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Abstract

Accurate alignment of intra-operative X-ray coronary angiography (XA) and pre-operative cardiac CT angiography (CTA) may improve procedural success rates of minimally invasive coronary interventions for patients with chronic total occlusions. It was previously shown that incorporating patient specific coronary motion extracted from 4D CTA increases the robustness of the alignment. However, pre-operative CTA is often acquired with gating at end-diastole, in which case patient specific motion is not available.

For such cases, we investigate the possibility of using population based coronary motion models to provide constraints for the 2D+t/3D registration. We propose a methodology for building statistical motion models of the coronary arteries from a training population of 4D CTA datasets. We compare the 2D+t/3D registration performance of the proposed statistical models with other motion estimates, including the patient specific motion extracted from 4D CTA, the mean motion of a population, the predicted motion based on the cardiac shape.

The coronary motion models, constructed on a training set of 150 patients, had a generalization accuracy of 1 mm root mean square point-to-point distance. Their 2D+t/3D registration accuracy on one cardiac cycle of 12 monoplane XA sequences was similar to, if not better than, the 4D CTA based motion, irrespective of which respiratory model and which feature based 2D/3D distance metric was used. The resulting model based coronary motion estimate showed good applicability for registration of a subsequent cardiac cycle.

Keywords: SSM, 2D+t/3D+t registration, reconstruction, 2D/3D alignment, respiratory alignment, cardiac contraction

1. Introduction

Percutaneous coronary intervention (PCI) is routinely performed for treating stenosed coronary arteries. During the procedure the site of lumenal narrowing is dilated and a stent is placed under X-ray coronary angiographic (XA) guidance. The XA sequence shows both the guide wire and the vessels due to the injection of contrast agent. PCI on non-occluded lesions has high success rates (99%). These rates drop to 60-80% in the case of treatment of chronic total occlusions (CTOs) (Di Mario et al., 2007; Soon et al., 2007). CTOs can not be fully visualized with XA as the contrast agent does not pass the occluded segment, which hampers percutaneous treatment. In order to successfully cross a CTO with a guide wire, the interventional cardiologist ideally requires visualization of the occluded segment including the vessel borders and plaque composition, because soft parts of the lesion are easier to cross than calcified parts. Pre-operative CT angiography (CTA) can be used to visualize the entire cardiac vasculature including occluded segments, and the possibility to distinguish calcified plaque (Magro et al., 2010). The combined visualization of the information from CTA and XA during percutaneous treatment of CTOs may increase the success rate of CTO treatment. Therefore, this paper deals with the registration of intra-operative XA sequences with pre-operative 3D CTA images. To account for cardiac motion throughout the registration, we investigate the possibility of employing statistical motion models of the coronary artery.

Many authors have addressed registration of a 3D vascular tree with its projection images. While calibrated bi-plane acquisitions enable direct reconstruction of the cen-
terline structure (Mourgues, 2001), often only a monoplane setup is available. Registration of the 3D vascular tree with one projection image has been investigated by several authors. Many of the works focus on anatomies which are inherently not moving, such as the cerebral arteries (Feldmar et al., 1995; Kita et al., 1998), or the coronary arteries using an XA frame taken at the same cardiac phase as the CTA image (Metz et al., 2009b; Ruijters et al., 2009; Turgeon et al., 2005). However, selecting the XA frame with the correct cardiac phase is not easy, and an inexact selection may deteriorate registration performance (Turgeon et al., 2005).

To account for slight differences in the vessel shapes, non-rigid 2D-3D alignment techniques have been proposed. Groher et al. (2009) allowed non-rigid deformation of vessel segments of the liver while constraining the length and smoothness of the vessel to ensure plausible deformations. Gatta et al. (2011) corrected for shape differences using 2D non-rigid registration between the projected coronary arteries and one XA frame. Serradell et al. (2011) generated a synthetic motion model of the coronary arteries to constrain the non-rigid motion while fitting the 3D vessel tree to the 2D projection image.

Registration of an entire cardiac cycle rather than a single time-frame provides more information to guide the alignment, but it requires coping with the cardiac and respiratory motion of the coronary arteries. Bouattour et al. (2005) performed frame-by-frame B-spline based 2D-3D fitting, with the previous frame’s fit as the initialization for the next frame. They reported a success rate of 56% on the evaluated three sequences. Metz et al. (2011) proposed simultaneous registration of all frames of a cardiac cycle, using the cardiac motion derived from 4D CTA data. They showed an increase in registration robustness compared to the single frame 2D-3D fitting of the end-diastolic XA frame. However, in clinical practice CTA images are typically acquired within a limited part of the cardiac cycle in order to minimize radiation dose. Therefore, information on the motion of the coronary arteries is often not available. Statistical motion models might in this case replace the patient specific motion.

Statistical motion models have been proposed for respiratory motion tracking in image guided radiotherapy of the liver (Blackall et al., 2001) and the lungs (Liu et al., 2010), in image guided interventions (Klinder et al., 2010), and for modeling heart deformation due to respiration (McLeish et al., 2002). These models were built from multiple images of a single patient to represent the intra-patient variability of breathing. If only one time-point in the cardiac cycle of the patient is known, construction and application of such models is not feasible.

