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(71) Applicant: KING'S COLLEGE LONDON [GB/GB];

Strand, London WC2R 2LS (GB).

(72) Inventors: **BROWN, Jemma**; IP & Licensing, Research Management & Innovation Directorate, King's College London, 5-11 Lavington Street, London, Greater London SE1 0NZ (GB). **ECKERSLEY, Robert**; IP & Licensing, Research Management & Innovation Directorate, King's College London, 5-11 Lavington Street, London, Greater London SE1 0NZ (GB).

(74) Agent: **SCRIPT IP LIMITED** et al.; Turnpike House, 18 Bridge Street, Frome, Somerset BA11 1BB (GB).

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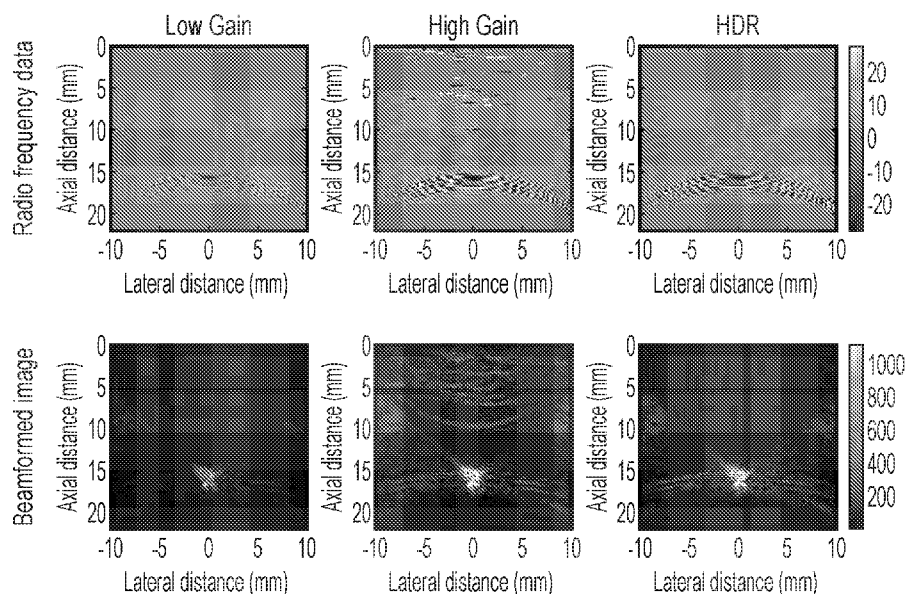


FIG. 2 B

(57) **Abstract:** Aspects and embodiments relate to a method of detecting and imaging non-linear components of ultrasound signals returned by a target including a non-linear scatterer, a computer program product configured to perform the method and an apparatus for detecting and imaging non-linear components of ultrasound signals returned by a target including a non-linear scatterer. The method comprises: (a) transmitting a first ultrasound pulse into the target; (b) receiving a first ultrasound signal including linear and non-linear components from the target at two gain levels, the gain levels having a relationship which is known and the gain levels being such that: at one of said the levels, the received first ultrasound signal comprises detectable non-linear components; (c) constructing a replacement first ultrasound signal for the received first ultrasound signal comprising detectable non-linear components by: combining a translation of the received first signal at a first gain level with the received first signal comprising detectable non-linear components, the translation and construction being based on the known relationship between gain levels; (d) transmitting a second pulse into the

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target and performing steps (b) and (c) in relation to the second pulse to construct a replacement second signal for the received second signal comprising detectable non-linear components; and (e) combining the replacement first signal and the replacement second signal to detect the non-linear components of the ultrasound signals returned by the target to produce an image of a non-linear scatterer in the target. Aspects and embodiments may provide a means to provide high dynamic range ultrasound imaging (HDR) techniques in relation to a target having a non-dominant non-linear response, and allow for effective imaging of scatterers in a target associated with that non-linear response.

HIGH DYNAMIC RANGE NON-LINEAR ULTRASOUND IMAGING

FIELD OF THE INVENTION

Aspects and embodiments relate to a method of detecting and imaging non-linear
5 components of ultrasound signals returned by a target including a non-linear scatterer,
a computer program product configured to perform the method and an apparatus for
detecting and imaging non-linear components of ultrasound signals returned by a
target including a non-linear scatterer.

10 BACKGROUND

Ultrasound is a widely used analysis tool. Advantages of ultrasound include safety and
low cost compared to other possible analysis tools. The fast imaging properties of
ultrasound can be further utilised to image targets. However, conventional ultrasound
systems are configured to successfully image ultrasound targets having a
15 predominantly linear response. It has been recognised that a non-linear response of a
target may include information of interest about the target.

SUMMARY

A first aspect provides: a method of detecting and imaging non-linear components of
20 ultrasound signals returned by a target including a non-linear scatterer, the method
comprising: (a) transmitting a first ultrasound pulse into the target; (b) receiving a first
ultrasound signal including linear and non-linear components from the target at two
gain levels, the gain levels having a relationship which is known and the gain levels
being such that: at one of said the levels, the received first ultrasound signal comprises
25 detectable non-linear components; (c) constructing a replacement first ultrasound
signal for the received first ultrasound signal comprising detectable non-linear
components by: combining a translation of the received first signal at a first gain level
with the received first signal comprising detectable non-linear components, the
translation and construction being based on the known relationship between gain
30 levels; (d) transmitting a second pulse into the target and performing steps (b) and (c)
in relation to the second pulse to construct a replacement second signal for the received
second signal comprising detectable non-linear components; and (e) combining the
replacement first signal and the replacement second signal to detect the non-linear
components of the ultrasound signals returned by the target to produce an image of a
35 non-linear scatterer in the target.

The first aspect recognises that ultrasound imaging can suffer from saturation issues and that typical ultrasound targets, particularly in relation to medical imaging applications, comprise targets in which highly echogenic linear features dominate a target response to application of an ultrasound pulse. The first aspect further
5 recognises that features which have a non-linear response to application of an ultrasound pulse may be of interest to those investigating a target and that those responses may be difficult to separate from a dominant linear response. In order to detect any non-linear response from a target, it may be necessary to receive at a high level of gain. At such a high level of gain, the linear response of the target may suffer
10 saturation at the receiver. As a result, standard techniques to recover a non-linear response from a signal may be inappropriate and artefacts associated with the receiver saturation may be difficult or impossible to distinguish from a non-linear signal of interest received from the target. The first aspect recognises that in response to an ultrasound pulse transmitted into a target, it is possible to use a signal received at a
15 relatively low gain in which a non-linear signal response may not be distinguishable but which does not suffer from saturation issues, together with a signal received at a relatively high gain to more effectively recover and process a signal relating to the non-linear response of a target to application of ultrasound.

