

(51) International Patent Classification:

A61B 5/00 (2006.01) A61B 1/00 (2006.01)
G02B 21/00 (2006.01) G02B 23/26 (2006.01)
G02B 23/24 (2006.01) G02B 26/10 (2006.01)

(21) International Application Number:

PCT/US2024/013172

(22) International Filing Date:

26 January 2024 (26.01.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/481,992 27 January 2023 (27.01.2023) US

(71) Applicant: REGENTS OF THE UNIVERSITY OF
MICHIGAN [US/US]; c/o Innovation Partnerships, 1600

Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).

(72) Inventors: WANG, Thomas, D.; 2880 Chaseway Drive, Ann Arbor, MI 48105 (US). OLDHAM, Kenn; 803 Barton Drive, Ann Arbor, MI 48105 (US). SHIRAZI, Ahmad; 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).

(74) Agent: RADDATZ, Brian, A.R.; Marshall, Gerstein & Borun LLP, 233 S. Wacker Drive, 6300 Willis Tower, Chicago, IL 60606-6357 (US).

(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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG,

(54) Title: SIDE-VIEW DUAL AXES CONFOCAL ENDOMICROSCOPE

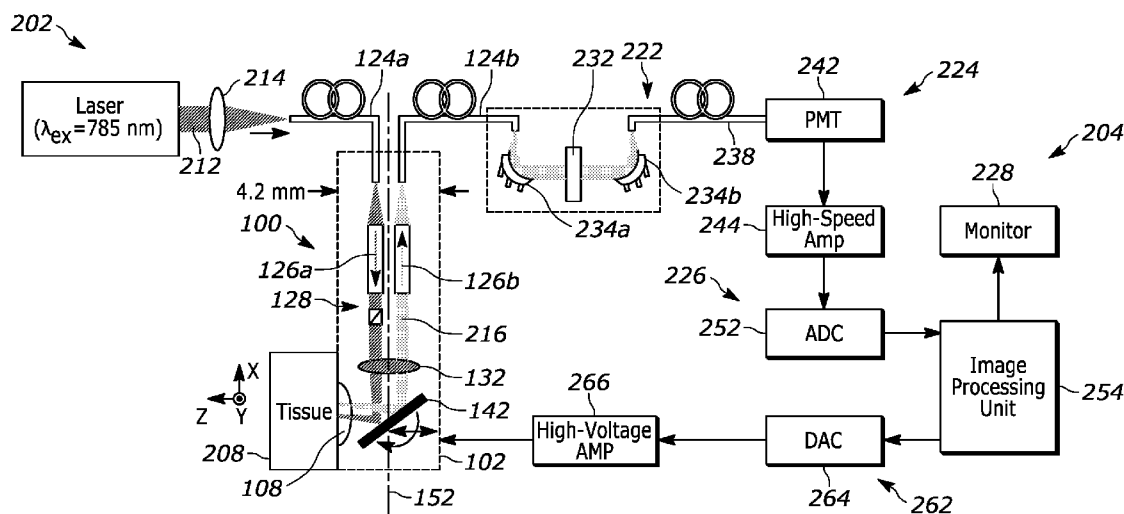


FIG. 2

(57) Abstract: An endomicroscope imaging system. The endomicroscope includes a housing having a proximal end and a distal end, the proximal end configured to receive a first optical fiber and a second optical fiber. The endomicroscope may further include an optical processing assembly disposed in the housing. The optical processing assembly generally includes a first collimator coupled to the first optical fiber, a second collimator coupled to the second optical fiber, and an objective disposed proximate the first collimator and the second collimator. The imaging system may further include a mirror scanning assembly disposed on the distal end of the housing and adjacent the objective. In various examples, the scanning assembly is configured to pivot about a first axis and a second axis. The endomicroscope may further include a lens disposed on a sidewall of the housing and aligned with the mirror scanning system.

KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY,
MA, MD, MG, MK, MN, MU, 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, ST, SV, SY, TH,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS,
ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, 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, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, 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))*

SIDE-VIEW DUAL AXES CONFOCAL ENDOMICROSCOPE**GOVERNMENT LICENSE RIGHTS**

[0001] This invention was made with government support under CA230669 and CA249851 awarded by the National Institutes of Health. The government has certain rights in the invention.

RELATED APPLICATION

[0002] This application claims the benefit of and priority to U.S. Provisional Patent Application 63/481,992, filed January 27, 2023. The content of which is incorporated by reference herein in its entirety and for all purposes.

FIELD

[0003] The present disclosure relates to endomicroscopes for in vivo imaging and, more particularly, to miniature side-view dual axes confocal endomicroscopes.

BACKGROUND

[0004] The background description provided herein is for the purpose of generally presenting the context of the disclosure. Work of the presently named inventor, to the extent it is described in this background section, as well as aspects of the description that may not otherwise qualify as prior art at the time of filing, are neither expressly nor impliedly admitted as prior art against the present disclosure.

[0005] Most internal and external body surfaces are covered with the epithelium, a thin layer of tissue with dimensions of a few hundred microns, that serves as the source of intense biological activity. The epithelium functions as a substrate for electrolyte transport, as well as a source for tissue regeneration. The epithelium also functions as the origin of tumorigenesis.

[0006] Because of its many different biological functions, researchers study the epithelium in various ways. Researchers, for example, have genetically engineered mice to express optical reporters that are used to investigate epithelial regulation of transport effects, barrier effects, and proliferation. These studies are usually validated by performing histologies on excised tissue. However, this approach has numerous limitations, including that it provides static information only at finite points in time. Real-time intravital microscopy, by contrast, has been developed to track cell movement over time in an innate host environment. In particular, confocal microscopy has become a powerful method of optical imaging of the epithelium. Confocal microscopy allows for sectioning that penetrates several hundred microns into tissue, which means that an instrument with proper dimensions and geometry can be used repetitively to monitor epithelial processes. Unfortunately, conventional confocal

microscopy devices are large and bulky, and require wide surgical exposure that may introduce significant trauma.

[0007] Until now, confocal techniques for investigating cellular behavior in the epithelium have been limited by a lack of instruments that can be easily maneuvered and accurately positioned to visualize individual cells. Generally, confocal endomicroscopy employs the use of flexible optical fibers for minimal invasiveness. Current confocal instruments use front-view optics that collect images in the horizontal plane only. Because firm contact with tissue is required to couple light, this orientation limits usefulness in many applications, including when examining the epithelium of small animals. There is a desire for an improved confocal microcopy instrument capable examining the epithelium in a more accurate and more flexible manner.

SUMMARY

[0008] The present disclosure is directed to an endomicroscope imaging system. The imaging system may include a housing having a proximal end and a distal end. The proximal end being configured to receive a first optical fiber and a second optical fiber. In some examples, the imaging system includes an optical processing assembly disposed in the housing, comprising: a first collimator coupled to the first optical fiber; a second collimator coupled to the second optical fiber; and an objective disposed proximate the first collimator and the second collimator. Additionally, the imaging system may have a mirror scanning assembly disposed on the distal end of the housing and adjacent the objective, the scanning assembly configured to pivot about a first axis and a second axis. Also, the imaging system may include a lens disposed on a sidewall of the housing and aligned with the mirror scanning system.

[0009] In some variations, the imaging system may further include a laser excitation source coupled to the first optical fiber. Additionally, the laser excitation source may be configured to generate an infrared or near-infrared laser. In some examples, the near-infrared laser has a light wavelength of between 750 nanometers (nm) and 800 (nm).

[0010] In other variations, the imaging system may further include a long pass filter coupled to the second optical fiber. In some examples, the housing defines an outer diameter between 4.0 millimeters (mm) and 4.25 mm.

[0011] In yet other variations, the first collimator and the second collimator are parallel. Additionally the objective may be aligned with both the first collimator and the second collimator. In some examples, the imaging system further includes an alignment prism aligned with the first collimator, the alignment prism including a first and second prism. In such examples, the first and second prisms comprise Risley prisms.

[0012] In further variations, the mirror scanning assembly includes a monolithic scan mirror. Additionally, the mirror scanning assembly may include at least two symmetric through holes symmetrically disposed on the mirror scanning assembly. Further, the mirror may be disposed between the objective and the lens.

[0013] In some other variations, the housing defines a central longitudinal axis and the lens defines a lens axis perpendicular to the central longitudinal axis. In such variations, the monolithic scan mirror may be disposed at 45 degrees (°) relative to the central longitudinal axis and the lens axis. Additionally, the mirror scanning assembly can be configured to pivot the monolithic scan mirror about an X-axis, a Y-axis, and translate the monolithic scan mirror along a Z-axis, the X-axis, Y-axis, and Z-axis each being perpendicular to each other. As a result, the mirror scanning assembly is configured to pivot the monolithic scan mirror at least 8.5 degrees (°) about the X axis; pivot the monolithic scan mirror at least 9 degrees (°) about the Y axis; and/or translate the monolithic scan mirror at least 150 micrometers (μm) along the Z axis. In some such variations, the mirror scanning assembly may be further configured to translate in a direction perpendicular to the first axis and the second axis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] This patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the United States Patent and Trademark Office upon request and payment of the necessary fee.

[0015] The above needs are at least partially met through provision of the marking system described in the following detailed description, particularly when studied in conjunction with the drawings, wherein:

[0016] FIG. 1 is a perspective view of an endomicroscope imaging system made in accordance with the present disclosure.

[0017] FIG. 2 illustrates a schematic diagram of the endomicroscope imaging system made in accordance with the present disclosure.

[0018] FIG. 3a is a side view of a mirror scanning assembly rotating about an axis in accordance with the present disclosure.

[0019] FIG. 3b illustrates an example field of view the endomicroscope can scan in an example horizontal plane.

[0020] FIG. 4a is a side view of a mirror scanning assembly translating in accordance with the present disclosure.

[0021] FIG. 4b illustrates an example field of view the endomicroscope can scan in an example vertical plane.

[0022] FIG. 5a is a perspective view of a mirror scanning assembly and corresponding effect of mirror scanning assembly movement on illumination and collection beams.

[0023] FIG. 5b illustrates an example field of view the endomicroscope can scan in both the horizontal and vertical planes.

[0024] FIG. 6 illustrates a front view of an example mirror scanning assembly.

[0025] FIG. 7 illustrates perspective views of example movement of the mirror scanning assembly of FIG. 6.

[0026] FIG. 8 illustrates perspective views of example micro-electro-mechanical system (MEMS) springs used in the mirror scanning system of FIG. 7.

[0027] FIG. 9 illustrates finite element analysis results for the first twelve eigenmodes when exciting the axes of the mirror scanning system of FIG. 7.

[0028] FIG. 10 is a perspective view of the example mirror scanning system of FIG. 7.

[0029] FIG. 11a is a front view of the mirror scanning system of FIGS. 7 and 10.

[0030] FIG. 11b is a side view of the mirror scanning system of FIGS. 7 and 10.

[0031] FIG. 12a is a perspective view of electrical connections for the mirror scanning system of FIGS. 7 and 10.

[0032] FIG. 12b is a front view of the electrical connections for the mirror scanning system of FIGS. 7 and 10.

[0033] FIG. 13 is a side view of an endomicroscope imaging system made in accordance with the present disclosure.

[0034] FIG. 14 illustrates the endomicroscope disposed in an anesthetized mouse.

[0035] FIG. 15 illustrates example image data for the endomicroscope imaging system of the present disclosure.

[0036] FIG. 16 illustrates example frequency response data for the endomicroscope imaging system of FIGS. 1 and 14.

[0037] FIG. 17a illustrates example imaging data obtained by the endomicroscope imaging system of FIGS. 1 and 14.

[0038] FIG. 17b illustrates example image data obtained by the endomicroscope imaging system of FIGS. 1 and 14.

[0039] Skilled artisans will appreciate that elements in the figures are illustrated for simplicity and clarity and have not necessarily been drawn to scale. For example, the dimensions and/or relative positioning of some of the elements in the figures may be exaggerated relative to other elements to help to improve understanding of various embodiments of the present invention. Also, common but well-understood elements that are useful or necessary in a commercially feasible embodiment are often not depicted in order to facilitate a less obstructed view of these various embodiments. It will further be appreciated that certain actions and/or steps may be described or depicted in a particular order of occurrence while those skilled in the art will understand that such specificity with respect to sequence is not actually required. It will also be understood that the terms and expressions used herein have the ordinary technical meaning as is accorded to such terms and expressions by persons skilled in the technical field as set forth above except where different specific meanings have otherwise been set forth herein.

DETAILED DESCRIPTION

[0040] Pursuant to these various embodiments, an optical probe scanning assembly is provided. The optical probe scanning assembly includes a housing having a proximal end configured to receive an optical fiber beam source and a distal end for positioning at a sample. The housing has a length that extends along a longitudinal axis extending from the proximal end to the distal end. An optical focusing assembly is included to focus an output beam, from the fiber beam source, along an axial beam path. Downstream of that optical focusing assembly (where downstream refers a position distal to, or afterwards in the direction of the output beam), is a 3-axis mirror scanning assembly. The mirror assembly is positioned at an angle relative to the axial beam path to deflect the output beam into a lateral axis for emitting the output beam from a side of the housing. For example, the lateral beam path may be orthogonal to the axial beam path for emitting the output beam from a side-view of the optical probe, instead of from a distal end. Further, the mirror assembly may be configured to rotate along a first and a second axes, e.g., x-axis and y-axis, for scanning the output beam along a lateral plane, such as a horizontal plane as defined by the side view. The mirror assembly may be further configured to translate along a third axis for scanning the output beam along an oblique plane.

[0041] The present techniques may be implemented in confocal endomicroscopy devices. Confocal endomicroscopy is a minimally invasive imaging technique used to study epithelial biology, e.g., in live animals. With the present techniques, we have developed a confocal endomicroscope that has both high numerical aperture (NA) optics and post-objective scanning. The confocal endomicroscope has allowed us to achieve sub-cellular resolution with a large field of view (FOV). With these devices, we have visualized individual

colonocytes, goblet cells, and inflammatory cells *in vivo* from images collected in mouse colonic epithelium. Other imaging methods, including X-ray, ultrasound, computer tomography (CT) and magnetic resonance imaging (MRI), provide structural rather than functional information, and positron emission tomography (PET) does not have adequate speed or resolution to visualize single cells.

[0042] In exemplary embodiments, the present techniques use a confocal endomicroscope with side-view operation. In comparison to front-view endoscopic devices, the side-view allows the user rotational and translational maneuverability of the endomicroscope. The user can move the side-view endomicroscope along the axial length of vessel and rotationally about the vessel axis. That means that the user may accurately position the side-view optics on any region of interest (ROI) in the vessel. A user may first identify the ROI, e.g., using wide-field endoscopy, and then image the exact location using the side-view confocal endomicroscope. When trying to image ROI in small vessels, including those found in small animals, front-view devices are cumbersome because adequate contact with the epithelium is difficult to achieve. These endomicroscopes may be small enough to pass into and within the vessel, but the front-end does not contact the tissue that one desires to examine. Moreover, there is no rotation dependent imaging. Further, the side-view arrangements may be implemented with an objective lens positioned to confine collimated beams which removes the need, as seen in various conventional systems, for parabolic mirrors known to limit performance. Larger spherical mirrors may now be used resulting in more light collection and more stable resolution.

