Diffusion weighted imaging of prostate cancer: mathematical modeling of signal obtained using low b values

Harri Merisaari[1], Parisa Movahedi[1], Ileana Montoya[1], Jussi Toivonen[1], Marko Pesola[1], Pekka Taimen[2], Peter Boström[2], Tapio Pahikkala[1], Hannu Juhani Aronen[1], and Ivan Jambor[1]

[1]University of Turku, Turku, Finland, [2]Turku University Hospital, Turku, Finland

Synopsis

Eighty-one patients with historically confirmed PCa underwent two repeated 3T DWI examinations performed using 14 b-values in the range of 0-500 s/mm² and diffusion time of 19.004 ms. Various fitting methods for IVIM and mathematical models were evaluated in the terms of fitting quality (Akaike information criteria), repeatability, and Gleason score prediction. Monoexponential model demonstrated the highest repeatability and clinical values in the regions-of-interest based analysis of PCa DWI, b-values in the range of 0-500 s/mm².

Purpose

Our aim was to evaluate different fitting methods for intravoxel incoherent motion imaging model (IVIM) (1) and compare these methods with the monoexponential, kurtosis, and stretched exponential models/functions in the terms of fitting quality, repeatability, and prediction of prostate cancer (PCa) aggressiveness

Methods

Eighty-one patients with histologically confirmed PCa underwent two MR examinations on the same day performed using a 3T MR scanner (Ingenuity PET/MR, Philips, Cleveland, USA). The DWI was performed using a single shot SE-EPI sequence, monopolar diffusion gradient scheme, and the following parameters: TR/TE 1394/44 ms, FOV 250x250 mm2, acquisition matrix size 124x124, reconstruction matrix size 256x256, slice thickness 5.0 mm, no intersection gaps, diffusion gradient timing (Δ) 21.204 ms, diffusion gradient duration (δ) 6.600 m, SENSE factor of 2, partial-Fourier acquisition 0.69, SPAIR fat suppression, NSA 2, b values 0, 2, 4, 6, 9, 12, 14, 18, 23, 28, 50, 100, 300, 500 s/mm², acquisition time 3 minutes 45 seconds. The mean signal intensity of squared shaped ROI (4.89x4.89x5.00 mm³), placed in the center of PCa area, peripheral zone (PZ), and central gland (CG), was fitted. The IVIM biexponential equation (Eq. 1) was fitted using the following five different fitting methods:

$$S(b)=S0(fe^{-bDp}+(1-f)e^{-bDf})\quad \text{S(b)=S0(fe−bDp+(1−f)e−bDf)}$$

Eq. 1

1. "Full method": All four parameters (S_0, D_p, D_f, f) were derived using least square fitting method, in-house written C++ code, utilizing Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm (2) in dlib library (3).

2. “Segmented method”: In the first step, the monoexponential equation (Eq. 2) was used to derive D_f parameter value by fitting signal intensities in the range 100 - 500 s/mm^2.

$$S(b)=S_0e^{-bD_f}\text{S(b)=S0e−bDf}$$

Eq. 2
In the second step, the D_f parameter value from the first step was inserted into the biexponential equation and the remaining three parameters (S_0, D_p, f) were fitted.

3. “Over-segmented method” (4, 5): The first step consisted of fitting signal intensities of b values equal to or higher than 100 s/mm^2 with the monoexponential model (Eq.2) identically to the first step of the “segmented method”. In the second step, the extrapolated signal of the fitted monoexponential model was used to estimate f according to the equation 3:

$$f=(S_0-intercept)/S_0\text{f=(S0−intercept)/S0}$$

Eq.3
, where the intercept is the S_0 estimated from the eq. 2

In the last step the D_f and f parameter values from the first and second step, respectively, were inserted into the biexponential equation (Eq.1) and the remaining 2 parameters (S_0, D_p) were fitted.

4. “Semi-continuous multi-exponential method ” (6-8): This fitting method utilizes Non-negative least Squares (NNLS). The assumption is that the decay curve is composed of multiple mono exponential components each with different fraction of contribution to the decay curve extracted by NNLS. Accordingly, arbitrarily number of coefficient between 0.1 and 1000 μm^2/ms were chosen to derive the diffusion distribution spectrum of the signal decay curve. Fraction f was determined from the spectrum by calculating the ratio of the integral between 10-100 μm2/ms and the total integral.

$$S(b)=\sum_i Nf_{(ADCi)}.e^{-bADC_i}\text{S(b)=∑iNf(ADCi).e−bADCi}$$

Eq.4
5. “Simplified IVIM Model” (9): The biexponential function was modeled using delta function (Dirac delta function, d). Diffusion signal decay reduces to a mono-exponential function for all non-zero b-values:

$$S(b)=S_0(f\delta(b)+(1-f)e^{-bD_f})\text{S(b)=S0(fδ(b)+(1−f)e−bDf)}$$

Eq. 5
In addition to the IVIM fitting methods the following mathematical models/functions were fitted:

