Validation of adc measurements with DW-EPI scans as a function of b-value using tensor acquisitions

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Authors: C. Biagini¹, C. Biagini¹, M. Cardullo², L. Natale¹; ¹Sesto Fiorentino/IT, ²Firenze/IT
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Diffusion-weighted imaging (DWI) has become an indispensable tool in clinical routine, both in neuro as in body MR imaging [1-3]. DWI has the ability to extract information about tissue micro-structure from MR signal intensities, giving 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 [2,4,5] to functional characterization to tissue geometry as in DTI [2].

A particular interest is devoted to quantitative approaches, i.e., the measurement of the water diffusion coefficient 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 diffusion coefficient itself, as for the so-called pseudo-diffusion and true diffusion [1]. In particular, very recently [6], it has been reported the ability of low b-value diffusion-weighted imaging of the prostate and rectal wall to identify and characterize heteroplasic lesions in the gland. Analogously, different quantitative approaches has been proposed in order to perform reliable and repeatable interpretations of diffusion data [7-9].

To distinguish between those contributions, and in particular to address the problem of characterization of tissue perfusion, or pseudo-diffusion, in Body MR imaging, it is necessary to rely on ADC measurements at different b-values, starting at very low b's, as in Ref. [6], to arrive at very high thresholds (b>3000 s/mm²) in particular districts of the Body (i.e., the prostate). All those measurements are certainly affected by fluctuations due to patients variability (collaboration, patho-physiological conditions and other contingent conditions), but should not be affected by the equipment: as a consequence, we will focus our attention on the problem of reliability of the quantitative measurement of the 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. [10-15]).

In our opinion, it is fundamental to understand deeply the mechanisms which generate the signal and, more importantly, the technical and technological aspects of its acquisition. In effect, all the clinical studies usually assume that the measurements are reliable and repeatable, and that the systematic errors are practically negligible; here, with the expression "systematic error" we intend exactly unpredictable errors due, for example, to misfunctioning of the equipment, which can modify the result of a measurement in a profound way (for a simple introduction to the theory of errors in experiments, see Ref. [16]). Therefore, an initial validation of the diffusion measurements is necessary. Unfortunately, by its nature, MRI is a complicated multi-parametric technique; the study of the ADC only as a function of the spatial direction of application of diffusion gradients for a single b-value as in Ref. [11] or of the effect of eddy currents produced by the diffusion
gradients on the imaging gradients, as in [12], even if well done and complete by itself, it is still not enough.

Our goal was twofold: first, we studied the reliability of the measurements of the ADC as a function of b both along different spatial directions, to estimate the effect of the imaging gradients. Having found important deviations from the expected values in this first run, we took a second step: using a non-commercial Work-In-Process advanced diffusion protocol (Siemens, Erlangen-Berlin, Germany), we extended our analysis to lower b-values and to the direct calculation of the components (diagonal and off-diagonal) of the diffusion tensor, to explore the possibility of a mis-calibration of a single gradient coil.
Methods and Materials

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

The phantom 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 [13,14], around $1.95 \times 10^{-3}$ mm$^2$/s (in the following, each value will be expressed in those units: ADC as mm$^2$/s and b-values as s/mm$^2$) at 20 Celsius degrees. The phantom has been kept inside the examination room at all times to minimize the movement and to keep it at the temperature of the environment, as 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.

The second run of measurements have been performed using a spherical 17cm phantom present in the standard phantom set of the Siemens Verio equipment, with ADC around $2 \times 10^{-3}$ at 20 Celsius degrees. The reason for that choice was its geometry (spherical vs. cylindrical): in fact, a cylindrical phantom could be affected by direction-dependent vibrations due to the mechanical vibrations of the equipment during the scans; moreover, the fact that the temperature inside the first phantom remained absolutely constant during a single experimental session, signaling a very low SAR, i.e., allowed to avoid the use of the internal thermometer.

Measurements have been performed in two distinct steps: initially, to check for gradient non-linearity, 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; $T_R=2000$ ms; $T_E=90$ 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.

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.2), which corresponds to a change of $(2.42\pm0.06)\%$ per degree around 20 degrees, in fair
agreement with what reported by the AOUC group [13,14]. Using this result, we re-normalize all the data to a reference temperature, taken arbitrarily at 20 Celsius degrees.

