An Alternating-Constraints Algorithm for Volume-Preserving Non-rigid Registration of Contrast-Enhanced MR Breast Images

Torsten Rohlfing[1], Calvin R. Maurer, Jr.[1],
David A. Bluemke[2], and Michael A. Jacobs[2]

[1] Image Guidance Laboratories, Department of Neurosurgery
Stanford University, Stanford, CA 94305, USA
rohlfing@stanford.edu
calvin.maurer@igl.stanford.edu
[2] The Russell H. Morgan Department of Radiology and Radiological Science
The Johns Hopkins University School of Medicine
Baltimore, MD 21205, USA
dbluemke@jhmi.edu, mikej@mri.jhu.edu

Abstract. We propose and evaluate in this work a novel optimization strategy for intensity-based non-rigid image registration of contrast-enhanced images with a volume-preservation constraint. Since patient motion correction and volume preservation are to some extent mutually exclusive goals, one is usually faced with a trade-off between volume preservation of contrast-enhancing structures and artifact reduction. We address this problem by repeatedly applying registration passes with alternating incompressibility constraint weights. The novel optimization method alternates between under-constrained registration (allowing the elimination of motion artifacts in the subtraction images) and over-constrained registration (enforcing volume preservation of contrast-enhancing structures). We apply our method to pre- and post-contrast MR breast images from 17 patients. We evaluate our method and compare it to unconstrained and fixed constraint non-rigid registration by blinded visual assessment of maximum intensity projections of subtraction images. The alternating-constraints algorithm was judged to reduce artifacts better then the fixed-constraint algorithm in 11 out of 17 patients and equally well in the remaining 6. The results of this study show the capability of our method to achieve volume preservation and at the same time reduce artifacts very similar to what can be achieved by unconstrained non-rigid registration.

1 Introduction

Non-rigid image registration algorithms based on free-form deformations have recently been shown to be a valuable tool in various biomedical image processing applications. One application of particular clinical interest is the registration of images acquired before and after contrast administration with the purpose

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of reducing motion artifacts. A major problem with existing algorithms is that when they are applied to pre- and post-contrast image pairs, they often produce transformations that substantially change (generally decrease, but sometimes increase) the volume of contrast-enhancing structures. Tanner *et al.* [1] documented this phenomenon contrast-enhanced magnetic resonance (MR) breast images. We observed the same behavior for lesions in MR breast images [2], as well as for contrast-enhancing vessels in three-dimensional (3-D) digital subtraction angiography using X-ray computed tomography head-and-neck images [3]. Contrast enhancement is an intensity inconsistency between the two images, which is what intensity-based registration algorithms are designed to minimize. This problem severely affects the usefulness of the resulting transformation for volumetric analysis, image subtraction, multi-spectral classification, and pharmacokinetic modeling.

To address this problem, an additional "energy" term is typically added to the intensity-based similarity measure to constrain the deformation to be smooth. We recently introduced a novel incompressibility (local volume preservation) constraint based on the Jacobian determinant of the deformation [2]. Soft tissue in the human body is generally incompressible for small deformations and short time periods. That is, the tissue can be deformed locally, but just like a gelatin-filled balloon, the volume (local and total) remains approximately constant. When computing non-rigid coordinate transformations between pre- and post-contrast images, this knowledge can be incorporated into the registration process by penalizing deviations of the local Jacobian determinant of the deformation from unity.

With an incompressibility constraint, volume preservation and motion artifact reduction are somewhat mutually exclusive goals of the registration. Therefore, there is usually a trade-off when adjusting the constraint weight: high weights lead to good volume preservation but prevent elimination of artifacts, while low constraint weights allow for good artifact reduction at the cost of increased volume loss of contrast-enhancing lesions. We hypothesize the existence of an approximately incompressible non-rigid coordinate transformation that correctly describes patient motion between the two acquisitions. In other words, we assume that motion artifact can in principle be eliminated while preserving the volume of contrast-enhancing lesions. We furthermore hypothesize that residual motion artifacts observed after non-rigid registration using an incompressibility constraint are an effect of the optimization algorithm getting stuck in a local minimum, which it cannot escape from without violating, at least temporarily, the volume preservation condition.