[0043] More specifically, the present application is directed to a small diameter, (approximately 4.2 mm) near-infrared, side-viewing, dual-axis, confocal imaging system. In some examples, the imaging system is configured to achieve a sub-cellular resolution. Compared to single-axis confocal imaging, the dual-axis configuration improves the axial resolution and reduces out-of-focus light, thereby improving the signal-to-noise ratio. The dual-axis configuration also increases the dynamic range of the imaging system and allows for imaging deeper inside the tissue. Also, compared to a front-viewing configurations, the side-view architecture helps with (1) further reducing imaging system size, (2) simplifying manufacturing processes, and (3) expanding the field of view of the imaging system inside an enclosed environment (e.g., a tubular organ such as a colon). To perform a distal Lissajous scanning inside an enclosed environment, an electrostatically actuated mirror is designed and fabricated based on micro-electro-mechanical systems (MEMS) technology. The capability of this MEMS mirror to combine out-of-plane motion with tilting enables increased frame rate acquisition (e.g., 5 frames per second (fps) or great, 10 fps or great, or 20 fps or greater). For example, the imaging system may obtain approximately five frames

per second for real-time imaging in both horizontal and vertical (enface and cross-sectional) images of the tissue. Additionally, in some examples, the frame may sweep with a field of view covering 900 microns by 660 microns when horizontally imaging and 900 microns by 310 microns when vertically imaging. Additionally, the imaging system of the present disclosure has a reduced size. As a result, the imaging system makes it feasible to perform *in vivo* endoscopy on a subject, for example, on genetically engineered mice used in testing to replicate many human disease models. The imaging systems may be used to examine any number of tissue regions within a subject. For example, the imaging system may be sized to allow for repetitive insertion into the colon of a subject to perform longitudinal and cross sectional imaging analysis to search for cancer. Further, by providing volumetric scanning, i.e., lateral XY plane and vertical Z-axis scanning, imaging systems herein can be used to detect for cancer below a tissue superficial layer. Indeed, the resolution is so good and the amount of backscattered illumination sufficiently large, that now clinicians can examine cancer morphology subsurface. This is particularly important given that the greater the depth of cancer tissue, the more severe the subject's cancer is likely to be. Of course, while various example uses are discussed herein, the imaging systems of the present invention may be used in other environments or on other animals.

[0044] FIG. 1 illustrates the endomicroscope imaging system 100 made in accordance with the present disclosure. In the illustrated example of FIG. 1, the imaging system includes a housing 102, an optical processing assembly 104, a mirror scanning assembly 106, and a lens 108. The lens 108 may be a solid immersion lens (SIL), for example. Yet, while called lens 108, the optical element may provide additional magnification or, alternatively, may simply be a transparent material without any additional optical processing characteristics, in either case, providing an optically transparent seal that prevents fluid from entering the imaging system 100. In some examples, the imaging system 100 may include more, fewer, or alternative components.

[0045] In the present example, the housing 102 is a cylinder. The housing 102 may include a sidewall 114 defining an outer diameter 116 of approximately 4.19 millimeters (mm). However, in various examples, the outer diameter of the housing 102 could be between 4.0 mm and 4.4 mm, but preferably less than 4.2 mm. As shown in FIG. 1, the sidewall 114 of the housing 102 defines a hollow cylinder, but in other examples, the housing 102 could include a bend (as visible in FIG. 14), handle, or other feature to improve user control over the imaging system 100 during a medical or other procedures. In various examples, the housing 102 may include a proximal end 118a and a distal end 118b.

[0046] The imaging system 100 may include the example optical processing assembly 104 as shown in FIG. 1. For example, the optical processing assembly 104 may include a

holder 122a and a spacer 122b. The holder 122a and the spacer 122b can be provided to properly orient the other components of the optical processing assembly 104. Additionally or alternatively, the holder 122a and the spacer 122b can protect the components of the optical processing assembly 104 during transportation and use.

[0047] As shown, the optical processing assembly 104 includes a first optical fiber 124a and a second optical fiber 124b. As shown, the first and second optical fibers 124a, 124b can be received by and secured to the holder 122a. Additionally, in the present example, both the first and second optical fibers 124a, 124b are single mode optical fibers, but in other examples, one or both of the optical fibers could be multimode optical fibers.

[0048] The first optical fiber 124a is functionally coupled to a first collimator 126a and the second optical fiber 124b is functionally coupled to a second collimator 126b. Each of the first and second collimators 126a, 126b are configured to process light. For example, collimators can narrow, align, and/or focus radiation including infrared or near-infrared light. In the present example, the first optical fiber 124a and the first collimator 126a are configured to convey illumination beams and the second collimator 126b and the second optical fiber 124b convey collection beams. Additionally, the optical processing assembly 104 may further include an alignment prism 128 proximate the first collimator 126a. In the illustrated example, the alignment prism 128 includes two Risley Prisms. The alignment prism 128 may be provided to align the light passing through the first collimator 126a with optical path of the second collimator 126b. Accordingly, the alignment prism 128 is optional and could be replaced with any structure or method of aligning the first collimator 126a with the second collimator 126b.

[0049] In the present example, the first and second collimators may be 1.8 millimeters (mm) diameter fiber-pigtailed gradient index (GRIN) collimating lenses. In some examples, the lenses could be plano-convex lenses. Further, the center-to-center distance of the collimating lenses may be approximately 1.9 mm. Additionally, the Risley prisms may consist of two 0.2 degree (°) optical wedges inserted into the illumination path and rotated for fine alignment of the illumination beam. In some examples, the Risley prisms are the same diameter as the first collimator (e.g., 1.8 mm).

[0050] Additionally, the optical processing assembly 104 includes an objective 132 to focus light passing through the first collimator 126a and also focuses light being collected by the second collimator 126b. In various embodiments, the objective 132 has a low numerical aperture (e.g., the objective has a narrow range of angles over which the system can accept/emit light). The objective 132 can be made of any material in common use for processing infrared or near-infrared light. In some examples, the objective 132 actually

comprises two objectives while in other examples, the objective includes two low numerical apertures. The objective 132 is illustrated as a plano-convex lens, but any suitable lens types may be used, including, by way of example, Fresnel lens, gradient-index lens, aspherical lens, etc. Further, the low numerical aperture of the objective 132 may be used to ensure a narrow light angular aperture that avoids collecting excess scatters from the tissue, which, in turn, allows for more accurate imaging throughout the scan volume (lateral and vertical scanning).

[0051] The imaging system 100 may further include the mirror scanning assembly 106 disposed proximate the objective 132. The mirror scanning assembly 106 includes a scanner 142 including a monolithic scan mirror and a micro-electric-mechanical system (MEMS) (discussed in greater detail in connection with FIGS. 6–10). Additionally or alternatively, the mirror scanning assembly 106 may include a wire 144 for powering and controlling the scanner 142.

[0052] As shown in FIG. 1, the first and second optical fibers 124a, 124b; the first and second collimators 126a, 126b; the alignment prism 128; the objective 132; and the mirror scanning assembly 106 are generally disposed coaxially or parallel to a central longitudinal axis 152 of the housing 102. Alternatively, the lens 108 is disposed on the sidewall of the housing 102 and defines a lens axis 154 disposed perpendicular to the central longitudinal axis 152. In accordance with the present disclosure the scanner 142 is disposed at approximately 45 degrees (°) relative to each of the central longitudinal axis 152 and the lens axis 154.

[0053] FIG. 2 is a schematic illustration of the imaging system 100 of FIG. 1 in connection with a light source 202 and an imaging processing system 204. As shown in FIG. 2, the imaging system 100 is configured to generate an image corresponding to a tissue 208 disposed against the lens 108. As shown in FIG. 2, the imaging system 100 operates as described in connection with FIG. 1.

[0054] Light source 202 may be a laser excitation source, but in various examples, the light source 202 could be any other type of light source. In the preferred example, the light source 202 generates a laser 212 having a wavelength of approximately 785 nanometers (nm) (near infrared light). In various other examples, the light source could generate light having shorter or longer wavelengths. For example, the light source 202 could generate infrared light (e.g., greater than approximately 800 nm), near infrared light (between approximately 620 nm to 800 nm), or other visible light (between approximately 380 nm to 800 nm). In some examples, the max power of the light source 202 could be approximately 200 milliwatts (mW), but the light source 202 could be more or less powerful.

[0055] In some examples, the laser 212 undergoes some initial processing before entering the imaging system 100. For example, as shown in FIG. 2, the laser 212 is focused using a first lens 214 and directed towards the first optical fiber 124a. In other examples, the laser 212 could undergo more or less pre-processing before entering the imaging system 100 via first optical fiber 124a.

[0056] In accordance with the present example, the scanner 142 is disposed after the objective 132 and angled relative to lens 108. As a result, the scanner 142 is configured to direct the laser 212 through the from the objective through the lens 108. For example, the angle of the scanner relative to both laser 212 passing through the objective 132 and the laser 212 passing through the lens 108 may be approximately 45 degrees ($^{\circ}$). As a result, the laser is reflected 90° .

[0057] In some examples, the tissue 208 includes fluorophores, such as florescent tags or florescent probes, that are configured to fluoresce. In some examples, the fluorescent dye or tags may be configured to respond to a specific range of light wavelengths (e.g., near-infrared light). In the example of FIG. 2, the laser 212 causes the fluorophores to fluoresce, providing fluorescing beam 216 from the tissue 208. The fluorescing beam 216 is provided through the lens 108, reflects off the scanner 142, through the objective 132 and collimated through the second collimator 126b. The second optical fiber 124b then provides the emitted radiation to the image processing system 204. In various examples, the fluorescing beam 216 is a different color than the laser 212. As a result, the fluorescing beam 216 may have a different light wavelength than the laser 212. The core of an optical fiber (e.g., second optical fiber 124b) acts as a spatial filter to allow only the light that originates from the focal plane below the tissue surface to be collected.

[0058] The dual axes confocal architecture shown in FIG. 2 utilizes separate illumination and collection beams 212, 216. The first and second optical fibers 124a, 124b and the first and second low numerical aperture objectives (e.g., the objective 132 and the lens 108) are oriented at an angle relative to the central longitudinal axis 152. The region of overlap between these beams defines the focal volume, and significantly reduces the resolution that can be achieved by either objective 132a, 132b alone. Light scattered by tissue along the illumination path 212 enters the collection optics (e.g., second objective 132b and second optical fiber 124b), is descanned by the mirror 142 at large angles and are not captured. This effect improves the dynamic range so that images can be collected in vertical and horizontal planes. Vertical cross-sections provide the same view as that of histology, and may be able to assess the depth of early tumor invasion (T1a versus T1b). The low numerical aperture objectives 132a, 132b create a long working distance so that the scan mirror 142 can be placed on the tissue side of the objective 132 (post-objective position). This configuration

allows for images to be collected with a very large field-of-view (FOV) (discussed in greater detail in connection with FIGS. 3b, 4b, 5b). As a result, the imaging system 100 is scalable, so that the housing 102 diameter and overall size can be reduced markedly without loss of resolution.

[0059] In various examples, the objective 132 and the lens 108 are both low numerical aperture objective lenses. For example, the objective 132 and the lens 108 may have numerical aperture values between approximately 0.3 and 0.6. Additionally, the illumination and collection beams may converge in the tissue at a half angle of 15.25 degrees (°). Further, as noted above, the objective 132 may be defined by an aspheric geometry to minimize spherical aberrations, but could, alternatively be a plano-convex or other lens geometry.

[0060] Image processing system 204 can include various electronic and mechanical components configured to enhance the image capture of the imaging system 100. For example, the imaging processing system 204 may include an optical filter 222, analog processors 224, digital processors 226, and a monitor 228.

[0061] The optical filter 222 may include a long pass filter 232 disposed between a first off-axis parabolic mirror 234a and a second off-axis parabolic mirror 234b. In some examples, the long pass filter 232 is an ultra-steep long pass filter. The optical filter 222 is configured to receive light from the second optical fiber 124b and passes light through the long pass filter 232 to a multimode optical fiber 238.

[0062] The analog processors 224 may include a photomultiplier tube detector 242 and a high-speed amplifier 244, but may include more or fewer processing features.

[0063] The digital processors 226 may include an analog-to-digital converter 252 and an image processing unit 254. The analog-to-digital converter 252 converts the analog signals into a digital signal for readily processing the image data. The imaging processing unit 254 is configured to receive the digital data from the analog-to-digital converter 252 and send an image to the monitor 228. The monitor 228 may be configured to present real time or near-real time images of the tissue 208. Additionally or alternatively, the image processing unit 254 can be configured to send image data to a memory to be stored and recalled for viewing later.

[0064] In some other examples, the image processing unit 254 may further send image data to through a digital to analog converter 264 to a high voltage amplifier 266 configured to control actuation of the mirror scanning assembly 106 via the wire 144 (shown in FIG. 1). In some examples, the image processing unit 254 may be in electronic communication with a processor or microprocessor that controls operation of the mirror scanning assembly 106.

[0065] In various examples, the scanner 142 and the image processing unit 254 are configured to follow a dense Lissajous scan pattern and still provide five frames of real time or near-real time images per second. To generate five frames per second, the analog-to-digital converter 252 may operate at 10,000 samples per second. In various other examples, the scanner and image processing unit may provide more or fewer frames per second. For example, if the scanner 142 were actuated quicker, or if the scanner 142 reduced the field-of-view, the image processing unit 254 may be able to generate more frames per second.

[0066] FIGS. 3a, 3b, 4a, 4b, 5a, and 5b illustrate operation of the mirror scanning assembly 106 in transmitting illumination light and collecting fluorescence light. FIGS. 3a and 3b illustrate pivoting the scan mirror about an axis. Additionally, FIGS. 4a and 4b illustrate translating the scan mirror in a Z-axis. Lastly, FIGS. 5a and 5b illustrate the potential scanning area for the example mirror scanning assembly 106. To simplify the illustration of FIGS. 3a, 4a, and 5a, the micro-electro-mechanical system (MEMS) is not shown.

[0067] As shown in FIG. 3a, the scan mirror 302 is configured to pivot about an axis 312. As discussed in greater detail in connection with FIG. 7, the mirror scanning assembly 106 can pivot about two perpendicular axes. In the present example, the scan mirror can scan approximately 900 micrometers (μm) in a horizontal direction and approximately 660 μm in a vertical direction (as shown in FIG. 3b) perpendicular to the horizontal direction. However, in other examples, the scan mirror 306 may be configured to scan larger regions, for example, up to approximately 1500 μm or 2500 μm .

[0068] As shown in FIG. 4a, the scan mirror 302 is configured to translate along an axis 412. When the scan mirror is actuated closer to the lens 108, the focal point of the illumination light can be disposed an additional 310 μm beyond the outer edge of the lens 108. Accordingly, the scan mirror 302 can generate a more three-dimensional image beyond the lens (as discussed in greater detail in connection with FIGS. 17a and 17b). FIG. 4b illustrates an example field of view for a vertical view beyond the lens 108. As shown, the scan mirror 302 can scan a field having approximately 900 μm in a horizontal direction and approximately 310 μm of depth. In various examples, the field of view may be larger and may scan a width of up to approximately 2500 μm of width and approximately 600 μm of depth.

[0069] FIG. 5a and 5b illustrates the three-dimensional bounds of an example field of view of the imaging system 100 by pivoting and translating the scan mirror. As shown in FIG. 5b, the largest region of scanning, along the lens 108, and reduced scanning regions further away from the lens 108. As shown in FIG. 5b, the size of the scanning field-of-view is at

least partially based on the size of the reflective surfaces of the mirror (e.g., reflective surfaces 636a, 636b described in greater detail in connection with FIG. 6).

