A Model Describing Diffusion in Prostate Cancer

Nima Gilani[1], MS, Paul Malcolm[2], MBBS,
Glyn Johnson[1], PhD.

[1]Norwich Medical School, University of East Anglia
[3]Norfolk and Norwich University Hospital

Corresponding author: Nima Gilani
Bob Champion Research and Educational Building
James Watson Road
University of East Anglia
Norwich Research Park
Norwich NR4 7UQ
UK
n.gilani@uea.ac.uk

Running title: A model for diffusion in prostate cancer

Abstract

Purpose: Quantitative diffusion MRI has frequently been studied as a means of grading prostate cancer. Interpretation of results is complicated by the nature of prostate tissue which consists of four distinct compartments: vascular, ductal lumen, epithelium and stroma. Current diffusion measurements are an ill-defined weighted average of these compartments. Here prostate diffusion is analyzed in terms of a model that takes explicit account of tissue compartmentalization, exchange effects and the non-Gaussian behaviour of tissue diffusion.

Methods: The model assumes exchange between the cellular (i.e., stromal plus epithelial) and the vascular and ductal compartments is slow. Ductal and cellular diffusion characteristics are estimated by Monte Carlo simulation and a two-compartment exchange model respectively. Vascular pseudo-diffusion is represented by an additional signal at b = 0. Most model parameters are obtained either from published data or by comparing model predictions with published results from 41 studies. Model prediction error is estimated using 10-fold cross-validation.

Results: Agreement between model predictions and published results is good. The model satisfactorily explains the variability of ADC estimates found in the literature.

Conclusions: A reliable model that predicts the diffusion behaviour of benign and cancerous prostate tissue of different Gleason scores has been developed.

Keywords: Prostate MRI, diffusion, kurtosis, Gleason score, biexponential diffusion

Introduction

Prostate cancer is the second most common cancer in men worldwide [1] and the most common cancer in US men [2]. It is the fifth leading cause of death from cancer in men worldwide [1] and the second leading cause of death in US men [2]. Despite these mortality statistics, most prostate tumours are indolent, low-grade tumours that will have no clinical consequences. The best assessment of tumour aggressiveness is the Gleason score obtained from whole-mount histology of the surgically excised prostate [3-5]. However, pre-surgical Gleason scores obtained from trans-rectal biopsy samples are much less reliable due to the inability to sample the whole prostate (sampling error) [6-9]. As a result prostate cancer is over-treated and it is currently estimated that as many as 37 men undergo prostatectomy for every cancer death prevented [10]. This not only entails great unnecessary expense and suffering, but the incidence of morbidity associated with the procedure (principally urinary and sexual dysfunction) is very high (up to 90%) [11]. Improved methods of assessing prostate tumours could greatly reduce the expense, anxiety and morbidity associated with excessive treatment.

Histology: Gleason score and grade

Histologically, the prostate consists of four distinct compartments or cell types: vascular (i.e., capillaries), fibro-muscular stroma, epithelium and glandular lumen. Vascular volume in the normal peripheral zone of the prostate is about 2% [12]. Of the remaining tissue approximately 39.5% is stroma, 31.5% epithelium and 29% ductal lumen [13]. The epithelial cells form the walls of the glandular ducts and separate them from the stroma. In tumours, the stromal and lumenal fractions decrease and the vascular and epithelial fractions increase; these changes are progressive with tumour aggressiveness.

Tumours are assigned a Gleason score as follows: each tumour is given two Gleason *grades* based on histological pattern of the two dominant tumour areas and these are then summed to give the Gleason *score*. Scores of less than 6 are considered low grade. It is thus most important to distinguish between Gleason grades 3, 4 and 5 [3]. Lumen volume decreases with grade by ~12% for Gleason 3, ~16% for Gleason 4 and ~21% for Gleason 5 [13]. The ratio of epithelial to stromal volumes doubles between grades 3 and 5 (~1.4 for Gleason 3, ~2.8 for Gleason 5). Furthermore, the density of epithelial cells also increases. Thus measurements of lumenal volume and cellular composition have great potential to provide a reliable means of identifying grade.

