X-ray and Magnetic Resonance Imaging (MRI) Fusion to Guide Clinical Revascularization of Peripheral Chronic Total Occlusions (CTOs)

by

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A thesis submitted in conformity with the requirements for the degree of Master of Health Science
Institute of Biomaterials and Biomedical Engineering
University of Toronto

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2018

Abstract

Percutaneous transluminal angioplasty (PTA) is a minimally invasive procedure used to revascularize blocked arteries of the heart and peripheries. However, endovascular approaches to treat chronic total occlusions (CTOs) of the superficial femoral artery (SFA) have proven challenging due to the presence of long and multiple occlusions, which cannot be visualized under x-ray fluoroscopy (XRF) alone. Devices can exit the artery leading to severe perforation. Magnetic resonance imaging (MRI) can produce three-dimensional vascular maps that are sufficient to identify the lesion extent and characterize the surrounding vasculature. Higher PTA success rates could be achieved for lengthy occlusions by merging 3D MRI data and XRF. This thesis develops a 3D MRI to 2D XRF registration method to guide revascularization of peripheral CTOs. The registration method utilizes bones in the MR and x-ray images as landmarks for registration. Furthermore, using an edge-based similarity measure the algorithm automatically maintains alignment together with C-arm tracking.
Acknowledgments

I would like to thank my supervisor Dr. Graham Wright for the continuous support of my MHSc study and related research, for his patience, motivation, and immense knowledge. His guidance helped me through the time of research and writing of this thesis. Besides my supervisor, I would like to thank my committee members, Dr. Anne Martel and Dr. Tony Easty, for their insightful comments and encouragement, and for the hard questions, which incented me to widen my research from various perspectives.

As part of a larger team effort, my responsibilities included conducting X-ray and MRI swine experiments to collect data for registration, extending and modifying methods in an existing respiratory motion compensation software framework to have it conform to and appropriate for guidance in peripheral vascular interventions, and finally running simulations to evaluate the accuracy and capabilities of the proposed registration method.

I would also like to express my sincere gratitude to:

- Bonny Biswas for providing me with invaluable trainings and information on software project management, VPN tunnelling protocols, and DICOM web servers.
- Sebastian Ferguson for his instrumental explanations on the in-house visualization software and continued support.
- Howard Chen for providing me with his knowledge, time, and support in the acquisition of MRI data
- Jennifer Barry for her persistent support in coordinating animal experiments and assistance in acquiring X-ray image data
- Dr. Normand Robert for the insights into X-ray image registration and clinical C-arm systems
- Dr. Michael Truong for his enlightenments on X-ray/MRI image registration and tender guidance
- Dr. Trisha Roy for clarifications on the various operational aspects of peripheral vascular intervention and image registration requirements
Last but not least, I would like to thank my parents for supporting me spiritually throughout the completion of this thesis and my life in general.
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Figure 27 Schematic workflow of a GPU-based biplane 2D/3D registration. Before the intervention, MRI (a) is used to obtain a volumetric data set of the femur (b) from the patient. During the intervention, with an initial estimate of the transformation parameters (c), obtained systematically or via an initial manual registration and which are to be optimized, two perspective projections of a 3D femur model extracted from the MR volume are taken (d) using the same projection matrices as for the biplane intra-procedural x-ray images (f). Biplane x-ray images from the dual plane x-ray system (e) are continuously fed into a graphical processing unit (g) where they are registered in real-time with the two perspective projection images previously generated by the GPU (d). The optimized registration parameters (c) are then used to accurately align the MR data with the biplane x-ray images.
# List of Abbreviations

| 2D | Two-dimensional equation |
| 3D | Three-dimensional MR Magnetic resonance |
| API | Application programming interface MRI Magnetic resonance imaging |
| A-P | Anterior-posterior |
| CIN | Contrast-induced OPAD Occlusive peripheral arterial disease |
| CLI | Critical limb ischemia PAD Peripheral arterial disease |
| CT | Computed tomography PTA Percutaneous transluminal angioplasty |
| CPU | Central processing unit |
| CTO | Chronic total occlusion PVD Peripheral vascular disease |
| DICOM | Digital imaging and communication in medicine PVI Peripheral vascular intervention |
| DOF | Degree of freedom RAO Right anterior oblique |
| DRR | Digitally reconstructed radiograph RCM Radiocontrast media |
| FFT | Fast Fourier transform RMS Root mean square |
| FOV | Field of view SFA Superficial femoral artery |
| FPS | Frames per second SID Source-to-detector distance |
| GPGPU | General-purpose graphical processing unit S-I Superior-inferior |
| GPU | Graphical processing unit SNR Signal-to-noise ratio |
| HFS | Head-first supine SOD Source-to-patient distance |
| ICM | Iodinated contrast media US Ultrasound |
| LAO | Left anterior oblique VTK Visualization Toolkit |
| LCA | Left carotid artery XMR X-ray/MRI |
| L-R | Left-right XRF X-ray fluoroscopy |
| ITK | Insight Toolkit |
| MCDE | Modified curvature diffusion- |
Chapter 1
Background

Chapter Overview

This chapter gives a detailed overview of the epidemiology and the role of image guidance in catheter interventions. Due to the depth and breadth of the disease at hand, the introduction section will only quickly touch upon subjects about changes that occur in the body with the development of the disease including statistical figures indicating morbidity and cost of treatment, a discussion on the current treatment options, benefits and limitations of each method, as well as the role of improved image guidance on the efficacy of interventions.

In the light of this, first a close look is taken at peripheral arterial disease (PAD), its classification based on two paradigms and the associated symptoms. The next section mostly covers information on percutaneous transluminal angioplasty (PTA) as the current treatment method and compares it to other revascularization procedures, followed by a section on x-ray imaging as the contemporary and most widely used imaging technique in PTA procedures and its limitations. The next section reviews the use of other imaging modalities and especially of MRI in guiding percutaneous interventions and describes the various aspects related to implementing a comprehensive visualization method that extracts the benefits of x-ray and MR imaging modalities. Finally, the hypothesis and goal of this thesis will be presented in the last section.
Peripheral Arterial Disease

Peripheral arterial disease (PAD), also known as peripheral vascular disease (PVD), is a slow and progressive circulation disorder associated with blockages in the peripheral vascular system. It is a widespread disease that affects at least 8-12 million people in the United States alone [1]. The worldwide prevalence of lower extremity peripheral arterial disease is between 3 and 12 percent with 202 million people around the world living with PAD in 2010. Although Europe and North America jointly account for an estimated population of 27 million individuals affected with PAD, the majority of individuals with PAD (70 percent) live in low/middle income regions of the world, including 55 million individuals in Southeast Asia and 46 million in the Western Pacific Region [2]. Despite advances in medical technology and better patient management, the incidence of PAD is on the rise and the associated morbidity remains high, especially as the population is aging [3]. The number of individuals with PAD increased by 29 percent in low/middle income regions and 13 percent in high income regions from 2000 to 2010 compared with the preceding decade [2]. The economic cost of amputations for patients with critical limb ischemia (CLI), which is considered the end stage of peripheral arterial disease and is linked to inadequate blood flow to supply vital oxygen demanded by the limb, was estimated at $25 billion in 2014 [4]. According to several observational studies of patients diagnosed with CLI, only 50% of the patients will remain amputation-free at 1 year, although they may still be symptomatic, whereas 25% will require a major amputation and the remaining 25% will have died [5].

The process by which PAD occurs is called atherosclerosis, whereby plaque builds up inside the artery walls. Plaque is primarily made up of fat, cholesterol, calcium, and other substances found in the blood [6]. Over time, the wall of an artery that is affected by atherosclerosis gradually hardens and the internal diameter decreases. This process of narrowing is referred to as stenosis. Although plaque accumulation happens in tiny amounts over long periods of time, if the abnormal narrowing of an artery occurs consistently, it can lead to a complete or nearly complete blockage of the artery, which is characterized as occlusive peripheral arterial disease (OPAD) or often referred to as a chronic total occlusion (CTO). Chronic total occlusion is the main cause of critical limb
ischemia (CLI), which accounts for 40% of patients treated for peripheral arterial disease [7]. Figure 1 illustrates the difference between a normal, healthy artery and an artery affected by atherosclerosis.

Figure 1 The illustration shows how P.A.D. can affect arteries in the legs. A. A normal artery with normal blood flow. The inset image shows a cross-section of the normal artery. B. An artery with plaque buildup that is partially blocking blood flow. The inset image shows a cross-section of the narrowed artery. Modified from [8].

Although the definition of PAD technically includes problems within the extracranial carotid circulation, the upper extremity arteries, and the mesenteric and renal circulation [9], the focus here will be on chronic arterial occlusive disease in the arteries to the legs. It is well documented that approximately 40-50% of all PAD patients undergoing interventions have total occlusions of the superficial femoral artery [3], [10], [11]. Not
surprisingly, these patients often have coexistent cardiac and cerebrovascular diseases, which are also linked to the presence of aggregated plaque in the coronary and cerebral arteries respectively and carry a 5-year mortality rate of 50% in patients with intermittent claudication, and a mortality rate of 60-70% in patients with critical limb ischemia [12]-[15].

PAD is classified based on the manifestations of the disease by the Fontaine classification or the Rutherford classification schemes (Table 1) [16]. One of the earliest indications of lower extremity PAD that patients most frequently present with is intermittent claudication, defined as pain in the muscles of the leg with ambulation. As the disease progresses in severity, patients might have pain at rest, which is aggravated by lifting the limb and relieved by dependency. In the late stages of PAD, tissue hypoperfusion leads to ischemic ulceration and gangrene, eventually requiring a major amputation in more than a third of these patients [17]. In fact, the presence of rest pain or tissue loss, also known as critical limb ischemia, is closely linked with the rate of mortality in this group of patients with a 1-year rate of about 20% in several series [18], [19].

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<td>Asymptomatic</td>
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<tr>
<td></td>
<td>IIa</td>
<td>Mild claudication</td>
</tr>
<tr>
<td></td>
<td>IIb</td>
<td>Moderate-to-severe claudication</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Rest pain</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Ulceration or gangrene</td>
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<td>Severe claudication</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Rest pain</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Minor tissue loss</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Severe tissue loss or gangrene</td>
</tr>
</tbody>
</table>

*Table 1 Classification schemes of peripheral arterial disease*

## 2 Managing patients with Peripheral Arterial Disease

The task of managing patients with lower extremity PAD is classically tackled from two directions, addressing the risk factors important in the progression of the generalized
atherosclerosis first, followed by interventions such as pharmacotherapy, endovascular therapy, or surgery [9]. Treatment is warranted for all classes of PAD and includes control of hypertension, diabetes mellitus and hypercholesterolemia, smoking cessation and antiplatelet therapy when dealing with the primary risk factors (Table 2) [20].

<table>
<thead>
<tr>
<th>Cardiovascular risk factor modification (class/level of evidence)</th>
<th>Claudication treatments (class/level of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation support, including behavior-modification therapy, nicotine replacement or bupropion (I/B)</td>
<td>Supervised exercise program (I/A)</td>
</tr>
<tr>
<td>Lipid-lowering agents to achieve target LDL-cholesterol: &lt;100 mg/dl; &lt;70 mg/dl in high-risk patients (I/B) Statins (IIa/B)</td>
<td>Pharmacotherapy Cilostazol in the absence of heart failure (I/A) Pentoxifylline (IIb/A)</td>
</tr>
<tr>
<td>Diabetes control: proper foot care (I/B) Target glycosylated hemoglobin: &lt;7.0% (IIa/C)</td>
<td>Revascularization Endovascular (I/A) Surgical (I/B)</td>
</tr>
<tr>
<td>Antihypertensive therapy to achieve blood pressure &lt; 140/90 mmHg; &lt; 130/80 mmHg in diabetes and chronic renal failure (I/A) β-blockers (I/A) Angiotensin-converting enzyme inhibitors (IIa/B)</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet therapy (I/A) Aspirin 75–325 mg/day (I/A) Clopidogrel 75 mg/day (I/B)</td>
<td></td>
</tr>
</tbody>
</table>

Class I: Conditions for which there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful and effective.
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Level of evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B: Data derived from a single randomized trial or nonrandomized studies. Data from [20].

Table 2 Management of peripheral artery disease

2.1 Percutaneous Transluminal Angioplasty vs Surgery

Percutaneous catheter interventions to treat occlusive lesions of the lower extremities were first described by Dotter and Judkins in 1964 [21]. Percutaneous transluminal
angioplasty (PTA) is a minimally invasive procedure that can open up a blocked blood vessel using a small, flexible plastic tube, or catheter, with a balloon at the end of it. When the tube is in place, it inflates to open the blood vessel, or artery, so that normal blood flow is restored [29].

PTA is currently the main procedure for revascularizing narrowings and blockages of the superficial femoral artery (SFA). At the beginning of the procedure, the patient is placed in a supine position on the procedure table in a catheterization lab. Although patients are given a sedative medication to help them relax, they normally remain awake, but sleepy, throughout the procedure. A sheath, or introducer, is then inserted into the blood vessel. This is a plastic tube through which the catheter will be inserted into the femoral artery. Next, a special catheter or guidewire is inserted into the femoral artery and advanced to the site of the blockage. The proper position of the catheter may be confirmed by injecting a small amount of contrast dye into the artery, which can then be seen on a monitor. Subsequently, the physician will insert an angioplasty catheter and advance it to the location of the blockage. A balloon at the tip of the catheter will be inflated to open the artery. At this stage, the physician may inflate and deflate the balloon several times to open the artery. In some situations, a stent may also be inserted into the newly opened area of the artery to help keep the artery from narrowing or closing again [22].

Other revascularization options include open surgical procedures such as bypass grafting and endarterectomy. However, because the risks of surgery are significantly greater than the risks of a less invasive percutaneous approach, in terms of not only mortality but also major morbidity and delay in return to normal activities, PTA is currently recommended as the preferred treatment option in situations where endovascular revascularization and bypass surgery give equivalent short-term and long-term symptomatic improvement [23]. The efficiency of PTA for the treatment of focal occlusive disease of the superficial femoral artery (SFA) and popliteal artery has been studied extensively in the literature and compared to surgery it has been found to be less invasive, less costly, and associated with a low incidence of complications [24]-[32]. According to published results, initial technical success rates of 90% to 95% have been achieved for stenotic lesions and of 80% to 95% for complete occlusions [27], [28], [30], [31]. Studies by other groups of
scientists have placed the primary 1-year patency rates of iliac lesions revascularized using PTA at 70% to 80% [33]-[36]. Undoubtedly, there is a wide variability among the gathered scientific data and the efficacy of PTA remains controversial, which is mainly due to differences in the criteria used to denote success, patient demographics, and the types of lesions treated [37].

Among the three distinct areas where OPAD occurs, the iliac arteries, the femoropopliteal arteries, and the infrapopliteal arteries, disease in the latter two arteries is much more common and lesions in these regions are often long and multiple [38], [39] (Figure 2).

Figure 2 Illustration of the aortoiliac, femoropopliteal, and infrapopliteal arterial segments. There is a higher incidence of OPAD within the femoropopliteal and
infrapopliteal regions in the leg [38], [39]. Modified from [40] Figure 21.3.

In a recent investigation, 1605 occlusive lesions were analyzed in 407 diabetic patients with CLI and it was found that except for 2 lesions, all others were located in the femoropopliteal and infrapopliteal arteries. Furthermore, 32% of the lesions in the femoropopliteal arteries and 77% in the infrapopliteal arteries were greater than 10 cm in length [41]. However, under the current guidelines, PTA is only recommended for occlusions that are 3-10 cm in length in the femoropopliteal region [23], which has a restenosis rate of up to 60% despite high initial success rates [42]. These figures indicate that there is a large population of patients with extended occlusions of femoropopliteal and infrapopliteal arteries who could readily benefit from technological improvements in existing PTA procedures. The development of a minimally invasive technique to address the limitations faced by the current PTA method in revascularizing long occlusions of the lower extremity would also prompt an increase in procedural accuracy and a decrease in procedural duration. This will in turn translate into higher technical success rates of PTA procedures at large.

There are many lesion properties that can influence the success of a PTA procedure, which essentially boils down to the ability to successfully cross the occluded vessel. A lot of these properties can be inferred from the literature associated with CTOs of the coronary vasculature [43]-[46]. Entrance characteristics such as the presence of collateral vessels and vessel branches negatively affect success rates. The presence of harder components in an occlusion also restricts guidewire passage. As mentioned previously, when occlusive lesions age a collagen rich matrix gradually replaces thrombus and calcium deposits begin to appear inside the lesion [47], [48]. Furthermore, the proximal entrance of the lesion, the fibrous cap, becomes hard and resistant to device crossing [48], [49].

The merits of a more interactive and comprehensive visualization technology that can be utilized during PTA procedures to provide lesion information can be well appreciated. An overlay of such information during these procedures would be beneficial to physicians not only due to providing local lesion property information but also due to providing a
general map of the vasculature. However, PTA procedures are currently performed under x-ray fluoroscopy (XRF) guidance, which inherently lacks soft tissue contrast. Hence, the visualization method should ideally be able to overlay soft tissue information such as the locations of the lesion and the surrounding vessels as well as lesion property information onto the XRF to provide enhanced real-time guidance with little change to the current workflow.

