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Chapter 111: The early days of modelling contrast agent kinetics

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1. First encounter with DCE-MRI; the stimulus to model multiple sclerosis data

In 1985 I was appointed as a 'new blood' lecturer at the Institute of Neurology, Queen Square, London, in the Multiple Sclerosis (MS) research group headed by the late Ian McDonald, the leading MS clinician in the UK at the time. A physicist by training, with a PhD in Nuclear Magnetic Resonance of solid helium at low temperatures, I was thrown into a clinical research environment, with the brief to develop the newly installed 'NMR imaging technology'. My passion had always been to use physics to contribute to human health, so this suited me perfectly. The UK Multiple Sclerosis Society had the previous year funded a 0.3T Picker MRI machine, and a whole range of techniques to study the biology of developing MS lesions was being developed.

In the next few years Schering AG, a company based in Berlin, produced the first MRI contrast agent (then called Gd-DTPA, now Magnevist), and Queen Square was one of the first centres to use it for MS imaging. Previous work at Hammersmith Hospital by Ian Young and colleagues had shown that MS lesions, having a defective Blood-Brain Barrier (BBB), would enhance after injection of the compound.

> *'Understanding the time course and degree of BBB (Blood-Brain Barrier) damage in plaques may give quantitative indices with which we can assess the efficacy of drugs aiming to correct BBB disturbances (e..g. steroids) and may prove to be of use in assessment of treatment in MS'.*[2] [box 1]

Allan Kermode was a curious and dynamic trainee neurologist, the son of an Australian surgeon in Perth; he asked me how long after injection of the contrast agent should he image to stand the best chance of seeing image signal enhancement. This provoked a creative discussion in which I suggested trying a range of times in order to optimise the procedure. I thought no more about it, at the time being preoccupied with writing up previous work on quantification in spectroscopy.

> *"When I started at Queen Square I was very junior. Perhaps being somewhat uninformed about existing dogma in MS was quite helpful in some ways and made me look at everything with a fresh view. John Prineas had seen large extracellular spaces in MS lesions; however everyone thought they were artefacts of the histology. The combination of dynamic MRI scanning with T_2 decay studies (analysis into two compartments) changed forever the way pathologists thought about lesions. These lesions are the 'black holes' seen in T_1-weighted imaging".*
>
> Personal communication from Allan Kermode (2012). He reports his conversations with John Prineas, the principle MS pathologist at the time. [box 2]

A week later Kermode came back to me with datasets from two patients showing very different enhancement patterns. In each he had measured the mean signal in a region-of-interest over periods of time up two nearly two hours (see fig 111.1). This was many years before ethical considerations came to slow down clinical research. The patients had come out of the scanner for a break during the long examination, and good manual repositioning by the radiographer (technologist) gave datasets in which the portions collected before and after the break were spatially registered. Imaging was slow (a single slice inversion recovery sequence gave data every 6 min or so, a lesson in patience compared to modern acquisition – see chapter 31).

This provoked a firestorm in my brain. For weeks I could think of nothing else. What was driving this process? What biological information was lurking underneath the image data? Weinmann at Schering had measured the arterial plasma concentration of Gd-DTPA using blood samples every 5 minutes or so[1], and these were fitted to a biexponential model. The notion of water compartments had been revealed to me as part of my exposure to technetium Tc99m

