



(51) International Patent Classification:

A61B 18/14 (2006.01) A61B 90/00 (2016.01)
A61B 18/22 (2006.01) A61B 1/00 (2006.01)

(21) International Application Number:

PCT/GB2018/051086

(22) International Filing Date:

25 April 2018 (25.04.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1706565.7 25 April 2017 (25.04.2017) GB

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: MICROMANIPULATION APPARATUS FOR CLINICAL APPLICATIONS

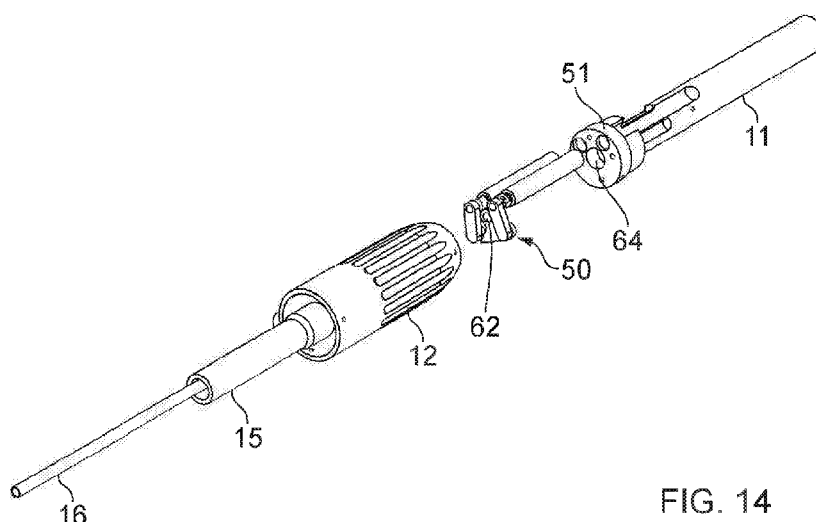


FIG. 14

(57) Abstract: A micromanipulation apparatus comprises an outer tube defining a longitudinal z-axis of the apparatus and an inner tube is at least partially disposed within the outer tube. The inner tube has a continuous working channel and an endoscopy probe extending therethrough. A steering mechanism controllably varies the lateral x, y position of a distal end of the inner tube, relative to the device z-axis, and an ablation energy delivery device extends through the apparatus along the z-axis. A contrast agent delivery mechanism delivers contrast agent to the distal end of the inner tube via the continuous working channel or via a lumen of the outer tube. An image processor analyses images from the endoscopy probe and a controller optically determines magnitudes of displacements of the distal end of the inner tube based on said analysed images which is used as feedback to the steering mechanism.



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))*

MICROMANIPULATION APPARATUS FOR CLINICAL APPLICATIONS

The present disclosure relates to micromanipulation apparatus suitable for use in clinical applications such as endomicroscopy and ablation.

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Biopsies can be carried out prior to, and during, a clinical intervention in order to characterise tissue. A physician may take a biopsy where it is suspected that a lesion might exist. Biopsies are currently performed using mechanical devices that remove a tissue sample for submission to a histologist who can assess the condition of the tissue in a laboratory.

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Clinical endomicroscopy is an imaging modality that enables histology-like images to be acquired from within the human body, in real-time, such as shown in Figure 1. These optical biopsies allow clinicians to make an in-situ, in-vivo assessment of a clinical site, aiding the diagnosis of lesions. There are a multitude of advantages to this approach. Patients can be diagnosed during a procedure and thus can avoid repeat interventions that would be occasioned by the wait for histology reports. This also shortens the length of the procedure in the case of samples being analysed intraoperatively. The biopsy is acquired without the need to mechanically interact with the specimen, so “crush artefacts” can be avoided.

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Histology images from common biopsies may be large (e.g. 2 to 3 mm or more) and endomicroscopy (optical biopsy images are very small, e.g. approximately 0.24 mm). Larger fields of view can be biopsied through mosaicing techniques that are not possible with traditional pinch biopsies. The acquired images can be “stitched” together to form a large map of the tissue region and tumour boundaries can therefore potentially be identified. This in turn, allows clinicians to be more conservative when resecting tumours, especially in surgical procedures such as breast tumour resection and endoscopic mucosal resection for early stage gastric cancer.

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The technology has been commercialised by Mauna Kea Technologies (Cellvisio, MKT, France) in the form of probe-based confocal endomicroscopy. The probes that have been developed can be deployed down standard endoscopes.

The endomicroscopy technique may have some disadvantages. High magnification probes may have a field of view of a few hundred microns. This means that it is often challenging for a clinician to maintain steady contact between the probe and the tissue. This is especially true in the presence of respiratory motion from the patient and tremor from the clinician. One solution is to use mechatronic hand-held instruments that adopt force control techniques [1, 2], spring-based techniques [3], [4] or pneumatic methods [5].

Another challenge is in the acquisition of large area mosaics. Researchers have integrated endomicroscopy probes into hand-held designs with hydraulic actuation [3], snake robots [6] and into precision industrial robots [7]. Researchers have also integrated probes into scanning mechanisms for use within a cavity. By actuating the probes through spiral trajectories, it is possible to build up large scale images of a cavity to aid the resection of breast tissue margins. One device uses an inflatable balloon to stabilise the surrounding tissue whilst the probe scans over the surface.

It is an object of the present invention to provide improvements in micromanipulation apparatus suitable for performing endomicroscopy techniques, and for providing additional functionality thereto.

According to one aspect, the present invention provides a micromanipulation apparatus comprising:

- an outer tube defining a longitudinal z-axis of the apparatus; and
- an inner tube, at least partially disposed within the outer tube, and having a continuous working channel extending therethrough, the inner tube further including an endoscopy probe extending therethrough;
- a steering mechanism configured to controllably vary the lateral x, y position of a distal end of the inner tube, relative to the device z-axis; and
- an ablation energy delivery device extending through the apparatus along the z-axis.

The ablation energy delivery device may comprise at least one ablation electrode at the distal end of the inner or the outer tube. The ablation energy delivery device may comprise an optical fibre for transmission of optical energy to the distal end of the inner tube. The ablation energy delivery device may comprise at least one electrical conductor passing through the inner tube and coupled to at least one electrode at the distal end of the inner

tube. The ablation electrode may be retractable. The micromanipulation apparatus may further include a contrast agent delivery mechanism configured to deliver contrast agent to the distal end of the inner tube. The contrast agent delivery mechanism may deliver contrast agent via the continuous working channel of the inner tube or via a lumen of the outer tube. The endoscopy probe may comprise an imaging fibre extending through the working channel of the inner tube. The inner tube may be coupled to the outer tube at a first longitudinal position to form a cantilever extending to the distal end of the inner tube. The steering mechanism may comprise a deflection device positioned within the outer tube at an intermediate position between the first longitudinal position and the distal end of the inner tube. The deflection device may be configured to deflect the cantilevered inner tube laterally within the outer tube so as to adjust the x, y position of the distal end of the inner tube relative to the device z-axis. The deflection device may comprise a pair of electrically-actuated rotatable cam surfaces configured to bear against two non-parallel bearing surfaces of the inner tube to effect motion of the inner tube in selected directions lateral to the device z-axis. The two bearing surfaces of the inner tube may comprise oblique two surfaces of a V-section component coupled to the inner tube. The first longitudinal position at which the inner tube is coupled to the outer tube may comprise an anchorage point laterally offset from the device z-axis to provide a bias from the device z-axis. The pair of cam surfaces may comprise a pair of driving elements each surrounding the inner tube. A part of the inner tube adjacent to the first longitudinal position may be profiled for a localised reduction in inner tube stiffness adjacent to the first longitudinal position. The steering mechanism may be further configured to controllably vary the longitudinal z-position of the distal end of the inner tube relative to the outer tube. The steering mechanism may be configured to control the longitudinal z-position of the inner tube relative to the outer tube to apply a pre-programmed axial force by the distal end of the inner tube on a specimen under examination.

The micromanipulation apparatus may further include an image processor configured to analyse images from the imaging fibre. The micromanipulation apparatus may further include a controller configured to optically determine magnitudes of displacements of the distal end of the inner tube based on the analysed images. The controller may be configured to use the optically determined displacement magnitudes as feedback to the steering mechanism.

Embodiments of the present invention will now be described by way of example and with reference to the accompanying drawings in which:

Figure 1 shows conventional images achievable with clinical endomicroscopy;

Figure 2 shows schematic views of biopsy sites encompassing a tumour and a
5 clinical ablation technique for marking a region for resection;

Figure 3 shows a perspective side view of a micromanipulation apparatus;

Figure 4 shows a close-up perspective view of a distal end of the micromanipulation
apparatus of figure 3;

Figures 5 and 6 show close-up perspective views of a distal end of possible
10 ablation contact arrangements for use with the micromanipulation apparatus of figure 4;

Figure 7 shows close-up perspective views of a distal end of possible ablation
electrode arrangements for use with the micromanipulation apparatus of figure 4;

Figure 8 is a schematic diagram illustrating design principles of a
micromanipulation apparatus;

15 Figure 9 shows a series of end views illustrating the operation of a
micromanipulation apparatus;

Figure 10 shows perspective views of the micromanipulation apparatus of figure 9;

Figure 11 shows a series of end views illustrating the operation of an alternative
micromanipulation apparatus;

20 Figure 12 shows a perspective view of the micromanipulation apparatus of figure
11;

Figure 13 shows perspective views of another configuration of micromanipulation
apparatus for improved control;

Figure 14 shows a perspective view of the micromanipulation apparatus of figure
25 10 in partially disassembled condition;

Figure 15 shows a schematic side view illustrating principles of operation of force
compensated diathermy electrodes of the apparatus of figures 5 to 7;

Figure 16 shows a perspective side view of a micromanipulation apparatus
incorporating an actuator for a contrast injection mechanism;

30 Figure 17 shows a perspective side view of a micromanipulation apparatus
incorporating a viewing screen;

Figure 18 shows two alternative positions for a micromanipulation cam system as
may be used in the apparatus of figures 10 and 12;

Figure 19 shows results of image scans of tissue paper taken using the apparatus
35 of figures 9 and 10;

Figure 20 shows results of image scans of stomach tissue taken using the apparatus of figures 9 and 10;

Figure 21 shows a framework overview of the system components;

Figure 22 shows a control schematic of the system;

5 Figure 23 shows an illustration of the effect of movement of the shaft and a graphical representation of the change in axial change versus shaft length;

Figure 24 shows an analysis of the cam-roller mechanism positions: (left) four different position configurations explored during the analysis and (right) simulated workspace results for the four different configurations;

10 Figure 25 (a – c) shows visual servoing results on a grid pattern;

Figure 26 shows visual servoing mosaic results when motion is introduced using the motorised translation stage, along with graphs showing the current position (real position from the mosaic) and the desired (commanded) position;

15 Figure 27 shows mosaic results without and with visual servoing on the grid pattern phantom with random motion disturbance of 1.25 mm/s

Figure 28 (a - b) shows mosaic results without and with visual servoing on lens paper (a) and colonic tissue (b) while an external disturbance is applied;

Figure 29 shows mosaic results for breast tissue scanning without and with visual servoing showing the difference in the scanning area covered;

20 Figure 30 (a – f) shows ex vivo tissue mosaics of (a) Human normal breast tissue (fibrous connective tissue), (b) human normal breast tissue (adipose tissue admixed with fibrous connective tissue), (c – d) human breast invasive carcinoma, (e) porcine large bowel and (f) porcine large bowel fat;

25 Figure 31 shows example mosaics of lens paper while manipulating the instrument in a hand-held manner or clamped on a robotic arm;

Figure 32 shows example ex vivo mosaic results using the in-house endocytoscopy with human normal breast tissue and the dual-wavelength slit scanning confocal system with lens paper;

30 Figure 33 shows (a) the tip of the instrument presenting the CO₂ laser and microscopy fibres, (b) instance from the laser ablation procedure on a paper card when the laser fired, (c) image from the custom tracking camera presenting the mechanical offset between the CO₂ fibre and the microscopy fibre, (d) two instances overlaid, from different timestamps, presenting the movement by the offset value in order that the offset dot can coincide with the initial position of the mechanical dot, and (e) real-time mosaic, from the
35 same region of a paper card, before and after the ablation in the centre of the spiral pattern;

Figure 34 shows an example of a real-time mosaic image from the same region of the grid patterns before and after the laser ablation.

In one aspect, a micromanipulation apparatus as described herein provides a means by which endomicroscopy image mosaics can be achieved rapidly and precisely, using hand-held instrumentation that is low cost, compact and easily integrated into a surgical workflow. Such a hand-held device facilitates the imaging of tissue, characterisation of the tissue and performance of an ablation procedure to remove any identified lesions or to mark out a region of tumour to be resected subsequently.

With reference to figure 2, a series of biopsy sites 1a, 1b, 1c, etc can be imaged in succession. A tumour or lesion region is schematically indicated by region 2 and is visible in the individual images. For each optical biopsy mosaic taken, the surgeon interprets the obtained image and makes a judgement as to whether the anatomy contains a lesion. Alternatively, this assessment process may be automated using a computer vision algorithm that can accurately classify images that imply cancerous tissue from healthy tissue. The obtained images can also be streamed through a network (local or internet) to a pathology lab for interpretation by a pathologist.

When a biopsy site 1 is identified as containing a tumour or lesion for treatment, the micromanipulation apparatus described herein enables the site to be ablated to remove the lesion, or to be marked by ablation, e.g. as seen by ablation marks 3a, 3b, 3c for subsequent resection within a resection margin 4.

With reference now to figures 3 and 4, a mechatronic micromanipulation apparatus 10 comprises a housing 11 including a hand grip portion 12. A distal end 14 of the micromanipulation apparatus 10 includes an outer tube 15 which defines a longitudinal axis of the apparatus (referred to herein as the z-axis) and an inner tube 16 which is at least partially disposed within the outer tube 15. The inner tube 16 may generally extend through the outer tube 15 so that its end coincides longitudinally with the end of the outer tube 15, or its end may be somewhat recessed within the distal end of the outer tube. The inner tube 16 may be retractable so that its distal end can be longitudinally repositioned relative to the distal end of the outer tube 15. The inner tube 16 may provide a working channel or lumen extending therethrough as seen in figure 4.

The outer tube 15 is preferably substantially rigid and may, when its distal end 14 is deployed against tissue, provide a means for stabilising the tissue near to the inner tube 16. The inner tube contains an endomicroscopy probe (not shown in figure 4) for imaging tissue at the distal end of the inner tube 16. The endoscopy probe may comprise an
5 imaging fibre extending through the inner tube, such as through the lumen of the tube 16 or integrated into the tube walls. Alternatively, the endoscopy probe could comprise an electronic imaging device disposed at the distal end of the inner tube 16 and an electrical communication channel extending along the inner tube to communicate images to a proximal end of the micromanipulation apparatus 10.

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As illustrated schematically in figure 4, the position of the distal end of the inner tube 16 can be manipulated, using a steering mechanism to be described later, to vary its lateral position relative to the distal end of the outer tube 15. Throughout the present specification, the lateral movement axes 17, 18 will be referred to as the x and y axes, i.e.
15 axes that are orthogonal to the longitudinal z-axis of the apparatus as defined by the outer tube 15.

The steering mechanism can be operated to manipulate the x-y position of the distal end of the inner tube 16 so as to generate a mosaic of images such as seen in figures 19 and
20 20.

With reference to figures 5 and 6, the micromanipulation apparatus 10 includes an ablation energy delivery device extending through the apparatus 10 along the z-axis. The energy delivery device may be disposed on either the inner tube 16, the outer tube 15, or a
25 combination of both and provides a means for performing tissue ablation. This enables both imaging and ablation to be carried out in quick succession, if required.

Figure 5a illustrates a pair of diathermy electrodes 20, 21 disposed at the distal end of the outer tube 15, suitable for bipolar diathermy. Figure 5b illustrates a single electrode 22
30 disposed at the distal end of the outer tube 15, suitable for monopolar diathermy. The diathermy electrical contacts or electrodes 20, 21 may be integrated into the outer tube that stabilises the tissue. In the case of the single monopolar electrode 22, a separate electrical contact may be placed on the patient elsewhere to provide an electrical ground.

Figure 6a illustrates a pair of diathermy electrodes 25, 26 disposed at the distal end of the inner tube 16, suitable for bipolar diathermy. Figure 6b illustrates a single electrode 27 disposed at the distal end of the inner tube 16, suitable for monopolar diathermy. The diathermy electrical electrodes 25, 26 may be integrated into the inner tube 16. Again, in the case of the single monopolar electrode 27, a separate electrical contact may be placed on the patient elsewhere to provide an electrical ground. This could be on the outer tube 15.

The endomicroscopy probe, which may pass through the lumen 28 of the inner tube 16 or along the walls thereof, may be retractable such that when an ablation is to be performed, the endomicroscopy probe is protected from damage which might otherwise be caused by electrical shorting from the diathermy electrode(s). For example, if the diathermy electrodes 20, 21, 22 are disposed on the outer tube 15, the endomicroscopy probe may be retracted by longitudinal displacement (i.e. retraction) of the inner tube 16 into the outer tube 15. Alternatively, if the diathermy electrodes 25, 26, 27 are disposed on the inner tube 16, the endomicroscopy probe may be retractable via the lumen 28 of the inner tube 16, for example.

