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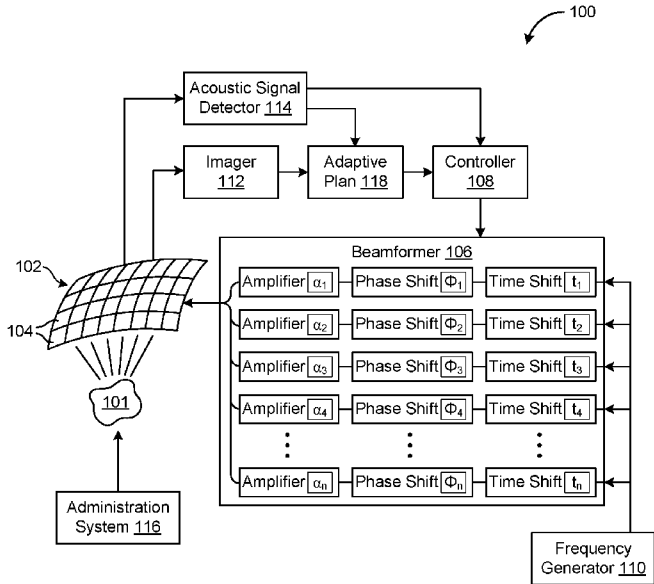


Figure 1

(57) **Abstract:** A controller communicatively coupled to an ultrasound transducer obtains image data of one or more subregions of the target region; determines a tissue type, a vasculature characteristic, or a microbubble concentration associated with each of the one or more subregions based on the image data; determines an acoustic treatment parameter for each of the one or more subregions based on the tissue type, the vasculature characteristic, or the microbubble concentration respectively associated with each of the one or more subregions; and causes the ultrasound transducer to sonicate the one or more subregions according to the acoustic treatment parameters respectively corresponding to each of the one or more subregions.

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TISSUE TYPE-BASED BLOOD-BRAIN BARRIER OPENING AND TREATMENT PARAMETER ESTABLISHMENT SYSTEMS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is related to U.S. Patent Application 18/176,978 (filed March 1, 2023), and International Patent Application PCT/IB2022/000747 (filed December 8, 2022), each of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The field of the disclosure relates generally to ultrasound systems and, more particularly, to systems and methods for selective, targeted opening of the blood-brain barrier using an ultrasound procedure.

BACKGROUND

[0003] The blood-brain barrier (BBB), formed by layers of cells in the central nervous system (CNS), excludes large molecules from entering the brain parenchyma, thereby protecting it from damage by toxic foreign substances. But the BBB also presents one of the largest obstacles to treating many brain diseases. Specifically, the BBB prevents many therapeutic agents, such as drugs and gene-therapy vectors, from reaching a patient's brain tissue. For example, treatments for CNS infections, neurodegenerative diseases, congenital enzyme defects and brain cancer are all hampered by the ability of the BBB to block passage of, inter alia, antibiotics, anti-retroviral drugs, enzyme replacement therapy, gene preparations and anti-neoplastic drugs. It is thus desirable to temporarily and locally "open" the BBB to permit therapeutic quantities of these agents to access the affected brain tissue.

[0004] Focused ultrasound (FUS) is a technique that enables mechanical opening of the BBB, allowing for the entrance of drugs and other molecules into the brain parenchyma. The opening of the BBB is achieved by sonicating gas bubbles that are circulating systemically, thus applying local mechanical strains on the endothelial cells. Currently, BBB opening operations are limited to small brain regions or produce variable results, due to the heterogeneous nature of the brain tissue. Different brain regions differ by their physiological properties (e.g., tissue composition, mechanical properties, vasculature density, vessel diameter distribution, vascular blood flow rate, etc.). Moreover, cancerous and benign tumors are known to have abnormal and deformed vasculature and unique heterogeneous microenvironment. Frequently, the tumor vasculature differs between the tumor core and its

rim, and in certain regions deformed vessels have unique mechanical properties. In some other pathologies like Alzheimer's disease (A.D.), the vascular system is known to be more leaky and fragile in comparison to healthy tissue. Using FUS to open the BBB in such varying regions and microenvironments can lead to overtreatment and damage or tissue-dependent BBB opening. Thus, there is a need for FUS treatment systems and methods that can achieve safe and confluent BBB openings in heterogenous brain regions and microenvironments, thereby avoiding permanent damage to the BBB and its surrounding tissue.

[0005] Moreover, the autonomic nervous system could change blood flow characteristics in between repeated sonications due to accumulated BBB opening effects and vasoconstriction. Therefore, there is a need for FUS treatment systems and methods that can achieve safe and confluent BBB openings in brain regions having changing physiological properties.

SUMMARY

[0006] The present disclosure provides systems and methods for adaptively treating target areas in a safe and effective manner, by identifying treatment-related properties of the target areas while accounting for the local microbubble concentration, blood flow patterns, and tissue types. This adaptive treatment planning enables safe and efficient BBB opening in large heterogenous brain regions. In addition, it details specific acoustic treatment parameters for optimal BBB opening with minimal treatment-related side effects. The techniques described herein estimate the optimal acoustic parameters for each different area or tissue to be treated, and tailor the treatment parameters to achieve optimal BBB opening in each specified treated area or tissue. Moreover, the techniques described herein adaptively modify the treatment parameters in real time in response to changes in blood flow patterns.

[0007] In some embodiments, the disclosure relates to a system and/or a method for providing focused ultrasound to a target region. A controller is configured to obtain image data of one or more subregions of the target region and/or a region surrounding the target region; determine a tissue type, a vasculature characteristic, or a microbubble concentration associated with each of the one or more subregions based on the image data; determine an acoustic treatment parameter for each of the one or more subregions based on the tissue type, the vasculature characteristic, or the microbubble concentration respectively associated with each of the one or more subregions; and cause an ultrasound transducer to sonicate the one or

more subregions according to the acoustic treatment parameters respectively corresponding to each of the one or more subregions.

[0008] In some embodiments, a first subregion of the one or more subregions comprises a first tissue type characterized by a first vascular density; a second subregion of the one or more subregions comprises a second tissue type characterized by a second vascular density lower than the first vascular density; and determining the acoustic treatment parameter for each of the one or more subregions comprises: determining a first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the first subregion; and determining a second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the second subregion. In some embodiments, the target region comprises portions of the blood-brain barrier that include gray matter and white matter; the first tissue type is gray matter; and the second tissue type is white matter. In some embodiments, the first tissue type can tolerate treatment rate 2-4 times higher than the second tissue type.

[0009] In some embodiments, a first subregion of the one or more subregions comprises a first tissue type characterized by a first tolerance level for the treatment; a second subregion of the one or more subregions comprises a second tissue type characterized by a second tolerance level for the treatment lower than the first tolerance level for the treatment; and determining the acoustic treatment parameter for each of the one or more subregions comprises: determining a first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the first subregion; and determining a second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the second subregion. In some embodiments, the target region comprises portions of the blood-brain barrier that include gray matter and white matter; the first tissue type is gray matter; and the second tissue type is white matter. In some other embodiments, the target region comprises portions of the blood-brain barrier that include more healthy tissue and less healthy tissue; the first tissue type is gray matter; and the second tissue type is white matter. In some embodiments, the less healthy tissue is a tissue that was heavily affected by a neurodegenerative disease such as Alzheimer's Disease.

[0010] In some embodiments, a first subregion of the one or more subregions is characterized by a first vascular density; a second subregion of the one or more subregions is characterized by a second vascular density lower than the first vascular density; and

determining the acoustic treatment parameter for each of the one or more subregions comprises: determining a first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the first subregion; and determining a second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the second subregion.

[0011] In some embodiments, a first subregion of the one or more subregions is characterized by a first microbubble concentration; a second subregion of the one or more subregions is characterized by a second microbubble concentration lower than the first microbubble concentration; and determining the acoustic treatment parameter for each of the one or more subregions comprises: determining a first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the first subregion; and determining a second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the second subregion.

[0012] In some embodiments, the controller is configured to determine the tissue type associated with each of the one or more subregions based on the image data; the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively lower pulse duration, pulse duty cycle, an acoustic frequency, acoustic power level, or treatment duration for subregions having tissue types that are characterized by relatively lower treatment tolerability, bubble concentration, vascular density or vascular flow velocity. In some embodiments, in those regions, the controller may select a lower acoustic frequency that produces more bubble activity. In other embodiments, in those regions, the controller might select an acoustic frequency that better matches the resonance frequency of the bubbles to maximize the bubble response. In some embodiments, the controller may manipulate the phases or time delay configuration to improve focusing or to smear the focus to get a less heterogenous treatment in the focal area according to the tissue tolerability.

[0013] In some embodiments, the controller is configured to determine the vasculature characteristic associated with each of the one or more subregions based on the image data, wherein the vasculature characteristic is a vascular density or a vascular flow velocity; the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively higher

acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having relatively lower vascular density or vascular flow velocity.

[0014] In some embodiments, the controller is configured to determine the microbubble concentration associated with each of the one or more subregions based on the image data; the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having relatively lower microbubble concentration.

[0015] In some embodiments, the controller is further configured to, after causing the ultrasound transducer to sonicate the one or more subregions: obtain subsequent image data of the one or more subregions of the target region; determine an updated vasculature characteristic or microbubble concentration associated with each of the one or more subregions based on the subsequent image data; determine an updated acoustic treatment parameter for each of the one or more subregions based on the updated vasculature characteristic or microbubble concentration respectively associated with each of the one or more subregions; and cause the ultrasound transducer to sonicate the one or more subregions according to the updated acoustic treatment parameters respectively corresponding to each of the one or more subregions.

[0016] In some embodiments, the controller is further configured to, for each sonication or pulse, determine an acoustic treatment parameter for each of the one or more subregions based on the tissue type, the vasculature characteristic, or the microbubble concentration respectively associated with each of the one or more subregions, together with the acoustic information received during previous sonication or pulse of the subregions; and cause the ultrasound transducer to sonicate the one or more subregions according to the updated acoustic treatment parameters respectively corresponding to each of the one or more subregions.

[0017] In some embodiments, wherein obtaining the image data comprises obtaining: contrast-enhanced ultrasound device (CEUS) data, ultrasound localization microscopy device

(ULM) data for obtaining ultrasound super-resolution images, magnetic resonance imaging (MRI) data, or computer tomography (CT) data.

[0018] In some embodiments, causing the ultrasound transducer to sonicate the one or more subregions comprises causing microbubbles to be generated and/or activated by application of ultrasound at the target region or causing the transducer to sonicate microbubbles administered by the system at the target region. In some embodiments, obtaining the image data comprises imaging the target region. In some embodiments, obtaining the image data comprises identifying the target region and using an atlas to determine the vasculature characteristic associated with each of the one or more subregions. In some embodiments, causing the ultrasound transducer to sonicate the one or more subregions comprises controlling acoustic power or energy emitted by transducer elements of the ultrasound transducer so that acoustic power or energy is above a threshold level to thereby induce microbubble generation or higher acoustic radiation force. In some embodiments, the acoustic treatment parameter is a frequency, an amplitude, or a phase associated with a plurality of transducer elements of the ultrasound transducer.

[0019] In some embodiments, the treatment controller has a distinct algorithm to maintain safety of the treatment based on the acoustic feedback during the treatment. Such implementations may be referred to as blind implementations since the controller is not aware of tissue types. A blind controller may use one set of one or more bands of the acoustic feedback in the treatment for efficacy (e.g., calculation of the treatment dose and treatment rate) and another independent set of one or more bands for maintaining safety (e.g., keeping the energy or power measured in the safety band below a threshold). In some embodiments, the bands for efficacy and the bands for safety may partially or entirely overlap.

[0020] In some embodiments, the safety information may be obtained by the controller using curve-fitting or other type of pre-processing that can separate narrowband signals indicative of overtreatment from broad-band efficacy indicators without prior knowledge of their specific frequency. Bifurcations are indicative of violent cavitation activity and appear in the PCD spectrum as symmetric peaks around the sub-harmonic peak, whose exact frequency could not be estimated in advance. A comb filter can separate narrowband peaks (harmonics) from broadband signals when their frequency is known (e.g., a sum-of-harmonics method for improved narrowband and broadband signal quantification during passive monitoring of ultrasound therapies). A slightly different approach with curve fitting could extend this to separating peaks with unknown frequencies from broadband signals.

[0021] In some embodiments, the safety algorithm can use the tissue type as determined by the controller as input to the safety algorithm. In some embodiments, the safety algorithm selects safety thresholds based on the tissue type (e.g., white matter vs. gray matter, or any other tissue type characteristic). In some embodiments, the controller selects lower safety thresholds for the tissues with lower vascular density; however, in some other embodiments, when possible, the controller might favor efficacy over safety and select higher safety thresholds for the tissues characterized by lower vascular density for which the treatment rate is lower.

[0022] As used herein, the terms “approximately” and “substantially” mean $\pm 20\%$, and in some embodiments, $\pm 5\%$. Reference throughout this specification to “one example,” “an example,” “one embodiment,” or “an embodiment” means that a particular feature, structure, or characteristic described in connection with the example is included in at least one example of the present technology. Thus, the occurrences of the phrases “in one example,” “in an example,” “one embodiment,” or “an embodiment” in various places throughout this specification are not necessarily all referring to the same example. Furthermore, the particular features, structures, routines, steps, or characteristics may be combined in any suitable manner in one or more examples of the technology. The headings provided herein are for convenience only and are not intended to limit or interpret the scope or meaning of the claimed technology.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] In the drawings, like reference characters generally refer to the same parts throughout the different views. Also, the drawings are not necessarily to scale, with an emphasis instead generally being placed upon illustrating the principles of the invention. In the following description, various embodiments of the present invention are described with reference to the following drawings.

[0024] Figure 1 schematically depicts an exemplary ultrasound system in accordance with various embodiments.

[0025] Figure 2 depicts presence of microbubbles in a target tissue region in accordance with various embodiments.

[0026] Figure 3 shows example image data of a target region in accordance with some embodiments.

[0027] Figure 4 shows example adaptive plan data of one or more subregions within the target region in accordance with some embodiments.

[0028] Figure 5 shows an example scenario in which acoustic treatment parameters may change according to a combination of tissue type and vascular characteristics in accordance with some embodiments.

[0029] Figure 6 shows a flowchart of an example method for providing focused ultrasound to a target region, according to some embodiments.

[0030] Figures 7-15 show experimental results of BBB opening in landrace pigs sonicated over widespread anatomical regions, according to some embodiments.

DETAILED DESCRIPTION

[0031] Figure 1 illustrates an exemplary ultrasound system 100 for generating and delivering a focused acoustic energy beam to a target region 101 within a patient's body. The applied ultrasound sonication may induce microbubble cavitation or acoustic radiation force and disrupt the target BBB region in a controlled and reversible manner. The applied ultrasound waves may be reflected from the target region and/or non-target region, and an image of the target and/or non-target regions may be generated based on the reflected waves. In addition, microbubbles may be introduced to the target region 101 and/or non-target region to increase ultrasound reflections, thereby improving the contrast of the ultrasound image. In some embodiments, the applied ultrasound waves may ablate tissue in the target region 101 and/or induce microbubble oscillation and/or cavitation to improve treatment effects.

