Force adaptive robotically-assisted endomicroscopy for intraoperative tumour identification

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Abstract

Purpose: For effective tumour margin definition for cancer surgery, there is an increasing demand for the development of real-time intraoperative tissue biopsy techniques. Recent advances in miniaturized biophotonics probes have permitted the development of endomicroscopy techniques that are clinically attractive. With these approaches, cellular-level imaging can be achieved through millimetre-scale flexible probes, and be performed in real-time, *in vivo* and *in situ*. Due to the limited field-of-view and flexibility of these probes, however, large area tissue coverage for acquiring histology-like images over complex three-dimensional surfaces is challenging. This is particularly the case because current surgical robots, such as the Da Vinci®, lack haptic feedback, making it difficult to maintain optimum tissue contact when these probes are deployed *in vivo*.

Methods: This paper proposes a simple force-controlled pick-up probe that can be integrated with the Da Vinci instruments for intraoperative endomicroscopy imaging. The device uses a new low-friction air bearing with adaptive axial force control to maintain constant contact between the tissue and the imaging probe, facilitating microscopy scans over complex surfaces. Detailed *ex vivo* user experiments have been conducted to demonstrate the effectiveness of the technique.

Results: The adaptive probe mount could achieve consistent low magnitude probe-sample contact forces compared to a rigid mount. In the user study, the adaptive probe combined with a high frame rate endomicroscopy system allowed larger mosaics to be generated over curved surfaces.

Conclusion: The device can improve the performance of large area mosaicking over complex 3D surfaces with improved handling and intraoperative control.

Keywords*: Endomicroscopy, Endoscopy, Adaptive control, Robotic-Assisted MIS, Mosaicking, Image Guidance*

Introduction

For oncological procedures, biopsy followed by postoperative histology remains the "gold standard" for the identification of cancerous tissue, despite this method relying on discrete sampling and not being real-time [1]. "Frozen section" analysis of surgical margins can be applied intraoperatively, but is less accurate than conventional histology. It requires discrete biopsies and requires a considerable amount of processing time [2, 3]. With the increasing use of robotically-assisted minimally invasive surgery for oncological procedures, there is an increasing demand for real-time, *in situ*, and *in vivo* tissue identification and characterization techniques, particular for the identification of tumour margins.

Optical imaging techniques, and endomicroscopy in particular, could provide the necessary cellular-level information. Endomicroscopy is an emerging technique, capable of highly magnified and continuous acquisition of cellular-level images for *in vivo* and *in situ* assessment of tissue pathology, a process known as "optical biopsy" [4]. There is increasing evidence for the application of endomicroscopy for the examination of various sites such as the bladder [5], peritoneal cavity [6], lung [7] and gastrointestinal tract lumen [8].

The most common approach is to use a fibre imaging bundle probe to relay excitation light to the tissue and a fluorescence image back to the rest of the imaging system. However, a disadvantage of using fibre bundles is that the resolution and field-of-view (FOV) are limited by the finite number of fibre cores in the bundle. In order to obtain resolution on the order of 1-2 microns, necessary for sub-cellular imaging, the FOV therefore has to be limited to less than half a millimeter. Due to this limited FOV it is challenging for the clinicians to correctly interpret the endomicroscopy images. This fact was clearly identified in the work of Patsias *et al.* [9] where the clinicians found it challenging to obtain a broad sense of tissue morphology.

In order to facilitate interpretation in the face of this difficulty, algorithms for video sequence mosaicking have been proposed as a solution to create images comparable in size to histology slides. These algorithms increase the effective FOV by stitching together the images while maintaining microscopic-level

resolution [10]. However, mosaicking is only a partial solution to this problem, as it remains difficult to study large complex 3D areas in practice. Probes are almost exclusively controlled manually by the clinician, leading to inconsistent velocities and poorly controlled trajectories.

Robot-assisted probe manipulation may provide a solution to this problem. In particular, the Da Vinci® robot (Intuitive Surgical, Inc.) incorporates motion scaling along with fine instrument handling and reduced tremor for consistent tissue handling and manipulation. All these features provide the necessary precision, accuracy and stability so that an endomicroscopy probe can be manipulated consistently and with stability [9]. The lack of haptic feedback however can result in unregulated surface contact forces. This hinders the operator from maintaining constant tissue-probe forces and therefore makes it difficult to scan over uneven or curved surfaces. Furthermore, if excessive pressure is applied, this tends to lead to severe tissue deformation and micro-structure damage, which in general also affects the quality of images and mosaics [11, 12].

The two main schemes that can facilitate constant force and probe-tissue contact, and hence obtaining consistent microscopy images over complex 3D surfaces, are the active and passive force control approaches. In particular, active control techniques, as the name implies, actively control the forces exerted on the tissue at the contact point so as to maintain them at a specific value. Passive force control approaches, on the other hand, maintain constant tissue forces independently of tissue motion using a passive physical system to exert high-magnitude forces on the tissue.

