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(54) **TISSUE PATHLENGTH RESOLVED NONINVASIVE ANALYZER APPARATUS AND METHOD OF USE THEREOF**

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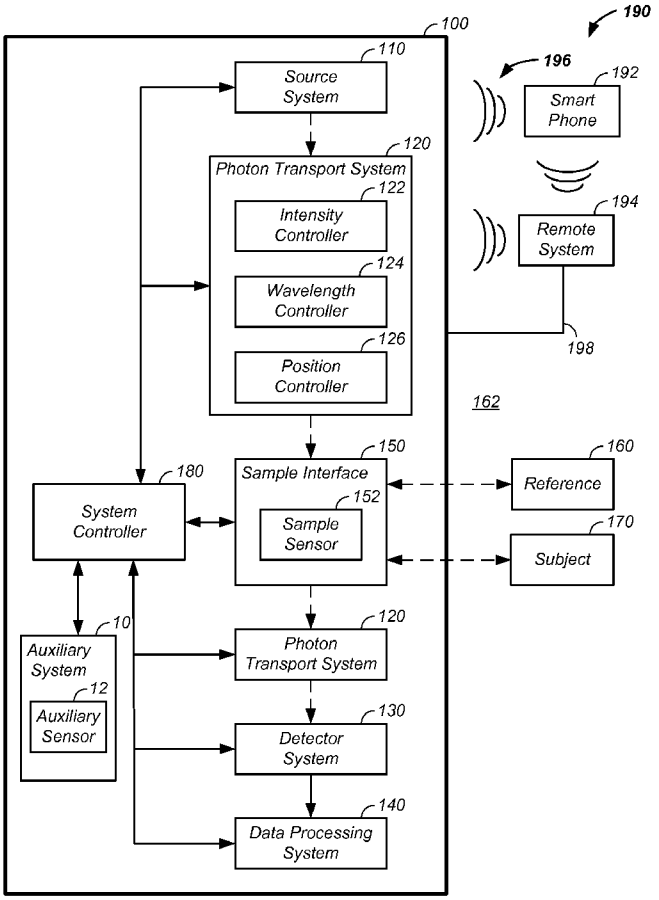
(57) **ABSTRACT**

An analyzer apparatus and method of use thereof is configured to dynamically interrogate a sample. For example, an analyzer using light interrogates a tissue sample using a temporal resolution system on a time scale of less than about one hundred nanoseconds. Optionally, near-infrared photons are introduced to a sample with a known illumination zone to detection zone distance allowing calculation of parameters related to photon pathlength in tissue and/or molar absorptivity of an individual or group through the use of the speed of light and/or one or more indices of refraction. Optionally, more accurate estimation of tissue properties are achieved through use of: knowledge of incident photon angle relative to skin, angularly resolved detector positions, anisotropy, skin temperature, environmental information, information related to contact pressure, blood glucose concentration history, and/or a skin layer thickness, such as that of the epidermis and dermis.



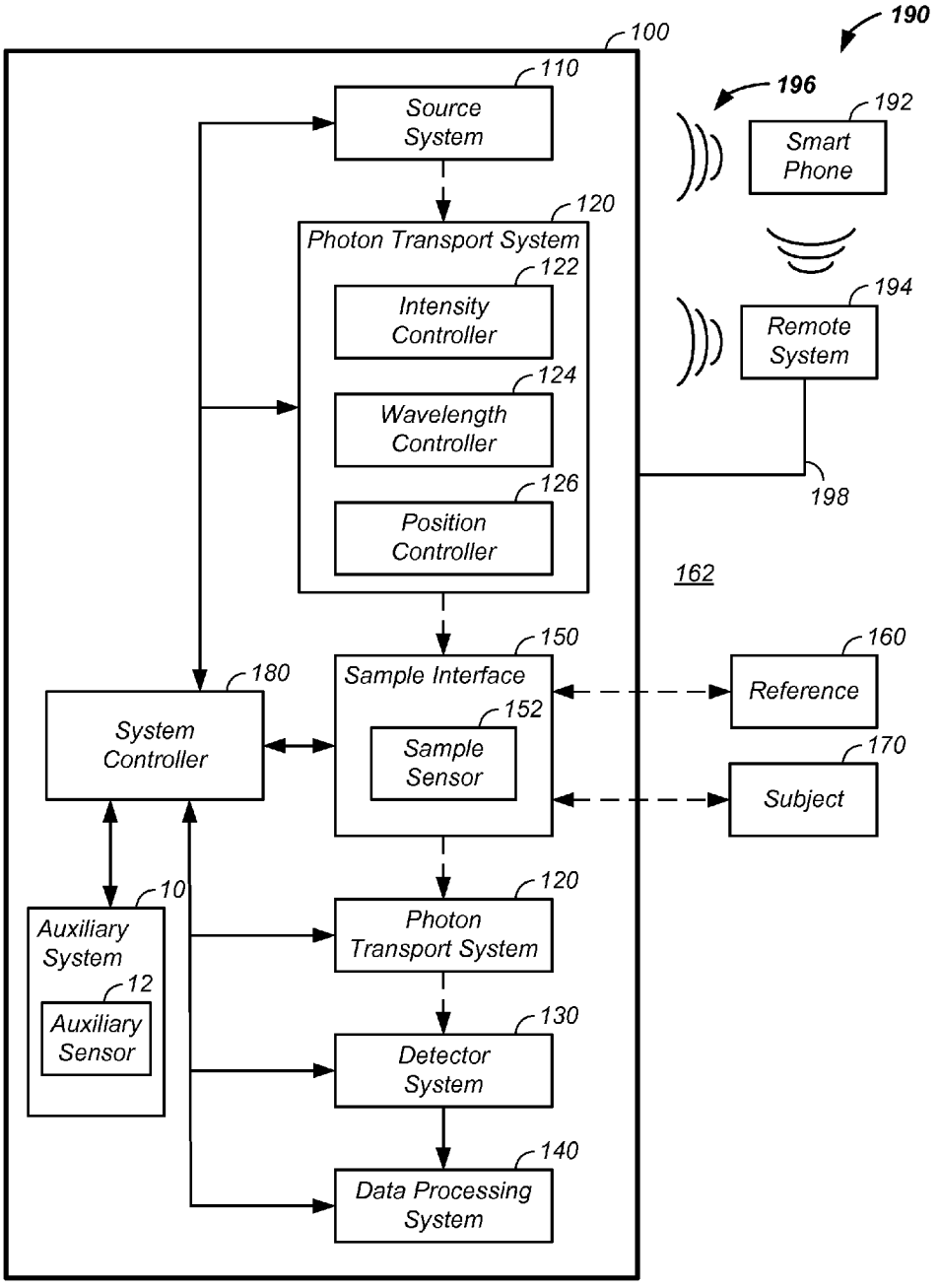

100
190
196
110
Source System
192
Smart Phone
120
Photon Transport System
122
Intensity Controller
194
Remote System
124
Wavelength Controller
126
Position Controller
198
162
150
160
180
Sample Interface
Reference
System Controller
152
Sample Sensor
170
Subject
10
120
Auxiliary System
Photon Transport System
12
Auxiliary Sensor
130
Detector System
140
Data Processing System

FIG. 1

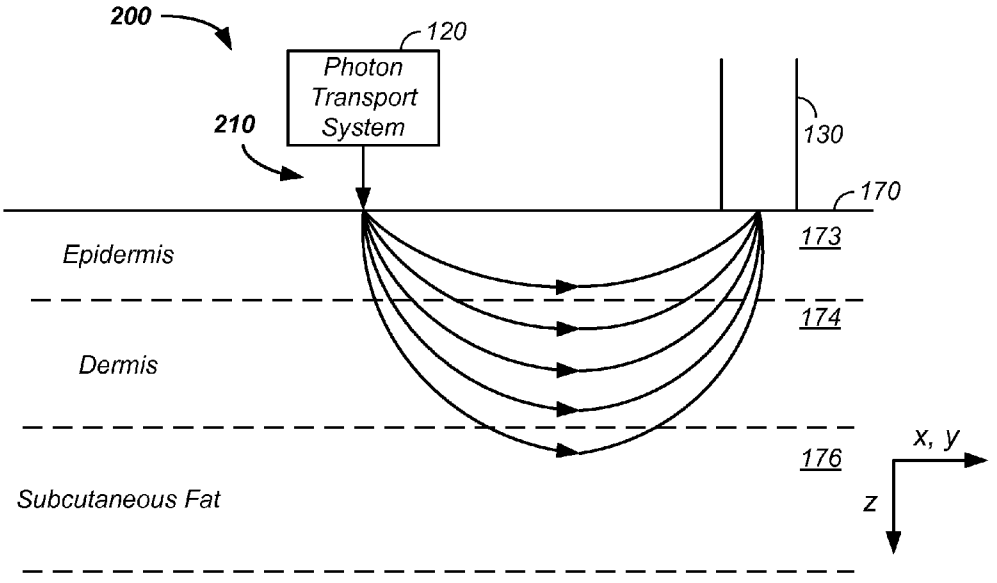

200
120
Photon Transport System
210
130
170
173
Epidermis
174
Dermis
176
Subcutaneous Fat
x, y
z

