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(54) METHODS FOR ACQUISITION AND DISPLAY IN ULTRASOUND IMAGING

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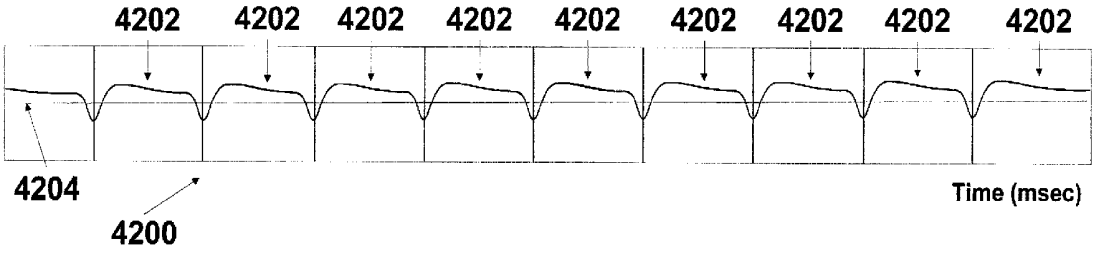
(57) **ABSTRACT**

In general, the invention provides methods for use in the acquisition and display of ultrasound images. In particular, the invention provides methods for displaying ultrasound images using a persistence algorithm, gating ultrasound acquisition based on subject respiration, triggering ultrasound acquisition based on subject ECG, and destroying bubble contrast agents during imaging. The methods may be employed with any suitable ultrasound system.



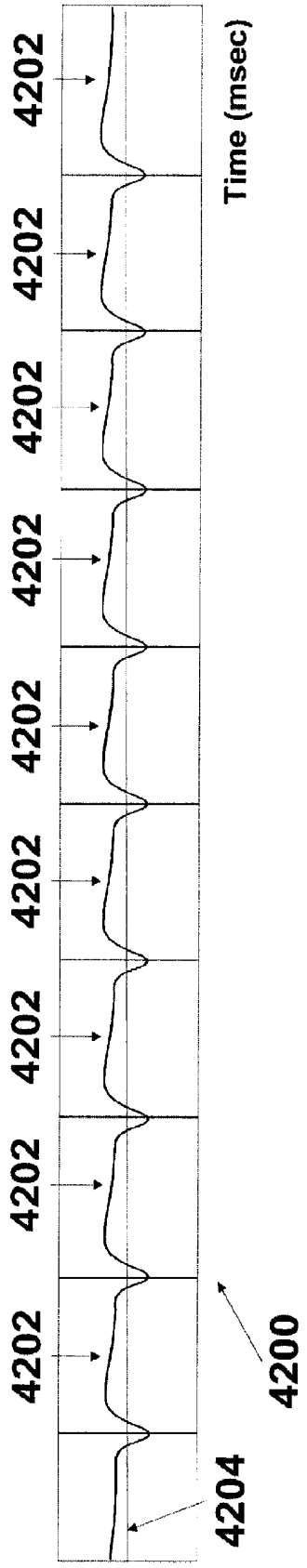


FIG. 1

FIG. 2

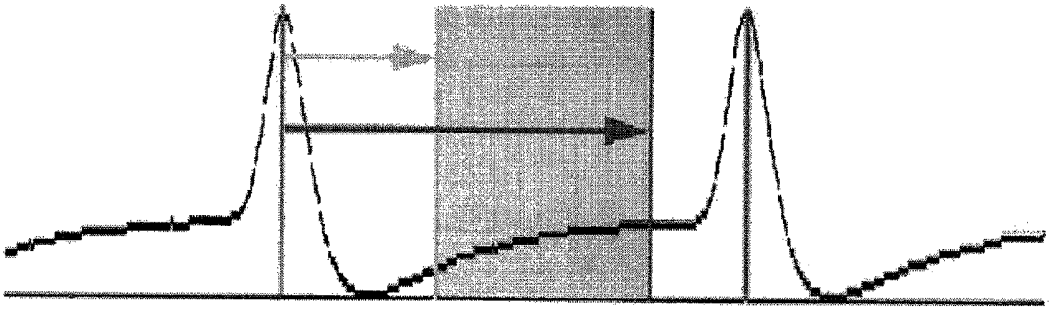


FIG. 3

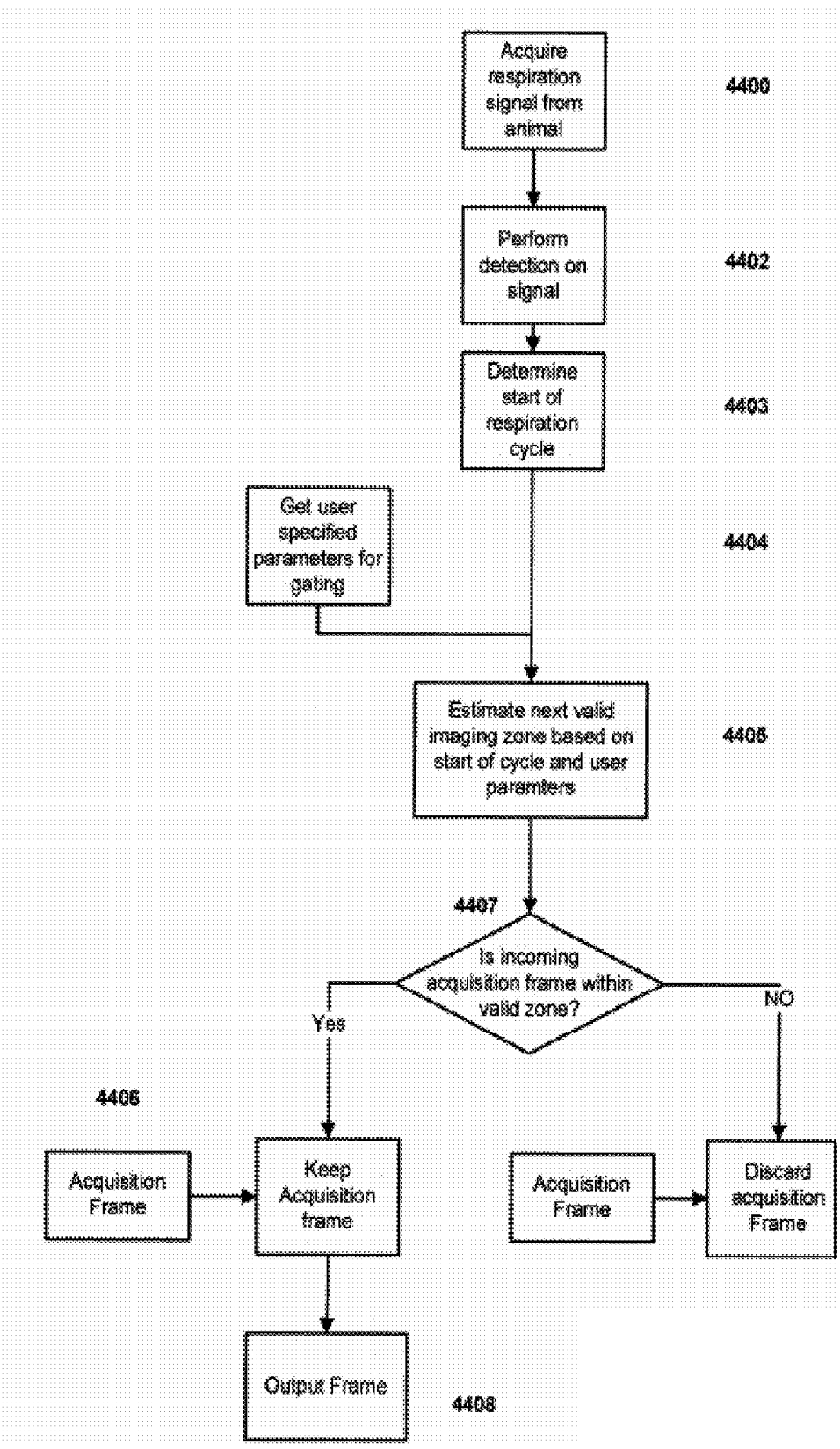

Acquire respiration signal from animal
4400
Perform detection on signal
4402
Determine start of respiration cycle
4403
Get user specified parameters for gating
4404
Estimate next valid imaging zone based on start of cycle and user paramters
4405
4407
Is incoming acquisition frame within valid zone?
Yes
NO
4406
Acquisition Frame
Keep Acquisition frame
Acquisition Frame
Discard acquisition Frame
Output Frame
4408