Quantitative Diffusion MRI

The use of quantitative diffusion magnetic resonance imaging (MRI) for assessment of prostate cancer has been investigated by many groups [14-43]. However, although there are clear differences in MRI parameters between tumours and normal prostate, differences between high and low grade tumours are small with considerable overlap. Quantitative measurements in the prostate are complicated by the complex nature of prostate tissue described above. In addition, blood flow in tortuous capillaries can lead to a "pseudo-diffusion" signal such as seen in intra-voxel, incoherent motion (IVIM) experiments. However, to date the heterogeneity of prostate tissue has not generally been taken into account and MRI parameter estimates represent a weighted average of the contributions of the different compartments.

In this paper we propose a model of prostate tissue diffusion that takes tissue compartmentalisation explicitly into account. By doing so, not only are ambiguities in previous measurements resolved, but also estimates of ductal, stromal and endothelial volumes become possible. Since these are the most important factors determining Gleason grade, this approach could provide an equivalent MRI score that might distinguish aggressive and indolent tumours. Furthermore, since this is an imaging method that can cover the whole prostate it avoids sampling error and could therefore provide greatly improved pre-operative assessment.

Tissue Model

The model is based on measured or estimated values for the different tissue volumes and diffusion coefficients in normal prostate and cancer. The net signal arising from the tissue will depend on these parameters and on the exchange of water between different compartments. If exchange is slow relative to the time over which the signal is acquired (typically 50–100 ms), then each water molecule will effectively be confined to a single compartment and will contribute a signal characteristic of that compartment alone. Conversely, if water exchange is very fast between two compartments they are well mixed and cannot be distinguished. At intermediate exchange rates, water molecules will spend time in both compartments and will contribute a signal that represents an average between them. In normal prostate the glandular lumen is 300μm in radius [44] compared with typical water diffusion distances of ~20 μm (assuming a total diffusion time of 80ms, typical of clinical scanners, and diffusion coefficient of 3 $\mu m^2 ms^{-1}$, similar to that of water [45, 46]). Thus

exchange of water between the lumen and the cellular (i.e., epithelial plus stromal) compartments is expected to be small. With increasing Gleason grade the lumenal volume decreases. Nonetheless, exchange between the two is likely to remain slow [44]. Similarly, the observation of an IVIM signal in most tissues suggests that exchange between the intra- and extra-vascular compartments is also slow [47]. Stromal and epithelial layers are relatively thin so that exchange will be significant but the two cannot be considered well mixed. The validity of these assumptions is confirmed by the finding of biexponential, but not triexponential T_2s in the prostate [48]. Our model (Fig. 1) is based on these assumptions, i.e., slow exchange between intra- and extravascular compartments; slow exchange between ductal and cellular compartments; moderate exchange between stroma and epithelium.

With this model, the total signal, *S*, is the sum of the signals from each slow-exchanging compartment, i.e.:

$$S = S_v + S_d + S_c \qquad [1]$$

where S_i is the signal from compartment *i* and the subscripts *v*, *d* and *c* indicate the vascular, ductal lumen and cellular compartments respectively.

Vascular Signal

The vascular fraction is small and becomes rapidly dephased at even low b values due to the relative rapidity of capillary flow [49]. S_v can thus be approximated by a delta function at b = 0.

Ductal signal

Both cellular and ductal compartments will display non-Gaussian diffusion (i.e., the probability density function describing diffusional motion is non-Gaussian) and so in principle should include a kurtosis term. The signal S_i from compartment *i* (*i* = *d* or *c*) is then

$$S_i = S_{i0} e^{-D_i b + \frac{D_i^2 K_i b^2}{6} + O(b^3)}, \qquad [2]$$

where S_{i0} is the signal in the absence of diffusion weighting, D_i is the apparent diffusion coefficient (ADC), K_i is the apparent kurtosis and $O(b^3)$ indicates terms on the order of b^3. In this report we use ADC to refer to any measured diffusion coefficient since all expressions relating signal to *b* value involve approximations. However, Monte Carlo simulations of semi-permeable cavities suggest that the ductal kurtosis term will contribute no more than 1% of the total ductal signal [44]. Consequently, although ductal kurtosis measurements might

provide useful information in principle, it is unlikely that the SNR of measurements will be sufficient for their accurate measurement. We have therefore assumed Gaussian ductal diffusion in our model.

