Tracer Kinetics Modeling Basics: Model Formulation

Tong San Koh, Ph.D
School of Electrical and Electronic Engineering
Nanyang Technological University, Singapore

Introduction

With the advances in fast MR imaging techniques, it is possible to monitor the traversal of a MR contrast agent within tissues at short time intervals (of the order of a few seconds or less), thereby allowing the possibility to study blood flow at the tissue level. Dynamic contrast-enhanced MRI (DCE MRI) is emerging as a promising approach for *in vivo* assessment of tissue microcirculation. Quantitative analysis of DCE MRI data has been performed by several approaches, of which the deconvolution approaches are popular among recent studies. Deconvolution analysis of DCE MRI data can in turn be broadly classified into two approaches: (i) numerical (model-independent) deconvolution [1,2] or (ii) model-dependent deconvolution [3-5]. For model-dependent deconvolution, tracer kinetics models (formulated with appropriate microcirculatory parameters) are employed to fit the tissue enhancement curves, and the deconvolution process becomes a parametric fitting process. In this presentation, we illustrate the formulation of such tracer kinetics models by walking through two example models encountered in the literature.

Impulse Response and Deconvolution

Assuming that blood flow and exchange within the tissue behaves linearly [6], the operational equation that relates the arterial plasma tracer concentration curve $C_A(t)$ as a function of time t, with the tissue concentration curve $C_{tiss}(t)$, involves a convolution $\otimes$:

$$C_{\text{tiss}}(t) = F_{\text{p}}\, C_{\text{A}}(t) \otimes R(t), \tag{1}$$

where F_p is blood (plasma) flow and $R(t)$ is commonly called the impulse residue function. The process to figure out $R(t)$ given $C_A(t)$ and $C_{tiss}(t)$, is called deconvolution. In tracer kinetics modeling, $R(t)$, which characterizes the tissue-tracer system, is the object to model. Once a model for $R(t)$ is assumed, in order to derive quantitative estimates, parameters defined in $R(t)$ are adjusted using optimization schemes to best-fit Eq.(1) to the actual tissue enhancement curve. In the following, we assume that $C_A(t)$ and $C_{tiss}(t)$ can be determined with confidence from DCE MR images (which is actually a significant challenge) and proceed with our discussion on modeling $R(t)$.

A conventional two-compartment model

In DCE MRI, the commonly-used gadolinium tracer may diffuse from the blood plasma within capillaries into the tissue interstitial (but not into the cells in the tissue). Thus, we may attempt to account for these two tracer distribution spaces by defining a compartment for the intra-vascular space (denoted by p) and a compartment for the extra-vascular, extra-cellular space (e). Within each compartment, tracer concentration $C_{p\text{ or }e}(t)$ is assumed to be spatially homogenous and changes with time t only. The tracer mass balance equations can be given by

$$v_{\text{p}} \frac{dC_{\text{p}}(t)}{dt} = -\, F_{\text{p}} C_{\text{p}}(t) \;-\; K_{\text{e}\leftarrow\text{p}} C_{\text{p}}(t) \;+\; K_{\text{p}\leftarrow\text{e}} C_{\text{e}}(t) \;+\; \delta(t) \tag{2a}$$

$$v_{\text{e}} \frac{dC_{\text{e}}(t)}{dt} = K_{\text{e}\leftarrow\text{p}} C_{\text{p}}(t) \;-\; K_{\text{p}\leftarrow\text{e}} C_{\text{e}}(t)\,, \tag{2b}$$

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where v_i and v_e are respectively the fractional volumes of the vascular and interstitial spaces, and $\delta(t)$ is the Dirac Delta function which denotes a impulse input of unit concentration per time. The transfer constants for transcapillary exchange, $K_{e\leftarrow p}$ and $K_{p\leftarrow e}$, should in general, differ by the partition coefficient [3,7]. However, for the typical tracers used in DCE imaging, the assumption of passive, iso-directional diffusion can be imposed and we may write $K_{e\leftarrow p} = K_{p\leftarrow e} = PS$, where PS denotes the permeability-surface area product. Hence, Eqs (2a) and (2b) can be expressed in the more familiar form:

