Towards Intraoperative Breast Endomicroscopy with a Novel Surface Scanning Device

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Abstract— Background: New optical biopsy methods such as confocal endomicroscopy represent a promising tool for breast conserving surgery, allowing real-time assessment of tumour margins. However, it remains difficult to scan over a large surface area because of the small field-of-view. **Methods:** This paper presents a novel robotic instrument to perform automated scanning with a fibre bundle endomicroscope probe to expand the effective imaging area. The device uses a rigid concentric tube scanning mechanism to facilitate large area mosaicing. It has a compact design with a diameter of 6 mm, incorporating a central channel with a diameter of 3 mm for passing through a fibre bundle probe. A bespoke bearing, an inflated balloon and a passive linear structure are used to control image rotation and ensure consistent tool-tissue contact. **Results:** Experimental results show that the device is able to scan a spiral trajectory over a large hemi-spherical surface. Detailed performance evaluation was performed and the bending angle ranges from -90 to 90 degrees with high repeatability and minimal rotational hysteresis errors. **Conclusion:** The device has also been validated with breast phantom and *ex vivo* human breast tissue, demonstrating the potential clinical value of the system.

Index Terms—Breast conserving surgery, confocal endomicroscopy, image mosaicing, mechanical design, surgical robot.

I. INTRODUCTION

Breast cancer is the most common type of cancer in women and is the second leading cause of cancer deaths among women in the United States and Europe [1]. Breast conserving surgery (BCS) is an operation that involves the excision of the tumour with a surrounding margin of healthy breast tissue (approximately 2-5 mm) while leaving the remainder of the breast intact [2]. It is well recognised that the margin status of the excised tissue is the strongest predictor for tumour recurrence following BCS [3]. If tumour cells are found on the edges of excised tissues (positive margins), these patients will require a reoperation [3]. National data from England and Wales highlights that a significant proportion of patients with invasive (18%) and non-invasive breast cancer (28%) require reoperation following failed attempts at BCS [4]. Reoperations will inevitably lead to unnecessary anxiety, poor cosmesis, and are

cost inefficient. However, there is increasing evidence that almost 50% of patients that underwent reoperations did not have any evidence of residual tumour cells in the re-excision specimens which suggests that a significant proportion of these patients might have been over-treated [5]. Currently, the adequacy of BCS relies on the predictive value of postoperative histological assessment of the margin of excised tissues and yet the residual in situ disease burden is not known. The value of direct intraoperative assessment of the cavity wall has yet to be investigated, arguably due to the lack of imaging technologies suitable for cavity deployment.

Confocal endomicroscopy has the technical advantage and physical properties to provide high-resolution, real-time, in vivo, in situ imaging at cellular and subcellular levels. Over the last decade, it has found promising applications in the gastrointestinal tract, most notably during endoscopic surveillance of Barrett's esophagus [6], assessment of indeterminate biliary strictures [7] and in the lung [8]. Utilising intravenous fluorescein [6-8] or topical acriflavine [9-10] as the contrast agent, real-time confocal endomicroscopic image acquisition of in vivo tissue morphology is achieved through the process of optical sectioning which involves point-by-point illumination of the tissue surface using a rapidly scanning laser. Given the difficulties of miniaturizing devices for high speed laser scanning, an optical fibre bundle (confocal miniprobe) is used to relay the light source, typically a 488 nm wavelength blue laser, to the tissue surface and the resulting emissions from fluorescing tissues are collected between 500 and 650 nm and focused through a pinhole to block out-of-focus light. With the advent of high-speed laser scanning units, confocal endomicroscopic images are displayed live on a display screen during image acquisition, thus allowing real-time clinical decisions to be made [6-8].

Thus far, bench-top confocal microscopes have been shown to have the ability to image breast cancer morphology and may have a role in imaging resection margins of excised tissues [11]. However, in situ imaging of breast cavity walls created during BCS warrants considerable miniaturization to allow insertion of the microscope through a small 3-4 cm skin incision and for deployment against the walls of the breast cavity. Evidently, the benefits of miniaturization for initial endoscopically-driven clinical applications could potentially be extrapolated to intraoperative use within a surgically created cavity. Recent work by Chang et al reported that morphological architecture of neoplastic and non-neoplastic breast tissues were readily visualised using confocal endomicroscopy [12]. This *ex vivo*

This work was supported by EPSRC grant EP/I027769/1: SMART Endomicroscopy. S. Zuo, M. Hughes, C. Seneci, T. P. Chang, and G.-Z. Yang are with the Hamlyn Centre for Robotic Surgery, Imperial College London, London SW7 2AZ, U.K. (e-mail: s.zuo@imperial.ac.uk; m.hughes@imperial.ac.uk; c.seneci@imperial.ac.uk; t.chang@imperial.ac.uk; g.z.yang@imperial.ac.uk).

study on acriflavine-stained human breast tissues demonstrated that the presence of hypercellularity and haphazard arrangement of morphological architecture correlated well with common pathognomic features of breast cancer seen on conventional histology. Additionally, surgeons were shown to be able to differentiate neoplastic from non-neoplastic morphology with accuracies equivalent to that of pathologists [13]. These intriguing results warrant validation in intraoperative *in situ* studies whereby the clinical impact of confocal endomicroscopy is evaluated based on its ability to identify residual cancer cells left *in situ* on the breast cavity walls, thereby guiding operative decision making during BCS based on real-time cavity scanning. It is envisaged that the presence of cancer cells detected *in situ* would allow further removal of the corresponding breast cavity wall during the same operation, whereas its absence reassures the surgeon that complete removal of cancer cells was achieved.