[0070] FIG. 6 is a front view of an example micro-electro-mechanical structure (MEMS) device 600 used in actuating a mirror in accordance with the present disclosure. The MEMS device 600 is a compact, monolithic 3-axis devices based on the principle of parametric resonance to achieve wide deflection angles and large axial displacements. The MEMS device 600 responds to electrical current and actuates corresponding linkages based on electrical current. In the illustrated example of FIG. 6, the MEMS device includes a substrate 602, anchored electrodes 604, actuating components 606, and a mirror 608. In the illustrated example, the device is generally symmetrical both vertically and horizontally.

[0071] In the illustrated example, the substrate 602 provides a semi-rigid structure that does not respond to electrical impulses. The substrate 602 may be made of any suitable material that is sufficiently rigid to hold the actuating components 606 and also nonconductive. In some examples, the substrate can include various island structures 612 disposed between various actuating components 606. In some examples, the island structures 612 may be configured to electrically isolate various components on the MEMS device 600. Additionally or alternatively, the island structures 612 can be configured to provide structural support to other components of the MEMS device 600. The substrate includes the anchored electrodes 604. The anchored electrodes 604 provide electrical connection to the actuating components 606. The anchored electrodes 604 are discussed in greater detail in connection with FIGS. 12a and 12b.

[0072] The MEMS device 600 includes actuating components 606. In various examples, the actuating components can include any typical MEMS components such as well known, actuators, sensors, gimbles, etc. In the present example, the actuating components 606 can include outer comb-drives 622 and inner comb-drives 624. Additionally, the MEMS device 600 could include passive components, including outer springs 626, inner springs 628, serpentine springs 632, and gimbals 634. In the present example, activating some or all of the outer comb-drives 622 and/or the inner comb-drives 624 causes the mirror 608 to pivot about the X-axis, Y-axis, and/or translate in the Z-direction. In various examples, some of the active components can be made passive and some of the passive components could be made active and the functionality of the MEMS device 600 could be maintained.

[0073] In the illustrated example, the inner springs 628 are configured to pivot the mirror 608 about the X-axis (e.g., X-tilt). Each inner spring 628 may include a single connection to the mirror 608 and two connections to the gimbal 634 (where these connections may be physical, sufficiently rigid couplings). Additionally, the outer spring 626 is configured to pivot

the mirror 608 about the Y-axis (e.g., Y-tilt). Lastly the serpentine springs 632 are configured to actuate the mirror 608 forward and backward along the Z-axis (e.g., Z-translation). The position of the serpentine springs 632, proximate the gimbals 634 and island structures 612 is conducive to not interfering with the mirror actuation. The pivoting and translation correspond to the pivoting and translating of the mirror 302 as described in connection with FIGS. 3a, 4a, and 5a. FIG. 7 illustrates an X-tilt 702, a Y-tilt 704, and a Z-translation 706.

[0074] In various examples, the mirror 608 may be configured to deflect ± 8.5 degrees ($^{\circ}$) about the X-axis. Additionally, the mirror 608 may be configured to deflect $\pm 9^{\circ}$ about the Y-axis. Further, the mirror 608 may be configured to translate ± 150 micrometers (μm). Lateral scan mirror deflections of $\pm 8.5^{\circ}$ and $\pm 9^{\circ}$ in the X- and Y-axes, respectively, produced a $900 \times 660 \mu\text{m}^2$ field-of-view in the horizontal plane. Also, the combined lateral deflection of $\pm 8.5^{\circ}$ in the X-axis with axial displacement of $\pm 150 \mu\text{m}$ in the Z-axis produced a $900 \times 310 \mu\text{m}^2$ field-of-view in the vertical plane.

[0075] The MEMS device 600 includes the mirror 608. The mirror 608 includes a first reflective surface 636a and a second reflective surface 636b. In some examples, the first reflective surface 636a reflects an illumination beam onto the sample (e.g., laser 212 of FIG. 2) and the second reflective surface 636b reflects captured scattered emissions from the sample (e.g., fluorescent beam 216 of FIG. 2). Additionally, the mirror 608 includes symmetric through holes to reduce air damping during motion of the mirror 608. The through holes may be positioned to have top/bottom and left/right symmetry over the mirror 608. For example, through holes may be formed in the mirror 608 to have horizontal and vertical symmetry about a centerpoint 648, as shown in FIG. 6. For example, the mirror 608 may include a central through hole 642. Additionally, the example mirror 608 includes top and bottom through holes 644a, 644b and left and right through holes 644c, 644d. The symmetric nature of the through holes 642, 644a, 644b, 644c, 644d permits uniform airflow around and through the mirror 608. In various examples, the mirror 608 may include more or fewer through holes than shown in FIG. 6.

[0076] The MEMS device 600 is configured to achieve more than $300 \mu\text{m}$ axial displacement of the focus. The gimbal 634 has 1.2 mm long lever arms, defined by the distance between the outer springs 626 and serpentine springs 632. This dimension was maximized to achieve the largest axial displacement allowed by the chip dimensions. Outer comb-drives 622 were arranged in 3 columns to generate a large force to produce angular deflections of greater than 23 degrees ($^{\circ}$) ($\pm 11.5^{\circ}$) and achieve out-of-plane mirror motion greater than $400 \mu\text{m}$ ($\pm 200 \mu\text{m}$). A $350 \mu\text{m}$ deep cavity on the backside was etched to provide space for the mirror to tilt at large angles and to displace vertically. Torsional springs were designed with a geometry and dimensions to achieve resonant scanning in the inner

(X) and outer (Y) axes (as shown in FIG. 7). Serpentine springs were fabricated to determine the frequency and displacement of the out-of-plane motion of the reflector in the Z-axis (as shown in FIG. 7).

[0077] FIG. 8 illustrates some of the passive components of the MEMS device 600, including the inner spring 628, outer torsional spring 626, and serpentine spring 632 in greater detail. Although the MEMS device 600 utilizes the inner spring 628, the outer spring 626, and the serpentine spring 632, in other examples, the MEMS device could utilize any suitable and/or comparable micro-spring structure.

[0078] The inner spring 628 includes a first connection point 802, a second connection point 804a, and a third connection point 804b. The first connection point 802 is configured to couple to the mirror 608 while the second and third connection points 804a, 804b are configured to couple to the gimble 634. The inner spring 628 is configured to pivot about the first connection point 802 when the mirror 608 pivots about the X-axis. As a result, the inner spring 628 is configured to evenly transfer the torque from the first connection point 802 to the second and third connection points 804a, 804b. The example MEMS device 600 includes two inner springs 628, one on either side of the mirror 608. In various examples, the MEMS device 600 could include more or fewer inner springs 628.

[0079] The outer torsional spring 626 includes a first connection 812 and a second connection 814. The outer torsional spring 626 is configured to resist the rotation of the mirror about the Y-axis. The example MEMS device 600 includes eight outer springs 626. In various examples, the MEMS device 600 could include more or fewer outer springs 626.

[0080] The serpentine spring 632 is configured to operate like serpentine springs known in the art. For example, the serpentine spring 632 includes a first connection point 822 and a second connection point 824. At least one of the first connection point 822 and the second connection point 824 may be coupled to the mirror 608 or the gimble 634. The serpentine spring 632 is configured to bend at least when the mirror 608 is translated in the Z-axis direction. The example MEMS device 600 includes four serpentine springs 632, two on either side of the mirror 608. In various examples, the MEMS device 600 could include more or fewer serpentine springs 632.

[0081] FIG. 9 illustrates various excitation modes of the MEMS device 600. In preferred embodiments, the MEMS device 600 is operated at a resonance of the structure. In the example MEMS device 600 illustrated in FIG. 9, the resonance of the MEMS device about the X-axis is approximately 4384.2 hertz (Hz). Additionally, the resonance of the MEMS device about the Y-axis frequency is approximately 1000.4 Hz. Further, the resonance of the

MEMS device in the Z-direction is approximately 852.2 Hz. But, in other examples, the frequency may be different if the MEMS device 600 is at least partially redesigned.

[0082] FIG. 10 illustrates the mirror scanning assembly 106 in greater detail. As shown in FIG. 10, the mirror scanning assembly includes the MEMS device 600. As shown in FIG. 10, the MEMS device includes the MEMS device 600 disposed on a MEMS holder 1002. In some examples, the mirror scanning assembly includes a cover 1006 and further includes a MEMS tail 1004. As shown in FIG. 10, the MEMS device is disposed on the proximate end 1012 of the mirror scanning assembly is disposed on a proximate end 1012 of the mirror scanning assembly 106 and the tail is disposed on the distal end 1014 of the mirror scanning assembly 106. In the present example, the MEMS device 600 is disposed at an angle 1016 relative to a sidewall of the mirror scanning assembly 106. In the present example, the angle 1016 is 45 degrees (°) to cause light reflecting off the mirror disposed on the MEMS device to reflect perpendicularly. In various examples, the mirror scanning assembly 106 may be configured to include apertures and throughholes to permit wiring to pass through the mirror scanning assembly. Additionally or alternatively, the apertures and throughholes may permit airflow around and through the mirror scanning assembly 106. In some examples, the tail 1004 can be snapped off after the mirror scanning assembly is manufactured.

[0083] FIGS. 11a and 11b illustrate the mirror scanning assembly 106 in a front view (FIG. 11a) and a side view (FIG. 11b). Additionally, FIGS. 12a and 12b illustrate the connection between the anchored electrodes 604 and a wire (e.g., wire 144 of FIG. 1). As shown in FIG. 11a, the wire is configured to wrap around the anchored electrodes 604. Additionally or alternatively, the wire could be soldered to the anchored electrode 604 or electrically coupled to the anchored electrode in any other known manner.

[0084] FIG. 13 is an assembled endomicroscope imaging system 1300 constructed in accordance with the present disclosure and held by an end user 1302. As shown, the imaging system 1300 defines an outer diameter 1312 of 4.19 millimeters (mm) and includes the lens 1314 disposed on a sidewall of the imaging system 1300. FIG. 14 illustrates the imaging system 1300 as disposed in a colon of a test subject 1400. As visible in FIG. 14, the imaging system 1300 may not be perfectly cylindrical, but may bend to increase user 1302.

[0085] The side view dual axes confocal endomicroscope 1300 was inserted into the colon of the test subject 1400, and the focusing optics was positioned at normal incidence to the mucosal surface and the lens 1314 came in direct contact with the mucosa. Although not necessary, a lubricating gel may be used for smoother insertion of the probe inside the colon of the test subject 1400. Near-infrared fluorescence images of normal and pre-malignant colon were collected in vertical and horizontal planes by tuning the drive frequency of the

scan mirror. Videos were captured at 5 frames per second. Streams that showed minimum motion artifact and absence of debris (stool, mucus) were identified. After completion of imaging, the test subject 1400 was euthanized, and the colon was resected, fixed in 10% buffered formalin, and processed for routine histology (H&E).

[0086] FIG. 15 illustrates the resolution capabilities of the endomicroscope 1300. For example, data 1502 illustrates the lateral resolution of the endomicroscope 1300, including simulated data 1504 and measured data 1506. Similarly, data 1512 illustrates the axial resolution of the endomicroscope 1300, including simulated data 1504 and measured data 1516. The reflectance image 1520 generated by the endomicroscope 1300 shows accurate imaging of the 7-6 target group of the United States Air Force standard pattern. The grid pattern 1530 shows accurate resolution of 50 μm grid pattern including curvature around the endomicroscope 1300. Lastly, image 1540 illustrates a 800x220 μm^2 field of view of an etched zig-zag pattern.

[0087] FIG. 16 illustrates the optical scan angle for each activation frequency. Based on the information shown, there is an optimal frequency for operating the MEMS device for each of the X-axis rotation, Y-axis rotation, and Z-axis translation. For example, graph 1602 illustrates that the largest scan angle about the X-axis occurs at approximately 8.7 or 8.8 kilohertz (kHz) (approximately double the eigenfrequency shown in FIG. 9). Similarly, graph 1604 illustrates that the largest scan angle about the Y-axis occurs at approximately 2.1 kHz (approximately double the eigenfrequency shown in FIG. 9). Further, the graph 1604 illustrates the largest translation of the mirror in the Z-axis occurs at approximately 1850 Hz (approximately double the eigenfrequency shown in FIG. 9). As a result, operating the MEMS device (e.g., the MEMS device 600) at the above frequency or the eigenfrequency will result in the largest field-of-view. But, in some examples, a partially modified version of the MEMS device 600 will result in different optimal frequencies.

[0088] FIGS. 17a and 17b are example images generated by the endomicroscope 1300. For example, FIG. 17a shows a first image 1702 and a second image 1704. Both the first and second images 1702, 1704 are collected in the horizontal plane. First image 1702 shows a normal colonic mucosa while the second image 1704 shows adenoma (benign cancerous cells). As can be seen from the first and second images 1702, 1704, the endomicroscope imaging system 1300 can generate images with individual cells being clearly distinguishable. Additionally, FIG. 17b includes a third image 1706 and a fourth image 1708. Both the third and fourth images 1706, 1708 are collected as a vertical cross section. The third and fourth images 1706, 1708 provide good mucosal detail. Images with sub-cellular resolution can be collected in vivo to track the behaviors of individual cells in the natural microenvironment. Repetitive imaging can be performed to extend the time course

for visualizing important dynamic events to better understanding the development and natural history of disease processes. Each animal can be used as its own control to reduce the numbers needed for statistical rigor. The reduced size may be compatible with medical endoscopes to perform “instantaneous” histology.

[0089] Conventional intra-vital microscopes are tabletop systems equipped with bulky optics and scanners. Either wide surgical exposure or surgically implanted optical windows are needed. These procedures can cause significant trauma, and application of pressure reduces blood flow, causes hypoxia, and incurs biological artifacts.

[0090] Throughout this specification, plural instances may implement components, operations, or structures described as a single instance. Although individual operations of one or more methods are illustrated and described as separate operations, one or more of the individual operations may be performed concurrently, and nothing requires that the operations be performed in the order illustrated. Structures and functionality presented as separate components in example configurations may be implemented as a combined structure or component. Similarly, structures and functionality presented as a single component may be implemented as separate components. These and other variations, modifications, additions, and improvements fall within the scope of the target matter herein.

[0091] Additionally, certain embodiments are described herein as including logic or a number of routines, subroutines, applications, or instructions. These may constitute either software (e.g., code embodied on a non-transitory, machine-readable medium) or hardware. In hardware, the routines, etc., are tangible units capable of performing certain operations and may be configured or arranged in a certain manner. In example embodiments, one or more computer systems (e.g., a standalone, client or server computer system) or one or more hardware modules of a computer system (e.g., a processor or a group of processors) may be configured by software (e.g., an application or application portion) as a hardware module that operates to perform certain operations as described herein.

[0092] In various embodiments, a hardware module may be implemented mechanically or electronically. For example, a hardware module may comprise dedicated circuitry or logic that is permanently configured (e.g., as a special-purpose processor, such as a field programmable gate array (FPGA) or an application-specific integrated circuit (ASIC)) to perform certain operations. A hardware module may also comprise programmable logic or circuitry (e.g., as encompassed within a general-purpose processor or other programmable processor) that is temporarily configured by software to perform certain operations. It will be appreciated that the decision to implement a hardware module mechanically, in dedicated

and permanently configured circuitry, or in temporarily configured circuitry (e.g., configured by software) may be driven by cost and time considerations.

