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Simulation study of the effect of golden-angle KWIC with generalized kinetic model analysis on diagnostic accuracy for lesion discrimination

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Abstract

Purpose—To quantitatively evaluate temporal blurring of dynamic contrast-enhanced MRI data generated using a k-space weighted image contrast (KWIC) image reconstruction technique with golden-angle view-ordering.

Methods—K-space data were simulated using golden-angle view-ordering and reconstructed using a KWIC algorithm with a Fibonacci number of views enforced for each annulus in k-space. Temporal blurring was evaluated by comparing pharmacokinetic model parameters estimated from the simulated data with the true values. Diagnostic accuracy was quantified using receiver operator characteristic curves (ROC) and the area under the ROC curves (AUC).

Results—Estimation errors of pharmacokinetic model parameters were dependent on the true curve type and the lesion size. For 10 mm benign and malignant lesions, estimated AUC values using the true and estimate AIFs were consistent with the true AUC value. For 5 mm benign and 20 mm malignant lesions, estimated AUC values using the true and estimated AIFs were 0.906 ± 0.020 and 0.905 ± 0.021 , respectively, as compared with the true AUC value of 0.896.

Conclusions—Although the investigated reconstruction algorithm does impose errors in pharmacokinetic model parameter estimation, they are not expected to significantly impact clinical studies of diagnostic accuracy.

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Introduction

Dynamic contrast enhanced MRI (DCE-MRI) is an important tool for the diagnosis of cancerous lesions. It provides morphological as well as pharmacokinetic information about lesions that can be combined to improve diagnostic accuracy. In an effort to balance morphological and kinetic information in DCE-MRI data sets, the clinical community often needs to trade-off spatial versus temporal resolution. This is particularly true, for example, when high-spatial resolution data are required for a large three-dimensional field of view, such as encountered in bilateral breast imaging [1].

There have been many approaches to balancing these two conflicting system requirements. One method is to improve scanner hardware (e.g., gradients, parallel imaging, coil arrays) and streamline pulse sequences so that data acquisition is faster. In this way, both spatial and temporal resolution can improve simultaneously. However, even when these methods are employed, current state-of-the-art hardware alone can not fulfill the ever-increasing demand for higher spatial and temporal resolution. Another approach is to take advantage of information redundancy in images to extract higher spatial and temporal resolution information from undersampled data [2]. Some examples of this method include keyhole imaging [3,4], compressed-sensing [5], and view sharing [6].

Although these algorithms show great promise, they can affect image quality in complicated, unexpected ways that hinder their acceptance by the clinical community [7]. In order to realize the full potential of these temporal acceleration techniques and facilitate their transition into the clinical workflow, image quality must be rigorously evaluated.

Two examples of methods that take advantage of information redundancy are k-space weighted image contrast (KWIC) [8] and golden-angle radial view sharing [9]. The combination of these two methods can be referred to as golden-angle KWIC (GA-KWIC). KWIC is a view sharing technique that uses a radial k-space acquisition and exploits the fact that the center of k-space is oversampled to reduce the number of views that contribute to lower resolution regions of k-space. Since the center of k-space is the primary determinant of image contrast, the temporal resolution can be increased to approximately the time it takes to acquire the reduced number of views in this region. This is achieved by continuously acquiring radial views and shifting the reconstruction window by the number of views in the center of k-space. With this method, the outer region of k-space maintains a full sampling of radial views in order to preserve spatial resolution. In this way, very high temporal resolution can be achieved in post-processing without detrimentally affecting the spatial resolution of the images. However, since different numbers of views contribute to different regions of k-space, the temporal resolution of a KWIC reconstructed data set is a complicated, poorly-defined quantity that depends on the combination of low- and high-frequency structures that make up an object under evaluation. Although temporal blurring of KWIC reconstructed data has been qualitatively examined [10], the authors are unaware of any published quantitative evaluations of this effect.

Golden-angle radial imaging is a method of continuously acquiring radial k-space data such that each view is separated by a constant angle, 111.25° , the so-called “golden angle” [9,11].

By acquiring data in this fashion, any number of consecutive views will provide a relatively even sampling of k-space and optimal k-space coverage is achieved when a Fibonacci number of consecutive views is selected [9,12,13]. This technique has the advantage that temporal resolution can be arbitrarily selected and optimized on an ex post facto basis. This property complements the KWIC algorithm since it allows the exact view weighting to be optimized in post-processing.

In this study, we quantitatively evaluate the temporal blurring of DCE-MRI images reconstructed using a GA-KWIC algorithm by examining the effect on estimated pharmacokinetic model parameters. Temporal blurring of both lesion and arterial input function (AIF) curves are taken into consideration. The dependence of model parameter estimation on kinetic curve type is examined since we expect quickly varying curves to be more strongly impacted than slowly varying curves. In addition, since KWIC reconstruction applies different weighting to low- and high-resolution regions of k-space, we explore how pharmacokinetic model parameter estimation depends on lesion size. Errors in model parameter estimation are directly translated into the impact of the GA-KWIC algorithm on diagnostic accuracy for the separation of benign and malignant lesions.

Methods

Object Model

The simulations in this study were performed using two different object models; Object A to assess the temporal blurring depending on lesion size and Object B to assess the temporal blurring depending on contrast enhancement characteristics (see Figure 1). Both objects consist of a two-dimensional (2D) circular component (150 mm diameter), representing normal tissue, in a flat background, representing air. Each object contains a set of internal circular shapes to represent lesions or arteries. Kinetic curves of the lesions and arteries are described by the generalized kinetic model (GKM) [14] and a population AIF [15], respectively.

Object A contains a 10.0 mm diameter artery and two sets of nine lesions. The first set of lesions, located in the outer region of the object, has kinetic curves with $K^{trans} = 0.08 \text{ min}^{-1}$ and $v_e = 0.30$, where K^{trans} is the volume transfer constant between blood plasma and extravascular extracellular space (EES) and v_e is the volume of the EES per unit volume of tissue, and diameters of 2.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.5, 15.0, and 20.0 mm. The second set of lesions is located in the inner region of the object and has $K^{trans} = 0.33 \text{ min}^{-1}$ and $v_e = 0.42$ and the same diameters as the first set of lesions.