In the second step, a multi-b sequence with $b=(10, 20, 40, 80, 150, 200, 300, 400, 600, 800, 1000, 1200, 1500, 1800, 2000)$ has been acquired in the axial plane at different environmental temperatures (20 to 23 Celsius degrees), with diffusion gradients aligned with the following six diffusion directions: $(1,0,1), (-1,0,1), (0,1,1), (0,1,-1), (1,1,0)$ and $(-1,1,0)$. Those directions are the standard acquisition directions for the six-directions DW-EPI in Siemens.

The other main parameters of the sequence are Field of View 200 mm; Read matrix 100; Phase matrix 100; Phase partial Fourier=Off; slice thickness/gap 9.0/4.5 mm; number of slices 7; $T_R=4000$ ms; $T_E=95$ ms; EPI factor=100; 2 averages; bandwidth=1516 Hz/pixel; iPAT factor=2; Scan duration=12'20".

The same acquisition has been repeated with different geometry: Axial (with the Phase encoding axis directed along the x direction, Read encoding axis along the y direction and the Slice selection axis along the z direction), Coronal (Phase again along x, Slice along y and Read along z) and Sagittal (Slice along x, Phase along y and Read along z). For completeness, a number of checks have been made, in particular Alternate Polarity and Monopolar diffusion gradients sequences have been used to acquire images in the Axial geometry to be compared with the standard Bipolar diffusion sequence [17].

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 [18-22].

During this run, having shown that the temperature of the solution inside the phantom of the first run did not change even after long scans, we recorded only the environmental temperature, keeping the phantom inside the magnet room at all times. We acquire data at three different temperatures (20, 21, 22 Celsius degrees) but we did not even try to obtain an ADC vs. temperature plot with only three points.
**Fig. 1:** 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 the internal temperature.

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**Fig. 2:** 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.
Results

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. 3.

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 \( \frac{S_b}{S_{b=0}}=e^{-bD} \): 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. 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.

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 \( b \), even after temperature normalization which can introduce further instability in the data. On the other hand, the ADC’s obtained with different diffusion gradient orientation are manifestly inconsistent; following the AOUC group, we take as a reference value the ADC obtained for the Trace at \( b=1000 \) (see Fig. 4); at low \( b \)’s, the deviation from this value is larger than 6\% for the Phase (ADC_{Phase}) and it is almost 5\% for the Slice (ADC_{Slice}). For these two directions, the deviations shrink till 2\% at the highest explored \( b \), where the ADC’s tend to different “asymptotic” values, i.e., there is no matching of ADC’s even at high \( b \).

The ADC_{Read} shows a completely different behavior, being almost constant for every \( b \), with a discrepancy with ADC_{Trace} of the order of 1\% at all \( b \)’s.

We analyzed the data in terms of the well-known concept of "cross-terms" [11,12]; one can assume that the imaging cross term \( b_{ci} \) in \( b=b_{d}+b_{ct}+b_{img} \) would be proportional to the square root of \( b \) across all nominal \( b \) values of the series (\( b_d \) is the effective diffusion \( b \)-value, \( b_{img} \) is the contribution to the overall \( b \) due to the imaging gradients, which is simplified out in the ratio \( S_b/S_0 \): in fact, all imaging parameters (FoV, Read Matrix and Phase Matrix) are obviously unchanged during the scan and, being \( b_d\sim G_d^2 \) and
$b_{\text{img}} \sim G_{\text{img}}^2$, one can reasonably assume $b_{\text{ct}} \sim G_d G_{\text{img}} \sim b_d$. As a consequence, one should be able to estimate $b_{\text{ct}}$ using the following (somewhat involved) approximate procedure:

- take the highest explored $b$ and assume $b^{\text{high}}_d b^{\text{high}}_{\text{ct}}$ at this value;
- calculate the ADC$_{\text{Trace}}$ at $b^{\text{high}}$ and assume it as a reference value ADC$_{\text{ref}}$ (it can be considered the most stable of all the ADC’s obtained till here);
- calculate the product $S_{\text{ref}} = (b^{\text{high}}_d \text{ADC}_\text{ref})$ which will be the reference signal intensity;
- calculate the $b$-dependent signal intensity $S_{b,\text{ref}} = \text{ADC}_\text{ref} b^{\text{high}}_d$;
- calculate the deviation from the reference signal intensity for each axis $S_{b,\text{axis}} = S_{b,\text{ref}} - S_{b,\text{axis}}$ (where "axis" = Phase, Slice or Read);
- fit the obtained curve as $S_{b,\text{axis}} = \alpha_{\text{axis}} b^{\text{high}}$.

