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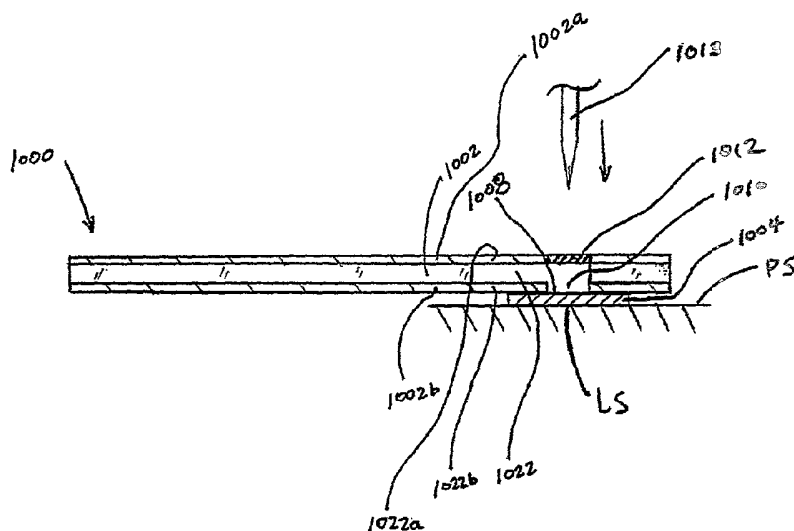
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[Continued on next page]

(54) Title: SAMPLE ELEMENT WITH BARRIER MATERIAL



(57) Abstract: Disclosed is a sample element (1000) for holding a volume of bodily fluid drawn from the skin of a patient (ps) at a withdrawal site (LS). The sample element comprises a housing defining a sample chamber (1002) therein, and a barrier (1004). The barrier has a first side configured to contact the skin of the patient at the withdrawal site, and a second side in fluid communication with the sample chamber. The barrier is configured to be pierced by a lance (1013), to permit the bodily fluid to pass from the first side to the second side. Also disclosed is a method of drawing a bodily fluid from the skin of a patient at a withdrawal site. The method comprises placing a first side of a barrier against the skin of the patient at the withdrawal site. The method further comprises forming a first opening through the barrier and a second opening in the skin of the patient at the withdrawal site. The first opening and the second opening are in fluid communication. The method further comprises placing a sample chamber in fluid communication with a second side of the barrier.



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SAMPLE ELEMENT WITH BARRIER MATERIAL

Background of the Invention

Field of the Invention

[0001] This invention relates generally to determining analyte concentrations in material samples.

Description of the Related Art

[0002] Millions of diabetics draw samples of bodily fluid such as blood on a daily basis to monitor the level of glucose in their bloodstream. A small test strip is often employed to hold the sample for analysis by a suitable analyte detection system. These test strips and detection systems suffer from a variety of problems and also have limited performance.

Summary of the Invention

[0003] One embodiment involves a sample element for holding a volume of bodily fluid drawn from the skin of a patient at a withdrawal site. The sample element comprises a housing defining a sample chamber therein, and a barrier. The barrier has a first side configured to contact the skin of the patient at the withdrawal site, and a second side in fluid communication with the sample chamber. The barrier is configured to be pierced by a lance, to permit the bodily fluid to pass from the first side to the second side.

[0004] Another embodiment involves a method of drawing a bodily fluid from the skin of a patient at a withdrawal site. The method comprises placing a first side of a barrier against the skin of the patient at the withdrawal site. The method further comprises forming a first opening through the barrier and a second opening in the skin of the patient at the withdrawal site. The first opening and the second opening are in fluid communication. The method further comprises placing a sample chamber in fluid communication with a second side of the barrier.

[0005] Another embodiment involves a sample element for holding a volume of bodily fluid. The sample element comprises a housing having a sample chamber therein, and a flow path extending from the sample chamber. The sample element further

comprises a barrier disposed across the flow path. The barrier has a first side configured to contact the skin of a patient at a lancing site. The flow path is enclosed on all sides except where the flow path joins the sample chamber such that, upon formation of an opening in the barrier, fluid may flow from the first side, through the flow path and into the sample chamber.

