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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 July 2021 (15.07.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/142090 A1

(51) International Patent Classification:
A61B 8/08 (2006.01) *A61B 8/14* (2006.01)
A61B 8/00 (2006.01) *A61B 34/20* (2016.01)
A61B 8/13 (2006.01)

(21) International Application Number:
PCT/US2021/012455

(22) International Filing Date:
07 January 2021 (07.01.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/958,209 07 January 2020 (07.01.2020) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,

(54) Title: SYSTEMS AND METHODS FOR ROBOTICALLY-ASSISTED HISTOTRIPSY TARGETING BASED ON MRI/CT SCANS TAKEN PRIOR TO TREATMENT

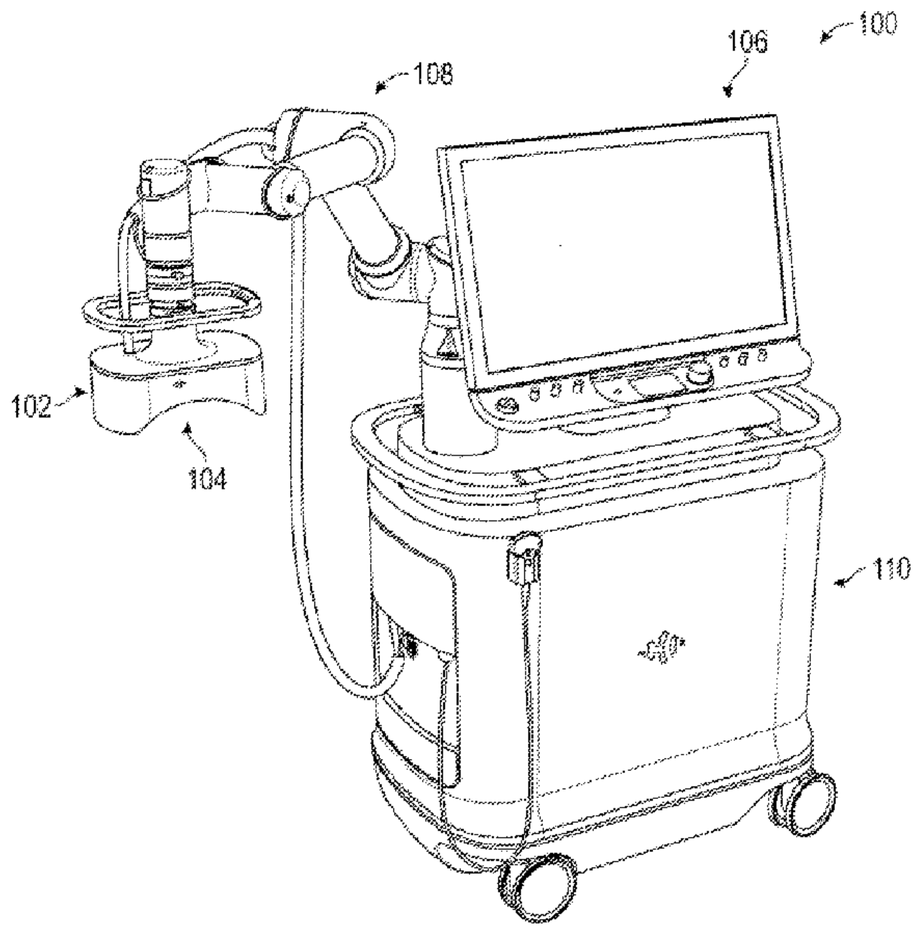


FIG. 1A

(57) Abstract: Methods and devices for producing cavitation in tissue are provided. Methods and devices are also provided for surgical navigation, including defining a target treatment zone and navigating a focus of a therapy transducer to the target treatment zone. Embodiments are provided for co-registering a plurality of surgical imaging and navigation systems. Systems for performing Histotripsy therapy are also discussed.

[Continued on next page]

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SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, 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).

Published:

— *with international search report (Art. 21(3))*

SYSTEMS AND METHODS FOR ROBOTICALLY-ASSISTED HISTOTRIPSY TARGETING BASED ON MRI/CT SCANS TAKEN PRIOR TO TREATMENT

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 62/958,209, filed January 7, 2020, titled "Systems and Methods for Robotically-Assisted Histotripsy Targeting Based on MRI/CT Scans Taken Prior to Treatment", incorporated herein by reference.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with Government support under NS108042 awarded by the National Institutes of Health. The Government has certain rights in the invention.

INCORPORATION BY REFERENCE

[0003] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

FIELD

[0004] The present disclosure details novel high intensity therapeutic ultrasound (HITU) systems configured to produce acoustic cavitation, methods, devices and procedures for the minimally and non-invasive treatment of healthy, diseased and/or injured tissue. The acoustic cavitation systems and methods described herein, also referred to Histotripsy, may include transducers, drive electronics, positioning robotics, imaging systems, and integrated treatment planning and control software to provide comprehensive treatment and therapy for soft tissues in a patient.

BACKGROUND

[0005] Histotripsy, or pulsed ultrasound cavitation therapy, is a technology where extremely short, intense bursts of acoustic energy induce controlled cavitation (microbubble formation) within the focal volume. The vigorous expansion and collapse of these microbubbles mechanically homogenizes cells and tissue structures within the focal volume. This is a very different end result than the coagulative necrosis characteristic of thermal ablation. To operate

within a non-thermal, Histotripsy realm; it is necessary to deliver acoustic energy in the form of high amplitude acoustic pulses with low duty cycle.

[0006] Compared with conventional focused ultrasound technologies, Histotripsy has important advantages: 1) the destructive process at the focus is mechanical, not thermal; 2) cavitation appears bright on ultrasound imaging thereby confirming correct targeting and localization of treatment; 3) treated tissue generally, but not always, appears darker (more hypoechoic) on ultrasound imaging, so that the operator knows what has been treated; and 4) Histotripsy produces lesions in a controlled and precise manner. It is important to emphasize that unlike thermal ablative technologies such as microwave, radiofrequency, and high-intensity focused ultrasound (HIFU), Histotripsy relies on the mechanical action of cavitation for tissue destruction.

SUMMARY OF THE DISCLOSURE

[0007] A method of surgical navigation is provided, comprising receiving, in a surgical navigation system, a first image of a target tissue volume, obtaining, with the surgical navigation system, a second image of the target tissue volume, co-registering, in the surgical navigation system, the first image with the second image to identify boundary coordinates of the target tissue volume in the first image, identifying, with the surgical navigation system, focal coordinates of a focus of a histotripsy therapy transducer, determining, in the surgical navigation system, movement coordinates that will place the histotripsy therapy transducer focus within the boundary coordinates of the target tissue volume in the first image, and moving the histotripsy therapy transducer focus based on the movement coordinates to place the histotripsy therapy transducer focus within the target tissue volume.

[0008] In some implementations, the moving step further comprises moving the histotripsy therapy transducer with a robotic positioning system. Alternatively, the moving step further comprises electronically steering the histotripsy therapy transducer focus.

[0009] In one implementation, the first image comprises a high-resolution image from an advanced diagnostic medical imaging system, such as a high-resolution MRI image, a high-resolution CT image, a cone beam CT image, or an augmented fluoroscopy image.

[0010] In other implementations, the second image comprises an ultrasound image, a photograph, or an optical image.

[0011] In some implementations, the co-registering step further comprises identifying a fiducial region in both the first image and the second image and using the fiducial region to correlate a coordinate system of the first image with a coordinate system of the second image.

[0012] In another implementation, identifying focal coordinates further comprises placing fiducial markers on the histotripsy therapy transducer and identifying the fiducial markers with the surgical navigation system.

[0013] In one implementation, the method further includes defining a treatment margin of the target tissue volume, calculating 3D grid locations to cover the target tissue volume and the treatment margin, and displaying the 3D grid locations over the first or second image. In another example, the treatment margin comprises a positive treatment margin that extends beyond the target tissue volume. In some implementations, the treatment margin comprises a negative treatment margin that extends within the target tissue volume.

[0014] In many implementations, the method further comprises applying histotripsy therapy to the target tissue volume.

[0015] In some implementations, the method further includes imaging the histotripsy therapy and peri-procedurally updating co-registration between the first image and the second image.

[0016] In one implementation, the method further comprises producing a histotripsy treatment map, and overlaying the histotripsy treatment map on the first or second image in real time.

[0017] In some examples, the robotic positioning system can move the histotripsy therapy transducer with 3 degrees of freedom. In other examples, the robotic positioning system can move the histotripsy therapy transducer with 6 degrees of freedom.

[0018] In one embodiment, the moving step further comprises a combination of electronically steering the histotripsy therapy transducer focus and moving the histotripsy therapy transducer with a robotic positioning system.

[0019] In various implementations, the target tissue volume can comprise a tumor, a clot, an organ, or a brain hemorrhage.

[0020] Another method of surgical navigation is provided, comprising inserting an acoustic detector into tissue within or near a target tissue volume, localizing a position of the target tissue volume relative to a focus of a histotripsy therapy transducer with the acoustic detector, and determining movement coordinates required to place the histotripsy therapy transducer focus within the target tissue volume.

[0021] In some embodiments, the method further comprises applying histotripsy therapy with the histotripsy therapy transducer.

[0022] In one implementation, the inserting step further comprises inserting a catheter into tissue within or near the target tissue volume, wherein the catheter includes the acoustic detector.

In another implementation, the inserting step further comprises inserting a needle into tissue within or near the target tissue volume, wherein the needle includes the acoustic detector.

[0023] A method of surgical navigation is provided, comprising inserting a fiducial marker into tissue within or near a target tissue volume, localizing a position of the target tissue volume relative to a focus of a histotripsy therapy transducer with the fiducial marker, and determining movement coordinates required to place the histotripsy therapy transducer focus within the target tissue volume.

[0024] In some embodiments, the method further comprises applying histotripsy therapy with the histotripsy therapy transducer.

[0025] A therapy system is provided, comprising a first imaging system, a surgical navigation system including a second imaging system, a robotic positioning arm, a histotripsy therapy transducer coupled to the robotic positioning arm, and an electronic controller operatively coupled to the first imaging system, the surgical navigation system, the second imaging system, the robotic positioning arm, and the histotripsy therapy transducer, the electronic controller being configured to co-register a first image of the target tissue volume from the first imaging system with a second imaging of the target tissue volume from the second imaging system to identify boundary coordinates of the target tissue volume, the electronic controller being further configured to determine movement coordinates of the robotic positioning arm requires to place a focus of the histotripsy therapy transducer within the target tissue volume.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] The novel features of the invention are set forth with particularity in the claims that follow. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0027] FIGS. 1A-1B illustrate an ultrasound imaging and therapy system.

[0028] FIG. 2 is a flowchart that describes one method for surgical navigation with a histotripsy therapy system.

[0029] FIG. 3 is one example of a stereotactic histotripsy therapy system.

[0030] FIGS. 4A-4C illustrate a method of performing stereotactic histotripsy.

[0031] FIG. 5 is a flowchart that describes another method for surgical navigation with a histotripsy therapy system.

DETAILED DESCRIPTION

[0032] The system, methods and devices of the disclosure may be used for the minimally or non-invasive acoustic cavitation and treatment of healthy, diseased and/or injured tissue, including in extracorporeal, percutaneous, endoscopic, laparoscopic, and/or as integrated into a robotically-enabled medical system and procedures. As will be described below, the acoustic cavitation system may include various sub-systems, including a Cart, Therapy, Integrated Imaging, Robotics, Coupling and Software. The system also may comprise various Other Components, Ancillaries and Accessories, including but not limited to computers, cables and connectors, networking devices, power supplies, displays, drawers/storage, doors, wheels, and various simulation and training tools, etc. All systems, methods and means creating/controlling/delivering histotripsy are considered to be a part of this disclosure, including new related inventions disclosed herein.

[0033] Fig. 1A generally illustrates histotripsy system 100 according to the present disclosure, comprising a therapy transducer 102, an imaging system 104, a display and control panel 106, a robotic positioning arm 108, and a cart 110. The system can further include an ultrasound coupling interface and a source of coupling medium, not shown.

[0034] FIG. 1B is a bottom view of the therapy transducer 102 and the imaging system 104. As shown, the imaging system can be positioned in the center of the therapy transducer. However, other embodiments can include the imaging system positioned in other locations within the therapy transducer, or even directly integrated into the therapy transducer. In some embodiments, the imaging system is configured to produce real-time imaging at a focal point of the therapy transducer.

[0035] The histotripsy system may comprise one or more of various sub-systems, including a Therapy sub-system that can create, apply, focus and deliver acoustic cavitation/histotripsy through one or more therapy transducers, Integrated Imaging sub-system (or connectivity to) allowing real-time visualization of the treatment site and histotripsy effect through-out the procedure, a Robotics positioning sub-system to mechanically and/or electronically steer the therapy transducer, further enabled to connect/support or interact with a Coupling sub-system to allow acoustic coupling between the therapy transducer and the patient, and Software to communicate, control and interface with the system and computer-based control systems (and other external systems) and various Other Components, Ancillaries and Accessories, including one or more user interfaces and displays, and related guided work-flows, all working in part or together. The system may further comprise various fluidics and fluid management components,

including but not limited to, pumps, valve and flow controls, temperature and degassing controls, and irrigation and aspiration capabilities, as well as providing and storing fluids. It may also contain various power supplies and protectors.

[0036] CART

[0037] The Cart 110 may be generally configured in a variety of ways and form factors based on the specific uses and procedures. In some cases, systems may comprise multiple Carts, configured with similar or different arrangements. In some embodiments, the cart may be configured and arranged to be used in a radiology environment and in some cases in concert with imaging (e.g., CT, cone beam CT and/or MRI scanning). In other embodiments, it may be arranged for use in an operating room and a sterile environment, or in a robotically enabled operating room, and used alone, or as part of a surgical robotics procedure wherein a surgical robot conducts specific tasks before, during or after use of the system and delivery of acoustic cavitation/histotripsy. As such and depending on the procedure environment based on the aforementioned embodiments, the cart may be positioned to provide sufficient work-space and access to various anatomical locations on the patient (e.g., torso, abdomen, flank, head and neck, etc.), as well as providing work-space for other systems (e.g., anesthesia cart, laparoscopic tower, surgical robot, endoscope tower, etc.).

[0038] The Cart may also work with a patient surface (e.g., table or bed) to allow the patient to be presented and repositioned in a plethora of positions, angles and orientations, including allowing changes to such to be made pre, peri and post-procedurally. It may further comprise the ability to interface and communicate with one or more external imaging or image data management and communication systems, not limited to ultrasound, CT, fluoroscopy, cone beam CT, PET, PET/CT, MRI, augmented fluoroscopy, optical, ultrasound, and image fusion and or image flow, of one or more modalities, to support the procedures and/or environments of use, including physical/mechanical interoperability (e.g., compatible within cone beam CT work-space for collecting imaging data pre, peri and/or post histotripsy).

[0039] In some embodiments one or more Carts may be configured to work together. As an example, one Cart may comprise a bedside mobile Cart equipped with one or more Robotic arms enabled with a Therapy transducer, and Therapy generator/amplifier, etc., while a companion cart working in concert and at a distance of the patient may comprise Integrated Imaging and a console/display for controlling the Robotic and Therapy facets, analogous to a surgical robot and master/slave configurations.