Object B has an artery, whose diameter can be selected to be either 5, 10, or 20 mm, and twenty circular lesions all with the same diameter, selected to be either 5, 10, or 20 mm. The K^{trans} values of the twenty lesions are 0.01 and 0.1 to 1.9 min^{-1} in increments of 0.1 min^{-1} and $v_e = 0.35$ for all the lesions.

For both objects, the relaxation times of normal tissue and lesions were set to $T_1 = 1495.0 \text{ ms}$ and $T_2 = 66.0 \text{ ms}$. These values were taken from published values measured *in vivo* of breast fibroglandular tissue in normal volunteers at 3T [16,17]. The relaxation times of blood were

set to $T_1 = 1932.0$ ms and $T_2 = 275.0$ ms [18]. In all cases, T_2^* was arbitrarily assumed to be equal to half of T_2 . Relaxivities were set to $r_1 = 3.3 \text{ s}^{-1} \text{ mM}^{-1}$ and $r_2 = 5.2 \text{ s}^{-1} \text{ mM}^{-1}$ [21] for all tissue types.

System Model

In order to generate simulated DCE-MRI data, a spoiled gradient echo (SPGR) imaging sequence (flip angle=12 degrees, repetition time=3.6 ms, echo time=1.47 ms, and 1.0 mm×1.0 mm pixel resolution) with golden-angle radial view-ordering scheme [Winkelmann 2007] and a three-dimensional (3D) stack-of-stars acquisition was assumed. Although data were generated in 2D, it was assumed that 35 total slices were acquired so that the time between acquisition of each radial view was $35 \times 3.6 \text{ ms} = 0.126$ seconds, as in a 3D acquisition.

Each acquired radial view was simulated by first calculating the relaxation values of each object component assuming the fast exchange limit and generating a true MR signal map with 1.0 mm×1.0 mm pixels using the SPGR signal equation [19]. The Fourier transform of this true MR signal map was then calculated to generate a cartesian-sampled version of k-space and the values for the radial view were estimated using bilinear interpolation. Relaxation values were updated for each radial view, but it was assumed that all the samples for a given view were acquired instantaneously. Each radial view was oversampled in the readout direction by a factor of two in order to simulate a two-fold oversampling scheme often used in radial sampling sequences.

Reconstructed images were produced from the series of radial views by selecting a continuous set of 610 radial views and then, optionally, applying a modified version of the k-space weighted image contrast (KWIC) algorithm [8]. The KWIC algorithm has been previously implemented using views that are acquired at sequential angles [8] as well as using bisectonal [10] and golden-angle [11] view-order strategies. In the current study, we implemented the KWIC algorithm using golden-angle view-ordering. Our implementation was similar to that of Ref. [11], except that we enforced a Fibonacci number of views for all annuli (see Figure 2). Using a Fibonacci number of views for all annuli results in the most uniform azimuthal spacing possible [9] and, therefore, minimizes streaking artifacts. Each image was reconstructed using 610 total radial views with annuli consisting of 8, 13, 21, 34, 55, 89, 144, 233, 377, and 610 views. The radius of each annulus was chosen to satisfy the Nyquist criterion under the assumption that the views had a uniform azimuthal spacing. A modified ramp filter was used to compensate for sampling distribution.

Radial k-space data were interpolated onto a cartesian grid before cropping by half and performing a 2D inverse fast Fourier transform to generate the reconstructed images. This was achieved using a 2D Kaiser-Bessel kernel on a 6×6 voxel grid [20]. All images were noiseless unless otherwise specified.

Temporal blurring of GA-KWIC reconstructed images

One of the primary objectives of the KWIC reconstruction algorithm is to improve the temporal resolution of DCE-MRI data while maintaining high spatial resolution. However,

since views acquired at different times still contribute to k-space for a single image, images reconstructed with the GA-KWIC algorithm can never achieve perfectly instantaneous temporal sampling. In order to quantify the amount of temporal blurring present in GA-KWIC reconstructed images, we examined the effect of the GA-KWIC algorithm on estimated pharmacokinetic parameters, K^{trans} and v_e , from GKM fits to data generated using Object A. The number of views in the central region of k-space was varied from 8 to 610 since the temporal resolution achievable with the GA-KWIC algorithm is largely dependent on how many views are used to reconstruct the central region of k-space. If our temporal sampling is set exactly equal to the number of views in the central region of GA-KWIC k-space, then our temporal sampling varies from 1.01 to 76.86 seconds per image for 8 to 610 views, respectively, in the central region. Each image, for both GA-KWIC and data with no KWIC weighting, was reconstructed using 610 total views.

The effect of noise and temporal sampling locations on the estimated pharmacokinetic parameters was also evaluated. The phrase “temporal sampling locations” refers to the temporal position of the data points that make up a given kinetic curve. These temporal sampling locations may be modified either by changing the temporal resolution of a data set or by shifting all of the data points along the time axis by a fixed amount. Fifteen independent, noisy data sets were generated with fixed temporal sampling locations and the mean and standard deviation of the pharmacokinetic model parameters fit to this data were recorded. Gaussian noise with a signal-to-noise ratio (SNR) of 20, as calculated on the lesions at baseline, was added to the real and imaginary components of the complex data in image space before calculation of the image magnitude. In addition, noiseless data sets were generated with 15 different temporal sampling location shifts and the mean and standard deviation of the model parameters were also recorded. The GKM model was fit to the data using the downhill simplex method [22] as implemented in the programming language IDL (Exelis Visual Information Solutions, Boulder, Co, USA). All fits were performed on data averaged over the entire lesion with initial guess coefficients set to the true coefficient values. This analysis was completed for both the 10 mm slow- and fast-enhancing lesions and KWIC weighting with 8, 13, 21, 34, 55, 89, 144, 233, 377, and 610 views in the central region of k-space. The case of 610 central views corresponds to no KWIC weighting.

