Tina Memo No. 2018-001
Internal, shortened version in preparation for Bioinformatics.

Maximising Tissue Characterisation from DCE-MRI using Haematocrit Corrections with the Tofts Model.

Scott V. Notley, Neil A. Thacker.

Last updated
8 / 5 / 2018

Imaging Science and Biomedical Engineering Division,
Medical School, University of Manchester,
Stopford Building, Oxford Road,
Manchester, M13 9PT.

Maximising Tissue Characterisation from DCE-MRI using Haematocrit Corrections with the Tofts Model

Scott V. Notley, Neil A. Thacker

To be distributed to G. Parker, R. Little and A. Jackson for comments

Introduction

DCE-MRI variables describing the vascular plasma volume (V_p), extra-vascular-extra-cellular volume (V_e) and the transfer constant (K^{trans}) may be derived from T_1-weighted images collected after the administration of a Gadolinium (Gd) based contrast agent using the Extended Tofts Model (ETM). The haematocrit for each subject is a measure of the fractional volume of blood constituent and may be measured from whole blood samples independently from the MRI scanning protocol. Model parameters are estimated using a conventional fitting process with the extended Tofts model. For these parameters to be of value they must be accurate and thereby capable of measuring changes between different voxels, regions (e.g. tumours) or subjects. Any uncontrolled variation induced in data is likely to reduce the accuracy of parameters and so its value for clinical or scientific investigations.

For pharmocokinetic modelling, as any measured signal change is driven by contrast concentration in plasma (solid blood constituents do not contribute), the haematocrit constitutes such an uncontrolled variation and measurements of pharmocokinetic parameters are potentially destabilised by its variations. Thus an independent characterisation of tumour microvascularity based on these DCE-MRI variables needs to account for this appropriately. The haematocrit can be measured from whole blood, and the theoretical models can be used to predict the correlated change, but further to this, the characterisation of tumour tissue may need to account for the Fahraeus effect. This predicts that the *local* haematocrit found in tissue is expected to be lower than that found (and therefore measured) in large blood vessels. The changes in haematocrit between tissue, and the differences between tumours and large blood vessels, have been measured using PET (Brooks, e.t.al. 1984, Lammertsma, et.al. 1986). Whilst we we cannot measure this variation in-vivo in MR, we can attempt to predict an average per-subject correction based upon a measurement from blood. In order to determine the correct approach we can appeal to our earlier argument, and seek the specific form of haematocrit correction which maximises parameter sensitivity. This can also be seen as using a correction to maximally de-correlate our parameters and haematocrit measurement, so standardising these parameters (e.g. to the value which would be measured for a nominal haematocrit) as a pure description of tissue properties.

1 Methods

Volume Independent Variance Model

In order to correct parameters derived for tumour regions for haematocrit variations between subjects an understanding of how our pharmocokinetic parameters are estimated is essential. The pharmocokinetic model is a formula for the contrast concentration expected in an MR voxel as a function of time $C(t)$. The extended Tofts model can be written in terms of a first pass peak (proportional to the arterial input $C_p(t)$) and a forward and backward leakage into the extra vascular space, described by rate parameters k_1 and k_2.

$$C(t) \;=\; V_p C_p(t) \;+\; k_1 \int_0^t C_p(\tau) exp(-k_2(t-\tau)/V_e)\; d\tau \qquad (1)$$

The convolution integral in the second term generates a scaling factor for C_p which is proportional to V_e/k_2. The parameters which control the overall normalisation of this curve are therefore the plasma volume V_p and extra-vascular volume V_e. In the extended Tofts model $k_1 = k_2 \;=\; k_{trans}$.

