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Sapozhnikov et al.

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(54) **METHODS OF SOFT TISSUE EMULSIFICATION USING A MECHANISM OF ULTRASONIC ATOMIZATION INSIDE GAS OR VAPOR CAVITIES AND ASSOCIATED SYSTEMS AND DEVICES**

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(51) **Int. Cl.**

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A61N 7/02	(2006.01)
A61N 7/00	(2006.01)

(52) **U.S. Cl.**

CPC . ***A61N 7/02*** (2013.01); ***A61B 8/00*** (2013.01); *A61N 2007/0039* (2013.01)

(58) **Field of Classification Search**

CPC ... A61N 2007/0039; A61N 7/02; A61B 8/00
USPC 601/2, 4
See application file for complete search history.

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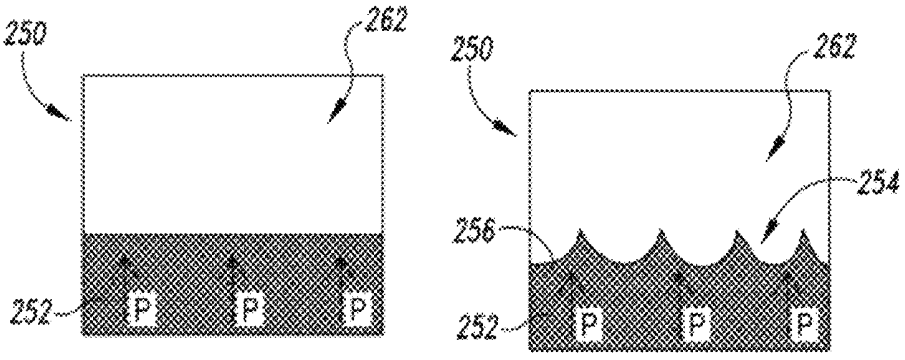
(57) **ABSTRACT**

The present technology is directed to methods of soft tissue emulsification using a mechanism of ultrasonic atomization inside gas or vapor cavities, and associated systems and devices. In several embodiments, for example, a method of non-invasively treating tissue includes pulsing ultrasound energy from the ultrasound source toward the target site in tissue. The ultrasound source is configured to emit high intensity focused ultrasound (HIFU) waves. The target site comprises a pressure-release interface of a gas or vapor cavity located within the tissue. The method continues by generating shock waves in the tissue to induce a lesion in the tissue at the target site. The method additionally includes characterizing the lesion based on a degree of at least one of a mechanical or thermal ablation of the tissue.

15 Claims, 5 Drawing Sheets



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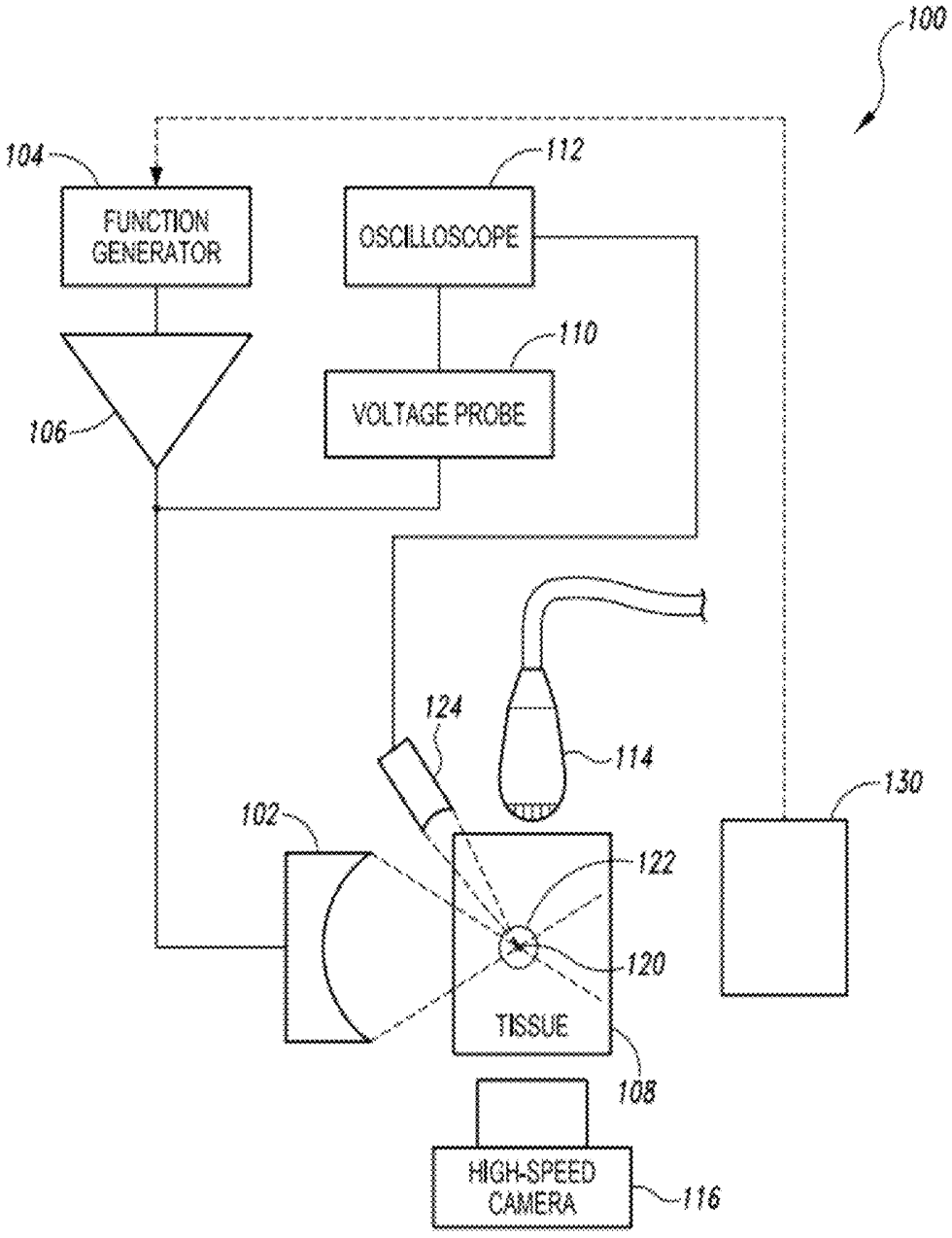
100
104
FUNCTION GENERATOR
112
OSCILLOSCOPE
110
VOLTAGE PROBE
106
124
114
130
102
122
120
TISSUE
108
HIGH-SPEED CAMERA
116

