Detection of microcalcifications by characteristic magnetic susceptibility effects using MR phase image cross-correlation analysis

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Purpose: To develop and evaluate a new method for detecting calcium deposits using their characteristic magnetic susceptibility effects on magnetic resonance (MR) images at high fields and demonstrate its potential in practice for detecting breast microcalcifications.

Methods: Characteristic dipole signatures of calcium deposits were detected in magnetic resonance phase images by computing the cross-correlation between the acquired data and a library of templates containing simulated phase patterns of spherical deposits. The influence of signal-to-noise ratio and various other MR parameters on the results were assessed using simulations and validated experimentally. The method was tested experimentally for detection of calcium fragments within gel phantoms and calcium-like inhomogeneities within chicken tissue at 7 T with optimized MR acquisition parameters. The method was also evaluated for detection of simulated microcalcifications, modeled from biopsy samples of malignant breast cancer, inserted *in silico* into breast magnetic resonance imaging (MRIs) of healthy subjects at 7 T. For both assessments of calcium fragments in phantoms and biopsy-based simulated microcalcifications in breast MRIs, receiver operator characteristic curve analyses were performed to determine the cross-correlation index cutoff, for achieving optimal sensitivity and specificity, and the area under the curve (AUC), for measuring the method's performance.

Results: The method detected calcium fragments with sizes of 0.14–0.79 mm, 1 mm calcium-like deposits, and simulated microcalcifications with sizes of 0.4–1.0 mm in images with voxel sizes between $(0.2 \text{ mm})^3$ and $(0.6 \text{ mm})^3$. In images acquired at 7 T with voxel sizes of $(0.2 \text{ mm})^3$ – $(0.4 \text{ mm})^3$, calcium fragments (size 0.3–0.4 mm) were detected with a sensitivity, specificity, and AUC of 78%–90%, 51%–68%, and 0.77%–0.88%, respectively. In images acquired with a human 7 T scanner, acquisition times below 12 min, and voxel sizes of $(0.4 \text{ mm})^3$ – $(0.6 \text{ mm})^3$, simulated microcalcifications with sizes of 0.6–1.0 mm were detected with a sensitivity, specificity, and AUC of 75%–87%, 54%–87%, and 0.76%–0.90%, respectively. However, different microcalcification shapes were indistinguishable.

Conclusions: The new method is promising for detecting relatively large microcalcifications (i.e., 0.6–0.9 mm) within the breast at 7 T in reasonable times. Detection of smaller deposits at high field may be possible with higher spatial resolution, but such images require relatively long scan times. Although mammography can detect and distinguish the shape of smaller microcalcifications with superior sensitivity and specificity, this alternative method does not expose tissue to ionizing radiation, is not affected by breast density, and can be combined with other

MRI methods (e.g., dynamic contrast-enhanced MRI and diffusion weighted MRI), to potentially improve diagnostic performance. © 2015 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4908009>]

Key words: magnetic susceptibility, breast cancer, MRI, microcalcifications, ROC analysis

1. INTRODUCTION

There continue to be major efforts to develop new methods to detect early breast cancers that present as microcalcifications. Although calcifications are common and frequently associated with benign changes, between 48% and 63% of malignant breast cancers contain microcalcifications and are often the sole mammographic feature indicating malignancy.¹ In fact, 86% of ductal carcinoma *in situ* (DCIS), which is an early form of noninvasive breast cancer, is detected by microcalcifications on mammograms.² Additionally, high risk lesions such as atypical hyperplasia (which suggest a long-term absolute risk of developing breast cancer of over 25% at 25 yr) can also be associated with microcalcifications.³

While x-ray mammography can detect calcifications due to the large mass attenuation coefficient differences (a factor of approximately 13) between calcium and surrounding breast tissue,⁴ leading to a sensitivity between 74% and 95% and a specificity between 89% and 99%,^{5–10} precise localization of calcium deposits is difficult due to the planar nature of mammography. Furthermore, screening mammography has a significantly lower sensitivity in women with extremely dense breasts than in those with almost entirely fatty breasts (62.2% vs 88.2%, respectively); women with breasts in the highest density category have a four- to sixfold greater risk of developing breast cancer compared with those who are least dense.¹¹ On the other hand, magnetic resonance imaging (MRI) sensitivity does not seem to be as affected by density as is mammography.¹¹ Indeed, MRI has higher sensitivity to breast cancer than mammography in women with a 15% or greater lifetime risk of the disease.¹² Another potential limitation of mammography is the cumulative effects of exposure of breast tissue to ionizing radiation. The updated 2007 International Commission on Radiological Protection estimated that the risk of breast cancer death due to exposure of breast tissue to ionizing radiation has approximately doubled compared to 1977 and 1991 estimates.¹³ The predicted number of cancers induced in 100 000 women who undergo annual screening mammograms from age 40 to 55 yr and biennially from 55 to 74 yr (for a total of 25 examinations, 3.7 mGy to both breasts for each exam) is 86.4.¹⁴ In addition, there are increased adverse consequences from the cumulative effects of ionizing radiation to breast tissue in women who start screening at a younger age, such as women with a BRCA mutation.^{15–17}

Due to these well-recognized limitations of mammography, MRI has become increasingly important for the detection and delineation of breast cancer. In fact, the American Cancer Society has issued guidelines that include annual breast MRI screening for high risk subjects: women with familial or genetic predisposition for breast cancer, dense breast tissue, and/or lifetime risk greater than 20%–25% based on family

and/or clinical history.^{18,19} MRI provides multiplanar sectioning, 3D views, and superior soft tissue contrast; contrast-enhanced breast MRI provides a sensitivity between 71% and 100% and specificity of 81%–99% in the detection of breast cancer.¹⁹ However, the sensitivity and specificity of MRI in characterizing and detecting breast cancers associated with microcalcifications are lower (45%–100% and 37%–95%, respectively).²⁰ As microcalcifications are a frequent feature of early breast cancer,^{20,21} breast MRI may be a more effective screening tool if microcalcifications were more readily detectable with MRI, particularly in high risk populations, such as women with dense breasts and females who begin screening at earlier ages, thus increasing risks associated with cumulative exposure to radiation.

In standard proton MRI, the small size of calcium deposits and their associated negligible signals render their direct detection impractical; however, methods that exploit the magnetic susceptibility difference between calcium and surrounding tissue water are more promising for calcium detection because these effects extend over a large scale. Calcium is more diamagnetic than tissue water and produces a disturbance in the magnetic field that can be observed in gradient echo phase images. In a right handed coordinate system,²² calcium produces positive phase shifts, whereas blood and iron, which are paramagnetic, generate negative shifts. To date, there have been several reported efforts to directly detect calcium deposits through their positive phase shifts. These include profiling of signal voids to identify positive phase shifts,²³ and magnetic susceptibility weighted imaging (SWI) in brain²⁴ and breast²⁵ that exploits the contrast from diamagnetic susceptibility differences.²⁶

We propose a new method for detecting microcalcifications within tissue using their characteristic magnetic susceptibility effects in magnetic resonance (MR) phase images. A small calcium deposit generates a dipole-like disturbance in the magnetic field, a shape that is distinct from those of other small inhomogeneities; therefore, we hypothesize an object with a similar phase signature is likely to be a calcification and pattern recognition should be capable of identifying its unique signature. To evaluate the conditions needed for the practical application of this method, and to ultimately provide insight into its clinical value for detecting microcalcifications in the human breast at high field (7 T), we performed three related studies. First, pattern recognition was implemented with cross-correlation using a library of templates to detect the phase signatures of spherical and nonspherical calcium deposits within homogeneous tissue in simulated MR phase images. The method was then applied to simulated images with different signal-to-noise ratios (SNR) and spatial resolutions containing calcium deposits of different sizes, shapes, and positions within a voxel in order to determine the

effects of these parameters on the method. Second, the cross-correlation method was applied to MR images of phantoms to validate the results found in simulations and to test the method for detecting deposits within tissue-like backgrounds. Finally, the method was used to detect simulated microcalcifications placed *in silico* within breast MR images of healthy controls to provide insight into the feasibility of the method for translation to patient studies at high field (7 T).

