(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 September 2015 (24.09.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/140782 A1

(51) International Patent Classification:
*A61B 5/00* (2006.01) *A61B 6/04* (2006.01)
*A61B 5/05* (2006.01) *A61B 8/00* (2006.01)
*A61B 5/055* (2006.01) *G21K 5/08* (2006.01)
*A61B 6/02* (2006.01)

(21) International Application Number:
PCT/IL2015/050207

(22) International Filing Date:
24 February 2015 (24.02.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/954,661 18 March 2014 (18.03.2014) US

(72) Inventor; and
(71) Applicant : **KWIAT, Doron** [IL/IL]; 17/2 Erez Street, 7680400 Mazkeret Batia (IL).

(74) Agents: **EHRLICH, Gal** et al.; G. E. Ehrlich (1995) LTD., 11 Menachem Begin Road, 5268104 Ramat Gan (IL).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *of inventorship (Rule 4.17(iv))*

**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))*

(54) **Title**: BIOPSY METHOD AND CLINIC FOR IMAGING AND BIOPSY

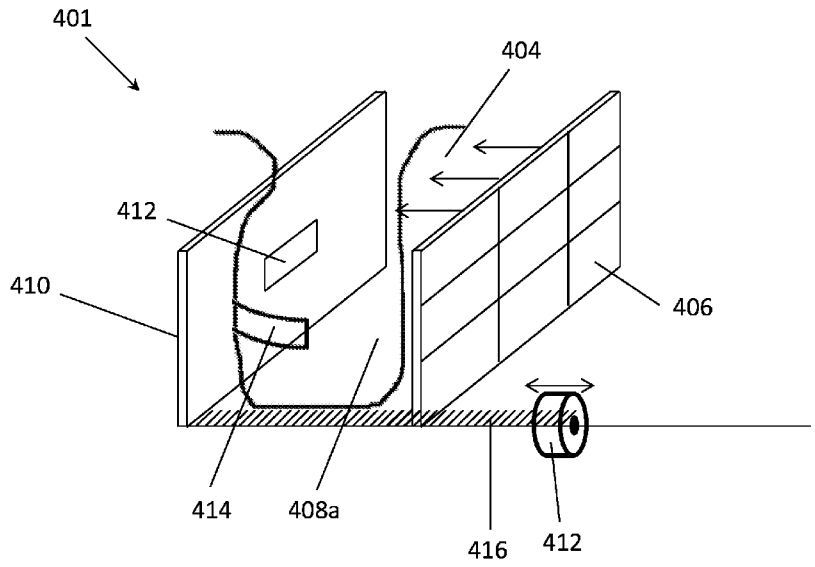



FIG. 4B

(57) **Abstract**: A method of preparing tissue for biopsy comprising: restraining non-rigid tissue by applying pressure to the non-rigid tissue; imaging restrained non-rigid tissue to provide at least one image thereof; releasing the non-rigid tissue; re-restraining the non-rigid tissue by applying pressure to the non-rigid tissue, after the imaging; and registering re-restrained tissue with the at least one image.

WO 2015/140782 A1

# BIOPSY METHOD AND CLINIC FOR IMAGING AND BIOPSY

## RELATED APPLICATION/S

This application claims the benefit of priority under 35 USC §119(e) of U.S. Provisional Patent Application No. 61/954,661 filed March 18, 2014, the contents of which are incorporated herein by reference in their entirety.

## FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to a method of biopsy, a clinic for imaging and biopsy and, more particularly, but not exclusively, to a method of biopsy of non-rigid tissue and a clinic for imaging and biopsy of non-rigid tissue.

Biopsy of patients inside imaging devices, e.g. MRI (Magnetic Resonance Imaging) and CT (Computed Tomography), guided by real time imaging is problematic, due to, for example, inaccessibility, limited space and the need for biopsy tools to be imager compatible (e.g. non-metallic for MRI compatibility). Current technologies correspondingly focus on biopsy taken outside of the imaging device.

Generally, biopsy involves several imaging procedures. Often, an initial scan is performed to identify suspected lesions. For breast tissue, identifying scans (e.g. MRI, CT, mammogram) are traditionally carried out on both breasts at the same time, where a patient lies on a rest and patient breasts hang into or are supported by one or more compartment of the rest. For MRI imaging, the imaging rest includes MRI coils and is sometime termed a 'breast cage'.

Once one or more region of interest (e.g. lesions) is identified from images for biopsy, generally, the breast to be biopsied is restrained by a compression and identification grid inserted into the rest. As movement of the patient and/or penetration of biopsy tools (e.g. needle and/or guiding stylus) can cause the breast to move, the grid holds breast tissue firmly. This means that, when biopsy is performed, based on the scanned images, shape and location of the breast and/or lesion location in the breast does not change.

The patient is scanned again, providing images of the region/s of interest (e.g. lesions) with respect to the grid. The patient is then removed from the imaging device and, generally, a biopsy tool is inserted 'blind' into patient tissue using a computer generated point of penetration pre-calculated from images.

So that the position of the tip of a biopsy tool is in a known position, generally, biopsy tool penetration angles are restricted, for example, to perpendicular to the grid. Techniques for angled penetration (e.g. at angles other than perpendicular to the grid) are time consuming and/or expensive, involving a special fixation mechanism and/or robotics.

Generally, where blind penetration is used, the patient is re-scanned once a needle guiding stylus is inserted, to validate the stylus position so that biopsy is taken of the desired region of tissue.

Although MRI provides more informative soft tissue images than other imaging techniques (e.g. x-ray, ultrasound), use is restricted, for example, due to high costs and/or lengthy biopsy procedures, for example associated with multiple scans.

Alternatively, biopsy of lesions identified from MRI/CT images can be guided by ultrasound imaging. Ultrasound provides real time images of the biopsy tool and patient tissue. However, in many cases, target lesions are not visible, as ultrasound images have lower resolution, tissue contrast, and conspicuity than MRI/CT. Locating target lesions in ultrasound can be particularly problematic where breast tissue is dense and/or where target lesions are small in size. Ultrasound guided biopsy is also limited to tissue unobscured by echogenic tissue (e.g. bone).

Additional background art includes U.S. Patent Application Publication No. 2012/271095, U.S. Patent No. 6,968,033, U.S. Patent Application Publication No. 2013/072963, U.S. Patent Application Publication No. 2013/165768, International Patent Application Publication No. WO 2012032308, International Patent Application Publication No. WO 2013119932, U.S. Patent Application Publication No. 2013/0317347, European Patent No. 1844712, European Patent No. 2561817, U.S. Patent No. 8587311, U.S. Patent No. 8473027, and U.S. Patent No. 8285361, and European Patent No. 1510182.

SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a method of preparing tissue for biopsy comprising: restraining non-rigid tissue by applying pressure to the non-rigid tissue; imaging restrained non-rigid tissue to provide at least one image thereof; releasing the non-rigid tissue; re-restraining the non-rigid tissue by applying pressure to the non-rigid tissue, after the imaging; and registering re-restrained tissue with the at least one image.

According to some embodiments of the invention at least 50% of an outer surface said re-restrained tissue is within at least 50mm of a geometry of said restrained non-rigid tissue.

According to some embodiments of the invention at least 90% of an outer surface the re-restrained tissue is within at least 1mm of a geometry of the restrained non-rigid tissue.

According to some embodiments of the invention registering comprises registering a biopsy tool with the at least one image.

According to some embodiments of the invention the non-rigid tissue is breast tissue.

According to some embodiments of the invention the imaging is by an imaging device; wherein the non-rigid tissue is of a first patient; wherein after the imaging the imaging device is free for imaging of a second patient.

According to some embodiments of the invention the restrained non-rigid tissue is restrained by an imaging restraining device; and wherein re-restraining is by a biopsy restraining device.

According to some embodiments of the invention the method comprises: measuring restrained tissue conditions; and wherein the re-restraining comprises re-restraining non-rigid tissue according to the restrained tissue conditions. According to some embodiments of the invention the tissue conditions comprise tissue dimensions. According to some embodiments of the invention the tissue conditions comprise tissue compression.

According to some embodiments of the invention the method comprises: collecting a biopsy with the biopsy tool.

According to some embodiments of the invention the collecting comprises: positioning the biopsy tool automatically based on a registered position of a target portion of the non-rigid tissue. According to some embodiments of the invention the collecting comprises insertion an interventional portion of the biopsy tool automatically, based on a registered position of the target portion of tissue.

According to some embodiments of the invention the non-rigid tissue is prostate tissue.

According to some embodiments of the invention imaging comprises imaging one or more fiducials; the method comprises measuring position of one or more fiducials; and registering comprises registering fiducials image space location with measured real space position of fiducials.

According to some embodiments of the invention, the method comprises: displaying the at least one image.

According to some embodiments of the invention, the method comprises: displaying a registered position of at least a portion of the biopsy tool on the displayed image.

According to some embodiments of the invention the registering re-restrained tissue with the at least one image comprises: sizing the image; rotating the image; and translating the image.

According to some embodiments of the invention the imaging is selected from the group consisting of CT imaging and MRI imaging.

According to some embodiments of the invention the at least one image is three dimensional image data; wherein the displaying comprises displaying a slice of the image data. According to some embodiments of the invention the slice is selected using a user input on the biopsy tool.

According to some embodiments of the invention the method comprises reimaging the re-restrained tissue to provide at least one re-restrained tissue image thereof; and wherein the displaying comprises displaying the re-restrained tissue image.

According to some embodiments of the invention, the method comprises wherein the displaying comprises displaying the slice side by side with the re-restrained tissue image. According to some embodiments of the invention reimaging is ultrasound imaging.

According to an aspect of some embodiments of the present invention there is provided a method of displaying image data comprising: imaging tissue with an imager, to provide three dimensional image data image thereof; registering tissue, outside the imager, with the three dimensional image data; registering a tool with the at least one image; and displaying a slice of the three dimensional image data, where the displayed slice is selected using a user input on the biopsy tool.

According to some embodiments of the invention the displaying comprises displaying a position of at least a portion of the biopsy tool on the displayed slice.

According to some embodiments of the invention the registering a tool comprises registering a position and orientation of the tool with respect to the image data; and wherein the displaying comprises displaying a slice of the image data at a tip of the tool and perpendicular to a tool long axis.

According to some embodiments of the invention, the displaying comprises displaying a slice of image data including a target portion of the image data.

According to an aspect of some embodiments of the present invention there is provided an imaging and biopsy clinic comprising: an imaging device; an imaging restraining device for restraining of non-rigid tissue inside the imaging device; a biopsy restraining device for restraining of non-rigid tissue outside the imaging device; and a biopsy tool.

According to some embodiments of the invention the imaging restraining device includes at least one measuring device for measuring restrained tissue conditions; and wherein the biopsy restraining device includes at least one sensor for replicating the restrained tissue conditions. According to some embodiments of the invention the at least one measuring device comprises a pressure gauge.

According to some embodiments of the invention the at least one measuring device comprises scale. According to some embodiments of the invention the at least one measuring device comprises a position sensor. According to some embodiments of the invention the biopsy tool includes at least one position sensor.

According to some embodiments of the invention the imaging and biopsy clinic comprises: a plurality of ultrasound pulse transmitters; wherein the biopsy tool position sensor is an ultrasound receiver.

According to some embodiments of the invention the imaging restraining device comprises a grid plate comprising a folding portion; and wherein the biopsy restraining device comprises a grid plate comprising a folding portion.

According to some embodiments of the invention the non-rigid tissue is breast tissue. According to some embodiments of the invention non-rigid tissue is prostate tissue.

According to some embodiments of the invention the imaging device is a MRI imaging device. According to some embodiments of the invention the imaging device is a CT imaging device.

According to some embodiments of the invention the biopsy tool includes an ultrasound probe.

According to some embodiments of the invention the clinic comprises an apparatus for support and automatic movement of the biopsy tool.

According to an aspect of some embodiments of the present invention there is provided a method of biopsy comprising: collecting first image data of patient tissue, including a tissue target, using a first imaging type; registering a patient and a biopsy tool position to the first image data; collecting a second image of the patient tissue using a second imaging type with a biopsy tool including an imager; displaying, side by side, the second image and a slice of the first image data corresponding to an orientation of the second image; superimposing on the display a biopsy tool position; and collecting a biopsy of the tissue target based on the display.

According to some embodiments of the invention the method comprises: displaying a registered position of at least a portion of the biopsy tool on the first image.

According to some embodiments of the invention the method comprises: restraining the patient tissue before the collecting a first image; and re-restraining the patient tissue before the collecting a second image.

According to some embodiments of the invention the second image is an ultrasound image using an ultrasound probe; and wherein the collecting a second image is through the ultrasound probe.

According to an aspect of some embodiments of the present invention there is provided a biopsy tool comprising: a user interface; at least one position sensor; and a processor to generate a control signal based on input to the user interface and

measurement by the position sensor; a transmitter to transmit the control signal to a remote display; an ultrasound transducer comprising a channel; and a needle positioned and sized to pass through the channel.

According to some embodiments of the invention the biopsy tool comprises an ultrasound probe. According to some embodiments of the invention the biopsy tool comprises more than one biopsy needle.

A method of prostate biopsy comprising: restraining prostate tissue by applying pressure using a first rectal probe and inflating a balloon to the prostate tissue;

imaging restrained non-rigid tissue to provide at least one image thereof; releasing the non-rigid tissue; re-restraining the non-rigid tissue by applying pressure using a second rectal probe and inflating a balloon to the prostate tissue; and registering re-restrained tissue with the at least one image; collecting a biopsy from a target portion of the prostate tissue.

According to some embodiments of the invention the imaging is MRI imaging and the first rectal probe includes MRI coils.

According to some embodiments of the invention the second rectal probe includes an ultrasound transducer.

According to some embodiments of the invention, the collecting comprises collecting biopsy through the ultrasound transducer.

According to some embodiments of the invention, the registering re-restrained tissue with the at least one image comprises: sizing the image; rotating the image; and translating the image.

## BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIG. 1 is a flowchart of a method of biopsy, according to some embodiments of the invention;

FIG. 2 is a flowchart of methods of biopsy, according to some embodiments of the invention;

FIG. 3A is a schematic drawing of a side view of a breast restraining device, according to some embodiments of the invention;

FIG. 3B is a schematic drawing of a patient lying on a simplified schematic of a breast restraining device, according to some embodiments of the invention;

FIG. 3C is a schematic drawing of a breast restraining device, according to some embodiments of the invention;

FIG. 3D is a schematic drawing of a breast restraining device, according to some embodiments of the invention;

FIG. 4A is a schematic drawing of at least a portion of a breast restraining device, and an un-restrained breast, according to some embodiments of the invention;

FIG. 4B is a schematic drawing of breast restraining device, and a restrained breast, according to some embodiments of the invention;

FIG. 4C is a schematic illustration of a breast restraining device including automatic features;

FIG. 4D is a schematic illustration of a breast restraining device, according to some embodiments of the invention;

FIG. 5 is a simplified schematic cross sectional view of a probe inserted into a patient rectum, according to some embodiments of the invention;

FIG. 6A is a simplified schematic of a user manually inserting a portion of a manually positioned biopsy tool into a patient, according to some embodiments of the invention;

FIG. 6B is a simplified schematic side view of a patient positioned on an automatic breast biopsy and/or treatment apparatus, according to some embodiments of the invention;

FIG. 6C is a simplified schematic side view of a patient positioned underneath an automatic biopsy and/or treatment apparatus, according to some embodiments of the invention;

FIG. 7A is a flowchart of a method of scanning and biopsy in an imaging and biopsy clinic, with time;

FIG. 7B is a flowchart showing scanning and biopsy in an imaging and biopsy clinic, with time, according to some embodiments of the invention;

FIG. 8 is a simplified top view of a clinic for imaging and biopsy, according to some embodiments of the invention;

FIG. 9A is a simplified top view of a clinic for imaging and biopsy, set up for imaging of a first patient, according to some embodiments of the invention;

FIG. 9B is a simplified top view of a clinic for imaging and biopsy, set up for biopsy of a first patient, and imaging of a second patient, according to some embodiments of the invention;

FIG. 10A is a simplified top view of a clinic for imaging and biopsy, set up for imaging of a first patient, according to some embodiments of the invention;

FIG. 10B is a simplified top view of a clinic for imaging and biopsy, set up for biopsy of a first patient, and imaging of a second patient, according to some embodiments of the invention;

FIG. 11 is a flowchart of a method of scanning and biopsy and/or treatment, according to some embodiments of the invention;

FIG. 12A is a simplified schematic illustration of a biopsy tool, according to some embodiments of the invention;

FIG. 12B illustrates a simplified schematic of a biopsy tool, according to some embodiments of the invention;

FIG. 13 illustrates a simplified schematic of a grid plate;

FIG. 14 illustrates a simplified schematic of a plate with a folding portion, according to some embodiments of the invention;

FIG. 15 illustrates a simplified schematic illustration of a compressed breast in a restraining device;

FIG. 16 illustrates a simplified schematic illustration of a compressed breast in a restraining device, according to some embodiments of the invention;

FIG. 17 is a simplified schematic illustration of an insertion unit, according to some embodiments of the invention;

FIG. 18 is a simplified schematic illustration of an insertion unit in place on one pane of a grid plate, according to some embodiments of the invention;

FIG. 19A is a simplified schematic illustration of a biopsy tool, according to some embodiments of the invention;

FIG. 19B is a simplified schematic illustration of a ring holder, according to some embodiments of the invention;

FIG. 20 is a simplified schematic cross sectional view of an exemplary biopsy tool, according to some embodiments of the invention;

FIG. 21A illustrates a biopsy tool, according to some embodiments of the invention;

FIG. 21B illustrates a biopsy tool, during biopsy collection, according to some embodiments of the invention;

FIG. 22 is a simplified schematic side view of a portion of a mobile unit including a user interface, according to some embodiments of the invention;

FIG. 23 is a simplified schematic side view of a tool including an ultrasound probe and a navigating unit, according to some embodiments of the invention;

FIG. 24 is a simplified schematic cross sectional view of a biopsy tool including more than one needle, according to some embodiments of the invention;

FIG. 25A is a simplified schematic side view of a tool including an ultrasound probe treating and/or collecting biopsy from a patient prostate, according to some embodiments of the invention;

FIG. 25B is a simplified schematic of a display, according to some embodiments of the invention;

FIG. 26A is a simplified schematic side view of a tool and displayed slices of image data, according to some embodiments of the invention;

FIG. 26B is a simplified schematic of a display, according to some embodiments of the invention;

FIG. 27A is a simplified schematic side view of a tool and displayed slices of image data, according to some embodiments of the invention;

FIG. 27B is a simplified schematic of a display, according to some embodiments of the invention; and

FIG. 28A and FIG. 28B show tool positioning adjustments that may be made by the operator to account for tissue flexibility under pressure, according to some embodiments of the invention.

## DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to a method of biopsy, a clinic for imaging and biopsy and, more particularly, but not exclusively, to a method of biopsy of non-rigid tissue and a clinic for imaging and biopsy of non-rigid tissue.

### Overview

An aspect of some embodiments of the invention relates to registration of one or more image (e.g. three dimensional image data) of restrained tissue, after imaging, with tissue which has optionally been released and re-restrained.

In some embodiments, re-restraining of the tissue is such that re-restrained tissue is under substantially the same conditions as during imaging (e.g. position and/or compression and/or geometrical shape). In some embodiments, a re-restrained tissue geometry is substantially the same as a restrained tissue geometry, where, for example, re-strained tissue is deformed to the same extent as restrained tissue.

For example, in some embodiments, re-restraining is accurate (e.g. re-restraining replicates restraining) such that at least 70%, or at least 80%, or at least 90%, or at least 95%, or at least 98% or lower, or higher, or intermediate percentages of an outer surface of re-restrained tissue is within at least 0.01-5mm, or at least 0.1-2mm, or at least 0.1-1mm or lower, or higher or intermediate measurements, of a geometry of an outer surface of the restrained tissue.

In some embodiments, re-restraining substantially replicates restrained compressions by approximately replicating restraining device dimensions and/or pressures (e.g. using one or more pressure gauge).

In some embodiments, re-restraining approximately replicates an imaging restraining procedure. For example, patient position and/or starting dimension/s of an imaging restraining device and/or finishing dimension/s of an imaging restraining device and/or speed of closure of an imaging restraining device are approximately replicated by a biopsy restraining device (e.g. using screws and/or marks on the

restraining device). For example, rate of inflation and/or pressure of inflation of a prostate balloon restraining device are approximately replicated by the biopsy restraining device.

In some embodiments, re-restraining is sufficiently accurate so that, for example, biopsy and/or treatment is carried out on one or more target, where registration of image/s does not include deforming the image/s, for example, registration of image/s including, scaling and/or rotation and/or translation.

In some embodiments, collected images are registered to patient tissue by registering a measured real-space position of marker/s, with corresponding imaged markers, where markers are, for example, attached to the patient.

In some embodiments, tissue restraining (e.g. by pressure applied to tissue) reduces deformation of tissue during collection of a biopsy (and/or treatment). In some embodiments, compressive force applied to tissue is 1-200N, 5-150N, or 10-100N, or lower, or higher, or intermediate forces. In some embodiments, during biopsy, restrained tissue is not substantially deformed, for example, under additional pressure exerted on the tissue by a biopsy tool. For example, in some embodiments, a dimension of restrained tissue, is deformed by at most 30%, or at most 20%, or at most 10%, or lower, or higher, or intermediate percentages, during collection of biopsy (and/or treatment). For example, in some embodiments, an outer surface of restrained tissue is deformed, during collection of biopsy (and/or treatment), by at most 2cm, or at most 1cm, or at most 0.5cm, or at most 0.1cm, or lower, or higher, or intermediate measurements. Potentially, lack of or minimal tissue deformation during biopsy improves accuracy of registration of images to re-restrained tissue, for example, improving accuracy of collection of biopsy from a desired target.

In some embodiments, insertion and/or penetration of an interventional portion of a tool (e.g. biopsy tool needle) into patient tissue and/or insertion of a probe (e.g. into the rectum) does not substantially deform tissue (e.g. as tissue is restrained). In some embodiments, a surface of the tissue is not deformed (e.g. as described herein). In some embodiments, a position of a target (e.g. a tumor) does not change upon insertion and/or penetration of an interventional portion of a tool (e.g. biopsy tool needle), for example, a target moving in position by at most 0.01-20%, or at most 0.01-10%, or at most 0.5-5%, or lower, or higher, or intermediate ranges or percentages of a target dimension axial

with a direction of insertion of the interventional portion. For example, a target moves at most 0.01-5mm, or at most 0.1-2mm, or lower, or higher, or intermediate measurements with respect to a tip of a tool interventional portion. In some embodiments through which a tool interventional portion passes e.g. tissue including one or more area to be avoided by the interventional tool (e.g. blood vessel/s and/or nerve tissue) is moved by penetration of the tool by at most 0.01-10%, or at most 0.5-5%, or lower, or higher, or intermediate percentages or ranges, of a depth of the tissue from a point of insertion of the interventional tool portion (e.g. biopsy needle). For example, a target moving at most 0.01-5mm, or at most 0.1-2mm, or lower, or higher, or intermediate distances or percentages with respect to a tip of a tool interventional portion.

In some embodiments, a measured real-space position of at least a portion of a tool (e.g. biopsy tool) is registered with the image/s. In some embodiments, biopsy and/or treatment of one or more region of interest within patient tissue is performed, using tool position with respect to the images and/or target tissue.

An aspect of some embodiments of the invention relates to biopsy and/or treatment guided by displaying an indication of a position of at least a portion of a tool registered (e.g. biopsy device needle) with respect to images (e.g. images of restrained tissue). For example, in some embodiments, a position of at least a portion of a tool is displayed with image/s (e.g. superimposed on images). In some embodiments, an indication of a distance of a portion of a tool to a target is displayed.

In some embodiments, a tool includes one or more user interface, through which a user controls displayed images, for example a user selects a slice of three dimensional image data for display.

In some embodiments, during restraining, imaging and re-restraining, the patient's body is substantially in the same position e.g. supine. Alternatively, in some embodiments, a position of a patient's body during restraining and imaging is different to a position of the patient's body during re-restraining and/or biopsy.

In some embodiments, patient tissue to be biopsied and/or treated is in a different configuration (e.g. position of different tissue types with respect to other tissue types and/or compression of tissue) to that when images were collected, for example, when a patient is placed in a different position for biopsy and/or treatment than the patient position during imaging. In some embodiments, tissue under different conditions (e.g.

position and/or compression) from the conditions the tissue was under during imaging is registered to the previously captured images using measured position of markers (scanning fiducials) e.g. by comparing measured position of markers to position of the markers in the image/s.

In some embodiments, measured and/or imaged markers (scanning fiducials) spatial separation in re-restraining is replicated by positioning and/or moving and/or compressing patient tissue.

In some embodiments, differences in marker position of a patient removed from the imager are used to register and/or align and/or distort previously collected image/s with the patient position.

In some embodiments, imaging and biopsy and/or treatment is of breast tissue. In some embodiments, imaging is of compressed breast tissue held in an imaging restraining device. In an exemplary embodiment, the imaging restraining device is a MRI breast coil cage, for example, including a plate (e.g. a grid plate).

In some embodiments, imaging and biopsy and/or treatment is of prostate tissue. In some embodiments, prostate tissue is compressed by a portion of an imaging restraining device, and re-compressed by a biopsy restraining device where, for example, the restraining device/s, include a balloon inflated within the rectum. In some embodiments, re-restraining of the prostate replicates a restrained and/or imaged position of the prostate within a patient body.

In some embodiments, image registration and accurate re-restraining, for example, enable biopsy and/or treatment of a region of interest identified and/or selected from images. In some embodiments, registration of a region of interest identified from images (e.g. lesion) and a biopsy device enable biopsy of the region of interest, outside of the imager.

An aspect of some embodiments of the invention relates to biopsy using previously collected image/s assisted using real time imaging (e.g. ultrasound imaging). In some embodiments, tissue is imaged using a first type of imaging (e.g. CT, MRI), the images are registered with a patient and/or a biopsy tool, optionally outside the imager and, in some embodiments, additional imaging is then performed. In some embodiments, additional imaging is used during positioning of a biopsy tool and/or collection of

biopsy. In some embodiments, previously collected image/s are displayed, for example, side by side, with real time images.

In some embodiments, a tool (e.g. biopsy tool) includes a navigating unit and an ultrasound probe. Alternatively or additionally, in some embodiments, an imager separate to a biopsy and/or treatment tool is used (e.g. ultrasound imager).

An aspect of some embodiments of the invention relates to imaging and biopsy of prostate tissue, where prostate tissue is restrained by a rectal probe and optionally a rectal balloon. In an exemplary embodiment, images are collected using a probe including MRI coils. The patient is then removed from the MRI imager and a biopsy tool including a probe is inserted into the rectum. Optionally, in some embodiments, the biopsy tool probe includes an ultrasound imager. In an exemplary embodiment, biopsy is collected through the ultrasound imager, for example, a biopsy needle is inserted through the probe. In some embodiments, the biopsy needle is axial with the ultrasound probe.

An aspect of some embodiments of the invention relates to biopsy and/or treatment, where, during biopsy and/or treatment of a first patient (e.g. of target tissue identified from images), the imaging device is free to accept a second patient, for example, reducing per-patient time inside the device and associated costs. In some embodiments, biopsy and/or treatment of the first patient is outside of the imaging device, for example outside a room housing the imaging device (e.g. in a biopsy and/or treatment room).

In some embodiments, after imaging, a patient is removed from an imaging restraining device, and biopsy and/or treatment is performed when the tissue is re-restrained by a different restraining device, a biopsy restraining device, outside the imaging device (e.g. in a different room). Optionally, in some embodiments, a biopsy restraining device does not include MRI coils.

Alternatively, in some embodiments, both the patient and the imaging restraining device (e.g. the patient remains attached to the restraining device) are removed from the imager to another location for biopsy and/or treatment.

In some embodiments, imaging is MRI imaging. In some embodiments, imaging is CT imaging.

In some embodiments, biopsy is taken automatically, for example, a biopsy and/or treatment tool is supported by a structure and one or more actuator controls position and/or movement of one or more portion of the tool.

In some embodiments, previously collected image/s registered with restrained tissue (e.g. re-restrained tissue) guide biopsy and/or treatment of one or more target or region of interest (e.g. identified and/or selected from images), optionally without re-imaging the tissue. For example, in some embodiments, biopsy and/or treatment is performed based on a single scan of patient tissue.

In some embodiments, a restraining device includes a non-planar plate (e.g. a folding plate).

In some embodiments, a biopsy and/or treatment tool is inserted into patient tissue at a desired inclination.

In some embodiments, registration of images guides further imaging of the tissue, for example, at a different time and/or by a different imaging device.

Additionally or alternatively to biopsy, in some embodiments, treatment of target tissue is guided by registered images. For example, in some embodiments, images are used in treatment of target region/s of tissue using ablation (e.g. laser ablation) and/or implanting of nuclear seeds, and/or positioning of a device (e.g. electrodes) and/or irradiation.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details of construction and the arrangement of the components and/or methods set forth in the following description and/or illustrated in the drawings and/or the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

**Exemplary biopsy outside the imager**

In some embodiments, a patient is scanned in an imaging device (also herein termed scanner, imager), for example, MRI machine, CT machine, the patient is then removed from the device and a biopsy is performed outside of the imaging device (e.g. outside a room housing the imaging device). In some embodiments, biopsy outside of

the imaging device reduces per-patient imaging time, potentially freeing the imaging device for additional patients, reducing costs.

In some embodiments, imaging is of non-rigid tissue (e.g. breast, prostate, testicle) restrained in an imaging restraining device.

