

**HISTOTRIPSY SYSTEMS AND METHODS FOR MANAGING THERMAL DOSE
DELIVERED TO A SUBJECT****PRIORITY CLAIM**

- 5 **[0001]** This patent application claims priority to U.S. Provisional Patent Application No. 63/549,826, titled "HISTOTRIPSY SYSTEMS AND METHODS," and filed on February 5, 2024, which is herein incorporated by reference in its entirety.

INCORPORATION BY REFERENCE

- 10 **[0002]** 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

- 15 **[0003]** 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
20 treatment planning and control software to provide comprehensive treatment and therapy for soft tissues in a patient.

BACKGROUND

- 25 **[0004]** 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
30 acoustic energy in the form of high amplitude acoustic pulses with low duty cycle.

[0005] 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, high-intensity focused ultrasound (HIFU) cryo or radiation, Histotripsy relies on the mechanical action of cavitation for tissue destruction and not on heat, cold or ionizing energy.

[0006] Problematically, treating a target volume of tissue with a transducer or other device with devices in Histotripsy procedure necessitates cooling periods (i.e. periods of no treatment) to prevent damage and overheating of tissues, particularly with higher driving voltages being emitted from a transducer for treatment at locations having greater depths within a target treatment volume of tissue.

[0007] Thus, what is needed is a method for determining and implementing cooling periods for various portions of a target treatment volume of tissue given various depths and driving voltages.

SUMMARY OF THE DISCLOSURE

[0008] An ultrasound therapy method is provided, comprising the steps of receiving a digital treatment plan that includes a target tissue volume of a subject divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes, receiving a treatment depth of the target tissue volume, receiving at least one driving voltage required for an ultrasound transducer to produce cavitation in at least one of the plurality of treatment volumes, determining a desired thermal profile for additional cooling time periods to be implemented in the digital treatment plan based on the treatment depth and at least one driving voltage, adding cooling time periods to one or more of the plurality of treatment volumes of the digital treatment plan according to the desired thermal profile, the cooling time periods varying as the treatment progresses through the plurality of treatment volumes, and commencing ultrasound treatment in the subject according to the digital treatment plan.

[0009] In some aspects, the cooling time periods increase as the treatment progresses through the plurality of treatment volumes.

[0010] In one aspect, the cooling time periods are between treatment pulses, wherein the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.

[0011] In other aspects, the treatment pathway starts at a distal-most region of the target tissue volume relative to a transducer configured to carry out the ultrasound treatment and moves towards a proximal-most region of the target tissue volume relative to the transducer.

[0012] In some aspects, the cooling time periods are off periods where no therapy is delivered.

[0013] In one aspect, the treatment depth is received via a user input.

5 [0014] In other aspects, the treatment depth is automatically determined based on patient imaging.

[0015] In some aspects, the driving voltage is determined based on a plurality of test pulses.

[0016] In one aspect, a total cooling time for the target tissue volume is based on the product of a cooling coefficient and a total number of the plurality of treatment volumes, wherein a cooling time period for each of the plurality of treatment volumes is based on a product of the cooling coefficient and a cooling weight for each treatment point.

[0017] In another aspect, a last one of the plurality of treatment volumes to be treated is excluded from cooling.

15 [0018] In one aspect, the ultrasound treatment progresses in a pattern based on one or more of: a sequence of points, a linear sequence, and a uniform distribution.

[0019] In other aspects, the plurality of treatment volumes are grouped and treated by size.

[0020] In another aspect, the desired thermal profile includes a range from a minimum cooling time to a maximum cooling time, wherein a number of segments in the treatment pathway is adjusted based on one or more of the minimum cooling time and maximum cooling time, wherein cooling time periods for the plurality of treatment volumes falling above the maximum cooling times or below the minimum cooling times are iteratively distributed across the plurality of treatment volumes to bring the cooling time period for each one of the plurality of treatment volumes within the range.

25 [0021] In one aspect, the plurality of treatment volumes having cooling time periods within the range are designated as free points to receive further cooling up to the maximum cooling time period, wherein the cooling time periods for treatment points falling above the maximum cooling times are iteratively distributed among the free points until no free points remain, wherein any cooling excess remaining after all free points have reached the maximum cooling time is added to the cooling time period for a last one of the plurality of treatment volumes to be treated.

[0022] In additional aspects, the cooling time periods increase linearly.

[0023] In some aspects, the cooling time periods increase exponentially.

[0024] In additional aspects, the cooling time periods increase in a stepwise manner.

[0025] In yet another aspect, the cooling time periods have a first value in a first region of the target tissue volume and a second value in a second region of the target tissue volume.

[0026] In one aspect, the second value is larger than the first value.

[0027] In other aspects, the first region is further from the ultrasound transducer than the
5 second region.

[0028] An ultrasound therapy system is provided, comprising; a robotic positioning system; an ultrasound therapy transducer array connected to the robotic positioning system; a generator operatively coupled to the ultrasound therapy transducer array, the generator and ultrasound therapy transducer array being configured to deliver histotripsy pulses into a
10 subject to generate a cavitation bubble cloud in the subject; and at least one processor operatively coupled to the robotic positioning system and the generator, the at least one processor being configured to: receive a digital treatment plan that includes a target tissue volume of a subject divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes; receive a treatment depth of the target tissue
15 volume; receiving at least one driving voltage required for an ultrasound transducer to produce cavitation in at least one of the plurality of treatment volumes; determine a desired thermal profile for additional cooling time periods to be implemented in the digital treatment plan based on the treatment depth and the at least one driving voltage; modify the digital treatment plan by adding cooling time periods to one or more of the plurality of treatment
20 volumes of the digital treatment plan according to the desired thermal profile, the cooling time periods varying as the treatment progresses through the plurality of treatment volumes; and control the robotic positioning system and the generator to provide histotripsy therapy to the subject according to the digital treatment plan that includes the cooling time periods.

[0029] In one aspect, the cooling time periods increase as the treatment progresses
25 through the plurality of treatment volumes.

[0030] In another aspect, the system further comprises a user input device configured for inputting the treatment depth.

[0031] In some aspects, the cooling time periods are between treatment pulses, wherein the cooling time periods are non-uniformly distributed throughout the volume of tissue to be
30 treated.

[0032] In another aspect, the treatment pathway starts at a distal-most region of the target tissue volume relative to the ultrasound therapy transducer array and moves towards a proximal-most region of the target tissue volume relative to the ultrasound therapy transducer array.

[0033] In some aspects, the cooling time periods are off periods where no ultrasound therapy is delivered.

[0034] In other aspects, the treatment depth is automatically determined based on patient imaging.

5 [0035] In one aspect, the driving voltage is determined based on a plurality of test pulses.

[0036] An ultrasound planning method is provided, comprising: dividing a target tissue volume of a subject into a plurality of treatment volumes; determining a treatment pathway to navigate through the plurality of treatment volumes; determining a treatment voltage for each of the plurality of treatment volumes to induce cavitation; determining cooling time periods
10 for one or more of the plurality of treatment volumes according to a desired thermal profile, the cooling time periods varying along the treatment pathway through the plurality of treatment volumes; and generating a digital treatment plan that includes the plurality of treatment volumes, the treatment pathway, the treatment voltage for each of the plurality of treatment volumes, and the cooling periods to be applied to the one or more treatment
15 volumes; and initiating ultrasound therapy of the target tissue volume with an ultrasound therapy system according to the digital treatment plan.

[0037] In one aspect, the cooling time periods increase as the treatment progresses through the plurality of treatment volumes.

[0038] In other aspects, the cooling time periods are between treatment pulses, wherein
20 the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.

[0039] In one aspect, the treatment pathway starts at a distal-most region of the target tissue volume relative to the ultrasound therapy transducer array and moves towards a proximal-most region of the target tissue volume relative to the ultrasound therapy transducer
25 array.

[0040] In some aspects, the cooling time periods are off periods where no ultrasound therapy is delivered.

[0041] A computer implemented ultrasound treatment planning system is provided, comprising: a processor; and a memory to store instructions, wherein executing the
30 instructions is configured to generate a treatment plan with cooling time, wherein the instructions include: dividing a target tissue volume of a subject into a plurality of treatment volumes, determining locations for a plurality of treatment points within the plurality of treatment volumes, determining a treatment pathway to navigate through the plurality of treatment volumes, and adding cooling time periods for the plurality of treatment points

according to a desired thermal profile, wherein the cooling periods vary along the treatment pathway through the plurality of treatment volumes.

5 [0042] In some aspects, the system receives one or more of: (i) a treatment depth of the target tissue volume, and (ii) a driving voltage required for the ultrasound transducer to produce cavitation in at least one location within the target tissue volume.

[0043] In another aspect, the cooling time periods are configured to be between treatment pulses, wherein the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.

10 [0044] In some aspects, the treatment pathway starts at a distal-most region of the target tissue volume relative to an ultrasound therapy transducer array and moves towards a proximal-most region of the target tissue volume relative to the ultrasound therapy transducer array.

[0045] In other aspects, the cooling time periods are off periods where no ultrasound therapy is delivered.

15 [0046] In one aspect, the treatment depth is received via a user input.