In practice it is more convenient to scale the arterial input function used to fit data to work with the whole blood volume V_b and the whole blood contrast concentration $C_b(t)$. This not only redefines the volume parameter in the first term (so that a 100% voxel of blood has $V_b \;=\; 1$), but also introduces a dependency on the haematocrit into

the second term.

$$C(t) \;=\; V_b(1-H)\frac{C_b(t)}{1-H} \;+\; k_1\int_0^t \frac{C_b(\tau)}{1-H} exp(-k_2(t-\tau)/V_e)\; d\tau \qquad (2)$$

Notice that the V_e term does not need to be modified if we can assume that there is no haematocrit in the extra-vascular space. However, if fitting a function of the form

$$C(t) \;=\; V_1 C_b(t) \;+\; k\int_0^t C_b(\tau) exp(-k(t-\tau)/V_2)\; d\tau \qquad (3)$$

In comparison to the original model of equation (1) we have

$$V_p \;=\; V_1(1-H)$$

$$k^{trans} \;=\; k(1-H)$$

and

$$V_e \;=\; V_2(1-H)$$

In the above expressions we have assumed that all parameters are ground truth and the haematocrit is taken from whole blood in each individual. However, if the assumed haematocrit is an inaccurate population average(H') then we will have incorrect values for our model parameters V_p' , k_{trans}' and V_e', which will need to be corrected when the correct H is subsequently determined.

Correcting Parameters with Measured Whole Blood Haematocrit

If we ignore for now other complicating factors, such as the Fahraeus effect, this would suggest that the correct V_p must be obtained by undoing the effect of the assumed haematocrit and replacing it with the correct one (H)

$$V_p \;=\; V_p'(1-H)/(1-H') \qquad (4)$$

Correcting the other parameters is done the same way

$$k^{trans} \;=\; k^{trans'}(1-H)/(1-H') \qquad (5)$$

$$V_e \;=\; V_e'(1-H)/(1-H') \qquad (6)$$

As the real biological system is likely to be more complicated than assumed here, we wish to evaluate the validity of this approach. We can do this by observing that a valid correction for haematocrit variation should improve the repeatability of measurements and so the sensitivity for detection of change.

Evaluating Whole Blood Haematocrit Correction

We present a method of empirically deriving general (tissue specific) haematocrit corrections from whole blood haematocrit measurements, based on the minimisation of mean of χ^2 distributions calculated for between subject tumour differences. In order to do this, and also test the standard correction process, the modification to the plasma volume fraction is generalised to have the form $\gamma = (1-H)^\theta$. As this allows us to apply a one parameter estimation of local tissue plasma fraction which has the correct limiting case values are preserved. The mean of the χ^2, for tumour differences, for each variable may be minimised with respect to the free parameter θ which is equivalent to minimising the variance of the variable with respect to the haematocrit. If the previous corrections were the best way to obtain stable parameters, then θ would have a value of 1 for all parameters in our experiment.

It is shown in Tina-Memo 2016-016 that the variables have parameter dependent noise distributions. As part of the analysis each DCE-MRI variable was transformed, with a function $f(\cdot)$, to stabilise the variance so that the measurement error was independent of the variable mean (Box and Cox, 1964). For each variable, a transformation function of the form $f(x) = x^\phi$, is estimated (with respect to ϕ) that stabilises the variance. The transformations estimated and used in this work are shown in Table 4 in the results section. The purpose of these transformations is to better control the effects of noise on measurements, so that parameter estimates are more accurate. As they can later be reversed (to regenerate the original variables) they do not impede the final interpretation of analysis results.

We assume that the total variance of each DCE-MRI variable seen in tumours is a summation of variations due to biology, measurement noise and haematocrit variations. i.e. $\sigma_V^2 = \sigma_{biology}^2 + \sigma_{noise}^2 + \sigma_H^2$. The χ^2 distribution for the differences between any two tumours, i and j, for variable V may then be defined as:

$$\chi_{i,j}^2(V) = \frac{(f(\gamma_i V_i/(1-H')) - f(\gamma_j V_j/(1-H')))^2}{var(f(\gamma_i V_i/(1-H')) - f(\gamma_j V_j/(1-H')))}$$

where $\sigma_{f(n)}$ is the standard deviation of differences between repeat measurements for the stabilised variable V and $\gamma_i/(1-H')$ is the subject dependant haematocrit correction factor.