[0006] Certain objects and advantages of the invention are described herein. Of course, it is to be understood that not necessarily all such objects or advantages may be achieved in accordance with any particular embodiment of the invention. Thus, for example, those skilled in the art will recognize that the invention may be embodied or carried out in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other objects or advantages as may be taught or suggested herein.

[0007] All of the embodiments summarized above are intended to be within the scope of the invention herein disclosed. However, despite the foregoing discussion of certain embodiments, only the appended claims (and not the present summary) are intended to define the invention. The summarized embodiments, and other embodiments of the present invention, will become readily apparent to those skilled in the art from the following detailed description of the preferred embodiments having reference to the attached figures, the invention not being limited to any particular embodiment(s) disclosed.

Brief Description of the Drawings

[0008] Figure 1 is a schematic illustration of one embodiment of an analyte detection system.

[0009] Figure 2 is a schematic illustration of another embodiment of the analyte detection system.

[0010] Figure 3 is a plan view of one embodiment of a filter wheel suitable for use in the analyte detection system depicted in Figure 2.

[0011] Figure 4 is a partial sectional view of another embodiment of an analyte detection system.

[0012] Figure 5 is a detailed sectional view of a sample detector of the analyte detection system illustrated in Figure 4.

[0013] Figure 6 is a detailed sectional view of a reference detector of the analyte detection system illustrated in Figure 4.

[0014] Figure 7 is a flowchart of one embodiment of a method of operation of various embodiments of the analyte detection system.

[0015] Figure 8 is a plan view of one embodiment of a sample element suitable for use in combination with various embodiments of the analyte detection system.

[0016] Figure 9 is a side elevation view of the sample element illustrated in Figure 8.

[0017] Figure 10 is an exploded view of the sample element illustrated in Figure 8.

[0018] Figure 11 is a cross-sectional view of one embodiment of a sample element configured for analysis of a sample at two separate pathlengths.

[0019] Figure 12 is a cross-sectional view of the sample element of Figure 11, as employed in an alternative method of analysis.

[0020] Figure 13 is a cross-sectional view of one embodiment of an analyte detection system configured for changing an optical pathlength of a sample element.

[0021] Figure 14 is a cross-sectional view of another embodiment of an analyte detection system configured for changing an optical pathlength of a sample element.

[0022] Figure 15 is a cross-sectional view of another embodiment of an analyte detection system configured for changing an optical pathlength of a sample element.

[0023] Figure 16 is a cross-sectional view of the analyte detection system of Figure 15, illustrating compression and expansion of a sample element employed therewith.

[0024] Figure 17 is a top plan view of another embodiment of a sample element configured for analysis of a sample at two separate pathlengths.

[0025] Figure 18 is a sectional view of the sample element of Figure 17.

[0026] Figure 19 is a bottom plan view of another embodiment of a sample element configured for analysis of a sample at two separate pathlengths.

[0027] Figure 20 is a sectional view of the sample element of Figure 19.

[0028] Figure 21 is an end sectional view of another embodiment of a sample element.

[0029] Figure 22 is a schematic view of one embodiment of a sample element employing a barrier material.

[0030] Figure 23 is a plan view of another embodiment of a sample element employing a barrier material.

[0031] Figure 24 is a sectional view of the sample element of Figure 23.

[0032] Figure 24A is a plan view of another embodiment of a sample element employing a barrier material.

[0033] Figure 24B is a sectional view of the sample element of Figure 24A.

[0034] Figure 25 is an elevation view of a sample extractor for use with the sample elements of Figures 22-24B.

[0035] Figure 26 is a sectional view of another embodiment of a sample extractor for use with the sample elements of Figures 22-24B.

[0036] Figure 27 is a sectional view of the function of the barrier.

[0037] Figure 28 is another sectional view of the function of the barrier.