Effect of lesion size on estimated pharmacokinetic model parameters

KWIC weighting achieves high temporal resolution, while preserving high spatial resolution, by using a small number of views in the central region of k-space and progressively increasing the number of views in the outer portions of k-space. Therefore, views from a larger temporal range contribute to the outermost, and higher frequency, regions of k-space. For this reason, one would expect smaller lesions, which have more contributions from the high-frequency region of k-space, to manifest more temporal blurring than larger lesions. To quantify the magnitude of this effect, pharmacokinetic model parameters were estimated on images reconstructed with the GA-KWIC algorithm with 55 central views. This analysis was completed for the fast-enhancing lesions (2.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.5, 15.0, and 20.0 mm diameters) of Object A using both the true AIF as well as the AIF estimated from the simulated data. Data were averaged over the entire lesion and

AIF before fitting. The results were then compared with the true model parameters used to generate the simulated data.

Spatial maps of pharmacokinetic model parameters were also created by fitting the data for each lesion on a voxel-by-voxel basis.

Effect of temporal blurring on diagnostic accuracy

The previously described simulations were performed to estimate how the uncertainty of pharmacokinetic parameter estimation is affected by various properties, including true kinetic curve shape and lesion size. In this section, we take this analysis a step further and evaluate the impact of these properties on diagnostic accuracy when using K^{trans} to separate benign and malignant lesions.

Simulations were performed using Object B in order to get a good sampling of K^{trans} estimation bias. The model parameter K^{trans} was estimated from data generated of Object B with the GA-KWIC algorithm and 34 central views. Pharmacokinetic model parameter fits were performed using both the true and estimated AIF. This was repeated for nine different versions of Object B with different lesion diameters (5, 10, and 20 mm) and artery diameters (5, 10, and 20 mm). The estimated K^{trans} value and its error were calculated by generating 15 independent realizations of noisy data (SNR=20) and 15 noiseless data sets with different temporal sampling location shifts. The mean of the K^{trans} values calculated from the 15 noiseless data sets was taken as the final estimated K^{trans} value. The two standard deviations of the K^{trans} values calculated from these two data sets were added in quadrature to produce the error of the estimated K^{trans} value. The bias in the K^{trans} value can be calculated by simply subtracting the true K^{trans} value from the final estimated K^{trans} value and the error in the bias is equivalent to the error in the estimated K^{trans} value.

Next, receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) values were generated to assess the effect of temporal blurring on the decision problem of discriminating between benign and malignant lesions. It was assumed that benign lesions had K^{trans} values that followed a Gamma distribution with an order of 2 and a peak at $K^{trans} = 0.08 \text{ min}^{-1}$. Malignant lesions were also assumed to have K^{trans} values that followed a Gamma distribution, but with an order of 4 and a peak at $K^{trans} = 0.33 \text{ min}^{-1}$. True K^{trans} values following these distributions were generated with 10^6 samples for both lesion types. These true K^{trans} values were then converted to measured K^{trans} values by interpolating the previously calculated values for K^{trans} estimation bias. Finally, ROC curves and AUC values were calculated for both the true and measured K^{trans} distributions to quantify the diagnostic error.

Errors in the calculated AUC values were estimated by calculating AUC values for 100 samples for both lesion types using interpolated K^{trans} bias with their corresponding errors. This process was repeated 10^5 times and the standard deviation of the resultant values was calculated.

Results

Temporal blurring of GA-KWIC reconstructed images

Kinetic curves generated from noiseless GA-KWIC data as well as data with no KWIC weighting are compared with true kinetic curves in Figure 3. Data reconstructed using the GA-KWIC algorithm in this figure used 8 central views. Comparisons are shown for the AIF, 10 mm slow enhancing lesion, and 10 mm fast enhancing lesion from Object A. The kinetic curves shown are the average over all voxels in the AIF or lesion.

The GA-KWIC data more closely match the true kinetic curves than data reconstructed using no KWIC weighting. GA-KWIC data is better at reproducing the true kinetic curve for components with more slowly varying kinetics. Qualitatively, both true lesion curves are relatively well matched by the GA-KWIC reconstructed data. While the true AIF is more closely approximated using the GA-KWIC reconstruction than without KWIC weighting, there is still substantial blurring resulting in a $2.5\times$ drop in the peak value of the AIF.

An analysis of the effect of GA-KWIC reconstruction on estimated pharmacokinetic model parameters is presented in Figure 4. Estimated K^{trans} and v_e values are plotted versus the number of views used in the central region of k-space for KWIC weighting. Results are shown for parameter estimation using the true and estimated AIF. Error bars corresponding to measurement noise and temporal sampling location shift are added in quadrature to produce the error bars shown. Results are shown for both the slow- and fast-enhancing 10 mm lesions in Object A. For both the slow- and fast-enhancing lesions, K^{trans} estimates have a slight negative bias when using the true AIF and a large positive bias when using the estimated AIF. These results indicate the importance of accurate AIF estimation. The bias and error in the K^{trans} values increase as the number of views in the central region of k-space for the KWIC algorithm increases. This is expected given the corresponding decrease in temporal resolution. The error and bias of the estimated K^{trans} values are relatively constant for a number of views less than or equal to 55 in the central region of k-space. This indicates that, for the cases considered in this study, there is no gain in parameter estimation accuracy when a smaller number of views are used. Estimates of v_e tend to have only small deviations from the true values and the bias is similar when using the true and estimated AIFs. Interestingly, using the measured AIF results in a negative v_e bias for the slow-enhancing lesion, but a positive bias for the fast-enhancing lesion.

