Model Comparison and Reproducibility Test of DCE-MRI in Glioblastoma Patients

P-J. Chen[1,2], W-T. Zhang[2,3], E. di Tomaso[3], D. G. Duda[3], R. K. Jain[3], T. T. Batchelor[3], and A. G. Sorensen[2,3]

[1]Department of Nuclear Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA, United States, [2]Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, United States, [3]Massachusetts General Hospital, Boston, MA, United States

Introduction:
We compare two pharmacokinetic analysis techniques: the generalized kinetic model (GKM) and one that attempts to incorporate the effects of a significant vascular contribution (mGKM) in thirteen patients with recurrent glioblastoma multiforme (GBM) undergoing Dynamic Contrast Enhanced MRI (DCE-MRI). The reproducibility of the principle parameters including transfer constants (Ktrans and Kep) of contrast agent between plasma and extravascular and extracellular space and blood plasma volume fraction (vp) from mGKM is also tested.

Materials and Methods:
Thirteen patients underwent DCE-MRI on the same 3 Tesla MRI system (TimTrio, Siemens Medical Solutions, Malvern, Pennsylvania). This is a series of acquisitions of a 50.6 mm thick slab consisting of 20 slices. All scans are 2.9 mm x 2.0 mm in-plane resolution, with a 2.1 mm slice thickness, 0.4 mm inter-slice gap, using a fast gradient echo technique (TR 5.7ms and TE 2.73ms). Data to allow computation of a T1 map of the tissue of interest is initial created using five different flip angles (2, 5, 10, 15, 30 degrees). Then, the same slab of tissue is sampled with a 10 degree flip angle every 5.04 seconds for 252 seconds (50 time points), and 0.1 mMol/kg of Gd-DTPA was injected 52 seconds after the beginning of the acquisition at 5 cc/second. All patients were scanned at two baseline time points, typically 3 to 7 days apart (average: 5.7). No drug intervention was given in between the two studies. T1 maps were then used to convert the signal intensity to concentration. Ktrans and Kep are estimated by GKM and mGKM model respectively (formulas for both models are shown below); vp could only be obtained by mGKM. Median values of the parameters of interest were calculated from the manually defined enhancing tumor as the volumes of interest for each visit. For each subjects, the reproducibility of each pairwise comparison was assessed using the test-retest root mean square (RMS) coefficient of variation (CoV) and Spearman's correlation test was used to see the correlation between two visits. A P-value < 0.05 was considered statistically significant.

$$C_t(t) = ktrans \int_0^t C_p(t)\exp(-kep\,(t-\tau))\,d\tau$$

GKM where Cp(t) is the vascular input function.

$$C_t(t) = v_p \bullet C_p(t) + ktrans \int_0^t C_p(t)\exp(-kep\,(t-\tau))\,d\tau$$

mGKM includes the intravascular signal contribution.

Results and Discussions:
Our results showed that the GKM could not adequately capture the details of the concentration change in our glioblastoma data while the mGKM fits nicely with the data. A representative fitting result from both models is shown in figure 1. Since blood volume could increase markedly in neoplasms, it is not surprising that the attempts to incorporate the effects of significant signal contribution from vasculature improve the modeling accuracy significantly. Figure 2 compares the root-mean-square (RMS) error between GKM and mGKM. mGKM shows convincingly better fitting result for all thirteen patients ($P < 0.0001$). Moreover, Ktrans estimation from GKM is higher than that from mGKM ($P < 0.0001$). The reason for this over-estimation is that GKM considered the contribution of intravascular contrast agent to the signal also caused by the tracer that enters extravascular extracellular space (EES), thus erroneously calculating pseudo-permeability. Since we consider that mGKM is the more adequate model for our glioblastoma data, the following discussions will only concern the results from mGKM. In order to apply the analysis technique for drug effect evaluation, the knowledge of the reproducibility is essential to determine the statistical power. Figure 3 showed a good correlation of Ktrans between two visits and a straight line with a slope of 1.062 was fitted by that set of data. The results from Spearman's correlation test also showed that median Ktrans values of two visits were highly correlated ($r = 0.8297$, $P < 0.001$), median Kep with a correlation coefficient $r = 0.7418$ ($P < 0.05$), and median vp with $r = 0.8297$ ($P < 0.001$). The test-retest RMS CoV of median Ktrans, Kep and vp were 0.08, 0.12 and 0.13 respectively. All three parameters from mGKM demonstrated good reproducibility between two visits. Figure 4 gave the summary of tumor volumes and fitted parameters of each visit where blue bar represents the result from the first visit and red bar the second.

Conclusions:
Our data suggest that mGKM is a more appropriate model for DCE-MRI of glioblastoma due to the significant increased vascular volume in the tumor regions. It also demonstrates robust reproducibility between visits. The results of our study clearly suggest that mGKM model is a valid choice for evaluate anti-angiogenic agent treatment for brain tumor in which bio-makers such as Ktrans, kep and vp can be estimated. These parameters offer us the possibility of insight into underlying physiology that in turn may allows us to more closely assess drugs effects.

References
1. Tofts, P.S., et al, J Magn Reson Imaging. 1999;10:223-32. **2**. Roberts C., et al J Magn Reson. Imaging. 2006;23:554-563

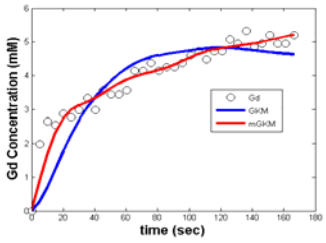

Fig. 1 shows mGKM (red line) is a more adequate model to describe the contrast signal dynamic in glioblastoma patients.

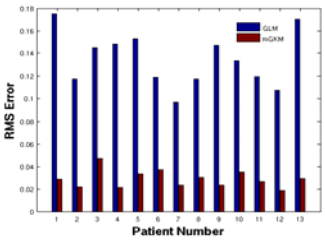

Fig. 2. RMS error comparison between GKM and mGKM. It showed that mGKM is a more adequate model to estimate permeability in glioblastoma patients

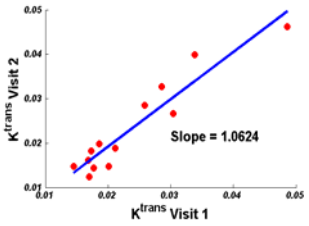

Fig. 3 Plot Ktrans of visit1 against visit2. It showed a good correlation of Ktrans between visits.

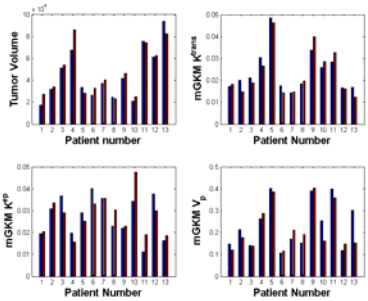

Fig. 4. Summary of tumor volumes and mGKM parameters where red and blue bar represent visit1 and visit2 respectively.