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α -Information Based Registration of Dynamic Scans for Magnetic Resonance Cystography

Hao Han,

Department of Radiology, Stony Brook University, Stony Brook, NY 11794 USA

Qin Lin⁺,

Southwest Institute of Electronic Technology of China, Chengdu, Sichuan 610036 China

Lihong Li [Senior Member, IEEE],

Department of Engineering Science and Physics, College of Staten Island of the City University of New York, Staten Island, NY 10314 USA

Chaijie Duan,

Department of Biomedical Engineering, Tsinghua University, Shenzhen, Guangdong 518055, China

Hongbing Lu,

Department of Biomedical Engineering, Fourth Military Medical University, Xi'an, Shaanxi 710032, China

Haifang Li,

Department of Radiology, Stony Brook University, Stony Brook, NY 11794 USA

Zengmin Yan,

Department of Radiology, Stony Brook University, Stony Brook, NY 11794 USA

John Fitzgerald, and

Department of Urology, Stony Brook University, Stony Brook, NY 11794 USA

Zhengrong Liang [Fellow, IEEE]

Department of Radiology, Stony Brook University, Stony Brook, NY 11794 USA

Hao Han: hanhao224@gmail.com; Qin Lin: qinlin.iris@gmail.com; Zhengrong Liang: jerome.liang@sunysb.edu

Abstract

To continue our effort on developing magnetic resonance (MR) cystography, we introduce a novel non-rigid 3D registration method to compensate for bladder wall motion and deformation in dynamic MR scans, which are impaired by relatively low signal-to-noise ratio in each time frame. The registration method is developed on the similarity measure of α -information, which has the potential of achieving higher registration accuracy than the commonly-used mutual information (MI) measure for either mono-modality or multi-modality image registration. The α -information metric was also demonstrated to be superior to both the mean squares and the cross-correlation

Correspondence to: Zhengrong Liang, jerome.liang@sunysb.edu.

⁺indicates the first two authors contributed equally to this work

metrics in multi-modality scenarios. The proposed α -registration method was applied for bladder motion compensation via real patient studies, and its effect to the automatic and accurate segmentation of bladder wall was also evaluated. Compared with the prevailing MI-based image registration approach, the presented α -information based registration was more effective to capture the bladder wall motion and deformation, which ensured the success of the following bladder wall segmentation to achieve the goal of evaluating the entire bladder wall for detection and diagnosis of abnormality.

Index Terms

Image registration; image segmentation; magnetic resonance; cystography; bladder cancer

I. Introduction

The awareness of bladder cancer has risen in the past decade. According to the latest statistics from American Cancer Society [1], urinary bladder cancer, after prostate, lung, and colon cancers, has been ranked as the fourth most common cancer among males in the United States. An estimated 74,690 new cases and 15,580 deaths of urinary bladder cancer are expected to occur in the United States in 2014. The five-year relative survival rate for bladder cancer is 70% if it is localized and decreases to 5% if it has metastasized. Therefore, it is critical to detect bladder cancer at earlier stages. Moreover, due to the high recurrence rate (as high as 80% [2]) after local tumor resection, an appropriate and timely follow-up procedure is extremely important.

Magnetic resonance (MR) cystography is a very promising, completely non-invasive procedure for detection and management of bladder lesions [3]–[5]. Since carcinoma tumors at early stages of penetration can be as small as less than 5mm [6], images with high spatial resolution and sufficient signal-to-noise ratio (SNR) are required to present the bladder wall, where bladder lesions reside. Unfortunately, MR scans though with satisfactory tissue contrast are usually prone to motion artifacts. Image registration is a sound approach to mitigate the motions, which ensures high spatial resolution and adequate SNR on the bladder wall. Following a good definition of the bladder wall, accurate segmentation of the inner and outer wall borders is another critical task to establish a precise three-dimensional (3D) model of the bladder for evaluation of the entire bladder by experts or radiologists [7]–[9]. Because normal thickness of the bladder wall is around 3 mm [10], abnormal wall thickness is generally recognized as a biomarker of potential lesions [10]–[12].

Our previous work has shown that retrospective motion correction (RMC) is a promising image processing approach for MR imaging of the moving, expanding, and deforming bladder wall [13], [14]. In this study, we further investigate the effect of selecting an effective image registration method for the RMC in bladder MR images. Mutual information (MI) made its entrance into the field of medical image registration in the mid-1990s [15], [16]. Previous studies [17], [18] have demonstrated that the MI is a very powerful and reliable information theory-based similarity measure for non-rigid or deformable image registration. However, the feasibility of using other information measures has also been

investigated for medical image registration applications. For instance, Wachowiak *et al.* [19] studied the feasibility of using Renyi and Havrda–Charvat entropies, respectively, as the similarity measure for rigid multi-modality image registration. Rougon *et al.* [20] proposed the f -information measure for image registration and then Pluim *et al.* [21] further investigated the performance of f -information in a rigid multi-modality registration framework. He *et al.* [22] and Bardera *et al.* [23] proposed to use the Jensen divergence as a similarity measure for solving their registration problems. Most of the aforementioned works focus on rigid registrations. As the urinary bladder is a hollow muscular and elastic organ, modeling the motion of bladder in a non-rigid fashion is expected to be more realistic for RMC in bladder MR images. In this paper, inspired by the tunable nature of the α -divergence, we presented a generalized information measure, α -information, as the similarity measure in a non-rigid registration framework.

The remainder of this paper is organized as follows. Section II presents the bladder MR data acquisition procedure, the details of the proposed α -information based image registration approach (called α -registration hereafter), and a brief review of the previously-developed bladder wall segmentation algorithm [9], which will be employed to extract the bladder wall from the registered volumetric image for 3D bladder model construction. Compared with the well-evaluated MI-registration approach [24], [25] as well as the commonly-used mean-squares registration (MS-registration) and cross-correlation registration (CC-registration) approaches, the gain of the proposed α -registration approach on the accuracy of constructing the 3D bladder model was demonstrated via both simulated phantom and real patient studies in Section III. This article ends with conclusion and discussion in Section IV.

