Doctoral theses at NTNU, 2018:81

Páll Jens Reynisson

Improved Bronchoscopy by new image guided Approach

Norwegian University of Science and Technology
Science and Technology

Doctoral thesis

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ISBN 978-82-326-2952-7 (printed ver.)
ISBN 978-82-326-2953-4 (electronic ver.)
ISSN 1503-8181

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Thesis for the Degree of
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Department of Circulation and Medical Imaging

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Trondheim, March 2018

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Printed by NTNU Grafisk senter

To my dear friend:

Magnús Freyr Sveinbjörnsson 1980-2002

And to my daughter:

Rebekka Elisabeth Pálsdóttir

Abstract

Navigation in bronchoscopy has developed into a feasible approach for lung diagnostics since introduced in 1998. The concept combines computer generated models from patient CT data with position and orientation tracking of the bronchoscope tip and/or other tools. Trials using navigational bronchoscopy have demonstrated increased diagnostics success rates. Despite higher diagnostic success rates and two decades of development in navigation for bronchoscopy, the use of the technology is still not common in lung diagnostics.

The pulmonologist is trained surveying and assessing CT and steering via video display from a flexible scope during bronchoscopy. Expanding the conventional work with additional display through techniques such as navigational bronchoscopy can be expensive to integrate in smaller hospitals and complicated for pulmonologists without proper training. Also, existing VB approaches only offers endoluminal view, an airway segmentation as a "road map" to lesions in lungs, and in best circumstances additional models of segmented lesions and vessels.

New solutions specifically for bronchoscopy visualization application was developed in this project. This thesis presents a development and evaluation of a new visualization approach for planning and guidance in bronchoscopy; *Anchored to Centerline Curved Surface* (ACCuSurf), consisting of more complete view for navigated bronchoscopy in tube-like structures. The technique may also be combined with other methods such as VB, PET and ultrasound images, by adding these data sources to the display. At the same time as providing overview of the lungs and tools, the ACCuSurf can be zoomed in and show more anatomical details than the conventional endoluminal view. First, a comparison of different approaches to airway segmentation was carried out to establish a route to target. Secondly, the ACCuSurf was developed by slicing the segmented airways in half, creating a 3D volume representing surrounding anatomy along the path to target. Finally, the ACCuSurf method was assessed by pulmonologists using it as a planning tool before performing bronchoscopy on a phantom with a mixed data set from a patient and the phantom. The conventional 2D (axial, sagittal, coronal) visualisation was comparison reference. The study is an effort to ease and simplify visualisation for navigation in bronchoscopy.

Preface and acknowledgements

This thesis is submitted for partial fulfilment of the requirements of the degree of PhD in Medical Technology at the Faculty of Medicine at the Norwegian University of Science and Technology (NTNU). The research work was performed as collaboration between Faculty of Medicine Department of Circulation and Medical Imaging at NTNU and the Department of Medical Technology at SINTEF, Technology and Society, in the years 2011-2017 in collaboration with St. Olavs Hospital Trondheim.

My main supervisors have been Thomas Langø, PhD, senior scientist, of Medical Technology, SINTEF Technology and Society, Professor Toril Anita Nagelhus Hernes, Håkon Olav Leira (MD, PhD) Postdoctoral Fellow at the Department Circulation and Medical Imaging NTNU, and Associate Professor Frank Lindseth at Department of Computer and Information Science NTNU, 2011-2017.

The PhD position was a part of Marie Curie Initial Training Network for the Integrated Interventional Imaging Operating System (IIIOS project), funded specially by the Dean Office of NTNU (DT-sak 267-11 Temporary position as PhD Candidate, Department of Circulation and Medical Imaging, Faculty of Medicine). The position was also granted from the Norwegian Research School in Medical Imaging and the Interventional Center (OUS/UiO), the 3rd National PhD Conference in Medical Imaging Oslo 21-22 November 2011.

I thank my supervisors Thomas Langø, Toril Anita Nagelhus Hernes, Håkon Olav Leira and Frank Lindseth for all their guidance, time and patience during these years. I also want to thank my other co-authors, friends and family for their time and contribution:

Special thanks to: Erlend Fagertun Hofstad, Erik Smistad, Tormod Selbekk, Geir Arne Tangen, Tore Amundsen, Peter Hatlen, Hanne Sorger, Ellen Fjellheim Opland, Mari Dyrset, Lars Christian, Finn Bakke Olsen, Sinara Vijayan, Marta Scali, Aimee Kok and Maryse Karsten. My beloved parents Ólöf Brynja Jónsdóttir and Reynir Snæfeld Stefánsson, Afi Sivi, Amma Mæja, my brothers Indriði and Sigurvin, Svala, my nephew Jón Stormur, Gunnar Logi, Bojana Kokinovic, Sigrún Reykdal, Ragnheidur&Solvi, Ásdís&Jónsi and family, Tryggvi&Ása and family, Pétur&Erna and family, Jón Kristinn&Perla and family, Jóhann Daníel&Mila and family, Logi&Ingibjörg and family, Sigurrós Yrja, Gísli, Valdimar, Ragga&Fannar, Einar&Kristín, Gunna&Ørger and family, Víðir, Thomas Fisichella, Runson, Halldór P, Guðrún S, and Thordur H. Finally thanks to Benhel and Paolo for the motivation. To the light in my life daughter Rebekka Elisabeth Pálsdóttir. And finally, remembrance to my dear friend Magnús Freyr Sveinbjörnsson who only shined transient upon our star.

Trondheim, February 2018

Páll Jens Reynisson

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Paper II

Páll Jens Reynisson, Erlend Fagertun Hofstad, Håkon Olav Leira, Christian Askeland, Thomas Langø, Hanne Sorger, Frank Lindseth, Tore Amundssen, Toril Anita Nagelhus Hernes. A New Visualisation Method for Navigated Bronchoscopy. Journal of Minimally Invasive Therapy & Allied Technologies 2017(30): p. 1-8.

Paper III

Páll Jens Reynisson, Håkon Olav Leira, Thomas Langø, Peter Hatlen, Tore Amundsen, Erlend Fagertun Hofstad. New CT visualization for guidance to peripheral lung tumours: Evaluation of operator performance. Journal of Minimally Invasive Therapy & Allied Technologies accepted February 2018.

Appendix Paper

Páll J. Reynisson, Håkon O. Leira, Erlend F. Hofstad, Tore Amundsen, Toril N. Hernes, Marta Scali, Hanne Sorger, Frank Lindseth, Thomas Langø. Navigated Bronchoscopy - A Technical Review. Journal of Bronchology and Interventional Pulmonology 2014 (21): 1-23

Note of contribution

Table 1: *Authors contribution on thesis papers.* ***Main:*** *most of the work,* ***Major:*** *large part of the work with co-authors,* ***Minor:*** *Contributions with co-authors,* ***NA:*** *not applicable.*

Work	Paper I	Paper II	Paper III	Appendix Paper I
Protocol and research design	Major	Main	Main	Main
Method development	Major	Main	Main	Main
Data Collection	Main	Main	Main	Main
Data analysis and statistics	Main	Main	Main	Main
Scientific discussions	Main	Main	Main	Main
Literature review	Main	Main	Main	Main
Writing the article	Main	Main	Main	Main

1. Lung diagnostics

1.1 Lung cancer and work-up

Lung cancer is a grave threat and has a five-year survival rate for early stage patients as low as 38% to 67% and 1% to 8% for later stages [1]. These facts underline the significance of earlier diagnostics of malignancy for better and right medical treatment to increase survival rate [2].

Screening for lung cancer has increased the detection of small lung lesions on computed tomography (CT) and have given a potential to diagnose more lesions at early stage. The literature mentioning early detection with screening has emphasized for faster, safer and inexpensive diagnostic approaches [3-5]. Lung cancer diagnostics involves radiology and tissue sampling. A CT scan of the chest (thorax CT) and upper abdomen is usually performed, which results in the initial staging according to size and location of the primary cancer, affection of nearby organs and distant spread. Other radiology examinations, like nuclear scans, MRI, PET, often supply the diagnosis. For tissue sampling most patients undergo a bronchoscopy, where an instrument (a bronchoscope) is inserted into the airways.

1.2 Bronchoscopy

The bronchoscope instrument and bronchoscopy has been in development from its invention in the end of the 19th century. Gustav Killian introduced the first rigid bronchoscopy for lung diagnostics in 1896 and defined it as direct bronchoscopy (figure 1 left). Rigid bronchoscopy did not develop considerably until developments on bronchoscope video carried out by companies like Storz and Wolf in the 50's [6]. The development of flexible bronchoscopy by Shigeto Ikeda in 1968 added a tool steering through the sharper branching turns of the airways, with additional flexible light fibre in the bronchoscope tip (figure 1 right) [6, 7].

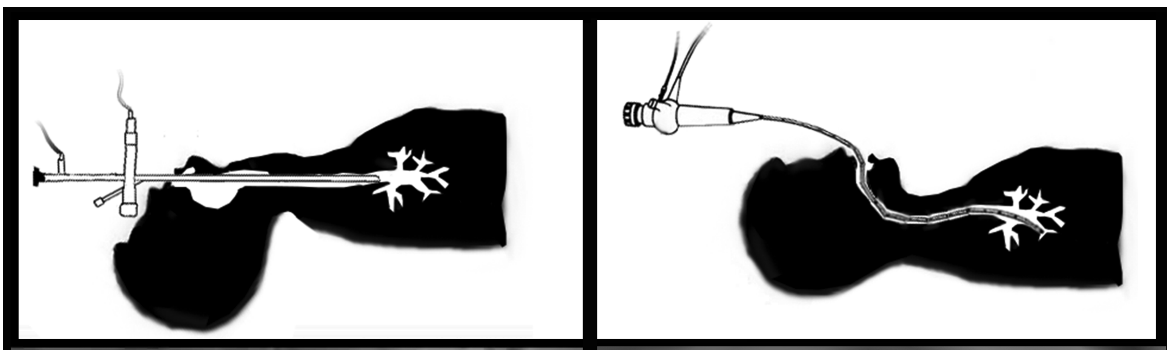

Figure 1. *ACS Rigid (left) and flexible (right) bronchoscopes, own image.*

1.3 Bronchoscopy success rates

Using a bronchoscope, the operator has a choice between needle aspirations, fluid washings, brushes, and forceps biopsies, and a combination of techniques is most often used. The overall success rate of bronchoscopic tumor diagnosis is 70-80% [8, 9]. But this varies greatly according to the position of the tumor in the lung and airways that are either centralized or peripherally located.

Centralized tumors are located in the central airways i.e. visible with the bronchoscope and are easy to find and sample. Diagnostic success rates for central tumors exceed 90%.

Peripheral tumors however is when the bronchoscope can, due to its diameter, not reach nor visualize the outer peripheral parts of the lung. Tumors beyond the visual reach of the bronchoscope are called peripheral tumors, and to sample these the operator has to forward a diagnostic instrument out in the peripheral airway tree beyond visual control. Accordingly, the diagnostic success rates drop sharply. Published success rates differ significantly, but most referred success rates for peripheral lesions states 63% for tumors >2 cm and 38% for <2 cm [5]. Note that publications presenting new technology or procedures in bronchoscopy are biased. The institutions circumstances vary in resource regarding high technical operation rooms, expert pulmonologist and technical staff behind them. Different studies regarding lesion criteria are also difficult to compare due to lack of standardization in what is considered peripherally located or not [10]. Diagnostic yield varies in the literature between 18-62% for conventional bronchoscopy [11]. An example is a report from Scottish multicentre study reporting success rate of 9% for peripheral lesion in 1998 [12].

2. Navigated bronchoscopy

Just before the end of the millennia, Ivan Bricult introduced endoluminal virtual bronchoscopy (VB) in 1998 [13]. This was the start of navigated bronchoscopy, where the operator is guided through the airways by 3D maps made from the patient's own radiology images. Introduction of navigation into bronchoscopy has increased success rates towards 80% in cutting edge lung diagnostic facilities [14-20].

VB is beneficial in procedure planning and during the image guided intervention in lungs especially when managing tracked tool such as steerable catheter or forceps outside visual range of the bronchoscope. Also, when the bronchoscope video is disturbed by blood, mucus or swollen tissue blocking the camera lens [21, 22].

Present visualization techniques demand multiple displays; traditional bronchoscope video, 3D endoluminal view of the airways, three orthogonal CT ACS views, x-ray, and vital signs monitor. The first decade of 2000 introduced a broad research and development on tool tracking via hybrid registration for navigated bronchoscopy, by utilization of electromagnetic fields and image registration for electromagnetic navigation bronchoscopy (ENB). Currently, there has been focus on the integration of EBUS for aspiration purposes inside the airways for lymph nodule biopsy [14, 23, 24].

Workflow including diagnostics, technologies and necessary steps for navigated bronchoscopy are listed in figure 2, but they involve these three phases;

1. Preoperative phase:
   - Acquisition of patient thorax CT, (including landmark fiducials if needed).
   - Data processing and 3D reconstruction from CT data; i.e. volume rendering and/or extraction of airways lumen (segmentation), targets (i.e. tumors) and centerlines typically, sometimes also vessels and other nearby structures.
   - Planning; visualization of data prior to procedure such as VB, 3D model of lesions or ACCuSurf
2. Intraoperative phase:
   - Image-to-patient registration with combinations of pattern recognition, electromagnetic field, centerlines and landmarks/fiducials, and also updating the registration during the procedure due to anatomic shifts. Registration may also include image-to-image registration for multimodal visualization if different data is available such as MR or PET-CT/MR [14].
3. Postoperative phase:
   - Documentation of procedure, presenting for clinicians

- Follow up on treatments and revaluation on patient condition, after the intervention that includes new CT data and medical inspections such as blood tests that could decide if the procedure should be repeated.

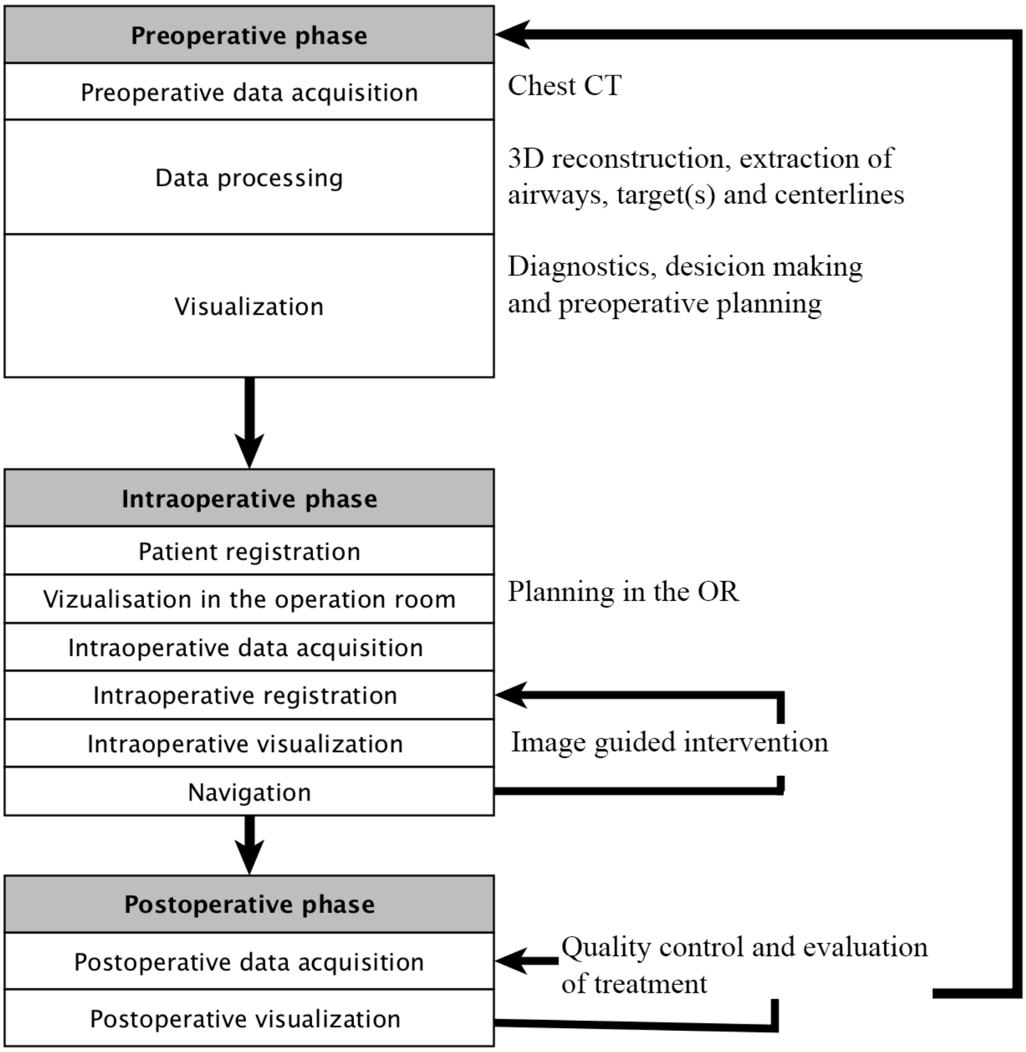

Figure 2. *Workflow of navigated bronchoscope.*

2.1 Patient registration

Before bronchoscopy with VB as a navigation application the airway model is linked and aligned with the real patient airways, so-called image-to-patient registration. Registration can also involve alignment to alternate radiology images such as magnetic resonance and positron emission images or other derived CT images or models from same patient, entitled image-to-image registration [25, 26].

