Modeling and Quantitative Analysis:

From Simple to Complex

David L Buckley, PhD - Division of Medical Physics, University of Leeds, Leeds, U.K.

Outline

1. Tracer kinetics principles – the building blocks
2. Simple – 1 compartment model
3. More complicated - 2 compartment models
4. Complex – distributed parameter and tissue-specific models

1. Tracer Kinetic Modeling

- Extracellular agents (such as Gd-DTPA[1]) accumulate in the interstitium of many tissues (e.g. muscle) but do not cross the normal blood-brain-barrier.
- Functional information may be obtained by treating Gd-DTPA as a tracer and following its kinetics (as opposed to the conventional 'static' 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.
- 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 perfusion 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.
- Transport of Gd-DTPA can be described using a number of parameters:
- Perfusion, F (or plasma perfusion, F_p); capillary permeability-surface area product, PS (a measure of vessel leakiness); plasma volume, v_p and interstitial volume, v_e.
- 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.

[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.

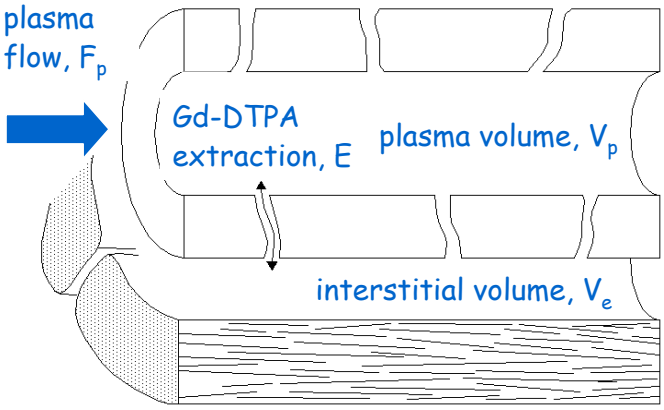


Fig. 1 - The basic capillary-tissue exchange unit (after Kuikka [2]). Two spaces (plasma and interstitium) are separated by a semi-permeable membrane. The plasma volume is replenished by flow of contrast agent and a fraction of this, E, is extracted to the interstitium in a single pass.

- 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 plasma of the feeding artery) with the tissue impulse residue function (IRF), the theoretical response in the tissue to an infinitely tight unit bolus [3].

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

  where $C_t(t)$ is the tissue concentration of Gd-DTPA, F_p is plasma perfusion, 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. This won't be considered further.
  - 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.

2. The one compartment model

- A compartment is defined as a well-mixed region of space, so that the tracer has a constant concentration throughout the volume. It is characterized by a monoexponential IRF.
- The most common models used to describe R(t) in dynamic contrast-enhanced (DCE)-MRI studies today [4] [5] [6] assume a mono-exponential form for R(t):

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

  where K^{trans} is the volume transfer coefficient [7].
- While simple and straightforward to use interpretation of the resulting parameter K^{trans} can be a challenge. It depends upon assumptions made about the tissue status; K^{trans} may reflect F_p, it may reflect PS. More generally, it reflects a variable mixture of the two.

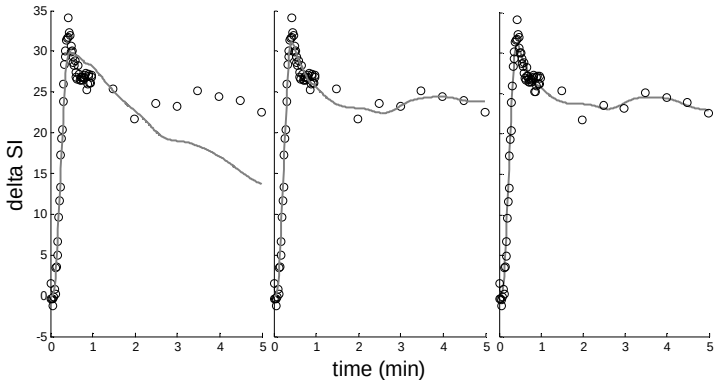
3. Two compartment models

- If the contribution of intravascular Gd-DTPA is thought to be significant, a second compartment is often added to the model. The simplest approach is often employed (e.g. [8]):

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

- However, like the use of K^{trans}, there are implicit assumptions in such an approach. In this case, the plasma transit time is assumed to be negligible (shorter than the data sampling interval). There is evidence to suggest that this is often not the case [9,10].
- If this assumption is relaxed the 2 compartment model has a biexponential IRF (see the notes from Dr. Koh's talk) and F_p and PS may be estimated separately [11]. Nevertheless, the data acquired may not have the necessary temporal characteristics or contrast-to-noise to provide precise estimates of the increasing number of parameters that result from the use of the 2 compartment model [12].
- It is possible to use statistical techniques to help in the selection of an appropriate model [10,13,14]. See Fig. 2.

Fig. 2 - The problem of model selection. DCE-CT data from a bladder tumour are poorly described by the 2-parameter 1-compartment model (left) and well described by a 4-parameter 2-compartment model (right). However, an F-test tells us that 3 parameters are sufficient to fit the data appropriately (centre).



4. Other models

- The 'well-mixed' assumption of a compartment, particularly with respect to the vascular space, can be avoided through use of distributed parameter models. These are now transferring from the fields of PET [15] and CT [16] into DCE-MRI [17]. While they have had limited exposure in the clinic to date, they show promise for the future [18,19].
- Measurement of liver perfusion is complicated by the organ's dual blood supply (hepatic artery and portal vein). However, techniques have been developed to model this system [6, 7]. Hepatic perfusion is described in terms of 3 parameters, an arterial blood flow, a portal blood flow and a liver mean transit time.
- Another functional application of tracer kinetic modeling is the assessment of glomerular filtration rate (GFR) [20]. 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 [21]. This is considered further in the talk by Dr. Bokacheva.

Recommended Reading

Books:

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)

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