(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 313 396 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
28.06.2006 Bulletin 2006/26

(21) Application number: **01958348.3**

(22) Date of filing: **09.08.2001**

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(86) International application number:
PCT/IL2001/000740

(87) International publication number:
WO 2002/015776 (28.02.2002 Gazette 2002/09)

(54) **PHOTOACOUSTIC ASSAY AND IMAGING SYSTEM**

PHOTOAKUSTICHE PRUFVORRICHTUNG UND BILDERZEUGUNGSSYSTEM

DOSAGE PHOTOACOUSTIQUE ET SYSTEME D'IMAGERIE

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

(30) Priority: **24.08.2000 IL 13807300**

(43) Date of publication of application:
28.05.2003 Bulletin 2003/22

(73) Proprietor: **Glucon Inc.**
Wilmington, DE 19805 (US)

(72) Inventors:
- **NAGAR, Ron**
  63417 Tel-Aviv (IL)
- **PESACH, Benny**
  48072 Rosh-Ha'ayin (IL)
- **BEN-AMI, Udi**
  48580 Rosh-Haayin (IL)

(74) Representative: **Jorritsma, Ruurd et al**
Nederlandsch Octrooibureau
Postbus 29720
2502 LS Den Haag (NL)

(56) References cited:
EP-A- 0 919 180
US-A- 4 385 634
US-A- 5 840 023

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 313 396 B1

Description

FIELD OF THE INVENTION

[0001] The invention relates to non-invasive *in-vivo* methods and apparatus for determining the concentration of a substance in a body and for determining the concentration of the substance as a function of position in the body.

BACKGROUND OF THE INVENTION

[0002] Methods and apparatus for *in-vivo* and *in-vitro* measurements of blood glucose levels are known in the art. Generally, the methods and apparatus are relatively complicated and measurements of a person's blood glucose levels are usually performed in a clinic or laboratory with the aid of a technician and costs of the measurements are relatively high.

[0003] Methods and apparatus for determining blood glucose levels for use in the home, for example by a diabetic who must monitor blood glucose levels frequently, are available. These methods and associated devices arc generally invasive and usually involve taking blood samples by finger pricking. Finger pricking is perceived as inconvenient and unpleasant and to avoid finger pricking diabetics tend to monitor their glucose levels less frequently than is advisable. Moreover, many conventional glucometers require routine purchasing of sample sticks and pricking needles, which is bothersome and adds cost to the user. There is a need for glucometers that are easy to use and that perform non-invasive *in-vivo* assays of blood sugar.

[0004] PCT Publication WO 98/38904, describes a "non-invasive, *in-vivo* glucometer" that uses a photoacoustic effect in which light energy is converted to acoustic energy to measure a person's blood glucose. Pulses of light at a wavelength for which light is absorbed by glucose is directed by the glucometer to illuminate a part of the person's body, such as a fingertip, comprising soft tissue. The light pulses are typically focused to a relatively small focal region inside the body part and light from the light pulses is absorbed by glucose and converted to kinetic energy in a region of tissue in the neighborhood of the focal region. The kinetic energy causes temperature and pressure of the absorbing tissue region to increase and generates acoustic waves, hereinafter referred to as "photoacoustic waves", that radiate out from the absorbing tissue region. An acoustic sensor comprised in the glucometer contacts the body part and senses the photoacoustic waves. Intensity of the waves is a function of the concentration of glucose in the absorbing tissue region and their intensity as measured by the sensor is used to assay the glucose.

[0005] However, light is scattered by body tissue and even though the light is focused to a small focal region inside the body, the location and size of the absorbing tissue region are not accurately known. As a result, the generated photoacoustic effect and measurements of the person's glucose levels are not necessarily the result only of glucose concentration in the person's blood. Characteristics of the absorbing tissue region, such as density of blood vessels therein, that can affect concentration of glucose in the absorbing region are often not accurately known. Measurements of blood glucose levels can therefore be affected by unknown variables that substantially compromise the reliability of the measurements.

[0006] US Patent 5,941,821 and EPO 0 919 180, which claims priority from the U.S. Patent describe another non-invasive *in-vivo* glucometer that uses a photoacoustic effect to assay blood glucose. Light at a wavelength at which glucose absorbs light is modulated at a suitable frequency and directed by the glucometer to illuminate a region of a person's body. Glucose in blood and interstitial fluid in tissue near the surface of the region absorbs the light and converts the absorbed energy to kinetic energy that heats the tissue. Temperature of the tissue increases and decreases cyclically in cadence with the modulation of the light. The alternate heating and cooling of the tissue results in periodic heating of air in contact with the surface of the illuminated region, which generates sound waves in the air. A microphone comprised in the glucometer provides measurements of intensity of the sound waves that are used to determine a concentration of glucose.

SUMMARY OF THE INVENTION

[0007] The invention is defined in claim 1.

[0008] An aspect of some embodiments of the present invention relates to providing a non-invasive, *in-vivo* glucometer that determines a person's glucose level substantially only from glucose concentration in the person's blood.

[0009] An aspect of some embodiments of the present invention relates to providing a glucometer that locates at least one blood vessel in a person's body using ultrasound. The glucometer determines the person's glucose level by assaying glucose present substantially only in blood in the located at least one blood vessel.

[0010] In embodiments of the present invention, the glucometer comprises at least one ultrasound transducer that radiates ultrasound into the person's body and at least one ultrasound sensor that receives energy from the radiated ultrasound that is reflected or transmitted by features in the body. The glucometer locates the at least one blood vessel from the reflected/transmitted energy using methods known in the art. In some embodiments of the present invention, the glucometer comprises at least one light source that illuminates a region of tissue in which the at least one blood vessel is located with at least one pulse of light at a wavelength for which light is absorbed by glucose. Glucose in a volume of blood, hereinafter referred to as a "bolus" of blood, in the at least one blood vessel absorbs energy from the at least one light pulse. The absorbed energy generates changes in the bolus that are a function of the amount of energy

absorbed, which in turn is a function, inter alia, of the concentration of glucose in the bolus.

[0011] At least one change in an acoustic property of the bolus and/or acoustic phenomena generated in the bolus by the absorbed energy is measured by the glucometer and used to assay glucose in the bolus. In some embodiments of the present invention a measurement of a change and/or phenomenon is performed during illumination of the bolus with the at least one light pulse. In some embodiments of the present invention a measurement is performed after illumination of the bolus with the at least one light pulse.

[0012] According to an aspect of some embodiments of the present invention a photoacoustic wave generated by the absorbed energy is used to assay glucose in the bolus,

[0013] When the region of tissue in which the at least one blood vessel is located is illuminated with the at least one light pulse, the bolus and generally tissue surrounding the bolus generate pbotoacoustic waves responsive to energy that they absorb from the at least one light pulse. The glucometer senses the photoacoustic waves and identifies locations of their origins using methods known in the art. The glucometer compares the identified locations with the location of the bolus to identify which of the photoacoustic waves originates in the bolus. The amplitude of the photoacoustic wave so identified is a function of the concentration of glucose in the bolus and is used to assay the person's glucose.

[0014] According to an aspect of some embodiments of the present invention the glucometer reflects ultrasound waves from the bolus at times during which a photoacoustic wave is being generated by the bolus to measure a change in the bolus from which to determine glucose concentration. During generation of the photoacoustic wave, the surface of the bolus is moving and ultrasound waves reflected from the bolus are therefore Doppler shifted. Generally, during generation of the photoacoustic wave, surface regions of the bolus move at speeds that are substantial fractions of the speed of sound in the illuminated tissue. As a result, frequencies of ultrasound waves that are reflected by the bolus from ultrasound waves incident on the bolus are Doppler shifted substantially compared to the frequency of the incident ultrasound waves. Intensities of these reflected waves and magnitude of their Doppler shifts are sensed and used to determine concentration of glucose in the bolus.

[0015] The glucometer has been described as illuminating the bolus with light at a wavelength for which light is absorbed by glucose. However, it is not possible to choose a wavelength for the light for which components of the bolus other than glucose do not absorb the light. As a result, an acoustic effect measured by the glucometer resulting from absorption of light by the bolus at any wavelength is due to absorption of the light by substances other than glucose in the bolus, such as cholesterol, albumin and various lipids, as well as by glucose. In order to isolate a contribution to the effect due to glucose, and thereby the concentration of glucose in the bolus, the bolus is preferably illuminated with pulses of light at a plurality of different wavelengths and the effect measured at the different wavelengths. Using known absorption cross-sections for light by substances in the blood, the contribution to the effect from glucose and thereby the concentration of glucose in the bolus is determined.

