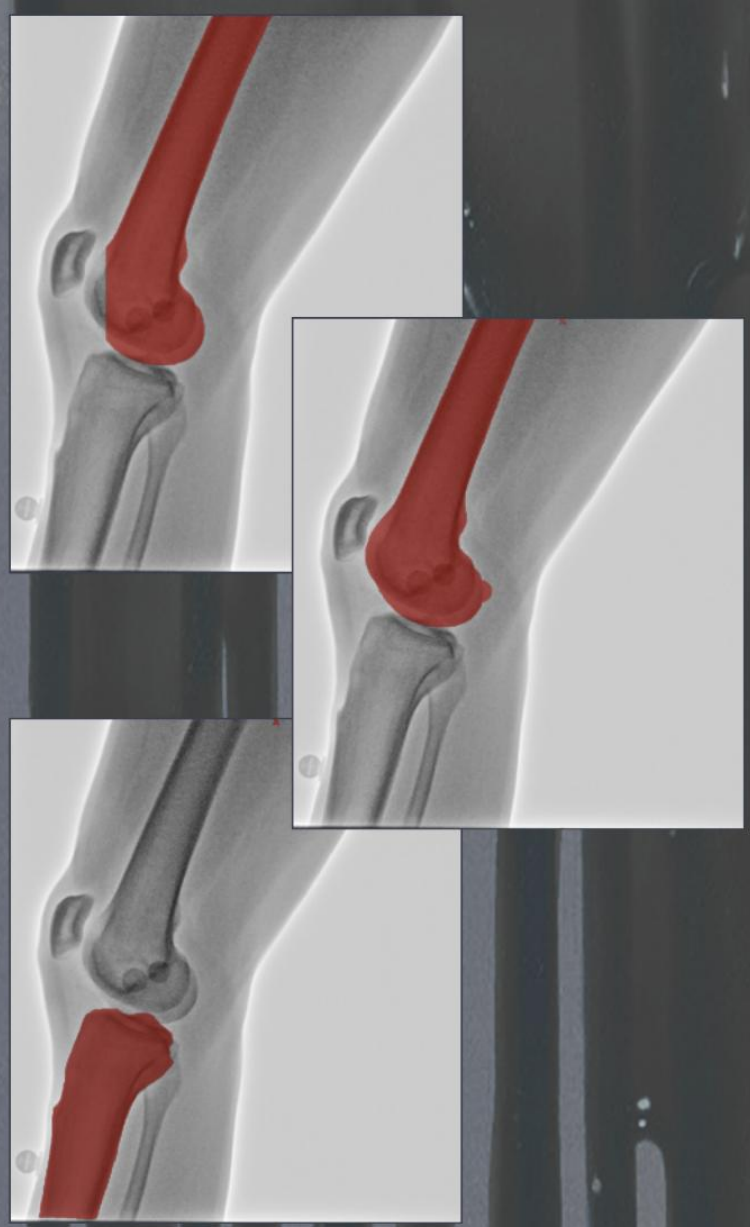
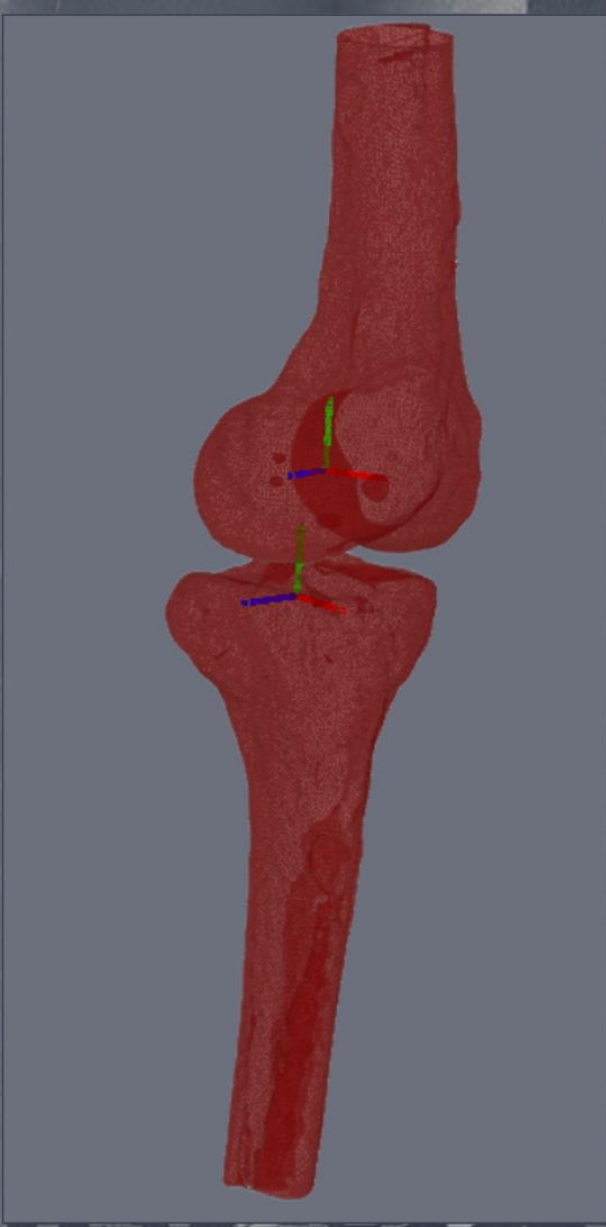




Registration of 3D MRI Bone Models on 2D Fluoroscopy Images of the Knee Joint:

Towards Clinical Practice



Sebastiaan Koninkx
Master Thesis | Technical Medicine
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REGISTRATION OF 3D MRI BONE MODELS ON 2D FLUOROSCOPY IMAGES OF THE KNEE JOINT: TOWARDS CLINICAL PRACTICE

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Sebastiaan Koninkx

Student number : 5116198

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Erasmus MC

Dept. of Radiology & Nuclear Medicine,
Erasmus MC

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Supervisor(s):

Dr. Rianne van der Heijden

Dr. Wouter Schallig

Dr. Jukka Hirvasniemi

Niels Dur

Thesis committee members:

Dr. ir. Bart Kaptein, LUMC (chair)

Dr. Rianne van der Heijden, Erasmus MC

Dr. Wouter Schallig, Erasmus MC

Dr. Jukka Hirvasniemi, Erasmus MC & TUD

Niels Dur, Erasmus MC

An electronic version of this thesis is available at <http://repository.tudelft.nl/>

Preface

My seven years at university come to an end with this Master thesis project at the Erasmus MC. First, I would like to thank Mariska Wesseling for giving me the opportunity to conduct my thesis project at the MOBI-lab. After a very pleasant experience during an earlier internship, I was excited to return to the Orthopedics department and continue my collaboration with her. When Mariska had to step down from the project, Wouter Schallig was thankfully willing to take her place as technical supervisor. I really appreciate his efforts throughout the project, even though parts of the project maybe were not exactly up his ally. I would also like to thank Jukka Hirvasniemi for stepping up as additional technical supervisor and providing the technical insights we thought were missing in our supervisory team. His efforts in data processing, i.e. providing automated segmentations of both 3D MRI bone models and fluoroscopic images, did not go unnoticed, which was a big part of this thesis project.

I am grateful that Rianne van der Heijden was willing to act as medical supervisor throughout my time at the Erasmus MC. I can imagine that it was not necessarily easy to oversee the clinical side of my project as we were operating on the intersection of radiology and orthopedics and I spent a lot of time at the orthopedics department. Nonetheless, Rianne provided me with valuable advice on how to present myself in clinic and how to reach my clinical goals. Last but not least, I want to thank Niels Dur for being my daily supervisor, from the first online meeting we had with Mariska over a year ago to present times. From fixing me a spot at the operating table to walking me through the code of previous students or providing manual segmentation to train the automated segmentation algorithm. Niels helped me a lot on both the technical and medical side of the project and was very easy to approach (pretty much 24/7). An honorable mention goes out to all the students at the MOBI-lab. We bonded quite quickly and every now and then we managed to unwind together from our research struggles.

Sebastiaan Koninkx
Rotterdam, October 2026

Abstract

Introduction: Osteoarthritis (OA) mainly affects weight-bearing joints such as the knee. The exact pathomechanics of OA remain a major focus of research, with the aim to slow down progression or prevent the development of OA altogether. By accurately characterizing knee kinematics during functional activities, mechanical factors contributing to the progression and onset of knee OA can be identified. Knee kinematics are obtained by registering a three-dimensional (3D) bone model derived from magnetic resonance imaging (MRI) to two dimensional (2D) fluoroscopic images, a process that relies on accurate bone segmentation. Automated segmentation is a promising way to reduce the workload of manual segmentation. This thesis evaluated what impact the variability in automated segmentation of the femur and tibia on monoplane fluoroscopy has on 3D-2D registration accuracy and knee kinematics.

Methods: A dataset consisting of a double-echo steady-state MRI sequence and 78 fluoroscopy images of one healthy subject. A nnU-net was trained to automatically segment the fluoroscopic images. One automated segmentation was selected as reference and visually checked for correctness. 14 typically occurring segmentation errors were identified based on visual inspection of the automated segmentations and applied as variant segmentations. 3D-2D registration was performed with the reference and variant segmentations. A descriptive analysis was carried out to compare reference and variant segmentations.

Results: Overall, typically occurring segmentation errors in automatic registration resulted in a submillimeter and subdegree error in registration and subdegree error in knee kinematics rotations compared to the reference segmentations. Larger errors existed for dilated, eroded, out-of-frame and altered tibial joint contour variants, especially for the out-of-plane direction (5.64 mm) and two rotational axes (2.71°). Kinematic translations showed larger errors across all variants with errors up to 11.10 mm in anterior/posterior direction.

Conclusion: Small, typical inaccuracies in automated femur and tibia segmentations in monoplane fluoroscopy do not have a substantial impact on the registration accuracy and knee kinematics. However, errors that omit (out-of-frame) or misrepresent (tibial joint contour) distinct bone contours can cause larger errors. In addition, caution should be exercised with the exact delineation, i.e. erosion or dilation, of bone contours. Future research should focus on evaluating the generalizability of the findings from this thesis and improving the registration accuracy in general.

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Abbreviations

Abbreviation	Definition
OA	Osteoarthritis
OMC	Optical motion capture
3D	Three-dimensional
2D	Two-dimensional
CT	Computed tomography
MRI	Magnetic resonance imaging
DRR	Digitally reconstructed radiograph
MOBI	Motion biomechanics & imaging
EMC	Erasmus Medical Center
DESS	Double-echo steady-state
LAVA	Liver acquisition volume acceleration
COM	Center of mass
ACS	Anatomical coordinate system
ML	Medial-lateral
AP	Anterior-posterior
PD	Proximal-distal
DoF	Degrees of freedom
MAE	Median absolute error
IQR	Interquartile range

1. Introduction

1.1. Osteoarthritis

1.1.1. Epidemiology and etiology

Arthritis is one of the most common chronic diseases and continues to be the leading cause of disability among adults (1-3). Osteoarthritis (OA), the most prevalent form of arthritis, is a joint disease, mainly affecting weight-bearing joints (4-6). OA is reported to affect about 3.3 to 4.6% of the population globally, with percentages going up as high as 30.4% for people aged 55 years and older (4, 6-8). Worldwide estimates of people suffering from OA are ranging from 250 to 654 million people (7, 9-11). Knee OA remains the most frequently affected joint site, accounting for almost four fifths of the burden of OA (9, 12, 13).

To a large extent, OA is a disease associated with older age. The proportion of adults aged 65 years or older is expected to increase at least 7% by 2030 (14). Other risk factors for developing OA include the female gender, obesity, genetics, muscle weakness and joint injury (4, 6, 7). According to data from the World Health Organization, the incidence of obesity has more than doubled in adults and tripled in adolescents worldwide since 1990 (10). Hence, the prevalence of OA increased significantly over the last decades and continues to rise. Currently, the total costs attributable to arthritis are approximately \$128 billion on a yearly basis, which is equivalent to 1.2% of the U.S. gross domestic product (1). In the next 30 years, the epidemiological trends highlight the growing burden of OA on an individual and global scale, putting pressure on healthcare systems (10, 15).

1.1.2. Clinical symptoms

OA is a disease of the whole joint (4). The cause is a combination of the risk factors mentioned above, mechanical stress and abnormal joint mechanics, leading to pro-inflammatory markers that eventually mediate joint destruction (16). The pathologic changes seen in joints affected by OA include degradation of articular cartilage, thickening of subchondral bone, osteophyte formation, synovial inflammation and degradation of ligaments (5, 17). Patients with OA experience pain as the most disabling symptom in their daily life (11). Other characteristic symptoms are reduced range of motion, morning stiffness, joint instability and swelling (18, 19). However, only 60% of people with radiographic evidence of OA has symptoms (4, 11). In other words, radiographic findings do not necessarily correlate to the severity of the disease.

1.1.3. Diagnosis and management

The clinical diagnosis of OA is made if the patient has symptoms related to OA. The characteristics of OA can be defined clinically, radiographically or pathologically. Criteria for classifying knee OA include less than 30 minutes of morning stiffness, the definite presence of osteophytes on plain radiographs and OA-specific synovial fluid findings (20). Knee OA starts with a gradual and subtle onset, characterized by vague knee pain that worsens when bearing weight (18). During the early stages, prolonged asymptomatic periods may be accompanied by short periods of increased pain. In advanced stages of OA, pain may become constant, even at rest. However, relying on symptoms to identify OA has limitations. Radiographic OA is often asymptomatic, and, conversely, some patients with knee pain show no radiographic abnormalities. Moreover, patients often seek care only once symptoms become persistent, by which time structural damage may already be advanced and largely irreversible (17, 18).

Most currently available treatments such as corticosteroids and lifestyle changes primarily target symptom management (21, 22). No treatment has been able to reverse or halt OA progression. In advanced stages of OA, joint replacement is the most effective treatment for relieving pain and improving quality of life (22, 23). Nonetheless, functional outcomes can be poor and the lifespan of prostheses is limited (17). Arthroplasty is also responsible for the substantial health costs of arthritis (24). Therefore, the research focus has shifted to an improved understanding of disease pathogenesis (17, 25). The goal is to identify modifiable risk factors that can slow down progression at an early stage or even prevent the development of OA altogether. Studies focus on providing preventive strategies that focus on lifestyle and dietary modifications (7, 11, 17, 25, 26). In addition, researchers have attempted to evaluate the role of biomechanics in the onset and progression of OA (27, 28).

1.2. Gait analysis

Abnormal loading of the joint has been identified as a contributor to the onset and progression of OA (28). Abnormal loading patterns can instigate and/or accelerate cartilage degeneration by increasing localized stress on joint surfaces. It is also believed that abnormal loading activates subchondral bone remodeling, which can alter load distribution across the joint and further promote cartilage damage (29, 30). The exact pathomechanics of OA, however, remain a major focus of research. Understanding the biomechanical behavior of the knee, being the most frequently affected joint, during functional activities is crucial for both researchers and clinicians. Daily activities experienced as problematic include heavy housework, kneeling down, climbing stairs and walking (31, 32). Given the high prevalence of difficulty walking and its substantial impact on daily life, identifying contributing factors is clinically important. Gait analysis has proven useful in identifying kinematic characteristics in people with knee OA (27, 33-37). Knee kinematics describe motion, expressed in joint angles and translations, without reference to the forces causing it (kinetics). Studies report on reduced knee flexion, increased adduction and internal rotation in patients with varying severities of OA (33-37). By accurately characterizing knee kinematics during functional activities, mechanical factors contributing to the progression and onset of knee OA can be identified and targeted preventive strategies can be developed, such as strength training and gait retraining (38).