In practice, the deployment of confocal miniprobes for large area tissue surface scanning presents unique challenges pertaining to precision, accuracy and economy of movement. Currently, the field-of-view of images obtained is less than 1 mm in diameter and this could be as low as 0.3 mm in diameter when high-resolution confocal miniprobes are used. It is unequivocal that the information obtained from a static miniprobe will not be truly representative of the corresponding cavity wall as adjacently placed cancer cells could easily be missed if they are not brought to the surgeon's view. A potential solution to this is to increase the field-of-view obtained by stitching adjacent image frames as the probe is moved across the tissue surface, a technique known as mosaicing [14-15]. However, in practice this is often difficult to achieve due to the surgeon's hand tremor, tissue surface deformation and the patient's respiratory movements. This is further compounded by the relatively large tissue surface area that needs to be assessed, which is a time-consuming process and inevitably induces fatigue to the surgeon. Moreover, this could lengthen the operation time, which in turn increases the risk of anaesthetic complications to the patient and reduces operating theatre productivity.

These inherent limitations are well-recognised and have motivated the development of several mechanical scanning devices to facilitate smooth and consistent translation of the miniprobe tip against the tissue surface. An articulated robot for manipulation of biophotonics probes was first developed by Noonan et al. for intra-operative integration of laparoscopic instruments [16]. Rosa et al. developed a scanning device using hydraulic micro-balloons [17], and a conic structure was developed by Erden et al. [18]. A cooperative robotic arm (KUKA Roboter GmbH, Augsburg, Germany) has also been used to generate a 3D map of the tissue [19]. However, the target of [17] and [18] were applications for which the scanning device must remain very compact. As a result, only relatively small areas of tissue could be mosaiced. Although large area mosaics were achieved by [19, 20], this work is difficult to adapt to clinical use due to the complex robotic arm used.

This motivates the development of a novel scanning device adapted to address the unique challenges during intraoperative

image acquisition in the breast cavity, with a specific emphasis on enhanced precision, accuracy and efficiency of probe-tip movement. To that end, a preliminary scanning device prototype was developed [21], where all parts of the bending unit were fabricated by a Direct Metal Laser Sintering technology. However, it was noted that the sintering technology was not precise enough for gear fabrication, thus a more precise processing technology needed be adopted. Moreover, inadvertent rotation occurred because the 2D motion of the scanner required rotation of the distal tip in the previous prototype [21], which resulted in an accumulation of errors during mosaicing. Furthermore, better control algorithms, which can maintain a stable tangential velocity at the tip for large area spiral scans, needed to be tested on *ex vivo* human breast tissue for further evaluation.

The aim of the study reported here was to develop a large area scanning device equipped with a robotized scanning tip to enable safe, efficient and accurate scanning of the breast cavity. Many existing robotic devices, including the da Vinci surgical instruments, incorporate multi degree-of-freedom (DOF) motion at the tip with wire driven mechanisms [22-24]. While the wire driven mechanism allows miniaturization of multi-DOF structures, problems of friction, wearing and extension are practical difficulties to consider.

Alternatively, linkage driven mechanisms can be considered [25, 26]. Although they provide a strong force to the target, backlash may be caused due to repeated use. In particular, it is difficult to satisfy the durability requirement while achieving miniaturization of the linkage.

Spring-shaped shape memory alloy (SMA) fabricated by laser profiling on a superelastic nitinol tube can also be used to improve the bending performance [27]. For SMA, insulation against electric leakage and heat generation needs to be treated carefully for safety. In practice, it is also difficult to achieve a small bending radius and apply a strong force to the target. In the case of tendon driven nitinol tubes, the demerits of wire extension and wearing should be considered. To address the snapping problem in a flexible concentric tube robot, Kim et al. designed groove patterns on superelastic nitinol tubes [28].

Another possible drive mechanism is to use rotational joints with bevel gears such as in [29, 30]. The gear driven mechanism makes it easy to achieve multi-DOFs together with miniaturisation. However, the traditional gear driven mechanisms often result in an increase in the number of parts. Furthermore, it is particularly difficult to reduce the backlash when there are a large number of gears.

Fig. 1 A concept of the system with an inflated balloon and a fibre bundle endomicroscope during breast conserving surgery for breast cancer.

In this study, we propose a simple and compact device, using a specially-designed gear-based rigid concentric tube scanning mechanism to achieve increased robustness, accuracy and durability. It is envisaged that this scanning device would be inserted through the incision created during BCS, and deployed against the cavity walls to allow for smooth and seamless image acquisition over a large tissue surface area, thus allowing high quality image mosaics to be created (Fig. 1). We also show how, in principle, an inflatable balloon can be used to help smooth the tissue surface, making it sufficiently regular for microscopic scanning.

The main design features of the device include the mechatronic design of the device, a rigid concentric tube architecture allowing the driver source to be placed outside of the body to facilitate device miniaturisation, and a simple, ergonomic design for clinical deployment. In the rest of this paper, detailed design considerations and mechanical performance analysis of the scanning structure are provided. Results from *ex vivo* breast cancer tissue experiments are demonstrated, demonstrating the capabilities of the device for large area endomicroscopy imaging and mosaicing.

II. MATERIALS AND METHODS

A. Scanning Mechanism

The proposed scanning device has the ability to scan a number of trajectories by combining bending and rotating motion of the tip. The scanning structure is illustrated in Fig. 2, in which the spur gear and rotation gear are in contact to enable a bending motion. The inner tube and outer tube are coaxially-arranged and able to rotate independently. This structure provides -90 to +90 degrees bending on one axis, and 360 degrees of rotation on a second axis.

