# Precision and accuracy of $K^{trans}$ estimated by fitting the extended Kety model parameters to DCE-MRI time course data is unaffected by the choice of optimisation algorithm or estimation of $T_1$ using linearisation

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Introduction Microvascular characteristics of tumours can be assessed by fitting a tracer kinetic model to contrast agent concentration time course data derived from dynamic contrast-enhanced (DCE-) MRI time series. The estimated model parameters, such as $K^{trans}$, can be used to monitor the efficacy of anti-angiogenic drugs[1]. Many optimisation algorithms are available for model fitting and it is important to ensure that the selected implementation gives precise and accurate results[2]. We present a comparison of optimisation algorithms used to fit the extended Kety model[3] to contrast agent concentration time course data. The parameter values could also be affected by the accuracy of the $T_1$ value (which is required to convert signal intensity to contrast agent concentration). Therefore, we also assess algorithms (including function linearisation[4]) used for estimating $T_1$ from the commonly used variable flip angle (VFA) spoiled gradient echo (SPGR) method[5].

Synthetic data We used a software phantom generator[6] to provide VFA SPGR images and DCE time-series with known ground truth. Pre-contrast SPGR images for $T_1$ estimation had flip angles of 2°, 10° and 30° and a TR of 4 ms. DCE time-series SPGR images were simulated using the extended Kety model and a functional form of a population AIF[7]. $K^{trans}$, $v_e$ and $v_p$ were varied along the 3 axes of the synthetic image volume to give 400 different parameter combinations. 20 evenly-spaced values of each parameter were used with ranges of 0.1 – 0.5 $min^{-1}$ for $K^{trans}$; 0.15 – 0.6 for $v_e$; and 0.025 – 0.1 for $v_p$. Three synthetic data sets with ground truth $T_1$ values of 600 ms, 1000 ms and 1400 ms were generated. For assessing $T_1$ estimation, VFA SPGR images were produced with 20 evenly-spaced $T_1$ values from 100 ms to 2000 ms. 400 samples were generated for each $T_1$ value. Zero mean Gaussian noise was added to the signal intensity data to give a signal-to-noise ratio equivalent to 10 in a 30° flip angle pre-contrast SPGR image.

Model fitting **For estimating $T_1$ values** from VFA SPGR images, we compared three commonly-used non-linear least squares (NLLS) optimisation algorithms: a C implementation of the Levenberg-Marquardt algorithm as described in Numerical Recipes[8]; the lsqcurvefit routine in Matlab (also Levenberg-Marquardt) and the routine eo4fc (an augmented Gauss-Newton method) from the NAG[9] toolbox for Matlab. We also assessed the results of fitting a linearised SPGR equation and performed the subsequent parameter estimation using the lsqcurvefit routine. **For the extended Kety model fitting optimisation**, we compared three commonly-used implementations of the Nelder-Mead simplex algorithm: a C implementation based on Numerical Recipes; the Matlab fminsearch routine; and the routine e04cc from the NAG toolbox for Matlab. We also assessed the lsqcurvefit Matlab routine. The maximum number of iterations, tolerance values and initial parameter values were matched for all optimisations. A dual start method (the optimisation is run twice with the output of the first run as input to the second but with one parameter ($v_e$) reset to its initial value) was used to reduce the likelihood of settling at local minima[10]. All the simplex implementations were constrained to prevent negative parameter estimates. Only the Numerical Recipes in C simplex implementation allowed the initial length of the simplex vertices to be set.