The results for $\alpha_{\text{axis}}$ and the linear regression coefficient $r$ are reported in Table 1, while the calculated $b_{\text{ct}}$ are listed in Table 2. Amazingly enough, given the amount of deviations in the various axis, the relative value of $b_{\text{ct}}$ with respect to the effective $b_d$ is almost the same in all axis.

<table>
<thead>
<tr>
<th></th>
<th>Phase</th>
<th>Slice</th>
<th>Read</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>-0.0011</td>
<td>0.0013</td>
<td>0.0004</td>
</tr>
<tr>
<td>$r$</td>
<td>0.989</td>
<td>0.983</td>
<td>0.980</td>
</tr>
</tbody>
</table>

Table 1: The values of the obtained angular coefficient between $S_b$ and $b$ for each axis, along with the linear regression coefficient $r$

<table>
<thead>
<tr>
<th>$b$</th>
<th>$b_{\text{ct}}/b_d%$ (Phase)</th>
<th>$b_{\text{ct}}/b_d%$ (Slice)</th>
<th>$b_{\text{ct}}/b_d%$ (Read)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>21.7</td>
<td>22.7</td>
<td>10.0</td>
</tr>
<tr>
<td>200</td>
<td>14.3</td>
<td>17.1</td>
<td>12.8</td>
</tr>
<tr>
<td>300</td>
<td>12.0</td>
<td>13.4</td>
<td>11.8</td>
</tr>
<tr>
<td>400</td>
<td>9.8</td>
<td>11.6</td>
<td>11.4</td>
</tr>
<tr>
<td>500</td>
<td>9.0</td>
<td>10.2</td>
<td>10.0</td>
</tr>
<tr>
<td>600</td>
<td>8.7</td>
<td>8.9</td>
<td>8.2</td>
</tr>
<tr>
<td>700</td>
<td>8.0</td>
<td>8.1</td>
<td>8.4</td>
</tr>
<tr>
<td>800</td>
<td>7.7</td>
<td>7.2</td>
<td>7.3</td>
</tr>
<tr>
<td>900</td>
<td>7.2</td>
<td>6.8</td>
<td>7.6</td>
</tr>
</tbody>
</table>
Table 2: The relative value of the cross term with respect to each $b_d$ along the three encoding axis

A comment is in order here: the theoretical interpretation of Ref. [12] only partially apply to our results; in particular it is opposite to our observations the assumption that the Phase direction would be the least sensible to cross terms.

It is worth to stress that, due to an almost complete compensation of the discrepancies in $\text{ADC}_\text{Phase}$ and $\text{ADC}_\text{Slice}$, $\text{ADC}_\text{Trace}$ shows a behavior which is comparable to the Read case. Anyway, this probably accidental cancellation should not be taken as an advantage.

In the second run, we directly acquired the diffusion tensor components; in our equipment, it is possible to acquire 6- or 12-direction diffusion scans but it is not present a post-processing software like a DTI reconstruction. As a consequence, only the final mean diffusivity $D$ map and a Trace map were automatically produced, together with the native images along each diffusion direction. Therefore, in the second experiment, we analyzed each native image in the following way: we took the central image of the seven previously acquired; draw a ROI covering at least the 80% of the phantom and register the signal intensity. This has been done for each $b$-value and diffusion direction, resulting in $1 + (6 \times 15)$ images to be analyzed, the first one being the $b=0$ reference. Then, the logarithm of the relative signal attenuation divided by the corresponding $b$-value has been calculated and registered as $s_i$ with $i=1$ to 6.

Reconstructing the $b$-matrix starting from the given diffusion directions and following standard linear algebra manipulations [23], from the six values obtained for each $b$-value, we recovered the six independent diffusion tensor elements $D_{ab}$.

For a homogeneous and isotropic phantom, the expected values are of course $D_{xx} = D_{yy} = D_{zz} = D # 2 \times 10^{-3}$ mm$^2$/s and $D_{xy} = D_{yz} = D_{zx} = 0$, within experimental errors.