Total signal is therefore given by

$$S = S_0 \left\{ f_v d(b) + f_d e^{-bD_d} + f_c e^{-bD_c + \frac{D_c^2 K_c b^2}{6}} \right\} \quad [3]$$

where S_0 is the signal without diffusion weighting, f_i is the signal fraction of compartment i, (so that $f_v + f_d + f_c = 1$), D_i is the apparent diffusion coefficient of compartment i, δ is the Dirac delta function, and b is the diffusion weighting constant.

We have previously shown that the reductions in lumenal diameter found in prostate cancer reduce D_d [44]. Values can be described approximately by the following biexponential function

$$D_d = D_d^{free}\left(1 - 0.46 \times e^{-0.0459b} - 0.54 e^{-0.4024b}\right) \quad [4]$$

where

$$b = \frac{r_d^2}{T_{TD} D_d^{free}}, \quad [5]$$

r_d is the lumenal radius (μm), T_{TD} is the total diffusion time and D_d^{free} is the diffusion coefficient in the absence of barriers. (See below for a discussion of the distinction between total diffusion time and diffusion time.)

Cellular Signal

The cellular compartment consists of the stroma and epithelial sub-compartments. Exchange between these sub-compartments is intermediate between fast and slow. In such circumstances diffusion behaviour is complex. Jensen et al. [50] have shown that the behaviour can be approximated by monoexponential diffusion with a kurtosis term (Eq. [2]). The cellular diffusion and kurtosis are then [50-52]

$$D_c = D_c^{nox} \quad [6]$$

$$K_c = K_c^{nox} \frac{2t}{T_D} \left\{ 1 - \frac{t}{T_D}\left(1 - e^{-T_D/t}\right) \right\} \quad [7]$$

where D_c^{nox} and K_c^{nox} are the diffusion coefficient and kurtosis with no exchange, T_D is the diffusion time, and τ is the exchange time between stromal and epithelial sub-compartments.

D_c^{nox} and K_c^{nox} are the given by

$$D_c^{nox} = \frac{v_s D_s + v_e D_e}{v_s + v_e} \quad [8]$$

$$K_c^{nox} = 3\frac{v_s\left(D_s - D_c^{nox}\right)^2 + v_e\left(D_e - D_c^{nox}\right)^2}{\left(v_s + v_e\right)D_c^{nox\,2}} \quad [9]$$

where v_i is the water volume fraction of compartment i and subscripts s and e refer to the stromal and epithelial sub-compartments respectively. The exchange time, τ, is given by

$$t = \frac{v_e t_s}{v_s + v_e} = \frac{v_s t_e}{v_s + v_e} \quad [10]$$

where τ_s and τ_e are the stromal and epithelial residence times respectively.

Thus, the diffusion coefficient of the cellular compartment is the average of the individual stromal and epithelial diffusion coefficients weighted by the relative amounts of water in each; the kurtosis is similarly a weighted measure of the variance of the diffusion coefficients. When $T_D >> \tau$, the compartments are effectively in fast exchange, are well mixed and behave as a single monoexponential compartment with K_c close to zero.

Diffusion Time

Note the distinction between the total diffusion time, T_{TD}, and diffusion time, T_D, as normally defined in the MRI literature. T_{TD} is the total period over which diffusion affects the outcome of the experiment

$$T_D = \Delta + \delta \quad [11]$$

where δ is the length of the diffusion gradients and Δ is the interval between their centers. T_D is a convenient constant that arises when calculating gradient b values

$$T_D = \Delta - \frac{\delta}{3}. \quad [12]$$

Diffusion time also occurs in other MRI diffusion equations, such as that for kurtosis, Eq. [7]. However, these expressions often only strictly apply when $\delta << \Delta$. In most *in vivo* imaging sequences the diffusion gradients are applied for as long as possible to maximize b for a

given echo time. It has recently been suggested [53] that in these circumstances T_D is better approximated by

$$T_D = \Delta + \delta. \qquad [13]$$

Diffusion time is not in any case generally available (and is usually unknown to all but the sequence designers). In developing the model we have therefore used the same approximation for T_D (in Eq. [7]) and T_{DF} (in Eq. [5])

$$T_D = T_{DF} \approx T_E - 25\text{ms}. \qquad [14]$$

This is based on the assumption that echo times have been minimized to improve SNR and a few milliseconds are required for the EPI imaging gradients following diffusion weighting.