1.2.1. Optical motion capture

The most common way of measuring knee kinematics is by means of an optical motion capture (OMC) system. These systems use multiple synchronized, high-speed cameras emitting and detecting infrared light. The cameras, positioned around the subject, can track the three-dimensional (3D) position of reflective markers attached to the skin of the subject. The markers are placed on specific bony landmarks across the limbs and upper body of the subject. The precise position and orientation of the bones can be derived, allowing for the reconstruction of knee kinematics (39). Although OMC systems provide high temporal resolution, their accuracy in quantifying knee kinematics is limited by soft tissue artifacts (STAs) (40). An STA is known as the movement of the skin markers relative to the underlying bone. The movement causes a discrepancy between the measured position of the skin marker and the true position of the bony landmark it was supposed to represent. STAs can be a substantial source of error when calculating knee kinematics, especially in obese individuals. Reported errors are up to 31 mm for skin marker trajectories and 9° for knee joint rotations (41, 42). The accuracy limitation is particularly relevant, as obesity is an important risk factor for developing knee OA. To overcome the influence of STAs, a technique is required that can directly visualize the underlying bone.

1.2.2. Fluoroscopy

Fluoroscopy is a medical imaging technique that uses low dose radiation to produce real-time images of anatomical structures. It does so by passing X-rays through the body and recording the attenuated radiation on a detector positioned on the opposite side of the body. This produces a series of two-dimensional (2D) images over time (Figure 1). Fluoroscopy can be performed using either a monoplanar or biplanar setup. In a monoplanar setup, images are acquired from a single direction. 3D anatomy is projected on a single 2D image plane, a process in which out-of-plane information is lost. Monoplanar fluoroscopy therefore suffers from depth-related ambiguity, as out-of-plane motion produces only subtle changes in the 2D image and is more challenging to estimate. In contrast, biplanar fluoroscopy simultaneously acquires images from two different directions. The additional information can partially resolve the depth-related ambiguities. Whereas OMC is limited by soft tissue artifacts, fluoroscopy can directly visualize the movement of bones due to high contrast between bone and surrounding soft tissue. Fluoroscopy is therefore particularly valuable for applications requiring precise knee kinematics, such as subtle kinematic changes potentially playing a role in the onset of OA.



Figure 1: Series of fluoroscopic images visualizing a part of the gait cycle.

1.2.3. 3D-2D Registration

To obtain knee kinematics, a 3D bone geometry model is registered to the 2D fluoroscopy projection images (Figure 2). The 3D geometry model is a representation of the 3D bone shape, derived from the bone segmentation of a 3D modality, such as computed tomography (CT) or magnetic resonance imaging (MRI). In general, 3D to 2D registration seeks to determine the 3D pose of the bone that best fits the 2D pose depicted in the fluoroscopic image. This requires the 3D geometry to be projected along a 2D imaging plane, such that the resulting projection can be compared with the 2D fluoroscopic image. The basic principle of 3D-2D registration involves generating a synthetic X-ray image of a 3D bone model, i.e. a digitally reconstructed radiograph (DRR). A DRR simulates the projection of a bone for a given pose as if it were a fluoroscopic image. The pose of the 3D bone model is iteratively adjusted and a new DRR is generated each time until the correspondence between the fluoroscopic image and the DRR is satisfactory (43). At the end of this process, the pose of the 3D bone model is assumed to correspond to the true in-vivo pose of the imaged bone.

CT is considered the gold standard to obtain the 3D bone geometries, because of its high geometric accuracy and similar tissue contrast compared to fluoroscopy (43). MRI is considered an alternative, which does not expose subjects to radiation and provides the ability to add soft tissues to the models. However, MRI suffers from lower bone contrast and spatial distortions. Additionally, MRI has fundamental differences in imaging physics compared to fluoroscopy in which MRI voxel intensities do not correspond to X-ray attenuation values (43). Therefore, 3D-2D registration of MRI with fluoroscopy remains challenging.

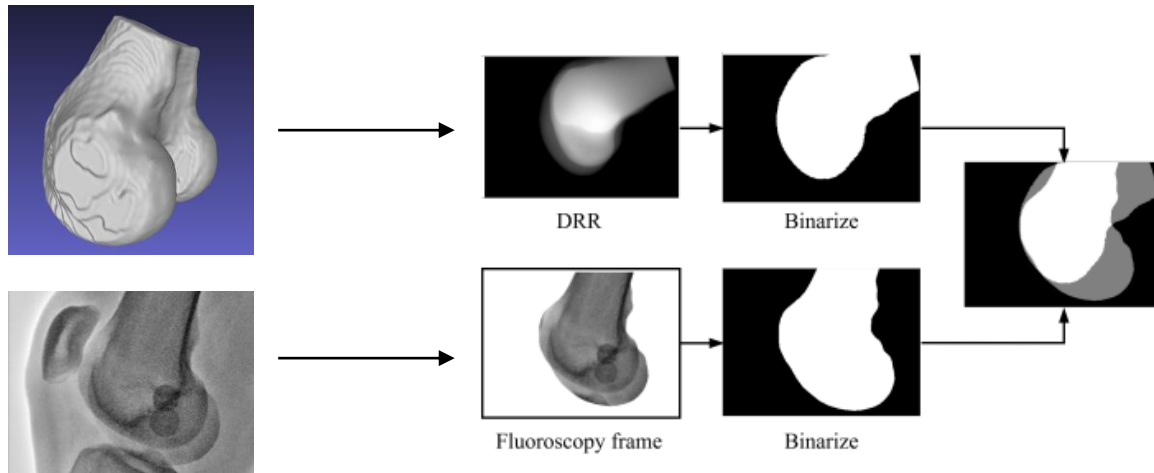


Figure 2: Contour-based pipeline of 3D-2D registration. A 2D projection of the 3D bone geometry model is created in the form of a synthetic X-ray image (DRR). The DRR is then compared to the segmented fluoroscopy image and iteratively adjusted until a satisfactory match is found. The image on the right shows the matched pixels in white and mismatched pixels in grey. DRR = Digitally Reconstructed Radiograph. Adapted from (44).

Typically, two categories of measures are used to evaluate the resemblance between the fluoroscopic image and the generated DRR. Intensity-based measures directly compare pixel intensities or distributions between two images. Intensity-based measures therefore heavily rely on the two images having corresponding intensity values. In fluoroscopy, signal intensity reflects the cumulative X-ray attenuation along each ray. In MRI, signal intensity instead depends on proton density and tissue relaxation times. As a result, MRI intensities do not map onto attenuation-based fluoroscopic intensities, leading to mismatched intensity values (43). Feature-based measures, on the other hand, focus on comparing specific image features, such as anatomical landmarks or bone contours. Consequently, the pipeline within our research group was built on a feature-based approach, only relying on identifying and matching bone contours.

Exploratory research from our research group has since focused developing a contour-based 3D-2D registration pipeline. An important step before registration is the accurate bone segmentation of the fluoroscopic images, since the registration purely relies on the contour of the bones. Other image features and intensity values are disregarded. Segmentation of the bones is challenging due to the complex structure of the knee in x-ray images. Images may be contaminated by noise, insufficient contrast and/or resolution and motion blur during dynamic studies, such that the contours of the bones become indistinct (Figure 3a). Interpatient bone shape, size, and variations in deformation, such as osteophytes, add complexity to bone contour identification. Moreover, the loss of bone contours may occur from overlapping neighboring bones and surrounding soft tissue (Figure 3b) (45, 46). Manual and automatic methods for segmentation result in contours that can vary significantly (47). It is argued that both manual and automatic segmentation methods can produce errors in the location of the 2D bone contours and in the resulting 3D pose. An additional drawback of manual segmentation is that it is extremely labor intensive. Hence, the goal is to use an automatic segmentation tool moving forward and assess the accuracy and downstream impact on our outcome measures.

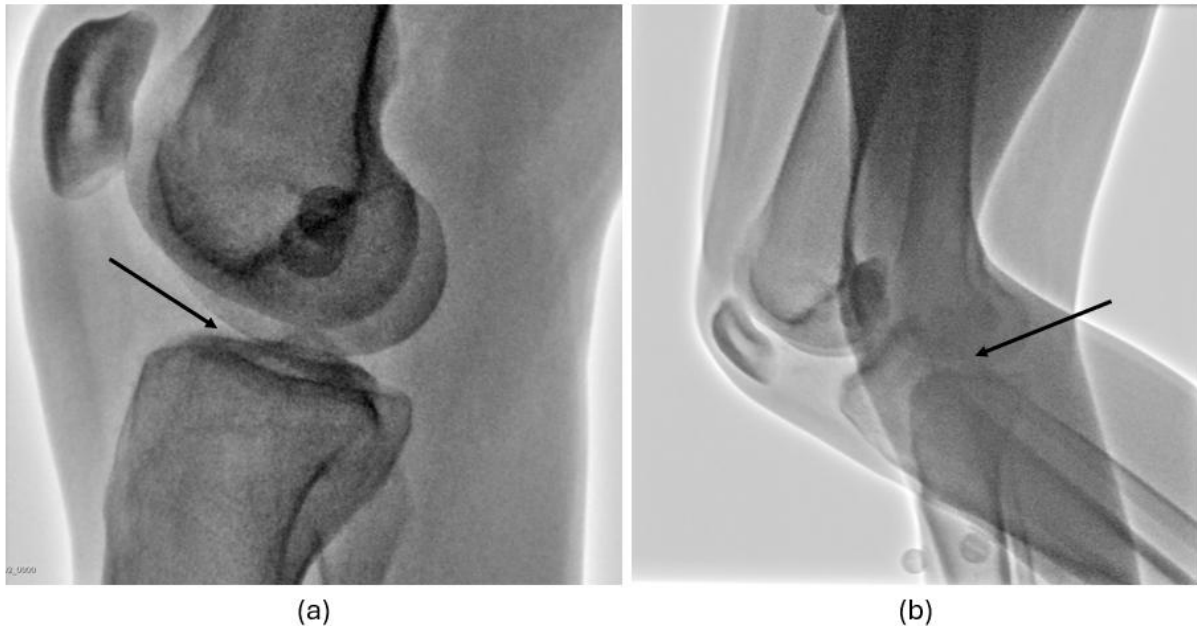


Figure 3: Two examples of fluoroscopic images with indistinct bone contours, either due to a) complex geometry in the joint space, especially the tibial contour or b) overlapping bones.

1.3. Research Question

This thesis aimed to answer the following research question:

What impact does the variability in automated segmentation of the femur and tibia on monoplanar fluoroscopic images have on the 3D-2D registration accuracy and knee kinematics?

2. Methods

2.1. Image acquisition and analysis

In order to perform large scale clinical research into the pathogenesis and biomechanics of OA, the Motion Biomechanics & Imaging (MOBI) lab has been established, a collaboration between the Erasmus Medical Center (EMC) and the Technical University of Delft (48). The lab, located in the EMC, is equipped with an OMC system, a monoplanar fluoroscope and a treadmill.

A dataset consisting of two MRI sequences and 78 fluoroscopy scans from one healthy subject from the MOBI-trial was available for this study. The primary MRI sequence was a high resolution double-echo steady-state (DESS) sequence acquired on a 3.0T GE SIGNA PET/MRI scanner. The field of view was represented by $512 \times 512 \times 340$ voxels with a corresponding voxel size of $0.625 \text{ mm} \times 0.625 \text{ mm} \times 0.500 \text{ mm}$ in the sagittal plane. The DESS was made with a flexible coil around the knee joint, containing approximately 81 mm of the distal femur and 85 mm of the proximal tibia. The DESS was segmented by a collaborating research group, using a deep learning-based segmentation nnU-Net (49). This process produced binary masks for the femur and tibia, isolating the bone structures from surrounding soft tissues and background (Figure 4). The second MRI sequence was Liver Acquisition Volume Acceleration (LAVA-flex), a rapid, fat-suppressed gradient-echo pulse sequence. The LAVA-flex contained $512 \times 512 \times 952$ voxels (voxel size of $0.977 \text{ mm} \times 0.977 \text{ mm} \times 1.500 \text{ mm}$) per bed position, with bed positions covering the whole leg. This was used in case a larger part of the femur and tibia bones was needed for the further development of the pipeline. The 78 fluoroscopic images were acquired from the same healthy participant as the MRI-scan, using a Canon Adora DFRi system. Pulsed fluoroscopic images were recorded at a frame rate of 15 frames per second during a walking task. The flat-panel detector measured $424 \times 414 \text{ mm}$ and consisted of square pixels with an image resolution of 1328×1296 pixels. The image series visualized the participant walking from a sagittal point of view (Figure 1).

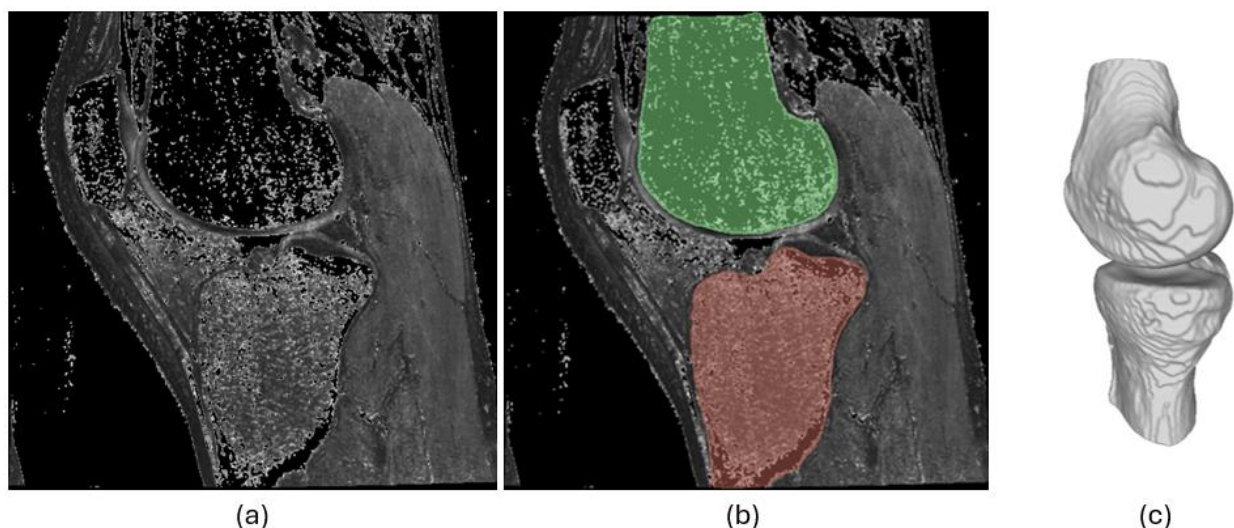


Figure 4: a) A sagittal DESS image from the MOBI-trial, b) The same sagittal DESS image with femur (green) and tibia (red) segmentations, c) The three-dimensional geometry bone model derived from the DESS. DESS = Double-Echo Steady-State sequence

2.2. Registration pipeline

The registration pipeline described in this chapter was available at the start of this project. As briefly mentioned in the introduction, a 3D-2D registration pipeline was built within our research group (Figure 5). The automated registration script requires a segmented MRI bone model, a manual initial pose and a segmentation of the fluoroscopic image. The available pipeline included a tool to provide a manual initial pose for the registration algorithm. At the start of this project, automated registration was only tested on cropped fluoroscopic images of individual bones, i.e. either femur or tibia.

