Toward Intraoperative Breast Endomicroscopy
With a Novel Surface-Scanning Device

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Abstract—New optical biopsy methods such as confocal endomicroscopy represent a promising tool for breast conserving surgery, allowing real-time assessment of tumor margins. However, it remains difficult to scan over a large surface area because of the small field-of-view. This paper presents a novel robotic instrument to perform automated scanning with a fiber bundle endomicroscope probe to expand the effective imaging area. The device uses a rigid concentric tube scanning mechanism to facilitate large-area mosaicking. 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 fiber 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. Experimental results show that the device is able to scan a spiral trajectory over a large hemispherical surface. Detailed performance evaluation was performed and the bending angle ranges from –90° to 90° with high repeatability and minimal rotational hysteresis errors. 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 (BCS), confocal endomicroscopy, image mosaicking, 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 tumor with a surrounding margin of healthy breast tissue (approximately 2–5 mm) while leaving the remainder of the breast intact [2]. It is well recognized that the margin status of the excised tissue is the strongest predictor for tumor recurrence following BCS [3]. If tumor cells are found on the edges of excised tissues (positive margins), these patients will require a reoperation [3]. National data from England and Wales highlight that a significant proportion of patients with invasive (18%) and noninvasive 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 tumor cells in the reexcision specimens which suggests that a significant proportion of these patients might have been overtreated [5]. Currently, the adequacy of BCS relies on the predictive value of the 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, and 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]. Utilizing 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 fiber 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 nonneoplastic breast tissues were readily visualized using confocal endomicroscopy [12]. This ex vivo study on acriflavine-stained human breast tissues demonstrated that the presence of hypercellularity and haphazard arrangement of morphological architecture correlated well with common pathognomonic features of breast cancer seen on conventional histology.

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Additionally, surgeons were shown to be able to differentiate neoplastic from nonneoplastic 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 adjacentily 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 anesthetic complications to the patient and reduces operating theatre productivity.

These inherent limitations are well-recognized 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 intraoperative integration of laparoscopic instruments [16]. Rosa et al. developed a scanning device using hydraulic microballoons [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 three-dimensional (3-D) 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 mosaicked. Although large-area mosaics were achieved by [19] and [20], this study 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 two-dimensional (2-D) motion of the scanner required rotation of the distal tip in the previous prototype [21], which resulted in an accumulation of errors during mosaicking. 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 merits 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] and [30]. The gear-driven mechanism makes it easy to achieve multi-DOFs together with miniaturization. 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.

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 (see 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 mechanical design of the device, a rigid concentric tube architecture allowing the driver source to be placed outside of the body to facilitate device miniaturization, 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 mosaicking.

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 are able to rotate independently. This structure provides $-90^\circ$ to $+90^\circ$ bending on one axis, and $360^\circ$ 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 $\alpha$, the outer tube rotation angle $\beta$, and the tip bending angle $\theta$ are related by the following equation:

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

where the lengths $R$ and $r$ are indicated in Fig. 2. Combination of the rotational and bending motions provides the hemispherical 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 between the tip frame length $H$ (Fig. 2) and tip bending angle $\theta$ (see Fig. 2), such that

$$h = H \sin \left( \frac{R}{r} (\beta - \alpha) \right).$$  \hspace{1cm} (2)

In our design, $R/r$ is 1, and the resulting relationship between $\theta$, $H$, and $h$ is shown in Fig. 3(b). The rotation angle around the center of the $xy$ plane is given by $\beta$. Hence, a suitable variation of $h$ and $\beta$ 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) and (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 setup 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 the 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 (see 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 (see Fig. 4 enlarged view). It works well since the probe itself has an inherent stiffness. It consists of a slider, a spring (labeled 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.

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 [see Fig. 5(a)]. The balloon was fixed on a guide tube, and the scanning device was inserted into the guide tube (8 mm 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 the guide tube and the scanning device. A highly flexible leached fiber 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 [see Fig. 5(b)]. Because the linear structure in Fig. 4 enlarged view is easy to be separated, we can change the position of the linear structure depending on probe types. The scanning device is connected to a microdiaphragm air pump (8018 Gt, Namiki Precision Jewel Co., Ltd., Japan). There is an inner spacer inserted into the 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 mm × 90 mm × 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) [see 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, $\alpha_1$ and $\mu$ are the input angle and function from input angle to the target rotational displacement of the inner tube, $X_1$ and $X_2$ are the target rotational displacement of the inner tube and current rotational displacement of the inner tube, $\Delta x$ 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 $\alpha_f$ are the output voltage and rotational angle of inner tube, respectively. 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 the rotation speed, the rotation angle, the effective scan speed, and the radial position. These data could be used to assist with the assembling of mosaics in future.

