Analysis of DCE-MRI in oncology: when should we use the Tofts models?

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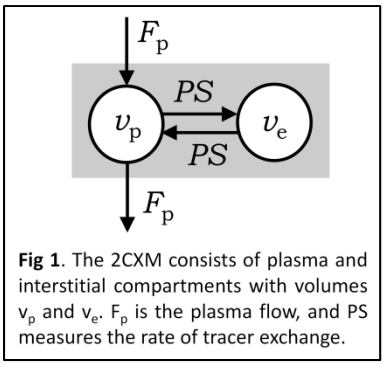

Fig 1. The 2CXM consists of plasma and interstitial compartments with volumes v_p and v_e. F_p is the plasma flow, and PS measures the rate of tracer exchange.

INTRODUCTION The Tofts Model (TM) and Extended Tofts Model (ETM) [1] have become a standard for the analysis of DCE-MRI data in oncology, but the scope of the models has never been identified rigourously. It is often assumed that the ETM applies to arbitrary tissues, but experimental data show otherwise [2], and it is recognised in [1] that a more complex model may sometimes be necessary. Hence when the Tofts models are applied blindly, the danger exists that measured values are inaccurate or misinterpreted. A thorough investigation of these issues is urgently needed, since the Tofts model parameter K^{trans} is increasingly recommended as a non-invasive biomarker to assess the effect of targeted therapeutics in oncology [3,4]. In this study, a mathematical analysis is used to identify necessary and sufficient conditions for which a TM and ETM can be applied.

METHODS Our approach is to start from a more general tracer kinetic model and identify the conditions under which it reduces to a TM or ETM. A suitable generalization is the two-compartment exchange model (2CXM) in fig 1 [5], which has the advantage that it can be solved analytically [6]. We evaluated the shape of the impulse response function (IRF) in all sections of the 4-dimensional parameter space (F_p, v_p, PS, v_e), and identified those sections where the IRF is the same as that of the TM or ETM, respectively. The analysis and conclusions are based exclusively on rigourous mathematical arguments, but simulations with a population-averaged arterial input function [7] are added as a verification and illustration of the results.

RESULTS The results show that the TM is accurate if and only if the tissue is weakly vascularised ($v_p \to 0$), and confirms that K^{trans} generally has a mixed flow-permeability weighting in this regime. The ETM is additionally accurate in highly perfused tissues ($F_p \to \infty$). If the ETM is applied outside the weakly vascularised regime ($F_p \to \infty$ and $v_p \neq 0$), the interpretation of K^{trans} is unambiguous: K^{trans} = PS. In tissues that are highly vascularised ($v_e \to 0$), or where tracer exchange between intra- and extravascular spaces is very fast (PS $\to \infty$) or very slow (PS $\to 0$), TM and ETM accurately fit the data but lead to a misinterpretation of the parameters. In tissue types with intermediate vascularity, perfusion and tracer exchange rates, neither model offers a good fit to the tissue concentrations. Simulations confirm that applying the TM or ETM outside the weakly vascularised or highly perfused regimes may lead to high errors (fig 2b). Reducing the temporal resolution improves the fit, but generally does not improve the accuracy of the measured parameters (fig 2c).

CONCLUSION The result that K^{trans} is always permeability-limited for tumors with non-negligible blood volumes is significant, and contradicts the conventional idea that K^{trans} in the ETM suffers from the same interpretation issues as the TM. Regarding the scope, the results show that the TM should only be used if prior knowledge is available which guarantees that the vascularity is small, a relatively uncommon situation in metabolically active tumors. The ETM has a broader scope and may also be used in tissues that are known to be highly perfused. In all other conditions, TM and ETM do not produce accurate values - even if they offer a good fit to the data. The implications for oncology are significant: due to the large physiological variability in tumor tissues, it is unlikely that a given tumor occupies the narrow regime where the TM or ETM apply, or that the required prior knowledge is available to decide whether this is the case. The problems can be addressed by optimizing data quality (temporal resolution, SNR, artefacts) so that a more complete model (2CXM or equivalent [8]) can be applied [2].

REFERENCES [1] Tofts et al (1999) JMRI 10: 223-32 **[2]** Donaldson et al 2010 MRM 63: 691-700 **[3]** Leach et al (2005) Br J Cancer 92: 1599-1610 **[4]** O'Connor et al (2008) Lancet Oncol 9:766-776 **[5]** Brix et al 2004 MRM 52: 420-429 **[6]** Sourbron et al (2009) *MRM* 62: 205-17 **[7]** Parker 2006 MRM 56: 993-1000 **[8]** Cheong et al (2004) Radiology 232: 921-930

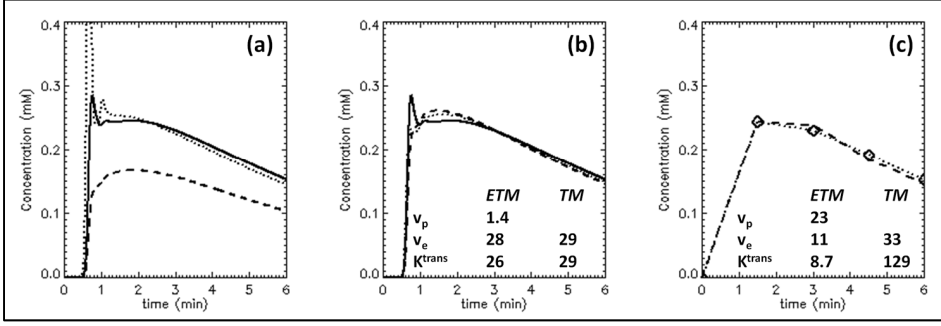

Fig 2. Illustration for an intermediate tissue with K^{trans} = 17ml/min/100ml, v_p = 10%, v_e = 20%. Fig 2a shows the exact concentrations generated by the 2CXM, the TM and the ETM. Figs 2b,c show the 2CXM concentrations downsampled at 1s and 90s, respectively, the best fits of TM and ETM, and the values of the fitted parameters. 2CXM curves are shown in a full line (a,b) or diamonds (c), the ETM in a dotted line, and the TM in a dashed line.