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(54) **HISTOTRIPSY THERAPY SYSTEMS AND METHODS FOR THE TREATMENT OF BRAIN TISSUE**

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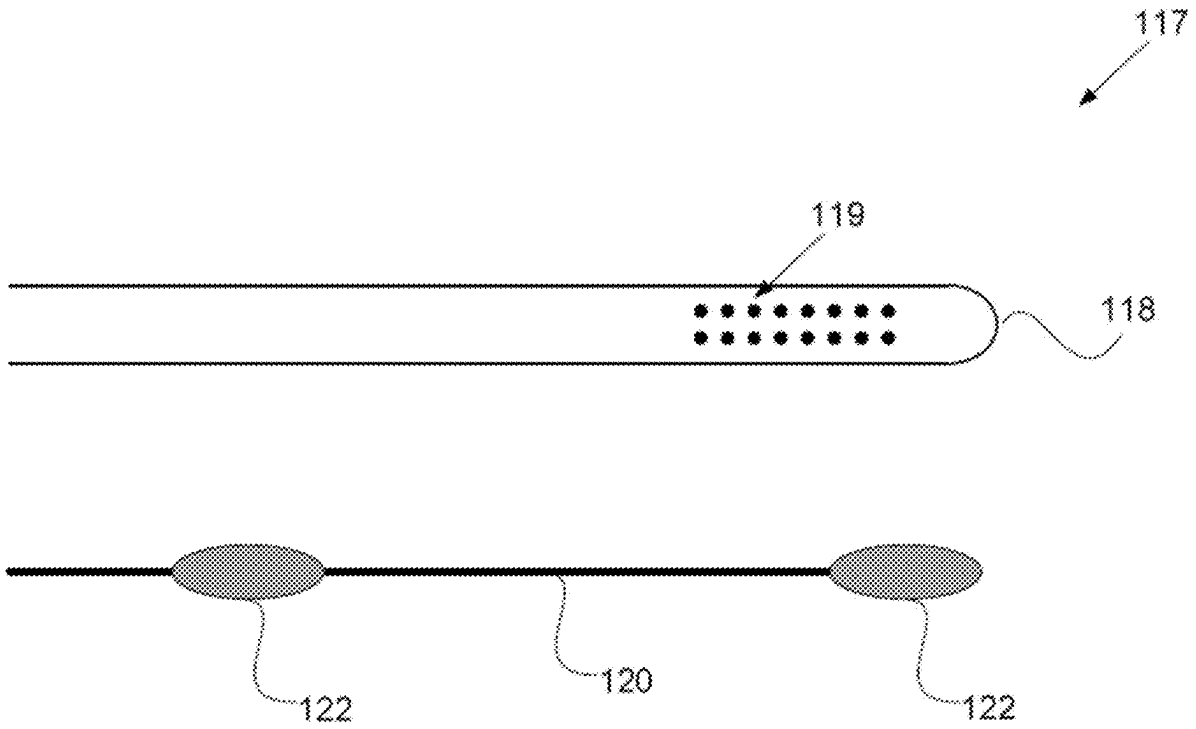
(57) **ABSTRACT**

A histotripsy therapy system configured for the treatment of brain tissue is provided, which may include any number of features. In one embodiment, the system includes an ultrasound therapy transducer, a drainage catheter, and a plurality of piezoelectric sensors disposed in the drainage catheter. The ultrasound therapy is configured to transmit ultrasound pulses into the brain to generate cavitation that liquefies a target tissue in the brain. The drainage catheter is configured to detect the ultrasound pulses. An aberration correction algorithm can be executed by the system based on the ultrasound pulses measured by the drainage catheter to automatically correct for an aberration effect caused by the ultrasound pulses passing through a skullcap of the patient.



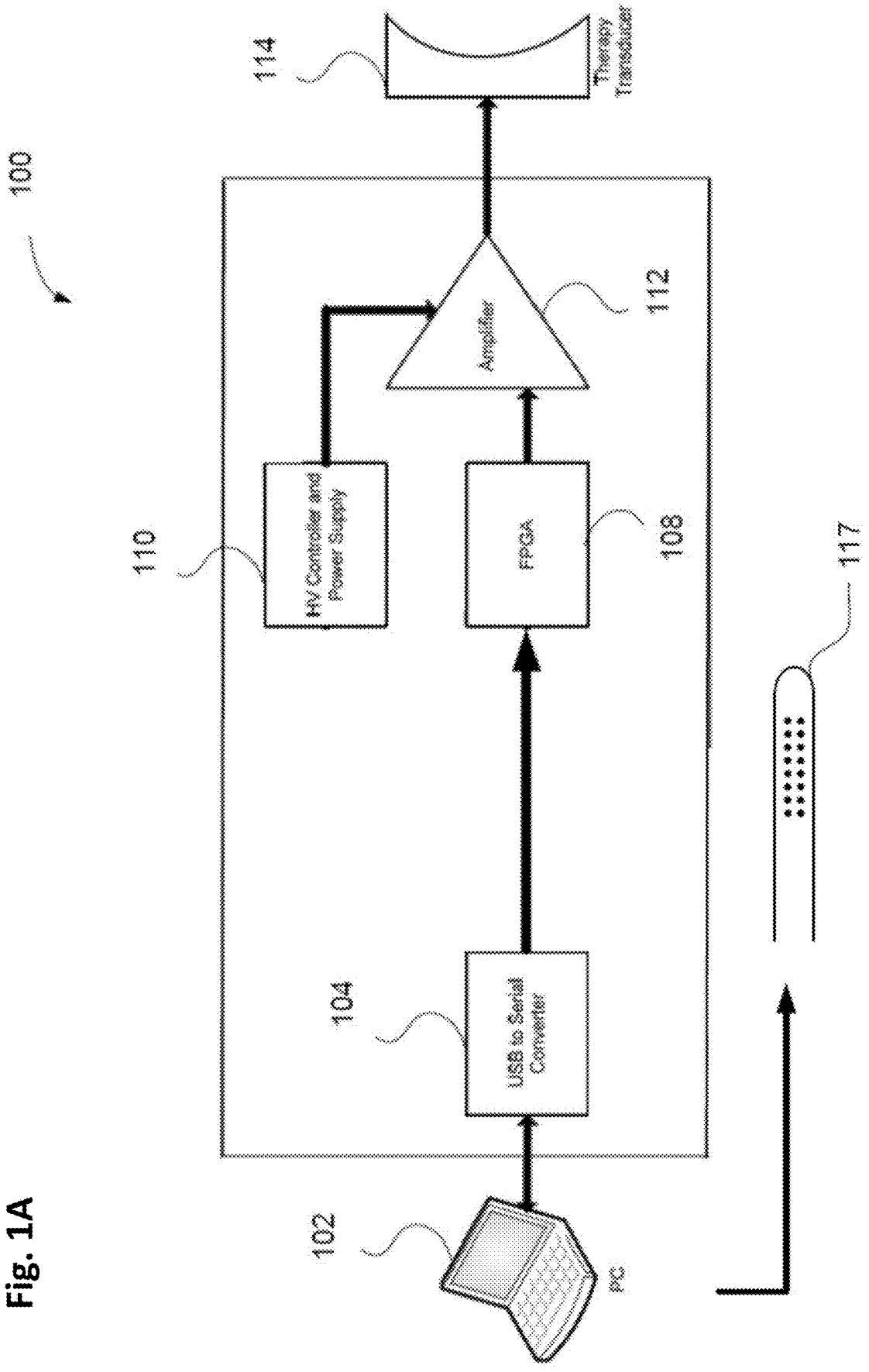
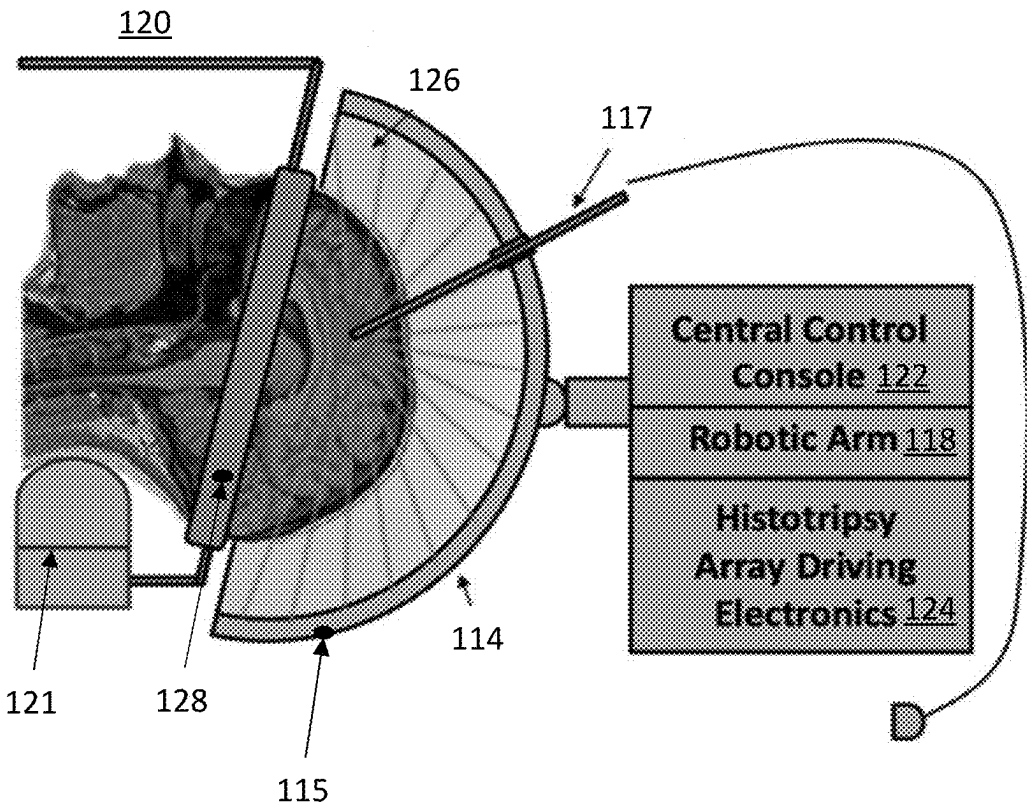

