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Tracer kinetic modelling issues

Bernd Müller-Bierl

November 9, 2010

1 The two compartment exchange model

A simple tracer-kinetic model that produces both blood flow and extraction flow is the two compartment exchange model [Sourbron 2009] [Brix 1999] [Brix 2004] [Brix 2010]. It is fully defined by the four parameters F_p (plasma flow), V_p (plasma volume), F_E (extraction flow) and V_E (volume of the extravascular, extracellular space or interstitial volume, for short). Applying conservation of tracer mass to each compartment produces the model equations:

$$V_p C_p' = -(F_E + F_p)C_p + F_E C_E + F_p C_{p,A} \quad (1)$$
$$V_E C_E' = F_E C_p - F_E C_E \quad (2)$$

with the amount of tracer in plasma $q_1 = V_p C_p$ and the amount of tracer in the interstitial space $q_2 = V_E C_E$ these equations read in terms of the kinetic transfer constants

$$q_1' = -(f_{01} + f_{21})q_1 + f_{12}q_2 + i_1 \quad (3)$$
$$q_2' = f_{21}q_1 - f_{12}q_2 \quad (4)$$

Here the flows are given in terms of the kinetic transfer constants by

$$F_E = f_{21}V_p \quad (5)$$
$$F_E = f_{12}V_E \quad (6)$$
$$F_p = f_{01}V_p \quad (7)$$

Denoting the convolution product of two functions with the symbol "$\otimes$" the solutions for C_p and C_E can be written as $V_p C_p = F_p R_p \otimes C_{p,A}$ and $V_E C_E = F_p R_E \otimes C_{p,A}$. The functions R_p and R_E are given by the following expressions:

$$R_p(t) = \exp(-\beta t) + T_B\,\alpha\,A\,(\exp(-\alpha t) - \exp(-\beta t)) \quad (8)$$
$$R_E(t) = (1 - T_B\alpha)\,A\,(\exp(-\alpha t) - \exp(-\beta t)) \quad (9)$$

where the parameters α, β and A are given in terms of transit times by

$$\alpha = \frac{1}{2}\left(T_p^{-1} + T_E^{-1} - \sqrt{(T_p^{-1} + T_E^{-1})^2 - 4\,T_p^{-1}T_E^{-1}}\right) \quad (10)$$
$$\beta = \frac{1}{2}\left(T_p^{-1} + T_E^{-1} + \sqrt{(T_p^{-1} + T_E^{-1})^2 - 4\,T_p^{-1}T_E^{-1}}\right) \quad (11)$$
$$A = \frac{T_B^{-1} - \beta}{\alpha - \beta} \quad (12)$$

and where the mean transit times in both compartments T_p and T_E and the mean transit time of an intravascular tracer T_B are given in terms of the flow by (compare Eqs. 1,2 with Eqs. 3,4)

$$T_p = \frac{V_p}{F_E + F_p} \quad (13)$$
$$T_E = \frac{V_E}{F_E} \quad (14)$$
$$T_B = \frac{V_p}{F_p} \quad (15)$$

The inverse mean transit times thus are given in terms of kinetic parameters and in terms of the parameters α, β and A as [Donaldson 2010]

$$T_p^{-1} = k_{21} = f_{01} + f_{21} = \alpha + \beta - k_{12} \quad (16)$$
$$T_E^{-1} = k_{12} = f_{12} = \frac{\alpha\beta}{k_{21}} \quad (17)$$
$$T_B^{-1} = k_{01} = f_{01} = A(\alpha - \beta) + \beta \quad (18)$$

This can easily be verified to be the inverse of Eqs. 10 - 12. Eqs. 13-15 and Eqs. 16-18 can easily be fulfilled by setting α and β, to the values in Eqs. 10-12.

The total tissue concentration $C = V_p C_p + V_E C_E$ takes the form $C = F_p R \otimes C_{p,A}$ with a biexponential residue function $R = R_p + R_E$

$$R(t) = \exp(-\beta t) + A(\exp(-\alpha t) - \exp(-\beta t)) \quad (19)$$

Fitting the model (Eq. 19) to the data $C(t)$ and $C_{p,A}(t)$ produces the four parameters A, α, β and F_p. The parameters T_p, T_E and T_B are found from their inverses (Eqs. 16, 17, 18) and the parameters V_p, V_E, and F_E are found from the inverses of Eqs. 13, 14 and 15:

$$V_p = F_p T_B \quad (20)$$
$$F_E = F_p\left(\frac{T_B}{T_p} - 1\right) \quad (21)$$
$$V_E = F_E T_E \quad (22)$$

This can most easily be verified by inserting Eqs. 20-22 into Eqs. 13-15.

Two important review papers are [Tofts 1997] and [Brix 2010].

2 The two compartment exchange model revisited

Tofts and Kermode have used a different approach [Tofts 1999]. They consider that the tracer has already been applied ($t = 0$ is the end of the tracer administration) and establish the bidirectional approach

$$V_p C_p' = \tilde{f}_{12} C_E - \tilde{f}_{21} C_p - f_p C_p \quad (23)$$

$$V_E C_E' = \tilde{f}_{21} C_p - \tilde{f}_{12} C_E \quad (24)$$

Elimination of C_E results in the ordinary differential equation

$$V_E V_p C_p'' + (\tilde{f}_{12} V_p + \tilde{f}_{21} V_E + f_p V_E)\, C_p' + \tilde{f}_{12} f_p C_p = 0 \quad (25)$$

A solution is of the form

$$C_p(t) = A_1 \exp(-b_1 t) + A_2 \exp(-b_2 t) \quad (26)$$

Eqs. 24 and 26 can be rewritten as

$$C_E' + k_2 C_E = k_1 (A_1 \exp(-b_1 t) + A_2 \exp(-b_2 t)) \quad (27)$$

where $k_1 = \tilde{f}_{21}/V_E = F_E^{21}/V_E$ and $k_2 = \tilde{f}_{12}/V_E = F_E^{12}/V_E$.

