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Pre-clinical Validation of Virtual Bronchoscopy Using 3D Slicer

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Abstract *Purpose* Lung cancer still represents the leading cause of cancer-related death and the long-term survival rate remains low. Computed Tomography (CT) is currently the most common imaging modality for lung diseases recognition. The purpose of this work was to develop a simple and easily accessible virtual bronchoscopy system to be coupled with a customised electromagnetic (EM) tracking system for navigation in the lung and which requires as little user interaction as possible, while maintaining high usability.
Methods The proposed method has been implemented as an extension to the open-source platform, 3D Slicer. It creates a virtual reconstruction of the airways starting from CT images for virtual navigation. It provides tools for pre-procedural planning and virtual navigation and it has been optimised for use in combination with a 5 degrees of freedom EM tracking sensor. Performance of the algorithm has been evaluated in *ex-vivo* and *in-vivo* testing.
Results During *ex-vivo* testing, nine volunteer physicians tested the implemented algorithm to navigate three separate targets placed inside a breathing pig lung model. In general, the system proved easy to use and accurate in replicating the clinical setting, and seemed to help choose the correct path

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without any previous experience or image analysis. Two separate animal studies confirmed technical feasibility and usability of the system.
Conclusions This work describes an easily accessible virtual bronchoscopy system for navigation in the lung. The system provides the user with a complete set of tools that facilitate navigation toward user-selected regions of interest. Results from *ex-vivo* and *in-vivo* studies showed that the system opens the way for potential future work with virtual navigation for safe and reliable airway disease diagnosis.

Keywords Virtual Bronchoscopy · Computed Tomography · Airway Segmentation · 3D Slicer

1 Introduction

Lung cancer still represents the leading cause of cancer-related death and the long-term survival rate remains low [1]. According to GLOBOCAN, there were 1.8 million new global cases of lung cancer in 2012 (12.9% of the total cancer incidence). In the United States, lung cancer is the second most common cancer diagnosed cancer in men and women [2].

When a patient is diagnosed with a suspiciously malignant lung cancer, the physician may decide to proceed with biopsy or cancer exportation. To do so, the CT image of the patient is analysed and anatomy of the airways is mentally reconstructed from the the CT scan to identify the best path toward suspect nodule. This is then followed by a physical bronchoscopy to evaluate or biopsy the nodule. However, image guidance based on CT images alone is tedious, due to noise, low image quality, or the complex structure of the different regions. Moreover, standard bronchoscopes do not reach thin peripheral airways. For this reason, in the last two decades the use of a virtual environment that reconstructs the lung anatomy and helps the physician during bronchoscopy procedures has emerged as a potential solution. This concept has been called virtual bronchoscopy (VB) and simulates the inside of the airway during navigation similar to images from a real bronchoscope, allowing for virtual exploration of the inside of the lung. Combined with a CT image, VB can also provide information about the real position of the probe within the lung, as well as information of structures that may be not visible on a CT image. Moreover, automatic reconstruction of an "optimal" pathway toward the lung cancer allows to focus on the procedure, without the need to memorize the path.

At present, there are three commercially available systems that implement virtual navigation; superDimension iLogic [3] and Veran SPINDrive [4] use electromagnetic navigation coupled with virtual reconstruction of the inside of the airways. Bronchus LungPoint [5] identifies the correct position of the bronchoscope within the lung using an image-based synchronization technique that aligns the virtual images obtained from the CT scan of the patient with the anatomy seen in the live bronchoscopic video. However, high costs and CT resolution as well as high sensitivity to external magnetic fields, such as those that could be used as a steering mechanism or imaging (e.g., in MRI), limit these systems.

In the last decade, several approaches have been proposed for virtual bronchoscopy. These aim at localising the actual position of the bronchoscope inside the lung in a virtual environment. Table 1 summarises some of the techniques developed to date. The most common approaches apply EM tracking, real-virtual image matching, or a combination of both.

EM Tracking Methods

EM tracking systems use a small sensor mounted on the tip of the bronchoscope (or inserted in the bronchoscope channel) to determine location and orientation of the tip in real time. These systems require calibration and registration between the real and the virtual environments before each bronschoscopic session [6]. Calibration and registration can be achieved either by using fiducial markers placed near the bony structure [6] or using anatomical landmarks of the airways, such as carina and main bronchi [7]. However, the EM field can be distorted due to the presence of ferromagnetic material around the EM system, while accuracy of EM tracking can be affected by unexpected movement of the patient and respiration during bronchoscopy.

Real-virtual Images Matching

Real-virtual matching tracking techniques, on the other hand, seek to track the position of the scope by finding the best match between the real image from the bronchoscope with the rendered view of the airways. The similarity between the two images can be accomplished using approaches that are either intensity-based [8,9] or geometry-based [10–12].

Intensity-based methods [8,9] compare the intensities between the two images. Bricault et al. [8] proposed a method that renders the virtual bronchial views using a ray tracing technique, while in [9], a novel approach that uses photo-realistic rendering has been proposed. However, intensity-based techniques may often require continuous manual lighting adjustment of the virtual camera and are very sensitive to illumination artefacts.

