

# What can quantitative DCE $T_1$ -weighted MR imaging tell us?

Paul S Tofts

Institute of Neurology (Queen Square), University College London, WC1N 3BG, UK

<http://www.ion.ucl.ac.uk/nmrphysics/paultofts/> [p.tofts@ion.ucl.ac.uk](mailto:p.tofts@ion.ucl.ac.uk)  
a more recent version of this note is accessible from [qmri.org](http://qmri.org)

Version December 13<sup>th</sup> 2005

## 1. Fundamentals of $T_1$ -weighted DCE

- a. Repeated imaging of a Multiple Sclerosis (MS) lesion after injection of Gd contrast agent shows an enhanced signal which increases with time, then decreases (figure 1)
- b. The time to peak, and the peak enhancement, both vary according to the kind of lesion.
- c. Why do we see this? Why is the signal changing? What underlying properties of the tissue and the MR imager drive this process?
- d. Gd is a contrast agent which decreases the value of  $T_1$ , and hence increases the signal intensity in a  $T_1$ -weighted sequence.
- e. In the normal brain, the Blood-Brain Barrier keeps Gd inside the blood capillaries; it cannot reach the brain tissue outside the capillaries.
- f. The blood volume in (normal) brain is small (about 2-4%), and no signal enhancement is seen.
- g. In MS or tumours, the capillary wall (endothelium) is damaged, Gd can escape into the relatively large Extravascular Extracellular Space (EES)
- h. In the EES there can be enough Gd to reduce  $T_1$  and hence increase signal.
- i. A mathematical pharmacokinetic compartmental model<sup>1</sup> enables the concentration of Gd in tissue to be calculated as a function of time after bolus injection of the contrast agent (figure 2 and appendix 1: eqn 2). The driving parameters in this model are:
  - i. PS the permeability surface area product of the endothelium
  - ii.  $v_e$  the fractional size of the EES ( $0 < v_e < 1$ )
  - iii. the dose of injected Gd (contrast agent CA or tracer)
  - iv. the time course of blood plasma Gd concentration ( $C_p(t)$  the Arterial Input Function – AIF; eqn 1))
- j. A 2<sup>nd</sup> (MRI) model is needed to relate the signal to the Gd concentration. The chief consideration here are:
  - i. How  $T_1$  depends on Gd concentration. An in-vitro value for relaxivity is often used (appendix eqn 3), and intravascular tracer is ignored. If the relaxivity is not known, then the rate constant  $k_{ep} = PS/v_e$  can be found, but PS and  $v_e$  cannot be found individually.
  - ii. How signal depends on  $T_1$  (eqns 4,5) A gradient echo sequence is usually used, for speed. Flip angle ( $B_1$ ) errors, including slice profile effects, limit the accuracy of this. The ‘native  $T_1$ ’, i.e. the  $T_1$  of the tissue before injection of Gd, must be known in order to

calculate signal enhancement. Sometimes a series of maps of  $T_1$  values is calculated.

- k. The model can be fitted to the data, by adjusting PS and  $v_e$  (fig 1). For the fitted values of PS and  $v_e$ , the sum of the squares of the differences between the model and the data are a minimum.
- l. These two parameters PS and  $v_e$  characterise the biology of the situation. In principle they are independent of the particular sequence, injection procedure or MRI machine used. They are truly quantitative parameters that can be compared in international multi-centre studies.
- m. Other parameters have been used to characterise Gd enhancement
  - i. Initial slope
  - ii. Time to peak
  - iii. Area under curve (AUC)
  - iv. These other parameters tend to be easier to measure; however they are usually less comparable between centres, and their biological interpretation is less clear.

## 2. Subtle leakage

- a. More subtle leakage can be detected and measured by optimising the MR sequence<sup>2</sup>
- b. Delayed scanning gives increased enhancement in subtle leaks (fig 1)
- c. Optimising the sequence parameters (e.g. TR, FA) enables tissue with smaller PS values to be measured
- d. Increasing the dose ('triple dose') increases the signal enhancement and enables more lesions to be detected in MS
- e. In MS, both 'nonenhancing' lesions and Normal-Appearing White Matter show leakage.