3 X-ray fluoroscopy guided PTA

The x-ray system (C-arm) is comprised of the x-ray source, x-ray detector, and the patient table (Figure 3). The x-ray source, located at one end of the C-arm, emits a cone-shaped beam of x-ray photons that passes through the patient at the preferred target site. The photons in the x-ray beam are attenuated in various degrees as they pass through the different tissues in the body. They hit the x-ray detector on the opposite end of the C-arm where they cast a 2-dimensional (2D) shadow image of the 3-dimensional (3D) object on their path depending on the level attenuation as experienced by individual photons (Figure 3 Right). The C-arm can be rotated around 3 axes (Figure 3 Left) to provide flexible imaging of the anatomy. Most of the clinically available x-ray systems come with a single C-arm, making them compact and portable. Biplane x-ray imaging systems are also available but are rarely utilized during PTA procedures.
As mentioned in the previous section, PTA procedures can benefit from readily available patient-specific information about the SFA anatomy, location and extent of the blockage along the vessel, and lesion properties. However, current PTA procedures are mainly performed in an x-ray catheterization laboratory. Therefore, the revascularization rates of long occlusions using PTA have been limited by the technical challenges associated with crossing occluded vessels with guidewires under x-ray’s poor soft-tissue visualization. While the x-ray fluoroscopy can provide high spatial and temporal resolution images of the SFA up to the entrance of the occlusion using contrast media injection, there is no opacification of the vessel lumen along the body of the blockage as there is no flow through a total occlusion (Figure 4). In this situation, the operator is unable to visualize the vessel path under x-ray fluoroscopy, which can make it very difficult to assess vessel tortuosity and to identify the position of a revascularization device with respect to the proximal and distal ends of the lesion and to the vessel wall. Devices may steer out of the artery, which can lead to severe perforation [52]. Consequently, attempts to recanalize extended occlusions are relatively rare. In addition, x-ray fluoroscopy’s limited soft tissue contrast also makes it difficult for the operator to assess properties of the lesion that directly affect procedural success as discussed in the previous section. Merging pre-acquired lesion and anatomical information with the live XRF display may permit upfront use of aggressive devices and improve procedural outcomes [52]. Finally, PTA typically involves a significant exposure to nephrotoxic contrast, which can adversely affect patients with pre-existing renal dysfunction and is of particular concern in the patient population with OPAD. Contrast-induced nephropathy (CIN) is a common complication in this patient group and is defined as acute renal failure occurring within 24-72 hours of exposure to radiocontrast media (RCM). In a study by Stegemann et al., it was found that the volume of iodinated contrast media (ICM) used during typical fluoroscopy-guided
Peripheral vascular procedures (i.e. PTA) was 113 ± 76 mL with a total irradiation time of 25 ± 16 minutes out of 89 ± 34 minutes of intervention time [53]. It is worthwhile to note that the elimination half-life of most ICM falls within the range of 90 to 120 minutes in patients with normal renal function and can be delayed, on the order of weeks, in patients with renal insufficiency, which further contributes to nephrotoxicity in patients suffering from OPAD [54].

The limitations stated above primarily apply to single-plane x-ray fluoroscopy. Bi-plane x-ray imaging systems that are found in advanced catheterization laboratories can create a 3D approximation of the imaged anatomy using two orthogonal 2D projections. However, this does not fully solve the 3D ambiguities associated with 2D projective images [55]-[57]. Furthermore, bi-plane x-ray imaging systems are rarely set up in standard catheterization labs. Finally, endovascular interventionalists with access to both single-plane and bi-plane imaging systems are often reluctant to use the bi-plane mode as the additional C-arm not only adds to the ionizing radiation exposure to the patient and staff but also increases the complexity of the workflow related to two simultaneous image acquisitions.

Figure 4 Peripheral arterial occlusive disease. This angiogram shows a superficial
femoral artery occlusion on one side and superficial femoral artery stenosis on the other side. This is the most common area for peripheral vascular disease. XRF does not display any information about the occlusive lesion or the vessel path/wall at the site of the occlusion. Reprinted with permission from [58].

As a result, the radiologist is effectively blind when guiding a catheter across an occlusion and solely relies on a mental image of the patient’s SFA morphology. These challenges have led to variable results in treating CTOs using standard guidewires, with procedural success rates ranging from 34% to 91% [59], [60].

4 Integrating soft tissue information into PTA procedures

Ideally, during a revascularization procedure, the imaging method should provide three things: First, clear visualization of the lesion, the device, and the vessel wall to ensure that the device remains within the lumen; Second, visualization and stiffness characteristics of the proximal entrance to facilitate guidewire entry; And third, mapping of hard and soft lesion constituents at a resolution that is sufficient to facilitate guidewire navigation.

Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) are all able to acquire images of occlusive lesions with soft-tissue contrast. These imaging modalities are able to characterize many lesion attributes including lesion length, tortuosity, and presence of collateral vessels, which may be predictors of procedural success. However, the use of CT is limited due to the associated large radiation dose and the incapability to characterize soft lesion components well. US also suffers from extensive shadowing associated with heavy calcification found in many occlusive lesions [61].

The use of MRI for direct lesion characterization is particularly promising. MRI has excellent soft-tissue contrast and is capable of differentiating between the vessel wall and many of the lesion constituents. MRI has been used to study atherosclerotic plaque
morphology using T2-weighted images [62]. Clarke et al. have demonstrated that MRI can achieve a sensitivity and specificity of 65.2% and 87.9% for identifying loose connective tissue, 97.6% and 94.9% for calcification, and 60.4% and 87.9% for fibrous tissue, respectively [63]. Furthermore, MRI has been shown to be able to image the vessel wall and to delineate it from the surrounding epicardial fat and blood in patent and diseased right coronary arteries [64]. In a recent study by Roy et al., MRI has shown promising results in distinguishing between hard and soft plaque components, which directly affects the ease of crossing [65].

4.1 MRI of vascular blockages

MRI is well suited for guiding the revascularization of extended lower extremity vascular lesions owing to its excellent soft-tissue contrast, capacity to acquire 3D volumetric anatomical images, and lack of ionizing radiation. By combining MRI and XRF the strengths of both modalities can be exploited [66], [67]. The visualization method will be able to produce vascular maps that are sufficient to identify the lesion extent and characterize the surrounding vasculature, including collateral vessels and vessel branching at the entrance of the occlusion, with respect to the revascularization device by superimposing soft-tissue information onto the XRF display. In addition, a pathway for the guidewire to follow through the occlusive lesion could be established by mapping lesion constituents using MR’s high soft-tissue contrast and providing the information to the operator in real-time via the comprehensive visualization technology. However, before any of this is achieved, pre-acquired 3D anatomical data from MRI must be correlated to the anatomy depicted in XRF. This requires the spatial co-registration of MRI and x-ray data.

4.2 Registration of pre-procedural maps with XRF

Image registration is one of the enabling technologies in the field of medical imaging and is concerned with bringing pre-intervention data (patient’s images or models of anatomical structures obtained from these images and treatment plan) and intra-
intervention data (patient’s images, positions of tools, radiation fields, etc.) into the same coordinate frame [68]-[75]. In the context of OPAD, image registration has received a smaller body of research as compared to cardiac applications, all of which have been devoted to finding precise alignment between pre-procedural 3D volumes (MRI/CT) and intra-procedural 2D x-ray fluoroscopy images.

The fusion of 2D x-ray and 3D pre-procedural data (MRI/CT) can be formulated as a rigid registration problem, finding 3 translations and 3 rotations around associated axes. Normally, there are no intrinsic movements within the leg during PTA procedures of the lower extremity and the anatomy remains fairly static. However, there could be minor displacements of the leg as these procedures are typically long in duration and the patients are not fully asleep. Thus, rigid registration is a reasonable first approach for this application.

A number of different registration methods have been developed to address the imaging limitations in PTA procedures as previously mentioned. All of these methods can be categorized as one of manual, semi-automatic, or fully automatic registration techniques according to the required user interaction. Semi-automatic and fully automatic registration algorithms usually require that the user provides the data as well as providing some initialization to the algorithm, such as segmentation, and validating the current registration result [76]. On the contrary, manual registration is performed entirely by the user using software tools that provide visual feedback of the current transformation [77], [78].

4.2.1 Manual Registration

As mentioned before, in terms of 3D/2D registration, most of the image registration literature pertains to cardiac interventions [79]-[81]. This is primarily due to a more demanding challenge that needs to be addressed while navigating a catheter through an occluded vessel in the presence of respiratory motion [76]. Most of the registration techniques fall into the manual registration category or possess some level of user interaction [82], [83]. The manual portion of the registration often encompasses segmentation of 3D features using a manual or automatic approach and then initializing
the algorithm using the obtained information in order to reduce subjectivity to local minima by performing rough registration.

Fully manual registration methods suffer from a few drawbacks. First, they are burdensome, time-consuming, and are associated with high levels of inter-operator variability as they directly depend on the skills of the user [76]. Also, without any automatic registration update, any movement of the extracted 3D feature cannot be accounted for in 3D space and the transformation is solely derived from 2D movements of the visible feature in the x-ray images that were used initially to register the two coordinate systems [82], [84]. Hence, the registration accuracy can be inconsistent or unacceptable.

4.2.2 Semi-automatic and automatic registration

While researchers make every effort to develop fully automated 3D/2D registration algorithms, some user interaction is usually still needed at least for the final verification of the results [85]. Semi-automatic registration methods involve manual extraction of a feature from the x-ray and MR images, i.e. identifying the distal/proximal femur or a CTO stump as a landmark [86], [87]. Some form of initialization of the registration algorithm often follows this, which can be a manual initialization on images. For example, the initialization procedure must achieve a registration that is within the capture range of a specific intrinsic 3D/2D registration method. Most of the intrinsic 3D/2D registration methods are semi-automatic [76]. Fully automatic registration methods have been mainly focused on radiotherapy applications [88]-[91], and are rarely employed in cardiovascular interventions, which is mainly due to the use of unconventional catheters [92], requirement for nonstandard hybrid XMR systems [93], and reliance on toxic contrast injection for repeated re-registration [94].

4.2.3 Registration landmarks

A few reliable landmarks exist inherently within the upper leg anatomy. The existence of these landmarks eliminates the need for artificial landmarks to be introduced into the anatomy and provides a consistent reference frame for sharing between the x-ray and MR
coordinate systems. An image based registration method can be performed using landmarks such as the proximal CTO stump in an artery, the curvature of a patent artery and arterial branches [52], [95] (**Figure 5 C-F**), as well as the bone [86] (**Figure 5 A-B**). All of these features readily exist in the upper leg anatomy. Other registration methods employ fiducial markers placed on the patient’s skin surface to achieve spatial alignment between the two coordinate systems [96]. These methods can achieve good registration results and provide an accurate alignment of the x-ray and MR coordinate systems, but the underlying anatomy can exhibit displacements relative to the affixed skin markers due to tissue elasticity, which could throw off the registration and cause discrepancies in accuracy.

Considering the application of registration in PTA procedures of the SFA, the two plausible landmarks that inherently exist in the upper leg are the superficial femoral artery and the femur bone. Given that the occlusive lesions are located within the SFA and PTA procedures attempt to cross the occlusion by blindly guiding a catheter inside the artery, choosing the SFA as the x-ray and MR registration landmarks may seem reasonable. However, in order for the automatic registration update to perform real-time refinement of the alignment, constant injection of nephrotoxic contrast is required, rendering the SFA structure less valuable as a landmark. The femur bone is the closest consistently available inherent feature to the SFA that can be utilized as a shared reference point between the two coordinate frames. The femur is a rigid object that resides a distance of $20 \pm 6$ mm from the superficial femoral artery in a neutral position [97] and possesses a 3D geometry that produces a unique shape when viewed from different angiographic angles. Hence, the femur bone can provide a reliable registration landmark in both the x-ray and MR images.
Figure 5 Image registration examples based on intrinsic registration landmarks. A-B. 3D/2D registration of a surface model of the distal femur extracted from 3D ultrasound to 2D x-ray image generated from a CT dataset using a projective feature-based approach. Reprinted with permission from [86] Figure 1. C-D. Intra-procedural angiograms from orthogonal views (45° RAO / 45° LAO) reveal the patent right carotid artery (RCA) and proximal stump of the left carotid artery (LCA) in a swine model. E-F. 3D models of the carotid arteries are registered to the angiograms by aligning the luminal edges of the RCA with its model. Reprinted with permission from [52] Figure 2.

4.2.4 Determining target registration accuracy - superficial femoral artery dimensions and movements

The choice of the registration landmark should be based not only on finding a reliable feature that can be identified in both modalities but also on an effort to minimize error. In addition to serving as a rigid reference object, the femur is located in close proximity of
the SFA as stated in the previous section. Selecting a landmark (i.e. the femur) nearest to
the anatomy where registration is required (i.e. the SFA) greatly reduces the effect of
tissue displacement as caused by elasticity. This is because anatomical structures in the
vicinity of one another tend to be displaced by the same proportion, which would
minimize misalignments in the final registration. By extension, achieving a desired target
registration accuracy using the femur as a landmark in the x-ray and MR images directly
translates to nearly the same accuracy at the site of the intervention, i.e. the SFA. The
diameter of the superficial femoral artery is approximately 6.3 ± 0.1 mm in healthy
subjects [98]. To this end, by achieving a registration accuracy of less than 3 mm
using the femur as the registration landmark ensures a final accuracy of at most
half of the vessel diameter within the SFA.

5 Objectives, Hypothesis and Scope

The previous sections indicated the inadequacies associated with current registration
methods that are geared towards development of a guidance technology for PTA
procedures. Drawbacks such as dependence on contrast injection, potential propagation
of error due to fiducial marker utilization, and the use of clinically nonstandard hybrid
XMR suites are to name a few.

Thus, the objective of this thesis is to develop an x-ray to MR registration method that
effectively refines the initial registration and continually corrects for misalignments
during the procedure in real-time, while utilizing features as landmarks that inherently
exist in the body and result in a reliable registration.

The hypothesis that will be tested in this thesis is as follows: The registration method
utilizing the femur bone as an inherent landmark, can co-register anatomical models
segmented from pre-acquired MR images to intra-procedural x-ray images with an
adequate target registration error (less than 3 mm based on half of the diameter of the
superficial femoral artery). In addition, the capture range of the registration method will
be characterized in this thesis.

The ultimate goal of XMR fusion in PTA procedures of the lower extremity is to
visualize the lesion and its properties, delineate the lesion from the vessel wall, and locate the revascularization device relative to the lesion and the vessel wall to provide a road map for the operator to follow. The scope of this thesis is to overlay pre-acquired MRI onto XRF to locate the revascularization device with respect to the vessel wall and the lesion where standard fluoroscopy fails to provide such information. The consequence of achieving this spatial registration reaches beyond providing ordinary anatomical and pathological structure location information. With evolving MR sequences, the lesion properties can be well characterized and superimposed using this registration method, which can aid in the upfront selection of the appropriate revascularization device and provides a pathway to follow through the occlusion.
Chapter 2
X-ray and MRI registration

Chapter Overview

This chapter is intended to provide a detailed description of the proposed registration method. As for any complete and reliable registration package, the basis utilized to implement the registration method in this thesis will be justified and the drawbacks of the existing registration tools will be mentioned briefly. For the large portion of this chapter, the methods used to construct and test the accuracy and performance of the registration method will be presented.

In order to keep a consistent flow between sections, the chapter will start off by explaining the requirements for implementing an efficient and robust registration method that can be used to guide percutaneous catheter interventions of the lower extremities. In the following section, the steps required to implement the registration pipeline as proposed by this thesis will be presented including the data acquisition and evaluation methods. Finally, the accuracy of the registration method will be demonstrated along with a discussion of the factors influencing the target registration error (TRE) and ways to improve it. The upper boundaries of the registration error tolerance will be assessed and their significance with respect to bulk patient motion will be highlighted.
6 Introduction

The application of image registration for the guidance of peripheral CTO revascularization has not received adequate attention in the literature and most of the medical image registration algorithms pertain to the coronary interventions. The current x-ray and MR (XMR) co-registration methods to guide clinical revascularization of chronic total occlusions can achieve high accuracy but rely on the placement of external fiducial markers and/or the use of expensive hybrid XMR systems [100], [101]. Klein et al. have employed segmented 3-dimensional surface models of the carotid artery in swine, extracted from MRI, to register onto live XRF images using established visual matching methods [52]. Other available methods require special catheters for active catheter tracking, which may not be present during a percutaneous vascular intervention (PVI) of the lower extremity. This chapter extends and validates an existing XMR registration method that will co-register a 3D surface mesh extracted from pre-procedural 3D MR images to 2D projective x-ray images. The registration method in this chapter is intended to provide guidance for the clinical revascularization of peripheral CTOs and is designed to account for patient bulk motion and x-ray gantry movements. The registration method as described in the following section will be based on anatomical landmarks that are readily visible in both x-ray and MR images.

7 Methods

7.1 Overview of the registration method

7.1.1 Landmarks

In order for two sets of data to be spatially aligned, reference points in each dataset or their metadata that are shared between the datasets are required. These shared reference points are used to locate the corresponding parts of the datasets and find the matching transformation that brings the coordinate system of one dataset in alignment with the coordinate system of another dataset. Shared reference points in image datasets ideally represent prominent features that are readily distinguishable in the set of images to be registered and retain a constant shape and size. Several research groups have utilized the
arterial centerline or key anatomic features such as arterial curvatures and branching as shared references for registration [52], [102]. However, since the artery is not visible in the region of occlusion under fluoroscopy, registration cannot be performed at totally occluded regions of the artery and may be subject to error if only the visible sections upstream are utilized. The registration method proposed in this thesis takes advantage of the consistently visible solid bone in the x-ray images as the shared reference for registration. The femur is easily detectable under XRF and is often present in the field of view of the C-arm during SFA revascularization. Hence, it can provide a reliable landmark within the x-ray images (Figure 6C) and removes the need for external fiducial markers to be placed on the skin or special interventional devices to be present at all times for utilization as landmarks. MRI can generate a high-resolution 3D image of the femur, which can be segmented and used as the MR landmark (Figure 6A). The 3D MR landmark can be projected onto x-ray’s 2D plane and compared to the x-ray landmark (Figure 6B, C). In this way, the registration pipeline possesses a basis for comparison and optimization in order to find the registration pose.