With reference to figure 7, in an alternative arrangement, the electrical diathermy electrodes 30, 31, 32 may themselves be extendible and retractable. The electrodes 30, 31, 32 may be actuatable to extend from the distal end of the inner tube 16 when ablation is required, and may be retractable into the inner tube when ablation is complete, ready for steering of the inner tube and the endoscopy probe to a new biopsy site 1. The electrodes 30, 31, 32 may be manufactured from an elastic material, or a superelastic material. The electrodes 30, 31, 32 may be actuated by axial movement of the inner tube 16 carrying the endomicroscopy probe, such that as the inner tube 16 is retracted, the electrodes effectively extend outwards and converge on a point where imaging had previously been taking place prior to the ablation phase.

Another form of ablation energy delivery device that can be incorporated into the micromanipulation apparatus 10 could be a laser ablation system. A laser ablation fibre may be inserted into the same working channel (e.g. the lumen 28 of the inner tube 16) as the endomicroscopy probe fibre for example, extending to the distal end of the inner tube 16. The laser ablation device fibre may be separated from the endomicroscopy probe at

the distal end of the inner tube by a small lateral offset. The laser ablation device fibre may also terminate with a z-axis offset from the microscopy probe, as discussed later.

5 The micromanipulation apparatus 10 may deploy a number of possible steering mechanisms for effecting lateral movement of the distal end of the inner tube 16 relative to the outer tube 15, thereby effecting x-y displacement of the endoscopy probe in a controlled manner. The steering mechanism may be configured to perform automated scanning functions to allow endomicroscopy imaging. There are a number of preferred features of such a mechanism, such as positioning accuracy and high repeatability. In one
10 example, an endomicroscopy probe may only have a field of view of between 100 and 300 microns and thus has to be carefully manipulated in order for images to be reliably generated using a mosaicking algorithm.

A micromanipulation mechanism therefore desirably provides a good positioning accuracy
15 and avoids backlash, hysteresis effects and other “dead zones”. There are designs that can provide such motion control attributes. Stewart-Gough platforms, are one such example. However, such designs tend to use many actuators and elaborate mechanical components that are large and heavy, and are thus not ideal for a hand-held micromanipulator implementation. Additionally, mechanisms that are based on gears or
20 rigid structures have inherent backlash that is often difficult to compensate for, or require such high levels of manufacturing precision that they are not practical for implementation in a low cost, lightweight device.

Compliant cantilever mechanisms are one means of circumventing these problems. A
25 micromanipulation or steering mechanism will now be described which provides excellent positioning accuracy and very low or negligible backlash, hysteresis effects and other “dead zones” and is lightweight for handheld operation. With reference to schematic figure 8, the principle of operation is to provide a beam 40 (corresponding to the inner tube 16) which is anchored to an anchorage point 45 and can be deflected to a position as indicated
30 by dashed line 41) by way of a cam mechanism indicated at 42. In this way, the distal end of the beam 46 can be manoeuvred.

With reference to figures 9 and 10, a steering mechanism 50 comprises a frame 51 onto which is mounted a pair of motors 52, 53 each of which drives a respective motor shaft 54,
35 55. Each motor shaft 54, 55 is coupled to drive a respective cam lever 56, 57 with a

respective bearing surface 58, 59. The bearing surfaces 58, 59 each bear against a respective edge or bearing surface 60, 61 of a cam follower 62, whose edge bearing surfaces 60, 61 are disposed in a "V" formation. The cam follower 62 is affixed to a tube 63 which corresponds to the inner tube 16 of the micromanipulation apparatus of figures 3 and 4. The tube 63 extends through an aperture 64 in the frame 51. The aperture 64 provides sufficient clearance to allow the tube 63 to be displaced laterally within the aperture. The tube 63 is affixed, at its proximal end 65, to an anchorage point 45 (figure 8) that is stationary with respect to the frame 51, e.g. as part of an outer casing of the micromanipulation apparatus 10 or the outer tube 15. The distal end 66 of the tube 63 is free to move laterally, i.e. in x and y directions under the control of the steering mechanism 50. An endomicroscopy probe (not shown) is firmly affixed to the distal end 66 of the tube by suitable means such as a grub screw, locking mechanism or some other form of bond.

In use, the motors 52, 53 are used to independently rotate the two cam levers 56, 57 so that the bearing surfaces 58, 59 apply required lateral forces to the tube 63 by way of the bearing surfaces 60, 61 of the cam follower 62, which deflects the tube 63 as required. In a general aspect, the cam follower 62 provides two non-parallel bearing surfaces 60, 61 to the tube 63 which bear against the rotatable cam bearing surfaces 58, 59 to enable the cam levers 56, 57 to cooperate in deflecting the tube 63 in the desired x, y directions. The tube 63 is preferably mounted at anchorage point 45 in an offset position relative to the centre of aperture 64 such that the tube 63 is somewhat deflected or biased in the x-y directions and there is always an inherent elastic return force being exerted on the cam levers 56, 57 by the deflection in the tube 63.

This is illustrated in figures 9a, 9b and 9c where: figure 9a illustrates rotation of the cam levers 56, 57 to diverging positions allowing the cam follower 62 and the tube 63 to return under self-bias towards a downward deflection position within the aperture 64; figure 9b illustrates rotation of the cam levers to parallel rightward positions thereby driving the cam follower 62 and the tube 63 against the downward bias to a right and upward deflection position within the aperture 64; figure 9c illustrates rotation of the cam levers 56, 57 to converging positions driving the cam follower 62 and tube 63 against the downward bias towards an upward central deflection position within the aperture 64. It will be understood that by independent control of the motors 52, 53, the cam follower 62 and tube 63 can be driven to any required x-y position within the available range of the deflection device.

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The bearing surfaces 58, 59 on the cam levers 56, 57 may comprise rotary bearings so as to reduce friction between the cam levers 56, 57 and the cam follower 62.

5 An advantage to the arrangement of the steering mechanism 50 as shown in figures 9 and 10 is a significant reduction in backlash as a result of the elastic restoring force provided by the tube 63 mounting / anchoring point 45 being offset from the central z-axis of the micromanipulation apparatus 10, e.g. the axis passing through the centre of the aperture 64. The micromanipulation apparatus 10 can manipulate the endomicroscopy probe tip to move in both lateral directions x and y and can be used to perform scanning trajectories, 10 for example, a raster scan or spiral scan.

In another embodiment of a steering mechanism 70 shown in figures 11 and 12, the cam lever components instead incorporate a slotted feature that is used to apply lateral forces to the tube 63. In this implementation, the tube 63 can be mounted centrally (e.g. on the 15 apparatus z-axis, and / or lying in unbiased condition in the centre of the aperture 64). The cam levers 71, 72 each have a slot or aperture 73, 74 through which the tube 63 passes, and the cam levers 71, 72 are in overlying relation to one another along the z-axis. The slots 73, 74 can each push the tube 63 in two opposing lateral directions, where the pushing directions of each of the cam levers 71, 72 are different to the other lever, e.g. 20 oblique or orthogonal thereto. Thus, by independent control of the cam levers by motors 52, 53, the cam levers 71, 72 can cooperate to drive the tube 63 to any position within the x-y space within the range of the steering mechanism 70. Thus, in a general aspect, the cam levers 71, 72 exemplify a pair of driving elements that each surround the inner tube 63.

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An advantage of this design is that the returning spring force of the tube 63 is lower and more homogeneous (e.g. not directionally dependent). A potential disadvantage may be that a dead zone could be introduced in to the steering mechanism, but this may be compensated by incorporating spring loaded features into the levers such that backlash is 30 minimised. This mechanism can also work with an inherent bias on the tube 63, e.g. in the downward direction within aperture 64 in the same manner as in the device of figure 9.

The slotted cam levers 71, 72 may incorporate low friction surfaces to improve control and reduce stiction effects. The low friction surfaces may be polished metal surfaces or polymer-based surfaces. They may incorporate ball bearings.

- 5 In the examples of figures 9-12, the steering mechanism 50, 70 generally exemplifies a deflection device having at least a pair of electrically-actuated rotatable cam surfaces which bear against two non-parallel bearing surfaces on the tube 63 to effect motion thereof in x-y space. The arrangement of figures 11 and 12 provides four rotatable cam surfaces and generally exemplifies an arrangement having a pair of driving elements
10 surrounding the tube 63. Other means for driving the cam levers can be envisaged such as hydraulic or pneumatic motors which are suitably electrically actuated / controlled by a microprocessor controller (not shown).

- An improvement in the flexibility of the tube 63 to deflect under the bias of a steering
15 mechanism such as 50 or 70 may be achieved using the arrangement shown in figure 13. The proximal end 65 of the tube 63 includes a profiled section 80 of tube near to the anchorage point 45 to the housing. The profiled section 80 is configured to locally reduce the stiffness of the tube 63 at a bending point and thus improve control by ensuring that the actuators do not experience large changes in force during the steering process.

- 20 In the example of figure 13, the profiled section 80 may be provided by a series of arcuate slots 81, 82 each extending part way around a circumference of the tube 63. The series of arcuate slots 81, 82 are centred on at least two different radial angles around the tube axis (z), preferably orthogonal radial angles, e.g. one set of slots 81 centred on the x-axis and one set of slots 82 centred on the y-axis. In this way, a reduction in bending stiffness
25 of the tube 63 around both the x- and y-axes is effected. Other slots could be disposed at other radial angles around the z-axis.

- In a further embodiment, strain gauges may be mounted to the proximal end 65 of the tube
30 63 so that deformation can be measured and this information used in the control of the micromanipulator mechanism. In another embodiment, this function could be carried out by encoders in the rotary motors 52, 53.

- Figure 14 shows a perspective view of the partly disassembled micromanipulation
35 apparatus 10 showing the housing 11 with handgrip portion 12, inner tube 16 partly

installed into outer tube 15, steering mechanism 50 with motors 52, 53 withdrawn from the frame 51 and housing 11. The aperture 64 through which the tube 16 passes is clearly seen as is the cam follower 62 through which the inner tube 16 is passed.

5 Other modifications may be made to the micromanipulation apparatus.

A force compensation mechanism may be provided which allows the endomicroscopy probe on the inner tube 16 to adapt to the tissue and make consistent contact. This may be achieved by a number of methods that have already been described in the art including
10 mechatronic force compensation, springs or pneumatics. The z-position of the inner tube 16, or the z-position of the endomicroscopy probe on the inner tube, relative to the outer tube 15, may be controlled as a function of the axial pressure placed on the apparatus by the tissue 19 against which it bears, as shown schematically in figure 15. In such an arrangement, the anchorage point 45 (figure 8) where the inner tube 16 is coupled to the
15 outer tube 15 may be configured to allow axial (z) movement of the inner tube relative to the outer tube, while maintaining fixed x-y axis relationship. Similarly, the inner tube 16 would be enabled for axial (z) movement through e.g. the cam follower 62 or through the slots 73, 74.

20 The micromanipulation apparatus may be provided with a contrast agent delivery system as illustrated in figure 16. Contrast agent is used to improve the image quality of the biological tissues being studied. The micromanipulation apparatus 160 may be provided with a nozzle for secretion / delivery of contrast agent 163 at the distal end 161 of the inner tube 16 / outer tube 15. Contrast agent 163 may be delivered through the lumen of either
25 the inner tube 16 or the lumen of the outer tube 15. The hand grip portion 12 may be provided with an actuation button 162. The actuation button 162 could be coupled to a deformable reservoir of a compliant pipette mechanism or may be an electrical control of a dispensing system such as a motor and leadscrew which are used to control a syringe that can deliver precisely controlled volumes of contrast agent.

30 Figure 17 shows a micromanipulation apparatus 170 which incorporates a display screen 171 for display of the images from the endomicroscopy device. The images may be mosaicked images from multiple biopsy sites as discussed in connection with figure 2.

With reference to figure 18, the steering mechanism (e.g mechanism 50 or 70) may be positioned at different locations along the z-axis of the micromanipulation apparatus, for different scaling of x-y movement. For example, when the steering mechanism 50 is in a position close to the distal end 66 of the inner tube 16 at the tip (as seen in figure 18b), the cam levers 56, 57 provide approximately 1:1 scaling of movement of the tip whereas when the steering mechanism 50 is in a position closer to the proximal end 65 (as seen in figure 18a), the motion at the distal end 66 of the tube 16 is amplified from the movement at the cam levers. The arrangement of figure 18b may provide improved stability, whereas the embodiment of figure 18a may provide improved accuracy of the distal end 66 (tip) due to z-axis position differences in the extreme displacement positions.

Figure 19 shows examples of raster scans of tissue paper using the endomicroscopy probe of figures 9 and 10 showing how the manipulation of the distal end of the inner tube 16 carrying the endoscopy probe, in a raster scan by the steering mechanism 50, enables a composite image to be created. Similarly, figure 20 shows examples of spiral scans of stomach tissue using the endomicroscopy probe of figures 9 and 10 showing how the manipulation of the distal end of the inner tube 16 carrying the endoscopy probe, in a spiral scan by the steering mechanism 50, enables a composite image to be created. Cellular scale images are enabled over a wide area or field of view, by generating a mosaic of images using the steering mechanism.

In a preferred arrangement, the mosaicking of the images is carried out under visual servo control based on the endomicroscope images, as will be described below.

Example 1

In one example, the micromanipulation apparatus as described above comprises two action buttons 162, an ergonomic casing 11, 12 and a 58 mm long steel outer tube 15 of 3.3 mm outer diameter with a channel for passing multiple fibres. An imaging probe and an energy delivery fibre can be passed through the 2.7 mm diameter bore / lumen of the tube and fixed via a locking mechanism. The same channel can be used with other types of optical imaging probes, providing to a surgeon an accurate, scanning platform for various optical biopsy techniques.

For actuation, two 6 mm diameter micro servomotors are used with a 256 : 1 reduction gearbox. These servomotors have an integrated magnetic encoding system that allows for

closed-loop position control using a dedicated motor controller. The motor controllers also provide the necessary power to drive the motors. The robotic scanning device can be either used in a handheld manner or attached to a robotic arm and be manipulated in a cooperative approach. The latter yields increased stability during scanning and would help avoid fatigue of the surgeon. An overall illustration of the system components is given in Figure 21.

The scanning device utilises a flexure mechanism to provide precise, controlled motions of the instrument tip with minimal backlash as described above. The steel tube is clamped in a cantilever configuration so that it can deflect in two planes at its free end. Two cam-roller mechanisms are then used in conjunction with micro servomotors to deflect the tube which yields an approximately planar motion of the tube tip. This configuration allows for a slender, low-profile actuation system that fits in to a 27 mm diameter hand-held device (including the exterior casing). A V-profiled steel cam is welded to the tube shaft; it is engaged by two steel levers with tip mounted bearings that exert lateral forces to the cantilevered tube. The levers are actuated by the two servomotors. The cantilevered tube is mounted in an unloaded position outside the nominal workspace of the device which ensures that the cantilevered tube is always deflected and thus preloaded against the cam-roller mechanisms so as to circumvent backlash errors. The cantilevered tube and micro servomotors are all integrated into a tubular chassis, which is enclosed by an ergonomic casing and can be handheld by the operator.

Different fibre-based optical imaging systems can be used in conjunction with the scanning device where the fibre fits through the, e.g. 2.7 mm diameter inner tube channel. The preferred endomicroscopy system allows high frame rate imaging and high speed scanning. The scanner has been used with a dual wavelength slit scanning system and an endocytoscopy system.

A mosaicking algorithm is used that can run in real-time in conjunction with the high-speed optical system with 120 fps acquisition rate. This algorithm is a pairwise image registration approach which provides the shift between each pair of individual images based on the location of a cross-correlation peak.

Trajectory generation

For the kinematic software of the instrument, different automatic scanning patterns, including linear, raster and spiral trajectories, can be used. As mentioned before, all the input signals have the form of voltage inputs and, therefore, all trajectories are in the “voltage” space rather than the Cartesian space. However, since it is a linear correspondence, a conversion factor can be determined by measuring and correlating the displacement in both spaces, as will be described later. An additional requirement is that the generated points should result in a constant linear or tangential velocity. This ensures that there is consistent overlap between consecutive endomicroscopy images frames, at least when there are no severe tissue deformations.

To generate a linear scanning trajectory, the operator specifies the scan point frequency f_s , the linear velocity u_s and the trajectory length l_s . Based on these inputs, every point (x_i, y_i) is generated as:

$$(x_i, y_i) = (x_c + \sum_{i=0}^{n_p} (\frac{i \cdot u_s}{f_s}), y_c) \quad (5.1)$$

where (x_c, y_c) is the initial centre point used as offset to the trajectory.