Model Parameters

The parameters that define the model are of two types. First, there are *a priori* parameters that are derived from literature values. Second are parameters for which no reliable estimates can be found. These are optimized by minimization of the mean square error (MSE) between model predictions and measured values.

The vascular, stromal, epithelial and ductal fractional volumes, and ductal radius of benign and cancerous prostate tissue were defined *a priori* using literature values [13, 44] (Table 1). Vascular volumes are based on the measurements of Schlemmer at al.[12] who found vascular volumes of 2% in normal peripheral zone, rising to 4% in prostate cancer. Gleason score was not specified so the value of 4% was assumed to correspond to Gleason 7 and other values derived using linear interpolation and extrapolation.

The difference in water density between the vascular, ductal and cellular compartments and differences in transverse relaxation time must also be taken into account when calculating signal fractions from volume fractions. In the absence of diffusion weighting, the signal from compartment i, is

$$S_{i0} = k\rho_i v_i e^{-T_E/T_{2i}} \qquad [15]$$

where k is a constant describing system gain, ρ_i is water spin density (water hydrogen atoms per unit volume), v_i is the volume fraction, T_E is the echo time of the diffusion sequence and T_{2i} is the transverse relaxation time. The fractional signal from compartment i, f_i, is therefore the ratio of S_{i0} to the sum of the signals from all compartments, i.e.,

$$f_i = \frac{r_i v_i e^{-T_E/T_{2i}}}{\sum_{i=v,d,s,e} r_i v_i e^{-T_E/T_{2i}}}. \qquad [16]$$

The glandular fluid contains few solids so that water content is ~100% whereas most soft tissues have a water content of about 75% [54, 55] and blood is about 80% water [56]. Long and short T_2s, which we assume correspond to the ductal and cellular (i.e., stromal plus epithelial) fractions respectively, have been measured to be about 450 ms and 60 ms [48, 57]. The T_2 of blood is about 280ms and largely independent of field strength [58]. Signal fractions calculated from Eq. [16] using the above figures are given in Table 1.

It is not simple to obtain independent estimates of ductal, stromal and epithelial diffusion coefficients *in vivo*. *Ex vivo* MRI measurements in formalin fixed tissue at 22°C give diffusion coefficients of 2.0-2.2, 0.7-0.9 and 0.3-0.5 $\mu m^2 ms^{-1}$ for ducts, stroma and epithelium respectively [59, 60]. However, changes in diffusion characteristics due to cell death, fixation and temperature differences make these measurements difficult to interpret [61-63]. Several studies have reported biexponential diffusion measurements in normal PZ [64-66]. However, the fast and slow diffusion coefficients (presumably corresponding to glandular and cellular diffusion respectively) covered very large ranges: 2.5 – 8.8 and 0.2 – 1.2 $\mu m^2 ms^{-1}$ respectively. The fast diffusion coefficient is difficult to interpret because it includes perfusion signals (the IVIM effect) and variations in this measurement will also affect the slow diffusion estimate. The values of D_s and D_e that gave the best agreement between the model and experimental results were therefore found empirically (see below).

Cellular kurtosis depends on the ratio of diffusion time to the exchange time between stroma and epithelium. Exchange time is also unknown but can be estimated from the average diffusion distance [67]:

$$\langle x \rangle = \sqrt{2 D_c T_{TD}} \qquad [17]$$

If we assume that τ is approximately the time it takes to diffuse from the centre of the stromal or epithelial layer to its edge, then

$$t \sim \frac{r_c^2}{2 D_c} \qquad [18]$$

where r_c is half the thickness of either the epithelial or stromal layer.

Diffusion coefficients are inversely correlated with cell density [68, 69] and consequently reduced in tumours. The precise relationship between ADC and cancer grade is unknown but ADC values typically decrease with increasing grade, dropping to about 50% of normal values in high-grade tumors [70-72]. We therefore assumed that the epithelial diffusion coefficient D_e drops linearly with Gleason score from a value D_e^{norm} at Gleason 0 (i.e., normal) to $0.5D_e^{norm}$ at Gleason 10, i.e.,

$$D_e = D_e^{norm}\left(1 - 0.05g\right) \quad [19]$$

where g is the Gleason score.