In this paper, we propose a new optimization strategy for intensity-based non-rigid image registration with an incompressibility constraint. Instead of simply constraining the free-form deformation with a weighted incompressibility constraint, we apply a scheme similar to simulated annealing. The underlying rationale is to first under-constrain (by using a smaller incompressibility constraint weight) the deformation, allowing the non-rigid registration to remove motion artifacts at the cost of shrinking contrast-enhancing lesions. In a subse-

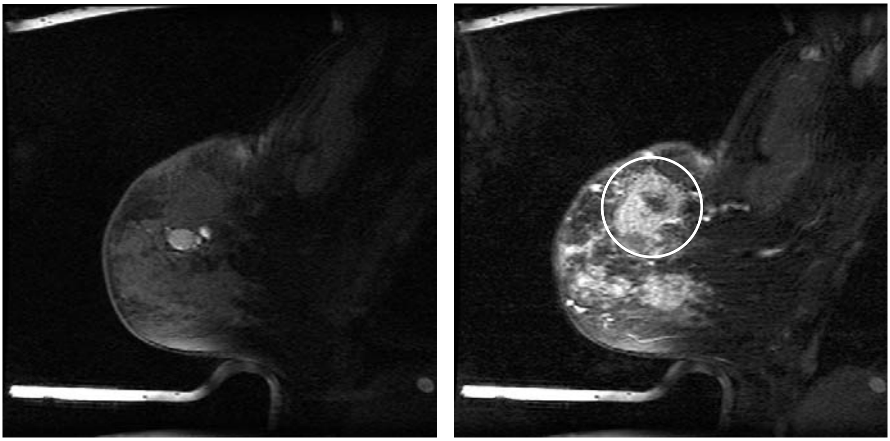


Fig. 1. Image data from one of the patients used in this study. *Left:* Pre-contrast image; *right:* corresponding post-contrast image. The contrast-enhancing lesion is marked with a circle in the post-contrast image.

quent step, the deformation is then over-constrained (by using a larger weight), re-expanding the previously shrunk regions (typically contrast-enhancing lesions) while de-emphasizing the image similarity measure. The purpose of this alternating-constraints strategy is to help the registration avoid local minima by allowing temporary volume loss that is compensated for in a subsequent step after the motion artifacts have been successfully eliminated. Our method is somewhat similar in concept to the alternation of deformation and Gaussian smoothing as described in Ref. [4]. Note, however, that the "smoothing" step in our case is not a purely mathematical operation as it is in Ref. [4], but instead is another deformation step with an increased weight on the regularization term.

To evaluate the efficacy and robustness of our alternating volume-preservation constraint algorithm and in order to validate its clinical value, we apply it to pre- and post-contrast MR breast images from 17 patients. Coordinate transformations were computed by four different algorithms: rigid registration, unconstrained non-rigid registration, fixed constraint non-rigid registration, and alternating constraints non-rigid registration. For all registrations, subtraction images were generated for the registered images and rendered by maximum intensity projection (MIP). The MIP renderings were then randomized and assessed for residual motion artifacts by an expert observer in a blinded evaluation study.

2 Materials and Methods

2.1 Image Data

We applied the non-rigid registration algorithm presented in this paper to MR breast images acquired before and after contrast injection. Seventeen patients (age range, 18–80 years; median, 45 years) were consecutively referred for MR evaluation of suspicious findings and/or extent of the breast lesion. Each pair of pre- and post-contrast images was first registered using a rigid transformation. Given the rigid registration as the initial alignment, various non-rigid registrations were then computed.

All MR scans were performed on a 1.5T MR scanner (General Electric Medical Systems, Milwaukee, WI), using a dedicated phased array breast coil (MRI Devices, Waukesha, WI) with the patient lying prone with the breast in a holder to reduce motion. Fat suppressed 3-D T_1-weighted FSPGR (T_R/T_E = 20/4 ms, FOV = 18×18 cm, matrix = 512×160, 60 slices, slice thickness 2 mm) pre- and post-contrast images were obtained after intravenous administration of Gd-DTPA contrast agent (Magnevist, Berlex, Wayne, NJ; patients received 0.1 mmol/kg as 0.2 mL/kg of 0.5 mol/l contrast solution). The contrast agent was hand injected over 10 seconds with MR imaging beginning immediately after completion of the injection. The contrast bolus was then followed by a 20 cc flush. The breast lesion was defined by contrast enhancement and identified by a radiologist. A sample pre- and post-contrast image pair is shown in Fig. 1.