The scanning motion is driven by rotating the inner and outer tubes as detailed in Fig. 2. In the proposed mechanical design, the inner tube rotation angle α , the outer tube rotation angle β , and tip bending angle θ are related by (1):

$$\theta = \frac{R}{r}(\beta - \alpha) \quad (1)$$

where the lengths R and r are indicated in Fig. 2. Combination of the rotational and bending motions provides the hemi-spherical workspace shown in Fig. 3(a). A spiral trajectory can be achieved by rotating the inner and outer tubes simultaneously at different angular velocities. The radial position h in xy dimensions can be represented from the between the tip frame length H (Fig. 2) and tip bending angle θ (Fig. 2), such that:

$$h = H \sin\left(\frac{R}{r}(\beta - \alpha)\right) \quad (2)$$

In our design, R/r is 1, and the resulting relationship between θ , H , and h is shown in Fig. 3(b).

The rotation angle around the centre of the xy plane is given by β . Hence, a suitable variation of h and β leads to a spiral trajectory for the tip.

B. Scanning Prototype

The proposed scanning prototype is 6 mm in diameter, incorporating a central hollow channel 3 mm in diameter, as shown in Fig. 4 (a - b). In this configuration, the distal end has a 1-DOF bending and a 1-DOF rotating mechanism. The device has a length of 85 mm, while the bending tip has a length of 20 mm. The prototype is equipped with a 3 mm diameter central channel, through which the endomicroscope probe can be deployed. A set-up tube, which fits concentrically around the device tip, is used to adjust the starting point of the scanning, making sure it begins with a straight tip. A bearing structure is fixed to the tip frame with embedded steel balls which rotate during scanning. Combined with the inherent stiffness of the probe, this prevents the endomicroscope probe from rotating around its axis during scanning.

The scanning structure was fabricated from stainless steel, while the bearing cap and set up tube were rapid prototyped (VeroBlackPlus, Objet Geometries Ltd., Israel). To minimize friction during rotation, there is a 1 mm clearance between the inner and outer tubes. The ends of the tubes are held by coaxially-mounted rotation gears in the driver unit to maintain this clearance during rotation. Hence the friction between the tubes is very low, allowing smooth rotational motion transmission and spiral scanning. Backlash is reduced by a spring (Spring 2 in Fig. 4 enlarged view) in the driver unit, which engages the rotation gear shaft against the spur gear link.

In case of passing a commercial endomicroscopy probe (Cellvizio UHD Miniprobe) through the channel, the passive linear structure is located posterior to the driver unit (Fig. 4 enlarged view). It works well since the probe itself has an inherent stiffness. It consists of a slider, a spring (labelled Spring 1) and a slide guider. The endomicroscope probe is fixed onto the slider, and the spring structure ensures consistent contact between the tip of the device and the tissue. The inner diameter of the bespoke bearing structure fits to the outer diameter of the probe tip precisely. The probe can easily be separated from this structure for cleaning.

Fig. 2. The configuration of the scanning mechanism, transforming rotational motion of the inner and outer tubes to tip scan motion.

Fig. 3. (a) Scanning space of the scanner tip with bending and rotating motions. The scanning space is a large and hemispherical. (b) Relationship of tip bending angle θ , tip frame length H , and radial position h .

Fig. 4. A prototype of the scanning device, showing (a) the image of scanner, (b) distal end showing dimensions; (c) details of the driver unit with rotation gear, brushless DC-servomotors, gear head and Hall effect sensor.

Fig. 5. The prototype with balloon attachment, (a) Image of scanning tip, (b) Passive linear structure.

C. Balloon mechanism

To achieve the balloon scanning, a balloon inflation system was developed. The urethane balloon was a medical balloon with inflated diameter of 30 -50 mm and a wall thickness of 0.02 mm (Fig. 5(a)). The balloon was fixed on a guide tube, and the scanning device was inserted into the guide tube (8mm in outer diameter) during scanning. There is a 1 mm clearance between the guide tube and the scanning tip. A heat shrink tube was used to seal the cap between guide tube and scanning device. A highly flexible leached fibre bundle (Schott) was inserted into the channel and fixed on the linear structure at the distal end for allowing the full scanning range to be used (Fig. 5(b)). Because linear structure in Fig. 4 enlarged view is easily to be separated, we can change the position of linear structure depending on probe types. The scanning device is connected to a micro diaphragm air pump (8018Gt, Namiki Precision Jewel Co., Ltd, Japan). There is an inner spacer inserted to working channel to seal the inner space from air leakage. The inner pressure of the balloon was 170 kPa during the scanning.

D. Drive Unit

The size of the drive unit is 75×90×55 mm, and the total weight of the scanning device is 324 g, thus making it suitable for use as a handheld device. For cleaning and sterilization purposes, the rigid concentric tube structure part can easily be

separated from the driver unit. The inner and outer tubes are placed concentrically, and driven by two high-resolution brushless DC-servomotors equipped with gear heads and Hall effect sensors (1226 E 012 B K1855, Faulhaber SA, Germany) (Fig. 4 (c)). The rotational angles of the tube are detected by Hall effect sensors for the purposes of feedback control. A standard computer calculates rotational displacements of the inner and outer tubes from inputted target angles. The control diagram of inner tube rotation is shown in Fig. 6. In Fig. 6, α_i and $P(\alpha_i)$ are the input angle and function from input angle to target rotational displacement of the inner tube, X_i and X_f are the target rotational displacement of the inner tube and current rotational displacement of the inner tube, Δx and $S(\Delta x)$ are the differential rotational displacement of the inner tube and function from the differential rotational displacement to output voltage, and V and α_f are the output voltage and rotational angle of inner tube. The independent control process of the outer tube rotation is the same as for the inner tube rotation.

We recorded and displayed the actual signal output of the motors, including rotation speed, rotation angle, the effective scan speed, and the radial position. These data could be used to assist with the assembling of mosaics in future.

Fig. 6. Inner tube rotation control

E. Control Algorithms and Trajectory

We developed a custom user interface to control the prototype from a standard PC. Once the scan parameters are entered, the device can scan the target surface automatically.

