Classical and Knowledge-Based Pharmacokinetic Model Selection Techniques in Analysis of Dynamic Contrast Enhanced MRI Studies: Performance and Bias Comparison

Hassan Bagher-Ebadian[1,2], Mohammadreza Mohammadian-Behbahani[3,4], Azimeh Noorizadeh Vahed Dehkordi[3,5], James R Ewing[2,6], Alireza Kamali-Asl[3], Siamak P Nejad-Davarani[7], Hamed Moradi[8], Stephen Brown[2,9], Brent Griffith[10], Ali S Arbab[11], Tom Mikkelsen[12], Lisa Scarpace[12], and Hamid Soltanian-Zadeh[1,13]

[1]Radiology and Research Administration, Henry Ford Hospital, Detroit, Michigan, United States, [2]Physics, Oakland University, Rochester, Michigan, United States, [3]Nuclear Engineering, Shahid Beheshti University, Tehran, Iran, [4]Nuclear Engineering, Amir-Kabir University of Technology, Tehran, Iran, [5]Nuclear Engineering, Najaf Abad Branch, Islamic Azad University, Isfahan, Iran, [6]Neurology, Henry Ford Hospital, Detroit, Michigan, United States, [7]Neurology, Henry Ford Hospital, Michigan, Iran, [8]Nuclear Engineering, Shiraz University, Shiraz, Fars, Iran, [9]Radiation Oncology, Henry Ford Hospital, Detroit, Michigan, United States, [10]Radiology, Henry Ford Hospital, Detroit, Michigan, United States, [11]GRU Cancer Center, Georgia Regents University, Atlanta, Georgia, United States, [12]Neurosurgery, Henry Ford Hospital, Detroit, Michigan, United States, [13]CIPCE, School of Electrical and Computer Engineering, University of Tehran, Tehran, Iran

Target Audience: Neuroradiologists, Neurologist, and medical physicists who are interested in pharmacokinetic modeling and brain tumor studies.

Introduction: Model selection (MS) techniques are inspired by the principle of parsimony[1] also known as *Ockham's razor*. MS techniques identify the model that is most closely supported by the observed data (referred to as the 'best model') among a set of candidate models[1]. Quantitative analysis of tissue vascular permeability and estimation of Pharmacokinetic (PK) model parameters[2,3] using Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) is achieved through a series of processing steps in which Pharmacokinetic Model Selection (PK-MS) is one of the most crucial steps. Given DCE-MRI data, accurate estimation of PK parameters strongly relies on appropriate selection of the best PK model to fit the data. In general, for DCE-MRI data analysis, one of the main challenges is to choose the best PK model among competing models to describe the behavior of the time trace of contrast agent (CA) concentration in DCE MR experiments. The F-Statistic (F-test)[4], Akaike Information Criterion (AIC)[5], Bayesian Information Criterion (BIC)[6] and Log-Likelihood Ratio (LLR)[7] tests are the most widely used members of classical MS techniques[4,5,6,7]. In addition to these classical MS techniques, our group has recently introduced an Adaptive MS method, based on an Artificial Neural Networks (ANN) to perform PK-MS for the analysis of DCE-MRI data. This study investigates the performance of different MS techniques (F-Test, AIC, reduced AIC, BIC, LLR, ANN) for selection of the PK model as well as the impact of the recruited MS technique on the estimation of PK parameters in DCE-MRI data analysis.

Material and Methods: In this study, three physiologically nested models derived from the standard Tofts model[8] were used to describe possible physiological conditions of underlying tissue pathology as following: Model 1: refers to the condition that the tissue vascular compartment is filled with CA with no outward leakage. Model 2: refers to the condition that the tissue vascular compartment is filled with CA with outward leakage but no evidence of back-flux. Model 3: refers to the condition that the tissue vascular compartment is filled with CA with both outward and backward-flux. Plasma volume (v_p), v_p and forward vascular transfer constant (k^{trans}), v_p, k^{trans} and reverse vascular transfer constant (k_{ep}) are the PK parameters for Models 1, 2 and 3 respectively[2,3]. A set of experimental Arterial Input Function (AIF) curves, manually picked by different experts from DCE-MRI data of the human brain was used to simulate the time trace of CA concentration for the three models. Twenty AIFs (manually chosen from the DCE-MRI data of 20 patients) plus one Averaged-AIF (constructed by averaging 60 different hand-picked AIFs) were used to generate CA concentration profiles for three different PK models according to the Tofts equations (Equation-1: $C_t(t)$ is the time trace of CA concentration) for Models 1, 2 and 3. In this study using the 21 AIFs and by varying different PK parameters for the three PK models (1, 2, and 3), 9072 time traces of CA concentration (with time resolution of 5.03 sec) for 12 levels of SNRs (Rician noises with SNRs of 5, 8, 10, 12, 15, 18, 20, 25, 30, 50, 100 and no noise) were generated. Simulating the CA concentration profiles at such SNRs and PK parameter variations assured the closest replication of CA concentration profiles acquired in DCE-MRI experiments. The simulated CA concentration profiles were fitted to the three different models (1, 2, and 3) using Maximum Likelihood technique[7]. This allowed generating Log-Likelihood measures for all models. Using the residual sum of squares and Log-Likelihood measures for each fitted model, six different MS techniques were employed to choose the best model among the three models (1, 2, and 3). Confusion matrices were computed for all the six MS techniques over the 9072 tested hypotheses to quantify the performance of different MS techniques in model judgment. PK parameters of each chosen model were estimated and compared to their ground truth values for quantification of bias and variance of each MS technique.