Figure 6 Femur as the x-ray and MR registration landmarks. A. The femur is segmented (in red) from the 3D MR data. B. The 3D MR landmark (segmented femur) is projected onto the 2D x-ray imaging plane to be compared to the x-ray landmark. C. The femur as visible in the x-ray image is used to compare against the 2D projection image of the MR landmark.
7.1.2 Workflow

The image registration workflow as implemented in this thesis includes a manual and an automatic component (Figure 7). The manual portion of the registration pipeline is comprised of a preprocessing step as well as the initial manual registration. The automatic portion of the workflow updates the registration pose every time the x-ray image undergoes a rigid body transformation, whether caused by the movement of the physical C-arm or patient motion. The manual and automatic pieces of the XMR registration pipeline are outlined as follow:

- Manual segmentation of the femur from MRI data
- Initial manual registration using segmented femur based on bi-plane x-ray images
- Automatic registration update and refinement based on single-plane x-ray images, which includes the following steps in a loop:
  - C-arm gantry tracking and updates to the registration pose
  - Computation of the similarity metric based on the comparison of the projected MR landmark and x-ray landmark
  - Updates to the registration pose based on the computed similarity metric
  - Visualization of the XMR fusion

The SFA and multi-modality fiducial markers are also manually segmented from the MR data for use in the analysis of accuracy. More specifically, the multi-modality markers will be used in the calculation of target registration error and the SFA segmentation is used to provide a qualitative visual assessment of the final overlay. All of the segmentations are performed using ITK-Snap 2.4.0 [103]. The rest of the registration components are implemented in C++ by taking advantage of open-source application programming interfaces (API) including the Insight Registration and Segmentation Toolkit (ITK), Visualization Toolkit (VTK), Qt Frameworks, and OpenGL. The registration workflow as currently implemented for the purpose of this thesis works retrospectively on the collected data. A clinical version of the registration workflow will have the same general sequence of activities as outlined here with a few exceptions that will be addressed briefly in the final chapter.
Figure 7 An overview of the image registration components and pipeline. The XMR image registration workflow begins by manual segmentation of the femur from the 3D MR volume followed by initial manual alignment of the segmented 3D model to bi-plane x-ray images. The automatic registration loop updates the registration pose continuously based on the orientation of the C-arm gantry, performs a finer feature-based registration based on the x-ray and projected MR landmarks using single-plane x-ray images and realigns the MR coordinate system accordingly. The resulting image fusion is then displayed on the screen.
7.2 Data

All of the x-ray and MRI data used to develop and evaluate the proposed registration method in this thesis are pre-acquired and have been retrospectively utilized in the development process. Pig experiments were conducted to collect the required data for registration. Some of the activities performed during x-ray experiments include insertion of a catheter into the SFA for contrast delivery, multi-modality marker placement on the pig’s skin around the area of the femur, and making measurement of the source-to-patient distance (SOD) after ensuring that the desired leg is properly isocentred on both of the required angiogram angulations. Once the required x-ray images are attained, the pig is transferred from the surgical C-arm table to the MRI table where a 3D scan of the femur including the SFA and surface markers is acquired.

7.2.1 X-ray image data

X-ray images are acquired in DICOM format using the Philips Veradius mobile C-arm. Image acquisition is performed using high-resolution Cine recording mode, which is the standard recording setting for angiographic systems and has a high radiation dose rate that can be up to 15 times greater than that used in fluoro mode to obtain a series of images with reduced image noise [104]. The x-ray DICOM image metadata from the Philips Veradius x-ray image acquisition and viewing system does not include specifications for the source-to-patient distance (SOD) given the fundamental physical structure of the system, which does not have a table of its own and, therefore, no inherent indication of where the object to be imaged may have been positioned during acquisition. As such, approximate measurement of the SOD is made during acquisition using a measuring tape by carefully measuring the distance from the flat detector panel on the C-arm to the animal’s right femur (Figure 8). The found value is then added into the DICOM metadata of the acquired x-ray images, which is utilized by the registration algorithm along with other DICOM tags such as the positioner primary angle and field of view dimensions to reconstruct the 3D scene of the C-arm. With a properly isocentred object within the radiation field of the C-arm, the source-to-patient distance (SOD) of an object should not change with oblique lateral rotations of the gantry. This fact will alternatively aid in finding the most accurate position for the isocentre point of the C-
Moreover, it should be evident that the source-to-detector distance (SID) stays the same at all times as this specification indicates the distance between the flat detector panel and the x-ray source, which is a fixed distance and is determined by the vendor (Figure 8).

The source-to-patient distance is a standard DICOM tag that is internally measured and provided by most clinical bi-plane x-ray systems that possess a calibrated table. Since the SOD tag is manually measured in the current study, significant error is expected. The error from the measurement of this distance propagates and affects the registration results to a certain degree. To minimize this error, the SOD can be measured at both angulations as previously described to confirm the same measurement from both x-ray views. The impact of the approximation to the SOD on the initial registration and automatic registration accuracies will be explored in more detail in the discussion section.

As mentioned before, the object, namely the pig’s right femur, is placed as close to the isocentre of the C-arm as possible by confirming that the relative SODs stay constant within both of the desired x-ray views as the object’s angular view changes through oblique lateral rotations of the gantry. With this achievement, the femur along with the multimodality markers and the SFA are imaged under x-ray in left anterior oblique (LAO) 35° (Figure 8 Left) and right anterior oblique (RAO) 35° (Figure 8 Right) while contrast is delivered to illuminate the artery. Further x-ray acquisition settings include field of view of 27 cm x 27 cm, image size of 1024 x 1024 pixels, tube voltage of 55 kV (RAO) and 64 kV (LAO), current of 4.13 mA (RAO) and 8.97 mA (LAO), and 15 frames per second (FPS) cine rate. The source-to-patient distance was found to be 635mm.
Figure 8 Illustration of the x-ray acquisition module attributes source-to-detector distances (SID) and source-to-patient distance (SOD). Left. C-arm in the left anterior oblique (LAO) 35° angulation. Right. C-arm in the right anterior oblique (RAO) 35° viewing angulation. With a properly isocentred object within the radiation field of the C-arm, the measured SOD at both angulations must match.

7.2.2 MRI data

Following x-ray image data acquisition, the pig is transferred to a GE Discovery MR750w 3T scanner and is placed on the MR table in head-first supine (HFS) orientation. The axial location of the femur is landmarked so that the acquired MR data appears close to the center of the coordinate system. The femur is imaged using a cardiac coil with the following protocol details: fat-suppressed 3D balanced binomial-pulse steady-state free precession (BP-SSFP) sequence, TR 6.4 ms, TE 4.0 ms, flip angle 45°, field of view of 240mm x 192mm, slice thickness of 1.0 mm, and sagittal plane prescription. The BP-SSFP sequence parameters are tailored in a way to achieve optimal distinguishability of the femur and SFA. The resulting 3D MR volume had an isotropic resolution of 1.0mm x 1.0mm x 1.0mm. The metadata of the DICOM MR images also
included information about the position and orientation of the patient within the MR coordinate system, which is employed by the registration algorithm to place the volume with the right orientation and at the correct location in order to initialize the starting position and orientation of the segmented 3D femur model prior to manual biplane registration.

7.3 Preprocessing

7.3.1 Femur and SFA segmentation

The features of interest from 3D MRI data are segmented using ITK-Snap 2.4.0 [103]. The segmentation produces the following three distinct meshes:

- Femur
- Superficial femoral artery
- XMR multi-modality markers

The 3D surface models were obtained by performing manual segmentation for each of the features. All of the resulting segmentation models were further processed to produce smoother boundaries and feature edges by incorporating a Gaussian blur function subsequent to the coarse segmentation of the features. The standard deviation used in the Gaussian smoothing function for each of the surface models is as follow: 1.2 mm for the femur, 0.7 mm for the SFA, and 1.0 mm for the multi-modality (XMR) markers. The standard deviation value for each feature was empirically chosen to attain sufficient smoothing of the 3D model and to diminish the discontinuity in appearance between the segmented slices.

7.3.2 Initial manual registration

Originally, there is no correspondence between the coordinate systems of the x-ray C-arm and MR scanner. Hence, data from the two imaging modalities can exhibit large initial misalignments. There have been efforts to calibrate the coordinate systems of the x-ray and MRI in an XMR facility in order to provide initial correspondence between the imaging modalities with the use of optical tracking to maintain the registration [67]. However, the complexity of the proposed method as well as long recalibration times
make this approach unfeasible for clinical adoption where real-time visualization with the least change in workflow is a priority. In any event, the initial misalignment between the x-ray and MR datasets still imposes a challenge and a potentially long computation time on the automatic registration’s ability to correct for the large translational and rotational transformations in the 6 degrees of freedom (DOF) that would result in an acceptable registration. One way to overcome this is to augment the automatic registration with a smaller search space in favor of faster computation by accounting for most of the large initial translational and rotational misalignments through a manual initial alignment. This way, though there will be a tradeoff between speed and search space, the required optimal registration accuracy can be preserved. Moreover, since the patient’s leg remains fairly static during a peripheral CTO revascularization procedure, the initial manual alignment will decrease the automatic registration’s computational burden in maintaining the continual pose of the registration by endowing it with a narrower search range.

There are quite a few examples of the employment of initial manual registration to either bring two datasets into coarse alignment or to accurately align intermodal datasets [82], [86]. In an attempt by Hsu et al. to register a 3D surface model of the distal femur obtained from CT data to 2D x-ray data with known perspective projection matrix, an initial transform was applied using manual alignment followed by an iterative, projective, feature-based approach to estimate the optimal transformation [86]. This thesis adopts a similar approach, using the femur as the shared x-ray and MR landmark for registration. Since the manual registration is performed only initially, a biplane x-ray image acquisition or two consecutive single-plane image acquisitions at the beginning of the procedure would provide sufficient anatomical information to bring the MR dataset in rough alignment with the two acquired x-ray views. In this fashion, the proposed workflow does not add complexity to the current procedure and is clinically achievable as the automatic registration requires only single-plane images to work with while the two x-ray views are only needed once in the beginning of the procedure or at any time bulk motion of the leg occurs beyond the capture range of the automatic registration method.

The manual initial registration is accurately performed using the femur while the accompanying multi-modality markers at the rendered positions at the end of the initial
registration will provide for a ground truth transformation against which the automatic registration’s target registration error (TRE) can be expressed. The manual registration is performed by interactively aligning the segmented 3D femur model from MRI to the femur as visible on the two x-ray views (Figure 9). Since the relative positions of the femur and XMR markers is suspected to have been distorted in between the x-ray and MR data acquisitions due to skin and femur displacements, the segmented 3D markers from MRI may not perfectly overlap with the markers as visible on the x-ray images following the accurate alignment of the femur. However, this will not affect the TRE measurement as with precise generation of the registration pose by the automatic registration using the femur, the markers are expected to return to the same starting positions, i.e. relative positions with respect to the femur. With this taken into account, a small human error in performing the initial manual registration may exist in this ground truth determination step that can be carried over to contribute to the final TRE. This negligible error can be measured during the validation of the automatic registration, and will be interpreted in more detail in the discussion section.
Figure 9 Demonstration of the initial manual registration of the x-ray and MR data using femur as the shared landmark. A, B. Initial unregistered coordinate systems of x-ray (background) and MR data (white) in the LAO and RAO projections. C, D. Manually registered coordinate systems of x-ray and MRI based on the segmented 3D femur model and x-ray images of the femur as visible in LAO 35° and RAO 35° x-ray projections.

7.4 Automatic registration update

The automatic registration is responsible for the continuous update of the registration pose throughout the procedure based on single-plane x-ray images. It achieves this task through the execution of two independent components: x-ray C-arm gantry tracking and automatic image-based registration (Figure 10). The x-ray C-arm gantry tracking operates by reading calibrated geometrical information about the x-ray C-arm position and orientation provided by the metadata and reflecting any new changes onto the 3D MR data by rotating and translating the registration pose in real-time. The tracking component, however, does not account for potential millimetric misalignments left behind from the initial manual registration step nor does it correct for possible bulk motions of the patient mid-procedure. In this case, the image registration component refines the results of the C-arm tracking and corrects for the slight misalignments that may have existed from the manual registration step by finding the accurate transformation parameters that re-establishes correspondence between the landmark features visible in x-ray and MRI. The automatic registration component also allows for patient bulk motions within the registration’s capture range by repeatedly searching for the transformations that re-institute the appropriate alignment, all using single-plane x-ray images as biplane images are not typically available during the procedure.
7.4.1 X-ray C-arm gantry tracking

C-arm tracking accounts for the physical rotations and translations of the gantry during the procedure and relays these changes onto the registered MR data by completely reflecting the required transformations. Thus, the registration pose is maintained throughout the movements of the C-arm without the use of imaging.

The C-arm gantry tracking tags, which are used to recreate the C-arm configuration in 3D space when a standard floor-mounted C-arm is used, include source-to-patient distance, source-to-detector distance, positioner primary angle, positioner secondary angle, and field of view dimensions (Figure 11). As noted earlier, in this experiment, the source-to-patient distance DICOM tag is not available for the mobile C-arm so is manually measured and added into the metadata of the acquired x-ray images. The 3D geometrical recreation of the C-arm orientation in preparation for registration within the visualization software’s environment assumes that the patient lies on the table in supine position.
Figure 11 Schematic depicting x-ray DICOM tags related to C-arm orientation required for registration. A. Source-to-detector distance (SID). B. Source-to-patient distance (SOD). C. Positioner primary angle. D. Positioner secondary angle. Adapted with permission from [50].

7.4.2 Image registration

The automatic image registration makes up the core of the proposed registration method and aims at finding the rigid-body transformations that accurately align the 3D MRI data to 2D projective x-ray images using only the features that are visible in the images. This process involves the identification of a moving dataset (M), which is transformed by the parameters y and is compared, in its transformed state (M[y]), with a fixed dataset (R), using the similarity metric (D) according to the following equation:

$$\arg \min_y \{D(M[y], R)\} \quad (1)$$

The 6-degree-of-freedom (6 DOF) transformation parameters \(y = \{T_x, T_y, T_z, R_x, R_y, R_z\}\), which define three translations \(\{T_x, T_y, T_z\}\) and three rotations \(\{R_x, R_y, R_z\}\) in 3D space, are optimized by minimizing the similarity metric D that results from the comparison between the fixed dataset R and the moving dataset in its transformed state M[y].

There are a number of steps that comprise the bulk of the automatic image registration
method. These components include projection of the 3D MR landmark onto the 2D x-ray imaging plane, anisotropic denoising of the x-ray image, generation of the normalized gradient fields (NGF) from the projected MR landmark and the denoised x-ray image, computation of the normalized cross correlation (NCC) similarity metric, and heuristic optimization of the NCC similarity metric (Figure 10).

In order for the NCC similarity measure to be successfully applied to the 3D MR data and 2D x-ray images with the aim of comparing and aligning the datasets, there must be correspondence in dimensions between the datasets. This correspondence must also account for the projective nature of the x-ray images that inherently possess a built-in magnification factor. Dimensional correspondence can be achieved by projecting the 3D MR data onto the x-ray imaging plane using the same projection matrix as for the acquired x-ray images.

Edge-based similarity measures have been shown to provide a reliable way of comparing projected MR data against 2D x-ray images [76], [105]-[107]. In preparation for the extraction of edge information from the x-ray image, an edge-sensitive anisotropic denoising algorithm is first applied to the image. Then, NGFs are generated for the denoised x-ray image and the projection image of the MR landmark. Eventually, the similarity between the generated NGFs is assessed using the NCC similarity metric. The NCC metric is computed and optimized to find the best registration pose using a heuristic optimization method. In order to reduce the computation time of the heuristic method, a Fourier domain calculation of the NCC (FFT NCC) with fast template matching is implemented. Using this approach, the computation of maximum correlation between the extracted NGFs is performed by applying the convolution theorem in the frequency domain using the fast Fourier transform of the spatial domain convolution, which can provide an order of magnitude speedup over spatial domain computation of normalized cross correlation [112].

The traditional gradient descent/ascent optimization methods are not suitable candidates for optimizing the similarity metric in the proposed registration method due to the intrinsic characteristics of the chosen metric, which could produce multiple local extrema in the cost function with the given datasets. On the other hand, global optimization with 6 DOF search space is resource intensive since not only each degree of freedom exponentially adds to the size of the search space but also the evaluation of each
optimization parameter is costly as it entails the calculation of the projection image for the 3D MR landmark [50].

### 7.4.2.1 Dimensional correspondence

As noted above, the 3D MRI images are projected to correspond to the 2D x-ray images using perspective projection parameters. The perspective projection parameters, $P$, of the 2D x-ray iamges can be obtained from the metadata of the acquired images. The parameters, $P = \{c_s, l_s, k_1, k_2\}$, are intrinsic to the x-ray device and are used to recreate the projection conditions of the C-arm for the forward projection of the 3D MR data (Figure 12). The parameters $k_1$ and $k_2$ are obtained using the following equations:

$$k_1 = \frac{f}{\Delta u} \quad (2)$$

$$k_2 = \frac{f}{\Delta v} \quad (3)$$

where $f$ is the focal distance and is equivalent to the source-to-detector distance, $\Delta u$ and $\Delta v$ are the pixel spacing in the horizontal and vertical directions of the imaging plane, and $c_s$ and $l_s$ are the coordinates in the image where the beam is normal to the projection plane [108].
**Figure 12** Projection of the 3D femur model and comparison based on edge information. Forward projection of the 3D model of the femur in the current alignment pose \( y = \{T_x, T_y, T_z, R_x, R_y, R_z\} \) is performed using x-ray’s perspective projection parameters \( P = \{c_x, l_s, k_1, k_2\} \). Edge information from the x-ray image and this projection are used to compare their similarity.