In some embodiments, restraining, imaging and re-restraining is used to minimize soft tissue movement (e.g. under biopsy needle or other interventional tool penetration) for biopsy of other organs and/or tissue, for example, in liver biopsy.

Referring now to the drawings, FIG. 1 is a flowchart of a method of biopsy, according to some embodiments of the invention.

At 100a, optionally, one or more marker is applied to a patient (e.g. as described herein).

At 100b, patient tissue is scanned in an imaging device (e.g. MRI device, CT device). In some embodiments, the optionally applied markers are scanning fiducials (e.g. are radiopaque) and appear in images collected by the imaging device.

At 102, the patient is removed from the imaging device.

At 103, optionally, markers are re-applied to patient tissue (e.g. as described herein). In an exemplary embodiment, at least four markers are applied to the patient.

At 103a, optionally, markers are registered, for example, a position of real space markers (e.g. re-applied markers) and position of markers in collected image/s is used to align real space with previously collected image.

At 102, patient tissue is biopsied outside of the imaging device.

In some embodiments, biopsy outside of the imaging device is such that the imaging device is now free for scanning of a different patient. In some embodiments, biopsy outside of the imaging device is in a different room to the imaging device (e.g. a biopsy room, a biopsy room in a different building).

FIG. 2 is a flowchart of methods of biopsy, according to some embodiments of the invention. At 200, patient tissue is restrained by a restraining device. At 202, patient tissue is scanned in an imaging device (e.g. MRI device, CT device).

Then, in some embodiments, at 206, the patient is detached from the imaging restraining device and the patient is removed from the imaging device.

At 208, the patient tissue is re-restrained in a second restraining device, outside of the imaging device.

Optionally, in some embodiments, there is a time delay between imaging and re-restraining for biopsy, for example, to provide time for analysis of images. In some embodiments, the time delay between imaging and re-restraining is 1-5 hours, or 1-5 days, or 1-5 weeks.

Alternatively, at 204, the patient and restraining device, where the patient remains attached to the restraining device, are removed from the imaging device. In some embodiments, the imaging breast restraining device, for example, including MRI coils, is removed to another location for biopsy. Alternatively, the MRI coils are removed from the restraining device.

In some embodiments, a restraining device forms part of and/or is located on a bed. In some embodiments, the patient remains on the bed, which is removed to another room.

In some embodiments, the restraining device, or a portion of the restraining device (e.g. not including the MRI coils), is removed from the imager (e.g. from the imager bed) and the patient attached to the restraining device or portion thereof is removed to a different location for biopsy.

At 210, patient tissue is biopsied outside of the imaging device. Meanwhile, in some embodiments, another patient is imaged.

*Exemplary restraining and re-restraining*

In some embodiments, re-restraining substantially replicates conditions (e.g. position, compression) of restrained patient tissue (e.g. breasts) during imaging. In some embodiments, re-restraining substantially replicates a geometrical shape of restrained patient tissue during imaging.

In some embodiments, patient tissue (e.g. breast/s) is re-positioned with respect to the restraining device with over 95% accuracy, or with over 99% accuracy, or with over 99.5% accuracy and/or over 3mm, or over 2mm, or over 1mm accuracy.

In some embodiments, one or more tissue target is substantially in the same position (e.g. with over 95% accuracy, or with over 99% accuracy, or with over 99.5% accuracy and/or over 3mm, or over 2mm, or over 1mm accuracy) during imaging and during re-restraining.

In some embodiments, an imaging restraining device includes a MRI breast cage, for example, including one or more plate.

In some embodiments, restraining of non-rigid tissue is by compression of the tissue between one or more plate. In some embodiments, restraining is of one or both breasts, each breast restrained between more than one plate. In some embodiments, each breast is restrained by at least one grid plate.

*Exemplary breast restraining device*

FIG. 3A is a schematic drawing of a side view of a breast restraining device 300, according to some embodiments of the invention. In some embodiments, breast restraining device 300 is an imaging restraining device. In some embodiments, breast restraining device 300 is a biopsy and/or treatment restraining device. In some embodiments, breast restraining device 300 includes one or more grid 306 through which at least a portion of an interventional tool (e.g. a biopsy tool) is inserted, e.g. for taking of a biopsy. Optionally, grid 306 is a plate for applying pressure to the breast.

Restraining device 300 includes a rest 302 over which the patient lies during scanning, and rest inlets 304, into which the patient's breasts, in some embodiments, protrude. FIG. 3B is a schematic drawing of a patient 301 lying on a simplified schematic of a breast restraining device 300b, according to some embodiments of the invention. In some embodiments, one or more breast is compressed, each breast inside one of inlets 304b.

In some embodiments, a restraining device (e.g. 300, 300b) includes one or more surface additional to the rest (e.g. 302, 302b) supporting one or more portion of the patient (e.g. 301). In some embodiments, the surface is a bed and/or platform, for example, on which the patient lies. For example, in some embodiments, rest 302, 302b is disposed on top of a bed and the patient lies on top of the bed, for example positioning breasts in rest inlets (e.g. 304, 304b).

In some embodiments, during scanning, one or more of the breasts are compressed, for example, in order to prevent movement of breast tissue due to respiration. In some embodiments, one or more breast is compressed by one or more plates in a medio-lateral direction. In some embodiments, one or more breast is compressed by one or more plates in a cranio- caudal direction.

FIG. 3C is a schematic drawing of a breast restraining device 300c, according to some embodiments of the invention. Restraining device 300c includes a first plate 306 and a second plate 310 for compression of the breast in a medio-lateral direction. In some embodiments, one or more plate (e.g. first plate 306 and/or second plate 310) are a grid, mesh, or other material with holes through which biopsy is taken (and/or tissue is treated). In some embodiments, biopsy is taken (and/or tissue is treated) by accessing patient tissue around plate/s, for example, plates 306, 310 (e.g. in a cranio- caudal direction). In an exemplary embodiment, first plate 306 is a grid through which biopsy is taken (and/or tissue is treated).

FIG. 3D is a schematic drawing of a breast restraining device 300d, according to some embodiments of the invention. Restraining device 300d illustrates a first plate 306 and a second plate 310 for compression of the breast in a cranio-caudal direction. In some embodiments, first plate 306 and/or second plate 310 are a grid, mesh, or other material with holes through which biopsy is taken (and/or tissue is treated). In some embodiments, biopsy is taken (and/or tissue is treated) by accessing patient tissue around plate/s around plates 306, 310 (e.g. in a medio-lateral direction).

Optionally, both breasts are compressed for scanning and one breast is re-restrained (e.g. for biopsy), for example, in the case where biopsy and/or treatment is performed by accessing breast tissue from between the breasts, e.g. in a medio-lateral direction.

In some embodiments, one breast is compressed for scanning and re-restrained for biopsy. In some embodiments, the non-compressed breast is blocked or prevented from protruding through the rest (e.g. by insertion of a blocking plate into the rest), for example, to improve access to the compressed breast (e.g. for biopsy). In some embodiments, the non-compressed breast hangs freely in a rest inlet.

In some embodiments, the imaging restraining device has the same components and/or features as the biopsy and/or treatment restraining device. Alternatively, the imaging restraining device differs from the biopsy and/or treatment restraining device (e.g. in an exemplary embodiment, an imaging restraining device does not include a biopsy grid, and/or a biopsy restraining device does not include MRI coils).

FIG. 4A is a schematic drawing of at least a portion of a breast restraining device 400, and an un-restrained breast 408, according to some embodiments of the invention.

Breast 408 rests inside a rest inlet 404. FIG. 4B is a schematic drawing of breast restraining device 401, and a restrained breast 408a, according to some embodiments of the invention.

In some embodiments, breast 408 is restrained by moving a first plate 406 towards a second plate 410, breast 408 being held and/or compressed therebetween. This process is illustrated by the movement of first plate 406, in FIG. 4A to the position illustrated in FIG. 4B.

Optionally, in some embodiments, more than one plate moves to restrain the breast (e.g. first plate 406 and second plate both move towards each other). In some embodiments, first plate 406 is a grid, through which biopsy can be taken. In some embodiments, second plate 410 is a grid. Some embodiments include more than two plates for each breast, each optionally including a biopsy grid, each optionally moving to restrain the breast.

In some embodiments, a breast restraining device includes, for example, the apparatus illustrated by FIG. 4A and FIG. 4B for each breast. In some embodiments, the apparatus for one breast is a mirror image of that for the other breast.

In some embodiments, breast restraining device 400, 401 includes one or more motion controller 412.

In some embodiments, the restraining device includes one or more pressure gauge. In some embodiments, one or more plate includes a plate pressure gauge 412.

Alternatively, or additionally, in some embodiments, one or more breast pressure gauge 414 is placed on and/or affixed to breast, for example a flexible pressure strip, e.g. Tekscan® FlexiForce® A401-25 sensor which produces a voltage signal corresponding to applied pressure.

In some embodiments, breast restraining device 400, 401 includes one or more scale 416 (e.g. a mm scale). In some embodiments, a scale is marked graduations, for example, on a surface of the restraining device (e.g. ruler markings). In some embodiments, dimensions of the imaging restraining device during imaging are measured, (e.g. using scale 416) and replicated (e.g. using scale 416) during re-restraining. In some embodiments, dimensions of the imaging restraining device are measured using one or more position sensor, for example, a position sensor on first plate 406, a position sensor on scale 416 (not illustrated).

In some embodiments, a position of one or more portion of a patient is measured (e.g. during restraining) and replicated (e.g. during re-restraining). In some embodiments, position of one or more portion of a patient with respect to a restraint is measured, for example a position of the patient's shoulders with respect to the rest and/or bed. In some embodiments, one or more marker on a restraining device is used to position the patient for restraining and/or re-restraining.

In some embodiments, compression of the patient tissue is measured and replicated during re-restraining. For example, measurement and/or replication of tissue compression is made using plate pressure gauge 412 and/or breast pressure gauge 414.

In some embodiments, a restraining procedure, used to restrain patient tissue before imaging, is replicated during re-restraining. For example, in some embodiments, a restraining procedure includes, for example, a restraining device starting position, a restraining device finishing position, speed and/or direction of movement of moving portions of the restraining device.

In some embodiments, one or more maker on the patient tissue is used to position the breast in an imaging restraining device and/or re-position the breast in a biopsy restraining device. In some embodiments, one or more marker for positioning the breast are visual markers (e.g. ink and/or pen marks made on the skin). In some embodiments, visual markers for positioning the breast are the same as scanning fiducials (as described below).

In some embodiments, restraining and/or re-restraining is manual, where a user takes measurements and/or records measurements and/or replicates measurements, for example position (e.g. using scale 416) and/or compression (e.g. using pressure gauge/s) manually. In some embodiments, the user then re-restrains patient tissue by manually positioning the plates, e.g. guided by recorded measurements.

In some embodiments, motion controller 412 includes one or more screw mechanism and/or dial and scale 416 is graduated markings on the surface of breast restraining device. In some embodiments, the use rotates the screw mechanism and/or dial to move one or more plate. In some embodiments, the user, for example, during movement and/or once a desired final plate position is reached, records one or more measurement using one or more scale (e.g. scale 416).

In some embodiments, the restraining device includes automatic features, for example, control of moving parts and/or measurement. FIG. 4C is a schematic illustration of a breast restraining device including automatic features 400, according to some embodiments of the invention. In some embodiments, a processor 418 receives signals from one or more sensor, for example, one or more pressure gauge (e.g. 412, 414) and/or one or more position sensor.

Optionally, processor 418 sends signals from one or more sensor for recording in a database 420. Optionally, additional information e.g. patient information, date, time, images is recorded and/or stored with measured conditions (e.g. manually measured dimensions and/or signals from one or more sensor).

Optionally, processor 418 sends signals from one or more sensor for display by a user interface 422.

In some embodiments, processor 418 controls one or more moving part of restraining device 400, for example, by controlling motion controller 412.

In some embodiments, processor is physically connected to one or more other component (e.g. sensor/s, motion controller/s). Alternatively, in some embodiments, processor wirelessly connects with one or more other component.

Optionally database 420 and/or processor 422 is hosted remotely.

Additionally or alternatively to biopsy and/or treatment, in some embodiments, patient tissue is re-restrained for re-imaging. For example, in some embodiments, re-imaging is to produce higher resolution images of one or more area of interest. For example, in some embodiments, re-imaging is used to analyze changes in imaged tissue with time e.g. to quantify movement and/or growth of patient tissue (e.g. tumor tissue) and/or an implanted device.

In some embodiments, re-imaging is by a second imaging device, for example, an imaging device in a different location, for CT imaging after MRI imaging, for MRI imaging after CT imaging. In some embodiments, re-imaging is using the same imager.

In some embodiments, scanning fiducial/s (e.g. radio opaque markers) are used (e.g. applied and/or attached to the patient and/or restraining device) in re-imaging. For example, in some embodiments, markers appearing in the initially collected images remain and/or are re-applied for re-imaging.

In some embodiments, 1-50, or 1-20, or 1-10 or larger or smaller or intermediate ranges or number of markers are used (e.g. applied to patient tissue). In some embodiments, markers are applied (e.g. stuck onto) patient tissue on and/or around a region to be scanned. For example, in some embodiments, markers are applied to a patient breast e.g. for scanning and/or restraining of breast tissue. In some embodiments, markers are applied to a patient torso and/or groin area e.g. for scanning and/or restraining of prostrate tissue.

In an exemplary embodiment, 4 or at least 4 markers are used.

A possible benefit of re-restraining for re-imaging is the ability to register images from different scans, e.g. scans carried out at different times. For example, in some embodiments, registering images is used to quantify tumor growth over time. For example, in some embodiments, registering different sets of images reduces the extent and/or duration of re-imaging.

FIG. 4D is a schematic illustration of a breast restraining device 400d, according to some embodiments of the invention.

In some embodiments, (e.g. as described previously) a grid 406d is positioned, for example by moving 403d, e.g. to compress a breast within a breast inlet 404d.

In some embodiments, a biopsy needle (and/or another interventional tool) is supported e.g. during insertion into patient tissue. In some embodiments, a biopsy needle (e.g. attached to a tool including a mobile unit) is supported by grid 406d and/or a holder 492d. In some embodiments, holder 492d includes a hole 494d through which a biopsy needle is inserted. In some embodiments, holder controls 490d, are used to position and/or secure holder 492d.

In some embodiments, controls 413d are tightened to fix a position of holder arms 496d on struts 498d which support holder with respect to grid 406d.

*Exemplary probe restraining device*

In some embodiments, images are collected by an imaging probe which is, for example, inserted into a body orifice. In an exemplary embodiment, images are collected by a probe inserted into the rectum, where images, for example, are collected of the prostate. In an exemplary embodiment, the probe is an MRI probe.

In some embodiments, an imaging probe is held in position by one or more restraining device. In some embodiments, the restraining device includes an element (e.g. a balloon) which holds the probe in position and/or applies pressure to patient tissue (e.g. directly and/or indirectly where the balloon applies pressure to the probe which then applies pressure to patient tissue). In some embodiments, a balloon is disposed next to the probe (e.g. inserted before and/or during and/or after insertion of the probe). The balloon is then inflated applying pressure to patient tissue and/or the probe.

In some embodiments, re-straining of prostate tissue replicates restraining of prostate tissue by replicating a measured length of a balloon pumping tube (e.g. length of the tube inserted and/or protruding from the patient) and/or by replicating a measured pressure of inflation of the balloon (e.g. assessed by reading of a pressure measure).

In some embodiments, the probe is inserted and/or positioned according to a restraining procedure e.g. during restraining and/or re-restraining. Where the procedure includes, for example, positioning the patient and/or position and/or speed and/or direction of insertion of the probe. In some embodiments, a probe restraining device includes one or more structure (e.g. bed and/or leg supports) supporting one or more portion of the patient. In some embodiments, positioning of the patient is with respect to the structure (e.g. using markers on the structure and/or on the patient).

FIG. 5 is a simplified schematic cross sectional view of a probe 592 inserted into a patient rectum 504, according to some embodiments of the invention. A balloon 506 pushes the probe towards a prostate 508. Exemplary positions for balloon 506 include positions within rectum 504, against proximal to prostate 508. Also illustrated are a bladder 512 and a urethra 514.

In some embodiments, a restraining procedure includes insertion and/or inflation of the balloon (e.g. a speed and/or volume and/or pressure of inflation of the balloon). In some embodiments, a controller 510 controls inflation of balloon 506. In some embodiments, controller 510 is connected to a processor which controls and/or measures and/or records details of inflation and/or positioning of balloon 506.

In some embodiments, images of the prostate are collected using external MRI coils (e.g. without an internal MRI probe). Optionally, prostate tissue is restrained e.g. during imaging using external MRI coils, using a probe and/or instrument inserted into

the rectum. Alternatively or additionally to the probe and/or instrument inserted into the rectum, a balloon is inserted and inflated (e.g. as described herein).

In some embodiments, during treatment and/or biopsy outside of the imager (e.g. outside of the MRI imager), prostate tissue is re-restrained by insertion of a probe and/or instrument, for example, sized to match the probe and/or instrument in place during imaging. Optionally, the probe and/or instrument is accompanied by a balloon. In an exemplary embodiment, the probe is an ultrasound probe (e.g. as described herein).

*Exemplary manual biopsy and/or treatment*

In some embodiments, biopsy and/or treatment is manual, where, for example, a user manually positions a tool and/or inserts a portion of the tool (e.g. a needle) into patient tissue. FIG. 6A is a simplified schematic of a user 637 manually inserting a portion of a manually positioned biopsy tool 624 into a patient 601, according to some embodiments of the invention.

In some embodiments, user 637 manually positions and/or angles biopsy tool d24. In some embodiments, user 637 manually inserts a needle 634 into patient tissue. In some embodiments, a user manually controls angle and/or entry position and/or speed of insertion and/or depth of insertion of a portion of a tool (e.g. needle 634) into patient tissue, for example, breast tissue, e.g. as illustrated in FIG. 6.

In some embodiments, patient 601 lies on a rest 602. In some embodiments, rest 602 and/or one or more portion of patient 601 are supported by a bed 638. In some embodiments, (e.g. as described herein) one or more marker 640 is applied to patient 601.

In some embodiments, (e.g. as described herein) user 637 uses images displayed on a display 636 to guide tool angle and/or position and/or insertion depth.

In some embodiments, tissue for biopsy is not compressed, for example, FIG. 6 illustrates biopsy of a freely hanging breast 690. In some embodiments, tissue for biopsy is compressed, for example, by a restraining device (e.g. 300, 506, as described herein).

*Exemplary automated biopsy*

In some embodiments, biopsy and/or treatment is partially or fully automatic. In

patient tissue are automatic. In some embodiments, an insertion point and/or depth of insertion and/or speed of insertion and/or angle of insertion of a portion of a biopsy tool are automatic. For example, in an exemplary embodiment, a biopsy tool is positioned (e.g. by one or more actuator), for example, based on a location of a selected target, and biopsy is taken automatically.

In some embodiments, biopsy is partially automatic. For example, in some embodiments, the biopsy tool is positioned automatically and biopsy is taken manually where a user inserts at least a portion of the tool (e.g. needle) manually.

In some embodiments, automatic biopsy (and/or treatment of a target region) is performed by an automatic biopsy (and/or treatment) apparatus. In some embodiments, the apparatus includes a structure which supports the tool. In an exemplary embodiment, a portion of the tool protrudes from the structure, for example allowing a user to grasp the tool and manually move it.

FIG. 6B is a simplified schematic side view of a patient 601 positioned on an automatic breast biopsy and/or treatment apparatus 699, according to some embodiments of the invention. In some embodiments, a tool 624 supported by apparatus 699 is automatically positioned (e.g. by actuators) with respect to a target (e.g. a breast).

FIG. 6C is a simplified schematic side view of a patient 601 positioned underneath an automatic biopsy and/or treatment apparatus 699c, according to some embodiments of the invention. In some embodiments, biopsy is automatically taken from the torso (e.g. spine) e.g. using apparatus 699c. In some embodiments, apparatus 699c is moved along bed 638, e.g. for biopsy and/or treatment of other portions of the body, for example, upper torso and/or head and/or lower torso and/or legs.

*Exemplary registration and display taking into account tissue elasticity*

In some embodiments, biopsy and/or treatment compresses tissue (e.g. insertion of a biopsy needle locally compresses tissue). In some embodiments, viscoelastic measurements are used to correct (e.g. deform) image/s during collection of biopsy.

In some embodiments, a mobile unit is used to measure tissue elasticity, for example, by registering a position of a marker under different pressures for example, as described in U.S. Patent Application Publication No. 2013/0317347 which describes "Improving Tool Positioning Accuracy by Accounting for Tissue Elastic Properties".

FIG. 28A and FIG. 28B show tool positioning adjustments that may be made by the operator to account for tissue flexibility under pressure, according to some embodiments of the invention.

Referring to FIG. 28A and FIG. 28B, U.S. Patent Application Publication No. 2013/0317347 states "The figure shows in (A) a tool 902 attached to a MU 904, the tool close to touching a body 908 that includes an organ 910. A marker 906 on the body is also shown. During or after the marker's position registration procedure, the operator may press marker 906 (as well as all other markers) with the tool tip, to compress the body tissue along a propagation pressure line (axis) 916. Under pressure, the body and the organ change shapes to respectively shapes 908′ and 910′. The marker moves to a pressed marker position 906′. The compression is done to a maximum compression distance (displacement) D that the operator feels is allowed without causing pain or damage. A point on the organ along axis 916 changes position from an un-pressed position 914 to a final pressed position 912. By pressing of a button (not shown) the operator then registers the marker's maximal displacement under pressure against the body's flexible texture. By doing so over at least three markers, an elasticity displacement map can be constructed using a known mathematical algorithm. Basically, it is assumed that an internal displacement d is directly proportional to D and inversely proportional to the initial distance between the marker and the internal organ L, i.e. d=cD/L where e is the elasticity of the intermediate tissue between the marker and the internal organ. This allows corrections in real time for the displacement of patient's organs under the pressure of the interventional tool during the interventional procedure. Corrections to reconstructed images obtained from the pre-scanned 3D data volume can be done accordingly and thus overcome inaccuracies expected due to non-rigidity of tissues under tool pressure during operation." In an exemplary embodiment, the mobile unit includes a pressure sensor and, for example, measurement of a position of a tissue surface under different measured pressures is collected using the mobile unit. In some embodiments, data including deformation of tissue (e.g. change in position of tissue with pressure) is used to calculate tissue viscoelastic properties.

In some embodiments, the tissue surface is at a marker location e.g. the mobile unit is contacted to the marker and pressure measurements are taken for different tissue deformations.

In an exemplary embodiment, viscoelasticity measurements of prostate tissue are collected using a tool including an anal probe and a mobile unit. For example, in some embodiments, viscoelasticity measurements are collected by pressuring the prostate by different degrees using the anal probe.

In some embodiments, images are corrected according to the pressure exerted on tissue by a tool (e.g. biopsy device). For example, in some embodiments, displayed images are distorted using pressure measurements collected from a pressure sensor at a tool tip in contact with patient tissue and/or tissue elasticity information. In some embodiments, a position of a target tissue area is corrected based on measured applied pressure where, for example, pressure is applied by a tool and measured by a tool pressure sensor.

In some embodiments, viscoelastic measurement/s are taken at a point of penetration. For example, in some embodiments, viscoelastic measurements are collected for each marker, biopsy is then taken at the marker position (e.g. through the marker, e.g. through a hole in the marker), optionally at the same angle that the viscoelastic measurements were taken.

In some embodiments, during biopsy and/or treatment, viscoelastic tissue information (e.g. a viscoelastic tissue map) is used to deform images based on pressure applied by an interventional tool (e.g. biopsy needle) and/or to correct a position of an identified target and/or to correct a position of the tool (e.g. needle) with respect to images.

**Exemplary Imaging and Biopsy Clinic**

FIG. 7A is a flowchart of a method of scanning and biopsy in an imaging and biopsy clinic, with time. At 700, first patient tissue is scanned in an imaging device (e.g. MRI device, CT device). At 702, the patient is removed from the imaging device and patient tissue is biopsied. Only at 704, after the first patient has undergone biopsy, is a second patient scanned in the imaging device. In some embodiments, the clinic is additionally or alternatively for treatment (e.g. as described herein).

FIG. 7B is a flowchart showing scanning and biopsy in an imaging and biopsy clinic, with time, according to some embodiments of the invention. At 700, first patient tissue is scanned in an imaging device (e.g. MRI device, CT device). At 702, the patient

is removed from the imaging device and patient tissue is biopsied. In some embodiments, for example, simultaneous to performing biopsy on the first patient, at 704, a second patient is scanned in the imaging device.

Optionally, in some embodiments, one or more maker is applied to first patient tissue and/or second patient tissue. In some embodiments, one or more marker is removed and re-applied between imaging and biopsy. In some embodiments, markers are visible in scanned image/s. In some embodiments, measured position of markers (e.g. re-applied markers) in real space is used to register previously collected images to patient tissue (e.g. outside the imager).

FIG. 8 is a simplified top view of a clinic 850 for imaging and biopsy, according to some embodiments of the invention. In some embodiments, clinic 850 includes an imager 852 (e.g. MRI device, CT device) located in an imaging room 854 and a location (e.g. a biopsy room 855) outside the imager where biopsy is performed.

In some embodiments, clinic 850 includes an imaging bed 856, which includes an imaging restraining device 858. In some embodiments, the patient (not illustrated) lies on imaging bed 856 where imaging restraining device 858 holds and/or compresses patient soft tissue (e.g. breasts).

Once scanning is finished, in some embodiments, the patient moves from imaging restraining device 858 and imaging bed 856 (the imager is now free for imaging of another patient) to a biopsy room 855 where the patient lies on a biopsy bed 860 and patient tissue is re-restrained by a biopsy restraining device 862. Images are registered to the re-restrained patient tissue and a biopsy tool and a biopsy is taken.

In some embodiments, biopsy restraining device 862 does not include MRI coils. Optionally, biopsy restraining device 862 is a former imaging restraining device (e.g. a worn-out imaging restraining device) optionally with non-functional MRI coils.

In some embodiments, a restraining device includes or is connected to a processor. For example, as described previously, in some embodiments, a processor hosts code for recording (e.g. to a database) and/or control and/or guiding replication (e.g. for biopsy) of conditions of the compressed tissue and/or imaging restraining device. Optionally, clinic 850 includes more than one processor, for example, an imaging processor 818 for imaging (e.g. located in imaging room 854) and a biopsy processor 818a (e.g. located in biopsy room 855).

Optionally, processor/s include and/or are connected to one or more user interface. In some embodiments, one or more user interface, for example, displays recorded conditions and/or accepts input of user instructions (e.g. for non-rigid tissue compression). In some embodiments, clinic 850 includes an imaging room restraining device user interface and/or a biopsy room restraining device user interface. Alternatively, in some embodiments, one or more restraining device user interface is hosted on a portable electronic device (e.g. a tablet).

Optionally, processor/s are hosted by an imaging device processor (e.g. MRI processor). Optionally, one or more restraining device user interface is hosted by and/or accessed through an imaging device user interface (e.g. MRI machine imager).

Optionally, imaging room 854 and biopsy room 855 are not adjoining rooms as illustrated, but in different locations. Optionally, one or more additional biopsy room is in a different location. For example, a central imaging clinic (e.g. in a hospital) includes an imager and imaging room and optionally a biopsy room. An (optionally additional) biopsy room is in a separate location, e.g. a in a local surgery.

Optionally, processors 818 and/or 818a and/or user interface 822 is hosted by the imager.

Optionally, processors 818, and/or 818a are hosted remotely (e.g. on a remote server).

Although, in FIG. 8, one imager 852 and one biopsy room 854 are illustrated, some clinic embodiments include more than one imager and/or more than one biopsy room.

In some embodiments, processor 818 and/or process 818a are hosted by a workstation, for example, including a display for display of images to the user. In some embodiments, a mobile workstation is moved between imaging room 854 and biopsy room 855. In some embodiments, processor 818 and an imaging room user interface is hosted by the imager and a workstation hosts processor 818a and a biopsy room user interface.

In some embodiments, a central workstation (not illustrated) is located in a third area or room. For example, in some embodiments, a radiologist analyzes images in a room separate to the biopsy and imaging rooms.

*Exemplary movable imaging restraining device*

FIG. 9A is a simplified top view of a clinic 950 for imaging and biopsy, set up for imaging of a first patient, according to some embodiments of the invention. In FIG. 9A a first patient (not illustrated) is imaged on an imaging bed 956, where patient tissue is held by a first restraining device 958. A second restraining device 962 is not in use.

FIG. 9B is a simplified top view of a clinic 951 for imaging and biopsy, set up for biopsy of a first patient, and imaging of a second patient, according to some embodiments of the invention. In FIG. 9B the first patient, attached to first restraining device 958, has been moved to a biopsy bed 960, located in a biopsy room 955. Optionally, once the first patient is moved from the imager to the biopsy room, a second patient, attached to second restraining device 962, is imaged in imager 952.

Optionally, if the imager is an MRI imager, MRI coils in the restraining device are unplugged and/or removed, for example, when the restraining device is moved after imaging.

*Exemplary clinic, more than one imaging bed*

FIG. 10A is a simplified top view of a clinic 1050 for imaging and biopsy, set up for imaging of a first patient, according to some embodiments of the invention. In FIG. 10A a first patient (not illustrated) is imaged on a first bed 1056, where patient tissue is held by a first restraining device 1058. A second bed 1056 and restraining device 1058 are not in use.