2. METHODS

2.A. Gradient echo magnitude and phase image simulations

Simulated MR images of calcium deposits surrounded by tissue were generated under different conditions of noise, spatial resolution, magnetic field strength, and position. All simulations and analyses employed MATLAB version 7.10.0.499 (Mathworks, Natick, MA). Each calcification was modeled as a spherical object immersed in a homogeneous material. Diameters of the deposits varied between 0.2 and 1.0 mm in steps of 0.1 mm, based on the dimensions of calcium deposits found in breast cancer.^{27–30} The volume magnetic susceptibility of each sphere was set to that of calcium phosphate (-11×10^{-6} , dimensionless SI units),²³ while the value for the surrounding medium was set to the value for water, -9×10^{-6} .

3D gradient echo MR magnitude and phase images were simulated separately. Simulated magnitude images were computed by setting the signal value inside the sphere to 0 arbitrary units (a.u.). The signal value in the surrounding material was computed using

$$S(r) = \rho_0 \cdot \frac{(1 - e^{-TR/T_1}) \cdot \sin(\alpha) \cdot e^{-TE/T_2^*}}{(1 - \cos(\alpha) \cdot e^{-TR/T_1})}, \quad (1)$$

where TR is the repetition time, α is the flip angle, T_1 is the longitudinal relaxation time, ρ_0 is the spin density in location r , and T_2^* is the apparent transverse relaxation time. T_1 was set to 1622 ms and T_2^* to 64 ms.³¹ Simulated phase images were generated using the relationship between the phase in gradient

echo images and the induced magnetic field, ΔB ,

$$\varphi(r) = -\gamma TE \Delta B(r), \quad (2)$$

where φ is the phase at position r , γ the gyromagnetic ratio, TE is the echo time, and ΔB the deviation of the induced magnetic field at r . This equation uses the right handed coordinate system. Salomir *et al.*³² derived a transformation for computing the field perturbation $\Delta B_z(x, y, z)$ due to a particular magnetic susceptibility distribution $\chi(x, y, z)$ that is exposed to a static magnetic field B_0 . In the Fourier domain,

$$\Delta \tilde{B}_z(\mathbf{k}) = B_0 \tilde{\chi}(k) \times \left(\frac{1}{3} - \frac{k_z^2}{\mathbf{k}^2} \right), \quad (3)$$

where the overstrike “~” denotes a 3D Fourier transform, k_z is the z -component of the k -space vector parallel to the main magnetic field, and $\mathbf{k}^2 = k_x^2 + k_y^2 + k_z^2$ is the squared magnitude of the k -space vector.

To mimic experimental conditions, noise was added to the real and imaginary components of the simulated images to yield SNR values between 5 and 95. Noise was generated using a normal random distribution function with a mean of zero.

Phase images can contain a wide range of values depending on TE, orientation and magnitude of B_0 , size of the spherical object, differences in magnetic susceptibilities, position of the spherical object within the voxel, and resolution of the image. The phase range was constrained to $[-\pi, \pi]$ (rad) by adjusting the TE to prevent phase wrapping. The TEs needed to appropriately restrict the phase in the 3D gradient echo simulations of spherical deposits with diameters between 0.2 and 1.0 mm (in steps of 0.1 mm) and isotropic voxel sizes between 0.2 and 1.0 mm (in steps of 0.2 mm) at the main static field of 7 T were computed and are summarized in Table I. The magnitudes of the images for these TEs are also computed and are expressed as a percentage of the initial maximum signal when TE = 0 (see Table I). For combinations with very long TEs, the signal drops close to zero and therefore the phase cannot be measured (see Table I).

TABLE I. Gradient echo simulations computed to constrain phase within $[-\pi, \pi]$.

Deposit size (mm)	TE (ms), signal intensity (%)				
	Resolution (mm)				
	0.2	0.4	0.6	0.8	1
0.2	12.5, 82	(595, 0)	(3336, 0)	(5350, 0)	(11710, 0)
0.3	3.72, 94	17.4, 76	(595, 0)	(2371, 0)	(5750, 0)
0.4	1.9, 97	12.6, 82	91, 24	(584, 0)	(2070, 0)
0.5	1.3, 98	6.4, 91	29, 63	(177, 6)	(595, 0)
0.6	1.3, 98	3.7, 94	12.5, 82	17.3, 76	197, 4
0.7	1.5, 98	2.5, 96	7.7, 89	17.7, 83	82, 27
0.8	1.2, 98	1.9, 97	5.3, 92	12.6, 82	12.1, 83
0.9	1.0, 98	1.6, 98	3.8, 94	8.9, 87	11.8, 83
1	1.3, 98	1.3, 98	2.7, 96	6.4, 91	12.5, 82

Note: “()” indicates combinations where deposits cannot be detected because their phase signatures cannot be measured.

2.B. Identifying calcifications via the cross-correlation method

In simulated and experimental phase images, the positions of calcium deposits and their sizes were determined using

$$C(i,j,k) = \frac{\sum_{l=1}^r \sum_{m=1}^r \sum_{n=1}^r T(l,m,n) A(i+l-\frac{r}{2}, j+m-\frac{r}{2}, k+n-\frac{r}{2})}{\sqrt{\left[\sum_{l=1}^r \sum_{m=1}^r \sum_{n=1}^r T(l,m,n)^2 \right] \left[\sum_{l=1}^r \sum_{m=1}^r \sum_{n=1}^r A(i+l-\frac{r}{2}, j+m-\frac{r}{2}, k+n-\frac{r}{2})^2 \right]}} \quad \text{for} \quad \begin{cases} \frac{r}{2} < i < q - \frac{r}{2} \\ \frac{r}{2} < j < q - \frac{r}{2} \\ \frac{r}{2} < k < q - \frac{r}{2} \end{cases}, \quad (4)$$

where $C(i,j,k)$ is the cross-correlation matrix with dimensions $q \times q \times q$, A is the matrix containing the target image also with dimensions $q \times q \times q$, and T is the matrix containing the template with dimensions $r \times r \times r$. Matrices A and C are of the same size while T is usually much smaller and depends on the deposit size (larger deposits will have large phase signatures and therefore large templates). The computed matrix contains cross-correlation coefficients with values between $[-1, 1]$. The coefficient value indicates the degree of similitude between the template and target; a coefficient of 1 indicates a perfect match while a -1 indicates a target with the exact opposite value of the template, in this case the same dipole shape but opposite polarity. In principle, the location in the matrix with the cross-correlation maximum value (CCMV) indicates the center position of the calcium signature in the phase image. Deposit size is determined by comparing the CCMVs obtained with the other templates in the library and is indicated by the maximum CCMV.