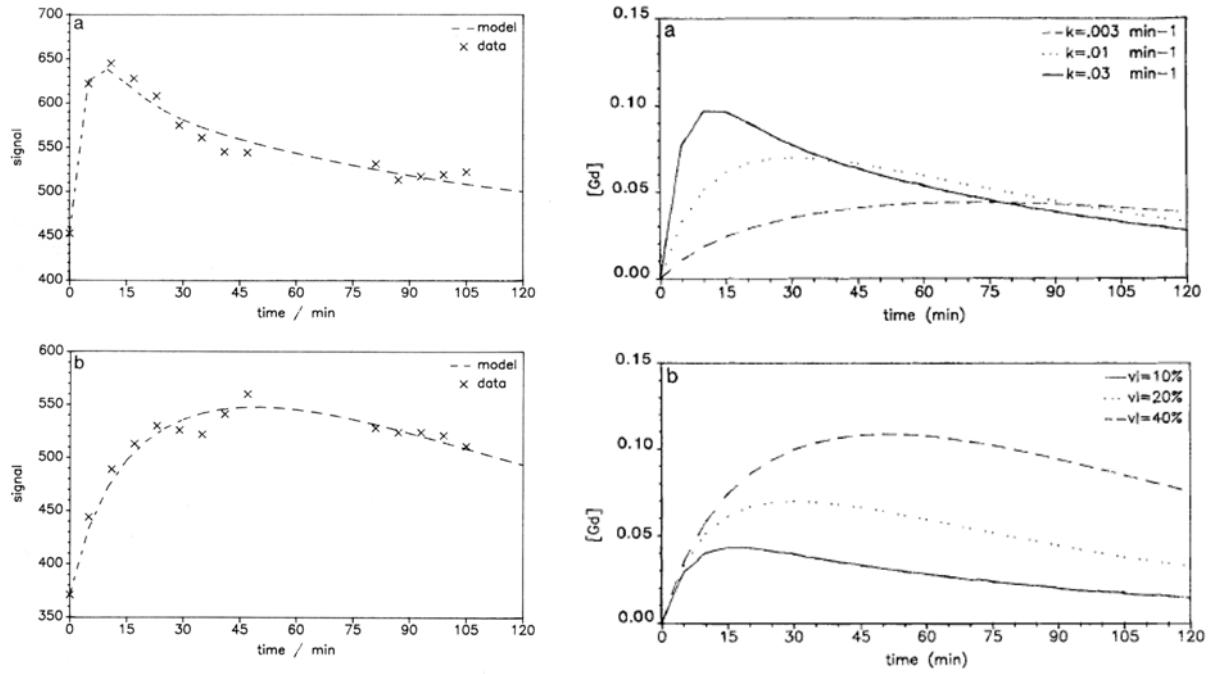
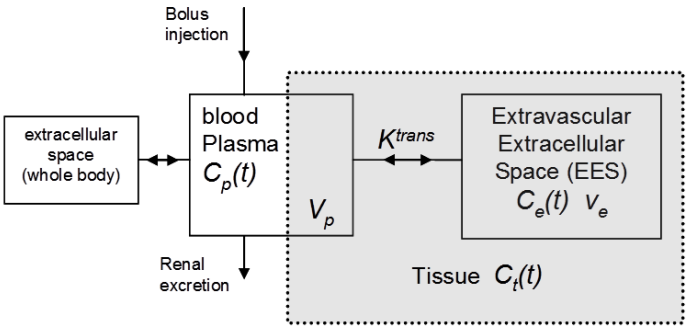


Figure 111.1: Left hand: Early DCE data[5] a) rapidly enhancing MS lesion K^{trans}=0.050 min^{-1}, v_e=21%; b) slowly enhancing lesion K^{trans}=0.013 min^{-1}, v_e=49%). Right hand: model enhancement curves[5] a) fixed v_e =20%, varying K^{trans} (k in the plot) showing how initial slope depends on K^{trans} ; b) fixed K^{trans} =0.01 min^{-1} varying v_e (v_i in the plot), showing how increased v_e gives increased and delayed peak enhancement

imaging at Hammersmith Hospital. I realised that the flow of Gd from the plasma through the leak in the endothelium to the extravascular space was governed by a mathematical differential equation, and that this related to permeability as measured for many years in semipermeable membranes by physiologists. Solving differential equations had been in my physics degree at Oxford University. Finally in a Eureka moment, during a day working at home, at a place high on the roof terrace of my attic apartment that I still remember, it all fell into place. It was clear how to model the signal enhancement as a function of time (see fig 111.2). (Much later on I because aware of the pharmacokinetic work already carried out by others – see section 3).

I rushed to the newly installed Sun Microsystems computer at Queen Square to set this up in Fortran (the programming language of the time).



$$v_e \frac{dC_e}{dt} = K^{trans}(C_p(t) - C_e(t))$$

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(\tau) e^{-k_{ep}(t-\tau)} d\tau$$

$$k_{ep} = K^{trans} / v_e$$

Figure 111.2: top: compartment model used in original model[5] (redrawn to use consensus[31] names K^{trans} v_e and explicit intravascular contribution v_p); bottom: key pharmacokinetic equations[22]: K^{trans} and v_e are defined in fig 111.4; C_p C_e and C_t are the Gd concentrations in plasma, EES and tissue.