For a spiral trajectory, the Archimedean spiral (also known as arithmetic spiral) model was selected as it has the property that any line originating from the origin intersects successive turnings of the spiral at constant intervals of distance. Every point (x_i, y_i) in the Archimedean spiral is described in Cartesian coordinates as:

$$\begin{cases} x_i = x_c + b \cdot \theta_i \cdot \cos(\theta_i) \\ y_i = y_c + b \cdot \theta_i \cdot \sin(\theta_i) \end{cases} \quad (5.2)$$

where (x_c, y_c) is the initial centre point used as offset to the trajectory, b is the angular velocity of the spiral and θ_i is the corresponding angle in this specific time instance. The initial spiral is considered to start from $\theta_0 = 0$. Since the distance between two successive turnings Δ_r is pre-defined as the desired overlap, then the angular velocity is:

$$b = \frac{\Delta_r}{2\pi} \quad (5.3)$$

The maximum circular area to be scanned defines the final radius of the spiral trajectory R_{max} and therefore the maximum angle at which the motion should end is:

$$\theta_{max} = \frac{R_{max}}{b} \quad (5.4)$$

5 The total length of the spiral trajectory can be defined as:

$$L_{max} = \frac{b}{2} \left[\theta_{max} \sqrt{1 + \theta_{max}^2} + \log(\theta_{max} + \sqrt{1 + \theta_{max}^2}) \right] \quad (5.5)$$

which can be approximated as:

$$L_{max} = \frac{b}{2} \cdot \theta_{max}^2 \quad (5.6)$$

By defining the scan point frequency f_s and the linear velocity u_s , the distance Δ_l between
10 successive points on the spiral can be defined as:

$$\Delta_l = \frac{u_s}{f_s} \quad (5.7)$$

Since the sampling should be performed at regular distances across the length of the spiral and given that the distance between successive points on the spiral is pre-defined as well
(Δ_l), then at each time instance i the angle θ_i is calculated as:

$$\theta_i = \sqrt{\frac{2}{b} \sum_{l=0}^{\lfloor L_{max}/\Delta_l \rfloor} (l \cdot \Delta_l)} \quad (5.8)$$

15

Then every point (x_i, y_i) can be derived based on equation 5.2. Due to the fact that the approximated form of the spiral length is used for the derivation, in the beginning of the spiral the points are only approximately uniformly spaced.

20 Closed-loop visual servoing using microscopic images

The positional information that microscopic mosaicking provides (in the form of integrated image shifts) can be used for controlling robotic instruments. In particular, a model-free visual servoing control algorithm is used in conjunction with the robotic scanning instrument. As the robot scans a planned trajectory, the microscopic image shifts are used
25 as the input to a closed loop proportional–integral–derivative (PID) control system. This method allows the robotic scanner to compensate for tissue deformation and low

frequency external motion effects. For the robotic design considered here, the rotation of the probe with respect to the tissue surface is considered negligible and can be ignored. A similar approach was initially described in the work of Rosa et al. [216] but here is the first time that external motion effects are explored and that such algorithm is implemented
 5 in a high-speed spiral handheld scanner.

The concept of this control algorithm is to use the image shifts, in the 2D mosaic image plane, to control the XY positions of the instrument in the Cartesian space (here also referred to as the “voltage” space). The Z-component is defined manually by the operator
 10 when the instrument is placed normal to the tissue surface and does not change during the scanning task as the area covered is very small (discussed below). To align, therefore, the x-axis of the probe’s space with the x-axis of the image space (and hence also align the y-axes), an angle φ should be calculated in order to find the matrix $\mathbf{R}$ and rotate the XY position of the mosaic frame of reference to the XY position in the voltage frame of
 15 reference:

$$p_v = \begin{bmatrix} x_v \\ y_v \end{bmatrix} = L \cdot \begin{bmatrix} \cos\varphi & \sin\varphi \\ -\sin\varphi & \cos\varphi \end{bmatrix} \cdot \begin{bmatrix} x_I \\ y_I \end{bmatrix} = L \cdot R \cdot \begin{bmatrix} x_I \\ y_I \end{bmatrix} \quad (5.9)$$

where L is the factor that transforms Cartesian coordinates to voltages.

The angle φ is calculated at the beginning of each experiment. The calculation of φ is
 20 manually performed through an optimisation process where the scanner is commanded to follow a straight line and, using the real-time mosaicking output, the error between the commanded and the real coordinate points is minimised.

At the beginning of each scanning task, the probe position in the mosaic image is initialised and set as: $p_i(t = 0) = (0, 0)$. This position corresponds to the centre $p_{ic} = (x_{ic}, y_{ic})$ of the
 25 mosaic image. As the scanning continues, the integral over time of the relative image shifts corresponds to the current probe position $p_v(t)$ at the time instance t . Consequently, at every time instance, the measured probe position $p_v(t)$ can be compared with $p^*_v(t)$, the desired probe position at time t'). Due to the different time sampling rate between the
 30 generated trajectory and the endomicroscopy images, the closest generated time instance t' to the actual measurement t is used as the desired probe position. To compensate for position differences, a PID based controller is implemented; here only the PI terms are used as the derivative term is prone to measurement and timing errors. In practice, the PI

controller is sufficient for the proposed visual servoing control algorithm as the P term eliminates the steady state error while the I term accelerates the movement towards the set-point faster and further eliminates the steady state error. Additionally, the scanning task is mainly quasi-static as the variables change slowly due to the velocity being approximately constant.

The required correction to the probe trajectory in voltage space can be calculated as:

$$\begin{bmatrix} \Delta p_{vx} \\ \Delta p_{vy} \end{bmatrix} = K_p \cdot \begin{bmatrix} p_{vx}^*(t') - p_{vx}(t) \\ p_{vy}^*(t') - p_{vy}(t) \end{bmatrix} + K_I \cdot \int_0^t \left(\begin{bmatrix} p_{vx}^*(\tau') - p_{vx}(\tau) \\ p_{vy}^*(\tau') - p_{vy}(\tau) \end{bmatrix} \right) d\tau \quad (5.10)$$

where the gains K_p and K_I are the proportional and integral terms respectively. The tuning of the gains is performed manually, using the standard method of eliminating the steady state error and minimising the overshoots. The selected PI terms are: $K_p = 10 \text{ min}^{-1}$ and $K_I = 0.4 \text{ min}^{-2}$.

A schematic of the control algorithm is depicted in Figure 22.

Mechanical Performance Evaluation and Characterisation

A potential issue with the cantilevered tube is that the motion of the tube tip is approximately planar which means that if the axial component (Z-component) difference is larger than the working distance of the optical imaging system, then optimal imaging results are not guaranteed. For this reason, a CAD simulation was performed in order to calculate the axial difference for various extreme positions of the workspace and the results are depicted in Figure 23. As can be seen, the selected length of 58 mm provides less than 50 microns difference. In practice this is sufficiently small to be compensated for by the elasticity of the tissue.

Furthermore, the position of the motors and consequently the configuration of the camroller mechanism is optimised to achieve the largest possible workspace in the smallest possible overall dimensions for the actuation system. A CAD simulation of four different configurations has been performed, as can be seen in Figure 24. Figure 24a shows four different position configurations explored during the analysis of the cam-roller positions. Figure 24b shows the simulated workspace results for the four different configurations of

Figure 24a. As a result, the configuration of 10 mm positional difference between the cam-roller mechanisms is chosen as it provides the largest simulated workspace (17.95 mm^2).

Custom Tracking Rig

5

The measuring system may provide accurate tracking measurements in the range of several μm , approximately less than 10 times smaller than the effective FoV of the microscope probe. Commercial measuring systems such as electromagnetic and optical trackers provide no more than $100 \mu\text{m}$ accuracy which is only 2 times smaller than the
10 FoV. Therefore, a custom tracking rig has been fabricated with tracking accuracy of several μm that may effectively measure the instrument's tip without imposing any additional weight on the instrument.

The rig consists of a camera fixed rigidly along the axis of the scanning mechanism of the
15 instrument, such as those examples provided in Figures 9 - 12, and a lens assembly between the two in order to focus the tip of the probe onto the camera. An imaging probe inserted into the tube is used to relay light to the tip of the instrument, and the camera may records 1280×1024 pixels video while the instrument scans. The output images have a dark background with a bright circle where the instrument's tip is. Further processing is
20 then needed to measure the circle's centre and consequently the instrument's relative tip position at any time.

After converting the output into a binary image, the tip of the instrument appears as a circle of 15 pixels diameter. Circle tracking, based on the two-stage Circular Hough Transform
25 method, is used and the centres of the circles are recorded online. The overall resolution of the tracking system is measured to be 7.5 microns which is 32 times smaller than the microscopic image FoV (240 microns) and, therefore, adequate for use as a tracking method for the system.

30 Workspace Evaluation

By using the optimal mechanical design parameters and the previously mentioned tracking device, the overall workspace of the instrument can be evaluated. By commanding the instrument to scan across the whole workspace, the linear and non-linear parts of the
35 workspace can be found and the optimal workspace can be identified. In the upper and

right edges of the workspace, the levers of the mechanism lose contact from the cam, whereas in the lower and left edges there is a mechanical stop in the cam mechanism. The resulting middle linear workspace is approximately 14 mm (3.7 X 3.7 mm area size). The resulting limits of the linear workspace are used to constrain the motion of the instrument so as to stay within this linear area.

The circle tracking method is also used to evaluate the repeatability and accuracy of the instrument. Two different scanning approaches (spiral and raster) have been evaluated. Three repeats of spiral trajectories and four repeats of raster trajectories, using the same parameters across the repeats, are performed in sequence. The position errors relative to the original plan were measured, with the maximum position error not exceeding 30 microns and the mean error across all the trajectories being 10.7 microns. The latter implies that the instrument has similar repeatability and accuracy to the tracking system while providing a FoV that is approximately 22 times larger than that of the microscopy probe. This is the first time that a custom large area robotic scanning device demonstrated such performance in terms of accuracy and repeatability.

Microscopic Visual Servoing Evaluation

The validation and evaluation of the visual servoing approach for microscopic images was performed, initially, using a custom phantom that exhibits a pre-defined grid pattern (see Figure 25a). The phantom was printed by a laser printer on a sheet of paper and coated by a fluorescent marker, making it visible by the endomicroscopy probe. Every square in the grid pattern has a line thickness of 73 μm and width of 237 μm . The accuracy of the printed phantom was confirmed using a bench-top microscope, showing that a maximum error of $\pm 6 \mu\text{m}$ and $\pm 5 \mu\text{m}$ respectively could be introduced to the ground truth by the printer. The mosaic results are presented in Figure 25b. The lines and width of the grid pattern are measured using the mosaic images to validate the visual servoing algorithm, as can be seen in Table 1. A total of 22 sample measurements are made on each image, recording the line thicknesses and the square widths. It should be mentioned that the measurements are performed manually, leading to minor segmentation errors for the distance calculation. However, these errors are not comparable to the overall FoV of the scanning device and therefore do not affect the final result. Despite the high accuracy of the instrument, the open loop performance is not perfect in terms of the grid visualisation, even in the situation that the surface is non-deforming. This can be explained by various mechanical imperfections and especially by the fact that the orientation of the instrument

cannot be exactly perpendicular to the scanning surface, leading to a minor drift in one direction.

Units: μm	Ground Truth	With Visual Servoing	Open Loop
Line Thickness	73 ± 6	69 ± 3	70 ± 3
Square width	237 ± 4	235 ± 10	236 ± 13

Table 1: Comparison between the bench-top measurements and the generated mosaics with and without visual servoing.

However, a significant difference in terms of open loop and closed loop control is observed when unexpected motions and deformations appear. In order to demonstrate and evaluate this, the rigid scanner was clamped and commanded to perform spiral scans on a moving surface. Initially, lens tissue paper stained with the topical fluorescent contrast agent acriflavine was placed on top of a motorised translation stage that was commanded to move in a random motion along both the x-axis and the y-axis within a range of $\pm 100 \mu m$ with velocity of 1 mm/s.

As can be seen in Figure 26, the spiral pattern cannot be formed in the open loop approach. This is evident in the position graph on the right-hand side which shows that the mosaic trajectory, which is approximately the real trajectory followed by the probe (allowing for any small deformations), deviates significantly from the commanded trajectory (whereas it would ideally coincide). Conversely, with the visual servoing algorithm, the effects of the motion are almost eliminated as the mosaic trajectory follows the desired spiral trajectory. Note that the control trajectory, which consists of the real output signals provided to the instrument, in the visual servoing result does not follow any specific model, demonstrating the importance of the model-free PID approach. A random motion such as an external disturbance when the probe is scanning a spiral over the grid pattern is presented in Figure 27. Further ex vivo results on lens paper and colonic tissue (also stained with acriflavine) are depicted in Figure 28. It is important to mention here that the colonic tissue results show not only the suppression of the external motion but also compensation for tissue deformation.

This, as a result, tends to increase the effective FoV for deformable surfaces, as can be seen in Figure 29 where the diameter of the area covered with visual servoing is 1.1 mm, whereas without it is 0.94 mm.

Mosaicking Results

The performance of the robotic scanning instrument was further assessed with ex vivo tissue experiments (see Figure 30). Human breast tissues (normal and tumour) were scanned with the instrument while clamped. Clamping was used as handheld operation introduced motion artefacts due to hand motions, creating issues with large area mosaicking. The primary goal of these experiments was to scan, with high-speed, specific areas of interest to assess their histological features. Therefore, tissue areas of approximately 1 mm (Figure 30a, e, f) and 1.7 mm (Figure 30b-d) outer diameter were covered in 13 and 8 seconds respectively. The time difference here is because a slower speed was selected in the scan in Figure 30a-c. Additional experiments on porcine colonic tissue were performed to assess the performance of the instrument on other types of tissue (Figure 30e-f).

The mosaics presented illustrate the performance of the instrument while rigidly clamped in order to demonstrate the enhanced scanning capabilities of the proposed work. This is the main reason that a robotic arm with cooperative-control function is included in this system. The operator can manipulate the arm in a hands-on manner, place it in the desired position and then press the button to scan the area under investigation. On the other hand, the operator has the option to unmount the instrument from the robotic arm and operate it in a handheld manner. Exemplar mosaicking results comparing use of the instrument handheld and clamped in the robotic arm are demonstrated in Figure 31. High resolution microscopic scanning of lens paper areas of 2 mm and 4.1 mm diameter is shown.

As mentioned before, the instrument features a tubular channel that different fibre-based optical imaging probes can be inserted into. To demonstrate use of the instrument with other endomicroscopes, an in-house dual wavelength slit scanning confocal system and an endocytoscopy system were tested. Exemplar ex vivo mosaic results for each system are presented in Figure 5.18. The human breast tissue scanned with the endocytoscopy system is stained topically with the contrast agent methylene blue. The lens paper mosaic using the dual-wavelength system was acquired by staining locally one part of the paper with the contrast agent acriflavine and the remaining part with methylene blue. Scanning was performed over the edge between the two parts in order to visualise both contrast agents and hence mosaicking of two wavelengths.

Energy Delivery Results

Finally, for the first time in robotic-assisted endomicroscopy, preliminary results showing how a fibred CO₂ laser ablation system can be integrated into the scanning device are presented. The concept for the use of a laser ablation system is that the operator can assess the tissue microscopically and, if cancer cells are identified or tumour margins, then, with the laser, can mark or cauterise the examined area in real-time. The laser was used in "Super Pulse" mode (single pulse, power 3 W and duration 40 ms) in order to deliver a small precise mark on the target. The laser fibre is inserted through the same channel as the microscopy fibre bundle and is separated by a small horizontal mechanical offset at the tip of the instrument (see Figure 33a-c). Also, at the tip of the instrument, the laser fibre is fixed in a vertical offset of 1 – 2 mm from the tip of the microscopy probe due to its working range (see Figure 33b). Since the two fibres are laterally offset, in order to be able to ablate at the centre of the microscopy mosaic, an offset is applied to the probe's position during CO₂ laser firing. Determining this offset requires that the mechanical offset should be accurately measured (see Figure 33c). For this, the custom tracking rig is used and the two fibres are tracked in real-time. Since using the CO₂ laser would damage the camera, this is replaced with a multi-mode fibre coupled to a first LED for the purpose of the calibration. The horizontal offset is found in the voltage space by commanding the tip to move so that the first circle 331 (CO₂ fibre) coincides with the initial position of the second circle 332 (microscopy fibre) (see Figure 33d).

To validate the previous approach, a laser pulse is shot at the centre of an area that has been mosaicked using a spiral pattern and then it is mosaicked again. Figure 33(e) shows the area before and after the ablation. The laser mark, as expected, is at the centre of the mosaic. The same process is followed using the grid pattern, described in relation to Figure 25, in Figure 34. The laser delivered a very short pulse, ablating an area of 104 µm in diameter with minimal thermal damage (< 50 µm radially), as can be seen in the bench-top microscope's image. Here, also, the real-time mosaicking does not provide as accurate pairwise registration as previous mosaicking examples due to the very small correlation of the images in the ablated area. However, the results demonstrate the potential for the combination of microscopy with a laser ablation fibre in the same reference frame to assist with intraoperative tumour marking and ablation.

Other embodiments are intentionally within the scope of the accompanying claims.

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CLAIMS

1. A micromanipulation apparatus comprising:
an outer tube defining a longitudinal z-axis of the apparatus; and
5 an inner tube, at least partially disposed within the outer tube, and having a continuous working channel extending therethrough, the inner tube further including an endoscopy probe extending therethrough;
a steering mechanism configured to controllably vary the lateral x, y position of a
distal end of the inner tube, relative to the device z-axis; and
10 an ablation energy delivery device extending through the apparatus along the z-axis.
2. The micromanipulation apparatus of claim 1 in which the ablation energy delivery device further comprises at least one ablation electrode at the distal end of the inner or
15 the outer tube.
3. The micromanipulation apparatus of claim 1 in which the ablation energy delivery device comprises:
an optical fibre for transmission of optical energy to the distal end of the inner tube;
20 or
at least one electrical conductor passing through the inner tube and coupled to at least one electrode at the distal end of the inner tube.
4. The micromanipulation apparatus of claim 2 or claim 3 in which the ablation
25 electrode is retractable.
5. The micromanipulation apparatus of claim 1 further including a contrast agent delivery mechanism configured to deliver contrast agent to the distal end of the inner tube via the continuous working channel of the inner tube or via a lumen of the outer tube.
30
6. The micromanipulation apparatus of claim 1 in which the endoscopy probe comprises an imaging fibre extending through the working channel of the inner tube.
7. The micromanipulation apparatus of claim 1 wherein:

the inner tube is coupled to the outer tube at a first longitudinal position to form a cantilever extending to the distal end of the inner tube, and

the steering mechanism comprises a deflection device positioned within the outer tube at an intermediate position between the first longitudinal position and the distal end of the inner tube, the deflection device configured to deflect the cantilevered inner tube laterally within the outer tube so as to adjust the x, y position of the distal end of the inner tube relative to the device z-axis.