Recent research developments demonstrate an improvement in the acquisition of endomicroscopy images with the use of a force control scheme. In the work of Newton et al. [13], an articulated robotic endoscope controlled a miniaturized probe with an integrated, motorized, force-adaptive control scheme to ensure a constant tissue-contact force. A handheld robotic device by Latt et al. [14] further demonstrated the benefits of force control schemes. In this work, while a front facing microscopic probe was used, a force sensor and an actuator were placed proximally to the instrument. The forces on the probe were then transferred

through the instrument shaft. Such devices have shown promising results for robotically controlled endomicroscopic imaging, but they are large, bespoke devices requiring complex motor actuation and sensing. They are designed as a standalone system rather than to be integrated as a pick-up probe for existing minimally-invasive surgical (MIS) platforms.

The purpose of this paper is to propose a versatile yet simple pick-up probe, which can be used by robotic instruments such as Da Vinci, with adaptive force control and consistent instrument-tissue contact. One of the significant challenges associated with adaptive force control with micro-force sensitivity is the sensitivity of the actuator friction control. The new approach uses a low-friction air bearing with adaptive axial force control. This facilitates microscopic scans over complex and curved surfaces, such as those that would be encountered during *in vivo* tumour margin delineation. As demonstrated below, the device can improve the performance of large area mosaicking over complex 3D surfaces with improved handling and intraoperative control.

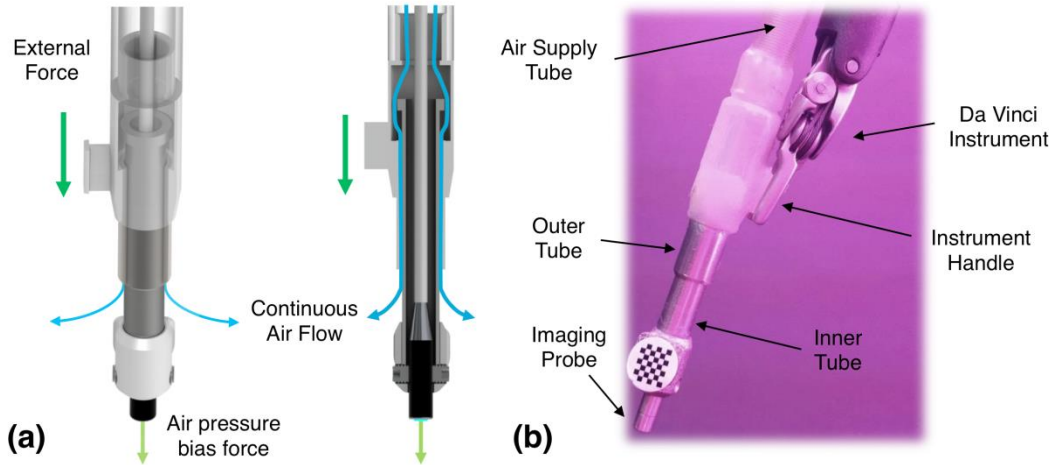

Figure 1 (a) Computer-Assisted Drawing (CAD) model of the proposed drop-in mount (left) and its section view (right) demonstrating the air flow path; (b) fabricated instrument handled by the Da Vinci Endowrist Needle Driver.

Materials and Methods

Robotic Pick-up Probe for in vivo Endomicroscopy

The fabricated instrument along with the CAD model is presented in Figure 1(a-b). The concept is based on the fact that an air cushion can be created between two cylinders, thus reducing the friction during their motion while acting as an

opposing force to elongate the probe mount when the probe is not pressed. During the operation, the air pressure and supply are kept constant in order to maintain a constant force at the tip of the mount. The operation is similar to a spring-based mechanism but the difference of this mechanism is that the air cushion keeps the force contact constant (rather than increase with shaft displacement), whilst at the same time minimizing the friction of the mechanism.

To simplify clinical deployment, the fabricated mount is used as a drop-in pick-up device delivering the imaging probe, and can fit inside a common 10 mm surgical trocar port. It can be dropped through the port at the operating site and then picked by an Endowrist® grasper or needle driver.

At the lower part of the device, the imaging probe is fixed and a marker for probe tracking is attached. This tracking, however, was not used for the experiments described here and is not discussed further. The outer tube of the proposed device has an outer diameter of 5 mm and inner diameter of 4.1 mm. The corresponding values for the inner tube are 4 mm and 3.2 mm, respectively. Both tubes are made of stainless steel, while the part that fixes the imaging probe and the other part that includes the pick-up handle were made of stainless steel through Direct Metal Laser Sintering process for improved durability. The supply of compressed air is by an air-compressor, with air tank for smoothing out the flow, through an 8 mm diameter flexible plastic tube.

