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(54) Title: IMAGE-BASED DYNAMIC ULTRASOUND SPECTROGRAPHY TO LOCATE BREAST MICRO-CALCIFICATION

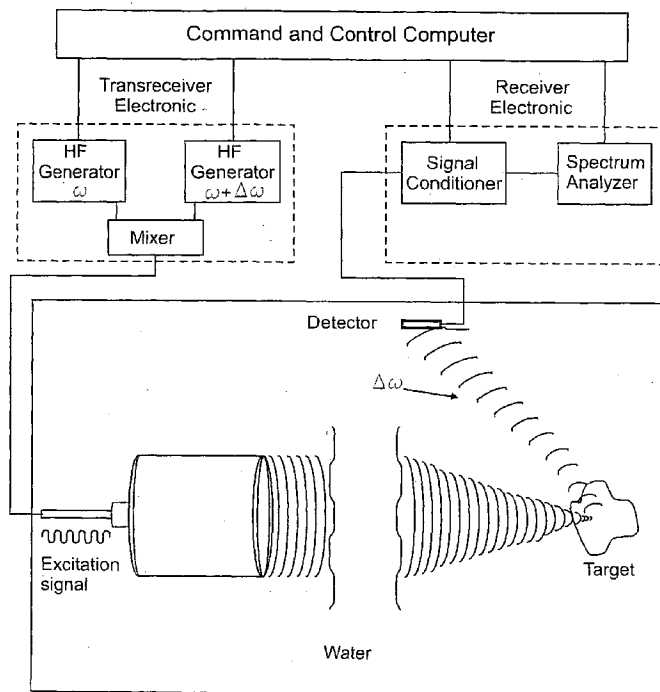


FIG. 1: IDUS™ - The Principle

(57) Abstract: It is an object of the present invention to provide a method for the detection and localization of breast micro-calcification through a precise method of ultrasound impacting and ultrasound frequency wave detection which will enable the system to detect not only if there is a micro-calcification in the breast, but the precise location of the micro-calcification and the mass of the micro-calcification. The invention is also a method and system that provides bi-modal image guided stimulation of a targeted mass within the breast to determine the location and nature of the micro-calcification within the breast.

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IMAGE-BASED DYNAMIC ULTRASOUND SPECTROGRAPHY TO LOCATE BREAST MICRO-CALCIFICATION

TECHNICAL FIELD

The present invention relates to the diagnosis of medical conditions and in particular to medical diagnosis of abnormalities within a female breast which is performed through the use of non-invasive ultrasound techniques to determine whether or not there is any micro-calcification in a female breast and further, to determine the location where the micro-calcification is located as well as the size of the micro-calcification.

BACKGROUND ART

In general, breast screening for cancer and micro-calcification detection have been performed using different imaging modalities in the prior art and there are several techniques that are currently in active use. The techniques are as follows:

X-ray Mammography

To date, X-ray mammography is the method of choice and the “*gold standard*” for breast screening and diagnosis with which other technologies are compared. In

order to perform this test a breast is exposed to an X-ray beam whose transmission is measured. The breast is rather strongly compressed between an X-ray sensitive screen and a transparent plate to:

- Obtain a uniform thickness,
- Reduce the total thickness in order to facilitate operation in the range of lower photon energy levels and higher contrast between tissues, to obtain a clearer image, and
- Reduce overlapping of the different inner breast tissues to increase clarity of the image and better sensitivity.

X-ray mammography was first pioneered by Warren in 1930 but it has been widely used only for the last 30 years. The identification of a breast lesion relies on the imaging of radiographic density changes caused by the lesion and associated changes in breast architecture, vascularity or skin contour. Radiographically, benign lesions are usually less dense than those that are malignant, and in general they have smooth outlines. Malignant lesions, on the other hand, have irregular outlines. When the breast is glandular it is more difficult to image its architecture than when the breast contains large amounts of fat. The breast might be so radiographically dense that breast structure cannot be imaged with sufficient clarity to identify a discrete mass. In the fatty breast the tumor may be clearly visible, as well as changes in vascularity and skin contour. Although, larger tumor in a dense breast can be seen less clearly, it may be identifiable by *micro-calcifications*. *In vivo* radiographic studies on the incidence of *micro-calcifications* show that they can be detected in 40% to 50% of malignant tumors and in

about 20% of benign tumors, and histological sections show even higher percentages. Several randomized controlled studies undertaken in different countries to assess the value of screening mammography have demonstrated a clear benefit of screening mammography for women over age 50 or even over the age of 40 in some countries. Although the results for women younger than age 50 are still controversial.

During the last fifteen years, mammography screening has reduced the mortality rate among women with breast cancer considerably¹, by detecting approximately 85% to 90% of breast cancers. The reported *sensitivity* of X-ray mammography varies from 83% to 95%. The reported *specificity* of X-ray mammography varies from 90% to 98%. However, the reported positive predictive value (PPV) which includes the prevalence of detecting the disease is quite poor, varying from 10% to 50%.

In many developed countries, the film-screen mammography (FSM) is being gradually replaced by full-field digital mammography (FFDM) which is identical to FSM except for the electronic detector that captures and facilitates display of the X-ray signals on a computer or laser-printed film. Although the resolution of the new FFDM instruments is not higher than the traditional FSM technique, additional data processing may help to find tumor marks with higher accuracy.

Two and Three Dimensional Ultrasound Imaging

Conventional ultrasound imaging utilizes megahertz frequency sound waves

¹ "Preventing Chronic Diseases: Investing Wisely in Health Screening to Prevent Cancer Deaths", U.S. Department of Health and Human Services.

which reflect at boundaries between tissue with different acoustic impedance, which is the product of the penetrating sound velocity and material density. The time interval of arrival of these reflections is proportional to the depth of field (boundaries of a targeted area). Thus, ultrasound can map acoustic tissue boundaries. Traditionally, 2-dimensional ultrasound imaging is used as an adjunct to X-ray mammography in the identification and differentiation of cysts or solid masses. Ultrasound imaging of the breast may also help radiologists to evaluate some lumps that can be felt but that are difficult to see on X-ray mammogram, especially in dense breast or implants. It is also in wide use in guided biopsy since it allows real time imaging of the breast. 3-Dimensional ultrasound imaging is seldom used in breast screening due to very limited added information.

Evaluation of the ultrasound technique in distinguishing malignant from benign tumors has shown the accuracy of benign condition detection to be 99.5%. Reportedly, a combination of ultrasonography and standard X-ray mammography has yielded a *sensitivity* of 92% and a *specificity* of 98%. With recent advancements in ultrasound platforms, some earlier-stage, clinically occult tumors, that were missed by screening mammography, could be detected. Since the speed of sound in fatty and less fatty breast tissues are approximately the same, ultrasound possesses a promising role in the future screening of younger women with dense breast and high risk factors.

Magnetic Resonance Imaging (MRI)

MR images are created by recording the signals generated after radiofrequency

excitation of hydrogen nuclei (or other elements) in tissue exposed to a strong static magnetic field. The signals have characteristics that vary according to the tissue type (fat, muscle, fibrotic tissue, etc.).

The method has minimal hazards from magnetic field effects and does not use ionizing radiation. The first MRI results of the human breast were disappointing, but subsequent use of an intravenous gadolinium based contrast agent has offered a clear advance and increased sensitivity. Reportedly, the *sensitivity* of contrast-enhanced MRI in detection of suspicious breast lesions varies from 88% to 100% (average reported *sensitivity* of about 95%). However the *specificity* of the contrast-enhanced MRI has been quoted as rather variable, ranging from 37% to 100%. This is mainly because of considerable exceptions and overlaps in contrast agent uptake and kinetics between benign and malignant tumors. The prevalence of cancer by MRI screening in high risk women is significantly greater than that reported in a similar population screened by ultrasound (4% vs. 1.3%)². However, neither the technique nor the interpretive criteria are standardized as of to date, leading to variability in performance and in results interpretation. In addition, MRI can only be performed in a setting in which it is possible to perform biopsy of lesions detected solely by MRI.

Despite its high accuracy in detecting malignancies in breast, MRI is not recommended as a routine examination for the differentiation of benign and malignant

² E.A Morris, L. Liberman, D.J. Ballow et al. 2003 " MRI of Occult Breast Carcenoma in a high risk population", *AJR* 2003;181:619-626.

lesions/tumors. MRI is a prohibitively expensive modality and it is unsuitable for large-scale screening programs. A US survey conducted by market research firm IVM has revealed that not more than 17% of US imaging facilities provide MRI imaging on site. Nonetheless, where available, MRI can be used as a complementary methodology to assist in differential diagnosis of uncertain lesions.

Positron Emission Tomography (PET) Scan

To conduct a PET scan, a short-lived radioactive tracer isotope, which decays by emitting a positron (chemically incorporated into a metabolically active molecule), is injected into the blood circulation. There is a waiting period while the metabolically active molecule becomes concentrated in tissues of interest; then the patient is placed in the imaging scanner where the positron encounters an electron, producing a pair of photons moving in almost opposite directions. These are detected when they reach a sensitive material in the scanning device, creating a burst of light which is detected by photomultiplier tubes.

Optical Mammography and Spectroscopy of Breast

In the past decade, optical imaging techniques using near-infrared light (NIR) have attracted considerable interest. Characterization, differentiation and localization of different lesions are possible due to the presence of optical absorption contrast between tumors and healthy tissues due to an increased hemoglobin concentration as a result of angiogenesis. The hemoglobin oxygen saturation of suspicious sites can be reconstructed by spectroscopic analysis and can additionally serve as a criterion for

diagnosing malignancies. Optical imaging techniques incorporate detection of photons that propagate through the breast with light propagation models to reconstruct the optical properties of the illuminated tissue. By altering the wavelength of the optical source, the spectroscopic dependence of optical properties can be obtained.

An early trans-illumination platform for breast lesion detection demonstrated low *sensitivity*, *specificity* and *reproducibility*. The optical imaging techniques can be split into three groups:

- Continuous wave (CW)
- Time-domain
- Frequency-domain

Each group has its own strengths and weaknesses. Optical imaging techniques have some advantages and drawbacks. The notable advantages are that they:

- Are relatively inexpensive
- Use NIR and do not impose ionizing radiation
- Have potential for portability

The major drawback associated with optical imaging remains light propagation in biological tissue, which is highly scattered, resulting in poor resolution. Improving spatial resolution and discriminating between absorption and scattering remain the biggest challenges that are faced by optical imaging.

Optical mammography has yet to demonstrate its potential to be a stand-alone imaging modality, mainly because of its poor *specificity* and *sensitivity*. Nevertheless,

it may supplement existing breast imaging techniques by characterizing lesions in suspicious cases, resulting in a reduction of the number of unnecessary biopsies.