2.2 Image Registration Algorithm

An initial alignment of pre- and post-contrast images is achieved using a rigid registration method with six parameters (three for rotation; three for translation). Our algorithm is an independent implementation of a technique for rigid and affine registration described in Ref. [5]. It uses normalized mutual information (NMI) as the image similarity measure [6]. In the first step, this method is used to find an initial rigid transformation to capture the global motion of the object. The rigid transformation is then used as the initial estimate for the non-rigid registration.

The intensity-based non-rigid registration algorithm is an independent, parallel implementation [7] of the technique introduced by Rueckert et al. [8]. The transformation model is a multilevel formulation of a free-form deformation (FFD) based on cubic B-splines. In addition to the NMI similarity measure E_{NMI}, our technique incorporates a penalty term $E_{\text{constraint}}$ to constrain the deformation of the coordinate space [2]. A user-defined weighting factor w ($0 \leq w \leq 1$) controls the relative influence of E_{NMI} and $E_{\text{constraint}}$, combining both into the overall cost function E_{Total} as follows:

$$E_{\text{Total}} = (1 - w)E_{\text{NMI}} - wE_{\text{constraint}}. \tag{1}$$

The design of our deformation constraint is motivated by the observation that most tissues in the human body, including the breast, are approximately incompressible for small deformations and short time periods. In a small neighborhood of the point (x, y, z), the local compression or expansion caused by the deformation can be calculated by means of its Jacobian determinant. The value of the Jacobian determinant is equal to 1 if the deformation at (x, y, z) is incompressible, greater than 1 if there is local expansion, and less than 1 if there is compression. The incompressibility constraint penalty term we use is the integral of the absolute logarithm of the Jacobian determinant, integrated over the domain of the reference image [2]. This term penalizes local deviations of the Jacobian determinant from unity, that is, it penalizes local tissue expansion and compression. Alternative forms of the incompressibility constraint term are possible [2].

Like Rueckert et al. [8], we aim to improve robustness and efficiency of the registration algorithm by employing a multiresolution approach, starting with a coarse control point spacing that is successively refined using a B-spline subdivision algorithm. The alternating-constraints strategy is applied at each level, starting with an under-constrained optimization pass[1], followed by an over-constrained pass. A B-spline subdivision, if the finest control point resolution has not yet been reached, takes places after an over-constrained pass. The constraint weight for the over-constrained pass was adjusted individually for each patient; the respective constraint weight for the under-constrained pass was defined as 1/100 of the over-constrained weight.

2.3 Study Design

We evaluate and compare the artifact reduction achieved by four different registration methods: rigid, unconstrained non-rigid, non-rigid with a fixed constraint weight, and non-rigid with alternating constraint weights. For this study, multiple constrained free-form deformations were computed, covering a large range of weighting factors for the the deformation constraint. For the fixed-constraint algorithm the weights ranged from 0.0001 to 0.5, while for the alternating-constraints algorithm the weights ranged from 0.01 to 1. The latter values refer to the over-constrained pass; the weights in the under-constrained pass were determined by multiplying the over-constraining weights by 0.01. All non-rigid registrations started with a 40 mm control point spacing that was successively refined to 20 mm, 10 mm, and finally 5 mm. In parallel, the image data resolution was refined from 4 mm voxel size to 2 mm, 1 mm, until at the final stage the original image data was used. Table 1 gives an overview of the parameters used at each level for fixed-constraint and alternating-constraints non-rigid registration.

A key question to answer is whether a given technique provides a way of compensating motion artifacts while preventing volume loss of contrast-enhancing structures. For each algorithm (fixed and alternating constraints) and each patient, we independently determined the smallest weighting factor for the respective algorithm that provided volume preservation of the identified lesion within 2% of the original volume. As reference methods, rigid and unconstrained non-rigid transformations were also computed. For the resulting four transformations, 3-D subtraction images of the registered pre- and post-contrast images

[1] The term “optimization pass” in this context refers to a complete optimization of the non-rigid transformation parameters at one particular voxel size and control point resolution.

