Optimizing Flip Angle Selection in Breast MRI for Accurate Extraction and Visualization of T1 Tissue Relaxation Time

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Abstract : Contrast enhanced MRI is a popular diagnostic technique for characterizing angiogenesis and detecting breast cancer. Though conventionally measured relative signal enhancement (RSE) is not linearly proportional to contrast agent concentration, relative enhancement of T_1 tissue relaxation time is. Therefore, measurement of T_1 using low flip angle acquisitions is essential for characterizing tumors. In this paper, we present a framework to select optimum flip angles analytically from minimizing the error in T_1. The method is flexible and adaptive to noise as reflected in a critical comparison with the most recent method for optimum flip angle selection. Evaluation of our method on clinical Breast MR data of 2 women shows consistent superiority in mapping accurately T_1 in pre contrast enhanced images.

Key-Words : *Magnetic Resonance Imaging, Breast Imaging, T_1 estimation.*

1 Introduction

Dynamic contrast-enhanced magnetic resonance imaging (CE-MRI) is an MRI technique which assesses tissue properties. Contrast agent (typically Gd-DTPA) is injected into the patient immediately prior to acquiring a series of T_1 weighted MRI volumes using eg. Fast Spoiled Gradient (FSPGR) echo sequences, with a temporal resolution currently around a minute [1, 2]. The presence of contrast agent within an imaging voxel results in an increased signal that can be observed during the time course of the experiment. Different tissue types have different contrast uptake properties and such signal-time curves enable their identification. Study of these curves has been used clinically to identify and characterize tumors into malignant or benign classes, although success has been variable with generally very good sensitivity ($> 95\%$) but often quite variable specificity.

The primary reason for the poor specificity is that pharmacokinetic modelling of uptake curves is based on the erroneous assumption that enhancement is linearly proportional to contrast agent concentration. It has been shown [3] that this relationship is non-linear and that it can be represented as a function of two variables: T_{10}, the T_1 tissue relaxation time before injection of the contrast agent, and the concentration of the contrast agent. Given the RSE, an accurate measurement of T_{10} suffices for determination of the contrast agent concentration and more reliable classification of breast tissues according to the uptake curves of the pharmacokinetic model.

In a recent study on the measurement of T_{10}, Armitage et al. [4] developed a method based on Monte Carlo simulations for minimizing the error in T_{10} estimation arising from signal noise with respect to the flip angle. However, neither the above, nor other methods, have yet produced a clear quantitative relationship between the noise model for the signal and the set of flip angles which minimize T_{10} error estimation. We fill this gap by providing a concise error

analysis which leads naturally to the establishment of this relationship. The analytic formula of the error in T_{10} estimation as a function of the flip angle, further FSPGR echo pulse sequence parameters and noise, is obtained. Its dependence on the transverse relaxation time T_2 leads to further selection of optimum angle acquisitions and the new protocol is completed. Section 3.2 provides a critical comparison of our proposed method against the method of Armitage et al. in terms of numerical stability, robustness and computational complexity. We conclude by comparing T_{10} maps obtained by our method and the method of Armitage et al. for the same FSPGR echo parameter protocol.

2 Signal Modelling

The standard model of the signal generated at a voxel by a gradient echo MR pulse sequence is given by:

$$S = g\rho e^{-\frac{TE}{T_{20}^*}} \sin(\alpha) \frac{1 - e^{-\frac{TR}{T_{10}}}}{1 - \cos(\alpha) e^{-\frac{TR}{T_{10}}}} \ , \qquad (1)$$

where S is the measured signal, g is the scanner gain, ρ is the proton density, TE the echo time, TR the repetition time, α the flip angle and T_{10} and T_{20}^* are the longitudinal and transverse relaxation times respectively. From now on, we write

$$k = g\rho e^{-\frac{TE}{T_{20}^*}} \ . \qquad (2)$$

Proposed methods for measuring T_{10} in current 3D breast imaging include inversion recovery protocols [5] and gradient echo sequences acquired with variable TR. Both are extremely time inefficient. Instead, variable flip angle methods are the most viable option. Our focus in this paper is to examine which selection of variable flip angle acquisitions produce T_{10} measurements with the highest accuracy.

