

Perfusion/Permeability 1:

Tracer Kinetic Modeling Using Contrast Agents

David L Buckley, PhD

Senior Lecturer, Imaging Science and Biomedical Engineering,
University of Manchester, Manchester, United Kingdom

Outline

1. Introduction to contrast agents, imaging methods and uptake dynamics
2. Introduction to time series models and tracer kinetic modeling
3. Standard methods of modeling and statistical estimation
4. Advanced methods and specific artifacts/errors/difficulties
5. Applications of methods in research and clinical practice

1. Contrast Agents and MRI

- Agents originally developed to enhance contrast-to-noise in anatomic images following intravenous administration.
- Their principal mode of action is to increase the relaxation rates ($1/T_1$, $1/T_2$, $1/T_2^*$) of nearby water molecules thereby modifying local signal intensity.
- Extracellular agents (such as Gd-DTPA¹) accumulate in the interstitium of many tissues (e.g. muscle) but do not cross the blood-brain-barrier (BBB) in normal brain tissue.
- Gd-DTPA is particularly useful for identifying breakdown of the BBB in conditions such as cancer, multiple sclerosis and ischemia.
- Extracellular agents are by far the most common contrast agents in use today. Others exist and numerous agents are in development but this discussion is limited to Gd-DTPA and its like.
 - Functional information may be obtained by treating Gd-DTPA as a tracer and following its kinetics (as opposed to the conventional approach, inject - wait - image once).
 - After intravenous administration (normally in the form of a bolus) Gd-DTPA transits the venous and arterial system leaking from capillary beds wherever the endothelial cell junctions allow. It is excreted via the kidneys [1].
- The choice of imaging method is crucially dependent on what is to be measured and the rate of tracer delivery and uptake.

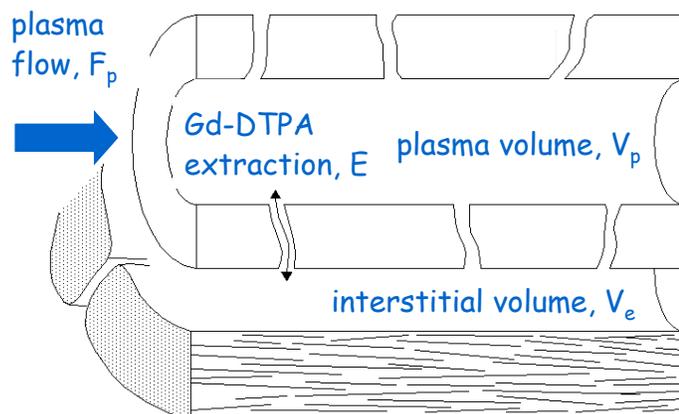
¹ A number of extracellular agents behave very similarly. The term Gd-DTPA is simply used for the sake of convenience and is not an endorsement of Magnevist specifically.

- In the brain with an intact BBB the conventional approach is to make rapid serial measurements using T2 or T2*-weighted sequences (often EPI) [2].
 - Gd-DTPA remains in the blood plasma; a very small fraction, < 5%, of the total tissue volume. T1 signal change is therefore small.
 - Its effect on T2/T2* relaxation rate is enhanced by susceptibility gradients between the vessels and surrounding parenchyma.
- When imaging tissues with leaky capillaries (e.g. tumors), measurements are typically made using rapid T1-weighted gradient echo sequences (often FLASH or TurboFLASH).
 - Gd-DTPA in the plasma has a relatively small influence on the signal except where the vascular volume is large (e.g. in the kidney, heart or certain tumors).
 - Gd-DTPA in the interstitial space has a significant effect since this often represents > 30% of the tissue volume.
- The temporal sampling requirements vary enormously. For first-pass T2/T2* studies a sampling interval of ~ 1 s is required to measure the rapid transit of the Gd-DTPA bolus. For so-called permeability studies the uptake of Gd-DTPA may take several minutes and sampling rates can be reduced to tens of seconds or even minutes.

2. Tracer Kinetic Modeling

- Transport of Gd-DTPA can be described using a number of parameters:
 - Blood flow, F (or plasma flow, F_p); transit time, T_c (time taken for a Gd-DTPA molecule to travel from the artery to the vein); capillary permeability-surface area product, PS (a measure of vessel leakiness); blood volume, V_b and interstitial volume, V_e .

Fig. 1 - The basic capillary-tissue exchange unit (after Kuikka [3]). Two spaces (plasma and interstitium) are separated by a semi-permeable membrane. The plasma volume is replenished by flow of contrast agent and a fraction of this, E , is extracted to the interstitium in a single pass. $E = 1 - \exp(-PS/F_p)$.