Table 1. Algorithm parameters during multi-level non-rigid registration.

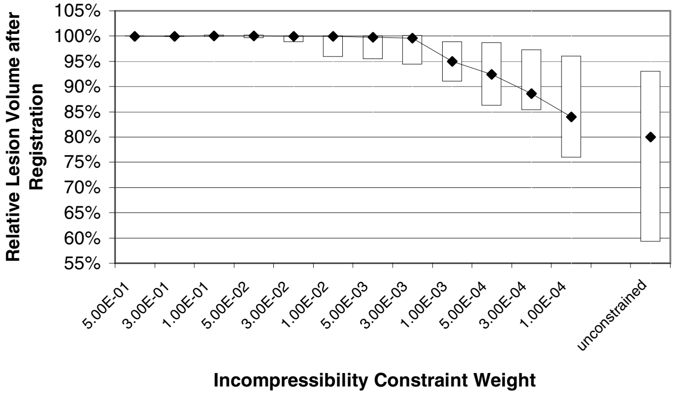
Algorithm	Level	CPG Spacing	Voxel Size	Constraint Weight
Fixed Constraint	1	40 mm	4 mm	w
	2	20 mm	2 mm	w
	3	10 mm	1 mm	w
	4	5 mm	original	w
Alternating Constraints	1	40 mm	4 mm	$10^{-2}w$
	2	40 mm	4 mm	w
	3	20 mm	2 mm	$10^{-2}w$
	4	20 mm	2 mm	w
	5	10 mm	1 mm	$10^{-2}w$
	6	10 mm	1 mm	w
	7	5 mm	original	$10^{-2}w$
	8	5 mm	original	w

were computed, rendered by lateral orthogonal maximum intensity projection[2] (MIP), randomized, and presented to an expert observer. The blinded observer ranked the four subtraction MIP images based on motion artifact reduction. Rank #1 was assigned to the image showing least residual artifact, while rank #4 was assigned to the image showing most residual artifact. Several images could be assigned the same rank, in which case an appropriate number of subsequent ranks would be left unassigned. For example, if one image clearly showed least artifact, another clearly showed most artifact, and the remaining two images were indistinguishable, then the ranks assigned would be #1, #2, #2, and #4 with rank #3 unassigned.

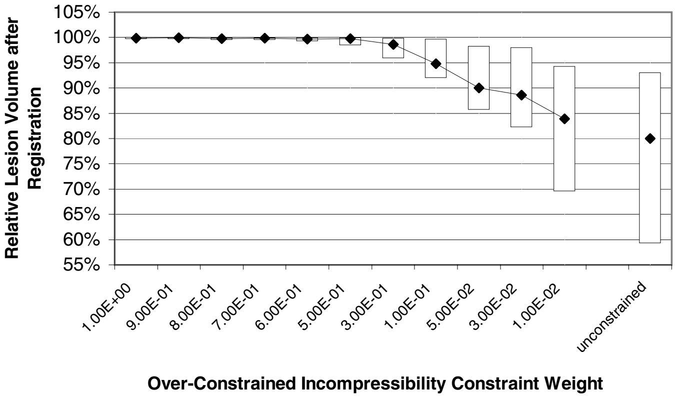
3 Results

Volume Preservation. The original volumes of the contrast-enhancing lesions in the images from 17 patients ranged from 0.2 to 77.7 ml (mean $\pm$ SD $=$ 9.1 $\pm$ 19.0 ml). These volumes were determined by semi-automatically segmenting the contrast-enhancing lesions in the subtraction image after rigid registration. As other groups have reported before, unconstrained non-rigid registration of pre- and post-contrast images often results in substantial volume loss of the contrast-enhancing structures. For the 17 patients considered in the present study, volume loss was between 1.3 and 61.8 percent (mean $\pm$ SD $=$ 23.4 $\pm$ 18.3 percent). On average, for both optimization strategies (fixed and alternating constraints), volume preservation improves as the relative weight of the constraint penalty term increases (Fig. 2). With sufficiently high relative weighting factors, the median volume change of contrast-enhancing lesions is less than 1% for both strategies.

