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Image registration and analysis for quantitative myocardial perfusion: application to dynamic circular cardiac CT

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Abstract

Large area detector computed tomography systems with fast rotating gantries enable volumetric dynamic cardiac perfusion studies. Prospectively, ECG-triggered acquisitions limit the data acquisition to a predefined cardiac phase and thereby reduce x-ray dose and limit motion artefacts. Even in the case of highly accurate prospective triggering and stable heart rate, spatial misalignment of the cardiac volumes acquired and reconstructed per cardiac cycle may occur due to small motion pattern variations from cycle to cycle. These misalignments reduce the accuracy of the quantitative analysis of myocardial perfusion parameters on a per voxel basis. An image-based solution to this problem is elastic 3D image registration of dynamic volume sequences with variable contrast, as it is introduced in this contribution. After circular cone-beam CT reconstruction of cardiac volumes covering large areas of the myocardial tissue, the complete series is aligned with respect to a chosen reference volume. The results of the registration process and the perfusion analysis with and without registration are evaluated quantitatively in this paper. The spatial alignment leads to improved quantification of myocardial perfusion for three different pig data sets.

(Some figures in this article are in colour only in the electronic version)
1. Introduction

Myocardial perfusion imaging can be used to measure the oxygen supply of muscle tissue in the heart. Therefore, the heart of the patient is imaged in 3D before and during injection of radio-opaque contrast material, and the differences in the reconstructed images can be attributed to the contrast material that is washed in George et al (2006). Myocardial perfusion imaging by multi-slice computed tomography (CT) represents a promising tool to detect the significance of a stenosis at the tissue level, i.e. to detect the presence of myocardial ischemia (Nikolaou et al 2005, Lardo et al 2006, Lessick et al 2007). Moreover, assessment of the heart muscle viability can allow distinguishing between necrotic and dysfunctional but viable tissues after acute or chronic ischemia, and can support the diagnosis and treatment of acute infarctions (Tilton et al 1983, Lessick et al 2007).

Hypoenhanced regions on the initial scan, and hyperenhanced regions on late scans obtained 5–15 min after contrast material injection represent two types of abnormal myocardial enhancement patterns which have been described in the literature (Nikolaou et al 2005, Lardo et al 2006, Lessick et al 2007). A strong relationship between the presence and size of these two abnormal myocardial defects and the degree of follow-up regional dysfunction after acute myocardial infarction was observed (Lessick et al 2007). Also, the probability of myocardial functional recovery is significantly inversely related to the presence and size of both early hypoenhanced and late hyperenhanced regions (Lessick et al 2007). Animal studies have shown early hypoenhancement to be a measure of low reflow regions, which may result from abnormal flow at the level of either the epicardial artery and/or the myocardial capillaries (Rochitte et al 1998, Mochizuki et al 1999, Paul et al 2005, Lardo et al 2006, Lessick et al 2007). Late hyperenhancement has been shown to be a marker of necrotic tissue (Rochitte et al 1998, Lessick et al 2007). The mechanism of hyperenhancement of healed myocardial infarction or collagenous scar is thought to be related to an accumulation of contrast media in the interstitial space between collagen fibers (Lardo et al 2006, Lessick et al 2007).

A cardiac CT scan (e.g. circular scanning-mode) can be applied to generate a sequence of volumes acquired during the first pass of a contrast agent (CA) bolus. Then, the x-ray attenuation changes for each voxel in the acquired images can be visually evaluated by using the corresponding time-intensity curves (Miles 1991, Stantz et al 2003). Moreover, these time–intensity curves can be used as an input for the assessment of quantitative perfusion-related parameters (Miles 1991, Stantz et al 2003). A consistent quantitative evaluation of the CA presence over time requires the alignment of corresponding voxels in all temporal frames of the 4D perfusion data set. Unfortunately, obtaining spatially aligned images is a difficult task in cardiac CT, in which image misalignment due to patient breathing and poor ECG synchronization is commonly observed.

Post-processing misalignment correction, also called image registration, represents a potential solution to increase time sequence alignment (Rueckert et al 1999, Hill et al 2001, Kybic and Unser 2003, Crum et al 2004). Registration techniques can be categorized according to the transformation’s degrees of freedom. The most well-known example is the rigid or affine transformation that can be described very compactly by 6 (3 translations and 3 rotations) to 12 (6 + 3 scalings + 3 shears) parameters for a whole image (Hill et al 2001). Rigid registration of bone and brain images has been frequently applied in the literature (Zhu and Cochhoff 2002). However, most of the human organs (e.g. the heart) do not conform to a rigid or even an affine approximation. To produce an optimal alignment non-rigid or elastic models are appropriate. Non-rigid registration techniques (Rueckert et al 1999, Kybic and Unser 2003, Crum et al 2004) treat images as linear, elastic solids and deform them using forces derived from an image dissimilarity measure.
The big challenge in perfusion CT image alignment is the dramatic change of the image intensity over time. This contrast variation has to be taken into account during the registration step. An explicit way to handle this problem is a registration process using time varying reference images. An example of this approach is the serial registration scheme registering pairs of consecutive images. Since the CA diffuses continuously, two consecutive images are almost similar and in principle this will lead to an accurate correction of misalignment. Nevertheless, errors in the registration of one image pair propagate through the whole temporal sequence and accumulate.