100
114
Therapy Transducer
112
Amplifier
110
HV Controller and Power Supply
108
FPGA
117
104
USB to Serial Converter
102
PC

Fig. 1A

Fig. 1B


120
126
117
Central Control Console 122
Robotic Arm 118
Histotripsy Array Driving Electronics 124
114
121
128
115

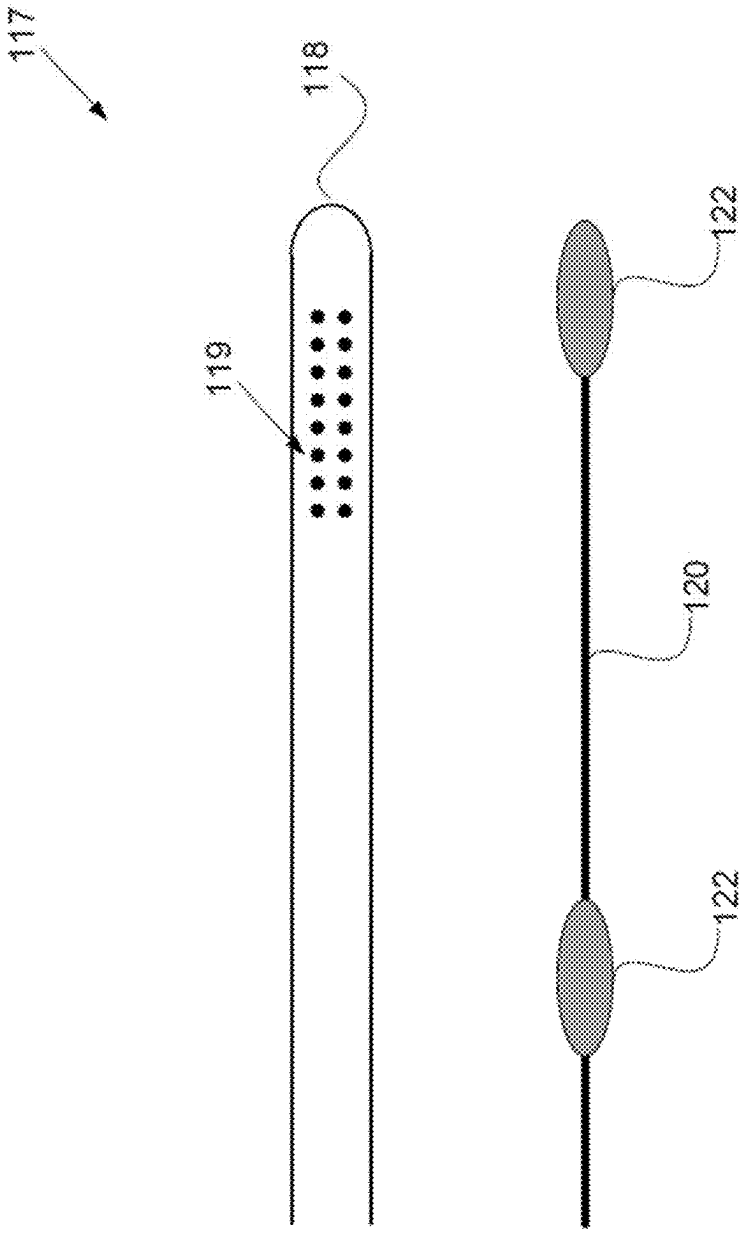


FIG. 2

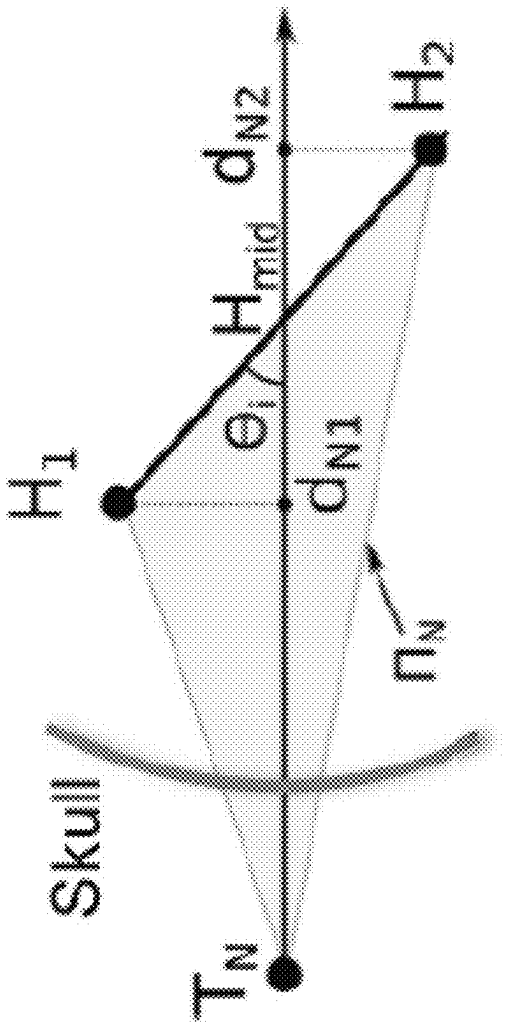


FIG. 3

FIG. 4

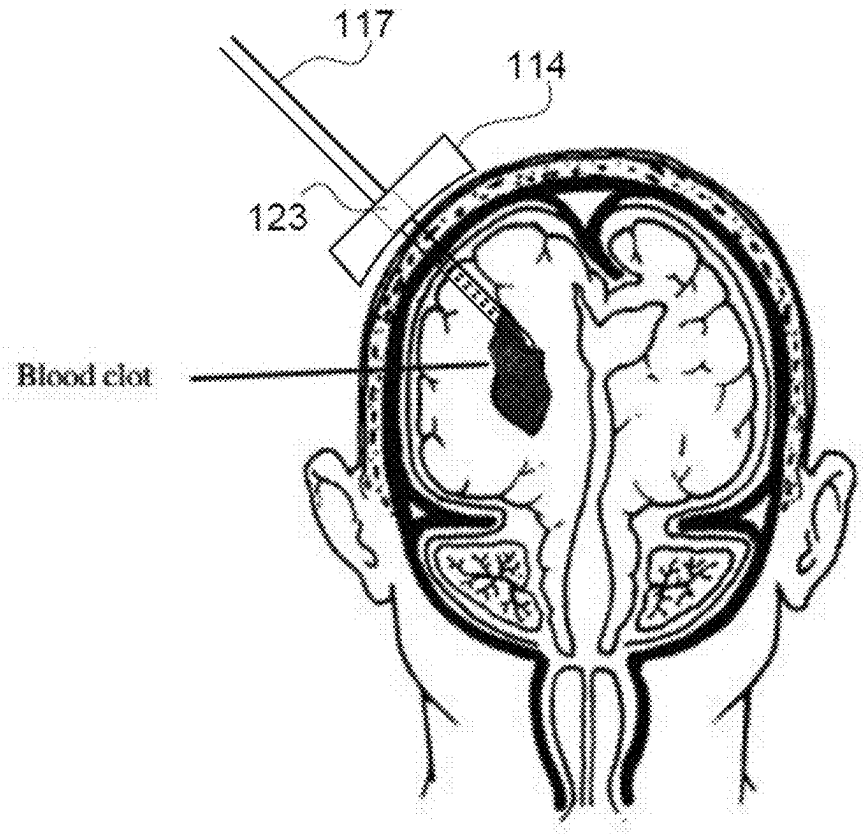


FIG. 5

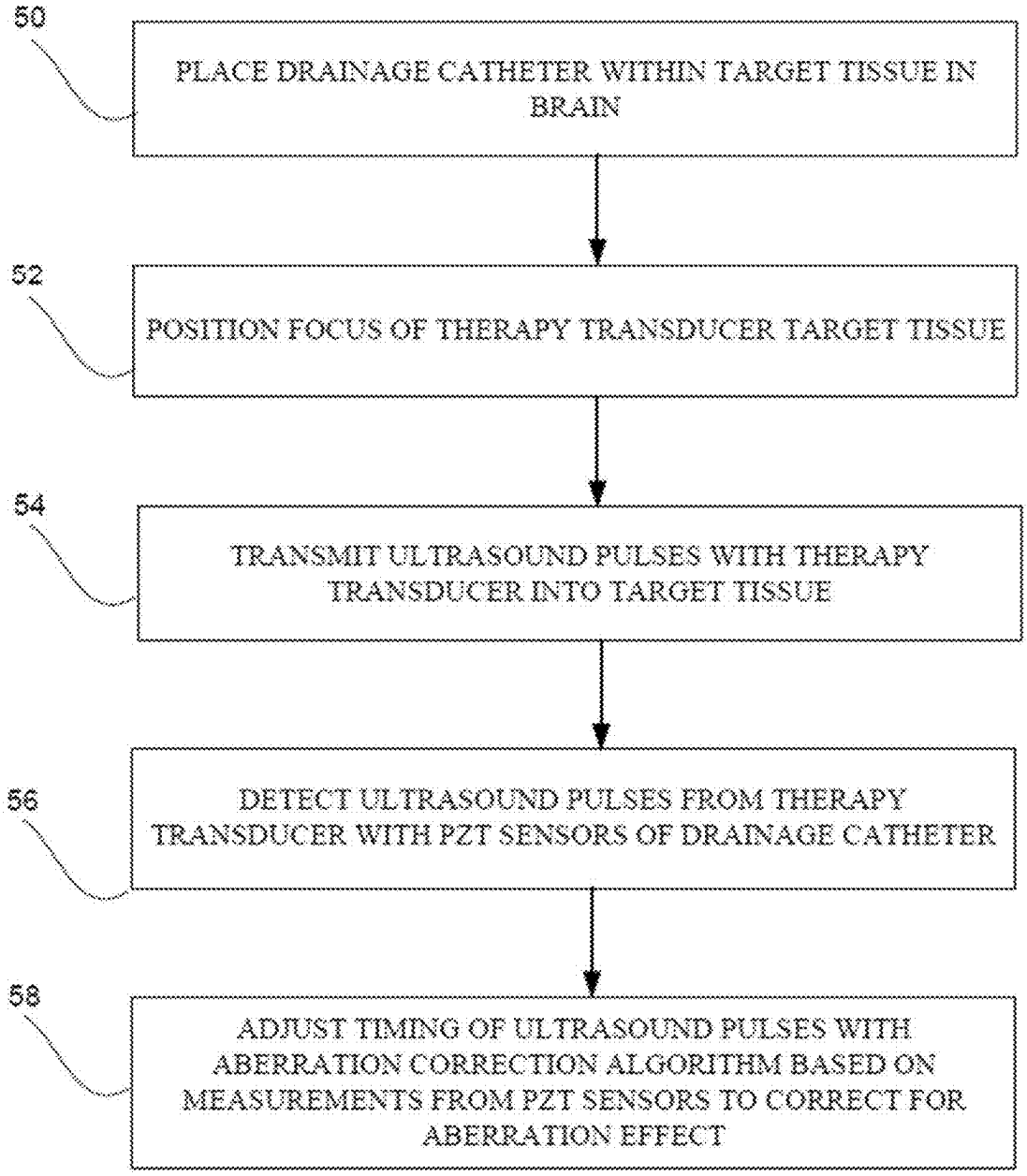
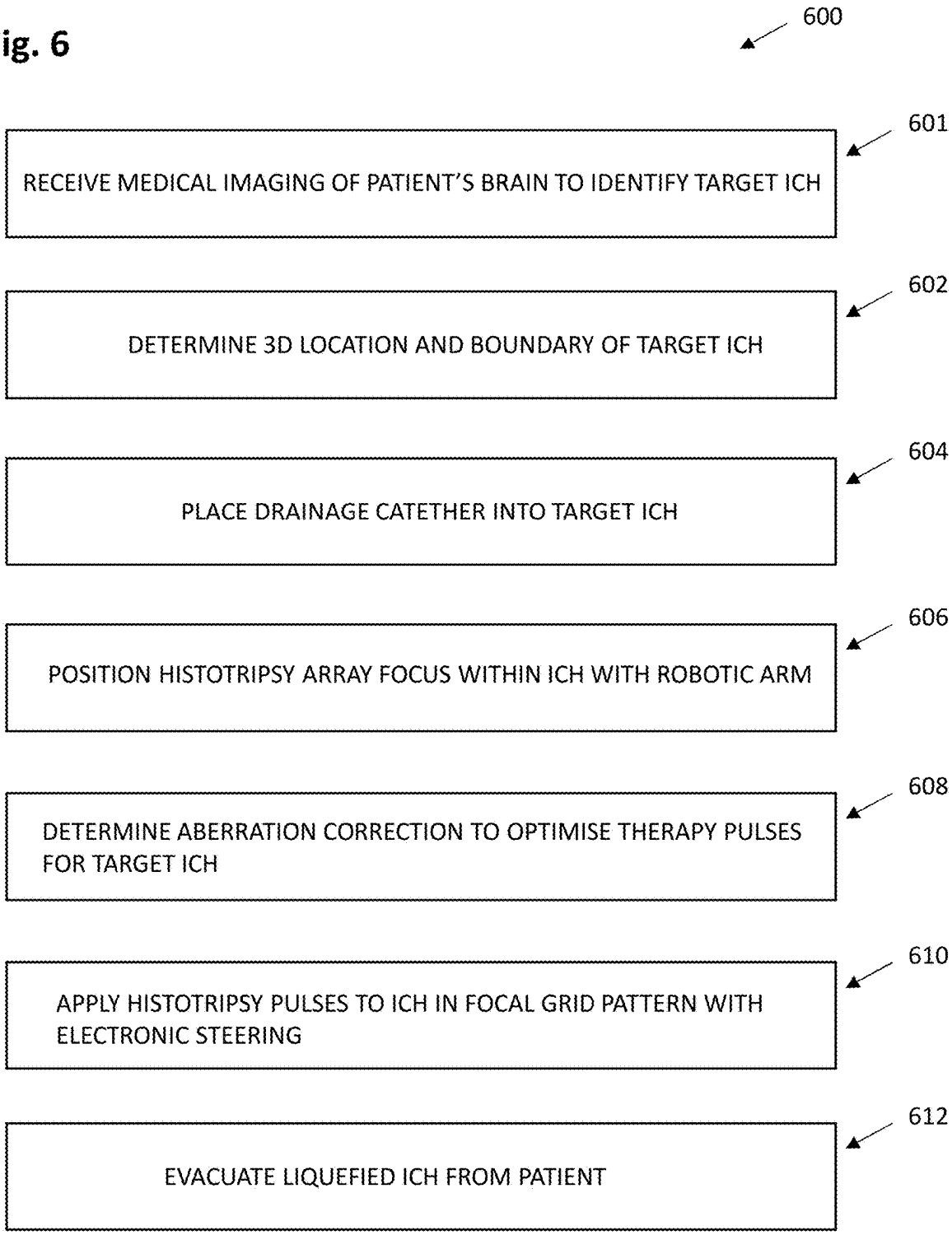

50
PLACE DRAINAGE CATHETER WITHIN TARGET TISSUE IN BRAIN
52
POSITION FOCUS OF THERAPY TRANSDUCER TARGET TISSUE
54
TRANSMIT ULTRASOUND PULSES WITH THERAPY TRANSDUCER INTO TARGET TISSUE
56
DETECT ULTRASOUND PULSES FROM THERAPY TRANSDUCER WITH PZT SENSORS OF DRAINAGE CATHETER
58
ADJUST TIMING OF ULTRASOUND PULSES WITH ABERRATION CORRECTION ALGORITHM BASED ON MEASUREMENTS FROM PZT SENSORS TO CORRECT FOR ABERRATION EFFECT

Fig. 6


600
601
RECEIVE MEDICAL IMAGING OF PATIENT'S BRAIN TO IDENTIFY TARGET ICH
602
DETERMINE 3D LOCATION AND BOUNDARY OF TARGET ICH
604
PLACE DRAINAGE CATETHER INTO TARGET ICH
606
POSITION HISTOTRIPSY ARRAY FOCUS WITHIN ICH WITH ROBOTIC ARM
608
DETERMINE ABERRATION CORRECTION TO OPTIMISE THERAPY PULSES FOR TARGET ICH
610
APPLY HISTOTRIPSY PULSES TO ICH IN FOCAL GRID PATTERN WITH ELECTRONIC STEERING
612
EVACUATE LIQUEFIED ICH FROM PATIENT

HISTOTRIPSY THERAPY SYSTEMS AND METHODS FOR THE TREATMENT OF BRAIN TISSUE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. application Ser. No. 19/006,948, filed Dec. 31, 2024, which is a continuation of U.S. application Ser. No. 17/407,780, filed Aug. 20, 2021, now U.S. Pat. No. 12,220,602, which is a continuation of U.S. application Ser. No. 15/737,761, filed Dec. 19, 2017, now U.S. Pat. No. 11,135,454, which is the national phase entry of International Application No. PCT/US2016/039020, filed Jun. 23, 2016, which claims the benefit of U.S. Provisional Patent Application No. 62/184,179, filed Jun. 24, 2015, titled "HISTOTRIPSY THERAPY SYSTEMS AND METHODS FOR THE TREATMENT OF INTRACEREBRAL HEMORRHAGE", all of which are incorporated by reference in their entirety.