1. Monoexponential model (10):

$$S(b)=S_0(e^{-bADC_m})\text{S(b)=S0(e−bADCm)}$$

Eq. 6
2. Kurtosis model (11):

$$S(b)=S_0(e^{-bADC_k+\frac{1}{6}b^2ADC^2_kK})\text{S(b)=S0(e−bADCk+16b2ADCk2K)}$$

Eq. 7
3. Stretched exponential model (12, 13):

$$S(b)=S_0(e^{-(bADC_s)_\alpha})\text{S(b)=S0(e−(bADCs)α)}$$

Eq. 8
The fitting quality was evaluated using corrected Akaike information criteria difference (ΔAICc) (14) while the repeatability of the fitted parameters was evaluated using coefficient of repeatability (CR) and Intraclass

Correlation Coefficient (ICC) values (15), specifically ICC(3,1). Receiver operating characteristic curve (ROC) analysis was used to evaluate ability of the fitted parameters (17 parameters in total) to discriminate PCa with Gleason score of 3+3 from those with Gleason score of >3+3. Spearman correlation coefficient (ρ) values were calculated between the fitted parameters and the Gleason score groups (n=3).

Results

Based on ΔAICc the monoexponential model was the preferred model over all of the remaining models/functions and IVIM fitting methods in PCa, PZ and CG (Figure 1). The CR, ICC(3,1), AUC, and ρ values of ADC parameters (ADC_m, ADC_s, ADC_k) were similar to the D_f parameters estimated using all of the IVIM fitting methods (Figure 3). In contrast all f and Dp parameters demonstrated low repeatability (CR, ICC(3,1) values) and diagnostic performance (AUC and ρ values).

Conclusion

Monoexponential model demonstrated the highest repeatability and clinical performance in the regions-of-interest based analysis of PCa DWI obtained using b values in the range of 0-500 . s/mm^2.

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Figures

AIC$_c$¶	PCa	PZ	CZ
mono vs kurtosis	78	78	67
mono vs stretched	58	57	40
mono vs "full method"	74	65	53
mono vs "segmented method"	80	69	61
mono vs "over-segmented method"	87	77	82
mono vs "semi-continuous multi-exponential fitting method"	85	84	77
kurtosis vs stretched	30	25	18
kurtosis vs "full"	74	64	56
kurtosis vs "segmented method"	76	68	60
kurtosis vs "over-segmented method"	86	82	78
kurtosis vs "semi-continuous multi-exponential fitting method"	79	78	72
stretched vs "full"	89	80	77
stretched vs "segmented method"	91	85	84
stretched vs "over-segmented method"	96	92	96
stretched vs "semi-continuous multi-exponential fitting method"	94	88	92
"full" vs "segmented method"	100	100	100
"full" vs "over-segmented method"	100	100	100
"full" vs "semi-continuous multi-exponential fitting method"	99	99	100
"segmented method" vs "over-segmented method"	100	100	100
"segmented method" vs "semi-continuous multi-exponential fitting method"	67	75	75
"over-segmented method" vs "semi-continuous multi-exponential fitting method"	38	44	46

¶- Corrected Akaike information criteria

Selection of preferred model in different groups, each comparing two models. Percentage of ROIs described better by the first model of the comparison is shown in the table.