By altering the transfer constant K^{trans} and the size of the extravascular extracellular space v_e (see figure 111.1) a set of model enhancement curves could be produced that really did have the behaviour of the data that Kermode had given me. There was a peak in the enhancement, and the size and time of that peak could be changed by altering the two driving physiological parameters K^{trans} and v_e. By adjusting these, the two datasets could be fitted with no apparent systematic error. Programming in the least squares fitting gave an automated process where the curves would lie satisfyingly close to the data.

The value of K^{trans} (at first called k, and in MS equal to the permeability surface area product per unit volume of tissue)) was reasonably close to values measured by physiologists in comparable tissues. The lowest observed value for the extracellular (interstitial) space volume fraction v_e (21%) was a little more than the normal value (about 16%). In the slowly-enhancing lesion the value of 49% was considered implausibly high by the clinicians involved in experimental animal studies.

Allan Kermode's abstract at SMRM in 1988 prepared the way[2]. My poster at Los Angeles in February 1989 at the 7th annual meeting of the Society for Magnetic Resonance Imaging (SMRI; now part of the International Society of Magnetic Resonance in Medicine - ISMRM) showed the essence of the method (fig 111.3)[3]. I did not go personally; when Allan returned from the meeting he reported that he had met someone who was measuring T_1 as a function of time after injection of Gd-DTPA in MS lesions, and that I had better publish my work quickly!

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MEASUREMENT OF BLOOD BRAIN BARRIER PERMEABILITY USING GD-DTPA SCANNING
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Introduction: Gd-DTPA can qualitatively visualise the activity of multiple sclerosis (MS) lesions. A quantitative model of dynamic scanning, i.e. of signal enhancement vs time, has been developed, based on compartmental analysis. Gd-DTPA tracer distributes into 3 compartments: a) plasma b) whole body extra-cellular space (ecs) and c) lesion leakage space within the brain. Two parameters relevant to the natural history of the MS lesion are estimated: 1) ki, the blood brain barrier (BBB) permeability surface area product per unit volume, or influx constant and 2) vl, the leakage space per unit volume of tissue ($0 \le vl < 1$).

Theory: The mathematical model involves the following steps:
1) Flow of tracer from capillary plasma to the lesion leakage space is

$$vl\ dCl/dt = ki(Cp-Cl) \quad [1]$$

where Cp and Cl are [tracer] in plasma and in lesion leakage space.
2) Plasma concentration Cp(t) is known to decay biexponentially
3) Solution of equation [1] gives a triexponential for Cl(t)
4) The dependence of T1 and T2 on Cl, i.e. [Gd] is known.
5) Dependence of IR or SE signal on T1 and T2 is known.
By adjusting ki and vl, early- or late-enhancing curves can be simulated, as seen in practice. These curves can be fitted to measured curves, with ki and vl as free parameters.

Method: The patient is scanned to determine spin density and T1 of the lesion. Gd-DTPA is injected and repeated IR scans made.

Results: An early enhancing lesion (plateau at 10min) gave ki=0.056min-1; vl=0.18. A late enhancing lesion (45min) gave ki=0.012min-1; vl=0.41. The values of vl are in broad agreement with measurements of ecs made using multi-echo biexponential T2 analysis.

Fig 111.3: Society of Magnetic Resonance Imaging 1989 abstract[3]. In later work[31] ki and vl became K^{trans} and v_e.

At the August meeting of the SMRM in Amsterdam in the same year there were abstracts with remarkably similar titles from myself and Henrik Larsson, a Danish clinician with a strong physiological background. He was the mysterious person at SMRI that Allan had told me about; we soon became friends. I proposed we write a joint note to reconcile the two approaches. Our own independent work[4, 5] was published, then the reconciliation[6] .

> *'First we describe dynamic scanning, which enables a curve of signal enhancement versus time to be produced, with a consequent differentiation between lesions that enhance with different time courses. Second we describe a quantitative analysis of the dynamic curve which enables absolute measurements of blood-brain barrier permeability and leakage space to be made'* [5] [box 3]

Histology studies showed that MS lesions could indeed have vast extracellular spaces (the 'open lesions'). Modelling of transverse magnetisation decay curves (where the signal from intracellular and extracellular water can be distinguished) showed that chronic lesions could have extracellular spaces up to 87% in MS[7], and that the large v_e estimates from DCE-MRI were indeed plausible! When asked what aspect of MRI physics I should concentrate on, Ian McDonald wisely pronounced: "well the quantitation does seem rather interesting".