[0047] In additional aspects, the treatment depth is automatically determined based on patient imaging.

[0048] In one aspect, the driving voltage is determined based on a plurality of test pulses.

20 [0049] A method for delivering ultrasound therapy to a subject with an ultrasound transducer array is provided, comprising the steps of: receiving a digital treatment plan that includes a target tissue volume of a subject divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes; dividing the target tissue volume into a first cooling region and a second cooling region, the second cooling region being positioned closer to the ultrasound transducer array than the first cooling region;
25 determining first cooling time periods to add to one or more of the plurality of treatment volumes in the first cooling region in the digital treatment plan according to a desired thermal profile; determining second cooling time periods to add to one or more of the plurality of treatment volumes in the second cooling region in the digital treatment plan according to the desired thermal profile; and commencing ultrasound treatment in the target tissue volume
30 with the ultrasound transducer array according to the digital treatment plan.

[0050] An ultrasound therapy system is provided, comprising; a robotic positioning system; an ultrasound therapy transducer array connected to the robotic positioning system; a generator operatively coupled to the ultrasound therapy transducer array, the generator and ultrasound therapy transducer array being configured to deliver histotripsy pulses into a

subject to generate a cavitation bubble cloud in the subject; and at least one processor operatively coupled to the robotic positioning system and the generator, the at least one processor being configured to: receive a digital treatment plan that includes a target tissue volume of a subject divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes; divide the target tissue volume into a first cooling region and a second cooling region, the second cooling region being positioned closer to the ultrasound transducer array than the first cooling region; determine first cooling time periods to add to one or more of the plurality of treatment volumes in the first cooling region in the digital treatment plan according to a desired thermal profile; determine second cooling time periods to add to one or more of the plurality of treatment volumes in the second cooling region in the digital treatment plan according to the desired thermal profile; and control the robotic positioning system and the generator to provide histotripsy therapy to the subject according to the digital treatment plan that includes the first and second cooling time periods.

15 BRIEF DESCRIPTION OF THE DRAWINGS

- [0051] 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:
- [0052] FIGS. 1A-1B illustrate an ultrasound imaging and therapy system.
- [0053] FIG. 2 is one embodiment of a histotripsy therapy and imaging system with a coupling system.
- [0054] FIG. 3 is one example of an ultrasound pulse for generating histotripsy via a shock scattering mechanism.
- [0055] FIGS. 4A-4B depict formulas for cooling weights w and normalized cooling weight w'_i for an index i along the treatment path, respectively.
- [0056] FIGS. 5A-5B illustrate depictions of cooling magnitudes along a cooling treatment pathway for a target treatment volume.
- [0057] FIG. 6A is a graph illustrating a distribution of treatment points vs. cooling times.
- [0058] FIG. 6B is a graph illustrating segmentation of treatment points vs. cooling times.
- [0059] FIG. 6C is a graph illustrating final cooling times for a treatment volume of tissue.
- [0060] FIG. 7 is a graph illustrating an example lookup table at a focus of a transducer.
- [0061] FIGS. 8A-8B illustrate an ultrasound therapy method.

[0062] FIG. 9 is an ultrasound planning method.

DETAILED DESCRIPTION

[0063] The system, methods and devices of the disclosure may be used for open surgical, minimally invasive surgical (laparoscopic and percutaneous), robotic surgical (integrated into a robotically-enabled medical system), endoscopic or completely transdermal extracorporeal non-invasive acoustic cavitation for the treatment of healthy, diseased and/or injured tissue including but not limited to tissue destruction, cutting, skeletonizing and ablation. Furthermore, due to tissue selective properties, histotripsy may be used to create a cytoskeleton that allows for subsequent tissue regeneration either de novo or through the application of stem cells and other adjuvants. Finally, histotripsy can be used to cause the release of delivered agents such as chemotherapy and immunotherapy by locally causing the release of these agents by the application of acoustic energy to the targets. 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.

[0064] 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.

[0065] 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. The system also allows for multiple imaging transducers to be located within the therapy transducer to provide multiple views of the target tissue simultaneously and to integrate these images into a single 3-D image.

[0066] 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

5 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

10 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.

[0067] As described herein, the histotripsy system may include integrated imaging.

15 However, in other embodiments, the histotripsy system can be configured to interface with separate imaging systems, such as C-arm, fluoroscope, cone beam CT, MRI, etc., to provide real-time imaging during histotripsy therapy. In some embodiments, the histotripsy system can be sized and configured to fit within a C-arm, fluoroscope, cone beam CT, MRI, etc.

HISTOTRIPSY

20 [0068] 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

25 ablation, including thermal and radiation-based modalities, histotripsy does not rely on heat cold 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.

[0069] Histotripsy can be applied in various forms, including:

30 [0070] 1) Intrinsic-Threshold Histotripsy: Delivers pulses typically 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),

[0071] 2) Shock-Scattering Histotripsy: Delivers typically pulses 1-20 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

[0072] 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.

[0073] 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.

[0074] 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). The application of histotripsy is not limited to a transdermal approach but can be applied through any means that allows contact of the transducer with tissue including open surgical laparoscopic surgical, percutaneous and robotically mediated surgical procedures. 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.

[0075] 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”.

[0076] 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.

[0077] 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”.

[0078] 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.

[0079] 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.”

[0080] 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., pre-focal 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.

CART

[0081] 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 for open surgical or laparoscopic surgical and endoscopic application, 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.).

[0082] 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, 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) and to provide access to and display of patient medical data including but not limited to laboratory and historical medical record data.

[0083] 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.

[0084] 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).

[0085] 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.

THERAPY COMPONENTS

[0086] 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.

[0087] 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.

[0088] 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 piezoelectric 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.

[0089] 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.

[0090] 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.

- 5 **[0091]** 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
10 voltage supply, and/or other service, diagnostic or treatment features.

- [0092]** 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
15 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.

- 20 **[0093]** 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
25 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.

- [0094]** Therapy transducer element(s) are excited with an electrical waveform with an
30 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.

[0095] FIG. 2 illustrates one embodiment of a histotripsy therapy and imaging system 200, including a coupling assembly 201. As described above, a histotripsy therapy and imaging system can include a therapy transducer 202, an imaging system, a robotic positioning arm 208, a fluidics cart 209, and a therapy cart 210.

5 [0096] The therapy and/or imaging transducers can be housed in a coupling assembly 201 which can further include a coupling membrane 214 and a membrane constraint 216 configured to prevent the membrane from expanding too far from the transducer. The coupling membrane can be filled with an acoustic coupling medium such as a fluid or a gel. The membrane constraint can be, for example, a semi-rigid or rigid material configured to
10 restrict expansion/movement of the membrane. In some embodiments, the membrane constraint is not used, and the elasticity and tensile strength of the membrane prevent over expansion. The coupling membrane can be a mineral-oil infused SEBS membrane to prevent direct fluid contact with the patient's skin. In the illustrated embodiment, the coupling assembly 201 is supported by a mechanical support arm 218 which can be load bearing in the
15 x-y plane but allow for manual or automated z-axis adjustment. The mechanical support arm can be attached to the floor, the patient table, or the fluidics cart 209. The mechanical support is designed and configured to conform and hold the coupling membrane 214 in place against the patient's skin while still allowing movement of the therapy/imaging transducer relative to the patient and also relative to the coupling membrane 214 with the robotic
20 positioning arm 208.

[0097] The fluidics cart 409 can include additional features, including a fluid tank 420, a cooling and degassing system, and a programmable control system. The fluidics cart is configured for external loading of the coupling membrane with automated control of fluidic sequences.

25 **MECHANICAL SUPPORT ARMS AND ARM ARCHITECTURES**

[0098] In order to support the acoustic and patient coupling system, including providing efficient and ergonomic work-flows for users, various designs and configurations of mechanical support arms (and arm architectures) may be employed. Support arms may be configured with a range of degrees of freedom, including but not limited to allowing, x, y, z,
30 pitch, roll and yaw, as well additional interfacing features that may allow additional height adjustment or translation.

[0099] Arms may comprise a varied number and type of joints and segments. Typically, arms may comprise a minimum of 2 segments. In some configurations, arms may comprise 3 to 5 segments.

[0100] Arms are also be configured to interface proximally to a main support base or base interface (e.g., robot, table, table/bed rail, cart, floor mount, etc.) and distally to the frame/assembly and overall “UMC” or “coupling solution”. This specific distal interface may further include features for controlling position/orientation of the frame/assembly, at the
5 frame/assembly interface.

[0101] For example, in some embodiments, the arm/frame interface may comprise a ball joint wrist. In another example, the interface may include use of a gimbal wrist or an adjustable pitch and roll controlled wrist. These interfaces may be further employed with specific user interfaces and inputs, to assist with interacting with the various wrists, of which
10 may include additional handles or knobs (as an unlimited example), to further enable positioning the UMC/coupling solution. For example, a gimbal wrist may benefit from allowing the frame/assembly to have 3 degrees of freedom (independent of the arm degrees of freedom), including pitch, roll and yaw adjustments.