The solution is

$$C_E(t) = \frac{k_1 A_1}{k_2 - b_1} \exp(-b_1 t) + \frac{k_1 A_2}{k_2 - b_2} \exp(-b_2 t) + c \exp(-k_2 t) \quad (28)$$

The constant c is determined by the initial condition $C_E(0) = 0$. The total signal is then given by

$$S_{\text{tissue}} = V_p C_p + V_E C_E \propto \gamma \left(\frac{A_1 k_1}{b_1 - k_2} + \frac{A_2 k_1}{b_2 - k_2} \right) \exp(-k_2 t) \quad (29)$$

$$+ A_1 \left(1 - \frac{\gamma k_1}{b_1 - k_2} \right) \exp(-b_1 t) \quad (30)$$

$$+ A_2 \left(1 - \frac{\gamma k_1}{b_2 - k_2} \right) \exp(-b_2 t) \quad (31)$$

where $\gamma = V_E/V_p$. This is of the form similar (but not equal) to S_{tissue} in the article of Roberts et al. [Roberts 2000] Since it is a variation of Toft's equations it is also referred sometimes as a (modified) Tofts model. It should, however, not be confused with the modified Tofts model in Section 5.

3 The two compartment uptake model

For the 2 compartment exchange model, there exist 3 limiting regimes:

1. no exchange limit $F_E \to 0$
2. one compartment limit $V_E \to 0$
3. fast exchange limit $F_E \to \infty$

A further simplification of the two compartment exchange model is the two compartment uptake model defined by $C_E(t) \ll C_p(t)$; The model equations for the uptake model are [Bazelaire 2005]

$$V_p C_p' = -(F_E + F_p) C_p + F_p C_{p,A} \quad (32)$$

$$V_E C_E' = F_E C_p \quad (33)$$

The residuum functions are

$$R_p(t) = \exp(-t/T_p) \quad (34)$$

$$R_E(t) = E\,(1 - \exp(-t/T_p)) \quad (35)$$

with $E = F_E/(F_E + F_p)$ being the extraction fraction.

The total tissue concentration is $C = F_p R \otimes C_{p,A}$ with

$$R(t) = \exp(-t/T_p) + E\,(1 - \exp(-t/T_p)) \quad (36)$$

Fitting the data to the total tissue concentration yields the 3 parameters T_p, E, and F_p. The parameters V_p and F_E can be found from

$$V_p(t) = \frac{T_p F_p}{1 - E} \quad (37)$$

$$F_E(t) = \frac{E F_p}{1 - E} \quad (38)$$

The model is fully define by the three parameters T_p, E, and F_p and has only one monoexponential limit ($E = 0$).

4 The Tofts model

A one-compartment model can be used when the blood-brain-barrier (BBB) is intact.The total tissue concentration is $C = F_p R \otimes C_{p,A}$ with

$$R(t) = \exp(-t/T_p) \quad (39)$$

A two parameter fit to the model produces F_p and T_p from which the blood volume can be computed as

$$V_p(t) = T_p F_p \quad (40)$$

In case of a broken BBB a more abstract notation is used for determining the total concentration:

$$C = \frac{K^{\text{trans}}}{1 - \text{Hct}} \exp(-t k_{\text{ep}}) \otimes C_{p,A} \quad (41)$$

where Hct is the blood haematocrit-value. A one-compartment model with these notations is commonly referred to in the literature as "Tofts model". The parameter K^{trans} must be interpreted as F_E when the signal from tracer in the microvasculature is negligible. In this permeability limited regime it can be derived that $V_E = K^{trans}/k^{ep}$. Conversely, K^{trans} equals plasma flow F_p when the microvascular signal is non-negligible. In this flow-limited regime, the value of K^{trans}/k^{ep} equals the extracellular volume. Note that the assumption of a well-mixed space in this regime is only valid if tracer extravasation is sufficiently rapid, so plasma and interstitium have equal concentrations.

5 The modified Tofts model

When the temporal resolution is not sufficient to measure the broadening of the arterial input function $C_{p,A}$ in the microvasculature, the concentrations in the tissue plasma and in the artery are often assumed to be equal:

$$C(t) = \frac{V_p}{1 - \text{Hct}} C_{p,A} + \frac{F_E}{1 - \text{Hct}} \exp(-t/T_E) \otimes C_{p,A} \tag{42}$$

This model we refer to as the *modified Tofts model*. It is T_E the mean transit time of the interstitium, so the model provides the means to estimate V_p, F_E and the volume of the interstitium $V_E = F_E T_E$.

