# Generating Coefficients for Regularization Terms in Nonrigid Registration of Contrast-Enhanced MRI

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**Abstract.** Nonrigid registration is a technique to recover spatial deformations between images. It can be formulated as an optimization problem to minimize the image dissimilarity. A regularization term is used to reduce undesirable deformations which are usually employed in a homogeneous or spatial-variant fashion. When spatial-variant regularization is used in nonrigid registration of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), the local coefficients have been determined by manual segmentation of tissues of interest. We propose a framework to generate regularization coefficients for nonrigid registration in DCE-MRI, where tumor locations are to be transformed in a rigid fashion. The coefficients are obtained by applying a sigmoid function on subtraction images from a pre-registration. All parameters in the function are automatically determined using $k$-means clustering. The validation study compares three regularization weighting schemes in nonrigid registrations: a constant coefficient for a volume-preserving term, binary coefficients obtained by manual segmentation and a real-value coefficients using the proposed method on a rigidity term. Evaluation is performed using displacements, intensity changes and volume changes of tumors on synthetic and clinical DCE-MR breast images. As a result, the registration using spatial-variant rigidity terms performs better than using homogeneous volume-preserving terms. For the coefficient generation methods of a rigidity term, the proposed method can replace the binary coefficients requiring manual tumor segmentation.

## 1 Introduction

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is used to differentiate between malignant and benign lesions in cancer diagnosis. A sequence of 3D MRI scans before and after the injection of a paramagnetic contrast agent is acquired to form a 4D (3D+time) DCE-MR image. The 4D imaging technique allows an analysis of the variation of the magnetic resonance (MR) signal intensity, before and after the injection of contrast enhancement. The time-intensity curve patterns can be used in the detection of tumors. However, the motion in between the image acquisitions can complicate the analysis. Image registration is used in DCE-MR image analysis to achieve alignment between images. Image registration is an optimization problem aiming to minimize the image dissimilarity. In registration of DCE-MRI, free-form deformation

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(FFD) based nonrigid registration is widely used to remove motions in between image acquisition of the pre- and post-contrast images [1]. All post-contrast images at different time steps are registered to the baseline pre-contrast image such that the same tissue is located at the same position in all images.

There are two reasons that lead to an intensity difference. One is motion occurred in between image acquisitions and the other is intensity enhancement caused by the injection of contrast agent. Therefore, minimizing the image dissimilarity during the image registration can reduce the occurred motion but also change the volume of the enhanced region [2]. This can be countered through the use of regularization.

An incompressibility constraint was proposed to preserve tumor volumes [2], which is applied on the whole breast region with the same weight for all types of tissues. The assumption is that the tissue volume does not change over a short period of time. However, most DCE-MR images require several minutes' acquisition time and the breath or body gesture changes of a patient might change the volume of soft breast tissues.

Spatial-variant rigidity constraints [3,4,5] were proposed to preserve the rigidity of tissues. When applying a rigidity term in the registration of DCE-MR images, it requires a coefficient or stiffness map on each post-contrast image to determine the penalty weight on various types of tissue. Tumors are usually assumed to be rigid while other tissue (e.g. fat) is relatively soft. Therefore a segmentation of the enhanced tumors on the post-contrast image can be used to build a binary stiffness map. Manual segmentation is usually regarded as the most accurate method but can be time consuming; and automatic enhanced tumor segmentation on subtraction images usually requires a preliminary successful registration to remove motion artifacts. Therefore, it is important to build a robust and reliable method to compute the regularization coefficients for the registration in DCE-MR images.

We propose a framework to compute the rigidity registration coefficients in application to 4D DCE-MR images. A pre-registration is performed that registers the pre-contrast image to each post-contrast image. A subtraction image is obtained, identifying corresponding tissue enhancement information. We subsequently apply a sigmoid function to map the voxel intensity in the smoothed subtraction image to form the regularization coefficients. All parameters of the sigmoid function are determined by a $k$-means clustering method.

In our validation study on synthetic and clinical DCE-MR breast images, we compare registration schemes with various methods to compute the coefficients of the rigidity regularization term: a constant term, a binary function that requires an explicit segmentation, and the proposed mapping method.

