MRI Estimation of Contrast Agent Concentration in Tissue Using a Neural Network Approach

H. Bagher-Ebadian[1], T. Nagaraja[2], R. Paudyal[1,3], P. Whitton[1], S. Panda[1], K. Ledbetter[1], J. D. Fenstermacher[2], and J. R. Ewing[1,3]

[1]Neurology, Henry Ford Health System, Detroit, Michigan, United States, [2]Anesthesiology, Henry Ford Health System, Detroit, Michigan, United States, [3]Physics, Oakland University, Rochester, Michigan, United States

Introduction:

The ability of MRI Contrast Agents (CA's) to quantify such physiological variables as blood flow, vascular volume, and vascular transfer constant can be limited by the mixed (e.g. $T2^*$ and T1), and/or nonlinear, contrast mechanisms encountered [1]. Physiological measurements in humans universally employ small CA's such as Gd-DTPA as a contrast agent. In animals, Gd-DTPA-albumin complex can be used in concentration-time studies to quantify tumor vascular transfer constant (K_1 or K^{trans}) and extravascular, extracellular leakage volume (v_e) [2, 3]. Since, in MRI physiological studies, the measurement of CA concentration plays a crucial role in quantification and estimation of kinetic model parameters, nonlinearities form a source of systematic error that can substantially undermine the reliability of the measurement. We hypothesized that, given a gold-standard map of CA concentration, an Adaptive Neural Network (ANN) might be trained to directly estimate CA concentration from MRI image sets. After a preliminary study in a set of tubular gel phantoms using TOMROP (T One by Multiple Read Out Pulses) image sets [4] showed promise, a new ANN was designed, trained, optimized, and tested by K-Fold Cross-Validation (KFCV) method [5] using real cases (9 male Fisher rats) for estimating the CA concentration from TOMROP signal changes after injection of Gd-albumin in a 9L rat model of cerebral tumor. Quantitative Autoradiography (QAR) using Radioiodinated Serum Albumin (RISA) immediately followed the MRI experiment; the autoradiogram of this latter procedure served as a gold-standard training set. We demonstrate that the ANN's prediction of in a very good agreement with other measures of concentration.

Materials and Method: To compare MRI estimates of transfer constant to QAR estimates, nine animals (Fisher rats) with 9L tumor were studied. Mean tumor age was 14.6 ± 0.7 days (range 14 to 16 days) for all animals. In MRI procedures, two initial TOMROP image sets were followed by the injection of a prepared Gd-labeled albumin (Gd-albumin) solution, and then ten more TOMROP data sets were collected [4]. The last set of TOMROP images in the animal data was used in training the ANN, since it corresponded most closely in time post-injection to the QAR data set subsequently taken using RISA as the indicator. In the rat model of cerebral tumor, TOMROP signals before, and 25 minutes after CA injection (i.e., one pre-contrast set and the last post-contrast set) were used to extract feature vectors for training the ANN. To generate a feature set U_n that was physically meaningful, independent from system gain, and sensitive to the amount of the Gd-albumin concentration, inputs to the ANN were formed using following equation 1. In this equation, S_{Pre} and S_{post} denote MR signal for pre- and post-injection and n denotes echo number. The ANN was trained and validated using KFCV method and optimized by maximizing the Area Under Receiver Operator Characteristic (AUROCC) [6] (ANN: 24:6:1 was optimal at AUROC=0.840). The ANN was trained and validated by 8100 samples with 50 folds and 162 samples in each randomly split fold.

$$U_n = \frac{S^n_{Post} - S^n_{pre}}{S^0_{pre}} \quad n \in [0,24] \qquad \text{Equation-1}$$

Results: Figure 1, illustrates the feature vectors *(U_n)* versus echo number (0 to 23) for a leaky tumor and a normal area of cerebral tissue in a rat brain.