[0032] In various embodiments, the system 100 includes a phased array 102 of transducer elements 104, a beamformer 106 driving the phased array 102, a controller 108 in communication with the beamformer 106 and configured to operate the beamformer 106 in accordance with an adaptive treatment plan 118, and a frequency generator 110 providing an input electronic signal to the beamformer 106.

[0033] In various embodiments, the ultrasound system 100 further includes an imager 112 for determining anatomical characteristics (e.g., the type, property, structure, thickness, density, etc.) of the tissue at the target region 101 and/or the tissue surrounding the target region (referred to as a non-target region). For example, the imager 112 may be a contrast-enhanced ultrasound device (CEUS), an ultrasound localization microscopy device (ULM) for obtaining ultrasound super-resolution images, a magnetic resonance imaging (MRI) device, a computer tomography (CT) device, a positron emission tomography (PET) device, a

single-photon emission computed tomography (SPECT) device, or an ultrasonography device. The ultrasound system 100 and/or imager 112 may be utilized to detect the presence, type, and/or location associated with microbubble cavitation.

[0034] In various embodiments, the ultrasound system 100 further includes an acoustic signal detector 114, also referred to as a cavitation detection device, to detect information associated with microbubble cavitation. For example, the acoustic signal detector 114 may be a passive cavitation detector (PCD), a hydrophone, or any suitable alternative.

[0035] The array 102 may have a curved (e.g., spherical or parabolic) shape suitable for placing it on the surface of the skull, or may include one or more planar or otherwise shaped sections. Its dimensions may vary between millimeters and tens of centimeters. The transducer elements 104 of the array 102 may be piezoelectric ceramic elements, and may be mounted in silicone rubber or any other material suitable for damping the mechanical coupling between the elements 104. Piezo-composite materials, or generally any materials capable of converting electrical energy to acoustic energy, may also be used. To assure maximum power transfer to the transducer elements 104, the elements 104 may be configured for electrical resonance at, e.g., 50 Ω to match (or substantially match) input connector impedance.

[0036] The transducer array 102 is coupled to the beamformer 106, which drives the individual transducer elements 104 so that they collectively produce a focused ultrasonic beam or field. For n transducer elements, the beamformer 106 may contain n driver circuits, each including or consisting of an amplifier, a phase shift circuit, and/or a time shift circuit. Each driver circuit drives one of the transducer elements 104. The beamformer 106 receives a radio frequency (RF) input signal, typically in the range from 0.1 MHz to 1.0 MHz, from the frequency generator 110. The input signal may be split into n channels for the n amplifiers, phase shift circuits, and time shift circuits of the beamformer 106. In some embodiments, the frequency generator 110 is integrated with the beamformer 106. The frequency generator 110 and the beamformer 106 are configured to drive the individual transducer elements 104 of the transducer array 102 at the same frequency, but at different amplitudes, different phases, and/or different time delays. Time delays shift all frequencies by the same amount of time, whereas phase delays shift some frequencies longer than others.

[0037] The amplification or attenuation factors α_1 - α_n , phase shifts Φ_1 - Φ_n , and/or the time shifts t_1 - t_n imposed by the beamformer 106 serve to transmit and focus ultrasonic

energy through the patient's skull onto a selected region 101 of the patient's BBB, and account for wave distortions induced in the skull and soft brain tissue. The amplification factors, phase shifts, and time shifts are computed using the controller 108, which may provide the computational functions through software, hardware, firmware, hardwiring, or any combination thereof. For example, the controller 108 may utilize a general-purpose or special-purpose digital data processor programmed with software in a conventional manner, and without undue experimentation, in order to determine an optimal value of an ultrasound parameter (e.g., a frequency, an amplification factor, a phase shift, and/or a time shift) associated with each element 104 so as to obtain a desired focus or any other desired spatial field patterns. The optimal value of the ultrasound parameter may be refined experimentally before, after, and/or at one or more times during the ultrasound procedure based on, for example, the focus quality, the focus location relative to the target 101 and/or the microbubble response to the ultrasound sonications. The quality and location of the focus may be monitored using the imager 112, and the microbubble response may be detected using the transducer 102 and/or the acoustic signal detector 114.

[0038] In certain embodiments, the optimal value of the ultrasound parameter is computationally estimated based on detailed information about the characteristics of the intervening tissue and their effects (e.g., reflection, refraction, and/or scattering) on propagation of acoustic energy. Such information may be obtained from the imager 112 and analyzed manually or computationally. Image acquisition may be three-dimensional or, alternatively, the imager 112 may provide a set of two-dimensional images suitable for reconstructing a three-dimensional image of the target and/or non-target regions. Image-manipulation functionality may be implemented in the imager 112, in the controller 108, or in a separate device.

[0039] In certain treatment scenarios, ultrasound waves propagating towards the target region 101 from different directions may encounter a highly variable anatomy, such as different vasculature density, different vasculature morphology (e.g., diameter distribution), different vasculature blood flow dynamics, different thicknesses of tissue layers, and different acoustic impedances. As a result, energy deposition at the target region 101 varies significantly and often nonmonotonically with frequency, and the optimum frequency for a particular patient is typically unpredictable. Accordingly, in some embodiments, the frequency of the ultrasound is optimized by sequentially sonicating the target region 101 with waves having different "test frequencies" within a test frequency range; for each tested

frequency, a parameter (e.g., temperature, acoustic force, tissue displacement, etc.) indicative of energy deposition in the target region 101 is measured. The test range may span the entire range of frequencies suitable for ultrasound treatment (e.g., in various embodiments, 0.1 MHz to 10 MHz), but is typically a much smaller sub-range thereof within which the optimal frequency is expected. Such a sub-range may be determined, e.g., based on computational estimates of the optimal frequency, the results of simulations, or empirical data acquired for the same target in other patients. Further details about determining the optimal frequency for the ultrasound application are provided, for example, in U.S. Patent Publication No. 2016/0008633, the entire content of which is incorporated herein by reference.

[0040] In some embodiments, optimizing the ultrasound frequency involves iteratively setting a test frequency, sonicating the target region 101 at the selected frequency, and quantitatively assessing the resulting focusing properties or energy deposition at the target region 101. This may be accomplished using, e.g., MRI thermometry to measure the temperature increase in the target region 101 resulting from the deposited energy, MR-ARFI to measure the tissue displacement resulting from the acoustic radiation force at the target region 101, ultrasound detection to measure the intensity of the ultrasound reflected from the target region 101, or generally any experimental technique for measuring a parameter that correlates with energy deposition at the target region 101 in a known and predictable manner. Following frequency optimization, the amplitude, phase, and/or time settings of the phased-array transducer 102 may be adjusted at the beamformer 106 to optimize the focus for the selected frequency. Approaches to assessing focusing properties at the target region 101 and, based thereon, adjusting the ultrasound frequency, amplitude, and/or phase settings of the phased-array transducer 102 are provided, for example, in International Patent Application PCT/IB2022/000747, filed December 8, 2022, the entire disclosure of which is hereby incorporated by reference.

[0041] Referring to Figure 2, in various embodiments, the acoustic energy emitted by the transducer elements 104 may be above a threshold and thereby cause generation of a small cloud of gas bubbles (or “microbubbles”) 202 in the liquid contained in the target BBB region 101. The microbubbles 202 can be formed due to the negative pressure produced by the propagating ultrasonic waves or pulses, when the heated liquid ruptures and is filled with gas/vapor, or when a mild acoustic field is applied on tissue containing cavitation nuclei. Generally, at a relatively low acoustic power (e.g., 1-2 Watts above the microbubble-generation threshold), however, the generated microbubbles 202 undergo oscillation with

compression and rarefaction that are equal in magnitude and thus the microbubbles generally remain unruptured. At a higher acoustic power (e.g., more than 10 Watts above the microbubble-generation threshold), the generated microbubbles 202 undergo rarefaction that is greater than compression, which may cause cavitation of the microbubbles. The microbubble cavitation may result in transient disruption (or “opening”) of the targeted BBB region 101, thereby allowing therapeutic or prophylactic agents present in the bloodstream to penetrate the “opened” BBB region 101 and effectively deliver therapy to the targeted tissue (e.g., targeted brain cells).

[0042] In various embodiments, microbubbles and/or other therapeutic agents are introduced intravenously or, in some cases, by injection proximate to the target region 101 using an administration system 116 (Figure 1) for enhancing the ultrasound procedure on the target region. For example, the microbubbles may be introduced into the patient’s brain in the form of liquid droplets that subsequently vaporize, or as gas-filled bubbles, or entrained with another suitable substance, such as a conventional ultrasound contrast agent. Because of their encapsulation of gas, the microbubbles may act as scatterers/harmonic oscillators or reflectors of the ultrasound. Reflections from the microbubbles may be more intense than the reflections from the soft tissue of the body and/or blood. Therefore, by using a microbubble-based contrast agent, the contrast level of an ultrasound image may be significantly increased.

[0043] To avoid undesired damage to the target BBB region 101 and/or its surrounding tissue resulting from the microbubble cavitation, in various embodiments, the formation and/or amount of induced microbubbles 202 in the target BBB region 101 are monitored by detecting acoustic signals emanating therefrom using the acoustic signal detector 114 (Figure 1), which then transmits the signals to the controller 108. Alternatively, the transducer elements 104 may possess both transmit and detect capabilities. In some embodiments, each individual transducer element 104 may alternate between transmitting ultrasound signals to the microbubbles and receiving ultrasound signals therefrom. For example, all transducer elements 104 may substantially simultaneously transmit ultrasound to the microbubbles 202 and subsequently receive echo signals therefrom. In some embodiments, the transducer array may be divided into multiple sub-regions, each comprising an array of transducer elements 104. The sub-regions may be assigned different amplitudes, frequencies, phases, and/or time delays from one another, and activated, one at a time, to transmit ultrasound to and receive echo signals from the microbubbles 202. For example, one sub-region may be operated as a receive region, and another sub-region may be operated as a transmit region. Transducer

elements in the transmit region transmit the ultrasound waves/pulses while transducer elements in the receive region receive the echo signals from the microbubbles 202. The received signals are then transmitted to the controller 108 for analysis. The transmit and receive regions of the transducer array may be configured in different patterns and shapes at various locations of the transducer array.

[0044] Referring to Figure 3, a target region 302 (corresponding to 101 in Figures 1-2) is depicted in a slice of the brain of a patient. The target region 302 is relatively larger than target regions in conventional focused ultrasound treatment systems. As a result, the target region 302 is heterogenous in nature, including one or more subregions having different physiological properties. For example, subregion 304 includes or is otherwise characterized by gray matter, and subregion 306 includes or is otherwise characterized by white matter. Gray matter contains neural cell bodies, axon terminals, dendrites, and nerve synapses, and largely functions to receive information and regulate outgoing information. White matter contains bundles of axons, and largely serves to transmit signals to other regions of the brain, spinal cord, and body. Importantly, these different tissue types behave differently during attempts to open the BBB during focused ultrasound treatment, because the different tissue types have different vascular properties. For example, since white matter is less vascularized and more delicate, it tends to get overtreated when subjected to the same treatment parameters as gray matter, which is more vascularized and, therefore, contains higher concentrations of microbubbles. Thus, using the same acoustic treatment parameters (e.g., frequency, amplitude, phase, and/or timing) to treat the entire target region 302 could result in overtreatment of the white matter 306, undertreatment of the gray matter 304, or a combination of both.

[0045] Referring to Figure 4, the target region 304 is divided into subregions 311-315, each corresponding to a tissue type, vascular characteristic, or microbubble concentration. The tissue types in subregions 311-314 correspond to gray matter and are therefore more vascularized than other the tissue type in subregion 315, which corresponds to white matter. Since the tissue in subregions 311-314 is more vascularized, it requires or accepts higher microbubble concentrations in order to open the BBB in those regions during focused ultrasound treatment. Likewise, since the tissue in subregion 315 is less vascularized, it requires or accepts lower microbubble concentrations in order to open the BBB in that subregion during focused ultrasound treatment. In order to address the different microbubble

concentration requirements, different acoustic treatment parameters (e.g., frequency, amplitude, phase, and/or timing) may be used in order to open the BBB in each subregion.

[0046] In some embodiments, acoustic treatment parameters may change according to a combination of tissue type and vascular characteristics. For example, referring to Figure 5, a combination of tissue type and relative distance from an interface affects treatment parameters. Specifically, for a given distance from the interface, gray matter and white matter respond differently from a given acoustic treatment dose. In another example, the same bubble density in a normal vessel and in a tumor vessel could have a different meaning due to the different mechanical properties of these vessels.

[0047] Figure 6 is a flow diagram illustrating an example process 600 for providing focused ultrasound to a target region in accordance with some implementations. The process may be governed by instructions that are stored in a computer memory or non-transitory computer readable storage medium. The instructions may be included in one or more programs stored in the non-transitory computer readable storage medium. When executed by one or more processors (e.g., controller 108), the instructions cause the system to perform the process. The non-transitory computer readable storage medium may include one or more solid state storage devices (e.g., Flash memory), magnetic or optical disk storage devices, or other non-volatile memory devices. The instructions may include source code, assembly language code, object code, or any other instruction format that can be interpreted by one or more processors.

[0048] In operation 602, a controller (e.g., 108) obtains image data of one or more subregions of a target region (e.g., subregions 311-315 of target region 302) and/or a region surrounding the target region. Depending on the embodiment and the use case, the controller may obtain image data of just one subregion of a target region, or two or more subregions of a target region. In addition, the controller may obtain image data of a region surrounding the target region, such as healthy tissue not meant for treatment. Such healthy tissue may still be subject to acoustic treatment dose and/or treatment rate limits, to ensure the healthy tissue is not damaged. Similar to the subregions within the target region, subregions in the surround tissue (associated with healthy tissue) may be subject to varying acoustic dose and/or treatment rate limits or thresholds based on tissue type and/or vasculature characteristics. Thus, any description within this disclosure regarding adaptive treatment of subregions of a target region apply equally to regions or subregions surrounding, or otherwise outside of, the target region. In various embodiments, the image data may be contrast-enhanced ultrasound

device (CEUS) data, ultrasound localization microscopy device (ULM) data for obtaining ultrasound super-resolution images, magnetic resonance imaging (MRI) data, computer tomography (CT) data, and/or anatomical information based on a medical atlas.

[0049] In operation 604, the controller determines a tissue type, a vasculature characteristic, or a microbubble concentration associated with each of the one or more subregions (or with just the one subregion, depending on the embodiment and the use case) based on the image data. In general, these factors may be referred to as physiological properties of the subregions. Example vasculature characteristics include vascular density, vascular morphology, vascular flow velocity, and vascular flow pattern (including flow direction). Additionally or alternatively, the physiological property determined by the controller for each subregion may be a disease status or condition (e.g., presence and/or location of tumor or protein aggregates such as amyloid plaques), general brain anatomy that is taken from one or more anatomical atlases, or in-situ microbubble concentration. Additionally or alternatively, the physiological property determined by the controller for each subregion may be one or more perfusion parameters that can be extracted from perfusion MRI scans, including blood flow, blood volume, mean transient time, permeability, or any other perfusion parameter. In some embodiments, MRI scans may enable the processor to characterize the tissue type, including quantitative or qualitative MRI data such as T1, T2, MT, Diffusion, susceptibility, and others. Such properties can also assist with the registration to brain anatomy.