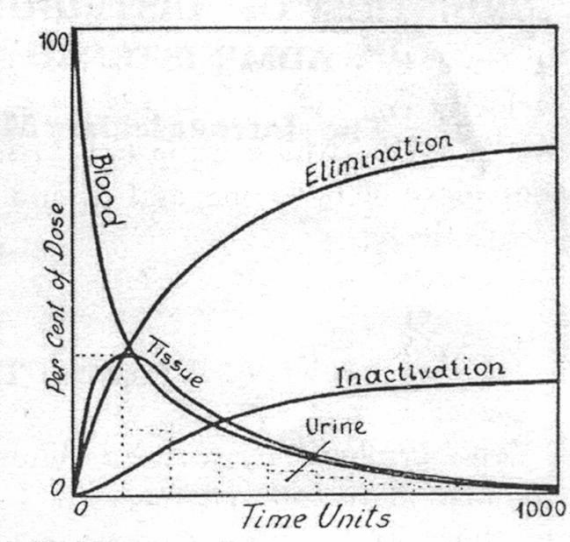
2. The first quantification in MR – absolute metabolite concentrations using spectroscopy

My first opportunity to quantify in biomedicine had been in the late 1970's using ^{31}P spectra, before ^{1}H MRI had got started. This was my first taste of how the application of quite specialised techniques from physics or mathematics could bring unexpected advances in biomedicine. A review was generously invited by John Griffiths, the editor of the newly formed journal NMR in Biomedicine; this appeared as its first article[8]. The discovery that quantification using medical imaging is a fertile ground for innovation by physicists later inspired the first book on quantification in MRI, focused on the brain[9]; recently a book on quantitative MRI in cancer has appeared[10].

3. Early pharmacokinetics by physiologists: Teorell, Kety and Patlak

Torsten Teorell has been called the father of pharmacokinetics[11]. The papers from this physiologist at Uppsala University (Sweden) published in 1937 in a French journal on 'The kinetics of distribution of substances administered to the body' are completely relevant to modern DCE modelling[12, 13]. He considers blood flow, blood volume and permeability. Transport from the blood is described by a rate constant; differential equations

are produced and solved[11]. The concepts of mass conservation (used by Fick the previous century) and differential equations (developed by Isaac Newton and others in the 17th century) led naturally to this work.



Tissue uptake and clearance curves by Teorell in 1937[13]. Teorell gave an equation: 'amount across boundary in [unit time] = permeability coefficient x concentration difference'. He made several numerical calculations and remarked that 'a marked change in the absorption properties may bring about a marked change in the magnitude and duration of the .. tissue concentration curves; [this] may have bearings upon practical therapeutics'.

According to Paalzow, who held the chair of pharmaco-kinetics at Uppsala University in 1995, Teorell's work was forgotten, and nothing really happened for more than 25 years, when US scientists rediscovered his work[11]. [box 4]

From the post-war University of Pennsylvania (USA) Seymour Kety MD published an influential review[14] in 1951 which shows his awareness of Teorell's work. He gives an equation from Teorell's work and discusses whether gas transport is diffusion, permeability or blood-flow limited. This equation is $dQ/dt=k(Q/V-C_b)$, where Q is an amount of substance diffusing into the blood, k is a permeability coefficient, V is a volume and C_b is the concentration in blood. This equation is similar to the first equation figure 111.2, although in a rather different context. Kety worked in a department of physiology and pharmacology; the context was the uptake of inert gas from the lung into blood capillaries, which is considered to be blood flow-limited. The 'Kety model' was widely taken up, particularly in PET. In MRI the model described in fig 111.2 is often described as a 'Kety model'; however Kety appears not to have published a general (convolution) solution to the differential equation. Moreover, to analyse imaging data requires extra equations related to the physiological behaviour of the contrast agent and its effect on imaging signal. Teorell made a strong contribution to pharmacokinetic modelling; history has still to decide which name or names will be used for our current DCE models – the 'Teorell model'?

At the University of Copenhagen (Denmark) Crone in the 1960's, using dogs, measured the permeability of the blood capillaries to an injected agent in various organs[15].

