# Model-based alignment of Look-Locker MRI sequences for calibrated myocardical scar tissue quantification

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**Abstract**

The characterization of myocardial scar tissue in Late Gadolinium Enhancement (LGE) MRI volumes is hampered by the non-quantitative nature of MRI image intensities. Using the widely available Look-Locker (LL) sequence a T1 map can be created per patient to calibrate the LGE datasets. However, during the LL acquisition, the myocardium is imaged at different phases of the cardiac cycle, resulting in deformations between frames of the LL stack and preventing accurate T1 map estimates.

In this paper a method is proposed for the concurrrent non-rigid alignment of the LL stack that uses a model of the exponential contrast development throughout the LL stack. The model based alignment is shown to be more robust than a pairwise mutual information based alignment. More importantly, correlations between the relaxivity (R1) map and the LGE intensities (needed for the LGE calibration) are higher using the proposed alignment than when using manual annotations.

The model based alignment allows the use of the LL sequence for LGE calibration without manually annotating the (typically) 33 frames in this sequence. Thereby the proposed calibration in feasible within clinical studies and eventually diagnosis.

## 1 Introduction

Scarring of myocardial tissue is often diagnosed using Late Gadolinium Enhancement (LGE) MR images. Although an LGE volume generally shows good contrast between infarcted and non-infarcted myocardium (Figure 1), the non-quantitative nature of the LGE acquisition gives rise to differences in appearance that may influence the estimated infarct size.

To calibrate the LGE acquisition, recently quantitative T1 mapping techniques have been proposed, particularly based on the Look-Locker (LL) and MOLLI (a modified Look-Locker, requiring an extra acquisition) sequences [3]. These sequences image the heart (after contrast injection) at multiple inversion times (TI) and estimate a T1 by fitting an exponential model

through corresponding pixels (Figure 1). The inverse T1 map, the relaxivity (R1) map, has a nearly affine relation with the intensities in the LGE acquisition [2].

To avoid an extra acquisition we propose to calibrate the LGE volume using the LL sequence. This low-resolution sequence is *by default* acquired before an LGE acquisition to estimate an appropriate inversion time (TI) for nulling out the healthy myocardium.

However, contrary to MOLLI, LL frames are acquired at different phases of the cardiac cycle. Alignment of the LL stack is not trivial as contrast differs considerably between frames. Currently the alignment problem is mainly solved by manual contour annotation of all (typically 33) frames in an LL sequence. Recent work on the alignment of (contrast varying) cardiac MR perfusion images uses independent component analysis in patients at rest [5] and free breathing [8] and frequency domain based registration in patients under induced stress [1]. These methods, however, only use a rigid alignment and use limited knowledge of the process that causes the contrast change. The LL contrast change is accurately described by an exponential model with an offset, similar to [7], but this method does not allow the inclusion of a spatially varying constant term in the exponential.

To enable the use of the readily available Look-Locker sequences for a reliable quantification of scar tissue in LGE a new method is proposed in this paper to simultaneously align the Look-Locker and estimate the model parameters. This method limits the user-input to the annotation of a single myocardium in the LGE slice and is validated on scans of 25 patients.

# 2 Methods

## 2.1 Calibration of late Gadolinium enhancement MRI

In standard MR protocols, the Look-Locker sequence is performed after contrast injection and precedes the LGE sequence to determine the optimal inversion time (TI), for which the healthy myocardium is nulled out. The LL sequence acquires images using different TI's to estimate the entire MR relaxation process (Figure 1). In general the Look-Locker sequence has a lower acquisition resolution than the LGE acquisition.