In order to understand the results presented in Figure 4, some explanatory curves are shown in Figure 5. The true and estimated AIFs are plotted in Figure 5a for noiseless data with 8 central views. As expected, the estimated AIF is more blurred and has a lower peak value than the true AIF. Figures 5b–5d display the measured lesion curve from the same data set for the 10 mm diameter slow-enhancing lesion. This is compared with lesion curves predicted using the true AIF with $K^{trans}=0.08$ and $v_e=0.30$ (correct model parameters), estimated AIF with $K^{trans}=0.08$ and $v_e=0.30$, and estimated AIF with $K^{trans}=0.102$ and $v_e=0.30$. When the true AIF is used with the correct model parameters, the predicted lesion curve is sharper than the measured lesion curve in the uptake region and higher than the measured lesion curve in the washout portion of the curve. This discrepancy is due to the fact that the measured lesion curves are generated by simulating the full imaging process,

while the model predicted curves only take into account the GKM equation and, therefore, neglect imaging related effects. In this case, the discrepancy between the predicted and measured lesion curves is due to the fact that the predicted curve does not take into account the drop off in K^{trans} values near the edges of the lesion (see Figure 7). This explains why slightly lower K^{trans} and v_e values are necessary to fit the measured data, as shown in Figure 4. When the estimated AIF is used with the correct model parameters, the predicted lesion curve is smoother than the measured lesion curve in the uptake portion of the curve and has a lower level than the measured lesion curve in the washout region. This suggests that a larger K^{trans} and v_e value might be necessary to fit the measured curves. However, Figure 4 indicates that the K^{trans} is overestimated, as expected, but that the v_e value is actually underestimated. This behavior can be explained by examining the predicted lesion curve using the estimated AIF with $K^{trans} = 0.102$ and $v_e = 0.30$. When this larger K^{trans} value is used, the predicted lesion curve has a slightly higher level than the measured lesion curve in the washout portion of the curve. Since the v_e value primarily controls the level of this area of the curve, a lower v_e value is necessary to better match the measured lesion curve. This result is consistent with Figure 4. A similar analysis of Figures 5e–5g shows that when a higher K^{trans} value is used with the estimated AIF, the washout portion of the predicted lesion curve has a lower value than that of the measured lesion curve, thus requiring a higher v_e value to properly match the measured lesion curve.

Effect of lesion size on estimated pharmacokinetic model parameters

The influence of lesion size on pharmacokinetic model parameter estimation is shown in Figure 6. Figure 6a shows the estimated kinetic curves generated from GA-KWIC data with 55 central views. From this figure it is clear that larger lesions have less temporal blurring than smaller lesions. Figures 6b and 6c quantify this temporal blurring in terms of its effect on the estimated pharmacokinetic model parameters, K^{trans} and v_e , respectively. From these plots, we see the same result from Figure 4, that fits performed using the true AIF result in a small negative bias and using the estimated AIF result in a larger positive bias in both K^{trans} and v_e . In addition, for the results generated using the true AIF, smaller lesions result in an increasing underestimation of K^{trans} , but not v_e . The same is true of results generated using the estimated AIF, however, when combined with the positive bias smaller lesions in this case produce values closer to the truth than larger lesions.

Figure 7 shows voxel-by-voxel maps of estimated K^{trans} values for several different lesion sizes and demonstrates the origin of the effect shown in Figure 6. These maps demonstrate that K^{trans} estimates are lower at the edges of lesions, where higher frequency information is located. Since high frequency information is contained in the outer region of k-space, where KWIC reconstructed images have larger temporal blurring, the corresponding estimated K^{trans} values are decreased.

Effect of temporal blurring on diagnostic accuracy

Estimation bias of K^{trans} values for a sampling of different true K^{trans} values and lesion and artery sizes is plotted in Figure 8. As expected, the K^{trans} bias increases for larger K^{trans} values. The estimated K^{trans} values decrease as the lesion size decreases and the artery size increases.

Figure 9a shows results for benign and malignant lesions with diameters fixed to 10 mm. The distribution of true and measured K^{trans} values for the benign and malignant lesions is shown on the left. The measured distributions for both the benign and malignant lesions are shifted to lower K^{trans} values and the effect is larger for the malignant lesions. These trends are expected given the biases presented in Figure 8. The right plot in Figure 9a shows the ROC curves for the true and measured K^{trans} values that correspond to the left plot. We can see that the two curves are indistinguishable and the AUC values are identical. Therefore, the kinetic-shape dependent bias, which is imposed on the estimated pharmacokinetic model parameter K^{trans} by the GA-KWIC reconstruction algorithm, does not affect diagnostic accuracy of benign and malignant lesion discrimination.

Figure 9b is similar to Figure 9a, but the benign and malignant lesions are simulated with different diameters, 5 and 20 mm, respectively. This analysis gives an indication as to how important the size-dependent temporal blurring of GA-KWIC reconstructions are to diagnostic accuracy. Again, in the left-hand plot, we see that the measured K^{trans} distributions are shifted to lower K^{trans} values than the true distributions. However, in this case, the malignant lesion distribution is shifted to a lesser extent. In this case, we can now see that the ROC curves of the true and measured K^{trans} values are distinguishable with the measured K^{trans} values giving an overall higher ROC curve. The AUC values are 0.896 for the true K^{trans} values and 0.906 for the measured K^{trans} values. Therefore, if one is comparing benign and malignant lesion samples with average lesion sizes of 5 and 20 mm, respectively, an overestimation of the AUC value on the order of 0.010 can be expected.

Figures 9c and 9d are the same as Figures 9a and 9b, respectively, except that they use the estimated AIF instead of the true AIF. The artery has a diameter of 10 mm for this data. The increased K^{trans} bias produces a larger shift in the K^{trans} distributions, but since this is true for both lesion types, the effect on the ROC curves and AUC values remains small. When comparing benign and malignant lesion samples with average lesion sizes of 5 and 20 mm, respectively, the AUC is overestimated by 0.009. This overestimation of the AUC is similar to that seen when using the true AIF. Therefore, while use of the estimated AIF does result in incorrect estimates of K^{trans} values, the estimated ROC curves and AUC values are not strongly affected.

In addition to the specific cases shown in Figures 9c and 9d, AUC values were calculated for every possible combination of benign and malignant lesion size. Artery sizes were set to either 5, 10, or 20 mm and the same artery size was used for the benign and malignant lesion populations. Changing the artery size had no effect on the AUC values. This is because the specific bias imposed by any given artery diameter was uniformly applied to the benign and malignant lesion K^{trans} estimates.

