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FULL PAPER

Performance of U-net based pyramidal lucas-kanade registration on free-breathing multi-*b*-value diffusion MRI of the kidney

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Objective: In free-breathing multi-*b*-value diffusion-weighted imaging (DWI), a series of images typically requires several minutes to collect. During respiration the kidney is routinely displaced and may also undergo deformation. These respiratory motion effects generate artifacts and these are the main sources of error in the quantification of intravoxel incoherent motion (IVIM) derived parameters. This work proposes a fully automated framework that combines a kidney segmentation to improve the registration accuracy.

Methods: 10 healthy subjects were recruited to participate in this experiment. For the segmentation, U-net was adopted to acquire the kidney's contour. The segmented kidney then served as a region of interest (ROI) for the registration method, known as pyramidal Lucas-Kanade. Our proposed framework confines the kidney's solution range, thus increasing the pyramidal Lucas-Kanade's accuracy. To demonstrate the feasibility of our presented framework, eight regions of interest were selected in the cortex and medulla, and data stability was estimated by comparing the normalized root-mean-square

error (NRMSE) values of the fitted data from the bi-exponential intravoxel incoherent motion model pre- and post- registration.

Results: The results show that the NRMSE was significantly lower after registration both in the cortex ($p < 0.05$) and medulla ($p < 0.01$) during free-breathing measurements. In addition, expert visual scoring of the derived apparent diffusion coefficient (ADC), *f*, *D* and *D** maps indicated there were significant improvements in the alignment of the kidney in the post-registered image.

Conclusion: The proposed framework can effectively reduce the motion artifacts of misaligned multi-*b*-value DWIs and the inaccuracies of the ADC, *f*, *D* and *D** estimations.

Advances in knowledge: This study demonstrates the feasibility of our proposed fully automated framework combining U-net based segmentation and pyramidal Lucas-Kanade registration method for improving the alignment of multi-*b*-value diffusion-weighted MRIs and reducing the inaccuracy of parameter estimation during free-breathing.

INTRODUCTION

Diffusion-weighted MRI (DW-MRI) of kidney is a growing field of research because it allows the tissue characteristics to be assessed.^{1–3} The method makes no use of ionizing radiation and does not require extraneous contrast agents that might impede kidney function. Living tissue contains cell compartments that restrict diffusion, which alters the signal intensity of DW-MRIs depending on the *b*-values. The apparent diffusion coefficient (ADC) is based on mono-exponential fitting, which refers to the linear fit of the logarithmic normalized signal attenuation of at least

two *b*-values.⁴ Intravoxel incoherent motion (IVIM), which was first described by Le Bihan et al⁵ is an interesting imaging technique for estimating tissue perfusion by calculating diffusivity parameters using multi-*b*-value diffusion-weighted magnetic resonance imaging. Recent advances in MR imaging have facilitated the application of IVIM imaging to estimate the tissue perfusion and diffusivity of protons in abdominal organs.⁶

However, diffusion-weighted imaging (DWI) is sensitive to molecular displacement, bulk motion and physiological

motion, which are caused by a variety of sources. DW-MRI of the abdomen is hindered by motion due to breathing, and the resulting multi- b -value DWIs are not aligned to each other. In human subjects, respiratory motion may displace the kidneys by 5–10 mm, and this relative motion between images acquired can introduce substantial error into the estimation of functional parameters.^{7,8}

At present, a simple approach to reduce respiratory motion artifacts is to acquire images during one or more breath-holds; however, this is often intolerable for elderly or severely ill patients.⁹ In addition, in order to reduce the scanning time, breath-hold acquisition is often limited to a relatively poor resolution in the phase-encoded direction. Navigator gating can reduce motion and improve image quality.^{10,11} This approach may lead to unpredictable scan times and inefficiency. The acquisition time is reproducible if the subject can breathe freely.¹² Thus, many retrospective image registration methods have been applied to further increase confidence in the estimated parameters. For example, Mazaheri et al¹³ used a special acquisition method combined with a pair of rectangular gradient pulses transmitted simultaneously along three orthogonal axes (x , y and z) to correct for liver motion. Later, Guyader et al¹⁴ presented a new acquisition sequence to improve the alignment of DW-MRIs of kidneys. Recently, a demons-based registration algorithm is introduced to correct motion artifacts, which leads to clearly reduced signal variations in kidney diffusion tensor imaging (DTI) scans.^{15,16} Also, a novel edge-based image registration⁸ was introduced to reduce respiratory motion artifacts effectively in free-breathing renographic acquisitions. Still, the problem remains challenging due to the serious displacements and deformations of kidney.