## 3. Generalisation to $K^{trans}$

- a. In tumours PS is higher than in MS, and often blood flow F (i.e. delivery of tracer to the site of leakage) is insufficient to maintain the local plasma concentration at the arterial level. Thus Gd uptake may reflect **flow not permeability**.
- b. Mathematical analysis of these two situations<sup>3</sup> shows that the shape and amplitude of the uptake curve can be identical for each, and cannot distinguish between the two. Thus the generalised solution has the transfer constant  $K^{trans}$  in place of PS.
- c. In a permeability-limited situation (as in MS),  $K^{trans}=PS$  ( $F \gg PS$ )
- d. In a flow-limited situation (as in most tumours),  $K^{trans}=flow$  ( $F \ll PS$ )
- e. Larger contrast agents have lower PS, so can give permeability-limited behaviour in tumours (hence measure F and PS separately)

## 4. Applications in cancer – major areas are

- a. Breast – see early example<sup>4</sup>
- b. Prostate – example of  $K^{trans}$  map by Padhani et al.

## 5. Other models

- a. Tissue homogeneity model (St Lawrence and Lee). Accounts for IV tracer, and the inflow effects during bolus arrival. In principle gives flow from the

bolus arrival portion and PS from the later portion, although good temporal resolution is required.

- b. Brix: no need to assume a plasma curve, relaxivity or native  $T_1$  value. Obtains plasma curve by fitting uptake data; obtains  $k_{ep}$  only<sup>3</sup>

## 6. 'Perfusion imaging'

- a. perfusion = blood flow  $F$  (ml blood  $g^{-1} \text{ min}^{-1}$ )
- b. can be measured most accurately by Arterial Spin Labeling (though noisy)<sup>5</sup>
- c.  $T_{1w}$ -DCE (after bolus passage) gives  $F$  under conditions of:
  - i. Low PS (i.e. flow-limited) AND
  - ii. Blood plasma volume  $v_p$  not too small
  - iii. However incomplete exchange of intravascular (IV) and extravascular water reduces the visibility of IV Gd.
- d.  $T_{2w}$ (\*)-DCE ('bolus tracking') gives  $F$  estimate:
  - i. Much more sensitive to IV Gd (magnetic susceptibility gradient dephases protons)
  - ii. Quantification still difficult (depends on capillary architecture)
  - iii. Blood volume also available
- e. Combined approach of Johnson<sup>6</sup> analyses leakage during bolus passage

## 7. Current problems in $T_{1w}$ DCE

- a. AIF – ideally measure it with MRI (but hard to get a slice). Larger agents slow the process down. Standardised injection may be enough?
- b. Modelling
  - i. IV tracer hard
  - ii. Distributed system (tissue homogeneity)
- c. Imaging - temporal vs spatial resolution
- d. Reproducibility – generally unknown and poor
- e. Interpretation – PS vs  $F$  (angiogenesis) – use larger agents (+ lower temporal resolution)
- f. Turnkey software for maps of  $K^{trans}$  and  $v_e$

## 8. Future of $T_{1w}$ DCE

- a. Cancer Research UK workshop<sup>7</sup> The assessment of anti-angiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations
- b. *Although  $K_{trans}$  is a complex function of tumour blood flow, endothelial surface and endothelial permeability (Tofts et al, 1999), an effective agent will be expected to reduce some or all of these fundamental physiological parameters and it should therefore decrease  $K_{trans}$ .*
- c. **Future requirements for clinical trials:**
  - i. Methods of supporting the MR developments required to underpin clinical trials need to be established.
  - ii. Trials using the MR techniques recommended here need the support of physicists and radiologists at all stages.
  - iii. For multicentre trials, this should include establishing and effecting cross site standardisation of measurements and evaluation.

## 9. Appendix – simulating BBB leakage

The mathematical equations needed in order to simulate Gd enhancement curves (such as in figure 1), and also to extract fitted lesion parameters from measured enhancement data, are given here. These equations follow those previously published<sup>1 2 8</sup>; however the naming conventions for some of the variables have since changed<sup>3</sup>, and revised versions are given here in a compact form for convenience.

