Precision of two-compartment exchange model parameter estimates: dependence on tissue physiology

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TARGET AUDIENCE Researchers interested in using the two-component exchange model[1] (2CXM) for perfusion and permeability measurement in DCE-MRI.

PURPOSE To determine how the error in 2CXM parameter estimates varies across a range of tissue types.

THEORY DCE-MRI data can be analysed by fitting a tracer kinetic model to the measured signal time curves, resulting in estimates of biophysical parameters such as plasma perfusion and capillary permeability. For this purpose, the model should be representative of the tissue. Most DCE-MRI analyses use the Tofts or extended-Tofts models, which are simplified versions of the more general two-compartment exchange model[1]. The Tofts-model is used on data with poor temporal resolution, and requires the prior assumption that plasma perfusion is infinite. The 2CXM requires no such assumptions, and can theoretically be applied to any tissue that can be adequately described as a two compartment system separated by a diffusible membrane. In pre-clinical and clinical DCE-MRI data, electronic scanner noise and patient motion lead to fluctuations in MR signal, which are unrelated to signal changes caused by underlying tissue physiology and therefore produce errors in the estimates of the model parameters. Previous simulation studies have assessed the error in 2CXM parameter estimates, but have been limited to a small numbers of tissue types[2]. It has been suggested that the 2CXM will not perform well for tissues near the boundary of parameter space due to model degeneracy, however no quantitative analysis has been carried out in the literature[3]. We perform simulations that show how the relative error in parameter estimates varies across a range of tissue types.

METHODS A total of 10,000 signal-time curves were simulated. All curves were generated with relative interstitial volume (v_e) and plasma volume (v_p) of 0.25 ml ml^{-1} and 0.05 ml ml^{-1} respectively, whereas F_p and F_E varied from curve to curve. The values chosen for v_e and v_p are representative of typical tumour physiology. Curves had values of F_p varying from 0.01 ml ml^{-1} min^{-1} to 1.00 ml ml^{-1} min^{-1} in increments of 0.01 ml ml^{-1} min^{-1}. For each value of F_p, 100 additional curves were generated by varying F_E from 0.01 ml ml^{-1} min^{-1} to 1.00 ml ml^{-1} min^{-1} in increments of 0.01 ml ml^{-1} min^{-1}. Curves were generated with the following input parameters: pre-contrast T_1 of 800 ms, M_0 of 10500 (unitless), TR of 3.2 ms, flip angle of 25°, using the spoiled gradient echo equation, 2CXM impulse response function, and a population based AIF[4]. Gaussian noise was added to each signal-time curve to yield an SNR of 5, a level typical in voxel-wise analyses. Least squares fitting was performed using the Levenberg-Marquardt least squares minimiser 'mpcurvefit' in IDL 8.2.2 (Exelis Visual Information Solutions, Boulder, CO, USA). During each optimisation, F_p, F_E and v_e were allowed to vary and v_p was held fixed. Fitting was repeated 100 times, incrementing v_p between 0.01 ml ml^{-1} and 1.00 ml ml^{-1} in 0.01 ml ml^{-1} increments. Parameter estimates corresponding to the fit with the lowest chi-square were chosen. Simulations were repeated 1,000 times in a Monte Carlo experiment. The bias between the estimated value and ground-truth value was determined for each parameter and repetition, and the interquartile range (IQR) of the bias was calculated as a measure of precision error. Relative error due to lack of precision was calculated by dividing the IQR by the ground-truth value and was plotted for each 2CXM parameter in Figure 1.

RESULTS Figure 1A shows that relative error in F_p is lower for well-perfused tissues than for poorly perfused tissues. The value of the exchange flow, F_E, is seen to have little effect on the relative error of F_p. Relative error in F_E (Figure 1B) is high in tissues with low F_E and F_p, but reduces as either F_E or F_p increase. Error in v_e (Figure 1C) is much better than F_p or F_E (less than 40% for all tissues types studied). v_p exhibits the lowest error (Figure 1D) averaged over all tissue types considered (less than 20%).