[0093] Accordingly, the term "hardware module" should be understood to encompass a tangible entity, be that an entity that is physically constructed, permanently configured (e.g., hardwired), or temporarily configured (e.g., programmed) to operate in a certain manner or to perform certain operations described herein. Considering embodiments in which hardware modules are temporarily configured (e.g., programmed), each of the hardware modules need not be configured or instantiated at any one instance in time. For example, where the hardware modules comprise a general-purpose processor configured using software, the general-purpose processor may be configured as respective different hardware modules at different times. Software may accordingly configure a processor, for example, to constitute a particular hardware module at one instance of time and to constitute a different hardware module at a different instance of time.

[0094] Hardware modules can provide information to, and receive information from, other hardware modules. Accordingly, the described hardware modules may be regarded as being communicatively coupled. Where multiple of such hardware modules exist contemporaneously, communications may be achieved through signal transmission (e.g., over appropriate circuits and buses) that connect the hardware modules. In embodiments in which multiple hardware modules are configured or instantiated at different times, communications between such hardware modules may be achieved, for example, through the storage and retrieval of information in memory structures to which the multiple hardware modules have access. For example, one hardware module may perform an operation and store the output of that operation in a memory device to which it is communicatively coupled. A further hardware module may then, at a later time, access the memory device to retrieve and process the stored output. Hardware modules may also initiate communications with input or output devices, and can operate on a resource (e.g., a collection of information).

[0095] The various operations of example methods described herein may be performed, at least partially, by one or more processors that are temporarily configured (e.g., by software) or permanently configured to perform the relevant operations. Whether temporarily or permanently configured, such processors may constitute processor-implemented modules that operate to perform one or more operations or functions. The modules referred to herein may, in some example embodiments, comprise processor-implemented modules.

[0096] Similarly, the methods or routines described herein may be at least partially processor-implemented. For example, at least some of the operations of a method may be performed by one or more processors or processor-implemented hardware modules. The

performance of certain of the operations may be distributed among the one or more processors, not only residing within a single machine, but deployed across a number of machines. In some example embodiments, the processor or processors may be located in a single location (e.g., within a home environment, an office environment or as a server farm), while in other embodiments the processors may be distributed across a number of locations.

[0097] The performance of certain of the operations may be distributed among the one or more processors, not only residing within a single machine, but deployed across a number of machines. In some example embodiments, the one or more processors or processor-implemented modules may be located in a single geographic location (e.g., within a home environment, an office environment, or a server farm). In other example embodiments, the one or more processors or processor-implemented modules may be distributed across a number of geographic locations.

[0098] Unless specifically stated otherwise, discussions herein using words such as "processing," "computing," "calculating," "determining," "presenting," "displaying," or the like may refer to actions or processes of a machine (e.g., a computer) that manipulates or transforms data represented as physical (e.g., electronic, magnetic, or optical) quantities within one or more memories (e.g., volatile memory, non-volatile memory, or a combination thereof), registers, or other machine components that receive, store, transmit, or display information.

[0099] As used herein any reference to "one embodiment" or "an embodiment" means that a particular element, feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. The appearances of the phrase "in one embodiment" in various places in the specification are not necessarily all referring to the same embodiment.

[0100] Some embodiments may be described using the expression "coupled" and "connected" along with their derivatives. For example, some embodiments may be described using the term "coupled" to indicate that two or more elements are in direct physical or electrical contact. The term "coupled," however, may also mean that two or more elements are not in direct contact with each other, but yet still co-operate or interact with each other. The embodiments are not limited in this context.

[0101] Those skilled in the art will recognize that a wide variety of modifications, alterations, and combinations can be made with respect to the above described embodiments without departing from the scope of the invention, and that such modifications, alterations, and combinations are to be viewed as being within the ambit of the inventive concept.

[0102] While the present invention has been described with reference to specific examples, which are intended to be illustrative only and not to be limiting of the invention, it will be apparent to those of ordinary skill in the art that changes, additions and/or deletions may be made to the disclosed embodiments without departing from the spirit and scope of the invention.

[0103] The foregoing description is given for clearness of understanding; and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.

WHAT IS CLAIMED IS:

1. An endomicroscope imaging system, comprising:
a housing having a proximal end and a distal end, the proximal end configured to receive a first optical fiber and a second optical fiber;
an optical processing assembly disposed in the housing, comprising:
a first collimator coupled to the first optical fiber;
a second collimator coupled to the second optical fiber; and
an objective disposed proximate the first collimator and the second collimator;
a mirror scanning assembly disposed on the distal end of the housing and adjacent the objective, the scanning assembly configured to pivot about a first axis and a second axis;
and
a lens disposed on a sidewall of the housing and aligned with the mirror scanning system.
2. The imaging system of claim 1, further comprising a laser excitation source coupled to the first optical fiber.
3. The imaging system of claim 2, wherein the laser excitation source is configured to generate an infrared or near-infrared laser.
4. The imaging system of claim 3, wherein the near-infrared laser has a light wavelength of between 750 nanometers (nm) and 800 (nm).
5. The imaging system of claim 1, further comprising a long pass filter coupled to the second optical fiber.
6. The imaging system of claim 1, wherein the first collimator and the second collimator are parallel.
7. The imaging system of claim 1, wherein the objective is aligned with both the first collimator and the second collimator.
8. The imaging system of claim 1, further comprising an alignment prism aligned with the first collimator, the alignment prism including a first and second prism.

9. The imaging system of claim 8, wherein the first and second prisms comprise Risley prisms.

10. The imaging system of claim 1, wherein the mirror scanning assembly includes a monolithic scan mirror.

11. The imaging system of claim 10, wherein the mirror scanning assembly includes at least two through holes symmetrically disposed on the mirror scanning assembly.

12. The imaging system of claim 10, wherein the mirror is disposed between the objective and the lens.

13. The imaging system of claim 12, wherein the housing defines a central longitudinal axis and the lens defines a lens axis perpendicular to the central longitudinal axis; and

wherein the monolithic scan mirror is disposed at 45 degrees (°) relative to the central longitudinal axis and the lens axis.

14. The imaging system of claim 13, wherein the mirror scanning assembly is configured to pivot the monolithic scan mirror about an X-axis, a Y-axis, and translate the monolithic scan mirror along a Z-axis, the X-axis, Y-axis, and Z-axis each being perpendicular to each other.

15. The imaging system of claim 14, wherein the mirror scanning assembly is configured to pivot the monolithic scan mirror at least 8.5 degrees (°) about the X-axis.

16. The imaging system of claim 14, wherein the mirror scanning assembly is configured to pivot the monolithic scan mirror at least 9 degrees (°) about the Y-axis.

17. The imaging system of claim 14, wherein the mirror scanning assembly is configured to translate the monolithic scan mirror at least 150 micrometers (μm) along the Z-axis.

18. The imaging system of claim 1, wherein the mirror scanning assembly is further configured to translate in a direction perpendicular to the first axis and the second axis.

19. The imaging system of claim 1, wherein the housing defines an outer diameter between 4.0 millimeters (mm) and 4.25 mm.