[0102] Support arms, configured with arm wrists, further interfaced with
15 frames/assemblies, may comprise features such as brakes, including cable or electronic actuated brakes, and quick releases, which may interact with one or more axis, individually, or in groupings. They may also include electronic lift systems and base supports. In some embodiments, these lift systems/base supports are co-located with robot arm bases, wherein said robot arm is equipped with the histotripsy therapy transducer configured to fit/work
20 within the enclosed coupling solution. In other embodiments, the support arm is located on a separate cart. In some cases, the separate cart may comprise a fluidics system or user console. In other embodiments, it is interfaced to a bed/table, including but not limited to a rail, side surface, and/or bed/table base. In other examples/embodiments, it's interfaced to a floor-based structure/footing, capable of managing weight and tipping requirements.

25 MEMBRANES / BARRIER FILMS AND RELATED ARCHITECTURES

[0103] Membranes and barrier films may be composed of various biocompatible materials which allow conformal coupling to patient anatomy with minimal or no entrapped bubbles capable of interfering with ultrasound imaging and histotripsy therapy, and that are capable of providing a sealed barrier layer between said patient anatomy and the ultrasound
30 medium, of which is contained within the work-space provided by the frame and assembly.

[0104] Membrane and barrier film materials may comprise flexible and elastomeric biocompatible materials/polymers, such as various thermoplastic and thermoset materials, as well as permanent or bioresorbable polymers. Additionally, the frame of the UMC can also

comprise the same materials. In some examples, the membrane may be rigid or semi-rigid polymers which are pre-shaped or flat.

ULTRASOUND MEDIUM

[0105] As previously described, the ultrasound medium may comprise any applicable medium capable of providing sufficient and useful acoustic coupling to allow histotripsy treatments and enable sufficient clinical imaging (e.g., ultrasound). Ultrasound mediums, as a part of this disclosure and system, may comprise, but are not limited to, various aqueous solutions/mediums, including mixtures with other co-soluble fluids, of which may have preferred or more preferred acoustic qualities, including ability to match speed of sound, etc. Example mediums may comprise degassed water and/or mixtures/co-solutions of degassed water and various alcohols, such as ethanol.

FLUIDICS SYSTEMS, CONTROL SYSTEMS AND SYSTEM ARCHITECTURES

[0106] As a part of overall fluidics management, histotripsy systems including acoustic/patient coupling systems, may be configured to include an automated fluidics system, which primarily is responsible for providing a reservoir for preparation and use of coupling medium, where preparation may include the ability to degas, chill, monitor, adjust, dispense/fill, and retrieve/drain coupling medium to/from the frame/assembly. The fluidics system may include an emergency high flow rate system for rapid draining of the coupling medium from the UMC. In some embodiments, the fluidics system can be configured for a single use of the coupling medium, or alternatively, for re-use of the medium. In some embodiments, the fluidics system can implement positive air pressure or vacuum to carry out leak tests of the UMC and membrane prior to filling with a coupling medium. Vacuum assist can also be used for removal of air from the UMC during the filling process. The fluidics system can further include filters configured to prevent particulate contamination from reaching the UMC.

[0107] The fluidics system may implemented in the form of a mobile fluidics cart. The cart may comprise an input tank, drain tank, degassing module, fill pump, drain pump, inert gas tank, air compressor, tubing/connectors/lines, electronic and manual controls systems and input devices, power supplies and one or more batteries. The cart in some cases may also comprise a system check vessel/reservoir for evaluating histotripsy system performance and related system diagnostics (configured to accommodate a required water volume and work-space for a therapy transducer).

[0108] FIG. 3 illustrates an ultrasound pulse that can be used for shock scattering histotripsy. As shown the ultrasound pulse can include a leading negative half cycle, a peak

positive half cycle, a peak negative half cycle, and a trailing peak positive half cycle (with the pulse traveling from right to left on the page). As shown, the trailing peak positive cycle has a lower amplitude than the peak positive cycle. 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 if the amplitude of those cycles is sufficient, 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.

[0109] When the amplitude(s) of positive half cycle(s) of each pulse are limited, 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”.

[0110] 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.

[0111] According to certain embodiments, threshold reduction in Histotripsy therapy may be defined as a pressure amplitude required to initiate a bubble cloud being reduced. Because thermal deposition is a function of the amplitude of the pressure wave traversing the tissue path, a reduction in the pressure required to generate a bubble cloud manifests in a reduction in thermal deposition at higher PRFs, providing a net thermal benefit.

[0112] 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.”

[0113] 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.

THERAPY COMPONENTS

[0114] 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.

[0115] 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.

[0116] The therapy transducer can comprise a single element or multiple elements configured to be excited with high amplitude electric pulses ($>1000\text{V}$ 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.

[0117] 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.

[0118] 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.

- 5 **[0119]** 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
10 voltage supply, and/or other service, diagnostic or treatment features.

- [0120]** 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
15 various combinations. Other systems may include other acoustic cavitation/histotripsy, HIFU, HITU, radiation therapy, radiofrequency, microwave, and cryoablation systems, navigation and localization systems, open surgical, 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.

- 20 **[0121]** 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
25 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.

- [0122]** Therapy transducer element(s) are excited with an electrical waveform with an
30 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.

[0123] The Therapy sub-system may also comprise therapy transducers of various designs and working parameters, supporting use in various procedures (and procedure settings). Systems may be configured with one or more therapy transducers, that may be further interchangeable, and work with various aspects of the system in similar or different ways (e.g., may interface to a robotic arm using a common interface and exchange feature, or conversely, may adapt to work differently with application specific imaging probes, where different imaging probes may interface and integrate with a therapy transducer in specifically different ways).

[0124] Therapy transducers may be configured of various parameters that may include size, shape (e.g., rectangular or round; anatomically curved housings, etc.), geometry, focal length, number of elements, size of elements, distribution of elements (e.g., number of rings, size of rings for annular patterned transducers), frequency, enabling electronic beam steering, etc. Transducers may be composed of various materials (e.g., piezoelectric, silicon, etc.), form factors and types (e.g., machined elements, chip-based, etc.) and/or by various methods of fabrication of.

[0125] Transducers may be designed and optimized for clinical applications (e.g., abdominal tumors, peripheral vascular disease, fat ablation, etc.) and desired outcomes (e.g., acoustic cavitation/histotripsy without thermal injury to intervening tissue), and affording a breadth of working ranges, including relatively shallow and superficial targets (e.g., thyroid or breast nodules), versus, deeper or harder to reach targets, such as central liver or brain tumors. They may be configured to enable acoustic cavitation/histotripsy under various parameters and sets of, as enabled by the aforementioned system components (e.g., function generator and amplifier, etc.), including but not limited to frequency, pulse repetition rate, pulses, number of pulses, pulse length, pulse period, delays, repetitions, sync delays, sync period, sync pulses, sync pulse delays, various loop sets, others, and permutations of. The transducer may also be designed to allow for the activation of a drug payload either deposited in tissue through various means including injection, placement or delivery in micelle or nanostructures.

INTEGRATED IMAGING

[0126] 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

5 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

10 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.

15 **[0127]** 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

20 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

25 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

30 positioning component may be determined.

[0128] 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).

5 [0129] 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).

10 [0130] 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
15 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
20 associated system parameters) to optimize the drug delivery and/or tissue erosion process.

[0131] In some embodiments, imaging including feedback and monitoring from backscatter, and speckle reduction, may be configured in the system.

[0132] For systems comprising feedback and monitoring via backscattering, and as means of background, as tissue is progressively mechanically subdivided, in other words
25 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
30 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.

5 [0133] 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 10 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 15 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. 20

[0134] 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 25 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 30 other quantitative means.

[0135] 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.

- 5 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
- 10 modality to enhance feedback and monitoring of the acoustic cavitation/histotripsy procedure.

- [0136] 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
- 15 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
- 20 efficacy, enables monitoring of the progress of therapy, and may be configured as a feature of the system.

- [0137] 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.
- 25 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
- 30 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.

[0138] 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.

[0139] 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).

[0140] 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).

[0141] 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.

ROBOTICS

[0142] The 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.

[0143] 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
5 robotic arm and other listed sub-systems are controlled by the user through the form factor of a single bedside Cart.

[0144] 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
10 a distance from said Cart.

[0145] 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
15 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 U.S. Patent Pub. No. 2013/0255426 to Kassow et al. which is disclosed herein by reference in its entirety.

[0146] The robotic arm receives control signals and commands from the robotic control
20 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.

[0147] Position may be configured to comprise fixed positions, pallet positions, time-controlled positions, distance-controlled positions, variable-time controlled positions,
25 variable-distance controlled positions.

[0148] Tracking may be configured to comprise time-controlled tracking and/or distance-controlled tracking.

[0149] 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.

30 [0150] 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.

[0151] 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.

- 5 **[0152]** 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
10 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,
15 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.

- [0153]** 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
20 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
25 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
30 transducer/coupling solution as a later/terminal set up step.

[0154] 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.

SOFTWARE

[0155] 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.

[0156] 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.).

[0157] 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.

[0158] 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.

[0159] 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).

[0160] 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
5 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
10 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.

[0161] Software may also be configured, by working with computer processors and one or more function generators, amplifiers and therapy transducers, to allow various
15 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
20 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
25 (e.g., dynamically adjusting amplitude across the treatment area/volume).