[2] Since the original plane orientation of the MR images used in this study was sagittal, a lateral projection showed the most image detail and was therefore considered most appropriate for image quality assessment.



(a) Fixed Constraint Weight



(b) Alternating Constraint Weights

Fig. 2. Relative volumes of contrast-enhancing lesions after non-rigid registration with different incompressibility constraint weights.

Artifact Reduction. The results of the expert assessments of the artifact reductions achieved on the 17 patients in this study are shown in Fig. 3. For each constrained non-rigid registration optimization strategy and each patient, we used the deformation produced by the smallest weight factor that produced volume preservation of the identified lesion within 2%. Unconstrained non-rigid registration was ranked best (least residual motion artifact) in all cases. The alternating-constraints algorithm clearly outperformed the fixed constraint algorithm: in 11 out of 17 cases, the alternating-constraints method was ranked better than the fixed-constraint method, and equally good in the remaining 6 cases. Paired two-sided t-tests on the distribution of ranks showed that the differences among all algorithms are statistically significant. The significance level

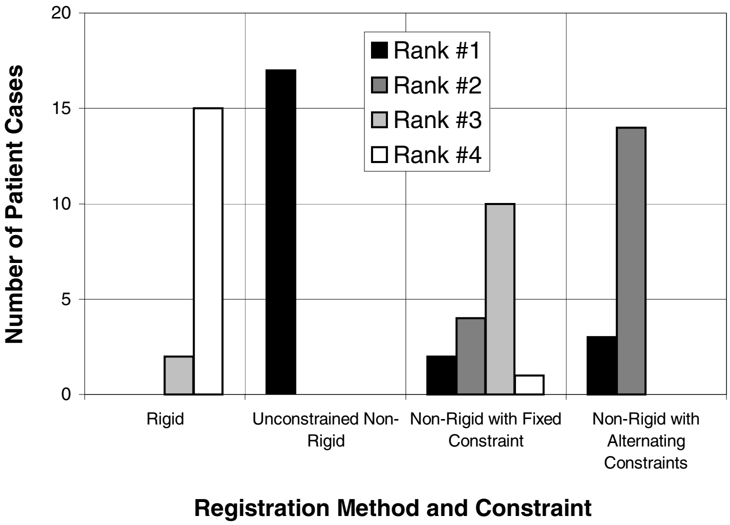


Fig. 3. Expert assessment of residual artifacts in subtraction MIP renderings after motion correction by four different registration methods. The bars show the number of patients for which each quality rank was assigned to the respective registration method (least artifact, Rank #1; most artifact, Rank #4).

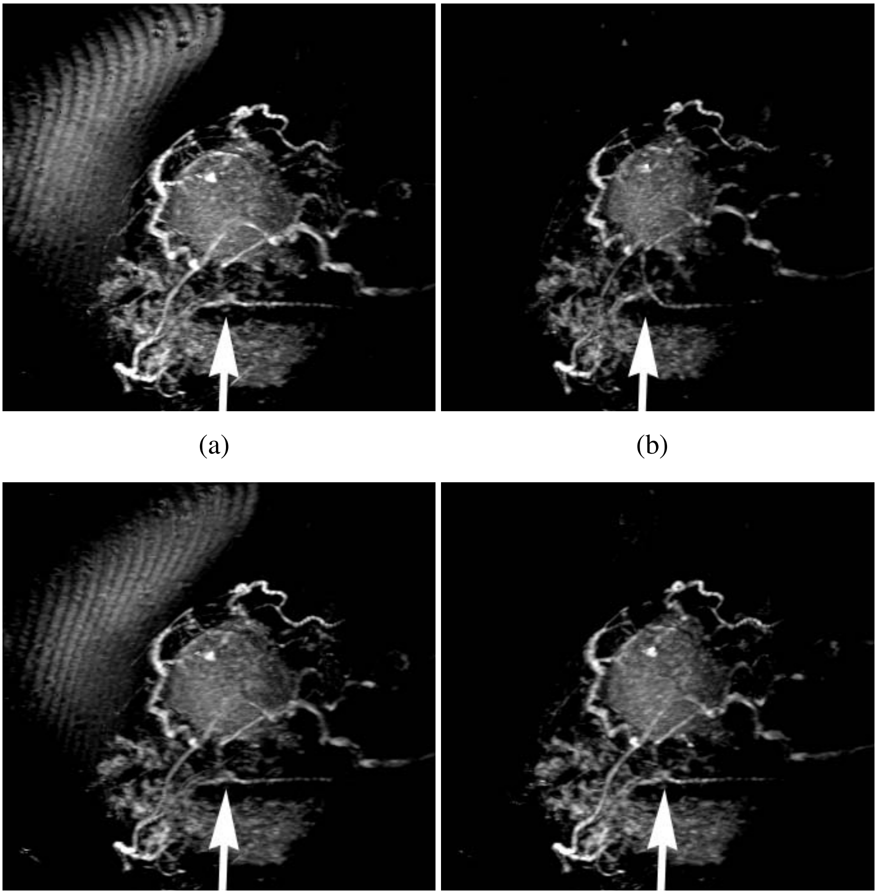
for the superiority of the alternating-constraints approach over fixed-constraint registration is $P < 2.2 \cdot 10^{-4}$.