The templates in the library containing the phase signatures of spherical calcium deposits of different sizes surrounded by tissue were generated by simulation using the same parameters (i.e., spatial resolution, TE, and B_0) used to acquire or simulate the target images. The field of view (FOV) of the template was set to three times the size of the deposit to include the characteristic phase changes. The matrix size of the template depends on the resolution; for example, using a resolution of $(0.2 \text{ mm})^3$ and a 1 mm diameter spherical object will result in a template size of $3 \times 3 \times 3 \text{ mm}$ and a template matrix size of $15 \times 15 \times 15$.

In order to determine if a template generated using a spherical deposit can be used to detect nonspherical deposits, cross-correlation was applied to simulated images of a spherical and a nonspherical object. The shape of the nonspherical deposit was obtained from high resolution micro CT (Sec. 2.G).

2.C. Measuring the effect of B_0 , spatial resolution, and deposit size, shape, and location on cross-correlation using simulations

To determine the sensitivity of the method to changes in spatial resolution, SNR, and intravoxel position of the deposit, we monitored CCMV changes to different parameters

cross-correlation between the phase images and a library of templates containing the phase disturbances of calcium deposits with different sizes. The cross-correlation coefficient matrix between a target image and an individual template was computed via Eq. (3),

for detection of spherical deposits (0.2–1.0 mm in steps of 0.1 mm). Simulated images had isotropic voxel sizes between 0.2 and 1.0 mm (in steps of 0.2 mm). SNR ranged from 5 to 95 (in steps of 10). The deposit was systematically moved, parallel to B_0 , in 25 equally spaced locations from the center of the voxel to 2.5 times the voxel size. Only the position of the simulated deposit changed; the location of the deposit in the template remained constant, centered within a voxel. For each SNR value and for each deposit location, 100 images were generated. Cross-correlation was applied to the images to locate the deposit, and the CCMV mean and confidence intervals (CI) were computed. The influence of both SNR and intravoxel position on CCMV mean and CI was also determined; for each SNR value, the deposit was systematically moved within the voxel in ten equally spaced locations on each orthogonal dimension, totaling 1000 different locations.

2.D. Validation of influences of spatial resolution, deposit size, shape, and location on cross-correlation using phantom experiments

The influences of spatial resolution, SNR, and deposit location on the method were measured and validated in MR images of a phantom mimicking a calcium deposit within tissue. The phantom consisted of a 1 mm spherical borosilicate glass bead (Aldrich, St. Louis, MO) immersed in agar gel, which has the same magnetic susceptibility ($\chi = -9 \times 10^{-6}$) as tissue. The bead was chosen for its shape, low water content, and a magnetic susceptibility equivalent to calcium ($\chi = -11 \times 10^{-6}$).³³ MR images were acquired using a 7 T Varian scanner (Palo Alto, CA) using 3D gradient recalled echo pulse sequences with $TR/\alpha = 10 \text{ ms}/7^\circ$. TE, B_0 , and voxel sizes were identical to those used in the simulations. Bandwidths (BW) of 1330 Hz/pixel and 2666 Hz/pixel were used for voxel sizes of $(0.2 \text{ mm})^3$ and $(0.4 \text{ mm})^3$, respectively. The FOV and acquisition matrix were varied to obtain these spatial resolutions and the number of signal averages was systematically increased to achieve different SNR values.

The influence of the deposit location on cross-correlation was determined by studying changes in CCMV obtained when detecting the deposit in different locations within the FOV. In MR images of the phantom acquired at 7 T with an isotropic

voxel size of 0.2 mm^3 , different positions of the deposit within the FOV were obtained by systematically increasing the offset of the center of the FOV. The offset was increased from 0 to 0.8 mm in steps of 0.02 mm in the readout direction parallel to B_0 and for each position six images were acquired. Cross-correlation was applied to the images to locate the deposit, and the CCMV mean and CIs were computed. We repeated similar experiments with images acquired with isotropic voxel sizes of 0.4 mm^3 , different SNRs, and different deposit positions.

2.E. Sensitivity and specificity of cross-correlation for detecting calcium fragments

While the above measurements examine the method for spherical calcium-like deposits, actual calcifications are grossly nonspherical. Thus, we studied four phantoms (C1, C2, C3, C4) that contained 6–11 nonspherical fragments of calcium hydroxyphosphate (Aldrich, St. Louis, MO) immersed in agar gel. Each fragment was less than 1 mm in the longest dimension and their exact dimensions were measured with high resolution micro CT (Table II). MR images of the phantoms were acquired using a 7 T Varian spectrometer using 3D gradient recalled echo pulse sequences with voxel sizes between $(0.2 \text{ mm})^3$ and $(1.0 \text{ mm})^3$ in steps of $(0.2 \text{ mm})^3$. In order to detect the phase signatures of different deposit sizes on images acquired with the same spatial resolution, different TEs were used (Table I). TR was set to the minimum allowed by the scanner (ranging from 4 to 32 ms), BWs were set to the maximum allowed by the scanner (1330–2666 Hz/pixel), and the flip angle (α) was set using the Ernst equation using a T_1 value of 1300 ms. The number of signal acquisitions was set to 1, except for images with voxel sizes of $(0.2 \text{ mm})^3$ where the number of acquisitions averages was set to 8 in order to obtain a $\text{SNR} > 30$. Cross-correlation was applied to the images to locate fragments C1–C4 and receiver operator characteristic (ROC) analysis applied to the cross-correlation indices to determine the CCMV cutoff needed to maximize the sensitivity and specificity of the method.

2.F. Identifying calcium-like deposits within a tissue-like phantom

MR images of a chicken breast with inserted calcium-like glass beads were also acquired to test the cross-correlation method. The beads were inserted approximately 1 cm into the chicken breast through a channel made with the tip of a #80 industrial sewing needle. The sample was then inserted into a glass bottle, and remaining space was filled with saline solution. MR images of the chicken breast were acquired with a 7 T Varian scanner using 3D gradient echo pulse sequence with $\text{TR}/\alpha = 10 \text{ ms}/7^\circ$. Images were acquired with spatial resolutions of $(0.2 \text{ mm})^3$ and $(0.4 \text{ mm})^3$ with BWs of 1330 Hz/pixel and 2666 Hz/pixel, respectively. Previously calculated TE values were used to obtain images with a phase range of $[-\pi, \pi]$ (see Table I). Cross-correlation was applied to the images to locate the fragments. CT was also performed to validate the findings obtained by the cross-correlation method.

TABLE II. Dimensions of calcium deposits measured in phantoms C1–C4 using microCT.