Thermo/Photo-Acoustic Breast Imaging

Thermo-acoustics exposes the breast to short pulses of externally applied electromagnetic energy. Differential absorption induces differential heating of the tissue followed by rapid thermal expansion. This generates sound waves that are detected by acoustic transducers positioned around the breast. Tissues that absorb more energy expand more and produce higher amplitude sound waves. The time-of-flight, amplitude and duration of acoustic pulses recorded on the tissue surface possess information regarding the location, absorption and dimensions of the source, thereby permitting a 3-dimensional reconstruction of the targeted absorber.

When the incident electromagnetic energy is visible or NIR light, the term “photo-acoustics” is used instead of thermo-acoustics. Photo-acoustics combines the advantages of two techniques. First, like optical mammography, photo-acoustics probes the optical contrast of the tumor site with respect to surrounding tissue. Secondly, all information about optical absorption inhomogeneities is carried to the breast surface by ultrasound waves which have low attenuation and scattering in soft tissue and thus, resulting in poor *sensitivity*. Similar to thermo-acoustic techniques, photo-acoustics retain 3-dimensional structural information of the targeted area.

One of the major disadvantages of these techniques is the difficulties in displaying and analyzing the 3-dimensional information retained from the targeted area.

Therefore, the time and cost required for image retrieval and analysis of the thermo/photo-acoustic techniques are potentially greater when compared with that of X-ray mammography and ultrasound. Moreover, these techniques have yet to demonstrate *reproducibility*, adequate *sensitivity*, *specificity* and practicality.

A summary of the prior art which will be more understandable after the detailed description of the preferred embodiment is set forth in Table 1 which compares the present invention IDUS technology with leading diagnostic imaging modalities. Also, reference is made to Table 2 at the end of the detailed description of the preferred embodiment which sets forth competing imaging technologies and the strengths and weaknesses of competing imaging technologies as compared with the present invention IDUS system.

There is a significant need for an improved method which will be able to determine not only whether a micro-calcification is present in the female breast, but also be able to evaluate the size the location of the micro-calcification and through a preset series of information, determine and evaluate whether or not the micro-calcification is possibly malignant which would result in further medical treatment and biopsy to remove the micro-calcification.

DISCLOSURE OF INVENTION

The present invention is based on the utilization of externally produced, noninvasive image-based dynamic ultrasound spectrography for real-time imaging and stimulation of breast micro-calcification masses which can be under 100 microns in size and confined within the breast tissue. The purpose of this design is to: 1) detect and 2) determine the three-dimensional positioning of the micro-calcification areas within the breast in vivo for follow-ups and guidance of various medical procedures.

It has been discovered, according to the present invention, that the improved technique to locate the micro-calcification includes the utilization of a disposable compliant O-ring which is designed to be placed around the breast, leaving the center portion available for an ultrasound scanner.

It has further been discovered, according to the present invention, that in the preferred embodiment, four round reusable sensors (receivers) are firmly housed at 90 degrees apart on the O-ring. Three of the sensors would determine the X-Y-Z coordinates of the exact location of the micro-calcification within the breast. The fourth sensor is used for correcting any errors in determining the X-Y-Z coordinates by the other three sensors. Another such sensor is positioned within the imaging scanner and used to provide a reference vertical axis to: 1) determine the depth of the micro-calcification sites and 2) relative to which the said X-Y-Z coordinates are determined. In the present invention, this vertical axis is important to ensure that the positioning of micro-calcification within the breast is performed irrespective of the geometry changes

that may occur in the breast at different times and between one examination to the other.

It has also been discovered, according to the present invention, that once the O-ring and the housed sensors are positioned around the breast, an ultrasound transducer (scanner) will then scan each of the four quadrants of the breast looking for the areas of interest with potential micro-calcification. Once an area of interest (AOI) is located, the scanner will remain steady on the breast, the imaging mode of the said IDUS device is turned off and the stimulation mode of the said device is activated. The area of interest will then be stimulated by a swept band of frequencies at a given range corresponding to the natural frequency of said micro-calcifications and modulated with a megahertz (1-14 MHz) carrier frequency. When micro-calcification is present, it will be stimulated by the sequential frequency schemes of the present invention resulting in a characteristic response proportional to its mass density. The response will be monitored and recorded in real time and will appear as a spectrum where the peak frequency will be recorded and spectrally analyzed. The recorded peak frequency will be compared in real-time with a predetermined database of frequencies which will provide information as to what specific micro-calcification size the frequency corresponds to based on a predetermined map of frequencies corresponding to specific micro-calcification masses. A pre-programmed color-coded scheme will then be applied to color the site with determined micro-calcification where different micro-calcification masses will be colored differently according to the color-coded scheme.

It has further been discovered that emitted frequencies from the targeted soft tissue is estimated at few Hertz (1-50 Hz), whereas corresponding emitted frequencies from a micro-calcification sites are estimated to be in the range of 100 Hz to one KHz. It has also been discovered according to the present invention that the modulated frequency band used to stimulate the micro-calcification sites is not in the range that can stimulate the soft tissue and therefore, the sites with micro-calcification are distinguished by a unique set of frequencies from the surrounding tissue.

It has further been discovered, according to the present invention, that utilizing specialized localization methodology the exact three dimensional position of the area of interest with micro-calcification is determined based on the signals received by the receiving sensors and analyzed respectively. The exact three-dimensional position of the targeted area will be displayed on the B-mode image and marked for future reference and follow up.

It is an object of the present invention to provide a method for the detection and localization of breast micro-calcification through a precise method of ultrasound impacting and ultrasound frequency wave detection which will enable the system to detect not only if there is a micro-calcification in the breast, but the precise location of the micro-calcification and the mass of the micro-calcification.

It is a further object of the present invention to provide a method and system that

provides bi-modal image guided stimulation of a targeted mass within the breast to determine the location and nature of the micro-calcification within the breast.

It is a further object of the present invention to provide real time qualitative imaging of the targeted area and quantitative data about the mass structural of the targeted area.

It is also an object of the present invention to provide a methodology to locate micro-calcification and determine the nature of the micro-calcification without providing the drawbacks of other imaging and screening modalities such as being invasive, having no ionization radiation, being safe, reliable, cost-effective, not Doppler based, not angular-dependent and being portable, suitable for field applications and suitable for operating room conditions.

It is a further object of the present invention to provide a pre-determined series of frequency map information which is programmed into the system so that once a specific micro-calcification site is located and once its peak response frequency is determined, the peak response frequency can be compared to a preset series of mapped frequencies for correlative detection and site identification.

Further novel features and other objects of the present invention will become apparent from the following detailed description, discussion and the appended claims, taken in conjunction with the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Referring particularly to the drawings for the purpose of illustration only and not limitation, there is illustrated:

FIG. 1 is a schematic diagram of the present invention IDUS technology demonstrating the insonification procedure imposing by the modulated ultrasound frequency on a target and the detection and analysis methodology of the response frequencies emanating from the target;

FIG. 2 is a flow diagram showing the sequence of the steps of the present invention IDUS technology;

FIG. 3 is a flow diagram and pictures of the components utilizing the present invention IDUS technology;

FIG. 4 is a flow diagram showing the process of the present invention in breast screening;

FIG. 5 in general illustrates the application of the technology in the present invention;

FIG. 5A is a perspective view of the disposable O-ring with four spaced apart housing for the receiving sensors;

FIG. 5B is an exploded view showing the O-rings with the specific receiving sensors positioned on the O-ring;

FIG. 5C is a bottom perspective view of the O-ring illustrating a receiving sensor within the O-ring and also illustrating the thin transparent film underneath the sensor separating it from contacting the skin;

FIG. 5D is an exploded view showing the disposable O-ring with the receiving sensors in place located above the breast before it is positioned on a breast;

FIG. 5E is a perspective view showing the disposable O-ring and the receiving sensors positioned on the breast contacting the skin;

FIG. 5F is a perspective view showing the disposable O-ring and the receiving sensors positioned on the breast and an ultrasound scanner scanning the breast;

FIG. 5G is a perspective view showing the device in its stimulation mode and stimulating signals transmitted by the ultrasound B-mode scanner towards the area of interest;

FIG. 5H is a perspective view showing the ultrasound scanner transmitting sweeping frequencies in search for a peak response frequency from the area of interest. The disposable O-ring is attached to the breast and the receiving sensors sense the response frequencies emanating from the area of interest. The detected response frequency will reach a peak when an area with micro-calcification of certain mass is detected; and

FIG. 5I shows that the recorded response frequency reaches a peak indicating an area with certain micro-calcification mass detected within the breast;

FIG. 6A shows the schematics of the relative locations of the five receiving sensors. Four sensors are positioned around the O-ring wherein the fifth one is embedded within the transmitting transducer and provide a reference axis relative to the other four receiving sensors.

FIG. 6B shows the schematics of the signal from the target received by the receiving sensors. The stimulated target emanates resonant frequency signals to all directions. The four receiving sensors determine the 3-D position of the target wherein the fifth one provides a reference axis to the target. This reference axis is used to refer the position of any detected target at any point of time to any future examination on the same subject. This will enable the technique to be used over different periods of time to examine the same targeted area.

MODES FOR CARRYING OUT THE INVENTION

Although specific embodiments of the present invention will now be described with reference to the drawings, it should be understood that such embodiments are by way of example only and merely illustrative of but a small number of the many possible specific embodiments which can represent applications of the principles of the present invention. Various changes and modifications obvious to one skilled in the art to which the present invention pertains are deemed to be within the spirit, scope and contemplation of the present invention as further defined in the appended claims.

The fundamental concept of the present invention is depicted in the enclosed Figure 1 which is a schematic representation of the present invention as described below.

The invention for the noninvasive remote ultrasound detection and localization of the targeted breast micro-calcification masses by sensing their emanating acoustic response is based on the insonification of the breast areas with micro-calcification masses with two or more sweeping ultrasound waves differing slightly in frequency, to result in application of a sweeping low frequency (Hertz or kilohertz) acoustic force, at the micro-calcification areas. This low frequency radiation force will stimulate the micro-calcification masses and instigate their vibration at frequencies typical of their masses, generating unique signatures. The vibrational response of the micro-

calcification which is related to the difference of the two or more transmitted ultrasound frequencies (low frequency modulation), is measured by an array of noninvasive remote low frequency (Hz or kHz) acoustic detectors. This measurement allows for the evaluation of the acoustic signatures according to a pre-defined frequency signature map corresponding to different masses of micro-calcification, thus providing information on the 3-dimensional real-time positioning of the micro-calcification areas within the breast tissue within the body. This technique involves two main components:

- (i) The aiming high frequency ultrasound scanner and insonifiers, and
- (ii) The wide angle, low frequency array of acoustic detectors/receivers.