Two classes of registrations are distinct; rigid and deformable registration. An assumption is made for rigid image-to-patient registration that the shape of the airways does not change after acquisition of a thorax CT. The drawbacks of the assumption are misalignment between the real patient and the airway model due to the respiratory motion of a breathing patient when the airway model remains static [27]. Also, misalignments due to the deformation while steering the bronchoscope inside the patient airways using a stationary airway model. Two rigid registration methods used for navigated bronchoscopy are centerline based and landmark based.

For centerline based registration, the centerlines of the airways must be extracted from the thorax CT. The bronchoscope tip is assumed to be located approximately at the centerline on average [28]. Accordingly, the centerline from the thorax CT is fitted with position data coming from a tracking senor on the tip of the bronchoscope. Tracking will be discussed in the next section. Registration is performed using orientation or the pointing direction of a sensor and running direction of the CT centerline [29, 30].

For landmark-based registration, anatomical landmarks and/or fiducials on/or inside patient body are matched with corresponding points in the CT images [17, 31, 32]. The fiducials are torus stickers filled with CT contrasts attached to patient while acquiring thorax CT and during image-to patient registration in the OR.

Future development in navigated bronchoscopy involves deformable registration aiming to compensate and correct issues that changes the patient anatomy after thorax CT such as;

- Progression of malignancies that change shape of the lungs [33-35].
- The alignment of the patient on the operation table vs. the table in the CT scanner.
- The patient respiration cycle that can change alignment by few cm, particularly in the lower peripheral parts of the airways [36].
- Pumping of heart and larger vessels [33-35].

The literature suggests compensating some of these issues by;

- Counteracting the patient breathing during the registration process through optimization on the respiratory movement with the anatomy using deformability [29, 37].

- Using local corrections on the airway model after the registration, during the navigation by either projecting the tool tip to the centerline on the airway model [28], or filter the VB image projection to match the bronchoscope video by continuous image based tracking [37, 38].

Deformable (or non-rigid) image-to-patient registration is not used in existing bronchoscopy platforms but the concept is to deform and align airway model to the movement of the real patient airway [39].

2.2 Instrument tracking

The concept of navigated bronchoscopy is to display the correct position and orientation of the bronchoscope as it is moved. Tracking position and orientation of the bronchoscope in real time and displaying this in 2D images and on 3D models created from CT is the second important part of achieving navigated bronchoscopy.

The most common tracking technology for navigated bronchoscopy is electromagnetic (EM) systems. Bronchoscopes and catheters can be integrated with and guided with EM tracking. EM tracking is based on use of small tracking sensor coils measuring an induced voltage, which is proportional to the flux of the magnetic field the sensor is located within, consequently the movement, rotation, and x, y, and z positions are possible to measure. The bronchoscope tool tip with attached tracking sensor is measured repeatedly, updating the position and orientation of the tool tip in the navigation system, which in turn displays an updated image on a monitor [40]. Two leading EM tracking systems for navigated bronchoscopy are NDI (Ascension Technology Corporation, Shelburn, VT, USA) and Polhemus (Vermont, Canada). NDI published an evaluation on magnetic tracking, comparing three different field generators [41]. Due to inductions in metallic objects there can be disturbance issues with EM tracking. Development in navigated bronchoscopy systems have accelerated since the EM tracking was introduced [42, 43]. The fiducials or anatomical landmarks mentioned earlier are pinpointed with an EM tracking pointer on patient during image-to-patient registration matching correspondent points in the airway model. Catheter tracking is only achieved by EM tracking. Yet, another alternative to EM tracking is the Anser system [44], which originally was consolidated onto a single printed circuit board (PCB). An ergonomic enclosure for the field generator was also constructed.

Another tracking approach for navigated bronchoscopy is image-based tracking. In image-based tracking, the bronchoscope tip location is found by comparison of airway model and bronchoscope video images and match these using mutual information techniques [26, 45, 46]. The mutual information is the intensity profile relationship between the airway model and bronchoscope video images [13, 25, 47]. The main drawback in image-based tracking are distortions such as mucus on the bronchoscope camera lens, consequently creating misalignments between the VB and video. Image-based tracking is also limited to the central airways as it requires the presence of the bronchoscope camera, and thus can't track instruments in the periphery of the lungs.

The third tracking approach is a combination of EM and image based, a hybrid tracking approach. For hybrid methods, the EM sensor location is used to estimate the initial location of the bronchoscope tip within the airway model, and the mutual information between the bronchoscope video and airway model is used as a correction. The airway model and the bronchoscope video is continuously registered (tracking correction) with time-varying filter to obtain more accurate position for the airway model to become VB [48, 49].

Some systems offer roadmaps without any tracking of the bronchoscope position. Instead the operator is given images of bronchial divisions along the path to the malignancy. When the operator advances further to the next division the system either manually or semi automatically provides image of next bronchial divisions. The images are from an airway model, without navigation [50]. The method is useful only to assist the operator during steering of the bronchoscope, i.e. choosing the correct division/path forward. The image-to-patient registration is performed with either electromagnetic (EM) field emitted through the patient, image based registration or a combination of both [51, 52].

2.3 Imaging of lung anatomy and visualization for planning and navigation

2.3.1 Imaging modalities in lung diagnostics

Visualisation in navigated bronchoscopy portrays medical images typically acquired from patient thorax CT, presenting the operator a better overview for planning or guidance to reach a target. There are two groups of modalities in medical imaging, anatomical modalities and functional modalities. The modalities are source for the different visualisation techniques in image guided surgery, therapy and diagnostic [53].

Anatomical modalities describe anatomical structures in the human body and are:

- Radiography or X-rays.
- Computed tomography (CT), also based on X-rays [54].
- Magnetic resonance imaging (MRI).
- Endoscope video.
- Ultrasonography or ultrasound (US) (also a functional modality).

Functional modalities reveal metabolism and functions of organs such as glucose consumption and blood flow, and include these imaging modalities:

- Single photon emission computed tomography (SPECT).
- Positron emission tomography (PET).
- Functional magnetic resonance imagery (fMRI).
- US such as pulsed Doppler for velocity measurements of fluids.
- Magnetic resonance angiography (MRA, from MRI).
- Digital subtraction angiography (DSA, from Xrays).
- Computed tomography angiography (CTA, from CT).

The most common image modality used for bronchoscopy is CT and is displayed in lung window figure 3.

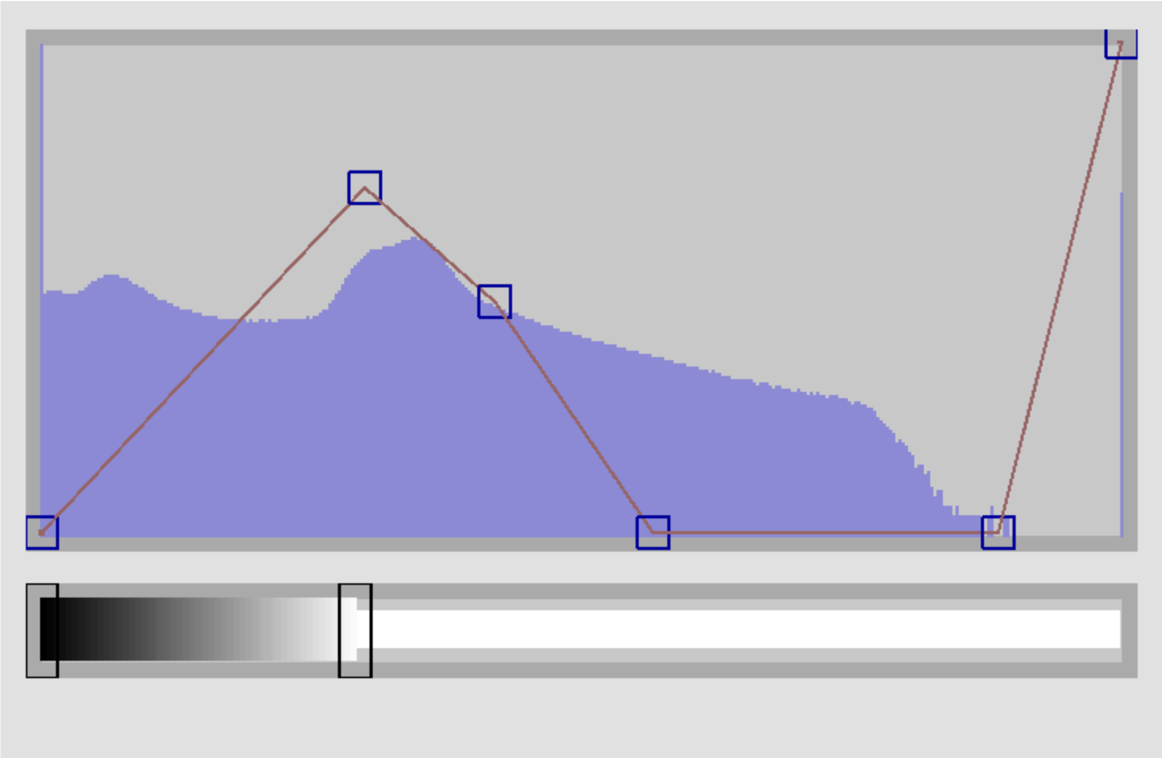

Figure 3. *Lung windowing transfer function. The scale to the left is HU= -1024 and the scale to the right is HU= 3096. Area under the red lines are the HU values displayed for the ACCuSurf and ACS views.*

The first stage of lung diagnostic is a thorax acquisition CT of a patient. A typical thorax CT includes set of 2D axial slices from trachea to diaphragm with a dimension of 512 × 512 pixels. The intensity scale in the CT pixels are called Hounsfield units (HU) with scale from -1024 to +3096 in the study. The characteristics of tissue has approximated values of [50]:

1. Air -1024 HU
2. Water 0 HU
3. Blood 10 to 30 HU
4. Solid organs 30 to 150 HU,
5. Bone >300 HU

2.3.2 Preoperative data processing (segmentation)

Segmentation of the airways is an extraction of the lumen part of the airways from the trachea and through as many divisions as possible, limited by the resolution of the images.

A recent review established five classes of segmentation methods [55]:

1. Thresholding-based.
2. Region-based.
3. Shape-based.
4. Neighbouring anatomy–guided.
5. Machine learning–based methods.

The Mansoor et al. review describes the classes thoroughly emphasising the use for abnormal pathological conditions of lungs [55]. The Tube detection filter (TSF) is a region based method for filtering tubular structures and centerlines such as airways and is used in this study [56, 57].

2.3.3 Visualization

Commonly available data sources for visualization during bronchoscopy are:

1. Video bronchoscope.
2. ACS from reconstructed 3D CT data.
3. Endoluminal display from segmented surface or volume modelled airways (based on CT).
4. Endobronchial ultrasound.
5. Fluoroscopy.

Other visualization displays available and can be taken from other modalities than CT for bronchoscopy are:

1. Any-plane (oblique plane) from 3D reconstructed CT or MRI.
2. Maximum intensity projection (MIP) from CT or MRI.
3. Stereoscopy of 3D data.
4. Image fusion approaches (PET, MRI, ultrasound).

The standard image guided intervention display for bronchoscopy is the intraoperative video display i.e. real-time imaging within the airway tract and preoperative 2D axial, coronal and sagittal (ACS) slices from thorax CT. The ACS slices exhibit different cross sections of the body within a 3D dataset see figure 4.

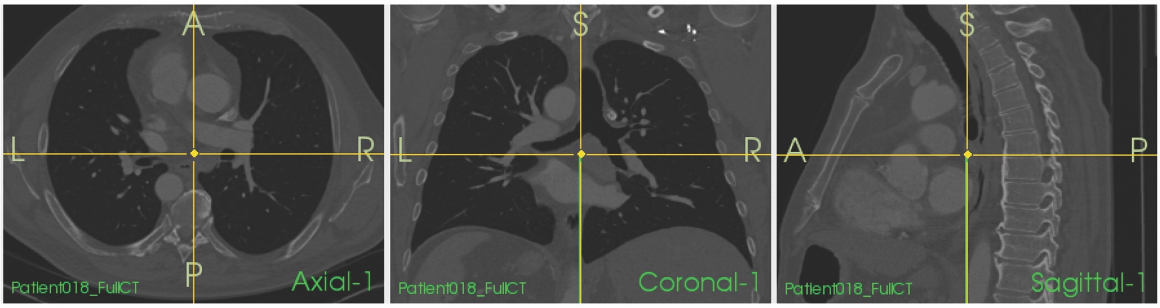

Figure 4. *ACS: Axial, coronal and sagittal views of CT data.*

A 3D CT volume has information of pixels between axial slices called voxels. A slice from 3D CT volume can be cut from any orientation and the display is called any-plane or oblique plane [58].

Visualization rendering are the techniques to create 2D perception of 3D volume or surface data on a screen [59]. Main rendering techniques for medical images are volume rendering and surface rendering, see figure 3 [59-61].

Volume rendering portrays 3D shaped structures from voxels onto a 3D grid or raster with all the information each voxel provides (see figure 5 left) [62]. The original data within the 3D images is preserved during the visualization process offering the possibility to display different information using thresholding. The disadvantage is the computational time and big amount of information compared to the surface rendering [61, 62].

Surface rendering portrays 3D models outer layer with no information inside or outside the models. The outer layer is constructed with multiple polygons identifying surface of interest (see figure 5 right) [63]. Airway models are mainly made from surface rendering of segmented structures via CT or MRI as the airways are hollow tubes and ideal for VB.