Finally, as prostate tumours primarily involve epithelial cells, we assumed that the stromal diffusion coefficient is independent of grade,

$$D_s = D_s^{norm} \quad [20]$$

where D_s^{norm} is the diffusion coefficient of normal stroma.

The model is thus Eq. [3] with D_d given by Eq. [4], D_c by Eq. [6], and K_c by Eq. [7], with signal fractions given by Eq. [16].

Materials and Methods

Only published data was used for this study so no ethical consent was sought.

Epithelial Thickness

To obtain the estimate of stromal/epithelial exchange times, for use in Eq. [7], the average thickness of epithelial cells was estimated by making measurements from histology images of normal and cancerous prostate [73] using ImageJ [74].

Optimum Compartmental Diffusion Coefficients, D_i

Forty-three papers were identified that presented diffusion measurements with associated Gleason scores [14-43, 75-87] and included b values. (No attempt was made to perform an exhaustive search and this does not represent a complete list of prostate diffusion studies.) In three studies, field strength was not reported and was assumed to be 3T [14, 17, 41]. Studies were divided into two categories according to the precision with which Gleason score was specified:

I ADC recorded for individual Gleason scores.

II ADCs recorded for groups with an average (mean or median) Gleason score.

Where separate ADC estimates were made for, e.g., Gleason 3+4 and 4+3, each measurement was included separately with a grade of 7. Similarly, when measurements for multiple readers were reported, each was treated as a separate measurement. In one case tertiary Gleason grades were given [21] but were ignored.

In all studies, measurements were made at two or more b values and ADCs were estimated assuming a single compartment displaying Gaussian diffusion so that signals were assumed to be given by

$$S = S_0 e^{-bD}. \qquad [21]$$

These data were used to find the values of the compartmental diffusion coefficients (i.e., D_d^{free}, D_e^{norm}, and D_s^{norm}), that maximise agreement with the model predictions. Fig. 2 gives a flow chart outlining the process. The initial data is derived from the published data. Gleason score and b values were passed to the model and used to generate a set of signals, $S(b)$ using Eq. [3], with trial values of D_i. Eq. [21] is then fitted to the model signal to obtain model estimates of ADC, D_{model}. Non-linear least squares fitting (Matlab function lsqcurvefit) is then used to find the set of D_i that minimize mean-square error, MSE,

$$\mathrm{MSE} = \frac{\sum_{i=1}^{N} \left(\Delta D_i\right)^2}{N}. \qquad [22]$$

where ΔD is the difference between measured and model ADC and the sum is over each measurement in the published data sets.

The above procedure was initially performed over all data sets to find an initial set of optimum D_i. The difference, ΔD, was calculated for all measurements and the mean and standard deviation of the differences found. Differences that were greater than 1.96 standard deviations away from the mean were considered outliers. Any data sets containing more than one outlier was removed from the analysis set since this suggested the possibility of a systematic error such as incorrectly calibrated b values. The optimization procedure was then repeated with the reduced set to generate the final results.

Cross-validation

Cross-validation was performed using 10-fold cross-validation [88]. Briefly, all tissue measurements from the 43 studies were collected into a single set of N measurements. This set was split into 10 folds, each with a group of ~N/10 test points used for testing with the

remaining points used for training. Each training group is used to find a set of optimum D_i. The differences between $D_{measured}$ and D_{model} were then found for all points in the test group using these parameters. The process was repeated for each fold and the MSE found over all test points in all folds. This method provides a moderately conservative estimate of the true MSE.

Results

Epithelial Thickness

Average epithelial thickness was 8.2±1.3 μm (12 measurements) and 18.3±5.4 μm (7 measurements) for healthy prostate and Gleason score 7, respectively. This gives an estimate of τ = 50ms from Eq. [18], assuming r_c (half thickness of the cellular layer) is ~10μm, and the cellular diffusion coefficient is 1 $\mu m^2 ms^{-1}$.

Compartmental Diffusion Coefficients

Two of the 43 papers produced more than one outlier each and were removed leaving 41 papers and a total of 140 different diffusion measurements. Optimum values of D_d^{free}, D_s^{norm} and D_e^{norm} for this reduced set were 2.368, 1.222 and 0.571 $\mu m^2 ms^{-1}$ respectively.