A potential implicit solution is registration based on a similarity measure that does not rely on a linear or monotonic relation between image intensities (e.g. mutual information (MI) Thévenaz and Unser 2000, Pluim et al 2003). This solution has already been applied in several prior studies where rigid or elastic image registrations (EIR) were applied for magnetic resonance (MR) myocardial perfusion dataset alignment (see Milles et al 2008 and references therein). The non-negligible drawback of the MI metric is its computational effort. In an earlier work, Wollny et al (2008) proposed to use a combination of modified normalized gradient fields (Haber and Modersitzki 2005) and sum of squared difference as registration criterion. This alternative normalized-gradient-based approach is deterministic, much simpler, fast to compute and also much more suitable to optimize than MI. The zero mean normalized cross-correlation (ZNCC) can be an alternative faster image registration metric. The inherent normalization of the ZNCC allows us to register variations in the images in the presence of brightness.

In this paper, it is proposed to apply a non-rigid registration method with ZNCC as a similarity measure to achieve an effective quantification of myocardial perfusion. Given a cardiac 4D CT data set (section 2.1), all frames are registered to a reference image where the myocardial region of interest (ROI) is well delineated (section 2.3). Subsequently, a quantitative analysis is performed by calculating the area under curve (AUC) and the peak intensity (PI) (section 2.4). The method is evaluated on three pigs (two healthy animals and one pig with myocardial infarction) and quantitative perfusion maps of the registered and non-registered data sets are calculated and presented (section 3). Sections 4 and 5 contain the discussion and conclusion, respectively.

2. Method

In the following subsections, the components of the proposed perfusion analysis are presented. First, the methods applied for the generation of the 4D CT image (subsection 2.1) and for image filtration (subsection 2.2) are briefly discussed. Subsequently, in subsection 2.3 the image registration applied for the spatio-temporal alignment of the data set is described. Finally, the calculation of the perfusion parameters is introduced (subsection 2.4).

2.1. Generation of 4D image data sets

A 4D cardiac image data set is required for the determination of the perfusion parameter. The images are obtained by continuously acquiring projection data \( p \) with a CT scanner equipped with a focus-centered 2D detector and an x-ray source moving on a circular path around the anatomy. The circular scan is performed with multiple rotations \( N_{\text{rot}} \). The ECG is recorded in parallel. Depending on the animals heart rate, data are acquired during \( M \) cardiac cycles. The acquisition with a cone–beam CT system can be described as follows. The x-ray source rotates around the object at the position \( z = z_0 \) on a circular trajectory \( S(\lambda) = (R \cos(\frac{\lambda}{N_{\text{rot}}} \pi), R \sin(\frac{\lambda}{N_{\text{rot}}} \pi), z_0) \). The rotation axis coincides with the \( z \)-axis. The
Figure 1. Circular CT data acquisition for dynamic cardiac imaging. An ECG is acquired simultaneously to the continuous circular CT scan. Thus, a certain number of time frames can be reconstructed out of the continuous axial scan, depending on the heart rate of the animal. The time frames are reconstructed from subsections (grey intervals) with an angular range of $220^\circ$ centered around the chosen cardiac phase point $P_t$.

Parameter $\lambda = 0..\Lambda_{\text{tot}}$ describes the discrete angular position of the source and $\Lambda_{\text{tot}}$ is the number of angular source positions per rotation. $\Lambda_{\text{tot}}$ is the total number of angular source positions, $N_{\text{rot}} = \Lambda_{\text{tot}}/\Lambda_{\text{rot}}$ denotes the total number of rotations, and $R$ is the radius of the circle.

In the same way as already known from helical cardiac CT, a phase-point position can be chosen as a percentage of the RR interval, resulting in $M$ phase points $P_t$, with $t = 0, \ldots, M-1$, at the angular position $\lambda (P_t)$ (Manzke et al 2003). The position of the phase points defines the motion state of the heart. A rectangular cardiac gating window (see figure 1) is centered at each phase point $P_t$ and only projections $p(\lambda)$ within this time window are used during each single-cycle reconstruction.

For the image reconstruction of each image $f_P (x, t)$ per cardiac cycle, a single-cycle variant of the reconstruction method described in Koken and Grass (2006) for the helical case and in van Stevendaal et al (2006) for the circular cone-beam case was used. The reconstruction formula per time frame reads

$$f_P (x, t) = \frac{1}{2\pi} \int_{\lambda (P_t) - \frac{W}{2}}^{\lambda (P_t) + \frac{W}{2}} w_{\text{ap}}(\lambda, x) \cdot p_f (\lambda, u, h) \, d\lambda.$$  \hfill (1)

Here, the backprojection interval is limited to an angular range of $\pi$ plus fan angle $\beta$ by $W = \pi + \beta$. Aiming at the best achievable temporal resolution an angular coverage of $W = 220^\circ$ is used per cardiac cycle. The aperture weighting function $w_{\text{ap}}$ defines a trapezoidal cone-beam weighting function (Koken and Grass 2006, van Stevendaal et al 2006) and $p_f$ are the rebinned and filtered cone-beam projections. They depend on the source angular position $\lambda$, the distance of the line integrals from the rotation axis $u$ and the detector height projected onto the rotation axis $h$.

