A Novel Luminal Water Model for DCE MRI of Prostatic Tissues

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Introduction Dynamic contrast-enhanced MRI has been shown to be useful in identifying prostate cancer compared to healthy glandular tissue. It has been suggested that Gd-DTPA does not reach intact prostatic ducts [1,2]. Standard pharmacokinetic modeling of DCE MRI data of the prostate does not take this into account and thus likely do not accurately represent the tissues. The purpose of this abstract is to present a novel pharmacokinetic model incorporating a Gd-inaccessible luminal water parameter and to demonstrate its differences versus an extended Tofts Kermode model [3] in simulations and in an in vivo example.

Methods A novel Luminal Water (LW) model of prostate tissue was designed based upon the assumption of Gd not reaching intact prostatic ductal lumen and the water in the lumen not having interacted with Gd through diffusion into the lumen. A luminal water volume parameter (V_L) was added to the extended Tofts Kermode (TK) model [3]. General assumptions of the Tofts Kermode model persist. The T1 outside of the lumen was assumed to change with time due to the change in Gd concentration in those tissues: $T1 = \frac{1}{\frac{1}{T_{10}} + R1 \times \frac{Vees \times Cv + Vp \times Cp}{1 - V_L}}$ T_{10} is the native T1, R1 = 4.5sec^{-1}mM^{-1}, Vees is the fractional volume of the extracellular, extravascular, extraluminar space, Cv is the concentration in this space, Vp is the fractional plasma volume, Cp is the plasma concentration of Gd. The tissue concentration is the weighted average of these concentrations, normalized to the non luminal water volume (1-V_L) (as water that has interacted with Gd can diffuse into cells, that volume is included). Cv is based upon simple diffusion of the Gd from the plasma and upon the arterial input function.

T1 in the ductal lumen was assumed to remain constant. The signal for the voxel was modeled as a linear combination of these two compartments, as follows, assuming a 3D spoiled gradient recalled echo acquisition:

$$S = \left[(1 - V_L) \frac{1 - \exp(-TR/T1)}{1 - \cos(\alpha)\exp(-TR/T1)} + V_L \times \frac{1 - \exp(-TR/T_{10})}{1 - \cos(\alpha)\exp(-TR/T_{10})} \right] \times \frac{1 - \cos(\alpha)\exp(-TR/T_{10})}{1 - \exp(-TR/T_{10})}$$

Inputs to this formula are α and TR, obtained from the sequence parameters, and T_{10}. T1 was given above. Fitting the data to this equation, using standard models for Cv, leads to output parameters of K^{trans}, Vees, Vp and V_L. For this study, the population AIF presented by Tofts [3] was used, with an additional, variable, amplitude parameter. MR signal intensities versus time for healthy peripheral zone tissue were simulated using the LW model and the extended TK model.

This model was applied to data from a subject with biopsy proven, untreated prostate cancer. 3T DCE MRI was performed with a series of 3D FSPGR images (TR/TE/flip=5/2.1ms/6°, 2.7mm slices, matrix=192x128, 100 timepoints, bolus injection of 0.1mmol/Kg Gd-DTPA). Regions of interest were identified and manually drawn on the aligned, T2-weighted images, maintaining homogeneous tissues. The time of initial enhancement was manually identified and subsequent intensities versus time data were fit to 1) the novel LW model and 2) the extended TK model. Native T1s were assumed to be 1.6sec.

Results Results of simulations with and without a luminal water component are shown in Table 1 and Figure 1. The extended Tofts Kermode tissue models are given, designed for matching the LW model with: 1) matching K^{trans}, 2) fitting the data, 3) matching late washout.

	K^{trans}	%Diff	V_L	Vees	%Diff
nPZ – modeled	0.0075		0.4	0.55	
1-Fit nPZ-Ktrans	0.0075	-	0	0.395	-28%
2-Fit nPZ	0.0055	-27%	0	0.415	-25%
3-Fit nPZ late washout	0.0042	-44%	0	0.43	-22%

Table 1 – Simulated normal peripheral zone tissue (nPZ) with fits using an extended Tofts-Kermode model with Vp=0.01 and an AIF amplitude of 2.