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tracer kinetic modelling

Tracer kinetic modelling issues

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1 The 2 compartment exchange model

The concentration of the contrast agent in the tissue $c_t(t)$ can be written as follows:

$$c_t(t) = F_p\, c_p(t) \otimes R_{2\mathrm{CXM}}(t)$$

where F_p is the tissue plasma perfusion, $c_p(t)$ is the concentration of the contrast agent in the feeding arteria (AIF) and $R_{2\mathrm{CXM}}$ is the input response function given by:

$$R_{2\mathrm{CXM}}(t) = A\exp(-\alpha t) + (1-A)\exp(-\beta t)$$

The relations to the transfer constants k_{01}, k_{12}, k_{21} are given according to Donaldson et al. by [Donaldson 2010]

$$\begin{aligned} k_{01} &= A(\alpha-\beta)+\beta \\ k_{12} &= \frac{\alpha\beta}{k_{01}} \\ k_{21} &= \alpha+\beta-k_{12} \end{aligned}$$

The relation to the model parameters are given by

$$\begin{aligned} v_p &= \frac{F_p}{k_{01}} \\ \mathrm{PS} &= (k_{21}-k_{01})\cdot v_p \\ v_e &= \frac{\mathrm{PS}}{k_{12}} \end{aligned}$$

This is a 4 parameter model with F_p, A, α, β.

2 The uptake model

In the uptake model we have $k_{12} \approx 0$ and we set $\alpha = 0$, $\gamma = \beta$, $B = A$ so that the input response function is given as

$$R_{2\mathrm{CUM}}(t) = B + (1-B)\exp(-\gamma t)$$

we therefrom get

$$B = \frac{k_{21}-k_{01}}{k_{21}}$$

and the standard parameters v_p and PS can be calculated as

$$v_p = \frac{F_p}{\gamma(1-B)};\quad \mathrm{PS} = \frac{B\cdot F_p}{(1-B)}$$

3 The 2 compartment exchange model revisited

In the notation of Sourbron [Sourbron 2009] we have the input response function as

$$R(t) = (1-E_-)\exp(-tK_+) + E_-\exp(-tK_-)$$

so that we have $E_- = A$, $\beta = K_+$, $\alpha = K_-$ and

$$\begin{aligned} k_{01} &= \frac{1}{T_B} = E_-(K_- - K_+) + K_+ \\ k_{12} &= \frac{1}{T_E} = (K_+K_-)T_B \\ k_{21} &= \frac{1}{T_P} = K_+ + K_- - \frac{1}{T_E} \end{aligned}$$

wherefrom the standard parameters v_p, v_e and PS can be calculated as

$$v_p = \frac{F_p}{k_{01}};\quad \mathrm{PS} = v_p\cdot(k_{21}-k_{01});\quad v_e = \frac{\mathrm{PS}}{k_{12}}$$

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[Donaldson 2010] Donaldson, S.B. et al. *A Comparison of Tracer Kinetic Models for T1-Weighted Dynamic Contrast-Enhanced MRI: Application in Carcinoma of the Cervix*, Magnetic Resonance In Medicine 63:691-700 (2010)

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Assessment of Plasma Flow from the Myocardium

Bernd Müller-Bierl

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1 The Fermi function model

The Fermi function method consists in replacing the residue function by a Fermi function model. In the following we will develop the theory of the Fermi function method. The amount of contrast agent (CA) in the region of interest (ROI) at any time is given by [Jerosch-Herold 1998]

$$q(t) = F \int_0^t [c_{in}(s) - c_{out}(s)]\, ds \tag{1}$$

where the outflow CA concentration $c_{out}(s)$ is given by the inflow $c_{in}(s)$ and the transfer function $h(t)$ according to

$$c_{out}(t) = \int_0^t c_{in}(s) h(s-t) ds = c_{in}(t) \otimes h(t) \tag{2}$$

where $\otimes$ denotes the convolution. Then equation 1 can be rewritten as a convolution of a residuum function with the inflow

$$q(t) = F \int_0^t c_{in}(s) \otimes (1 - h(s-t)) ds = R_F \otimes c_{in}(t) \tag{3}$$

with the residuum function given by

$$q(t) = F \left(1 - \int_0^t h(s-t) ds\right) = F \cdot R(t) \tag{4}$$

where the transfer function at $t = 0$ is given by $h(0) = 0$ and thus $R_F(0) = F$.

We now use the Fermi function model

$$\begin{aligned} R_F(t) &= F \left[\frac{1}{\exp((t - t_0 - t_d)k + 1)}\right] u(t - t_d) \\ u(t - t_d) &= \begin{cases} 0 & t < t_d \\ 1 & t > t_d \end{cases} \end{aligned} \tag{5}$$

The solution process now uses as input c_{in}: the inflow tracer concentration or *arterial input function* which is known as amount of contrast agent delivered

to the ROI, and $q(t)$: the quantity of contrast agent in a tissue ROI or *tissue function*.

Then $q(t) = R_F \otimes c_{in}$ is solved in Fourier space and R_F is fitted to the measured data $q(t)$ and c_{in} using the Levenberg-Marquard algorithm.

The experimental conditions are

1. The signal intensity is linerily proportional to the CA concentration for the CA dosage used in the study
2. The relationship between image intensity and CA concentration is the same in the blood pool and the myocardium
3. Effects of water exchange in the myocardium are minimized (short TR, high flip angle) and a no-exchange model can be applied
4. The signal time course in the left ventricular blood pool can be used as an input function
5. The shape of the tissue impulse response $R(t)$ can be approximated with a Fermi-function

2 The model-free deconvolution

In the model-free approach again the tissue function $q(t)$ is given by the convolution of the arterial input function c_{in} with an impulse response function $r(t)$ where the flow F is given by the impulse response at $t = 0$ [Jerosch-Herold 2002].

$$\begin{aligned} q(t) &= c_{in}(t) \otimes r(t) \\ r(0) &= F \end{aligned} \tag{6}$$