II. Materials and Methods

A. Bladder MR Data

Most previous MR cystography studies [3], [7], [9–11] found that T_1 –/ T_2 – rather than PD-weighted scanning protocol is in favored for assessing the anatomical structures or pathologies in the urinary bladder. Compared with T_2 -weighed MR imaging, T_1 -weighted imaging enhances the desired signals or the bladder wall by lowering the lumen intensity as shown in Fig. 1(a), while with T_2 -weighted imaging the lumen intensity is enhanced and the partial volume effect from the high-intensity lumen to the low-intensity wall tends to “swallow” small pathological structures on the bladder wall [7], [10], see Fig. 1(b). Hence, in our study, T_1 -weighted MR imaging was primarily used to enhance the definition of the bladder wall borders.

Our MR cystography study was approved by the institutional review board at the Stony Brook University Medical Center. All subjects were examined on a clinical 3.0 Tesla whole body MR scanner with informed consent. The 3D T_1 high resolution isotropic volume excitation (THRIVE) pulse sequence was adopted with 0.9375mm isotropic, 224×224 axial-plane dimension, 21cm field of view (FOV), 1mm slice thickness, 84 or 95 slices, and TR/TE of 6.3/3.9ms. Prior to scanning, the subjects were instructed to empty the bladder and drink three cups (about 500 ml) of water aiming at making small structures of the bladder wall more visible. In addition, the bladder was slowly stretching by the urine inflow which serves as a natural contrast agent for the imaging. Three short-time dynamic scans were

acquired for each subject. The number of signal averages (NSA) equals 2 for each scan, and the acquisition time for a single short-time scan was approximately 2 minutes. For comparison purpose, a single long-time scan was acquired with NSA = 6, and the corresponding acquisition time is about the same as the total time of three short-time scans. The entire examination for each subject lasted about 40 minutes (including 15 minutes waiting after drinking water, 5 minutes subject preparation, and initial scanning for FOV positioning, followed by the above described T₁ scanning). During the data acquisition, patient voluntary motions were suppressed by instructing the subject to keep still and with the help of a belt motion suppression system. Then the major motions in this study were involuntary bladder motions due to the urine filling, intestines' peristalsis, and lung breath, *etc.*

B. Motion Correction by Dynamic Scans via α -Registration

Regarding the RMC strategy, instead of a single long-time scan averaged (on the signals) by the MR scanner, we aim to acquire multiple repeated short-time scans for the purpose of shifting bladder motion from intrascan into interscans. Then the interscan motions can be corrected by registering the short-time scans to a selected reference, and finally we can obtain a motion-corrected image by averaging all the registered images with the reference image. Based on the judgment from an experienced radiologist, the short-time scan with the best definition of the bladder wall was selected as the reference image for the RMC registration task. All other short-time scans (i.e., moving images) were registered to the reference image before averaging them. A flow chart of the RMC strategy for 3D dynamic scans registration is illustrated in Fig. 2. While the short-time scans are less affected by the motion, they have lower SNR on the bladder wall or the region of interest (ROI) of this study. Therefore, a suitable registration method must consider this aspect. More details on the proposed registration method are given below.

1) A Combined Global and Local Transformation Model—Motion correction for bladder MR images is the problem of determining transformations that capture the motion of every pixel or voxel in the ROI across the short-time acquisitions. As we know that urinary bladder is a hollow muscular and elastic organ, the motion of the bladder follows a non-rigid fashion, including the motion of the bladder as a whole and the deformation of bladder soft tissues. Therefore, global transformation models, such as rigid or affine transformation, are not sufficient to describe the non-rigid motion. In this study the registration task was adapted into a well-established framework using an affine transform followed a B -splines approach [26]. A combined transformation model, consisting of both global and local transformations, is desired and then adapted in this study. The combined transformation model is represented by

$$T(\mathbf{x}) = T_{\text{global}}(\mathbf{x}) + T_{\text{local}}(\mathbf{x}), \quad (1)$$

where $(\mathbf{x})$ represents a position in the 3D volumetric image. $T_{\text{global}}(\mathbf{x})$ denotes an affine transformation which has a degree of freedom of 12. This global term describes the overall

bladder motions, such as rotations, translations and scaling. $T_{local}(\aleph)$ represents a local transformation for capturing the local deformations of the bladder soft tissues. In this study, it is parameterized by the free-form deformation (FFD) model based on B -splines [25], [27], which has been proven to be powerful for modeling the 3D deformations. The basic idea of FFD model is to deform an image by manipulating a regular grid of control points that are distributed across the whole image. The deformation result of the grid is applied to generate a smooth and C^2 continuous transformation. The spacing of the control point grid determines the resolution of the control points. When a higher resolution of the control point grid is set, a finer local non-rigid deformation will be obtained at the cost of more intensive computation. The spacing setting would be determined according to the requirement of accuracy and computational efficiency. Let Φ represent an $n_x \times n_y \times n_z$ grid of control points $\{\Phi_{i,j,k}\}$ with uniform 3D spacing in the X-Y-Z coordinate system, the degree d of cubic B -splines is three. Thus, at any position $\aleph$, the FFD can be written as a 3D tensor product of 1D cubic B -splines

$$T_{local}(\aleph) = \sum_{l=0}^3 \sum_{m=0}^3 \sum_{n=0}^3 B_l(u) B_m(v) B_n(w) \Phi_{i+l, j+m, k+n}, \quad (2)$$

where $i = \lfloor x/n_x \rfloor - 1$, $j = \lfloor y/n_y \rfloor - 1$, $k = \lfloor z/n_z \rfloor - 1$, $u = x/n_x - \lfloor x/n_x \rfloor$, $v = y/n_y - \lfloor y/n_y \rfloor$, $w = z/n_z - \lfloor z/n_z \rfloor$ and B_l denotes the l -th basis function of the B -spline [27], [28],

$$B_0(u) = (1 - u)^3 / 6 \quad (3)$$

$$B_1(u) = (3u^3 - 6u^2 + 4) / 6 \quad (4)$$

$$B_2(u) = (-3u^3 + 3u^2 + 3u + 1) / 6 \quad (5)$$

$$B_3(u) = u^3 / 6. \quad (6)$$

In this study, we employ the FFD model to guide the displacement field. As illustrated through Fig. 3, after defining a grid of control points over the moving image, a displacement field for the control points is generated by image forces, and then the displacement of each voxel is generated by B-spline interpolation under the guidance of the control points.

