

NMR Shutter-Speed Discrimination of Malignant and Benign Breast Tumors Using ROI Data

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INTRODUCTION Recent results suggest that quantitative analyses of Dynamic-Contrast-Enhanced (DCE) MRI pharmacokinetic data using the Shutter-Speed Model (SSM) can yield very high breast cancer screening specificity [1]. The SSM differs from the Standard Model (SM) normally used for DCE-MRI only by allowing that equilibrium intercompartmental water exchange processes can have finite kinetics [1,2]. The SM intrinsically assumes that each MR system is in the fast-exchange-limit [FXL]. But, during the peak tumor contrast reagent (CR) bolus passage, the equilibrium transcytlemmal water exchange system (CWX) departs the FXL. This happens for benign and malignant breast tumors and the SM underestimates the extracellular extravascular volume fraction (v_e) values by similar factors for each [1]. However, the volume-weighted CR extravasation rate constant (K^{trans}) values are greater for angiogenic malignant than benign lesions. Thus, FXL departure is greater for malignant tumors, and the SM underestimates K^{trans} values for these – but *not* for benign lesions. The earlier paper used lesion K^{trans} maps for 3 malignant and 3 benign cases to demonstrate perfect SSM discrimination. Only malignant tumors exhibited “hot spots” ($K^{trans} > 0.08 \text{ min}^{-1}$), and in only SSM maps [1]. However, the production of DCE-MRI parametric maps is signal-to-noise (S/N) demanding: it entails pixel-by-pixel analyses. The data in [1] were acquired without adipose -¹H₂C- signal suppression - common for breast screening MRI, which can decrease even ¹H₂O S/N. Here, we use both -¹H₂C- suppressed and unsuppressed DCE-MRI data to show that SSM analyses of ROI intensities still allows complete malignant and benign tumor discrimination.

METHODS A 22 patient cohort had already undergone a clinical MRI protocol prior to the research DCE-MRI study. All had CR-enhanced lesions classified in the BIRADS 4 (n = 17) or 5 (n = 5) categories based on lesion morphology and qualitative CR kinetics (persistent, plateau, or washout), and were referred for biopsy. Under IRB-approved protocols, the research DCE-MRI data from 16 patients were acquired during clinical MRI-guided preoperative needle localization or core biopsy, *just before* needle insertions, and those from the 6 other patients as part of a combined MRI/MRS protocol *prior* to excisional or core biopsy. 1.5T DCE-MRI used body transmit and 4- or 7-channel phased-array bilateral breast receive RF coils. A 3D SPGR pulse sequence was used for 12-20 continual serial sagittal image volume sets, spatially covering the whole breast with the suspicious lesion. Other parameters were: $\alpha = 10^\circ$ or 30° , 3-4 ms TE, 6-9 ms TR, 3 mm slice thickness, 18-24 cm FOV. For 16 patients, the fat -¹H₂C- signal was suppressed with narrow-band RF saturation centered on its frequency. Depending on breast size, 16-32 planes were acquired per set, resulting in 13-26 s temporal resolutions. At the start of the second volume set acquisition, Gd CR was delivered intravenously [0.1 mmol/kg at 2 mL/s]. ROIs circumscribing the enhanced lesion and within an axillary artery produced the tumor and arterial input function (AIF) intensity time-courses, respectively, which were then subjected to both SM and SSM analyses [1-3].

RESULTS **Figure 1a** shows the 3.3 min. fat-suppressed pharmacokinetic image plane of a 57 year-old. One ROI [65 mm², 194 μL] is in normal-appearing-glandular (NAG) tissue and one [10 mm², 31 μL] contains the tiny lesion evident, subsequently pathology proven as a malignant invasive ductal carcinoma (IDC). **Fig. 1c** shows the 3.6 min. image of a 52 year-old. One ROI [127 mm², 381 μL] is in NAG and one [81 mm², 243 μL] contains the lesion evident, subsequently found to comprise benign lobular carcinoma *in situ* [LCIS] and stromal fibrosis (SF). In contrast to those without -¹H₂C-suppression [1,2], these darker images show glandular regions brighter than fatty tissue. The 4 ROI ¹H₂O R₁ time-courses are shown in **Figs. 1b,d** (circles). The CR injection is suggested by the bottom rectangular function. The NAG ROIs show very weak CR uptake, while the IDC ROI data shape (1b) is that characteristic of such tumors; much faster and greater uptake compared with a benign lesion (1d) [1]. The mean AIF, from axillary artery ¹H₂O time-courses in 3 patients, shows the plasma CR concentration, [CR_p], peaking at almost 5 mM at -0.75 minutes (1d inset).