FIG. 2

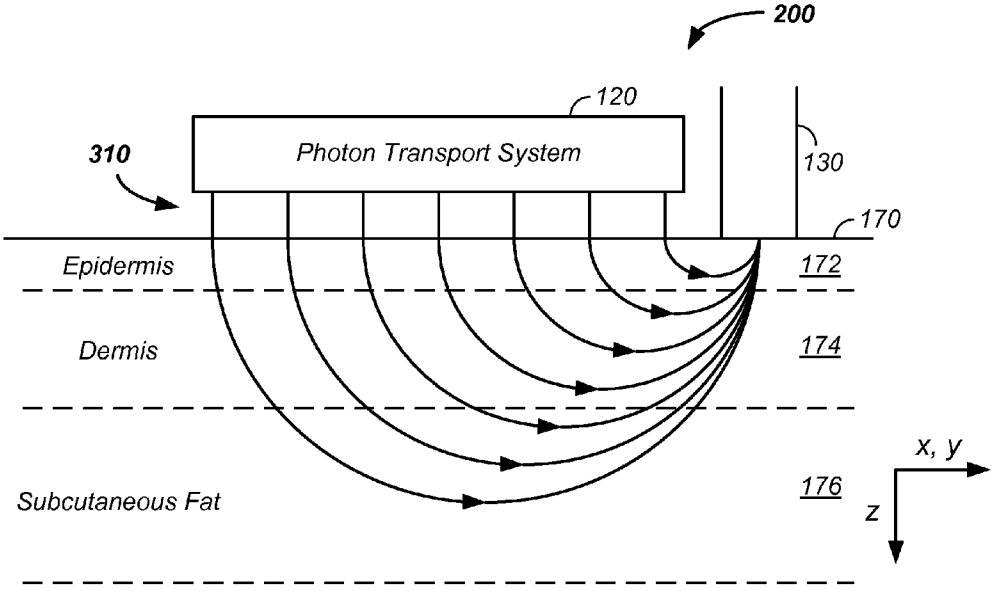

200
120
Photon Transport System
310
130
170
Epidermis
172
Dermis
174
176
Subcutaneous Fat
x, y
z