[0050] In operation 606, the controller determines one or more acoustic treatment parameters for each of the one or more subregions (or for just one subregion, depending on the embodiment and the use case) based on the tissue type, the vasculature characteristic, or the microbubble concentration (or, in general, any physiological property discussed above) respectively associated with each of the one or more subregions (e.g., determine an acoustic treatment parameter associated with subregion 311, determine an acoustic treatment parameter associated with region 312, and so forth). In some embodiments, the acoustic treatment parameters are stored in data storage communicatively coupled to the controller and they comprise an adaptive treatment plan 118.

[0051] The acoustic treatment parameters are responsible for achieving an overall treatment effect. The treatment effect may be expressed in terms of treatment dose and/or treatment rate.

[0052] The treatment dose (also referred to as the acoustic dose or acoustic treatment dose) denotes a cumulative quantity that represents the overall effect of the focused ultrasound treatment. The treatment dose may be measured by summing the overall acoustic signal or energy or power measured by the acoustic signal detector 114 on selected spectral bands.

[0053] The treatment rate is related to the time it takes to achieve the treatment dose. The higher the treatment rate, the faster the treatment dose is achieved.

[0054] In some embodiments, determining an acoustic treatment parameter includes determining a level of heterogeneity of subregions of the tissue within the focal zone (referred to as focal zone heterogeneity). Based on the heterogeneity, a treatment rate and/or treatment dose may be determined. For example, the more heterogeneous the tissue is in the focal zone, the greater the variation treatment rates and/or treatment doses across the various subregions of tissue in the focal zone.

[0055] Some types of tissue are more sensitive to the treatment dose, and some types of tissue are more sensitive to the treatment rate. For example, tissue that is more sensitive to the treatment dose is more affected by the cumulative amount of acoustic energy absorbed, regardless of the rate of absorption. On the other hand, tissue that is more sensitive to the treatment rate is more affected by the rate of absorption of the acoustic energy, regardless of how much acoustic energy gets absorbed. Thus, the controller 108 may manage the treatment dose and the treatment rate for various types of tissue in parallel.

[0056] Depending on the optimal treatment effect (treatment dose and/or treatment rate) for the tissue type, vasculature characteristic, or microbubble concentration associated with a given subregion of the target region, the controller 108 determines one or more treatment parameters that will achieve that treatment effect (treatment dose and/or treatment rate). For example, the controller 108 may determine a specific pulse duration, pulse duty cycle, acoustic frequency, acoustic power level, and/or treatment duration in order to achieve a specific treatment dose and/or treatment rate for a given subregion.

[0057] In operation 608, the controller causes the ultrasound transducer to sonicate the one or more subregions (or just the one subregion, depending on the embodiment and the use case) according to the acoustic treatment parameters respectively corresponding to each of the one or more subregions (e.g., sonicate subregion 311 using an acoustic treatment parameter specifically determined for that subregion, sonicate subregion 312 using an

acoustic treatment parameter specifically determined for that subregion, and so forth). For embodiments in which the acoustic treatment parameters are stored as part of an adaptive treatment plan 118, the controller operates the ultrasound transducer according to the acoustic treatment parameters currently stored in the adaptive treatment plan 118.

[0058] In some embodiments, the sonication in operation 608 comprises one treatment in a multi-treatment procedure. After a given treatment (or during the treatment), the tissue in the subregions being treated may react to the treatment. In order to prevent overtreatment, the acoustic treatment parameters may need to be normalized before proceeding with the next treatment in the procedure. Thus, the acoustic treatment parameters (stored in the adaptive treatment plan 118) may be adaptively replanned and controlled for subsequent sonications. In these embodiments, after performing a sonication in operation 608, the process repeats. Specifically, operation 602 is performed again in order to obtain updated image data (since the subregions were affected by the previous sonication, causing the image data to be different). Then, operation 604 is performed again, during which an updated vasculature characteristic or microbubble concentration may be determined (based on the updated image data). Then, operation 606 is performed again, during which acoustic treatment parameters for one or more of the subregions are updated (and thus, the adaptive treatment plan 118 is updated). Then, a subsequent sonication is performed in operation 608. Operations 602-608 may be successively repeated for each subsequent sonication treatment in the multi-treatment procedure.

[0059] The following discussion includes several examples of operations 602-606. Specifically, these examples include discriminating between tissue types in healthy and pathological brain conditions (e.g., Alzheimer's, Parkinson, Cancer, Huntington disease, and the like) for the purpose of establishing tissue-related acoustic treatment parameters in operation 606.

[0060] Example 1: One example involves usage of CEUS or ultrasound super-resolution imaging (e.g., using ultrasound localization microscopy or ULM) for calculating vascular maps before and during the BBB opening treatment.

[0061] The ultrasound imaging-based analysis in operation 604 may include tailoring the treatment parameters according to the estimated local microbubble concentration, vasculature density, vasculature morphology (e.g., diameter distribution), and vasculature blood flow

dynamics, using either or both of the calculations described below with reference to (I) and (II).

[0062] (I) CEUS or ultrasound super-resolution scans performed prior to the treatment to infer the vascular density. Harmonic or temporally changing echoes are known to come from intravascular bubbles. After producing a spatial map of the bubbles in each frame, in a process known as beamforming, the tissue-related clutter may be removed from the desired bubble signals. CEUS processing may include denoising of the beam-formed bubble images over time to produce a clear low-resolution image of the vasculature. ULM processing may include finding the exact locations of resolvable bubbles and aggregating this information over many frames to produce a super-resolved image of the vasculature. High and/or low microbubble concentration, long (ms) and/or short (ms) pulses, and long and/or short acquisitions may be used according to the specific implementation. These calculations can be aided by information from co-registered vascular maps acquired using different imaging modalities such as MRI and CT.

[0063] (II) Super-resolved acoustic maps of therapeutic BBB opening doses, calculated based on the pre-treatment ULM maps. Since microbubbles are purely intravascular, their possible locations can be constrained according to the calculated super-resolved vascular map. Since BBB pulses are typically long, short echoes can be generated for producing super-resolved passive acoustic maps by slightly modulating the transmitted frequency (ultrasonic waves encoding) and filtering out the desired frequencies on receive. Enforcing constraints such as sparsity and an allowed reconstruction grid on the passive acoustic mapping calculations could improve the reconstruction resolution beyond the diffraction limit, revealing details that are missing in classic passive acoustic maps. These sparsity priors may be determined according to the bubble density in each vascular region. These calculations can be aided by information from co-registered vascular maps acquired using different imaging modalities such as MRI and CT.

[0064] The ultrasound imaging-based analysis in operation 604 may include monitoring the treatment according to CEUS or super-resolved vascular changes (vasculature integrity, vasculature diameter changes, vasoconstriction) by comparing vascular maps and flow velocities and patterns during the treatment to pre-treatment vasculature maps (or maps taken at previous sessions of the BBB opening treatment) for tracking functional vasculature changes (density of functional vessels, diameter histogram, integrity, and flow patterns) and updating the treatments' acoustic parameters (in operation 606) accordingly. The vascular

map sampling can be (i) in between repeated pulses, (ii) in between sonications, and/or (iii) in between treatment sessions.

[0065] Any or all of the data analysis operations above may rely on artificial intelligence (AI) or heuristic algorithms for achieving optimal results. For example, the algorithms can be used to detect vascular changes in real-time from short scans and partial vascular information. Similarly, the reconstruction can be based on fitting an assumed bubble shape or rely on the sparsity of the underlying vasculature.

[0066] Example 2: Another example involves usage of an MRI scan acquired during the planning stages of the BBB treatment to adjust the treatment parameters to MRI-related tissue values.

[0067] In some embodiments, the MRI analysis can include T1 and T2-based treatment planning. In these embodiments, the method includes review of treatment area T1 and T2 values (in operation 604) and tailoring the acoustic treatment parameters according to the obtained values (in operation 606), using empirical formulas obtained in experimental results. The data analysis in these embodiments can include AI usage for optimal results.

[0068] In some embodiments, the MRI analysis can include MR-angiography (MRA)-based treatment planning. In these embodiments, the treatment parameters may be determined according to diffusion images (DTI), using empirical formula obtained in experimental results. The data analysis in these embodiments can include AI usage for optimal results.

[0069] Example 3: Another example involves usage of CT-angiography during the planning stages of the BBB treatment to adjust the treatment parameters to tissue vasculature properties. For this technique, CT is performed using contrast agents. The treatment parameters may be determined (in operation 606) according to tissue-dependent vasculature properties (determined in operation 604) using empirical formula obtained in experimental results. The data analysis in these embodiments can include AI usage for optimal results.

[0070] Example 4: Another example involves usage of anatomical, physiological, and neuro-physiological brain atlases to tailor the treatment parameters. In these embodiments, the treatment parameters may be determined (in operation 606) according to atlas-based vascular properties (determined in operation 604), using empirical formulas obtained in experimental results.

[0071] In some embodiments, any combination of the usages described in Examples 1-4 above may be used to determine physiological properties in operation 604 and determine acoustic treatment parameters in operation 606 based on the determined physiological properties.

[0072] The following discussion describes examples of acoustic and auxiliary parameters that may be tailored (in operation 606) according to BBB treated area/tissue type (determined in operation 604).

[0073] In one example, one or more acoustic treatment parameters include total energy (treatment dose) and energy rate (treatment rate) of specific spectrum frequency bands (all bands together and each band separately). This may determine the pulse duration, acoustic power, maximal power levels, treatment duration, pulse duty cycle, and/or acoustic frequency for each treated area (e.g., each subregion 311-315). For example, the local microbubble concentration and vascular density may be factored in when determining the acoustic treatment parameter (e.g., PCD power) in operation 606. In doing so, the system aims for a lower treatment effect when treating regions with low vascular density, instead of increasing the transmitted power in order to reach a uniform treatment effect. Similarly, the treatment effect may be normalized to the local microbubble concentration, accounting for variability in bubble manufacturing and administration.

[0074] In another example, tailoring one or more acoustic treatment parameters includes adaptively adjusting microbubble concentration and/or flow rate while injecting microbubbles into the subregions. This ability allows the system to compensate for heterogeneous tumor vasculature.

[0075] In another example, tailoring one or more acoustic treatment parameters includes adaptively adjusting blood flow rate at the treatment area, using different pharmaceuticals. For example, the microbubble concentration or injection rate can be increased by slowing down blood flow rate when treating poorly perfused regions.

[0076] In another example, tailoring one or more acoustic treatment parameters includes producing acoustic holography patterns to match the vascular geometry and distinguish between different neurological regions. For example, the direction of the beam could be adjusted to fit the borders between white and gray matter regions.

[0077] In another example, tailoring one or more acoustic treatment parameters includes selecting targets to fit the expected efficiency and safety profile of the ultrasound treatment. For example, locations in the tissue that are close to sensitive blood vessels may be avoided.

[0078] In another example, tailoring one or more acoustic treatment parameters includes planning a target sequence opposite to blood flow direction, so microbubbles are not increasingly depleted as subsequent targets are treated.

[0079] In another example, tailoring one or more acoustic treatment parameters includes planning longer sonications with lower rates to get a higher effect in subregions sensitive to high treatment rates.

[0080] In another example, tailoring one or more acoustic treatment parameters includes planning sonications with a smeared focal spot for more sensitive subregions (e.g. tissue with A.D.).

[0081] The following discussion describes example implementations with respect to method 600.

[0082] In some implementations, the one or more subregions is a plurality of subregions, a first subregion of the plurality of subregions (e.g., 311) comprises a first tissue type characterized by a first vascular density (e.g., gray matter having a relatively high vascular density), and a second subregion of the plurality of subregions (e.g., 315) comprises a second tissue type characterized by a second vascular density lower than the first vascular density (e.g., white matter having a relatively low vascular density). In these implementations, determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises: determining a first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the first subregion; and determining a second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the second subregion. This is because the lower the vascular density in a given tissue type, the lower the microbubble concentration (since there are fewer blood vessels in which microbubbles may be injected or otherwise formed), and lower microbubble concentrations do not require an acoustic treatment dose, treatment rate, and/or focal zone heterogeneity that is as high as that used for subregions having higher microbubble concentrations. Tailoring the acoustic treatment dose, treatment rate, and/or focal zone heterogeneity to the specific microbubble concentration of a given subregion prevents one subregion from being overtreated at the expense of another.

Conversely, if the second tissue type is characterized by a second vascular density higher than the first vascular density, then the second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity is higher than the first acoustic dose and/or treatment rate for the second subregion.

[0083] In some implementations, the one or more subregions is a plurality of subregions, a first subregion of the plurality of subregions (e.g., 311) is characterized by a first vascular density, and a second subregion of the plurality of subregions (e.g., 315) is characterized by a second vascular density lower than the first vascular density. In these implementations, determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises: determining a first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the first subregion; and determining a second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the second subregion. This is because the lower the vascular density in a given subregion, the lower the microbubble concentration, and lower microbubble concentrations do not require an acoustic treatment dose, treatment rate, and/or focal zone heterogeneity that is as high as that used for higher microbubble concentrations. Conversely, if the second vascular density is higher than the first vascular density, then the second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity is higher than the first acoustic dose and/or treatment rate for the second subregion

[0084] In some implementations, the one or more subregions is a plurality of subregions, a first subregion of the plurality of subregions (e.g., 311) is characterized by a first microbubble concentration, and a second subregion of the plurality of subregions (e.g., 315) is characterized by a second microbubble concentration lower than the first microbubble concentration. In these implementations, determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises: determining a first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the first subregion; and determining a second acoustic treatment dose, treatment rate, and/or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, and/or focal zone heterogeneity for the second subregion. This is because lower microbubble concentrations do not require an acoustic treatment dose, treatment rate, and/or focal zone heterogeneity that is as high as that used for subregions having higher microbubble concentrations. Conversely, if the second microbubble concentration is higher than the first microbubble concentration, then the second

acoustic treatment dose, treatment rate, and/or focal zone heterogeneity is higher than the first acoustic dose and/or treatment rate for the second subregion.

[0085] To achieve an overall treatment effect (treatment dose and/or treatment rate), the phased array 102 delivers a series of pulses of ultrasonic waves to the target subregions at a particular timing or energy level, which can be varied by modifying the frequency, amplitude, phase, and/or timing used by the beamformer 106. Thus, a lower treatment effect may be achieved with a higher frequency or lower amplitude, or with a modified phase or timing delay resulting in lower energy at a given target subregion. Likewise, a higher treatment effect may be achieved with a lower frequency or higher amplitude, or with a modified phase or timing delay resulting in higher energy at a given target subregion. It should be noted that beyond the optimal treatment dose and dose rate, further increasing the amplitude dose or dose rate can result in overtreatment and, thus, in some cases, reduced payload delivery.

