Published in final edited form as:

IEEE Trans Ultrason Ferroelectr Freq Control. 2010 July ; 57(7): 1548–1557. doi:10.1109/TUFFC.

2010.1585.

A High-Frequency High Frame Rate Duplex Ultrasound Linear Array Imaging System for Small Animal Imaging

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Abstract

High-frequency (HF) ultrasound imaging has been shown to be useful for non-invasively imaging anatomical structures of the eye and small animals in biological and pharmaceutical research, achieving superior spatial resolution. Cardiovascular research utilizing mice requires not only real-time B-scan imaging, but also ultrasound Doppler to evaluate both anatomy and blood flow of the mouse heart. This paper reports the development of a high frequency ultrasound duplex imaging system capable of both B-mode imaging and Doppler flow measurements, using a 64-element linear array. The system included a HF pulsed-wave Doppler module, a 32-channel HF B-mode imaging module, a PC with a 200 MS/s 14-bit A/D card, and real-time LabView software. A 50dB signal-to-noise ratio (SNR) and a depth of penetration of larger than 12 mm were achieved using a 35 MHz linear array with 50 μ m pitch. The two-way beam widths were determined to be 165 μ m to 260 μ m and the clutter energy to total energy ratio (CTR) were 9.1 dB to 12 dB, when the array was electronically focused at different focal points at depths from 4.8 mm to 9.6 mm. The system is capable of acquiring real-time B-mode images at a rate greater than 400 frames per second (fps) for a 4.8×13 mm field of view, using a 30 MHz 64-element linear array with 100 μ m pitch. Sample *in vivo* cardiac high frame rate images and duplex images of mouse hearts are shown to assess its current imaging capability and performance for small animals.

I. Introduction

Small animals such as mice, rats, and zebrafish are preferred models for biological and pharmacological studies. However, in order to visualize anatomical structures and monitor physiological activities on such a small scale, high resolution imaging modalities are required. Currently, computed tomography (CT) [1], magnetic resonance imaging (MRI) [2], positron emission tomography (PET) [3], single photon emission computed tomography (SPECT) [4], optical coherent tomography (OCT) [5], have been developed and used for small animal imaging. But their cost effectiveness and real-time capability are still significant issues. Also, due to the fast heart rate of a mouse (400–800 beats/minute) [6], cardiovascular research utilizing mice requires imaging modalities with high frame rate capability (>100 fps), which cannot yet be realized by modalities other than ultrasound.

High-frequency (HF) ultrasound imaging provides a non-invasive method of superior spatial resolution for imaging small animals [7], [8]. Commercial HF ultrasound systems dubbed ultrasonic biomicroscope or UBMs, in which images are acquired by mechanically scanning a single element ultrasonic transducer, can obtain a spatial resolution better than 15 μ m [9], and detect blood velocities less than 0.5 mm/s in capillaries as small as 20 μ m in diameter [10]. Commercial UBMs have been utilized in preclinical cancer and cardiovascular research [8]. Since UBM systems are based on mechanical scanning of a single-element transducer, it is very difficult to achieve a very high frame rate (>100 fps) with a wide field of view. The fixed focal point of the single-element transducer also limits the image quality at depths away from the focus. Current state-of-the-art commercial UBMs are capable of

performing high frame rate (>240 fps) B-mode imaging for a limited FOV (<1 mm) [11]. In addition, a frame rate higher than 1000 fps can be realized using electrocardiogram (ECG) gating and off-line reconstruction algorithms [12], [13]. However, UBMs based upon mechanically scanned single element transducers and may have reached their limit in image quality and frame rate.

HF ultrasonic linear arrays (>30 MHz) system utilizing electronic beam steering provides a better solution to high frame rate imaging. A linear array allows for dynamic focusing in the imaging plane to improve the lateral resolution throughout the depth of view. Electronic scanning provides a jitter free method for acquiring high frame rate real-time images. Significant progress in the development of HF linear arrays has been achieved in the past few years. [14] – [17]. Preliminary B-mode images have been reported [18], [19]. Mouse heart imaging at 100 fps was achieved using a system with analog beamformer [19]. Quite recently linear array based HF ultrasound systems have become commercially available (Vevo 2100, Visualsonics Inc., Toronto, Canada) as described in [20] and [21].

