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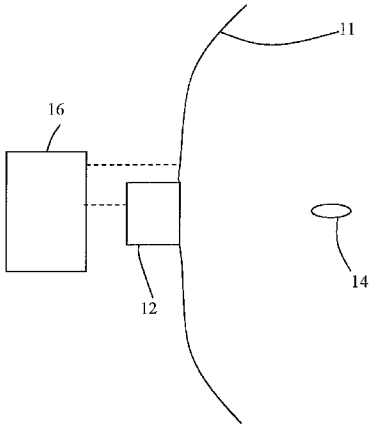

Fig. 1

(57) Abstract: An ultrasound system comprises a transducer, a controller arranged to generate control signals arranged to control the transducer to generate pressure waves directed at a target volume, and sensing means arranged to sense cavitation in the target volume. The controller is arranged to receive sensing signals from the sensing means and to vary the control signals in response to the sensing signals thereby to control the cavitation.

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Ultrasound Systems

Field of the Invention

The present invention relates to ultrasound systems and in particular to therapeutic ultrasound systems arranged to generate cavitation in tissue during therapy.

Background to the Invention

Having been traditionally perceived as a diagnostic modality, ultrasound is rapidly emerging as a most promising therapeutic tool for non-invasive ablation of cancerous and other tissues, for enhanced drug delivery, and for a range of other therapeutic applications that include thrombolysis, opening of the blood-brain barrier, tendon and bone repair, tissue erosion, vaccine delivery and acoustic haemostasis. In all of these applications, ultrasound-induced bubble activity (acoustic cavitation) has been found to play a major role in enhancing several desirable bioeffects (heating, cell permeability, drug diffusion lengthscales, etc). The term 'cavitation' is used hereafter to encompass all possible bubble behaviours in an ultrasound field, including transient or inertial cavitation; stable cavitation including shape oscillations of the bubble wall; and the response of thermally stabilized bubbles (such as boiling bubbles) in an ultrasound field. The process of cavitation itself could have been initiated through spontaneous, acoustically driven nucleation, or through the injection of stabilized gas bodies such as ultrasound contrast agents, or of solid microparticles that are designed with appropriate surface characteristics (hydrophobicity and surface roughness) to facilitate cavitation inception.

Cavitation is an inherently unstable phenomenon and, once initiated in the body (which is by itself quite unpredictable), tends to decay rapidly whilst the associated bubble cloud readily shifts positions. Being unable to sustain cavitation activity at the desired location for prolonged periods of time means that the potential benefits of cavitation cannot be fully exploited.

Summary of the Invention

The present invention provides an ultrasound system comprising a transducer, a controller arranged to generate control signals arranged to control the transducer to generate pressure waves directed at a target volume, and sensing means arranged to sense cavitation in the target volume. The controller may be arranged to receive sensing signals from the sensing means and may be arranged to vary the control signals, for example in response to the sensing signals, thereby to control the cavitation.

The pressure waves may be ultrasound waves or audible sound waves.

The controller may be arranged to measure from the sensing signals the position of the cavitation, for example by measuring the position of an edge of a cavitation bubble cloud, or by imaging the cavitation bubble cloud to determine its position in two or three dimensions.

The controller may be arranged to measure from the sensing signals variations in either or both of the type and the level of cavitation activity. The controller may be arranged to control the level of cavitation activity so as to maintain at least a predetermined level of cavitation, so as to maintain the level of cavitation at or below a predetermined level, which may be zero, or so as to maintain the level of cavitation within a range between a predetermined minimum and a predetermined maximum level.

The controller may be arranged to define one or more parameters of the sensing signals, which may be a magnitude, a time-average, a mean, a peak value, a variance, or any similar metric of a sensing signal that has been post-processed in the time-domain or frequency-domain, and a target range of the one or more parameters, and to change the control signals in response to the one or more parameters being outside the respective target ranges. The target range

may have an upper limit and a lower limit or it may have just an upper limit, or just a lower limit.

The sensing means may comprise at least one pressure wave detector arranged to detect pressure waves generated by the cavitation. The pressure waves may be ultrasound or audible sound waves. The controller may be arranged to measure an arrival time of pressure waves at the pressure wave detector thereby to measure the position of the cavitation.

The present invention further provides a method of controlling cavitation in a subject comprising generating pressure waves directed at a target volume, sensing changes in the cavitation in the target volume, and controlling the pressure waves in response to the changes thereby to control the cavitation. The pressure waves may be controlled by a controller, but may also, or alternatively, be controlled manually.

The present invention further provides a method of setting up a pressure wave control system comprising producing a control signal to control a pressure wave transmitter so as to produce cavitation in a subject, sensing the cavitation using sensing means arranged to output a sensing signal indicative of one or more parameters of the cavitation, varying the control signal so as to vary the cavitation, defining one or more sensing parameters of the sensing signal, measuring one or more controlled parameters of the cavitation which are to be controlled by the system, determining how the one or more sensing parameters vary with variations in the one or more measured parameters, and selecting a target value of the one or more measured parameters corresponding to a target value of the one or more sensing parameters.

For example the sensing parameter may be indicative of the level of cavitation activity. The sensing parameter may be the magnitude of the sensing signal, or a variance of the sensing signal, or the timing of the sensing signal. The sensing

means may comprise a passive cavitation detector, such as a pressure sensor. The controlled parameter may comprise, for example, a temperature, or a position of the cavitation, or a cell permeability, or drug diffusion lengthscale.

Some embodiments of the present invention provide a procedure to identify the set-point or range of set-points for quantifiable cavitation activity, in order to achieve optimal energy transfer to the surrounding medium (in terms of heat, momentum transfer, tissue erosion, bubble cloud position, or whichever other quantifiable cavitation-induced effect).

Some embodiments of the invention provide an adaptive cavitation controller which varies the input signal (for example by varying one or more of the frequency, amplitude, duty cycle, pulse duration, etc.) to a single or multiple pressure wave transducers in order to maintain the level of cavitation activity as continuously detected by a single or multiple cavitation detectors within the desired range for prolonged periods of time.

The controller can be implemented for continuous or pulsed pressure wave exposure and with the intention of maintaining stable or inertial cavitation activity for a very broad range of therapeutic bioeffects, such as heating for ablation or hyperthermia, momentum transfer for drug delivery to tumours, tissue erosion by cavitation, lipolysis, thrombolysis, opening of the blood-brain barrier, acoustic haemostasis, and any other emerging application where cavitation activity is found to play a key role.

The ability to detect and quantify cavitation activity in a reproducible manner and to monitor it continuously and in real-time, in some cases whilst identifying the position of the bubble cloud using those same measurements from a passive cavitation detector, makes it possible to use this data in order to control cavitation in a closed feedback loop. In some cases, by continuously altering one or more of the amplitude, duty cycle, pulse duration and frequency of the input signal to the

source pressure wave transducer, cavitation activity can be sustained over a broad range of experimental conditions.