FIG. 4

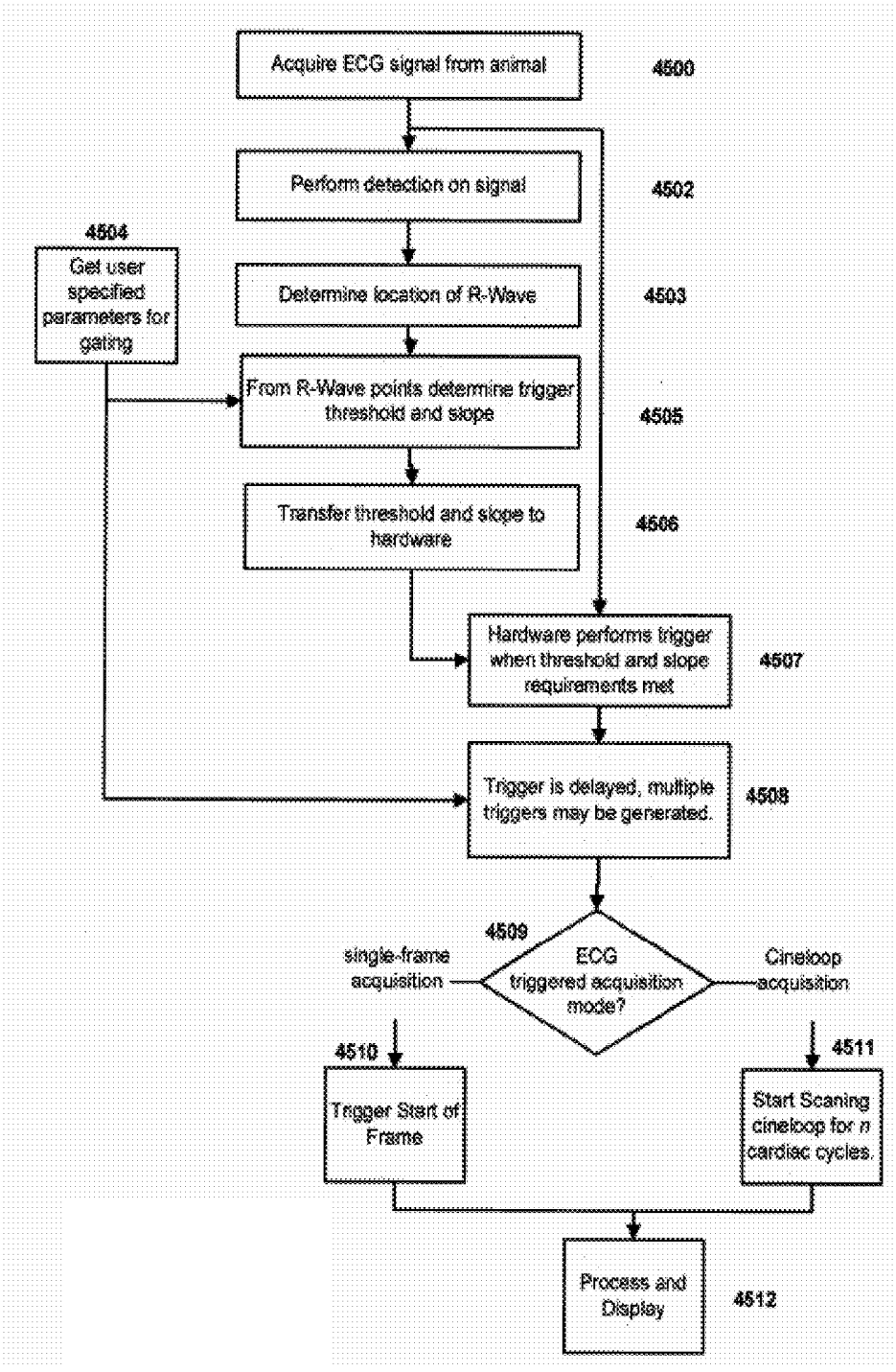

Acquire ECG signal from animal
4500
Perform detection on signal
4502
4504
Get user specified parameters for gating
Determine location of R-Wave
4503
From R-Wave points determine trigger threshold and slope
4505
Transfer threshold and slope to hardware
4506
Hardware performs trigger when threshold and slope requirements met
4507
Trigger is delayed, multiple triggers may be generated.
4508
4509
single-frame acquisition
ECG triggered acquisition mode?
Cineloop acquisition
4510
Trigger Start of Frame
4511
Start Scaning cineloop for n cardiac cycles.
Process and Display
4512

FIG. 5

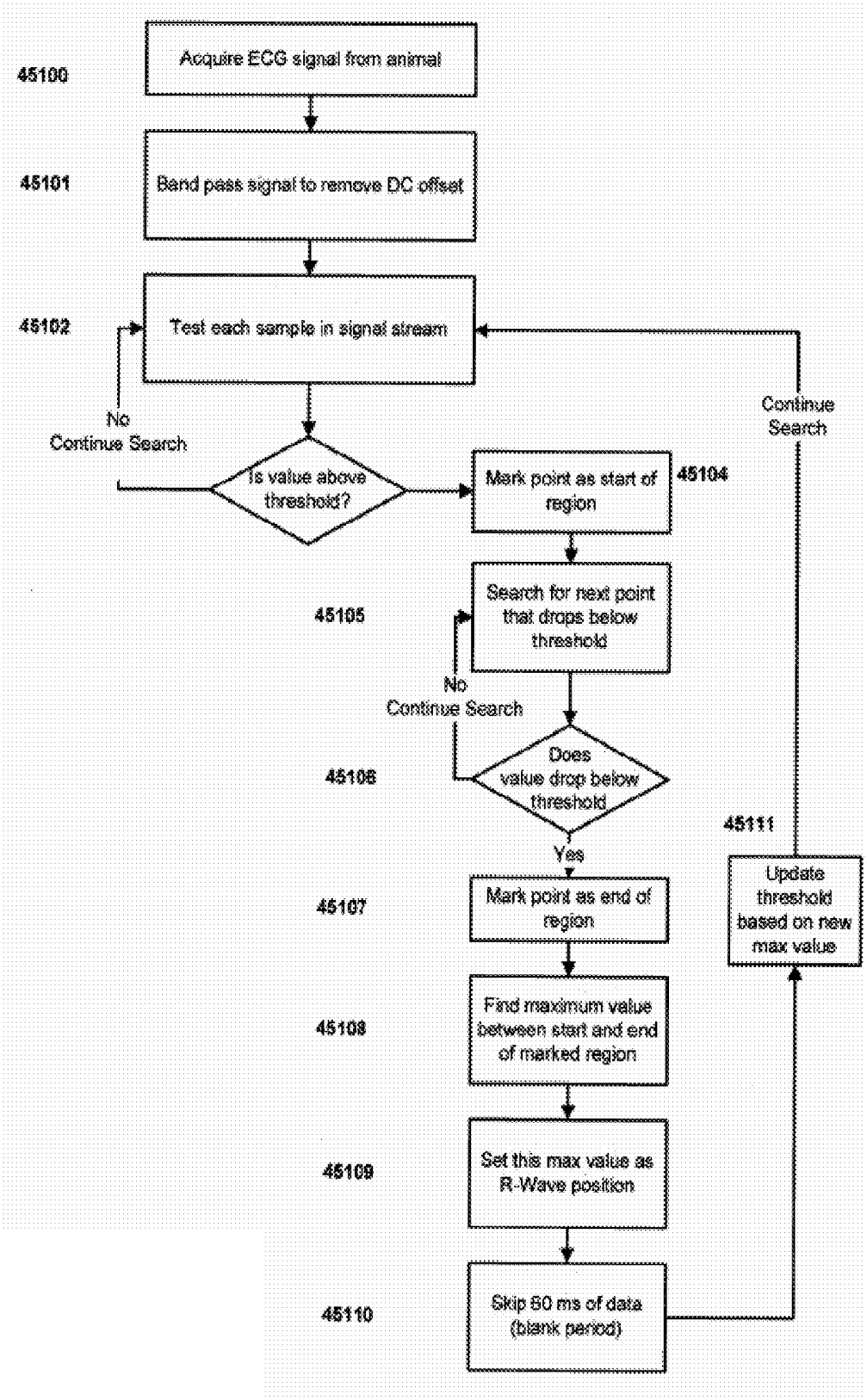
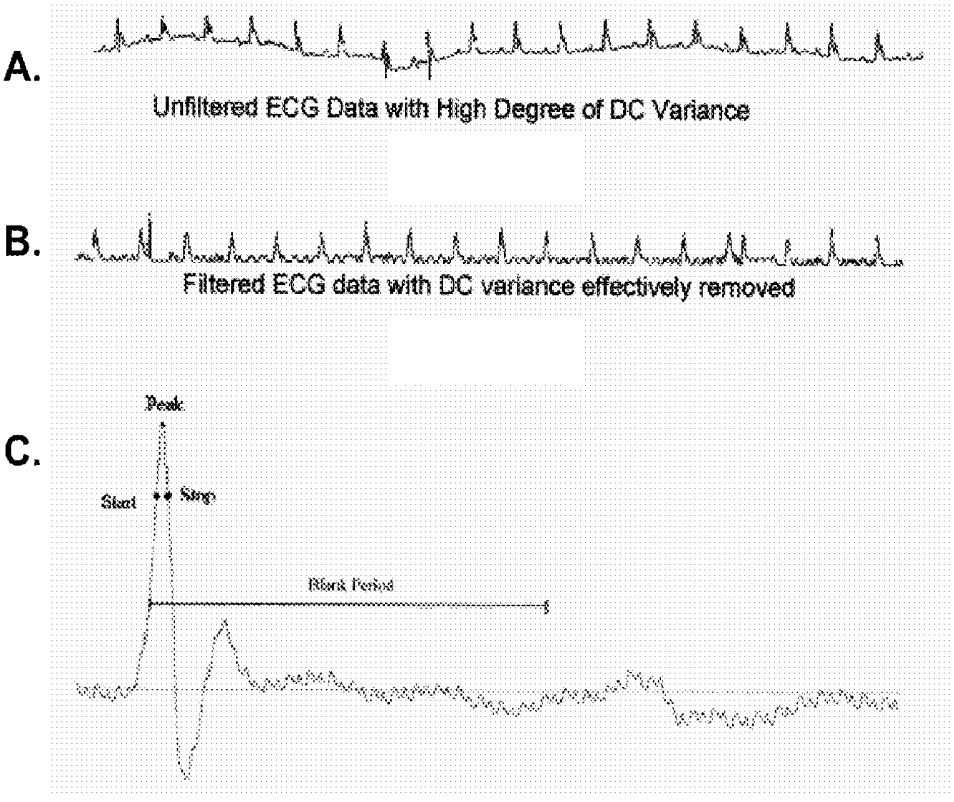

