Gradient and RF non linearity in ADC measurement using EPI Diffusion-Weighted MRI

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Purpose

Diffusion-weighted imaging (DWI) has become an indispensable tool in clinical routine, in neuro as in body MR imaging [1-3]. DWI has the ability to extract informations about tissue microstructure from MR signal intensities, giving to the Radiologist useful details to assess the presence or absence of abnormalities, and even their nature. Its application ranges from treatment monitoring in different physiological regions [2,4] to functional characterization to tissue geometry as in DTI [2].

A particular interest is devoted to quantitative approaches, i.e., to the evaluation of ADC of a particular region, or lesion, or tissue and its direct comparison with some other "paradigmatic" value obtained from other studies. Even more intriguing is the possibility to separate different contributions to the ADC itself, as for the so-called pseudo-diffusion and true diffusion [1].

Due to this broad field of interest, it is important to understand deeply the mechanisms which generate the signal and, maybe more importantly, the technical and technological aspects of its acquisition.

The physics behind the phenomenon of self-diffusion of molecules in fluids and its relation with the MR signal has been the topic of many important reviews and even books [2,3]. We will focus our attention on the problem of reliability of the quantitative measurement of the so-called apparent diffusion coefficient (ADC) using diffusion-weighted Spin-Echo Echo-Planar Imaging (EPI): a number of technical works and reviews have been already devoted to this field, in order to clarify advantages and drawbacks of such technique (as a little extract of such a large literature, see for example Refs. [5-9]).

Unfortunately, by its nature, MR signal is a complicated multi-parametric technique; the study of the ADC only as a function of the spatial direction for a single \(b\)-value as in [7] or of the effect of eddy currents produced by the diffusion gradients on the imaging gradients, as in [9], even if well done and complete by itself, it is still not enough.

Our goal is to study the reliability of the measurements of ADC as a function of \(b\) both along different spatial directions and using different fat saturation techniques: the first part will regard the effect of imaging gradients and the second the effect of RF pulses.
Methods and Materials

The measurements have been realized on a 3 Tesla MRI Equipment (Siemens Verio), with a 12-channel receive Matrix Head Coil, using a phantom realized by the Medical Physics Unit of the AOUC in Careggi (Florence, Italy), in the configuration shown in Fig. 1.

The phantom (see Fig. 2) is a plexiglass cylinder filled with an aqueous solution of Agarose (1.2% weight fraction) with an ADC, as reported in the AOUC group work [8], around $1950 \times 10^{-3} \text{m}^2/\text{s}$ (or 1950 mm$^2$/s, i.e. squared millimeter per second; in the following, each value will be expressed in those units: ADC as mm$^2$/s and b-values as s/mm$^2$). The phantom has been kept inside the examination room at all times to minimize the movement and to keep it at the temperature of such environment, so to avoid to perform measurements far from thermal equilibrium. Further, to take into account thermal effect on ADC measurements, a thermometer was inserted in the phantom, in contact with the solution.

Measurements have been performed in three distinct steps: initially, to check for gradient non-linearities, following the AOUC Medical Physics Unit, three series of diffusion-weighted images have been acquired with a multi-b scan, varying the orientation of the diffusion gradients (along the Readout, Phase and Slice gradient, respectively); a fourth series has been obtained with all the three orientation, in order to obtain a Trace image. In these series, the scan parameters were: nominal $b$ ranging from 0 to 1000, with steps of 100; Field of View 200 mm; Read matrix 128; Phase matrix 64; Phase partial Fourier=7/8; slice thickness/gap 9.0/2.7 mm; number of slices 5; $T_R=2000 \text{ ms}$; $T_E=90 \text{ ms}$; EPI factor=64; 2 averages; bandwidth=1446 Hz/pixel; iPAT factor=2; Scan duration=44" for the single-axis scan and 2'12" for the Trace series.