- When put together in a physiologic model (e.g. Fig. 1) and formulated in mathematical terms the tracer kinetic parameters provide a powerful tool for data analysis.
- One important step so far missing is the link between the models and the image data. The models require Gd-DTPA concentrations as inputs; the images contain only signal intensities.
- Conversion between signal and concentration relies upon the assumption that changes in relaxation rate are linearly related to Gd-DTPA concentration and that relaxation rate change can be measured sufficiently quickly (see, for example, Gareth Barker's talk).

3. Models and Data Fitting

- One way of describing the tracer kinetics is to calculate the convolution of the arterial input function (AIF, the concentration of Gd-DTPA in the feeding artery) with the tissue impulse residue function (IRF), the theoretical response in the tissue to an infinitely tight unit bolus [4].

$$C_t(t) = F \cdot AIF \otimes R(t)$$

where $C_t(t)$ is the tissue concentration of Gd-DTPA, F is blood flow, $R(t)$ is the IRF and \otimes is the convolution operator.

- The shape of the IRF can be determined in two ways:
 - No assumption about $R(t)$. A deconvolution may be performed using C_t and the AIF and this results in an estimate of $R(t)$ directly
 - Model assumed. A mathematical description of $R(t)$ may be derived and then data fitting (usually non-linear regression) to the C_t and AIF data is used to estimate the model parameters.
- Deconvolution is commonly used to estimate blood volume, transit time and flow (via the central volume theorem $F = V_b/T_c$) [5, 6] in dynamic susceptibility studies. Here $R(t)$ represents the combination of AIF dispersion and transit time heterogeneity since Gd-DTPA doesn't leave the vascular space.
- Model fitting is commonly employed once Gd-DTPA leaves the vasculature. $R(t)$ typically incorporates V_e and K^{trans} , the volume transfer coefficient, combining a mixture of flow and permeability ($K^{\text{trans}} = E \cdot F_p$) [7].
- The most common models used to describe $R(t)$ in dynamic contrast-enhanced (DCE)-MRI studies today [8] [9] [10] assume an exponential form for $R(t)$:

$$C_t(t) = K^{\text{trans}} \cdot AIF \otimes \exp\left(\frac{-K^{\text{trans}} t}{v_e}\right)$$

- If the contribution of intravascular Gd-DTPA is thought to be significant, a simple additional compartment can be added to the model [11]:

$$C_t(t) = v_b \cdot AIF + K^{\text{trans}} \cdot AIF \otimes \exp\left(\frac{-K^{\text{trans}} t}{v_e}\right)$$

- Vital to the application of all these techniques is the measurement of an AIF. In clinical practice this may not always be possible and the use of a population AIF has been proposed [9].

4. Problems and Possible Solutions

- Central to the application of these techniques is the requirement for good quality, artifact-free data with an appropriate spatial, temporal and contrast resolution. Perhaps the most difficult aspect of this is the measurement of the AIF. Techniques have been described for such measurements [12, 13].
- A confound for dynamic susceptibility studies is the complex relationship between Gd-DTPA concentration and $1/T2^*$. It may be that relative measures of flow are the best that can be obtained [14].
- Estimating the IRF. Deconvolution is a noisy process [15] and many of the models of $R(t)$ are overly simplistic [16].
- A combination of approaches is one way to proceed. Incorporating leakage into $T2^*$ models is complicated by the competing effects of intravascular and interstitial Gd-DTPA [17] while $T1$ techniques are confusingly reported as either perfusion or permeability studies while in reality either designation is premature.
- However, a recent development is the wider introduction of distributed parameter models into the CT-perfusion community [18] and now for $T1$ -weighted DCE-MRI [19]. Flow and PS can be separated provided data sampling rates exceed the minimum transit time of the tissue studied (in the same way that $T2^*$ measurements must).
- The $T1$ relaxivity of Gd-DTPA may not be the same in blood plasma and tissue [20]. This, if confirmed *in vivo*, would significantly complicate tracer kinetic modeling using MR data.
- Debate surrounds the issues of water exchange; whether a single $T1$ (or $T2$) is an appropriate measure of Gd-DTPA concentration [21, 22]. This remains a fertile area of study.
- Numerous additional issues must be considered. Fitting complex models to limited data requires careful interpretation [23]. Measures of tracer kinetic parameters need to be corrected for tissue density (if quoted per g) and hematocrit. This can be significantly lower at the capillary level than systemically [24].