Endomicroscopy Imaging System

The endomicroscope is a Gastroflex UHD fibre bundle probe (Cellvizio, Mauna Kea Technologies) fitted to an in-house, high speed laser line-scanning system. The probe is designed to be placed in direct contact with the tissue under study, having a working distance of only a few 10s of microns. It incorporates an approximately x2.5 magnification distal micro-objective, resulting in a field-of-view of 240 microns with a resolution of approximately 2.4 microns, limited by the bundle diameter and inter-fibre spacing respectively.

The line-scanning system operates under a well-established principle of slit-scanning [15]. Specific details of this implementation, which allows for high

speed imaging, are available in the work of Hughes et al. [16], and so only a brief description is given here. A 488 nm laser is shaped to a horizontal line, and scanned vertically over the proximal face of the fibre bundle probe by a scanning mirror. The bundle transfers the laser line to the tissue (with approximately 4 mW of power), where it excites a line of fluorescent stained tissue. The line of fluorescence returns along the bundle, where it is de-scanned, wavelength-filtered to remove reflected illumination light and imaged onto a linear CCD (2048 x 1 pixels). Fluorescence from out-of-focus regions of the tissue is defocused onto the camera and so largely undetected, resulting in an optical sectioning effect which reduces background blur and allows imaging of thick tissue. 2D fluorescence microscopy images, with a frame rate of up to 120 fps, are assembled from 500 lines acquired for consecutive positions of the scanning mirror. The system is shown in Figure 2.

They key functional differences between the line-scanning endomicroscope and conventional point-scanning confocal endomicroscopes, such as Cellvizio [11], are the higher frame rate (120 fps compared to typically 12 fps) and slightly reducing optical sectioning strength (i.e. a greater fraction of background blur survives to impact on the image) [15, 16]. The higher frame rate tends to improve mosaicking because of greater overlap between adjacent images [16]. However, the general approach described in this paper is not specific to a line-scanning system, and could be used with other fibre bundle based endomicroscopes.

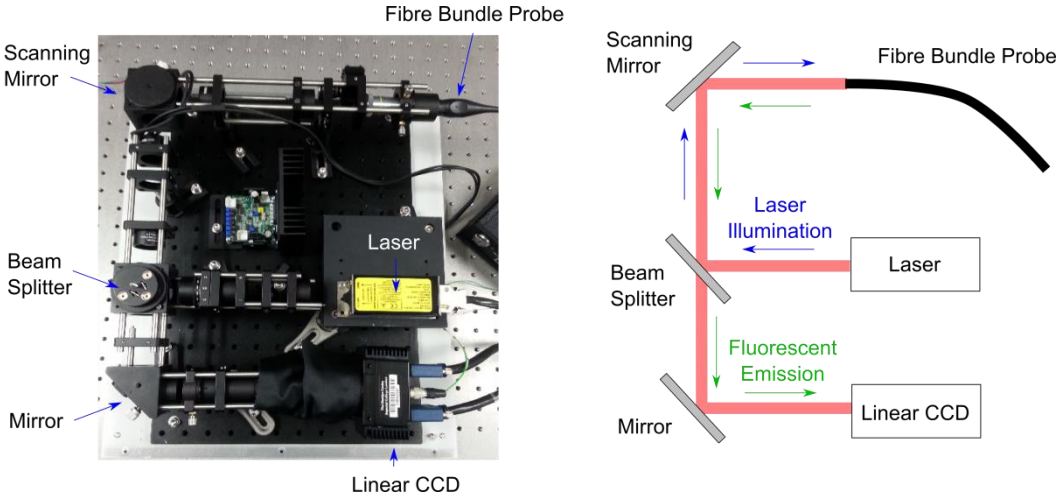

Figure 2 Photograph and schematic of the endomicroscopy imaging system, showing only the key components. Intermediate relay optics, and optomechanics are not shown for clarity.

Image Processing and Mosaicking

The raw image was streamed directly to disk at 120 fps, while an on-screen preview was shown at 20 fps. This preview was fed to the Da Vinci console, and displayed to the user in the upper-right corner of the normal 3D endoscope view. Endomicroscopy image processing is relatively straightforward: the raw 12 bit data is converted to uncompressed AVI, being downsampled to 8 bits in the process. A Gaussian spatial filter of 1.4 px (corresponding to 0.7 microns on the surface of the tissue) is applied to reduce the effect of the 'honeycomb' pattern of the fibre cores, and a circular window is applied to hide the periphery of the bundle. A background image is then subtracted to remove signal from along the length of the bundle.