Preferred embodiments of the present invention will now be described by way of example only with reference to the accompanying drawings.

Brief Description of the Drawings

Figure 1 is a diagram of a therapeutic ultrasound system according to an embodiment of the invention;

Figure 2 is a graph showing the decay in cavitation detector signal variance during a pulsed ultrasound insonation in the system of Figure 1;

Figure 3 is a graph showing detector signal as a function of time during a pulsed ultrasound insonation in the system of Figure 1;

Figure 4 is a plot showing position of cavitation relative the transducer in the system of Figure 1 during each of three pulsed ultrasound insonation periods;

Figure 5 is a graph showing variation of cavitation-induced temperature with cavitation detector signal variance in the system of Figure 1;

Figure 6 is a graph showing variation of position of cavitation with cavitation detector signal variance in the system of Figure 1;

Figure 7 is a high level system diagram showing operation of the system of Figure 1;

Figure 8 is a functional flowchart showing operation of the system of Figure 1;

Figure 9 is a graph of detector signal variance over time for different frequencies during operation of the system of Figure 1 with cavitation control;

Figure 10 is a graph of peak focal pressure over time during operation of the system of Figure 1 with cavitation control;

Figure 11 is a graph of temperature over time during operation of the system of Figure 1 with cavitation control;

Figure 12 is a graph of cavitation cloud position over time during operation of the system of Figure 1 with cavitation control;

Figure 13 is a graph of detector signal variance over time for different ultrasound frequencies during operation of the system of Figure 1 without cavitation control with a first input energy;

Figure 14 is a graph of temperature over time during operation of the system of Figure 1 without cavitation control with the first input energy;

Figure 15 is a graph of cavitation cloud position over time during operation of the system of Figure 1 without cavitation control with the first input energy;

Figure 16 is a graph of detector signal variance over time for different ultrasound frequencies during operation of the system of Figure 1 without cavitation control with a second input energy;

Figure 17 is a graph of temperature over time during operation of the system of Figure 1 without cavitation control with the second input energy;

Figure 18 is a graph of cavitation cloud position over time during operation of the system of Figure 1 without cavitation control with the second input energy.

Referring to Figure 1, a high intensity focused ultrasound system according to an embodiment of the invention comprises a high intensity focused ultrasound (HIFU) transducer 11 with a coaxial passive cavitation detector (PCD) 12 mounted at its centre. The ultrasound transducer 11 has a focal point 14 at which the ultrasound it produces is at the highest intensity and tissue to be treated is therefore located in a volume at and around that focal point 14. The PCD 12 comprises an ultrasound detector which is a pressure sensor arranged to output a signal having a voltage that varies with the pressure it detects. The pressure varies at the frequency of the ultrasound detected, and the sensor may include a high pass filter so as to avoid saturation by signals at the frequency of the ultrasound transducer 11, which can be around 1MHz, being most sensitive to signals with a frequency range significantly higher than the frequency of the ultrasound transducer 11, for example around 5 to 15MHz, which makes it sensitive to the acoustic emissions associated with inertial cavitation.

A controller 16 is arranged to drive the ultrasound transducer 11 using a drive signal. This drive signal is generated by an oscillator and has a frequency which determines the frequency of the ultrasound generated, and an amplitude which determines the intensity of the ultrasound generated. It is also pulse width modulated, and the controller is arranged to vary the pulse width and duty ratio (and hence frequency) of the drive pulses that generate pulses of ultrasound from the transducer 11.

Referring to Figure 2, in the system such as that of Figure 1, if a sample of tissue is targeted with a pulsed ultrasound signal, in this case with around 100μs between pulses, the inertial cavitation starts quite abruptly, but then decays over time during the ultrasound exposure, in this case over about 2s, in the absence of any kind of active cavitation control. Figure 2 shows the variance of the detector signal σ^2 as a function of time. It can be seen from this that the signal variance gives a clear indication of the level of cavitation and how it changes over time.

Referring to Figure 3, at the start of an ultrasound pulse, the distance of the closest part of the cavitation cloud to the detector 12 can be determined by measuring the time between the start of transmission of the ultrasound pulse by the HIFU transducer 11 and the time at which the detector signal first increases above the background noise level. Figure 3 shows an example of a raw output voltage trace from the PCD 12. The broken horizontal lines show the threshold voltage that is used to define the level of background noise, and the signal first exceeds this level at a time of about $0.9x10^{-4}$ seconds. Thereafter the signal continues to vary significantly outside this threshold voltage. The time at which the signal first exceeds the threshold level can be used to determine the distance from the detector to the front of the cavitation bubble cloud, i.e. the closest part of the cavitation cloud to the HIFU transducer 11. This measurement can be repeated for each ultrasound pulse, so that the position of the cavitation cloud can be monitored over time.

Referring to Figure 4, the position of the front of the cavitation cloud varies over time during any exposure to ultrasound. In Figure 4, the three traces show the distance between the ultrasound transducer 11 and the front of the cavitation cloud over the cavitation period of about 2s in each of three separate exposures of pulsed ultrasound. As can be seen, the distance varies considerably between exposures, and also varies significantly over the course of each exposure.

In order to control treatment using the system of Figure 1, it is necessary to know how the cavitation itself and its effects, which are the parameters to be controlled, vary with the parameters which can be directly measured. In this case, the variance of the detector signal is measured, and is generally indicative of the level of cavitation. Variations in the level of cavitation result in variation in the induced temperature rise and the position of the cavitation cloud. In order to measure the relationship between detector signal variance and temperature rise, a test sample (such as a phantom or excised tissue) is placed at the focal

point 14, and pulsed ultrasound used to insonate the sample over a test period. During the insonation, the temperature of the sample is measured using a thermometer, while the detector signal variance σ^2 is also measured. The results of this process are shown in Figure 5, which shows that the cavitation induced temperature rise increases significantly with signal variance for low levels of variance (and hence cavitation), but then reaches a plateau. During this test process, the distance of the cavitation cloud from the ultrasound transducer 11 can also be measured as a function of signal variance, and the results from several such exposures are shown in Figure 6. It can be seen that the cavitation cloud tends to get closer to the transducer 11 as the variance increases, which is consistent with the cloud increasing in size as the level of cavitation increases. From these two graphs a target signal variance, shown by the vertical broken line, can be chosen, which provides sufficient temperature rise without the cavitation cloud getting too large, and therefore affecting too great a volume of tissue. This target signal variance can then be used to define a setpoint value, or range, of the variance for use in control of the system as will be described below.