GOVERNMENT LICENSE RIGHTS

[0002] This invention was made with government support under Grant Number NS093121 and EB028309 awarded by the National Institute of Health. The government has certain rights in the invention.

INCORPORATION BY REFERENCE

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

FIELD

[0004] This disclosure generally relates to treating tissue with cavitation created by ultrasound therapy. More specifically, this disclosure relates to treatment of brain tissue or disorders of the brain, such as intracerebral hemorrhage (ICH) or brain tumors, with ultrasound therapy.

BACKGROUND

[0005] Histotripsy, or pulsed ultrasound cavitation therapy, is a technology where extremely short, intense bursts of acoustic energy induce controlled cavitation (microbubble formation) within the focal volume. The vigorous expansion and collapse of these microbubbles mechanically homogenizes cells and tissue structures within the focal volume. This is a very different end result than the coagulative necrosis characteristic of thermal ablation. To operate within a non-thermal, Histotripsy realm; it is necessary to deliver acoustic energy in the form of high amplitude acoustic pulses with low duty cycle.

[0006] Compared with conventional focused ultrasound technologies, Histotripsy has important advantages: 1) the destructive process at the focus is mechanical, not thermal; 2) bubble clouds appear bright on ultrasound imaging thereby confirming correct targeting and localization of treatment; 3) treated tissue appears darker (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 microwave, radiofrequency, or high-intensity focused ultrasound (HIFU), Histotripsy is not a thermal modality.