FIG. 10B is a simplified top view of a clinic 1051 for imaging and biopsy, set up for biopsy of a first patient, and imaging of a second patient, according to some embodiments of the invention. In FIG. 10B the first patient, attached to first restraining device 1058 and on first bed 1056 has been moved to a biopsy room 1055. Optionally, once the first patient is moved from the imager to the biopsy room, a second patient, on a second bed 1060, held by a second restraining device 1062, is imaged in imager 1052.

**Exemplary Method**

FIG. 11 is a flowchart of a method of scanning and biopsy and/or treatment, according to some embodiments of the invention.

At 1100, in some embodiments, a patient is assessed, for example, a doctor examines a patient and/or assesses patient medical history and/or patient medical tests

(e.g. blood tests and/or imaging). In some embodiments, for example, based upon the assessment, the doctor selects one or more portion of the patient for imaging using one or more imaging type (e.g. CT and/or MRI). For example, in an exemplary embodiment, a doctor assesses a patient who has found a lump in her breast and/or a patient for which a mammogram shows abnormal breast tissue and selects MRI imaging of the breast including the lump and/or abnormity.

At 1102, in some embodiments, fiducial markers are attached to a patient's body (e.g. by gluing to the skin). In some embodiments, position of markers is measured. In an exemplary embodiment, markers are attached to a patient breast to be scanned and/or treated and/or biopsied, for example markers 640 on FIG. 6A. In an exemplary embodiment, markers are attached to a patient around the pelvis, for example, for scanning and/or biopsy and/or treatment of prostate tissue.

At 1104, in some embodiments, patient tissue is restrained (e.g. as described herein). In some embodiments, the patient is positioned according to one or more marker on the restraining device and/or the imager, for example, to aid positioning of the patient in a known (e.g. replicable) position. In some embodiments, the patient is placed on the restraining device and, for example, a patient breast is compressed with grid plates. In some embodiments, the applied pressure of the plates is measured and recorded (e.g. using one or more plate pressure sensor and/or using one or more pressure sensor coupled to the patient). In some embodiments, distances between the plates are measured and recorded (e.g. using one or more position sensor and/or using one or more scale).

Alternatively, in some embodiments, patient tissue is not restrained (and/or is not re-restrained, for example, as illustrated in FIG. 6A). In some embodiments, measured visco-elastic properties of patient tissue (e.g. measured using a tool) are used to correct images in accordance with tissue compression.

At 1106, in some embodiments, at least a portion of patient tissue is scanned. In some embodiments, a restrained portion of patient tissue is scanned. In some embodiments, after scanning, the patient is removed from the restraint and/or leaves the imager and/or imaging room. In some embodiments, the scan is performed by an imaging device and fiducials appear in the scan, along with target lesions. In some

embodiments, e.g. once scanning is finished, the patient leaves the imaging device (scanner) and the scanner is now free to scan another patient.

At 1108, in some embodiments, the images are then analyzed by physician. In some embodiments, the doctor selects one or more portion of patient tissue for biopsy and/or treatment. In some embodiments, a doctor selects one or more portion of patient tissue for re-imaging (e.g. using a different type of imaging). In some embodiments, a doctor inputs a target (e.g. for biopsy and/or treatment). For example, inputting a selection of a portion of patient tissue and/or inputs a selection of a point on an image through a user interface. In some embodiments, the selection is saved.

At 1110, in some embodiments, e.g. if image analysis (e.g. by a physician) indicates the need for a biopsy, patient tissue is re-restrained. In some embodiments, re-restraining is performed while fiducial markers are still attached (e.g. the fiducial markers remain in the same position as in scanning). Additionally or alternatively fiducials are later re-attached (e.g. patched back at ink marked points on patient skin, e.g. one or more marker which has fallen off is re-attached).

In some embodiments, a position of one or more marker is indicated on patient tissue e.g. using pen and/or ink marks on patient skin, before and/or during and/or after attachment of the markers. In some embodiments, marker/s are re-applied at a later time, e.g. a few days later, the position of which is guided by the indication on the patient tissue. In some embodiments, tattoo is used to indicate marker position on patient tissue. In some embodiments, one or more marker is inserted into patient tissue, e.g. under the skin.

In some embodiments, (e.g. when the fiducials are in position), the patient, for example, in a biopsy room, separate from the room housing the imaging device (also termed imager), is re-restrained on a biopsy restraining device. Optionally, in some embodiments, re-restraining is using the same pressure and distances (e.g. between restraining device plates), for example giving the tissue (e.g. breasts) a similar geometrical shape as in imaging and/or positioning one or more target region (e.g. lesion) in the same position as in imaging.

At 1112, in some embodiments, patient tissue position (e.g. position of fiducials attached to the patient) is registered to a known position within a biopsy room and/or with respect to a mobile unit (e.g. as described herein). In some embodiments,

registering markers includes touching a portion of a tool (e.g. tool tip), where the tool includes a mobile unit, to each fiducial, giving fiducial coordinates in real space. In some embodiments, comparing image space co-ordinates of fiducials to real space coordinates of fiducials provides a transformational algorithm mapping between compressed tissue (e.g. breast tissue) to image/s of the compressed tissue.

At 1114, in some embodiments, previously scanned image/s are displayed, for example, on a user interface. In some embodiments, a position of a mobile unit (e.g. biopsy tool) is displayed on the images. In some embodiments, a position of the mobile unit tip (e.g. needle tip) is displayed on images.

In some embodiments, a position of the biopsy tool tip is tracked and displayed with images (e.g. by a user interface), guiding biopsy of target lesions. In some embodiments, a position of an interventional portion of a tool is displayed, for example, a biopsy needle. In some embodiments, a position of more than one portion of a tool is displayed, for example, a tip and/or portion of a biopsy needle which collects tissue and a shaft of the needle. For example, a portions of the tool which is inserted into patient tissue.

In some embodiments, a target tissue selection is displayed, for example, the target is marked on image/s.

At 1116, in some embodiments, three dimensional image data is displayed from an angle which corresponds to an angle of the mobile unit (e.g. biopsy tool) in real space. In some embodiments, a user selects an angle from which to view image data. In some embodiments, a slice of three dimensional image data is displayed e.g. a slice which is shows a target and/or is perpendicular to a long axis real space direction of the tool. In some embodiments, a user selects one or more slice of image data for display. In an exemplary embodiment, a user selects slice/s of image data for display using a user interface (e.g. a tool user interface).

FIG. 26A is a simplified schematic side view of a tool 2624 and displayed slices of image data 2602, 2604, according to some embodiments of the invention. FIG. 26B is a simplified schematic of a display 2636, according to some embodiments of the invention. In some embodiments, display 2636 is the display corresponding with tool 2624 as illustrated in FIG. 26A.

FIG. 26A and FIG. 26B show display of images perpendicular to a long axis of tool 2610. In some embodiments, a tool tip image slice 2602, corresponding to a position of a tool tip 2610 is displayed on display 2626. In some embodiments, one or more slice including a target (e.g. a target portion of tissue selected by a doctor), for example, target image slice 2604 is displayed on display.

In some embodiments, one or more additional slice, for example, located between target 2606 and tool tip 2610 is displayed.

In some embodiments, tool 2624 includes one or more user interface 2618. In some embodiments, a user selects a slice of image data to display using user interface 2618. In an exemplary embodiment, user interface 2618 includes a scroll wheel the movement of which, for example, selects a position of displayed image slice 2603.

In some embodiments, additional data is displayed, for example, in some embodiments, a distance D between tool tip 2610 and a target 2606 is displayed 2616 on display 2636.

In some embodiments, one or more slice parallel to the long axis of the tool is displayed. FIG. 27A is a simplified schematic side view of a tool 2724 and displayed slices of image data, 2702, 2704, 2712, 2714, according to some embodiments of the invention. FIG. 27B is a simplified schematic of a display, according to some embodiments of the invention. In some embodiments, display 2636 is the display corresponding with tool 2624 as illustrated in FIG. 26A. In some embodiments, one or more slice parallel to the tool long axis including target tissue 2706 is displayed 2712, 2714.

Returning now to FIG. 11, optionally, in some embodiments, at 1118, additional images are collected. For example, in some embodiments, real time images are collected of patient tissue (e.g. including a target identified from previously acquired images).

In an exemplary embodiment, additional images are collected by an ultrasound probe. In some embodiments, ultrasound image/s are displayed side by side with previously collected first images (e.g. MRI and/or CT). In some embodiments, ultrasound images are used to verify a position of a portion of tissue and/or a target (e.g. identified and/or selected from first images), for example the prostate. In some embodiments, recent (e.g. collected less than 5seconds, or less than 1 second ago)

and/or real time ultrasound images are used, for example, accounting for movement of the patient e.g. within a restraint.

Optionally, in some embodiments, a user plans a trajectory of insertion of an portion of a tool (e.g. biopsy needle) into patient tissue, for example, by moving the tool according to a planned trajectory, without contacting the patient, and viewing images corresponding to the trajectory e.g. viewing the movement of a tip of the interventional portion of a tool superimposed on previously collected images.

At 1122, in some embodiments, patient tissue is biopsied and/or treated. In some embodiments, biopsy and/or treatment is performed by a hand-held tool including a mobile unit. In some embodiments, collection of biopsy and/or treatment is guided by displayed images.

In some embodiments, a biopsy needle is inserted into patient tissue from a desired direction and inclination through an insertion unit. Optionally, biopsy is then collected from a target region.

In some embodiments, biopsy is taken using a grid plate (e.g. the insertion unit is a grid plate), as is known in the art of biopsy (e.g. of breast biopsy). In some embodiments, biopsy is taken using a pillar and post method, as is known in the art of biopsy (e.g. of breast biopsy). In some embodiments, biopsy is taken directly from the skin surface, without support of the biopsy tool, for example without using a grid or plate.

In some embodiments, additionally or alternatively to biopsy, the tool is used for placement of one or more device, for example, nuclear seed/s and/or electrode/s (e.g. deep brain stimulation electrodes).

In some embodiments, additionally or alternatively to biopsy, the tool is used for targeted treatment of tissue, for example, irradiation and/or ablation of tissue (e.g. ablation of uterine fibroids).

In some embodiments, additionally or alternatively to biopsy, the tool is used in measurement, for example, geometrical measurement of tissue (e.g. a tumor or suspected tumor). In some embodiments, position and/or size in one or more dimension and/or volume, e.g. of a selected and/or identified area of tissue is calculated.

For example, in some embodiments, a mobile unit is attached to a tool able to perform one or more of biopsy, ablation, insertion of nuclear material, irradiation, attachment of electrode/s.

Optionally, upon insertion of an interventional portion of a tool (e.g. biopsy needle), the patient is returned to an imaging device for an additional scan, for example, to confirm that the tool is in the desired position (e.g. at a target lesion).

In some embodiments, the tool and/or method is used in biopsy and/or treatment of, for example, tissue in the head and/or neck, the spinal area (e.g. spinal lesion/s), liver tissue (e.g. primary and/or secondary liver tumors), bone tissue (e.g. benign and/or metastatic bone tumor, e.g. osteoid osteoma), pancreatic tissue, extra peritoneal tissue (e.g. extra peritoneal tumor/s), uterine tissue (e.g. uterine fibroids), neuroblastoma, renal tissue (e.g. renal cell carcinoma).

*Exemplary registration of images and biopsy tool position with images*

In some embodiments, image/s collected of tissue (for example compressed tissue) inside the imager are registered to the compressed tissue outside of the imager.

In some embodiments, registering includes sizing and/or rotating and/or translating the collected image/s.

In some embodiments, imaged features are used to register image space with real space. In some embodiments, registration uses location of features in image space and location of the same features in real space. In some embodiments, a transformational algorithm provides a 1:1 mapping between the re-restrained tissue to images of the restrained breast by comparing image co-ordinates of features (e.g. fiducials, markers, restraining device features) to measured real space coordinates of the features.

In some embodiments, fiducials on the patient during scanning (e.g. affixed to patient skin with glue prior to scanning) are used for registering image space with real space. In some embodiments, fiducials on the patient during scanning remain on the patient until biopsy. Alternatively, in some embodiments, fiducials are removed and replaced before re-restraining and biopsy.

Alternatively, in some embodiments, feature/s, appearing in images, of the imaging restraining device, which match features of the biopsy restraining device, are used to register image space to real space.

In some embodiments, position of features (e.g. fiducials and/or markers and/or restraining device features) are measured using a mobile unit, for example, within a room which includes transmission unit/s, for example as described in U.S. Patent Application Publication No. 2013/0317347, which is herein incorporated by reference as if fully set forth herein in its entirety.

In some embodiments, a mobile unit includes a position sensor, for example, which includes one or more than one ultrasound sensor (e.g. two sensors). In some embodiments, a plurality of transmitting units (e.g. located in biopsy room 855), each of which emit ultrasound pulses, are sensed by the mobile unit sensors. The received signals provide the position of each mobile unit sensor (from which the mobile unit inclination and/or a direction of a long axis of the mobile unit, in some embodiments, is inferred). Alternatively or additionally, in some embodiments, the mobile unit includes transmitter/s and position of the unit (e.g. within a biopsy room) is inferred from signals received by ultrasound sensors (e.g. which are within the biopsy room).

In some embodiments, ultrasound pulses are used to read four distances to a point in space (e.g. from four transmitting units, each in a different location). For example, transmitting units produce ultrasound pulses, which are sensed by the mobile unit sensors. Reading the four distances, triangulation is used to find the spatial position of the point, with respect to the room's isocenter.

In some embodiments, a biopsy tool includes a position sensor, for example, providing a location of the biopsy tool with respect to a restraining device and/or patient tissue. For example, in some embodiments, a biopsy tool includes or is attached to a mobile unit.

In some embodiments, location of the tool is measured regularly (e.g. once a second, several times a second e.g. more than 5 times a second, more than 10 times a second, more than 50 times a second), and, optionally, the tool's real time position is displayed together (e.g. by a user interface) with images (e.g. images previously collected from imaging, for example MRI/CT imaging).

In some embodiments, position of markers (e.g. scanned fiducials and/or markers re-applied to the patient in the substantially same position as scanned fiducials) is measured within the room for example, using a measured position of a mobile unit e.g. by touching the mobile unit to scanned fiducial markers. In some embodiments, patient

tissue in real space is registered to imaged tissue in image space using the measured real space position of the markers and an identified position of the scanned fiducials within image/s.

In some embodiments, registration of a measured biopsy tool position with images is used to guide biopsy, for example, tool location is updated with time. In some embodiments, real time registration of the biopsy tool with images enables biopsy of a region of interest identified from images.

In some embodiments, a user interface displays an image of the biopsy tool (and/or a portion of the tool) superimposed on images (e.g. images previously collected from imaging, for example MRI/CT imaging), the user collecting the biopsy is then able to perform biopsy as if the user were collecting biopsy inside of an imaging device guided by real time imaging.

**Exemplary biopsy tool**

*Exemplary biopsy tool with navigating unit*

FIG. 12A is a simplified schematic illustration of a biopsy tool 1224, according to some embodiments of the invention. In some embodiments, biopsy tool 1224 includes a mobile unit 1226, also termed hand held navigating unit. Mobile unit 1226 includes position sensors 1228, 1230.

In some embodiments, mobile unit 1226 is attached to a biopsy tool 1232, optionally by an attachment adaptor 1240. In some embodiments, position sensors are collinear with a biopsy tool tip 1234. In some embodiments, position sensors 1228, 1230 are ultrasound position sensors.

In some embodiments, position of the biopsy tool is inferred from measured mobile unit position, known biopsy tool dimensions, and by assuming that attachment between the mobile unit and biopsy tool is constant.

In some embodiments, a position of a biopsy tool tip 1234 is tracked, using position sensors 1228, 1230. In some embodiments, tip 1234 is calibrated by touching the tip to a known location and recording a first position measured by sensors 1228, 1230. In some embodiments, when biopsy tool 1224 is moved, a second position of sensors 1228 and 1230 and the known location of tip 1234 with respect to sensors is used to infer the new tip location.

In some embodiments, a biopsy tool includes sensors which are not collinear with the biopsy tool. FIG. 12B illustrates a simplified schematic of a biopsy tool 1224, according to some embodiments of the invention. In some embodiments, position sensors, 1228, 1230 are not collinear with a biopsy tool tip 1234. In some embodiments, a tip location is inferred from position provided by position sensors and a means of a tilt angle and/or rotational measurement (e.g. an accelerometer). In some embodiments, position of biopsy tool tip 1234 is inferred from measurement provided by position sensors 1228, 1230, for example, using known dimensions of the biopsy tool and/or given that attachment between the sensors and the tool is rigid and/or constant.

In some embodiments, a tool (e.g. biopsy tool) includes one or more pressure sensor. In some embodiments, a pressure sensor at a tool tip measures a contact pressure between the tool tip and, for example, patient tissue.

In some embodiments, pressure sensor measurements are used to measure viscoelastic properties of tissue, e.g. as described herein.

In some embodiments, pressure sensor measurements are used to validate measured positions of markers attached to the patient. For example, if pressure measured by the pressure sensor/s is outside a range for example, too low (e.g. corresponding with lack of contact) and/or too high (e.g. corresponding with repositioning of tissue) then, for example, the position measurement of the marker is not validated. In some embodiments, if an attempted registration of a marker (e.g. a user touches a tool tip to the marker, and inputs into a user interface e.g. pressing a “collect position” button) fails, an alarm is issued to the user, e.g. an audio and/or visual alarm e.g. by a tool user interface and/or by a display.

*Exemplary non-planar restraining device plate*

In some embodiments, for example, as biopsy does not rely on a geometrical relationship between a grid and a target tissue area for biopsy, plates for compression of the breast are non-planar.

In some embodiments, one or more plate has a folding portion. FIG. 13 illustrates a simplified schematic of a grid plate 1306.

FIG. 14 illustrates a simplified schematic of a plate 1406 with a folding portion 1468, according to some embodiments of the invention. In some embodiments, plate

1406 is a grid through which biopsy optionally is taken. In some embodiments, plate 1406 includes a first portion 1466 and a second portion 1468 where second portion 1468 folds about a bending axis 1464 (e.g. a hinge). In some embodiments, a plate includes more than one folding portion.

FIG. 15 illustrates a simplified schematic illustration of a compressed breast 1308a in a restraining device 1500.

FIG. 16 illustrates a simplified schematic illustration of a compressed breast 1608a in a restraining device 1600, according to some embodiments of the invention. In some embodiments, a folding portion 1686 folds towards a second plate 1610, compressing a nipple end of breast 1608a. A potential benefit of a plate with a folding portion is more uniform compression of the breast. A further potential benefit of a grid plate with a folding portion is better access of biopsy tool 1632 to the breast (e.g. the nipple end of breast 1608a). For example, a needle of a biopsy tool extends a smaller distance from the biopsy tool in order to biopsy a region of the breast.

*Exemplary angled insertion of biopsy tool*

In some embodiments, biopsy is taken by inserting a biopsy tool (e.g. needle) at an angle (e.g. non-perpendicular) to a surface of the patient tissue. FIG. 17 is a simplified schematic illustration of an insertion unit 1770, according to some embodiments of the invention.

In some embodiments, insertion unit 1770 enables penetration of patient skin at a desired inclination, for example between 0.5° and 179.5° to a surface of the patient tissue. Insertion unit 1770 includes a gripping hole 1772 through which a biopsy tool (e.g. leading pipeline) is inserted for penetration of patient tissue. In some embodiments, gripping hole 1772 holds the leading pipeline firmly in place. In some embodiments, gripping hole 1772 is located inside a grip unit 1774.

In some embodiments, the inclination and/or position of gripping hole 1772 is moved by a user to a desired inclination and/or position. In some embodiments, gripping hole 1772 moves linearly inside guide rails 1776. In some embodiments, guide rails 1776 are coupled to (attached and/or part of) a first rotational wheel 1778. In some embodiments, a second rotational wheel 1780 is coupled to first rotational wheel. In some embodiments, first rotation wheel has a rotation axis 1782 perpendicular to a

rotation axis 1784 of section rotation wheel. In some embodiments, first wheel 1778 rotates about first rotational axis 1782 (in the figure, around the x-axis). In some embodiments, second wheel 1780 rotates about a second rotational axis 1784 (in the figure, around the y-axis). In some embodiments, third wheel 1786 rotates freely (in some embodiments, there is a gap 1789 between third wheel 1786 and ring 1788) within a plane of a third ring 1788 (in the figure, around the z-axis). In some embodiments, wheels 1778, 1780, 1786 allow motion of the needle to any desired inclination.

FIG. 18 is a simplified schematic illustration of an insertion unit 1870 in place on one pane of a grid plate 1806, according to some embodiments of the invention. In some embodiments, insertion unit 1870 is used with a grid plate 1806 with one or more folding portion 1868 and bending axis 1864.

*Exemplary biopsy tool*

In some embodiments, biopsy of one or more target (e.g. lesion) is obtained using a biopsy tool. FIG. 19A is a simplified schematic illustration of a biopsy tool 1932, according to some embodiments of the invention. In some embodiments, a biopsy tool 1932 includes ultrasound position sensors 1928, 1930, which, for example, are used in measuring position of the biopsy tool for registering the biopsy tool position with images (e.g. for image guided biopsy).

In some embodiments, biopsy tool 1932 includes a driving mechanism (e.g. mechanical and/or electrical) for insertion and/or withdrawal of a needle 1934. Optionally, the driving mechanism includes a push unit 1935 and/or electrical motor 1938 for insertion and/or withdrawal of needle 1934.

In some embodiments, biopsy tool 1932 includes a ring holder 1942. In some embodiments, needle 1934, for example under pressure exerted by a user and/or driving mechanism, penetrates ring holder 1942 and ring holder 1942 holds needle 1934 in place after insertion. In some embodiments, ring holder 1942 prevents needle collapse (e.g. bending) under insertion pressure exerted by a user (e.g. physician).

FIG. 19B is a simplified schematic illustration of a ring holder 1942, according to some embodiments of the invention.

FIG. 20 is a simplified schematic cross sectional view of an exemplary biopsy tool 2024, according to some embodiments of the invention. In some embodiments,

biopsy tool 2024 includes a first ultrasound position sensor 2028 and a second ultrasound position sensor 2030. In some embodiments, first position sensor 2028 is a 25kHz ultrasound sensor array. In some embodiments, second position sensor 2030 is a 40kHz ultrasound sensor array.

In some embodiments, a user holds biopsy tool 2024 by a handle 2032. In some embodiments, one or more control buttons 2044 for biopsy tool are located on handle 2032. In some embodiments, measurement of a location of tool tip 2034 is taken upon pressing a control button 2044 on handle 2032.

In some embodiments, penetration and/or withdrawal of a needle 2034 is by a motor 2038. In some embodiments, needle is within a magazine tube 2046. In some embodiments, magazine tube 2046 is disposable and/or sterile. In some embodiments, a sticker 2048 at the end of magazine tube, for example, prevents needle from bending during penetration of patient tissue and/or attaches to patient skin.

In some embodiments, a plunger 2049 pushes or pulls needle, (e.g. through a plunger slider bearing 2049a) according to control of motor. As described previously, knowledge of biopsy tool geometry (e.g. tool length, needle length) combined with position sensors 2028, 2030 measurements is used to calculate needle tip location.

FIG. 21A illustrates a biopsy tool 2132, according to some embodiments of the invention. FIG. 21B illustrates a biopsy tool 2132, during biopsy collection, according to some embodiments of the invention. In some embodiments, biopsy tool 2132 includes a replaceable cartridge (or magazine) 2146 (e.g. removable and/or disposable). In some embodiments, replaceable cartridge 2146 is placed, for example stuck (e.g. with adhesive) into a recess inside biopsy tool 2132. In some embodiments, cartridge 2146 and/or needle 2134 and/or portions of biopsy tool 2132 which come into contact with patient tissue are sterile.

In some embodiments, replaceable cartridge 2146 includes a leading needle 2134 and a plunger 2149. In some embodiments, plunger 2149 pushes leading needle 2134 into patient tissue. In some embodiments, plunger 2149 is controlled with an electrical propagation mechanism (not illustrated). In some embodiments, when a user pulls on a trigger 2133, leading needle 2134 is launched through a ring holder 2142 into patient tissue 2108, as illustrated by the position of leading needle 2134 in FIG. 21B. In some embodiments, biopsy tool 2132 includes one or more actuator (e.g. an electrical

actuator), and, for example, when a user pulls on trigger 2133 an actuator launches leading needle 2134. In some embodiments, a speed of movement of leading needle 2134 is controlled by how hard a user presses on trigger 2133.

In some embodiments, ring holder 2142 holds leading needle 2134 in place and prevents bending of leading needle 2134.

In some embodiments, a user taking the biopsy uses biopsy tool 2132 to penetrate the patient to a partial depth. The user removes the tool, leaving ring holder 2142 and leading needle 2134 in position. In some embodiments, the leading needle is hollow and the user (e.g. manually) inserts a second needle into the hollow needle, to a desired depth, for example, to collect a biopsy. In some embodiments, leading needle is inserted to a penetration depth of between 10 and 200mm, or lower, or higher, or intermediate penetration ranges or depths.

In some embodiments, a biopsy tool and/or mobile unit includes a user interface through which a user controls the tool.

For example, in some embodiments, a tool includes a handle on which a user interface is disposed, for example, a button and/or control which a user grasping the handle can operate e.g. using the same hand which holds the handle. For example, in some embodiments, a tool (e.g. biopsy gun) includes one or more button in a trigger position, e.g. trigger 2133 on FIG. 21.

In some embodiments, one or more tool user interface e.g. button is disposed on the tool such that a user inputs into the user interface using a single hand grasping the tool. For example, in some embodiments, a user interface is located on a handle of a tool, similar to a trigger of a gun. In some embodiments, a tool lacks a handle and a shaft or body of a tool is grasped directly by a user and, for example, a user interface is located on the tool body, such that a user grasping the tool inputs into the user interface using one or more finger of the hand which is grasping the tool. For example, referring to FIG. 26A, tool 2624 includes a user interface 2618 which, in some embodiments, includes a scroll wheel which, for example, is controlled by a thumb or finger of a user hand grasping tool 2624.

FIG. 22 is a simplified schematic side view of a portion of a mobile unit including a user interface, according to some embodiments of the invention.

In an exemplary embodiment, the user interface includes an "acquire marker position" button 2202. In some embodiments, when a user measures and/or registers position of markers on a patient's body (e.g. as described herein) a portion (e.g. a tip) of the mobile unit (e.g. biopsy tool) is touched to each marker, and acquire maker position button is pressed by a user, to enter the position of the maker into the system.

In some embodiments, a tool user interface includes one or more control for control of a display, e.g. of images displayed on the display. In some embodiments, a displayed angle of one or more slice of image data is selected and/or changed using the control.

In some embodiments, the mobile unit includes one or more rotational wheel 2204. For example, in an exemplary embodiment, referring to FIG. 27A, rotation of rotational wheel rotates slices parallel to the tool long axis 2712 and/or 2714 about the long axis of the tool.

In some embodiments, a directional pad input controls zoom on one or more displayed image. In an exemplary embodiment, a zoom on a display window (e.g. displaying an image data slice) is controlled by rotation of a rotational wheel.

In some embodiments, the tool user interface includes a directional pad 2206 where a selected window and/or cell in a display is changed by pressing on a portion of directional pad 2206.

In some embodiments, a tool including a mobile unit includes a user input for registering markers (e.g. as described with reference to method step 1112 illustrated in FIG. 11). For example, in some embodiments, a position of each marker is registered by touching a portion of a tool including a mobile unit (e.g. a tool tip) to each marker and inputting into a tool user interface an input to register the position of the tool, where inputting, in an exemplary embodiment, includes pressing on an acquisition button 2202.

Alternatively or additionally, in some embodiments, button 2202 changes a selected window on the display.

In some embodiments, a mobile unit and/or biopsy tool includes a screen, for example, for display of image/s and/or information to the user (e.g. distance from target). In some embodiments, a user controls the mobile unit and/or biopsy tool through a touch-screen (e.g. mounted on the device).

*Exemplary tool with ultrasound probe e.g. prostate biopsy and/or treatment*

In some embodiments, a biopsy and/or treatment tool (e.g. as described herein) includes an ultrasonic probe. In some embodiments, ultrasound images are used to verify a position of a portion of patient tissue, for example, a position of the prostate. In some embodiments, previously acquired images are aligned to a patient using registration with patient markers and/or ultrasound images.

FIG. 23 is a simplified schematic side view of a tool 2324 including an ultrasound probe 2392 and a navigating unit, according to some embodiments of the invention.

In some embodiments, tool 2324 includes an extendable portion 2334 (e.g. a biopsy needle). In some embodiments, tool 2324 includes one or more user interface (e.g. trigger 2344, button 2345) for control of the tool and/or of displayed images. In some embodiments, tool 2334 includes inlets and/or vents 2393, 2395 in a tool outer shell, for example, to improve broadcast and/or reception of tracking signals (e.g. ultrasound signals). Alternatively, in some embodiments, transceiver/s are externally coupled and/or mounted on the tool.

In some embodiments, a biopsy tool includes more than one biopsy needle, for example, for taking more than one biopsy of a region of tissue. FIG. 24 is a simplified schematic cross sectional view of a biopsy tool 2424 including more than one needle 2434, according to some embodiments of the invention. For example, in some embodiments, the biopsy tool illustrated in FIG. 19A and/or FIG. 20 and/or FIG. 21A and/or FIG. 21B and/or FIG. 22 and/or FIG. 23 includes a cartridge with more than one needle. In some embodiments, a tool is positioned, a biopsy needle is inserted, and retracted, optionally back into the cartridge, collecting a sample of tissue. In some embodiments, the tool remains in position and a second tissue sample is collected, for example, by inserting and retracting a second needle. In some embodiments, a position and/or angle of the tool is changed between collections of tissue. In some embodiments, a depth of insertion of the needle is varied between needle insertions. In some embodiments, the tool includes 1-50, or 1-20, or 1-10, or 1-5, or 1-3 or larger, or smaller or intermediate numbers or ranges of needles.