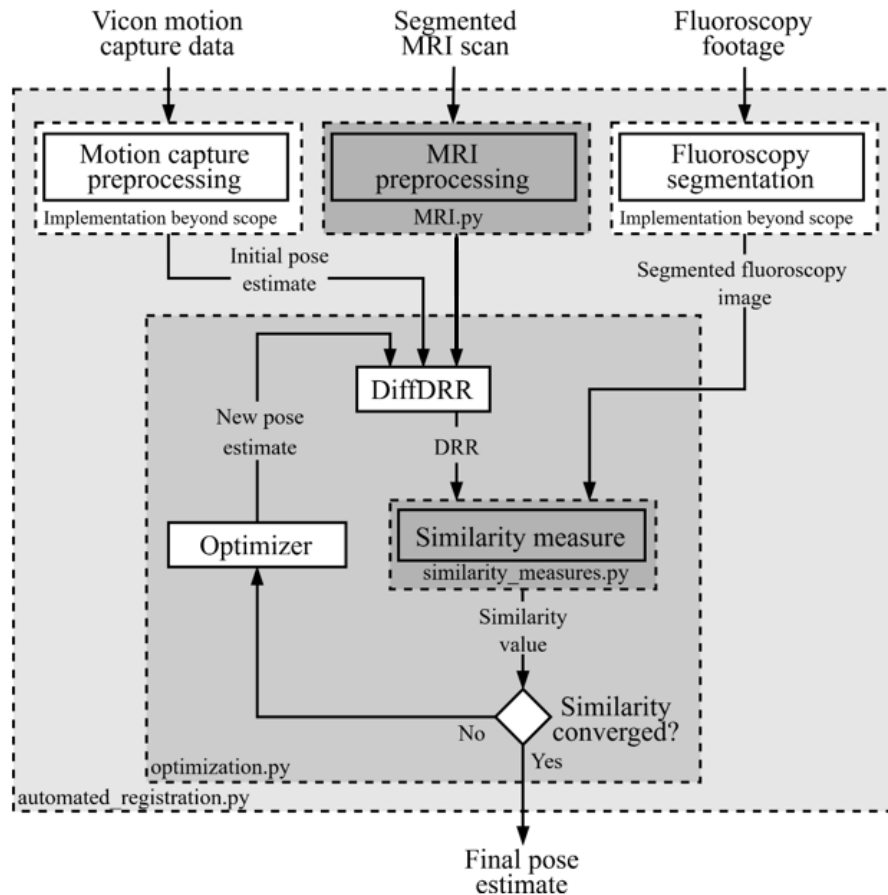


Figure 5: Full registration pipeline (44). The dashed white blocks were beyond the scope of previous research from our research group. The optimizer and DiffDRR are existing open source software libraries.

2.2.1. MRI preprocessing and DRR formation

To prepare the segmented MRI bone models for use in the registration pipeline, the solid bone model as shown in Figure 4b was turned into a hollow shell. This preprocessing step enhanced visibility of the interior bony features (Figure 6), which was highly valuable for initial pose estimation, as described in Chapter 2.2.2. For example, interior features of the femur include intercondylar fossa, lateral and medial femoral epicondyles. The DiffDRR Python library was selected to generate DRR's during the optimization process (50). The primary advantage of DiffDRR's implementation is its computational efficiency. In addition, DiffDRR integrates smoothly with existing Python-based tools for image processing and optimization.

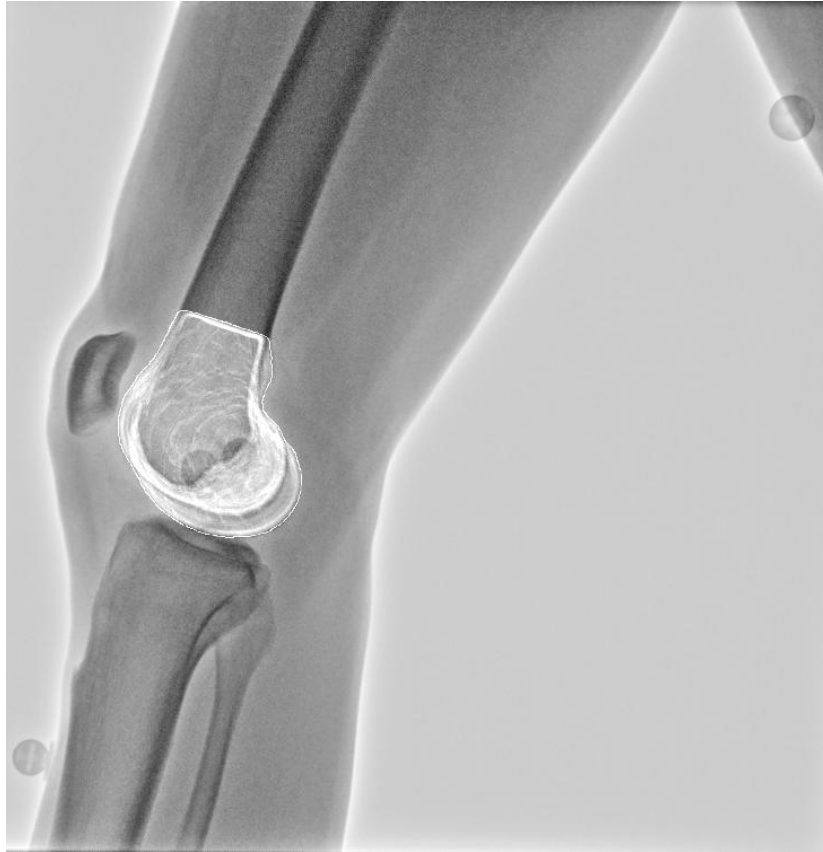


Figure 6: A visualization of the manual pose estimation. The pose of the DRR can be adjusted in six degrees of freedom. In this image, the hollowed-out DRR of the DESS bone model (white contour) is registered to a full fluoroscopic image from the MOBI-trial. The hollow shell enables the visualization of interior features such as intercondylar fossa, lateral and medial femoral epicondyles.

DRR = Digitally Reconstructed Radiograph; DESS = Double-Echo Steady-State sequence

2.2.2. Registration

Registration was performed based on the shape matching similarity measure. Shape matching tries to minimize the symmetric differences between the contour of the DRR and the fluoroscopic image. The symmetric difference is the amount of pixels that is part of the contour of either the DRR or the fluoroscopic image, but not both (grey area in the far right image of Figure 1). The main advantage of shape matching compared to other contour-based measures was its computational efficiency. Powell's method was used to maximize the image similarity (51). Powell's method is an optimization algorithm that iteratively refines a set of directions along which to perform line minimizations. It is well suited for problems, in which the intensity gradient information is unreliable, as is the case in MRI-based 3D-2D registration.

The optimizer of the automated registration requires an initial pose estimation. The initial pose was estimated by manually registering the DRR to the fluoroscopic image using the tool created by a previous student (44). To facilitate direct comparison between the manual and automated registration, the manual registration tool utilized the same render engine as the automated registration pipeline.

2.3. Registration pipeline extension

The automated registration pipeline, as described in Chapter 2.2., was tailored to individual bones and cropped fluoroscopic images. This means that either the femur or tibia could be registered on a cropped version of the 1328 x 1296 fluoroscopy pixels. This was done to only include the part of the bones on the fluoroscopic images that was also covered by the DESS. One of the aims of this project was to further develop this pipeline and derive six degrees of freedom (DoF) knee kinematics from the estimated pose and orientation of the femur and tibia.

Calculating knee kinematics requires the femur and tibia to be in an anatomically correct position relative to each other. Directly applying the pose estimates obtained from the 3D-2D registration to the 3D MRI bone models of the tibia and femur would put the bones in a random position in 3D space (Figure 7a). First, a method was developed to put the tibia and femur in the anatomically correct position relative to each other and ensure correct alignment within the voxel space. The first step was a ‘center bone to voxel space’ correction, i.e. moving the bone so that the center of mass (COM) aligns with the center of the 3D voxel space. When rendering the DRRs, rotations are applied around the center of the voxel space, rather than around the centroid of the segmented structure. If the bone is not centered, rotational adjustments will inadvertently introduce large translations, degrading registration performance. To mitigate this, the centroid of the bone was automatically aligned with the center of the voxel space. This alignment ensured that subsequent rotations during DRR generation would preserve the position of the bone within the fluoroscopic frame. Center bone to voxel space was applied in both manual and automated registration and therefore had to be corrected for. A number of additional translation and rotation adjustments were needed to correctly align both bones relative to each other (Figure 7b).

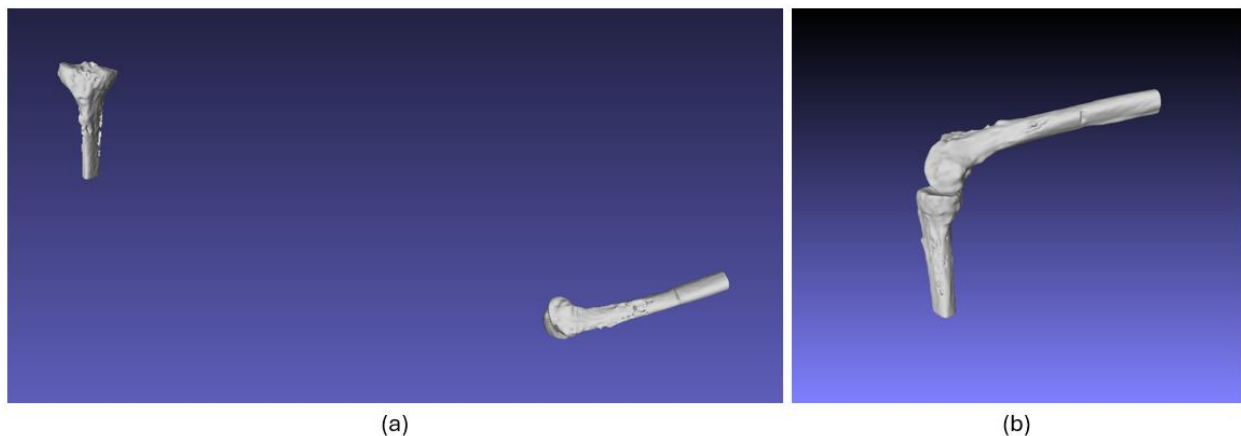


Figure 7: To illustrate with 3D MRI (LAVA) bone models, a) Directly applying the final registration pose versus b) Creating a custom method to go from the final registration pose to an anatomically correct pose relative to the other bone. LAVA was used at this stage of the pipeline development. The rationale is given in Chapter 2.4.2. LAVA = Liver Acquisition Volume Acceleration.

The full fluoroscopy image provides the registration algorithm with more potentially valuable information to achieve accurate registrations compared to a cropped version of it. However, the optimizer computes the similarity measure for every pixel in the fluoroscopy segmentation, causing significantly increased runtimes. After confirming that cropping the fluoroscopy segmentation still resulted in correct relative bone positions, automated cropping was introduced. The maximum and minimum pixel coordinates of the segmentation were determined along both the horizontal and vertical axes, with an additional padding of 50 pixels

applied to each boundary (Figure 8a). To correct for the shift of the image center between the full and cropped fluoroscopy images, the offset between their middle pixels was passed to the DRR renderer, ensuring alignment of the DRR with the fluoroscopy segmentation (Figure 8b+c).

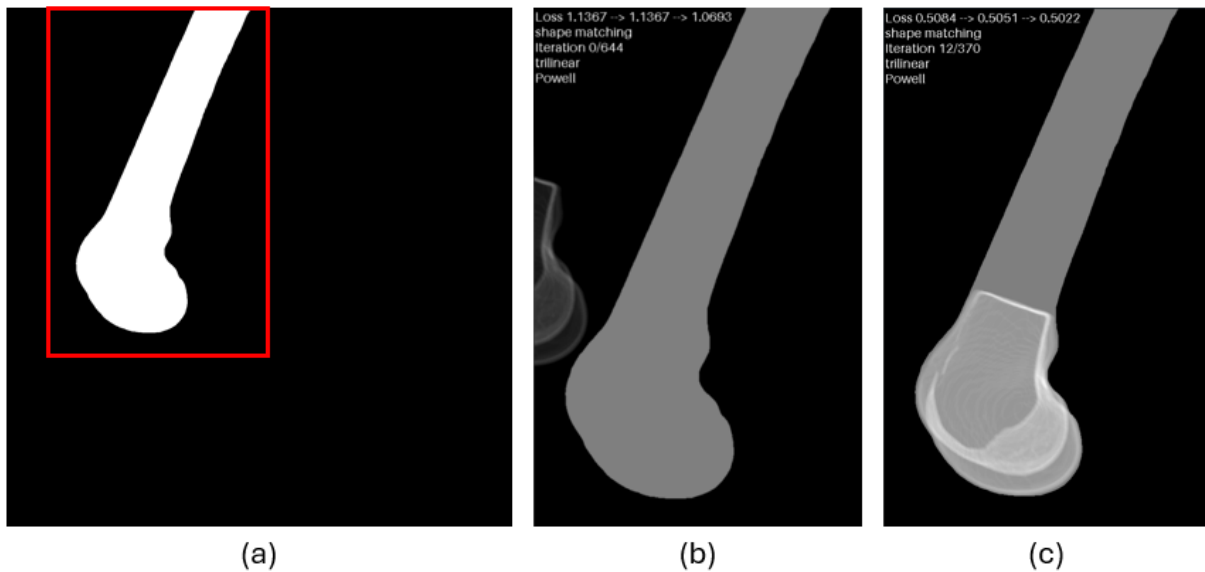


Figure 8: a) Proposed automated cropping of segmented region with padding, b) Registration before correcting for cropping offset, c) Registration after correcting for cropping offset

2.4. Anatomical coordinate systems

2.4.1. Open-source method

In order to compute knee kinematics from the corrected final position and orientation of the femur and tibia, the motion of each bone must first be expressed relative to a consistent anatomical reference frame. Anatomical coordinate systems (ACS) provide this reference by defining an origin and clinically and anatomically meaningful axes for each bone, allowing the relative position and orientation of the femur and tibia to be quantified and subsequently used to derive knee kinematics. Therefore, a method was implemented to calculate ACSs for both bones. This method was originally created by Miranda et al. (52) and adapted by Chen et al. (53). The method is suited for automation and is reasonably insensitive to anatomical variability (54).

The coordinate systems consist of three orthogonal axes: the medial-lateral (ML) axis, the anterior-posterior (AP) axis and the proximal-distal (PD) axis. The method computes the femoral ACS from the articular surfaces of the femoral condyles.

1. First, the inertial axes of the femur were calculated (Figure 9a).
2. Axial cross-sections were determined along the femur's length. Three locations were identified along the femur: (1) the maximum cross-sectional area; (2) half the maximum cross-sectional area; (3) 30% farther from the distal end of the femur than the second location (Figure 9b). The femoral diaphysis was isolated with a plane oriented using the femur's inertial axis and positioned at the third location.
3. The inertial axes of the femoral diaphysis were computed. Point 1 (pt_1) was determined by extending a vector distally until it intersected with the femoral cortex (Figure 9c).
4. Point 2 (pt_2) was established using the same axial cross-sections. A plane at the second axial location was oriented using the femur's inertial axes. pt_2 was determined by

extending the femur's inertial axis pointing in the anterior–posterior (AP) direction through the posterior femur (Figure 9d).

