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Diffusion weighted imaging of the prostate and rectal wall: comparison of biexponential and monoexponential modelled diffusion and associated perfusion coefficients

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Short Title: Modeling diffusion in the prostate and rectal wall
ABSTRACT

This study compares parameters from monoexponential and biexponential modelling of diffusion-weighted imaging (DWI) of normal and malignant prostate tissue and normal rectal wall (RW) tissues. 50 men with Stage Ic prostate cancer were studied using endorectal T2-weighted imaging and DWI with 11 diffusion sensitive values (b-values=0,1,2,4,10,20,50,100,200,400,800 s/mm²). Regions of interest (ROIs) were drawn within non-malignant central gland (CG) and peripheral zone (PZ), malignant prostate tissue (TU) and RW tissue. Both a monoexponential and biexponential model was fitted over varying b-value ranges, giving an apparent diffusion coefficient (ADC) from the monoexponential model and a diffusion coefficient (D), perfusion coefficient and perfusion fraction from the biexponential model. In all tissues, over the full range of b-values, the ADC from the monoexponential model was significantly higher than the corresponding D from the biexponential model. As the minimum b-value increased, the ADC decreased and was equal to D for some b-value ranges. The biexponential model best described the data when low b-values were included suggesting there is a fast perfusion component. Neither model could distinguish between benign prostate tissues based on diffusion coefficients, but the rectal wall tissue and malignant prostate tissue had significantly lower diffusion coefficients than normal prostate tissues. Perfusion coefficients and fractions were highly variable within the population so their clinical utility may be limited, but removal of this variable perfusion component from reported diffusion coefficients is important when attributing clinical differences to diffusion within tissues.

Keywords: Diffusion-weighted-MRI, prostate, biexponential decay, IVIM.

List of Abbreviations:

DWI – Diffusion Weighted Imaging
RW – Rectal Wall
ROI – Region of Interest
CG – Central Gland
PZ – Peripheral Zone
ADC – Apparent Diffusion Coefficient
D – Diffusion Coefficient
IVIM – Intra Voxel Incoherent Motion
PSA – Prostatic Specific Antigen
TU - Tumour
Introduction

Prostate cancer is currently diagnosed using endorectal sonographically guided saturation biopsy, but due to the morbidity and poor patient acceptability, a reliable technique for tumour detection which then enables targeted biopsy is desirable. T2-weighted MRI with external pelvic coils has been shown to have good specificity (90%) but low sensitivity (27.3%) for tumour detection (1). Endorectal receiver coils offer greater signal to noise ratio and hence allow greater spatial resolution and give a sensitivity of 85.3% for tumours larger than 1cm in diameter, but this falls to 26.2% for tumours less than 1cm (2). In order to improve on these values, other contrast methods used in conjunction with T2-weighted imaging are being investigated.

Diffusion weighted MRI (DWI) which exploits the differences in water diffusion between tissues is showing potential for improving prostate cancer detection (3,4) as the increased cellularity of many tumours is associated with reduced tissue water diffusion (5,6). Studies have used a range of diffusion-sensitisation values (signified by b-values), but most have assumed a monoexponential model to describe the changing signal from the prostate associated with an increasing diffusion gradient. In the brain, use of multiple diffusion-sensitisation values up to 6000 s/mm$^2$ in value produces a signal decay curve that is better described by a biexponential fit indicating two components of diffusion in tissue (7). These fast and slow components are believed to arise from extracellular and intracellular diffusion processes respectively, with slow diffusion also showing correlation with cell membrane density (8). Fast and slow diffusion coefficients in normal central gland (CG) and peripheral zone (PZ) tissue have been investigated using extended b-value ranges up to 3000 s/mm$^2$ (9). The intravoxel incoherent motion (IVIM) model (10-12) also suggests the existence of a third, much faster component of exponential signal decay associated with the effects of perfusion rather than diffusion. It has been shown that it is possible to improve distinction between tumour, oedema and normal tissue in the brain by increasing the minimum diffusion gradient to exclude these fast perfusion-based effects (13).
Accurate determination of the coefficients associated with diffusion and perfusion would enable them to be separately investigated for their clinical utility. The purpose of this study was therefore to use the IVIM biexponential model over a range of b-values in order to determine the coefficients associated with diffusion and perfusion in normal PZ, CG and rectal wall tissue (RW) and in malignant prostate tissue (TU). The apparent diffusion coefficient (ADC) obtained from a monoexponential fit was compared with the coefficients of diffusion (D) and perfusion (D*) obtained from a biexponential fit. The b-values used in this experiment were chosen to separate the effects of the very fast signal decay associated with perfusion and the combined decay arising from fast and slow diffusion.