Referring to Figure 7, the controller 14 is arranged to operate on a closed loop control basis. The controller 14 is arranged to provide control signals to the ultrasound transducer 11, so as to control the amplitude and other parameters of the ultrasound generated. The detector 12 is arranged to sense any cavitation produced, and send sensor signals back to the controller 14. The controller is also arranged to receive a reference demand, which may correspond to a value or range of values of a parameter of the sensor signals, to compare the sensor signals, or the appropriate parameter of the sensor signals defined by the reference demand, with the reference demand and to calculate an error, and then to adjust the control signals if the error meets conditions stored in the controller. In other embodiments this basic feedback system can take many forms depending on the nature of the detector 12, which can be different from the PCD 12 as described above, on the parameter of the cavitation that is to be controlled, and

on the relationship between that parameter and the parameter of the cavitation that can be directly measured, or the parameter of the sensor signals.

Referring to Figure 8, in this particular embodiment, the controller is arranged to receive the voltage signal V from the PCD 12, and includes a data acquisition card (DAQ) 13 which feeds digitized data to a software routine running on a computer, enabling calculation of the variance σ^2 of that voltage signal. The controller has stored in it a setpoint range of variance values, defined as maximum and minimum values of the variance σ^2. This setpoint range is based around the target variance value shown in Figures 5 and 6. This setpoint range forms a reference demand, and can be input and updated depending on the nature of the cavitation that is required. The controller is arranged to calculate the log of the measured detector signal variance and the log of the max and min setpoint variances, and to compare the log of the measured variance with the logs of the max and min values, and to control the amplitude of the drive signal to the transducer depending on the result. The part of the controller 14 that generates the drive signals for the HIFU transducer 11 is referred to as the function generator 18, and this controls the amplitude, as well as any other appropriate parameters, of the ultrasound generated by the HIFU transducer 11. If the measured variance σ^2 is within the desired range between the max and min values, then the function generator 18 that generates the control signal is arranged to keep the amplitude of the drive signal constant. If the measured variance is greater than the maximum variance, then a comparator 15 calculates an error e_1, which is the amount by which it is too high. The controller then calculates a reduced amplitude, reducing the current amplitude by a correction value, calculated as the product of the error e_1 and a first gain factor k_1, which is input to the function generator. If the measured variance is less than the minimum variance, then a separate comparator 17 calculates an error e_2, which is the amount by which it is too low. The controller then calculates an increased amplitude, increasing the current amplitude by a correction value, calculated as the product of the error e_2 and a second gain factor k_2, which is input to the

function generator. The function generator 18 therefore alters the amplitude of the control signal to the transducer 11 so as to keep the PCD detector signal variance, and hence the level of cavitation, within the desired range of values.

Referring to Figures 9 to 12 it can be seen that the control system described above can maintain cavitation for an extended test period of, in this case, over 20s. In Figure 9 the upper line is a plot of PCD signal variance over time for a broadband ultrasound frequency range indicative of inertial cavitation in the system of Figure 8. The lower line is a plot of variance for frequencies corresponding to harmonic emissions indicative of stable cavitation. It can be seen that, while it varies significantly, some level of cavitation is maintained throughout the 20s period. It can also be seen that the variances for the broadband and harmonic frequencies vary in different ways over time. Because they generate ultrasound of different frequency content, the different types of cavitation activity can be detected and controlled separately. Figure 10 shows the peak focal pressure, i.e. the amplitude of the ultrasound output of the ultrasound transducer, as controlled by the controller 14. As can be seen, this pressure, and hence the output power of the transducer, increases steadily to maintain the cavitation. The peaks in the focal pressure are a result of the gain values used in the feedback control. Figure 11 shows the resulting temperature of the sample through the 20s period. As can be seen this rises up to a target temperature, shown by the broken line, and then fluctuates around that level throughout the 20s period. This shows good control of the tissue temperature which can be used to provide controlled treatment. Figure 12 shows how the distance between the front edge of the cavitation cloud and the transducer 11 varies during the test period. In this case the distance decreases steadily throughout the test period, but remains within acceptable limits.

For comparison, Figures 13 to 15 show the detector signal variances, the temperature increase, and the distance from cavitation cloud to ultrasound transducer for a pulsed ultrasound signal with a fixed peak focal pressure of

7.3MPa, and Figures 16 to 18 are similar plots for a fixed 10.5MPa peak focal pressure. As can be seen, in each case, the temperature rise starts significantly higher than desired, and is not maintained, falling below the desired level quite quickly.

The controller of Figure 8 can be modified in various ways to provide further or alternative types of control. For example, the position of the cavitation cloud, as measured by its distance from the ultrasound transducer, can be used as a control input. The response of the controller to that data can be very simple. For example a threshold distance can be defined and, if the distance becomes less than that threshold, the transducer 11 can be switched off and the ultrasound transmission ended, on the assumption that heat is being applied to a region of tissue where it is not desirable. Alternatively a set point range of acceptable values for that distance can be defined, and the control signal amplitude varied so as to maintain the distance within the setpoint range. The system can be arranged to control just bubble cloud position, and not the degree of cavitation. Alternatively it can be arranged to control both cloud position and the degree of cavitation, in which case both of these can be measured, as described above, and the ultrasound amplitude controlled so as to obtain the best compromise, or combination, of cloud position and degree of cavitation. In some embodiments, or under some circumstances, it may be desirable to avoid cavitation altogether. In that case the target value of the PCD signal variance can be set to zero, or a target range of PCD signal variance set with a low upper limit. The system is then arranged to modify or stop the ultrasound transmission when cavitation is detected so as to bring the PCD signal variance back to the target value or range.

In a further modification the controller is arranged to measure the detector signal variance for both the broadband range and a range of harmonics of the transducer frequency. It can then monitor variations in the relative magnitudes of those variances which can be used as an indication of changes in the type of cavitation activity. The driving signal for the ultrasound transducer can be

controlled in response to these changes to control the type of cavitation activity being produced.

While the examples described above rely on varying the amplitude of the driving signal to the ultrasound transducer, and hence the amplitude of the ultrasound waves generated in the subject, other parameters of the driving signal and hence of the ultrasound generated can also be varied by the feedback control. For example the frequency of the ultrasound can be varied, or where the ultrasound is pulsed, the pulse duration, duty cycle, or pulse repetition frequency can be varied. Rather than having a single ultrasound transducer, two or more transducers can be included in the system. This gives greater control over the position of the cavitation being produced, as the relative amplitudes of the transducers can be controlled to control the focus or centre of the cavitation.

Similarly other types of sensor can be used to measure, directly or indirectly, parameters of the cavitation produced, or the resultant heating generated, and these parameters can be used as at least a part of the feedback signals for the feedback control. For example, rather than a single detector, an array of ultrasound detectors, i.e. pressure sensors, can be used. The signals from these sensors, filtered so as to be sensitive to cavitation, can be used to locate the cavitation in two or three dimensions, rather than simply in one dimension as described above. Such a sensing system can be used together with multiple ultrasound transducers to provide control of cavitation position in two or three dimensions.

