Tina Memo No. 2001-003
Short Version published in: Proc. MIUA, pp 137-140, London. 10th-11th July, 2000.

A New Approach for the Estimation of MTT in Bolus Passage Perfusion Techniques.

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Last updated
7 / 2 / 2002

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The importance of accurate measurement of cerebral perfusion in clinical practice cannot be overestimated. Changes in blood flow occur in all cerebral diseases and can provide valuable diagnostic and prognostic data for patient management. More important is the ability to measure reductions in blood flow which may produce ischaemic cell death either due to ischaemic apoptosis or stroke. Until recently accurate measurements of blood flow within the capillary beds of the brain could be produced only by use of ^{15}O labeled water molecules and positron emission tomography. This technique is accurate but extremely unsatisfactory for clinical examinations since it is extremely expensive, invasive and requires prior scheduling of the examinations which can be completely impossible in clinical emergencies. In order to overcome these problems two alternative clinical methodologies were developed. The first of these is the use of 99mTc HMPAO as a marker of perfusion in combination with single photon emission computed tomography (SPECT). This tracer is highly lipophilic and passes into the brain in quantities proportional to regional blood flow. Once in the brain the isotope is trapped and its distribution can be imaged for several hours after the injection. Unfortunately the method still requires exposure to radiation and produces low spatial resolution images which contain no other anatomical or structural data. As a result the SPECT examination must be routinely supplemented with other cross-sectional imaging such as CT or MRI. The introduction of Xe enhanced CT has provided a potential solution to these problems by providing high resolution anatomical images in combination with accurate high resolution measurements of cerebral blood flow. Despite this the Xe technique has not been widely accepted for clinical use due to the high radiation dose required and the potential clinical complications produced by the anaesthetic activity of the Xe. In clinical practice MRI is now the investigation of first choice in the vast majority of cerebral disease. The ability to produce accurate cerebral perfusion maps on standard clinical MR scanners is therefore highly desirable. Two generic methods have been described to produce MR based measurements of perfusion. The first, which is the basis of this application, is to derive measurements of perfusion from images which document the passage of a single bolus of contrast medium through the brain. The second is to magnetically label protons in blood which is passing through the brain and to use resulting, flow induced changes in signal intensity to calculate flow. These spin labeling techniques are attractive since they do not require contrast injection and can be repeated as often as is necessary without risk. Unfortunately, spin labeling techniques suffer from physical limitations imposed by the half life of the "spin tag". These problems have excluded the spin labeling methods from clinical practice at the present time.

The use of first-pass bolus studies to measure cerebral perfusion is fundamentally attractive. The use of contrast injection produces controllable decreases in signal intensity, whilst basing the analysis purely on first pass data imposes a short image acquisition which can be easily incorporated into existing clinical imaging protocols. First-pass bolus kinetics are also well documented and highly generic, so that any successful technique can be used with a range of imaging technologies. In clinical practice, the need is for a technique that will work with both MRI and CT, which currently form the basis of all clinical scanning protocols. Equally important is the ability of first-pass techniques to provide no first-pass analysis methods to produce maps of cerebral blood flow from MR data. These techniques use the area under the contrast concentration curve as an estimate of blood volume within the pixel (CBV) and the width of the contrast bolus as an estimate of the mean transit time (MTT). The MTT parameter can be estimated from the temporal width of the measured bolus by assuming that the net shape of the bolus can be modeled as a convolution of the arterial bolus shape with the within voxel molecular transit time distribution. This in turn can be approximated to first order by a quadrature addition of widths (analogous to addition of variance in error analysis). The importance of deconvolution with an input response function has recently been identified in order to obtain quantitative measurement [4]. These techniques and others, involving fitting of the bolus to a gamma variate based on varying assumptions regarding measurement noise [1], are now being applied in medical research for the estimation of blood flow from MR data sets. This allows calculation of relative cerebral blood flow (CBF=CBV/MTT) and the production of parametric maps of each parameter. One major restriction of this technique is that the estimates of CBV and CBF are relative and not absolute which restricts clinical interpretation. Production of absolute measures of CBF requires absolute accurate measures of CBV and MTT. The production of accurate CBV measures is possible if inflow effects and other non-linear MR variables can be compensated for. We have previously published techniques at MIUA which allow quality control of the derived perfusion parameters. Production of accurate measurements of MTT is far more difficult and has not been adequately addressed. It is increasingly clear that current methods for the measurement of MTT are flawed, resulting in parametric images of flow which are inaccurate and potentially clinically dangerous. This paper attempts to explain and illustrate these problems and suggests a possible solution.