[0086] Additionally or alternatively, an overall treatment effect (treatment dose and/or treatment rate) may be attained by setting particular values for acoustic treatment parameters such as pulse duration, pulse duty cycle, an acoustic frequency, acoustic power level, or treatment duration. Thus, in some implementations, the controller is configured to determine the tissue type associated with each of the one or more subregions based on the image data (as in operation 604); the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having tissue types that are characterized by relatively lower vascular density or vascular flow velocity. Conversely, determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises determining a relatively lower acoustic frequency, a relatively higher pulse duration, a relatively higher pulse duty cycle, a relatively higher acoustic power level, or a relatively higher treatment duration for subregions having tissue types that are characterized by relatively higher vascular density or vascular flow velocity.

[0087] In some implementations, the controller is configured to determine the vasculature characteristic associated with each of the one or more subregions based on the image data (as in operation 604), wherein the vasculature characteristic is a vascular density or a vascular flow velocity; the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an

acoustic frequency, an acoustic power level, or a treatment duration; and determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having relatively lower vascular density or vascular flow velocity. Conversely, determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises determining a relatively lower acoustic frequency, a relatively higher pulse duration, a relatively higher pulse duty cycle, a relatively higher acoustic power level, or a relatively higher treatment duration for subregions having relatively higher vascular density or vascular flow velocity.

[0088] In some implementations, the controller is configured to determine the microbubble concentration associated with each of the one or more subregions based on the image data (as in operation 604); the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having relatively lower microbubble concentration. Conversely, determining the acoustic treatment parameter for each of the one or more subregions in operation 606 comprises determining a relatively lower acoustic frequency, a relatively higher pulse duration, a relatively higher pulse duty cycle, a relatively higher acoustic power level, or a relatively higher treatment duration for subregions having relatively higher microbubble concentration.

[0089] In some implementations, the controller is configured to, for each sonication or pulse in which an acoustic treatment parameter is determined, determine the acoustic treatment parameter for each of the one or more subregions based further on acoustic information obtained during a previous sonication or pulse of the one or more subregions. Stated another way, in some scenarios, the adaptive treatment plan 118 considers, for each sonication or pulse in a series of sonications or pulses, both tissue-based information as described above (e.g., tissue type and/or vasculature characteristics) and the acoustic feedback received during previous sonications or pulses, to determine the treatment parameter for the next sonication or pulse. For example, if the acoustic feedback received during a previous sonication or pulse indicates that a particular tissue type experienced a dose

or dose rate that deviated from the plan corresponding to the particular tissue type or associated vasculature characteristic, then the controller takes this acoustic feedback into account when determining treatment parameters for the next sonication or pulse (e.g., by raising the acoustic frequency, lowering the pulse duration, lowering the pulse duty cycle, lowering the acoustic power level, blurring the focus, and/or lowering the treatment duration for the next sonication). Blurring of the focus can be done by changing the phase configuration of the elements (e.g., adding a random phase per element for elements from a range of optional phases). The larger the range and the number of effected elements, the bigger the blurring is.

[0090] In some implementations, the controller is further configured to, after causing the ultrasound transducer to sonicate the one or more subregions, obtain subsequent (updated) image data of the one or more subregions of the target region (by repeating operation 602); determine an updated vasculature characteristic or microbubble concentration associated with each of the one or more subregions based on the subsequent image data (by repeating operation 604 using the updated image data); determine an updated acoustic treatment parameter for each of the one or more subregions based on the updated vasculature characteristic or microbubble concentration respectively associated with each of the one or more subregions (by repeating operation 606); and cause the ultrasound transducer to sonicate the one or more subregions according to the updated acoustic treatment parameters respectively corresponding to each of the one or more subregions (by repeating operation 608 using the updated acoustic treatment parameter).

[0091] In some embodiments, the controller is configured to operate the ultrasound transducer according to a safety algorithm that maintains safety of the treatment based on the acoustic feedback during the treatment. Such implementations may be referred to as blind implementations since the controller is not aware of tissue types. A blind controller may use one set of one or more bands of the acoustic feedback in the treatment for efficacy (e.g., calculation of the treatment dose and treatment rate) and another independent set of one or more bands for maintaining safety (e.g., keeping the energy or power measured in the safety band below a threshold). In some embodiments, the bands for efficacy and the bands for safety may partially or entirely overlap.

[0092] As such, a system for providing focused ultrasound to a target region may comprise an ultrasound transducer and a controller. The controller may be configured to obtain acoustic feedback associated with a sonication operation involving the ultrasound

transducer treating one or more subregions of the target region and/or a region surrounding the target region; determine a treatment dose and/or a treatment rate of the sonication operation for each of the one or more subregions according to a first set of one or more frequency bands of the acoustic feedback; determine an energy level and/or a power level of the sonication operation for each of the one or more subregions according to a second set of one or more frequency bands of the acoustic feedback; and determine an acoustic treatment parameter for each of the one or more subregions based on (i) the treatment dose and/or the treatment rate respectively associated with each of the one or more subregions, and (ii) the energy level and/or the power level respectively associated with each of the one or more subregions; and cause the ultrasound transducer to sonicate the one or more subregions according to the acoustic treatment parameters respectively corresponding to each of the one or more subregions. The acoustic treatment parameter may be a frequency, an amplitude, or a phase associated with a plurality of transducer elements of the ultrasound transducer.

[0093] In some embodiments, determining the acoustic treatment parameter based on the treatment dose and/or the treatment rate includes adjusting the acoustic treatment parameter to maintain the treatment dose and/or the treatment rate with respect to an efficacy threshold. For example, the acoustic treatment parameter may be adjusted to keep the treatment dose in a first subregion above an efficacy threshold (e.g., in order to treat a target region) and to keep the treatment dose in a second subregion below an efficacy threshold (e.g., in order to minimize damage outside a target region).

[0094] In some embodiments, determining the acoustic treatment parameter based on the energy level and/or the power level includes adjusting the acoustic treatment parameter to maintain the energy level and/or the power level with respect to a safety threshold. For example, the acoustic treatment parameter may be adjusted to keep energy and/or power levels below a safety threshold in order to minimize damage.

[0095] In some embodiments, the controller may obtain the safety information (acoustic feedback) using curve-fitting or other type of pre-processing that can separate narrowband signals indicative of overtreatment from broad-band efficacy indicators without prior knowledge of their specific frequency. Bifurcations are indicative of violent cavitation activity and appear in the PCD spectrum as symmetric peaks around the sub-harmonic peak, whose exact frequency could not be estimated in advance. A comb filter can separate narrowband peaks (harmonics) from broadband signals when their frequency is known (e.g., a sum-of-harmonics method for improved narrowband and broadband signal quantification

during passive monitoring of ultrasound therapies). A slightly different approach with curve fitting could extend this to separating peaks with unknown frequencies from broadband signals.

[0096] In some embodiments, the safety algorithm can use the tissue type as determined by the controller as input to the safety algorithm. In some embodiments, the safety algorithm selects safety thresholds based on the tissue type (e.g., white matter vs. gray matter, or any other tissue type characteristic). In some embodiments, the controller selects lower safety thresholds for the tissues with lower vascular density; however, in some other embodiments, when possible, the controller might favor efficacy over safety and select higher safety thresholds for the tissues characterized by lower vascular density for which the treatment rate is lower.

[0097] Functionality for providing focused ultrasound to a target region in order to disrupt the BBB as described above, whether integrated within the controller 108 of the ultrasound system 100, the imager 112 and/or the administration system 116 or provided by a separate external controller, may be structured in one or more modules implemented in hardware, software, or a combination of both. In addition, the imager 112 and/or the administration system 116 may be controlled by the controller 108 or other separate processor(s). For embodiments in which the functions are provided as one or more software programs, the programs may be written in any of a number of high level languages such as PYTHON, FORTRAN, PASCAL, JAVA, C, C++, C#, BASIC, various scripting languages, and/or HTML. Additionally, the software can be implemented in an assembly language directed to the microprocessor resident on a target computer; for example, the software may be implemented in Intel 80x86 assembly language if it is configured to run on an IBM PC or PC clone. The software may be embodied on an article of manufacture including, but not limited to, a floppy disk, a jump drive, a hard disk, an optical disk, a magnetic tape, a PROM, an EPROM, EEPROM, field-programmable gate array, or CD-ROM. Embodiments using hardware circuitry may be implemented using, for example, one or more FPGA, CPLD or ASIC processors.

[0098] Although the previous discussion focused on microbubbles, microbubbles represent one example of treatment enhancers. Similar results can be expected with bubbles in different size ranges, such as bubbles in the sub-micron range (referred to as nanobubbles). Additionally or alternatively, nanodroplets or nanoparticles such as gold seeds may be employed.

[0099] Figures 7-15 show experimental results of BBB opening in landrace pigs sonicated over widespread anatomical regions using the Exablate Neuro 220kHz transducer. Pre- and post-treatment MRI scans were performed with a SIGNA™ 1.5T GE scanner and a 3T Siemens Lumina system. Anatomical SPGR (GE) or MPRAGE (Siemens) scans were used for tissue-aware treatment planning.

[0100] Figure 7 depicts the need for factoring in vascular densities of different tissues. White and gray matter respond differently to ultrasound-assisted BBB opening due to differences in vasculature densities and mechanical properties characterizing these tissues. As a result, higher acoustic power is needed for the same acoustic dose in white matter regions. Experiments demonstrated that overtreatment can be observed when the same acoustic parameters ($AD = 0.7$ without changing the treatment rate) are used for different tissues. The effects of over-treatment are shown as dark spots in the post-treatment GRE MRI scans. Here, treatment regions, including gray and white matter regions, were defined using an anatomical SPGR MRI scan. In some embodiments, imaging is used to characterize tissue type of sub regions. In some embodiments, the controller selects a lower treatment dose and/or treatment rate for the white matter to avoid over treatment.

[0101] Figures 8-10 depict how a wide focal spot can lead to heterogeneous BBB opening due to differences between tissue type and vascular density. Typically, the focal spot of the ultrasound system is much larger in the axial dimension. When using a large focal spot, for example, by selecting a small aperture, the central lobe of the beam covers large sections of the tissue, frequently including different tissue types and vascular densities. The treatment planning is commonly performed based on the middle imaging plane (Figure 8). Here, the post-treatment T1-weighted scan with gadolinium, displaying regions with high degree of BBB opening, is overlayed in red on top of the matching anatomical SPGR image in blue (left). The treatment plan shows the sonicated sub-spots in green on top of the anatomical SPGR image (right). Therefore, when the tissue composition in neighboring axial planes is different from that of the planning section, the BBB opening patterns depend on the local tissue composition in addition to the geometry of the treatment plan (Figures 9-10). Here again, the post-treatment T1-weighted scan with gadolinium, displaying regions with high degree of BBB opening, is overlayed in red on top of the matching anatomical SPGR image in blue (left). The anatomical SPGR image is also presented without the overly to show the location of bright white tissue regions and darker gray tissue region (right).

[0102] In some embodiments, the controller chooses the smallest focal point in areas with mixed tissue types to minimize the situation of treating multiple tissue types within the same spot. In some embodiments, when tissue health is above all other considerations, the controller treats a mixed area based on the parameters of the weakest tissue type in the mix. In some embodiment (e.g. oncological treatment), when treatment efficacy is too important to be totally sacrificed, the controller might treat the mixed tissue based on the dominant tissue type in the mix or on parameters that are an average of the parameters that were supposed to be applied for each tissue by itself. In some embodiments, the controller selects a mixed approach in which the treatment rate is selected based on the most sensitive tissue type in the mix and the treatment dose is higher than the desired treatment dose for the most sensitive tissue type in the mix or vice versa.

[0103] Figure 11 depicts when anatomy-based treatment planning leads to BBB opening in white and gray matter. Here, treatment regions, including gray (G) and white (W) matter regions were defined using an anatomical SPGR MRI scan (left). The acoustic dose and dose rates in white matter regions were set to a third of that used in gray matter regions. This tissue adaptive treatment planning led to a more homogenous opening of the said heterogeneous tissue observed as bright regions in post-treatment T1-weighted MRI scans after injection of gadolinium.

[0104] In some embodiments, the homogenous opening is a key for successful treatment (e.g. when treatment is used for delivery of toxic drug), and controller tries to get the opening as homogeneous as possible. In some embodiments the controller may open the tissue as much as possible under the constraints of safety, treatment time, bubbles dose and, in those treatments, the controller treatment plan favor more opening over homogeneous opening. For example, it aims to achieve higher payload delivery in gray matter regions that have higher vascular density compared to gray matter regions.

[0105] Figure 12 depicts how anatomy-based treatment planning enables more homogenous opening of heterogeneous tissue. The tissue-adaptive BBB opening treatment planning methodology described above repeatably led to extensive opening of gray and white tissue regions. BBB opening is observed as bright regions in post-treatment T1-weighted MRI scans after gadolinium injection. The results were consistent over many experiments with different animals.

[0106] Figure 13 depicts when anatomy-based treatment planning leads to repeatable BBB opening. The repeatability of the described methodology was quantified using multi-echo sequences and calculation of the R1 parameter in Hz. When calculating success probabilities per area, the treatment in a given pixel was considered successful if the maximal axial R1 value was above 0.1Hz. When calculating success probabilities per voxel, the treatment in a given voxel was considered successful if its R1 value was above 0.1Hz. Repeatable BBB opening was observed in gray matter, white matter, and sulcus gray matter. A lower degree of repeatability was presented in white matter in the sulcus areas. In some embodiments, the patient should do multiple treatments. Post treatment images may be used to further characterize the sub region tissue types based on the tissue response for actual treatments (efficacy – Figure 13 and safety – Figure 14).

[0107] Figure 14 depicts when anatomy-based treatment planning leads safer opening with minimal signs of edema and microbleeding. The high level of BBB opening achieved using tissue-adaptive planning with a lower acoustic dose for white matter regions showed good signs of treatment safety. The post-treatment GRE MRI scans showed a few weak dark spots without evidence of significant microbleeding (center-right). The post-treatment T2-weighted scans showed minimal signs of edema in the form of bright areas that didn't appear in the pre-treatment scans. When observed, these signs of edema concentrated around tissue interface regions (right).

[0108] Figure 15 depicts the importance of precise treatment in tissue interface regions. Tissue interface regions are relatively sensitive and demand careful treatment monitoring to avoid overtreatment and therapeutic under-delivery. In the anatomical MPRAGE MRI image, we can see a thin white matter region in the middle of gray/mixed matter (left, red arrow). In cases when the controller didn't provide this region with adequate protection, the gadolinium delivery to this region was considerably lower in post-treatment T1-weighted scans compared to the neighboring tissue regions, suggesting overtreatment (middle). Similarly, signs of edema appeared around it in the T2-weighted follow-up scans 1 day after the procedure (right). Therefore, adaptive planning and the Exablate transducer's high spatial resolution are critical for adaptive BBB opening.

