US 20100113932A1

(19) **United States**

(12) **Patent Application Publication**

(10) **Pub. No.: US 2010/0113932 A1**

(43) **Pub. Date: May 6, 2010**

Antich et al.

(54) **RAPID AND ACCURATE DETECTION OF BONE QUALITY USING ULTRASOUND CRITICAL ANGLE REFLECTOMETRY**

(75) Inventors: **Pietro Antich**, Richardson, TX (US); **Charles Y.C. Pak**, Dallas, TX (US); **Billy Smith**, Duncanville, TX (US); **Edmond Richer**, Dallas, TX (US); **Matthew A. Lewis**, Farmers Branch, TX (US)

Correspondence Address:
CHALKER FLORES, LLP
2711 LBJ FRWY, Suite 1036
DALLAS, TX 75234 (US)

(73) Assignee: **BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM**, Austin, TX (US)

(21) Appl. No.: **12/609,445**

(22) Filed: **Oct. 30, 2009**

Related U.S. Application Data

(62) Division of application No. 10/630,330, filed on Jul. 30, 2003, now Pat. No. 7,611,465.

(60) Provisional application No. 60/487,334, filed on Jul. 15, 2003.

Publication Classification

(51) **Int. Cl.**
A61B 8/00 (2006.01)

(52) **U.S. Cl.** **600/449**

(57) **ABSTRACT**

The present invention is an apparatus, method and system for determining the coefficient of elasticity of a target by detecting an ultracritical reflection of ultrasound waves directed at the target using an ultrasound transducer at two or more angles simultaneously and calculating the elasticity coefficient of the target.

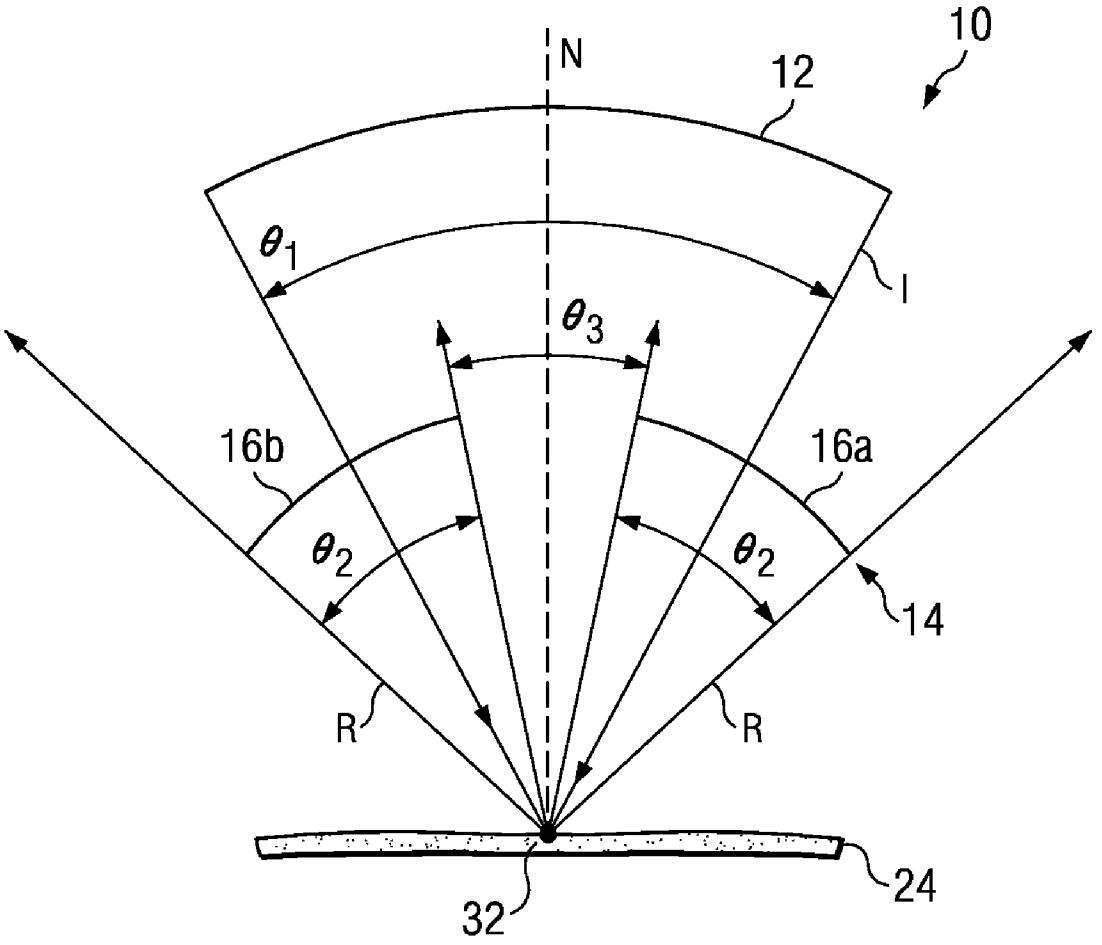


FIG. 1

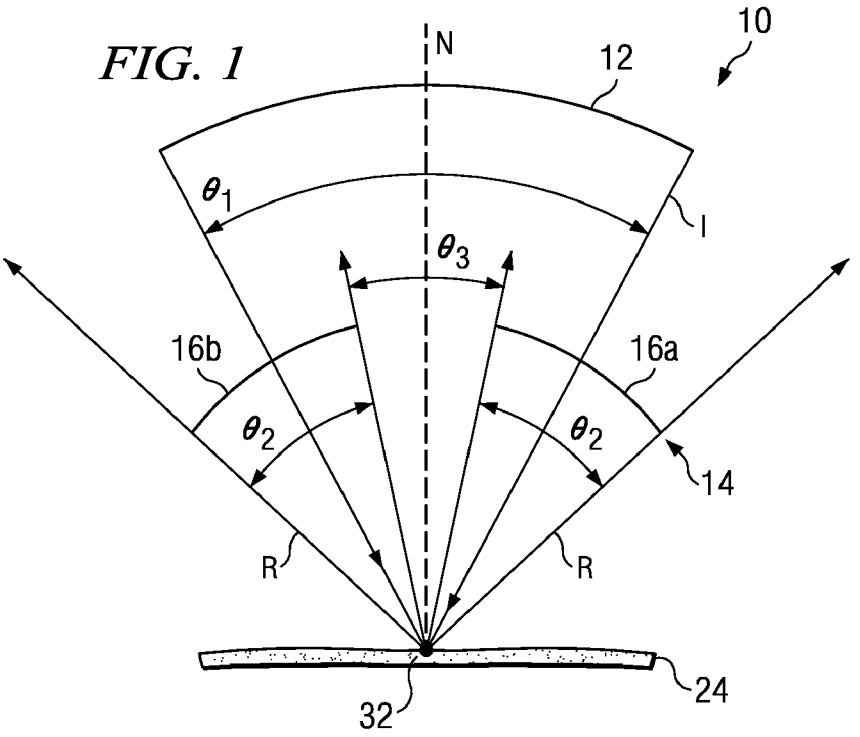

10
N
12
θ1
I
θ3
16b
16a
θ2
θ2
14
R
R
24
32

FIG. 2

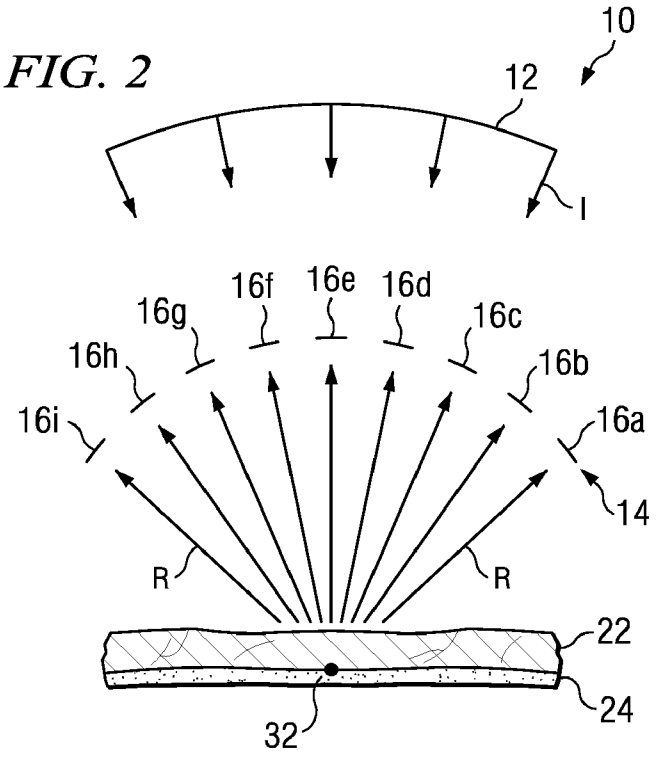
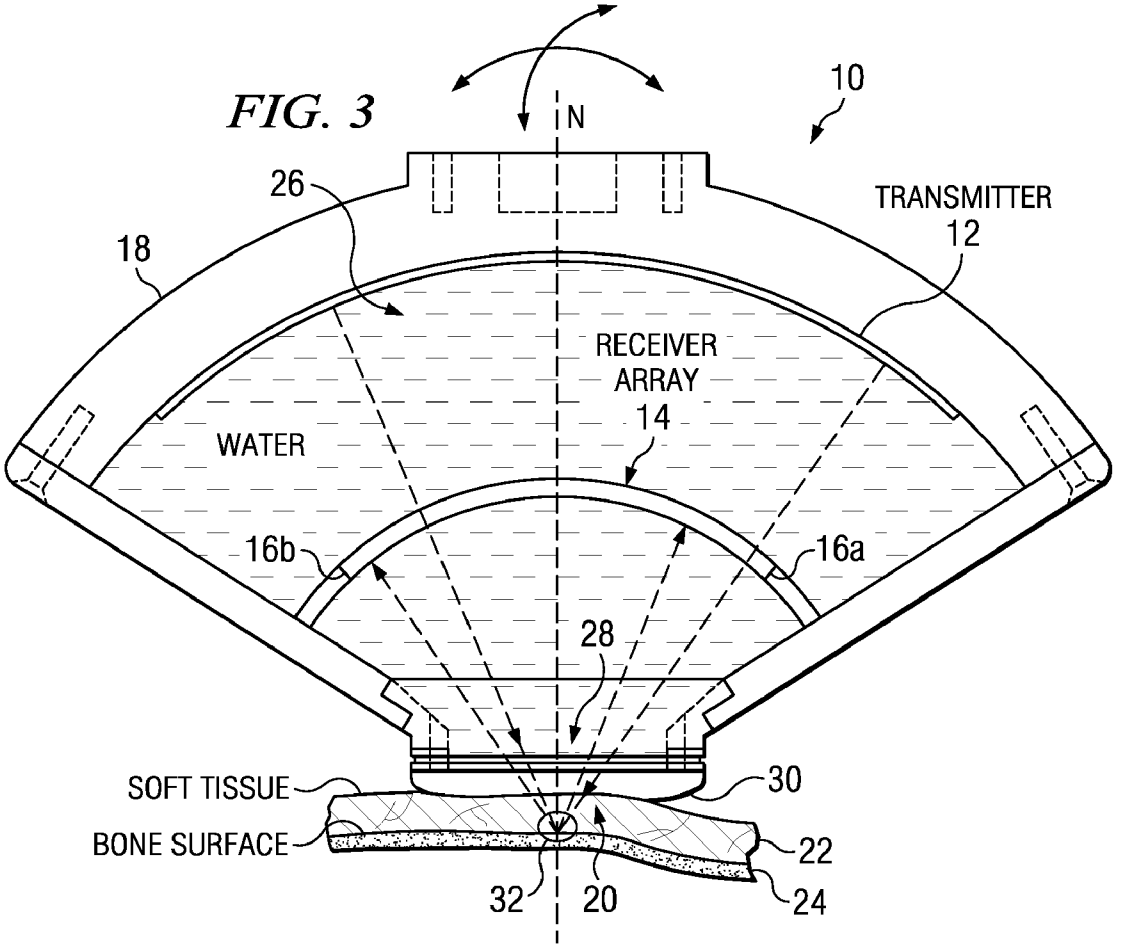