As f is a simple power function, the $(1-H')$ terms cancel in the ratio we can simplify this expression to

$$\frac{(f(\gamma_i V_i) - f(\gamma_j V_j))^2}{var(f(\gamma_i V_i) - f(\gamma_j V_j))}$$

Assuming that noise on the measured V_j and V_j are independent we have

$$\frac{(f(\gamma_i V_i) - f(\gamma_j V_j))^2}{var(f(\gamma_i V_i)) + var(f(\gamma_j V_j))}$$

which, due to the use of the homoscedastic transform, can be further simplified to

$$\chi_{i,j}^2(V) \;=\; \frac{2(f(\gamma_i V_i) - f(\gamma_j V_j))^2}{(f(\gamma_i)\sigma_{f(n)})^2 + (f(\gamma_j)\sigma_{f(n)})^2} \qquad (7)$$

Tumour Volume Dependent Haematocrit Correction

The above model makes the rather unrealistic assumption that the contributions to the variance in pharmocokinetic parameters from all sources are fixed factors. However, as these parameter estimates are obtained as the median from a distribution, we know there must be an overall scaling effect on variance which comes from the sample size (i.e. enhancing tumour volume). We would expect that our ability to estimate the best haematocrit correction is impeded by not taking appropriate account of this, as poorly measured parameters have proportionately more significance during fitting than they should. We can attempt to reduce the significance of volume change by selecting only large tumours, but this would be statistically inefficient.

In this second model it would be assumed that the total variance of each DCE-MRI has an additional scaling, due to the enhancing tumour volume N. i.e. $\sigma_V^2 = \frac{1}{N}(\sigma_{biology}^2 + \sigma_{noise}^2 + \sigma_H^2)$. This new model changes the relative weightings of the data both during the estimation of homoscedastic transforms and also in the χ^2 distribution for the differences between any two tumours, which may then be defined as:

$$\chi_{i,j}^2 = \frac{(f(\gamma_i V_i) - f(\gamma_j V_j))^2}{f(\gamma_i)^2\sigma_{f(V_i)}^2 + f(\gamma_j)^2\sigma_{f(V_j)}^2}$$

where:

$$\sigma_{f(v_i)}^2 = \left(\frac{1}{N_i} + \frac{1}{k}\right)\sigma_{f(n')}^2 = \omega_i \cdot \sigma_{f(n')}^2 \qquad (8)$$

N_i is the tumour volume, k is an effective maximum tumour size above which the statistical errors have been reduced to a level where systematic errors are dominant. $\sigma_{f(n')}^2$ is the *per* voxel transformed variable variance estimated as:

$$\sigma_{f(n')}^2 = \frac{1}{2}\frac{1}{I}\sum_i \frac{(f(v_i) - f(v_i'))^2}{\omega_i}$$

v_i' is the repeat measurement. By substitution we obtain:

$$\chi_{i,j}^2 = \frac{(f(\gamma_i V_i) - f(\gamma_j V_j))^2}{\omega_i f(\gamma_i)^2 + \omega_j f(\gamma_j)^2} \cdot \frac{1}{\sigma_{f(n')}^2} \qquad (9)$$

Data

The patients included in this study were undergoing imaging with DCE-MRI as a part of a clinical trial and had given written informed consent to participate in the study. A data-set composed of three DCE-MRI variables (V_p, V_e and K^{trans}) measured from 77 liver metastases from 30 subjects. All patients had undergone 2 baseline DCE-MRI scans, median 4 days (range 2-7 days) prior to treatment. Analysis was performed using in-house software (Manchester Dynamic Modelling) (Jackson *et al*, 2005)and the extended Tofts and Kermode pharmacokinetic model (Tofts, 1997).

Haematocrit measurements were made prior to the first baseline scan. Whole blood was collected in standard EDTA tubes immediately prior to each DCE-MRI scan. Samples were processed using an automated analyser (Advia 2120, Siemens, Germany) and the Hct was calculated as $RCC \times MCV$ (RCC:red cell count per litre; MCV: mean cell volume in femto litres). The demographics of the haematocrit values are shown in table 1.