## 2 Image registration

Image registration is defined as a problem of finding a spatial transformation $\boldsymbol{T}$ relating two images of dimension $d$, one of which is fixed ($I_F$) and the other moving ($I_M$). In this paper, we employ intensity-based image registration, formulated as an optimization problem in which the cost function $\mathcal{C}$ is minimized with respect to the spatial transformation $\boldsymbol{T}$. The cost function defines the quality of the match, in combination with a

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regularization of the transformation. The optimization problem can be formulated as:

$$\widehat{\boldsymbol{\mu}} = \arg\min_{\boldsymbol{\mu}} \mathcal{C}_{\text{sim}}(\boldsymbol{T}_{\boldsymbol{\mu}}; I_F, I_M) + w\mathcal{C}_{\text{reg}}(\boldsymbol{T}_{\boldsymbol{\mu}}), \tag{1}$$

where the subscript $\boldsymbol{\mu}$ indicate the transformation parameters, $\mathcal{C}_{\text{sim}}$ denotes the image similarity, which is mutual information [6] in this paper, and $\mathcal{C}_{\text{reg}}$ is used to penalize nonrigid deformations as a soft constraint weighted by a scalar $w$. A rigidity regularization term proposed by Staring *et al.* [5] is employed in the registration package `elastix`[7]. We adopt a B-splines based transformation model [1] in this paper, called free-form deformation (FFD).

## 3 Method

Let $\boldsymbol{F}$ be a regularization term that can be applied on transformation $\boldsymbol{T}$ with a coefficient map function $\gamma : \mathbb{R} \rightarrow \mathbb{R}$. A general form of this term can be represented as:

$$\mathcal{C}_{\text{reg}}(\boldsymbol{T}) = \frac{\int_{x\in\Omega} \gamma(x)\boldsymbol{F}(\boldsymbol{T};x)^2}{\int_{x\in\Omega}\gamma(x)} \tag{2}$$

The coefficient mapping function $\gamma$ maps each voxel in a moving image to a value that suggest the weight of the regularization term applied on it. The simplest mapping function is a constant number where all voxels $x$ in an image are equally weighted, $\gamma(x) = \alpha$. For instance, Rohlfing [2] applied a uniformly weighed incompressibility term on all breast regions.

Another commonly used function is a binary function that requires a preliminary segmentation of various tissues. For instance by performing a tumor segmentation on the DCE-MR images, the weight on tumor tissue is 1 and non-tumor tissue is 0.

Another kind of function is to map the intensity of an image to another range when the intensity can imply the tissue types. Ruan *et al.* [4] maps a CT image into a new range where most of voxels have either value 1 (bone tissues) or 0. The assumption is the voxel intensity value that falls in a certain range in a CT image suggests the bone tissues.

In DCE-MR images, the intensity does not always link to tissue types. However, most tumors are more rigid than healthy tissue and are usually enhanced in post-contrast images. Subtraction images of pre- from post-contrast image show enhancement of tissues provided there is no motion in between. Based on the assumption that tumors get enhanced in post-contrast images, we obtain regularization coefficients by applying a sigmoid mapping function on subtraction images from a pre-registration.

Given a pre-contrast image $f$ and post-contrast image $g$, $f$ is registered to $g$ using a rigid and then nonrigid (FFD) registration algorithm, obtaining a registered pre-contrast image $f'$. A subtraction image denoted as $h$ shown in Figure 1(a) is obtained by subtracting $f'$ from $g$ and then smoothed by a Gaussian filter ($\sigma = 2$) shown in Figure 1(b). A non-linear mapping function, sigmoid function, is then applied on the subtraction image $h$, resulting in the coefficient image (Figure 1(c)).

In the pre-registration, the tumor volume in pre-contrast might have changed, but the intensity of post-contrast image will dominate the intensity in subtraction image,

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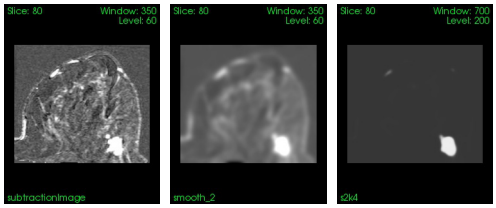


(a) Subtraction image (b) After smoothed (c) Coefficients

Fig. 1: Central slices of image volume of a subtraction image, after being smoothed and after applying sigmoid function on the subtract image.

therefore, the tumor volume change in pre-contrast image will not effect the resulting coefficient image.