The ultimate goal of projecting the 3D data onto the 2D imaging plane is to achieve dimensional correspondence and to allow for the use of 2D similarity metrics in the comparison of datasets. A common method of obtaining digitally generated projection data for comparison against data from perspective projection imaging modalities such as x-ray is via generating digitally reconstructed radiographs (DRR). However, this is not the technique utilized in this thesis as it involves lengthy computation times even with the most efficient implementation due to the need for the calculation of x-ray attenuation through the voxels of the 3D data [50]. Since the proposed registration algorithm is only concerned with the overall shape of the projected feature as dictated by its edges and not the varying grayscale intensities as x-rays pass through the 3D structure (as may be the case with intensity-based registration methods), a simpler projection algorithm called the fast perspective projection rendering with binary output is chosen for this task. The fast perspective projection rendering is based on the modified pinhole camera model (Figure 13), which reduces the complexity of the projection step as compared with the DRR generation by bypassing the calculation of x-ray attenuation to different grayscale intensities and only casting a binary shadow of the 3D structure with known perspective projection parameters on a white background. This projection method will also work well for comparing feature edges since this projection rendering technique captures the overall contour of the 3D feature from the same perspective as for the x-ray images.

The pinhole camera model is implemented using OpenGL and is adjusted to match the x-ray C-arm’s perspective projection matrix by setting its perspective attributes to that of the acquired x-ray images. This is achieved by placing the object to be projected between the aperture and the x-ray imaging plane with the distance between the aperture and the object matching the source-to-patient distance (SOD). The 3D object is then rendered on
the 2D detector plane by the camera as a black shadow on white background.

**Figure 13** The modified pinhole camera model as used in fast perspective projection rendering. A point \( q \) on plane \( p_1 \) is projected onto the image plane \( p_2 \) using the pinhole camera model. \( C \): aperture or x-ray source. \( f \): focal length or C-arm’s source-to-detector distance (SID). \( m \): point on plane \( p_2 \) which is the projection of point \( q \) located on plane \( p_1 \) using the camera \( C \) perspective projection parameters. \( c_z \) and \( l_z \): image coordinates where the x-ray beam is normal to the image plane \( p_2 \).

Following the projection of the 3D MR landmark (segmented 3D femur model), according to the perspective projection parameters of the C-arm, a 2D binary image is obtained. The normalized gradient field images are then computed from the projected MR landmark and the denoised x-ray image as explained in the later section (**Figure 14**). The NGFs are compared using the normalized cross correlation similarity metric in its Fourier domain, which is optimized by a heuristic global optimization method to find the appropriate registration pose.

7.4.2.2 Normalized gradient field
There is no global intensity correspondence between the projected MR landmark and the x-ray image since the projection rendering process casts only a binary shadow of the MR landmark on the image plane. On the other hand, there is a strong correspondence between the 2D shapes of the binary projection image of the segmented right femur and the actual x-ray image of the right femur. As a consequence, local intensity changes can provide a more consistent assessment of similarity when dealing with binary perspective projections and x-ray images [76], [105]-[107].

The projection image of the MR landmark and the x-ray landmark (x-ray image of the physical right femur) both exhibit strong edges in their respective images, which means that the shift of pixel intensity (i.e. gradient) around these regions is large. However, this change of pixel intensity around the edges, also called the edge magnitude, is likely to vary between the binary projection image of the MR landmark and the x-ray landmark due to the aforementioned global intensity variation between the images. This variance in edge magnitude can also be further exacerbated during x-ray image acquisition by the use of different x-ray exposure parameters, which can augment or diminish femur contrast in the x-ray image [50]. As such, it is not recommended to directly tie a similarity metric to the crudely extracted gradients [109]. However, it is possible to take advantage of the strong shape correspondence between the projected MR and x-ray landmarks to assess similarity by extracting the edge information from the projection image of the MR landmark and the x-ray landmark in their normalized forms in order to disregard the differences in edge magnitude. In this thesis, the regularized normalized gradient field (NGF) developed by Haber et al. is adopted, which is described by the following formula for an image [109]:

\[ n_\varepsilon(I, x) := \frac{\nabla I(x)}{\|\nabla I(x)\|_\varepsilon} \quad (4) \]

where \( \|x\|_\varepsilon = \sqrt{\sum_{i=1}^{d} x_i^2 + \varepsilon^2} \) and \( \nabla I := (\partial_1 I, \ldots, \partial_d I)^T \) for \( x \in \mathbb{R}^d \). Furthermore, the parameter \( \varepsilon \) determines the magnitude of the gradient that can be interpreted as a jump or an edge. If \( \varepsilon \) is much larger than the gradients in a region of the image, then the edge
maps $n_\varepsilon(I, x)$ are almost zero and therefore the gradients are removed from the mapping. However, in regions where $\varepsilon$ is much smaller than the gradients, the regularized maps are close to the non-regularized ones [109].

For the x-ray image, the parameter $\varepsilon$ is empirically determined in this thesis in a way that accentuates the edges produced by the femur and undermines the gradients produced by soft tissue and other irrelevant features. Ultimately, the value of $\varepsilon$ was determined to be 10. Moreover, the magnitude of the gradients allowed for inclusion in the mapping of edges were further restricted to a characteristic range for the bone in order to filter out the edges resulting from noise that fall outside of this interval (Figure 14 top). The range of edge magnitudes that are characteristic of the bone and result in sufficient isolation of the femur was empirically determined to be between 2 and 15 on a scale of 0 (black, no edge) to 255 (white, strong edge).
**Figure 14** Normalized gradient fields as extracted from the denoised x-ray and projected MR landmarks. **Top left:** Denoised x-ray image. **Top right:** Normalized gradient field of the denoised x-ray image. **Bottom left:** Projection image of the 3D model of the femur. **Bottom right:** Normalized gradient field of the projection image.

### 7.4.2.3 Anisotropic denoising

Medical images consist of structures of varying scales such as noise, which is considered a small-scale structure [110]. For the computation of the NGF, noise can be falsely detected as a gradient in the image, obstructing the critical edge information. Thus, the x-ray image is denoised prior to NGF computation using the modified curvature diffusion equation (MCDE) developed by Whitaker et al. [111]. As opposed to standard isotropic diffusion methods that move and blur all light-dark boundaries indiscriminately, anisotropic diffusion methods are formulated to specifically preserve image features (i.e., edges) while reducing noise. Given the reliance on edges for registration, it is a desirable attribute of the denoising method to have an edge-preserving property while smoothing away the noise everywhere else in the image.

The MCDE is a level-set analog of the anisotropic diffusion equation and does not exhibit the edge-enhancing properties of classic anisotropic diffusion, which in certain conditions can undergo a “negative” diffusion that increases the contrast of edges. Equations of the form of MCDE always undergo positive diffusion with the conductance term only varying the strength of that diffusion, which causes smoothing proportional to the level-set curvature of the image with reduced smoothing near the edges. The formula for the MCDE is as follows:

\[
\frac{\partial f}{\partial t} = |\nabla f| \nabla \cdot (|\nabla f| \frac{\nabla f}{|\nabla f|})
\]  

(5)

where the conductance modified curvature term is \( \nabla \cdot \frac{\nabla f}{|\nabla f|} \) and \( f = f(x, y, t) \). The initial image prior to denoising is given by \( f(x, y, 0) \). The image \( I \) becomes progressively smoother through changes that occur at each iteration \( i \) with time step \( \Delta t \). The discrete changes that are applied to the initial image over time \( i\Delta t \) in order to obtain a smoother
image are described in terms of the following formula:

\[ f_{t+\Delta t} = f_t + \frac{\partial f}{\partial t} \quad (6) \]

The MCDE is a type of partial differential equation for which appropriate time steps \( \Delta t \) depend on the dimensionality of the image as well as the order of the equation. In general, the time step should be kept below \( \text{PixelSpacing}/2^{N+1} \), where \( N \) is the number of image dimensions, to maintain stability of the function.

The conductance parameter \( c \) controls the sensitivity of the conductance term in the basic anisotropic diffusion equation, which in turn varies the strength of diffusion anisotropically. In other words, the conductance term determines the aggressiveness of the edge-preserving property and the ITK implementation of the MCDE, as adopted in this thesis, describes the conductance function using the following formula:

\[ c(|\nabla f|) = \frac{k^2}{(k^2 + |f|^2)^\frac{3}{2}} \quad (7) \]

The parameters for the denoising algorithm used in this thesis have been empirically determined to achieve sufficient signal-to-noise ratio (SNR) in the x-ray image, and are as follows: \( \Delta t = 0.1 \), \( k = 3.0 \), and number of iterations \( i = 50 \). The appropriateness of the found values was later confirmed by the capacity to adequately visualize sharp edges of the x-ray landmark and the reduction to insignificance of smoothed noise gradients in the NGF image.

### 7.4.2.4 Optimization

The goal of the optimization process is to find registration parameters according to equation (1) that minimize the difference between the x-ray and MR landmarks. This can be achieved by minimizing the NCC similarity metric as explained in Section 7.4.2.5. The NGF image obtained from projection of the 3D MR landmark is compared against the NGF of the 2D x-ray landmark using FFT NCC as the 2D-2D similarity measure, which is minimized by a heuristic global optimization method.
Conventional optimization methods can be classified into two general categories: iterative gradient descent/ascent methods and global evaluation methods. The iterative methods, which are considered local search techniques, are useful when the similarity metric/cost function is relatively smooth and is monotonically increasing/decreasing with changes in transformation parameters. Iterative optimization methods, therefore, are prone to error with a similarity metric that results in a multimodal cost function with numerous local extrema or when the similarity metric is relatively flat over the misregistration parameters. On the other hand, global optimization methods can evaluate the similarity metric over the full space of candidate solutions/transformation parameters and, therefore, can generate accurate registration results. However, with increasing degrees of freedom and search space, the computational cost of global methods can become increasingly inefficient.

The FFT NCC similarity metric, which computes the correlation between pixels that make up the edges (NGFs) within two images to be registered, demonstrates an important characteristic that leads to the choice of the optimization method in this thesis. The width of the lines that form the feature edges in the NGF images is on the order of a few pixels and, as a result, can lose overlap with slight rotations or translations during the matching process (Figure 15A-C). The cost function for the similarity metric in this case displays low-similarity flat regions with a large number of local minima and maxima whereby the thin feature edges cross one another, as well as a global minimum that represents the correct registration pose (Figure 15D). As mentioned earlier, the iterative optimization methods perform poorly with metrics that exhibit a large number of local extrema as they can get trapped in these local valleys of the cost function. On the contrary, a 6-DOF global optimization method can outperform its iterative local optimizer counterpart resulting in a more accurate registration but will require the computation of all the possible combinations of the similarity metric over the degrees of freedom, which can enormously increase the computational overhead and runtime.
Figure 15 Edge overlap scenarios and cost function characteristics. A. Perfect overlap between edges (high similarity). B. Slight translational misalignment (no overlap, zero similarity). C. Slight rotational misalignment (little overlap, low similarity). D. FFT NCC cost function values over rotational misalignment measured in degrees. This graph illustrates the inadequacy of a gradient descent/ascent optimizer in choosing the correct registration parameter due to the depicted local minima. Adapted with permission from [50].

The global optimization method as implemented in this thesis follows a heuristic model. Here, instead of calculating all of the possible permutations of the transformation parameters for the 6 degrees of freedom, the optimizer computes only a subset of the permutations in favor of shorter runtime and less computational complexity. Following this method, the $n^6$ possible permutations of the transformation parameters for the 6-DOF search are structured as $n^4 \times n^2$ combinations of possible permutations by dividing the 6-DOF search into a 4-DOF and a 2-DOF search, which offers a few advantages. The number of required perspective projection renderings will be reduced by a factor of $n^2$ as compared to an exhaustive 6-DOF 3D search that will require a projection for every permutation of the transformation parameters. Moreover, the 2-DOF 2D search is
delegated to the fast template matching technique, which is an inherently fast 2D image registration algorithm as explained later. The results of the 4-DOF and 2-DOF searches can then be recombined to deliver the complete 6-DOF 3D search equivalent.

Before going into details about this search procedure, the reader needs some information about the coordinate systems being used. The visualization software, namely visual understating of real-time image-guided operations (VURTIGO), places the 3D MR data and the x-ray imaging planes according to a global coordinate system \((x_{global}, y_{global}, z_{global})\) that is initially in alignment with the MR data’s coordinate system. The anatomical mapping between the MR data and VURTIGO’s global coordinate system is automatically established based on the patient orientation within the MR scanner. For the purpose of this thesis, a pig was positioned inside the MRI bore in head-first supine (HFS) orientation and the acquired data was later mapped within the visualization software as follow: \(x_{global} = Left - Right, y_{global} = Superior - Inferior, z_{global} = Anterior - Posterior\). With this mapping in mind, the x-ray imaging planes are intentionally positioned within the global coordinate system according to the position and orientation of the MR data in a way that would allow the recreation of the x-ray images’ geometrical environment. As an outcome of such positioning, the MR data’s \(S - I\) axis becomes perfectly aligned with the x-ray imaging plane’s y-axis. The MR volume’s position and translation transformations can be expressed in terms of either the global coordinate system or the x-ray imaging plane’s coordinate system \((x_{x-ray}, y_{x-ray}, z_{x-ray})\), which has its y-axis \((y_{x-ray})\) in alignment with \(y_{global}\) \((S - I\) anatomical axis) as mentioned above (Figure 16).

In the search for the correct registration pose, translation parameters operate with respect to the x-ray imaging plane’s coordinate system whereas rotation parameters are investigated according to the global coordinate system. As noted earlier, the search is divided into a 4-DOF 3D search, which entails finding three rotational parameters for the three rotational degrees of freedom \((R_{x global}, R_{y global}, R_{z global})\) and one translational parameter along the through-plane axis in relation to the x-ray imaging plane \((T_{z x-ray})\), and a 2-DOF 2D search that optimizes the remaining 2 translational parameters along the
in-plane axes of the x-ray imaging plane ($T_{x\ x\-ray}$, $T_{y \ x\-ray}$). The 2D optimization for the in-plane translational parameters is executed at every evaluation of the 3D parameters using the template matching technique as described in the following section, for which the FFT NCC similarity metric is computed and considered by the 3D optimizer in its pick for the best-matching rotational and through-plane translational parameters (Figure 16).

![Diagram](image)

**Figure 16** An overview of the heuristic global optimization method. The 4-DOF 3D search attempts to find registration parameters along three rotational axes ($R_{x\ global}$, $R_{y\ global}$, $R_{z\ global}$) and one translational ($T_{z\ x\-ray}$) dimension (red-enclosed arrows on the left) via heuristic evaluation of the parameters within a prescribed search space. The 3D search is augmented and completed by the 2-DOF 2D search, which entails finding the remaining registration parameters along the two translational axes ($T_{x\ x\-ray}$, $T_{y\ x\-ray}$) (red-enclosed arrow cross on the right) and is executed at every evaluation of the 3D optimization parameters.

The percutaneous transluminal angioplasty procedure for the treatment of chronic total occlusions is a relatively static procedure in terms of the amount of patient leg movement.
aside from the sporadic bulk motions that may occur when a discomforted patient twitches their leg through a larger rotation or distance. As such, the expectation is for only small-scale movements of the femur arising from tissue compression as caused by the patient flexing or the interventionalist pressing down on the leg. In the light of the anticipated motion, and in order to limit the size of the 4-DOF search space and its associated computational time, the small likely displacements of the femur due to flexing and compression during PTA procedures are assumed to be contained according to the aforementioned prior knowledge in the motion interval \( M = \{ R_{L-R}, R_{S-I}, R_{A-P}, T_{L-R}, T_{S-I}, T_{A-P} \} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3, -3 \ldots 3, -3 \ldots 3 \} \) where the interval \{A…B\} represents uniformly distributed integers in the range A to B, \( T_{S-I} \) represents the maximum possible translation of the femur in millimeters along the superior-inferior axis, \( T_{L-R} \) along the left-right axis, and \( T_{A-P} \) along the anterior-posterior axis. Likewise, \( R_{S-I} \) represents the maximum possible rotation of the femur in degrees around the superior-inferior axis, \( R_{L-R} \) around the left-right axis, and \( R_{A-P} \) around the anterior-posterior axis. The optimization of the translational parameters for both the 4-DOF and 2-DOF searches occurs in relation to the x-ray imaging plane. Hence, at the end of each optimization, the relative translational registration parameters are changed back to the global coordinates to be applied to the MR data (Figure 16).

The sequence of steps that are carried out by the 4-DOF 3D optimizer to find the three rotational and one through-plane translational registration parameters are as follows: with a predetermined search space \( S = \{ \pm R_{x\, global}, \pm R_{y\, global}, \pm R_{z\, global}, \pm T_{x\, global}, \pm T_{y\, global}, \pm T_{z\, global} \} \), the three rotational axes are searched through the allocated rotational search space \( \{ \pm R_{x\, global}, \pm R_{y\, global}, \pm R_{z\, global} \} \); the axis and the angle of that axis that results in the lowest cost (highest similarity) is selected and applied to the MR data. With the first axis netting the highest similarity optimized, the other two axes follow suit. If the first optimized axis happens to be \( R_{x\, global} \), then the similarity metric for the rotational parameters in the range defined by \( \{ \pm R_{y\, global}, \pm R_{z\, global} \} \) is computed and the axis along with its angle scoring the lowest cost is selected and applied to the current pose. Finally, the last axis is optimized through its degrees of permitted rotation and its minimum-cost angle is applied to the MR data. With the rotation
parameters optimized, a depth search along the through-plane axis of the x-ray imaging plane \((z_{x-ray})\) begins with its search threshold computed from mapping of \(\pm T_{x\ global} \) and \(\pm T_{z\ global}\) components in the \(z_{x-ray}\) direction in the relative x-ray imaging plane coordinate system, which then utilizes the golden section search algorithm to iteratively optimize the depth parameter. At the end of the depth optimization, the through-plane registration parameter \((T_{z\ x-ray})\) is mapped back to \(T_{x\ global}\) and \(T_{z\ global}\) before being applied to the existing registration pose of the MR data.

