Development and clinical applications of the time intensity curve shape analysis in dynamic contrast enhanced MRI: a pixel-by-pixel approach
Lavini, C.

Citation for published version (APA):
APPENDIX 2

Summary of Pharmacokinetic modelling in DCE-MRI and related problems.

Explanation of the algorithms used in the software DYNAMO
SUMMARY OF PHARMACOKINETIC MODELLING IN DCE-MRI AND RELATED PROBLEMS.

In DCE-MRI a low molecular weight paramagnetic contrast agent is injected intravenously as a bolus (i.e. as very quick injection, by means of a pump), while MRI data are being acquired. Data generated by DCE-MRI carry information about the microvascularisation and the status of the capillaries in the tissue, and the aim of pharmacokinetic (PK) modelling is to extract those physiological parameters from the available data by means of a mathematical model.

Between 1990 and 1991 three investigators [1-3] independently published three pharmacokinetic models meant to describe the exchange of contrast agent in the tissue and the resulting MR signal. The three models were later shown to be substantially the same model [4], which is nowadays often referred to as “Tofts’ model”, or PK generalised model. This is nowadays the most widespread model used in clinical studies, and was chosen for the work in this thesis, where it was implemented with some modifications.

The explanation given here refers to this model, which was used for the program Dynamo described in Appendix 1. The PK model was used in the brain study in chapter 7, and as a reference standard to which to compare the TIC shape analysis in chapters 8 and 9.

Besides, the procedure to apply PK modelling and the problems related are summarised.

![Figure 1: Schematic representation of a voxel.](image)

1. **Tofts’ model**

The tissue is modelled as made up of three different compartments; the plasma (where the contrast agent is carried to the tissue), the extravascular extracellular space (EES), where the contrast medium can diffuse into when it crosses the
capillary membrane, and the cellular space, which is inaccessible to the contrast agent.

When the paramagnetic contrast agent (CA) reaches the tissue, it decreases the relaxation time $T_1$ of the tissue water with which it comes into contact. As the water signal acquires different magnetic properties, the CA becomes “apparent” (indirectly) by means of an appropriately weighted MR sequence. Contrast agents used in DCE-MRI are complexes containing the paramagnetic ion Gd$^{3+}$, encapsulated in a cage (the “chelate”) to reduce its toxicity.

**General assumptions of the model**

The basic assumptions are summarised here [4]

1) that compartments exist, containing a well mixed tracer in a uniform concentration throughout the compartment.

2) that flux of contrast agent between the plasma and the extracellular extravascular space is driven by concentration differences: the flux between compartments is linearly dependent of the concentration difference between two compartments.

3) that the parameters describing the model do not change for the duration of the measurement (time invariance).

4) that there exist a compartment (the EES) where the contrast agent can leak into, and that the concentration in any particular point in the tissue is the result of diffusion from only one (the closest) capillary.

5) that the relaxivity $\mathcal{R}_1$ (the constant through which $1/T_1$ changes because of the contrast agent) is time invariant.

6) that the tissue relaxes with one single $T_1$ value, i.e. that the mixing of the contrast agent in the tissue is instantaneous (fast exchange limit).

**Derivation of the Concentration-time curve**

Tofts model is directly derived from Kety’s model, developed for small freely diffusible gaseous contrast agents [5]. In Tofts’ original formulation, the main difference with Kety’s model consists in the fact that the contrast medium in MRI is non–freely diffusible, and that the amount that can leak into the tissue is not determined by flow in the capillary, but by the vessel permeability. This is commonly called the “permeability limited” case. In other words, it is assumed that diffusion into the EEC has little or no effect on the concentration in the vessel, and that only permeability can limit the build-up of the CA in the EEC.
With this assumption the difference in Gd amount (mMoles) in the extravascular space per unit time \( \Delta Q_e/\Delta t \) is proportional to the concentration difference between the plasma compartment and the extravascular compartment itself \((C_p - C_e)\) (mMol/ml), and the proportionality constant is the product between the permeability \( P \) (the velocity of the Gd passing through the vessel wall, expressed in mm/min) and the surface per unit mass of the capillary \( S \) \((cm^2/gr)\) through which the contrast agent can pass (the larger the surface available in the pixel, the more Gadolinium passes through), multiplied by the mass of the voxel \( m_{vox} \) (gr). In each voxel it is therefore

\[
\Delta Q_e/\Delta t = PS m_{vox} (C_p - C_e).
\]

As long as the concentration in the plasma is larger than that in the extracellular space, the difference will be a positive one, leading to an increase in the amount of Gd in the extravascular space.

In terms of differential equations, we can write

\[
\frac{dQ_e}{dt} = PSm_{vox} (C_p (t) - C_e (t))
\]  
(Eq. 1)

\( Q_e \) can be expressed in terms of concentration:

\[
Q_e = C_e \times V_e,
\]

where \( V_e \) is the volume of the voxel EES. If related to the whole volume of the voxel (tissue)

\[
Q_e = C_e \times v_e \times V_{vox}
\]

where \( V_{vox} \) is the volume of the voxel, and \( v_e \) is the fractional volume of the extracellular space (with respect to the pixel).

