Automated Registration of Sequential Breath-Hold DCE-MRI Images

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Introduction: Dynamic Contrast Enhanced (DCE)-MRI has emerged as a valuable investigational tool for assessing tumor microcirculatory changes following therapy using anti-angiogenic or anti-vascular agents. In the clinical setting, DCE-MRI images of the chest or abdominal region are typically acquired during sequential breathholds by the patient, following injection of a Gadolinium (Gd)-based MRI contrast agent. Pixel-by-pixel pharmacokinetic (PK) analysis of DCE-MRI images can yield physiologically meaningful model parameters which contain quantitative information pertaining to tumor microvascular leakage, vascular volume fraction and perfusion [1,2]. The expectation is that changes in these PK model parameters will serve as imaging biomarkers of tumor response to anti-angiogenic and anti-vascular therapies. Such pixel-by-pixel PK analysis of DCE-MR images is extremely susceptible to misregistration of successive images in the DCE-MRI series arising from inconsistent breath-holding by the human subjects. Hence, it is imperative to spatially register DCE-MR images prior to PK analysis. Fast and efficient non-rigid registration schemes are therefore of great interest in this setting. We introduce a novel method for DCE-MRI registration in which images at adjacent time-samples are registered sequentially. The driving assumption behind this Sequential Elastic Registration (SER) method is that intensity variations between adjacent time-sample images are relatively small. Thus, a general-purpose non-rigid registration algorithm which explicitly incorporates local changes in brightness and contrast would be expected to perform well at registering adjacent time-sample images. Additionally, we have employed a 3-D rigid-body registration with mutual information similarity metric as a pre-processing step for correcting global registration errors. We have compared the performance of SER to two schemes previously published by other groups. The first technique is a PK model-driven non-rigid registration (PMDR) scheme, based on an algorithm proposed by Buonaccorsi et al. [3]. The second technique is the progressive principal component registration (PPCR) scheme proposed by Melbourne et al. [4]. A novel DCE-MRI phantom data series, created by adapting the work reported elsewhere [5] is used to compare the performance of the three registration schemes. The best-performing algorithm, in terms of registration accuracy in the DCE-MRI phantom, was then used to register DCE-MRI images collected from human subjects in clinical studies.

Methods: A software phantom of DCE-MRI images was created by adapting the work reported previously [5]. Briefly, mean values of K^{trans}, v_e, v_p and pre-contrast T1 were assigned to 14 hand-segmented tissue types based on a poll of values reported in the literature as well as from our own measurements. These 4 parameters were treated as independent, and their values were distributed randomly among the pixels within a tissue type by assuming a normal distribution with standard deviation of 5% about the mean (**figure 1**). The phantom dataset comprised of 5 slices and 30 time samples, and these were mathematically misregistered using 3 different polynomial functions. Given the known "ground truth" values of the PK model parameters, a quantitative comparison of the performance of the SER, PMDR and PPCR in correcting the misregistration was possible.

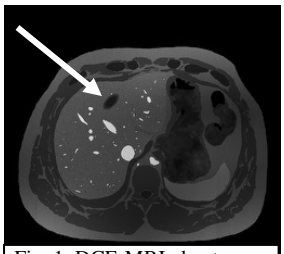

Fig. 1: DCE-MRI phantom (arrow marks tumor).

DCE-MRI images were collected from 12 volunteer subjects with advanced solid tumors who participated in two unrelated cancer clinical trials. Each subject was imaged twice (baseline & post-therapy). Target lesion(s) > 1 cm, with well-defined margins and without significant necrosis, were identified by experienced radiologists at each participating site. Metastatic lesions were imaged in a variety of locations, including liver, uterus, lung and chest wall. Subjects were imaged under repeated "held exhalation" breath-holding. DCE-MRI was performed using a GRE sequence with TR = 43 ms & α=50º. Gadolinium (0.1 mmole/Kg) was administered by power-injection at 4 mL/s after 2-4 pre-contrast GRE images had been acquired, and chased with 20 mL saline.

The 3 registration schemes are depicted in **figure 2**. In the SER scheme, adjacent time-sample images were registered directly using a general purpose elastic registration scheme [6]. For example, the image at the first time-sample (t_0) is used as the template against which the image at the next time-sample (t_1) is registered. The registered t_1 image is then used as the template against which the image at the next time-sample (t_2) is registered, and so on. This process was carried out sequentially through to the final time-sample. While SER is non-iterative, PMDR & PPCR are both iterative schemes. Three quantitative metrics were employed to evaluate the performance of the 3 registration schemes on the deformed phantom data: the mean PK parameter values post-registration *vs.* the known ground truth values, the mean squared error (*MSE*) between the actual and the fitted concentration of Gd over time, and multiple linear correlation coefficient values obtained from the PK model fitting.