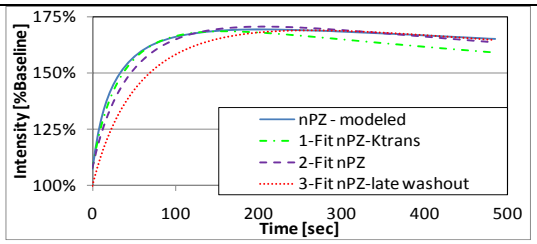

Figure 1- Simulation of normal peripheral zone (solid line) using luminal water, Tofts-Kermode models without luminal water (dashed)

The in vivo example case had a region of high signal intensity on the T2-weighted image, representing benign glandular tissue (highly ductal) and extensive regions with MR measures indicative of cancer (Bx=Gleason Grades 3 and 4) (Figure 2). Data was modeled as shown in Figure 3 and Table 2.

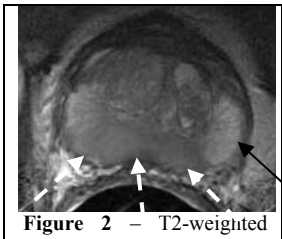

Figure 2 – T2-weighted image with highly glandular/ductal (black arrow) and cancer (white dashed arrows)

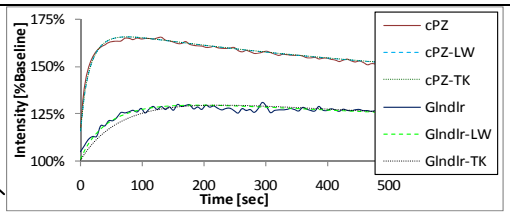

Figure 3 - Corresponding intensity vs. time curves and fits. The cancerous fits match (top) while the glandular (bottom) Tofts-Kermode fit (dotted) shows a slower enhancement than the data and than the Luminal Water model

	Model	K^{trans}	V_L	Vees	Vp
Glandular Tissue	**Luminal**	0.0021	0.4562	0.1689	0.0011
	Tofts-Kermode	0.0018	0	0.1519	0.0007
%Difference		-14%		-10%	-36%
Cancerous Tissue	**Luminal**	0.0139	0.0001	0.2827	0.0137
	Tofts-Kermode	0.0138	0	0.2827	0.014
%Difference		-1%		0%	2%

Table 2- Fits. The Luminal Water model yields a luminal water volume for the glandular tissue, but not the cancerous tissue, as expected biologically. The resultant Tofts-Kermode fit results in an underestimation of K^{trans}, Vees, and Vp for the glandular tissue.

Discussion This Luminal Water model of prostate tissues reflects underlying histology, as theorized and as demonstrated *in vivo*. The major difference between the LW and TK models is the luminal water compartment in the LW model which allows for a slower washout, quite common in healthy and benign, glandular prostate tissues. Simulations demonstrated that the standard extended TK model would greatly underestimate K^{trans} and vees in glandular tissues (-27% in example given). K^{trans} reductions less than this (12.5%) have been used to monitor therapy for prostate cancer [4]). Therefore, error in K^{trans} accuracy may be relevant for treatment response, as cancerous tissues are frequently mixed with healthy tissue, particularly in the low and moderate grades, so changes in the relative percentages of healthy and cancerous tissues can result in changes in K^{trans} without actual changes in the underlying vascular volume or permeability. Another implication of these simulations is that the K^{trans} with TK fits will be affected by the DCE MRI acquisition time, relevant for comparing studies. A limitation of this model is that it introduces an additional fit parameter; some data may be overparameterized, leading to difficulty in finding optimal fits. As this model provides a metric of benign glands, it has promise to help in understanding prostate tissue histopathology and potentially aid in tissue discrimination.

References 1-Noworolski et al. MRI 2008;1071-1080; 2-Storaas et al. ISMRM 2009;2235; 3-Tofts JMRI 1997;91-101; 4-Checkley et al. Br J Cancer 2003;1889-1895.
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