[0040] In some embodiments, the system may comprise a plurality of Carts, all slave to one master Cart, equipped to conduct acoustic cavitation procedures. In some arrangements and

cases, one Cart configuration may allow for storage of specific sub-systems at a distance reducing operating room clutter, while another in concert Cart may comprise essentially bedside sub-systems and componentry (e.g., delivery system and therapy).

[0041] One can envision a plethora of permutations and configurations of Cart design, and these examples are in no way limiting the scope of the disclosure.

[0042] **HISTOTRIPSY**

[0043] Histotripsy comprises short, high amplitude, focused ultrasound pulses to generate a dense, energetic, "bubble cloud", capable of the targeted fractionation and destruction of tissue. Histotripsy is capable of creating controlled tissue erosion when directed at a tissue interface, including tissue/fluid interfaces, as well as well-demarcated tissue fractionation and destruction, at sub-cellular levels, when it is targeted at bulk tissue. Unlike other forms of ablation, including thermal and radiation-based modalities, histotripsy does not rely on heat or ionizing (high) energy to treat tissue. Instead, histotripsy uses acoustic cavitation generated at the focus to mechanically effect tissue structure, and in some cases liquefy, suspend, solubilize and/or destruct tissue into sub-cellular components.

[0044] Histotripsy can be applied in various forms, including: 1) Intrinsic-Threshold Histotripsy: Delivers pulses with a 1-2 cycles of high amplitude negative/tensile phase pressure exceeding the intrinsic threshold to generate cavitation in the medium (e.g., ~24-28 MPa for water-based soft tissue), 2) Shock-Scattering Histotripsy: Delivers typically pulses 3-20 cycles in duration. The shockwave (positive/compressive phase) scattered from an initial individual microbubble generated forms inverted shockwave, which constructively interfere with the incoming negative/tensile phase to form high amplitude negative/rarefactional phase exceeding the intrinsic threshold. In this way, a cluster of cavitation microbubbles is generated. The amplitude of the tensile phases of the pulses is sufficient to cause bubble nuclei in the medium to undergo inertial cavitation within the focal zone throughout the duration of the pulse. These nuclei scatter the incident shockwaves, which invert and constructively interfere with the incident wave to exceed the threshold for intrinsic nucleation, and 3) Boiling Histotripsy: Employs pulses roughly 1-20 ms in duration. Absorption of the shocked pulse rapidly heats the medium, thereby reducing the threshold for intrinsic nuclei. Once this intrinsic threshold coincides with the peak negative pressure of the incident wave, boiling bubbles form at the focus.

[0045] The large pressure generated at the focus causes a cloud of acoustic cavitation bubbles to form above certain thresholds, which creates localized stress and strain in the tissue and mechanical breakdown without significant heat deposition. At pressure levels where

cavitation is not generated, minimal effect is observed on the tissue at the focus. This cavitation effect is observed only at pressure levels significantly greater than those which define the inertial cavitation threshold in water for similar pulse durations, on the order of 10 to 30 MPa peak negative pressure.

[0046] Histotripsy may be performed in multiple ways and under different parameters. It may be performed totally non-invasively by acoustically coupling a focused ultrasound transducer over the skin of a patient and transmitting acoustic pulses transcutaneously through overlying (and intervening) tissue to the focal zone (treatment zone and site). It may be further targeted, planned, directed and observed under direct visualization, via ultrasound imaging, given the bubble clouds generated by histotripsy may be visible as highly dynamic, echogenic regions on, for example, B Mode ultrasound images, allowing continuous visualization through its use (and related procedures). Likewise, the treated and fractionated tissue shows a dynamic change in echogenicity (typically a reduction), which can be used to evaluate, plan, observe and monitor treatment.

[0047] Generally, in histotripsy treatments, ultrasound pulses with 1 or more acoustic cycles are applied, and the bubble cloud formation relies on the pressure release scattering of the positive shock fronts (sometimes exceeding 100 MPa, P+) from initially initiated, sparsely distributed bubbles (or a single bubble). This is referred to as the "shock scattering mechanism".

[0048] This mechanism depends on one (or a few sparsely distributed) bubble(s) initiated with the initial negative half cycle(s) of the pulse at the focus of the transducer. A cloud of microbubbles then forms due to the pressure release backscattering of the high peak positive shock fronts from these sparsely initiated bubbles. These back-scattered high-amplitude rarefactional waves exceed the intrinsic threshold thus producing a localized dense bubble cloud. Each of the following acoustic cycles then induces further cavitation by the backscattering from the bubble cloud surface, which grows towards the transducer. As a result, an elongated dense bubble cloud growing along the acoustic axis opposite the ultrasound propagation direction is observed with the shock scattering mechanism. This shock scattering process makes the bubble cloud generation not only dependent on the peak negative pressure, but also the number of acoustic cycles and the amplitudes of the positive shocks. Without at least one intense shock front developed by nonlinear propagation, no dense bubble clouds are generated when the peak negative half-cycles are below the intrinsic threshold.

[0049] When ultrasound pulses less than 2 cycles are applied, shock scattering can be minimized, and the generation of a dense bubble cloud depends on the negative half cycle(s) of

the applied ultrasound pulses exceeding an "intrinsic threshold" of the medium. This is referred to as the "intrinsic threshold mechanism".

[0050] This threshold can be in the range of 26 – 30 MPa for soft tissues with high water content, such as tissues in the human body. In some embodiments, using this intrinsic threshold mechanism, the spatial extent of the lesion may be well-defined and more predictable. With peak negative pressures (P–) not significantly higher than this threshold, sub-wavelength reproducible lesions as small as half of the –6dB beam width of a transducer may be generated.

[0051] With high-frequency Histotripsy pulses, the size of the smallest reproducible lesion becomes smaller, which is beneficial in applications that require precise lesion generation. However, high-frequency pulses are more susceptible to attenuation and aberration, rendering problematical treatments at a larger penetration depth (e.g., ablation deep in the body) or through a highly aberrative medium (e.g., transcranial procedures, or procedures in which the pulses are transmitted through bone(s)). Histotripsy may further also be applied as a low-frequency "pump" pulse (typically < 2 cycles and having a frequency between 100 kHz and 1 MHz) can be applied together with a high-frequency "probe" pulse (typically < 2 cycles and having a frequency greater than 2 MHz, or ranging between 2 MHz and 10 MHz) wherein the peak negative pressures of the low and high-frequency pulses constructively interfere to exceed the intrinsic threshold in the target tissue or medium. The low-frequency pulse, which is more resistant to attenuation and aberration, can raise the peak negative pressure P– level for a region of interest (ROI), while the high-frequency pulse, which provides more precision, can pin-point a targeted location within the ROI and raise the peak negative pressure P– above the intrinsic threshold. This approach may be referred to as "dual frequency", "dual beam histotripsy" or "parametric histotripsy."

[0052] Additional systems, methods and parameters to deliver optimized histotripsy, using shock scattering, intrinsic threshold, and various parameters enabling frequency compounding and bubble manipulation, are herein included as part of the system and methods disclosed herein, including additional means of controlling said histotripsy effect as pertains to steering and positioning the focus, and concurrently managing tissue effects (e.g., prefocal thermal collateral damage) at the treatment site or within intervening tissue. Further, it is disclosed that the various systems and methods, which may include a plurality of parameters, such as but not limited to, frequency, operating frequency, center frequency, pulse repetition frequency, pulses, bursts, number of pulses, cycles, length of pulses, amplitude of pulses, pulse period, delays, burst repetition frequency, sets of the former, loops of multiple sets, loops of multiple and/or different

sets, sets of loops, and various combinations or permutations of, etc., are included as a part of this disclosure, including future envisioned embodiments of such.

[0053] THERAPY COMPONENTS

[0054] The Therapy sub-system may work with other sub-systems to create, optimize, deliver, visualize, monitor and control acoustic cavitation, also referred to herein and in following as "histotripsy", and its derivatives of, including boiling histotripsy and other thermal high frequency ultrasound approaches. It is noted that the disclosed inventions may also further benefit other acoustic therapies that do not comprise a cavitation, mechanical or histotripsy component. The therapy sub-system can include, among other features, an ultrasound therapy transducer and a pulse generator system configured to deliver ultrasound pulses into tissue.

[0055] In order to create and deliver histotripsy and derivatives of histotripsy, the therapy sub-system may also comprise components, including but not limited to, one or more function generators, amplifiers, therapy transducers and power supplies.

[0056] The therapy transducer can comprise a single element or multiple elements configured to be excited with high amplitude electric pulses (>1000V or any other voltage that can cause harm to living organisms). The amplitude necessary to drive the therapy transducers for Histotripsy vary depending on the design of the transducer and the materials used (e.g., solid or polymer/piezoelectric composite including ceramic or single crystal) and the transducer center frequency which is directly proportional to the thickness of the piezo-electric material. Transducers therefore operating at a high frequency require lower voltage to produce a given surface pressure than is required by low frequency therapy transducers. In some embodiments, the transducer elements are formed using a piezoelectric-polymer composite material or a solid piezoelectric material. Further, the piezoelectric material can be of polycrystalline/ceramic or single crystalline formulation. In some embodiments the transducer elements can be formed using silicon using MEMs technology, including CMUT and PMUT designs.

[0057] In some embodiments, the function generator may comprise a field programmable gate array (FPGA) or other suitable function generator. The FPGA may be configured with parameters disclosed previously herein, including but not limited to frequency, pulse repetition frequency, bursts, burst numbers, where bursts may comprise pulses, numbers of pulses, length of pulses, pulse period, delays, burst repetition frequency or period, where sets of bursts may comprise a parameter set, where loop sets may comprise various parameter sets, with or without delays, or varied delays, where multiple loop sets may be repeated and/or new loop sets introduced, of varied time delay and independently controlled, and of various combinations and permutations of such, overall and throughout.

[0058] In some embodiments, the generator or amplifier may be configured to be a universal single-cycle or multi-cycle pulse generator, and to support driving via Class D or inductive driving, as well as across all envisioned clinical applications, use environments, also discussed in part later in this disclosure. In other embodiments, the class D or inductive current driver may be configured to comprise transformer and/or auto-transformer driving circuits to further provide step up/down components, and in some cases, to preferably allow a step up in the amplitude. They may also comprise specific protective features, to further support the system, and provide capability to protect other parts of the system (e.g., therapy transducer and/or amplifier circuit components) and/or the user, from various hazards, including but not limited to, electrical safety hazards, which may potentially lead to use environment, system and therapy system, and user harms, damage or issues.

[0059] Disclosed generators may allow and support the ability of the system to select, vary and control various parameters (through enabled software tools), including, but not limited to those previously disclosed, as well as the ability to start/stop therapy, set and read voltage level, pulse and/or burst repetition frequency, number of cycles, duty ratio, channel enabled and delay, etc., modulate pulse amplitude on a fast time-scale independent of a high voltage supply, and/or other service, diagnostic or treatment features.

[0060] In some embodiments, the Therapy sub-system and/or components of, such as the amplifier, may comprise further integrated computer processing capability and may be networked, connected, accessed, and/or be removable/portable, modular, and/or exchangeable between systems, and/or driven/commanded from/by other systems, or in various combinations. Other systems may include other acoustic cavitation/histotripsy, HIFU, HITU, radiation therapy, radiofrequency, microwave, and cryoablation systems, navigation and localization systems, laparoscopic, single incision/single port, endoscopic and non-invasive surgical robots, laparoscopic or surgical towers comprising other energy-based or vision systems, surgical system racks or booms, imaging carts, etc.

[0061] In some embodiments, one or more amplifiers may comprise a Class D amplifier and related drive circuitry including matching network components. Depending on the transducer element electric impedance and choice of the matching network components (e.g., an LC circuit made of an inductor L1 in series and the capacitor C1 in parallel), the combined impedance can be aggressively set low in order to have high amplitude electric waveform necessary to drive the transducer element. The maximum amplitude that Class D amplifiers is dependent on the circuit components used, including the driving MOSFET/IGBT transistors, matching network

components or inductor, and transformer or autotransformer, and of which may be typically in the low kV (e.g., 1-3 kV) range.

[0062] Therapy transducer element(s) are excited with an electrical waveform with an amplitude (voltage) to produce a pressure output sufficient for Histotripsy therapy. The excitation electric field can be defined as the necessary waveform voltage per thickness of the piezoelectric element. For example, because a piezoelectric element operating at 1 MHz transducer is half the thickness of an equivalent 500 kHz element, it will require half the voltage to achieve the same electric field and surface pressure.

[0063] INTEGRATED IMAGING

[0064] The disclosed system may comprise various imaging modalities to allow users to visualize, monitor and collect/use feedback of the patient's anatomy, related regions of interest and treatment/procedure sites, as well as surrounding and intervening tissues to assess, plan and conduct procedures, and adjust treatment parameters as needed. Imaging modalities may comprise various ultrasound, x-ray, CT, MRI, PET, fluoroscopy, optical, contrast or agent enhanced versions, and/or various combinations of. It is further disclosed that various image processing and characterization technologies may also be utilized to afford enhanced visualization and user decision making. These may be selected or commanded manually by the user or in an automated fashion by the system. The system may be configured to allow side by side, toggling, overlays, 3D reconstruction, segmentation, registration, multi-modal image fusion, image flow, and/or any methodology affording the user to identify, define and inform various aspects of using imaging during the procedure, as displayed in the various system user interfaces and displays. Examples may include locating, displaying and characterizing regions of interest, organ systems, potential treatment sites within, with on and/or surrounding organs or tissues, identifying critical structures such as ducts, vessels, nerves, ureters, fissures, capsules, tumors, tissue trauma/injury/disease, other organs, connective tissues, etc., and/or in context to one another, of one or more (e.g., tumor draining lymphatics or vasculature; or tumor proximity to organ capsule or underlying other organ), as unlimited examples.

[0065] Systems may be configured to include onboard integrated imaging hardware, software, sensors, probes and wetware, and/or may be configured to communicate and interface with external imaging and image processing systems. The aforementioned components may be also integrated into the system's Therapy sub-system components wherein probes, imaging arrays, or the like, and electrically, mechanically or electromechanically integrated into therapy transducers. This may afford, in part, the ability to have geometrically aligned imaging and therapy, with the therapy directly within the field of view, and in some cases in line, with

imaging. In some embodiments, this integration may comprise a fixed orientation of the imaging capability (e.g., imaging probe) in context to the therapy transducer. In other embodiments, the imaging solution may be able to move or adjust its position, including modifying angle, extension (e.g., distance from therapy transducer or patient), rotation (e.g., imaging plane in example of an ultrasound probe) and/or other parameters, including moving/adjusting dynamically while actively imaging. The imaging component or probe may be encoded so its orientation and position relative to another aspect of the system, such as the therapy transducer, and/or robotically-enabled positioning component may be determined.

[0066] In one embodiment, the system may comprise onboard ultrasound, further configured to allow users to visualize, monitor and receive feedback for procedure sites through the system displays and software, including allowing ultrasound imaging and characterization (and various forms of), ultrasound guided planning and ultrasound guided treatment, all in real-time. The system may be configured to allow users to manually, semi-automated or in fully automated means image the patient (e.g., by hand or using a robotically-enabled imager).

[0067] In some embodiments, imaging feedback and monitoring can include monitoring changes in: backscatter from bubble clouds; speckle reduction in backscatter; backscatter speckle statistics; mechanical properties of tissue (i.e., elastography); tissue perfusion (i.e., ultrasound contrast); shear wave propagation; acoustic emissions, electrical impedance tomography, and/or various combinations of, including as displayed or integrated with other forms of imaging (e.g., CT or MRI).