Detailed Description of the Preferred Embodiment

[0038] Although certain preferred embodiments and examples are disclosed below, it will be understood by those skilled in the art that the invention extends beyond the specifically disclosed embodiments to other alternative embodiments and/or uses of the invention and obvious modifications and equivalents thereof. Thus it is intended that the scope of the invention herein disclosed should not be limited by the particular disclosed embodiments described below. In any method or process disclosed herein, the acts or operations making up the method/process may be performed in any suitable sequence, and are not necessarily limited to any particular disclosed sequence. For purposes of contrasting various embodiments with the prior art, certain aspects and advantages of these embodiments are described where appropriate herein. Of course, it is to be understood that not necessarily all such aspects or advantages may be achieved in accordance with any particular embodiment. Thus, for example, it should be recognized that the various embodiments may be carried out in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other aspects or advantages as may be taught or suggested herein.

[0039] Section I below discloses various embodiments of an analyte detection system that may be used to detect the concentration of one or more analytes in a material sample. Section II discloses various embodiments of a cuvette or sample element which are suitable for use with the embodiments of the analyte detection system discussed in Section I. The disclosed embodiments of the sample element are configured to support or contain a material sample for analysis by the analyte detection system. In Section III, there are disclosed a number of methods for sample-element referencing, which generally comprises compensating for the effects of the sample element itself on the measurement of analyte concentration. Any one or combination of the methods disclosed in Section III may be executed wholly or partly by appropriate processing hardware in the analyte detection system to support computation of the concentration of the analyte(s) of interest in the sample. Section III also discloses further variations of the analyte detection system and sample element, which are adapted for use in practicing the disclosed methods of sample-element referencing.

[0040] Section IV below discusses a number of computational methods or algorithms which may be used to calculate the concentration of the analyte(s) of interest in the sample, and/or to compute or estimate other measures that may be used in support of calculations of analyte concentrations. Any one or combination of the algorithms disclosed in Section IV may be executed by appropriate processing hardware in the analyte detection system to compute the concentration of the analyte(s) of interest in the sample. Section V discloses further embodiments of a sample element and a barrier that may be used with a sample element.

I. ANALYTE DETECTION SYSTEM

[0041] Figure 1 is a schematic view of one embodiment of an analyte detection system 10. The detection system 10 is particularly suited for detecting the concentration of one or more analytes in a material sample S, by detecting energy transmitted through the sample, as will be discussed in further detail below.

[0042] The detection system 10 comprises an energy source 20 disposed along a major axis X of the system 10. When activated, the energy source 20 generates an energy beam E which advances from the energy source 20 along the major axis X. In one embodiment, the energy source 20 comprises an infrared source and the energy beam E comprises an infrared energy beam.

[0043] The energy beam E passes through a filter 25, also situated on the major axis X, before reaching a sample element or cuvette 120, which supports or contains the material sample S. After passing through the sample element 120 and the sample S, the energy beam E reaches a detector 145.

[0044] With further reference to Figure 1, the detector 145 responds to radiation incident thereon by generating an electrical signal and passing the signal to a processor 180 for analysis. Based on the signal(s) passed to it by the detector 145, the processor computes the concentration of the analyte(s) of interest in the sample S, and/or the absorbance/transmittance characteristics of the sample S at one or more wavelengths or wavelength bands employed to analyze the sample. The processor 180 computes the concentration(s), absorbance(s), transmittance(s), etc. by executing a data processing algorithm or program instructions residing within memory 185 accessible by the processor 180.

[0045] In the embodiment shown in Figure 1, the filter 25 may comprise a varying-passband filter, to facilitate changing, over time and/or during a measurement taken with the detection system 10, the wavelength or wavelength band of the energy beam E that may pass the filter 25 for use in analyzing the sample S. (In various other embodiments, the filter 25 may be omitted altogether.) Some examples of a varying-passband filter usable with the detection system 10 include, but are not limited to, a filter wheel (discussed in further detail below), electronically tunable filter, Fabry-Perot interferometer, or any other suitable varying-passband filter.