Inspired by Conlin et al¹⁸ in this study, we propose a novel framework of registration with a prior segmentation method to address motion-related artifacts during free-breathing in multi- b -value diffusion-weighted imaging. The segmentation is obtained using a deep learning method called U-net in order to emphasize the exact location during registration. Results are assessed by comparing to manual segmentations. The pyramidal lucas-kanade method is used to register multi- b -value diffusion-weighted images ($b > 0$) to the template image ($b = 0$). The

normalized root-mean-square error (NRMSE) is regarded as a measure of the ability of our registration algorithm to correct for motion.

METHODS AND MATERIALS

Subjects

Written informed consent for the MRI procedures was obtained from each subject. 10 healthy volunteers (5 males and 5 females aged 23.8 ± 2.2 years) with no potential kidney or other dysfunctions were recruited. The subjects were instructed to eat and drink moderately before the MR examination.

MRI data acquisition

The MRI was performed using a 3-Tesla whole-body MR imaging unit (Discovery MR750; GE Medical Systems, Waukesha, WI) equipped with a 32-channel phased-array coil. The IVIM images were acquired in the free-breathing state using a diffusion-weighted single shot echo-planar imaging fat saturated sequence. The repetition time (ms)/echo time (ms) was 3300/57; the flip angle was 90° ; the results of two excitations were averaged; the field of view was 30×30 cm; the matrix size was 128×128 ; 10 coronal slices were acquired with a thickness of 5 mm and a gap of 2 mm; the parallel imaging (ASSET) factor was 3; and the scan time was 180 s. 10 different b values were used: 0, 10, 20, 50, 100, 180, 300, 420, 550 and 700 s mm^{-2} .

Description of the image registration pipeline

The whole registration pipeline is shown in Figure 1. Firstly, the original DWIs were fed to the modified U-net based on the methods of Ronneberger et al¹⁷ for kidney segmentation. Then, we segmented the contour of the kidney and cropped it from the original images. At this point, displacement and direction of the moving images ($b > 0$) could be obtained by aligning them to the template image ($b = 0$) using pyramidal lucas-kanade registration method.

Kidney segmentation based on U-net

Architecture of modified U-net

Our modified U-net is based on the methods of Ronneberger et al.¹⁷ The only difference is that in the final layer, a 1×1

Figure 1. Pipeline of our proposed framework. Multi- b -value DWIs were segmented by U-net and then registered by pyramidal Lucas-Kanade registration method. DWI, diffusion-weighted imaging.

convolution is used to map each 32-component feature vector to the desired number of classes.

U-net training

For U-net based segmentation, datasets were randomly split into a training set (80% of the original dataset) and a test set (20% of the original dataset). During training, the effective features were extracted gradually by our modified U-net. To minimize errors between the real labels and the output labels, the network's parameters were updated by an Adam optimizer, with a $1e-5$ learning rate. An epoch is a step in the training course in which the whole training dataset is presented to the U-net at once for parameter adjustments.¹⁸ Small epochs may lead to poor performance if parameter adjustments are incomplete. Here, our model is trained for 6000 epochs on NVIDIA GPUs (GTX 1080). Loss of function for the training is a negative of the dice coefficient.¹⁹ The formula used to calculate dice coefficient is defined as:

$$Dice = \frac{2|X \cap Y|}{|X| + |Y|} \quad (1)$$

Dice coefficients evaluate the overlap between the automated segmentation, X, and the manual segmentation, Y. The value is between 0 and 1, with 0 indicating no overlap and 1 denoting a perfect match. Keras²⁰ is a high-level neural networks library, originally written in Python. Here, it was used to implement this model on a Linux machine (Ubuntu 14.04 LTS; Cuda 7.5).

Pyramidal lucas-kanade registration

After segmentation we used a 3-level multiresolution pyramidal Lucas-Kanade^{21,22} registration method. In summary, an image pyramid is used to perform a top-down estimation of the flow, where the apex represents the MR image at a coarse scale. Based on the optical flow constraint, the optical flow field at every image level is calculated.²³ The calibration of the resulting motion field at this level is resized and passed on to the next. This continues based on the estimated flow at the preceding scale until the original scale is reached.