[0007] The rupture of blood vessels in the brain can lead to bleeding and clotting (hematoma) inside the brain, termed as hemorrhagic stroke or intracerebral hemorrhage (ICH). ICH accounts for 10-15% of all strokes. Current mainstay treatment remains craniotomy, a highly invasive surgery to remove the clot, associated with severe damage to the brain neurological function.

[0008] Minimally invasive (MIS) stereotactic approaches have been investigated to drain the hematoma via a catheter and thrombolytic drug (tPA) over several days. However, there are severe complications associated with tPA, and the functional outcome for ICH survivors is not improved, likely due the long treatment time allowing neurological damage to develop.

[0009] Recent preclinical studies show that, using magnetic resonance guided focused ultrasound (MRgFUS) applied outside the skullcap, the clot in the brain can be liquefied without drugs and aspirated out with a needle. However, the MRgFUS treatment time is still not short enough to avoid neurological damage (up to 3 hours for 40 mL clot). It is highly costly due to the long MRI time required, and cannot treat clots within 2 cm distance from the skullcap.

[0010] A skullcap in the ultrasound pathway can cause significant attenuation and defocusing (aberration effect) of ultrasound signals passing through the skullcap. For aberration correction, MRgFUS uses a skullcap profile extracted from prior 3D CT scans of the patient brain. However, during MRgFUS treatment, as it is impossible to put the patient in the exact same position as the previous scan, MRI is needed to guide and monitor precise focusing through the skullcap. The process is complex and highly costly.

[0011] Furthermore, all the current methods are not effective for large hematoma (>40 mL). There is a clear unmet need for a better ICH therapy that can minimally invasively and rapidly reduce the hematoma in the brain without tPA, which will allow the ICH patients to recover without significant neurological damage.

SUMMARY OF THE DISCLOSURE

[0012] Histotripsy produces tissue fractionation through dense energetic bubble clouds generated by short, high-pressure, ultrasound pulses. When using pulses shorter than 2 cycles, the generation of these energetic bubble clouds only depends on where the peak negative pressure (P−) exceeds an intrinsic threshold for inducing cavitation in a medium (typically 26-30 MPa in soft tissue with high water content).

[0013] A method of transmitting ultrasound energy into a brain of a human patient is provided, comprising the steps of: imaging the brain to identify a target intracerebral hemorrhage (ICH); determining 3D coordinates of the ICH and a margin of the ICH; placing a drainage catheter within the ICH; attaching a stereotactic frame to the patient's skull; coupling a semi-spherical therapy transducer array and an acoustic coupler to the stereotactic frame; positioning a focus of a plurality of transducer elements of the therapy transducer array within the target tissue; transmitting test ultrasound pulses from each of the plurality of transducer elements towards a natural focus of the therapy transducer array; detecting the test ultrasound pulses with one or more

piezoelectric sensors positioned on or in the drainage catheter; and determining a set of time delays to add to ultrasound pulses from the plurality of transducer elements based on the detected ultrasound pulses to automatically correct for an aberration effect caused by the ultrasound pulses passing through the patient's skull; delivering histotripsy pulses with the set of time delays to liquefy the ICH; and evacuating the liquefied ICH from the patient with the drainage catheter.

[0014] In one aspect, the method includes delivering histotripsy pulses in a focal grid pattern without treating the margin.

[0015] In another aspect, the method includes transmitting second test ultrasound pulses from each of the plurality of transducer elements towards one or more discrete electronically steered focal locations; detecting the test ultrasound pulses with the one or more piezoelectric sensors positioned on or in the drainage catheter; and determining additional sets of time delays to add to ultrasound pulses from the plurality of transducer elements based on the detected ultrasound pulses to automatically correct for an aberration effect caused by the electronically steered ultrasound pulses passing through the patient's skull at each of the discrete electronically steered focal locations.

[0016] In some aspects, the method includes forming a bubble cloud on the target tissue with the histotripsy pulses.

[0017] In one aspect, the method includes adjusting the transmission of ultrasound pulses from the plurality of transducer elements with the aberration correction algorithm based on the detected ultrasound pulses further comprises: determining a propagation time for the ultrasound pulses to travel from each of the plurality of transducer elements of the therapy transducer to the one or more piezoelectric sensors; calculating a time delay of the propagation time between each of the plurality of transducer elements and a reference element of the therapy transducer; and adjusting the transmission of ultrasound pulses from the plurality of transducer elements based on the calculated time delays.

[0018] In some aspects, the one or more piezoelectric sensors comprises first and second piezoelectric sensors.

[0019] In other aspects, adjusting the transmission of ultrasound pulses from the plurality of transducer elements with the aberration correction algorithm based on the detected ultrasound pulses further comprises: determining a propagation time for the ultrasound pulses to travel from each of a plurality of transducer elements of the therapy transducer to the first and second piezoelectric sensors; calculating a distance between the first and second piezoelectric sensors using projections of the first and second piezoelectric sensors onto a ray from each of the plurality of transducer elements to a midpoint of the first and second piezoelectric sensors; calculating a travel direction and a time of travel of the ultrasound pulses from each of the plurality of transducer elements to the to the midpoint of the first and second piezoelectric sensors; calculating a stand-off distance between the focus and the midpoint for each of the plurality of transducer elements; and calculating a time delay of each of the plurality of transducer elements based on the distance between the first and second piezoelectric sensors, the midpoint, and the stand-off distance.

[0020] In some aspects, the method includes placing the one or more piezoelectric sensors within or adjacent to the focus.

[0021] In additional aspects, the placing step further comprises advancing the drainage catheter through a hole of the therapy transducer.

[0022] In some aspects, the method includes electronically steering the focus to fully liquefy the target tissue.

[0023] Additionally, the method includes mechanically steering the focus to fully liquefy the target tissue.

[0024] An ultrasound system configured to treat a target tissue in a brain of a human patient is provided, comprising: a pulse generator and an amplifier; a stereotactic frame configured to be attached to a skull of the patient; an acoustic coupler configured to be attached to the stereotactic frame; an ultrasound therapy transducer operatively coupled to the pulse generator and having a plurality of transducer elements configured to transmit ultrasound pulses through a skullcap of the human patient towards a focal point within the target tissue in the brain to generate cavitation, the ultrasound therapy transducer being configured to couple to the stereotactic frame such that the acoustic coupler provides acoustic coupling between the plurality of transducer elements and the patient; a drainage catheter comprising one or more piezoelectric sensors, the drainage catheter adapted to be placed within the brain near the focal point to measure the ultrasound pulses; an electronic controller coupled to the pulse generator, the ultrasound therapy transducer, and the piezoelectric sensors of the drainage catheter, the electronic controller being configured to control transmission of the ultrasound pulses and adjust the transmission of ultrasound pulses from each of the plurality of transducer elements by executing an aberration correction algorithm based on the ultrasound pulses detected by the drainage catheter to automatically correct for an aberration effect caused by the ultrasound pulses passing through the skullcap of the human patient.

[0025] In some aspects, the ultrasound therapy transducer is configured to transmit histotripsy therapy pulses to generate cavitation to liquefy the target tissue within the brain of the human patient.

[0026] In other aspects, the drainage catheter including drainage ports configured to drain the liquefied target tissue from the human patient.

[0027] In one aspect, the one or more piezoelectric sensors comprises exactly one piezoelectric sensor.

[0028] In some aspects, the aberration correction algorithm comprises: determining a propagation time for the ultrasound pulses to travel from each of the plurality of transducer elements of the therapy transducer to piezoelectric sensor; calculating a time delay of the propagation time between each of the plurality of transducer elements and a reference element of the therapy transducer; and adjusting the transmission of ultrasound pulses from the plurality of transducer elements based on the calculated time delays.

[0029] In some aspects, the one or more piezoelectric sensors comprises first and second piezoelectric sensors.

[0030] In one aspect, the aberration correction algorithm comprises: determining a propagation time for the ultrasound pulses to travel from each of the plurality of transducer elements of the therapy transducer to the first and second piezoelectric sensors; calculating a distance between the first and second piezoelectric sensors using projections of the first and second piezoelectric sensors onto a ray from each of the plurality of transducer elements to a midpoint of the first and second piezoelectric sensors; calculating a travel direction and a time of travel of the ultrasound pulses

from each of the plurality of transducer elements to the to the midpoint of the first and second piezoelectric sensors; calculating a stand-off distance between the focus and the midpoint for each of the plurality of transducer elements; and calculating a time delay of each of the plurality of transducer elements based on the distance between the first and second piezoelectric sensors, the midpoint, and the stand-off distance.

[0031] In one aspect, the therapy transducer comprises a hole through which the drainage catheter is configured to be advanced into the brain of the human patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] 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:

[0033] FIG. **1**A shows one embodiment of a Histotripsy therapy system that includes a drainage catheter.

[0034] FIG. **1**B is another embodiment of a Histotripsy therapy system having a stereotactic frame, a hemispherical therapy array mounted on a robotic positioning system, and a drainage catheter.

[0035] FIG. **2** shows schematic of drainage catheter and the guidewire with miniature piezoelectric sensors.

[0036] FIG. **3** illustrates the ray tracing algorithm to correct aberration of ultrasound pulses propagating through the skullcap in order to achieve focusing of histotripsy therapy through the skullcap.

[0037] FIGS. **4-5** illustrate one embodiment and method for treating brain tissue with Histotripsy ultrasound therapy.

[0038] FIG. **6** is another embodiment and method for treating brain tissue with Histotripsy ultrasound therapy.

