Ultrasound Stimulated Vibro-acoustography

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Abstract. Vibro-acoustography is a method of imaging and measurement that uses ultrasound to produce radiation force to vibrate objects. The radiation force is concentrated laterally by focusing the ultrasound beam. The radiation force is limited in depth by intersecting two beams at different frequencies so that there is interference between the beams at the difference frequency only at their intersection. This results in a radiation stress of limited spatial extent on or within the object of interest. The resulting harmonic displacement of the object is detected by acoustic emission, ultrasound Doppler, or laser interferometery. The displacement is a complicated function of the object material parameters. However, significant images and measurements can be made with this arrangement. Vibro-acoustography can produce high resolution speckle free images of biologically relevant objects such as breast micro-calcification and vessel calcifications, heart valves, and normal arteries. Vibro-acoustography can also make spot measurements such as microbubble contrast agent concentration in vessels. Several examples of these results will be described.

1 Introduction

It is well known that changes in the elasticity of soft tissues are often related to pathology. Traditionally, physicians use palpation as a simple method for estimating the mechanical properties of tissue. Physicians use a static force applied with their hands and obtain a crude estimation of tissue elasticity the sense of touch. Thus, the force is applied on the body surface and the result is a collective response of all the tissues below. Clinicians can sense abnormalities if the response to palpation is sufficiently different from that of normal tissue. However, if the abnormality lies deep in the body, or if is too small to be resolved by touch, then palpation fails. The dynamic response of soft tissue to a force is also valuable in medical diagnosis. For instance, rebound of tissue upon sudden release of pressure exerted by the physician's finger on the skin provides useful diagnostic information about the tissue.

Quantitative measurement of the mechanical properties of tissues and their display in raster format is the aim of a class of techniques generally called elasticity imaging, or elastography. The general approach is to measure tissue motion caused by an external (or, in some methods, internal) force and use the degree of displacement to reconstruct the elastic parameters of the tissue. The excitation stress can be either

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static or dynamic (vibration). Dynamic excitation is of particular interest because it provides more comprehensive information about tissue properties over a spectrum of frequencies. In many elasticity imaging methods, ultrasound is used to detect the motion or displacement resulting from the applied stress. Magnetic resonance elastography is a recently developed method [1] that employs a mechanical actuator to vibrate the body surface and then measures the resulting strain waves with a phase sensitive magnetic resonance imaging (MRI) machine.

The majority of elasticity imaging methods is based on an external source of force in which the object is pressed by a known amount of force or displacement, and the resulting internal deformations are measured by means of pulse-echo ultrasound. The elasticity of the region of interest is then calculated based on the resulting deformation in relation to the magnitude of the applied force (or displacement). Normally, the region of interest rests deep in the body and away from the source of the force. The problem with this method, termed elastography, is that the force actually exerted on the region of interest depends on the elastic properties of the tissues located between the source and the region of interest. Hence, the deformation and the estimated elasticity of the region of interest are subject to the variability of the intervening tissues.

An alternative strategy is to apply a localized stress directly in the region of interest. One way to accomplish this is to use the radiation pressure of ultrasound. Acoustic radiation force is the time average force exerted by an acoustic field on an object. This force is produced by a change in the energy density of an incident acoustic field [2]; for example, due to absorption or reflection. The use of ultrasound radiation force for evaluating tissue properties has several benefits, for example:

(a) Acoustic (ultrasound) energy is a non-invasive means of exerting force.
(b) Existing ultrasound technology and devices can be readily modified for this purpose, thus eliminating the need for developing a new technology.
(c) Radiation force can be generated remotely inside tissue without disturbing superficial layers.
(d) The radiation stress field can be highly localized, thus allowing for interrogation of a small excitation point.
(e) Radiation force can be produced in a wide range of frequencies or temporal shapes.

These features make radiation force methods highly attractive compared to other, mostly mechanical excitation methods used in elasticity imaging. Tissue probing with the radiation force of ultrasound can be accomplished with a variety of methods depending on the excitation and detection methods used. Similar to elasticity imaging methods with mechanical excitation, radiation force methods can use either a static or dynamic stress.

Using a dynamic radiation force to remotely probe tissue has certain unique characteristics and capabilities that can provide a new family of methods in the field of tissue characterization and imaging. It is insightful to set this new field apart from conventional ultrasound tissue characterization imaging. A major difference is that the dynamic radiation stress allows one to analyze the object based on its low frequency structural vibration properties as opposed to its ultrasonic parameters.

