Scope and interpretation of the modified Tofts model

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INTRODUCTION: The 3-parameter modified Tofts model [1] for bolus-tracking MRI provides a relation between the tracer concentrations C(t) and C_A(t) in tissue and arterial plasma, respectively, in terms of the plasma volume V_P, the transfer constant K^{trans} and the rate constant k_{ep}:

$$C(t) = V_P C_A(t) + K^{\mathrm{trans}}\, e^{-tk_{\mathrm{ep}}} * C_A(t)$$

The model has become a standard for the analysis of DCE-MRI data, but it remains unclear under which conditions it applies. It cannot be valid for general two-compartment tissues, since those are defined by 4 parameters: the volumes V_P and V_E of plasma and extravascular, extracellular space, the plasma flow F_P, and the extraction flow F_E (also known as permeability-surface area product PS). The aim of this theoretical study is to identify exactly under which conditions the modified Tofts model applies, and to derive expressions for the parameters K^{trans} and k_{ep}.

METHODS: The general bi-exponential solution for the residue function of the two-compartment exchange model [2] was expressed in the representation {F_P, T, f, v}:

$$T = \frac{V_P + V_E}{F} \qquad f = \frac{F_E}{F_P + F_E} \qquad v = \frac{V_E}{V_P + V_E}$$

In this representation, F_P and T act as parameters of scale: any change in their values for fixed f and v is fully equivalent to a change in the units of flow and time, respectively. Hence for the purposes of classification, F_P and T can be fixed without loss of generality. The dimensionless parameters f and v take values on the square [0,1]x[0,1], where the edges correspond to the four physical regimes of interest: $v \cong 0$ is the highly vascularized regime $V_E << V_P$, $v \cong 1$ is the weakly vascularized regime $V_P << V_E$, $f \cong 0$ is the slow-exchange regime $F_E << F_P$, and $f \cong 1$ is the fast exchange regime $F_P << F_E$. Approximations to the bi-exponential solution are derived by power-expanding the rate constants and amplitudes of the exponentials up to first order in v, 1-v, f, and 1-f, respectively. In regimes where a time constant of one of the exponentials was first order in the small parameter, the following "no-broadening" approximation was used to eliminate the exponential ($\varepsilon \cong 0$):

$$\frac{e^{-t/\epsilon}}{\epsilon} * C_A(t) \approx C_A(t)$$

	Highly vascularized $V_P >> V_E$	Intermediate	Weakly vascularized $V_P << V_E$
Fast Exch. $F_P << F_E$	$K^{\mathrm{trans}} = F_P$ $V_P^{\mathrm{app}} = V_E \frac{F_P}{F_E}$	$K^{\mathrm{trans}} = F_P$ $V_P^{\mathrm{app}} = \frac{V_P V_E}{V_P + V_E} \frac{F_P}{F_E}$	$K^{\mathrm{trans}} = F_P$ $V_P^{\mathrm{app}} = V_P \frac{F_P}{F_E}$
Intermediate	$K^{\mathrm{trans}} = F_P$ $V_P^{\mathrm{app}} = V_E \frac{F_P}{F_E}$	Exchange	$K^{\mathrm{trans}} = \frac{F_P F_E}{F_P + F_E}$ $V_P^{\mathrm{app}} = V_P \frac{F_P}{F_P + F_E}$
Slow Exch. $F_E << F_P$	Exchange	Exchange	$K^{\mathrm{trans}} = F_E$ $V_P^{\mathrm{app}} = V_P$

Table 1. The different regimes where a generalized Tofts model arises, with the corresponding expressions for the model parameters K^{trans} and V_P^{app}. In each of these regimes, the ratio K^{trans}/k_{ep} equals the total extracellular volume V_P+V_E.

RESULTS: The modified Tofts model arises in one regime only, the weakly vascularized ($V_P << V_E$), slow exchange ($F_E << F_P$) regime. In this regime, K^{trans} equals the permeability F_E. In most other regimes, a model with the same structure as the modified Tofts model arises, but with a different interpretation of the amplitude of C_A(t). For this reason, we introduce a generalized Tofts model in terms of an *apparent* plasma volume V_P^{app}:

$$C(t) = V_P^{\mathrm{app}} C_A(t) + K^{\mathrm{trans}}\, e^{-tk_{\mathrm{ep}}} * C_A(t)$$

The modified Tofts model is then a special case of the generalized Tofts model defined by $V_P^{app} = V_P$. The regimes where a generalized Tofts model arises, as well as an expression for the model parameters, are summarized in Table 1.

CONCLUSION: We conclude that the modified Tofts model can only be applied to tissues that are weakly vascularized and have a low permeability. This might exclude many tissues to which the model is often applied, in particular (malignant) tumors. In other regimes, a model of exactly the same form applies, but the amplitude of the C_A(t) term cannot be interpreted as the plasma volume V_P, and K^{trans} has a mixed interpretation. The implications for measurement are significant. If a modified Tofts model is found to describe the data well, none of the physical parameters V_P, V_E, F_P, F_E are directly measureable without making further assumptions on the nature of the tissue. In particular, the assumption that the plasma volume V_P can be derived from a modified Tofts model, is generally untrue. This may have significant implications for the interpretation of results in past and future studies. The ambiguity in the interpretation can only be resolved by sampling the data fast and precise enough, so that the no-broading approximation does not apply, and the complete two-compartment exchange model can be fitted [2].

REFERENCES: [1] Tofts et al 1999. JMRI 10: 223-232 [2] Sourbron et al 2009. MRM 62: 205-217.