In order to enlarge the field-of-view of the imaging probe, a low-complexity mosaicking algorithm is implemented, similar to previously reported approaches [17]. For successive pairs of images, I_1 and I_2, a central template of smaller dimensions (here 200 pixels in both directions) is extracted from I_1 and the 2D cross correlation between the template and the image I_2 is calculated. Then, based on the maximum cross-correlation value, the location of this peak is used as an estimate of the shift between the images I_1 and I_2. The algorithm is a two-way approach as both forward (I_1 to I_2) and reverse directions (I_2 to I_1) are used to find the location of the cross-correlation peak, with the result with the highest cross-correlation value taken as the best estimate of the shift. Furthermore, if the confidence is low, i.e. less than 30%, then the shift is considered as zero. For this study, all mosaicking was performed off-line.

Mosaicking with only 2D cross correlation leaves overlapping edges, due to the non-uniform lighting characteristics of the fibre bundle. Blending, specifically distance weighting, was used to minimise these differences. Both the current mosaic and the next image frame are converted into a binary image and a distance transform is performed on each image. The resultant values are then used as weights, and the weighted mean intensity is calculated from both images, for each pixel of the mosaic. To reduce the calculation time and maintain the latter independent of the mosaic size, only a defined area of the mosaic around the successive frame is considered for the blending calculation.

Experimental Validation and Results

Force Adaptive Mount Demonstration

Figure 3 shows the results of a simple but illustrative demonstration of the force adaptive system. The force-adaptive mount, with the probe inserted, was grasped by the Da Vinci Endowrist instrument, and driven across the surface of a scientific weighing scale for 60 s, showing an approximately constant force averaging to 97 mN (standard deviation: 21 mN). The same experiment was conducted with a rigid mount for comparison, with the user attempting to maintain a small and

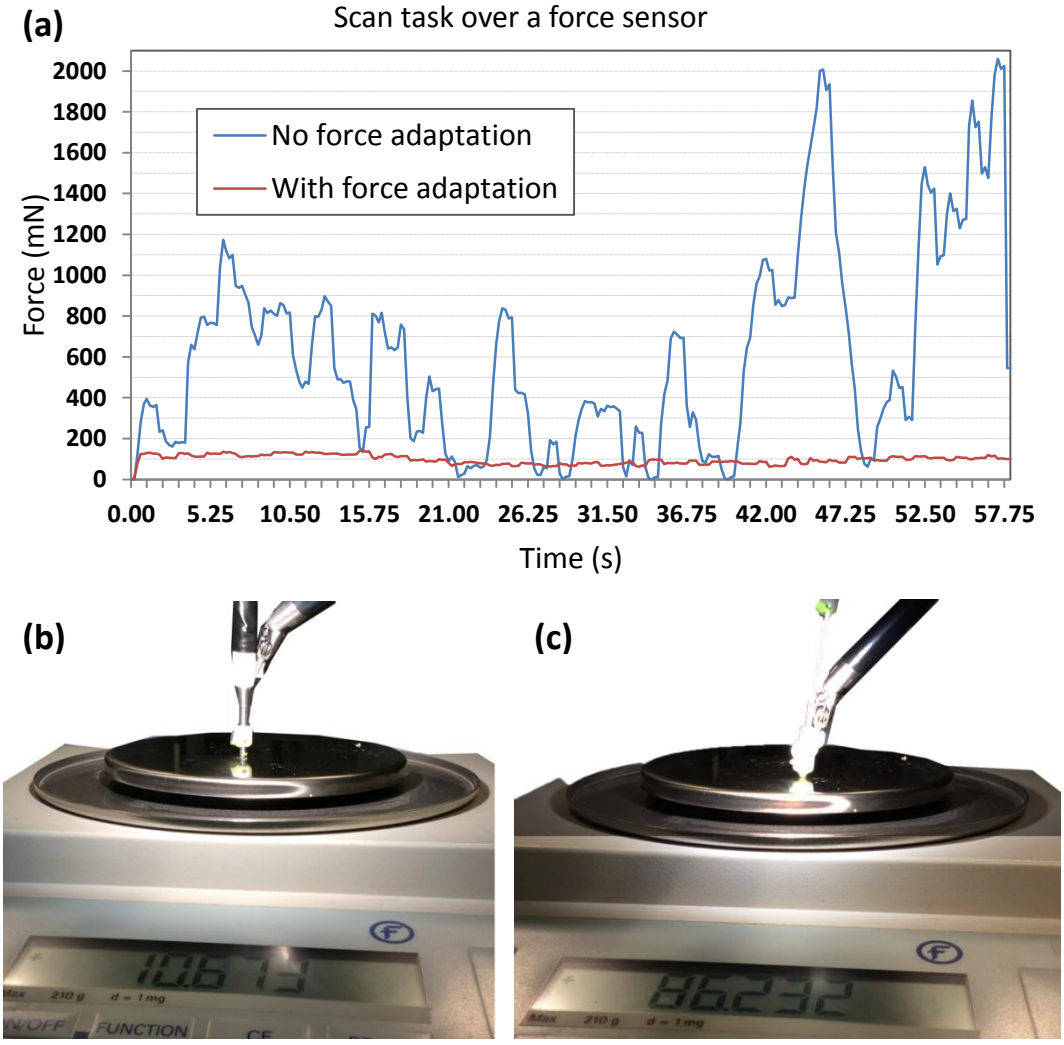

Figure 3 (a) Graph of a 60 s sample recording of the scale demonstrating that the adaptive probe proposed can apply consistent low magnitude forces to the surface of a scientific scale. Force measurements were made by recording a video of the scales as the probe was driven across. Then, from this video, each measured weight value was manually recorded every 0.22s; (b-c) Frames from the recorded video presenting the adaptive probe (b) and the rigid mount (c) and their respective weight values in grams.