Bi-exponential and mono-exponential diffusion models

The following three IVIM parameters were chosen: the non-perfusion-based molecular diffusion coefficient ($D \times 10^{-3} \text{ mm s}^{-1}$), which represents extravascular molecular diffusion; the perfusion-based molecular diffusion coefficient ($D^* \times 10^{-3} \text{ mm s}^{-1}$), which represents intravoxel microcirculation or perfusion; and the perfusion fraction ($f\%$).

These IVIM parameters were calculated using the IVIM model equations described by Le Bihan et al.^{5, 24, 25}

$$S(b) = S(0) \cdot [(1 - f) \cdot \exp(-b \cdot D) + f \cdot \exp(-b \cdot D^*)] \quad (2)$$

where $S(b)$ and $S(0)$ represent the signal intensity with and without the diffusion gradients or b -value, and D , D^* and f were estimated using the least squares approach. For comparison, the conventional ADC, which contains both D and D^* , was also calculated using mono-exponential decay²⁶:

Figure 2. Eight ROIs positioned on anatomical image ($b = 0$). The red and yellow circles indicate parts of the cortex and medulla, respectively. ROIs, regions of interest.

$$S(b)/S_0 = \exp(-b \cdot ADC) \quad (3)$$

Data analysis

Validation of the results from image registration algorithms is limited due to the lack of a gold standard. Therefore, an indirect measure should be proposed to establish the reliability of an image registration method.

The NRMSE is defined as the root-mean-square error between the data points and bi-exponential model divided by the range of values:

$$NRMSE = \frac{1}{x_{data,max} - x_{data,min}} \sqrt{\frac{\sum_{i=1}^N (x_{data,i} - x_{mod,i})^2}{N}} \quad (4)$$

where $x_{data,max}$ is the pre- or post-registered data, $x_{mod,i}$ is the pre- or post-registered bi-exponential fit and N is the number of voxels in the region of interest (ROI). A lower NRMSE indicates a better match. Thus, the NRMSE of each ROI for each patient can be regarded as an indirect measure of the ability of the registration algorithm to correct for motion.^{13, 27}

To obtain the IVIM parameters and ADC values, four ROIs were manually drawn in each cortex and medulla of the kidney by an experienced abdominal radiologist. As shown in Figure 2, a total of eight ROIs were placed on the anatomical image ($b = 0$) and then copied-and-pasted onto the four maps (D , D^* , f and ADC).

Statistical analysis

The parameters were then quantitatively analyzed in terms of the NRMSE of the fitting procedure to test the results of our registration algorithm. The statistics and diffusion parameter values are presented as median $\pm$ standard deviation (SD) for the ROI. The statistical testing was performed using a paired t -test with the significance defined at $p < 0.05$.

The resulting maps were scored on a 5-point scale^{28, 29} (where "5" indicates a superior image) by two independent experts who were unaware of the process used to create each image. The images were scored in the following categories: overall image quality, degree of blurring and clarity of the physiological

Figure 3. (a) Training and validation dice values for each training and validation epoch. (b) Segmentation result (red edge) with manual ground truth (green border).

structures. The overall image quality and clarity of the physiological structure were scored as follows: (1) very poor; (2) poor; (3) fair; (4) good; and (5) excellent. The visual blurring was scored as follows: (1) extreme; (2) major; (3) significant; (4) minor; and (5) no blurring. Statistical significance of these scores were also evaluated using a paired *t*-test (*p*-value of <0.05 considered significant). The study protocol was approved by the BioMed-X Research Center Ethical Review Committee of the Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, 100871, China.

RESULTS

It can be seen in Figure 3a, using 6000 epochs, the model converged nicely with high dice scores. In addition, the performance of kidney segmentation on the test images acquired from four subjects is shown in Figure 3b. The presented results show very good consistency between the U-net based segmentation and the manual segmentation.

Figure 4 shows a comparison of a reference image ($b = 0$) and pre- and post-registration target images ($b = 50$ and $b = 550 \text{ s mm}^{-2}$). In the pre-registered image, the kidney and contour do not match. However, there was a significant improvement in the alignment between the kidney edge in each post-registered image and the kidney edge in the reference image.