20 A method of detecting and imaging non-linear components of ultrasound signals returned by a target including a non-linear scatterer may be provided. The method may comprise the following steps: (a) transmitting a first ultrasound pulse into the target. Step (a) may comprise transmitting the first ultrasound pulse into the target more than once. Step (b): receiving a first ultrasound signal including linear and non-
25 linear components from the target at two gain levels. The method may comprise receiving at more than two gain levels. The gain levels may be different. The gain levels may have a relationship which is known. That is to say, it may be possible to map a signal received at one gain level to a signal expected at the second gain level. The gain levels may be such that: at one of said the levels, the received first ultrasound signal
30 comprises linear components which have passed a known receiver saturation threshold. That is to say, at a higher gain level, highly echogenic features of a received signal may be dominant and may suffer from saturation at a receiver. The saturation threshold may depend upon the ultrasound apparatus being used and the target under study. Step (c) may comprise: constructing a replacement first ultrasound signal for
35 the received first ultrasound signal comprising linear components which have passed the known receiver saturation threshold by: combining a translation of the received first signal for which saturation of linear components is avoided with the received first

signal comprising linear components which have passed the known receiver saturation threshold, the translation and construction being based on the known relationship between gain levels and the known receiver saturation threshold. That is to say, a saturated portion of a signal received at a high gain level may be replaced by a portion of a signal it might be expected to receive, had the receiver been capable of receiving at that level. The replacement portion may be calculated or estimated by assuming a linear translation of the signal received when a “low” receiver gain is used. Step (d) may comprise: transmitting a second pulse into the target and performing steps (b) and (c) in relation to the second pulse to construct a replacement second signal for the received second signal comprising linear components which have passed the known receiver saturation threshold. Step (e) may comprise: combining the replacement first signal and the replacement second signal to detect the non-linear components of the ultrasound signals returned by the target to produce an image of a non-linear scatterer in the target. In other words, a replacement “hybrid” signal formed partly from measured data, and partly from estimated data from the low gain signals can be formed for each of the first as second ultrasound pulses transmitted into a target for which a response signal is received. The replacement hybrid signals created in accordance with a method of the first aspect can be used in standard multi-pulse non-linear imaging methods.

20

In some embodiments, the first ultrasound signal comprises an ultrasound pulse having a known amplitude and phase and the second ultrasound signal comprises an ultrasound signal having a known amplitude and phase. The first and second ultrasound pulses comprise different pulses. The first and second pulses have a different amplitude and/or phase (or combination thereof). The first pulse is identical in relation to receiving the first ultrasound signal at the two gain levels. In other words, the response of the target is substantially identical at the two gain levels, only the gain level at the receiver is changed. This may be achieved in various ways: In some embodiments, receiving from the target at the two gain levels comprises: reception of distinct transmissions of the first or second ultrasound pulse. That is to say, the first pulse may be transmitted into the target more than once, for example, in adjacent pulses introduced into a target. In some embodiments, receiving from the target at the two gain levels comprises: concurrent reception of a single transmission of the first or second ultrasound pulse. Receiver technology may allow for a single introduction of a first pulse to be concurrently received at both a high and low gain level by a receiver.

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In some embodiments, the translation of the first received signal comprises: linearly mapping the first received signal at the first gain level to the gain level at which the received first signal comprising detectable non-linear components is received. For example, if the low gain is half that of the high gain, the signal received at low gain may
5 be translated by multiplying by a factor of two.

In some embodiments, construction of the replacement first ultrasound signal comprises: replacing a saturated portion of the received first signal comprising detectable non-linear components with an equivalent portion of signal from the
10 translation of the first received signal. It will be appreciated that saturation of a response may be visualised as the clipping of a received signal. The flattened or truncated portion may be replaced by an equivalent portion calculated from the translated low gain signal. That is to say, the unclipped portion of a high gain signal may be stitched together with an estimate of what the clipped portion of signal is likely
15 to be. The estimate is created from the signal received at low gain.

In some embodiments, constructing the replacement first or second ultrasound signal further comprises: smoothing a transition of signal associated with the translation of said received first signal to a portion of the received first signal comprising detectable
20 non-linear components. It will be appreciated that the stitching together process referred to above may result in a jagged replacement signal. Abrupt or jagged signals can themselves cause unwanted artefacts in an image resulting from non-linear processing techniques and it may be advantageous to use mathematical smoothing methods to smooth a transition between “real” acquired signal and a calculated signal
25 used to replace a clipped (saturated) portion of that real acquired signal.

In some embodiments, combining the replacement first signal and the replacement second signal to detect the non-linear components of the ultrasound signals returned by the target comprises use of a multi-pulse non-linear imaging ultrasound method. In
30 some embodiments, the multi-pulse non-linear imaging ultrasound method comprises: a multi-pulse amplitude modulation technique. In some embodiments, the multi-pulse non-linear imaging ultrasound method comprises: a multi-pulse phase modulation technique. It will be appreciated that the multi-pulse technique may comprise a phase and amplitude modulation technique.

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In some embodiments, the non-linear scatterer included in the target comprises: an ultrasound contrast agent. In some embodiments, the ultrasound contrast agent

comprises: one or more of: microbubbles or nanodroplets. In some embodiments, an amplitude of the first and second ultrasound signals is selected to be above a threshold at which a non-linear response from said ultrasound contrast agent is activated. It will be appreciated that non-linear responses in ultrasound are associated with the use of contrast agents. Contrast agents include, for example, microbubbles (MBs) and nanodroplets. Furthermore, it will be appreciated that MB responses can depend on applied ultrasound pulse amplitude and whilst they require application of a particular amplitude above an activation amplitude to oscillate and operate as desired, they can be destroyed/damaged if the amplitude increases over a certain threshold.

Ultrasound contrast agents have various uses, in particular in relation to vascular imaging, where microbubbles can be placed in the blood, but also have applications in tumour/necrosis imaging as described in [17].

In some embodiments, the method may comprise calibration steps to identify appropriate gain levels to apply. A test sequence over a possible range of receiver gain levels can be performed to determine a set of operating parameters at which saturation of a receiver is likely to occur. An ultrasound transmitter may then be configured such that a non-linear pulse sequence is transmitted into a target, reflected/scattered by the target and then received by an ultrasound transducer at an ultrafast frame rate. A transmission is made and received at a maximum gain before which saturation occurs, immediately followed by reception at, for example, maximum system gain. In this way, it is possible to ensure at least one received signal is substantially unsaturated and thus, that any received signal which does suffer from saturation can be augmented/corrected using the unsaturated received signal. The signal received at a lower gain level may be amplified during post processing in various implementations of methods in accordance with the first aspect and data “lost” due to saturation of the signal received at a higher gain regained. In particular, data at amplitudes beyond receive saturation level can be combined or “stitched” onto signals received at a higher gain level which includes saturated portions. A calibration step may help to ensure detectability of non-linearities in a received signal from a target. It will be appreciated that in some instances, in order to detect non-linear components in a signal, it may be necessary to increase gain to a level at which saturation of a signal from highly echogenic (linear) features of a target occurs.