[0068] In some embodiments, imaging including feedback and monitoring from backscatter from bubble clouds, may be used as a method to determine immediately if the histotripsy process has been initiated, is being properly maintained, or even if it has been extinguished. For example, this method enables continuously monitored in real time drug delivery, tissue erosion, and the like. The method also can provide feedback permitting the histotripsy process to be initiated at a higher intensity and maintained at a much lower intensity. For example, backscatter feedback can be monitored by any transducer or ultrasonic imager. By measuring feedback for the therapy transducer, an accessory transducer can send out interrogation pulses or be configured to passively detect cavitation. Moreover, the nature of the feedback received can be used to adjust acoustic parameters (and associated system parameters) to optimize the drug delivery and/or tissue erosion process.

[0069] In some embodiments, imaging including feedback and monitoring from backscatter, and speckle reduction, may be configured in the system.

[0070] For systems comprising feedback and monitoring via backscattering, and as means of background, as tissue is progressively mechanically subdivided, in other words homogenized, disrupted, or eroded tissue, this process results in changes in the size and distribution of acoustic scatter. At some point in the process, the scattering particle size and density is reduced to levels where little ultrasound is scattered, or the amount scattered is reduced significantly. This results in a significant reduction in speckle, which is the coherent constructive and destructive interference patterns of light and dark spots seen on images when coherent sources of illumination are used; in this case, ultrasound. After some treatment time, the speckle reduction results in a dark area in the therapy volume. Since the amount of speckle reduction is related to the amount of tissue subdivision, it can be related to the size of the remaining tissue fragments. When this size is reduced to sub-cellular levels, no cells are assumed to have survived. So, treatment can proceed until a desired speckle reduction level has been reached. Speckle is easily seen and evaluated on standard ultrasound imaging systems. Specialized transducers and systems, including those disclosed herein, may also be used to evaluate the backscatter changes.

[0071] Further, systems comprising feedback and monitoring via speckle, and as means of background, an image may persist from frame to frame and change very little as long as the scatter distribution does not change and there is no movement of the imaged object. However, long before the scatters are reduced enough in size to cause speckle reduction, they may be changed sufficiently to be detected by signal processing and other means. This family of techniques can operate as detectors of speckle statistics changes. For example, the size and position of one or more speckles in an image will begin to decorrelate before observable speckle reduction occurs. Speckle decorrelation, after appropriate motion compensation, can be a sensitive measure of the mechanical disruption of the tissues, and thus a measure of therapeutic efficacy. This feedback and monitoring technique may permit early observation of changes resulting from the acoustic cavitation/histotripsy process and can identify changes in tissue before substantial or complete tissue effect (e.g., erosion occurs). In one embodiment, this method may be used to monitor the acoustic cavitation/histotripsy process for enhanced drug delivery where treatment sites/tissue is temporally disrupted, and tissue damage/erosion is not desired. In other embodiments, this may comprise speckle decorrelation by movement of scatters in an increasingly fluidized therapy volume. For example, in the case where partial or complete tissue erosion is desired.

[0072] For systems comprising feedback and monitoring via elastography, and as means of background, as treatment sites/tissue are further subdivided per an acoustic cavitation/histotripsy effect (homogenized, disrupted, or eroded), its mechanical properties change from a soft but

interconnected solid to a viscous fluid or paste with few long-range interactions. These changes in mechanical properties can be measured by various imaging modalities including MRI and ultrasound imaging systems. For example, an ultrasound pulse can be used to produce a force (i.e., a radiation force) on a localized volume of tissue. The tissue response (displacements, strains, and velocities) can change significantly during histotripsy treatment allowing the state of tissue disruption to be determined by imaging or other quantitative means.

[0073] Systems may also comprise feedback and monitoring via shear wave propagation changes. As means of background, the subdivision of tissues makes the tissue more fluid and less solid and fluid systems generally do not propagate shear waves. Thus, the extent of tissue fluidization provides opportunities for feedback and monitoring of the histotripsy process. For example, ultrasound and MRI imaging systems can be used to observe the propagation of shear waves. The extinction of such waves in a treated volume is used as a measure of tissue destruction or disruption. In one system embodiment, the system and supporting sub-systems may be used to generate and measure the interacting shear waves. For example, two adjacent ultrasound foci might perturb tissue by pushing it in certain ways. If adjacent foci are in a fluid, no shear waves propagate to interact with each other. If the tissue is not fluidized, the interaction would be detected with external means, for example, by a difference frequency only detected when two shear waves interact nonlinearly, with their disappearance correlated to tissue damage. As such, the system may be configured to use this modality to enhance feedback and monitoring of the acoustic cavitation/histotripsy procedure.

[0074] For systems comprising feedback and monitoring via acoustic emission, and as means of background, as a tissue volume is subdivided, its effect on acoustic cavitation/histotripsy (e.g., the bubble cloud here) is changed. For example, bubbles may grow larger and have a different lifetime and collapse changing characteristics in intact versus fluidized tissue. Bubbles may also move and interact after tissue is subdivided producing larger bubbles or cooperative interaction among bubbles, all of which can result in changes in acoustic emission. These emissions can be heard during treatment and they change during treatment. Analysis of these changes, and their correlation to therapeutic efficacy, enables monitoring of the progress of therapy, and may be configured as a feature of the system.

[0075] For systems comprising feedback and monitoring via electrical impedance tomography, and as means of background, an impedance map of a therapy site can be produced based upon the spatial electrical characteristics throughout the therapy site. Imaging of the conductivity or permittivity of the therapy site of a patient can be inferred from taking skin surface electrical measurements. Conducting electrodes are attached to a patient's skin and small

alternating currents are applied to some or all of the electrodes. One or more known currents are injected into the surface and the voltage is measured at a number of points using the electrodes. The process can be repeated for different configurations of applied current. The resolution of the resultant image can be adjusted by changing the number of electrodes employed. A measure of the electrical properties of the therapy site within the skin surface can be obtained from the impedance map, and changes in and location of the acoustic cavitation/histotripsy (e.g., bubble cloud, specifically) and histotripsy process can be monitored using this as configured in the system and supporting sub-systems.

[0076] The user may be allowed to further select, annotate, mark, highlight, and/or contour, various regions of interest or treatment sites, and defined treatment targets (on the image(s)), of which may be used to command and direct the system where to image, test and/or treat, through the system software and user interfaces and displays. In some arrangements, the user may use a manual ultrasound probe (e.g., diagnostic hand-held probe) to conduct the procedure. In another arrangement, the system may use a robot and/or electromechanical positioning system to conduct the procedure, as directed and/or automated by the system, or conversely, the system can enable combinations of manual and automated uses.

[0077] The system may further include the ability to conduct image registration, including imaging and image data set registration to allow navigation and localization of the system to the patient, including the treatment site (e.g., tumor, critical structure, bony anatomy, anatomy and identifying features of, etc.). In one embodiment, the system allows the user to image and identify a region of interest, for example the liver, using integrated ultrasound, and to select and mark a tumor (or surrogate marker of) comprised within the liver through/displayed in the system software, and wherein said system registers the image data to a coordinate system defined by the system, that further allows the system's Therapy and Robotics sub-systems to deliver synchronized acoustic cavitation/histotripsy to said marked tumor. The system may comprise the ability to register various image sets, including those previously disclosed, to one another, as well as to afford navigation and localization (e.g., of a therapy transducer to a CT or MRI/ultrasound fusion image with the therapy transducer and Robotics sub-system tracking to said image).

[0078] The system may also comprise the ability to work in a variety of interventional, endoscopic and surgical environments, including alone and with other systems (surgical/laparoscopic towers, vision systems, endoscope systems and towers, ultrasound enabled endoscopic ultrasound (flexible and rigid), percutaneous/endoscopic/laparoscopic and minimally invasive navigation systems (e.g., optical, electromagnetic, shape-sensing, ultrasound-enabled,

etc.), of also which may work with, or comprise various optical imaging capabilities (e.g., fiber and or digital). The disclosed system may be configured to work with these systems, in some embodiments working alongside them in concert, or in other embodiments where all or some of the system may be integrated into the above systems/platforms (e.g., acoustic cavitation/histotripsy-enabled endoscope system or laparoscopic surgical robot). In many of these environments, a therapy transducer may be utilized at or around the time of use, for example, of an optically guided endoscope/bronchoscope, or as another example, at the time a laparoscopic robot (e.g., Intuitive Da Vinci* Xi system) is viewing/manipulating a tissue/treatment site. Further, these embodiments and examples may include where said other systems/platforms are used to deliver (locally) fluid to enable the creation of a man-made acoustic window, where on under normal circumstances may not exist (e.g., fluidizing a segment or lobe of the lung in preparation for acoustic cavitation/histotripsy via non-invasive transthoracic treatment (e.g., transducer externally placed on/around patient). Systems disclosed herein may also comprise all or some of their sub-system hardware packaged within the other system cart/console/systems described here (e.g., acoustic cavitation/histotripsy system and/or sub-systems integrated and operated from said navigation or laparoscopic system).

[0079] The system may also be configured, through various aforementioned parameters and other parameters, to display real-time visualization of a bubble cloud in a spatial-temporal manner, including the resulting tissue effect peri/post-treatment from tissue/bubble cloud interaction, wherein the system can dynamically image and visualize, and display, the bubble cloud, and any changes to it (e.g., decreasing or increasing echogenicity), which may include intensity, shape, size, location, morphology, persistence, etc. These features may allow users to continuously track and follow the treatment in real-time in one integrated procedure and interface/system, and confirm treatment safety and efficacy on the fly (versus other interventional or surgical modalities, which either require multiple procedures to achieve the same, or where the treatment effect is not visible in real-time (e.g., radiation therapy), or where it is not possible to achieve such (e.g., real-time visualization of local tissue during thermal ablation), and/or where the other procedure further require invasive approaches (e.g., incisions or punctures) and iterative imaging in a scanner between procedure steps (e.g., CT or MRI scanning). The above disclosed systems, sub-systems, components, modalities, features and work-flows/methods of use may be implemented in an unlimited fashion through enabling hardware, software, user interfaces and use environments, and future improvements, enhancements and inventions in this area are considered as included in the scope of this

disclosure, as well as any of the resulting data and means of using said data for analytics, artificial intelligence or digital health applications and systems.

[0080] ROBOTICS

[0081] They system may comprise various Robotic sub-systems and components, including but not limited to, one or more robotic arms and controllers, which may further work with other sub-systems or components of the system to deliver and monitor acoustic cavitation/histotripsy. As previously discussed herein, robotic arms and control systems may be integrated into one or more Cart configurations.

[0082] For example, one system embodiment may comprise a Cart with an integrated robotic arm and control system, and Therapy, Integrated Imaging and Software, where the robotic arm and other listed sub-systems are controlled by the user through the form factor of a single bedside Cart.

[0083] In other embodiments, the Robotic sub-system may be configured in one or more separate Carts, that may be a driven in a master/slave configuration from a separate master or Cart, wherein the robotically-enabled Cart is positioned bed/patient-side, and the Master is at a distance from said Cart.

[0084] Disclosed robotic arms may be comprised of a plurality of joints, segments, and degrees of freedom and may also include various integrated sensor types and encoders, implemented for various use and safety features. Sensing technologies and data may comprise, as an example, vision, potentiometers, position/localization, kinematics, force, torque, speed, acceleration, dynamic loading, and/or others. In some cases, sensors may be used for users to direct robot commands (e.g., hand gesture the robot into a preferred set up position, or to dock home). Additional details on robotic arms can be found in US Patent Pub. No. 2013/0255426 to Kassow et al. which is disclosed herein by reference in its entirety.

[0085] The robotic arm receives control signals and commands from the robotic control system, which may be housed in a Cart. The system may be configured to provide various functionalities, including but not limited to, position, tracking, patterns, triggering, and events/actions.

[0086] Position may be configured to comprise fixed positions, pallet positions, time-controlled positions, distance-controlled positions, variable-time controlled positions, variable-distance controlled positions.

[0087] Tracking may be configured to comprise time-controlled tracking and/or distance-controlled tracking.

[0088] The patterns of movement may be configured to comprise intermediate positions or waypoints, as well as sequence of positions, through a defined path in space.

[0089] Triggers may be configured to comprise distance measuring means, time, and/or various sensor means including those disclosed herein, and not limited to, visual/imaging-based, force, torque, localization, energy/power feedback and/or others.

[0090] Events/actions may be configured to comprise various examples, including proximity-based (approaching/departing a target object), activation or de-activation of various end-effectors (e.g., therapy transducers), starting/stopping/pausing sequences of said events, triggering or switching between triggers of events/actions, initiating patterns of movement and changing/toggling between patterns of movement, and/or time-based and temporal over the defined work and time-space.

[0091] In one embodiment, the system comprises a three degree of freedom robotic positioning system, enabled to allow the user (through the software of the system and related user interfaces), to micro-position a therapy transducer through X, Y, and Z coordinate system, and where gross macro-positioning of the transducer (e.g., aligning the transducer on the patient's body) is completed manually. In some embodiments, the robot may comprise 6 degrees of freedom including X, Y, Z, and pitch, roll and yaw. In other embodiments, the Robotic sub-system may comprise further degrees of freedom, that allow the robot arm supporting base to be positioned along a linear axis running parallel to the general direction of the patient surface, and/or the supporting base height to be adjusted up or down, allowing the position of the robotic arm to be modified relative to the patient, patient surface, Cart, Coupling sub-system, additional robots/robotic arms and/or additional surgical systems, including but not limited to, surgical towers, imaging systems, endoscopic/laparoscopic systems, and/or other.

[0092] One or more robotic arms may also comprise various features to assist in maneuvering and modifying the arm position, manually or semi-manually, and of which said features may interface on or between the therapy transducer and the most distal joint of the robotic arm. In some embodiments, the feature is configured to comprise a handle allowing maneuvering and manual control with one or more hands. The handle may also be configured to include user input and electronic control features of the robotic arm, to command various drive capabilities or modes, to actuate the robot to assist in gross or fine positioning of the arm (e.g., activating or deactivating free drive mode). The work-flow for the initial positioning of the robotic arm and therapy head can be configured to allow either first positioning the therapy transducer/head in the coupling solution, with the therapy transducer directly interfaced to the arm, or in a different work-flow, allowing the user to set up the coupling solution first, and

enabling the robot arm to be interfaced to the therapy transducer/coupling solution as a later/terminal set up step.

[0093] In some embodiments, the robotic arm may comprise a robotic arm on a laparoscopic, single port, endoscopic, hybrid or combination of, and/or other robot, wherein said robot of the system may be a slave to a master that controls said arm, as well as potentially a plurality of other arms, equipped to concurrently execute other tasks (vision, imaging, grasping, cutting, ligating, sealing, closing, stapling, ablating, suturing, marking, etc.), including actuating one or more laparoscopic arms (and instruments) and various histotripsy system components. For example, a laparoscopic robot may be utilized to prepare the surgical site, including manipulating organ position to provide more ideal acoustic access and further stabilizing said organ in some cases to minimize respiratory motion. In conjunction and parallel to this, a second robotic arm may be used to deliver non-invasive acoustic cavitation through a body cavity, as observed under real-time imaging from the therapy transducer (e.g., ultrasound) and with concurrent visualization via a laparoscopic camera. In other related aspects, a similar approach may be utilized with a combination of an endoscopic and non-invasive approach, and further, with a combination of an endoscopic, laparoscopic and non-invasive approach.