[0016] It is readily concluded from remarks made in the previous paragraph that the invention is not limited to assaying blood glucose. In the process of determining glucose concentration, in accordance with an embodiment of the present invention, absorption coefficients of other substances in the blood are determined and the absorption coefficients may be used to determine concentrations of these substances. For example if "N" different wavelengths of light are used to determine glucose concentration, in accordance with an embodiment of the present invention, absorption coefficients of N different components of the blood bolus are determined and may be used to estimate concentrations of the components in the bolus. Different particular substances in the bolus whose concentrations are to be estimated can be assayed, in accordance with an embodiment of the present invention, by proper "tuning" of frequencies used to illuminate the blood bolus. Furthermore, the present invention is not limited to assaying blood components. Some embodiments of the present invention can be used to assay components of other tissues and features of the body, such as for example, components of interstitial fluid, blood clots or plaque in blood vessels that are located using ultrasound.

[0017] Whereas only light has been described as being used to introduce energy to a blood bolus, other forms of electromagnetic radiation, such as microwave or RF radiation, may be used to impart energy to components being assayed in a tissue volume, in accordance with an embodiment of the present invention. Some embodiments of the present invention are used to provide a spatial map of concentration of a substance in a region of the body. In some embodiments, a sub-region of the region of the body for which concentration of the substance is to be mapped is illuminated with collimated light that is absorbed by the substance. As noted above, because of scattering of light in body tissue, the size and location of the sub-region is not accurately known. However, changes in acoustic properties of tissue in the sub-region can be determined for highly localized "voxels" in the sub-region. The changes can be determined by sensing photoacoustic waves generated in the voxels and/or characteristics of ultrasonic waves that are, reflected from and/or transmitted through the voxels, in accordance with embodiments of the present invention. Any of the changes in acoustic properties that affect transmitted, reflected or generated acoustic waves, such as those discussed above, can be localized to voxels in the sub-region having dimensions in a range from a few to about ten wavelengths of ultrasound that is used to probe the sub-region.

Since these changes are a function of concentration of the substance, the concentration of the substance in different voxels of the sub-region can be determined, in accordance with preferred embodiments of the present invention. A map of the concentration of the substance in the body region is acquired by moving the illuminated sub-region to different "scan" positions in the body region.

[0018] Since different organs and/or features in the body region will usually be distinguished by different levels of concentration of a substance, a concentration map of the substance, provided in accordance with an embodiment of the present invention, will, in general, image the organs and/or features. As a result some embodiments of the present invention are used to imago organs and or features of organs in a region of a body. For example, LDL cholesterol and oxidized LDL cholesterol are highly concentrated in plaque. By mapping concentration of LDL cholesterol or oxidized LDL cholesterol in a region of a person's body, images of plaque deposits on walls of blood vessels in the region can be acquired.

BRIEF DESCRIPTION OF FIGURES

[0019] Non-limiting examples of embodiments of the present invention are described below with reference to figures attached hereto. In the figures, identical structures, elements or parts that appear in more than one figure are generally labeled with the same numeral in all the figures in which they appear. Dimensions of components and features shown in the figures are chosen for convenience and clarity of presentation and are not necessarily shown to scale. The figures are listed below.

Figs. 1A-1C schematically show a glucometer measuring a person's blood glucose by sensing photoacoustic waves generated in blood in a region of the person's body by illumination of the region with light absorbed by glucose, in accordance with an embodiment of the present invention;

Figs. 2A and 2B schematically show a glucometer measuring blood glucose by sensing changes in velocity of sound in blood, in accordance with an embodiment of the present invention;

Figs. 3A-3B schematically show a glucometer assaying and imaging cholesterol in a person's body, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF EMBODIMENTS

[0020] Figs. 1A-1C schematically show a glucometer 20 measuring a person's blood glucose by sensing photoacoustic waves generated in blood in a part 24 of the person's body, in accordance with an embodiment of the present invention. Glucometer 20 comprises at least one ultrasound transducer 26, a light source 28 that provides light at a wavelength at which light is absorbed by glucose and a controller 30 that controls the at least one ultrasound transducer and the light source.

[0021] At least one ultrasound transducer 26 is acoustically coupled to region 24 and is used to profile acoustic impedance and velocity of sound in region 24 and identify and locate features in the region using ultrasound imaging techniques and methods known in the art. In particular, at least one ultrasound transducer 24 is used to identify and locate at least one blood vessel 22 in body part 24 using methods known in the art. For example, location of blood vessel 22 can be performed by detecting a Doppler shift in ultrasound reflected from the blood vessel caused by velocity of blood in the blood vessel, assuming that a component of the velocity of the blood is parallel to ultrasound incident on the blood vessel. Or, location of a blood vessel can be performed by sensing reflections of ultrasound from walls of the blood vessel.

[0022] Numerous and varied ultrasound transducers, configurations of transducers and ultrasound imaging methods suitable for use in practicing the present invention and locating blood vessels are known in the art.

[0023] At least one transducer 26 may comprise a single transducer or a plurality of transducers. At least one transducer 26 may compriso a relatively small transducer that performs as a point source when generating ultrasound waves and performs as a point sensor that senses ultrasound waves in a relatively large solid angle. At least one transducer 26 may comprise a shaped transducer that generates a collimated beam of ultrasound and senses ultrasound in a relatively small solid angle. At least one transducer may comprise a phased array of ultrasound transducers that can be controlled by controller 30 to generate and steer a beam of ultrasound.

[0024] At least one transducer 26 may comprise a piezoelectric transducer or other transducer known in the art, such as an "optical" ultrasound transducer that converts pulses of optical energy into acoustic energy. Optical ultrasound transducers are described in an article entitled "Theory of Detection of Shear Stress Pulses with Laser Picosecond Acoustics", by O. Matsuda, 11th ICPPP, Japan 2000. Such transducers can provide and detect ultrasound pulses having sub-picosecond pulse lengths.

[0025] In some embodiments of the present invention same transducers are used to both generate and sense ultrasound waves. In some embodiments of the present invention at least one transducer that is used to transmit ultrasound is not used to sense ultrasound.

[0026] In Figs 1A - 1C and figures that follow, for convenience of presentation, at least one ultrasound transducer 26 is assumed, by way of example, to both transmit and sense ultrasound and to be controllable to generate a collimated and/or focused pulse of ultrasound. In Fig. 1 A controller 30 controls at least one ultrasound transducer 26 to transmit at least one collimated pulse of ultrasound waves into body part 24, which ultrasound pulse

is represented by arc line segments 32. Some of the energy in at least one ultrasound pulse 32 is reflected from a localized region 36 of at least one blood vessel 22 and returns to at least one transducer 26 as a reflected at least one ultrasound pulse 38.

[0027] A reflected pulse 38 is sensed by at least one ultrasound transducer 26, which generates signals responsive thereto that the ultrasound transducer transmits to controller 30. Controller 30 processes the received signals, using methods known in the art, to identify and locate at least one blood vessel 22. For example, assume a bolus of blood 40 moving through region 36 of at least one blood vessel 22 has a component of velocity parallel to pulse 32 or reflected pulse 38. Reflected pulse 38 may then be identified as originating in at least one blood vessel 22 by sensing a Doppler shift in the reflected pulse resulting from the pulse being reflected from bolus 40. The location of blood vessel 22 may be determined from a time lapse between a time at which the pulses of ultrasound waves 32 are transmitted and a time at which Doppler shifted ultrasound pulse 38 arrives at ultrasound transducer 26. In addition, reflected pulses 38 may arise from reflections of energy from transmitted pulses 32 by walls of at least one blood vessel 22 as a result of the walls having acoustic impedance different from the acoustic impedance of tissue adjacent to the walls.