As a second step, to evaluate RF non-linearities, a diffusion-weighted Trace scan with only two $b$-values (0 and 1000) has been repeated on the phantom, checking carefully the identity of all parameters but the fat suppression technique: one without RF pulse (no fat suppression), three with a spectrally selective pulse (Spectral Adiabatic Inversion Recovery pulse -SPAIR-, FatSat and Water Excitation) and a fifth with a non spectrally selective pulse (Inversion Recovery, $T_I=220 \text{ ms}$). The scan parameters for these sequences were: nominal $b=0$, 1000; Field of View 200 mm; Read matrix 128; Phase matrix 128; Phase partial Fourier=7/8; slice thickness/gap 9.0/2.7 mm; number of slices 5; $T_R=2000 \text{ ms}$; $T_E=90 \text{ ms}$; EPI factor=100; 4 averages; bandwidth=1428 Hz/pixel; iPAT factor=2; Scan duration=40". Each sequence has been repeated twice, in order to evaluate the SNR reliably, even in the presence of a Phased-Array Coil together with a parallel imaging technique, using the method of the difference [10].
Finally, to check for the significance of the Signal-to-Noise Ratio (SNR) in a ADC measurement, a third series of multi-b scans have been performed, with nominal b ranging from 0 to 3000, with steps of 300; again, this series has been repeated four times, with the four different fat suppression technique described above. The scan parameter were: nominal b ranging from 0 to 3000, with steps of 300; Field of View 200 mm; Read matrix 128; Phase matrix 64; Phase partial Fourier=7/8; slice thickness/gap 9.0/2.7 mm; number of slices 5; TR=2600 ms; TE=116 ms; EPI factor=64; 4 averages; bandwidth=1446 Hz/pixel; iPAT factor=2; Scan duration=2'04". The diffusion gradients were applied only along the least perturbed direction in our measurements (see below), i.e., the Readout gradient one. Each sequence has been repeated twice, in order to evaluate the SNR reliably, even in the presence of a Phased-Array Coil together with a parallel imaging technique, using the method of the difference [10].

In each single case, the temperature of the phantom prior and after the measurement has been recorded, without noticing any significant heating due to RF power (SAR) released inside the phantom. However, due to a careful variation of the environmental conditions, we had the possibility to acquire ADC values in a temperature range between 18.0 and 23.0 Celsius degrees, allowing to evaluate the temperature dependence of the ADC (Fig.6), which corresponds to a change of (2.42±0.06)% per degree around 20 degrees, in fair agreement with what reported by the AOUC group [8]. Using this result, we re-normalize all the data to a reference temperature, taken arbitrarily at 20 Celsius degrees.
Fig. 1: The 12-channel Matrix Coil used in our experiments, with the phantom described in Fig. 2 inside, placed on a soft mattree to minimize vibration effects.

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Fig. 2: The phantom realized by the Medical Physics Unit of the AOUC of Florence, Italy. It is a plexiglass cylinder, filled with an aqueous solution of Agarose (1.2% weight fraction) with a thermometer in close contact with the solution, to keep track of thermal effects on measured ADC.

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Fig. 3: A typical series of images obtained with the multib sequence used in our first experiment. Those images are obtained with a very basic multi-b diffusion-weighted EPI scan, and parameters have been set to match the experiment in Ref.[AOUC].

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**Fig. 4:** Five ADC maps from experiment 2. It is apparent, even at glance, the discrepancy in the IR ADC map.

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**Fig. 5:** Four sets of images from experiment 3: even at a glance, the IR scan has a strongly lower SNR and the high b images are unreadable.

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Results

Experiment 1

The first run of acquisitions, with b ranging from 0 to 1000 with step of 100, has been analyzed as follows: on the third image for each b-value acquisition, we have drawn a Region-of-Interest (ROI) on at least the 80% of the image; we have recorded the mean signal intensity in the ROI; copying the ROI from one b-value acquisition to another, and also from one diffusion gradient direction to another, we have calculated the ADC values for each b and for each diffusion direction. Taking the average for each b and for each direction, we have obtained a representation of the ADC as a function of b from 0 to 1000 for the three different diffusion directions and also for the Trace, see Fig. 7.

It has to be noted that the Trace values, obtained from direct evaluation of the images or from the arithmetical average of the ADC value over the three directions, were strictly consistent.

As a further check, we obtained the ADC as a linear fit of the logarithm of the signal intensities, normalized to the $b=0$ value, following the well-known formula $S_b/S_{b=0}=e^{-bD}$: it has to be stressed that our values did not coincide with those obtained from the automated post-processing of the MRI equipment, even if we used exactly the same procedure as they do. Our calculated ADC have shown a slight deviation towards higher values with respect to the automated ones, and this deviation has shown a temperature dependence itself, being higher for higher temperatures. This bias, even if well below the experimental error (see below), is reproducible and seems to be a systematic error in the calculation. No explanation of this deviation has been received till now from the manufacturing company.