X (mm)	Y (mm)	Z (mm)
0.225	0.142	0.158
0.172	0.188	0.218
0.345	0.218	0.232
0.128	0.172	0.172
0.375	0.285	0.248
0.607	0.600	0.300
0.397	0.427	0.375
0.593	0.698	0.607
0.232	0.397	0.277
0.532	0.352	0.412
0.128	0.135	0.195
0.232	0.263	0.202
0.517	0.375	0.750
0.390	0.397	0.375
0.705	0.495	0.443
0.165	0.172	0.240
0.397	0.375	0.263
0.652	0.938	0.772
0.517	0.330	0.457
0.277	0.158	0.142
0.180	0.255	0.142
0.270	0.308	0.323
0.300	0.202	0.277
0.277	0.472	0.270
0.292	0.517	0.532
0.525	0.645	0.375
0.517	0.765	0.578
0.345	0.232	0.248
0.135	0.255	0.270
0.232	0.270	0.308
0.292	0.158	0.412
0.427	0.435	0.308
0.397	0.585	0.412
0.375	0.337	0.270
0.547	0.427	0.367
0.405	0.472	0.352
0.480	0.330	0.367
0.930	0.457	0.270
0.135	0.180	0.105

2.G. Computed tomography

All CT images of phantoms C1, C2, C3, and C4 were acquired using a Scanco Medical microCT50 (Brüttisellen, Switzerland). For phantoms C1–C4, a tube voltage of 55 kVp, exposure time of 300 ms, and an anode current of 200 μA were used. A 3D volume ($\text{FOV} = 22 \times 22 \times 30 \text{ mm}$) was obtained using images from adjacent slices ($10 \mu\text{m}$ separation). Each slice was reconstructed from 1000 projections acquired over 180° to yield an isotropic voxel of size $(10 \mu\text{m})^3$.

For CT scans of the chicken breast phantom, we used a tube voltage of 45 kVp, exposure time of 300 ms, and an anode current of 177 μA . A 3D volume ($\text{FOV} = 24 \times 24 \times 33 \text{ mm}$) was obtained using images from adjacent slices ($30 \mu\text{m}$ separation). Each slice was reconstructed from 500 projections acquired over 180° to yield an isotropic voxel size of $(30 \mu\text{m})^3$.

CT images were coregistered to MR images using previously described software.³²

2.H. Detecting simulated microcalcifications in breast MRI

Realistic phase signatures of microcalcifications were computed using the shape of microcalcifications extracted from high resolution CT images of breast cancer biopsy samples and then inserted *in silico* into breast MR images of healthy control subjects. The biopsy samples (S1, S2, and S3) were prepared in paraffin blocks. The images were acquired using a Scanco Medical microCT50 (Brüttisellen, Switzerland) with the following parameters: tube voltage of 45 kVp, exposure time of 300 ms, anode current of 200 μ A, 500 projections acquired over 180°. The reconstructed volume had an isotropic voxel of size $(7.5 \mu\text{m})^3$. Threshold based segmentation was applied to mask calcium from background and tissue. The MATLAB function “BWCONCOMP” was applied to the binary image to identify all the connected components, their locations, dimensions (length, width, and thickness), and shapes. Components with dimensions >0.1 mm surrounded by tissue were classified as microcalcifications.

Breast MR images were acquired using an Achieva 7 T (Philips Healthcare, Cleveland, OH) with a local transmit/receive breast coil³⁴ for unilateral focused transmission/reception using two circular elements 15 cm in diameter, orthogonally aligned and driven in quadrature.³⁵ A 3D gradient echo sequence with ProSet fat suppression (a selective excitation technique that employs a frequency and spatially selective excitation pulse to dephase fat and water proton signal) was used to obtain images sensitive to the phase signature of microcalcifications with a clinically practical acquisition time limit of 12 min and two spatial resolutions. (By “clinically practical,” we mean a single scan with a duration that is well-tolerated by the patient so as to have minimal subject motion.) For the $(0.4 \text{ mm})^3$ data, we employed TR/TE/ $\alpha = 10 \text{ ms}/6.9 \text{ ms}/10^\circ$, BW = 661 Hz/pixel, FOV of $140 \times 140 \times 80 \text{ mm}^3$, acquisition matrix of $350 \times 350 \times 200$ for an acquisition time of 12 min. For the $(0.6 \text{ mm})^3$ data, we used TR/TE/ $\alpha = 6.7 \text{ ms}/3.0 \text{ ms}/10^\circ$, BW = 531 Hz/pixel, FOV of 150×150

$\times 120 \text{ mm}^3$, acquisition matrix of $250 \times 250 \times 200$, for an acquisition time of 7 min.

The phase signatures of the microcalcifications were computed as described above. The signatures were inserted *in silico* into the MRI data by adding the phase of the signatures to the phase of the acquired images. Microcalcifications, individual and clustered, with sizes between 0.3 and 1.0 mm were inserted into four different locations within glandular tissue in each set of breast MR images, one with voxel size of $(0.4 \text{ mm})^3$ and the other with voxel size of $(0.6 \text{ mm})^3$. In order to consider partial volume effects, each microcalcification was systematically moved within the voxel in four equally spaced locations on each dimension, totaling 64 different locations. Cross-correlation analysis was applied to breast MRI data to detect the microcalcifications. ROC analysis was then used to compare the sensitivity and specificity of this method with published data on mammography.

3. RESULTS

3.A. Gradient echo magnitude and phase image simulations

Figure 1 shows the simulated MR magnitude and phase images (SNR = 20) of a 1 mm spherical calcium deposit within a homogeneous background. In the magnitude image [Fig. 1(a)], there is a circular signal void created by the deposit, and the phase image [Fig. 1(b)] shows the characteristic phase signature of the deposit: a dipole shape with the positive lobe parallel to the main magnetic field and twice the magnitude of the negative shifts perpendicular to the main magnetic field.

Simulated images matched experimental 3D gradient echo magnitude and phase images of a 1 mm calcium-like deposit immersed in gel. Figure 2 depicts a picture of the phantom [Fig. 2(a)] and corresponding MR images [Figs. 2(b)–2(f)]. In the magnitude image [Fig. 2(b)], there is a circular signal void generated by the deposit, and in the phase image [Fig. 2(d)], the deposit’s characteristic dipole shape is present within the slowly varying phase artifacts (due to gel/air interfaces and subtle shimming errors). The artifacts were removed with a high-pass frequency Hanning filter with size $21 \times 21 \times 1$ that

FIG. 1. MRI simulation of a 1 mm calcium deposit within tissue. The gradient echo magnitude image (a) shows a signal void created by calcium, and the phase image (b) depicts the characteristic phase signature of the deposit.

FIG. 2. MRI of a 1 mm calcium-like object immersed in agar gel. Photograph of the phantom containing a 1 mm glass bead within gel (a), the corresponding gradient echo magnitude image shows a signal void created by the deposit (b) while the corresponding phase image (d) shows the phase signature of the deposit altered by air/gel interface phase artifacts. The phase image after high-pass filtering shows a clean phase signature of the deposit (e). Magnified views of the inset show, in more detail, the signal void (c) and the phase signature (f) of the deposit.

had no apparent effects on the dipole shape; the phase image after filtering shows a clean phase signature of the deposit [Fig. 2(e)]; magnified views of the inset show a more detailed view of the signal void [Fig. 2(c)] and the phase signature [Fig. 2(f)].