[0028] It should be noted that energy from at least one ultrasound pulse 32 is not only reflected by at least one blood vessel 22 and features thereof. In general, energy from at least one ultrasound pulse 32 is reflected by tissue interfaces and regions in body part 24 in which the acoustic impedance is changing rapidly. In some embodiments of the present invention, energy in the reflections that is sensed by at least one transducer 26 is used to determine acoustic properties, such as for example acoustic impedance and the speed of sound, of regions in body part 24. In some embodiments of the present invention acoustic energy reflections are used to determine acoustic properties of coupling of at least one transducer 26 to body part 24. Measurements of the acoustic properties of body part 24 and of the coupling of at least one transducer 26 to the body part are hereinafter referred to as "acoustic calibration measurements".

[0029] In some embodiments of the present invention, ultrasound generated by at least one transducer 26 has a frequency greater than 5MHz. In some embodiments of the present invention the frequency is substantially equal to or greater than 10MHz. Sound propagates in body tissue at a velocity of about 1.5mm per microsecond and has a useful penetration depth for detection of features in tissue, which is limited by absorption and decreases as frequency increases. For an ultrasound frequency of about 10MHz, the wavelength of ultrasound generated by the transducer is about 0.15 mm and a useful penetration depth of about 35 mm. For this frequency, glucometer 20 can determine location of at least one blood vessel 22 in a direction along which the transducer transmits ultrasound pulses with an accuracy of about 0.15mm (*i.e.* about a wavelength). In some embodiments of the present invention, transmitted ultrasound pulses 32 are collimated so that they have a cross-sectional diameter of about 1.5mm. Glucometer 20 therefore has spatial resolution and penetration depth sufficient to locate blood vessels having dimensions typical of dimensions of blood vessels located, by way of example, in a person's wrist, forearm or groin.

[0030] In Fig. 1B, after at least one blood vessel 22 has been located, controller 30 controls light source 28 to illuminate body part 24 with at least one pulse 42 of collimated light "aimed" at region 36 of at least one blood vessel 22. As light pulse 42 enters body part 24, tissue in body part 24 scatters the light and the collimated light spreads out laterally. Therefore as light pulse 42 penetrates deeper into body part 24 it illuminates an increasing volume of tissue in the body part. In the region of bolus 40 a volume of tissue greater than the volume of bolus 40 is illuminated. It is therefore seen that, because of scattering, collimated light cannot, generally, be used to illuminate substantially only a relatively small, accurately defined region of tissue in body part 24. As a result, photoacoustic waves can be generated by light pulse 42 in locations in body part 24 that are not restricted to blood bolus 40 and the light pulse may generate photoacoustic waves at locations substantially removed from the location of the blood bolus. In Fig. 1B, lines 44 schematically represent an envelope that defines the spatial extent of at least one light pulse 42 perpendicular to the direction of travel of the light pulse and spreading of lines 44 inside body part 24 indicate lateral spreading of at least one light pulse 42.

[0031] It should be noted that whereas light source 28 is shown, by way of example, located at a side of ultrasound transducer 26 other positions of light source 28 are possible and can be advantageous. In some embodiments of the present invention, for example, ultrasound transducer 26 is formed with a hole and light source 28 is positioned to transmit light pulses through the hole. Transmission of light pulses through a hole in ultrasound transducer 26 provides relatively uniform and more symmetric illumination of a "field of view" of the transducer in body part 24 in which the transducer detects features of the body part. Furthermore whereas light source 28 is shown as a single light source, light source 28 may comprise a plurality of light sources that provide light at wavelengths suitable for determining glucose concentration in bolus 40.

[0032] Fig. 1C schematically shows photoacoustic waves, which are represented by sets of concentric circles, that are generated in body part 24 as a result of illumination by light 42. An innermost concentric circle in a set of concentric circles schematically represents a location of an origin of a photoacoustic wave. Sets of concentric circles 48 drawn with dashed lines schematically represent photoacoustic waves that are generated by absorption of energy from light pulse 42 at locations outside of blood vessel 22 and bolus 40. Set 50 of concentric

circles drawn in solid lines schematically represents a photoacoustic wave having an origin in bolus 40.

[0033] Ultrasound transducer 26 senses photoacoustic waves 48 and 50 and transmits signals responsive thereto to controller 30. In accordance with an embodiment of the present invention controller 30 determines a location for the origin of each of photoacoustic waves 48 and 50 using results of acoustic calibration measurements performed previously and noted in the discussion of Fig. 1A. Controller 30 than compares the locations to the location of bolus 40, which was determined previously, as indicated in Fig. 1A. Methods for determining the locations of origins of photoacoustic waves are described in PCT Publication WO 98/14118 and US Patent 5,713,356.

[0034] Controller 30, in accordance with an embodiment of the present invention, is therefore able to discriminate between photoacoustic waves that are generated in bolus 40 and photoacoustic waves that are generated outside of bolus 40. Controller 30 determines that photoacoustic wave 50 is located in bolus 40 and that photoacoustic waves 48 are located outside of bolus 40. In accordance with an embodiment of the present invention, controller 30 therefore uses the locations and amplitudes of photoacoustic waves 50 and 48 and calibration measurements to determine a concentration of glucose in the person's blood.

[0035] The amplitude of pressure from photoacoustic wave 50 and the shape of photoacoustic wave 50 that is sensed by ultrasound sensor 26 is a function of an amount of energy absorbed by bolus 40 from at least one light pulse 42. The amount of energy absorbed from at least one light pulse 42 is, of course, a function of an absorption coefficient in blood for light in light pulse 42. In general the amount of energy absorbed is relatively small, as a result of which, the amount of energy is approximately proportional to the absorption coefficient of light 42 in blood. The relationship between the amplitude of a photoacoustic wave and an amount of energy absorbed by a region of tissue that generates the photoacoustic wave is described in US Patent 4,385,634 to Bowen and in PCT publication WO 98/14118 referenced above. Expressions for the amplitude of a photoacoustic wave arc also given in an article by Lai, H. M. and Young, K.J. in Acoust. Soc. Am. Vol 76, pg 2000 (1982), in an article by MacKenzie et al., "Advances in Photoacoustic Noninvasive Glucose Testing", Clin. Chem. Vol 45, pp 1587-1595 (1999) and in an article by C.G.A. Hoelen et al., "A New Theoretical Approach To Photoacoustic Signal Generation", Acoust. Soc. Am. 106 2 (1999).

[0036] If P represents the amplitude of photoacoustic wave 50 then, adopting the expression for amplitude given by Hoelen et al., $P = A(\beta C^2/H)(I_o \tau e^{-\alpha d})\alpha_b$, where A is a constant of proportionality, β is the temperature expansion coefficient for blood, C the speed of sound and H the specific heat capacity of blood. I_o and τ are respectively the intensity and pulse length of at least one light pulse 42. α is the absorption coefficient for light in at least one light pulse 42 in tissue of body part 24 and d is a path length that light pulse 42 travels in the body part to reach blood bolus 40. α_b is the absorption coefficient of blood in bolus 40, which is a function of glucose concentration in the blood, for light in at least one light pulse 42. The exponential factor $e^{-\alpha d}$ is an attenuation factor by which intensity of at least one light pulse 42 is attenuated along the path length d. The attenuation factor may be estimated from d, which is known from the location of blood bolus 40 and experimentally known values for α. In some embodiments of the present invention, the absorption coefficient a is determined as a function of distance along the path length d using the equation for P given above or in one of the other referenced documents and a finits element analysis of the measured photoacoustic signal.

[0037] The wavelength of light in at least one light pulse 42 is chosen so that the light is absorbed by glucose. The absorption coefficient α_b is therefore a function of a known absorption cross section of glucose for light at the wavelength of light in at least one light pulse 42 and an unknown concentration of glucose in the blood of bolus 40. A measure of the amplitude P of photoacoustic waves generated in blood bolus 40 can therefore be used to determine concentration of glucose in blood bolus 40. In some embodiments of the present invention, controller 30 adjusts amplitude P using results of the acoustic calibration measurements to remove biases in P introduced by acoustic properties of tissue in body part 24 and coupling of at least one transducer 26 to the body part Controller 30 uses the adjusted P to determine glucose concentration.