$$v_p \frac{dC_p(t)}{dt} = F_p C_p(t) - PS\left[C_p(t) - C_e(t)\right] + \delta(t) \tag{3a}$$

$$v_e \frac{dC_e(t)}{dt} = PS\left[C_p(t) - C_e(t)\right] \quad . \tag{3b}$$

The initial conditions are

$$C_p(t=0) = 0, \quad C_e(t=0) = 0 . \tag{3c}$$

Using the method of Laplace transform, Eqn.3 can be solved (will be illustrated) to yield the impulse residue function in a bi-exponential form

$$R_{CC}(t) = A\exp(\alpha t) + (1-A)\exp(\beta t) , \tag{4a}$$

where

$$\begin{pmatrix}\alpha \\ \beta\end{pmatrix} = \frac{1}{2}\left[-\left(\frac{PS}{v_p} + \frac{PS}{v_e} + \frac{F_p}{v_p}\right) \pm \sqrt{\left(\frac{PS}{v_p} + \frac{PS}{v_e} + \frac{F_p}{v_p}\right)^2 - 4\frac{PS}{v_e}\frac{F_p}{v_p}}\right] \tag{4b}$$

$$A = \frac{\alpha + \frac{PS}{v_p} + \frac{PS}{v_e}}{\alpha - \beta} \quad . \tag{4c}$$

A two-compartment distributed-parameter (DP) model

Suppose one would not want to consider a homogeneous vascular compartment, and would like to model the concentration of contrast agent as a function of both time and position (z) along the length (L) of a cylindrical capillary space. The mass-balance equations can be formulated as follows [8,9] (for an alternative formulation, see [10,11]) :

$$v_p \frac{\partial}{\partial t} C_p(t,z) = - F_p L \frac{\partial}{\partial z} C_p(t,z) - PS\left[C_p(t,z) - C_e(t,z)\right] \tag{5a}$$

$$v_e \frac{\partial}{\partial t} C_e(t,z) = PS\left[C_p(t,z) - C_e(t,z)\right] \tag{5b}$$

with the initial and boundary conditions as

$$C_p(z=0,t) = \delta(t), \; C_p(z>0, t=0) = 0, \; C_e(z, t=0) = 0 . \tag{5c}$$

In this form, the model accounts for the processes of convective transport and capillary-tissue exchange.

Using the method of Laplace transform, Eqs 5 can be solved simultaneously and the impulse residue function can be given by [10,11]

$$R(t) = \begin{cases} 1 & 0 < t \le t_1 \\ 1 - \exp(-PS/F_p)\left[1 + X(t - t_1)\right] & t > t_1 \end{cases} \tag{6a}$$

where t_1 ($=v_p/F_p$) denotes the mean vascular transit time. Here,

$$X(t) = \int_0^t \exp\left(-\frac{PS}{v_e}\tau\right)\sqrt{\frac{PS}{v_e}\frac{PS}{F_p}\frac{1}{\tau}}\, I_1\left(2\sqrt{\frac{PS}{v_e}\frac{PS}{F_p}\tau}\right) d\tau \tag{6b}$$

and I_1 is the modified Bessel function. The first-pass extraction fraction E of the DP model can be formally evaluated as $E = 1 - \exp(-PS/F_p)$ [10,11], which is consistent with the Renkin-Crone equation [12,13].

Some comments on the usage of the models

The major difference between the formulation of the two models is the assumption of homogeneous mixing in the vascular compartment (capillary space), which sheds light on the applicability of these models. If a compartment is observed at time intervals much longer than the time needed for the movement/mixing of its contents, it would appear to be well-mixed. In DCE MRI, each dynamic scan is an attempt to observe/monitor the retention of contrast agent within the tissue. If the time taken to traverse the vascular space of a particular tissue is short, and the time interval between scans (observations) is much longer, then the conventional compartmental model which assumes well-mixed compartments would be applicable. On the other hand, if the time interval between dynamic scans is comparable to the vascular transit time of the tissue, then we might not be able to assume that the vascular compartment is homogenous and the DP model might be appropriate.

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