Quantification of Prostate Spectra at 3T Using LCModel with a Simulated Basis Set

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INTRODUCTION: Three-dimensional spectroscopic imaging (3DSI) of the prostate has been shown to aid in diagnosis and staging of disease with the potential to guide and monitor therapy. However, it may be that the full potential of this data has not been realized because of the limitations of the current standard quantitation method which involves the integration of the spectra over frequency ranges to determine relative amounts of metabolites. While being a simple and robust method, the challenge comes when more quantitative information is desired on the metabolites under investigation. Integration has difficulties addressing many issues including linewidth variations resulting from typical field inhomogeneities across the prostate and overlapping resonances especially when they have unique phases. While other methods for quantifying prostate spectra have been investigated (1), they fall short of fully modeling the spin systems involved. In this work we present a "true" model of the prostate metabolites. Through simulation, a set of basis functions was constructed and subsequently used in the frequency domain fitting of LCModel (2) to quantitate *in vivo* 3T prostate spectra.

METHODS: In order to quantitate spectra with LCModel, basis functions were created for each metabolite of interest by simulation using software developed by Henry *et. al.* (3). In brief, this software uses the Liouville equation to model the effects of both metabolite and sequence specific factors. For metabolites, the chemical shift and J-coupling constants are included while for the sequence, detailed RF pulse descriptions and timing information are included. Several prostate metabolites are not coupled and can be modeled based on their chemical shift alone. These signals include glycerophosphocholine (GPC at 3.212 ppm) phosphocholine (PCho at 3.208 ppm), choline (Cho at 3.185 ppm), and creatine (Cre: CH_3 at 3.027 and CH_2 at 3.913 ppm). Citrate (Cit) and Spermine (Spm), on the other hand, are coupled resonances. Citrate, which has been previously characterized, contains strongly coupled methylene resonances where the two doublets are centered at 2.550 and 2.686 ppm with a coupling constant of 16.1 Hz (4).

Spermine, which is the primary contributor to the polyamine signal between choline and creatine, was inadequately described in the literature. To assign chemical shifts and *J*-coupling for spermine's 20 protons, we ran high field NMR studies. A solution of 100 mM spermine tetrahydrochloride was mixed in distilled water and 10% D_2O. A spectrum was acquired on a 600 MHz vertical bore spectrometer (Varian, INOVA) with a simple excite-acquire sequence: repetition time of 6 s and a bandwidth of 8 kHz. The primary spectral features of spermine (NH_2-$CH_{2,1}$-$CH_{2,2}$-$CH_{2,3}$-NH-$CH_{2,3}$-$CH_{2,4}$-$CH_{2,4}$-$CH_{2,3}$-NH-$CH_{2,3}$-$CH_{2,2}$-$CH_{2,1}$-NH_2) were determined from the 1 dimensional spectrum (**Fig.1**) along with a *J*-resolved study. Each methylene was assigned with a subscript which links it to one of the 4 multiplets in the spectrum. The chemical shifts and coupling constants for the different methylene groups were as follows: $CH_{2,1}$: triplet at 3.15 ppm, $CH_{2,2}$: triplet at 3.11 ppm, $CH_{2,3}$: quintuplet at 2.09 ppm, and $CH_{2,4}$: triplet at 1.78 ppm. Coupling may also exist with the amine and amide groups but these assignments were not yet investigated. In addition, some protons assumed to be magnetically equivalent might require additional consideration.

In vivo data were acquired with a 3DSI acquisition on a Philips 3T scanner (Philips Medical Systems, Best, NL). The 3DSI PRESS sequence used had a 970 ms repetition time, 100 ms echo time and a nominal voxel size of 0.22 cm^3. Water suppression was achieved with an optimized saturation pulse along with a dual band BASING-type pulse for residual water and lipid suppression. The simulation of the basis set included modeling of the excitation and refocusing pulses used for PRESS localization but did not include the other RF pulses used for signal suppression as they ideally should not impact the evolution of the observed spins.