By rewriting Eq 1 in terms of concentrations:

\[
v_e \frac{dC_e (t)}{dt} = \frac{PSm_{vox}}{V_{vox}} (C_p (t) - C_e (t)) \quad \text{or} \quad \frac{dC_e (t)}{dt} = \frac{PS \rho}{v_e} (C_p (t) - C_e (t))
\]  
(Eq. 2)

where \( \rho \) is the density of the tissue expressed as \((g*ml)\): \( \rho = m_{vox}/V_{vox} \).

The function \( C_p (t) \), or concentration in the plasma, is the Arterial Input Function, which needs to be known a priori (as a known term in this differential equation).

When we measure the MR signal, and therefore (indirectly) the contrast agent concentration, we measure the total concentration in the pixel, not in the extravascular space only. So the equation needs to be rewritten in terms of \( C_l(t) \) (concentration in the tissue).
The solution of equation 2 depends on the assumptions made. In a first approach, which is valid in some diseases, it can be assumed that the intravascular component in figure 1 is so small that the signal coming from the plasma does not contribute substantially to the total signal measured in the tissue (Case 1). Otherwise the intravascular component needs to be taken into account (Case 2).

**CASE 1**: Negligible intravascular component: \( C_t \approx \frac{v_e}{v_e} \cdot C_e \)

We can approximate the relation between the two spaces with \( C_t \approx \frac{v_e}{v_e} \cdot C_e \), this meaning that the “diluted” concentration measured in the tissue \( (C_t) \) is lower than the concentration in pure extravascular space \( (C_e) \). This is a rough approximation for most tumours, but in lesions such as multiple sclerosis it was shown to be a valid approximation.

As \( C_e = C_t / v_e \), the following holds:

\[
\frac{dC_t(t)}{dt} = PS\rho \left( C_p(t) - \frac{C_t(t)}{v_e} \right) \quad \text{(Eq. 3)}
\]

The product \( PS\rho \) is called \( K_{\text{trans}} \).

With this, equation (3) becomes

\[
\frac{dC_t(t)}{dt} = K_{\text{trans}} C_p(t) - \frac{K_{\text{trans}}}{v_e} C_t(t) \quad \text{(Eq. 4)}
\]

or, by defining

\[
k_{ep} := \frac{K_{\text{trans}}}{v_e} \quad \text{(Eq. 5)}
\]

\[
\frac{dC_t(t)}{dt} = K_{\text{trans}} C_p(t) - k_{ep} C_t(t) \quad \text{(Eq. 6)}
\]

which is the generalized kinetic model according to Tofts [4].

The equation is of the type

\[
\frac{dy(t)}{dt} + k(t)y(t) = Q(t) \quad \text{(Eq. 7)}
\]

whose general solution is

\[
\left\{
\begin{array}{l}
y(t) = y(a)e^{-A(t)} + e^{-A(t)} \int_a^t Q(u)e^{A(u)} \, du \\
A(t) = \int_0^t k(u) \, du
\end{array}
\right.
\quad \text{(Eq. 8)}
\]

With the substitution \( C_t(t) = y(t) \), \( k(t) = k_{ep} \) and \( Q(t) = K_{\text{trans}} C_p(t) \), it results
\[ A(t) = K_{ep} t \]

resulting in
\[ C_t(t) = C_t(a) e^{-K_{ep} t} + e^{-K_{ep} t} \int_a^t e^{K_{ep} \mu} \cdot K_{trans} C_p(\mu) d\mu \]  
(Eq. 9)

where \( a \) is arbitrary: if \( a := 0 \), the initial condition \( C(a) = C(0) = 0 \) leads to
\[ C_t(t) = K_{trans} e^{-K_{ep} t} \int_0^t e^{K_{ep} \mu} \cdot C_p(\mu) d\mu \]  
(Eq. 10)

**CASE 2:** \( C_t = v_e C_e + v_p C_p \)  
(Eq. 11)

Eq 11 means that the concentration measured in the tissue \( C_t \) comes partially from the extracellular space and partly from the capillary.

In this case, rewriting eq 2 we obtain
\[ \frac{dC_e(t)}{dt} = \frac{K_{trans}}{v_e} (C_p(t) - C_e(t)) \]  
(Eq. 12)

Solving eq 12 in \( C_e(t) \) instead of \( C_t(t) \) and using equation 5 and 7, with
\[ Q(t) = K_{ep} C_p(t) \]  
and \( K(t) = K_{ep} \)

we obtain
\[ C_e(t) = C_e(a) e^{-K_{ep} t} + e^{-K_{ep} t} \int_a^t C_p(\mu) \cdot K_{ep} \cdot e^{K_{ep} \mu} d\mu \]  
(Eq. 13).