DETAILED DESCRIPTION

[0039] Histotripsy is a noninvasive, cavitation-based therapy that uses very short, high-pressure ultrasound pulses to generate a dense, energetic, lesion-producing bubble cloud. This Histotripsy treatment can create controlled tissue erosion when it is targeted at a fluid-tissue interface and well-demarcated tissue fractionation when it is targeted within bulk tissue. Additionally, Histotripsy has been shown to be capable of fragmenting model kidney stones using surface erosion that is mechanistically distinct from conventional shockwave lithotripsy (SWL). Histotripsy therapy can be guided and monitored using ultrasound B-mode imaging in real-time, since 1) the cavitating bubble cloud appears as a temporally changing hyperechoic region in B-mode imaging, allowing the treatment to be precisely targeted, and 2) the echogenicity of the targeted region decreases as the degree of tissue fractionation increases, which can be used as a way of monitoring lesion production (image feedback) in real-time.

[0040] 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 has been called the "shock scattering mechanism". 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 these intense shock fronts developed by nonlinear propagation, no dense bubble clouds are generated when the peak negative half-cycles are below the intrinsic threshold.

[0041] When ultrasound pulses less than 2 cycles are applied, shock scattering can be minimized, and the generation of a dense bubble cloud depends on one or two negative half cycle(s) of the applied ultrasound pulses exceeding an "intrinsic threshold" of the medium (the "intrinsic threshold mechanism"). 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. Using this intrinsic threshold mechanism, the spatial extent of the lesion is 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 −6 dB beamwidth of a transducer can be generated.

[0042] Histotripsy has the potential to overcome the drawbacks of conventional treatment of ICH to provide minimally invasive, rapid reduction of hematoma in the brain, without thrombolytic drugs and regardless the size of the hematoma. Systems and methods described herein transmit microsecond-length ultrasound pulses at high pressures to generate a dense cavitation cloud of microbubbles using pre-existing gas nuclei in the clot within the focal region. The rapid expansion and collapse of the microbubbles induces high strain and stress to adjacent cells to fractionate the cells to liquid-like acellular homogenate.

[0043] According to some embodiments, Histotripsy can be used treat brain tissue or disorders of the brain, such as ICH or brain tumors. In one embodiment, Histotripsy can be used to liquefy a clot or a brain tumor through a skullcap of a human patient, and the resulting liquid can then be drained via a drainage catheter, without the use of thrombolytic drugs or external agents. For example, Histotripsy can be used to liquefy in vitro clots of 40 mL through a human skullcap within 30 minutes, which is six-fold faster than MRgFUS. With parameter optimization, the treatment time can be shortened by more than an order of magnitude compared to MRgFUS. These optimized parameters can be used to treat clots larger than 40 mL and at locations within 2 cm to the skullcap. The systems and methods described herein enable rapid clot removal even for clots >40 mL, in a minimally invasive approach, and eliminate the need for thrombolytic drugs and MRI, thereby substantially improving ICH and brain tumor therapy.

[0044] According to embodiments described herein that use histotripsy for treating the brain, a catheter can be placed

in a target tissue, such as a clot or tumor within the brain of a patient. One or more acoustic hydrophones or PZT sensors can be integrated to a guidewire placed inside the catheter, which can then be inserted into the target tissue in the brain to directly measure ultrasound signals from a histotripsy therapy transducer positioned outside the patient. The timing of pulse transmission from all elements of the histotripsy therapy transducer can be re-aligned to refocus through the skullcap by using the timing of the ultrasound signal received at the sensor from each element of histotripsy therapy transducer. The sensor(s) and associated aberration correction algorithm for transcranial histotripsy therapy described herein is novel and can provide a cost-effective and simplified device to guide and monitor transcranial histotripsy therapy without CT or MRI.

[0045] FIG. **1**A illustrates a Histotripsy system configured to generate cavitation bubbles or bubble clouds in tissue according to the methods and embodiments described herein. A Histotripsy system and generator is configured to generate complex waveforms in order to support the ultrasound pulse sequences described herein. A simplified block diagram of system **100** is shown in FIG. **1**A. The main components of the system are: Computer/controller **102**, USB to Serial Converter **104**, FPGA (Field Programmable Gate Array) **108**, High Voltage Controller and Power Supply **110**, Amplifier **112**, and Therapy Transducer **114**, and Drainage Catheter **117**.

[0046] All controls for the generator can be established using a "Histotripsy Service Tool" software that can run on the computer/controller **102** (e.g., a standard PC, laptop, tablet, or other electronic computing system) and communicates to the generator via a connector such as a wireless, USB, or serial communication **104**. The controller **102** can include a non-transitory computer-readable storage medium configured to store a set of instructions capable of being executed by the controller.

[0047] The system **100** can be configured to receive multiple sets of different driving parameters and loop them, which give the ability to the user to create wide range of custom sequences where all parameters (pulse repetition frequency (PRF), voltage amplitude, number of cycles, number of pulses per set, frequency, transducer element channels enabled, and time delays) can be set differently for every pulse generated. Time delays between pulses can be specified by the PRF for a parameter set or by specifying them manually/individually on a pulse-by-pulse basis.

[0048] For overall voltage amplitude regulation, level of high voltage can be changed accordingly through the HV Controller **110**. This method cannot be used for dynamic voltage amplitude changes between two pulses since it will take too long for all capacitors on the HV line to discharge. For dynamic voltage amplitude changes between pulses, PWM (pulse width modulation) can be used at the FPGA **108** where the duty cycle of the capacitor-charging pulse may be modulated in order to produce the desired pulse voltage and resultant pressure amplitude.

USB to Serial Converter

[0049] USB to Serial converter **104** can convert USB combination to serial in order to communicate from the PC or electronic controller to the FPGA. It should be understood that other converters (or none at all) may be used in embodiments where the connection between the generator and the controller is not a USB connection.

FPGA

[0050] The FPGA **108** receives the information from the PC or electronic controller **102** and it can generate the complex pulsing sequence that is required to drive the amplifier **112**. The FPGA can run on 100 MHz clock since speed of pulsing is critical to be timed in at least 10 ns increments.

High Voltage Controller and Power Supply

[0051] The High Voltage Controller and Power Supply **110** determines the level of DC voltage that needs to be supplied to the amplifier circuitry in order to have an adequate voltage amplitude level at the output of the amplifier.

Amplifier

[0052] The Amplifier **112** receives pulses generated by the FPGA and is supplied with high voltage from High Voltage Controller and Power Supply. It generates high voltage amplitude pulses that are fed to the Therapy Transducer **114** through the matching network components which properly matches the impedance of the therapy transducer to the impedance of the amplifier. It can be necessary to use a large number of capacitors that can store enough energy to support peak current demand during the generation of high voltage amplitude pulses.

Therapy Transducer

[0053] The Therapy Transducer **114** can be a single element transducer, or a multi-element ultrasound therapy transducer comprising a plurality of transducer elements and configured to generate and deliver the ultrasound therapy pulses described herein into tissue or other mediums. In some embodiments, the multi-element ultrasound therapy transducer can generate ultrasound pulses in two or more frequencies. The active transducer elements of the Therapy Transducer can be piezoelectric transducer elements. In some embodiments, the transducer elements can be mounted to an acoustic lens with a common geometric focus.

[0054] In other embodiments, the transducer elements can comprise a phased array that is optimized with steering parameters to maximize treatment speed and locations for transcranial histotripsy clot liquefaction without overheating the skullcap. Overheating the skullcap is the major limitation to restrain the treatment speed and location for transcranial ultrasound therapy. Proposed parameter optimization will ensure a rapid brain tissue treatment and minimize the heating to the skullcap. In some embodiments, the therapy transducer can achieve brain tissue liquefaction rates greater than 1 mL/min, which is orders of magnitude faster than passive thrombolytic action.

[0055] The therapy transducer can be configured to generate cavitation through the skullcap with a single ultrasound pulse having one high negative pressure phase lasting approximately 1-4 μs, where the peak negative pressure of the pulse directly exceeds the "intrinsic threshold" for cavitation of the medium (approximately 27 MPa for brain tissue such as clots). The focus of the therapy transducer can be electrically steered to other locations to cover a large treatment volume, and the treatment time can be shortened by more than an order of magnitude compared to other

therapy modalities. In some embodiments, the focal steering rate can be kept below 1% duty cycle to avoid overheating the skullcap.

[0056] According to the systems and methods described herein, histotripsy brain therapy can be performed without real-time imaging. CT scan may be needed as part of the target tissue diagnosis but is performed prior to the treatment. Using prior CT scan and stereotactic approach, the drainage hydrophone can be placed inside the clot, and the precise position of the catheter tip with regard to the clot position is known. The focus from the histotripsy therapy transducer can then be steered to liquefy a large portion of the brain tissue, leaving a thin rim of the tissue to avoid damage to adjacent brain tissue.

[0057] FIG. **1**B shows another embodiment of a Histotripsy therapy system **100** configured for treating a target tissue in a brain of a subject, such as an intracerebral hemorrhage (ICH), which can include a transcranial histotripsy array **114** coupled to a robotic positioning system or arm **118** and a drainage catheter **117**. The system can further include a central control console **122**, which can include all the components required to drive and control the robotic positioning system and the transcranial histotripsy array **114**, such as the histotripsy array driving electronics **124**. The console can further include, for example, one or more displays and user inputs to present therapy and imaging information to a user, and receive inputs from the user.

[0058] The transcranial histotripsy array **114** can include a plurality of transducer elements with a common natural focus, and be configured to generate microsecond pulses with a peak negative pressure that exceeds the cavitation threshold in tissue through the human skull (e.g., >30 MPa). The transcranial histotripsy array can be, for example, hemispherically shaped with a focal distance of 10-20 cm. It should be understood that other semi-spherical or concave shapes can be employed. In one specific example, the transcranial histotripsy array has a center frequency of 200 kHz-1 MHz and 200-2000 transducer elements.