Conversely, geometry-based approaches [10–12] consist in extracting anatomical structures from the two images to find the best match. Deligianni et al. [10–12] presented a method that uses a linear local shape-from-shading (SFS) algorithm derived from the unique camera/lighting constraints of the endoscope to extract surface normal and accomplish a *pq* space-based 2D/3D registration process. The system also incorporates a patient-specific airway deformation model. This approach proved more robust to illumination artefacts and tissue deformation than intensity-based techniques. However, recovering geometrical structures from the bronchoscope video can be challenging, due to the fact that conventional methods to extract the structure, such as the SFS, assume orthogonal projection and light source at infinity. These assumptions cannot be used in the bronchoscopic scenario. To overcome this problem, Shen et al [13] recently proposed a method which first extracts depth information of the bronchoschopic image using a SFS approach based on the assumption that the light source is near the surface. Next, depth information from CT data is recovered by linearisation of depth buffering from perspective projections of the CT model. Finally, the camera position is estimated as that which maximises the similarity between the two extracted depth maps.

Hybrid Methods
Virtual bronchoscopy can also be achieved using an hybrid approach that combines EM tracking and image registration. A hybrid method that combines EM tracking and intensity-based image registration has been proposed by Mori et al [14]. The approximate position and orientation of the bronchoscope in the coordinate system of the CT image is determined using EM tracking. This is used as a starting point for an intensity-based registration between the real bronchoscopic image and the virtual image generated with a highly-optimized software-based volume rendering. A similar approach has been developed by Luo et al [15]. This system is based on three main steps. First, a camera and hand-eye calibration to obtain intrinsic parameters of the bronchoschopic camera and to perform sensor-camera alignment is undertaken. Then, a rigid registration between EM and CT tracking coordinates is performed. Finally, an intensity-based image registration is combined with the result of the EM system to improve the camera tracking. Another methodology using both EM tracking and image registration, based on differential surface analysis in a *pq* space, was outlined by Soper et al [16,17]. As part of this framework, the positional and orientational error between the CT and EM tracking system is adaptively estimated by means of Kalman filtering. The local deformation at each video frame is then intra-operatively estimated to compensate for respiratory motion.

Hybrid method improves the performance of the registration, but have the drawback to complicate the registration algorithm and the sensor calibration. One of the biggest issues is due to the high time consumption of image registration. For this reason, methods that use motion prediction have also been proposed to achieve faster convergence during registration. Higgins et al. [18] investigated an approach that estimates the optical-flow from the bronchoscope video and uses the tracked 3D trajectory to assist localisation in the virtual world. This allows for tracking of the 3D motion of the bronchoscope. A different approach that employs a Kalman filter to predict the 3D motion of the bronschoscope has been proposed by Nagao et al. [19]. However, the final image registration still relies on the matching between real and virtual images, as the 3D motion prediction from 2D video images may be not accurate enough.

Present Work
In this work, we describe the implementation of a novel hybrid method for virtual bronchoschopy (VB). The system combines EM tracking of 5 DOF sensing and intensity-based image registration has been investigated. A novel landmark-free registration approach for EM tracking is proposed.

Table 1: Summary of some of the VB methods developed to date.

Method	Main Features
Bricault et al. [8]	Intensity-based; ray tracing technique.
Chung et al. [9]	Intensity-based; photo-realistic rendering.
Deligianni et al. [10–12]	Geometry-based; linear local SFS for pq space-based registration.
Shen et al. [13]	Geometry-based; SFS; depth information from CT.
Mori at al. [14]	Hybrid method; EM tracking; intensity-based registration.
Luo et al. [15]	Hybrid method; sensor-camera alignment; rigid registration; intensity-based registration.
Soper et al. [16, 17]	Hybrid method; EM tracking; image registration (differential surface analysis); respiratory motion compensation.
Higgins et al. [18]	Optical flow estimation; 3D trajectory for localisation.
Nagao et al. [19]	Kalman filtering for 3D motion prediction; real/virtual images matching.

To compensate for possible respiratory motion, a centreline matching approach similar to that proposed in Wegner et al. [20] and Gergel et al. [21]. This method was originally tested in a virtual environment reproducing a bronchoscopic intervention. In this work the method is tested both in a phantom study and in animal studies.

The 5 DOF sensor inserted through the bronchoscope channel allows for navigation in peripheral branches, but does not provide information about roll rotation of the scope. For this reason, an intensity-based image registration based on multi-scale pyramid registration is employed to compensate for possible roll-rotation misalignment. The final goal of the work is to create a system to be used in in combination with the EM tracking system described in [22–25], and which requires as little user interaction as possible, while maintaining high usability. The EM system uses planar magnetic coils transmitting low frequency magnetic fields (< 30 kHz) and implemented on printed circuit board (PCB), as well as a miniature pick-up coil, or sensor, placed at the distal end of a catheter (inserted in the bronchoscope channel) [22–25]. The sensor position and orientation can be determined by measuring an induced voltage and by solving a non-linear system of equations.

One of the key aspects in developing a system for VB is the set up of a proper testing method. For this reason, we performed two tests to evaluate performance of the method. First, a phantom study where different physicians are required to evaluate usability of the system was accomplished. Next, two different animal studies were used to test the ability of the system to help blind navigation during bronchoscopy.