Rewriting Eq 11
\[ C_e = \frac{1}{v_e} C_t - \frac{v_p}{v_e} C_p \]

and by substituting the above in (13) we obtain
\[ \frac{1}{v_e} C_t - \frac{v_p}{v_e} C_p = \left\{ \frac{1}{v_e} C_t(a) - \frac{v_p}{v_e} C_p(a) \right\} e^{-K_{ep} t} + e^{-K_{ep} t} \int_a^t C_p(\mu) \cdot K_{ep} \cdot e^{K_{ep} \mu} d\mu \]  
(Eq. 14), or
\[ C_t(t) = v_e \left\{ \frac{v_p}{v_e} C_p(t) + \left\{ \frac{1}{v_e} C_t(a) - \frac{v_p}{v_e} C_p(a) \right\} e^{-K_{ep} t} + e^{-K_{ep} t} \int_a^t C_p(\mu) \cdot K_{ep} \cdot e^{K_{ep} \mu} d\mu \right\} \]  
(Eq. 15)

With the same assumptions as before \( (a = 0 \Rightarrow C_t(a) = 0) \)
\[ C_t(t) = v_p C_p(t) + K_{trans} \cdot e^{-K_{ep} t} \int_0^t C_p(\mu) \cdot e^{K_{ep} \mu} d\mu \]  
(Eq. 16)

which is the known form of the extended Tofts model.
\( v_p \) (plasma fractional volume) is sometimes also called \( v_i \) (intravascular fractional volume)

The **Transfer Coefficient** \( K_{\text{trans}} \) is the volume transfer constant between plasma and EES (min\(^{-1}\)).

The **Rate constant** \( K_{ep} \), that is the rate constant between EES and plasma (min\(^{-1}\)).

The **Extravascular Extracellular Space (EES) fractional volume** \( v_e \) (also called interstitial space, leakage space), is the volume of EES per unit volume of tissue (no units), \( 0 < v_e < 1 \).

It has to be remarked that the definition \( K_{\text{trans}} = PS \rho \) is valid in the assumption of a permeability–limited model, the assumption that was used in Tofts model and in this thesis. In the flow-limited approximation (i.e. for small, diffusible tracers, such as the gaseous diffusible tracers as in Kety’s model) \( K_{\text{trans}} \) is proportional to flow instead of permeability: \( K_{\text{trans}} = F \rho (1-Hct) \), where \( Hct \) is the haematocrit.

Hybrid cases have been studied (partially flow, partially permeability limited case), for which the concept of “extraction fraction” was introduced by Renkin [6]:

\[
E=1-\exp(-PS/F(\rho(1-Hct)))
\]

However, in order to decouple \( PS \) and \( F \), models other than Tofts are used [7]: furthermore, the intravascular tracer has to be completely visible in the imaged voxel, and scanned at a very high rate. As we were dealing with clinical DCE-MRI data with relatively low temporal resolution (5-20 sec), this model was not applicable to the data in this thesis.

**2. The arterial input function and the PK model**

The term \( C_p(t) \) in Eq 10 or Eq16 represents the Arterial Input Function (AIF). This is the concentration in the plasma in the capillaries feeding the tissue imaged.

Though the contrast agent is delivered intravenously as a bolus (so, ideally, a “delta” function), once in the vascular system it is dispersed (by two passages through the heart and one through the lungs, and by the capillary network structure itself) so that by the time it reaches the tissue via the capillary system it assumes a characteristic “bell” shape, whose characteristics are dependent on the patient, on the tissue location and physiological parameters, such as, for example, heartbeat.

Unfortunately it is not possible to measure the AIF directly in the capillary, and the AIF is always approximated. Many authors use standard AIF (i.e. standard functions with fixed parameter, such as a patients-averaged AIF), though it is now commonly accepted that a measured AIF significantly improves the results of the PK model and should always be preferred.
When the AIF is measured, it is sampled in an artery close to the tissue to be imaged. The resulting concentration-time curve is either entered numerically in the model, or fitted to a model function. In the last case, a multiexponential form is often used in the literature

\[ C_a(t) = \sum_{i=1}^{N} A_i e^{-m_i t} \]  
(Eq. 17)

with \( N=1,2,3 \). (single, bi- or tri-exponential form).

Most often (and in the original Tofts’ formulation [1]) a bi-exponential form is used

\[ C_a(t) = \left( A_1 e^{-m_1 t} + A_2 e^{-m_2 t} \right). \]

This form (as well as the single exponential) neglects the initial rise in the signal, and assumes instantaneous growth to the maximum concentration value. A triexponential is used when one wants to take into account the initial concentration uptake.

3a. Closed form of Tofts’ model (AIF=multiexponential)

Equation 10 and 16 with a biexponential AIF can be solved in closed form as follows. Here an example is given for the bi-exponential form of the AIF. Single and tri-exponential forms are obtained in the same way

\[ C(t) = e^{-k_{ep}t} \int_{u} e^{k_{ep}u} \cdot K_{trans} \left( A_1 e^{-m_1 u} + A_2 e^{-m_2 u} \right) du \]  
(Eq. 18)

thus

\[ C(t) = K_{trans} \cdot e^{-k_{ep}t} \left[ \frac{A_1}{K_{ep} - m_1} e^{(K_{ep} - m_1)u} + \frac{A_2}{K_{ep} - m_2} e^{(K_{ep} - m_2)u} \right] \]

or

\[ C(t) = K_{trans} \cdot e^{-k_{ep}t} \left[ \left( \frac{A_1}{K_{ep} - m_1} e^{(k_{ep} - m_1)u} + \frac{A_2}{K_{ep} - m_2} e^{(k_{ep} - m_2)u} \right) - \left( \frac{A_1}{K_{ep} - m_1} + \frac{A_2}{K_{ep} - m_2} \right) \right] \]

with the substitution \( K_{trans} = K_{ep} v_e \)

\[ C(t) = K_{ep} v_e \cdot \left\{ \frac{A_1}{K_{ep} - m_1} e^{-m_1 t} + \frac{A_2}{K_{ep} - m_2} e^{-m_2 t} - \left[ \frac{A_1}{K_{ep} - m_1} + \frac{A_2}{K_{ep} - m_2} \right] e^{-k_{ep} t} \right\} \]  
(Eq 19)

The term \( K_{ep} \) is determined by the exponential decay, whereas \( v_e \) is the “rescaling factor” of the curve.
A similar solution can be obtained for a single and triexponential form, which were also used in the software described in appendix 1.