OTHER COMPONENTS, ANCILLARIES AND ACCESSORIES

[0162] 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
30 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.

SYSTEM VARIATIONS AND METHODS / APPLICATIONS

5 [0163] 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
10 plan.

[0164] Feedback may include various energy, power, location, position, tissue and/or other parameters.

[0165] 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
15 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.

20 [0166] 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. The disclosure also considers the application of histotripsy as a means to activate previously delivered in active drug payloads
25 whose activity is inert due to protection in a micelle, nanostructure or similar protective structure or through molecular arrangement that allows activation only when struck with acoustic energy.

[0167] 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
30 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.

[0168] 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).

[0169] 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.).

[0170] 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 pulmonary and/or neurocranial-related spaces, cosmetics/aesthetics, metabolic (e.g., type 2 diabetes), plastic and reconstructive, ocular and ophthalmology, orthopedic, gynecology and men’s health, and other systems, devices and methods of treating diseased, injured, undesired, or healthy tissues, organs or cells.

[0171] 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 pre-focal tissue heating delivered to patients.

USE ENVIRONMENTS

[0172] 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), aero and marine

- 5 transportation vehicles such as planes and ships, 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
- 10 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.

COUPLING

- [0173] 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
- 15 acoustic access for ultrasound visualization and acoustic cavitation/histotripsy (e.g., provide acoustic window and medium between the transducer(s) and patient, and support of). These may include different form factors of such, including open and enclosed device 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,
- 20 volume, composition, etc.). Such dynamic control components may be directly integrated to the system (within the Cart), or may be in temporary/intermittent or continuous communication with the system, but externally situated in a separate device and/or cart.

- [0174] The Coupling sub-system typically comprises, at a minimum, coupling medium (e.g., degassed water or water solutions), a reservoir/container to contain said coupling
- 25 medium, and a support structure (including interfaces to other surfaces or devices). 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 its intended use/application.

- 30 [0175] The reservoir or medium container may be formed and shaped to various sizes and shapes, and to adapt/conform to the patient, allow the therapy transducer to engage/access 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. As a representative example, this may include a support frame. The container may be of various shapes, sizes, curvatures, and dimensions, and may be comprised of a variety of materials compositions (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, of which may be used to conform to the patient and assist in confining/containing the medium within the container. It may further contain various sensors (e.g., volume/fill level), drains (e.g., inlet/outlet), lighting (e.g., LEDs), markings (e.g., fill lines, set up orientations, etc.), text (e.g., labeling), etc.

[0176] 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 treatment head/therapy transducer) as an interface to the patient, that further provides a barrier to the medium (e.g., water) between the patient and therapy transducer). In other embodiments, the membrane and/or film may comprise an opening, the patient contacting edge of which affords a fluid/mechanical seal to the patient, but in contrast allows medium communication directly with the patient (e.g., direct degassed 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).

[0177] 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. The membrane form factor can be flat or pre-shaped prior to use. In other embodiments, the membrane could be inelastic (i.e., a convex shape) and pressed against the patient's skin to acoustically couple the transducer to the tissue. Systems and methods are further disclosed to control the level of contaminants (e.g., particulates, etc.) on the membrane to maintain the proper level of ultrasound coupling. Too many particulates or contaminants can cause scattering of the ultrasound waves. This can be

achieved with removable films or coatings on the outer surfaces of the membrane to protect against contamination.

[0178] Said materials may be formed into useful membranes through molding, casting, spraying, ultrasonic spraying, extruding, and/or any other processing methodology that produces useful embodiments. They may be single use or reusable/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 or over molded frame to provide mechanical stability to the membrane during handling including assembly, set up and take down 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, additives, plasticizers, etc.), including optimizing specifically to maximize acoustic transmission properties, including minimizing impact to cavitation initiation threshold values, and/or ultrasound imaging artifacts, including but not limited to membrane reflections, as representative examples.

[0179] Open reservoirs or medium containers may comprise various methods of filling, including using pre-prepared medium or water, that may be delivered into the containers, in some cases to a defined specification of water (level of temperature, 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.). These features may be further configured into or to interface to other devices, including for example, a fluidics system. In some cases, the fluidics system may be an in-house medium preparation system in a hospital or care setting room, or conversely, a mobile cart-based system which can prepare and transport medium to and from the cart to the medium container, etc.

[0180] 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 and to allow for changes in the focal length to the target area without moving the transducer. 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, pumping, filtering and control systems, etc. The reservoir may also be configured to receive signals that cause it to
5 deform or change shape in a specific and controlled manner to allow the target point to be adjusted without moving the transducer.

[0181] 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, floor, etc.). In some embodiments, the support system comprises a mechanical arm with 3 or
10 more degrees of freedom. Said arm may have a proximal 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 distal locations of the reservoir or container. The arm may also 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
15 supporting and providing the disclosed support structure.

[0182] 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
20 to actuate/control the robotic arm (e.g., positioning into/within coupling medium) and/or Coupling solution features (e.g., filling, draining, etc.). In some examples, the support structure robotic arm positional encoders may be used to coordinate the manipulation of the second arm (e.g. comprising the therapy transducer/treatment head), such as to position the therapy transducer to a desired/known location and pose within the coupling support
25 structure.

[0183] Overall, significant unmet needs exist in interventional and surgical medical procedures today, including those procedures utilizing minimally invasive devices and approaches to treat disease and/or injury, and across various types of procedures where the unmet needs may be solved with entirely new medical procedures. Today's medical system
30 capabilities are often limited by access, wherein a less or non-invasive approach would be preferred, or wherein today's tools aren't capable to deliver preferred/required tissue effects (e.g., operate around/through critical structures without serious injury), or where the physical set up of the systems makes certain procedure approaches less desirable or not possible, and

where a combination of approaches, along with enhanced tissue effecting treatments, may enable entirely new procedures and approaches, not possible today.

[0184] In addition, specific needs exist for enabling histotripsy delivery, including robotic histotripsy delivery, wherein one or more histotripsy therapy transducers may be configured to acoustically couple to a patient, using a completely sealed approach (e.g., no acoustic medium communication with the patient's skin) and allowing the one or more histotripsy transducers to be moved within the coupling solution without impeding the motion/movement of the robotic arm or interfering/disturbing the coupling interface, which could affect the intended treatment and/or target location.

[0185] Disclosed herein are histotripsy acoustic and patient coupling systems and methods, to enable histotripsy therapy/treatment, as envisioned in any setting, from interventional suite, operating room, hybrid suites, imaging centers, medical centers, office settings, mobile treatment centers, and/or others, as non-limiting examples. The following disclosure further describes novel systems used to create, control, maintain, modify/enhance, monitor and setup/takedown acoustic and patient coupling systems, in a variety of approaches, methods, environments, architectures and work-flows. In general, the disclosed novel systems may allow for a coupling medium, in some examples degassed water, to be interfaced between a histotripsy therapy transducer and a patient, wherein the acoustic medium provides sufficient acoustic coupling to said patient, allowing the delivery of histotripsy pulses through a user desired treatment location (and volume), where the delivery may require physically moving the histotripsy therapy transducer within a defined work-space comprising the coupling medium, and also where the coupling system is configured to allow said movement of the therapy transducer (and positioning system, e.g., robot) freely and unencumbered from by the coupling support system (e.g., a frame or manifold holding the coupling medium).

COUPLING SYSTEM AND SUB-SYSTEMS / COMPONENTS

[0186] The disclosed histotripsy acoustic and patient coupling systems, in general, may comprise one or more of the following sub-systems and components, an example of which is depicted in FIG. 2, including but not limited to 1) a membrane/barrier film to provide an enclosed, sealed and conformal patient coupling and histotripsy system interface, 2) a frame and assembly to retain the membrane and provide sufficient work and head space for a histotripsy therapy transducers required range of motion (x, y and z, pitch, roll and yaw), 3) a sufficient volume of ultrasound medium to afford acoustic coupling and interfaces to a histotripsy therapy transducer and robotic arm, 4) one or more mechanical support arms to

allow placement, positioning and load support of the frame, assembly and medium and 5) a fluidics system to prepare, provide and remove ultrasound medium(s) from the frame and assembly.

[0187] In some embodiments, the coupling system may be fully sealed, and in other 5 embodiments and configurations, it may be partially open to afford immediate access (physical and/or visual).

[0188] The acoustic and patient coupling systems and sub-systems may further comprise various features and functionality, and associated work-flows, and may also be configured in a variety of ways to enable histotripsy procedures as detailed below.

10 Treatment Pulse Sequences and Thermal Management

[0189] A given Histotripsy therapy or treatment session can be defined in terms of a set number of pulses N that are to be delivered to a target tissue volume over a set total treatment time T. The number of pulses delivered every second by the systems described herein is defined by the pulse repetition frequency (PRF) of the system, which can be adjusted during 15 therapy depending on the cavitation threshold, the tissue type, depth, etc. Thus, the total number of pulses N delivered over the total treatment time T (in seconds) is equal to the total treatment time T multiplied by the PRF of the system. For example, a system operating at a constant 200 Hz PRF for a total treatment time of 10 minutes (600 seconds) will have a total number of pulses N equal to 120,000. The systems and methods described herein can include 20 PRFs of 400 Hz or greater to generate acoustic cavitation, including PRFs ranging from 400 to 900 Hz. According to certain embodiments, frequent short cooling periods (lower PRFs) distributed along the treatment path are beneficial. According to other embodiments, higher PRFs result in a lower bubble cloud threshold, providing a net thermal benefit. According to yet other embodiments, pulses with high PRFs along with short cooling periods may be 25 interspersed throughout the treatment pathway.