[0094] **COUPLING**

[0095] Systems may comprise a variety of Coupling sub-system embodiments, of which are enabled and configured to allow acoustic coupling to the patient to afford effective acoustic cavitation/histotripsy (e.g., provide acoustic medium between transducer and patient, and support of). These may include different form factors of such, including open and enclosed solutions, and some arrangements which may be configured to allow dynamic control over the acoustic medium (e.g., temperature, dissolved gas content, level of particulate filtration, sterility, etc.). Such dynamic control components may be directly integrated to the system (within the Cart), or may be in communication with the system, but externally situated.

[0096] The Coupling sub-system typically comprises, at a minimum, coupling medium, a reservoir/container to contain said coupling medium, and a support structure. In most embodiments, the coupling medium is water, and wherein the water may be conditioned before or during the procedure (e.g., chilled, degassed, filtered, etc.). Various conditioning parameters may be employed based on the configuration of the system and it's intended use/application.

[0097] The reservoir or medium container may be formed and shaped to adapt/conform to the patient, allow the therapy transducer to engage and work within the acoustic medium, per defined and required working space (minimum volume of medium to allow the therapy transducer to be positioned and/or move through one or more treatment positions or patterns, and

at various standoffs or depths from the patient, etc.), and wherein said reservoir or medium container may also mechanically support the load, and distribution of the load, through the use of a mechanical and/or electromechanical support structure. The container may be of various shapes, sizes, curvatures, and dimensions, and may be comprised of a variety of materials (single, multiple, composites, etc.), of which may vary throughout. In some embodiments, it may comprise features such as films, drapes, membranes, bellows, etc. that may be insertable and removable, and/or fabricated within. It may further contain various sensors, drains, lighting (e.g., LEDs), markings, text, etc.

[0098] In one embodiment, the reservoir or medium container contains a sealable frame, of which a membrane and/or film may be positioned within, to afford a conformable means of contacting the reservoir (later comprising the therapy transducer) as an interface to the patient, that further provides a barrier to the medium (e.g., water) between the patient and transducer). In other embodiments, the membrane and/or film may comprise an opening, the edge of which affords mechanical sealing to the patient, but in contrast allows medium communication with the patient (e.g., direct water interface with patient). The superstructure of the reservoir or medium container in both these examples may further afford the proximal portion of the structure (e.g., top) to be open or enclosed (e.g., to prevent spillage or afford additional features).

[0099] Disclosed membranes may be comprised of various elastomers, viscoelastic polymers, thermoplastics, thermoplastic elastomers, thermoset polymers, silicones, urethanes, rigid/flexible co-polymers, block co-polymers, random block co-polymers, etc. Materials may be hydrophilic, hydrophobic, surface modified, coated, extracted, etc., and may also contain various additives to enhance performance, appearance or stability. In some embodiments, the thermoplastic elastomer may be styrene-ethylene-butylene-styrene (SEBS), or other like strong and flexible elastomers.

[0100] Said materials may be formed into useful membranes through molding, casting, spraying, ultrasonic spraying and/or any other processing methodology that produces useful embodiments. They may be single use or reposable/reusable. They may be provided non-sterile, aseptically cleaned or sterile, where sterilization may comprise any known method, including but not limited to ethylene oxide, gamma, e-beam, autoclaving, steam, peroxide, plasma, chemical, etc. Membranes can be further configured with an outer molded frame to provide mechanical stability during assembly of the coupling sub-system. Various parameters of the membrane can be optimized for this method of use, including thickness, thickness profile, density, formulation (e.g., polymer molecular weight and copolymer ratios), including optimizing specifically to

maximize acoustic properties, including minimizing impact to cavitation initiation threshold values, and/or ultrasound imaging artifacts, including but not limited to membrane reflections.

[0101] Open reservoirs or medium containers may comprise various methods of filling, including using pre-prepared medium or water, that may be delivered into the such, in some cases to a defined specification of water (level of temperature and gas saturation, etc.), or they may comprise additional features integral to the design that allow filling and draining (e.g., ports, valves, hoses, tubing, fittings, bags, pumps, etc.).

[0102] Enclosed iterations of the reservoir or medium container may comprise various features for sealing, in some embodiments sealing to a proximal/top portion or structure of a reservoir/container, or in other cases where sealing may comprise embodiments that seal to the transducer, or a feature on the transducer housings. Further, some embodiments may comprise the dynamic ability to control the volume of fluid within these designs, to minimize the potential for air bubbles or turbulence in said fluid. As such, integrated features allowing fluid communication, and control of, may be provided (ability to provide/remove fluid on demand), including the ability to monitor and control various fluid parameters, some disclosed above. In order to provide this functionality, the overall system, and as part, the Coupling sub-system, may comprise a fluid conditioning system, which may contain various electromechanical devices, systems, power, sensing, computing and control systems, etc.

[0103] Coupling support systems may include various mechanical support devices to interface the reservoir/container and medium to the patient, and the workspace (e.g., bed). In some embodiments, the support system comprises a mechanical arm with 3 or more degrees of freedom. Said arm may interface with one or more locations (and features) of the bed, including but not limited to, the frame, rails, customized rails or inserts, as well as one or more locations of the reservoir or container. The arm may be a feature implemented on one or more Carts, wherein Carts may be configured in various unlimited permutations, in some cases where a Cart only comprises the role of supporting and providing the disclosed support structure.

[0104] In some embodiments, the support structure and arm may be a robotically-enabled arm, implemented as a stand-alone Cart, or integrated into a Cart further comprising two or more system sub-systems, or where in the robotically-enabled arm is an arm of another robot, of interventional, surgical or other type, and may further comprise various user input features to actuate/control the robotic arm (e.g., positioning into/within coupling medium) and/or Coupling solution features (e.g., filling, draining, etc.).

[0105] SOFTWARE

[0106] The system may comprise various software applications, features and components which allow the user to interact, control and use the system for a plethora of clinical applications. The Software may communicate and work with one or more of the sub-systems, including but not limited to Therapy, Integrated Imaging, Robotics and Other Components, Ancillaries and Accessories of the system.

[0107] Overall, in no specific order of importance, the software may provide features and support to initialize and set up the system, service the system, communicate and import/export/store data, modify/manipulate/configure/control/command various settings and parameters by the user, mitigate safety and use-related risks, plan procedures, provide support to various configurations of transducers, robotic arms and drive systems, function generators and amplifier circuits/slaves, test and treatment ultrasound sequences, transducer steering and positioning (electromechanical and electronic beam steering, etc.), treatment patterns, support for imaging and imaging probes, manual and electromechanical/robotically-enabling movement of, imaging support for measuring/characterizing various dimensions within or around procedure and treatment sites (e.g., depth from one anatomical location to another, etc., pre-treatment assessments and protocols for measuring/characterizing in situ treatment site properties and conditions (e.g., acoustic cavitation/histotripsy thresholds and heterogeneity of), targeting and target alignment, calibration, marking/annotating, localizing/navigating, registering, guiding, providing and guiding through work-flows, procedure steps, executing treatment plans and protocols autonomously, autonomously and while under direct observation and viewing with real-time imaging as displayed through the software, including various views and viewports for viewing, communication tools (video, audio, sharing, etc.), troubleshooting, providing directions, warnings, alerts, and/or allowing communication through various networking devices and protocols. It is further envisioned that the software user interfaces and supporting displays may comprise various buttons, commands, icons, graphics, text, etc., that allow the user to interact with the system in a user-friendly and effective manner, and these may be presented in an unlimited number of permutations, layouts and designs, and displayed in similar or different manners or feature sets for systems that may comprise more than one display (e.g., touch screen monitor and touch pad), and/or may network to one or more external displays or systems (e.g., another robot, navigation system, system tower, console, monitor, touch display, mobile device, tablet, etc.).

[0108] The software, as a part of a representative system, including one or more computer processors, may support the various aforementioned function generators (e.g., FPGA), amplifiers, power supplies and therapy transducers. The software may be configured to allow

users to select, determine and monitor various parameters and settings for acoustic cavitation/histotripsy, and upon observing/receiving feedback on performance and conditions, may allow the user to stop/start/modify said parameters and settings.

[0109] The software may be configured to allow users to select from a list or menu of multiple transducers and support the auto-detection of said transducers upon connection to the system (and verification of the appropriate sequence and parameter settings based on selected application). In other embodiments, the software may update the targeting and amplifier settings (e.g., channels) based on the specific transducer selection. The software may also provide transducer recommendations based on pre-treatment and planning inputs. Conversely, the software may provide error messages or warnings to the user if said therapy transducer, amplifier and/or function generator selections or parameters are erroneous, yield a fault or failure. This may further comprise reporting the details and location of such.

[0110] In addition to above, the software may be configured to allow users to select treatment sequences and protocols from a list or menu, and to store selected and/or previous selected sequences and protocols as associated with specific clinical uses or patient profiles. Related profiles may comprise any associated patient, procedure, clinical and/or engineering data, and maybe used to inform, modify and/or guide current or future treatments or procedures/interventions, whether as decision support or an active part of a procedure itself (e.g., using serial data sets to build and guide new treatments).

[0111] As a part of planning or during the treatment, the software (and in working with other components of the system) may allow the user to evaluate and test acoustic cavitation/histotripsy thresholds at various locations in a user-selected region of interest or defined treatment area/volume, to determine the minimum cavitation thresholds throughout said region or area/volume, to ensure treatment parameters are optimized to achieve, maintain and dynamically control acoustic cavitation/histotripsy. In one embodiment, the system allows a user to manually evaluate and test threshold parameters at various points. Said points may include those at defined boundary, interior to the boundary and center locations/positions, of the selected region of interest and treatment area/volume, and where resulting threshold measurements may be reported/displayed to the user, as well as utilized to update therapy parameters before treatment. In another embodiment, the system may be configured to allow automated threshold measurements and updates, as enabled by the aforementioned Robotics sub-system, wherein the user may direct the robot, or the robot may be commanded to execute the measurements autonomously.

[0112] Software may also be configured, by working with computer processors and one or more function generators, amplifiers and therapy transducers, to allow various permutations of delivering and positioning optimized acoustic cavitation/histotripsy in and through a selected area/volume. This may include, but not limited to, systems configured with a fixed/natural focus arrangement using purely electromechanical positioning configuration(s), electronic beam steering (with or without electromechanical positioning), electronic beam steering to a new selected fixed focus with further electromechanical positioning, axial (Z axis) electronic beam steering with lateral (X and Y) electromechanical positioning, high speed axial electronic beam steering with lateral electromechanical positioning, high speed beam steering in 3D space, various combinations of including with dynamically varying one or more acoustic cavitation/histotripsy parameters based on the aforementioned ability to update treatment parameters based on threshold measurements (e.g., dynamically adjusting amplitude across the treatment area/volume).

[0113] OTHER COMPONENTS, ANCILLARIES AND ACCESSORIES

[0114] The system may comprise various other components, ancillaries and accessories, including but not limited to computers, computer processors, power supplies including high voltage power supplies, controllers, cables, connectors, networking devices, software applications for security, communication, integration into information systems including hospital information systems, cellular communication devices and modems, handheld wired or wireless controllers, goggles or glasses for advanced visualization, augmented or virtual reality applications, cameras, sensors, tablets, smart devices, phones, internet of things enabling capabilities, specialized use “apps” or user training materials and applications (software or paper based), virtual proctors or trainers and/or other enabling features, devices, systems or applications, and/or methods of using the above.

[0115] SYSTEM VARIATIONS AND METHODS/APPLICATIONS

[0116] In addition to performing a breadth of procedures, the system may allow additional benefits, such as enhanced planning, imaging and guidance to assist the user. In one embodiment, the system may allow a user to create a patient, target and application specific treatment plan, wherein the system may be configured to optimize treatment parameters based on feedback to the system during planning, and where planning may further comprise the ability to run various test protocols to gather specific inputs to the system and plan.

[0117] Feedback may include various energy, power, location, position, tissue and/or other parameters.

[0118] The system, and the above feedback, may also be further configured and used to autonomously (and robotically) execute the delivery of the optimized treatment plan and protocol, as visualized under real-time imaging during the procedure, allowing the user to directly observe the local treatment tissue effect, as it progresses through treatment, and start/stop/modify treatment at their discretion. Both test and treatment protocols may be updated over the course of the procedure at the direction of the user, or in some embodiments, based on logic embedded within the system.

[0119] It is also recognized that many of these benefits may further improve other forms of acoustic therapy, including thermal ablation with high intensity focused ultrasound (HIFU), high intensity therapeutic ultrasound (HITU) including boiling histotripsy (thermal cavitation), and are considered as part of this disclosure.

[0120] In another aspect, the Therapy sub-system, comprising in part, one or more amplifiers, transducers and power supplies, may be configured to allow multiple acoustic cavitation and histotripsy driving capabilities, affording specific benefits based on application, method and/or patient specific use. These benefits may include, but are not limited to, the ability to better optimize and control treatment parameters, which may allow delivery of more energy, with more desirable thermal profiles, increased treatment speed and reduced procedure times, enable electronic beam steering and/or other features.

[0121] This disclosure also includes novel systems and concepts as related to systems and sub-systems comprising new and "universal" amplifiers, which may allow multiple driving approaches (e.g., single and multi-cycle pulsing). In some embodiments, this may include various novel features to further protect the system and user, in terms of electrical safety or other hazards (e.g., damage to transducer and/or amplifier circuitry).

[0122] In another aspect, the system, and Therapy sub-system, may include a plethora of therapy transducers, where said therapy transducers are configured for specific applications and uses and may accommodate treating over a wide range of working parameters (target size, depth, location, etc.) and may comprise a wide range of working specifications (detailed below). Transducers may further adapt, interface and connect to a robotically-enabled system, as well as the Coupling sub-system, allowing the transducer to be positioned within, or along with, an acoustic coupling device allowing, in many embodiments, concurrent imaging and histotripsy treatments through an acceptable acoustic window. The therapy transducer may also comprise an integrated imaging probe or localization sensors, capable of displaying and determining transducer position within the treatment site and affording a direct field of view (or representation of) the treatment site, and as the acoustic cavitation/histotripsy tissue effect and

bubble cloud may or may not change in appearance and intensity, throughout the treatment, and as a function of its location within said treatment (e.g., tumor, healthy tissue surrounding, critical structures, adipose tissue, etc.).

[0123] The systems, methods and use of the system disclosed herein, may be beneficial to overcoming significant unmet needs in the areas of soft tissue ablation, oncology, immuno-oncology, advanced image guided procedures, surgical procedures including but not limited to open, laparoscopic, single incision, natural orifice, endoscopic, non-invasive, various combination of, various interventional spaces for catheter-based procedures of the vascular, cardiovascular and/or neuro-related spaces, cosmetics/aesthetics, metabolic (e.g., type 2 diabetes), plastics and reconstructive, ocular and ophthalmology, gynecology and men's health, and other systems, devices and methods of treating diseased, injured, undesired, or healthy tissues, organs or cells.

[0124] Systems and methods are also provided for improving treatment patterns within tissue that can reduce treatment time, improve efficacy, and reduce the amount of energy and prefocal tissue heating delivered to patients.