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 $V_{\text{tangential}}$, and the loop spacing in the radial direction, $\Delta h$. The parameters $R$ and $r$ are shown in Fig. 2. $V_{\text{tangential}}$ is given by

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

(3)
where \( \mu \) 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 \( r_{\text{sphere}} \) and the number of turns \( N \) [see Fig. 7(a)]. The equation of the spherical helix in spherical coordinates is given by [31]

\[
\begin{align*}
    r_{\text{sphere}} &= H \\
    \theta_i &= \cos^{-1}\left(\frac{\beta_i}{\pi N} - 1\right) \quad 0 \leq \beta_i \leq 2N\pi.
\end{align*}
\]

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

\[
L_t = \int_0^{\delta_t} H \sqrt{1 + (N\pi)^2 \sin^4 \theta_i} d\theta_i \\
0 \leq \delta_t \leq \frac{\pi}{2}.
\]

The spacing between loops \( \Delta h \) is given by (7). The loop spacing is a geodesic distance between the loops of the spiral trajectory on the sphere [see Fig. 7(a)]

\[
\Delta h = \frac{\pi H}{N}. \tag{7}
\]

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 \( \Delta p \) by (8)

\[
L_t = \Delta p \cdot F \cdot t. \tag{8}
\]

Empirically, it was found that a shift of 40 \( \mu m \) between images, and hence, an overlap of 200 \( \mu m \) for a 240-\( \mu m \) field-of-view, was necessary to ensure consistent mosaicking. Given the imaging frame rate of 10 frames/s, 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

\[
\begin{align*}
S_i &= \int_0^{2\pi} \int_0^{\delta_i} H^2 \sin(\theta_i) \, d\beta_i \, d\theta_i = 2\pi H^2 \int_0^{\delta_i} \sin(\theta_i) \, d\theta_i \\
&= 2\pi H^2 (1 - \cos \delta_i) \quad 0 \leq \delta_i \leq \frac{\pi}{2}.
\end{align*}
\]

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.

\[\text{Fig. 7. (a) Co-ordinates for spherical spiral and (b) mosaic envelope area that the device can scan over in a given time for values of the loop spacing } \Delta h \text{ between 0.24 and 1 mm.}\]

\[\text{Fig. 8. Optical layout of the laser scanning confocal endomicroscopy system. MO = microscope objective. APD = avalanche photodiode.}\]
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 2-D images frames using synchronization 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 synchronized 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 fiber core pattern and a background subtracted to remove the fluorescence signal from the fiber bundle. Processed and auto-contrasted images were displayed live to the user at 10 frames/s, 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 mosaicking algorithm in MATLAB was used. From each 670-pixel diameter image, we extracted a rectangular subimage, 250 pixels wide. The normalized 2-D 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, overwriting 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 the 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 the assessment of the bending performance, measurements were made in four parts: (a) bending from 0° to +90°, (b) returning to 0°, (c) bending from 0° to −90°, and (d) returning again to 0°. The bending angles were measured by a digital camera that had a resolution of 4272 × 2848 pixels, which was equivalent to a resolution of 0.05 mm at the imaging plane. The camera was setup 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 (e) from 0 to 360°, and then (f) returned to 0° [see Fig. 9(c) and Table II]. The measurement setup is shown in Fig. 9(d).
Tip positioning accuracy was used to evaluate the dispersion of the tip position in a one-way trip (see, a–f in Fig. 9). In addition, the 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.

### TABLE III

<table>
<thead>
<tr>
<th>DOF</th>
<th>Direction (°)</th>
<th>Power [N]</th>
<th>Torque [N-mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bending</td>
<td>−90 to 90</td>
<td>0.9</td>
<td>19.8</td>
</tr>
<tr>
<td>Rotating (Bending 45°)</td>
<td>−360 to 360</td>
<td>2.1</td>
<td>46.2</td>
</tr>
</tbody>
</table>

B. Trajectory Performance Evaluation

The workspace and trajectory of the tip were evaluated by an NDI Aurora electromagnetic tracking system (NDI Corp., USA). 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 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 Fig. 10(a) and (b).