5. The femoral condyles were isolated by cutting with a plane perpendicular to the pt_1 - pt_2 vector (Figure 9e).
 6. A cylinder was fit to the condyles using a Matlab-based Gauss–Newton algorithm. The adapted method used two cylinders, one for the medial and lateral condyles separately (Figure 9f). This allowed for asymmetry among the condyles and restricted the fit to the mechanically relevant articular surfaces (55). The articular surface centers (COM of the faces) were computed and projected on their respective cylinder axis. A line going through both points defined the ML axis.
 7. The femoral ACSs secondary axis (AP) was calculated by crossing the vector through the diaphysis with the ML axis.
 8. The femoral ACSs third axis (PD) was calculated by re-crossing the AP and ML axes.
- Finally, the origin of the femoral ACS was defined as the middle of the two points used to define the ML axis.

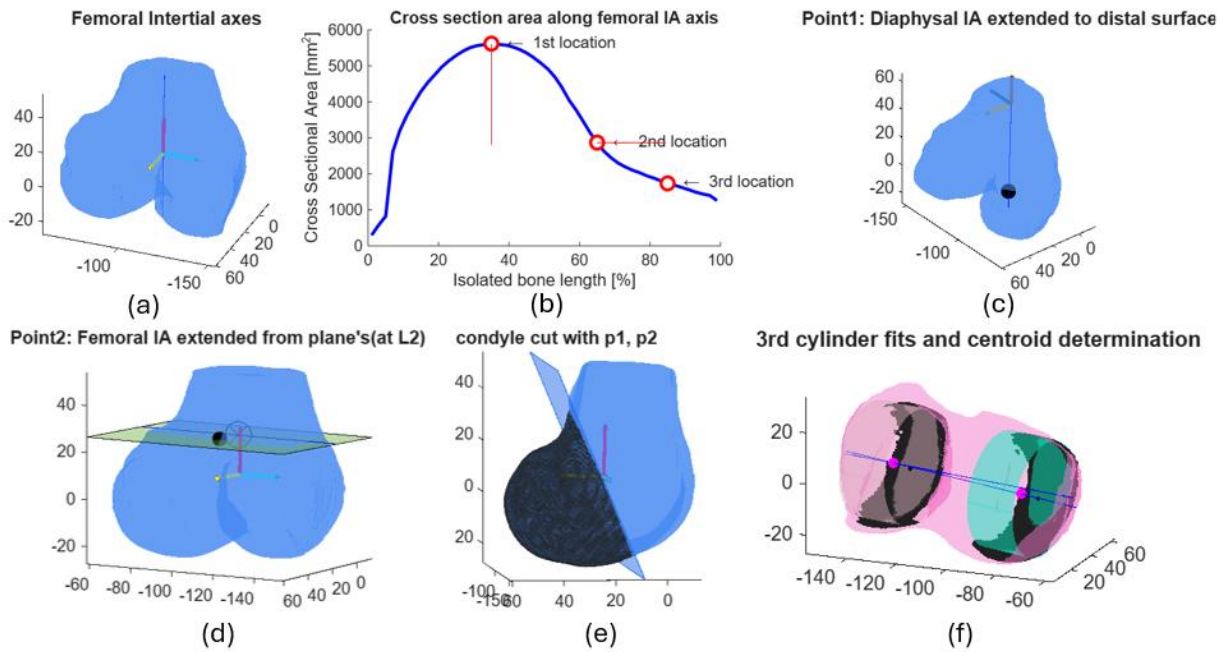


Figure 9: a) Inertial axes (IA) of the whole femur, b) Axial cross sections of the femur, c) Point 1 was determined by extending the long, red axis distally to the edge of the femur, d) Point 2 was determined by extending the AP axis posteriorly at the 2nd cross sectional location to the edge of the femur, e) The condyles were cut by connecting the two points, f) Two cylinders were separately fitted to the two femur condyles.

The determination of the tibial ACS was not altered in the adapted method. The articular surface of the tibial plateau was used to define the ML, AP, and PD axes of the tibial ACS.

1. First, the inertial axes of the tibia were calculated (Figure 10a).
2. A plane oriented using the inertial axes of the tibia and positioned at the largest cross-sectional area was used to isolate the tibial plateau (Figure 10b+c).
3. The inertial axes of only the plateau were designated as the ML, AP, and PD axes of the tibial ACS (Figure 10d). The origin of the tibial ACS was positioned at the plateau's COM.

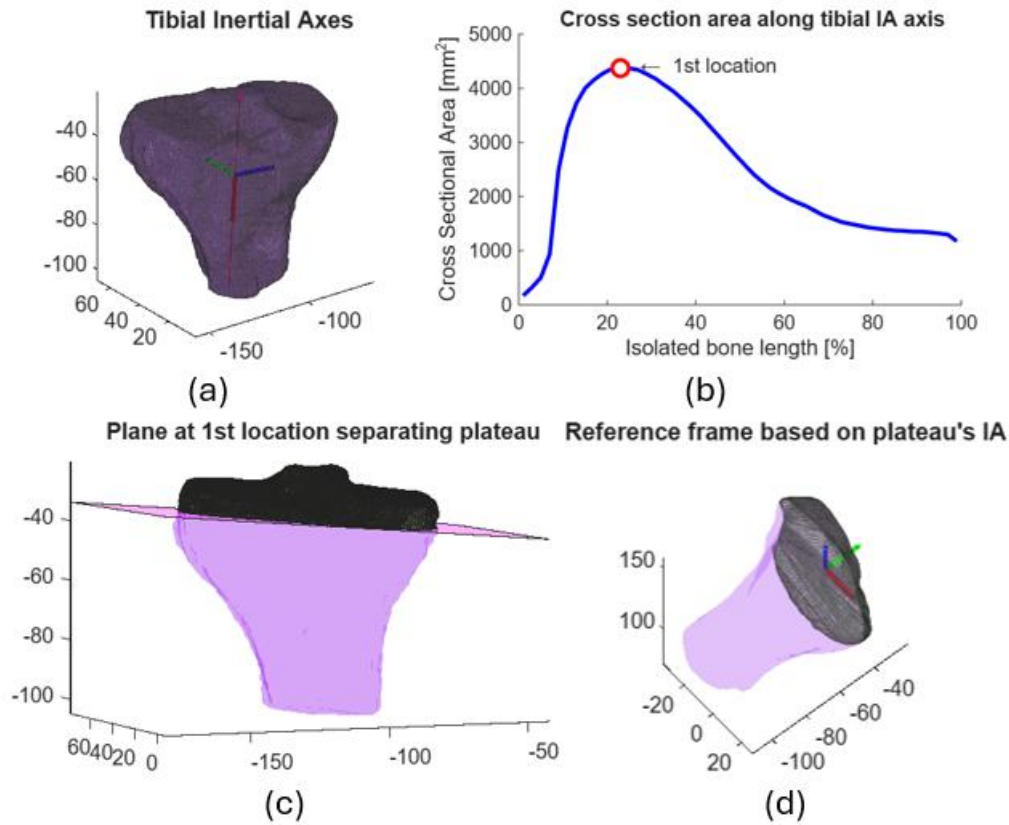


Figure 10: a) Inertial axes (IA) of the whole tibia, b) Axial cross sections of the femur, c) Tibia plateau cut, d) Inertial axes of tibial plateau.

2.4.2. Manual adjustment

As described in chapter 2.1, the DESS was intended to serve as input for the 3D bone model. However, the ACS method had one major limitation as described by the creators: “For instance, too short diaphysis causes the method to crash”. An adjustment to the code was required in order to use the method and get plausible results. Researcher from the Cardiff University came up with an additional manual step to the original method by Miranda et al. (52). Their code took a user click and isolated the 'top surface' of the femur by using the clicked point to define the proximal direction, then calculating the geometric center of all the points within a given range from the most proximal point on the bone. The proximal-distal axis is then defined as the line between the calculated geometric center and the centroid of the entire bone model.

Their method was also faced with limitations. The proximal-distal axis was highly dependent on the centroid of the bone model. In the case of a very short or absent diaphysis, the femur's COM was located more posteriorly due to the condyles (Figure 11a). The tibial centroid also resulted in skewed axes (Figure 11c). Therefore, the manual method had to be altered and then adapted to Chen et al.'s method (53). The final method also selected all the points within a given range, after which a plane was fitted through these points. For the femur, this plane was then used to create the axis perpendicular to the plane. For the tibia, the orientation of the plane was used to select a range of points and calculate the centroids of the cross sectional areas within this range. The proximal-distal axis was then calculated by fitting a line through these centroids. The final method was created and validated based on visual inspection. ACSs were visually compared to the ACSs of the LAVA computed using the method described in Chapter 2.4.1. (Figure 11e).

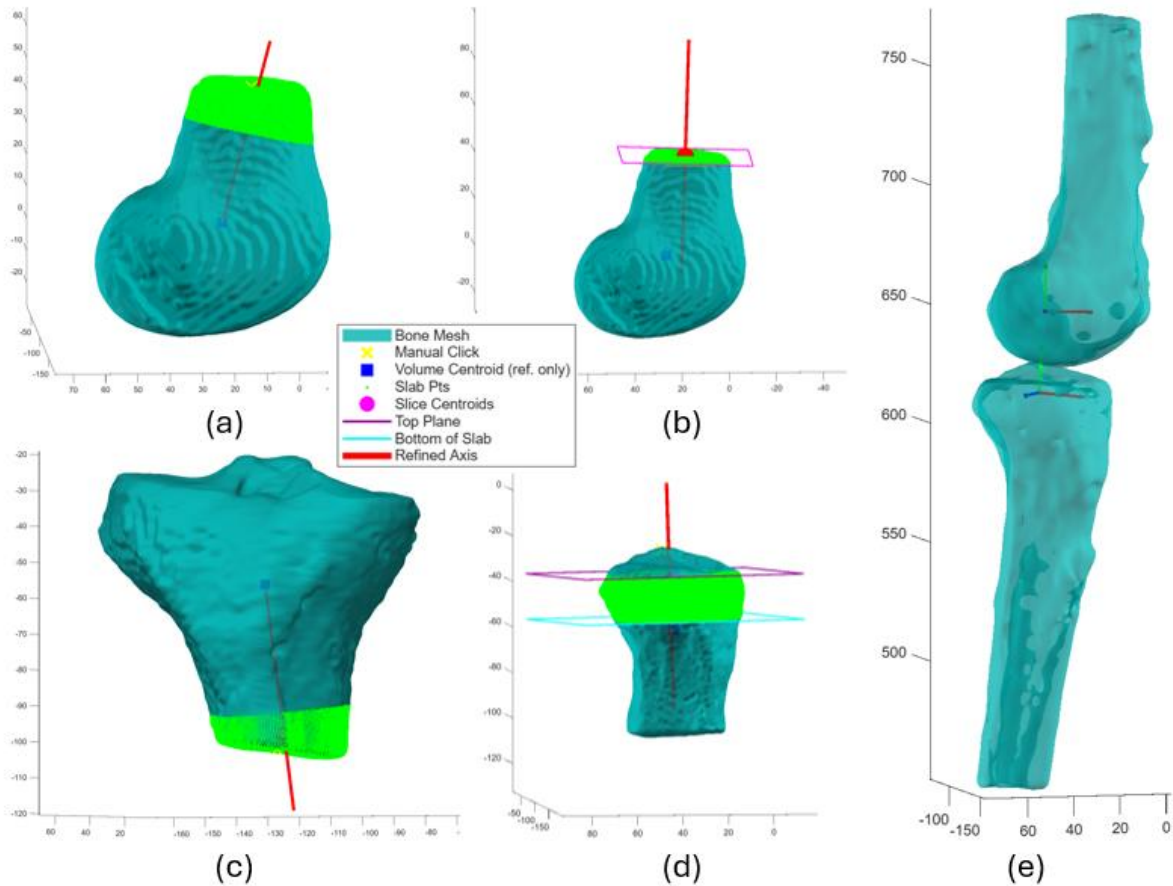


Figure 11: a) Cardiff's fix of femoral inertial axes, b) Adapted fix of femoral inertial axis, c) Cardiff's fix of tibial inertial axes, d) Adapted fix of tibial inertial axis, e) The anatomical coordinate systems of the LAVA computed using the method described in Chapter 2.4.1. LAVA = Liver Acquisition Volume Acceleration

The extended registration pipeline is visualized in Figure 12. Additions are shown in red.

- The 3D MRI bone model was moved in order to align the model's COM with the center of voxel space.
- Fluoroscopic images were segmented and cropped automatically, which will be explained in Chapter 2.5.
- A method was implemented to compute ACSs for the tibia and femur. A manual step was added to enable ACS computation for the DESS.
- Knee kinematics ('static') were computed for the 3D MRI bone model using Cardan angle decomposition of rotation matrices (56). The orientation of the 3D bone is stored in one rotation matrix. Cardan decomposition breaks the matrix down into three sequential rotations, i.e. flexion/extension, abduction/adduction and endorotation/exorotation.
- After automatic registration of the 3D MRI bone model on the fluoroscopic image, the femur and tibia were put in an anatomically correct position relative to each other.
- Knee kinematics ('dynamic') were computed for the registered position using the knee kinematics of the 3D MRI bone model and the corrected registration results.

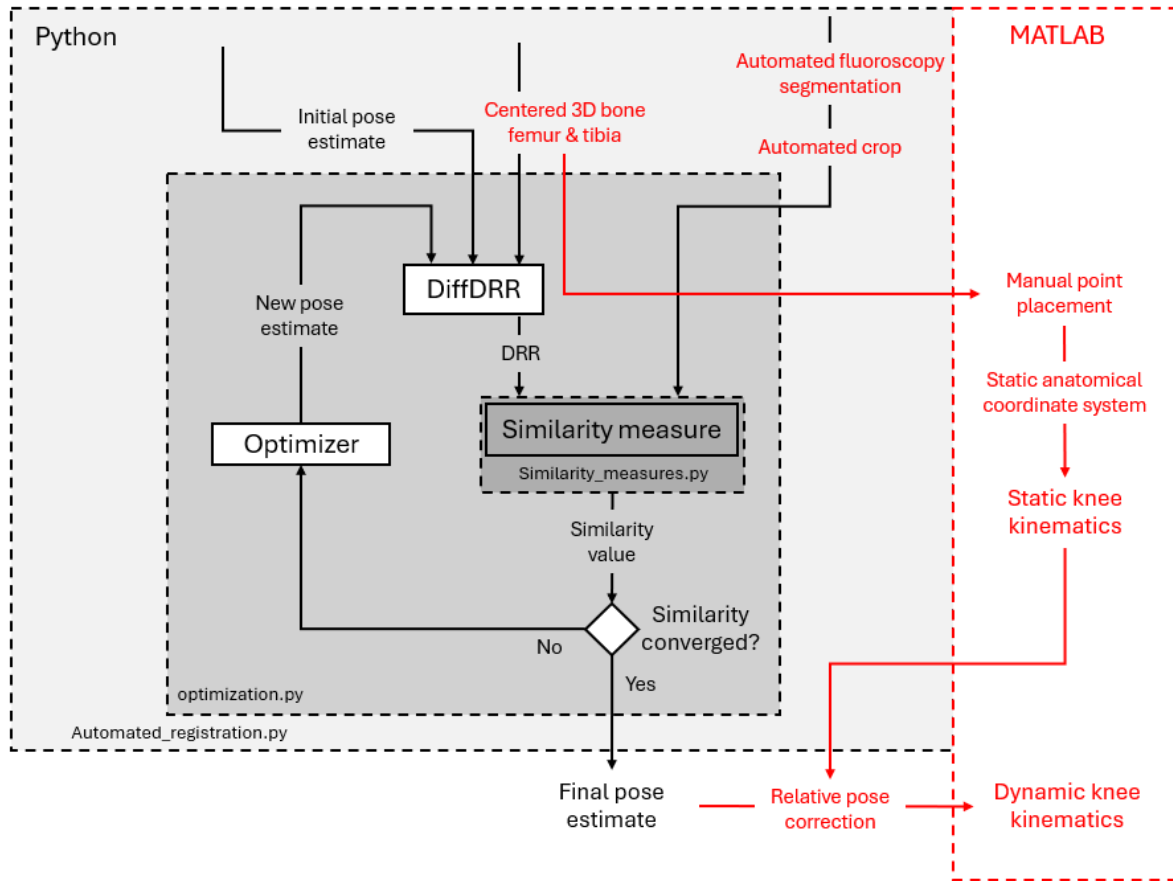


Figure 12: Extended registration pipeline, additions in red; image adapted from (44).