A second aspect provides a computer program product operable, when executed on a computer, to perform the method of the first aspect.

A third aspect provides: an ultrasound apparatus configured to detect and image non-linear components of ultrasound signals returned by a target including a non-linear scatterer, the apparatus comprising a transducer configured to: (a) transmit a first
5 ultrasound pulse into the target; and (b) receive a first ultrasound signal including linear and non-linear components from the target at two gain levels, the gain levels having a relationship which is known and the gain levels being such that: at one of said the levels, the received first ultrasound signal comprises detectable non-linear components; processing logic configured to (c) construct a replacement first ultrasound
10 signal for the received first ultrasound signal comprising detectable non-linear components by: combining a translation of the received first signal with the received first signal comprising detectable non-linear components, the translation and construction being based on the known relationship between gain levels; the transducer and processing logic also being configured to: transmit a second pulse into the target
15 and perform steps (b) and (c) in relation to the second pulse to construct a replacement second signal for the received second signal comprising detectable non-linear components; and detection and imaging logic configured to combine the replacement first signal and the replacement second signal to detect the non-linear components of the ultrasound signals returned by the target and produce an image of a non-linear
20 scatterer in the target.

In some embodiments, the first ultrasound signal comprises: an ultrasound pulse having a known amplitude and phase and the second ultrasound signal comprises an ultrasound signal having a known amplitude and phase.

25

In some embodiments, receiving from the target at the two gain levels comprises: reception of distinct transmissions of the first or second ultrasound pulse. In other words, the transducer may be configured to transmit a pulse (first and/or second) having a particular form more than once. That multiple transmission may occur in
30 consecutive transmissions. The timing of those consecutive transmissions may be set by the depth of the features of interest in a target, since when using acoustic pressure waves as a means of interrogation or investigation of the target it will be appreciated that time and depth are related.

35 In some embodiments, the transducer may be configured to receive from the target at the two gain levels as concurrent reception of a single transmission of the first or second ultrasound pulse.

In some embodiments, the translation of the first received signal comprises: linearly mapping the first received signal at a first gain level to the gain level at which the received first signal comprising detectable non-linear components is received.

5

In some embodiments, construction of the replacement first ultrasound signal comprises: replacing a saturated portion of the received first signal comprising detectable non-linear components with an equivalent portion of signal from the translation of the first received signal.

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In some embodiments, combining the replacement first signal and the replacement second signal to detect the non-linear components of the ultrasound signals returned by the target comprises use of a multi-pulse non-linear imaging ultrasound method.

15 In some embodiments, the multi-pulse non-linear imaging ultrasound method comprises: a multi-pulse amplitude modulation technique.

In some embodiments, the multi-pulse non-linear imaging ultrasound method comprises: a multi-pulse phase modulation technique.

20

In some embodiments, the non-linear scatterer included in the target comprises: an ultrasound contrast agent.

In some embodiments, the ultrasound contrast agent comprises: one or more of:
25 microbubbles or nanodroplets.

In some embodiments, an amplitude of the first and second ultrasound signals is selected to be above a threshold at which a non-linear response from said ultrasound contrast agent is activated.

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In some embodiments, constructing the replacement first or second ultrasound signal further comprises: smoothing a transition of signal associated with the translation of said received first signal at a first gain level to a portion of the received first signal comprising detectable non-linear components.

35

Further aspects provide: a method, computer program product and apparatus for detecting and imaging non-linear components of ultrasound signals returned by a

target including a non-linear scatterer, the method comprising: (a) transmitting a first ultrasound pulse into the target; (b) receiving a first ultrasound signal including linear and non-linear components from the target at two gain levels, the gain levels having a relationship which is known and the gain levels being such that: at one of said the
5 levels, the received first ultrasound signal comprises detectable non-linear components; (c) constructing a replacement first ultrasound signal for the received first ultrasound signal comprising detectable non-linear components by: combining a translation of the received first signal at a first gain level with the received first signal comprising detectable non-linear components, the translation and construction being
10 based on the known relationship between gain levels; (d) using the replacement first signal and to identify non-linear components of the ultrasound signal returned by the target to produce an image of a non-linear scatterer in the target.

Further aspects recognise that by receiving an ultrasound signal from a target more
15 than one gain level can be advantageous. In particular, receiving a response signal from a target at both high and low gain may allow for effective tissue harmonic imaging. It will be appreciated that techniques described above in relation to multi-pulse imaging may also be applied in a scenario in which a user is seeking to perform tissue harmonic imaging. The non-linear components may be more accurately
20 identified in, for example the replacement first ultrasound signal, and thus processing may occur on a signal for which saturation complications are mitigated.

Aspects and embodiments may relate to plane wave ultrasound imaging techniques.

25 Aspects may operate to mathematically combine signals received at different gains, before doing a multi-pulse technique to extract non-linear signal. Aspects may require that a first ultrasound pulse is received at least twice. The pulse is received at different gain levels. The second ultrasound pulse, which may, for example, be transmitted at a different intensity or phase to the first ultrasound pulse, may also be received at two
30 different gain levels. Aspects may operate to construct a “replacement” received signal by mathematically combining signals corresponding to transmit pulses of the same excitation level but received at different gain levels. It will be appreciated that a nonlinear signal is extracted by mathematically combining the replacement signals. Aspects may operate such that a method and apparatus are provided in which signals
35 are received at different gains, but those received signals correspond to the same transmit pulse properties. As a result, artifacts which occur in a received signal due to

saturation of strong linear signals when imaging non-linear targets using a high gain can be avoided or accounted for.

Aspects may provide methods and apparatus which can improve non-linear ultrasound
5 imaging. Aspects may operate to improve non-linear ultrasound imaging by receiving pulses at different gains, those received pulses corresponding to transmission pulses transmitted with the same transmit properties. Received signals at different gain levels can then be combined to construct replacement signals. These replacement signals are not affected by saturation due to the limited dynamic range of the ultrasound
10 transducer. Therefore, mathematical manipulation to extract a non-linear signal can be performed without producing a saturation artifact.