Statistical motion models have also been proposed to represent the motion variation in a population, thus modeling the inter-patient variability. The straightforward extension of statistical shape models to incorporate motion is by concatenating the landmark coordinates of every frame to derive the modeled coordinate vector. Such 4D shape models have been proposed for dynamic segmentation, such as for left ventricle segmentation from ultrasound images (Bosch et al., 2002), and segmentation of the entire heart from 4D CTA (Ordas et al., 2007) and MRI images (Zhang et al., 2010). Others solely modeled motion, thus the difference in point coordinates from a reference frame. Such models have been proposed for recognizing pathologies (Chandrashekara et al., 2003; Perperidis et al., 2005; Srinivasan et al., 2009), and for predicting cardiac contraction patterns either for the entire cardiac cycle, or a few phases ahead (Hoogendoorn et al., 2009; Metz et al., 2012).

Coronary artery geometry has previously been studied by Lorenz and von Berg (2006), who built a mean end-diastolic heart surface and coronary artery tree model. Due to the topological variation between patients, the coronary artery model was restricted to the largest arteries, which have a relatively well defined position. A synthetic coronary artery motion model was proposed by Serradell et al. (2011), based on the 3D vessel centerlines. The motion model was generated by hierarchical simulated random movements of the centerline points, where each movement of a point affected the entire sub-tree below that point. The resulting movements remained realistic by smoothing and by constraining movements in the vessel direction. To our knowledge, no population based statistical coronary motion models have been reported in literature. This might be due to the high variability in coronary artery anatomy, and the difficulty to reliably segment coronary arteries in a large number of 4D datasets.

In this paper, we perform 2D++/3D registration of single-plane XA sequences with pre-operative end-diastolic CTA images. We turn this registration into a 2D++/3D+t registration by employing a coronary artery motion prior. The primary focus of the paper is the question whether the coronary artery motion prior needs to be patient specific, i.e., derived from a 4D CTA scan (as proposed in Metz et al. (2011)), or could other sources be used, such as a statistical motion model or the mean motion over a population. To investigate this, we propose a methodology to construct patient specific statistical coronary motion models based on 4D CTA images of a training population. The aforementioned problems with population based coronary artery motion models are circumvented by estimating the coronary motion from the motion of the cardiac surface. Four different population based coronary artery motion models are proposed and evaluated for 2D++/3D alignment: the mean motion, a statistical motion model, the most probable motion based on cardiac shape, and a shape conditional motion model.

The main contributions of this paper are the following:

1. We propose a technique for constructing statistical coronary artery motion models from 4D CTA datasets by coronary motion estimation from the cardiac surface, and generate two types of models: a classic statistical motion model and a shape conditional motion...
model.

2. We investigate if inclusion of the derived motion models can lead to a similar 2D+t/3D registration accuracy as the 2D+t/3D+t registration employing a 4D CTA based patient specific motion model.

Furthermore, we investigate if the motion estimated with a statistical model can be applied in registration of subsequent cardiac cycles. This is of interest, as a patient specific motion prior recovered from high contrast frames could then be used in subsequent cycles with fading contrast. This paper is an extension of our preliminary work investigating the use of the mean and predicted coronary artery motion estimates for 2D+t/3D+t registration (Baka et al., 2012).

The paper is structured as follows. First, we describe the construction of the proposed statistical coronary motion models (Section 2). Then, in Section 3, we introduce the feature based 2D-3D distance metric used in the registration, and describe the strategy of incorporating different models for the whole cardiac cycle registration. After discussing implementation details in Section 4, and the data in Section 5, the experiments and results are presented in Section 6. Finally, we discuss the results, and present the conclusions in Section 7.

2. Statistical coronary motion model construction

Building a statistical motion model directly from a training set of 4D coronary artery centerlines would be very challenging due to the variations in coronary topology, which seriously complicates establishing correspondence. Instead, we propose to shift the correspondence definition from the 4D arteries to the 4D cardiac surfaces. We theorize that coronary arteries are attached to the cardiac muscles they are feeding, and therefore move together with that tissue. Coronary artery motion can thus be implicitly derived by extrapolating the motion of the nearby cardiac surface. As a consequence, if 4D cardiac surfaces with point correspondence are available, different motion patterns for the same region can be extracted, which can be extrapolated to different motion patterns of the same coronary artery. We can therefore build a coronary artery motion model, that is specific to the coronary artery used to determine the nearby cardiac surface, thus to the patient to be modeled.

As a first step of creating the model, the cardiac surface region nearby the coronary arteries of the patient has to be selected. This can be done by extracting the artery centerline and the cardiac surface from the patient’s 3D CTA scan. If the cardiac surface is represented with points corresponding to the training set of 4D cardiac surfaces, the selected surface points can be retrieved on all training surfaces. These surface motions can then be used to estimate coronary centerline motions, on which the statistical model can be created. Due to the differences in coronary artery configurations, the motion model has to be newly created for every new patient or new artery to be modeled.

The above proposed steps could be implemented in many ways. We, for example, investigate two ways to create the coronary artery motion model. First, the classical statistical model defining the space of allowable motion estimates, and second, a shape conditional motion model, that takes the cardiac shape of the patient into account. The following sections describe our implementation of the coronary motion model step by step.

2.1. Cardiac training set with point correspondence

We automatically segment and landmark the four heart chambers and the aorta from a training set of 4D CTA scans, as described in Metz et al. (2012). End diastolic segmentation is performed with multi-atlas registration using eight atlases. Point correspondence in the end-diastolic segmentations is achieved by defining corresponding landmark points on the atlases. The end-diastolic segmentations are then propagated to the other cardiac phases by 4D registration (Metz et al., 2009a). The resulting shapes are temporally aligned using the left ventricle volume curves to compensate for heart rate differences. Further details on landmarking, segmentation, and temporal alignment can be found in Metz et al. (2012).