2.2. Spatio-temporal bilateral filtration

Image noise and artefacts can hamper an accurate quantitative analysis of myocardial perfusion. Here, a spatio-temporal diffusion filtration for dynamic CT data (Bruder et al 2009) is applied.
to overcome this problem. This bilateral filter is applied to the 4D data set \(f_P\) in two different steps. First, given a certain temporal position (i.e. cardiac cycle) \(t^*\) of the dynamic CT data set, with \(t^* \in [0, M - 1]\), a filtration is performed in the spatial domain by

\[
\hat{f}_P(x, t^*) = \frac{1}{N^S_{\text{norm}}(x, t^*)} \sum_{y \in \Omega_{26}(x)} d(|y - x|) \cdot K(\|f_P(y, t^*) - f_P(x, t^*)\|) \cdot f_P(y, t^*). \tag{2}
\]

Here, \(\Omega_{26}(x)\) is the 26-connected neighbourhood of the image voxel at position \(x = (x, y, z)\), \(\hat{f}_P\) denotes the filtered image, while the normalization factor \(N^S_{\text{norm}}(x, t)\) reads

\[
N^S_{\text{norm}}(x, t) = \sum_{y \in \Omega_{26}(x)} d(|y - x|) \cdot K(\|f_P(y, t) - f_P(x, t)\|), \tag{3}
\]

where \(d\) indicates the inverse Euclidean distance and \(K\) is a function of the local gradient of the grey values.

In a second step, the filter operates on image data of adjacent temporal positions, and for a given image voxel \(x^*\) it reads

\[
\hat{f}_P(x^*, t) = \frac{1}{N^T_{\text{norm}}(x^*, t)} \sum_{m \neq 0} d(|(t + m) - t|) \cdot K(\|f_P(x^*, t + m) - f_P(x^*, t)\|) \cdot f_P(x^*, t + m). \tag{4}
\]

Here, \(\nu\) denotes the temporal window radius, while \(N^T_{\text{norm}}\), similar to \(N^S_{\text{norm}}\) in equation (3), denotes a normalization factor which operates along the temporal direction.

The right choice of the range filter \(K\) is crucial for smoothing noise in homogeneous regions maintaining at the same time spatial and temporal sharpness of the images. As proposed in Bruder et al (2009), a Gaussian weight is applied as a stop function in the spatial domain:

\[
K(\|f_P(y, t) - f_P(x, t)\|) = \exp\left(-\left(\frac{\|f_P(y, t) - f_P(x, t)\|}{S_\sigma}\right)^2\right). \tag{5}
\]

The parameter \(S_\sigma\) is correlated to the level of the image noise and has to be carefully adjusted for preserving edges while reducing noise in homogeneous image regions. A corresponding function is applied in the temporal direction and its parameter \(T_\sigma\) has to be adapted (Bruder et al 2009).

In this work, for the selection of \(S_\sigma\) and \(T_\sigma\), the image noise in the myocardium in a ROI in one time frame was calculated. For this purpose, a muscle ROI with limited contrast enhancement over time (muscle region outside the myocardium) was selected to measure the spatial standard deviation. The same measurement was applied along the temporal axis for the same ROI to determine the standard deviation along the temporal axis. Both \(S_\sigma\) and \(T_\sigma\) have been chosen in this study as 1.5 times the noise value (standard deviation in HU) as suggested by Bruder et al (2009). Since the presented studies were all similar with regard to the x-ray dose applied in one time frame (in mAs), they had similar noise characteristics, and therefore the same \(S_\sigma\) and \(T_\sigma\) could be used for all studies. In subsection 3.2, a study on the sensitivity of the calculation of the perfusion parameter to the parameters \(S_\sigma\) and \(T_\sigma\) will be given.

2.3. The EIR framework

Even in the case of highly accurate ECG gating or triggering and stable heart rate, spatial misalignment of the cardiac volumes acquired and reconstructed per cardiac cycle may occur due to small motion pattern variations from cycle to cycle. These misalignments reduce the
accuracy of the quantitative analysis of myocardial perfusion parameters on a per voxel basis. An image-based solution to this problem is 3D–3D EIR (Rueckert et al 1999, Kybic and Unser 2003) of dynamic volume sequences with variable contrast. Given the filtered 4D image data set, the time frame with the maximum image energy $E_{\text{ref}}$ is automatically selected as the reference image:

$$\hat{f}_P(x_{\text{ref}}) = \hat{f}_P(x, t_{\text{ref}})$$

with $E(\hat{f}_P(x, t_{\text{ref}})) = \max_{t = 0, \ldots, M-1} \left\{ \sum_{j=0}^{N_{\text{vox}}-1} \hat{f}_P(x_j, t)^2 \right\}$, (6)

where $N_{\text{vox}}$ denotes the number of image voxels. Generally, this frame corresponds to the time when a large amount of CA is present within the heart chambers. Hence, the myocardium is well delineated. Subsequently, the reference volume $\hat{f}_P(x, t_{\text{ref}})$ is propagated to the other time frames $\hat{f}_P(x, t)$ using an EIR approach. The basic EIR technique can be summarized as follows. Given a pair of images $\hat{f}_P(x, t_{\text{ref}})$ and $\hat{f}_P(x, t)$, which can be called reference and test images, the main task of the EIR is to find a deformation field $g$ such that $\hat{f}_w(x, t) = \hat{f}_P(g(x), t) \approx \hat{f}_P(x, t_{\text{ref}})$, where $\hat{f}_w(x, t)$ is the warped test image. A minimization problem is solved to determine the deformation field $g$ which minimizes an image dissimilarity measure that is computed for each grid position in the reference $\hat{f}_P(x, t_{\text{ref}})$ and warped test $\hat{f}_w(x, t)$ images.