constant contact force. The latter experiment showed an average force of 613 mN (standard deviation: 498 mN). This illustrates that the passive mount is indeed able to maintain a small and constant probe-sample contact force in comparison to a rigid mount.

Robotic-assisted endomicroscopy scanning study over complex surface

A pilot *ex vivo* user study was conducted to perform an initial assessment of the potential of the proposed device. The five users range from novice to experienced, both in the use of the Da Vinci system and in their knowledge of endomicroscopy and mosaicking, as presented in Table 1. A phantom was fabricated using 3D printing technology, which incorporates a tubular structure and a curved surface in

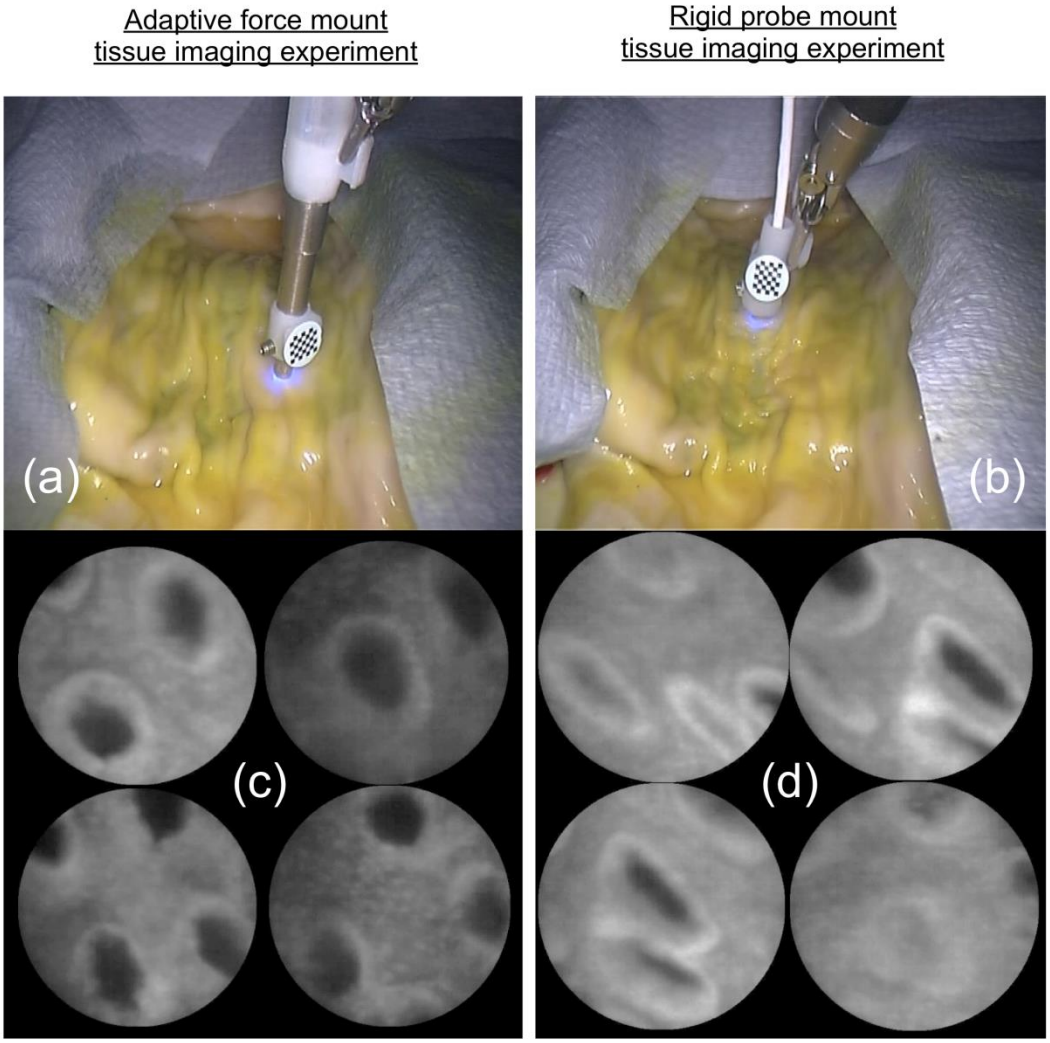

Figure 4 (a-b) Snapshots during the tissue task where the users had to scan, with the adaptive robotic mount (a) and a rigid mount (b), a large curved 3D surface and acquire consistent microscopy images. (c-d) Indicative microscopy images sampled during the tissue task with the adaptive probe (c) and the rigid probe (d).