2.2. Coronary artery segmentation and landmark selection

To create the patient specific motion model, the cardiac surface nearby the patient’s coronary arteries has to be determined. The coronary artery centerlines of the patient are extracted from the end-diastolic 3D CTA scan. We use a centerline extraction method based on a vesselness filter (Frangi et al., 1998) and a minimum cost path between the manually annotated ostium and a manually clicked vessel end point. Centerlines are thereby extracted up till the point where the vessel is visible in the end-diastolic CTA scan. This centerline is then refined using vessel wall segmentation based on Schaap et al. (2011). A detailed description of the procedure can be found in Metz et al. (2011).

The cardiac structures are segmented using multi-atlas segmentation as described in Section 2.1, resulting in surface points corresponding to the training set. Landmark points far from the coronary arteries are eliminated, and nearby landmark points are retained for further analysis. For each coronary artery centerline point, we select the closest 30 surface landmark points, resulting in a maximum distance of about one cm. Figure 1 shows an example segmentation with coronary centerlines in blue, and selected nearby landmark points marked white.

2.3. Coronary artery motion estimation on the training set

This section describes how the coronary artery motion is extrapolated from the cardiac surface motion for coronary motion model building. First, the landmark points
that were selected in the previous subsection are extracted from all training surfaces. Subsequently, the selected part of the training surfaces is aligned based on the end-diastolic phase (translation, rotation, isotropic scaling), and this alignment is propagated to the rest of the phases. The surface motion $l$ is derived by subtracting the end-diastolic landmark point coordinates $d_c$ from the coordinates $d_j$ $j \in [1,T]$ of all phases\footnote{Due to space considerations all vectors are represented as row vectors in Equation 1}:

$$l = [l_1, l_2, \ldots l_T] = [d_1 - d_c, d_2 - d_c, \ldots d_T - d_c] .$$  \tag{1}

The motion $m_j^i$ of vessel point $i$ in cardiac phase $j$ is then calculated as the weighted average of the motion $l_k^i$ of their 30 closest cardiac surface landmark points $k$ in phase $j$:

$$m_j^i = \frac{\sum_{k=1}^{30} \nu_k^i l_k^i}{\sum_{k=1}^{30} \nu_k^i} .$$  \tag{2}

The weights $\nu_k^i$ are pre-calculated based on the distances $D(k, i)$ between cardiac surface landmark point $k$ and vessel point $i$ on the cardiac segmentation of the patient to be treated. The exponential function used provides a higher weight for surface landmark points that are closer:

$$\nu_k^i = \exp(-D(k, i)/\sigma_v) ,$$  \tag{3}

where $\sigma_v$ controls the steepness of the weight function.

This step results in a coronary artery motion estimate for every subject in the training set, based on the coronary artery geometry of the patient to be treated.

### 2.4. Statistical motion model (SMM)

To build a classical statistical motion model, principal component analysis (PCA) is used on the coronary artery motion estimates from the previous subsection. The coronary motion for a given subject can then be approximated as

$$m \approx \bar{m} + \Phi b ,$$  \tag{4}

where $m = [m_1^1, m_1^2, \ldots m_N^1, \ldots, m_1^N, \ldots, m_N^N]$ contains the motion of all vessel points $i \in [1,N]$ in all phases $j$, $\bar{m}$ is the mean motion, $\Phi$ represents the main modes of variation, and $b$ is the vector of motion parameters. In this paper we keep 95% variance in the model, assuming that the residual variance is caused by noise.

### 2.5. Shape conditional motion model

In previous work we showed that the motion of the four cardiac chambers and the aorta was correlated with their end-diastolic shape (Metz et al., 2012). As we estimate the coronary motion from the cardiac motion, coronary motion is also expected to be correlated with the end-diastolic shape. The most probable motion $\bar{m}$ of a coronary artery can therefore be estimated from the end-diastolic heart surface $d_e$ nearby the artery via linear regression. In this work we use ridge regression, as that was found to slightly outperform other linear regression methods for large dimensional, small sample size data (Baka et al., 2011b). The regression can be formalized as

$$m = \bar{m} + \epsilon = (d_e - \bar{d}_e)\beta + \bar{m} + \epsilon$$  \tag{5}

where $\bar{m}$ is the predicted motion, $\bar{d}_e$ is the mean motion, $d_e$ and $\bar{d}_e$ are the population mean shape and the current shape of the end-diastolic heart surface nearby the coronary arteries, $\beta$ is the vector of regression coefficients, and $\epsilon$ is the remaining error. $\beta$ is calculated from the training set as

$$\beta = (\Sigma_{d_e} + \lambda I)^{-1} \Sigma_{d_e,m} ,$$  \tag{6}

where $\Sigma_{d_e}$ denotes the shape variance of the nearby region, $\Sigma_{d_e,m}$ denotes the cross-covariance between shape and motion, $I$ is the identity matrix, and $\lambda$ is the ridge parameter. We refer to Hastie et al. (2009) for a detailed description of ridge regression. The ridge parameter can be optimized by cross validation on the training set.