The absolute intensities in the LGE are not directly related to tissue specific T1 times such as 338.9±44.1ms for viable tissue and 264.8±35.3ms for fibrotic tissue [4]. However, by scanning corresponding frames in both LL and LGE sequences, the LGE intensities can be calibrated. Assuming that pixelwise correspondence is available between all frames of the LL sequence and the corresponding LGE slice, a T1 map can be obtained by least-squares fitting an exponential function $f_t$ to the intensities $i_t$ per TI for each pixel:

$$i(t) \approx f(t) = a - be^{-t/T1^*} \tag{1}$$

where $t$ is the TI used for one of the frames in the LL stack. When fitting, one should take into account that only absolute intensity values are measured, as in the example curve in Figure 2(a). From this, the T1 value can be obtained as [4]:

$$T1 = T1^* \left((b/a) - 1\right) \tag{2}$$

and R1 as 1/T1. The R1 map is then related to the intensities in the LGE slice by sampling both the R1 values and corresponding LGE intensities between the annotated contours (Figure 1) and performing a linear regression between LGE intensities and the R1 values [2].

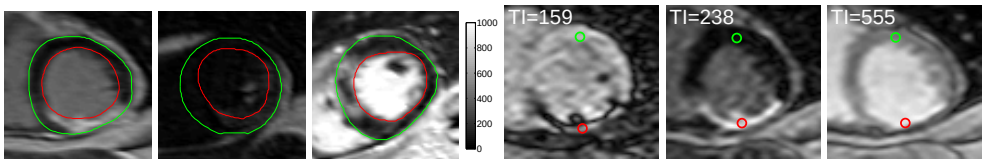



Figure 1: Left: Example LGE slices from three patients, where annotated epi (green) and endo (red) contours denote the mycardium. Infarcted tissue in the myocardium is bright (high Gadolinium uptake), non-infarcted tissue is dark, but the absolute values (see colorbar) vary widely. Right: Example LL frames corresponding to the leftmost LGE slice

### 2.2 Model based Look-Locker stack alignment

The fitting in (1) requires alignment of all frames within the LL stack. The final calibration also requires alignment between the LL stack and the LGE slice to account for patient motion and cardiac phase differences. We propose to first align all frames within the LL stack and subsequently register this stack to the LGE slice using the fit (1).

Mewton, et al. [4], for example, show that the exponential model (1) closely approximates the actual intensity values (See also Figure 2(a)). Therefore it is to be expected that in the case of misalignment the fitting error increases. When using a least-squares fitting to obtain an estimated model $f_x(t,\theta)$ at each pixel location $x$ with intensities $i_x(t,\theta)$, the error to be minimized by adapting the transformation parameters $\theta$ becomes:

$$C = \sum_{x\in\Omega}\sum_{t\in\mathcal{T}_i} \|i_x(t,\theta) - f_x(t,\theta)\|_2^2 \tag{3}$$

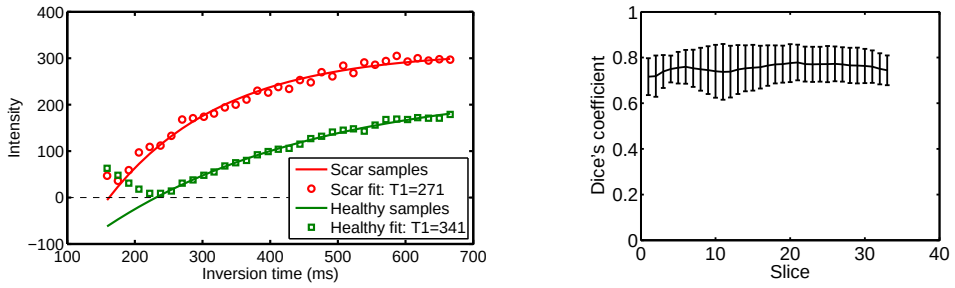
where $\Omega$ is the image domain and $\mathcal{T}_i$ is the set of inversion times in the LL stack. Both $i_x(t,\theta)$ and $f_x(t,\theta)$ are affected by the transformation parameters $\theta$. In this work a b-spline deformation model is used to parameterize the non-rigid transformation, regularized with a bending energy penalty [6]. B-spline spacing was experimentally determined to be optimal in the order of 16 mm with a low bending energy penalty such that only severe local deformations were suppressed. Because of the large number of model parameters to estimate (per pixel: $a$, $b$, and $T1^*$), an expectation-maximization approach is used to minimize $C$: alternatingly the models $f_x(t,\theta)$ are estimated (in closed form) and the frames of the LL stack are registered. Convergence to a local minimum is guaranteed as both steps minimize $C$ (3).