Let $\boldsymbol{I}(x)$ be the intensity value at voxel $x$ in subtraction image $h$, the mapping function $\gamma(x)$ transform $\boldsymbol{I}(x)$ to a new range with a center $\alpha$ and scale $\beta$:

$$\gamma(x) = \frac{\max - \min}{\left(1 + e^{-\left(\frac{\boldsymbol{I}(x)-\beta}{\alpha}\right)}\right)} + \min, \tag{3}$$

where $\max$ and $\min$ are maximum and minimum intensity of the image, $\alpha$ and $\beta$ are determined by performing a $k$-means clustering method on the smoothed subtraction image $h$ and partitioning it into $k$ groups with various intensity means. The highest intensity mean value is assigned to $\beta$ and the standard deviation of that cluster is assigned to $\alpha$. Therefore, the only user-defined parameter is the number of clusters $k$. The performance of the registration is demonstrated to be insensitive to the value of $k$ in the range of 2 to 5.

## 4 Validation

All DCE-MR breast images were acquired with a Siemens 1.5 MR system, where $T_R = 5.11$ms, $T_E = 2.7$ms, field of view $= 340$mm. The voxel dimensions were around $0.68 \times 0.68 \times 1$mm. The slice orientations were axial and reformatted to identity orientation for visualization convenience. The total acquisition time was 6.24 minutes, including 6 time steps in a four-dimensional DCE-MR breast image (1 before and 5 after injection of contrast agent).

### 4.1 Synthetic datasets

We select 3 clinical DCE-MR breast images without obvious motions to generate $3 \times 10$ synthetic images with simulated deformations. The three images show various tumor volumes ($1.5\text{cm}^3, 11.8\text{cm}^3, 22.3\text{cm}^3$) or enhancement patterns (homogeneous, heterogeneous). The subtraction images of the pre- from post-contrast images are shown in Figure 2. Two image volumes in each clinical DCE-MR breast image series are used in

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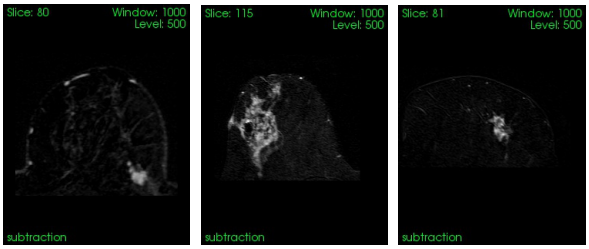


Fig. 2: Selected slices of subtraction image of pre- from post-contrast images in the three clinical image series, which are used to generate synthetic images.

building a synthetic image set: a pre- and a post-contrast image volumes at the second time point after injection of contrast agent ($f_0, g_0$). We manually segment the enhanced tumors $s_0$ from the post-contrast images, which will be used in the validation study as a ground truth of tumor volume, location and intensity.

For the deformation simulation, we randomly generate two rigid transformations ($\boldsymbol{T}_{r_1}, \boldsymbol{T}_{r_2}$), and two B-spline transformations with a grid point space of 10mm and 20mm. We later update these B-spline transformations to $\boldsymbol{T}_{b_1}, \boldsymbol{T}_{b_2}$ such that the tumors are rigidly deformed by enforcing the related control points to be zero. We subsequently compose all transformations to $\boldsymbol{T}_{\rm gt}(x) = \boldsymbol{T}_{b_1} \circ \boldsymbol{T}_{r_1} \circ \boldsymbol{T}_{b_2} \circ \boldsymbol{T}_{r_2}$, which are used to construct synthetic pre- and post-contrast images $f_1, m_1$ and tumor mask $s_1$, where $f_1 = f_0$, $g_1 = \boldsymbol{T}_{\rm gt}(g_0)$, and $s_1 = \boldsymbol{T}_{\rm gt}(s_0)$.

### 4.2 Evaluation method

The Target Registration Error (TRE) [8] is used to evaluate the degree of alignment between two corresponding voxels in terms of deformations:

$$\mathrm{TRE} = \sum_{x \in \Omega} ||\boldsymbol{T}_{\rm est} \circ \boldsymbol{T}_{\rm gt}(x) - x||, \tag{4}$$

where $\boldsymbol{T}_{\rm gt}$ is the simulated deformation, $\boldsymbol{T}_{\rm est}$ is the estimated transformation obtained from various registration schemes. A smaller $\mathrm{TRE}$ value suggests a registration can better recover the simulated motion.