A 2-DOF 2D global optimization along the in-plane axes of the x-ray imaging plane \((x_{x-ray}, y_{x-ray})\) is performed at every evaluation of the above-mentioned 3D optimization parameters. The FFT NCC similarity metric computation occurs with the global 2D optimization of the two in-plane translational parameters using the fast template matching technique, which is subsequently considered by the 3D optimizer in its heuristic search for the rotational and through-plane translational registration parameters that produce the lowest FFT NCC cost. The final 2D in-plane registration parameters are back-projected from in-plane 2D movements \((T_{x\ x-ray}, T_{y\ x-ray})\) to 3D movements within the x-ray coordinate system and are applied to the MR data in terms of their global coordinates \((T_{x\ x-ray}\) is mapped to components of \(T_{x\ global}\) and \(T_{z\ global}\) while \(T_{y\ x-ray}\) is mapped to \(T_{y\ global}\)).

7.4.2.5 2D 2-DOF global search using fast Fourier transform normalized cross correlation

The normalized cross correlation of two images is defined by the following formula:

\[
NCC = \frac{\sum_{x,y}(T(x,y)-\bar{T})(R(x,y)-\bar{R})}{\sqrt{\sum_{x,y}(T(x,y)-\bar{T})^2 \sum_{x,y}(R(x,y)-\bar{R})^2}} \tag{8}
\]

where \(T\) is the template image with size \(M_x \times M_y\) and \(R\) is the reference image with the same size as \(T\). \(\bar{T}\) and \(\bar{R}\) represent the mean values of the images \(T\) and \(R\), respectively.
The fast template matching technique is a 2D based image registration method that measures the similarity between the pixels in the fixed image (reference image) and the pixels in the moving image (template image). Having sufficiently extracted the NGFs from the denoised x-ray image and the projection image, the NCC template matching technique is utilized to compare them and find the point of maximum correspondence between the NGFs. J. P. Lewis has previously described a fast Fourier domain implementation of the NCC template matching, which calculates the normalized cross correlation of two images using FFTs instead of spatial correlation [112]. This is particularly favorable as it yields a much faster computation compared to spatial correlation due to the use of pre-computed tables and large structuring elements. The global minimum of the NCC metric can thus be calculated simultaneously with the metric values for all possible transformations with a single iteration of the template over the reference image [112]. This thesis adopts the 2D-2D fast Fourier transform normalized cross correlation (FFT NCC) registration method as described by D. Padfield in ITK for the registration of the NGF images, which completes the 2-DOF 2D search optimization [113]. Moreover, since the FFT NCC registration finds the global minimum of the similarity metric, the mapping of the prescribed translational search space \( \{ \pm T_x \text{ global}, \pm T_y \text{ global}, \pm T_z \text{ global} \} \) to the x-ray imaging plane’s coordinate system (in-plane axes) does not need to be performed as opposed to the through-plane search threshold determination. The 3D heuristic optimizer considers the resulting FFT NCC cost from this 2D optimization step, which is executed at every evaluation of the 3D optimization parameters, and the global minimum of the cost function is selected (Section 7.4.2.4).

In order to prepare the NGFs for FFT NCC computation, first, the feature of the femur within the projection NGF image is enclosed in a box and extracted from the whole image (Figure 17A). The extracted feature is then translated to the origin of the image with the offset \((x, y)\) (Figure 17A, B). The computation of the FFT NCC between the NGF of the x-ray image (Figure 17C) and the extracted feature is performed and the translation \((u, v)\) to the pixel with the maximum intensity is found (Figure 17D). These 2D translational parameters \((u, v)\) represent the translation registration pose of the extracted feature of the femur (Figure 17E). The initial offset of the extracted feature is
then used to calculate the registration pose of the original projection NGF image to the x-ray NGF \((T_{x x-ray}, T_{y x-ray}) = (u - x, v - y)\) (Figure 17F). These 2D in-plane registration parameters are back-projected to the x-ray imaging plane’s 3D coordinate system and are translated in terms of the global coordinates before being applied to the MR data to achieve XMR registration.

*Figure 17* 2D-2D fast Fourier transform normalized cross correlation (FFT NCC) registration. *A.* The landmark feature of the femur is located with the offset \((x, y)\) within the projection NGF image. *B.* The extracted feature is translated to the origin. *C.* The NGF of the denoised x-ray image depicting the x-ray landmark (femur) within the image. *D.* Fast Fourier transform normalized cross correlation is computed and the location of the maximum pixel intensity is found \((u, v)\). *E.* The extracted femur feature is registered to the x-ray NGF using the found offset \((u, v)\). *F.* The registration pose of the original projection NGF image to the x-ray NGF is determined by calculating the difference between the feature registration parameters and the feature extraction offset \((T_{x x-ray}, T_{y x-ray}) = (u - x, v - y)\).
7.5 Evaluation

7.5.1 Initial manual registration evaluation

The first evaluation measures the variation in position of the 3D femur model following the initial manual registration. For this evaluation, an experienced user performed a total of 20 manual alignments of the 3D femur model to the two x-ray projections (see section 7.3.2). Each x-ray projection (i.e. LAO 35°, RAO 35°) is utilized 10 times to measure the variations in position in each view. In order to measure the position of the 3D femur model, a projection of it is taken using the utilized x-ray image’s perspective. Then, a 2D-2D registration using FFT NCC template matching is performed using the method outlined in the previous chapter, which measures the in-plane distance between the edges of the x-ray femur (x-ray landmark) and the projection image of the femur (MR landmark). For the purpose of evaluating the automatic registration in this thesis, the ground truth registration is established by performing the initial manual registration, and any deviation from the manually registered position is assumed to be TRE (as explained in detail in the later section). In this way, the average noise present in the final target registration error (i.e. at the end of the automatic registration) due to the variation in position of the 3D femur model at the end of the initial manual registration can be determined. The mean, 10th percentile, 90th percentile, minimum, and maximum of the variations in position following the initial manual registration will be calculated. In addition, using a timer to record and average the durations that the user takes to perform each of the 20 manual alignments (i.e. as soon as the alignment process begins until the manual registration is done), the average manual registration time will be evaluated.

7.5.2 Automatic registration evaluation

This evaluation scheme assumes that the femur remains relatively stationary during typical recanalization procedures of the superficial femoral artery where the potential small-scale movements demonstrated by the femur can be contained in the motion interval \( M = \{R_{L-R}, R_{S-I}, R_{A-P}, T_{L-R}, T_{S-I}, T_{A-P}\} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3, -3 \ldots 3, -3 \ldots 3, -3 \ldots 3\} \) as mentioned in Section 7.4.2.4. Here, the automatic registration’s stability is evaluated based on its ability to maintain the registration pose within the
following prescribed search space: \( \{ R_x^{\text{global}}, R_y^{\text{global}}, R_z^{\text{global}} \} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3\} \), \( \{ T_{x^{\text{x-ray}}}, T_{y^{\text{x-ray}}} \} = \{ \text{x-ray FOV} \} \) (global in-plane search), \( \{ T_{z^{\text{x-ray}}} \} = \{ T_{x^{\text{global}} | x^{\text{ray}}, T_{z^{\text{global}} | x^{\text{ray}}} \} = \{-3 \ldots 3 z^{\text{x-ray}}, -3 \ldots 3 z^{\text{x-ray}} \} \) (through-plane search based on through-plane components of \( T_{x^{\text{global}}} \) and \( T_{z^{\text{global}}} \)), which sufficiently covers the range of potential small-scale movements of the femur as mentioned above. Under the fixed scenario, the manually registered 3D model of the femur from the MR data exhibits no movement, meaning that the introduced perturbations will be \( \{ R_{L-R}, R_{S-I}, R_{A-P}, T_L-R, T_{S-I}, T_{A-P} \} = \{ 0, 0, 0, 0, 0, 0 \} \), while the automatic registration attempts to confirm the registration pose by searching through its predetermined search space and reporting the target registration error (TRE).

The automatic registration will continuously update the registration pose by using the femur as the shared x-ray and MR landmark (i.e. the femur as visible on the x-ray image and the segmented 3D model of the femur from MRI) and by utilizing single-plane x-ray images (LAO 35° or RAO 35°). The evaluation dataset contains two evaluation instances that only differ by the utilized x-ray viewing angle. In order to assess the stability of the automatic registration in maintaining the specified registration pose (with the 3D femur model undergoing zero perturbation), the automatic registration is executed following each manual alignment as performed in the previous section (i.e. total of 20 evaluation runs, 10 runs using each x-ray view). The mean, 10th percentile, 90th percentile, minimum, and maximum TRE values as well as the automatic registration runtime are recorded.

In order to measure the target registration error, first, the 3D ground truth transformations that accurately align the MR data to the two x-ray images in LAO 35° and RAO 35° are found by interactively aligning the segmented 3D femur model from MRI to the x-ray images on both views. With the ground truth registration pose established based on the manual alignment of the femur, the positions of the multi-modality markers, which are segmented from the same MR volume as the femur and therefore always maintain the same distance away from it, are also noted in 3D space by calculating their centroids. Once the automatic registration updates the registration pose based on the realignment of the femur, the XMR marker centroids, which ideally should have moved back to their
ground truth positions along with the realignment of the femur, are then used to calculate the 3D target registration error (TRE). The root mean square (RMS) of the 3D distances between the pairs of markers is used to compute the 3D TRE. Moreover, the measured 3D distances are computed in terms of their x-ray coordinate axes components \((x_{x-ray}, y_{x-ray}, z_{x-ray})\) and the 2D TREs are calculated in directions parallel and perpendicular to the utilized x-ray imaging plane (i.e. 2D TRE_{In-plane} and 2D TRE_{Through-plane}). The 2D TRE_{In-plane} is calculated by summing the components in the \(x_{x-ray}\) and \(y_{x-ray}\) axes, and the 2D TRE_{Through-plane} by summing the components of the 3D distances in the \(z_{x-ray}\) axis. The 2D TRE_{In-plane} is of utmost importance in this context as the XMR fusion is presented as an overlay of 3D MR data on top of x-ray images to the vascular surgeon and, hence, reveals alignment information on the two most apparent axes.

### 7.5.3 Evaluation of upper bound of capture range

After the evaluation of the automatic registration’s ability to maintain the registration pose of the fixed femur within the allocated search space, a second evaluation is performed to characterize the upper bounds of the misregistration that the automatic registration method can reliably realign within. Strictly speaking, this characterization answers the question of how much the femur can be perturbed before the automatic registration fails to realign within the tolerable registration accuracy \((<3\text{mm }3\text{D TRE})\). The upper bound evaluation is performed in the LAO 35° x-ray viewing angle and contains two evaluation instances; the upper translational bound evaluation instance and the upper rotational bound evaluation instance. Each evaluation instance uses different predetermined search spaces and various amounts of perturbation applied to the femur. There are 600 randomly generated perturbation cases in every evaluation and while they may differ between evaluation instances, they are the same within an evaluation instance (i.e. within a given perturbation range).

#### 7.5.3.1 Upper translational bounds

The first instance of the evaluation deals with the upper translational bounds that the automatic registration can satisfactorily capture and correct for. The perturbation parameters for this scenario are contained in the interval \(\{R_{L-R}, R_{S-I}, R_{A-P}, T_{L-R}, T_{S-I}\}\).
\[ T_{A-p} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3, -30 \ldots 30, -20 \ldots 20, -40 \ldots 40\} \] where the interval \{A \ldots B\} represents uniformly distributed integers in the range A to B. The reason behind the chosen range of translational perturbations is to keep the movements of the 3D femur model within the x-ray FOV. Here, the search space used for the automatic registration will be the same as in the first evaluation, namely \( \{R_{x\ global}, R_{y\ global}, R_{z\ global}\} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3\}, \{T_{x\ x-ray}, T_{y\ x-ray}\} = \{\text{x-ray FOV}\} \) (global in-plane search), \( \{T_{z\ x-ray}\} = \{T_{x\ global}\mid z\ x-ray, T_{z\ global}\mid z\ x-ray\} = \{-3 \ldots 3_{z\ x-ray}, -3 \ldots 3_{z\ x-ray}\} \) (through-plane search based on through-plane components of \( T_{x\ global} \) and \( T_{z\ global} \)).

A quick look makes it manifest that both the rotational and in-plane translational search spaces adequately cover the induced perturbations in these directions. However, with the calculation of the \( T_{x\ global} \) and \( T_{z\ global} \) components in the \( z_{x-ray} \) direction, it becomes apparent that the through-plane search space does not fully contain the introduced through-plane perturbations. As such, a second scenario for this evaluation instance is performed whereby all of the aspects of the new scenario stay the same as before including the perturbation cases. The only change is that the through-plane search space will be increased by a factor of 3 to \( \{T_{z\ x-ray}\} = \{T_{x\ global}\mid z\ x-ray, T_{z\ global}\mid z\ x-ray\} = \{-9 \ldots 9_{z\ x-ray}, -9 \ldots 9_{z\ x-ray}\} \), which would allow for a more thorough assessment of the through-plane capture range based on the prescribed search spaces.

The idea here is to avoid confusion by keeping the perturbations consistent across related evaluations, and while there may be perturbations greater than the allocated search space (as with the through-plane perturbations), by expanding the allocated search space in that direction and performing another evaluation, the trend can be discerned that will allow us to infer what happens to the automatic registration’s capture range capability with increasing its search space. This method of evaluation is performed in part because it may not be practical to evaluate the upper bound of capture range by solely testing one prescribed search space since the capture range itself depends on the range of the allocated search space. Furthermore, it may not be practical to allocate an infinitely large search space and, therefore, by looking at the changes in TRE between the allocated search spaces for a given set of perturbations, the trend can be visualized, at which point there may be indications as to what the optimal search space should be for the automatic
registration to achieve a 3D TRE < 3 mm. The evaluated 3D translational upper bound is then presented in terms of 2D in-plane \((T_{x x-ray,y x-ray})\) and 2D through-plane upper translational bounds \((T_{z x-ray})\).

### 7.5.3.2 Upper rotational bounds

In the second evaluation instance, the upper rotational bounds are addressed with perturbation parameters contained in the interval \(\{R_{L-R}, R_{S-I}, R_{A-P}, T_{L-R}, T_{S-I}, T_{A-P}\} = \{-10 \ldots 10, -10 \ldots 10, -10 \ldots 10, 0, -20 \ldots 20, 0\}\). Here, translation perturbations in the \(L - R\) and \(A - P\) anatomical directions are set to 0 to eliminate the effect of through-plane perturbation on the final TRE. Similar to the translational upper bound evaluation, two scenarios of the rotational upper bound evaluation are performed with the only difference being in their prescribed search spaces. As noted earlier, a comparative assessment of the TREs as produced by the allocated search spaces can give directions to what would have happened to the TRE if the rotational search space (i.e. capture range) were to be further expanded to contain all possible degrees of perturbation. As before, the search space for the first scenario in this evaluation instance will be identical to the one used in the automatic registration’s evaluation, namely \(\{R_{x global}, R_{y global}, R_{z global}\} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3\}\), \(\{T_{x x-ray}, T_{y x-ray}\} = \{x-ray \ FOV\}\) (global in-plane search), \(\{T_{z x-ray}\} = \{T_{x global} | x x-ray, T_{z global} | z x-ray\} = \{-3 \ldots 3_{x x-ray}, -3 \ldots 3_{z x-ray}\}\) (through-plane search based on through-plane components of \(T_{x global}\) and \(T_{z global}\)).

The second scenario, however, will have its rotational search space increased to \(\{R_{x global}, R_{y global}, R_{z global}\} = \{-7 \ldots 7, -7 \ldots 7, -7 \ldots 7\}\). The evaluated 3D rotational upper bound is then presented in terms of the total rotation in relation to the x-ray imaging plane, which is calculated by \(R_{total} = |R_{x x-ray}| + |R_{y x-ray}| + |R_{z x-ray}|\), where \(R_{x x-ray}\) is the rotation around the \(x_{x-ray}\) axis relative to the x-ray image, \(R_{y x-ray}\) is the rotation around \(y_{x-ray}\), and \(R_{z x-ray}\) is the rotation around \(z_{x-ray}\).
8 Results

8.1 Variation in position following initial manual registration

The in-plane differences between the edges of the x-ray femur and projection femur as measured by the FFT NCC template matching method following the initial manual registration were characterized for 10 manual registrations performed in each of the LAO and RAO projections (Figure 18). In other words, this graph illustrates how much the automatic registration initially shifts the manually registered position of the 3D femur model (i.e. ground truth shift or can be regarded as the automatic registration’s ground truth). The variation in manually registered positions is, therefore, evaluated with respect to the automatic registration’s ground truth and by measuring the shift amounts from the manually registered positions to this ground truth location. On average, the manually registered ground truth positions were shifted by 0.67 mm in the LAO and 0.65 mm in the RAO projections due to variation in positions of the 3D femur model (with respect to the underlying x-ray femur) following the initial manual registration. The minimum and maximum shifts were 0.34 mm and 1.07 mm in both the LAO and RAO projections. The 10th and 90th percentile shifts were 0.34 mm and 1.07 mm in both views. The average duration of the initial manual registration as performed by an experienced user was found to be 113 seconds for 20 manual registrations.
Figure 18 Shift statistics of the manually registered positions (due to variation in positions of the 3D femur model with respect to the x-ray femur) by the automatic registration. Left: shift statistics in the LAO projection. The top and bottom whiskers represent the maximum and minimum shifts in mm, which were 1.07 mm and 0.34 mm, respectively. The bottom box represents 25% of the shifts that were between 0.42 mm and 0.68 mm (median). The top box represents 25% of the shifts that were between 0.68 mm (median) and 0.76 mm. Right: shift statistics in the RAO projection. The top and bottom whiskers represent the maximum and minimum shifts in mm, which were 1.07 mm and 0.34 mm, respectively. The bottom box represents 25% of the shifts that were between 0.48 mm and 0.68 mm (median). The top box represents 25% of the shifts that were between 0.68 mm (median) and 0.74 mm.

