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**Abul-Haj et al.**

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(54) **NONINVASIVE APPLIED FORCE / OPTICAL GLUCOSE CONCENTRATION DETERMINATION ANALYZER APPARATUS AND METHOD OF USE THEREOF**

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**A61B 5/1455** (2006.01)  
**A61B 5/00** (2006.01)  
**G01N 21/47** (2006.01)  
(Continued)

(52) **U.S. Cl.**  
CPC ..... **A61B 5/14532** (2013.01); **A61B 5/0051** (2013.01); **A61B 5/1455** (2013.01); **A61B 5/6841** (2013.01); **G01N 21/1717** (2013.01); **G01N 21/359** (2013.01);  
(Continued)

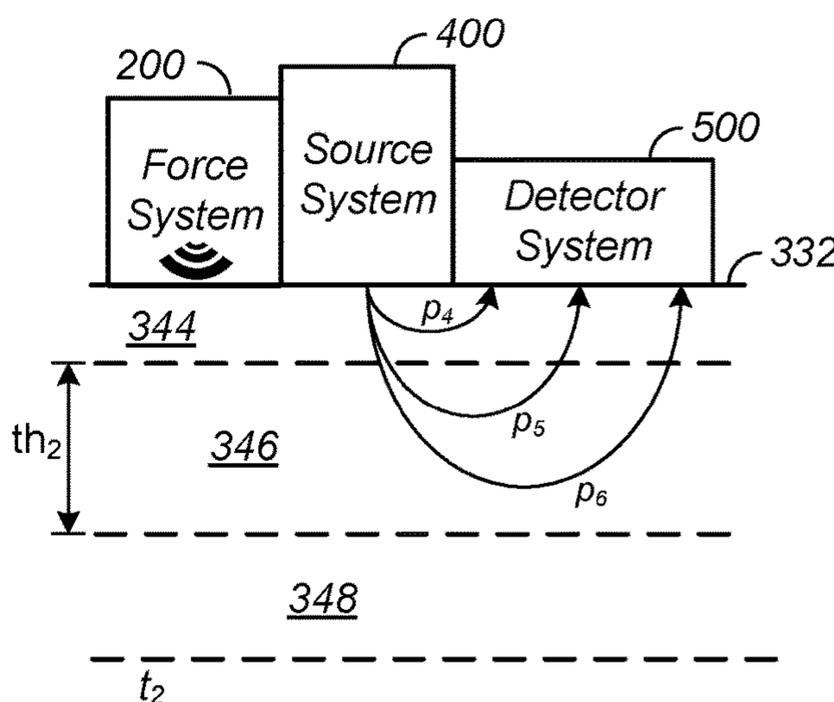
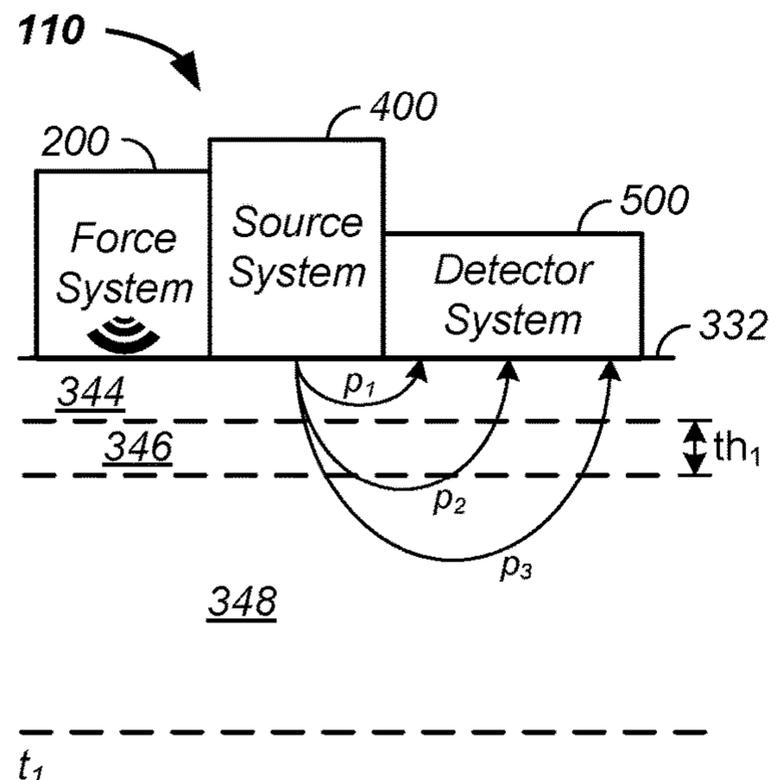
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See application file for complete search history.

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*Primary Examiner* — Dominic J Bologna

(57) **ABSTRACT**  
The invention comprises an applied force-optic analyzer used to determine a sample constituent concentration, a physical measure of the sample, and/or a state of the sample. The analyzer comprises: an electro-mechanical transducer affixed to skin of a subject; a controller, the controller providing a voltage waveform to the electro-mechanical transducer driving displacement of the skin and inducing a pressure wave into the skin; and a spectrometer interfaced to a sample site of the skin, the spectrometer comprising a set of sources and a set of detectors, where the controller is configured to collect signal from the set of detectors as a function of timing of the voltage waveform and apply a calibration model to the signal to determine the analyte concentration.

**18 Claims, 9 Drawing Sheets**



**Related U.S. Application Data**

filed on Apr. 25, 2019, provisional application No. 62/838,283, filed on Apr. 24, 2019.

(51) **Int. Cl.**

**G01N 21/17** (2006.01)

**G01N 21/49** (2006.01)

(52) **U.S. Cl.**

CPC ..... **G01N 21/474** (2013.01); **G01N 21/49** (2013.01); **G01N 2021/1729** (2013.01)

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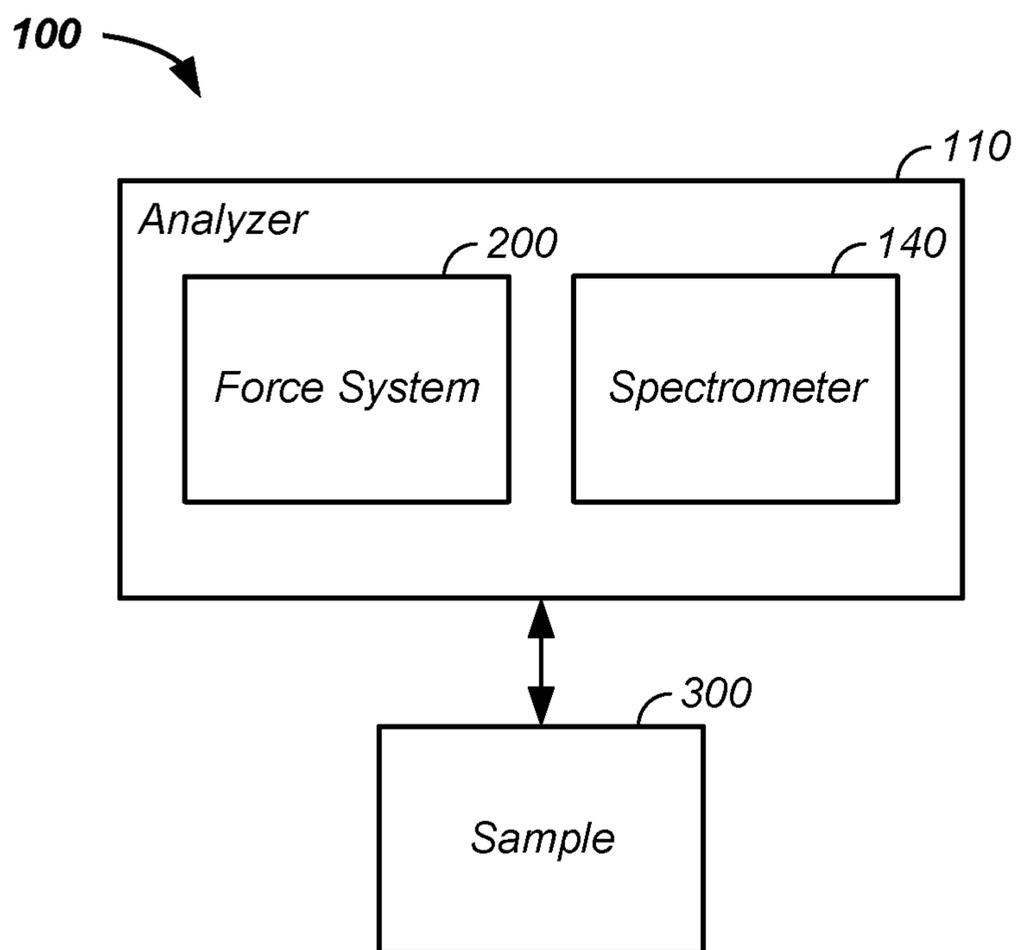