[0125] USE ENVIRONMENTS

[0126] The disclosed system, methods of use, and use of the system, may be conducted in a plethora of environments and settings, with or without various support systems such as anesthesia, including but not limited to, procedure suites, operating rooms, hybrid rooms, in and out-patient settings, ambulatory settings, imaging centers, radiology, radiation therapy, oncology, surgical and/or any medical center, as well as physician offices, mobile healthcare centers or systems, automobiles and related vehicles (e.g., van), and/or any structure capable of providing temporary procedure support (e.g., tent). In some cases, systems and/or sub-systems disclosed herein may also be provided as integrated features into other environments, for example, the direct integration of the histotripsy Therapy sub-system into a MRI scanner or patient surface/bed, wherein at a minimum the therapy generator and transducer are integral to such, and in other cases wherein the histotripsy configuration further includes a robotic positioning system, which also may be integral to a scanner or bed centered design.

[0127] COORDINATION BETWEEN IMAGING AND ROBOTICS SUBSYSTEMS

[0128] To effectively treat tissue with histotripsy ultrasound therapy, the ultrasound focus of the therapy system needs to be precisely placed to the target tissue (e.g., tumor and clot) inside the body. For a non-invasive treatment such as histotripsy, precise targeting can be guided by real-time imaging such as ultrasound or MRI. The advantage of using ultrasound imaging is that ultrasound is low-cost, widely available, and can visualize cavitation from the histotripsy clearly.

However, ultrasound imaging has many limitations in histotripsy therapy, including: 1) Many clinical targets such as tumors may not be viewed clearly on ultrasound, 2) native Ultrasound imaging is typically 2D and does not provide precise 3D volume information of the tissue, 3) Targets inside the brain cannot be imaged with ultrasound due to the skull and limitations in acoustic windows required for imaging.

[0129] Histotripsy targeting can also be guided with real-time MRI. Tumor and clots can be viewed on MRI clearly, and MRI commonly provides 3D imaging. However, real-time MRI guidance also has limitations in histotripsy therapy, including: 1) High cost of the MRI scan time, 2) Requirement of specialized MRI-compatible and directly integrated histotripsy equipment, and 3) Limited MRI scanner availability.

[0130] The present disclosure hereby describes novel approaches for histotripsy targeting that do not require real-time imaging. Systems and methods are described herein that achieve precise targeting based on imaging scans (e.g., MRI or CT) taken prior to, or during, the treatment. The approaches described herein may include combining histotripsy with a surgical navigation capabilities and/or systems, stereotactic setup, and/or inserted fiducial markers.

[0131] The methods and systems of histotripsy targeting based on prior imaging scans can leverage the capability of MRI/CT for 3D imaging and clear visualization of tumor/clot contrast. These techniques use software and hardware components that may interact and communicate/interface with a histotripsy system, or as part of a histotripsy system, but that do not require a specialized histotripsy system wherein the system requires the physical and electromechanical integration of MRI/CT. In some embodiments, as only imaging scans prior to treatment are used, these techniques do not require real-time MRI/CT during the entire duration of the treatment, thus significantly reducing the cost of therapy while maintaining a high targeting accuracy. In some embodiments, the histotripsy system may communicate and interact with the interoperative MRI/CT, but in working in concert only (not integrated as part of the scanner itself).

[0132] The histotripsy targeting systems and methods described herein generally require a specific set of hardware and software systems which may be configured in a variety of ways, including but not limited to a histotripsy therapy transducer, a robotic positioning system coupled to the histotripsy therapy transducer and configured to control and move the position and orientation of the histotripsy therapy transducer during therapy, a surgical navigation system or sub-system, capable of producing variable-resolution (low or high) images of a target tissue volume, and prior high-resolution imaging scans of the target tissue volume such as imaging scans from a MRI or CT system. For example, the histotripsy therapy transducer and robotic

positioning arm described herein (in FIG. 1) can be used for these novel targeting systems and methods. Any surgical navigation system can be used, but generally the surgical navigation system can be further configured to obtain low-resolution images of the target tissue volume, such as ultrasound or still camera images. The robot and navigation systems/sub-systems may be used to further register the robot encoded positional data, low resolution real-time images (e.g., ultrasound or optical camera), to the MRI/CT pre-procedure images, to afford real-time navigation in the MRI/CT. In some embodiments, and as previously described herein, the MRI/CT data may be registered using rigid and/or elastic and deformable models, to best fit the pre-op imaging data with the real-time data, to achieve the highest accuracy registration possible with minimal MRI/CT to body divergence.

[0133] FIG. 2 depicts a flowchart 200 that describes steps for some representative embodiments, for performing histotripsy targeting and therapy using the system components described above, including a histotripsy therapy transducer, a robotic positioning system, and a surgical navigation system. At step 202 of flowchart 200, the surgical navigation system can receive or access prior high-resolution image(s) of the patient including a target tissue volume on or within the patient. The high-resolution image(s) can comprise, for example, 2D or 3D MRI or CT scans, cone beam CT, augmented fluoroscopy images, etc., of the patient including the target tissue volume. These images may be anatomically segmented and reconstructed into various 2D or 3D models, including deformation models accounting for any divergence or shift due to coupling or other pre/peri-procedural anatomical changes. The target tissue volume can comprise, for example, diseased or abnormal tissue such as a tumor or cancerous growth, clots, polyps, nodules, organs, etc.

[0134] Next, at step 204, the surgical navigation system can obtain a low-resolution image(s) of the target tissue volume. Typically, surgical navigation systems have their own imaging systems that can include optical imaging, near-infrared, confocal, coherence tomography, photographic, ultrasonic, etc. Thus, for purposes of discussion in this disclosure, "high-resolution image(s)" generally refers to the types of images obtained by advanced medical imaging and diagnostic systems including MRI and CT. These images can be 2D or 3D images, or further post-processed including various segmentation, reconstruction, deformation, etc. Furthermore, "low-resolution image(s)" as discussed herein generally refers to the types of images obtained with more ubiquitous, less detailed imaging and diagnostic systems such as diagnostic ultrasound and still image/camera/optical imaging.

[0135] Next, at step 206 of flowchart 200, the surgical navigation system or sub-system can be configured to localize the target tissue volume by co-registering the lower-resolution image(s)

generated with the surgical navigation system/sub-system with the higher-resolution image(s) previously obtained (e.g., prior or peri-operative CT or MRI image(s)). Co-registering the images from the navigation system with the prior CT/MRI images allows the navigation system to correlate the coordinate systems between the images to identify the precise location of the target tissue volume in 2D or 3D space. In some examples, the low-resolution image(s) generated with the surgical navigation system can comprise ultrasound images, wherein the ultrasound probe is located in fixed geometry within, and relative to the histotripsy transducer, or in other embodiments the low-resolution images can comprise a digital optical image of the patient's skin surface with identifying landmarks. Co-registering the low-resolution image(s) with the high-resolution image(s) can include, at a high level, identifying a landmark or fiducial region in both the high-resolution image(s) and the low-resolution image(s) and using the landmark or fiducial region (e.g., certain features on the skull or face co-registering the brain scans) to correlate a coordinate system of the high-resolution image with a coordinate system of the low-resolution image. Since the low-resolution image may be obtained with the navigation system itself and using the robot, then the navigation system can use this correlation of coordinate systems (base to tool) to effectively navigate using the high-resolution image(s), where the robotic encoded positional data is registered to the imaging data sets. The register work-flow as presented in the system user interface may comprise fully automated work-flows, partially automated or fully manual procedure steps. Further, given histotripsy produces highly visible treatment zones, the treatment itself, as visualized by ultrasound, MRI and/or CT, may be further used peri-procedurally to update/enhance registration as needed or desired as well.

[0136] Next, at step 208 of flowchart 200, the surgical navigation system or sub-system can identify the location of the histotripsy transducer focus. In some examples, the surgical navigation can use the position and orientation of the histotripsy transducer itself, combined with the focal distance of the transducer, to determine the location of the focus. Many techniques can be used to identify the location of the histotripsy transducer focus, including placing fiducial markers (e.g., optical, electrical, or magnetic) on the transducer and identifying those fiducial markers with the surgical navigation system. By placing fiducial markers on the histotripsy ultrasound transducer that the surgical navigation system can detect, the position of the histotripsy transducer can be recognized in the coordinate system of the surgical navigation system. In one example, the fiducial markers can comprise a set of markers with a unique constellation to a known tool/device. A unique marker constellation (e.g., five sphere optical markers arranged in a specific pattern, such as the optical tracking markers for Stealth Station or Brainlab surgical navigation system) can be attached to the surface of the histotripsy transducer

that can be detected by the surgical navigation system (e.g., by imaging or sensing the markers). As such, the surgical navigation system can then automatically locate and identify the histotripsy focal location on the surgical navigation system co-ordinates based on the marker constellation location/orientation and the histotripsy transducer focal length. In other embodiments, given the known geometries and predicted focal length of the transducer, a peri-procedural scan may be used to predict location using the robotic position encoder data (and pose relative to image set), to predict the ultimate bubble cloud location.

[0137] Next, at step 210 of flowchart 200, the surgical navigation system, or the robotic positioning system that controls the position and motion/movement of the histotripsy transducer, can then calculate the movement coordinates that are needed to place the histotripsy focus onto the target tissue volume. These movement coordinates are then input to the robotic positioning system to move the histotripsy transducer accordingly, and can reconcile base/tool coordinate systems. In some embodiments, software watchdogs may monitor position and pose to verify the planned versus actual location/position are accurate. In additional embodiments, movement of the histotripsy therapy focus can be achieved with a combination of electronic steering of the focus with the transducer (phased array) and mechanical movement of the transducer with the robotic positioning system.

[0138] At step 212, when the histotripsy transducer is in the proper position (e.g., the focus is located on or within the target tissue volume as verified using registered real-time and virtual imaging data), histotripsy therapy can be applied to the target tissue volume with the histotripsy therapy transducer. Typically, the target tissue is a volume, for example, a volume of tumor or a clot. To treat a target volume, the user can outline and contour the target tissue volume boundaries on the high-resolution MRI/CT scans. For example, the surgical navigation system can include input features that allows the user to define a positive margin (e.g., a treatment margin that extends beyond or is larger than the target tissue volume, such as for treating a cancerous tumor) or a negative margin (e.g., a treatment margin that is within or smaller than the target tissue volume, such as for treating a clot) and the extent of the treatment margin (e.g., 1 cm). For example, if a tumor is the target tissue volume, the treatment margin can cover the entirety of the tumor with a margin pre-defined by the user surrounding the tumor to ensure that all the tumor cells are treated. If, for example, a clot is the target tissue volume, the treatment margin can cover a majority of the clot but leave the rim of the clot untreated to prevent damage to the surrounding normal tissue as defined by the user. After the treatment margin is defined, the surgical navigation system or the robotic arm can calculate and create treatment parameters to cover the target tissue volume and display the treatment margins overlaid on the prior MRI/CT

scans of the patient. Fine tuning or further adjustments to the treatment margin or coordinates can be made if desired by the user. The treatment margin location coordinates can then be fed to the robotic control system to move the histotripsy transducer accordingly to deliver the treatment, including through desired pathway, pattern, direction and order, and including any determined cooling and/or off-time (to prevent any non-target tissue effect). These parameters may be further displayed through one or more user interfaces and displays as previously disclosed herein.

[0139] STEREOTACTIC HISTOTRIPSY

[0140] Another embodiment for histotripsy targeting uses a stereotactic approach. Similar to the approach described above in FIG. 2 with the surgical navigation system, targeting using stereotactic histotripsy also relies on prior MRI or CT scans of the patient and while it may use real-time imaging, it does not require it. However, stereotactic histotripsy requires a stereotactic frame for targeting. FIG. 3 illustrates one embodiment of a stereotactic histotripsy treatment system, which can include a treatment bed 0, a stereotactic frame 1, a histotripsy therapy transducer 3, and one or more fiducial markers 4. Referring to FIG. 3, the stereotactic frame 1 can be attached to the treatment bed, and the histotripsy transducer can be affixed to the stereotactic frame. The histotripsy transducer must be in a fixed position relative to the stereotactic frame, such that the position/orientation of the histotripsy therapy transducer is always known with respect to the position of the stereotactic frame.

[0141] In most examples, the stereotactic frame can be rigidly mounted to the patient's head or torso depending on the target tissue volume. MRI or CT scans of the patient and the target tissue volume can be obtained with the stereotactic frame prior to treatment. Since the stereotactic frame includes fiducial markers that are detectable by MRI or CT, those fiducial markers will be imaged in the pre and/or peri procedural MRI or CT scans (See fiducial markers 4 in FIG. 4A). Based on these scans, the locations of the fiducial markers with regard to the tumor locations T can be localized based on the positions of the fiducial markers (See FIG. 4B). The histotripsy transducer can then be mechanically mounted to the stereotactic frame, such that the location of the histotripsy transducer and focus will be known with regard and relative to the fiducial markers on the stereotactic frame. With these conditions satisfied, the robotic positioning control system that controls the histotripsy transducer and its position, location and motion, and the histotripsy system software, can calculate or determine the location of the current histotripsy focus F with regard to the target tissue volume and target/region of interest (See FIG. 4C). The robotic positioning system can then be used to move the therapy transducer to align the histotripsy focus to the target location(s).

[0142] When the target tissue volume is a tumor, the locations of the tumor boundary can be outlined and contoured on the pre or peri-procedural MRI or CT scans, and the tumor boundary coordinates with regard to the fiducial markers and the current histotripsy focus can be calculated by the robotic positioning and histotripsy system. As described above, the system can be configured to allow the user to define positive vs. negative treatment margins (e.g., positive margin to extend beyond the tumor or negative margin to treat within the clot) and the extent of the margin (e.g., 1 cm). After the treatment margin is defined, the system can calculate and create 3D grid locations to cover the target tissue volume and display the 3D grid locations overlaid on prior MRI/CT scans of the patient. If the user believes that adjustment of the grid locations is needed, he/she can make adjustment to the treatment margin or coordinates on the fly. In some embodiments, adjustments may be made using elastic and deformation models to further visualize grid and planned cloud locations in the most clinically relevant image sets. Once the user confirms the coordinates, the 3D grid location coordinates are then fed to the robotic positioning system and software to move the histotripsy transducer accordingly to deliver the treatment per the defined plan, including but not limited to the pattern, pathway and any predetermined cooling and/or off-times to manage prefocal thermal or other undesired tissue effects. In addition to robotic mechanical delivery, the system may use electronic focal steering in part, or full, to deliver the desired plan, including any treatment planning steps (e.g., test pulses) and/or therapy itself (e.g., full volumetric ablation).

[0143] TARGETING WITH CATHETER INSERTION

[0144] In certain treatments, insertion of a catheter or needle is needed. One example is the treatment of intracerebral hemorrhage, where a catheter is typically used to drain a clot liquefied by histotripsy therapy. In this example, a catheter or needle is inserted into the target tissue. The insertion of the needle or catheter can be guided by a surgical navigation system or some form of imaging as routinely performed clinically. To guide the catheter or needle during therapy, the tip of the catheter or needle with regard to the boundary of the target tissue volume should be known at the point of insertion. In one embodiment, the tip of the catheter or needle can include an acoustic detector and/or source, configured to receive or emit, ultrasound signals from the and/or measured by, the histotripsy transducer, respectively. Alternatively, the catheter or needle can include fiducial markers. These ultrasound signals or fiducial markers can be used to localize the position of the target tissue volume relative to the position of the histotripsy transducer. The robotic positioning system that controls movement of the histotripsy transducer can then calculate the coordinates of the histotripsy transducer or focus with regard to the catheter tip, and thus the target tissue. The robotic positioning system can then calculate the movement

coordinates required to align the histotripsy focus onto the target tissue volume. Treatment margins of can be calculated and adjusted, as described above. Further, if a peri-procedural image set (MRI or CT) is captured, including catheter location, the robotic encoder positional data may be used to further register this data stream to the acoustic data to further enhance registration accuracy.

