Optimised VERDICT MRI protocol for prostate cancer characterisation

Eleftheria Panagiotaki[1], Andrada Ianus[1], Edward Johnston[2], Rachel W Chan[2], Nicola Stevens[2], David Atkinson[2], Shonit Punwani[2], David J Hawkes[1], and Daniel C Alexander[1]

[1]Centre for Medical Image Computing, University College London, London, London, United Kingdom, [2]Centre for Medical Imaging, University College London, London, United Kingdom

Target Audience Biophysical modellers, diffusion MRI researchers, cancer imaging researchers, prostate cancer clinicians

Introduction Vascular Extracellular and Restricted DIffusion for Cytometry in tumours (VERDICT) uses a three-compartment model to characterise diffusion in the vascular, extracellular-extravascular space (EES) and intracellular (IC) compartments in tumours[1]. Previous studies use VERDICT with long imaging protocols for microstructural tumour characterisation of colorectal xenograft models[1] and human prostate[2]. Clinical adoption of the technique would be made more likely if the scan time requirements could be limited to approximately 10 minutes, 3-4 times shorter than the current experimental prostate protocol. This work uses a computational optimization framework[3] with VERDICT to meet the clinical scan duration that will enable larger clinical trials to judge suitability for widespread translation.

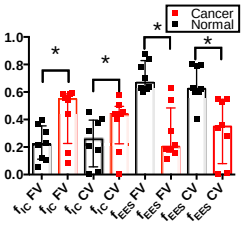

Figure 1 VERDICT volume fraction estimates from the FV, CV protocols for 8 patients. The CV has significantly different (Wilcoxon matched pairs p=0.05) estimates between tissue types as the FV.

Methods Protocol Optimisation We use the experiment optimisation framework[3] with the VERDICT prostate model[2] to find the measurements that provide the most accurate and precise parameter estimation within clinical and hardware constraints. The optimisation produces protocols with 5 measurements (equal to the number of free model parameters) for 3 directions. By minimising the Cramer-Rao-Lower-Bound of the estimates we obtain the optimal combination of b values and Δ, δ, |G|, where Δ is the gradient separation time, δ is the gradient duration and |G| is the gradient strength. The method is optimised for the configuration of a 3T clinical scanner and a maximum b value of 3000 s/mm^2.

Diffusion model We perform the optimisation for the 5 free parameters of the prostate model: f_{EES} (EES volume fraction), f_{IC} (IC volume fraction), cell radius R, diffusivity D and pseudo-diffusion P. The vascular volume fraction is $f_{VASC}=1-f_{IC}-f_{EES}$.

MRI Acquisition protocols We acquire DW-MR images with a Philips Achieva 3T MRI using a pulse-gradient spin-echo sequence and a 32 channel cardiac coil with b values of 90-3000s/mm^2 in 3 orthogonal directions. For b<500 the number of averages (N_{AV})=6, for 500<b<1000 N_{AV}=12 and for b>1000 N_{AV}=18 with voxel size=1.3×1.3×5mm, matrix size=176×176, TR=2000ms. Table 1 shows the imaging parameters. We normalised the data with a b=0 image for every echo time (TE) to avoid T_2 dependence.

Table 1. Diffusion MRI protocol details for VERDICT analysis.

b value s/mm^2	Δ/ δ ms	TE ms	|G| T/m
3000	31.6 / 13.5	65	0.0921
2500	30.7 / 12.6	63	0.0910
2000	29.4 / 11.3	60	0.0923
1500	28.1 / 10.0	58	0.0919
1000	26.6 / 8.5	55	0.0901
800	25.7 / 7.6	53	0.0913
400	23.7 / 5.6	49	0.0903
200	22.2 / 4.1	46	0.0893
100	21.2 / 3.1	44	0.0848
3000	24.7/43.8	90	0.0439
2000	13.2/32.3	67	0.0758
1500	24.7/43.4	90	0.0311
500	12.2/31.3	65	0.0415
90	12.2/23.8	50	0.0506

Model fitting and regions of interest (ROI) We use a similar iterative optimization procedure to[1, 2] that accounts for local minima and Rician noise. We fit the model to areas of normal and cancerous peripheral zone (PZ) tissue before averaging the signal over the whole region. For the 5 volunteers we used healthy PZ.