45100
Acquire ECG signal from animal
45101
Band pass signal to remove DC offset
45102
Test each sample in signal stream
No
Continue Search
Is value above threshold?
Continue Search
Mark point as start of region
45104
45105
Search for next point that drops below threshold
No
Continue Search
45106
Does value drop below threshold
Yes
45107
Mark point as end of region
45108
Find maximum value between start and end of marked region
45109
Set this max value as R-Wave position
45110
Skip 60 ms of data (blank period)
45111
Update threshold based on new max value

FIG. 6


A.
Unfiltered ECG Data with High Degree of DC Variance
B.
Filtered ECG data with DC variance effectively removed
C.
Peak
Start
Stop
Blank Period

METHODS FOR ACQUISITION AND DISPLAY IN ULTRASOUND IMAGING

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Application Nos. 61/192,690 and 61/192,661, both filed Sep. 18, 2008 and both of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention relates to the field of high frequency ultrasound imaging systems.

SUMMARY OF THE INVENTION

[0003] The invention provides various methods for use in the acquisition and display of ultrasound imaging. The methods are preferably employed in conjunction with high frequency ultrasound imaging using an arrayed transducer.

[0004] In one aspect, the invention features a method for frame persistence implemented by an ultrasound imaging system by obtaining a plurality of frames of ultrasound at a baseline frame rate (FR_0); processing a portion of the plurality of frames of ultrasound at a processing rate (PR), wherein the portion includes a first frame having a first plurality of data points; applying a persistence routine to at least one of the first plurality of data points, wherein the persistence routine combines the at least one of the first plurality of data points with a corresponding stored data point based on a user defined persistence setting, FR_0, and PR, to produce at least one persistence processed data point; storing the at least one persistence processed data point to replace the previously stored data point; and generating a persistence processed output frame from the at least one persistence processed data point. The persistent routine is for example:

$$y(n)=(1-(1-\alpha)^p)\cdot x(n)+(1-\alpha)^p\cdot y(n-1),$$

where p is the ratio FR_0/PR, α is the user defined persistence setting and is greater than 0 and less than 1, n is the frame index, y(n) is the persistence processed data point, x(n) is the at least one of the first plurality of data points, and y(n−1) is the corresponding stored data point, wherein the value of y(n−1) is set to 0 for n=1. The plurality of frames may include B-Mode data, Color Flow image data, or Power Doppler image data. The method may further include displaying the persistence processed output frame on a display. The method may also be repeated for subsequent frames.

[0005] The invention further features a method for destroying contrast agent bubbles by providing a subject to which has been administered contrast agent bubbles; scanning a region of interest in the subject with ultrasound; receiving a bubble destruction command; transmitting at least one ultrasound pulse into the region of interest, wherein the ultrasound pulse is transmitted at a mechanical index sufficient to destroy bubbles in the region of interest (e.g., greater than about 0.6); and resuming scanning of the region of interest. The region of interest may include one or more focal zones, and the destruction of bubble may occur in each focal zone. A specific bubble destruction sequence of ultrasound includes transmission at 10-20 MHz with a 4 cycle pulse, with a plurality of focal zones evenly spaced over a depth of the region of interest (ROI), at 100% TX power at a mechanical index (MI) greater than 0.6, wherein 10-20 MHz pulses are fired at a Pulse Repetition Frequency (PRF) of 25 kHz and above for up to 1 s. In various embodiments, scanning of the region of interest is discontinued prior to bubble destruction. Alternatively, the mechanical index of ultrasound transmission is increased in response to the bubble destruction command, while scanning the region of interest. The ultrasound employed in scanning may have a wider bandwidth than ultrasound employed in bubble destruction. Scanning of the region of interest and bubble destruction may occur using the same or different transducers. After bubble destruction, the method may include monitoring for reperfusion of bubble contrast agent into the region of interest or monitoring for determining the circulating amount of bubble contrast agent, e.g., when the contrast agent is targeted to a particular tissue.

[0006] The invention also features a method for respiration gating during ultrasound imaging by acquiring a respiration signal from a subject; determining a start of a respiration cycle in the respiration signal; setting a valid zone based on the start of the respiration cycle and user defined offset and/or duration; acquiring a plurality of frames of ultrasound, e.g., at an acquisition rate of at least 200 frames per second; discarding one or more frames of the plurality of frames acquired outside the valid zone; and outputting remaining frames of the plurality of frames acquired inside the valid zone. The acquired plurality of frames may also be time-stamped to indicate when each frame is acquired.

[0007] The invention further features a method for ECG triggered acquisition during ultrasound imaging by acquiring, at a host computer, an ECG signal from a subject; determining, at the host computer, an R-wave point in the ECG signal; determining, at the host computer, a trigger point threshold and a trigger slope based on the R-wave point; transferring the trigger point threshold and the trigger slope to a programmable logic device; and triggering, by the programmable logic device, the acquisition of ultrasound based on the trigger point threshold and the trigger slope, e.g., at a rate of at least 200 frames per second. The method may be employed to acquire a cineloop that starts at a specified point in a cardiac cycle and runs for a specified number of cardiac cycles. The method may be used to acquire one or more of B-Mode data, Color Doppler Mode data, Power Doppler Mode data, Contrast Mode data, and 3D Mode data.

[0008] Any of the methods of the invention may be employed with each other and with any of the ultrasonic systems described herein. The methods are particularly useful in high frequency ultrasound imaging (greater than 20 MHz) and/or in imaging small animals.

[0009] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. **1** shows an exemplary respiration waveform **4200** from a subject where the x-axis represents time in milliseconds (ms) and the y-axis represents voltage in millivolts (mV).

[0011] FIG. **2** shows a valid acquisition zone where the start of the respiration cycle combined with the user's specifications denotes the valid acquisition zone.

[0012] FIG. **3** illustrates an exemplary method for respiration gating.

[0013] FIG. **4** illustrates an exemplary method of ECG triggered acquisition.