**Experimental**

*Patient population:* This was a prospective, single-institution study with institutional approval from the local research ethics committee. The study population consisted of 50 patients with Stage Ic prostate cancer (elevated PSA and octant transrectal ultrasound guided biopsy positive for cancer on one side, either right or left of mid-line, of the gland alone) who were willing to undergo additional endorectal scanning. Patients were aged 53-78 yrs (mean±sd, 66 ± 6 yrs). Over a 12-week period, patients were imaged using DWI of the prostate in the same examination as the routine staging MRI done at a median of 104 days (lower and upper quartiles 63.5 days and 344 days) following the most recent biopsy.

*MRI:* MR studies were done on a 1.5T Intera clinical system (Philips Medical Systems, Netherlands) using a balloon design endorectal coil (Philips Medical Systems, Netherlands) inflated with 55 ml of air. 20 mg of hyoscine butyl bromide was administered intramuscularly immediately prior to centering the patient in the scanner in order to reduce peristalsis: this is routine at our institution for abdomino-pelvic MRI and is preferred to glucagon because it offers more effective antiperistalsis. Conventional T2-weighted fast spin echo images were obtained in 3 orthogonal planes (2000/90 ms [TR/effective TE], echo train length: 16, 2 signal averages)
with a 256 by 512 matrix, 3 mm slice thickness, no gap between consecutive slices and a 140 mm field of view (total imaging time 12 mins). Echo-planar DWI (2500/69 ms [TR/TE]) with b-values of 0, 1, 2, 4, 10, 20, 50, 100, 200, 400 and 800 s/mm\(^2\) were obtained transverse to the prostate and parallel to the corresponding set of T2-weighted images. Three orthogonal directions were used resulting in a rotationally invariant trace image at each b-value. The phase-encoding was performed in the left-right direction in order to minimize motion artifacts in the prostate, observed in the AP direction due to breathing. Twelve 4mm slices (no gap, 20 cm field of view, matrix 128\(^2\)) provided coverage of the prostate with an image acquisition time of 287s.

**Data Analysis:** Regions of interest (ROI) were drawn around areas of normal PZ, CG and RW tissue (defined as T2-weighted isointense regions in an octant that was biopsy negative for tumour (within dark stromal areas in the central gland)) and areas of TU (defined as T2-weighted hypo-intense regions in an octant that was biopsy positive for tumour) by a radiologist on the b=0 mm/s\(^2\) diffusion weighted images. The mean ROI sizes were 174 ± 40 mm\(^2\) (mean ± sd) for the CG, 81 ± 11 mm\(^2\) for the PZ, 56 ± 6mm\(^2\) for the RW and 126 ± 31 mm\(^2\) for TU. The DWI were checked for motion throughout the sequence and no registration was found to be necessary. Two methods of data analysis were employed for comparison; a voxel-by-voxel fitting method and an ROI averaged fitting method. For the voxel-by-voxel method the chosen models were fitted for each voxel within the image and the ROIs were then placed on the resulting parametric map and a mean parameter value obtained for each ROI. For the ROI based method, the mean signal intensity value (average of the voxels in the ROI) was found for each ROI and the models fitted to these averaged values. Data was fitted with monoexponential and biexponential models using in-house software developed using Interactive Data Language (IDL, ITTVIS Ltd).
For the biexponential model, values for the diffusion coefficient ($D$), perfusion coefficient ($D^*$) and perfusion fraction ($f$) were calculated for each tissue using a weighted least-squares solution to

$$S_n = S_0 \left[ (1 - f) e^{-b_D} + fe^{-b_{D^*}} \right] (1)$$

where $S_n$ is the signal intensity of the diffusion-weighted image with the $n$th $b$-value. For the monoexponential model, values for the diffusion coefficient (ADC) were found for each tissue using a weighted least-squares solution to

$$S_n = S_0 e^{-b_{ADC}}. (2)$$

The range of $b$-values included in each model was from $X$ to 800 s/mm$^2$, where $X$ was varied from 0, 1, 2, 4, 10, 20, 50, 100, 200 s/mm$^2$ to investigate how the range of $b$-values used affects the parameters obtained. Parameters calculated using only 400 and 800 s/mm$^2$ could not be obtained as the curve-fitting models the $S_0$ value to reduce variability(14) and therefore requires at least three data points.