A spiral trajectory is an effective means of covering a scan area [19] and so was adopted here. For spiral scanning, the parameters include the tangential velocity of the probe $V_{tangential}$, and the loop spacing in the radial direction, Δh . The parameters R and r are shown in Fig. 2. $V_{tangential}$ is given by (3).

$$V_{tangential} = \frac{H \sin(\theta_t) W_{m2t}}{\mu} \quad (3)$$

Where μ is the gear reduction ratio and W_{m2t} is the angular velocity of Motor 2. Here we have made the approximation that the tangential velocity is dominated by the rotational, rather than the bending, motion.

The spherical spiral with equal spacing between turns has two parameters: the radius of the sphere r_{sphere} and the number of turns N (Fig. 7 (a)). The equation of the spherical helix in spherical coordinates is given by [31].

$$r_{sphere} = H \quad (4)$$

$$\theta_t = \cos^{-1} \left(\frac{\beta_t}{\pi N} - 1 \right) \quad 0 \leq \beta_t \leq 2N\pi \quad (5)$$

We note that the length L_t of a spiral can be calculated by (6).

Fig. 7. (a) Co-ordinates for spherical spiral, (b) The mosaic envelope area that the device can scan over in a given time for values of the loop spacing Δh between 0.24 and 1 mm.

Fig. 8. Optical layout of laser scanning confocal endomicroscopy system. MO = microscope objective, APD = avalanche photodiode.

$$L_t = \int_0^{\delta_t} H \sqrt{1 + (N\pi)^2 \sin^4 \theta_t} d\theta_t \quad 0 \leq \delta_t \leq \frac{\pi}{2} \quad (6)$$

The spacing between loops, Δh , is given by (7). The loop spacing is a geodesic distance between the loops of the spiral trajectory on the sphere (Fig. 7(a)).

$$\Delta h = \frac{\pi H}{N} \quad (7)$$

The length of the spiral, L_t , achievable in a given time, t , is related to the imaging frame rate, F , and the required fractional overlap between successive image frames to allow image stitching, Δp , by (9):

$$L_t = \Delta p \cdot F \cdot t \quad (8)$$

Empirically, it was found that a shift of 40 μm between images, and hence an overlap of 200 μm for a 240 μm field-of-view, was necessary to ensure consistent mosaicing. Given the imaging frame rate of 10 fps, a maximum acceptable

tangential velocity of 0.4 mm/s was selected.

The mosaic envelope area, and to a good approximation the equivalent spiral, is given by (9). This approximate formula can be derived by considering integral to sum the circles' circumferences of the sphere.

$$\begin{aligned} S_t &= \int_0^{2\pi} \int_0^{\delta_t} H^2 \sin(\theta_t) d\beta_t d\theta_t \\ &= 2\pi H^2 \int_0^{\delta_t} \sin(\theta_t) d\theta_t \\ &= 2\pi H^2 (1 - \cos \delta_t) \quad 0 \leq \delta_t \leq \frac{\pi}{2} \quad (9) \end{aligned}$$

The relationship between mosaic envelope area, time and loop spacing are illustrated in Fig. 7 (b). Note that the field-of-view of the probe is 0.24 mm, so that if the spacing between spiral loops is set at 0.24 mm, then the loops of the spiral will just touch.

F. Visualisation and Mosaicing

The endomicroscopy system used to test the scanning device was an in-house laser scanning and detection system. For the imaging probe we used both a fibre bundle and lens assembly from a commercial endomicroscopy system (Cellvizio UHD Miniprobe, Mauna Kea Technologies, France) and a 17000 core, 8 μm core-spacing bare leached fibre bundle (Schott) with a 1 mm diameter. The imaging system is shown in Fig. 8. This custom acquisition system allows a combination of imaging, mosaicing and scanner control for real-time use. The system was illuminated by a 488 nm, 50 mW laser (Vortran Stradus), which was reflected off a dichroic mirror (Thorlabs MD498) into a laser scanning system. The laser scanning system comprised a galvo scanning mirror (Thorlabs GVS011) and a resonant scanning mirror (Cambridge Technologies CRS), which provided the slow and fast axis laser scanning respectively. Both mirrors were imaged onto the rear focal plane of a 20X microscope objective by a pair of telescopes. The proximal end of the fibre bundle was placed at the focus of the microscope objective, resulting in a 2D laser raster scanning pattern across the bundle. This was transferred to the tissue by the bundle and a distal micro-objective. The time-average power to the tissue was approximately 5 mW.

Fluorescence signal returning from the tissue travelled back along the fibre bundle and was de-scanned. It was then

Fig. 9. Results of 2-DOFs scanning characteristic test, showing relationship between target angles and actual bending and rotating angles. (a) 1-DOF bending mechanism with, (b) set up of the bending experiment, (c) 1-DOF rotating mechanism, (d) set up of the rotating experiment.

transmitted by the dichroic mirror and a 500 nm long pass filter (Thorlabs FEL0500) and focused through a 15 micron pinhole by a 20X microscope objective. A second 20X objective focused light that had passed through the pinhole onto an avalanche photodiode. Signal from the photodiode was digitised by a high speed, 12 bit analogue to digital converter (ADC) board (National Instruments National Instruments PCI-5105).