5. Applications

- Dynamic susceptibility techniques are now standard in the field of neuroradiology. In particular, they provide a frontline tool in the assessment of stroke and other vascular abnormalities of the brain [25].
- $T1$ DCE-MRI techniques are particularly popular in oncological imaging. More recently they have found a niche in the field of drug development [26].
- Another functional application of tracer kinetic modeling is the assessment of glomerular filtration rate (GFR) [27]. Gd-DTPA is filtered in the same way as many radioisotope markers of GFR and can be studied as part of a comprehensive renal exam [28].
- More advanced techniques employing distributed parameter models are now transferring from the fields of PET and CT into DCE-MRI [29]. While still far from the clinical mainstream, they show promise for the future [19].

Recommended Reading

Books:

G.J.P. Parker and A.R. Padhani
 T1-weighted dynamic contrast-enhanced MRI
In: Quantitative MRI of the brain (Ed, Tofts, P. S.)
 John Wiley & Sons, pp. 341-364 (2003).

A. Jackson, D.L. Buckley, G.J.M. Parker, Editors.
 Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology
 Springer-Verlag – Medical Radiology Series (2005).

Review articles:

P.S. Tofts, Modeling tracer kinetics in dynamic Gd-DTPA MR imaging
J Magn Reson Imaging **7**:91-101 (1997)

A.M. Peters, Fundamentals of tracer kinetics for radiologists
Brit J Radiol **71**:1116-1129 (1998)

F. Calamante et al., Measuring cerebral blood flow using magnetic resonance imaging techniques
J Cereb Blood Flow Metab, **19**, 701-735 (1999).

References

- Weinmann, H. J., Laniado, M. and Mutzel, W. (1984) Pharmacokinetics of Gd-DTPA/dimeglumine after intravenous injection into healthy volunteers *Physiological Chemistry and Physics and Medical NMR*, **16**, 167-172.
- Calamante, F., Thomas, D. L., Pell, G. S., Wiersma, J. and Turner, R. (1999) Measuring cerebral blood flow using magnetic resonance imaging techniques *J Cereb Blood Flow Metab*, **19**, 701-735.
- Kuikka, J. T., Basingthwaite, J. B., Henrich, M. M. and Feinendegen, L. E. (1991) Mathematical modeling in nuclear-medicine *European Journal of Nuclear Medicine*, **18**, 351-362.
- Ostergaard, L., Weisskoff, R. M., Chesler, D. A., Gyldensted, C. and Rosen, B. R. (1996) High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. 1. mathematical approach and statistical analysis *Magn Reson Med*, **36**, 715-725.
- Zierler, K. L. (1962) Theoretical basis of indicator-dilution methods for measuring flow and volume *Circ.Res.*, **10**, 393-407.
- Zierler, K. L. (1965) Equations for measuring blood flow by external monitoring of radioisotopes *Circ.Res.*, **16**, 309-321.
- Tofts, P. S., Brix, G., Buckley, D. L., Evelhoch, J. L., Henderson, E., Knopp, M. V., Larsson, H. B., Lee, T. Y., Mayr, N. A., Parker, G. J., Port, R. E., Taylor, J. and Weisskoff, R. M. (1999) Estimating kinetic parameters from dynamic contrast-enhanced T1-weighted MRI of a diffusable tracer: Standardized quantities and symbols *J Magn Reson Imaging*, **10**, 223-232.
- Larsson, H. B. W., Stubgaard, M., Frederiksen, J. L., Jensen, M., Henriksen, O. and Paulson, O. B. (1990) Quantitation of Blood-Brain Barrier Defect by Magnetic Resonance Imaging and Gadolinium-DTPA in Patients with Multiple Sclerosis and Brain Tumors *Magn Reson Med*, **16**, 117-131.
- Tofts, P. S. and Kermode, A. G. (1991) Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts *Magn Reson Med*, **17**, 357-367.
- Brix, G., Semmler, W., Port, R., Schad, L. R., Layer, G. and Lorenz, W. J. (1991) Pharmacokinetic parameters in CNS Gd-DTPA enhanced MR imaging *J Comput Assist Tomogr*, **15**, 621-628.

