A New Similarity Measure for Non-Rigid Breathing Motion Compensation of Myocardial Perfusion MRI

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Abstract— **Breathing movements during the image acquisition of first-pass gadolinium enhanced, myocardial perfusion *Magnetic Resonance Imaging* (MRI) hinder a direct automatic analysis of the blood flow of the myocardium. In addition, a qualitative readout by visual tracking is more difficult as well. Non-rigid registration can be used to compensate for these movements in the image series. Because of the local contrast and intensity change over time, the registration criterion needs to be chosen carefully. We propose a measure based on *Normalized Gradient Fields* (NGF) in order to obtain registration. Since this measure requires strong gradients in the images, we also test combining the measure with the *Sum of Squared Differences* (SSD) to maintain registration forces over the whole image area. To ensure smoothness, we employ a Laplacian regularizer and use the B-spline based approach to describe the transformation of the image space. Our experiments show that by using NGF good registration results can be obtained for image exhibiting a high intensity contrast. For images with a low intensity contrast, combining NGF and SSD improves the registration results significantly over using NGF only. Both measures are differentiable making possible the application of fast, gradient based optimizers.**

I. INTRODUCTION

First-pass gadolinium enhanced, myocardial perfusion *magnetic resonance imaging* (MRI) can be used to observe and quantify blood flow to the different regions of the myocardium. Ultimately such observation can lead to diagnosis of coronary artery disease that causes narrowing of these arteries leading to reduced blood flow to the heart muscle.

A typical imaging sequence includes a pre-contrast baseline image, the full cycle of contrast agent first entering the right heart ventricle (RV), then the left ventricle (LV), and finally, the agent perfusing into the LV myocardium (Fig. 1). Images are acquired to cover the full first pass (typically 60 heartbeats) which is too long for the patient to hold their breath. Therefore, a non-rigid respiratory motion is introduced into the image sequence which results in a mis-alignment of the sequence of images through the whole acquisition. For the automatic analysis of the sequence, a proper alignment of the heart structures over the whole sequence is desired.

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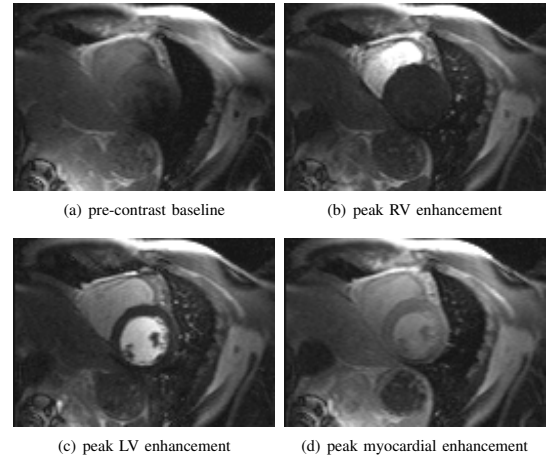
(a) pre-contrast baseline   (b) peak RV enhancement

(c) peak LV enhancement   (d) peak myocardial enhancement

Fig. 1. Images from a first-pass gadolinium enhanced, myocardial perfusion MRI of a patient with chronic myocardial infarction (MI).

A. State of the art

To achieve such alignment, various registration methods have been proposed [1]. The challenge in the registration of the contrast enhanced perfusion imaging is that the contrast and intensity of the images change locally over time, especially in the region of interest, the left ventricular myocardium.

Some approaches to compensate the breathing movement use rigid registration only: Breeuwer and Spreeuwers [2] use a translation/rotation based registration with normalized cross-correlation as a similarity measure. Milles et al. [3] proposed to identify three images (base-line, peak RV enhancement, peak LV enhancement) by using *independent component analysis* (ICA) of the intensity curve within the left and the right ventricle. These three images then form a vector base that is used to create a reference image for each time step by a weighted linear combination, hopefully exhibiting a similar intensity distribution like the according original image to be registered. Image registration of the original image to the composed reference image is then done by a rigid transformation minimizing the *sum of squared differences* (SSD). However, it is not clear, how the displacements between the three base images are corrected (if at all), and how their mis-alignment might influence the overall registration. Also with rigid registration only, the method does not account for the non-rigid deformations of the heart.