In each case where the control is based on feedback using an error between a measured parameter and a setpoint value or range for that parameter, the setpoint can be determined by varying the drive signals to the ultrasound transducer or transducers so as to produce a variation in the cavitation and hence a variation in the measured parameter, and also measuring a further parameter, such as tissue temperature or other therapeutically desirable bioeffect such as cell permeability,

drug diffusion lengthscale, etc, and identifying the setpoint value or range of the measured parameter that corresponds to a desired value of the further parameter. This can be done in a similar way to that described above with reference to Figures 5 and 6. Once the setpoint range has been determined, suitable gain factors can be determined for the feedback control. The setpoint values and the gain factors are then stored in memory in the controller so that it can be used for cavitation control.

Embodiments of the invention provide both a procedure and the implementation of an adaptive feedback controller that utilizes the signal received from one or several passive cavitation detectors (PCD) to affect the input signal to the therapeutic ultrasound transducer(s) in order to both maintain and localize cavitation activity for prolonged periods of time. The controller has thus far been implemented in the context of maximizing cavitation-enhanced heating, but the procedures are directly extendable to optimizing other therapeutically desirable bioeffects and could also extend to applications outside the biomedical arena, for example in ultrasound cleaning baths, cavitation control in nuclear reactors, etc.

Claims

1. An ultrasound system comprising a transducer, a controller arranged to generate control signals arranged to control the transducer to generate pressure waves directed at a target volume, and sensing means arranged to sense cavitation in the target volume, wherein the controller is arranged to receive sensing signals from the sensing means and to vary the control signals in response to the sensing signals thereby to control the cavitation.

2. A system according to claim 1 wherein the controller is arranged to measure from the sensing signals the position of the cavitation.

3. A system according to claim 1 or claim 2 wherein the controller is arranged to measure from the sensing signals variations in the amount of the cavitation.

4. A system according to any of claims 1 to 3 wherein the controller is arranged to measure from the sensing signals variations in the type of the cavitation.

5. A system according to any foregoing claim wherein the controller is arranged to define a parameter of the sensing signals, and a target range of the parameter, and to change the control signals in response to the parameter being outside the target range.

6. A system according to any foregoing claim wherein the sensing means comprises at least one pressure wave detector arranged to detect pressure waves generated by the cavitation.

7. A system according to claim 6 wherein the controller is arranged to measure an arrival time of pressure waves at the pressure wave detector thereby to measure the position of the cavitation.

8. A system according to claim 6 wherein the controller is arranged to measure the frequency content within one or more frequency bands of the pressure waves generated by cavitation and detected by the pressure wave detector.

9. A system according to any of claims 6 to 8 wherein the controller is arranged to calculate the variance of the sensing signals and vary the control signals in a manner dependent on the variance.

10. A method of controlling cavitation in a subject comprising generating ultrasound directed at a target volume, sensing changes in the cavitation in the target volume, and controlling the ultrasound in response to the changes thereby to control the cavitation.

11. A method according to claim 10 wherein the step of sensing comprises sensing the position of the cavitation.

12. A method according to claim 10 or claim 11 wherein the step of sensing comprises sensing variations in the amount of the cavitation.

13 A method according to any of claims 10 to 12 wherein the step of sensing comprises sensing the type of the cavitation.

14. A method according to any of claims 10 to 12 including defining a parameter of sensing signal generated by the sensing means, and a target range of the parameter, and varying the pressure waves in response to the parameter being outside the target range.

15. A method according to any of claims 10 to 14 including measuring an arrival time of pressure wave at a pressure wave detector thereby to measure the position of the cavitation.

16. A method of setting up a pressure wave control system comprising producing a control signal to control an pressure wave transmitter so as to produce cavitation in a subject, sensing the cavitation using sensing means arranged to output a sensing signal indicative of a parameter of the cavitation, varying the control signal so as to vary the cavitation, defining a sensing parameter of the sensing signal, measuring a controlled parameter of the cavitation which is to be controlled by the system, determining how the sensing parameter varies with variations in the controlled parameter, and selecting a target value of the sensing parameter corresponding to a target value of the controlled parameter.

17. A method according to claim 16 wherein the sensing means comprises a pressure sensor arranged to detect pressure waves generated by the cavitation.

18. A method according to claim 17 wherein the controlled parameter comprises a temperature, or a position of the cavitation, or an amount of mass transport or a measure of thermal damage or a measure of mechanical damage due to cavitation.