In some embodiments, a biopsy tool including a mobile unit and more than one needle includes an ultrasound probe 2492. In some embodiments, ultrasound probe

2492 includes an ultrasound transducer 2495 with a channel, for example, a ring shaped ultrasound transducer. In some embodiments, a biopsy needle is inserted into patient tissue through a channel 2494 in probe 2492, where channel 2494 runs through ultrasound transducer 2495. In some embodiments, a largest dimension of the channel through ultrasound transducer 2495, perpendicular to a long axis of probe 2592 (e.g. inner diameter when ultrasound transducer 2495 is ring-shaped), is small, for example, 0.01mm-5mm, or 0.1mm-2mm, or smaller, or larger, or intermediate ranges or values. In some embodiments, a small channel through ultrasound transducer 2495 maintains image quality collected by the transducer. In some embodiments, a biopsy tool including an ultrasound probe and a mobile unit includes a single biopsy needle.

FIG. 25A is a simplified schematic side view of a tool 2524 including an ultrasound probe 2592 treating and/or collecting biopsy from a patient prostate, according to some embodiments of the invention. FIG. 25B is a simplified schematic of a display 2536, according to some embodiments of the invention. In some embodiments, display 2536 is the display corresponding with tool 2524 as illustrated in FIG. 25A. In some embodiments, (not illustrated in FIG. 25B) an indication of a position of a portion of tool 2534 is displayed on the ultrasound and/or the previously collected image. For example, in some embodiments, a position of a biopsy needle is imaged by the ultrasound probe and displayed on the display, optionally, at the same time, a registered position of the biopsy needle is displayed on the displayed previously collected image/s.

In some embodiments, a needle 2434 is used to collect biopsy, e.g. from a target region of a prostate 2508.

In some embodiments, previously collected image/s (e.g. MRI images) are displayed (e.g. on display 2536) next to and/or side by side (e.g. in different portions and/or windows of a display) to ultrasound image/s collected by probe 2592. In some embodiments, an identified and/or selected target region 2506 is displayed on a previously collected image 2552. In some embodiments, image slice/s of previously collected image data 2524 are displayed (e.g. as described herein) optionally next to (e.g. side by side to) images collected by ultrasound probe 2592. In an exemplary embodiment, an ultrasound image representing a slice through tissue (e.g. prostate tissue) proximal (e.g. 0-5cm, 0-2cm, 0-1cm from the tip) to a tip of probe 2592 and/or

perpendicular to a long axis of probe 2592 is displayed, for example, side by side with a slice of previously collected image data, where the slice is perpendicular to the long axis of probe 2592 and approximately at the same distance from the probe tip. In some embodiments, as the probe is moved, the displayed slice of previously collected image data is changed, for example, the displayed slice corresponding to the orientation and position of the probe (e.g. within the patient's body).

In an exemplary embodiment, ultrasound probe 2592 includes a canal through which biopsy needle 2534 is inserted into patient tissue. In some embodiments, a position of one or more portion of probe 2592 and/or a position of an interventional portion (e.g. needle 2534) are displayed on previously acquired image/s (e.g. MRI and/or CT). In some embodiments, a position of the interventional portion (e.g. needle 2534) is displayed on image/s collected by probe 2592. In some embodiments, needle 2534 position is displayed simultaneously on previously collected image/s (e.g. MR and/or CT) and on real time image/s (e.g. collected by probe 2592). In some embodiments, display of previously collected image/s and real time collected image/s are side by side. In some embodiments, previously collected image/s and real time collected image/s are displayed overlapping and/or fused.

In some embodiments, ultrasound images are used to verify position of a target, for example, a user positioning a portion of a biopsy device (e.g. needle) to access a target selected from and/or identified from previously collected images (e.g. MRI and/or CT) uses collected ultrasound images to verify that the biopsy device is in a correct and/or desired location (e.g. a biopsy needle contacts the target). In some embodiments, ultrasound and/or probe images provide additional information to a user, for example, enabling refining of the desired target (e.g. selection of a portion of an identified region of tissue and/or in selecting direction of access to a target).

**General**

As will be appreciated by one skilled in the art, aspects of the present invention may be embodied as a system, method or computer program product. Accordingly, aspects of the present invention may take the form of an entirely hardware embodiment, an entirely software embodiment (including firmware, resident software, micro-code, etc.) or an embodiment combining software and hardware aspects that may all generally

be referred to herein as a "circuit," "module" or "system." Furthermore, aspects of the present invention may take the form of a computer program product embodied in one or more computer readable medium(s) having computer readable program code embodied thereon. Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of embodiments of the method and/or system of the invention, several selected tasks could be implemented by hardware, by software or by firmware or by a combination thereof using an operating system.

For example, hardware for performing selected tasks according to embodiments of the invention could be implemented as a chip or a circuit. As software, selected tasks according to embodiments of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In an exemplary embodiment of the invention, one or more tasks according to exemplary embodiments of method and/or system as described herein are performed by a data processor, such as a computing platform for executing a plurality of instructions. Optionally, the data processor includes a volatile memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. Optionally, a network connection is provided as well. A display and/or a user input device such as a keyboard or mouse are optionally provided as well.

Any combination of one or more computer readable medium(s) may be utilized. The computer readable medium may be a computer readable signal medium or a computer readable storage medium. A computer readable storage medium may be, for example, but not limited to, an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system, apparatus, or device, or any suitable combination of the foregoing. More specific examples (a non-exhaustive list) of the computer readable storage medium would include the following: an electrical connection having one or more wires, a portable computer diskette, a hard disk, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory), an optical fiber, a portable compact disc read-only memory (CD-ROM), an optical storage device, a magnetic storage device, or any suitable combination of the

foregoing. In the context of this document, a computer readable storage medium may be any tangible medium that can contain, or store a program for use by or in connection with an instruction execution system, apparatus, or device.

A computer readable signal medium may include a propagated data signal with computer readable program code embodied therein, for example, in baseband or as part of a carrier wave. Such a propagated signal may take any of a variety of forms, including, but not limited to, electro-magnetic, optical, or any suitable combination thereof. A computer readable signal medium may be any computer readable medium that is not a computer readable storage medium and that can communicate, propagate, or transport a program for use by or in connection with an instruction execution system, apparatus, or device.

Program code embodied on a computer readable medium may be transmitted using any appropriate medium, including but not limited to wireless, wire line, optical fiber cable, RF, etc., or any suitable combination of the foregoing.

Computer program code for carrying out operations for aspects of the present invention may be written in any combination of one or more programming languages, including an object oriented programming language such as Java, Smalltalk, C++ or the like and conventional procedural programming languages, such as the "C" programming language or similar programming languages. The program code may execute entirely on the user's computer, partly on the user's computer, as a stand-alone software package, partly on the user's computer and partly on a remote computer or entirely on the remote computer or server. In the latter scenario, the remote computer may be connected to the user's computer through any type of network, including a local area network (LAN) or a wide area network (WAN), or the connection may be made to an external computer (for example, through the Internet using an Internet Service Provider).

Aspects of the present invention are described below with reference to flowchart illustrations and/or block diagrams of methods, apparatus (systems) and computer program products according to embodiments of the invention. It will be understood that each block of the flowchart illustrations and/or block diagrams, and combinations of blocks in the flowchart illustrations and/or block diagrams, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general purpose computer, special purpose computer, or other

programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer or other programmable data processing apparatus, create means for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

These computer program instructions may also be stored in a computer readable medium that can direct a computer, other programmable data processing apparatus, or other devices to function in a particular manner, such that the instructions stored in the computer readable medium produce an article of manufacture including instructions which implement the function/act specified in the flowchart and/or block diagram block or blocks.

The computer program instructions may also be loaded onto a computer, other programmable data processing apparatus, or other devices to cause a series of operational steps to be performed on the computer, other programmable apparatus or other devices to produce a computer implemented process such that the instructions which execute on the computer or other programmable apparatus provide processes for implementing the functions/acts specified in the flowchart and/or block diagram block or blocks.

As used herein the term “about” refers to ± 20 %.

The terms "comprises", "comprising", "includes", "including", “having” and their conjugates mean "including but not limited to".

The term “consisting of” means “including and limited to”.

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible

limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

WHAT IS CLAIMED IS:

1. A method of preparing tissue for biopsy comprising:

restraining non-rigid tissue by applying pressure to said non-rigid tissue;

imaging restrained non-rigid tissue to provide at least one image thereof;

releasing said non-rigid tissue;

re-restraining said non-rigid tissue by applying pressure to said non-rigid tissue, after said imaging; and

registering re-restrained tissue with said at least one image.

2. The method according to claim 1, wherein at least 50% of an outer surface said re-restrained tissue is within at least 50mm of a geometry of said restrained non-rigid tissue.

3. The method according to claim 1, wherein at least 90% of an outer surface said re-restrained tissue is within at least 1mm of a geometry of said restrained non-rigid tissue.

4. The method according to any one of claims 1-3, wherein registering comprises registering a biopsy tool with said at least one image.

5. The method according to any one of claims 1-4, wherein said non-rigid tissue is breast tissue.

6. The method according to any one of claims 1-5, wherein said imaging is by an imaging device;

wherein said non-rigid tissue is of a first patient;

wherein after said imaging said imaging device is free for imaging of a second patient.

7. The method according to any one of claims 1-6, wherein said restrained non-rigid tissue is restrained by an imaging restraining device; and

wherein re-restraining is by a biopsy restraining device.

8. The method according to any one of claims 1-7, comprising:

measuring restrained tissue conditions; and

wherein said re-restraining comprises re-restraining non-rigid tissue according to said restrained tissue conditions.

9. The method of claim 8, wherein said tissue conditions comprise tissue dimensions.

10. The method according to any one of claims 8-9, wherein said tissue conditions comprise tissue compression.

11. The method according to any one of claims 1-10, comprising:

collecting a biopsy with said biopsy tool.

12. The method according to any one of claims 1-11, wherein said collecting comprises positioning said biopsy tool automatically based on a registered position of a target portion of said non-rigid tissue.

13. The method according to any one of claims 1-12, wherein said collecting comprises insertion an interventional portion of said biopsy tool automatically, based on a registered position of said target portion of tissue.

14. The method according to any one of claims 1-13, wherein said non-rigid tissue is prostate tissue.

15. The method according to any one of claims 1-14,

wherein imaging comprises imaging one or more fiducials;

the method comprising measuring position of one or more fiducials; and

registering comprises registering fiducials image space location with measured real space position of fiducials.

16. The method according to any one of claims 1-15, comprising:

displaying said at least one image.

17. The method according to claim 16, comprising:

displaying a registered position of at least a portion of said biopsy tool on said displayed image.

18. The method according to any one of claims 1-17, wherein said registering re-restrained tissue with said at least one image comprises:

sizing said image;

rotating said image; and

translating said image.

19. The method according to any one of claims 1-18, wherein said imaging is selected from the group consisting of CT imaging and MRI imaging.

20. The method according to any one of claims 1-19, wherein said at least one image is three dimensional image data; wherein said displaying comprises displaying a slice of said image data.

21. The method according to claim 20, wherein said slice is selected using a user input on said biopsy tool.

22. The method according to claim 21, comprising reimaging said re-restrained tissue to provide at least one re-restrained tissue image thereof; and wherein said displaying comprises displaying said re-restrained tissue image.

23. The method according to claim 22, comprising wherein said displaying comprises displaying said slice side by side with said re-restrained tissue image.

24. The method according to any of claims 22-23, wherein said reimaging is ultrasound imaging.

25. A method of displaying image data comprising:

imaging tissue with an imager, to provide three dimensional image data image thereof;

registering tissue, outside said imager, with said three dimensional image data;

registering a tool with said at least one image; and

displaying a slice of said three dimensional image data, where said displayed slice is selected using a user input on said biopsy tool.

26. The method according to claim 25, wherein said displaying comprises displaying a position of at least a portion of said biopsy tool on said displayed slice.

27. The method according to any one of claims 25-26, wherein said registering a tool comprises registering a position and orientation of said tool with respect to said image data; and

wherein said displaying comprises displaying a slice of said image data at a tip of said tool and perpendicular to a tool long axis.

28. The method according to any one of claims 25-27, wherein said displaying comprises displaying a slice of image data including a target portion of said image data.

29. An imaging and biopsy clinic comprising:

an imaging device;

an imaging restraining device for restraining of non-rigid tissue inside said imaging device;

a biopsy restraining device for restraining of non-rigid tissue outside said imaging device; and

a biopsy tool.

30. The imaging and biopsy clinic of claim 29,

wherein said imaging restraining device includes at least one measuring device for measuring restrained tissue conditions; and

wherein said biopsy restraining device includes at least one sensor for replicating said restrained tissue conditions.

31. The imaging and biopsy clinic according to claim 30, wherein said at least one measuring device comprises one or more selected from the group comprising a pressure gauge, a scale, a position sensor.

32. The imaging and biopsy clinic according to any one of claims 29-31, wherein said biopsy tool includes at least one position sensor.

33. The imaging and biopsy clinic according to any one of claims 29-32, comprising:

a plurality of ultrasound pulse transmitters;

wherein said biopsy tool position sensor is an ultrasound receiver.

34. The imaging and biopsy clinic according to any one of claims 29-33,

wherein said imaging restraining device comprises a grid plate comprising a folding portion; and

wherein said biopsy restraining device comprises a grid plate comprising a folding portion.

35. The imaging and biopsy clinic according to any one of claims 29-34, wherein said non-rigid tissue is selected from the group consisting of breast tissue and prostate tissue.

36. The imaging and biopsy clinic according to any one of claims 29-35, wherein said imaging device is selected from the group consisting of a MRI imaging device, a CT imaging device.

37. The imaging and biopsy clinic according to any one of claims 29-36, wherein said biopsy tool includes an ultrasound probe.

38. The imaging and biopsy clinic according to any one of claims 29-37, comprising an apparatus for support and automatic movement of said biopsy tool.

39. A method of biopsy comprising:

collecting first image data of patient tissue, including a tissue target, using a first imaging type;

registering a patient and a biopsy tool position to said first image data;

collecting a second image of said patient tissue using a second imaging type with a biopsy tool including an imager;

displaying, side by side, said second image and a slice of said first image data corresponding to an orientation of said second image;

superimposing on said display a biopsy tool position; and

collecting a biopsy of said tissue target based on said display.

40. The method according to claim 39, comprising:

displaying a registered position of at least a portion of said biopsy tool on said first image.

41. The method according to any one of claims 39-40, comprising:

restraining said patient tissue before said collecting a first image; and

re-restraining said patient tissue before said collecting a second image.

42. The method according to any one of claims 39-41, wherein said second image is an ultrasound image using an ultrasound probe; and

wherein said collecting a second image is through said ultrasound probe.

43. A biopsy tool comprising:

a user interface;

at least one position sensor; and

a processor to generate a control signal based on input to said user interface and measurement by said position sensor;

a transmitter to transmit said control signal to a remote display;

an ultrasound transducer comprising a channel; and

a needle positioned and sized to pass through said channel.

44. The biopsy tool according to claim 43, comprising an ultrasound probe.

45. The biopsy tool according to any one of claims 43-44, comprising more than one biopsy needle.

46. A method of prostate biopsy comprising:

restraining prostate tissue by applying pressure using a first rectal probe and inflating a balloon to said prostate tissue;

imaging restrained non-rigid tissue to provide at least one image thereof;

releasing said non-rigid tissue;

re-restraining said non-rigid tissue by applying pressure using a second rectal probe and inflating a balloon to said prostate tissue; and

registering re-restrained tissue with said at least one image;

collecting a biopsy from a target portion of said prostate tissue.

47. The method according to claim 46, wherein said imaging is MRI imaging and said first rectal probe includes MRI coils.

48. The method according to any one of claims 46-47, wherein said second rectal probe includes an ultrasound transducer.

49. The method according to any one of claims 46-48, wherein said collecting comprises collecting biopsy through said ultrasound transducer.

50. The method according to any one of claims 47-49, wherein said registering re-restrained tissue with said at least one image comprises:

sizing said image;

rotating said image; and

translating said image.

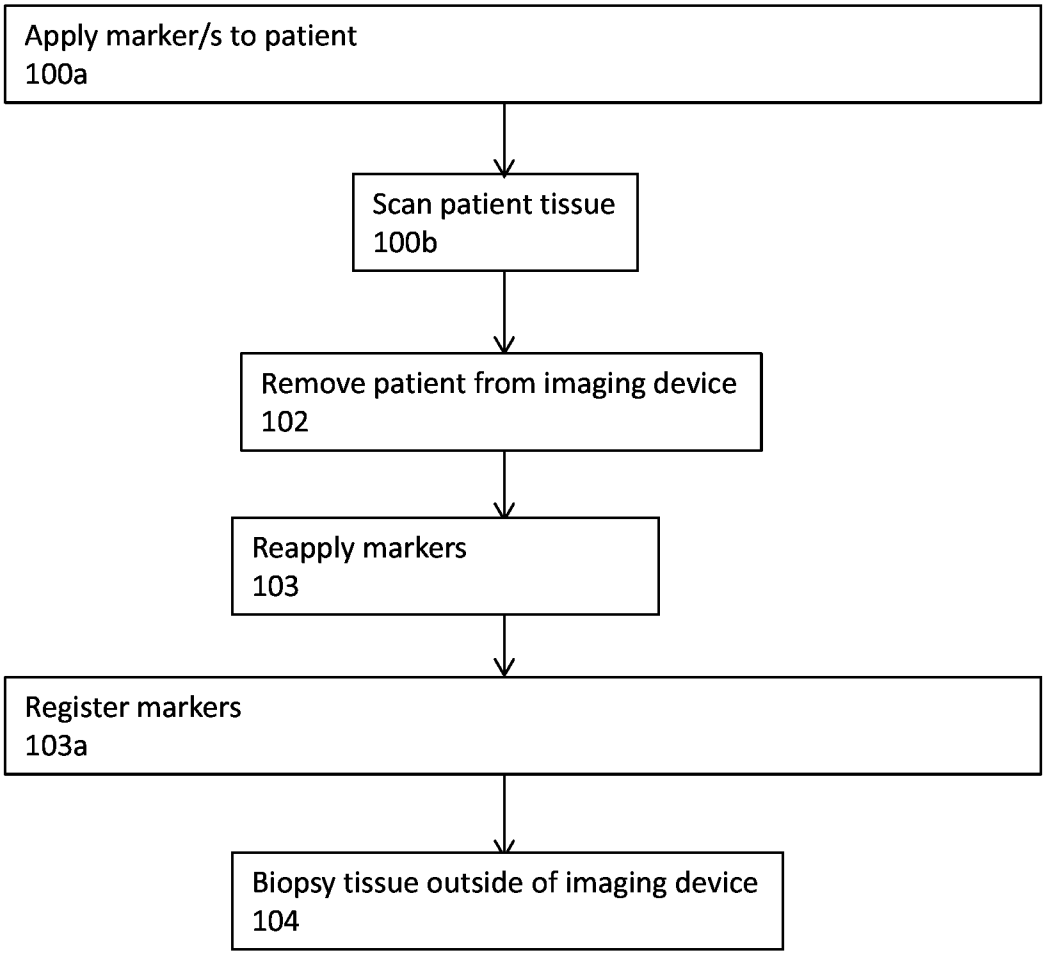

Apply marker/s to patient
100a
Scan patient tissue
100b
Remove patient from imaging device
102
Reapply markers
103
Register markers
103a
Biopsy tissue outside of imaging device
104

FIG. 1

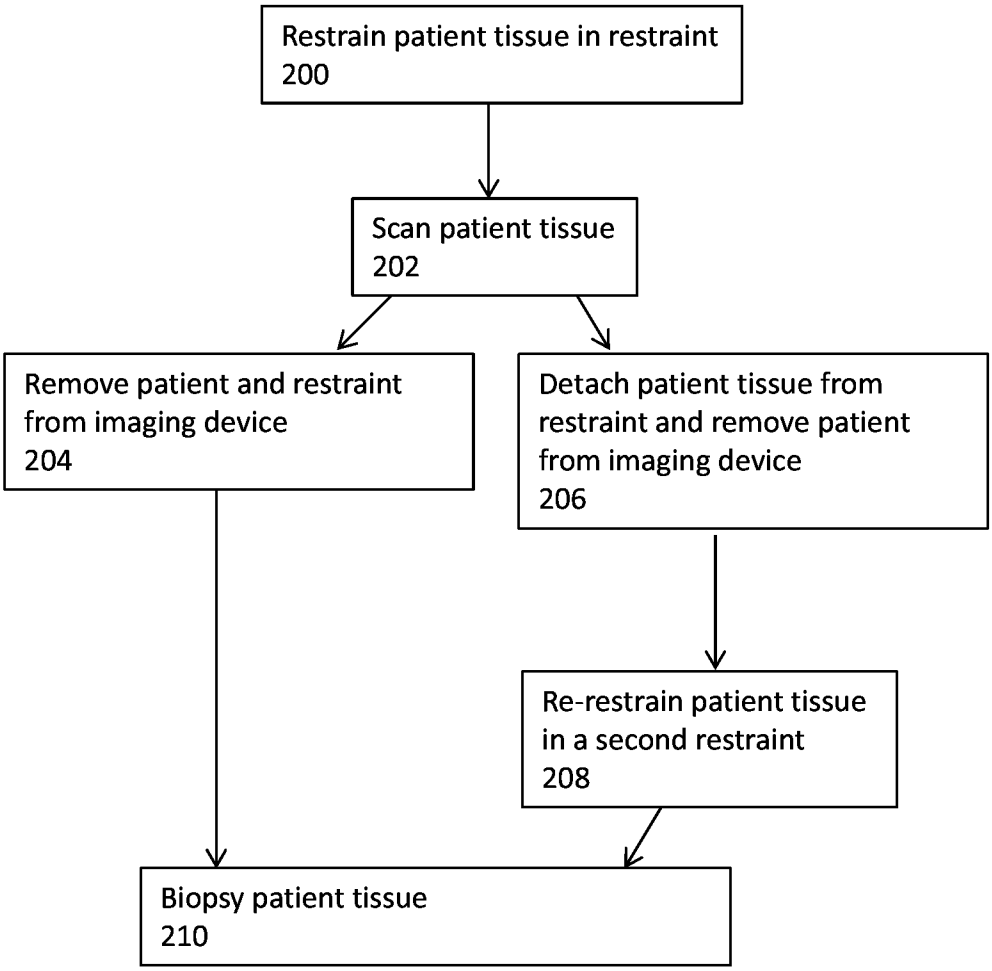

Restrain patient tissue in restraint
200
Scan patient tissue
202
Remove patient and restraint from imaging device
204
Detach patient tissue from restraint and remove patient from imaging device
206
Re-restrain patient tissue in a second restraint
208
Biopsy patient tissue
210

