Bayesian Estimation Improves Plasma Volume Repeatability with Compartmental Modelling of DCE-MRI Data

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Introduction   The Extended Kety model (also known as the Modified Tofts model [1]) is a compartmental model that is widely used for modelling DCE-MRI data. It is well known that estimates of the plasma volume fraction parameter (v_p) are subject to large errors compared with other parameters that can be obtained with this model, which limits the utility of such estimates in trials and clinical practice. In this abstract we present a Bayesian estimation methodology that reduces test-retest repeatability of v_p estimates by around 50% in comparison to standard least-squares estimates. This results in a more reliable measure that has similar repeatability to DC-CT based measures, and therefore has the potential to detect smaller changes as a result of therapeutic interventions. In practice errors on v_p have two principle causes: 1) estimates of v_p are essentially determined from data acquired between 0 and 10-15 seconds after the start of enhancement, and in the worst case there may be no data points acquired in this period, depending on the temporal resolution of the acquisition; 2) v_p estimates therefore tend to be small relative to their statistical uncertainty, and as they are restricted to positive values, estimates of $v_p = 0$ are common, even with data showing clear enhancement. Such estimates are logically incompatible with the compartmental model assumptions since $v_p = 0$ implies that contrast is not delivered to the imaged tissue. Cause 1) can be mitigated by acquiring data as quickly as possible, though depending on the application, other constraints on the acquisition protocol may still restrict the sampling rate, resulting in worst-case data. Cause 2) typically occurs when a least-squares curve-fitting algorithm is used that minimises the sum of squared errors between the data and the model curve, subject to the constraint $v_p \geq 0$. Incompatible cases with $v_p = 0$ could be fixed by modifying the constraint to $v_p \geq \varepsilon$ for a suitable ε, but an objective method for selecting ε would be needed. Here we present a Bayesian estimation methodology that provides a minimum mean-squared error (MMSE) estimate of v_p. While this estimate is not obtained by explicitly deriving a lower bounding ε, the natural properties of the MMSE estimator closely mimic those of a lower bound derived from the apparent noise level for each voxel. The implicit lower bound is such that differences between uptake curves with $v_p = x$ and $v_p = x + \varepsilon$ are within the limits of the data noise.

Methods   The Extended Kety model has the form $C_t(t) = v_p C_p(t) + v_e C_e(t)$, where $C_t(t)$ is the tissue concentration-time curve (CTC), $C_p(t)$ is the plasma CTC, and $C_e(t) = C_p(t) \otimes k_{ep} \exp(-k_{ep}t)$ is the extra-vascular extra-cellular CTC. The data model is $y_n = C_t(t_n - \tau_0) + E_n$ for n = 1, 2, … N, where E_n are independent Gaussian noise terms and the unknown parameters are v_p, v_e, k_{ep} and τ_0. The data model is used to derive a (complete) likelihood function for the probability density function of the data conditioned on values for the unknown parameters and unknown noise variance, $p(y_{1:N} \mid v_p, v_e, k_{ep}, \tau_0, \sigma^2)$. Since the error model is Gaussian, the maximum likelihood estimate (MLE) is the same as the least-squares estimate. For the Bayesian estimator a prior distribution is used to encode the lower-bound on v_p, that is $p(v_p) = 1$ for $0 \leq v_p \leq 1$, $p(v_p) = 0$ otherwise. (A more detailed prior distribution would be derived from the combined constraint $v_p + v_e \leq 1$, but this is unnecessary in practice as this upper limit is rarely reached.) With this prior distribution a
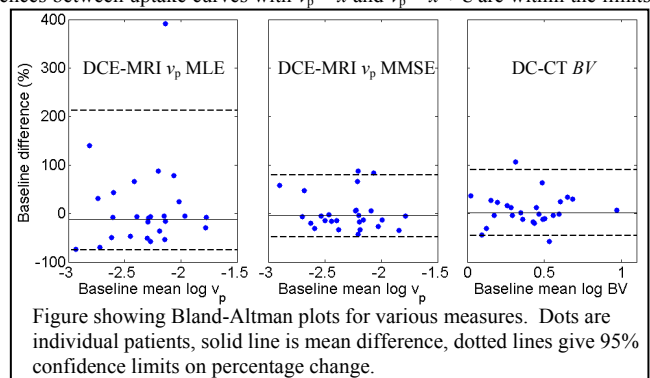

Figure showing Bland-Altman plots for various measures. Dots are individual patients, solid line is mean difference, dotted lines give 95% confidence limits on percentage change.