We have distinguished the measurements in two steps: in the first step, a number of acquisitions have been repeated in the same geometry (Axial) in order to check the statistical fluctuations; we stop after only twelve repetitions for each environment temperature, having observed a strong repeatability of our measurements and being sufficiently confident of the stability of the results after the first run (see above). In the second step, we simply acquired just two set of images per geometry (Axial, Coronal, Sagittal) and compared the results. Moreover, in the second step, we acquired another set of images disabling the built-in image filter typical of our equipment in order to evaluate its impact in particular on low $b$-values acquisitions.

**Bipolar diffusion gradients in fixed Geometry**
The results are displayed in Fig. 5 for the diagonal components of the Diffusion Tensor and in Fig. 6 for its off-diagonal components. A large deviation from the expected fully diagonal tensor is apparent at low b-values, and a stable diagonal matrix is recovered only at b's of the order of 400 s/mm², manifesting a strong disturbance on the effective b-value at lower values. The deviations tend to the same "asymptotic" value, together with the Mean Diffusivity (MD) calculated by us, and also the MD automatically calculated by the equipment: this last value has a very disturbing behavior at low b's, showing an even higher degree of deviation with respect to the diffusion tensor components and their average. All the values almost merge at b larger than 1000 s/mm² and then one can trustfully take those values of the MD (or even of a single tensor component) as a reference value.

The statistical error (three standard deviations) is much smaller than the observed discrepancies (about 3 times smaller in the worst case) signaling a high stability and repeatability of the measurements. In particular, the pattern of the results is very robust, showing always a very high value of $D_{xx}$, an intermediate value of $D_{yy}$ and a low value of $D_{zz}$ for b less than 300-400 s/mm². Furthermore, the off-diagonal components of the tensor show high $D_{xy}$ and $D_{zx}$ for low-to-intermediate b-values but a $D_{yz}$ compatible with zero at all b-values.

It is worth to stress that the deviations $D_{ii}-D_{2000}$ (where $ii=xx,yy,zz$ and $D_{2000}$ is the MD value at b=2000 s/mm²) do not have a square-root of b behavior, at least in the high deviations interval; this is in contrast with the usual assumption that those deviations are related to cross-term interference [11,12], as for our initial conclusion in the first run. To better assess this statement, we realized a number of acquisitions using the Alternate Polarity of the diffusion gradients, without changing any other parameters; taking the geometric mean of the signal intensity between two acquisitions [11], we recalculate the diffusion tensor components and we could not observe any significant change in the final result.

The Monopolar diffusion gradients acquisitions were not significant, owing to a higher degree of deviations but also a higher value of the diffusion tensor components: these deviations are still to be analyzed by our group.

**Bipolar Diffusion Gradients in variable Geometry and comparison with unfiltered acquisitions**

In the previous experiments, a very high grade of "repeatable variability" of the diffusion coefficient measurement has been demonstrated as a function of the b-value and of the direction of application of the diffusion gradients with respect to the image axis. Unfortunately, this observation does not by itself allow the Physicist or the Technologist to distinguish if the affected image axis is the physical magnet axis or the relative (parallel) encoding axis. To decide between the two, it is necessary to repeat the acquisition in different geometries and changing the encoding axis.
**Axial Geometry:** In this geometry, the magnet coordinate system corresponds to the following orientation of the imaging gradient coordinate system (x,y,z)# (P,R,S) where P is the phase encoding gradient direction, R the frequency encoding (or readout) one and S the slice selection gradient direction. The result of this measurement is reported in Fig. 7 for the diagonal components only. Note that the curve of the diffusion components can be identified also by the sign of their second derivative with respect to b, i.e. by their convexity: the P curve has a monotonic decreasing behavior, the S a monotonic increasing behavior while the R behavior is initially increasing and then decreasing, even if of much smaller amplitude than the other two. The overall pattern is strictly matched on what we observed in the Experiment 1 of first run (see e.g. Fig. 4): the non-monotonic behavior of the R component shows up for b less than 100 and therefore cannot be observed in our first set of measurements.

The MD (both "man" and "auto") curve is monotonically increasing in this geometry. Actually, its value should be considered almost meaningless at b-values at which the components of the diffusion tensor are not consistent among themselves.

Switching off the built-in image filter do not change qualitatively the results. However, a small "rigid" shift of the curves towards slightly smaller values can be seen.