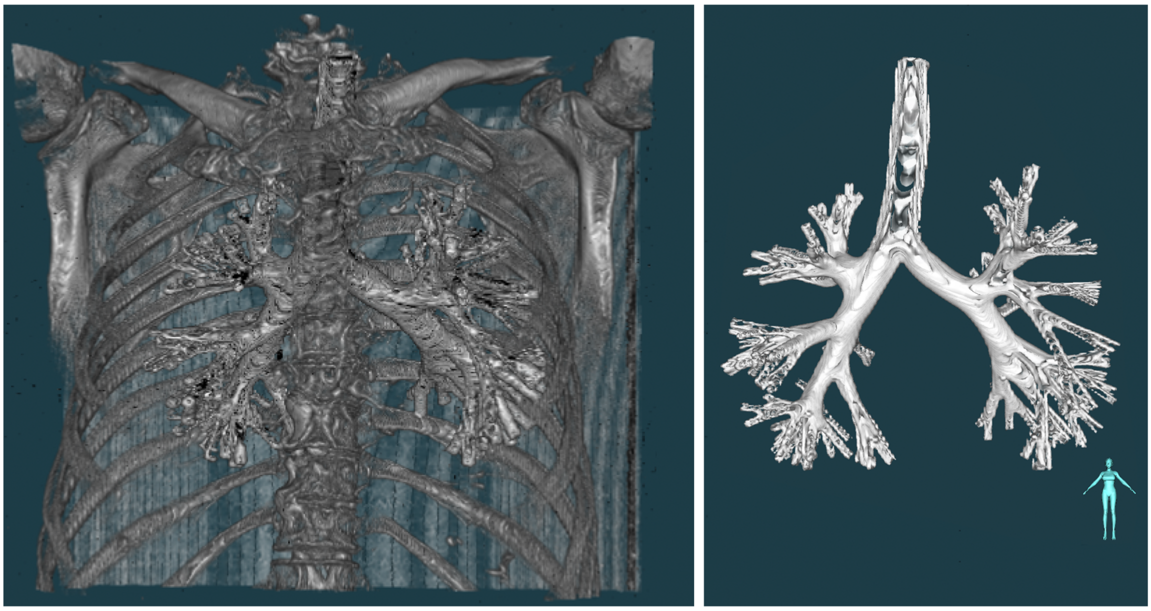

Figure 5. *Volume (left) and surface (right) models of phantom airways. Part of published image from own journal paper submitted [63].*

One visualization method is MIP, visualizing a projection of the maximum intensity of voxels from a CT volume [64]. MIP uses ray projection through a stack of 3D thorax CT volume and the highest HU value encountered by the ray crossing the stack is projected to an image. The anatomical advantages of MIP are clear tubular and branching structures versus discrete nodules [65].

Another visualization display is a slice projection technique called curved planar reformatting (CPR), projecting one defined path and displaying it stretched in a 2D projection [66].

Other possible visualization display for airways is image fusion exploiting multiple volume or surface based models from CT, MRI, PET or along with e.g. EBUS taken from inside the patient airway [14, 67, 68]

Ultrasound is only used with EBUS within the airways because ultrasound does not emit through air when a US probe is put between the patient's ribs [14]. One interesting approach could be a real-time image fusion of the pre-stated modalities with the video bronchoscope.

Stereoscopy is a visualization display used to express 3D information of volume data from two reference points. The two images are created as seen from each of the human eyes and can be merged with 3D viewing glasses for 3D display. The effect provides the viewer an awareness of depth of the 3D model [69].

The purpose of bronchoscopy is to steer an endoscope from mouth via trachea to a lesion for an inspection or biopsy in or outside the airways. The bronchoscopy procedure includes a planning phase using ACS CT slice views following a bronchoscopy. One of the main challenges in current bronchoscopy procedure is the accuracy in manoeuvring the endoscope tip to the right destination. The main aim of including navigation into bronchoscopy is the intention to improve the guidance to the right target with more confidence and accuracy [70]. Existing image guided approach for navigated bronchoscopy is video bronchoscope with VB see figure 6.

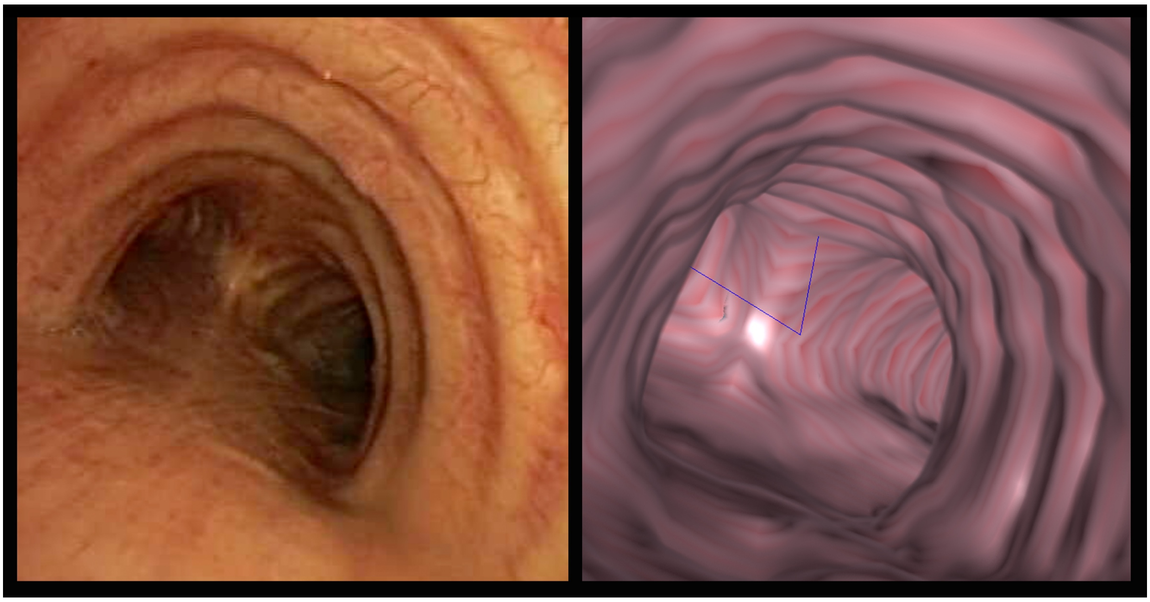

Figure 6. *Video bronchoscope(left) and VB (right) using surface model. Own image.*

3. Aims of study

The overall goal of the study was to develop a new visualization technique for navigated bronchoscopy that would ease planning before procedure. The work focuses on expansions of existing visualization procedures in navigated bronchoscopy, i.e. technology proposing a map display during computer aided navigated VB.

The aims were as follow:

1. Evaluation on a new segmentation method developed by scientists in SINTEF and NTNU for use in bronchoscopy.
2. Development of a new visualisation technique for VB.
3. Demonstration of the new visualisation technique as a planning tool for pulmonologists before bronchoscopy using lung phantom.

4. Materials and Methods

The PhD project was a collaboration between Department of circulation and medical imaging (ISB) and SINTEF. Three research applications (three scientific papers) on fulfilment of the research aims included;

1. Evaluation study; Evaluation of the Tube detection filter (TSF) method and the Mimics (Materialize, Leuven, Belgium) pulmonology module was performed on 17 in-house thorax CT data and the EXACT 09' lung reference data including 20 thorax CT. The data was processed with Matlab (Mathworks Inc., USA).
2. Visualization development; Anchored to centerline curved surface (ACCuSurf) visualisation method development was performed in Matlab using raw format to process the eight patient thorax CT scans.
3. Experiment on new visualisation technique; Experimental data was generated by fusing real patient thorax CT data and CT data of a silicon lung phantom (Ultrasonic Bronchoscopy Simulator LM-099 from KOKEN CO., LTD, Tokyo, Japan). Four targets were created on the silicon phantom and 12 pulmonologists used the experimental data as a planning tool before steering a bronchoscope with forceps to each target using either segmented airway model augmented onto the ACCuSurf or conventional ACS as a planning tool. The planning time, procedure time and successful navigation grade in percentage were measured.

All visualisation representation during the method development and experimentation was performed with the CustusX research platform. Additionally, our research group performed an extensive literature review on technical aspects of navigated bronchoscopy.

4.1 Background facilities

Rune Aaslid and Bjørn Angelsen started development on ultrasound at NTNU in early 1970's under the Department of Engineering Cybernetics. In 1984 the research headed by Bjørn Angelsen and Hans Torp was integrated into the Department of Biomedical Engineering. The Department of circulation and medical imaging was established in 2002 as part of the Faculty of Medicine.

Image-guided intervention focusing on intraoperative ultrasound was established in Trondheim in 1996 with the Norwegian National Advisory Unit for Ultrasound and Image-Guided Therapy (www.usigt.org). The intention is to perform clinical and technological research aiming at improving minimally invasive therapy. Today, about 20 clinicians at St. Olavs hospital/NTNU and 20 research scientists at SINTEF Medical Technology (including on-going and finished PhDs and Postdocs) are related to the National Advisory Unit. The collaboration between physicians from St. Olavs hospital, Trondheim University Hospital and research scientists from NTNU and SINTEF has resulted in productive and innovative efforts, verifying to be one of the leading groups within the field of image-guided intervention and navigation.

The basis of the navigation software technology (www.custusx.org) and competence for the bronchoscopy/lung project was offered and developed from the National Advisory Unit. Other equipment available to the project are ultrasound probe scanners, research and development navigation system platform exploiting tracking systems (optical and electromagnetic), navigation tools and tracking frames for several clinical applications, conventional bronchoscopes for lung diagnosis, other endoscopes like high-definition video laparoscopes and phantoms for bronchoscopy including EBUS phantom. SINTEF Medical Technology, and their collaborators within the Norwegian National Advisory Unit for Ultrasound and Image-Guided Therapy (St. Olavs hospital and NTNU), have devoted resources to create a multimodal navigation research platform CustusX.

4.2 Navigation platform CustusX/Fraxinus

The research and development platform CustusX (see figure 7) combines modalities such as preoperative CT / MRI data with intraoperative ultrasound and tracking systems for the improvement of navigated interventions. The platform is for image-guided interventions with focus on intraoperative use and supports data import in DICOM or meta-header format (.mhd and .raw).

The SINTEF research group and collaborators have been developing the research software for image-guided interventions since 1995, the last decade based on the open-source toolkits VTK (Visualization Toolkit, Kitware Inc., Clifton Park, New York, USA), ITK (Insight Segmentation and Registration Toolkit, Kitware Inc., Clifton Park, New York, USA), IGSTK (The Image-Guided Surgery Toolkit Kitware Inc., Clifton Park, New York, USA) and Qt (Qt Development Frameworks, Oslo, Norway). Though the present study focuses on bronchoscopy, the research platform for navigation in image-guided therapy also includes research within neurosurgery, laparoscopy and endovascular treatment at St. Olav University hospital [71]. In 2017, development of the Fraxinus planning application for bronchoscopy is based on CustusX [72].

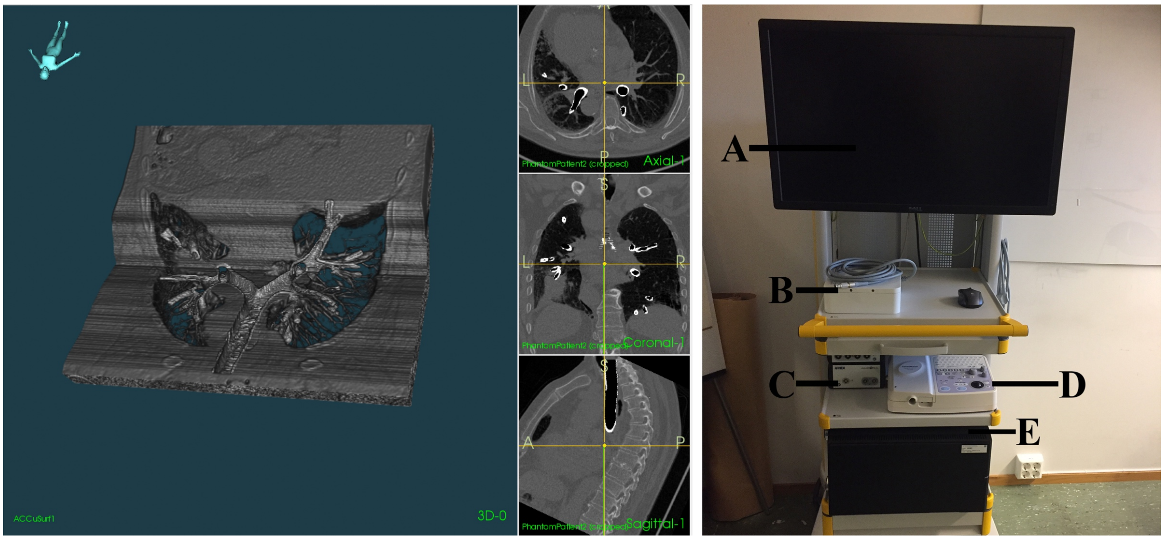

***Figure** 7. Left: Layout organised 3D+ACS View, ACCuSurf and ACS of fused silicon CT data and patient thorax CT. Right: CustusX rack; A) monitor, B) electromagnetic field generator, C) inlets for tool sensors, D) keyboard for ultrasound probe, E) Computer hardware.*

4.3 Trondheim lung group

The research with navigated bronchoscopy at St. Olavs hospital started in 2007 after professor Rolf Walstad and associate professor Tore Amundsen initiated a collaboration with SINTEF and could establish funding for a PhD candidate (Håkon O. Leira), one of the co-supervisors for current PhD project [36].

The partnership developed a research platform for navigation bronchoscopy including:

- Electromagnetic based navigated bronchoscopy [36, 73, 74].
- Registration method testing [51, 75, 76].
- Accuracy tests and measurements during respiratory movements [73, 77].
- EBUS tests with phantom [23].
- Airway segmentation development and testing [56, 57, 78, 79].
- Technical literature study on existing commercial software and Research and Development platforms/groups within navigated bronchoscopy [39].
- Development on new visualization display for navigated bronchoscopy and Performance test with pulmonologists using the display on patient phantom [63, 80].

4.4 Research applications

4.4.1 Evaluation study

The study was twofold; First an evaluation of our own 17 in-house thorax CT data with four different methods in three different software applications:

1. Dynamic region growing provided with Mimics basic module (MBM).
2. Deep airway segmentation provided by Mimics pulmonology module (MPM).
3. Tube detection filter (TSF) included in CustusX.
4. Threshold-based region growing algorithm in OsiriX (Pixmeo, Geneva, Switzerland).

To distinguish the difference between the methods regarding time consumption and quality, following parameters were surveyed:

1. Number of mouse click user needed to achieve segmented airways.
2. Number of branches and length of branches.
3. Total of branches in each branch generation.
4. Total volume of the segmented airways.

Secondly an evaluation on the MPM and TSF in CustusX by using an airway extraction global comparison study data of 20 patients with various conditions [81]. The overall percentage averages of airway branches extracted and total length of the whole study data were examined by the EXACT 09 experiments committee [81].

4.4.2 Visualization development

Development on Anchored to centerline curved surface (ACCuSurf) visualisation method using eight patient thorax CT data sets. The method algorithm exploits "route to target" an airway centerline extracted from patient airways from trachea to a virtual target.

ACCuSurf is prepared by following steps; For the demonstration in the paper two "route to target" centerlines from each side of a patient lungs are used to create the ACCuSurf. Lines between corresponding points in each centerline path are interpolated along with points from paths to the lateral edge of the thorax CT volume. These lines are made for all points in both centerline paths to form a 3D point cloud surface. Then HU values from the thorax CT data are extracted to the 3D point cloud surface. The results are displayed in CustusX using lung windowing. The visualization technique was implemented in Matlab.

4.4.3 Experiment on new visualisation

An operator performance experiment with 12 pulmonologists using either half airway augmented on ACCuSurf or ACS as a planning tool. Experiment data was produced by fusing real patient thorax CT data and CT data of a silicon lung phantom. The airways in the patient data were removed by assigning random HU values between 1-160 instead of the airway values of -1024 corresponds to HU values in the surrounding tissue (lung and heart). Next the patient thorax CT data and CT data of a silicon lung phantom were fused using centerline based registration method aligning the tracheas and the carinas in both datasets together. Then four peripheral targets, two in each side of the lung phantom were seeded separately into the ACCuSurf algorithm to create four different ACCuSurf. A half 3D airway tree was overlaid transparently on each ACCuSurf to demonstrate the upper half of the airways. CustusX generated the standard ACS of the fused CT data.