As $b$-values increased, the signal to noise ratio associated with the resulting diffusion weighted image decreased. This was reflected in the subsequent calculation of the bi- or monoexponential by incorporating differential weightings for signals measured at a particular $b$-value; these ‘Gaussian weightings’ reflected the signal to noise ratio associated with a specific $b$-value. For the ROI-based method, the Gaussian weight given to observed point $Y_i$ was $(\sigma_{Y_i})^{-2}$, where $\sigma_{Y_i}$ is the standard deviation of the signal in the ROI (15). For the voxel-based method, the weights for the diffusion weighted image acquired at a particular $b$-value were approximated from the average weighting calculated via the ROI-based method. Reduced-$\chi^2$ values of the fit of the models in all tissues (accounting for the varying degrees of freedom in each model) were found and compared.
**Quality Assurance:** A spherical phantom containing a uniform solution of distilled water and 1.8g/l of Cu$_2$SO$_4$ (monoexponential ADC of $2060 \times 10^{-6} \text{mm}^2/\text{s}$ at 21°C and T2 relaxation rate of 150ms) was imaged three times using the echo planar DWI sequence with the same sequence parameters as used in-vivo. A circular ROI (area 314mm$^2$) was drawn on the central slice and the ADC was calculated using a weighted least-squares solution to equation 2. As in-vivo, the range of b-values included in each model was from $X$ to 800 s/mm$^2$, where $X$ was varied from 0, 1, 2, 4, 10, 20, 50, 100, 200 s/mm$^2$ to investigate how the range of b-values used affects the parameters obtained.

**Statistical Analysis:** Statistical analysis of the data was performed using SPSS, version 11.0 for Windows. The Shapiro-Wilk test for normality was performed on datasets and the graphical spread of the data was inspected visually. Wilkoxen (signed rank) tests were used to detect differences between the $\text{ADC}_{[X-800]}$ and $\text{D}_{[X-800]}$ obtained for each tissue type and to detect differences in tissue types for $\text{ADC}_{[0-800]}$, $\text{D}_{[0-800]}$, $\text{D}^*_{[0-800]}$, and $f_{[0-800]}$. Significance tests were 2-sided and a p-value of less than 0.05 was chosen as the criterion for statistical significance.

**Results**

Figure 1 shows example ROIs for CG, PZ, RW and TU (TU identified in 43 cases as low signal-intensity lesions on T2W images with positive biopsy from that octant) tissue with corresponding graphs of the signal intensity for each model overlaid. The logarithmic vertical scale for the signal intensity will display a monoexponential curve as a straight line. The data displays a deviation from a straight line at low b-values, indicating a second component in the data, which is not modeled adequately by a monoexponential fit. The gradient of the monoexponential straight line including the b=0s/mm$^2$ value, which determines the ADC calculated, can be seen to overestimate the slow component in the data. Table 1 gives the mean and standard deviation (for normal datasets) and median and ranges (for normal and non-normal
datasets) for all parameters obtained for each tissue using the two models with an ROI analysis method.

Normality plots and the Shapiro-Wilk test for normality showed the monoexponential diffusion coefficients to be normally distributed for all tissues. The biexponential diffusion coefficients were normally distributed for the PZ and CG but not the RW or TU. The perfusion coefficients and perfusion fractions were not normally distributed. \( \chi^2 \) values of the fit of the models in all tissues were not normally distributed.