3.B. Identifying calcifications via cross-correlation

The cross-correlation method was applied to the simulated phase images in Fig. 1 to detect the deposit. Figure 3 shows the cross-correlation between the template containing the phase signature of a 1 mm deposit [Fig. 3(a)] and a library of templates containing the phase signatures of calcium deposit with sizes between 0.2 and 2.0 mm in steps of 0.2 mm [Fig. 3(b) shows the templates of deposits with sizes 0.2, 1.0, and 2.0 mm] resulted in cross-correlation matrices where the position of the deposit is indicated by a CCMV. Figure 3(c) depicts the cross-correlation between the phase and the template of a 1.0 mm deposit with a CCMV of 0.8. The size of the deposit was determined by comparing the CCMVs obtained with the cross-correlation between the image and the templates in the library [Fig. 3(d)]; the maximum CCMV indicates the method's estimate of the size of the deposit. Deposits with sizes between 0.9 and 1.1 mm will also be detected with the same maximum CCMV, so the estimated size of the deposit is $1.0 \text{ mm} \pm$ a margin of error of 0.1 mm. In the cross-correlation example shown in Fig. 3, the CCMV of 0.8 indicates that the phase signature in the image does not exactly match the phase signature in the template even though both contain the same phase signature of a 1 mm deposit. The decrease in

CCMV from a perfect match of 1–0.8 is due to the presence of noise in the image. By studying changes in CCMVs similar to this one, we were able to determine the influences of various sample and acquisition parameters on the method in simulation experiments.

3.C. Measurement of influence of spatial resolution, and deposit size, shape, and location on cross-correlation using simulations

The influence of deposit shape on the method was assessed by comparing the phase signature of two deposits with different shapes and their corresponding CCMVs. High resolution simulations of the phase image of a spherical and nonspherical object are depicted in Figs. 4(a) and 4(b), respectively. Both objects are 0.3 mm in cross-sectional size. To show the phase signatures in detail, the simulations were made using voxel sizes of $(0.03 \text{ mm})^3$. There are some differences between both signatures at the boundaries of the deposits; however, the phase signatures of the deposits simulated with voxel sizes of $(1 \text{ mm})^3$ [Figs. 4(c) and 4(d)], a size more common in clinical MRI, are very similar. Figures 4(c) and 4(d) show the signatures generated with the spherical and nonspherical deposits, respectively. Even though both signatures can be differentiated at $(0.03 \text{ mm})^3$ spatial resolution, they appear very similar at $(1 \text{ mm})^3$ spatial resolution. In fact, when the cross-correlation method is applied to the low resolution images, the CCMVs obtained are almost identical, 1.0 for the spherical deposit and 0.9996 for the nonspherical deposit. This result suggests that the method can also detect deposits with nonspherical shapes

FIG. 3. Detection of calcium deposits via cross-correlation method. Cross-correlation between the simulated phase of a deposit (a) and a library of templates containing the phase signatures of deposits with various sizes [three shown in (b)] results in cross-correlation matrices (1.0 mm template) shown in panel (c), where the position of the deposit is indicated by a CCMV, the size of the deposit (1 mm) by a maximum CCMV across cross-correlation matrices (d), and the measurement error (± 0.1 mm) by the step size between deposits used to generate the templates.

in images obtained with spatial resolutions available in current gradient echo MRI.

The influence of image SNR on the method's response was determined by comparing the CCMVs obtained when applying cross-correlation to simulated MR phase images of a 1 mm calcium deposit with different levels of noise. Figure 5(a) displays the CCMV obtained when cross-correlation was applied to images generated using $B_0 = 7$ T and a voxel size of $(0.4 \text{ mm})^3$ for SNR values between 5 and 95 (in increments of 10). The CCMV plot shows an asymptotic recovery starting at 0.5 when the SNR is 5, reaching 90% of its terminal value of 1.0 at a SNR of approximately 20. The 95% CI (indicated by the error bars) of the CCMVs decreased gradually for increasing SNR values; the initial CI range of 0.23 for a SNR of 5 reduced to 0.10 at a SNR of 20. In simulations with voxel sizes of $(0.2 \text{ mm})^3$ (not shown), a similar CCMV response was obtained. The method is influenced by noise in an asymptotic manner with smaller CCMV and larger CI for lower SNR values and larger CCMVs and smaller CI for higher SNR.

The influence of deposit position on cross-correlation was determined by studying changes in CCMV obtained when detecting the deposit in different locations. Figure 5(b) shows the CCMV measured in simulated MR phase images of a 1 mm calcium deposit systematically positioned from the center of a voxel to 1.0 mm, or two and a half times the size of the voxel, in the direction parallel to B_0 in steps of 0.04 mm. The CCMV is the highest (0.98) when the deposit is centered in a voxel (locations 0, 0.4, and 0.8 mm) and the lowest (0.69) when it is

located between two voxels (locations 0.2, 0.6, and 1.0 mm). The CCMV CI is the same (0.018) for the different positions. Similar results (not shown) were found when the position of the object was changed in the other orthogonal directions. Similar CCMV curves were also obtained in simulations with a voxel sizes of $(0.2 \text{ mm})^3$ (not shown). Since the template is made with the object centered in a voxel, the largest CCMVs are expected when the deposit is located in the center of the voxel and the results confirm this. In addition, the results indicate that the CCMV range and CI are different for the voxel size and deposit size combination; and that the template and the phase signature are less alike when the deposit is centered at the boundaries of the voxels, indicated by the lowest CCMV values at these locations.

The combined effects of noise and location in the voxel on the method were determined by comparing the CCMVs obtained with images containing deposits at different locations and with different SNRs. The CCMV measured on simulated MR phase images of a 1 mm calcium deposit for different SNR values and different positions of the deposit is displayed in Fig. 5(c). For each SNR value, the object was moved in ten equally spaced locations in each dimension, totaling 1000 different locations, within the voxel. The CCMV shows an asymptotic recovery shape starting at 0.43 when the SNR is 5, and reaching 90% of its terminal mean value of 0.8 at a SNR of 15. The CCMV CI range had the same value of 0.2 for all SNR values. Similar results were obtained when using simulations with voxel size of $(0.2 \text{ mm})^3$ [Fig. 5(d)], but with

FIG. 4. Phase signatures of spherical and nonspherical deposits. High spatial resolution phase signatures of a spherical (a) and nonspherical (b) deposit show differences at the boundaries; however, their lower resolution signatures (c) and (d), respectively, are very similar and cross-correlation detects them with CCMVs of 1.0 and 0.9996, respectively.

increased terminal CCMV (0.85) and lower CI (0.12) across all SNR realizations, reflecting decreased partial volume effects. These results indicate that lower CCMVs are obtained with decreased SNR, but that beyond a SNR of 30, the CCMV reaches a terminal value with constant CI. The CCMV terminal value and CI depend on the deposit size and the voxel size combination. Larger deposit sizes in images with smaller voxel result in larger CCMV terminal values with smaller CI.

3.D. Validation of influences of spatial resolution, and deposit size, shape, and position on cross-correlation using phantom experiments

Figure 6(a) shows the CCMV measured on MR images of a 1 mm calcium-like deposit within gel with readout offsets of 0–0.5 mm in steps of 0.02 mm. The voxel size for these images was $(0.2 \text{ mm})^3$. The CCMV plot shows a cyclical shape with a period equal to 0.2 mm, the size of the voxel. The same maximum value of 0.92 was reached when the offset has values of 0.12 mm and 0.32. Similarly, the minimum value of 0.78 was found at offsets of values of 0.02, 0.22, and 0.42 mm. The cyclical shape found experimentally matches those predicted by the simulations [Fig. 5(b)]. The CCMV depends on the location of the deposit within the voxel with the largest CCMVs achieved when the deposit is located in the center of the voxel. Figure 6(b) presents the CCMV obtained

on MR images of the same phantom for different SNR values and spatial resolution from data with voxel size of $(0.4 \text{ mm})^3$ acquired at 7 T. Figure 6(c) shows the CCMV measured from data with voxel size of $(0.2 \text{ mm})^3$; the higher CCMV and decreased CI reflect decreased partial volume effects. The asymptotic CCMV response to different SNR values (determined by simulations) can only be observed in [Fig. 6(c)]; images acquired at lower spatial resolution [Fig. 6(b)] had higher SNR range and did not show the lower SNR end of the asymptotic response.