[0038] Glucose has absorption peaks at a number of different wavelengths that can be used in the practice of the present invention. For example, glucose has absorption peaks in the mid infrared (IR) at 9.7 microns in the combination region at 2.10, 2.27, and 2.32 microns, in the first overtone region at 1.73, 1.69, and 1.61 microns, and in the near infrared, with relatively low absorption, in bands centered at 0.76, 0.92, and 1.00 micron that can be used in the practice of the present invention. However, there is no wavelength for the light at which only glucose in the blood absorbs the light. Many different substances in the blood such as cholesterol, albumin and various fats and proteins absorb light at or near wavelengths of light at which glucose absorbs light. As a result, the absorption coefficient α_b is a function not only of glucose concentration in blood bolus 40 but also of the concentrations (and absorption coefficients) the other absorbing substances in the blood bolus. Therefore, in accordance with an embodiment of the present invention, to assay the person's blood glucose, absorption coefficients α_b of light by a bolus 40 of the person's blood are determined from measured amplitudes of photoacoustic waves for a plurality of different wavelengths of light. The concentration of glucose in the person's blood is then determined from analysis of the determined absorption coefficients using algorithms known in the art.

[0039] Appropriate criteria for the choice different wavelengths of light used to determine glucose concentration and the methods and techniques for analyzing the absorption coefficients are well known. US patent 5,957,841 to Maruo et aL, US Patent 5,452,716 to V. Clift, US Pat 5,348,002 to Caro, and U.S. Patent 4,975,581 to Robinson et al., describe methods of determining glucose concentration from absorption measurements at a plurality of wavelengths. US Patent 5,957,841 describes determining glucose concentration in tissue from measurements of absorption of light in the tissue in three wavelength bands: 1.48 microns - 1.55 microns, 1.55 microns -1.65 microns and 1.65 microns - 1.88 microns. Suitable light sources, such as lasers, laser diodes (LDs), and light emitting diodes (LEDs) for providing light at wavelengths used to assay glucose, in accordance with embodiments of the present invention, are readily available. For methods of assaying glucose, in accordance with embodiments of the present invention, such as a method discussed below with reference to Fig. 4, in which continuous illumination of a blood bolus at desired frequencies is required, filtered lamps can also be used for providing light.

[0040] In some embodiments of the present invention, photoacoustic waves generated in blood bolus 40 by at least one light pulse 42 are detected by heterodyning the photoacoustic waves with a reference acoustic wave, in accordance with an embodiment of the present invention.

[0041] To illustrate the heterodyning detection technique, in accordance with an embodiment of the present invention, assume that at least one light pulse 42 comprises a train of light pulses radiated at a first frequency. Photoacoustic waves will then be generated by blood bolus 40 at substantially the first frequency. Assume that the reference source is controlled to generate "reference" acoustic waves at a second frequency, offset from the first frequency, which are focused on blood bolus 40. Assume further that the reference acoustic waves are sufficiently intense so that in the presence of the reference acoustic waves the blood bolus has a substantial non-linear response to acoustic stimuli. As a result, photoacoustic waves generated in blood bolus 40 by light pulses 42 are a function not only of the intensity and frequency of the light pulses but are a function also of the intensity and frequency of the reference acoustic waves. The "acoustic non-linearity" of blood bolus 40 caused by the reference waves couples the reference waves and the photoacoustic response of the blood bolus to light pulses 42.

[0042] In particular, if the phase of the reference waves and the envelope of optical energy of light pulses 42 at blood bolus 40 are stable, the coupling of the reference waves and the photoacoustic response of the blood bolus will generate a "heterodyned photoacoustio signal". The heterodyned photoacoustic signal will have a frequency substantially equal to the beat frequency of the first and second frequencies will be transmitted from the blood bolus. The pressure amplitude of the heterodyned signal is proportional to the power in the reference beam and can be substantially larger than the pressure amplitude of photoacoustic waves generated by blood bolus 40 responsive to illumination by light pulse 42. The heterodyned signal can be detected by appropriate filtering of signals generated by at least one transducer 26 using techniques well known in the art.

[0043] The inventors estimate that a reference acoustic beam that focuses about 1mW of power in a blood bolus having a volume of about 1 mm^2, focuses sufficient energy in the blood bolus to couple the photoacoustic response to the reference acoustic beam. The coupling of two acoustic signals in the human body to generate a heterodyned signal is discussed in a book entitled "Physical Ultrasonics" by Robert T. Beyer and Stephen V. Letcher, Academic Press 1969. Calculations in the book indicate possible gain factors.

[0044] It is to be noted that using a heterodyning detection technique, in accordance with an embodiment of the present invention, enables simultaneous excitation and subsequent simultaneous detection of photoacoustic waves generated in bolus 40 by light at a plurality of different wavelengths. For example, assume that blood bolus 40 is simultaneously illuminated with light at three different wavelengths in order to determine glucose concentration in the blood bolus. Assume further that the pulse rate of the light is different for each wavelength and that during illumination a reference acoustic wave is focused on the bolus. The photoacoustic response of the blood bolus will result in generation of a strong photoacoustic signal at a different beat frequency for each of the three wavelengths. The signals at each of the frequencies can be simultaneously detected and identified using appropriate filtering and signal processing techniques known in the art.

[0045] It is to be further recognized that a heterodyning detection technique, in accordance with an embodiment of the present invention, can be used to determine a location of the source of photoacoustic waves generated in a body. Energy in a reference acoustic beam can be focused to a relatively small focal volume at a known location. Photoacoustic signals generated in the body that are characterized by a frequency equal to a beat frequency must have originated in the reference beam focal volume.

[0046] In some embodiments of the present invention, at least one light pulse 42 comprises a train of light pulses and glucometer 20' measures a change in reflectance following each light pulse in the train of light pulses. Optionally, the pulse width and pulse repetition rate are such that between light pulses bolus 40 cools down to a temperature substantially equal to the ambient temperature. Optionally, energy reflectance of bolus 40 is measured by reflecting an ultrasound pulse 46 from the bolus before and after each light pulse in the train of light pulses to determine a change in reflectance resulting from illumination by the light pulse. In some embodiments of the present invention, the pulse width of the light pulses is

about 10 nanoseconds and the pulse repetition rate is about 10 kHz. In some embodiments of the present invention, ultrasound pulses 46 are pulses of ultrasound waves at a frequency of at least 10 MHz.

[0047] In some embodiments of the present invention changes in acoustic impedance of blood bolus 40 are measured to determine blood glucose levels while bolus 40 is being heated by at least one light pulse 42 or shortly thereafter. To perform the measurements glucometer 20' reflects ultrasound from bolus 40 while the bolus is being heated by light pulse 42, or shortly thereafter, during a time period in which photoacoustic waves are being generated in bolus 40 responsive to illumination by the light pulse.

[0048] Ultrasound waves reflected from bolus 40 while it is expanding following absorption of energy from light pulse 42 often carry a very definite and relatively easily identified signature - a very large Doppler shift. During expansion, while a photoacoustic wave is being generated in blood bolus 40 a surface of a volume of blood in bolus 40 expands at a speed close to the speed of sound. As a result, sound waves reflected from bolus 40 while it is being heated by light pulse 42, are generally characterized by very large Doppler shifts.

[0049] Figs. 2A and 2B show a glucometer 21, similar to glucometer 20, operating to assay glucose in a person's blood by reflecting ultrasound waves from blood bolus 40 while the blood bolus is being heated by light that is absorbed by blood.

[0050] In Fig. 2A, glucometer 21 locates at least one blood vessel 22 and blood bolus 40 and, optionally, performs acoustic calibration measurements. In Fig. 2B controller 30 controls light source 28 to illuminate bolus 40 with a light pulse 42 and while bolus is being illuminated by the light pulse, controls ultrasound transducer 26 to transmit a pulse 51 of ultrasound that is focused on the blood bolus. As a result of illumination of bolus 40 by light pulse 42, bolus 40 expands rapidly. The surface of the bolus moves outward from the bolus at speeds close to the speed of sound and generates a photoaconstic wave. Energy from ultrasound pulse 51 is reflected from the rapidly moving surface of bolus 40 in an ultrasound pulse 54 having a large Doppler shift generated by the velocity at which the surface moves. The intensity of Doppler shifted pulse 54 is a function of the energy reflectance of the surface of bolus 40 which in turn is a function of a difference between the absorption coefficieat of light in blood bolus 40 and the absorption coefficient of tissue surrounding the bolus.