The predicted motion $\bar{m}$ is the most probable motion for the coronary artery given the cardiac shape. To model the distribution of possible motions, we calculate the amount of motion variation from the remaining error $\epsilon$ as

$$\Sigma_\epsilon = E\{\epsilon \epsilon^T\} = \Sigma_m - 2\Sigma_{m,d_e}S^{-1}\Sigma_{m,d_e} + \Sigma_{m,d_e}S^{-1}\Sigma_{d_e}S^{-1}\Sigma_{m,d_e} ,$$  \tag{7}

with

$$S = \Sigma_{d_e} + \lambda I .$$  \tag{8}

This equation can be derived by combining Equation 5 with 6, and substituting the resulting $\epsilon$ into the left hand
side of Equation 7. Similar to the SMM case, we can decompose the variance $\Sigma$ into its principal directions creating the conditional model

$$m \approx \hat{m} + \Phi \beta.$$  

(9)

Also in this model, we keep 95% of the variance of the training data.

The conditional model allows variations around the predicted motion rather than around the population mean motion and restricts the allowable motions more than the classical SMM.

3. 2D+t/3D coronary centerline registration

A 2D-3D registration through time consists of two main components: the 2D-3D distance measure evaluating the alignment in one frame, and the strategy in which the frame-by-frame measures are combined and optimized to derive the alignment of the entire cardiac cycle. In this section we describe both components in detail.

3.1. 2D-3D distance measure

This measure quantifies the distance between the projected 3D vessel centerlines and automatically extracted 2D vessel centerlines in the XA image. The 3D vessels are projected to the image plane using perspective projection. The required C-arm orientation and source-to-detector distance are obtained from the DICOM header. The 2D vessel centerlines are extracted from the X-ray images by first enhancing dark longitudinal structures with a Frangi vesselness filter (Frangi et al., 1998). Subsequently, ridges are found via local non-maximum suppression, and hysteresis thresholding. Finally, single pixel long centerlines are removed. This automatic extraction produces true and false centerline candidates. In the remainder of the paper we denote all extracted centerline candidates as 2D centerlines. An example frame with original intensities, the vesselness filtered image, and the centerline image is shown in Fig. 2.

The 2D-3D distance measure of a frame is based on the distances between projected 3D vessel points and extracted 2D centerlines. To determine corresponding points and their distances, we adapted the distance function $\Theta_{ij}$ from Baka et al. (2011a), which comprises a 2D Euclidean centerline points $j$, such that their distances, we adapted the distance function $\Theta$ for the distances between projected 3D vessel points and extracted vessel points after projection. This weighting ensures that all vessels have a similar influence on the optimization independent of their orientation with respect to the projection direction. Centerline points outside the FOV are weighted zero.

In the second measure, correspondences in both directions are created, meaning that also every 2D centerline point is matched with its closest projected 3D centerline point. The resulting symmetric frame distance measure is

$$G_2 = \frac{1}{M} \sum_{i=1}^{M} \sum_{j=1}^{N} w_i \min \Theta_{ij} + \frac{1}{M} \sum_{i=1}^{M} \min \Theta_{ij},$$  

(12)

where $M$ is the number of extracted 2D centerline pixels.

3.2. 2D+t/3D registration

We register a complete cardiac cycle by minimizing the sum of all frame-wise 2D-3D distances

$$G = \sum_{l=1}^{L} G_1(t) \quad \text{or} \quad G = \sum_{l=1}^{L} G_2(t),$$  

(13)

where $L$ is the number of frames in the cardiac cycle. Minimization is performed by optimizing four groups of parameters: heart pose parameters relating the CT coordinate system with the angiography coordinate system, respiratory motion parameters, coronary artery motion parameters, and temporal alignment parameters. A more detailed explanation of the motion parameters and the temporal alignment is provided below. An overview of the number of parameters optimized in the different models is shown in Table 1.

3.2.1. Temporal alignment

The coronary artery motion model describes the shapes of the coronary arteries in different cardiac phases. A temporal alignment is needed to relate these cardiac phases to the XA frames, accounting for differences in temporal resolution and heart rate between the model and the angiography sequence. As heart rate influences the relative duration of systole and diastole, a piecewise linear

with higher vesselness. Due to the exponential function all distances $D_{ij}$ are mapped to the [0,1] interval, resulting in small gradients for large distances. The parameter $\sigma$ regulates this non-linear behavior.

Two different methods to calculate frame-wise 2D-3D distances are proposed and used in the experiments.

For the first distance measure every 3D centerline point $i$ is matched with a 2D centerline pixel $j$, such that $\Theta_{ij}$ is minimal. The final 2D-3D frame distance is the weighted average of the individual minimum distances:

$$G_1 = \frac{1}{\sum_{i=1}^{N} w_i} \sum_{i=1}^{N} w_i \min \Theta_{ij},$$  

(11)

where $N$ is the number of 3D centerline points, and weight $w_i$ is the average of the distances between vessel point $i$ and its neighboring vessel points after projection. This weighting ensures that all vessels have a similar influence on the optimization independent of their orientation with respect to the projection direction. Centerline points outside the FOV are weighted zero.

