GRADIENT ECHO SIGNAL DECAYS IN HEALTHY AND CANCEROUS PROSTATE AT 3T REQUIRE A GAUSSIAN AUGMENTATION OF THE MONO-EXPONENTIAL (GAME) MODEL

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Introduction: Hypoxia is prevalent in prostate cancer [(1)] and maybe associated with poor patient outcomes, with higher metastatic potential, chemo- and radiation-therapy resistance [(2)]. MRI attempts to detect hypoxia via R_2^* ($1/T_2^*$) measurements using multiple gradient echo (GRE) signals with a standard **M**ono-**E**xponential (ME) decay model had some success at 1.5T [(3, 4)], which might be improved at 3T. In this work, we report that proper characterization of GRE signals requires a **G**aussian **A**ugmentation of the **M**ono-**E**xponential (GAME) decay model at 3T in the prostate, as recently found in the brain [(5)].

Theory: GRE signal decay with echo time (TE) is generally assumed to follow a ME decay model: $S = \rho\, e^{-R_2^* TE}$, where $R_2^* = R_2 + R_2'$ is the sum of irreversible (R_2) and reversible (R_2') decay rates, R_2' being the half-width-at-half-maximum (HWHM) of a Lorentzian intra-voxel frequency distribution and ρ the pseudo-spin density [(6)]. However, if the intra-voxel frequency distributions are better characterized with Gaussian rather than Lorentzian functions, then S vs. TE follows a GAME decay model: $S = \rho\, e^{-R_2 TE} e^{-(\sigma TE)^2/2}$, where the Gaussian HWHM is $\sigma\sqrt{2ln2}$ [(5)].

Methods: Twenty men undergoing 3T in-bore MR-guided prostate biopsy participated in this IRB-approved study (ages: 65 ± 9 years, weights: 88 ± 16 kg, prostate-specific antigen: 10.72 ± 10.81 ng/mL, range 1.90 to 42.80). Imaging was performed at 3T (Verio, Siemens, Erlangen, Germany) using body and spine matrix coils. The protocol included T2-weighted turbo-spin-echo (TSE, TE/TR=102/5190ms, flip=140, FOV=22x22cm, 256x320 matrix, 4mm slices) and 2D multi-slice multi-echo GRE imaging (TE= 3, 9, 18, 27, 36, and 45ms, TR=494-985ms, flip=43-58, FOV=30x30cm, 192x192 matrix, 4mm slices). Regions of interest (ROIs) were delineated on T2-TSE images in the healthy prostate (central gland, CG; peripheral zone, PZ). Twenty-nine biopsy targets (15 in CG and 14 in PZ) from pre-operative multi-parametric MRI were also registered and delineated. Tissues were classified as normal, suspicious (positive by imaging alone), or cancerous (positive by imaging and confirmed by biopsy). GRE signal decay was fitted to these two models using Matlab (Mathworks, Natick MA). For the ME model, ρ and R_2^* were extracted. For the GAME model, ρ, R_2 and σ were extracted. F-tests were performed to test whether improvements were statistically significant.

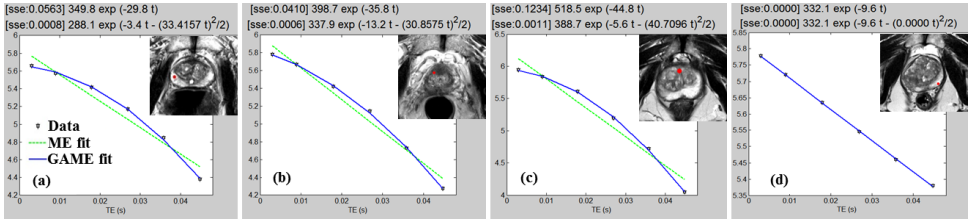

Figure 1: Data ($log(S)$ vs. TE, black) and fits (a-c) GAME (blue) outperforms ME (green) (d) As $\sigma \rightarrow 0$ and $R_2 \rightarrow R_2^*$, the models become equivalent (Red dots: location, SSE: sum of squared errors).