Cardiovascular and tumor research using small animals requires not only B-mode imaging, but also ultrasound Doppler to evaluate blood flow [22]. A HF ultrasonic linear array Pulsed-wave (PW) Doppler system capable of detecting the blood flows as low as 0.1 mm/s and as high as 1 m/s has been developed [23]. By combining the linear array B-mode imaging system with the Doppler function, the HF imaging system can be expanded to a duplex system which is capable of acquiring high frame rate B-mode images as well as performing image-guided Doppler flow measurements. The commercial HF linear array system was reported to be capable of obtaining B-mode images with frame rates up to 1000 fps over limited field of view, as well as performing PW Doppler measurements [20], [21].

In this paper, we report the development and the potential application of a 30 MHz linear array duplex HF ultrasound system capable of both real-time high frame rate B-mode imaging and pulsed-wave Doppler measurements. The system has the capability of acquiring >400 B-mode images per second with a 4.8 mm lateral view. Under the guidance of B-mode imaging, PW Doppler can be used to detect the blood flow at specified location. Details of the system are first described, followed by a discussion on phantom images acquired to assess the B-mode imaging performance of this system. *In vivo* study on mice was also carried out using this duplex system. Representative images and Doppler waveforms from various structures are given to demonstrate its capability for small animal research.

II. MATERIALS AND METHODS

A block diagram of the duplex system with HF arrays is illustrated in Fig. 1. The system included three separated blocks: a B-mode imaging block, a HF directional PW Doppler block, and a PC for data acquisition. The control and timing circuits communicating with the PC were used to manage the timing signals for these two blocks, as well as the data acquisition. It would change the setting accordingly when users switched between B-mode imaging and PW Doppler.

A. B-mode Imaging Circuits

The B-mode imaging system was controlled by a control and timing circuit, which generates a pulse repetition frequency (PRF) clock, a current scan line number to synchronize the operations of the system. A 64-channel transmit beamformer was implemented using Complex Programmable Logic Device (CPLD) to send out up to 32 delayed trigger signal to trigger the excitation of the array elements, which were driven by 64 bipolar pulsers [24].

The analog receiving front-end consisted of a limiter and an amplification circuit. In order to prevent high voltage pulses from entering the amplifiers, a limiter including a pair of back-to-back diodes was added before the pre-amplifier of each channel [25]. Then the received echoes from each element were amplified by a variable gain amplifier AD8331 (Analog Devices, Norwood, MA), followed by a band-pass filter PBP-35W (Mini Circuits, Brooklyn, NY), and a second amplifier MAX4106 (Maxim Integrated Products, Sunnyvale, CA). The total achievable amplification was 70 dB. The measured minimum detectable signal can be as low as 20 μ Vpp [23].

The analog receiving beamformer applied delays to each of the 32 received radio-frequency (RF) signals. It consisted of five fixed analog delay lines FDC1005~FDD15005 (ELMEC Technology of America Inc., San Mateo, CA) and three dual channel 2-to-1 multiplexers AD8182 (Analog Devices, Norwood, MA) in cascade. By setting the 2-to-1 multiplexer, each delay line might be incorporated or bypassed. During imaging, the control signals, carrying delay information for each channel, were distributed during the initializing period. Then the 32 delayed signals were summed to form the ultrasound beam. The characteristics of the analog receiving beamformer [23] are listed in Table I.