2 Materials and Methods

The proposed VB system has been developed as an extension of the freely available and easily extendible software platform, 3D Slicer [26]. The VB method

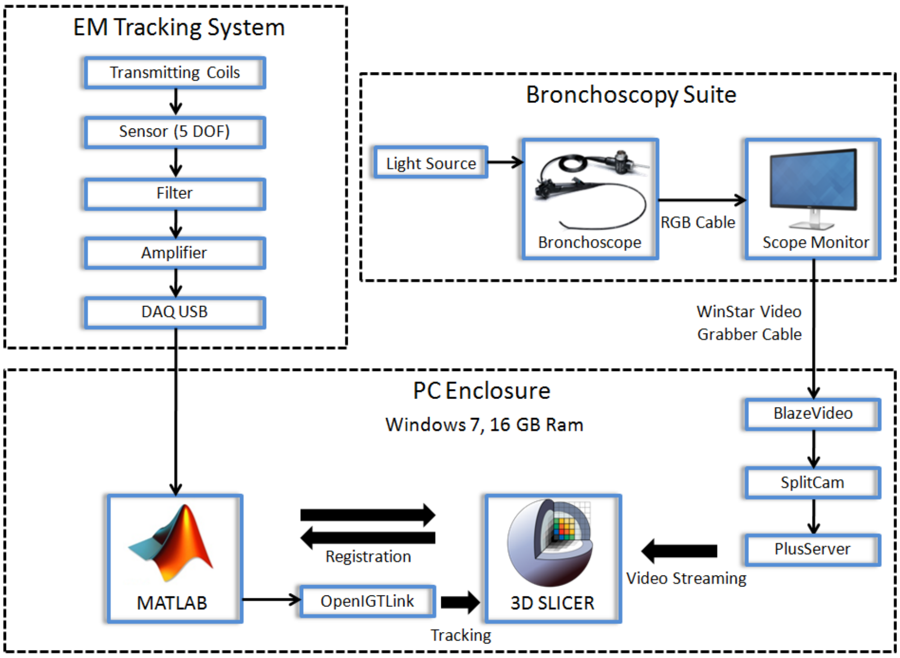


Fig. 1: Block diagram of system hardware/software interfaces.

can be used for (1) real navigation, but also (2) procedural simulation and planning.

The system has a modular structure, enabling direct pre-operative CT-based procedure planning and provides direct guidance during bronchoscopy. A 3D representation of the target is provided. This virtual target changes colour once the bronchoscope (with the sensor inserted in the working channel) reaches the desired region. Distance information between the current location and the biopsy site is interactively provided as the physician advances the bronchoscope. Since the system was used incombination with EM tracking using a 5 DOF sensing, video image registration between the real and the virtual camera has been implemented to compensate for possible roll angle misalignment. The centreline of the 3D rendered airway view is extracted and used to avoid registration errors between the real and virtual environments.

Figure 1 shows a block diagram of the system hardware. A desktop Windows 7 computer, with 16 GB RAM is used as the main CPU. A WinStar[1] frame grabber connects the bronschope monitor to one of the PC's USB ports. The video grabber is connected to Slicer through the open-source Public Software Library for Ultrasound Imaging (PLUS) research framework [27]. PLUS is a toolkit for data acquisition, pre-processing, and calibration in navigated image-guided interventions which was originally developed for ultrasound-

[1] http://www.win-star.com/

guided interventions. However, it is now widely used in all kinds of interventions, with and without ultrasound imaging. In our case, it was to stream the video from the bronchoscope into 3D Slicer. The PC is also connected to the EM tracking system, with tracking implemented using MATLAB (Mathworks Corp, Natick, MA) [22,23]. MATLAB is also used to register the real and virtual environments created from 3D Slicer. Note that MATLAB is necessary due to customised EM tracking system. To read the sensor position tracked by the EM system in 3D Slicer, the open-source OpenIGTLink[2] software, available as 3D Slicer extension, is used. We are currently working to integrate the registration system into the Slicer environment.

The system works in two main steps; (1) a pre-procedure step followed by (2) an image-guided bronchoscopy step. The pre-procedure step involves centreline airway extraction, real-virtual registration and procedure planning (with paths to target creation). The second step represents the operations involved during the procedure, including intensity-based image registration. The methods are written mostly in C++ (using ITK classes) and Python and are run through a Python graphical user interface. The system is composed of different tools that can be interactively used by the user, before or during the procedure. Figure 2 shows the system user interface as it is presented to a user in Slicer during the pre-processing step. As shown, the interface is divided into four different sections: centreline extraction, procedure planning, path visualization, distance to target information, and fiducial registration.

Centreline Extraction

Centreline of the airway model is extracted using ITK-based[3] classes to implement the algorithm described in [28]. We chose this approach as it is based on theoretical properties that have been previously thoroughly justified [29] and because the algorithm is completely automatic. The algorithm extracts the centreline of the specified airway label using an AOF implementation of the label followed by a thinning of the medial surface to obtain a structure with only one curve, defined as the medial curve, and a pruning operation to obtain the final centreline.

Procedure Planning

This section represents the area where the user can select the biopsy targets, or regions of interest, to create the paths for guidance. As shown in Figure 2, this section consists of different buttons and a combination box that facilitate the targets selection. This area permits also the selection of areas outside the 3D airway model, so that guidance can be provided even in peripheral areas virtually not reconstructed. In this case, a spline interpolation of user-specified points is used. Once the biopsy targets have been selected, pathways towards the regions of interest are automatically extracted using VMTK[4] classes as