[0059] Histotripsy therapy can be delivered by the histotripsy array to liquefy the targeted ICH by electronically steering the array focus to the pre-programmed focal scan path positions. In some examples, Histotripsy parameters can include a 500 kHz-1 MHz center frequency, pulses of 1-5 cycles in duration, pulse repetition frequency (PRF) ≤5 kHz or a duty cycle ≤0.5% to avoid overheating to skull, peak negative pressure >20 MPz, and 10-500 pulses per focal location.

[0060] Most arrays include an upper limit of electric focal steering range (e.g., 5 cm diameter). If the ICH is larger than the upper limit of the electric steering range, the ICH can be treated by combining mechanical focal steering and electric focal steering. The ICH can be divided into multiple segments. The histotripsy array can then be mechanically moved to the center of each segment by the robotic arm, and each segment can be treated by electric focal steering. Alternatively, the large ICH can be treated with multiple sessions.

[0061] A focal grid pattern can be determined by the system to treat the ICH with 1-2 mm rim or margin remaining to prevent the surrounding normal brain tissue from being damaged and to prevent the hemotoxic components in the clot lysates from leaking to the surrounding tissue. The ICH boundary is known to the neuronavigation system coregistered to the pre-treatment imaging (e.g., the pre-treatment CT scan). The coordinates of the ICH boundary can then be exported to the robotic arm, and a focal grid pattern can be created with predetermined spacing between adjacent focal positions (e.g., 0.2-2 mm) and leaving the margin of ICH untreated. The focal grid pattern can be used for treating the ICH with electric focal steering, thus, the largest dimension of the focal grid pattern is limited by the upper limit of the electric focal steering (e.g. 5 cm).

[0062] There may be an upper limit of the ICH that can be treated in one session (e.g., 40-60 mL). If the ICH is too large, then the scan path can be defined based on the upper limit of the electric steering range. It is worth noting that removal of 100% of the ICH volume is not critical. Improvement in ICH induced edema has been demonstrated for patients who have >65% of the ICH volume evacuated.

[0063] During treatment, the cavitation emission signals can be received by the histotripsy array and processed to produce a 3D map of the cavitation zone (i.e., treatment zone) in real-time. The 3D cavitation map can be overlaid onto the ICH from the prior CT scan to ensure the treatment zone is within the ICH. The histotripsy array elements can also receive reflection signals from the skull to form a skull map. The skull map formed by the histotripsy array can be overlaid and co-registered with the skull outer surface shown on the CT scan to ensure accuracy of the 3D cavitation feedback. In one example, if the cavitation feedback indicates any cavitation generation outside the ICH, the treatment will be halted.

[0064] The histotripsy array can optionally include one or more fiducial markers **115** (e.g. electromagnetic or optical markers) disposed on or within the array or array shell to co-register the array location and orientation with surgical navigation system.

[0065] The histotripsy array can be acoustically coupled to the patient and the target tissue with an acoustic coupler **126**. The acoustic coupler provides an acoustic path (e.g., via an acoustic coupling medium) to ensure efficient transmission of ultrasound from the histotripsy array to the target tissue. In one embodiment, the acoustic coupler **126** comprises a deformable, compliant, stretchable membrane or material. The acoustic coupler can comprise a sheet coupled to or sealed around edges of the histotripsy array (e.g., around the perimeter of the array shell), or alternatively, can be a sealed bag or balloon that can be adhered or coupled to the inner surface of the transducer array. In either embodiment, the acoustic coupler may include a supporting structure or frame configured to support the membrane. The supporting structure or frame may then be coupled to the histotripsy array, the stereotactic frame, or both. The acoustic coupler may further include an inlet and/or outlet to facilitate filling and draining with an acoustic coupling medium, such as degassed sterile water or saline, as needed.

[0066] In some embodiments, one or more sensors or other electronics can be included within or on the acoustic coupler **126** for the detection of bubbles or gas within the acoustic coupling medium. For example, a camera or optical sensor could be used inside the acoustic coupler to detect any air bubbles on the interface between the acoustic coupler and the patient. If bubbles or gas or detected, a physical device, such as a bendable tubing can be inserted into the acoustic coupler via the inlet or outlet to remove any air bubbles.

[0067] The console **122** and driving electronics **124** of the histotripsy array can include transmit-and-receive capabili-

ties, being configured to drive the array to transmit high-pressure histotripsy pulses into tissue, and receive the signals from cavitation emissions in the tissue along with reflection and scatter signals from the skull and tissue.

[0068] The console **122** and robotic positioning system can further include a surgical navigation system or neuronavigation system, which can be used to guide the insertion of the catheter hydrophone and target the histotripsy focus within the target tissue. The surgical navigation system can, for example, receive or generate imaging of the patient, including the target tissue, and use the imaging for targeting and therapy progression. The pre, peri, and/or post operative imaging can be any known medical imaging, including CT, CBCT, ultrasound, x-ray, or MRI imaging.

[0069] Referring still to FIG. **1**B, the system can further include a stereotactic frame **120** which can be rigidly attached to the patient's head (e.g., right above the eyebrow) and rigidly connected to the water coupling and the histotripsy array. There can be fiducial markers **128** on the stereotactic frame for co-registration with the surgical navigation system.

[0070] The drainage catheter **117** can be configured for insertion into the patient's brain. In one example, the drainage catheter is guided for insertion by the surgical navigation system. For example, the catheter hydrophone can be placed into the ICH center via a small burr hole in the skull. The ICH boundary locations with regards to the catheter hydrophone location can be calculated by the surgical navigation system. The drainage catheter can be affixed or attached to the histotripsy array, or separate from the array. In some examples, the array has a hole or bore to receive the catheter.

[0071] The liquefied ICH will be evacuated via the catheter after or during treatment. The catheter will be removed after treatment, and the burr hole will be patched up. For treatment of a large clot (e.g. >40 mL), the treated ICH may need to be treated by histotripsy and evacuated multiple times. Typically when the clot is evacuated, the brain will need to be imaged by CT again to re-evaluate the ICH boundary before the histotripsy is delivered again following the workflow described above.

[0072] The drainage catheter **117** can include one or more sensors or hydrophones incorporated into one or more portions of the catheter for receiving signals from the histotripsy array. These sensors can be used by the system to correct for aberrations as a result of transmitting ultrasound pulses through the skull. For example, when the histotripsy array elements transmit an ultrasound pulse, the catheter sensor(s) can measure the ultrasound signal generated by each of the element and calculate the travel time from each element to the catheter sensor(s). Using the travel time set based on catheter sensor signals, a set of time delays can be calculated by the system that can be input to each of the histotripsy array element to allow them to arrive at the catheter hydrophone location at the same time, i.e., aberration correction.

[0073] To maximize the electronic focal steering range, aberration correction can also be performed at discrete electronically-steered focal points. The array can be electronically steered to generate cavitation at discrete locations off the focus (e.g., locations separated by 5 mm apart in a 3D volume around the focus), and the shockwave emitted from these cavitations can be received by each of the histotripsy array elements and processed to calculate the travel time. This travel time set will be used to calculate a transmission delay set, which will then be applied to each of the elements for aberration correction at the discrete electronically-steered focal points.

Drainage Catheter

[0074] FIG. **2** is an expanded view of the drainage catheter **117** of the system, which can comprise a sheath portion **118** and a guidewire portion **120**. The sheath portion can comprise a flexible material and can include one or more drainage ports **119** to facilitate the removal of bodily fluids or tissues through the catheter. The guidewire portion **120** can be insertable into the sheath portion **118** for steering the catheter to the target region in tissue. The drainage catheter can further include one or more piezoelectric (PZT) sensors **122** disposed along the guidewire portion **120**. The embodiment of FIG. **2** shows 2 PZT sensors, but it should be understood that any number of PZT sensors can be implemented. For example, some embodiments utilize a single PZT sensor. The PZT sensors of the catheter can be configured to measure ultrasound pulse waveforms from individual elements of the therapy transducer **114** to extract time delays between waveforms transmitted by the therapy transducer. The time delays can then be used by the system for aberration correction.

[0075] In addition, the PZT sensors can also be used to monitor the initiation and maintenance of cavitation, which is an indication of successful histotripsy therapy and can be monitored as increased acoustic emission from the cavitation site. As the attenuation caused by the skullcap can vary across patients, such real-time cavitation detection can be used to identify the power needed to initiate cavitation for an individual patient.

[0076] Software and hardware can be configured to automatically control the pulse transmission from each element of the therapy transducer sequentially and to collect and store the signals from the PZT sensors. With only a few microseconds necessary to transmit a single pulse from one element at one time and ~100 μs for the ultrasound to travel from the element to the hydrophone, the entire data acquisition can be accomplished rapidly within a second using the automatic package.

Histotripsy Service Tool and Electronic Controller

[0077] Histotripsy Service Tool is software that can be run on any PC or computing system (e.g., electronic controller) and may be used for controlling the system. The Histotripsy Service Tool can start/stop the therapy with the therapy transducer, set and read the level of high voltage, therapy parameters (PRF, number of cycles, duty ratio, channel enabled and delay, etc.), and set and read other service and maintenance related items. The Histotripsy Service tool and Electronic Controller can be configured to set/read working parameters, start/stop the therapy, etc. It can use internal flash memory or other electronic storage media to store all the parameters. The Histotripsy Service Tool and Electronic Controller can communicate to the FPGA **108** all driving parameters that are necessary to generate complex pulsing. They can also communicate using serial communication or other electronic communication to the high voltage controller and power supply **110** where it can set/read the proper level of driving voltage.