Fig. 1

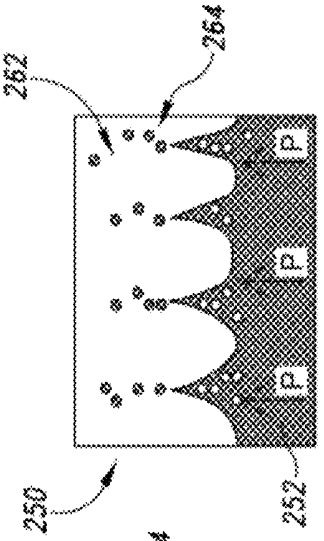

Fig. 2C

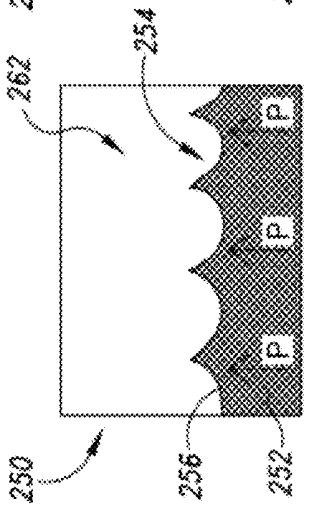

Fig. 2B

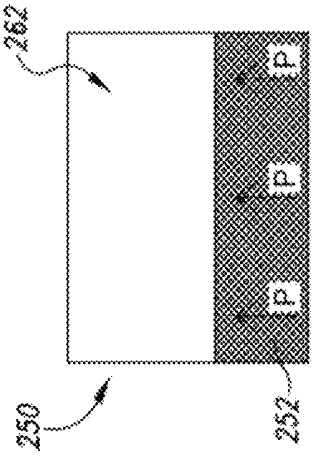

Fig. 2A

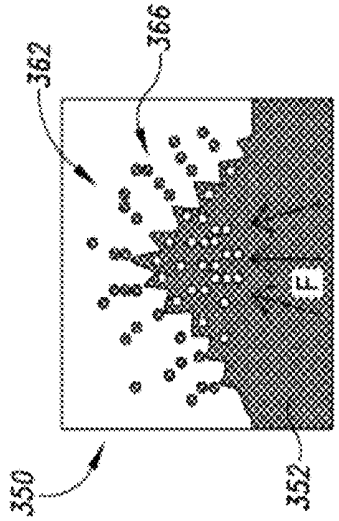

Fig. 3C

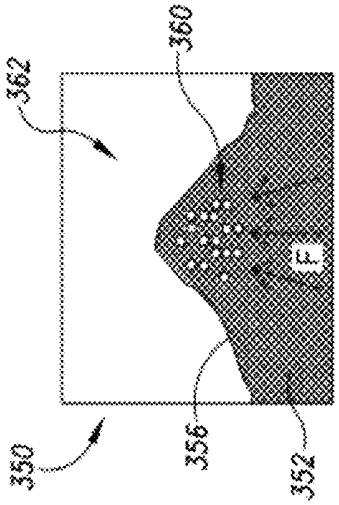

Fig. 3B

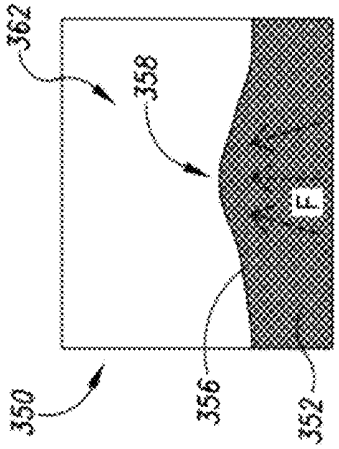

Fig. 3A

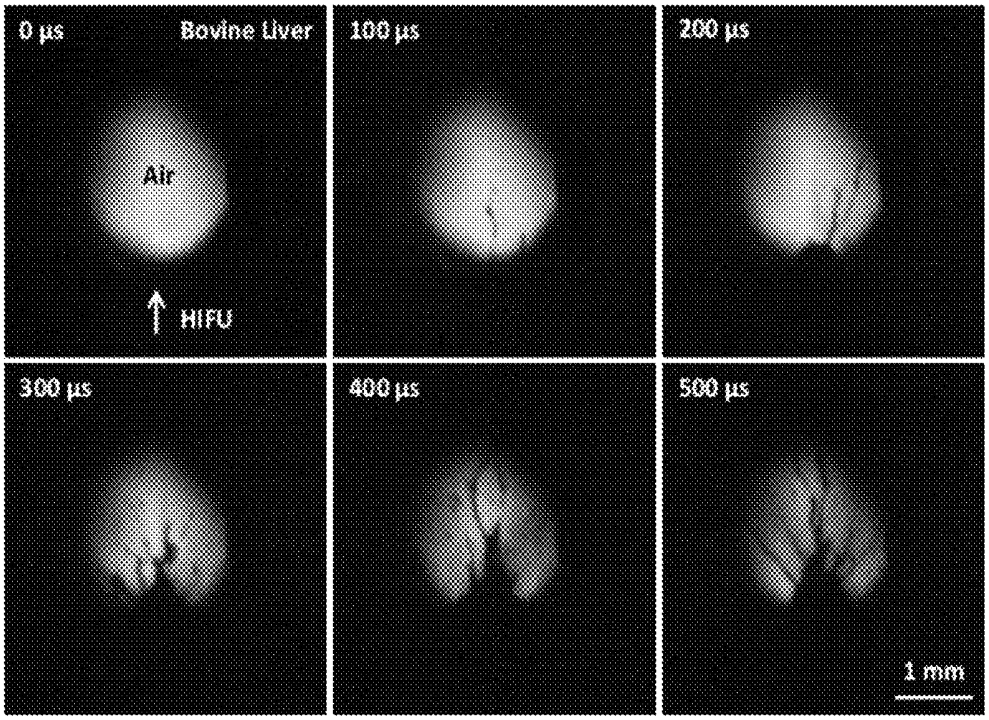

Fig. 3D

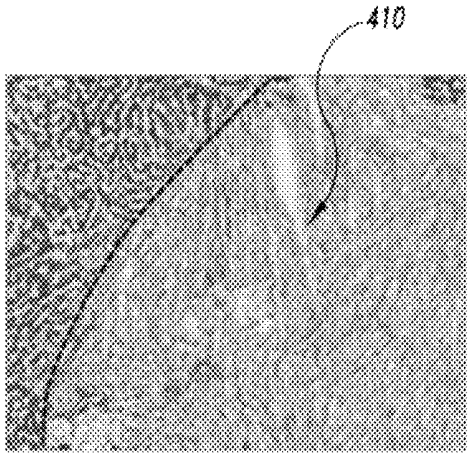

Fig. 4A

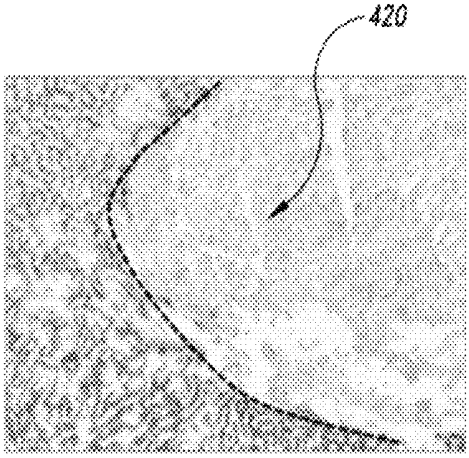

Fig. 4B

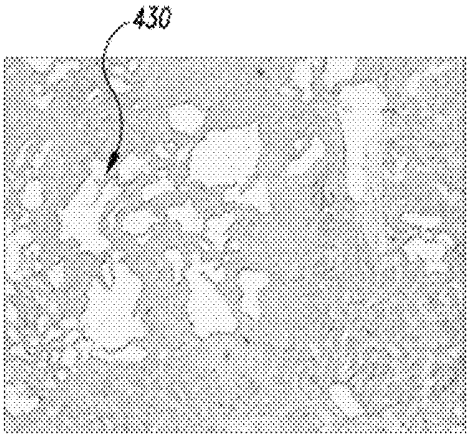

Fig. 4C

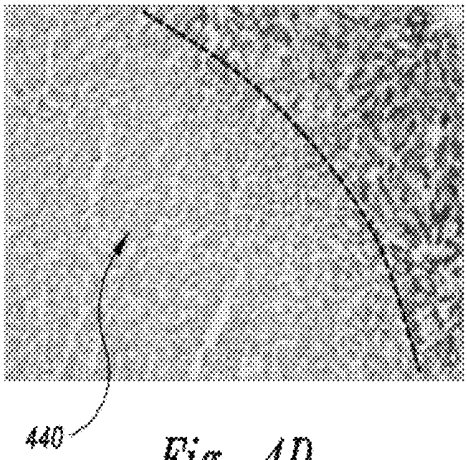