**AIF expressed as convolution.**

For the work presented in this thesis we have also made use of a functional form of the AIF proposed by Orton at al [8]. In this functional form, the AIF is a convolution of two functions:

\[ C_p(t) = C_b(t) + C_b(t) \otimes B(t) \]  

(Eq. 20)

where

\[ C_b(t) = b \cdot m^2 \cdot t \cdot e^{-mb \cdot t} \]

\[ B(t) = a \cdot e^{-ma \cdot t} \]

Eq (20) can be written out as

\[ C_p(t) = b \cdot m^2 \cdot t \cdot e^{-mb \cdot t} + \int_0^t (b \cdot m^2 \cdot u \cdot e^{-mb \cdot u}) \cdot (a \cdot e^{-ma \cdot (t-u)}) du \]

\[ C_p(t) = b \cdot m^2 \cdot t \cdot e^{-mb \cdot t} + a \cdot b \cdot m^2 \cdot e^{-ma \cdot t} \int_0^t u \cdot e^{-(mb-ma) \cdot u} \cdot du \]

\[ C_p(t) = b \cdot m^2 \cdot t \cdot e^{-mb \cdot t} + a \cdot b \cdot m^2 \cdot e^{-ma \cdot t} \left[ \frac{e^{-(mb-ma) \cdot u}}{-(mb-ma)} \left( u - \frac{1}{- (mb-ma)} \right) \right] \bigg|_0^t \]

or, rearranging:

\[ C_p(t) = e^{-mb \cdot t} \left[ b \cdot m^2 \cdot t + a \cdot b \cdot m^2 \cdot \frac{t - a \cdot b \cdot m^2}{(ma - mb)^2} \right] + e^{-ma \cdot t} \frac{a \cdot b \cdot m^2}{(ma - mb)^2} . \]

(Eq. 21)

By defining:

\[ \beta := \frac{a \cdot b \cdot m^2}{(ma - mb)^2} \]  

(Eq. 23)

\[ \alpha := \left[ b \cdot m^2 + \frac{a \cdot b \cdot m^2}{(ma - mb)} \right] \]  

(Eq. 24)

Eq 22 can be written as

\[ C_p(t) = (\alpha \cdot t \cdot e^{-mb \cdot t} - \beta \cdot e^{-mb \cdot t} + \beta \cdot e^{-ma \cdot t}) \]  

(Eq. 25)

This functional form takes into account the initial uptake of the Gd. The dependence of the AIF shape on the parameters can be seen in figure 1.
3b. Closed form of the PK model (AIF=Convolution)

With the AIF as in Eq 25, Tofts generalised model can be expressed in closed form as follows

\[ C_t(t) = K_{\text{trans}} \cdot e^{-K_{ep} t} \int_0^t e^{K_{ep} u} \left( \alpha \cdot u \cdot e^{-mb \cdot u} - \beta \cdot e^{-mb \cdot u} + \beta \cdot e^{-ma \cdot u} \right) du \]

(Eq. 26)

Writing out equation 26 we obtain:

\[
C_t(t) = K_{\text{trans}} \cdot e^{-K_{ep} t} \left\{ \frac{\alpha \cdot t}{(K_{ep} - mb)} + \frac{\beta}{(K_{ep} - mb)} \cdot e^{(K_{ep} - mb) t} - \frac{\beta}{(K_{ep} - mb)} \cdot e^{(K_{ep} - mb) t} \right\} \\
+ \frac{\alpha}{(K_{ep} - mb)^2} \cdot e^{(K_{ep} - mb) t} - \frac{\beta}{(K_{ep} - mb)} \cdot e^{(K_{ep} - mb) t} - \frac{\beta}{(K_{ep} - mb)} \cdot e^{(K_{ep} - mb) t} \\
+ \frac{\alpha}{(K_{ep} - ma)^2} \cdot e^{(K_{ep} - ma) t} - \frac{\beta}{(K_{ep} - ma)} \cdot e^{(K_{ep} - ma) t} - \frac{\beta}{(K_{ep} - ma)} \cdot e^{(K_{ep} - ma) t} \right\} \\
\]

\[ C_t(t) = K_{\text{trans}} \left\{ \frac{\alpha \cdot e^{-mb \cdot t}}{(K_{ep} - mb)} - \frac{\alpha \cdot e^{-mb \cdot t}}{(K_{ep} - mb)^2} + \frac{\alpha \cdot e^{-(K_{ep} - mb) \cdot t}}{(K_{ep} - mb)^2} \right\} \\
- \frac{\beta \cdot e^{-(K_{ep} - mb) \cdot t}}{(K_{ep} - mb)} + \frac{\beta \cdot e^{-(K_{ep} - mb) \cdot t}}{(K_{ep} - mb)^2} + \frac{\beta \cdot e^{-(K_{ep} - ma) \cdot t}}{(K_{ep} - ma)} - \frac{\beta \cdot e^{-(K_{ep} - ma) \cdot t}}{(K_{ep} - ma)^2} \right\} . \\
\]