In Fig. 10(c)–(f) shows 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 in the opposite direction to the confocal probe (i.e., it did not run through the device’s probe channel). In Fig. 10(c) and (d), the amplitude [see 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 [see Fig. 11(a) and (b)]. The breast phantom was designed for use in training of surgeons to conduct wide local excision of breast tumors, 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 fiber-core spacing of 8 μm, and the lack of distal objective. The working distance is also suboptimal, 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°). The results show that the probe could maintain almost constant tissue contact when scanning over large distances of up to 48 mm. [see Fig. 11(c) and (d)]. Because the balloon is not a perfect spherical shape, there is a risk of loss of contact in some places [see 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 mosaicking 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 optimized 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 license and ethics approval was obtained from Imperial College Tissue Bank (R12047 and R12047 a). For these experiments, the balloon was not necessary to flatten the tissue. However, to simulate its presence, a transparent disposable drape (Clinicon, Bristol, U.K.) was fixed onto a support window, as shown in Fig. 12(a). The scanning device and support window were held by passive arms.

First, 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-colored 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 mosaicking 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. 10(d), two large areas of hypercellular foci (clusters of hyperfluorescent dots) can be seen.
in the center 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 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 between adipocytes and fibrous tissues.

The performance of the probe bearing was analyzed 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 normalized cross-correlation between the two sinograms. The average rotation was $(0.1 \pm 0.1)^\circ$, 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 ($-90.97^\circ$ to $90.05^\circ$) was slightly over $\pm 90^\circ$. The cause of this was the overrun of the inner tube. However, the 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 $-0.65^\circ$ to $359.67^\circ$. 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 $0.73^\circ$ for the bending motion and $0.41^\circ$ 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 fiber bundle probes is between 0.24 and 1 mm in diameter. The positioning accuracy should be acceptable for scanning with fiber bundles for which the field-of-view is over 0.5 mm in diameter.
For miniprobes 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 visualization 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 wirecut 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 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 [see 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 center 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 setup tube, and then initialized the motors. However, as there was a small gap between the setup tube and scanning tip, there was sometimes 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 center by the reactive force. Both of these effects could have led to a “hole” in the center 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 setup tube and to avoid 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 and 0.5 N [32], [33]. The bending and rotating forces, which were 0.9 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 tumor is generally small (between 1–2 cm). Provided there is no distant spread, the bearing structure is much less stiff, so the bearing structure will not be damaged even in the event of air leakage. Actually, the air leakage problem has not occurred in 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 s to reach the targeted tangential velocity of 0.4 mm/s; this time can be minimized by controlling the angular velocity of Motor 2 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 s, 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 s 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 min. Intraoperative specimen X-ray may take as little as 5–10 min 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 visualized in a single field-of-view while providing the microscopic means of visualizing 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 preemptively 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 mosaicking 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 minimize 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 mosaicking 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 pressurized 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 a 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 artifacts 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] and [30]. In particular, because of the size and shape restrictions of bevel gears, the mechanisms in [29] and [30] make it difficult to achieve a small outer diameter with a large channel.

Studies in [18] aimed to generate a mosaic under 3 mm² in area without any gaps. Our scanning device is able to scan both overlapping trajectories in a focused area (under 3 mm²) and nonoverlap 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 judgment 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 minimized. 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 the 3-D space, and hence provide the position of a mosaic. The aim for future trials is a 3-D 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. While it increases the amount of information visualized 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 the probe tip and the tissue surface are also required to achieve uninterrupted and continuous scanning. Our scanning device is an economical, robust, and intelligent platform to generate accurate spatio–temporal localization 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 regard to the practical application of the scanning device, the simple mechanical design will make commercial manufacturing straightforward.