It was not possible to fit the data accurately with the biexponential model using the voxel-by-voxel method. For the example shown in Figure 1, the number of voxels within a 42x42 voxel region covering the prostate that could be successfully fitted using the monoexponential model was 1735/1764 compared with 1178/1764 for the biexponential model. To improve the signal to noise ratio a boxcar 2D smoothing algorithm of dimension X by X was applied, with X varied from 1-5. This only improved the number of pixels which could be successfully fitted by around 50 pixels. It was therefore decided to proceed only with the ROI method of analysis.

The least-squares fitting algorithm converged for the monoexponential model in all cases; however the biexponential converged using the ROI analysis method in only 32/50 of CG cases, 39/50 of PZ cases, 39/43 of TU cases and 45/50 RW cases.

**Diffusion Coefficients using all b-values:** Comparison of the diffusion coefficients obtained by each model for each tissue showed that the values obtained using the monoexponential method with all b-values were significantly higher than the diffusion coefficient determined from the biexponential method \((p<0.001)\) in all tissues. Figure 2 shows the diffusion coefficients for the monoexponential and biexponential models for each tissue using all b-values \([b=0-800s/mm^2]\)
over all patients. The diffusion coefficient obtained from the monoexponential model \( \text{ADC}_{[0-800]} \) could not distinguish between the CG and PZ tissues \((p=0.438)\), but both RW and TU were highly significantly lower than the PZ \((p<0.001)\) and CG \((p<0.001)\). The diffusion coefficient from the biexponential model, \( D \), could not distinguish between the CG and PZ tissues \((p=0.819)\) or between the RW and CG tissues \((p=0.245)\) but the TU was significantly lower than the PZ \((p<0.001)\) and CG \((p<0.001)\) and there was a significant difference between the RW and PZ tissue \((p=0.015)\).

**Diffusion coefficients with varying b-value ranges:** When the range of b-values used in the monoexponential model was varied, the monoexponential \( \text{ADC}_{[X-800]} \) was significantly larger \((p<0.001)\) than the biexponential \( D_{[0-800]} \) when \( X \) was less than 20 s/mm\(^2\) for TU and RW, when \( X \) was less than 10s/mm\(^2\) for PZ and when \( X \) was less than100 s/mm\(^2\) for CG (Figure 3). The monoexponential \( \text{ADC}_{[X-800]} \) was statistically indistinguishable from \( D_{[0-800]} \) when \( X \) was 50,100 or 200 s/mm\(^2\) for TU and RW, when \( X \) was 20, 50,100 or 200 s/mm\(^2\) for PZ and when \( X \) was equal to 200 s/mm\(^2\) for CG \((p>0.05\) in all cases).

The reduced-\( \chi^2 \) values for the biexponential model using a minimum b-value of 0 s/mm\(^2\) were significantly lower \((p<0.001)\) than the reduced-\( \chi^2 \) values of the monoexponential model with a minimum b-value varied between 0 and 200 s/mm\(^2\) indicating that the biexponential model over the full b-value range offers the best description of the acquired data. When the minimum b-values in the biexponential model and monoexponential model were simultaneously varied from 0-20 s/mm\(^2\), the biexponential model showed significantly lower reduced-\( \chi^2 \) values compared with the monoexponential model \((\text{all } p< 0.001)\) for all tissues, indicating that when the minimum b-value is less then 20 s/mm\(^2\) the biexponential model offers a better fit to the data. However, when the minimum b-value was increased above 20 s/mm\(^2\) in both models, the
monoexponential model had a significantly lower reduced-$\chi^2$ values indicating the monoexponential model better describes data acquired with no low b-values.

**Biexponential Perfusion Coefficients:** The perfusion coefficients from the biexponential model had a very large variation across this patient population. The perfusion coefficient ($D^*$) was significantly lower in the CG than in the RW ($p=0.003$), but there was no significant difference between the PZ and CG ($p=0.081$), the PZ and RW ($p=0.072$), the PZ and TU ($p=0.347$) or the CG and TU ($p=0.976$) (Figure 4).

There was no difference between the perfusion fractions ($f$) of the PZ and RW ($p=0.870$), between the CG and RW ($p=0.285$), or between the CG and PZ ($p=0.051$) (Figure 5). The perfusion fraction of the TU had a large spread in the data across the patient population, but was not significantly different from with the PZ ($p=0.909$) or the CG ($p=0.158$).