3.E. Sensitivity and specificity of cross-correlation for detecting calcium fragments

The sensitivity and specificity of the method for detecting calcium deposits ($<1 \text{ mm}$) with different shapes were measured using MR images of phantoms containing calcium fragments. Cross-correlation was applied to MR phase images of the phantoms (C1, C2, C3, and C4) to detect calcium fragments. Figure 7 shows the detection of a deposit with dimensions $0.52 \times 0.37 \times 0.75 \text{ (mm)}$. The plot shows the CCMVs obtained with cross-correlation between the image and a library of templates generated with deposit sizes between 0.4 and 0.9 mm. The estimated size of the detected deposit is indicated by the maximum CCMV. Since deposits with sizes between 0.55 and 0.65 mm will also be detected with the same

FIG. 5. SNR and partial volume effects on cross-correlation method measured in simulations of a 1 mm deposit. CCMV curves obtained for different conditions of (a) noise indicates the method's asymptotic response to SNR; (b) different positions show fluctuations of CCMV between 0.65 and 1.0; (c) varying SNR and position of the deposit yield a terminal CCMV with constant CI, or error, for $\text{SNR} > 35$; (d) spatial resolution shows less partial volume effects (increased terminal CCMV and decreased CI, or error) when the resolution increases from $(0.4 \text{ mm})^3$ (c) to $(0.2 \text{ mm})^3$ (d).

maximum CCMV, the estimated size of the deposit is $0.6 \text{ mm} \pm$ a margin of error of 0.05 mm .

ROC analysis was applied to the CCMVs obtained from cross-correlation analysis on phantoms C1–C4. Figure 8 presents the ROC analysis applied to the method for detecting calcium fragments via cross-correlation, specifically microcalcifications with a size range between 0.14 and 0.79 mm in images with a $(0.4 \text{ mm})^3$ voxel. Different cutoff thresholds

and their corresponding sensitivity, specificity, true positive rate (TPR), and false positive rate (FPR) were calculated. The optimal threshold was 0.3 , yielding a sensitivity, specificity, and area under the curve (AUC) of 94% , 58% , and 0.85% , respectively.

ROC analysis was also applied to the method for detecting calcium fragments of different sizes in images acquired at different spatial resolutions. Table III shows the CCMV cutoff

FIG. 6. SNR and partial volume effects on cross-correlation method measured in gel phantom containing a 1 mm calcium-like deposit. Panel (a) shows the CCMV curve obtained for different positions of the deposit indicates fluctuations of the CCMV between 0.81 and 0.93 ; panels (b) and (c) indicate increased terminal CCMV and decreased CI, or error, when spatial resolution increases from $(0.4 \text{ mm})^3$ (b) to $(0.2 \text{ mm})^3$ (c). Panel (c) illustrates the method's asymptotic response with a terminal CCMV of 0.91 for $\text{SNR} > 25$.

FIG. 7. Calcium fragment size detected via cross-correlation. The size of the fragment is determined in the plot of CCMVs obtained from the phase image and templates generated with deposit sizes between 0.4 and 0.9 mm. The estimated size of 0.6 mm is indicated by the maximum CCMV across the templates and the uncertainty by the difference between phase signature sizes in the library. In this case, it is ± 0.05 mm.

that maximizes sensitivity and specificity for detection of calcium fragments with sizes between 0.2 and 0.6 mm, in steps of 0.1 mm in images with voxel sizes of $(0.2 \text{ mm})^3$, $(0.4 \text{ mm})^3$, and $(0.6 \text{ mm})^3$. The results indicate that similar CCMV cutoff values optimized sensitivity and specificity for detection of fragments with different sizes in images with the same spatial resolution. This suggests that the same CCMV cutoff can be

FIG. 8. ROC curve analysis applied to detection of calcium fragments via the cross-correlation method. The ROC curve was generated using FPR and TPR. ROC curve analysis applied to detection of calcium fragments via the cross-correlation method. The ROC curve was generated using FPR and TPR.

TABLE III. ROC analysis of detection of calcium fragments in gel via cross-correlation; data presented as sensitivity (%), specificity (%), AUC.

Deposit size(mm)	Image voxel size (mm) ³		
	0.2	0.4	0.6
0.2	71, 50, 0.60	X	X
0.3	90, 52, 0.77	X	X
0.4	89, 51, 0.85	78, 68, 0.88	X
0.5	—	75, 67, 0.84	50, 68, 0.74
0.6	—	67, 67, 0.70	67, 80, 0.86

Note: "X" indicates combinations with unavailable TE (too short); "—" indicates combinations producing very low SNR images (TE too long).

used to detect calcium fragments of different sizes in images with the same spatial resolution.

3.F. Identifying calcifications via cross-correlation within a tissue-like phantom

Figure 9 shows the gradient echo, cross-correlation matrix, and CT images of a chicken breast tissue acquired with voxel size of $(0.2 \text{ mm})^3$ containing two glass beads (GB1 and GB2). While both were detected, for simplicity, only GB1 is shown. A white arrow indicates the location of GB1 while the black arrows indicate the location of air bubbles. Figure 9(a) displays the MR magnitude image in which the potential location of GB1 can be any region with a circular signal void; however, a signal void can also indicate the location of an air bubble. The corresponding phase image [Fig. 9(b)] suggests the presence of the calcium deposit signature, but the image has many dipole shapes generated by air bubbles and 2D dipole shapes generated by blood vessels orthogonal to the slice. The corresponding CCMV image [Fig. 9(c)] clearly indicates the location of the GB1 with the presence of a CCMV. The locations of the air bubbles are also detected and indicated by the presence of negative values in the matrix. The minimum occurs because the shape of the phase signature of an air bubble within tissue is similar to the shape of the phase signature of a calcium deposit, but with lobes of opposite sign. Therefore, the coefficients corresponding to bubbles will have values close to -1 . The corresponding CT image corroborates the location of GB1 [Fig. 9(d)]. Figures 9(e)–9(h) depict the enlarged views of Figs. 9(a)–9(d). GB1 produced a CCMV of 0.73 while GB2 a CCMV of 0.40; none of CCMVs are within the range determined by simulations $[0.75, 1.0]$. The reason for this smaller CCMV value for GB2 is explained by the presence of other small structures near the bead that appear as signal voids [Fig. 9(e)]. These structures alter the phase signature of the bead [Fig. 9(f)], rendering it less similar to the template and therefore decreasing the CCMV.