After a bolus injection of dose D (mmole/kg), the blood plasma concentration follows a biexponential decay<sup>9</sup>. (This expression is convenient, although it ignores any initial mixing effects, and inter-subject differences in compartment size and renal function).

$$C_p(t) = D \sum_{i=1}^2 a_i \exp(-m_i t) \quad \text{Equation 1}$$

$$a_1=3.99 \text{ kg litre}^{-1}; m_1=0.144 \text{ min}^{-1}; a_2=4.78 \text{ kg litre}^{-1}; m_2=0.0111 \text{ min}^{-1}$$

The tissue concentration is then:

$$C_t(t) = D K^{trans} \sum_{i=1}^2 a_i [\exp(-k_{ep} t) - \exp(-m_i t)] / [m_i - k_{ep}] \quad \text{Equation 2}$$

$K^{trans}$  is the transfer constant (which for a small leak such as in MS equals the permeability surface area product per unit mass of tissue PS).  $k_{ep}$  is the rate constant;  $k_{ep}=K^{trans}/v_e$  (where  $v_e$  is the fractional volume of the Extravascular Extracellular Space (EES)).

The reduction in  $T_1$  is related to the Gd concentration by:

$$R_1(t) = R_{10} + r_1 C_t(t) \quad \text{Equation 3}$$

where  $R_1$  is the relaxation rate ( $=1/T_1$ ),  $R_{10}$  is the rate before injection of Gd, and the  $T_1$  value before injection is  $T_{10} \equiv R_{10}$ .  $r_1$  is the relaxivity (i.e. the increase in relaxation rate per unit concentration of Gd); usually the in-vitro value is used for this ( $4.5 \text{ s}^{-1} \text{ mM}^{-1}$ ).

Using eqns 1-3, then  $T_1(t)$ , the  $T_1$  value as a function of time, can be predicted, given the lesion characteristics ( $K^{trans}$ ,  $v_e$  and  $T_{10}$ ). If  $T_{10}$  is known (or can be estimated), then these predictions can be least-square fitted to measured  $T_1$  data to obtain  $K^{trans}$  and  $v_e$ .

If we have  $T_1$ -weighted signal data (instead of  $T_1$  values or maps) then we can use simple expressions for the signal as a function of  $T_1$  (although we have to rely on the slice profile being good, the flip angle being set correctly and the  $B_1$  field being uniform). We still need an estimate of  $T_{10}$ . The signal for a  $T_1$ -weighted spin echo (at short echo time) is:

$$S(t) = S_0 (1 - \exp(-R_1(t) TR)) \quad \text{equation 4}$$

where  $S_0$  is the fully relaxed signal. For a spoiled gradient echo signal it is

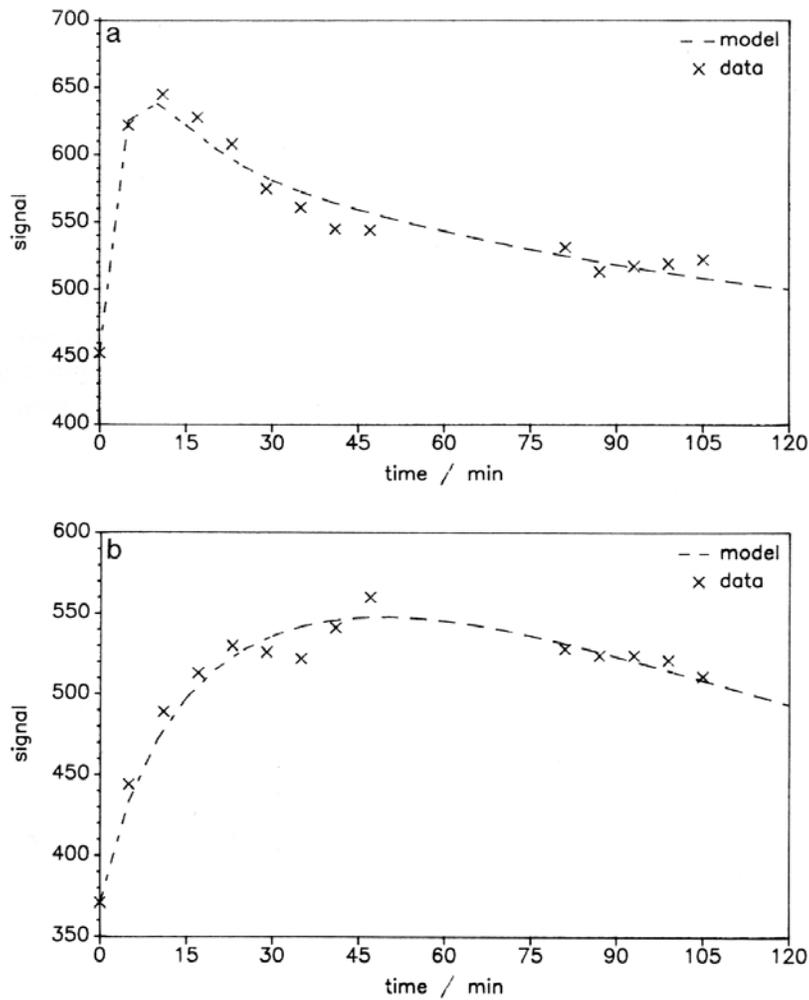
$$S(t) = \frac{S_0 (1 - \exp(-R_1(t)TR)) \sin(\theta)}{1 - \exp(-R_1(t)TR) \cos(\theta)} \quad \text{equation 5}$$