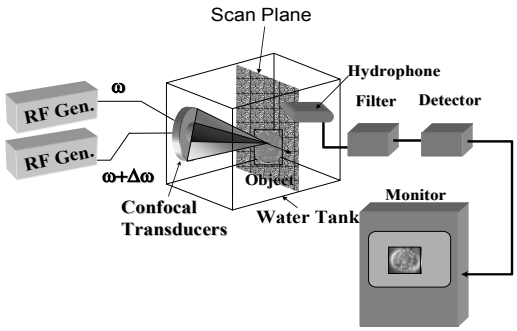

Fig. 1. Schematic of experiment setup

The dynamic radiation force methods may be categorized as:

(a) Transient methods, where an impulsive radiation force is used and the transient response of the tissue is detected by Doppler ultrasound [3].
(b) Shear-wave methods, where an impulsive or oscillating radiation is applied to the tissue and the resulting shear wave is detected by ultrasound or other methods [4,5,6].
(c) Vibro-acoustography, a method recently developed by the authors, where a localized oscillating radiation force is applied to the tissue and the acoustic response of the tissue is detected by a hydrophone or microphone [7].

Fig. 2. Vibro-acoustic image of US quarter obtained with the setup of Fig. 1.

2 Theory

Acoustic radiation force is a time average force exerted by a propagating acoustic wave on an object. This force is an example of a universal phenomenon in any wave motion that introduces some type of unidirectional force on absorbing or reflecting targets in the wave path. For a review of this topic the reader may refer to [2].

Consider a plane ultrasound beam interacting with a planar object of zero thickness and arbitrary shape and boundary impedance that scatters and absorbs. The radiation force vector, $\boldsymbol{F}$, arising from this interaction has a component in the beam direction and another transverse to it. The magnitude of this force is proportional to the average energy density of the incident wave E at the object, where $<>$ represents the time average, and S the area of the projected portion of the object [8]:

$$\boldsymbol{F} = \boldsymbol{d}rS <E> . \qquad (1)$$

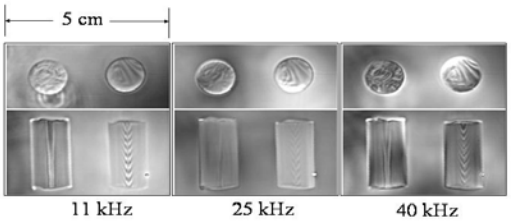

Fig. 3. Vibro-acoustic image of a hard (left) and a soft (right) urethane cylinder embedded within agar gel. Top row are images from the ends of the cylinders and bottom row are imaged from the side of the cylinders. The low difference frequencies, 11 kHz and 25 kHz. show the difference in stiffness of the two cylinders.

Here $\boldsymbol{d}r$ is called the vector drag coefficient with a component in the incident beam direction and another transverse to it. The coefficient $\boldsymbol{d}r$ is defined per unit incident energy density and unit projected area. For a planar object, the magnitude of $\boldsymbol{d}r$ is numerically equal to the force on the unit area of the object per unit energy density. Physically, the drag coefficient represents the scattering and absorbing properties of the object. The drag coefficient can also be interpreted as the ratio of the radiation force magnitude on a given object to the corresponding value if the object were replaced by a totally absorbing object of similar size. For simplicity, we assume a planar objected oriented perpendicular to the beam axis. In this case, the transverse component vanishes, thus, the drag coefficient (force) will have only a component normal to the target surface which we denote by scalar $dr(F)$. To produce a time-varying radiation force, the intensity of the incident beam can be modulated in various ways.

For example, a short ultrasound pulse can produce a transient pulsed radiation force, and a sinusoidally modulated beam can result in a sinusoidally varying force.

3 Experimental Setup for Imaging

The experimental setup is shown in Fig. 1. The experiments were conducted in a water tank. (In a system designed for *in vivo* imaging the transducers can be placed in contact with the skin instead of using water. The hydrophone would also be placed in contact with the skin. At low frequencies the sound wave propagates almost uniformly in all directions. Hydrophone position is not critical, as long as it is relatively close to the exposure site but not in the ultrasound path.) A two-element confocal ultrasound transducer array was positioned such that the beams meet the object at their joint focal point. Transducer was a confocal 38mm diameter transducer with a center frequency of 3MHz. The elements were driven by two stable RF synthesizers (HP 33120A) at frequencies of 3 MHz and 3 MHz+Δf. Sound produced by the object vibration was detected by a submerged hydrophone (ITC model 680) placed within the water tank. The received signal was filtered and amplified by a programmable filter (Stanford Research Systems, SR650) to reject the noise, then digitized by a 12-bits/sample digitizer (National Instruments VXI-1000) at a rate sufficiently higher than the Nyquist rate. Data are recorded on a computer disc.