[0109] The terms and expressions employed herein are used as terms and expressions of description and not of limitation, and there is no intention, in the use of such terms and expressions, of excluding any equivalents of the features shown and described or portions thereof. In addition, having described certain embodiments of the disclosure, it will be

apparent to those of ordinary skill in the art that other embodiments incorporating the concepts disclosed herein may be used without departing from the spirit and scope of the disclosure. Accordingly, the described embodiments are to be considered in all respects as only illustrative and not restrictive.

[0110] The foregoing description has been described with reference to specific implementations. However, the illustrative discussions above are not intended to be exhaustive or to limit the claims to the precise forms disclosed. Many variations are possible in view of the above teachings. The implementations were chosen and described to best explain principles of operation and practical applications, to thereby enable others skilled in the art.

[0111] The various drawings illustrate a number of elements in a particular order. However, elements that are not order dependent may be reordered and other elements may be combined or separated. While some reordering or other groupings are specifically mentioned, others will be obvious to those of ordinary skill in the art, so the ordering and groupings presented herein are not an exhaustive list of alternatives.

[0112] As used herein: the singular forms “a”, “an,” and “the” include the plural forms as well, unless the context clearly indicates otherwise; the term “and/or” encompasses all possible combinations of one or more of the associated listed items (e.g., A and/or B means A only, B only, or both A and B); the terms “first,” “second,” etc. are only used to distinguish one element from another and do not limit the elements themselves; the term “if” may be construed to mean “when,” “upon,” “in response to,” or “in accordance with,” depending on the context; and the terms “include,” “including,” “comprise,” and “comprising” specify particular features or operations but do not preclude additional features or operations.

CLAIMS

What is claimed is:

1. A system for providing focused ultrasound to a target region, the system comprising:
 - an ultrasound transducer; and
 - a controller configured to:
 - obtain image data of one or more subregions of the target region and/or a region surrounding the target region;
 - determine a tissue type, a vasculature characteristic, or a microbubble concentration associated with each of the one or more subregions based on the image data;
 - determine an acoustic treatment parameter for each of the one or more subregions based on the tissue type, the vasculature characteristic, or the microbubble concentration respectively associated with each of the one or more subregions; and
 - cause the ultrasound transducer to sonicate the one or more subregions according to the acoustic treatment parameters respectively corresponding to each of the one or more subregions.
2. The system of claim 1, wherein:
 - the one or more subregions is a plurality of subregions;
 - a first subregion of the plurality of subregions comprises a first tissue type characterized by a first vascular density;
 - a second subregion of the plurality of subregions comprises a second tissue type characterized by a second vascular density lower than the first vascular density; and
 - determining the acoustic treatment parameter for each of the one or more subregions comprises:
 - determining a first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the first subregion; and
 - determining a second acoustic treatment dose, treatment rate, or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the second subregion.
3. The system of claim 2, wherein:
 - the target region comprises portions of the blood-brain barrier located within gray matter and white matter;
 - the first tissue type is gray matter; and

the second tissue type is white matter.

4. The system of claim 1, wherein:

the one or more subregions is a plurality of subregions;

a first subregion of the plurality of subregions is characterized by a first vascular density;

a second subregion of the plurality of subregions is characterized by a second vascular density lower than the first vascular density; and

determining the acoustic treatment parameter for each of the one or more subregions comprises:

determining a first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the first subregion; and

determining a second acoustic treatment dose, treatment rate, or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the second subregion.

5. The system of claim 1, wherein:

the one or more subregions is a plurality of subregions;

a first subregion of the plurality of subregions is characterized by a first microbubble concentration;

a second subregion of the plurality of subregions is characterized by a second microbubble concentration lower than the first microbubble concentration; and

determining the acoustic treatment parameter for each of the one or more subregions comprises:

determining a first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the first subregion; and

determining a second acoustic treatment dose, treatment rate, or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the second subregion.

6. The system of claim 1, wherein:

the controller is configured to determine the tissue type associated with each of the one or more subregions based on the image data;

the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and

determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having tissue types that are characterized by relatively lower vascular density or vascular flow velocity.

7. The system of claim 1, wherein:

the controller is configured to determine the vasculature characteristic associated with each of the one or more subregions based on the image data, wherein the vasculature characteristic is a vascular density or a vascular flow velocity;

the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and

determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having relatively lower vascular density or vascular flow velocity.

8. The system of claim 1, wherein:

the controller is configured to determine the microbubble concentration associated with each of the one or more subregions based on the image data;

the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and

determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having relatively lower microbubble concentration.

9. The system of any of claims 1-8, wherein for each sonication or pulse in which an acoustic treatment parameter is determined, determining the acoustic treatment parameter for

each of the one or more subregions is further based on acoustic information obtained during a previous sonication or pulse of the one or more subregions.

10. The system of any of claims 1-9, wherein the controller is further configured to, after causing the ultrasound transducer to sonicate the one or more subregions:

- obtain subsequent image data of the one or more subregions of the target region;
- determine an updated vasculature characteristic or microbubble concentration associated with each of the one or more subregions based on the subsequent image data;

- determine an updated acoustic treatment parameter for each of the one or more subregions based on the updated vasculature characteristic or microbubble concentration respectively associated with each of the one or more subregions; and

- cause the ultrasound transducer to sonicate the one or more subregions according to the updated acoustic treatment parameters respectively corresponding to each of the one or more subregions.

11. The system of any of claims 1-10, wherein obtaining the image data comprises obtaining:

- contrast-enhanced ultrasound device (CEUS) data,
- ultrasound localization microscopy device (ULM) data for obtaining ultrasound super-resolution images,

- magnetic resonance imaging (MRI) data,
- computer tomography (CT) data, and/or
- anatomical information based on a medical atlas.

12. The system of any of claims 1-11, wherein causing the ultrasound transducer to sonicate the one or more subregions comprises causing microbubbles to be generated and/or activated by application of ultrasound at the target region or causing the transducer to sonicate microbubbles administered by the system at the target region.

13. The system of any of claims 1-12, wherein obtaining the image data comprises imaging the target region.

14. The system of any of claims 1-13, wherein obtaining the image data comprises identifying the target region and using either an atlas or a diagnosed pathology to determine the vasculature characteristic associated with each of the one or more subregions.

15. The system of any of claims 1-14, wherein causing the ultrasound transducer to sonicate the one or more subregions comprises controlling acoustic power or energy emitted by transducer elements of the ultrasound transducer so that acoustic power or energy is above a threshold level to thereby induce microbubble generation or higher acoustic radiation force.
16. The system of any of claims 1-15, wherein the acoustic treatment parameter is a frequency, an amplitude, or a phase associated with a plurality of transducer elements of the ultrasound transducer.
17. A method for providing focused ultrasound to a target region, the method comprising:
at a controller communicatively coupled to an ultrasound transducer:
obtaining image data of one or more subregions of the target region and/or a region surrounding the target region;
determining a tissue type, a vasculature characteristic, or a microbubble concentration associated with each of the one or more subregions based on the image data;
determining an acoustic treatment parameter for each of the one or more subregions based on the tissue type, the vasculature characteristic, or the microbubble concentration respectively associated with each of the one or more subregions; and
causing the ultrasound transducer to sonicate the one or more subregions according to the acoustic treatment parameters respectively corresponding to each of the one or more subregions.
18. The method of claim 17, wherein:
the one or more subregions is a plurality of subregions;
a first subregion of the plurality of subregions comprises a first tissue type characterized by a first vascular density;
a second subregion of the plurality of subregions comprises a second tissue type characterized by a second vascular density lower than the first vascular density; and
determining the acoustic treatment parameter for each of the one or more subregions comprises:
determining a first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the first subregion; and
determining a second acoustic treatment dose, treatment rate, or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the second subregion.

19. The method of claim 18, wherein:
the target region comprises portions of the blood-brain barrier that include gray matter and white matter;
the first tissue type is gray matter; and
the second tissue type is white matter.
20. The method of claim 17, wherein:
the one or more subregions is a plurality of subregions;
a first subregion of the plurality of subregions is characterized by a first vascular density;
a second subregion of the plurality of subregions is characterized by a second vascular density lower than the first vascular density; and
determining the acoustic treatment parameter for each of the one or more subregions comprises:
determining a first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the first subregion; and
determining a second acoustic treatment dose, treatment rate, or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the second subregion.
21. The method of claim 17, wherein:
the one or more subregions is a plurality of subregions;
a first subregion of the plurality of subregions is characterized by a first microbubble concentration;
a second subregion of the plurality of subregions is characterized by a second microbubble concentration lower than the first microbubble concentration; and
determining the acoustic treatment parameter for each of the one or more subregions comprises:
determining a first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the first subregion; and
determining a second acoustic treatment dose, treatment rate, or focal zone heterogeneity lower than the first acoustic treatment dose, treatment rate, or focal zone heterogeneity for the second subregion.

22. The method of claim 17, wherein:

determining the tissue type, the vasculature characteristic, or the microbubble concentration associated with each of the one or more subregions comprises determining the tissue type associated with each of the one or more subregions based on the image data;

the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and

determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having tissue types that are characterized by relatively lower vascular density or vascular flow velocity.

23. The method of claim 17, wherein:

determining the tissue type, the vasculature characteristic, or the microbubble concentration associated with each of the one or more subregions comprises determining the vasculature characteristic associated with each of the one or more subregions based on the image data, wherein the vasculature characteristic is a vascular density or a vascular flow velocity;

the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and

determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having relatively lower vascular density or vascular flow velocity.

24. The method of claim 17, wherein:

determining the tissue type, the vasculature characteristic, or the microbubble concentration associated with each of the one or more subregions comprises determining the microbubble concentration associated with each of the one or more subregions based on the image data;

the acoustic treatment parameter is a pulse duration, a pulse duty cycle, an acoustic frequency, an acoustic power level, or a treatment duration; and

determining the acoustic treatment parameter for each of the one or more subregions comprises determining a relatively higher acoustic frequency, a relatively lower pulse duration, a relatively lower pulse duty cycle, a relatively lower acoustic power level, or a relatively lower treatment duration for subregions having relatively lower microbubble concentration.

25. The method of any of claims 17-24, wherein for each sonication or pulse in which an acoustic treatment parameter is determined, determining the acoustic treatment parameter for each of the one or more subregions is further based on acoustic information obtained during a previous sonication or pulse of the one or more subregions.

26. The method of any of claims 17-25, further comprising, after causing the ultrasound transducer to sonicate the one or more subregions:

- obtaining subsequent image data of the one or more subregions of the target region;
- determining an updated vasculature characteristic or microbubble concentration associated with each of the one or more subregions based on the subsequent image data;

- determining an updated acoustic treatment parameter for each of the one or more subregions based on the updated vasculature characteristic or microbubble concentration respectively associated with each of the one or more subregions; and

- causing the ultrasound transducer to sonicate the one or more subregions according to the updated acoustic treatment parameters respectively corresponding to each of the one or more subregions.

27. The method of any of claims 17-26, wherein obtaining the image data comprises obtaining:

- contrast-enhanced ultrasound device (CEUS) data,
- ultrasound localization microscopy device (ULM) data for obtaining ultrasound super-resolution images,
- magnetic resonance imaging (MRI) data,
- computer tomography (CT) data, and/or
- anatomical information based on a medical atlas.

28. The method of any of claims 17-27, wherein causing the ultrasound transducer to sonicate the one or more subregions comprises causing microbubbles to be generated by

application of ultrasound at the target region or causing the transducer to sonicate microbubbles administered by the system at the target region.

29. The method of any of claims 17-28, wherein obtaining the image data comprises imaging the target region.

30. The method of any of claims 17-29, wherein obtaining the image data comprises identifying the target region and using an atlas to determine the vasculature characteristic associated with each of the one or more subregions.

31. The method of any of claims 17-30, wherein causing the ultrasound transducer to sonicate the one or more subregions comprises controlling acoustic power or energy emitted by transducer elements of the ultrasound transducer so that acoustic power or energy is above a threshold level to thereby induce microbubble generation.

32. The method of any of claims 17-31, wherein the acoustic treatment parameter is a frequency, an amplitude, or a phase associated with a plurality of transducer elements of the ultrasound transducer.

33. A system for providing focused ultrasound to a target region, the system comprising:
an ultrasound transducer; and
a controller configured to:

obtain acoustic feedback associated with a sonication operation involving the ultrasound transducer treating one or more subregions of the target region and/or a region surrounding the target region;

determine a treatment dose and/or a treatment rate of the sonication operation for each of the one or more subregions according to a first set of one or more frequency bands of the acoustic feedback;

determine an energy level and/or a power level of the sonication operation for each of the one or more subregions according to a second set of one or more frequency bands of the acoustic feedback;

determine an acoustic treatment parameter for each of the one or more subregions based on (i) the treatment dose and/or the treatment rate respectively associated with each of the one or more subregions, and (ii) the energy level and/or the power level respectively associated with each of the one or more subregions; and

cause the ultrasound transducer to sonicate the one or more subregions according to the acoustic treatment parameters respectively corresponding to each of the one or more subregions.

34. The system of claim 33, wherein:

determining the acoustic treatment parameter based on the treatment dose and/or the treatment rate includes adjusting the acoustic treatment parameter to maintain the treatment dose and/or the treatment rate with respect to an efficacy threshold; and

determining the acoustic treatment parameter based on the energy level and/or the power level includes adjusting the acoustic treatment parameter to maintain the energy level and/or the power level with respect to a safety threshold.

35. The system of any of claims 33-34, wherein the acoustic treatment parameter is a frequency, an amplitude, or a phase associated with a plurality of transducer elements of the ultrasound transducer.

36. A method for providing focused ultrasound to a target region using an ultrasound transducer, the method comprising:

at a controller communicatively coupled to the ultrasound transducer:

obtaining acoustic feedback associated with a sonication operation involving the ultrasound transducer treating one or more subregions of the target region and/or a region surrounding the target region;

determining a treatment dose and/or a treatment rate of the sonication operation for each of the one or more subregions according to a first set of one or more frequency bands of the acoustic feedback;

determining an energy level and/or a power level of the sonication operation for each of the one or more subregions according to a second set of one or more frequency bands of the acoustic feedback;

determining an acoustic treatment parameter for each of the one or more subregions based on (i) the treatment dose and/or the treatment rate respectively associated with each of the one or more subregions, and (ii) the energy level and/or the power level respectively associated with each of the one or more subregions; and

causing the ultrasound transducer to sonicate the one or more subregions according to the acoustic treatment parameters respectively corresponding to each of the one or more subregions.

37. The method of claim 37, wherein:

determining the acoustic treatment parameter based on the treatment dose and/or the treatment rate includes adjusting the acoustic treatment parameter to maintain the treatment dose and/or the treatment rate with respect to an efficacy threshold; and

determining the acoustic treatment parameter based on the energy level and/or the power level includes adjusting the acoustic treatment parameter to maintain the energy level and/or the power level with respect to a safety threshold.