**Coronal Geometry:** In this geometry, the magnet coordinate system corresponds to the following orientation of the imaging gradient coordinate system (x,y,z)# (P,S,R). The result of this measurement is reported in Fig. 8 for the diagonal components only. With respect to the Axial geometry, the convexity of the R curve has been inverted and its value has significantly been varied (it has been reduced of about 10%); the amplitude of the deviation of the P and S curve has quantitatively but not qualitatively changed. The spread in the values between different directions is enlarged while the mean diffusivity at b=2000 is almost equal.

Switching off the built-in image filter do not change qualitatively the results. However, a small "rigid" shift of the curves towards slightly smaller values can be seen.

**Sagittal Geometry:** In this geometry, the magnet coordinate system corresponds to the following orientation of the imaging gradient coordinate system (x,y,z)# (S,P,R). The result of this measurement is reported in Fig. 9 for the diagonal components only. Here an amazing qualitative change has happened with respect to the Axial geometry: again the P curve is the most deviated with respect to the mean diffusivity at high b, but now the deviation has changed sign and the curve is monotonically increasing. On the other hand, the other two directions (R and S) remain almost unchanged and this is reflected by the fact that the mean diffusivity curve is highly non constant, in a much worst way than in the other two directions; on the other hand, the fact that Axial and Coronal mean diffusivity is more constant cannot be taken as a quality check: in fact, it is only related to a probably accidental cancellation of systematic errors.
Switching off the built-in image filter do not change qualitatively the results. However, a small "rigid" shift of the curves towards slightly smaller values can be seen.

**A single case:** As a final check of our work, we studied a single patient in our Onco-DWI research protocol [24] for the study of the efficacy of the therapy in prostate carcinoma (conventional MRI, DWI and DCE PWI) and add to it a multi-b scan with b ranging from 0 to 2000, qualitatively and quantitatively comparing the results of the different perfusion and diffusion techniques. In our protocol are included two different diffusion-weighted scans (with b=0, 500, 1000 and b=0, 1100, 2200) and a dynamic contrast-enhanced (DCE) perfusion-weighted scan with 90 phases of about 4 s each, with comparable spatial resolution. We recorded the automatically evaluated ADC for normal tissue and for a single lesion (respectively, $1.57 \times 10^{-3}$ and $1.01 \times 10^{-3}$ for the first scan and $1.21 \times 10^{-3}$ and $0.790 \times 10^{-3}$ for the second scan); the DCE series has been processed with a dedicated software (Tissue4D, Siemens, Erlangen) to obtain Tofts's model parameters [25] ($K_{\text{trans}}=0.288$ and $0.565 \text{ min}^{-1}$ and $v_{\text{e}}=0.285$ and 0.194 for normal tissue and lesion) in the same ROI's than in the DWI scans. The results, in fair agreement with the literature, signal a pathological region with a very fast perfusion with respect to the normal one, and with a reduced extravascular-extracellular space. This second observation is an indirect confirm of the "high cellularity" of the lesion with respect to the normal tissue, as is usually interpreted a reduction in ADC as what we have found in DWI scans. Nothing can be said, though, on the first statement about the high rate of perfusion of the lesion.

Using an IVIM post-processing software built-in the Work-In-Progress "advanced diffusion" package already mentioned, we re-analyzed the images of the multi-b scan; we copied the ROI’s onto this scan and evaluated the IVIM parameters $D_{\text{slow}}$, $D_{\text{fast}}$ and PF (in IVIM language, $D$, $D^*$ and $f$); the $D_{\text{slow}}$ parameter has been evaluated using only the "perfusion-free" region, i.e. $b>400$, then the $D_{\text{fast}}$ and PF parameters have been obtained by a two-parameter fit of the remaining points of the decaying signal. The value of the "slow" diffusion coefficient returned by the IVIM software is in very good agreement with the standard $b=2200$ DWI scan: $1.13 \times 10^{-3}$ and $0.795 \times 10^{-3}$ for normal tissue and lesion, respectively. On the other hand, the pseudo-diffusion coefficient (or fast diffusion coefficient) reads $10.0 \times 10^{-3}$ and $10.4 \times 10^{-3}$ while the perfusion fraction results 30% and 20%, respectively. This sounds at least "at odd" with the suggestion of the (robust) PWI technique that the tumor tissue is much more quickly perfused than the normal one.

It is not known how to quantitatively relate PWI and DWI but, qualitatively, our result is an apparent paradox. In our opinion, there is no reason to invoke complicated physiopathological phenomena to explain such a mystery, but only to realize that the so-called "perfusion region" at low-b's is the much affected by unpredictable and wild deviations from the expected value in phantom studies.
Fig. 3: 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.
**Fig. 4:** 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 errors along the Phase and the Slice.