FIG. 1

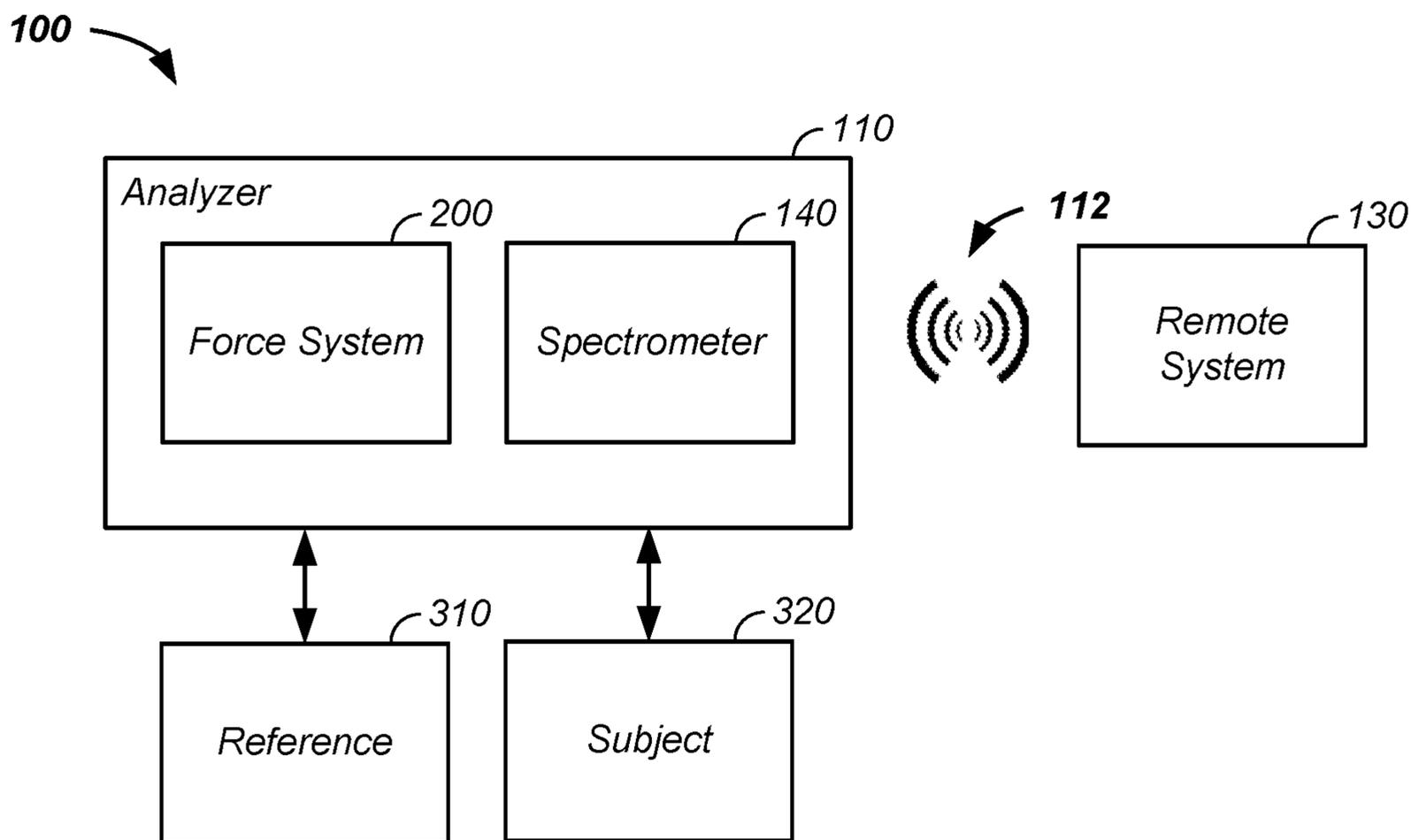


FIG. 2

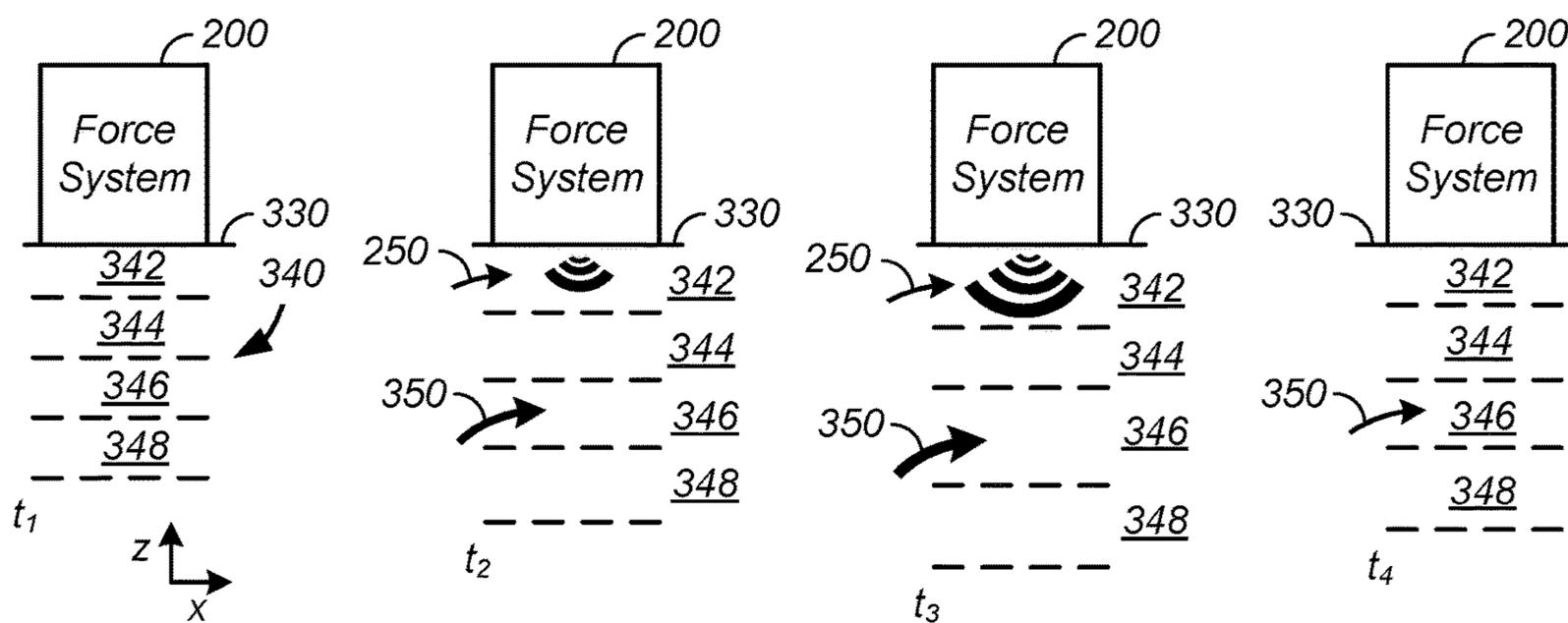


FIG. 3A

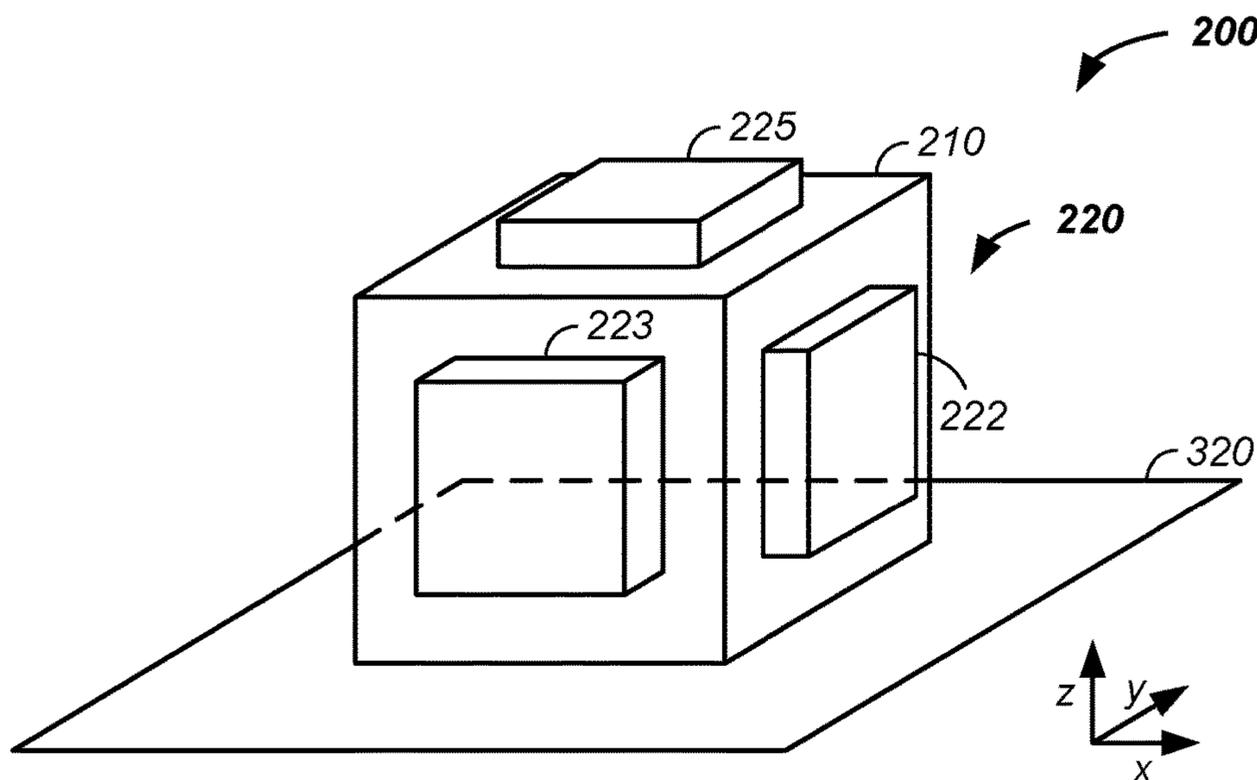


FIG. 3B

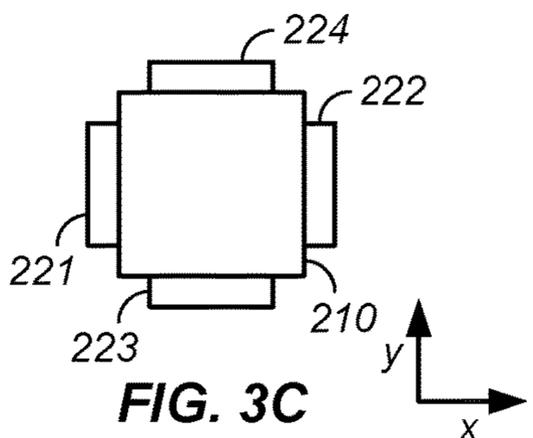


FIG. 3C

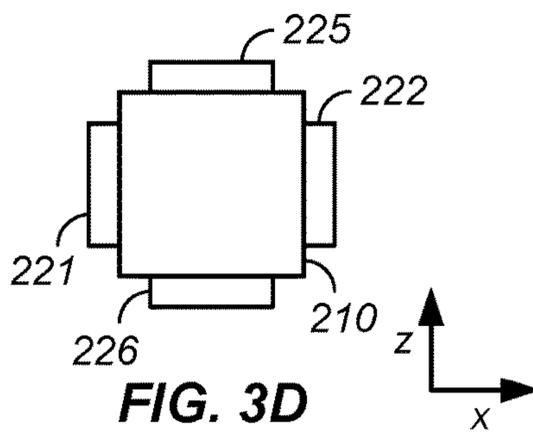


FIG. 3D

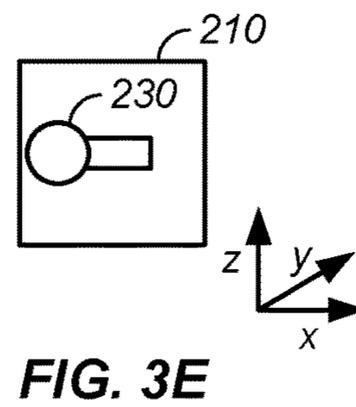


FIG. 3E

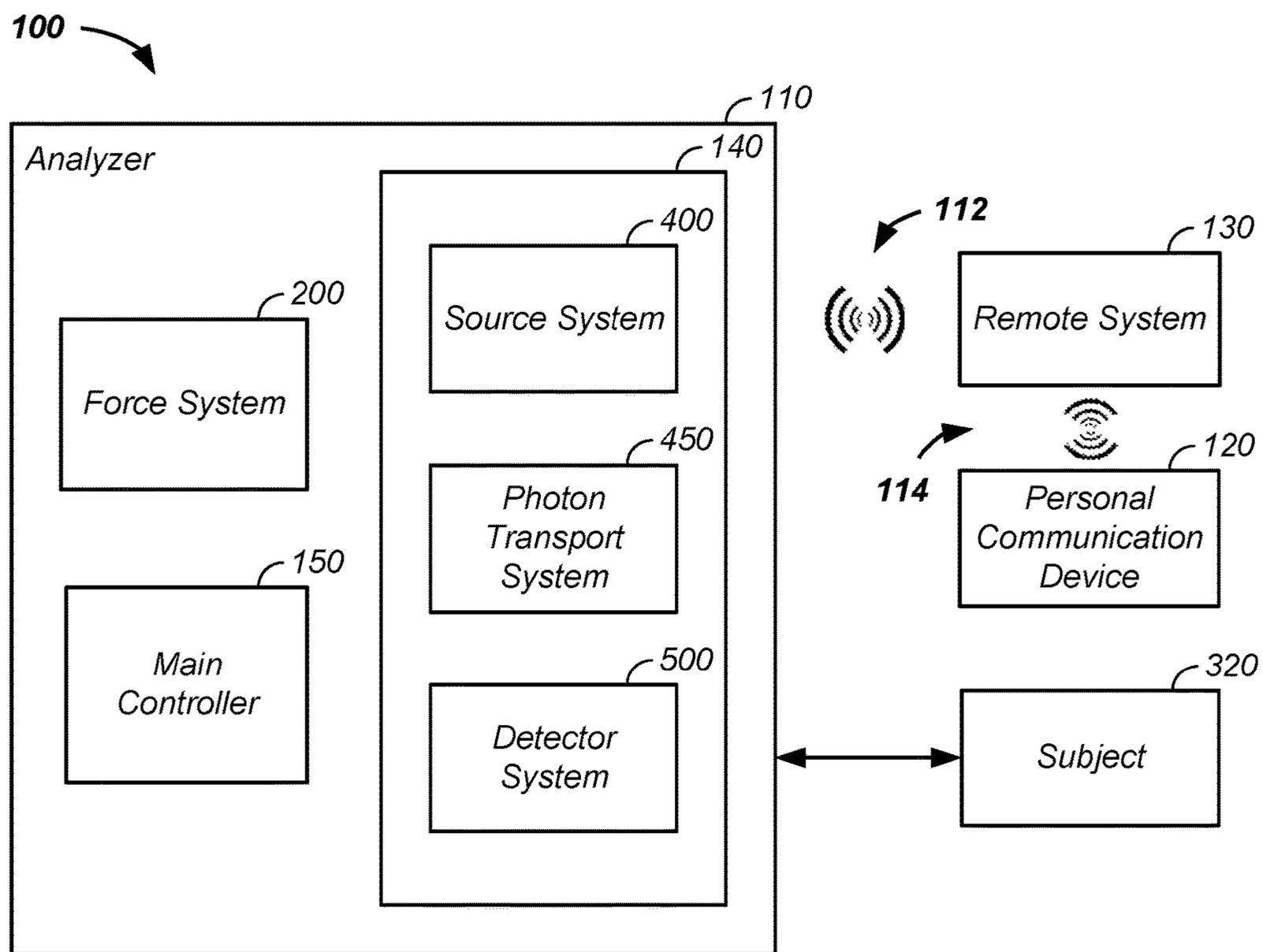