With the substitutions

Figure 2: meaning of the AIF parameters in Eq. 22 or 25
\[ a_1 := \frac{\alpha}{(k_{ep} - mb)} \quad a_3 := \frac{\beta}{(k_{ep} - mb)} \]

\[ a_2 := \frac{\alpha}{(k_{ep} - mb)^2} \quad a_4 := \frac{\beta}{(k_{ep} - ma)} \]  

(Eq. 27)

Eq 10 becomes

\[
C_t(t) = K^{trans} \left\{ a_1 e^{-mbt} \cdot t + a_2 \left( -e^{-mbt} + e^{-K_{ep}t} \right) + \ldots \right. \\
+ a_3 \left( -e^{-mbt} + e^{-K_{ep}t} \right) + a_4 (e^{-ma} - e^{-K_{ep}t}) \right\} 
\]  

(Eq. 28)

and Eq 16 becomes

\[
C_t(t) = v_i \left\{ a \cdot t \cdot e^{-mbt} - \beta \cdot e^{-mbt} + \beta \cdot e^{-mat} \right\} + \ldots \\
+ K^{trans} \left\{ a_1 e^{-mbt} \cdot t + a_2 \left( -e^{-mbt} + e^{-K_{ep}t} \right) + a_3 \left( -e^{-mbt} + e^{-K_{ep}t} \right) + a_4 (e^{-mat} - e^{-K_{ep}t}) \right\} 
\]  

[Chapter 8]  

(Eq. 29)

Remarks:

1) In the work presented in this thesis it was chosen to fit a measured AIF to these 4 different functional forms (single, bi, tri exponential ad convolution as in eq 20), and to write out Tofts’ model in an analytical fashion. The fitting of the PK is non-linear in both cases (when AIF=multiexponential and when AIF=Convolution). This is in general a slow procedure and fitting a whole ROI can take many minutes, up to one hour in case of large ROIs and high resolution.

2) The arterial input function (AIF) represents the input of contrast agent arriving in the tissue, and it is represented in Tofts model by the term \( C_p(t) \) in equation 16. The form of the AIF does influence the final results of the model (i.e. \( v_i, v_e \) and \( K_{ep} \)). It is important to observe how the AIF “enters” the solution of Tofts model, namely as a scaling factor. If \( \kappa \times C_p(t) \) is used instead of \( C_p(t) \) in eq 10 and 16, the solution will result in \( v_e \) and \( v_i \) being rescaled to \( v_e/\kappa \) and \( v_i/\kappa \). Thus any error on the scaling of the AIF is “projected” into the parameters \( v_e \) and \( v_i \), and consequently by \( K^{trans} \) (as \( K^{trans} = K_{ep} \times v_e \)).

4. Measurement of the tissue Concentration

Tofts’ model (as well as other models) uses contrast agent concentration as the basis of the model. Unfortunately, in MRI the signal is, though related, not linearly dependent on the contrast agent concentration. The relationship between contrast agent concentration and the signal depends on the MR sequence chosen. In DCE-MRI it is customary to use gradient echo sequences for which, under steady-state conditions and perfect spoiling of the transverse signal, the following holds:
\[ S = N(H) \cdot \sin \alpha \cdot \frac{1 - \exp(-TR/T_1)}{1 - \cos \alpha \cdot \exp(-TR/T_1)} \cdot \exp(-TE/T_2^*) \]  
(Eq. 30)

where \( TR \) and \( TE \) are respectively the Repetition and Echo Time of the sequence, \( \alpha \) the flip angle and \( N(H) \) the proton density multiplied by an arbitrary factor (the scaling factor used by the scanner).

It is assumed that \( TE << T_2^* \), so that the last exponential term can be neglected. In this case \( S \) is approximated to
\[ S = N(H) \cdot \sin \alpha \cdot \frac{1 - \exp(-TR/T_1)}{1 - \cos \alpha \cdot \exp(-TR/T_1)} \]  
(Eq. 31)

The (varying) \( T_1 \) is assumed to be dependent on the concentration of Gadolinium in the tissue via
\[ \frac{1}{T_1} = \frac{1}{T_{10}} + \mathcal{R}_1 C, \]  
(Eq. 32)

with \( \mathcal{R}_1 \) being the tissue relaxivity.

The relaxivity of the tissue is dependent on many parameters, such as the magnetic field strength, the density of the tissue, the structure of the tissue, and in blood it is dependent on haematocrit. Often a standard, average value is assumed, such as \( \mathcal{R}_1 = 4.52 \text{ s}^{-1} \text{mM}^{-1} \text{liter} \), a value used in the literature at 1.5 Tesla.

By substituting Eq 32 in Eq 31, we obtain
\[ S = N(H) \cdot \sin \alpha \cdot \frac{1 - \exp(-TR/T_1)}{1 - \cos \alpha \cdot \exp(-TR/T_1)} \left( 1 + \mathcal{R}_1 C(t) \right) \]  
(Eq. 33)

The dependence of the relative signal ratio \( S/N(H) \) against the Gd concentration can be seen below, where curves are plotted against the Gd concentration, for a concentration range between 0 and 0.1 mMol, making use of 3 different flip angles of the FGRE sequence: \( \alpha = 10, 30 \) and 60 degree and using \( TR = 4.2 \) ms. In the example below the native \( T_1 \) of the tissue is 450 ms (typical value for liver at 1.5T).