[2] http://openigtlink.org/
[3] https://www.itk.org/
[4] http://www.vmtk.org

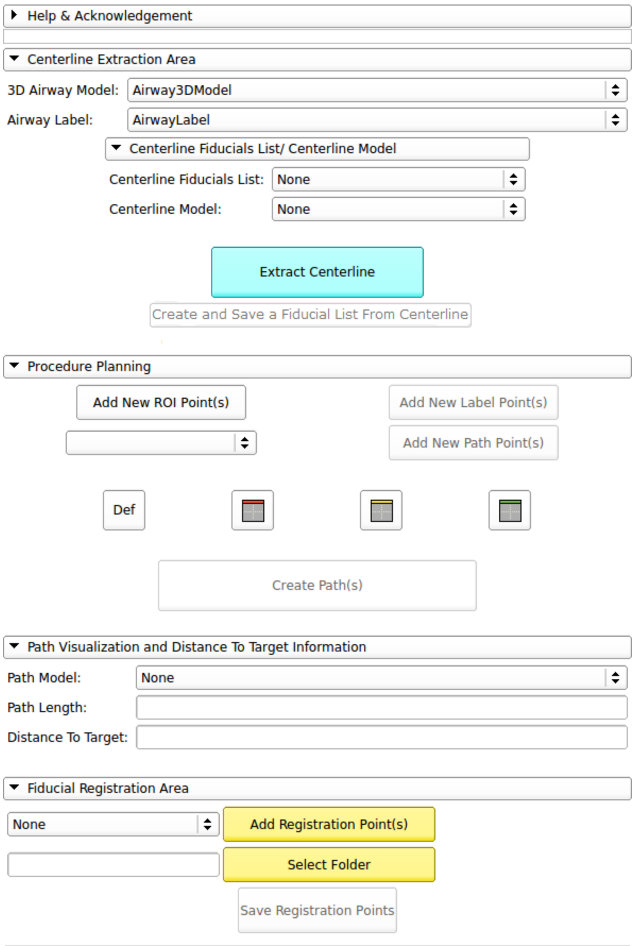


Fig. 2: The Slicer Virtual Bronchoscopy interface as shown during the preprocessing step.

the weighted shortest path traced between the trachea and the target point. In order to ensure that the final lines are in fact central, the pathway is bound to run on the Voronoi diagram [30] of the 3D airway model.

Path Visualization and Distance to Target Information
In this section, the user can select and visualize each path on the 3D model. This tool is also used during the procedure to move from one path to another. Once a path is selected, the total length of the path from the trachea to the ROI is shown. The Distance to Target is only used during the procedure to provide distance information between the actual position and the biopsy target. This information is duplicated on the 3D view showing the virtual navigation.

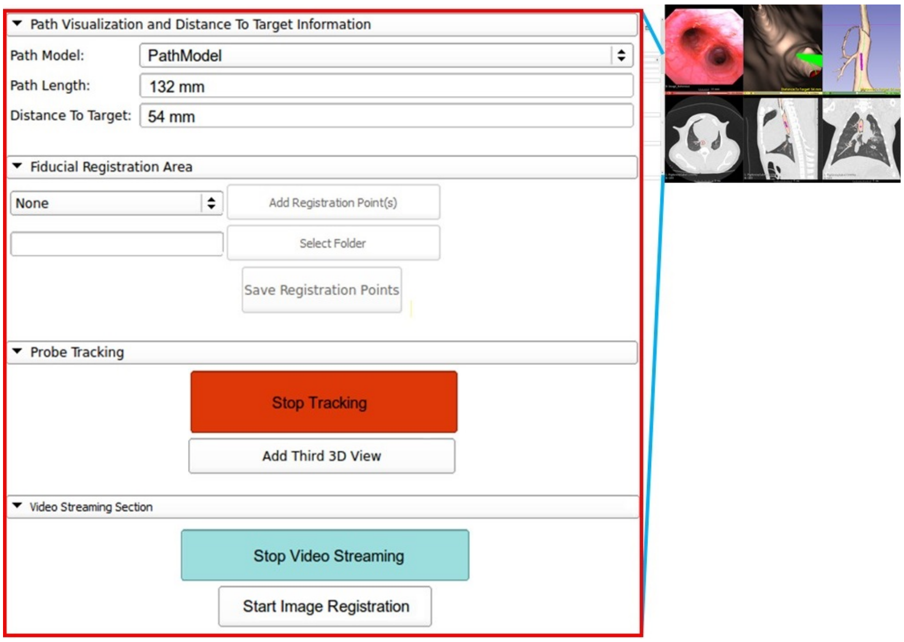


Fig. 3: The Slicer Virtual Bronchoscopy system as shown during image-guided bronchoscopy. On the left side, the user interface is presented. On the right, the visualization area shows the user different views that help during navigation.

Registration
The last area of the pre-procedural interface consists of the tools for helping in the real-virtual registration process. For registration, we used the landmark-based registration technique described in [23]. With this method, four or five physical fiducials easily identifiable both in the real and in the virtual airways are touched with the sensor inserted in the bronchoscope channel.

Image-guided Bronchoscopy
On the right of Figure 2, the visualization area is shown. This includes six different windows. At the bottom, the axial (red), sagittal (yellow), and coronal (green) views are presented. On the top, the first window represents the bronchoscope's video stream. The second two windows represent two 3D views of the airway model. During the pre-processing step, these are identical. However, these provide the user with two different views of the 3D model; one of the inside of the airway, while the other of the complete model as seen from distance.