Ultrasound radiation modalities have a very small wavelength, to demonstrate the necessary spatial resolution for exact targeting of the interrogated breast micro-calcification areas. Generally, it is well known in the art that many rigid structures, especially those characterized by distinguished vibratory mass, shapes and materials, manifest acoustic natural resonances at particular frequencies, which can serve as their acoustic signatures. The acoustic signature is strongly dependent on the structure, density and material strain coefficients and the targeted areas relative to the surrounding environment. These resonances can be experimentally measured by the excitation of the modes of vibrations and listening to the radiated acoustic waves by known listening devices, like our ears, microphones, accelerometers, etc. Additionally, such acoustic resonances can be theoretically predicted using different computer programs, like the Finite Elements Method.

The present invention remotely measures the characteristic acoustic signature/s of the micro-calcification areas/masses, using high frequency ultrasound (1-14 MHz), which is well known to be able to penetrate the human body (skin, fat, muscle, etc) and image the area of interest with high precision. By interrogating the imaged areas of interest, characteristic response frequencies will be recorded if micro-calcification is present. Real-time detection and analysis of the emitted acoustic response signature from an area with micro-calcification by a single detector/receiver can provide a single dimension position of the targeted area. Time-of-Flight and other triangulation techniques are used, with at least three receivers positioned such as to obtain the three-dimensional real-time position of the targeted area. The advantage of this invention is in its spatial resolution, which is independent of the ultrasound imaging resolution and ultrasound imaging capabilities which is safe compared to other X-ray-based imaging modalities.

The IDUS™ Technology – The Rationale

The Image-based Dynamic Ultrasound Spectrography (IDUS)™ has already been shown to provide a real-time, safe, reliable and cost-effective diagnostic technique for detection of structural flaws in implanted medical devices. The fundamental concept of IDUS™ is to excite the target externally and then measure its response by using specialized sensor/s. By measuring the emanating response of the target, its structural state can be determined relative to the surrounding environment.

IDUSTM - The Principle

Image-based Dynamic Ultrasound Spectrography (IDUS)TM is an active acoustic technology in which the targeted site is imaged first and then stimulated using proprietary and specialized ultrasound schemes delivered by the same ultrasound imaging transducer (see Figure 1). The frequency response of the resulting stimuli is detected by a detector or a series of detectors positioned externally on the body and in the immediate vicinity of the transmitting transducer, and analyzed in real-time using proprietary algorithm.

IDUSTM – The Sequence

Following the conventional ultrasound imaging, the Active Acoustics Approach (AAA) uses multiple ultrasound beams at differential frequencies to stimulate the target (Figure 2, Step 1). By projecting these beams onto the object, an oscillating radiation point-force is applied onto the object, which in return produces unique acoustic signals (Step 2). The emitted acoustic signal is recorded by a sensitive detector or a series of detectors located in the vicinity of the targeted object (Step 3). The recorded response is subsequently analyzed and compared with pre-defined frequency maps and characterized (Step 4).

IDUSTM is a platform technology that utilizes AAA to offer a real-time, bi-modal methodology based on non-invasively imaging of the area of interest (AOI), and

A) Stimulating the AOI with specialized ultrasound-based waveform schemes,

- B) Performing spectral analysis of the target's response to external stimulation,
- C) Correlating the response with pre-existing frequency maps and identifying the target, and
- D) Navigating and positioning of the AOI in 3-dimension.

Identification of the target is performed according to its characteristic peak response frequency signature, which is unique to its mechanical and material properties (viscosity, elasticity, plasticity, visco-elasticity, etc). Based on the recorded acoustic fingerprint, the target is classified in different categories of frequency bands. In IDUS™, each of the defined categories is investigated by sweeping the ultrasound energy imposed onto the target in each frequency band. The response frequency could deviate from a few Hz to several KHz and the response could be in the form of a narrow peak or a band of frequencies, based on the mass density and stiffness coefficient of the targeted area/material. A combination of IDUS™ and other modalities for measuring the elasticity of the targeted area will provide a complete and unique methodology for breast screening. For example, early detection of micro-calcification in breast tissue (<100 micrometers typical dimension) and an assessment of the elasticity/stiffness of the AOI will provide important diagnostic information on the targeted area.

Presenting the IDUS™ System for Breast Micro-Calcification Detection

IDUS™ has been designed to either standalone as a dual-mode diagnostic ultrasound platform or be integrated to and perform in conjunction with a standard ultrasound

imaging platform. The IDUS™ system uses *BioQuantetics*' proprietary ultrasound technology to stimulate the area of interest (AOI) in the breast and subsequently analyzes and characterizes the response frequency of the targeted area in search for micro-calcification based on spectrography techniques. The dual-mode platform technology may utilize state-of-the-art ultrasound platforms and acoustic technologies for imaging, stimulating, frequency recording and localizing the AOI. Real-time spectral analysis determines the target's particular spectral resonance signature corresponding to its state.

Using IDUS™ system, detection of breast micro-calcification (<100 micrometer) will be done during a routine clinical ultrasound examination providing additional quantitative information (stored in individual libraries for every patient). Since the examination is cost-effective and does not expose the examinee to any ionizing radiation whatsoever, it can be repeated on a more frequently basis (if required) for guidance, more effective follow-ups and selection of treatment/s. The components of the IDUS™ system for breast screening are described in the Figure 3. In addition to the software for stimulation scheme, data analysis and processing and 3-D navigation, the most important hardware components of the IDUS™ system are: 1) the specialized power amplifier, 2) the sensors and 3) the modified imaging transducer. The power amplifier is an integral part of any standard ultrasound platform which may be modified to meet IDUS™ specifications. The sensors have to be custom-made to meet the sensitivity requirements for the range of emitted frequencies from breast

micro-calcification. The only modification to the imaging transducer is related to the 3-D localization capability of the IDUS™ system. Other devices required for implementation of the IDUS™ system are standard components of any ultrasound platform and can be accommodated within the platform itself. These include: A) electronic filters, B) high-speed processors, C) display monitors and C) video card, a keyboard and a trackball.

It is important to note, that the IDUS™ also includes a disposable “O-ring”, made out of biocompatible material, available in five different sizes according to the breast size (i.e., x-small, small, medium, large and x-large) and houses four sensors. The ring stably surrounds the breast by biocompatible adhesive material prior to the examination, facilitating the sensors to firmly couple with the breast skin via a thin film. The film will prevent formation of an air gap between the sensor and the skin, thus enhancing returned data acquisition and eliminating the possibility of signal attenuation or distortion. It is expected that two rings will be used for screening two breasts in one examinee.

How Does It Work?

Imaging Mode - The imaging feature of an ultrasound platform provides a 2 or 3-dimensional B-mode (grayscale) image of the targeted area (commonly performed during any routine procedure), Figure 4. The image is obtained by using a linear-array transducer with a center frequency ranging from 1.0 megahertz (MHz) to 14 MHz depending on the application and depth of the AOI. Higher frequency provides imaging

of smaller depth. For example, a 3 MHz transducer can provide images at depth of 12 to 15 centimeters in the body, whereas a 14 MHz transducer (typically used in pediatric applications) can provide images of targets at approximately 1.5 centimeters depth. The grayscale imaging resolution of the advanced ultrasound platforms are reasonably high and thus their improved mapping capabilities.

Stimulation Mode – Once the grayscale image of the targeted area (any cross sectional scanned area) has been obtained and AOI marked, the procedure is switched to the stimulation mode where the AOI is projected with specific ultrasound waveform (energy) scheme/s delivered by IDUSTM via the same imaging transducer. By projection of the ultrasound energy scheme/s onto the target, an oscillating force is generated that sets the object to vibrate at or near its lowest natural frequency. The resulting vibration produces sound signals (a unique signature), which is received by a series of receiving sensors positioned on the body (i.e., breast) in the vicinity of the ultrasound imaging scanner. A typical receiver is about 19 millimeters in diameter. The emitted frequencies may vary from a few Hz to several KHz depending on the physical nature of the stimulated target.

IDUSTM analyzes the recorded signals in real-time to identify maximum emitted frequencies. The maximum peak of the frequency spectrum is then compared to a pre-defined map of frequencies corresponding to a potential targeted area (i.e., micro-calcification). The pre-defined frequency map can be programmed into the ultrasound platform software. When a correlation between the recorded peak frequency and the

programmed frequency map is found, the AOI on the B-mode image is colored according to a programmed color-coded scheme. The procedure is then switched back to the imaging mode and another area is screened and the sequence is repeated.

A specific frequency map will be developed for each medical application of the IDUS™ platform technology (breast, cardiac, orthopedic, etc.) and embedded into the ultrasound imaging platform database. The transition between different applications of IDUS™ is expected to be straightforward and will essentially be the same as done at present.

IDUS™ possesses a number of unique advantages:

Non-invasive detection of structural differences in a targeted area can be achieved based on spectral analysis of the response frequency as a result of external stimulation - The characteristics of the vibrations of various targets (breast micro-calcification, stress fractures, fractures in implanted mechanical devices, injured knee cartilage, muscle infract, etc.) and resultant sound signals are different and distinguishable in different material and mediums. Thus, detection and classification of unique frequency signatures allows differentiation and diagnosis of mechanical characteristics.

Real-time imaging - Saves on time-consuming image acquisition and post-processing, and especially streamlines guided biopsy and surgery.

High sensitivity and specificity - Different targets have different and yet specific frequency response signatures corresponding to their state. These will result in

enhanced sensitivity and specificity of the IDUS™ technology.

User intuitive - The system is based on common ultrasound screening technology.

Therefore, no complex or extraordinary training is required.

No ionizing radiation - IDUS™ allows frequent screening of populations at high risk, and frequent treatment follow-ups, with no hazard of radiation involved in X-ray based screening modalities.

Low cost capital equipment - The system is based on conventional ultrasound imaging technology, and will be marketed by ultrasound manufacturers as a standalone system or as an integral part of a high-end ultrasound platform at acceptable premium price.

High accessibility for patient follow-up - The IDUS™ system will be potentially available in every hospital, field and clinical setup currently hosting ultrasound equipment. Additionally, it may be used in operating rooms, field hospitals and rural areas without a need for major real-estate and special infrastructure.

Cost-effective treatments - The reimbursement cost of the new modality is expected to be much lower than competing functional imaging modalities such as MRI.

Multiple applications – For example, breast, cardiac, orthopedic, cranial, abdominal, etc.