[0145] TARGETING WITH MARKER INSERTION

[0146] For cases that do not require catheter or needle insertion, it is also possible to implant fiducial markers at the time of biopsy either inside or near the target tissue volume. These fiducial markers can then be visualized on MRI or CT. These markers can also preferable be ultrasound reflective to allow the histotripsy transducer to receive acoustic reflection signals from these markers to localize these markers during therapy. This allows the histotripsy therapy system to identify the coordinates of the current histotripsy focus with regard to the fiducial markers in real-time. Based on the locations of the markers relative to the target tissue volume, the treatment margin coordinates relative to the current histotripsy focus will be calculated. The target tissue volume can be treated using the techniques described above.

[0147] Referring to FIG. 5, a flowchart 500 is provided that describes steps for some representative embodiments, for performing histotripsy targeting and therapy using the system components described above, including a histotripsy therapy transducer, a robotic positioning system, and/or a surgical navigation system.

[0148] At step 502 of flowchart 500, the method can include inserting a fiducial marker or acoustic detector into a patient near the tissue volume. As described above, in some embodiments a surgical procedure can include inserting a catheter or a needle near a target tissue site. The catheter or needle can include, for example, fiducial markers disposed thereon or therein as described above. Alternatively, the catheter or needle can include an ultrasound sensor or transmitter. In an alternative embodiment, fiducial markers or an acoustic sensor/transmitter can be injected into the patient's tissue within or near the target tissue site.

[0149] Next, at step 504 of flowchart 500, the method can include localizing the target tissue volume relative to the position of the histotripsy transducer. In some embodiments, localizing the position of the target tissue volume can include transmitting ultrasound energy from the histotripsy therapy transducer towards a needle or catheter in the tissue that includes an ultrasound sensor. The signals received by the ultrasound sensor can be used to determine the location of the target tissue volume relative to the histotripsy therapy transducer. In other embodiments, fiducial markers on the needle or catheter, or alternatively, fiducial markers

injected into the tissue, can be used to correlate a coordinate system of the histotripsy therapy system and/or surgical navigation system to the location of the target tissue volume.

[0150] In some implementations, the surgical navigation system or sub-system can identify the location of the histotripsy transducer focus. In some examples, the surgical navigation can use the position and orientation of the histotripsy transducer itself, combined with the focal distance of the transducer, to determine the location of the focus. Many techniques can be used to identify the location of the histotripsy transducer focus, including placing fiducial markers (e.g., optical, electrical, or magnetic) on the transducer and identifying those fiducial markers with the surgical navigation system. By placing fiducial markers on the histotripsy ultrasound transducer that the surgical navigation system can detect, the position of the histotripsy transducer can be recognized in the coordinate system of the surgical navigation system. In one example, the fiducial markers can comprise a set of markers with a unique constellation to a known tool/device. A unique marker constellation (e.g., five sphere optical markers arranged in a specific pattern, such as the optical tracking markers for Stealth Station or Brainlab surgical navigation system) can be attached to the surface of the histotripsy transducer that can be detected by the surgical navigation system (e.g., by imaging or sensing the markers). As such, the surgical navigation system can then automatically locate and identify the histotripsy focal location on the surgical navigation system co-ordinates based on the marker constellation location/orientation and the histotripsy transducer focal length. In other embodiments, given the known geometries and predicted focal length of the transducer, a peri-procedural scan may be used to predict location using the robotic position encoder data (and pose relative to image set), to predict the ultimate bubble cloud location.

[0151] Next, at step 506 of flowchart 500, the surgical navigation system, or the robotic positioning system that controls the position and motion/movement of the histotripsy transducer, can then calculate the movement coordinates that are needed to place the histotripsy focus onto the target tissue volume. These movement coordinates are then input to the robotic positioning system to move the histotripsy transducer accordingly, and can reconcile base/tool coordinate systems. In some embodiments, software watchdogs may monitor position and pose to verify the planned versus actual location/position are accurate.

[0152] At step 508, when the histotripsy transducer is in the proper position (e.g., the focus is located on or within the target tissue volume as verified using registered real-time and virtual imaging data), histotripsy therapy can be applied to the target tissue volume with the histotripsy therapy transducer. Typically, the target tissue is a volume, for example, a volume of tumor or a clot. To treat a target volume, the user can outline and contour the target tissue volume

boundaries on the high-resolution MRI/CT scans. For example, the surgical navigation system can include input features that allows the user to define a positive margin (e.g., a treatment margin that extends beyond or is larger than the target tissue volume, such as for treating a cancerous tumor) or a negative margin (e.g., a treatment margin that is within or smaller than the target tissue volume, such as for treating a clot) and the extent of the treatment margin (e.g., 1 cm). For example, if a tumor is the target tissue volume, the treatment margin can cover the entirety of the tumor with a margin pre-defined by the user surrounding the tumor to ensure that all the tumor cells are treated. If, for example, a clot is the target tissue volume, the treatment margin can cover a majority of the clot but leave the rim of the clot untreated to prevent damage to the surrounding normal tissue as defined by the user. After the treatment margin is defined, the surgical navigation system or the robotic arm can calculate and create treatment parameters to cover the target tissue volume and display the treatment margins overlaid on the prior MRI/CT scans of the patient. Fine tuning or further adjustments to the treatment margin or coordinates can be made if desired by the user. The treatment margin location coordinates can then be fed to the robotic control system to move the histotripsy transducer accordingly to deliver the treatment, including through desired pathway, pattern, direction and order, and including any determined cooling and/or off-time (to prevent any non-target tissue effect). These parameters may be further displayed through one or more user interfaces and displays as previously disclosed herein.

[0153] ADDITIONAL IMAGING AND TREATMENT PLANNING FEATURES

[0154] In some examples, the surgical navigation system can include a modeling tool that can be used to capture the boundary mesh coordinates of the target tissue volume from the pre-treatment MRI or CT scan. These mesh coordinates can be used directly to calculate the 3D grid points of the treatment margin, which can be overlaid onto the pre-treatment MRI or CT scan. Alternatively, these mesh coordinates can be fed to the robotic arm to calculate the 3D grid points and/or histotripsy therapy controls system to provide electronical focal steering coordinates/commands, to cover target tissue volume and treatment margin.

[0155] Once the high and low-resolution images are co-registered, the surgical navigation system can be used to measure the distance between anatomical landmarks in the MRI or CT scans. For example, the surgical navigation system can measure the distance from the center of the target tissue volume and a boundary of the target volume at different axes. These distance values can be fed to the robotic arm to calculate the upper limit that can limit the maximum distance used for the steering distance for treating the target tissue volume.

[0156] Histotripsy mechanically disrupts cells to destroy the target tissue through cavitation. A histotripsy ultrasound transducer can have both transmit capability to generate cavitation and receive capability to receive emission signals from cavitation. As such, cavitation mapping generated by the histotripsy transducer during treatment in real-time can be overlaid onto prior MRI/CT scans of the patients to ensure that the treatment is within the boundary defined by the targeting. If cavitation is generated outside the outlined target volume. Treatment can be stopped. A histotripsy transducer array with transmit-receive capability can produce a 3D cavitation map (i.e., histotripsy treatment map) during treatment to indicate precisely the tissue locations that are being treated with cavitation in real-time. This cavitation map can be overlaid onto the MRI/CT scans in real time to allow the user to monitor the treatment in high-resolution in real-time. In some examples, a treatment cavitation map can be imported to the surgical navigation system or the robotic positioning system and/or overlaid onto the pre-treatment MRI/CT scans showing the planned treatment volume.

[0157] In another example, the surgical navigation system can include a "merge" feature for co-registering MRI, CT, or any other images of the same body part or anatomical landmark (e.g., head, abdomen, etc.) of the same patient, but at different orientations. Post-treatment images can be imported to co-register with pre-treatment images on the same image plan to allow accurate post-treatment volume matches with the planned treatment volume.

[0158] If the target tissue volume is a moving target, e.g., an abdominal organ with breathing motion, the motion can result in targeting errors in the systems described above. In this example, the implementation of histotripsy can be gated with the patient's respiration/ventilation, such that histotripsy is only applied when the target is at the resting position, for a fixed focus transducer. For example, an accelerometer or other sensor can be placed on the body of the patient near to the target tissue volume to detect movement and the measurements from the sensor can be fed to the histotripsy therapy system. If the system detects movement above a threshold value, delivery of histotripsy therapy can be halted or delayed until the movement value returns below the threshold value. Similarly, a simple respiratory monitor can be applied to the patient, and respiratory data can be used by the system to deliver therapy only when the patient is at the resting position. It is also possible to ask the patient to perform breath hold during the therapy delivery. If the patient is actually on a ventilator during the procedure, the therapy can be delivered when the ventilation machine delivery is below a pre-define threshold. In the case when histotripsy is delivered with a phased array transducer and the transducer focus can be moved instantaneously via electronic steering, the histotripsy focal location can be moved along with the breathing to track the moving target in real-time. For example, the location of the

moving target can be estimated based on the output of an accelerometer or other sensor can be placed on the body of the patient, a respiratory monitor, or a ventilator. In another example, triggered imaging may be used, wherein the registered real-time and virtual data are used to plan treatment triggers where therapy is triggered on when the target is in a desired focal zone location, and may be also turned off when said target migrates out of the desired focal zone location.

[0159] When the targeting is based on prior CT/MRI scans using the methods described above, it should be noted that deformation of the body may occur. For example, patients may lay in a different position during the treatment compared to in a prior scan; ultrasound coupling device used to acoustically couple the histotripsy transducer to the patient's skin can also cause the patient's body to deform. In these cases, to ensure treatment accuracy, prior MRI or CT scan datasets can be processed (e.g., rotated) to co-register with the deformed elastic body parts at the treatment using the existing radiological tools.

[0160] **EXAMPLES**

[0161] Example 1 - Histotripsy targeting with surgical navigation system. In this example, a robotic positioning system with a histotripsy therapy transducer is guided by a surgical navigation system to treat a tumor, in particular a liver tumor. The targeting can be implemented in the steps as described below.

[0162] 1. Prior CT/MRI scan – As part of the diagnosis, the patient's abdomen can be scanned by CT or MRI with fine resolution prior to the treatment. Prior to the treatment, the abdomen can also be imaged with the surgical navigation system with coarse resolution (e.g., ultrasound or a digital camera).

[0163] 2. Identifying the target location with surgical navigation system – Based on the prior CT or MRI scans, the surgical navigation system can be used to identify the 3D location and boundaries of the target tumor. For example, the images with coarse resolution taken with the surgical navigation system can be co-registered with the CT or MR image taken with fine resolution prior to the treatment. The tumor boundary coordinates can then be known and calculated by the surgical navigation system.

[0164] 3. Identifying histotripsy transducer location - Fiducial sensors can be placed in a fixed location on or near the histotripsy therapy transducer that are detectable by the surgical navigation system. The surgical navigation system can then know the coordinates of the histotripsy transducer use those coordinates to determine the location of the histotripsy focus.

[0165] 4. Align the histotripsy focus to the target tissue volume - Based on above coordinates, the movement coordinates required to move the histotripsy transducer to align the

histotripsy focus to align onto a central location within the target tissue volume can be calculated by the surgical navigation system or the robotic positioning system that moves the histotripsy transducer. The robotic positioning system can then be configured to move the histotripsy transducer to align the histotripsy focus to the target tissue volume.

[0166] 5. Create 3D grid coordinates to target the tumor volume with a treatment margin – The user of the system can identify the boundaries of the tumor in each slice or image of the prior MR or CT scans. The user can also input the desired treatment margin (e.g., a margin of 1 cm beyond the tumor boundary). The surgical navigation system or the robotic positioning system can then calculate and create 3D grid locations that cover the entirety of the tumor with the desired 1 cm treatment margin surrounding the tumor. The surgical navigation system or the robotic positioning system can then display the 3D grid locations overlaid onto the prior MRI/CT scans of the patient. The 3D grid location coordinates can then be fed to the robotic positioning system to move the histotripsy transducer accordingly during the treatment.

[0167] Example 2 – as detailed in Example 1, but wherein the navigation system, histotripsy system and robotic delivery system are all configured as one integrated electromechanical and software controlled system and form factor.

[0168] Example 3 – as detailed in Example 1 and 2, but wherein the pre-procedure MRI/CT is obtained with the coupling solution in place on the patient, so any observed MRI/CT-body divergence is calculated and known prior to planning the histotripsy ablation/treatment.

[0169] Example 4 - Stereotactic histotripsy. In this example, stereotactic histotripsy is used to target a brain tumor. The targeting can be implemented in the steps as described below.

[0170] 1. Prior CT/MRI scan – Prior to the treatment, a stereotactic frame can be rigidly fixed to the patient's head. The stereotactic frame can include a plurality (e.g., four) of fiducial markers. The patient's head along with the stereotactic frame can be scanned by MRI or CT to image the target tissue volume and the fiducial markers.

[0171] 2. Identifying the target location – Since the CT or MRI scans visualize both the fiducial markers and the brain tumor, the location of the tumor relative to the fiducial markers is known.

[0172] 3. Identifying histotripsy transducer location – A histotripsy transducer can attached to the stereotactic frame rigidly at the pre-designed connecting points, such that the location of the histotripsy transducer focus relative to the fiducial markers on the stereotactic frame is fixed and always known.

[0173] 4. Align the histotripsy focus to the target - Based on the coordinates of the fiducial markers, the selected tumor center, and the histotripsy focus, the movement coordinates to move

the histotripsy focus to align onto a central location within the tumor can be calculated by the robotic positioning system. The robotic positioning system can then be configured to move the histotripsy transducer to align the current histotripsy focus to the tumor center. For the brain target, the ultrasound propagates through the skull with varying thickness, which can introduce aberration and cause defocusing and reduced focal pressure. An aberration correction algorithm can be applied based on prior CT scan to improve focusing the focal pressure.

[0174] 5. Create 3D grid coordinates to target the tumor volume with a margin – Once the histotripsy focus is moved to the tumor center. The user can identify the target tissue volume boundaries on each image of the MR or CT scans. Then the user can input the desired treatment margin (e.g., a margin of 1 cm beyond the tumor boundary circled out on prior MRI/CT scans). The robotic positioning system can be configured to calculate and create 3D grid locations that cover the entirety of the tumor with the 1 cm treatment margin surrounding the tumor. The robotic arm system can display the 3D grid locations overlaid on the prior MRI/CT scans of the patient

[0175] Example 5 - Histotripsy targeting with catheter insertion. In this example, histotripsy targeting can be guided by a catheter insertion, and the target treatment volume is a blood clot in the brain for the treatment of hemorrhagic stroke or intracerebral hemorrhage (ICH). For ICH treatment, histotripsy applied from outside the skull can be used to rapidly liquefy the clot, and the catheter inserted into the clot can be used to drain the clot after it is liquefied. The targeting can be implemented in the steps as described below.

[0176] 1. Prior CT scan – Prior to the treatment, the patient's brain can be scanned by CT or MRI with fine resolution.