FIG. 4A

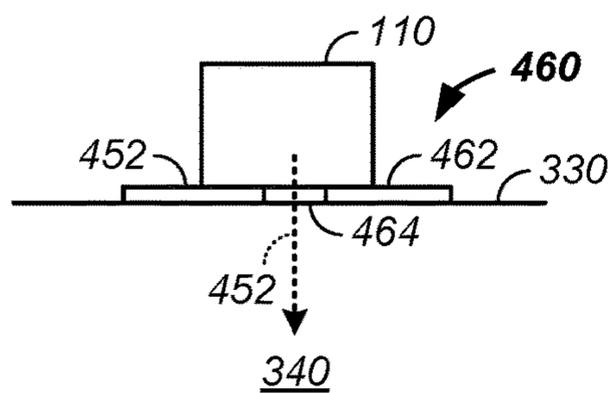


FIG. 4B

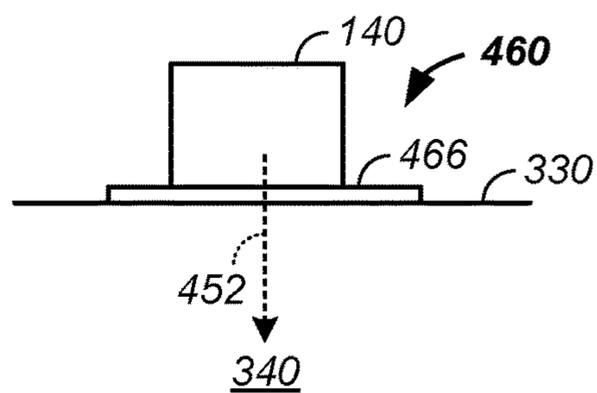


FIG. 4C

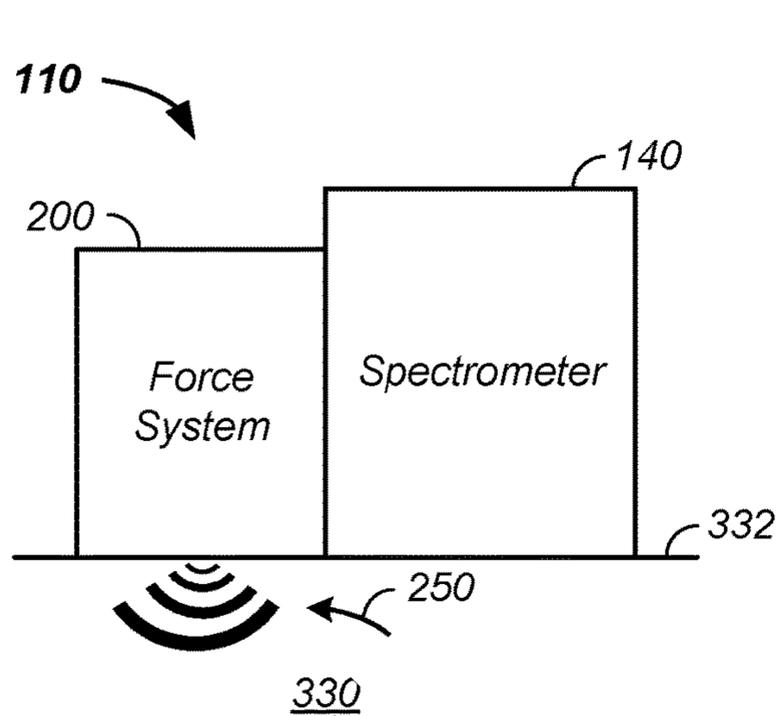


FIG. 5A

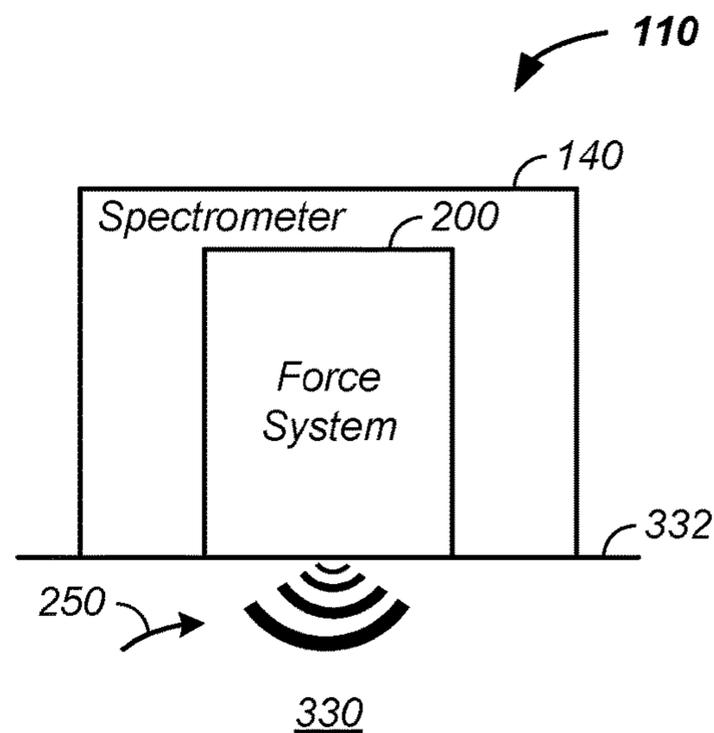


FIG. 5B

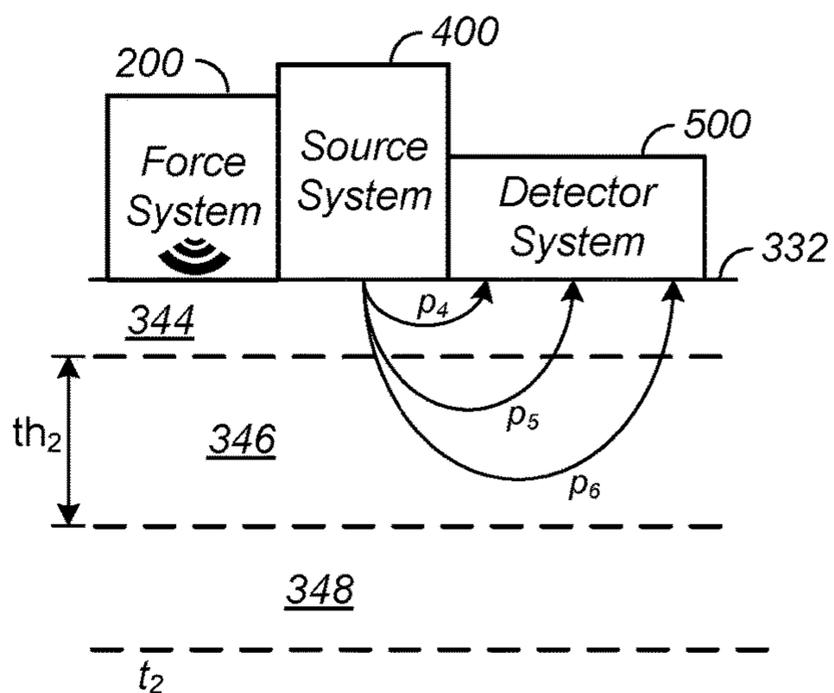
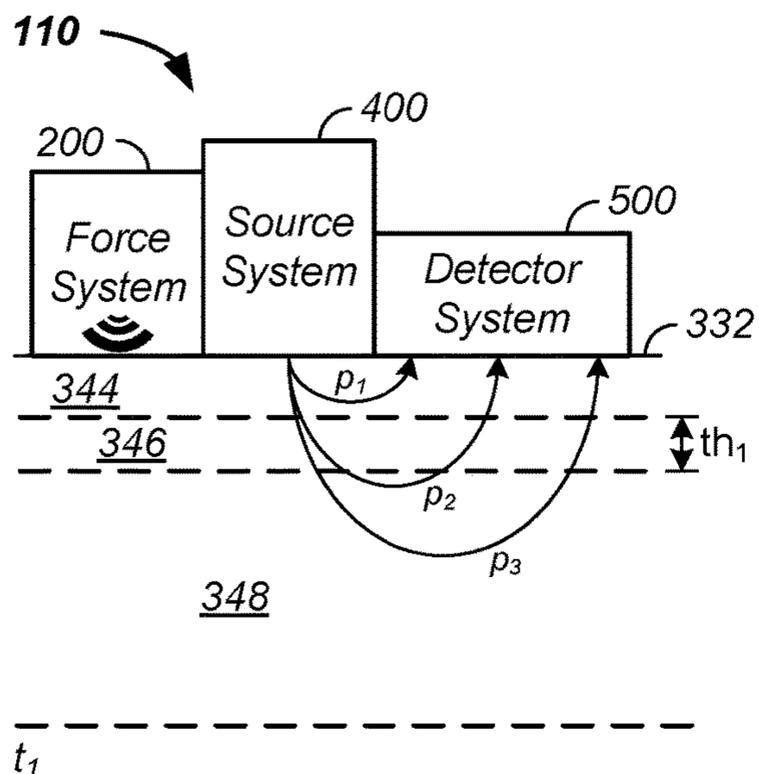
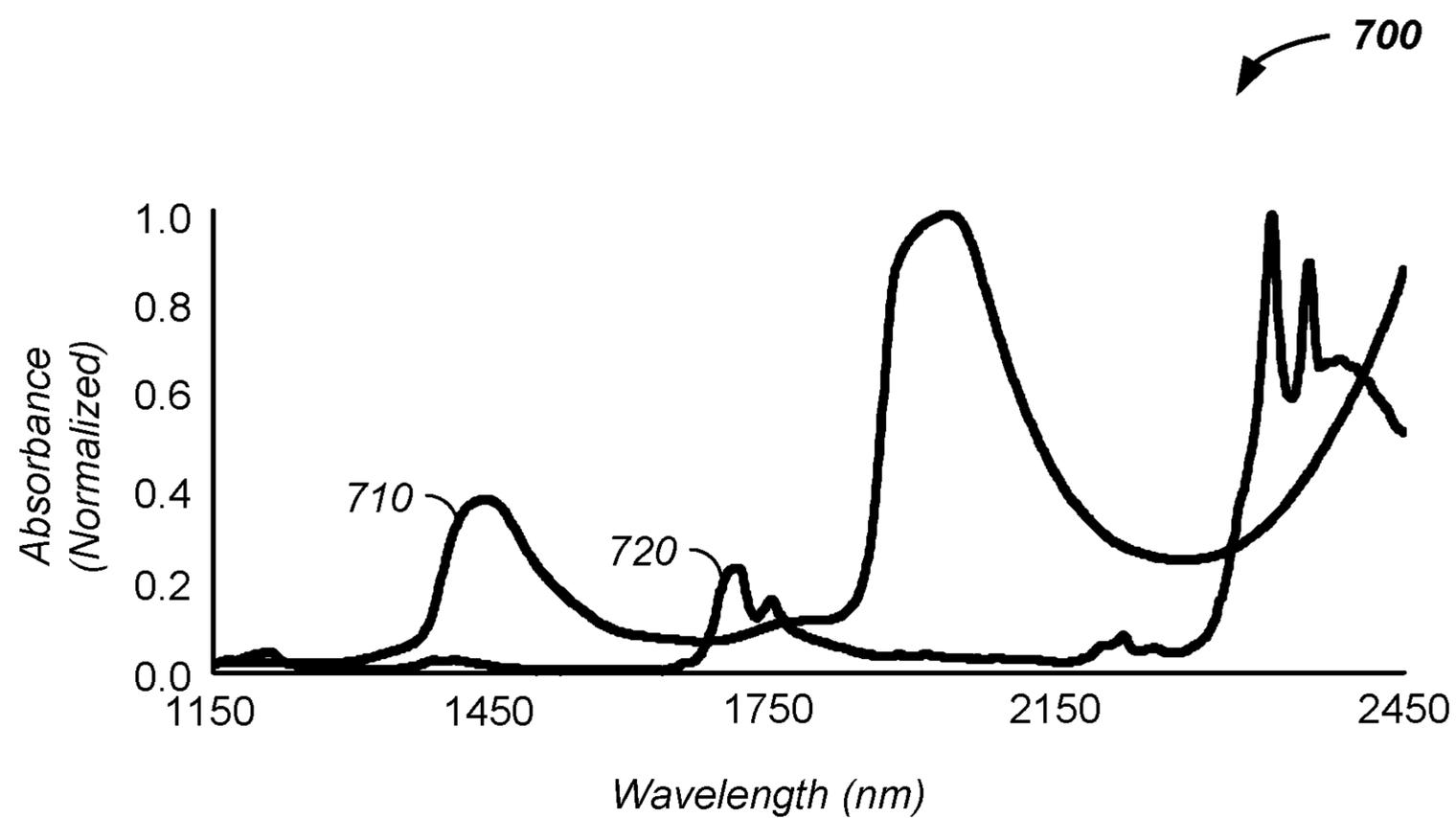