In this paper, a voxel intensity-based registration algorithm similar to that described in section II.C of Isola et al (2010) is applied. Here, the images and the deformation field $g$ are represented by cubic B-spline bases (Unser et al 1993a, Isola et al 2010, section II.C.1):

$$g(x) = x + \sum_{l \in L_q} k_l \beta_3(x/q - 1),$$

(7)

where $\beta_3$ is a 3D tensor product of 1D centered cubic B-spline, $k_l$ denote the corresponding expansion coefficients, $L_q$ is a grid of control points and $q = (q_x, q_y, q_z)$ is the knot spacing. The scale parameter $q$ can be used to set the desired node spacing, which determines the level of smoothness of the deformation field $g$.

A characteristic feature of myocardial perfusion imaging is the dramatic contrast variation with time that has to be taken into account for proper registration. Taking into account contrast variations over time leads to the application of the ZNCC as a dissimilarity measure. To encourage invertible solution, a topology-preserving smooth penalty function (Chun and Fessler 2009) is combined with the previous dissimilarity measure (Isola et al 2010, section II.C.2). In order to minimize the dissimilarity criterion, differently from what was proposed in Isola et al (2010), section II.C.3, here a stochastic gradient descent optimization method with adaptive step size prediction (ASGD) (Klein et al 2009) is applied. The stopping criterion for the optimization process is represented by reaching the maximum number of iteration, or when the relative and absolute improvement of the criterion value are smaller than a fixed threshold. Finally, a multi-resolution approach (Unser et al 1993b) is applied to avoid a local minimum (Isola et al 2010, section II.C.4). The registration method’s workflow is summarized by the diagram in figure 2.

2.4. Perfusion parameters

A 4D perfusion CT sequence consists of a set of frames $\hat{f}_P(x, 0), \ldots, \hat{f}_P(x, M - 1)$. For a given image voxel $x^* = (x^*, y^*, z^*)$, the time series of the corresponding values $\hat{f}_P(x^*, t)$ of all volumes of the perfusion sequence yields the individual local time–intensity (T–I) curve.
2.4.1. The CA arrival time. In order to determine the perfusion-related parameters, the arrival time \( t_0 \) of the CA in each point of the reconstructed field of view (FOV) is required. The way to evaluate the CA arrival time can change with regard to the particular application and the tissue perfusion model used. Generally, the local CA arrival time \( t_0 \) is the earliest significant intensity increase in the perfused tissue after the injection of the CA bolus. It corresponds to the frame number when the T–I curve begins to rise. In this work, a global temporal parameter \( t_0 \) is automatically evaluated by the following procedure (figure 3(a)): first, a mean T–I curve \( \bar{f}_P(t) \) consisting of the mean voxel–intensity values in each frame of the 4D CT data set is determined by

\[
\bar{f}_P(t) = \sum_{j=0}^{N_{\text{vox}}-1} \hat{f}_P(x_j, t) \quad \text{with} \quad t \in [0, M-1].
\] (8)

Subsequently, the maximum up-slope of this curve is determined as the maximum of the first derivative, while the second derivative changes from positive to negative:

\[
\bar{f}_P'(t_{mu}) = \max_{t=0, \ldots, M-1} \left\{ \bar{f}_P'(t) \right\}
\] (9)

with \( \bar{f}_P''(t_{mu} - 1) < 0 \) and \( \bar{f}_P''(t_{mu} + 1) > 0 \).

Starting from the timepoint \( t_{mu} \), the curve is back-traced until the slope either becomes insignificantly small or negative (figure 3(a)):

\[
\bar{f}_P'(t_0) < \epsilon \quad \text{with} \quad t_0 \in [0, t_{mu}], \quad \epsilon > 0.
\] (10)
Figure 3. Perfusion parameters. In (a) the automatic global CA arrival time determination approach is shown. In (b) a sketch of a T–I curve is shown. Here, all described parameters except $t_0$ are calculated locally.

2.4.2. Area under curve. The parameter AUC is achieved by the summation of the intensities for each voxel starting with the frame $\hat{f}_P(x, t_0)$, which corresponds to the frame of first occurrence of the CA (i.e. global arrival time $t_0$). The local baseline intensity $I_0(x)$ of each voxel is subtracted before the summation. The baseline intensity $I_0$ represents the pure tissue intensity without any CA (figure 3(b)). It can be estimated by the voxel-wise mean of all images acquired before the global CA arrival time $t_0$, and reads

$$I_0(x) = \frac{1}{t_0} \sum_{t=0}^{t_0} \hat{f}_P(x, t).$$

(11)

The interesting part of the T–I curve for the AUC parameter starts where the curve begins to rise and should include the peak. To be able to compare the sum within the parametric image, the summation must always include the same number of frames. It is not possible to let the summation stop at the peak frame since the number of this frame varies between different voxels. The solution is to let the summation stop at time $t_0 + r$ with $r$ set manually. The AUC parameter is given by

$$\text{AUC}(x) = \sum_{t=t_0}^{t_0+r} \hat{f}_P(x, t) - I_0(x).$$

(12)

The AUC parameter gives information about the blood volume passing through the selected myocardial tissue (figure 3(b)).