**Quality Assurance:** The monoexponential ADC was found to be $2035 \pm 4 \times 10^{-6}$ mm$^2$/s (mean ± standard deviation). When the minimum b-value included in the monoexponential model was increased from 0-200s/mm$^2$, the ADC calculated remained the same (minimum $p=0.139$) (Figure 6).

**Discussion**

This study showed that using a sequence with high sampling at very low b-values gave data which could be fitted using a biexponential model and ROI method in 90% patients in the rectal wall, 78% of patients in the peripheral zone, and 88% of patients with confirmed tumour in the malignant region, but was not as successful at fitting the central gland. Overall, the biexponential model better described the data suggesting that there are two components in the signal decay of these tissues over these b-values, one associated with slower small scale
movement from diffusion of water within the voxels, and a very fast component associated with
large scale bulk movement believed to originate from perfusion of tissue (11). Even if the fast
large scale movement is not a direct measure of actual tissue perfusion (10), the ability to
characterize it separately provides additional information about normal and pathological tissue
while removing its influence from the differences in true diffusion between these tissues.

Endorectal T2-weighted MRI is a well established method of local staging and identifying
extracapsular tumour extension (16,17), but newer treatment strategies such as brachytherapy,
photodynamic therapy and cryoablation (18-21) demand more precise localisation of the
tumour. DWI of the prostate has shown differences between normal and potentially pathological
tissue types (5,6,22,23) and recent studies have shown that the addition of DWI to conventional
T2-weighted imaging significantly improved tumour detection (5). Previous studies have
concentrated on determining ADC values for prostate tissues using a monoexponential model
and have contradictory results. Issa et al (24) used six b-values between 68 and 786 s/mm² and a
monoexponential model to give the true diffusion coefficient for 19 patients and found a
difference between normal PZ (1880 ± 480 x10⁻⁶ mm²/s) and normal CG (1620 ± 410x10⁻⁶
mm²/s), and between peripheral zone tumour (1380 ± 520 x10⁻⁶ mm²/s) and normal CG . Our
values of the true diffusion coefficient are in agreement with this, but whilst both studies show
the CG to have a lower diffusion coefficient than the PZ, this was not statistically significant in
our study of a larger number of patients. Gibbs et al (25) found diffusion coefficients of 3430 ±
690 x10⁻⁶ mm²/s for normal peripheral zone and 2730 ± 700 x10⁻⁶ mm²/s for malignant tissue in
12 cancer patients but this was calculated using 4 b-values ranging from 0-720 s/mm². Our
study suggests this b-value range will be influenced by the perfusion component and so will be
increased significantly, although their values remain very high compared with our ADC values.
In the same study, they found lower ADC values (1250 ± 230 x10⁻⁶ mm²/s) for PZ in healthy
volunteers using the same b-values, which are in much closer agreement with the values found
in this study, and suggest something other than perfusion may account for the difference in ADC found in the two studies. We are unaware of published values of normal rectal wall diffusion parameters.

The significantly higher diffusion component obtained from the monoexponential model in all tissues is due to the inclusion of the large-scale intravoxel movement in the calculation. The minimum b-values required to give diffusion coefficients not significantly different to the diffusion coefficient obtained by the full range biexponential model varies from 20 s/mm\(^2\) in the peripheral zone, 50s/mm\(^2\) for the rectal wall and tumour tissue and 200 s/mm\(^2\) in the central gland. Thus, we have identified minimum b-values by which mono- and biexponential models are fitted equally well and provide similar values of diffusion coefficient removing the need for a lengthier DWI acquisition sequence with increased number of b-values and a more complicated method of analysing the data. Although the slower moving diffusion coefficient identified using the biexponential model was not better at discriminating between the tissues within the prostate, the separation between normal and malignant prostate tissues was greater for the biexponential diffusion coefficient than for the monoexponential model. This may prove useful in patients with reduced diffusion contrast between normal and malignant tissue due to treatments such as androgen deprivation therapy(26).