2) α -Information Theoretic Measure—Since short-time scans in the studied dataset are with relatively low SNR, the information-theoretic measure based registration approaches would be preferred for our registration task. The advantage of such approaches is

that the image statistics are estimated using a large quantity of voxel samples, and therefore the image noise effects on the metrics can be attenuated.

In probability theory or information theory, the α -divergence is a function $D_\alpha(P, Q)$ that measures the discrepancy between two probability distributions. Given two discrete probability distributions $P = \{p_i | i = 1, 2, \dots, n\}$ and $Q = \{q_i | i = 1, 2, \dots, n\}$, the α -divergence is defined as:

$$D_\alpha(P, Q) = \frac{1}{\alpha(1-\alpha)} \sum_i [\alpha p_i + (1-\alpha)q_i - p_i^\alpha q_i^{1-\alpha}] = \frac{1}{\alpha(1-\alpha)} (1 - \sum_i \frac{p_i^\alpha}{q_i^{\alpha-1}}), \quad (7)$$

where $\alpha \in [0, 1]$ and $\sum_i p_i = \sum_i q_i = 1$. Some important properties of α -divergence can be summarized as:

1. $D_\alpha(P, Q)$ is convex with respect to both P and Q ;
2. $D_\alpha(P, Q) \geq 0$; and $D_\alpha(P, Q) = 0$ if and only if $P = Q$.

Moreover, some well-known divergences are special cases of α -divergence with different α settings. For example, as can be verified with L'Hopital's rule, α -divergence specializes to Kullback-Leibler divergence in the limit of α approaching 1. Hellinger divergence and Neyman's chi-square divergence are individually obtained when α equals 0.5 or 2 [29].

A variant of α -divergence in the information theory is the α -information measure, which applies only to two specific discrete probability distributions; namely, the joint probability distribution $\tilde{P} = (P_1, P_2) = \{p_{ij} | i, j = 1, 2, \dots, n\}$ of two random variables P_1 and P_2 and the product of their marginal probability distributions $\tilde{Q} = P_1 \times P_2 = \{p_i p_j | i, j = 1, 2, \dots, n\}$. Hence the α -information measure between two probability distributions P_1 and P_2 can be formulated as follows:

$$I_\alpha(P_1, P_2) = D_\alpha(\tilde{P}, \tilde{Q}) = \frac{1}{\alpha(1-\alpha)} (1 - \sum_{i,j} \frac{p_{ij}^\alpha}{(p_i p_j)^{\alpha-1}}), \quad (8)$$

where $\alpha \in [0, 1]$ and $\sum_i p_i = \sum_j p_j = \sum_{i,j} p_{ij} = 1$. Note that when α approaches 1, we have:

$$I_{\alpha=1}(p_1, p_2) = D_{\alpha=1}(\tilde{P}, \tilde{Q}) = \sum_{i,j} p_{ij} \log\left(\frac{p_{ij}}{p_i p_j}\right), \quad (9)$$

which is actually the definition of mutual information [17]. Similar to the properties of α -divergence, the α -information measure is convex and nonnegative, and it equals 0 if and only if P_1 and P_2 are mutually independent (i.e., $\tilde{p} = \tilde{q}$).

Information measures have been recognized as theoretically sound criteria for medical image registration [21]. The interpretation of evaluating such information is actually a measure of dependence between two images. The assumption is that, when the two images are correctly registered, the maximal dependence of the images is reached and the underlying information measure is maximized. Misalignment between the two images will decrease the value of this information.

When using the α -information as a similarity measure for image registration problems, the to-be-estimated transformation parameters have to be considered in the similarity measure formulation. Suppose the tunable parameter α has been preset, the similarity measure S between the reference image R and the moving image M can be expressed as a function of the transformation parameters μ , and the corresponding optimization problem can be formulated as:

$$\arg \max_{\mu} S(\mu) = \arg \max_{\mu} \left[\frac{1}{\alpha(1-\alpha)} \left(1 - \sum_{l,k} \frac{[p(l,k|\mu)]^{\alpha}}{[p_M(l|\mu)p_R(k)]^{\alpha-1}} \right) \right], \quad (10)$$

where $p(l, k)$, $p_M(l)$ and $p_R(k)$ are the joint, marginal moving, and marginal reference probability distributions, respectively. If let the H_R and H_M represent specified numbers of uniformly sized bins along the respective dimensions of the joint histogram of the reference and moving images, the integer values of l and k denote the indexes of the histogram bins ($0 \leq l < H_R, 0 \leq k < H_M$). Therefore, the B -spline Parzen window [30] can be employed to estimate the underlying image intensity distributions. From Eq. (10), it is noted that the distribution of moving image is dependent on the transformation model, so is the joint probability distribution, although the reference image is always fixed and independent of the transformation parameters. Therefore, an optimization method is needed to iteratively optimize the to-be-estimated transformation parameters.

3) Optimization Method for α -Registration—In our preliminary work on bladder MR image registration [31], the optimization problem was addressed using the Powell's conjugate directions method [32]. While it can generate reasonable results, the Powell's method is computational intensive and may attract to local maxima. Although the gradient-based optimization methods may also suffer from the local maxima problem, it is known that direct calculation of the gradient of the objective function has its advantage in computational efficiency. Therefore, we employ a quasi-Newton method based optimizer to solve the optimization problem. For the transformation parameters μ or a set of n -independent parameters $(\mu_1, \mu_2, \dots, \mu_n)$, the gradient of similarity measure $S(\mu)$ is given as:

$$\nabla S(\mu) = \left[\frac{\partial S}{\partial \mu_1}, \frac{\partial S}{\partial \mu_2}, \dots, \frac{\partial S}{\partial \mu_i}, \dots, \frac{\partial S}{\partial \mu_n} \right]. \quad (11)$$