3 Error Analysis

Suppose that at each voxel location $\vec{\mathbf{x}}$ there exists a random error to the signal due to noise (from RF field and inhomogeneities of the magnet of the scanner) denoted by $\mathcal{E}_S(\vec{\mathbf{x}})$ and a corresponding error for k denoted by $\mathcal{E}_k(\vec{\mathbf{x}})$. The following theorem provides the error in the measurement of the parameter T_{10} using a FSPGR echo pulse sequence by describing how the errors in the signal propagate through to the measurement of T_{10} [6]. We are able to prove [7]

Theorem 3.1. *Let $\hat{S} = S + \mathcal{E}_S(\vec{\mathbf{x}})$ and $\hat{k} = k + \mathcal{E}_k(\vec{\mathbf{x}})$, where S, k are the real values of the signal and the parameter k respectively and $\mathcal{E}_*$ denotes the corresponding random errors. If T_{10} represents the actual value of T_{10} at $\vec{\mathbf{x}}$, the resulting value of T_{10} using a FSPGR echo pulse sequence is*

$$\hat{T}_{10} = T_{10} - \frac{\left[\mathcal{E}_S(e^{\frac{TR}{T_{10}}} - \cos(\alpha)) - \mathcal{E}_k \sin(\alpha)(e^{\frac{TR}{T_{10}}} - 1)\right] T_{10}^2}{TR(k\sin(\alpha) - S\cos(\alpha))} + \mathcal{O}(\max(\mathcal{E}_S, \mathcal{E}_k)^2). \qquad (3)$$

To minimize the error in T_{10} with respect to the choice of flip angles, we need to minimize the following quantity:

$$\mathcal{W} = \frac{\left[\mathcal{E}_S(e^{\frac{TR}{T_{10}}} - \cos(\alpha)) - \mathcal{E}_k \sin(\alpha)(e^{\frac{TR}{T_{10}}} - 1)\right]}{k\sin(\alpha) - S\cos(\alpha)} \ . \qquad (4)$$

The denominator $F = F(\alpha; TR, T_{10}, k) = k\sin(\alpha) - S\cos(\alpha)$ is an increasing function of the flip angle α for all TR, T_{10} and k. Thus, there exists a constant $C > 0$ such that $F(\alpha; TR, T_{10}, k) > C$ for all α, TR, T_{10} and k. We deduce

$$|\mathcal{W}| \leq \frac{\left|\left[\mathcal{E}_S(e^{\frac{TR}{T_{10}}} - \cos(\alpha)) - \mathcal{E}_k \sin(\alpha)(e^{\frac{TR}{T_{10}}} - 1)\right]\right|}{C} \ . \qquad (5)$$

Therefore $\min_{\alpha} |\mathcal{W}|$ is less than the minimum of the RHS of (5) with respect to α. Thus, the minimization problem reduces to the minimization of $\mathcal{E} = \|\mathcal{X}_1 - \mathcal{X}_2\|$ with respect to the flip angle α, where $\mathcal{X}_1$ and $\mathcal{X}_2$ denote the random variables

$$\mathcal{X}_1 = \mathcal{E}_S(e^{\frac{TR}{T_{10}}} - \cos(\alpha)), \quad \mathcal{X}_2 = \mathcal{E}_k \sin(\alpha)(e^{\frac{TR}{T_{10}}} - 1) \ . \qquad (6)$$

Assuming Gaussian errors $\mathcal{E}_S \sim N(0, \sigma_S)$ and $\mathcal{E}_k \sim N(0, \sigma_k)$ for every pixel, it follows that $\mathcal{X}_1 \sim N(0, \sigma(\mathcal{X}_1))$ and $\mathcal{X}_2 \sim N(0, \sigma(\mathcal{X}_2))$, where

$$\begin{aligned} \sigma(\mathcal{X}_1) &= \sigma_S(e^{\frac{TR}{T_{10}}} - \cos(\alpha)), \\ \sigma(\mathcal{X}_2) &= \sigma_k \sin(\alpha)(e^{\frac{TR}{T_{10}}} - 1). \end{aligned}$$