2.5. Segmentation trial

To assess the sensitivity of 3D-2D registration and subsequent knee kinematics to errors in automated bone segmentation, a controlled segmentation-variation experiment was performed. The aim was to determine to what extent segmentation errors that may occur in automated fluoroscopic segmentation affect the registration and kinematic measurements.

2.5.1. Segmentation

A collaborating research group trained an nnU-net to automatically segment the femur and tibia in the 78 fluoroscopic images. The nnU-net was trained with 10 manual segmentations by a single researcher. A reference fluoroscopic image was selected from the 78 images and the automated segmentations of the femur and tibia were visually checked for correctness by a segmentation expert. These served as reference segmentations for the experiment. Subsequently, a list of typically occurring segmentation errors was identified based on visual inspection of the automated segmentations of the 78 images (Table 1). Most segmentation errors result from ambiguous bone contours, caused by overlapping bones or insufficient contrast, and bones being out-of-frame. Additionally, cortical bone edges are less well defined in fluoroscopic images, e.g. due to insufficient contrast or surrounding soft tissue (45, 46). To simulate the uncertainty in the exact bone contour, dilated and eroded segmentations were added. Dilation and erosion of two pixels was chosen based on visual inspection of the new bone contours. 14 variant segmentations of the reference segmentations were manually created using ITK Snap software and evaluated by two segmentation experts (Figure 13). This means that all segmentations were of the same fluoroscopic image to be able to compare registration results and knee kinematics.

Table 1: List of typically occurring segmentation errors in automated fluoroscopy segmentation

Femur	Tibia
Femur partially out-of-frame	Tibia partially out-of-frame
OMC marker wrongfully segmented	Trouble segmenting tuberositas tibiae
Femur contour unreliable with an overlapping patella	Inaccurate segmentation posterior condyle of tibia
Inaccurate segmentation posterior condyle of femur	Inaccurate segmentation tibial joint contour 1 (contour removed)
Inaccurate segmentation posterior contour of femur	Inaccurate segmentation tibial joint contour 2 (contour added)

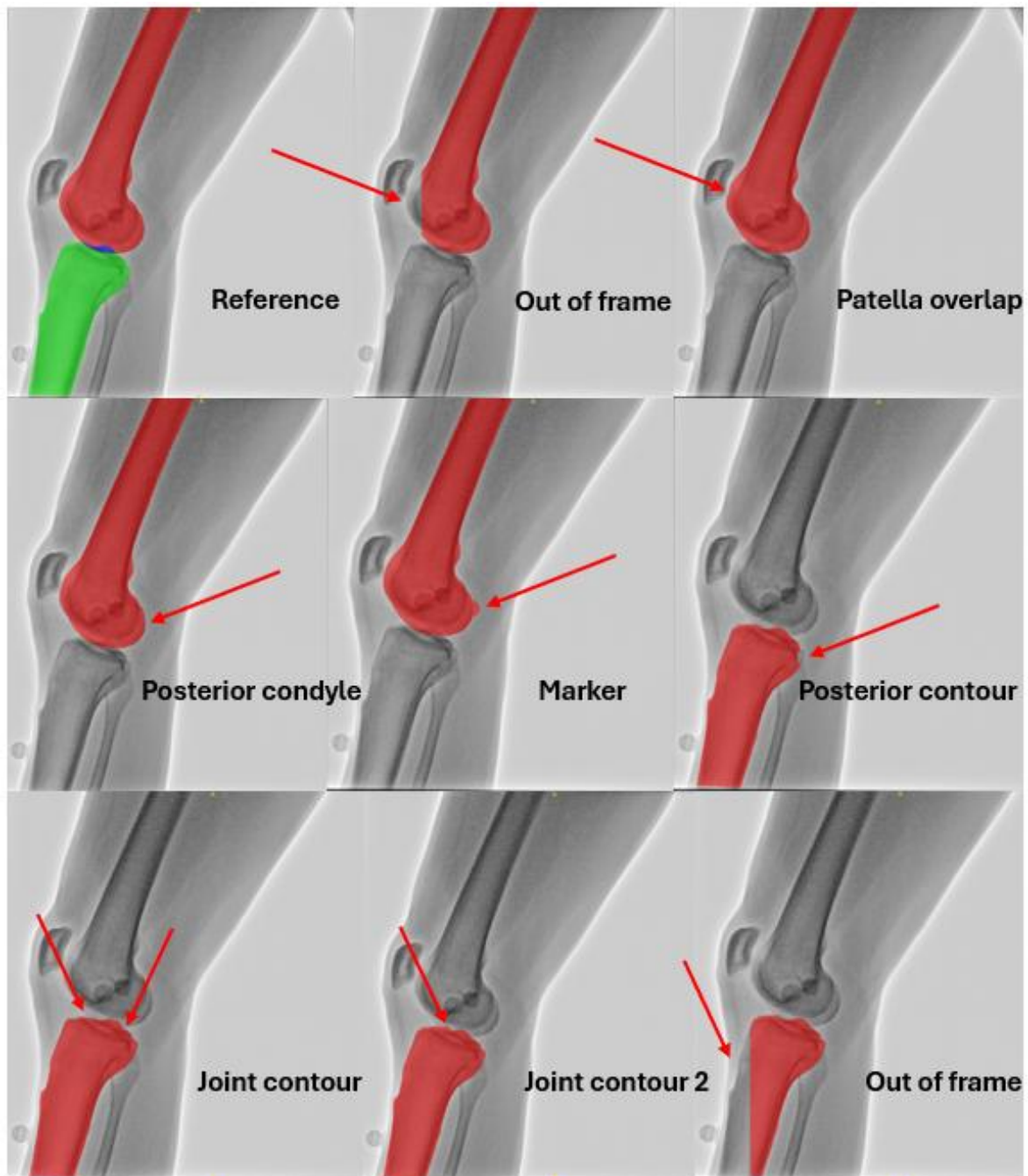


Figure 13: The reference segmentation of the femur and tibia and eight examples of segmentations containing an error. The remaining six segmentation errors were too subtle to visualize in this figure.

2.5.2. Registration

The reference segmentations of femur and tibia and 14 variant segmentations were used as input for the registration pipeline. The DESS was used to create the 3D bone model. A manual initial pose estimation was provided to the algorithm with the DESS and selected fluoroscopic image, using the tool described in Chapter 2.2. The segmentations were cropped consistently, with the exception of the out-of-frame variants. All segmentations were loaded at once per bone, after which the maximum and minimum pixel coordinates of the segmentations were determined along both the horizontal and vertical axes across the reference and seven variant segmentations. Figure 13 shows that the out-of-frame variants contain significantly less pixels compared to the other variants. As a result of the constant cropping, those segmented images will contain more background, i.e. zeros. This so called zero-padding is subject to uncertainty in contour prediction and algorithms may return misleading outputs (57, 58). Hence, the out-of-frame variants were cropped to its own contour, i.e. without zero-padding. A total of 16 registrations were performed using shape matching as similarity measure, once for every segmentation variant and reference segmentations. The 16 registrations were run six times each to evaluate the optimizer's stochastic behavior.

2.5.3. Data analysis

The registration pose was expressed as six DoF, translations in mm and rotations in degrees. Knee kinematics were expressed as flexion/extension, ab/adduction, internal/external rotation in degrees and ML, AP, PD translation in mm. For each outcome measure, the absolute error between each variant and the reference was calculated. Total translation and rotation absolute errors were calculated to visualize the overall performance of the variants compared to the reference. The total translation errors were calculated using Euclidean distance. While not routinely used for angular measures, the same method is allowed for small rotations (59).

$$\text{Total translation error} = \sqrt{x^2 + y^2 + z^2} \quad (1)$$

$$\text{Total rotation error} = \sqrt{\alpha^2 + \beta^2 + \gamma^2} \quad (2)$$

To summarize the overall effect of segmentation errors, differences were pooled across variants and reported as median absolute error (MAE) and interquartile range (IQR). Median values were used because of the small sample size and expected outliers, as the median is robust to outliers and does not assume normality. Considering the small sample size, i.e. one reference segmentation compared to seven variant segmentations per bone, no statistical testing was applied to the data. A descriptive analysis was based on the MAE with IQR, violin plots of the six DoF absolute differences and bar plots, in which the variants were compared to each other.

3. Results

3.1. Automated registration results

The total registration time for 16 registrations was 37 minutes and 18 seconds. Thus, each registration was performed in roughly two minutes, assuming that starting MATLAB, performing the manual point placement step and calculating the ACSs took about five minutes. The 16 registrations were run six times, yielding the exact same results each run. Therefore, the results of a single run are reported. Table 2 shows the registration MAE with IQR of all variant segmentations combined per bone. The direction of the translations and orientation of the rotations are visualized in Figure 14. It can be seen that overall the translation and rotation MAEs are below 1 mm and 1 degree.

Table 2: Median absolute registration error of the seven variant segmentations per bone compared to the reference segmentation for the six degrees of freedom (DoF), with interquartile range (IQR). Translational errors are in millimeter and rotational errors in degrees.

		Femur (n=7)	Tibia (n=7)
		MAE [IQR]	MAE [IQR]
Translation (mm)	x	0.03 [0.02–0.11]	0.29 [0.26–0.42]
	y	0.36 [0.18–0.38]	0.12 [0.04–0.20]
	z	0.12 [0.05–0.14]	0.60 [0.34–0.63]
Rotation (°)	α	0.31 [0.16–0.60]	0.56 [0.11–0.90]
	β	0.29 [0.20–0.69]	0.36 [0.17–0.80]
	γ	0.20 [0.08–0.46]	0.30 [0.11–0.34]

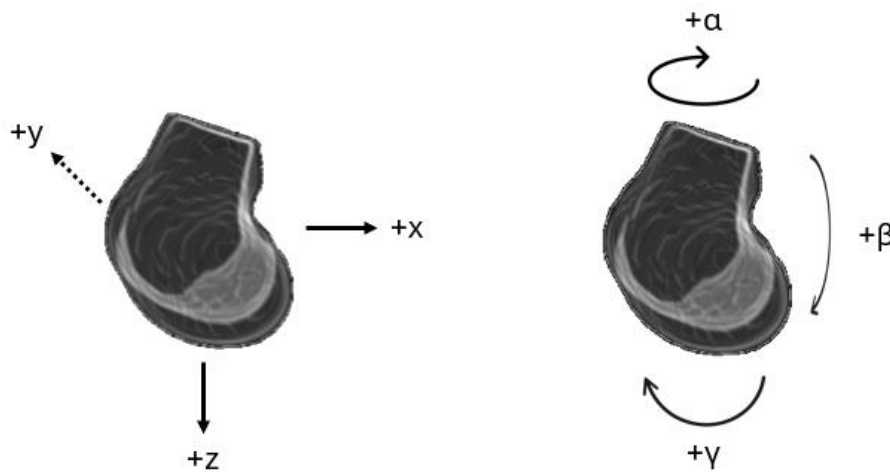


Figure 14: The direction and orientation of the translational and rotational registration axes.

However, some variant segmentations result in bigger MAEs. The violin plots (Figure 15) show the absolute errors in registration between the reference segmentations and variant segmentations across the separate six DoF. The out-of-frame, dilated, eroded and adjusted tibial joint contour variants are the cause of outliers, for both femur and tibia. The only translational error larger than 1 mm is the eroded femur in y (5.64 mm), which is the out-of-plane direction. Alpha and beta rotations shows larger errors compared to gamma. Rotational outliers are not as extreme as the one translational outlier, i.e. no more than 2.74°.

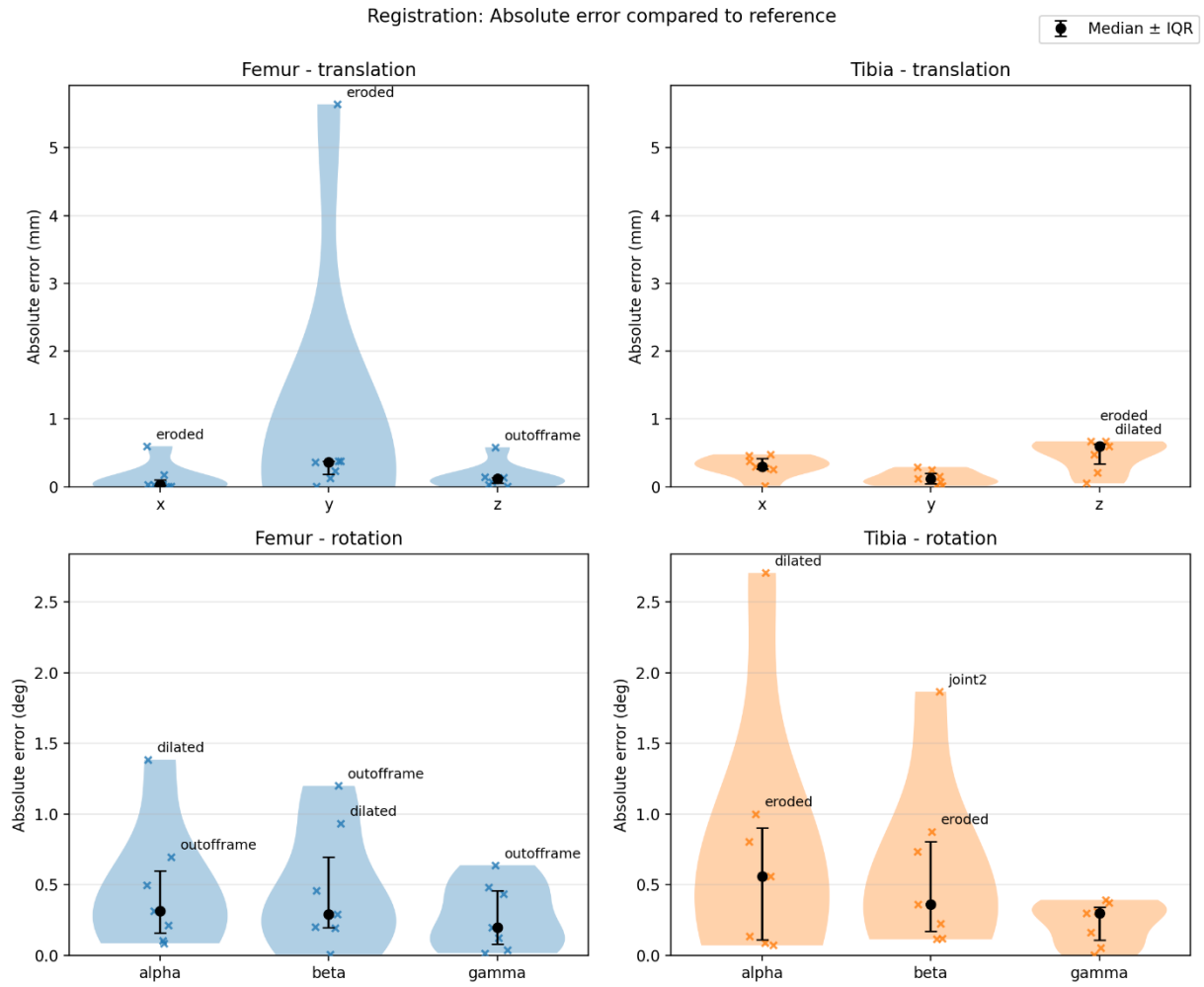


Figure 15: Violin plots of the absolute registration errors of the seven variant segmentations per bone compared to the reference segmentation six degrees of freedom (DoF). The median absolute error (MAE) and interquartile range (IQR) are also shown. Translational errors are in millimeter and rotational errors in degrees.