8. The micromanipulation apparatus of claim 7 in which the deflection device comprises a pair of electrically-actuated rotatable cam surfaces configured to bear against two non-parallel bearing surfaces of the inner tube to effect motion of the inner tube in selected directions lateral to the device z-axis.

9. The micromanipulation apparatus of claim 8 in which the two bearing surfaces of the inner tube comprise oblique two surfaces of a V-section component coupled to the inner tube.

10. The micromanipulation apparatus of claim 7 in which the first longitudinal position at which the inner tube is coupled to the outer tube comprises an anchorage point laterally offset from the device z-axis to provide a bias from the device z-axis.

11. The micromanipulation apparatus of claim 8 in which the pair of cam surfaces comprise a pair of driving elements each surrounding the inner tube.

12. The micromanipulation apparatus of claim 6 in which a part of the inner tube adjacent to the first longitudinal position is profiled for a localised reduction in inner tube stiffness adjacent to the first longitudinal position.

13. The micromanipulation apparatus of claim 1 in which the steering mechanism is further configured to controllably vary the longitudinal z-position of the distal end of the inner tube relative to the outer tube.

14. The micromanipulation apparatus of claim 1 in which the steering mechanism is configured to control the longitudinal z-position of the inner tube relative to the outer tube

to apply a pre-programmed axial force by the distal end of the inner tube on a specimen under examination.

15. The micromanipulation apparatus of claim 1 further including:
- 5 an image processor configured to analyse images from the imaging fibre; and
a controller configured to optically determine magnitudes of displacements of the distal end of the inner tube based on said analysed images.
16. The micromanipulation apparatus of claim 15 in which the controller is configured
- 10 to use said optically determined displacement magnitudes as feedback to the steering mechanism.

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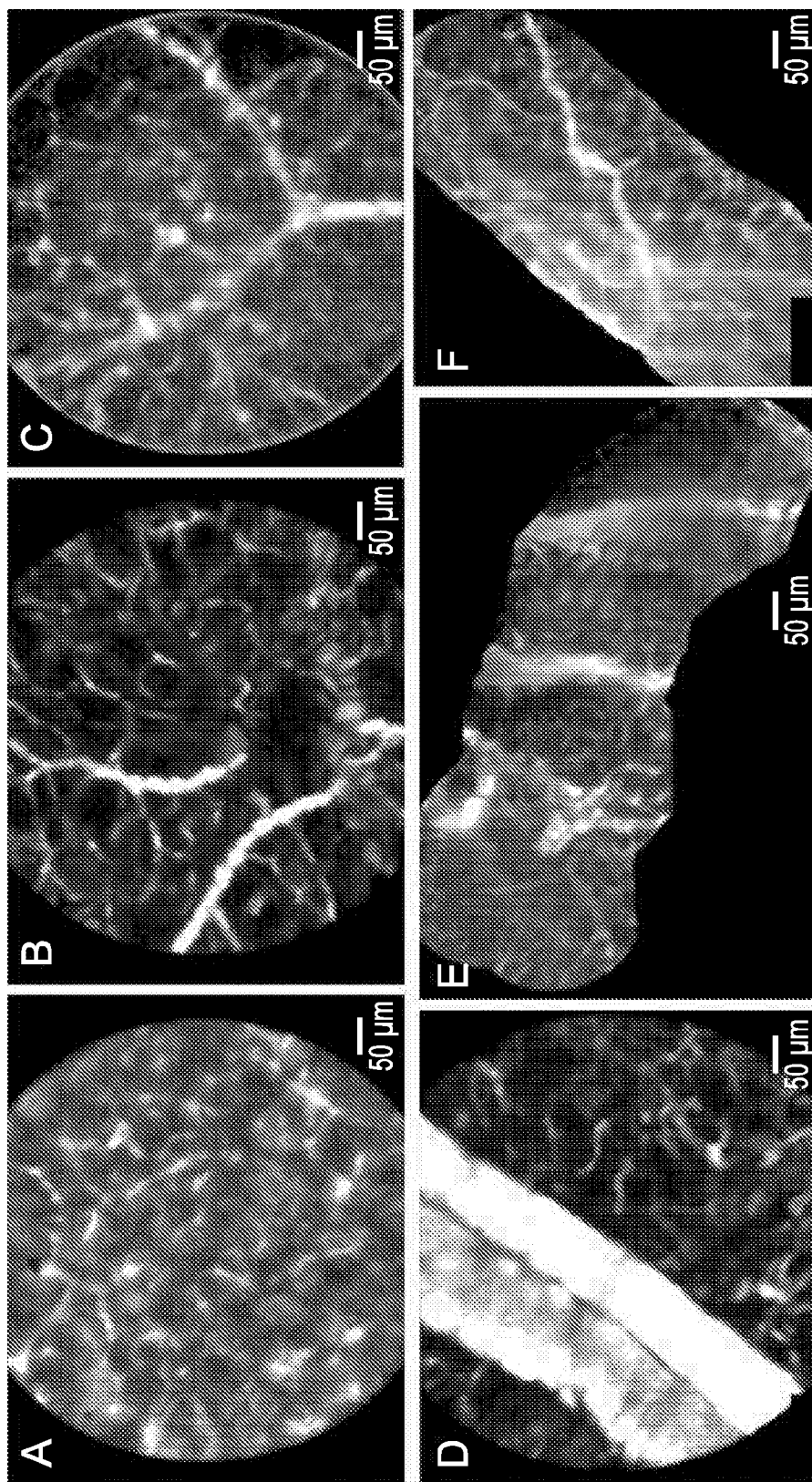


FIG. 1

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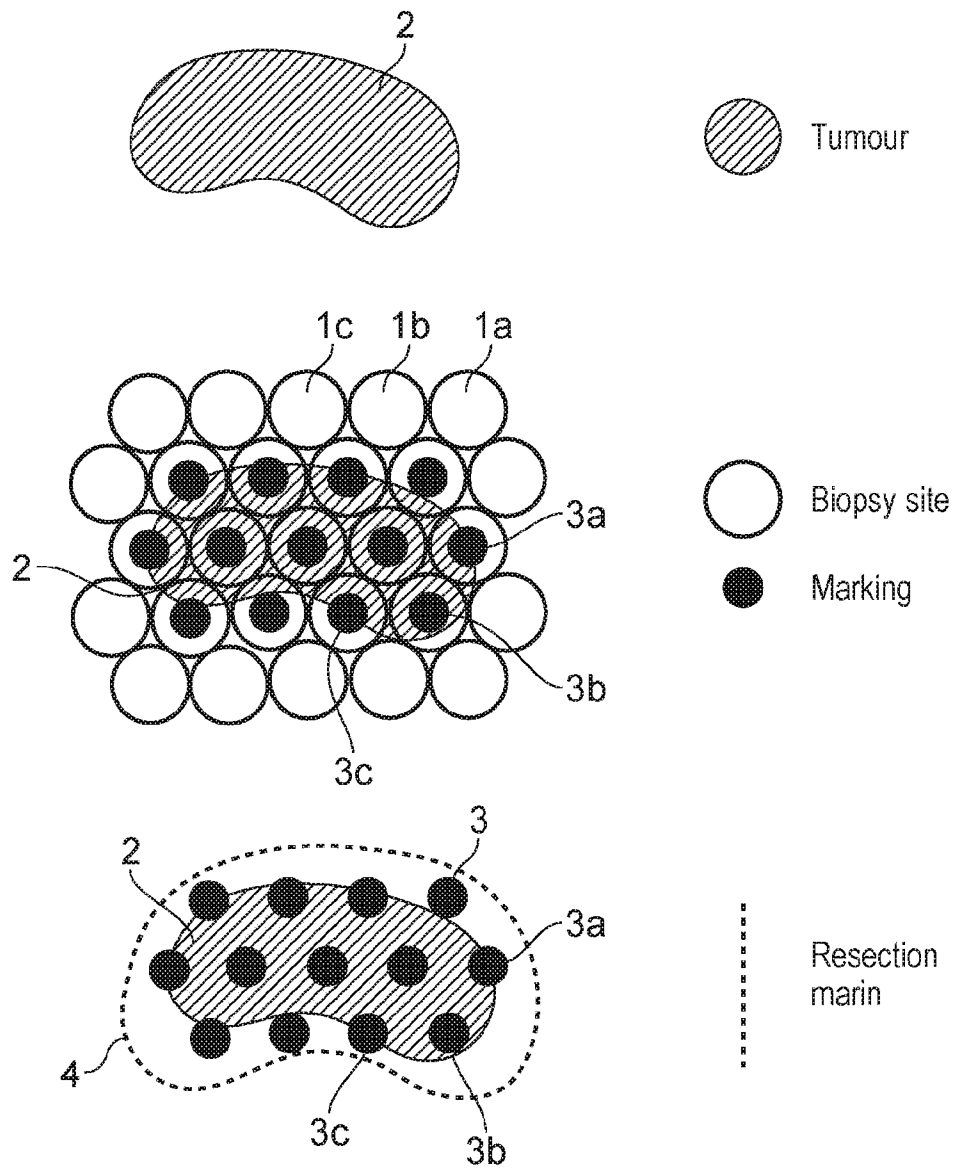


FIG. 2

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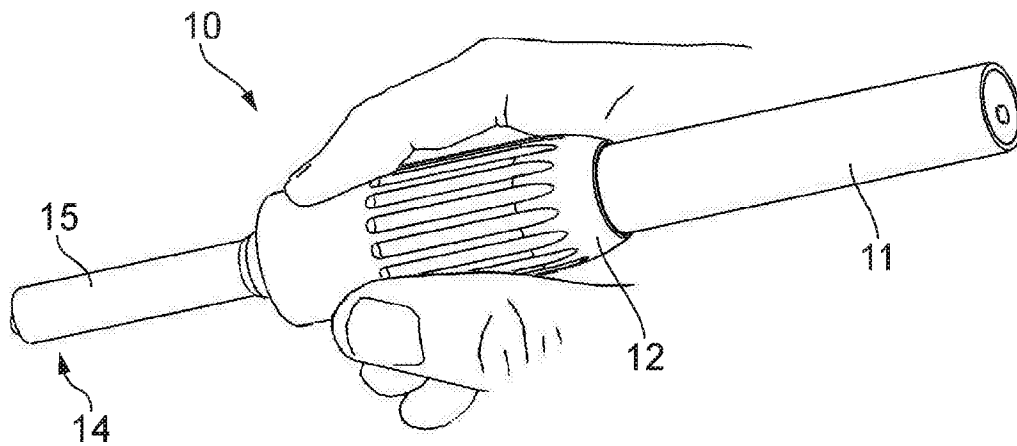


FIG. 3

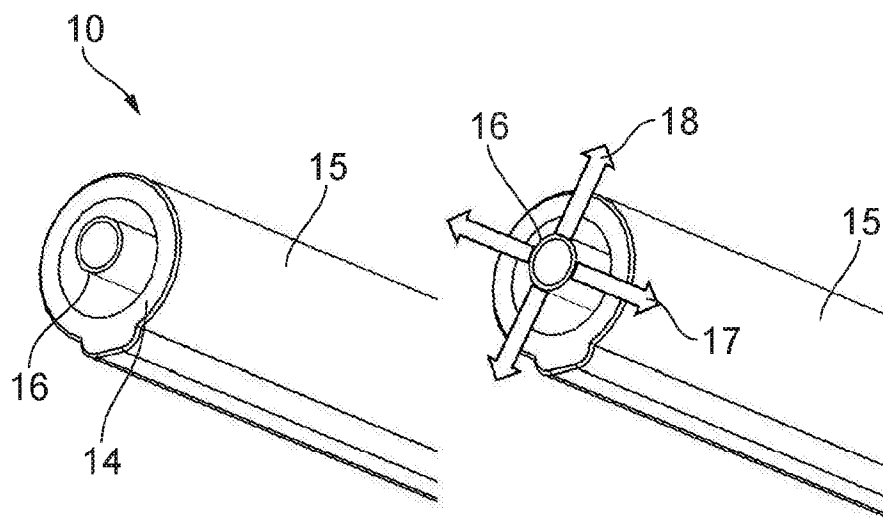


FIG. 4

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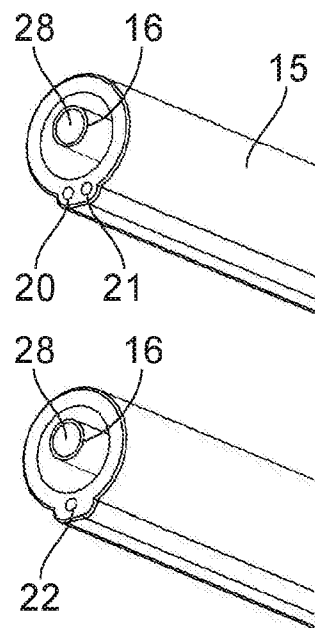


FIG. 5

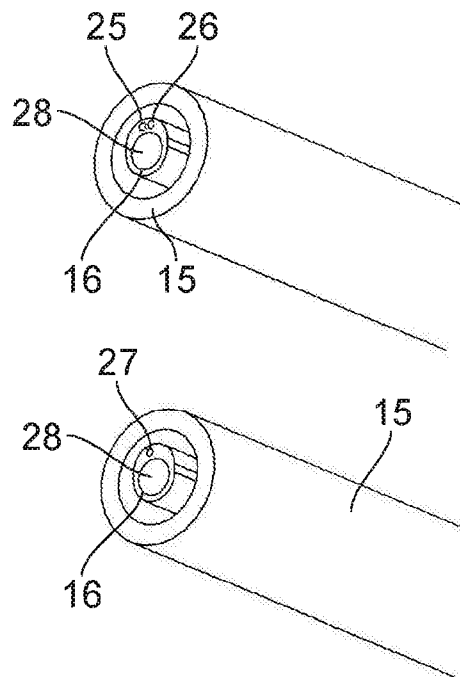


FIG. 6

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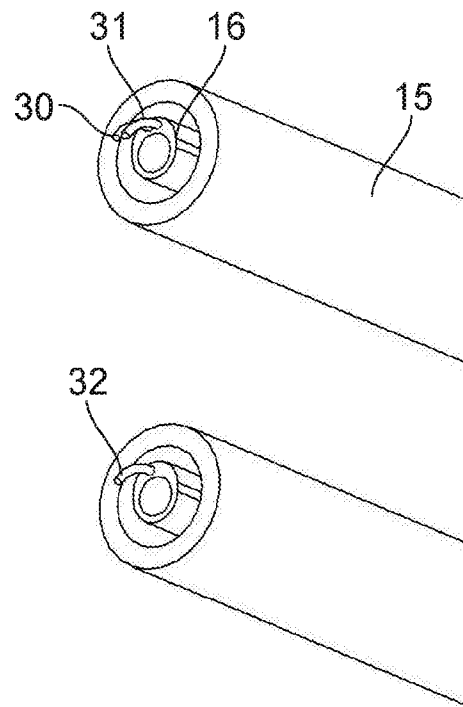


FIG. 7

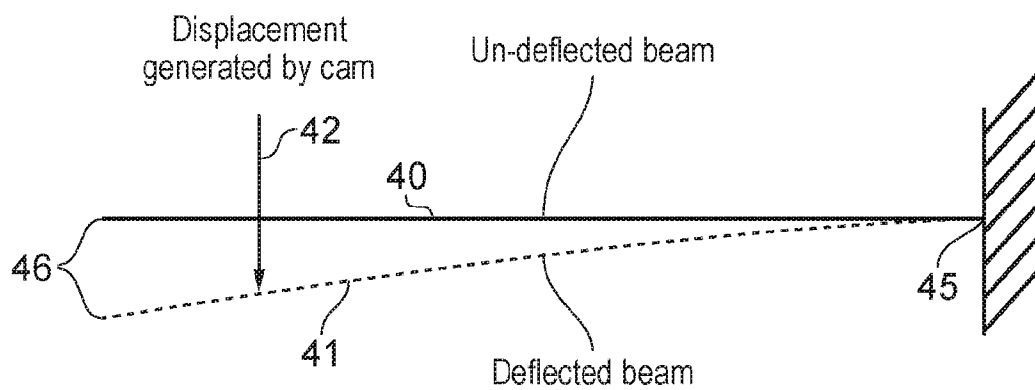


FIG. 8

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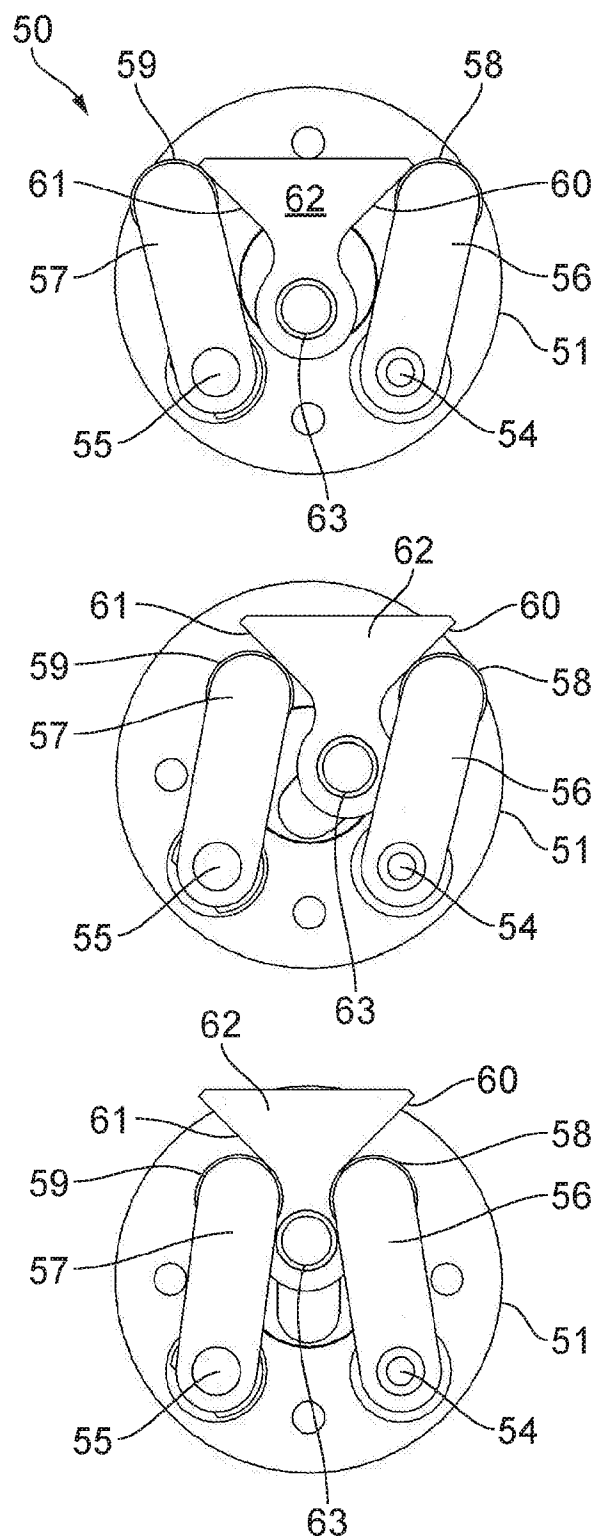