10
12
I
16f
16e
16d
16g
16c
16h
16b
16i
16a
14
R
R
22
24
32

FIG. 3


10
N
26
TRANSMITTER
12
18
RECEIVER
ARRAY
14
WATER
16b
16a
28
SOFT TISSUE
30
BONE SURFACE
22
32
20
24

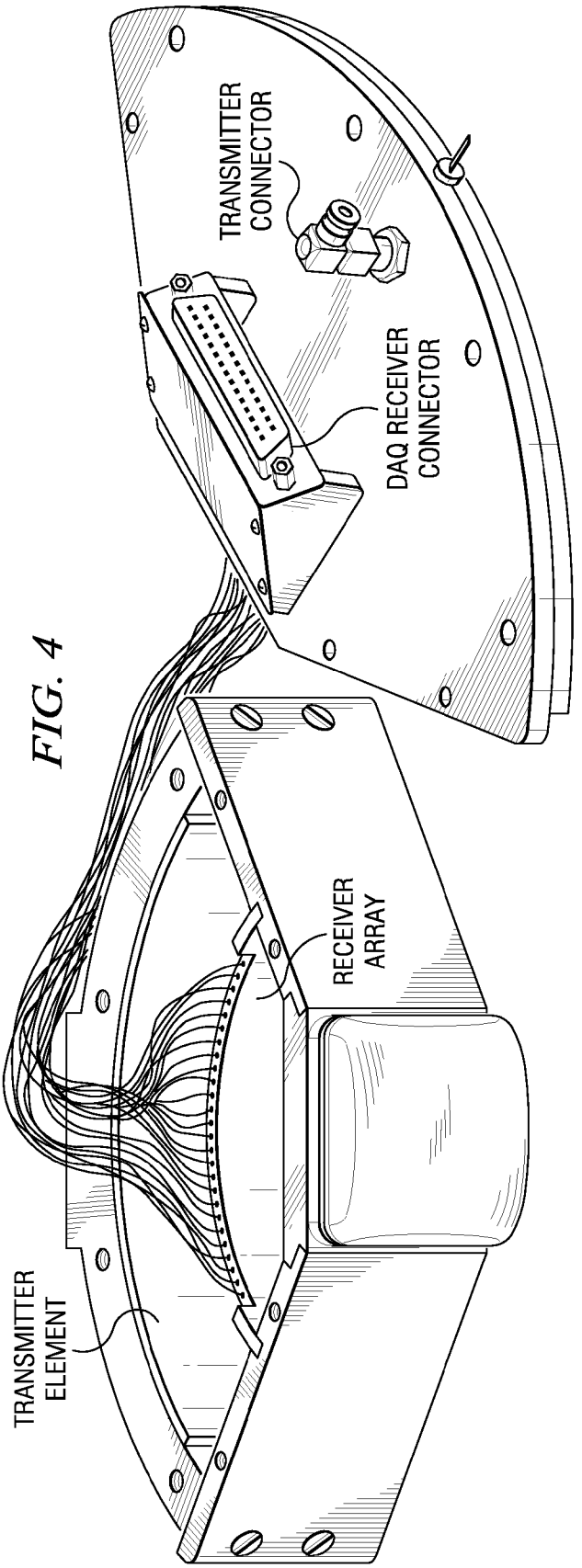

TRANSMITTER CONNECTOR
DAQ RECEIVER CONNECTOR
RECEIVER ARRAY
TRANSMITTER ELEMENT

FIG. 4

FIG. 5

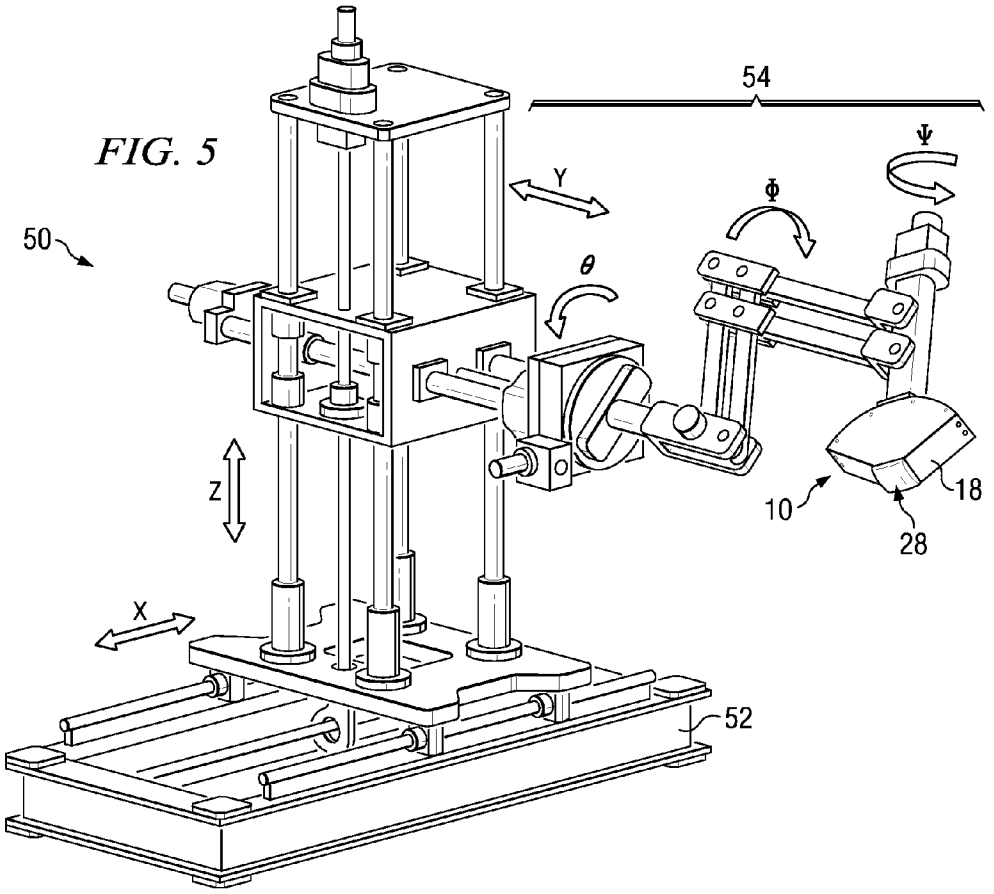
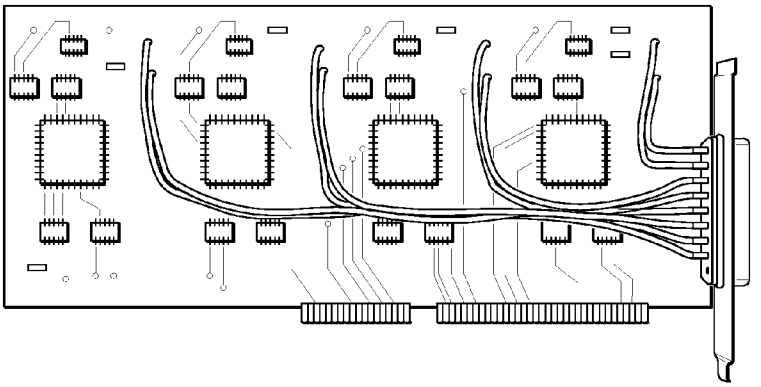


FIG. 6



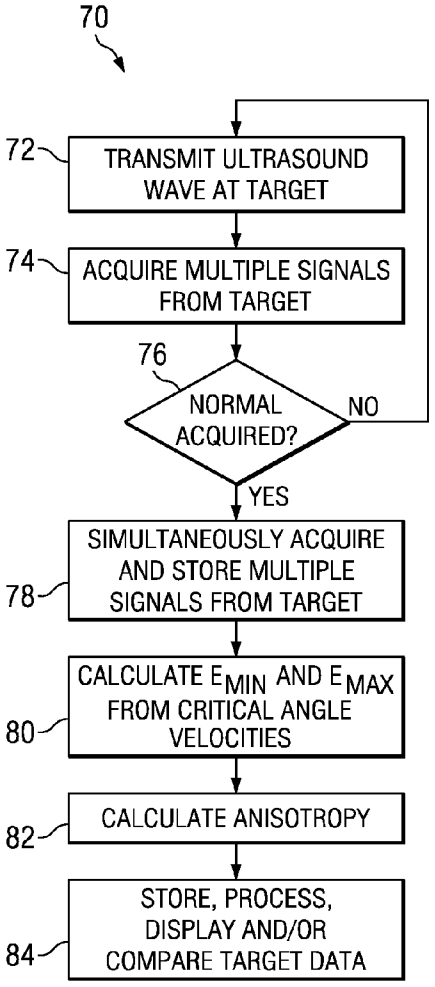

70
72
TRANSMIT ULTRASOUND WAVE AT TARGET
74
ACQUIRE MULTIPLE SIGNALS FROM TARGET
76
NORMAL ACQUIRED?
NO
YES
78
SIMULTANEOUSLY ACQUIRE AND STORE MULTIPLE SIGNALS FROM TARGET
80
CALCULATE E_{MIN} AND E_{MAX} FROM CRITICAL ANGLE VELOCITIES
82
CALCULATE ANISOTROPY
84
STORE, PROCESS, DISPLAY AND/OR COMPARE TARGET DATA

FIG. 7

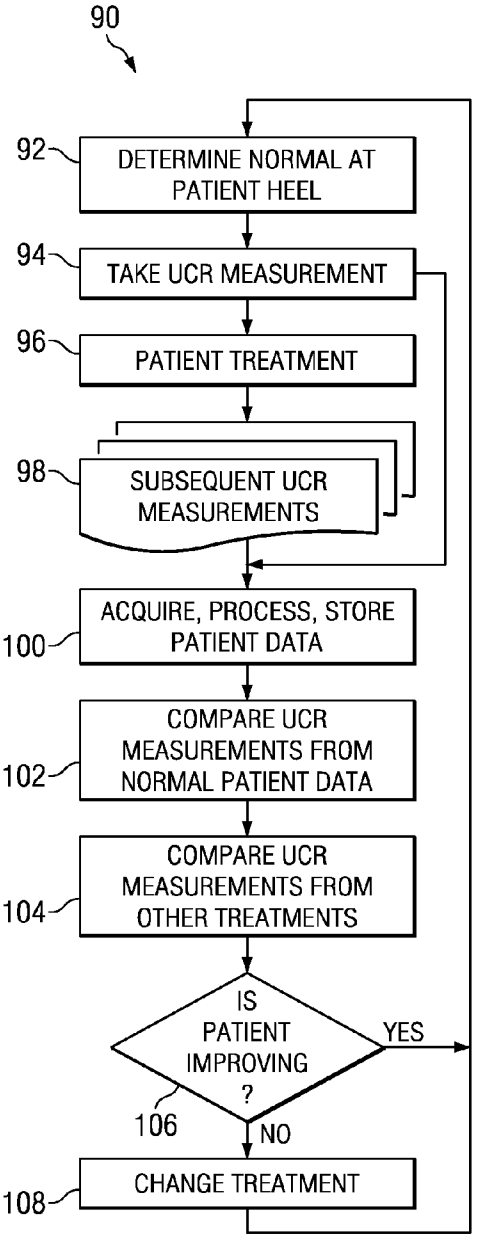
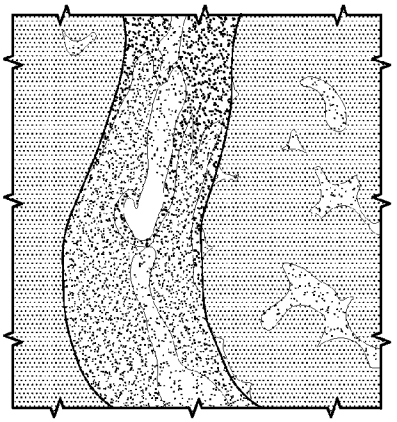

90
92
DETERMINE NORMAL AT PATIENT HEEL
94
TAKE UCR MEASUREMENT
96
PATIENT TREATMENT
98
SUBSEQUENT UCR MEASUREMENTS
100
ACQUIRE, PROCESS, STORE PATIENT DATA
102
COMPARE UCR MEASUREMENTS FROM NORMAL PATIENT DATA
104
COMPARE UCR MEASUREMENTS FROM OTHER TREATMENTS
IS PATIENT IMPROVING ?
YES
106
NO
108
CHANGE TREATMENT

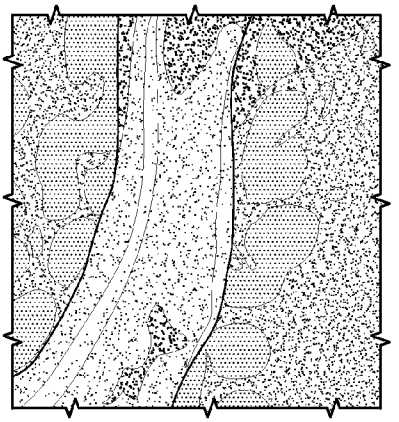
FIG. 8

FIG. 9A



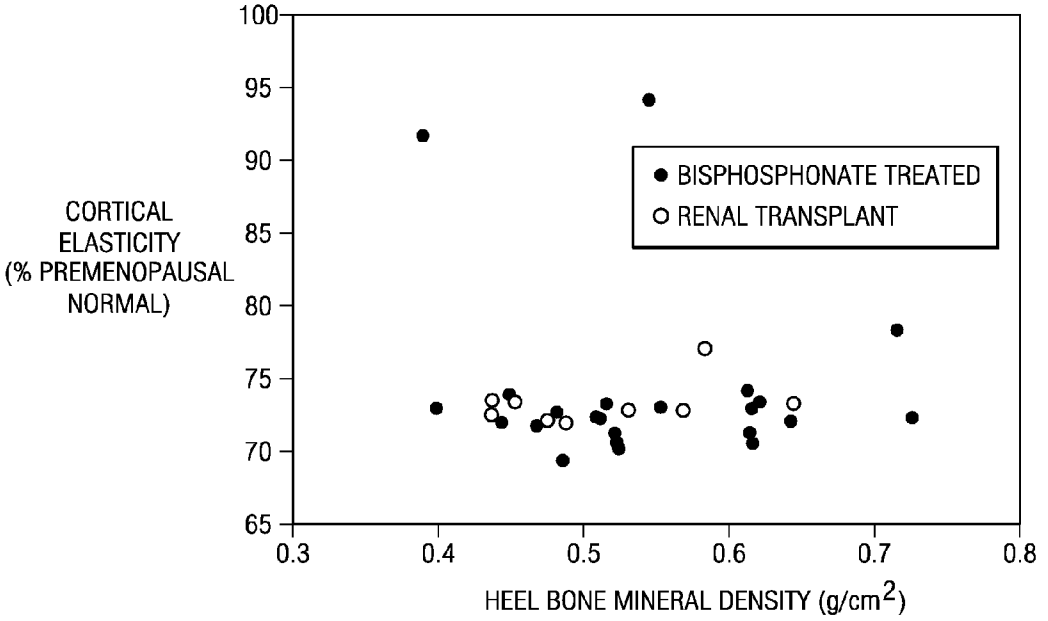
PATIENT

FIG. 9B



NORMAL

FIG. 10



RAPID AND ACCURATE DETECTION OF BONE QUALITY USING ULTRASOUND CRITICAL ANGLE REFLECTOMETRY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to provisional patent application Ser. No. 60/487,334, filed Jul. 15, 2003, and co-pending U.S. patent application Ser. No. 10/630,330 filed Jul. 30, 2003, to issue as U.S. Pat. No. 7,611,465 on Nov. 3, 2009.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates in general to the field of bone quality determination, and more particularly, to the rapid and accurate measurement of elasticity coefficients, in vivo of cortical and trabecular bone.