Fig. 4D

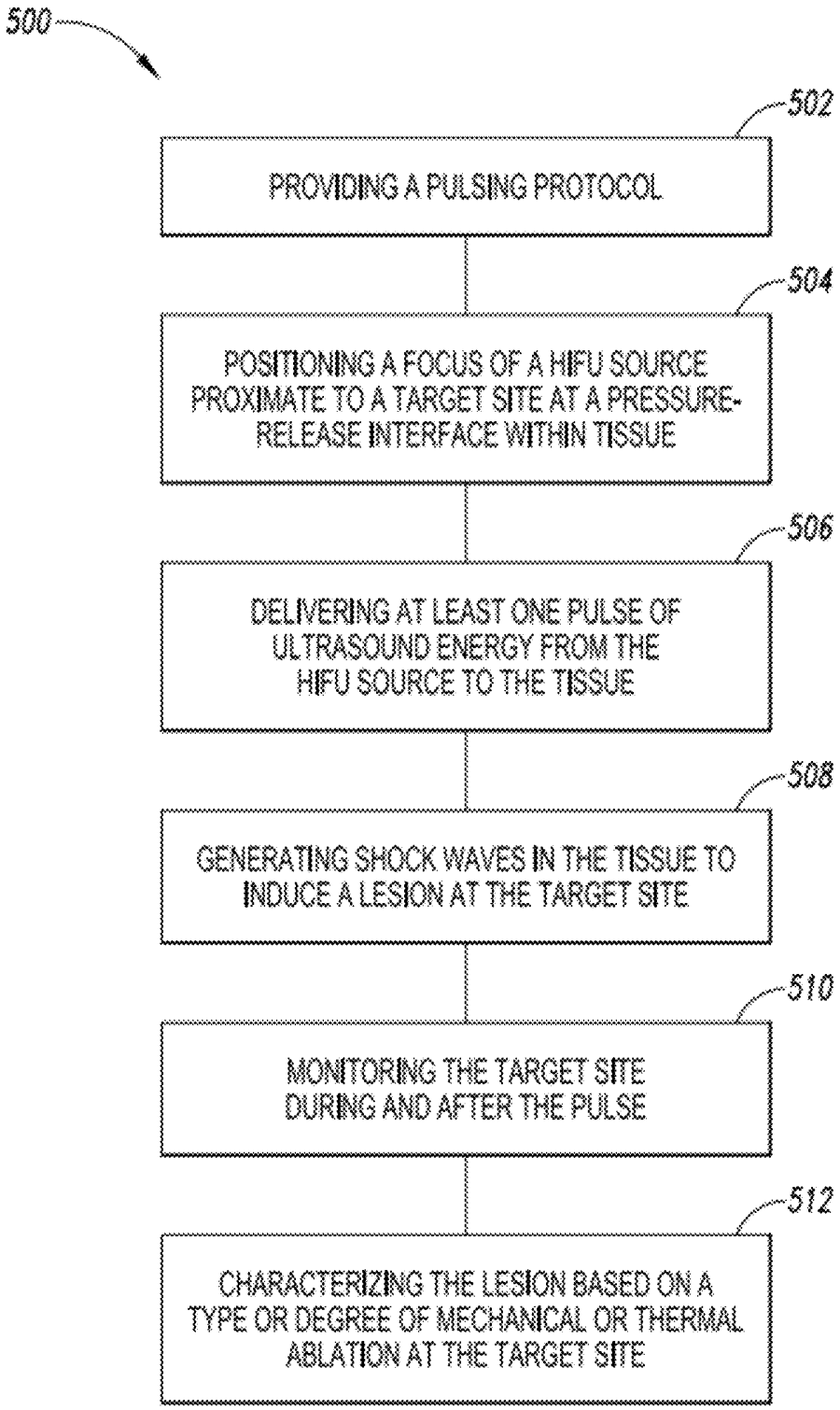
500
502
PROVIDING A PULSING PROTOCOL
504
POSITIONING A FOCUS OF A HIFU SOURCE PROXIMATE TO A TARGET SITE AT A PRESSURE-RELEASE INTERFACE WITHIN TISSUE
506
DELIVERING AT LEAST ONE PULSE OF ULTRASOUND ENERGY FROM THE HIFU SOURCE TO THE TISSUE
508
GENERATING SHOCK WAVES IN THE TISSUE TO INDUCE A LESION AT THE TARGET SITE
510
MONITORING THE TARGET SITE DURING AND AFTER THE PULSE
512
CHARACTERIZING THE LESION BASED ON A TYPE OR DEGREE OF MECHANICAL OR THERMAL ABLATION AT THE TARGET SITE