Figs. 3 and 4 gives plots comparing measured values of diffusion coefficient with values predicted by the model. Fig. 3 is plot of $D_{measured}$ vs. D_{model}; Fig. 4 is a Bland-Altman plot of ADC difference vs. mean ADC. As might be expected field strength shows little or no influence on the measurements. There appears to be a slight suggestion that the scatter is greater for Category II than Category I as might be expected. Overall agreement is very good and the 10-fold cross-validation gave an MSE of 0.046 equivalent to a root MSE of 0.21 $\mu m^2 ms^{-1}$

Fig. 5 gives plots of D_d, D_s, D_e, D_c and K_c vs. Gleason score. (Diagnostically the most important distinction is between scores of less than and greater than six.)

Fig. 6 gives a plot of signal intensity predicated by the model vs. b value for normal prostate and Gleason scores 5 – 9.

Discussion

The value of an accurate model of tissue diffusion is fourfold. First, it allows association of diffusion measurements with specific cellular changes, which may have valuable diagnostic implications. In this case, diffusion changes are direct consequences of changes in the relative

volumes of ductal lumen, stroma and epithelium. These volumes are a key aspect of histopathological analysis and largely determine Gleason score. Hence estimates from diffusion measurements may allow calculation of an "MR Gleason Score" that predicts tumour aggressiveness. Second, knowing how changes in individual tissue compartments influence signal changes allows optimization of acquisitions (specifically choice of *b* values) to minimize errors in tissue estimates. Thirdly, a model simplifies fitting procedures. Increasing the number of parameters in a model will inevitably reduce the size of the residuals but increases the risk of overfitting (i.e., fitting to noise). Moreover, multiple parameters which have similar effects on the signal can lead to instabilities when two entirely different parameters sets can produce similar fits. This is a notorious problem in fitting biexponential signals. However, the model we propose has only a single free parameter – the Gleason score. Finally, the model explains the contradictions and ambiguities found in the literature. For example, a number of studies have described the b value dependence of measured ADCs [18, 27, 38, 75]. However, this is entirely to be expected as a linear relationship between ln(*S*) and *b* will only be found for diffusion in a single Gaussian compartment. In any more complex system, the ln(*S*) vs. *b* is non-linear and cannot be described by a single ADC (i.e., a single value for the slope). The problem is particularly acute in the prostate since the two main compartments, ductal and cellular, have markedly different diffusion coefficients. The optimum prostate diffusion protocol is not then a simple matter of finding a single optimum *b* value [89] but of acquiring images at a sufficiently large number of *b* values to fully describe the data. Similarly, the model explains the finding of a lowered IVIM "perfusion fraction" in tumours [64, 90]. This finding is not only counterintuitive since tumour angiogenesis generally increase blood volume, it is also contradictory to DCE perfusion measurements [90]. However, changes in signal at low *b* values are determined by two components: flowing blood displaying pseudo-diffusion and signal from the rapidly diffusing ductal compartment. The latter is reduced in cancer resulting in a reduction in the signal labelled perfusion fraction in IVIM experiments.

Others have previously investigated multi-exponential diffusion in the prostate. The Mulkern group observed bi-exponential diffusion behaviour in both normal prostate [65] and cancer [84] but offered no explanation of its origin. Bourne and colleagues [91] also observed bi-exponential diffusion in fixed samples. Panagiotaki et al. [29] previously proposed a three compartment model consisting of vascular (i.e., IVIM), intracellular and extracellular compartments. However, previous attributions of biexponential behaviour to intra- and

extracellular compartments in the brain have been questioned for a number of reasons. First, it is unnecessary since non-Gaussian diffusion will always occur in the presence of hindered diffusion [50]. Second the signal fractions do not agree with known intra- and extracellular volumes obtained by other means [92, 93]. Third, magnetization transfer rates are similar for both components which would not be expected for intra- and extracellular water [94]. Furthermore, if the two non-vascular diffusion components are assigned to intra- and extracellular spaces in the prostate then the cellular and ductal signals must be well mixed. This is biophysically difficult to explain and we believe that ductal/cellular compartmentalization is a more plausible explanation of bi-exponential diffusion behaviour.

Several groups have also used non-Gaussian fits, either with a kurtosis term or using a stretched exponential equation to describe diffusion in the prostate [32, 34, 91]. These methods will naturally provide better fits than simpler models. However, without explicitly taking into account the multi-compartment nature of the prostate, these models provide little biophysical insight into the relationship between diffusion measurements and the changes that occur in cancer.