The relationship between $\mathcal{X}_1$ and $\mathcal{X}_2$ is revealed by the following:

Lemma 3.2. *If $\mathcal{E}_S$ and $\mathcal{E}_k$ denote the quantities defined in Theorem 3.1, then $sgn(\mathcal{E}_S) = sgn(\mathcal{E}_k)$.*

Proof. The partial derivative of the signal with respect to k is

$$\frac{\partial S}{\partial k} = \sin(\alpha)\frac{1 - e^{-\frac{TR}{T_{10}}}}{1 - \cos(\alpha)e^{-\frac{TR}{T_{10}}}} > 0, \qquad (7)$$

for all α, TR, T_{10}. Equation (7) can be approximated by a finite difference $\Delta S/\Delta k$ for sufficiently small ΔS and Δk. If we denote $\Delta S = \mathcal{E}_S$ and $\Delta k = \mathcal{E}_k$, substitution into (7) completes the proof. □

Because $\mathcal{X}_1$ and $\mathcal{X}_2$ have the same sign, the error in T_{10} estimation becomes smallest when these standard deviations are as close to each other as possible for appropriate choice of flip angle. We can therefore obtain the unique optimum flip angle if we choose it such that:

$$e^{-\frac{TR}{T_{10}}}(\sigma_S\cos(\alpha) - \sigma_k\sin(\alpha)) - (\sigma_S - \sigma_k\sin(\alpha)) = 0\ . \qquad (8)$$

This non-linear function of α may be solved using the Gauss-Newton method. We can overcome the spatial constraint that (8) imposes by choosing a global (independent of T_{10}) flip angle which minimizes the error in the larger T_{10} values by taking:

$$e^{-\frac{TR}{T_{10\,\max}}}\frac{(\sigma_S\cos(\alpha) - \sigma_k\sin(\alpha))}{(\sigma_S - \sigma_k\sin(\alpha))} = 1. \qquad (9)$$

In doing so, we do not lose accuracy in the optimum flip angle and T_{10} estimation. The reason is that the resulting flip angle does not depend strongly on the exponential factor: for given TR from the pulse sequence protocol, the optimum flip angle as a function of T_{10} in the allowable range for the breast[a] is practically constant, with variations that do not exceed one degree. In general, the flip angle variation is an increasing function of the ratio σ_S/σ_k. Thus the method is also robust for variable T_{10}.

3.1 Obtaining the value of k and a corresponding noise model

The method for determining optimum flip angle acquisition requires a Gaussian white noise model for the signal S and k. The former can be determined by an off-line phantom experiment, or following [8]. To obtain the value of T_{10} we require also the value of k at each voxel, so we need to determine the optimum angle acquisitions for k estimation. To find k we need two signal acquisitions using (1) at two different angles α_1, α_2, so that by cancelling out T_{10} between them we obtain:

$$k = \frac{S_1S_2(\cos(\alpha_1) - \cos(\alpha_2))}{S_2\sin(\alpha_1)(1 - \cos(\alpha_2)) - S_1\sin(\alpha_2)(1 - \cos(\alpha_1))}. \qquad (10)$$

We determine the two flip angles α_1, α_2 so that the error in the resulting value of k obtained from (10) is the minimum possible, working as follows: for given TR and randomly chosen T_{10} within $\{T_{10}\}$, we find the corresponding value of k by solving from (1) at $\alpha_1 = 10^o$ for random signal S_1 chosen from a uniform distribution on the interval [0,1]. This flip angle was chosen to optimise signal and contrast properties for enhancing tumours in post-contrast images [9]. We then generate the signal S_2 which corresponds to any angle $\alpha_2 \leq 90^o$, different from α_1. We corrupt both S_1 and S_2 by the same Gaussian white noise model for the signal (chosen to be 1% noise as is the case in most clinical MR applications) and compute the resulting noisy value of k from (10), which we denote by $\tilde{k}$. In this way we obtain the mean $\bar{k}$ and the standard deviation σ_k of the Gaussian white noise model for k with respect to the choice of α_2. We minimize the quantity $\sigma_k \cdot \|k - \bar{k}\|$ as a function of the flip angle α_2. For $TR = 0.0089$sec we find $\alpha_2 = 2^o$.