FIG. 3

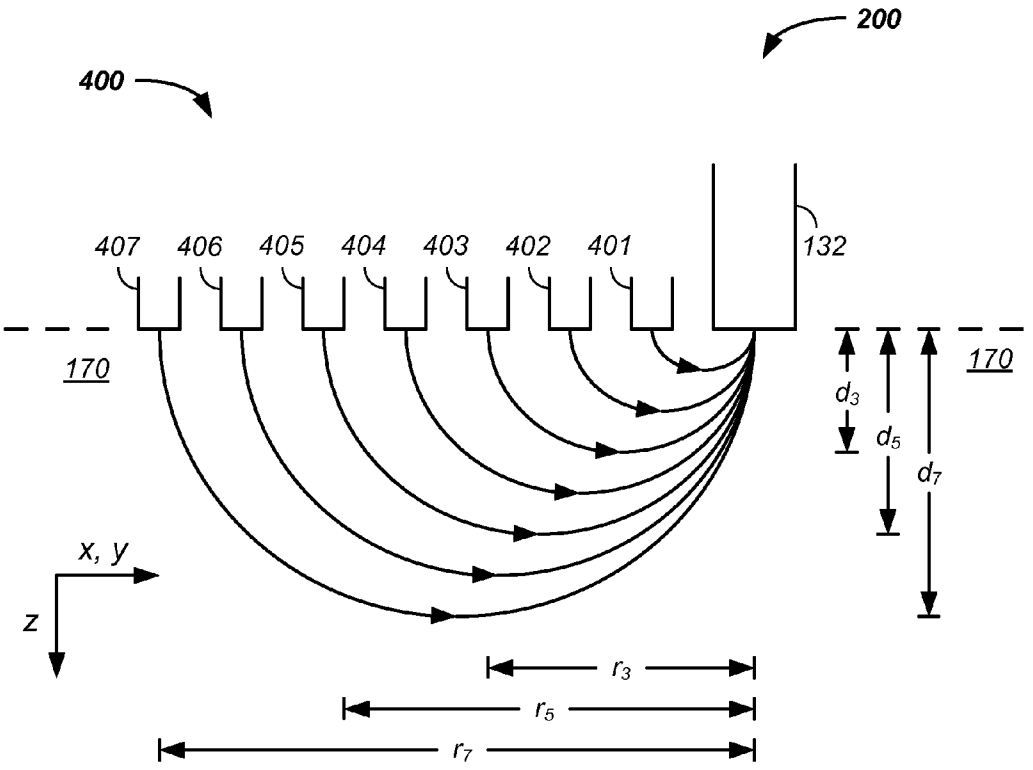

200
400
407
406
405
404
403
402
401
132
170
170
d_3
d_5
d_7
x, y
z
r_3
r_5
r_7

FIG. 4

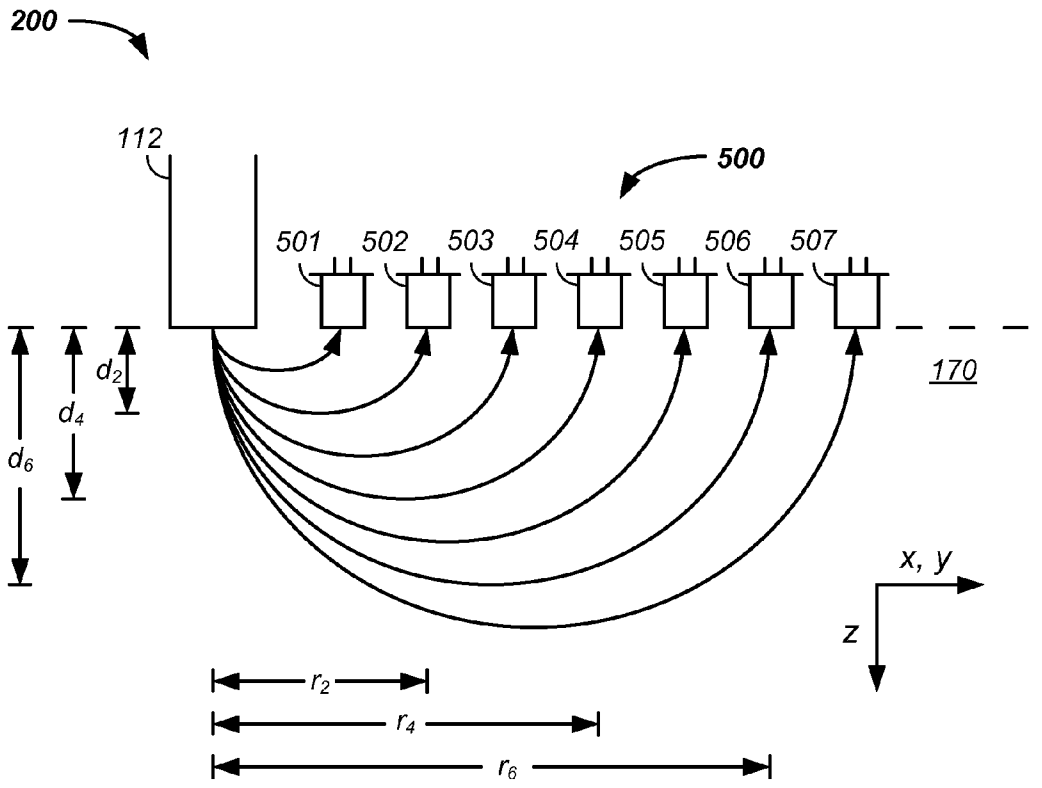


FIG. 5

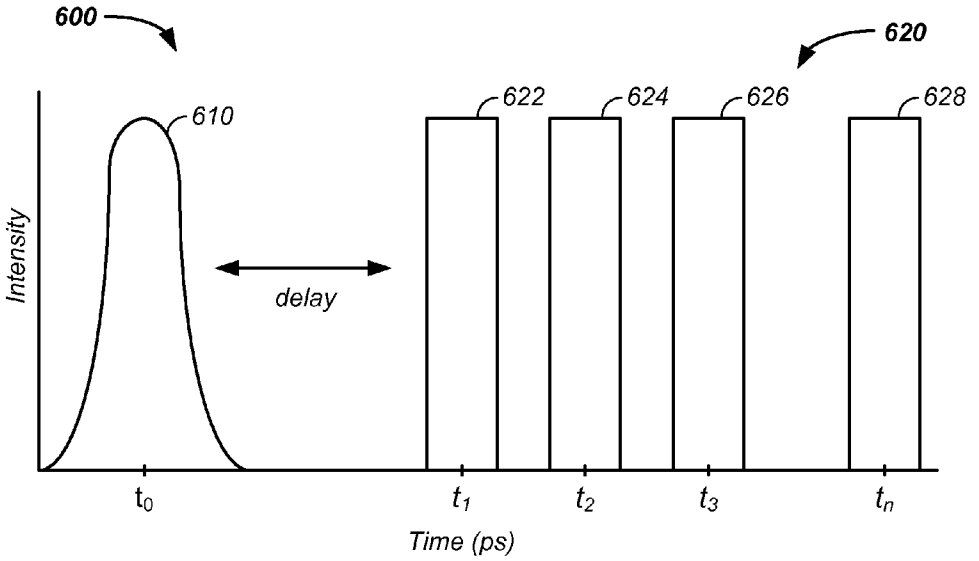


FIG. 6A

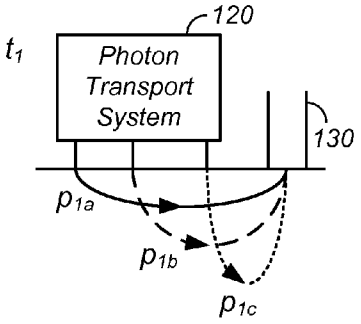


FIG. 6B

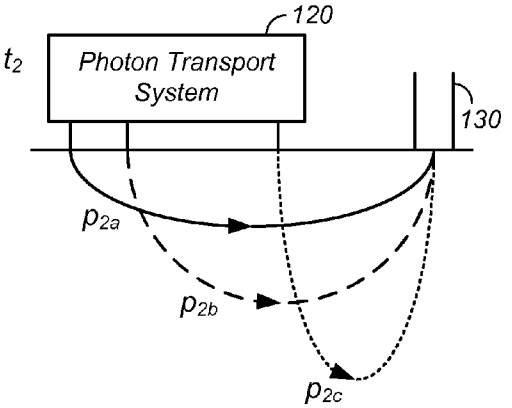


FIG. 6C

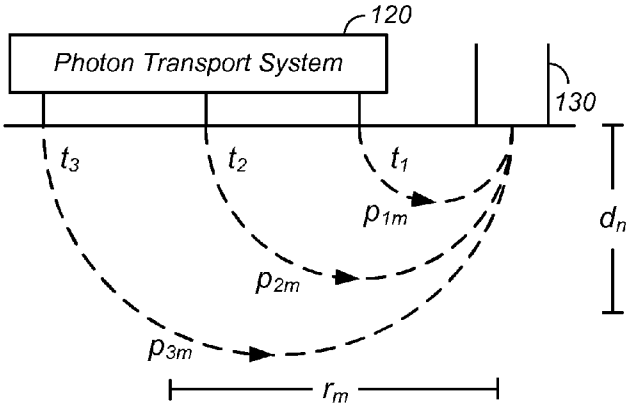


FIG. 6D

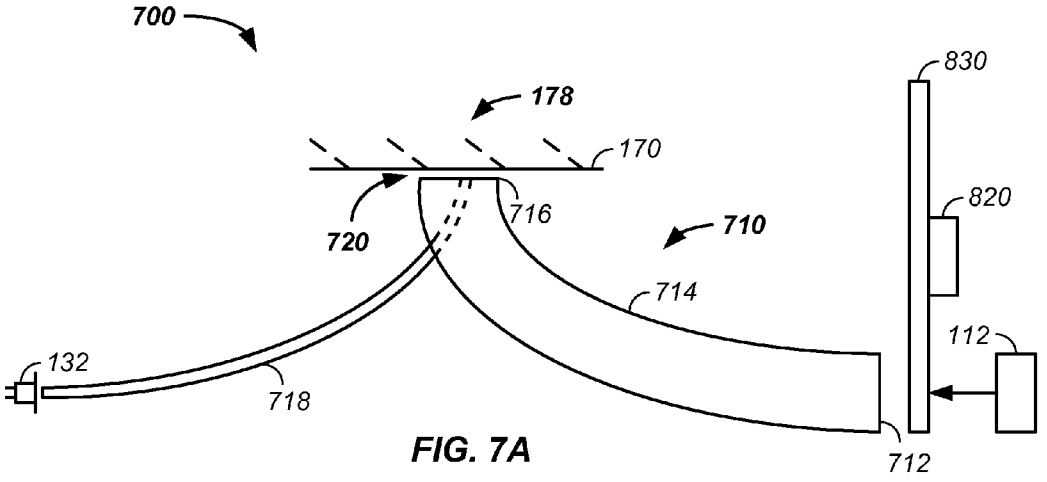


FIG. 7A

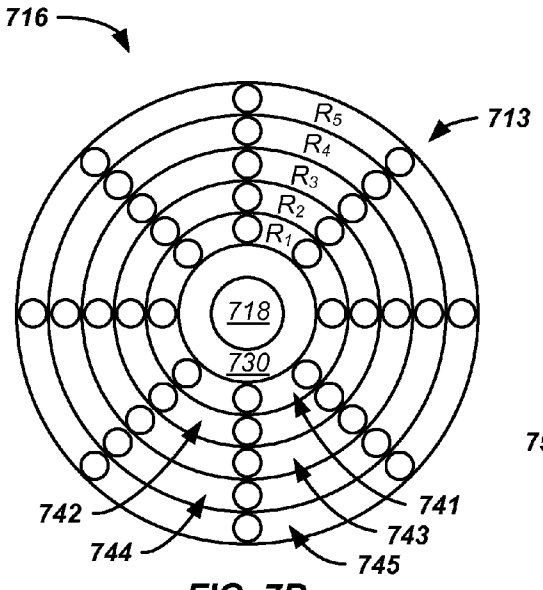


FIG. 7B

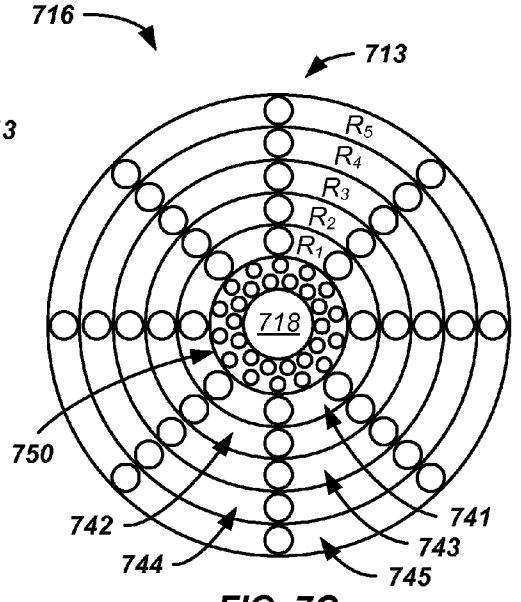


FIG. 7C

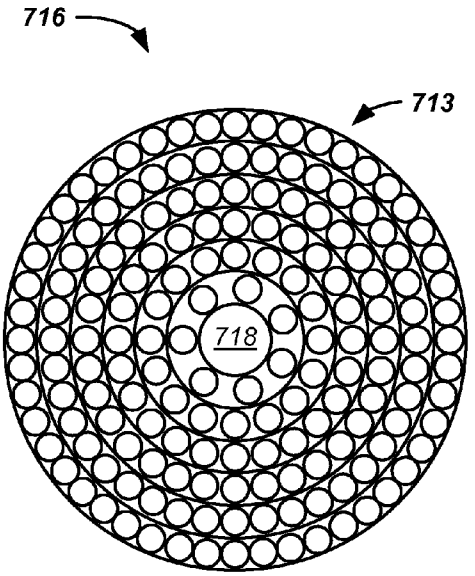


FIG. 8A

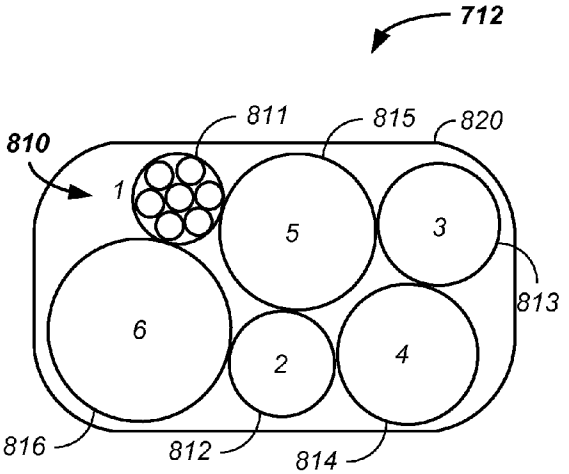


FIG. 8B

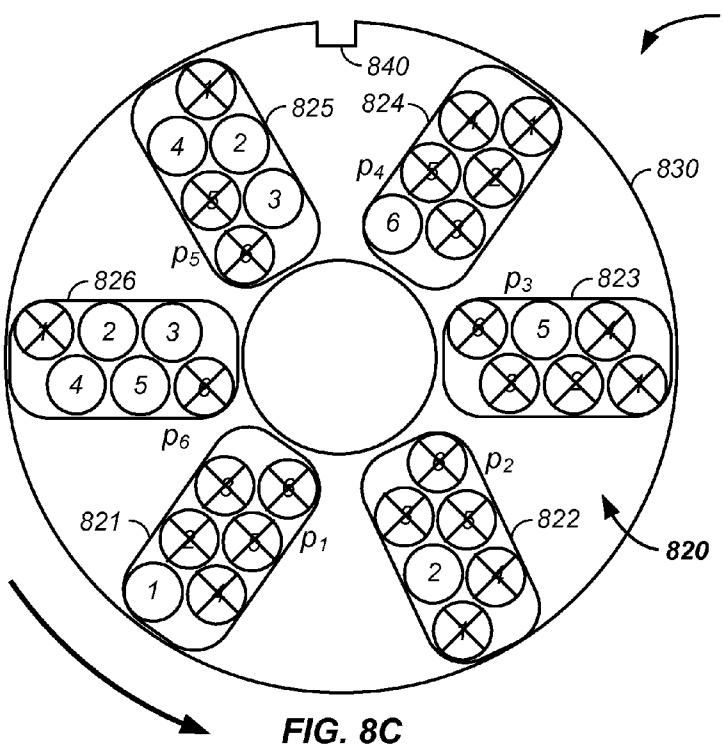


FIG. 8C

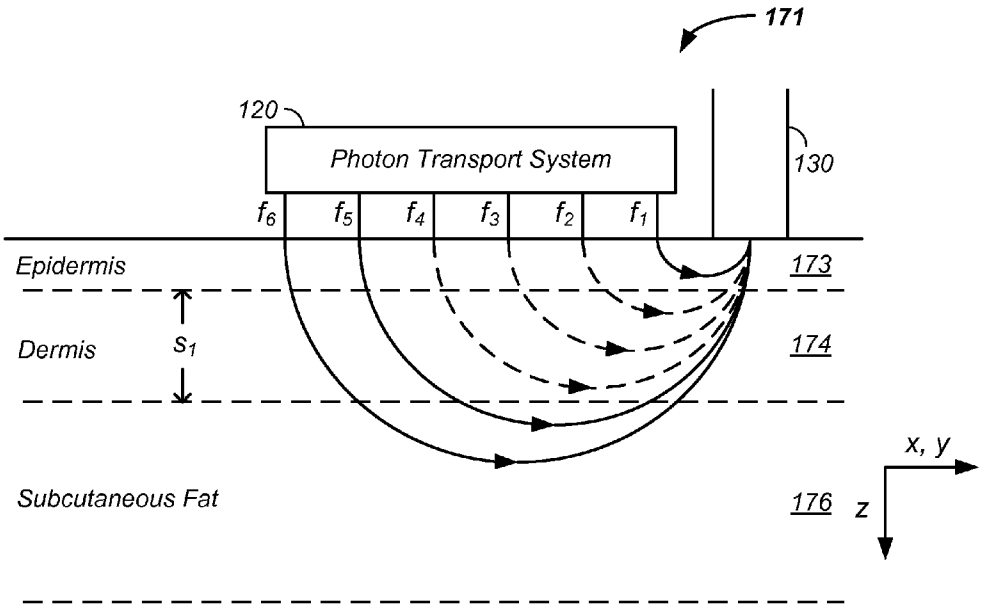

171
120
Photon Transport System
130
f_6 f_5 f_4 f_3 f_2 f_1
Epidermis
173
Dermis
s_1
174
x, y
Subcutaneous Fat
176
z

