

Original Article

An Automated Non-Rigid Registration Method for Accurate Quantification of Dynamic Contrast Enhanced MR Imaging (DCE-MRI) in Complex Adnexal Masses Employing Residual Complexity Framework

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ABSTRACT

Purpose- Quantification of dynamic contrast enhanced (DCE-) MRI of ovarian masses is susceptible to errors caused by motion artifacts and intensity inhomogeneity induced by bias fields. Motion artifacts and bias fields introduce signal intensity variations in the images that must be resolved from intensity changes caused by the passage of contrast agent. Thus, registration of DCE-MR image sequence is a challenging issue. In this work, we proposed a solution to misregistration problem of DCE-MR images.

Methods- We acquired pre-operative DCE-MR images of 16 patients diagnosed with solid or solid/cystic complex ovarian masses on ultrasound examination (with post-operative histopathological assessment showing 8 benign and 8 malignant cases). The residual complexity (RC) similarity measure was exploited in a non-rigid registration framework in order to account for complex intensity variations. Performance of the proposed method was evaluated by computing semi-quantitative parameters, determined in the regions of interest (ROIs) selected on the solid portion of the tumor and the psoas muscle. The results were compared with unregistered data and registered images using mutual information (MI) similarity measure.

Results- The registered data using RC similarity measure indicated lower variations in signal intensity over the time course of contrast agent passage. The derived quantitative parameters showed an improved discrimination of benign from malignant tumors using RC registration in comparison with unregistered and MI-registered data.

Conclusion- RC registration is a useful tool for correcting misalignments of DCE-MR image series in the presence of bias field artifacts, while it conserves the quantitative information of the contrast enhancement.

1. Introduction

Ovarian cancer is the dominant cause of death from gynecological cancer in women and is usually the leading indication for

surgery [1, 2]. Rapid and precise decisions about the type of ovarian mass could significantly affect the patient outcome: while unnecessary and extensive operation could be avoided in patients with benign

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masses, increased survival rate could be offered to patients with malignant masses [3, 4]. In this light, a quantitative image analysis plays a central role in preoperative characterization of adnexal masses. While ultrasonography (US) is the first-line examination technique for investigating ovarian masses due to its availability and low costs [5], magnetic resonance imaging (MRI) plays a pivotal role in characterizing indeterminate complex adnexal masses in US examination as it provides a superb spatial and tissue contrast resolution [4, 6, 7].

Recently, dynamic contrast enhanced (DCE-) MRI technique has evolved into a helpful imaging technique for distinguishing complex adnexal masses by providing noninvasive and quantitative biomarkers of tumor progression [8, 9]. In this context, semi-quantitative analysis of the time-intensity curves could present several descriptive parameters for differentiating benign from malignant complex adnexal tumors [8, 10, 11].

One major assumption in quantification of DCE-MRI is spatially-fixed regions of interest over the time course of contrast agent passage. However, this assumption becomes invalid when motion artifacts occur [10]. Therefore, an accurate quantification of DCE-MR image series highly depends on minimization of motion artifacts.

Two types of motion occur in DCE-MR images of abdominal organs: 1) the complex motion resulting from breathing, pulsation, and the natural movement of the organ of interest or its surrounding organs; 2) motion of contrast agent in the tissue [12]. Motion correction of DCE-MR image series becomes a challenging issue in that the proposed registration algorithm for rectifying the first type of motion must be unaffected by signal intensity changes during the bolus passage [13]. Apart from intensity variations caused by motion, spatially-varying intensity distortions induced by bias fields in high-field MRI, increase the complexity of the interrelationships of pixel intensities, which compromise the performance of registration procedures.

The problem of image registration has not been much tackled in DCE-MR images of ovarian cancers. The widely-used similarity measures, such as normalized mutual information (NMI), are mostly defined based on the assumption of pixel-wise independence and stationarity of

image intensities in the spatial domain [14, 15]. Consequently, the complexity resulting from time-varying image contrast induced by spatially-varying kinetics of contrast agent and bias fields, where the former is a desirable intensity change and the latter is undesirable, cannot be resolved by the aforementioned image registration similarity measures [16].