FIG. 6



**FIG. 7**

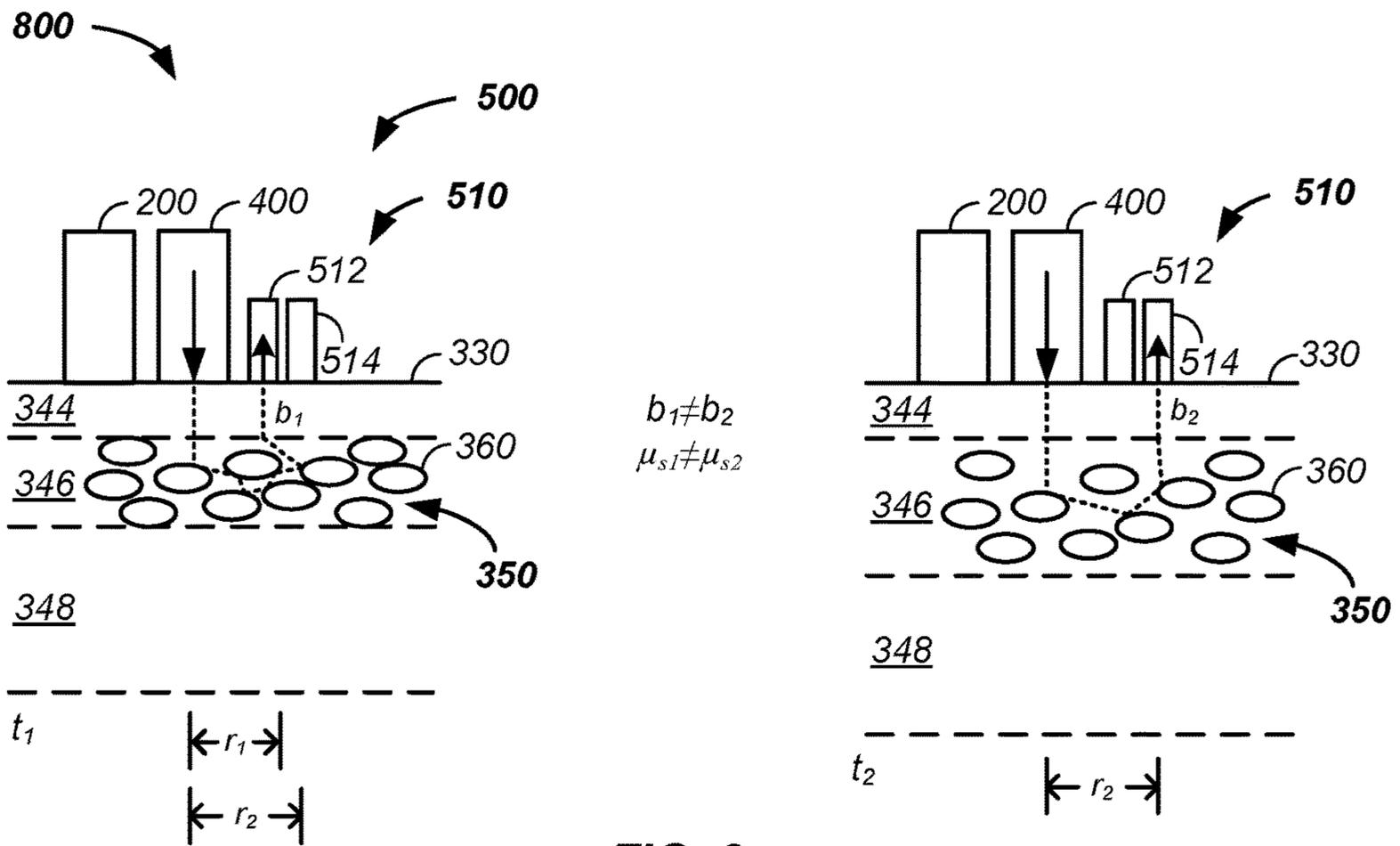


FIG. 8

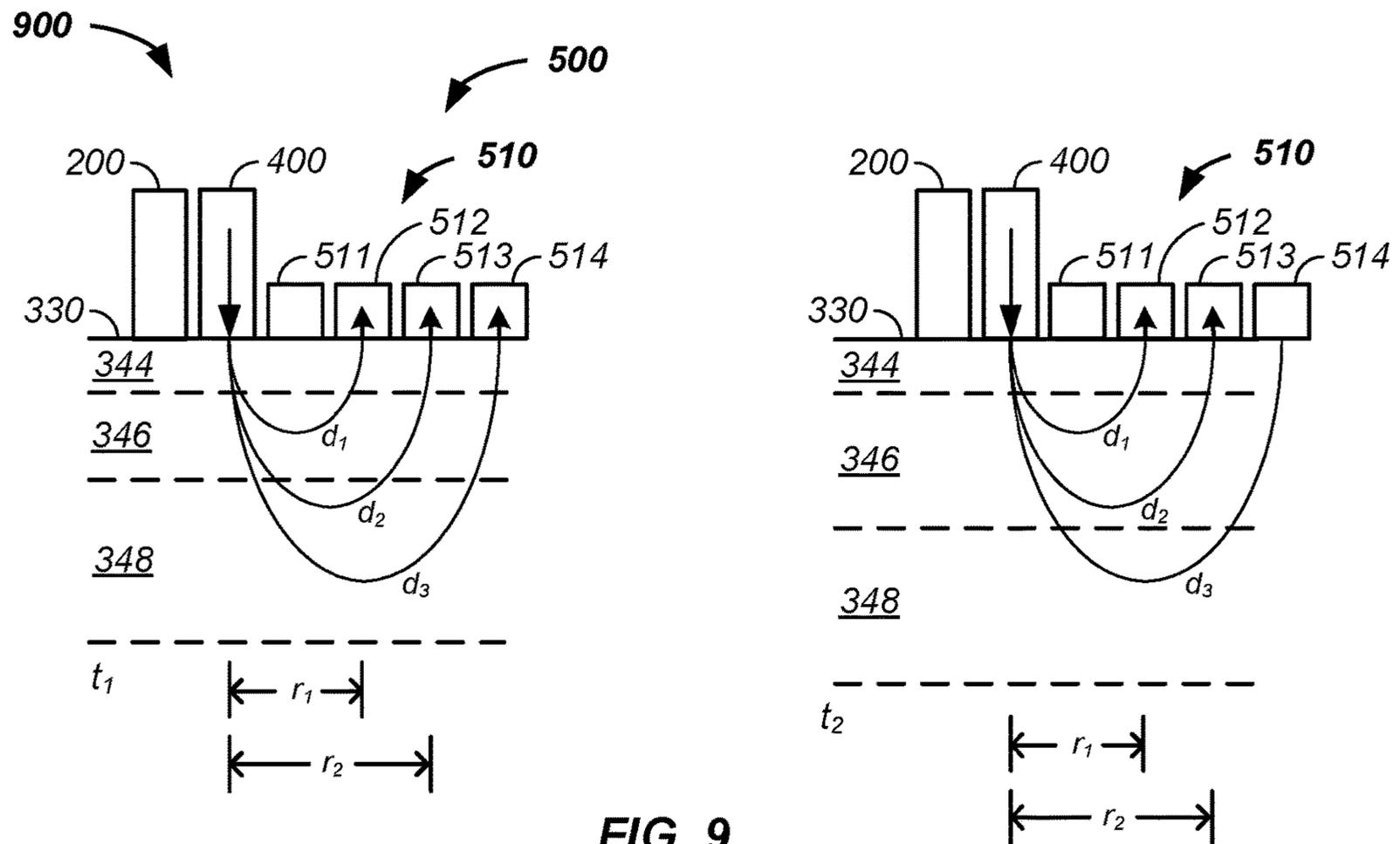


FIG. 9

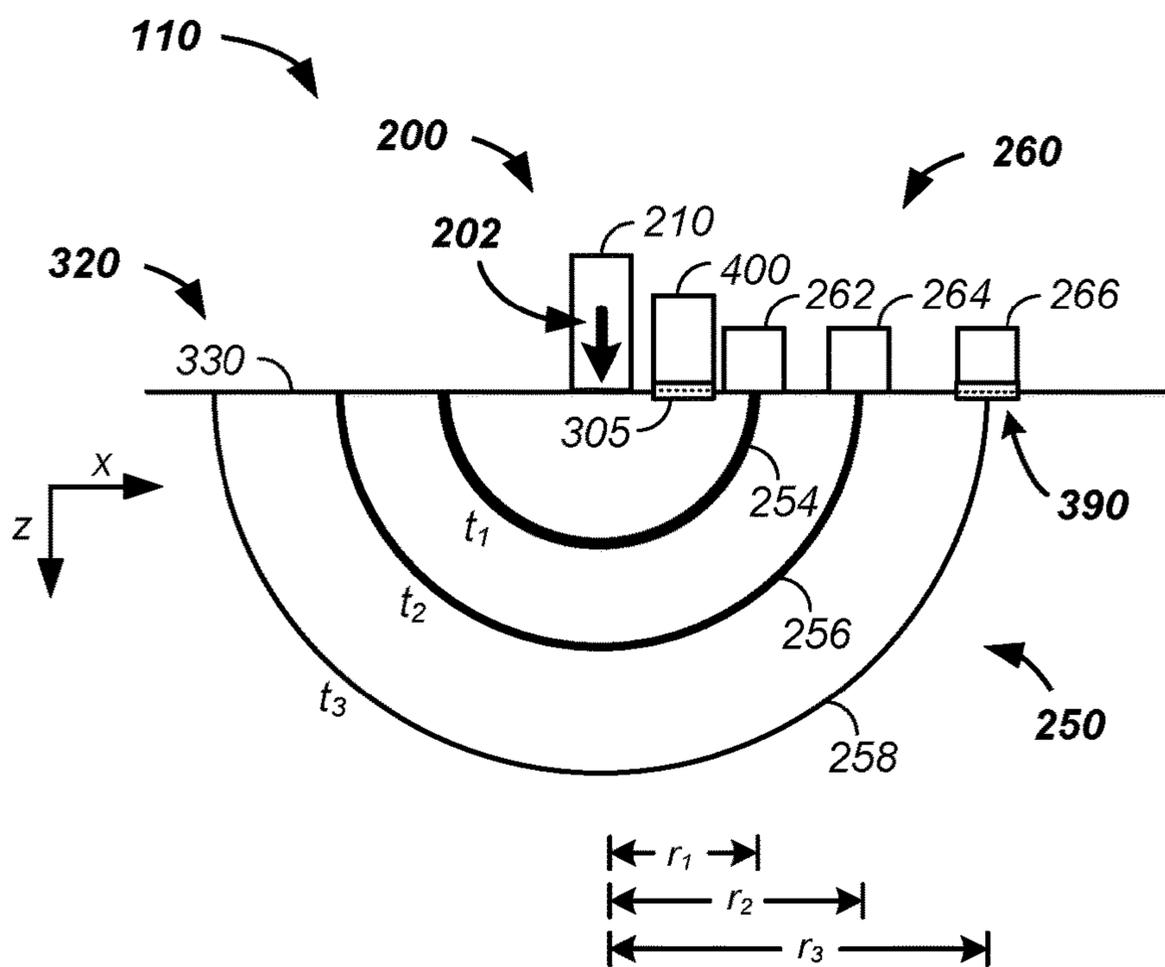


FIG. 10A

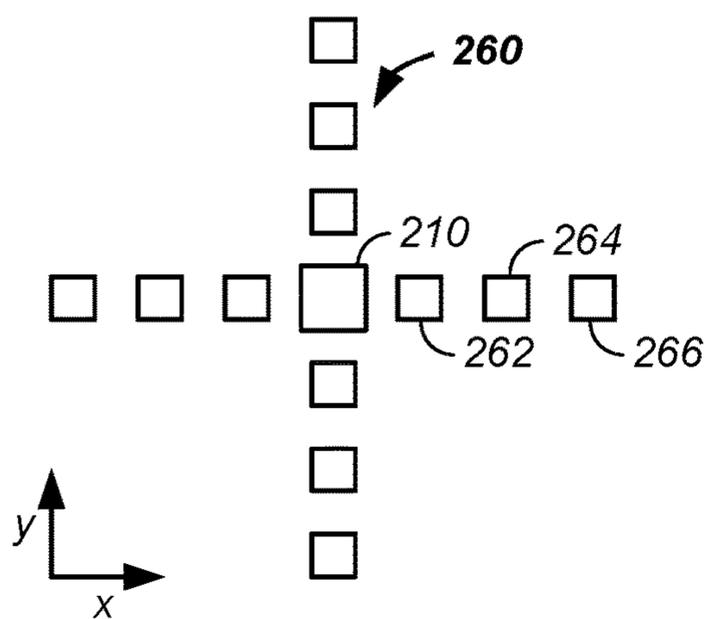


FIG. 10B

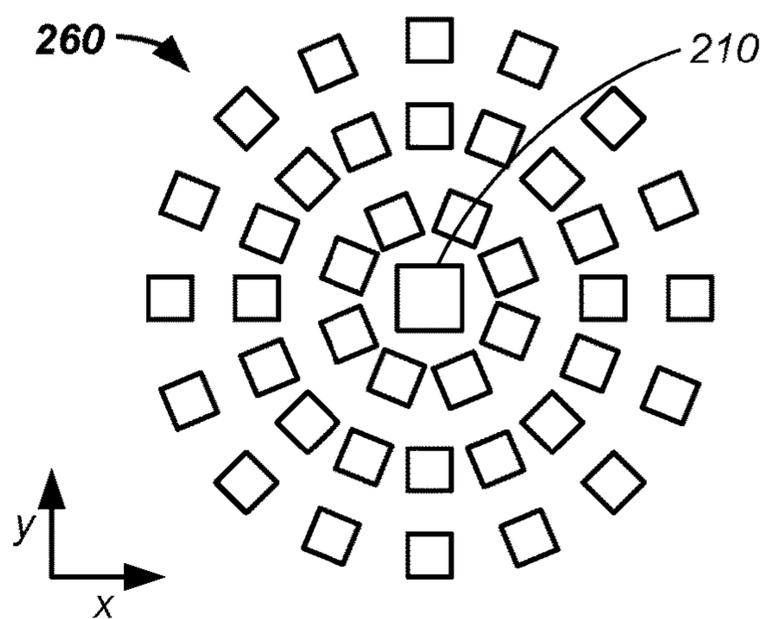


FIG. 10C

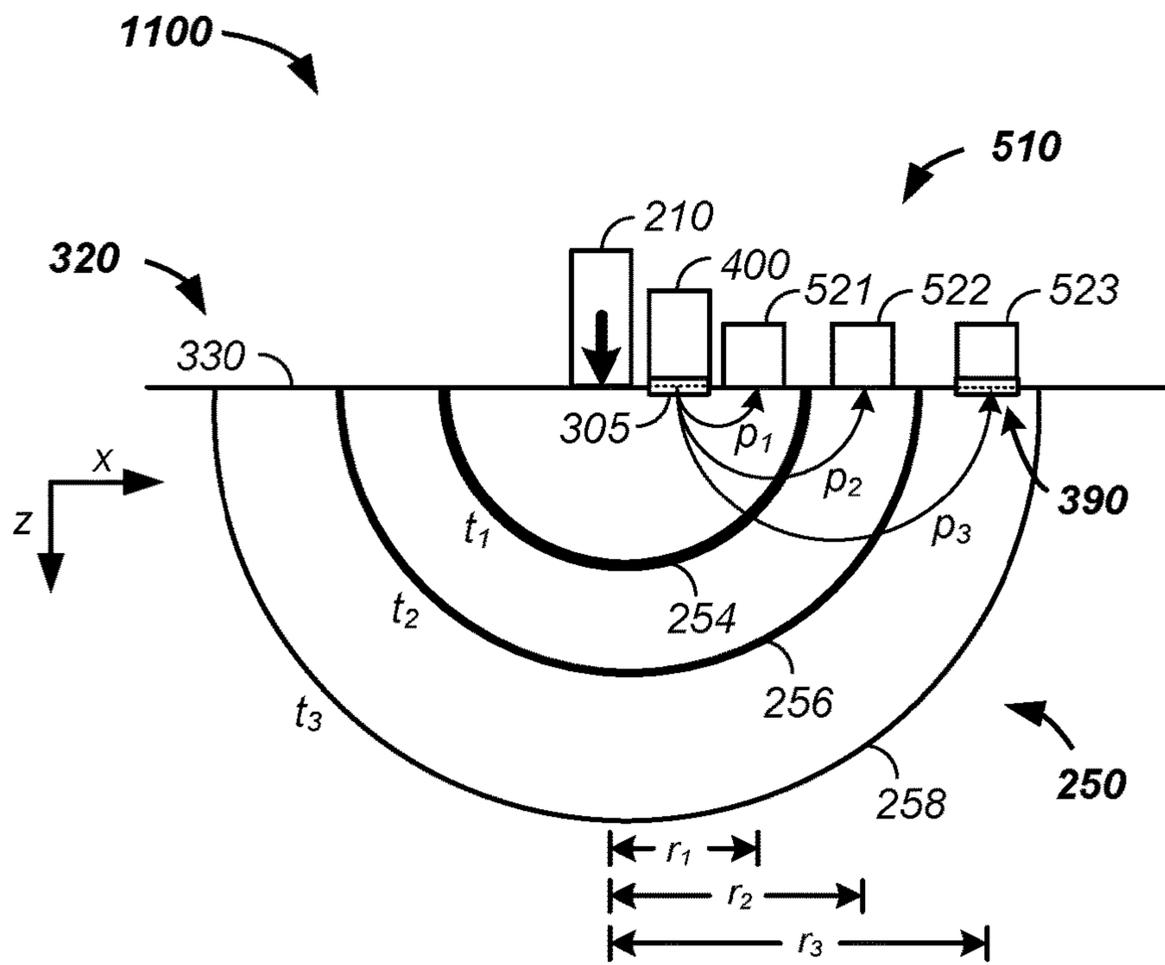


FIG. 11A

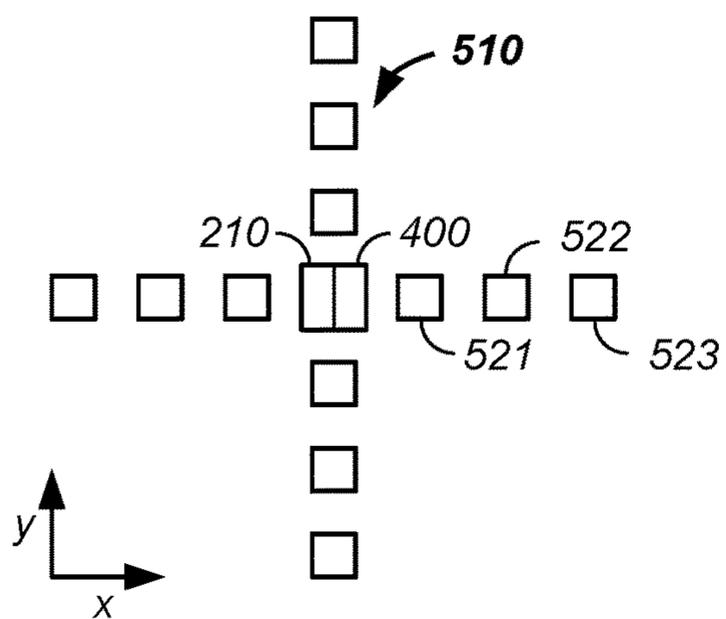


FIG. 11B

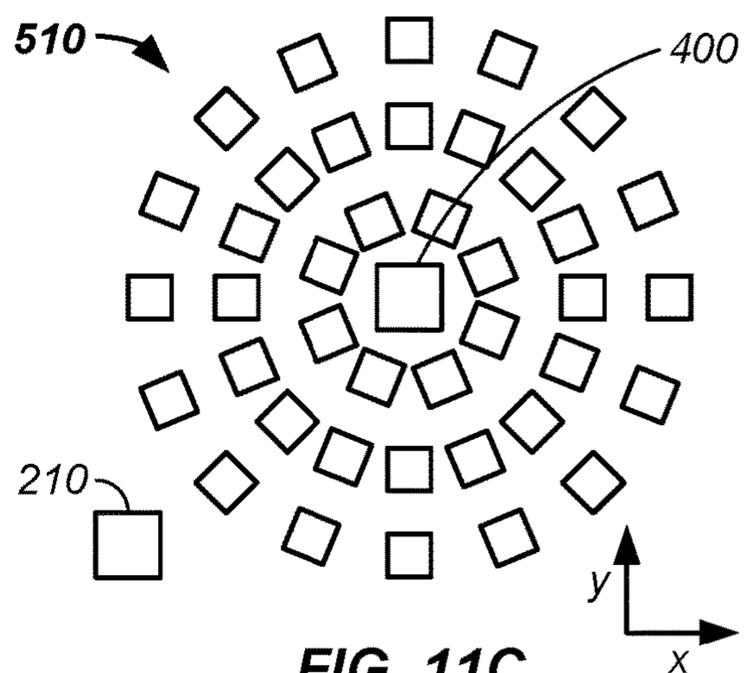


FIG. 11C

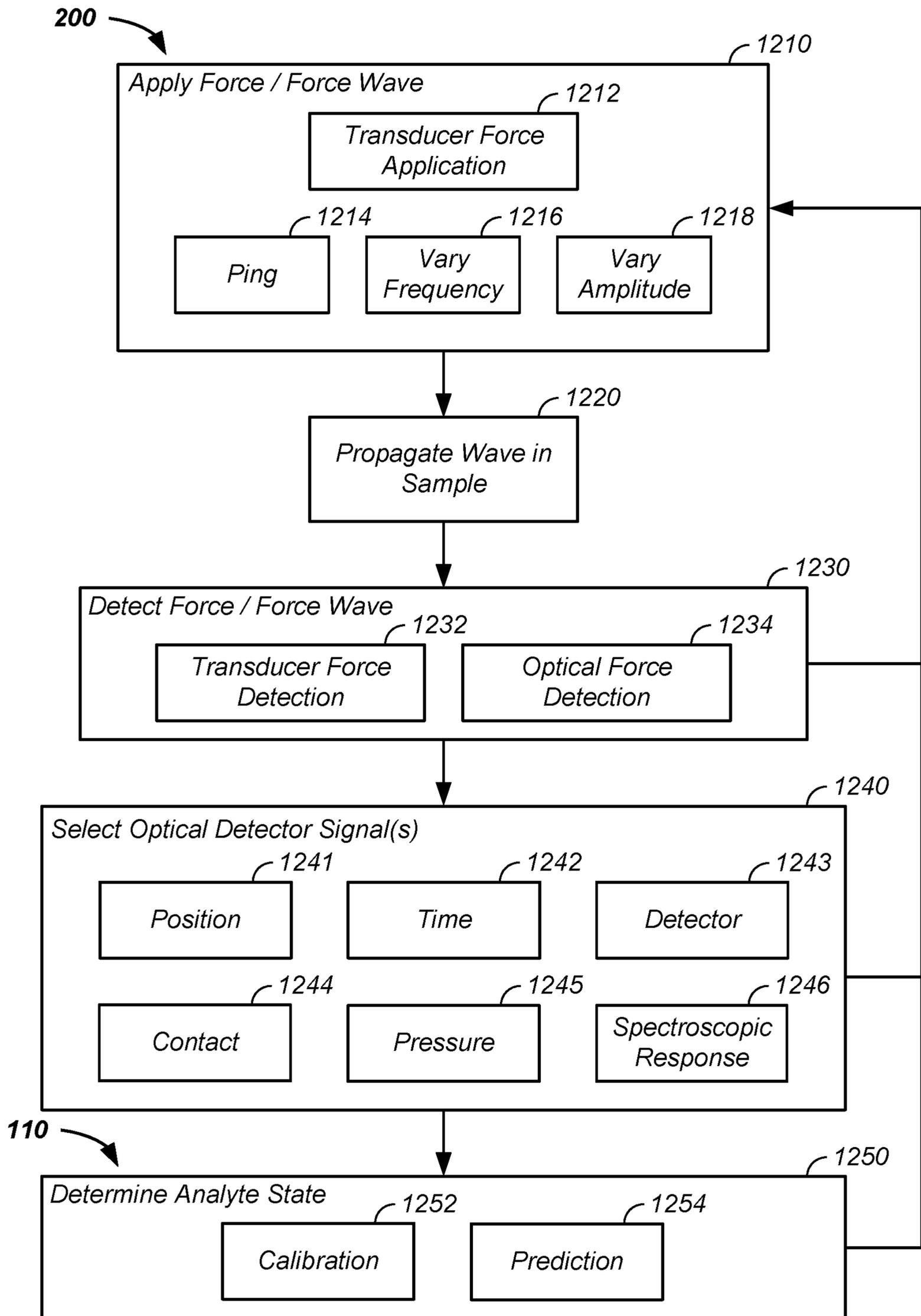


FIG. 12

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**NONINVASIVE APPLIED FORCE / OPTICAL  
GLUCOSE CONCENTRATION  
DETERMINATION ANALYZER APPARATUS  
AND METHOD OF USE THEREOF**

CROSS-REFERENCES TO RELATED  
APPLICATIONS

This application:

claims the benefit of U.S. provisional patent application

No. 62/838,283 filed Apr. 24, 2019;

claims the benefit of U.S. provisional patent application

No. 62/838,838 filed Apr. 25, 2019; and

claims the benefit of U.S. provisional patent application

No. 62/846,521 filed May 10, 2019.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates generally to noninvasively determining glucose concentration in a living body using an applied force to the body in combination with use of an optical analyzer, such as a visible/near-infrared noninvasive glucose concentration determination analyzer.

Discussion of the Prior Art

There exists in the art a need for noninvasively determining glucose concentration in the human body.

SUMMARY OF THE INVENTION

The invention comprises an applied force-optical glucose concentration analyzer apparatus and method of use thereof.

DESCRIPTION OF THE FIGURES

A more complete understanding of the present invention is derived by referring to the detailed description and claims when considered in connection with the Figures, wherein like reference numbers refer to similar items throughout the Figures.

FIG. 1 illustrates use of an applied force-optic analyzer;

FIG. 2 illustrates a noninvasive analyzer;

FIG. 3A illustrates an applied force system, FIG. 3B illustrates a transducer, FIG. 3C illustrates transducer movement normal to an optical axis, FIG. 3D illustrates a z-axis transducer, and FIG. 3E illustrates a multi-axes off-center spinning mass transducer;

FIG. 4A illustrates spectrometer components, FIG. 4B illustrates an affixing layer, and FIG. 4C illustrates a coupling fluid enhanced affixer;

FIG. 5A illustrates a force system coupled to a spectrometer and FIG. 5B illustrates a force system embedded in a spectrometer;

FIG. 6 illustrates photons interacting with applied force wave(s) in tissue;

FIG. 7 illustrates absorbance of skin constituents;

FIG. 8 illustrates detector selection;

FIG. 9 illustrates changing detector selection with tissue change;