Each of the 12 operators had four unique test planning routines (none did the same routine) of experimenting two ACCuSurf and two ACS on targets 1-4 a total of 24 samples for each visualisation approach. The routine difference gave none of the targets or the visualisation methods an advantage.

A mark indicator resembled each of the four targets in CustusX while an operator figured out the right route to target from his/her own perspective in planning phase. When the operator was confident enough, he/she steered a bronchoscope to the closest branch, one thought was right and pushed forceps out of the end. The time during the planning and procedure were measured. The navigation percentage was graded based on number of right branch generation passed towards each target.

4.4.4 Appendix paper - technical review

During the research time, we made an extensive review on existing software and technology in Navigated bronchoscopy. We used peer review journal databases; **GoogleScholar, IEEE, SpringerLink, PubMed and ScienceDirect** ***using following keywords:*** *navigation, tracking, registration, image tracking, medical image guided navigation platforms, platform names, and R&D platforms, always limiting these to bronchoscopy.* After chasing the journal papers, we iterated the discovered references using the relevant papers from the last ten years (2003-2013) and emphasised specially on the last five years, though few older key papers were included such as the first development papers of virtual navigated bronchoscopy.

5. Summary of Papers

Paper I - Airway Segmentation and Centerline Extraction from Thoracic CT – Comparison of a New Method to State of the Art Commercialized Methods.

Surface models of airways are used for image guided intervention such as navigated bronchoscopy. Optimized time and logistics during planning phase before navigated bronchoscopy ease the complexity of the intervention. Trondheim research group developed and published a tube segmentation filter (TSF) for airway segmentation and centerline extraction [56, 57]. This paper compared three different software applications for airway segmentation and centerline extraction from CT data. The software applications used were open source CustusX (SINTEF, Trondheim, Norway), free software package OsiriX (Pixmeo, Geneva, Switzerland) and the commercially available Mimics (Materialize, Leuven, Belgium). Mimics provides a Basic module (MBM) and Mimic Pulmonology module (MPM). These four different approaches were evaluated with lung data from 17 of our patients. The freeware OsiriX was the least accurate software compared to the other approaches regarding segmentation results and number of mouse clicks required for the airway extraction. The results from the MBM was also time consuming in the aspects of number of mouse clicks to achieve segmented airways and centerlines.

The two most automatic approaches; MPM and TSF method in CustusX were also evaluated specially with 20 patient data sets standardized from the EXACT 09 study [81]. The MPM segments the highest number of branches and generations, on the other hand the MPM needs a seed point while the TSF is fully automatic. The TSF is able to extract the airways and the centerlines in one single step. The EXACT 09 protocol data sets are part of an international evaluation study on airway segmentation algorithms. Main results regarding the PhD study is that TSF is compatible with overall averages published from the EXACT 09 segmentation study. The comparison on the results in the study to the overall segmentation methods in the EXACT 09 was close or within the standard deviation for branch detection and tree length. The mean and standard deviation for the branch detection were 42.9±9.6% and 31.3±10.4% for the MPM and the TSF methods, respectively, both lower than the reference segmentation average but within the standard deviation range of 51.8±13.5%. Mean and standard deviation for the tree length detected was 37.5±7.1% and 27.4±9.6% for the MPM and the TSF methods, respectively, both lower than the reference segmentation average but within the standard deviation range of 46.0±12.9% [79].

Paper II - A New Visualisation Method for Navigated Bronchoscopy.

Visualisation methodology development using airway lumen and centerline obtained from TSF. Endoluminal display of airways alone fails pulmonologist's needs to locate and sample the frequent targets outside the bronchial wall during navigated bronchoscopy. The paper demonstrates creation of anchored to centerline curved surface (ACCuSurf). ACCuSurf is a method that includes, in addition to the route to target, the anatomical features surrounding the airways for diagnostic purposes. The ACCuSurf method is presented using eight patient lung data sets with shortest path from trachea to target lesion (i.e. route to target) with an auxiliary branch from the other side of the lung for visualization in navigated bronchoscopy. The ACCuSurf algorithm extracts voxel segments from the CT data beginning in the shortest paths and the branch on each side of the lung and ending in the CT datasets boundaries. The new technique was tested on non-selective CT data from eight patients using random artificial lung targets deep in the lung periphery on the left side the most lateral branch and peripherally on the right side. The ACCuSurf was displayed in CustusX with appropriate lung window setting used by lung doctors. A comparison argument was made between airway endoluminal view, ACCuSurf, and both combined. The ACCuSurf display is more informative compared to endoluminal view alone. ACCuSurf combines into one view the anatomical structures such as airway route to target with surrounding information of vessels and lesions. The conclusion suggested that ACCuSurf might be feasible addition to bronchoscopy and could simplify planning before bronchoscopy and aid the guidance during.

Paper III - Pulmonologist evaluation on new CT visualization for guidance to lung lesions during bronchoscopy

Feasibility study on combined visualising methods ACCuSurf with airway model. In the previous study, we suggested that the new visualisation method ACCuSurf would simplify planning before bronchoscopy. A performance test was made with 12 pulmonologists using ACCuSurf alongside airway model versus standard ACS displays on a phantom as a planning tool before bronchoscopy. The data was a mix between patient CT and a high-resolution scan of the phantom. Each pulmonologist targeted four virtual targets in the physical phantom, using the navigation system for planning and guidance during bronchoscopy. The navigation system displayed the image data in either ACS or ACCuSurf visualization with a transparent version of the top half of the airways overlaid. Each pulmonologist was given two targets for each of two visualization methods. No pulmonologist made the same combination of routine, using different visualization and target order. The planning and procedure time were measured, in addition to a score for navigation success. As mentioned, a CT scan of the phantom was fused with an anonymized thorax CT scan of a patient to create a convincing bronchoscope presentation to the pulmonologists. There were two targets in each side of the lung phantom. The pulmonologists were then given either ACCuSurf with airway model sliced in half or ACS display of a target to aid the planning procedure.

The experiment setup proved realistic corresponding to the pulmonologists. ACCuSurf with sliced airways proved better than ACS in planning time and navigation success grading. The study concluded that improvements in visualization technique would improve planning and navigation in bronchoscopy and might consequently contribute to more accurate lung diagnostics.

Appendix paper - Navigated Bronchoscopy - A Technical Review.

Navigated bronchoscopy is not currently in widespread use. A broad literature review included in the appendix found four commercial software based systems and ten research groups working actively and publishing in the field of navigated bronchoscopy and associated software solutions. The commercial platforms available are [82];

1. **SuperDimension** (Minneapolis, USA)
2. **Lungpoint** (Broncus Technologies, Inc., Mountain View, USA)
3. **Veran SpinDrive** (Veran Medical Technologies Inc., St Louis, USA)
4. **bf-NAVI** virtual bronchoscopic navigation (Emergo Group, Austin, USA) [13].

The ten research groups are:

1. **Atlas group** (The University of Iowa, USA)
2. **Pluto group** (Nagoya University, Japan),
3. **DKFZ group** (Heidelberg, Germany)
4. **BRONCHOVID group** (Krakow, Poland)
5. **Medizinische Klinik I and Workgroup MITI group** (Munich and Erlangen, Germany)
6. **V-Ninja group**, Olympus prototype (Sapporo, Fukushima, Tokyo, Japan). Commercialized into bf-NAVI.
7. **Pennsylvania group** (Pennsylvania State University,, USA) Partly commercialized into Lungpoint
8. **HPL group**, ((University of Washington, USA)
9. **Trondheim group** (Trondheim, Norway)
10. **BioElectromagnetics group** [82], (University College Cork)

There has been research and testing of navigation technology since our publication of the literature review, mainly within EBUS navigation [14, 23, 24, 68]. One positive feasibility study was found combining navigation bronchoscopy with fluoroscopy and near-infrared fluorescence thoracoscopy with injecting green indocyanine transbronchially into the lesions [83]. Furthermore, there have been tests on magnetic interference from navigational bronchoscopy on implanted cardioverter defibrillators and pacemakers. No patients underwent arrhythmias or other disturbance to their pacemakers during ENB [50, 84]. Regarding image to patient registration; improvements on gradient detection of lumen centre could potentially improve the image to patient registration [84].

6. Discussion and Future Work

The first objective was to evaluate TSF and compare it to three other airway segmentation methods. The evaluation proved the TSF to be comparable to other state-of-the-art segmentation method MPM used to extract human airways, regarding the least number of mouse clicks to obtain a result of segmented airways. Of the four different approaches the freeware OsiriX was the most manual and time consuming (number of mouse clicks to obtain a result of segmented airways using our own patients. MBM performed better than TSF finding more branches and more branch generations while using our own patients but it was not as automatic. We compared TSF and MPM to a reference standard because both were semi- or automatic or. Both TSF and MPM were close or within standard deviation for branch detection and tree length.

The second objective introduced the utilization of route to target and a curved anyplane anchored to the centerline, a curved surface (ACCuSurf), a surface that mimics the current guidance road maps in global positioning system (GPS) display monitors but within the lungs. The route to target was obtained from the Airway centerlines extracted from TSF. The method developed used as inspiration from the Any-plane/Oblique plane view feature combined with airway centerline path leading from the trachea to a target lesion, i.e. route to target [58, 85]. We used thorax CT from 8 patients and demonstrated ACCuSurf on all of them. Compared to three ACS orthogonal views the ACCuSurf surpasses the conventional way by representing the directional/orientation info additionally to the anatomical information. The ACS view do not correspond clearly the direction of the airways and are therefore less suited as a map guidance for bronchoscopy tool, that indication was confirmed with planning study using the silicon phantom. VB is an excellent visualisation approach for instrument guidance as it resembles the real-time bronchoscopy video while using tool tracking. The VB however lacks information about surrounding anatomical structures outside the endoluminal view and if VB does not include the tracking then it lacks the orientation and direction to target. We acknowledge that all three have limitations and pulmonologists need to use both VB and ACS with two different monitor feeds unfortunately making the methods more complicated than it should be, and therefore failing the purpose of simplification. We suggest that ACCuSurf could combine both VB and ACS information in one view.

Third objective focused on a feasibility test for the new ACCuSurf visualization technique. The visualization was tested on pulmonologists using it as a planning tool before performing bronchoscopy on a patient phantom [63]. We image fused a CT of silicon phantom and patient CT to let the regular ACS and ACCuSurf visualisations appear more real and the pulmonologists. All of the lung doctors were capable of transferring the knowledge gained from the planning phase to perform bronchoscopy procedure on the silicone phantom. Every pulmonologist mentioned that the patient phantom data were realistic, though it lacked respiratory motion that made it easier to perform bronchoscopy on compared to real patient. On the other hand, they commented that it was stiffer to perform bronchoscope on the phantom than on a patient. We compensated the stiffness by spraying silicone lubricant on the bronchoscope before the pulmonologists performed bronchoscopy. The ACCuSurf visualisation with 3D airway overlay proved better planning tool than ACS regarding the how close to target the pulmonologist were able to get.

Finally, during the PhD research project, a literature review on navigation platforms was performed to extract an overview of the research field found in the appendix [39]. There were four commercial and nine research and development based software found globally. The paper evaluates all the software based on peer reviewed and published material in 5-7-year period. The literature review confirmed peripheral diagnostic accuracy improvements using navigated bronchoscopy. The review also confirmed that virtual endoluminal view and the CT three orthogonal views are still the main existing display approach. Overall the SuperDimension system, specially designed and built for navigated bronchoscopy, has an advantage on the market being the first system to be commercially available, four years ahead the next system introduced to the market. SuperDimension is the most tested system in the literature. We found over 30 journal papers describing and testing the navigation system, compared to 15 journal papers in total on the other three commercially available systems.

The future development that are crucial for navigated bronchoscopy are:

- EM tracking integrated in tools.
- Automated segmentation and centerline extraction.
- Compensation for lung movement.
- Level of integration into bronchoscopy suite.
- Possibly 3D visualization.

For successfully guiding and navigating peripherally in the lungs, the tools need to be tracked. Also, the visualization needs to be easy to interpret and understand, including the route to target. Using the centerline seems to be one of the most promising methods to perform registration. Using the centerline can also be used to update the registration, the common assumption is made that the tool tip is always in the centre of the lumen. The most important developments will be to increase the diagnostic success rate further, particularly to target small peripheral lesions more accurately during biopsies. To achieve that, methods compensating the respiratory movements might be necessary.

For navigational bronchoscopy to gain wide acceptance in lung medicine, a more integrated solution in the operation suite is essential, i.e. tracking system integrated in table and visualizations routed to monitors used currently during bronchoscopy [39].

We evaluated the 3D visualisation less important in the literature review, but this may prove wrong in the next years. We demonstrated that 3D visualisation might be superior to the traditional 2D ACS view in one of the studies [63].

The virtual visualization, i.e. the 3D modelling of lung structures, have been mainly concentrated on endoluminal viewing of the airway structures for navigation, attempting to replicate the bronchoscope video display. Motivation for using navigation in bronchoscopy is the potential increase in diagnostic success rates and yield on lung lesions, as mentioned earlier. The aim of navigated bronchoscopy is to ease and improve guidance to lesions for improving diagnostic yield. One of these improvement factors is the visualization technique that this PhD project has developed. The ACCuSurf combines the CT data and extracted models into one single view. The ACCuSurf displays the route to target and has a potential to reduce procedure time and add to the improvements, quality and success rates during navigation with easier planning and guidance to a central or peripheral part of the lungs. Improved visualisation approach such as ACCuSurf would add to other potential future work that includes navigation into peripheral parts of the lungs and better airway segmentation. We proved that usage of ACCuSurf with 3D airways overlay is a better planning tool than conventional ACS. The ACCuSurf needs to be tested in an animal study before concluding more of it.

An interesting addition to ACCuSurf could be deformability to simulate respiratory motion. Using ACCuSurf as a test object for deformation would be less computationally expensive than using the complete 3D thorax volume.

The main challenge for using navigated bronchoscopy is the accessibility due to cost and complex technology for lung doctors that are used to current visualisation approach with orthogonal CT slicing, only. Education and practice on navigation systems in early stages of pulmonologists training would add to its future integration for lung diagnostics. ACCuSurf represent simpler overview than conventional ACS. ACCuSurf could ease the complexity of teaching navigated bronchoscopy as a standard routine versus the conventional way using ACS and no navigation.

Operation theatres in a research hospital such as St. Olavs are state of the art and not standard circumstances in every hospital. Making navigation software freeware would contribute to make navigation in bronchoscopy more accessible. I believe that by creating an optimal visualisation display for planning and procedure guidance would make it more appealing for pulmonologist to use navigation in bronchoscopy.

Future work could include improvements on the visualization and display to appeal more to lung doctors to practice navigated bronchoscopy as a standard diagnostic tool. Improvements might further enable and encourage pulmonologists to increase the use of navigated bronchoscopy. Repeated surveys and experiments correspondingly applied in the current PhD research include lung doctors training bronchoscopy on lung phantoms and consequently introducing new pulmonologist into the field of navigated bronchoscopy.