8.2 Automatic registration accuracy

The automatic registration was able to maintain the XMR registration pose within the prescribed search space (see section 7.5.2) with an average 3D TRE of 1.56 mm in the LAO 35° x-ray viewing angle and 2.05 mm in the RAO 35° x-ray view. The 3D TRE at 90th percentile was < 2 mm using the LAO 35° view and < 2.5 mm using the RAO 35° view. The 10th percentile 3D TREs in the LAO 35° and RAO 35° views were 1.13 mm and 1.62 mm, respectively. The minimum and maximum TREs were 1.13 mm and 1.95 mm using the LAO 35° view, and 1.62 mm and 2.44 mm in the RAO 35° view, respectively (Figure 18).

The 2D TRE_{in-plane} values were < 1.5 mm and < 2 mm at 90th percentile, 0.35 mm and 0.75 mm at 10th percentile, and 1.02 mm and 1.46 mm on average for the LAO 35° and RAO 35° projections, respectively (Figure 18). The mean 2D TRE_{through-plane} values were 1.13 mm and 1.35 mm in the LAO 35° and RAO 35° projections, respectively. Both the 3D TRE and 2D TRE_{in-plane} meet the required 3 mm target registration accuracy based on half of the diameter of the superficial femoral artery as stated by the hypothesis in this thesis. The automatic registration’s runtime to achieve XMR registration was, on average, 112 seconds in either view with the current implementation including computation of all
of its components using a 2.8 GHz quad-core Intel Xeon processor. A breakdown of the automatic registration’s runtime into its respective components will be given in Section 9.5 with a discussion of how it could potentially be accelerated.

![Automatic registration’s 3D TRE and 2D TRE<sub>in-plane</sub> in the absence of 3D femur model’s movement. Left (blue): TRE statistics computed using the LAO 35° evaluation instance. The bars represent, from left to right, the 3D TRE and 2D TRE<sub>in-plane</sub> statistics. Right (purple): TRE statistics computed using the RAO 35° evaluation instance. The bars indicate, from left to right, the 3D TRE and 2D TRE<sub>in-plane</sub> statistics. The top and bottom whiskers on each bar represent the maximum and minimum TRE values in mm, respectively. The lower and upper boxes in each bar represent the middle 50% of TRE values in mm (i.e. second and third quartile groups).](image)
8.3 Characterization of upper bound of capture range

The misregistration bounds (i.e. capture range) of the automatic registration were analyzed in terms of the allowed in-plane and through-plane translations as well as total rotation using different allocated search spaces (see Sections 7.5.3.1 and 7.5.3.2).

8.3.1 Upper translational bounds

For the first scenario of this evaluation instance, the upper in-plane bounds were analyzed using perturbations in the interval \( \{R_{L-R}, R_{S-1}, R_{A-P}, T_{L-R}, T_{S-1}, T_{A-P}\} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 30 \ldots 30, -20 \ldots 20, -40 \ldots 40\} \). This scenario was performed with the following automatic registration’s search space: \( \{R_{global}, R_{global}, R_{global}\} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3\} \), \( \{T_{x-ray}, T_{y-ray}\} = \{x-ray \text{ FOV}\} \) (global in-plane search), \( \{T_{x-ray}\} = \{T_{x-global} \mid z \text{-ray} , T_{y-global} \mid z \text{-ray}\} = \{-3 \ldots 3_{x-ray}, -3 \ldots 3_{x-ray}\} \) (through-plane search based on through-plane components of \( T_{x-global} \) and \( T_{z-global} \), which is \( \pm 4.1 \) mm. It should be noted that the golden section search algorithm uses the golden ratio for its search through the interval instead of randomly distributed integers in the aforementioned range).

![Figure 20](image)

**Figure 20** In-plane registration accuracy for various amounts of 3D femur model’s in-plane perturbation (600 simulated perturbation cases). *Left*: plot of 2D TRE\(_{\text{in-plane}}\) vs initial 2D\(_{\text{in-plane}}\) perturbation. Almost all of the induced in-plane perturbations
were adequately corrected as suggested by the final 2D TRE\textsubscript{in-plane}. Right: from left to right, the bars represent 2D TRE\textsubscript{in-plane} statistics for in-plane perturbations of up to 10 mm, 20 mm, 30 mm, 40 mm, and 50 mm. The top and bottom whiskers on each bar represent the maximum and minimum 2D TRE\textsubscript{in-plane} values in mm, respectively. The lower and upper boxes in each bar represent the middle 50\% of 2D TRE\textsubscript{in-plane} values in mm (i.e. second and third quartile groups).

As Figure 20 illustrates, in-plane perturbations of up to 50 mm were corrected with an average 2D TRE\textsubscript{in-plane} of 2.1 mm. This means that the automatic registration method can tolerate any amount of in-plane perturbation using the allocated search space, as long as the landmark remains within the x-ray field of view, with an acceptable accuracy for peripheral vascular interventions. There are two outliers that exhibit a large 2D TRE\textsubscript{in-plane} (Figure 20 left), which were excluded from the statistical analysis and will be further analyzed in the Discussion section.

The second scenario in this evaluation instance analyzed the upper through-plane bounds of the automatic registration using two prescribed search spaces that only differed in the amount of their through-plane search threshold, namely \(\{T_{z\text{-ray}}\} = \{-4.1 \ldots 4.1\}\) (mapped from \(T_{x\text{ global}} = \pm 3\) and \(T_{z\text{ global}} = \pm 3\)) and \(\{T_{z\text{-ray}}\} = \{-12.5 \ldots 12.5\}\) (mapped from \(T_{x\text{ global}} = \pm 9\) and \(T_{z\text{ global}} = \pm 9\)). As Figure 21 left suggests, 2D TRE\textsubscript{through-plane} generally increased with increasing amounts of initial through-plane perturbation under both search spaces. In fact, by increasing the through-plane search space to \(\{T_{z\text{-ray}}\} = \{-12.5 \ldots 12.5\}\), the 2D TRE\textsubscript{through-plane} is exacerbated as indicated by the TRE statistics for each search space (Figure 21 right). The findings here suggest that the smaller search space cannot correct for through-plane perturbations that are contained in the search space, and, the larger search space not only results in the larger through-plane perturbations to be carried over but also potentially worsens the 2D TRE\textsubscript{through-plane} for smaller through-plane perturbations in comparison to the smaller search space. This ultimately means that the golden-section search is not an appropriate through-plane search candidate for this application as it cannot adequately correct for through-plane perturbations using any allocated search space and can be omitted from the automatic registration. However, if kept as part of the automatic registration algorithm,
the through-plane search space should be restricted to \(\{T_{z-x-ray}\} = \{-4.1 \ldots 4.1\}\), which would both account for the small-scale through-plane movements of the femur (i.e. \(M = \{T_{L-R}, T_{A-P}\} = \{-3 \ldots 3\}\)) and achieve an acceptable 2D \(T_{\text{R through-plane}}\) with respect to the target registration error requirements of SFA revascularization procedures. This would allow for up to 3 mm of through-plane translation with an average 2D \(T_{\text{R through-plane}}\) of 2.3 mm (**Figure 21 top right, leftmost bar**). The underlying reasons for the insufficiency of the through-plane search with respect to resolving through-plane perturbations will be further investigated in the Discussion section.
Figure 21 Through-plane registration accuracy for various amounts of 3D femur model’s through-plane perturbation (600 simulated perturbation cases per search space). Left: 2D \( \text{TRE}_{\text{through-plane}} \) vs initial through-plane perturbation under the smaller (top) and larger (bottom) search spaces. For the smaller search space, the through-plane perturbations generally remain uncorrected and contribute to the final 2D \( \text{TRE}_{\text{through-plane}} \). Under the larger search space, there is a “forking” effect generated by the golden section search method with the worsening of the average 2D \( \text{TRE}_{\text{through-plane}} \). Right: from left to right, the bars in each graph represent the 2D \( \text{TRE}_{\text{through-plane}} \) statistics for initial through-plane perturbations of up to 3 mm, 6 mm, 9 mm, 12 mm, and 15 mm using the smaller (top) and larger (bottom) search spaces. The top and bottom whiskers on each bar represent the maximum and minimum 2D \( \text{TRE}_{\text{through-plane}} \) values in mm, respectively. The lower and upper boxes in each bar represent the middle 50% of 2D \( \text{TRE}_{\text{through-plane}} \) values in mm (i.e. second and third quartile groups). The required 3 mm target accuracy (dashed red line) cannot be met using a larger through-plane search space. However, an acceptable 2D \( \text{TRE}_{\text{through-plane}} \) can be achieved with through-plane perturbations of \( \leq 3 \) mm using the smaller search space.

8.3.2 Upper rotational bounds

In this evaluation instance the automatic registration’s upper rotational bounds were examined. As before, two prescribed search spaces were utilized that only differed in the amount of their rotational search threshold, namely \( \{R_{x_{\text{global}}}, R_{y_{\text{global}}}, R_{z_{\text{global}}}\} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3\} \) and \( \{R_{x_{\text{global}}}, R_{y_{\text{global}}}, R_{z_{\text{global}}}\} = \{-7 \ldots 7, -7 \ldots 7, -7 \ldots 7\} \). The in-plane and through-plane search spaces remain as \( \{T_{x_{\text{x-ray}}}, T_{y_{\text{x-ray}}}\} = \{\text{x-ray FOV}\} \) (global in-plane search), \( \{T_{z_{\text{x-ray}}}\} = \{-4.1 \ldots 4.1\} \). The induced perturbations for both search spaces in this evaluation were contained in the interval \( \{R_{L_{-R}}, R_{S_{-I}}, R_{A_{-P}}, T_{L_{-R}}, T_{S_{-I}}, T_{A_{-P}}\} = \{-10 \ldots 10, -10 \ldots 10, -10 \ldots 10, 0, -20 \ldots 20, 0\} \).

As Figure 22 indicates, there is a general increasing trend of 3D TRE with increasing degrees of induced rotational perturbation. Starting at 9° of total initial rotation, it becomes difficult for the automatic registration to find the rotation transformations that
accurately register the 3D femur model to the x-ray images using a total rotation search space (i.e. 9°) smaller than that of the total induced rotation perturbations as indicated by the larger 3D TREs (Figure 22 top). In the second scenario of this evaluation, the search space of the automatic registration was increased to examine its ability in fixing larger rotation perturbations, and, as expected, more of the cases with total rotation perturbations of up to 25° were registered with an average 3D TRE of 6.69 mm (Figure 22 bottom).

Figure 22 Automatic registration’s accuracy for various amounts of 3D femur model’s total rotational perturbation (600 simulated perturbation cases per search)
space). Top left: graph of 3D TRE vs total initial rotation perturbation in degrees for the smaller search space. As the graph indicates, total initial rotations of more than 9°, which represents the limit of the total rotational search space of the automatic registration, remain largely uncorrected. Bottom left: graph of 3D TRE vs total initial rotation perturbation in degrees for the larger search space. Most of the induced rotation perturbations have been corrected by the automatic registration due to the larger rotational search. Right: from left to right, the bars indicate 3D TRE statistics for rotations of up to 5°, 9°, 15°, 20°, and 25° using the smaller (top) and larger (bottom) search spaces. The top and bottom whiskers on each bar represent the maximum and minimum 3D TREs in mm, respectively. The lower and upper boxes in each bar represent the middle 50% of 3D TRE values in mm (i.e. second and third quartile groups). Although the larger search space can correct more of the larger perturbations with a better TRE, the smaller search space seems to be a slightly better candidate when only considering 3D TRE < 3 mm, which includes total rotation perturbations of up to 9°, likely to be exhibited by small-scale rotations of the femur.

Total initial rotation perturbations of ≤ 9° resulted in a fairly similar 3D TRE using both search spaces, which was on average 2.9 mm. Considering the tremendously lower computational time and the sufficiency of the smaller search space in addressing total initial rotation perturbations of up to 9° (i.e. small scale rotations likely to occur during SFA revascularization procedures) with 3D TRE < 3 mm, it may be a better candidate unless the computational time of the larger search space can be comparably reduced. Furthermore, the fact that the larger search space does not yield a better 3D TRE for total rotation perturbations of ≤ 9° renders it incompetent compared to the smaller search space in achieving < 3 mm 3D TRE for perturbations in that range. As noted earlier, the reason behind the cluster of 3D TREs that represent total rotation perturbations of greater than 9° (Figure 22 top left) is mainly due to the cases being out of the total range of the search space (i.e. 9°), which will be addressed further in the Discussion section.

The misregistration limits that the automatic registration was able to correct with an acceptable accuracy (both 3D TRE and 2D TRE_{in-plane} < 3 mm) using the more
appropriate search space for SFA revascularization procedures (i.e. \( \{ R_{x\_global}, R_{y\_global}, R_{z\_global} \} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3\} \), \( \{ T_{x\_x\_ray}, T_{y\_x\_ray} \} = \{ \text{x-ray FOV} \} \), \( \{ T_{z\_x\_ray} \} = \{-4.1 \ldots 4.1\} \)) are summarized in Table 3.

<table>
<thead>
<tr>
<th>Perturbation</th>
<th>&lt; 3 mm 3D TRE</th>
<th>&lt; 3 mm 2D TRE&lt;sub&gt;in-plane&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-plane</td>
<td>X-ray Field of View</td>
<td>X-ray Field of View</td>
</tr>
<tr>
<td>Through-plane</td>
<td>( \leq 3 \text{ mm} )</td>
<td>20 mm</td>
</tr>
<tr>
<td>Rotation</td>
<td>( 9^\circ )</td>
<td>( 9^\circ )</td>
</tr>
</tbody>
</table>

Table 3 A summary of the automatic registration’s tolerable (< 3 mm 3D TRE or 2D TRE<sub>in-plane</sub>) capture range. Using a fixed automatic registration search space that is suitable for the requirements of SFA CTO revascularization procedures, an average 3D TRE < 3 mm was achieved with through-plane translations of \( \leq 3 \text{ mm} \) and \( R_{\text{total}} = 9^\circ \). An average in-plane registration accuracy of 2D TRE<sub>in-plane</sub> < 3 mm was achieved following through-plane translations of on average 20 mm and \( R_{\text{total}} = 9^\circ \). Any magnitude of in-plane translations were sufficiently corrected to meet 3D TRE < 3 mm and 2D TRE<sub>in-plane</sub> < 3 mm as long as the MR landmark remained fully visible under the utilized x-ray view.
9 Discussion

Several observations require more detailed consideration when considering sources of error and opportunities for improvement. These include interpretation of the initial manual registration error, the impact of manual segmentation on registration accuracy, influence of image acquisition and quality, the effectiveness of the golden section depth search, the automatic registration’s speed and accuracy, and the potential of employing biplane x-ray views to improve the automatic registration’s operation. In addition, a translation of the final registration error to the perceived registration error at the superficial femoral artery will be provided. Before examining the individual components, however, an analysis of the obtained TRE results and their implications in terms of patient bulk motion will be presented.

Referring back to the collected TRE data, it was observed that a 3D TRE < 3 mm was achieved using the adequate peripheral vascular intervention’s search space (i.e. \( \{ R_x\text{ global}, R_y\text{ global}, R_z\text{ global} \} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3\} \), \( \{ T_{x\text{x-ray}}, T_{y\text{x-ray}} \} = \{\text{x-ray FOV}\} \), \( \{ T_{z\text{x-ray}} \} = \{-4.1 \ldots 4.1\}\) ) with a through-plane movement of \( \leq 3 \) mm and an unlimited movement of the MR landmark within the x-ray field of view. The identified through-plane and in-plane translations are a breakdown of the total 3D movement of the patient relative to the x-ray imaging plane and coordinate system. Recalling the mapping of the coordinate systems as depicted in Figure 16, it can be seen that the S-I axis coincides perfectly with \( y_{x\text{-ray}} \) in the vertical direction of the x-ray image, and, the horizontal direction or \( x_{x\text{-ray}} \) translates to a sum of components from of the L-R and A-P axes. However, a component sum from the L-R and A-P axes is also mapped in the \( z_{x\text{-ray}} \) direction. Now, considering that the patient motion during a peripheral revascularization procedure can mainly occur on the patient table and, therefore, in the L-R and S-I directions, the maximum through-plane movement of 3 mm directly translates to 7.1 mm in the L-R anatomical direction. Moreover, although the \( x_{x\text{-ray}} \) component of the in-plane translation will be capped by the calculated L-R displacement of the patient, due to its decomposed through-plane contribution and the limitation on through-plane translation to meet 3D TRE < 3 mm, there are no limitations imposed by the \( y_{x\text{-ray}} \) axis as it only maps to the S-I anatomical axis, and given unlimited tolerable in-plane
translations in the \( y_{x\text{-}ray} \) direction, any magnitude of movement by the patient in the S-I direction within the x-ray FOV can be reliably registered.

