Multimodality Imaging of Tumor Angiogenesis:

Perfusion Modeling for Tumor Angiogenesis

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1. Introduction

When a tracer, such as Gd-doped or iodinated extracellular contrast, is introduced into the blood stream of a patient its transport through the vascular system, heart and lungs and eventual excretion via the kidneys is a well-established process [1,2]. At the level of the imaging voxel (for example, in the centre of a breast tumor) we can only speculate as to the precise nature of the tracer kinetics. We can, however, form a hypothesis. The tracer kinetic model helps us to formulate such a hypothesis, provides us with the opportunity to predict the behavior of the system and subsequently test our predictions [3]. With time, like most hypotheses, our models become more complex attempting to describe the system with greater realism.

The following syllabus contribution will briefly summarize several important tracer kinetic models used in body MRI and CT research and clinical practice, highlight the latest developments in the field and identify some important limitations of the techniques and sources of error inherent in their use.

2. Building blocks

The indicator-dilution technique developed from physiological studies dating back to the 19th century and the mathematical foundations of today’s models were laid in the late 1940s and early 1950s [4-6]. In the nuclear medicine community the field has matured and practitioners have employed sophisticated models in their analyses [7].

Many of these approaches contain a set of model building blocks (Fig. 1). For the purposes of this discussion the tissue may be said to be composed of plasma (vascular) and interstitial spaces separated by a semi-permeable endothelial cell layer (the capillary wall). Their fractional volumes, in ml/(ml tissue), are defined as \( v_p \) and \( v_e \), respectively. A third compartment, mainly intra-cellular space but also composed of membranes, fibrous tissues and so on, is present but usually excludes tracers. This discussion is limited to those models that incorporate capillary-tissue exchange and we may consider two principal exchange parameters: plasma flow, \( F_p \) measured in ml/min/ml tissue and capillary permeability-surface area product, PS measured in ml/min/ml tissue. A conversion to the common units of ml/min/g is achieved by the inclusion of the tissue density, g/ml [8] while a measure of whole blood volume and flow is obtained by multiplication by \( 1/(1 – \text{hematocrit}) \).
Fig. 1 – Tracer transport and exchange in tumors may be described using a set of basic building blocks. Flow (plasma flow, \( F_p \)); Shunt (flow where there is no exchange of nutrients with the tissue); Perfusion (nutritive flow); PS (permeability-surface area product); E (extracted fraction); VD* (volume of distribution – not all of the tissue volume is ‘available’ to the extracted tracer; in the case of most MRI and CT contrast agents this represents the interstitial volume, \( v_e \)). Modified from ref. [9].

The kinetic modeling of tracer distribution has a basis in the simple rate equation describing diffusive flux across a permeable membrane [10,11]. This is determined by the difference in concentration between two compartments that are separated by the membrane and the membranes permeability. For the case of transport across the capillary wall the flux is equal to \( PS(C_p - C_e) \), where \( P \) is the capillary permeability, \( S \) is the total effective surface area of the capillary wall and \( C_p \) and \( C_e \) are the concentrations of tracer in the plasma and interstitial spaces, respectively. In reality the concentrations of tracer in these compartments are not stable, the plasma concentration (and therefore capillary-tissue exchange) is dependent upon flow. The extraction fraction, \( E \), is the relative difference between arterial and venous concentrations of tracer and is defined as the fractional reduction of tracer in the plasma during its passage through the tissue [10]. The combined effect of these parameters is often summarized using the parameter \( K_{\text{trans}} \) [12] (see below).

3. Compartamental models

The tracer kinetic models used in many CT and most MRI studies to date are essentially based upon a modified version of Kety’s original one-compartment model in which the plasma input function is convolved with the tissue impulse response derived above to arrive at an estimate of the whole tissue concentration of tracer \( (C_t(t)) \):

\[
C_t(t) = K_{\text{trans}} \int_0^t C_p(t') \exp \left( -\frac{K_{\text{trans}}(t-t')}{{v_e}} \right) dt'.
\]  

(1)

The MRI techniques described in the early 1990s by both Larsson and Tofts follow this pattern [13,14]. Brix et al. used the same principles [15] and common to all three approaches is the


calculation of the rate constant $k_{ep} (= K_{trans}/v_e)$ [8]. The differences between these techniques are in the details of their individual measurement schemes. With baseline estimates of $T_1$ and independent estimates of $C_p(t)$, they broadly reduce to the same form [16]. All require dynamic imaging following the administration of tracer for a time period of a few minutes or more (until equilibrium between plasma and interstitial tracer concentrations is achieved). Absolute estimates of $K_{trans}$ can only be obtained when the dynamic imaging is accompanied by an estimate of baseline $T_1$ and a measurement of $C_p(t)$, the arterial input function (AIF).