Fig. 5

METHODS OF SOFT TISSUE EMULSIFICATION USING A MECHANISM OF ULTRASONIC ATOMIZATION INSIDE GAS OR VAPOR CAVITIES AND ASSOCIATED SYSTEMS AND DEVICES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/474,080, filed Apr. 11, 2011, and U.S. Provisional Application No. 61/488,552, filed May 20, 2011, both of which are incorporated herein by reference in their entireties.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with government support under 1R01EB007643-01A2 awarded by National Institutes of Health (NIH) and SMST01601 (NASA NCC 9-58) awarded by National Space Biomedical Research Institute (NSBRI). The government has certain rights in the invention.

TECHNICAL FIELD

The present technology relates generally to high intensity focused ultrasound. In particular, several embodiments are directed toward methods and systems for non-invasive treatment of tissue using high intensity focused ultrasound therapy.

BACKGROUND

Minimally invasive and non-invasive therapeutic ultrasound treatments can be used to ablate, necrotize, and/or otherwise damage tissue. High intensity focused ultrasound ("HIFU"), for example, is used to thermally or mechanically damage tissue. HIFU thermal treatments increase the temperature of tissue at a focal region such that the tissue quickly forms a thermally coagulated treatment volume. HIFU treatments can also cause mechanical disruption of tissue with well-demarcated regions of mechanically emulsified treatment volumes that have little remaining cellular integrity. For certain medical applications, tissue emulsification may be more favorable than thermal damage because it produces liquefied volumes that can be more easily removed or absorbed by the body than thermally coagulated solid volumes.

HIFU treatments can utilize a sequence of pulses, rather than continuous-wave HIFU exposures, to reduce undesirable thermal effects on the surrounding tissue. In histotripsy exposures, for example, HIFU sources operate with low duty cycles (e.g., 1%), use relatively short pulses (e.g., 10-20 microseconds), and deliver high pulse average intensities of up to 40 kW/cm^2 to form bubbles that mechanically disrupt tissue. Histotripsy techniques, for example, can induce cavitation by delivering pulses of high peak negative pressures that are significantly higher than the tensile strength of the tissue. The repetition of such pulses can increase the area of tissue affected by cavitation to create a "cavitation cloud" that emulsifies the tissue. Cavitation, however, is generally stochastic in nature, making cavitation-based HIFU treatments somewhat unpredictable and difficult to reproduce. Therefore, there is a need to enhance the reliability, predictability, and repeatability of mechanical disruption of tissue damage (e.g., emulsification).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic view of a HIFU system configured in accordance with an embodiment of the present technology.

FIGS. **2**A-**2**C are illustrations of planar ultrasound waves modeled at a pressure-release interface in tissue in accordance with several embodiments of the present technology.

FIGS. **3**A-**3**C are illustrations of focal ultrasound waves modeled at a pressure-release interface in tissue in accordance with several embodiments of the present technology.

FIG. **3**D is a set of photographs of focal ultrasound waves applied to a pressure-release interface in tissue in accordance with several embodiments of the present technology.

FIGS. **4**A-**4**D are photographs of various types of lesions formed in tissue using HIFU in accordance with embodiments of the present technology.

FIG. **5** is a block diagram illustrating a method of treating tissue at a target site in accordance with an embodiment of the present technology.

DETAILED DESCRIPTION

The present technology is directed to methods of soft tissue emulsification using a mechanism of ultrasonic atomization inside gas or vapor cavities, and associated systems and devices. In several embodiments, for example, a method of non-invasively treating tissue includes pulsing ultrasound energy from the ultrasound source toward the target site in tissue. The ultrasound source is configured to emit HIFU waves. The target site comprises a pressure-release interface of a gas or vapor cavity located within the tissue. The method continues by generating shock waves in the tissue to induce a lesion in the tissue at the target site. The method additionally includes characterizing the lesion based on a degree of at least one of a mechanical or thermal ablation of the tissue. These HIFU systems and methods have a number of both therapeutic and cosmetic applications, such as producing bulk ablation of benign and malignant tumors.

Certain specific details are set forth in the following description and in FIGS. **1-5** to provide a thorough understanding of various embodiments of the technology. For example, several embodiments of HIFU treatments that destroy tissue are described in detail below. The present technology, however, may be used to destroy multi-cell structures similar to tissue. Additionally, the term "target site" is used broadly throughout the disclosure to refer to any volume or region of tissue that may benefit from HIFU treatment. Other details describing well-known structures and systems often associated with ultrasound systems and associated devices have not been set forth in the following disclosure to avoid unnecessarily obscuring the description of the various embodiments of the technology. A person of ordinary skill in the art, therefore, will accordingly understand that the technology may have other embodiments with additional elements, or the technology may have other embodiments without several of the features shown and described below with reference to FIGS. **1-5**.

FIG. **1** is a schematic view of a HIFU system **100** configured in accordance with an embodiment of the present technology. The HIFU system **100** can include a HIFU source **102** operably coupled to a function generator **104** and an amplifier **106**. The HIFU source **102** can be an ultrasound transducer that emits high levels of ultrasound energy to a

focus **120**. The focus **120** can be a point, plane, or region at which the intensity from the HIFU source **102** is the highest. In other embodiments, the HIFU source **102** can include a single-element device, a multi-element device, an extracorporeal device, an intracavitary device, and/or other devices or systems configured to emit HIFU energy to a focus. The HIFU source **102** can have a frequency range of approximately 0.5-20 MHz. In other embodiments, the frequency of the HIFU source **102** can vary. The function generator **104** (e.g., an Agilent 33250A function generator from Agilent of Palo Alto, Calif.) and the amplifier **106** (e.g., an ENI A-300 300 W RF amplifier from ENI of Rochester, N.Y.) can drive the HIFU source **102** to generate pulsed shock waves proximate to the focus **120**. Accordingly, the HIFU system **100** can implement a pulsing protocol in which ultrasound frequency, pulse repetition frequency, pulse length, duty cycle, pressure amplitude, and/or other factors associated with the HIFU treatment can be adjusted to generate shock waves proximate to the focus **120**.