[0190] Systems and methods are provided herein that implement Histotripsy pulse sequences with cooling periods that are distributed within a treatment plan or protocol that advantageously improve the thermal profile generated by histotripsy treatment as the treatment progresses through a target treatment tissue volume, with the limiting case of N 30 pulses distributed over the treatment time T. These pulse sequences can further be characterized in terms of the amount of time in which therapy is actively delivered to tissue relative to the amount of cooling time in which no therapy pulses are delivered to tissue. For example, a system delivering therapy pulses at a 400 Hz PRF for 5 minutes, followed by a 5

minute cooling time in which no therapy pulses are delivered (for a total treatment time of 10 minutes) would have a ratio of therapy (5 minutes) to cooling (5 minutes) of 1:1.

[0191] According to certain embodiments, cooling time can be non-uniformly distributed throughout a treatment tissue volume in order to achieve a desired thermal profile. Desired thermal profiles may be dictated by a combination of treatment pathway through discrete treatment locations of the target tissue volume and cooling distribution. In some aspects, the cooling periods vary throughout the treatment tissue volume to achieve the desired thermal profile. For example, cooling periods may increase as treatment progresses (backloaded cooling), or alternatively, may be frontloaded towards the beginning of treatment and decrease as treatment progresses.

[0192] When Histotripsy is used to ablate a target volume larger than the cavitation bubble clouds created by the system, the cavitation focus of the Histotripsy therapy system is moved (mechanically and/or electronically) through a plurality of discrete treatment locations within the target tissue volume as defined by a treatment pathway to ablate the entire target tissue volume. This disclosure provides methods and techniques that can improve the thermal profile of Histotripsy therapy when ablating a target tissue volume larger than the cavitation bubble cloud.

[0193] Many factors for a given Histotripsy procedure can dictate the amount and location of cooling for a given target tissue volume, including the size of the target tissue volume, the depth of the target tissue volume in the patient (e.g., the depth from the skin or some other obstruction like bone), the average driving voltage required to treat a target tissue volume, and/or the type of volume treatment path employed by the Histotripsy systems. In some implementations, the system is configured to use Lookup Tables based on one or more system inputs to determine the cooling profile to implement for a given treatment. Lookup Tables as discussed herein are reference tables that provide a multiplication factor, x_{cool} , which is used to scale how much cooling is needed for a target tissue volume treatment at a specified depth d and average driving voltage of the therapy transducer array. According to this disclosure, the x_{cool} factor can be defined as the variable that dictates the total amount of cooling time to be incorporated into a given treatment, whereas the weights w dictate how that given amount of cooling time is distributed throughout the treatment. According to certain embodiments, a Histotripsy system may be configured to use a plurality of different treatment heads (e.g., treatment heads with varying transducer array sizes or numbers of transducer elements), and each transducer array or treatment head may have its own

corresponding Lookup Table. According to yet other embodiments, each tissue type and/or treatment pathway may have its own Lookup Table.

[0194] According to certain embodiments, inputs for the Lookup Table including depth of the target tissue volume and/or average driving voltage of the therapy transducer may be automated, or alternatively, a user selects or inputs depth d and/or driving voltage(s) via a user interface. According to certain embodiments, the $xcool$ factor is not an input for the pattern generation, as in certain situations it can be adjusted after the pattern has been generated. When cooling is needed, $xcool$ can range between some minimum, non-zero, and maximum value which will need to be accounted for by the algorithm. If no cooling is needed during treatment $xcool$ is set to zero. The actual cooling time for a treatment point is calculated by multiplying $xcool$ by a cooling weight w returned from the pattern library.

[0195] FIG. 4A depicts a formula or algorithm that can be used by any of the histotripsy systems, or planning/treatment software described herein, for initially setting cooling weights w 402 along a treatment path for a given treatment depth d 403, in mm, with time factor t 405 representing progress along the treatment path from 0 to 1. The type of cooling applied may depend on a number of factors, including but not limited to the target tissue type, the depth of the target tissue, and/or the pattern/pathway the system is using to treat the target tissue (e.g., the manner in which the cavitation bubble cloud is navigated through the target tissue volume to treat the entire volume).

[0196] Early in the treatment pattern, cooling may not be necessary. For example, bottom-up treatment pathways where a target tissue volume is treated distally to proximally relative to the transducer location result in slower thermal build up in critical tissue locations. Bottom-up treatment pathways refer to treatment protocols where the location within the tissue volume furthest from the transducer is treated first, and the treatment progresses through the volume and generally towards the transducer until completion. As the treatment moves distal to proximal, variations such as in-out patterns or bottom-up spiral patterns, or other patterns, can be used to fill out the tissue volume. In these scenarios, cooling may not be needed during the first 35% or so of treatment, or may be minimal during this portion of treatment. It should be understood that the 35% value can be adjusted based on specific depths or tissue types of the target tissue volume and intervening tissue path. Therefore, a cooling value or weight of zero or near-zero may be applied for the first portion (e.g., up to the first 35%, or whatever time factor t 405 is chosen by the user or the system) of the treatment. Subsequently, as treatment progresses along the path towards a transducer beyond time factor t 405 (here, set to 35% of the total treatment time), cooling may increase with

more cooling at the top/proximal portion of the target tissue volume closest to the transducer according to the second equation provided in FIG. 4A. In some examples, the amount of cooling may increase exponentially. In other examples, the cooling may increase linearly, or alternatively, by a pre-set or predetermined increase depending on the location within the target tissue volume and/or the time into the treatment. Additionally, in other embodiments,

cooling may be distributed based on the composition of the intervening tissue path (e.g., more cooling in a region in which the acoustic field includes an aberrator such as a bone/rib). [0197] Distal to proximal, or bottom-up spiral patterns may also be advantageous for mitigation of treating through residual cavitation/bubbles. Furthermore, the bottom-up spiral patterns may reduce the redundant motions associated with patterns that have a high degree of spatial variability incorporated as a means to spread out thermal deposition. The benefits in therapeutic effectiveness afforded by this pathway (reducing the potential for pre-focal shielding of stable bubbles) outweigh the thermal consequences. According to other embodiments, other pathways, such as pathways having enhanced spatial variability, may be utilized. Non-ideal thermal properties associated with pathways having a lack of spatial variability may be compensated for via a non-uniform distribution of cooling time.

[0198] FIG. 4B depicts a formula or algorithm that can be used by any of the histotripsy systems, or planning/treatment software described herein, for a normalized cooling weight w'_i for an index i along a given treatment path, respectively. The total cooling time added (in seconds) for a treatment volume having a plurality of discrete treatment locations is the x_{cool} factor multiplied by the total number of treatment locations (excluding the last treatment location), denoted by N . In one embodiment, the last point in the pattern is excluded because it only returns to the start, the center of the plan, at the end of treatment without any further application of therapy.

[0199] FIG. 5A illustrates a depiction of cooling zones with varying cooling magnitudes or cooling times along a treatment pathway for a target treatment volume.

[0200] As shown in FIG. 5A, a target tissue volume 504 can be divided into a plurality of discrete treatment locations 505 according to a treatment plan. According to certain embodiments, the net direction 512 of traversal through the treatment volume can be towards transducer 502 from a distal point in the target tissue volume 504 relative to transducer 502 (e.g., bottom-up traversal). The target volume 504 is segmented into treatment locations based on packing parameters that optimize placement of the locations within the target tissue volume to fill the target tissue volume while also optimizing a treatment pathway through the target tissue volume.

[0201] Additionally, the treatment plan can identify a magnitude of cooling periods to achieve a target thermal dose throughout the target tissue volume. In some examples, the cooling periods implemented into the treatment plan can be weighted or backloaded towards the latter treatment locations of the treatment plan. For example, Distal regions 506 of target tissue volume 504 (e.g., treatment locations distal within the target tissue volume relative to the transducer/located at great depths in the target volume) may require little to no cooling periods in the treatment plan. Central regions 508 of target tissue volume 504 (e.g., treatment locations centrally located within the target tissue volume relative to the transducer) may require increased cooling periods in the treatment plan relative to the cooling periods implemented in distal regions 506. Furthermore, proximal regions 510 of target tissue volume 504 (e.g., treatment locations most proximal to transducer 502/located at more shallow depths in the target volume) may require the most cooling periods in the treatment plan relative to the cooling periods implemented in distal regions 506 and/or central regions 508, given that more ultrasound energy is transmitted through regions 510 and 508 compared to region 506, therefore potentially providing higher heating. The example of FIG. 5A shows three discrete cooling regions (proximal, central, distal), but it should be understood that any number of cooling regions can be implemented (e.g., up to three regions, four regions, five regions, more than five regions).