V. CONCLUSION

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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Authors’ photographs and biographies not available at the time of publication.
Toward Intraoperative Breast Endomicroscopy With a Novel Surface-Scanning Device

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Abstract—New optical biopsy methods such as confocal endomicroscopy represent a promising tool for breast conserving surgery, allowing real-time assessment of tumor margins. However, it remains difficult to scan over a large surface area because of the small field-of-view. This paper presents a novel robotic instrument to perform automated scanning with a fiber bundle endomicroscope probe to expand the effective imaging area. The device uses a rigid concentric tube scanning mechanism to facilitate large-area mosaicking. 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 fiber 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. Experimental results show that the device is able to scan a spiral trajectory over a large hemispherical surface. Detailed performance evaluation was performed and the bending angle ranges from –90° to 90° with high repeatability and minimal rotational hysteresis errors. 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 (BCS), confocal endomicroscopy, image mosaicking, 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 tumor with a surrounding margin of healthy breast tissue (approximately 2–5 mm) while leaving the remainder of the breast intact [2]. It is well recognized that the margin status of the excised tissue is the strongest predictor for tumor recurrence following BCS [3]. If tumor cells are found on the edges of excised tissues (positive margins), these patients will require a reoperation [3]. National data from England and Wales highlight that a significant proportion of patients with invasive (18%) and noninvasive 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 tumor cells in the reexcision specimens which suggests that a significant proportion of these patients might have been overtreated [5]. Currently, the adequacy of BCS relies on the predictive value of the 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, and 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]. Utilizing 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 fiber 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 fluorescent 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 nonneoplastic breast tissues were readily visualized using confocal endomicroscopy [12]. This ex vivo study on acriflavine-stained human breast tissues demonstrated that the presence of hypercellularity and haphazard arrangement of morphological architecture correlated well with common pathognomonic features of breast cancer seen on conventional histology.
Additionally, surgeons were shown to be able to differentiate neoplastic from nonneoplastic 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 adjacentely 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 mosaicking [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 anesthetic complications to the patient and reduces operating theatre productivity.

These inherent limitations are well-recognized and have motivated the development of several mechanical scanning devices to facilitate smooth and consistent translation of the miniprobe against the tissue surface. An articulated robot for manipulation of biophotonics probes was first developed by Noonan et al. for intraoperative integration of laparoscopic instruments [16]. Rosa et al. developed a scanning device using hydraulic microballoons [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 three-dimensional (3-D) 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 mosaicked. Although large-area mosaics were achieved by [19] and [20], this study 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 two-dimensional (2-D) motion of the scanner required rotation of the distal tip in the previous prototype [21], which resulted in an accumulation of errors during mosaicking. 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] and [30]. The gear-driven mechanism makes it easy to achieve multi-DOFs together with miniaturization. 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.

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 (see 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 miniaturization, 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 mosaicking.

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 are able to rotate independently. This structure provides $-90^\circ$ to $+90^\circ$ bending on one axis, and $360^\circ$ 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 $\alpha$, the outer tube rotation angle $\beta$, and the tip bending angle $\theta$ are related by the following equation:

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

where the lengths $R$ and $r$ are indicated in Fig. 2. Combination of the rotational and bending motions provides the hemispherical 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 between the tip frame length $H$ (Fig. 2) and tip bending angle $\theta$ (see Fig. 2), such that

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

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

The rotation angle around the center of the $xy$ plane is given by $\beta$. Hence, a suitable variation of $h$ and $\beta$ 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) and (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 setup 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 the 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 (see 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 (see Fig. 4 enlarged view). It works well since the probe itself has an inherent stiffness. It consists of a slider, a spring (labeled 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.

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 [see Fig. 5(a)]. The balloon was fixed on a guide tube, and the scanning device was inserted into the guide tube (8 mm 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 the guide tube and the scanning device. A highly flexible leached fiber 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 [see Fig. 5(b)]. Because the linear structure in Fig. 4 enlarged view is easy to be separated, we can change the position of the linear structure depending on probe types. The scanning device is connected to a microdiaphragm air pump (8018 Gt, Namiki Precision Jewel Co., Ltd., Japan). There is an inner spacer inserted into the 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 mm × 90 mm × 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) [see 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, \( \alpha \) and \( P(\alpha) \) are the input angle and function from input angle to the target rotational displacement of the inner tube, \( X_t \) and \( X_f \) are the target rotational displacement of the inner tube and current rotational displacement of the inner tube, \( \Delta x = S(\Delta x) \) are the differential rotational displacement of the inner tube and function from the differential rotational displacement to output voltage, and \( V \) and \( \alpha_f \) are the output voltage and rotational angle of inner tube, respectively. 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 the rotation speed, the rotation angle, the effective scan speed, and the radial position. These data could be used to assist with the assembling of mosaics in future.