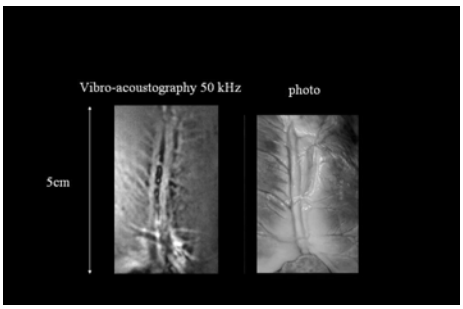

Fig. 4. Vibro-acoustic images of coronary vessels of an excised pig heart, left, compared to photograph, right.

4 Vibro-acoustography Results

An example of resolution is shown in Fig. 2 in which a US quarter was scanned with the set up of Fig. 1. The resolution of the method depends on the power point source function of the ultrasound transducers used to produce the ultrasound beam at the intersection of the confocal beams. To test the ability of vibro-acoustography to de-

tect differences in stiffness we prepared a phantom consisting of a block of agar gel with two urethane cylinders about 2.5 cm in diameter and 4 cm in length. One of the cylinders was stiffer than the other. We scanned the phantom using the setup of Fig. 1. The resulting images at three separate difference frequencies are shown in Fig. 3. At the two lowest frequencies the difference in hardness is shown by the variation in brightness of the cylinders. Fig. 4 illustrates the capability of vibro-acoustography to image vessels on the surface of a heart. Of course this could not be done in the intact chest but the image illustrates the capability of the method to obtain very high resolution images of vessels with no speckle.

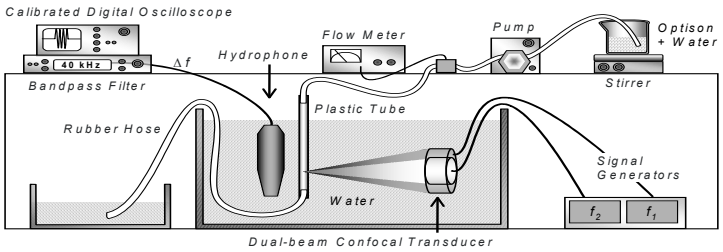

Fig. 5 Set up for measuring acoustic emission from contrast microbubbles.

5 Contrast Vibro-acoustography and the Experimental Setup

We used a customized dual-beam confocal transducer, 25 mm in diameter, to intersect 2 ultrasound beams at 7-cm focal distance. Bursts of 40-kHz vibrations were obtained from interference of 3.48-MHz and 3.52-MHz frequencies, calibrated to a peak negative pressure of 350 kPa at 3.5 MHz and originating from 2 separate signal generators (Model 33120A, Agilent Technologies, Palo Alto, CA). Each tone burst formed a narrow, approximately cylindrical (2 mm in diameter, 10 mm in length) region of radiation force. In a water tank, a thin (0.25 mm) plastic tube (11 mm in diameter) was centered at the beam intersection Fig. 5. Using rubber conduits, diluted contrast agent was continuously run through the plastic tube by means of a peristaltic flow pump (Model 7518-10, Cole-Parmer Instrument Co., Vernon Hills, IL). A flow meter (Model T106, Transonic Systems Inc., Ithaca, NY) was used to set and maintain a constant flow rate. An underwater microphone (Model 8106, Bruel & Kjaer, Naerum, Denmark) detected the emitted audio signals via a band-pass filter (Model SR650, Stanford Research Systems, Sunnyvale, CA) centered at 40 ± 4 kHz for a -6 dB cutoff. The filter eliminated confounding audio signals from the surrounding environment, while passing the emitted audio signal. A digital oscilloscope (Model 3014, Tektronix Inc., Beaverton, OR) measured the peak amplitude of the stimulated audio signals.

A suspension of Optison™ (Mallinckrodt Inc., St. Louis, MO) is provided in 3 mL vials at a concentration of approximately 6.0×10^8 bubbles/mL and with 3.8-μm mean diameter. Using a tuberculin syringe, small amounts of the pre-mixed Optison were subsequently diluted in degassed distilled water to achieve the desired incremental testing concentrations.

6 Agent Vibrometry Results

We found that with increasing concentration of Optison, the amplitude of the stimulated audio signal reached a plateau. However, for concentrations of Optison less than about 4.0×10^5 bubbles/ml, the peak audio signal amplitude was linear (Fig. 6). We related pulsing intervals of the radiation force bursts to the peak audio signal amplitude for various flow rates (Fig. 7). Quantitative analysis of flow was based on the replenishment method described by Wei et al.[10]. Briefly, contrast microbubbles administered in a continuous infusion can be destroyed by a burst of ultrasound energy. The replenishment rate of the bubbles then provides a relative measure of mean microbubble velocity. Higher pulsing rates destroy more bubbles and the acoustic emission would be expected to decrease. Greater flow rate or bubble concentration will increase the acoustic emission. The relationship between the pulsing interval and the peak acoustic amplitude is described by a least-square fitted exponential function $y = A(1\text{-}e^{-\beta t})$, where y is the resulting peak acoustic amplitude, A represents the plateau value of the peak amplitude, β is the rate constant of the peak amplitude, and t is the pulsing interval [10,11].