Figure 5 provides examples of the computed D , D^* , f and ADC maps for two typical subjects. A visual inspection of the four diffusion maps suggests that the proposed method improved the visual quality of these maps. The contours of the kidney are better defined, and the number of voxels for which the fitting failed decreased. The edges in the “post-registration” images are indicated by white arrows, and appear sharper.

The results of the visual scoring are listed in Table 1, where the mean score $\pm$ SD in each of the assessment criteria are shown for

Figure 4. Registration of the target image to the reference image of two typical subjects. (a) Subject #1. Left: Reference image (frame 1, $b = 0 \text{ s mm}^{-2}$). For comparison, the contour of the kidney (green) from frame 1 is copied in its original location in each subsequent frame. Pre-(middle) and Post-(right) registration images of the same slice from frame ($b = 50 \text{ s mm}^{-2}$). (b) Subject #2. Left: Reference image (frame 1, $b = 0 \text{ s mm}^{-2}$). Similarly, the contour of the kidney (green) from frame 1 is copied in its original location in each subsequent frame. Pre- (middle) and Post-(right) registration images of the same slice from frame ($b = 550 \text{ s mm}^{-2}$).

Figure 5. Computed f , D , D^* and ADC maps of two typical subjects (the arrows indicate some major differences). In contrast to the non-processed images, the visual quality of the four computed parameter maps was clearly improved in the registration case. ADC, apparent diffusion coefficient.

both experts. Both experts reported a clearly significant improvement in image quality across all categories after our proposed method was applied (all $p < 0.05$).

The results from fitting the ADC and IVIM diffusion models for the cortex and medulla are presented in Table 2, and only show significant differences for the ADC in the kidney cortex. For all other parameters and in all tissues, no significant differences were observed between the pre- and post-registered images.

In the datasets of the 10 subjects, the cortical and medulla NRMSE values were similar for the non-motion-corrected scans (0.30 ± 0.06 and 0.31 ± 0.05 , respectively). However, after registration, the NRMSE values were 0.25 ± 0.06 and 0.22 ± 0.05 in the cortex and medulla, respectively. As shown in Figure 6, the NRMSE was significantly lower after registration in both the cortex ($p < 0.05$) and medulla ($p < 0.01$) of the free-breathing measurements.

DISCUSSION

In this study, we proposed a fully automated framework combining U-net based segmentation and pyramidal Lucas-Kanade registration method to reduce artifacts caused by motion during the acquisition of images at multiple b -values. We assumed that respiratory motion blurring in abdominal DWIs

could result in errors of the quantification of perfusion fraction, pseudo-diffusivity and true diffusion. To evaluate our assumptions, we compared the mean NRMSE values for the data fit to the bi-exponential model of ROIs and four diffusion parameter maps (D , D^* , f and ADC) between the pre- and post-registered images. The results for the 10 subjects showed that our method effectively corrected the respiratory motion artifacts.

Segmentation results show that our model is robust against slice misalignments and different subject as well as various sizes of kidneys. The U-net architecture achieves very good performance on very different biomedical segmentation applications.^{17,30} As shown in Figure 3a, dice similarity of our training and validation is over 95%. It is because U-net has skip connections, which enables the network to not only learn to generalize in the compressed representation but also recover latent generalizations to a spatial representation. The fully automated and accurate contour extraction is helpful for the following registration.

Our results suggest that the registration of DW-MRIs of the kidney acquired with multiple b -values is significantly improved using the proposed method. As shown in Figure 4, the contour of the kidney is somewhat aligned after registration. Meanwhile, as shown in Figure 5 and Table 1, the post-registered diffusion parameter maps are shown to be visually superior to those

Table 1. Visual scoring from expert readers on a 5-point scale, where “5” denotes superior quality

Criterion	Expert 1		Expert 2	
	Pre-registered	Post-registered	Pre-registered	Post-registered
Overall	2.8 ± 0.3	4.5 ± 0.5	2.7 ± 0.7	4.4 ± 0.9
Blurring	2.7 ± 0.6	4.4 ± 0.6	2.9 ± 0.5	4.3 ± 0.4
Structures	2.9 ± 0.4	4.3 ± 0.8	3.1 ± 0.2	4.4 ± 0.7

The bold values are considered significant ($p < 0.05$) vs the pre-registered data.

