

Improving the accuracy and precision of DCE-MRI tracer kinetic modelling by imposing inter-variable constraints

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INTRODUCTION Tracer kinetic modelling of dynamic contrast-enhanced (DCE-) MRI time series has proven to be a valuable tool for studying the microvascular characteristics of tumours and organs¹. Inherent to this task is the estimation of model parameters via nonlinear regression: this is typically approached as an optimisation problem in which the model's parameters are varied such to minimise some measure of dissimilarity—e.g., the sum of squared differences (SSD)—between the observed contrast agent concentrations and those predicted by the model. Because the parameters of tracer kinetic models have physiological interpretations, there exist certain constraints that they must satisfy. While some of these constraints can easily be imposed using widely available fitting routines, others cannot. In this work we consider the constraints that exist between the parameters of the extended Tofts model², explore how often those constraints are violated in an example clinical data set, propose a simple way in which those constraints can be imposed and, using simulations, compare the proposed solution to a conventional approach. We show that the proposed approach provides constrained parameter estimates that are more accurate and precise.

Eqn. 1 shows the extended Tofts model, which is parameterised in terms of the bulk transfer coefficient K^{trans} (min^{-1}), the relative extravascular extracellular volume v_e , and the relative plasma volume v_p ; $C_p(t)$ is the concentration of contrast agent in the arterial blood plasma at time t (in min), and $C_t(t)$ is the measured contrast agent concentration at time t . The model is subject to the following constraints: $K^{\text{trans}} \geq 0$, and $0 \leq v_e + v_p \leq 1$ (the total relative volume of a voxel is unity, and the model does not parameterise the intracellular space, v_i). Fig. 1 shows the latter constraint: parameter values outside the shaded area are non-physiological. Most fitting software, e.g., Matlab's `lsqcurvefit`, allows constraints like $0 \leq v_e \leq 1$ and $0 \leq v_p \leq 1$ to be enforced, but not inter-variable constraints.

$$C_t(t) = v_p C_p(t) + K^{\text{trans}} \int_0^t C_p(t') e^{-\frac{K^{\text{trans}}}{v_e} t'} dt' \quad (1)$$

$$\Theta^* = \arg \min_{\Theta'} \sum_{i=1}^N \left(C_t(t_i) - \left(C_t(t_i; \Theta') + \begin{cases} 0 & \text{if } v_e + v_p \leq 1 \\ \frac{c_1}{1+c_2 e^{-c_3(v_e+v_p)}} & \text{otherwise} \end{cases} \right)^2 \right) \quad (2)$$

METHOD Parameters estimated (without imposing constraints) for 42 tumours (~38,000 voxels) were analysed to determine the frequency with which non-physiological estimates occur. To allow inter-variable constraints to be imposed during model fitting, we modified the conventional SSD loss function to include a term to penalise non-physiological parameter combinations (see Eqn. 2). Here, the parameters $\Theta^* = (K^{\text{trans}}, v_e, v_p)$ are estimated by the Θ' that minimises the SSD between the observed contrast agent concentrations at the i^{th} time point (of N), $C_t(t_i)$, and the sum of the model's prediction of those contrast agent concentrations, $C_t(t_i; \Theta')$, and the penalty term. The penalty term is a piecewise function that is zero for physiological parameters, and a sigmoid when they are not. The sigmoid has three parameters, c_1 , c_2 , & c_3 that control its shape; we set these to 500, 7,600, & 6.4, respectively, but have not systematically identified optimal values. The sigmoid was chosen so that the loss function changes smoothly at the boundary of the physiological and non-physiological spaces. (The conventional SSD loss function is identical to Eqn. 2 except it lacks the piecewise term.) We evaluated the modified loss function's ability to enforce the constraint at the boundary by: choosing known parameters ($K^{\text{trans}}=0.9 \text{ min}^{-1}$, $v_e=1/2$, $v_p=1/2$); generating 1000 corresponding contrast agent concentration time series (using a population averaged³ $C_p(t)$); adding noise to the resulting time series; and then estimating the model parameters using the conventional SSD loss function and the method described above. The accuracy and precision of the two methods were compared by computing 95% confidence intervals on the mean and variance of the absolute difference between the estimated and known values of v_e and v_p . Finally, the mean time required to estimate parameters for a single time series was calculated for each method. All work was performed using Mathematica v7 (Wolfram Research Inc., Champaign, IL).