FIG. 2

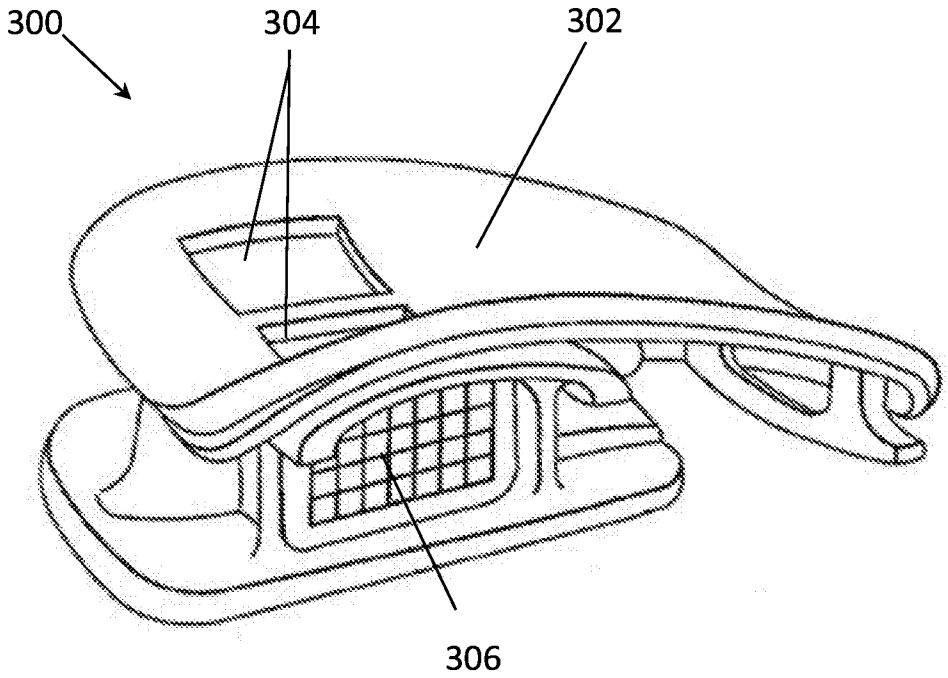



FIG. 3A

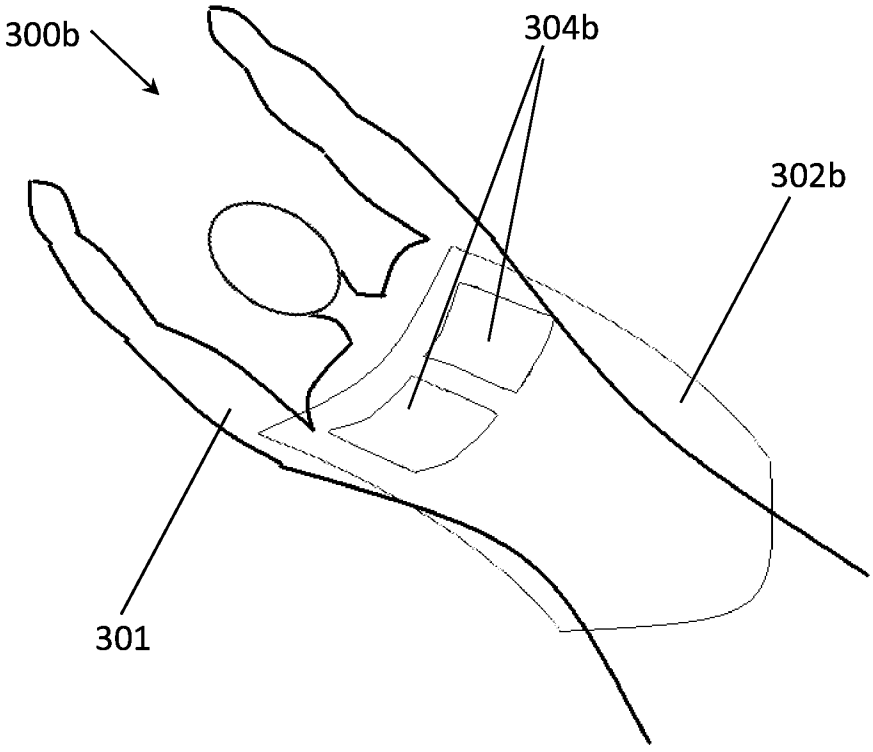



FIG. 3B

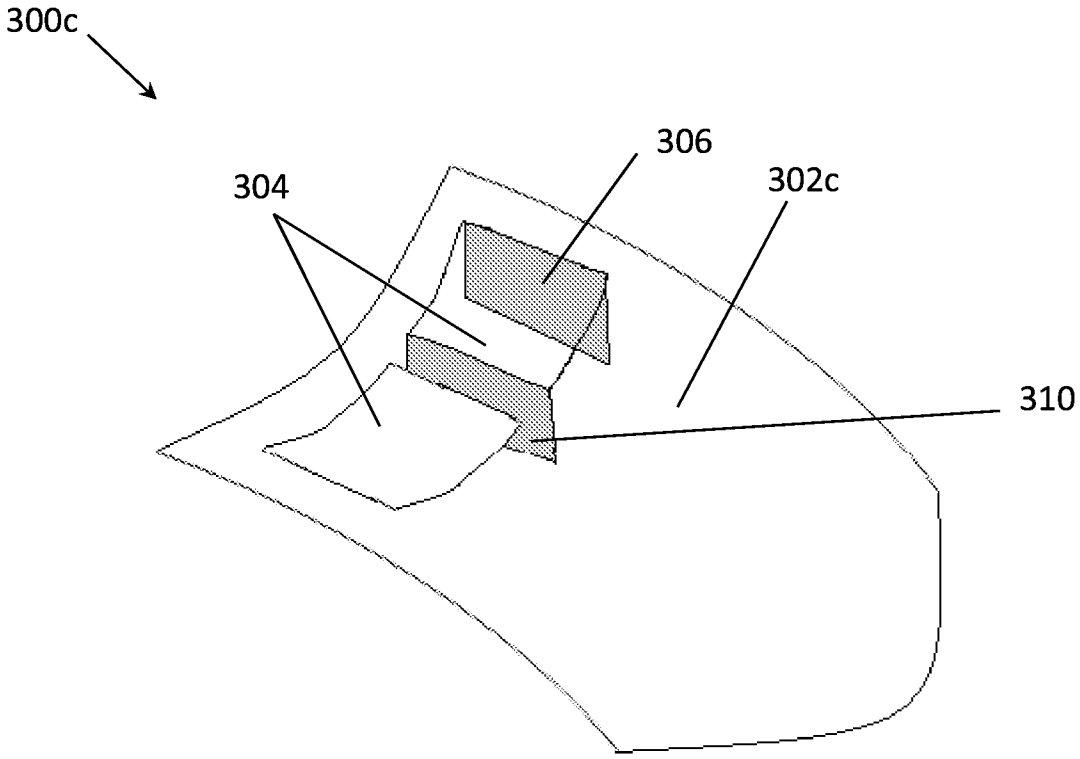



FIG. 3C

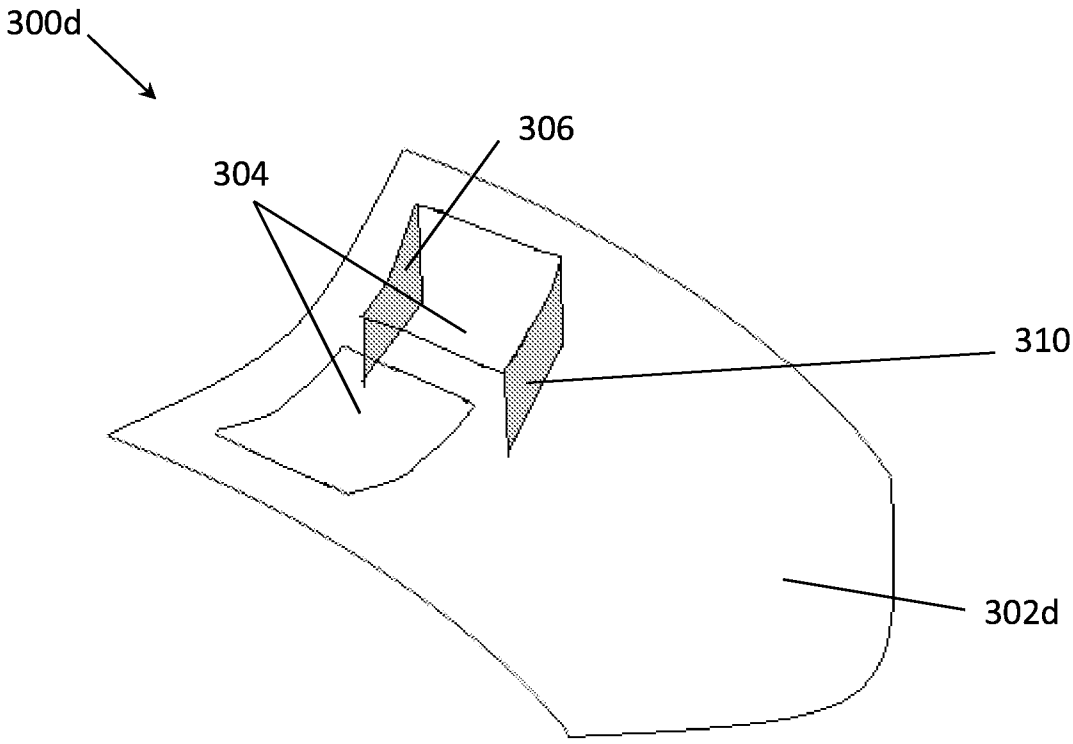



FIG. 3D

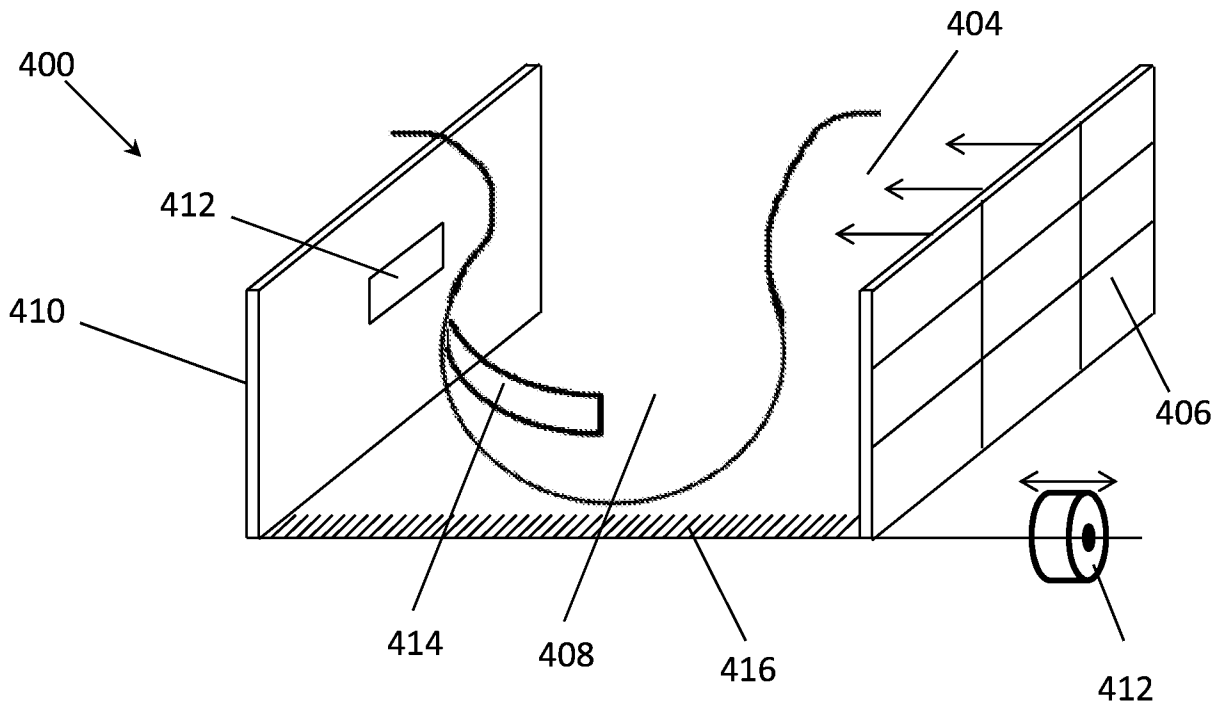

400
404
412
410
406
414
408
416
412

FIG. 4A

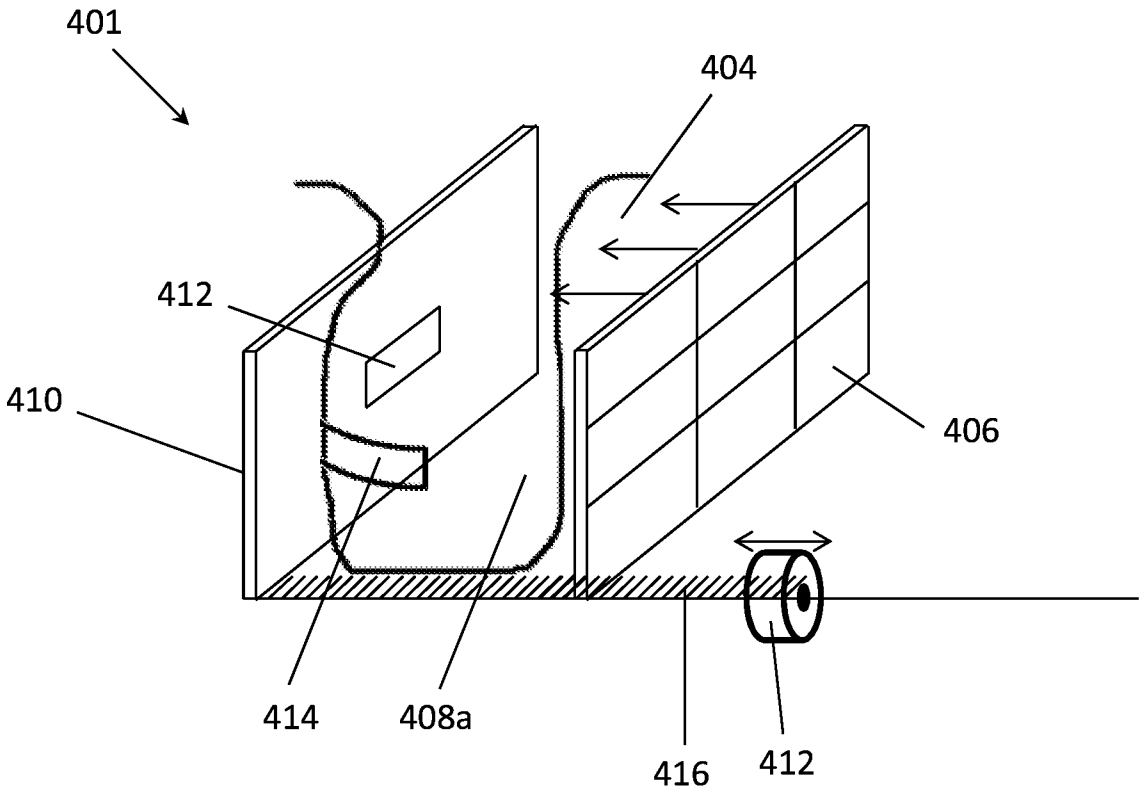

401
404
412
410
406
414
408a
416
412

FIG. 4B

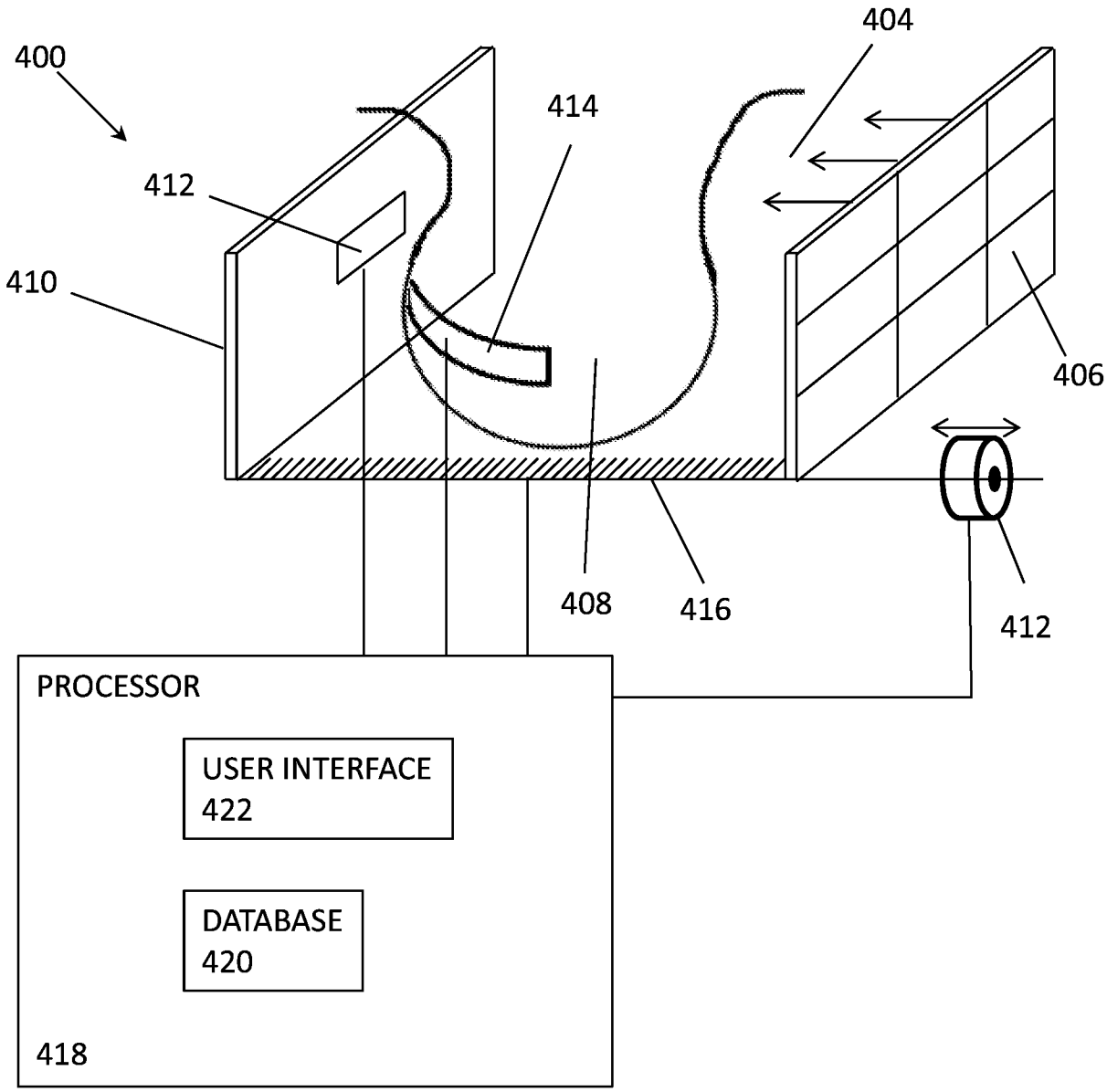

400
404
414
412
410
406
408
416
412
PROCESSOR
USER INTERFACE
422
DATABASE
420
418

FIG. 4C

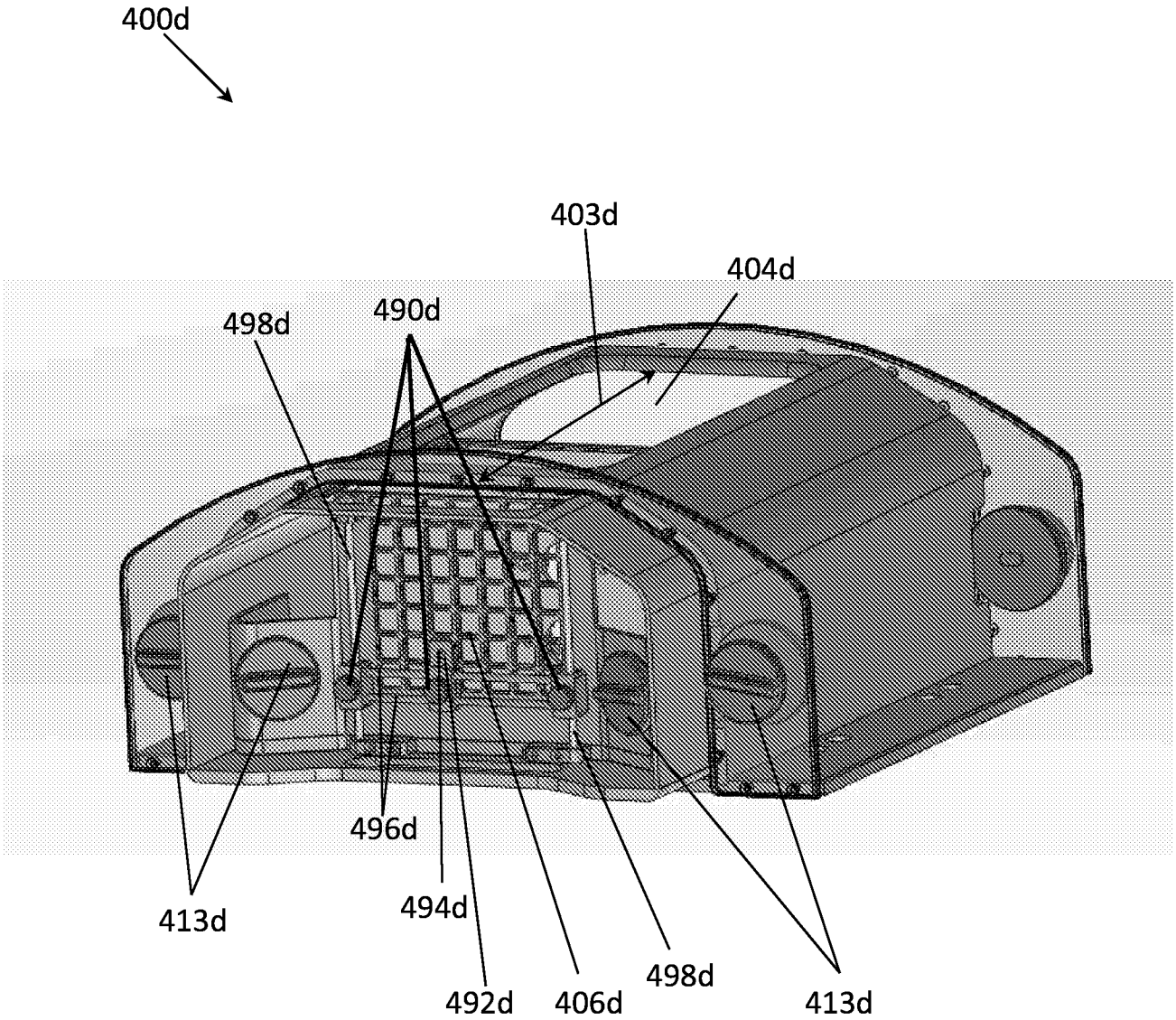



FIG. 4D

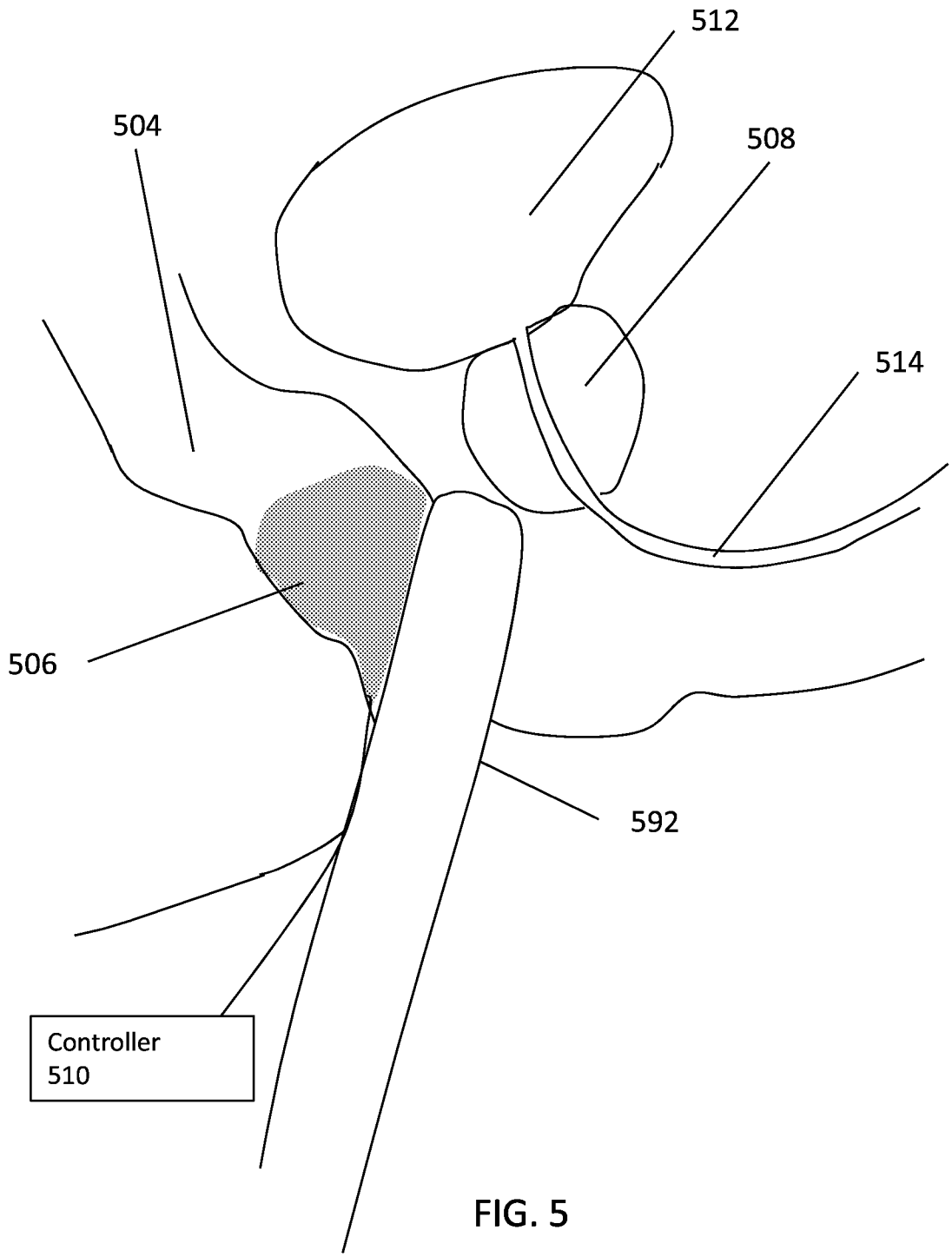



FIG. 5

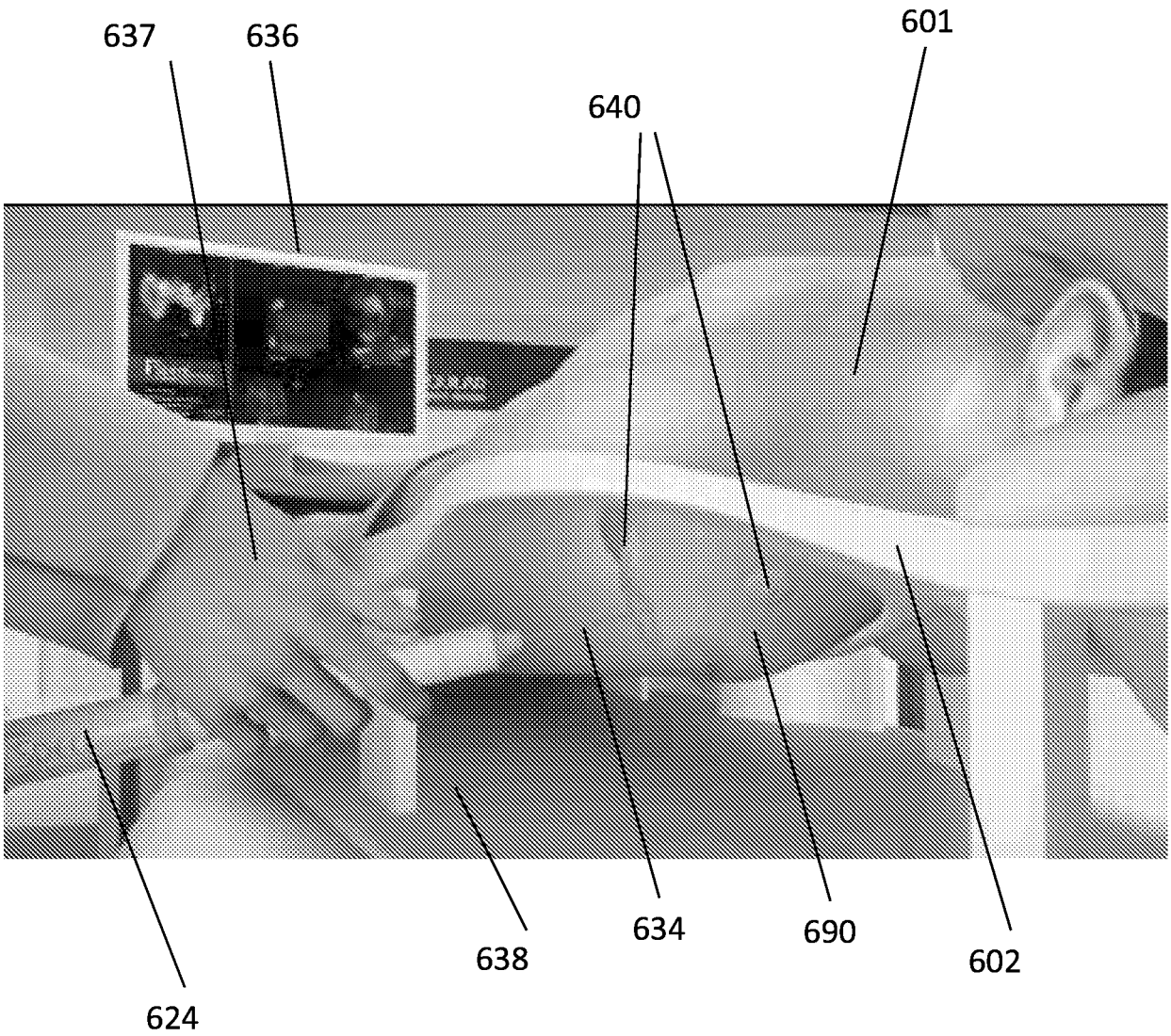



FIG. 6A

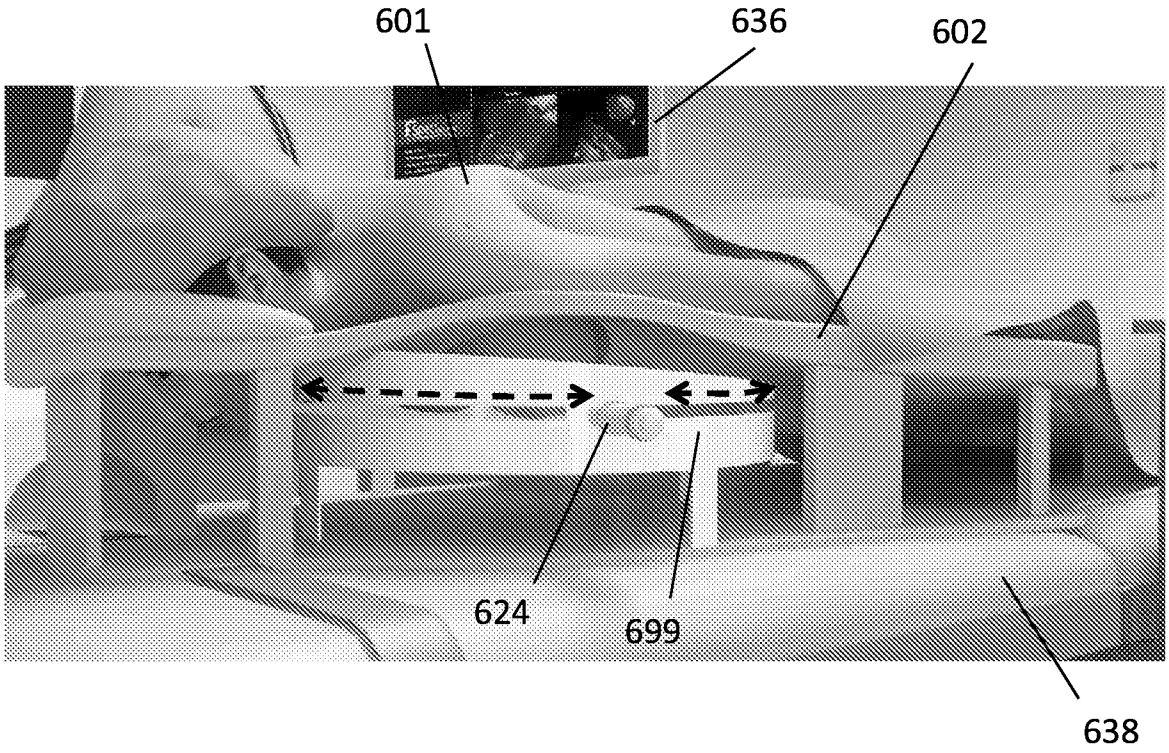



FIG. 6B

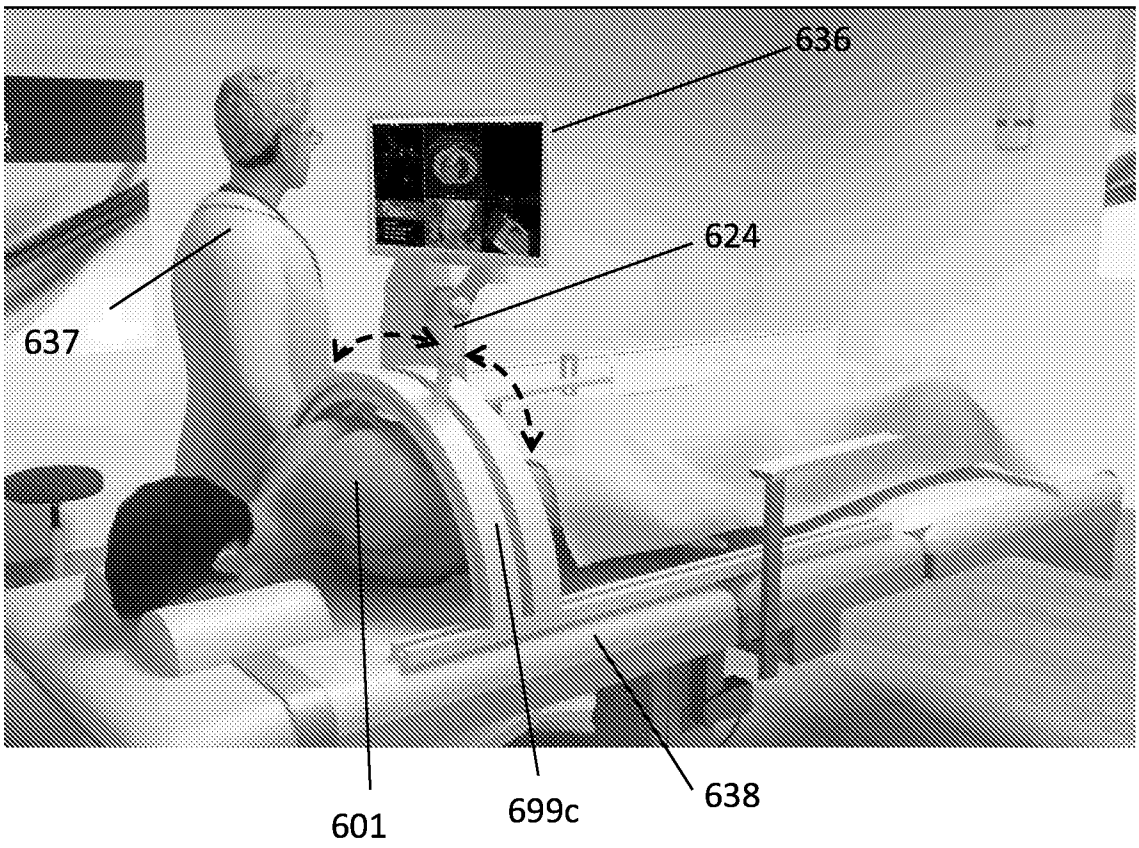
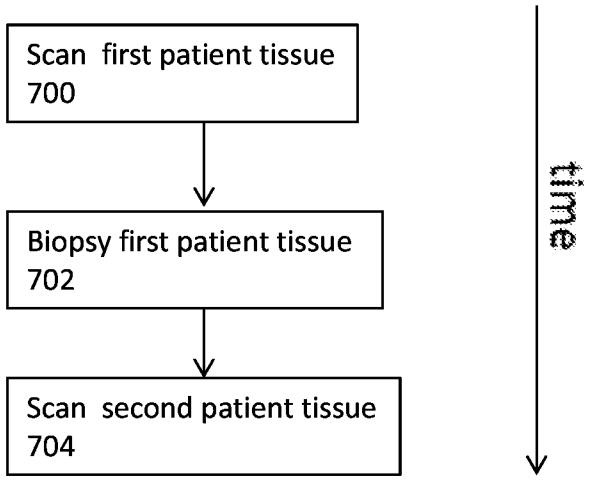