From the standpoint of a vascular surgeon or an interventional radiologist, a more meaningful presentation of the XMR fused images may be a measure of the apparent registration accuracy as visible on the 2D plane of the x-ray image. When considering only the 2D \( \text{TRE}_{\text{in-plane}} < 3 \text{ mm} \), up to 20 mm of through-plane misregistration can be tolerated, which in anatomical axes terms converts to 47.3 mm L-R motion, assuming there is no A-P movement of the patient occurring off the table. Patients requiring peripheral vascular interventions are normally either locally anesthetized to remain awake and follow the doctor’s instructions or receive general anesthesia. In both cases the pain and discomfort will be minor, which causes the leg to remain relatively stationary throughout the procedure. The above noted limits of allowed movement in relation to the patient (\( T_{L-R} = 7.1 \text{ mm}, R_{total} < 9^\circ \) for 3D \( \text{TRE} < 3 \text{ mm} \) and \( T_{L-R} = 47.3 \text{ mm}, R_{total} < 9^\circ \) for 2D \( \text{TRE}_{\text{in-plane}} < 3 \text{ mm} \), \( T_{S-I} = \text{unlimited within x-ray FOV, assuming } T_{A-P} = 0 \) for both \( \text{TRE} \) scenarios) as tolerated by the automatic registration in order to meet the 3D and 2D \( \text{TRE} \) requirements are sufficient to encompass minor displacements of the femur due to tissue compression and small-scale patient movement. Any magnitude of displacement larger than defined by these intervals will require recalibration of the registration by repeating the initial manual registration using two newly acquired x-ray images from different angles, which may happen with bulk motions of the patient resulting from sudden surge of pain and discomfort following catheter manipulation in the leg.

The limitations of the through-plane search that only allow the moderate correction of through-plane translations of up to 3 mm (i.e. 3D \( \text{TRE} \) of on average 2.23 mm) using the smaller depth search space will be further investigated in Section 9.2. Moreover, the current restriction on the upper rotational bound is mainly due to the required high target registration accuracy. As observed in Figure 22, increasing the rotational search space does not improve the 3D \( \text{TRE} \) for total perturbations of up to 9°, which remained just below 3 mm. In general, applications that require high levels of registration accuracy should not have a large registration search space as it only reduces constraints and allows
for more potential matches between the images. Hence, bulk patient movements beyond 9° of total rotation perturbation cannot be accounted for using a larger rotational search space when 3D TRE < 3 mm is required. Furthermore, the bulk motions cannot solely be detected using the automatic registration’s cost function since out-of-range rotations can at times produce cost values that are comparable to within-range rotation perturbations. As such, these movements need to be detected via another mechanism and manually re-registered, which will be further discussed in next chapter.

9.1 Initial manual registration error

The automatic registration method is primarily designed with a clinical focus to refine any residual errors that might remain from the manual alignment step. Although the residual error refinement notion applies to the clinic, for the simulation and validation studies performed in this thesis a small error is often carried over that contributes to the final TRE measurements due to the variability in the position of the manually aligned edges of the projected MR and x-ray landmarks at the end of the initial manual registration. This base level of error is initially measured by the FFT NCC template matching technique to be 0.67 mm and 0.54 mm on average in the LAO 35° and RAO 35° views, respectively (refer to Section 8.1). Consequently, the automatic registration’s error, mainly 2D TRE_{in-plane}, is slightly underestimated by the amount of this initial error.

Having a more detailed 3D segmentation of the femur from MR data can augment the manual alignment process and accuracy of the initial manual registration. Various automatic segmentation methods have been proposed for the extraction of bone and cartilage from MRI data [114], [115]. However, these methods rely on prior knowledge of the variations in bone dimensions, require statistical shape models, and are still inaccurate across different datasets. The manual segmentation as performed in this thesis, depends on the operator’s ability in delineating the pixels that represent the bone’s contours. A rather accurate 3D model can be manually segmented from magnetic resonance data with prior knowledge of the particular bone’s shape and anatomy, and experience in its segmentation. Not only can the initial manual registration benefit from a
well-segmented 3D model of the femur, but also the automatic registration’s performance can be improved as its accuracy directly depends on how well it can detect the lowest cost when the edges of the landmarks (i.e. segmented 3D femur model and x-ray image of the femur) are perfectly overlapping. Moreover, the manual measurement of the SOD from the C-arm further contributes to the above noted base error since any inaccuracy in the SOD value causes the edges of the landmarks to never be able to perfectly overlap. Although improvements in these fronts can produce a sub-millimeter improvement in the TRE, the manual segmentation of the femur from MRI and the manual measurement of the SOD from the C-arm still remain a bottleneck in the accuracy of the registration.

Considering that the manual segmentation relies on the operator’s ability to delineate the bordering pixels that represent the femur’s contour from the MR images, the segmentation process itself can benefit from better image resolution and quality. Generally, air and hard bone do not give an MRI signal so these areas appear black. In this thesis, a fat-suppressed BP-SSFP MR sequence (see Section 7.2.2) was used with a voxel size of 1.0 x 1.0 x 1.0 mm$^3$ to acquire images of the femur. With better tuning of the sequence parameters to generate additional contrast between the bone and surrounding soft tissue as well as increasing the resolution (at the cost of increased acquisition time) the segmentation process, whether automatic or manual, can readily benefit from the added image information and quality.

9.2 Golden section depth search and the through-plane accuracy

With an understanding of how L-R patient motion contributes to through-plane translations and essentially defines the upper limit of the registration method’s capacity for achieving a target registration accuracy of 3D TRE < 3 mm, the underlying weakness of the automatic registration in through-plane correction will be analyzed.

The rotational and through-plane translational search methods implemented in this thesis follow a heuristic approach where the search optimizers receive their cost information
from the FFT NCC template matching technique, which performs a global in-plane optimization at every heuristic evaluation of the rotational and through-plane translational candidate parameters. The heuristic optimization of the through-plane parameter is delegated to the golden-section search technique. The search starts with a bounding search interval (through-plane threshold) and iteratively shrinks the search interval based on function values at newly selected intervals. The process continues until the interval is sufficiently small, at which point the function’s minimum is found by taking the average of the function values at the detected final upper and lower intervals. The selection of a new interval occurs based on the golden ratio, which is 0.618 (Figure 23).

**Figure 23** Diagram depicting the golden-section search technique. By iteratively closing the upper \( (u) \) and lower \( (l) \) boundaries based on the calculated function values at the new intervals \( x_1 \) and \( x_2 \), the function’s maximum can be found. \( x_1 \) and \( x_2 \) are selected based on the golden ratio in a way that \( x_1 = x_l + 0.618 (a + b) \), \( x_2 = x_u - 0.618 (a + b) \), and \( x_u - x_2 = x_1 - x_l = a = 0.618 (x_u - x_l) \).

As Figure 23 illustrates, the golden-section search is only suitable for use with functions that are unimodal with a single maximum/minimum existing in the search threshold. In other words, it must be ensured that a single maximum/minimum exists in between the selected intervals for the golden-section search to work properly. However, with a through-plane search threshold of \( \pm 12 \) mm, as with the case of the larger through-plane
search space, the in-plane magnification changes with shifts of only a few pixels, which can generate an equally better or worse cost in the matching process. Thus, a multimodal cost function with random minima that lie within the allocated through-plane threshold results. Increasing the through-plane search interval as was observed with the through-plane upper translational bound evaluation will only increase the number of minima that lie in between, thus making the search outcome more random and inaccurate (Figure 21). In that case, though the search did not take more time to complete as opposed to the smaller through-plane search threshold due to use of larger intervals according to the golden ratio, it did become less accurate. This is because of the converging of the search at random on either side of the current depth using the larger search space (which could make the 2D TRE_{through-plane} better or worse) because of the random presence of local minima in the cost function with through-plane translations; hence a perceived “forking” effect results with a larger through-plane search space using the golden-section search algorithm on a non-unimodal cost function. In contrast, using the smaller through-plane search space, the optimizer inevitably converges within the same local minimum (i.e. can act randomly within a smaller interval) and so only the initial through-plane perturbation is largely carried over to the final 3D TRE.

In order to better understand the process behind the creation of the “forking” trend, let’s consider how the search progresses with 6 mm of through-plane perturbation. As discussed in the following paragraphs, only a millimeter of magnification can be detected on the screen for every 3 mm of through-plane translation, which means that with 6 mm of depth movement there is going to be approximately 2 mm of detectable in-plane magnification. Furthermore, the cost is the same for through-plane translations in steps of 3 mm (i.e. 3 – 5 mm = a, 6 – 8 mm = b, and 9 – 11 mm = c, where a, b, and c are cost values). With this in mind, for the observed “forking” trend to be created, the search must converge in a local minimum that represents 3 – 5 mm or 9 – 11 mm of through-plane movement (which indicates 1 mm or 3 mm of detectable in-plane magnification with cost values being a or c, respectively). The convergence of the through-plane search in these local minima, situated on either side of the global minimum, is primarily due to the selection of search intervals according to the golden ratio, which places the lower and upper intervals within the neighboring local minima. At this point, the local minimum
that results in a lower FFT NCC cost is selected and the search eventually converges in that neighboring minimum (Figure 24). This selection is governed by whether a one-millimeter decrease or increase in magnification produces a greater degree of overlap between the edges of the x-ray and projection image NGFs (Figure 25), and the results vary randomly across independent trials.

Figure 24 FFT NCC cost vs through-plane translation of the 3D femur model in mm. Due to a 3:1 ratio of through-plane movement to in-plane magnification, the costs for through-plane movements in the range 3 – 5 mm are equal (as are in the ranges 6 – 8 mm and 9 – 11 mm). In this case, though the true depth movement should be identified as being 6 mm, the golden-section search incorrectly converges in one of the neighboring local minima (indicated by the circled search interval here) that correspond to an in-plane magnification of a millimeter larger or smaller (Figure 25). The correct magnification (i.e. 2 mm) corresponding to 6 mm of depth movement is never evaluated by the golden-section algorithm because of the selection of the search intervals according to the golden ratio, which initially places the lower and upper intervals in the neighboring local minima and drives the search to converge in the minimum with the lowest cost.

With the convergence of the search in one of the neighboring local minima, according to whether the 1 mm larger or smaller magnification produces more overlap regions (Figure 25), the resultant depth is adjusted by translating the current location 3 mm in either the
positive or negative through-plane direction; thereby increasing or decreasing the current 6 mm through-plane error by 3 mm. This results in a final 2D TRE$_{\text{through-plane}}$ value of 3 mm or 9 mm for a through-plane perturbation of 6 mm, according to whichever local minimum the golden-section search converges in, which produces the observable “forking” trend on graph under the larger search space (Figure 21 bottom left).

Figure 25 A visual representation of the edge matching process during through-plane optimization and the shortcoming of the golden-section algorithm. The magnification of the projection image NGF changes by a millimeter for every 3 mm of through-plane translation. This means that in order to achieve a 1-mm larger projection image (femur in dashed green line) the 3D femur model must be moved 3 mm towards the camera, and, 3 mm away from the camera to achieve a 1-mm smaller projection image (femur in dashed red line). With 6 mm of through-plane movement in the above example, since the golden-section search fails to calculate the cost for 2 mm in-plane magnification (corresponding to 6 mm through-plane translation) due to its predetermined intervals, the global minimum is missed (Figure 24). However, the costs for 3 mm and 9 mm through-plane translations are calculated by the search, which entail generating projection images that have 1 mm smaller and larger in-plane magnifications than the target magnification (femur in
solid black line), respectively. The outcome of the search is determined by choosing the projection image that yields a greater degree of overlap with the x-ray NGF. The selected in-plane magnification is then translated to the appropriate through-plane movement and applied to the 3D femur model, which moves it 3 mm towards or away from the camera, resulting in the observed “forking” effect when repeated across numerous through-plane perturbation cases.

The choice of the depth search optimizer becomes further pronounced by the projective nature of the registration problem. The automatic registration naturally relies on the extraction of edge information from the fixed and moving images to find a best match based on this information. However, through-plane movements do not generate a great deal of apparent pixel shift on the projected plane. For the purposes of this thesis, the performed x-ray experiment placed a pig’s femur at a SOD of 630 mm. Given the length of the pig’s femur (~14 cm), an in-plane magnification of 1 mm on the x-ray image would require ~3 mm of through-plane movement of the femur. Thus, through-plane movements of < 3 mm will only generate sub-millimeter in-plane magnifications that would be unrecognizable by the automatic registration. The automatic registration’s ability to correct through-plane translations also becomes limited due to this 3:1 ratio. With the optimizer’s through-plane search space close to the 3 mm mark, any through-plane translations smaller than 3 mm would be unnoticed by the automatic registration and inevitably carried over to the 3D TRE. Anything larger would be susceptible to the detection of random neighboring local minima in the multimodal cost function by the golden-section search. Rotation transformations also generate small through-plane translations due to a slightly off-center axis of rotation in relation to the 3D femur model, which can directly contribute to the final TRE.

One approach to concurrently circumvent the limitation associated with projective through-plane translation detection and the above noted weakness of the golden section search, or any other search prone to the limitations of inferring projected depth motion for that matter, is to incorporate a biplane optimization method into the automatic registration. Currently, the automatic registration utilizes single-plane x-ray images as these systems are more commonly employed during endovascular procedures. Having a
second x-ray plane register depth information (in-plane as opposed to through-plane) using the FFT NCC template matching, the fast speed, high accuracy, and global search advantage of the technique can be exploited, which can readily solve the limitations of extracting depth information from single-plane x-ray images as previously mentioned. In this manner, the through-plane accuracy is expected to reach the current in-plane accuracy of, on average, 2.1 mm with its capture range increased to the x-ray plane’s field of view. Increased workflow complexity and radiation exposure to the patient and staff are the main drawbacks of biplane image guidance.

The uncorrected through-plane errors in the current implementation of the automatic registration can be minimized by deliberately placing the A-P axis of the patient in alignment with the \(z_{x-ray}\) axis. This would require imaging the patient in A-P radiological view, and since most of the patient bulk motions are likely to happen on the patient table, the \(z_{x-ray}\) vector component can be made negligible in the 3D TRE even without performing any depth search.

### 9.3 Femur rotational ambiguity

As illustrated in Figure 22 top left, the automatic registration is unable to find the correct rotational transformations that accurately register the 3D femur model to the x-ray image using a total rotational search space that is smaller than the induced total rotations. This is indicated by the cluster of TRE points in the middle and on the right side of the graph that result from total rotations of \(R_{tot} > 9^\circ\). Here, since some of the degrees of induced rotation perturbations are not searched for, the FFT NCC template matching unsurprisingly finds random matches based on the minimum NNC cost at locations in the image that may or may not be close to the true registration pose. This situation can occur even with rotation perturbations that are contained within the search space as illustrated by the cases to the far right of Figure 22 bottom left. Here, even though most of the induced total rotation perturbations are successfully corrected by the larger rotational search space of the automatic registration, there are a few cases that still exhibit large 3D TRES. Out of these, most cases are caused by perturbations that are comprised of greater
than 7° of rotation in one axis and less than 7° of rotation in other axes leading to a total rotational perturbation of $R_{tot} \leq 21°$ (i.e. allocated total search space), which as mentioned earlier, are affected by the problem of having a larger induced rotation than the allocated search space within that axis. Leaving those reasonably faulty cases aside, there was one case out of the total 600 evaluation runs that exhibited a large 3D TRE for induced axial rotations that were contained within the rotational search space of the automatic registration. This is because under certain and usually large rotations (i.e. close to the limit of the axial rotational search space, 7° in this case), mainly occurring along the A-P anatomical axis, an ambiguous projection can at times result that leads to an erroneous match generation by the FFT NCC template matching technique (Figure 26).

Figure 26 An incorrect match produced by FFT NCC template matching as caused by rotational ambiguity. The unusual registration pose generated by the 2D-2D registration technique is due to the ambiguous shape of the femur in the current projection, which results in a smaller FFT NCC cost than the true registration pose.
Although uncommon (as with the case of 1 out of 600 ≈ 0.2% of the time in the evaluation tests, for which the case exhibited 7° or the maximum allowed rotation around the A-P axis along with 3° around the S-I axis), rotational ambiguity can still exist. Shapes that lack morphological uniqueness can produce ambiguous projections, which is why the femur can, to a great extent, provide a reliable landmark due to its rather constrained shape close to the bone ends. Under certain angles, however, the femur can become less exclusive in terms of providing for a unique landmark as is the case with RAO 35° radiological view, which results in a slightly higher average target registration error (i.e. an average 3D TRE = 2.05 mm in RAO 35° compared to an average 3D TRE = 1.56 mm in LAO 35°, see Section 8.2). As such, it is recommended that the registration be performed in the angle of LAO 35°, which offers a slightly more restricted shape of the femur and, thus, fewer ambiguous registration poses in comparison to RAO 35°.

9.4 Registration error propagation

The registration method in this thesis utilizes the femur as the shared landmark to overlay prior MR data onto x-ray images while the intervention site for the peripheral revascularization of CTOs (where the registration’s accuracy is of utmost concern) is within the superficial femoral artery. This means that any registration error resulting from matching of the femur is propagated and affects the overlay of the SFA from MRI to x-ray. With rotational registration errors, the SFA shifts from a perfect overlay position according to the misalignment angle with the axis of rotation located at the landmark. The amount of the SFA’s shift from a perfect overlay position is directly proportional to the misalignment angle of the landmark and the distance away of the SFA from the landmark. The amount of this shift (i.e. translational offset) due to rotational error propagation can be described by the following formula:

$$T = 2D \sin \frac{\theta}{2}$$ (9)
where \( \theta \) represents the misregistration angle in degrees, \( D \) is the distance from the centerline of the femur to the centerline of the SFA in millimeters, and \( T \) is the amount of translational offset of the SFA in millimeters due to the propagation of rotational error.