FIG. 10A illustrates a transducer force applicator and FIG. 10B and FIG. 10C illustrate transducer force detectors in lines and arcs respectively;

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FIG. 11A illustrates radial optical detection of force waves, FIG. 11B illustrates an array of optical detectors, and FIG. 11C illustrates arcs of optical detectors; and

FIG. 12 illustrates optical probes observing tissue modified by force waves in a noninvasive glucose concentration determination system/analyzer.

Elements and steps in the figures are illustrated for simplicity and clarity and have not necessarily been rendered according to any particular sequence. For example, steps that are performed concurrently or in different order are illustrated in the figures to help improve understanding of embodiments of the present invention.

PROBLEM

There remains in the art a need for a noninvasive glucose concentration analyzer.

DETAILED DESCRIPTION OF THE  
INVENTION

The invention comprises an applied force-optic analyzer used to determine a sample constituent concentration, a physical measure of the sample, and/or a state of the sample. The analyzer comprises: an electro-mechanical transducer affixed to skin of a subject; a controller, the controller providing a voltage waveform to the electro-mechanical transducer driving displacement of the skin and inducing a pressure wave into the skin; and a spectrometer interfaced to a sample site of the skin, the spectrometer comprising a set of sources and a set of detectors, where the controller is configured to collect signal from the set of detectors as a function of timing of the voltage waveform and apply a calibration model to the signal to determine the analyte concentration.

Herein, generally, when describing an optical portion of the applied force-optic analyzer, a z-axis is aligned with a mean direction of the photons in a given sub-portion of the analyzer, such as along a longitudinal path of the photons into skin of a subject, and x- and y-axes form a plane perpendicular to the z-axis, such as at an interface point of incident photons into the skin of the subject. At the point of contact of the applied force-optic analyzer with the biological sample, the z-axis is normal/perpendicular to the sample and the x/y-plane tangentially contacts the sample. For instance, the light moves dominantly along the z-axis along vectors approaching perpendicular to an upper arm of a subject or a patient and the x/y-plane tangentially touches the upper arm along the z-axis. In particular cases, a second x,y,z-axis system is used to describe the sample itself, such as a z-axis being along the longitudinal length of a body part, such as along a digit or a finger or along the length of an arm section and the x/y-plane in this case is a cross-section plane of the body part.

