Bias and precision for hemodynamic parameters resulting from 'best model' and 'weighted model' strategies based on the Akaike Information Criterion

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Introduction

One of the approaches recently advocated for pharmacokinetic modelling of dynamic contrast enhanced MRI is to fit the data using several models of varying complexity and to rank the models on the basis of an information criterion. The Akaike Weight (AW), for instance, expresses the probability for a model to be the best amongst a set of models, taking into account the trade-off between the goodness-of-fit and the number of fit parameters for the models involved [1]. The two-compartment exchange and Tofts models (2CXM and 2CTM) are commonly used in the context of tumour perfusion studies [2]. Both models can provide an estimate of the plasma volume fraction PV, the extraction flow EF and the interstitial volume fraction EV of the tissue. The first model is general and contains a fourth parameter, the plasma flow PF. The second one is known to be a valid approximation for tissues with negligible plasma mean transit time MTTp and delivers a flow parameter Ktrans that is assumed to coincide with EF for tissues with PF>>EF (permeability limited regime [3]). The aim of this study was to investigate whether the Akaike criterion can be used to optimize estimates for PV, EF and EV. Bias and precision for the native fit models were compared with the bias and precision obtained by (1) systematically selecting the results of the model with highest AW ('best model' approach) or (2) by calculating weighted averages of the results based on the AW ('weighted model' approach, e.g. [4]). Tissues with varying validity of the 2CTM were considered by varying MTTp.

Materials and methods

The 2CXM was used to simulate measured tissue time courses [5] which were analysed using least-squares fitting by both the 2CXM and the 2CTM. The input parameters PFin, EFin, EVin were fixed at 100ml/min/100ml, 10ml/min/100ml, 25ml/100ml, respectively. PVin was varied from 0.1 to 10.0ml/100ml (step 0.1ml/100ml), leading to MTTp ranging from 0.06 to 6sec and variable validity for the 2CTM. The experimental set-up was characterized by a temporal sampling step of 1sec and a time window of 250sec. The noise was normally distributed, with a fixed SD corresponding to 10% of the maximum concentration of the noise-free time course for PVin=0.1ml/100ml. For each value of PVin (therefore of MTTp), 500 time courses were generated. For each time course, the AW of both models (AWx and AWt for the 2CXM and 2CTM, respectively) and the corresponding estimates for the parameters were calculated. On the basis of the results for 500 time courses, the 5^{th}, 50^{th} and 95^{th} percentiles of the AW and of the relative deviation of the estimated parameters from the input values were determined and plotted as a function of MTTp. All calculations were performed in IDL (Research Systems, Boulder, CO, USA).

Results

In Fig.1 the time courses corresponding to the lowest and highest MTTp considered were plotted. Fig. 2 showed, with increasing MTTp, a transition from situations where 2CTM was the best model (high AWt) to situations where the 2CXM prevailed (high AWx). In Fig. 3, the EFx, EFt, EFb and EFw, respectively obtained with 2CXM fitting, 2CTM fitting and the 'best model' and 'weighted model' approaches were plotted. The estimates from 2CTM had lower spread than those from 2CXM, but were more sensitive to bias. The 'best model' approach delivered median values that reflected those obtained by the 2CTM for MTTp<1sec and those obtained by the 2CXM for MTTp>1sec. The 'weighted model' approach led to similar results, with improved bias. In both cases, the spread about these median values resembled the one encountered using the 2CXM. Analogous results were obtained for PV and EV.

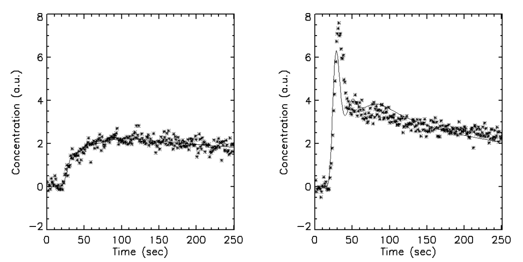

Fig. 1: Simulated time courses (dots) and 2CTM fits (line) for MTTp=0.06sec (left) and 6sec (right).

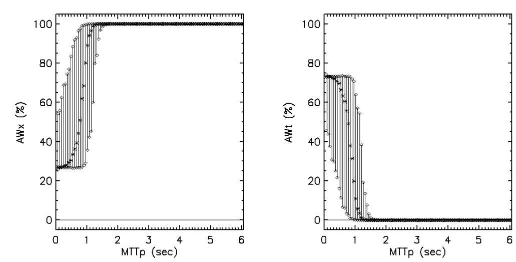

Fig. 2: Dependence of AWx (left) and AWt (right) on MTTp

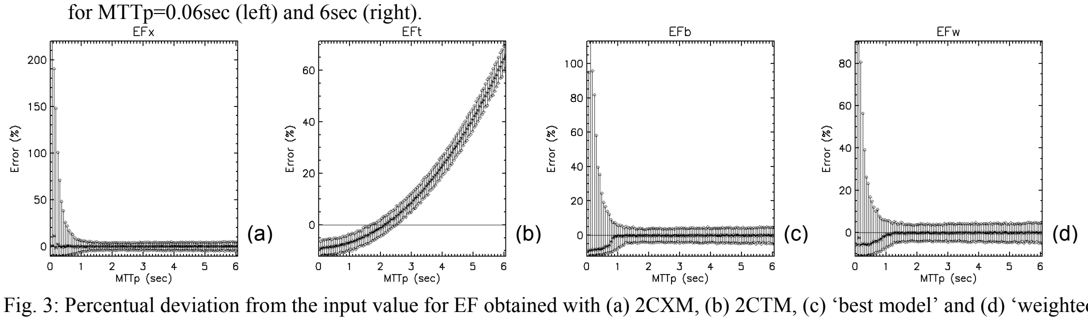

Fig. 3: Percentual deviation from the input value for EF obtained with (a) 2CXM, (b) 2CTM, (c) 'best model' and (d) 'weighted model' approach.

Discussion and conclusion

Fig. 1 confirms that the 2CTM provides a good fit for low MTTp, while it does not for high ones. The results in Fig. 3 can be understood when looking at Fig. 2: for MTTp<1sec the median of AWt becomes larger than that of AWx, indicating that, at these low values of MTTp, the 2CTM fit becomes sufficiently good to outperform the 2CXM. On the other hand, there is considerable spread about the median AW values, leading to a corresponding spread in 'best model' and 'weighted model' estimates. Even at the lowest MTTp there remains a nonzero bias for EFt, EFb, EFw, showing that, although PF is ten times EF, the permeability limited regime where Ktrans = EF is not reached: a good fit does not guarantee a valid interpretation of the derived quantities [6]. The very large uncertainty encountered at low MTTp was not anticipated: as 2CTM scores better here than 2CXM, a low spread resembling the one in Fig. 3(b) was expected.

These examples show that, although the 'best model' and 'weighted model' approaches based on Akaike do lead to optimized estimates, these estimates can have unexpected and undesirable properties that could hamper the usefulness of these approaches.

References

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