Fig. 1

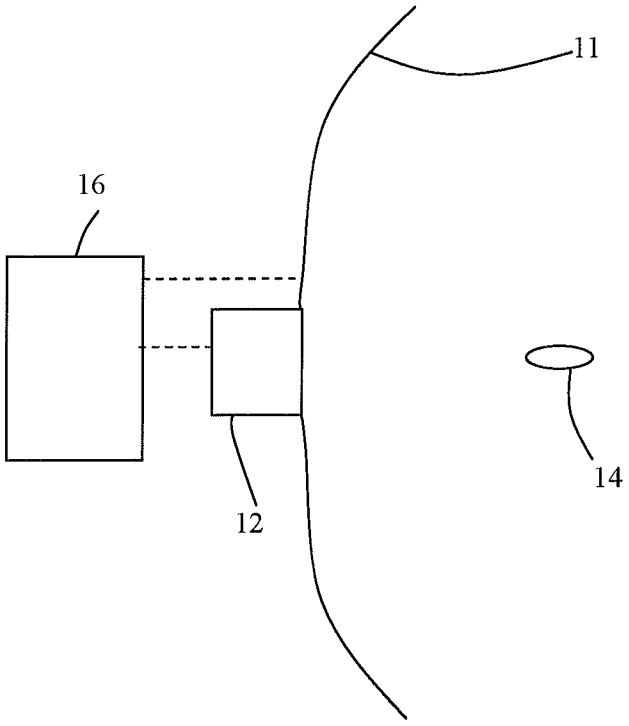


Fig. 2

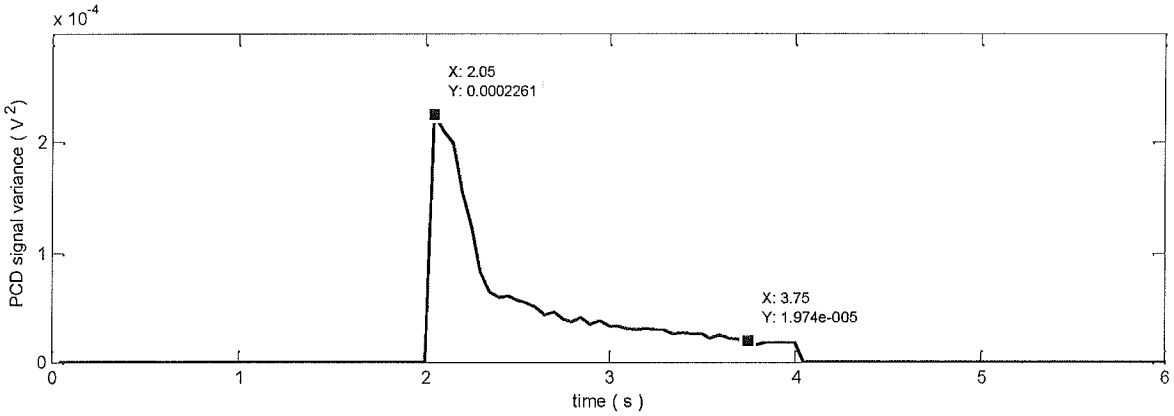


Fig. 3

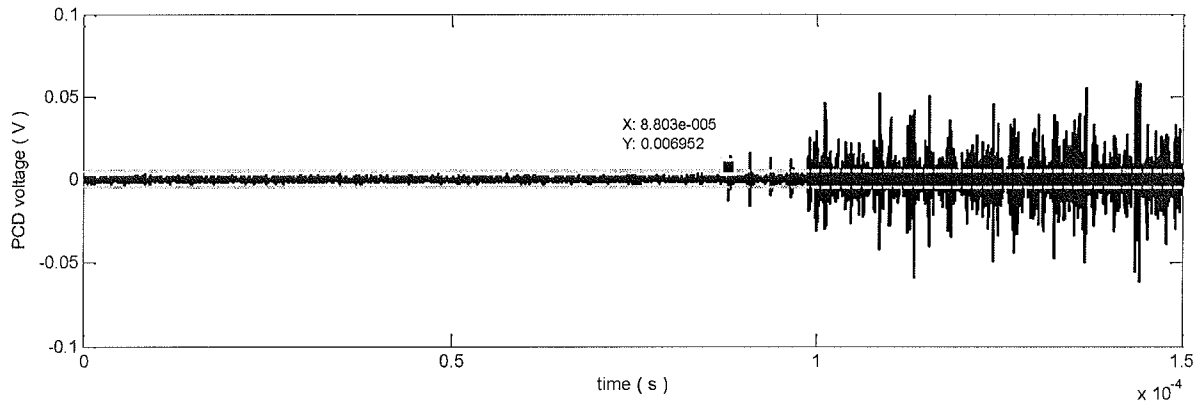


Fig. 4

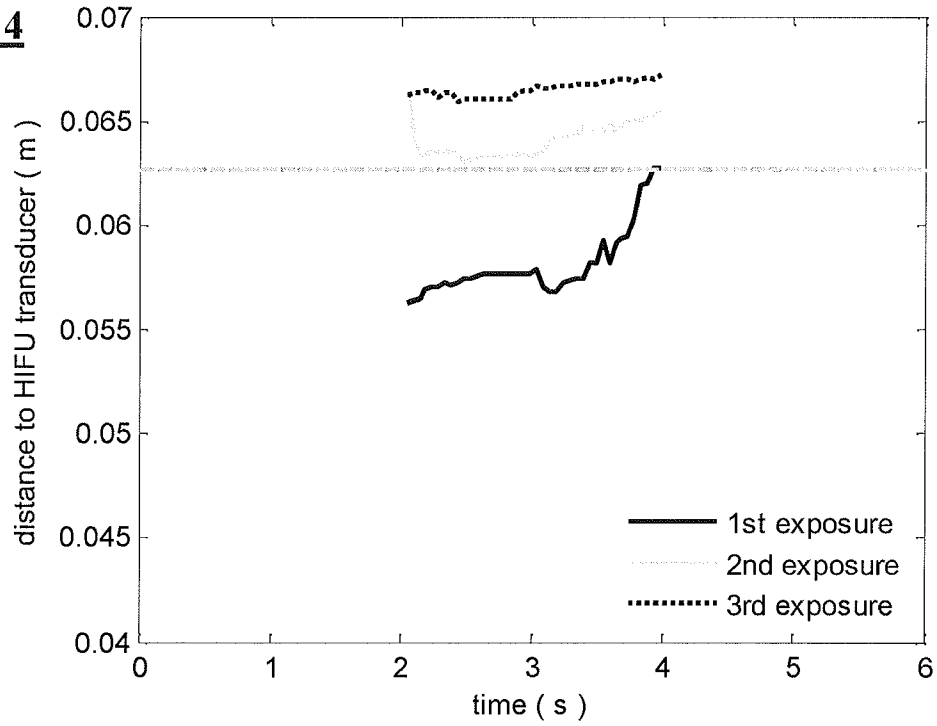


Fig. 5

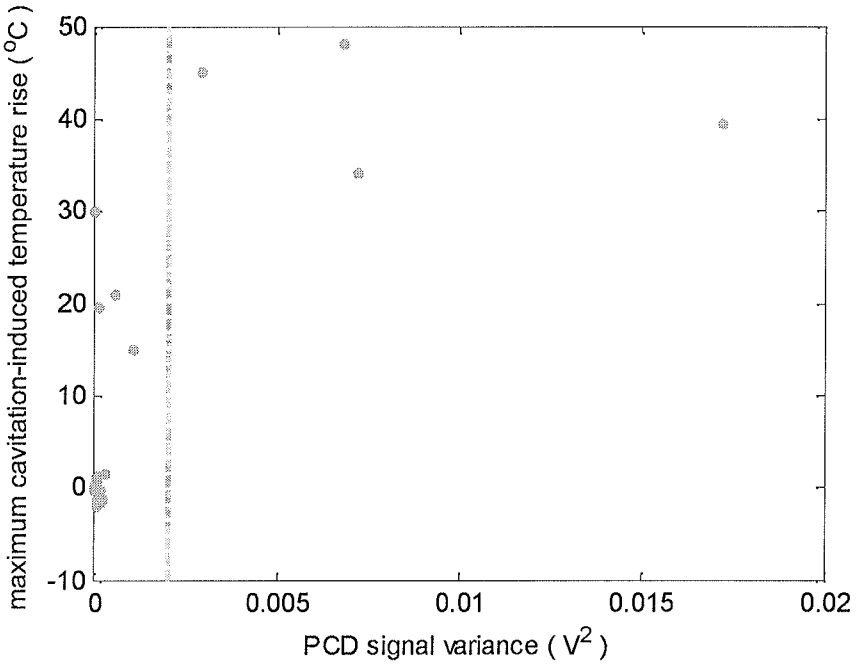
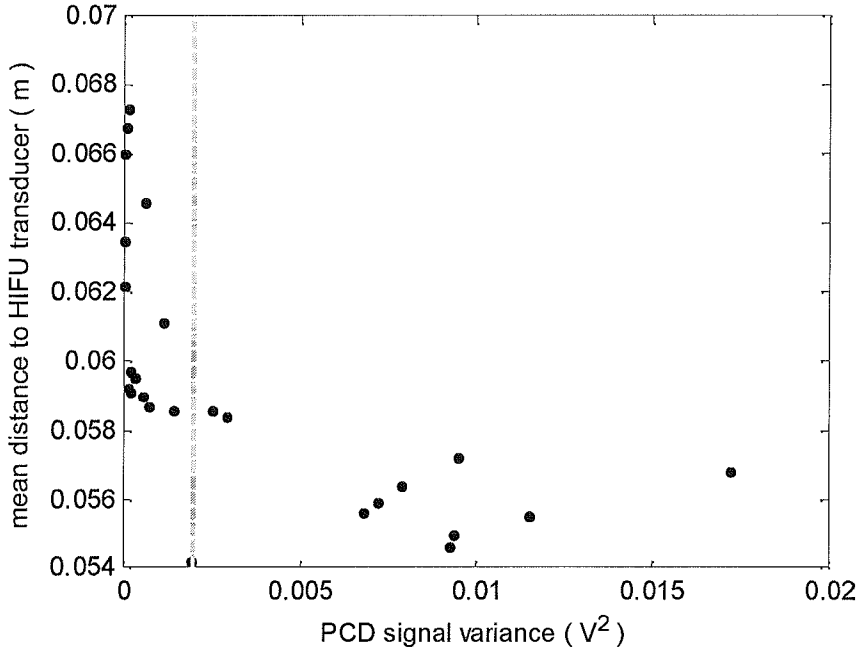