We can write the convolution in form of a matrix product

$$q_i = \sum_{j=1}^{i} A_{ij} r_j + \epsilon_i \tag{7}$$

where

$$A = \begin{bmatrix} c_{in}(t_1) & 0 & 0 & 0 & 0 \\ c_{in}(t_2) & c_{in}(t_1) & 0 & 0 & 0 \\ c_{in}(t_3) & c_{in}(t_2) & \ddots & 0 & 0 \\ \ddots & \ddots & \ddots & \ddots & 0 \\ c_{in}(t_N) & c_{in}(t_{N-1}) & \ddots & \ddots & c_{in}(t_1) \end{bmatrix} \tag{8}$$

We determine the impulse response r_j from the matrix A where we develop the impulse response into basis functions. As basis functions we use the j'ths B-splines of order k.

$$r_i = \sum_{j=1}^{p} \alpha_j B_j^{(k)}(t_i) \qquad \alpha_j \in \Re \tag{9}$$

We write

$$q_i = \sum_{j=1}^{i} D_{ij}\alpha_j \qquad \vec{\alpha} :: \min\{\| D\vec{\alpha} - \vec{q} \|; \vec{\alpha} \in \Re^p\} \tag{10}$$

with

$$D_{ij} = \sum_{0}^{t_i} B_j^{(k)}(u) c_{in}(t_i - u)du \tag{11}$$

Regularization

Instead of solving the matrix equation

$$D\vec{\alpha} = \vec{q} \tag{12}$$

directly by inversion, we use the original model + side constraints (the so-called normal equation)

$$D^T D\vec{\alpha} + \lambda^2 L^T L\vec{\alpha} = D^T\vec{q} \tag{13}$$

For $L = I$ (standard form) the solution is given by

$$\vec{\alpha} = \sum_{i=1}^{s}\left[\frac{\sigma_i^2}{\sigma_i^2 + \lambda^2}\right]\frac{\vec{u_i}^T\vec{q}}{\sigma_j}\vec{v_i} \qquad \text{SVD}(D) = U\Sigma V^T \tag{14}$$

For $L \neq I$ we transform the normal equations numerically into standard form and again we have

$$\vec{\alpha} = \sum_{i=1}^{s}\left[\frac{\sigma_i^2}{\sigma_i^2 + \lambda^2}\right]\frac{\vec{u_i}^T\vec{q}}{\sigma_j}\vec{v_i} \qquad \text{GSVD}(D) = U\Sigma V^T \tag{15}$$

where we determine the parameter λ in both cases from the L-curve.

3 The two compartment exchange model

A simple tracer-kinetic model that produces both blood flow and extraction flow is the two compartment exchange model [Sourbron 2009] [Brix 1999] [Brix 2004] [Brix 2010]. It is fully defined by the four parameters F_P (plasma flow), V_P (plasma volume), F_E (extraction flow) and V_E (volume of the extravascular, extracellular space or interstitial volume, for short). Applying conservation of tracer mass to each compartment produces the model equations:

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$$V_E C_E' = F_E C_P - F_E C_E \tag{17}$$

with the amount of tracer in plasma $q_1 = V_P C_P$ and the amount of tracer in the interstitial space $q_2 = V_E C_E$ these equations read in terms of the kinetic transfer constants

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$$q_2' = f_{21}q_1 - f_{12}q_2 \tag{19}$$

Here the flows are given in terms of the kinetic transfer constants by

$$F_E = f_{21}V_P \tag{20}$$
$$F_E = f_{12}V_E \tag{21}$$
$$F_P = f_{01}V_P \tag{22}$$

Denoting the convolution product of two functions with the symbol "$\otimes$" the solutions for C_P and C_E can be written as $V_P C_P = F_P R_P \otimes C_{P,A}$ and $V_E C_E = F_P R_E \otimes C_{P,A}$. The functions R_P and R_E are given by the following expressions:

$$R_P(t) = \exp(-\beta t) + T_B\,\alpha\,A\,(\exp(-\alpha t) - \exp(-\beta t)) \tag{23}$$
$$R_E(t) = (1 - T_B\alpha)\,A\,(\exp(-\alpha t) - \exp(-\beta t)) \tag{24}$$

where the parameters α, β and A are given in terms of transit times by

$$\alpha = \frac{1}{2}\left(T_P^{-1} + T_E^{-1} - \sqrt{(T_P^{-1} + T_E^{-1})^2 - 4\,T_B^{-1}T_E^{-1}}\right) \tag{25}$$
$$\beta = \frac{1}{2}\left(T_P^{-1} + T_E^{-1} + \sqrt{(T_P^{-1} + T_E^{-1})^2 - 4\,T_B^{-1}T_E^{-1}}\right) \tag{26}$$
$$A = \frac{T_B^{-1} - \beta}{\alpha - \beta} \tag{27}$$

and where the mean transit times in both compartments T_P and T_E and the mean transit time of an intravascular tracer T_B are given in terms of the flow by (compare Eqs. 16,17 with Eqs. 18,19)

$$T_P = \frac{V_P}{F_E + F_P} \tag{28}$$
$$T_E = \frac{V_E}{F_E} \tag{29}$$
$$T_B = \frac{V_P}{F_P} \tag{30}$$

The inverse mean transit times thus are given in terms of kinetic constants and in terms of the parameters α, β and A as [Donaldson 2010]

$$T_P^{-1} = f_{01} + f_{21} = \alpha + \beta - f_{12} \tag{31}$$
$$T_E^{-1} = f_{12} = \frac{\alpha\beta}{f_{01}} \tag{32}$$
$$T_B^{-1} = f_{01} = A(\alpha - \beta) + \beta \tag{33}$$

This can easily be verified to be the inverse of Eqs. 25 - 27. Eqs. 28-30 and Eqs. 31-33 can easily be fulfilled by setting α and β, to the values in Eqs. 25-27.