BACKGROUND OF THE INVENTION

[0003] Without limiting the scope of the invention, its background is described in connection with bone density measurements, as an example.

[0004] Need for Non-Invasive Measurement of Bone Quality. Osteoporosis is a major medical problem, with a large percentage of elderly persons being susceptible to sustain non-traumatic fractures (bone fractures from minimum trauma). Bone strength is a primary predictor of bone fractures. Bone strength is determined by both bone density and bone quality.

[0005] Currently, bone density can be measured by several methods, including: dual energy x-ray absorptiometry, computer-assisted tomography and transmission ultrasound. From epidemiological studies, bone density is inversely correlated with the rate of skeletal fractures. Thus, bone density has been used to define osteoporosis, with a value below 75% of normal peak value referred to as osteoporosis even in the absence of fractures. Recent discoveries, however, have presented situations in which severe impairment of bone quality can occur. Introduced in 1996, a new class of drugs called "bisphosphonate" has been widely used for the treatment of osteoporosis (Liberman et al., *N. Engl. J. Med.* 333:1437-1443, 1995). With long-term use, new studies suggest that these drugs can severely impair bone quality, leading to recurrent fractures that do not heal properly (Ott, *J. Clin. Endo. Metab.* 86:1835, 2001; Odvina, et al., *J. Bone Miner. Res.*, September, 2003; Richer et al., *J. Bone Miner. Res.*, September, 2003; Li et al., *Calc. Tissue Intern.* 69:281-286, 2001). Moreover, with improvement in surgical techniques and in medical treatments to prevent rejection, more patients are living longer after kidney (renal) transplantation. These patients are known to have increased susceptibility to fractures, since they probably have defective bone from taking steroids and suffer from other factors that are harmful to bone. These clinical conditions presented situations wherein a much more prominent reduction in ultrasound elasticity might be expected by the UCR device, than previously disclosed in untreated postmenopausal osteoporosis.

[0006] Another recent development that emphasizes the need for an improved UCR device is the recognition that bone quality, aside from bone density, is a critical determinant of fractures in osteoporosis. In 1994, the World Health Organization defined osteoporosis based on bone density alone. In 2000, the NIH Consensus Conference on Osteoporosis defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture".

[0007] What is needed is a device that can measure reliably, quickly and non-invasively the quality of bone in vivo. The device should permit for the rapid, accurate, consistent detection of critical bone density, elasticity and strength data. A need also exists for the development of a system that may be automated and which has a design, engineering and software for data acquisition that is user-friendly. Also needed are a new system, method and apparatus that minimizes the need for water or other media-baths that are needed with current technology. Finally, a need has arisen for a reliable, inexpensive method for monitoring the status of a patient's bone density information during treatment of, e.g., osteoporosis.

SUMMARY OF THE INVENTION

[0008] The apparatus, method and system of the present invention use ultrasound critical angle reflectometry to improve patient care. The present invention is used to make the measurement of critical bone density information practical and faster than in previous devices, and expands the method to take explicitly into account the anisotropy of bone, assumed to be hexagonally symmetric. The device is designed to make measurements at multiple sites of bone. An integral part of the device is a robotic gantry of specific design, constructed to permit the rapid determination of the "normal" to bone and to automate the measurement of spectra at different orientations. The normal to bone must be determined with considerable accuracy, as it represents the initial angle (degrees) in the angular system, and thus dominates the accuracy of the measurement. Using this gantry, once the normal has been determined, the head can be rotated using the normal as the axis of rotation to obtain the spectra at different orientations. This activity is now rapid and automated. When made for a specific site, the size of the device can be made smaller, while encompassing the same basic features.

[0009] In one embodiment, the present invention is a transducer that includes at least one ultrasound transmitter and two or more receivers separated by an angle that form a receiver array that is concentric and shares a focal point with the transmitter and, wherein the receiver array detects simultaneously the reflected ultrasound energy from a target. The transducer may include a transmitter that is concave in at least two dimensions and/or two or more receivers that form a concave array in at least two dimensions; and/or a transmitter and two or more receivers that are concave and concentric, e.g., about a common focal point. The transducer may have an odd or even number of receiver elements or receivers greater than one, e.g., 2, 4, 8, 16, 24, 36, 48, 64, 128 or more independent receivers. In one embodiment, the two or more receivers form a receiving array system that includes at least one transmitter and a 48-element receiver array located in a housing, wherein the receiver array measures simultaneous the velocity of an ultrasound wave across 120 degrees from a point of examination that is at or about the focal point of the transmitter. The housing for the transmitter and the at least two receivers, the housing having at least one opening at or about the focal point of the transmitter and receivers.

[0010] In one particular embodiment, the transducer includes a housing for the transmitter and the at least two receivers, the housing having at least one opening, a latex membrane at or about the opening of the housing and an ultrasound conductive material within the housing. In one

example, the ultrasound conductive material may include water, saline and the like. The transducer may be part of a ultrasound system that further includes a computer-controlled positioning arm connected to the transducer, wherein the movement of the transducer permits accurate positioning of device on a point of examination. The transducer may also include a pressure detector in communication with the ultrasound conductive material that detects when pressure within the housing increases that may break the latex membrane. The at least one computer may be connected to transmitter and receivers of the transducer, the computer including at least one code segment that gathers one or more reflected spectra from each receiver at each angle, and calculates from the spectra the critical angles for a cortical and a trabecular bone. From the data acquired, the computer may also include at least one code segment that determines critical angle velocities, and fits them to a linear-quadratic equation for the determination of at least two principal coefficients of elasticity.

[0011] Yet another embodiment of the present invention is a transducer that includes at least one ultrasound transmitter and a receiver array that is concentric and shares a focal point with the transmitter, wherein the receiver array detects simultaneously the reflected ultrasound energy from a target at multiple angles. The transducer detects pressure waves that may be used to determine reflected spectra from a bone that is undergoing bone treatment therapy, e.g., for osteoporosis, that determined critical cortical and a trabecular bone data, which may be used to calculate bone anisotropy. The critical angle velocities may be used to determination at least two principal coefficients of elasticity, which correlate with bone density and strength data that may be used to track improvements or degeneration of bone during treatment with, e.g., bisphosphonate treatment versus other forms of bone therapy.

[0012] The present invention also includes a method for determining the coefficient of elasticity of a target, comprising the steps of, detecting simultaneously two or more ultracritical reflections of an ultrasound wave from the target using an ultrasound transducer comprising a transmitter and two or more receivers separated by an angle and calculating the elasticity coefficient of the target. The target may be bone, e.g., a human bone, that may be suspected of having osteoporosis. The method may further include the determination of disease progression of a human bone suspected of having osteoporosis that is treated with bisphosphonate, its salts or mixtures thereof. The present invention includes the use of a transducer that is non-invasive and that does not require the use of water baths to obtain UCR data. The present invention may be used to determine the elasticity coefficient by comparing the square of the velocity of an ultrasound wave with the intrinsic orientation of bone at a fixed position using values detected at multiple orientations from the ultrasound transducer. Using the maximum elasticity coefficient and a minimum elasticity coefficient the degree of target anisotropy (e.g., bone anisotropy) may be estimated in a rapid and automated manner. To achieve more reliable results, the apparatus, method and system disclosed herein also includes the use of an automated arm to rapidly and consistently determine the normal of the transducer to the target. Data processing and calculations are also may more efficient by the concurrent or simultaneous detection from, e.g., 2, 4, 8, 16, 24, 36, 48, 64 or 128 receivers.

[0013] Ultracritical reflection value of a ultrasound wave at two or more receivers that are concentric with a transmitter may also be detected and stored, displayed and/or printed for further analysis. As such, the present method may also include storing the detected ultracritical reflection of ultrasound waves at different points in time and comparing the measurements to track changes in the coefficient of elasticity of the target over time.

[0014] The present invention may also be used to determine the effect on a coefficient of elasticity of a bone undergoing therapy for osteoporosis, comprising the steps of detecting simultaneously at two or more angles the ultracritical reflection of ultrasound waves directed at a bone using an ultrasound transducer with one or more transmitters and two or multiple receivers and calculating the anisotropy of the bone by calculating an elasticity coefficient for the bone by comparing the square of the velocity of an ultrasound wave with the intrinsic orientation of bone at a fixed position using values detected at each of the two or more receivers. The apparatus, method and system disclosed herein may also include the steps of storing a first detected ultracritical reflection of ultrasound waves at two or more receivers prior to, or concurrent with, treatment with a bisphosphonate or derivative thereof, storing a second detected ultracritical reflection of ultrasound waves at two or more receivers after a period of time and comparing the first and second measurements to track changes in the coefficient of elasticity of the bone during treatment with the bisphosphonate or derivative thereof. The detection and calculation of the maximum and a minimum elasticity of a cortical and a trabecular region of the bone may be used to estimate the anisotropy of the bone in vivo, before and during the treatment of a patient with bisphosphonate, and for those patients that do not respond positively to treatment, or that respond negatively to treatment, to identify those patients and change the treatment prior to further damage. The present invention allows the determination of the elasticity of cortical bone, trabecular bone, and anisotropy of a patient's bone in a manner that is non-invasive, e.g., at a patient's heel. Using the data acquired, stored and/or processed, the user may calculate the anisotropy of the bone (determining a maximum and a minimum elasticity of a cortical and a trabecular bone region), wherein the measurements correspond to an axis of a weight-bearing and a non-weight-bearing bone, respectively.

[0015] The present invention also includes a system for measuring bone anisotropy that includes a computer-controlled ultrasound ultracritical reflectometry transducer that detects ultrasound velocities at multiple angles simultaneously and automatically, an articulated arm that permits motion in three-dimensions that supports the ultrasound transducer and a computer connected to and capable of receiving a signal from the ultrasound transducer to calculate ultracritical reflectometry data from the ultrasound transducer. The computer is connected to one or more controllers of the articulated arm that direct the position of the transducer in three dimensions. The transducer may be used to measure the elasticity coefficient of a human bone suspected of having osteoporosis, e.g, the elasticity coefficient of a human bone suspected of having osteoporosis treated with bisphosphonate. The computer can determine an elasticity coefficient by comparing the square of the velocity of an ultrasound wave with the intrinsic orientation of bone at a fixed position using values detected at multiple orientations using the ultrasound transducer and/or calculate a maximum elasticity coefficient and a minimum elasticity coefficient to estimate a degree of target anisotropy. Using the data, the computer of the present system may also calculate a maximum elasticity coefficient

and a minimum elasticity coefficient to estimate a degree of bone anisotropy. To automate the determination of bone anisotropy with results that are rapid and consistent, the computer of the present invention automates the determination of the normal of the transducer to the target. The computer may stores a value for an ultracritical reflection of ultrasound waves at different points in time, and even compare and provide the user with a user-friendly output that shows the effect on a coefficient of elasticity of a bone undergoing therapy for osteoporosis by storing a first and a second value for the coefficient of elasticity of a patient at a first and a second point in time, and calculates a bone anisotropy value by calculating an elasticity coefficient for the bone by comparing the square of the velocity of an ultrasound wave with the intrinsic orientation of bone at a fixed position using the first and second values to determine the effect of treatment on bone quality.

[0016] In yet another embodiment, the system of the present invention determines the effect on a coefficient of elasticity of a bone undergoing bisphosphonate therapy for osteoporosis by storing a first and a second value for the coefficient of elasticity of a patient at a first and a second point in time, and calculates a bone anisotropy value by calculating an elasticity coefficient for the bone by comparing the square of the velocity of an ultrasound wave with the intrinsic orientation of bone at a fixed position using the first and second values to determine the effect of bisphosphonate treatment on bone quality.