maximum cavitation-induced temperature rise (°C)
50
40
30
20
10
0
-10
0
0.005
0.01
0.015
0.02
PCD signal variance (V2)

Fig. 6


mean distance to HIFU transducer (m)
0.07
0.068
0.066
0.064
0.062
0.06
0.058
0.056
0.054
0
0.005
0.01
0.015
0.02
PCD signal variance (V2)

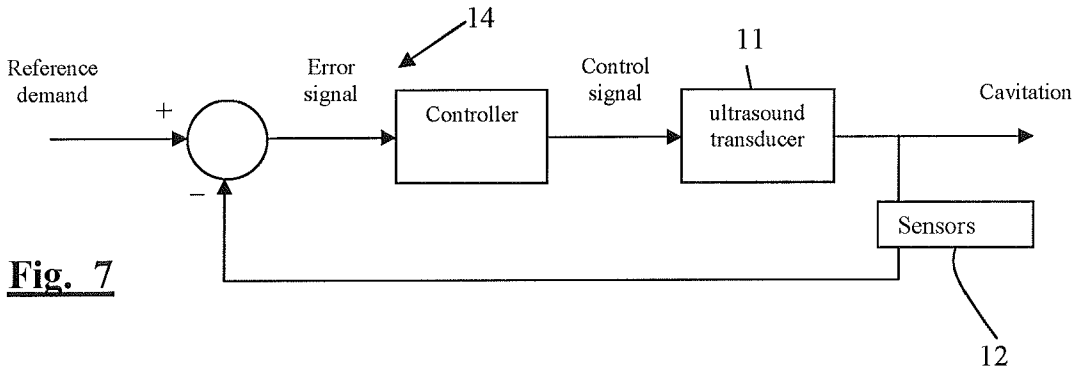

14
11
Reference demand
Error signal
Control signal
Cavitation
+
Controller
ultrasound transducer
−
Sensors
12

Fig. 7

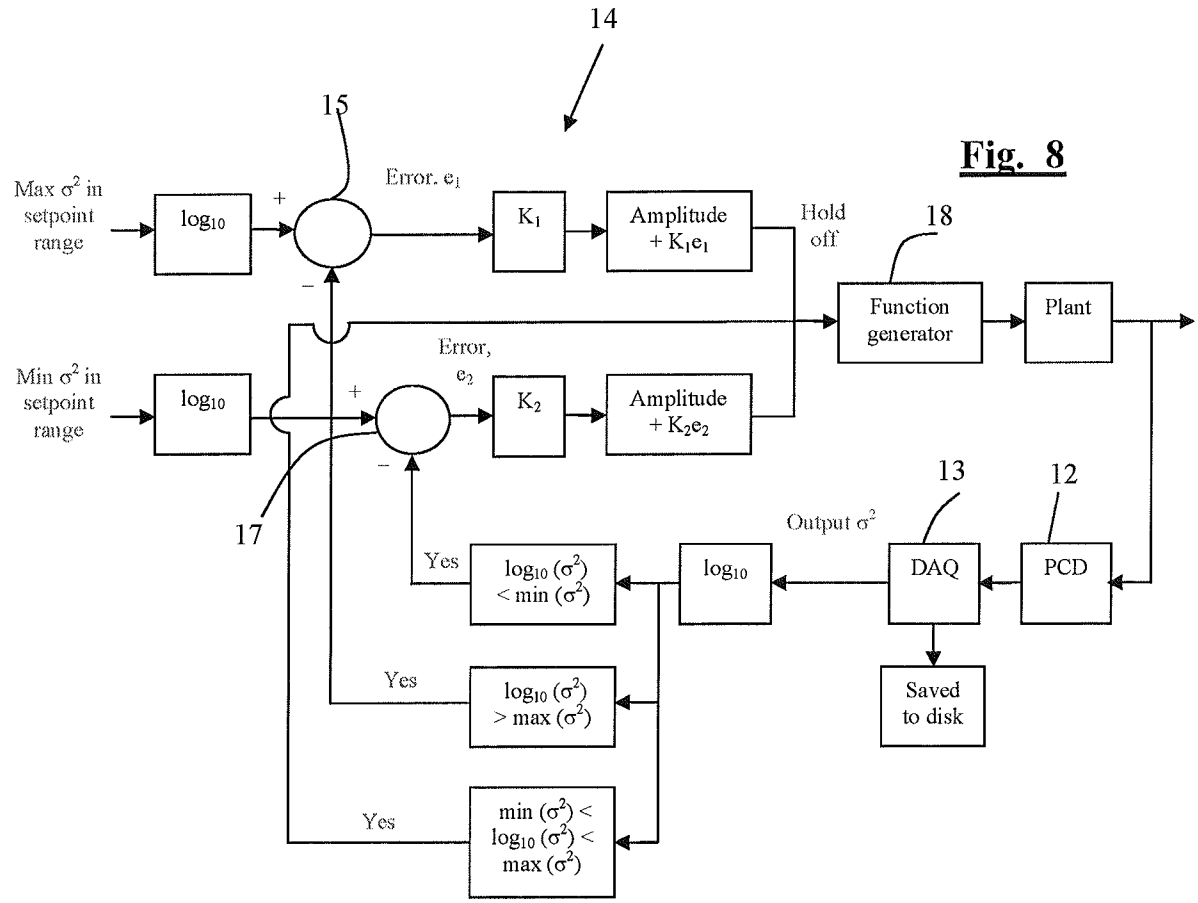

14
15
Max σ^2 in setpoint range
$\log_{10}$
+
Error. e_1
K_1
Amplitude + K_1e_1
Hold off
18
Function generator
Plant
−
Min σ^2 in setpoint range
$\log_{10}$
+
Error, e_2
K_2
Amplitude + K_2e_2
−
17
13
12
Output σ^2
Yes
$\log_{10}$ (σ^2) < min (σ^2)
$\log_{10}$
DAQ
PCD
Yes
$\log_{10}$ (σ^2) > max (σ^2)
Saved to disk
Yes
min (σ^2) < $\log_{10}$ (σ^2) < max (σ^2)