Drive signals for the scanning mirrors were generated by an input/output board (National Instruments PCI-6366). For the galvo scanner, which generated the slow axis of the raster scan, the drive signal was a voltage ramp. The resonant scanner, which generated the fast axis, was free-running at a frequency of 8 kHz, and it was only necessary to control the scan amplitude via a voltage signal. The ADC formed 2D images frames using synchronisation pulses from the resonant scanner for the start of each line, and from its internal clock for the start of each frame. The start of the ramp of the galvo scan was synchronised with the start of each frame acquisition via a digital trigger from the ADC. The system was controlled by a Labview program, which also reconstructed images based on the data acquired from the ADC board. Raw images had a Gaussian filter applied to remove the fibre core pattern, and a background subtracted to remove fluorescence signal from the fibre bundle. Processed and auto-contrasted images were displayed live to the user at 10 frames per second, and both processed and raw images were saved to disk after being converted to 8 bits per pixel. To validate the scanning approach and demonstrate the potential to reconstruct large area scans, an offline, cross-correlation based mosaicing algorithm in Matlab was used. From each 670 pixel diameter image we extracted a rectangular sub-image, 250 pixels wide. The normalised two dimensional cross correlation was then computed between this template and the previous image. The position of the peak of the cross correlation was taken to be the shift between the two images. To create the mosaic, each image was inserted into the mosaic with the correct shift relative to the previous image, over-writing any existing pixel values.

III. RESULTS

A. Mechanical Performance Evaluation

For performance evaluation, we examined bending and rotating characteristics of the 2-DOF scanning mechanism, and generated power at the tip of scanning distal end. These measurements were made initially with no imaging probe inserted.

Repeatability measurements were performed unloaded over five trials, measuring actual bending and rotating angles against the target angles. For assessment of the bending performance, measurements were made in four parts: (a) bending from 0 degrees to +90 degrees, (b) returning to 0 degrees, (c) bending from 0 to -90 degrees, and (d) returning again to 0 degrees. The bending angles were measured by a digital camera that had a resolution of 4272 x 2848 pixels, which was equivalent to a resolution of 0.05 mm at the imaging plane. The camera was set up to image the tip as shown in Fig. 9 (b). The accuracy of the

camera image was checked by capturing a regular grid image (pitch 0.05 mm) before the experiments. The maximum errors on x axis and y axis were smaller than one pixel (0.05 mm), thus, the accuracy was sufficient to evaluate the bending angle of the scanning tip.

The measured hysteresis curve with the maximum differences between the experimental and theoretical values is shown in Fig. 9(a), and the measured values of bending range, bending repeatability error (standard deviation), tip positioning accuracy (calculated by the tip length and repeatability error), and hysteresis error are presented in Table I. We also tested in detail the rotating performance. The scanning device was first rotated from 0 to 360 degrees (e), and then returned to 0 degrees (f) (Fig. 9(c) and Table II). The measurement setup is shown in Fig. 9 (d).

TABLE I
RESULTS OF REPEATABILITY MEASUREMENT IN EACH BENDING MECHANISM

Measurement item	(a)	(b)	(c)	(d)
Bending range (°)	0 to 90.05	90.05 to -0.41	-0.41 to -90.97	-90.97 to -0.61
Repeatability (°)	0.72	0.68	0.73	0.80
Tip positioning accuracy (mm)	0.25	0.23	0.25	0.28
Hysteresis error(°)	1.58±0.44			

TABLE II
RESULTS OF REPEATABILITY MEASUREMENT IN ROTATING MECHANISM

Measurement item	(e)	(f)
One circle rotational range (°)	0 to 359.67	359.67 to -0.65
Repeatability (°)	0.4	0.42
Tip positioning accuracy (mm)	0.13	0.14
Hysteresis error(°)	0.51±0.04	

TABLE III
GENERATED POWER AND TORQUE AT TIP

DOF	Direction (°)	Power [N]	Torque [Nmm]
Bending	-90 to 90	0.9	19.8
Rotating (Bending 45°)	-360 to 360	2.1	46.2

Tip positioning accuracy was used to evaluate the dispersion of the tip position in a one-way trip (a-f in Fig. 9). In addition, hysteresis error was used to evaluate the repeatability between bending back and forth (from a to b, from c to d, and from e to f in Fig. 9).

Finally, we examined the generated powers and torques using a digital force gauge. These results are shown in Table III.

B. Trajectory performance evaluation

The workspace and trajectory of the tip were evaluated by an NDI Aurora Electromagnetic Tracking System (NDI Corp, CA). A mini electromagnetic sensor with 6 DOFs (2.5 mm diameter × 2 m in length, the sensor itself is 11 mm in length) was inserted into the channel of the scanning device to measure the tip position. We performed the spiral scans four times. We chose one set of data randomly to evaluate the workspace and trajectory. A Kalman filter was used to smooth EM data and

Fig. 10. Trajectory of a sample scan measured. (a) Working space of the tip, (b) 3D trajectory of spiral scan, (c) x position, (d) y position, (e) z position, (f) the radial position of the spiral, (g) the linear velocity of the tip of the device, (h) Comparison of the spiral trajectory generated by motor output and the theoretical spiral.

hence reduce noise. Here, we used a constant velocity model as the state-equation. The state vector includes the location and velocity. The workspace and trajectory of a full spiral scan are shown in Figs. 10 (a)-(b).

Figs. 10(c)-(f) show the target and actual x, y, z and radial positions, while the spiral trajectory is shown in Fig. 10(h), both for the target value and the value calculated from the read-out

of the motor positions. In Fig 10(g), the tangential velocity of the scanner tip is plotted. This demonstrates that the tip velocity can be controlled to maintain a constant speed, set at 0.4 mm/s for these experiments. The confocal probe (Cellvizio UHD Miniprobe) was inserted into the working channel of the scanning device during this evaluation. The EM probe was concentrically fixed by a tube connector at the scanning tip with

the cable running the opposite direction to the confocal probe (i.e. it did not run through the device's probe channel). In Figs. 10 (c) and (d), the amplitude (the radial position in Fig. 10(f)) of the cosine and sine functions were increased, leading to a corresponding increase in the tip velocity noise. This is reflected in the noise value changing on the vertical scale with time. For this dataset, the spacing between each loop of the spiral was set to be 1 mm.