A sample is optionally any material responding to an applied physical force in a manner observed by a probing optical system. However, for clarity of presentation and without loss of generality, the sample is described as a person, subject, patient, and/or a living tissue, such as skin and/or a portion of a human or animal. While the analyzer is described as a noninvasive analyzer probing into and optionally through the outer layers of skin, the noninvasive analyzer is optionally used as and or in conjunction with a minimally invasive glucose concentration analyzer and/or in conjunction with an invasive glucose concentration analyzer.

Herein, an illumination zone and/or an imaging zone is a point, region, or area of intersection of the illumination/imaging beam and/or pulse with an incident surface of the sample to yield a spectrum and/or an image of a desired volume of the sample. Herein, a detection zone is a point, region, or area of the sample sampled and/or visualized by one or more detectors. Similarly, herein an applied force zone is an incident point, region, or area of intersection at which an applied force is applied to the sample and a detected force zone is a point, region, or area of the sample interfacing with a force detector.

#### Applied Force-Optic Analyzer

Referring now to FIG. 1, a noninvasive analysis system 100 using an analyzer 110, such as an applied force-optic analyzer system is illustrated. Generally, an optional force system 200 is used to apply one or more applied forces, physical distortions, and/or force waves to a sample 300. The applied force travels with a wave front, as a wave, in a pattern of compression and rarefaction, and/or as a traveling displacement through the sample 300 or portions thereof. With or without application of the force waves, a spectrometer 140 is used to noninvasively collect spectra of the sample 300 and photometrically determine one or more properties of the sample, such as a glucose concentration. As described infra, the applied force is optionally in the form of an acoustic wave. However, the applied force is optionally and preferably a physical displacement of a portion of skin of a person, where the physical displacement is caused by movement of a mechanical object relative to the body to yield a time varying displacement of skin and/or constituents of the skin by the mechanical object. As described, infra, a variety of force provider technologies are available to variably displace the skin in a controlled manner. For clarity of presentation and without loss of generality, a transducer is used as an example to represent an applied force section of the force system 200, where a transducer comprises a device that receives a signal/force in the form of one type of energy and converts it to a signal/force in another form. Again for clarity of presentation and without loss of generality, a piezoelectric actuator is used to represent a transducer and an off-center spinning mass is used to represent a transducer. Hence, again for clarity of presentation and without loss of generality, a piezoelectric-optical analyzer or simply a piezo-optic analyzer, a transducer, and/or a transducer force applicator is used to describe any and all applied force electromechanical sources in the force system 200.

Referring now to FIG. 2, use of the analyzer 110 is described. Generally, the analyzer 110 is optionally calibrated using a reference 310 and is used to measure a subject 320, where the subject 320 is an example of the sample 300. Optionally and preferably, the analyzer 110 and/or a constituent thereof communicates with a remote system 130 using a wireless communication protocol 112 and/or a wired communication protocol.

#### Force System

Referring now to FIGS. 3(A-E), the force system 200 is further described. Generally, the force system 200 comprises a force delivery transducer that directly and/or indirectly contacts the sample 300, such as an outer skin surface 330 of the subject 320 and/or a patient. The subject 320 has many skin layers 340. For clarity of presentation, the skin layers 320 are represented as having a first skin layer, such as a stratum corneum 342; a second skin layer, such as an epidermis 344 or epidermal layer; a third skin layer, such as a dermis 346 or dermis layer; and a fourth layer, such as subcutaneous fat 348 or a subcutaneous fat layer. It is recognized that skin is a complex organ with many addi-

tional layers and many sub-layers of the named layers that vary in thickness and shape with time.

However, for clarity of presentation and without loss of generality, the stratum corneum, epidermis, dermis, and subcutaneous fat layers are used to illustrate impact of the force delivery transducer on the skin layers 340 of the subject 320 and how the applied force waves alter optical paths of probing photons in the spectrometer 140 of the analyzer 110 in the noninvasive analysis system 100.

Still referring to FIG. 3A, at a first time,  $t_1$ , the tissue layers 340 are in a first state. As illustrated, the tissue layers 340 are in a compressed state 340, such as a result of mass of the force system 200 sitting on the skin surface 330, as a result of dehydration of the subject 320, and/or as a result of a physiological and/or environmental force on the tissue layers 340 of the subject. At a second time,  $t_2$ , the force system 200 applies a force wave 250 to the skin surface 330 of the patient 320, which sequentially propagates into the stratum corneum 342, epidermis 344, dermis 346, and given enough force into the subcutaneous fat 348. In addition to the force wave propagating into the skin layers 340 along the z-axis, the force wave propagates radially through the skin layers, such as along the x/y-plane of the skin layers. As illustrated at the second time,  $t_2$ , as the force wave 250 propagates into the tissue layers 340, the tissue layers expand and/or rarefy, such that the thickness of the epidermis 344 and/or the dermis 346 layers expands. The rarefaction of the epidermis 344 and particularly the dermis 346 allows an increased and/or enhanced perfusion of blood 350 into the rarefied layers. The increased perfusion increases water concentration in the perfused layers, increase and/or changes distance between cells in the perfused layers, and/or changes shapes of cells in the perfused layers, such as through osmolarity induced changes in concentration in and/or around blood cells, such as red blood cells. Generally, scattering coefficients of the epidermis layer and/or especially the dermis layer changes, which is observed by the spectrometer 140 in the range of 400 to 2500 nm with larger changes at smaller wavelengths in the visible, 400 to 700 nm, and/or near-infrared, 700 to 2500 nm, regions. As illustrated at the third time,  $t_3$ , as the force wave 250 continues propagation in the tissue layers 340, the perfusion 350 continues to increase, such as to a maximum perfusion. As illustrated at the fourth time,  $t_4$ , after discontinuation of the force wave 250, the skin layers 340 revert toward the initial state of the non-force wave induced perfusion to a local minimum perfusion, which may match the initial perfusion, is likely higher than the initial perfusion, and is at times less than the initial perfusion due to changes in state of the environment, such as temperature, and/or generalized state of the subject 320, such as hydration, localized hydration of skin, such as due to food intake, insulin response to food intake, exercise level, blood pressure, and/or the like. Generally, the tissue layers 340 of the subject increase in thickness and/or rarefy during application of the transducer applied force wave 250 and decrease and/or compress after termination of the transducer applied force wave 250 to the skin surface 330 of the subject 320. The process of applying the force wave 250 is optionally and preferably repeated n times, where n is a positive integer of greater than 1, 2, 5, 10, 100, 1000, or 5000 times in a measurement period of an analyte of the subject 320, such as a glucose concentration. Generally, the cycle of applying the force wave 250 results in a compression-rarefaction cycle of the tissue that alters an observed scattering and/or absorbance of probing photons in the visible and near-infrared regions. The force wave 250 is optionally and preferably applied as a single ping force in

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a tissue state classification step, as multiple pings in a tissue classification step, and/or as a series of waves during a tissue measurement step. Individual waves of a set of force waves are optionally controlled and varied in terms of one or more of: time of application, amplitude, period, frequency, and/or duty cycle.

Still referring to FIG. 3A and referring now to FIGS. 3(B-D), a force wave input element 210 of the force system 200 is illustrated. As illustrated, the force wave input element 210 is equipped with one or more transducers: a left transducer 221, a right transducer 222, a front transducer 223, a back transducer 224, a top transducer 225, and/or a bottom transducer 226. For instance, the left and/or right transducers 221, 222 move the force wave input element 210 left and/or right along the x-axis; the front and/or back transducers 223, 224 move the force wave input element 210 forward and/or back along the y-axis; and/or the top and bottom transducers 225, 226 move the force wave input element 210 up and/or down along the z-axis along and/or into the skin surface 330 of the subject 320, which moves the skin, skin layers 340, and/or skin surface 330 of the subject relative to the spectrometer 140 and/or is a source of the force wave 250 moving, in the skin layers 340, along the z-axis into the skin, and/or radially outward from an interface zone of the force wave input element 210 of the force system 200. A transducer itself is optionally used as the force wave impulse element 210. Referring now to FIG. 3E, one or more off-center mass elements 230 is optionally spun or rotated, such as with an electric motor, along one or more of the x,y,z-axes to move the force wave input element 210 relative to the skin surface 330 of the subject 320 resulting movement of the skin of the subject 320 relative to the spectrometer 140 and/or cycling and/or periodic displacement of the tissue layers 340 of the subject 320 due to movement of the force wave input element 210 resulting in the force wave(s) 250. Generally, the force system 200 induces a movement of a sampled zone of skin of the subject 320, applies a displacement of a sampled zone of the skin of the subject 320, and/or applies a propagating force wave into and/or through a sample zone of tissue layers 340 of the subject, where the sampled zone is probed using photons from the spectrometer 140 and/or is measured using a set of detection zone transducers, described infra. The force wave(s) are optionally and preferably applied as a single input ping wave, a set of input ping waves, and/or are applied with a frequency of 0.01 Hz to 60 Hz. Optionally and preferably, the force waves 250 are applied with a frequency greater than 0.01, 0.02, 0.05, 0.1, or 1 Hz. Optionally and preferably, the force waves 250 are applied with a frequency of less than 200, 100, 50, 40, 30, or 20 Hz. Optionally and preferably, the force waves 250 are applied with a frequency within 5, 10, 25, 50, or 100 percent of 2, 4, 6, 8, 10, 12, 15, and 20 Hz.

## Optical System

Referring now to FIG. 4A, the spectrometer 140 of the analyzer 110 is further described. The spectrometer 140 comprises a source system 400, which provides photons 452 in the visible and/or infrared regions to the subject 320, such as via a photon transport system 450, at an illumination zone. After scattering and/or absorbance by the tissue layers 340 of the subject 320, a portion of the photons are detected at a detection zone by a detector system 500. The source system 400 includes one or more light sources, such as any of one or more of a light emitting diode, a laser diode, a black body emitter, and/or a white light source, that emits at any wavelength, range of wavelengths, and/or sets of wavelengths from 400 to 2500 nm. Each source system photon source is optionally controlled in terms of time of illumina-

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tion, intensity, amplitude, wavelength range, and/or bandwidth. The photon transport system 450 comprises any fiber optic, light pipe, air interface, air transport path, optic, and/or mirror to guide the photons from the light source to one or more illumination zones of the skin surface 330 of the subject 320 and/or to guide the photons from one or more detection zones of the skin surface 330 of the subject 320 to one or more detectors of the detector system 500. Optionally and preferably, the photon transport system 450 includes one or more optical filters and/or substrates to selectively pass one or more wavelength regions for each source element of the source system 400 and/or to selectively pass one or more wavelength ranges to each detector element of the detector system 500. Herein, the reference 310 is optionally an intensity and/or wavelength reference material used in place of the sample and/or is used in an optical path simultaneously measured by the analyzer 110.

Still referring to FIG. 4A and referring now to FIG. 4B and FIG. 4C, the subject 320 optionally and preferably wears the analyzer 110 in the physical form of a watch head, band, and/or physical element attached to the body with a band and/or an adhesive. For example, the analyzer 110, the spectrometer 140, the source system 400, and/or the photon transport system 450 is optionally attached to the subject 320, such as at the wrist or upper arm, using thin affixing layer 460, such as a double sided adhesive 462. Referring now to FIG. 4B, the double sided adhesive 462 optionally contains an aperture 464 therethrough. The photons 452 optionally and preferably pass through the aperture 452 to the skin surface 330 of the subject. The force wave 250 optionally moves the skin surface 330 through the aperture into intermittent contact with the analyzer 110. Optionally, referring now to FIG. 4C, a thin affixing layer 466, such as less than 1, 0.5, or 0.25 mm thick, is continuous in nature in front of the incident surface and/or incident photon coupling zone and/or is continuous in nature in front of the detection zone, where photons exiting the skin surface 330 are detected by the detector system 500. The affixing layer 466 is optionally permeated with a fluid, such as a coupling fluid, an air displacement medium, an optical coupling fluid, a fluorocarbon liquid, a fluorocarbon gel, an index of refraction matching medium, and/or any fluid that increases a percentage of photons from the source system 400 entering the skin surface 330 compared to an absence of the fluid and/or is any fluid that increases a percentage of photons from the tissue layers 340 exiting the detection zone and reaching the detector system 500 as compared to a case where the fluid is not embedded into the affixing layer. Hence, the affixing layer serves several purposes: attaching the analyzer or a portion thereof to the skin surface 330 of the subject 320, coupling forces from the force system 200 to the skin surface 330 of the subject 320, forming a constant sampling interface location on the skin surface 330 of the subject, and/or altering a coupling efficiency, angular direction, and/or reproducibility of coupling of photons enter the skin of the subject 320 and/or exiting the skin surface 330.

## Coupled Force System/Spectrometer

Referring now to FIG. 5A and FIG. 5B, the force system 200 is illustrated working in conjunction with the spectrometer 140. Referring now to FIG. 5A, the analyzer 110 is illustrated with the force system 200 being attached to and/or within 1, 2, 3, 5, 10, 20, or 50 mm of the spectrometer 140. Referring now to FIG. 5B, the analyzer 110 is illustrated with the force system 200 being integrated into the spectrometer 140, such as within 20, 10, 5, 2, or 1 mm of the source system 400 of the analyzer 110 and/or in a single housing unit of the analyzer 110.