The total tissue concentration $C = V_p C_p + V_E C_E$ takes the form $C = F_p R \otimes C_{p,A}$ with a biexponential residue function $R = R_p + R_E$

$$R(t) = \exp(-\beta t) + A(\exp(-\alpha t) - \exp(-\beta t)) \tag{34}$$

Fitting the model (Eq. 34) to the data $C(t)$ and $C_{p,A}(t)$ produces the four parameters A, α, β and F_p. The parameters T_p, T_E and T_B are found from their inverses (Eqs. 31, 32, 33) and the parameters V_p, V_E, and F_E are found from the inverses of Eqs. 28, 29 and 30:

$$V_p = F_p T_B \tag{35}$$

$$F_E = F_p \left(\frac{T_B}{T_p} - 1 \right) \tag{36}$$

$$V_E = F_E T_E \tag{37}$$

This can most easily be verified by inserting Eqs. 35-37 into Eqs. 28-30.

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$$V_E C_E' = \tilde{f}_{21} C_p - \tilde{f}_{12} C_E \tag{39}$$

Elimination of C_E results in the ordinary differential equation

$$V_E V_p C_p'' + (\tilde{f}_{12} V_p + \tilde{f}_{21} V_E + f_p V_E)\, C_p' + \tilde{f}_{12} f_p C_p = 0 \tag{40}$$

A solution is of the form

$$C_p(t) = A_1 \exp(-b_1 t) + A_2 \exp(-b_2 t) \tag{41}$$

Eqs. 39 and 41 can be rewritten as

$$C_E' + k_2 C_E = k_1 (A_1 \exp(-b_1 t) + A_2 \exp(-b_2 t)) \tag{42}$$

where $k_1 = \tilde{f}_{21}/V_E = F_E^{21}/V_E$ and $k_2 = \tilde{f}_{12}/V_E = F_E^{12}/V_E$.

The solution is

$$C_E(t) = \frac{k_1 A_1}{k_2 - b_1} \exp(-b_1 t) + \frac{k_1 A_2}{k_2 - b_2} \exp(-b_2 t) + c \exp(-k_2 t) \tag{43}$$

The constant c is determined by the initial condition $C_E(0) = 0$. The total signal is then given by

$$S_{\text{tissue}} = V_p C_p + V_E C_E \propto \gamma \left(\frac{A_1 k_1}{b_1 - k_2} + \frac{A_2 k_1}{b_2 - k_2} \right) \exp(-k_2 t) \tag{44}$$

$$+ A_1 \left(1 - \frac{\gamma k_1}{b_1 - k_2} \right) \exp(-b_1 t) \tag{45}$$

$$+ A_2 \left(1 - \frac{\gamma k_1}{b_2 - k_2} \right) \exp(-b_2 t) \tag{46}$$

where $\gamma = V_E/V_p$. This is of the form similar (but not equal) to S_{tissue} in the article of Roberts et al. [Roberts 2000] Since it is a variation of Toft's equations it is also referred sometimes as a (modified) Tofts model. It should, however, not be confused with the modified Tofts model in Section 7.

5 The two compartment uptake model

For the 2 compartment exchange model, there exist 3 limiting regimes:

1. no exchange limit $F_E \to 0$
2. one compartment limit $V_E \to 0$
3. fast exchange limit $F_E \to \infty$

A further simplification of the two compartment exchange model is the two compartment uptake model defined by $C_E(t) \ll C_p(t)$, The model equations for the uptake model are [Bazelaire 2005]

$$V_p C_p' = -(F_E + F_p) C_p + F_p C_{p,A} \tag{47}$$

$$V_E C_E' = F_E C_p \tag{48}$$

The residuum functions are

$$R_p(t) = \exp(-t/T_p) \tag{49}$$

$$R_E(t) = E\,(1 - \exp(-t/T_p)) \tag{50}$$

with $E = F_E/(F_E + F_p)$ being the extraction fraction.

The total tissue concentration is $C = F_p R \otimes C_{p,A}$ with

$$R(t) = \exp(-t/T_p) + E\,(1 - \exp(-t/T_p)) \tag{51}$$

Fitting the data to the total tissue concentration yields the 3 parameters T_p, E, and F_p. The parameters V_p and F_E can be found from

$$V_p(t) = \frac{T_p F_p}{1 - E} \tag{52}$$

$$F_E(t) = \frac{E F_p}{1 - E} \tag{53}$$

The model is fully define by the three parameters T_p, E, and F_p and has only one monoexponential limit ($E = 0$).

6 The Tofts model

A one-compartment model can be used when the blood-brain-barrier (BBB) is intact.The total tissue concentration is $C = F_p R \otimes C_{p,A}$ with

$$R(t) = \exp(-t/T_p) \tag{54}$$

A two parameter fit to the model produces F_p and T_p from which the blood volume can be computed as

$$V_p(t) = T_p F_p \tag{55}$$

In case of a broken BBB a more abstract notation is used for determining the total concentration:

$$C = \frac{K^{\text{trans}}}{1 - \text{Hct}} \exp(-t k_{ep}) \otimes C_{p,A} \tag{56}$$

where Hct is the blood haematocrit-value. A one-compartment model with these notations is commonly referred to in the literature as "Tofts model". The parameter K^{trans} must be interpreted as F_E when the signal from tracer in the microvasculature is negligible. In this permeability limited regime it can be derived that $V_E = K^{\text{trans}}/k^{ep}$. Conversely, K^{trans} equals plasma flow F_p when the microvascular signal is non-negligible. In this flow-limited regime, the value of K^{trans}/k^{ep} equals the extracellular volume. Note that the assumption of a well-mixed space in this regime is only valid if tracer extravasation is sufficiently rapid, so plasma and interstitium have equal concentrations.