2.4.3. Peak intensity. The PI (also called peak enhancement) flow parameter is obtained by the intensity difference between the baseline intensity $I_0(x)$ and the maximum intensity $I_{\text{max}}(x)$ at a point $x$. This is because the PI takes into account only the tissue intensity in the image based on the CA (figure 3(b)):

$$PI(x) = I_{\text{max}}(x) - I_0(x) \quad \text{with} \quad I_{\text{max}}(x) = \max_{t=0,...,M-1} \left\{ \hat{f}_P(x, t) \right\}.$$

(13)
Table 1. CT scanning and reconstruction parameters.

<table>
<thead>
<tr>
<th>Clinical case</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan trajectory</td>
<td>Circular</td>
<td>Circular</td>
<td>Circular</td>
</tr>
<tr>
<td>ECG gating</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>Collimation (mm)</td>
<td>64×0.625</td>
<td>64×0.625</td>
<td>64×0.625</td>
</tr>
<tr>
<td>Rotation time (s)</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
</tr>
<tr>
<td>Tube voltage (keV)</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Anode current (mA)</td>
<td>238</td>
<td>238</td>
<td>120</td>
</tr>
<tr>
<td>Mean heart rate (bpm)</td>
<td>56</td>
<td>71.5</td>
<td>153</td>
</tr>
<tr>
<td>No of heart beats</td>
<td>25</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td>Scanning duration (s)</td>
<td>27</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Systolic phase point (% RR)</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Diastolic phase point (% RR)</td>
<td>75</td>
<td>84</td>
<td>-</td>
</tr>
<tr>
<td>Image FOV (mm)</td>
<td>140×140×32</td>
<td>220×220×30</td>
<td>220×220×30</td>
</tr>
<tr>
<td>Image dimensions</td>
<td>256×256×58</td>
<td>256×256×26</td>
<td>256×256×40</td>
</tr>
<tr>
<td>Voxel size (mm)</td>
<td>0.55×0.55×0.55</td>
<td>0.86×0.86×1.15</td>
<td>0.86×0.86×0.75</td>
</tr>
</tbody>
</table>

Here, for each image point x the corresponding baseline intensity $I_0(x)$ is calculated as given in equation (11). The maximum local intensity $I_{\text{max}}(x)$ represents the highest CA response and it is identified as the maximum of the intensity time series at each image position (figure 3(b)).

Additional and detailed information on the AUC, the PI and many other perfusion-related parameters can be found in the literature (see Axel 1980, Gobbel et al 1991, Peters 1993, Miles and Griffiths 2003, Seidel et al 2006 and references therein).

3. Experiments and results

To validate the sequence of processing steps described in the previous section a series of experiments was performed. The CT data acquisition and image reconstruction settings of these experiments are given in subsection 3.1. The filtration approach applied to deal with image noise and artefacts is evaluated in subsection 3.2. Subsequently, qualitative and quantitative results of the geometric misalignment correction achieved using the proposed technique on three pig cases are presented in subsection 3.3. Finally, visual inspections and quantitative evaluations of the corrected perfusion-related parametric maps for the pig myocardium tissue only are given in subsection 3.4.

3.1. CT scanning and reconstruction settings

Three pig data sets (A–C) were acquired on a Brilliance 64 CT scanner (Philips Healthcare, Cleveland, OH, USA). The animal’s ECG was recorded synchronously with the scan. Pig data have been acquired under ethic commission approval at the University Hospital Hamburg-Eppendorf, Germany, and at the Louis Pradel University Hospital, France. Cases A and B represent two normal healthy pigs, whereas case C is a pig with a coronary artery occlusion (angioplasty balloon inflation) of the left anterior descending coronary artery. Heart rate statistics of the pigs and parameters of the CT acquisition are listed in table 1.

In this work, images are reconstructed at phases of slow cardiac motion. To select suitable quiet motion phases within the RR interval, a motion map (MM) technique is used (Manzke et al 2004). Therefore, retrospective ECG-gated reconstructions at the systolic and diastolic
Figure 4. Image dataset temporal filtering. The CT axial views of the pig case C without (a) and with (b) spatio-temporal diffusive filtration, and the corresponding T–I curves (c) of a myocardial ROI (red circles, (a–b)) are shown (pig case C, at systole (40% RR), L/W: 0/500 HU).

phase points 40 and 75%, and 40 and 84% of the R–R cycle were performed for cases A and B, respectively. For the pig case C a prospectively ECG-gated reconstruction was performed at the systolic phase of 40% RR. Thus, 25, 33 and 52 heart beats were reconstructed from 220° subsections centered around the chosen cardiac phase point, for cases A–C, respectively.

3.2. The effect of noise and artefacts on perfusion parameters

The perfusion parameter determination requires first and second temporal derivative calculation. Due to the presence of noise, a spatial low-pass filter can be applied to the image data set in order to stabilize the derivative calculation. Another problem in perfusion parameter evaluation is the occasional presence of artefacts inside a subset of frames (e.g. beam hardening, cone-beam artefacts, rings, etc). These artefacts can lead to myocardial regions with inconsistent hyper- or hypo-enhancement. As discussed in section 2.2, in this work, a spatio-temporal bilateral filter is applied to each data set to reduce this problem. For the temporal filtration only the two adjacent timeframes are used for filtering. Finally, the range filter parameters $S_\sigma = 40$ HU and $T_\sigma = 260$ HU are utilized, in space and time, respectively.