Discussion

In order to meet the ever-increasing demands on temporal and spatial resolution for clinical DCE-MRI applications, a variety of methods have been introduced that extract high-resolution information from under-sampled data. The impact of these methods on image quality must be rigorously evaluated to understand the corresponding influence on pathology

diagnosis. In the current study, we have investigated the use of the GA-KWIC reconstruction algorithm for evaluation of benign and malignant lesions. The effect of this method on the estimation of pharmacokinetic model parameters was quantified as well as the corresponding repercussions on diagnostic accuracy for lesion discrimination.

Estimation of K^{trans} values is improved, in the presence of noise and temporal sampling location shifts, when the number of views in the central region of k-space is less than or equal to about 55. For the conditions investigated in this study, no gain in K^{trans} estimation accuracy is seen for smaller numbers of central views. In general, v_e values are well estimated with a bias that depends on the true curve shape. The plateau in K^{trans} estimation improvement at 55 central views is due to a plateau in the ability of the GA-KWIC algorithm to provide increasing temporal information. As seen in Figure 3a, even with only 8 central views, the true AIF cannot be reproduced using GA-KWIC reconstructed data because the true temporal resolution is not completely determined by the number of central views.

The ability of the GA-KWIC algorithm to accurately measure kinetic curves is dependent on the shape of the true curve itself, with more slowly-varying kinetic curves faring better than more rapidly varying curves. Pharmacokinetic model parameter estimation accuracy is then dependent on the true kinetic curve shape. This effect is of concern since the diagnostic power of temporal information in DCE-MRI data relies on the ability to measure an inherent difference in curve shapes between different lesion populations. However, we have shown that this has a negligible impact on diagnostic accuracy as measured by ROC curves and AUC. Temporal blurring using the GA-KWIC algorithm is dependent on the size of the lesion being evaluated. This is due to the fact that different numbers of views contribute to low- and high-frequency regions of k-space for the GA-KWIC algorithm. For a KWIC algorithm with a bisectional view-ordering strategy, Song and Dougherty [10] demonstrated that a 5 pixel diameter phantom had more temporal blurring than a 20 pixel diameter phantom by qualitatively comparing their temporal curves. For our study, using GA-KWIC, we also found that measured kinetic curves are more blurred for smaller lesion sizes, resulting in an under-estimation of K^{trans} . This effect is most pronounced for lesions smaller than 10 mm. While this effect is present, it has a negligible impact on diagnostic accuracy. For our case, with 5 mm diameter benign lesions and 20 mm diameter malignant lesions, the estimated AUC, using an artery of 10 mm in diameter, differed from the true AUC by only 0.009 and its error was 0.021, more than twice that. For additional comparison, for a large American College of Radiology Imaging Network (ACRIN) study evaluating the diagnostic accuracy of digital and film mammography in 42,760 women with verified breast cancer status, the estimated AUC errors were 0.02 [23]. Although some studies have reported AUC values for lesion discrimination in DCE-MRI [24,25], these studies have not provided errors estimates, thereby rendering a comparison with our estimated AUC errors impossible. We also found that using arteries of different sizes to estimate the AIF did not affect the estimate of diagnostic accuracy in the case where the AIF was the same size for both the benign and malignant lesion populations. If there is a large discrepancy in artery size for these two populations, there may be a corresponding affect on the diagnostic accuracy. This was beyond the scope of this study, not to mention that there is a paucity of studies on the artery

sizes used to perform pharmacokinetic model analysis on enhancing benign and malignant lesions.

For the current study, we have focused on the GKM model and a conventionally sampled AIF to evaluate the effect of the GA-KWIC algorithm on temporal information in DCE-MRI data and estimation of pharmacokinetic model parameters. There exist many alternative approaches to DCE-MRI pharmacokinetic modeling, including more complicated pharmacokinetic models [26,27,28,29,30,31,32,33,34,35,36,37,38,39] as well as AIF estimation using reference region models [40,41,42,43]. Use of a different pharmacokinetic model and/or AIF estimation method will likely produce results that differ from those presented in the current study. For example, pharmacokinetic models that include a plasma volume fraction can produce sharper contrast agent uptake behavior. Since GA-KWIC is better able to reproduce more slowly varying kinetic, its use may result in larger parameter estimation errors for such models. In addition, models that include a temporal delay between the AIF and lesion kinetic curves impose an additional source of uncertainties that may be more strongly affected by temporal sampling location and frequency [44]. In terms of AIF estimation, reference region models relax the requirement for high temporal resolution data since only relatively slowly varying tissue kinetic curves must be measured [45]. Therefore, we expect that GA-KWIC will provide better pharmacokinetic model parameter estimates if this approach is employed. In light of these considerations, results presented in the current study should be interpreted only in the context of the specific models used to generate and fit the data and not generalized to more complex cases. Future studies to explore these additional parameter spaces would provide further insight into the utility of GA-KWIC for DCE-MRI data analysis.

Another interesting topic for future study is the effect of GA-KWIC on spatial information since lesion morphology is an important aspect of cancer diagnosis. Due to the fact that the total number of radial spokes is preserved, we expect that the effect of GA-KWIC on spatial resolution is small. However, it would be interesting to investigate how the temporal blurring of high resolution structures affects morphological evaluation.

We have demonstrated that the GA-KWIC method produces diagnostic accuracy estimates that are well matched to the truth. Despite this, there are biases in the pharmacokinetic model parameter estimates themselves. If accurate pharmacokinetic model parameter estimation is the primary objective of a study, and not diagnostic accuracy, there is additional flexibility in the GA-KWIC method that could be exploited in an attempt to produce more accurate results. For example, GA-KWIC does allow for kinetic curves for the AIF and lesion with different temporal resolutions to be extracted from the same data. In this case, higher temporal resolution data could be extracted for the AIF and lower resolution data for the lesion. The effect of resampling higher resolution model curves to fit lower resolution lesion curves would need to be quantitatively evaluated to determine how it affects the final result. In addition, it is not necessary for temporal data locations to be evenly spaced as GA-KWIC can reconstruct images for any arbitrary set of time points. Therefore, more rapidly varying portions of the kinetic curves could be more frequently sampled than more slowly varying portions. Furthermore, the Nyquist criteria used to define the size of the annuli could be relaxed to minimize the temporal blurring [10]. The

additional noise incurred by this approach could be ameliorated by using a region-of-interest analysis such that multiple voxels are averaged to produce a given kinetic curve. It is also possible that spatial filtering applied to images could impose some unintentional temporal blurring. Although it was beyond the scope of this study to investigate all of the flexible features of GA-KWIC with respect to diagnostic accuracy, future study is warranted to investigate optimal strategies to utilize GA-KWIC for different clinical applications.