A single component, S/μ_i of the gradient is computed by differentiating Eq. (10) with respect to a single transformation parameter. Straightforward derivation shows that the i -th component of the gradient is formulated as:

$$\frac{\partial S}{\partial \mu_i} = \frac{1}{\alpha(\alpha-1)} \sum_{l,k} \frac{A-B}{c}, \quad (12)$$

Where

$$A = \alpha [p(l, k|\mu)]^{\alpha-1} \frac{\partial p(l, k|\mu)}{\partial \mu_i} \quad (13)$$

$$B = (\alpha-1) [p(l, k|\mu)]^\alpha [p_M(l|\mu)]^{-1} \sum_k \frac{\partial p(l, k|\mu)}{\partial \mu_i} \quad (14)$$

$$C = [p_M(l|\mu) p_R(k)]^{\alpha-1}. \quad (15)$$

From Eq. (12), we can see that the calculation of each component of the gradient requires differentiating the joint distribution of the intensity values of the reference and moving images. Please refer to [25] for details on the estimation of marginal and joint distributions as well as the calculation for the partial derivative of the joint distribution.

In this study, we employ the limited memory, quasi-Newton optimization package – the L-BFGS-B (limited-memory Broyden-Fletcher-Goldfarb-Shannon optimization with simple Bounds) [33] for the optimization calculation. Of note, the L-BFGS-B has its advantage here because the moderate requirement of memory makes it well suitable for the optimization problems with a large number of variables. Instead of estimating the entire Hessian matrix as in the commonly-used Newton-Raphson optimization method, a low-rank approximation is calculated which allows linear convergence rates. Another advantage of using the L-BFGS-B method is that it allows bound constraints on the independent variables. In order to avoid local maxima and to reduce the computation time, a hierarchical multi-resolution optimization scheme is used in the non-rigid registration stages.

The process of moving image alignment can be divided into two registrations. First, the global affine transformation, that contains only rigid body parameters, is optimized. The resultant affine transformation is then used to initialize a low-resolution deformation field with a coarse grid of FFD control points. Then the local deformations are gradually refined by increasing the resolution of control point grid distributed across the moving images. In each resolution level, the optimal set of deformation parameters is reached when the

similarity measure between moving images and the reference image is maximized. The set of optimal deformation parameters at a coarser resolution level is up-sampled to initialize the transformation parameters for the next resolution level. The process of applying α -registration in a multi-resolution fashion can be summarized by Fig. 4.

C. Metrics for Registration Method Evaluation

The proposed α -registration method was evaluated through both phantom and patient studies. For simulated phantom studies with known ground truth, we employed root mean squared error (RMSE) and correlation coefficient (CC) as quantitative metrics to assess the consistency of the registered image to the ground truth. These two metrics can be calculated as follows.

$$\text{RMSE} = \sqrt{\frac{1}{n} \sum (I_{\text{GT}} - I_{\text{Reg}})^2} \quad (16)$$

$$\text{CC} = \frac{\sum (I_{\text{GT}} - \bar{I}_{\text{GT}})(I_{\text{Reg}} - \bar{I}_{\text{Reg}})}{\sqrt{\sum (I_{\text{GT}} - \bar{I}_{\text{GT}})^2 \sum (I_{\text{Reg}} - \bar{I}_{\text{Reg}})^2}} \quad (17)$$

In Eqs. (16) and (17), $\bar{I}_{\text{GT}}$ and $\bar{I}_{\text{Reg}}$ represent the average intensity of the ground truth image and the average intensity of the registered image, respectively. RMSE and CC can provide direct and quantitative measures of the performance of a registration method. Smaller RMSE and larger CC usually indicate better registration accuracy.

Due to the lack of ground truth for real patient studies, we alternatively adopted the SNR of the bladder wall as a quantitative metric to evaluate the quality of the motion corrected image. Under the guidance of an experienced radiologist, we manually outlined the bladder wall ROI on each motion-corrected MR image. The signal is estimated as the averaged intensity of bladder wall voxels, and the noise is estimated as the standard deviation of voxel intensities of the bladder lumen inside the wall. Then the SNR of the bladder wall can be calculated by

$$\text{SNR} = \mu_{\text{wall}} / \sigma_{\text{lumen}} \quad (18)$$

In addition to direct quantitative measure of the registration accuracy, we are also interested in assessing the gain of the proposed α -registration method to the automatic and accurate segmentation of the bladder wall for various clinical tasks. In this work, the automatic extraction of the bladder wall is performed via a unified image segmentation approach, as outlined below.

D. A Unified Bladder Wall Segmentation Method

In order to evaluate the gain of the proposed α -registration method for motion compensation, the motion-corrected image was subsequently segmented for the inner and outer borders of the bladder wall. The segmentation was performed by a unified maximum *a posteriori* expectation-maximization (MAP-EM) approach with coupled level-set (CLS) constraints as the *a-priori* penalty on the image data statistics or likelihood [9]. First, the inner border was automatically segmented via the evolution of inner level set surface inside the bladder lumen. Then, the outer border was segmented by expanding the outer level set surface outwards from the inner border surface. Finally, both borders were refined by an interleaved operation of voxel classification via MAP-EM and surface evolution via CLS.

III. Experimental Results

In order to evaluate the effectiveness of the proposed α -registration method, we compared it with three commonly-used registration methods including the MI-registration, the MS-registration, and the CC-registration via both simulated phantom and real patient studies. Note that all the registration algorithms were implemented under the Insight Toolkit platform [34]. In simulated phantom studies, the method comparison was conducted by solving either mono-modality or multi-modality image registration problems. While in real patient studies, T_1 -weighted MR cystography was utilized as a clinical task to assess the effectiveness of the proposed α -registration method for the motion correction of dynamic bladder MR scans.