Evaluation Ideally we would like to compare the full version (FV) protocol with the optimised (Opt) protocol to see which provides the most accurate and precise parameter estimates. However it was not possible to image further patients that underwent the FV protocol. The FV protocol lasts 35 minutes and is indicated by the first 9 rows of Table 1. The Opt protocol is 10 minutes long and highlighted in blue in Table 1, and in grey we indicate a cut-down version (CV) of the FV with similar b values as the Opt, which is 15 minutes long. Hence we use i) data from 8 patients with PZ prostate cancer (Gleason score 3+3 (n=1), 3+4 (n=6) and 4+3 (n=1)) that underwent the FV to compare the CV with the FV, ii) simulations and 5 healthy volunteers to compare the CV with the Opt, and iii) data from 4 additional patients with radiologically suspicious prostate lesions with the Opt protocol. The fitting with the FV and CV estimates 4 parameters as in [2] for comparison: f_{IC}, f_{EES}, f_{VASC}, R, and with the Opt protocol all 5 parameters.

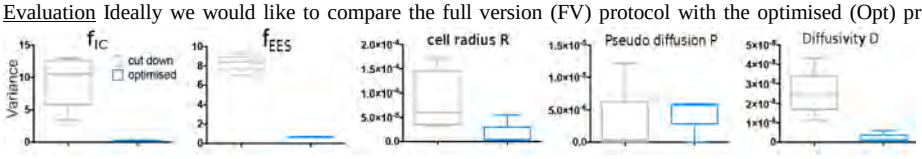

Figure 2 Variance for VERDICT estimates from the Fisher Information matrix for 5 healthy volunteers using Opt and CV. The Opt protocol has smaller variance for all the parameters.

Simulations: We simulate data with VERDICT for normal and cancerous tissue using estimates from the 8 patients with SNR_{Opt}=15, 20, 25. The Opt protocol has longer TEs compared to the CV, so we calculate the reduced SNR according to: $SNR_{Opt}=SNR_{CV}\times\exp(-(TE_{Opt}-TE_{CV})/T_2)$, using a median value of T_2 for PZ tissue of 100ms[4].

Results *FV-CV comparison*: The CV performed similarly to the FV revealing significant differences between the f_{IC}, f_{EES} of cancer and benign tissue (Fig.1), trends previously shown in[2]. There was no significant change in the cell radius. *CV-Opt comparison*: Simulation results (omitted) showed that the Opt protocol estimated more accurately the parameters for all SNR levels compared to CV with lower standard deviation. Figure 2 shows the variance for all the parameters from the Fisher Information matrix for healthy volunteers using Opt and CV. All estimates with Opt have lower variance than with CV. *Parameter estimation in patients with Opt*: Figure 3 presents VERDICT parameters for normal and cancer suspicious ROIs. There is higher f_{IC} and lower f_{EES} in cancer as in[2], but also lower values for cancer than normal tissue in the P, D coefficients.

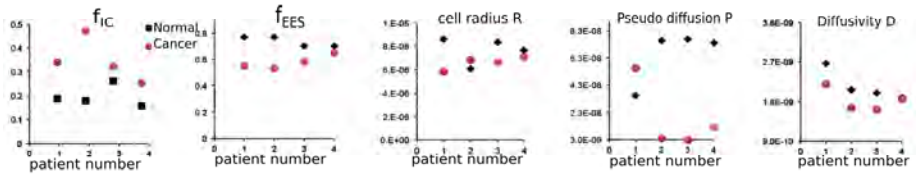

Figure 3 VERDICT estimates with the Opt protocol for normal and suspicious for cancer tissue from 4 patients.

Discussion This method provides a clinically feasible imaging protocol of 10 minutes for prostate microstructure characterization with VERDICT. Comparison of a CV version of the original protocol reproduced the findings of the FV in patients with confirmed cancer. Computer simulations and healthy volunteers then showed greater accuracy of the Opt protocol compared to CV. VERDICT analysis of additional patients with the Opt protocol showed promising results for cancer discrimination by differences in the estimates f_{IC} f_{EES}, P, D of suspicious lesions and normal tissue. We note that for the model fitting the FV and CV protocols required constraints for stable fitting[2] whereas the optimisation allowed stable fitting and sensible estimation for all the parameters. Future work will look at a larger patient cohort as well as histological analysis of the lesions for validation.

References & Acknowledgements 1 Panagiotaki et al Cancer Research 2014, **2** Panagiotaki et al Investigative Radiology (in Press) 2014 **3** Alexander MRM 2008 **4** Langer et al JMRI 2009. **This work is funded by the grants EP/H046410, EP/0I018700/1, EP/G007748.**