Conclusions

We have performed a quantitative evaluation of the effect of a GA-KWIC algorithm on the temporal fidelity of DCE-MRI data. The effect of this reconstruction algorithm on estimated pharmacokinetic model parameters has been investigated as well as the resultant impact on diagnostic accuracy for benign and malignant lesion discrimination. Although use of the GA-KWIC algorithm does impose model parameter estimation errors that are dependent on the lesion size and kinetic curve shape, the resultant errors in diagnostic accuracy are small compared to other sources of error typically encountered in clinical studies. Therefore, we expect that the GA-KWIC algorithm can be reasonably utilized for clinical studies to improve temporal resolution without detrimentally affecting diagnostic accuracy estimations.

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References

1. Kuhl CK, Schild HH, Morakkabati N. Dynamic bilateral contrast-enhanced MR imaging of the breast: trade-off between spatial and temporal resolution. *Radiology*. 2005; 236:789–800. [PubMed: 16118161]
2. Tsao J, Kozerke S. MRI temporal acceleration techniques. *J Magn Reson Imaging*. 2012; 36:543–560. [PubMed: 22903655]
3. Jones RA, Haraldseth O, Müller TB, Rinck PA, Øksendal. K-space substitution: a novel dynamic imaging technique. *Magn Reson Med*. 1993; 29:830–834. [PubMed: 8350729]
4. van Vaals JJ, Brummer ME, Dixon WT, Tuithof HH, Engels H, Nelson RC, Gerety BM, Chezmar JL, den Boer JA. “Keyhole” method for accelerating imaging of contrast agent uptake. *J Magn Reson Imaging*. 1993; 3:671–675. [PubMed: 8347963]
5. Lustig M, Donoho D, Pauly JM. Sparse MRI: The application of compressed sensing for rapid MR imaging. *Magn Reson Med*. 2007; 58:1182–1195. [PubMed: 17969013]
6. Markl M, Hennig J. Phase contrast MRI with improved temporal resolution by view sharing: k-space related velocity mapping properties. *Magn Reson Imaging*. 2001; 19:669–676. [PubMed: 11672625]
7. Sharma SD, Fong CL, Tzung BS, Law M, Nayak KS. Clinical image quality assessment of accelerated magnetic resonance neuroimaging using compressed sensing. *Invest Radiol*. 2013; 48:638–645. [PubMed: 23538890]
8. Song HK, Dougherty L. *k*-Space weighted imaging contrast (KWIC) for contrast manipulation in projection reconstruction MRI. *Magn Reson Med*. 2000; 44:825–832. [PubMed: 11108618]
9. Winkelman S, Schaeffter T, Koehler T, Eggers H, Doessel O. An optimal radial profile order based on the golden ratio for time-resolved MRI. *IEEE Trans Med Imaging*. 2007; 26:68–76. [PubMed: 17243585]

10. Song HK, Dougherty L. Dynamic MRI with projection reconstruction and KWIC processing for simultaneous high spatial and temporal resolution. *Magn Reson Med*. 2004; 52:815–824. [PubMed: 15389936]
11. Lin W, Guo J, Rosen MA, Song HK. Respiratory motion-compensated radial dynamic contrast-enhanced (DCE)-MRI of chest and abdominal lesions. *Magn Reson Med*. 2008; 60:1135–1146. [PubMed: 18956465]
12. Koehler T. A projection access scheme for iterative reconstruction based on the golden section. *Proc IEEE Nucl Sci Med Imag Conf*. 2004:M10–200.
13. Kazantsev IG, Matej S, Lewitt RM. Optimal ordering of projections using permutation matrices and angles between projection subspaces. *Electronic Notes in Discrete Mathematics*. 2005; 20:205–216.
14. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging*. 1999; 10:223–232. [PubMed: 10508281]
15. Parker GJM, Roberts C, Macdonald A, Buonaccorsi GA, Cheung S, Buckley DL, Jackson A, Watson Y, Davies K, Jayson GC. Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI. *Magn Reson Med*. 2006; 56:993–1000. [PubMed: 17036301]
16. Rakow-Penner R, Daniel B, Yu H, Sawyer-Glover A, Glover GH. Relaxation times of breast tissue at 1.5T and 3T measured using IDEAL. *J Magn Reson Imaging*. 2006; 23:87–91. [PubMed: 16315211]
17. Edden RAE, Smith SA, Barker PB. Longitudinal and multi-echo transverse relaxation times of normal breast tissue at 3 Tesla. *J Magn Reson Imaging*. 2010; 32:982–987. [PubMed: 20882630]
18. Stanisz GJ, Odobina EE, Pun J, Escaravage M, Graham SJ, Bronskill MJ, Henkelman RM. T-1, T-2 relaxation and magnetization transfer in tissue at 3T. *Magn Reson Med*. 2005; 54:507–512. [PubMed: 16086319]
19. Bernstein, MA.; King, KF.; Zhou, XJ. *Handbook of MRI Pulse Sequences*. Amsterdam: Elsevier; 2004. Basic pulse sequences; p. 579–647.
20. Jackson JI, Meyer CH, Nishimura DG, Macovski A. Selection of a convolution function for Fourier inversion using gridding. *IEEE Trans Med Imaging*. 1991; 10:473–478. [PubMed: 18222850]
21. Pintaske J, Martirosian P, Graf H, Erb G, Lodemann K-P, Claussen CD, Schick F. Relaxivity of Gadopentetate Dimeglumine (Magnevist), Gadobutrol (Gadovist), and Gadobenate Dimeglumine (MultiHance) in human blood plasma at 0.2, 1.5, and 3 Tesla. *Invest Radiol*. 2006; 41:213–221. [PubMed: 16481903]
22. Nelder JA, Mead R. A simplex method for function minimization. *Computer J*. 1965; 7:308–313.
23. Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med*. 2005; 353:1773–1783. [PubMed: 16169887]
24. Kriege MK, Brekelmans CTM, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med*. 2004; 351:427–437. [PubMed: 15282350]
25. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA*. 2004; 292:1317–1325. [PubMed: 15367553]
26. Hoffmann U, Brix G, Knopp MV, Hess T, Lorenz WJ. Pharmacokinetic mapping of the breast: a new method for dynamic MR mammography. *Magn Reson Med*. 1995; 33:506–14. [PubMed: 7776881]
27. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging*. 1997; 7:91–101. [PubMed: 9039598]
28. St Lawrence KS, Lee TY. An adiabatic approximation to the tissue homogeneity model for water exchange in the brain: I. Theoretical derivation. *J Cereb Blood Flow Metab*. 1998; 18:1365–77. [PubMed: 9850149]

