Joint estimation of precontrast T_1 and DCE-MRI perfusion and permeability parameters significantly improves precision of parameter estimates

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TARGET AUDIENCE Imaging scientists who use DCE-MRI to study perfusion and permeability, particularly in preclinical and clinical studies of cancer.

PURPOSE DCE-MRI can be used to spatially map estimates of biophysical parameters related to tumour perfusion and capillary permeability [1]. These parameters are commonly used in pre-clinical and clinical trials of novel anti-vascular and anti-angiogenic agents as they can provide early quantitative measurements of treatment efficacy [2]. Improving the precision of parameter estimates is important ethically and economically, as greater precision can help minimise the number of animal or human subjects required. We present a novel method for estimating DCE-MRI perfusion and permeability parameters from data acquired using a typical DCE-MRI protocol. The key contribution of this work is that parameter estimate precision can be improved significantly by estimating precontrast T_1 and M_0, and tracer kinetic parameters, ***jointly*** instead of sequentially.

THEORY DCE-MRI involves the acquisition of a series of images during the administration, uptake and washout of a contrast agent. Biophysical parameters related to tumour perfusion and capillary permeability may be estimated by fitting a tracer kinetic model, such as the two-compartment exchange model (2CXM; Eqn. 1), to measured signal-time curves via the spoiled gradient echo equation (Eqn. 2):

$$C_t(t) = F_p[Ae^{-K_+t} + (1-A)e^{-K_-t}] \otimes AIF(t) \qquad (1)$$

$$S(T_{1,0}, M_0, C_t) = \frac{M_0 \sin(\alpha) e^{-TR(rC_t + 1/T_{1,0})}}{1 - \cos(\alpha) e^{-TR(rC_t + 1/T_{1,0})}} \qquad (2)$$

where C_t is the modelled contrast agent concentration, F_p, A, K_+, and K_- are the 2CXM parameters, AIF is the arterial input function, S is the modelled MR signal, $T_{1,0}$ is the pre-contrast T_1, M_0 is the equilibrium longitudinal magnetization, r is the T_1 relaxivity of the contrast agent, and α and TR are the flip angle and repetition times of the MR sequence. Conventionally, $T_{1,0}$ and M_0 are estimated prior to model fitting using a dedicated MR experiment. This can be done using a variable flip angle (VFA) experiment by fitting Eqn. 2 (with $C_t(t) = 0$) to signal intensities acquired at each of a number of flip angles. The estimates of $T_{1,0}$ and M_0 are then substituted into Eqn. 2 as fixed parameters, and $C_t(t)$ is varied (by performing an optimization) to fit the modelled signal to the measured dynamic data. In this approach $T_{1,0}$ and M_0, and the 2CXM parameters, are estimated sequentially. Measurement error in the VFA experiment will propagate through to error in $T_{1,0}$ and M_0 estimation, to error in calculation of $C_t(t)$, to errors in estimates of the biophysical parameters of ultimate interest. Here we present an alternative approach, which recognises that while DCE-MRI sequences are not designed to measure $T_{1,0}$ or M_0, they nonetheless carry information about them, and that the above propagation of errors can be mitigated via joint estimation of all parameters of interest. If VFA images are misregistered due to subject motion, then additional errors will be introduced into the estimates of $T_{1,0}$ and M_0 due to poor tissue-voxel mapping. We propose that joint estimation can again mitigate such errors by reducing the dependence of the $T_{1,0}$ and M_0 estimates on misregistered VFA images.