[0017] More particularly, the present invention includes a custom designed transducer head, which permits a nearly instantaneous measurement over a complete set of angle of reflection. The head includes two ultrasound elements encased within a water-tight enclosure with an elastic pliant interface (placed over the bone tissue under examination). In one embodiment, the single-element transmitter and the 48-element receiver array are separate. Both are sections of right cylinders of different radii but with a common axis, subtending 120 degrees. The midpoint of the axial segment is the nominal center of the transducers. The two elements are mounted in a fixed geometry within a water-tight solid container, which is filled with water and terminates in a window covered by a latex membrane, in a configuration such that the common center of the transducers projects 1.5 cm beyond the window. In operation, the liquid is under a slight pressure controlled by gravity (by using a reservoir of water placed at a slight higher elevation than the transducer head on the support base) and the latex membrane bulges at least 0.5 cm beyond the rim of the window. When the bulge is in contact with the patient's skin (overlying bone being examined), the transducer center is a virtual point projected under the skin at depth.

[0018] The positioning arm is a pantograph that includes two segments shaped as parallelograms, one attached to the base and one supporting the transducer head. The arm can be moved vertically and horizontally (three degrees of freedom) by means of motors mounted on the base. The arm is articulated so that the transducer head pivots around a fixed point, coincident with the center of the transducers. This geometric property makes it possible to determine the normal by changing the tilt angles ϕ and θ at two mutually orthogonal values of rotation angle ψ. In this fashion, the axis of the transducer head can be rotated with two degrees of freedom to coincide with the normal to bone at the fixed point and the transducer head can be rotated by an angle ψ around that axis to assume any orientation along the bone surface.

[0019] During an examination, the operator places the transducer head over the site of interest (bone tissue being examined), and the transducer head is advanced by the operator using precise, sub-millimeter steps of the arm using computer controls until the transducer center is at the surface of the bone under study. This advance, for the heel, is restricted to 0.5-1.0 cm, and the patient's skin remains in contact with the flexible membrane and does not come in contact with the rim or any other element of the solid surface. Excessive pressure (which may occur, for example, from a sudden movement of the foot that is being measured) causes the advance to stop and the head to retract. A single (imploding cylindrical) wave is emitted by the transmitter, and each receiving element detects the reflected amplitude over a set of angles of reflection, operationally determined as successive elements of the receiving array. A critical angle β_c, corresponds to a maximum in this distribution. The velocity V is then given by $V=V_c/\mathrm{Sin}\,\beta_c$ where V_c is the velocity of sound in the calibration medium (water). For each orientation ψ, a different value of V is obtained, $V(\psi)$. As bone has an intrinsic hexagonal symmetry, the distribution is determined a priori to be $V(\psi)=A\mathrm{Cos}^4\psi+B\mathrm{Cos}^2\psi+C$. In classic textbook notations, these are expressed in terms of the elements of the stiffness matrix $\{C\}$ as $A=C_{11}+C_{33}-k$, $B=k-2C_{11}$, $C=C_{11}$ and $k=2(C_{13}+2C_{44})$. The present invention permits the determination of two principal coefficients: $E^*_{min}=C\ (=C_{11})$ and $E^*_{max}=A+B+C\ (=C_{33})$. These coefficients are intrinsic properties of bone reflective of its mechanical properties.

[0020] Thus, key innovations of this UCR transducer and system are: (a) "dual array" system of single transmitter and multiple receiver elements, e.g., 48-receiver elements, which allow simultaneous measurement of critical angle velocities across the whole spectrum of angles of scattering; (b) a robotic arm engineered to accommodate naturally the movements that permit accurate positioning and alignment along the normal to bone of the transducer head over the site of bone tissues being examined; (c) the use of latex membrane containing water in the transducer head avoiding immersion of bone tissue in a water bath; (d) special engineering features that prevent excessive pressure to build on the membrane or the patient; (e) data acquisition software to obtain the reflected spectra from measurements of the reflected wave train at each angle and to extract from the spectra the critical angles for cortical and trabecular bone; and (f) special post-processing software to determine the critical angle velocity V at each angle ψ, and then fit the data onto a linear-quadratic formula relating V^2 on the Cos^2 of the angle ψ, in order to determine two principal coefficients of elasticity.

[0021] For example, the apparatus, method and system of the present invention permits for a simple, fast determination of the vector "normal" to the transducer for a more accurate and repeatable measurement. The invention permits the simultaneous and automated detection for the velocity of the sound signal with less dependence on the orientation of the transducer. Furthermore, the system allows for a rapid, automated and fast determination of elasticity coefficients and hence permits, for the first time, a calculation of anisotropy. Using the transducer, methods and system disclosed herein, a more complex and hence more accurate determination and measurement with full automation may be taken at, e.g., 3 points in 6 orientations with a reduction in the time for measurement time of one-third or less than currently possible.

The method is non-invasive and does not require immersion of the patient or a patient's body part in an immersion bath containing an ultrasound carrier media. Furthermore, the present invention may be used to determine and track the effect of patient therapy using, e.g., a bisphosphonate, salt or derivatives thereof. Other patients, e.g., renal transplant and patients undergoing sodium fluoride treatments will also benefit from the present invention.

[0022] The present inventors have recognized that bone density alone is not predictive of the risk of fractures. Some patients with normal bone density develop non-traumatic fractures, and some with low bone density do not sustain fractures. One explanation for this finding is that bone quality may be "out of line" from bone density. Thus, some subjects with low bone density may be less susceptible to fracture, if bone quality is superior. On the other hand, some with high bone density may be susceptible to fractures if bone quality is poor.

[0023] Measurement of bone quality is important, because there are some conditions or treatments that are associated with, or may cause, deterioration of bone quality. Examples where bone quality is presumed to be impaired are: Paget's disease of bone (with excessive formation of abnormal bone with fibrosis), osteomalacia or rickets (with poorly mineralized bone), immobilization and fluorosis (toxic fluoride exposure with abnormal mosaic bone). Unfortunately, there is no commercial device that can measure bone quality non-invasively (safely). The available ultrasound method is based on transmission of ultrasound across bone tissue and thus only yields a measure largely of bone density.

[0024] Clinical applications of the present invention permit the determination of critical bone density, elasticity and strength data. A device capable of measuring elasticity coefficients at different sites of bone has been constructed by the new UCR method, tested in the calcaneus (heel), and its important clinical applications have been identified. With this new UCR device, multiple measurements can be made rapidly and reliably, yielding elasticity coefficients of cortical and trabecular bone non-invasively in vivo (in living persons). The transducer disclosed herein can determine peak and minimum elasticity coefficients, where the peak elasticity coefficient is an intrinsic property of bone that is critical in weight bearing, and minimum elasticity coefficient is one that is less critical in weight bearing. From the ratio of maximum and minimum elasticity coefficients, anisotropy (asymmetry) of bone can be estimated. This device has shown to be clinically useful in detecting inferior bone quality during treatment with bisphosphonate (a widely used drug for osteoporosis) and in renal transplantation (on steroid treatment). As will be described below, the reductions in bone quality shown in these conditions was much greater than disclosed previously in postmenopausal osteoporosis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] For a more complete understanding of the features and advantages of the present invention, reference is now made to the detailed description of the invention along with the accompanying figures in which corresponding numerals in the different figures refer to corresponding parts and in which:

[0026] FIGS. **1** and **2** are diagrammatic renderings that show the general principles of UCR using two alternative embodiments of the device and system of the present invention;

[0027] FIG. **3** is a diagrammatic rendering of another embodiment of the present invention that shows a cross-section of the transducer head placed over a bone tissue ready for UCR measurement in close contact with a soft tissue overlying a bone by a latex membrane filled with water;

[0028] FIG. **4** shows an isometric view of the transducer head, the main body being on the left hand side and the cover on the right. Water fills the volume between transducers and window. A single coaxial cable transports the low current (xA), low voltage (xV) 1.5 MHz signals from the generator to transmitter element and a set of coaxial cables transports the signal from the receiver to the data acquisition system via a multi-element connector.

[0029] FIG. **5** shows the kinematics of the transducer support arm; three motors mounted on the base and elevator support three-dimensional translations, while three motors mounted on the arm support two tilt rotations (θ and ϕ, necessary to identify and select the "normal" to bone) and the rotation of the head around the normal (ψ);

[0030] FIG. **6** shows the analog-to-digital acquisition board designed to connect with and receive data from the transducer of the present invention;

[0031] FIG. **7** is a basic flowchart that summarizes the basic data acquisition model of the present invention;

[0032] FIG. **8** is a basic flowchart that shows the use of the present invention in patient evaluation and treatment;

[0033] FIGS. **9**A and **9**B are photographs of polarized light microscopy that shows the absence of tetracycline labeling in a patient on long-term bisphosphonate treatment (**9**A), and normal labeling in a normal subject (**9**B); and

[0034] FIG. **10** is a graph that shows independence of bone elasticity from bone density during bisphosphonate treatment and in renal transplantation.

DETAILED DESCRIPTION OF THE INVENTION

[0035] While the making and using of various embodiments of the present invention are discussed in detail below, it should be appreciated that the present invention provides many applicable inventive concepts which can be embodied in a wide variety of specific contexts. The specific embodiments discussed herein are merely illustrative of specific ways to make and use the invention and do not delimit the scope of the invention.

[0036] Ultrasound Critical Angle Reflectometry (UCR). In the early 1990s, the present inventors introduced a novel method, called ultrasound critical angle reflectometry or UCR, for measuring bone quality based on the "reflection" of ultrasound across small parts of bone surfaces of about 0.2 mm (Antich, et al., *J. Bone Min. Res.* 6:417-426, 1991). Bone quality may be derived or inferred from ultrasound velocity. The original UCR device determined velocity in cortical bone ("hard bone" on outer parts of bone tissue) as well as in trabecular bone ("spongy bone" in the inner core of bone tissue).

[0037] The present invention describes an improvement of methods for ultrasound critical angle reflectometry (UCR), which allows a rapid and reliable measurement of elasticity coefficients (quality) of cortical (hard) and trabecular (spongy) bone non-invasively in vivo in human beings. The refinement permits simultaneous detection of reflected ultrasound amplitudes at multiple angles, e.g., on an array that includes 48 receivers separated by 47 angles, and the measurement of ultrasound velocity at critical angle over a range of orientations using a special "array system" and novel engi-

neering and software designs. The software implements from these data the calculation of the principal elasticity coefficients from the square of velocity. Both the maximum elasticity coefficient C_{33} (approximately along the vertical axis, critical in weight-bearing) and minimum elasticity coefficient C_{11} (approximately along the horizontal axis, less critical in weight-bearing) are separately calculated in cortical and trabecular bone. This measurement is more precise than that obtained at a fixed anatomical direction because the intrinsic orientation of bone changes with position, causing the velocity along a given anatomical direction to vary by more than the measurement error, while the velocity along a given intrinsic direction is affected only by measurement uncertainties. As deterministic relationship exists between the square of velocity and the intrinsic orientation, a fit to the values at multiple orientations minimizes the measurement errors. Moreover, the measurement is more accurate because acoustic waves that do not propagate along a principal axis have a mixed nature (they are quasi-pressure waves), obscuring correlations with mechanical properties such as elasticity and strength. From the ratio of maximum and minimum elasticity coefficients, the degree of "anisotropy" (asymmetry) can be accurately estimated. The UCR apparatus and method disclosed herein has been applied to detect impaired bone quality that contributes to osteoporotic fractures.

[0038] In patients with kidney transplantations taking steroids, a condition known to be associated with impaired bone quality and increased susceptibility to fractures, cortical and trabecular elasticity coefficients were decreased by 15-30% from the normal premenopausal state. Treatment with bisphosphonate, a widely used drug to treat osteoporosis, can cause "adynamic bone disease" (severe depression of bone turnover) after long-term use, resulting in fractures of long bones that heal poorly. By the new UCR method, the elasticity coefficients of cortical and trabecular bone were also reduced by 15-30% during long-term bisphosphonate treatment, indicative of impaired bone strength. Thus, this invention claims a reliable and rapid method for measuring non-invasively in human beings, the intrinsic (material) quality of cortical and trabecular bone, that is useful in detecting conditions with inferior bone strength, and in alerting to the development of defective bone among patients taking bisphosphonate or steroid.

[0039] Three patents have been issued to the present inventors to methods and applications of the original UCR device (U.S. Pat. No. 5,038,787, No. 5,197,475, and No. 5,228,445, relevant teachings of UCR are incorporated herein by reference). In this approach, ultrasound signal in bone was measured while varying the angle of incidence and analyzing the amplitude of the ultrasound wave reflected by bone. An apparatus that can measure ultrasound velocity at the critical angle was described (Antich, et al., *J. Bone Miner. Res.* 6:417-426, 1991; Antich, et al., *J. Bone Miner. Res.* 8:301-311, 1993). Using this apparatus, ultrasound velocity in trabecular bone was shown to be reduced by 7% in normal postmenopausal women and by 13% in patients with untreated postmenopausal osteoporosis, compared with normal premenopausal women. Treatment with sustained-release sodium fluoride, that increases bone density and inhibit fractures of the spine by delivering therapeutic subtoxic amounts of fluoride (Pak, et al., *Arch. Intern. Med.* 123:401-408, 1995), was found to increase ultrasound velocity of trabecular bone to the level of normal postmenopausal women (Antich, et al., *J. Bone Miner. Res.* 8:301-311, 1993; Zerwekh et al., *J. Bone Miner. Res.* 6:239-244, 1991).