Our data indicates that with minimum b-values greater than 20 s/mm\(^2\), the monoexponential model describes the data better than the biexponential model in all three tissues. This suggests that the perfusion component is not dominant at these length scales, although the significantly higher monoexponential diffusion coefficients show the signal acquired at these b-values will still have a contribution from large scale bulk movement. Thus the b-values used in the calculation of the monoexponential diffusion coefficient are important and must be carefully considered when comparing apparent diffusion coefficients from different studies as there will be varying amounts of perfusion affecting the coefficients calculated. The combination of both
perfusion and diffusion components into one quantitative apparent diffusion coefficient parameter may not be ideal for determining diagnosis or treatment response.

The perfusion coefficients calculated by the biexponential model had very large associated standard deviations, possibly reflecting physiologically based variability. This limits their clinical value, but further demonstrates the need for this highly variable perfusion component to be excluded in order to increase the clinical utility of the diffusion coefficient in diagnosis, prognosis or treatment response. There was no difference in the fraction of the tissues that exhibited perfusion, although this may be masked by the patient variability in this cohort and a follow-up of these trends in a larger series is needed in order to establish the utility of the perfusion coefficient separately from the diffusion coefficient. For example, the difference in diffusion coefficient between the rectal wall tissue and the peripheral zone tissue is not seen in the perfusion coefficient, suggesting the perfusion in these tissues is similar but the cellularity is different. The perfusion fraction for tumour tissues has a much larger variation than in the normal tissues, which is agreeable with observations from dynamic contrast enhanced MRI studies which show increased but very heterogeneous vascularity and perfusion within tumour tissue (27-29).

The comparison of the two analysis methods found the biexponential model to be problematic in the voxel-based method due to the signal to noise ratio. Smoothing the data using a simple boxcar algorithm to improve the signal to noise ratio did not improve the number of voxels that could be fitted substantially. Whilst the ROI based method which allowed the biexponential model to be fitted in the majority of cases was sufficient for this study where conservative regions of normal tissue were chosen, ROI-based analysis may mask inherent heterogeneity in the clinical situation and reduce the information available. Whilst the SNR of the data is not sufficient to allow biexponential voxel analysis, we have demonstrated minimum b-values which can be used to allow monoexponential analysis to produce the same diffusion coefficient
and as monoexponential fitting is possible with lower SNR data, heterogeneity could be
explored in the diffusion coefficients. However, in order to explore tissue heterogeneity of
perfusion coefficients, higher signal to noise data is required to allow biexponential modelling.

As the DWI was acquired with an echo-planar read-out, some distortion was visible in tissue
boundaries of discontinuous magnetic susceptibility. Additionally a shift in the phase-encode
direction owing to a slight offset of the water resonance frequency was observed occasionally.
We have previously quantified both distortions compared with a standard spin-echo readout,
which yielded a bulk shift of 0.11 - 4.28 mm (median 1.10 mm), and a residual disagreement
between echo-planar and T2-weighted prostate outlines of 1.2+0.5 mm. As the ROIs were
drawn directly onto the DWI with prior knowledge from the T2-weighted images, conservative
ROIs in normal tissue areas ensured this was not problematic. A further limitation of this study
is that malignant lesions not visible on T2-weighted images may have been included in the
analysis of normal tissues. It was not possible to remove these regions without histological
proof of their involvement with tumour. The high prevalence of benign prostatatic hyperplasia
(BPH) in this central gland of this patient population means there is a high degree of tissue
heterogeneity in this tissue. To reduce the heterogeneity in the data we chose to analyse only
stromal central gland, but cannot discount the inclusion of areas of BPH in the normal tissue.

Tissue heterogeneity within the central gland is a likely explanation for the decreased ability to
fit the central gland tissue with the biexponential model. Further investigation into a voxel-
based analysis method within the central gland ROI, together with increased correction of the
signals to ensure no signal to noise ratio biasing of the data at high b-values would be useful.

We have used a biexponential model to characterise a very fast coefficient associated with
perfusion, but the true perfusion decay is more likely to be sinc-shaped due to the random
direction of flow in microvasculature over these timescales (11,30). Adaptation of the model to
better describe this perfusion decay may decrease the variation seen in the fast coefficient
associated with perfusion. The perfusion coefficient and perfusion fraction derived offer additional information from conventional tracer methods of measuring perfusion where an increased blood flow in malignant compared with normal prostate tissue (29.4ml/minute versus 15.7ml/minute) has been shown (31). The perfusion coefficient is a function of average blood velocity and mean capillary segment length, whereas the perfusion fraction represents the ratio of water movement within capillaries compared to the total volume of water in a voxel (10,11).