A major limitation of such one-compartment models is the difficulty in interpreting the parameter $K_{trans}$. If the single compartment reflects $v_e$ alone (i.e. the vascular signal is negligible) and $F_p \gg PS$, the so-called permeability limited regime, then $K_{trans}$ reflects PS. Conversely, if $PS \gg F_p$ (the capillary wall presents almost no barrier to the tracer) then $K_{trans}$ reflects $F_p$ and the distribution volume is the sum of $v_e$ and $v_p$. How do we know, a priori, which (if either) regime applies? If the contribution to the signal from tracer in the vascular space, $v_p$, of the tissue is significant then a two-compartment model is needed. This has long been recognized in PET studies [17] and explicitly modeled in the popular Patlak approach to data analysis [18]. Measurement of an AIF becomes increasingly important and a number of investigators have developed methods to achieve this in animals [19] and humans [20]. A simple extension of equation 1 allows its incorporation:

$$C_i(t) = v_pC_p(t) + K_{trans}\int_0^t C_p(t') \exp\left(-\frac{K_{trans}(t-t')}{v_e}\right) dt'$$

(2)

This model spans the fields of PET, contrast-enhanced CT and MRI and represents a popular standard for tracer kinetic analysis. An interesting limiting case for this model, popular in the CT field using short acquisition times, occurs when tracer transport is largely one way (e.g. in the early phases of tissue enhancement). In this case, the interstitial volume is neglected and a simplified version of equation 2 may be derived [18]:

$$C_i(t) = v_pC_p(t) + K_{trans}\int_0^t C_p(t') dt'$$

(3)

Finally, it should be noted that two-compartment models of this form (equations 2 & 3) do include an important implicit assumption (beyond those normally associated with compartmental models). The transit time of the tracer in the vascular space is negligible (we measure no dispersion of the AIF in the tissue) and this has important implications as sampling times get shorter.

4. Advanced models

Compact and relatively straightforward to fit, Eqn. 2 provides a useful tool for the hypothesis-driven analysis of contrast-enhanced MR and CT data. However, it lacks an important characteristic, the isolation of flow as a separable parameter. There has subsequently been considerable interest in developing methods to isolate flow and PS-product. This has taken on added significance in the last few years with the introduction of commercial software addressing
this issue directly (e.g. GE Healthcare’s CT Perfusion software). Numerous clinical groups have started using such software and a number of papers have now appeared in the literature reporting flow and PS values obtained from dynamic contrast-enhanced CT acquisitions [21,22] and emphasizing some of the complications inherent in using such complex techniques [23].

Advanced models capable of separating the effects of flow and PS-product were pioneered very early [3,5,24] and have been tested in PET [7], CT [25,26] and MRI studies [27,28]. Central to their foundation is the concept of a measurable vascular transit time. That is, the tracer takes a finite time to transit the vascular volume of the tissue and we are able to measure this with our imaging system. Typically this transit time will be on the order of seconds and this places an increased strain on image acquisition requiring sampling intervals on the order of 1 or 2 s. However, the transport of tracer to the tissue during this initial period is solely due to tissue flow (i.e. extravasation may or may not occur in this initial phase; this can’t be established until the tracer begins to appear in the venules) [29]. Thus the early phase of enhancement provides information about flow alone and this, combined with late phase K\text{trans} estimates, can be used to extract estimates of PS. When the transit time is on the order of a few seconds (such as in the normal brain), measurement precision is limited; very few data points can be acquired in this time. However, transit time may be significantly longer in other tissues. MRI studies of the prostate gland using a sampling interval of 1.5 s [30] have provided estimates of flow and PS with good precision (coefficient of variation 4\% and 10\%, respectively). The transit time estimated in prostate tumors was \sim 20 s and this reflects the relatively low blood flow to these cancers combined with a large blood volume [31]. While these advanced models have yet to be fully validated in a clinical setting, the prostate results compare extremely well with the current gold standard, H\textsubscript{2}O-15 PET. In a study of 11 tumor-bearing prostates, Inaba used H\textsubscript{2}O-15 PET to estimate a mean perfusion of the whole prostate gland of 29 ml/min/100 ml [32]. The mean value in 9 normal prostates was 16 ml/min/100 ml. The compares with MR and CT estimates of blood flow made in regions of interest encompassing prostate tumor of 36 & 38 ml/min/100 ml and normal prostate peripheral zone of 13 & 13 ml/min/100 ml [31] and [33], respectively. Allowing for the partial volume averaging of central gland inherent in the PET regions, these numbers are remarkably consistent. Furthermore, the same MR & CT data also provide estimates of blood volume, PS-product and interstitial volume.