[0051] In accordance with an embodiment of the present invention, glucometer 21 measures intensity of Doppler shifted waves reflected from a blood bolus while the blood bolus is being illuminated with light for different wavelengths of the illuminating light. The measurements are used to determine absorption coefficients for blood at the wavelengths and a concentration of glucose in the blood. In some embodiments of the present invention, the measurements are corrected responsive to acoustic calibration measurements and the corrected measurements are used to determine glucose concentration.

[0052] By way of another example of assaying substances other than glucose, in accordance with embodiments of the present invention, by choosing an appropriate set of wavelengths for light used to illuminate regions of a person's body, concentrations of cholesterol in the regions can be determined. Light at wavelengths between 1.70-1.80 microns is absorbed by cholesterol and light at these wavelengths can be used in the practice of the present invention to determine cholesterol concentrations in regions of a person's body.

[0053] Methods of determining concentration of a substance in a body, in accordance with an embodiment of the present invention provide the concentration of the substances as a function of position in the body. In some embodiments of the present invention a spatial map of concentrations of a substance in a body is used to image features and/or components of the body.

[0054] Figs. 3A and 3B schematically show a "glucometer" 100, hereinafter referred to as "assay imager 100", used, by way of example, to assay and image cholesterol in a person's body in accordance with an embodiment of the present invention. Assay imager 100 comprises a visual display 102. In Fig. 3A, controller 30 controls at least one transducer 26 to locate a region 36 of at least one blood vessel 22. In Fig. 3B assay imager 100 then illuminates region 36 with light at wavelengths suitable for assaying cholesterol and determines concentrations of cholesterol in region 36 using methods similar to those described above for determining concentrations of glucose. Controller 30 then controls transducer 26 to locate other regions of at least one blood vessel 22 and proceeds to determine concentrations of cholesterol in these other regions. A map 110 of cholesterol concentration as a function of position for regions scanned by assay imager 100 is displayed on visual display 102. At least one blood vessel 22 is compromised by plaque deposits 104 and 106 at two locations. The locations of plaque deposits 104 and 106 are visible on cholesterol concentration map 110 shown on display 102.

[0055] By way of another example, assay imager 100 may also be used to image tumors. Tumorous growths generally have an unusually high concentration of blood vessels in the growths and in tissue surrounding the growths. By imaging a region of tissue with assay imager 100 using light at a wavelength that is strongly absorbed by blood, in accordance with an embodiment of the present invention, tissue having an unusually high density of blood vessels can be clearly contrasted against tissue having normal blood vessel density. As a result, tumor tissue in the imaged region can often be clearly contrasted with healthy tissue.

[0056] In some embodiments of the present invention, an "assay image" of a region of the body responsive to concentration of a substance in the region that is provided by an assay imager is overlaid on an image of the region provided by another imaging modality, such as for exam-

ple an MRI or CT image. In some embodiments of the present invention, the image on which the assay image is overlaid is an ultrasound image. Optionally the ultrasound image is acquired using the same ultrasound detectors that are used to acquire the assay image. By using the same ultrasound detectors for acquiring both the assay image and the ultrasound image on which the assay image is overlaid the assay image is automatically registered to the ultrasound image.

[0057] In the description and claims of the present application, each of the verbs, "comprise" "include" and "have", and conjugates thereof, are used to indicate that the object or objects of the verb are not necessarily a complete listing of members, components, elements or parts of the subject or subjects of the verb.

[0058] The present invention has been described using detailed descriptions of embodiments thereof that are provided by way of example and are not intended to limit the scope of the invention. The described embodiments comprise different features, not all of which are required in all embodiments of the invention. Some embodiments of the present invention utilize only some of the features or possible combinations of the features. Variations of embodiments of the present invention that are described and embodiments of the present invention comprising different combinations of features noted in the described embodiments will occur to persons of the art. The scope of the invention is limited only by the following claims.

Claims

1. Apparatus (20, 21, 100) for assaying a component of a blood bolus in a body comprising:

a light source (28) controllable to provide pulses of light having a wavelength at which the radiation is absorbed by the component and generates photoacoustic waves in the region;
at least one transducer (26) for sensing ultrasound that generates signals responsive to ultrasound energy incident thereon; and
a controller (30) that:

a) locates the blood bolus in a volume of the body comprising the blood bolus;
b) controls the light source to illuminate the volume comprising the blood bolus with at least one pulse of light having a wavelength at which light is absorbed by the component so as to generate photoacoustic waves in the volume that arc incident on the at least one sensing transducer;
c) receives signals generated by the at least one sensing transducer (26) responsive to the photoacoustic waves and uses them to determine locations of the origins of the photoacoustic waves;
d) uses signals generated by the at least one sensing transducer (26) responsive to those photoacoustic waves having an origin determined to be located in the blood bolus to determine an absorption coefficient for the light in the blood bolus; and
e) uses the determined absorption coefficient to determine concentration of the component in the blood bolus.

2. Apparatus according to claim 1 and wherein the controller (30) controls the light source (28) to illuminate the volume with at least one pulse of light at at least one other wavelength, and repeats c-e.

3. Apparatus according to claim 1 or claim 2 wherein to locate the blood bolus the controller (30):

a) controls the light source (28) to illuminate the volume of the body that comprises the bolus with at least one pulse of light having a wavelength at which light is preferentially absorbed by blood so as to generate photoacoustic waves in the volume that are incident on the at least one sensing transducer;
b) uses signals generated by the at least one sensing transducer (26) responsive to the photoacoustic waves to map concentration of blood in the volume as a function of position; and
c) uses the determined concentration map to determine a location for the blood bolus.

4. Apparatus according to claim any of claims 1-3 and comprising at least one transducer (26) controllable to transmit ultrasound into the body.

5. Apparatus according to claim 4 wherein the controller (30) controls the at least one transmitting transducer (26) to transmit ultrasound into the volume and processes signals from the at least one sensing transducer responsive to reflections from the transmitted ultrasound to determine the location of the bolus.

6. Apparatus according to claim 5 wherein the bolus is located to within an uncertainty of less than 5 wavelengths of the ultrasound in at least one direction.

7. Apparatus according to claim 5 wherein the bolus is located to within an uncertainty of less than 3 wavelengths of the ultrasound in at least one direction.

8. Apparatus according to claim 5 wherein the bolus is located to within an uncertainty of about a wavelength of the ultrasound in at least one direction.

9. Apparatus according to any of claims 4-8 wherein the at least one light pulse comprises at least one

train of light pulses radiated at a pulse repetition rate.

10. Apparatus according to claim 9 wherein the controller (30):

controls a transmitting transducer (26) of the at least one transmitting transducer to focus an acoustic reference beam on the blood bolus, which reference beam has a frequency that is shifted from the pulse repetition frequency of the at least one light pulse train by an offset frequency and has an intensity that causes the bolus to respond non-linearly to acoustic stimuli;
receives signals provided by a sensing transducer responsive to acoustic waves at the offset frequency that are incident on the transducer; and
uses the signals to determine the absorption coefficient.

11. Apparatus according to claim 10 wherein the controller (30) controls the light source (28) to illuminate the volume with at least one other light pulse train **characterized by** a different wavelength and pulse repetition rate and repeats c-e.

12. Apparatus according to claim 11 wherein the light pulse train and at least one other light pulse train illuminate the region substantially simultaneously.

13. Apparatus according to any of claims 4-12 wherein a transducer (26) of the at least one transmitting and/or sensing transducer is coupled to the body and the controller (30):

controls the at least one transmitting transducer (26) to transmit ultrasonic waves, which are incident on a sensing transducer (26) that generates signals responsive thereto;
receives the generated signals; and
processes the signals to determine acoustic properties of the coupling between the transducer (26) coupled to the body and the body.

14. Apparatus according to any of the preceding claims wherein the controller (30) processes signals from the at least one sensing transducer (26) to determine acoustic properties of material in the body.

15. Apparatus according to claim 14 wherein the determined absorption coefficient is adjusted responsive to the measured acoustic properties.

16. Apparatus according to any of the preceding claims wherein the component is LDL cholesterol or oxidized LDL cholesterol.