In the second measure, correspondences in both directions are created, meaning that also every 2D centerline point is matched with its closest projected 3D centerline point. The resulting symmetric frame distance measure is

$$G_2 = \frac{1}{\sum_{i=1}^{N} w_i} \sum_{i=1}^{N} w_i \min \Theta_{ij} + \frac{1}{M} \sum_{j=1}^{M} \min \Theta_{ij},$$  

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Table 1: The number of parameters optimized during 2D+t/3D+t registration with different motion model configurations. The number of frames of a cardiac cycle is denoted by L, and the number of modes of the statistical model by K.

function is proposed for the temporal alignment, with one parameter \( \tau \) representing the relative length of systole in a cardiac cycle. The function is shown in Figure 3, with phases parameterized between 0 and 1.

3.2.2. Coronary motion models

The investigated coronary motion models can be grouped in two categories: motion estimates, and statistical motion models. While in the latter the motion pattern is optimized, in the first one the actual motion is fixed. Therefore, registration with a motion estimate is computationally cheaper.

The considered motion estimates are the 4D CTA motion as proposed in Metz et al. (2011), the static end-diastole, where no cardiac motion is assumed, the mean motion of the training population, and the predicted motion from the cardiac shape as explained in Section 2.

The statistical models considered are the statistical motion model (SMM) and the conditional motion model as described in Section 2. These models were fitted by optimizing the motion parameters \( b \) in Equation 4 and 9 respectively.

3.2.3. Respiratory motion models

We investigate two strategies to account for the respiratory motion during XA acquisition. In both we consider only the rigid part of the respiratory induced movement of the heart, which was shown to account for the largest part of the motion (Shechter et al., 2004, 2006).

In the first strategy we model the respiration induced movement of the heart in one cardiac cycle as a quadratic function. In this case, beside the pose in the first frame, the pose (translation and rotation) in the center frame and the last frame of the sequence are also optimized. The respiratory motion of all other frames is calculated by quadratic interpolation. Thus next to the 6 pose parameters, 12 respiratory parameters are required to represent the respiratory motion in one cardiac cycle.

In the second, unconstrained strategy we optimize the pose of the heart in every frame solely based on the image information. Optimization of this approach is the slowest, due to the large amount of parameters (6 DoF per frame).

4. Implementation details

4.1. Optimization

We used the non-linear least squares optimizer implemented in the optimization toolbox of Matlab R2011. This is a subspace trust-region method based on the interior-reflective Newton method. We set 20 mm and 20° bounds on the initial displacement parameter, and 10 mm and 10° bounds on the initial rotation parameter.
degree bounds on the respiratory model following Shechter et al. (2006). These bounds ensure that the out of plane motion stays within realistic bounds. The motion model parameters were restricted to lie within 3 standard deviations from the mean shape for both the classical statistical and the conditional models. In order to increase registration speed we sub-sampled the automatic 2D centerlines by a factor of 6 resulting in a neighboring centerline point distance of about 1.5 mm, and the 3D coronary artery centerline by a factor of 3 resulting in a 3D centerline point distance of about 2.4 mm.

Our optimization strategy was slightly different for the different breathing models. When using the quadratic breathing model, all parameters were optimized at once (parameters were weighted such that a unit change caused the same order of magnitude difference in the distance measure as a unit translation in plane). When optimizing the unconstrained breathing we alternately optimized the respiratory motion parameters, and shape parameters (including the temporal fit) to keep the number of parameters to optimize within reasonable limits.

4.2. Parameter settings

The vesselness filter parameters used for the automatic centerline extraction were set as proposed in Frangi et al. (1998). Vesselness was calculated on three scales (0.5, 1, and 2 mm). The high and low threshold values for the hysteresis thresholding of the vessel centerlines were manually set to 0.45 and 0.1 after visual inspection of 3 sequences.

For the coronary artery motion estimation from the cardiac surface motion we set the parameter $v_1$ in Equation 3 to 4 mm. In this manner the furthest selected landmark points are weighted less than 0.1 in the motion estimation.

The $\sigma^2$ parameter of Equation 10 was set to 50 mm$^2$, preventing distances larger than 15 mm to influence the alignment. The weighting constant $\alpha$ of the same equation was set to 0.1.

5. Data

5.1. Training data for the motion model

The 4D heart segmentations from Metz et al. (2012) were used to build the statistical motion models of the coronary arteries. The data consisted of 151 ECG gated 4D CTA images acquired between 2006 and 2010 as part of the clinical diagnosis of patients with acute or stable chest pain, or for research purposes. The data therefore includes a large variety of anatomies and pathologies. 20 of the originally 171 datasets were excluded due to pacemakers (10 cases), and other large anatomical deviations causing the multi-atlas segmentation to fail (10 cases). CTA reconstructions were made every 5% of the cardiac cycle resulting in 20 images per sequence. The voxel size of the 3D+T CTA sequence was approximately 0.7x0.7x0.9 mm$^3$.

5.2. Test data

For evaluation, 12 XA datasets of 10 patients (two patients underwent two interventions) were used. The same patients were analyzed in Metz et al. (2011) for the case of known patient specific coronary motion. Images were acquired between 2007 and 2009 using a Siemens Axiom Artis biplane system. As no calibration data was available, in this work only sequences of the primary C-arm were included. Images contain 512x512 pixels with a pixel size of 0.22x0.22 mm$^2$. We selected two consecutive cardiac cycles from each sequence for analysis, both cycles containing contrast enhanced coronary arteries. The average number of frames in a cardiac cycle was 13 frames, and ranged from 9 to 22 frames. One sequence was acquired at a frame rate of 30 frames per second (fps), the others at 15 fps. Five of the sequences contained the right coronary artery, the others the left coronary tree. Six of the sequences were confirmed CTO cases. For all but one procedure we chose a sequence that was acquired before the opening of the occlusion. Every patient in the test set underwent a 4D CTA scan prior to PCI. These CTA scans were also part of the training data described in the previous subsection. To derive the patient specific coronary artery motion from the 4D CTA, we first extracted the centerlines at end diastole as described in Section 2.2, and then propagated these to the other cardiac phases. We refer to Metz et al. (2011) for further details on 4D centerline extraction.