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 [34,35]. Hepatic perfusion is described in terms of 3 parameters, an arterial blood flow, a portal blood flow and a liver mean transit time and this can be extended to incorporate changes resulting from malignant growth [36]. Of course, the more complex the model the more important it becomes for the investigator to interpret their results judiciously [37]. Nevertheless, many of these advanced studies will surely prick the interest of the MR community in much the way that similar introductions to the CT community has.

5. Limitations and sources of error

While the acquisition of good quality DCE-CT data is a relatively robust process, there are a myriad of potential pitfalls in the acquisition of DCE-MRI data and these are not covered here other than to emphasize the importance of acquiring good quality, artifact-free data with an
appropriate spatial, temporal and contrast resolution. A common mistake is to assume that the measurement of an arterial input function is trivial and this is far from the case. A suitable artery (+ portal vein in liver studies) must be identified and inflow effects must be considered for MR studies [38,39]. A dominant source of artifact in many abdominal studies is motion caused by patient breathing. Respiratory-triggered or navigator techniques can be employed but such techniques compromise temporal resolution. Breath-hold techniques have limited application as the timescale of the hemodynamics (tens of seconds) rather than the hardware tends to dictate the imaging time required. Considerable effort has been directed at post-processing techniques to register images after acquisition particularly in the kidney but these largely remain limited to specialist sites.

One important step so far missing is the link between the models and the image data. The models require tracer concentrations as inputs; the images contain only signal intensities. Conversion between signal and concentration in CT is very straightforward; a simple subtraction suffices [40]. The conversion in MRI relies upon either the assumption that relaxation rate change can be measured sufficiently quickly or that an accurate calibration step is performed prior to the perfusion measurements. Without discussing these issues further, it is worth emphasizing that considerable debate surrounds the issues of water exchange (whether a single $T_1$ is really an appropriate measure of Gd-DTPA concentration) [41,42] and the relaxivity of Gd-DTPA in plasma and tissue [43].

When it comes to analyzing experimental data using a tracer kinetic model a number of issues should be considered. Is the model appropriate and not over-parameterized? Data from a slow enhancing multiple sclerosis lesion should not require the same level of model sophistication as a lung tumor. Conversely, a rapidly enhancing bladder tumor may have a significant vascular component and estimates of $K_{trans}$ made using equations 1 to 3 may be inaccurate [44]. As noted above, data fitting is not a trivial problem even with the simplest model. Delay and dispersion of the AIF is common [45] and correlation between parameters and error in their estimates should all be considered [37].

6. Summary

Tracer kinetic models can play a major role in the characterization of tumors, help provide prognostic information and assess the progress of treatments [46]. Importantly, they can be used to test hypotheses and provide specific physiological insight. These techniques have been used for many years in the PET and, more recently, CT communities and a considerable body of literature is available to help expedite their introduction into a variety of MR applications. They are not without their limitations and the results must be interpreted with caution but as tools for the study of cancer and its treatment they are invaluable.

Recommended Reading

Book:
A. Jackson, D.L. Buckley, G.J.M. Parker, Editors.
Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology
Review articles:
P.S. Tofts  
Modeling tracer kinetics in dynamic Gd-DTPA MR imaging  

A.M. Peters  
Fundamentals of tracer kinetics for radiologists  

References


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