3-D positioning – A unique advantage of the IDUS™ system which will allow for better imaging when combined with 3-dimensional ultrasound capabilities or for better positioning and localization of the AOI by using GPS compatible technologies.

Table 1 compares the IDUS™ technology with leading imaging technologies (currently available for breast screening or under development) according to several critical success factors. Note that complete information on some of the new modalities under development is not readily available and thus, the evaluation presented in this Table has been done based on preliminary assessments and estimations. For instance, the opto/thermo acoustic technologies have yet to be introduced to the market and proven practical and reliable. Their true evaluation will be possible following initial employment in clinical settings.

Introducing the IDUS™ Breast Screening Application

IDUS™ functional imaging diagnostic technology will provide a safe, cost-effective, and reliable methodology with no ionizing radiation that can accurately detect small areas of micro-calcification (<100 microns) in breast based on their characteristic emitted frequencies.

How does it work in breast screening?

Referring to Figures 4 and 5 and subfigures 5A through 5I, the IDUS™ functional imaging diagnostic procedure is carried out according to the following steps:

1. The patient is asked to lie supine on the examination bed.
2. A disposable and compliant O-ring will be placed around the breast, leaving the center portion available for the ultrasound r/scanner. The disposable O-ring has four

housing openings for the receiving sensors, which are spaced 90 degrees apart. In each O-ring there is received a reusable sensor designed to be placed within a respective housing. A perspective view of a reusable sensor is shown in Figure 5B.

3. Four small (round, approximately 20 mm in diameter) and sensitive reusable sensors will be placed into their designed housings around the O ring (Step 2). Once in their housing, the sensors will be coupled with a thin and transparent film as illustrated in Figure 5C, which will be firmly coupled with the skin by a layer of biocompatible adhesive surrounding the opening. Referring to Figure 5D, the disposable O-ring with the sensors in place is located above the breast and thereafter as shown in Figure 5E is positioned on the breast and affixed to the breast by removable adhesive around the bottom of the disposable O-ring as well as adhesive on the thin transparent film so that the disposable O-ring is firmly positioned on the breast during the scanning procedure.
4. Referring to Figures 5F to 5I, the B-mode ultrasound scanner will then scan each of the four quadrants of the breast looking for AOI with potential micro-calcification. The transmitted ultrasound frequency can be varied from 1-14 MHz covering a range of depths. The automatic frequency transition is a standard feature of the advanced ultrasound platforms to date. Once located, the scanner will remain steady, the B-mode image will be "locked" and the AOI marked. AOI will be then stimulated by a swept band of ultrasound frequencies generated by proprietary sequence of specialized schemes via the same ultrasound imager/scanner.

4.A. FIG. 5F shows a perspective view showing the disposable O-ring and the receiving sensors positioned on the breast and an ultrasound scanner scanning the breast. The B-mode ultrasound image is generated. Figure 5G is a perspective view showing the device in its stimulation mode and stimulating signals transmitted by the ultrasound B-mode scanner toward the area of interest. Figure 5H is a perspective view showing the ultrasound scanner transmitting sweeping frequencies in search for a peak response frequency from the area of interest. The disposable O-ring is attached to the breast and the receiving sensors sense the response frequencies emanating from the area of interest. The detected response frequency will reach a peak when an area of micro-calcification of a certain mass is detected. Finally, Figure 5I shows that the recorded response frequency reaches a peak indicating an area with certain micro-calcification mass detected within the breast. The detected area of micro-calcification is then marked on the B-mode image according to a pre-defined color-code scheme and subsequently, the exact three-dimensional position of the area with micro-calcification is determined and marked on the B-mode image and recorded for future follow-ups.

5. When micro-calcification is present, it will be stimulated by the sequential frequency schemes, resulting in emitted characteristic response proportional to its mass. The response will be monitored in real-time and will appear as a spectrum where the peak frequency will be recorded and spectrally analyzed. Preliminary experiments with IDUSTM used in breast phantoms have indicated that the emitted frequencies from targeted soft tissues can vary from 50-200 Hertz (Hz), whereas corresponding emitted frequencies from a micro-calcification site are estimated to be in the range of 250 Hz to

6. If the recorded response correlates with a pre-defined frequency database, the marked AOI on the B-mode image is colored according to a particular color-coded scheme similar to velocity classification in ultrasound color-Doppler flow mapping.
7. Using specialized localization software, the 3-dimensional position of the AOI is determined based on the signals received by the receiving sensors and analyzes respectively. The exact 3-D position of the targeted area will be displayed on the B-mode image and marked on a separate reference device for future reference.

Four round reusable sensors (receivers) are firmly housed at 90 degrees apart on the O-ring. Three of the sensors would determine the X-Y-Z coordinates of the exact location of the micro-calcification within the breast. The fourth sensor is used for correcting any errors in determining the X-Y-Z coordinates by the other three sensors. Another such sensor is positioned within the imaging scanner and used to provide a reference vertical axis (Figure 6A and 6B) to: 1) determine the depth of the micro-calcification sites and 2) relative to which the said X-Y-Z coordinates are determined. In the present invention, this vertical axis is important to ensure that the positioning of micro-calcification within the breast is performed irrespective of the geometry changes that may occur in the breast at different times and between one examination to the other.

Competing Imaging Technologies

Table 2 presents the competition among imaging technologies, their strengths and weaknesses when compared to IDUSTM technology.

| Table 1: IDUS™ Technology Compared with Leading Diagnostic Imaging Modalities | | | | | | |
|--|--------------|---------------------------|--------------------------|-----------|----------------|-------------------------------|
| Imaging Technology | IDUS™ | Imaging Ultrasound | X-ray Mammography | CT | MRI | Opto/Thermo Acoustics* |
| Principle | Ultrasound | Ultrasound | X-ray | X-ray | Magnetic Field | Light/Laser |
| Penetration Depth | ≤ 20 cm | ≤ 20 cm | Whole | Whole | Whole | ~ 5 cm |
| Real-Time | Yes | Yes | Yes | No | No | No |
| Sensitivity | ≤ 100 μm | ≤ 200 μm | ≤ 100 μm | ≤ 100 μm | ≤ 100 μm | ~ 5 mm |
| Dual-Mode | Yes | No | No | No | Yes | No |
| Ionizing Radiation | No | No | Yes | Yes | No | No |
| Interventional | Yes | Yes | Yes | No | No | No |
| Cost | Low | Low | Low | High | High | Low** |
| Market DIC/PO | DIC & PO | DIC & PO | DIC | DIC | DIC | DIC |

* These techniques have yet to demonstrate data reproducibility and practicality in clinical settings

** The cost of the opto/thermo acoustic techniques is unknown and the evaluation has been done based on initial assessments

DIC – Diagnostic imaging center

PO – Physician office

Table 2: Competing Imaging Technologies

| Technology | Strengths | Weaknesses | Selected Manufacturers |
|--------------------------|---|---|--|
| IDUS™ | <ul style="list-style-type: none"> • Bi-modal, image guided excitation of the target • Provides real-time qualitative image of the targeted area and quantitative data about the structural integrity of the targeted area. • 3-D GPS-like positioning capability • Non-invasive • No ionizing radiation • Safe • Reliable • Cost-effective • Not Doppler based • Portable • Suitable for field applications • Suitable for operating room applications | <ul style="list-style-type: none"> • Frequency dependent penetration depth • Requires certain hardware modifications of conventional ultrasound platforms • Requires an specialized power amplifier | <ul style="list-style-type: none"> • <i>BioQuantetics,</i> |
| X-Ray Mammography | <ul style="list-style-type: none"> • Used in mammography and is the only FDA approved technology for cancer detection. • High penetration depth • Low cost • High resolution • Real time imaging | <ul style="list-style-type: none"> • Affected by tissue density • X-ray radiation • Requires special setting • Allows for morphologic imaging only | <ul style="list-style-type: none"> • Eastman Kodak • Fischer Imaging • GE Healthcare • Medical Systems • Lorad Corporation • Philips • Siemens • Barco • Hologic • Dalsa Life Sciences |
| MRI | <ul style="list-style-type: none"> • High resolution • Detailed images of the soft-tissue structures • High penetration depth • Allows for morphologic, as well as functional imaging | <ul style="list-style-type: none"> • The most expensive imaging technology • Requires special setting • Cannot detect calcium present in a tumor • Image degradation due to motion artifact effects | <ul style="list-style-type: none"> • Fonar Corp. • GE Healthcare • Hitachi • Philips • Siemens • Toshiba |

Table 2 (Cont.): Competing Imaging Technologies

| Technology | Strengths | Weaknesses | Selected Manufacturers |
|-----------------------------------|--|---|---|
| 2/3-Dimensional Ultrasound | <ul style="list-style-type: none"> • High Resolution • Real-Time qualitative image of the targeted area • Does not require special logistics, real-estate or settings • No ionizing radiation • Non-invasive • No ionizing radiation • Safe • Cost effective • Portable | <ul style="list-style-type: none"> • Medium penetration depth • Allows for morphologic imaging only • Low specificity | <ul style="list-style-type: none"> • B-K Medical • Siemens • GE Healthcare • Medison Co. • Philips • Shimadzu • Aloka • Hitachi • Terason • Toshiba |
| CT | <ul style="list-style-type: none"> • High penetration depth • High resolution • Identify normal and abnormal structures | <ul style="list-style-type: none"> • Not real-time • High Cost • Ionizing radiation • Requires special setting • Allows for morphologic imaging only | <ul style="list-style-type: none"> • Shimadzu Corp • Schaerer Mayfield • Siemens • Toshiba • GE Healthcare • Medrad • Xoran Technologies • Prism Microsystems • Philips |
| Digital Mammography | <ul style="list-style-type: none"> • High Penetration depth • Real Time • Display of sections as thin as 1mm • Allows for detection of cancer hiding within overlapping tissue | <ul style="list-style-type: none"> • Ionizing radiation • Requires special logistics and settings • High cost • Short life span | <ul style="list-style-type: none"> • GE Healthcare • Siemens • Hologic |
| Nuclear Imaging | <ul style="list-style-type: none"> • High penetration depth • Allows for functional imaging | <ul style="list-style-type: none"> • Medium resolution • Radiation • Requires special settings • Medium Costs • Time consuming | <ul style="list-style-type: none"> • Positron Corp. PET • Naviscan Systems • Transphoton • GE Healthcare • Siemens • Syntermed • Philips • Toshiba • Ultraspect • Hamamatsu Photonics |