A. Simulated Phantom Studies

In the phantom study on mono-modality image registration, three $128 \times 128 \times 128$ digital images were simulated to mimic the entire process of the RMC for dynamic bladder MR images. Since urinary bladder generally appears as a hollow muscular and distensible organ, we simplified its shape as either a hollow ellipsoid or a hollow spheroid. As shown in Fig. 5(a), the first volume of hollow ellipsoid shape represents a “bladder” of half filling state. The major semi-axis of inner ellipsoid (i.e., the inner surface of “bladder wall”) is set to be 30 units, and the other two minor semi-axes are both set to be 20 units. While the major semi-axis for the outer ellipsoid is 35 units and the minor semi-axes are 25 units. The image intensity of “bladder wall” is set to be 1000 and the intensity for inside “lumen” and outside “air” is set to be 500. In order to make the phantom to be more realistic, the partial volume effect (PVE) was added to both sides of the “bladder wall” so that the intensity gradually changes from 1000 to 500 within five layers of voxels. Finally, the white noise with a standard deviation of 20% of the voxel intensity, and the Gaussian smoothing filter with a convolution kernel size of 3 were imposed on the entire image. Similarly, the second and third volumes were generated with the same configurations except the shape of the phantom. The second volume in Fig. 5(b) represents the “bladder” with medium filing as time goes on, and the radius of inner and outer spherical surface is 35 and 40, respectively. While in the third phantom in Fig. 5(c) represents the “bladder” with full filling, and the radius of inner and outer spheroid is 40 and 45, respectively. This series of volumes mimics the change of the bladder shape given the condition that the subject has been asked to drink a bottle of water prior to the scanning.

In this mono-modality phantom study, the second “bladder” phantom with medium filling was selected as the reference image, and the corresponding image without random noises as shown in Fig. 5(d) was set as the ground truth for method evaluation. Table I summarizes the α -registration results by registering the first and third volumes to the second volume. Given the ground truth, we can calculate the RMSE and CC metrics for α -registration with different α values. When tuning the value of α between 0 and 2, we observed that the α -registration achieved the smallest RMSE and the largest CC when α equals 0.2, and it outperformed the MI-registration approach (i.e., $\alpha = 1$). The corresponding MI-registration and α -registration results are shown in Fig. 5(g) and Fig. 5(h), respectively. It is noted that the α -registration severely deteriorated when α equals 0.01 or 0.1. Moreover, we also observed that the CC-registration failed to register the three volumes as shown in Fig. 5(f). The MS-registration, in comparison with the α -registration, showed slightly better performance in terms of both RMSE and CC as listed in Table III, though the difference between the registered images is not evident as can be seen from the MS-registration result in Fig. 5(e).

We further conducted another phantom study, which demonstrated the inferior performance of both CC-registration and MS-registration methods in the multi-modality registration scenario. Two $128 \times 128 \times 128$ volumes were simulated to mimic both the T_1 - and T_2 -weighted bladder MR images. The T_1 -weighted MR image in Fig. 6(b) was generated in a similar manner as in the mono-modality phantom study. However, as shown in Fig. 6(a), the “lumen” and “air” in T_2 -weighted image were enhanced with an image intensity of 1000, while the intensity for “bladder wall” is decreased to 500. It is noted that we particularly embedded a spherical “tumor” of radius 10 inside the “bladder wall”. In T_2 -weighted image, the radius for the inner and outer bladder wall surface is 35 and 40, respectively. The T_1 -weighted image was enlarged in shape with inner radius of 45 and outer radius of 50. Same as the previous study, five layers of PVE, 20% noise and Gaussian smoothing were imposed on all simulated images.

In this phantom study on multi-modality registration, the T_2 -weighted image was used as the reference image, and the corresponding ground truth is given in Fig. 6(c). The accuracy of α -registration with different α values are summarized in the first two rows of Table II. As the value of α was tuned between 0 and 2, we observed that the optimal α -registration with the smallest RMSE and the largest CC was achieved when α equals 0.8, and it outperformed the MI-registration (i.e., $\alpha = 1$) in terms of both metrics. Fig. 6(f) and Fig. 6(g) show the registered images from MI-registration and α -registration, respectively. In addition, we observed that the α -registration severely deteriorated when α is near 0 or larger than 1.4. The last three rows in Table II demonstrate the convergence performance of α -registration. The number of iterations can range from 10 to 236 depending on the value of α , and dividing the change of cost function value we obtained the speed of the convergence for different settings of the α value. The fastest convergence of α -registration was observed when α equals 0.1 or 0.2. Furthermore, Table III summarizes the performance of the commonly-used MS-registration and CC-registration approaches. The abnormally high RMSE and negative CC indicated the poor performance of these two registration methods in this multi-modality registration scenario. The registered image from MS-registration is shown in Fig. 6(d), and we can see that the image intensity was largely influenced by the T_2 -

weighted reference image and the “tumor” area was severely distorted. While the CC-registration result in Fig. 6(e) kept the intensity information from the T_1 -weighted image, it failed to converge to the optimal solution and the “tumor” was also distorted.

B. Real Patient Studies

The presented α -registration approach was further evaluated on eight patient datasets (7 males and 1 female) undergoing clinical bladder MR imaging. The ages of the studied subjects were 65 ± 11 (mean $\pm$ standard deviation) years of old. Each MR scan consists of 84 or 95 image slices covering the bladder volume. Before registration, we manually defined a sufficiently large cubic ROI enclosing the whole bladder. (It is noted that all MR T_1 -weighted images were directly registered without correction for field inhomogeneity because this effect is not obvious visually). We typically started the non-rigid registration with a coarse control point mesh of 20 voxels grid spacing and ended it with a finer control point mesh of 15 voxels grid spacing on an image slice. Both the α -information and the mutual information were computed using 1) number of spatial samples = 20% of total voxels, 2) number of histogram bins = 32, 3) termination criterion with respect to the projected gradient = 10^{-7} , and 4) maximization number of iterations per resolution = 2000. In particular for α -registration, some discrete α values between 0 and 3 were investigated. By visual judgment, we found good registrations on all the subjects were achieved when α value was less than 2, and when α is larger than 2 the α -registration showed deteriorating results as α increased. Hence for the registration task in this study, the value of α was confined between 0 and 2.