During treatment the HIFU source **102** can be positioned proximate to tissue **108**, and the focus **120** of the HIFU source **102** can be aligned with at least a portion of a target site **122** within the tissue **108**. For example, the HIFU source **102** can be positioned over a patient's kidney, heart, or liver, and the focus **120** can be aligned with infected or otherwise adverse tissue therein. In still other embodiments, a variety of other types of tissue may be treated using the HIFU system **100**. Larger target sites **122** can be mechanically fractionated by scanning the HIFU source **102** over the treatment region using either mechanical or electronic scanning. Such scanning and the initial positioning of the HIFU source **102** can be performed manually or mechanically (e.g., using a three-axis positioning system, not shown). The function generator **104** can initiate the pulsing protocol to generate shock waves with amplitudes between approximately 10 MPa and approximately 80 MPa at the focus **120** with the HIFU source **102** having a frequency of approximately 2 MHz. In other embodiments, such as at lower or higher ultrasound frequencies, the shock wave amplitudes of the HIFU source **102** can be greater or smaller. Absorption of ultrasonic energy occurs primarily at the shock front and induces heating of the tissue **108** that can exceed boiling temperature in the tissue **108**.

During each HIFU pulse, one or more boiling bubbles can be formed in the tissue. In several embodiments, for example, the boiling bubbles can have cross-sectional dimensions of approximately 2-4 mm when the ultrasound frequency is approximately 2 MHz. In other embodiments, however, the boiling bubbles can be larger or smaller. For example, the boiling bubbles in the tissue can have a cross-sectional dimension between approximately 100 μm and approximately 4 mm on the order of the beam-width of the ultrasound source **102** at the focus **120**. The superheated vapor of the boiling bubbles provides a force pushing outward from the bubble. This repetitive explosive boiling activity and interaction of the ultrasound shock waves with the boiling bubbles emulsifies the tissue **108** at the target site **122** to form a liquid-filled lesion, at least partially devoid of cellular structure, with little to no thermal coagulation within the treated region. The reflection of the shock wave from the surface of these millimeter-sized boiling bubbles can also form cavitation bubbles proximate to the boiling bubble that can also induce mechanical damage to tissue.

Mechanical tissue destruction can occur consistently within localized treatment volumes when the temperature of the tissue reaches 100° C. and boiling bubbles form during each pulse or after a series of consecutive pulses. For example, boiling bubbles are generally produced proximate to the focus **120** of the HIFU source **102** (i.e., where shock wave amplitude is the highest). Alternatively, cavitation bubbles can be induced randomly over a larger region. In selected embodiments, for example, the energy deposition of the ultrasound beam can focus within 100 microns of the target site **122**. In other embodiments, however, this distance may vary.

In selected embodiments, the pulsing protocol of the HIFU system **100** can be adjusted to control the type of lesion formed in the tissue (e.g., a "liquid" lesion—a completely liquefied mechanical lesion; a "paste" lesion—a partially denatured mechanical lesion; a "thermal" lesion—a thermal lesion with no mechanical damage; or a "boiling" lesion—a thermally denatured lesion with mechanical damage). For example, repeating 10 ms duration shock waves at a pulse repetition frequency that is slow enough (e.g., approximately 2 MHz or 1% duty cycle) to allow cooling between the pulses such that lesion content within the target site **122** and the surrounding tissue **108** shows minimal to no evidence of thermal denaturation. A duty cycle of less than approximately 10% also allows cooling between pulses that minimizes thermal denaturation. In selected embodiments, the duration of the pulses can be reduced over the course of the pulsing protocol to account for a decreasing time to boil caused by the retention of heat in the tissue **108** between pulses. Additionally, the duration of each pulse can be such that the thermally denatured volume of the tissue **108** within each pulse is negligible. For example, in selected embodiments, the duration of each pulse is less than approximately 10 ms. In other embodiments, however, the pulse length can be longer.

In several embodiments, the target site **122** comprises a pressure-release interface within the tissue **108**. For example, the target site **122** can include tissue **108** adjacent to an inherent or induced gas or vapor cavity. The gas or vapor cavity can be natural, e.g., gas pockets in the lungs or intestine. Alternately, the bubbles can be created in the tissue **108** by other physical means, including laser ablation or vaporization droplets, e.g., liposomes injected in the vascular system by mild heating. The bubbles can also be introduced by HIFU in the form of cavitation or boiling bubbles in the soft tissue. For example, as discussed above, HIFU has been shown to extracoporeally emulsify regions of bulk tissue by shock wave heating and millisecond boiling, creating bubbles or cavitation bubble clouds. As will be discussed in further detail below with reference to FIGS. **2**A-**3**D, the bubbles or bubble clouds are large enough to act as a pressure-release interface, allowing acoustic atomization and fractioning the tissue into submicron-sized fragments.

The HIFU system **100** can also include systems or devices that detect and monitor tissue ablation initiation and the activity (e.g., heating or bubble activity) in the tissue **108**. In some embodiments, for example, these devices can be used during treatment to distinguish boiling bubbles from cavitation bubbles and ensure the pulsing protocol is set to parameters that will induce the desired lesion type. In the embodiment illustrated in FIG. **1**, for example, the HIFU source **102** is operably coupled to a voltage probe **110** and an oscilloscope **112** that can monitor and record, respectively, the drive voltage at the HIFU source **102**. In other embodiments, however, the HIFU source **102** may be coupled to additional detection and/or monitoring devices.