Table 2 (Cont.): Competing Imaging Technologies

| Technology | Strengths | Weaknesses | Selected Manufacturers |
|---------------------------------|---|--|---|
| Tomosynthesis | <ul style="list-style-type: none"> • High resolution • 3D imaging application • Low cost | <ul style="list-style-type: none"> • Requires special setting • Short life span • Ionizing radiation | <ul style="list-style-type: none"> • GE Healthcare • Siemens • Hologic |
| Digital Infrared Imaging | <ul style="list-style-type: none"> • Detection of pre-cancerous state of the breast or the presence an early tumor that is not yet large enough to be detected by physical examination, mammography, or other types of structural imaging • No radiation • Non invasive • Real time | <ul style="list-style-type: none"> • Requires special settings • Most Effective in detecting tumors that are close to the skin surface but not tumors deeper in the breast. • Not sensitive enough to detect small tumors or micro-calcification. | <ul style="list-style-type: none"> • OptoSonics |

THE CLAIMS

1. A non-invasive method of identifying micro-calcification in a breast of a human body comprising:
- 5 a. positioning a disposable biocompatible, circular and compliant ring on the breast (O-ring) which contains four housings spaced approximately 90 degrees apart around the O-ring and each housing retaining an acoustic receiving sensor which is positioned within the O-ring;
- b. the lower surface of each sensor housing is open and retains a thin transparent biocompatible plastic film which separates the receiving sensor from contacting skin on the breast;
- 10 c. the lower surface of the O-ring around the location of the receiving sensors is covered with biocompatible self-adhesive material coupled with a removable protective material selected from the group consisting of paper or plastic material;
- d. the biocompatible self-adhesive material is exposed by peeling-off and removing the protective paper or plastic material;
- 15 e. positioning the disposable O-ring on and around a human breast and removably adhering the O-ring onto the breast so that the sensor housings and the thin film firmly coupled with the skin of the breast and located at positions approximately 90 degrees apart on the breast;
- 20 f. utilizing a bi-modal IDUS functional imaging system with “Imaging Mode” and “Stimulation Mode”;
- g. the IDUS system is switched to its “Imaging Mode”;

- 25 h. a modified ultrasound imaging scanner is utilized to scan different segments of the breast and impact the breast with ultrasound imaging frequencies in the range of 1 megahertz (MHz) to 14 MHz to image the segments of the breast at each given time;
- 30 i. an ultrasound B-mode gray scale image is created whereby ultrasound frequencies are transmitted towards specific segments of the breast and subsequently reflected from the specific segment of the breast towards the scanner;
- j. the scanner is then held stationary and the IDUS system is switched to its “Stimulation Mode”;
- k. the selected segment of the breast is stimulated by a non-invasive burst or a chirp scheme delivered by the same imaging scanner;
- 35 l. when the stimulation frequency is delivered as chirp scheme, one signal generator provides chirps of different frequency ranges while the other signal generator provides a fixed frequency so that due to the difference in the applied frequencies, certain acoustic forces are generated proportional to the natural frequency of targeted micro-calcification masses that stimulates and vibrates the targeted masses;
- 40 m. a single chirp is broken down into different segments so that the frequency scan occurs in a particular and controlled sequence called “one presentation” so that the chirps can scan the desired frequency spans and search for any resonance of the target in order to maximize the time for
- 45 which each frequency span is introduced, which in turn increases the

signal-to-noise ratio (S/N);

- 50 n. when the stimulation frequency is delivered as burst sweep form the data is acquired over time wherein a fixed megahertz frequency is applied to the targeted micro-calcification masses in the form of a burst and another different megahertz frequency is incremented;
- o. in detection of stationary breast micro-calcification, said burst-sweep stimulation scheme is preferred wherein a first-hand estimate of the response is obtained and then a chirp frequency scheme is applied;
- 55 p. in either chirp or burst sweep schemes, the stimulation signal is swept over a band of Hertz or kilohertz range frequencies and the frequencies are modulated on a megahertz ultrasound carrier frequency;
- q. as a result of stimulation, the micro-calcification masses produce acoustic signals specific to their mass density and that are received by the receiving sensor positioned on the O-ring;
- 60 r. utilizing an acoustic readout means whereby certain frequencies received by one or more of the sensors positioned on the disposable O-ring;
- s. the obtained swept frequencies by each receiving sensor is compared and correlated with a predetermined map of peak frequencies corresponding to different micro-calcification masses;
- 65 t. if a detected (received) frequency by sensor/s correlates with a predetermined frequency in the frequency signature map, the targeted site on the B-mode image is color-coded using a predetermined color scheme and the exact coordinates of the site within the breast is determined based

on the readout from every sensor using certain triangulation technique;

and

- 70
- u. incorporating a fifth sensor with an imaging-stimulating transducer in the IDUS, the fifth sensor creating a reference axis in conjunction with the four acoustic receiving sensors, the fifth sensor used to create a reference axis so that the relative location of a detected micro-calcification site can
75 be marked to determine the exact location.

- 2. The apparatus in accordance with Claim 1, wherein soft breast tissues which are impacted by an acoustic force delivered by the carrier ultrasound frequency emit a response frequency of 1-50 Hz and micro-calcification masses emit frequencies in the range of 100 Hz to 1 KHz.
- 3. A non-invasive method to identify micro-calcification in a human breast comprising:
 - a. placing a disposable and compliant O-ring around the breast and leaving the center portion of the breast available for scanning by an ultrasound
5 scanner;
 - b. positioning four sensitive reusable sensors on a disposable O-ring which is placed around and removably adhered to the breast, each sensor respectively coupled with a thin and transparent film which is firmly coupled to skin on the breast by a layer of bio-compatible adhesive
10 surrounding the thin film on the O-ring;

- 15
- 20
- 25
- 30
- c. utilizing a B-mode ultrasound scanner to scan each of the four quadrants of the breast creating a gray-scale B-mode image of the area of interest with potential micro-calcification masses;
 - d. the transmitted ultrasound frequency being varied from 1 MHz to 14 MHz covering a range of depths;
 - e. once an image of the area of interest is obtained, the scanner is maintained stationary relative to the breast imaged quadrant, the B-mode image is frozen and the area of interest marked;
 - f. the area of interest is then stimulated by a swept band of frequencies generated by proprietary sequence of specialized schemes delivered by the same ultrasound imaging scanner;
 - g. when a micro-calcification mass is present, it is stimulated by sequential frequency schemes resulting in emanating a characteristic response frequency proportional to its mass;
 - h. monitoring the response in real time so that a spectrum including a peak resonant frequency is recorded and spectrally analyzed;
 - i. having the detected peak resonant frequency correlated with a predetermined database of predefined peak resonant frequencies to determine presence of a specific micro-calcification mass;
 - j. if the detected response frequency or band of frequencies correlate with peak value or values in a predefined frequency signature map, the exact three-dimensional coordinates of the area from where the frequency or frequencies have been detected is marked on the B-mode image and

colored according to particular predetermined color-coded scheme; and

35

- k. utilizing certain specialized triangulation technique, the exact three dimensional position of the area of interest is determined based on the signals received by the receiving sensors and analyzers respectively, with the exact three dimensional position of the targeted area displayed on a B-mode image and recorded for future reference.

4. The method in accordance with Claim 3, wherein frequencies of soft tissue of the breast are in the range of 1-50 Hz and frequencies which detect a micro-calcification are in the range of 100 Hz to 1 KHz.

5. The method in accordance with Claim 3, further comprising incorporating a fifth sensor within the IDUS, the fifth sensor used to create a reference axis in conjunction with the four acoustic receiving sensors, the fifth sensor used to create a reference axis so that the relative location of a detected micro-calcification can be marked to determine the exact location.

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6. A non-invasive method of identifying micro-calcification in a breast of a body, comprising:

- a. positioning a multiplicity of acoustic receiving sensors on a sensor retaining means so that the acoustic receiving sensors are spaced apart from each other;
- b. positioning the sensor retaining means on and around a human breast so

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that the multiplicity of acoustic sensors are positioned on and around the breast;

- 10 c. utilizing a bi-modal IDUS functional imaging system which has an Imaging Mode and a Stimulation Mode;
- d. utilizing the Imaging Mode of the IDUS with a modified ultrasound imaging scanner to scan different segments of the human breast and impact the human breast with ultrasound imaging frequencies in the range of 1 megahertz to 14 megahertz to image segments of the breast at given times to thereby create an ultrasound B-mode gray scale image wherein
15 ultrasound frequencies are transmitted toward specific segments of the breast and subsequently reflected from each specific segment of the breast toward the scanner;
- e. utilizing the Simulation Mode of the IDUS with said modified ultrasound imaging scanner and stimulating selected segments of the breast with a
20 non-invasive chirp scheme delivered by the modified ultrasound imaging scanner utilizing two signal generators so that one signal generator provides chirps of different frequency ranges while the other signal generator provides a fixed frequency so that due to the difference in the
25 applied frequencies, certain acoustic forces are generated proportional to the natural frequency of targeted micro-calcification masses that stimulates and vibrates the targeted masses;
- f. a single chirp is broken down into different segments so that the frequency scan occurs in a particular and controlled sequence called "one

- 30 presentation” so that the chirps can scan the desired frequency spans and
search for any resonance of the target in order to maximize the time for
which each frequency span is introduced to thereby increase the signal-to-
noise ratio;
- 35 g. the stimulation signal is swept over a band of Hertz or kilohertz range
frequencies and the frequencies are modulated on a megahertz ultrasound
carrier frequency so that the micro-calcification masses produce acoustic
signals specific to their mass density and that are received by the acoustic
receiving sensors and read out by an acoustic readout means to obtain
swept frequencies; and
- 40 h. comparing and correlating the obtained swept frequencies with a
predetermined map of peak frequencies corresponding to different micro-
calcification masses so that when a detected frequency correlates with a
predetermined frequency in the frequency signature map, the targeted site
on the B-mode image is color-coded utilizing a predetermined color
- 45 scheme and the exact coordinates of the site within the breast is
determined.
7. The method in accordance with Claim 6, further comprising incorporating an
additional sensor within the IDUS, the additional sensor used to create a reference
axis so that the relative locations of a detected micro-calcification can be marked
to determine the exact location.

8. The non-invasive method in accordance with Claim 6 wherein the exact coordinates of the site within the breast are determined based on readouts from each of the acoustic receiving sensors and utilizing triangulation techniques.
9. The non-invasive method in accordance with Claim 6 wherein said sensor retaining means is a circular compliant ring which contains spaced apart housings to respectively retain each of the multiplicity of acoustic retaining sensors.
10. The non-invasive method in accordance with Claim 9 further comprising four acoustic receiving sensors each respectively placed in a housing wherein the housing are spaced 90 degrees apart.
11. The non-invasive method in accordance with Claim 6 wherein each acoustic receiving sensor has a thin transparent biocompatible plastic film on a lower surface to separate each respective acoustic receiving sensor from the skin on the breast.
12. The non-invasive method in accordance with Claim 11 further comprising biocompatible self-adhesive material on each biocompatible plastic film.
13. The non-invasive method in accordance with Claim 12 wherein each biocompatible self-adhesive material is covered by a removable protective material.