The noise model for k is the final requirement of our previous section and can be determined from a unique signal acquisition as follows: from

$$\frac{\|\partial S\|}{\|\partial k\|} \sim \frac{\|\Delta S\|}{\|\Delta k\|} = \frac{\Delta S}{\Delta k} = \sin(\alpha)\frac{1 - e^{-\frac{TR}{T_{10}}}}{1 - \cos(\alpha)e^{-\frac{TR}{T_{10}}}}\ , \qquad (11)$$

let us denote the coefficient of $\sin(\alpha)$ in (11) by $Q(\alpha, TR, T_{10})$. For every fixed α, Q is a monotonically decreasing function of T_{10} and for all TR, α, T_{10}, satisfies $0 < Q < 1$. It follows that for every fixed flip angle α, we have:

$$\frac{\|\Delta S\|}{\sin(\alpha)Q(T_{10\,\min})} < \|\Delta k\| < \frac{\|\Delta S\|}{\sin(\alpha)Q(T_{10\,\max})}, \qquad (12)$$

which enables us to choose

$$\|\Delta k\| = \frac{\|\Delta S\|}{\sin(\alpha)Q(T_{10mean})}. \qquad (13)$$

[a] From now on, we denote the set of allowable T_{10} values for the breast by $\{T_{10}\}$.

For $\Delta S \sim N(0, 0.01)$ (1% noise as chosen above) and $TR = 0.0089$sec, we find the standard deviation σ_k for the Gaussian white noise model for k to be 0.2073 at $\alpha = \alpha_2$.

This completes the requirements of Sect. 2 and an optimum third flip angle for estimating T_{10} is obtained by substituting σ_S and σ_k in (9) and solving for α. The obtained k from (10) at $\alpha_1 = 10^o$, $\alpha_2 = 2^o$ is substituted into (1) along with the value of the signal at the third optimum flip angle α, to deduce T_{10}.

3.2 Comparison with the most recent method for T10 estimation

The cost of our method for optimum flip angle selection arises from determining α_2. Let $\mathcal{O}(p)$ denote the order of magnitude of any given number p. If N is the number of noise corruptions performed on S_1 and S_2 as required for the computation of $\tilde{k}$ in Sect. 3.1, the optimization scheme for obtaining α_2 requires operations (flops) of the order of magnitude $4 \times \mathcal{O}(N)$. The method of Armitage et al. [4] for determining the critical flip angles in a FSPGR echo pulse sequence which minimize the error in T_{10} estimation is summarized as follows: For a fixed value of T_{10} in $\{T_{10}\}$ and for given TR and randomly chosen k, the authors obtain the value of the signal S_i subject to a random flip angle α_i via (1). If $\aleph(\S)$ denotes the number of elements of the set $\S$, it follows that the order of magnitude of flops needed for their optimization scheme is $4 \times \mathcal{O}(\aleph(\{T_{10}\})) \times \mathcal{O}(N)$. Because $\mathcal{O}(\aleph\{T_{10}\})$ equals the order of magnitude of the number of image voxels, it follows that our proposed method is significantly computationally cheaper than the method of Armitage et al.