Figure 3 gives an example of what the module looks like during the image-guided bronchoscopy step. As shown, in this case three sections are active. The first one is the path visualization area already described. During the procedure, the distance to target is presented in this area. The second section, the fiducial registration area is disabled and cannot be used until navigation is stopped. The third section, Probe Tracking, represents the key area that starts navigation. The red button is initially white, and changes colour to signal that virtual navigation has started. Here, along with the navigation button, a second button called "Add Third 3D View" is inserted. This button allows for changes to layout of the visualization area, when needed. When this button is pressed, the sagittal view is removed to make space for a new 3D view which shows the probe position from a proximal point of view. This may help the physician recognize the correct path in some procedures. An example of this view is given in Figure 4.

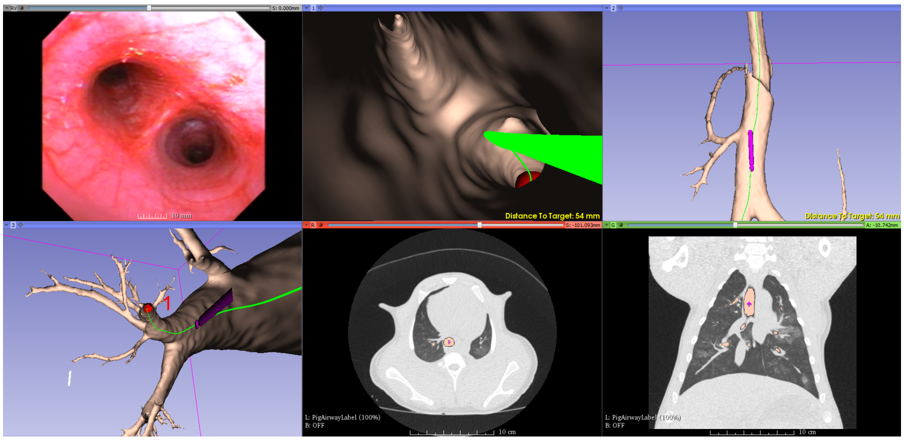


Fig. 4: Visualization area of the system when a third 3D view is selected by the user. The sagittal CT view is suppressed, the axial view is shifted to the right, and the third 3D view is placed on the initial axial view position. The third 3D view shows the airway model, the probe (purple), and the paths from a proximal perspective. This may be helpful in cases where branches seem to overlap in other views.

During navigation, a method to compensate for possible registration errors is activated. The idea underlying the method is to exploit the fact that physicians tend to move the bronchoscope on the medial axis of the airways. Therefore, assuming that registration errors are not excessive, the centreline of the airway model can be exploited. The probe position as tracked by the EM system is compared to the centreline points list (extracted during the preprocessing step) and the centreline position with smallest Euclidean distance to the actual position is used as a new position.

Finally, the last section of the interface is called Video Streaming and consists of two buttons. The first one connects Slicer to the PLUS research framework to start the streaming of the real bronchoschopic video. The second button allows to start an image registration process that provides error compensation for the roll rotation term that is not provided by the 5 DOF EM sensor placed at the tip of the bronchoscope. When started, image registration triggers an intensity-based multi-resolution pyramid registration method at every bifurcation point (previously computed from the centreline extracted from the airway model) to compute the optimal angle which matches the real and virtual images.

During the bronschoscopic procedure, the three views of the CT (bottom-right side of Figure 3) are aligned with the probe position (i.e., slices corresponding to the location of the bronchoscope are automatically identified and presented). On the top-right of Figure 3, the remaining views are shown. The first window represents the real image from the bronchoscope. The second one shows the virtual image representing the inside of the airway in the 3D model. A green line indicates the virtual path to follow to reach the target, shown as a red dot. To further help the physician understand the position of the scope, a third window shows a 3D view from outside the model. Again, the green line indicates the virtual path, while the purple object symbolizes the sensor at the tip of the bronchoscope. This view automatically zooms in and out as the scope moves according to distance to the target. This way, before the physician starts the navigation (s)he is provided with a complete view of the model and the path to navigate. When the bronchoscope reaches branching points and peripheral areas where airways become smaller and more difficult to distinguish, the virtual camera zooms in to help better find the correct direction. Finally, distance to target information is shown on the two 3D views with continuous updates, so that the physician knows in real time how far the ROI is. Figure 5 provides a diagram of system in the operating setup.

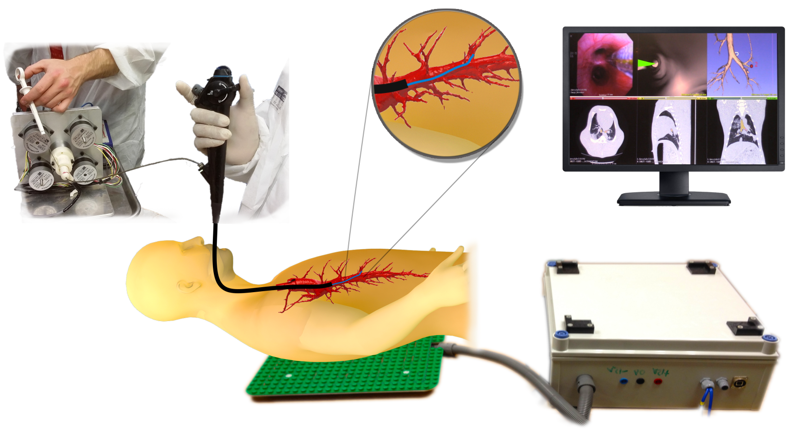


Fig. 5: Diagram of the system in the operating setup.