where  $\theta$  is the flip angle in radians. Thus the signal can be plotted as a function of time (with an assumed or fitted value of  $S_0$ ), and this is the principle of how the curves in figure 1 were plotted and fitted to obtain the lesion parameters.

## Reference List

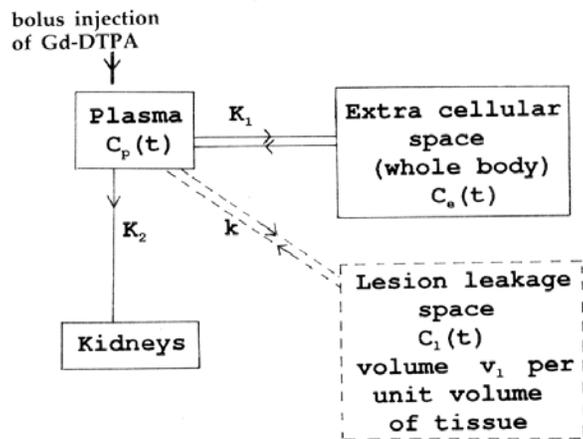
1. Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. *Magn Reson Med* 1991; 17(2):357-367.
2. Tofts PS. Optimal detection of blood-brain barrier defects with Gd-DTPA MRI- the influences of delayed imaging and optimised repetition time. *Magn Reson Imaging* 1996; 14(4):373-380.
3. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999; 10(3):223-232.
4. Tofts PS, Berkowitz B, Schnall MD. Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumors using a permeability model. *Magn Reson Med* 1995; 33(4):564-568.
5. Parkes LM, Rashid W, Chard D, Tofts PS. Normal cerebral perfusion measurements using arterial spin labelling; reproducibility, stability, age and gender effects. submitted 2003.
6. Johnson G, Wetzel SG, Cha S, Babb J, Tofts PS. Measuring blood volume and vascular transfer constant from dynamic, T(2)\*-weighted contrast-enhanced MRI. *Magn Reson Med* 2004; 51(5):961-968.
7. Leach MO, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A, Jayson GC, Judson IR, Knopp MV, Maxwell RJ, McIntyre D, Padhani AR, Price P, Rathbone R, Rustin GJ, Tofts PS, Tozer GM, Vennart W, Waterton JC, Williams SR, Workman P. The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations. *Br J Cancer* 2005; 92(9):1599-1610.
8. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging* 1997; 7(1):91-101.
9. Weinmann HJ, Laniado M, Mutzel W. Pharmacokinetics of GdDTPA/dimeglumine after intravenous injection into healthy volunteers. *Physiol Chem Phys Med NMR* 1984; 16(2):167-172.

**Figure 1 dynamic imaging of multiple sclerosis lesions.**



Dynamic changes in signal from two series of inversion-recovery images lasting nearly 2 hours, after injection of Gd-DTPA contrast agent. In the first example, from an acute MS lesion, peak enhancement is relatively early (about 12 min), and the fitted model parameters are permeability  $K^{\text{trans}} = 0.050 \text{ min}^{-1}$ , extracellular space  $v_e = 21\%$ . In the second example, from a chronic lesion, enhancement is slower, reaching a peak at about 50 min. Fitting the model shows a much lower permeability  $K^{\text{trans}} = 0.013 \text{ min}^{-1}$ , and a much larger extracellular space  $v_e = 49\%$ , both consistent with what is known from post-mortem studies.. From Tofts and Kermode<sup>1</sup>

**Figure 2 compartmental model**



Original mathematical model of water compartments into which Gd-DTPA can distribute. Initial bolus injection is into the blood plasma compartment; there is rapid equilibration with body water; irreversible removal by the kidneys; and reversible flow into the small extravascular extracellular space of the lesion. From Tofts and Kermode<sup>1</sup>