There are 3 fitted curves for each lesion R₁ plot. The dashed and solid curves represent SM and SSM best-fittings, respectively [indistinguishable for all but the IDC (1b)], and the dotted curves show SM expectations with K^{trans} and v_e fixed at the respective SSM values. The comparisons of the SM and SSM curves with their respective data have *random* fitting errors [1,3] that are not widely different, and this may contribute to a general, but unwarranted, sense of SM success. However, the **Fig. 1b** residuals exhibit significant temporal correlation. The dashed curve for the IDC tumor shows clearly the signature mismatch for malignant tumors [1-3]; lagging during CR uptake then leading then lagging during washout. The SM cannot match the data *shape* – a *systematic* error – due to the SM assumption of FXL for the CWX system [$\tau_i \rightarrow 0$] (τ_i : the mean intracellular water molecule lifetime) [1-3]. This results in a systematic underestimation in the SM-returned values (\pm s.d.) of K^{trans} [0.18 (± 0.002) min^{-1}], v_e [0.33 (± 0.001)], and τ_i [$\rightarrow 0$]. The SSM finds for the same (1b) data: K^{trans} [0.30 (± 0.04) min^{-1}], v_e [0.58 (± 0.08)], and τ_i [0.38 (± 0.04) s]. For the benign LCIS/SF lesion (**Fig. 1d**) data, the analogous results are: (SM fitting) K^{trans} [0.035 (± 0.0005) min^{-1}], v_e [0.36 (± 0.02)], and τ_i [$\rightarrow 0$]; (SSM fitting) K^{trans} [0.036 (± 0.001) min^{-1}], v_e [0.60 (± 0.07)], and τ_i [0.40 (± 0.12) s].

The extent of SM inadequacy is more dramatically displayed by the **Fig. 1b** dotted curve ($K^{trans} = 0.30 \text{ min}^{-1}$, $v_e = 0.58$, and [implicitly] $\tau_i \rightarrow 0$). This is the behavior the SM would expect for K^{trans} and v_e values returned by the SSM. The SM brings its expectation down to the IDC data only by reducing its K^{trans} and v_e values by significant factors; ~ 2 in this case. The analogous systematic discrepancy is very small for the **Fig. 1d** benign LCIS/SF lesion. Though the SM can reasonably match the data for the benign lesion, it fails for the malignant tumor – just when most needed. This is the same as observed for a lesion pair acquired without -¹H₂C- suppression [1], and suggests the particular SSM potential to discriminate malignant from benign breast tumors. Theory and simulations [3] and experimental animal model results [4] show that the SM-returned parameter values decrease with increasing CR dose and/or injection rate. Of course, these pharmacokinetic and physiological parameters should not depend on CR administration details. Most such CR dose-dependence is removed by SSM analyses [4].

For screening purposes, the most striking **Fig. 1** aspect is that the malignant tumor ROI K^{trans} is decreased by the SM, but not for the benign lesion. Thus, in **Figure 2**, we present the 1D scatter plot for the lesion ROI $\Delta K^{trans} [\equiv K^{trans}(\text{SSM}) - K^{trans}(\text{SM})]$ values for each of the 22 patients. There is a wide gap between all 7 of the gold standard, biopsy/pathology proven malignancies (black circles) [one is plotted in an inset] in this population, and all 15 of the proven benign lesions (red triangles), which cluster very near zero. A clean cut-off line is drawn at 0.029 min^{-1} .

DISCUSSION Since the only difference between these two models is the NMR shutter speed effect, this suggests that it is significant with the capillary wall permeability obtaining for the vascular beds of only malignant breast tumors. Thus, this is very encouraging that DCE-MRI ROI data analyses first with the SM and then with the SSM (each accomplished in only seconds) can lead to extremely high breast cancer screening specificity.

REFERENCES 1. Li, Huang, Yankeelov, Tudorica, Rooney, Springer, *MRM* 53:724-729(2005). 2. Yankeelov, Rooney, Huang, Dyke, Li, Tudorica, Lee, Koutcher, Springer, *NMRB* 18:173-185(2005). 3. Yankeelov, Rooney, Li, Springer *MRM*. 50: 1151-1169 (2003). 4. Zhou, Pickup, Yankeelov, Springer, Glickson, *MRM* 52:248-257(2004).

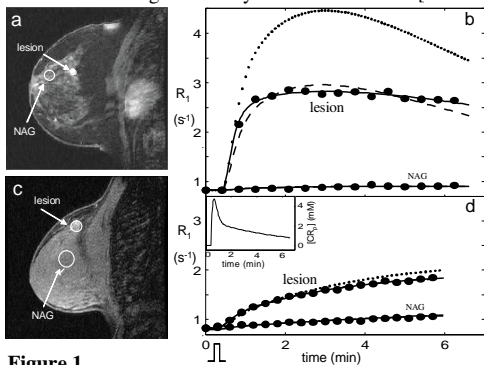


Figure 1.

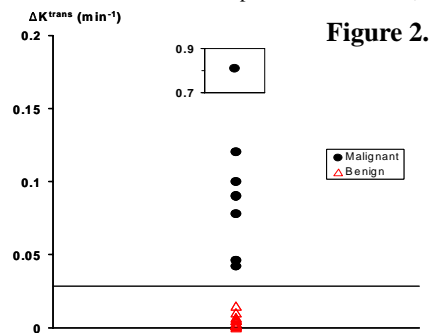


Figure 2.