Several examples are provided that illustrate how the force system 200 alters the tissue layers 340 of the subject 320 and how a selection of detected signals from the spectrometer 140 is performed as a function of time and respective radial separation between the one or more illumination zones and the one or more detection zones, such as using water signal, fat signal, and/or protein signal to determine the correct detection signals to use for noninvasive glucose concentration determination.

#### Example I

Referring now to FIG. 6, a first example of the analyzer 110 using the force system 200 and the source system 400 at the same time and/or within less than 60, 30, 15, 10, 5, or 1 second of each other is provided. In this example, the force system 200 applies a force to the tissue layers 340 at a first time,  $t_1$ , when the dermis has a first mean z-axis thickness,  $th_1$ . Optionally and preferably, the analyzer 110 acquires signals representative of the tissue layers 340 of the subject 320 using the source system 400 and the detector system 500. Illustrated are three representative photon pathways,  $p_{1-3}$ , reaching the detector system 500, such as at a first detector element, a second detector element, and a third detector element, respectively, at the first time,  $t_1$ , and/or within less than 60, 30, 15, 10, 5, or 1 second from the first time,  $t_1$ . Notably, at the first time, the first photon pathway,  $p_1$ , has an average path that does not penetrate into the dermis 346, while the second and third photon pathways,  $p_{2-3}$ , have mean pathways that penetrate through the dermis into the subcutaneous fat 348. In at least one preferred use of the analyzer, noninvasive glucose concentration determination is performed using a mean photon pathway that penetrates into the dermis 346 and not into the subcutaneous fat 348 and/or uses signal from a detector element at a first/minimal radial distance from the illumination zone, where the first/minimal radial distance is the smallest radial distance observing an increase in a fat signal/dominantly fat related signal, such as from the subcutaneous fat 348, compared to a water signal/dominantly water related signal from skin layers 340 closer to the skin surface 332 than that subcutaneous fat 348. Examples of wavelengths containing dominantly water absorbing signals are wavelengths correlating with the peaks of the water absorbance bands 710, FIG. 7, and examples of wavelengths containing an increased fat absorbance to water absorbance ratio when a mean photon path enters the subcutaneous fat 348 are at the fat absorbance bands 720. Still referring to FIG. 6, at a second time,  $t_2$ , the force wave 250 from the force system 200 has expanded the dermis layer to a second thickness,  $th_2$ , which is at least 0.1, 0.2, 0.3, 0.5, 1, 2, 5, 10, 20, or 50% thicker than the first thickness,  $th_1$ , and/or has an increased water absorbance, as measure by the first, second, and/or third detector element of the detector system 500, representative of the first through third photon pathway,  $p_{1-3}$ , in the condition of the larger dermis thickness at the second time,  $t_2$ , as represented by a fourth, fifth, and sixth photon pathway,  $p_{4-6}$ . Notably, the fifth and sixth photon pathways,  $p_{5,6}$ , with the same illumination zone to detection zone radial distance as the first and second photon pathways,  $p_{1-2}$ , have mean photon pathways that penetrate into the dermis 346 and not into the subcutaneous fat 348. Thus, the water-to-fat ratio of the observed signal continues to increase with radial distance for the second and third detectors after the force system 200 increased the thickness of the dermis 346 to the second thickness,  $th_2$ . Again, at least one preferred measurement is a measurement with a higher water-to-fat absor-

bance ratio. In this example, at the second time, the water-to-fat absorbance ratio of the fifth optical path,  $p_5$ , is greater than observed with the second optical path,  $p_2$ , despite have the same source zone-to-detector zone radial distance. Further, in this example a preferred optical signal is from the sixth optical path,  $th_6$ , at the second time,  $t_2$ , with a largest ratio of mean pathlength in the dermis 346 to total mean detected pathlength.

#### Example II

Referring now to FIG. 8, a second example is provided where the analyzer 110 uses the force system 200 to alter the sample 300 to enhance a noninvasive analyte property determination using the spectrometer 140. As above, the force system 200 provides one or more force waves 250 into the subject 320, which alters positions of cells 260 in the dermis 346 relative to the illumination zone of the illumination system 400 and or relative to one or more detection zones associated with a single element detector and/or one or more detectors of an array of detector elements 510. As illustrated, the cells 360 have a first average intercellular distance at a first time,  $t_1$ , which is altered by application of the force wave 250 to a second average intercellular distance at a second time,  $t_2$ , where the net change in cell position alters detected spectrophotometric absorbance signals at a give detector element of the detector system 500 by greater than 0.01, 0.02, 0.05, 0.1, 0.5, 1, 2, 5, or 10 percent, such as by a change in observed scattering and/or observed absorbance at a fixed radial distance between an illumination zone and a detection zone. Similarly, the average percentage volume of the intercellular fluid 350 in the dermis layer differs by greater than 0.01, 0.02, 0.05, 0.1, 0.5, 1, 2, 5, or 10 percent as a result of the applied force wave(s) 250. All of a change in thickness, change in observed mean pathlength, change in radial distance of detection, change in mean intercellular spacing, change in scattering, and change in water concentration, related to perfusion, are illustrated between the first time,  $t_1$ , and the second time,  $t_2$ , as a result of the applied force wave 250. Notably, a selected detector signal from the array of detectors 510 changed from a second detector element 512 at a first radial distance,  $r_1$ , from the illumination zone to a fourth detector element 514 at a second radial distance,  $r_2$ , from the illumination zone based on the above described larger observed water signal-to-observed fat signal ratio and/or as the second pathlength,  $b_2$ , is longer than the first pathlength,  $b_1$ , in the dermis layer. Similarly, absorbances of skin constituents, such as protein, albumin, globulin, keratin, and/or elastin increase relative to fat absorbance for the second pathlength,  $b_2$ , as the mean pathlength spends more time in the dermis layer compared to the subcutaneous fat layer 348, as described supra.

#### Example III

Referring now to FIG. 9, a third example of using the force system 200 to alter properties of the subject 330 to enhance performance of a noninvasive glucose concentration determination using the spectrometer 140 is provided. In this example, the detector array 510 of the detector system 500 contains n detector elements at differing radial distances from a time correlated illumination zone. For clarity of presentation, the detector array 510 is illustrated with four detector elements: a first detector element 511, a second detector element 512, a third detector element 513, and a fourth detector element 514. At a first time,  $t_1$ , the large water absorbance, protein absorbance, and/or protein and

water absorbance-to-fat ratio is observed using the second detector element **512** having a first illumination zone-to-detection zone radial distance,  $r_1$ , and a first mean optical pathway,  $d_1$ , penetrating into the dermis **346** with minimal to no mean penetration into the subcutaneous fat **348**. However, at a second time,  $t_2$ , after the provided force wave **250** has altered the skin of the subject **320**, the third detector element is observed, at a selected detection point in time, to have the largest metric for detector selection, such as a smoothly falling observed intensity with radial distance at a fat absorbance wavelength, where a sudden decrease in observed intensity at the fat absorbance wavelength indicates mean penetration of the observed optical pathway into the subcutaneous fat **348**, such as at the second radial distance,  $r_2$ . Notably, the largest radial distance is selected for a given water, protein, and/or fat based metric as at the larger radial distance a difference between a shortest possible pathlength between the illumination zone and the detection zone, the radial distance, is closest to the largest possible observed pathlength, which is based upon a maximum observable absorbance by a detector type for a fixed number of photons. For example, if the maximum observable absorbance is 3.9 and the absorbance per millimeter is 1.3, then a maximum observable pathlength is 3.0 mm. If the observed radial pathlength is 1.5 mm then a first range of observed pathlengths is 1.5 to 3.0 mm with a difference of 1.5 mm. Hence, a first ratio of observed pathlength difference to radial distance is 1:1 (1.5 mm:1.5 mm), which is a 100% error. However, if the observed radial pathlength is 2.5 mm, then a second range of observed pathlengths is 2.5 to 3.0 mm with a difference of 0.5 mm. Hence, a second ratio of observed pathlength difference-to-radial distance is 1:5 (0.5 mm:2.5 mm), which is a second pathlength error of 20% or one-fifth of the pathlength error of the first case. In general, the largest radial distance yielding and intensity-to-noise ratio beyond a threshold, such as 0.5, 1, 1.5 or 2, is preferred as error in a range of observed pathlengths decreases, which reduces the error in b, in Beer's Law: equation 1,

$$A = \text{molar absorptivity} * b * C \quad (\text{eq. 1})$$

where b is pathlength and C is concentration, which is central to visible and near-infrared absorbance and/or scattering models used to determine an analyte property, such as a noninvasive glucose concentration as measured using photons optically probing skin.

#### Skin State Classification

Skin state is optionally classified using a single force pulse or single impulse function, also referred to herein as a ping. Generally, an applied force, such as the force wave **250** provided by the force system **200**, takes time to propagate through the subject **320**. The travel time of the force wave varies as a function of state of the body, such as hydration, temperature, glucose concentration, triglyceride concentration, hematocrit and/or any constituent of skin, blood, and/or interstitial fluid. Hence, the amount of time to travel radial distances to force wave detectors is optionally used to classify the state of the subject and/or to map the state of the subject in regions probed by the force wave. For clarity of presentation and without loss of generality, two example of force wave detection are provided here using: (1) a transducer force detector and/or (2) an optical force wave classifier.

#### Example I

Referring now to FIGS. **10(A-C)**, transducer force detectors are optionally used to detect transit times of the force

wave **250** from the force wave input element **210** to one or more detectors of a set of transducer force detectors **260**. Generally, a transducer force detector converts mechanical motion, such as passage of the force wave **250** and/or skin movement into a measured electrical signal. Referring now to FIG. **10A**, for clarity of presentation and without loss of generality, a first transducer force detector **262**, a second transducer force detector **264**, and a third transducer force detector **266** are illustrated that represent n transducer based force detectors, where n is a positive integer of greater than 1, 2, 3, 5, 10, or 20. As illustrated in FIGS. **10B** and **10C**, the n transducer based force detectors are optionally positioned in a linear array, in a two-dimensional array, and/or along arcs, such as at differing radial distances from one or more light sources in the source system **400**. Referring still to FIG. **10A**, as illustrated, at a first time, the force wave **250** has propagated to the first transducer force detector **262** as a first wave front position **254**; at a second time,  $t_2$ , the force wave **250** has propagated to the second transducer force detector **264** as a second wave front position **256**; and at a third time,  $t_3$ , the force wave **250** has propagated to the third transducer force detector **266** as a third wave front position **258**. Timing of each wave front to each transducer based force wave detector allows: (1) generation of a sub-surface tissue map of constituents of the skin of the subject **320** using mathematical techniques used for seismic mapping known to those skilled in the art of seismic mapping and/or (2) a classification of state of the subject **320** versus a calibration set of classifying states of force wave propagation radial translation times. For instance, the classification is as simple as slow, medium, or fast translation times to a given transducer detector or a more involved combination of translation times for one or more of: (1) responses at a single detector position and (2) responses at a set of detector positions and/or responses to varying inputs of the force wave, such as time, direction, amplitude, and/or frequency of one or more pings from the force wave input elements and/or time varying induced applied pressure and/or displacement of a portion of the skin of the subject **320** by the force system **200**.

#### Example II

Referring now to FIGS. **11(A-C)**, propagation of the force wave(s) **250**, such as force wave fronts **254**, **256**, **258** is detected using a set of optical detectors and using the results in a manner similar to detecting the force wave **250** using the set of transducer based wave detectors. For instance, as the force wave **250** propagates through the tissue layers **340**, the density, absorbance, and/or scattering of voxels of the skin of the subject **320** change, which alters an observed mean optical path between a given source of photons and a photon/photonic detector. One or more sources of the source system **400** coupled to the array of optical detector elements **510** via the subject **320** is optionally used to detect propagation times of the force wave(s) **250**. For clarity of presentation and without loss of generality, a first optical detector **521**, a second optical detector **522**, and a third optical detector **523** are illustrated that represent n optical detectors, where n is a positive integer greater than 0, 1, 2, 3, 5, 10, 15, 16, 20, 25, 100, 500, 1000, and 5000. As illustrated in FIGS. **11B** and **11C**, the n optical detectors are optionally positioned in a linear array, in a two-dimensional array, and/or along arcs, such as differing radial distances from one or more light sources in the source system **400** and/or from one or more force wave sources. Notably, one or more detectors of the array of optical detector elements

510 are optionally and preferably used to detect photons from the source system 400 during a measurement phase of an analyte and/or tissue property with or without a tissue classification step. As illustrated, the first optical detector 521 detects a first optical signal, modified by the force wave 250, with a first pathlength,  $p_1$ , at a given point in time; the second optical detector 522 detects a second optical signal, modified by the force wave 250, with a second pathlength,  $p_2$ , at the given point in time; and the third optical detector 523 detects a third optical signal, modified by the force wave 250, with a third pathlength,  $p_3$ , at the given point in time. Each detected optical signal contains absorbances due to any sample constituent, such as water, protein, fat, and/or glucose and/or is representative of state of the tissue, such as a measure of scattering and/or temperature. As the force wave(s) propagate through the tissue, the first, second, and third pathlengths,  $p_1$ ,  $p_2$ ,  $p_3$ , vary. Hence, the state of the subject 320 is optionally characterized and/or mapped in a manner similar to the transducer wave detection classification and/or mapping; however, optical signals with chemical meaning are used in the process, such as detected intensity, absorbance, and/or scattering related to temperature, one or more tissue layer properties, collagen, elastin, water, albumin, globulin, protein, fat, hematocrit, and/or glucose, such as a concentration, change in tissue state, or a physical structure.