Clifford Patlak was also influential. A mathematician at the National Institute of Mental Health, Bethesda, USA, from 1975 onwards he carried out important work on compartments[16 17]. He solved an important problem. Fitting of nonlinear equations to data was almost impossible in this era before the widespread availability of computing. For a short time after contrast agent administration there is no backflow from the extracellular space to the plasma; for this period the model can be simplified, and the data can be fitted to the model manually[18]. His 'graphical evaluation' method is still used today. In 1978 Ohno et al[19] from Baltimore and from Patlak's department at Bethesda published a model that contains all the pharmacokinetic essentials of later MRI-based work. This was to measure blood-brain barrier permeability in the rat using a ^{14}C tracer.

4. Diffusion of the MRI model into cancer imaging; building a global consensus

In the early 1990's, although the MRI DCE model had been published as 'part 1: fundamental concepts' in 1991[5], it was not taken up by the MS imaging community (and 'part 2: practical aspects' was never written!). However it was clear from the annual ISMRM meetings that the cancer imaging community was starting to use DCE-MRI, and that they were in danger of re-inventing the wheel. For several years I would have crucial chance interactions with radiologists working in cancer, who gave me continuing encouragement. Anwar Padhani, then at the Institute of Cancer Research (ICR), London would point out some of the first DCE imaging in cancer, and Michael Knopp, then in Heidelberg was always enthusiastic. These encounters were often in the vast ISMRM poster jungle. Bruce Berkovitz's persistence in tracking me through the same jungle enabled me to show that the model would fit cancer data (in breast)[20] and it became clear how sensitive the enhancement is to the tumour T_1 value (although this had been hinted at earlier[5]). I gave a seminar at the ICR which provoked Martin Leach and David Collins into using DCE for cancer trials.

I started to shamelessly advertise my work; asking questions at oral presentations, and contacting poster presenters, seeking to accelerate the diffusion

process. Some years I systematically went through the meeting program to find the presentations using DCE-MRI and then emailed my work to the presenter, stating that they might find my model useful!

Michael Knopp organised a series of key meetings in Heidelberg. Here I met Gunnar Brix, who had also published in this area, coming from a cancer background[21]. William Yuh, a radiologist from Iowa, then editor of JMRI, was also a key encouraging figure. He virtually instructed me to write a review article[22] on DCE modelling; this reconciled and extended the three almost contemporary approaches of Larsson[4], Brix[21] and myself[5], and reported other relevant modelling that had not been apparent to me earlier on.

Three refinements were added in this article[22], as a result of discussion with cancer researchers. The v_p term was added (figure 111.2), to describe the contribution of intravascular Gd, which had been ignored in MS but could be considerable in tumours. It was recognised that the AIF could have an arbitrary numerically-defined shape, and that a convolution would better describe its effect (figure 111.2). Whether Gd leakage is dominated by permeability or blood flow (perfusion) was clarified (see fig 111.4 caption and chapter 44). In MS permeability is usually low and hence it dominates leakage; conversely in cancer permeability may be high in which case leakage is then flow-limited. The paper reviewer correctly pointed out that v_e was the *extravascular* extracellular space (previously we had just called it the extracellular space), and hence the abbreviation EES came into use in MRI (in CT this term had already been in use for 5 years! [23]).

In an era before the internet and easy access to scientific journals, it was hard to be aware of relevant work carried out in other imaging fields. In the field of nuclear medicine, Tc99m-DTPA had been available since 1971[24]; however no resulting measurements of BBB transfer seem to exist. Using PET, in 1987 in Italy the blood-brain barrier permeability of 68Ga-EDTA (a contrast agent with similar pharmacokinetics to the modern MRI and CT agents) was measured[25] using the Patlak method. The complete model with backflow was also used [26 27]. More detail on early PET pharmacokinetics is given elsewhere [23 28].

CT was able to give blood volume soon after its invention in the 1970's [29 30] but the modelling could not give BBB leakage. Only in 1992 were the first measurements of blood-brain barrier (BBB) permeability in humans published by the group of Ting-Yim Lee at London Ontario (Canada) using the contrast agent Iopamidol [23]. The inspiration for the modelling is from Patlak, with an awareness of the PET work. The mathematics is close to that developed in the MRI community, and Lee was a co-author on the consensus paper[31] that followed (see below).

