Breast Pharmacokinetic Mapping with Dispersion Models for Improved Tumor Classification

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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}), fractional volume of extravascular extracellular space (v_e) and rate constant (k_{ep}). These models require an 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 the Tofts model [2] without dispersion, from the tissue concentration $C_t(t) = K^{trans} \int C_p(\tau) e^{-k_{ep}(t-\tau)} d\tau$ 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.

Axial 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 17 patients (age=53±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. Voxel-by-voxel pharmacokinetic mapping was performed in 22 tumors with histology proven 11 IDC, two ILC, three DCIS and 6 benign tumors. A Naive Bayes classifier was used to classify benign and malignant tumors using each pharmacokinetic parameter for the three models.

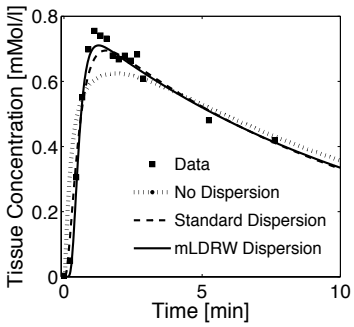

Fig.1. *The measured tissue concentration (black squares) and the fits for Tofts model without dispersion (dotted), standard dispersion (dashed) and mLDRW dispersion (solid). The dispersion models fit the measured data well compared to the Tofts model without dispersion.*

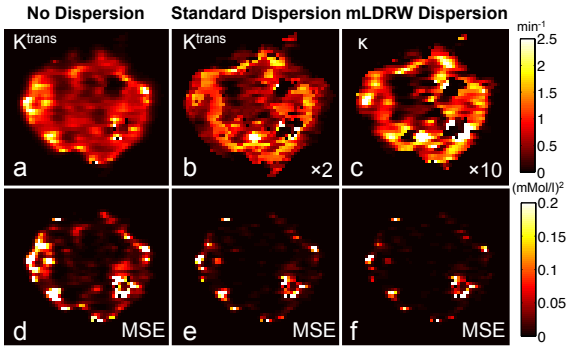

Fig.2. *The K^{trans} map estimated using Tofts model without dispersion (a), standard dispersion (b) and the κ (dispersion) using the mLDRW dispersion model (c). The scales of b and c are 2 and 10 times the scale of a. The corresponding MSE (d-f) indicates increased error in the model without dispersion compared to dispersion models.*

	Parameters	Se (%)	Sp (%)	AUC
mLDRW	**κ**	**94**	**100**	**0.91**
	k_{ep}	75	83	0.79
	MTT	94	17	0.65
	κ vs. k_{ep} (2D)	**94**	**100**	**0.91**
Standard	**K^{trans}**	**81**	**100**	**0.90**
	v_e	88	83	0.83
	t_d	88	83	0.81
	(1/d)	38	100	0.71
	K^{trans} vs. v_e (2D)	**88**	**100**	**0.84**
No	K^{trans}	44	83	0.67
	k_{ep}	**94**	**67**	**0.90**
	K^{trans} vs. k_{ep} (2D)	**75**	**100**	**0.87**

Table 1. *Sensitivity (Se), Specificity (Sp) and area under the ROC curve (AUC) for tumor classification. Both the dispersion models improve the accuracy of tumor classification.*

RESULTS: Fig.1 shows the estimated tissue concentration at time points acquired using DISCO DCE images measured within a tumor ROI. Both dispersion models fit the data points better than the standard Tofts model without dispersion especially in the wash-in phase.

Fig.2 shows the K^{trans} map from the Tofts model without dispersion, K^{trans} from the standard dispersion and dispersion (κ) from the mLDRW dispersion model [4] with the corresponding mean squared errors (MSE) in the bottom row. Both the dispersion models significantly reduce the fitting errors compared to the standard model without dispersion (P<0.01). The MSE is also significantly reduced in mLDRW model compared to standard dispersion model (P<0.01).

Table 1 shows the sensitivity, specificity and area under the ROC curve (AUC) for tumor classification. The standard dispersion model improves the sensitivity and specificity of K^{trans} compared to the model without dispersion due to the improved fitting of the rapid wash-in phase. The dispersion (κ) of mLDRW yields the highest sensitivity of 94%, specificity of 100% and AUC of 0.91.

DISCUSSION: The improved fits of pharmacokinetic parameter maps using dispersion models improve the accuracy of differentiating benign and malignant tumors and may be useful for monitoring the tumor response to chemotherapy.

CONCLUSION: The mLDRW and standard dispersion models fit the rapid wash-in phase better that a Tofts model without dispersion. In this small study, this resulted in improved accuracy of tumor classification.

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