7 The modified Tofts model

When the temporal resolution is not sufficient to measure the broadening of the arterial input function $C_{p,A}$ in the microvasculature, the concentrations in the tissue plasma and in the artery are often assumed to be equal:

$$C(t) = \frac{V_p}{1 - \text{Hct}} C_{p,A} + \frac{F_E}{1 - \text{Hct}} \exp(-t/T_E) \otimes C_{p,A} \tag{57}$$

This model we refer to as the *modified Tofts model*. It is T_E the mean transit time of the interstitium, so the model provides the means to estimate V_p, F_E and the volume of the interstitium $V_E = F_E T_E$.

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Assessment of Plasma Flow from the Myocardium

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1 The Pulsed Arterial Spin Labeling Model according to Detre et al.

The Bloch Eqs. for the longitudinal magnetisation of a continuously perfused system which include T_1 relaxation, brain perfusion and cross relaxation between brain water and macromolecular spins, are given by

$$\frac{dM_b}{dt} = \frac{M_b^0 - M_b}{T_{1b}} - k_{for}M_b + k_{rev}M_m + fM_a - fM_v \quad (1)$$

$$\frac{dM_m}{dt} = \frac{M_m^0 - M_m}{T_{1m}} + k_{for}M_b - k_{rev}M_m \quad (2)$$

where f = tissue perfusion in $ml/g/s$, T_{1b}, T_{1m} are the spin lattice relaxation time at brain water and macromolecule spins in the absence of perfusion and cross-relaxation, M_b, M_m are the magnetization of brain water and macromolecular spins per gramm, M_b^0, M_m^0 are the equilibrium values, M_a, M_v are the magnetizations of water per ml arterial/ venous blood and k_{for}, k_{rev} are the magnetization transfer rates between brain water and macromolecules.

Assuming that venous blood from the tissue is in equilibrium with the tissue itself means that there is a proportionality

$$M_v = \frac{1}{\lambda}M_b \quad (3)$$

then, under equilibrium conditions the amount of water magnetization flowing into the brain equals what is leaving so that $fM_a^0 = fM_v^0 = fM_b^0/\lambda$ or

$$M_a^0 = \frac{1}{\lambda}M_b^0 \quad (4)$$

The Bloch Eqn. 1 can be simplified to

$$\frac{dM_b}{dt} = \frac{M_b^0 - M_b}{T_{1b}} - k_{for}M_b + k_{rev}M_m - (2\alpha - 1)\frac{f}{\lambda}M_b^0 - \frac{f}{\lambda}M_b \quad (5)$$

with λ = brain/blood partition coefficient and

$$\alpha = \frac{M_a^0 - M_a}{2M_a^0} \quad (6)$$

being the degree of spin labeling.

Ignoring cross-relaxation in the case where macromolecular spins are not perturbed, the general solution of Eqn. 5 for an inversion recovery experiment where spins are not labeled ($\alpha = 0$) gives:

$$M_b(\tau) = M_b^0 - 2M_b^0\exp(-(\frac{1}{T_{1b}} + \frac{f}{\lambda})\tau) \quad (7)$$

The steady state solution of Eqn. 5 when macromolecular spins are saturated $M_m = 0$ without arterial spin labeling ($\alpha = 0$), gives

$$M_b^{ss1} = \frac{1/T_{1b} + f/\lambda}{1/T_{1b} + k_{for} + f/\lambda}M_b^0 \quad (8)$$

The steady state solution of Eqn. 5 when macromolecular spins are saturated with ASL ($\alpha \neq 0$) gives

$$M_b^{ss2} = \frac{1/T_{1b} - (2\alpha - 1)f/\lambda}{1/T_{1b} + f/\lambda}M_b^{ss1} \quad (9)$$

From Eqs. 8 and 11 the tissue perfusion can be calculated from the steady state tissue water magnetization according to

$$f = \frac{\lambda}{T_{1b}}\left(\frac{M_b^{ss1} - M_b^{ss2}}{M_b^{ss2} + (2\alpha - 1)M_b^{ss1}}\right) \quad (10)$$

where for $\alpha = 1$ we have complete inversion, whereas for $\alpha = 0.5$ we have saturation.

When arterial spin tagging is advised without saturation of macromolecular spins, the steady state solution of Eqs. 2 and 5 (see [Detre 1994]) gives

$$M_b^{ss2} = \frac{1/T_{1b} - (2\alpha - 1)f/\lambda + \delta}{1/T_{1b} + f/\lambda + \delta}M_b^{ss1} \quad (11)$$

with

$$\delta = \frac{k_{for}}{1 + T_{1m}k_{rev}} \quad (12)$$

Tissue perfusion can then be calculated from the steady state tissue water magnetization according to

$$f = \lambda\left(\frac{1}{T_{1b} + \delta}\right)\left(\frac{M_b^{ss1} - M_b^{ss2}}{M_b^{ss2} + (2\alpha - 1)M_b^{ss1}}\right) \quad (13)$$

2 The Pulsed Arterial Spin Labeling Model according to Buxton et al.

After the inversion pulse, the arterial magnetization difference is $2\tilde{\alpha}M_{0b}$, where M_{0b} is the equilibrium magnetization of arterial blood and the factor $\tilde{\alpha}$ accounts

for incomplete inversion during the tagging pulse: $\tilde{\alpha}$ is the maximum possible change in the longitudinal magnetization that was achieved [Zhang 1993] [Alsop 1996].