To compare our method with that of Armitage et al. [4] in terms of numerical stability and robustness, we work as follows: for any random value of T_{10} within $\{T_{10}\}$, fixed $TR = 0.0089$sec as chosen in [4] and a random value of k, we evaluate the signals corresponding to the three flip angles predicted by [4] $(3^o, 10^o, 17^o)$. We corrupt each of these three signals according to a given Gaussian white noise model with standard deviation σ_S which is fixed from now on. We then fit the signals to compute the estimated T_{10} following [4]. Using the same Gaussian white noise model for the signal and the corresponding k noise model obtained from (12), we determine the optimum flip angle from (9). For the given T_{10}, k and the provided TR, we evaluate the signals at the flip angles $\alpha_{1n} = 2^o$ (predicted by our method) and $\alpha_{2n} = 10^o$, which we then corrupt by the Gaussian white noise model with standard deviation σ_S and determine our predicted noisy value of k from (10). Finally, we use our derived value of k along with the optimum flip angle predicted by (9) and the provided TR in order to evaluate the corresponding signal, which we then corrupt by the Gaussian white noise model with standard deviation σ_S. This provides our prediction for the estimated T_{10} solving for it directly from (1).

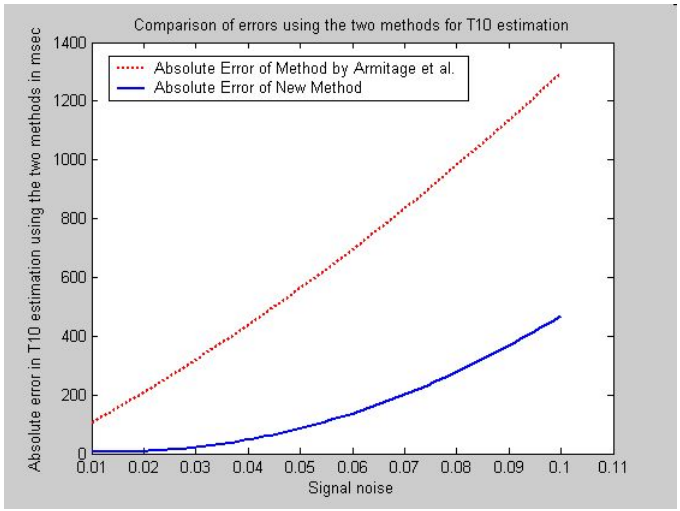
We repeat the above comparisons of the two methods for the whole set $\{T_{10}\}$ and for σ_S ranging from 1% up to 10%. In all comparisons, our method proved superior to that of Armitage et al. Our comparative results for $TR = 0.0089$sec are summarized in the following figures : Fig. 1 (a) compares stability of the two algorithms and Fig. 1 (b) compares their numerical robustness. The new algorithm takes 13.8sec to run on an Intel Pentium III/1.3-GHz CPU.

3.3 T10 Visualization

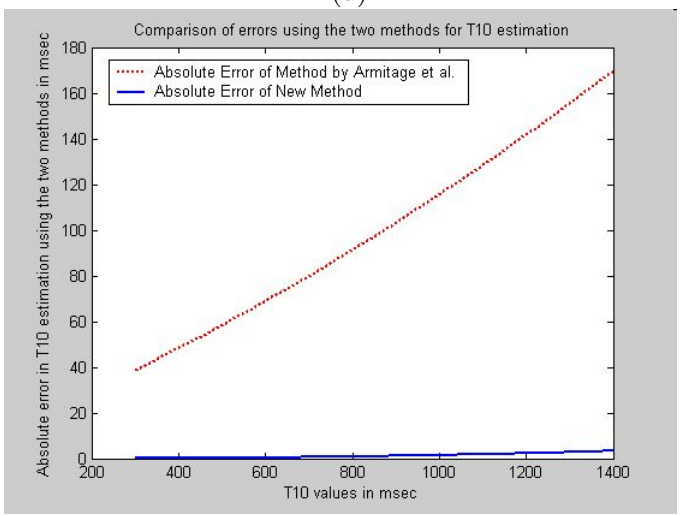
Because high T_{10} values are associated with malignancies, the latter could be located if T_{10} maps were readily available from breast images. Such maps would distinguish T_{10} values by intensity and suspicious areas would look bright in comparison with healthy tissue. Following our proposed protocol, we have produced T_{10} maps of three patient cases which can be compared with a T_{10} map of another patient produced by the method of Armitage et al. for the same pulse sequence parameters, in Fig. 2. Apart from the substantially greater artificial enhancement of the breast boundaries, Fig. 2 (c) also displays poorer specificity of different breast tissues in comparison with Fig. 2 (b), showing the superiority of the new method.