14. A non-invasive method of identifying micro-calcification in a breast of a body, comprising:
- a. positioning a multiplicity of acoustic receiving sensors on a sensor retaining means so that the acoustic receiving sensors are spaced apart from each other;
 - b. positioning the sensor retaining means on and around a breast so that the multiplicity of acoustic sensors are positioned on and around the breast;
 - c. utilizing a bi-modal IDUS functional imaging system which has an Imaging Mode and a Stimulation Mode;
 - d. utilizing the Imaging Mode of the IDUS with a modified ultrasound imaging scanner to scan different segments of the breast and impact the human breast with ultrasound imaging frequencies in the range of 1 megahertz to 14 megahertz to image segments of the breast at given times to thereby create an ultrasound B-mode gray scale image wherein ultrasound frequencies are transmitted toward specific segments of the breast and subsequently reflected from each specific segment of the breast toward the scanner;
 - e. utilizing the Simulation Mode of the IDUS with said modified ultrasound imaging scanner and stimulating selected segments of the breast with a non-invasive burst sweep form so that data is acquired over time wherein a fixed megahertz frequency is applied to the targeted

micro-calcification masses in the form of a burst and another
different megahertz frequency is incremented to obtain a first hand
estimate of the response;

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f. the stimulation signal is swept over a band of Hertz or kilohertz range
frequencies and the frequencies are modulated on a megahertz ultrasound
carrier frequency so that the micro-calcification masses produce acoustic
signals specific to their mass density and that are received by the acoustic
receiving sensors and read out by an acoustic readout means to obtain
swept frequencies; and

30

g. comparing and correlating the obtained swept frequencies with a
predetermined map of peak frequencies corresponding to different micro-
calcification masses so that when a detected frequency correlates with a
predetermined frequency in the frequency signature map, the targeted site
on the B-mode image is color-coded utilizing a predetermined color
scheme and the exact coordinates of the site within the breast is
determined.

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15. The method in accordance with Claim 14, further comprising incorporating an additional sensor within the IDUS, the additional sensor used to create a reference axis so that the relative locations of a detected micro-calcification can be marked to determine the exact location.
16. The non-invasive method in accordance with Claim 14 wherein the exact

coordinates of the site within the breast are determined based on readouts from each of the acoustic receiving sensors and utilizing triangulation techniques.

17. The non-invasive method in accordance with Claim 14 wherein said sensor retaining means is a circular compliant ring which contains spaced apart housings to respectively retain each of the multiplicity of acoustic retaining sensors.
18. The non-invasive method in accordance with Claim 17 further comprising four acoustic receiving sensors each respectively placed in a housing wherein the housing are spaced 90 degrees apart.
19. The non-invasive method in accordance with Claim 14 wherein each acoustic receiving sensor has a thin transparent biocompatible plastic film on a lower surface to separate each respective acoustic receiving sensor from the skin on the breast.
20. The non-invasive method in accordance with Claim 19 further comprising biocompatible self-adhesive material on each biocompatible plastic film.
21. The non-invasive method in accordance with Claim 20 wherein each biocompatible self-adhesive material is covered by a removable protective material.

22. A non-invasive method to identify micro-calcification in a human breast, comprising:
- a. positioning a multiplicity of acoustic receiving sensors on a sensor retaining means so that the acoustic receiving sensors are spaced apart from each other;
 - b. positioning the sensor retaining means on and around a breast so that the multiplicity of acoustic sensors are positioned on and around the breast and leaving the center portion of the breast available for scanning by an ultrasound transducer;
 - c. utilizing a B-mode ultrasound scanner to scan each of the four quadrants of the breast creating a gray-scale B-mode image of the area of interest with potential micro-calcification masses;
 - d. the transmitted ultrasound frequency being varied from 1 MHz to 14 MHz covering a range of depths;
 - e. once an image of the area of interest is obtained, the scanner is maintained stationary relative to the breast imaged quadrant, the B-mode image is frozen and the area of interest marked;
 - f. the area of interest is then stimulated by a swept band of frequencies generated by proprietary sequence of specialized schemes delivered by the same ultrasound imaging scanner;
 - g. when a micro-calcification mass is present, it is stimulated by sequential frequency schemes resulting in emanating a characteristic response frequency proportional to its mass;
 - h. monitoring the response in real time so that a spectrum including a peak

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resonant frequency is recorded and spectrally analyzed; and

- i. having the detected peak resonant frequency correlated with a predetermined database of predefined peak resonant frequencies to determine presence of a specific micro-calcification mass.

23. The method in accordance with Claim 22 utilizing an additional sensor to create a reference axis so that the relative location of a detailed micro-calcification can be marked to determine the exact location.
24. The non-invasive method in accordance with Claim 22 wherein said sensor retaining means is a circular compliant ring which contains spaced apart housings to respectively retain each of the multiplicity of reusable sensors.
25. The non-invasive method in accordance with Claim 24 further comprising four acoustic receiving sensors each respectively placed in a housing wherein the housing are spaced 90 degrees apart.
26. The non-invasive method in accordance with Claim 22 wherein each respective acoustic sensor is reusable.
27. The non-invasive method in accordance with Claim 26 wherein each reusable sensor has a thin transparent biocompatible plastic film on a lower surface to separate each respective acoustic receiving sensor from the skin on the breast.

28. The non-invasive method in accordance with Claim 27 further comprising biocompatible self-adhesive material on each biocompatible plastic film.
29. The non-invasive method in accordance with Claim 28 wherein each biocompatible self-adhesive material is covered by a removable protective material.
30. The method in accordance with Claim 22, wherein frequencies of soft tissue of the breast are in the range of 1-50 Hz and frequencies which detect a micro-calcification are in the range of 100 Hz to 1 KHz.
31. The method in accordance with Claim 23, further comprising:
- a. if the detected response frequency or band of frequencies correlate with peak value or values in a predefined frequency signature map, the exact three-dimensional coordinates of the area from where the frequency or frequencies have been detected is marked on the B-mode image and colored according to particular predetermined color-coded scheme; and
 - b. utilizing certain specialized triangulation technique, the exact three dimensional position of the area of interest is determined based on the signals received by the receiving sensors and analyzers respectively, with the exact three dimensional position of the targeted area displayed on a B-mode image and recorded for future reference.