2.1 System Testing Approach

The system was tested on both *in-vitro* and *in-vivo* pre-clinical animal studies. This serves as a precursor for future clinical work on human trials. First, the VB technology was tested *in-vitro* in a breathing lung model [31] to verify performance in a simulated setting. Next, to further evaluate VB in a realistic setting, two animal studies were carried out.

2.1.1 Breathing Lung Model Evaluation

Tests with the breathing pig lung model were conducted at the Irish Thoracic Society (ITS) Conference[5], that took place in Cork, Ireland, in November 2015. The breathing model consists in plasticised pig lungs which are placed in a vacuum chamber, with the trachea connected to atmospheric pressure. When the chamber is evacuated, the pressure differential between the outside and the inside of the lungs causes them to inflate.

The complete EM tracking system was connected to the VB technology as described above, and the 3D virtual model of the phantom was created using the Slicer airway segmentation extension described in [31]. Three different targets were selected inside the airway model in order of difficulty. The position of the three targets (red, blue and green) are shown in Figure 6. Physical "tumour" targets made of Blu-Tack^{TM} (volume $< 5mm^3$) were placed within the lung phantom at the corresponding positions. Nine different physicians in the field of respiratory medicine were asked to navigate through the model lungs in order to reach three pre-defined physical targets. The VB system was presented on screen to the physicians who had to follow the different paths created in the virtual environment to reach the regions of interest.

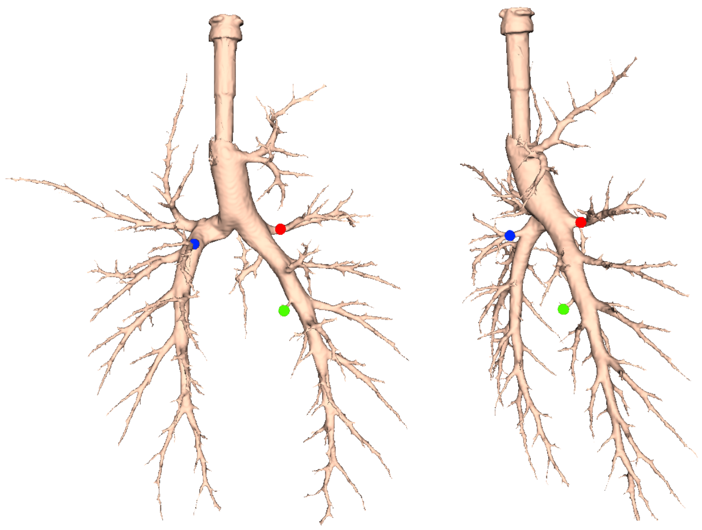
At the end of the procedure, all participants were asked to complete a questionnaire to evaluate their personal experience and usability of the VB system. Each was first asked five questions about the overall system usability and value. The questions are reported in Table 2.

Table 2: Questions to evaluate overall system usability.

Question	**Score (1-5)**
How was the overall ease of use of the system?	Poor to Excellent
Does the system accurately replicate the clinical setting?	Not at all to Excellent
How valuable do you consider the system as a training tool?	Not at all to Extremely Valuable
How valuable do you consider the system as a clinical tool?	Not at all to Extremely Valuable
Would you use image-guided navigation in bronchoscopy?	Yes/No

The second part of the questionnaire concerned the system usability. A questionnaire provided by the system usability scale (SUS) [32] method was presented to the physicians to evaluate usability. The SUS system is a simple,

[5] http://www.irishthoracicsociety.com/its-conference/its-asm-2015



(a) (b)

Fig. 6: Position of the three targets inside the airways. Two different views are shown. The first, second, and third targets are indicated in red, blue, and green, respectively. First and third targets were placed in the right lung. The second target was in the left lung.

Table 3: The SUS questionnaire.

1)	I think that I would like to use this system frequently.
2)	I found the system unnecessarily complex.
3)	I thought the system was easy to use.
4)	I think that I would need the support of a technical person to be able to use this system.
5)	I found the various functions in this system were well integrated.
6)	I thought there was too much inconsistency in this system.
7)	I would imagine that most people would learn to use this system very quickly.
8)	I found the system very cumbersome to use.
9)	I felt very confident using the system.
10)	I needed to learn a lot of things before I could get going with this system.

ten-part scale giving a global view of subjective assessments of usability. The ten questions are characterized by five response options, from strongly agree to strongly disagree. The ten questions are reported in Table 3. However, scores for particular items are not meaningful on their own. To calculate the SUS score, first all the score contributions from each item are summed and this sum is multiplied by 2.5 to obtain the overall value of system usability. SUS scores have a range of 0 to 100, but this is not a percentage. Based on research [32,33], a SUS score above a 68 would be considered above average and anything below 68 is below average. However, the best way to interpret the results involves “normalizing” the scores to produce a percentile ranking [33]. During the testing, time to reach the targets was also recorded.

2.1.2 Animal Studies

Two separate animal studies were carried out on pigs to evaluate the VB algorithm in a clinical settings. One pig for each study was used. Both tests were approved by both the Irish Department of Health and UCC Animal Experimentation Ethics Committee and followed similar protocols, with incremental improvements to instrumentation between studies. As well as testing the VB system, these studies were also used to evaluate performance of a novel semi-automated robotic navigation method, compared to manual navigation, and to investigate novel radiopaque tumour models [34]. The robotic system consists of a specifically designed catheter with the tracking sensor incorporated at the tip. The proximal end of the catheter contains four pull wires whose tension can be monitored through individual force sensing loadcells on each wire member. A joystick connected to the loadcells allows for different forces on each of the wires to steer the catheter’s tip.