FIG. 6C




PRIOR ART
FIG. 7A

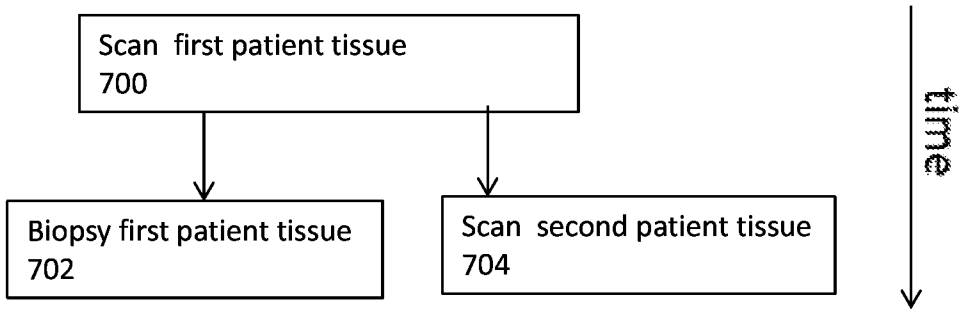



FIG. 7B

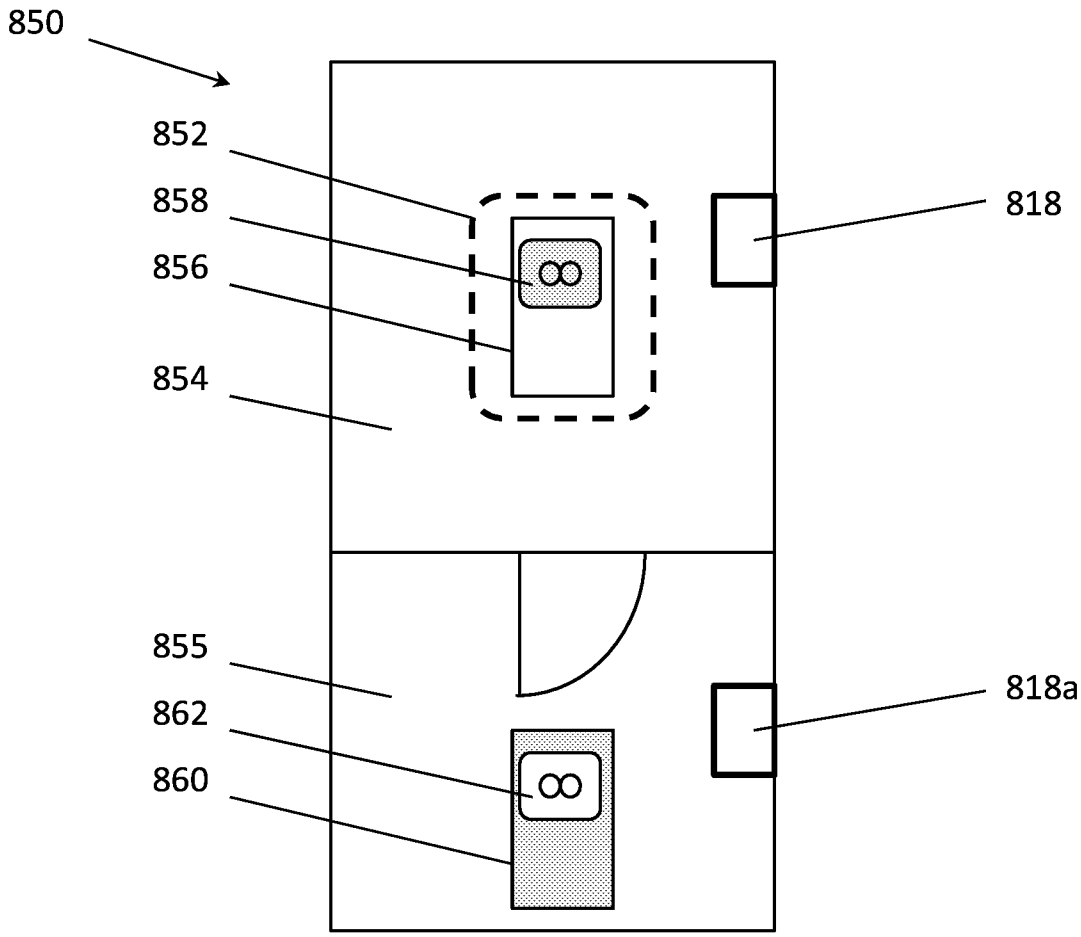



FIG. 8

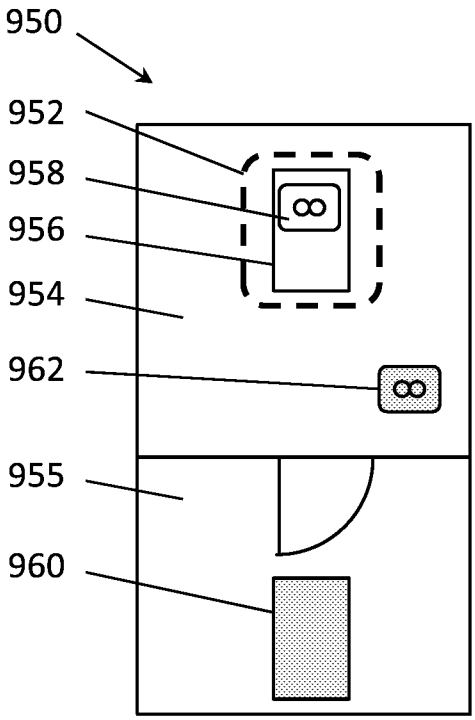



FIG. 9A

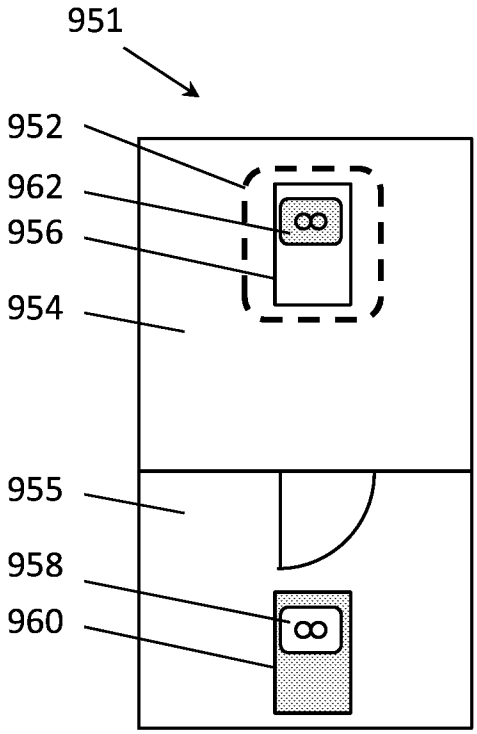



FIG. 9B

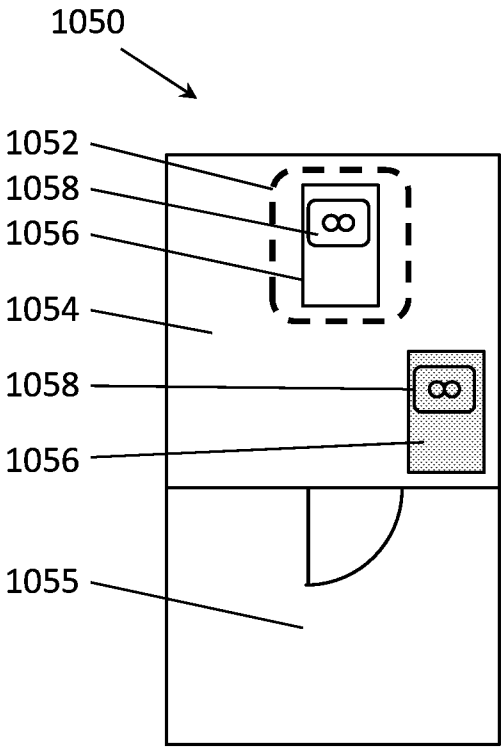



FIG. 10A

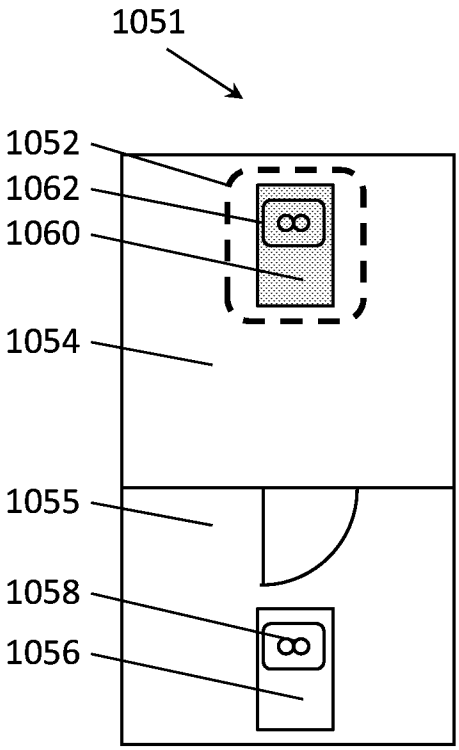



FIG. 10B

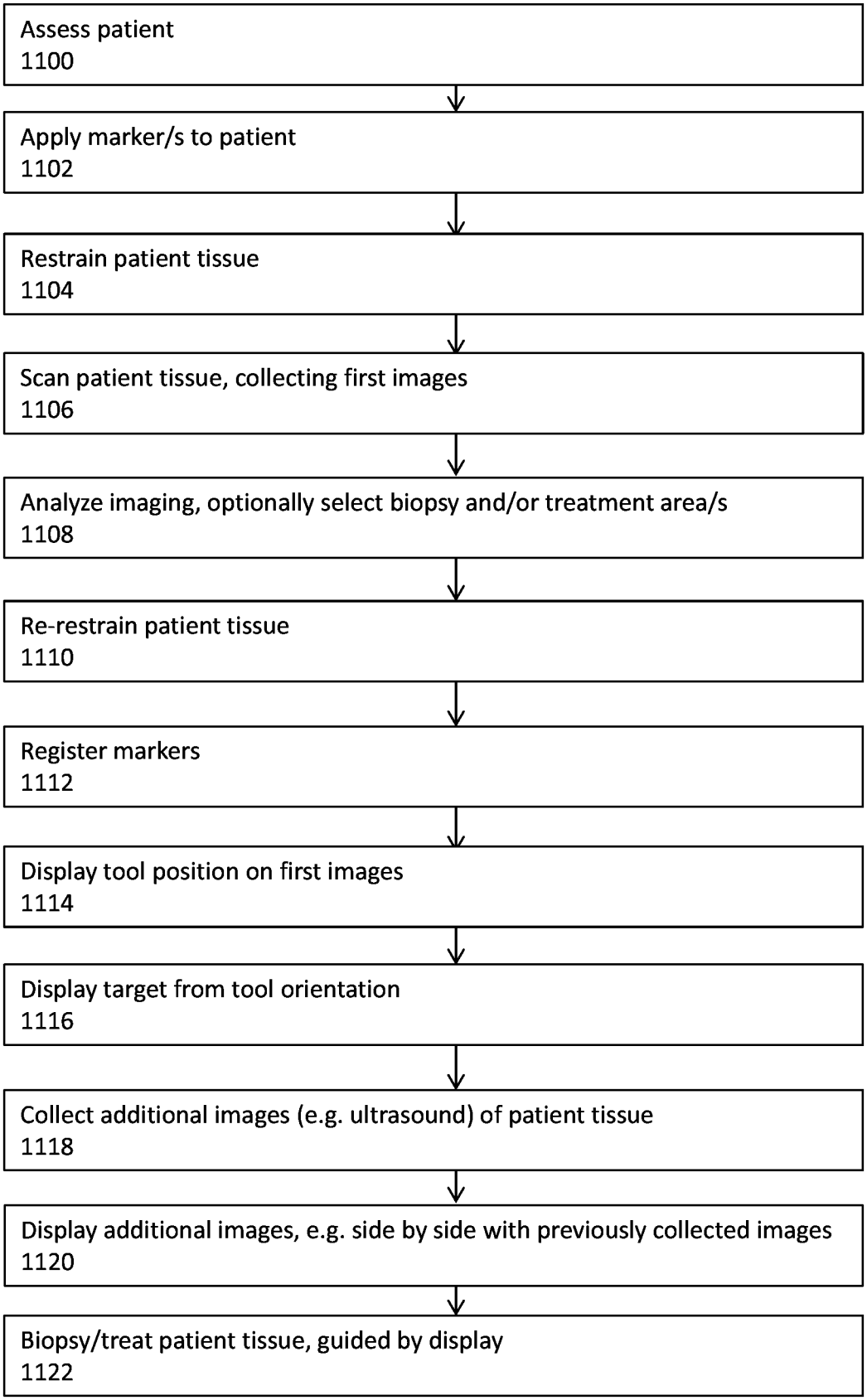

Assess patient
1100
Apply marker/s to patient
1102
Restrain patient tissue
1104
Scan patient tissue, collecting first images
1106
Analyze imaging, optionally select biopsy and/or treatment area/s
1108
Re-restrain patient tissue
1110
Register markers
1112
Display tool position on first images
1114
Display target from tool orientation
1116
Collect additional images (e.g. ultrasound) of patient tissue
1118
Display additional images, e.g. side by side with previously collected images
1120
Biopsy/treat patient tissue, guided by display
1122

FIG. 11

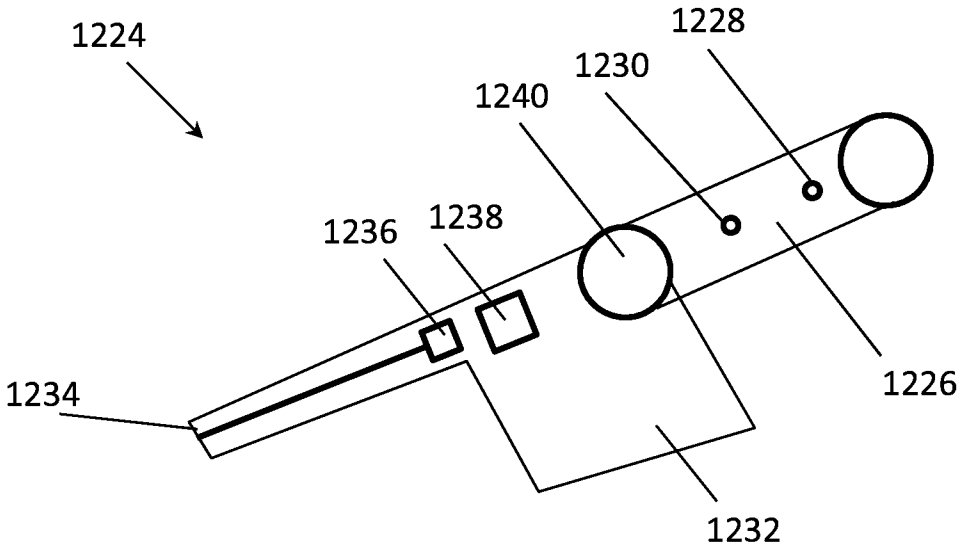



FIG. 12A

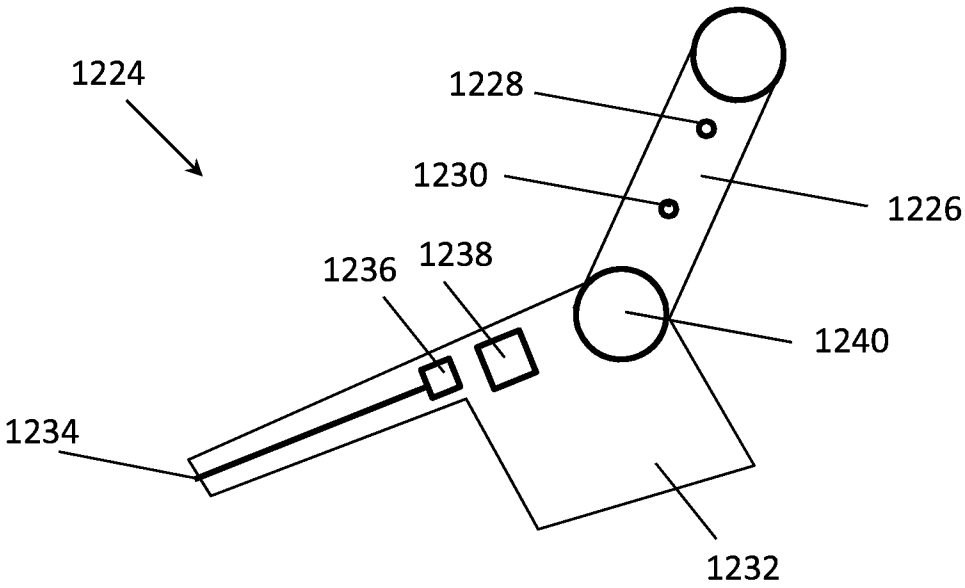
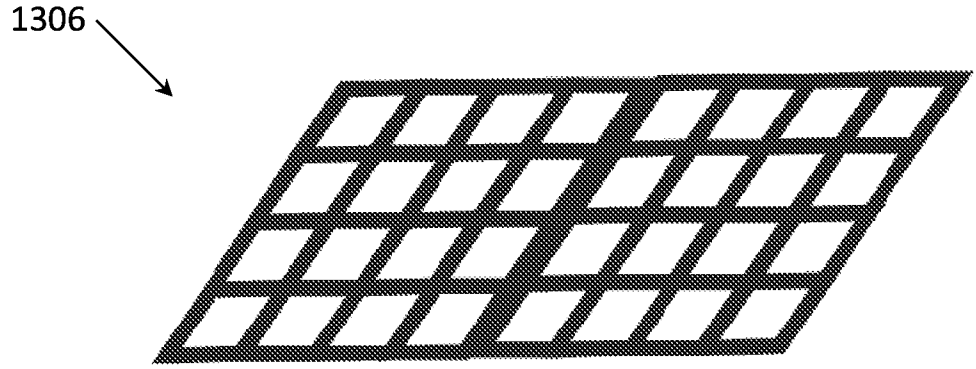



FIG. 12B




PRIOR ART

FIG. 13

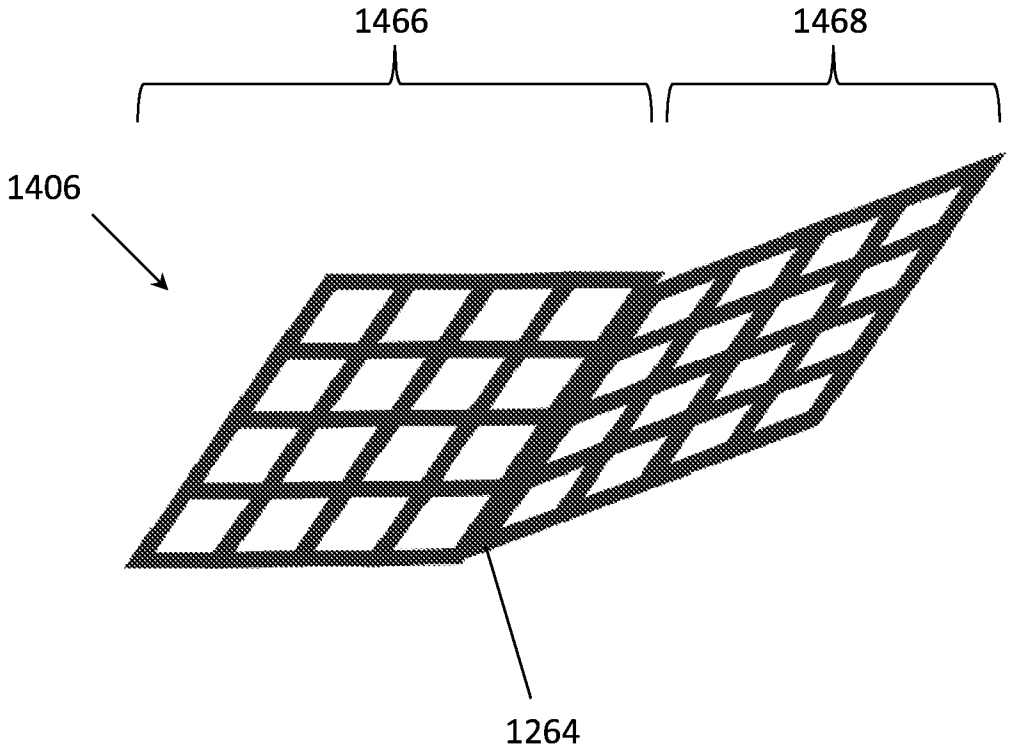
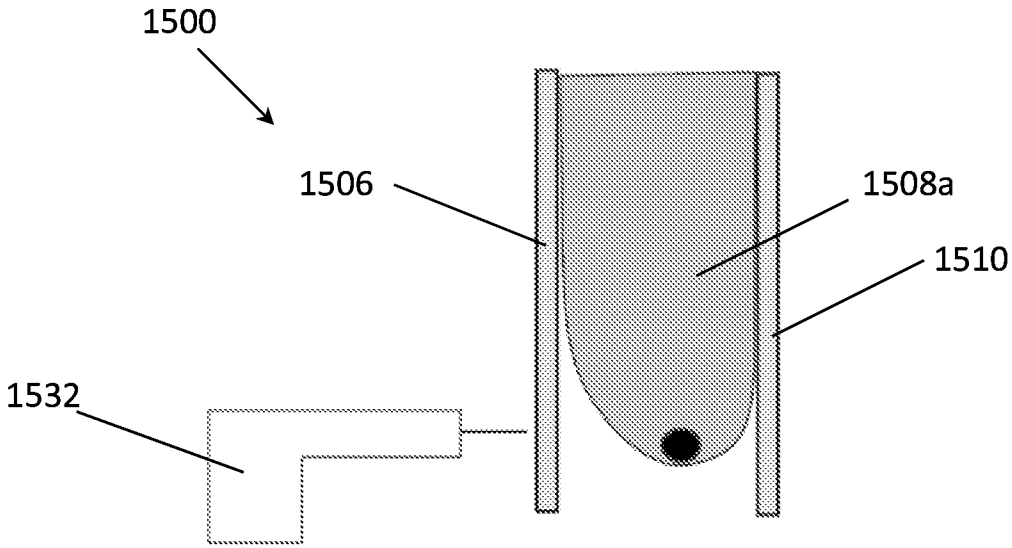