In figure 4, CT axial images of the pig case C without (a) and with (b) filtration, and the corresponding T–I curves (c) of a myocardial ROI (red circles, (a–b)) are depicted. Spatio-temporal filtering helps to reduce both noise and artefacts. Typical over- and undershoot present along the non-filtered T–I curve ((c), blue dashed curve) are strongly reduced by the spatio-temporal filter ((c), red curve). The residual slight T–I curve variations ((c), red curve) are mainly caused by spatial misalignment which will be removed by a subsequent registration step.

In the next subsection, colour-coded perfusion-related parametric maps will be presented for all three pigs. For the sake of comparison, in the pig case C, the results with and without spatio-temporal filtration will be shown (figure 12).

Moreover, for the pig case B, a sensitivity study of the proposed technique to the range filter parameters $S_\sigma$ and $T_\sigma$ is given (figure 5). Here, for different $S_\sigma$ and $T_\sigma$ combinations, the filtered CT images and the corresponding AUC parameter maps are shown. First, in order to evaluate the spatial filtration parameter effects on image quality, $T_\sigma$ was kept fixed at 260 HU and three different values of 5, 40 and 100 HU were assigned to $S_\sigma$ (figures 5(b)–(d)). When $S_\sigma = 5$ HU was used the filtered image appears grainy (figure 5(b)). In contrast, a value of $S_\sigma = 100$ HU leads to smoothed image and with a decreased spatial resolution (figure 5(d)).
Figure 5. Image data set with spatio-temporal bilateral filtering. In order, in (a–g) the CT axial views (upper rows) and the corresponding colour-coded perfusion-related AUC parameter maps (lower rows) of the pig case B at diastole are given. In (a) the original CT image and AUC map is given, in (b–d) the corresponding images obtained keeping fixed the parameter \( T_\sigma = 260 \text{ HU} \) and varying \( S_\sigma = (5, 40, 100) \text{ HU} \) are shown, while in (e–g) the corresponding images achieved keeping fixed \( S_\sigma = 40 \text{ HU} \) and varying \( T_\sigma = (10, 260, 500) \text{ HU} \) are presented. The red box indicates the images achieved with the optimal parameters combination (pig case B, heart rate: 71.5 bpm, reconstruction phase: 84\% \text{ RR}, CT images L/W: 0/500 HU, AUC parameter colour map min(blue)/max(red): 0/10 000 HU).

Second, the spatial range filter parameter \( S_\sigma \) was kept fixed to the value of 40 HU, while the values 10, 260 and 500 HU were assigned to \( T_\sigma \) (figures 5(b)–(d)). While the spatial resolution in each frame showed a low dependence of \( T_\sigma \), the homogeneity of regions in the perfusion map increased with larger \( T_\sigma \) values (260 and 500 HU). This was due to the increased smoothness of the T–I curves which is advantageous for the calculation of temporal derivatives used for the determination of the perfusion parameters. Finally, the range filter
parameters $S_\sigma = 40$ HU and $T_\sigma = 260$ HU represented the optimal tradeoff among image noise suppression and sharp edge preservation.

### 3.3. Misalignment correction

Subsequent to 4D data reconstruction and filtration, reference images with the maximum image energy were automatically selected and non-rigidly registered to all other volumes of the 4D data sets. Here, the adaptive optimizer randomly selected 3500 image samples at each optimization’s iteration. The stochastic gain settings were automatically estimated by this optimizer. For the multi-resolution approach two levels were used, and in each level the deformation field B-spline knot spacing was every eight voxels. At each resolution level 1500 optimization iterations were performed. Each 3D–3D registration took approximately 2 min on a 2.8 GHz AMD Opteron. As a direct measure of registration quality, statistics on the ZNCC criterion calculated within an elliptical ROI which contained the heart only before and after the registrations are listed in table 2, while the corresponding ZNCC curves evaluated on the whole images are depicted in figure 6. Additionally, for the pig case A, an exemplary rendering of the registration result as checker-board visualization is given in figure 7. The results clearly show applicability of the proposed approach to reduce misalignment.

The ZNCC metric values are mainly affected from both spatial misalignment and typical variation of CA over time (table 2, figure 6). The increased ZNCC’s mean values and the decreased ZNCC’s STD values which are visible in the registered data sets confirm as image registration allowed us to improve spatial alignment along all frames in the temporal sequences (table 2, figure 6, red curves).

Finally, the AUC and PI perfusion parameters were determined. In figures 8–11, the axial, coronal and sagittal views of the AUC and PI perfusion parametric maps for the pig cases A–B without (left) and with (right) registration are presented. Here, the white arrows indicate the artificial hyper-perfusion caused by the spatial misalignment. Image regions which are close to the heart borders suffer more from image misalignment than voxels which are placed within homogeneous image regions (e.g. within the heart chambers or the lungs). Generally, artificial hyper-(or hypo-)perfusion is observable along the myocardial borders.