The HIFU system **100** can also include a passive cavitation detector ("PCD") **124** that monitors acoustic signals associated with tissue ablation. For example, the PCD **124**

can include an acoustic receiver (e.g., an ultrasound transducer) separate from the HIFU source **102**, but confocally aligned with the focus **120** of the HIFU source **102** such that the PCD **124** can receive real-time acoustic feedback during HIFU treatment. In general, boiling bubbles scatter frequencies that already exist in the incident wave, whereas cavitation bubbles create short pops when they collapse and have a broadband frequency noise. Boiling bubbles may also generate lower frequency noise (e.g., kilohertz frequencies) that can be recorded and used to monitor treatments. As shown in FIG. **1**, similar to the voltage probe **110**, the PCD **124** can also be coupled to the oscilloscope **112** to record acoustic signals during HIFU treatment.

Echogenic ablation activity and/or the thermal effects of the HIFU treatment can also be monitored using separate devices and systems. The HIFU system **100** illustrated in FIG. **1**, for example, includes an imaging system **114** that can create a visual image to monitor the boiling bubbles and thus temperatures of approximately 100° C. in real-time at a depth within the tissue **108**. The imaging system **114** can be a separate confocal transducer, an unfocused transducer, another type of confocal or unfocused ultrasound source, one or more sub-element(s) of a multi-element array, and/or a separate imaging system. For example, in one embodiment the imaging system **114** includes an HDI-1000 scanner with a CL 10-5 scanhead made by Philips Medical Systems of Bothell, Wash. In other embodiments, the imaging system **114** can include a magnetic resonance imaging ("MRI") system that can monitor temperature and boiling activity during HIFU treatments or other suitable devices.

In the embodiment shown in FIG. **1**, the HIFU system **100** also includes a high-speed camera **116** (e.g., video, still frame) to take video or still images of the target site **122** during HIFU treatment to capture the effects of the HIFU treatment on the tissue **108**. Such a camera **116** is generally used with initially transparent tissues or tissue phantoms to capture the thermal effects of HIFU treatment within the tissue **108**. Accordingly, the high-speed camera **116** can be especially suited for experiments and testing that include transparent gel phantoms to simulate tissue. The high-speed camera **116** is an optional component that may not be used in some embodiments.

The HIFU system **100** can also simulate the shock waves and heating in water or tissue. Resultant modeling can be used to calculate heating from the shock amplitude of the focal waveform, and for extrapolating pressure waveforms at the focus **120** in water to the equivalent waveforms in tissue. One such method for this extrapolation is called "derating," and is useful for regulatory oversight and HIFU treatment planning. For example, derating can be used to determine values of the acoustic field parameters in the tissue region exposed to HIFU (e.g., the target site **122** and the surrounding tissue **108**). During the derating process, low level ultrasound measurements can be taken at the focus **120** in water and scaled to the higher level outputs used during therapeutic HIFU treatments.

The HIFU system **100** can also include a testing apparatus **130** that can assess the extent of mechanical and/or thermal ablation and distinguish among lesion types. In some embodiments, for example, the testing apparatus **130** can send feedback to the function generator **104** or other components of the HIFU system **100** to cause the function generator **104** to select ultrasound parameters designed to achieve a particular type of mechanical or thermal ablation. For example, as will be discussed in further detail below with reference to FIGS. **4**A-**4**D, a user may desire to create a lesion that can be categorized as one of a liquid lesion, a paste lesion, a boiling lesion, or a thermal lesion. The testing apparatus **130** can determine the type of lesion created by the ultrasound source **102** and then automatically instruct the function generator **104** to alter or fine-tune HIFU parameters to better achieve the characteristics of the desired lesion. In further embodiments, the testing apparatus **130** may supply information to a user to allow the user to manually adjust HIFU settings as necessary to achieve the desired lesion type. As will be discussed in further detail below, the testing apparatus **130** can characterize or distinguish ablated tissue at the target site **122** according to at least one of a histological or biochemical trait.

Further details regarding HIFU system components and operating parameters can be found in U.S. patent application Ser. No. 13/085,368, filed Apr. 12, 2011 and entitled "Methods and Systems for Non-Invasive Treatment of Tissue Using High Intensity Focused Ultrasound Therapy," which is hereby incorporated by reference in its entirety.

FIGS. **2**A-**3**D illustrate various steps of atomizing tissue at pressure-release interfaces using a suitable HIFU system (e.g., the HIFU system **100** of FIG. **1**). The techniques for atomizing tissue described below, for example, are directed to particular applications of the HIFU system and associated methods described above. FIGS. **2**A-**2**C, for example, are sequential illustrations of planar waveforms modeled at a pressure-release interface **250** between tissue **252** and a gas or vapor cavity **262** in accordance with several embodiments of the present technology.

FIG. **2**A illustrates the pressure-release interface **250** after the initial application of planar shock waves P. FIG. **2**B illustrates the pressure-release interface **250** when capillary waves **254** have been parametrically excited on a surface **256** of the tissue **252**. In some embodiments, the capillary waves **254** are excited at half of the ultrasound frequency. FIG. **2**C illustrates the pressure-release interface **250** after cavitation and instability of sharp cusps of the capillary waves **254** have caused the emission of droplets or atomization **264** in the tissue **252**.

FIGS. **3**A-**3**C are sequential illustrations of focal waveforms modeled at a pressure-release interface **350** between tissue **352** and a gas or vapor cavity **362** in accordance with several embodiments of the present technology. FIG. **3**A, for example, illustrates the pressure-release interface **350** upon initial application of focused shock waves F. The radiation force from the shock waves F causes a surface **356** of the tissue **352** to become concave at a focal point **358** of the radiation. FIG. **3**B illustrates the pressure-release interface **350** after cavitation bubbles **360** have appeared under the surface **356** of the tissue **352**. FIG. **3**C illustrates the pressure-release interface **350** after cavitation and capillary waves have caused an acoustic fountain and atomization **366** of the tissue **352**. The gas or vapor cavity **362** provides the space for the tissue **352** to excite and atomize in this manner. FIG. **3**D is a set of photographs of focal ultrasound waves applied to a pressure-release interface in tissue in accordance with several embodiments of the present technology.

Referring to FIGS. **3**A-**3**D together, in some embodiments, the projectiles atomizing from the acoustic fountain **366** can include both fragmented and whole cells and nuclei. In some embodiments, the water content of the tissue **352** can contribute to the degree of tissue erosion. For example, the water content of the tissue **352** can decrease the tissue stiffness and/or the tissue cavitation threshold, thereby increasing the ease of emulsification. Further, water may contribute to tissue emulsification by forming a slurry that is recirculated within the boiling bubble or cavitation bubble cloud. Accordingly, a portion of the tissue **352** can be wetted

(e.g., misted with water or a saline solution) prior, during, or after a HIFU treatment. Many types of tissue can exhibit this acoustic fountain effect, including, for example, kidneys, esophageal tissue, skeletal muscle, blood clots, spleen tissue, and/or other suitable tissue.