29. Koh TS, Zeman V, Darko J, Lee TY, Milosevic MF, Haider M, Warde P, Yeung IW. The inclusion of capillary distribution in the adiabatic tissue homogeneity model of blood flow. *Phys Med Biol*. 2001; 46:1519–38. [PubMed: 11384068]
30. Buckley DL. Uncertainty in the analysis of tracer kinetics using dynamic contrast-enhanced T1-weighted MRI. *Magn Reson Med*. 2002; 47:601–6. [PubMed: 11870848]
31. Dennis Cheong LH, Tchoyoson Lim CC, Koh TS. Dynamic contrast-enhanced CT of intracranial meningioma: comparison of distributed and compartmental tracer kinetic models—initial results. *Radiology*. 2004; 232:921–30. [PubMed: 15247436]
32. Larsson HB, Courivaud F, Rostrup E, Hansen AE. Measurement of brain perfusion, blood volume, and blood-brain barrier permeability, using dynamic contrast-enhanced T(1)-weighted MRI at 3 tesla. *Magn Reson Med*. 2009; 62:1270–81. [PubMed: 19780145]
33. Bartos M, Keunen O, Jirik R, Bjerkvig R, Taxt T. Perfusion analysis of dynamic contrast enhanced magnetic resonance images using a fully continuous tissue homogeneity model with mean transit. *Anal Biomed Sign Images*. 2010; 20:269–274.
34. Kershaw LE, Cheng HL. Temporal resolution and SNR requirements for accurate DCE-MRI data analysis using the AATH model. *Magn Reson Med*. 2010; 64:1772–80. [PubMed: 20715059]
35. Luybaert R, Sourbron S, Makkat S, de Mey J. Error estimation for perfusion parameters obtained using the two-compartment exchange model in dynamic contrast-enhanced MRI: a simulation study. *Phys Med Biol*. 2010; 55:6431–43. [PubMed: 20952813]
36. Koh TS, Cheong DL, Hou Z. Issues of discontinuity in the impulse residue function for deconvolution analysis of dynamic contrast-enhanced MRI data. *Magn Reson Med*. 2011; 66:886–92. [PubMed: 21465544]
37. Sourbron SP, Buckley DL. On the scope and interpretation of the Tofts models for DCE-MRI. *Magn Reson Med*. 2011; 66:735–45. [PubMed: 21384424]
38. Brix G, Ravesh MS, Zwick S, Griebel J, Delorme S. On impulse response functions computed from dynamic contrast-enhanced image data by algebraic deconvolution and compartmental modeling. *Phys Med*. 2012; 28:119–28. [PubMed: 21497123]
39. Schabel MC. A unified impulse response model for DCE-MRI. *Magn Reson Med*. 2012; 68:1632–1646. [PubMed: 22294448]
40. Kovar DA, Lewis M, Karczmar GS. A new method for imaging perfusion and contrast extraction fraction: input functions derived from reference tissues. *J Magn Reson Imaging*. 1998; 8:1126–1134. [PubMed: 9786152]
41. Yang C, Karczmar GS, Medved M, Stadler WM. Estimating the arterial input function using two reference tissues in dynamic contrast-enhanced MRI studies: fundamental concepts and simulations. *Magn Reson Med*. 2004; 52:1110–1117. [PubMed: 15508148]
42. Yankeelov TE, Luci JJ, Lepage M, Li R, Debusk L, Lin PC, Price RR, Gore JC. Quantitative pharmacokinetic analysis of DCE-MRI data without an arterial input function: a reference region model. *Magn Reson Imaging*. 2005; 23:519–29. [PubMed: 15919597]
43. Yang C, Karczmar GS, Medved M, Stadler WM. Multiple reference tissue method for contrast agent arterial input function estimation. *Magn Reson Med*. 2007; 58:1266–1275. [PubMed: 17969061]
44. Henderson E, Rutt BK, Lee T-Y. Temporal sampling requirements for the tracer kinetics modeling of breast disease. *Magn Reson Imaging*. 1998; 16:1057–1073. [PubMed: 9839990]
45. Planey CR, Welch EB, Xu L, Chakravarthy AB, Gatenby JC, Freehardt D, Mayer I, Meszeoly I, Kelley M, Means-Powell J, Gore JC, Yankeelov TE. Temporal sampling requirements for reference region modeling of DCE-MRI data in human breast cancer. *J Magn Reson Imaging*. 2009; 30:121–134. [PubMed: 19557727]

Figure 1.

a) Object A consists of a circular region of normal tissue that contains one circular artery and two sets of 9 lesions with varying sizes. One set of lesions (outer ring) has a slow enhancing kinetic curve and the second set (inner ring) has a fast enhancing kinetic curve. b) Kinetic curve for the artery (a population AIF). c) Slow and fast enhancing kinetic curves for the lesions. d) Object B consists of one 10 mm circular artery and twenty circular lesions (diameter=5, 10, or 20 mm) in a circular background of normal tissue (diameter=150 mm). Each of the lesions has a different kinetic curve. Objects A and B are shown with the background areas cropped for ease of visualization. See text for detailed object specifications. label fig-phantom A

Figure 2.