The IVIM signal in this model is described by a delta function at $b = 0$. I.e., it is assumed that any diffusion weighting effectively eliminates the perfusion signal. This is a simplification and it might be possible to develop a more accurate model with a pseudo-diffusion term that would help in diagnosis. However, there are a number of problems with this approach. First, the perfusion signal is very sensitive to low b values. However, the "$b = 0$" signal includes a small amount of diffusion weighting due to the imaging gradients. This is especially true with the large, repeated gradient pulses that are used in the EPI sequences. This introduces errors into estimates of the pseudo-diffusion parameters. Second, although blood volume is increased with tumour angiogenesis, it is not certain that blood *flow* is also increased since increased interstitial pressure caused by hyperpermeable vessels can retard flow decreasing the IVIM signal [95-97]. Given the difficulty in interpretation we think it preferable to use b ~150smm^{-2} for the "$b = 0$" signal.

Our results primarily show that the diffusion properties of benign and cancerous prostate tissue can be described by a simple model. Most model parameters were defined *a priori* using non-MRI data. Three, D_d^{free}, D_s^{norm}, and D_e^{norm}, were obtained by fitting the model to empirical data. The estimated values seem reasonable. D_d^{free} is somewhat lower than that of free water at 37°C (3.08 μm^{2}ms^{-1}) [45, 46] and is similar to the *ex vivo* estimate of Bourne et

al. [60]. D_s^{norm} and D_e^{norm} are both of the same order as the slow ADCs found by Shinmoto et al. [84]. Furthermore, the relative sizes are similar to those found by Bourne et al. [59] in fixed tissue and are consistent with histological observations of greater cell density in epithelium than in stroma [20]. All the *a priori* parameters are subject to noise and could undoubtedly be improved with further experiment.

One interesting implication of this study is that diffusion values are a product of the diffusion coefficients of the individual tissue types and Gleason score alone. Gleason score can, in principle, be determined by a diffusion measurement using only two *b* values provided the minimum is sufficient to completely dephase the IVIM signal (Fig. 6). However, as is well known, noise in these measurements is relatively large. Furthermore changes in Gleason score affect the shape of the signal curve, not just the overall decay rate so that multiple *b* values will help in accurately determining Gleason score.

There are a number of limitations of this study. First, and most importantly, the data to construct and test the model were obtained from the literature. Our approach has the advantage that the model is tested against a very large body of data, acquired with multiple different protocols, thus demonstrating the generality of model predictions. Similarly, the success of model predictions demonstrates that it is capable of explaining many of the ambiguities and contradictions in the literature. However, it would be better to construct the model from measurements specifically designed for the purpose (i.e., to characterize D_d^{free}, D_s^{norm} and D_e^{norm}) and to test the model by comparing signal predictions against actual signal measurements. We are currently acquiring data for this purpose. Second, the histological diagnoses reported were derived from either biopsy samples or post-surgical whole-mount histology. It is well known that the former are much less reliable than the latter due to sampling error [6-9]. Similarly association between diffusion measurements and the corresponding histopathological assessments was by a variety of different methods (quadrant by quadrant, MRI visible abnormality vs. overall Gleason score, etc.). Optimally, comparisons should be made between co-registered histological and MRI images. Third, some model parameters were estimated by informed guesswork rather than direct measurement. In particular, diffusion in cancerous epithelium was assumed to decrease linearly with Gleason score to a minimum of 50% of normal. Neither linearity nor the magnitude of the effect can be fully justified. A more complex relationship is probable given the complexity of biological processes and certainly has the potential to improve agreement between model and measurement. However, we believe it is unlikely to provide substantial

improvement given the noise levels involved, and runs the danger of over-fitting. The maximum reduction of 50% is also a guess but within the range reported in the literature for other tumours. However, all estimated parameters should be replaced, where possible, by direct measurement. (Some could also be made free parameters of the model but the advantage of this approach would be offset by the danger of overfitting.) Similarly, several model parameter estimates were obtained by linear interpolation between known measurements at particular Gleason scores. Although, replacement by direct measurements should improve the model, we believe the difference is likely to be a relatively small. Finally, there are limitations to the Jensen/Kärger exchange model that have been investigated in Fieremans et al. [98]. Although the model appears accurate for brain tissue, it is not clear that this is so in the cellular compartment of prostate. Additionally both stroma and epithelium consist of cellular and extra-cellular compartments potentially with a corresponding kurtosis term. Considerably more work is required to elucidate these issues. Nonetheless, the predicted range of K_c appears reasonable and, since K_c has only second order effects on diffusion signal, any errors are unlikely to be seriously detrimental to the model presented here.