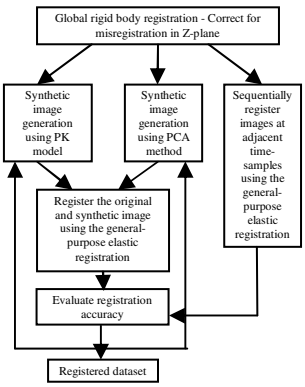

Fig. 2: PMDR, PPCR & SER.

Results: For the phantom dataset, post-deformation, the average deviations in the PK parameter values in tumor core and tumor rim were as large as 196% relative to the ground truth values. All three registration schemes satisfactorily restored the PK values (average deviation of 5.7 % from the ground truth) in larger ROIs like muscle, spleen and liver. In the case of tumor core and tumor rim, the SER scheme was able to restore the values closer to the ground truth (average deviation of 14.7 $\pm$ 7.7 % from the ground truth) when compared to PPCR (average deviation of 39.5 $\pm$ 24.67 % from the ground truth) and PMDR (average deviation of 39.2 $\pm$ 15.85 % from the ground truth). For muscle rim, the average deviation post-deformation was 43.07 $\pm$ 17.07 % from the ground truth. SER was able to restore the PK values closer to ground truth (average deviation of 4.23 $\pm$ 2.11 % from the ground truth) when compared to PPCR (average deviation of 33.65 $\pm$ 30.45 % from the ground truth) and PMDR (average deviation of 17.82 $\pm$ 16.32 % from the ground truth). SER was therefore selected as the algorithm for registering clinical DCE-MRI datasets. **Figure 3** depicts absolute difference images demonstrating successful registration with SER: **(a)** unregistered post-contrast image; **(b)**, **(c)** and **(d)** are SER registered post-contrast images at the initial, middle and late enhancement stages; **(e)**, **(f)**, **(g)** and **(h)** are the corresponding difference images with the preceding time-sample image in the DCE-MRI series. All the difference images were scaled between 0-255 using the same scaling factor. A qualitative comparison of panels **(f)**, **(g)** and **(h)** against panel **(e)** illustrates that SER is able to significantly improve timepoint-to-timepoint registration, particularly in the liver and tumor pixels. A significant reduction in the *MSE* metric was also obtained for 56 out of 63 tumor ROIs in the 12 subjects.

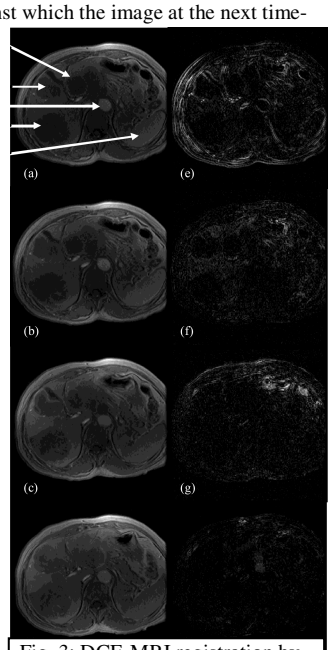

Fig. 3: DCE-MRI registration by SER. Arrows point to the aorta, spleen & 3 large hepatic tumors.

Conclusion: A sequential technique for registration of DCE-MRI data using a general-purpose elastic registration scheme is described which explicitly accounts for time-varying changes in pixel brightness due to contrast enhancement. Quantitative comparison of the performance of SER vis-à-vis two other schemes was performed using a computer-generated DCE-MRI phantom, and based on the superior performance of SER, it was chosen to register DCE-MRI data obtained from volunteer subjects in ongoing cancer clinical trials. The significant differences between PK parameter maps calculated from unregistered *vs.* registered DCE-MRI data underlines the importance of image registration.

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References: [1] Kety, *Pharmacol Rev.* 3:1-41, 1951; [2] Tofts, *JMRI* 7:91-101, 1997; [3] Buonaccorsi et al., *MRM* 58:1010-1019, 2007; [4] Melbourne et al., *Phys Med Biol* 52:5147-5156, 2007; [5] Graff et al., *Proc. ISMRM 2008*, 492; [6] Periaswamy et al., *IEEE Trans Med Imaging* 22:865-874, 2003.