FIG. 9A

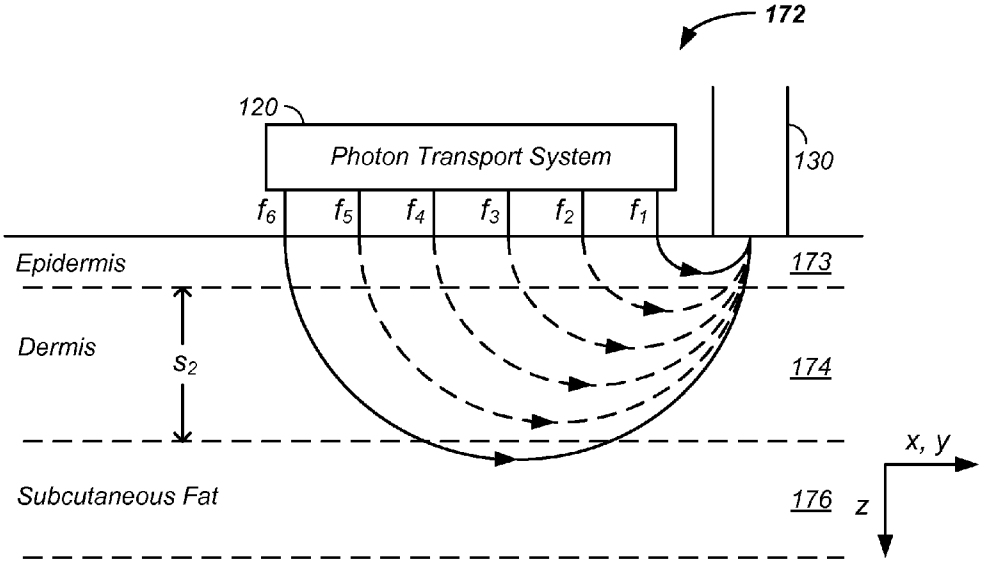

172
120
Photon Transport System
130
f_6 f_5 f_4 f_3 f_2 f_1
Epidermis
173
Dermis
s_2
174
x, y
Subcutaneous Fat
176
z

FIG. 9B

TISSUE PATHLENGTH RESOLVED NONINVASIVE ANALYZER APPARATUS AND METHOD OF USE THEREOF

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of:

[0002] U.S. provisional patent application No. 61/672,195 filed Jul. 16, 2012;

[0003] U.S. provisional patent application No. 61/700,291 filed Sep. 12, 2012; and

[0004] U.S. provisional patent application No. 61/700,294 filed Sep. 12, 2012,

[0005] all of which are incorporated herein in their entirety by this reference thereto.

TECHNICAL FIELD OF THE INVENTION

[0006] The present invention relates to a temporal resolution gating noninvasive analyzer for use in analyte concentration estimation.

DESCRIPTION OF THE RELATED ART

[0007] Patents and literature related to the current invention are summarized herein.

Diabetes

[0008] Diabetes mellitus or diabetes is a chronic disease resulting in the improper production and/or use of insulin, a hormone that facilitates glucose uptake into cells. Diabetes is broadly categorized into four forms grouped by glucose concentration state: hyperinsulinemia (hypoglycemia), normal physiology, impaired glucose tolerance, and hypoinsulinemia (hyperglycemia).

[0009] Diabetics have increased risk in three broad categories: cardiovascular heart disease, retinopathy, and/or neuropathy. Complications of diabetes include: heart disease, stroke, high blood pressure, kidney disease, nerve disease and related amputations, retinopathy, diabetic ketoacidosis, skin conditions, gum disease, impotence, and/or fetal complications.

[0010] Diabetes is a common and increasingly prevalent disease. Currently, diabetes is a leading cause of death and disability worldwide. The World Health Organization estimates that the number of people with diabetes will grow to three hundred million by the year 2025.

[0011] Long term clinical studies show that the onset of diabetes related complications is significantly reduced through proper control of blood glucose concentrations, The Diabetes Control and Complications Trial Research Group, "The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus", N. Eng. J. of Med., 1993, vol. 329, pp. 977-986.

Problem Statement

[0012] What is needed is a noninvasive glucose concentration analyzer having precision and accuracy suitable for treatment of diabetes mellitus.

SUMMARY OF THE INVENTION

[0013] The invention comprises a temporal resolution gating noninvasive analyzer apparatus and method of use thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] 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.

[0015] FIG. **1** illustrates an analyzer;

[0016] FIG. **2** illustrates diffusely reflecting optical paths;

[0017] FIG. **3** illustrates probing tissue layers using a spatial distribution method;

[0018] FIG. **4** illustrates varying illumination zones relative to a detector;

[0019] FIG. **5** illustrates varying detection zones relative to an illuminator;

[0020] FIGS. **6**(A-D) illustrate temporal resolution gating, FIG. **6**A; probabilistic optical paths for a first elapsed time, FIG. **6**B; probabilistic optical paths for a second elapsed time, FIG. **6**C; and a temporal distribution method, FIG. **6**D;

[0021] FIGS. **7**(A-C) illustrate a fiber optic bundle, FIG. **7**A; a first example sample interface end of the fiber optic bundle, FIG. **7**B; and a second example sample interface end of the fiber optic bundle, FIG. **7**C;

[0022] FIGS. **8**(A-C) illustrate a third example sample interface end of the fiber optic bundle, FIG. **8**A; a mask, FIG. **8**B; and a mask selector, FIG. **8**C;

[0023] FIGS. **9**(A-B) illustrate a pathlength resolved sample interface for (1) a first subject, FIG. **9**A and (2) a second subject, FIG. **9**B.

[0024] 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 a different order are illustrated in the figures to help improve understanding of embodiments of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0025] The invention comprises a temporal resolution gating noninvasive analyzer apparatus and method of use thereof.

[0026] In one embodiment, a temporal resolution gating noninvasive analyzer is used to determine an analyte property of a biomedical sample, such as a glucose concentration of a subject using light in the near-infrared region from 1000 to 2500 nanometers.

[0027] In another embodiment, a data processing system analyzes data from an analyzer to estimate and/or determine an analyte property, such as concentration.

[0028] In still another embodiment, an analyzer using light interrogates the sample using one or more of:

[0029] a spatially resolved system;

[0030] a radial distance resolved system;

[0031] a time resolved system, where the times are greater than about 1, 10, 100, or 1000 microseconds;

[0032] a picosecond timeframe resolved system, where times are less than about 1, 10, 100, or 1000 nanoseconds;

[0033] an incident angle resolved system; and

[0034] a collection angle resolved system.

[0035] Data from the analyzer is analyzed using a data processing system capable of using the information inherent in the resolved system data.

[0036] In another embodiment, a data processing system uses interrelationships of chemistry based a-priori spectral information related to absorbance of a sample constituent and/or the effect of the environment, such as temperature, on the spectral information.

[0037] In yet still another embodiment, a data processing system uses a first mapping phase to set instrument control parameters for a particular subject, set of subjects, and/or class of subjects. Subsequently, the control parameters are used in a second data collection phase to collect spectra of the particular subject or class of subjects.

[0038] In yet another embodiment, a data processing system uses information related to contact pressure on a tissue sample site.

[0039] In still yet another embodiment, a data processing system uses a combination of any of:

[0040] spatially resolved information;

[0041] temporally resolved information on a time scale of longer than about one microsecond;

[0042] temporally resolved information on a sub one hundred picosecond timeframe;

[0043] incident photon angle information;

[0044] photon collection angle information;

[0045] interrelationships of spectral absorbance and/or intensity information;

[0046] environmental information;

[0047] temperature information; and

[0048] information related to contact pressure on a tissue sample site.

Axes

[0049] Herein, axes systems are separately defined for an analyzer and for an interface of the analyzer to a patient, where the patient is alternatively referred to as a subject.

[0050] Herein, when referring to the analyzer, an x-, y-, z-axes analyzer coordinate system is defined relative to the analyzer. The x-axis is the in the direction of the mean optical path. The y-axis crosses the mean optical path perpendicular to the x-axis. When the optical path is horizontal, the x-axis and y-axis define a x/y horizontal plane. The z-axis is normal to the x/y plane. When the optical path is moving horizontally, the z-axis is aligned with gravity, which is normal to the x/y horizontal plane. Hence, the x, y, z-analyzer coordinate system is defined separately for each optical path element. In any case where the mean optical path is not horizontal, the optical system is further defined to remove ambiguity.

[0051] Herein, when referring to the patient, an x, y, z-axes patient coordinate system is defined relative to a body part interfaced to the analyzer. Hence, the x, y, z-axes body coordinate system moves with movement of the body part. The x-axis is defined along the length of the body part, the y-axis is defined across the body part. As an illustrative example, if the analyzer interfaces to the forearm of the patient, then the x-axis runs longitudinally between the elbow and the wrist of the forearm and the y-axis runs across the forearm. Together, the x,y plane tangentially touches the skin surface at a central point of the interface of the analyzer to the body part, which is referred to as the center of the sample site, sample region, or sample site. The z-axis is defined as orthogonal to the x,y plane. Rotation of an object is further used to define the orientation of the object to the sample site. For example, in some cases a sample probe of the analyzer is rotatable relative to the sample site. Tilt refers to an off z-axis alignment, such as an off z-axis alignment of a probe of the analyzer relative to the sample site.