Computation Times. For the fixed-constraint algorithm, the median computation time over 204 registrations (17 patients, 12 constraint weights per patient) was 24,344 seconds. For the alternating-constraints algorithm, the median computation time over 187 registrations (11 constraint weights per patient) was 27,406 seconds. The alternating-constraint algorithm, despite running twice as many optimization passes, was only about 12% slower than the fixed-constraint algorithm. We observed that the over-constrained passes typically required substantially fewer optimization steps than the under-constrained passes, thereby explaining the comparatively low additional computational cost.

4 Conclusion

Results on contrast-enhanced MR breast images from 17 patients suggest that the incompressibility constraint improves non-rigid registration of pre- and post-contrast images by substantially reducing the problem of shrinkage of contrast-enhancing structures. Motion artifacts can still be reduced substantially, but the more strictly the constraint is enforced (larger relative weight in the cost function), the more residual artifacts remain.

Using a novel alternating-constraints registration optimization strategy, artifact reduction and lesion volume preservation were both reasonably well achieved simultaneously. In a blinded assessment study, the alternating-constraints algo-



(a) (b) (c) (d)

Fig. 4. Effect of alternating constraints on motion artifacts in MIP of subtraction images. (a) After rigid registration. (b) After unconstrained non-rigid registration (30% volume loss). (c) After non-rigid registration with single incompressibility constraint (1% volume loss). (d) After non-rigid registration with alternating incompressibility constraints (1% volume loss). In the blinded evaluation of the MIP renderings from this patient, the expert rated unconstrained non-rigid registration slightly superior (i.e., as having slightly less residual artifacts) to the alternating-constraints algorithm. The fixed-constraint algorithm left substantial residual artifacts and was ranked third, followed by rigid registration. The unconstrained non-rigid registration reduces motion artifacts but shrinks the contrast enhancing lesion by 30% and also causes some change in the shape of structures, e.g., the arrow points to a bending that appears in a contrast-enhancing vessel after unconstrained registration. The incompressibility constraint with the normal search strategy preserves the lesion volume and the vessel morphology but does not in this case compensate for motion artifacts. The incompressibility constraint with alternating constraints optimization preserves the lesion volume and the vessel morphology and also substantially reduces motion artifacts.

rithm clearly outperformed the fixed-constraint algorithm. Although the unconstrained non-rigid registration resulted in the fewest residual artifacts, in many cases the perception of the expert observer was that the differences between the alternating-constraints method and unconstrained non-rigid registration were very subtle or indistinguishable. An example result is illustrated in Figure 4. The additional computational cost incurred by the alternating-constraints optimization strategy was found to be only approximately 12%.

We conclude that our method is an important step towards simultaneously achieving the two goals of motion artifact reduction and volume preservation in a fully automated, computationally efficient algorithm.

Acknowledgments

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