FIGS. **4**A-**4**D are photos of various types of lesions formed in tissue using HIFU in accordance with embodiments of the present technology. The photos are arranged in order of decreasing liquid and increasing thermal components. For example, FIG. **4**A illustrates a "liquid" lesion **410**, FIG. **4**B illustrates a "paste" lesion **420**, FIG. **4**C illustrates a "boiling" lesion **430**, and FIG. **4**D illustrates a "thermal" lesion **440**. FIGS. **4**A, **4**B, and **4**D include dashed lines to more clearly delineate the ablated and unscathed tissue. For purposes of this disclosure, a liquid lesion **410** is one in which the tissue is nearly or completely emulsified. The lesion **410** includes only mechanical ablation, and no thermal effects. As shown in FIG. **4**A, the lesion **410** includes active enzymes in the ablated region. For purposes of this disclosure, a paste lesion **420** can be considered slightly more viscous than a liquid lesion **410**, with some non-active enzymes remaining in the lesion **420**. For purposes of this disclosure, a boiling lesion **430** includes some pieces of non-emulsified tissue, while a thermal lesion **440** has been at least partially ablated by heat, with a blurrier boundary line between treated and untreated tissue.

A testing method or apparatus, such as testing apparatus **130** described above with reference to FIG. **1**, can be used to distinguish among the various types of lesions. In some embodiments, for example, a lesion can be analyzed for microscopic anatomical/structural changes or changes in the quantity or type of cells, molecules, or cellular components. In further embodiments, the testing apparatus can perform biochemical analyses of samples at or around a target site. In some embodiments, a frozen embed of the treatment site can be sectioned and stained to determine cellular structure or contents. In particular embodiments, Haeomatoxylin and Eosin stain and/or nicotinamide adenine dinucleotide diaphorase stain are used to better view changes to the general tissue structure and effects of thermal treatment, respectively. In other embodiments, however, other suitable techniques may be used to test/analyze the treated tissue.

In still further embodiments, the extent of thermal ablation in a lesion can be determined by analyzing the quantity of protein in a lesion sample, as heated proteins denature and become less soluble in water. The contents of the lesion can be removed and a serial salt extraction applied. A Bradford assay or other suitable test can quantify proteins in the sample. In some embodiments, for example, the lesion is characterized as liquid if there is no denatured protein relative to a control sample; as paste if there is approximately 20%-40% denatured protein relative to the control; as boiling if there is approximately 80-85% denatured protein relative to the control; and as thermal if there is approximately 85% or more denatured protein relative to the control. Liquid lesions are purely mechanical lesions, and therefore have not suffered from thermally-induced protein denaturation. In further embodiments, a spectrophotometric determination can distinguish among lesion types.

As discussed above, a HIFU system can be configured to implement pulsing parameters that correspond to a particular, desired type of lesion. The feedback based on the lesion characterization can be used to modify ultrasound parameters. Referring to general histological trends, an increased pulse length, duty cycle, or thermal component will create a more thermal, less liquid lesion (and vice versa) while increasing structural disruption of the tissue will create a more liquid, less thermal lesion. In further embodiments, other desired bioeffects can be induced based on the results of the lesion characterization.

FIG. **5** is a block diagram illustrating a method **500** of treating tissue at a target site in accordance with an embodiment of the present technology. The method **500** can include providing a pulsing protocol (block **502**). As discussed above, a pulsing protocol can take into account the ultrasound frequency at a HIFU source, peak positive pressure at the focus, shock amplitude, pulse length, pulse repetition frequency, and duty cycle. In other embodiments, additional factors related to tissue boiling and shock wave heating can be included in the pulsing protocol. In selected embodiments, a derating process can be used to estimate values of acoustic field parameters of the exposed tissue, and therefrom calculate the requisite peak positive pressures and pulse lengths for shock wave heating and millisecond boiling. The pulsing protocol can also be configured to minimize thermal effects of the HIFU treatment on the tissue. For example, as described above, the duty cycle can be less than 10% to ensure sufficient cooling occurs between shock wave pulses and prevent thermal denature. As another example, the pulse length can be less than approximately 100 ms such that any thermally denatured volume formed within each pulse is negligible. In a particular embodiment, atomization can occur in liver tissue at 60 MPa with individual pulses having a pulse duration of at least 20 μs. When the amplitude is reduced to 15 MPa, atomization can occur when the pulse duration is increased to 10 ms. The pressure threshold can be even lower and reach diagnostic ultrasound levels for a larger number of consecutive pulses or for tissues with less structure. In a particular embodiment, blood clots can atomize at 4 MPa in less than 70 μs and heparinize blood at 2 MPa in less than 70 μs. In several embodiments, the time required to achieve atomization is related to the shock wave amplitude, wherein quicker atomization can correspond to higher amplitudes, and vice versa. The pulsing protocol can be set to take this and other treatment variable relationships into account. Various other pulsing protocols can be established to induce a desired type of lesion as described above.

Once the pulsing protocol is established, the method **500** can continue by positioning a focus of a HIFU source proximate to a target site at a pressure-release interface within tissue (block **504**). The pressure-release interface can be similar to the pressure-release interfaces described above with reference to FIGS. **1**-**3**C. For example, the pressure-release interface can include an inherent or induced gas or vapor cavity within tissue. The pressure-release interface can be induced by any of the techniques described above, such as laser ablation, vaporization droplets, injected liposomes, cavitation clouds, etc.

The method **500** can further include delivering at lease one pulse of ultrasound energy from the HIFU source to the tissue (block **506**) and generating shock waves in the tissue to induce a lesion at the target site (block **508**). In some embodiments, each pulse of shock waves at the target site can generate boiling bubbles within milliseconds. This rapid millisecond boiling can mechanically disrupt the tissue without evident thermal damage. Additionally, as described above, the HIFU source can deliver shock waves to its focus to consistently induce boiling within a localized treatment area or can be planar to induce boiling over a larger area of tissue. Therefore, the millisecond boiling provided by this HIFU method **200** provides a repeatable, directable, and predictable mechanical destruction of tissue to produce a desired type of lesion. Alternatively, thermal treatment can be applied. Optionally, the target site can be monitored

during HIFU treatment to ensure boiling and/or otherwise observe the effects of the HIFU treatment (block **210**).