<table>
<thead>
<tr>
<th>Case</th>
<th>ECG gating</th>
<th>Registered</th>
<th>Mean[±STD]</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Retrospective (40% RR)</td>
<td>No</td>
<td>0.80[±0.105]</td>
<td>0.71</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.96[±0.033]</td>
<td>0.91</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Retrospective (75% RR)</td>
<td>No</td>
<td>0.79[±0.095]</td>
<td>0.69</td>
<td>0.92</td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.94[±0.040]</td>
<td>0.89</td>
<td>0.99</td>
</tr>
<tr>
<td>B</td>
<td>Retrospective (40% RR)</td>
<td>No</td>
<td>0.92[±0.025]</td>
<td>0.88</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>0.99[±0.008]</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Retrospective (84% RR)</td>
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<td>0.87</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.99[±0.008]</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>C</td>
<td>Prospective (40% RR)</td>
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<td>0.92[±0.025]</td>
<td>0.89</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>0.99[±0.007]</td>
<td>0.98</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Figure 6. Registration results as ZNCC curves. The ZNCC values for the registered (red) and non-registered (dashed blue) data sets are given. The metric is evaluated between the selected reference volumes and all other volumes of the 4D data sets. All data were calculated on the whole image domain. In order, in (a, b) and (c, d) the ZNCC curves for the systolic and diastolic data sets of the pig cases A and B are given, respectively. In (e) the corresponding curve for the systolic data set of the pig case C is shown (reference frames: 13 (a), 13 (b), 16 (c), 13 (d) and 22 (e)).

which could lead to rather difficult or erroneous diagnoses of its condition. As an example, in figures 8(a) and (b) (left, white arrows), it is well visible as image misalignment produced very big parameter values along the heart borders (AUC > 11 000 HU and PI > 1100 HU), while after image registration, smoother T–I curves are recovered and more consistent perfusion maps are obtained (figures 8(a) and (b) (right, white arrows)). Similar observations can be made regarding all other cases presented in figures 9–11.

In figure 12, the perfusion parameters of the pig case C determined without (left column) and with (middle column) spatio-temporal filtering are shown. Moreover, the filtered and registered perfusion parametric maps are shown in the right column. Again, the white arrows indicate the artificial hyper-perfusion visible on the myocardium borders caused by the geometric misalignment. This misalignment is well corrected by the image registration technique (right column).

For the pig case A, in figure 13 the T–I curves of the non-registered (dashed black lines) and registered (red-blue lines) systolic reconstructed data sets are given for four different ROIs. Hereto, the registrations are performed using the MI (blue lines) and ZNCC (red lines) dissimilarity metrics. Despite of its simplicity, the ZNCC measure (figure 13, red lines) led to results very similar to those produced using the more sophisticated and slower MI criterion (figure 13, blue lines).

The evaluated colour-coded perfusion parametric maps confirm that image registration can help to reduce the severe artefacts caused by the motion state inconsistencies, and to provide quantitative information of the dynamic CA uptake of the myocardium (figures 8–12). The usual artificial myocardial hyper- (or hypo-) perfusion caused by the cardiac and pulmonary motions (figure 13, dashed black lines) was strongly reduced (figure 13, blue and red lines).
3.4. Visual inspection and quantitative evaluation of myocardial perfusion

In order to highlight the blood perfusion within the myocardium, level and window have been adjusted (figures 14 and 16). Moreover, the determined colour-coded perfusion maps were superimposed to the axial CT images to better locate possible necrotic areas positions. Assuming that an ideal mixture of CA is injected in blood, that the blood flow is constant over time and that the intrinsic permeability and CA response of healthy and homogeneous cardiac tissue are ideally constant in each point, we can conclude that all the perfusion parameters should be approximately constant inside a viable myocardium. A myocardial infarction is strictly related to a suspicious variation of the perfusion parameter visible in the regions where the blood flow is strongly reduced or totally absent, e.g. a reduction is observable in the local AUC or PI parameters.

Therefore, for the healthy pig cases A and B a uniform perfusion was expected within the whole myocardium. In contrast, in the third pig case C, a hypo-attenuated region was expected in correspondence to the myocardial ischemic zone related to coronary artery occlusion.

In figure 14, the perfusion parametric maps for cases A (a) and B (b) are given. As expected, for both pigs, the whole myocardium presents an almost uniform and homogeneous AUC and PI parameter value distribution.

In figure 15, selected frames to the time series of pig C are presented. Here, the red arrows indicate the penumbral myocardial tissue. The corresponding perfusion maps are presented in figure 16. In contrast to the first two healthy pigs, in this case the perfusion maps clearly show a strong reduction of the AUC and PI parameters (black arrows).
Figure 8. Axial, coronal and sagittal views of the AUC (a, c, e) and PI (b, d, f) of the pig case A at systole. In order, the colour-coded perfusion-related parameter maps for the non-registered (left) and registered (right) image data sets are given. The white arrows indicate regions with perfusion artefacts which are removed by the proposed method (heart rate: 56 bpm, reconstruction phase: 40% RR).

Figure 9. Axial, coronal and sagittal views of the AUC (a, c, e) and PI (b, d, f) of the pig case A at diastole. In order, the colour-coded perfusion-related parameter maps for the non-registered (left) and registered (right) image data sets are given. The white arrows indicate regions with perfusion artefacts which are removed by the proposed method (heart rate: 56 bpm, reconstruction phase: 75% RR).
Figure 10. Axial, coronal and sagittal views of the AUC (a, c, e) and PI (b, d, f) of the pig case B at systole. In order, the colour-coded perfusion-related parameter maps for the non-registered (left) and registered (right) image data sets are given. The white arrows indicate regions with perfusion artefacts which are removed by the proposed method (heart rate: 71.5 bpm, reconstruction phase: 40% RR).