The registered LL stack and the fit model are aligned with the corresponding LGE slice by generating an artificial image $I_f$ from the fit model using the same inversion time $t$ as used for the LGE acquisition. Normalized cross correlation is used as similarity measure. The transformation model is the same regularized b-spline as during the LL stack alignment. All registrations are performed using `elastix (www.elastix.org)`.

## 3 Experiments

### 3.1 Data description

Data from 25 patients was acquired using a 1.5-T MRI scanner (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands). A Look-Locker sequence was acquired 15 minutes after injection of gadolinium DPTA. The slice in the LL sequence contained the myocardium part where scar was expected. Typically 33 LL frames were acquired at uniformly




(a) (b)

Figure 2: (a) Example model fits from samples in the frames in Figure 1 at the red (scar) and green (healthy) annotated points that describe the relation between TI and signal intensity, including T1 estimates. (b) Average Dice coefficients per slice after the proposed model based alignment. Error bars denote standard deviations.

spaced inversion times, with T1-weighted LGE images three to four minutes later. The *reconstruction* pixel sizes of both the LL and LGE acquisitions was $1.56 \times 1.56$ mm.

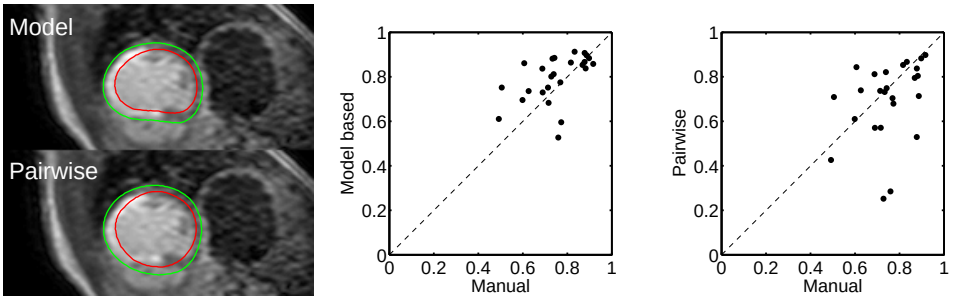
## 3.2 Registration accuracy

The registration accuracy of the proposed alignment method was evaluated by manually annotating the contours of the myocardium in the original LL stack and evaluating the alignment of these contours after registration. To this end, the Dice coefficients of the area between the epi and endo contours of the middle slice and each of the other frames were computed as well as the distances between contours. The latter were estimated as distances between closest points with both contours used for closest point search. These numbers were compared to aligned LL stacks that were obtained by pairwise registering the frames of the LL stack to the middle slice using normalized mutual information as similarity criterion.

After the model based alignment the mean Dice coefficients over all 33 frames of 25 patients was 0.76 with a standard deviation (SD) of 0.09 (Results per frame in Figure 2(b)). The mean pairwise Dice coefficient was lower, at 0.70 (SD 0.16). A clear trend was visible in both the model based alignment and the pairwise results, where especially the frames for low inversion times (and low constrast) were less accurately registered. The average epi and endo contour distances after model based alignment were 2.7 (SD 1.0) and 2.1 (SD 0.7) mm, respectively. For the pairwise registration these numbers were 3.6 (SD 2.0) and 2.8 (1.7) mm, respectively. The contour distances also showed the worst results for small inversion times. For the pairwise registration, larger errors tended also to occur for the endo contour for larger inversion times, even excluding the scar tissue as in Figure 3(a).