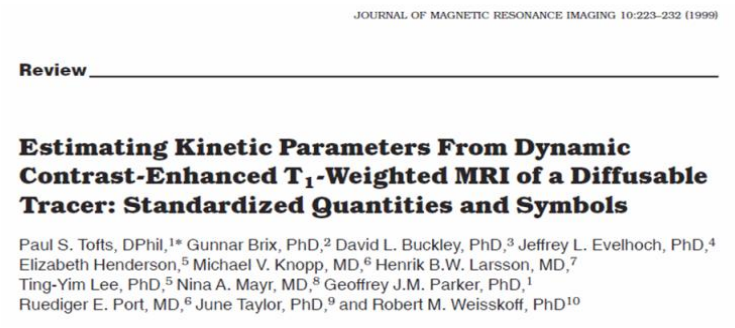
Back in the world of MRI, in the mid-1990's there was a half-day meeting in the USA organised by NCI (National Cancer Institute) at the same time as an ISMRM meeting (probably in Washington or Philadelphia), on the subject of DCE-MRI in cancer. The field seemed disorganised; North American investigators were not aware of the European work (I believe Gd-DTPA came to the US after Europe and Japan). After I spoke briefly, Robert Gillies (who I did not know but was a senior figure connected to the NCI) came to me and said I should exercise some leadership in the field; this was a message I took to heart.

"I do remember that meeting. At the time, I was an Associate Professor of Biochemistry at University of Arizona, and was an interested bystander during the early DCE debates. My involvement with this primarily came though association with the Cancer MR subgroup, where interpretation of DCE data was pretty hotly debated. (Personally, I was more focused on developing diffusion MRI at the time). I remember at that time that you emerged as a thought leader in this area. I became aware of your work and your approaches primarily through my friends and colleagues (Bhujwalla, Evelhoch, Padhani). While I do enjoy a good debate, it seemed to me at the time that the discussions on our side of the pond were fruitless, as they were occurring without your involvement, and no consensus opinion was emerging. It was on this backdrop that I approached you at that NCI meeting, and as you said, implored you to take the lead to organize further discussions with the goal of achieving a consensus approach that the rest of us could rely on. Evelhoch was standing there and we were able to bring Dan Sullivan in to the conversation. He was the senior leader at NCI (Head of the Cancer Imaging Program) who made the subsequent meeting [in Heidelberg] *possible. As I was not expert in DCE (just an interested bystander), I did not attend this subsequent meeting. I do believe, however, that that meeting and its white paper [*i.e. reference[31]] *were instrumental in developing more unified approaches to the interpretation of DCE data, which I use to this day."*

Personal communication to the author by email from Robert Gilles May 30th 2012 concerning the NCI meeting held in the mid 1990's. This shows the importance of building and funding connections at a key time in the evolution of the modelling technology applied to DCE cancer imaging. [box 5]

From a further meeting in Heidelberg (Germany) with Yuh and Knopp came the impetus to produce a consensus paper. The variety of models and terms for the quantities was holding back the technique from being used clinically. The major world players in the field of DCE-MRI would be invited to sign up to a consensus paper in which all authors agreed to use the standard terms (see fig 111.4). Anyone who did not sign up would be outside the consensus, facing the wrath of paper reviewers. The mathematics were reconciled, with detailed help from Rudi Port a

physiologist who I met in Heidelberg. Agreement was reached on standard terms, the names K^{trans} , v_e and k_{ep} were born (see fig 111.4 caption). The terms r_1 (relaxivity) and T_{10} (native T_1) were also agreed.



JOURNAL OF MAGNETIC RESONANCE IMAGING 10:223–232 (1999)

Review

Estimating Kinetic Parameters From Dynamic Contrast-Enhanced T_1-Weighted MRI of a Diffusable Tracer: Standardized Quantities and Symbols

Paul S. Tofts, DPhil,[1*] Gunnar Brix, PhD,[2] David L. Buckley, PhD,[3] Jeffrey L. Evelhoch, PhD,[4] Elizabeth Henderson,[5] Michael V. Knopp, MD,[6] Henrik B.W. Larsson, MD,[7] Ting-Yim Lee, PhD,[5] Nina A. Mayr, MD,[8] Geoffrey J.M. Parker, PhD,[1] Ruediger E. Port, MD,[6] June Taylor, PhD,[9] and Robert M. Weisskoff, PhD[10]