[0040] The original UCR device was mounted on a simple gantry that allowed linear motions and rotations; its transducer head may include two transducers moving in unison. While the design was simple, it requires considerable manual adjustments and complex movements in order to measure critical angle velocity at different orientations at a given site of bone (Antich, et al., *J. Bone Miner. Res.*, 6:417-426, 1991). Thus, only a single measurement of velocity could be obtained in vivo in cortical bone and trabecular bone. The maximum and minimum velocities could not be reliably determined, and thus an accurate estimation of anisotropy ("asymmetry" of bone material) was not possible. Moreover, the original device was cumbersome and time-consuming to use. Lastly, the degree of change in ultrasound velocity with disease shown by the original UCR device was modest as previously mentioned, with the value in postmenopausal osteoporosis being about 13% below that of normal premenopausal state (Antich, et al., *J. Bone Miner. Res.* 8:301-311, 1993).

[0041] As used the term "emitting" is used to describe the transmission of an ultrasound wave or pulse by an ultrasound wave transmitter. As used herein the term "receiving" is used to describe the reception by an ultrasound wave receiver of an ultrasound pressure pulse or wave reflected by a material. Together the transmitter and the receiver are described as forming a "transducer" that is able to emit and receive an ultrasound wave reflected from a target material, whether the wave hits the target directly and/or if the wave traverses an ultrasound conductive or transmissive material prior to striking the target, which may be a target point or plane.

[0042] As used herein, the term "ultracritical reflection" is used to describe the reflection an ultrasound wave emitted from an ultrasound transmitter after striking a target, where the reflected ultrasound wave travels back toward the ultrasound transmitter. In order to receive or detect an ultrasound wave reflected from a target as an ultracritical reflection, the receivers of the ultrasound wave are at, behind or about the ultrasound transmitter, e.g., in the direction of the ultracritical reflection, which is generally the normal of the transmitter and the receivers.

[0043] The receiver array is connected to one or more signal analyzers that operable to determine at least one characteristic of the received ultrasound wave, e.g., amplitude and phase of the received ultrasound wave. The receivers transmit data to an analyzer, e.g., a computer that includes a code segment that acquires, processes and/or stores data from the two or more receivers with respect to, e.g., the amplitude of the received ultrasound wave; parameters such as maxima, minima (collectively referred to as "extrema"); and edges used to determine various velocities; and/or estimates of the mechanical properties of the target material. With respect to phase, parameters such as the angle of incidence at which phase first appreciably deviates from zero can also be acquired, processed and/or stored and used to calculate and/or estimate the mechanical properties of the target material.

[0044] Using data acquired from the receiving array the present invention also includes a system and method for determining, acquiring and automating the detection of the normal using, e.g., a computer from data acquired by the receiving array. Automated determination of the "normal" increases the accuracy of present, past and future measure-

ments to the target, e.g., the surface of the bone that is undergoing bone therapy, which permits the use of a rational set of measurements to align the detectors and the bone in a present and future measurements. Consistent, automated determination of the normal is important because the normal defines the zero angle as well as the emitting plane (or plane of scattering), which must contain the normal and the incident wave (I). When the plane and zero are chosen incorrectly, the measurements obtained would be of little value as the angles are not well measured. The method and system of the present invention increase both the accuracy and speed of the determination of the normal, and hence the rapid, precise and repeatable measurement and calculation of critical target data, e.g., a patient's critical bone density, with a great reduction in patient waiting time. By reducing patient processing time, more patients may be served and cost per determination is reduced. Furthermore, by acquiring and processing data more accurately, a reduced number of visits is required to improve patient data, patient compliance and improve patient treatment.

[0045] General Description and Mode of Operation of the New UCR Device. The transducer disclosed herein was designed to implement the methodology of ultrasound critical angle reflectometry (Antich, et al., *J. Bone Min. Res.* 6:417-426, 1991; Antich, et al., *J. Bone Min. Res.* 8:301-311, 1993) by making the measurement practical and faster than in previous devices and expands the method to take explicitly into account the anisotropy of bone, assumed to be hexagonally symmetric. The apparatus disclosed herein is designed to make measurements at multiple sites of bone. When made for a specific site, the size of the device should be much smaller, though encompassing the same basic features.

[0046] FIGS. **1** and **2** illustrate the general critical angle of reflection apparatus and method of the present invention. FIG. **1** illustrates an ultrasound transducer **10** functioning as a transmitter **12** and a receiver array **14** that includes two or more receivers (**16***a*, **16***b*). An ultrasound wave (I) having an angle θ_1 strikes a solid target **22** (e.g., a bone tissue). For convenience, the plane defined by the direction of propagation of the transmitted wave is defined from the Normal (N) to the surface of the target **24**, which includes a focal point **32** for the transmitter **12** and the receiving array **14**. The reflected (R) ultrasound waves arrive at the receivers **16***a*, **16***b* with a pre-defined targeting angle θ_2, which are separated be predefined angle θ_3.

[0047] FIG. **2** shows another embodiment of the present invention in which the transmitted wave (I) contacts the target **24** after crossing a soft layer **22** (e.g., a soft tissue like skin) and which shows an alternative receiver array **14** that includes an odd number of receivers **16***a* through **16***i* after striking the focal point **32** that is about the focal point **32** of the transmitter **12** and the receiving array **14**. The receiving array **14** detects simultaneously the reflections R from the target **24** after the pressure waves cross the soft layer **22**.

[0048] FIG. **3** is a diagrammatic rendering of another embodiment of the present invention that shows a cross-section of the transducer head **10** ready for UCR measurement in close contact with a target **24**. The central elements of the transducer head **10** are a transmitter **12** and a receiver array **14** (together ultrasound elements **12**, **14**) that includes two or more receivers **16***a*, **16***b* in the receiver array **14**. The transducer **12** includes two ultrasound elements (**12**, **14**) encased in a housing **18** or container with patient interface **20** depicted here in contact with a soft tissue **22** (e.g., skin) at or about a bone tissue **24** under examination), as shown in FIGS. **2-4**. In one example, a single-element transmitter **12** and the 48-element receiver array **14** are separate. Both are sections of a right cylinder with a common axis, subtending 120 degrees. The midpoint of the axial segment is the nominal center of the transducer elements **12**, **14**. The two ultrasound elements **12**, **14** may be mounted with a fixed geometry within, e.g., a water-tight solid housing **18**, which is filled with an ultrasound conductive material **26** (e.g., water) and terminates in a window **28** covered by, e.g., a latex membrane **30**, in a configuration such that the common center or focal point **32** of the ultrasound elements **12**, **14** projects, e.g., about 1.5 cm beyond the window **28**.

[0049] In operation, the ultrasound conductive material **26** is under a slight pressure controlled by gravity (e.g., by a reservoir of water placed at a slight higher elevation than the transducer head **10** on a support base (not depicted in FIG. **3**)) and the latex membrane **30** bulges to, e.g., 0.5 cm beyond the rim of the window **28**. When the latex membrane **30** bulge is in contact with the patient's soft tissue **22** (overlying bone 24 being examined), the transducer common center **32** is a virtual point projected under the soft tissue **22** at depth.

[0050] A positioning arm **50** for the transducer head **10** is shown in FIG. **5**, which is a pantograph that includes two segments shaped as parallelograms, one attached to the base 52 and one supporting the transducer head **10**. The arm **54** can be moved vertically and horizontally (three degrees of freedom) by, e.g., motors mounted on the base 52. The arm **54** is articulated so that the transducer head **10** pivots around a fixed point, coincident with the center of the ultrasound elements. In this fashion, the axis of the transducer head **10** can be rotated with two degrees of freedom to assume any orientation around the fixed point.

[0051] During an examination, the operator places the transducer head **10** over the site of interest (bone tissue being examined), and the transducer head **10** is advanced by the operator using precise, submillimeter steps of the arm **54** using computer controls until the transducer center is at the surface of the bone under study. This advance, for the heel, is restricted to 0.5-1 cm and the patient's skin remains in contact with the flexible membrane, and does not come in contact with the rim or any other element of the solid surface. Excessive pressure, which occurs, for example, from a sudden movement of the foot that is being measured, causes the advance to stop and the head to retract.

[0052] Transducer Head. The ultrasound transducer head includes two elements built on, e.g., PVDF (poly-vinyl-difluorene) substrates. The element used as transmitter is single and spans a large interval of degrees from the center, terminating in a latex-covered window. A single coaxial cable transports the low current (xA), low voltage (xV) 1.5-MHz signals from the generator to the transmitter and a set of coaxial cables transports the signal from the receiver to the data acquisition system. A diagram of the head is shown in FIG. **3** and an expanded close-up of the view is shown in FIG. **4**, which further includes the leads or connections that transfer a signal acquired by the individual receivers to, e.g., a computer.

[0053] While ultrasound has traditionally used ceramics and crystals such as PZT (lead zirconate titanate) and quartz to translate acoustical energy to electrical and visa versa, PVDF is ideally suited in its properties for use in medical ultrasound as it is matched to tissue and pliable. In addition, it is generally cheaper and easier to integrate than traditional

ceramics and crystals. The present invention is not limited to the actual materials described herein, as those skilled in the art will know how to match materials to specific target to maximize, e.g, data accuracy, signal strength and/or optimize the signal-to-noise ratio. Compared to PZT, PVDF has two significant advantages as a receiving element. It has a wide frequency response (0.001 to 1 GHz), easily spanning the standard range of biomedical ultrasound. In addition, it has a low acoustic impedance, approaching that of water and human tissue. In contrast, PZT is in general a high Q material that requires multiple matching layers to couple to liquids and soft tissues.

[0054] In the UCR transducer head disclosed herein, PVDF may also be used to as the receiving element, because of the ease of working with it and integrating it into receiver arrays. As a film, PVDF can be obtained in a variety of thicknesses, and therefore a variety of sensitivities. With the use of a commercial adhesive (micro-measurements AE-10 thin glue-line epoxy), PVDF films were glued to support structures of non-traditional design and shape. In addition, developed unique methods for gluing PVDF films together were developed to create novel detector elements. Also developed were techniques for coupling these multi-layer films to 1D and 2D electric arrays to create novel ultrasound detectors capable of both full waveform reception and excellent beam shape sampling. The receiver array pattern is etched on, e.g., 0.005"-thick fiberglass copper-clad board. The integrated PVDF receiver arrays are integrated with specially designed, multi-channel amplifier and digitization systems that are well-matched to the intrinsic electrical properties of PVDF, which is well matched to human soft tissues.

[0055] In order to improve and automate the accurate of UCR measurements, the system of the present invention was developed. It has been found that patient compliance and reproducible measurement are best achieved when the ultrasound head is oriented perpendicular to the bone surface at each measurement site. The system of the present invention achieves the goals of patient compliance and reproducibility by using two orthogonal rotating (pivoting) motions around the center of the transmitter, one longitudinal and the other transversal. These motions were found to provide minimal requirements for normal alignment. The longitudinal rotation is implemented using a pantograph mechanism that may include two parallelograms, the first one linked to a base shaft and the second to the transducer head. The mechanism is actuated by, e.g., one or more A-max 12V-DC gear motors (Maxon Precision Motors, Inc., Burlingame, Calif.). The actual angular position of the arm is read using a 24,000 steps/revolution optical encoder (model 755A—high precision, Encoder Products Co., Sagle, Id.) for an effective angular resolution of 0.9 minutes of angle (MOA). The range of motion is ±45° from the vertical central position.

[0056] The transversal rotation is performed by the base shaft and includes both the transducer head and the pantograph mechanism. The actuating mechanism may include a precision rotary table (model 200RT, Parker Hannifin Corporation, Daedal Division, Irwin, Pa.), and a motor/optical encoder assembly. The angular resolution for the transversal rotation is 0.12 MOA, and the range of motion is 180°.

[0057] In addition to these two pivoting motions, a third rotation around the surface normal is required for the measurement of the anisotropy. The motion may be implemented using the same Maxon 12V DC motor and a 10,000 steps/revolution optical encoder (model 260 accu-coder, Encoder Products Co., Sagle, Id.), for an angular resolution of 2.16 MOA and a range of motion off 180°.

[0058] Precision ball bearings (ABEC 3) may be used for all the rotating parts in order to insure the mechanical precision of the mechanisms. The scanning on the measured surface requires three linear motions oriented along the axis of an orthogonal coordinates system. Each motion is implemented using precision linear ball bearings and shafts, actuated by Maxon 12 V DC motors and precision ball screw and nut mechanisms. The position of each moving element is read by 4,000 steps/rev optical encoders providing a linear resolution of 1.25 μm.