Mean	Standard Deviation	Min	Max
0.37	0.04	0.27	0.48

Table 1. Haematocrit demographics for subject group.

Correction Estimation

Prior to analysis the tumours for each subject were sorted by tumour size (in descending order). To investigate possible bias due to combinatorial effects subsets of the full data-set were defined using a tumour threshold. Sub sets were defined using a maximum of 2, 3, 4 and 5 tumours per subject with largest tumours preferentially chosen.

For each variable a value for θ was found that minimised the mean of the χ^2 distribution for differences between tumours. A search over θ was made in the range -3 to 4.5 in steps of 0.005. Since there is only a single haematocrit measurement for each subject this method may only be applied across subjects.

Errors on the value of θ, that minimise the χ^2 means, were estimated from the χ^2 curves after normalisation to the number of data points (pairs of tumours). The error was measured as half the width of the χ^2 function for a change of one from the minimum.

Monté-Carlo Evaluation

The above estimation methods were evaluated using Monté-Carlo data sets with a known local haematocrit correction factor, θ. The number of subjects, number of tumours for each subject, enhancing tumour volumes and whole blood haematocrit values from the measured data was used in the generation of the surrogate data.

For each subject, a biological ground truth, in terms of the pharmacokinetic parameters, was defined for each tumour. Biological variation was modelled by defining a clonal centre, for each subject, and was drawn from a uniform distribution that models inter-subject variability. Intra-subject variability was modelled by distributing individual tumours, for each subject, normally around the subject specific clonal centre.

A repeated measures data-set was then generated by adding measurement noise the biological ground truth data generated in the previous step. The variance the simulated measurement noise was tumour specific, calculated using equation 8. The effective maximum tumour size was defined as 0.3 of the largest enhancing tumour volume in the measured data-set.

A local multiplicative haematocrit variation was modelled, for the i-th subject, as $(\frac{1-\overline{Hct}}{1-Hct_i})^{\theta}$.

For a given value of θ the inter-subject variability was adjusted such that overall distribution for a parameter matched that found in the real data. Intra-subject variability was always defined as half the inter-subject variability in accordance with signal-to-noise estimates previously made on this data set (Notley *et al*, 2016).

One hundred surrogate data-sets were generated for each value of θ: 0, 1, 1.5 and 2.

Results

Monté-Carlo Data

Tables 2 and 3 show the results found from the evaluation using Monté-Carlo data-sets for k^{trans} using 4 values of θ with tumour thresholds at 2 and 5 respectively. Results are shown for the volume dependent analysis and the unweighted analysis.

For a tumour thresholds of 2 and 5 (tables 2 and 3 respectively) the results from both forms of analysis are consistent with each other and on average giving a correct estimation of θ. Since the data-sets are restricted to the two largest tumours from each subject, it may be expected that both forms of analysis give similar results as the effect of including tumour volumes in the analysis is reduced or redundant.

The spread of values (σ_θ) from this testing are estimates of the actual parameter spread and match those found on the real data from the width of the χ^2 (tables 5 and 6 below).

	Volume Dependent		Unweighted	
Ground Truth	μ_θ	σ_θ	μ_θ	σ_θ
0.0	-0.02 ± 0.005	.28	0.02 ± 0.005	.27
1.0	1.04 ± 0.004	.22	1.04 ± 0.004	.23
1.5	1.49 ± 0.003	.17	1.50 ± 0.003	.18
2.0	2.02 ± 0.002	.13	2.03 ± 0.002	.13

Table 2. Results of Monté-Carlo testing for k^{trans} (tumour threshold 2).

	Volume Dependent		Unweighted	
Ground Truth	μ_θ	σ_θ	μ_θ	σ_θ
0.0	-0.02 ± 0.004	0.29	0.01 ± 0.003	0.28
1.0	1.04 ± 0.002	0.22	1.05 ± 0.002	0.22
1.5	1.51 ± 0.002	0.17	1.52 ± 0.002	0.17
2.0	2.02 ± 0.002	0.13	2.02 ± 0.002	0.14

Table 3. Results of Monté-Carlo testing for K^{trans} (tumour threshold 5).