[0046] When the energy beam E is filtered with a varying-passband filter, the absorption/transmittance characteristics of the sample S can be analyzed at a number of wavelengths or wavelength bands in a separate, sequential manner. As an example, assume that it is desired to analyze the sample S at four separate wavelengths (Wavelength 1 through Wavelength 4). The varying-passband filter is first operated or tuned to permit the energy beam E to pass at Wavelength 1, while substantially blocking the beam E at most or all other wavelengths to which the detector 145 is sensitive (including Wavelengths 2-4). The absorption/transmittance properties of the sample S are then measured at Wavelength 1, based on the beam E that passes through the sample S and reaches the detector 145. The varying-passband filter is then operated or tuned to permit the energy beam E to pass at Wavelength 2, while substantially blocking other wavelengths as discussed above; the

sample S is then analyzed at Wavelength 2 as was done at Wavelength 1. This process is repeated until all of the wavelengths of interest have been employed to analyze the sample S. The collected absorption/transmittance data can then be analyzed by the processor 180 to determine the concentration of the analyte(s) of interest in the material sample S.

[0047] By analyzing the sample S at each wavelength or wavelength band in this separate, sequential fashion, greater precision can be attained because the noise, interference, etc. otherwise caused by the detection of wavelengths other than the wavelength of immediate interest, is minimized. However, any other suitable detection methodology may be used with the detection system 10, whether or not the system 10 includes a varying-passband filter.

[0048] Although the use of a varying-passband filter offers certain advantages as discussed above, a fixed-passband filter may be used as an alternative filter 25, to permit a selected wavelength or wavelength band to pass through the sample S for analysis thereof.

[0049] As used herein, the term “material sample” (or, alternatively, “sample”) is a broad term and is used in its ordinary sense and includes, without limitation, any collection of material which is suitable for analysis by the analyte detection system 10. For example, the material sample S may comprise whole blood, blood components (e.g., plasma or serum), interstitial fluid, intercellular fluid, saliva, urine, sweat and/or other organic or inorganic materials, or derivatives of any of these materials. In one embodiment, whole blood or blood components may be drawn from a patient's capillaries. As used herein, the term “analyte” is a broad term and is used in its ordinary sense and includes, without limitation, any chemical species the presence or concentration of which is sought in the material sample S by the analyte detection system 10. For example, the analyte(s) which may be detected by the analyte detection system 10 include but not are limited to glucose, ethanol, insulin, water, carbon dioxide, blood oxygen, cholesterol, bilirubin, ketones, fatty acids, lipoproteins, albumin, urea, creatinine, white blood cells, red blood cells, hemoglobin, oxygenated hemoglobin, carboxyhemoglobin, organic molecules, inorganic molecules, pharmaceuticals, cytochrome, various proteins and chromophores, microcalcifications, electrolytes, sodium, potassium, chloride, bicarbonate, and hormones.

[0050] Figure 2 depicts another embodiment of the analyte detection system 10, which may be generally similar to the embodiment illustrated in Figure 1, except as further

detailed below. Where possible, similar elements are identified with identical reference numerals in the depiction of the embodiments of Figures 1 and 2.

[0051] The detection system 10 shown in Figure 2 includes a collimator 30 through which the energy beam E passes before reaching a primary filter 40 disposed downstream of a wide end 36 of the collimator 30. The primary filter 40 is aligned with the source 20 and collimator 30 on the major axis X and is preferably configured to operate as a broadband filter, allowing only a selected band, e.g. between about 2.5 μm and about 12.5 μm , of wavelengths emitted by the source 20 to pass therethrough, as discussed below. In one embodiment, the energy source 20 comprises an infrared source and the energy beam E comprises an infrared energy beam. One suitable energy source 20 is the TOMA TECHTM IR-50 available from HawkEye Technologies of Milford, Connecticut.