FIG. 14




PRIOR ART
FIG. 15

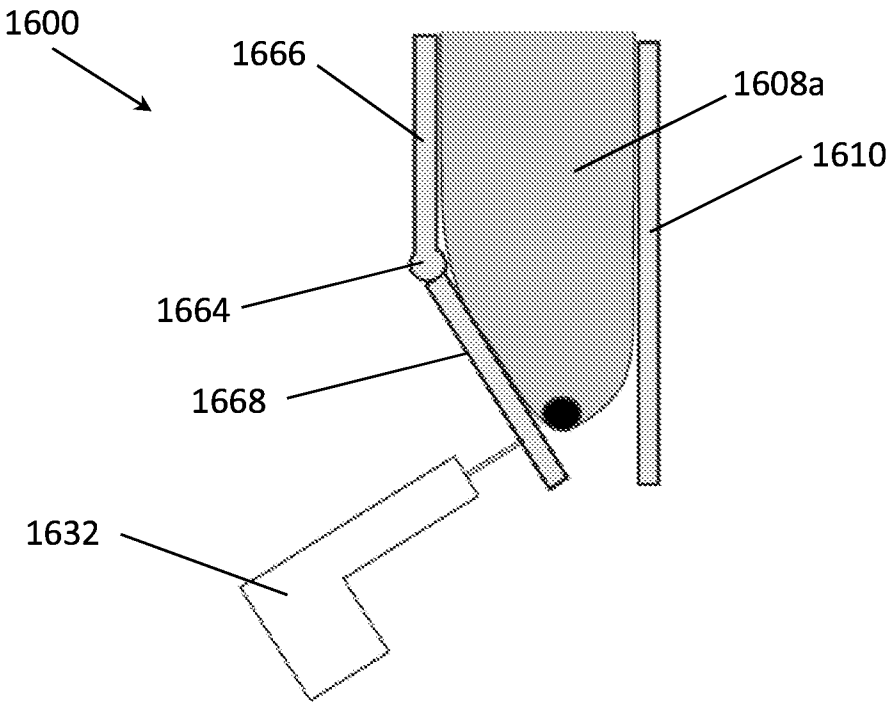



FIG. 16

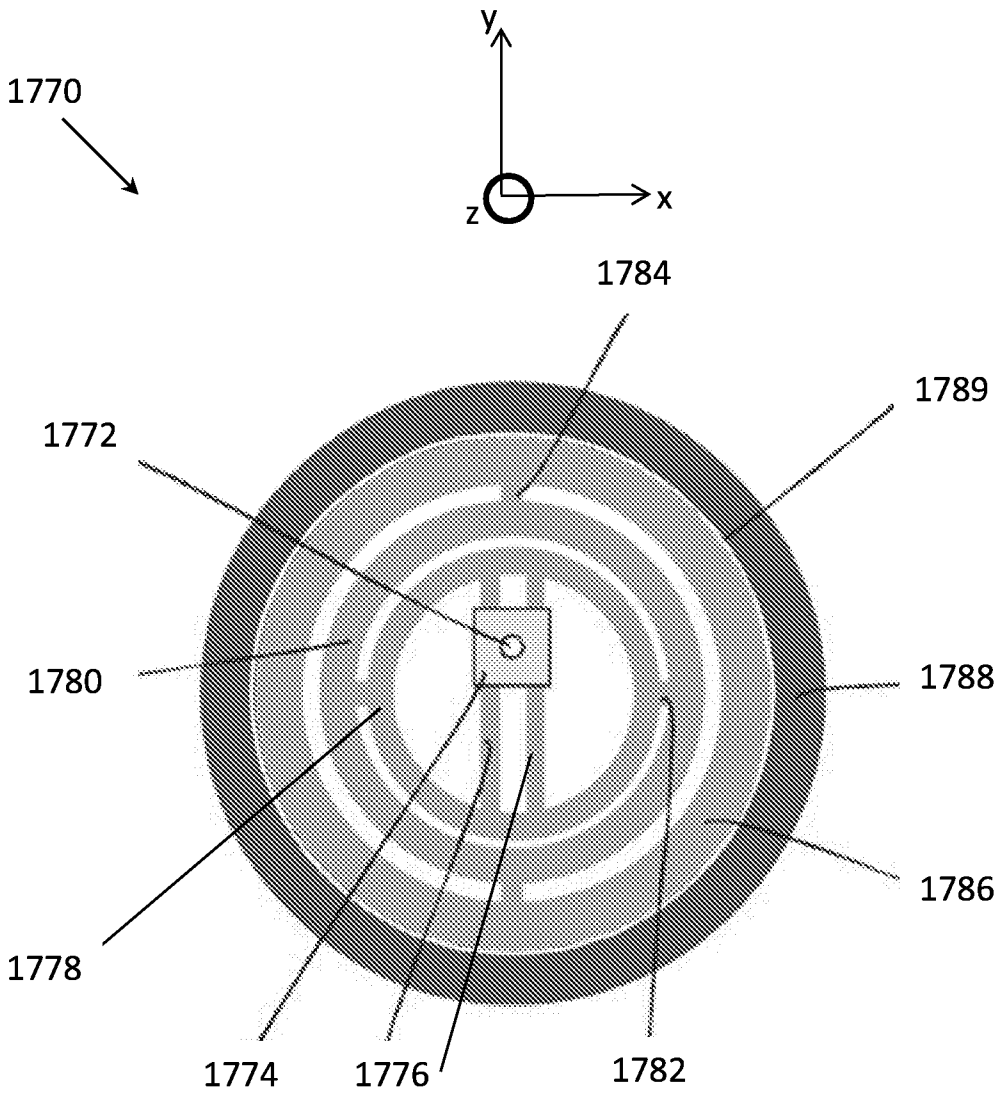



FIG. 17

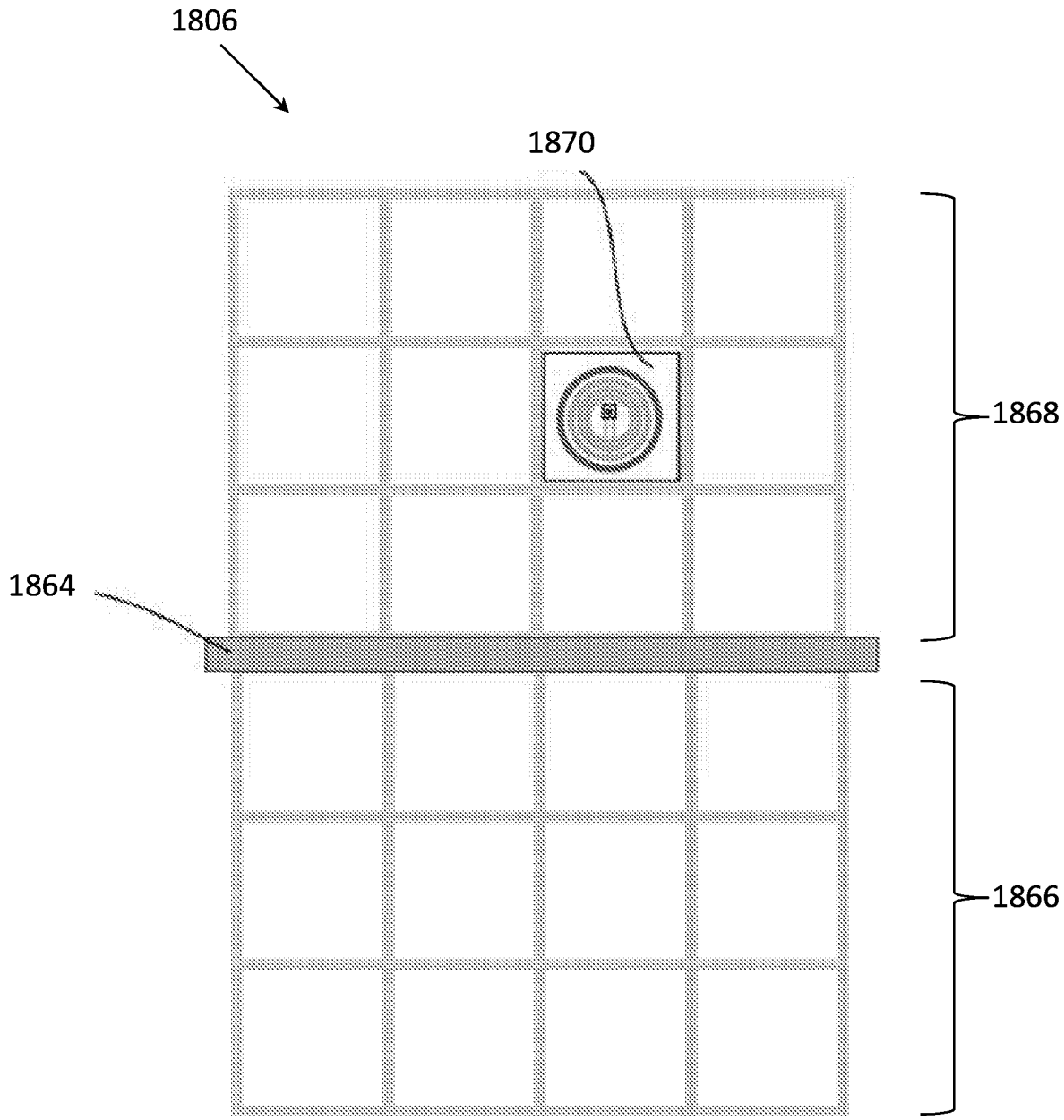



FIG. 18

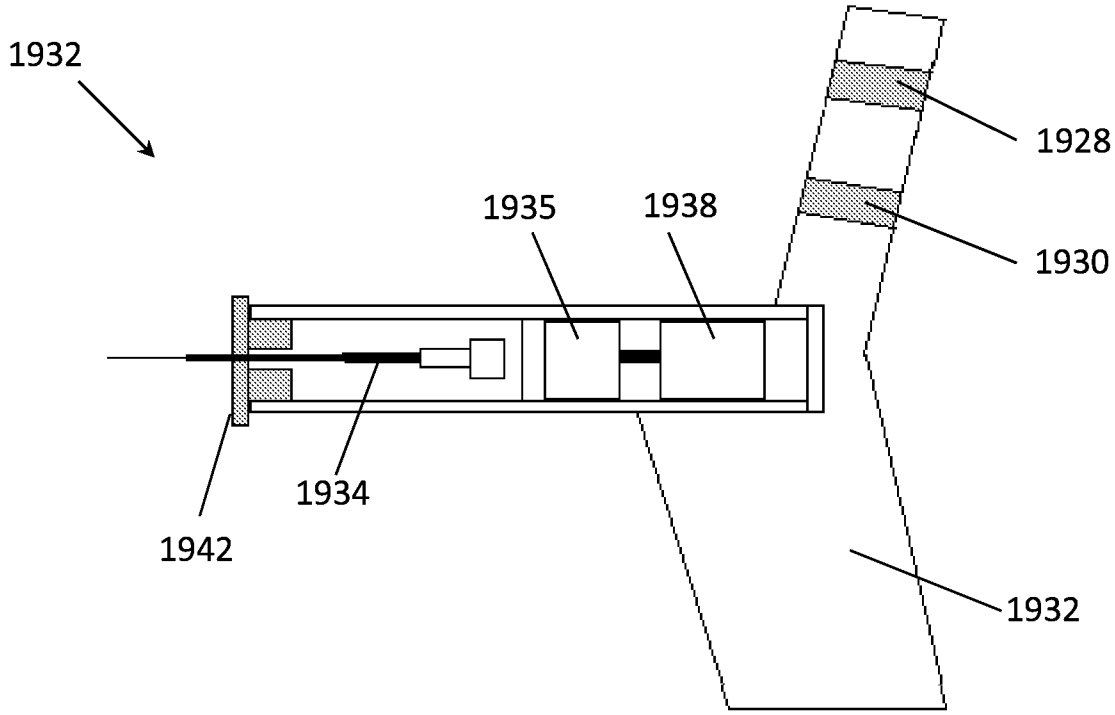



FIG. 19A

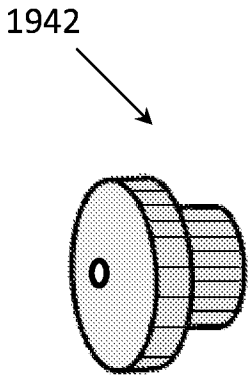



FIG. 19B

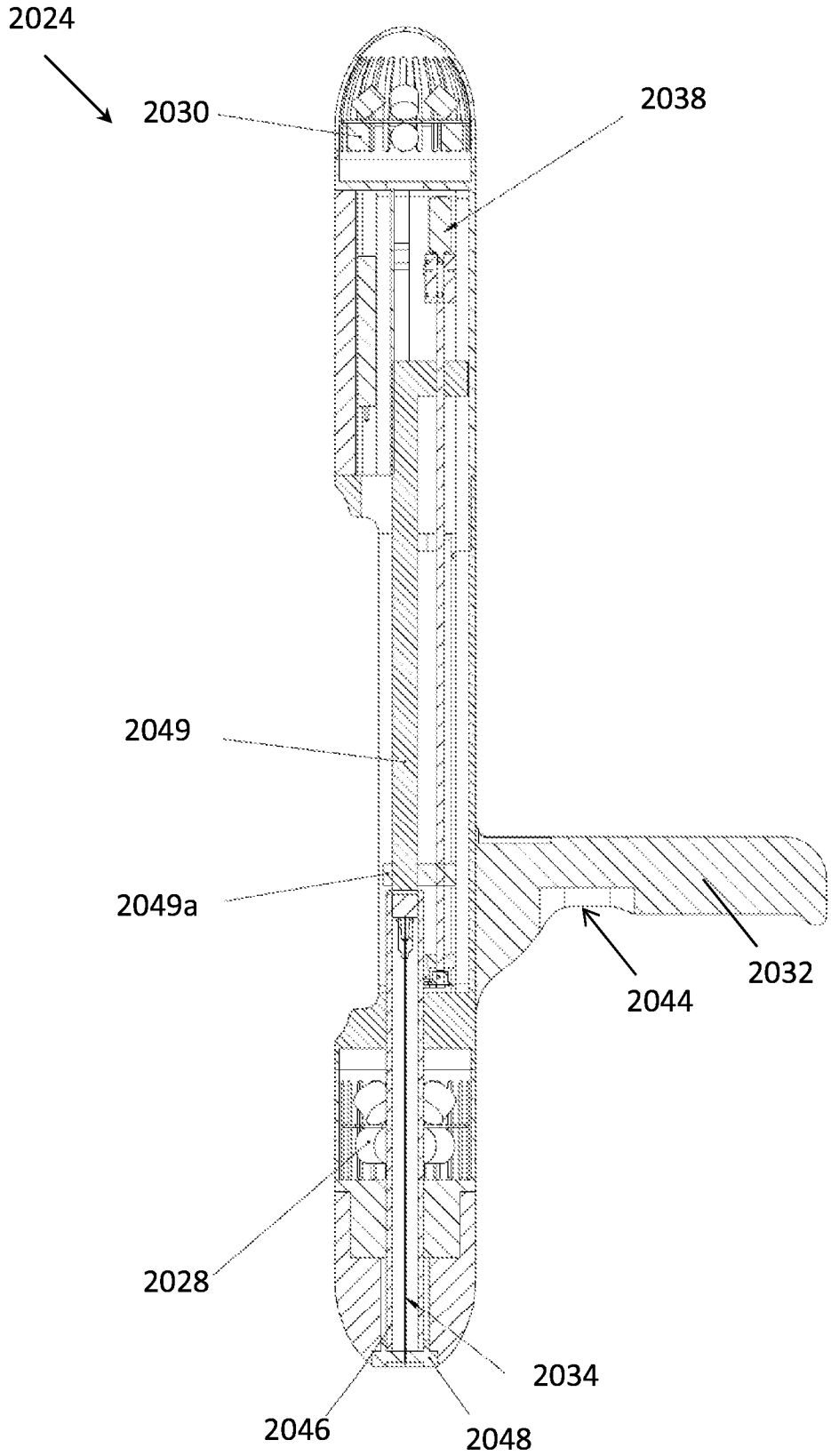



FIG. 20

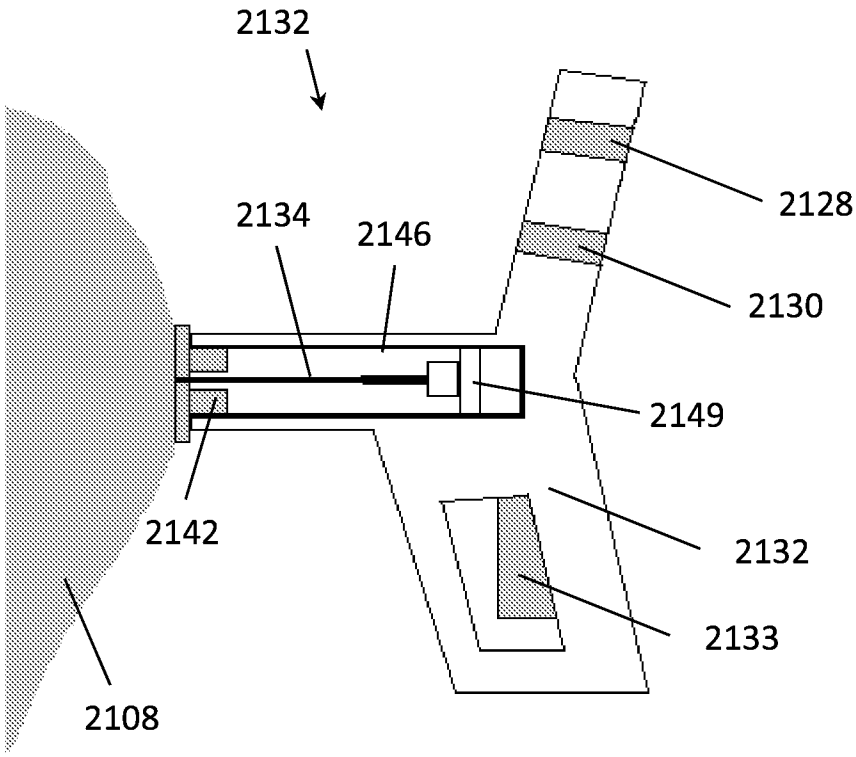



FIG. 21A

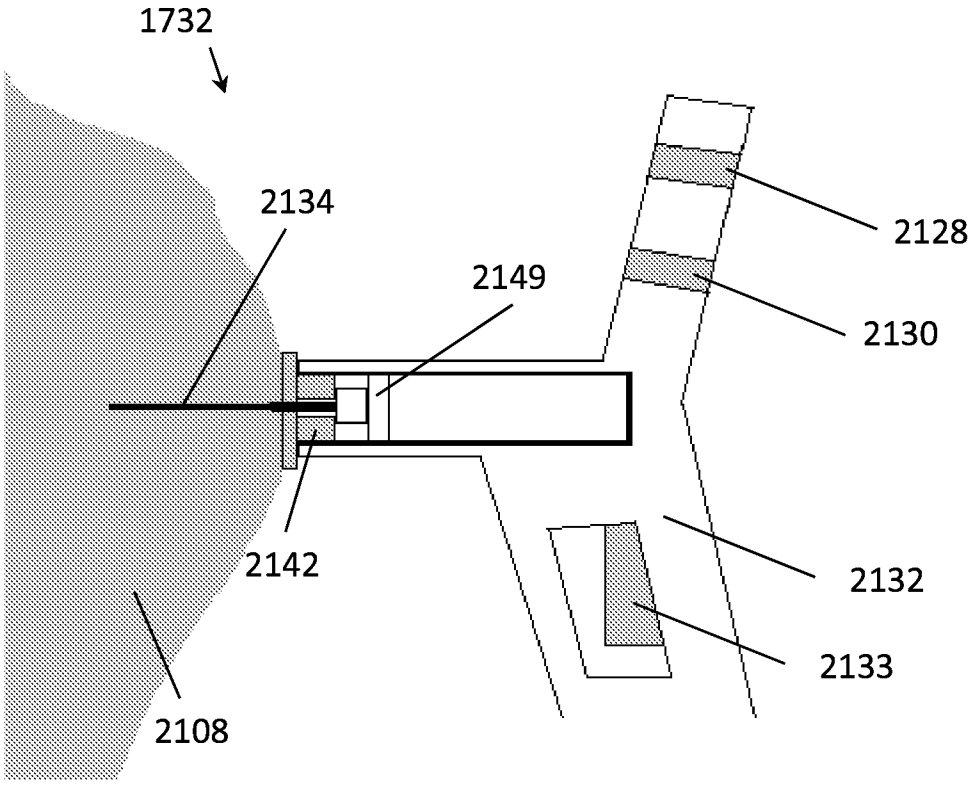



FIG. 21B

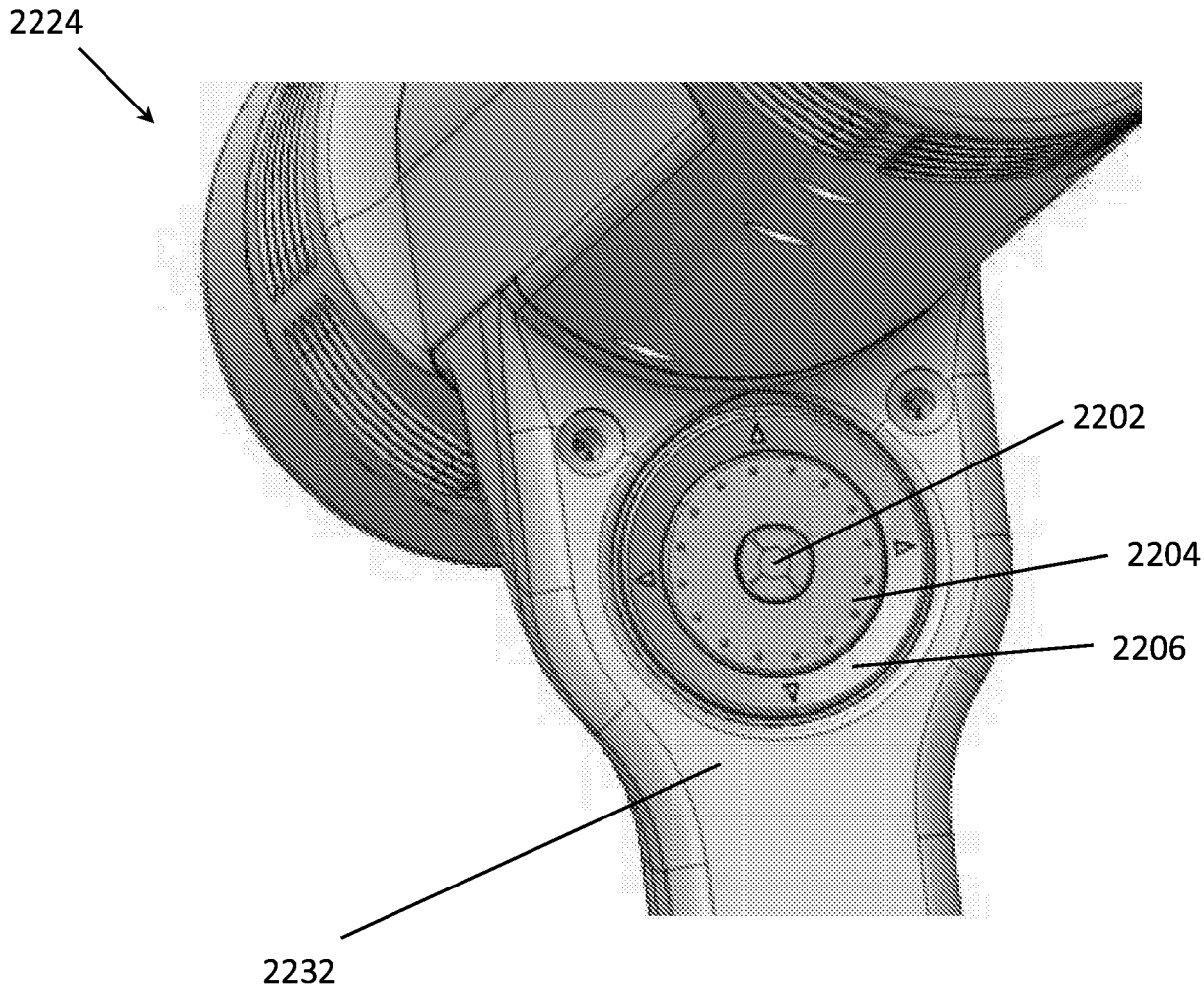



FIG. 22

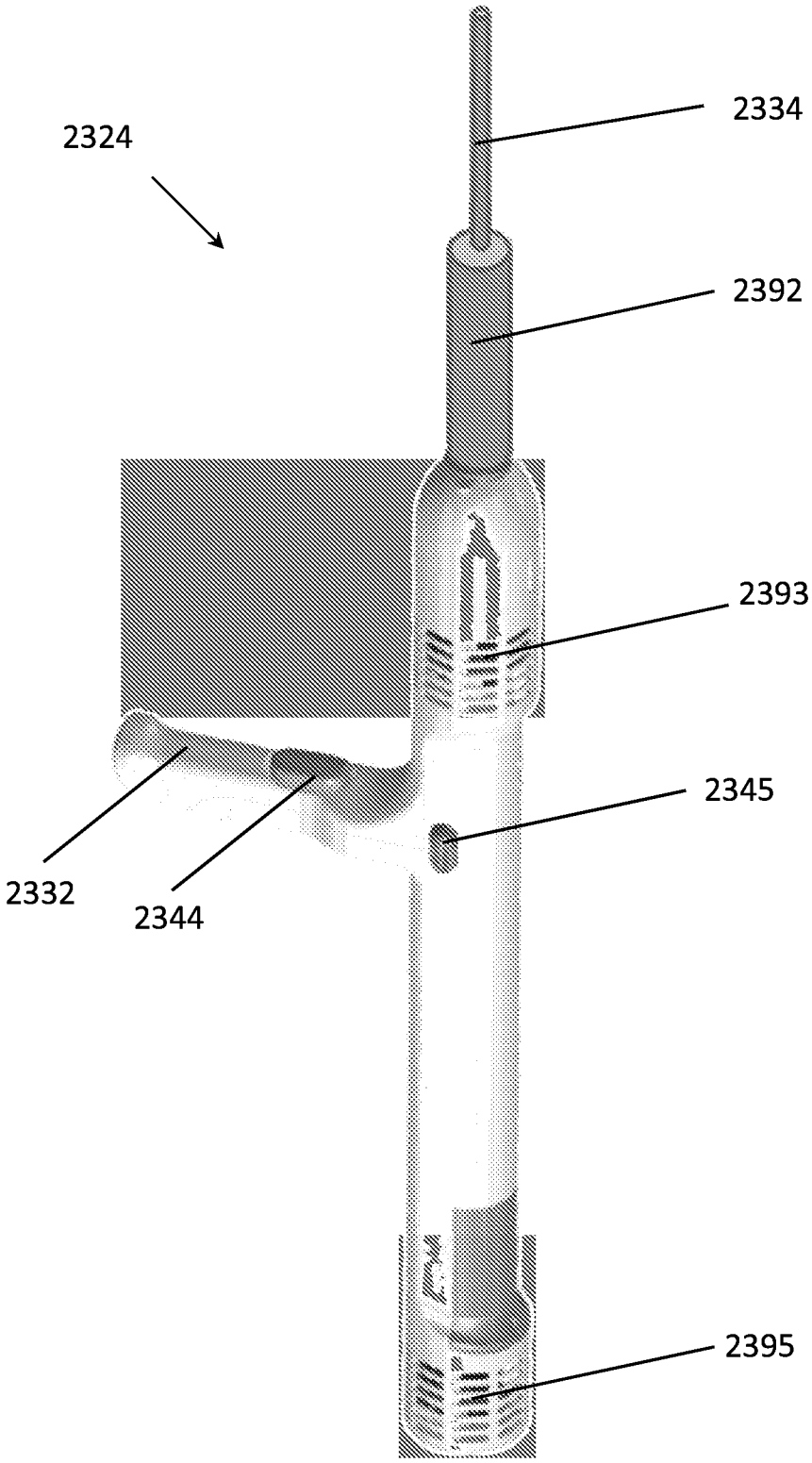



FIG. 23

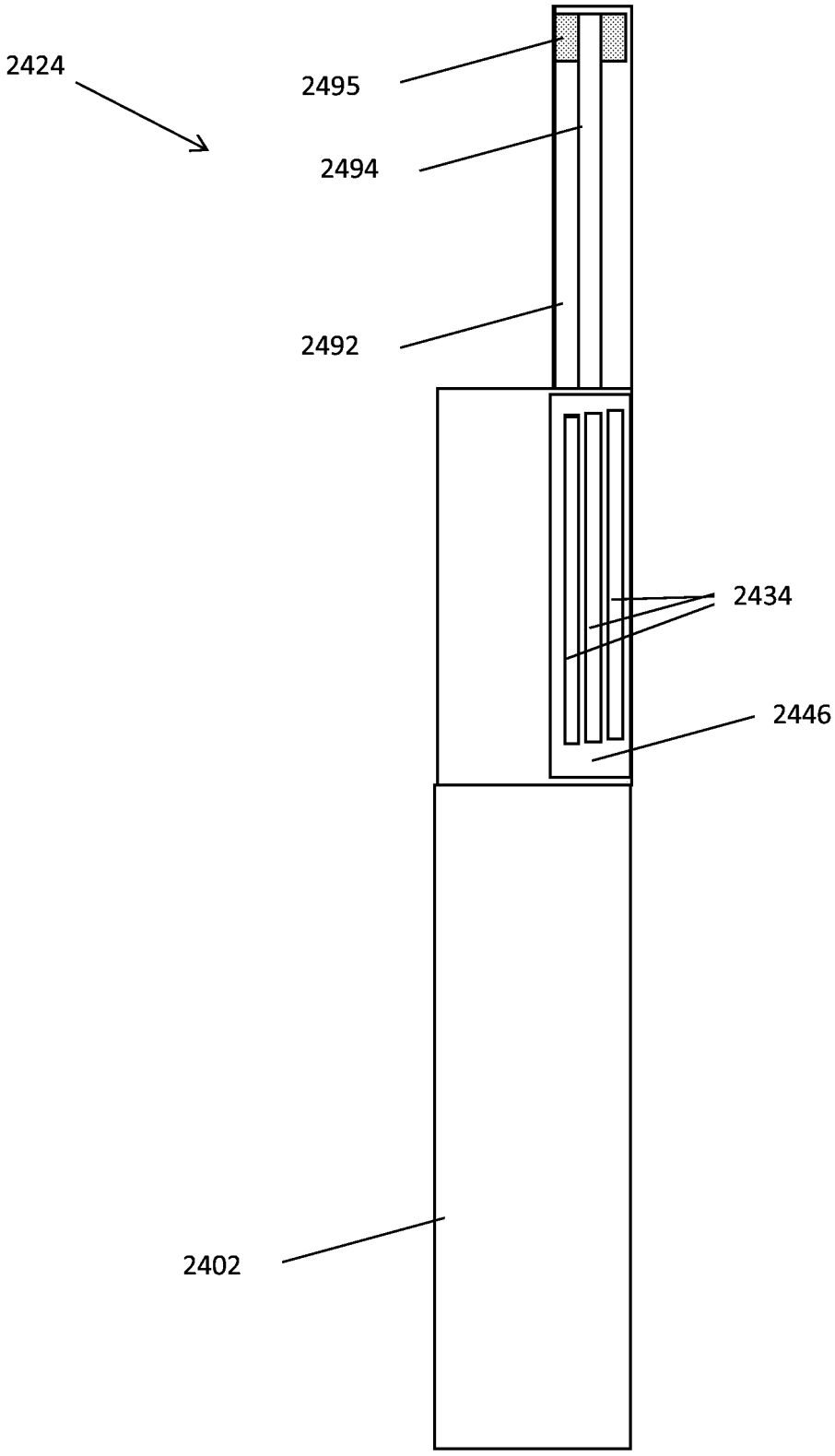



FIG. 24

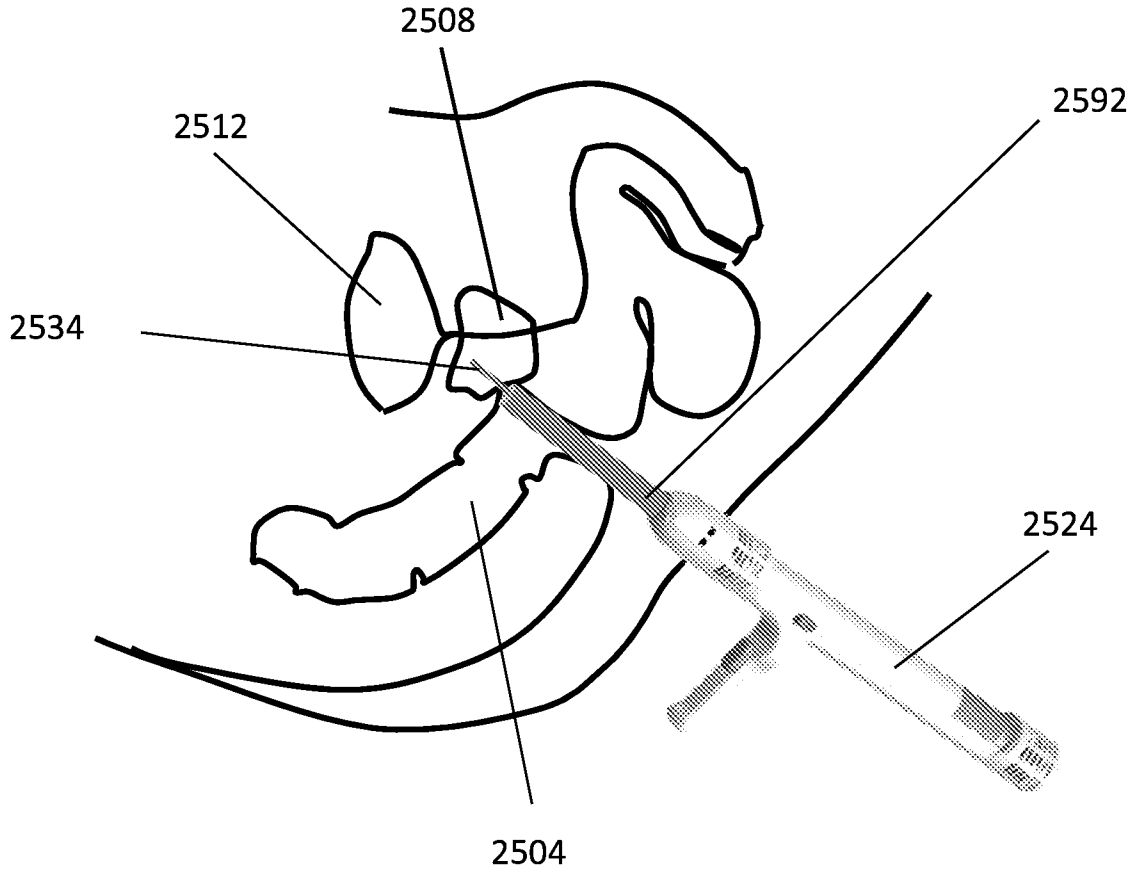



FIG. 25A

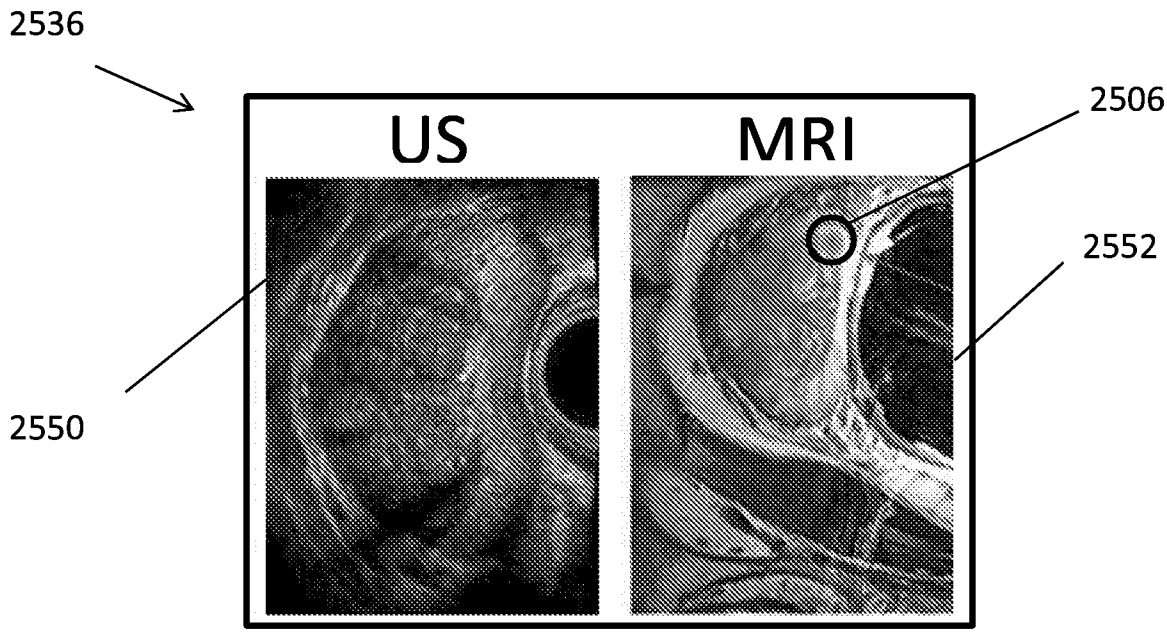



FIG. 25B

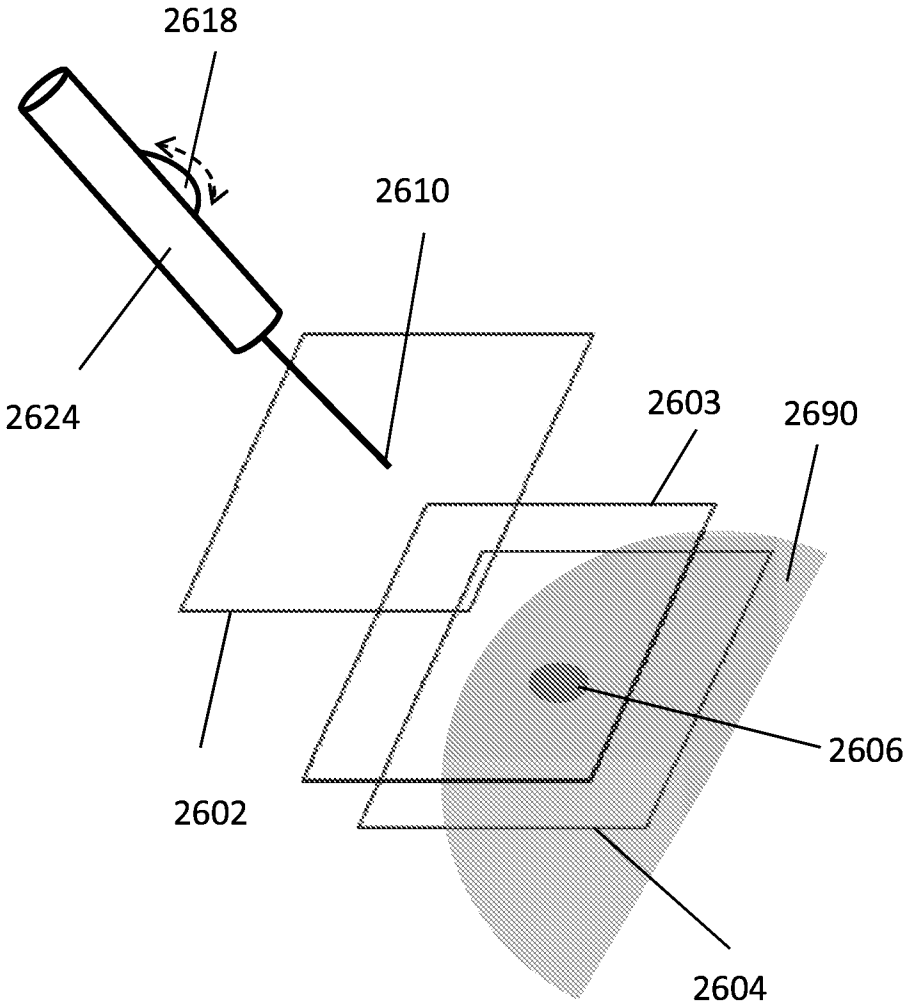



FIG. 26A

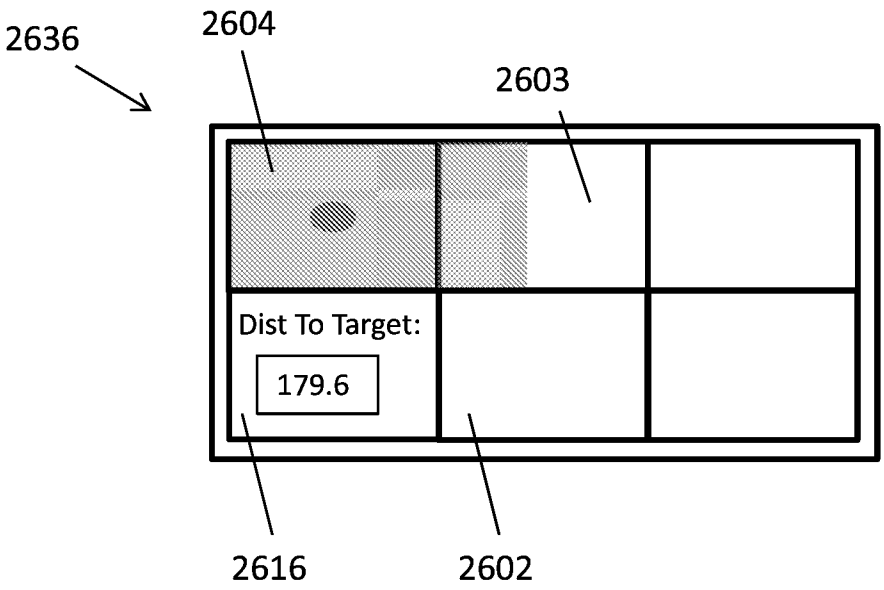



FIG. 26B

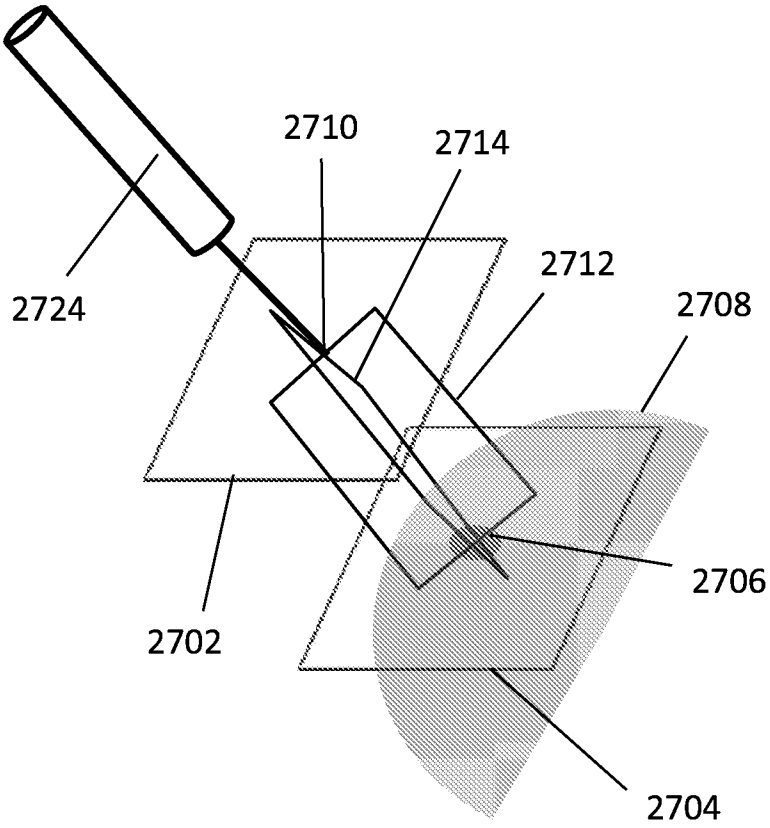



FIG. 27A

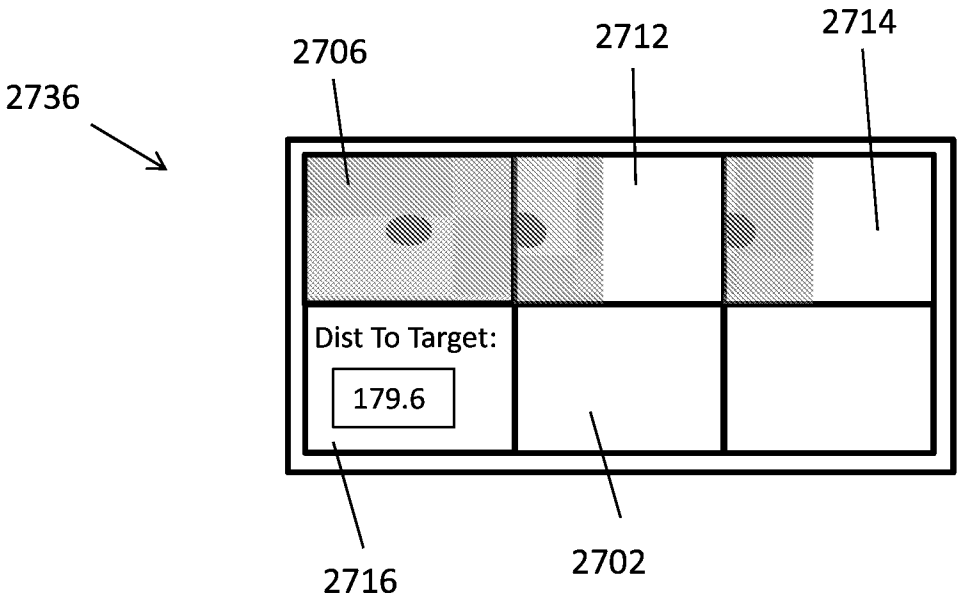



FIG. 27B

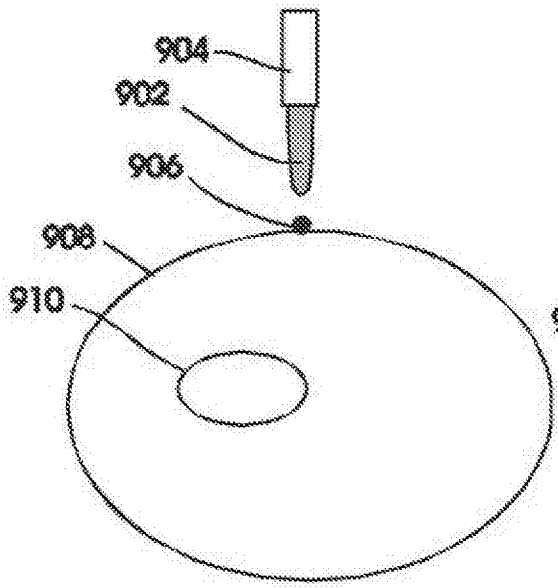



FIG. 28A

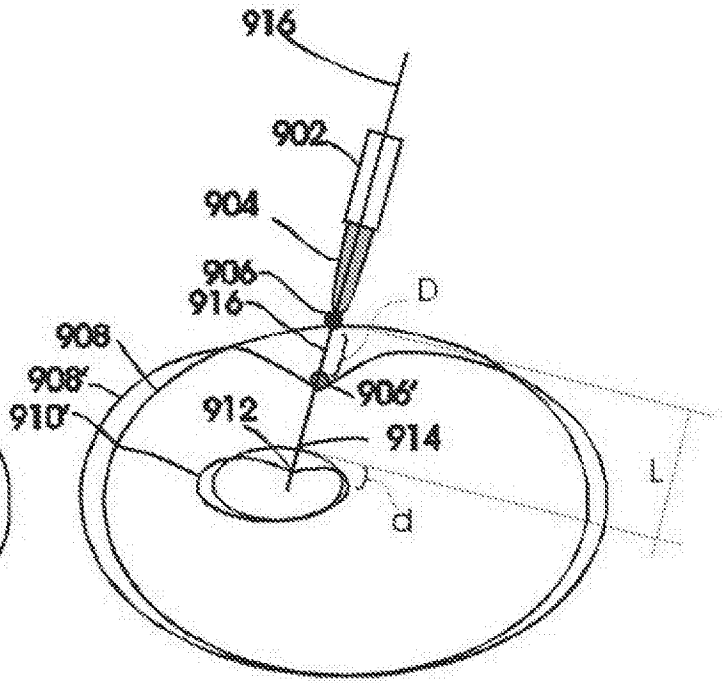



FIG. 28B

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2015/050207

A. CLASSIFICATION OF SUBJECT MATTER

IPC (2015.01) A61B 5/00, A61B 5/05, A61B 5/055, A61B 6/02, A61B 6/04, A61B 6/04, A61B 8/00, G21K 5/08

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)

IPC (2015.01) A61B 5/00, A61B 5/05, A61B 5/055, A61B 6/02, A61B 6/04, A61B 6/04, A61B 8/00, G21K 5/08

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)

Databases consulted: THOMSON INNOVATION, Esp@cenet, Google Patents

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2005080333 A1 Piron et al.<br>14 Apr 2005 (2005/04/14)<br>(The whole document especially abstract, Figs. 1a-b, 5a1, 5a2, 6C, 9a, 15, 17, 18, 28-31, paragraphs 11, 14-17, 21, 24-26, 28, 35-37, 75-97, 105, 107, 108, 125, 135, 140, 142, 144, 146, 148, 151, 160-161, 163, 224). | 1-24,41,42,46-50 |
| Y | US 2010246760 A1 Li et al.<br>30 Sep 2010 (2010/09/30)<br>(The whole document especially abstract, Figs. 3-5, 9, 10, paragraphs 7, 9, 27, 28-30, 32, 37-48). | 1-24,41,42,46-50 |
| X | US 2009143674 A1 Nields et al.<br>04 Jun 2009 (2009/06/04)<br>(The whole document especially abstract, Fig. 1-4, 18-20, paragraphs 2, 5, 12-13,23, 37, 39, 40-41, 43, 45, 46, 54, 70-73, 76, 90-91). | 25-28 |
| Y | (The whole document especially abstract, Fig. 1-4, 18-20, paragraphs 2, 5, 12-13,23, 37, 39, 40-41, 43, 45, 46, 54, 70-73, 76, 90-91). | 1-24,41,42,46-50 |
| | | |

[X] Further documents are listed in the continuation of Box C. [X] 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 |
|---|---|
| 15 Jul 2015 | 16 Jul 2015 |
| Name and mailing address of the ISA:<br>Israel Patent Office<br>Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel<br>Facsimile No. 972-2-5651616 | Authorized officer<br>NIMER Emad<br><br>Telephone No. 972-2-5657801 |

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/IL2015/050207

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2009326363 A1 Li et al.<br>31 Dec 2009 (2009/12/31)<br>(Co-registration MRI, and Ultrasound images, Abstract, Figs. 1, 2, 5-10). | 1-50 |
| A | US 2011178389 A1 Kumar et al.<br>21 Jul 2011 (2011/07/21)<br>(co-registration MRI and ultrasound images of prostate tissue, 3D construction, and transformation for alignment ultrasound and MRI images, abstract, Figs. 8, 10, 11). | 1-50 |
| Y | US 2008043905 A1 Hassanpourgol.<br>21 Feb 2008 (2008/02/21)<br>(The whole document especially abstract, Figs. 1, 4, 5, paragraphs 7, 51-57). | 1-24,41,42,46-50 |
| Y | US 3971950 A Evans et al.<br>27 Jul 1976 (1976/07/27)<br>(The whole document especially abstract, Figs. 1-4, col. 2 lines 63-65). | 1-24,41,42,46-50 |
| X | US 4875478 A Chen.<br>24 Oct 1989 (1989/10/24)<br>(The whole document especially abstract, Figs. 1-2, 8, 9, col.10 lines 50-62). | 29 |
| Y | (The whole document especially abstract, Figs. 1-2, 8, 9, col.10 lines 50-62). | 1-24,30-38,41,42, 46-50 |
| Y | US 2008230074 A1 Zheng et al.<br>25 Sep 2008 (2008/09/25)<br>(The whole document especially abstract, Figs. 1-10). | 1-24,41,42,46-50 |
| Y | US 2007016003 A1 Piron et al.<br>18 Jan 2007 (2007/01/18)<br>(The whole document especially abstract, Figs. 1-12). | 1-24,41,42,46-50 |
| X | US 2013090554 A1 Zvuloni et al.<br>11 Apr 2013 (2013/04/11)<br>(The whole document especially abstract, Figs. 4, 6, paragraphs 24, 29, 52, 67, 78, 104, 111, 150, 176). | 25-28,39,40,43-45 |
| Y | (The whole document especially abstract, Figs. 4, 6, paragraphs 24, 29, 52, 67, 78, 104, 111, 150, 176). | 12,13,32-38 |
| Y | US 2008132782 A1 Rueckmann et al.<br>05 Jun 2008 (2008/06/05)<br>(The whole document especially title, abstract, Fig. 1, paragraphs 14-15, 17-21). | 14-24,46-50 |
| Y | US 2006100529 A1 Rueckmann et al.<br>11 May 2006 (2006/05/11)<br>(Title, abstract, Fig. 1-3, paragraphs 17, 23, 24, 36, 37). | 14-24,46-50 |
| Y | US 5506877 A Niklason et al.<br>09 Apr 1996 (1996/04/09)<br>(breast compression device comprising motor, Force sensor, processor, abstract, Fig. 3, Fig. 6A, col. 8 lines 37-49). | 30,31 |
| Y | US 2011034796 A1 Ma et al.<br>10 Feb 2011 (2011/02/10)<br>(folding plate paddle, Abstract, Figs. 1, 3, 5, 8, 9, 10E, 11A). | 34 |

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/IL2015/050207

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2010104063 A1 Bindra et al.<br>29 Apr 2010 (2010/04/29)<br>(processor control compression mechanism, Fig. 6). | 30,31 |
| A | US 2013131509 A1 Rafaeli et al.<br>23 May 2014 (2014/05/23)<br>(Controllable paddle pressure, Fig. 2). | 30,31 |
| A | US 5190046 A Shturman.<br>02 Mar 1993 (1993/03/02)<br>(MRI imaging probe having inflatable balloon for maintaining or restraining/re-restraining prostate tissue, abstract, Figs. 1-3, 7-13). | 46-50 |
| A | US 5476095 A Schnall et al.<br>19 Dec 1995 (1995/12/19)<br>(MRI imaging probe having inflatable balloon for maintaining or restraining/re-restraining prostate tissue, abstract, Figs. 1-2, 7-13). | 46-50 |

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/IL2015/050207

**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 extra 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 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.:

**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.

**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:

| | | |
|---|---|---|
| Invention/s 1 | An imaging system and methodology configured to perform co-registration to a 3-D constructed MRI and 3-D constructed ultrasound images of a non-rigid tissue, while said non-rigid tissue are immobilized and compressed by an independent compression device(s), said MRI images are acquired by MRI modality, and said ultrasound images are acquired by ultrasound modality, wherein said independent breast compression device is functionally associated to said ultrasound imaging modality independently to said MRI imaging modality, said independent compression operation enables removing one patient from said MRI imaging modality and performs examination to another patient using said MRI modality, while the first patient is transferred to said ultrasound imaging modality. Said methodology is configured to optimize the utilization of the resources of said imaging modalities, increases throughput and reduces waiting time of patients for a free imaging resources. | Claim/s 1-24,39-42,46-50 |