[0014] FIG. **5** illustrates one of various methods that exist to detect the R-Wave events on an ECG signal.

[0015] FIG. **6**A shows unfiltered ECG data with a high degree of DC variance.

[0016] FIG. **6**B shows filtered ECG data with the DC variance effectively removed.

[0017] FIG. **6**C illustrates an exemplary single pulse of ECG data showing a threshold trigger point and a blank period.

DETAILED DESCRIPTION OF THE INVENTION

[0018] In general, the invention provides methods for use in the acquisition and display of ultrasound images. In particular, the invention provides methods for displaying ultrasound images using a persistence algorithm, gating ultrasound acquisition based on subject respiration, triggering ultrasound acquisition based on subject ECG, and destroying bubble contrast agents during imaging. The methods may be employed with any suitable ultrasound system. An exemplary system is disclosed in U.S. Publication No. 2007/0239001. Suitable ultrasound systems are also available from VisualSonics, Inc. (VEVO® 2100).

Persistence Processing

[0019] Typically, persistence processing combines information from previous frames of B-Mode detected data with the most recent frame of B-Mode detected data to produce an output frame. Persistence can also be applied to other data sets such as Color Flow or Power Doppler overlays or image data processed with harmonic imaging methods. A persistence algorithm is applied to each data point in the image. An equation used to apply persistence is:

$$y(n)=\alpha\cdot x(n)+(1-\alpha)\cdot y(n-1) \quad \text{Eq. 1}$$

where $0<\alpha<1$, n is the frame index, y(n) is the new persisted output value, x(n) is the new incoming data point, and y(n−1) is the previous persisted output value. Data represented by x(n) and y(n) have the same spatial coordinates, which have been left out for clarity. The parameter α is selected for each specific persistence setting (e.g. "low", "med", "high", etc.) in order to impart the desired degree of persistence to the displayed data. If α is 1.0, then no persistence is applied. For low, medium and high persistence, typical settings for α are in the ranges 0.71 to 0.99, 0.31 to 0.7 and 0.01 to 0.3 respectively.

[0020] For small animal imaging and other high frequency applications, the B-Mode acquisition frame rates may vary over a wide range, for example from less than 100 frames per second (fps) to approximately 500 frames per second. During real time acquisition and display of data, otherwise known as "live scanning," it may be necessary to decimate the frames prior to processing and display. All acquisition frames can be saved in an RF buffer. Data transfer bandwidth over busses from hardware to a host machine, for example, PCI express or ethernet, is limited, and the total number of acquisition frames may not be able to be transferred in real time to the host machine. For example, the hardware might acquire frames at 300 fps (acquisition frame rate), but, if the data transfer rate is 100 fps, then during live scanning only every third frame is processed. The difference in the time of acquisition of sequential frames that are processed by the persistence algorithm will vary depending on the number of frames that are skipped. In some cases, it is desirable that the amount of persistence applied be approximately constant relative to the acquisition time frame. For example, during live scanning, frames acquired at 300 fps designated F**1**, F**2**, F**3**, F**4**, . . . have acquisition times of 0, 3.33, 6.67, 10, 13.33, 16.67, . . . milliseconds relative to the start time. Because of data transfer restrictions, every third frame is transferred and processed, so frames F**1**, F**4**, F**7**, . . . etc. will undergo persistence processing. The time of acquisition of the frames being persistence processed during live scanning will then be 0, 10, 20, . . . milliseconds, and the acquisition rate of the data set being processed is 100 frames per second. If, once live scanning is halted, all acquired frames that had been saved in RF Buffer are transferred sequentially, the frames being persistence processed will have acquisition times of 0, 3.33, 6.67, 10, 13.33, 16.67, . . . milliseconds.

[0021] Equation 1 can be modified so that that regardless of whether all acquisition frames are processed or some frames are skipped, the frames corresponding to equivalent acquisition times have the approximately the same amount of persistence applied.

[0022] In Equation 1, y(n) can also be expressed as the convolution of x(n) with a function h(n):

$$y(n)=\alpha\cdot x(n)*h(n) \quad \text{Eq. 2,}$$

where $h(n)=(1-\alpha)^n$, * is the convolution operator, and n is the frame index.

[0023] The factor α may be chosen for each persistence setting for a baseline frame rate (FR_0). If the acquisition rate of the data set being processed (PR) is different from the baseline rate FR_0 by a factor p, i.e., $p=FR_0/PR$, the signal x(n) that is undergoing processing is effectively resampled at a lower rate, that is, it is decimated by a factor p. The function h(n) must then be replaced by the function $h'=(1-\alpha)^{pn}$, and the persistence algorithm becomes:

$$y(n)=\text{persistScale}\cdot\alpha\cdot x(n)+(1-\alpha)^p\cdot y(n-1) \quad \text{Eq. 3}$$

where p is the ratio FR_0/PR, and persistScale is the ratio of the areas under the functions h(n) and h'(n) given by

$$persistScale=\frac{\sum_{k=0}^{\infty}(1-\alpha)^k}{\sum_{k=0}^{\infty}(1-\alpha)^{kp}}=\frac{1-(1-\alpha)^p}{\alpha}. \quad \text{Eq. 4}$$

[0024] For example, for a "med" persistence setting and a baseline frame rate of 300 fps, the value for α is selected as 0.5. If the data are processed and displayed at a rate of 100 fps, the persistence algorithm is:

$$y(n)=\frac{1-(1-0.5)^3}{0.5}\cdot(0.5)\cdot x(n)+(1-0.5)^3\cdot y(n-1). \quad \text{Eq. 5}$$

[0025] Typically, all data in a frame are subjected to the persistence processing, but, in certain embodiments, only a portion of the data is subjected to the processing. It will also

be appreciated by one skilled in the art that the above method of applying persistence to frames of data which may have variable processing rates may be applied to any such data, e.g., Color Flow image data and Power Doppler image data.

Respiration Gating

[0026] The invention also features a method of gating ultrasound acquisition based on the respiration waveform of a subject, typically a small animal. FIG. **1** shows an exemplary respiration waveform **4200** from a subject where the x-axis represents time in milliseconds (ms), and the y-axis represents voltage in millivolts (mV). A typical respiration waveform **4200** includes multiple peak positions or plateaus **4202**, one for each respiration cycle of the subject. As shown in FIG. **1**, a reference line **4204** can be inserted on the waveform **4202**. The portions of the respiration waveform **4200** above the reference line **4204**, are peaks or plateaus **4202**, and generally represent the period when the subject's movement due to breathing has substantially stopped. By "substantially stopped" is meant that a subject's movement due to breathing has stopped to the point at which the collection of ultrasound data is desirable because of a reduction in artifacts and inaccuracies that would otherwise result in the acquired image due to breathing motion. A subject's motion due to breathing substantially stops for a period of approximately 100 to 2000 milliseconds during a respiration cycle. The period during a subject's respiration cycle during which that subject's motion due to breathing has substantially stopped may vary depending on several factors including, animal species, body temperature, body mass, or anesthesia level.

[0027] The invention features a method for gating retention of ultrasound based on the respiration cycle. For example, a threshold value can be selected, and a time position can be recorded when the respiration signal exceeds the threshold. When the signal falls below the threshold again, a second time position can be recorded. The highest signal value between these two points can denote a peak position. The peak position can indicate the start of the respiration cycle. The user can specify additional information such as a custom offset from the start of the cycle. The user can also specify a duration during which to allow acquisition. As shown in FIG. **2**, the start of the respiration cycle combined with the user's specifications denotes a valid acquisition zone, e.g., when frames can be acquired without motion artifact.

[0028] Frames can be continuously acquired at a high rate. Following acquisition, each frame can be tested to determine if the frame was acquired during the valid period. If not, the frame can be discarded. An exemplary method for respiration gating is illustrated in FIG. **3**. At **4400**, a respiration signal is acquired from an animal. At **4402**, the respiration signal is processed. At **4403**, a start of a respiration cycle is determined from the processed respiration signal. At **4404**, one or more user supplied values, such as a requested offset, a duration, and the like, is received. The one or more user supplied values allows the user to control the timing of a valid region of acquisition within a respiration cycle. At **4405**, the start of the respiration cycle and the one or more user supplied values is used to define a valid region. At **4406**, frames can be continuously acquired at an acquisition rate. The acquisition rate can be, for example, 200 frames per second. Each frame can be time-stamped to indicate when the frame is acquired. At **4407**, frames that are acquired outside the valid zone can be discarded. At **4408**, frames acquired inside the valid region are output.