All the data presents a strong repeatability. The statistical error (three standard deviations) for each b-value is not larger than 2.5% at low b and 1.7% at high b (see Fig. 8), even after temperature normalization which can introduce further instability in the data. On the other hand, a strong discrepancy between ADC obtained with different diffusion gradient orientation is apparent; following the AOUC group, we take as a reference value the ADC obtained for the Trace at $b=1000$ (see Fig. 9); at low b's, the deviation from this value is larger than 6% for the Phase (ADC$_{\text{Phase}}$) and it is almost 5% for the Slice (ADC$_{\text{Slice}}$). For these two directions, the deviations shrink till 2% at the highest explored b, where the ADC's look to tend to different "asymptotic" values, i.e., there is no matching of ADC's even at high b.

The ADC$_{\text{Read}}$ shows a completely different behavior, being almost constant for every b, with a discrepancy with ADC$_{\text{Trace}}$ of the order of 1% at all b's.
A possible explanation of the different behavior of ADC along the various spatial directions has to be found in the temporal diagram of the sequence. Assuming that the deviations are a consequence of eddy currents due to the imaging gradients [6,7] applied along the same spatial direction, we can consistently conclude that the temporal diagram of our sequence should have the form in Fig. 10; this is consistent both with the amplitude of the deviation (larger for ADC\textsubscript{Phase} and ADC\textsubscript{Slice}, smaller for ADC\textsubscript{Read}) and their sign (positive for ADC\textsubscript{Phase}, negative for ADC\textsubscript{Slice}). We are waiting a definitive answer from the manufacturing company to check our conclusions (sequence temporal diagrams are considered "absolutely confidential" informations). If the MPG are on the Phase axis, due to the presence of the pre-phasing gradient, the diffusion dephasing lobe will be more affected than the rephasing one; if they are on Slice axis, the situation will be the opposite, resulting in a sign inversion in the deviation of the ADC. Finally, if the MPG are on the Read axis, due to the fact that the pre-phasing lobe falls after the diffusion sequence, the deviation will be minimal.

We analyzed the data in terms of the well-known concept of "cross-terms" [6,7]; following Ref. [7], one can assume that the imaging cross term $b\textsubscript{ct}$ in $b=b_d+b\textsubscript{ct}$ would be constant across all nominal $b$ values of the series ($b_d$ is the effective $b$-value): in fact, all imaging parameters (FoV, Read Matrix and Phase Matrix) are obviously unchanged during the scan. As a consequence, one should be able to estimate $b\textsubscript{ct}$ taking the highest explored $b$ and assuming $b\approx b_d$ at this value. Unfortunately, this is not the case: $b\textsubscript{ct}$ is $b$-dependent, varying in the range 2-5% and showing a systematic increase in absolute value when $b$ grows from 0 to 1000; therefore, the theoretical interpretation of Ref. [7] does not apply to our results and in particular it is opposite to our observations the assumption that the Phase direction would be the least sensible to cross terms.

Amazingly enough, due to an almost complete compensation of the discrepancies in ADC\textsubscript{Phase} and ADC\textsubscript{Slice}, ADC\textsubscript{Trace} shows a behavior which is comparable to the Read case. This cancellation should not be taken as an advantage, due to the fact the experimental errors in the Phase and Slice directions must add in the Trace error value, as it is reported in Fig. 11. As one can see, the uncertainty in ADC\textsubscript{Trace} is three times larger than in each single directions.

**Experiment 2**

The second series of acquisition have been boosted by the incidental observation that different fat saturation techniques gave different ADC on heteroplastic breast lesions.

After temperature normalization, we have taken the average of the obtained ADC and compared them, taking as an experimental error three standard deviations (99.3% of the data).