11. Larsson, H. B. W., Fritz-Hansen, T., Rostrup, E., Sondergaard, L., Ring, P. and Henriksen, O. (1996) Myocardial perfusion modeling using MRI *Magn Reson Med*, **35**, 716-726.
12. Fritz-Hansen, T., Rostrup, E., Larsson, H. B., Sondergaard, L., Ring, P. and Henriksen, O. (1996) Measurement of the arterial concentration of Gd-DTPA using MRI: a step toward quantitative perfusion imaging *Magn Reson Med*, **36**, 225-31.
13. Zhu, X. P., Li, K. L., Kamaly-Asl, I. D., Checkley, D. R., Tessier, J. J., Waterton, J. C. and Jackson, A. (2000) Quantification of endothelial permeability, leakage space, and blood volume in brain tumors using combined T1 and T2* contrast-enhanced dynamic MR imaging *J Magn Reson Imaging*, **11**, 575-85.
14. Kiselev, V. G. (2001) On the theoretical basis of perfusion measurements by dynamic susceptibility contrast MRI *Magn Reson Med*, **46**, 1113-22.
15. Wirestam, R., Andersson, L., Ostergaard, L., Bolling, M., Aunola, J. P., Lindgren, A., Geijer, B., Holtas, S. and Stahlberg, F. (2000) Assessment of regional cerebral blood flow by dynamic susceptibility contrast MRI using different deconvolution techniques *Magn Reson Med*, **43**, 691-700.
16. Buckley, D. L. (2002) Uncertainty in the analysis of tracer kinetics using dynamic contrast-enhanced T1-weighted MRI *Magn Reson Med*, **47**, 601-606.
17. Johnson, G., Wetzell, S. G., Cha, S., Babb, J. and Tofts, P. S. (2004) Measuring blood volume and vascular transfer constant from dynamic, T*(2)-weighted contrast-enhanced MRI *Magn Reson Med*, **51**, 961-968.
18. Sahani, D. V., Kalva, S. P., Hamberg, L. M., Hahn, P. F., Willett, C. G., Saini, S., Mueller, P. R. and Lee, T. Y. (2005) Assessing tumor perfusion and treatment response in rectal cancer with multisection CT: initial observations *Radiology*, **234**, 785-92.
19. Buckley, D. L., Roberts, C., Parker, G. J., Logue, J. P. and Hutchinson, C. E. (2004) Prostate Cancer: Evaluation of Vascular Characteristics with Dynamic Contrast-enhanced T1-weighted MR Imaging--Initial Experience *Radiology*, **233**, 709-15.
20. Stanisz, G. J. and Henkelman, R. M. (2000) Gd-DTPA relaxivity depends on macromolecular content *Magn Reson Med*, **44**, 665-667.
21. Landis, C. S., Li, X., Telang, F. W., Coderre, J. A., Micca, P. L., Rooney, W. D., Latour, L. L., Vetek, G., Palyka, I. and Springer, C. S. (2000) Determination of the MRI contrast agent concentration time course in vivo following bolus injection: Effect of equilibrium transcytolemmal water exchange *Magn Reson Med*, **44**, 563-574.
22. Larsson, H. B. W., Rosenbaum, S. and Fritz-Hansen, T. (2001) Quantification of the effect of water exchange in dynamic contrast MRI perfusion measurements in the brain and heart *Magn Reson Med*, **46**, 272-281.
23. Jerosch-Herold, M., Wilke, N., Wang, Y., Gong, G. R., Mansoor, A. M., Huang, H., Gurchumelidze, S. and Stillman, A. E. (1999) Direct comparison of an intravascular and an extracellular contrast agent for quantification of myocardial perfusion *International Journal of Cardiac Imaging*, **15**, 453-464.
24. Desjardins, C. and Duling, B. R. (1987) Microvessel hematocrit: measurement and implications for capillary oxygen transport *Am J Physiol*, **252**, H494-503.
25. Schaefer, P. W., Romero, J. M., Grant, P. E., Wu, O., Sorensen, A. G., Koroshetz, W. and Gonzalez, R. G. (2002) Perfusion magnetic resonance imaging of acute ischemic stroke *Semin Roentgenol*, **37**, 230-6.
26. Laking, G. R., West, C. M., Buckley, D. L., Matthews, J. and Price, P. M. (2006) Imaging vascular physiology to monitor cancer treatment *Critical Reviews in Oncology/Hematology*, **In Press**.
27. Hackstein, N., Heckrodt, J. and Rau, W. S. (2003) Measurement of single-kidney glomerular filtration rate using a contrast-enhanced dynamic gradient-echo sequence and the Rutland-Patlak plot technique *J Magn Reson Imaging*, **18**, 714-725.
28. Schoenberg, S. O., Essig, M., Bock, M., Hawighorst, H., Sharafuddin, M. and Knopp, M. V. (1999) Comprehensive MR evaluation of renovascular disease in five breath holds *J Magn Reson Imaging*, **10**, 347-356.
29. Henderson, E., Sykes, J., Drost, D., Weinmann, H. J., Rutt, B. K. and Lee, T. Y. (2000) Simultaneous MRI measurement of blood flow, blood volume, and capillary permeability in mammary tumors using two different contrast agents *J Magn Reson Imaging*, **12**, 991-1003.