Real Data

Figure 1a shows the minimum χ^2's as a function of θ for each variable using the tumour volume dependent analysis for a data subset with a tumour threshold of 2. The minimums found for K^{trans}, V_e, and V_p were 1.48 ± 0.20,1.91 ± 0.10 and -0.11 ± 0.22 (errors found via width of χ^2 function). For the cases of K^{trans} and V_e the correction factors have reduced the correlation with haematocrit making the measurement more biologically relevant.

Tables 5 and 6 show the results found for subsets with tumour threshold ranging from 2 to 5 for the unweighted and volume dependent analysis respectively. It may be seen, for both forms of analysis, that as the tumour threshold is increased there is a trend towards a final value. A number of reasons may be the cause of this trend one of which is that there is a bias towards a subject or subjects with 5 tumours due to combinatorial effects.

Method	k^{trans}	v_e	v_p
Unweighted	-0.10	0.45	0.33
Weighted	0.24	0.74	0.37

Table 4. Variance stabilisation transform parameters for unweighted and weighted analysis.

Tumour Thresh	k^{trans}	v_e	Average k^{trans} and v_e	v_p
2	1.51 ± 0.18	1.82 ± 0.09	1.75 ± 0.20	-0.46 ± 0.21
3	1.51 ± 0.15	1.50 ± 0.07	1.50 ± 0.16	-1.08 ± 0.18
4	1.40 ± 0.15	1.43 ± 0.08	1.42 ± 0.17	-1.52 ± 0.18
5	1.22 ± 0.14	1.44 ± 0.07	1.40 ± 0.18	-1.73 ± 0.17