Therefore, it is highly desirable to adaptively remove undesirable intensity inhomogeneity artifacts arising from bias fields while maintaining the informative intensity changes of image contrast in a unified framework with the registration procedure. Since intensity inhomogeneity arising from the bias field is a low frequency distortion, correlated with the pixels, its elimination can be better performed by decorrelating the intensities of pixels in the transform domain. Recently, Residual Complexity (RC) has been introduced as a new similarity measure for non-rigid registration which can capture non-stationarity and complex spatially-varying pixel intensities [14, 15]. The idea of exploiting RC is to minimize the complexity of the residual of images in the Discrete Cosine Transformation (DCT) domain rather than in pixel domain.

Based on this idea, we utilized RC to perform the registration procedure more locally and sparsely, which is suited for the registration of DCE-MR images, in order to cope with complex motion artifacts for an accurate quantification of DCE-MRI in ovary.

2. Materials and Methods

2.1. Patients

Study approval for this prospective study was obtained from the Institutional Review Board (IRB), and patients were included only if they provided a written informed consent. A total of sixteen patients were enrolled in this study. Prior to the MRI examination, all study subjects were assessed by transvaginal ultrasound and accordingly Ultrasound score (U-score) was estimated for the patients. Each U-score point for a patient was added if any of the following features existed: multilocular cyst, solid components, bilateral lesions, metastases, and ascites. Patients with U-score of 1 or more who did not show any contraindications for MR imaging or

receiving contrast agent were scheduled for an MRI acquisition. All included patients were scheduled for the surgical removal of suspicious ovarian masses and postoperative histopathological assessment within two weeks of MR imaging.

2.2. MR Imaging

MR imaging was performed on a 3T scanner (MAGNETOM Tim TRIO, Siemens, Erlangen, Germany). DCE-MR images were acquired using a surface phased array coil, with TE/TR, 1.74/5 ms; flip angle, 60°; image matrix, 156×192; FOV, 23×23cm²; slice thickness, 5mm; number of measurements, 52 at 6 sec/volume; and number of slices, 16. The acquisition was performed before and immediately after the injection of 0.2mL/kg of Gadolinium (DOTAREM; Guerbet, Aulnay, France), followed by the injection of 20cc normal saline solution with 3mL/min injection rate.

2.3. DCE-MR Image Registration

2.3.1. Definition of Residual Complexity

Residual Complexity (RC) is an intensity-based similarity measure which is suitable for registration of images distorted by spatially-varying intensity inhomogeneity. RC is defined by eliminating the intensity inhomogeneity from the similarity measure formulation simultaneously with the registration problem. This is undertaken by introducing an intensity correction field that enforces the alignment of the images in the intensity domain. An adaptive regularization term is defined for the intensity correction field. The registration problem is then solved for the intensity correction field and the regularization term. The registration problem using RC is optimized when the difference (residual) of the images achieves its minimum complexity.

Consider two images I and J, which are aligned using the geometric transformation defined by T. By analytically solving the registration formulation and in the same time eliminating the intensity inhomogeneity from the formulation, the final form of the RC similarity measure can be represented by:

$$E_{RC}(T) = \sum \log\left(\frac{(q_n^T r)^2}{\alpha + 1}\right),$$

$$r = (I - J(T)). \quad (1)$$

where ‘ q_n ’s are of a form of basis functions, and α is a trade-off parameter.

In order to specify Q, the discrete cosine transform (DCT) coefficients are selected. Therefore, the matrix multiplication of $Q^T r$ is a DCT of r. The DCT-II form of basis functions, which is commonly used in image processing, is used for defining eigenvalues of Q. For 1-D, we have:

$$q_n(k) = \frac{w_n}{\sqrt{N}} \cos\left(\frac{\pi(2k-1)(n-1)}{2N}\right), \quad (2)$$

for $k = 1, 2 \dots N, n = 1, 2 \dots N$ and,

$$w_n = \begin{cases} 1, \dots n=1, \\ \sqrt{2}, \dots n=2 \dots N. \end{cases}$$

As it can be seen in the above formulas, smaller DCT coefficients are more penalized with respect to the larger ones, due to the existence of the term $\log(x^2+1)$. The \log function decreases rapidly to zero as the number of points is increased, causing the DCT coefficients to become sparse [15, 17]. RC reaches its optimum more accurately, by imposing sparseness on the DCT coefficients of the residual image. For this purpose, we set a threshold value, which is obtained by taking the mode of the coefficient matrix. The coefficients below this threshold (mostly occurring in higher frequencies) are set to zero.

