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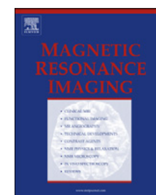

Simulating the effect of input errors on the accuracy of Tofts' pharmacokinetic model parameters

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ABSTRACT

Pharmacokinetic modeling in Dynamic Contrast Enhanced (DCE)-MRI is an elegant and useful method that provides valuable insight into angiogenesis in cancer and inflammatory diseases. Despite its widespread use, the reliability of the model results is still questioned, as many factors hamper the calculation of the model's parameters, resulting in the poor reproducibility and accuracy of the method. Pharmacokinetic modeling relies on the knowledge of inputs such as the Arterial Input Function (AIF) and of the tissue contrast agent concentration, both of which are difficult to accurately measure. Any errors in the measurement of either of the inputs propagate into the calculated pharmacokinetic model parameters (**PMP**s), and the significance of the effect depends on the source of the measurement error.

In this work we systematically investigate the effect of the incorrect estimation of the parameters describing the inputs of the model on the calculated **PMP**s when using Tofts' model. Furthermore, we analyze the dependence of these errors on the native values of the **PMP**s. We show that errors on the measurement of the native T_1 as well as errors on the parameters describing the initial peak of the AIF have the largest impact on the calculated **PMP**s. The parameter whose error has the least effect is the one describing the slow decay of the AIF.

The effect of input parameter (**IP**) errors on the calculated **PMP**s is found to be dependent on the native set of **PMP**s: this is particularly true for the errors in the flip angle, and for the errors in parameters describing the initial AIF peak. Conversely the effect of T_1 and AIF scaling errors on the calculated **PMP**s is only slightly dependent on the native **PMP**s.

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1. Introduction

The analysis of Dynamic Contrast Enhanced (DCE-MRI) data by means of Pharmacokinetic Models (PKMs) has become a widely used tool used to assess microvascular status in cancer and to monitor treatment response [1–3]. A commonly used pharmacokinetic model, generally known as "Tofts' model" [4], describes the exchange of low-molecular weight gadolinium (Gd)-based contrast agents (CA) between the tissue and the blood as a function of the time-dependent changes in the measured CA concentration in the tissue. The data used for the model are MRI images generated by a dynamic scan acquired for about 5–10 min by means of a fast T_1-weighted MRI scan during and after the injection of the contrast agent. One of the greatest advantages of using PKM over other DCE-MRI data analysis methods is that it allows the direct measurement of intrinsic physiological properties, the results being therefore portable and independent of the MR scanner or DCE-MRI protocol used. The method produces the physiology-related **PMP**s v_e (the Extravascular Extracellular Space (EES) fractional volume), K^{trans} (the volume transfer constant between plasma and EES), k_{ep}, (the rate constant between EES and plasma) and v_p (the fractional plasma space) [4]. Its value in various clinical applications has been proven and recommendations have been made on how to apply it in practice [2,5].

Despite the advantages a number of problems hamper the correct calculation of the **PMP**s. Tofts' model, as well as other models, requires the knowledge of the CA absolute concentrations in the tissue as well as of the Arterial Input Function (AIF) *i.e.* the time-dependent plasma contrast agent concentration in the capillaries feeding the modeled tissue. As the native MRI data do not directly provide a measurement of the CA's concentration, a conversion from signal intensity to concentration should first take place, and errors may occur in this process. As the conversion is derived from the observed changes in the T_1 in the tissue, the values of the native T_1 maps need to be measured separately or approximated, and any errors in these values will propagate through the signal-to-concentration conversion. B1 field inhomogeneities (leading to discrepancies between the imposed flip angles and the actual flip angle experienced by the tissue) and other assumptions made about

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the value of various constants used in the conversion (e.g. the CA relaxivity r_1 in blood and tissue) will also affect the estimation of the CA concentration.

Errors also enter the model through the estimation of the AIF. Its calculation is hampered not only by flow effects and saturation due to the high contrast agent concentration, but also by partial volume effects, and by insufficient temporal sampling, affecting especially the description of the CA first pass [6,7]. Furthermore, other factors such as the unknown hematocrit (*Hct*) also affect the amplitude of the AIF and can be a significant source of error in the calculated **PMP**s [8].

Though it is commonly accepted that measuring the AIF during the DCE scan significantly improves the results of the PKM [7,9,10], in the absence of a measurable arterial signal, fixed values of the AIF [11] or a population-based AIF [12,13] are used. Some authors also advocate the use of a standard T_1 (population based) value [14] to infer the CA concentration. Both approaches represent a source of systematic error, and therefore reduced accuracy.

A substantial effort has been made by many investigators to improve the reliability of the **PMP**s, and a wealth of correction algorithms is proposed to improve the AIF calculation [15–19], or tissue input data [20,21]. Alternative algorithms to improve the model [22] have also been proposed.

The work behind these efforts is justified by one simple fact: the results of the Tofts model are as good as the input used. Knowing the relative effect of each of the different input measurement errors on the final results might help researchers focus on the most effective way of improving their PKM results.