6. Experiments and results

We performed two sets of experiments. The first set of experiments focused entirely on the coronary motion model, which was evaluated independently of the task of 2D+T/3D registration. The second set of experiments focused on the 2D+T/3D registration and assessed registration accuracy as well as the quality of the final motion estimate.

6.1. Coronary motion model evaluation

In these experiments the coronary artery locations extracted from the 4D CTA datasets of the 10 test patients were used as ground truth.

6.1.1. Coronary motion extrapolation from nearby heart landmarks

First, we evaluated the accuracy of estimating coronary motion from the motion of nearby cardiac surface landmark points. The resulting coronary artery centerlines were compared to the arteries extracted from the 4D CTA.

Results indicate an average root mean square (RMS) point-to-point distance of 0.53 mm, and a maximum RMS distance of 1.39 mm. Figure 4 shows the distances of all 10 patients over the cardiac cycle. As a reference the average coronary motion (mixed left and right trees) is plotted in black.
6.1.2. Model generalization

The generalization power of a statistical model indicates the accuracy with which the model is able to represent a previously unseen subject. We evaluated generalization on the 10 test subjects, with a model built on 150 training samples (excluding the current test subject). The statistical models contained about 45 modes of variation after dimensionality reduction, and the parameters of each mode were restricted to lie within the ±3 standard deviation bound. The representation accuracy of the model was compared with the mean motion, predicted motion, and static estimates. Prediction was performed as described in Section 3.2.2, with λ, the ridge parameter being optimized on the training set excluding the test subjects.

The results in Table 2 indicate that both statistical models were able to represent the motion with about 1 mm average root mean square point-to-point accuracy, and thereby significantly outperformed the motion estimates (p<0.001). The predicted motion tends to have a better accuracy than mean motion, though the difference was not found to be significant (p=0.07). The static motion estimate, as expected, performed significantly the worst (all p<0.005). All significance tests were performed at the 5% significance level with a two-sided paired t-test. Plotting the errors versus cardiac phase revealed no dependency between cardiac phase and the model generalization with the SMM and the conditional models. Mean and predicted motion on the other hand had larger errors at systole. We also investigated whether generalization accuracy was dependent on the vessel diameter, and found no dependency.

<table>
<thead>
<tr>
<th></th>
<th>Accuracy [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± std</td>
</tr>
<tr>
<td>SSM repr.</td>
<td>1.02 ± 0.29</td>
</tr>
<tr>
<td>Conditional repr.</td>
<td>1.02 ± 0.29</td>
</tr>
<tr>
<td>Predicted</td>
<td>2.29 ± 0.43</td>
</tr>
<tr>
<td>Mean</td>
<td>2.52 ± 0.74</td>
</tr>
<tr>
<td>Static</td>
<td>4.4 ± 1.39</td>
</tr>
</tbody>
</table>

6.2. 2D+t/3D registration evaluation

We compared in total 12 registration strategies varying both the coronary and breathing motion models respectively. Coronary motion models were built on 150 training subjects leaving the test subject out from the training set. Every registration strategy was run nine times on all test data with different manual initializations. The manual initializations were collected from three independent observers (three initializations from each), who were asked to translate the end-diastolic coronary artery in the projection plane (2 DoF) such that the projection of the 3D vessels matched the first angiographic frame of the cardiac cycle well.

The XA data contained images of patients with metallic stitches from previous heart surgeries, and in some cases the guiding catheter was visible in the field of view (FOV). We therefore performed stitch and catheter removal in a preprocessing step. We first semi-automatically delineated the stitches in the first frame using a live-wire approach, and then tracked their position using intensity based rigid registration through time. Finally the stitches were masked, and replaced with the gray-value morphological closed image intensities. A similar strategy was used for the catheters.

Corresponding centerline distance. For evaluation purposes, we adapted the centerline distance measure from Metz et al. (2011). First, centerline segments were manually drawn on the XA frames. The corresponding closest projected 3D centerline branch for every annotated centerline segment was determined, and subsequently the distances of all points in the annotated centerline segment to the projected 3D centerline branch were calculated. The mean of all annotated centerline point distances resulted in the corresponding centerline distance measure for each frame.

6.2.1. Experiment 1: Comparison of motion models

We compared registration performance of the coronary and respiratory motion models described in Section 3.2. One cardiac cycle per sequence was used for evaluation, with nine different manual initializations each. We performed registrations with both 2D-3D distance measures, $G_1$ and $G_2$. In prior experiments we found that the convergence range of $G_2$ was smaller than that of $G_1$, as $G_1$...
is less sensitive to false 2D centerline detections. Therefore, in our experiments $G_2$ was always applied after an optimization with $G_1$.