C. Breast phantom experiments

We confirmed the ability of the system to obtain consistent images with an inflated balloon using a silicon breast phantom (Fig. 11(a-b)). The breast phantom was designed for use in training of surgeons to conduct wide local excision of breast tumours, and had previously been used for this purpose, leaving a realistically sized cavity. The cavity was lined with tissue paper stained with acriflavine to allow imaging and mosaicking, since the phantom did not have sufficient features at a microscope scale. For this experiment we used a leached imaging bundle. This bundle is highly flexible, allowing the full scanning range to be used, but has a low intrinsic resolution due to its large fibre-core spacing of 8 μm , and the lack of distal

objective. The working distance is also sub-optimal, with the optimal image plane lying exactly on the surface of the bundle, and so some of the available depth of field was taken up by the balloon wall thickness. We performed long linear scans across the hemisphere (bending range: -70° to $+70^\circ$). The results show that the probe could maintain almost constant tissue contact when scanning over large distances of up to 48 mm. (Fig. 11 (c-d)). Because the balloon is not a perfect spherical shape, there is a risk of loss of contact in some places (Fig. 11(e)). Fig. 11(f), shows a circular scan, demonstrating that in practice it is possible to maintain good contact for a 360° scan. We used a mosaicing algorithm that checks for rotations as well as translation [21].

D. Ex vivo breast cancer tissue experiments

We evaluated the ability of the scanning system to obtain consistent ex vivo images on freshly excised, acriflavine-stained human breast cancer tissues. For this study, the Cellvizio UHD microprobe was used so as to provide sufficient resolution and an optimised working distance, but with the disadvantage that the imaging range is limited due to its stiffness. All subjects gave prior written informed consent and Human Tissue Authority licence and ethics approval was obtained from Imperial College Tissue Bank (R12047 and R12047a). For these experiments the balloon was not necessary to flatten the tissue. However, to simulate its presence, a transparent disposable drape (Clinicon[®], Bristol, UK) was fixed onto a support window, as shown in Fig. 12(a). The scanning device and support window were held by passive arms.

Firstly, we scanned a sample of normal breast fatty tissue. For this test, linear scans were performed by controlling only the bending motor. Fig. 12(b) shows a mosaic of a linear scan which is approximately 5 mm in length. A large number of polygonal-shaped, dark-coloured cells with thin hyperfluorescent borders depict the typical appearances of fat cells in Fig. 12(b). Then, we scanned the breast cancer tissues. A mosaic of a linear scan is given in Fig. 12(c). In Fig. 12(c), disorganized architecture with hypercellularity and haphazard arrangement of cells can be observed. Fig. 12(d) shows a mosaic created from a spiral scan which is approximately 2.2 mm in diameter. The spacing between spiral loops is set at 0.24 mm which makes the loops of the spiral just touch. There are small gaps between the loops of the spiral. One reason for this was that the probe was not positioned vertically when scanning started. As the tip of the device is pressed onto the target tissue, there is a residual bending due to a small backlash of the gear. The other cause of the gaps is likely to be the combination of mosaicing errors, positioning errors and deformation of the scanned surface. Nevertheless, the creation of the large image mosaics enables global appreciation of the tissue characteristics. In Fig. 12(d), two large areas of hypercellular foci (clusters of hyperfluorescent dots) can be seen in the centre and left of the mosaic. In addition, the background architecture on the upper left and right quadrant appeared to be haphazard with cells seen to be loosely dispersed throughout the breast connective tissue.

Fig. 12(e) shows a second scan, with the spacing between loops of the spiral set to 1 mm. Note that the diameter of the

Fig. 11. Breast phantom experiment. (a) Scanning tip with balloon and probe, (b) Set up, (c-d) Linear mosaics: (c) and (d) were vertically-placed, and covered a length of 48mm, (e) Position of circle scan tests, (f) Circle scans at corner of the flat and curve surface, (g) Co-ordinates for scanning tip

Fig. 12. Human breast tissue mosaic images, (a) Setup, (b) Linear mosaic of human breast fat, (c) Linear mosaic of human breast cancer, (d) Human breast cancer: spiral mosaic result which makes the loops of the spiral just touch, (e) Human breast cancer: large area spiral without overlap.

spiral is approximately 5.2 mm. We observed that the gaps between the spirals get slightly larger in the outer branches during a large spiral scan. The main cause is likely to be the positioning errors of the tip. On the magnified insets of Fig 12(e), morphological constituents of the human breast such as fibrous tissues and adipocytes are readily visualized. The former is represented by fine, grey and linear strands of collagen fibers on a relatively acellular background, whereas the latter is depicted as dark-colored, polygonal-shaped cells with thin well-defined bright borders. Clusters of hyperfluorescent dots can be seen in between adipocytes and fibrous tissues.

The performance of the probe bearing was analysed by calculating the average rotation between consecutive frames of 500 images during a spiral scan acquisition. The rotation was estimated by taking the radon transform of each pair of images to obtain a sinogram, followed by finding the peak of the normalised cross-correlation between the two sinograms. The average rotation was (0.1 ± 0.1) degrees, confirming that there was no net rotation above random jitter.

IV. DISCUSSION

In this paper, a large area scanning device has been developed for breast endomicroscopy. The mechanical design and motor control allow the tip of the device to scan a spiral trajectory and maintain a constant tip velocity. The bending range (-90.97 degrees to 90.05 degrees) was slightly over ± 90 degrees. The cause of this was the overrun of the inner tube. However, this difference was small, and a larger maximum bending range has adverse effect on the performance of the device. The range for a single rotation varies from -0.65 degrees to 359.67 degrees. For a spiral scan, the device rotates continuously, so the scanning performance is determined by the bending and rotating accuracy rather than the range values. Overall, the scanning device achieved high scanning repeatability with 0.73 degrees for the bending motion and 0.41 degrees for the rotational motion on average, and high accuracy with 0.25 mm for bending motion and 0.13 mm for rotational motion at the tip, respectively. The field-of-view of commercial fibre bundle probes is between 0.24 mm and 1 mm in diameter.