B. High Frame Rate Design

The most novel aspect of the system is its capability to image at a much higher frame rate than mechanical scanners. In order to do so, the system configuration time overhead must be reduced. The configuration time included the time of selecting appropriate analog channels for electronic scanning and the time of programming the appropriate delay time to each delay channel. High speed Static RAMs (CY7C128A, Cypress Semiconductor, San Jose, CA) were used to distribute all of these configuration data as shown in Fig. 2. Before imaging, all line-by-line configuration data were written to RAMs from the microcontroller. During imaging, either a Complex Programmable Logic Device (CPLD) or an external source provided an image line trigger that drove an image line counter at the falling edge. Based on the image line number from the counter, corresponding data saved in RAM were distributed to destination circuits, such as the analog channels and the programmable delay circuits. From the timing analysis diagram shown in Fig. 2b, the total time consumed for configuration was only the time delays of chips, which were around several nanoseconds. Therefore the theoretical frame rate of the new system relied only on the field of view. This frame rate is given by:

$$FR = \frac{c}{2dN} \quad (1)$$

where FR is the frame rate, c is the sound velocity in a medium (1480 m/s in water), d is the image depth, and N is the total number of image scan lines of each frame. Another limitation factor on the frame rate is the PRF on the pulser, which requires a certain amount of time to recover for next firing. The system was able to be operated under 20 kHz PRF, and achieved a frame rate at about 400 fps for 49 line/frame image.

C. HF Pulsed-Wave Doppler Module

When the system was switched to the Doppler function, the control and timing circuit would select a specified B-mode image line and set the desired PRF for Doppler measurements. The pulser would generate a multi-cycle bipolar pulse, instead of a single cycle pulse for B-mode imaging, to drive the selected array elements. Trade-off between signal-to-noise ratio (SNR) and resolution should be considered when selecting the number of cycles of the pulse. The control and timing circuit also set the sample gate width to the same as the transmit pulse length. The beamformed echoes from the selected B-mode image line were

fed to the Doppler block via a band-pass filter BBP-30 (Mini-Circuits, Brooklyn, NY). The detail of the Doppler system was described in [23]. It used in-phase and quadrature demodulation and sample-and-hold circuits [26] to produce the directional PW Doppler audio signal. The system was capable of detecting motion velocity of the wire phantom as low as 0.1 mm/s, and detecting blood-mimicking flow velocity in a 127 μm tube lower than 7 mm/s.

D. Data Acquisition and Imaging

The RF data from the receive beamformer was digitized by a Gage A/D card CS14200 (Gage Applied Technologies Inc., Montreal, Quebec, Canada) at a sampling frequency of 200 MHz. This ADC helped to maintain a high SNR and provided good signal resolution and large dynamic range. For normal frame rate B-mode acquisition, the RF data of each line were transferred to PC once they were digitized into the Gage card. The subsequent line would be activated after the transfer was finished. When a frame was received on the PC, it would be then processed and displayed by LabView (National Instruments Corp., Austin, TX) before the acquisition for next frame. To form a B-mode image, the RF echo signal was demodulated and compressed logarithmically. Then the signal was linearly mapped to gray scale levels. For the high frame rate B-mode acquisition, to avoid the overhead of data transfer from the Gage card to PC, the RF data of all the frames were stored at the local buffer on the Gage card during the data digitization. They were then transferred to PC for display or storage. When using the Doppler mode, after identifying the area of interest from the B-mode image, the objects were moved to the location where the area of interest shows on the preset Doppler measurement location on the image. The Doppler audio signals were digitized by an integrated sound card of the PC. The digitized signals were processed and converted into a directional spectrogram by LabView.

E. System Architecture

In order to expand the system to support future arrays with more elements, the system was designed as a mother-daughter board structure illustrated in Fig. 3. The motherboard included the clock generator and driver, timing circuits, multiplexers, and a Doppler processing unit. Each pulser daughter board included eight channel N-cycle bipolar pulsers and corresponding analog front-ends. Each analog receiving beamformer board included 8-channel 6-bit programmable delay circuits. Therefore a 16 to 64-channel receiving beamformer could be constructed by using multiple daughter boards to support 128 to 256 element arrays. A photo of the complete system is shown in Fig. 4.

