Information Criteria weighted Parameter Estimates in DCE-MRI

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Target Audience: Investigators using DCE-MRI in clinic or in preclinical models, who are interested in optimizing the achievable parameter precision and accuracy through choice of the appropriate modelling procedure.

Introduction: Pharmacokinetic models are widely used for the data analysis of DCE-MRI[1]. They map the physiological properties of tissues onto a set of haemodynamic parameters. These models vary in their complexity and in their underlying assumptions. Thus, the accuracy and the precision of their parameter estimates is varied and depends on the data quality and the tissue physiology. It seems therefore promising to take the decision for a certain model on a voxel-wise basis and to combine estimate from different models. The application of information criteria for obtaining a weighted mixed-model estimate has been addressed in a previous simulation study[2] and the absence of a systematic benefit has been reported. The mentioned study focused on the model complexity by using nested models, where the most complex model defines the ground truth. Our approach is different in two ways. In order to closely resemble an experimental situation, a more complex model for tissue uptake simulations was chosen and a larger set of partially nested models was considered. We aim to describe the performance of mixed-model inference in DCE-MRI from a most applied perspective. **Methods:** Based on published arterial input functions in mice[3] and humans[4], tissue uptake curves are simulated using the Multiple path, Multiple tracer, Indicator Dilution, 4 region model (MMID4)[5]. This model simulates blood tissue exchange and accounts for flow dispersion and heterogeneity. From the large number of parameters, that are variable within the MMID4, only the mean plasma flow (F_p), the permeability surface area (PS), the fractional plasma and interstitial volume (v_p, v_e) are modified. Tissue uptake curves were simulated for the eight possible combinations of F_p[ml/g/min]=0.5,1.2; PS[ml/g/min]=0.2,0.6; v_p=0.001,0.05; v_e=0.4. The volume transfer constant is calculated according to $K^{trans} = F_p \cdot PS / (F_p + PS)$. Gaussian noise (SNR=30) is added to the associated FLASH signal, whereupon five pharmacokinetic models are fit to derive estimates of the volume transfer constant K^{trans}. The simple Tofts Model (TM), the extended Tofts Model (ETM), the 2-compartment exchange model (2CXM), the adiabatic approximation to the tissue homogeneity model (AATH), and the distributed parameter model (DPM) have recently been discussed[1]. A parametric bootstrap procedure approximates the statistical distribution of each model's K^{trans} estimates with 500 iterations. The best fit parameters for each model are determined by a brute force search with noise-free data. Initial guesses for the subsequent application of a least-squares search algorithm are sampled from a uniform distribution around the best guesses with a width of 25%, in order to resemble a realistic case, where the researcher has limited prior knowledge of the true tissue parameters. Fit parameters are constricted to be positive and fractional volumes to be smaller than one. Based on the Akaike (AIC) and the Bayesian information criterion (BIC), each model's probability to be the best among the five models is calculated[6]. The probabilities are used as weights to calculate a weighted mean estimate. **Results:** Examples for AIC weights and the resulting K^{trans} distributions for the five models and their AIC weighted means are shown in Fig. 1, for a human AIF and a tissue with low F_p and PS, and a significant v_p. Fig. 2 summarizes all investigated tissues and shows the mean coefficient of variation (precision, top) and the mean deviation from the true parameter (accuracy, bottom). Either TM, ETM, 2CXM are chosen as *best* model, while ATHM and DPM have lower model weights, throughout. AIC-weighted K^{trans} estimates are roughly as precise and accurate, as the most precise and the most accurate model. This is observed for the average (Fig. 2), as well as for every single tissue (not shown). The model weights vary distinctly for different tissue types, while AIC-weighted parameter estimates improve the precision and the accuracy of K^{trans} estimates, throughout. The BIC favors models with fewer parameters, while its mixed-models estimates are of similar overall goodness, as those from the AIC (data not shown). **Discussion/Conclusion:** The mixed-model derived predictions were never worse than the individual model parameters in terms of precision and accuracy. Especially for heterogeneous tissues, mixed-model estimates are an advisable strategy and attach weight to the models, which describe the data in each voxel appropriately. The chosen set of models is partially nested, which limits the theoretical justification of the suggest procedure. Nevertheless, this simulation study shows, that such multi-model inference practically improves the quality of haemodynamic parameter estimates. Different models and model sets, as well as other haemodynamic parameters are subject of further investigation.

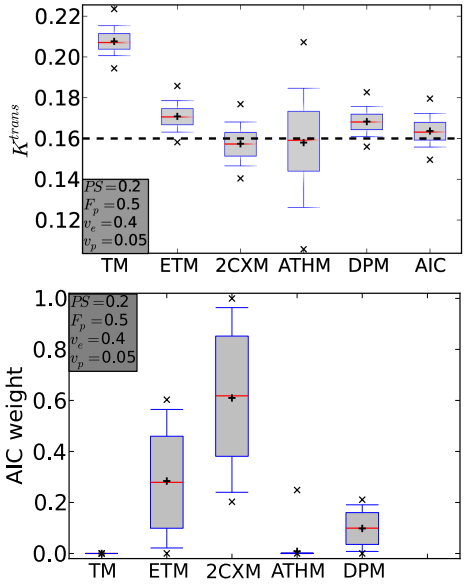

Fig 1: Bootstrap distribution of the model weights (top) and the resulting estimates (bottom) from a mouse AIF. The box-whisker plot shows the median (red) and limits of 1st and 3rd quartiles. The mean is indicated using a '+'. The whiskers extend to the 10th and 90th percentile, respectively, while the 1st and 99th percentile are shown using an 'x'.

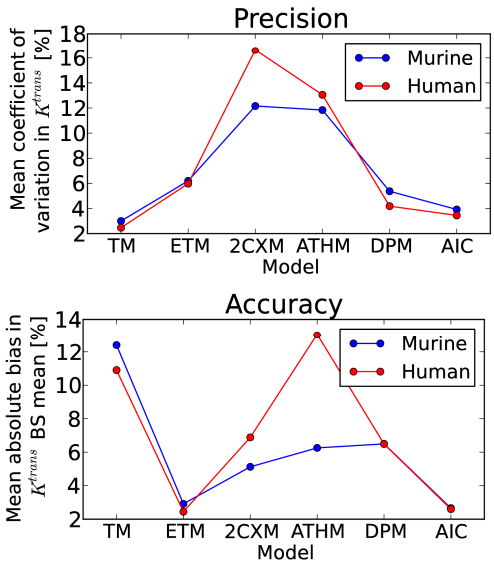

Fig 2: Mean precision (top) and accuracy (bottom) for eight different tissues and human and mouse AIFs. The AIC weighted mean features high accuracy and high precision.

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