Let the delivery function $c(t)$ be the normalized arterial concentration of magnetization arriving at the voxel at time t. Let $r(t,t')$ be the residue function that is the fraction of tagged water molecules that arrived at time t' and are still in the voxel at time t. Furthermore the magnetization relaxation function $m(t,t')$ is the fraction of the original longitudinal magnetization tag carried by the water molecule that arrived at time t' that remains at time t. The amount delivered to a particular voxel between t' and $t'+dt'$ is $2\tilde{\alpha}M_{0b}fc(t')$ where f is the cerebral blood flow $[ml/ml/s]$. The fraction of the magnetization that remains at time t is $r(t-t')m(t-t')$. Then [Buxton 1998]

$$\begin{aligned}\Delta M(t) &= 2M_{0b}f\int_0^t c(t')r(t-t')m(t-t')dt' \\ &= 2M_{0b}f\{c(t)\otimes[r(t)m(t)]\}\end{aligned} \tag{14}$$

The standard ASL kinetic model takes into account the effect of transit delay from the tagging region to the imaged voxel. We summarize the standard model as

$$\begin{aligned}c(t) &= \begin{cases}0 & 0<t<\Delta t \\ \tilde{\alpha}\exp(-t/T_{1b}) & \Delta t<t<\tau+\Delta t \\ 0 & \tau+\Delta t<t\end{cases} \quad \text{pulsed ASL} \\ r(t) &= \exp(-ft/\lambda) \\ m(t) &= \exp(-t/T_1)\end{aligned} \tag{15}$$

Inserting Eqn. 15 into Eqn. 14 leads to the following expressions for the pulsed ASL difference signals

$$\Delta M(t) = \begin{cases}0 & 0<t<\Delta t \\ 2M_{0b}f(t-\Delta t)\tilde{\alpha}\exp(-t/T_{1b})q_p(t) & \Delta t<t<\tau+\Delta t \\ 2M_{0b}f(\tau)\tilde{\alpha}\exp(-t/T_{1b})q_p(t) & \tau+\Delta t<t\end{cases} \quad \text{pulsed ASL} \tag{16}$$

with

$$\begin{aligned}q_p(t) &= \begin{cases}\frac{1}{k(t-\Delta t)}\exp(kt)(\exp(-k\Delta t)-\exp(-kt)) & \Delta t<t<\tau+\Delta t \\ \frac{1}{k\tau}\exp(kt)(\exp(-k\Delta t)-\exp(-k(\tau+\Delta t))) & \tau+\Delta t<t\end{cases} \\ k &= \frac{1}{T_{1b}}-\frac{1}{T_1'} \\ \frac{1}{T_1'} &= \frac{1}{T_1}+\frac{f}{\lambda}\end{aligned}$$

Eqn. 16 is the standard model for pulsed ASL-signals.

3 The Pulsed Arterial Spin Labeling Model according to Wang et al.

We start from the simple differential equation [Ye 1997]

$$\frac{dM(t)}{dt} = -\delta R(M(t)-M_{ss}(\alpha,\omega_1,\Delta\omega)) \tag{17}$$

where R_{1a} $(0.83s^{-1})$ and R_1 are the longitudinal relaxation rate of the blood and myocardium at 1.5 T [Wang 2010], with $\delta R = R_1 - R_{1a}$ being the water relaxation rate in the presence of the off-resonance RF irradiation.

A general solution is [Ye 1997], Eqn. (A2)

$$M(t) = M(0)\exp(-\delta Rt) + \int_\tau^t \exp(-\delta R(t-\tau))\delta R\, M_{ss}d\tau \tag{18}$$

The normalized difference between the amplitude of signal from the tagged scan and the control scan is [Ye 1997], Eqn. (A3)

$$\frac{\Delta M(t)}{M_0} = \frac{M(\alpha,t)-M(\alpha=0,t)}{M_0} \tag{19}$$

Then, from $\delta R(M_{ss}(\alpha,\omega_1,\Delta\omega)-M_{ss}(\alpha=0,\omega_1,\Delta\omega)) = -2\alpha F_p/\lambda M_0$ [McLaughlin 1997], Eqn. (36), where F_p is the metabolic blood flow, we get [Ye 1997], Eqn. (A4)

$$\frac{\Delta M(t)}{M_0} = -2F_p/\lambda\int_0^t \exp(-\delta R(t-\tau))\,a(\tau)\,d\tau \tag{20}$$

where we further defined

$$a(t) = h(t)\cdot\exp(-R_{1a}\tau_a) \tag{21}$$

where $h(t)$ is defined as

$$h(t) = \begin{cases}0 & t<\tau \\ 1 & \tau<t<\tau_d \\ 0 & \tau_d<t\end{cases} \tag{22}$$

where τ is the "arterial transit time," is the time for the leading edge of the tagged bolus to reach the capillary exchange site, τ_d is the time for the trailing edge of the tagged bolus to reach the capillary exchange site. R_{1a} is the longitudinal relaxation rate of arterial blood.