We have shown that rectal wall tissue has a similar perfusion fraction but an increased perfusion coefficient compared to normal prostate tissue, suggesting that the two tissues have a similar amount of water movement within capillaries per voxel, but that this movement is faster within the rectal wall. It is possible that the wide variation in the perfusion data is hiding a converse effect where similar perfusion coefficient but increased perfusion fraction of malignant compared with normal prostate tissue suggests water movement within blood vessels is similar in these regions, but that the overall water movement per voxel is larger presumably due to increased vascularity within malignant regions. Thus, the IVIM model may offer the potential of determining the mechanism of increased blood flow within tumours.

In conclusion, the biexponential model better describes the DWI signal loss associated with low b-values in the normal and malignant prostate tissues and normal rectal wall tissues and the diffusion coefficients determined are dependent on the b-values used in the calculation. There is very large variation in the perfusion coefficients obtained which may currently limit its clinical utility, but differences between central gland and peripheral zone suggest that the perfusion parameters may offer additional information useful in determining diagnosis and treatment response. The importance of the perfusion coefficient appears to be increased in malignant tissues, which exhibit a highly variable perfusion fraction, and the removal of this variable perfusion component from the reported diffusion coefficients is important when attributing clinical differences to diffusion within tissues.
REFERENCES


Figure 1 - Example ROIs for CG, PZ and RW tissue (isointense regions on T2-weighted imaging) (top left) and TU ROI (hypointense regions on T2-weighted imaging) (top right) from one patient with corresponding graphs of the signal intensity with both models overlaid (bottom).
Figure 2 – Comparison of the median (horizontal line), interquartile range (box), and ranges (tails) of the diffusion coefficients calculated for the CG, PZ, TU and RW tissues using the monoexponential and biexponential models.
Figure 3 - Monoexponential diffusion coefficients as a function of minimum b-value used in the calculation for CG (top left), PZ (top right), TU (bottom left) and RW (bottom right). The horizontal line represents the biexponential diffusion coefficient using 11 b-values and the grey shaded area represents two standard deviation of the biexponential coefficient. ADC data points shown in white are not statistically different from the biexponential diffusion coefficient D (p>0.05).
Figure 4 – Comparison of the median (horizontal line), interquartile range (box), and ranges (tails) of the perfusion coefficients calculated for the CG, PZ, TU and RW tissues using the biexponential model. The stars denote extreme values in the data.
Figure 5 – Comparison of the median (horizontal line), interquartile range (box), and ranges (tails) of the perfusion fractions calculated for the CG, PZ, TU and RW tissues using the biexponential model. The stars denote extreme values in the data.
Figure 6: Monoexponential diffusion coefficients as a function of minimum b-value used in the calculation for the cooper sulphate quality assurance phantom.
Table 1. Mean ± standard deviation of monoexponential ADC and biexponential D obtained for each tissue, and the median and ranges (in italics) for the ADC, D, D* and f.

<table>
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<th>Parameter</th>
<th>CG</th>
<th>PZ</th>
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<th>RW</th>
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<tr>
<td></td>
<td>(x10^6 mm^2/s)</td>
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<tr>
<td>ADC</td>
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<td>1660 ± 340</td>
<td>1330 ± 520</td>
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<td>1460 (770-2000)</td>
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<td>1290 ± 250</td>
<td>1340 ± 280</td>
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<td></td>
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<td>1340 (690-1920)</td>
<td>850 (0-1820)</td>
<td>1210 (0-1780)</td>
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<tr>
<td>D*</td>
<td>10,900 (3800 – 87,600)</td>
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<td>25,200 (0-122,000)</td>
<td>31,300 (3320-316,000)</td>
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<td>23 (6-53)</td>
<td>15 (3-77)</td>
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<td>1210 (0-1780)</td>
</tr>
<tr>
<td>f (%)</td>
<td>18 (8-42)</td>
<td>23 (6-53)</td>
<td>15 (3-77)</td>
<td>24 (5-82)</td>
</tr>
</tbody>
</table>