Other authors target for non-rigid registration and use *mutual information* (MI) based criterions as image similarity measures [4], [5]. However, the evaluation of MI is quite

expensive in computational terms.

B. Our contribution

In order to compensate for the breathing movements, we use non-rigid registration, and to avoid the difficulties in registration induced by the local contrast change, we follow Haber and Modersitzki [6] using a modified version of their proposed image similarity measure that is based on *Normalized Gradient Fields* (NGF). Since this cost function does not induce any forces in homogeneous regions of the images, we also combine the NGF based measure with SSD.

The remainder of the paper first discusses non-rigid registration, then, we focus on the NGF based cost measure and our modifications to it as well as combining the new measure with the well known SSD measure F_{SSD}. Finally, we present and discuss these results and point to future work.

II. THE METHODS

A. Non-Rigid Registration

Image registration can be defined as follows: consider an image domain $\Omega \subset \mathbb{R}^d$ in the d-dimensional Euclidean space, a test image S and a reference image R, and a transformation of an image as a mapping $T : \Omega \to \Omega$. Then, the registration of S to R aims at finding a transformation T according to

$$T = \min_{T \in \Theta} \left(F(S_T, R) + \kappa E(T) \right). \quad (1)$$

F measures the similarity between the (deformed) test image S and the reference, E ensures a steady and smooth transformation T, and κ is a weighting factor between smoothness and similarity. In non-rigid registration, the transformation T is only restricted to be neighborhood-preserving. In our application, the similarity measure F is derived from a so called voxel-similarity measure that takes into account the intensities of the whole image domain. In consequence, the driving force of the registration will be calculated directly from the given image data.

B. A similarity measure based on normalized gradient fields

The use of *normalized gradient fields* (NGF) has been proposed by Haber and Modersitzki for the registration of images with different intensity distributions as an alternative to mutual information [6]. Given an image $I(\mathbf{x})$ $\mathbf{x} \in \Omega$ and its noise level η, a measure ϵ for boundary "jumps" (locations with a high gradient) can be defined as

$$\epsilon := \eta \frac{\int_\Omega |\nabla I(\mathbf{x})| d\mathbf{x}}{\int_\Omega d\mathbf{x}}, \quad (2)$$

and with

$$\|\nabla I(\mathbf{x})\|_\epsilon := \sqrt{\sum_{i=1}^{d} (\nabla I(\mathbf{x}))_i^2 + \epsilon^2}, \quad (3)$$

the NGF of an image I is defined as follows:

$$\mathbf{n}_\epsilon(I, \mathbf{x}) := \frac{\nabla I(\mathbf{x})}{\|\nabla I(\mathbf{x})\|_\epsilon}. \quad (4)$$

NGF based similarity measures for the image registration of a test image S to a reference image R have been formulated based on either the scalar product or the cross product of the vectors of the NGF [6]:

$$F_{\text{NGF}}^{(\cdot)}(S, R) := -\frac{1}{2} \int_\Omega \|\mathbf{n}_\epsilon(R, \mathbf{x}) \cdot \mathbf{n}_\epsilon(S, \mathbf{x})\|^2 d\mathbf{x} \quad (5)$$

$$F_{\text{NGF}}^{(\times)}(S, R) := \frac{1}{2} \int_\Omega \|\mathbf{n}_\epsilon(R, \mathbf{x}) \times \mathbf{n}_\epsilon(S, \mathbf{x})\|^2 d\mathbf{x} \quad (6)$$

However, both similarity measures exhibit problems when it comes to their application. Even though the gradient of the scalar product based cost function $F_{\text{NGF}}^{(\cdot)}$(5) is analytically zero at the optimum, for practical implementations of the gradient evaluation, like e.g., finite differences, the gradient is non-zero at the optimum (i.e. even if $S = R$) making the optimization using gradient based methods difficult. On the other hand, when using the cross product based version (6), $F_{\text{NGF}}^{(\times)}(\mathbf{x})$ is not only zero when $\mathbf{n}_\epsilon(R, \mathbf{x})(\mathbf{x}) \parallel \mathbf{n}_\epsilon(S, \mathbf{x})(\mathbf{x})$ (as desired), but also when either $\mathbf{n}_\epsilon(R, \mathbf{x})$, or $\mathbf{n}_\epsilon(S, \mathbf{x})$ have zero norm.