¶ - Corrected Akaike information criteria

Parameter	CR			ICC(3,1)			AUC	ρ
	PCa	PZ	CG	PCa	PZ	CG		
ADC_m	18.8 (16.0 21.7)	22.4 (14.1 32.2)	15.7 (12.7 18.7)	0.92 (0.88 0.95)	0.72 (0.47 0.88)	0.78 (0.65 0.86)	0.77 (0.68 0.85)	-0.326 (-0.457 -0.181)***
ADC_k	36.4 (30.7 41.8)	45.7 (29.5 64.6)	33.0 (27.4 38.2)	0.76 (0.65 0.85)	0.37 (-0.01 0.72)	0.45 (0.27 0.6)	0.78 (0.69 0.86)	-0.392 (-0.515 -0.253)***
K	158.0 (129.0 186.0)	126.0 (109.0 144.0)	106.0 (87.3 124.0)	0.17 (-0.07 0.40)	0.30 (0.11 0.48)	0.17 (-0.08 0.42)	0.55 (0.46 0.64)	-0.14 (-0.29 +0.02)
ADC_s	34.7 (29.0 40.4)	25.6 (14.7 38.2)	23.1 (18.9 27.1)	0.84 (0.77 0.90)	0.72 (0.43 0.9)	0.72 (0.58 0.82)	0.72 (0.63 0.81)	-0.20 (-0.34 -0.05)**
α	31.1 (25.4 36.8)	24.2 (20.1 28.1)	32.2 (25.5 38.8)	0.43 (0.19 0.62)	0.34 (0.089 0.55)	0.17 (-0.06 0.4)	0.64 (0.55 0.74)	+0.24 (+0.08 +0.38)**
f_{FULL}	1250.0 (972.0 1500.0)	1250.0 (998.0 1470.0)	834.0 (612.0 1030.0)	0.05 (-0.18 0.32)	0.10 (-0.081 0.32)	0.01 (-0.16 0.29)	0.63 (0.53 0.73)	-0.17 (-0.32 -0.02)*
$D_{p,FULL}$	2060.0 (1730.02370.0)	1610.0 (1290.0 1900.0)	919.0 (774.0 1050.0)	-0.07 (-0.23 0.12)	0.43 (0.22 0.62)	0.06 (-0.17 0.29)	0.55 (0.39 0.69)	-0.06 (-0.21 +0.09)
$D_{f,FULL}$	112.0 (88.3 134.0)	98.1 (79.5 115.0)	83.5 (62.6 103.0)	0.20 (-0.03 0.44)	0.26 (0.087 0.44)	0.13 (-0.12 0.41)	0.69 (0.53 0.83)	-0.23 (-0.37 -0.08)**
f_{SEG}	659.0 (425.0 898.0)	619.0 (361.0 898.0)	236.0 (166.0 299.0)	0.18 (-0.11 0.59)	-0.10 (-0.19 -0.01)	-0.10 (-0.28 0.13)	0.55 (0.45 0.65)	-0.03 (-0.18 +0.12)
$D_{p,SEG}$	2320.0 (1730.0 2900.0)	2290.0 (1690.0 2820.0)	1490.0 (1070.0 1860.0)	-0.04 (-0.12 0.06)	0.32 (0.09 0.55)	0.33 (0.03 0.6)	0.64 (0.52 0.77)	-0.19 (-0.340 -0.04)*
$D_{f,SEG}$	24.2 (18.9 29.8)	17.6 (14.5 20.7)	19.6 (15.8 23.8)	0.88 (0.81 0.93)	0.83 (0.75 0.9)	0.69 (0.54 0.81)	0.73 (0.64 0.83)	-0.27 (-0.41 -0.13)***
f_{OVER}	242.0 (202.0 284.0)	231.0 (195.0 267.0)	162.0 (131.0 191.0)	0.48 (0.27 0.66)	0.32 (0.08 0.54)	0.05 (-0.17 0.28)	0.71 (0.60 0.80)	-0.26 (-0.40 -0.11)**
$D_{p,OVER}$	2440.0 (1890.02950.0)	2780.0 (2150.0 3350.0)	1990.0 (1520.0 2410.0)	0.01 (-0.18 0.18)	0.18 (-0.04 0.41)	0.25 (-0.00750.51)	0.59 (0.47 0.73)	-0.19 (-0.33 -0.04)*
f_{DECON}	256.0 (205.0 308.0)	304.0 (252.0 354.0)	227.0 (178.0 274.0)	0.53 (0.34 0.69)	0.22 (-0.06 0.46)	0.14 (-0.05 0.34)	0.63 (0.52 0.73)	-0.28 (-0.42 -0.13)***
$D_{p,DECON}$	1370.0 (1150.0 1570.0)	930.0 (754.0 1080.0)	725.0 (612.0 828.0)	-0.04 (-0.21 0.17)	0.36 (0.16 0.55)	0.07 (-0.16 0.3)	0.56 (0.43 0.69)	-0.03 (-0.19 +0.12)
$D_{f,DECON}$	19.1 (16.1 22.2)	28.2 (14.9 42.8)	37.9 (17.2 55.6)	0.93 (0.89 0.95)	0.65 (0.39 0.87)	0.33 (0.058 0.78)	0.76 (0.67 0.84)	-0.30 (-0.43 -0.16)
f_{DELTA}	198.0 (167.0 230.0)	199.0 (164.0 237.0)	157.0 (127.0 187.0)	0.52 (0.33 0.68)	0.36 (0.082 0.61)	0.05 (-0.18 0.29)	0.71 (0.61 0.80)	-0.26 (-0.39 -0.11)**
$D_{f,DELTA}$	23.6 (18.8 28.1)	17.8 (14.6 21.1)	19.4 (15.5 23.6)	0.89 (0.83 0.93)	0.82 (0.74 0.89)	0.69 (0.53 0.81)	0.75 (0.65 0.83)	-0.28 (-0.42 -0.14)***

Coefficient of repeatability (CR), ICC(3,1), area under the curve values (AUC), and spearman correlation coefficient values (ρ). 95% confidence intervals are shown in brackets. PCa= regions of interest placed in prostate cancer lesions; PZ= regions of interest placed in normal tissue of the peripheral zone, CG= regions of interest placed in normal tissue of the central gland; *=p value < 0.05; **=p value < 0.01; ***=p value < 0.001