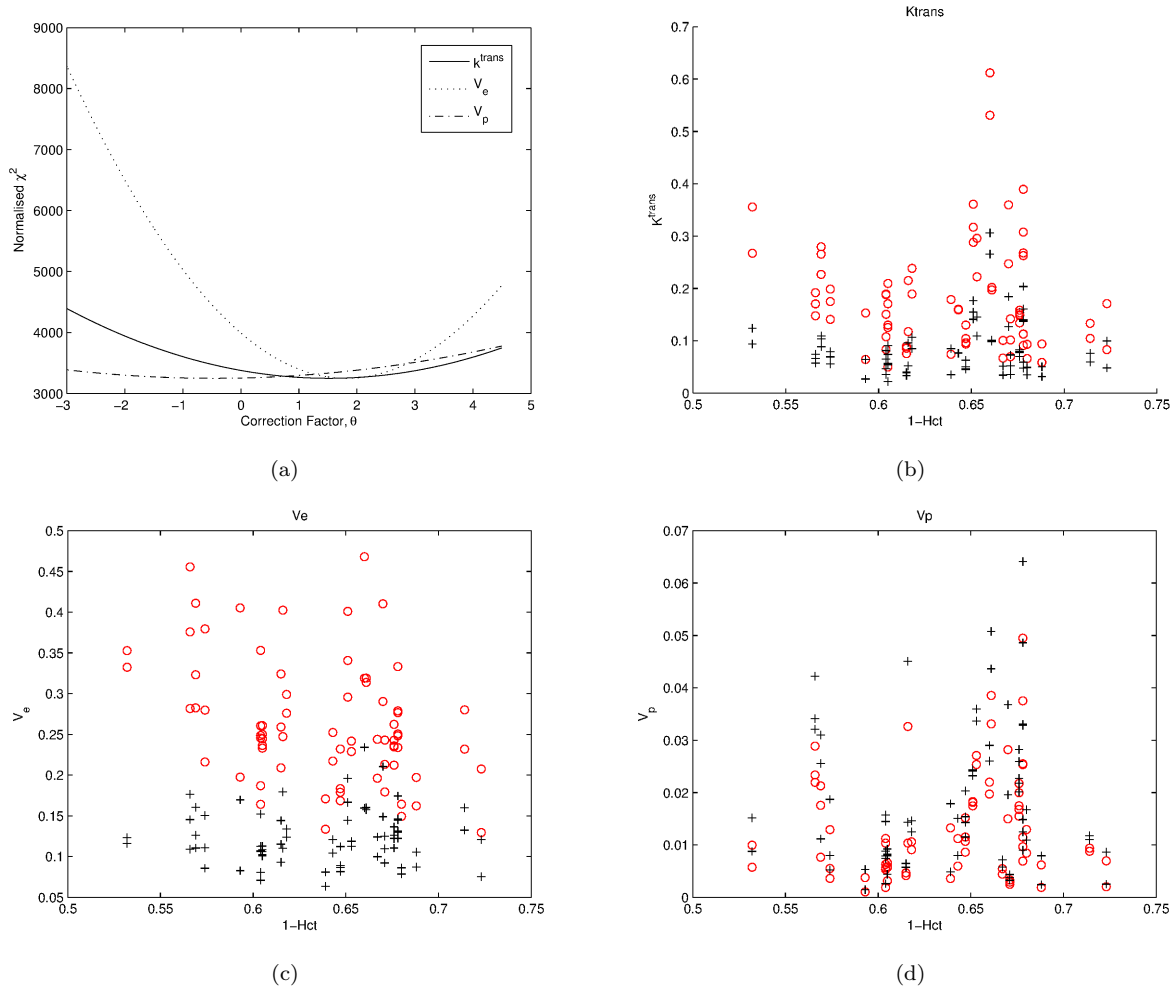

Figure 1: a) Minimum of χ^2, (b),(c) and (d) De-correlation of variables from haematocrit (circle - raw, crosses - corrected)

Table 5. Unweighted analysis.

Tumour Thresh	K^{trans}	V_e	Average K^{trans} and V_e	V_p
2	1.48 ± 0.20	1.91 ± 0.10	1.82 ± 0.22	-0.11 ± 0.22
3	1.29 ± 0.17	1.76 ± 0.08	1.66 ± 0.19	-0.85 ± 0.20
4	1.23 ± 0.15	1.65 ± 0.07	1.58 ± 0.17	-1.12 ± 0.19
5	1.00 ± 0.15	1.66 ± 0.07	1.54 ± 0.17	-1.34 ± 0.19

Table 6. Tumour volume weighted analysis.

Discussion

The standard Tofts pharmocokinetic model describes the tissue uptake and decay of contrast agent in a region of interest in terms of a transfer rate (k^{trans}) and extra-cellular extra-vascular volume (V_e); the extended Tofts model further accounts for the contrast agent concentration in plasma. Conventionally, the plasma concentration is estimated from the whole blood concentration using a nominal haematocrit to whole blood ratio of $H = 0.42$. For a given individual, it may be acceptable to observe longitudinal changes in measured parameters for a region of interest under the assumption of a constant haematocrit level for that subject. However, this assumption is weak for both an individual and for a group level study. Since, the Tofts models do not explicitly model the haematocrit ratio, any variations in the haematocrit across a group will lead to unwanted variations in the measured

parameters that a) do not reflect changes in the tissue micro-structure and b) reduces the discrimination power of the estimated parameters. Further to this it known that, due to the Farhaeus effect, that local haematocrit values are lower in smaller capillaries compared to the whole blood levels. The work of Lammertsma *et al*, 1984, measured cerebral-to-large vessel haematocrit ratios ranging from 0.59 to 0.80 for a range of pathologies.

The data set used in this work has measured whole blood haematocrit values for each individual subject, and thus allows for correction of the estimated pharmacokinetic parameters on a *per* subject basis. The analysis removes this variation via a correction factor that is a power law version of the standard correction. Thus, if the standard corrections are valid the power factor estimated would be consistent with a value of 1. This interpretation relies on the assumption that an appropriate parameter correction should eliminate correlation with the haematocrit. By this we mean that the correlations will not be generated due to pathology e.g. a tumour with a large k^{trans} is associated with a large whole blood haematocrit value as a consequence of tumour progression. If such correlations did exist then not only would the optimal de-correlation of data not re-generate expected values but the haematocrit would contain information of potential clinical value for prognosis.