[0059] Thus, a total of six degrees of freedom (DOF), three translations and three rotations, are implemented for the precise positioning of the ultrasound transducer head. The motion of each of the six DOF is controlled using a PCI-Flexmotion motion control card (National Instruments, Austin, Tex.). This card uses PID closed loop feedback control algorithm for each axis and allows the implementation of complex 3D trajectories.

[0060] The control algorithm monitors the "error" (the difference between the actual position at a certain time and the desired position on the requested trajectory); it will stop the motion of the device if the error becomes larger then a threshold value set at 1 mm for the linear motions and 1° for rotations. Thus, the correct execution of the programmed trajectory of the transducer head is permanently monitored.

[0061] In addition, a pressure sensor monitors the contact force between the patient and the elastic membrane of the transducer head. If the contact force becomes larger than 10 N, for example, from a sudden movement of the patient or error in programming of the trajectory of the transducer head, the transducer head is retracted along the direction of the normal to the measured surface, thus preventing potential injury to a subject being examined. Also, the motion control card limits the torque generated by the electrical motors such that the maximum force exerted by the mechanism cannot be larger than 20 N.

[0062] UCR Data Acquisition System and Motor Control Electronics. All of the electronic equipment required to operate the UCR system is contained in one 32 inch tall, 19 inch wide, relay rack, with wheels to make it mobile. The tabletop height allows the monitor and computer keyboard to be mounted on top of the rack, and all equipment is connected to a 120-volt, surge protected, rack-mount power strip. There are five rack-mounted modules in the system, containing the following six devices:

[0063] (1) Computer. The computer has a 1.3 GHz AMD Athlon motherboard with four PCI slots, and one ISA slot. It has 512 MB of PC100 memory, and a 10 GB hard drive. It contains a PCI bus, 48-bit, digital I/O card used to communicate with a delay module (described later) and a proprietary ISA bus interface card, which essentially buffers the address and data lines to transfer data to and from the Data Acquisition Module. A PCI GPIB card is used to program the transmitter, and a PCI card is installed that controls the six DC motors and reads the encoders used to provide the motion in the UCR system. The computer is in a seven-inch high industrial rack-mount case. One or more computers for use with the present invention will generally include code segments that permit data acquisition, normal acquisition and arm positioning, data storage, data processing and a user-interface that permits the user to start a measurement cycle, conduct the data acquisition and capture, interpret the data and graph

and/or output the data in a format for immediate analysis, analysis over time, integration with other data and/or data export.

[0064] (2) Data Acquisition Module. Also mounted in a seven inch high case (FIG. **7**) data acquisition module, which as depicted is a 12-slot ISA passive back plane that has had the connector pin numbers redefined to match signals on a set of proprietary cards developed to digitize the signals from the UCR receiver.

[0065] The A/D cards mounted in this rack may include four dual eight-bit analog-to-digital converters (Analog Devices AD9059) for a total of eight channels per board. In one example, there are six boards per system, giving forty-eight channels of digitized data, which are sent to the computer for analysis via the ISA bus interface card in the computer. All six A/D cards operate from a 40-MHz, crystal controlled, master clock to assure that all A/D converters start digitizing at the same point on the signal. This gives 25 nanoseconds per point resolution. Sixty-four 8-bit points are collected per acquisition cycle. The digitized data from all A/D converters is read simultaneously into dual-port static ram chips, which is 16 bits wide, organized into two bytes. One-half of the dual A/D converter writes into the upper byte, and the other half writes into the lower byte. This arrangement allows use of the 16-bit ISA to transfer data from two channels at once for faster throughput. The data is stored in the primary port of the ram chip, and read out from the secondary port by the 12-MHz ISA computer bus. It is simply read as external memory at location C000h, which is a space reserved for add-on cards in the IBM computer architecture. A DIP-switch can change this address if there are conflicts with another board in the computer.

[0066] The read-and-write addressing function is performed by an address decoder card on the passive back plane. The address decoder card generates the master clock and the write address for the ram chips, and also decodes the memory address for each board. The decoder card in the Acquisition chassis is connected to the ISA bus interface card in the computer chassis by a 50-pin ribbon cable. Linear type power supplies are used to supply the 1 ampere, minus 5 volts and the 10 ampere, plus 5 volts required by all six A/D cards, in order to eliminate the noise generated by the more commonly used switching regulator power supplies.

[0067] (3) Transmitter. The transmitter, which is used to excite the transmit section of the UCR transducer, includes two components: a rack-mounted, synthesized function generator (Stanford Research Systems model DS345), and a Mini-Circuits model ZHL-32A RF power amplifier which is mounted in the back of the rack with its 24-volt power supply. The transmitter configuration puts out a 24-volt peak-to-peak, 3-cycle, 1 MHz, sine wave burst into a 50-ohm load. The transmitter has the capability of being programmed by the computer via a GBIB interface mounted in one of the PCI slots.

[0068] (4) Preamplifier Assembly. The function of the preamplifiers is to amplify the low-level (millivolt range) signals from the receiver section of the UCR transducer to match the 100-millivolt peak-to-peak input sensitivity of the A/D cards. The A/D converters have, e.g., a 1-volt sensitivity, with a X10 amplifier at each A/D input. The preamplifiers have a gain of 100 (40 dB), which gives an overall gain of 1000. There may be eight channels per board, with six boards in the system, for a total of 48 channels. Each channel contains a 50-ohm pulse transformer to match the input impedance of the A/D cards and prevent ground loops by isolating the preamplifier assembly. The input impedance of the preamplifiers (Analog Devices AD844) is set at 10,000 ohms to match the high impedance of the PVDF film used in the receiver construction. As depicted, the preamplifier cards are mounted in a EIA-standard sub-rack with a built-in linear, plus and minus 15-volt power supply. The input connectors are standard DB37S, as are the connectors on the A/D card inputs.

[0069] (5) Motor Controller Chassis. There are six, 12-volt DC motors, each with their own position encoder, used to control the motion of the platform, arm, and transducer assembly in the UCR system. The motor controller chassis contains power supplies, drivers for the motors, and an interface to the motor controller board, in the computer. The motor drives are National Semiconductor LM1875 power amplifiers used in a direct-coupled configuration. This arrangement allows clockwise and counter-clockwise rotation at any velocity, and the 4-phase position encoders provide precise positioning.

[0070] (6) Programmable Delay Generator. It is programmed by three of the 8-bit ports on the PIO card in the computer, and simply sets a delay between the software instruction to fire the transmitter and the signal to start the data acquisition. The velocity of sound through the water the transducer is 1.5 Km per second, and only 64 points are captured. The above arrangement prevents the digitization of all the dead time between the transmitted and received signals. The counter is programmable up to 4096 microseconds, with 100-nanosecond resolution. It may include three 74F163 pre-settable binary counters, and a 10-MHz crystal clock. It is housed in a small chassis, with power supply, in the back of the rack.

[0071] Operational Description of Data Acquisition. The Scalable Multichannel Data Acquisition System (SMDAS) is a high frequency digital system for collecting data in the standard ultrasonic frequency range (50 kHz to 10 MHz). The SMDAS hardware component generally includes multiple channels with two stages: pre-amplification and digitization. The system is scalable with a granularity of, e.g., 8 channels.

[0072] The SMDAS is a triggerless, computer-controlled system, based on a low-cost, 8-bit, 60-MHz analog-to-digital converter. Because traditional UCR used three-cycle, 4-MHz pulses, a 40-MHz solution was chosen so as to permit 10 times oversampling of these signals. A sampling memory of 64 samples (1.6 μs) provides sufficient storage for each channel. A total of 48 channels were chosen because each channel maps to a specific angle of incidence, and all pressure critical angles and 2-gamma shear dynamics occur for angles less than 40 degrees in solids of interest.

[0073] Digitization Subsystem. The heart of digitization is the AD9059 (Analog Devices, Norwood, Mass.), a dual channel IC package capable of sampling at 40 million samples per second. Although this chip can be supplied a reference voltage, the AD9059 can self-generate the required level to operate the internal pipeline of comparators. With self-referencing enabled, the AD9059 accepts two single-ended inputs with a voltage range between 1.5 and 2.5 Volts. Upon cycling with a TTL compatible clock, the 16 digital output pins on the AD9059 will output 8-bit digital samples for the two input channels. While digital crosstalk is negligible, the AD9059 is rated with 1.5 bits of noise. For 8 channels, a two-layer printed circuit board was designed, wire-wrap tested, and built (Alpha Printed Circuits, Mesquite, Tex.) to accommo-

date four independent subsystems of two channels. For each AD9059, a 16-bit dual port static RAM (CY7C133, Cypress Semiconductor, San Jose, Calif.) with ~25 ns access time is used to record the 64 samples for two channels, although in principle only 128 bytes of memory should suffice. The PCBs are equipped with DB37F connectors (Amphenol, Wallingford, Conn.), and each channel is routed to a pre-amplification stage with a coaxial wire to avoid the noise associated with a trace on the PCB.

[0074] Before digitization, each channel passes through an operational amplifier (CLC440, ComLinear/Nationional Semiconductor, Santa Clara, Calif.) with a gain of 10. The amplification stage expects all inputs to be 50 ohms in impedance. Each board has a 98-pin on-board edge connector designed to fit into a 14-slot ISA standard backplane (JDR Microdevices, San Jose, Calif., part number BP141) mounted in a separate computer chassis. For each board, there is also a selectable board identification jumper needed for reading from a given card. A special decoder board also in the bus associates each digitizing board with a memory address relative to some selectable base address, in steps of 128 bytes (0x080h). The decoder board is in turn connected with a parallel ribbon cable to a buffer board on the computer system's ISA bus. If the base address is set to be in the x86 architecture's high memory area (that is, 0xD0000h to 0xE0000h), this configuration allows direct memory access to samples stored in the memories for each individual channel. If a 2-byte read is utilized, data can be read for two channels simultaneously. In the initial design, sampling was initiated by a memory write to the base address. It should be noted that memory reads are limited in time by clocking of the ISA bus, which on recent motherboards was maximized at 12.5 MHz.

[0075] Pre-Amplification Subsystem. Although the digitization subsystem includes some amplification, it is often necessary to condition signals from transducers with additional amplification. With certain transducers, there may also be issues involved with impedance matching, especially for high impedance, polymer based piezoelectric system. A high impedance input amplification system was designed and built around a 44-pin EIA card subrack (Vector Electronics, North Hollywood, Calif.). Each amplifier cards uses high impedance operation amplifiers (Analog Devices, AD844) to amplify signals ideally from PVDF transducers. With a nominal gain of 100 for 10,000 ohm input impedance, these amplifiers also resist oscillations that can occur with impedance mismatches. The AD844 has a bandwidth-gain product of over 300 MHz, so signal distortion should be negligible at typical ultrasonic frequencies. Output of each channel is transformer (Mini Circuits, Brooklyn, N.Y., part number T1-1) coupled to prevent catastrophic ground loops. The EIA rack is connected to the chassis containing the digitization subsystem with shielded, coaxial cables.

[0076] Signal Generation and Timing. In order to have precise timing between pulse generation and the start of the sampling, it was necessary with the original SMDAS design to have a computer system with little or no overhead. With a data acquisition window of 1.6 μs, precise timing could be guaranteed with a real time operating system (RTOS). With a Windows (Microsoft, Redmond, Mass.) or Linux brand operating system, the system timing granularity is on the order of 1 millisecond. Rather than going with an expensive embedded solution, the flexibility of an industry standard operating system was retained, and the timing for signal generation and sampling was moved to a custom-made external module. The timing module is enclosed in a rack mountable case. It contains three 4-bit binary counters operating at 10 MHz, programmable with the digital output from a PIO card (PCI-DIO48H, Measurement Computing, Middleboro, Mass.). Twelve bits of programmability at 10 MHz translates to a delay range of 409.6 μs. For typical ultrasonic velocities in water and soft tissues, this window accounts for propagations up to 60 cm. After the pulse generator firing is commenced, the counters complete their programmed delay, and then a TTL level signal is transmitted via external co-axial cable to the decoder board in the DAQ chassis to commence sampling.

[0077] Software for Data Acquisition. The SMDAS software component includes, e.g., several layers of libraries for accessing the SMDAS hardware component. It offers entry points at several layers of system programming, providing maximum flexibility for application development and future systems integration.

[0078] Memory Mapping. As designed, the data acquisition board memory that contains sampled data is mapped to a physical memory address in the upper memory area of the Intel x86 architecture. By reading at this address and storing the information in a variable array, the sampled data can be transferred from board memory to system memory without need for complex communications or system drivers. Because reading of sampled data is ultimately multiplexed across the ISA bus, it is most efficient to read in two-byte words to maximize the bus bandwidth. After transfer, the 8-bit samples must be separated. On a modern microprocessor, such as a Pentium (Intel Corporation, Santa Clara, Calif.) or Athlon (AMD, Sunnyvale, Calif.) class chips, this separation should be accomplished in a single clock cycle instruction. An arbitrary bit shift (also known as a barrel shift) or a bit-wise AND operation can be used to extract the upper or lower 8 bits from the 16-bit word.