[0078] The Histotripsy Service Tool and the Electronic controller can be coupled to the therapy transducer and the

PZT sensors of the drainage catheter to use feedback from the drainage catheter during transcranial Histotripsy therapy. When ultrasound pulses propagate through a human skullcap, an aberration effect results in the peak negative pressure of the ultrasound pulses being reduced. In some experiments, the aberration effect of the skullcap has been shown to reduce the peak negative pressure to approximately 20% or less of the free-field condition of the pulses.

[0079] In one embodiment, the PZT sensors of the drainage catheter can measure the ultrasound pulse signal from each transducer element of the therapy transducer, and the Histotripsy Service Tool and the Electronic control can use these measurements and execute and aberration correction algorithm to adjust the timing of electrical pulses to each transducer element to correct for the aberration effect. The software and hardware can then automatically control the pulse transmission from each element sequentially and collect and store the measured signals. With only a few microseconds necessary to transmit a single pulse from one element at one time and ~100 μs for the ultrasound to travel from each element to the PZT sensors, the entire data acquisition can be accomplished within a second using the proposed automatic package.

[0080] An aberration correction algorithm based on ray-tracing is configured to process the measured signal from the PZT sensors to achieve precise focusing and electrical or mechanical focal steering of the therapy transducer through the skullcap. In the specific embodiment described below, the system can include two or more PZT sensors. The algorithm contains three steps, and is illustrated in FIG. **3**. The steps are as follows: 1) Using the known locations of two or more PZT sensors within the catheter (H_1,H_2) and the emitting transducer element (T_N) of the therapy transducer, a plane, Π_N, is defined onto which the travel direction of the rays are restricted. H_1 and H_2 are assumed to be far enough from T_N that the emitted signals from each individual element are effectively traveling as plane waves. The propagation time (t_1 and t_2) for the ultrasound to travel from T_N to H_1 and H_2 can be calculated based on the time period between the signal arrival at the PZT sensor and its transmission from the transducer element. Using $\Delta t=t_1-t_2$, the distance between d_{N1} and d_{N2} is calculated as $dist(d_{N1}-d_{N2})=C_{tissue}*\Delta t$, where d_{N1} and d_{N2} are the projections of H_1 and H_2 onto the ray from T_N to the midpoint of the two sensors, H_{mid}. The travel direction θ_i and the time of travel of the wave from T_N to H_{mid} can then be calculated. 2) Knowing θ_i, a plane orthogonal to this wave propagation, Π_{orth}, can be defined and centered at the H_{mid}. Then assuming plane wave propagation, the requisite time delay of each transducer element can be calculated for a given focal location, f_n, by calculating the stand-off distance, d_x, between Π_{orth} and f_n, and plugging into the equation $T(f_n)=t_{mid}+d_x/c_{tissue}$. 3). Based on the time delay calculated for all steering locations within the treatment volume, a steering pattern can be generated in the software. The software can be configured to control steering parameters as well as cavitation monitoring, and can incorporate the aberration correction algorithm to automatically collect and process the PZT sensor signals and generate adjusted steering patterns.

[0081] In one embodiment, and aberration correction algorithm based on time delays is used to achieve precise focusing and electrical or mechanical focal steering of the therapy transducer through the skullcap. In the specific embodiment described immediately below, a single PZT sensor can be used. According to this embodiment, the algorithm comprises determining a propagation time for the ultrasound pulses to travel from each of the plurality of transducer elements of the therapy transducer to the piezoelectric sensor, calculating a time delay of the propagation time between each of the plurality of transducer elements and a reference element of the therapy transducer, and adjusting the transmission of ultrasound pulses from the plurality of transducer elements based on the calculated time delays.

[0082] One limitation of ultrasound transcranial therapy is overheating to the skullcap. To address this issue, a number of strategies may be employed in addition to parameter optimization. The order in which certain elements are fired can be alternated to reduce the local heating caused by individual elements. Heat may also be reduced by using cold water as the ultrasound coupling medium to the skullcap.

[0083] FIGS. **4-5** illustrate one embodiment and method for treating brain tissue with Histotripsy ultrasound therapy. FIG. **4** illustrates a therapy transducer **114** positioned adjacent to a skullcap of a patient, and a drainage catheter **117** positioned partially inside the brain of the patient such that drainage ports of the catheter are positioned within or adjacent to a target tissue of the brain, such as a blood clot or a brain tumor. To obtain precise focusing and focal steering, the PZT sensors in the catheter can be placed close to the geometrical focus of the transducer. In one embodiment, the therapy transducer **114** can include a hole **123** to facilitate catheter insertion through the transducer array. A catheter holder can be screwed into the hole, with scale markings on the catheter, which allows the operator to know the precise position of the catheter tip based on the insertion position, angle, and distance.

[0084] First, referring to step **50** of FIG. **5** and also to FIG. **4**, the drainage catheter **117** can be inserted through the skullcap of the patient and placed within or adjacent to the target tissue in the brain. Next, referring to step **52** of FIG. **5** and also to FIG. **4**, a focus of the therapy transducer **114** can be positioned on the target tissue. The therapy transducer itself can be acoustically coupled to the skull of the patient. Next, referring to step **54** of FIG. **5**, ultrasound pulses can be transmitted from the therapy transducer into the target tissue. At step **56** of FIG. **5**, PZT sensors of the drainage catheter can detect or measure ultrasound pulses from the therapy transducer. Finally, at step **58** of FIG. **5**, the software and electronic controller of the system can adjust timing of the ultrasound pulses with an aberration correction algorithm based on the measurements from the PZT sensors to correct for the aberration effect caused by the skullcap.

[0085] The ultrasound pulses can be configured to generate cavitation or bubble clouds within the target tissue of the brain to liquefy the target tissue. In some embodiments, the liquefied target tissue can be drained with the catheter. In further embodiments, the focus of the therapy transducer can be electronically or mechanically steered to fully liquefy the target tissue.

[0086] FIG. **6** is a workflow **600** describing a method of treatment using the system of FIG. **1**B. In one embodiment, the workflow for the histotripsy ICH treatment includes the following steps.

[0087] At step **601**, prior to treatment, the patient's brain can be scanned by medical imaging such as CT, which can be used to identify and localize the ICH.

[0088] Next, at step **602**, the workflow can include determining the 3D location, boundary, and/or coordinates of the target ICH. In some examples, this can include co-registration between the medical imaging coordinate system and the surgical navigation system coordinate system. In some examples, the co-registration can use fiducial markers on the patient's skull, on the stereotactic frame, or on other components of the system. The surgical navigation system can then be used to identify the 3D location, coordinates, and boundary of the target ICH.

[0089] At step **604**, the workflow can include catheter hydrophone insertion into the patient. For example, guided by the surgical navigation system, the catheter hydrophone can be placed into the ICH center via a small burr hole in the skull. The ICH boundary locations with regards to the catheter hydrophone location can also be calculated by the surgical navigation system.

[0090] At step **606**, the histotripsy array can be placed on or near the patient's skull. In one example, the stereotactic frame is rigidly attached on the patient's head. The histotripsy array and acoustic coupler are then connected to the stereotactic frame. With the fiducial markers on the histotripsy array surface, the position coordinates of the histotripsy array can be recognized by the surgical navigation system. The catheter hydrophone position coordinates are also known to the surgical navigation system. These coordinates will be exported to the robotic arm via the central control console so that the robotic arm can move the histotripsy array to place the array focus at or near the ICH center. One histotripsy array element can be removed to allow the catheter to go through to keep the catheter hydrophone remaining inserted in the brain.

[0091] At step **608**, the system can perform aberration correction to correct for the ultrasound energy passing through the patient's skull. In one example, each of the histotripsy array elements is controlled to transmit an ultrasound pulse, and the drainage catheter sensor(s) measure the ultrasound signal generated by each of the elements to calculate the travel time from each element to the catheter. Using the travel time set based on catheter signals, a set of time delay will be calculated that can be input to each of the histotripsy array elements to allow them to arrive at the catheter (or ICH) location at the same time, i.e., aberration correction.

[0092] To maximize the electronic focal steering range, aberration correction can also be performed at discrete electronically-steered focal points. Cavitation will be generated at discrete locations electronically steered off the focus (e.g., locations separated by 5 mm apart in a 3D volume around the focus), and the shockwave emitted from the cavitation will be received by each of the histotripsy array element and processed to calculate the travel time. This travel time set will be used to calculate the transmission delay set, which will then be applied to each of the element for aberration correction at the discrete electronically-steered focal points.

[0093] At step **610**, the histotripsy treatment can be applied in a focal grid pattern to treat the ICH. This can include a margin or rim of a predetermined size (e.g., 1-2 mm rim) remaining to prevent the surrounding normal brain tissue from being damaged and to prevent the hemotoxic components in the clot lysates from leaking to the surrounding tissue. The ICH boundary is known to the neuronavigation system co-registered to the pre-treatment CT scan. The coordinates of the ICH boundary can be exported to the robotic arm, and a focal grid pattern can be created with predetermined spacing between adjacent focal positions and leaving the margin or rim of ICH untreated. The focal grid pattern will be used for treating the ICH with electric focal steering, thus, the largest dimension of the focal grid pattern is limited by the upper limit of the electric focal steering (e.g. 5 cm).

[0094] There may be an upper limit of the ICH that can be treated in one session (e.g., 40-60 mL). If the ICH is too large, then the scan path can be defined based on the upper limit of the electric steering range. It is worth noting that removal of 100% of the ICH volume is not critical. Improvement in ICH induced edema has been demonstrated for patients who have >65% of the ICH volume evacuated.