FIG. 9

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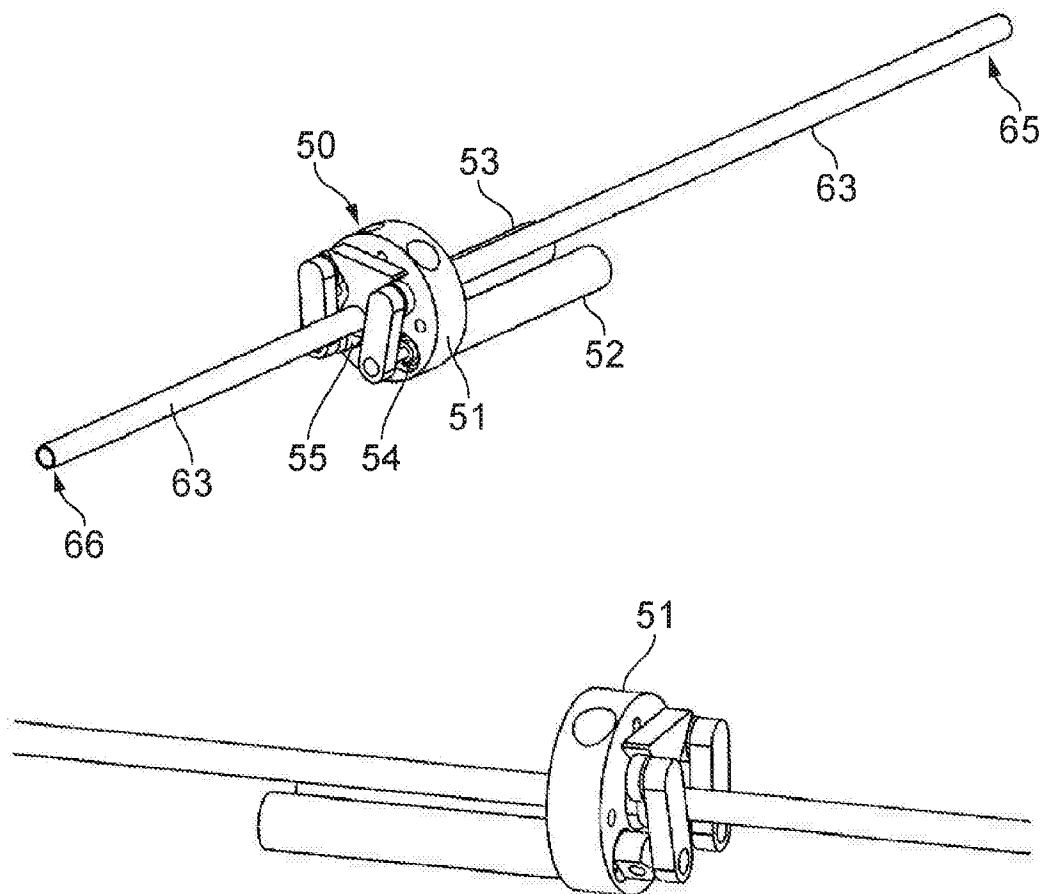


FIG. 10

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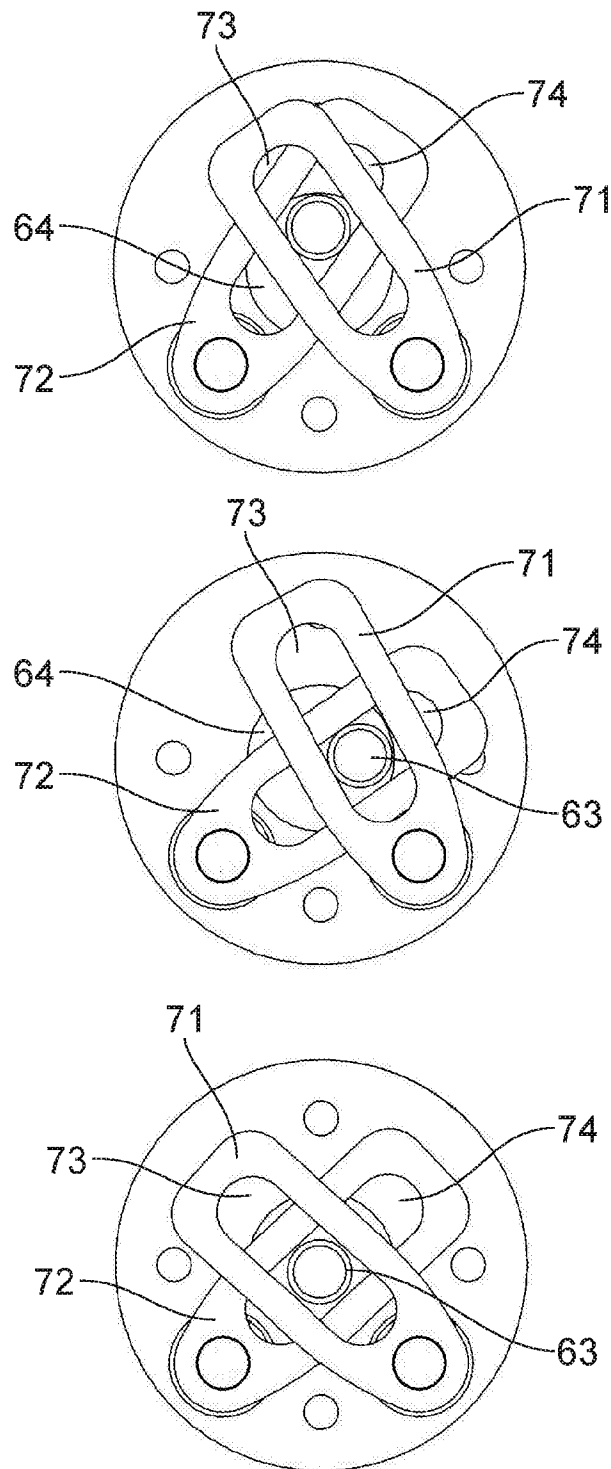


FIG. 11

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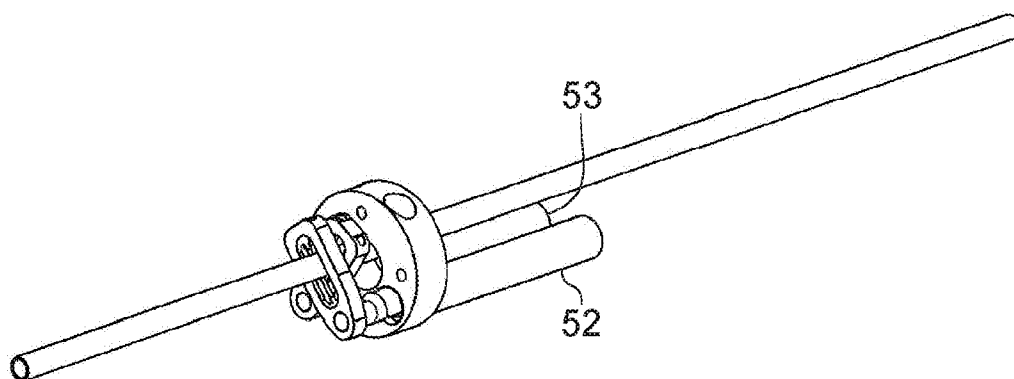


FIG. 12

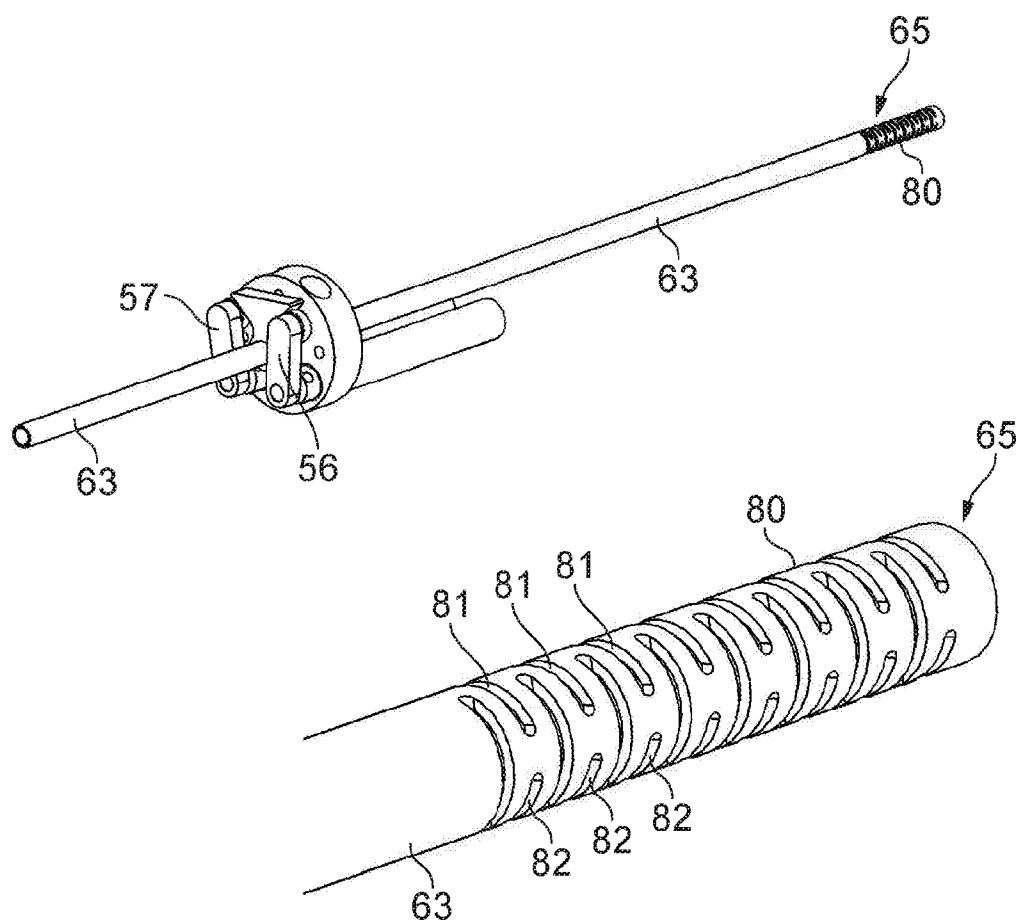


FIG. 13

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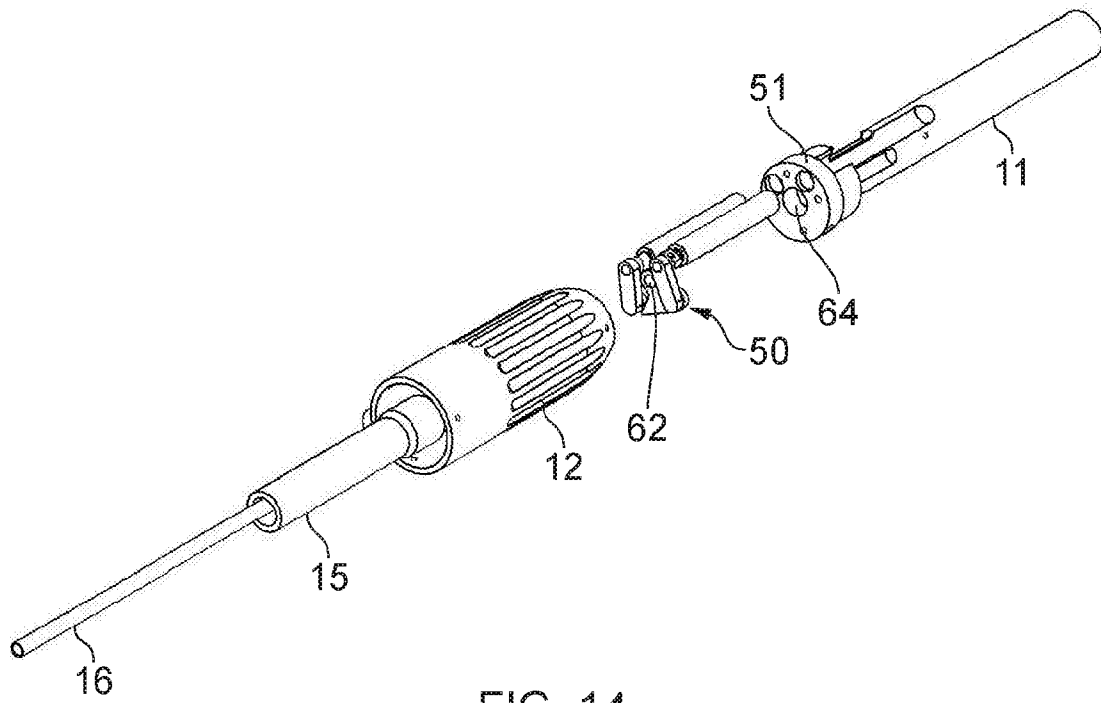


FIG. 14

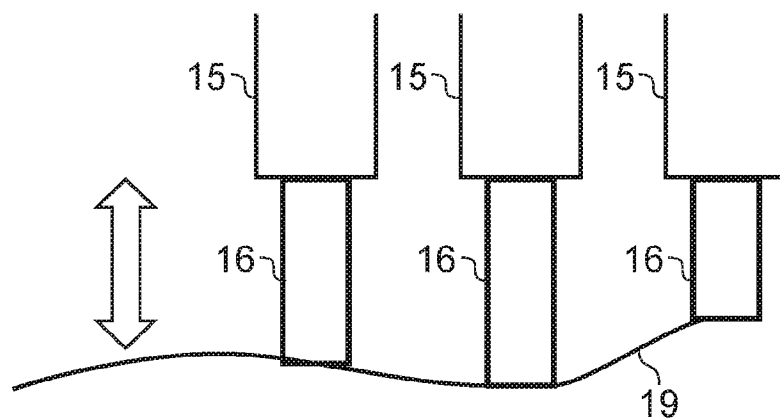


FIG. 15

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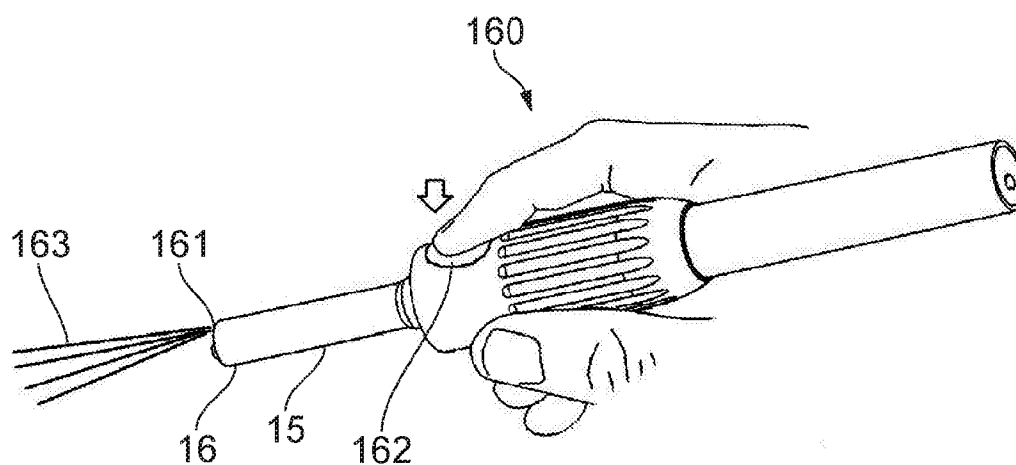