Therefore, we propose a different similarity measure as

$$d(\mathbf{a}, \mathbf{b}) := \begin{cases} \mathbf{a} - \mathbf{b}, \text{if } \mathbf{a} \cdot \mathbf{b} > 0, \\ \mathbf{a} + \mathbf{b}, \text{otherwise} \end{cases} \quad (7)$$

$$F_{\text{NGF}}(S, R) := \frac{1}{2} \int_\Omega \|\mathbf{n}_\epsilon(R) \cdot d(\mathbf{n}_\epsilon(R), \mathbf{n}_\epsilon(S))\|^2 d\mathbf{x}. \quad (8)$$

This cost function needs to be minimized, is differentiable and its evaluation as well as the evaluation of its derivatives is straightforward, making it easy to use it for non-rigid registration. In the optimal case, $S = R$ the cost function and its first order derivatives are zero and the evaluation is numerically stable. $F_{\text{NGF}}(\mathbf{x})$ is minimized when $\mathbf{n}_\epsilon(R, \mathbf{x})(\mathbf{x}) \parallel \mathbf{n}_\epsilon(S, \mathbf{x})(\mathbf{x})$ (as desired) and even zero when $\mathbf{n}_\epsilon(R, \mathbf{x})(\mathbf{x})$ and $\mathbf{n}_\epsilon(S, \mathbf{x})(\mathbf{x})$ have the same norm, but also when $\mathbf{n}_\epsilon(R, \mathbf{x})$ has zero norm, thereby, reducing the number of undesired cases in comparison with (6).

C. The complete non-rigid registration method

The proposed similarity measure F_{NGF} is a local measure and is, therefore, well suited for the registration of images that exhibit local intensity change. However, the cost function is also zero (or close to zero) in homogeneous areas of the reference image. Therefore, good registration can only be achieved if either the images do not contain large homogeneous areas, or if a very "smooth" regularization $E(T)$ (eqn. 1) is used, and/or the transformation T is rather restricted.

To overcome these problems, our registration method uses a Laplacian regularization [7],

$$E_{\text{L}} := \int_\Omega \left\| \frac{\partial^2 T(\mathbf{x})}{\partial x^2} \right\|^2 d\mathbf{x} + \int_\Omega \left\| \frac{\partial^2 T(\mathbf{x})}{\partial y^2} \right\|^2 d\mathbf{x} \quad (9)$$

and the transformation is formulated in terms of B-splines [8], introducing a smoothness that can be adjusted by the number of control points.

In addition, we also compare a minimization of F_{NGF} (8) only with the minimization of a combination of the both functions F_{NGF} and F_{SSD} (10) to achieve registration.

$$F_{\text{SSD}}(S, R) := \int_\Omega (S(\mathbf{x}) - R(\mathbf{x}))^2 d\mathbf{x}. \quad (10)$$

As minimizer we use a Levenberg-Marquardt optimizer [9].

The image series to be registered consists of approximated 60 2D images. In order to reduce the influence of the changing intensities, a registration of all frames to one reference frame has been rules out and replaced by a serial registration. To reduce the accumulation of registration errors and in order to be able to choose a reference frame easily, the following procedure is applied: For each pair of subsequent images registration is done twice, one selecting the earlier image of the series as a reference (backward registration), and the second by using the later image as the reference (forward registration). Therefore, for each pair of subsequent images I_i and I_{i+1}, a forward transformation $T^{i,i+1}$ and a backward transformation $T^{i+1,i}$ is obtained. Consider the concatenation of two transformations

$$T_a(T_b(\mathbf{x})) := (T_b \oplus T_a)(\mathbf{x}); \qquad (11)$$

in order to align all image of the series a reference frame i_{ref} is chosen, and all other images S_i are deformed to obtain the aligned image $S_i^{(\text{align})}$ by applying the subsequent forward or backward transformations

$$S_i^{(\text{align})} := \begin{cases} S_i\left(\bigoplus_{k=i_{\text{ref}}}^{i+1} T^{k,k-1}(\mathbf{x})\right) & \forall i < i_{\text{ref}}, \\ S_i\left(\bigoplus_{k=i_{\text{ref}}}^{i-1} T^{k,k+1}(\mathbf{x})\right) & \forall i > i_{\text{ref}}, \\ S_{i_{\text{ref}}} & \text{otherwise.} \end{cases} \qquad (12)$$

In order to minimize the accumulation of errors for a series of n images one would usually choose $i_{\text{ref}} = \lfloor \frac{n}{2} \rfloor$ as the reference frame. Nevertheless, with the full set of forward and backward transformations at hand, any frame can be chosen.