Figure 11. Axial, coronal and sagittal views of the AUC (a, c, e) and PI (b, d, f) of the pig case B at diastole. In order, the colour-coded perfusion-related parameter maps for the non-registered (left) and registered (right) image data sets are given. The white arrows indicate regions with perfusion artefacts which are removed by the proposed method (heart rate: 71.5 bpm, reconstruction phase: 84% RR).
Figure 12. Axial views of the AUC (top) and PI (bottom) of the pig case C at systole. In order, the colour-coded perfusion-related parameter maps for the non-registered and non-filtered (left), the non-registered and filtered (center) and the registered and filtered (right) image data sets are given. The white arrows indicate regions with perfusion artefacts which are removed by the proposed method (heart rate: 153 bpm, reconstruction phase: 40% RR).

Corresponding quantitative results for the AUC and PI are given in table 3. Here, seven different regions have been selected within the myocardium muscle (figure 16, R1–5 regions) and the left ventricle (figure 16, R6 and R7 regions). The mean and STD of the AUC and PI were calculated for the non-registered and non-filtered (NORF) and the registered and filtered (RF) image data sets inside selected ROIs. The same results for the myocardium muscle only (R1–5 regions) are presented in figure 17. If neither registration nor filtration were applied, image noise, reconstruction artefacts and especially spatial misalignment due to motion yielded strong AUC and PI standard deviations within the myocardium and the left ventricle (table 3, R1–7 regions, NORF columns). The proposed image filtration and registration led to reduced AUC and PI STD values (table 3, R1–7 regions, RF columns). A clear reduction of both perfusion parameters (AUC and PI) in the infarcted myocardial tissue regions (table 3, figure 17, R1 and R2 regions) compared to normal regions of the myocardial muscle (table 3, figure 17, R3–5 regions) can be observed.

4. Discussion

Early perfusion defects in multi-slice cardiac CT are closely related to the degree of significance of a coronary artery stenosis. Therefore, it is important to accurately detect the presence of myocardial ischemia to support diagnosis and treatment. Myocardial perfusion imaging
by follow-up CT scanning is a promising diagnostic tool to assess the extent of infarcted myocardial regions. However, the limited synchronization accuracy of the ECG with the real heart movement and respiratory induced motion causes a deformation of the myocardium shape and a spatio-temporal misalignment between successive perfusion sequence frames.

In this work, an EIR approach was used to align the 4D data sets. EIR represents an essential tool to perform myocardial perfusion CT imaging with a higher quantitative accuracy. The proposed overall approach allowed us to reduce the effects of image misalignment on myocardial perfusion analysis. Promising results have been achieved by applying image registration to a number of animal cases (figures 6–12, tables 2–3).
Figure 14. Axial views of the registered AUC (left) and PI (right) colour-coded perfusion-related parameter maps of the pig cases A (top) and B (bottom) at systole. The perfusion maps are superimposed to the CT axial images (heart rate case A(B): 56(71.5) bpm, reconstruction phase: 40% RR).

A bilateral spatio-temporal filtration has shown to be a good solution to avoid image corruption by noise and artefacts which can hamper an accurate quantitative and qualitative perfusion evaluation (figure 12). This filter is based on the noise level in the image sequence. The two additional parameters which define the strength of the filtering process in the spatial and temporal domain have been tested within a suitable range and the selected values have been applied to all image series evaluated in this paper.

In the pig case C (suffering from myocardial infarction), both AUC and PI parameters showed a strong perfusion deficit in correspondence to the ischemic myocardial region (table 3, figure 16, figure 17). However, the sensitivity of these two and other time-dependent perfusion
parameters (e.g. time to peak, maximum up-slope) needs to be carefully evaluated on a larger data base. Similarly, the sensitivity and robustness of the approach to the various parameters chosen (e.g. $S_\sigma$ and $T_\sigma$) should be more extensively studied in future work.
Despite the encouraging results, some limitations of the proposed approach are not negligible. First, in this work, the perfusion parameters were calculated assuming a global CA arrival time. This assumption is generally false for a cardiac ROI. Second, the vascular physiology of the myocardial tissue is based on changes in concentration of the CA within tissue as a function of time. The use of time-concentration data to calculate blood flow and its transit time is not optimal because these data reflect not only the vascular physiology of the tissue, but also the input function, which is the concentration of the arterial CA when it enters the ROI. Therefore, a more accurate perfusion model should be applied. A potential solution could be a model describing the flow of CA into and through the myocardial tissue to be linear and stationary. Here, the measured myocardial tissue CA concentration time curve corresponds to the convolution of a given input arterial CA concentration time curve with the corresponding impulse response of the tissue (Gobbel and Fike 1994, Ostergaard et al 1996). Several deconvolution approaches have been proposed in the literature to determine the unknown impulse response of the tissue and to derive the corresponding perfusion-related parameters (Gobbel and Fike 1994, Ostergaard et al 1996, Orten et al 2008, Al-Mallah et al 2010). The integration of deconvolution approaches in the current processing chain will be a topic of future research.

5. Conclusions

In conclusion, an elastic image registration-based method was proposed to improve the characterization of CT-based estimates of myocardial perfusion. The performance of this technique was assessed visually and quantitatively on three animal data sets. A reduced variability of measured perfusion parameters has been shown. In an animal data set with myocardial infarction, the measured PI and AUC enabled the quantification of perfusion parameter changes due to myocardial ischemia. The proposed method may also be applied to other perfusion studies being limited by inconsistent motion states.
Acknowledgments

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