Two different types of effects/errors have to be distinguished: those originating from the lack of *accuracy* (i.e. the ability to determine the true value of a parameter) and those due to the *uncertainty* (i.e. the measurement-linked variation of the estimate due to the standard deviation of the measurement, a factor linked to the reproducibility) [23].

Uncertainty arises from non-reproducible results due to accidental errors. Signal noise and insufficient temporal sampling are among the major causes of uncertainty, though not the only ones. The *accuracy* in the determination of the pharmacokinetic parameters is affected, among other factors, by systematic errors in the input of the model, or by the use of a model inadequate for describing the data [10,12].

In the present work we concentrate on errors affecting the *accuracy*, and especially on the relative importance of each of the parameters describing these inputs (the **IP**s) on the accuracy of the calculated **PMP**s.

Previous work has already been published in which the propagation of errors in PKM was addressed [9,23–30]. These studies either concentrate on the error generated on the **PMP**s by measurement limitations such as noise [24] or insufficient temporal sampling [26,27], or focus on only one of the two PKM inputs (either AIF [9] or tissue concentration [24,25,28]). In the present study we compare the different sources of inaccuracy in both the PKM inputs (AIF and tissue concentration) and their relative effect on the calculated **PMP**s. We analyze how the different factors and **IP** errors affect the results of Tofts' model, and try to distinguish which **IP***s* need high measurement accuracy in order to insure reliable **PMP**s, and which **IP***s* have a comparatively smaller effect. Furthermore, we investigate the dependence of these effects on the native values of the **PMP**s. The inputs will be then related to the sources of error causing the **PMP**s inaccuracy.

2. Model

2.1. Theoretical background

Tofts' model describes the exchange of a CA moving across the plasma space and the EES through the capillary membrane. Under a number of assumptions, extensively described by Tofts et al. [4], the exchange of of CA between the plasma and the EES can be described by

$$C_t(t) = v_p C_p(t) + K^{trans} \cdot C_p(t) \otimes e^{-k_{ep} \cdot t} \tag{1}$$

with

$$k_{ep} := K^{trans}/v_e \tag{2}$$

where $C_p(t)$ is the CA concentration in the plasma, or AIF, and $C_t(t)$ is the CA concentration in the whole tissue (assuming $C_t = v_e C_e + v_p C_p$ where $C_e(t)$ is the CA concentration in the EES). The physiological meaning of K^{trans} depends on the specific balance between blood flow and capillary permeability for a specific contrast agent [4].

With the assumption of negligible plasma space ($v_p = 0$), Eq. (1) takes the simplified form

$$C_t(t) = K_{trans} \cdot C_p(t) \otimes e^{-k_{ep} \cdot t} \tag{3}$$

which neglects the contribution of the intravascular compartment in the final measured CA concentration. The term $C_p(t)$ (plasma concentration in the feeding vessel) represents the AIF. The **PMP***s* calculated through this model will be therefore (v_e, k_{ep}, K^{trans}, v_p). Eqs. (3) and (1) will be respectively referred to as the Tofts model (*TM*) and the extended Tofts Model (*ETM*).

2.2. Implementation of the pharmacokinetic model

The *TM* and *ETM* are widely used in publications using PKM of DCE-MRI data, yet the implementation of the *TM* and *ETM* varies considerably among published studies. The largest implementation differences are to be found in the way the AIF $C_p(t)$ is measured or input, the way the tissue contrast agent concentration $C_t(t)$ is calculated, and the way the data are fitted to the model [31].

2.2.1. Calculation of the contrast agent concentration from signal intensity

The *TM* and *ETM* apply to input data ($C_t(t)$ and $C_p(t)$) representing concentrations of CA measured in the tissue and in the plasma. As the signal intensity in MR data has no straightforward relationship with the contrast medium concentration (this relation varying according to the MR sequence chosen and its T_1 weighting), it needs to be transformed into Concentration Time Curves (*CTCs*). This can be achieved in different ways, such as with calibration phantoms, lookup tables, or using the theoretical relation between the signal intensity and the absolute pre-contrast T_1 values. When using the latter, the calculation of the native T_1 of the tissue (T_{10}) is required and the relation between T_1 and concentration should be known. T_{10} maps can be calculated using different techniques, such as the variable flip angle [32] or the Look–Locker [33] sequence. The theoretical relation between the contrast agent concentration and the signal depends on the MR sequence used for the DCE-MRI acquisition. If DCE-MRI data are acquired using a spoiled gradient echo sequence, the signal dependence on T_1 is represented by

$$S = kN(H) \cdot \sin\alpha \cdot \frac{1-\exp(-TR/T_1)}{1-\cos\alpha \cdot \exp(-TR/T_1)} \cdot \exp(-TE/T_2^*) \tag{4}$$

where α is the flip angle, N(H) is the proton density and *k* a sequence dependent multiplying factor dependent on the MR signal gain [32].

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