A New Approach for the Estimation of MTT in Bolus Passage Perfusion Techniques.

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Abstract

In clinical practice MRI is now the investigation of first choice in the vast majority of cerebral disease. The ability to produce accurate cerebral perfusion maps on standard clinical MR scanners is therefore highly desireable [7]. In particular, the use of first-pass bolus studies to measure cerebral perfusion is fundamentally attractive. The use of contrast injection produces controllable increases in signal to noise ratio whilst basing the analysis purely on first pass data imposes a short image acquisition which can be easily incorporated into existing clinical imaging protocols. This has led to the description of first-pass analysis methods to produce maps of cerebral blood flow from MR data. These techniques use the area under the contrast concentration curve as an estimate of blood volume within the voxel (RCBV) and the width of the contrast bolus as an estimate of the mean transit time (MTT). This allows calculation of relative cerebral blood flow (RCBF=RCBV/MTT) and the production of parametric maps of each parameter. The production of accurate CBV measures is possible if inflow effects and other non-linear MR variables can be compensated for. Production of accurate measurements of MTT is far more difficult and it is increasingly clear that current methods for the measurement of MTT are flawed [10]. This paper attempts to examine why these methods are flawed and how the flaws may be corrected.

Introduction

The standard approach is to assume that the width of the gamma variate time curve, generated by the passage of the bolus is representative of the time taken for the bolus to pass through a voxel. Clearly such an approach is highly dependent upon the shape of the active region and isotropic voxels would be preferred in order to eliminate net flow direction dependencies. Attempts to account for differences in cardiac output and administration of contrast are generally based on deconvolution. However, as the spatial resolution of the data improves the expected contribution of MTT to the width of the curve will decrease.

Before the advent of Perfusion MR much was already known from standard physiology regarding the expected flow of blood through the brain. In particular, given the quantity of brain tissue, the blood flow into the head and known cerebral blood volume fractions it is possible to estimate the mean velocity of blood plasma to be approximately 2mm per second. Such velocities can be directly visualised on imaging modalities other than MR, such as CT angiography. An analysis of the expected accuracy of MTT, for typical bolus width measurement accuracy (0.6 seconds) and RMS arterial width (4 seconds), is shown in table 1. This table illustrates that for typical blood flow, velocities of 2 mm per second in grey matter and white matter capillaries, MTT should not be reliably measurable in high resolution MR data sets (3mm voxels) with the RMS width of the bolus rising from 4.0 to a maximum of 4.02 seconds in the capillaries.

MTT	1.0	1.5	2.0	3.0	4.0	5.0
$error fraction$	28.9	12.8	7.2	3.2	1.8	1.2

Table 1: Proportional error estimates on MTT computed using the method of error propagation for the calculation of MTT based on a quadrature subtraction.

However, typically quoted values of MTT from deconvolution in the literature are of the order of 4 seconds and these numbers have been demonstrated to give derived flow measurements which correlate with independent flow estimates [9, 4]. This result, which is the commonly accepted view in the literature, demands an explanation. In this paper we attempt to construct a new model to better describe the

observed measurements and go on to suggest an alternative method for estimation of MTT which should make fully quantitative perfusion measurement possible.

Theory and Method

The conventional approach to modelling the perfusion measurement process relies upon three key stages concerning;

- a relationship between contrast density and MR signal loss.
- a relationship between the integrated contrast density and flow variables.
- a relationship between the shape of the contrast density distribution and the transit time.

