How to assess the quality of microcirculation parameters of tumors from CE-MRI fitting, by combining reliability criteria and the Fisher matrix

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Introduction: Microcirculation quantification by contrast–enhanced magnetic resonance (CE-MRI) has a lot of potentials in cancer diagnostic and in therapeutic evaluation [1]. However, it is mandatory to evaluate the relevance of the model used for fit the time-enhancement curves and the accuracy of the parameters resulting from this fit. Firstly, we have proposed two "reliability" criteria [2] called the *Fraction of Modeled Information* (FMI) and the *Fraction of Residual information* (FRI), which are more efficient than conventional criteria (such as square error or correlation coefficient R^2) to detect poor fits. These criteria can be used to detect over-simplified models that cannot fit time-enhancement curve. Secondly, Fisher matrix is conventionally used to estimate covariance matrix of physiological parameters, which indicates standard deviation of each parameter (diagonal elements of the matrix) and the redundancy between each pair of parameters (no diagonal elements of the matrix). The Fisher matrix can be used to detect over-complex models, i.e. models with surfeit parameters which are not detectable in the data. The aim of this study is to show how reliability criteria (FMI and FRI) and Fisher matrix can be used as complementary tools to choose the best fitting model, that is to say the most adapted model for a set of CE-MRI data.

Methods: Experimental MRI studies were undertaken on nude mice bearing human prostatic adenocarcinomas (PC3). A rapid-clearance blood pool macromolecular contrast agent (Vistarem®, Guerbet) was used for injections. Dynamic MRI was undertaken with a bolus injection of a dose of 0.045 mMol(Gd)/kg of contrast agent. A series of 512 2D FSPGR images (TR/TE 15/2.2 ms, FA 60°, thickness: 5mm, matrix 256x128, FOV 70x30mm, temporal resolution 1.1s per image) was acquired on a 1.5-T clinical device (Signa®, GE). After each acquisition, the same sequence was applied to a regular set of six tubes of Vistarem to convert the signal enhancement of the arterial input function (selected in the left ventricle) and the tumor tissue into concentration of contrast agent [3]. Parametric images of tissue blood perfusion (TBF), tissue blood volume (TBV) and permeability-surface product (PS) were calculated by modeling the time enhancement curve of each pixel, with a one- (M1) and a two-compartment model (M2) on the whole series of 512 images (long series) and on the first 51 selected images of the series (first-pass series). The one compartment model M1 does not take into account the leakage of the contrast agent into the extra-capillary space, and therefore should be best suited to fit the first-pass series, whereas the two compartment model M2, that takes into account the leakage, should be best suited to fit the long series which includes the steady state. For each fitting, the FMI and FRI criteria were calculated, with a previously described method [2] on a pixel by pixel basis, to estimate fit success, and the diagonal elements of Fisher matrix where used to estimate the confidence interval (CI) of each parameter (i.e. 1.96 x relative standard deviation, expressed in %).

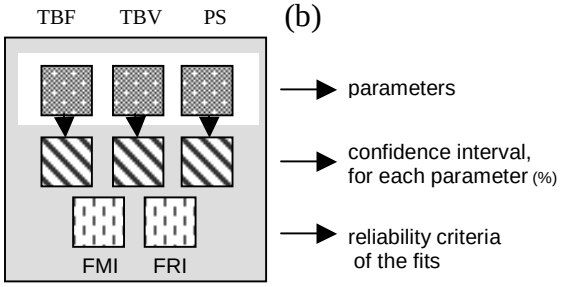
Results:

1) *Reliability criteria maps* (fig. 1(a)-3rd line of each square): the pixels in the FMI maps are mostly in red (FMI ≈ 1), and they are mostly in blue in the FRI maps (FRI ≈ 0). These reliability criteria maps indicate successful fits over the entire tumor, except for the long series fitted with the M1 model (surrounded in orange).

2) *Confidence intervals maps* (fig. 1(a)-2nd line of each square): estimated confidence intervals of each parameter, performed with Fisher matrix, are mostly around or fewer than 30%, except for the first-pass series fitted with the M2 model, where the CI of the PS values are very large (surrounded in green).

3) *Parameter maps*: there is a remarkable similitude between the TBF and TBV maps obtained with M1 on the first-pass series and the TBF and TBV maps obtained with M2 on the long series (fig.1(a) -1st line of the top left square and of the bottom right square). These maps were obtained with the models which appear to be well adapted to the set of time-enhancement data according to both set of criteria. Whereas, the TBF and TBV maps obtained with M1 on the long series are different and PS maps obtained with M2 on the first-pass series are very noisy.

Conclusion: These results indicated that permeability information is not available in first-pass series whereas it has to be taken into account for long series (doing so: it does not only offer new information (PS) but it also avoids bias in TBF and TBV measurement). Both the reliability criteria and the Fisher matrix have to be used to get selection of models which are adapted to each study, by detecting over-simplified models and over-complex models. These sets of criteria could also be used to adapt an acquisition protocol to a specific model, for example to establish the required acquisition duration for a one-compartment model.



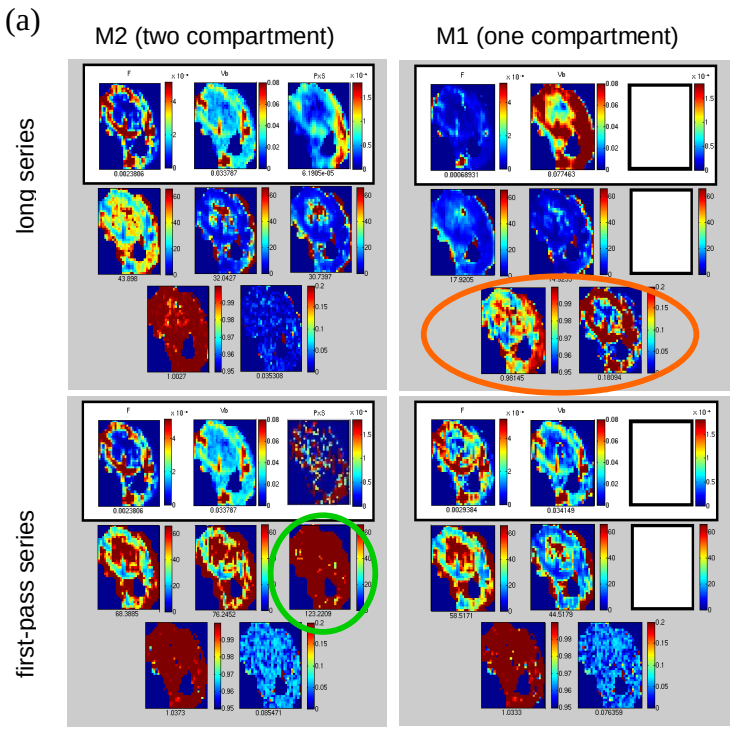


Figure 1: Parametric images of a PC3 tumor in a nude mouse. The color-coded maps (a) depict the perfusion parameters and the criteria used to assess the quality of the fit performed for first-pass and long series, with one- and two-compartmental models. Each result is presented as indicated in the diagram (b). Reliability criteria indicate over-simplified modeling of long study by M1 (orange ellipse) and confidence intervals detect an over-complex modeling of first pass by M2 (green circle).

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