Analyzer

[0052] Referring now to FIG. **1**, an analyzer **100** is illustrated. The analyzer comprises at least: a light source system **110**, a photon transport system **120**, a detector system **130**, and a data processing system **140**. In use the analyzer **100** estimates and/or determines a physical property, a sample state, a constituent property, and/or a concentration of an analyte.

Patient/Reference

[0053] Still referring to FIG. **1**, an example of the analyzer **100** is presented. In this example, the analyzer **100** includes a sample interface **150**, which interfaces to a reference material **160** and/or to a subject **170**. Herein, for clarity of presentation a subject **170** in the examples is representative of a person, animal, a prepared sample, and/or patient. In practice, the analyzer **100** is used by a user to analyze the user, referred to herein as a subject **170**, and is used by a medical professional to analyze a patient.

Controller

[0054] Still referring to FIG. **1**, the analyzer **100** optionally includes a system controller **180**. The system controller **180** is used to control one or more of: the light source system **110** or a light source **112** thereof, the photon transport system **120**, the detector system **130** or a detector **132** thereof, the sample interface **150**, position of the reference **160** relative to the sample interface **150**, position of the subject **170** relative to the sample interface **150**, and communication to an outside system **190**, such as a smart phone **192**, and/or a remote system **194** using a wireless communication system **196** and/or hard wired communication system **198**. For example, the remote system includes a data processing system, a data storage system, and/or a data organization system.

[0055] Still referring to FIG. **1**, the optional system controller **180** operates in any of a predetermined manner or in communication with the data processing system **140**. In the case of operation in communication with the data processing system **140**, the controller generates control statements using data and/or information about the current state of the analyzer **100**, current state of a surrounding environment **162** outside of the analyzer **100**, information generated by the data processing system **140**, and/or input from a sensor, such as a sample interface sensor **152** or an auxiliary system **10** or an auxiliary sensor **12** thereof. Herein, the auxiliary system **10** is any system providing input to the analyzer **100**.

[0056] Still referring to FIG. **1**, the optional system controller **180** is used to control: photon intensity of photons from the source using an intensity controller **122**, wavelength distribution of photons from the source **110** using a wavelength controller **124**, and/or physical routing of photons from the source **110** using a position controller **126**.

[0057] Still referring to FIG. **1**, for clarity of presentation the optional outside system **190** is illustrated as using a smart phone **192**. However, the smart phone **192** is optionally a cell phone, a tablet computer, a computer network, and/or a personal computer. Similarly, the smart phone **192** also refers to

a feature phone, a mobile phone, a portable phone, and/or a cell phone. Generally, the smart phone **192** includes hardware, software, and/or communication features carried by an individual that is optionally used to offload requirements of the analyzer **100**. For example, the smart phone **192** includes a user interface system, a memory system, a communication system, and/or a global positioning system. Further, the smart phone **192** is optionally used to link to the remote system **194**, such as a data processing system, a medical system, and/or an emergency system. In another example at least one calculation of the analyzer in noninvasively determining a glucose concentration of the subject **170** is performed using the smart phone **192**. In yet another example, the analyzer gathers information from at least one auxiliary sensor **12** and relays that information and/or a processed form of that information to the smart phone **192**, where the auxiliary sensor is not integrated into the analyzer **100**.

Source

[0058] Herein, the source system **110** generates photons in any of the visible, infrared, near-infrared, mid-infrared, and/or far-infrared spectral regions. In one case, the source system generates photons in the near-infrared region from 1100 to 2500 nm or any range therein, such as within the range of about 1200 to 1800 nm; at wavelength longer than any of 800, 900, 1000, and 1100 nm; and/or at wavelengths shorter than any of 2600, 2500, 2000, or 1900 nm.

Photon/Skin Interaction

[0059] Light interacts with skin through laws of physics to scatter and transmit through skin voxels.

[0060] Referring now to FIG. **2**, for clarity of presentation and without limitation, in several examples provided herein a simplifying and non-limiting assumption is made, for some wavelengths and for some temperatures, that mean photon depth of penetration increases with mean radial distance between a photon illumination zone and a photon detection zone.

[0061] Referring still to FIG. **2**, a photon transit system **200** through skin layers of the subject **170** is illustrated. In this example, the photon transport system **120** guides light from a source **112** of the source system **110** to the subject **170**. Optionally, a contact gap **210** is present between a last optic of the photon transport system **120** and skin of the subject **170**. Further, in this example, the photon transport system **120** irradiates skin of the subject **170** over a narrow illumination zone, such as having an area of less than about 9, 4, 1, or ¼mm^2. Optionally, the photons are delivered to the skin of the subject **170** through an optic proximately contacting, but not actually contacting, the skin, such as within about 0.5, 1.0, or 2.0 millimeters of the skin. Optionally, the distance between the analyzer and the skin of the subject **170** is maintained with a vibration and/or shake reduction system, such as is used in a vibration reduction camera or lens. For example, the skin position is monitored with a sensor, output from the sensor is sent to the controller, and the controller controls an electro-mechanical element used to control a position of an element of the analyzer. For clarity of presentation, the photons are depicted as entering the skin at a single point. A portion of the photons traverse, or more particularly traverse through, the skin to a detection zone. The detection zone is a region of the skin surface where the detector system **130** gathers the traversing or diffusely reflected photons. Various photons traversing or diffusely scattering through the skin encounter an epidermis **173** or epidermis layer, a dermis **174** or dermis layer, and subcutaneous fat **176** or a subcutaneous fat layer. As depicted in FIG. **2**, the diffuse reflectance of the various photons through the skin detected by the detection system **130** follow a variety of optical paths through the tissue, such as shallow paths through the epidermis **173**, deeper paths through the epidermis **173** and dermis **174**, and still deeper paths through the epidermis **173**, dermis **174**, and subcutaneous fat **176**. However, for a large number of photons, there exists a mean photon path for photons from entering the skin that are detected by the detection system **130**.

Pathlength

[0062] Herein, for clarity, without loss of generality, and without limitation, Beer's Law is used to described photon interaction with skin, though those skilled in the art understand deviation from Beer's Law result from sample scattering, index of refraction variation, inhomogeneity, turbidity, and/or absorbance out of a linear range of the analyzer **100**.

[0063] Beer's Law, equation 1, states that:

$$A = abC \quad \text{(eq. 1)}$$

where A is absorbance, b is pathlength, and C is concentration. Typically, spectral absorbance is used to determine concentration. However, the absorbance is additionally related to pathlength. Hence, determination of the optical pathlength traveled by the photons is useful in reducing error in the determined concentration. Two methods, described infra, are optionally used to estimate pathlength: (1) spatial resolution of pathlength and (2) temporal resolution of pathlength.

Algorithm

[0064] The data and/or derived information from each of the spatial resolution method and temporal resolution method are each usable with the data processing system **140**. Examples provide, infra, illustrate: (1) both cases of the spatial resolution method and (2) the temporal resolution method. However, for clarity of presentation and without limitation, the photons in most examples are depicted as radially traversing from a range of input zones to a detection zone. Similarly, photons are optionally controlled from an input zone to a range of detection zones. Still further, photons are optionally directed to a series of input zones, as a function of time, and for each input zone or set of input zones one or more detection zones are used.

Spatial Resolution

[0065] The first method of spatial resolution contains two cases. Herein, in a first case photons are depicted traversing from a range of input points on the skin to a radially located detector to derive photon interrogated sample path and/or depth information. However, in a second case, equivalent systems optionally use a single input zone of the photons to the skin and a plurality of radially located detector zones to determine optical sample photons paths and/or depth information. Still further, a combination of the first two cases, such as multiple sources and multiple detectors, is optionally used to derive photon path information in the skin.

[0066] In the first system, Referring now to FIG. **3**, the photon transit system **200** of FIG. **2** is illustrated where the photon transport system **110** irradiates the skin of the subject **170** over a wide range of radial distance from the detection

zone, such as at least about 0.1, 0.2, 0.3, 0.4, or 0.5 millimeters from the detection zone to less than about 1.0, 1.2, 1.4, 1.6, or 1.8 millimeters from the detection zone. In this example, a mean photon path is provided as a function of radial distance from the illumination zone to the detection zone. Generally, over a range of about zero to less than about two millimeters from the detection zone, the mean optical path of the detected diffusely scattering photons increases in depth for photons in the near-infrared traveling through skin.

[0067] In the first case of the spatial resolution method, referring now to FIG. **4**, the photon transit system **200** uses a vector or array of illumination sources **400**, of the source system **110**, in a spatially resolved pathlength determination system. For example, the illumination sources are an array of fiber optic cables. In this example, a set of seven fiber optics **401**, **402**, **403**, **404**, **405**, **406**, **407** are positioned, radially along the x,y plane of the subject **170** to provide a set of illuminations zones, relative to a detection fiber at a detection zone. As illustrated the third illumination fiber optic **403**/detector **132** combination yields a mean photon path having a third depth of penetration, d_3, for a third fiber optic-to-detector radial distance, r_3; the fifth illumination fiber optic **405**/detector **132** combination yields a mean photon path having a fifth depth of penetration, d_5, for a fifth fiber optic-to-detector radial distance, r_5; and the seventh illumination fiber optic **407**/detector **132** combination yields a mean photon path having a seventh depth of penetration, d_7, for a seventh fiber optic-to-detector radial distance, r_7. Generally, for photons in the near-infrared region from 1100 to 2500 nanometers both a mean depth of penetration of the photons and a total optical pathlength increases with increasing fiber optic-to-detector distance, where the fiber optic-to-detector distance is less than about three millimeters.