To visualize the overall performance of the variant segmentations compared to the reference segmentation, bar plots were created for total translation and rotation absolute error (Figure 16). The variants on the x-axis are sorted by femur-only (left), both femur and tibia (middle) and tibia-only (right). The total translation and rotation absolute errors were calculated using equations 1 and 2.

Figure 16 shows the separate differences for each variant. It can be seen that a large total translation error exists for the eroded femur (5.67 mm). A different pattern can be seen for the total rotation error. The dilated femur and tibia, eroded tibia, out-of-frame femur and adjusted tibial joint contour show larger total registration errors compared to the other variants. The dilated tibia shows the largest total rotation error of 2.71 degrees.

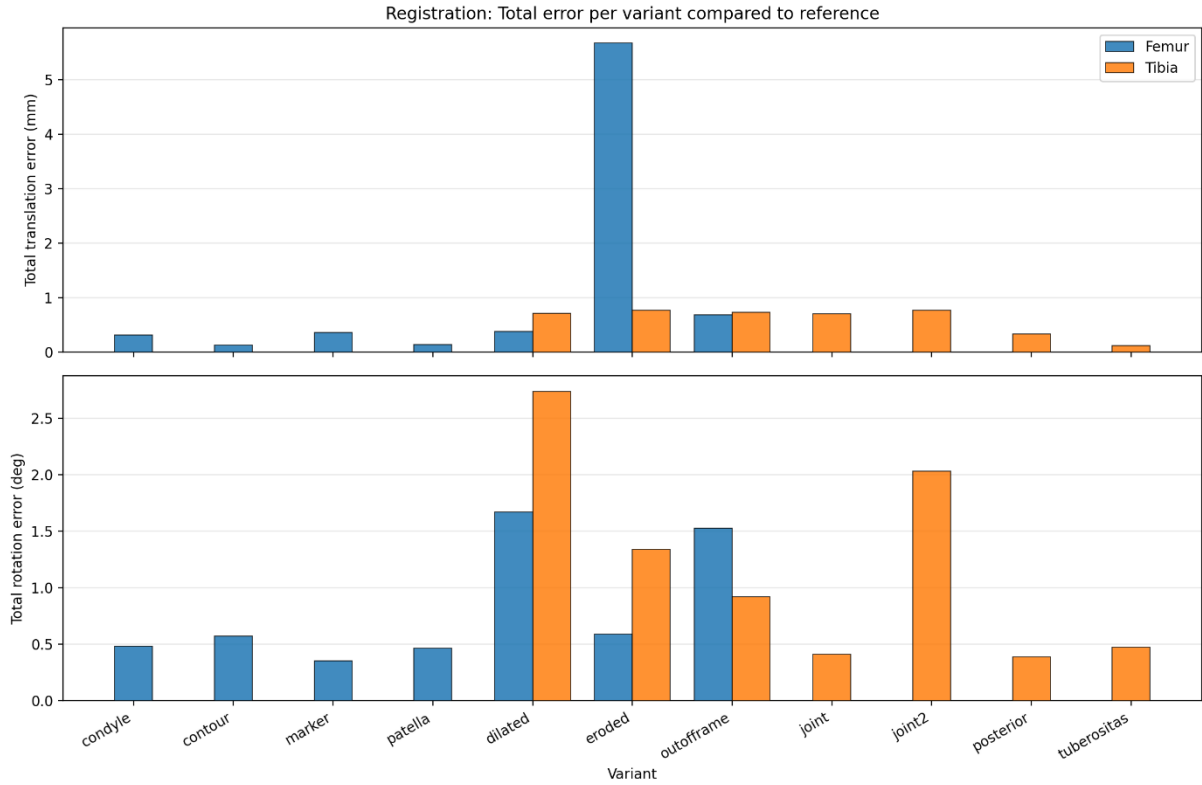


Figure 16: Bar plots of the total translation and rotation registration error per segmentation variant. Total translation and rotation error are calculated by means of Euclidean distance (Equation 1 and 2). Translational errors are in millimeter and rotational errors in degrees. The variants on the x-axis are sorted by femur-only (left), both femur and tibia (middle) and tibia-only (right).

3.2. Knee kinematics results

Table 3 and 4 show the kinematics MAE with IQR of the 14 variant segmentation x reference segmentation combinations compared to the reference x reference segmentation. It can be seen that all three rotations have MAEs below one degree, with the flexion/ extension angle being the least affected by segmentation errors in either bone. Separating the femur and tibia segmentations shows that the three rotations are slightly more robust against femur variant segmentations. Regarding the three translations, only the ML translation has an MAE below one millimeter. The AP translation is more affected by tibial segmentation errors compared to femoral segmentation errors, while the ML translation is more affected by femoral segmentation errors.

Table 3: Median absolute kinematics error (MAE) of the 14 segmentation combinations (reference x variant segmentation) compared to the reference x reference segmentation, with interquartile range (IQR). Translational errors are in millimeter and rotational errors in degrees.

Knee kinematics (n=14)		
MAE [IQR]		
Translation (mm)	Medial-Lateral	0.58 [0.31–1.71]
	Anterior-Posterior	1.84 [0.62–3.09]
	Proximal-Distal	1.54 [0.91–2.67]
Rotation (°)	Flexion/Extension	0.21 [0.11–0.42]
	Abduction/Adduction	0.33 [0.17–0.82]
	Internal/External Rotation	0.40 [0.13–0.76]

Table 4: Median absolute kinematics error (MAE) of the 14 segmentation combinations (reference x variant segmentation) compared to the reference x reference combination, with interquartile range (IQR), separated by which bone contained the segmentation error. Translational errors are in millimeter and rotational errors in degrees.

Knee kinematics		Femur (n=7)	Tibia (n=7)
		MAE [IQR]	MAE [IQR]
Translation (mm)	Medial-Lateral	0.62 [0.48–2.07]	0.29 [0.16–1.05]
	Anterior-Posterior	1.30 [0.67–2.82]	2.57 [0.76–3.30]
	Proximal-Distal	1.54 [0.73–2.60]	1.54 [1.14–2.54]
Rotation (°)	Flexion/Extension	0.13 [0.11–0.45]	0.22 [0.16–0.34]
	Abduction/Adduction	0.24 [0.17–0.65]	0.41 [0.17–0.80]
	Internal/External Rotation	0.29 [0.17–0.61]	0.56 [0.13–0.89]

The violin plots (Figure 17) show the absolute errors in knee kinematics. Similar to the registration results, the out-of-frame, dilated, eroded and adjusted tibial joint contour variants are the main contributors to outliers in the knee kinematics.

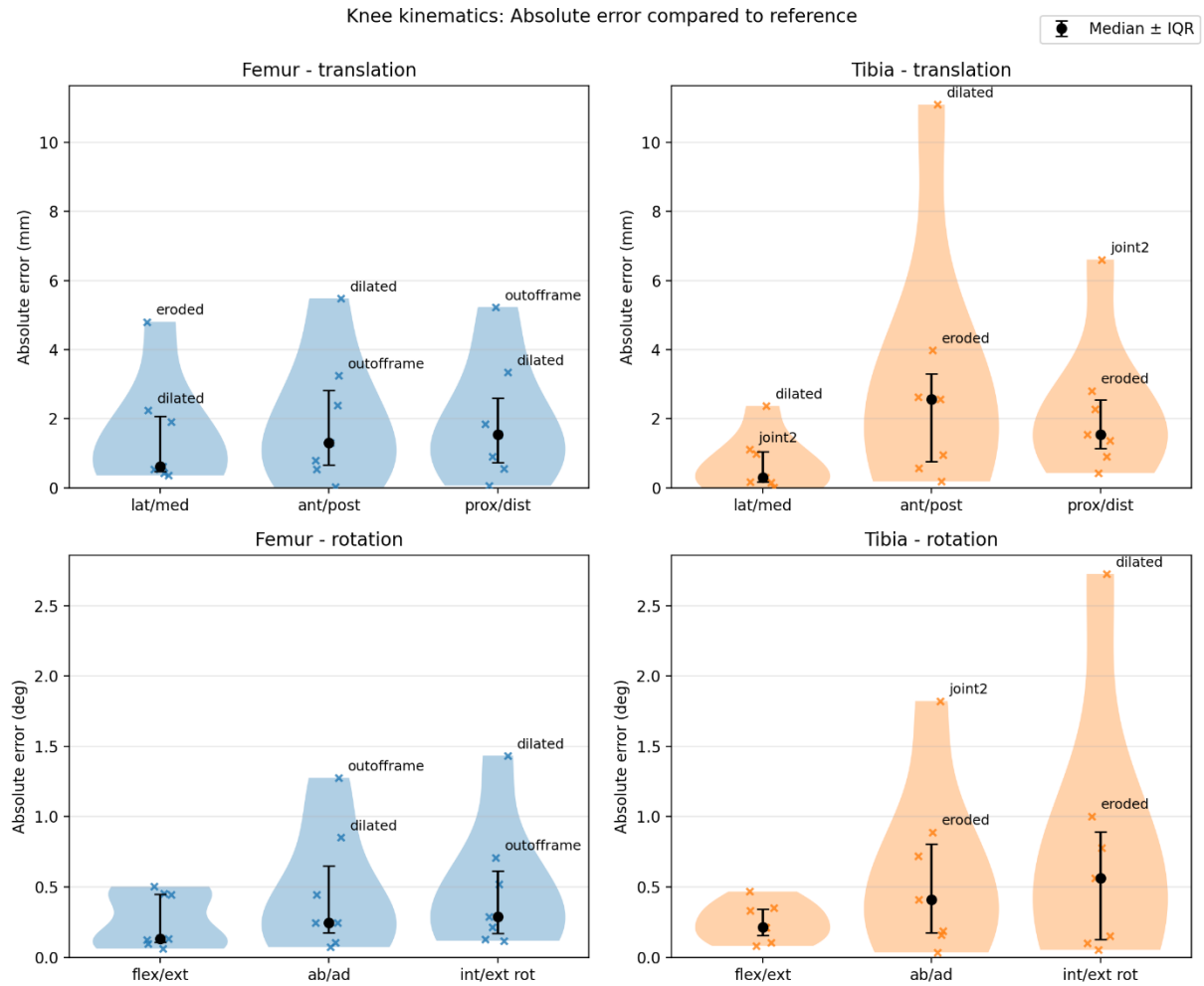


Figure 17: Violin plots of the absolute kinematics errors of the variant segmentation x reference segmentation compared to the reference x reference segmentation six degrees of freedom (DoF). The median absolute error (MAE) and interquartile range (IQR) are also shown. Translational errors are in millimeter and rotational errors in degrees.

The bar plots (Figure 18) show that the total rotation errors for knee kinematics are nearly identical to the total rotation errors for registration. This is not the case for the total translation errors. Whereas only the eroded femur showed a total translation error above 1 mm, total translation errors for knee kinematics are increased across all variant segmentations. Similar to the rotation results, large total translation errors exist for the out-of-frame, dilated, eroded and adjusted tibial joint contour variants. The dilated tibia shows the largest total translation error with 11.38 mm.

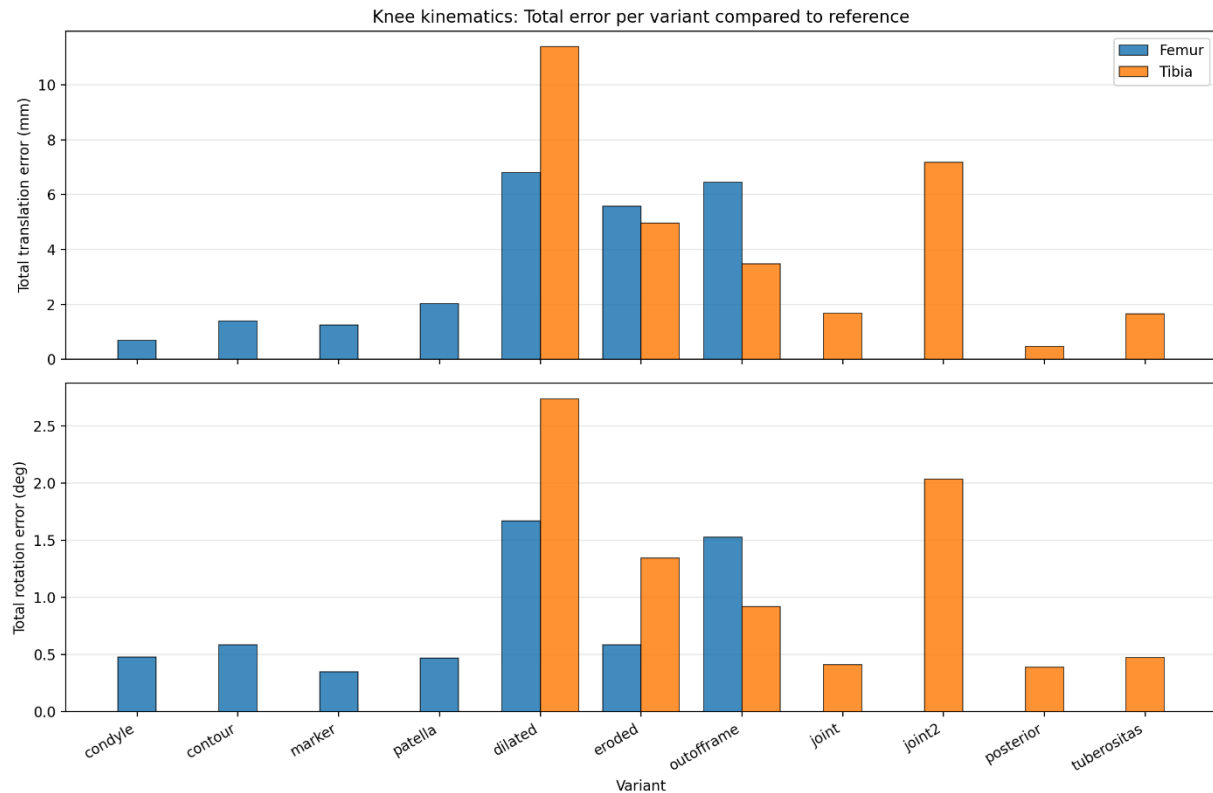


Figure 18: Bar plots of the total translation and rotation error per segmentation variant. Total translation and rotation error are calculated by means of Euclidean distance (Equation 1 and 2). Translational errors are in millimeter and rotational errors in degrees. The variants on the x-axis are sorted by femur-only (left), both femur and tibia (middle) and tibia-only (right).