1/18

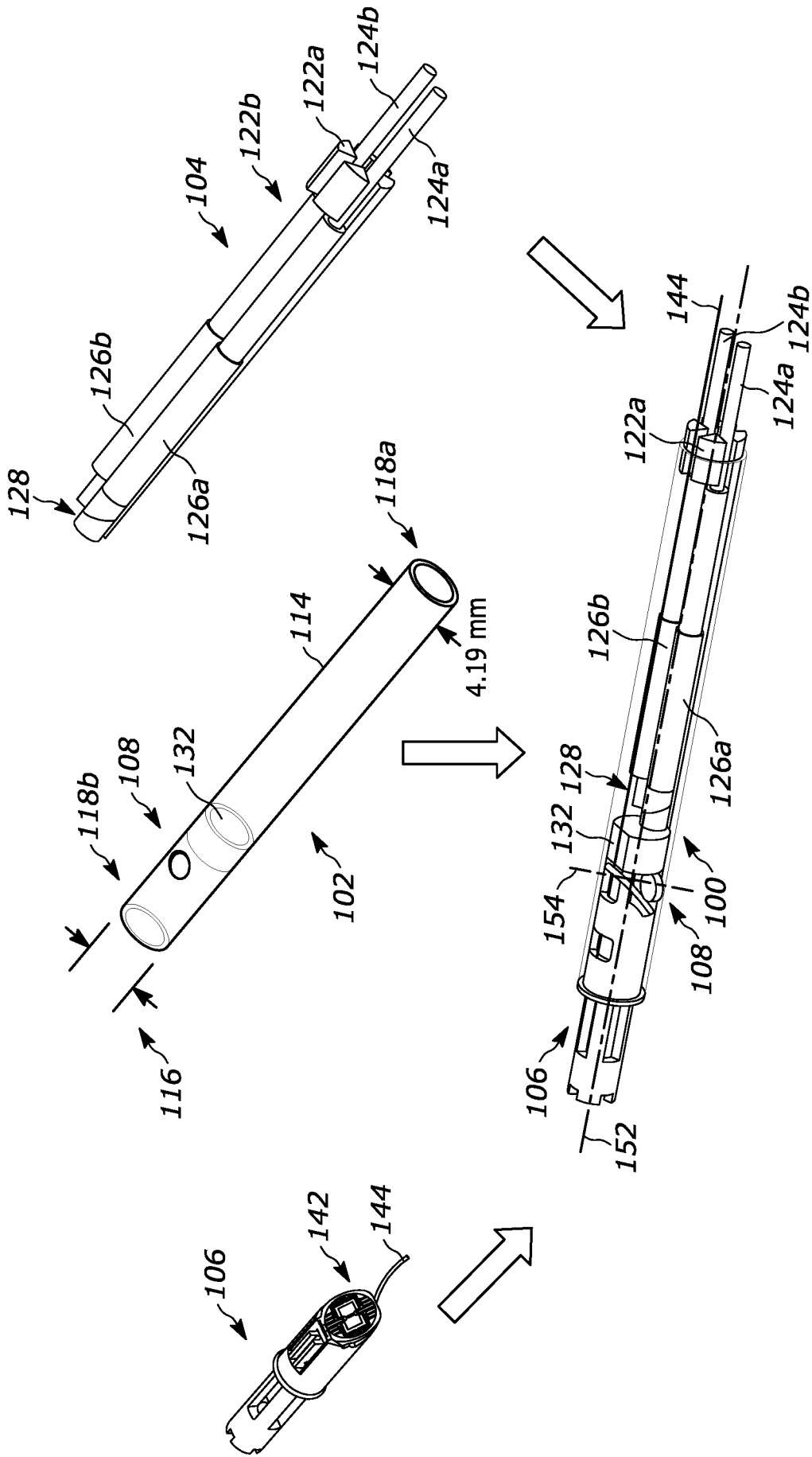


FIG. 1

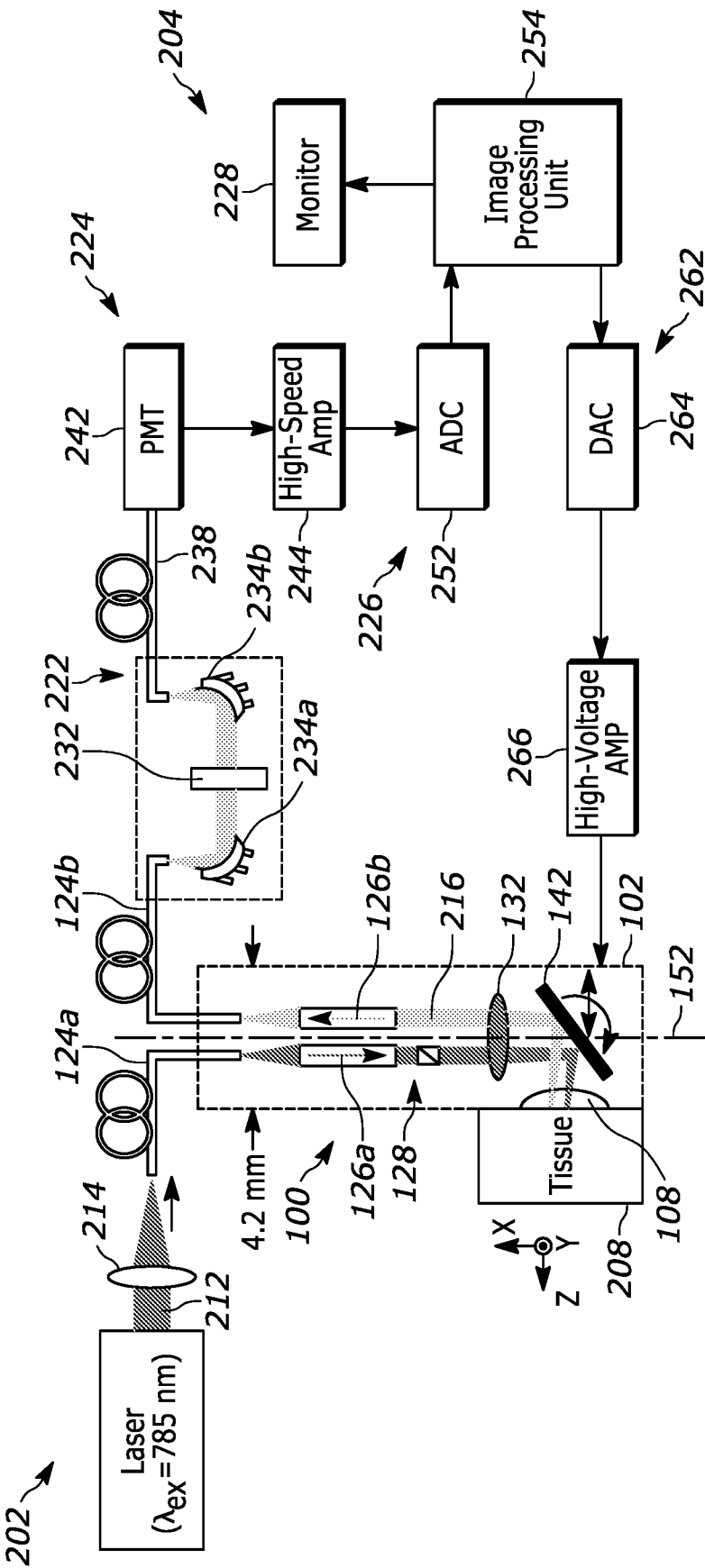


FIG. 2

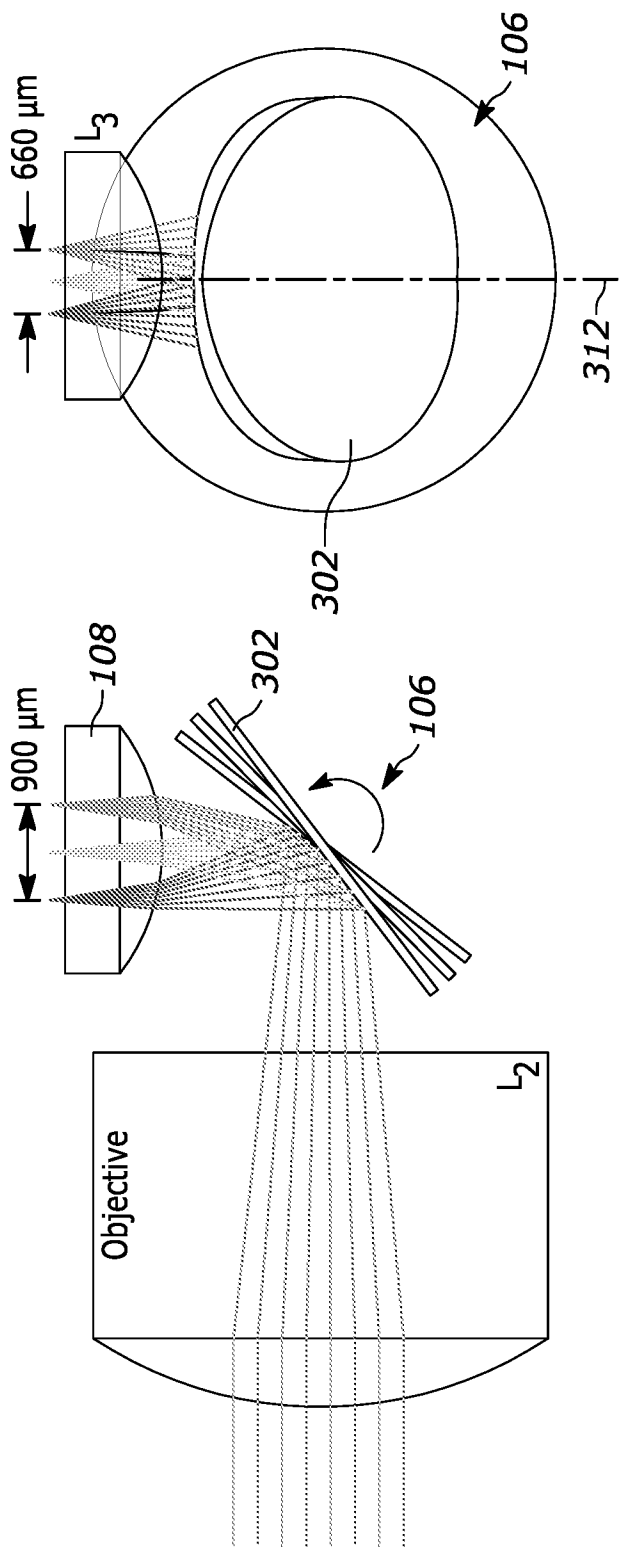


FIG. 3A

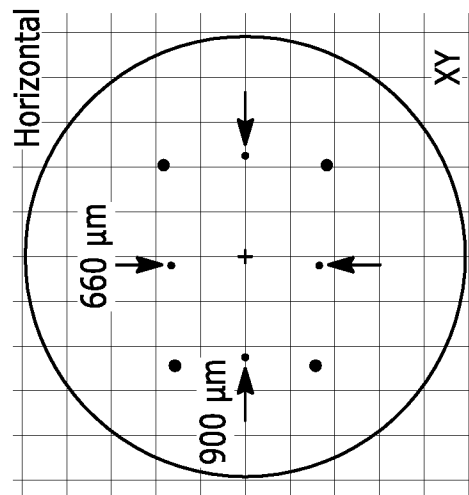


FIG. 3B

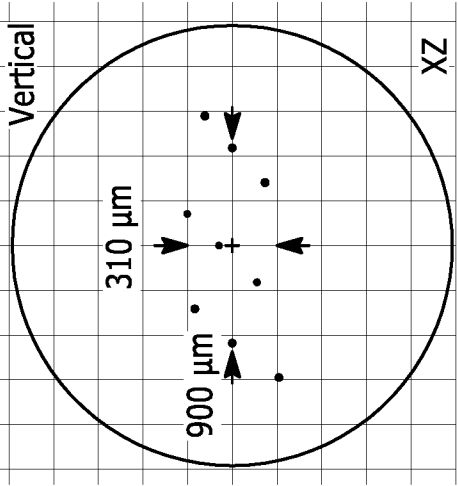
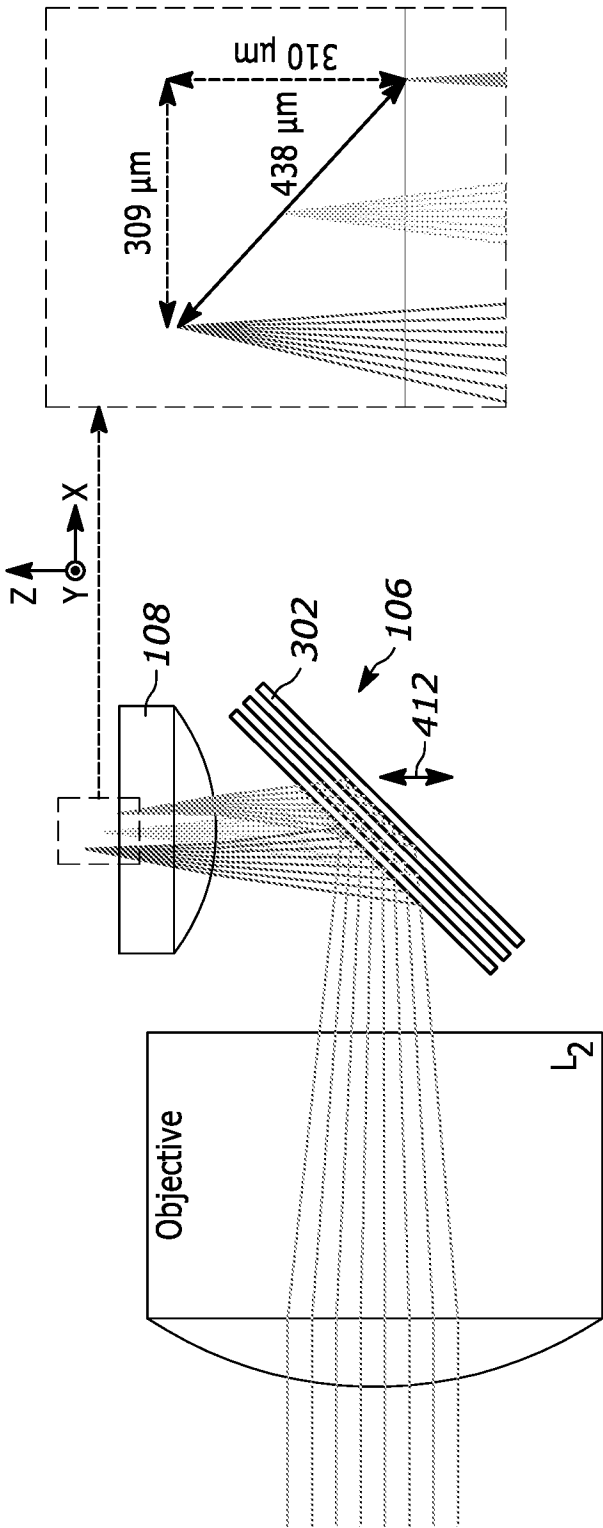