1) Evaluation of Registration Quality by Quantitative Metrics—To correct motions among three short-time dynamic scans, the short-time scan with the best definition of the bladder wall was chosen as the reference image. The other two short-time scans were moving images that ought to deform to the reference. Then the deformed moving images together with the reference image were averaged to generate the motion-corrected average image. In order to demonstrate how the population-wise optimal α value was selected for the proposed α -registration approach, we summarized, in Table IV, the registration of three short-time scans for each patient study with the value of α varying from 0 to 2. When using the SNR of the bladder wall as an evaluation metric, it can be observed that the optimal α value for α -registration may be different for different patient studies, and the optimal α -registration always outperformed the MI-registration (i.e., when α approaches 1.0) for all the patient studies. In order to determine the population-wise optimal α value from our patient studies, we further conducted statistical hypothesis testing to test whether the α -registration with a specific α value can significantly enhance the SNR of bladder wall compared with the widely-used MI-registration approach. As shown in Table V, the Wilcoxon signed rank test indicated that the α -registration with a fixed α value of 0.6 significantly (one-sided p -value=0.004) outperformed the mutual information approach in terms of the SNR of bladder wall. While the improvement from α -registration with other α values was not statistically significant.

Furthermore, the α -registration with an optimal α value of 0.6 was compared with the commonly-used MS-registration or the CC-registration method. Table V summarizes the

SNR of bladder wall from either MS-registration or CC-registration for each patient study. The Wilcoxon signed rank test indicated that the α -registration with α equals 0.6 significantly outperformed (one-sided p -value=0.039) the MS-registration at a significance level of 0.05. However, there was no significant difference between the α -registration (with $\alpha=0.6$) and the CC-registration. In addition, the average runtime for different registration methods was summarized in Table VI. Note that the implementation was based on a standard PC with 2.20GHz processor and 4GB memory. We can see that the runtimes for two information measure based methods were comparable while the runtimes for the conventional MS- and CC-registration methods were relatively less.

Fig. 7 shows examples of three dynamic bladder MR scans for each patient study as well as the corresponding RMC results from MS-registration, CC-registration, MI-registration, and α -registration with $\alpha=0.6$, respectively. We can see that the SNR of the whole bladder was significantly improved after averaging three dynamic scans, and the definition of the bladder wall was enhanced after motion correction. By visual inspection of the motion-corrected bladder wall in Fig. 7, we observed that, in comparison to the MS-registration, the other three registration methods clearly generated a sharper definition of the bladder wall where severe motion artifacts exist.

In addition, we compared the quality of the registered image from the proposed α -registration based RMC approach with the long-time MR scan acquired from the commercial scanner. The bladder wall edges in the long-time scans of Fig. 8(a)–(c) were severely blurred, while the bladder walls in the motion-corrected average images, as shown in Fig. 8(d)–(f), were more clearly defined in terms of edge details and wall uniformity. This observation indicated that the developed RMC strategy is obviously advantageous to the long-time scanning for bladder MR image acquisition.

2) Evaluation of Registration Quality by an Observer Study—As a means of evaluating the registered image quality for clinical usage, five experts were asked to score on the definition of the bladder wall from two different averaging methods: (1) the motion-corrected average by the α -registration and (2) the motion-corrected average by the MI-registration. For each subject, two volume images were obtained by the two different averaging methods, respectively. Experts performed evaluation tasks by simultaneously observing the two averaged volumes of each subject slice by slice. This expert evaluation study was a blinded process, because we set the display order of motion-corrected images to be random and the experts had no knowledge of which method was used for each display. By comparing the relative definition of the bladder wall, five experts were instructed to give scores between 1 (worst) to 5 (best) on each display.

Fig. 9 illustrates the pair-wise scatter plot of expert scores in comparing the motion-corrected image from α -registration against the image from MI-registration. Jittering technique was employed to assure the visualization of overlapped score pairs. We can see that most data points (about 70%) fell above the 45 degree concordance line, which suggests the α -registration tends to have a higher score than the MI-registration. As a compliment to the straightforward analysis via scatter plots, statistical analysis was applied to the scores from the five experts on the eight patient subjects. We employed a linear mixed effect model

[35], [36] to test the statistical significance of each effect of interest. The considered fixed effects included two main effects of registration method and selected expert as well as their interaction effect, while the patient subject effect is random. Statistical hypothesis testing showed that the expert scores on α -registration was significantly higher than the scores for MI-registration (one-sided p -value < 0.0001), and the corresponding 95% confidence interval of the score difference was (0.66, 1.39). The expert-by-method interaction effect was not significant (p -value = 0.697), which can be concluded that different experts were in agreement in terms of ranking the two methods.

3) The Effect of Registration on Bladder Wall Segmentation—Since our goal in developing MR cystography technology is to extract the bladder wall accurately. For that goal, we have developed a sound 3D automatic bladder wall segmentation algorithm [9]. This algorithm was applied to the motion-corrected images from the baseline method (i.e., MI-registration) and the proposed approach (i.e., α -registration), respectively. The outputs of the segmentation are the outlines of the inner and outer surfaces of the bladder wall. Fig. 10 shows exemplary 3D bladder wall segmentation results via 2D axial views. Given the same bladder wall segmentation algorithm, we assume that a better motion-corrected image should lead to better bladder wall segmentation in a point-by-point fashion. As we can see from Fig. 10, compared with the wall segmentation resulted from motion-corrected image of the baseline registration method of mutual information, the proposed α -registration approach led to comparable or better segmentation of the bladder wall, which implied better edge details were preserved that facilitated our automatic segmentation algorithm. It is noted that although some registered images in Fig. 10 look similar their difference in segmentation was mainly due to the cumulative contribution from the entire volume as our segmentation algorithm was performed in a 3D manner. The most experienced radiologist among the above five experts was asked to examine and give scores on the segmented bladder wall for each of our studied dataset. The expert scores ranged from 0 (worst) to 4 (best) based on the segmentation accuracy. Student's paired t-test indicated that the scores on the α -registration based segmentation results are significantly higher (one-sided p -value = 0.025) than the baseline method based segmentation results at a significance level of 0.05, and the 95% confidence interval of the score difference is (0.003, 1.247). Therefore, we can conclude that the presented α -registration approach can outperform the MI-registration approach in terms of increasing the bladder wall segmentation accuracy or extracting an accurate bladder wall model for clinical evaluation of the entire wall.