4. Discussion

The aim of this thesis was to answer the following question: What impact does the variability in automated segmentation of the femur and tibia on monoplanar fluoroscopic images have on the 3D-2D registration accuracy and knee kinematics? A common method for 3D-2D registration is a contour-based approach, in which the contours of the bones are segmented from a fluoroscopic image. However, errors in the segmentation of bone contours can lead to errors in the estimated pose of the object. Image quality, limited field of view and overlapping bones can make the exact location of the contour challenging to determine. This applies to both manual and automated segmentation. Manual segmentation is still the common approach for registration in clinical practice, but is a time-consuming task and places a considerable burden on clinicians. Automated segmentation methods offer a promising way to reduce this workload. Hence, an nnU-net was trained to automatically segment the femur and tibia on fluoroscopic images. However, efficiency gains should not come at the expense of segmentation and subsequent registration accuracy.

This thesis has shown that, overall, typically occurring segmentation errors in automatic registration result in a submillimeter and subdegree error in registration and subdegree error in knee kinematics compared to the reference segmentations. Submillimeter accuracy has been identified as desirable for quantifying knee kinematics in the context of OA using monoplanar fluoroscopy (60). Small segmentation errors have shown to achieve this target. Small errors include an OCM marker being segmented, an unreliable femur contour with an overlapping patella and an inaccurate segmentation of the femoral or tibial condyle.

Based on the results, the dilated, eroded, out-of-frame and tibial joint contour variants were the main contributors to errors in registration and knee kinematics. Absolute errors of these variants were consistently higher across all six DoF compared to the other variants. This makes sense considering the magnitude of the segmentation error and the impact it has on the bone contour. The out-of-frame variant is the clearest example of this. A significant part of the bone and distinctive contour is missing due to the bone being partially located outside the field of view. Depending on the cut off, a large part of the shaft and a part of the distinct joint contour might be missing. To a lesser extent, an inaccurate segmentation of the tibial joint contour, which is a distinctive part of the tibial contour, has shown to impact the registration. Dilation or erosion of 2 pixels might not seem much, but every part of the contour is either enlarged or shrunk. Instinctively, this would mainly affect the registration in the out-of-plane (y) direction. Changes in the y-direction would not change the contours of the segmentation, only the size. Surprisingly, only the registration of the eroded femur met this expectation. The direction of error, however, was inexplicable. The DRR was moved further away in the +y-direction (Appendix A, Table A.1) and therefore shrunk.

Whereas the total rotation errors for kinematics were nearly identical to the total rotation errors for registration, increased total translation errors existed for kinematics compared to those for registration. For registration, rotations and translations are calculated from the bone's COM. The kinematic translations, however, are calculated from a different 'center'. A point between the condyles for the femur and the COM of the tibial plateau. This means that a small rotational error around the bone's COM will have a bigger impact on a point located further away from the center of rotation.

Furthermore, the out-of-frame variant segmentations were cropped differently compared to the other variants. In a real dataset, the bone would be located at the edge of the frame. Once the

edge is reached, the segmentation transitions into nothing. Before collecting the main results, an experiment was carried out by cropping the out-of-frame variants consistent to the other variants, reported in Appendix B. The segmentation image of the out-of-frame variant included a large area of zeros, which can be interpreted as zero-padding. In a real dataset this would mean that a layer of zeros is added at the edge of the image. The registration algorithm gets fed more information, but might also misinterpret this information. Zero-padding introduces a hard transition from valid segmented pixels to the padded zeros, i.e. an artificial structural edge. The algorithm may incorrectly force background or truncated edges to match unrelated bone contours. The registration algorithm did in fact show this considering the absolute errors across all six DoF for registration and knee kinematics (Figures B.2 and B.3). The removal of the padded zeros resulted in reduced errors in most translational and rotational directions, which is why the out-of-frame variants were cropped around their own contours.

Only one study was found that also reported on the effect of segmentation errors on 3D-2D registration in X-ray images (47). After registration, they found rotational errors up to 0.84° and translational errors up to 5.19 mm in the out-of-plane direction. Overall, translation and rotation errors between their study and this thesis are comparable. They did, however, focus on implant delineation. Knee implants are usually more clearly delineated than bone contours on fluoroscopic images. Therefore, segmentation errors are expected to be less frequent and registration errors to be smaller. The differences in methodology prevent a clear comparison.

The findings of this thesis should be put in perspective. Results show that most of the included segmentation errors do not differ from the reference segmentation regarding registration results and kinematics. In other words, the accuracies of registration and knee kinematics do not get worse. A previous study from our research group has shown that the registration pipeline only achieves submillimeter accuracy compared to a registration gold standard for translations in the xz-plane and γ -rotation (44). High errors exist for the out-of-plane (y) translation, which remains a challenge for monoplanar fluoroscopy. Two studies with a methodology comparable to that of our 3D-2D registration pipeline reported comparable accuracy results (61, 62). The outcomes, however, should be interpreted in the context of their experimental setup, i.e. with soft tissue-less cadaver bones (61) and the absence of a golden standard (62). Additionally, our registration pipeline outperformed two studies that used artificial femur and tibia bones (63, 64). Three of the four studies performed CT-based 3D-2D registration (61, 63, 64). Only one study reported substantially better, CT-based, registration accuracy across most DoF (65). The same study also found low errors for kinematics, the poorest being 0.42 mm for AP translation and 0.33° for internal-external rotation. Two studies, however, reported on kinematic errors comparable to this thesis, with one reported an accuracy of 2 mm for sagittal plane translations and 1.5° for rotations (60, 63). These findings are similar to the results presented in this thesis. Interestingly, one study performed an experiment in which the fluoroscopic image was partially blocked (62). Their reasoning is that monoplanar fluoroscopy may capture only a part of the knee joint in dynamic studies, which is very similar to the out-of-frame variants from this thesis. Errors from partially blocking the image by 20% are comparable to the errors of the out-of-frame variants that were cropped around their own contour. They also found that the accuracy of the knee kinematics decreased with increased blockage (up to 80%) of the fluoroscopy images.

4.1. Anatomical coordinate system method

The method used to compute anatomical coordinate systems is suited for automated pipelines and is reasonably insensitive to anatomical variability (53). It is also quite robust for several scenarios, including several combinations of bones (e.g. patella-femoral without tibia) and bone

sizes (e.g. also including the proximal part of the femur). However, one scenario the method is not robust for is short bone models such as the 3D bone models derived from the DESS. A short diaphysis causes the ACS method to crash. This makes sense, looking at the steps described in Chapter 2.4.1. The ACS method aims to isolate the femoral diaphysis. Hence, little to no diaphysis may prevent the method from being able to continue with further steps. Similarly, the tibia plateau cannot be isolated well without a sufficiently long diaphysis.

Therefore, manual input was added to the ACS method. For both the femur and tibia, it is essential for the method to have an accurate PD-axis. Researchers from Cardiff came up with a solution, placing a manual point on the proximal end of the femur and distal end of the tibia. In their proposed solution however, the direction of the PD-axis heavily relied on the centroid of the 3D bone model. In our short femur model, the centroid is located posteriorly due to the condyles. For the same reason, the tibial PD-axis was skewed (Figure 10a+c). For this thesis, a different manual method was created and tailored to the short DESS 3D bone models. The method comes with two important caveats. It is specifically tailored to the bone models of a single subject from the MOBI-trial. Its robustness is yet to be evaluated. The solution for the femur now heavily relies on the proximal cut off of the femur bone. If the DESS was not well aligned with a straight leg, the proximal cut off will be skewed and so will the PD-axis. The solution for the tibia is more robust. A point is placed on the proximal end of the tibia. Subsequently, cross sectional areas are identified and a line is fitted through the centroids of these areas. The method therefore relies on the anatomy of the proximal tibia rather than the distal cut off of the DESS. Secondly, the method has not been quantitatively validated. Despite the PD-axis looking accurate visually, it can be argued that quantitative validation is needed to compare the results to the original automated method on long bones. Regardless, it is nearly impossible to reconstruct the PD-axis of long bones without the actual diaphysis, purely based on the 8 cm surrounding the knee joint. If the method turns out not to be robust and/or accurate enough, additional 3D-3D registration of the DESS and LAVA could be an alternative solution. The ACSs would be calculated on a longer bone model (LAVA scan), after which the long bone is registered to the shorter bone model (DESS scan). The long bone would then be used for ACS computation and the short bone for registration. The long bone would probably not suffice for registration, because of its inferior resolution.

4.2. Limitations

A number of considerations should be taken into account when interpreting the results from this thesis. First, the generalizability of the segmentation experiments. The experiments consist of 7 variant segmentations for femur and tibia, all applied to one, reference, fluoroscopic image. The variants were based on visual inspection by a single researcher and were derived from 78 fluoroscopic images of one healthy subject. Simulating them was arbitrary at times. For example, where the out-of-frame segmentation was cut off. As mentioned above, blocking or cutting off a bigger part of the bone might decrease the accuracy of registration and kinematics (62). Additionally, the data used in this thesis were collected from one healthy subject. The registration pipeline is eventually intended to be used for an OA population, which means that data could contain anatomy different to healthy subjects. Osteophyte formation is one of the pathological changes seen in OA (5). Osteophytes might contribute to the complex geometry in the knee joint and therefore complicate accurate segmentation of the bones. Furthermore, the automated fluoroscopy segmentation nnU-net trained was only trained with 10 segmentations of a single healthy subject by a single researcher. As stated in the Introduction, manual segmentations can vary significantly (47). Segmentation experts might disagree on the exact

delineation of bone contours, e.g. in the joint space where femur and tibia overlap (Figure 3a). Hence, the U-net's robustness is unknown.

The MRI segmentations used to generate the DRRs in this thesis were only validated against manually segmented MRI scans. Previous research has reported that manually segmented MRI-based bone masks differ from CT-based bone masks by approximately 0.61 mm for the femur and 0.45 mm for the tibia (66). The potential error could negatively impact the registration accuracy and the way the registration algorithm deals with segmentation errors. Caution should also be exercised with the accuracy and robustness of the ACS computation method, as discussed in Chapter 4.1.

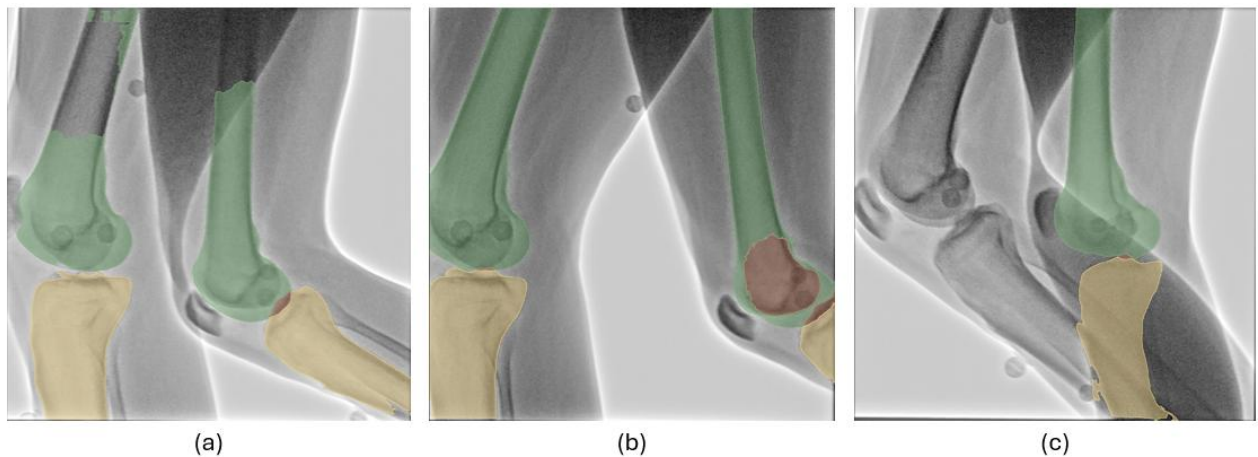


Figure 19: Three examples of inaccurate automated segmentations from the 78 fluoroscopic images, with a) unsegmented femur shaft, b) femur and tibia mix up (red means both bones are segmented for those pixels) and c) the leg in front not being segmented.

4.3. Future research

This thesis focused on evaluating the impact of the segmentation errors made by the automated nnU-net. The U-net should be provided with more training data to improve automated segmentation. The segmentation experiment was carried out with the assumption that a researcher or clinician would flag major segmentation errors, such as the ones shown in Figure 19. Not only do small segmentation errors exist, but also more obvious errors: both legs being segmented, a big part of the shaft missing or random noise. Multiple segmentation experts should manually segment more fluoroscopic images. Potentially even the same images multiple times, to account for both intra- and inter-rater variability. In addition, attempts should be made to validate the robustness and accuracy of the manual ACS computation method. Ideally, the method should be fully automated as intended by Miranda et al. and Chen et al. (52, 53), also to ensure repeatability and eliminate human error when placing the manual points.

The registration pipeline is quite computationally expensive. Several choices have been made to reduce runtimes, both in ACS computation and registration. The DESS models consisted of a large amount of faces and vertices, so the registration pipeline has been adapted to handle large amounts of 3D model data more efficiently. Additionally, the similarity measure for registration was mainly chosen on the basis of computational efficiency. Despite all of this, it still takes a lot of manual steps before running the automated registration. Every fluoroscopic image requires a manual initial pose and with the current state of the nnU-net most automated segmentation should be checked. Given the high frame rate of fluoroscopic recordings, this would be a time-consuming task for clinical studies involving large patient groups. An alternative approach to the manual initial pose estimation would be to use an optical motion capture (OMC) system to

provide an initial six DoF pose estimate for each frame, which could serve as the starting point for the optimization algorithm. To enable this, it is necessary to calibrate the coordinate systems of the OMC system and the fluoroscope relative to one another.

Lastly, the current registration algorithm does not provide an accurate registration in all 6 DoF (44). Especially, the out-of-plane direction remains a challenge in a monoplanar setup. While the achieved accuracy exceeded what an OMC system could provide under ideal conditions, it remains insufficient for applications that require reliable sub-degree and sub-millimeter kinematics for all DoFs for the quantification of small-scale knee kinematics or cartilage deformations. Therefore, inventive solutions should be explored to improve the registration process, such as patient-specific neural networks (67). Approaches like this directly address limitations of the current registration pipeline, such as slow convergence and the reliance on contour-based similarity measures. Integrating these techniques into future iterations of the registration pipeline could substantially enhance both accuracy and robustness.

5. Conclusion

Overall, typically occurring segmentation errors in automatic segmentations of femur and tibia in monoplanar fluoroscopy do not have a substantial impact on the 3D-2D registration accuracy and knee kinematics. This holds particularly true for small inaccuracies in the bone contours. However, segmentation errors that leave out (out-of-frame) or inaccurately segment (tibial joint contour) distinct bone contours could cause larger errors. In addition, caution should be exercised with the exact delineation of bone contours, as eroded or dilated might impact registration and subsequent kinematics. Future research should focus on evaluating the generalizability of the findings from this thesis and improving the overall registration accuracy.

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Appendix A - Supplementary results

This appendix contains the, non-absolute, errors between the variant segmentations and the reference segmentations. Figure 15 shows the +/- directions of the registration. For kinematics, flexion, abduction, internal rotation, and lateral, anterior, and proximal translations are defined as positive. The total translation and rotation errors are added, supplementary to the bar plots.