FIG. 4A

FIG. 4B

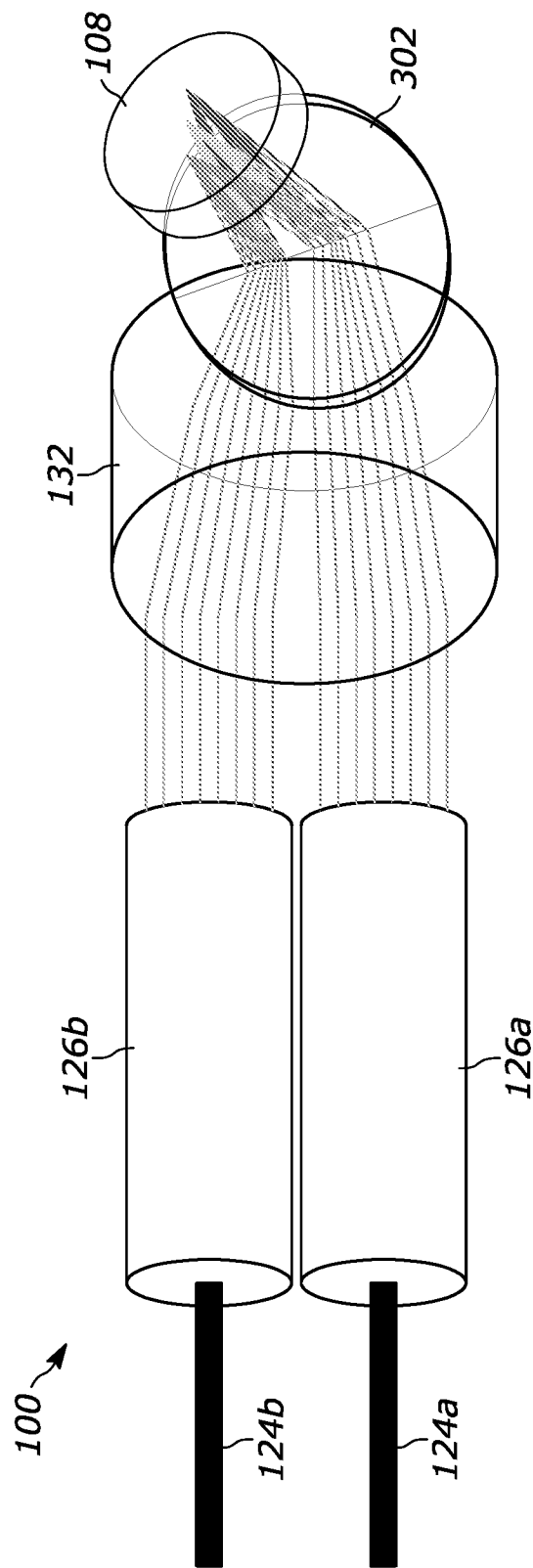


FIG. 5A

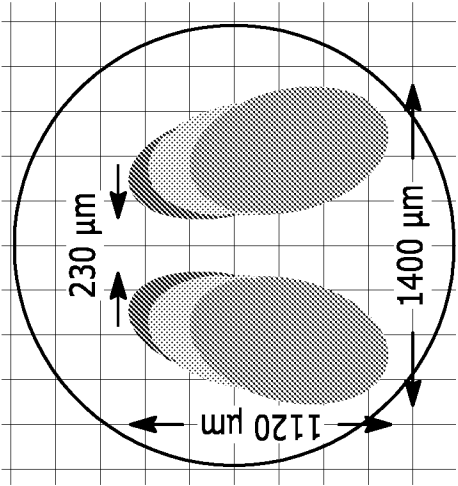


FIG. 5B

6/18

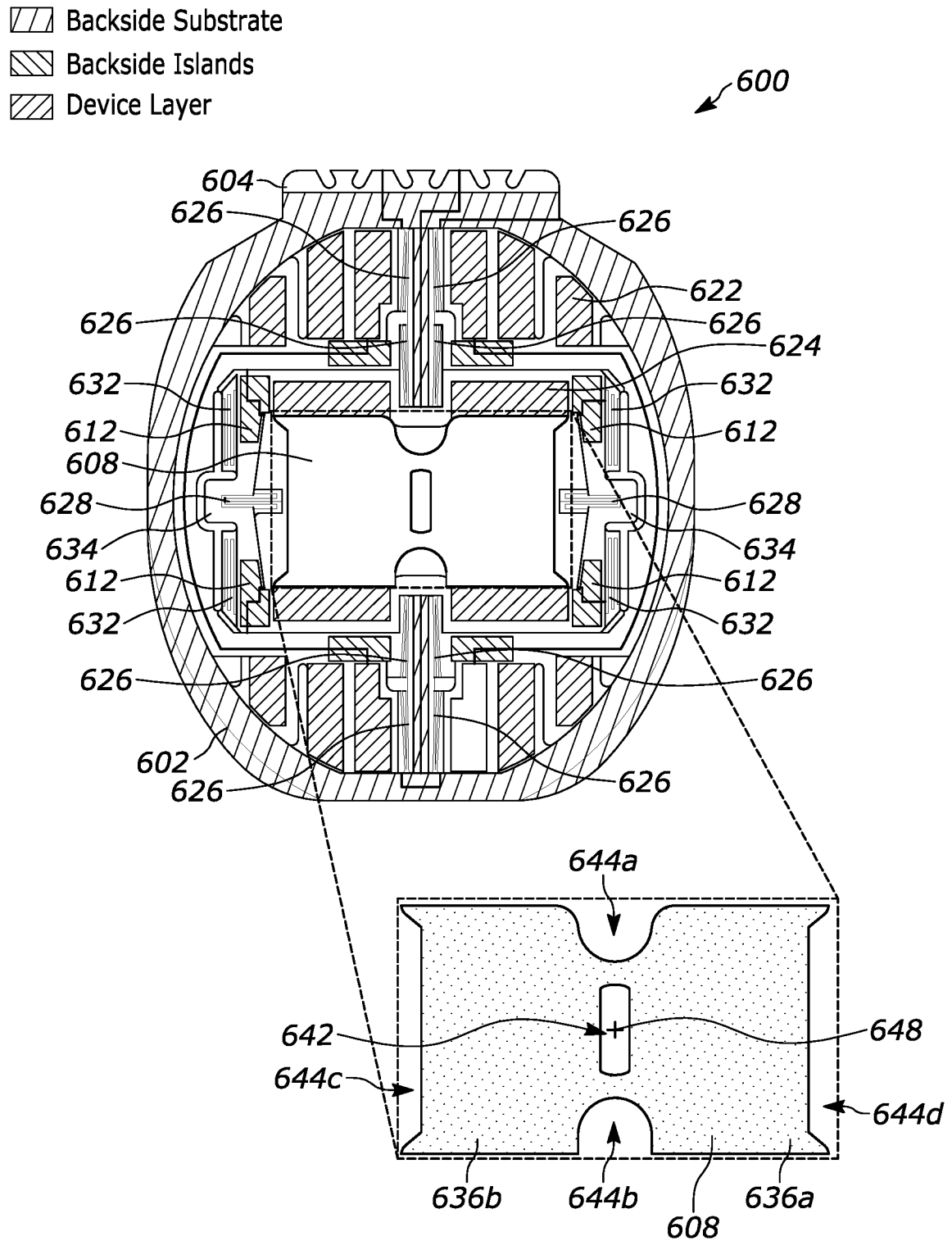


FIG. 6

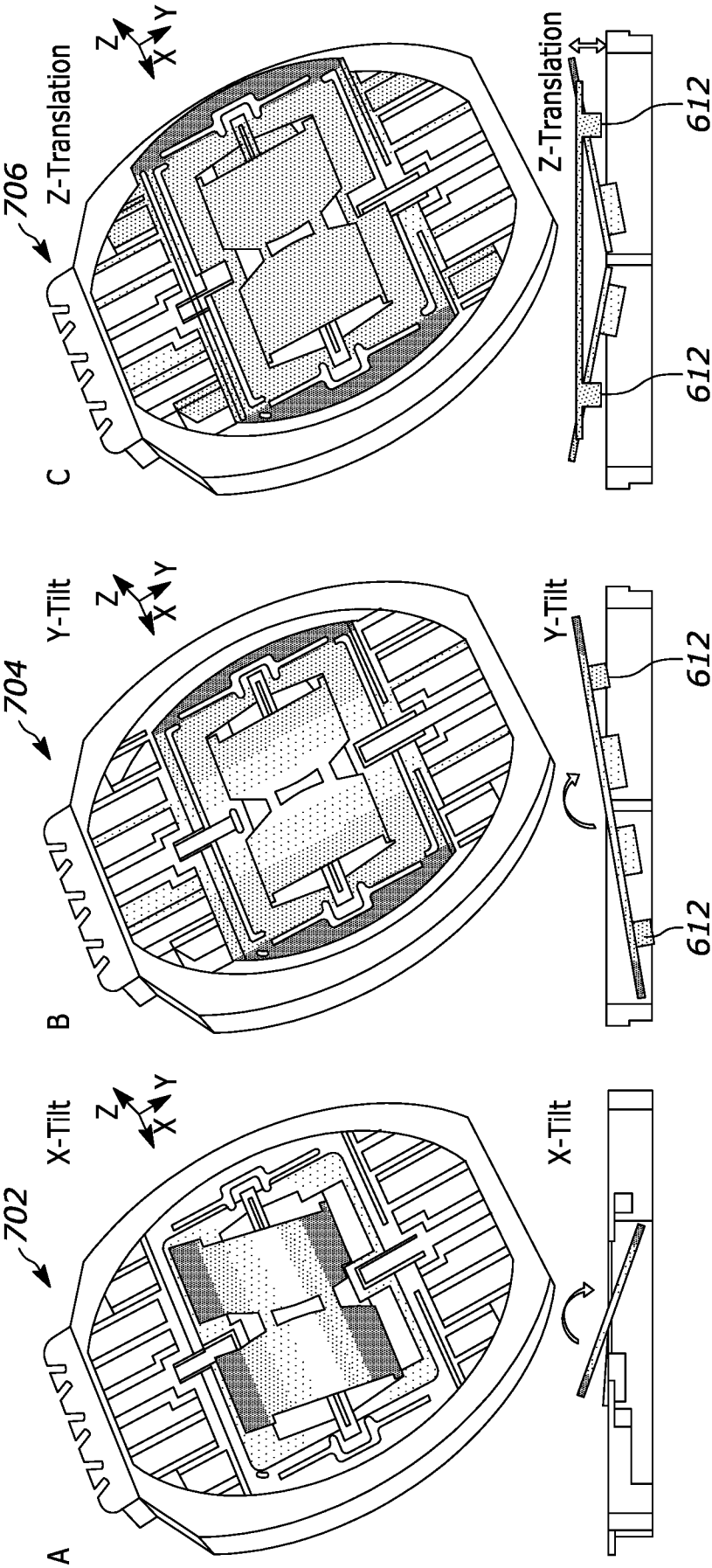
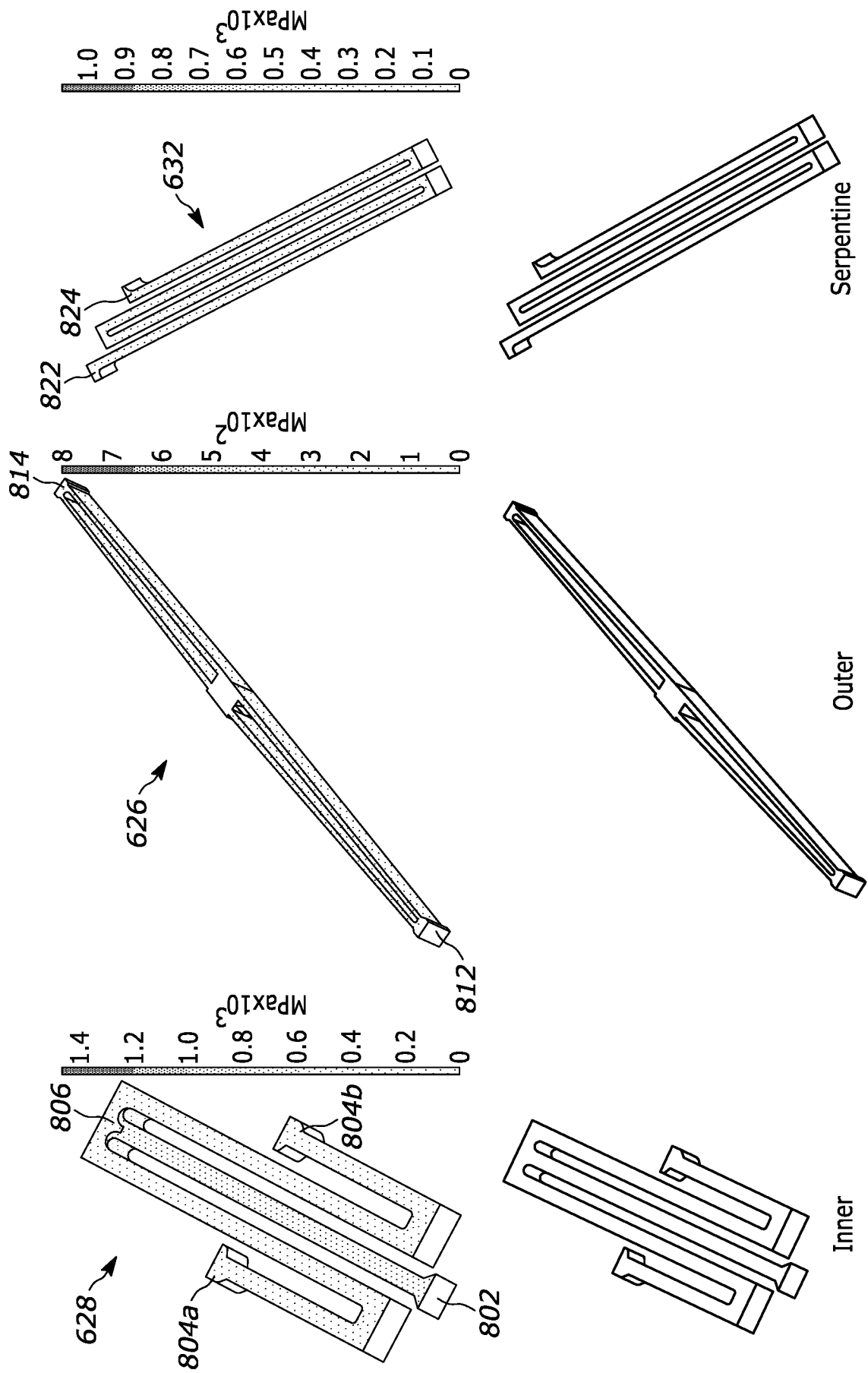