38. The method of any of claims 36-37, wherein the acoustic treatment parameter is a frequency, an amplitude, or a phase associated with a plurality of transducer elements of the ultrasound transducer.

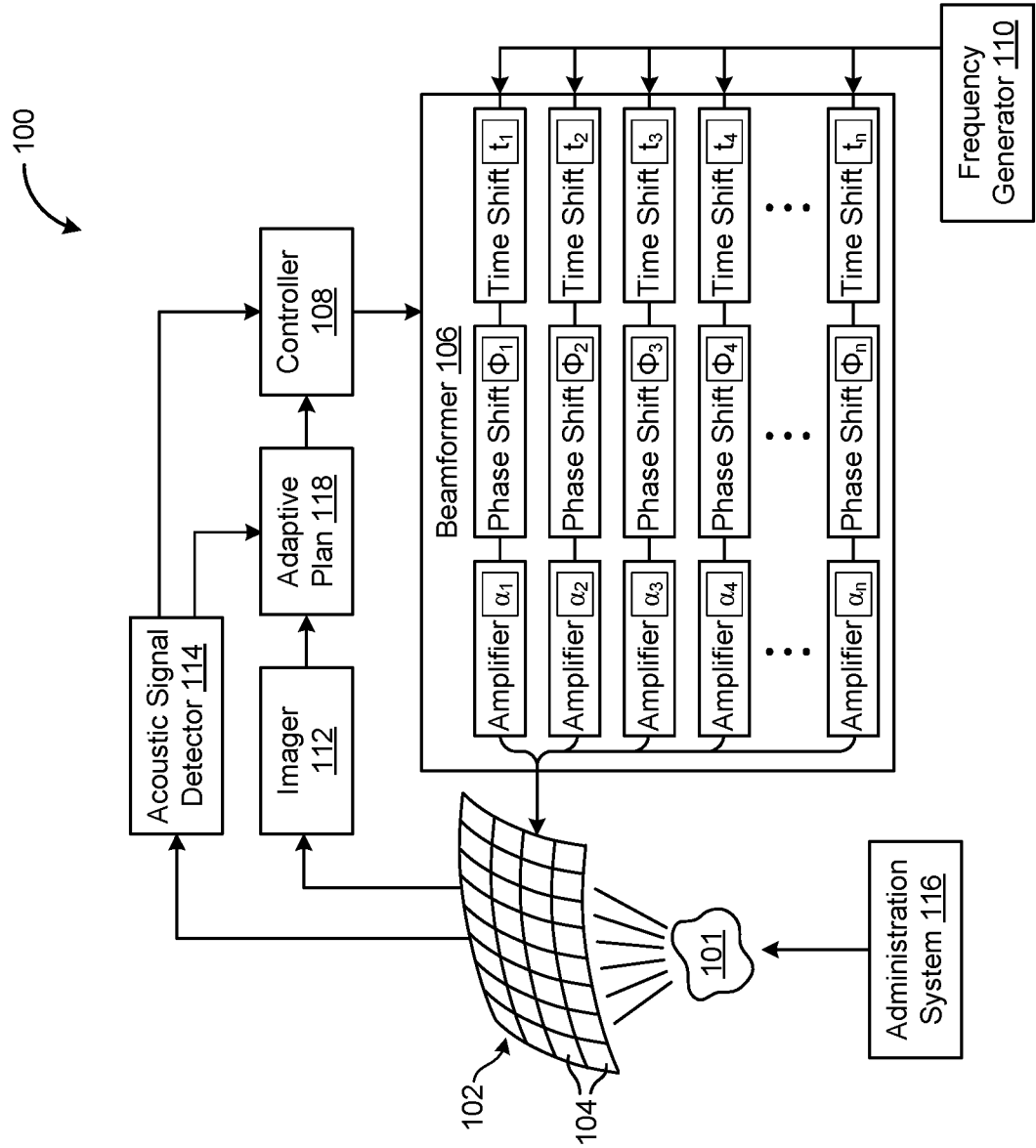


Figure 1

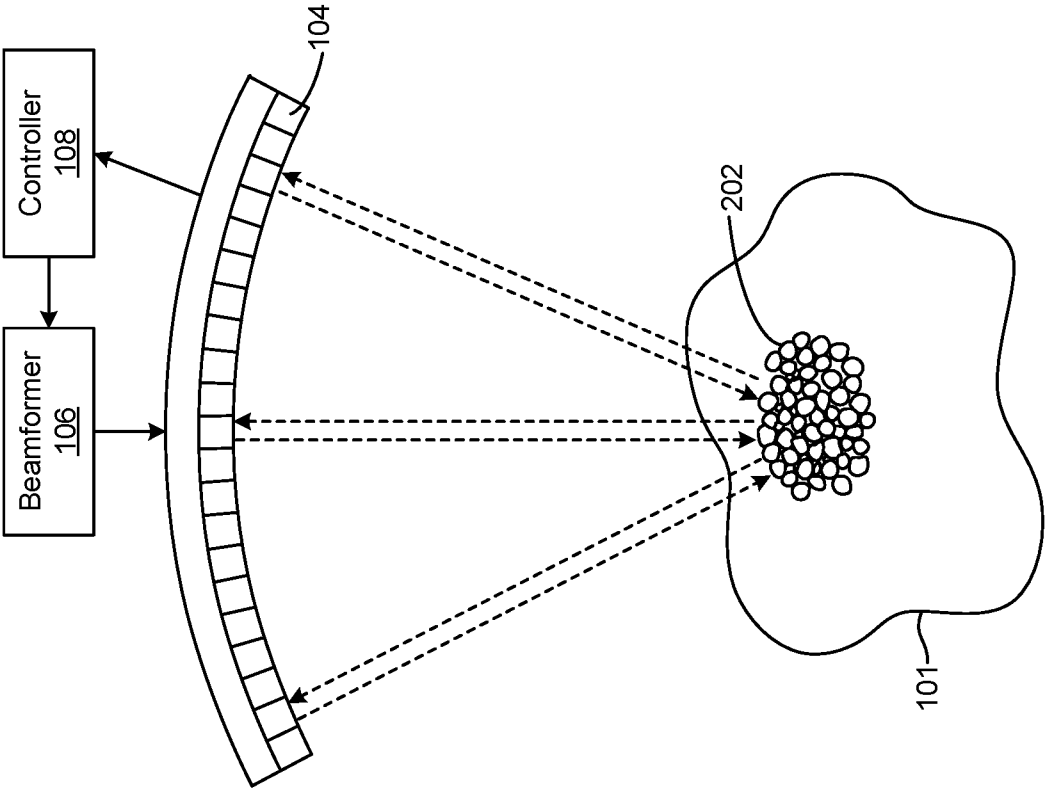


Figure 2

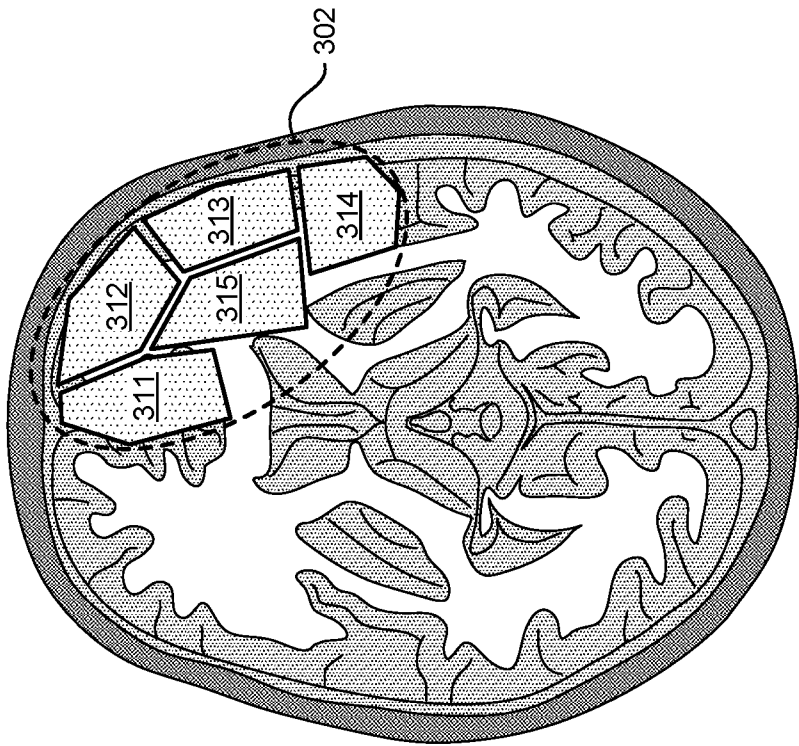


Figure 4

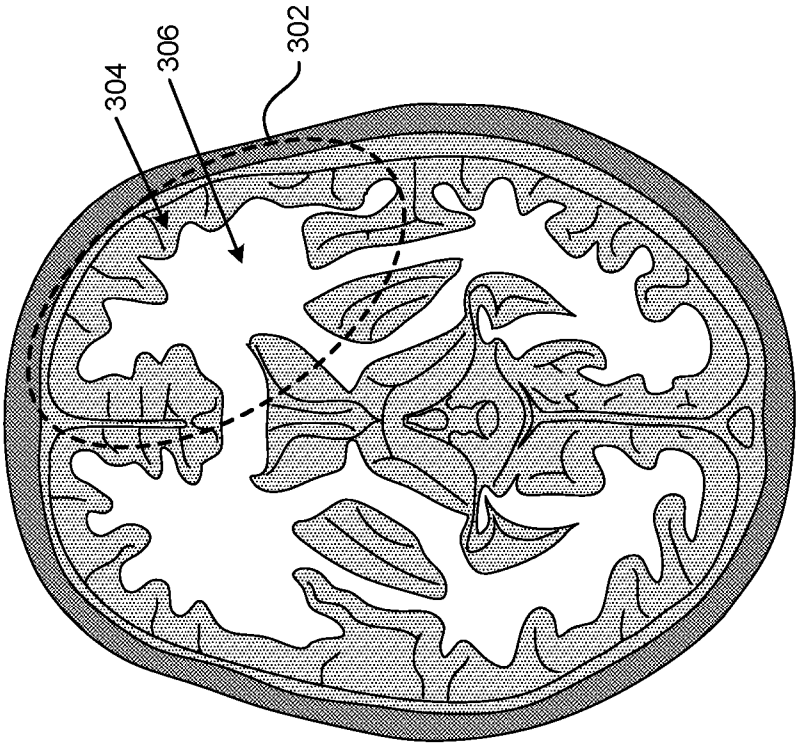


Figure 3

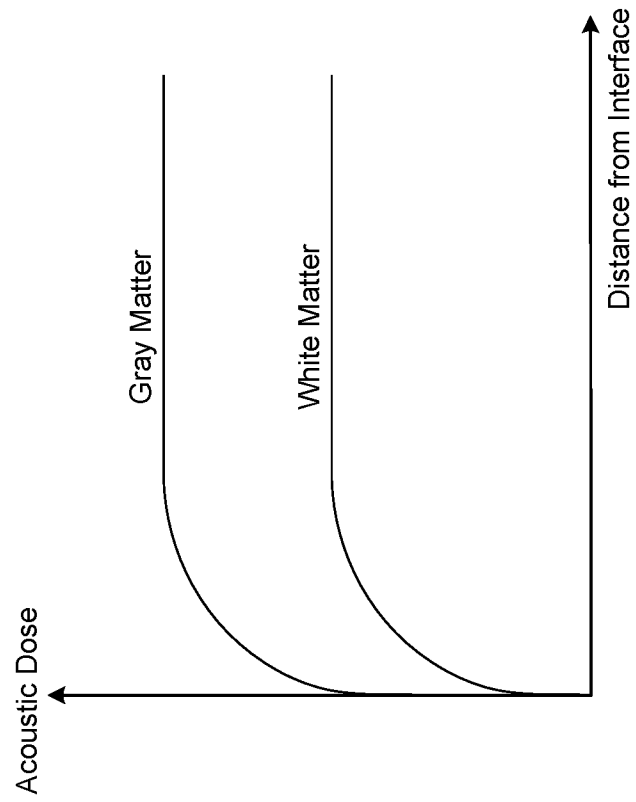


Figure 5

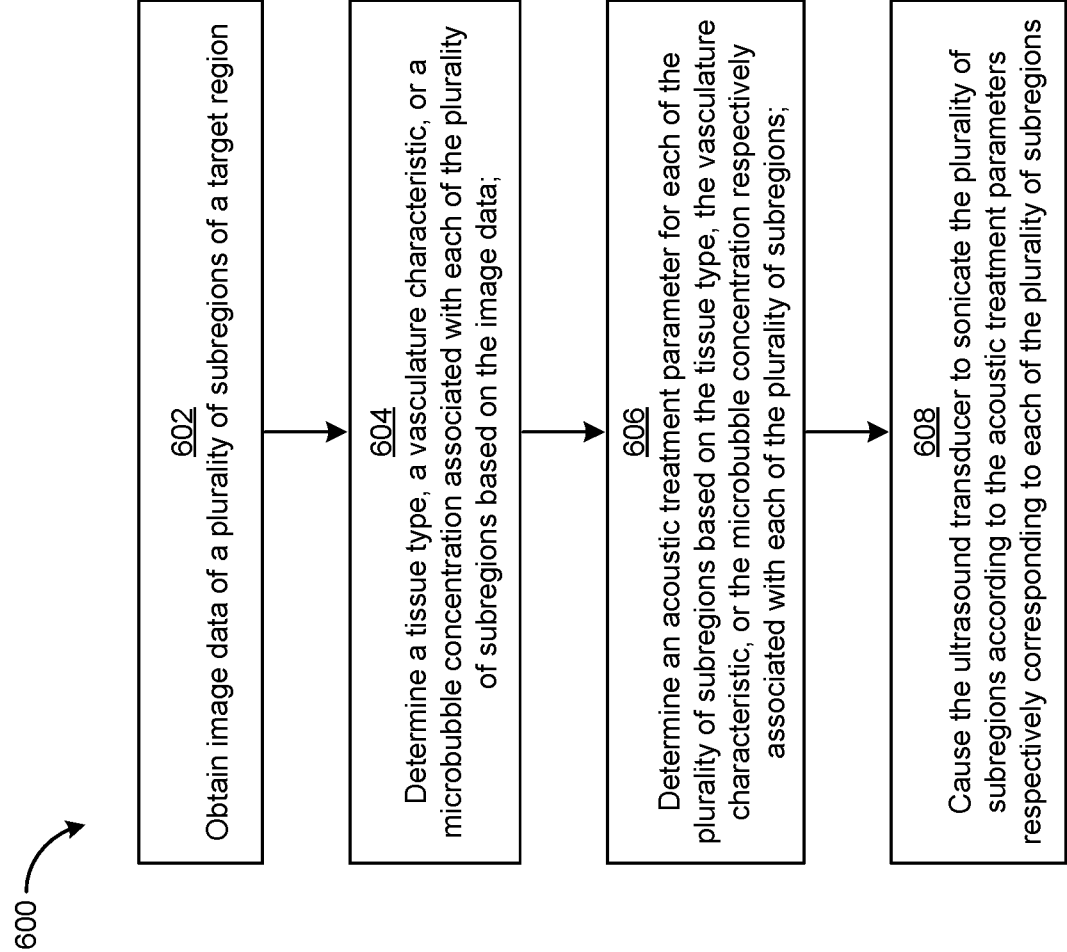


Figure 6

Need for Factoring in Vascular Densities of Different Tissues

- * White and gray matters respond differently to BBB opening due to different vasculature densities
- * Higher acoustic power is needed for the same acoustic dose
- * Overtreatment can be observed when the same acoustic parameters ($AD_2 = 0.7$) are used for different tissues (bottom)