4 Conclusion

This paper presents a new approach in determining optimum angle acquisitions for MR breast cancer diagnosis, using measurements of the T_{10} longitudinal relaxation time. The method is based on error analysis of the signal model that enables an analytic formulation of the error in T_{10} estimation, in terms of pulse sequence parameters and noise. This is used to

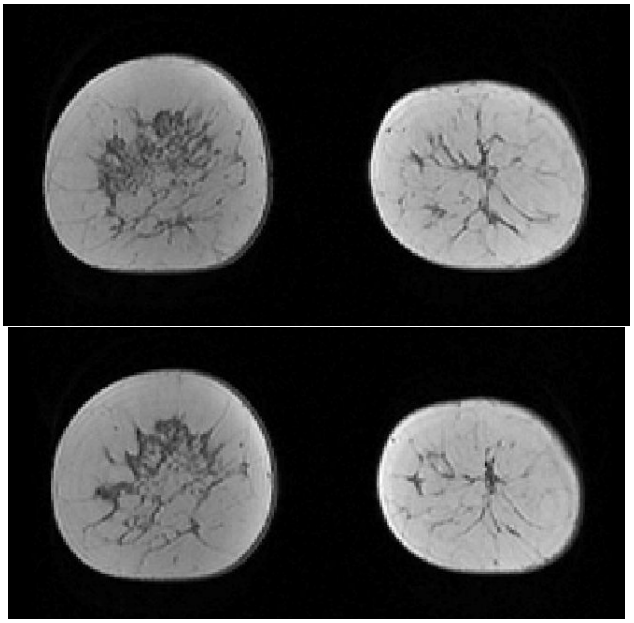


(a)

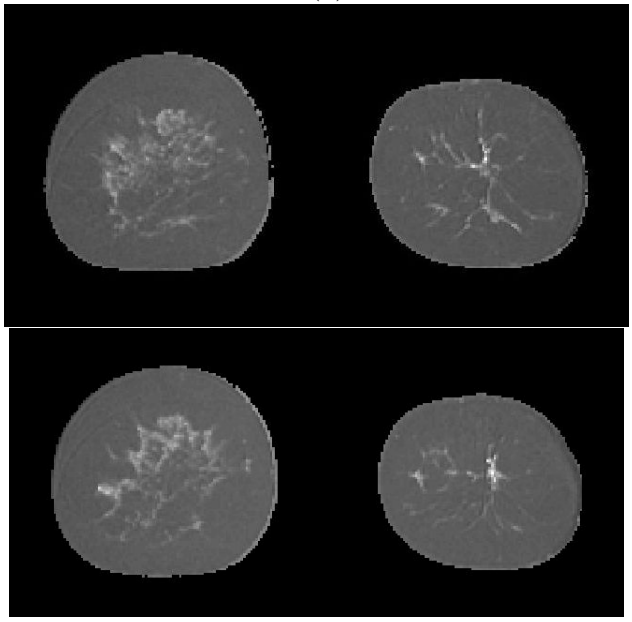


(b)

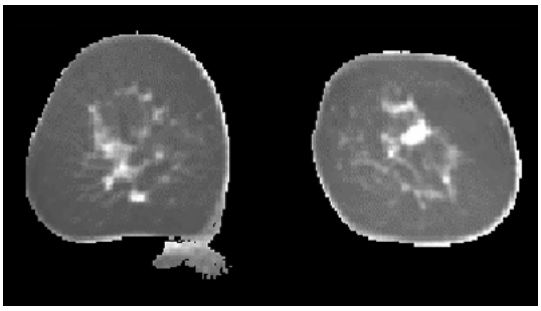
Figure 1: (a) Plot of the absolute error in T_{10} estimation for different noise model for the signal (standard deviation) using the method of Armitage et al. and the new method. The noise model is chosen in the standard range for good quality MR images, from 1% up to 10% of the original signal and $T_{10} = 1.35$sec. (b) Plot of the absolute error in T_{10} estimation for different T_{10} values using the method of Armitage et al. and the new method, for noise standard deviation being 1% of the signal value.