$$C_t(t) = v_p\, C_p(t) + K^{trans} \int_0^t AIF(\tau) e^{-k_{ep}(t-\tau)} d\tau \qquad \text{Equation-1}$$

Table -1	C_{11}	C_{12}	C_{13}	C_{21}	C_{22}	C_{23}	C_{31}	C_{32}	C_{33}
Perfect MS	1.00	0	0	0	1.00	0	0	0	1.00
ANN	1.00	0	0	0	0.98	0.02	0	0.01	0.99
F-Test	0.35	0.42	0.13	0	0.85	0.15	0	0.12	0.88
AIC	0.77	0.13	0.10	0	0.71	0.29	0	0.14	0.86
AIC_c	0.78	0.13	0.09	0	0.73	0.27	0	0.15	0.85
BIC	0.93	0.05	0.02	0	0.84	0.16	0	0.27	0.73
LLR	0.93	0.06	0.01	0	0.83	0.17	0	0.25	0.75

Table -2	v_{p1}(%)	v_{p2}(%)	v_{p3}(%)	$K^{trans}{}_2$(%)	$K^{trans}{}_3$(%)	k_{ep3}(%)
ANN	-0.46	-4.10	-1.01	-2.52	-0.36	1.23
F-Test	-0.30	-65.64	7.86	24.63	14.64	3.94
AIC	-0.50	-55.08	13.10	7.51	18.66	14.24
AIC_c	-0.47	-55.32	12.84	6.31	17.28	13.27
BIC	-0.38	-59.08	10.86	-5.10	7.71	5.52
LLR	-0.39	-57.82	11.43	-4.07	6.98	6.22

Results and Conclusions: Table 1 illustrates the 9 elements of the Confusion Matrices (CMs) for all the six MS techniques as well as the perfect MS. C_{mn} represents the ratio of number of judgments in favor of model ***n*** when model ***m*** is judged by the MS technique. As shown in this table, the performance of the Adaptive MS technique is superior (close to the perfect MS) to the other MS techniques. Other techniques show reasonable performances in the following order: LLR, BIC, AICc, AIC and F-Test. According to this table, the C_{21} and C_{31} elements being zero for all MS techniques implies that all MS techniques (Adaptive and Classical) would never miss any tissue with leaky vasculature (Model 2 and 3). Table 2 shows the bias of estimates for all PK parameters (Model 1, 2 and 3) for all MS techniques in percentile (negative and positive signs indicates over and under-estimation respectively). Results imply that the Adaptive MS technique generates significantly less biased estimates of PK parameters compared to the classical MS techniques while both the LLR and BIC methods outperform the other classical MS techniques. This pilot study suggests that Adaptive models (ANN), LLR and BIC are the best candidates among the MS techniques for PK analysis of DCE-MRI data.

References:

[1] Hansen MH., et al, J of the Am. Stat. Assoc. 96(45):746-774(2001).
[2] Bagher-Ebadian H., et al, Magn Reson Med, 68(1):241-251(2012).
[3] Ewing JR., et al, NMR in Biomed., 26(8):1028-1041(2013).
[4] Chernoff H., et al, Math. Statist. 1: 579-586(1954).
[5] Akaike H., 2nd Int. Symp. on IT, Vol. 1: 267-281(1973).
[6] Reid MC., et al, Am J Med 104, 374-380(1998).
[7] Schwarz G., et al, Annals of Statist. 6, 461-464(1978).
[8] Tofts PS., et al, Magn Reson Med 1, 17:357-367(1991).