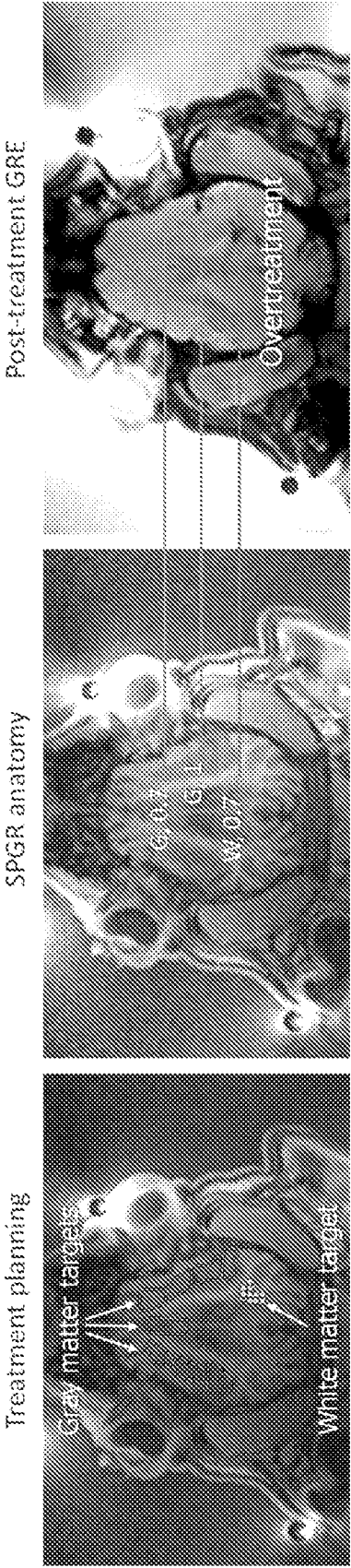


Figure 7

Wide Focal Spot Can Lead to Heterogeneous BBB Opening due to Differences Between Tissue Type and Vascular Density

- * When using a wide focal spot, the central lobe of the beam covers large sections of the tissue, frequently with different tissue types, and vascular densities
- * The treatment planning is performed based on the middle imaging plane

Tissue Anatomy vs. BBB Opening (Dotarem)



Tissue Anatomy Image



MRI plane used for treatment planning

Figure 8

Tissue-based BBB Opening due to Wide Beam

- The tissue composition in the upper and lower imaging planes are different leading to BBB opening patterns that depend on the tissue composition and not the targeted anatomical region

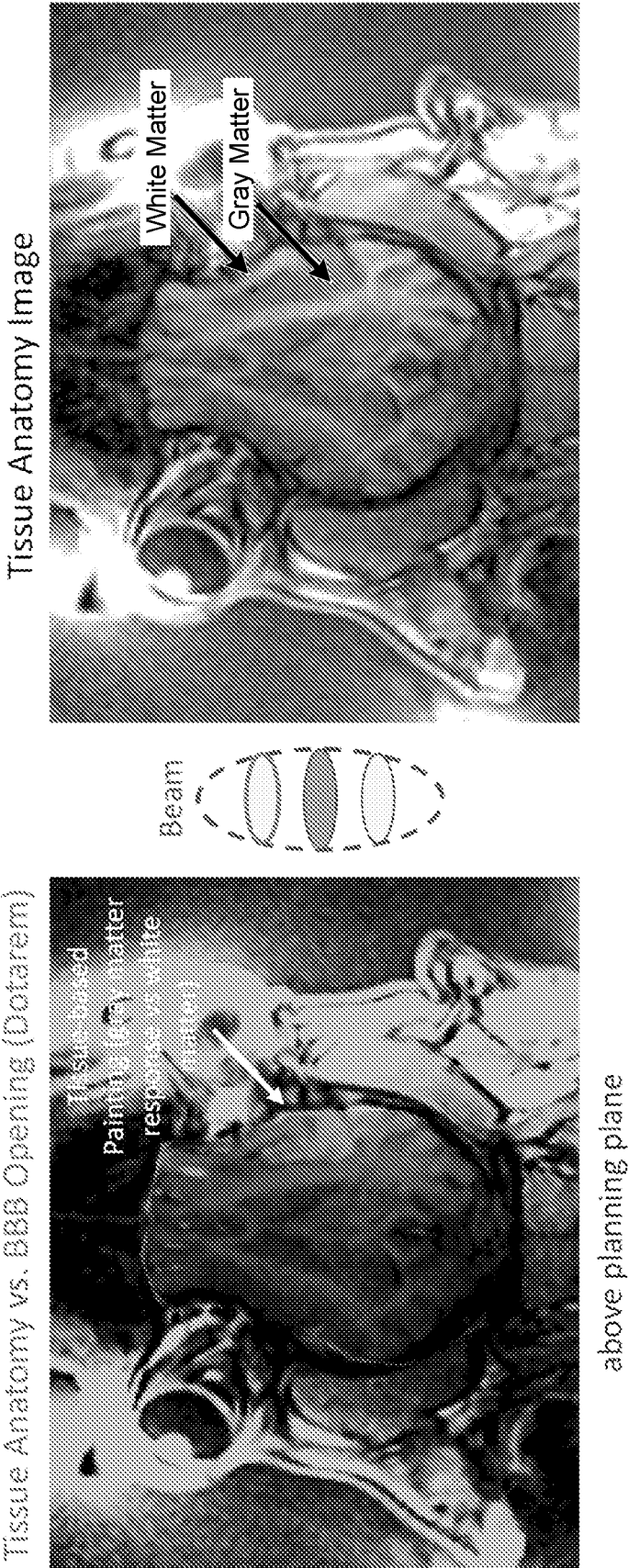
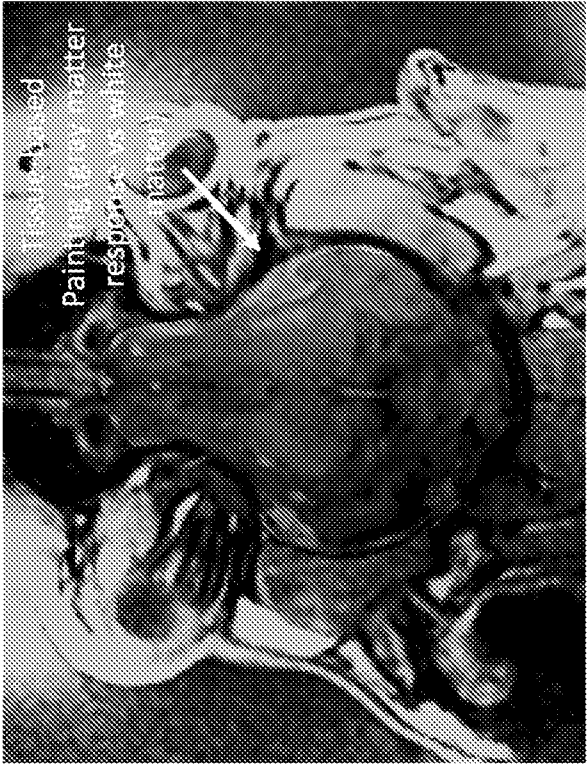


Figure 9

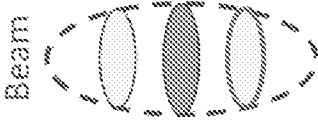
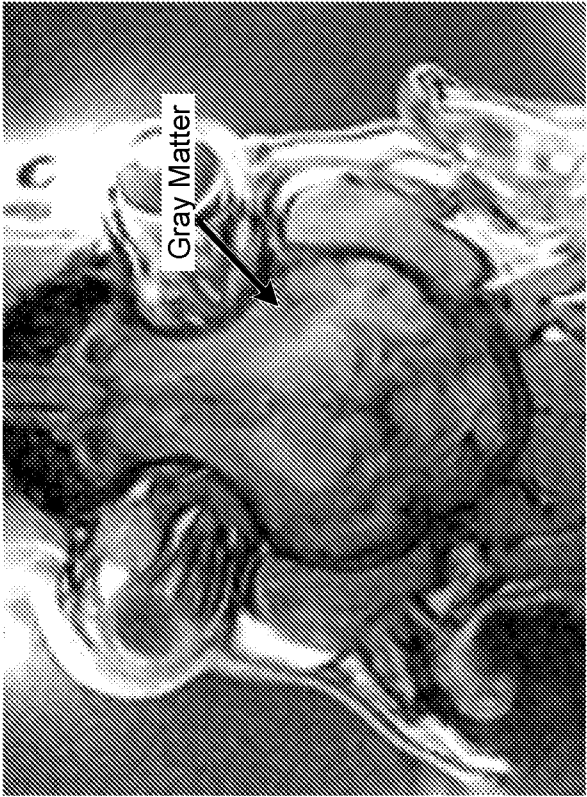
Tissue-based BBB Opening due to Wide Beam

- * The tissue composition in the upper and lower imaging planes are different leading to BBB opening patterns that depend on the tissue composition and not the targeted anatomical region

Tissue Anatomy vs. BBB Opening (Dotarem)



Tissue Anatomy Image



below planning plane

Figure 10

Anatomy-Based Treatment Planning Leads to BBB Opening in Both White and Gray Matter

• Adaptive treatment planning leads to opening of both white and gray brain regions

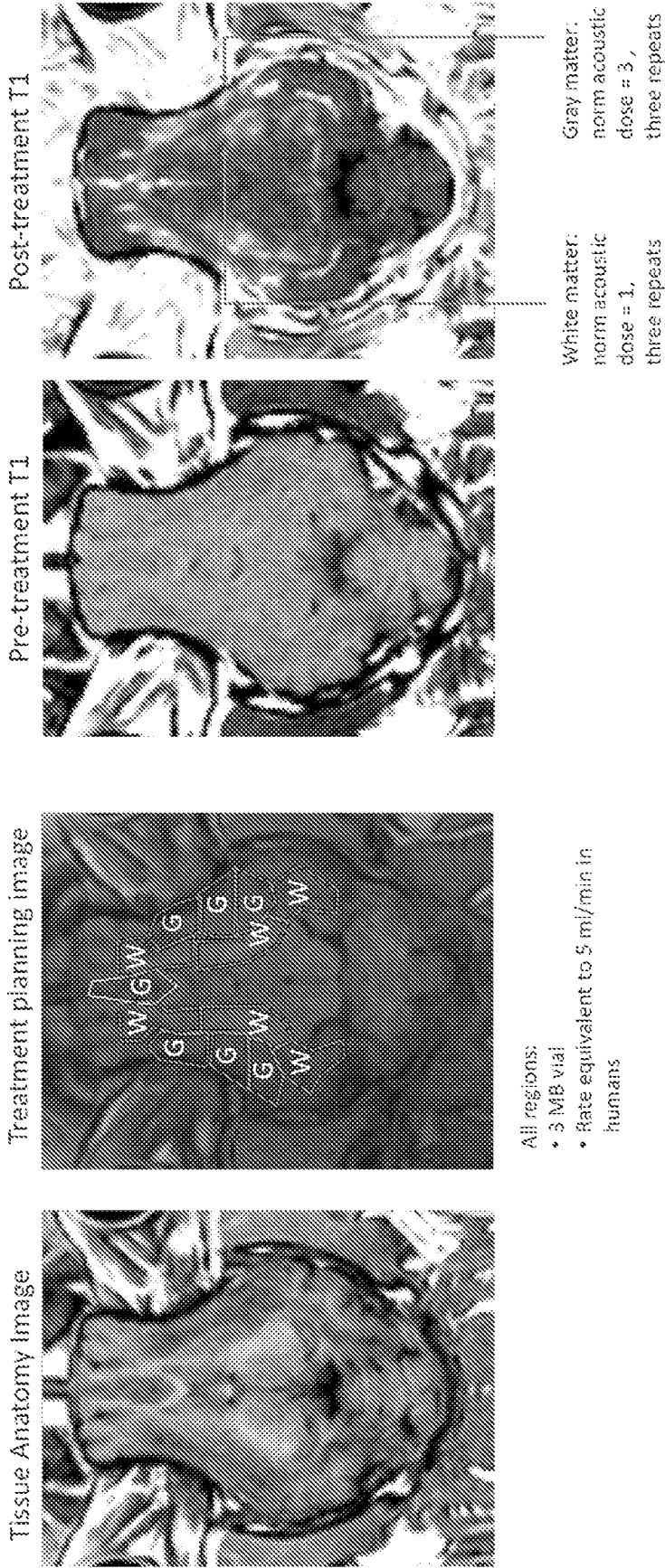


Figure 11

Anatomy-Based Treatment Planning Enables Homogenous Opening of Heterogenous Tissue