Monté-Carlo evaluation shows that, on average, the presented method of minimising variance with respect to haematocrit values returns the correct power factor. However, the values seen the real data (Tables 5 and 6) are significantly different to those expected for a standard correction and leads to consideration of other physical interpretations over and above pure volumetric arguments.

V_p vs V_b

Our aim is to determine the parameters which are a most reliable description of the tissue micro-structure. What we can see from above is that, by definition, V_p is a function of the haematocrit value. The parameter which better describes the biological properties of tissue by being independent of the haematocrit is V_b. However, by choosing an arterial input function which gives $V_b = 1$ in large vessels, and computing V_p' using a population haematocrit, this only served to re-scale V_b by a fixed constant. Therefore, as a tissue description V_p' is effectively the same as $V_1 = V_b$. This being the case, the V_p' correction which should give the best repeatability between subjects would be $V_p'(1-H)^0$.

Taking into account the Fahraeus effect, we now assume a relationship between whole blood (H) and tissue haematocrit (H_t). A simple one parameter approach which has the correct boundary conditions is $(1-H_t) = (1-H)^\tau$. If V_b' is scaled (by the normalisation of the arterial input function), so that a voxel of 100% blood (e.g. in the SSS) has $V_b = 1$, then for the expected reduction in haematocrit in tissue ($\theta < 1$) the estimated V_b' (and also V_p) will be too large by a factor of

$$V_b = V_b'(1-H)/(1-H)^\tau \qquad (10)$$

However, when using $\gamma = (1-H)^\theta$ the corresponding correction requires $\theta \approx -1.0$. As $(1-H)$ is less than 1 this suggests the plasma fraction has increased rather than reduced as predicted.

k^{trans} and V_e

The correction for Fahraeus effect seen in V_b is due to the reduction in signal from a fixed contrast concentration. However, having corrected the arterial input function for the whole blood haematocrit (first term in equation (1)) the plasma concentration (used in the second term) is **correct** regardless of later local changes in haematocrit, provided the extra-vascular space associated with V_e fills with plasma not whole blood [1]. Therefore it should be unnecessary to correct k_{trans} and V_e for the Fahraeus effect.

Permeability and Porosity

Even if the Tofts model is capable of correctly estimating a permeability, it is still not necessarily the most reliable way of characterising a property of tissue micro-structure. We have already made the point that V_b is a better description of tissue than V_p. We now need to consider if k_{trans} is a good way to describe tissue structure.

k_{trans} can be interpreted as a surface area and permeability product. Permeability is a function of both the physical damage in tissue and properties of the leaking blood. If we consider a fluid leaking through holes, and imagine a change to the properties of the fluid by introducing large components which cannot pass though these

[1] If the extra-vascular space were to fill with whole blood the the measured V_e even following the standard corrections would be too small by a factor of $(1-H)$.

holes, then the rate of leakage is likely to change. The correct term for the physical damage might be better described as *porosity*. The way in which a tissue porosity is related to the observed measured leakage rate might be quite complicated, and include effects due to the local concentrations of plasma and haematocrit within a vessel. However, a reduction in permeability due to blockage would appear to operate in the opposite direction to the effects we see in data.

Modelling Errors

It is known that susceptibility of blood changes with haematocrit (Blockley *et al*, 2008; Silvennoinen *et al*, 2003; Koenig *et al*, 1986), however, the effect on T_1 relaxation times is accounted by using differences between pre- and post-contrast measurements; T_2^* effects are minimised due to the protocol (small TE). Thus, changes in signal intensity due to variations in haematocrit do not propagate to estimates of the AIF. However, the reasons for over-corrections may be partially or wholly due to inadequacies in the assumptions of the Tofts model. For instance, when the Tofts model is compared to a two compartment exchange system (Sourbron and Buckley, 2011) it is possible to identify an assumption that the flow/leakage rate ratio is high enough that there is minimal net depletion of the contrast agent in the vascular space. A failure of this assumption may well lead to biases in parameter estimation which have some correlation with haematocrit. Further understanding of this effect is however beyond the scope of this work.