Bronchoscopy simulation is recommended for future advancement of navigated bronchoscopy for training new pulmonologists in lung diagnostics until a certain level of competence is achieved [86]. Familiarizing new pulmonologist in early medical training would accordingly integrate navigation as a standard procedure in lung diagnostics. Parallel the endobronchial ultrasound could be integrated in a standard bronchoscope training and procedure [87]. A review on bronchoscopy simulation as a training tool suggested two approaches to teach and practise pulmonologists in navigated bronchoscopy [86]:

1. Bronchoscopy skills and tasks assessment tool (BSTAT) [88, 89].
2. Bronchoscopy step-by-step evaluation (BSSE).

The BSTAT was concluded to be a tool to measure improvements on pulmonologist's technical skills after course training. BSTAT failed to distinguish between intermediate and expert pulmonologist and therefore BSSE was suggested as an additional training tool and tested. BSSE approach was able to discriminate among novices, intermediates, and experts [86].

Our pulmonologist evaluation on ACCuSurf had not enough test subjects to estimate any difference between novice, intermediate, and expert operators. But as mentioned all of our test subjects said that our experiment was realistic. One future study could test our method and phantom as a training tool with BSTAT and BSSE.

Of all the navigation platform SuperDimension was the first on the market in 2003, four years ahead the next one (LungPoint). Consequently, due to the head start, if there is a navigation platform in any hospital it is almost certain to be SuperDimension. Our literature study confirmed that SuperDimension is mentioned in more peer review papers than the other three navigation platforms combined. As this study is published there is a prospective, multicenter, global, cohort study of electromagnetic navigation bronchoscopy going on specifically on SuperDimension [90, 91].

Usage of electromagnetic navigated bronchoscopy is more expensive than conventional CT-guided method. A recent paper estimated the biopsy cost difference between those two as means of \$6.633 (95% Confidence interval \$1.518–18.511) vs. \$2.913 (95% Confidence interval \$1.248–18.241) in the electromagnetic navigation and CT-guided bronchoscopy, respectively [92]. The study referred only to the SuperDimension system hence the computations are based on the SuperDImension iLogic system. The expenses are bigger using electromagnetic navigation bronchoscopy biopsy approach than CT-guided bronchoscopy. But the diagnostic yields are higher using electromagnetic navigation bronchoscopy (80%) than CT-guided bronchoscopy (9-62%) [11, 12, 14-20, 93]. The challenge for the other commercial and research based software and platforms is to compete with SuperDimension on economical position, but not on technological ground. The other commercialized and research based platforms and software are compatible to SuperDimension. The main assignment to the future pulmonologists and hospital directors is to make navigational bronchoscopy a standard procedure in lung diagnostics. One way would be making a navigation platform or software a freeware or open source.

Making the navigation software open source and optimizing the visualisation exercising survey and experiments give benefits such as;

1. Attracting more physicians to exercise proper planning and navigated bronchoscopy for more accuracy.
2. Increasing probability of right diagnostic for patients in the first intervention and therefore the correct necessary cancer treatment earlier.
3. Consequently, saving hospital resources, decreasing the necessary repetition of bronchoscopy, and providing lung doctors with better confirmation of a successful procedure.
4. Enabling researchers to contribute by using a common software platform (e.g. CustusX) to develop new techniques within minimally invasive interventions.

By attracting more lung doctors to perform navigated bronchoscopy, for diagnostics, the lung physicians' community would also increase its technology skills and hence promoting use of navigated bronchoscopy as a standard practise.

The methodologies, knowledge and techniques done in one practise, such as navigated bronchoscopy can be used in other clinical applications where flexible endoscope is applied inside the body/cavities. For example, the ACCuSurf could be a useful tool to better navigate a catheter in endovascular therapy similar to CPR that offers stretched surface without the depth in 3D that ACCuSurf provides.

The actual display of the ACCuSurf in combination with other sources can also be optimized with respect to the specific phase of a procedure, e.g. overview in the start, more zoom in as you get to the target, and other images such as ultrasound mini-probe at the target. Default display for the different phases of the intervention may also be defined in collaboration with several pulmonologists and based on observation studies. Phase detection software have to be used in conjunction to automate such dynamic displays during the procedure.

Image fusion of 3D CT and bronchoscope video real time data is something that has not been done before. The study already established a new visualisation approach, the ACCuSurf view and next step would be the fusion integration with bronchoscope video and other medical image modalities like PET and EBUS/ultrasound.

Other improvements in lung navigation would be improvements on steerable catheters and better CT data resolution. Development on thin steerable catheters such as ultrathin single scanning fibre bronchoscopy for the peripheral parts of the lungs have been reported with diameters as small as 1.6mm [37, 48, 94].

Better airway segmentation could possibly be obtained by decreased voxel dimensions, i.e. the spacing and pitch in and between the CT images needs to be decreased for increased lung patient data resolution. Current CT scanners at St. Olavs hospital give pixel spacing of 0.70 mm and pitch of 0.50 mm giving diagonal spacing of 1.1 mm while state of the art scanner has diagonal spacing of 0.33 mm (SOMATOM Definition Flash, Siemens). These concerns are confirmed by the literature as the one of the main limitations in navigated bronchoscopy [14, 95]. Increased resolution provides more details and visual edges of the voxels in thorax CT. Increased resolution would therefore give opportunities for detecting more branches and segment thinner airways in higher branch generations; consequently, generate routes further into the peripheral parts of the lungs. The study was only able to obtain two branches in 13th generation from one patient with Mimics Pulmonology module and the study could only detect all branches in 2nd generation precisely in all patients [79]. One fundamental study concluded a human lung is branching up to 25th generations and diameter and branch length decreasing from 16 mm down to 0.8 mm and from 100 mm down to 3.1 mm respectively once airway divides in the route to alveolar ducts [96].

As mentioned the diagonal voxel spacing in our study is 1.1 mm but could be 0.33 mm with state of the art CT scanners. Improved resolution would improve the ACCuSurf visualization presenting more details for detecting smaller lesions, perhaps not noticed on CT scans today. It would also provide more complete routes for peripheral targets.

One possible future development in lung diagnostics utilizing navigated bronchoscopy is twofold concerning model movement;

1. *Deformability:* Integrating breathing motion on present 3D visualization combining deformation on static CT scan via respiratory measurement on patient chest and lungs.
2. *Four dimensional (4D) helical CT scanning:* Using data sample from a 4D helical scanner during one respiratory cycle on patient then proceeding implementing a lung model and register to patent before navigation.

A first approach for model movements could be using intensity based deformation. Deforming medical images for registration purposes among others was recently developed in a software called elastix (elastix.isi.uu.nl/) [97], which also is integrated to the CustusX platform.

Another approach would be finite element modelling (FEM). FEM can potentially be integrated to predict deformability based on Hounsfield to lung tissue material properties. Hounsfield values in thorax CT vary and are therefore non-homogeneous. There exists a method developed for FEM in bones that smears Hounsfield values to bone converted material properties on models that includes movements [98, 99]. Methods such as these could be implemented on static lung data models for deformation after establishing a proper Hounsfield to material conversion and boundary conditions on movements.

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7. Conclusion

From all three research applications, I conclude;

1. The evaluation of the segmentation methods using the EXACT 09 reference data proved the TSF and MPM to be equivalent to other state-of-the-art segmentation used to extract human airways.
2. Development of a new visualisation technique for VB was accomplished with Anchored to Centerline Curved Surface (ACCuSurf).
3. The usage of the new visualisation technique ACCuSurf with 3D airway overlay proved better than ACS view as planning tools before bronchoscopy on a silicone phantom.

The ACCuSurf display represents a future add-on and new visualization approach in navigated bronchoscopy. ACCuSurf is suitable for both planning and navigation and as CT scanners technology progresses there will be more information available than today. Many different image modalities may be displayed and fused in the ACCuSurf visualization through co-registration of the data during the planning phase. PET, ultrasound, and VB view are examples of such multimodal views that could be combined with ACCuSurf, which I believe could be useful to the clinicians, both in planning and guidance of bronchoscopy.

Improved CT scanners will offer better microscale features detection and accordingly improve the results from airway segmentation, giving increased number of segmented airway branches. Increased number of segmented airway branches will give more detailed route to target navigation maps such as ACCuSurf and endoluminal airway views than offered by existing data acquisition.

Research on lung deformability such as measurements on respiratory motion and movement simulations with finite element added together with better route to target navigation maps would give an opportunity for micro scale instruments to advance further into a human lung than today.

Finally, the navigation in bronchoscopy could be more widespread with more accessibility to the technology that would reduce cost and ease the education for pulmonologists to use it as a future practise in lung diagnostics. I believe that navigation platforms for guidance of bronchoscopy will be the golden standard and principal practice in the future of lung medicine. Navigated bronchoscopy is still a developing field and display options have not been fully optimized and exploited. Perhaps the contribution of this thesis research work will help improving the user-friendly aspect of planning and navigation in bronchoscopy, to make it a common practice.

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Paper I

RESEARCH ARTICLE

Airway Segmentation and Centerline Extraction from Thoracic CT – Comparison of a New Method to State of the Art Commercialized Methods

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OPEN ACCESS

Citation: Reynisson PJ, Scali M, Smistad E, Hofstad EF, Leira HO, Lindseth F, et al. (2015) Airway Segmentation and Centerline Extraction from Thoracic CT – Comparison of a New Method to State of the Art Commercialized Methods. PLoS ONE 10 (12): e0144282. doi:10.1371/journal.pone.0144282

Editor: Josué Sznitman, Technion - Israel Institute of Technology, ISRAEL

Received: August 26, 2015

Accepted: November 15, 2015

Published: December 11, 2015

Data Availability Statement: Data are available from Dryad (doi:10.5061/dryad.mj76c).

Funding: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Funding for MS EFH HOL ES FL TANH TA HS TL is from: This work was supported by the Liaison Committee between the Central Norway Regional Health Authority (RHA), the local Cancer Fund at St. Olavs University hospital, SINTEF Department of Medical Technology, the Ministry of Health and Social Affairs of Norway through the Norwegian National Advisory Unit for

Abstract

Introduction

Our motivation is increased bronchoscopic diagnostic yield and optimized preparation, for navigated bronchoscopy. In navigated bronchoscopy, virtual 3D airway visualization is often used to guide a bronchoscopic tool to peripheral lesions, synchronized with the real time video bronchoscopy. Visualization during navigated bronchoscopy, the segmentation time and methods, differs. Time consumption and logistics are two essential aspects that need to be optimized when integrating such technologies in the interventional room. We compared three different approaches to obtain airway centerlines and surface.

Method

CT lung dataset of 17 patients were processed in Mimics (Materialize, Leuven, Belgium), which provides a Basic module and a Pulmonology module (beta version) (MPM), OsiriX (Pixmeo, Geneva, Switzerland) and our Tube Segmentation Framework (TSF) method. Both MPM and TSF were evaluated with reference segmentation. Automatic and manual settings allowed us to segment the airways and obtain 3D models as well as the centrelines in all datasets. We compared the different procedures by user interactions such as number of clicks needed to process the data and quantitative measures concerning the quality of the segmentation and centrelines such as total length of the branches, number of branches, number of generations, and volume of the 3D model.

Results

The TSF method was the most automatic, while the Mimics Pulmonology Module (MPM) and the Mimics Basic Module (MBM) resulted in the highest number of branches. MPM is

Ultrasound and Image-Guided Therapy (Trondheim, Norway), and the project 196726/V50 eMIT (enhanced Minimally Invasive Therapy) in the FRIMED program of the Research Council of Norway. The research leading to these results has also received funding from EEA Financial Mechanism 2009 - 2014 under the project EEA-JRP-RO-NO-2013-1-0123 - Navigation System For Confocal Laser Endomicroscopy To Improve Optical Biopsy Of Peripheral Lesions In The Lungs (NAVICAD), contract no. 3SEE/30.06.2014. PhD position of PJR is funded by following: The work is also a part of a Marie Curie Initial Training Network for the Integrated Interventional Imaging Operating System (IIIOS project) funded specially by the Dean Office of Norges teknisk-naturvitenskapelige universitet (NTNU) (DT-sak 267-11 Temporary position as PhD Candidate, Department of Circulation and Medical Imaging, Faculty of Medicine). The work is also granted from Norwegian Research School in Medical Imaging and the Interventional Center (OUS/UiO).

Competing Interests: The authors have declared that no competing interests exist.

the software which demands the least number of clicks to process the data. We found that the freely available OsiriX was less accurate compared to the other methods regarding segmentation results. However, the TSF method provided results fastest regarding number of clicks. The MPM was able to find the highest number of branches and generations. On the other hand, the TSF is fully automatic and it provides the user with both segmentation of the airways and the centerlines. Reference segmentation comparison averages and standard deviations for MPM and TSF correspond to literature.

Conclusion

The TSF is able to segment the airways and extract the centerlines in one single step. The number of branches found is lower for the TSF method than in Mimics. OsiriX demands the highest number of clicks to process the data, the segmentation is often sparse and extracting the centerline requires the use of another software system. Two of the software systems performed satisfactory with respect to be used in preprocessing CT images for navigated bronchoscopy, i.e. the TSF method and the MPM. According to reference segmentation both TSF and MPM are comparable with other segmentation methods. The level of automaticity and the resulting high number of branches plus the fact that both centerline and the surface of the airways were extracted, are requirements we considered particularly important. The in house method has the advantage of being an integrated part of a navigation platform for bronchoscopy, whilst the other methods can be considered preprocessing tools to a navigation system.

Introduction

Lung cancer is among the most frequent malignant diseases and overall only 10–15% of patients are expected to survive five years. Early diagnosis and selection of appropriate therapy is essential for survival, as among early stage cancer patients, 38–67% will live for at least five years, compared to 1–8% in the more advanced stages of the disease [1].

The early stage lung cancers are most often small, single tumors in the peripheral parts of the lungs, and they may be hard to reach with biopsy tools in current diagnostic methods. Peripheral parts of the lungs are the locations that the bronchoscope cannot reach, which depends on the diameter of the scope used and the airway lumen. Reaching tumors in the periphery also depends on operator skills and the access to navigation.

It is fundamental that the preoperative preparation and planning is optimal in order to enable accurate diagnosis during the first investigation of the patient.

Navigated bronchoscopy is a fairly new diagnostic method that emerged as an attempt to increase the diagnostic success rate for peripheral lung tumours. There are four image-guidance bronchoscopy systems commercially available and nine research and development platforms [2]. In navigated bronchoscopy systems, the position of the bronchoscope and/or biopsy tools are tracked and displayed real-time in a map made from the patient's preoperative computed tomography (CT) images, providing the operator an endobronchial pathway towards a predefined target, e.g. a lesion. Important technological components of navigated bronchoscopy are the isolation and extraction of anatomical structures of interest from the CT images (segmentation), and the registration of preoperative images to the patient′s anatomy. Centerline-based registration, one of several options for image-to-patient registration, is a method where the position data from the bronchoscope tip is matched to the center path of the lumen in the bronchi from the preoperative CT images. A recent review state eleven different segmentation methods available for centerline extraction but we consider only the most collective [3].

Region growing is a common method to segment airways from a CT data set [4]. It starts with a predefined seed point and if criteria of intensity threshold are satisfied, adjacent voxels are added to the segmentation. This growing procedure continues until no more valid voxels can be added. Sometimes image noise and other artefacts create holes in the thin wall that separates the airway lumen and lung parenchyma. As these structures have similar voxel intensities in CT images, the region may grow outside the airway lumen. This common problem in region growing algorithms is called leakage.

Segmentation of the airways can be performed by manual, semi-automatic or automatic methods. Manual segmentation is impractical and time-consuming due to the structural complexity of the airways and the dimensions of a typical patient CT data set. The new generation of CT scanners generates a data set of the human airways, which often contain more than 400 slices, each 512x512 pixels [5]. During manual segmentation the user has to perform the entire structure delineation slice by slice. The role of the user in semi-automatic approach is basically reduced to set an initial threshold and place a seed point in one of the slices of the CT data.