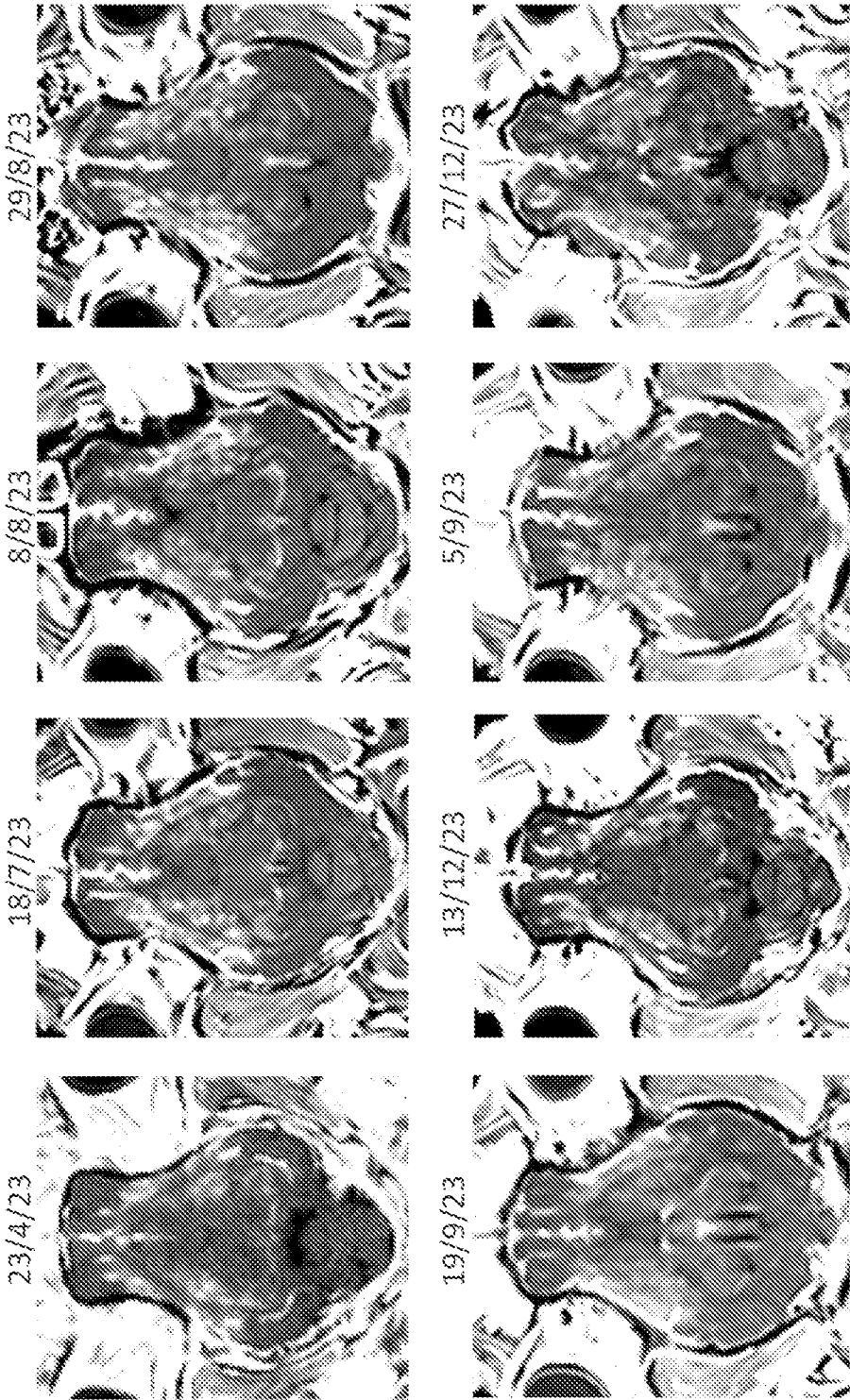


Figure 12

Anatomy-Based Treatment Planning Leads to Repeatable BBBO

- Repeatable BBBO opening in gray matter, white matter, and sulcus gray matter
- Room for improvement in sulcus white
- Lower delivery potential in white matter

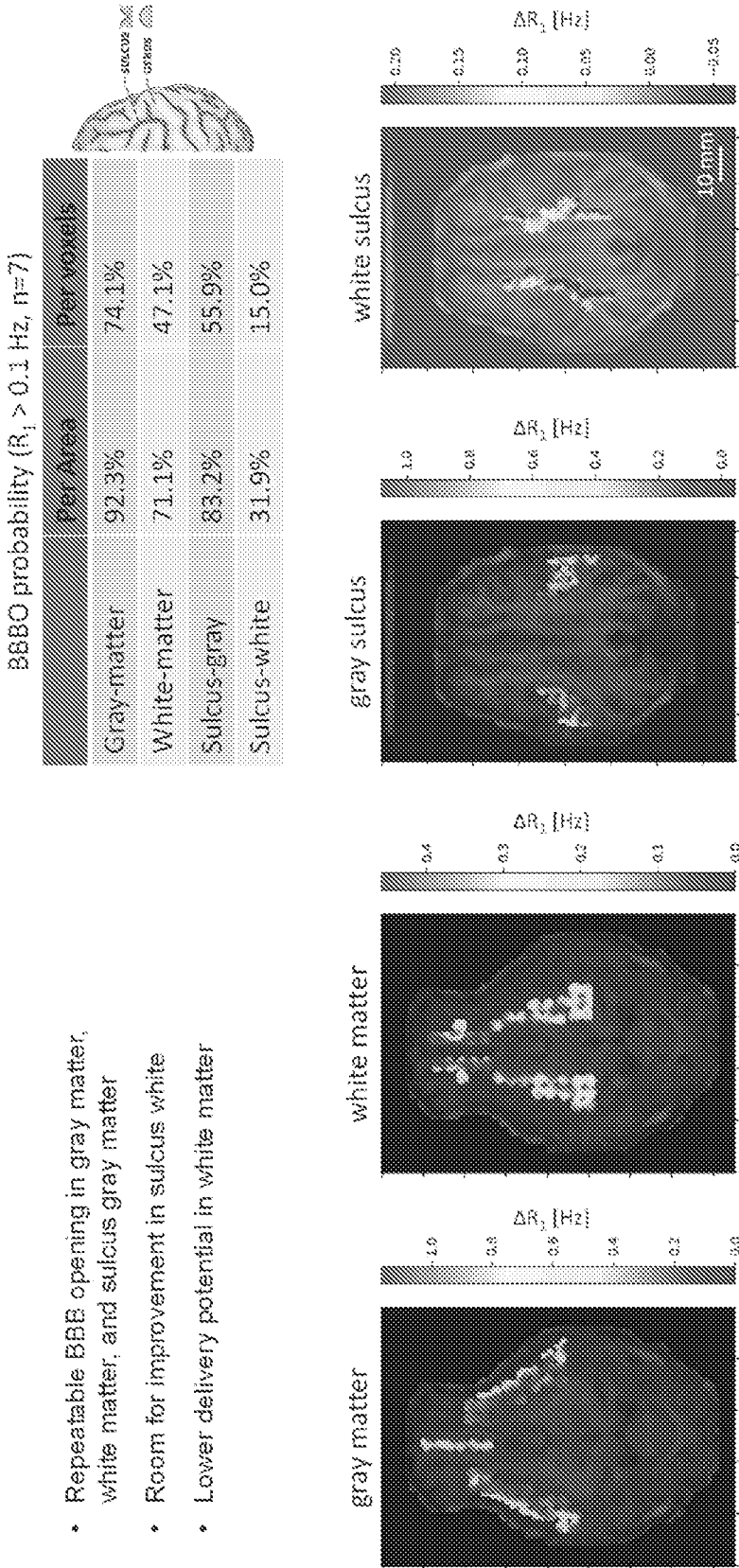
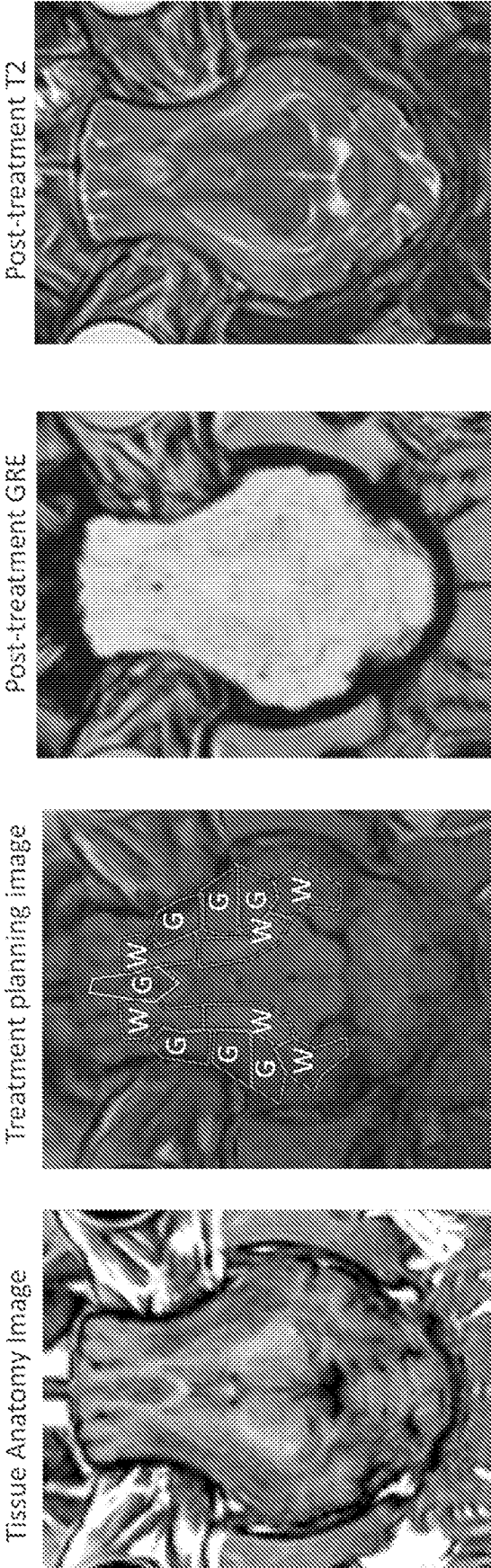


Figure 13

Anatomy-Based Treatment Planning Leads to BBB Opening in Both White and Gray Matter

- * Safe opening with minimal signs of edema and micro-bleeding



All regions:
• 3 MB vial
• Rate equivalent to 5 ml/min in humans

Figure 14

Importance of Precise treatment In Tissue Interface Regions

- Tissue interface regions demand careful treatment monitoring to avoid overtreatment and under-delivery
- Therefore, adaptive planning and the transducer's high-spatial resolution of the are critical for adaptive BBBO opening

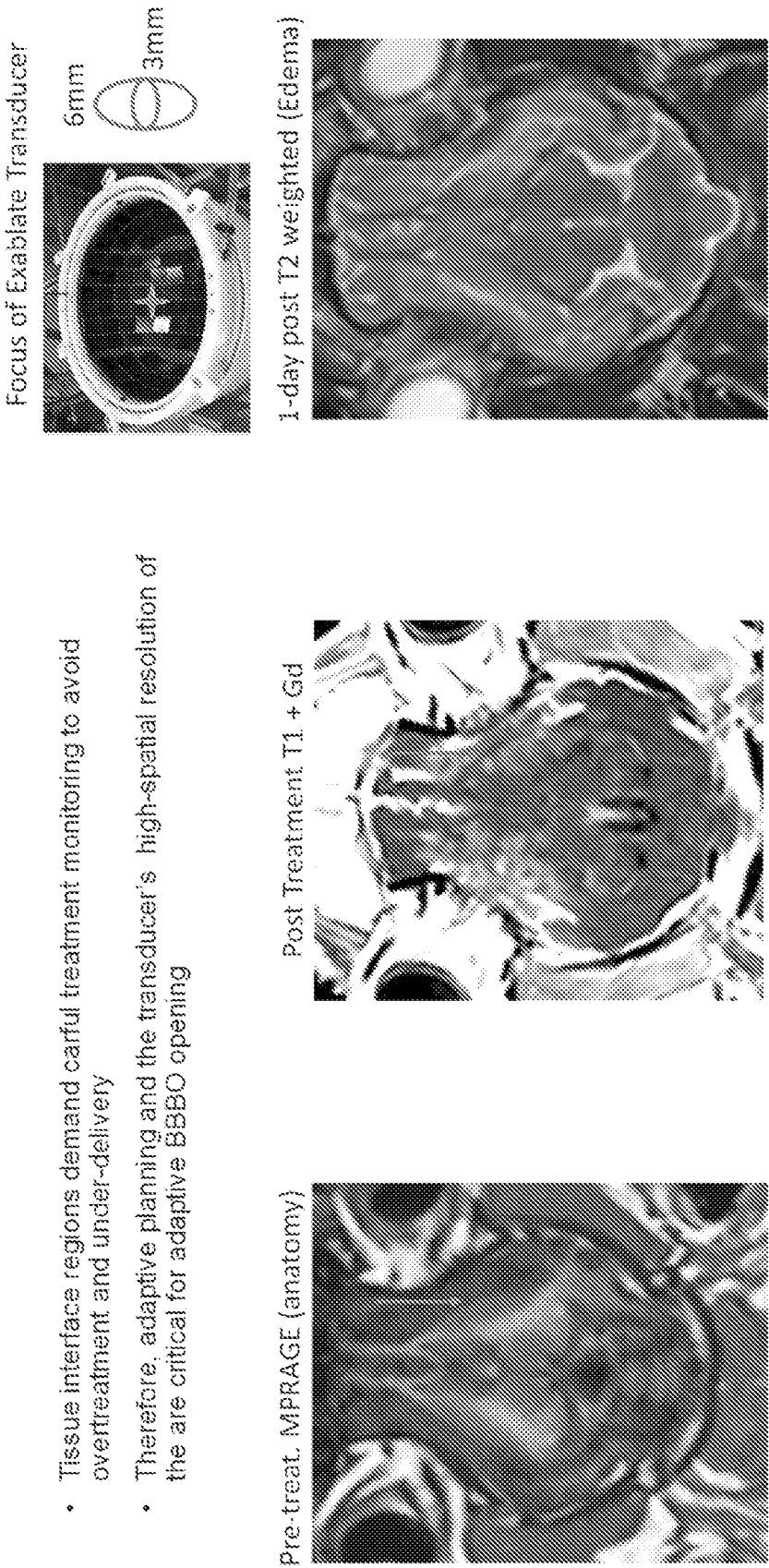


Figure 15

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/055813

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61N7/02
ADD. A61N7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61N

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 3 645 118 A1 (INSIGHTEC LTD [IL]) 6 May 2020 (2020-05-06)	1,3,9-16
Y	paragraphs [0021], [0022], [0027], [0040], [0045], [0050]; figures 1,3a -----	2,4-8
Y	US 2023/158171 A1 (SHAPIRO MIKHAIL [US] ET AL) 25 May 2023 (2023-05-25) paragraph [0246] -----	2,4-8
A	US 2022/273929 A1 (KONOFAGOU ELISA E [US]) 1 September 2022 (2022-09-01) paragraph [0089] ----- - / - -	2,4-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 September 2024

Date of mailing of the international search report

02/12/2024

Name and mailing address of the ISA/

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Schmidt, Matthias

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/055813

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	DURHAM PHILLIP G. ET AL: "Current clinical investigations of focused ultrasound blood-brain barrier disruption: A review", NEUROTHERAPEUTICS : THE JOURNAL OF THE AMERICAN SOCIETY FOR EXPERIMENTAL NEUROTHERAPEUTICS, vol. 21, no. 3, 17 April 2024 (2024-04-17), XP093206474, ISSN: 1878-7479, DOI: 10.1016/j.neurot.2024.e00352 Retrieved from the Internet: URL:https://www.sciencedirect.com/science/article/pii/S1878747924000382> paragraph [0003] -----	2, 4-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2024/055813

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17 - 32, 36 - 38
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
1 - 16

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-16

treatment parameters are generated determined according to
tissue type

2. claims: 33-35

unaware of the treated tissue type, the controller may use
acoustic feedback for efficacy and for maintaining safety

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 17-32, 36-38

Method claims 17-32,36-38 define methods for treatment of the human or animal body by surgery practised on the human or animal body. They include the step of "causing the ultrasonic transducer to sonicate [...] subregions [of tissue] according to treatment parameters", which is a surgical step. Therefore no search has been performed for the subject-matter of these claims (see Article 17 (2) PCT and Rule 39.1.(iv) PCT) and no written opinion is required for the subject-matter of these method claims (see Rule43bis.1 and Rule 67.1 (iv) PCT).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2024/055813

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