CONCLUSION For tissues with typical v_p and v_e, errors in the estimates of the 2CXM are shown to depend on the perfusion and permeability status of the tissue of interest. Relative error in F_p (interquartile range/ground truth) is found to exceed 60% for tissues with plasma perfusion below 0.1 ml ml^{-1} min^{-1}. Furthermore, relative errors in F_E are found to exceed 40% if both F_p and F_E are less than or equal to 0.1 ml ml^{-1} min^{-1}. These results confirm that the 2CXM fails to describe well those tissues with near zero F_p or F_E, confirming predictions made by Sourbron et al[3]. If v_p and v_e are the only parameters of interest, one can have confidence that relative errors in either parameter are largely independent of tissue type. In summary, users of the 2CXM should be aware of the dependency of parameter precision on the type of tissue being studied, and must bear this in mind when interpreting results.

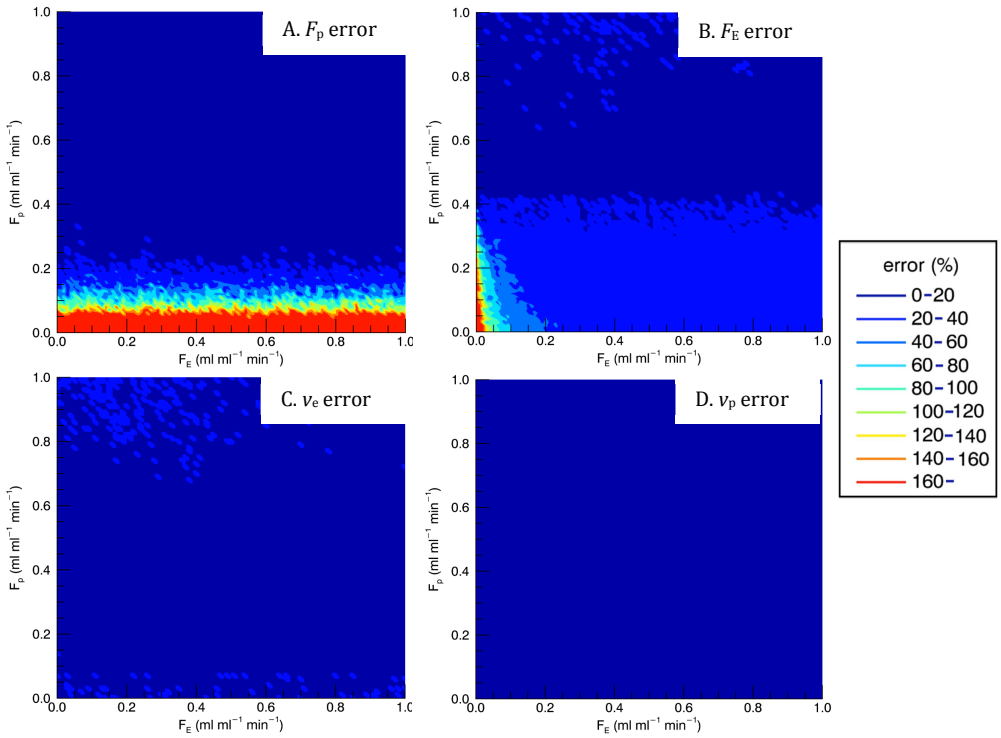

Figure 1. *Plots showing the relative error (interquartile range/groundtruth) in each 2CXM parameter as a function of F_p and F_E.*

REFERENCES 1. Sourbron et al, *Magn Reson Med*, 2009, 62:205-17 **2.** Luypaert et al, *Phys. Med. Biol*, 2010, 55:6431-6443, **3.** Sourbron et al, *Magn Reson Med*, 2011, 66: 735-745**, 4.** Parker et al. *Magn Reson Med*, 2006, 56:993-1000.