The method **500** can also include characterizing the lesion based on a type or degree of mechanical or thermal ablation at the target site (block **512**). As described above, histological and/or biochemical testing or observation can be performed to distinguish or categorize among lesion types. Based on the characterization, feedback can be sent to alter or fine-tune the pulsing protocol to achieve a desired type of lesion.

From the foregoing, it will be appreciated that specific embodiments of the technology have been described herein for purposes of illustration, but that various modifications may be made without deviating from the disclosure. For example, the HIFU system **100** of FIG. **1** can include additional devices and/or systems to facilitate shock wave heating of the tissue **108**. For example, the HIFU system **100** can include a timing board to trigger the function generator **104**, additional amplifiers **106**, high-pass or other suitable filters, a computer to drive the entire HIFU system **100**, and/or other suitable devices related to HIFU treatments. Additional assays, stains, or alternate testing devices or methods can be used to characterize lesions. Certain aspects of the new technology described in the context of particular embodiments may be combined or eliminated in other embodiments. For example, the HIFU system **100** does not need to include some of the devices shown in FIG. **1**. In selected embodiments, the HIFU system can include only one of or a combination of the voltage probe **110**, the PCD **124**, the imaging system **114**, and/or the high-speed camera **116** to monitor the thermal and mechanical effects of the HIFU treatment. Additionally, while advantages associated with certain embodiments of the new technology have been described in the context of those embodiments, other embodiments may also exhibit such advantages, and not all embodiments need necessarily exhibit such advantages to fall within the scope of the technology. Accordingly, the disclosure and associated technology can encompass other embodiments not expressly shown or described herein. Thus, the disclosure is not limited except as by the appended claims.

We claim:

1. A method of non-invasively treating tissue, the method comprising:

pulsing ultrasound energy from an ultrasound source to a target site in tissue, wherein the ultrasound source is configured to emit high intensity focused ultrasound (HIFU) waves, and wherein the target site comprises a pressure-release interface located between tissue and a gas or vapor cavity;

generating shock waves in the tissue to induce a lesion in the tissue at the target site;

atomizing the tissue at the pressure-release interface to create an acoustic fountain; and

characterizing the lesion based, at least in part, on a degree of at least one of a mechanical or thermal ablation of the tissue at the target site.

2. The method of claim **1** wherein characterizing the lesion based on a degree of at least one of a mechanical or thermal ablation of the tissue comprises characterizing the lesion based on a change of at least one of a cellular structure, molecular structure, protein structure, protein quantity, protein solubility, or cellular quantity at the target site.

3. The method of claim **1** wherein characterizing the lesion based on a degree of at least one of a mechanical or thermal ablation of the lesion comprises using at least one of a Haematoxylin and Eosin stain or a nicotinamide adenine dinucleotide diaphorase stain to characterize the lesion.

4. The method of claim **1** wherein characterizing the lesion based on a degree of at least one of a mechanical or thermal ablation of the tissue comprises using at least one of a serial salt extraction, protein-quantifying assay, or spectrophotometric determination to characterize the lesion.

5. The method of claim **1** wherein characterizing the lesion based on a degree of at least one of a mechanical or thermal ablation of the tissue comprises characterizing the lesion as a liquid lesion, a paste lesion, a boiling lesion, or a thermal lesion.

6. The method of claim **1** wherein the target site comprises a naturally-occurring gas or vapor cavity located within the tissue.

7. The method of claim **1**, further comprising wetting the pressure-release interface of the gas or vapor cavity located within the tissue.

8. The method of claim **1** wherein generating shock waves in the tissue comprises generating planar waves in the tissue.

9. The method of claim **1** wherein generating shock waves in the tissue to induce a lesion in the tissue at the target site comprises generating a focused beam of waves in the tissue to create the acoustic fountain and atomize the tissue at the target site.

10. The method of claim **1** wherein:

pulsing ultrasound energy comprises pulsing ultrasound energy to the pressure-release interface at a pulse length comprising multiple cycles of the ultrasound wave; and

generating shock waves in the tissue comprises generating shock waves having amplitudes between 10 MPa and 80 MPa.

11. The method of claim **1**, further comprising selecting a setting of the ultrasound source corresponding to a desired mechanical or thermal phase of the lesion.

12. The method of claim **1**, further comprising establishing a pulsing protocol taking into account factors comprising ultrasound frequency of the ultrasound source, pulse length, pulse repetition frequency, and duty cycle.

13. The method of claim **1** wherein generating shock waves in the tissue comprises generating shock waves such that a surface of the tissue becomes concave.

14. The method of claim **1**, further comprising creating the pressure-release interface of the gas or vapor cavity located within the tissue by introducing or inducing a gas or vapor at the target site.

15. The method of claim **14** wherein inducing a gas or vapor at the target site comprises inducing cavitation bubbles or boiling bubbles in the tissue with HIFU.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,498,651 B2
APPLICATION NO. : 13/444466
DATED : November 22, 2016
INVENTOR(S) : Oleg A. Sapozhnikov et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

In Column 4, Line 44, delete “extracoporeally” and insert -- extracorporeally --, therefor.

In Column 7, Line 37, delete “Haeomatoxylin” and insert -- Haematoxylin --, therefor.

In Column 8, Line 52, delete “lease” and insert -- least --, therefor.

Signed and Sealed this
Seventeenth Day of October, 2017

Joseph Matal

Joseph Matal
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

专利名称(译)	使用气体或蒸汽腔内的超声雾化机制及相关系统和装置进行软组织乳化的方法		
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申请号	US13/444466	申请日	2012-04-11
[标]申请(专利权)人(译)	华盛顿大学		
申请(专利权)人(译)	华盛顿大学		
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摘要(译)

本技术涉及使用气体或蒸汽腔内的超声雾化机制的软组织乳化方法，以及相关的系统和装置。在若干实施例中，例如，非侵入性地处理组织的方法包括将来自超声源的超声能量朝向组织中的目标部位脉冲。超声源被配置为发射高强度聚焦超声（HIFU）波。目标部位包括位于组织内的气体或蒸汽腔的压力释放界面。该方法通过在组织中产生冲击波以在目标部位处诱导组织中的病变而继续。该方法另外包括基于组织的机械消融或热消融中的至少一个的程度来表征病变。