Given these relationships it is then possible to calculate tissue perfusion from the time varying MR signal following contrast administration. The approach outlined above initially involves computation of relative cerebral blood volume [1, 7, 9] which is a well defined and easily measured parameter. The equations describing formation of T2* weighted image intensity values I_i for voxel i ignores flow based and partial volume measurement artifacts and is written as

$$R_i(t) \;=\; -\frac{ln\left(I_i(t)/I_i(0)\right)}{\alpha T_E}$$

Where $R_i(t)$ is the relaxivity and α is a constant. The assumption of a linear relationship between relaxivity and concentration of the contrast agent has been shown to be valid both by experiment and simulation for the blood volume fractions in the physiological and pathological range [2]. For a bolus with time varying contrast concentration we can thus write:

$$\int_0^\infty R_i(t)dt \;=\; \beta \oint_{V_i} \int_0^\infty C(\mathbf{p},t)dtd\mathbf{p}$$

Where $C(\mathbf{p},t)$ is the spatio-temporal contrast density and β is a constant. This quantity is generally referred to as relative cerebral blood volume (RCBV), implying that the integrated time varying contrast concentration must have the same value at all locations $\mathbf{p}$ such that;

$$\int_0^\infty R_i(t)dt \;=\; \beta V_i \int_0^\infty C_i(t)dt$$

Where C_i is the concentration of contrast in the fractional volume V_i of the voxel. This amounts to an assumption of zero dispersion in an incompressible fluid, where changes in cross-sectional volume are accompanied by compensating changes in velocity. If correct our integral can now be re-written as

$$\int_0^\infty R_i(t)dt \;=\; \beta V_i \langle C_a\rangle \langle T_a\rangle$$

where $\langle T_a\rangle$ is the time taken for some proportion of the bolus to pass any point $\mathbf{p}$ in an arterial voxel. This equation then defines the effective arterial inflow concentration $\langle C_a\rangle$. RCBV can thus be estimated from a sum over the appropriate measured image data although a non-linear correction for variation in the haematocrit may be required. Division by a parameter generally referred to as mean transit time (MTT) recovers relative blood flow measurements (RCBF).

$$RCBF \;=\; RCBV/MTT$$

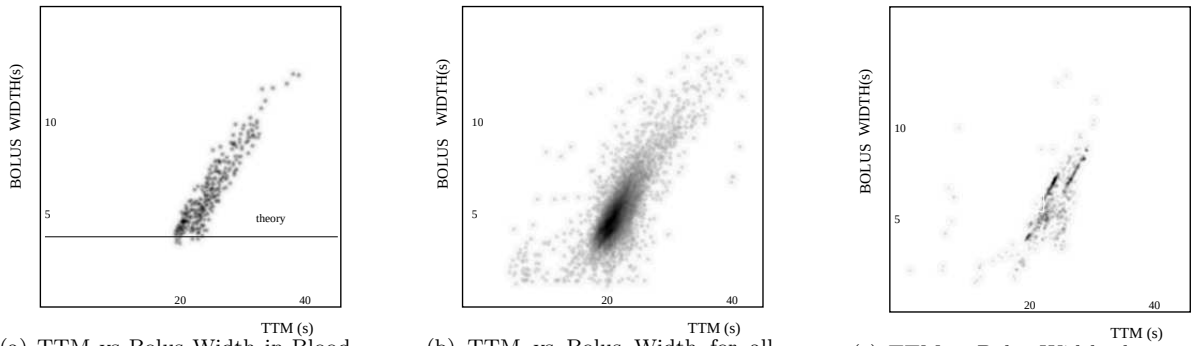
This process defines MTT as a direct estimate of the average time taken for a molecule of the bolus to pass through an image voxel. We note here that **in order for the value of MTT to be independent of the net flow direction the active area of a voxel must be isotropic**, though the most frequently cited publications in this area make no attempt to satisfy this requirement and generally define large regions of interest using arbitrary spatial geometry.

The MTT parameter can be estimated from the temporal width of the measured bolus by assuming that the net shape of the bolus can be modelled as a convolution of the arterial bolus shape with the

within-voxel molecular transit time distribution. The importance of deconvolution with an input response function has recently been identified in order to obtain quantitative measurement [4, 9]. These techniques and others, involving fitting of the bolus to a gamma variate based on varying assumptions regarding measurement noise [1], are now being applied in medical research for the estimation of blood flow from MR data sets.