FIG. 16

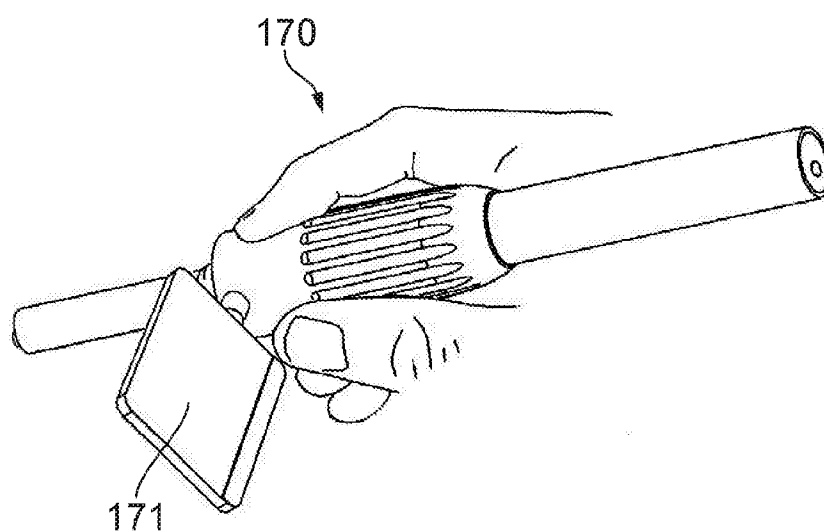


FIG. 17

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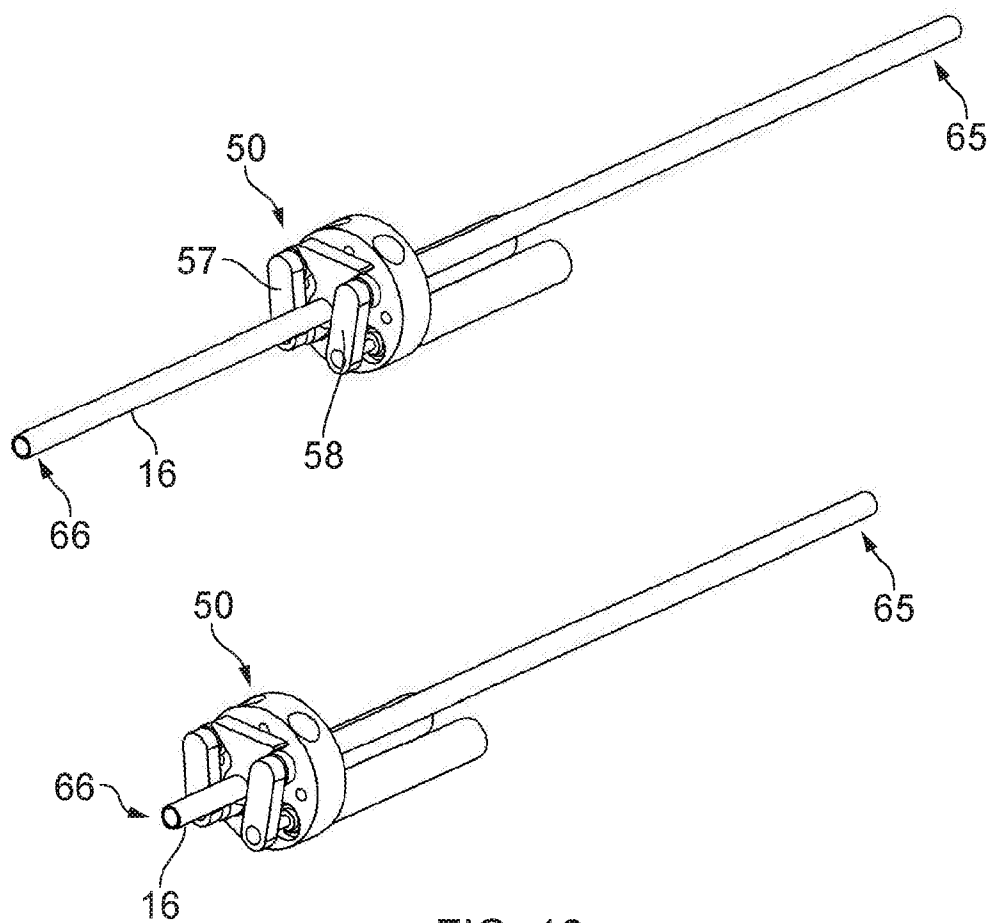


FIG. 18

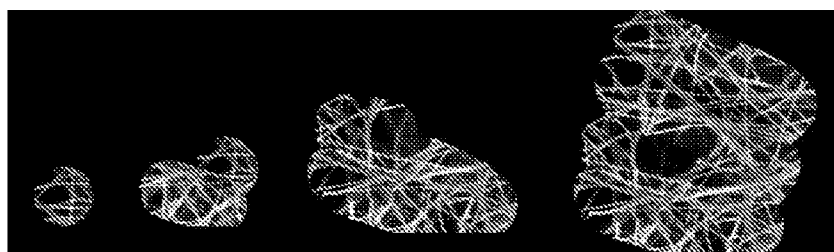


FIG. 19

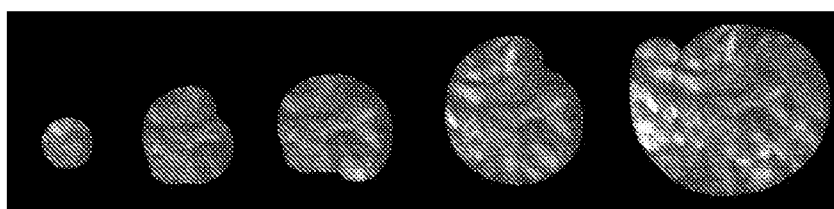


FIG. 20

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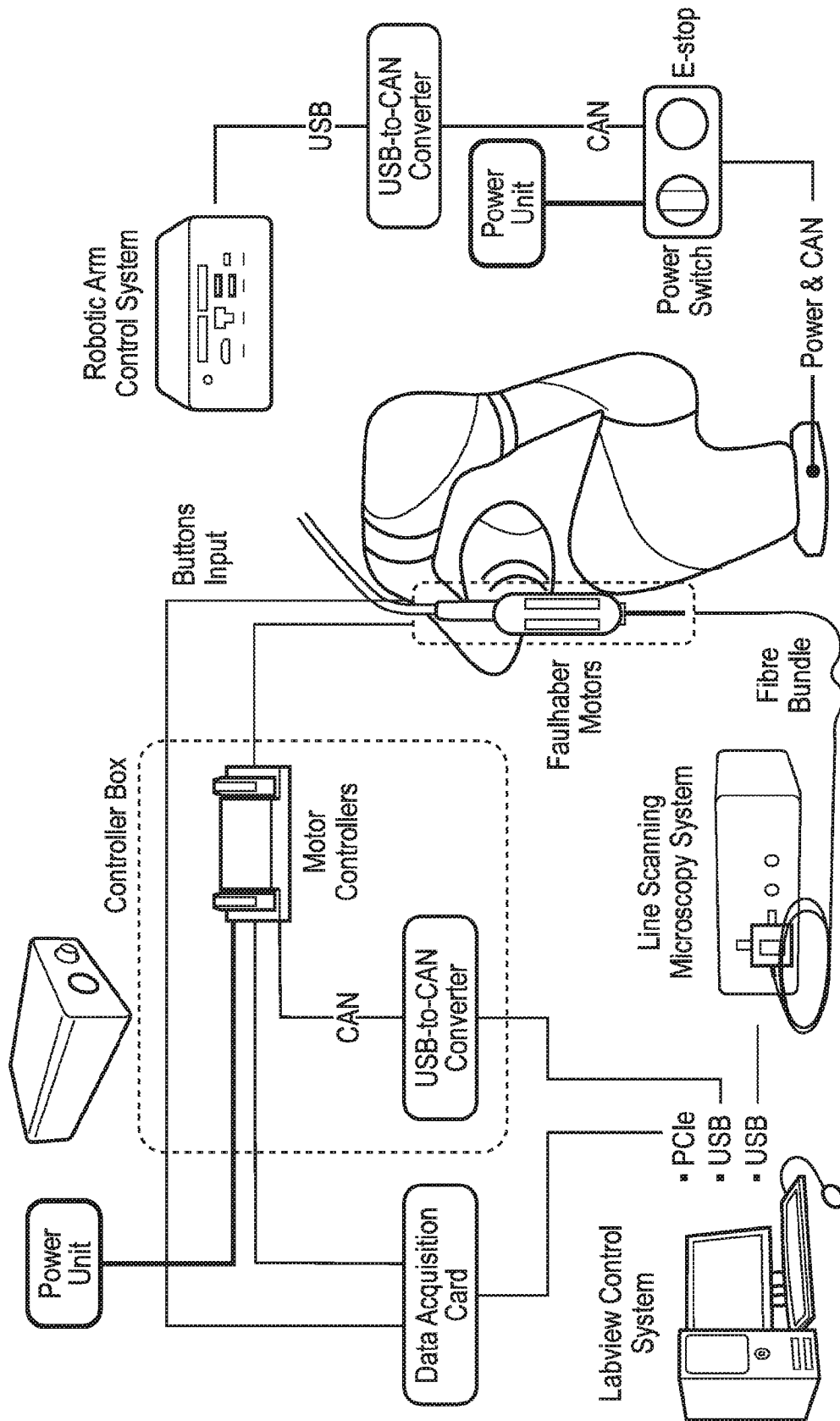


