Joint Estimation of AIF and Perfusion Parameters from Dynamic Susceptibility Contrast MRI in Mouse Gliomas Using a Tissue Model

K. E. Chaffee[1], J. S. Shimony[1], G. L. Bretthorst[1], and J. R. Garbow[1]
[1]Radiology, Washington University, Saint Louis, MO, United States

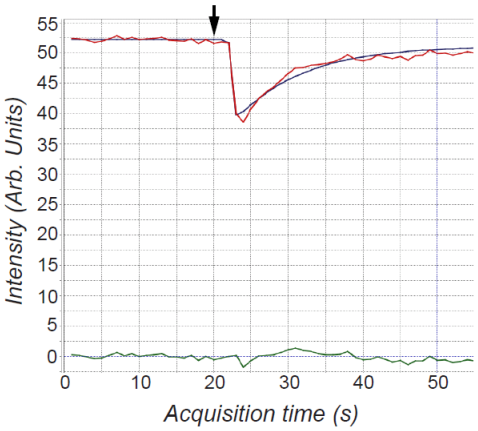

Fig. 1. Perfusion MRI was used to analyze perfusion parameters in mouse DBT gliomas. Signal intensity vs. time (red) during the passage of the contrast bolus in a region of interest with tumor of a mouse at POD 14. Model estimation of the signal intensity is shown in blue and the residual in green.

Introduction: MRI perfusion measurements have been shown to correlate with angiogenesis and brain tumor progression [1], and are, thus, a potential source of information about both tumor development and response to therapy. Traditionally, quantification of perfusion depends on accurate measurement of the contrast agent concentration in the blood, the so-called arterial input function (AIF). AIF measurements are particularly difficult in rodents, where partial volume effects and motion present significant challenges. Using a modification of standard tracer kinetic principles, we applied a tissue perfusion model that allows both the AIF and residue curve to be determined for each pixel in the image in a mouse glioma model. The parameters appearing in this model are estimated by Bayesian probability theory (BPT) using Markov chain Monte Carlo simulations to sample the joint posterior probabilities for the parameters [2].

Materials and Methods: *Mice and tumor implantation.* DBT glioblastoma cells were implanted into the brains of female Balb/c mice as previously described [3]. *μMRI and pMRI.* Nine mice were imaged between 7 to 18 days after the DBT cells were injected intracerebrally. Prior to each imaging experiment, mice were anesthetized with isoflurane/O_2 [2% (v/v)], intravenous catheters were surgically inserted into the jugular veins for contrast agent administration, and isoflurane/O_2 was reduced to [1% (v/v)] for maintenance. Experiments were performed on an 11.7-T Varian scanner using an actively decoupled volume (transmit) / surface (receive) coil pair. The brain of each mouse was imaged with a multislice T_2-weighted spin-echo pulse sequence (echo time (TE) = 30 ms; repetition time (TR) = 2 s; field of view (FOV) = 15 × 15 mm^2; matrix= 256 × 128; 21 slices; slice thickness = 750 μm; NT = 4; total imaging time = 17 min), data not shown, and a T_1-weighted spin-echo pulse sequence (TE = 20 ms; TR = 1000 ms; other parameters same as T_2-weighted spin echo; total imaging time = 8.5 min). For perfusion MRI (pMRI), a series of T_2*-weighted gradient echo fast low-angle shot (FLASH) (TE = 10 ms; TR = 15.65 ms, FA = 20°; FOV = 15 × 15 mm^2; matrix = 64 × 64; 1 slice; slice thickness = 750 μm) images were acquired from a slice through the center of the tumor, determined from the T_2-weighted images. Images were acquired every second for 100 seconds following a 1-s injection of Multihance (Gd-BOPTA) at 0.2-mmol/kg via the jugular vein catheter. The contrast bolus was injected after the 20th image acquisition. These data sets were analyzed using the model described below.