[0068] In the second case of the spatial resolution method, referring now to FIG. **5**, the photon transit system **200** uses a vector or array of detectors **500** in the detection system **130**. For example, a single fiber optic source is used, which sends radially distributed light to an array of staring detectors or collection optics coupled to a set of detectors. In this example, a set of seven detectors **501**, **502**, **503**, **504**, **505**, **506**, **507** are positioned, radially along the x,y plane to provide a set of detection zones, relative to an illumination zone. As illustrated the source **112**/second detector **502** combination yields a mean photon path having a second depth of penetration, d_2, for a second source-to-detector radial distance, r_2; the source **112**/fourth detector **504** combination yields a mean photon path having a fourth depth of penetration, d_4, for a fourth source-to-detector radial distance, r_4; and the source **112**/sixth detector **506** combination yields a mean photon path having a sixth depth of penetration, d_6, for a sixth source-to-detector radial distance, r_6. Again, generally for photons in the near-infrared region from 1100 to 2500 nanometers both the mean depth of penetration of the photons into skin and the total optical pathlength in skin increases with increasing fiber optic-to-detector distance, where the fiber optic-to-detector distance is less than about three millimeters. Hence, data collected with an analyzer configured with a multiple detector design generally corresponds to the first case of a multiple source design.

[0069] Referring again to FIGS. **4** and **5**, the number of source zones is optionally 1, 2, 3, 4, 5, 10, 20, 50, 100 or more and the number of detection zones is optionally 1, 2, 3, 4, 5, 10, 20, 50, 500, 1000, 5000, 10,000, 100,000 or more.

Temporal Resolution

[0070] The second method of temporal resolution is optionally performed in a number of manners. For clarity of presentation and without limitation, a temporal resolution example is provided where photons are timed using a gating system and the elapsed time is used to determine photon paths in tissue.

[0071] Referring now to FIGS. **6**A-D, an example of a temporally resolved gating system **600** is illustrated. Generally, in the temporal gating system **600** the time of flight of a photon is used to determine the pathlength, b. Referring now to FIG. **6**A, at an initial time, t_0, an interrogation pulse **610** of one or more photons is introduced to the sample, which herein is skin of the subject **170**. The interrogation pulse **610** is also referred to as a pump pulse or as a flash of light. At one or more subsequent gated detection times **620**, after passing through the sample the interrogation pulse **610** is detected. As illustrated, the gated detection times are at a first time **622**, t_1; a second time **624**, t_2; a third time **626**, t_3; and at an n^{th} time **628**, t_n, where n is a positive number. Optionally, the gated detection times **620** overlap. For the near-infrared spectral region, the elapsed time used to detect the interrogation photons **610** is on the order of picoseconds, such as less than about 100, 10, or 1 picosecond. The physical pathlength, b, is determined using equation 2:

$$OPD = \frac{c}{n}(b) \qquad \text{(eq. 2)}$$

where OPD is the optical path distance, c is the speed of light, n is the index of refraction of the sample, and b is the physical pathlength. Optionally, n is a mathematical representation of a series of indices of refraction of various constituents of skin and/or skin and surrounding tissue layers. More generally, observed pathlength is related to elapsed time of photon capture where the relationship of pathlength to temperature is optionally further determined using a measure of a tissue, such as an index of refraction.

[0072] Referring now to FIG. **6**B, illustrative paths of the photons for the first gated detection time **622** are provided. A first path, p_{1a}; second path, p_{1b}; and third path, p_{1c}, of photons in the tissue are illustrated. In each case, the total pathlength, for a constant index of refraction, is the same for each path. However, the probability of each path also depends on the anisotropy of the tissue and the variable indices of refraction of traversed tissue voxels.

[0073] Referring now to FIG. **6**C, illustrative paths of the photons for the second gated detection time **624** are provided. A first path, p_{2a}; second path, p_{2b}; and third path, p_{2c}, of photons in the tissue are illustrated. Again, in each case the total pathlength for the second elapsed time, t_2, is the same for each path. Generally, if the delay to the second gated detection time **624** is twice as long as the first gated detection time **622**, then the second pathlength, p_2, for the second gated detection time **624** is twice as long as the first pathlength, p_1, for the first gated detection time **622**. Knowledge of anisotropy is optionally used to decrease the probability spread of paths observed in the second set of pathlengths, p_{2a}, p_{2b}, p_{2c}. Similarly a-priori knowledge of approximate physiological thickness of varying tissue layers, such as an epidermal thickness of a patient, an average epidermal thickness of a population, a dermal thickness of a patient, and/or an average

dermal thickness of a population is optionally used to reduce error in an estimation of pathlength, a product of pathlength and a molar absorptivity, and/or a glucose concentration by limiting bounds of probability of a photon traversing different pathways through the skin layers and still returning to the detection element with the elapsed time. Similarly, knowledge of an index of refraction of one or more sample constituents and/or a mathematical representation of probable indices of refraction is also optionally used to reduce error in estimation of a pathlength, molar absorptivity, and/or an analyte property concentration estimation. Still further, knowledge of an incident point or region of light entering she skin of the subject relative to a detection zone is optionally used to further determine probability of a photon traversing dermal or subcutaneous fat layers along with bounding errors of pathlength in each layer.

[0074] Referring now to FIG. **6**D, mean pathlengths and trajectories are illustrated for three elapsed times, t_1, t_2, t_3. As with the spatially resolved method, generally, for photons in the near-infrared region from 1100 to 2500 nanometers, both a mean depth of penetration of the photons, d_n; the total radial distance traveled, r_m; and the total optical pathlength increases with increasing time, where the fiber optic-to-detector distance is less than about three millimeters. Preferably, time gates range from shorter than 100 picoseconds to about 1 picosecond or 100 nanoseconds.

Spatial and Temporal Resolution

[0075] Hence, both the spatial resolution method and temporal resolution method yield information on pathlength, b, which is optionally used by the data processing system **140** to reduce error in the determined concentration, C.

Analyzer and Subject Variation

[0076] As described, supra, Beer's Law states that absorbance, A, is proportional to pathlength, b, times concentration, C. More precisely, Beer's Law includes a molar absorbance, ϵ, term, as shown in equation 3:

$$A=\epsilon bC \quad \text{(eq. 3)}$$

[0077] Typically, spectroscopists consider the molar absorbance as a constant due to the difficulties in determination of the molar absorbance for a complex sample, such as skin of the subject **170**. However, information related to the combined molar absorbance and pathlength product for skin tissue of individuals is optionally determined using one or both of the spatially resolved method and time resolved method, described supra. In the field of noninvasive glucose concentration determination, the product of molar absorbance and pathlength relates at least to the dermal thickness of the particular individual or subject **170** being analyzed. Examples of spatially resolved analyzer methods used to provide information on the molar absorbance and/or pathlength usable in reduction of analyte property estimation or determination are provided infra.

Spatially Resolved Analyzer

[0078] Herein, an analyzer **100** using fiber optics is used to describe obtaining spatially resolved information, such as pathlength and/or molar absorbance, of skin of an individual, which is subsequently used by the data processing system **140**. The use of fiber optics in the examples is used without limitation, without loss of generality, and for clarity of presentation. More generally, photons are delivered in quantities of one or more through free space, through optics, and/or off of reflectors to the skin of the subject **170** as a function of distance from a detection zone.

[0079] Referring now to FIG. **7**A, an example of a fiber optic interface system **700** of the analyzer **100** to the subject **170** is provided, which is an example of the sample interface system **150**. Light from the source system **110** of the analyzer **100** is coupled into a fiber optic illumination bundle **714** of a fiber optic bundle **710**. The fiber optic illumination bundle **714** guides light to a sample site **178** of the subject **170**. The sample site **178** has a surface area and a sample volume. In a first case, a sample interface tip **716** of the fiber optic bundle **710** contacts the subject **170** at the sample site **178**. In a second case, the sample interface tip **716** of the fiber optic bundle **710** proximately contacts the subject **170** at the sample site **178**, but leaves a gap **720** between the sample interface tip **716** of the fiber optic bundle **710** and the subject **170**. In one instance, the gap **720** is filled with a contact fluid and/or an optical contact fluid. In a second instance, the gap **720** is filled with air, such as atmospheric air. Light transported by the fiber optic bundle **710** to the subject **170** interacts with tissue of the subject **170** at the sample site **178**. A portion of the light interacting with the sample site is collected with one or more fiber optic collection fibers **718**, which is optionally and preferably integrated into the fiber optic bundle **710**. As illustrated, a single collection fiber **718** is used. The collection fiber **718** transports collected light to the detector **132** of the detection system **130**.

[0080] Referring now to FIG. **7**B, a first example of a sample side light collection end **716** of the fiber optic bundle **710** is illustrated. In this example, the single collection fiber **718** is circumferentially surrounded by an optional spacer **730**, where the spacer has an average radial width of less than about 200, 150, 100, 50, or 25 micrometers. The optional spacer **730** is circumferentially surrounded by a set of fiber optic elements **713**. As illustrated, the set of fiber optic elements **713** are arranged into a set of radial dispersed fiber optic rings, such as a first ring **741**, a second ring **742**, a third ring **743**, a fourth ring **744**, and an n^{th} ring **745**, where n comprises a positive integer of at least 2, 3, 4, 5, 6, 7, 8, 9, or 10. Optionally, the fiber optic elements **713** are in any configuration, such as in a close-packed configuration about the collection fiber **718** or in an about close-packed configuration about the collection fiber **718**. The distance of each individual fiber optic of the set of fiber optic elements **713**, or light collection element, from the center of the collection fiber **718** is preferably known.