2.3.2. The Algorithm

Image registration is composed of three main steps: similarity measure, transformation, and optimization. As explained earlier, in this work, RC is selected as the similarity measure to be compared with NMI similarity measure. In the transformation step, Free Form Deformation (FFD) Bspline is used for modeling local deformations of abdominal organs. In the transformation selection step of image registration, the goal is to find an optimal transformation that corresponds each point in the source image to its corresponding point in the reference image. The FFD model based on Bsplines deforms the object by operating on a mesh of control points. In order to define the Bspline-based FFD, we consider the image domain. The $n_x \times n_y \times n_z$ mesh of control points $p_{i,j,k}$ with a uniform spacing can be defined on the image domain. The FFD can be denoted as the 3D tensor product of 1-D cubic Bsplines:

$$T(x, y, z; p) = \sum_{n=0}^3 \sum_{m=0}^3 \sum_{l=0}^3 B_n(u_x) B_m(v_y) B_l(w_z) p_{i+k, j+m, k+l} \quad (3)$$

where

$i = \lfloor x/n_x \rfloor - 1, j = \lfloor y/n_y \rfloor - 1, k = \lfloor z/n_z \rfloor - 1, u_x = x/n_x - \lfloor x/n_x \rfloor, v_y = y/n_y - \lfloor y/n_y \rfloor, w_z = z/n_z - \lfloor z/n_z \rfloor$, and B_n is the n -th basis function of B-spline [18]:

$$\begin{aligned} B_1(u) &= (1-u)^3/6 \\ B_2(u) &= (3u^3 - 6u^2 + 4)/6 \\ B_3(u) &= (-3u^3 + 3u^2 + 3u + 1)/6 \\ B_4(u) &= u^3/6 \end{aligned} \quad (4)$$

For the optimization of the cost function, the gradient descent method is applied.

For more information about RC similarity measure and the choice of DCT basis functions as well as transformation function, the interested readers could refer to [14, 17].

2.3.3. Implementation

In the current study, RC was considered as a potential similarity measure for the registration of DCE-MR images since it can correct for bias fields along with the motion correction. Misalignments of DCE-MR images of adnexal masses were corrected by registering each frame to a reference frame, selected from the same series. The proposed registration approach composed of two steps: (1) 2-D rigid registration for aligning the whole dynamic images with the frame of reference (the initial dynamic scan); by employing a normalized Mutual Information (MI) as the similarity measure: the first image in the sequence of images was used as the reference and the consequent images were aligned with this image; (2) 2-D non-rigid registration using RC similarity measure, along with 2-D Free Form Deformation (FFD) Bspline transformation, and the gradient descent optimization method, as explained in the previous section.

In the 2-D non-rigid registration framework, the regularization term, which is used as the trade-off between the alignment of two images and the smoothness of FFD Bspline transformation, was set to 0.01 and the value of α was selected to be 0.05. The algorithm was performed hierarchically

in 3 different scales, with 200 iterations and grid spacing equal to 5.

The above mentioned registration approach was implemented and performed in MATLAB (MathWorks, Inc) on a Windows-based platform (64-bit OS, Intel® Core™ i5 CPU, 2.67 GHz, 4 GB RAM). The computation time was calculated using the developed software code. In order to indicate the capability of RC in resolving intensity changes from motion artifacts in DCE-MR images of the ovarian masses, we have compared the performance of RC with the widely-used MI similarity measure.

In the following steps, the DCE-MRI before and after the motion-correction using both MI and RC similarity measures were analyzed and compared with each other. The registration parameters for both RC and MI are set at their best operational condition in a way that they achieved the highest accuracy in the average sense for all patients.

2.4. DCE-MRI Quantification

2.4.1. Semi-quantitative Analysis

Two Regions of Interest (ROIs) were drawn for each examination: one within the solid portion of the adnexal tumor and the other one in the psoas muscle as an internal reference. Signal intensity-time courses of tumor ROIs were determined over all the time frames and normalized to the mean signal intensity of the corresponding psoas ROI. (Figure 1).