[0029] The respiration waveform **4200** including the peaks **4202** can be determined by the respiration detection software from electrical signals delivered by ECG electrodes which can detect muscular resistance when breathing. For example, muscular resistance can be detected by applying electrodes to a subject's foot pads. By detecting changes in muscular resistance in the foot pads, the respiration detection software can generate the respiration waveform **4200**. Thus, variations during a subject's respiration cycle can be detected, and ultrasound data can be acquired during the appropriate time of the respiration cycle when the subject's motion due to breathing has substantially stopped. For example, ultrasound data samples can be captured during the approximate 100 milliseconds to 2000 millisecond period when movement has substantially ceased. A respiration waveform **4200** can also be determined by the respiration detection software from signals delivered by a pneumatic cushion (not shown) positioned underneath the subject. Use of a pneumatic cushion to produce signals from a subject's breathing is known in the art. A respiration waveform can be produced with a strain gauge plethysmograph. Methods for detecting respiration waveforms are also known in the art, e.g., as described in U.S. Publication No. 2006/0241446.

[0030] The respiration detection software can convert electrical information from the ECG electrodes (or other detector) into an analog signal that can be transmitted to the ultrasound system. The analog signal can be further converted into digital data by an analog-to-digital converter, which can be included in a signal processor or can be located elsewhere, after being amplified by an ECG/respiration waveform amplifier. In one embodiment, the respiration detection element can comprise an amplifier for amplifying the analog signal for provision to the ultrasound system and for conversion to digital data by the analog-to-digital converter. Using digitized data, respiration analysis software located in a memory can determine characteristics of a subject's breathing including respiration rate and the time during which the subject's movement due to respiration has substantially stopped.

[0031] Cardiac signals from the electrodes and the respiration waveform signals can be transmitted to an ECG/respiration waveform amplifier to condition the signals for provision to an ultrasound system. It is recognized that a signal processor or other such device may be used instead of an ECG/respiration waveform amplifier to condition the signals. If the cardiac signal or respiration waveform signal from the electrodes is suitable, then use of the amplifier is unnecessary.

ECG Triggered Acquisition

[0032] ECG triggered acquisition can be used to acquire and display images at a specified point in a cardiac cycle. ECG triggered acquisition can also be used to acquire a cineloop that starts at a specified point in the cardiac cycle and runs for a specified number of cardiac cycles. ECG triggered acquisition is supported, for example, in B-Mode, Color Doppler Mode, Power Doppler Mode, Contrast Mode, 3D Mode, etc. In one aspect, ECG triggered acquisition can be combined with respiration gating, e.g., as described herein or in U.S. Publication No. 2006/0241446.

[0033] Generally, there are two components to ECG triggered acquisition: software signal processing and hardware triggering. Software signal processing determines the trigger threshold and slope from an incoming physiological ECG signal, while hardware triggering uses the slope and threshold to perform the actual triggering in real time. This method

permits a complicated algorithm to be executed on a host computer, while a very small but fast segment is run on the hardware.

[0034] An exemplary method of ECG triggered acquisition is illustrated in FIG. **4**. At step **4500**, an ECG signal is acquired from a subject, e.g., a small animal. At step **4502**, the signal is processed, e.g., according to a detection algorithm. At step **4503**, a R-Wave point is identified in the ECG signal. Various methods exist to detect R-Wave events on an ECG signal. An exemplary method is described here. Other methods may be used as would be understood by one skilled in the art. The operations are shown in FIG. **5**.

[0035] In FIG. **5**, an incoming ECG signal **45100** is first filtered using a band-pass FIR filter **45101** with a pass band between 100 Hz and 200 Hz. Other frequency bands may be used depending on the application (for example, in a human the ECG rate is much slower than a small animal and these values may be modified). Filtering effectively removes most of the DC offset. FIGS. **6**A and **6**B show the pre and post filtered signal.

[0036] The detection algorithm can use a threshold detection scheme with a dynamically updating threshold value. Each value in the filtered ECG signal stream is then tested to determine if it is above a threshold value **45102**. If the value exceeds the threshold **4504**, this point is marked as the start of a region (labelled as "Start" in FIG. **6**C). Stream values are tested to determine when the value drops below the threshold **45105**. If the value drops below the threshold **45106**, this point is marked as the end of the region **45107** (labelled as "Stop" in FIG. **6**C).

[0037] The maximum value is then found between the start and stop points of the region **45108**. This point is the peak value and is thus the R-Wave position **4509** (labelled as "Peak" in FIG. **6**C). The slope value may be obtained around the start point.

[0038] A period of about 60 ms measured from the start of the first threshold detection can be skipped to eliminate any possible subsequent peaks from being detected too close to the pulse **45110**. This is called the Blank Period as labeled in FIG. **6**C. The duration of the blank period may depend on the time between R-Wave positions. For example, a small animal with a high heart rate may use a short blank period (for example, 30-90 ms). A larger animal, such as a human, with a slower heart rate may employ a longer blank period (for example 100-600 ms).

[0039] The current threshold point is updated based on the new peak value **45111**. The threshold can be set, for example, at about 80% of the peak value.

[0040] Returning to FIG. **4**, at step **4504**, user supplied values are collected. These user supplied values can include, for example, a requested offset from the R-Wave to perform triggering. Multiple trigger points may be selected. At step **4505**, a trigger threshold is determined, and a slope is calculated using the detected R-Wave points. In one aspect, the trigger threshold is selected to be about 80 percent of the peak of the R-Wave, although other values can be selected, for example, 70 percent or 90 percent. The slope can be determined as the slope of the ECG signal at the threshold point on the leading edge of the signal. At step **4506**, the calculated slope and the trigger threshold are transferred to hardware. The calculated slope and trigger threshold values are updated in real time approximately once per second. Updating the calculated slope and trigger threshold values allow for accounting of changes to the ECG signal. At step **4507**, the hardware performs triggering based on threshold and slope information. In another aspect, the hardware can also trigger based on a peak detection method or use an external trigger. At step **4508**, the trigger event can be delayed by a user specified amount of time, or multiple triggers may be enabled. Each subsequent trigger can be delayed by a different user specified amount of time. At step **4509**, it is determined which mode is used for ECG triggered acquisition, single-frame acquisition or cineloop acquisition. Depending on the ECG triggered acquisition mode, the trigger is used differently. If single-frame acquisition is used, then at step **4510** a single frame of data is acquired. If at step **4509** it is determined that cineloop acquisition is used, then at step **4511** a cineloop is acquired. The length of the cineloop is a user specified number of cardiac cycles. At step **4512**, the acquired data are processed and displayed.

Bubble Destruction

[0041] Contrast agents, such as microbubbles, can be used in high-frequency ultrasound imaging. For example, U.S. Publication 2006/0078501, hereby incorporated by reference, describes systems and methods for the use of microbubbles in ultrasound imaging.

[0042] Disruption-replenishment techniques typically use a continuous infusion of microbubble contrast agents, generally with a syringe pump. While the agent is flowing through the imaging plane, high power ultrasound is applied, which clears the imaging plane of microbubbles by disrupting (destroying) them. The subsequent refilling of the agent into the imaging plane can be tracked over time, giving functional information about the perfusion of tissue, namely the blood flow (slope of refill) and blood volume (plateau level). This type of functional information is valuable to the pre-clinical researcher studying differences in the perfusion of normal and diseased tissues.

[0043] A different approach to imaging microbubbles preclinically is to use the contrast agent as a marker of a particular disease state. This is accomplished by attaching (targeting) microbubbles to endothelial cells of blood vessels that express a surface marker indicative of the disease state. After allowing microbubbles to circulate for an appropriate time, e.g., at least 4 minutes, the targeted signal in a region of interest can be quantified. Then disrupting the microbubbles and performing another quantification, gives the signal level of residual freely circulating untargeted microbubbles. This allows a normalization of the measurement so that the amount of targeted signal, proportional to the level of cell surface marker being targeted, is accurately quantified.

[0044] In another embodiment, the bubble contrast agent compositions can be disrupted or popped by the ultrasound energy at a given frequency. As used throughout, "disrupted" or "destroyed" means that a microbubble is fragmented, ruptured, or cracked such that gas escapes from the microbubble. The compositions may be disrupted by ultrasound at a frequency at or above 15 MHz, 20 MHz, 30 MHz, 40 MHz, 50 MHz or 60 MHz. The destruction or popping creates a means of probing perfusion of selected tissues or a means for releasing a therapeutic payload. It will be understood that destruction of 100% of bubbles in a given region of interest is not necessary. An exemplary level of disruption is at least 75%, 80%, 85%, 90%, 95%, or even 99%.