3.G. Detection of simulated microcalcifications in breast MR images using cross-correlation

Microcalcifications were inserted *in silico* into breast MR images of healthy controls and detected via cross-correlation. Figure 10(a) shows the magnitude image of a healthy control

FIG. 9. Detection MR magnitude (a) and phase images (b) of chicken breast containing a 1 mm glass bead do not indicate the presence of the bead. However, the cross-correlation matrix (c) reveals the deposit's presence and position, which were validated by CT (d). Panels (e)–(h) depict the enlarged views of panels (a)–(d), respectively. In the region denoted by the green square in panel (a), the enlarged views in panels (e) and (f) indicate the location of the bead with a white arrow, while the two black arrows indicate the locations of air bubbles. The magnified view of the magnitude image (e) also indicates the presence of structures adjacent to the bead that alters the dipole shape of the deposit phase signature.

FIG. 10. Detection of simulated microcalcification in breast MRI via cross-correlation. The insertions were made within the fibroglandular tissue, indicated by the high intensity regions in the magnitude image (a); the exact locations are indicated by the arrows in the inset (b). Panel (c) shows the 3D shape of the microcalcification. Panels (d)–(f) display the similarity matrix. Panel (e) depicts the image before insertion and panel (f) after insertion.

subject acquired with voxel size of $(0.6 \text{ mm})^3$. Figure 10(b) depicts a magnified view of the location of the insertion, indicated by the white inset in the magnitude image; the insertions were made within glandular tissue, at the locations indicated by white arrows. Figure 10(c) displays the shape of the microcalcification used to simulate the phase signature and its dimensions, $0.64 \times 0.71 \times 1.065 \text{ mm}^3$. Figure 10(d) displays the cross-correlation matrix obtained from a template generated with a deposit size of 0.8 mm and the phase image after the insertions. The magnified views of the similarity matrix are shown before [Fig. 10(e)] and after the insertions [Fig. 10(f)] after high-pass filtering. Simulated microcalcifications, located far from fat and fibroglandular tissue borders, were detected [Fig. 10(f), left pointing arrows] with a CCMV of 0.68; before insertion, the cross-correlation index at these locations was 0.16. Simulated microcalcifications next to the boundary (right pointing arrows) were not detected. The size of the microcalcification was determined from the plot of CCMVs obtained between the phase image and the library of templates generated with deposit sizes between 0.4 and 1.0 mm. Figure 11 shows the CCMV plot where the maximum CCMV across the templates indicates the size of the deposit, in this case 0.8 mm, and the uncertainty is indicated by the difference between phase signature sizes in the library as $0.8 \pm 0.05 \text{ mm}$.

To estimate the clinical value of cross-correlation, ROC analysis was applied to the detection of simulated calcifications in breast MR via cross-correlation and the sensitivity and specificity of the method were measured. Figure 12(a) shows the ROC curve for detection of 0.8 mm microcalcifications in images with voxel size of $(0.4 \text{ mm})^3$ with sensitivity of 75%, specificity of 75%, and AUC of 0.89; the sensi-

tivity and specificity refer to one specific operating point (the fourth point on the ROC curve), not the entire curve. Figure 12(b) shows the ROC curve for detection of 1.0 mm microcalcifications in images with voxel size of $(0.6 \text{ mm})^3$ with sensitivity of 78% and specificity of 87% (these values correspond to the fourth operating point on the curve) and AUC of 0.90. Table IV presents the sensitivity, specificity, and AUC

FIG. 11. Detection of simulated microcalcification size in breast MRI via cross-correlation. The size of the microcalcification is determined in the plot of CCMVs obtained from the phase image and templates generated with deposit sizes between 0.4 and 1.0 mm. The estimated size of 0.8 mm of the detected deposit is indicated by the maximum CCMV across the templates and the uncertainty by the difference between phase signature sizes in the library. In this case, it is $\pm 0.05 \text{ mm}$.

FIG. 12. ROC curve analysis of detection of simulated microcalcifications in breast MRI via cross-correlation. ROC curve for detection of 0.8 mm microcalcifications in MR images with voxel size of $(0.4 \text{ mm})^3$ (a) and 1.0 mm microcalcifications in images with voxel size of $(0.6 \text{ mm})^3$ (b).

obtained when ROC analysis was applied to the detection of microcalcifications with sizes between 0.4 and 1.0 in steps of 0.1 mm in images with voxel sizes of $(0.4 \text{ mm})^3$ and $(0.6 \text{ mm})^3$. Mammographic calcium detection sensitivity has been shown to be 84% with a specificity of 71%.³⁶ The specificity of the cross-correlation technique is comparable to mammography only for large calcium deposits (1.0 mm); in all other cases demonstrated, both sensitivity and specificity of calcification detection are lower for the MR method compared to recently reported mammography data.

4. DISCUSSION

A similar method to the one implemented here has previously been used for detection of iron-oxide-labeled cells.³⁷ Superparamagnetic iron oxide (SPIO) nanoparticles have a large magnetic susceptibility difference with tissue water, thereby perturbing the local magnetic field over length scales much greater than the particles' dimensions. The distortion has a dipole shape and is recorded in high resolution gradient echo phase images; cross-correlation between the dipole pattern and the phase images indicated the occurrences of the nanoparticles. In the method implemented here, we also used cross-correlation to detect a dipole shape, in this case one generated

by a more subtle magnetic susceptibility difference between calcium and tissue water in MR phase images. In addition, we studied how the method is affected by various MR parameters; understanding these effects will help determine the optimum gradient echo parameters for detecting calcium deposits in practice. In simulation experiments, we quantified the partial volume effects and determined the TE needed to obtain detectable phase signatures of deposits of different sizes for typical spatial resolutions. These results indicate that we can only detect deposits of certain sizes when using a fixed TE and that the size depends on the spatial resolution (see Table I); therefore, in order to reliably detect deposits of different sizes, we need to acquire images using multiple TEs. Multiecho sequences can be used to generate the data required for the proposed method, but only with a concomitant reduction in spatial resolution and field of view coverage per unit time.

Our simulation experiments also led to another practical finding concerning the method's ability to characterize deposits in images of different spatial resolutions (see Fig. 5). These values can be used as a reference to determine if a calcium deposit is present in an image or not. For example, if we obtain a CCMV of 0.8 with a template generated with a 1.0 mm deposit when performing cross-correlation between a template library and a phase image with voxel size of $(0.4 \text{ mm})^3$ and SNR of 50, we can state with confidence that there is a 1.0 mm deposit in the image.

The simulations also provided insight on the method's specificity. We found that deposits with different shapes are detected with very similar cross-correlation indices, particularly in images with voxel sizes larger than the deposit size (see Fig. 4). While nonspherical calcifications can be detected, our results suggest that the method cannot discern different shapes. Conversely, x-ray mammography can detect very fine details of the object. The fine details of calcium deposits associated with breast cancer are clinically relevant because the shapes and dimensions can be used to help distinguish between benign tumors and malignant cancer; for example, nonspherical calcifications with fine pleomorphic and fine linear morphologies are likely to be indicators of precancerous lesions or early invasive breast cancer.²⁷ Since distinguishing the different shapes

TABLE IV. ROC analysis of detection of simulated microcalcifications in breast MRI via the cross-correlation method; data presented as sensitivity (%), specificity (%), AUC.

Deposit size (mm)	Image voxel size (mm) ³	
	0.4	0.6
0.4	75, 19, 0.42	43, 32, 0.45
0.5	50, 50, 0.61	33, 41, 0.48
0.6	87, 54, 0.80	78, 47, 0.65
0.7	87, 54, 0.80	56, 44, 0.56
0.8	75, 75, 0.89	78, 66, 0.80
0.9	75, 52, 0.76	78, 66, 0.80
1.0	87, 54, 0.81	78, 87, 0.90

of microcalcifications associated with benign and malignant tumors is of central importance in diagnosing breast cancer, the clinical value of the MR-based cross-correlation method used alone will be reduced.