Proof of Eqn. (20) from Eqn. (19) and Eqn. (18):

$$\begin{aligned}\Delta M(t) &= \int_\tau^t \exp(-\delta R(t-\tau))\delta R(M_{ss}(\alpha=0)-M_{ss}(\alpha\neq 0))d\tau \\ &= \int_\tau^t \exp(-\delta R(t-\tau))(-2\alpha F_p/\lambda M_0)d\tau \\ &\Leftrightarrow \\ \frac{\Delta M(t)}{M_0} &= -2F_p/\lambda\int_\tau^t \exp(-\delta R(t-\tau))a(\tau)d\tau\end{aligned}$$

Proof of Eqn. (18): from Eqn. (17). The Integral of Eqn. (17) is

$$M(t) - M(\tau) = \int_\tau^t \frac{dM(t)}{dt} dt = -\int_\tau^t \delta R M(t) dt + \int_\tau^t \delta R M_{ss}(\alpha) dt \qquad (23)$$

Insertion of $M(t)$ from Eqn. (18) yields

$$\begin{aligned}
M_0 \exp(-\delta R t) &- M_0 \exp(-\delta R \tau) + \int_\tau^t \exp(-\delta R(t-\tau)) \delta R M_{ss}(\alpha) d\tau \\
&= -\int_\tau^t \delta R M(t) dt + \int_\tau^t \delta R M_{ss}(\alpha) dt \\
&= -\int_\tau^t \delta R \left(M_0 \exp(-\delta R t) + \int_\tau^t \exp(-\delta R(t-\tau)) \delta R M_{ss} d\tau \right) dt \\
&\quad + \int_\tau^t \delta R M_{ss}(\alpha) dt \\
&= M_0(\exp(-\delta R t) - \exp(-\delta R \tau)) \\
&\quad + \int_\tau^t \int_\tau^t (-\delta R) \exp(-\delta R(t-\tau)) \delta R M_{ss} d\tau dt \\
&\quad + \int_\tau^t \delta R M_{ss}(\alpha) dt \\
&\Leftrightarrow
\end{aligned}$$

$$\int_\tau^t \exp(-\delta R(t-\tau)) M_{ss}(\alpha) d\tau = \int_\tau^t (\exp(-\delta R(t-\tau)) - 1) M_{ss}(\alpha) d\tau + \int_\tau^t M_{ss}(\alpha) dt \qquad (24)$$

Derivation with respect to t yields

$$\exp(-\delta R(t-\tau)) = \exp(-\delta R(t-\tau)) - 1 + 1 \qquad (25)$$

This is true, thus we have proved Eqn. (18).

Finally, we get [Ye 1997], Eqn. (A6)

$$\frac{\Delta M(t)}{M_0} = \frac{-2\alpha F_p}{\lambda \delta R} (1 - \exp(-\delta R(t - \tau_a))) \qquad (26)$$

or, in the interval $\tau_a < t < \tau_d$ we have [Yang 1998]

$$\frac{\Delta M(t)}{M_0} = \frac{-2F_p}{\lambda \delta R} \exp(-R_{1a} t)(1 - \exp(-\delta R(t - \tau_a))) \qquad (27)$$

Now, flow-sensitive alternating inversion recovery (FAIR) is implemented for spin-tagging using alternating slice-selective and non-selective inversion pulses. The dynamic myocardial dM signals at multiple T_Is were simultaneously fitted for the plasma flow F_p and for arterial transit time τ based on the following kinetic model [Yang 1998]:

$$dM/M_0 = \begin{cases} \frac{2F_p}{\lambda} \frac{1}{\delta R} \exp(-R_{1a} T_I)\{1 - \exp(-\delta R(T_I - \tau))\} & T_I \geq \tau \\ 0 & T_I < \tau \end{cases} \qquad (28)$$

where F_p is the metabolic blood flow, R_{1a} ($0.83 s^{-1}$) and R_1 are the longitudinal relaxation rate of the blood and myocardium at 1.5 T [Wang 2010], respectively, $\delta R = R_1 - R_{1a}$, M_0 is the equilibrium magnetization of myocardium, λ is the blood tissue water partition coefficient (0.92ml/g) and τ is arterial transit time.

M_0 and R_1 of myocardium were fitted from experimental data at multiple T_Is according to the standard saturation recovery model

$$M(T_I, T_E) = M_0 \exp\{-T_E/T_2\}(1 - \exp(-T_I/T_1)) \qquad (29)$$

where the non-selective pulse images are used. This equation can be evaluated at $T_E \ll T_2$.

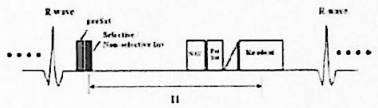

Figure 1: *Sequence for pulsed ASL. Combines ASL (FAIR in this study) with a navigator gated, ECG triggered TrueFISP readout sequence.*

The Figure 1 shows the pulse diagram of the pulsed ASL FAIR TrueFISP sequence. Selective and non-selective inversion pulses are used for label and control acquisitions respectively. A slice-selective saturation pulse is applied prior to labeling pulses to minimize the variations in heart beat. Navigator echo is placed on the diaphragm that allows image readout during the end-expiration phase. Image acquisition is always during the mid-diastole cardiac phase.

The Fig. 2 shows the evolution of the magnetization. To the left the evolution of the magnetization is shown without saturation pulse and to the right with saturation pulse. The image is given by the difference A-B, where A stands for the slice selective inversion and B stands for the non-slice-selective inversion.

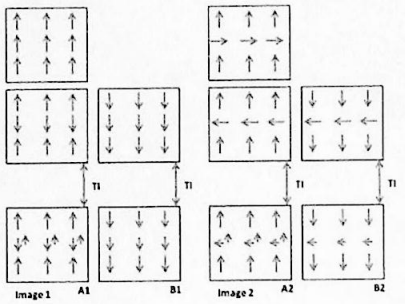

Figure 2: *Magnetization during pulsed ASL sequence. To the left. Without saturation pulse. To the right: With saturation pulse.*

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