III. EXPERIMENTS AND RESULTS

A. Experiments

First pass contrast enhanced myocardial perfusion imaging data was acquired during free-breathing using 2 distinct pulse sequences: a hybrid GRE-EPI sequence and a trueFISP sequence. Both sequences were ECG triggered and used 90 degree saturation recovery imaging of several slices per R-R interval acquired for 60 heartbeats. The pulse sequence parameters for the true-FISP sequence were 50 degree readout flip angle, 975 Hz/pixel bandwidth, TE/TR/TI= 1.3/2.8/90 ms, 128x88 matrix, 6mm slice thickness; the GRE-EPI sequence parameters were: 25 degree readout flip angle, echo train length = 4, 1500 Hz/pixel bandwidth, TE/TR/TI=1.1/6.5/70 ms, 128x96 matrix, 8 mm slice thickness. The spatial resolution was approximately 2.8mm x 3.5mm. Parallel imaging using the TSENSE method with acceleration factor = 2 was used to improve temporal resolution and spatial coverage. A single dose of contrast agent (Gd-DTPA, 0.1 mmol/kg) was administered at 5 ml/s, followed by saline flush. Motion compensation was performed for seven distinct slices of two patient data sets covering different levels of the LV-myocardium.

The Registration procedure used B-Splines of degree 2 and varying parameters for the number $l \in \{1,2,3\}$ of multi-resolution levels, the knot spacing $c_{\text{rate}} \in$

$\{32mm, 16mm, 12.8mm\}$ for the B-Spline coefficients, and the weight $\kappa \in \{0.8, 1.0, 2.0, 3.0\}$ of the Laplacian regularization term. Estimating the noise level of images is a difficult problem, we approximated η by $\sigma(\nabla I)$ standard deviation of the intensity gradient.

To ensure registration driving forces exist over the whole image domain, we also run experiments with the combined cost function $F_{\text{NGF}} + \frac{1}{10}F_{\text{SSD}}$ so that F_{NGF} would take precedence where both images exhibit strong gradients, and F_{SSD} otherwise. Since all images are of the same modality, we expect that combining the two measures will yield the same or better results. Tests showed that applying F_{SSD} as only registration criterion doesn't yield usable results.

B. Registration results

The quality of the registration was assessed visually observing videos as well as horizontal and vertical profiles through the time-series stack. An example of the profiles location is given in Fig. 2.
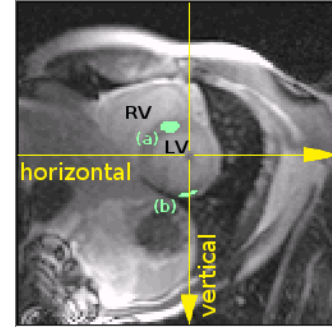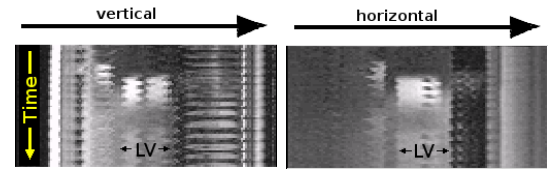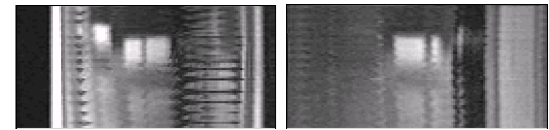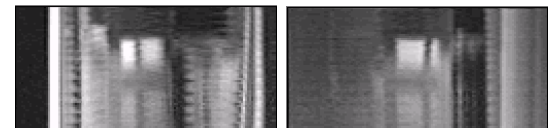

Fig. 2. Location of the vertical and horizontal profiles through the time series stack, and the septal (a) and inferior (b) ROIs for intensity tracking.