[0081] Referring now to FIG. **7**C, a second example of the sample side light collection end **716** of the fiber optic bundle **710** is provided. In this example, the centrally positioned collection fiber **718** is circumferentially surrounded by a set of spacer fibers **750**. The spacer fibers combine to cover a radial distance from the outside of the collection fiber of less than about 300, 200, 150, 100, 75, 60, 50, or 40 micrometers. The spacer fibers **750** are circumferentially surrounded by the radially dispersed fiber optic rings, such as the first ring **741**, the second ring **742**, the third ring **743**, the fourth ring **744**, and the n^{th} ring **745**. Optionally, fiber diameters of the spacer fibers **750** are at least ten, twenty, or thirty percent larger or smaller than fiber diameters of the set of fiber optic elements **713**. Further, optionally the fiber optic elements **713** are arranged in any spatial configuration radially outward from the spacer fibers **750**. More generally, the set of fiber optic

elements **713** and/or spacer fibers **750** optionally contain two, three, four, or more fiber optic diameters, such as any of about 40, 50, 60, 80, 100, 150, 200, or more micrometers. Optionally, smaller diameter fiber optics, or light collection optics, are positioned closer to any detection fiber and progressively larger diameter fiber optics are positioned, relative to the smaller diameter fiber optics, further from the detection fiber.

Radial Distribution System

[0082] Referring now to FIG. **8**A-**8**C, a system for spatial illumination **800** of the sample site **178** of the subject **170** is provided. The spatial illumination system **800** is used to control distances between illumination zones and detection zones as a function of time.

[0083] Referring now to FIG. **8**A, a third example of the sample side light collection end **716** of the fiber optic bundle **710** is provided. In this example, the collection fiber **718** or collection optic is circumferentially surrounded by the set of fiber optic elements **713** or irradiation points on the skin of the subject **170**. For clarity of presentation and without loss of generality, the fiber optic elements **713** are depicted in a set of rings radially distributed from the collection fiber **718**. However, it is understood that the set of fiber optics **713** are optionally close packed, arranged in a random configuration, or arranged according to any criterion. Notably, the distance of each fiber optic element of the set of fiber optic elements **713** from the collection fiber **718** is optionally determined using standard measurement techniques through use of an algorithm and/or through use of a dynamically adjustable optic used to deliver light to the sample, such as through air. Hence, the radial distribution approach, described infra, is optionally used for individual fiber optic elements and/or groups of fiber optic elements arranged in any configuration. More generally, the radial distribution approach, described infra, is optionally used for any set of illumination zone/detection zone distances using any form of illuminator and any form of detection system, such as through use of the spatially resolved system and/or the time resolved system.

[0084] Referring now to FIG. **8**B, an example of a light input end **712** of the fiber optic bundle **710** is provided. In this example, individual fibers of the set of fiber optics **713** having the same or closely spaced radial distances from the collection fiber **718** are grouped into a set of fiber optic bundles or a set of fiber optic bundlets **810**. As illustrated, the seven fibers in the first ring circumferentially surrounding the collection fiber **718** are grouped into a first bundlet **811**. Similarly, the sixteen fibers in the second ring circumferentially surrounding the collection fiber **718** are grouped into a second bundlet **812**. Similarly, the fibers from the third, fourth, fifth, and sixth rings about the collection fiber **718** at the sample side illumination end **716** of the fiber bundle **710** are grouped into a third bundlet **813**, a fourth bundlet **814**, a fifth bundlet **815**, and a sixth bundlet **816**, respectively. For clarity of presentation, the individual fibers are not illustrated in the second, third, fourth, fifth, and sixth bundlets **812**, **813**, **814**, **815**, **816**. Individual bundles and/or individual fibers of the set of fiber optic bundlets **810** are optionally selectively illuminated using a mask **820**, described infra.

[0085] Referring now to FIG. **8**C and FIG. **7**A, a mask wheel **830** is illustrated. Generally, the mask wheel **830** rotates, such as through use of a wheel motor **820**. As a function of mask wheel rotation position, holes or apertures through the mask wheel **830** selectively pass light from the source system **110** to the fiber optic input end **712** of the fiber optic bundle **710**. In practice, the apertures through the mask wheel are precisely located to align with (1) individual fiber optic elements of the set of fiber optics at the input end **712** of the fiber optic bundle or (2) individual bundlets of the set of fiber optic bundlets **810**. Optionally an encoder or marker section **840** of the mask wheel **830** is used for tracking, determining, and/or validating wheel position in use.

[0086] Still referring to FIG. **80**, an example of use of the mask wheel **830** to selectively illuminate individual bundlets of the set of fiber optic bundlets **810** is provided. Herein, for clarity of presentation the individual bundlets are each presented as uniform size, are exaggerated in size, and are repositioned on the wheel. For example, as illustrated a first mask position, p_1, **821** is illustrated at about the seven o'clock position. The first mask position **821** figuratively illustrates an aperture passing light from the source system **110** to the first bundlet **811** while blocking light to the second through sixth bundlets **812-816**. At a second point in time, the mask wheel **830** is rotated such that a second mask position, p_2, **822** is aligned with the input end **712** of the fiber optic bundle **710**. As illustrated, at the second point in time, the mask wheel **830** passes light from the illumination system **110** to the second bundlet **812**, while blocking light to the first bundlet **811** and blocking light to the third through six bundlets **813-816**. Similarly, at a third point in time the mask wheel uses a third mask position, p_3, **823** to selectively pass light into only the fifth bundlet **815**. Similarly, at a fourth point in time the mask wheel uses a fourth mask position, p_4, **824** to selectively pass light into only the sixth bundlet **816**.

[0087] Still referring to FIG. **80**, thus far the immediately prior example has only shown individual illuminated bundlets as a function of time. However, combinations of bundlets are optionally illuminated as a function of time. In this continuing example, at a fifth point in time, the mask wheel **830** is rotated such that a fifth mask position, p_5, **825** is aligned with the input end **712** of the fiber optic bundle **710**. As illustrated, at the fifth point in time, the mask wheel **830** passes light from the illumination system **110** to all of (1) the second bundlet **812**, (2) the third bundlet **813**, and (3) the fourth bundlet **814**, while blocking light to all of (1) the first bundlet **811**, (2) the fifth bundlet **815**, and (3) the sixth bundlet **816**. Similarly, at a sixth point in time a sixth mask position, p_6, **826** of the mask wheel **830** passes light to the second through fifth bundlets **812-815** while blocking light to both the first bundlet **811** and sixth bundlet **816**.

[0088] In practice, the mask wheel **830** contains an integral number of n positions, where the n positions selectively illuminate and/or block any combination of: (1) the individual fibers of the set of fiber optics **713** and/or (2) bundlets **810** of the set of fiber optic optics **713**. Further, the filter wheel is optionally of any shape and uses any number of motors to position mask position openings relative to selected fiber optics. Still further, in practice the filter wheel is optionally any electro-mechanical and/or electro-optical system used to selectively illuminate the individual fibers of the set of fiber optics **713**. Yet still further, in practice the filter wheel is optionally any illumination system that selectively passes light to any illumination optic or illumination zone, where various illumination zones illuminate various regions of the subject **170** as a function of time. The various illumination zones alter the effectively probed sample site **178** or region of the subject **170**.

Adaptive Subject Measurement

[0089] Referring now to FIG. **9**A and FIG. **9**B, examples of use of the spatial illumination system **800** is illustrated for a first subject **171** and a second subject **172**. However, more generally the photon transport system **120** in FIGS. **9**A and **9**B is used in any spatially resolved system and/or in any time resolved system to deliver photons as a function of radial distance to a detector or to a detection zone.

[0090] Referring now to FIG. **9**A, FIG. **8**A, and FIG. **8**C, an example of application of the spatial illumination system **800** to the first subject **171** is provided. At a first point in time, the first position, p_1, **821** of the filter wheel **830** is aligned with the light input end **712** of the fiber bundle, which results in the light from the first bundlet **811**, which corresponds to the first ring **741**, irradiating the sample site **178** at a first radial distance, r_1, and a first depth, d_1, which as illustrated in FIG. **9**A has a mean optical path through the epidermis. Similarly, at a second point in time, the filter wheel **830** at the second position **822** passes light to the second bundlet **812**, which corresponds to the second ring, irradiating the sample site **178** at a second increased distance and a second increased depth, which as illustrated in FIG. **9**A has a mean optical path through the epidermis and dermis. Similarly, results of interrogation of the subject **170** with light passed through the six illustrative fiber illumination rings in FIG. **8**A is provided in Table 1. The results of Table 1 demonstrate that for the first individual, the prime illumination rings for a blood analyte concentration determination are rings two through four as the first ring, sampling the epidermis, does not sample the blood filled dermis layer; rings two through four probe the blood filled dermis layer; and rings five and six penetrate through the dermis into the subcutaneous fat where photons are lost and the resultant signal-to-noise ratio for the blood analyte decreases.

TABLE 1

Subject 1	
Illumination Ring	Deepest Tissue Layer Probed
1	Epidermis
2	Dermis
3	Dermis
4	Dermis
5	Subcutaneous Fat
6	Subcutaneous Fat

[0091] Referring now to FIG. **9**B and FIG. **8**A, an example of application of the spatial illumination system **800** to the second subject **172** is provided. Results of interrogation of the subject **170** with light passed through the six illustrative fiber illumination rings in FIG. **8**A is provided in Table 2. For the second subject, it is noted that interrogation of the sample with the fifth radial fiber ring, f_5, results in a mean optical path through the epidermis and dermis, but not through the subcutaneous fat. In stark contrast, the mean optical path using the fifth radial fiber ring, f_5, for the second subject **172** has a deepest penetration depth into the dermis **174**. Hence, the fifth radial fiber ring, f_5, yields photons probing the subcutaneous fat **176** for the first subject **171** and yields photons probing the dermis **174** of the second subject **172**. Hence, for a water soluble analyte and/or a blood borne analyte, such as glucose, the analyzer **100** is more optimally configured to not use both the fifth fiber ring, f_5, and the sixth fiber ring, f_6, for the first subject **171**. However, analyzer **100** is more optimally configured to not use only the sixth fiber ring, f_6, for the second subject **172**, as described infra.