Figure 2 illustrates the fact that in order to obtain reliable values of the Gd concentration it is mandatory to weight the MR sequence properly. A sequence with a large flip angle (i.e 60 degrees) is highly \( T_1 \) weighted and almost-linearity is reached in this Concentration range. For little \( T_1 \)- weighted (or Proton Density weighted) sequence, such as with a low flip angle (i.e. 10 degrees) the signal soon reaches a plateau, and an increase of Gd is not corresponded by an increase in
the MR signal. Usual concentrations of Gd in DCE-MRI can reach up to 10 mMol (in the artery) and 1 mMol (in tissue).

![Figure 2](image)

### 5. Derivation of the Concentration from MR signal

For proper PK modelling, it is necessary to calculate the Gd concentration at each point in time.

Different methods are used in the literature, including the use of look up tables after calibration. For the work presented in this thesis it was chosen to accurately measure the T1 values prior to contrast delivery - by means of different methods - as described later in this appendix.

The Concentration Time Curve (CTC) was then calculated as follows.

The ratio between the signal at time $S(t)$ and the signal before contrast delivery is given (using Eq 31) by

$$\frac{S(t)}{S(0)} = \frac{1 - \exp(-TR/T_1)}{1 - \cos \alpha \cdot \exp(-TR/T_{10})} \cdot \frac{1 - \cos \alpha \cdot \exp(-TR/T_{10})}{1 - \exp(-TR/T_{10})}$$  \hspace{1cm} (Eq. 34)

Assuming linearity between Gd concentration and $1/T_1$ as in eq 32, equation 34 can be rewritten as:

$$\frac{S(t)}{S(0)} = \frac{1 - \exp(-TR \cdot (R0 + \mathbb{R}[Gd]))}{1 - \cos \alpha \cdot \exp(-TR \cdot (R0 + \mathbb{R}[Gd]))} \cdot \frac{1 - \cos \alpha \cdot \exp(-TR/T_{10})}{1 - \exp(-TR/T_{10})}$$

or, with the following substitutions:

- $E = \exp(-TR \times R0)$
- $RR = \exp(-TR \times \mathbb{R}[Gd])$
- $a = \cos(\alpha)$
- $S10 = S(t)/S(0)$
The solution of which is

\[ RR(t) = -\frac{S10 - S10 \cdot E - 1 + a \cdot E}{E \cdot (S10 \cdot a \cdot E - S10 \cdot a + 1 - a \cdot E)} \]  
(Eq. 36)

resulting in

\[
TR \cdot R \cdot [Gd] = -\ln\left\{ -\frac{S10 - S10 \cdot E - 1 + a \cdot E}{E \cdot (S10 \cdot a \cdot E - S10 \cdot a + 1 - a \cdot E)} \right\}, \text{ or }
\]

\[
[Gd(t)] = -\frac{1}{TR \cdot R} \ln\left\{ \frac{S10(t) \cdot (1 - E) - (1 - a \cdot E)}{E \cdot (S10(t) \cdot a \cdot (1 - E) - (1 - a \cdot E))} \right\} \]  
(Eq. 37)

In this way only the \( T_1 \) before contrast is needed, and the \( T_1 \) after contrast delivery is derived theoretically through eq 32 and 34.

6. \( T_1 \) measurement.

\( T_1 \) maps can be created by fitting sets of \( T_1 \) weighted images acquired with different parameters.

Different methods were used for the work presented in this thesis.

1) Fitting to the SPGR signal equation

One popular method is to use a gradient Echo Sequence with different flip angles. As the signal intensity for a Gradient echo sequence is given by eq 30, neglecting \( T_2^* \) decay.

By fitting \( S(\alpha) = N(H) \cdot \sin \alpha \cdot \frac{1 - \exp(-TR/T_1)}{1 - \cos \alpha \cdot \exp(-TR/T_1)} \)  
(Eq. 38)

to the signal acquired with different flip angles \( \alpha \) (usually a set of 3 or 4 flip angles), the pre-contrast \( T_1 \) values can be obtained.

2) Linearised SPGR signal equation

As the fitting to eq 30 is non-linear, in order to speed up the calculation, in the program Dynamo a modified version of this algorithm is used according to the algorithm published by Gupta [10].

By rewriting Eq 38,

\[ \xi = \rho_0 \cdot \sin \alpha \cdot \frac{1 - E_1}{1 - \cos \alpha \cdot E_1} \]  
(Eq. 39)

where \( E_1 := \exp(-TR/T_1) \),

Eq 39 can be rewritten as
This transformed signal equation is in the form of a straight line in XY space, where

\[ X = \frac{\xi}{\sin \alpha} \quad \text{and} \quad Y = \frac{\xi}{\tan \alpha} \]

The slope of this line is given by \( \rho_0(1 - E_1) \)

As a result if images at several flip angles are available, a transformation into this XY space gives a set of points for each pixel that can be fitted to a straight line. The slope yields an estimate of the \( T_1 \), whereas the intercept yields an estimate of the \( \rho_0 \). The advantage of the linearization lies in much faster fitting.