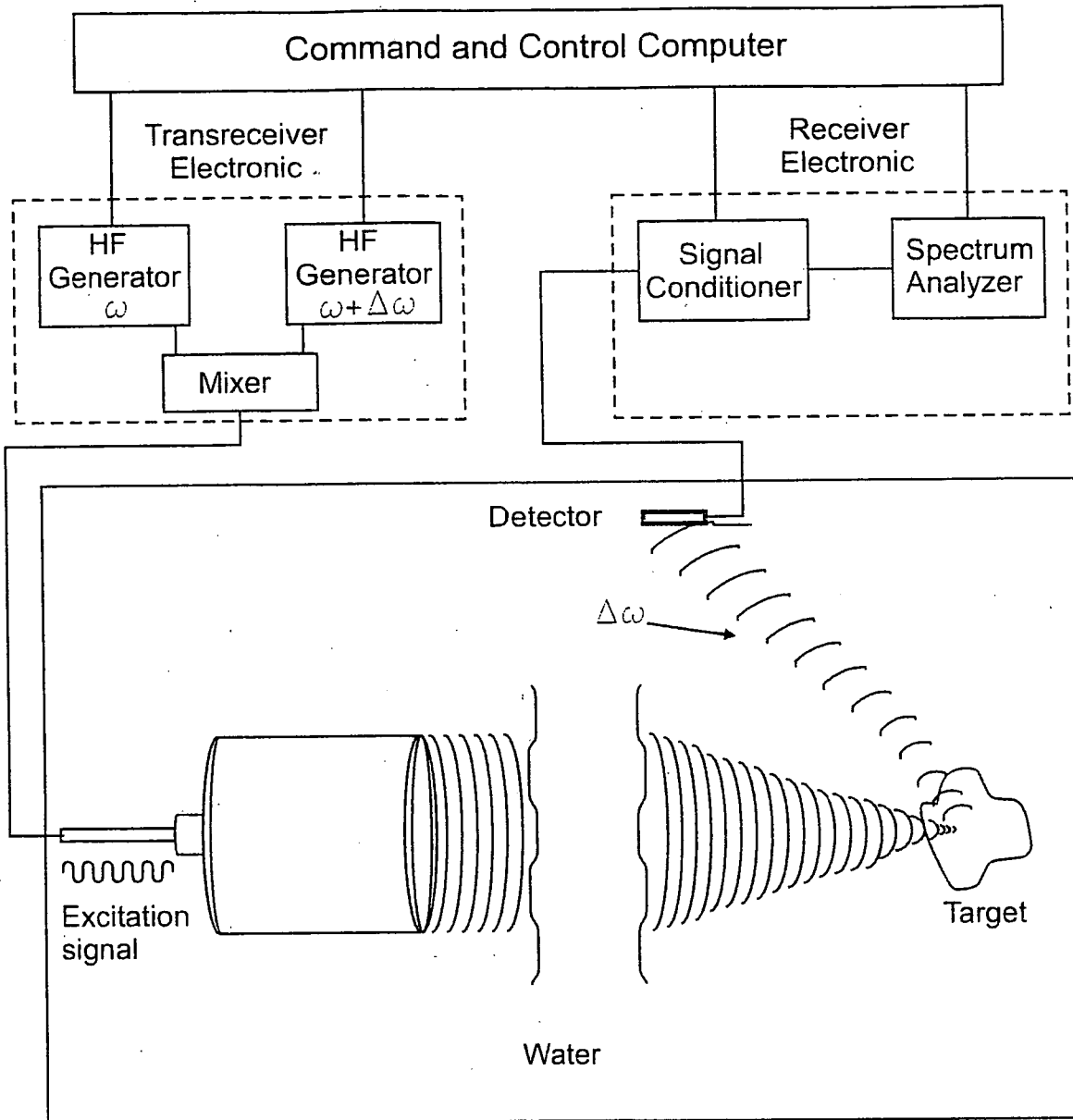


FIG. 1: IDUS™ - The Principle

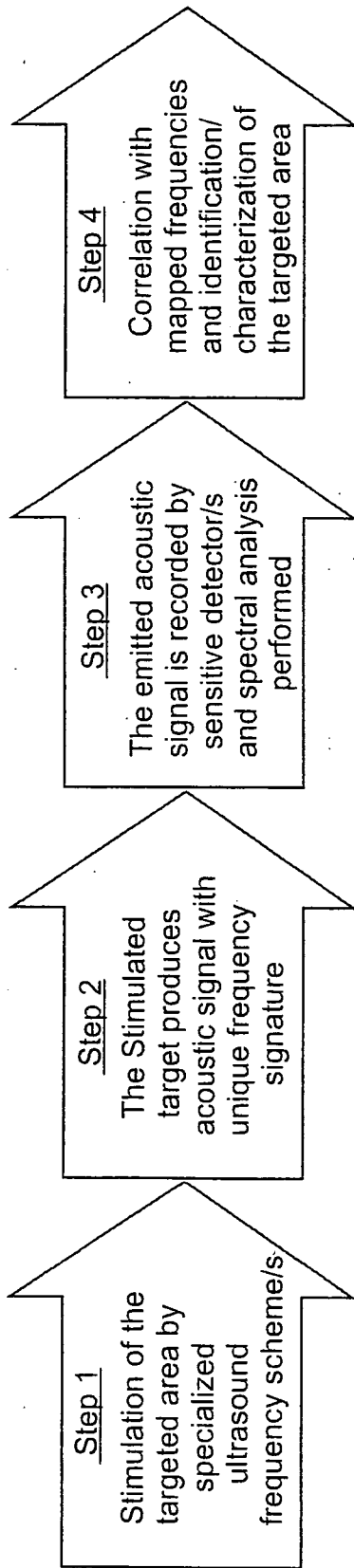


FIG. 2: IDUS™ - The Sequence

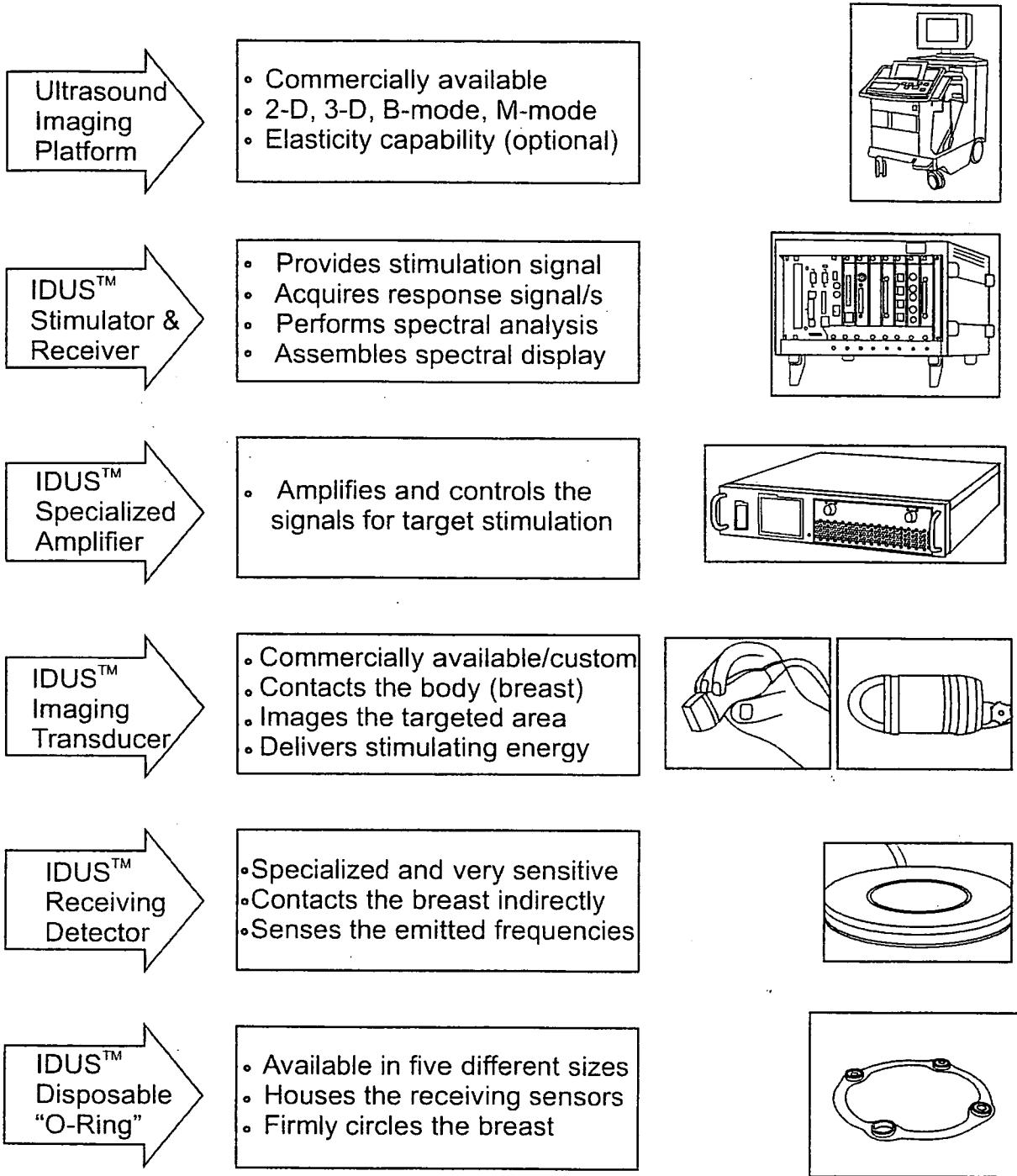


FIG. 3: IDUS™ - System Components

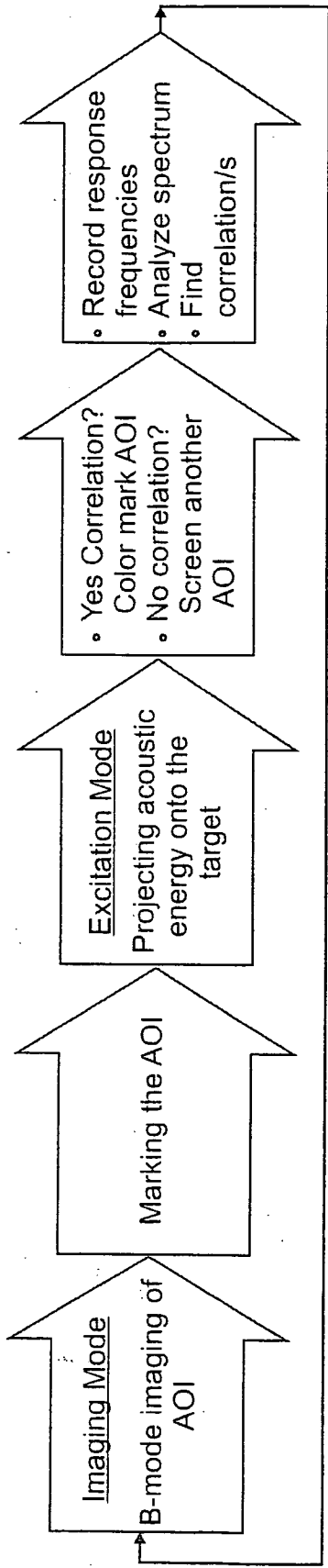
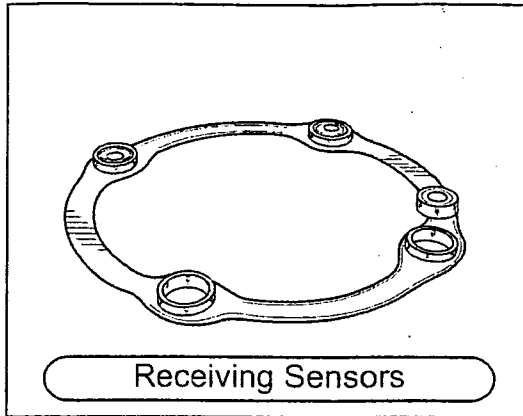
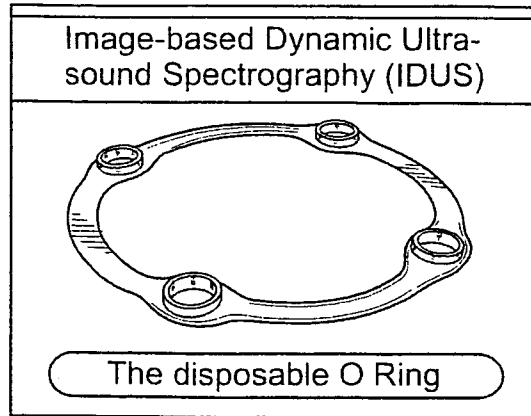