the centre. A piece of porcine colon tissue was stained with a fluorescent dye (proflavine) and laid over the phantom. Colon tissue was chosen for these initial experiments as it has strong features for mosaicking, particularly the mucosal crypts. Also, previous studies have shown that the probe-tissue contact force alters the colonic crypt morphology seen in the endomicroscopy images, making this an ideal candidate for assessing the consistency of the contact force [12]. Users were asked to attempt to make several linear scans over this large area, from back to front, for one minute, following an initial training period of five minutes. The

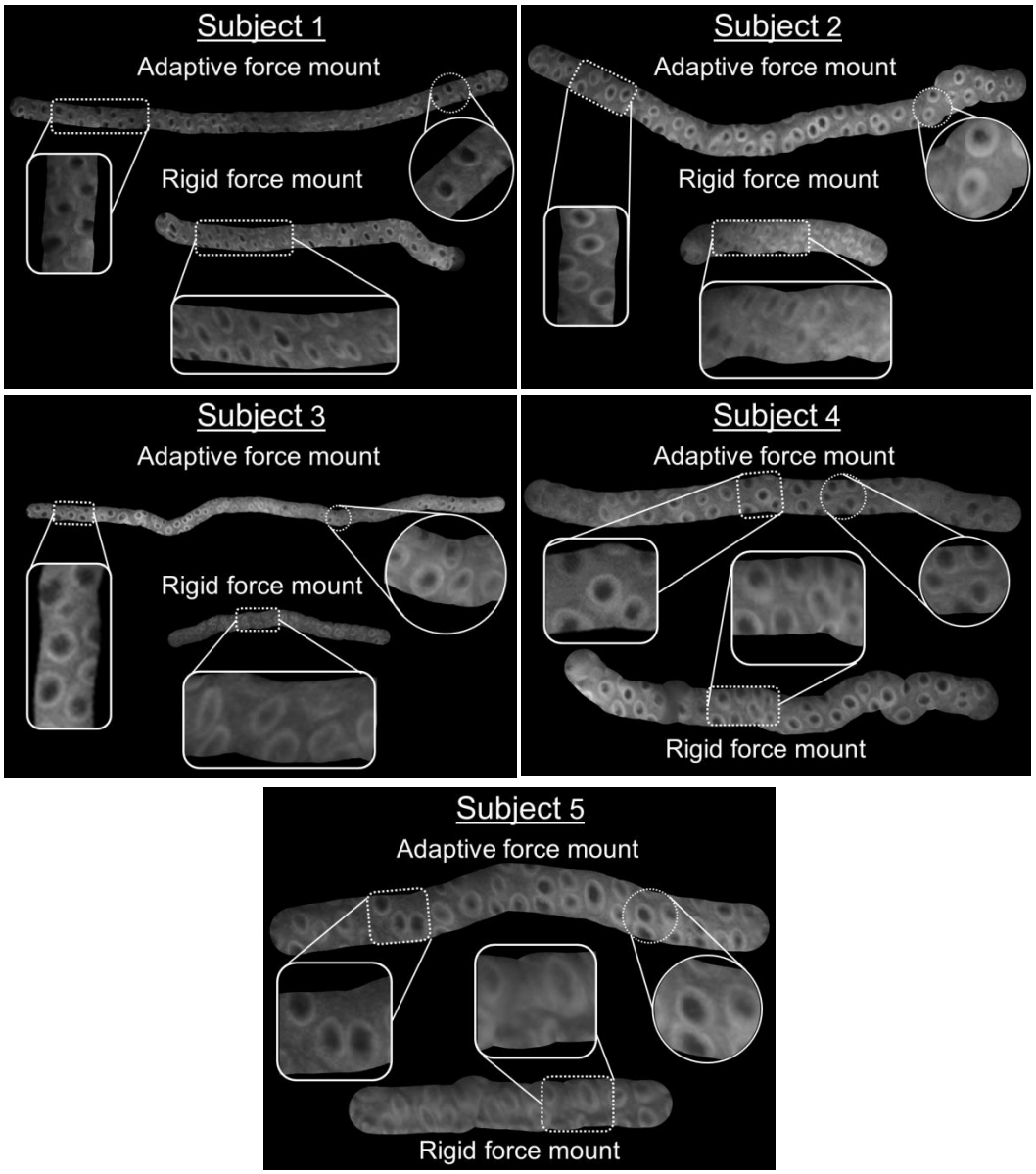

Figure 5 Indicative mosaic results of all the subjects that participated at the tissue study, demonstrating the largest mosaics achieved with the adaptive mount and the rigid probe. The mosaics depicted have been scaled with the same ratio to allow comparison of their lengths. Zoomed versions of microscopy segments are presented to assess the changes in the morphology of the cells, with and without the adaptive force mount.

users performed this experiment both with the adaptive force mount, and with a rigid probe mount in a random sequence. Example images from the Da Vinci endoscope view, showing the two mounts being grasped by the Da Vinci, can be seen in Figure 4(a-b). Example endomicroscopy image frames can be seen in Figure 4(c-d); those were chosen to highlight the increased distortion of the crypts that tended to occur when the passive force control was not used.