[0202] While the proximal regions of the plan are subject to thermal accumulation during treatment of distal (or even central) regions, this isn't the only motivation for adding more cooling during treatment of the proximal regions. A key factor in determining cooling revolves around the depth input for cooling considerations, which is the distance between the treatment volume and the patient's body wall, a critical pre-focal absorber in the ultrasound beam path. The proximal regions of the target tissue volume typically need more cooling because the critical absorber, or body wall, is typically in a more focused portion of the acoustic field from the therapy transducer during therapy of the proximal region, and therefore absorbs energy at a higher rate in this location.

[0203] In some embodiments, referring to FIG. 5A, the amount of cooling in a given cooling zone or region may be consistent within that cooling region. Alternatively, the amount of cooling may increase linearly, exponentially, or by a fixed amount within a given cooling zone or region. In some embodiments, cooling within a given zone or region may be linear, or increase linearly, while cooling in subsequent regions may increase exponentially. In another example, a first region may have cooling applied at a first value of zero or near zero, a second region may have cooling at a second value larger than zero, and a third region

may have cooling applied at a third value greater than the second value, and so forth. The cooling could be applied in a step-function as the treatment passes through the various regions. The cooling value could be a fixed value, a linearly increasing/decreasing value, or an exponential value within a given region.

5 **[0204]** FIG. 5B depicts a similar embodiment to that of FIG. 5A, however there are only two distinct cooling zones, distal region 506 and proximal region 510. The same principles may apply to the embodiment of FIG. 5B, namely, that cooling times may increase (either linearly, exponentially, or as a step function) as the treatment progresses through the treatment volume in the direction 512 of the transducer.

10 **[0205]** FIG. 6A is a graph illustrating a distribution of treatment points or treatment locations 608 vs. cooling times 610 in a treatment plan of a target tissue volume.

[0206] According to certain embodiments, graph 600 represents normalized weights for a 2cm sphere of treatment volume at a depth of 30 mm 601. The pattern shows a cooling time 610 of 0 seconds for point #s 0 to around point #125 (602) and increasing cooling times of
15 greater than 0 to 5 seconds for around point #s 125-350 (604). As described above, the increase in cooling times as treatment progresses can be exponential, linear, or stepwise.

[0207] In one embodiment, the treatment plan of cooling times as depicted in FIG. 6A can be applied to the embodiment of FIG. 5B. For example, the linear or zero cooling times applied to points 602 may represent distal region 506 in FIG. 5B, and the increasing cooling
20 times applied to points 604 may represent proximal region 510 in FIG. 5B.

[0208] According to certain embodiments, the pattern of treatment points within the target tissue volume is split into different sequences of points, for example linear sequences, rings, and single point treatments.

[0209] FIG. 6B is a graph illustrating segmentation of treatment points 608 vs. cooling
25 times 610 in a treatment plan of a target tissue volume.

[0210] To avoid cooling at every single point in the treatment path, the points in each sequence of graph 600 can be grouped 603 into as equally sized groups 606 as possible. By default, the group size can be set to 5 in one example. For example, a sequence with 29 points can be distributed 603 in groups of [5, 5, 5, 4, 5, 5] points 606. The cooling weights within
30 each group can then be summed together and the total is set as the cooling weight for the last point in the group. This avoids cooling at the beginning of a point sequence and ensures the last point has cooling. All the other points in the group can be set to 0. To correspond with the range that *xcool* can span, there may be minimum 620 and maximum 622 allowable cooling times 610 chosen to avoid too short and excessive cooling. The algorithm can then

look at the cooling times 610 in each point sequence and increase the number of segments if the maximum cooling time 622 is too large or decrease the number of segments if the minimum cooling time 620 is too small.

[0211] FIG. 6C is a graph illustrating final cooling times for a treatment volume of tissue.

5 The present embodiment includes a 2 cm sphere at 30 mm depth and an *xcool* of 1 (605).

[0212] In some examples, this resizing of treatment point segments may not be able to deal with single point treatments or if the number of segments in the point sequence cannot be further decreased or increased, i.e. all the cooling is already at a single point in the sequence or every point has cooling. The next step in the algorithm can be to redistribute the excessive or deficient cooling times 610 over the entire path instead of just the point sequence. This may be accomplished by iterating through the cooling points 608 in the path, dropping a point 608 if it is below the minimum cooling time 620 and adding its time into a reservoir of cooling time 610 that needs to be distributed. If the algorithm comes across a point where adding some of the now extra cooling time 610 would bring it up to the minimum cooling time 620, it may do so, but only to the minimum cooling time 620. Going through all the points this way ensures that no point is below the minimum cooling time 620.

[0213] Dealing with points that are above the maximum cooling time 622, a similar approach may be used by iterating through each cooling point and capping it to the maximum cooling time 622. Any time above the maximum cooling time 622 is added to the bank of cooling time to be distributed. As it goes through the points, the algorithm may store which points are within the minimum cooling times 620 and maximum cooling times 622. These are called free points, as in free to receive more cooling without going over the limit. The algorithm can then try to add remaining time divided by the number of free points to each free point without going over the maximum cooling time 622. If there are points that end up reaching the maximum cooling time 622, the extra time may then be redistributed in the same manner until no more extra cooling time is available or there are no more free points. In the case that there are no free points, any remaining time can be added to the last cooling point.

[0214] In some examples, the algorithm can add an extra point to the end to return to the center. This extra point can be assigned a cooling time of 0. During treatment, the actual cooling times are $c_i * xcool$, where c_i are the redistributed cooling weights.

[0215] FIG. 7 is a graph illustrating an example Lookup Table.

[0216] The Lookup Table can inform users or the system/algorithm of the appropriate volume treatment parameters to minimize the likelihood of unwanted thermal effects in a given treatment scenario. Specifically, this lookup table can specify the extent of additional

cooling time to be imposed during automated volume treatment based on two inputs: (1) the treatment depth (from the center of the body wall to the center of the planned treatment volume (PTV)), and (2) the average treatment voltage. Automated volume treatment guided by the lookup table can produce favorable treatment outcomes without the generation of thermal adverse events when targeting tissue within a subject.

[0217] In some embodiments, the lookup table utilized for a given treatment is dependent on the therapy transducer and amount of global focal steering selected by the user. For example, lookup tables can be developed specific to each possible transducer/global focal steering combination. For a system with two different therapy transducers (A and B), and three global focal steering settings (natural focus, +1 cm global focal steering, and +2 cm global focal steering), this results in 6 possible lookup tables:

[0218] 1) Therapy transducer A + natural focus

[0219] 2) Therapy transducer A + 1 cm global focal steering

[0220] 3) Therapy transducer A + 2 cm global focal steering

[0221] 4) Therapy transducer B + natural focus

[0222] 5) Therapy transducer B + 1 cm global focal steering

[0223] 6) Therapy transducer B + 2 cm global focal steering

[0224] Based on the therapy transducer that is connected to the system and the user's choice of global focal steering in the UI, the software is configured to automatically consult the appropriate lookup table.

[0225] As previously discussed above, for a given lookup table the primary inputs are 1) the user-measured depth from the center of the target tissue volume to the absorptive structure of interest within the body wall (e.g. a rib), 2) the average voltage defined for treatment of the planned treatment volume (e.g., the average of planned transducer voltages for each of the treatment locations/points within the tissue volume), and 3) the size of the target tissue volume/treatment plan.

[0226] In some embodiments, the system can account for different plan sizes by modifying the depth input to the lookup table. Specifically, in one example, treatment plans/target tissue volumes with a maximum diameter ≤ 3 cm may use the appropriate lookup table without depth input modification. However, plans with a maximum diameter > 3 cm may use a formula to modify the depth input to the lookup table. Essentially, the formula is designed such that the temperature rise generated by treating the larger plan (with diameter > 3 cm) will be less than or equal to that produced by a 3 cm sphere at the same voltage. This

allows the system to have one lookup table to account for all plan sizes, simplifying the overall software implementation.

[0227] According to certain embodiments, 2D lookup tables for the natural focus of a transducer of interest may be generated for planned treatment volumes (PTVs) with given spherical margin contours. As shown here, treatment in portion 708 of the parameter space is prohibited with the current cooling coefficient options 705. Voltage 703 in the figure is displayed as a percentage of maximum, where 100% may correspond, for example, to 150 VDC. Depiction of voltage 703 as a percentage may match, for example the user-facing voltage readout of the system. For a given depth 701 and voltage 703, a cooling coefficient 705 may be assigned. As shown here, the lookup table graph can include a portion with a cooling coefficient of 0 (region 702) and a portion with a maximum allowable cooling coefficient (region 706). At greater depths 701 for a given voltage 703, cooling coefficient 705 may approach 0. At most depths 701 with moderate to higher voltages, treatment may be prohibited (region 708), as the lookup table is unable to provide sufficient cooling periods to reduce or eliminate unwanted tissue heating at the given driving voltages and depths.

[0228] FIGS. 8A-8B illustrate an ultrasound therapy method 800-801. Method 800-801 begins with block 805 by receiving a digital treatment plan that includes a target tissue volume of a subject divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes.

[0229] At block 810, a treatment depth of the target tissue volume is received.