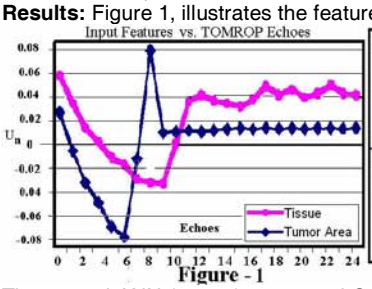

Figure - 1

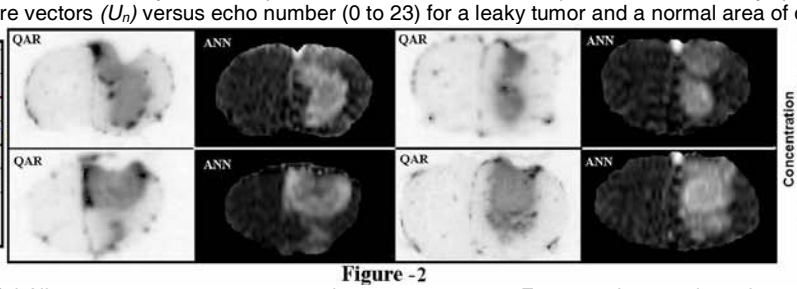

Figure -2

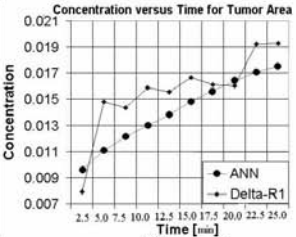

Figure -3

The trained ANN (24:6:1) generated Gd-Albumin concentration maps in the range 0 to 1.00. Figure 2 shows selected outputs of the trained ANN in four animals, along with the corresponding autoradiogram. The left-hand images in first and third columns illustrate the QAR gold standard maps taken 30 minutes past injection of RISA, while the right-hand images in the second and fourth columns present the ANN response in the same animal and corresponding slice. There is a clear visual correspondence between the ANN measures of CA concentration and autoradiographic measures of RISA concentration. To evaluate the accuracy of the ANN as an estimator of CA concentration, ΔR1 and ANN maps were compared to each other and to the corresponding autoradiogram, with sampling performed at prevalence of ~0.5 by choosing two similar regions of interest from normal tissue and leaky area. The ANN measure of CA concentration is in excellent agreement($r=0.92$, $p<0.0001$) with the ΔR1 map; the ANN measure of CA concentration and QAR measure of RISA concentration are better correlated ($r=0.82$, $p<0.0001$) than are the ΔR1 map with QAR ($r=0.75$, $p<0.0001$). As a final test to check the ANN's ability to characterize the time-dependence of Gd leakage in different areas of rat brain, the ANN was applied to a full set of TOMROP experiments - all 10 time points after injection. After calibrating the resulting maps to maps of ΔR1 (calibration factor of [CA] *=a+b*[ANN], *a=0.01 and b=4.08*), the final results were used to generate concentration-time curves for normal tissue and tumor (See Figure 3). In the tumor, both ANN and ΔR1 agree that the CA concentration increases with time. The ANN estimate appears to be more stable, and much less noisy than the ΔR1 estimate.

Discussion

This work addresses a fundamental problem in the matter of physiological estimates via time-concentration studies using MRI. While these results are promising, there are refinements that might be introduced to the practice of training an Adaptive technology for the analysis of Look-Locker image sets. First, the autoradiogram chosen for training was one 20 μm slice that corresponded to the center of the 2 mm thick MRI slice. An image formed by summing autoradiogram slices across a 2 mm section corresponding to the MRI slice should provide a better source of truth than only the central slice and should improve the correlation between QAR and ANN results, presently lower than ANN *vs* ΔR1. Generally, we believe that misregistration between QAR and LL images is a major source of error in the matching of QAR-ΔR1 and QAR-ANN data sets. In the future, a refinement in the testing of other adaptive technologies will be explored, e.g. support vector regression (SVR) [5], a subset of support vector machines (SVM's), appears to be promising. Also of interest are Local Linear Neuro-Fuzzy Models (LLNFM) [5] and neuro- fuzzy systems that provide robust learning capabilities.

Acknowledgement Supported by NIH grants NS 1RO1 HL70023 and PO1 NS 23393

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