[0095] Histotripsy can be delivered to liquefy the targeted ICH by electronically steering focus to the pre-programmed focal scan path positions.

[0096] Histotripsy parameters used may include 500 kHz-1 MHz center frequency, pulses of 1-5 cycles in duration, pulse repetition frequency (PRF) ≤5 kHz or a duty cycle ≤0.5% to avoid overheating to skull, peak negative pressure >20 MPz, and 10-500 pulses per focal location.

[0097] There is an upper limit of electric focal steering range (e.g., 5 cm diameter) depending on the array geometry. If the ICH is larger than the upper limit of the electric steering range, the ICH can be treated by combining mechanical focal steering and electric focal steering. The ICH can be divided into multiple segments. The histotripsy array will be mechanically moved to the center of each segment by the robotic arm, and each segment will be treated by electric focal steering. Alternatively, the large ICH can be treated with multiple sessions.

[0098] Optionally the workflow and treatment can include treatment monitoring. During treatment, the cavitation emission signals can be received by the histotripsy array and processed to produce a 3D map of the cavitation zone (i.e., treatment zone) in real-time. The 3D cavitation map can be overlaid onto the ICH from the prior CT scan to ensure the treatment zone is within the ICH. The histotripsy array elements can also receive reflection signals from the skull to form a skull map. The skull map formed by the histotripsy array can be overlaid and co-registered with the skull outer surface shown on the CT scan to ensure accuracy of the 3D cavitation feedback. If the cavitation feedback indicates any cavitation generation outside the ICH, the treatment can be halted.

[0099] After treatment is completed, or during treatment, at step **612**, the liquefied ICH can be evacuated via the catheter. The catheter is then removed, and the burr hole can be patched up.

[0100] For treatment of a large clot (e.g. >40 mL), the treated ICH may need to be treated by histotripsy and evacuated multiple times. Every time the clot is evacuated, the brain may need to be imaged again to re-evaluate the ICH boundary before the histotripsy is delivered again following the workflow described above.

[0101] The examples and illustrations included herein show, by way of illustration and not of limitation, specific embodiments in which the subject matter may be practiced. As mentioned, other embodiments may be utilized and derived there from, such that structural and logical substitutions and changes may be made without departing from the scope of this disclosure. Such embodiments of the

inventive subject matter may be referred to herein individually or collectively by the term "invention" merely for convenience and without intending to voluntarily limit the scope of this application to any single invention or inventive concept, if more than one is, in fact, disclosed. Thus, although specific embodiments have been illustrated and described herein, any arrangement calculated to achieve the same purpose may be substituted for the specific embodiments shown. This disclosure is intended to cover any and all adaptations or variations of various embodiments. Combinations of the above embodiments, and other embodiments not specifically described herein, will be apparent to those of skill in the art upon reviewing the above description.

What is claimed is:

1. A method of transmitting ultrasound energy into a brain of a human patient, comprising the steps of:

imaging the brain to identify a target intracerebral hemorrhage (ICH);

determining 3D coordinates of the ICH and a margin of the ICH;

placing a drainage catheter within the ICH;

attaching a stereotactic frame to the patient's skull;

coupling a semi-spherical therapy transducer array and an acoustic coupler to the stereotactic frame;

positioning a focus of a plurality of transducer elements of the therapy transducer array within the target tissue;

transmitting test ultrasound pulses from each of the plurality of transducer elements towards a natural focus of the therapy transducer array;

detecting the test ultrasound pulses with one or more piezoelectric sensors positioned on or in the drainage catheter; and

determining a set of time delays to add to ultrasound pulses from the plurality of transducer elements based on the detected ultrasound pulses to automatically correct for an aberration effect caused by the ultrasound pulses passing through the patient's skull;

delivering histotripsy pulses with the set of time delays to liquefy the ICH; and

evacuating the liquefied ICH from the patient with the drainage catheter.

2. The method of claim **1**, further comprising delivering histotripsy pulses in a focal grid pattern without treating the margin.

3. The method of claim **1**, further comprising:

transmitting second test ultrasound pulses from each of the plurality of transducer elements towards one or more discrete electronically steered focal locations;

detecting the test ultrasound pulses with the one or more piezoelectric sensors positioned on or in the drainage catheter; and

determining additional sets of time delays to add to ultrasound pulses from the plurality of transducer elements based on the detected ultrasound pulses to automatically correct for an aberration effect caused by the electronically steered ultrasound pulses passing through the patient's skull at each of the discrete electronically steered focal locations.

4. The method of claim **1**, further comprising forming a bubble cloud on the target tissue with the histotripsy pulses.

5. The method of claim **1**, wherein adjusting the transmission of ultrasound pulses from the plurality of transducer elements with the aberration correction algorithm based on the detected ultrasound pulses further comprises:

determining a propagation time for the ultrasound pulses to travel from each of the plurality of transducer elements of the therapy transducer to the one or more piezoelectric sensors;

calculating a time delay of the propagation time between each of the plurality of transducer elements and a reference element of the therapy transducer; and

adjusting the transmission of ultrasound pulses from the plurality of transducer elements based on the calculated time delays.

6. The method of claim **1**, wherein the one or more piezoelectric sensors comprises first and second piezoelectric sensors.

7. The method of claim **6**, wherein adjusting the transmission of ultrasound pulses from the plurality of transducer elements with the aberration correction algorithm based on the detected ultrasound pulses further comprises:

determining a propagation time for the ultrasound pulses to travel from each of a plurality of transducer elements of the therapy transducer to the first and second piezoelectric sensors;

calculating a distance between the first and second piezoelectric sensors using projections of the first and second piezoelectric sensors onto a ray from each of the plurality of transducer elements to a midpoint of the first and second piezoelectric sensors;

calculating a travel direction and a time of travel of the ultrasound pulses from each of the plurality of transducer elements to the to the midpoint of the first and second piezoelectric sensors;

calculating a stand-off distance between the focus and the midpoint for each of the plurality of transducer elements; and

calculating a time delay of each of the plurality of transducer elements based on the distance between the first and second piezoelectric sensors, the midpoint, and the stand-off distance.

8. The method of claim **1** further comprising placing the one or more piezoelectric sensors within or adjacent to the focus.

9. The method of claim **1**, wherein the placing step further comprises advancing the drainage catheter through a hole of the therapy transducer.

10. The method of claim **3**, further comprising electronically steering the focus to fully liquefy the target tissue.

11. The method of claim **3**, further comprising mechanically steering the focus to fully liquefy the target tissue.

12. An ultrasound system configured to treat a target tissue in a brain of a human patient, comprising:

a pulse generator and an amplifier;

a stereotactic frame configured to be attached to a skull of the patient;

an acoustic coupler configured to be attached to the stereotactic frame;

an ultrasound therapy transducer operatively coupled to the pulse generator and having a plurality of transducer elements configured to transmit ultrasound pulses through a skullcap of the human patient towards a focal point within the target tissue in the brain to generate cavitation, the ultrasound therapy transducer being configured to couple to the stereotactic frame such that

the acoustic coupler provides acoustic coupling between the plurality of transducer elements and the patient;

a drainage catheter comprising one or more piezoelectric sensors, the drainage catheter adapted to be placed within the brain near the focal point to measure the ultrasound pulses;

an electronic controller coupled to the pulse generator, the ultrasound therapy transducer, and the piezoelectric sensors of the drainage catheter, the electronic controller being configured to control transmission of the ultrasound pulses and adjust the transmission of ultrasound pulses from each of the plurality of transducer elements by executing an aberration correction algorithm based on the ultrasound pulses detected by the drainage catheter to automatically correct for an aberration effect caused by the ultrasound pulses passing through the skullcap of the human patient.

13. The ultrasound system of claim **12**, wherein the ultrasound therapy transducer is configured to transmit histotripsy therapy pulses to generate cavitation to liquefy the target tissue within the brain of the human patient.

14. The ultrasound system of claim **13**, the drainage catheter including drainage ports configured to drain the liquefied target tissue from the human patient.

15. The ultrasound system of claim **12**, wherein the one or more piezoelectric sensors comprises exactly one piezoelectric sensor.

16. The ultrasound system of claim **15**, wherein the aberration correction algorithm comprises:

determining a propagation time for the ultrasound pulses to travel from each of the plurality of transducer elements of the therapy transducer to piezoelectric sensor;

calculating a time delay of the propagation time between each of the plurality of transducer elements and a reference element of the therapy transducer; and

adjusting the transmission of ultrasound pulses from the plurality of transducer elements based on the calculated time delays.

17. The ultrasound system of claim **12**, wherein the one or more piezoelectric sensors comprises first and second piezoelectric sensors.

18. The ultrasound system of claim **17**, wherein the aberration correction algorithm comprises:

determining a propagation time for the ultrasound pulses to travel from each of the plurality of transducer elements of the therapy transducer to the first and second piezoelectric sensors;

calculating a distance between the first and second piezoelectric sensors using projections of the first and second piezoelectric sensors onto a ray from each of the plurality of transducer elements to a midpoint of the first and second piezoelectric sensors;

calculating a travel direction and a time of travel of the ultrasound pulses from each of the plurality of transducer elements to the to the midpoint of the first and second piezoelectric sensors;

calculating a stand-off distance between the focus and the midpoint for each of the plurality of transducer elements; and

calculating a time delay of each of the plurality of transducer elements based on the distance between the first and second piezoelectric sensors, the midpoint, and the stand-off distance.

19. The ultrasound system of claim **12**, wherein the therapy transducer comprises a hole through which the drainage catheter is configured to be advanced into the brain of the human patient.

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