We describe a standard set of quantity names and symbols related to the estimation of kinetic parameters from dynamic contrast-enhanced T1-weighted magnetic resonance imaging data, using diffusable agents such as gadopentetate dimeglumine (Gd-DTPA). These include a) the volume transfer constant K^{trans} (min^{-1}); b) the volume of extravascular extracellular space (EES) per unit volume of tissue v_e ($0< v_e < 1$); and c) the flux rate constant between EES and plasma k_{ep} (min^{-1}). The rate constant is the ratio of the transfer constant to the EES ($k_{ep} = K^{trans}/ v_e$). Under flow-limited conditions K^{trans} equals the blood plasma flow per unit volume of tissue; under permeability-limited conditions K^{trans} equals the permeability surface area product per unit volume of tissue. We relate these quantities to previously published work from our groups; our future publications will refer to these standardized terms, and we propose that these be adopted as international standards.

Fig 111.4: The JMRI 1999 consensus paper[31].title and abstract showing the key agreed quantities:

The consensus paper[31] appeared in JMRI in 1999; armed with this I would (exercising leadership!) fearlessly approach any presenter at SMRM who dared to use their own terms and insist that they conform. By 2013 this paper had been cited over 1000 times. Having agreed on the modelling definitions, and given the clinical users a well-defined tool, the clinical applications started to flow. Martin Leach and Cancer Research UK led initiatives to promote K^{trans} as an agreed imaging biomarker to evaluate anti-angiogenic drug treatments in cancer [32] [33].

5. Recent advances in DCE modelling.

Bringing DCE imaging to the clinic enables it to be used more widely to benefit patients. Yet there are major costs in producing a push button (turnkey) system that requires little technical expertise. As research centres demonstrate the clinical usefulness of DCE-MRI, vendors become more willing to implement it on their platforms. Two major MRI-vendors now offer K^{trans} mapping, although the software is at an early stage. Several third parties offer dedicated software for fitting. The use of widely-available commercial spreadsheet software for fitting enables curves to be analysed conveniently on a personal computer[34].

Modelling has developed some more refined aspects in the quarter century since the initial work. In lesions with significant blood volume, the simple v_p term (figure 111.2) may not provide a good fit to the initial bolus transit peak[35] , and a more complex model of the vascular bed may be needed[36] [37]. If capillary permeability is high (i.e. leakage is flow-limited), then the vascular bed and EES will function as a single compartment [38, 39], and v_p and v_e cannot be determined separately, only their sum (see chapter 42). In necrotic tumours diffusion through the EES may limit and influence Gd concentration; at long times after injection non-vascularised tissue may enhance[40].

In CT the DCE imaging is called 'perfusion imaging', although it involves a degree of pharmacokinetic modelling (see chapter 34). CT and MRI use contrast agents with very similar pharmacokinetics. CT has a more clear relationship between the concentration of the contrast agent and the signal enhancement; with MRI repeated measurements can be made in controls to establish the reproducibility, and it can be used to study most patients. Thus cross-fertilisation between the two modalities could make important contributions; a reconciliation of MRI and CT models would advance the field enormously.

Access to renal data enabled the concepts to be tested and developed in a new arena. The complex and large vascular bed was best modelled by rather arbitrary response functions chosen heuristically (ideally constrained to have an initial flat portion), and evaluated using reproducibility as a main criterion[34]. Values of renal perfusion and filtration parameters in healthy volunteers agreed with published normal values. The influence on blood perfusion estimation of the reduced value of haematocrit in capillaries (compared to large vessels) was recognised; estimates of plasma perfusion (as distinct from blood perfusion) are more robust[34].

Within the imaging community it is now recognised that a good biomarker needs to have demonstrably good reproducibility (whilst still being sensitive to biological change); this enables smaller changes to be detected, or conversely in trials the effect can be seen in a smaller study. Some workers have measured reproducibility from repeated imaging [41] [34]; keeping models simple, with a minimum number of free parameters, contributes to a reduced variance in tissue parameter estimates[34]. Pharmacokinetic modelling is now ubiquitous (e.g. in Arterial Spin Labelling and ^{13}C) as a way of accessing quantitative physiological information.

We are living through a scientific and technical revolution that makes it possible to measure aspects of physiology in the living human body; DCE modelling is making an important contribution to this.

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