[0079] To facilitate this memory mapped read, a dynamic linked library (DLL) was created using Visual Studio Professional 6.0 (Microsoft Corporation, Redmond, Wash.) using the C programming language. This low level library provides a function for reading a 2-byte word at an arbitrary address in the upper memory area (unsigned short int 1v48chdaq(int addr)) and two functions for extracting upper and lower samples (unsigned char left/right(unsigned short int a)). This portable DLL can, e.g., be linked into Windows applications developed in a variety of programming languages, and by cycling through memory address all sampled data can be transferred to system memory for analysis or for saving to storage media.

[0080] Noise Reduction. The visual programming environment LabVIEW (National Instruments, Austin, Tex.) was chosen for development of data acquisition software due to its rapid development scheme, its ease of use, and its recognition as an industry standard. In order to maximize flexibility for future applications, an intermediate library of "virtual instruments" (VIs) was developed using a bottom-up approach where a special global VI contains parameters common to all components (that is, number of channels, base memory address).

[0081] At the lowest level, the "download 2 channels" VI is attached to the DLL described above and cycles through the appropriate memory addresses to transfer 128 bytes to system memory. Each channel possesses repeatable error that is measurable with the pre-amplification stage disabled or the open inputs. Fourier analysis of averages of this residual indicates

contributions at 40 MHz and its subharmonics. This is entirely consistent with reference voltage noise due to a lack of shielding on the address lines for the buffer memories. Because 6 address lines are required, one would not be surprised to find noise at the fundamental and at the 5 subharmonics (20, 10, 5, 2.5, and 1.25 MHz).

[0082] The "download 2 cleaner channels" VI subtracts this repeatable signal from sampled data, and the resultant noise is consistent with the manufacturer's specifications. An application can either generate these average background waveforms itself, or it can use the default ones produced by the "calibrate average background waveforms" VI. The "download n cleaner channels" VI packages multiple channels into an n by 64 matrix.

[0083] The pipeline architecture of the AD9059 requires a 1-MHz minimum sampling rate. At slower rates, the internal registers are degraded, and the sampling is extremely inaccurate. Because the transfer of one block of 64 two-channel words occurs at ISA bus speeds (in the order of 10 MHz), the effective rate for sequential acquisitions is less than 200 kHz. Thus, the first 5 samples of every acquisition of each channel may be suspect. Because the granularity of the time delay subsystem is 0.1 μs, it is convenient to drop the first 8 samples (0.2 μs).

[0084] Multiple Frame Acquisition. The real power of this intermediate library is its ability to construct time windows larger than the 1.6 μs given by 64 samples. In one determination using steady-state dynamics, it is possible to adjust the delay time between sequential acquisitions so that they are properly aligned in time. The "acquire" VI uses the "set delay time" VI to form contiguous frames from "download n cleaner channels". The process is repeated a number of times, with each sequential acquisition appending to the previous set of data. The resulting output of N channels and M 1.4 μs frames gives a matrix of dimensions N×(56×M). It should be noted that the rate-limiting step in the data acquisition process is the transfer of information across the ISA bus. Increasing the number of frames and time window increase the scan time, which in general grows at a linear rate.

[0085] Stochastic Frame Acquisition. In some imaging situations, the alignment of contiguous time frames will lead to spurious signals. This problem is especially evident with large blocks of time (order of 100 μs) in scenarios where secondary reflections or reverberations from early pulses are captured in later frames. These signals cannot be removed by taking an average. In order to minimize these unwanted data, it is sometimes necessary to gather multiple frames in a stochastic manner. For a given time window, the 1.4 μs frames are selected at random from a list until exhausted and the window is filled. If this method is repeated and averaged, the cross-correlated signals from separate frame pulses may be eliminated.

[0086] In operation, the system of the present invention is summarized in the flowchart **70** of FIG. **7**. In step **72**, an ultrasound wave or pulse is transmitted toward a target, e.g., a bone, and the reflected signals are captured by two or more receivers in step **74**. Based on the signals acquired from the receptors a determination is made as to whether the normal was found is made at step **76**, which is made by a computer that directs, e.g., the articulated arm to either move the transducer or begin data acquisition. If the normal was found, then the final data from the target is acquired simultaneously in final data acquisition step **78**, and the results stored as an analog signal or a digital equivalent. Based on the data acquired from the final acquisition step **78**, the Emax and Emin are calculated at step **80** to determine the ultracritical reflectometry data of the target, from which the anisotropy may be calculated in step **82**. Finally, the raw data, processed data and/or the calculated results may be stored, processed, displayed, printed and/or compared to earlier or later target data and calculations to provide the user with useful results at step **84**.

[0087] In FIG. **8**, the ultracritical reflectometry data acquisition transducer, method and system are used in flowchart **90** to make a determination for treatment of a patient. In step **92**, the normal is determined for bone, in this example at the heel. Upon acquisition of the normal, the transducer takes the critical UCR measurements. If the patient is concurrently or about to begin a treatment regimen, that occurs at step **96**, with subsequent measurements taken at time-intervals (e.g., weekly, bi-weekly, monthly, depending on the physicians instructions and type of treatment) in step **98**. Data from before patient treatment (step **94**) and subsequent treatments (step **98**) are acquired, processed and/or stored as patient data (step **100**). The measurements, data and processed patient information is then compared at step **102** with normal patient data, and with the UCR measurements from the same or other treatments (step **104**) from the same and/or other patients and a determination is made to see if the patient is improving at step **106**. If the patient is improving then they may be returned to the bone scanning regime. If the patient is not improving or getting worse, then the physician can direct a change in treatment and the patient is returned to the monitoring regime (step **84**).

[0088] The collection of reflected signal begins when bone surface is reached. This time is operationally defined by an abrupt increase in the reflected signal over all angles. The operator then initiates a series of automated steps to accurately identify the normal. These steps control the acquisition of reflected angular spectra from at least two orthogonal directions on the bone surface. For each direction the plane of the normal is found by tilting the transducer head until the integrated signal is maximum; the intersection of the two orthogonal planes defines the normal. The reflected spectra (signals at all receiver elements) are then obtained by rotating the head around the normal in 15-degree intervals over 120 degrees; the two orientations at which the first critical angle is smallest and greatest identify the two principal axes of bone.

[0089] Calculation of Key Indices of Bone Quality from UCR. In general practice, measurements are made at three discrete areas of bone tissue being examined. At each site, multiple critical angle velocities (v) are obtained over 120 degrees. The data for v are mathematically fitted to the formula: $v^2=a+bx^2+cx^4$, where x=cos (orientation), and v^2 is elasticity normalized to a density of 1 g/cc. From the resulting graph, the minimum (E_{min}) and maximum (E_{max}) elasticities of trabecular and cortical bone are calculated as a measure of bone material quality. The term "elasticity" may be used interchangeably with the term "elasticity coefficient". From the area-under the curve of v data, "integrated" or "mean" elasticity (E_{int}) is calculated. E_{int} is essentially the same as the square of average velocity. Anisotropy (A) is calculated as the ratio of corresponding maximum and minimum elasticities.

[0090] Clinical Application of New UCR Device. Development of adynamic bone disease during bisphosphonate treatment of osteoporosis. Bisphosphonates (such as Fosamax® and Actonel®) are widely used for the treatment of postmenopausal osteoporosis throughout the world. This treatment is

known to increase bone density and decrease fractures (Liberman, et al., *N. Engl. J. Med.*, 333:1437-1443, 1995). The primary action of this drug is to inhibit bone resorption (destruction). There is secondary reduction in bone formation that lags behind the fall in bone resorption during the first 1-3 years of treatment. During this period, a gain in bone mass occurs resulting in increased bone density. The inhibition of fractures has been ascribed to this rise in bone density. From studies in experimental animals, however, a concern has been raised that bisphosphonate may produce a profound suppression of bone turnover that could cause microdamage and compromise bone quality (Li, et al., *Calc. Tissue Intern.*, 69:281-286). Moreover, in human beings, it has been suggested that chronic bisphosphonate treatment may impair bone quality from marked suppression of bone turnover, causing increased rate of fracture after long-term bisphosphonate treatment (Ott, *J. Clin. Endo. Metab.* 86:1835, 2001).

[0091] The study summarized below was undertaken in order to determine if such complication can occur in human beings, using the apparatus, method and system disclosed herein. Using the present invention, it was discovered that long-term bisphosphonate treatment causes "adynamic bone disease," a histologic appearance of bone displaying a marked suppression of bone turnover with virtual absence of cellular activity (Odvina, et al., *J. Bone Miner. Res., publication expected September* 2003).

[0092] A transiliac crest bone biopsy was performed in 6 postmenopausal osteoporotic women (49-76 years), who developed fractures after they had been on long-term bisphosphonate treatment for 3-7 years. Besides bisphosphonate, 3 patients took hormone replacement therapy, 2 prednisone (one for fibromyalgia, the other for asthma), 4 vitamin D, and all 6 patients received calcium supplements. Fractures occurred in finger in 1 patient, pelvis in 3, hip in 1, foot in 1, and femur in 2. In four patients, bone biopsy was obtained because patients displayed delayed healing of fractures (of ischium, femur, pelvis) for 3 months to 2 years while maintained on bisphosphonate treatment. In two patients, the biopsy was taken shortly after they developed fractures (sacrum, pubic rami, rib), because the physician felt that the index of suspicion for adynamic bone disease was high.

[0093] Histomorphometric findings in trabecular bone are summarized in Table 1. As shown in FIGS. **9**A and **9**B, bone formation were markedly diminished with low osteoblast surface (Ob.S/BS) and absence of double tetracycline label (dLS) and absent or diminished single label (sLS) in all specimens. Before a biopsy was obtained, tetracycline was given in two coursed 10 days apart. Tetracycline is picked up in area of active bone formation, imparting yellow lines under polarized light microscopy. FIGS. **9**A and **9**B are photographs of polarized light microscopy that shows the absence of tetracycline labeling in a patient on long-term bisphosphonate treatment (**9**A), and normal labeling in a normal subject (**9**B). Two courses of tetracycline were given 10 days apart. Tetracycline is picked up in area of active bone formation, imparting yellow lines under polarized light microscopy. The distance between two labels represent the amount of new bone formed over 10 days. Absence of tetracycline labeling indicated markedly impaired bone formation. Bone resorption (destruction) parameters (ES/BS and Oc.S/BS) were also decreased in 3 patients. A similar trend was observed in cortical bone (data not shown).

TABLE 1

Histomorphometric Findings in 6 Patients with Adynamic Bone Disease After Long-Term Bisphosphonate Treatment

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Normal Mean ± SD
BV/TV (%)	9.4	8.9	14.3	15.2	12.2	10.9	21.17 ± 4.9
OV/BV (%)	0	0.05	0.42	0.66	0	0.89	0.38 ± 0.25
Oc.S/BS	0	0.12	1.0	0.3	0.17	0.29	0.7 ± 0.7
ES/BS (%)	0.85	1.7	9.5	9.3	2.1	1.3	4.0 ± 2.0
Ob.S	0	0.19	1.7	0	0	3.6*	4.4 ± 3.2
dLS/BS (%)	0	0	0	0	0	0	4.3 ± 2.9
SLS/BS (%)	0	0.3	0.58	0	0	0	6.0 ± 4.1

Abbreviations:
BV = bone volume;
TV = total volume;
OV = osteoid volume;
Os.S/BS = osteoclastic surface/bone surface;
ES = eroded surface;
Ob.S = osteoblactic surface;
dLs = double-label tetracycline label;
sLS = single tetracycline label.
*= probably falsely high, since osteoclasts appeared flat and inactive.

[0094] The results suggest that bisphosphonate may cause adynamic bone disease with markedly reduced bone formation. "Bone turnover", a process by which "old" or damaged parts of bone are removed and replaced by new healthy bone, is markedly suppressed as well. Following a chronic suppression of bone turnover, bone microdamage may accumulate (Li, et al., *Calc. Tissue Intern.* 69:281-286, 2001). This explanation can account for recurrent fractures that display delayed healing.

[0095] UCR Reflectometry in vivo Among Patients with Adynamic Bone Disease. Bone elasticity was measured in vivo by new UCR in two patients from the preceding study with adynamic bone disease on bisphosphonate treatment, 8 months and 12 months after withdrawal of bisphosphonate treatment. At the beginning of this study the UCR device was not available. In the former patient, the mean (integrated) cortical and trabecular elasticities were depressed by 15.4%

and 27.1%, respectively, from the mean of normal premenopausal women. In the latter patient, the mean (integrated) cortical and trabecular elasticities were within the range of values in normal premenopausal women, indicative of eventual correction of defective bone quality after stopping bisphosphonate treatment.

[0096] In two patients, UCR analysis of the heel was performed in vivo when they presented with fractures while still on bisphosphonate treatment. Mean cortical elasticity was decreased by 25% and 26%, and mean trabecular velocity by 16% and 15%, compared to mean values for normal premenopausal women. The remaining two patients underwent bone biopsies elsewhere and were not available for UCR measurements.

[0097] The finding of reduced elasticities of cortical and trabecular bone in patients with adynamic bone disease from bisphosphonate treatment strongly suggests that abnormal structural derangement in bone (shown on histomorphometry) is correlated with impaired bone quality, affirming the previously stated hypothesis.