Table 2. Mean $\pm$ SD of all pixels within ROIs of the parameters in cortex and medulla

	Kidney	ADC (10–3)	D* (10–3)	D (10–3)	f (%)
Cortex	Orig.	2.06 $\pm$ 0.08	73.6 $\pm$ 6.6	1.93 $\pm$ 0.06	9.6 $\pm$ 1.8
	Reg.	2.01 $\pm$ 0.06	77.0 $\pm$ 7.9	1.91 $\pm$ 0.07	9.8 $\pm$ 1.6
	<i>p</i> -values	<0.05 ^a	>0.05	>0.05	>0.05
Medulla	Orig.	1.84 $\pm$ 0.04	72.5 $\pm$ 6.8	1.85 $\pm$ 0.09	7.6 $\pm$ 1.9
	Reg.	1.85 $\pm$ 0.05	89.6 $\pm$ 8.2	1.80 $\pm$ 0.08	8.2 $\pm$ 1.7
	<i>p</i> -values	>0.05	>0.05	>0.05	>0.05

ADC, apparent diffusion coefficient; ROIs, regions of interest; SD, standard deviation.

^aSignificant difference.

derived from the pre-registered images for both the ADC and IVIM models.

The mean values of the ADC, D* and D in the medulla and cortex are in agreement with the results of previous studies.^{12,31,32} However, the values of *f* in the medulla are a little lower than those mentioned in Jerome et al¹², which may be due to the shorter echo times used in the present study. Moreover, the ADC for the kidney cortex was higher after registration. This could be explained by the fact that the ADC was calculated using fewer data points, and thus was more susceptible to variations and noise in the data. Because each method attempts to measure the same true tissue ADC, discrepancies necessarily arise from sources such as organ movement during respiration, which is present in both strategies and is problematic when considering small ROIs on the same order as the range of motion.

The pyramidal Lucas-Kanade optical flow algorithm has been applied in many studies^{33,34} for magnetic resonance fluid motion estimation. These studies have demonstrated that this algorithm can capture the motion of objects while excluding expansions, contractions and deformations. As shown in

Figure 6. Comparison of the NRMSE of the cortex and medulla between the original and registered measurements for the eight ROIs of ten subjects. NRMSE, normalized root-mean-square error; ROIs, regions of interest.

Figure 4, in the cortex regions with low NRMSEs, the reduction in image-based motion artifacts is very small since the remaining artifacts are mostly caused by through-plane motion. After registration, the NRMSEs of the medulla are reduced more than those of the cortex. The benefit of the registration algorithm appears to be more substantial for medulla with stronger deviations (higher NRMSEs). This may be due to the fact that the medulla consists of many separate small regions and is sensitive to movement. In contrast, the cortex is a relatively contiguous zone.

When compared to the methods of Mazaheri et al¹³, our proposed method does not require the development of new sequences, and is therefore widely applicable. Meanwhile, the effectiveness obtained by Choi et al¹¹ was only verified on axial images, although the coronal position is the main direction of motion. In addition, edge-based image registration⁸ requires the kidney images to be manually cropped ahead of time. In contrast, our method is fully automatic, which can enhance efficiency and save time. The demons³⁵ algorithm mentioned in¹⁵ is based on gradient images and can be interpreted as an interactive optimization approach using the steepest descent algorithm. Due to the fact that the gradient image contrast within structures naturally suffers from noise, demons registration is known for a relatively low convergence rate, especially in the neighborhood of the solution.³⁶ However, the Lucas-Kanade algorithm, which has been previously applied to optic flow estimation in 2-D video images, can be interpreted as an iterative Gauss-Newton optimization method, which is superior in convergence and accuracy compared to the steepest descent method.^{36,37}

It should be noted that our study has some limitations. First, no breath-hold DWI data were available for the same volunteer as a gold standard. In addition, the number of subjects was small; thus, it may be insufficient for demonstrating that our proposed method can render breath-hold unnecessary. A final limitation is that our subjects were young, healthy participants with no diseases that would cause structural abnormalities in the kidney. The potential benefit of this method for the assessment of abnormal kidney function will be explored in the future.

CONCLUSION

This study demonstrates the feasibility of our proposed fully automated framework combining U-net based segmentation

and pyramidal Lucas-Kanade registration method for improving the alignment of multi-*b*-value diffusion-weighted MRIs and reducing the inaccuracy of parameter estimation during free-breathing.

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