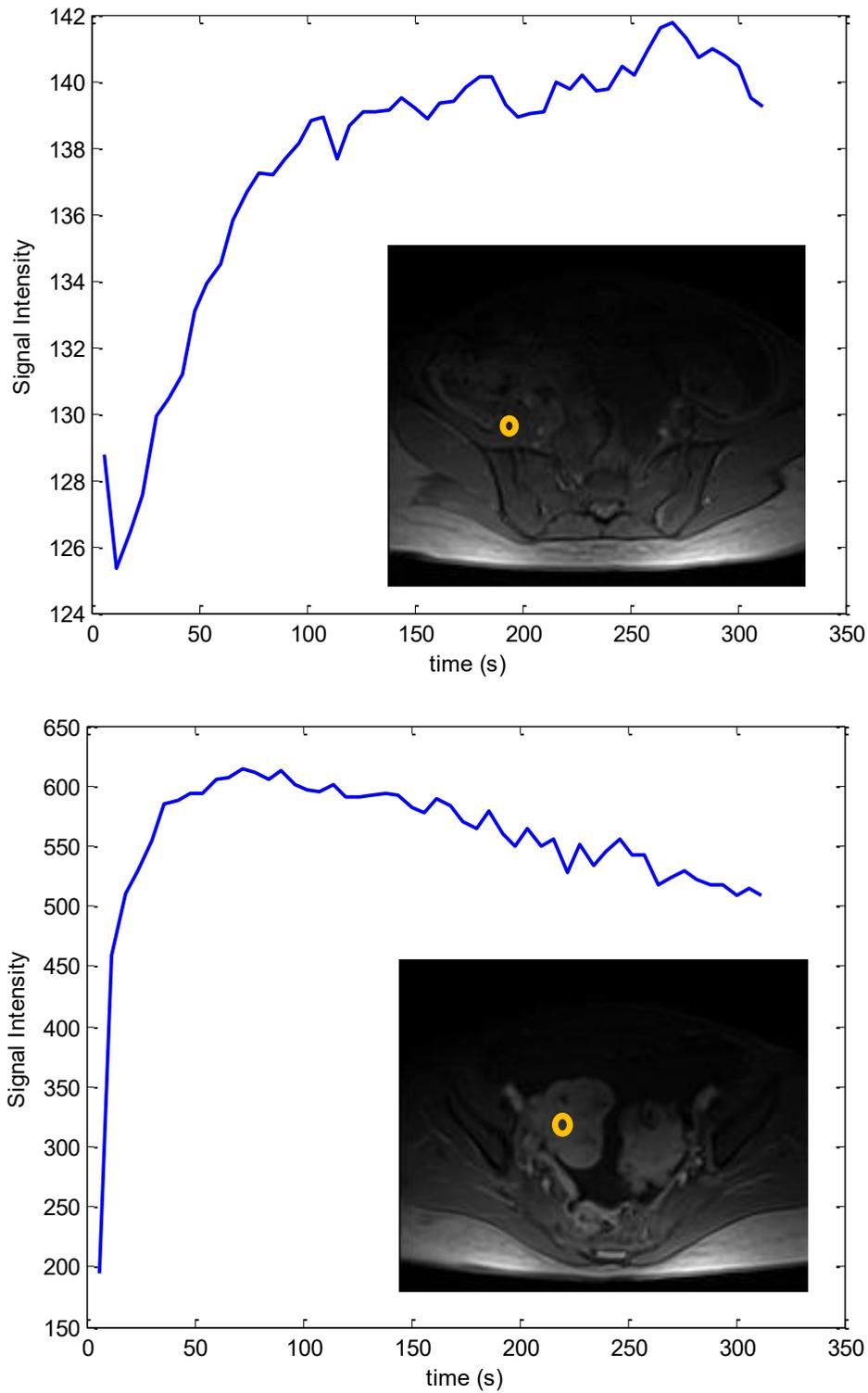


Figure 1. Region of interest (ROI) selection from psoas which is considered as the internal reference tissue (up) and solid portion of the tumor (bottom) for quantitative assessment of the complex adnexal cancers.

The semi-quantitative enhancement parameters were then calculated using an in-house software implemented in MATLAB (MathWorks, Inc), as summarized in Table 1.