FIG. 7



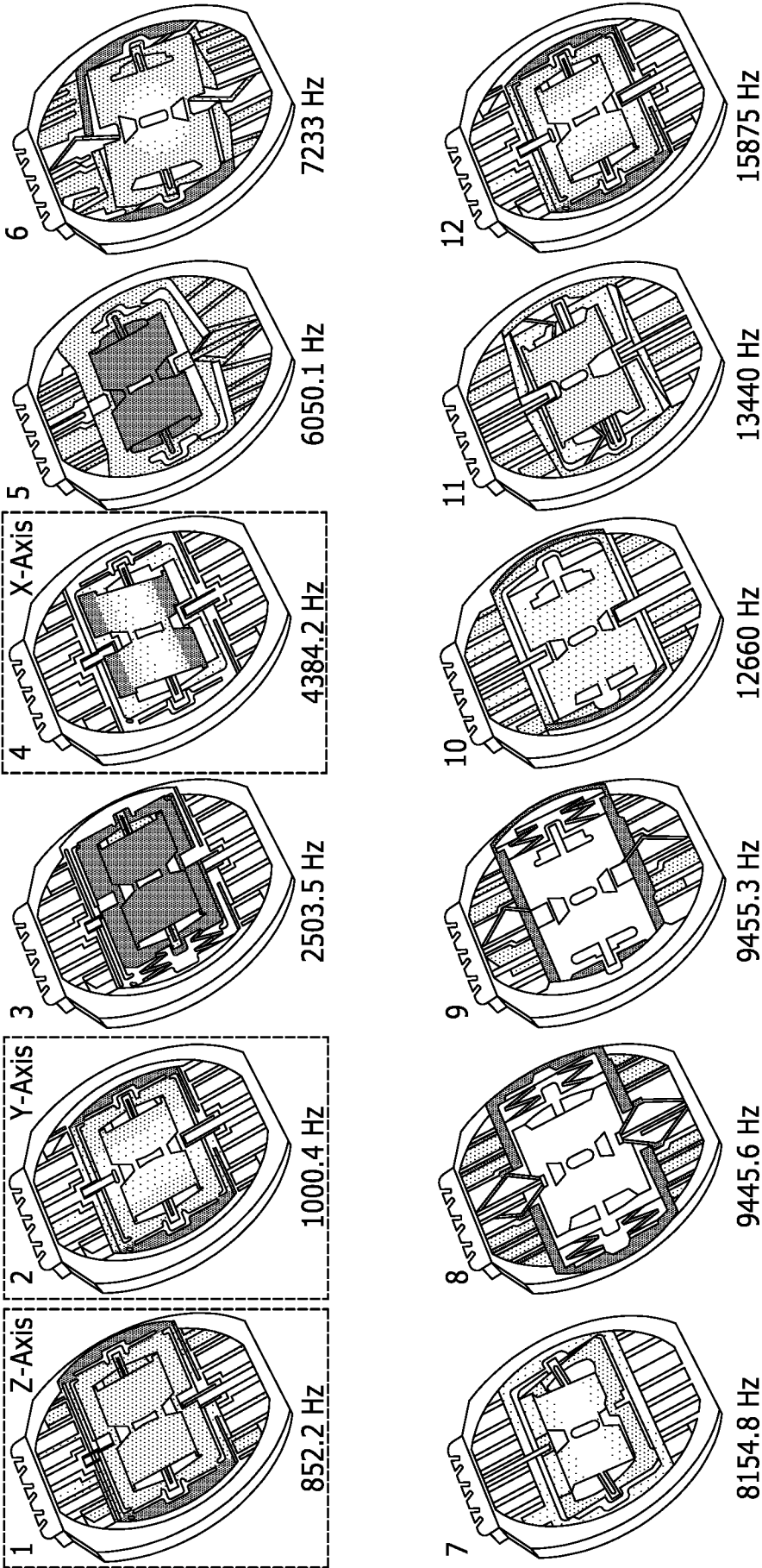


FIG. 9

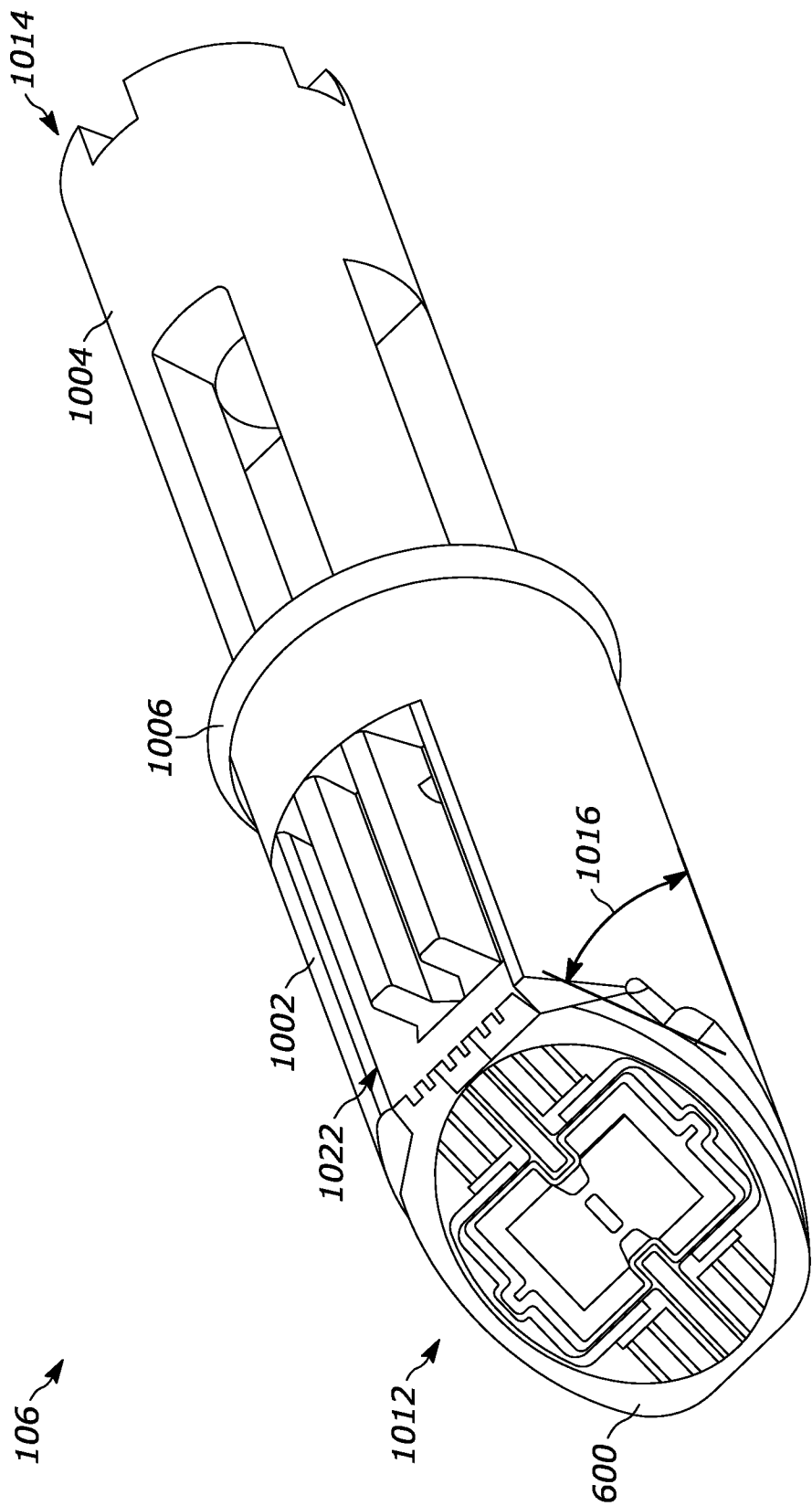


FIG. 10

11/18

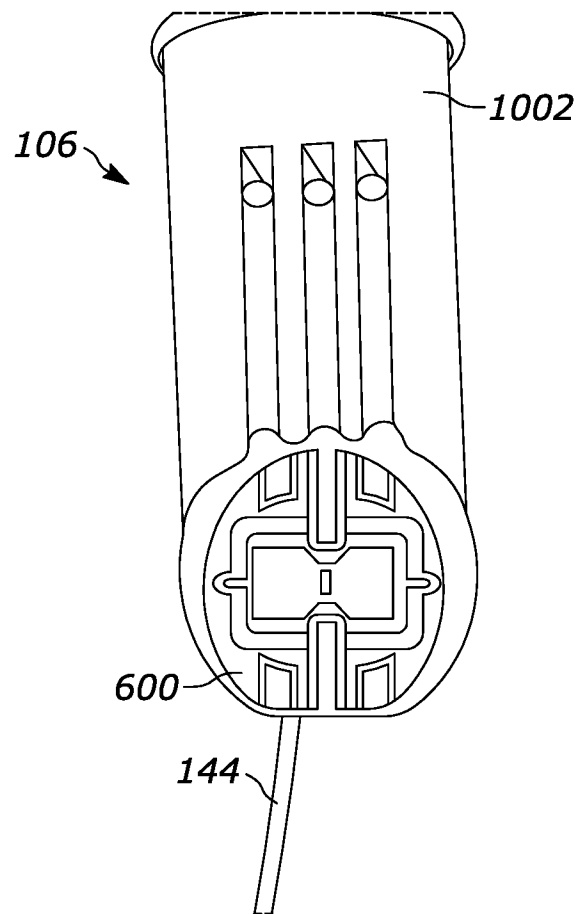


FIG. 11A

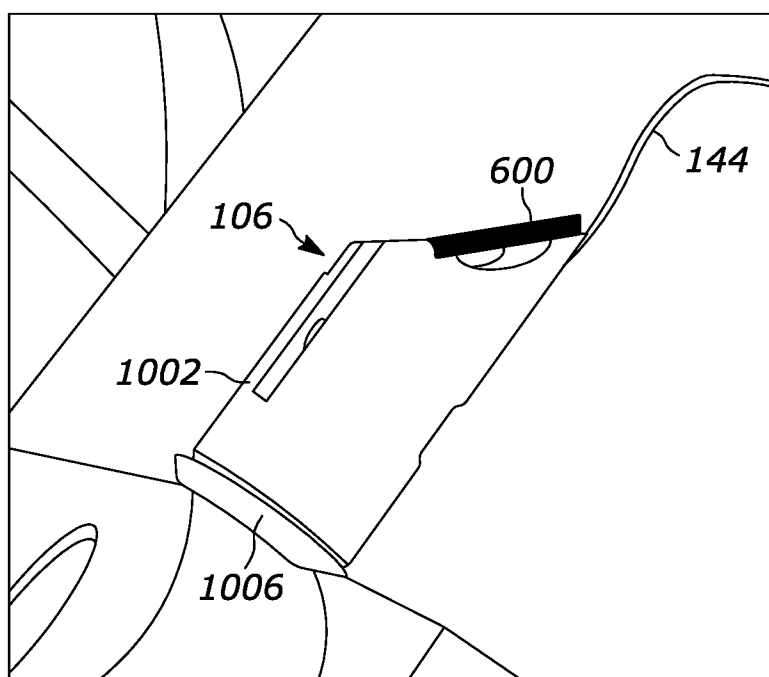


FIG. 11B

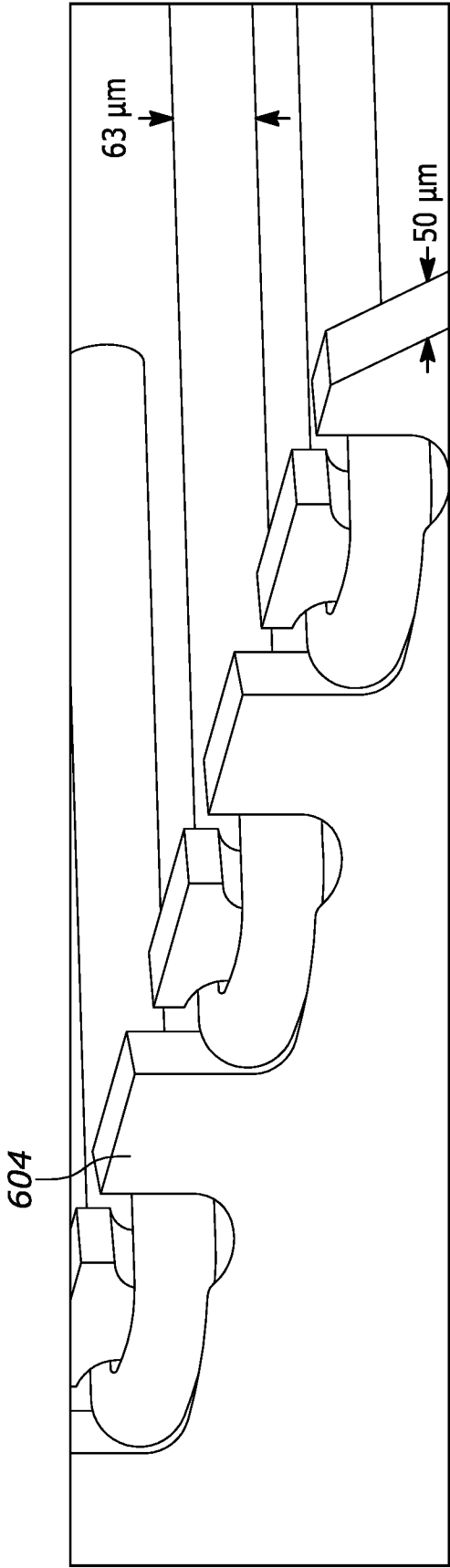


FIG. 12A

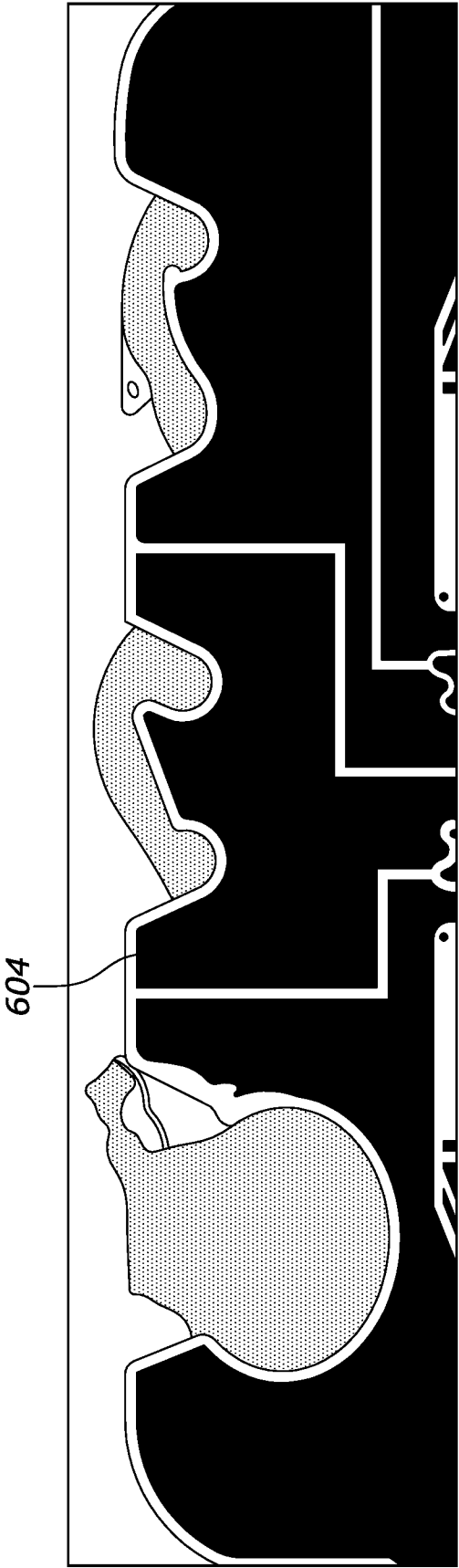


FIG. 12B

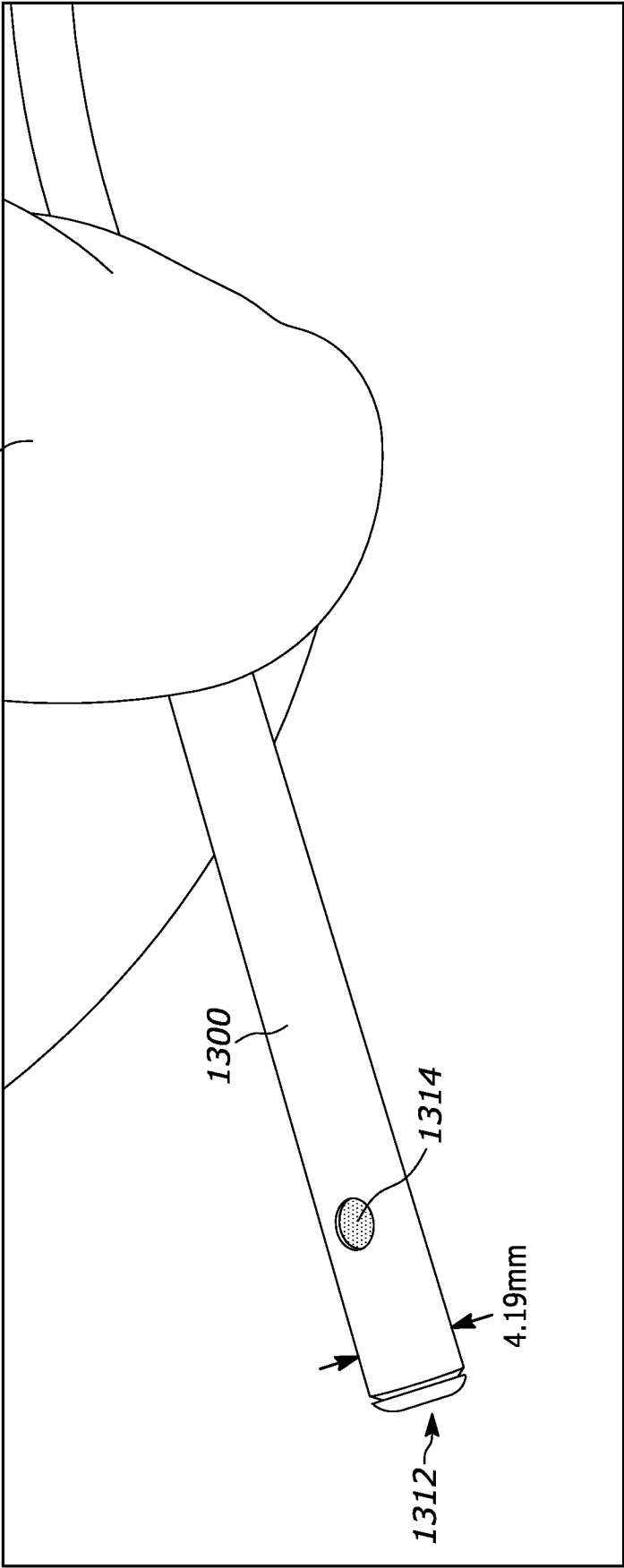


FIG. 13

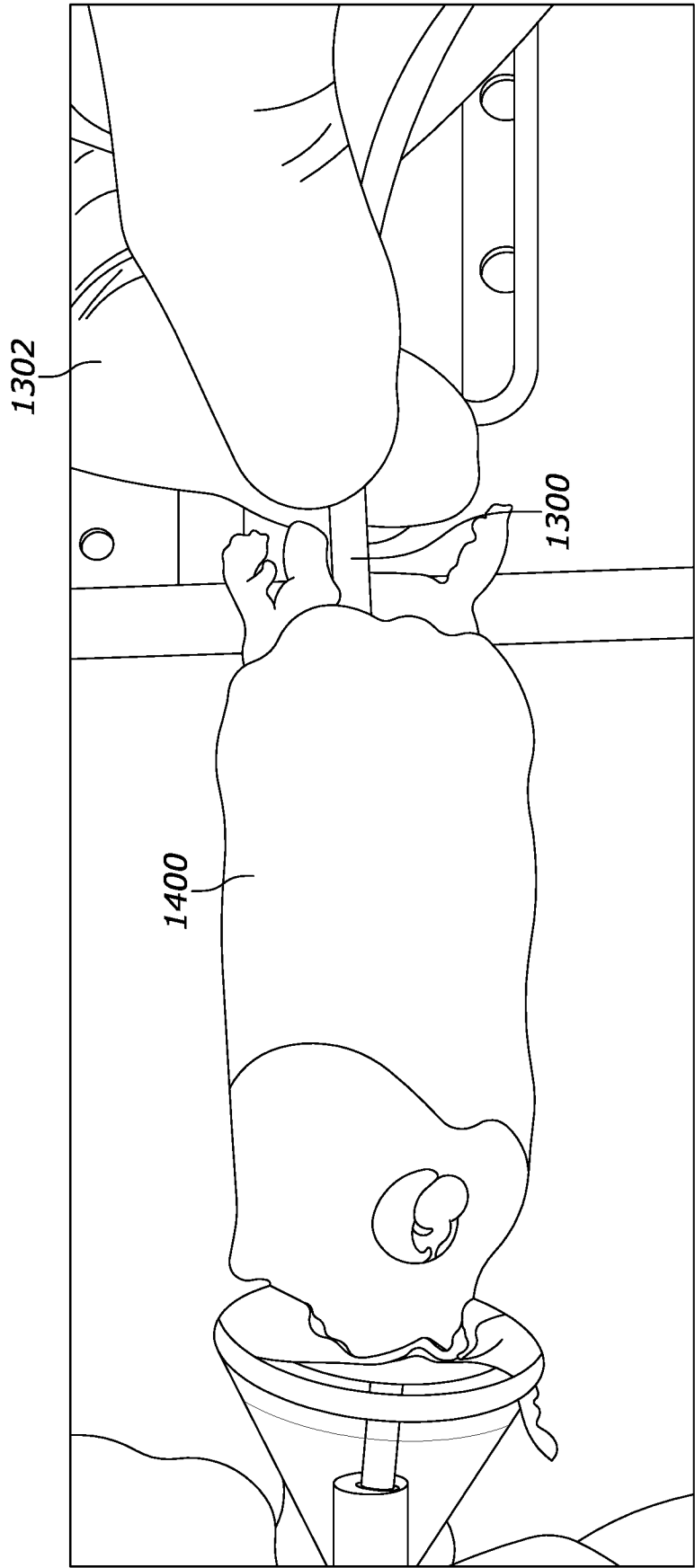


FIG. 14

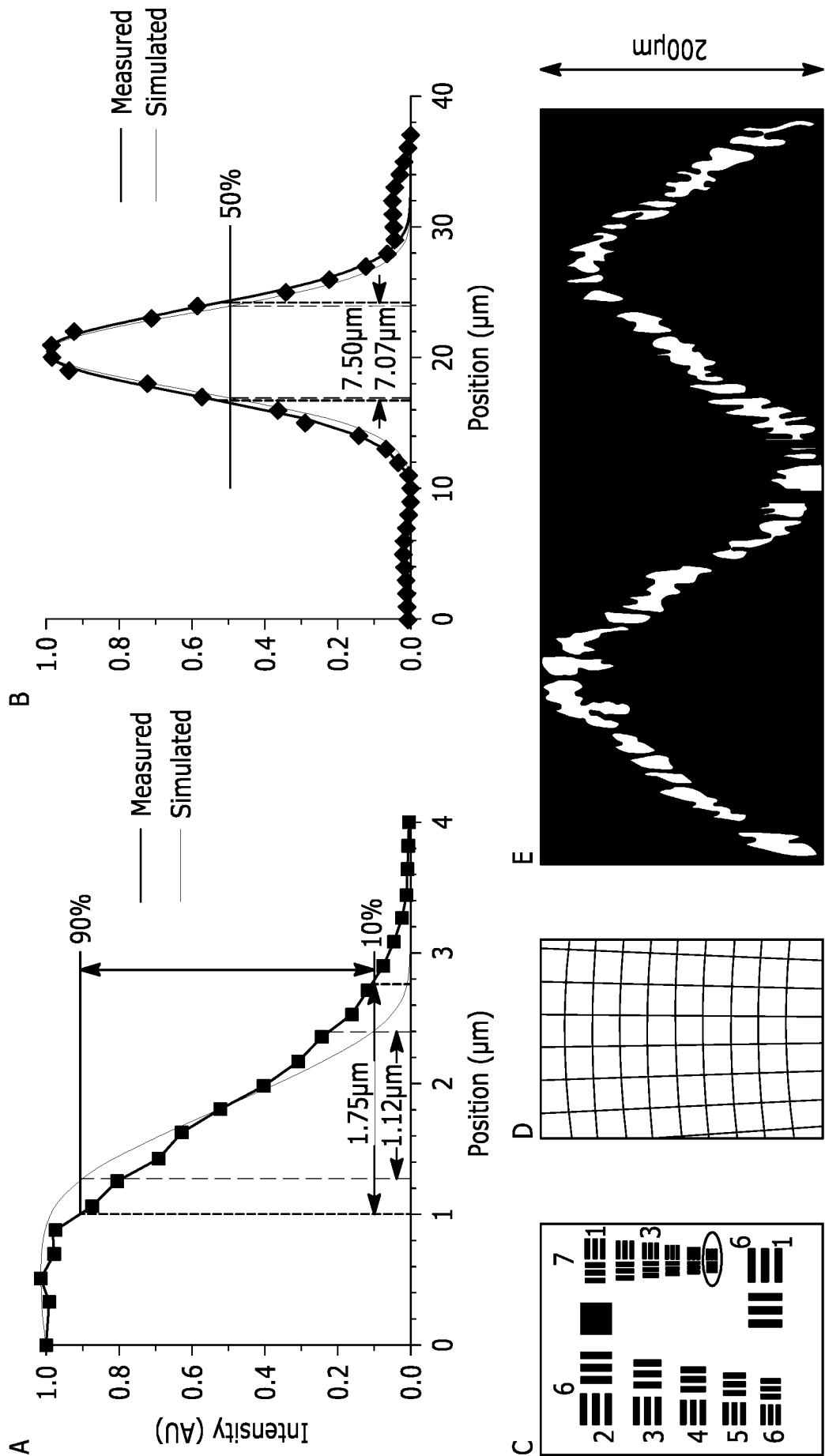


FIG. 15

16/18

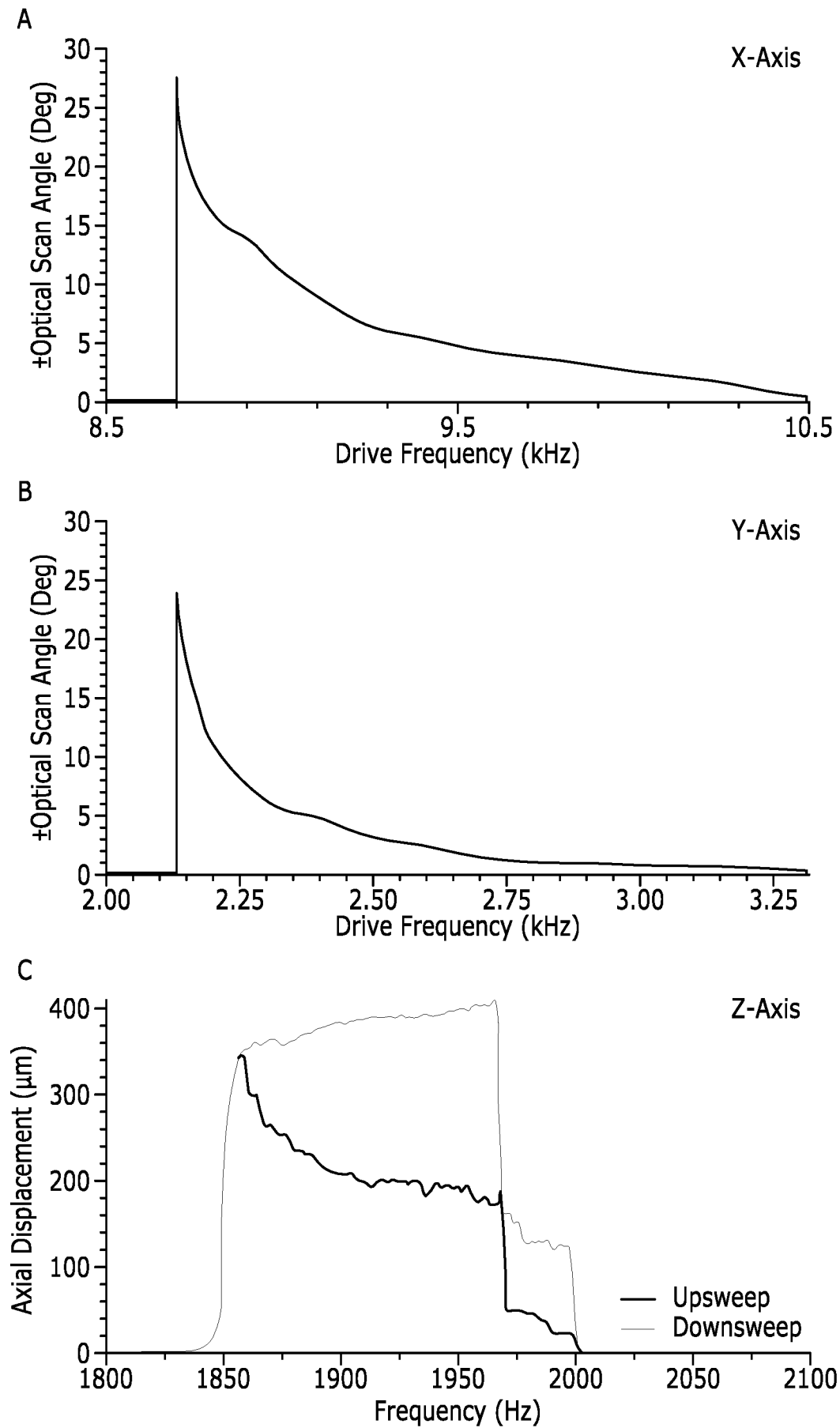


FIG. 16

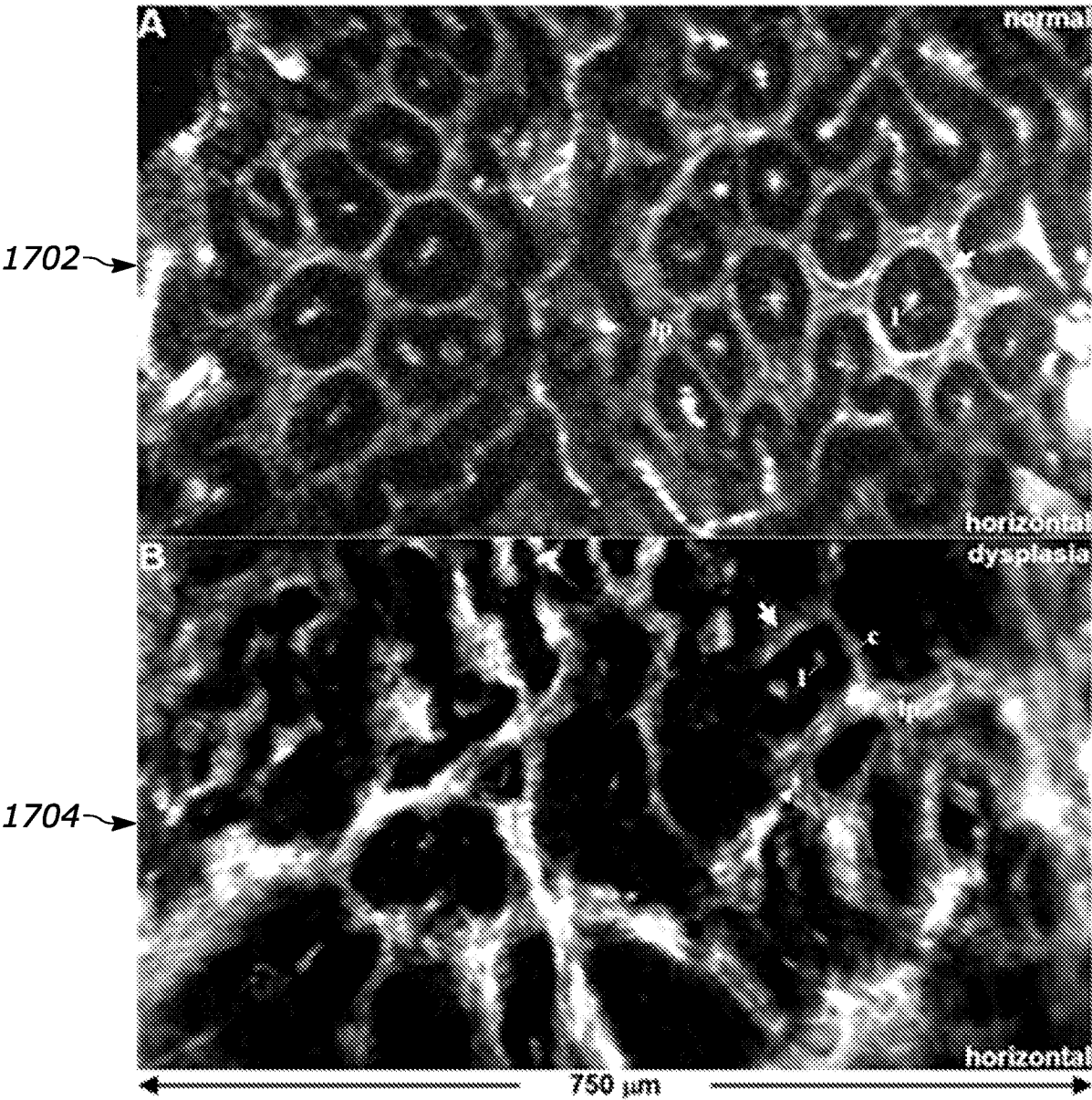


FIG. 17A

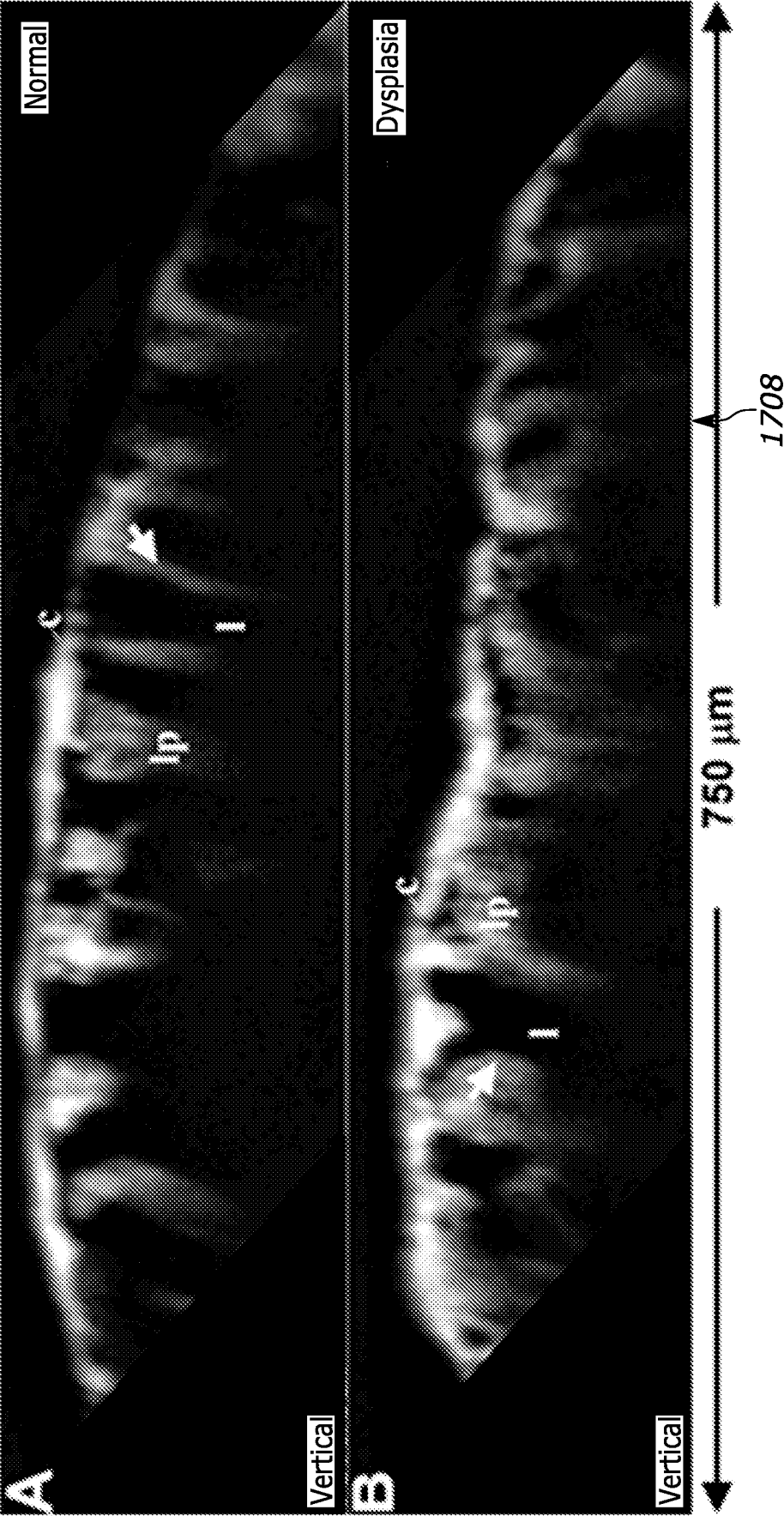


FIG. 17B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/013172

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61B5/00	G02B21/00
	G02B23/24	A61B1/00
	G02B26/10	G02B23/26
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)		
EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	XIYU DUAN ET AL: "Visualizing epithelial expression of EGFR in vivo with distal scanning side-viewing confocal endomicroscope", SCIENTIFIC REPORTS, vol. 6, no. 1, 22 November 2016 (2016-11-22), pages 1-9, XP055570870, DOI: 10.1038/srep37315 the whole document ----- -/--	1-19
☒ 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		Date of mailing of the international search report
8 May 2024		27/05/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Wolf, Steffen

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2024/013172