Fig. 8

Fig. 9

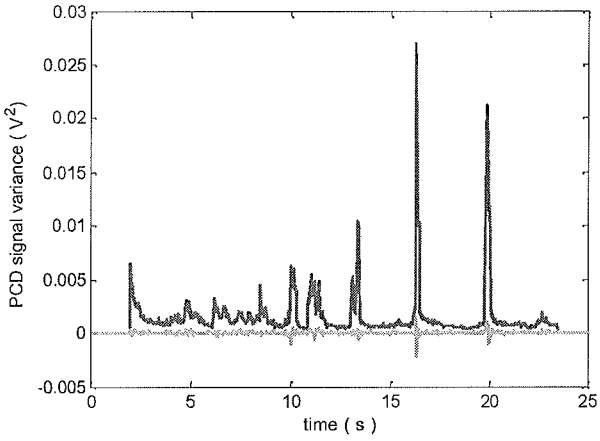
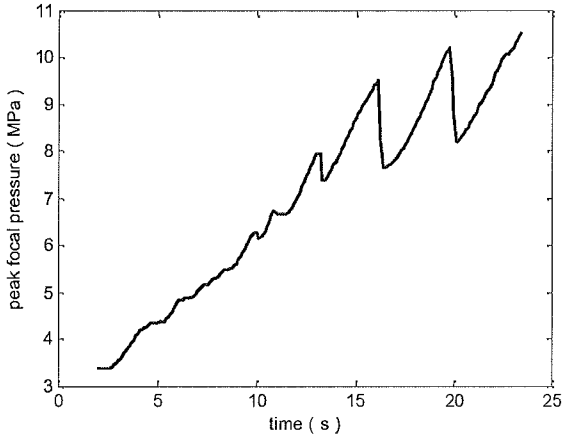


Fig. 10



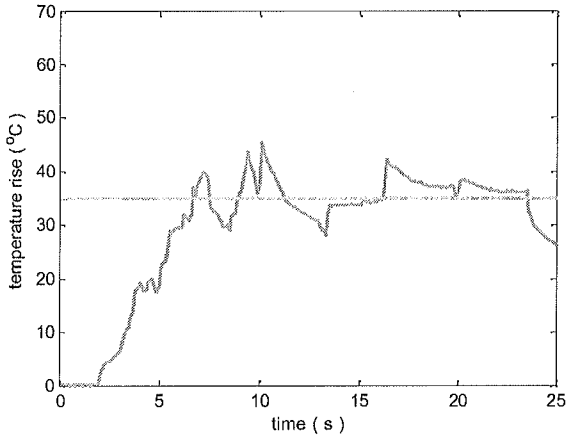


Fig. 11

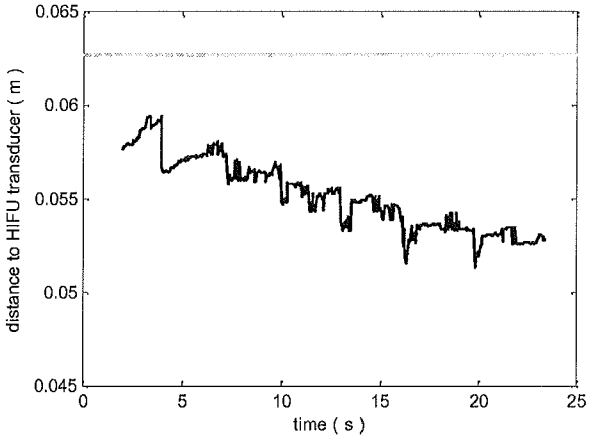
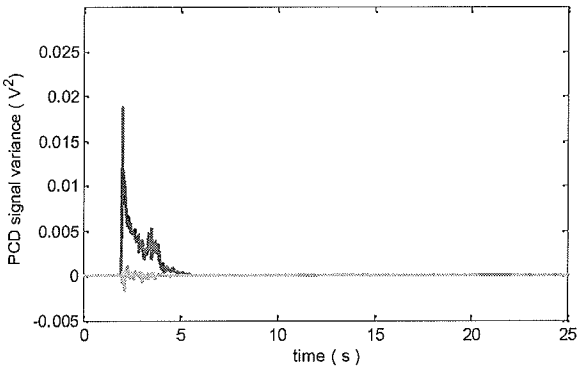


Fig. 12

Fig. 13



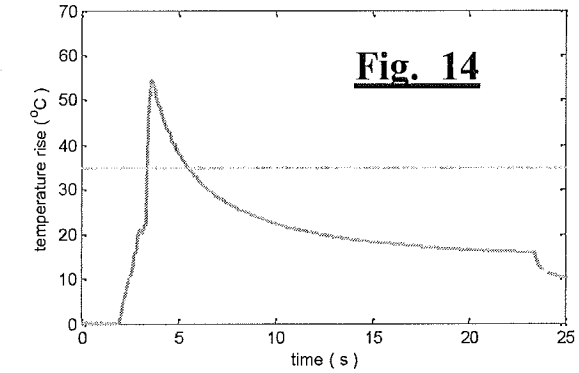


Fig. 14

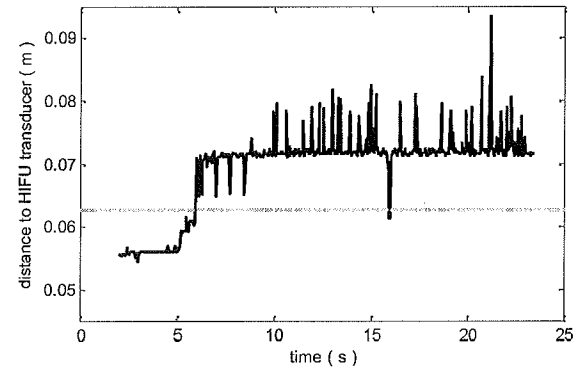
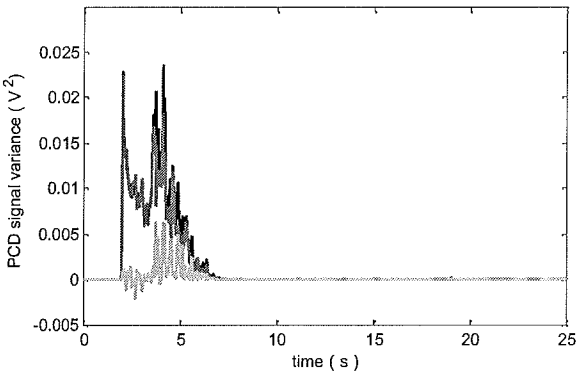