17. Apparatus according to any of the preceding claims wherein the component is glucose.

Patentansprüche

1. Vorrichtung (20, 21, 100) zum Analysieren einer Komponente eines Blutbolus in einem Körper mit:

einer Lichtquelle (28), die so steuerbar ist, daß sie Lichtimpulse mit einer Wellenlänge liefert, bei der die Strahlung durch die Komponente absorbiert wird und
photoakustische Wellen in dem Bereich erzeugt;
mindestens einem Wandler (26) zum Erfassen von Ultraschall, der Signale als Reaktion auf darauf auftreffende Ultraschallenergie erzeugt; und
einer Steuerung (30), die:

a) den Blutbolus in einem Volumen des Bluts lokalisiert, das den Blutbolus aufweist;
b) die Lichtquelle so steuert, daß sie das den Blutbolus aufweisende Volumen mit mindestens einem Lichtimpuls mit einer Wellenlänge bestrahlt, bei der Licht durch die Komponente absorbiert wird, um so photoakustische Wellen im Volumen zu erzeugen, die auf den mindestens einen Erfassungswandler auftreffen;
c) Signale empfängt, die durch den mindestens einen Erfassungswandler (26) als Reaktion auf die photoakustischen Wellen erzeugt werden, und sie verwendet, um Lagen der Ursprünge der photoakustischen Wellen zu bestimmen;
d) Signale verwendet, die durch den mindestens einen Erfassungswandler (26) als Reaktion auf jene photoakustischen Wellen mit einem Ursprung erzeugt werden, von dem bestimmt wird, daß er im Blutbolus liegt, um einen Absorptionskoeffizienten für das Licht im Blutbolus zu bestimmen; und
e) den bestimmten Absorptionskoeffizienten verwendet, um die Konzentration der Komponente im Blutbolus zu bestimmen.

2. Vorrichtung nach Anspruch 1 und wobei die Steuerung (30) die Lichtquelle (28) so steuert, daß sie das Volumen mit mindestens einem Lichtimpuls mit mindestens einer anderen Wellenlänge bestrahlt, und c) bis e) wiederholt.

3. Vorrichtung nach Anspruch 1 oder Anspruch 2, wobei die Steuerung (30) zum Lokalisieren des Blutbolus:

a) die Lichtquelle (28) so steuert, daß sie das

Volumen des Körpers, das den Bolus aufweist, mit mindestens einem Lichtimpuls mit einer Wellenlänge bestrahlt, bei der Licht durch Blut vorzugsweise absorbiert wird, um so photoakustische Wellen im Volumen zu erzeugen, die auf den mindestens einen Erfassungswandler auftreffen;

b) Signale verwendet, die durch den mindestens einen Erfassungswandler (26) als Reaktion auf die photoakustischen Wellen erzeugt werden, um die Blutkonzentration im Volumen als Funktion der Position in einem Kennfeld abzubilden; und

c) das bestimmte Konzentrationskennfeld verwendet, um eine Lage für den Blutbolus zu bestimmen.

4. Vorrichtung nach einem der Ansprüche 1 bis 3 und mit mindestens einem Wandler (26), der so steuerbar ist, daß er Ultraschall in den Körper sendet.

5. Vorrichtung nach Anspruch 4, wobei die Steuerung (30) den mindestens einen Sendewandler (26) so steuert, daß er Ultraschall in das Volumen sendet, und Signale vom mindestens einen Erfassungswandler als Reaktion auf Reflexionen vom gesendeten Ultraschall verarbeitet, um die Lage des Bolus zu bestimmen.

6. Vorrichtung nach Anspruch 5, wobei der Bolus innerhalb einer Unsicherheit von weniger als 5 Wellenlängen des Ultraschalls in mindestens einer Richtung liegt.

7. Vorrichtung nach Anspruch 5, wobei der Bolus innerhalb einer Unsicherheit von weniger als 3 Wellenlängen des Ultraschalls in mindestens einer Richtung liegt.

8. Vorrichtung nach Anspruch 5, wobei der Bolus innerhalb einer Unsicherheit von etwa einer Wellenlänge des Ultraschalls in mindestens einer Richtung liegt.

9. Vorrichtung nach einem der Ansprüche 4 bis 8, wobei der mindestens eine Lichtimpuls mindestens eine Folge von Lichtimpulsen aufweist, die mit einer Impulsfolgefrequenz abgestrahlt werden.

10. Vorrichtung nach Anspruch 9, wobei die Steuerung (30):

einen Sendewandler (26) des mindestens einen Sendewandlers so steuert, daß er einen akustischen Referenzstrahl auf den Blutbolus fokussiert, wobei der Referenzstrahl eine Frequenz hat, die gegenüber der Impulsfolgefrequenz der mindestens einen Lichtimpulsfolge um eine Versatzfrequenz verschoben ist, und eine Stärke hat, die den Bolus veranlaßt, auf akustische Stimuli nichtlinear zu reagieren;

Signale empfängt, die durch einen Erfassungswandler als Reaktion auf akustische Wellen mit der Versatzfrequenz bereitgestellt werden und auf den Wandler auftreffen; und

die Signale verwendet, um den Absorptionskoeffizienten zu bestimmen.

11. Vorrichtung nach Anspruch 10, wobei die Steuerung (30) die Lichtquelle (28) so steuert, daß sie das Volumen mit mindestens einer anderen Lichtimpulsfolge bestrahlt, die durch eine unterschiedliche Wellenlänge und Impulsfolgefrequenz **gekennzeichnet** ist, und c) bis e) wiederholt.

12. Vorrichtung nach Anspruch 11, wobei die Lichtimpulsfolge und mindestens eine andere Lichtimpulsfolge den Bereich im wesentlichen gleichzeitig bestrahlen.

13. Vorrichtung nach einem der Ansprüche 4 bis 12, wobei ein Wandler (26) des mindestens einen Sende- und/oder Erfassungswandlers mit dem Körper gekoppelt ist und die Steuerung (30):

den mindestens einen Sendewandler (26) so steuert, daß er Ultraschallwellen sendet, die auf einen Erfassungswandler (26) auftreffen, der Signale als Reaktion darauf erzeugt;

die erzeugten Signale empfängt; und

die Signale verarbeitet, um akustische Eigenschaften der Kopplung zwischen dem mit dem Körper gekoppelten Wandler (26) und dem Körper zu bestimmen.

14. Vorrichtung nach einem der vorstehenden Ansprüche, wobei die Steuerung (30) Signale vom mindestens einem Erfassungswandler (26) verarbeitet, um akustische Eigenschaften von Material im Körper zu bestimmen.

15. Vorrichtung nach Anspruch 14, wobei der bestimmte Absorptionskoeffizient als Reaktion auf die gemessenen akustischen Eigenschaften justiert wird.

16. Vorrichtung nach einem der vorstehenden Ansprüche, wobei die Komponente LDL-Cholesterin oder oxidiertes LDL-Cholesterin ist.

17. Vorrichtung nach einem der vorstehenden Ansprüche, wobei die Komponente Glucose ist.

Revendications

1. Appareil (20, 21, 100) de dosage d'un composant

d'un bolus sanguin dans un corps comprenant :

une source lumineuse (28) commandable pour fournir des impulsions de lumière ayant une longueur d'onde à laquelle le rayonnement est absorbé par le composant et génère des ondes photo-acoustiques dans la région ;
au moins un transducteur (26) pour détecter des ultrasons qui génère des signaux en réponse à l'énergie ultrasonore incidente sur celui-ci ; et
un dispositif de commande (30) qui :

a) localise le bolus sanguin dans un volume du corps comprenant le bolus sanguin ;
b) commande la source lumineuse pour illuminer le volume comprenant le bolus sanguin avec au moins une impulsion de lumière ayant une longueur d'onde à laquelle la lumière est absorbée par le composant afin de générer des ondes photo-acoustiques dans le volume qui sont incidentes sur ledit au moins un transducteur de détection ;
c) reçoit des signaux générés par ledit au moins un transducteur de détection (26) en réponse aux ondes photo-acoustiques et les utilise pour déterminer des emplacements des origines des ondes photo-acoustiques ;
d) utilise des signaux générés par ledit au moins un transducteur de détection (26) en réponse à ces ondes photo-acoustiques ayant une origine déterminée à localiser dans le bolus sanguin pour déterminer un coefficient d'absorption pour la lumière dans le bolus sanguin ; et
e) utilise le coefficient d'absorption déterminé pour déterminer une concentration du composant dans le bolus sanguin.