Further particular and preferred aspects are set out in the accompanying independent and dependent claims. Features of the dependent claims may be combined with
15 features of the independent claims as appropriate, and in combinations other than those explicitly set out in the claims.

Where an apparatus feature is described as being operable to provide a function, it will be appreciated that this includes an apparatus feature which provides that function or
20 which is adapted or configured to provide that function.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the present invention will now be described further, with reference to the accompanying drawings, in which:

- 25 Figure 1A illustrates schematically amplitude modulation techniques and artefacts that can be introduced when strong linear signal is saturated;
Figure 1B illustrates graphically recovery of an example non-linear signal by application of illustrative techniques;
Figure 2 illustrates schematically ultrasound techniques used on an in silico target;
30 Figure 2A shows simulation target geometry including a colour map of tissue impedance values;
Figure 2B illustrates images created from multi-pulse ultrasound data collected from an in silico arrangement such as that shown in Figure 2A at low gain, high gain and according to one possible imaging method;
35 Figure 3 illustrates schematically ultrasound techniques used on an in vitro phantom target;

Figure 3A illustrates images created from multi-pulse ultrasound data collected from an in vitro phantom target at low gain, high gain and according to one possible imaging method;

Figure 3B shows a quantification of a comparison of the images of Figure 3A; and

5 Figure 3C shows a difference image between a high gain image and an image created according to one possible imaging method.

DESCRIPTION OF THE EMBODIMENTS

Before describing one particular embodiment in detail, a general overview of methods
10 and devices utilising concepts described is provided.

Ultrasound images are generated by reconstructing reflections of acoustic waves incident at tissue boundaries. Ultrasound transducers typically transmit acoustic waves and use piezoelectric sensors to convert pressure waves returned by a target into
15 electrical signals. Such a received signal undergoes analogue amplification before being digitised, typically into 8 bit data [1]. The amplitude of the returned wave, reflected by a scatterer in a target, is dependent on a difference in acoustic impedance (product of speed of sound and density) between boundary media. There is a finite range over which an analogue amplifier can ensure linear amplification of an input voltage with
20 respect to the output voltage [2]. As a result, relatively high amplitude input voltages are typically saturated by a receiver after amplification.

It has been recognised that it is possible to use ultrasound contrast agents to enhance the information available about a target via ultrasound imaging. Possible ultrasound
25 contrast agents include, for example, nanodroplet and microbubble (MB) contrast agents. Microbubble contrast agents comprise spheres of gas enclosed in a shell engineered for stability. Microbubbles can be used as blood pool agents, used to increase the contrast of vasculature [3]. In an in vivo ultrasound target, microbubbles act to strongly reflect acoustic waves due to the large impedance mismatch between
30 microbubbles and typical surrounding tissue and the high compressibility of the microbubbles. At some ultrasound acquisition parameters, MBs can exhibit a non-linear response to an incident ultrasound pulse. The non-linear response of the MBs can be extracted from the response of surrounding (predominantly linearly scattering), tissue using non-linear image processing techniques [4]. Non-linear image processing
35 techniques include ultrasound techniques known as multi-pulse imaging.

One example non-linear imaging processing technique, amplitude modulation, involves transmitting pulses with different amplitudes before rescaling and combining received data from a target to extract a linear signal [5]. For example, a target may be exposed to an ultrasound transmission at an amplitude of P and then ultrasound transmission at an amplitude of $P/2$. According to an amplitude modulation non-linear image processing technique, the received signal from transmitting a pulse with amplitude $P/2$ can be multiplied by a factor of two and subtracted from the received signal from transmitting a pulse with amplitude P . Such an approach operates to remove any linear part of the received signal.

It will be appreciated that ultrasound contrast agents, such as microbubbles, operate such that the non-linear components of the MB signals are much weaker than the linear. As a result, the receive gain of an ultrasound system will typically need to be high so that the non-linear components are sufficiently well received. However, use of a high receive gain can cause the signal from strong tissue scattering to become saturated. This means that linear signals may no longer be readily removed by using the non-linear processing techniques referred to above. Saturation at high gain can be a common problem in commercial ultrasound systems, with the saturated signal appearing as bright structures in a resulting ultrasound image.

Similar problems have been approached in other modalities, namely optics [6]. In the case of linear optics systems tone mapping techniques are used such that combining images acquired using high and low exposures can be used to visualise both bright and dark features. Analogous techniques have been applied to linear ultrasound targets, in which no contrast agents are used [7-8].

Application of known tone mapping techniques to a system or ultrasound target in which a non-linear response is expected does not yield a successful imaging outcome. It is desired to provide an ultrasound method and apparatus which can be used to image targets in which a non-linear response is expected and in which the non-linear response is a feature of interest in an ultrasound target.

It will be appreciated that non-linear responses in ultrasound are associated with the use of contrast agents. Furthermore, it will be appreciated that MB responses depend on pulse amplitude and they will be destroyed/ damaged if the amplitude increases over a certain threshold [9]. In looking for techniques to successfully image non-linear responses of targets including contrast agents, various approaches have been

considered: Volterra filtering has been reported as an alternative to pulse inversion (PI) and AM in order to extract MB contrast with improved dynamic range [10-11]. More simply, some authors have investigated automatically adjusting display settings [12]. Ishihara, Tanaka et al. 2015, describe a system which also looks at the effect of

5 saturation on amplitude modulated data [2]. In particular: if a pulse of amplitude A is flagged as being saturated, amplification applied to subsequent pulses of lower transmit amplitude is increased prior to the digitisation.

Overall, the problem of visualising non-linear signals in ultrasound targets, without

10 encountering saturation of signals associated with strong linearly scattering structure, has not been sufficiently addressed for successful contrast enhanced ultrasound imaging.

Illustrated methods recognise ways in which it may be possible to mitigate some issues associated with the imaging of ultrasound targets in which a non-linear response is

15 expected. Such targets include, for example, systems including ultrasound contrast agents such as nanodroplets and/or microbubbles.

In general, the illustrative methods for imaging features with which a non-linear response to an ultrasound pulse is associated use multi-pulse non-linear imaging

20 methods. In order to mitigate some of the problems associated with saturation issues, some methods illustrated are such that an identical pulse signal is transmitted into a target and received at more than one gain level. The gain levels used are selected such that at least one does not suffer from saturation issues. The relationship between gain levels at which the identical pulse signal is received is known. As a result, if another

25 receive gain level is such that a signal suffers saturation issues, the predominantly linear response of a signal received at a lower gain level and the known relationship between gain levels can be used to augment and adapt the signal suffering from saturation issues. By using an appropriately enhanced signal at a higher gain level (thus being likely to include the information associated with the non-linear response of

30 the target), standard multi-pulse methods for performing non-linear image processing become applicable to targets from which a non-linear response is expected.