The centerline can be extracted from a surface model of the airways by e.g. a thinning algorithm [6]. A different approach is used in the method we developed, the Tube Segmentation Framework (TSF), where first the centerline is detected and then the tubular structure, the airways, "grow" from the extracted centerline [7].

The centerline is used both for alignment of positioning system to CT images [8], but also to indicate the path during navigation. It may also be used for a simplified overview of the airways during navigated bronchoscopy.

Pu et al. [9] presented a review of methods developed primarily for computerized analysis of human airways; they also consider the use of segmentation for path planning in virtual bronchoscopy. Results from manual segmentation are not reliable in a strict sense, since manual delineation typically suffers from relatively large inter- and/or intra reader variability in particular related to small airways [9]. There have been several semi-automatic and automatic methods presented in the literature. Lo et al. [10] presented a review of 15 different methods for bronchial tree segmentation from CT images and today their study is considered a reference for airway segmentation methods. We found studies where the authors mainly compared their own method with a manual segmentation [11–13]. Kiraly et al. [14] compared different segmentation methods but specify few details about the parameters achieved such as number of branches and number of generations. Tschirren et al. [15] also compared other segmentation methods, mentioning number of branches and number of generations achieved but did not compare it to any available commercialized segmentation tool. We have only found two studies that have evaluated the accuracy of segmentation methods in commercially available software. Weissheimer et al. [16] and El et al. [17] presented comparison work between different image processing software for segmentation, but only of the upper airways. None of the studies we found compares results from a commercial system, with segmentation of the bronchial tree including some of the lower peripheral lung segments.

We wanted to examine our own developed method versus commercial software for segmentation of the airways, also for the purpose of seamless preparation, user interaction aspects, and planning and guidance of bronchoscopic procedures. Our work focuses on segmentation of the airways and centerline extraction to be acquired automatically and as quickly as possible before image-to-patient registration and image-guided bronchoscopy, all steps performed in the interventional room. We studied and compared an automatic open access TSF filter [18–19] integrated into our research and development platform for image-guided interventions, CustusX

[20], two semi-automatic methods in a commercial system, the Mimics Pulmonology Module (MPM) and the Mimics Basic Module (MBM) (Materialise, Leuven, Belgium) (http://biomedical.materialise.com/mimics), and a semi-automatic method in the freely available DICOM processing application OsiriX [21] (http://www.osirix-viewer.com). We also compared the MPM and the TSF method to the reference segmentation as defined in the study by Lo et al. [10]. As stated on the reference segmentation web page, the images are volumetric chest CT scans acquired at different sites using several different scanners, scanning protocols, and reconstruction parameters. The dataset ranges from clinical dose to ultra-low dose scans, from healthy volunteers to patients with severe lung disease, and from full inspiration to full expiration (http://image.diku.dk/exact/).

The visual representation results from the analysis of our patients' data were evaluated visually by pulmonologists, radiologists and medical engineers, with emphasis on automaticity and clinically useful segmentations, e.g. complete branches at each generation. We also surveyed the interaction needed to obtain the segmentation. The study should be of interest for those who are considering implementation of navigated bronchoscopy in their clinical practice, in particular with respect to pre-processing of images before intervention.

Materials and Methods

The anonymized CT data was collected from patients included in a clinical study approved by the Regional Ethical Committee, and all patients signed an informed consent. In the first part of this study we processed 17 CT patient datasets with four different methods in three different software applications; Dynamic region growing provided by MBM, Deep airway segmentation provided by MPM, our own developed TSF method (freely available online) (https://github.com/smistad/Tube-Segmentation-Framework/), implemented in our platform for image-guided interventions, CustusX (an open source platform, SINTEF, Trondheim, Norway) (http://www.custusx.org) and a threshold-based region growing algorithm in OsiriX (Pixmeo, Geneva, Switzerland) (Table 1). Our research group has used OsiriX as a segmentation tool for several years. To obtain airway segmentation in OsiriX the user needs to perform multiple iterations manually to find a proper model mask, which may not always be achievable. Our open source platform for medical image-guided interventions, CustusX, is based on the open access toolboxes VTK (http://www.vtk.org) and ITK (http://www.itk.org).

To compare the feasibility of the different solutions we registered the amount of user interaction as number of clicks needed by the operator. The segmentation results were measured as number of branches, total length of branches (without discontinuation), and number of branches segmented for each generation and total volume of the segmented airways.

Table 1. Software used in this study.

Software	Description	Operating system	Method / Algorithm
Mimics	Version 15.01 Materialise, Leuven, Belgium Commercial	Windows	Dynamic region growing (Basic Module) (MBM)
Mimics	Version 15.01 Materialise, Leuven, Belgium Commercial	Windows	Deep airway segmentation (Pulmonology Module) (MPM)
OsiriX	Version 5.5, 64 bit [a] Pixmeo, Geneva, Switzerland Freely available	Mac OS	Region growing threshold-based algorithm
CustusX	Version 3.5.0 SINTEF, Trondheim, Norway Research platform in development	Ubuntu Linux	Tube Segmentation Framework (TSF) [b]

[a] The 32 bit version is free.

[b] Freely available online

doi:10.1371/journal.pone.0144282.t001

In the second part of the study we compared our results from the MPM and the TSF methods to the reference segmentation standard by Lo et al. [10]. The reference segmentation is based on 20 different patient datasets with difference in acquisition parameters such as slice thickness, scanner type, image quality and electronic emittance. By following the reference segmentation protocol on their webpage one can evaluate the results to other segmentation methods (http://image.diku.dk/exact/).

The results are interpreted in main three performance measurements: branch detection, tree length detected and false positive rates. Included are also leakage count and volume i.e. voxels outside the correct volume.

1. Branch detection: The count and percentage of branches detected correctly N_{seg} from segmentation with respect to the total number of branches present in the reference N_{ref} defined as

$$\frac{N_{seg}}{N_{ref}} \times 100\%$$

2. Branch length: The total tree length and percentage of tree length in the reference i.e. the fraction of tree length that is detected correctly L_{seg} by the segmentation relative to the total tree length in the reference L_{ref} defined as:

$$\frac{L_{seg}}{L_{ref}} \times 100\%$$

3. False positive rates: The fraction of the segmented voxels that is not marked as "correct" in the reference, defined as:

$$\frac{N_w}{N_c + N_w} \times 100\%$$

Where N_C and N_w are the number of voxels in the segmented airway that overlap with the "correct" and "wrong" regions in the reference, respectively. Note that "unknown" regions in the reference are not included in the calculations of the false positives rates. The trachea is excluded from all measures in the reference segmentation, furthermore for the false positive rate the left and right main bronchi are excluded as well.

The Norwegian Regional Committees for Medical and Health Research Ethics (http://helseforskning.etikkom.no) approved the retrospective use of the CT data used in this study. Written informed consent was given by participants for their clinical CT data to be used in this study. The CT data was anonymized and de-identified before data analysis.

Software used in this study

Mimics. Mimics is a commercial medical image processing and analysis software. The user can import various data formats such as DICOM and create 3D models of the patient's anatomy. Mimics provide both basic functionality and an additional Pulmonology module to process the airways in lung CT scans. For our study we used two modules in Mimics, i.e. a Basic Module and the Pulmonology Module. Both modules used in this study must be purchased separately.

Mimics Basic Module. The MBM provides a "Dynamic region growing" segmentation method, which segments an object based on the connectivity of gray scale values in a certain range. The pre-processing starts with manually setting a seed point inside the trachea and selecting a gray value range. For the airway segmentation the minimum value is -990

Fig 1. Mimics Graphical User Interface (GUI). In green the result of the segmentation with "Dynamic region growing" in MBM. **A** coronal, **B** axial, **C** sagittal view of the CT data and **D** the 3D model of the airway.

doi:10.1371/journal.pone.0144282.g001

Hounsfield unit (HU) and the maximum is usually between -50 HU and -120 HU. Trial and error work is needed to find an appropriate range of gray levels that results in a segmentation mask of the airway without leakage. When the mask is set, the option "calculate 3D model from the mask" allows creating a 3D model of the airway that is shown in the right corner of the screen (Fig 1). The model is then smoothed with a smoothing factor (0.9 was used in the example in Fig 1), and a number of iterations factor (1 was used in our cases), which determine respectively how much smoothing and how many smoothing iterations will be performed.

The MBM does not have a tool to extract the centerline, this is provided by a MedCad module, which requires an additional purchase. In this study the centerline of the 3D model made with dynamic region growing has been extracted with the option "centerline labelling" tool of the MPM.

Mimics Pulmonology Module. The MPM provides the tool "Deep airways segmentation", where the airways are segmented based on two seed points in the trachea set in the axial view. The first point is the start point of the trachea and by scrolling down a few axial slices from the first slice the second point is set to define the direction of the trachea. After the seed point step, a preview of the airway segmentation appears, and next a 3D model is calculated based on the segmentation mask. During the pre-processing it is possible to select five levels of leakage detection. If the leakage detection level is increased the 3D preview will contain less leakage but the 3D structure will become thinner and have fewer branches, smaller branches will therefore be less likely to be detected. During the following study of the 17 datasets, the level of leakage detection was first put to the third level (default), in order to use as few clicks as possible without leakage. However, if leakage was detected the leakage detection level was increased to fourth or fifth level. In some cases it was not enough to increase the detection level to avoid leakage, consequently requiring some manual work to obtain the most appropriate 3D model possible, by deleting leakages (Fig 2). Leakages may be removed by simply pinpointing (manually clicking) them. The centerline has been extracted by using the tool "centerline extraction", which also output the name of the branches.

OsiriX. OsiriX (http://www.osirix-viewer.com) is image processing software for Mac OSX (Apple, Cupertino, USA) dedicated to DICOM image viewing and processing. The OsiriX software offers several algorithms for segmentation; threshold (interval), neighborhood, confidence,

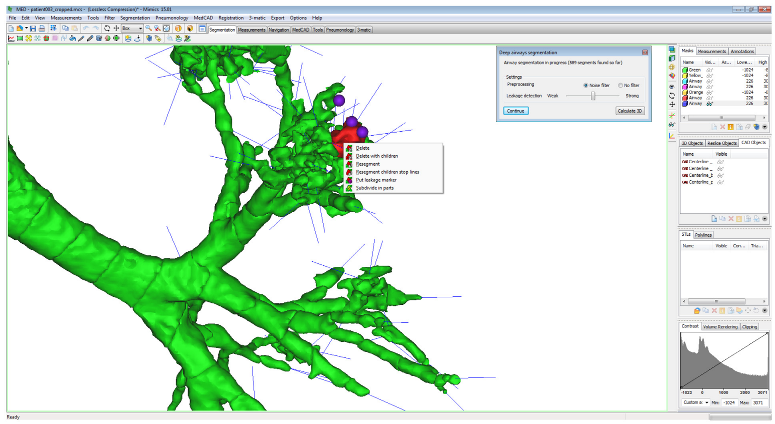

Fig 2. The figure shows a detail of segmentation in MPM. The leakage is well visible at the end of the branches as "clouds" around the branch. The user can select manually the leakage that has to be removed (red segment) and put the leakage marker in its place (purple ball).

doi:10.1371/journal.pone.0144282.g002

threshold (upper/lower), all based on 2D or 3D region growing. Based on initial testing and trial and error we decided to use the Region growing threshold-based (upper/lower) algorithm in our study (Fig 3a). First a range of gray scale values was chosen in order to achieve a segmentation of the airways without leakage. Next, a seed point within the trachea was set and a mask computed. This procedure is time consuming because if the gray scale range chosen is not appropriate, the user has to start over, change the range and compute the mask again. When the 3D model has been obtained, it can be displayed in the OsiriX 3D panel (Fig 3b). A meta-header and raw volume export plug-in was used to export the 3D model for extraction of the centerlines in our own software (CustusX) as OsiriX does not have an option for this.

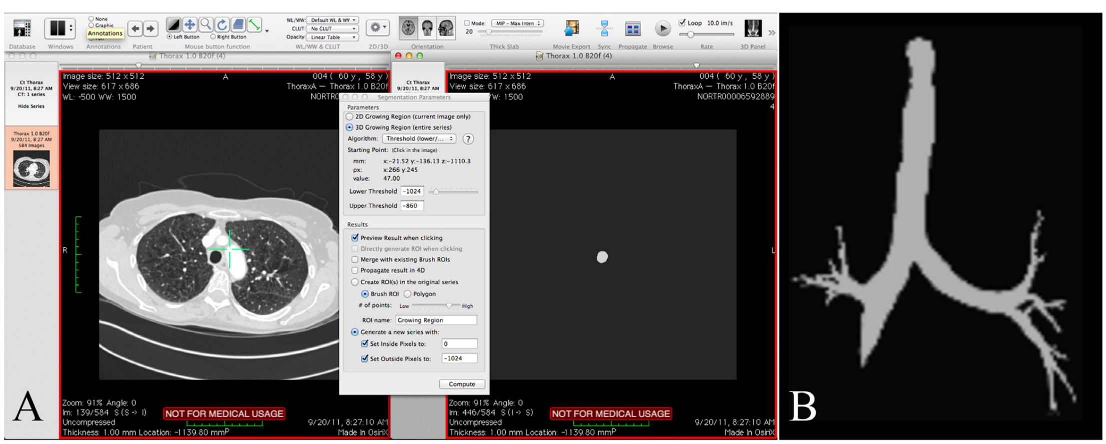

Fig 3. OsiriX GUI. A) axial view of the original CT data, 2D result of the segmentation with threshold upper/lower algorithm, window of the region growing with threshold (upper/lower) algorithm; B) 3D panel.

doi:10.1371/journal.pone.0144282.g003

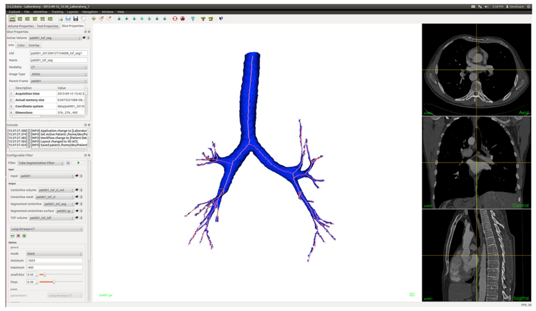

Fig 4. CustusX GUI for TSF. axial, coronal, sagittal view (right side), 3D model of the airway with centerline (center) and configuration filter parameters (left side).

doi:10.1371/journal.pone.0144282.g004

CustusX. CustusX is a research and development platform for image-guided interventions with focus on intraoperative use [20]. The user can import data in DICOM or meta-header format (.mhd and.raw). The airways are extracted automatically using the open access TSF module (https://github.com/smistad/Tube-Segmentation-Framework/) integrated into the CustusX platform. The TSF, which is the core part being used in this study, uses the graphic processing unit (GPU) to quickly calculate a probability for each voxel whether it is inside a tubular structure or not. First, the method removes data that is not part of the lungs by using a novel automatic cropping algorithm, this is done to reduce memory usage and execution time. Next, a centerline is extracted by automatically selecting a subset of voxels that have a high probability of being inside the airways. These are then linked together to represent the airway structure. Finally, an optional segmentation can be performed by means of a seeded region-growing algorithm using the dilated centerline as seeds and the image gradients to avoid segmentation leakage. Further details of this implementation can be found elsewhere [18–19] (https://github.com/smistad/Tube-Segmentation-Framework/). After the patient CT dataset is imported the user has to choose which parameter preset to use. A parameter preset has to be selected because the TSF can be used to extract blood vessels from different modalities as well as airways from CT. In this case the parameter preset of lung airways was used. The TSF provides the user with both the airways segmentation and centerlines of the airways at the same time (Fig 4).

Parameters used in the study are overall visual inspection and user interaction. Fig 5 summarizes the work performed in each software application used in this study.