In both tests, tumour models were placed in different positions of the animals’ lungs and image-guided navigation was tested. Two different physicians carried out the tests; one to place the tumour models; the second one to navigate to the targets. Navigation success, defined as correctly guiding the physician to the final pre-defined target was undertaken. Tumour model samples from the target’s positions were extracted to validate the navigation. Finally, time required to guide the physician to the different regions of interest was recorded. The usability evaluation system used for the breathing model was not meaningful in this case, as only two physicians carried out the test.

Animal studies were achieved using the same bronchoscope and the EM tracking system used for the pre-clinical testing. In both cases the 3D airway model was reconstructed using the method described in [31]. In both studies the pig was anaesthetized before placing the tumour models [34], taking the CT scan and starting the procedure. The first trial served as pilot study. Seven targets were placed in the pig’s lungs. Image registration was not used, as not yet optimised. The second test was carried out to evaluate performance and usability of the system. In this case, six different targets were considered. Figure 7 shows the system as used by the physician during the second animal procedure.

3 Results

3.1 Results for the Breathing Pig Lung Model

For testing with the breathing pig lung model, all targets were reached by the users. Table 4 shows the times required to every user to reach the three targets. On average, target 1 was reached in 58.2±56.5 seconds, target 2 in 44.8±30.04

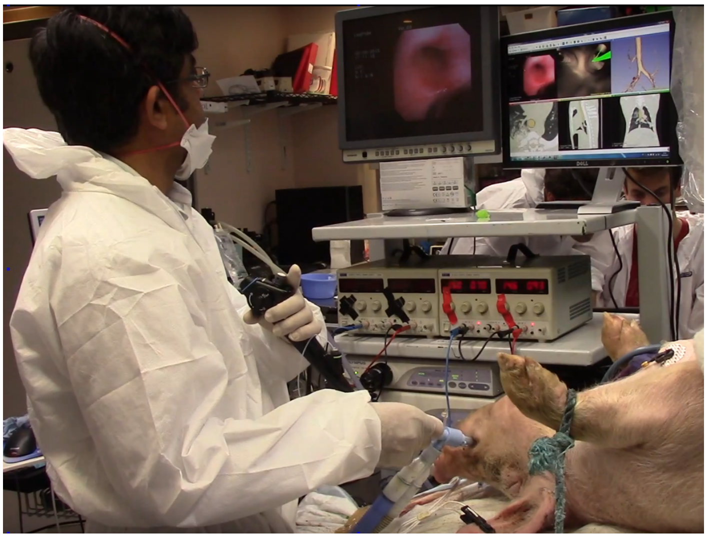


Fig. 7: The VB system as used by the physician during the second animal trial.

Table 4: Time (in seconds) required to each participant to reach the three targets.

Participant ID	**Target 1**	**Target 2**	**Target 3**
V1	58	80	40
V2	20	17	17
V3	45	34	36
V4	59	82	241
V5	200	82	130
V6	40	20	32
V7	25	15	68
V8	10	18	40
V9	57	55	62
Average	58.2	44.8	74.0
Std. Dev.	56.5	30.04	70.7

seconds, and target 3 in 74.0 ± 70.7 seconds. As expected, target 3 was the most complicated to reach, while the high time required to reach target one (placed in a quite easy to reach position), can be explained by the fact that participants were familiarizing with the bronchoscope and the system.

In general, considering that volunteers had never tried the system previously and could not analyse the CT image or the lungs prior to the procedure, this can be considered as a positive result, indicating the help that the image-guided system can provide. Moreover, even participants who never performed a bronchoscopy before were able to reach targets in reasonable clinical time frames, indicating that the image-guided system helps choose the correct path

Table 5: Results of overall satisfaction of participants. For all questions a score 1-5 was requested. For question 1 (Q1), 1 represented poor and 5 excellent. For Q2, 1 was not at all, whereas 5 stood for excellent. For Q3 and Q4 scores ranged from not al all (1) to extremely valuable.

Participant ID	**Q1**	**Q2**	**Q3**	**Q4**	**Q5 (Y/N)**
V1	4	4	5	4	Yes
V2	4	4	2	4	Yes
V3	4	4	4	4	Yes
V4	2	4	5	5	Yes
V5	4	5	5	5	Yes
V6	5	4	4	4	Yes
V7	4	3	5	5	Yes
V8	5	4	4	3	Yes
V9	4	3	5	4	Yes
Average	4	3.89	4.33	4.22	//
Std. Dev.	0.87	0.6	1	0.67	//

without any previous experience or image analysis. Comparison with navigation without help of the VB system would give a better indication of the real help the system could provide in a blinded comparative study. However, this was not possible in our study, as the results would be biased by the participants already knowing the position of the target. The end points of the study were technical feasibility rather than comparative analysis. While a blinded study is certainly something that will be included in the future, the limited cohort number to date meant that such analysis was difficult to achieve to date.

Table 5 reports the results in terms of overall satisfaction of the participants. As shown, the system has been considered easy to use and accurate in replicating the clinical setting. Also, participants evaluated the system as valuable both as a training and as a clinical tool. All the volunteers stated that they would use the system during a bronchoscopy procedure.