F. System Evaluation

We used a 35 MHz 64-element linear array with 50 μm pitch [15] to assess the B-mode imaging performance. The characteristics of the array are listed as Array 1 in Table II. A scan line was formed by a 32-element sub-aperture, which was equivalent to an aperture size of 1.6 mm. The lateral field of view was 1.6 mm. The beam was electronically focused at 8 mm for transmission, and 4.8 mm, 6.4 mm, 8 mm, 9.6 mm for reception. A 40 MHz single element transducer UBM system described in [27] was used to make a direct comparison with the array system. The transducer was constructed with lithium niobate (LNO) single crystal. It had an aperture diameter of 3 mm, with a focal distance of 7.5 mm and a -6 dB fractional bandwidth of 65%. The transducer was mechanically scanned by a motor controller DMC-1802 (Galil Motion Control Inc., Mountain View, CA). The Panametrics 5900PR pulser/receiver (Olympus NDT Inc., Waltham, MA) was used to excite the transducer and receive the echoes. The echoes were then digitized by Gage A/D card CS14200 (Gage Applied Technologies Inc., Montreal, Quebec, Canada) at a sampling frequency of 200 MHz.

Cross-sectional images of a wire-target phantom were used to assess the lateral resolution. The phantom consisted of four 20 μm diameter tungsten wires, which were arranged diagonally with axial distance of 1.6 mm. The wires were placed at different depths in order to demonstrate the lateral resolution variation of the two systems. The SNR, depth of penetration, and the contrast resolution were evaluated using a tissue mimicking phantom, which was designed to have attenuation and scattering properties similar to human soft tissue [28]. The SNR was measured by the ratio of the RMS signal from the phantom to the RMS noise level as a function of depth [29]. The surface of the phantom was placed at 4 mm away from the linear array for the array measurement. And for the UBM measurement, in order to evaluate the signal at and away from the focal point, the phantom surface was moved to 7.5 mm and 4.5 mm which were at the transducer's focal point and 3 mm above it respectively. The depth of penetration was determined by the depth at which SNR fell below 6 dB. The phantom also contains a 0.5-mm-diameter cylindrical anechoic cyst R that was filled with water. The contrast resolution at different depths was measured by clutter energy to total energy ratio (CTR), which is the ratio of the average energy level of the background to the cyst's center given by:

$$CTR = 10 \log_{10} \frac{S_b}{S_c}$$

where S_c and S_b is the average energy inside the cyst, and its neighbor background region of the same size respectively.

G. In Vivo Experiments

In vivo experiments were carried out on mice under the protocols approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Southern California. In order to obtain sufficiently large field of view for imaging the mouse anatomy, a 30 MHz 64-element linear array with 100 μm pitch [14] was used for the experiments. The characteristics of the array are listed as Array 2 in Table II. It had a lateral width of 4.8 mm with a 16-element sub-aperture, which was 1.6 mm wide. Even though a pitch of around 2λ would cause degradation to the image quality, it still allowed us to demonstrate the high frame rate imaging capability of the system.

Ten Balb/c mice (Simonsen Laboratories, Gilroy, CA) at an age of 4 to 8 weeks were anesthetized with Avertin (2-2-2 Tribromoethanol) (Sigma-Aldrich, St. Louis, MO) given intraperitoneally at a dose of 0.5-mg/g body weight. When adequate anesthesia was obtained (typically in 5–10 minutes), animal chest areas were shaved and further cleaned with a chemical hair remover to minimize ultrasound energy loss. A heat lamp was used to maintain the body temperatures of the mice in order to ensure their normal physiological activities. The 30 MHz linear array transducer was applied to the shaved chest area coupled through ultrasound gel (Parker Lab, Fairfield, NJ). After locating the area of interest by monitoring the real-time images at a lower frame rate (30 fps), the system was switched to the high frame rate mode. The high frame rate images (400 fps) were acquired and played back at slow motion, whose speed was defined by the user. Under the guidance of B-mode images, the Doppler signals from different locations around the mouse heart were measured. The duration of the experiments lasted for less than two hours. After the procedure the animals were euthanized by placing them in a chamber with a carbon dioxide concentration of 60–70% for at least 10 minutes.