The phantom experiments validated the findings from simulations, in particular, the method's response to SNR, position of the deposit, and spatial resolution. Additionally, these experiments also identified some practical implementation challenges not considered during simulations. During simulations, the TEs needed to detect deposits of different sizes in images with different spatial resolutions were computed; however, not all of these values were practical. Some small TE values were not available in gradient echo 3D for certain spatial resolutions (see Table II). Other TE values were too large and produced images with very low SNR that are impractical for cross-correlation. Acquisition time was kept as low as possible by using the minimum TR allowed in gradient echo 3D imaging. However, when increasing the TE, the TR needed to be increased which increases acquisition time.

Detection of calcium-like deposits within tissue was more challenging than detecting deposits within gel. We obtained CCMVs of 0.91 when detecting 1 mm glass beads within gel in images with voxel size of $(0.2 \text{ mm})^3$; however, the CCMV range for a 1 mm deposit obtained when the deposit was within tissue was [0.34,0.70]. The decrease in CCMVs was due to the heterogeneity of the tissue, specifically the presence of structures adjacent to the bead that altered the dipole shape of the deposit phase signature.

Accurate and precise detection of microcalcifications in breast MRI at 7 T via cross-correlation is limited by the available MR parameters for a gradient echo 3D sequence (e.g., TE, spatial resolution, and SNR). Only spatial resolutions of $(0.4 \text{ mm})^3$ and $(0.6 \text{ mm})^3$ and their corresponding TEs of 6.9 and 3.0 ms, respectively were feasible with conventional methods. Smaller TE values were not available for these voxel sizes, and larger TE values produced images with very low SNR and increased acquisition time. According to Table II, only microcalcifications with sizes $>0.4 \text{ mm}$ can be detected in images acquired at these spatial resolutions. Detection of smaller simulated microcalcifications will require higher spatial resolution of $(0.2 \text{ mm})^3$. The proposed technique is not practical at lower field strengths (1.5 T or 3 T) as the phase signature of a deposit depends on the product of B_0 and TE. If B_0 is reduced, SNR decreases and the longer TEs required reduce SNR even further. Reducing the bandwidth can recover some SNR, but at the cost of distortions due to increased chemical shift. In addition, the longer TEs needed at lower field strengths will require longer TRs and increase total scan time. This longer scan time may not be practical for clinical MRI. One option is to increase voxel size, which raises SNR; however, the lower spatial resolution will only allow for detection of larger calcium deposits that are not clinically relevant in the context of breast cancer. Thus, the translation of the technique to clinical MRI (1.5 T or 3 T) will require a method such as compressed sensing for shortening the total scan time to render the acquisition more practical for clinical use. The emerging method of compressed sensing³⁸ can, in principle, be used to (a) shorten total scan time for a fixed

acquisition, (b) increase the spatial resolution per unit time, or (c) allow for combined implementation of (a) and (b). Thus, compressed sensing may allow for acquisition of 3D gradient echo images with a voxel size of $(0.2 \text{ mm})^3$ to potentially detect microcalcifications via cross-correlation.

ROC analysis indicated that the cross-correlation method detected 0.4–0.9 mm simulated microcalcifications with sensitivities between 75% and 78%, specificities of 32%–75% (Table IV), which worsened with decreasing deposit size (0.7 mm and below). The sensitivity and specificity depended directly on the CCMV cutoff used to determine if a deposit was present or not. Calcium detection via x-ray mammography is superior to the MR method as demonstrated by mammography's sensitivity (84%) and specificity (71%).³⁶ Only in the case of the 1.0 mm calcifications was the specificity (87%) of detecting calcifications by MR comparable to that of mammography. Smaller calcium deposits are possible to detect ($<0.4 \text{ mm}$) by the MR method, and according to Table I, calcifications with size of 0.3 mm should be detected on gradient echo 3D images with voxel size of $(0.2 \text{ mm})^3$ with a TE of 3.72 ms, but these data will take longer than 20 min to acquire using conventional methods. The ability to distinguish calcification size is critical and there are benefits to detecting calcium deposits below 0.6 mm, as well as their shapes, because calcifications associated with malignancy are smaller than 1 mm each (in a cluster of 4–5 deposits or fine, linear and branching), while, in general, benign calcium deposits are macrocalcifications $>1 \text{ mm}$ with smooth and dense shapes over a larger area.²⁷

While the proposed MR method may not on its own outperform x-ray mammography in detecting microcalcifications associated with premalignant and malignant lesions, it could readily be combined with dynamic contrast-enhanced MRI and diffusion weighted MRI to provide a multiparameter assessment of suspicious lesions under investigation and this combination may outperform mammography without ionizing radiation. The cumulative effects of radiation exposure to breast tissue are a potential issue associated with x-ray mammography as it increases the risks of breast cancer induction and breast cancer death.^{13,14} Therefore, MRI is a modality that could particularly benefit women identified with a high risk of developing breast cancer, including women with a BRCA mutation who start mammography screening at a younger age, those with childhood chest radiation exposure, and other predispositions for breast cancer.^{18,19} The American Cancer Society has recently issued guidelines that include annual MRI screening for these high risk patients,^{18,19} and breast MRI is also recommended for women with dense breast tissue, in part, because increased breast density is associated with a higher risk of breast cancer.¹¹ Also, MRI has higher sensitivity to breast cancer than mammography in women with a 15% or greater lifetime risk of developing the disease.¹² In contrast, MRI is not affected by breast tissue density. The sensitivity of contrast-enhanced breast MRI to breast cancer is between 71% and 100% in the detection of breast cancer,¹⁹ while the sensitivity of MRI in detecting breast cancers associated with microcalcifications is 45%–100%.²⁰ Current drawbacks of MRI for breast cancer screening include cost, lack of standardization in examination techniques, the inability of MRI to detect

microcalcifications, scanner and coil variability, and the need for a dedicated breast coil.¹⁹ However, the inability of MRI to detect microcalcifications is the fundamental barrier for its use as a sole screening or diagnostic tool for breast cancer. As the presence of microcalcifications in breast tissue can be an early indicator of cancer, the ability to detect calcium deposits with MRI is potentially of great clinical importance, particularly for the aforementioned high risk groups who already undergo MRI examinations. The method proposed here is an effort to identify calcium deposits using MRI and the results indicate its feasibility at high field (7 T).

5. CONCLUSIONS

We have evaluated a new MRI-based method for detecting calcium deposits, using their characteristic magnetic susceptibility effects in practical conditions to provide insight into its clinical value for detecting breast microcalcifications at high field (7 T). The method was designed to detect the characteristic, unique dipole signatures of calcium deposits in phase images via cross-correlation between those images, and a library of templates containing simulated phase signatures of deposits. The influences of SNR and various MR parameters on the method were determined using simulations and validated in experiments with phantoms and *in silico* insertions of microcalcifications into breast MR images of healthy controls. While x-ray mammography can detect smaller microcalcifications with superior sensitivity and specificity, as well as distinguish their morphologies, the ROC results indicate that the proposed MR method is promising for detecting microcalcifications greater than 0.4 mm and, therefore, warrants further investigation.

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