The results are reported in Fig. 12.
The ADC values obtained by the scans with spectrally selective fat saturation RF pulses, even if always higher than the ADC of the non saturated scan, are pretty consistent, at least taking as experimental error three times the standard deviation. The scan with non spectrally selective RF pulse gives always smaller values of ADC, and there is only a slight overlap of the error bar with the non saturated scan, and it is inconsistent with the other saturated scans. The interpretation of such an effect is not simple; in fact, the typical underestimation of the IR-saturated scan can be explained due to a rapid fall of SNR of the image at high $b$ with respect to the one at $b=0$ (see below, Experiment 3). On the other hand, the spectrally-selective saturated scans show anyway a reproducible deviation from the non saturated scan, which is a symptom of a RF cross-term in the nominal $b$.

**Experiment 3**

The third series have been motivated by both the experimental result reported above. We have taken again the ADC values for each $b$-value, and observed the deviation from almost constancy in the Readout direction. The results regarding the effect of the SNR on the ADC values, are summarized in the Figs. 13 and 14. The measured ADC (for sake of simplicity, normalized at the value at $b=300$) shows a plateau till a sequence-dependent $b$ value, at which a strong deviation can be seen towards lower values. This can be explained by the fall in SNR at the same $b$ value: the threshold at which the deviation is observed corresponds to a SNR value around 4. At larger $b$ values SNR and ADC show again a plateau: the first is related to an overestimate due to the registration of noise and the second to a subsequent underestimate, due to the "saturation" of the value of SNR for the images at high $b$.

In Fig. 15, a detail of Fig. 14 is shown to stress the importance of the threshold at SNR=4. The IR-saturated scan falls very rapidly under the threshold (with $b$ between 900 and 1200), while the spectrally-saturated scans are able to explore a much more deep region of high $b$, falling below the threshold only when $b$ is larger than 2100.

Obviously, intrinsic SNR depends on the true value of the diffusion coefficient of the sample: if this value is sufficiently low (strongly restricted diffusion), SNR can be higher and the exploitable region grows towards higher values of $b$. On the other hand, when the diffusion coefficient is pretty high, as in our phantom, this region shrinks to very low values of $b$. 
Fig. 6: The temperature dependence of the measured ADC. The higher values have been calculated by us, by a linear fit of the logarithm of the signal intensities at various b; the lower values have been given by the automated post-processing of the MRI equipment. The linear fit versus the temperature is shown for both curves.

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Fig. 7: The ADC values measured on the phantom, with diffusion gradients directed along three spatial directions (Phase, Slice, Read), and with an isotropic Trace scan. Note the discrepancy in ADC even at high b-values.

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Fig. 8: The relative statistical error (three standard deviations, corresponding to take into account more than 99% of the data) in percent, for the various series along all the spatial directions and for the Trace.
**Fig. 9:** The relative deviations, in percent, with respect to the value of the ADC for the Trace at \(b=1000\). It is evident the strong deviation when the diffusion gradients are applied along the Phase and Slice directions. The ADC in the Read direction is instead pretty constant, showing a small dependence on \(b\). The Trace is almost constant, too, but this can be due only to an almost exact cancellation of the errors along the Phase and the Slice.
Fig. 10: A possible explanation of the pattern of our deviations can reside in the temporal diagram of our sequence itself.

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**Fig. 11:** Same Figure as in Fig.7, with the full experimental error bars as expected from the error propagation. It's easy to see that the ADC value obtained from the Trace has a very large error with respect to the single axis measurement,

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![Graph showing ADC values with error bars](image)

**Fig. 12:** Five different values of ADC obtained on the phantom, under the same conditions and with the same scan, apart for different fat saturation techniques: one is non saturated (no RF pulse), three are spectrally selective methods (SPAIR, FatSat, Water Excitation) and the fifth is non spectrally selective (Inversion Recovery). Note the discrepancy between the non saturated scan (reasonably the least affected by RF cross terms) and the other results. In particular, the IR value is evidently inconsistent with all the other techniques. The error bars are not single standard deviations, but full statistical errors, i.e., three times the standard deviation.

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Fig. 13: The deviation in ADC in multi-b scan due to the fall of SNR at high b-values, for the same scan but with four different fat saturation technique, three spectrally-selective (SPAIR, FatSat, Water Excitation) and one non-spectrally selective (Inversion Recovery).

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Fig. 14: The SNR as a function of the nominal b-value for all the four fat saturation techniques used in our experiment 3. It is immediately apparent the very low starting value of the Inversion Recovery sequence and its almost immediate saturation below the threshold of reliability (see text).