[0177] 2. Catheter hydrophone insertion – The catheter hydrophone can be inserted into the center of the clot through a burr hole in the skull. The insertion can be guided by a surgical navigation system or real-time imaging. The location of the catheter tip with regard to the clot boundary should be known. This catheter can include a miniature hydrophone incorporated at the tip of its guiding wire.

[0178] 3. Align the histotripsy focus to the target – This catheter hydrophone can be used to measure the ultrasound signal from the histotripsy ultrasound array elements. The signals can be used to calculate the ultrasound travel time from each histotripsy array element to the catheter hydrophone. Based on the hydrophone signals, and the location of the catheter tip with regard to the current histotripsy focus can be calculated, and aberration correction can be performed. The robotic arm system can then use these coordinates to move the histotripsy transducer to align the histotripsy focus to the catheter tip.

[0179] 4. Create 3D grid coordinates to target the clot volume – The user can identify the clot boundaries in each image of MR or CT scans. To avoid damage to the normal brain tissue surrounding the clot, the clinician can input a desired negative margin (e.g., liquefying the clot with histotripsy but leaving a margin of ~5 mm rim of intact clot). The robotic positioning system can then calculate and create 3D grid locations that would cover the entirety of the clot while leaving a ~5mm clot margin to preserve the normal brain tissue surrounding the clot. The robotic positioning system can also be configured to display the 3D grid locations overlaid on prior MRI/CT scans.

[0180] OTHER SYSTEMS AND METHODS OF USE

[0181] The systems and methods described herein are related to the systems and methods described in International Application No. PCT/US2019/063728, filed November 27, 2019, which is incorporated herein by reference. Any of the systems described herein can be further configured to perform the methods described in International Application No. PCT/US2019/063728.

CLAIMS

What is claimed is:

1. A method of surgical navigation, comprising:

receiving, in a surgical navigation system, a first image of a target tissue volume;

obtaining, with the surgical navigation system, a second image of the target tissue volume;

co-registering, in the surgical navigation system, the first image with the second image to identify boundary coordinates of the target tissue volume in the first image;

identifying, with the surgical navigation system, focal coordinates of a focus of a histotripsy therapy transducer;

determining, in the surgical navigation system, movement coordinates that will place the histotripsy therapy transducer focus within the boundary coordinates of the target tissue volume in the first image; and

moving the histotripsy therapy transducer focus based on the movement coordinates to place the histotripsy therapy transducer focus within the target tissue volume.

2. The method of claim 1, wherein the moving step further comprises moving the histotripsy therapy transducer with a robotic positioning system.

3. The method of claim 1, wherein the moving step further comprises electronically steering the histotripsy therapy transducer focus.

4. The method of claim 1, wherein the first image comprises a high-resolution image from an advanced diagnostic medical imaging system.

5. The method of claim 4, wherein the first image comprises a high-resolution MRI image.

6. The method of claim 4, wherein the first image comprises a high-resolution CT image.

7. The method of claim 1, wherein the second image comprises an ultrasound image.

8. The method of claim 1, wherein the second image comprises an optical image.

9. The method of claim 1, wherein the co-registering step further comprises identifying a fiducial region in both the first image and the second image and using the fiducial region to correlate a coordinate system of the first image with a coordinate system of the second image.

10. The method of claim 1, wherein identifying focal coordinates further comprises placing fiducial markers on the histotripsy therapy transducer and identifying the fiducial markers with the surgical navigation system.

11. The method of claim 1, further comprising:

defining a treatment margin of the target tissue volume;

calculating 3D grid locations to cover the target tissue volume and the treatment margin; and

displaying the 3D grid locations over the first or second image.

12. The method of claim 11, wherein the treatment margin comprises a positive treatment margin that extends beyond the target tissue volume.

13. The method of claim 11, wherein the treatment margin comprises a negative treatment margin that extends within the target tissue volume.

14. The method of claim 1, further comprising applying histotripsy therapy to the target tissue volume.

15. The method of claim 14, further comprising imaging the histotripsy therapy and peri-procedurally updating co-registration between the first image and the second image.

16. The method of claim 1, further comprising producing a histotripsy treatment map; and overlaying the histotripsy treatment map on the first or second image in real time.

17. The method of claim 2, wherein the robotic positioning system can move the histotripsy therapy transducer with 3 degrees of freedom.

18. The method of claim 2, wherein the robotic positioning system can move the histotripsy therapy transducer with 6 degrees of freedom.

19. The method of claim 1, wherein the moving step further comprises a combination of electronically steering the histotripsy therapy transducer focus and moving the histotripsy therapy transducer with a robotic positioning system.

20. The method of claim 4, wherein the first image comprises a cone beam CT image.

21. The method of claim 4, wherein the first image comprises an augmented fluoroscopy image.

22. The method of claim 1, wherein the target tissue volume comprises a tumor.

23. The method of claim 1, wherein the target tissue volume comprises a clot.

24. The method of claim 1, wherein the target tissue volume comprises a brain hemorrhage.

25. A method of surgical navigation, comprising:

inserting an acoustic detector into tissue within or near a target tissue volume;

localizing a position of the target tissue volume relative to a focus of a histotripsy therapy transducer with the acoustic detector; and

determining movement coordinates required to place the histotripsy therapy transducer focus within the target tissue volume.

26. The method of claim 25, further comprising applying histotripsy therapy with the histotripsy therapy transducer.

27. The method of claim 25, wherein the inserting step further comprises inserting a catheter into tissue within or near the target tissue volume, wherein the catheter includes the acoustic detector.

28. The method of claim 25, wherein the inserting step further comprises inserting a needle into tissue within or near the target tissue volume, wherein the needle includes the acoustic detector.

29. A method of surgical navigation, comprising:

inserting a fiducial marker into tissue within or near a target tissue volume;

localizing a position of the target tissue volume relative to a focus of a histotripsy therapy transducer with the fiducial marker; and

determining movement coordinates required to place the histotripsy therapy transducer focus within the target tissue volume.

30. The method of claim 29, further comprising applying histotripsy therapy with the histotripsy therapy transducer.

31. A therapy system, comprising:

a first imaging system;

a surgical navigation system including a second imaging system;

a robotic positioning arm;

a histotripsy therapy transducer coupled to the robotic positioning arm; and

an electronic controller operatively coupled to the first imaging system, the surgical navigation system, the second imaging system, the robotic positioning arm, and the histotripsy therapy transducer, the electronic controller being configured to co-register a first image of the target tissue volume from the first imaging system with a second imaging of the target tissue volume from the second imaging system to identify boundary coordinates of the target tissue volume, the electronic controller being further configured to determine movement coordinates of the robotic positioning arm requires to place a focus of the histotripsy therapy transducer within the target tissue volume.