The deconvolution approach is based on several assumptions, one of which is that of zero dispersion of the contrast agent, either due to Brownian motion or inflow heterogeneity. If this were not true it would be wrong to deconvolve with the same arterial input function in all regions of the data. Unfortunately, the observed time curve may be affected not only by the input response at the base of the brain, but also by any intervening tissues en-route to a voxel. We can validate this assumption by investigating the relationship between bolus width (statistical variance) and TTM (mean arrival time ie: midpoint of the bolus) in blood vessels. If bolus dispersion does not occur then the width of the bolus in veins should be the same as in the arteries. We have therefore constructed a simple experiment in order to investigate this assumption.

Typical results from Susceptibility Perfusion Measurement



(a) TTM vs Bolus Width in Blood Vessels

(b) TTM vs Bolus Width for all data

(c) TTM vs Bolus Width phantom

Figure 1: Data Distributions demonstrating the correlation between TTM and bolus width indicative of an effective dispersion process and the distribution of the new MTT estimate.

Figures 1 (a) and (b) show a typical distribution of width versus TTM values estimated in the brain of a normal subject in a 256x256 (0.9mm x 0.9mm x 12.5 mm) MR perfusion data set using gamma variate fitting. Figure 1 (a) is for high RCBV regions only (greater than 0.3 of the maximum arterial value), and cannot therefore be attributed to cappilary beds in grey or white matter. Figure 1 (b) demonstrates that the bolus width versus TTM distribution is identical in the rest of the data. Though the dynamic range of the data is consistent with published values, broadening of the function due to increased MTT in capillary beds is not seen. A flow phantom, constructed with typical flow velocities for the passage of plasma through the brain from physiology, generates exactly the same distribution (Figure 1(c)). As the phantom contains only MTT's less than 1 second for this data, one must conclude that the range of bolus width values must be accounted for by some other mechanism, such as flow heterogeneity, which has only recently been acknowledged as a potentially important factor [6]. We would go further and suggest that **MTT estimation based on changes in bolus width is impossible in high resolution MR** and that bolus broadening, which is currently being interpreted as MTT is actually an estimate of the amount of dispersion of the bolus.

In order to modify our previous expression for RCBV now to deal with such a dispersive process and a different local mean contrast concentration $\langle C_i \rangle$ we need only notice that conservation of matter would require a proportional increase in bolus passage time $\langle T_i \rangle$ in voxel i (by a factor $d_i > 1.0$) which would be inversely proportional to the contrast concentration,

$$\langle C_i \rangle \;=\; \langle C_a \rangle / d_i \qquad\qquad \langle T_i \rangle \;=\; d_i \langle T_a \rangle$$

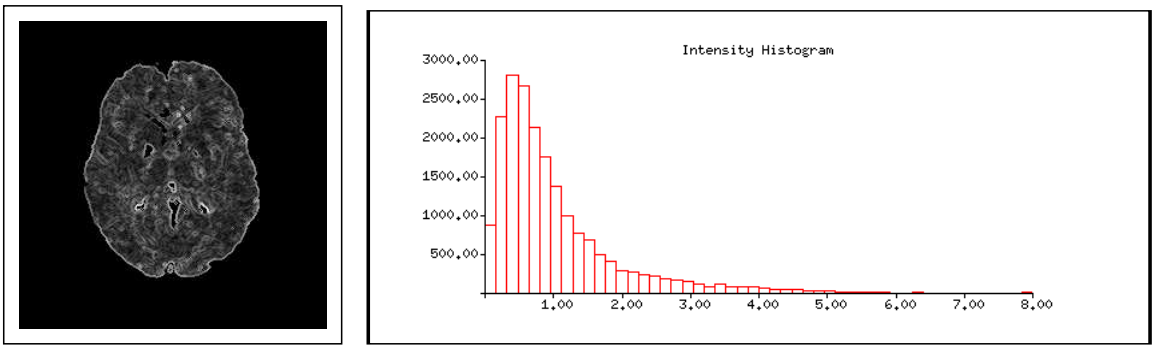
Grouping all of the constant factors for a given bolus into one term γ_a gives a modified expression for $RCBV$.

$$RCBV_i \;=\; \gamma_a V_i \langle T_i \rangle / d_i$$

The numerical value of which is independent of d_i under these assumptions. However, for the purposes of calculating perfusion, differing T_i will result in spatially varying bolus widths which invalidate conventional approaches for estimation of MTT. Correlations of RCBF with independent estimates of flow [3, 5] could be accounted for by the expected correlation between RCBV and actual flow and coincidental changes in bolus width in regions of low flow due to the increased time available for dispersion.