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**Fig. 5:** Diagonal tensor components ($D_{xx}, D_{yy}, D_{zz}$) and Mean Diffusivity (MD) calculated manually by our group ("man") and automatically by the equipment ("auto") as a function of the $b$-value, at 20 Celsius degree. Note that the $b$ axis is not in scale to emphasize the region 0.

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**Fig. 6:** Off-diagonal tensor components (Dxy, Dyz, Dzx) as a function of the b-value, at 20 Celsius degree. It is apparent the anomalous deviation of the components regarding the correlation of the x axis with the other two. The Dyz component alone remains always compatible with zero.

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**Fig. 7:** Diagonal components of the Diffusion tensor in the Axial geometry (see text).

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Fig. 8: Diagonal components of the Diffusion tensor in the Coronal geometry (see text).

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Fig. 9: Diagonal components of the Diffusion tensor in the Sagittal geometry (see text).

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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 ADC's along the various axis tend to join at high b-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 mainly by the imaging gradients.

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, 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 [13].

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 are expected to be important [1-3].

A scan technique to cancel out imaging cross terms has been proposed some year ago by Neeman et al. [11]: 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.

Motivated by the results of our first run of measurements, we moved forward to the acquisition of the entire diffusion tensor which was expected to be a diagonal matrix, proportional to the identity matrix $D=D_0I$, where $I$ is a 3x3 matrix with only 1 on the diagonal elements and 0 on the other components. Unfortunately, this was not the case: very large deviations has been observed as a function of the b-value and the spatial direction. No correlation with the expected usual behavior #b-like of the cross-term disturbances [11,12] could be found, and alternating the polarity of the diffusion gradients together with
the geometric mean of the signal intensities did not show any substantial modification of the results, as it should be the case in the presence of simple cross-term interference. The derivative of the deviations with respect to the b-value is very large and shows a quickly increasing importance of the discrepancies when b moves toward lower values. This is in contrast with our conclusions in our first run of experiments, and remain in our experience completely un-interpreted.

To gain further insight into the possible origin of the deviations, we acquired the same 6-direction diffusion scan in different spatial geometries, Axial, Coronal and Sagittal, varying as a consequence the encoding direction with respect to the magnet axis, as described in the previous section.

By close inspection of the results, a number of conclusions can be drawn: first of all, one can say that the R encoding direction is the less quantitatively affected by the errors, being the most constant of all, even if it changes convexity passing form Axial to Coronal geometry and again from Coronal to Sagittal. The S and P directions are strongly affected, the second one both quantitatively as qualitatively, changing sign in different geometries (positive in Axial and Coronal geometry, negative in Sagittal geometry). In particular, in the Sagittal geometry, even the mean diffusivity results strongly deviated, due to the fact that all the tensor components have a negative difference from the reference value at b=2000.

The most important conclusion of our second run of measurements is that the errors manifest themselves in all the three magnet directions (x,y,z) without differences, while they depend both quantitatively and qualitatively from the gradient encoding directions, i.e. from the sequence design itself and the relative automated post-processing. It is worth to stress that deviations are present, and very large, in the interval 0<b<250, where the phenomenon of the pseudo-diffusion is assumed to be important in DWI measurements in the Body, in particular in the Liver. In this view, any IVIM interpretation [1] of multi-b sequences cannot be considered trustworthy, because of the presence of such large systematic errors, as it can be inferred from our direct comparison between IVIM results and DCE-PWI analysis in a patient with a hystologically proven prostate carcinoma.

Our results strongly recommend a careful periodical calibration of each single MRI equipment, even by the Medical Physicist or the Radiologist, to avoid wrong conclusions due to the described pitfalls, and in particular to establish the threshold below which the diffusion quantification becomes unstable of unreliable. In particular, this could explain the broad disagreement on the behavior of the IVIM parameters present to date in the Literature. Further insight is needed and a careful validation of multi-b sequences seems mandatory, before starting any in vivo evaluation.
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Personal Information

Cristiano Biagini
Physicist, Radiology Technician

Centro Oncologico Fiorentino
Via A. Ragionieri 101, 50019 Sesto F.no (Firenze), Italy
Phone: +39.0555301914
Mob: +39.3496272041

Email: cristiano.biagini@lacittadellasalute.it