One technique which may provide a method of detecting and imaging non-linear components of ultrasound signals returned by a target including a non-linear scatterer

35 may comprise: (a) transmitting a first ultrasound pulse into the target; (b) receiving a first ultrasound signal including linear and non-linear components from the target at two gain levels, those gain levels having a relationship which is known and those gain

levels being selected such that: at one of the gain levels the received first ultrasound signal is sufficiently amplified to render weak non-linear signals detectable but which may result in linear components which have passed a known receiver saturation threshold; c) constructing a replacement first ultrasound signal for the received first
5 ultrasound signal comprising linear components which have passed the known receiver saturation threshold by: combining a translation of the received first signal for which saturation of linear components is avoided with the received first signal comprising linear components which have passed the known receiver saturation threshold, that translation being based on the known receiver saturation threshold and the known
10 relationship between gain levels; (d) transmitting a second pulse into the target and performing steps (b) and (c) in relation to the second pulse to construct a replacement second signal for the received second signal comprising linear components which have passed the known receiver saturation threshold; and (e) combining the replacement first signal and the replacement second signal to detect the non-linear components of
15 the ultrasound signals returned by the target to produce an image of a non-linear scatterer in the target.

It will be appreciated that, in some implementations, methods may include a step to determine whether saturation artifacts in received signals are significant enough to
20 warrant collecting at multiple gains. Accordingly, a test sequence over a possible range of receiver gain levels can be performed. That test sequence may operate such that a test signal is received at a plurality of receive gain levels, the received signals can then be analysed to determine a set of operating parameters at which saturation of the receiver is likely to occur.

25 For example, an ultrasound transmitter may then be configured such that a non-linear pulse sequence is transmitted into a target, reflected/ scattered by the target and then received by an ultrasound transducer at an ultrafast frame rate. A transmission is made and received at a maximum gain before which saturation occurs, immediately
30 followed by reception at, for example, maximum system gain. In this way, it is possible to ensure at least one received signal is substantially unsaturated and thus, that any received signal which does suffer from saturation can be augmented/ corrected using the unsaturated received signal. The signal received at a lower gain level may be amplified during post processing and the data "lost" due to saturation of the signal
35 received at a higher gain regained.

In particular, data at amplitudes beyond receive saturation level can be combined or “stitched” onto signals received at a higher gain level which includes saturated portions. A non-linear processing technique, such as amplitude modulation, may then be applied to the reconstructed data, thus enabling a non-dominant non-linear signal, such as a
5 signal associated with microbubbles, without being limited by saturation.

Some implementations may recognise that it is possible that the optimum gain settings may vary as different planes within the body are scanned during an imaging session. Accordingly, the ‘test sequence’ referred to above may be performed if a significant
10 change in saturation properties of the field of view is detected. In other words, the test sequence may be periodically repeated, and/or repeated in response to detection of a change beyond a threshold in saturation properties a given field of view is detected.

By way of specific illustrative example:
15

Figure 1(A) illustrates schematically an amplitude modulation image processing technique and artefacts that can be introduced when a strong linear signal received from a target is saturated. As shown in Figure 1A, an input ultrasound pulse of amplitude P is transmitted into a target and the resulting response received. The
20 received response is shown in the left hand column in relation to: linear tissue; non-linear tissue and “saturated” tissue. The central column illustrates the received signal after transmission of a pulse having an amplitude $P/2$ into the target, again for each of: linear tissue; non-linear tissue and “saturated” tissue. The right column of Figure 1A illustrates schematically the use of the received signals of the left and central columns
25 in a multi-pulse non-linear imaging technique which uses amplitude modulation.

It can be seen in Figure 1A that for linear tissue, amplitude modulation processing causes complete cancellation of signal. For a non-linear (for example, a target including microbubbles) signal, the amplitude modulation processing extracts a non-
30 linear signal component. For a saturated (linear) tissue sample, the saturation means that amplitude modulation techniques cannot achieve cancellation of the tissue signal. The features shown in such a scenario could be mistaken or interfere with a genuine non-linear response from a target.

35 Figure 1(B) illustrates graphically recovery of an example microbubble non-linear signal by means of illustrated “high dynamic range (HDR)” methods. Figure 1B shows example modelling of HDR correction on a signal comprising linear tissue and

microbubble components in which a signal above a threshold microbubble activation amplitude has been saturated and amplitude modulation processing applied. Without the presence of surrounding tissue, a target comprising microbubbles is such that amplitude modulation non-linear imaging methods perfectly extracts the nonlinear microbubble signal. When a strong saturated linear response is introduced, amplitude modulation techniques introduce unwanted artefacts. By using illustrated HDR techniques, a microbubble signal can be recovered, even in the case where a strong saturated linear response is introduced.

Plane wave ultrasound enables ultrasound frames to be acquired with high temporal resolution of the order of milliseconds [13]. This can enable receive and transmit settings of an ultrasound apparatus to be changed on a fast timescale, for example, when using a programmable research scanner, such as ULA-OP (Univ. degli Studi di Firenze, Florence, Italy) [14]. As described above, illustrated methods may allow for extraction of a non-linear signal received from a target by combining frames acquired at high and low receiver gain levels.

According to one illustrative example, the following steps for ultrasound imaging of a target from which a non-linear response is expected may be performed:

A test sequence over a possible range of receiver gain levels can be performed to determine a set of operating parameters at which saturation of the receiver is likely to occur. An ultrasound transmitter may then be configured such that a non-linear pulse sequence is transmitted into a target, reflected/ scattered by the target and then received by an ultrasound transducer at an ultrafast frame rate. A transmission is made and received at a maximum gain before which saturation occurs, immediately followed by reception at, for example, maximum system gain. In this way, it is possible to ensure at least one received signal is substantially unsaturated and thus, that any received signal which does suffer from saturation can be augmented/corrected using the unsaturated received signal. The signal received at a lower gain level may be amplified during post processing and the data “lost” due to saturation of the signal received at a higher gain regained. In particular, data at amplitudes beyond receive saturation level can be combined or “stitched” onto signals received at a higher gain level which includes saturated portions. A non-linear processing technique, such as amplitude modulation, may then be applied to the reconstructed data, thus enabling a non-dominant non-linear signal, such as a signal associated with microbubbles, without being limited by saturation.

Figure 2 illustrates the results of an illustrative method obtained using a simulated ultrasound apparatus and target. In particular, k-Wave [15], a simulation package used to model acoustic wave propagation in tissue, has been combined with the Marmottant model of microbubble dynamics [16] to simulate 2D plane wave ultrasound images received with different gains.