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 \( V_{\text{tangential}} \), and the loop spacing in the radial direction, \( \Delta h \). The parameters \( R \) and \( r \) are shown in Fig. 2. \( V_{\text{tangential}} \) is given by

\[
V_{\text{tangential}} = \frac{H \sin (\theta_t) W_{m2t}}{\mu}
\]
where $\mu$ 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 $r_{\text{sphere}}$ and the number of turns $N$ [see Fig. 7(a)]. The equation of the spherical helix in spherical coordinates is given by [31]

$$r_{\text{sphere}} = H$$

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

We note that the length $L_t$ of a spiral can be calculated by

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

The spacing between loops $\Delta h$ is given by (7). The loop spacing is a geodesic distance between the loops of the spiral trajectory on the sphere [see Fig. 7(a)]

$$\Delta h = \frac{\pi H}{N}.$$  

(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 $\Delta p$ by (8)

$$L_t = \Delta p \cdot F \cdot t.$$  

(8)

Empirically, it was found that a shift of 40 $\mu$m between images, and hence, an overlap of 200 $\mu$m for a 240-$\mu$m field-of-view, was necessary to ensure consistent mosaicking. Given the imaging frame rate of 10 frames/s, 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

$$S_t = \int_0^{2\pi} \int_0^{\delta_t} H^2 \sin(\theta_t) \, d\beta_t \, d\theta_t = 2\pi H^2 \int_0^{\delta_t} \sin(\theta_t) \, d\theta_t$$

$$= 2\pi H^2 (1 - \cos \delta_t) \quad 0 \leq \delta_t \leq \frac{\pi}{2}.$$  

(9)

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. Visualization and Mosaicking

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 fiber bundle and lens assembly from a commercial endomicroscopy system (Cellvizio UHD Miniprobe, Mauna Kea Technologies, France) and a 17000 core, 8-$\mu$m core-spacing bare leached fiber bundle (Schott) with a 1-mm diameter. The imaging system is shown in Fig. 8. This custom acquisition system allows a combination of imaging, mosaicking, 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 microscopic objective by a pair of telescopes. The proximal end of the fiber bundle was placed at the focus of the microscope objective, resulting in a 2-D laser raster scanning pattern across the bundle. This was transferred to the tissue by the bundle and a distal microobjective. The time-average power to the tissue was approximately 5 mW.

Fluorescence signal returning from the tissue travelled back along the fiber bundle and was descanned. It was then 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. A signal from the photodiode was digitized by a high speed, 12-bit analog-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 2-D images frames using synchronization 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 synchronized 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 fiber core pattern and a background subtracted to remove the fluorescence signal from the fiber bundle. Processed and auto-contrasted images were displayed live to the user at 10 frames/s, and both processed and raw images were saved to disk after being converted to 8 bits per pixel.

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 the 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 the assessment of the bending performance, measurements were made in four parts: (a) bending from 0° to +90°, (b) returning to 0°, (c) bending from 0° to −90°, and (d) returning again to 0°. The bending angles were measured by a digital camera that had a resolution of 4272 × 2848 pixels, which was equivalent to a resolution of 0.05 mm at the imaging plane. The camera was setup 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 (e) from 0 to 360°, and then (f) returned to 0° [see Fig. 9(c) and Table II]. The measurement setup is shown in Fig. 9(d).
Tip positioning accuracy was used to evaluate the dispersion of the tip position in a one-way trip (see, a–f in Fig. 9). In addition, the 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., USA). 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 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 Fig. 10(a) and (b).

Fig. 10(c)–(f) shows the target and actual $x$, $y$, 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 in the opposite direction to the confocal probe (i.e., it did not run through the device’s probe channel). In Fig. 10(c) and (d), the amplitude [see 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 change 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 [see Fig. 11(a) and (b)]. The breast phantom was designed for use in training of surgeons to conduct wide local excision of breast tumors, 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 fiber-core spacing of 8 μm, and the lack of distal objective. The working distance is also suboptimal, 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°). The results show that the probe could maintain almost constant tissue contact when scanning over large distances of up to 48 mm. [see Fig. 11(c) and (d)]. Because the balloon is not a perfect spherical shape, there is a risk of loss of contact in some places [see 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 mosaicking 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 optimized 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 license and ethics approval was obtained from Imperial College Tissue Bank (R12047 and R12047 a). For these experiments, the balloon was not necessary to flatten the tissue. However, to simulate its presence, a transparent disposable drape (Clinicon, Bristol, U.K.) was fixed onto a support window, as shown in Fig. 12(a). The scanning device and support window were held by passive arms.