Referring again to FIG. 11A and FIG. 12A, the applied pressure/force wave/displacement optionally generates a gap and/or varies an applied pressure at a first interface 305 of the source system 400 and the skin surface 330 and/or at a second interface 390 of the detector system 500 and/or any element thereof and the skin surface 330. A resulting air gap between the analyzer 110 and the subject 320 and/or a time varying change between an air gap and contact between the analyzer 110 and the subject 320 is used to determine times of contact/relative contact, which is in turn optionally and preferably used in a selection of detected signals step, described infra. For example, loss of optical contact yields a sudden increase in observed intensity in a wavelength region of high absorbance, such as a region dominated by water absorbance in the range of 1350 to 1550 nm, 1400 to 1500 nm, and/or within 5, 10, 15, 25, and/or 50 nm of 1450 nm. Removal of non-contacting signals aids in the development of an outlier analysis algorithm and/or in determining state of the tissue and/or in determination of a degree of applied force from the source system 400, detector system 500, and/or analyzer 110 to the skin surface 330 of the subject 320 as a function of time and/or position.

#### Force Wave/Optical Probe Analyte State Determination

Referring now to FIG. 12, a process of determining an analyte property, such as a glucose concentration, using one or more optical signals optionally and preferably modified by an applied force, force wave, and/or displacement is provided.

Referring still to FIG. 12, in a process, such as a first process or a second process, a force is applied 1210, such as in the form of a force wave and/or displacement induced force wave. For example, the force wave/displacement is generated with a transducer to generate application of a transducer force 1212, which is a single ping 1214/displacement and/or a series of pings and/or is a force/displacement varied in frequency 1216 and/or varied in amplitude 1218, such as via a controller, such as a main controller of the analyzer 110. Subsequently, the force wave 250/tissue displacement induced pressure propagates in the sample 1220.

Referring still to FIG. 12, in another process, such as a first or second process, a result of the tissue displacement

induced force wave is measured and/or detected 1230, such as through a transducer force detection 1232 and/or an optical force detection 1234.

Referring still to FIG. 12, in still another process, such as a second and/or third process, selection of a sub-set of detected signals 1240 is performed, such as a function of position 1241, time 1242, detector 1243, contact 1244, pressure 1245, and/or spectroscopic response 1246 and an analyte state is determined 1250, such as via generation of a calibration 1252 and/or use of a generated calibration in a prediction step 1254.

#### Acousto-Optic Analyzer vs. (1) UPI and (2) an AOTF

An applied force-optic analyzer is described herein. Optionally and preferably, the applied force results in a mechanical disturbance of the tissue resulting in a force being applied to the sample. However, in a sub-case of the applied force-optic analyzer, the applied force comprises an acoustic force yielding an acousto-optic analyzer. Notably, in the sub-case of the applied force-optic analyzer being an acousto-optic analyzer, as used herein an acousto-optic analyzer starkly contrasts with both: (1) an ultrasonic photoacoustic imaging (UPI) system and (2) an acousto-optic tunable filter (AOTF) spectrometer, as described infra.

#### Acousto-Optic Analyzer

As described, an acousto-optic analyzer (AOA) introduces an acoustic vibration wave to the sample to impact the state of the sample, such as tissue, and the state of the sample is measured using an optical probe.

#### Photoacoustic Imaging

In stark contrast, according to Wikipedia, ultrasonic photoacoustic imaging, also referred to as (UPI), photoacoustic imaging (PI), and/or optoacoustic imaging, delivers non-ionizing laser pulses to biological tissue, which results in absorbed energy and resultant heat in the form of transient thermoelastic expansions detected as wideband megaHertz ultrasonic emissions detected by ultrasonic transducers. The detected signals are used to produce images. As optical absorbance relationships exist with physiological properties, such as hemoglobin concentration and oxygen saturation, the detected pressure waves may be used to determine hemoglobin and oxygen concentration.

Hence, an acousto-optic analyzer starkly contrasts with photoacoustic imaging. Stated again, while the acousto-optic analyzer described herein may induce a heat wave like in photoacoustic imaging, in photoacoustic imaging the sound wave is detected whereas photons, from an external source, are detected in the acousto-optic analyzer described are detected after interacting with the sample being displaced/heated/disturbed by the sound wave.

#### Acousto-Optic Tunable Filter

According to Wikipedia, an acousto-optic tunable filter (AOTF), diffracts light based on an acoustic frequency. By tuning the frequency of the acoustic wave, the desired wavelength of the optical wave can be diffracted acousto-optically.

Hence, an acousto-optic analyzer (AOA) starkly contrasts with an acousto-optic tunable filter (AOTF) as, while the input sound wave of the AOA may diffract light, the separation of the input light is not the primary use of the sound wave. Indeed, a narrow-band light emitting diode (LED) is optionally used in conjunction with a broadband detector in the acousto-optic analyzer making any separation of the narrow band light source pointless. Further, in the AOA, the sound wave is used to change the state of the biological sample itself, whereas in the AOTF the sound wave is

introduced to a birefringent crystal in a wavelength separation module of the spectrometer and is not introduced into the sample.

Still yet another embodiment includes any combination and/or permutation of any of the elements described herein.

The main controller, a localized communication apparatus, and/or a system for communication of information optionally comprises one or more subsystems stored on a client. The client is a computing platform configured to act as a client device or other computing device, such as a computer, personal computer, a digital media device, and/or a personal digital assistant. The client comprises a processor that is optionally coupled to one or more internal or external input device, such as a mouse, a keyboard, a display device, a voice recognition system, a motion recognition system, or the like. The processor is also communicatively coupled to an output device, such as a display screen or data link to display or send data and/or processed information, respectively. In one embodiment, the communication apparatus is the processor. In another embodiment, the communication apparatus is a set of instructions stored in memory that is carried out by the processor.

The client includes a computer-readable storage medium, such as memory. The memory includes, but is not limited to, an electronic, optical, magnetic, or another storage or transmission data storage medium capable of coupling to a processor, such as a processor in communication with a touch-sensitive input device linked to computer-readable instructions. Other examples of suitable media include, for example, a flash drive, a CD-ROM, read only memory (ROM), random access memory (RAM), an application-specific integrated circuit (ASIC), a DVD, magnetic disk, an optical disk, and/or a memory chip. The processor executes a set of computer-executable program code instructions stored in the memory. The instructions may comprise code from any computer-programming language, including, for example, C originally of Bell Laboratories, C++, C#, Visual Basic® (Microsoft, Redmond, Wash.), Matlab® (MathWorks, Natick, Mass.), Java® (Oracle Corporation, Redwood City, Calif.), and JavaScript® (Oracle Corporation, Redwood City, Calif.).

Herein, any number, such as 1, 2, 3, 4, 5, is optionally more than the number, less than the number, or within 1, 2, 5, 10, 20, or 50 percent of the number.

Herein, an element and/or object is optionally manually and/or mechanically moved, such as along a guiding element, with a motor, and/or under control of the main controller.

The particular implementations shown and described are illustrative of the invention and its best mode and are not intended to otherwise limit the scope of the present invention in any way. Indeed, for the sake of brevity, conventional manufacturing, connection, preparation, and other functional aspects of the system may not be described in detail. Furthermore, the connecting lines shown in the various figures are intended to represent exemplary functional relationships and/or physical couplings between the various elements. Many alternative or additional functional relationships or physical connections may be present in a practical system.

In the foregoing description, the invention has been described with reference to specific exemplary embodiments; however, it will be appreciated that various modifications and changes may be made without departing from the scope of the present invention as set forth herein. The description and figures are to be regarded in an illustrative manner, rather than a restrictive one and all such modifica-

tions are intended to be included within the scope of the present invention. Accordingly, the scope of the invention should be determined by the generic embodiments described herein and their legal equivalents rather than by merely the specific examples described above. For example, the steps recited in any method or process embodiment may be executed in any order and are not limited to the explicit order presented in the specific examples. Additionally, the components and/or elements recited in any apparatus embodiment may be assembled or otherwise operationally configured in a variety of permutations to produce substantially the same result as the present invention and are accordingly not limited to the specific configuration recited in the specific examples.

Benefits, other advantages and solutions to problems have been described above with regard to particular embodiments; however, any benefit, advantage, solution to problems or any element that may cause any particular benefit, advantage or solution to occur or to become more pronounced are not to be construed as critical, required or essential features or components.

As used herein, the terms “comprises”, “comprising”, or any variation thereof, are intended to reference a non-exclusive inclusion, such that a process, method, article, composition or apparatus that comprises a list of elements does not include only those elements recited, but may also include other elements not expressly listed or inherent to such process, method, article, composition or apparatus. Other combinations and/or modifications of the above-described structures, arrangements, applications, proportions, elements, materials or components used in the practice of the present invention, in addition to those not specifically recited, may be varied or otherwise particularly adapted to specific environments, manufacturing specifications, design parameters or other operating requirements without departing from the general principles of the same.

Although the invention has been described herein with reference to certain preferred embodiments, one skilled in the art will readily appreciate that other applications may be substituted for those set forth herein without departing from the spirit and scope of the present invention. Accordingly, the invention should only be limited by the Claims included below.

The invention claimed is:

1. An apparatus for noninvasively determining an analyte property of a subject having skin and skin layers, comprising:

an electro-mechanical transducer affixed to the skin of the subject;

a controller, said controller providing a voltage waveform to said electro-mechanical transducer driving displacement of the skin and inducing a pressure wave into the skin; and

a spectrometer interfaced to a sample site of the skin, said spectrometer comprising a set of sources and a set of detectors,

said controller configured to collect signal from said set of detectors as a function of timing of said voltage waveform and apply a calibration model to the signal to determine the analyte concentration.

2. The apparatus of claim 1, said electro-mechanical transducer comprising:

at least one piezo-electric material configured to convert the voltage waveform into mechanical movement against the skin resulting in the displacement of the skin.

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3. The apparatus of claim 1, said electro-mechanical transducer comprising:

a motor rotating an off-center mass around an axis.

4. The apparatus of claim 1, further comprising:

a double-sided adhesive, said double-sided adhesive affixing said electro-mechanical transducer to the skin.

5. The apparatus of claim 1, further comprising:

an analyzer comprising said electro-mechanical transducer, said controller, said spectrometer, and an interface zone, at least one of said set of sources coupling photons through a fluorocarbon, embedded in a flexible material covering at least a portion of said interface zone, and into the skin.

6. The apparatus of claim 5, said flexible material further comprising:

an adhesive surface, said adhesive surface configured to temporarily affix said analyzer to the skin of the subject.

7. The apparatus of claim 1, further comprising:

a first detection transducer at a first radial distance from the sample site,

said controller configured to use an electric signal from said first detection transducer, induced in said first detection transducer by the pressure wave in the skin, to determine a transport time from said electro-mechanical transducer to said first detector and to classify the subject with the transport time.

8. The apparatus of claim 1, further comprising:

a first detection transducer contacting the skin at a first radial distance from the sample site; and

a second detection transducer contacting the skin at a second radial distance from the sample site.

9. A method for noninvasively determining an analyte property of a subject having skin and skin layers, comprising the steps of:

affixing an electro-mechanical transducer to the skin of the subject;

a controller driving said electro-mechanical transducer with a voltage waveform to induce displacement of the skin and generate a pressure wave in the skin;

a spectrometer collecting a near-infrared optical signal, said spectrometer interfaced to a sample site of the skin, said spectrometer comprising a set of sources and a set of detectors;

a controller collecting a set of signals from said set of detectors as a function of timing of said voltage waveform; and

applying a calibration model to selected signals from the set of signals to determine the analyte concentration.

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10. The method of claim 9, further comprising the step of: selecting the selected signals as a function of time of peaks of said voltage waveform.

11. The method of claim 9, further comprising the step of: selecting the selected signals as a function of detected signal from a dermis layer of the skin layers.

12. The method of claim 9, further comprising the step of: selecting the selected signals as a function of time of transport of the pressure wave in the skin to a detector of said set of detectors.

13. The method of claim 9, said step of displacing further comprising the step of: said electro-mechanical transducer applying said pressure wave as an analog varying wave responsive to said voltage waveform repeating with a frequency and an amplitude.

14. The method of claim 13, further comprising the step of:

selecting the selected signals as a function of time of transport of the pressure wave in the skin to a detector of said set of detectors.

15. An apparatus for noninvasively determining an analyte property of a subject having skin and skin layers, comprising:

an analyzer comprising:

an electro-mechanical transducer configured to displace skin of the subject generating a force wave propagating into the skin layers;

a near-infrared spectrometer, comprising:

a set of sources;

a set of detectors; and

coupling optics, configured to couple photons from said set of sources to said set of detector via the skin layers of the subject; and

a controller configured to drive said electro-mechanical transducer and select responses from said set of detectors as a function of timing of operation of said electro-mechanical transducer.

16. The apparatus of claim 15, said apparatus further comprising:

a housing, both said electro-mechanical transducer and said spectrometer at least partially embedded in said housing.

17. The apparatus of claim 16, further comprising: an adhesive layer affixed to said housing, an adhesive side of said adhesive layer configured to removably attach said housing to the skin of the subject.

18. The apparatus of claim 17, further comprising: a fluorocarbon embedded into said adhesive.

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