[0045] In one aspect, bubble destruction can be performed with embodiments described herein using a high-frequency arrayed transducer. One method includes scanning a region of

interest using an ultrasound system equipped with an arrayed transducer. The region of interest is divided into one or more focal zones. A bubble destruction command provided to the ultrasound system causes scanning of the region of interest to discontinue and a pulse of ultrasound, e.g., having a narrower bandwidth than the scanning ultrasound and having a mechanical index, e.g., greater than 0.6, sufficient to destroy the bubbles, is transmitted into each focal zone, thereby destroying the bubbles. Scanning of the region of interest can then resume, e.g., to measure the rate of reperfusion with additional contrast agent or the background level of contrast agent. In an alternative approach, scanning is not discontinued, but rather the bubble destruction command results in an increase in mechanical index of the transmitted ultrasound, thereby transmitting a pulse into each focal zone and destroying the bubbles. Scanning transmission power can then be re-set to a lower mechanical index. In yet another embodiment, two different transducers are employed: one is used for scanning, and the other is used to destroy bubbles.

[0046] For example, embodiments as described herein can perform bubble destruction by initiating bubble destruction while imaging in Contrast Mode, by receiving a bubble destruction command (e.g., by pressing a key or entering a command into an ultrasound system). In one exemplary approach, embodiments of systems described herein stop scanning and the transmit (TX) beamformer is reconfigured to Burst Mode. In Burst Mode the receive (RX) beamformer is disabled (there is no image data being collected). In one aspect, Burst Mode operates at 10-20 MHz (regardless of the transducer being used), with a narrowband (e.g., 4 cycle) pulse, with a plurality (e.g., 4) of focal zones evenly spaced over the depth of the region of interest (ROI), at 100% TX power at high mechanical index (MI>0.6). Burst Mode fires 10-20 MHz pulses at a Pulse Repetition Frequency (PRF) of 25 kHz and above for the duration specified by the user (e.g., up to a max of 1 s). There are 4 pulses per image line to make up the 4 TX foci. After the specified duration is over, the TX beamformer is reconfigured for the prior state of Contrast Mode, and the system resumes imaging.

[0047] In another exemplary approach, embodiments of systems described herein continue scanning in Contrast Mode after bubble destruction is initiated, however, the TX power is set to 100% for the duration specified by the user (e.g., up to a max of 1 s), and the transmit pulse may become more narrowband. All other imaging parameters remain the same. After the specified duration is over, the TX power is reset to the prior setting of Contrast Mode, and the system continues imaging.

[0048] In yet another exemplary approach, embodiments of systems described herein stop scanning, and both the transmit TX and RX beamformer are disabled (there is no image data being collected). Embodiments of systems described herein trigger an external device such as a low frequency ultrasound therapy unit delivering energy at, for example, 1 MHz. In one aspect this external device can be a SoniGene™. The external device (e.g., SoniGene) destroys bubbles for the duration specified by the user (e.g., up to a max of 1 s). After the specified duration is over the SoniGene stops transmitting, the TX and RX beamformers are reconfigured to the prior state of Contrast Mode, and the system resumes imaging.

[0049] A typical contrast agent comprises a thin flexible or rigid shell composed of albumin, lipid or polymer confining a gas such as nitrogen or a perfluorocarbon. Other examples of representative gases include air, oxygen, carbon dioxide, hydrogen, nitrous oxide, inert gases, sulfur fluorides, hydrocarbons, and halogenated hydrocarbons. Liposomes or other microbubbles can also be designed to encapsulate gas or a substance capable of forming gas as described in U.S. Pat. No. 5,316,771. In another embodiment, gas or a composition capable of producing gas can be trapped in a virus, bacteria, or cell to form a microbubble contrast agent.

[0050] A contrast agent can be modified to achieve a desired volume percentage by a filtering process, such as by micro or nano-filtration using a porous membrane. Contrast agents can also be modified by allowing larger bubbles to separate in solution relative to smaller bubbles. For example, contrast agents can be modified by allowing larger bubbles to float higher in solution relative to smaller bubbles. A population of microbubbles of an appropriate size to achieve a desired volume percentage can subsequently be selected. Other means are available in the art for separating micron-sized and nano-sized particles and can be adapted to select a microbubble population of the desired volume of submicron bubbles such as by centrifugation. The number of micro and nanobubbles of differing sizes can be determined, for example, using an optical decorrelation method. The diameter of micro and nanobubbles making up given volume percentage can also be determined and the number percentage of micro and nanobubbles at different sizes can also be determined. For optical decorrelation methods a Malvin™, Zetasizer™ or similar apparatus may be used.

[0051] Microbubble contrast agent may also produce non-linear scattering when contacted by ultrasound at a frequency above 30 MHz, 40 MHz, 50 MHz or 60 MHz. Non-linear scattering can be measured, for example, as described in U.S. Publication No. 2006/0078501. Further, transducer operating frequencies significantly greater than those mentioned above are also contemplated.

Uses

[0052] Among many possible applications, the described embodiments may be used in conjunction with visualization, assessment, and measurement of anatomical structures and hemodynamic function in longitudinal imaging studies of small animals. The systems can provide images having very high resolution, image uniformity, depth of field, adjustable transmit focal depths, multiple transmit focal zones for multiple uses. For example, the ultrasound image can be of a subject or an anatomical portion thereof, such as a heart or a heart valve. The image can also be of blood and can be used for applications including evaluation of the vascularization of tumors. The systems can be used to guide needle injections.

[0053] The described embodiments can also be used for human clinical, medical, manufacturing (e.g., ultrasonic inspections, etc.) or other applications where producing an image at a transmit frequency of 15 MHz or higher is desired.

Ultrasound Systems

[0054] As stated, the methods of the invention may be employed with any suitable ultrasound system, such as those described in U.S. Publication No. 2007/0239001 and the VEVO® 2100. Suitable systems can include one or more of the following: an array transducer that can be operatively connected to a processing system that may be comprised of one or more of signal and image processing capabilities; digital transmit and receive beamformer subsystems; analog front end electronics; a digital beamformer controller sub-

system; a high voltage subsystem; a computer module; a power supply module; a user interface; software to run the beamformer; a scan converter, and other system features as described herein.

[0055] An arrayed transducer used in the system can be incorporated into a scanhead that, in one embodiment, may be attached to a fixture during imaging which allows the operator to acquire images free of the vibrations and shaking that usually result from "free hand" imaging. A small animal subject may also be positioned on a heated platform with access to anesthetic equipment, and a means to position the scanhead relative to the subject in a flexible manner. The scanhead can be attached to a fixture during imaging. The fixture can have various features, such as freedom of motion in three dimensions, rotational freedom, a quick release mechanism, etc. The fixture can be part of a "rail system" apparatus, and can integrate with the heated mouse platform.

[0056] The systems can be used with platforms and apparatus used in imaging small animals including "rail guide" type platforms with maneuverable probe holder apparatuses. For example, the described systems can be used with multi-rail imaging systems, and with small animal mount assemblies as described in U.S. Pat. No. 7,133,713; U.S. Pat. No. 6,851,392, U.S. Pat. No. 7,426,904, and U.S. Publication No. 2005/0215878, each of which are each fully incorporated herein by reference.

[0057] Small animals can be anesthetized during imaging and vital physiological parameters such as heart rate and temperature can be monitored. Thus, an embodiment of the system may include means for acquiring ECG and temperature signals for processing and display. An embodiment of the system may also display physiological waveforms such as an electro-cardiogram (ECG), respiration or blood pressure waveform.

Ultrasound

[0058] Any of the methods of the invention are compatible with systems adapted to receive ultrasound signals having a frequency of at least 15 megahertz (MHz) with a transducer having a field of view of at least 5.0 millimeters (mm) at a frame rate of at least 20 frames per second (fps). In other embodiments, the ultrasound signals can be acquired at an acquisition rate of 50, 100, or 200 (fps). Optionally, ultrasound signals can be acquired at an acquisition rate of 200 frames per second (fps) or higher. In other examples, the received ultrasound signals can be acquired at a frame rate within the range of about 100 fps to about 200 fps. In some exemplary aspects, the length of the transducer is equal to the field of view. The field of view can be wide enough to include organs of interest such as the small animal heart and surrounding tissue for cardiology, and full length embryos for abdominal imaging. In one embodiment, the two-way bandwidth of the transducer can be approximately 50% to 100%. Optionally, the two-way bandwidth of the transducer can be approximately 60% to 70%. Two-way bandwidth refers to the bandwidth of the transducer that results when the transducer is used both as a transmitter of ultrasound and a receiver—that is, the two-way bandwidth is the bandwidth of the one-way spectrum squared.