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOEY M JABBOUR ET AL: "Confocal Endomicroscopy: Instrumentation and Medical Applications", ANNALS OF BIOMEDICAL ENGINEERING, KLUWER ACADEMIC PUBLISHERS-PLENUM PUBLISHERS, NE, vol. 40, no. 2, 13 October 2011 (2011-10-13), pages 378-397, XP035016172, ISSN: 1573-9686, DOI: 10.1007/S10439-011-0426-Y pages 379-386; figures 1, 2 -----	1-19
Y	US 2020/000341 A1 (MESSERSCHMIDT BERNHARD [DE] ET AL) 2 January 2020 (2020-01-02) paragraphs [0002] - [0061]; figures 1-3 -----	1-19
Y	US 2012/330157 A1 (MANDELLA MICHAEL [US] ET AL) 27 December 2012 (2012-12-27) paragraphs [0066] - [0101]; figures 1-7 -----	1-19
Y	US 2011/125029 A1 (WANG THOMAS D [US] ET AL) 26 May 2011 (2011-05-26) paragraph [0076]; figure 9 -----	9
A	LI GAOMING ET AL: "Ultra-Compact Microsystems-Based Confocal Endomicroscope", IEEE TRANSACTIONS ON MEDICAL IMAGING, IEEE, USA, vol. 39, no. 7, 3 February 2020 (2020-02-03), pages 2406-2414, XP011796116, ISSN: 0278-0062, DOI: 10.1109/TMI.2020.2971476 [retrieved on 2020-06-30] the whole document -----	1-19
A	M. ATIF ET AL: "Catheters for optical coherence tomography", LASER PHYSICS LETTERS, vol. 8, no. 9, 1 July 2011 (2011-07-01), pages n/a-n/a, XP055049797, ISSN: 1612-2011, DOI: 10.1002/lapl.201110035 the whole document -----	1-19
A	US 2012/140302 A1 (XIE HUIKAI [US] ET AL) 7 June 2012 (2012-06-07) paragraphs [0035] - [0054]; figures 1-6 -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/013172

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2020000341 A1	02-01-2020	DE 102017104617 A1 EP 3592210 A1 US 2020000341 A1 WO 2018162303 A1	06-09-2018 15-01-2020 02-01-2020 13-09-2018
US 2012330157 A1	27-12-2012	NONE	
US 2011125029 A1	26-05-2011	US 2011125029 A1 WO 2011053828 A2	26-05-2011 05-05-2011
US 2012140302 A1	07-06-2012	US 2012140302 A1 WO 2011028595 A2	07-06-2012 10-03-2011