Table A.1: Error between femur variant segmentation and reference segmentation for registration.

Registration	Translation			Rotation		
Femur variants	x	y	z	α	β	γ
Condyle	-0,18	-0,23	-0,13	0,09	-0,19	0,43
Contour	-0,03	-0,13	0,03	0,31	0,01	-0,48
Dilated	0,03	-0,38	0,00	-1,39	0,93	-0,04
Eroded	-0,60	5,64	-0,12	0,50	-0,29	0,12
Marker	0,00	-0,36	0,07	-0,21	-0,20	-0,20
Out-of-frame	-0,01	-0,37	-0,58	-0,70	1,20	0,64
Patella	-0,03	0,00	-0,14	-0,10	0,46	0,02

Table A.2: Error between tibia variant segmentation and reference segmentation for registration.

Registration	Translation			Rotation		
Tibia variants	x	y	z	α	β	γ
Dilated	0,27	0,02	-0,67	-2,71	0,11	-0,39
Eroded	-0,29	0,25	0,67	1,00	0,88	0,16
Joint	-0,38	0,01	0,60	-0,13	-0,12	-0,37
Joint2	0,46	0,15	-0,60	-0,80	-1,87	0,05
Out-of-frame	0,48	0,29	-0,47	0,56	-0,73	0,00
Posterior	-0,25	0,07	0,21	0,07	0,22	-0,31
Tuberositas	-0,01	0,12	-0,05	-0,09	-0,36	-0,30

Table A.3: Total translation and rotation error between variant segmentation and reference segmentation for registration.

Registration	Total translation error (mm)		Total rotation error (°)
Femur	Condyle	0,32	0,48
	Contour	0,14	0,57
	Dilated	0,38	1,67
	Eroded	5,67	0,59
	Marker	0,37	0,35
	Out-of-frame	0,69	1,53
	Patella	0,14	0,47
Tibia	Dilated	0,72	2,74
	Eroded	0,77	1,34
	Joint	0,71	0,41
	Joint2	0,77	2,03
	Out-of-frame	0,73	0,92
	Posterior	0,33	0,39
	Tuberositas	0,13	0,48

Table A.4: Error between femur variant segmentation x reference segmentation and reference x reference segmentation for kinematics.

Registration	Translation			Rotation		
Femur variants	Lat/med	Ant/post	Prox/dist	Flex/ext	Ab/ad	Int/ext rot
Condyle	0,42	-0,02	0,55	0,45	0,10	0,12
Contour	0,53	1,30	0,06	-0,50	0,07	0,29
Dilated	-2,24	-5,48	-3,34	-0,10	-0,85	-1,43
Eroded	-4,80	2,38	1,54	0,12	0,24	0,52
Marker	0,36	-0,79	0,91	-0,13	0,24	-0,21
Out-of-frame	-1,91	-3,25	-5,23	0,44	-1,28	-0,71
Patella	-0,62	-0,54	-1,85	-0,06	-0,45	-0,13

Table A.5: Error between tibia variant segmentation x reference segmentation and reference x reference segmentation for kinematics.

Registration	Translation			Rotation		
Tibia variants	Lat/med	Ant/post	Prox/dist	Flex/ext	Ab/ad	Int/ext rot
Dilated	2,37	11,10	0,91	0,21	0,04	2,73
Eroded	-0,98	-3,98	2,81	0,08	0,89	-1,00
Joint	0,17	0,96	-1,36	0,33	-0,19	0,15
Joint2	1,11	2,57	-6,61	-0,47	-1,82	0,78
Out-of-frame	-0,15	-2,62	-2,28	-0,10	-0,72	-0,56
Posterior	0,00	0,18	0,43	0,35	0,16	-0,05
Tuberositas	0,29	0,57	-1,54	0,22	-0,41	0,10

Table A.6: Total translation and rotation error between variant segmentation and reference segmentation for kinematics.

Kinematics	Total translation error (mm)		Total rotation error (°)	
Femur	Condyle	0,69	0,48	
	Contour	1,40	0,58	
	Dilated	6,80	1,67	
	Eroded	5,58	0,59	
	Marker	1,25	0,35	
	Out-of-frame	6,45	1,53	
	Patella	2,03	0,47	
Tibia	Dilated	11,38	2,73	
	Eroded	4,97	1,34	
	Joint	1,67	0,41	
	Joint2	7,18	2,03	
	Out-of-frame	3,47	0,92	
	Posterior	0,46	0,39	
	Tuberositas	1,67	0,47	

Appendix B - Zero-padding test

As described in Chapter 2.5.2., the segmentations were cropped consistently with the exception of the out-of-frame variants. The segmentations were cropped as shown in Figure B.1a. The out-of-frame variants, however, contain significantly less pixels compared to the other variants (Figure B.1b). Initially, the out-of-frame variants were cropped consistently to the other variant segmentations. It was hypothesized that the zero-padding would cause misleading registration results (57, 58). An experiment was carried for the out-of-frame variant to compare the consistent cropping method to cropping the segmentation to its own contour (Figure B.1b).

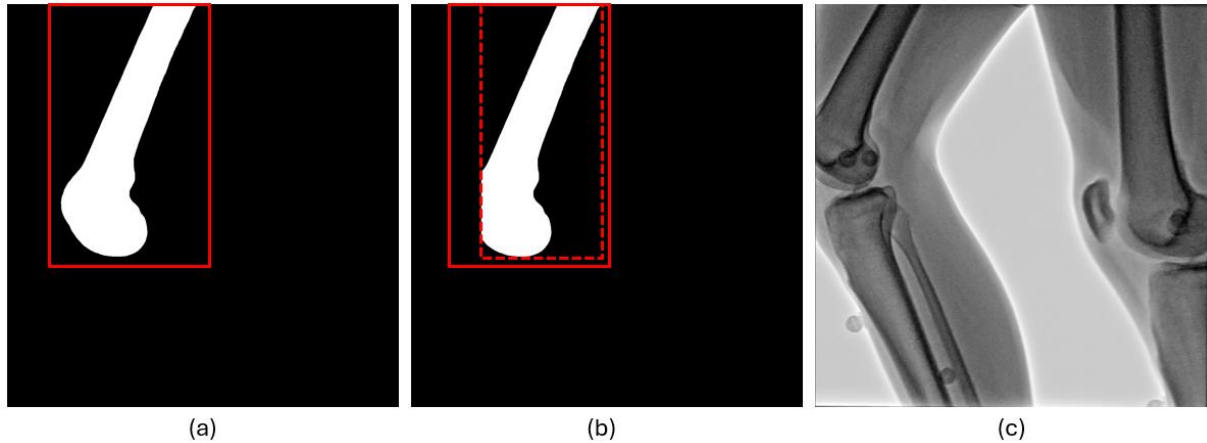


Figure B.1: a) Proposed automated cropping of segmented region with padding, b) Proposed automated cropping of out-of-frame segmentation to its own contour, c) Exemplary fluoroscopy image containing a partially out-of-frame femur.

The absolute registration errors compared to the reference segmentations are visualized in Figure B.2. The out-of-frame variant results with consistent cropping are shown in grey and results with contour cropping are visualized in green. The largest translation errors, femur x-direction and tibia y-direction, are significantly decreased, while the other axes are slightly increased with contour cropping. All rotation errors are decreased compared to consistent cropping. Absolute errors for joint kinematics are also decreased across all 6 DoF, except for the ML-direction of femoral segmentation errors (Figure B.3).

The hypothesis that zero-padding would cause misleading registration results was confirmed. Consistent cropping with zero-padding caused larger absolute errors compared to contour cropping. Because of this, contour cropping was applied to the out-of-frame variant segmentations in Chapter 3. Results.

Out-of-frame registration error: original vs new

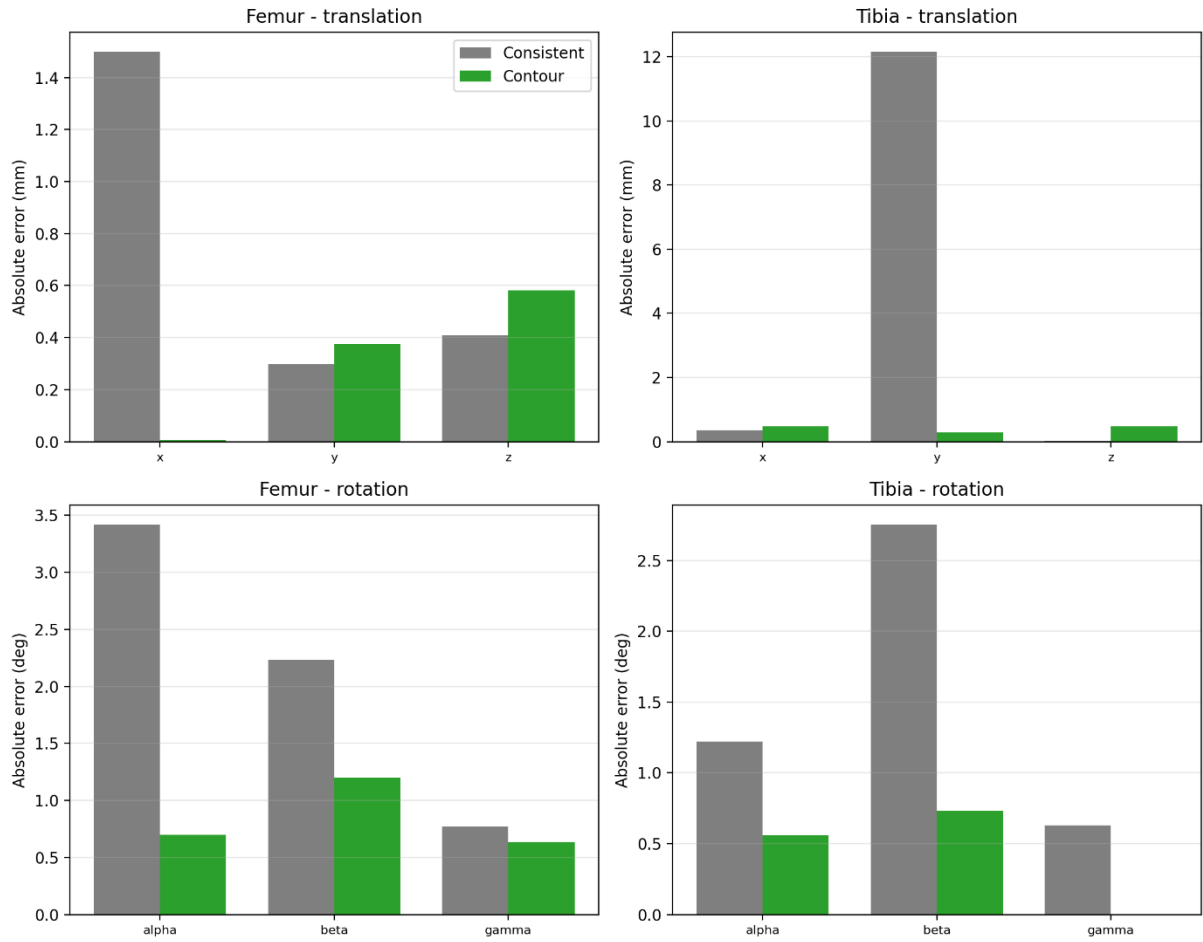


Figure B.2: Bar plots of the absolute registration errors. The out-of-frame variants cropped with zero-padding are shown in grey. The out-of-frame variants cropped without zero-padding are visualized in green. Results are separated by which bone contained the segmentation error. Translational errors are in millimeter and rotational errors in degrees

Out-of-frame knee kinematics error: original vs new

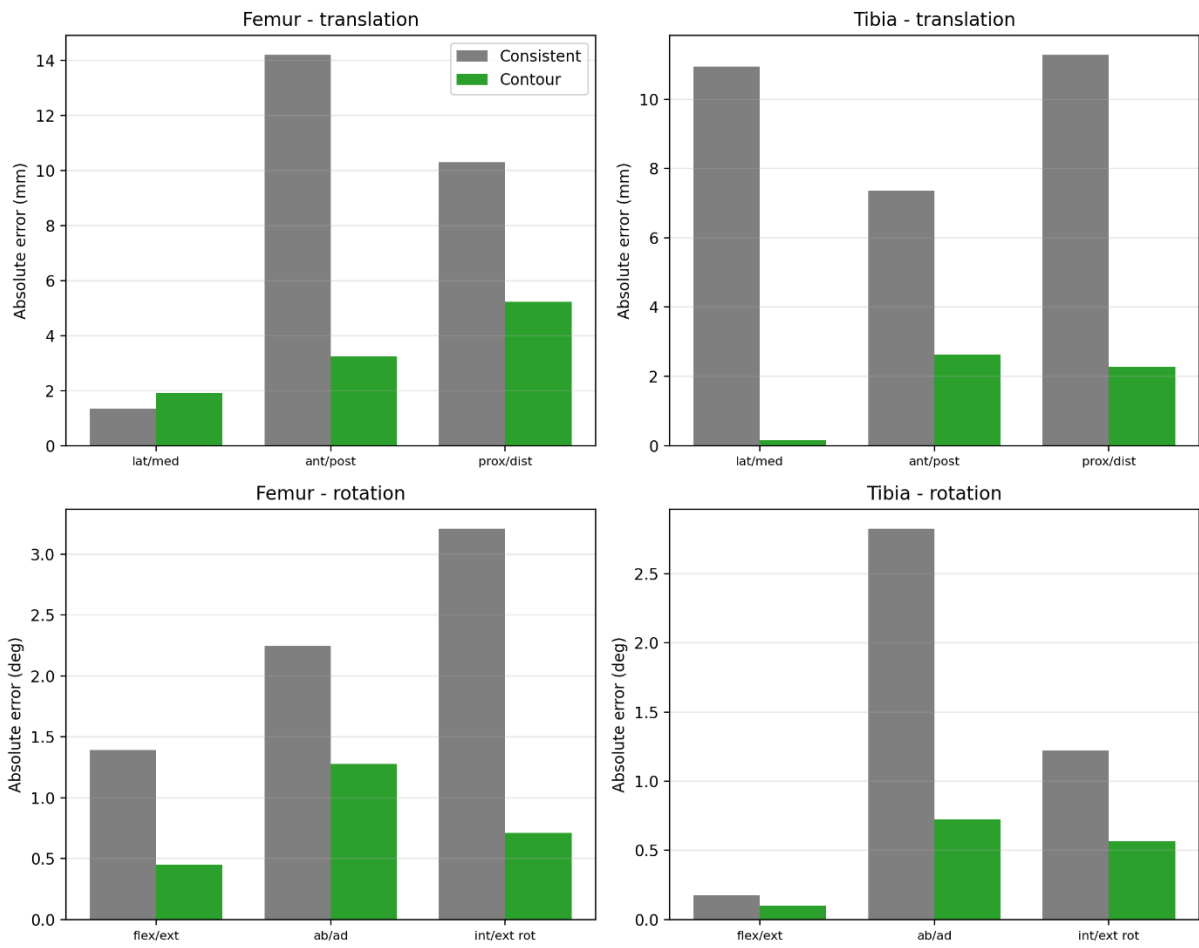


Figure B.3: Bar plots of the absolute joint kinematics errors. The out-of-frame variants cropped with zero-padding are shown in grey. The out-of-frame variants cropped without zero-padding are visualized in green. Translational errors are in millimeter and rotational errors in degrees