First, 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-colored 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 mosaicking 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.

### TABLE III

<table>
<thead>
<tr>
<th>DOF</th>
<th>Direction (°)</th>
<th>Power [N]</th>
<th>Torque [N-mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bending</td>
<td>−90 to 90</td>
<td>0.9</td>
<td>19.8</td>
</tr>
<tr>
<td>Rotating (Bending 45°)</td>
<td>−360 to 360</td>
<td>2.1</td>
<td>46.2</td>
</tr>
</tbody>
</table>

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The table above provides the generated power and torque at the tip for different degrees of bending and rotation.
in the center 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 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 between adipocytes and fibrous tissues.

The performance of the probe bearing was analyzed 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 normalized cross-correlation between the two sinograms. The average rotation was $(0.1 \pm 0.1)^\circ$, confirming that there was no net rotation above random jitter.

Fig. 11. Breast phantom experiment: (a) scanning tip with balloon and probe, (b) Setup, (c) and (d) linear mosaics: (c) and (d) were vertically placed and covered a length of 48 mm, (e) position of circle scan tests, (f) circle scans at corner of the flat and curve surface, and (g) co-ordinates for the 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, and (e) human breast cancer: large-area spiral without overlap.

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 $(-90.97^\circ$ to $90.05^\circ$) was slightly over $\pm 90^\circ$. 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 $-0.65^\circ$ to $359.67^\circ$. 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 $0.73^\circ$ for the bending motion and $0.41^\circ$ 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 fiber bundle probes is between 0.24 and 1 mm in diameter. The positioning accuracy should be acceptable for scanning with fiber bundles for which the field-of-view is over 0.5 mm in diameter.
For miniprobes 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 visualization 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 wirecut 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 [see 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 center 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 setup tube, and then initialized the motors. However, as there was a small gap between the setup 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 center by the reactive force. Both of these effects could have led to a “hole” in the center 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 setup 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 and 0.5 N [32], [33]. The bending and rotating forces, which were 0.9 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 tumor is generally small (between 1–2 cm). Provided there is no distant spread, BCS is generally performed to remove the tumor 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 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. Furthermore, 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 the 3-D 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 mosaicking 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 did not 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 fiber from rotating during rotational scanning. The mosaicking algorithm will therefore need to check for rotations, as well as translations, between images.

Nevertheless, these experiments showed that the probe could maintain tissue contact when moving over a large bending range of $-70^\circ$ 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 170 kPa 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 the 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 s to reach the targeted tangential velocity of 0.4 mm/s; this time can be minimized by controlling the angular velocity of Motor 2 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 s, 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 s 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 min. Intraoperative specimen X-ray may take as little as 5–10 min 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 panoramric scenes through the creation of large-area tissue mosaics has enabled more morphological features to be visualized in a single field-of-view while providing the microscopic means of visualizing 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 preemptively 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 mosaicking 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 minimize 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 mosaicking 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 pressurized 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 a 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 artifacts 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] and [30]. In particular, because of the size and shape restrictions of bevel gears, the mechanisms in [29] and [30] make it difficult to achieve a small outer diameter with a large channel.

Studies in [18] aimed to generate a mosaic under 3 mm² in area without any gaps. Our scanning device is able to scan both overlapping trajectories in a focused area (under 3 mm²) and nonoverlapping 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 judgment 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 minimized. 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 the 3-D space, and hence would provide the position of a mosaic. The aim for future trials is a 3-D 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. While it increases the amount of information visualized 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 the probe tip and the tissue surface are also required to achieve uninterrupted and continuous scanning. Our scanning device is an economical, robust, and intelligent platform to generate accurate spatio–temporal localization 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 regard to the practical application of the scanning device, the simple mechanical design will make commercial manufacturing straightforward.

V. Conclusion

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.

REFERENCES


Authors’ photographs and biographies not available at the time of publication.