Conclusions

The above analysis and results indicate that standard software packages for measurement of perfusion from MR data could well be providing misleading flow measurements due to dispersion. Instead of attempting to estimate MTT from the effects of bolus broadening the very nature of high resolution MR offers up an alternative. If we can locate a feature on a bolus curve which is independent of dispersion we may be able to track this feature across voxels in order to directly estimate MTT. One such possibility is the TTM parameter, which is independent of symmetrical diffusion and dispersion. Given sufficient accuracy, the spatial derivative of this parameter should this give a direct estimate of MTT in regions of uniform flow. Figure 2 shows the in-plane derivative for the previous data set along with its distribution. Though there is some structure which can be related to anatomical boundaries, the distribution of values peaks at a sensible estimate for MTT from physiology with an accuracy of around 50% which is already far greater than expected from bolus broadening techniques in the same data. This data makes possible the estimation of RCBF within the image plane and would seem to suggest that with some care (to avoid fitting failiures) it might be possible to estimate MTT from the 3D spatial derivative of TTM within a local region. All software and data used in this study are available as open source from our web site [11].



(a) Differential MTT Estimate

(b) MTT Distribution

Figure 2: Estimated value of MTT from the derivative of TTP demonstrating good regional coherence and reasonable agreement with physiological prediction.

References

1. M.M. Bahn, A Single step method for Estimation of Local Cerebral Blood Volume from Susceptibility Contrast MRI, MRM, 33, 309-317, 1995.
2. J.L.Boxerman, B.R.Rosen, and R.M.Weisskoff, Signal to Noise Analysis of Cerebral Blood Volume Maps from Dynamic NMR Imaging Studies, J.Mag.Res.Imag. 7,3, 528-537, 1997.
3. T. Hagen, K. Bartylla and U. Piepgras, Correlation of Regional Cerebral Blood Flow Measured by Stable Xenon CT and Perfusion MRI, JCAT, 2 , 3(2), 257-264, 1999.

   of Packaging
4. L.Ostergaard, A.G. Sorensen, K.K. Kwong, R.M.Weisskoff, C.Gyldensted and B.R.Rosen. High Resolution Measurement of Cerebral Blood Flow Using Intravascular Tracer Bolus Passages, Parts I and II, Experimental Comparison and Preliminary Results. MRM, 36, 715-736, 1996.
5. L.Ostergaard, P.Johannsen, P.Host-Poulsenm P.Vestergaard-Poulsen, H.Asboe, A.D.Gee, S.B.Hansen, G.E.Cold, A.Gjedde and C.Gyldensted, Cerebral Blood Flow Measurements by Magnetic Resonance Imaging Bolus Tracking: Comparison With (O^15 H_2O) Positron Emission Tomography in Humans. JCBF and M, 18, 9356-940, 1998.
6. L.Ostergaard, D.A.Chelser, R.M.Weisskoff, A.G.Sorensen and B.R.Rosen, Modelling Cerebral Blood Flow and Flow Heterogeneity From Magnetic Resonance Residue Data, JCABF and M, 19, 690-699, 1999.

7. D.R.Pickens, Perfusion/Diffusion Quantification with Magnetic Resonance Imaging.
8. J.Luettin and N.A.Thacker. "Speechreading Using Probabilistic Models". Computer Vision and Image Understanding, 65(2),163-178, 1997.
9. K.A.Remp, G.Brix, F.Wenz, C.R.Becker, F.Guckel, W.J.Lorenz, Quantification of Regional Cerebral Blood Flow and Volume with Dynamic Susceptibility Contrast-enhanced MR Imaging. Radiology, 193, 637-641, 1994.
10. R.M.Weiskoff, D.Chesler, Jerold L.Boxerman, Bruce R.Rosen. Pitfalls in MR Measurement of Tissue Blood Flow with Intravascular Tracers: Which Mean Transit Time? MRM, 29, 553-559, 1993.
11. Neuro-imaging analysis centre (niac), ISBE, Faculty of Medicine, University of Manchester, http: //www.niac.man.ac.uk.