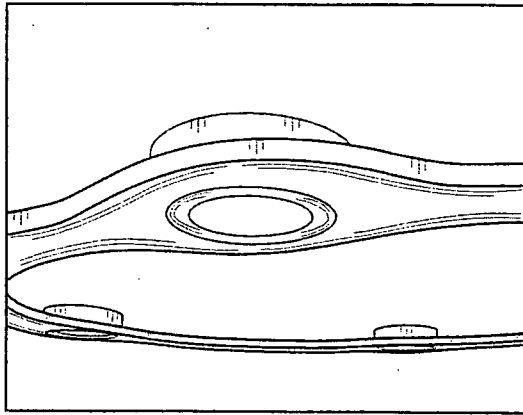
FIG. 4: IDUS™ - Flow Diagram



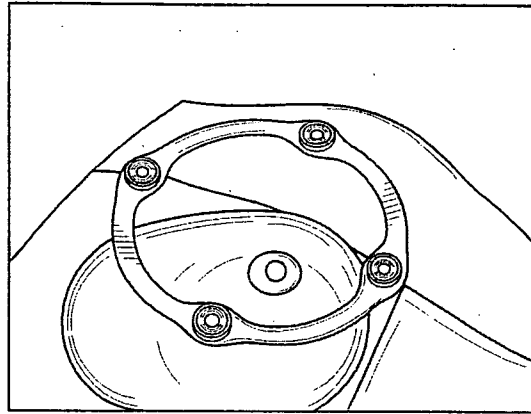
A



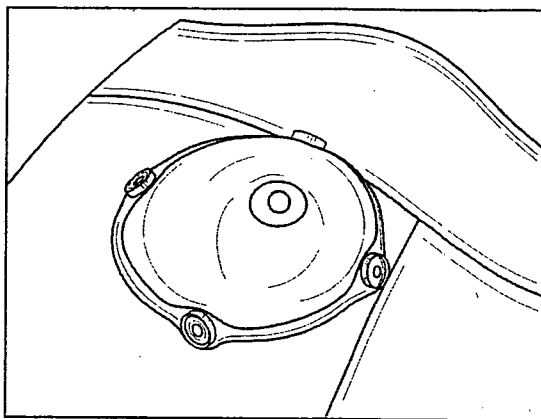
B



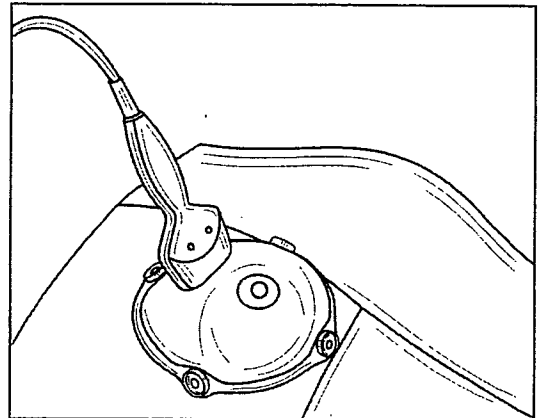
C



D

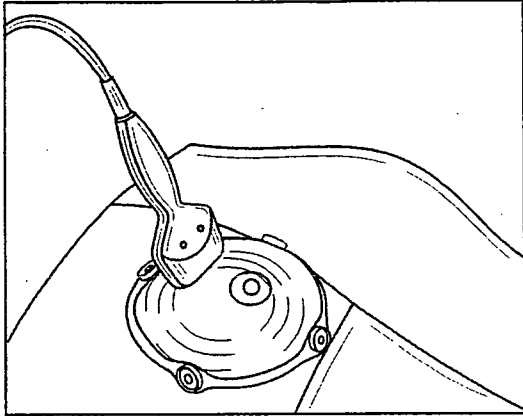


E

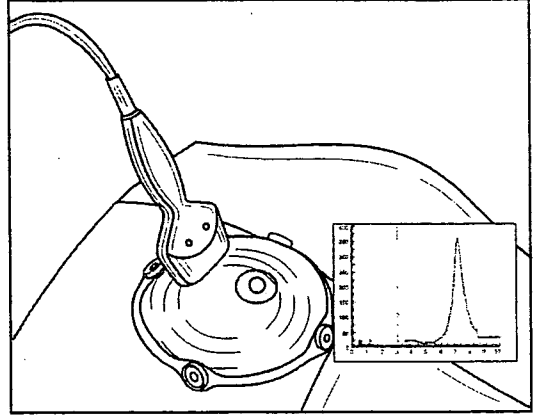


F

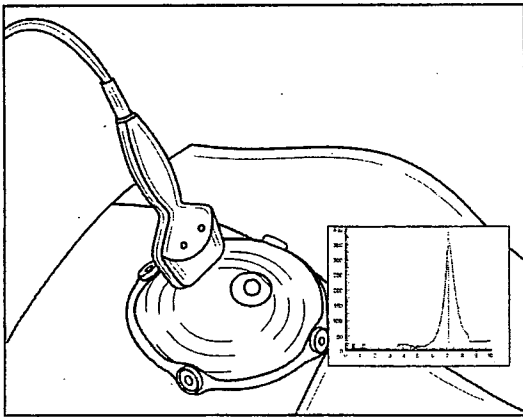
FIG. 5



G



H



I

FIG. 5

7/7

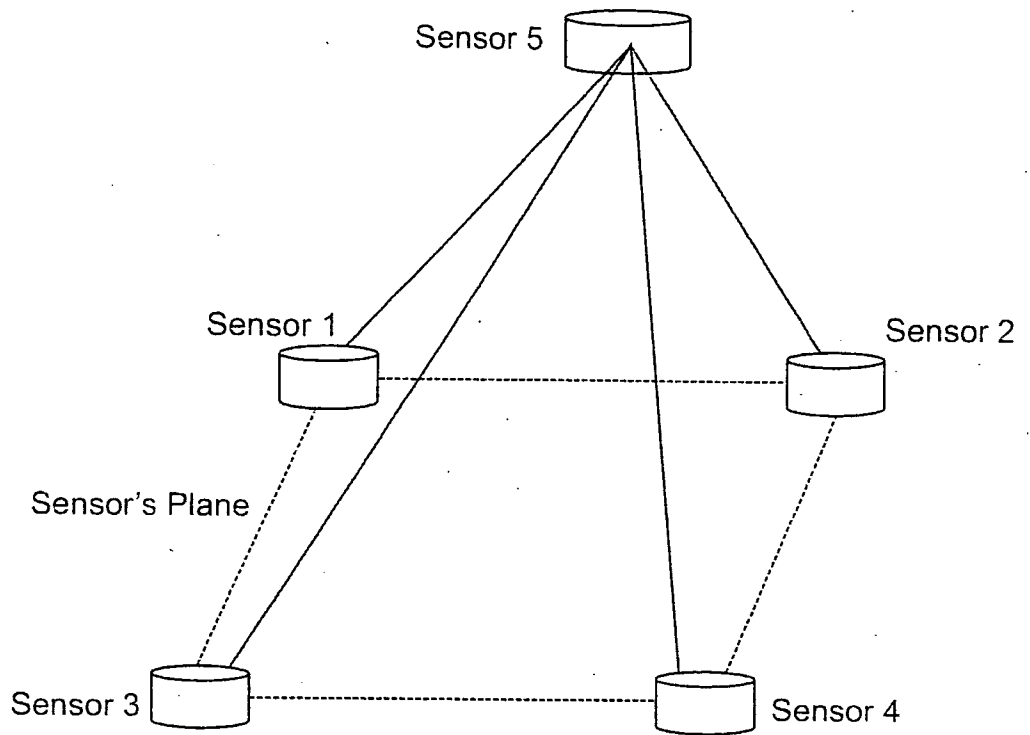


Figure 6A: Schematics of the relative locations of the five receiving sensors.

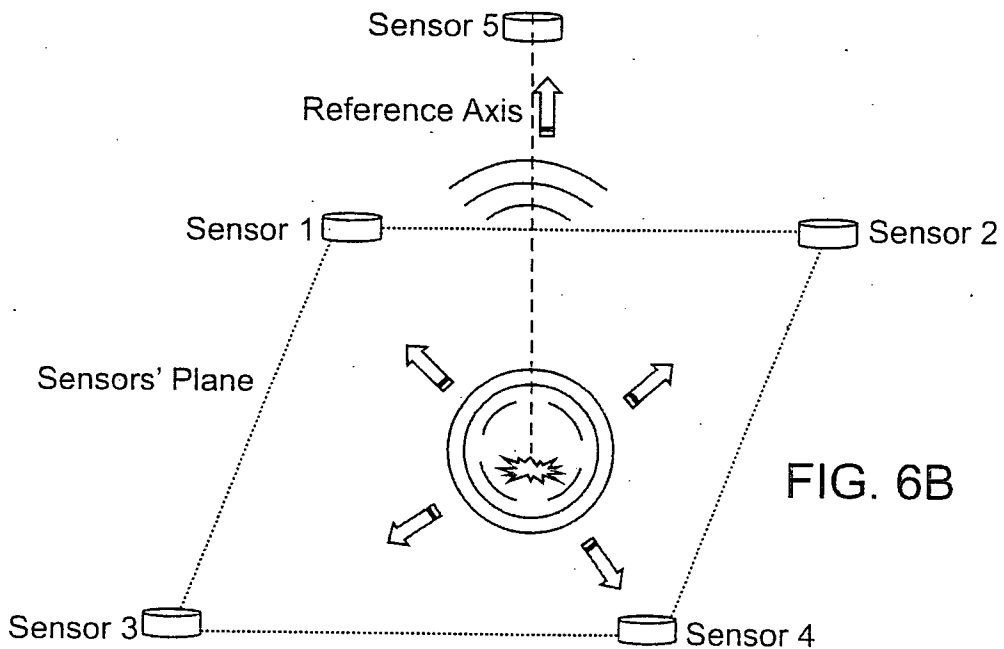


Figure 6B: Schematics of the signal from the target received by the receiving sensors.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/01652

| A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61B 8/00 USPC - 600/437 According to International Patent Classification (IPC) or to both national classification and IPC | | |
|--|--|--|
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) USPC: 600/437 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 128/915, 916, 922, 898; 600/301, 407, 437, 441, 443, 444, 445, 446; 378/37, 128 (text searched-see terms below) | | |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWest (PGPB, USPT, USOC, EPAB, and JPAB); Google Scholar Search Terms: dynamic, ultras\$, doppler, tumor, calcification, benign, malignant, cancer, growth, disease\$, breast, ring, holder, cup, compartment, placement, frequency, sweep, chirp, adher\$, adhesive, attach\$, stick\$, and "o ring" | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | US 2002/0065466 A1 (RATHER et al.) 30 May 2002 (30.05.2002), entire document, more specifically, Fig 1a, 1b, 5, para[0007], [0008], [0012], [0013], [0020], [0025], [0028], [0051], [0053]-[0059], [0060]-[0063], [0069]-[0074], [0080], [0085], [0089], and [0118]. | 22, 23, 26, and 30 ----- 1-21, 24, 25, 27-29 and 31 |
| Y | US 5,749,364 A (SLIWA, Jr. et al.) 12 May 1998 (12.05.1998), entire document, more specifically, col 3, ln 57-61 and col 12, ln 54-59. | 1-21 and 31 |
| Y | US 2004/0087851 A1 (LEE) 6 May 2004 (06.05.2004), Fig 1, 3F, para[0039]. | 1-5, 9, 10, 17, 18, 24, and 25 |
| Y | US 2007/0016030 A1 (STRINGER) 18 January 2007 (18.01.2007), Fig 9A-9D, para[0056]. | 1-5, 11-13, 19-21, and 27-29 |
| Y | US 2006/0241455 A1 (SHVARTS) 26 October 2006 (26.10.2006), para[0006]. | 1, 2 and 6-13 |
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| Date of the actual completion of the international search 06 May 2009 (06.05.2009) | | Date of mailing of the international search report 13 MAY 2009 |
| Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201 | | Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774 |

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| 当前申请(专利权)人(译) | BIOQUANTETICS INC. | | |
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| 优先权 | 12/079272 2008-03-26 US | | |
| 其他公开文献 | EP2257223A1 | | |
| 外部链接 | Espacenet | | |

摘要(译)

一种通过超声冲击和超声频率波检测的精确方法检测和定位乳腺微钙化的方法，该方法不仅能够检测乳房中是否存在微钙化，还能检测微钙化和质量的精确位置微钙化。本发明还是一种方法和系统，其提供乳房内目标肿块的双模引导刺激，以确定乳房内微钙化的位置和性质。