Overall visual inspection

The involved personnel (see author list), initially performed a simple visual inspection of the result to ensure it was anatomically correct and did not contain extensive false positive branches or missing major bronchi in the segmentations. This was performed by visualizing the centerlines and the segmented volumes with the possibility to interactively zoom in and out and rotate the entire structure at the same time as viewing the original CT axial slices.

User interaction

Number of clicks. Operator time is not an exact measure as it depends on the amount of experience the operator has had with the software, therefore we measured the number of clicks in the present study.

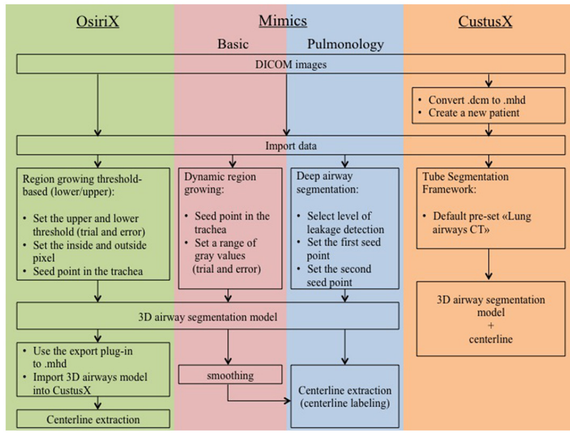

Fig 5. The figure shows a flowchart of analysis of CT data. In OsiriX, MBM, MPM and CustusX.

doi:10.1371/journal.pone.0144282.g005

In Mimics and OsiriX the user can import DICOM CT images directly. For the TSF method integration of CustusX, the CT data had to be converted into meta-header (.mhd and.raw) format, with a simple file format converter, at the time of comparison. In the newest version of the CustusX platform there is a possibility of importing DICOM images directly. Dynamic region growing in MBM demands manual and iterative manual input in order to find the appropriate range of gray scale values for the segmentation. This is a procedure of trial and error that requires a certain number of clicks, which is different for each patient. The MBM does not have the option of centerline extraction. In this study we used the centerline-labeling tool provided by the MPM (Fig 6).

Deep airway segmentation in MPM allows the user to choose the level of leakage detection, which is medium as default (third level). Additional clicks are needed when the user decides to change the level. In our study the fourth level was chosen for five of the patients and level five for three of the patients. This was done to reduce or eliminate the leakage in the final 3D model. Leakages in five patients were removed manually; in this case the number of clicks increases depending on the quantity of leakage to be deleted.

OsiriX does not have the option for centerline extraction. The airways segmented with OsiriX were imported into CustusX where the centerlines were extracted using a thinning algorithm.

Segmentation. Included number of branches, number of generations and total length displayed. Text files with coordinates of the centerlines from Mimics were processed in MATLAB (Mathworks Inc., USA) to calculate the number of branches, number of generations and total length of the centerline of the segmented airway branches. MATLAB was also used to process the Visualization Toolkit (VTK) files from CustusX to obtain the parameters of the 3D model and centerline obtained from the TSF in CustusX. The actual number of branches for each of the five first generations in a few control datasets was found by manually identifying airway bifurcations in the CT volumes.

Volume. The first step in the TSF method used in CustusX is to crop the dataset in order to save processing time. Each dataset contained between 241 and 843 slices with a percentage of reduction in number of slices from 5.65% to 29.03%. The slice increment was 0.5 mm, except in one patient, where it was 1.25 mm. This information was used to set the same starting point in the trachea in the other two software applications.

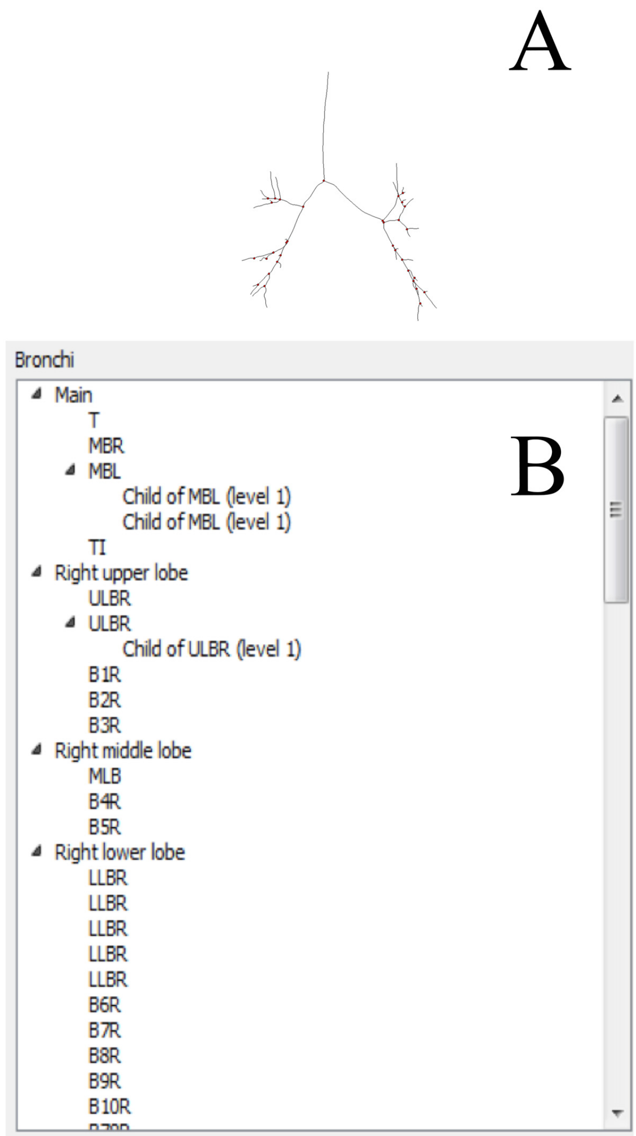

Fig 6. Labeling in Mimics. The figure shows the centerline labeling in MPM. fig B display centerline extracted and fig B list labelling with Mimics.

doi:10.1371/journal.pone.0144282.g006

Dynamic region growing in the MBM creates a mask, which is then cropped with the tool “crop mask”. The crop is automatically performed with the TSF method. The same crop is performed on the data before processing in Mimics in order to have comparable results for the different methods. The volume was calculated in the software directly after the 3D model had been created. In the MPM we set the same starting point as used in the Basic module and the volume is provided directly from the user interface of the software. In OsiriX we imported the dataset starting with the first (axial) slice after the cropping position. After segmentation, we were not able to measure the volume directly from the software or with other methods. The volume of the airways in TSF method was calculated from the number of voxels multiplied by the volume of a single voxel. This procedure was automated with a simple MATLAB script.

A total of 51 measurements of each parameter were made. To evaluate the correlation between the software, the Pearson correlation coefficient was used.

Results

User interaction

Number of clicks. The number of clicks needed to import the data for both Mimics modules were six, in OsiriX four, and in TSF it was 14. If we do not count the extra clicks needed to convert the file format for TSF, the number of clicks for importing the data was six. This is the case for the newest version of CustusX used for TSF, but an older version without DICOM import was used in this study. MPM demanded different number of clicks for the segmentation procedure depending on the level of leakage detection chosen. Seven clicks were necessary to provide segmentation and centerlines for TSF. The number of clicks for both Mimics modules does not include the process of cropping which can increase the number of clicks by nine clicks. All the results are summarized in Table 2.

Segmentation. Examples of segmentation and centerline of patient #1 are shown in Fig 7.

Following results for number of branches, total length and number of generations gave following. The mean and standard deviation of the total length of airways branches in millimeters (mm) in MBM, MPM and TSF were, respectively, 954 ± 406 mm, 1261 ± 565 mm and 806 ± 208 mm. The centerlines were not possible to extract in three patients (10, 12 and 14) in MBM due to the presence of holes in the 3D model. The correlation factor for the total length was 0.944 between the two modules in Mimics, 0.590 between MBM and TSF and 0.633 between MPM and TSF.

The average highest generation found by using MBM was 8.28 ± 1.43 and the average total number of branches was 59.42 ± 28.20, in MPM the highest generation was 9.53 ± 2.00 and 81.00 ± 40.50 branches were segmented, and in TSF the highest generation was 7.06 ± 1.60 and 41.52 ± 15.42 branches were segmented. In the four control datasets, where the actual number

Table 2. Number of clicks, mean ± standard deviation needed to import data and, perform a segmentation and centerlines extraction.

Software	Import	Segmentation and centerline extraction	Total
MBM	6	22 ± 4	28 ± 4
MPM*	6	11[a]	17
MPM*	6	17[b]	23
MPM*	6	24[c]	30
MPM*	6	33 ± 11[d]	39 ± 11
OsiriX	4	41 ± 4	45 ± 4
TSF (CustusX)	14	7	21

* In MPM we distinguished between four cases:
[a]Segmentation with the third level of leakage detection;
[b]Segmentation with the fourth level of leakage detection;
[c]Segmentation with the fifth level of leakage detection;
[d]Segmentation with leakage, we need to clean it manually.

doi:10.1371/journal.pone.0144282.t002

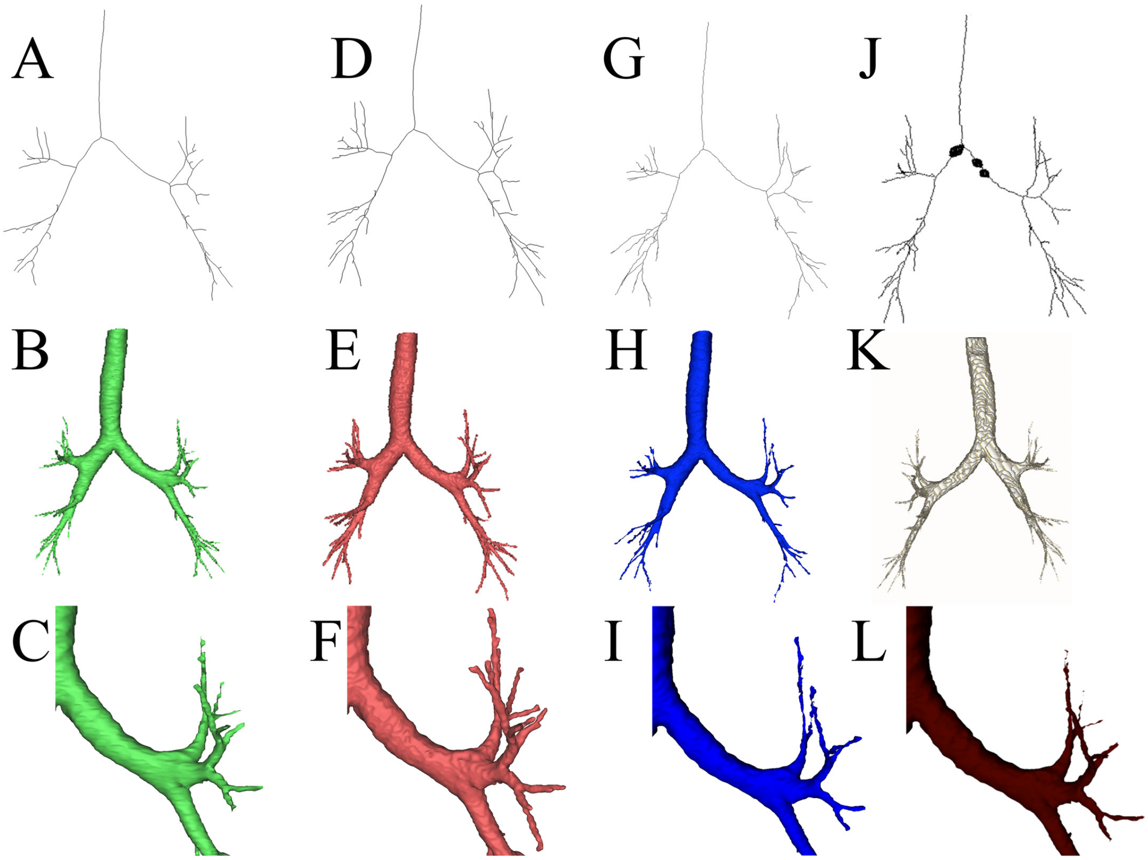

Fig 7. The figure shows segmentation, centerline, model and a detail of the airways of patient #1 in MBM (A,B,C), MPM (D,E,F), TSF(G,H,I) (CustusX) and OsiriX(J,K,L) respectively (left to right). The centerline for Osirix was produced in CustusX by using the standard filter for centerline extraction (thinning algorithm). In the centerline of OsiriX there are three black circles caused by holes in the segmentation.

doi:10.1371/journal.pone.0144282.g007

of branches was manually counted for the first five generations, all methods found all branches up to the fourth generation (± one branch for the fourth generation) for three of the datasets. In the data from patient 17, MBM missed branches from the third generation and all methods missed branches from the fourth generation. All methods missed branches at the fifth generation for all control datasets, MBM found 53% of the fifth generation branches, MPM 69% and TSF 51%.

The segmentations from OsiriX were sparse and that made it nearly impossible to get true centerlines of the airways. For only three of the patients it was possible to obtain the centerlines from the segmentation in OsiriX.

Method comparison based on number of branches in each generation for all patient cases is presented in Table 3. Fig 8 shows for how many patients each method is able to detect branches of each generation, starting from the sixth generation.

The mean and the standard deviation of the number of branches segmented per generation (until sixth) detected by each software are reported Fig 9.

Table 3. Method comparison, number of branches in each generation for all patients.

Patient number	Software	Generation												
		1	2	3	4	5	6	7	8	9	10	11	12	13
1	MBM	1	2	5	12	16	8	4	6					
1	MPM	1	2	5	12	20	12	12	10	6				
1	TSF	1	2	5	13	9	4	2	2					
1	Manual counting	1	2	5	13	27								
2	MBM	1	2	4	8	14	22	12	4	2				
2	MPM	1	2	4	8	14	16	15	7	2				
2	TSF	1	2	4	9	13	10	4	4					
3	MBM	1	2	4	9	19	29	20	16	10	6			
3	MPM	1	2	4	8	17	29	38	19	14	8	2		
3	TSF	1	2	4	9	20	17	10	5	4	2			
4	MBM	1	2	4	8	10	8							
4	MPM	1	2	4	6	10	16	4	2					
4	TSF	1	2	4	8	5	4							
5	MBM	1	2	4	6	4	4	2						
5	MPM	1	2	4	6	4	6							
5	TSF	1	2	4	8	4								
6	MBM	1	2	4	9	12	23	12	9	2	2			
6	MPM	1	2	4	9	16	24	24	16	8	4	2		
6	TSF	1	2	4	8	14	21	15						
6	Manual counting	1	2	4	8	17								
7	MBM	1	2	4	8	14	22	12	8	4	4	4		
7	MPM	1	2	4	8	14	24	30	18	12	4	6	2	2
7	TSF	1	2	4	9	13	12	7	6					
8	MBM	1	2	4	10	20	20	15	8	4				
8	MPM	1	2	4	9	18	32	27	17	7	6	4		
8	TSF	1	2	4	10	13	9	3						
9	MBM	1	2	4	6	8	4	4						
9	MPM	1	2	4	6	8	10	10	8	6	2			
9	TSF	1	2	4	6	12	10							
10	MBM													
10	MPM	1	2	4	6	12	12	10	6	4	6	6	2	
10	TSF	1	2	4	9	12	9	2						
11	MBM	1	2	4	8	14	22	14	6					
11	MPM	1	2	4	8	16	24	24	16	6	4			
11	TSF	1	2	4	6	6	6							
12	MBM													
12	MPM	1	2	4	8	17	27	28	14	11	7	2		
12	TSF	1	2	4	10	19	11	9	4	2	2	2		
13	MBM	1	2	4	9	10	10	4						
13	MPM	1	2	4	8	12	12	4	2					
13	TSF	1	2	5	10	10								
13	Manual counting	1	2	4	9	18								
14	MBM													
14	MPM	1	2	2	4	9	14	8	4	6				
14	TSF	1	2	4	10	16	7							
15	MBM	1	2	4	8	16	20	21	12	2				