The resulting videos were processed as described above to generate mosaics. All viable mosaics were extracted from each video, where a mosaic was considered to be viable if the NCC value between each successive pair of frames was greater than 0.85, and where the total length of the mosaic was greater than 10 frames. The videos were then downsampled to 30 fps and reprocessed in order to assess the necessity of using a high frame-rate endomicroscopy system.

The longest mosaics generated by each user, using each mount, and for the 120 fps videos are shown in Figure 5. The increased length of the mosaics from use of the adaptive force mount can clearly be seen, as can a reduction in distortion of the crypts. The latter is due to the generally lower contact forces resulting in reduced tissue deformation.

Table 1 Demonstration of each user's expertise (+ = Limited experience, ++ = Intermediate experience, +++ = Expert) and total mosaic length in mm achieved by each user over a large 3D tissue surface in the period of 1 minute.

Subjects		1	2	3	4	5
Expertise	Endomicroscopy	+++	+	+	+	++
	Da Vinci	+	++	+++	++	+
120 Frames / s						
Adaptive force mount		**45.6**	**46.1**	**74.9**	**51.7**	**67.4**
Rigid mount		37.9	24.6	42.8	44.7	46.2
30 Frames / s						
Adaptive force mount		**31.4**	**20.3**	**19.9**	**16.5**	**7.8**
Rigid mount		16.6	19.1	21.5	20.3	7.8

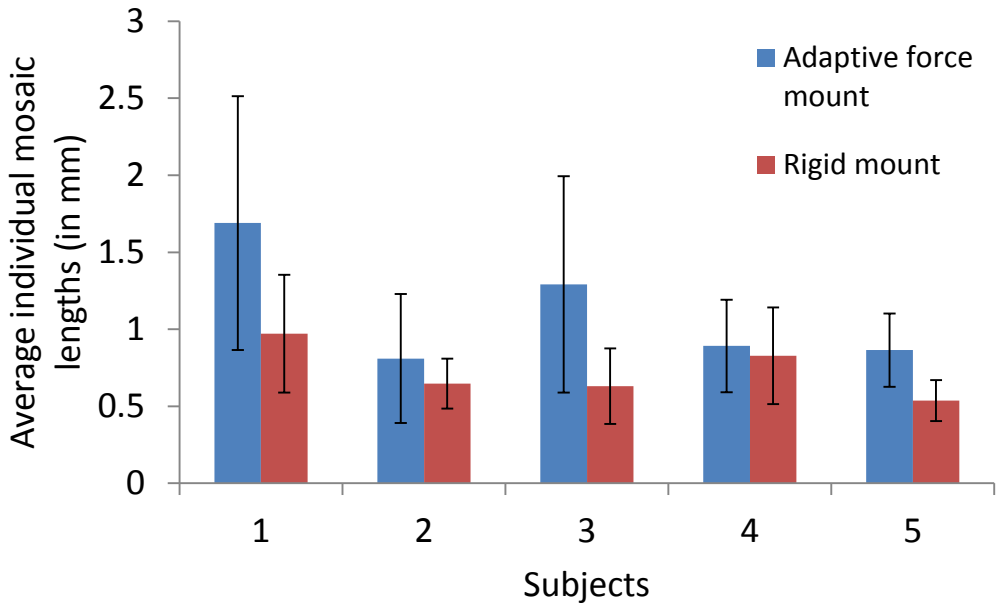

Figure 6 Average size of generated mosaics from each user during the 1 minute allowance for the tissue task. The images correspond to the raw acquisition rate of 120 fps.