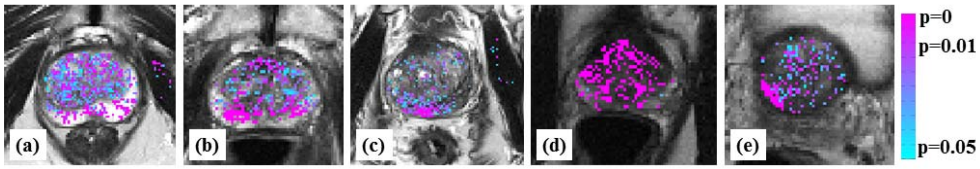

Figure 2: GAME statistically significantly improves fits over ME (p<0.05). F-test p-values of five different subjects are shown (a-e) Highly significant improvements are seen across the entire gland.

Results: GAME characterized signal decays better than or equivalent to ME in the prostate (Figure 1). GAME performed significantly better (p<0.05) in 21%, and highly significantly better (p<0.005) in 15% of all ROIs overall (Figure 2). Cancer was found in 12 biopsy targets: 6 Gleason 3+3, 4 Gleason 3+4 and 2 Gleason 4+3. GAME outperformed ME in 17%, 10%, 16% of the healthy CG, suspicious CG and cancerous CG, and 18%, 30%, 26% of the healthy PZ, suspicious PZ and cancerous PZ, respectively (p<0.05). Parametric maps from the ME and GAME model fits are shown in Figure 3 for a typical case. Note that high R_2^* values observed with ME model fits in the PZ may have different proportions of irreversible and reversible relaxation rate contributions, which are distinctly separated by the GAME model fit

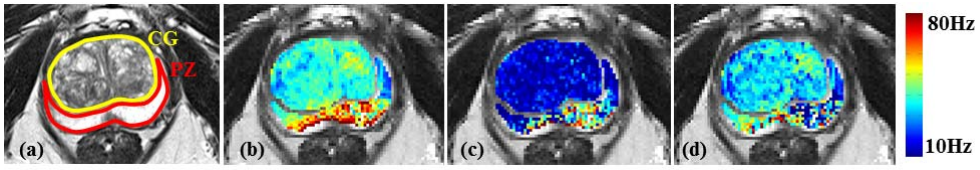

Figure 3: Anatomy and ME vs. GAME model fitting results,for the same subject as Figure 2a (a) T2-TSE, with CG and PZ contours outlined, along with maps of (b) ME R_2^* (c) GAME R_2 (d) GAME σ.

Discussion: In previous prostate hypoxia studies at 1.5 T, R_2^* values were directly estimated from GRE decays using a ME decay model, and high R_2^* values were assumed to be indicative of hypoxic regions within tumors [(3,4)]. Many factors besides oxygenation can influence the shape and rate of GRE signal decay in the prostate, including air/tissue and air/bone interfaces (e.g. rectum, pubis), blood products (e.g. hemosiderin), calcifications, temperature, etc. The ME model appears inadequate at 3T, due to the distinct curvature on semi-log plots observed in both normal and cancerous tissue (Figure 1, a-c). It is likely, that increased susceptibility induced gradients from air/tissue and air/bone interfaces at 3T, in combination with realistic, Gaussian-like, slice profiles, are responsible for this curvature [(7)]. In this case, methods such as susceptibility matching (e.g. fluorocarbon filled balloon in the rectum) or direct modeling of these effects [(7)] may be required to recover intrinsic R_2^* values.

Conclusion: Appropriate characterization of signal decay curves is essential for their use in quantitative MR studies. Improved fits are obtained in the prostate with the GAME vs the ME model at 3T. The degree to which R_2 or σ values correlate with hypoxia remains unknown. However, improved characterization of GRE signal decay curves increases the potential for determining correlates of the fit parameters with biomarkers of, e.g. oxygenation status. A hypoxia biomarker, as an indicator of cancer aggressiveness, would have critical impact in guiding treatment decisions, e.g. in the prostate, between treatment morbidity (urinary incontinence, erectile dysfunction, etc.) vs. mortality from slow-growing non-aggressive cancers.

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References: [(1)] Vaupel in W.J. Welch 2013 doi 10.1007/978-1-4614-4989-8_42 [(2)] Milosevic et.al. Clin Cancer Res 2012;18(7):2108-14 [(3)] Hoskin et.al. Int J Radiat Oncol Biol Phys. 2007;68(4):1065-71 [(4)] Chopra et.al. Int J Radiat Biol. 2009;85(9):805-13 [(5)] Mulkern, Balasubramanian, Mitsouras. MRM 2014 doi: 10.1002/mrm.25365 [(6)] Ma, Wehrli. J Magn Reson B. 1996;111(1):61-9 [(7)] Hernando et.al. MRM 2012;68(3):830-40.