2. Appareil selon la revendication 1 et dans lequel le dispositif de commande (30) commande la source lumineuse (28) pour illuminer le volume avec au moins une impulsion de lumière à au moins une autre longueur d'onde, et répète les points c à e.

3. Appareil selon la revendication 1 ou la revendication 2 dans lequel pour localiser le bolus sanguin, le dispositif de commande (30) :

a) commande la source lumineuse (28) pour illuminer le volume du corps qui comprend le bolus avec au moins une impulsion de lumière ayant une longueur d'onde à laquelle la lumière est préférentiellement absorbée par le sang afin de générer des ondes photo-acoustiques dans le volume qui sont incidentes sur ledit au moins un transducteur de détection ;
b) utilise des signaux générés par ledit au moins un transducteur de détection (26) en réponse aux ondes photo-acoustiques pour cartographier une concentration de sang dans le volume en fonction de la position ; et
c) utilise la carte de concentration déterminée pour déterminer un emplacement du bolus sanguin.

4. Appareil selon l'une quelconque des revendications 1 à 3 et comprenant au moins un transducteur (26) commandable pour émettre des ultrasons dans le corps.

5. Appareil selon la revendication 4 dans lequel le dispositif de commande (30) commande ledit au moins un transducteur d'émission (26) pour émettre un ultrason dans le volume et traite des signaux reçus dudit au moins un transducteur de détection en réponse à des réflexions provenant de l'ultrason émis pour déterminer l'emplacement du bolus.

6. Appareil selon la revendication 5 dans lequel le bolus est situé dans une plage d'incertitude inférieure à 5 longueurs d'onde de l'ultrason dans au moins une direction.

7. Appareil selon la revendication 5 dans lequel le bolus est situé dans une plage d'incertitude inférieure à 3 longueurs d'onde de l'ultrason dans au moins une direction.

8. Appareil selon la revendication 5 dans lequel le bolus est situé dans une plage d'incertitude d'environ une longueur d'onde de l'ultrason dans au moins une direction.

9. Appareil selon l'une quelconque des revendications 4 à 8 dans lequel ladite au moins une impulsion de lumière comprend au moins un train d'impulsions de lumière irradiée à une fréquence de répétition d'impulsions.

10. Appareil selon la revendication 9 dans lequel le dispositif de commande (30) :

commande un transducteur d'émission (26) dudit au moins un transducteur d'émission pour focaliser un faisceau acoustique de référence sur le bolus sanguin, lequel faisceau de référence a une fréquence qui est décalée de la fréquence de répétition d'impulsions dudit au moins un train d'impulsions de lumière d'une fréquence de décalage et a une intensité qui fait que le bolus répond non linéairement aux stimuli acoustiques ;
reçoit des signaux fournis par un transducteur de détection en réponse à des ondes acoustiques à la fréquence de décalage qui sont inci-

dentes sur le transducteur ; et
utilise les signaux pour déterminer le coefficient d'absorption.

11. Appareil selon la revendication 10 dans lequel le dispositif de commande (30) commande la source lumineuse (28) pour illuminer le volume avec au moins un autre train d'impulsions de lumière **caractérisé par** une longueur d'onde différente et une fréquence de répétition d'impulsions et répète les points c à e.

12. Appareil selon la revendication 11 dans lequel le train d'impulsions de lumière et ledit au moins un autre train d'impulsions de lumière illuminent la région substantiellement simultanément.

13. Appareil selon l'une quelconque des revendications 4 à 12 dans lequel le transducteur (26) dudit au moins un transducteur d'émission et/ou détection est couplé au corps et le dispositif de commande (30) :

commande ledit au moins un transducteur d'émission (26) pour émettre des ondes ultrasonores, qui sont incidentes sur un transducteur de détection (26) qui génère des signaux en réponse à celles-ci ;
reçoit les signaux générés ; et
traite les signaux pour déterminer des propriétés acoustiques du couplage entre le transducteur (26) couplé au corps et le corps.

14. Appareil selon l'une quelconque des revendications précédentes dans lequel le dispositif de commande (30) traite des signaux reçus à partir dudit au moins un transducteur de détection (26) pour déterminer des propriétés acoustiques du matériau dans le corps.

15. Appareil selon la revendication 14 dans lequel le coefficient d'absorption déterminé est ajusté en réponse aux propriétés acoustiques mesurées.

16. Appareil selon l'une quelconque des revendications précédentes dans lequel le composant est du cholestérol LDL ou du cholestérol LDL oxydé.