| Invention/s 2 | A method and system for registration a tissue, registration a biopsy tool, determining the position of said biopsy tool, and determining the condition of a restrained tissue. | Claim/s 25-38,43-45 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/IL2015/050207

| Patent document cited search report | Publication date | Patent family member(s) | Publication Date |
|---|---|---|---|
| US 2005080333 A1 | 14 Apr 2005 | US 2005080333 A1 | 14 Apr 2005 |
| | | US 7379769 B2 | 27 May 2008 |
| | | AU 2004216658 A1 | 14 Apr 2005 |
| | | CA 2483718 A1 | 30 Mar 2005 |
| | | CA 2483718 C | 27 Jan 2015 |
| | | EP 2063776 A1 | 03 Jun 2009 |
| | | EP 2063776 A4 | 04 Apr 2012 |
| | | EP 2096454 A2 | 02 Sep 2009 |
| | | EP 2096454 A3 | 18 Nov 2009 |
| | | JP 2010501294 A | 21 Jan 2010 |
| | | JP 5313899 B2 | 09 Oct 2013 |
| | | JP 2013176602 A | 09 Sep 2013 |
| | | US 2008216239 A1 | 11 Sep 2008 |
| | | US 7908690 B2 | 22 Mar 2011 |
| | | US 2008132785 A1 | 05 Jun 2008 |
| | | US 7937132 B2 | 03 May 2011 |
| | | US 2007016003 A1 | 18 Jan 2007 |
| | | US 7970452 B2 | 28 Jun 2011 |
| | | US 2008255443 A1 | 16 Oct 2008 |
| | | US 8050736 B2 | 01 Nov 2011 |
| | | US 2012172704 A1 | 05 Jul 2012 |
| | | US 8560051 B2 | 15 Oct 2013 |
| | | US 2008306377 A1 | 11 Dec 2008 |
| | | US 8571632 B2 | 29 Oct 2013 |
| | | US 2008077005 A1 | 27 Mar 2008 |
| | | US 2014024926 A1 | 23 Jan 2014 |
| | | US 2014128883 A1 | 08 May 2014 |
| | | WO 2008025146 A1 | 06 Mar 2008 |
| | | WO 2008141447 A1 | 27 Nov 2008 |
| US 2010246760 A1 | 30 Sep 2010 | US 2010246760 A1 | 30 Sep 2010 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/IL2015/050207

| Patent document cited search report | Publication date | Patent family member(s) | Publication Date |
|---|---|---|---|
| | | US 7831015 B2 | 09 Nov 2010 |
| US 2009143674 A1 | 04 Jun 2009 | US 2009143674 A1 | 04 Jun 2009 |
| | | AU 2706500 A | 21 Sep 2000 |
| | | AU 4900997 A | 11 May 1998 |
| | | DE 69739947 D1 | 09 Sep 2010 |
| | | EP 0936889 A2 | 25 Aug 1999 |
| | | EP 0936889 A4 | 01 Dec 1999 |
| | | EP 0936889 B1 | 28 Jul 2010 |
| | | EP 0936889 B8 | 24 Nov 2010 |
| | | EP 1143845 A1 | 17 Oct 2001 |
| | | EP 1143845 A4 | 06 Oct 2004 |
| | | US 5776062 A | 07 Jul 1998 |
| | | US 6102866 A | 15 Aug 2000 |
| | | US 6459925 B1 | 01 Oct 2002 |
| | | US 2003073895 A1 | 17 Apr 2003 |
| | | US 7496398 B2 | 24 Feb 2009 |
| | | WO 0051484 A2 | 08 Sep 2000 |
| | | WO 0051484 A3 | 12 Feb 2004 |
| | | WO 9816149 A2 | 23 Apr 1998 |
| | | WO 9816149 A3 | 22 Oct 1998 |
| US 2009326363 A1 | 31 Dec 2009 | US 2009326363 A1 | 31 Dec 2009 |
| | | US 2011178389 A1 | 21 Jul 2011 |
| US 2011178389 A1 | 21 Jul 2011 | US 2011178389 A1 | 21 Jul 2011 |
| | | US 2009326363 A1 | 31 Dec 2009 |
| US 2008043905 A1 | 21 Feb 2008 | US 2008043905 A1 | 21 Feb 2008 |
| US 3971950 A | 27 Jul 1976 | US 3971950 A | 27 Jul 1976 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/IL2015/050207

| Patent document cited search report | Publication date | Patent family member(s) | Publication Date |
|---|---|---|---|
| | | CA 1058334 A1 | 10 Jul 1979 |
| | | GB 1546660 A | 31 May 1979 |
| US 4875478 A | 24 Oct 1989 | US 4875478 A | 24 Oct 1989 |
| | | EP 0288187 A1 | 26 Oct 1988 |
| | | JP H01256942 A | 13 Oct 1989 |
| US 2008230074 A1 | 25 Sep 2008 | US 2008230074 A1 | 25 Sep 2008 |
| | | US 7597104 B2 | 06 Oct 2009 |
| US 2007016003 A1 | 18 Jan 2007 | US 2007016003 A1 | 18 Jan 2007 |
| | | US 7970452 B2 | 28 Jun 2011 |
| | | AU 2004216658 A1 | 14 Apr 2005 |
| | | CA 2483718 A1 | 30 Mar 2005 |
| | | CA 2483718 C | 27 Jan 2015 |
| | | EP 2063776 A1 | 03 Jun 2009 |
| | | EP 2063776 A4 | 04 Apr 2012 |
| | | EP 2096454 A2 | 02 Sep 2009 |
| | | EP 2096454 A3 | 18 Nov 2009 |
| | | JP 2010501294 A | 21 Jan 2010 |
| | | JP 5313899 B2 | 09 Oct 2013 |
| | | JP 2013176602 A | 09 Sep 2013 |
| | | US 2005080333 A1 | 14 Apr 2005 |
| | | US 7379769 B2 | 27 May 2008 |
| | | US 2008216239 A1 | 11 Sep 2008 |
| | | US 7908690 B2 | 22 Mar 2011 |
| | | US 2008132785 A1 | 05 Jun 2008 |
| | | US 7937132 B2 | 03 May 2011 |
| | | US 2008255443 A1 | 16 Oct 2008 |
| | | US 8050736 B2 | 01 Nov 2011 |
| | | US 2012172704 A1 | 05 Jul 2012 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/IL2015/050207

| Patent document cited search report | Publication date | Patent family member(s) | Publication Date |
|---|---|---|---|
| | | US 8560051 B2 | 15 Oct 2013 |
| | | US 2008306377 A1 | 11 Dec 2008 |
| | | US 8571632 B2 | 29 Oct 2013 |
| | | US 2008077005 A1 | 27 Mar 2008 |
| | | US 2014024926 A1 | 23 Jan 2014 |
| | | US 2014128883 A1 | 08 May 2014 |
| | | WO 2008025146 A1 | 06 Mar 2008 |
| | | WO 2008141447 A1 | 27 Nov 2008 |
| US 2013090554 A1 | 11 Apr 2013 | US 2013090554 A1 | 11 Apr 2013 |
| | | EP 2584990 A2 | 01 May 2013 |
| | | WO 2011161684 A2 | 29 Dec 2011 |
| | | WO 2011161684 A3 | 12 Apr 2012 |
| US 2008132782 A1 | 05 Jun 2008 | US 2008132782 A1 | 05 Jun 2008 |
| | | CN 1913826 A | 14 Feb 2007 |
| | | CN 100473338 C | 01 Apr 2009 |
| | | DE 102005004768 A1 | 27 Oct 2005 |
| | | EP 1559363 A2 | 03 Aug 2005 |
| | | EP 1559363 A3 | 23 May 2007 |
| | | JP 2007519493 A | 19 Jul 2007 |
| | | US 2008132777 A1 | 05 Jun 2008 |
| | | US 7894876 B2 | 22 Feb 2011 |
| | | US 2006100529 A1 | 11 May 2006 |
| | | WO 2005074797 A1 | 18 Aug 2005 |
| US 2006100529 A1 | 11 May 2006 | US 2006100529 A1 | 11 May 2006 |
| | | CN 1913826 A | 14 Feb 2007 |
| | | CN 100473338 C | 01 Apr 2009 |
| | | DE 102005004768 A1 | 27 Oct 2005 |
| | | EP 1559363 A2 | 03 Aug 2005 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/IL2015/050207

| Patent document cited search report | Publication date | Patent family member(s) | Publication Date |
|---|---|---|---|
| | | EP 1559363 A3 | 23 May 2007 |
| | | JP 2007519493 A | 19 Jul 2007 |
| | | US 2008132777 A1 | 05 Jun 2008 |
| | | US 7894876 B2 | 22 Feb 2011 |
| | | US 2008132782 A1 | 05 Jun 2008 |
| | | WO 2005074797 A1 | 18 Aug 2005 |
| US 5506877 A | 09 Apr 1996 | US 5506877 A | 09 Apr 1996 |
| US 2011034796 A1 | 10 Feb 2011 | US 2011034796 A1 | 10 Feb 2011 |
| | | US 8452374 B2 | 28 May 2013 |
| | | WO 2011014966 A1 | 10 Feb 2011 |
| US 2010104063 A1 | 29 Apr 2010 | US 2010104063 A1 | 29 Apr 2010 |
| | | US 7801267 B2 | 21 Sep 2010 |
| | | DE 102009044300 A1 | 06 May 2010 |
| US 2013131509 A1 | 23 May 2014 | US 2013131509 A1 | 23 May 2013 |
| US 5190046 A | 02 Mar 1993 | US 5190046 A | 02 Mar 1993 |
| | | AU 3609293 A | 29 Nov 1993 |
| | | WO 9321829 A1 | 11 Nov 1993 |
| US 5476095 A | 19 Dec 1995 | US 5476095 A | 19 Dec 1995 |
| | | US 5348010 A | 20 Sep 1994 |