In the above experiments, the sample gate for the PW Doppler was located at the depth of 8.0 mm and its sample volume duration was selected as 233 ns (seven cycles of the transmitted signal). The lateral location is at the 0.7 mm (#32 of the total 49 image lines).

An oscilloscope LeCroy 9350AL (LeCroy Corp., Chestnut Ridge, NY, USA) was used to monitor the sample gate and the beamformed echoes, ensuring that the sample gate was located at the correct positions of the wire, tube or blood vessel.

III. RESULTS

A. System Evaluation

The wire phantom images obtained by both the linear array and Field II [30] simulation of the array are shown in Fig. 5. The measured -6 dB lateral width at the wire targets was 175 μm , 165 μm , 200 μm , 260 μm at depth of 4.8 mm, 6.4 mm, 8 mm, 9.6 mm respectively. The simulated -6 dB lateral width by Field II was 155 μm , 165 μm , 175 μm , 245 μm at the same depths respectively. The UBM system, on the other hand, can achieve 85 μm for -6 dB lateral width near its focal point at 7.5mm, whereas outside the focal zone the resolution and the signal is significantly worse (Fig. 5c). It is worth noting that the lateral resolution of this array-based system may be further improved by expanding the sub-aperture from 32 elements to 64 elements. Fig. 6a indicates that the linear array system can achieve an SNR larger than 50 dB at the depth of 4 mm and depth of penetration beyond 12 mm. The UBM system has an SNR around 40 dB at its focal point with approximately only 3 mm of penetration (Fig. 6b). Meanwhile, the SNR changes to around 27 dB at the phantom surface when it is 3 mm above the focal point, and the depth of penetration increases to approximately 6.5 mm (Fig. 6c). The images of the cylindrical cyst obtained by the two systems at different axial locations are shown in Fig. 7 with 40 dB dynamic range. The measured CTR of the array system was 9.1 dB, 12 dB, and 10.6 dB for the cyst centered at the depth of 4.8 mm, 6.4 mm, and 9.6 mm respectively. The low level of contrast indicates a high side lobe level that can also be observed from Fig. 5a. It is likely due to the fact that there are inactive array elements which caused the generation of undesired grating lobes. The resulted image with the UBM system shows CTR of 3.8 dB, 15.9 dB, and 7.3 dB at the depth of 5 mm, 7 mm, and 9 mm respectively. Although the single element system can provide better contrast at its focal zone, the array system performed more consistently over the entire field of view.

B. In Vivo Experiments

A sample image acquired from the long-axis parasternal view of a mouse heart is displayed in Fig. 8. At the top of the image it can be seen that small air bubbles were trapped in the ultrasound gel showing bright reverberation artifact. Below the ultrasound gel was a layer of skin with relatively high echogenicity. Rib cage was located beneath the skin layer displaying bright entry echo followed by dark shadow. Three ribs could be identified in this view. Under the ribs were the right atrium (RA), aorta, and partial left ventricle due to the limited lateral view. The bright diaphragm was located at the bottom of this image because of mirror reflection. Although a number of landmark anatomical structures in the mouse heart could be identified in this image, it is evident that the performance of the current configuration of 2λ pitch array with 1.6 mm aperture size was simply not adequate to produce images that yield finer details needed for making a diagnosis. Further improvements, for instance, expanding the aperture from 32 to 64 elements must be made to make it a useful diagnostic tool. The cardiac cyclic motion could be visualized in a slow-motion display (**video clip 1**) at a frame rate of 30 fps, given the acquisition frame rate of 400 fps. The video clip shows that the high frame rate imaging technique is needed for the examination of rapidly moving mouse hearts.

