Improved Fitting of Breast Pharmacokinetic Parameters using Dispersion Models

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PURPOSE: Rapid dynamic contrast enhanced breast MRI is used to characterize tumors and monitor treatment response. The DCE MRI signal can be fit to models to determine pharmacokinetic parameters such as transfer constant (K^{trans}) and fractional volume of extravascular extracellular space (v_e). These models require the measurement of arterial input function (AIF) for estimation. The AIF is usually measured in a large enough blood vessel to reduce partial volume effects or is modeled based on population studies (Weinmann, Fritz Hansen and modified Fritz Hansen [1]). The standard models assume that the tumor tissue is also fed by the identical AIF measured in a distant artery. However, angiogenesis occurring adjacent to the tumor can delay and disperse the input AIF to the tumor, resulting in poor quantification of the pharmacokinetic parameters. The purpose of this study was to evaluate the goodness-of-fit using delay and dispersion models compared to the standard Tofts model without dispersion, for breast pharmacokinetic mapping.

METHODS: The pharmacokinetic parameters were estimated using Tofts model [2] without dispersion, from the tissue concentration $C_t(t) = K^{trans} \int C_p(\tau) e^{-(K^{trans}/ve)(t-\tau)} d\tau$ where $C_p(t)$ was a population AIF (modified Fritz Hansen) [1]. In addition, two different dispersion models of $C_p(t)$ were evaluated: (i) Standard dispersion model with delay (t_d) and dispersion (d) of modified Fritz Hansen given by $C_p'(\tau) = (1/d) \int C_p(\tau - t_d) e^{(-(t-\tau)/d)} d\tau$ [3], and (ii) modified local density random walk (mLDRW) dispersion model with $C_p(t) = \alpha \sqrt{\frac{\kappa}{2\pi t}} e^{-\frac{\kappa(t-MTT)^2}{2t}}$ [4], where κ is dispersion and MTT is the mean transit time. Both the dispersion models used Tofts model to estimate the pharmacokinetic parameters.

3D SPGR DCE images were acquired using DISCO [5], a pseudorandom k_y-k_z sampling scheme that enables a tradeoff between temporal and spatial resolution, on 3T scanner (GE Heathcare, Waukesha, WI) in 10 patients (age=56±10 yrs) with known masses. The imaging parameters were: FOV= 270×324 mm, TR/TE_1/TE_2= 6.3/2.2/3.3 ms. One pre-contrast and four post-contrast images were acquired with high spatial resolution of 0.5×0.6×1.0 mm and low temporal resolution of ~2 min. Fifteen images were acquired during the wash-in period with high temporal resolution of ~13s and lower spatial resolution of 0.5×1.2×2.0 mm. The mean measured signals at different time points within an ROI in 10 tumors were converted to tissue concentrations and fitted to the three models. The bolus arrival time for all the models was estimated by assuming that the concentration-time curve is a linear-quadratic piecewise continuous function after the bolus arrival [6]. Voxel by voxel pharmacokinetic mapping was also performed over 10 tumors.

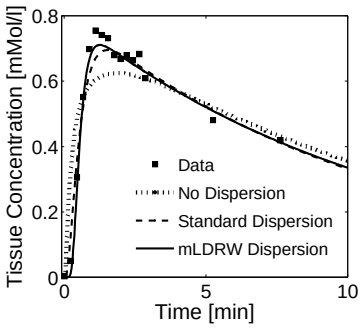

Fig.1. *The measured tissue concentration (black squares) and the fits for Tofts model without dispersion (dotted), standard dispersion model (dashed) and mLDRW dispersion model (solid). The dispersion models fit the measured data well compared to the Tofts model without dispersion.*

RESULTS: Fig.1 shows the estimated tissue concentration at time points acquired using DISCO DCE measured within a tumor ROI. Both the dispersion models fit the data points similarly and are both better than the standard Tofts model without delay and dispersion especially in the wash-in phase. The mean of the sum of squared errors (SSE) between the fitted curves and acquired data in 10 tumor ROIs using a Tofts model without dispersion=1.1±2.0(mMol/l)^2, standard dispersion model=0.5±1.0(mMol/l)^2, and mLDRW dispersion model=0.3±0.6 (mMol/l)^2.

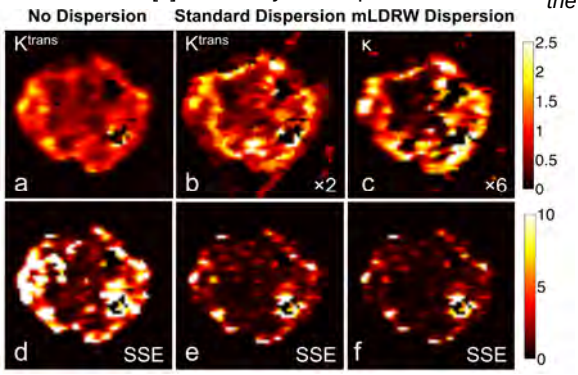

Fig.2. *The K^{trans} map estimated using Tofts model without dispersion (a), standard dispersion (b) and the κ (dispersion) using the mLDRW dispersion model (c). The scales of b and c are 2 and 6 times the scale of a. The corresponding SSE (d-f) indicates increased error in the model without dispersion compared to dispersion models.*

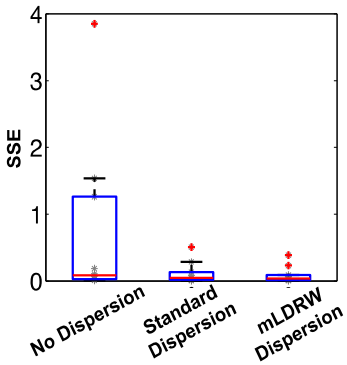

Fig.3. *Box plot of the mean of the sum of squared errors of voxel by voxel pharmacokinetic maps measured in 10 tumor volumes. The inner quartile range of the error is reduced in the dispersion models.*

Fig.2 shows the K^{trans} map from the Tofts model without dispersion, K^{trans} from the standard dispersion model and Dispersion (κ) from the mLDRW dispersion model [4] with the corresponding sum of squared errors in the bottom row. Both the dispersion models fit the tissue concentration better than the Tofts model without dispersion with reduced SSE. Fig.3 shows a box plot of the mean of the SSE of the voxel by voxel fitting over the 10 tumor volumes. The dispersion models significantly reduce the fitting errors compared to the standard model (P<0.01). The errors are also significantly reduced in mLDRW model compared to standard dispersion model (P<0.01).

DISCUSSION: The improved fits of pharmacokinetic parameter maps using dispersion models may be useful for improving the accuracy of differentiating benign and malignant tumors as well as monitoring the tumor response to chemotherapy, and require further clinical studies.

CONCLUSION: The mLDRW dispersion model and standard dispersion model fit the rapid wash-in phase better and hence reduce the errors in fitting and thereby pharmacokinetic parameters compared to Tofts model without dispersion.

ACKNOWLEDGEMENT: Research support from GE Healthcare and NIH.

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