Table 3 shows the median centerline distances of all frames with both distance measures and both respiratory motion compensation strategies. We report results on all 12 available datasets, as the registration accuracy on the datasets used for setting the method parameters were not better than the results of the other datasets. To check for statistical significance, we averaged all results per patient, and applied a paired Wilcoxon signed rank test on these averages. Significant differences between the proposed methods and the 4D CTA motion based fitting are reported at the 5% significance level in Table 3 as bold typeset. All results were significantly different from the initialization. Initializations using the mean motion gave a median centerline distance of 3.88 mm. Figure 7 shows the centerline distances achieved with the $G_2$ distance measure. The numbers at the top indicate the number of frames with a centerline distance larger than 6 mm. Example alignments for one frame with different coronary motion models and quadratic breathing are shown in Figure 8. Figure 9 shows further results for three time-points of four patients using the 4D CTA motion and using the statistical coronary motion models, with the quadratic breathing model. To investigate whether the rigid cardiac motion obtained with the unconstrained breathing optimization could be approximated with a second order function, we plotted the resulting pose parameters in the in- and out-of-plane directions for all patients. An example is given in Figure 8, showing the translation parameter trajectories for one of the sequences.

We also evaluated the difference between the estimated motion of the statistical models and the 4D CTA motion, while focusing strictly on the intrinsic cardiac motion. We separated this motion by reconstructing it from the optimized coronary artery motion model parameters. To gain insight in the directional dependency of the error, we report in-plane and out-of-plane 3D motion differences. A box plot of the per patient per initialization average of these errors is given in Figure 6, showing no obvious direction dependency.

To have an indication of the capture range of the 2D/3D fitting procedure, we calculated the intra-observer variability of the initializations as the average distance between the initializations as the average distance between the mean initializations of each observer. The intra- and inter-observer variabilities were 2.17 mm and 1.82 mm respectively. For all but one patient the individual initializations were within 5.16 mm from the mean initialization. We then performed further experiments with the conditional coronary motion model and quadratic respiratory model progressively degrading the initialization. We added random in-plane displacements in the range 0 to 5 mm to the mean initialization. Our results showed a steady, approximately 73% convergence rate for all initial displacement distances, if convergence was defined with a 2 mm average corresponding centerline distance threshold (averaged over all frames). This shows that within the normal variability of the manual initialization, the performance of the method is stable, and is similar to the results presented in Figure 7.

Investigating the relation between 2D/3D fitting accuracy achieved with the conditional motion model and the vessel diameter we found a slight increase in the error for smaller vessels, as shown in Figure 5.

6.2.2. Experiment 2: Reusability of the optimized motion

In this proof of concept experiment we investigated if the resulting coronary artery motion estimate of one cardiac cycle can be applied for the 2D+t/3D+t registration of a subsequent cycle. Hereto, we fixed the resulting motion from the first cardiac cycle, and only optimized the pose and respiratory motion for the next cardiac cycle. We compared the accuracy of this approach with the full optimization of heart pose, respiratory-, coronary-, and temporal parameters. The heart pose was initialized by extrapolating the quadratic breathing motion of the first
Table 3: Median 2D corresponding centerline distance measures [mm] of all frames in one cardiac cycle of all patients. The first row indicates the used coronary motion model, and the first column the used breathing model (quadratic and unconstrained). Bold numbers represent statistically significant differences with the Wilcoxon signed rank test at the 5% level, compared to the 4DCT motion fit of the same row. The small scripts show the corresponding p values.

<table>
<thead>
<tr>
<th>Parameters optimized</th>
<th>SMM</th>
<th>Cond.</th>
<th>4DCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pose and respiration</td>
<td>1.74</td>
<td>1.78</td>
<td>1.90</td>
</tr>
<tr>
<td>All</td>
<td>1.83</td>
<td>1.81</td>
<td>1.88</td>
</tr>
</tbody>
</table>

Table 4: Reusability of the optimized coronary motion with quadratic respiratory model. The table shows the median 2D centerline distance [mm] of all frames of all patients in the second cardiac cycle with initialization based on the first cardiac cycle. In the first row the coronary motion estimate from the first cycle was used, in the second row all model parameters were newly optimized. Bold numbers represent statistically significant differences from the 4DCT at the 5% level within a row.

<table>
<thead>
<tr>
<th>Parameters optimized</th>
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<th>Cond.</th>
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<td>1.81</td>
<td>1.88</td>
</tr>
</tbody>
</table>

cardiac cycle. Registration was performed with the $G_2$ distance measure.

Table 4 summarizes the results, and shows that the reused motion (first row) performs similar to, or slightly better than, a complete new fit of the cardiac motion model (second row).

7. Discussion and Conclusions

In this paper we investigated the possibility of using coronary motion models combined with a single end-diastolic CTA acquisition for aligning the CTA data with dynamic XA data. Several 4D coronary motion models were investigated, including motion estimates representing a specific motion pattern (such as the mean motion of a population, the predicted motion and no motion), and statistical models, which are able to adapt the motion pattern to the image information.

The proposed statistical models were constructed by extrapolating cardiac surface motion close to the coronary arteries. This extrapolation was shown to have an average root mean square (RMS) point-to-point accuracy of about half a mm, which is smaller than the voxel size of the CTA scans (0.7x0.7x0.9 mm), showing the viability of the proposed extrapolation (Section 6.1 and Figure 4). The remaining slight differences may be due to partial volume effect, inaccuracies in the 4D centerline extraction, a suboptimal region representation for extrapolation, or actual differences between cardiac and coronary artery motion.