Fig. 15

Fig. 16



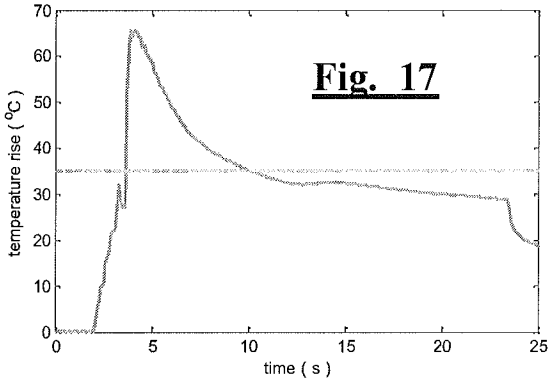


Fig. 17

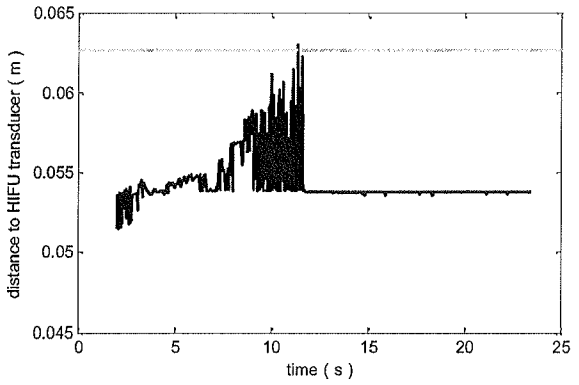


Fig. 18

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/051570

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B8/00 A61N7/02
ADD.

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)
A61B 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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 508 774 B1 (ACKER DAVID E [US] ET AL) 21 January 2003 (2003-01-21) column 7, line 22 - column 11, line 12 figure 1	1-9
X	US 2006/184075 A1 (RESTLE KARL-HEINZ [CH] ET AL) 17 August 2006 (2006-08-17) paragraph [0020] - paragraph [0029]; figure 1	1-9
X	WO 02/051501 A1 (INSIGHTEC IMAGE GUIDED TREAT L [IL]) 4 July 2002 (2002-07-04) page 12 - page 15 page 30 - page 33	1-9

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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	Date of mailing of the international search report
2 February 2011	10/02/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dydenko, Igor

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2010/051570

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. [X] Claims Nos.: 10-18
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:

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.:

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/051570

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/094554 A2 (UNIV MICHIGAN [US]; MAXWELL ADAM [US]; XU ZHEN [US]; GURM HITINDER S []) 30 July 2009 (2009-07-30) paragraphs [0035], [0 37], [0 42], [0 47], [0 57], [0 71]; figure 1	2,3,6,7
A	US 2007/265560 A1 (SOLTANI AZITA [US] ET AL) 15 November 2007 (2007-11-15) paragraph [0160]	4
A	WO 03/070105 A1 (LIPOSONIX INC [US]) 28 August 2003 (2003-08-28) paragraphs [0106], [111]	8
A	TRAN B C ET AL: "Correlation between acoustic backscatter variability and tissue damage produced by pulsed cavitational ultrasound therapy", ULTRASONICS SYMPOSIUM, 2004 IEEE MONTREAL, CANADA 23-27 AUG. 2004, PISCATAWAY, NJ, USA,IEEE, vol. 2, 23 August 2004 (2004-08-23), pages 1461-1464, XP010784237, DOI: DOI:10.1109/ULTSYM.2004.1418077 ISBN: 978-0-7803-8412-5 the whole document	1,9
A,P	WO 2010/052494 A1 (ISIS INNOVATION [GB]; COUSSIOS CONSTANTIN C [GB]; GYONGY MIKLOS [GB];) 14 May 2010 (2010-05-14) the whole document	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2010/051570

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6508774 B1	21-01-2003	NONE	
US 2006184075 A1	17-08-2006	DE 10102317 A1	14-08-2002
		JP 2002224127 A	13-08-2002
		US 2003130599 A1	10-07-2003
WO 02051501 A1	04-07-2002	AT 273051 T	15-08-2004
		DE 60104899 D1	16-09-2004
		DE 60104899 T2	18-08-2005
		EP 1345657 A1	24-09-2003
WO 2009094554 A2	30-07-2009	NONE	
US 2007265560 A1	15-11-2007	EP 2015846 A2	21-01-2009
		WO 2007127176 A2	08-11-2007
WO 03070105 A1	28-08-2003	AU 2003219843 A1	09-09-2003
		CA 2476873 A1	28-08-2003
		EP 1476080 A1	17-11-2004
		JP 4551090 B2	22-09-2010
		JP 2005517488 T	16-06-2005
WO 2010052494 A1	14-05-2010	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 10-18

Claims 10 - 18 all relates to a method for treatment of the human or animal body by surgery, because they all comprise the step of producing cavitation in a subject by delivering ultrasound. As is well known and is also clear from page 1 of the description of the present application, cavitation has an effect on the physical integrity of the living tissue, producing e.g. opening a blood-brain barrier tissue erosion, and this is considered a surgical procedure. Because ultrasound-induced cavitation is also a therapeutic tool (see page 1 of the description of the present application), claims 10-18 are also considered to relate to a method for treatment of the human or animal body therapy. This Authority is not required to search the present application with respect to the aforementioned claims (Article 17(2)(b) PCT and Rule 39.1(iv) PCT). Consequently, no International Search Report has been established with respect to them.

专利名称(译)	超声系统		
公开(公告)号	EP2480135A1	公开(公告)日	2012-08-01
申请号	EP2010768048	申请日	2010-09-20
[标]申请(专利权)人(译)	ISIS创新有限公司		
申请(专利权)人(译)	ISIS创新有限公司		
当前申请(专利权)人(译)	牛津大学创新有限公司		
[标]发明人	COUSSIOS CONSTANTIN ARORA MANISH HOCKHAM NATALIE ROY RONALD AURELE		
发明人	COUSSIOS, CONSTANTIN ARORA, MANISH HOCKHAM, NATALIE ROY, RONALD AURELE		
IPC分类号	A61B8/00 A61N7/02 A61N7/00 A61B17/22 A61B18/00 B06B1/02		
CPC分类号	A61B8/00 A61B17/22004 A61B2018/00642 A61B2018/00666 A61N7/00 A61N7/02 A61N2007/0008 A61N2007/0039 B06B1/0207 B06B2201/76		
代理机构(译)	WILSON，ALAN STUART		
优先权	2009016634 2009-09-22 GB		
其他公开文献	EP2480135B1		
外部链接	Espacenet		

摘要(译)

超声系统包括换能器，控制器，其被设置为产生控制信号，该控制信号被设置为控制换能器以产生指向目标体积的压力波，以及被设置为感测目标体积中的空化的感测装置。控制器设置成接收来自传感装置的传感信号并响应传感信号改变控制信号，从而控制空化。