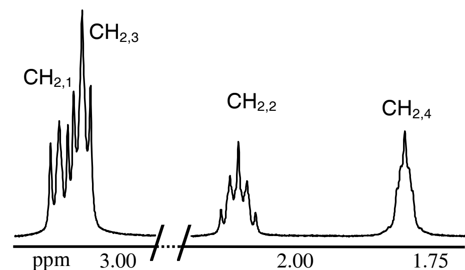

Fig 1: 600 MHz spectrum of 100 mM spermine tetrahydrochloride. The assignment of chemical shifts for the four types of methylene groups are shown.

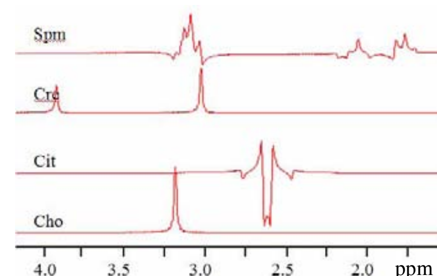

Fig 2: Simulated basis functions. GPC and PCho were excluded for display purposes.

RESULTS AND DISCUSSION: The basis functions are shown in **Fig. 2**. This basis set was used in LCModel to fit *in vivo* prostate spectra from a voxel in normal tissue (**Fig. 3a**) and cancer (**Fig. 3b**). The fitted amplitudes for the peaks from the two spectra along with the Cramer-Rao lower bounds (CRLB) are given in **Table 1** where tCho stands for total choline (Cho+PCho+GPC). The use of tCho is necessary as we cannot reliably quantify the individual choline compounds as they are highly correlated while the combined sum can be reliably quantified based on CRLB values. In addition, the justification for including both PCho and Cho in the fitting comes from HRMAS results where it was shown that both resonances are present in normal tissue and both increase in prostate cancer (5). While GPC was not explicitly identified in the HRMAS study it can be used synonymously with PCho in terms of fitting as GPC and PCho are only 0.5 Hz apart at 3T. As choline is approximately 3.5 Hz from GPC, it may be that including this resonance in the fit will improve characterization of tCho and allow Spm to be quantified more accurately. While this might not be significant for obviously cancerous spectra as in Fig. 3b, it may be important for monitoring changes in metabolite signals during treatment or to improve sensitivity to lower grade cancers. With respect to analyzing tCho, a useful feature of LCModel is its ability to automatically combine the results of several peaks, such as those of tCho, along with calculating their combined CRLB.

	Normal		Cancer	
	Amp.	CRLB	Amp.	CRLB
tCho	0.104	7%	0.31	4%
Spermine	0.208	5%	-	-
Creatine	-	-	0.146	22%
Citrate	2.81	3%	0.58	12%
Cit / tCho	0.037		0.534	

Table 1

Finally, a model based fitting approach provides the potential to improve quantification of overlapping resonances especially when different metabolites have different phases as in the case of Cre and Spm. While more complex to implement, this method should provide improved quantitation of prostate spectra over integration and heuristic models. However, further studies are required to justify such claims along with their clinical significance.

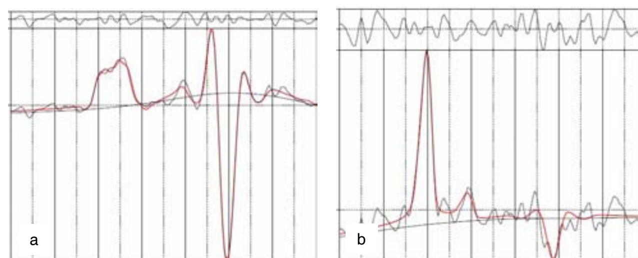

Fig. 3: Fitted prostate spectra from normal tissue (a) and cancer (b) with LCModel using the simulated basis set. The lower window shows the original spectrum (black curve) with the fitted results (red curve) along with the resulting baseline (smooth black curve). The upper curve shows the residual of original data minus the fit.

REFERENCES: Pels et. al. NMR Biomed 2006;19(2): 188., Provencher. MRM 1993;30(6): 672., Henry et. al. MRM 2006;55(2):250., Trabesinger et. al. MRM 2005;54(1):51., Cheng et. al. FEBS Lett 2001;494(1-2):112.

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