Finally, individual results obtained on system usability are reported in Table 6. Sixty-eight resulted as the 20^{th} percentile for this test, indicating that 80% of participants found the system usable above average. In fact, as shown by Table 6 only two participants score the system below 68, with V6 close to the usability limit. Furthermore, comments of the participants' report that most of them preferred to follow the path in the virtual environment to move the bronchoscope, rather than looking at the real image.

The results obtained in the pre-clinical setting are promising and show that an image-guided system coupled with electromagnetic tracking to recognize the current position of the scope inside the lung may be of great benefit for diagnosis and assessment of pathological conditions in the lung.

Table 6: System usability for all participants. Each question was given a score from 1 to 5, with 1 indicating strongly disagree, and 5 strongly agree. Scores higher than 68 indicate usability above average.

Participant ID	**Usability Score**
V1	77.5
V2	77.5
V3	57.5
V4	70
V5	90
V6	65
V7	75
V8	72.5
V9	70
Average	72.78
Std. Dev.	9.05

3.2 Pilot Animal Study: Results

During the pilot animal study, all the tumour models were successfully navigated using manual bronchoscopic steering with virtual navigation. An average time of 9.71 seconds was necessary for navigation to the targets. Table 7 reports the specific time required for each target. For each tumour model, a tissue sample was extracted and visually inspected to confirm successful targeting of the region of interest. Tumour 1 and 5 were also successfully navigated with automated navigation, as confirmed by biopsy of the tumour models. After the preliminary study, user comments were gathered. General satisfaction at the system was noted, although two main aspects were underlined; registration between the real and virtual world should be improved. In deeper branches the centreline compensation method is not sufficient to guarantee good guidance. Real and virtual frame images were often mismatched when the bronschoscope was rotated. Therefore, a method to compensate for the use of 5 DOF sensing should be implemented to help align the two images.

Table 7: Time (in seconds) required to reach every target using VB.

Target ID	**Time to Reach Target (sec)**
T1	18
T2	14
T3	10
T4	8
T5	6
T6	7
T7	5
Average Time	9.71
Std. Dev.	4.71

3.3 Pre-clinical Study In-Vivo: Results

During the pre-clinical study, four targets were successfully navigated, whereas targets 3 and 6, positioned in difficult locations, were not reached (more than 5 minutes attempting). Table 8 reports the time required to reach every target. An average time of 45.75 seconds was registered. In terms image intensity, the placed tumour models proved more representative of real tumours on CT scans. The study aimed at testing the robotic navigation system with VB. During navigation, the image registration approach successfully aligned real and virtual images at branching points and satisfaction at the VB system was noted. As well as in the case of the breathing model, comparison with "normal" navigation (without VB) was not possible, as the physician would already know the tumour position in the lung. This is an aspect that will be definitely considered in the future.

The study outlined a few aspects to be improved for future work. First, the sensor at the tip of the catheter is fragile and easy to break. Design of the catheter should be modified to guarantee higher reliability. Also, the physician noted mis-matching between joystick movements and catheter orientation. To this end, a label indicating how to insert the catheter into the bronchoscope's channel may help. Finally, landmark-based registration did not provide a true alignment between real and virtual images, and centreline compensation cannot be considered a long-term solution. Removing the centreline extraction stage would also reduce time required in pre-procedural planning. For this purpose, an optimized landmark-free registration, such as the use of a balanced survey method that uses an ICP algorithm to match the airway model centreline with the survey points, represents a possible solution. Accurate testing for this method should be carried out with animal studies to evaluate the benefits which the approach brings to VB. A comparison between the two registration methods should be performed.

Table 8: Time (in seconds) required to reach every target using automated steering and VB. Targets 3 and 6 were not reached.

Target ID	**Time to Reach Target (sec)**
T1	115
T2	20
T3	Not reached
T4	25
T5	23
T6	Not reached
Average Time	45.75
Std. Dev.	46.21

4 Conclusions

In this work, we presented a novel open-source virtual bronchoscopy system to be coupled with a 5 DOF sensing EM tracking system. Real and virtual environments are registered using a landmark-based registration algorithm. During a pre-procedure phase, centreline of the the 3D airway model is extracted. This is used during the virtual navigation for compensating for possible registration errors. Tools are provided to the user to select regions of interest on the patient CT image. Pathways towards the selected targets are automatically created for image-guided navigation. The 5 DOF sensing does not provide information on the roll orientation of the probe. For this reason, during the navigation, an intensity-based registration method is triggered at every bifurcation point to rotate the virtual image to match the real one.

Ex-vivo and *in-vivo* testing showed that the algorithm is easy to use and help the physician reach the selected targets. However, registration between real and virtual lungs should be improved to ensure more correct information of the bronchoscope position during navigation. To this end, we are currently working towards the implementation of a fiducial-free registration system based on reported methods, such as balanced survey and ICP techniques [36,37].

The created pathways are static in the 3D environment. This leads to confusion if the pathways exit the camera field of view. A method to automatically update the pathway real-time based on the probe position would be of great benefit for the navigation.

Moreover, image registration is computationally expensive and, at present can be only used at bifurcation points. A better method to compensate for the 5 DOF sensing should be developed. This solution may be either on the hardware system, such as the use of sensor to be placed on the bronchoscope to identify the applied roll rotation, or on the software side, using a system based on the inverse-compositional formulation proposed by Merritt et al [38] to register real-time the real and virtual world.

Finally, we are currently working at a method to compensate for torso movement due to breathing and coughing. This system consists in using a second 5 DOF sensor placed on the patient's torso to create a new reference system to remove breathing and coughing issues.

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