FIG. 21

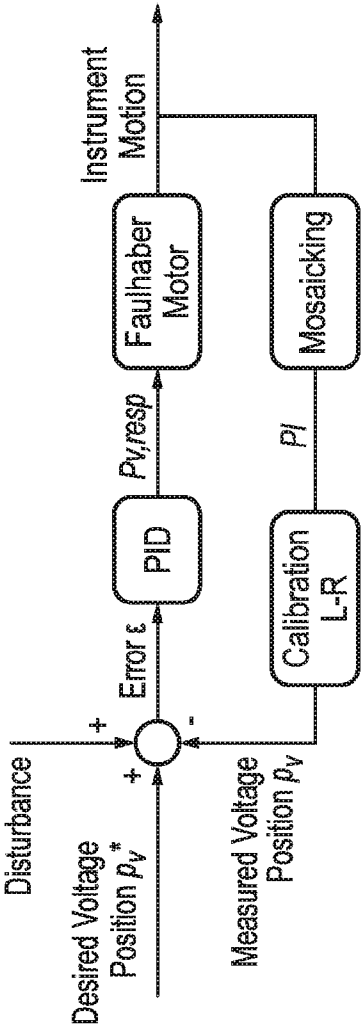


FIG. 22

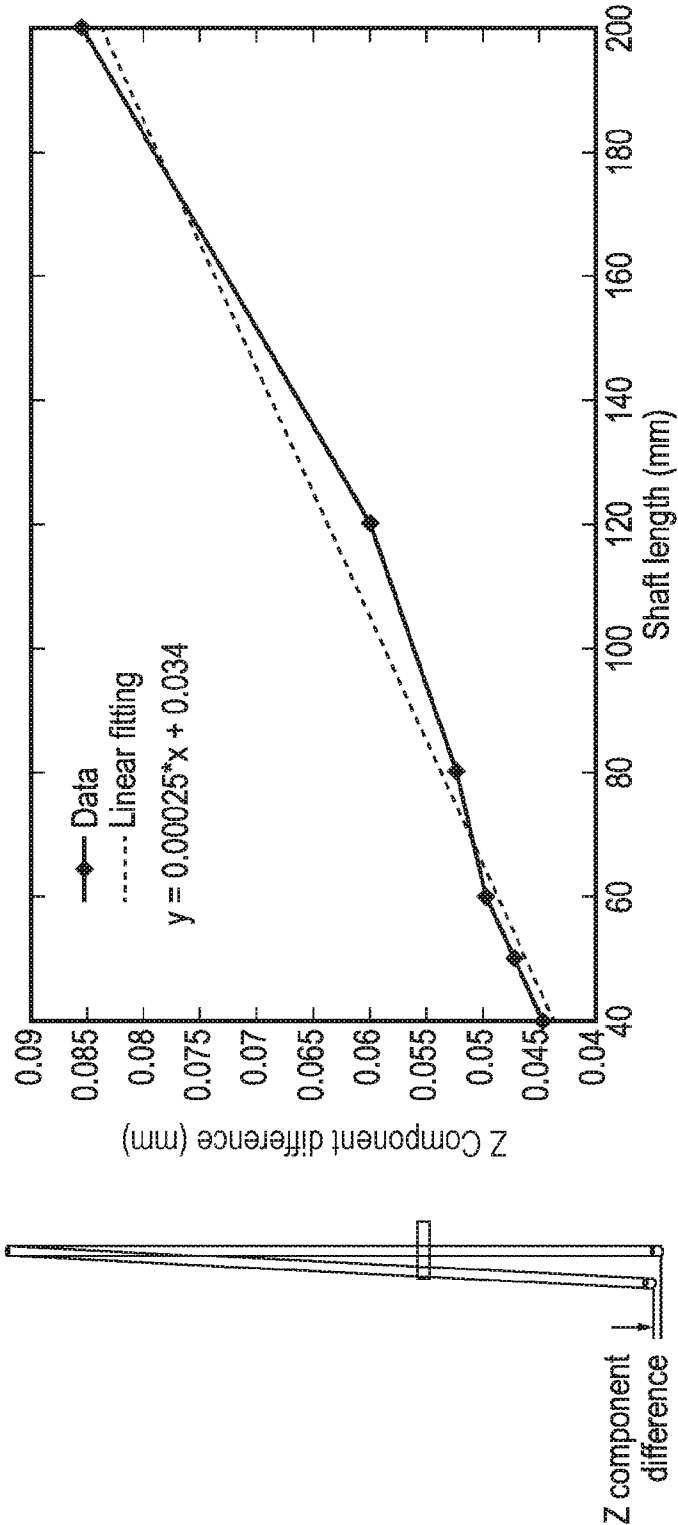


FIG. 23

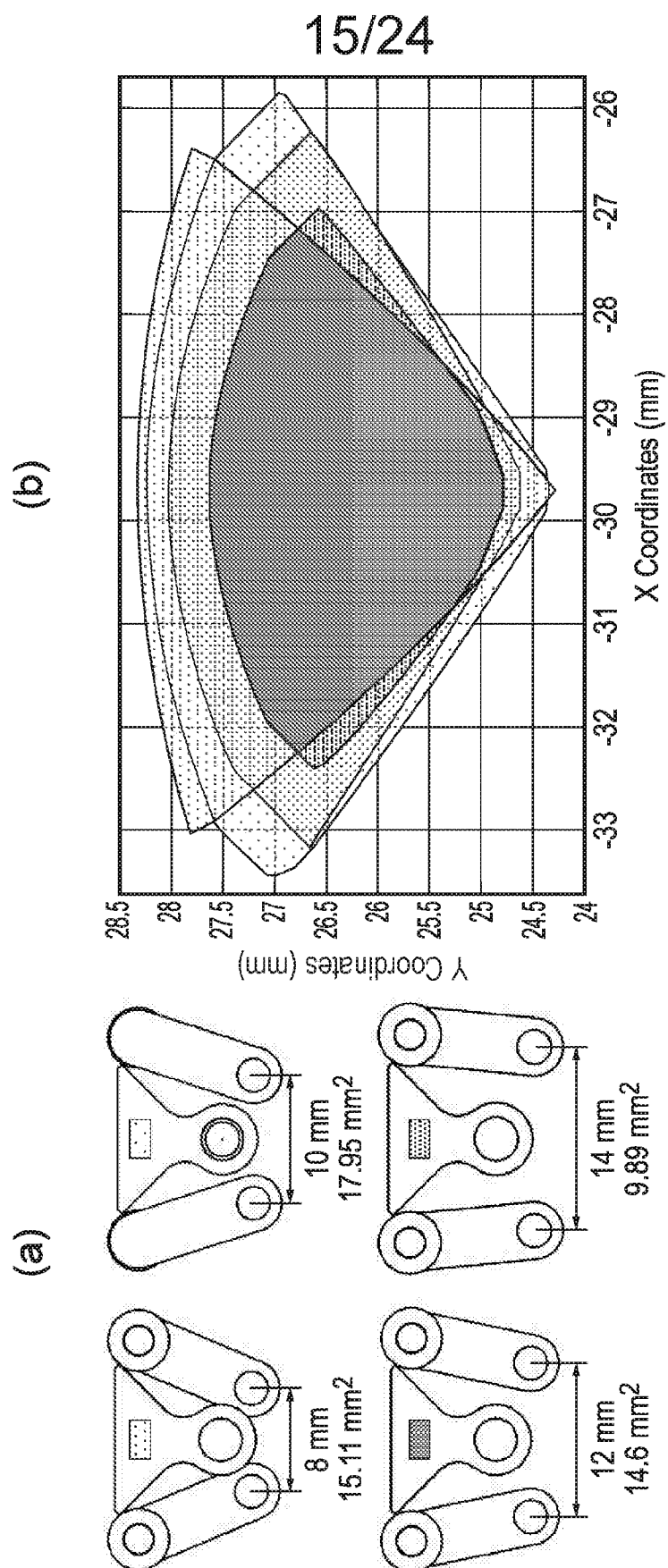


FIG. 24

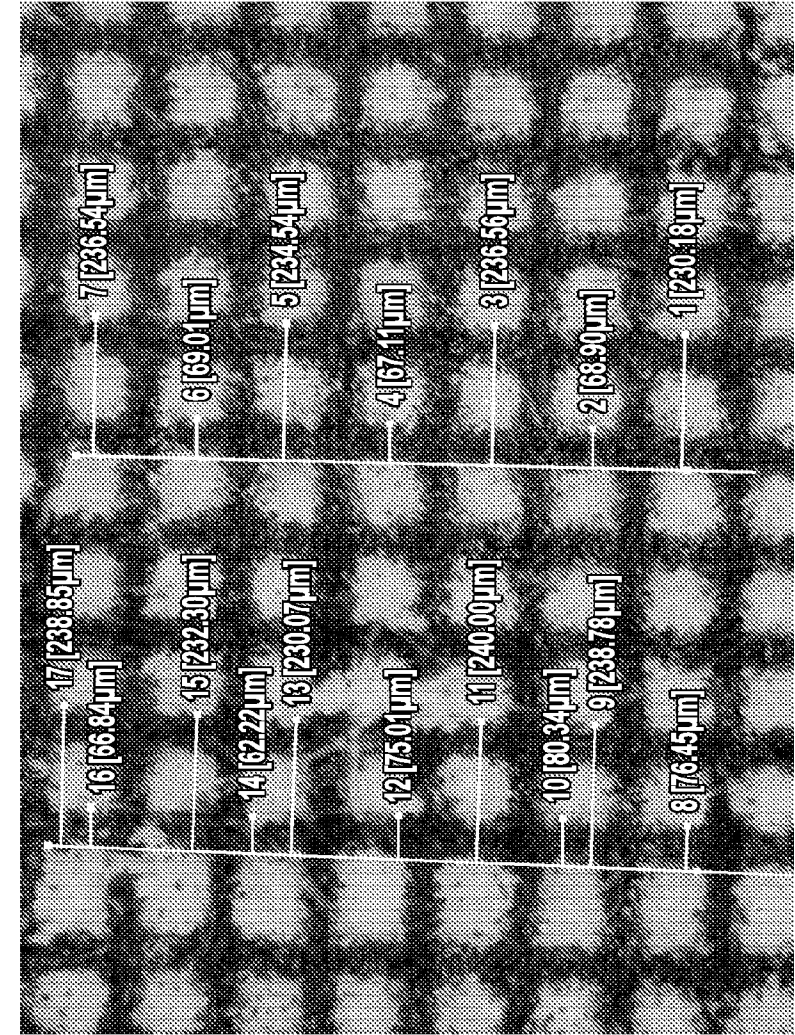
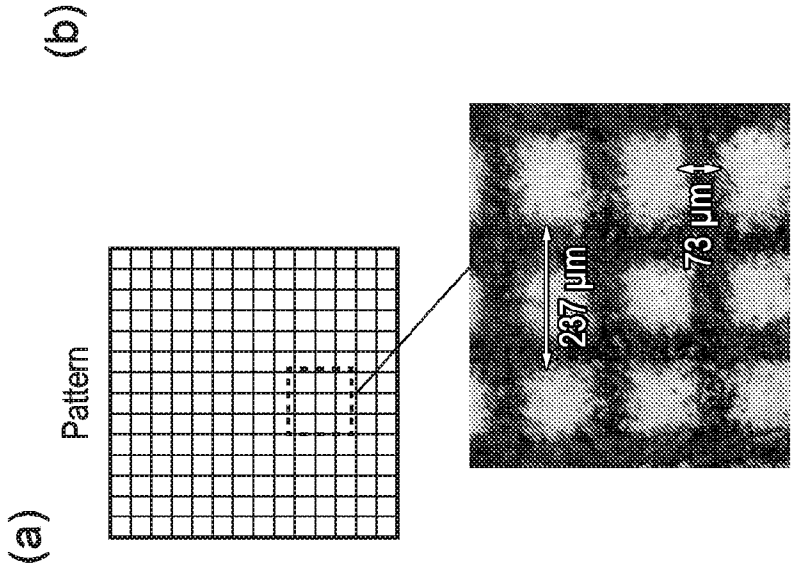
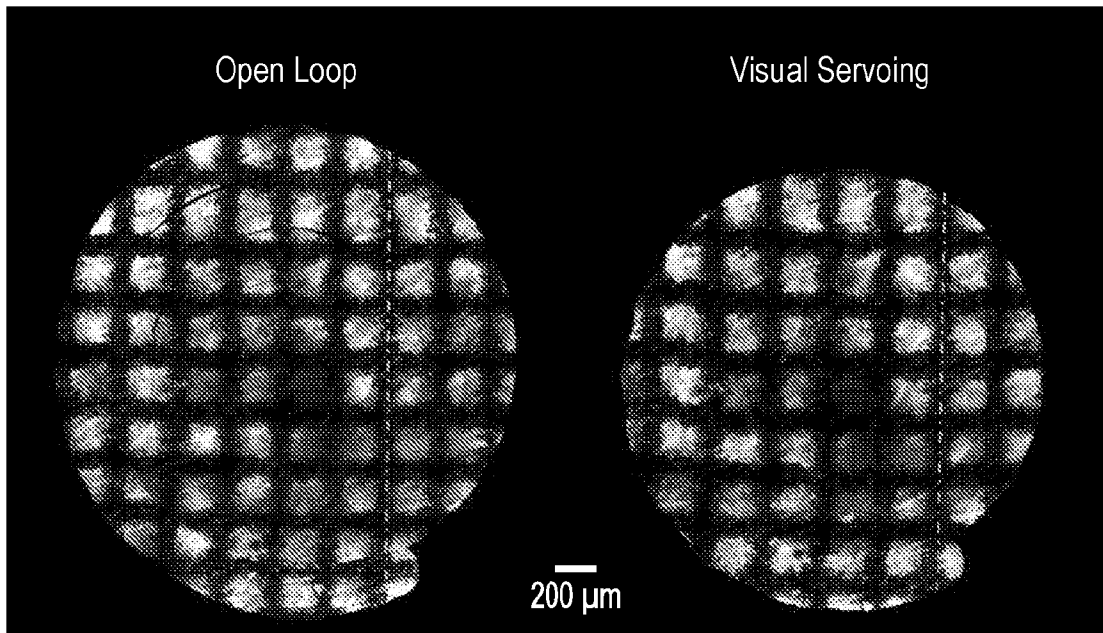


FIG. 25



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(b)



(c)

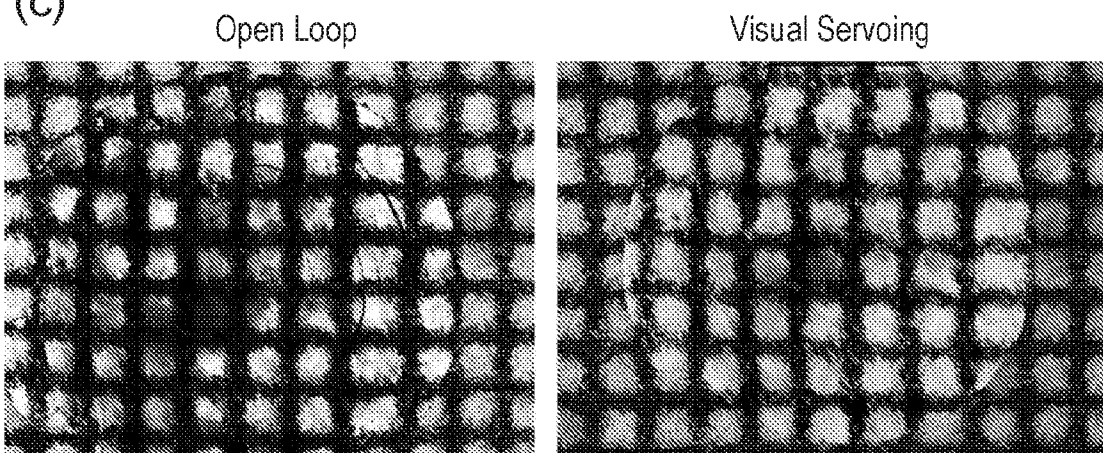


FIG. 25 (Continued)

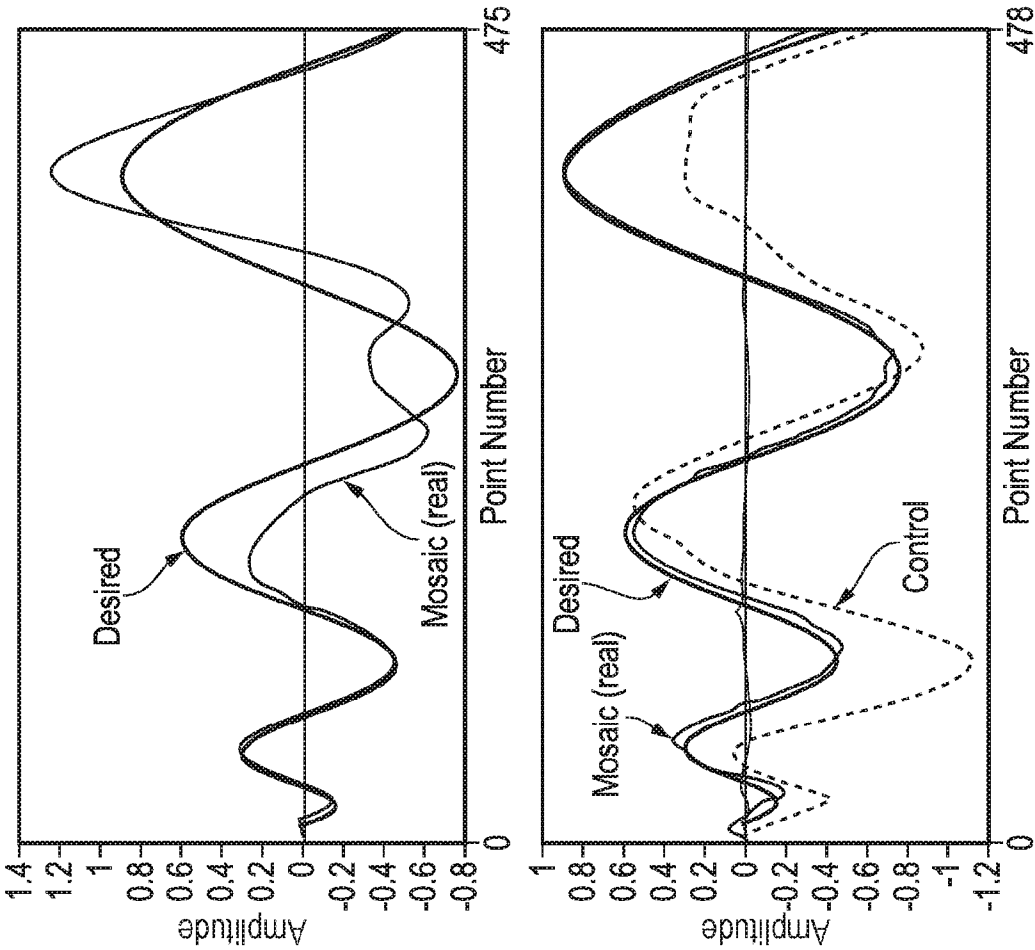
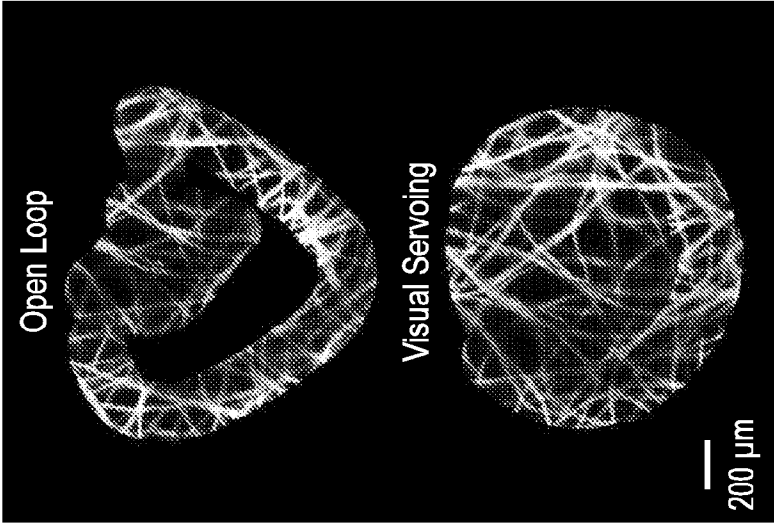


FIG. 26



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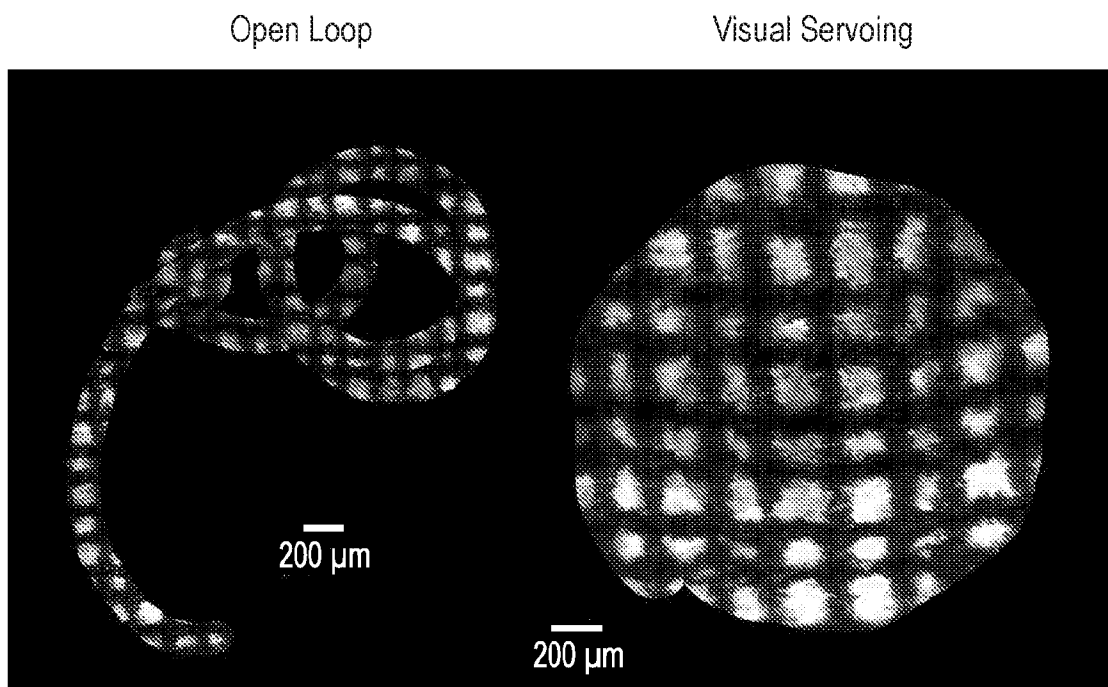


FIG. 27

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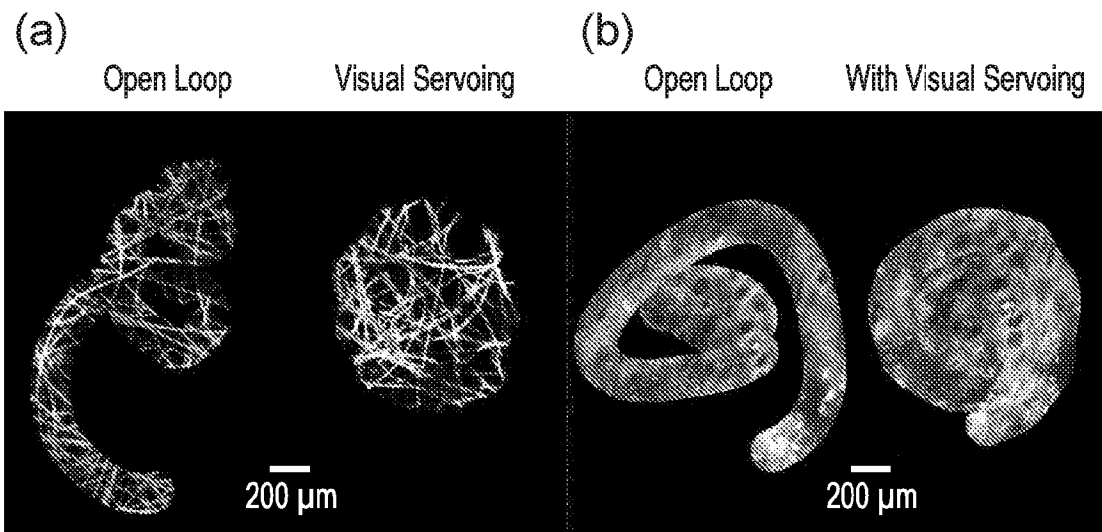