[0059] The processing unit produces an ultrasound image from the acquired ultrasound signal(s). The acquired signals may be processed to generate an ultrasound image at display rate that is slower than the acquisition rate. Optionally, the generated ultrasound image can have a display rate of 100 fps or less. For example, the generated ultrasound image has a display rate of 30 fps or less. The field of view can range from about 2.0 mm to about 30.0 mm. When a smaller field of view is utilized, the processing unit can acquire the received ultrasound signals at an acquisition rate of at least 300 frames per second (fps). In other examples, the acquisition rate can be 50, 100, 200 or more frames per second (fps).

[0060] In one embodiment, in which a 30 MHz center frequency transducer is used, the image generated using the disclosed systems may have a lateral resolution of about 150 microns (μm) or less and an axial resolution of about 75 microns (μm) or less. For example, the image can have an axial resolution of about 30 microns (μm). Furthermore, embodiments according to the present invention transmit ultrasound that may be focused at a depth of about 1.0 mm to about 30.0 mm. For example, the transmitted ultrasound can be focused at a depth of about 3.0 mm to about 10.0 mm. In other examples, the transmitted ultrasound can be focused at a depth of about 2.0 mm to about 12.0 mm, of about 1.0 mm to about 6.0 mm, of about 3.0 mm to about 8.0 mm, or of about 5.0 mm to about 30.0 mm.

Transducers

[0061] In various embodiments, the transducer can be, but is not limited to, a linear array transducer, a phased array transducer, a two-dimensional (2-D) array transducer, or a curved array transducer. A linear array is typically flat, i.e., all of the elements lie in the same (flat) plane. A curved linear array is typically configured such that the elements lie in a curved plane. The transducers described herein are "fixed" transducers, meaning that the transducer array does not utilize movement in its azimuthal direction during transmission or receipt of ultrasound in order to achieve its desired operating parameters, or to acquire a frame of ultrasound data. Moreover, if the transducer is located in a scanhead or other imaging probe, the term "fixed" may also mean that the transducer is not moved in an azimuthal or longitudinal direction relative to the scan head, probe, or portions thereof during operation. The transducers can be moved between the acquisition of ultrasound frames; for example, the transducer can be moved between scan planes after acquiring a frame of ultrasound data, but such movement is not required for their operation. As one skilled in the art would appreciate however, the transducer of the present system can be moved relative to the object imaged while still remaining fixed as to the operating parameters. For example, the transducer can be moved relative to the subject during operation to change position of the scan plane or to obtain different views of the subject or its underlying anatomy.

[0062] Arrayed transducers have a number of elements. In one embodiment, the transducer used to practice one or more aspects of the present invention has at least 64 elements, e.g., 256 elements. The transducer can also include fewer or more than 256 elements. The transducer elements can be separated by a distance equal to about one-half the wavelength to about two times the wavelength of the center transmit frequency of the transducer (referred to herein as the "element pitch."). In one aspect, the transducer elements are separated by a distance equal to about the wavelength of the center transmit frequency of the transducer. Optionally, the center transmit frequency of the transducer used is equal to or greater than 15 MHz. For example, the center transmit frequency can be approximately 15 MHz, 20 MHz, 30 MHz, 40 MHz, 50 MHz, 55 MHz or higher. In some exemplary aspects, the ultrasound

transducer can transmit ultrasound into the subject at a center frequency within the range of about 15 MHz to about 80 MHz. In one embodiment according to the present invention, the transducer has a center operating frequency of at least 15 MHz and the transducer has an element pitch equal to or less than 2.0 times the wavelength of sound at the transducer's transmitted center frequency. The transducer can also have an element pitch equal to or less than 1.5 times the wavelength of sound at the transducers transmitted center frequency.

[0063] By non-limiting example, one transducer that may be used with the described system can be an arrayed transducer as described in U.S. Pat. No. 7,230,368, U.S. Publication No. 2007/0222339, and U.S. Provisional Application No. 61/192,661, which are hereby incorporated by reference. The transducer may also comprise an array of piezoelectric elements that can be electronically steered using variable pulsing and delay mechanisms. The processing system according to various embodiments of the present invention may include multiple transducer ports for the interface of one or more transducers or scanheads. As previously described, a scanhead can be hand held or mounted to rail system and the scanhead cable can be flexible. Transducers are also commercially available from VisualSonics, Inc.

Ultrasound Signal Acquisition

[0064] The system can further comprise one or more signal samplers for each receive channel. The signal samplers can be analog-to-digital converters (ADCs). The signal samplers can use direct sampling techniques to sample the received signals. Optionally, the signal samplers can use bandwidth sampling to sample the received signals. In another aspect, the signal samplers can use quadrature sampling to sample the received signals. Optionally, with quadrature sampling, the signal samplers comprise sampling clocks shifted 90 degrees out of phase. Also with quadrature sampling the sampling clocks also have a receive period, and the receive clock frequency can be approximately equal to the center frequency of a received ultrasound signal but may be different from the transmit frequency. For example, in many situations, the center frequency of the received signal has been shifted lower than the center frequency of the transmit signal due to frequency dependent attenuation in the tissue being imaged. For these situations the receive sample clock frequency can be lower than the transmit frequency.

[0065] An acquired signal can be processed using an interpolation filtration method. Using the interpolation filtration method a delay resolution can be used, which can be less than the receive clock period. In an exemplary aspect, the delay resolution can be, for example, 1/16 of the receive clock period.

[0066] The processing unit can comprise a receive beamformer. The receive beamformer can be implemented using, for example, at least one field programmable gate array (FPGA) device. The processing unit can also comprise a transmit beamformer. The transmit beamformer can also be implemented using, for example, at least one FPGA device.

[0067] In one aspect, 512 lines of ultrasound are generated, transmitted into the subject and received from the subject for each frame of the generated ultrasound image. In a further aspect, 256 lines of ultrasound can also be generated, transmitted into the subject and received from the subject for each frame of the generated ultrasound image. In another aspect, at least two lines of ultrasound can be generated, transmitted into the subject and received from the subject at each element of the array for each frame of the generated ultrasound image. Optionally, one line of ultrasound is generated, transmitted into the subject and received from the subject at each element of the array for each frame of the generated ultrasound image.

[0068] The ultrasound systems described herein can be used in multiple imaging modes. For example, the systems can be used to produce an image in B-mode, M-mode, Pulsed Wave (PW) Doppler mode, power Doppler mode, color flow Doppler mode, RF-mode and 3-D mode. The systems can be used in Color Flow Imaging modes, including directional velocity color flow, Power Doppler imaging and Tissue Doppler imaging. The systems can also be used with Steered PW Doppler, with very high pulse repetition frequencies (PRF). The systems can also be used in M-Mode, with simultaneous B-Mode, for cardiology or other applications where such techniques are desired. The system can optionally be used in Duplex and Triplex modes, in which M-Mode and PW Doppler and/or Color Flow modes run simultaneously with B-Mode in real-time. A 3-D mode in which B-Mode or Color Flow mode information is acquired over a 3-dimensional region and presented in a 3-D surface rendered display can also be used. A line based image reconstruction or "EKV" mode, can be used for cardiology or other applications, in which image information is acquired over several cardiac cycles and recombined to provide a very high frame rate display. Line based image reconstruction methods are described in U.S. Pat. No. 7,052,460, which is hereby incorporated by reference. Such line based imaging methods image can be incorporated to produce an image when a high frame acquisition rate is desirable, for example when imaging a rapidly beating mouse heart. In the RF acquisition mode, raw RF data can be acquired, displayed and made available for off-line analysis.

[0069] In one embodiment, the transducer can transmit at a pulse repetition frequency (PRF) of at least 500 hertz (Hz). The system can further comprise a processing unit for generating a color flow Doppler ultrasound image from the received ultrasound. Optionally, the PRF is between about 100 Hz to about 150 KHz. In M-Mode or RF Mode the PRF is between about 100 Hz and about 10 KHz. For Doppler modes, the PRF can be between about 500 Hz and about 150 KHz. For M-Mode and RF mode, the PRF can be between about 50 Hz and about 10 KHz.