Table 1. Description of semi-quantitative parameters.

Parameter	Description	Unit
SI_{rel}	Relative Signal Enhancement = $(SI_{max} - SI_0)/SI_0 \times 100$ (SI_{max} : maximum signal intensity over the time course of contrast agent passage; SI_0 : initial signal intensity prior to contrast agent injection)	(Ratio)
$IAUC_{60}$	Initial area under the time-intensity curve over the first 60 seconds after gadolinium injection, normalized to that of psoas muscle	(Ratio)
TTP	Time-to-Peak: the time to the maximum absolute enhancement	s
WIR	Wash-in-Rate = $(SI_{max} - SI_0)/TTP$	a.u./s
WOR	Wash-out-Rate = $(SI_{max} - SI_{end})/SI_{max}$	(Ratio)

For a better comprehension, parameter definitions are also depicted in Figure 2. The area under the curve was determined by calculating the trapezoids constructed from the data points.

Performance of the proposed registration scheme was evaluated based on derived semi-quantitative parameters, namely SI_{rel} , $IAUC_{60}$, TTP, WIR,

and WOR. The parameters were calculated on the specified ROIs. The comparison of the mean values of benign and malignant groups for each parameter was carried out by calculating p-values using Mann-Whitney test (as the distributions were not normal) with assumptions of equality and non-equality of variances wherever appropriate and the significance level was assumed to be 0.05.

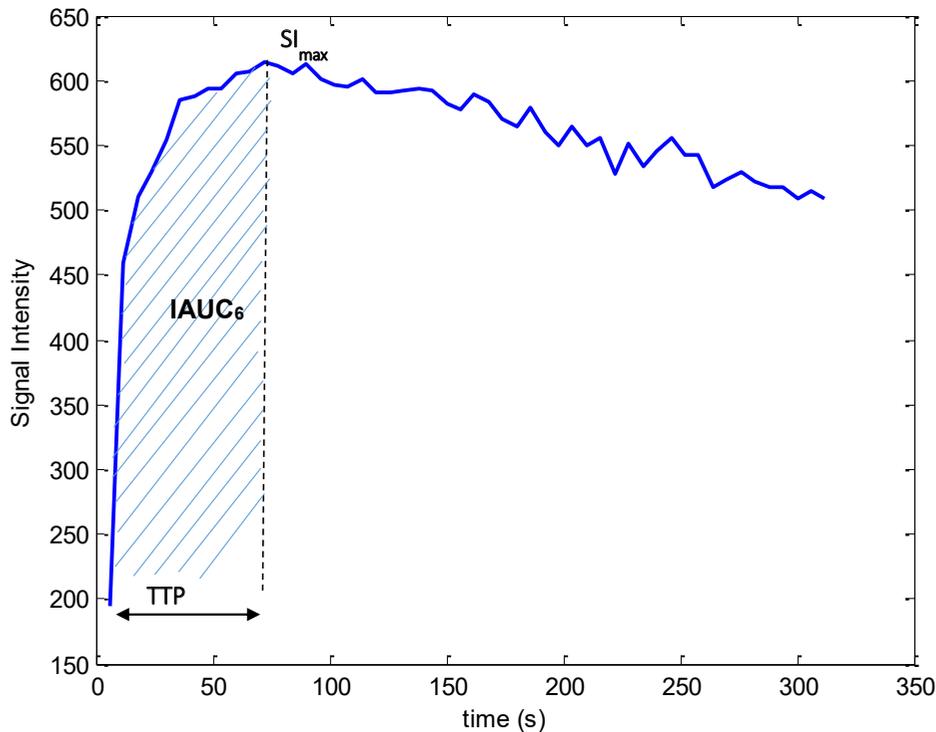


Figure 2. Definitions of the semi-quantitative parameters: SI_{max} is considered as the maximum signal intensity and $IAUC_{60}$ is defined as the initial area under the signal intensity-time curve over the first 60 seconds of image acquisition. TTP is the time interval to the maximum absolute enhancement.

3. Results

Sixteen women with complex adnexal masses, who provided informed consent, were included in the quantification. All subjects were scheduled for consequent surgery to remove at least one ovary and postoperative histopathological assessment, among which 8 were diagnosed with benign and 8 with malignant complex adnexal masses. The mean age was 39.7 (age range 14-70).