B-mode images and Doppler waveforms acquired in Duplex mode are display in Fig. 9. The sample volume is marked by a long line with two short bars. The Doppler angle was assumed to be 45° . Fig. 9a shows a long-axis parasternal view of a mouse heart. The pulsed-

wave Doppler waveform in Fig. 9b displays the blood flow acquired at the location marked in Fig. 9a. The large positive inflow followed by a negative outflow pattern suggested the filling and emptying of the left ventricle, indicating a typical ventricular blood flow. Fig. 9c shows another parasternal long axis view of cardiac structures. Under the guidance of the B-mode imaging, the Doppler signals in the aorta were acquired at the location marked in Fig. 9c. The spectrogram shown in Fig. 9d illustrates a standard aortic waveform with a large unidirectional blood flow caused by the powerful ventricular contraction followed by the closure of aortic valves to prevent the blood flowing backwards to the left ventricle. The peak aortic velocity was estimated to be 57 ± 5.5 cm/s.

IV. CONCLUSIONS

As an initial attempt, a real-time HF high frame rate duplex system with 30 MHz linear arrays was implemented. High speed electronic scanning allowed acquiring real-time B-mode images at a rate greater than 400 fps for a 4.8×13 mm field of view, making it feasible for imaging the motion of heart walls or heart valves of small animals. The duplex capability of the system offers a multitude of opportunities for cardiovascular and tumor investigation in small animals. The B-mode imaging performance was evaluated with phantom studies and compared to those with a single element transducer UBM system. The array system achieved an SNR of 50dB and a depth of penetration of larger than 12 mm. The results also demonstrated that the array system provided more uniform SNR, lateral resolution and contrast resolution at various depths, although the UBM system still had the advantages at its focal zone. *In vivo* experiments were carried out on mice. The resolution offered by the current system may not be adequate for many imaging applications. In the future spatial resolution improvements may be made by utilizing the 64-channel beamformer currently under development, and by increasing array center frequency.

Acknowledgments

The authors would like to thank the National Institute of Health (NIH) for providing the funding for this work through grants # P41-EB002182 and R01HL079976.

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Fig. 1.
Block Diagram of the HF high frame rate duplex ultrasound linear array imaging system.

Fig. 2. Block diagrams of RAMs based control structure (a) and corresponding timing sequences (b).

Fig. 3.
The mother-daughter board structure of the system.

Fig. 4.
Photo of the entire system.

Fig. 5. Wire phantom image obtained with the linear array system with a 35 MHz array (a), Field II simulation of the array (b) and the 40 MHz UBM system (c).

(a)

(b)

(c)

Fig. 6.

The measured SNR from tissue mimicking phantom as a function of depth: (a) 35 MHz linear array system (b) 40 MHz UBM system with phantom surface at 7.5 mm (c) 40 MHz UBM system with phantom surface at 4.5 mm.

Fig. 7.

Images of a tissue mimicking phantom consisting of a 0.5 mm cyst at different depths: (a) – (c) 35 MHz linear array system (d) – (e) 40 MHz UBM system.

Fig. 8.
In vivo image of an adult mouse cardiovascular system using the duplex linear array imaging system with a 30 MHz linear array.

(a)

(b)

(c)

(d)

Fig. 9.

A duplex B-mode image of a mouse heart (a) and its corresponding Ventricular Doppler waveform from the marked location (b). Another duplex B-mode image of a mouse of a mouse heart (c) and its corresponding aortic Doppler waveform from the marked location (d).

Table I

Characteristics of the analog receiving beamformer.

Characteristic	Value
−6dB bandwidth	90 MHz
Maximum delay	31ns
Minimum delay	1ns

Table II

Characteristics of the ultrasound linear arrays.

Characteristic	Array 1	Array 2
Number of elements	64	64
Center frequency	35 MHz	30 MHz
Average bandwidth	55%	56 %
Element dimensions	3 mm×36 μ m	2 mm×85 μ m
Kerf width	14 μ m	15 μ m
Pitch	50 μ m	100 μ m
Elevation focal distance	9.5 mm	8 mm
Aperture size	1.6mm	1.6mm
Number of lines/frame	33	49
Lateral FOV	1.6mm	4.8mm