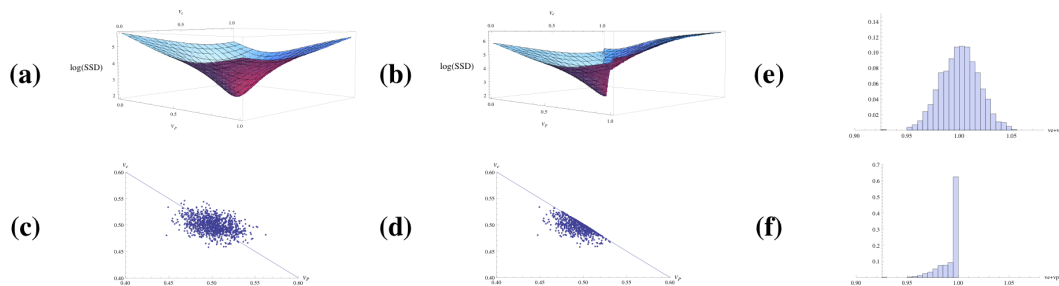


Fig. 2 The topology of the conventional (a) and penalised (b) SSD loss function: see text. Estimated values of v_e and v_p for the conventional (c) and penalised (d) SSD loss functions. Histograms of $v_e + v_p$ for the conventional (e) and penalised (f) loss functions.

RESULTS Of the ~38,000 voxels studied, ~550 had non-physiological parameter estimates. Figs. 2(a) & 2(b) show the topologies of the conventional SSD and penalised loss functions, respectively, in the absence of noise: optimal values of v_e and v_p correspond to the functions' minima; Fig. 2(b) illustrates the smooth penalisation of non-physiological estimates. Figs. 2(c) & 2(d) show the results of the evaluation. Fig. 2(c) shows unconstrained fitting results: the variation around the true parameter values is the result of the noise added to the simulated contrast agent concentration time series. Fig. 2(d) demonstrates that the penalty term eliminates non-physiological estimates. Figs. 2(e) & 2(f) show histograms of the quantity $v_e + v_p$ for the two methods, demonstrating the elimination of non-physiological estimates and the improved accuracy and precision of the constrained fitting method. The table below presents the 95% confidence intervals on the accuracy and precision for the two methods for the parameter v_e : the constrained fitting method gave parameter estimates that were both more accurate and precise; results for v_p were similar. The mean time required to estimate parameters for one time series was 4.6 s for the unconstrained method and 8.5 s for the constrained method.

	Accuracy (95% Confidence Intervals)	Precision (95% Confidence Intervals)
Unconstrained	$(1.10 \times 10^{-2}, 1.20 \times 10^{-2})$	$(6.73 \times 10^{-5}, 8.02 \times 10^{-5})$
Constrained	$(0.82 \times 10^{-2}, 0.92 \times 10^{-2})$	$(5.19 \times 10^{-5}, 6.19 \times 10^{-5})$

CONCLUSION We have proposed a penalised SSD loss function that imposes inter-variable constraints on the extended Tofts model. We have shown using simulations that, at the boundary of the physiological space, the approach can successfully eliminate non-physiological estimates of v_e and v_p , and that those estimates are more accurate and precise than those delivered by the conventional SSD loss function.

REFERENCES 1 Tofts, J Magn Reson Imag 1999, 10:223–32. 2 Tofts, J Mag Reson Imag 1997, 7:91–101. 3 Parker, Mag Reson Med 2006, 56:993–1000.