Considering an average distance of 28 mm between the centerlines of the femur and SFA in humans according to Sun et al. [116], a translational offset of \(~0.5\) mm can result at the SFA due to rotational error propagation for every degree of rotational misalignment at the landmark. On the other hand, there is no propagation of error attributed to translational misregistration of the landmark. This means that with translational registration errors, the SFA overlay will be directly affected by the amount of the translational TRE.

### 9.5 Automatic registration speed and runtime

The automatic registration currently completes a full registration cycle within the prescribed peripheral intervention’s search space (i.e. \( \{R_{x\text{global}}, R_{y\text{global}}, R_{z\text{global}}\} = \{-3 \ldots 3, -3 \ldots 3, -3 \ldots 3\}, \{T_{x\text{xy-ray}}, T_{y\text{xy-ray}}\} = \{\text{x-ray FOV}\}, \{T_{z\text{xy-ray}}\} = \{-4.1 \ldots 4.1\} \) in 112 seconds. Although not real-time, the present runtime of the XMR registration may not be suitable even for a relatively fixed procedure such as peripheral revascularization of the SFA. The long computational time of the registration can be attributed to several factors, namely, inherent requirements of 2D-3D registration that demands projection rendering of the 3D femur model, hardware limitations of the CPU in parallel processing, and inefficiencies in the current implementation. A breakdown of the registration’s runtime into its respective components is provided in Table 4. The NGF generation times were insignificant compared to their prior x-ray image denoising and projection image rendering runtimes. A single registration cycle includes one iteration of x-ray image denoising and NGF generation, which accounts for 15% of the total registration runtime, close to 50 iterations of projection image rendering along with their NGF generations, which account for 54% of the total runtime, and close to 50 iterations of the FFT NCC template matching that make up 31% of the total registration runtime.
<table>
<thead>
<tr>
<th>Number of runs</th>
<th>Description</th>
<th>Average time (s)</th>
<th>Percentage time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X-ray image denoising and NGF generation</td>
<td>17</td>
<td>15%</td>
</tr>
<tr>
<td>50</td>
<td>Projection image rendering and NGF generation</td>
<td>61</td>
<td>54%</td>
</tr>
<tr>
<td>50</td>
<td>2D 2DOF in-plane global search with FFT NCC</td>
<td>35</td>
<td>31%</td>
</tr>
</tbody>
</table>

Table 4 Average runtimes of the automatic registration’s components listed in the order of execution (N.B. the order of execution after x-ray image denoising and NGF generation is one iteration of projection image rendering along with its NGF generation followed by one iteration of FFT NCC template matching, which is repeated 50 times).

More recently, general-purpose graphics processing units (GPGPUs) have been employed to carry out computationally demanding tasks such as medical image processing [117]. A lot of the mentioned registration elements such as normalized cross-correlation computation, projection image rendering, and denoising are well suited for processing using GPU-accelerated computation in tandem with a central processing unit (CPU). GPU-based medical image processing can benefit from crucial advantages such as high throughput computing, specialized hardware for interpolation, high memory bandwidth, and excellent price-to-performance ratio [117]. Especially true of highly computationally intensive 2D-3D registration problems as described herein, a parallel implementation of the registration algorithm entirely on the GPU can significantly speed up the optimization process [118]. Moreover, the need to make duplicate copies of the rendered projection images between GPU memory, where perspective projection rendering is performed, and CPU memory, where the projection image is connected to the rest of the registration pipeline, is eliminated. Hence, having a unified GPU implementation can dramatically
reduce the registration runtime and allows for adaptation of the system into clinical applications that demand real-time image guidance.

10 Interpretation of findings in the clinical context

The XMR registration method developed in this thesis can be used to guide the clinical revascularization of chronic total occlusions. Though not in real-time, the method can provide a path for the clinician to follow when there is a lack of anatomical visualization as is in the case of CTO revascularization under x-ray guidance. It enables clinicians to have a sense of the position of the revascularization device with respect to the vessel wall and lesion location. However, the efficacy of such framework in improving the clinical practice of PTA procedures can better be acknowledged through the interpretation of the method’s capabilities in terms of sensible clinical numbers. This section provides a statistical analysis of the obtained results within the clinical context.

Using the registration approach outlined herein, two nearly orthogonal x-ray images of the femur must be acquired at the beginning of the procedure to perform the initial manual registration. As section 8.1 indicated, the in-plane variability in position of the 3D femur model at the end of the initial manual registration had a median of 0.68 mm with a range of 0.73 mm in either projection. The findings from this evaluation ensure that the variability in the location of the 3D femur model following the initial manual registration is less than 1.07 mm at 90th percentile. The variability in manually registered position was evaluated for two main reasons; to get a sense of an experienced user’s performance in accomplishing the initial alignment and to ensure that the 3D model can be sufficiently brought within the automatic registration’s search space, and, to obtain a benchmark for the purpose of ground truth evaluation in this dissertation. However, this amount of variability in the 3D model’s position is of minor concern during clinical practice, as the initial manual alignment only aims to bring the 3D femur model from MRI into rough correspondence with the x-ray image and is corrected in the next stage of the workflow by the automatic registration, which is initially responsible for providing the finer alignment between the MR and x-ray femur using one of the acquired projections. The more accurate, millimetric adjustment to the coarse registration can be achieved by
simply selecting one of the previously acquired x-ray views for the automatic registration to continue with and takes approximately 112 seconds to execute.

In the next evaluation, the stability of the automatic registration in maintaining a reliable registration (3D TRE < 3 mm) was examined. This evaluation was performed with the clinical aspect in mind where the femur/leg would remain static during the procedure while the automatic registration provides periodic updates to the registration pose every 112 seconds. The median of the 3D registration error for 10 independent runs of the automatic registration each starting from a prior initial manual registration (i.e. 3D error measured by comparing the final automatic registration pose against the starting manually registered ground truth location) was 1.46 mm with a range of 0.82 mm in LAO 35° and 2.03 mm with a range of 0.82 mm in RAO 35°. This evaluation indicated that the 3D TRE of the automatic registration, starting from an initial registration position without any movement of the femur (i.e. stability error), was 1.94 mm (LAO 35°) and 2.43 mm (RAO 35°) at 90th percentile, and, 1.95 mm (LAO 35°) and 2.44 m (RAO 35°) at maximum. It should be noted that the reported 3D TRE of the automatic registration includes a ground truth shift error resulting from a non-perfect alignment in the prior manual registration step, and therefore, is underestimated by the amount of the above-mentioned in-plane variability during initial registration. Though rather close to the target registration accuracy of 3 mm as demanded during PTA procedures of the SFA, the registration framework can provide a 3D path for the revascularization device to follow within the vessel.

Perhaps the most important piece of information relevant to a clinician is to have a sense of not only the tolerable ranges of femur movement for which the XMR registration remains reliable (i.e. 3D TRE < 3 mm), but also the statistics of registration failure within those ranges. In the last part of the evaluation, the upper bounds of femur/leg movement that the automatic registration was able to fix within the required target registration accuracy were analyzed. As section 8.3.1 indicated, in-plane perturbations of up to 50 mm were tolerated with a median 2D TRE_{in-plane} of 1.87 mm with the third-quartile 2D TRE_{in-plane} at 2.83 mm (Figure 20 right). The 2D TRE_{in-plane} values varied within a range of 10.69 mm for cases that had up to 50 mm of perturbation, which causes the percentage
of failed cases (i.e. had 2D TRE_{in-plane} > 3 mm) to be approximately 21% in 592 randomly perturbed cases. The percentage failure was rather similar for cases that lesser in-plane perturbation (i.e. up to 20 mm), which was roughly 23%. As mentioned earlier, the shortcomings of the golden-section depth search results in the through-plane perturbations to be largely carried over to the final TRE. However, in order to achieve an acceptable 2D TRE_{through-plane}, the search space can be kept small (i.e. ± 4.1 mm). In this case, though the average 2D TRE_{through-plane} will be 2.3 mm (Figure 21 top right, leftmost bar), the percentage failure remains at 27%. Lastly, even though section 8.3.2 mentioned an average 3D TRE of 2.9 mm for total rotation perturbations of up to 9°, the percentage of cases that had 3D TRE > 3 mm is 42%, with the median of 3D TRE values at 2.89 mm within a 5.09 mm range, which may not be suitable for clinical adoption. For a more reliable registration within the clinical setting, total rotation perturbations of up to 5° can be confidently corrected with a percentage failure of 6% using the smaller search space (i.e. ± 3°). The average 3D TRE for total rotations of ≤ 5° is 1.79 mm with a median of 1.63 mm and a range of 1.92 mm (Figure 22 top right, leftmost bar).

11 Conclusion

The registration method developed in this thesis utilizes bony landmarks that are inherently available in the body to register a 3D model of the femur extracted from prior 3D MR data to 2D x-ray images. This method can directly address catheter navigation limitations of x-ray faced during revascularization of peripheral CTOs by providing a path through the obstructed vessel for the operator. The registration pose is reliably maintained throughout the movements of the C-arm gantry and L-R patient bulk motions of up to 47 mm can be corrected with an average 2D TRE_{in-plane} < 3 mm. Any amount of S-I patient bulk motion can be adequately corrected as well as 9° of total 3D rotation. The method can provide periodic updates of the registration pose every 112 seconds with an average 3D TRE of 1.56 mm in LAO 35° x-ray view using the peripheral intervention’s search space (i.e. \{R_{x\ global}, R_{y\ global}, R_{z\ global}\} = \{-3 ... 3, -3 ... 3, -3 ... 3\}, \{T_{x\ x-ray}, T_{y\ x-ray}\} = \{x\-ray FOV\}, \{T_{z\ x-ray}\} = \{-4.1 ... 4.1\}). The 90th percentile 3D TREs were < 2 mm and < 2.5 mm using LAO 35° and RAO 35° projections,
respectively. The 90\textsuperscript{th} percentile 2D \text{TRE}_{\text{In-plane}} values were < 1.5 mm and < 2 mm in LAO 35° and RAO 35° projections, respectively. The average 2D \text{TRE}_{\text{In-plane}} was, on average, 1.02 mm in LAO 35° x-ray view. The target registration accuracies achieved herein are in agreement with the required 3 mm target registration accuracy as necessitated by half of the diameter of the superficial femoral artery for the purpose of guiding peripheral vascular interventions of the SFA. By adaptation of the proposed registration method into CTO revascularization procedures of the SFA, the imaging limitations related to current x-ray fluoroscopy guidance and the associated perforation risks can be reduced.
Chapter 3
Future work

Chapter Overview

In this chapter, potential future work into further development of the method will be studied. The strengths and disadvantages of the current implementation will be analyzed briefly and future improvements with considerations for clinical adoption will be discussed.
11 Introduction

The presented XMR registration workflow can establish an accurate overlay of 3D MR data onto 2D x-ray images with adequate accuracy for the purpose of guiding clinical revascularization of chronic total occlusions. However, the current runtime of 112 seconds and restricted search space of the automatic registration need improvement for broad adoption of the registration workflow. The following sections will primarily focus on ways to improve the registration runtime, accuracy, and capture range. Additionally, important considerations for a successful transition of the method into clinical practice will be reviewed. Lastly, distinctions between the current animal data and human data will be made and potential future development towards collecting and validating the established results with respect to patient data will be mentioned.

11.1 Runtime and accuracy

As mentioned earlier, although SFA revascularization is considered a rather static procedure in terms of leg movement throughout the intervention since the patient receives local anesthesia to relax and block their pain (i.e. conscious sedation), it is not guaranteed that the leg will not exhibit small-scale displacements or bulk motions over a larger angle or distance. In such scenarios, the registration runtime of 112 seconds may pose a challenge to the operator and, therefore, needs to be brought closer to the real-time scale (i.e. under 1-second periodic update). However, even in the absence of bulk patient motion, the XMR registration may generally be helpful in guiding the course of the catheter through the vessel due to misregistrations associated with C-arm movement tracking errors or due to the operator’s applied force on the tissue. In addition, the capability of the registration method to provide an accurate registration is limited due its current narrow range of capture. These issues motivate an effort to reduce the registration runtime and increase the registration accuracy and capture range.

One approach to increasing the accuracy and overall 3D capture range of the automatic registration is by utilizing a dual plane x-ray system to guide the intervention, as explained in Section 9.2 (Figure 27). In short, the biplane registration will employ the same fundamental methods as described in this thesis whereby instead of conducting a
through-plane search, the problem is transformed to an in-plane search using the second orthogonal x-ray imaging plane. This method is expected to increase the 3D translational accuracy; also the 3D rotational accuracy can benefit from such biplane implementation of the registration since the rotational pose is now being computed using two views, which reduces the likelihood of an ambiguous match, thereby increasing the reliability of the fit. This way, the increased accuracy and capture range of the registration method (surpassing the current 3 mm depth and 9° total rotation for 3D TRE < 3 mm) may prove significant enough to outweigh the added complexity of the procedure associated with the use of a biplane x-ray system and, therefore, may reduce the reluctance of operators in employing such systems for peripheral revascularization interventions.

At first glance, the use of two nearly orthogonal x-ray views and two projections of the 3D model of the femur from MRI to perform two simultaneous registrations may seem computationally more time-consuming than single-plane registration. However, with the reduction in the 3D 4-DOF search space by way of eliminating the depth search (which is now optimized simultaneously with the 3D 4-DOF rotational search using the second x-ray plane) and the ancillary benefit of the fast template matching technique realized as its surrogate, the runtime may not be compromised. Additionally, the biplane registration runtime can be greatly reduced by exploiting the parallelism inherent in medical image processing tasks (i.e. denoising of the x-ray images, taking perspective projections of the 3D MR landmark, computation of the normalized gradient fields, and calculation of the normalized cross-correlation) and realizing the registration algorithm on the highly parallel GPU. Restructuring the sequential automatic registration components (Table 4) in parallel could provide speedups of several orders of magnitude [118], which puts the current registration runtime closer to the real-time scale. It is also important how the memory resources are managed to fully utilize the GPU and obtained maximum speedup [117]. Having the registration algorithm entirely implemented within the GPU context will also get rid of the need to make duplicate copies of the images between the CPU and the GPU, hence, further reducing the runtime (Figure 27).
Figure 27 Schematic workflow of a GPU-based biplane 2D/3D registration. Before the intervention, MRI (a) is used to obtain a volumetric data set of the femur (b) from the patient. During the intervention, with an initial estimate of the transformation parameters (c), obtained systematically or via an initial manual registration and which are to be optimized, two perspective projections of a 3D femur model extracted from the MR volume are taken (d) using the same projection matrices as for the biplane intra-procedural x-ray images (f). Biplane x-ray images from the dual plane x-ray system (e) are continuously fed into a graphical processing unit (g) where they are registered in real-time with the two perspective projection images previously generated by the GPU (d). The optimized registration parameters (c) are then used to accurately align the MR data with the biplane x-ray images.
11.2 Clinical integration

A few considerations with respect to the current implementation are worth noting prior to clinical adoption. These include understanding when the registration needs to be recalibrated mid-procedure and conducting further retrospective feasibility studies using patient data.

Considering the capture range of 3 mm through-plane and 9 degrees total rotation in the current implementation of the registration method, it may be necessary for the operators to recognize when the registration needs to be recalibrated mid-procedure (i.e. at what point the information provided by the registration cannot be trusted and a re-registration must be executed from the beginning starting with the acquisition of two nearly orthogonal x-ray images to perform the initial manual registration). With the placement of optical or radiofrequency tracking markers on the leg at the axial location of the distal femur, the position of the femur in 3D space can be monitored. The recorded marker displacements can be translated in terms of both through-plane movements and total rotations with respect to predefined axes of rotation, and any displacement resulting in a depth movement of greater than 3 mm or total rotations of greater than 9 degrees will raise a flag in the registration interface. This way, the operators can be notified of a movement of the femur outside of the registration’s capture range, indicating an unreliable registration. Furthermore, by feeding the tracked leg motion information back into the registration algorithm, the out-of-range transformation parameters can be simultaneously applied to the automatic registration’s coordinate space so that the femur remains in its capture range. This will also remove the need to perform another manual registration using two newly acquired x-ray images and does not disrupt the procedure.

This type of identification may not be as essential for a future version of the registration whereby sub-millimeter accuracy and unlimited capture range within the FOV are achieved via the application of a biplane registration method as previously described. Moreover, a GPU-based biplane registration (Figure 27) can ensure a rapid update of the registration in real-time, giving us the confidence that no on-the-fly movement would reach the extremes of the capture range within a single update.
Finally, the current registration algorithm requires further development, testing, and validation with retrospectively collected patient data. The human and swine femurs mainly differ from each other in their dimensions. The longer human femur with a more complex distal structure can potentially provide a less ambiguous landmark and ultimately a more accurate registration. A patient study can be conducted by collecting pre-procedural MRI scans of patients with peripherally occluded SFA and retrospective x-ray images from the intervention can be taken at nearly orthogonal angles. The registration algorithm can then be evaluated and further developed in terms of the appropriateness of the selected similarity metric and optimization method with respect to the patient data.

11.3 Conclusion

The current implementation of the registration method can be improved in several major aspects: the accuracy and capture range can be increased while simplifying the 3D 4-DOF search into two 2-DOF in-plane searches by utilizing nearly orthogonal biplane x-ray images to perform the registration. Moreover, implementing the registration entirely within the highly parallel and considerably faster GPU context can reduce the registration runtime. In the current implementation, optical or RF markers may need to be placed on the patient’s leg to monitor bulk patient movements and assess the registration’s reliability according to its capture range, ultimately providing a cautionary mechanism for the operator to instigate a re-registration. Finally, the method should be evaluated using retrospectively collected patient data and potentially modified in terms of the preprocessing parameters as well as the choice of similarity metric and optimization method.
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