Schematic of GA-KWIC weighting of first three annuli in k -space for the current study. The radii of the annuli are selected to satisfy Nyquist sampling and are not to scale in this figure. The numbers indicate the order of acquisition of the views and each annulus is labeled with the views used for that annulus. A Fibonacci number of views (8, 13, 21, 34, 55, 89, 144, 233, 377, and 610) is used for all annuli, which provides the most uniform azimuthal sampling possible. a) Color coding indicates which views are used in which annuli. Views that extend through all annuli are blue, those that extend through the outer two annuli are green, and those that are only present in the outermost annulus are red. b) Color coding indicates the order of acquisition of the views. The central portion of k -space has views that were all acquired at about the same time, as indicated by the relatively small color spread. As we move outward in k -space each annulus contains views acquired over a progressively larger time interval, as indicated by the larger spread in colors.

Figure 3.

Kinetic curves for the a) AIF, b) 10 mm slow enhancing lesion, and c) 10 mm fast enhancing lesion from Object A. The true kinetic curve is shown in black. The kinetic curve calculated from data with GA view-ordering, but no KWIC weighting is shown with a solid green line. Finally, the kinetic curve calculated using GA-KWIC with 8 central views, is shown with a red dashed line. These data were simulated without noise. Data reconstructed using the GA-KWIC algorithm more closely matches the true kinetic curves than data reconstructed using no KWIC weighting.

Figure 4.

Pharmacokinetic model parameters, K^{trans} and v_e , fit to data simulated with the GA-KWIC algorithm with different numbers of views in the central region of k-space. Results are shown for the 10 mm (left) slow- and (right) fast-enhancing lesions. A value of 610 views in the central region corresponds to no KWIC weighting. Results from fits using the true AIF and the AIF as estimated from the simulated data are shown in blue with circle symbols and red with triangle symbols, respectively. True parameter values are indicated with a solid black line. Errors due to measurement noise (SNR=20 in complex images) and temporal sampling location shift are added in quadrature to produce the error bars shown. The data points are the average of values from all of the noiseless data sets generated with the different temporal sampling location shifts.

Figure 5.

Example curves to demonstrate the origin of trends shown in Figure 4. a) True and estimated AIFs from GA-KWIC data of Object A with 8 central views. The estimated AIF is blurred and has a lower peak value than the true AIF. b) Measured lesion curve for the 10 mm slow-enhancing lesion as well as predicted lesion curves using the true AIF with the correct model parameters ($K^{trans}=0.08$, $v_e=0.30$), the estimated AIF with the correct model parameters ($K^{trans}=0.08$, $v_e=0.30$), and the estimated AIF with $K^{trans}=0.102$ and $v_e=0.30$. c) Zoomed version of plot b) to highlight enhancement portion of curve. d) Zoomed version of plot b) to highlight enhancement of washout portion of curve. e) Measured lesion curve for the 10 mm fast-enhancing lesion as well as predicted lesion curves using the true AIF with the correct model parameters ($K^{trans}=0.33$, $v_e=0.42$), the estimated AIF with the correct model parameters ($K^{trans}=0.33$, $v_e=0.42$), and the estimated AIF with $K^{trans}=0.478$ and $v_e=0.42$. f) Zoomed version of plot e) to highlight enhancement portion of curve. g) Zoomed version of plot e) to highlight enhancement of washout portion of curve.

Figure 6.

Temporal blurring for different lesion sizes. a) Kinetic curves for lesions of different sizes as estimated from simulated data. The data were simulated using a GA-KWIC algorithm and 55 central views. Color coding for the lesion sizes is as follows: (red) 20 mm, (orange) 15 mm, (yellow) 12.5 mm, (light green) 10 mm, (dark green) 8 mm, (light blue) 6 mm, (blue) 5 mm, (dark blue) 4 mm, and (purple) 2 mm. The inset is a zoom of the early uptake region of the plot. Estimated b) K^{trans} and c) v_e values versus lesion size are also shown. Results are presented for fits using the estimated AIF and the true AIF. The true parameter values are indicated with a solid black line.

Figure 7.

Spatial maps of estimated K^{trans} values for different lesion sizes. The data were simulated using a GA-KWIC algorithm with 55 central views. The measured AIF was used for the pharmacokinetic model fit and the true K^{trans} value was 0.33 min^{-1} . K^{trans} values tend to be lower at the edges of lesions, where contributions from the high frequency region of k-space are larger. For this reason, K^{trans} values averaged over the entire lesion are lower for smaller lesions.

Figure 8.

Estimated versus true K^{trans} values for 5, 10, and 20 mm lesion diameters. Simulations were performed using Object B, a GA-KWIC algorithm with 34 central views, and both the true and estimated AIF. For the estimated AIF, three different artery diameters were considered; 5, 10, and 20 mm. The solid black line indicates zero bias. The bias increases as K^{trans} gets larger, lesions with smaller diameters have smaller estimated K^{trans} values, and using an AIF with a smaller diameter results in a higher K^{trans} estimate.

Figure 9.

Comparison of true diagnostic accuracy with diagnostic accuracy as estimated from measured data. a) Analysis for 10 mm benign and 10 mm malignant lesion samples. b) Analysis for 5 mm benign and 20 mm malignant lesion samples. The left-hand plots show the distributions of true and measured K^{trans} values for benign and malignant lesions. The right-hand plots show the resultant ROC curves and corresponding AUC values. In both cases, the ROC curves of measured K^{trans} values are similar to those of true K^{trans} values, indicating that the GA-KWIC algorithm does not significantly impact estimation of diagnostic accuracy of breast DCE-MRI for separation of benign and malignant lesions.