[0070] Exemplary specifications of the system may include those specifications listed in Table 1, below:

TABLE 1

System Specifications	
Number of transducer elements supported	Up to 256
Transmit channels (active aperture)	64
Receive channels	64
Transducers supported	Linear, curved linear
Center frequency range	15 to 55 MHz
Data acquisition method	Quadrature sampling
BF sampling frequency range	12 to 62 MHz
Receive BF fine delay implementation	Interpolation filter
Receive delay resolution	T/16
ADC number of bits	10
Transmit delay resolution	T/16
TGC	yes
Synthetic Aperture	yes
Maximum transmit voltage	80 Vpp
Transmit power control	yes
Multiple Transmit focal zones	yes
Transmit cycle adjustment	1-32
B-mode frame rate max	200
CFI frame rate max	160

TABLE 1-continued

System Specifications	
PW Doppler maximum PRF	150 KHz
CFI maximum PRF	75 KHz
Doppler beam steering	yes
Cine buffer size	300 frames
Physiological signal acquisition	yes
Transducer connectors	One or more

Other Embodiments

[0071] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference.

[0072] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

[0073] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

[0074] Other embodiments are in the claims.

What is claimed is:

1. A method for frame persistence implemented by an ultrasound imaging system, comprising:

a. obtaining a plurality of frames of ultrasound at a baseline frame rate (FR_0);

b. processing a portion of the plurality of frames of ultrasound at a processing rate (PR), wherein the portion comprises a first frame comprising a first plurality of data points;

c. applying a persistence routine to at least one of the first plurality of data points, wherein the persistence routine combines the at least one of the first plurality of data points with a corresponding stored data point based on a user defined persistence setting, FR_0, and PR, to produce at least one persistence processed data point;

d. storing the at least one persistence processed data point to replace the stored data point of (c); and

e. generating a persistence processed output frame from the at least one persistence processed data point.

2. The method of claim **1**, wherein the persistent routine comprises:

$$y(n)=(1-(1-\alpha)^p)\cdot x(n)+(1-\alpha)^p\cdot y(n-1),$$

where p is the ratio FR_0/PR, α is the user defined persistence setting and is greater than 0 and less than 1, n is the frame index, y(n) is the persistence processed data point, x(n) is the at least one of the first plurality of data points, and y(n−1) is the corresponding stored data point, wherein the value of y(n−1) is set to 0 for n=1.

3. The method of claim **1**, wherein the plurality of frames comprises B-Mode data, Color Flow image data, or Power Doppler image data.

4. The method of claim **1**, further comprising displaying the persistence processed output frame on a display.

5. The method claim **1**, further comprising repeated steps (c)-(e) with subsequent frames.

6. A method for destroying contrast agent bubbles present in a region of interest of a subject, comprising:

(a) providing the subject to which has been administered contrast agent bubbles;

(b) scanning the region of interest in the subject with ultrasound;

(c) receiving a bubble destruction command;

(d) transmitting at least one ultrasound pulse into the region of interest, wherein the ultrasound pulse is transmitted at a mechanical index sufficient to destroy bubbles in the region of interest; and

(e) resuming scanning of the region of interest.

7. The method of claim **6**, wherein the region of interest comprises one or more focal zones, and the ultrasound pulse of step (d) is transmitted into each focal zone.

8. The method of claim **6**, wherein the mechanical index of step (c) is greater than about 0.6.

9. The method of claim **6**, wherein step (d) comprises operating at 10-20 MHz with a 4 cycle pulse, with a plurality of focal zones evenly spaced over a depth of the region of interest (ROI), at 100% TX power at a mechanical index (MI) greater than 0.6, wherein 10-20 MHz pulses are fired at a Pulse Repetition Frequency (PRF) of 25 kHz and above for up to 1 s.

10. The method of claim **6**, wherein scanning of the region of interest is discontinued between steps (b) and (c).

11. The method of claim **6**, wherein ultrasound employed in steps (b) and (e) has a wider bandwidth than ultrasound employed in step (d).

12. The method of claim **6**, wherein the ultrasound employed in steps (b) and (e) is produced by one transducer, and the ultrasound transmitted in step (d) is produced by a different transducer.

13. The method of claim **6**, wherein a single transducer is employed in steps (b), (d), and (e).

14. The method of claim **6**, wherein step (e) comprises monitoring for reperfusion of bubble contrast agent into the region of interest.

15. The method of claim **6**, wherein step (e) comprises monitoring for determining the circulating amount of bubble contrast agent.

16. A method for respiration gating during ultrasound imaging, comprising:

acquiring a respiration signal from a subject;

determining a start of a respiration cycle in the respiration signal;

setting a valid zone based on the start of the respiration cycle and user defined offset and/or duration;

acquiring a plurality of frames of ultrasound;

discarding one or more frames of the plurality of frames acquired outside the valid zone; and

outputting remaining frames of the plurality of frames acquired inside the valid zone.

17. The method of claim **16**, wherein acquiring a plurality of frames comprises acquiring the plurality of frames at an acquisition rate of at least 200 frames per second.

18. The method of claim **16**, wherein each of the acquired plurality of frames are time-stamped to indicate when each frame is acquired.

19. A method for ECG triggered acquisition during ultrasound imaging, comprising:

(a) acquiring, at a host computer, an ECG signal from a subject;

(b) determining, at the host computer, an R-wave point in the ECG signal;

(c) determining, at the host computer, a trigger point threshold and a trigger slope based on the R-wave point;

(d) transferring the trigger point threshold and the trigger slope to a programmable logic device; and

(e) triggering, by the programmable logic device, the acquisition of ultrasound based on the trigger point threshold and the trigger slope.

20. The method of claim **19**, wherein triggering based on the trigger point threshold and the trigger slope is used to acquire a cineloop that starts at a specified point in a cardiac cycle and runs for a specified number of cardiac cycles.

21. The method of claim **19**, wherein triggering based on the trigger point threshold and the trigger slope is used to acquire one or more of B-Mode data, Color Doppler Mode data, Power Doppler Mode data, Contrast Mode data, and 3D Mode data.

22. The method of claim **19**, further comprising:

(i) acquiring a respiration signal from a subject;

(ii) determining a start of a respiration cycle in the respiration signal;

(iii) setting a valid zone based on the start of the respiration cycle and user defined offset and/or duration;

(iv) discarding ultrasound acquired outside the valid zone during step (e); and

(v) outputting ultrasound acquired inside the valid zone during step (e).

23. The method of claim **22**, wherein ultrasound is acquired at a rate of at least 200 frames per second.

24. The method of claim **22**, wherein ultrasound frames are time-stamped to indicate when each frame is acquired.

* * * * *

专利名称(译)	超声成像中的采集和显示方法		
公开(公告)号	US20110144494A1	公开(公告)日	2011-06-16
申请号	US12/562935	申请日	2009-09-18
[标]申请(专利权)人(译)	MEHI JAMES WHITE克里斯托弗 针ANDREW 文JERROLD 刘凯文 HIRSON戴斯蒙德		
申请(专利权)人(译)	MEHI JAMES WHITE克里斯托弗 针ANDREW 文JERROLD 刘凯文 HIRSON戴斯蒙德		
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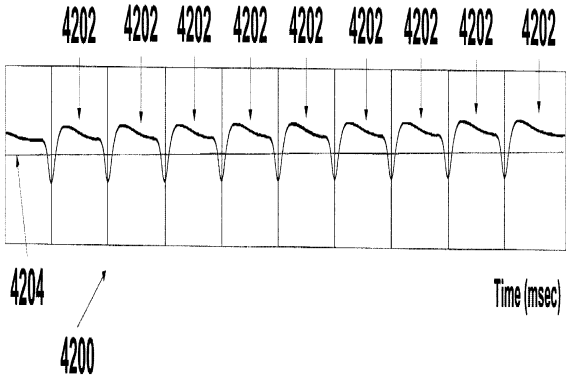
摘要(译)

通常，本发明提供了用于获取和显示超声图像的方法。特别地，本发明提供了使用持久性算法显示超声图像，基于受试者呼吸选通超声采集，基于受试者ECG触发超声采集以及在成像期间破坏气泡造影剂的方法。该方法可以与任何合适的超声系统一起使用。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