The positioning accuracy should be acceptable for scanning with fibre bundles for which the field-of-view is over 0.5 mm in diameter. For miniprobe with a field-of-view of less than 0.5 mm, there is a possibility for small gaps to occur between the loops of the spiral due to positioning inaccuracies. Nevertheless, this still allows visualisation of a large area and should be satisfactory for diagnosis purpose.

The rotation gear was specially designed and fabricated by Micro-EDM, while the spur gear part was manufactured by wire-cut EDM. These processing methods achieve high precision for the gears, thus allowing smaller bending hysteresis error and higher repeatability. The extension and deformation of the engagement parts were minimized by increasing the thickness of the rotation gear. The backlash was minimized to an acceptable level by pushing the rotation gear against the spur gear during scanning. Furthermore, backlash often occurs when changing the rotational direction of the gears. Although the hysteresis of the scanning device is fairly large, it can only affect the trajectories, which move back and forth in bending motion. There is only one way bending (process (a) or (c) in Section III-A) during spiral scanning, which results in backlash.

The starting position of the scan was not always exactly at the desired centre of the spiral due to a small initial bending of the tip. Prior to each scan, we adjusted the motors to ensure a straight condition using a set up tube, and then initialized the motors. However, as there was a small gap between the set-up tube and scanning tip there was sometime still a small initial bend. Additionally, if the scanning tip touched the target tissue with a large force, the tip could bend slightly from the centre by the reactive force. Both of these effects could have led to a 'hole' in the centre of the mosaic. The mosaics suggest that the initial tip positioning error is larger than the 0.25 mm repeatability we measured in general (although this may partly be explained due to deformation of the tissue rather than inaccuracies in the scanning.) One solution to this problem may be to adopt a more precise set up tube and to avoid an unnecessarily large contact force between the tip and the tissue at the beginning of the scan. The endomicroscopy probe can obtain stable images when the probe tip contact force is between 0.1 N and 0.5 N [32, 33]. The bending and rotating forces, which were 0.9 N and 2.1 N respectively, were sufficient in order to carry out a spiral scan.

Most breast cancers are detected early due to screening mammography and hence the average size of the tumour is generally small (between 1-2 cm). Provided there is no distant spread, breast-conserving surgery is generally performed to remove the tumour in its entirety with a surrounding cuff of normal tissue. The actual size of the specimen removed is variable and this could range between 4 cm and 8 cm in larger sized breasts. These correspond to a similar sized breast cavity and we therefore chose a 4 cm diameter cavity as an arbitrary starting point to test the feasibility of using the device. A smaller sized cavity provides a more realistic test of the robustness and accuracy of the device. Further increments to the radius could be tailored according to clinical needs and this can be modified accordingly for our prototype device.

In this study, we have presented detailed results of workspace and trajectory evaluation using an NDI Aurora EM tracking system, with a 6 DOF probe. The results indicate that the distal end can cover a smooth large spiral trajectory in 3D space. It is worth noting that the Aurora sensor itself has certain stiffness.

To generate high quality images from tissue we used a Cellvizio UHD Miniprobe which has a minimum bending radius of the order of 70 mm. With this probe, the bearing structure prevents rotation, making the mosaicing process simpler and more accurate. This allowed us to obtain high quality mosaics using a simple and fast normalized cross-correlation algorithm, as we did not need to consider rotations.

To avoid damaging the Cellvizio UHD Miniprobe, we didn't attempt a full hemispherical scan test with this probe. However, a full sized scan was demonstrated using a leached imaging bundle inside a breast phantom, and using an inflatable balloon to provide a smooth surface to scan over. Further work will be needed to enhance the resolution of this type of probe by incorporating a distal objective. A side-effect of using this type of bundle is that it is much less stiff, so the bearing structure is no longer effective in preventing the fibre from rotating during rotational scanning. The mosaicing algorithm will therefore need to check for rotations, as well as translations, between images.

Nevertheless, these experiments showed shown that the probe could maintain tissue contact when moving over a large bending range of -70° to $+70^\circ$, covering a total length of 48 mm. The working distance of the passive linear structure was 3 mm which means that the scanning tip hemispherical diameter could be varied by approximately 6 mm. Therefore a range of differently sized balloons could be used to suit the size of the cavity. To deal with larger variation, several removable scanning tips with different lengths could be customized. The rupture of the balloon should be possible problem during scanning. However, because the air pressure is 170kPa which is a low pressure, the tissues around the scanning device will not be damaged even in the event of air leakage. Actually the air leakage problem has not occurred in breast phantom experiment.

In all the experiments conducted it was possible to control the trajectory and the velocity of the distal end accurately. A hemispherical scanning area with a radius of 20 mm is considerably larger than for previously reported endomicroscopy scanning devices. It took almost 20 seconds to reach the targeted tangential velocity of 0.4 mm/s; this time can be minimized by controlling the angular velocity of Motor2 in the beginning. As shown by the ex vivo breast cancer tissue experiments, endomicroscopy image acquisition was feasible at this speed. After the first 20 seconds, the actual motor output matches the theoretical value. The spiral trajectory generated from the motor output follows the ideal spiral path very well, meaning the time delay of 20 seconds has little influence on the spiral trajectory. At present, the waiting time for existing methods of assessing tumor margins such as frozen section can be as long as 40 minutes. Intraoperative specimen x-ray may

take as little as 5-10 minutes but it has a low accuracy. The ability to obtain information on cavity margins within a minute of commencement of imaging is certainly well within the acceptable limits of the operation time and highly justified if it is proven to be an accurate method of ruling out the presence of residual tumor deposits in the cavity.