TABLE 2

Subject 2	
Illumination Ring	Deepest Tissue Layer Probed
1	Epidermis
2	Dermis
3	Dermis
4	Dermis
5	Dermis
6	Subcutaneous Fat

[0092] In yet another example, light is delivered with known radial distance to the detection zone, such as with optics of the analyzer, without use of a fiber optic bundle and/or without the use of a filter wheel. Just as the illumination ring determines the deepest tissue layer probed, control of the irradiation zone/detection zone distance determines the deepest tissue layer probed.

[0093] In still yet another example, referring again to time resolved spectroscopy, instead of delivering light through the filter wheel to force radial distance, photons are optionally delivered to the skin and the time resolved gating system is used to determine probably photon penetration depth. For example, Table 3 shows that at greater elapsed time to the n^{th} gated detection period, the probability of the deepest penetration depth reaching deeper tissue layers increases.

TABLE 3

Time Resolved Spectroscopy	
Elapsed Time (picoseconds)	Deepest Tissue Layer Probed
1	Epidermis
10	Dermis
50	Dermis
100	Subcutaneous Fat

Two-Phase Measurement(s)

[0094] Still referring to FIG. **9**A and FIG. **9**B, a first optional two-phase measurement approach is herein described. Optionally, during a first sample mapping phase, the photon transport system **120** provides interrogation photons to a particular test subject at controlled, but varying, radial distances from the detection system **130**. One or more spectral markers, or an algorithmic/mathematical representation thereof, are used to determine the radial illumination distances best used for the particular test subject. An output of the first phase is the data processing system **140** selecting how to illuminate/irradiate the subject **170**. Subsequently, during a second data collection phase, the system controller **180** controls the photon transport system **120** to deliver photons over selected conditions to the subject **170**. For clarity, several illustrative examples are provided, infra.

[0095] In a first example, a first spectral marker is optionally related to the absorbance of the subcutaneous fat **176** for the first subject **171**. During the first sample mapping phase, the fifth and sixth radial positions of the fiber probe illustrated in FIG. **8**A, yield collected signals for the first subject **171** that contain larger than average fat absorbance features, which

indicates that the fifth and sixth fiber rings of the example fiber bundle should not be used in the subsequent second data collection phase. Still in the first sample mapping phase, probing the tissue of the subject with photons from the fourth fiber ring yields a reduced signal for the first spectral marker and/or a larger relative signal for a second spectral marker related to the dermis **174**, such as a protein absorbance band or an algorithmic/mathematical representation thereof. Hence, the data processing system **140** yields a result that the fifth and sixth radial fiber optic rings or distance of the fiber bundle **170** should not be used in the second data collection phase and that the fourth radial fiber optic ring or distance should be used in the second data collection phase. Subsequently, in the second data collection phase, data collection for analyte determination ensues using the first through fourth radial positions of the fiber bundle, which yields a larger signal-to-noise ratio for dermis constituents, such as glucose, compared to the use of all six radial positions of the fiber bundle.

[0096] In a second example, the first sample mapping phase of the previous example is repeated for the second subject **172**. The first sample mapping phase indicates that for the second subject, the sixth radial illumination ring of the fiber bundle illustrated in FIG. **8**A should not be used, but that the fourth and fifth radial illumination ring should be used.

[0097] Generally, a particular subject is optionally probed in a sample mapping phase and results from the sample mapping phase are optionally used to configure analyzer parameters in a subsequent data collection phase. Optionally, the mapping phase and data collection phase occur within thirty seconds of each other. Optionally, the subject **170** does not move away from the sample interface **150** between the mapping phase and the data collection phase.

[0098] Further, generally each of the spatial and temporal methods yield information on pathlength, b, and/or a product of the molar absorptivity and pathlength, which is not achieved using a standard spectrometer.

[0099] In yet another embodiment, the sample interface tip **716** of the fiber optic bundle **710** includes optics that change the mean incident light angle of individual fibers of the fiber optic bundle **716** as they first hit the subject **170**. For example, a first optic at the end of a fiber in the first ring **741** aims light away from the collection fiber optic **718**; a second optic at the end of a fiber in the second ring **742** aims light nominally straight into the sample; and a third optic at the end of a fiber in the third ring **742** aims light toward the collection fiber **718**. Generally, the mean direction of the incident light varies by greater than 5, 10, 15, 20, or 25 degrees.

[0100] Still yet another embodiment includes any combination and/or permutation of any of the analyzer and/or sensor elements described herein.

[0101] 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.

[0102] 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 modifications 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.

[0103] 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.

[0104] 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.

[0105] 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.

1. An apparatus for determination of an analyte property of a subject, comprising:

a near-infrared analyzer, comprising:

a source configured to deliver a sub-microsecond burst of near-infrared light in the range of 1000 to 2500 nanometers;

a temporal resolution gating system configured to collect signal from the burst of near-infrared light during a time period of at least one time delayed gated window, the time period comprising a period greater than one femtosecond and less than one nanosecond after a midpoint of the burst of the near-infrared light; and

a data processing system configured to use the signal and the time period of the at least one delayed gated window in determination of a glucose concentration.

2. The apparatus of claim 1, said data processing system configured to resolve a pathlength of the near-infrared light in the subject using the signal from the burst of near-infrared light in the at least one time delayed gated window, the pathlength used in said data processing system in the determination of the glucose concentration.

3. The apparatus of claim 1, said data processing system configured to use the time period of the at least one time delayed gated window in determination of a product of pathlength and molar absorptivity.

4. The apparatus of claim 1, wherein said analyzer further comprises:

at least one optic configured to vary radial distance, by at least one millimeter as a function of time, between a middle of an illumination zone of the burst of near-infrared light on the subject and a middle of a detection zone of a detection optic of said analyzer.

5. The apparatus of claim 4, wherein the radial distance comprises a set of at least four mean distances as a function of scan number, wherein the signal comprises a set of at least ten sub-signals correlating to said set of four mean distances.

6. The apparatus of claim 1, wherein said data processing system uses a database, said database configured to store at least one physiology parameter, said physiology parameter comprising at least one of an epidermal thickness and a dermal thickness, said data processing system configured to use at least one of the epidermal thickness and the dermal thickness in the determination of the glucose concentration.

7. The apparatus of claim 1, in the determination of the glucose concentration, said data processing system configured to use at least one of:

an anisotropy value; and

an index of refraction.

8. The apparatus of claim 1, in the determination of the glucose concentration, said data processing system configured to use at least one of:

a scattering coefficient; and

an absorbance of any of water, protein, and fat.

9. The apparatus of claim 1, wherein said analyzer further comprises:

a sample interface configured to not contact the subject during collection of the signal.

10. The apparatus of claim 1, wherein said analyzer further comprises:

a sample interface configured to contact at least one of the subject and a coupling fluid during collection of the signal.

11. The apparatus of claim 1, wherein said analyzer further comprises:

a fiber optic bundle comprising:

a first fiber optic configured to deliver the burst of the near-infrared light to the subject, said first fiber optic comprising a first cross-sectional area; and

a second fiber optic configured to deliver the burst of the near-infrared light to the subject, said second fiber optic comprising a second cross-sectional area, said second cross-sectional area at least ten percent larger than said first cross-sectional area.

12. The apparatus of claim 1, wherein said analyzer further comprises:

a vibration reduction system, wherein said vibration reduction system maintains a gap between a sample interface of said analyzer and the subject by monitoring shaking of the subject and adjusting physical position of said sample interface relative to the subject.

13. The apparatus of claim 1, wherein said analyzer further comprises:

a first sample side optic configured to deliver the burst of light to the subject at a first mean incident angle relative to an axis normal to a sample site of the subject,

a second sample side optic configured to deliver the burst of light to the subject at a second mean incident angle relative to the axis normal to the sample site of the subject, the first mean incident angle at least ten degrees larger than the second mean incident angle.

14. A method for determination of an analyte property of a subject having skin, comprising the steps of:

delivering a spectral burst of near-infrared light at least within the range of 1000 to 2500 nanometers from a source of an analyzer to an illumination region of the skin of the subject;

generating a signal during at least one time period using a temporal resolution gating system to detect the burst of light in at least one time delayed gated window between one hundred picoseconds and one hundred nanoseconds after origination of the burst of the near-infrared light; and

processing the signal using the at least one time period and the signal to generate a glucose concentration of the subject.

15. The method of claim 14, wherein said step of processing uses the time of said at least one time delayed gated window and the signal to generate an optical pathlength of the burst of the near-infrared light in the subject.

16. The method of claim 14, wherein said step of processing estimates a molar absorptivity of the subject.

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

adapting an optical configuration of the analyzer using the molar absorptivity.

18. The method of claim 14, wherein said step of processing further comprises the steps of:

sending a form of the signal to a smart phone;

analyzing the form of the signal using the smart phone to generate a result; and

using said smart phone to convey the result to the subject.

19. The method of claim 14, further comprising the steps of:

using said analyzer to gather information from a sensor external to said analyzer; and

relaying a form of the information to a cell phone.

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

varying radial distance of the burst of light onto the subject relative to a zone monitored by a detector of said analyzer by at least one millimeter in a ten second time period.

21. A method for determination of a glucose concentration of a subject, comprising the steps of:

using a temporal resolution analyzer to time near-infrared photon traversal through skin using a time resolved gating system and to gather a signal at a detection time period of the time resolved gating system; and

using the detection time period and the signal to noninvasively determine a glucose concentration of the subject.

22. The method of claim 21, wherein said detection time comprises a time period greater than one femtosecond and

less than one nanosecond after generation of a burst of light by said analyzer, wherein the signal is collected during said time period.

23. The method of claim **21**, wherein said detection time comprises a time period greater than ten microseconds and less than one-tenth of a second after generation of a burst of light by said analyzer, wherein the signal is collected during said time period.

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