MR Estimation of Permeability Parameters in Dynamic Contrast Enhanced Studies Using Model Averaging Technique and Nested Model Selection Method

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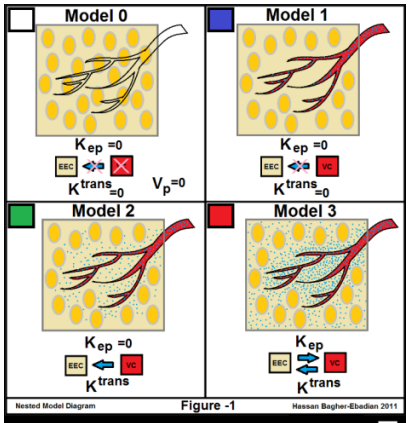
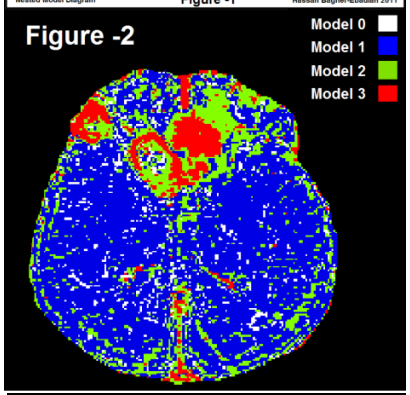
Target Audience: Neuroradiologists, neurologists, and medical physicists who are interested in compartmental modeling and brain tumor permeability

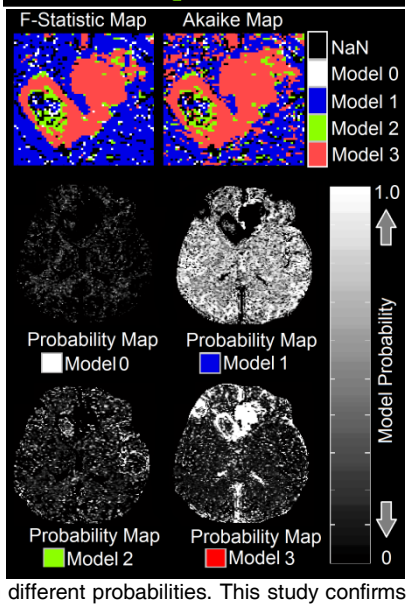
Purpose: Reasoning that assessment of the pathological physiology of solid tumors can aid in treatment planning and assessing drug therapy, researchers and clinicians are increasingly employing dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) to study high-risk brain tumors and breast cancers[1,2]. A number of pharmacokinetic models are in use, including the widely used Tofts models, the shutter-speed model (which accounts for water-exchange effects), and the Brix model[1,2]. Our group has recently shown[2] that a standard statistical approach can appropriately address the problem of model selection in DCE-MR data analysis. Although the conventional model selection approaches provide a more precise way of processing DCE-MR data, they have been constructed based on this assumption, which may not hold true: The measured time trace of contrast agent (CA) concentration for each voxel belongs to only one possible model. However, in a given voxel's time trace of CA concentration, different models may exist with varying probabilities. Herein, we recruit a '*model averaging*' concept in DCE-MR model selection using the Akaike Information Criterion (AIC)[3] that provides a unique set of probability maps for estimating the contribution of each model in a specific voxel. These probabilities allow combining and averaging the estimated parameters from different models, and thus generating a more accurate estimate of permeability parameters.



Methods: We have shown[2] that a set of nested models with as many as three parameters can be employed to estimate plasma volume (v_p), or v_p and forward vascular transfer constant (K^{trans}) for the CA molecules such as Gd-DTPA, or v_p, K^{trans}, and the reverse vascular transfer constant (k_{ep}). As shown in Figure 1 and 2, these constitute Models 1, 2 and 3 respectively, with Model 0 introduced for the areas with no evidence of CA vascular filling ($\Delta R_1(t)=0$, no change in profile of relaxivity rate change) and NaN Model for voxels not having enough information in their signal to calculate ΔR_1. Thus, Model 0 refers to areas with no vasculature or the areas with no evidence of CA filling in presumably necrotic areas. In this pilot study, the AIC was recruited for model selection (Models 0, 1, 2, and 3) and also for model averaging to estimate permeability parameters from DCE-MR data of 10 patients suffering from cerebral Glioblastoma Multiforme. In the MR experiment, a Variable-Flip-Angle (VFA-DESPOT1) pulse sequence (3D-Spoiled-Gradient Echo, flip angles: 2, 5, 10, 15, 20, and 25) was followed by a DCE-T1 (3D-SPGRE, flip angle: 30 degree, TR/TE: 5.8/1.3ms, matrix size: 256X256, 5.7 sec time res., 16 slices, Magnevist: 0.1mol/kg, 4ml/sec) experiment using a 3T GE scanner. The VFA MR experiment was used to calculate resting T_1 maps. Using the pre-contrast T_1 maps and dynamic data, the time trace of the CA concentration (ΔR_1) was calculated. Arterial input functions (AIFs) were picked by a trained Neuroradiologist. For each voxel, 4 nested models were fitted to the time trace of CA concentration using Levenberg-Marquardt nonlinear least squares fitting technique. Fitting residues were used to construct an F- statistic and sample-corrected AIC maps. The corrected AIC[3] was used to estimate Akaike's weights or model probabilities for the purpose of model selection and model averaging for estimation of permeability parameters from 4 different nested models.



Results: Figure 1 and 2 illustrate the physiological concept along with an exemplary regional model choice map for the nested model selection technique. Figure 3 represents model selection and model averaging maps for an exemplary case. The top row of this figure illustrates model selection maps for a zoomed part of the lesion obtained from different model selection techniques as follows: F-Statistic (at %90 confidence level), and sample corrected AIC. The two bottom rows of this figure show the maps of probabilities for 4 different nested models (0, 1, 2, and 3) generated from the AIC's weights. These probability maps clearly show the uncertainty and also the confidence levels in the selection of each of the four different models. As shown in this figure, the model map generated by the 2 different techniques (F-Statistic and AIC) are in substantial agreement. Note that the model selection maps in Figure 2 and 3 have been produced using different confidence level.



Discussion: In this pilot study we studied and tested the feasibility of recruiting the AIC and model averaging concept in DCE-MR data analysis. Results imply that the AIC technique is capable for correcting deficiencies (uniqueness of selected models for each voxel) associated with the conventional model selection techniques such as F-statistic. The probability maps estimated by the AIC can directly address the level of uncertainty in the estimation of permeability parameters pertinent to each model. To the best of our knowledge in the field of DCE-MR, recruiting the model averaging concept and its application in real DCE-MR experiments is novel for the estimation of pharmacokinetic parameters. Results of this pilot study point to the rich potential for model averaging in DCE studies using the Nested Model Selection technique.

Conclusion: Model averaging technique can address the problem of heterogeneity that exists in evaluating cerebral glioblastomas, and possibly in other pathologies such as breast cancers. AIC model averaging provides quantitative and useful information relevant to the level of the contribution of each model in a certain voxel in form of probability measure. Thus, a leaky voxel could be consisting of different models with different probabilities. This study confirms that while the conventional model selection techniques are the best and appropriate approaches in DCE-MR data analysis, their uncertainty levels in their model selection need to be quantified and also taken into account in order to produce relatively unbiased estimate of permeability parameters.

References:

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3. Luypaert R, Ingrisch M, Sourbron S, de Mey J. The Akaike information criterion in DCE-MRI, *J Phys Med Biol* 2012;57(11):3609-3628.