Results $T_1$ values estimated using all three NLLS optimisation algorithms gave identical results. Linearising the SPGR equation reduced the precision of the estimated $T_1$ values (see Fig. 1) with an interquartile range (IQR) as a percentage of the ground truth value of 17% for linearisation compared with 13% for the NLLS algorithms at a ground truth $T_1$ of 1000 ms. The loss in precision when using linearisation increased with ground truth $T_1$. The accuracy decreased slightly for linearisation with an error in the median value of 0.9% for linearisation compared with 0.1% for the NLLS algorithms at a ground truth $T_1$ of 1000 ms. Estimated $K^{trans}$ values for the model fitting optimisation algorithms are shown in Fig. 2 along with the effect of using $T_1$ estimated by linearisation. The accuracy and precision for $K^{trans}$ are comparable for all techniques as demonstrated by the median values and IQR. The error in the median values remains below 2% for all algorithms and the percentage IQR is between 10–14% for a ground truth $T_1$ value of 1000 ms. Similar results are seen for ground truth $T_1$ values of 600 and 1400 ms. Results for intermediate ground truth values not shown in Figures 1 and 2 follow the displayed trends. The results for $v_e$ (not shown), displayed similar trends except a reduction in precision and accuracy was seen for the NAG routine e04cc. For $v_p$ (results not shown) the Numerical Recipes simplex had the lowest accuracy with a mean percentage error in the median across all values of $v_p$ of 6.0% compared to 1.65% for fminsearch which had the best accuracy. All algorithms had similar precision for $v_p$.

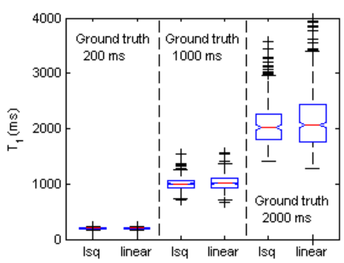


Fig 1. $T_1$ values estimated using lsqcurvefit and linearisation. Red lines are medians, the boxes are the IQR, and the whiskers are the most extreme values within 1.5 times the IQR.

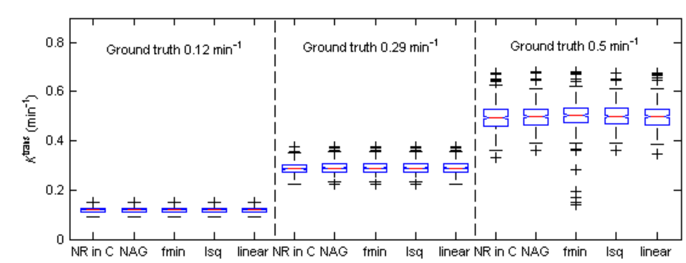


Fig 2. $K^{trans}$ values estimated using 3 different implementations of the simplex algorithm and lsqcurvefit. The effect of using linearisation for estimating $T_1$ (linear) is also shown (lsqcurvefit was used for model fitting). A ground truth $T_1$ value of 1000 ms was used for all voxels. For each ground truth value of $K^{trans}$ there are multiple different combinations of $v_e$ and $v_p$.

Conclusion The accuracy and precision of $T_1$ estimation from VFA images was unaffected by the choice of least squares optimisation routine. However, linearisation reduced the precision and accuracy particularly at higher $T_1$ values, but this did not influence the accuracy and precision of the subsequent model parameter estimation. The accuracy and precision of the estimated $K^{trans}$ values were not affected by the implementation used to fit the extended Kety model to the concentration time course data. Our results are in contrast to those of Buckley et al[2], who found that the simplex method gave superior results to a NLLS approach when fitting the Tofts model (a simplified form of the extended Kety model).

References [1] O'Connor JPB et al. Br J Cancer 96:189(2007).[2] Buckley DL et al. Magn Reson Med 3:646(1994). [3] Tofts P. J Magn Reson Img 7:101(1997). [4] Deoni SC et al. Magn Reson Med 49:515(2003). [5]Fram E et al. Magn Reson Img 5:201(1987). [6] Banerji A et al. Proc16th ISMRM. 2008. [7] Parker G et al. Magn Reson Med 56:993(2006). [8] Press W et al. 'Numerical Recipes in C'. ed (1992). CUP. [9] Numerical Algorithms Group. www.nag.co.uk. (Accessed Nov 2010). [10] Ahearn TS et al. Phys Med Biol 50:N85(2005).