marginalised likelihood is derived using $p(y_{1:N} \mid v_e, k_{ep}, \tau_0) = \iint p(y_{1:N} \mid v_p, v_e, k_{ep}, \tau_0, \sigma^2) \, p(v_p) \, p(\sigma^2) \, dv_p \, d\sigma^2$, where the prior on the noise variance is a conjugate inverse-gamma distribution. An explicit form for this double integral is derived in terms of the incomplete beta function, which is computed using standard library functions. Estimates, denoted $\hat{v}_e, \hat{k}_{ep}$ and $\hat{\tau}_0$ are obtained with standard function optimisation methods using the marginalised likelihood $p(y_{1:N} \mid v_e, k_{ep}, \tau_0)$ as the objective function. (This is equivalent to a Bayesian *a posteriori* estimate with uniform prior distributions for v_e, k_{ep} and τ_0.) Minimum mean-squared error (MMSE) estimates of v_p are derived using $\hat{v}_p = p(y_{1:N} \mid \hat{v}_e, \hat{k}_{ep}, \hat{\tau}_0)^{-1} \times \iint v_p \, p(y_{1:N} \mid v_p, \hat{v}_e, \hat{k}_{ep}, \hat{\tau}_0) \, p(v_p) \, p(\sigma^2) \, dv_p \, d\sigma^2$ which can also be computed using standard library functions. Due to the integral forms of the marginalised likelihood and the MMSE v_p estimate, estimates derived from the marginalised likelihood are affected by *all* probable v_p values, whereas estimates derived from the complete likelihood are only affected by v_p at the MLE. In cases where the MLE of $v_p = 0$, there will nevertheless be a range of $v_p > 0$ that have non-negligible likelihood values, and it is this range that relates to the implicit threshold ε discussed in the introduction. Another key consequence of this is that $\hat{v}_p$ is strictly greater than zero.

DCE-MRI data were acquired with the following set-up. 0.2mg/kg Magnevist followed by 20mls saline both at 3mls/sec; 1.5T Siemens Avanto; 3D FFE sequence with TR/TE = 3.05/0.89 ms, FA = 16°, 14×5mm slices NSA = 1, IPAT = 2, FOV = 308x320mm, 208x256 matrix. Dynamic scans were preceded by a calibration scan with the same parameters except FA = 3°, NSA = 8 to enable contrast quantification. 26 patients were imaged twice at baseline, 7 days apart. 17/26 patients were imaged coronally using a sequential breath-hold technique optimised for liver lesions; two image volumes were acquired during each 6 sec breath-hold, followed by a 6 sec breathing gap, 40 volumes were acquired over a 4 minute period. 9/26 patients were imaged axially with a free breathing technique; 80 image volumes acquired continuously at 3.3 sec/vol for 4.3 min. MLE and MMSE estimates of v_p were obtained voxel-wise from tumour ROIs drawn on four central slices, from which median values were used to summarise each volume. The plasma CTC used in the fitting was based on a population-averaged curve [2]. DC-CT data were acquired from the same patients on the same days with the following set-up. GE Lightspeed; Omnipaque 300 0.5ml/kg followed by 20 mls saline both at 3-5mls/sec; 5 second delay followed by breath hold cine covering 4x5mm, at 0.5 sec/volume in centre of lesion of interest over 55 sec at 120 kV, 60 mA; following this, twelve breath acquisitions at 10 sec intervals. Blood volume (BV) estimates were obtained from ROIs drawn on all 4 slices within the GE Perfusion 3 Software which uses an algorithm based on the St Lawrence and Lee model and reports the mean value from the tumour volume.

Results   Bland-Altman plots were generated for $\log(v_p)$ for the DCE-MRI data and $\log(BV)$ for the DC-CT data, from which limits of repeatability expressed as percentage changes were derived, as shown in the figure. The 95% confidence intervals were: MLE = -75.4 to 212%, MMSE = -48.5 to 79.2% and DC-CT BV -45.5 to 90.5%. For the DCE-MRI, separate statistics can be calculated for the breath-hold and free-breathing cases and these are: Free-breathing, MLE = -75.1 to 172%, MMSE = -52.3 to 71.1%; Breath-hold, MLE = -87.6 to 675%, MMSE = -60.9 to 146%.

Discussion and Conclusions   The repeatability limits of the MMSE are around 50% smaller than the MLE, and thus this estimator will be sensitive to treatment effects that are proportionately smaller. The MMSE repeatability is very similar to that obtained for BV, which is the nearest equivalent DC-CT parameter. Comparison of the MR estimates with the CT estimates is not direct since they are obtained using very different acquisition and post-processing methods, but we include these data as they give some indication of the relative performance of MR and CT for measuring vascular volumes. Further work is needed to assess the sensitivity of these measures to treatment effects. The repeatability of free-breathing DCE-MRI estimates are better than the breath-hold estimates, which is expected due to the higher sampling rate, although the statistics are strongly influenced by a small number of possibly outlying cases.

[1] Tofts PS, *J. Magn. Reson. Imaging*. 1997; **7**(1):91-101.   [2] Parker GJ, et. al., *Magn Reson Med*. 2006; **56**(5):993-1000.