(a) Original image series

(b) Registration using NGF only, $\kappa = 1.0$, note the bad alignment and the drift in the second (lower) half of the series


(c) Registration using NGF + 0.1 SSD, $\kappa = 2.0$, the drift vanished and alignment is in general better then with NGF only

Fig. 3. Registration result by using $l = 3$ multi-resolution levels, and a knot spacing $c_{\text{rate}} = 16mm$. Left: vertical cut, right: horizontal cut.

We obtained the best results using $l = 3$ multi-resolution levels and a knot-spacing of $c_{\text{rate}} = 16mm$ in each spacial direction. For the registration using NGF, a regularizer weight $\kappa = 1.0$ yielded best results, whereas for the combination of NGF and SSD $\kappa = 2.0$ was best. The registration by using F_{NGF} yields good results for the first half of the sequence, where the intensity contrast is higher, and the gradients are, therefore, stronger. In the second half, the sequential registration resulted in a bad alignment and a certain drift of the left ventricle (Fig. 3 (b)). Combining F_{NGF} and F_{SSD} results in a significant improvement of the alignment for the second part of the sequence (Fig. 3 (c)) and provided similar results for the first half. Following this scheme, a good reduction of the breathing motion was achieved in six of the seven slices. In the seventh slice, which was located near the apex, the motion reduction was not as good, mainly due to strong out-of-plane motion.

The good registration results were confirmed by observing the (average) signal intensities time courses in different regions of the myocardium. Fig. 4 show the corresponding intensity curves of the ROIs (a) and (b) represented in Fig. 2. A clear improvement is observed that would definitely affect quantitative analysis.
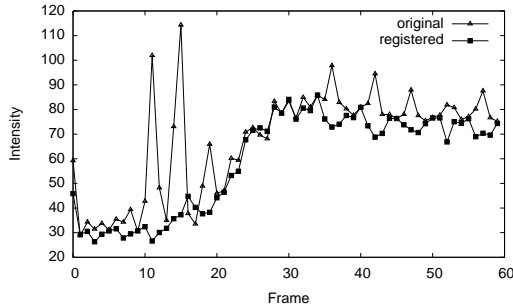
(a) Septal wall: good reduction of the strong intensity changes in the ROI, the residual fluctuation at the end of the series can actually be found in the original image series.
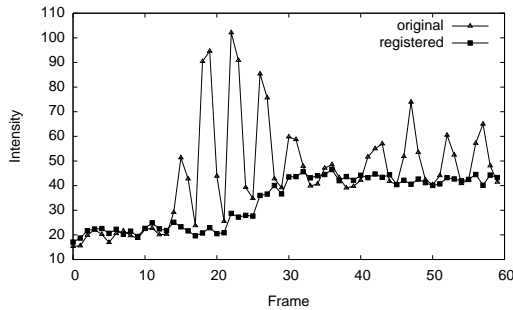
(b) Inferior wall: an infarcted area, the strong intensity changes due to the breathing movement are removed.

Fig. 4. Comparison of intensity change before and after registration in two regions of interest (a) and (b) as specified in Fig. 2 of a patient with chronic MI in the mid-posterior region (inferior to inferolateral).

IV. CONCLUSIONS AND FUTURE WORK

We have introduced a new measure F_{NGF} (8) that is based on a proposal by Haber and Modersitzki [6] and uses normalized gradient fields as a similarity measure for series of images obtained by non-rigid registration of myocardial perfusion MRI. Our experiments show that using this measure alone yields a good registration only for images of the series that exhibit a high contrast and, hence, strong gradients in the ROI, but results in a smooth shift of the registered series and a bad alignment, when the intensity contrast is low.

We were able to improve the latter results by combining F_{NGF} (8) and F_{SSD} (10) in a way that the NGF based cost function takes precedence in regions with strong gradients, while SSD ensures a steady registration in areas with low contrast.

In the future work, we will focus on validating the automatically registered areas of interest by comparing with manually tracked contours. Based on this we will apply a further tuning to the registration parameters. Specifically, the weighting between F_{NGF}, F_{SSD}, and the weighting of the regularizer need a further review. With a proper validation protocol in place, we would like to compare our method with approaches utilizing MI based criteria in terms of registration accuracy and speed as well.

V. ACKNOWLEDGMENTS

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