Conclusions

We have investigated the process of de-correlating the residuals on repeated estimates of pharmocokinetic parameters using a subject dependant whole blood haematocrit estimate. It has been found that the correction required to maximally reduce variations due haematocrit is significantly more than that found using pure volumetric arguments. Having considered other possible confounding factor, such as the Fahraeus effect and porosity, the reasons for this over correction are not immediately obvious, but appear to lie with the modelling process itself.

It is clear that, given the range of measured whole blood haematocrit and the corrections found, that a significant proportion of the variance in the data-set is due to variation in the haematocrit. The full correction of variables is consistent with the haematocrit accounting for approximately 25% of the measurement variance (repeatability). As methodology is improved it is very likely that the contribution to measurement uncertainty form other sources could be significantly reduced (Krokos, 2017), so that the contribution from the unknown haematocrit will become the most significant factor.

As the purpose of parameter correction is to reduce unwanted variations and so increase sensitivity to measured change, this suggests that a linear correction for plasma volume is sub-optimal, in the case of this study removing approximately only 60% of the unwanted correlation. We suggest that analysis of pharmacokinetic variables should include haematocrit measurements as a possible nuisance variable.

References

Box, G. E. P. and Cox, D. R.; *An analysis of transformations.*, J. of The Royal Statistical Society. Series B (Methodological), **26(2)**, 211–252, 1964.

Jackson, A., Parker, G. J. M., and Buckley, D. L.; *Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology.*, Springer-Verlag Berlin Heidelberg,2005.

Tofts, P. S.; *Modeling tracer kinetics in dynamic gd-dtpa MR imaging.*, J. Magn. Reson. Imaging, **7(1)**,91–101, 1997.

Lammertsma, A.A, Brooks, D.J., Beaney R.P., Turton, D.R., Kensett, M.J., Heather, J.D., Marshall, J. and Jones, T. *In-vivo Measurement of Cerebral Haematocrit Using Positron Emission Tomography.*, JCBF & M. **4**, 317-322, 1984.

Brooks, D.J., Beaney R.P., Lammertsma, A.A, Turton, D.R., Marshall, J., Thomas,. D.J.T. and Jones, T. *Studies on Regional Cerebral Haematocrit and Blood Flow in Patients with Cerebral Tumpurs Usinf Positron Emission Tomography.* Microvascular Research, **31**, 267-276, 1986.

Notley, S. V., Thacker, N. A. , Horsley, L., Little, R., Watson, Y., Mullamitha, S., Jayson, G. C., Jackson, A, *Computing Similarity Measures on Multi-Dimensional DCE-MRI Variables for Hepatic Colorectal Metastases.*, Tina-Memo 2016-16.

Sourbron, S. P. and Buckley, D. L., *On the Scope and Interpretation of the Tofts Models for DCE-MRI*, Magn. Reson. in Medicine, **66**,735–744), 2011.

Krokos, G., *Integratde Analysis of Dynamic PET and MR Brain Images for the Development of Imaging Biomark-*

ers of Drug Delivery, Ph.D Thesis, University of Manchester, 2017.

Blockley, N.P., Jiang, L., Gardener, A. G., Ludman, C. N., Francis, S. T., and Gowland, P.A., *Field Strength Dependence of R 1 and R* 2 Relaxivities of Human Whole Blood to ProHance, Vasovist, and Deoxyhemoglobin*, Magn. Reson. in Medicine, **60**,1313–1320), 2008.

Johanna Silvennoinen, M., Kettunen, M. I., and Kauppinen, R. A.*Effects of Hematocrit and Oxygen Saturation Level on Blood Spin-Lattice Relaxation*, Magn. Reson. in Medicine, **49**,568–571), 2003.