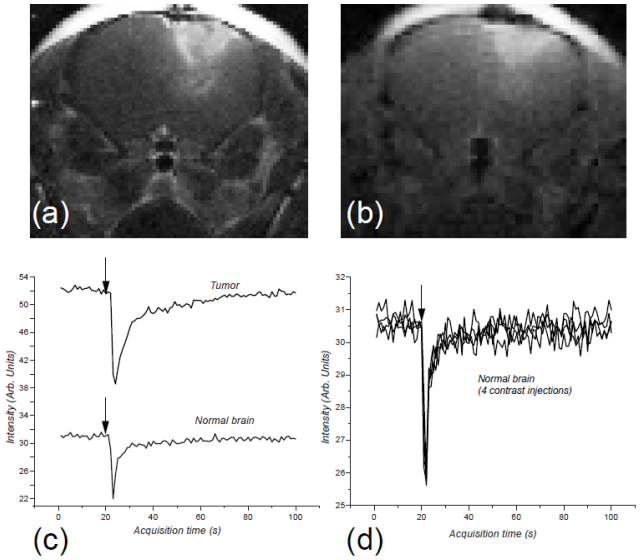

Fig. 2. Axial, postcontrast (a) T_1-weighted, and (b) dynamic T_2*-weighted μMR images of a 2-week tumor. Signal-intensity time-course data are shown for (c) a comparison between tumor and normal brain (same mouse as in Figs. 1 and 2 (a-b)) and (d) four contrast boluses, injected at 10-min intervals in a normal, control mouse brain. Arrows indicate the time of bolus injection.

Theory: In the standard tracer kinetic model [2,4] the tissue concentration is represented as a convolution of the AIF and the residue function: $C_T(t)=\mathrm{CBF}\cdot C_A(t)*R(t)$. In order to derive an analytical expression, we model the residue function as an exponential: $R(t)= \exp[-(t-t_0)/\mathrm{MTT}]$ and the AIF as a gamma-variate with an additive constant to represent the steady state level of contrast: $C_A(t) = N(t-t_0)^{\alpha} \exp[-\beta(t-t_0)] + b$. These expressions were substituted into the equation above and convolved analytically. Finally, the contrast agent concentration was converted to signal intensity (shown in Fig. 1 in red) measured in the pMRI experiment as: $S(t) = S_0 \exp[-kC_T(t)]$, where C_T is the concentration of contrast agent in the tissue and k is a constant dependent on the echo time. Given the time series data, the posterior probabilities for the model parameters were calculated for each region using Bayesian probability theory; the joint posterior probability was then sampled using a Markov chain Monte Carlo simulation with simulated annealing [5].

Results and Discussion: Perfusion parameters were measured in tumors from pMRI data (only one representative data set is shown here) on 8 and 14 post operative days (POD). Fig. 2 (a-b) show clear contrast enhancement in the tumor region. Using our perfusion model [2] to fit the data shown in Fig. 2(c), we calculated a relative cerebral blood flow (rCBV) of 1.70 ± 0.06, in good agreement with literature values [1]. An example of signal modeling using BPT is presented in Fig. 1. The original data (from the tumor region in the same mouse in Fig. 2 (a-c), POD 14) is shown in red and the model in blue. The model provides a good estimate of the data, with a small residual shown in green. A comparison of perfusion parameters for POD 8 and 14 of the same mouse is summarized in Table 1. As expected, all tumors displayed enhanced CBV values in the tumor region, which has been shown to correlate with an increase in microvascular density [1]. In addition, analysis of normal mouse brain (no tumor implantation) demonstrated reproducibility of perfusion parameters (see Fig. 2 (d)) made with multiple contrast boluses, administered at 10-min intervals (rCBV = 1.07 ± 0.02, rMTT = 1.0 ± 0.01, and rCBF = 1.09 ± 0.02).

Table 1

	POD 8	POD 14
rCBV	1.18 ± 0.13	1.70 ± 0.06
rCBF	1.12 ± 0.01	0.73 ± 0.02
rMTT	1.05 ± 0.08	2.33 ± 0.02

Conclusion: DSC perfusion imaging can be performed in a mouse glioma model and demonstrates characteristic elevations of CBV compared to normal brain tissue. The perfusion data are modeled using BPT methods that do not require independent measurement of an AIF. Ongoing studies are aimed at validation of the CBV finding by histological measurement of microvascular density.

References: 1. Cha S et al, MRM, 2003: 49(5):848-855. 2. Lee JJ et al, MRM, 2009 in press. 3. Jost S, et al, Neurosurgery 2007, 60(2):360-371. 4. Zierler K et al, Circ. Res., 1962: 10(3):393-407. 5. Bretthorst, GL, Probability Theory: the logic of science, 2003, Cambridge.