3) Inversion recovery

T1 maps are obtained from fitting the images obtained from repeated Inversion Recovery (IR) sequences with variable inversion times (TI)

\[ S(TI) = M_0(1 - 2\exp(-TI/TR)) \]

(Eq. 40)

This is a lengthy procedure, as acquiring multiple IR sequences can take more than 10 minutes, but it provides very accurate T1 values.

This method was used for the brain study in chapter 7 and 8.

4) Fitting to a Look Locker Sequence.

The Look-Locker sequence consists of repetitive excitations with small flip angles \( \alpha \), applied after a 180 degrees inversion.

The signal intensity is modelled by \( S(t_n) = \beta(1 - \gamma \exp(-t_n/T_{1*})) \). [11]

where \( t_n \) is the time of the \( n \)th excitation, or \( t_n = n\tau \) where \( \tau \) is the time interval between excitations.

\( T_{1*} \) is a fictitious \( T_1 \), which is related to the real \( T_1 \) by

\[ T_{1*} = \tau \frac{\tau - \ln(\cos \alpha)}{T_1} \]

(Eq. 41)

from which the \( T_1 \) can be calculated.

This approach was used in the study on fistulising Crohn’s disease on the 3.0T scanner.

7. PK Modelling: calculation workflow

The DCE-MRI is preceded by a scan which is performed to acquire the necessary data for the \( T_1 \) measurement. Gadolinium is delivered during the scan (about a minute after starting the scan), images acquired and transferred to a workstation.
For the analysis, first the $T_1$ maps must be calculated according to the algorithm chosen.

Concentration time curves are generated. The Concentration time curve is dependent on the $\mathcal{R}_1$ relaxivity value chosen. Standard values exist for each type of Gd contrast agent, but the same $\mathcal{R}_1$ is applied to the whole scan, independent of the tissue.

Then the artery/vein must be selected in order to generate an AIF.

The arterial signal is converted to Concentration time curve making used of a fixed $T_1$ value (as the $T_1$ maps do not correctly estimate $T_1$ in flowing blood). $T_1$ is dependent on the unknown haematocrit. Therefore this conversion is highly susceptible to errors.

Possible correction for the CTC of the blood can be carried out at this stage.

The CTC is fitted to a model function (in the program described in Appendix 1, the CTC is fitted to 4 different functional forms as described earlier in this appendix).

The ROI is selected, and PK modelling is performed on a pixel-by-pixel basis in the whole ROI. In the program Dynamo, the PK model is run using both Eqs 19 and 29.

8. Limitations of the PK model

Basic assumptions

A number of assumptions must hold for the PK model to be valid.

Contrast agent.

Permeability is usually high for small molecules like gadopentate dimeglumine, meaning that the uptake of these molecules is only partly permeability-limited, but also flow-limited. This means that the assumption of permeability-limited flow, made at the very beginning is not completely true. Permeability to larger agents (e.g. Gd-DTPA albumin) is usually lower, and these are probably better suited for detecting changes in the leakiness of the capillary endothelium. In tumours, the situation is probably the mixed flow and PS-limited case; however in the brain (e.g. low grade brain tumours) most cases are PS limited.

What is $K^{\text{trans}}$? It is often referred to $K^{\text{trans}}$ as to “permeability”. It has to be pointed out that $K^{\text{trans}}$ is not actually (pure) permeability, and that alterations in the transfer constant $K^{\text{trans}}$ may reflect increases in the capillary surface area rather than permeability.

It was assumed that the transfer constant between blood plasma and the EES is the same in both directions. There is no evidence, so far, of unequal transfer.
APPENDIX 2  Pharmacokinetic Modelling

constants in the case of low molecular weight Gd\(^{3+}\) contrast agents. Models other than Tofts’ take into account this inbalance.

**Fast Exchange limit.**
The model assumes immediate exchange between intra and extra vascular compartment, as well that the interstitium behaves as a well mixed homogeneous solution with respect to the contrast agent. This is equivalent to saying that the system remains in the fast exchange limit (FXL). It is recognised that this assumption does not hold. The parenchyma is not a single homogeneous solution, but it is highly compartmentalised on the scale of a MR imaging voxel. In most tissue water is intracellular, and thus cannot directly access the CA molecule. The use of the linear equation in Eq 32 for the entire H\(_2\)O signal from a voxel requires that the water exchange between compartments be sufficiently fast compared with the relaxation rate constant in each compartment (i.e. the water exchange is in the FXL). It has been shown that the exchange is not frequent enough for this assumption to be true [12], and the water relaxation can show a bi-exponential decay rate.

The combination of this bi-exponential decay rate to calculate apparent \(T_1\) decay times leads to cumbersome expressions, and has been dealt with by some authors [12]. However, the complexity of the treatment is far beyond the scope of the work presented in this thesis.

**Gadolinium concentration**
The calculated value of the Gd concentration is dependent on the assumptions made. The largest error can come from the value of the relaxivity \(\mathcal{R}_1\) assumed in Eq 32. The relaxivity is known to change in different tissue, and for different contrast media. In practice, a single value of the relaxivity is chosen for the whole image, but this is a rough assumption.