(a)



(b)



(c)

Figure 2: (a) Original MRI breast slices of two different patients. (b) Resulting T_{10} maps with intensity corresponding to T_{10} value magnitude. (c) T_{10} map of another patient produced by the method of Armitage et al. The striking difference in quality of the resulting T_{10} maps is because the method of Armitage et al. suffers from large fitting errors that do not affect our method.

define an optimum angle acquisition via a single equation. This single equation requires the knowledge of quantities obtained most accurately when further selection of optimum angles is performed. The analytic formulation of the method clarifies for first time explicitly the role of noise and pulse sequence parameters in selecting optimum flip angles in FSPGR echo sequences. In vitro experiments demonstrated the proposed method to be more stable to signal noise and more robust for all T_{10} values in $\{T_{10}\}$ when compared with the method of Armitage et al [4]. This is because the pure Monte-Carlo simulation of Armitage et al. did not take into account special relationships between the simulated parameters and because their objective minimization function is not optimum. In addition, the computational cost of the new method is significantly smaller because of its substantial analytical formulation. Reliable T_{10} visualization obtained using the same FSPGR echo parameter protocol, demonstrates the superiority of the new method in practice, providing better specificity of breast tissue from T_{10} values.

Acknowledgement We thank Paul Armitage for providing the images of breast slices and for helpful discussions.

References

[1] Bone B., Pentek Z., Perbeck L., and Veress B. Diagnostic accuracy of mammography and contrast-enhanced MR imaging in 238 histologically verified breast lesion. *Acta. Radiol.*, vol. 38, 1997, pp. 489–496.

[2] Kacl G., Liu P., Debatin J., Garzoli E., Caduff R., and Krestin G. Detection of breast cancer with conventional mammography and contrast-enhanced MR imaging. *Eur. Radiol.*, vol. 8, 1998, pp. 194–2000.

[3] Tofts P.S., Berkowitz B., and Schnall M.D. Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumors using a permeability model. *Magnetic Resonance in Medicine*, vol. 33, 1995, pp. 564–568.

[4] Armitage P., Behrenbruch C., Brady J., and Moore N. Optimising flip-angles for improved T_1 calculation in 3D contrast-enhanced breast MR imaging. In *Proc. ISMRM*, 2001.

[5] Hulka C., Smith B., Sgroi D., Tan L., Edmister W., Semple J., Campbell T., Kopans D., Brady T., and Weisskoff R. Benign and malignant breast lesions: differentiation with echo-planar MR imaging. *Radiology*, vol. 197, 1995, pp. 33–38.

[6] Pihler J. Pattern Recognition Using Advanced Error Back-Propagation Methods. In *Electronic Proceedings of the WSEAS conference in Neural Networks and Applications, NNA*, 2004.

[7] Ketsetzis G. and Brady M.J. Optimum flip angle selection in Contrast enhanced Magnetic Resonance imaging, 2004. Submitted for publication.

[8] Wahab A., Quek C., and Chong T.E. Softcomputing Approach to Noise Modeling. In *Electronic Proceedings of the WSEAS conference in Fuzzy Systems, SOSM*, 2004.

[9] Venkatesan R., Lin W., and Haacke E.M. Accurate Determination of Spin-Density and T_1 in the Presence of RF-Field Inhomogeneities and Flip-Angle Miscalibration. *Magnetic Resonance Medicine*, vol. 40, 1998, pp. 592–602.