Figure 3 illustrates the mean signal intensity time courses for the selected ROI obtained from unregistered image sequence and the images registered by MI and RC similarity measures in two patients with benign and malignant complex adnexal tumor. RC significantly improved the

signal intensity time courses. In the cases with solid malignant masses, the MI and RC returned almost similar results because the lesion is mostly solid and contains a little cystic portion. In addition, the mean and the median of standard deviation in tumor ROIs were computed (Table 2). The standard deviation of a specific ROI over the whole time course was considered and the mean and median of this signal standard deviation were computed afterwards. The decrease in the mean and median of this standard deviation represent the amount of motion, which is corrupting the signal intensity-time course. The results suggest that MI and RC methods significantly improve the signal intensity-time courses, in contrast to the unregistered method, in the average sense.

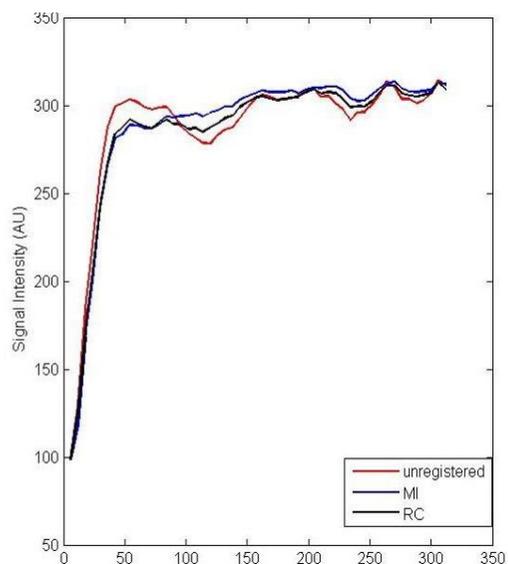
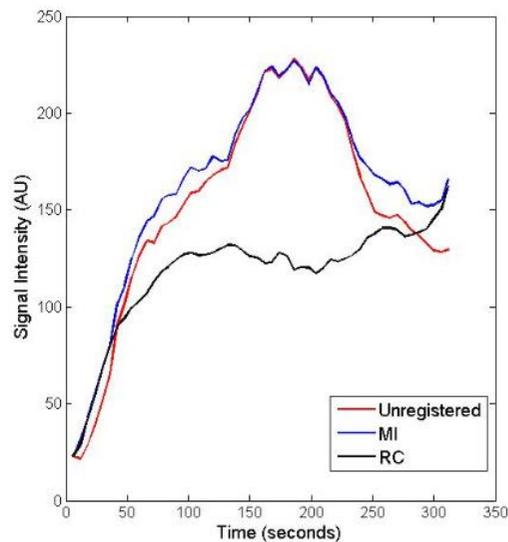
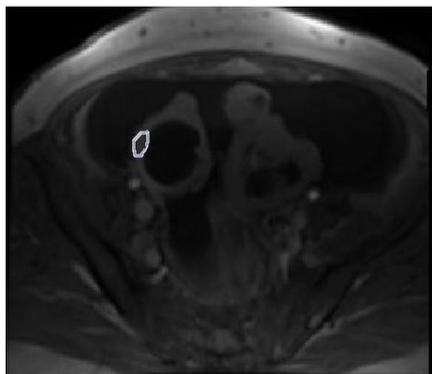
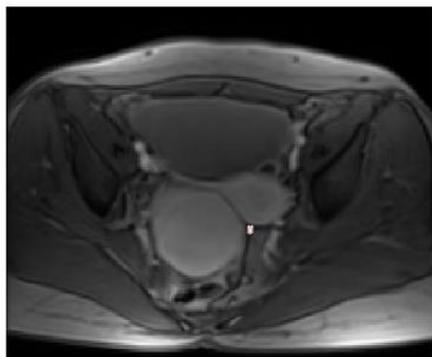


Figure 3. Signal intensity-time curves from unregistered images, and registered images by MI, RC in: (up) benign and (bottom) malignant masses. It is apparent that RC registration can significantly improve image alignment.