17. Appareil selon l'une quelconque des revendications précédentes dans lequel le composant est du glucose.

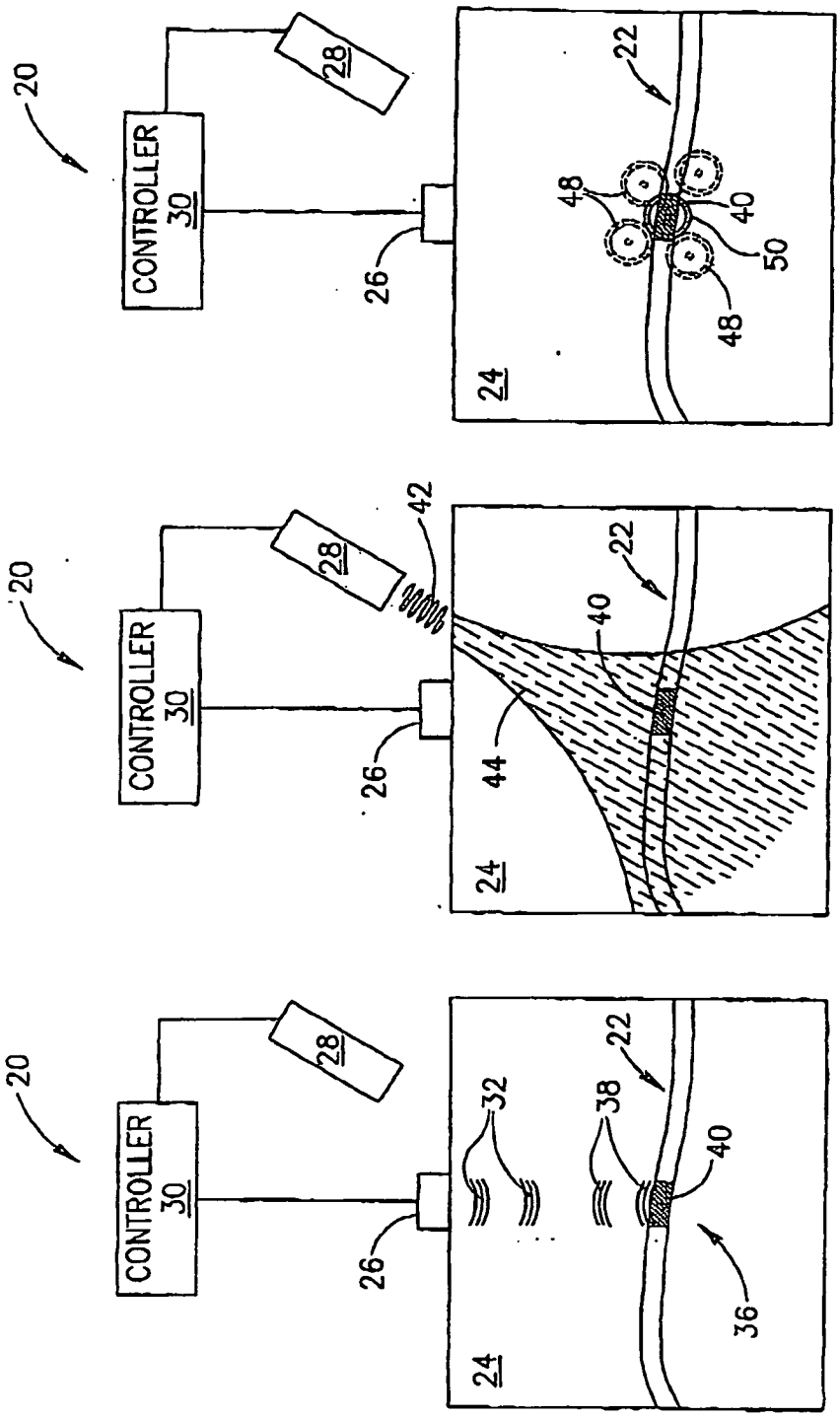

FIG.1A

FIG.1B

FIG.1C

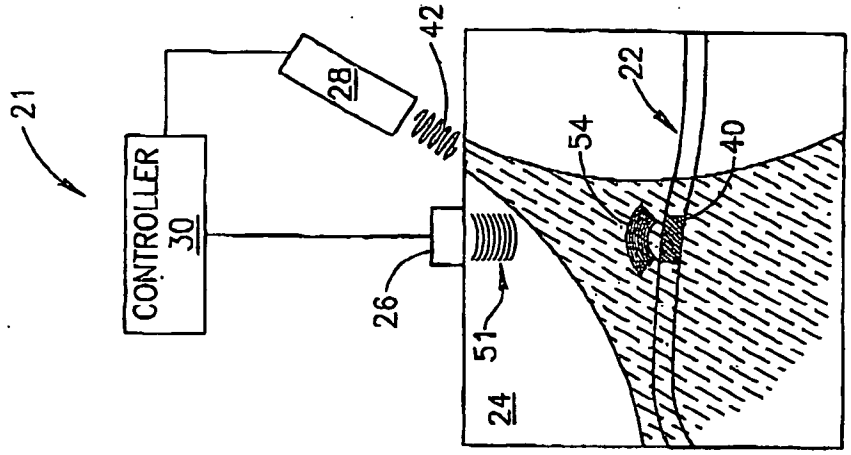
21
CONTROLLER
30
28
42
26
51
24
22
54
40

FIG.2B

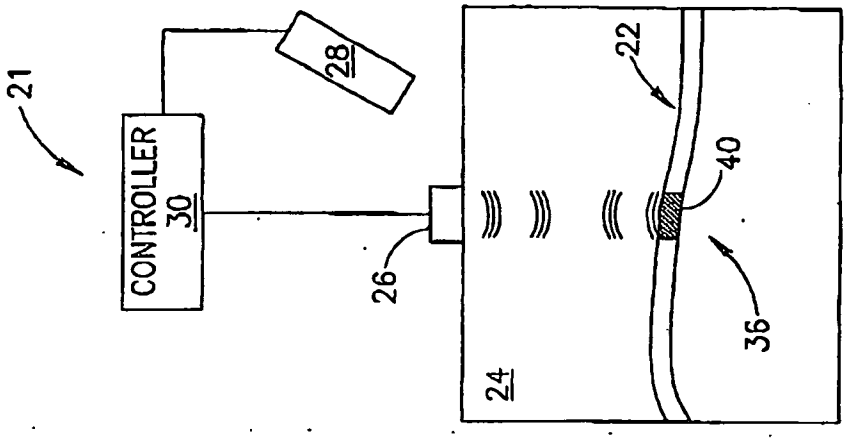
21
CONTROLLER
30
28
26
24
22
40
36

FIG.2A

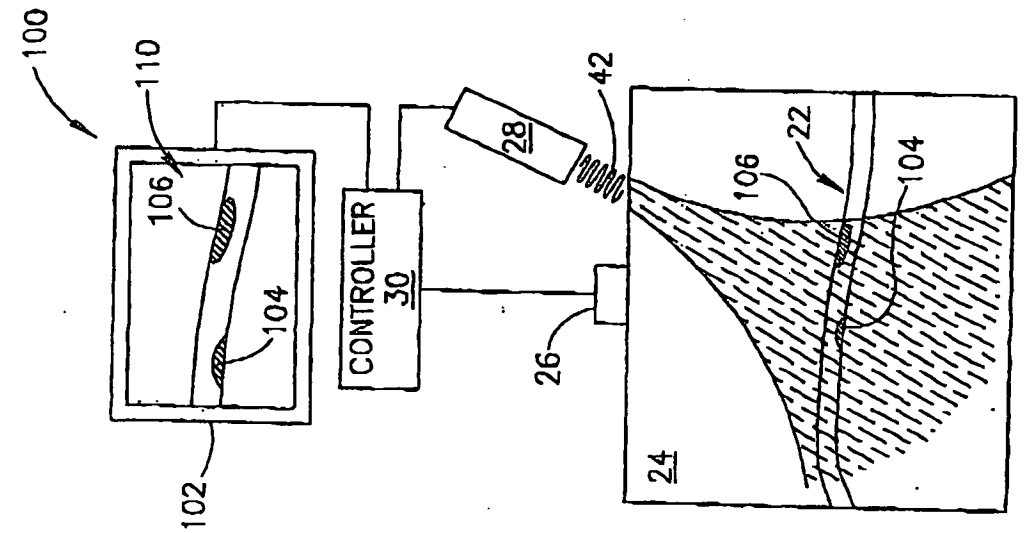
100
110
106
104
102
CONTROLLER
30
28
42
26
24
22
106
104

FIG.3B

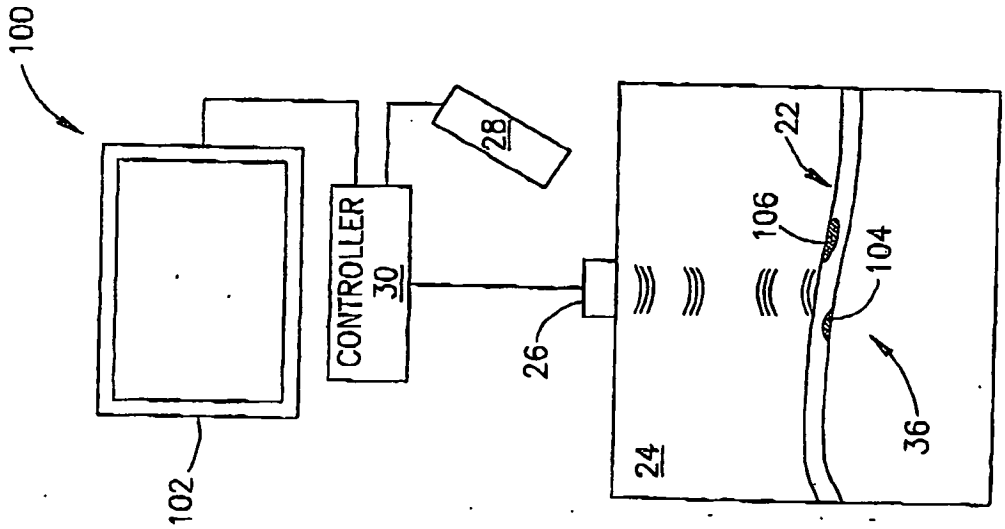
100
102
CONTROLLER
30
28
26
24
22
106
104
36

FIG.3A

专利名称(译)	光声测定和成像系统		
公开(公告)号	EP1313396B1	公开(公告)日	2006-06-28
申请号	EP2001958348	申请日	2001-08-09
[标]申请(专利权)人(译)	GLUCON		
申请(专利权)人(译)	GLUCON INC.		
当前申请(专利权)人(译)	GLUCON INC.		
[标]发明人	NAGAR RON PESACH BENNY BEN AMI UDI		
发明人	NAGAR, RON PESACH, BENNY BEN-AMI, UDI		
IPC分类号	A61B5/00 G01N29/00 A61B5/145 A61B5/1455 A61B8/00 A61B10/00		
CPC分类号	A61B5/1455 A61B5/0095 A61B5/14532 A61B8/00 A61B8/085		
优先权	138073 2000-08-24 IL		
其他公开文献	EP1313396A1		
外部链接	Espacenet		

摘要(译)

一种用于测定体内局部感兴趣区域的组分的方法，包括：用至少一个辐射脉冲照射所述区域，所述辐射脉冲具有所述辐射被所述组分吸收的波长，以产生所述区域的声学特性的变化。 ;发射超声波使其入射到该区域;测量变化对入射超声波的至少一种影响;使用测量的至少一种效应来确定该区域中辐射的吸收系数;并使用所确定的吸收系数来确定该区域中组分的浓度。