Figure 2 illustrates benefits associated with use of illustrative high dynamic range techniques with a non-linear processing technique, in this case: amplitude modulation. Layers of fat and muscle, visualised using a tissue impedance map such as that shown in Figure 2A, generate strong linear reflections which are saturated upon receive. Figure 2B illustrates how using a high gain reception mode operates to allow generation of a stronger contrast signal from MBs when compared to a low gain reception mode such as that which results in the image on the left of Figure 2B. However, regions of an image highlighted in a dashed box show artefacts in the image introduced due to signal saturation. The right-hand column of Figure 2B presents an image created as a result of an illustrative HDR technique: it can be seen that a strong contrast signal is captured, without saturation artefacts.

Figure 3 illustrates results of application of illustrative techniques in an in vitro demonstration. The empirical target arrangement comprised: an arrangement in which a 200 μm copper wire provided as a strong linear scatterer. The wire was located approximately 20 mm deep in the empirical target. The empirical target also included a 200 μm cellulose tube located approximately 50 mm deep in the empirical target. A diluted solution of Sonovue™(Bracco) MBs was drawn through the 200 μm cellulose tube using a syringe pump at a rate of 30 $\mu\text{l/min}$.

Plane wave ultrasound data was acquired using a programmable ULA-OP system (MSD Lab, University of Florence). Receive gains were chosen such that the “low” gain was the maximum possible before image saturation occurred (22dB), and the “high” gain was the maximum possible before the half amplitude pulse was saturated (30dB). A pulse repetition frequency of 4000Hz was used to ensure as little MB flow between frames as possible. A pulse sequence: [A_{low_gain}, -A_{low_gain}, (A/2)_{low_gain}, A_{high_gain}, -A_{high_gain}, (A/2)_{high_gain}] was repeated 100 times, where A represents pulse amplitude.

The results shown in Figure 3 illustrate a mean 9.3dB increase in contrast to tissue ratio (CTR) for the so called “HDR” images created using techniques illustrated when

compared to those images processed using just “high” gain data. Furthermore, the results illustrate a 29% average increase in contrast to acoustic noise ratio (CANR) in relation to the HDR images when compared to images processed using just the low gain data.

5

It will be appreciated that techniques in accordance with the illustrative methods and examples may offer various advantages when imaging non-linear responses from an ultrasound target. In particular, the techniques described do not change MB behaviour since transmit pulse is unchanged. Techniques can make use of a high frame rate so
10 that information on a fast physiological timescale is not sacrificed. Techniques can be easily implemented by existing ultrasound systems. Techniques can be used in existing commercially available systems to reduce any obscuring signal due to saturation of strong linear signals during use of non-linear imaging modes. Techniques can be useful in research scenarios when it is required to extract MB signal from a vasculature
15 phantom, for example, experiments testing new imaging techniques and characterisation of MB properties. Techniques can be used to investigate non-linear propagation in tissue.

Although illustrative embodiments of the invention have been disclosed in detail
20 herein, with reference to the accompanying drawings, it is understood that the invention is not limited to the precise embodiment and that various changes and modifications can be effected therein by one skilled in the art without departing from the scope of the invention as defined by the appended claims and their equivalents.

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CLAIMS

1. A method of detecting and imaging non-linear components of ultrasound signals returned by a target including a non-linear scatterer, said method comprising:
 - 5 (a) transmitting a first ultrasound pulse into said target;
 - (b) receiving a first ultrasound signal including linear and non-linear components from said target at two gain levels, said gain levels having a relationship which is known and said gain levels being such that: at one of said gain levels, said received first ultrasound signal comprises detectable non-linear components;
 - 10 (c) constructing a replacement first ultrasound signal for said received first ultrasound signal comprising detectable non-linear components by: combining a translation of said received first signal at a first gain level with said received first signal comprising detectable non-linear components, said translation and construction being based on said known relationship between gain levels;
 - 15 (d) transmitting a second pulse into said target and performing steps (b) and (c) in relation to said second pulse to construct a replacement second signal for said received second signal comprising detectable non-linear components; and
 - (e) combining said replacement first signal and said replacement second signal to detect said non-linear components of said ultrasound signals returned by said target to
 - 20 produce an image of a non-linear scatterer in said target.
2. A method according to claim 1, wherein said first ultrasound signal comprises an ultrasound pulse having a known amplitude and phase and said second ultrasound signal comprises an ultrasound signal having a known amplitude and phase.
- 25 3. A method according to claim 1 or claim 2, wherein receiving from said target at said two gain levels comprises: reception of distinct transmissions of said first or second ultrasound pulse.
- 30 4. A method according to claim 1 or claim 2, wherein receiving from said target at said two gain levels comprises: concurrent reception of a single transmission of said first or second ultrasound pulse.
5. A method according to any preceding claim, wherein said translation of said
- 35 first received signal at said first gain level comprises: linearly mapping said first received signal at said first gain level to said gain level at which said received first signal comprising detectable non-linear components is received.

6. A method according to any preceding claim, wherein construction of said replacement first ultrasound signal comprises: replacing a saturated portion of said received first signal comprising detectable non-linear components with an equivalent portion of signal from said translation of said first received signal at said first gain level.
7. A method according to any preceding claim, wherein combining said replacement first signal and said replacement second signal to detect said non-linear components of said ultrasound signals returned by said target comprises use of a multi-pulse non-linear imaging ultrasound method.
8. A method according to claim 7, wherein said multi-pulse non-linear imaging ultrasound method comprises: a multi-pulse amplitude modulation technique.
9. A method according to claim 7 or claim 8, wherein said multi-pulse non-linear imaging ultrasound method comprises: a multi-pulse phase modulation technique.
10. A method according to any preceding claim, wherein said non-linear scatterer included in said target comprises: an ultrasound contrast agent.
11. A method according to claim 10, wherein said ultrasound contrast agent comprises: one or more of: microbubbles or nanodroplets.
12. A method according to claim 10 or 11, wherein an amplitude of said first and second ultrasound signals is selected to be above a threshold at which a non-linear response from said ultrasound contrast agent is activated.
13. A method according to any preceding claim, wherein constructing said replacement first or second ultrasound signal further comprises: smoothing a transition of signal associated with said translation of said received first signal at said first gain level to a portion of said received first signal comprising detectable non-linear components.
14. A computer program product operable, when executed on a computer, to perform the method of any one of claims 1 to 13.