[0098] Detection of impaired bone quality by new UCR in vivo among patients on long-term bisphosphonate treatment. Using the new UCR device disclosed herein, the ultrasound elasticity of cortical and trabecular bone was measured at multiple orientations in the calcaneous in vivo. UCR analysis using the present invention was performed in 14 normal postmenopausal women, 9 with postmenopausal osteoporosis on conventional treatment (untreated PO), and 25 on bisphosphonate treatment (mean duration 3.5 years). Values were expressed as percentage of values in 14 normal premenopausal women (Table 2). Mild or no decreases (<5%) were observed in normal postmenopausal women. A mild-moderate reduction in elasticity (~10%) was disclosed in untreated postmenopausal women. In bisphosphonate treatment, trabecular elasticity (both maximum and minimum) significantly declined by about 15%, and cortical elasticity decreased by about 25%. Anisotropy of cortical and trabecular bone decreased during bisphosphonate treatment, owing to a more prominent decline in maximum elasticity. Thus, bone material became less anisotropic after this treatment, signaling an abnormal character of bone. Integrated cortical elasticity decreased significantly by 25.9% in cortical bone and by 17.5% in trabecular bone from normal premenopausal values following bisphosphonate treatment.

[0099] Much of the decline in elasticity occurred during the first 3 years of bisphosphonate treatment. In bisphosphonate treatment, elasticity was independent of heel bone mineral density obtained simultaneously by dual photon x-ray absorptiometry.

[0100] FIG. **10** is a graph that shows the independence of bone elasticity from bone density during bisphosphonate treatment and in renal transplantation. The integrated (mean) elasticity coefficient of cortical bone by new UCR and bone density by dual photon x-ray absorptiometry were simultaneously measured in the calcaneus in vivo. There were two "outliers" with elasticity coefficients that were much higher than in the rest. One of them was a patient in whom bisphosphonate treatment had been stopped for 1 year.

[0101] This finding confirms earlier conclusion (Antich, et al., *J. Bone Miner. Res.*, 8:301-311, 1993) that UCR measures material or intrinsic bone quality, not bone density at the organ level. In normal pre- and postmenopausal women and in postmenopausal osteoporotic patients on conventional treatment, elasticity was modestly correlated with bone density.

TABLE 2

Trabecular and Cortical Elasticities Measured in vivo by UCR

		Normal	Osteoporotic	
Elasticity		Postmenopausal	Untreated PO	BISPHOS
Trabecular	E_{min}	100.1 ± 3.1	94.2 ± 5.7	85.1 ± 5.5^{+}
	E_{max}	98.6 ± 4.3	89.9 ± 6.2*	82.3 ± 6.0^{+}
	E_{int}	98.3 ± 3.6	91.8 ± 5.9*	82.5 ± 5.6^{+}
	A	98.5 ± 3.4	95.3 ± 1.4**	96.8 ± 3.4^{+}
Cortical	E_{min}	97.4 ± 5.0	91.7 ± 1.8^{+}	75.4 ± 5.5^{+}
	E_{max}	96.8 ± 5.9	87.4 ± 1.4^{+}	72.1 ± 6.9^{+}
	E_{int}	97.4 ± 4.7	90.8 ± 2.0^{+}	74.1 ± 6.2^{+}
	A	99.4 ± 4.3	95.4 ± 2.7*	95.6 ± 6.8**

Elasticities are presented as percentage of normal premenopausal women.

*$p < 0.05$;

**$p < 0.01$;

$^{+}p < 0.001$ vs. normal premenopausal women.

PO = postmenopausal osteoporosis;

BISPHOS = bisphosphonate;

E_{max} = maximum elasticity;

E_{min} = minimum elasticity;

E_{int} = integrated elasticity;

A = anisotropy;

± = plus/minus standard deviation.

[0102] Inferior Bone Quality in Renal Transplantation Shown by New UCR. Ultrasonic analysis was performed in vivo using the new UCR device in 9 patients who underwent kidney transplantation and taking steroids (Table 3). In renal transplantation, a condition known to be associated with weakened bone and propensity to fractures, maximum and minimum elasticities in trabecular bone were significantly lower by 15-17% compared to normal premenopausal women. Cortical elasticities were reduced by 25-29%. The decline in maximum elasticities was more prominent than that of minimum elasticities, resulting in significantly lower anisotropy, compared with the normal premenopausal state. Findings were remarkably similar to those of bisphosphonate treatment (Table 2 vs. Table 3).

TABLE 3

Trabecular and Cortical Elasticities in Renal Transplantation and During Treatment with Sustained-Release Sodium Fluoride

Elasticity		RT-St	SR-NaF
Trabecular	E_{min}	85.1 ± 1.8^{+}	96.3 ± 4.6
	E_{max}	83.2 ± 1.8^{+}	93.3 ± 2.5^{+}
	E_{int}	83.4 ± 1.4^{+}	94.9 ± 2.1^{+}
	A	97.8 ± 2.0*	97.1 ± 3.7
Cortical	E_{min}	75.0 ± 2.4^{+}	95.0 ± 6.2
	E_{max}	71.4 ± 2.6^{+}	95.4 ± 6.9

TABLE 3-continued

Trabecular and Cortical Elasticities in Renal Transplantation and During Treatment with Sustained-Release Sodium Fluoride

Elasticity	RT-St	SR-NaF
E_{int}	73.2 ± 1.5^{+}	94.1 ± 4.8**
A	95.2 ± 2.1^{+}	100.5 ± 5.1

Elasticities are presented as percent of normal premenopausal women.
*$p < 0.05$;
**$p < 0.01$;
$^{+}p < 0.001$ vs. normal premenopausal women.
RT-St = renal transplantation on steroids;
SR-NaF = sustained-release sodium fluoride;
E_{max} = maximum elasticity;
E_{min} = minimum elasticity;
E_{int} = integrated elasticity;
A = anisotropy;
± = plus/minus standard deviation.

[0103] Improved bone quality following treatment with sustained-release sodium fluoride. The treatment of osteoporotic patients with sustained-release sodium fluoride was shown to increase trabecular bone velocity when measured by the original UCR device (Zerwekh, et al., *J. Bone Miner. Res.* 6:239-244, 1991; Antich, et al., *J. Bone Miner. Res.* 8:301-311, 1993, see also U.S. Pat. No. 5,228,445, relevant portions incorporated herein by reference). Ultrasonic analysis was performed in vivo using new UCR device in 8 patients with osteoporosis after treatment with sustained-release sodium fluoride. The elasticities of cortical and trabecular bone from patients undertaking this treatment resided between the values in normal postmenopausal women and postmenopausal osteoporotic patients on conventional treatment (Table 2 vs. Table 3). Anisotropy in patients undergoing sustained-release sodium fluoride treatment was found to be intact.

[0104] While this invention has been described in reference to illustrative embodiments, this description is not intended to be construed in a limiting sense. Various modifications and combinations of the illustrative embodiments, as well as other embodiments of the invention, will be apparent to persons skilled in the art upon reference to the description. It is therefore intended that the appended claims encompass any such modifications or embodiments.

1. A method for determining an elasticity coefficient of a target, comprising the steps of:
- determining simultaneously two or more critical-angle reflections of an ultrasound wave from the target using an ultrasound transducer comprising a transmitter and two or more receivers; and
- calculating the elasticity coefficients of the target.

2. The method of claim **1**, wherein the target comprises bone.

3. The method of claim **1**, wherein the target comprises human bone.

4. The method of claim **1**, wherein the target comprises a human bone from a human being suffering from or suspected of having osteoporosis.

5. The method of claim **1**, wherein the target comprises bone from a human being suffering from or suspected of having osteoporosis under treatment with bisphosphonate.

6. The method of claim **1**, wherein the detection step is non-invasive.

7. The method of claim **1**, wherein one or more elasticity coefficients are determined from the square of ultrasound velocity as determined from the identified critical angle.

8. The method of claim **1**, further comprising the steps of:
- determining a maximum elasticity coefficient and a minimum elasticity coefficient to estimate a degree of target anisotropy; and
- using the critical-angle reflection values detected at multiple rotational orientations from the ultrasound transducer fixed at a position normal to a bone surface.

9. The method of claim **2**, further comprising the step of determining a maximum elasticity coefficient and a minimum elasticity coefficient to estimate a degree of bone anisotropy.

10. The method of claim **1**, further comprising the step of automating the determination of the normal of the transducer to the target.

11. The method of claim **1**, wherein the step of detecting simultaneously is further defined as comprising the simultaneous reception from 2, 4, 8, 16, 24, 36, 48, 64 or 128 receivers.

12. The method of claim **1**, further comprising the step of storing the critical-angle values detected in the reflection of an ultrasound wave at two or more receivers that are concentric with a transmitter.

13. The method of claim **1**, further comprising the steps of:
- storing the detected critical-angle reflections of ultrasound waves at different points in time; and
- comparing the measurements to track changes in the coefficient of elasticity of the target.

14. The method of claim **1**, wherein the step of detecting at two or more angles uses a transducer head comprising at least one transmitter and two or more receivers that detect simultaneously the reflected ultrasound energy from the target, wherein the transmitter and the two or more transducers have a common focal point.

15. The method of claim **1**, wherein the transmitter is concave.

16. The method of claim **1**, wherein the two or more receivers for part of a concave array in at least two dimensions.

17. The method of claim **1**, wherein the transmitter and the two or more receivers are concave and concentric.

18. The method of claim **1**, wherein the transmitter is concave and the two or more receivers are concave and the transmitter and the two or more receivers are concentric about a common focal point.

19. The method of claim **1**, wherein the receivers are further defined as a receiving array and the array comprises 48 independent receiving transducers that are concentric and concave and share a focal point with the transmitter.

20. The method of claim **4**, wherein the human has bone disease, a bone-losing condition other than osteoporosis, or a condition suspected of causing inferior bone strength.

21. The method of claim **5**, wherein the treatment of osteoporosis comprises drugs other than bisphosphonate, e.g., an estrogen, an estrogen analog, a parathyroid hormone peptide, a fluoride, a vitamin D, and a calcitonin.

22. The method of claim **5**, wherein the treatment is suspected of causing bone loss.

23. The method of claim **5**, wherein the treatment is suspected of causing bone loss caused by a steroid or anticonvulsant.

24. The method of claim **5**, wherein the step of detecting simultaneously two or more critical-angle reflections of an ultrasound wave from the target is taken prior to initiation of

bisphosphonate treatment, in order to identify patients with inferior bone quality in whom bisphosphonate should be used with caution.

25. A method for determining the effect on a coefficient of elasticity of bone from a patient undergoing treatment for osteoporosis, comprising the steps of:

detecting simultaneously at two or more angles the critical-angle reflections of ultrasound waves directed at a bone using an ultrasound transducer with one or more transmitters and two or more receivers; and

calculating the anisotropy of the bone from the ratio of a maximum elasticity coefficient and a minimum elasticity coefficient, wherein elasticity coefficients are derived as the square of the velocities of an ultrasound waves as determined from the critical angle.

26. The method of claim **25**, further comprising the steps of:

storing a first detected critical-angle reflection of ultrasound waves at two or more receivers prior to, or concurrent with, treatment with a bisphosphonate or derivative thereof

storing a second detected critical-angle reflection of ultrasound waves at two or more receivers after a period of time; and

comparing the first and second measurements to track changes in the elasticity coefficient of the bone during treatment with the bisphosphonate or derivative thereof.

27. The method of claim **25**, wherein the step of detecting simultaneously at two or more angles the critical-angle reflection of ultrasound waves directed at a bone using an ultrasound transducer further comprises measuring a maximum and a minimum elasticity of a cortical and a trabecular region of the bone; and

estimating the anisotropy of the bone in vivo.

28. The method of claim **27**, wherein determining the elasticity of cortical bone, trabecular bone, and anisotropy of a patient's bone is non-invasive.

29. The method of claim **28**, wherein the measurement of elasticity is at a heel.

30. The method of claim **28**, wherein the step of calculating the anisotropy of the bone further comprises determining the maximum and the minimum elasticity coefficient of a cortical and a trabecular bone region, wherein the measurements correspond to an axis of a weight-bearing and a non-weight-bearing bone, respectively.

31. The method of claim **25**, wherein the patient has bone disease, a bone-losing condition other than osteoporosis, or a condition suspected of causing inferior bone strength.

32. The method of claim **26**, wherein the treatment of osteoporosis comprises an estrogen, an estrogen analog, a parathyroid hormone peptide, a fluoride, a vitamin D, and a calcitonin.

33. The method of claim **26**, wherein the treatment is suspected of causing bone loss caused by steroid or anticonvulsant.

34. The method of claim **26**, wherein the step of detecting simultaneously two or more critical-angle reflections of an ultrasound wave from the target is prior to initiation of bisphosphonate treatment, in order to identify patients with inferior bone quality in whom bisphosphonate should be used with caution.

35.-**84**. (canceled)

85. A method for simultaneously measuring maximum and minimum elasticity coefficients and anisotropy of bone non-invasively in vivo in accordance with the method of claim **1**.

86. A method for taking simultaneous measurements of maximum and minimum elasticity coefficients and anisotropy of cortical and trabecular bone non-invasively in vivo in accordance with the method of claim **25**.

87-**89**. (canceled)

* * * * *