Table 1. Tissue fractional volumes, v_i, signals, f_i, and ductal radii, r_d, used in the model for benign peripheral zone (PZ) and different Gleason scores. Fractional vascular volumes are interpolated from Schlemmer assuming that the measured value of v_v for cancer refers to Gleason 7. Other fractional volumes are derived from measurements made by Chatterjee et al.[13] for different Gleason *grades*. The value for Gleason score 7, for example, was obtained by averaging measurements for Gleason grades 3 and 4. Lumenal radius was obtained from Gilani et al. [44]. Interpolation was used when measurements were missing for individual scores.

Tissue	Fractional Volumes (Signals)				Ductal radius, r_d / μm
	Vascular	Ductal lumen	Stroma	Epithelium	
Normal PZ	0.020 (0.031)	0.284 (0.614)	0.382 (0.195)	0.314 (0.160)	300
Gleason 1	0.023 (0.037)	0.264 (0.588)	0.365 (0.192)	0.349 (0.184)	258
Gleason 2	0.026 (0.043)	0.244 (0.561)	0.357 (0.194)	0.373 (0.202)	216
Gleason 3	0.029 (0.050)	0.223 (0.530)	0.350 (0.197)	0.398 (0.224)	173
Gleason 4	0.031 (0.055)	0.203 (0.500)	0.333 (0.194)	0.433 (0.252)	135
Gleason 5	0.034 (0.062)	0.183 (0.467)	0.325 (0.196)	0.457 (0.275)	95
Gleason 6	0.037 (0.070)	0.164 (0.432)	0.318 (0.198)	0.481 (0.300)	65
Gleason 7	0.040 (0.079)	0.144 (0.394)	0.298 (0.193)	0.518 (0.335)	45
Gleason 8	0.043 (0.088)	0.124 (0.353)	0.278 (0.187)	0.555 (0.373)	32
Gleason 9	0.046 (0.099)	0.100 (0.299)	0.253 (0.179)	0.601 (0.424)	25
Gleason 10	0.049 (0.111)	0.076 (0.239)	0.228 (0.169)	0.647 (0.481)	20

Figure Captions

Fig. 1 Block diagram of the model for prostate diffusion. The model consists of four compartments, vascular, fluid filled ductal lumen, stroma and epithelium. Water exchange between both the vascular space and the ductal lumen and the other compartments is assumed to be negligible. Exchange between stroma and epithelium occurs but the two are not well mixed.

Fig. 2 Flow chart of the method used to determine empirical parameters of the diffusion model.

Fig. 3 Plot comparing measured values of measured ADC ($D_{measured}$) with values predicted by the model (D_{model}). Measurements made at 1.5T and 3T respectively are in blue and red respectively. Triangles and circles represent Category I (measurements represent a single Gleason score) and II (measurements represent an average Gleason score) papers respectively. The solid line is the line of identity.

Fig. 4 Bland-Altman plot of ADC difference, $D_{model} - D_{measured}$, vs. mean, $(D_{model} + D_{measured})/2$. Measurements made at 1.5T and 3T respectively are in blue and red respectively. Triangles and circles represent Category I (measurements represent a single Gleason score) and II (measurements represent an average Gleason score) papers respectively. The solid, dotted and dashed lines represent the mean difference, and the mean ± 1.96 standard deviations (i.e., the 95% confidence limits) respectively.

Fig. 5 Plot of ductal, epithelial, stromal and cellular (stromal and epithelial combined) ADC and cellular kurtosis vs. Gleason score. A score of 0 corresponds to normal peripheral zone tissue.

Fig. 6 Plot of signal vs. b value for normal peripheral zone (PZ) and Gleason scores 5 – 9. Note the discontinuity near b = 0 due to the delta function in Eq. [3].

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