(*Continued*)

Table 3. (*Continued*)

Patient number	Software	Generation									
15	MPM	1	2	4	8	17	26	32	29	15	2
15	TSF	1	2	4	9	16	5				
16	MBM	1	2	4	8	17	8	2			
16	MPM	1	2	4	8	12	6				
16	TSF	1	2	4	8	13	4	2			
17	MBM	1	2	2	5	6	6	2	2		
17	MPM	1	2	4	6	9	6	4	2		
17	TSF	1	2	4	8	9	9	6			
17	Manual counting	1	2	4	10	21					

doi:10.1371/journal.pone.0144282.t003

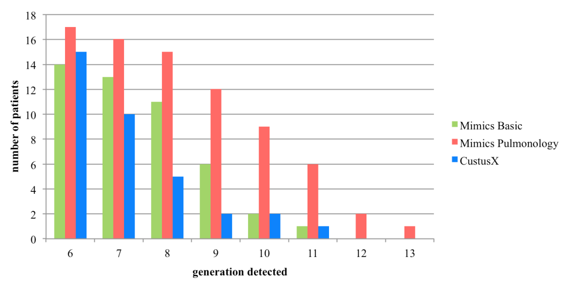

Fig 8. Number of patients in each generation. The plot shows the number of patients that each software is able to detect, up to the sixth generation.

doi:10.1371/journal.pone.0144282.g008

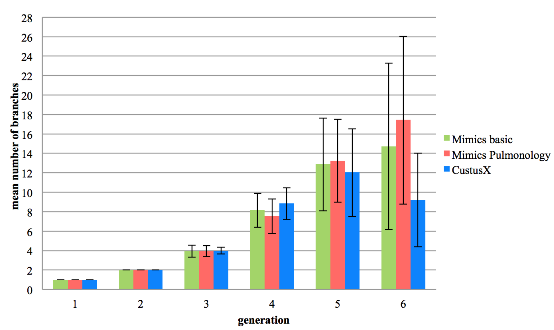

Fig 9. Average branches detected in each generation. The plot shows the mean and standard deviation of number of branches per generation for each method.

doi:10.1371/journal.pone.0144282.g009

Volume. The mean and standard deviation of the volume was found to be 37736 ± 15948 mm^3 in MBM, 46759 ± 20511 mm^3 in MPM and 34302 ± 15346 mm^3 in TSF. The segmentation of one patient (#12) in MBM was sparse making it impossible to achieve a measure of the volume. The reason why Dynamic region growing in MBM failed with this patient data might be due to the presence of a tumor. The correlation factor was 0.98 between the two modules of Mimics, 0.99 between MBM and TSF, and 0.98 between MPM and TSF.

Table 4. Reference segmentation results, comparison for MPM and TSF method, one can compare to results in EXACT09 webpage (http://image.diku.dk/exact/).

	Branch count	Branch detected (%)	Tree length (cm)	Tree length detected (%)	Leakage count	Leakage volume (mm3)	False positve rate (%)
Mean (MPM)	104.7	42.9	78.7	37.5	4.4	120.4	0.9
SD (MPM)	55.2	9.6	41.7	7.1	5.9	249.2	1.6
Mean (TSF)	72.4	31.3	54.3	27.4	34.5	344.8	3.6
Std. dev. (TSF)	37.8	10.4	33.9	9.6	23.4	397.8	3.4
Average (Overall for reference segmentation)	124.0	51.8	95.0	46.0	9.8	700.6	2.8
Std. dev. (Overall for reference segmentation)	62.9	13.5	52.1	12.9	10.1	856.1	3.4

doi:10.1371/journal.pone.0144282.t004

Reference segmentation

A reference segmentation comparison from MPM and our in-house method are shown in Table 4 with computed overall reference segmentation averages and standard deviations for branch count, branch detection percentage, percentage for path length detection, leakage count, leakage volume and percentage of false positive rate.

The mean and standard deviation for the branch detection were 42.9±9.6% and 31.3±10.4% for the MPM and the TSF methods, respectively, both lower than the reference segmentation average but within the standard deviation range of 51.8±13.5%. Mean and standard deviation for the tree length detected was 37.5±7.1% and 27.4±9.6% for the MPM and the TSF methods, respectively, both lower than the reference segmentation average but within the standard deviation range of 46.0±12.9%. Mean and standard deviation for the leakage count was 4.4±5.9% and 34.5±23.4% for the MPM and the TSF methods, respectively, compared to reference segmentation average of 9.8±10.1. The mean and standard deviation for the leakage volume was 120.4 ±249.2 mm^3 and 344.8±397.8 mm^3 for the MPM and the TSF methods, respectively, are both lower than the reference segmentation average of 700.6±856.1 mm^3. The mean and standard deviation for the false positive rate was 0.9±1,6% and 3.6±3.4% for the MPM and the TSF methods, respectively, which is at a similar level as the reference segmentation average of 2.81±3.3%.

Discussion

We have compared three different software applications for lung airways segmentation and centerline extraction and evaluated their performance. Overall, the results show that all the applications were feasible for processing lung CT images, but the applications differed regarding completeness of segmentation, automaticity and user interactions.

The ideal approach, according to the literature, for the assessment of the airway segmentation is using a manual segmentation as a reference [9]. This was not possible in our case due to the time and the complexity of such a task. Another accepted approach is the reference segmentation, by Lo et al. [10], which we used successfully for comparison in this study. Both MPM and TSF are compatible with the overall for reference segmentation averages and standard deviations of the reference segmentation except for the leakage number and volume that TSF got.

In addition, the segmentation methods were investigated using our own CT data from 17 patients. The number of branches for each generation was automatically counted and the volume was found. As a control we also performed a manual count of the number of branches for each of the first five generations in four selected control data sets. Counting beyond the fifth generation would be technically challenging and time consuming, and it would not add much extra information as none of the segmentation methods were able to identify all branches of the fifth generation, thus, none would be able to identify all branches of higher generations either. For navigated bronchoscopy it is also of higher importance to reveal if a method is able to identify, segment and find the centerline of a branch, than that the exact volume and branch radius is found. The total length of airways branches in millimeters (mm) depends on the number of branch detected.

User interaction

Number of clicks. The main goal of our work is the use of 3D airways model visualizations for guidance in navigated bronchoscopy. In this work we are seeking a seamless procedure with as little necessary user interaction as possible to be able to use guiding techniques in as many patients as possible. The preparations for each case should therefore be quick and as automatic as possible. Hence, limited user interaction, measured in clicks, are important in a clinical setting.

The segmentation in OsiriX and Mimics, particularly the MBM, require a manual and iterative procedure in order to set the right range of gray scale values, i.e. the user has to change the range until there is no leakage into the lung parenchyma. With Dynamic region growing in Mimics the results are displayed in the CT images immediately while one changes the upper and lower gray scale value, but with OsiriX the user needs to change settings and manually iterate to obtain the most appropriate results from the user's personal perspective. Changing one setting, the result in one 2D slice can be viewed and the slice can be changed, but the 3D result is only visible after running the segmentation with a chosen setting. During the processing, no feedback is provided, and the user has to "wait and see". This might have to be done several times, until the 3D model is segmented without leakage.

After the choice of the two seed points in MPM the segmentation mask is created automatically. If the results show leakages, some manual work is necessary to "clean" the model. The user decides when to stop by visual analysis of the model.

The segmentation process of the TSF in CustusX is fully automatic and the user interaction is reduced to only importing data and choosing the parameter preset for the structure of interest, e.g. CT airways. The parameter set for each type of image modality (CT/MR) and organ combination can be optimized and set for all future cases [20]. These parameters have been optimized manually.

The MPM is the software that demands fewest clicks to achieve a segmentation of the airways and their centerlines. However, this is not the case when we need to increase the level of leakage detection or when the result presents leakage that has to be removed manually. TSF on the other hand requires more clicks than the other methods to import the data since the data format has to be changed. If the importing of data is excluded, TSF has the fewest clicks to segment the airways, only seven clicks are needed for segmentation and centerline extraction compared to both modules of Mimics. When performing segmentation of the bronchial tree intraoperatively it is of course an advantage that the user has to perform as few clicks as possible and that the method is as automatic as possible. An intraoperative TSF integrated solution such as CustusX, is less time consuming than a preoperative system, such as Mimics or OsiriX. Nevertheless, robustness and accuracy are important as well.

Segmentation and Volume. The MBM failed segmentation in one patient due to a tumor in the trachea. It also failed centerline extraction in three patients due to the presence of holes in the segmentation. TSF and the MPM were both successful in segmenting the airways in all 17 patients CT scans.

The number of branches per generation and highest generation detected, and hence also total length of the airways was largest in the Mimics modules. The highest correlation factor between the measures of the total lengths was between the MBM and the MPM, indicating the similarity of the algorithms in the two modules.

The total number of branches detected in all patients was highest for the MPM, followed by the MBM and TSF. Only in one patient (#17) TSF detected more branches than the Mimics modules. The differences were less evident in the histogram of the number of generations. Both modules in Mimics have the highest generation detected. Nevertheless, TSF is able to achieve the same maximum level of generation as MBM in four patients, and the average highest generation detected between the two methods differs only by one generation. All methods are able to detect the trachea (first generation) and the main carina (second generation), but there are difference in branch number from third generation (Table 3). In seven patients TSF was not able to segment beyond the sixth generation, by comparison to the MPM, where the result was up to eighth generation in more than 50% of the patients. TSF was able to detect more branches of the fourth generation in ten patients compared to both Mimics modules. Compared to both Mimics modules, TSF detected the least number of branches but it has the smallest standard deviation, which means it is more consistent than Mimics in detecting branches between datasets. In four of the datasets branches up to the fifth generation were counted as a control. One dataset (patient #17) appeared to be challenging as none of the segmentation methods found all branches beyond the third generation. In the other three datasets all branches up to the fourth generation were found by all methods. In a few instances the number of branches for the fourth generation was one less or even one more compared to what was found by manual counting. This small inaccuracy is likely caused by an ambiguity whether a bifurcation point connects a branch with three branches of the next generation or two branches where one is very short followed by a new division. This assumption is based on the fact that we inspected the segmentation result for false positive detected branches. None of the methods found all branches at the fifth generation.

The volume results are linked with the results of number of branches and total length of the airways. Branches of the first generations are larger than in the latest generations, therefore they have a higher influence on the total volume. Defined volume of any patient lung data is not known but can give an idea of the difference between them. The MPM and the TSF methods also had lower leakage on average than the reference segmentation.

All software were able to detect branches up to the sixth generation in all the patients, then, since the volume measurement strongly depend on the first generation of the airways, the correlation factors for the volume results are very high. The correlation factor between the software applications is relative due to the fact that the real volume for each airway is unknown. But the difference between the volume measurement from each software changes in appropriate proportion between patient datasets.

The necessary number of branches and to what generation is needed for clinical application depends on the specific clinical case. The smallest diameter of existing bronchoscope technology is 2.4 mm, which is enough to maneuver to the fifth generation, considering that the average diameter in human lungs of apical bronchus and basal bronchus are 2.8 ± 0.6 mm and 2.7 ± 0.6 mm respectively [22]. Steerable catheter added into the navigation can be advanced into sixth-seventh generation, depending on the catheter diameter, which normally is 2 mm. When thinner bronchoscopes enters the market, the accuracy concerning the number of branches in each generation will become more valuable and specially when sampling peripheral lung lesions. Still, it is more important that the method is able to find as many of the bronchial branches as possible up to the sixth generation, compared to finding some of the branches in higher generations.

Table 5 shows advantages and disadvantages of the three different software systems used in this study.

Table 5. Advantages and disadvantages between Mimics (Basic and Pulmonology module), CustusX and OsiriX.

Software	Advantages	Disadvantages
Mimics	Quick segmentation, semi-automatic process, large segmentation parameters range	Commercial software (not free, relatively expensive), no navigation functionality
Mimics	Pulmonology module contains all tools needed for segmentation and centerline extraction, better results than Basic module in airways segmentation.	Basic module needs another tool for centerline extraction, manual steps needed to find the scale of gray level and can fail in data extraction.
Mimics	The MPM performed better than CustusX on average, at the same time there is no statistically significant difference on the results for the two methods.	Pulmonology module has additional cost
CustusX	Quick segmentation with automatic process, segmentation and centerline extraction at the same time. Available to collaboration partners via agreement	Need to convert DICOM to internal platform data first (plans to integrate DICOM import)
CustusX	Method more consistent than Mimics (smallest STD values)	Detects less generations and branches in general than Mimics
CustusX	Possible to perform all steps in operational room and navigation platform in same system	
CustusX	Available to collaboration partners via agreement	
OsiriX	Freely available	Manual steps to find the scale of gray levels (trial and error).
OsiriX		Need another software for the centerline extraction
OsiriX		Segmentation time consuming compared to the other software solutions

doi:10.1371/journal.pone.0144282.t005

Segmentation parameters difference in reference data vs. our patient data

There is a difference in terms between the reference segmentation and our patient data measurement. If there is a correct or true volume not connected to the branch tree we count it within our results but the reference segmentation demands a complete volume and all disconnected volumes from the bigger volume are not counted as results.

Reference segmentation comparison

The leakage count average and standard deviation for TSF method is higher than the reference segmentation but the leakage volume is low compared to the reference segmentation. The TSF method does thus create an extensive number for small leakages. That demonstrates the usage of the reference segmentation because the TSF method is automatic with no manual segmentation or post-segmentation smoothing algorithm to remove noisy additional voxels. MPM could have post-segmentation smoothing algorithm to ignore small leakages and disconnection of one or a few voxels. Finally the false positive rate averages and standard deviations for MPM and TSF methods are similar to the reference segmentation. The mean and standard deviation for the branch detection were 42.9±9.6% and 31.3±10.4% for the MPM and the TSF methods, respectively. The MPM performsed better than CustusX on average. At the same time there is no statistically significant difference on the results for the two methods.

Conclusion

The segmentation results from both MPM and TSF are sufficient for navigated bronchoscopy. Segmentation and centerline extraction of the airways are obtained with the least number of clicks in MPM if no leakage occurs. TSF demands more clicks than the other solutions to import the data since the data format has to be changed. Once the data is imported into CustusX, TSF provides a fast and automatic segmentation and centerline extraction, without using any extra manual pre-processing work (setting seed point and/or range of gray values) or time consuming manual post-processing work (removing leakages). OsiriX requires the highest number of clicks to process the data, the segmentation is often sparse and extracting the centerline requires the use of additional software. Mimics can detect a higher number of generations and branches than TSF, while TSF is more consistent in detecting almost the same number of branches in each generation over several data sets. Future work for TSF can be adding post-segmentation smoothing algorithm to remove noisy additional voxels and increase the possibility to detect more airway generations. We believe that navigated bronchoscopy will become more regularly used in lung medicine in the near future. To accomplish integration of such guidance technology it is important that preprocessing of data is precise, fast, and automatic and is integrated in a seamless manner into the workflow. This is particularly true for preoperative work in a busy clinical setting.

Author Contributions

Conceived and designed the experiments: PJR MS ES EFH HOL FL TANH TA HS TL. Performed the experiments: PJR MS ES EFH HOL FL TANH TA HS TL. Analyzed the data: PJR MS ES EFH HOL FL TANH TA HS TL. Contributed reagents/materials/analysis tools: PJR MS ES EFH HOL FL TANH TA HS TL. Wrote the paper: PJR MS ES EFH HOL FL TANH TA HS TL.

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Paper II

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Paper III

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Appendix I

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