15. An ultrasound apparatus configured to detect and image non-linear components of ultrasound signals returned by a target including a non-linear scatterer, said apparatus comprising a transducer configured to:
- (a) transmit a first ultrasound pulse into said target; and
 - 5 (b) receive a first ultrasound signal including linear and non-linear components from the target at two gain levels, said gain levels having a relationship which is known and the gain levels being such that: at one of said levels, said received first ultrasound signal comprises detectable non-linear components;
- processing logic configured to: (c) construct a replacement first ultrasound signal for
- 10 said received first ultrasound signal comprising detectable non-linear components by: combining a translation of said received first signal at a first gain level with said received first signal comprising detectable non-linear components, said translation and construction being based on the known relationship between gain levels;
- said transducer and processing logic also being configured to:
- 15 transmit a second pulse into the target and perform steps (b) and (c) in relation to said second pulse to construct a replacement second signal for said received second signal comprising detectable non-linear components; and
- detection and imaging logic configured to combine said replacement first signal and said replacement second signal to detect said non-linear components of said ultrasound
- 20 signals returned by the target and produce an image of a non-linear scatterer in said target.

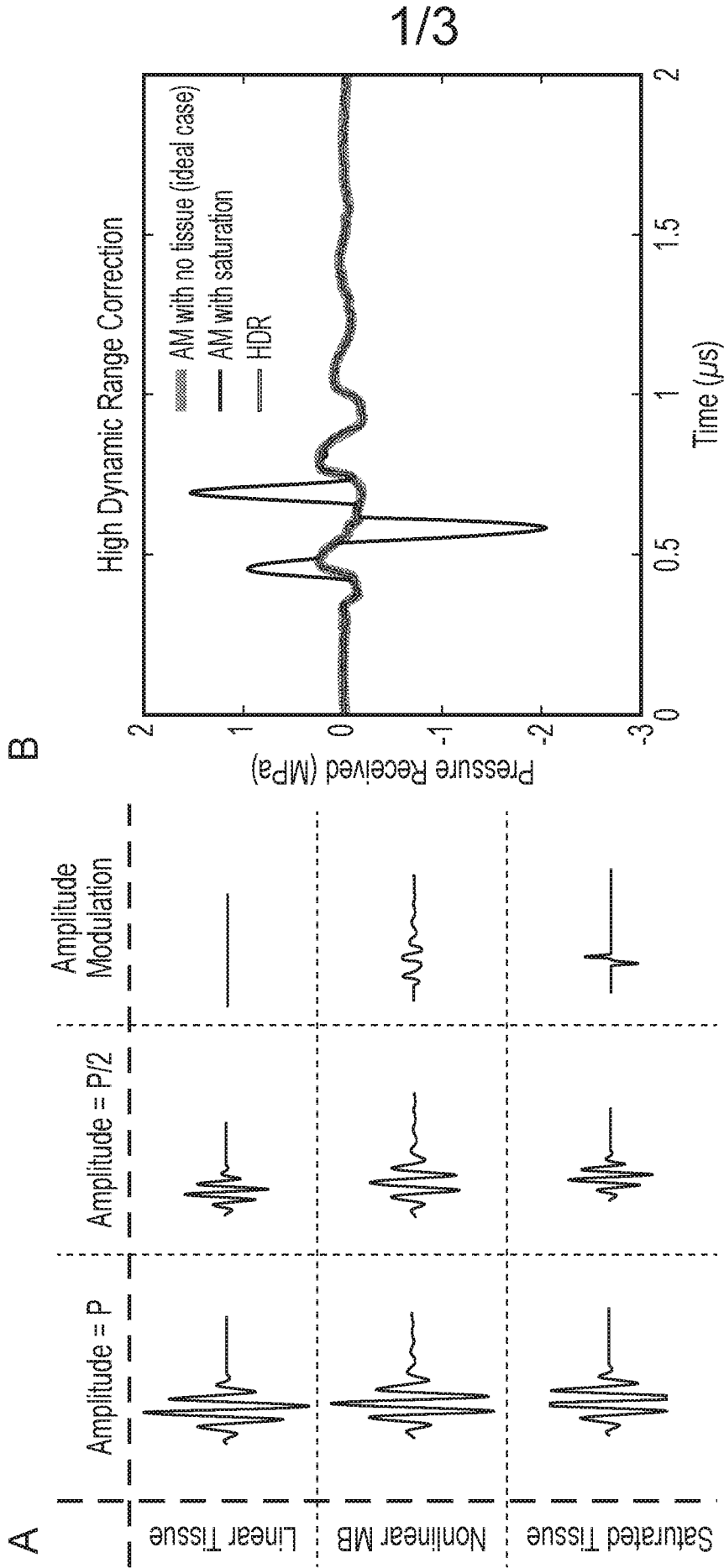


FIG. 1

2/3

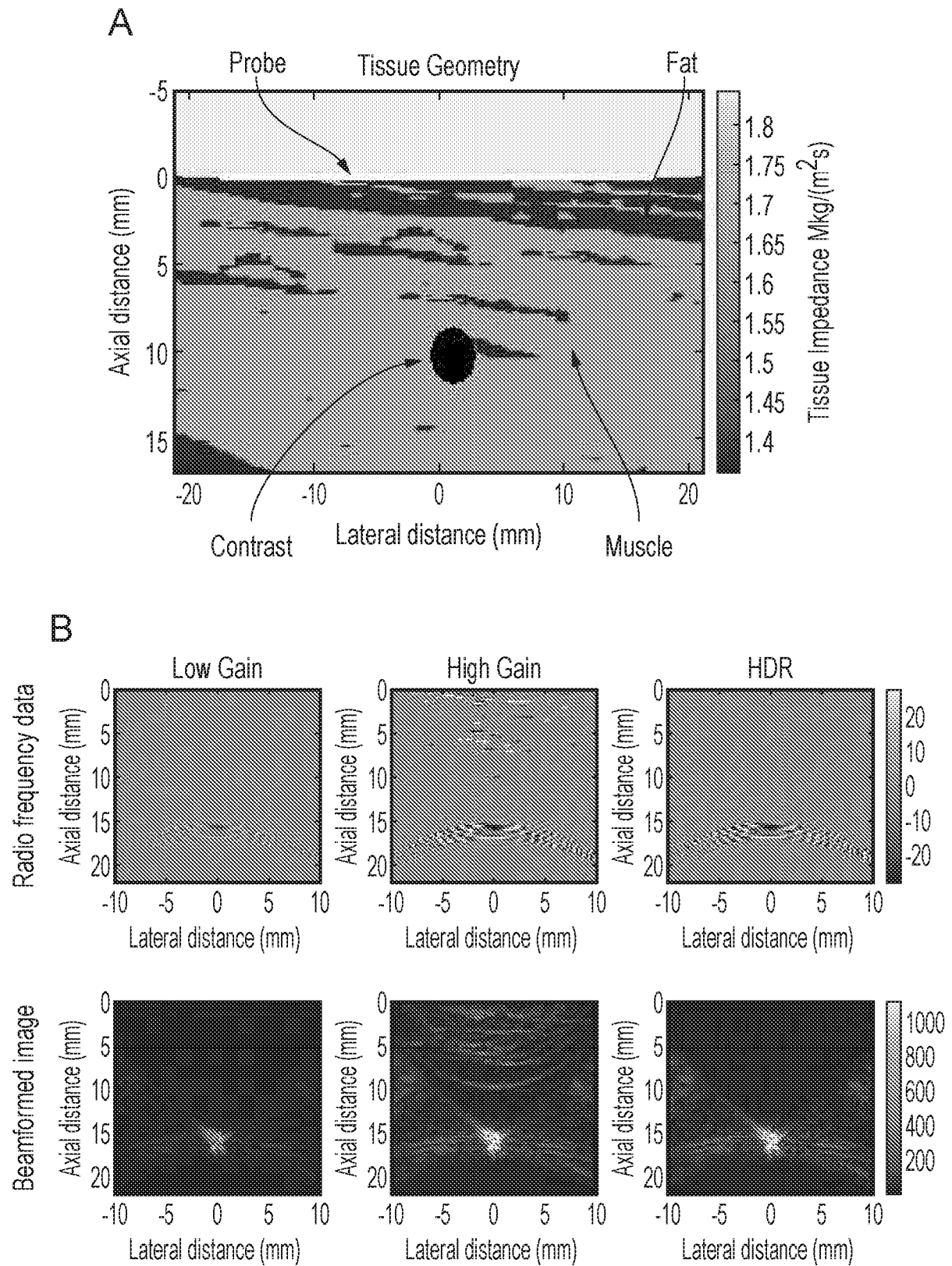


FIG. 2

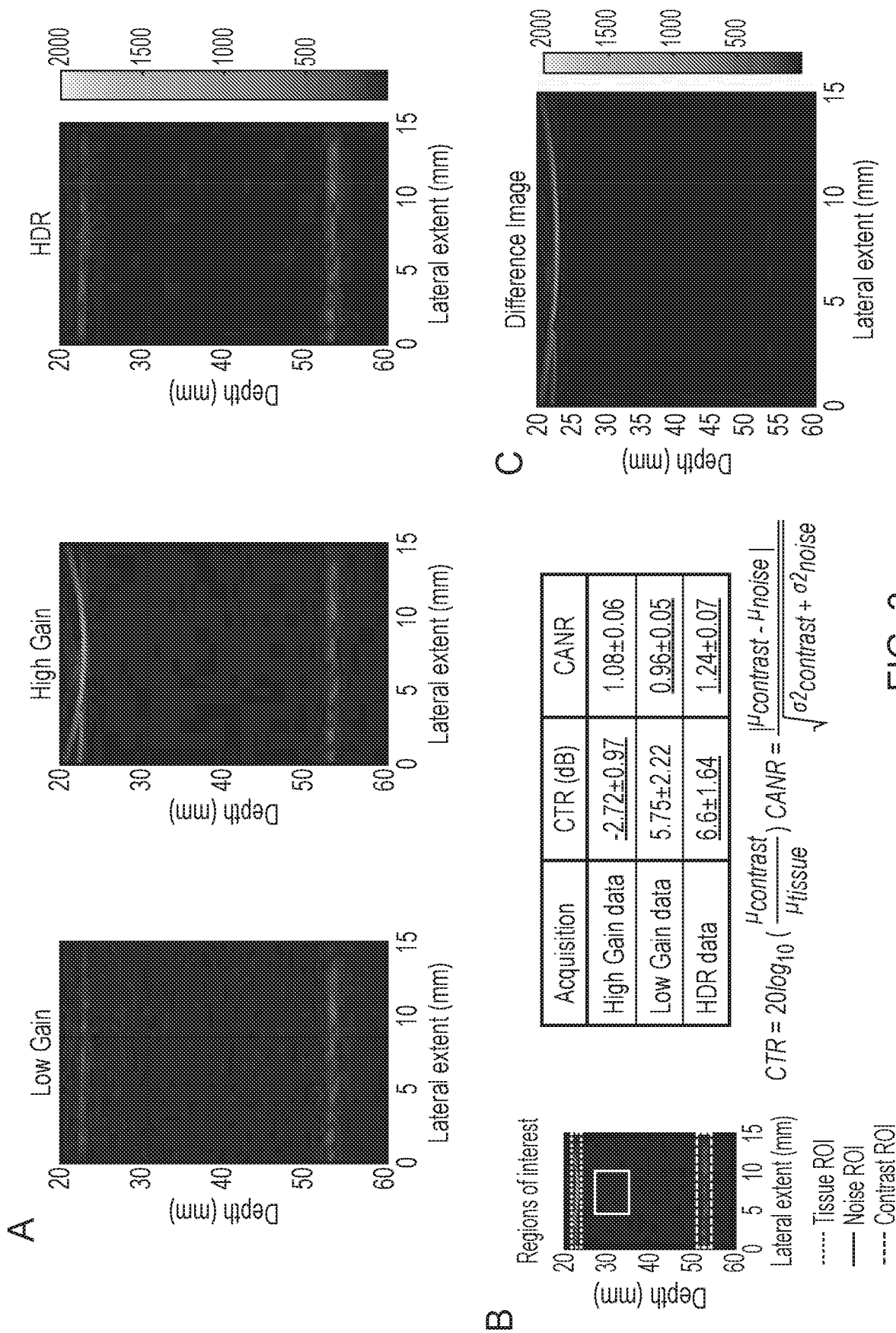


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/053623

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01S7/52 A61B8/08
ADD. G01S15/89

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)
G01S A61B

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)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017/071569 A1 (SATO TAKESHI [JP]) 16 March 2017 (2017-03-16)	1-5,7-15
A	abstract; figures 9, 14 paragraphs [0087], [0088] paragraph [0090] - paragraph [0096] paragraphs [0137], [0139], [0140] paragraphs [0143], [0158], [0159] -----	6
A	EP 2 952 137 A1 (HITACHI ALOKA MEDICAL LTD [JP]) 9 December 2015 (2015-12-09) abstract; figure 4 paragraphs [0007], [0033] - [0051] -----	1,8,14, 15



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

3 March 2020

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10/03/2020

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Knoll, Bernhard

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2019/053623

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP W02014119746 A1	26-01-2017
		US 2015351723 A1	10-12-2015
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