In the *ex vivo* human tissue evaluation, the device was shown to be able to scan the tissue stably. It is evident that the construction of panoramic scenes through the creation of large area tissue mosaics has enabled more morphological features to be visualised in a single field-of-view whilst providing the microscopic means of visualising carcinomatous foci. In practice, it is often difficult to obtain high quality interpretable images consistently due to the presence of tissue deformation and surgeon's hand tremor even on a uniformly flat tissue surface. The ergonomic challenges vastly restrict its true clinical potential which we believe includes provision of real-time *in situ* oncological information of global cavity margins intraoperatively. The scanning device has shown strong potential for solving these ergonomic challenges in BCS.

Deformation of the tissue plays an important role in endomicroscopy, and is a significant limiting factor in the generation of large mosaics. To an extent this problem is unavoidable, as any contact based imaging method will result in tissue deformation if the probe is driven across the tissue. Previously, Rosa et al. [20] have used a cooperative robotic arm to generate a mosaic with consideration of tissue deformation, suggesting there may be some scope to pre-emptively adjust the trajectory of the scan to account for deformation. This remains a topic for further research. Correction of distortions due to tissue deformation may also be achieved using a more sophisticated mosaicing algorithm which does not assume rigid transformations [34]. These algorithms are unlikely to be suitable for real time image reconstruction [35] but could be used for retrospective analysis. However, development of such algorithms is not the focus of this paper. In this study, we attempted to minimise tissue deformation by imaging the tissue through a thin plastic membrane held in place by the supporting arm. Imaging through the membrane was possible because the probe has a finite working distance, and, indeed, image quality through the membrane was comparable to image quality without membrane. This membrane appeared to help stabilize the tissue to some extent, limiting deformation. Selection of an optimum material and thickness, and a comparison of the mosaicing performance compared to direct probe-on-tissue scanning, will require further studies.

We also showed how, in principle, this membrane could be replaced by an inflatable balloon for *in vivo* studies. In future, this could include an automated balloon shaping mechanism using pressure control to allow a precise fit to the size of the cavity. Since a pressurised balloon would tend to smooth out the walls of the cavity, the scanning device would be better able to make stable tissue contact even with very irregular cavities. In the case of using the device as handheld instrument, maintaining a proper optical contact during the scanning becomes more challenging. In this case, a tightly fitting balloon might tend to reduce motion artefacts during the scan, including

those due to breathing or other patient motion, as the device would simply move with the patient.

Because it has a small number of parts, the proposed scanning device would be easy to manufacture, assemble and maintain. The special design of the spur and rotation gears allows the scanning device to achieve a large inner diameter (i.e. working channel) with a small outer diameter. Our design is different from the other rotational joints mechanism using bevel gears such as [29, 30]. In particular, because of size and shape restrictions of bevel gears, the mechanisms in [29, 30] make it difficult to achieve a small outer diameter with a large channel.

Studies in [18] aimed to generate a mosaic under 3 mm^2 in areas without any gaps. Our scanning device is able to scan both overlapping trajectories in a focused area (under 3mm^2) and non-overlap trajectories in a large hemispherical area (under 20 mm in radius). Depending on the clinical need, it may be preferable to create a small mosaic focusing on user-specified points of interest guided by the surgeon's clinical judgement or intraoperative specimen radiography. On the other hand, if we want to rule out the presence of cancer cells on several cavity walls a large mosaic will be more useful.

It is worth noting that the overall time to acquire a mosaic is limited by the frame-rate of the imaging system. If the scanner is to find a place in the clinical workflow then it is essential that the time taken to achieve a scan is minimised. Hence, when large area coverage is required, a sparse mosaic (i.e. one with gaps between the arms of the spiral) may be preferable. We have demonstrated that both large, sparse mosaics and small, continuous mosaics can be accommodated by our proposed mechanical design and control system.

It should be noted that the scanning device itself does not provide global positional information. However, by using optical tracking systems or intraoperative imaging (such as ultrasound) it could be possible to measure the position of the device. Combined with information from the motors, this would then allow calculation of the tip position in 3D space, and hence would provide the position of a mosaic. The aim for future trials is a 3D reconstruction technology that gives both imaging and positional information to the surgeon.

The process of scanning a large surface area will generate long and continuous mosaics. Whilst it increases the amount of information visualised for image interpretation, it requires an automated mechanism that allows abnormal images detected at multiple locations to be spatially located accurately without interrupting the scanning process – a task that induces fatigue and is almost impossible to achieve manually with precision. Given that the cavity surface is often uneven, multiple adjustments to the direction and contact forces between probe tip and tissue surface is also required to achieve uninterrupted and continuous scanning. Our scanning device is an economical, robust and intelligent platform to generate accurate spatio-temporal localisation in real-time to aid intraoperative decision making. The suitable combination of inner and outer tubes with gear bending mechanism realized accurate scanning (especially spiral scanning motion) and a larger scanning range. With regards to the practical application of the scanning device,

the simple mechanical design will make commercial manufacturing straightforward.

V. CONCLUSIONS

In conclusion, we have demonstrated a practical scanning device that can cover a large field-of-view in confocal endomicroscopy, specifically for use during breast endomicroscopy. This device can scan over a large spherical surface by bending and rotating the tip with highly repeatable positioning accuracy. We have shown the creation of a mosaic over a substantial portion of the scanning workspace, demonstrating the potential to provide a large field-of-view for 'optical biopsy'. In ex vivo human cancer tissue evaluation, the scanning device enables speedy and efficient large area imaging. We further showed how the device can be used with an inflatable balloon to allow scanning over very large arcs. These results demonstrate the potential clinical value of the device to improve the prospects for intraoperative cavity margin evaluation.

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