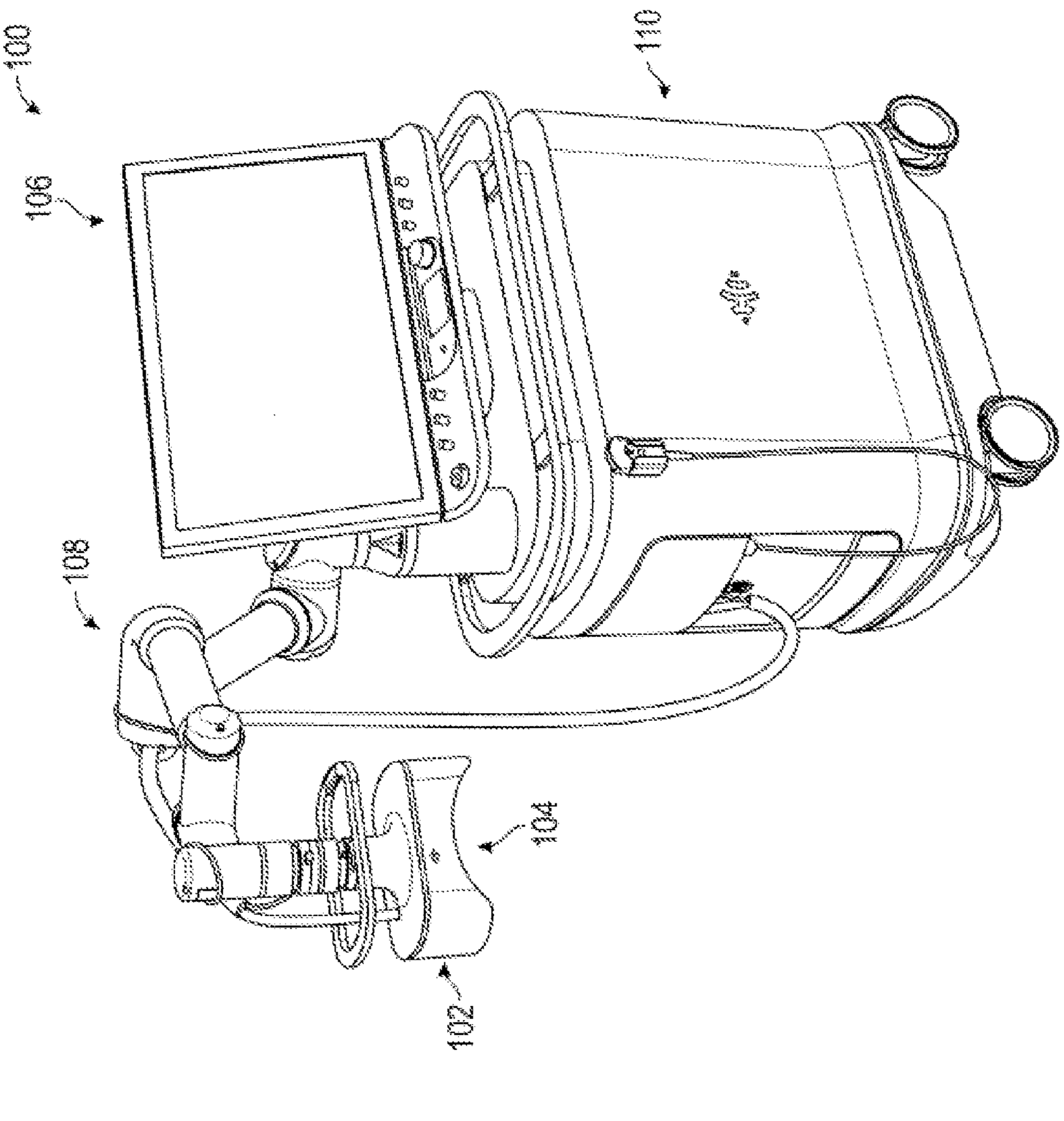


FIG. 1A

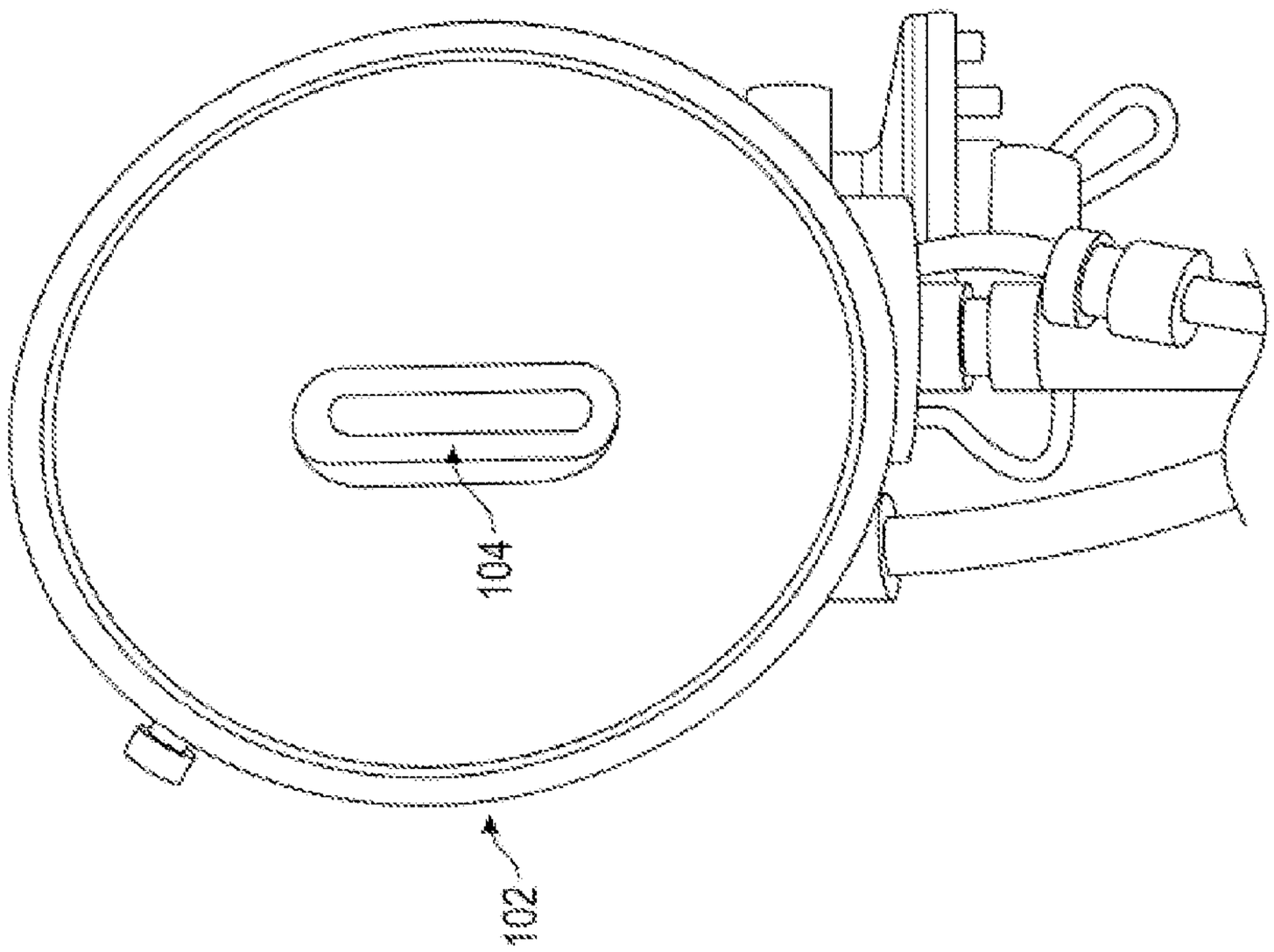


FIG. 1B

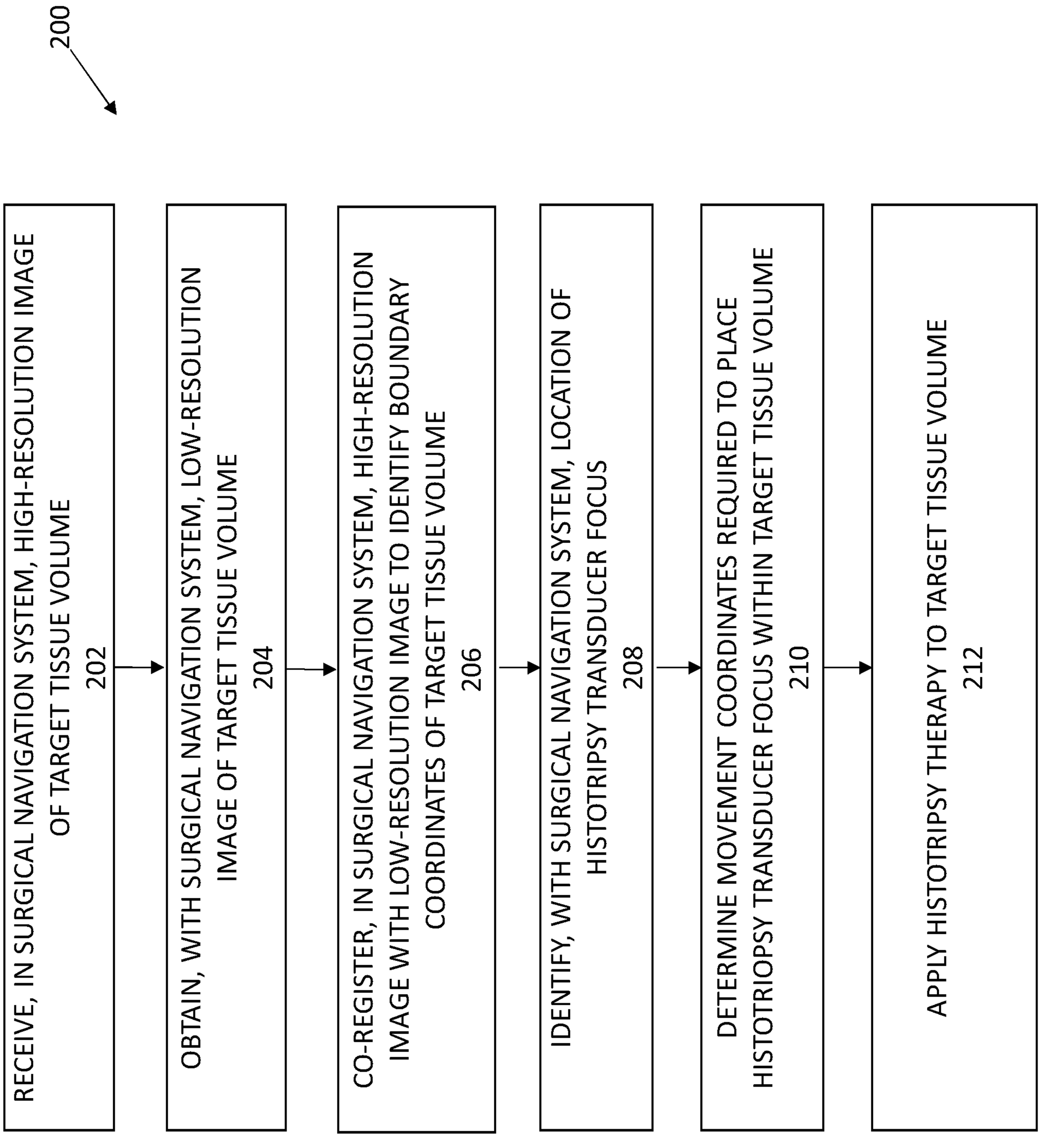

200
RECEIVE, IN SURGICAL NAVIGATION SYSTEM, HIGH-RESOLUTION IMAGE OF TARGET TISSUE VOLUME
202
OBTAIN, WITH SURGICAL NAVIGATION SYSTEM, LOW-RESOLUTION IMAGE OF TARGET TISSUE VOLUME
204
CO-REGISTER, IN SURGICAL NAVIGATION SYSTEM, HIGH-RESOLUTION IMAGE WITH LOW-RESOLUTION IMAGE TO IDENTIFY BOUNDARY COORDINATES OF TARGET TISSUE VOLUME
206
IDENTIFY, WITH SURGICAL NAVIGATION SYSTEM, LOCATION OF HISTOTRIPSY TRANSDUCER FOCUS
208
DETERMINE MOVEMENT COORDINATES REQUIRED TO PLACE HISTOTRIOPSY TRANSDUCER FOCUS WITHIN TARGET TISSUE VOLUME
210
APPLY HISTOTRIPSY THERAPY TO TARGET TISSUE VOLUME
212

FIG. 2

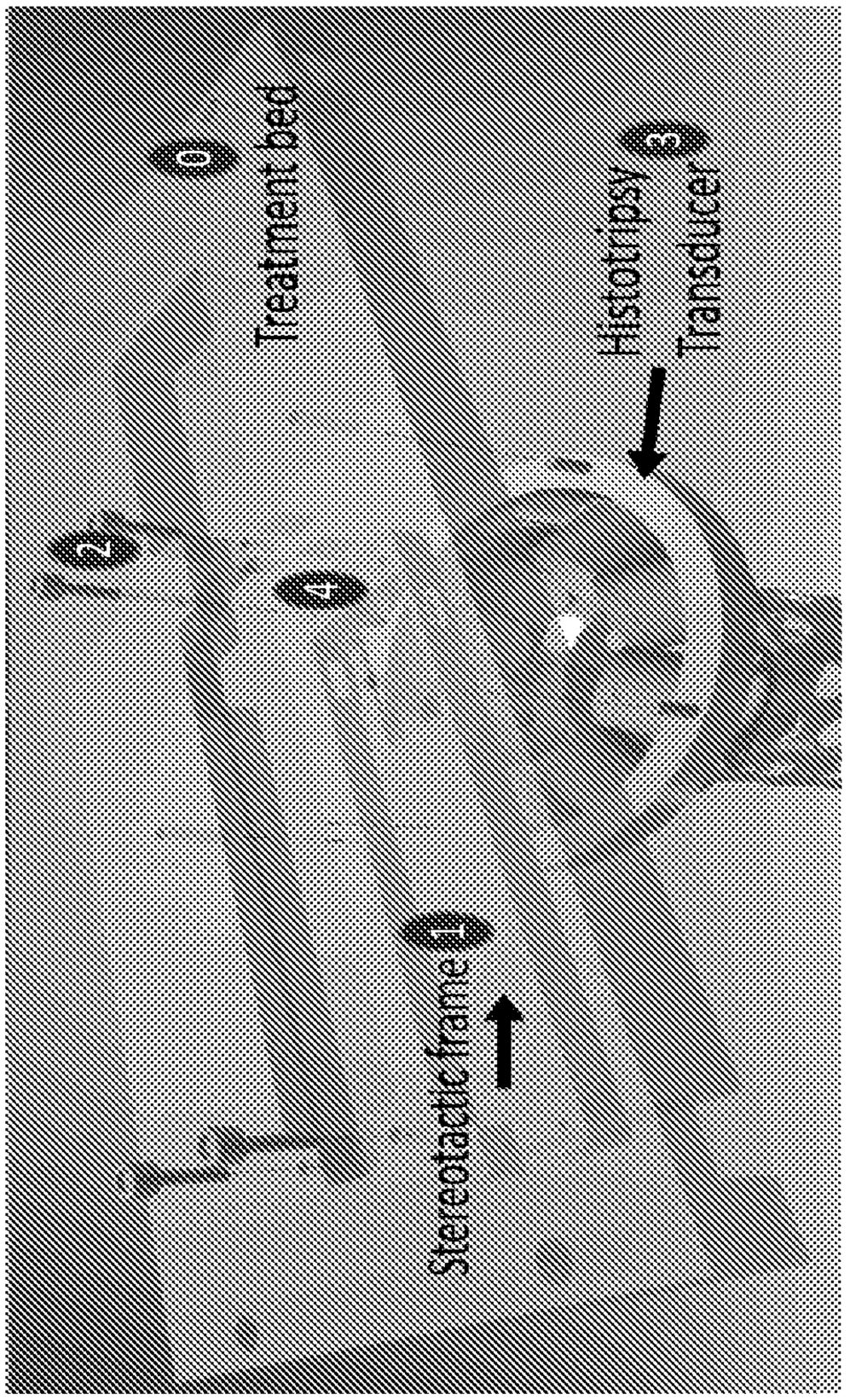

6
Treatment bed
Histotripsy
3
Transducer
2
4
7
Stereotactic frame
1

Fig. 3

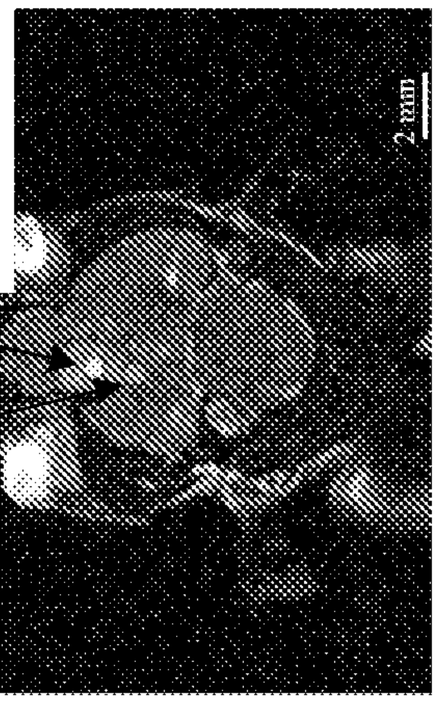


Fig. 4C

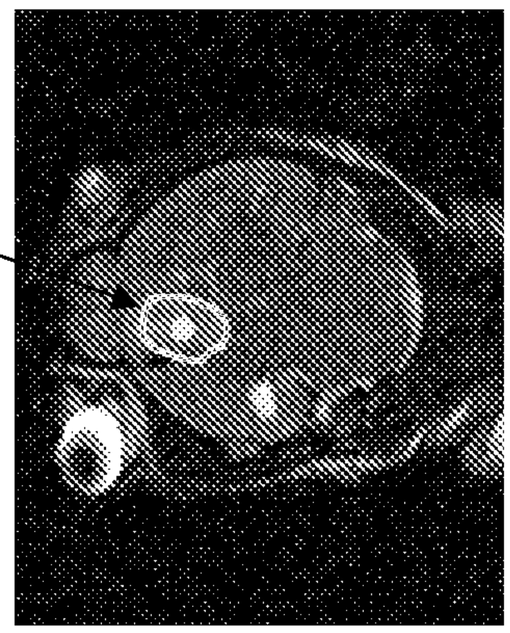


Fig. 4B



Fig. 4A

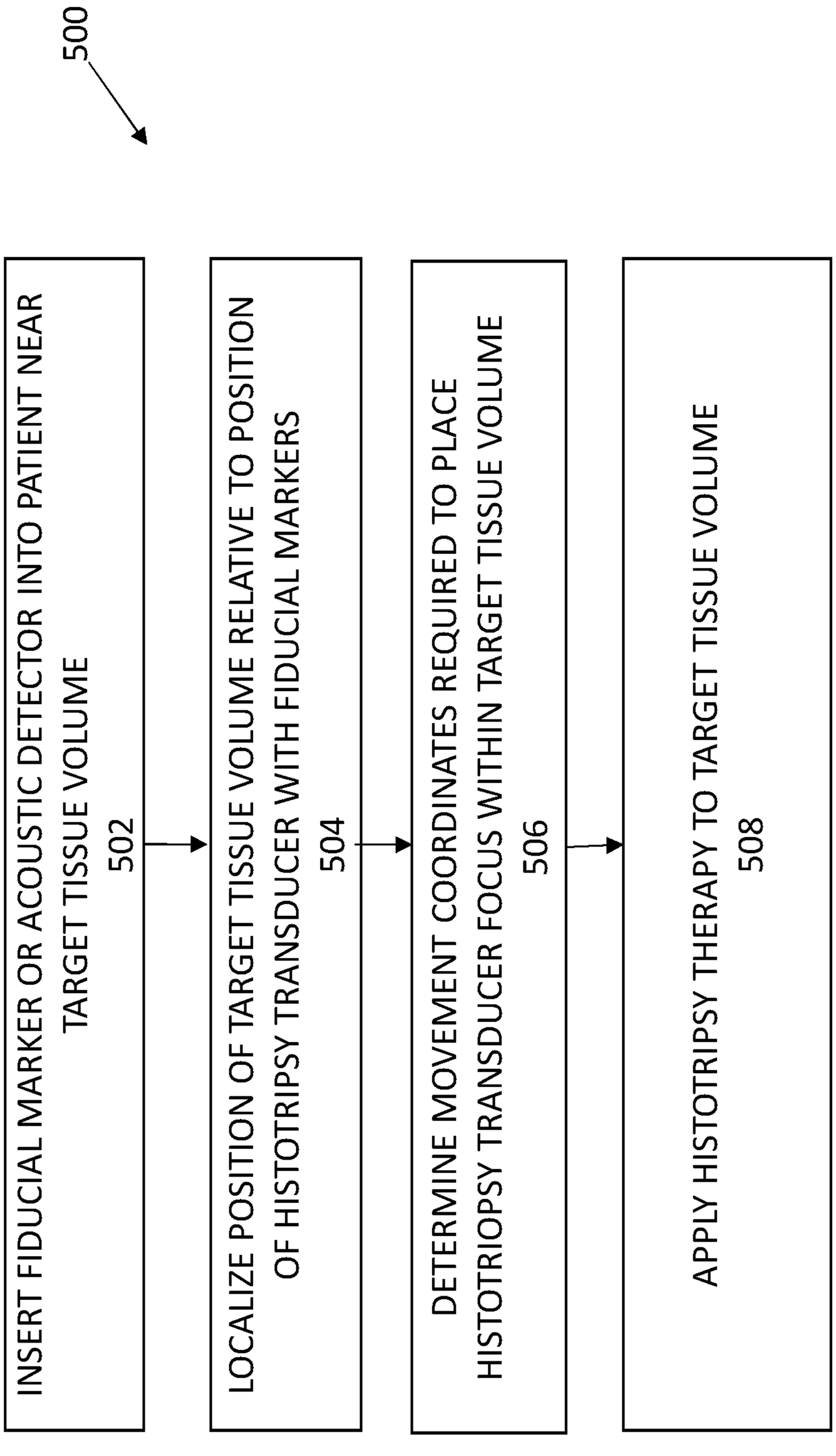

500
INSERT FIDUCIAL MARKER OR ACOUSTIC DETECTOR INTO PATIENT NEAR TARGET TISSUE VOLUME
502
LOCALIZE POSITION OF TARGET TISSUE VOLUME RELATIVE TO POSITION OF HISTOTRIPSY TRANSDUCER WITH FIDUCIAL MARKERS
504
DETERMINE MOVEMENT COORDINATES REQUIRED TO PLACE HISTOTRIOPSY TRANSDUCER FOCUS WITHIN TARGET TISSUE VOLUME
506
APPLY HISTOTRIPSY THERAPY TO TARGET TISSUE VOLUME
508

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/012455

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 8/08; A61B 8/00; A61B 8/13; A61B 8/14; A61B 34/20 (2021.01)

CPC - A61B 8/085; A61B 8/00; A61B 8/08; A61B 8/0833; A61B 8/13; A61B 8/14; A61B 8/5238; A61B 8/5261; A61B 34/20 (2021.02)

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)

see Search History document

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

see Search History document

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

see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0074076 A1 (KONA MEDICAL, INC.) 13 March 2014 (13.03.2014) entire document	1-19, 21, 22, 25-31
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Y		20, 23, 24
Y	US 2008/0033417 A1 (NIELDS et al) 07 February 2008 (07.02.2008) entire document	20
Y	US 2018/0154186 A1 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN) 07 June 2018 (07.06.2018) entire document	23, 24
A	US 2009/0177085 A1 (MAXWELL et al) 09 July 2009 (09.07.2009) entire document	1-31
A	US 2013/0102932 A1 (CAIN et al) 25 April 2013 (25.04.2013) entire document	1-31
A	US 2017/0049463 A1 (KONINKLIJKE PHILIPS N.V.) 23 February 2017 (23.02.2017) entire document	1-31

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

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"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
24 February 2021	MAR 18 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver Telephone No. PCT Helpdesk: 571-272-4300