[0230] At block 815, a driving voltage required for an ultrasound transducer to produce cavitation in at least one location within the target tissue volume is received.

[0231] At block 820, a desired thermal profile for additional cooling time (“cooling factor”) to be implemented into the digital treatment plan is determined.

[0232] Method 800-801 continues at FIG. 8B.

[0233] At block 825, cooling time periods are added to the digital treatment plan according to the desired thermal profile that may increase (“backload”) as the treatment progresses through the plurality of treatment volumes. As described above, the increase can be linear, exponential, or stepwise.

[0234] At block 830, ultrasound treatment is commenced in a subject according to the digital treatment plan.

[0235] According to other embodiments of method 800-801, the cooling time periods are between treatment pulses, in which the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.

[0236] According to other embodiments of method 800-801, the treatment pathway starts at a distal-most region of the target tissue volume relative to a transducer configured to carry out the ultrasound treatment and moves towards a proximal-most region of the target tissue volume relative to the transducer.

- 5 [0237] According to other embodiments of method 800-801, the cooling time periods are off periods where no therapy is delivered.

[0238] According to other embodiments of method 800-801, the treatment depth is received via a user input.

- 10 [0239] According to other embodiments of method 800-801, the treatment depth is automatically determined based on patient imaging.

[0240] According to other embodiments of method 800-801, the driving voltage is determined based on a plurality of test pulses.

- 15 [0241] According to other embodiments of method 800-801, the total cooling time for the target tissue volume is based on the product of a cooling coefficient (“*xcool*”) and a total number of the plurality of treatment volumes, in which a cooling time period for each of the plurality of treatment volumes is based on a product of the cooling coefficient and a cooling weight for each treatment point.

[0242] According to other embodiments of method 800-801, a last one of the plurality of treatment volumes to be treated is excluded from cooling.

- 20 [0243] According to other embodiments of method 800-801, the ultrasound treatment progresses in a pattern based on one or more of: a sequence of points, a linear sequence, and a uniform distribution.

[0244] According to other embodiments of method 800-801, the plurality of treatment volumes are grouped and treated by size.

- 25 [0245] According to other embodiments of method 800-801, the desired thermal profile includes a range from a minimum cooling time to a maximum cooling time, in which a number of segments in the treatment pathway is adjusted based on one or more of the minimum cooling time and maximum cooling time, wherein cooling time periods for the plurality of treatment volumes falling above the maximum cooling times (“cooling excess”) or below the minimum cooling times are iteratively distributed across the plurality of
30 treatment volumes to bring the cooling time period for each one of the plurality of treatment volumes within the range.

[0246] According to other embodiments of method 800-801, the plurality of treatment volumes having cooling time periods within the range are designated as free points to receive

further cooling up to the maximum cooling time period, in which the cooling time periods for treatment points falling above the maximum cooling times are iteratively distributed among the free points until no free points remain, in which any cooling excess remaining after all free points have reached the maximum cooling time is added to the cooling time period for a

5 last one of the plurality of treatment volumes to be treated.

[0247] FIG. 9 is an ultrasound planning method 900.

[0248] Method 900 begins at block 905 by dividing a target tissue volume of a subject into a plurality of treatment volumes.

10 [0249] At block 910, a treatment pathway to navigate through the plurality of treatment volumes is determined.

[0250] At block 915, cooling periods (“cooling factor”) are determined for the plurality of treatment volumes according to a desired thermal profile.

15 [0251] At block 920, the cooling time periods are added to the plurality of treatment volumes according to a desired thermal profile, in which the cooling time periods may increase (“backload”) along the treatment pathway through the plurality of treatment volumes. As described above, the increase can be linear, exponential, or stepwise.

[0252] According to other embodiments of method 900, the cooling time periods are between treatment pulses, in which the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.

20 [0253] According to other embodiments of method 900, the treatment pathway starts at a distal-most region of the target tissue volume relative to the ultrasound therapy transducer array and moves towards a proximal-most region of the target tissue volume relative to the ultrasound therapy transducer array.

25 [0254] According to other embodiments of method 900, the cooling time periods are off periods where no ultrasound therapy is delivered.

[0255] It should be understood that any feature described herein with respect to one embodiment can be substituted for or combined with any feature described with respect to another embodiment.

30 [0256] When a feature or element is herein referred to as being “on” another feature or element, it can be directly on the other feature or element or intervening features and/or elements may also be present. In contrast, when a feature or element is referred to as being “directly on” another feature or element, there are no intervening features or elements present. It will also be understood that, when a feature or element is referred to as being “connected”, “attached” or “coupled” to another feature or element, it can be directly

connected, attached or coupled to the other feature or element or intervening features or elements may be present. In contrast, when a feature or element is referred to as being “directly connected”, “directly attached” or “directly coupled” to another feature or element, there are no intervening features or elements present. Although described or shown with respect to one embodiment, the features and elements so described or shown can apply to other embodiments. It will also be appreciated by those of skill in the art that references to a structure or feature that is disposed “adjacent” another feature may have portions that overlap or underlie the adjacent feature.

[0257] Terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. For example, as used herein, the singular forms “a”, “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms “comprises” and/or “comprising,” when used in this specification, specify the presence of stated features, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, steps, operations, elements, components, and/or groups thereof. As used herein, the term “and/or” includes any and all combinations of one or more of the associated listed items and may be abbreviated as “/”.

[0258] Spatially relative terms, such as “under”, “below”, “lower”, “over”, “upper” and the like, may be used herein for ease of description to describe one element or feature’s relationship to another element(s) or feature(s) as illustrated in the figures. It will be understood that the spatially relative terms are intended to encompass different orientations of the device in use or operation in addition to the orientation depicted in the figures. For example, if a device in the figures is inverted, elements described as “under” or “beneath” other elements or features would then be oriented “over” the other elements or features. Thus, the exemplary term “under” can encompass both an orientation of over and under. The device may be otherwise oriented (rotated 90 degrees or at other orientations) and the spatially relative descriptors used herein interpreted accordingly. Similarly, the terms “upwardly”, “downwardly”, “vertical”, “horizontal” and the like are used herein for the purpose of explanation only unless specifically indicated otherwise.

[0259] Although the terms “first” and “second” may be used herein to describe various features/elements (including steps), these features/elements should not be limited by these terms, unless the context indicates otherwise. These terms may be used to distinguish one feature/element from another feature/element. Thus, a first feature/element discussed below could be termed a second feature/element, and similarly, a second feature/element discussed

below could be termed a first feature/element without departing from the teachings of the present invention.

[0260] Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and

5 “comprising” means various components can be co-jointly employed in the methods and articles (e.g., compositions and apparatuses including device and methods). For example, the term “comprising” will be understood to imply the inclusion of any stated elements or steps but not the exclusion of any other elements or steps.

[0261] As used herein in the specification and claims, including as used in the examples
10 and unless otherwise expressly specified, all numbers may be read as if prefaced by the word “about” or “approximately,” even if the term does not expressly appear. The phrase “about” or “approximately” may be used when describing magnitude and/or position to indicate that the value and/or position described is within a reasonable expected range of values and/or positions. For example, a numeric value may have a value that is +/- 0.1% of the stated value
15 (or range of values), +/- 1% of the stated value (or range of values), +/- 2% of the stated value (or range of values), +/- 5% of the stated value (or range of values), +/- 10% of the stated value (or range of values), etc. Any numerical values given herein should also be understood to include about or approximately that value, unless the context indicates otherwise. For example, if the value “10” is disclosed, then “about 10” is also disclosed. Any numerical
20 range recited herein is intended to include all sub-ranges subsumed therein. It is also understood that when a value is disclosed that “less than or equal to” the value, “greater than or equal to the value” and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value “X” is disclosed the “less than or equal to X” as well as “greater than or equal to X” (e.g., where X is a numerical value) is also
25 disclosed. It is also understood that the throughout the application, data is provided in a number of different formats, and that this data, represents endpoints and starting points, and ranges for any combination of the data points. For example, if a particular data point “10” and a particular data point “15” are disclosed, it is understood that greater than, greater than or equal to, less than, less than or equal to, and equal to 10 and 15 are considered disclosed as
30 well as between 10 and 15. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0262] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are

provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope
5 of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

What is claimed is:

1. An ultrasound therapy method, comprising the steps of:
5 receiving a digital treatment plan that includes a target tissue volume of a subject divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes;
receiving a treatment depth of the target tissue volume;
receiving at least one driving voltage required for an ultrasound transducer to produce
10 cavitation in at least one of the plurality of treatment volumes;
determining a desired thermal profile for additional cooling time periods to be implemented in the digital treatment plan based on the treatment depth and at least one driving voltage;
adding cooling time periods to one or more of the plurality of treatment volumes of
15 the digital treatment plan according to the desired thermal profile, the cooling time periods varying as the treatment progresses through the plurality of treatment volumes; and
commencing ultrasound treatment in the subject according to the digital treatment plan.
20
2. The method of claim 1, wherein the cooling time periods increase as the treatment progresses through the plurality of treatment volumes.
3. The method of claim 1, wherein the cooling time periods are between treatment
25 pulses, wherein the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.
4. The method of claim 1, wherein the treatment pathway starts at a distal-most region of the target tissue volume relative to a transducer configured to carry out the ultrasound
30 treatment and moves towards a proximal-most region of the target tissue volume relative to the transducer.
5. The method of claim 1, wherein the cooling time periods are off periods where no therapy is delivered.