IV. Conclusion and Discussion

In this paper, we presented a non-rigid image registration approach using the α -information measure. With respect to its application for MR cystography, the intrinsic bladder motion in short-time dynamic MR scans was compensated using the proposed α -registration method. As a pilot study, the registration method was validated on only eight patients under the T_1 -weighted MR imaging modality. More datasets from patients or volunteers shall be sought as this MR cystography research moving on and included into our current database to evaluate the methodology. Other MR scanning protocols or pulse sequences shall be examined, e.g.

T₂-weighted MR imaging modality, as additional information to improve the wall extraction and perform clinical wall evaluation for tumor detection and staging quantification [37].

Our experimental results demonstrated that the involuntary bladder wall motion can be effectively captured by the RMC strategy via averaging several short-time dynamic scans rather than acquiring a long-time scan. This observation is consistent with our previous studies reported in [13], [14]. Furthermore, with respect to comparing different methods for dynamic scans registration, the presented α -registration approach outperformed the well-known mutual information approach in terms of RMSE/CC for phantom studies and in terms of SNR of the bladder wall for patient studies. In particular, statistical test based on our patient studies revealed that the α -registration, when tuning the value of α between 0 and 2, achieved significantly better performance than the mutual-information when α equals 0.6. Both phantom and patient studies demonstrated that the α -registration performance was prone to decrease as α approaches 0 and deteriorated dramatically when the value of α was greater than 2. Regarding the computing time, the α -registration is computationally comparable to the MI-registration as both methods used the L-BFGS-B optimization algorithm and both were implemented using the ITK package. Regarding the clinical impact of the proposed registration method, human observer studies on the definition of the bladder wall and computer observer studies by segmenting the wall in a point-by-point fashion confirmed a noticeable gain by using α -information rather than the well-known mutual information as a similarity measure for registration.

We also compared the presented information measure based similarity metric with two commonly-used similarity metrics. Our multi-modality phantom study demonstrated that the MS-metric or the MS-registration failed to register images of different modalities. This metric relies on the assumption that image intensity representing the same homologous point must be the same in both reference and moving images. Therefore the use of this metric is limited to images obtained using the same imaging modality. Also note that any linear changes in the intensity result in a poor match value. This was confirmed by the poor performance of MS-registration for bladder motion correction in our patient studies. The other commonly-used metric under comparison is the CC-metric or the CC-registration. Although this metric showed a similar performance to the information measure based metrics in our patient studies, the CC-registration failed in phantom studies on either mono-modality or multi-modality registration problems. One possible reason is that in the use of CC-metric is restricted to images of the same modality, and the CC-registration may even fail in the mono-modality scenario because this metric has a relatively small capture radius as it produces a cost function with sharp peaks.

Of note, it has been observed that the success of the information-based similarity measures is highly dependent on the modalities being registered [19], [21]. With respect to the motion correction of dynamic scans in MR cystography, our experiments showed that the commonly-used mutual information approach, as a special case of α -registration when α approaches 1, often cannot yield the optimal performance, while $\alpha=0.6$ is likely to be a population-wise optimal α value for the proposed α -registration approach. On the other hand, whether the optimal α value exists for multi-modality applications is still an open question that cannot be concluded from the results of this study. A generally applicable

value of α may sacrifice its adaptation for each registration problem. Establishing a similarity measure based on the α -information gives us more freedom to choose the patient-specific similarity metrics by adjusting the value of α . Minimizing a similarity measure over a tractable family of divergences tends to seeking a shorter “distance” between the reference image and the moving image, and hence improving the registration accuracy. At the same time, the associated intensive computation may arise when searching for the optimal α value from a set of possible choices. A promising future direction is to adaptively adjust α value in the similarity metric during a single course of the optimization. It may prove beneficial to start registration with $\alpha = 1$ (i.e., mutual-information) and to adjust α value in subsequent iterations for improved accuracy [21]. In order to implement this adjustment, a careful selection of the optimization algorithm is desirable to provide enough feedback for adaptation of the value of α .

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Fig. 1. Axial view of both (a) T_1 -weighted and (b) T_2 -weighted bladder MR images. The bladder wall is more distinguishable in the T_1 - rather than the T_2 -weighted image, especially when comparing the upper side of the bladder wall in this example.

Fig. 2.
Flowchart of the RMC strategy for dynamic scans.

Fig. 3.
Illustration of B -spline-based FFD on a 2D grid of control points.

Fig. 4.

Flowchart of the α -information based registration in a multi-resolution fashion. I_R and I_M are the reference and moving images, respectively. $\mathbf{x}$ is any geometric location in the reference image, $\boldsymbol{\mu}$ is the set of transformation parameters. p , p_M , p_R , and ∇p are the joint, marginal moving, marginal reference, and gradient of the joint distribution, respectively. S and ∇S are the values of α -information and its gradient, respectively, between the two images. L-BFGS-B is a quasi-Newton method-based optimizer to search the parameter space of $\boldsymbol{\mu}$.

Fig. 5.

Axial view of a series of simulated mono-modality phantoms. (a) The ellipsoid phantom to mimic a bladder of half filling state; (b) the spheroid phantom to mimic a bladder with medium filling; (c) the spheroid phantom to mimic a bladder with full filling; (d) the ground truth for the phantom shown in (b) which is selected as the reference; (e) the MS-registration result; (f) the CC-registration result; (g) the MI-registration result; (h) the result from α -registration with $\alpha=0.2$.

Fig. 6.

Axial view of simulated multi-modality phantoms. (a) The reference phantom to mimic T2-weighted bladder MR image; (b) the moving phantom to mimic deformed T1-weighted bladder MR image; (c) the ground truth of registering phantom in (b) using the phantom in (a) as reference; (d) the MS-registration result; (e) the CC-registration result; (f) the MI-registration result; (g) the result from α -registration with $\alpha=0.8$.

Fig. 7.

Retrospective motion correction for dynamic bladder MR scans. (a)-(c) Three short-time dynamic scans and the first one serves as the reference image; (d) averaged image from MS-registration; (e) averaged image from CC-registration; (f) averaged image from MI-registration; (g) averaged image from α -registration with α equals 0.6.