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Fig. 15: The detail of the SNR at high b-values for the same scan but with four different fat saturation techniques, three spectrally selective (SPAIR, FatSat, Water Excitation) and a fourth non spectrally selective (Inversion Recovery). The "threshold" line is only a guide for the eye.

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Conclusion

In our experiment 1, measuring the ADC of a homogeneous and isotropic phantom with multi-\(b\) sequences, we have found strong deviations depending on the various spatial directions of application of the diffusion gradients. The differences in ADC along the various axes tend to join at high \(i\)-values, while the imaging parameters remain unchanged.

Therefore, the deviations can be interpreted as due to corrections to the nominal \(b\) given by \(b\)-dependent cross-terms generated by the imaging gradients; in our sequence, the cross-terms are likely to be originated by the pre-phasing Phase gradient and by the Slice selective gradient associated to the refocusing pulse in SE-EPI. We are waiting a hint from the manufacturing company, in order to analyze directly the temporal diagram of the sequence.

Our guess cannot be considered conclusive due to the fact that the diffusion-weighted sequences commercially available on our MRI equipment use bipolar diffusion gradients [11], i.e., the motion-probing procedure contains two dephasing and two rephasing lobes, and as a consequence the sequence is twice-refocused. For the same reason, a direct comparison with the results of the AOUC group is impossible (the motion-probing procedure in this case is likely to be a standard Stejskal-Tanner technique, with unipolar gradients and a single refocusing pulse): in fact, in their measurement they found quantitatively comparable discrepancies but a completely different pattern of the deviations [7].

In our results, one axis (Read) gives an almost constant ADC as a function of \(b\). We can conclude that this is the least disturbed direction and the one we can use to study isotropic systems reliably (with the advantage of using a shorter \(T_E\), for example). The problem arises in the clinical suspect of a bi-exponential decay in non isotropic tissues: in those cases, the bi-exponential fit can be strongly affected by systematic errors, in particular at low \(b\)'s, where perfusion effects should be important [1-3].

A scan technique to cancel out imaging cross terms has been described some year ago by Neeman et al. [6]: any diffusion sequence should be acquired twice, inverting the direction of the diffusion gradients (i.e., changing their phase by 180°); then, the geometric mean of the signal intensities will be free of cross terms. This approach should be easily implementable on every MRI equipment; unfortunately, it is usually just a step ahead of the commercially available software, even when the diffusion tensor imaging have been acquired. A second drawback is that the scan time will be doubled, but this should not be a strong concern when dealing with DWI.
In experiment 2, we have observed a discrepancy in the ADC when using different fat saturation techniques: in particular, the non spectrally selective pulse saturation (inversion recovery) gives inconsistent results with the spectrally selective pulse saturations (SPAIR, FatSat and Water Excitation) and barely consistent with the non saturated scan; on the other hand, the non saturated scan gives again a different result, signaling the presence of an RF interference (RF cross-term) which, even at high b's (1000), can induce errors in direct comparisons of quantitative results: great attention must be payed in using absolute values of ADC, obtained with different sequences or with the same sequence but on different MRI equipments.

The technique described above for the diffusion gradients to avoid imaging cross terms should work even in the case of RF pulses: again, the scan time will be doubled.

Finally, our experiment 3 has allowed us to estimate an SNR threshold for the reliability of the ADC measurements, which we evaluated to be around 4. For SNR lower than the threshold, a fatal underestimation of the ADC is to be expected, even if the measurements are repeatable. From this point of view, the Inversion Recovery technique tends to be much less robust of the other saturation techniques, even if much less prone to susceptibility artifacts. As it is well-known, the SNR in DWI is related to the amount of diffusion of the underlying tissue and to b-value: therefore, there is a limitation in the b-value, as a function of the fat saturation technique used for DWI.

As a final remark, it is worth to stress the fact that we used deliberately a low-resolution sequence. Increasing the pixel inevitably will require higher pre-phasing gradients, increasing consequently the discrepancies [7]. Our results strongly recommend a careful calibration of each single MRI equipment, even by the Medical Physicist or the Radiologist, to avoid wrong conclusions due to the described pitfalls.

Furthermore, a re-examination of the calibration procedures is probably in order here.
References


Personal Information