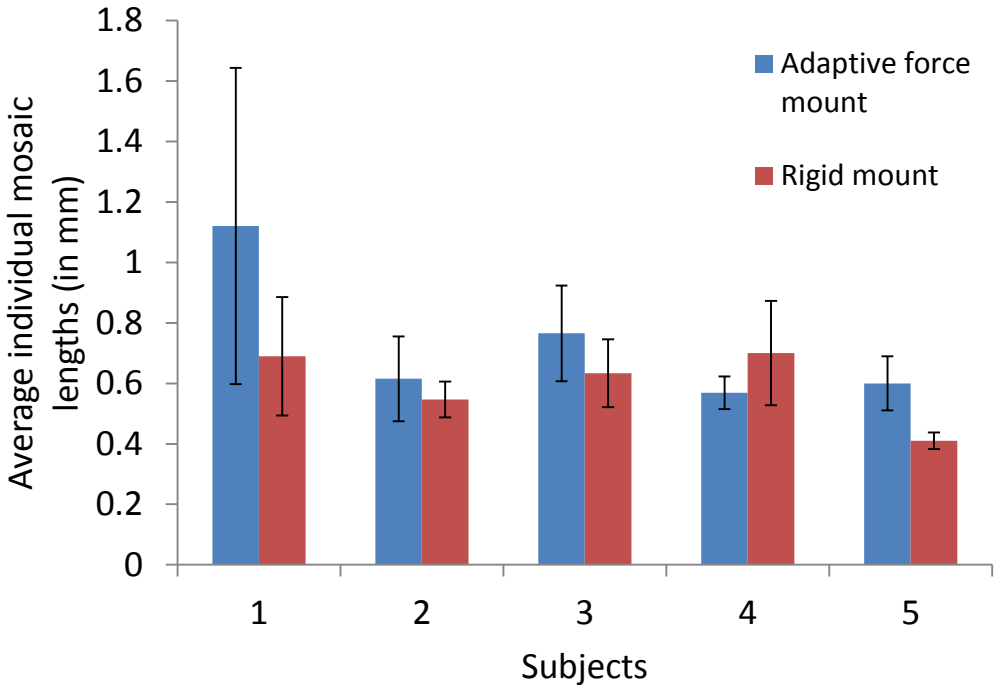

Figure 7 Average size of generated mosaics from each user during the 1 minute allowance for the tissue task. The images correspond to the downsampled acquisition rate of 30 fps.

Statistics relating to the mosaics are shown in Table 1 (total length of all mosaics from each video) and in Figure 6 and 7 (average length and standard deviation of all mosaics from each 1 minute video), for both the 30 fps and 120 fps videos. The improvement is clear for the 120 fps videos, in the sense that longer mosaics are generated by the force adaptive mount, but there appears to be little or no

improvement at 30 fps. There is also a clear improvement between the 30 fps and 120 fps videos, as expected, since for a given probe velocity there is an increased opportunity for the frame overlap required for mosaicking.

Discussion and Conclusions

In this paper, we have developed a simple yet versatile pick-up probe that can be used by robotic instrument, such as the Da Vinci, with adaptive force control and consistent instrument-tissue contact. The use of an ultra-low friction air bearing has permitted adaptive axial force control to facilitate large area image mosaicking over complex and curved surfaces. The proposed device requires a limited compressed air supply, which for MIS is convenient as it is readily available for maintaining pneumoperitoneum. User studies were performed to demonstrate the practical clinical value of the device compared to a rigid mount. The latter was designed shorter in size in order to provide better control as the user manipulates the probe near the tip of the instrument.

The results derived suggest that the passive force adaptive probe holder, combined with a high frame rate endomicroscopy system, allows large mosaics to be generated over curved surfaces. The device is able to maintain a small and consistent contact force between the probe and the tissue, offering the best prospect for good quality images and mosaics. However, these results are only preliminary, and further work will be needed to demonstrate that a similar improvement can be attained *in vivo*, under more realistic conditions and across a more representative range of skill levels. A more extensive study on the effects of the overall air pressure versus the force exerted to the tissue will, also, provide a better insight on the benefits of this device. Further, since endomicroscopy is not currently used in surgical procedures, manual or robotic, the eventual utility of this approach will depend on whether clinical research trials are able to demonstrate clinical effectiveness of optical biopsy techniques in intraoperative tumour margin delineation.

It is important to note that the probe holder is not specific to the Da Vinci, and so it should be possible to use this device with manual laparoscopic surgical instruments. The results of this work may therefore be extended to a much wider

range of surgical procedures than those currently conducted using the Da Vinci. In principle the device is not limited to surgical procedures, and with further miniaturisation it may be possible to make use of the technique in standard diagnostic procedures where the endomicroscope is introduced through the working channel of an endoscope.

Interestingly, for the 30 fps imaging, the benefits of the force adaption do not appear to be realised. This may be for one of several reasons. The force adaptive probe tended to make it easier to scan across the surface, possibly encouraging the user to scan at a higher speed than when using the non-adaptive holder. This higher speed may have led to insufficient overlap between frames at 30 fps for the mosaicking algorithm to calculate the shift, resulting in apparently degraded performance for the force adaptive holder. A second, related, possibility is that the users were always scanning too fast for mosaicking at 30 fps, but that without the force adaption, the probe tended to drag the tissue along with it to some extent, reducing the effective velocity and allowing mosaics to be created. Further work will be needed to confirm these effects.

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Conflict of interest

The authors declare that they have no conflict of interest.

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