## 3.3 Correlation between T1 map and LGE intensities

The suitability of using the automatically aligned LL stack for the calibration of LGE slices was investigated by computing the correlation between the R1 map and the intensities of the LGE slice in the myocardium as annotated in the LGE slice. Furthermore the fitting errors are reported for both aligned (model based and pairwise) and manually annotated LL stacks.




(a) (b) (c)

Figure 3: (a) Example with correctly propagated contours (model based) and incorrectly propagated contours (pairwise). (b,c) Correlation between R1 maps and LGE intensities for three different alignment methods: (b) manual vs. model based (c) manual vs. pairwise.

The measured correlations between the R1 map and the LGE intensities for the 25 datasets are in Figure 3 for all three methods. The average correlations over the 25 datasets were 0.79 (model based, SD 0.11), 0.70 (pairwise, SD 0.18) and 0.75 (manual, SD 0.12). Figure 3(b) shows that in a patient by patient comparison the model based approach tended to give higher correlations between R1 map and LGE intensities than the manual method, while the Figure 3(c) showed poor correlations for the pairwise alignment. The model based correlations were statistically significantly ($P<0.05$) higher than after pairwise alignment but not statistically significantly higher ($P=0.078$) than when based on the manual annotations.

Due to large differences in intensities between LL stacks of different patients, reported fitting errors are normalized to the average intensities. The mean fitting errors were 0.157 (model based, SD 0.025), 0.163 (pairwise, SD 0.025) and 0.167 (manual, SD 0.025). Using a pairwise t-test, the fitting errors were statistically significantly ($P<0.05$) smaller when using the proposed model based alignment, compared to both other methods.

# 4 Discussion

To calibrate late Gadolinium enhancement acquisitions of myocardial scar tissue using readily available Look-Locker sequences, an alignment method was proposed that uses a model of the LL intensity dependence on the inversion time.

The accuracy of the model based alignment compared favourably to a pairwise registration using manually drawn contours as the ground truth. Especially in low contrast LL frames the model based alignment was more robust than the pairwise alignment. The robustness of the model based alignment can be appreciated from Figure 4 where the LL sequence is correctly aligned despite a clear artifact.

Correlations between R1 maps and LGE intensities showed higher correlations based on the model based alignment than from manual annotations and especially compared to the pairwise alignment. Although the relation between the R1 map and the LGE intensity values is only approximately linear, the high correlations, despite the noisy images, showed that the aligned LL sequences are indeed suitable for LGE calibration. This is further illustrated in Figure 4 where scar tissue is identified by simply thresholding the LGE intensities based on their correlation with the R1 map. Although a better segmentation procedure is needed to

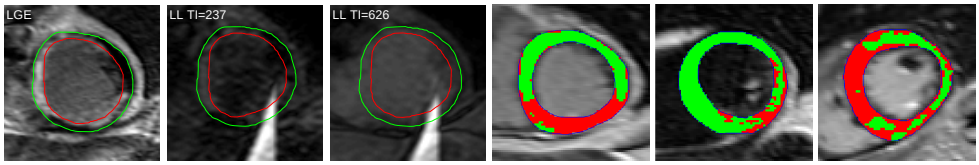



Figure 4: Left: LGE slice and corresponding LL frames with artifacts. The contours in the LL frames are propagated from the LGE slice. Right: The example LGE slices from Figure 1 with identified scar (red) and healthy (green) tissue through a simple thresholding T1 values at $(338.9+264.8)/2 = 301.9$ (See the T1 values in Section 2.1)

reliably identify the scar tissue, this shows that using the proposed alignment and calibration scars can be identified robustly in LGE acquisitions with greatly varying intensity ranges.

The implementation of the current expectation-maximization is non-optimized and requires approximately 15 minutes per sequence for about 20 iterations. In future work this implementation will be improved, expecting a 10-fold reduction in computation time.

The improved R1 vs. LGE correlations compared to manual annotations were especially encouraging because the manual annotation of the 33 frames is no longer needed. This may greatly help the introduction of calibrated myocardial scar tissue quantification in the clinic.

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