FIG. 28

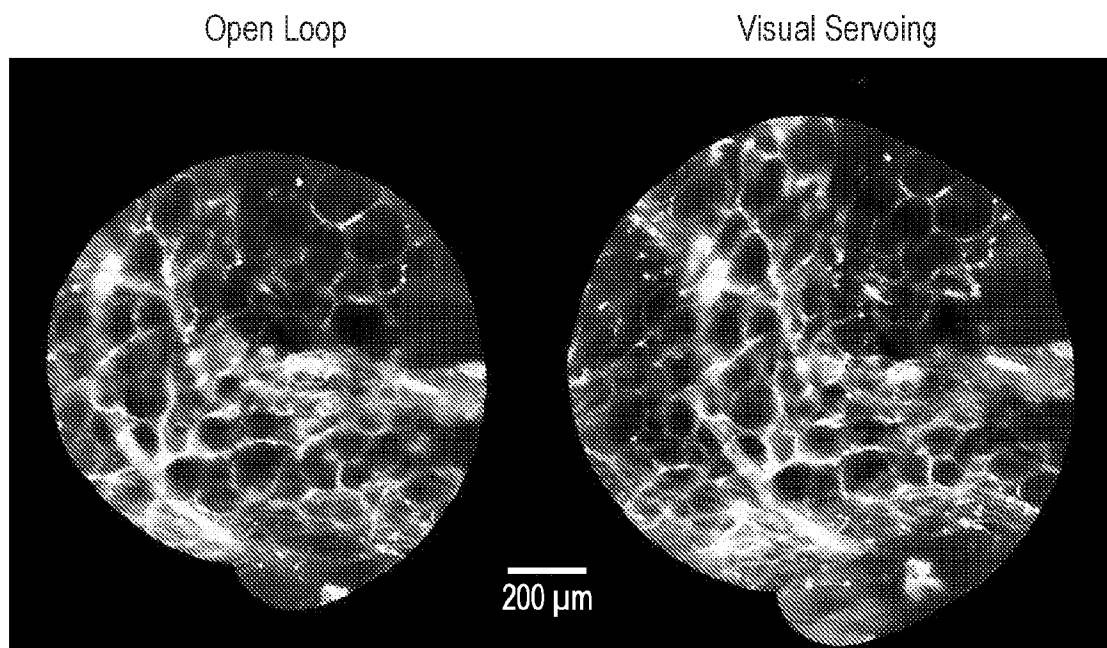


FIG. 29

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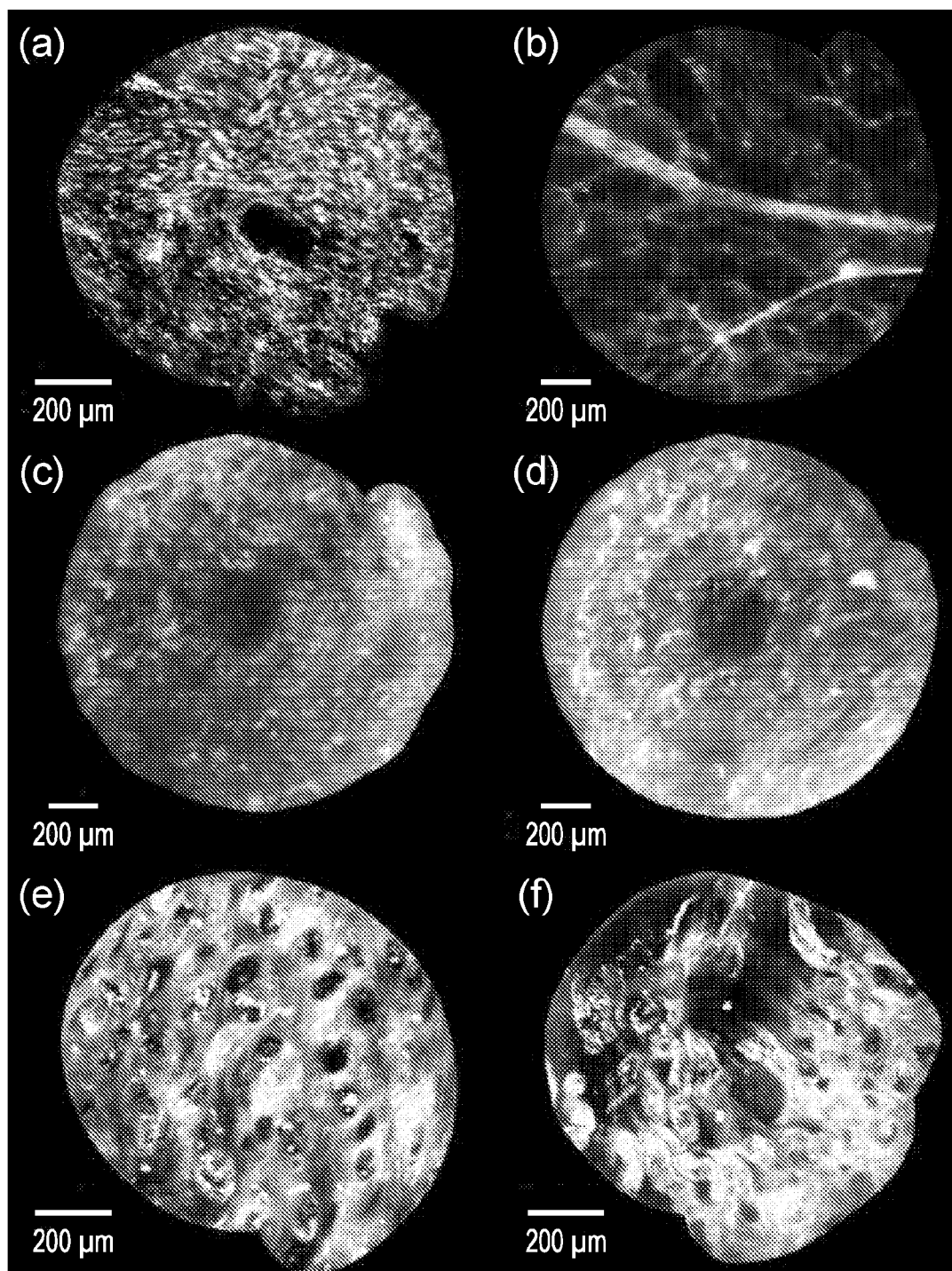


FIG. 30

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Handheld Operation

Clamped Operation

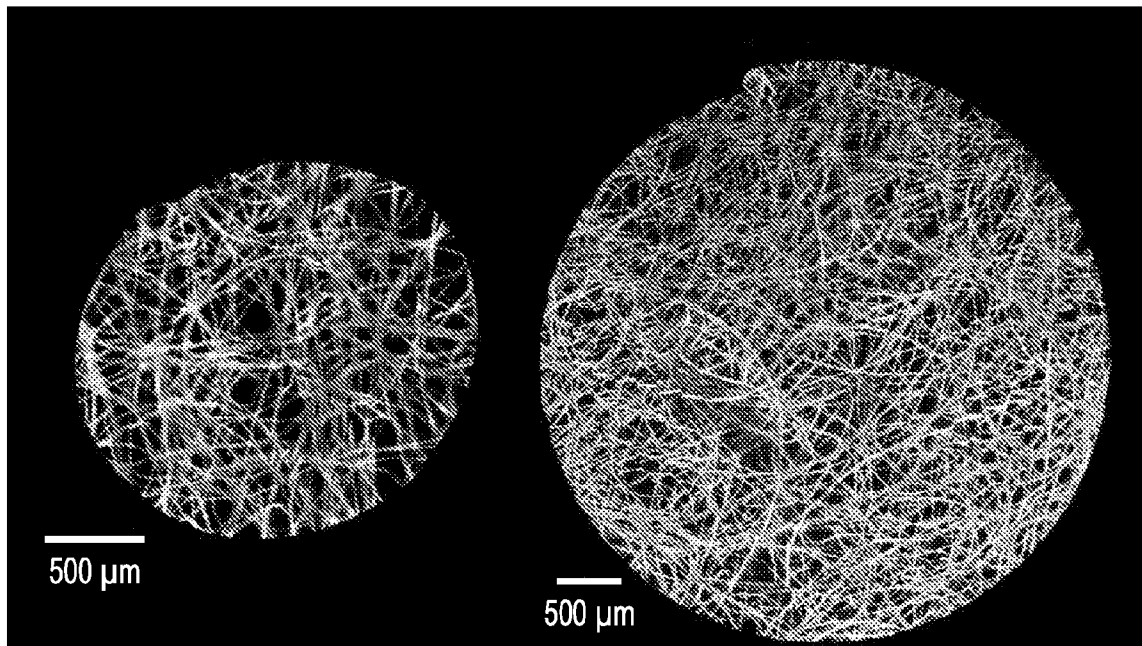


FIG. 31

Endocytoscopy

Dual-Wavelength Confocal Microscopy

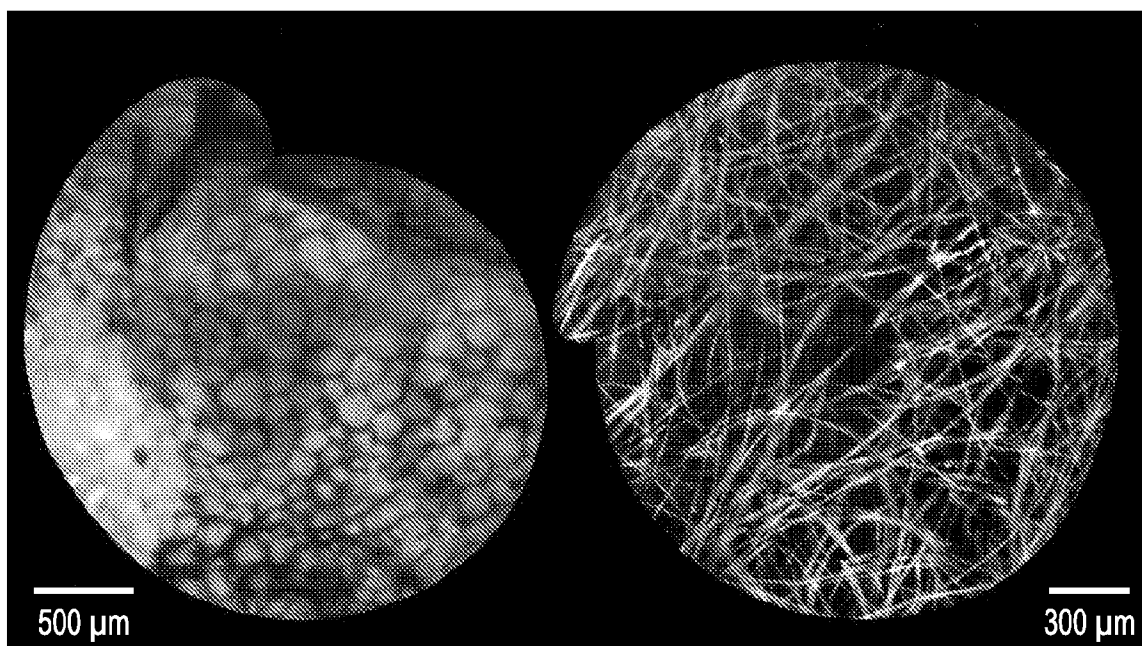


FIG. 32

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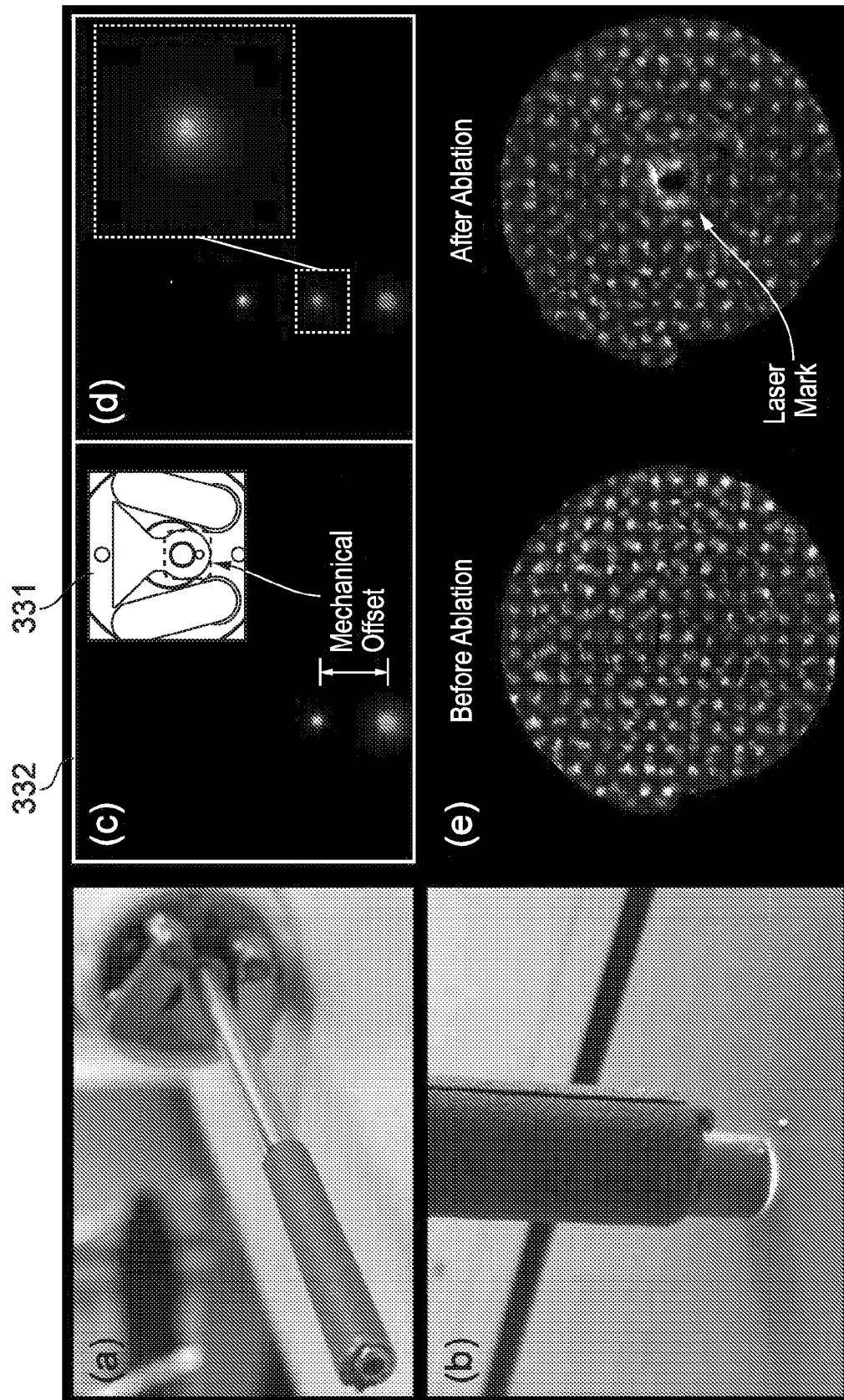


FIG. 33

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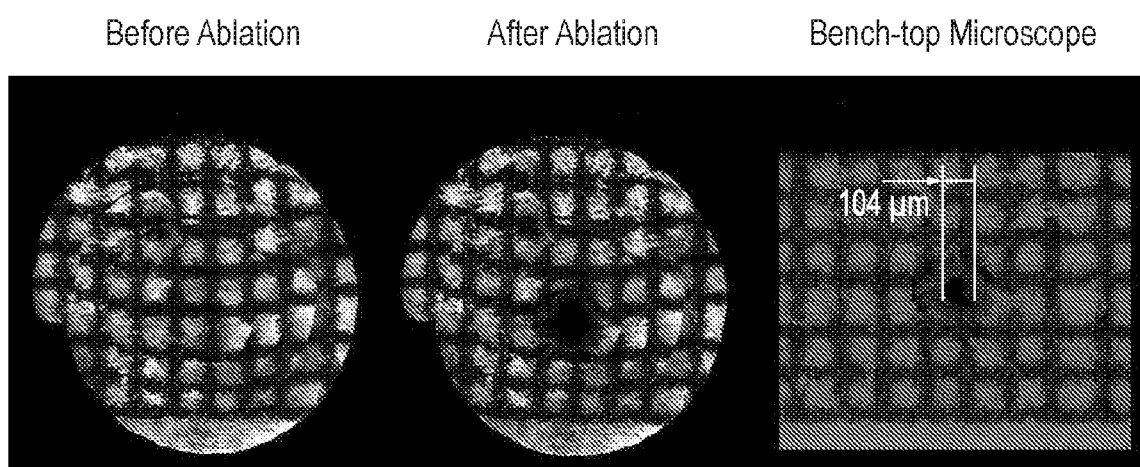


FIG. 34

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/051086

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61B18/14 A61B18/22 A61B90/00 A61B1/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/143640 A1 (SAADAT VAHID [US] ET AL) 4 June 2009 (2009-06-04)	1-6, 13
A	paragraph [0062] - paragraph [0082]; figures 8-14	7-12
X	US 2001/055462 A1 (SEIBEL ERIC J [US]) 27 December 2001 (2001-12-27)	1, 3, 6, 7, 12
	figure 3d paragraph [0157] - paragraph [0158]; figures 10, 11a, 11b, 11c paragraph [0141] paragraph [0151]	
A	US 2009/137893 A1 (SEIBEL ERIC [US] ET AL) 28 May 2009 (2009-05-28)	7-12
	paragraph [0016] - paragraph [0018] paragraph [0077] - paragraph [0079]; figures 11a, 12	

☐

Further documents are listed in the continuation of Box C.

☒

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 July 2018

Date of mailing of the international search report

27/09/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Petter, Erwin

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2018/051086

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-13

Deflection device configured to deflect a cantilevered inner tube laterally within the outer tube.

2. claims: 14, 15

Steering mechanism that applies a pre-programmed axial force by the distal end of the inner tube on a specimen under examination.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2018/051086

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009143640	A1	04-06-2009	NONE

US 2001055462	A1	27-12-2001	AU 7493301 A 02-01-2002
			JP 5025877 B2 12-09-2012
			JP 2003535659 A 02-12-2003
			US 2001055462 A1 27-12-2001
			WO 0197902 A2 27-12-2001

US 2009137893	A1	28-05-2009	NONE