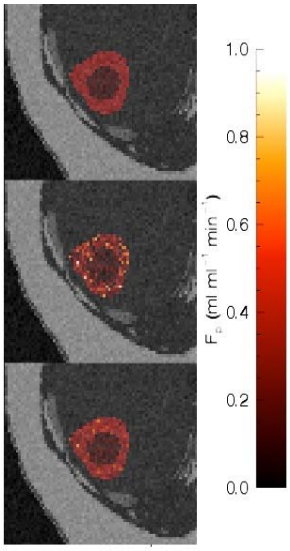

Figure 1. *Plasma perfusion maps. Top: Ground truth map. Centre: Sequential estimation map Bottom: Joint estimation map*

METHODS We used data simulated from a high fidelity software phantom [3] to test the null hypotheses of equal precision in parameter estimates, with no and substantial motion, between the conventional sequential and proposed joint estimation methods. The phantom can realistically model VFA and dynamic images of the abdomen, and can include non-linear local tissue deformations if required. The phantom anatomy is based on a DCE-CT scan of a patient with a liver tumour. Motion was emulated using displacement fields using finite element modelling and an acquired breathing trace. Zero mean Gaussian noise was added to the images to give a SNR of 5. The motion-corrupted data were registered prior to analysis using 3D translational registration. Plasma perfusion, F_p, and model parameters A, K_+ and K_- are analytically related to plasma-interstitial exchange flow (F_E), relative plasma volume (v_p), and relative interstitial volume (v_e) [4]**.** Ground-truth values for F_p, F_E, v_p and v_e were randomly sampled from one of two uniform distributions (tumour rim or core distribution); the limits of these distributions were based on 2CXM parameters estimated using DCE-MRI in patients with cervical cancer [5]. For sequential estimation, $T_{1,0}$ and M_0 were estimated from the VFA images, and the values were substituted as fixed parameters during model fitting. A population based AIF with temporal resolution of 2.5s was used to simulate a bolus input [6]. For joint estimation, $T_{1,0}$, M_0, and the model parameters were estimated simultaneously (all six parameters were allowed to vary). In both optimizations, all parameters were constrained to be greater than 0, and v_p and v_e were constrained to be less than 1. Curve fitting was performed using the Levenberg-Marquardt least squares minimiser in IDL 8.2.2 (Exelis Visual Information Solutions, Boulder, CO, USA). Precision was quantified by inter-quartile range of bias over all tumour voxels (bias = estimated value – groundtruth value).

Table 1. Interquartile range of the bias for sequential and joint estimation (IQR (95% CI)). Bold signifies significant improvements ($p < 0.05$) in precision compared to sequential estimation. Bonferroni correction has been applied.

	Motion-free		Motion with registration	
Parameter	**Sequential**	**Joint**	**Sequential**	**Joint**
F_p (ml ml^{-1} min^{-1})	0.17 (0.15, 0.19)	**0.10 (0.09, 0.11)**	0.12 (0.11, 0.14)	**0.09 (0.08, 0.11)**
F_E (ml ml^{-1} min^{-1})	0.07 (0.06, 0.07)	**0.05 (0.04, 0.05)**	0.21 (0.18, 0.25)	0.17 (0.14, 0.20)
v_p (ml ml^{-1})	0.05 (0.04, 0.06)	**0.04 (0.03, 0.04)**	0.07 (0.06, 0.08)	0.07 (0.06, 0.08)
v_e (ml ml^{-1})	0.20 (0.17, 0.23)	**0.13 (0.11, 0.16)**	0.09 (0.09, 0.11)	**0.08 (0.07, 0.09)**

RESULTS Table 1 shows that joint estimation leads to significant improvements ($p < 0.05$) in the precision of all 2CXM parameters in the motion-free data. Joint estimates of F_p and v_e in the registered motion-corrupted data are significantly more precise than for sequential estimation. Figure 1 shows better agreement with ground truth using joint versus sequential estimation.

CONCLUSION Joint estimation improves the precision of all tumour perfusion and permeability measurements in motion-free data, and of F_p and v_e in registered motion-corrupted data. Improved registration should result in significantly more precise estimates of F_E and v_p also. In the context of DCE-MRI studies of cancer, joint estimation may help reduce required sample sizes, conferring both ethical and economic benefits.

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