Things are even more complicated in the calculation of the arterial concentration. Whereas the \(T_1\) maps calculation in the tissue is quite reliable, because of flow problems the \(T_1\) calculation in blood is not feasible. For this reason we used fixed values of the \(T_1\) in blood only taking into account differences in field strength. (1700 ms at 3T, and 1540 ms at 1.5T). Unfortunately the \(T_1\) (as well as relaxivity) is known to be very sensitive to the haematocrit in the blood, so that little changes in the haematocrit can result in large variations in the final \(T_1\) concentration [13]. Though the difference between the haematocrit in the artery (where the AIF is measured) and in the capillary (where the model is applied) were taken into
account, it is not possible to correctly identify the $T_1$ in the blood. This results in large variation in the $C_p(t)$ that are not linear in $T_1$.

9. Uncertainty in the AIF

The AIF remains the weakest link in the PK modelling chain and uncertainties in the estimation of the AIF have large repercussions of the final results.

One of the major uncertainties in the measurement of the AIF arises from the unknown haematocrit. Errors in the haematocrit estimation result in huge differences in the final AIF concentration, as pointed out by Just and colleagues [13].

The uncertainty in the AIF has important consequences on the final results of the PK model. As explained in the paragraph on the AIF, uncertainties in the amplitude of the AIF are “absorbed” by the parameters $v_e$ and $v_i$. If the AIF is therefore scaled by a factor $\kappa$, both $v_i$ and $v_e$ are automatically scaled by a factor $1/\kappa$.

Errors in the decay constants in the exponential factor affect the final PK parameters in a more subtle way. An underestimation of these factors will “push up” the $K_{ep}$, and consequently the $K_{trans}$ value (as also described by [14]).

Other sources of incorrect AIF estimation come from the limited time resolution, flow and saturation problems.

An important source of miscalculation of the AIF arises from the limited time resolution (i.e. a time interval between successive dynamic measurements of more than 5 sec) of the DCE-MRI protocol in most clinical studies. This problem is unavoidable if both large volume coverage and high spatial resolution are required, resulting in a time resolution that does not allow to detect the initial peak concentration of the AIF as well as the exact moment when the enhancement begins. The limitations and problems arising from the low temporal resolution have been discussed in details elsewhere [14,15]. Briefly, we mention here the fact that this results in inaccurate fitting, especially of the part of the function describing the initial peak, as well as underestimation of the parameters. This problem was addressed in chapter 6.

Location of the AIF.

The artery where the AIF is sampled is not necessarily the closest in term of physiology. This introduces further bias on the AIF.

Flow

Other problems are just as important: one is the fact that the signal measured with a Gradient echo sequence in flowing blood is not a real reflection of the Gd
concentration. Because the RF excited spins are not the same spins that are measured (as they flow out of the imaging plane after the excitation), these sequences result in a hyperintense signal, whether or not the contrast medium is present. This does not permit the correct estimation of the change in contrast agent concentration. The problem has been amply discussed by [16], and correction methods proposed. It has to be noted though that correcting for these inflow effects is very challenging, and requires a thorough knowledge of the flow velocity, resistance in the vessel, dispersion, and direction of the vessel with respect to the imaging plane.

The third problem is especially relevant when the AIF is measured in large vessels, such as the aorta. In this case the initial concentration of Gadolinium is so large that it affects also the $T_2^*$ to the point that signal decays so shortly that the signal intensity, which should increase due to the $T_1$ shortening effect, actually decreases (see eq 30). This results in the peak being either underestimated or completely missed.

**Fitting**

Low SNR and low temporal resolution (not enough data) severely hamper the non linear (3 parameters) fitting. Furthermore, the $\chi^2$ of the Eq 16 has many local minima, and it is not always easy to recognise the location of the $\chi^2$ paraboloid where the real minima lie. Because fitting is done on a pixel-by-pixel basis, the SNR is always a limiting factor in PK modelling. For improvement of the data often a single slice is acquired, limiting therefore coverage.

The fitting is non linear (and not linearisable), so that computation times are long.

**When is the AIF good?**

Eq 1 says that in this model, only when a negative difference exists in concentrations between plasma and extravascular space (i.e. higher concentration in the extravascular space), the concentration the extravascular space starts decreasing. Therefore it is expected that the plasma concentration and the extravascular concentration will touch at some point, and this is where the differential term will change sign.

Being the extravascular concentration $C_e = C/v_e$, $C/v_e$ must cross the AIF the moment when the $C_t$ reaches its maximum (first derivative = 0). In order to “make this happen” (i.e. to have the $C_e$ cross the AIF at this point) the model adjusts the parameter $v_e$, resulting (sometimes) in $v_e >1$. As $v_e$ cannot physically be $v_e >1$, this is a sign that the AIF is underestimated.
It is possible to rescale the AIF in order to correct for this overestimation, but the scaling affects only the amplitude AIF, whereas the source of uncorrect scaling is also to be found in the exponential term in Eq 37.

**Consequences on the calculation of the PK parameters.**

The uncertainties described above all contribute to the incorrect determination of the PK parameters. It has been accepted that the knowledge of the AIF plays a pivotal role in the determination of the PK parameters. In Tofts’ model, it can actually be assumed that it greatly influences them, to the point that the AIF determination is the largest source of error. Besides the AIF, SNR plays an important role. In order to obtain reliable data for PK modelling, i.e. with good temporal and spatial resolution, together with high SNR, protocols must be reduced to a single slice, severely limiting its applicability in the clinical practice.

**REFERENCES**