Both the classical statistical motion model and the more specific conditional statistical motion model were able to represent previously unseen motions with the same average accuracy of 1.02 mm (Table 2). This demonstrates that all relevant variation was retained during variance reduction in the conditional model. Furthermore, the mean of the conditional model tended to predict the coronary motion better than the population average. However, most probably due to the small sample size, this difference was not found to be statistically significant.

We compared the 2D+t/3D registration accuracy of the coronary motion models and estimates using two different distance metrics, $G_1$ and $G_2$ (Table 3). The trends
obtained with both metrics were the same. The 4D CTA motion consistently outperformed the mean and predicted motion estimates. The best results, however, were achieved by the statistical motion models. This might be due to slight differences in the cardiac cycle between intervention time and CTA acquisition. Such differences can be caused e.g. by beat-to-beat variations, by non-rigid deformations due to respiration or inserted instruments, or by a deviation from the 0% and 100% cardiac phase at the first and last frames of the XA sequence resulting from the finite acquisition frequency. The statistical motion models have the advantage to be able to adapt to such changes in the cardiac cycle, and hence outperform the reference standard motion derived from a 4D CTA acquisition. The conditional and classical statistical motion models did not show a large difference in performance, though the conditional model tended to have somewhat lower median centerline errors. These trends hold for both quadratic and unconstrained respiratory motion models.

The additional degrees of freedom in the unconstrained respiratory motion model enabled compensating some of the shape variations during a cardiac cycle. This is especially visible with the static end-diastolic coronary motion model, where the difference in accuracy using the quadratic and unconstrained respiratory models was the largest (Table 3). The same conclusions can be drawn from the inspection of the time-curves of the resulting pose parameters of the unrestricted respiratory motion models (Figure 8). The motion pattern of the static estimate differed considerably from the other motion models, suggesting that frame-wise rigid pose optimization could partially reproduce the non-rigid deformations of the vessel tree in the projection images. We also observed that the time-curves of the population based motion estimates and statistical models were generally close to each other. The figure furthermore shows that the optimization of the out of plane translation is less consistent than in-plane translations, and also appears less plausible. This is due to the fact that the translation of the vessel toward (or away from) the source causes relatively small changes in the projected shape.

When investigating the effect of the projection direction on the coronary motion pattern, no obvious direction dependency was found (Figure 6). This might be caused by the global nature of the motion modes resulting from the PCA analysis, equally affecting all three dimensions.

We furthermore found in our proof of concept experiment that using the estimated coronary motion of one cardiac cycle in a consecutive cycle, performed similar to, if not better than a complete new registration with the statistical models (Table 4). A possible explanation is the lower contrast in the vessels due to wash-out, which caused some of the centerlines detected in the first cycle to be missed in the second cycle. The derived motion from the first heart cycle also outperformed the registration using the 4D CTA derived motion on the second cycle. This result indicates that the motion parameters, though highly varying for registration of the same patient with different initializations, hold meaningful information about the current patient specific contraction pattern.

Investigating the relation between 2D/3D fitting accuracy and vessel diameter revealed a slight increase in the error for smaller vessels, as shown in Figure 5. We believe this is because the error metric has a higher weight around bifurcations due to the larger number of centerline points in the vicinity, than at simple vessel segments or at vessel endings. The modeled bifurcations are typically at larger vessel diameters.

A qualitative evaluation of the overlay with all models showed that registration to sequences where most vessels were over-projected on each other were more susceptible to errors than sequences taken from other angles.

As no geometrically calibrated second view was available in our dataset, in this paper, we solely rely on performance evaluation in the projection plane. A tighter fit in the projection plane does not necessarily indicate a better 3D motion estimate. However, the measured overlay quality is important for several applications, such as for over-projecting lesion information from CTA on the XA sequence.

Registration time required for the evaluated methods depends on the number of frames in the cycle, and the
number of parameters optimized. While the final goal would be a real time registration, our unoptimized Matlab implementation takes about an hour to run on a current laptop computer for an average length cardiac cycle using a statistical coronary motion model and quadratic breathing. We believe this time can be greatly reduced by optimizing the code and parallelizing computations.

In this work we rely on the Frangi vesselness filter results for the 2D/3D matching. This filter is well known to produce lower response at bifurcation points. As our method relies on the entire vessel tree for the 2D/3D matching, the deteriorated filter response at bifurcations has negligible influence on the cost function. Furthermore, if desired, other vessel extraction methods could be employed.

In conclusion, this paper proposed the construction of population based coronary motion models, and showed their applicability for turning the 2D+t/3D registration of end-diastolic CTA and XA sequences into a 2D+t/3D+t registration. The registration performance using the motion models was similar, if not better than the registration performance using the patient specific motion extracted from 4D CTA. This result was found for all tested distance measures and respiratory models. Furthermore, the fitted coronary motion patterns were applicable for registration of a subsequent cardiac cycle with lower contrast. Therefore, we believe that statistical models may substitute the patient specific motion for the task of 2D+t/3D+t alignment of XA sequences and patient specific coronary arteries. Future work could focus on computation time issues, automatic initialization and evaluation on a larger dataset.

8. Acknowledgements

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Figure 10: 2D+t/3D registrations of 3D vessels (blue) to XA data of four patients. Frames are taken at 15%, 50%, and 85% of the selected cardiac cycle in the fluoroscopic sequence. First and third columns use the 4D CTA based coronary motion, the second and last columns use the SMM. A quadratic respiratory model was used in all cases.