Simultaneous Determination of Perfusion and Microvascular Permeability: Measurement Precision with T_1-weighted DCE-MRI

L. E. Kershaw[1], D. L. Buckley[1]

[1]Imaging Science and Biomedical Engineering, University of Manchester, Manchester, United Kingdom

Introduction Dynamic contrast-enhanced MRI (DCE-MRI) is increasingly used to estimate microvascular parameters by tracer kinetics analysis. Distributed parameter models are of particular interest since they allow simultaneous measurement of perfusion (F) and microvascular permeability-surface area product (PS). Bolus arrival time (BAT) must be measured in such studies as inaccurate estimates introduce a large degree of uncertainty into model fitting. It important to define this uncertainty but the precision of parameters estimates is rarely reported. To address these issues two investigations were undertaken. Simulated data were used to test the performance of two methods for estimating BAT and a bootstrap error analysis [1] was performed using the adiabatic approximation to the tissue homogeneity (AATH) model [2], fitted to experimental data acquired in prostate and muscle tissue [3].

Methods Curves simulated using the AATH model were used to assess the accuracy and precision of two methods for estimating the BAT. 37 different parameter sets were used, each with 5 different BATs between 0.05 and 0.3 min. For each of these curves, six different levels of Gaussian noise were added to produce SNRs between 20 and 4.1. The arterial input function used for these simulations was taken from one of the prostate datasets. The first method for estimating BAT involves fitting the Kety model, (including a v_p term [4]) to the uptake curve, including BAT as a free parameter in the model equation. The second method was described by Cheong [5], and uses a linear-quadratic function to model the baseline and first few points of the uptake curve. Each timepoint in turn is used as the point where the linear and quadratic functions meet. The point which produces the fit with the lowest χ^2 is chosen as BAT.

The AATH model was used to extract physiological parameter estimates by fitting to DCE-MRI data obtained from regions of interest in prostate tumour, contralateral normal peripheral zone and muscle from 22 prostate cancer patients [3]. Free parameters in the fit were the extraction fraction E, plasma flow F_p, mean capillary transit time T_c and interstitial volume v_e. Uncertainties associated with these parameter estimates were calculated using the bootstrap method, where residuals from the fit are used to create a large number of simulated datasets which are also fitted with the model to provide an error estimate (coefficient of variation, CoV) for each parameter.

Results The fitted values for BAT are shown in Fig 1 for the different noise levels as the median value over all 37 parameter sets. The grey lines show the simulated BAT values, and error bars show the 25th and 75th percentiles. Over a wide range of noise values Kety fits resulted in an overestimate of BAT whereas the Cheong approach gave a fitted BAT closer to the actual value. At low noise levels the Cheong method also improved precision but this effect was less marked at higher noise levels. Mean error over all noise levels ranged from 0.04-0.05 min (Kety), and from -0.005-0.04 min (Cheong). Median parameter estimates for the three region types are shown with their interquartile ranges in table 1 (cases where fitted v_e>1 were excluded). Two patients had no identifiable areas of normal tissue. Haematocrit was assumed to be 0.4, and PS and v_b were calculated from the fitted parameters. Fig 2 shows histograms of the estimated CoV when the AATH model was fitted to uptake curves in tumour and normal prostate tissue. In general, the data from muscle were noisy with low enhancement and the parameter estimates obtained from them have been excluded from the summary statistics.

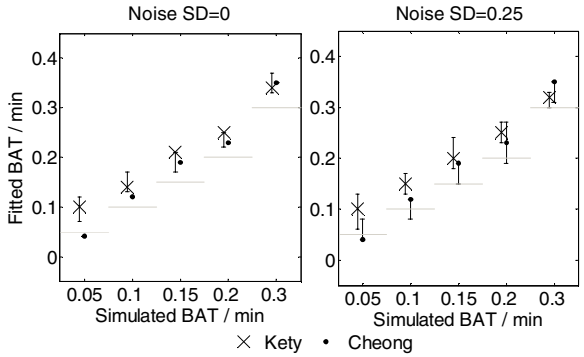

Figure 1 – Fitted BAT *vs.* simulated BAT for each method at lowest and highest noise levels

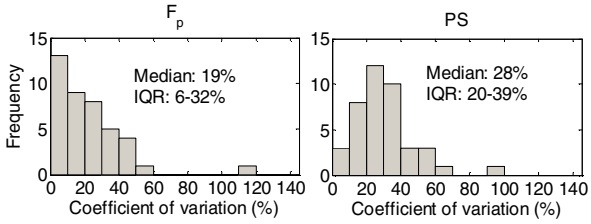

Figure 2 – Histograms of precision (CoV) in estimates of F_p and PS for all prostate tissue

Discussion The Cheong method was shown to be both quick and accurate for estimation of BAT. Such a method has benefits over the inclusion of an additional unknown to a model with an already large number of free parameters. Fitting the AATH model to clinical data was not straightforward, however, in all but 4 cases an acceptable fit was found. Parameter estimates are in close agreement with previous studies (e.g. [6]) and F and PS can be measured in the prostate with acceptable levels of precision (median CoV 19% and 28%, respectively). Large uncertainties in v_e (median CoV 35%) result from fitting to data yet to reach equilibrium. Longer acquisitions should decrease this uncertainty. Estimates of T_c are longer than previously reported, highlighting the importance of using distributed parameter models. In conclusion, we can estimate both F and PS with acceptable precision using the AATH model.

Table 1. Model fits to uptake curves in tumour, normal prostate and muscle

Parameter	F_b /ml ml^{-1} min^{-1}	T_c /min	v_e /ml ml^{-1}	v_b /ml ml^{-1}	PS /ml ml^{-1} min^{-1}
Tumour, n=21	**0.36** (0.19-0.51)	**0.31** (0.09-0.54)	**0.35** (0.26-0.49)	**0.12** (0.04-0.13)	**0.24** (0.18-0.34)
Normal, n=20	**0.13** (0.10-0.19)	**1.00** (0.55-1.26)	**0.21** (0.15-0.33)	**0.11** (0.09-0.18)	**0.12** (0.06-0.17)
Muscle, n=19	**0.06** (0.04-0.13)	**0.68** (0.31-1.15)	**0.08** (0.05-0.15)	**0.03** (0.02-0.06)	**0.02** (0.01-0.05)

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