Table 2. For each manually delineated ROI and each frame, the Standard Deviation (SD) of signal intensity was calculated: (a) mean and (b) median of these SD values for all patients. It is apparent that on average, the mean and median of deviation of signal intensity in patients decrease significantly after RC registration in comparison with unregistered data. In most cases, RC outperforms MI in registration of DCE-MRI data.

	Unregistered		MI		RC	
	Mean	Median	Mean	Median	Mean	Median
Benign Group (n=8)	34.2	35.5	28.7	29.2	21.1	20.8
Malignant Group (n=8)	21.8	19.7	16.2	15.3	12.6	11.5

Table 3 provides the parameter calculations averaged over benign and malignant patients, along with their corresponding p-values and confidence intervals. It is apparent from the results that the p-values of the quantification parameters obtained after RC registration method improved in comparison with unregistered and MI techniques,

suggesting that RC can better discriminate complex adnexal masses. It is worthwhile mentioning that TTP and IAUC₆₀ are the most relevant parameters in differentiating benign from malignant ovarian masses [19], which here show the least p-values (p<0.05). SI_{rel} and WOR did not show significant differences among benign and malignant patients.

Table 3. An assessment of the performance of RC registration in comparison with unregistered data and MI registration approach through quantitative parameter investigation. The calculations of the semi-quantitative parameters, namely Initial Area Under the Curve in the first 60 seconds (IAUC₆₀), Time-to-Peak (TTP), and Wash-in-Rate (WIR), with statistically significant p-values averaged over the benign and malignant patients, are summarized.

		Mean ± SD		p-value	Confidence Interval (Lower Limit-Upper Limit)
		Benign	Malignant		
IAUC60	Unregistered	72.0 ± 13.8	112.6 ± 21.8	0.0013	(-61.8)-(-19.3)
	MI	66.0 ± 10.1	107.6 ± 24.9	0.0035	(-65.1)-(-18.1)
	RC	70.1 ± 14.0	115.1 ± 19.8	0.00036	(65.0)-(-25.1)
TTP	Unregistered	165 ± 65.2	44.6 ± 17.9	0.0023	(59.9)-(181)
	MI	161.1 ± 61.5	42.0 ± 18.3	0.0017	(61.9)-(-176.4)
	RC	138 ± 28.1	45.4 ± 15.4	0.000006	(66.1)-(-119.0)
WIR	Unregistered	0.0093 ± 0.0059	0.045 ± 0.026	0.01	(-0.059)-(-0.01)
	MI	0.01 ± 0.01	0.04 ± 0.02	0.0064	(-0.048)-(0.01)
	RC	0.0095 ± 0.0062	0.047 ± 0.021	0.0026	(0.057)-(-0.018)

4. Discussion

The problem of DCE-MRI motion compensation in discrimination of benign and malignant complex adnexal masses has been ignored when analyzing dynamic image series using quantitative parameters [10, 20]. Nevertheless, image registration should be considered an essential element of DCE-MR image quantification for complex adnexal masses, as the corrupted signal intensity-time curve could negatively impact the differentiation of benign and malignant tumors.

Most importantly, the registration of DCE-MR images has not been tackled in the view of separating the components of motion and bias field artifact from the contrast agent enhancement changes. This is of great importance, as the registration process should accomplish motion and bias field artifact reduction while it preserves the quantitative information of contrast agent enhancement.

The work presented here addresses the motion correction problem of DCE-MR images in

complex adnexal masses, exploiting an automatic registration scheme. The proposed registration approach is composed of a rigid registration step, using normalized mutual information as the similarity measure, followed by a non-rigid registration step, employing Residual Complexity (RC) similarity measure. RC similarity measure spares the opportunity to differentiate the mentioned components in the frequency domain and eliminate the unnecessary components through registration process.

To assess the performance of the proposed registration framework in motion compensation of DCE-MR image series, we both probed variations of signal intensity over the time points and investigated the effects of registration in separating benign and malignant tumors. The indicated results on comparing the registered and unregistered data are suggestive of the positive impact of registration for improving the diagnostic accuracy.

In summary, we conclude that the proposed RC registration framework shows potential for a reliable registration and quantification of DCE-MR images of complex adnexal masses. Without a gold standard, explanation of the significance of the work could be limited. In future works, testing on a larger data population could provide a better insight about the feasibility of the proposed method for being incorporated in clinical applications.

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