6. The method of claim 1, wherein the treatment depth is received via a user input.
7. The method of claim 1, wherein the treatment depth is automatically determined based on patient imaging.
- 5 8. The method of claim 1, wherein the driving voltage is determined based on a plurality of test pulses.
9. The method of claim 1, wherein a total cooling time for the target tissue volume is based on the product of a cooling coefficient and a total number of the plurality of treatment volumes, wherein a cooling time period for each of the plurality of treatment volumes is based on a product of the cooling coefficient and a cooling weight for each treatment point.
- 10 10. The method of claim 1, wherein a last one of the plurality of treatment volumes to be treated is excluded from cooling.
- 15 11. The method of claim 1, wherein the ultrasound treatment progresses in a pattern based on one or more of: a sequence of points, a linear sequence, and a uniform distribution.
12. The method of claim 1, wherein the plurality of treatment volumes are grouped and treated by size.
- 20 13. The method of claim 1, wherein the desired thermal profile includes a range from a minimum cooling time to a maximum cooling time, wherein a number of segments in the treatment pathway is adjusted based on one or more of the minimum cooling time and maximum cooling time, wherein cooling time periods for the plurality of treatment volumes falling above the maximum cooling times or below the minimum cooling times are iteratively distributed across the plurality of treatment volumes to bring the cooling time period for each one of the plurality of treatment volumes within the range.
- 25 14. The method of claim 13, wherein the plurality of treatment volumes having cooling time periods within the range are designated as free points to receive further cooling up to the maximum cooling time period, wherein the cooling time periods for treatment points falling above the maximum cooling times are iteratively distributed among the free points until no free points remain, wherein any cooling excess remaining after all free points have reached
- 30

the maximum cooling time is added to the cooling time period for a last one of the plurality of treatment volumes to be treated.

15. The method of claim 1, wherein the cooling time periods increase linearly.
16. The method of claim 1, wherein the cooling time periods increase exponentially.
- 5 17. The method of claim 1, wherein the cooling time periods increase in a stepwise manner.
18. The method of claim 1, wherein the cooling time periods have a first value in a first region of the target tissue volume and a second value in a second region of the target tissue volume.
- 10 19. The method of claim 18, wherein the second value is larger than the first value.
20. The method of claim 18, wherein the first region is further from the ultrasound transducer than the second region.
21. An ultrasound therapy system, comprising;
 - a robotic positioning system;
 - 15 an ultrasound therapy transducer array connected to the robotic positioning system;
 - a generator operatively coupled to the ultrasound therapy transducer array, the generator and ultrasound therapy transducer array being configured to deliver histotripsy pulses into a subject to generate a cavitation bubble cloud in the subject; and
 - at least one processor operatively coupled to the robotic positioning system and the
 - 20 generator, the at least one processor being configured to:
 - receive a digital treatment plan that includes a target tissue volume of a subject
 - divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes;
 - receive a treatment depth of the target tissue volume;
 - 25 receiving at least one driving voltage required for an ultrasound transducer to produce cavitation in at least one of the plurality of treatment volumes;
 - determine a desired thermal profile for additional cooling time periods to be
 - implemented in the digital treatment plan based on the treatment depth and the
 - at least one driving voltage;

modify the digital treatment plan by adding cooling time periods to one or more of the plurality of treatment volumes of the digital treatment plan according to the desired thermal profile, the cooling time periods varying as the treatment progresses through the plurality of treatment volumes; and

- 5 control the robotic positioning system and the generator to provide histotripsy therapy to the subject according to the digital treatment plan that includes the cooling time periods.

22. The system of claim 21, wherein the cooling time periods increase as the treatment
10 progresses through the plurality of treatment volumes

23. The system of claim 21, further comprising a user input device configured for inputting the treatment depth.

15 24. The system of claim 21, wherein the cooling time periods are between treatment pulses, wherein the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.

25 25. The system of claim 21, wherein the treatment pathway starts at a distal-most region of the target tissue volume relative to the ultrasound therapy transducer array and moves
20 towards a proximal-most region of the target tissue volume relative to the ultrasound therapy transducer array.

26. The system of claim 21, wherein the cooling time periods are off periods where no
25 ultrasound therapy is delivered.

27. The system of claim 21, wherein the treatment depth is automatically determined based on patient imaging.

30 28. The system of claim 21, wherein the driving voltage is determined based on a plurality of test pulses.

29. An ultrasound planning method, comprising:
dividing a target tissue volume of a subject into a plurality of treatment volumes;

determining a treatment pathway to navigate through the plurality of treatment volumes;

determining a treatment voltage for each of the plurality of treatment volumes to induce cavitation;

5 determining cooling time periods for one or more of the plurality of treatment volumes according to a desired thermal profile, the cooling time periods varying along the treatment pathway through the plurality of treatment volumes; and

generating a digital treatment plan that includes the plurality of treatment volumes, the treatment pathway, the treatment voltage for each of the plurality of treatment volumes, and the cooling periods to be applied to the one or more treatment volumes; and

10 initiating ultrasound therapy of the target tissue volume with an ultrasound therapy system according to the digital treatment plan.

30. The method of claim 29, wherein the cooling time periods increase as the treatment progresses through the plurality of treatment volumes.

31. The method of claim 29, wherein the cooling time periods are between treatment pulses, wherein the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.

20 32. The method of claim 29, wherein the treatment pathway starts at a distal-most region of the target tissue volume relative to the ultrasound therapy transducer array and moves towards a proximal-most region of the target tissue volume relative to the ultrasound therapy transducer array.

25 33. The method of claim 29, wherein the cooling time periods are off periods where no ultrasound therapy is delivered.

30 34. A computer implemented ultrasound treatment planning system, comprising;
a processor; and
a memory to store instructions, wherein executing the instructions is configured to generate a treatment plan with cooling time, wherein the instructions include: dividing a target tissue volume of a subject into a plurality of treatment volumes, determining locations for a plurality of treatment points within the plurality of treatment volumes, determining a

treatment pathway to navigate through the plurality of treatment volumes, and adding cooling time periods for the plurality of treatment points according to a desired thermal profile, wherein the cooling periods vary along the treatment pathway through the plurality of treatment volumes.

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35. The system of claim 34, wherein the system receives one or more of: (i) a treatment depth of the target tissue volume, and (ii) a driving voltage required for the ultrasound transducer to produce cavitation in at least one location within the target tissue volume.

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36. The system of claim 34, wherein the cooling time periods are configured to be between treatment pulses, wherein the cooling time periods are non-uniformly distributed throughout the volume of tissue to be treated.

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37. The system of claim 34, wherein the treatment pathway starts at a distal-most region of the target tissue volume relative to an ultrasound therapy transducer array and moves towards a proximal-most region of the target tissue volume relative to the ultrasound therapy transducer array.

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38. The system of claim 34, wherein the cooling time periods are off periods where no ultrasound therapy is delivered.

39. The system of claim 35, wherein the treatment depth is received via a user input.

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40. The system of claim 35, wherein the treatment depth is automatically determined based on patient imaging.

41. The system of claim 32, wherein the driving voltage is determined based on a plurality of test pulses.

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42. A method for delivering ultrasound therapy to a subject with an ultrasound transducer array, comprising the steps of:

receiving a digital treatment plan that includes a target tissue volume of a subject divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes;

- dividing the target tissue volume into a first cooling region and a second cooling region, the second cooling region being positioned closer to the ultrasound transducer array than the first cooling region;
- determining first cooling time periods to add to one or more of the plurality of treatment volumes in the first cooling region in the digital treatment plan according to a desired thermal profile;
- determining second cooling time periods to add to one or more of the plurality of treatment volumes in the second cooling region in the digital treatment plan according to the desired thermal profile; and
- commencing ultrasound treatment in the target tissue volume with the ultrasound transducer array according to the digital treatment plan.
43. An ultrasound therapy system, comprising;
- a robotic positioning system;
- an ultrasound therapy transducer array connected to the robotic positioning system;
- a generator operatively coupled to the ultrasound therapy transducer array, the generator and ultrasound therapy transducer array being configured to deliver histotripsy pulses into a subject to generate a cavitation bubble cloud in the subject; and
- at least one processor operatively coupled to the robotic positioning system and the generator, the at least one processor being configured to:
- receive a digital treatment plan that includes a target tissue volume of a subject divided into a plurality of treatment volumes, and a treatment pathway through the plurality of treatment volumes;
- divide the target tissue volume into a first cooling region and a second cooling region, the second cooling region being positioned closer to the ultrasound transducer array than the first cooling region;
- determine first cooling time periods to add to one or more of the plurality of treatment volumes in the first cooling region in the digital treatment plan according to a desired thermal profile;
- determine second cooling time periods to add to one or more of the plurality of treatment volumes in the second cooling region in the digital treatment plan according to the desired thermal profile; and

control the robotic positioning system and the generator to provide histotripsy therapy to the subject according to the digital treatment plan that includes the first and second cooling time periods.