Fig. 8.
(a)-(c) Long-time acquisitions (i.e., k -space average); (d)-(f) the corresponding motion-corrected average of three short-time scans via α -registration.

Fig. 9.

Scatter plot of expert scores on the definition of the bladder wall resulted from motion correction by α -registration against by MI-registration. The p -value is based on statistical testing of score differences from two methods. With p -value < 0.0001, it can be concluded that the α -registration obtained significantly higher score than the MI-registration.

Fig. 10.

3D bladder wall segmentation results illustrated via 2D axial views (yellow curves). (a) Motion corrected image by MI-registration; (b) segmented bladder wall resulted from deformed image of MI-registration; (c) motion corrected image by α -registration; (d) α -registration based bladder wall segmentation.

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Table I
Accuracy of Alpha-Registration with Different Alpha Values in Mono-Modality Phantom Study

Metric	α	0.01	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0 (MI)	1.2	1.4	1.6	1.8	2.0
RMSE		81.373	80.575	20.309	20.376	41.587	30.328	30.714	30.223	37.513	23.242	25.575	27.451	28.713	29.914	29.931	28.596
CC		0.9166	0.9150	0.9931	0.9931	0.9746	0.9866	0.9863	0.9866	0.9792	0.9918	0.9905	0.9893	0.9885	0.9877	0.9877	0.9887

Entries in **bold** indicate that the optimal α -registration result with the smallest RMSE and the largest CC was achieved when $\alpha=0.2$.

Table II
Accuracy and Convergence of Alpha-Registration with Different Alpha Values in Multi-Modality Phantom Study

Metric	α	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0(MD)	1.2	1.4	1.6	1.8	2.0	
RMSE		297.37	34.976	35.307	32.059	31.809	31.132	30.801	30.518	30.468	30.705	32.312	30.750	31.596	291.42	313.99	315.14
CC		-0.202	0.9806	0.9804	0.9836	0.9838	0.9844	0.9847	0.9850	0.9851	0.9850	0.9840	0.9850	0.9845	-0.008	-0.146	-0.155
# Iteration		10	58	80	97	77	85	105	77	118	114	116	110	236	154	125	116
CostFin		0.0284	1.2956	1.2979	0.9667	0.7694	0.6607	0.5977	0.5559	0.5403	0.5412	0.5351	0.6336	0.7958	0.2619	0.2427	0.2362
Cvg.Speed		0.0028	0.0223	0.0162	0.0100	0.0100	0.0078	0.0057	0.0072	0.0046	0.0047	0.0046	0.0058	0.0034	0.0017	0.0019	0.0020

Entries in **bold** indicate the most accurate α -registration achieved when $\alpha=0.8$, and the fastest convergence was observed when $\alpha = 0.1$ or 0.2 .

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Table III
Accuracy of Two Conventional Registration Methods in Simulated Phantom Studies

Method	Study	Mono-Modality		Multi-Modality	
		RMSE	CC	RMSE	CC
MS-Registration		19.629	0.9936	452.82	-0.9335
CC-Registration		59.755	0.9556	275.44	-0.2788

Table IV
Summary of Alpha-Registration Performance in Terms of SNR of Bladder Wall for Patient Studies

ID	α	0.01	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0 (MI)	1.2	1.4	1.6	1.8	2.0
AB		11.446	12.218	10.746	10.735	11.101	11.197	11.279	11.150	11.036	11.118	11.243	11.162	11.300	11.386	12.062	11.431
BB		15.848	15.809	15.778	16.552	15.243	15.874	16.109	15.724	15.305	15.669	15.587	15.738	15.238	15.931	16.173	15.703
FB		9.466	9.544	9.206	9.733	9.793	9.901	10.007	9.884	9.550	9.627	9.665	10.082	9.695	9.383	9.397	9.262
FH		8.628	8.432	8.165	9.619	10.046	9.829	10.134	9.301	9.338	9.356	9.647	9.263	9.578	8.782	8.774	8.753
GF		13.956	13.795	12.558	12.423	12.866	12.958	12.962	12.963	13.110	12.550	12.907	12.796	12.860	14.238	13.180	12.505
GG		11.289	12.053	12.089	12.588	12.558	12.217	12.545	12.706	12.361	12.767	12.433	12.594	12.176	12.176	10.774	9.237
LC		7.670	7.662	7.400	7.357	7.420	7.445	7.216	7.119	6.995	7.000	7.037	6.650	6.707	7.028	7.799	7.574
MM		7.952	8.168	8.291	8.478	8.695	9.115	9.142	9.240	9.176	9.182	8.910	9.068	8.967	8.540	8.249	7.827
<i>p</i> -value		0.629	0.473	0.973	0.578	0.422	0.055	0.004	0.191	0.875	0.680	N/A	0.422	0.926	0.680	0.629	0.926

Entries in **bold** indicate the optimal α -registration result with the highest SNR of bladder wall for each patient study. The last row summarizes the p -values for hypothesis testing that α -registration statistically outperforms MI-registration, and the p -value in **bold** indicates the α -registration with $\alpha=0.6$ significantly outperformed the MI-registration at a significance level of 0.05.

Table V
Performance of Two Conventional Registration Methods in Patient Studies

Method	Patient ID	AB	BB	FB	FH	GF	GG	LC	MM	p-value
MS-Registration		10.565	16.029	9.116	9.713	13.181	11.923	7.602	7.749	0.039
CC-Registration		11.748	16.214	9.353	8.973	14.476	12.125	7.501	8.385	0.371

Entries for each patient study are the SNR of the bladder wall. The last column shows the p-value for hypothesis testing that α -registration with $\alpha=0.6$ statistically outperforms the conventional registration method, and the p-value in **bold** indicates the MS-registration was significantly outperformed at a significance level of 0.05.

Table VI
Average Runtime (Seconds) of Different Registration Methods in Patient Studies

α-Registration ($\alpha = 0.6$)	MI-Registration	MS-Registration	CC-Registration
417	431	69	264