We also measure the recovery of the motion in synthetic post-contrast images by measuring the intensity similarity with the corresponding original post-contrast images, using root mean squared error (RMS) and normalized correlation (NC):

$$\mathrm{RMS}(A,B) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(A_i - B_i)^2}, \qquad \mathrm{NC}(A,B) = \frac{\sum_{i=1}^{N}(A_i \cdot B_i)}{\sqrt{\sum_{i=1}^{N} A_i^2 \cdot \sum_{i=1}^{N} B_i^2}}$$

where $A_i, B_i$ is the intensity of $i$-th voxel of images $A$ and $B$, and $N$ is the total number of voxels considered. Smaller RMS values and higher NC values suggest higher image similarity and hence better registration performance.

We also compute the tumor volume changes by applying the estimated transformation $\boldsymbol{T}_{\rm est}$ on the tumor mask $s_1$.

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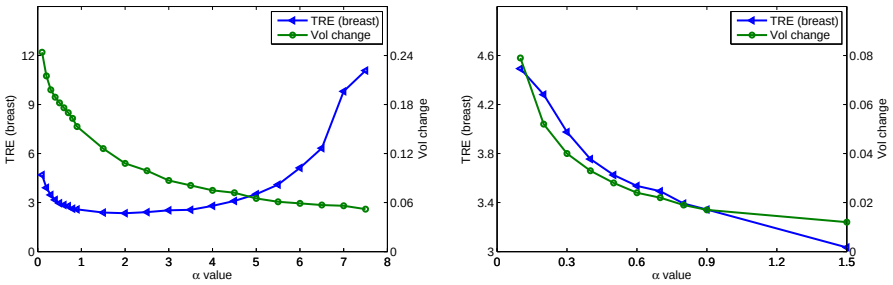


(a) VPC (b) ARC(5)

Fig. 3: TRE over the breast region is shown on left y-axis and volume change over the tumor region is on the right y-axis. (a) shows VPC registration scheme results for $\alpha \in [0.1, 7]$. The tumor volume change decreases as the weight $\alpha$ increase. TRE for breast region increases fast for $\alpha > 5$. (b) shows ARC(k=5) results for $\alpha \in [0.1, 1.5]$. The running time for $\alpha > 1.5$ are more than 15 minutes. Note the axes scales of (a) and (b) are different

### 4.3 Experiment and results

We perform registrations using three methods to compute regularization coefficients: constant number $\gamma(x) = 0$ for unconstrained FFD (denoted as UC) and $\gamma(x) = 1$ for volume-preserving constraint (VPC) [2], binary function based on manual segmentation of tumors (MRC) and our proposed automatic method (ARC($k$)) for rigidity constraint [5]. We evaluate the robustness of the proposed method to the number of clusters $k$ of range 2 to 5, used in determining the parameters of sigmoid function. Each registration scheme is tested on 30 synthetic and 5 clinical images and the performance is evaluated on the whole breast and tumor regions. Initial rigid registrations are employed in all tests. A multi-resolution scheme using 4 resolutions is employed for all nonrigid registrations, from 8, 16, 32 to 64mm. This is designed to be different from the resolution and grid space in the deformation simulation in order to reduce the evaluation bias. The breast regions are selected by performing a thresholding segmentation on cropped one-side breast images and followed by a morphology closing to remove holes. The parameter $\alpha$ in equation (1) is determined by finding the value that can best preserve the tumor volume while maintaining comparable or better result than unconstrained FFD scheme and the computation time is less than 15 minutes. Figure 3 shows an example of registration results on a synthetic image set using a range of $\alpha$ value.