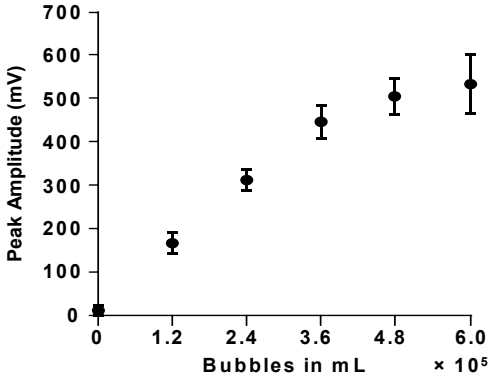

Fig. 6 Acoustic emission from contrast microbubbles is linear with concentration up to about 4 x 10^5 bubbles/mL.

Using a least-square exponential curve fit, we obtained values of A and β. The A-value, which is a function of microbubble concentration, ultimately reached a plateau that was similar for all testing flow rates, because microbubble concentration was kept constant. The value of β is proportional to volumetric flow. Figure 8 shows data

that demonstrate that β is highly correlated with flow, as expected, because the cross-sectional area of the flow conduit was unchanged in our model.

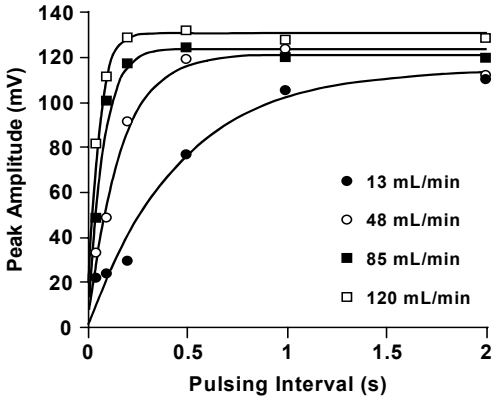

Fig. 7. Variation of Acoustic emission peak amplitude as function of pulsing rate and flow. Higher pulsing rates cause lower emission because fewer bubbles have traversed into the intersection of the two beams.

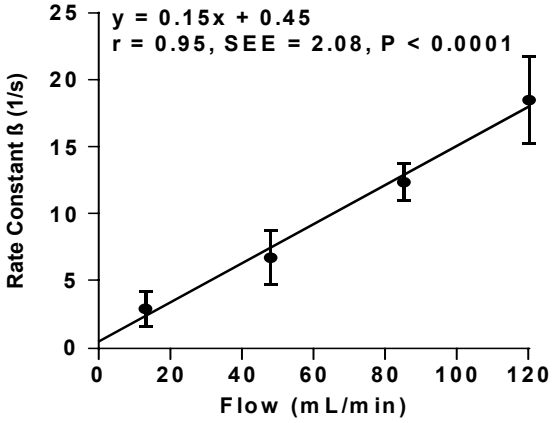

Fig.. 8. Rate constant versus flow from the bubble destruction/Vibro-acoustic flow curves of Fig. 5. Highly linear flow measurements are possible with Vibro-acoustographic point measurements within a vessel.

7 Discussion

Vibro-acoustography provides high contrast, high resolution and speckle free images that are related to object stiffness and acoustic characteristics. The format is the C-scan mode. Rather than obtaining a line in the image for each transmit Vibro-acoustography requires one transmit per pixel. The range of audio frequencies that can be used is very broad, as broad as the bandwidth of the ultrasound transducer, e.g., from DC to several hundred kilohertz. Vibro-acoustography provides objective, quantitative, and highly-localized assessment of contrast microbubble concentration and flow. The signal exhibits a linear response to low concentrations of microbubbles over a range applicable to *in vivo* use. The rate constant of a model of the response to varying pulsing intervals correlates with flow.

8 Summary

Vibro-acoustography can provide images of vessels within tissue and of objects with differing stiffness. The resolution of vibro-acoustography is similar to that of the ultrasound used to produce the radiation pressure. The images are free of speckle rivaling those of MRI in quality and time of acquisition. We demonstrate for the first time that contrast microbubbles can be detected and flow quantitated based on localized "remote tapping" of bubbles rather than on their harmonic response to high-frequency ultrasound. Additional work must concentrate on development of more realistic models and - ultimately - tests in humans before the technique can be introduced to a clinical environment.

9 Acknowledgment

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