Table 1 shows the registration results on synthetic images with ground-truth. Volume-preserving constrained scheme (VPC), with higher RMS and lower NC value on breast region, shows worse result than UC. However, VPC has smaller TRE than UC and the difference could come from distortion of tumors. Rigidity constrained schemes (ARC($k$) for $k = 3, 4, 5$ and MRC) perform better than volume-preserving constrained (VPC) schemes in terms of smaller mean TRE and RMS, higher NC over the whole breast and tumor regions and less tumor volume loss. It demonstrates that using spatial

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| | Breast regions | | | Tumor regions | | | |
|---|---|---|---|---|---|---|---|
| | TRE | RMS | NC | TRE | RMS | NC | Vol change |
| UC | 3.42±3.11 | 36.20±4.56 | 0.90±0.01 | 1.09±0.79 | 53.11±2.15 | 0.79±0.03 | 0.20±0.11 |
| VPC | 2.40±1.36 | 37.30±4.50 | 0.89±0.02 | 0.33±0.19 | 49.32±3.36 | 0.82±0.03 | 0.04±0.02 |
| ARC(2) | 1.32±1.04 | 35.61±4.67 | 0.90±0.01 | 0.16±0.15 | 45.35±6.22 | 0.85±0.04 | 0.04±0.04 |
| ARC(3) | 1.55±0.95 | 34.91±3.56 | 0.90±0.01 | 0.13±0.11 | 45.22±5.97 | 0.85±0.03 | 0.03±0.02 |
| ARC(4) | 1.60±0.97 | 34.62±3.87 | 0.91±0.01 | 0.10±0.07 | 44.59±5.41 | 0.85±0.03 | 0.01±0.01 |
| ARC(5) | 1.60±0.71 | 34.75±3.94 | 0.91±0.01 | 0.10±0.07 | 44.72±5.07 | 0.85±0.02 | 0.01±0.01 |
| MRC | 1.50±0.86 | 34.40±3.87 | 0.91±0.01 | 0.10±0.06 | 44.76±4.88 | 0.85±0.02 | 0.01±0.01 |

Table 1: Evaluation result for 30 synthetic images.

variant rigidity constraint can achieve better overall and local registration performance. Within rigidity constrained registration schemes, ARC(4,5) shows similar performance on both breast and tumor regions. As $k$ increases from 2 to 4, the registration performance improves, except for the TRE getting larger over the breast regions. The reason could be ARC(2) apply penalty on larger enhanced regions, and preserve the deformation of these enhanced regions as well in addition to enhanced tumors.

Table 2 shows registration results on 5 clinical images. Only NC is used to compute the image similarity between the registered post- to the pre-contrast images due to their different intensity levels. Note this is different from the tests on synthetic data where ground-truth is available. All registrations schemes show similar performance over breast regions in terms of NC value. ARC(2,3,4,5) and MRC preserved the volume of the tumors to an accuracy of $100\%$, compared to $2\% \pm 2\%$ volume change in VPC schemes. All registration schemes with constraints show significantly better than the unconstrained method (UC) of $32\% \pm 33\%$ tumor volume change. The global and local registration results obtained from clinical data are roughtly consistent with the synthetic data.

## 5 Discussion and conclusions

We proposed a framework to compute regularization coefficients in nonrigid registration using a sigmoid mapping method on a subtraction image obtained from a pre-registration. The evaluation results show that using a homogeneous volume-preserving constraint in nonrigid registration of DCE-MR beast images can reduce the tumor volume changes. Spatial variant rigidity constraint can further improve the volume preservation performance while showing better overall performance on the whole breast regions. The proposed method can replace the manual segmentation method to compute the rigidity term coefficients by showing comparable local and global registration performance. Note that our focus is not to create a better tumor segmentation method, but a framework that can replace the manual segmentation in computing the rigidity term coefficients.

In this framework, unconstrained FFD is used in pre-registration to remove enhancement artifact caused by motion in subtraction image, where the tumor volume in pre-

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| | Breast regions | tumor regions |
|---|---|---|
| | NC | Vol change |
| UC | 0.81±0.04 | 0.32±0.33 |
| VPC | 0.81±0.04 | 0.02±0.02 |
| ARC(2) | 0.81±0.04 | 0.00±0.00 |
| ARC(3) | 0.81±0.05 | 0.00±0.00 |
| ARC(4) | 0.81±0.04 | 0.00±0.00 |
| ARC(5) | 0.81±0.04 | 0.00±0.00 |
| MRC | 0.81±0.04 | 0.00±0.00 |

Table 2: Evaluation results for the 5 clinical data.

contrast image may change. Since the intensity of tumor region in subtraction image is dominated by post-contrast image, in our study we observed that the effect of volume change in pre-contrast image on the sigmoid mapping on the subtraction image is shown to be very limited. A possible future work is to evaluate the effect of pre-registration on the rigidity coefficients generation.

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