[0052] With further reference to Figure 2, the primary filter 40 is mounted in a mask 44 so that only those portions of the energy beam E which are incident on the primary filter 40 can pass the plane of the mask-primary filter assembly. The primary filter 40 is generally centered on and oriented orthogonal to the major axis X and is preferably circular (in a plane orthogonal to the major axis X) with a diameter of about 8 mm. Of course, any other suitable size or shape may be employed. As discussed above, the primary filter 40 preferably operates as a broadband filter. In the illustrated embodiment, the primary filter 40 preferably allows only energy wavelengths between about 4 μm and about 11 μm to pass therethrough. However, other ranges of wavelengths can be selected. The primary filter 40 advantageously reduces the filtering burden of secondary filter(s) 60 disposed downstream of the primary filter 40 and improves the rejection of electromagnetic radiation having a wavelength outside of the desired wavelength band. Additionally, the primary filter 40 can help minimize the heating of the secondary filter(s) 60 by the energy beam E passing therethrough. Despite these advantages, the primary filter 40 and/or mask 44 may be omitted in alternative embodiments of the system 10 shown in Figure 2.

[0053] The primary filter 40 is preferably configured to substantially maintain its operating characteristics (center wavelength, passband width) where some or all of the energy beam E deviates from normal incidence by a cone angle of up to about twelve degrees relative to the major axis X. In further embodiments, this cone angle may be up to about 15 degrees or 20 degrees. The primary filter 40 may be said to "substantially maintain" its operating characteristics where any changes therein are insufficient to affect

the performance or operation of the detection system 10 in a manner that would raise significant concerns for the user(s) of the system in the context in which the system 10 is employed.

[0054] In the embodiment illustrated in Figure 2, a filter wheel 50 is employed as a varying-passband filter, to selectively position the secondary filter(s) 60 on the major axis X and/or in the energy beam E. The filter wheel 50 can therefore selectively tune the wavelength(s) of the energy beam E downstream of the wheel 50. These wavelength(s) vary according to the characteristics of the secondary filter(s) 60 mounted in the filter wheel 50. The filter wheel 50 positions the secondary filter(s) 60 in the energy beam E in a “one-at-a-time” fashion to sequentially vary, as discussed above, the wavelengths or wavelength bands employed to analyze the material sample S.

[0055] In alternative arrangements, the single primary filter 40 depicted in Figure 2 may be replaced or supplemented with additional primary filters mounted on the filter wheel 50 upstream of each of the secondary filters 60. As yet another alternative, the primary filter 40 could be implemented as a primary filter wheel (not shown) to position different primary filters on the major axis X at different times during operation of the detection system 10, or as a tunable filter.

[0056] The filter wheel 50, in the embodiment depicted in Figure 3, can comprise a wheel body 52 and a plurality of secondary filters 60 disposed on the body 52, the center of each filter being equidistant from a rotational center RC of the wheel body. The filter wheel 50 is configured to rotate about an axis which is (i) parallel to the major axis X and (ii) spaced from the major axis X by an orthogonal distance approximately equal to the distance between the rotational center RC and any of the center(s) of the secondary filter(s) 60. Under this arrangement, rotation of the wheel body 52 advances each of the filters sequentially through the major axis X, so as to act upon the energy beam E. (However, depending on the analyte(s) of interest or desired measurement speed, only a subset of the filters on the wheel 50 may be employed in a given measurement run.) In the embodiment depicted in Figure 3, the wheel body 52 is circular; however, any suitable shape, such as oval, square, rectangular, triangular, etc. may be employed. A home position notch 54 may be provided to indicate the home position of the wheel 50 to a position sensor 80.

[0057] In one embodiment, the wheel body 52 can be formed from molded plastic, with each of the secondary filters 60 having a 5 mm x 5 mm square configuration and a thickness of 1 mm. Each of the filters 60, in this embodiment of the wheel body, is axially aligned with a circular aperture of 4 mm diameter, and the aperture centers define a circle of about 1.70 inches diameter, which circle is concentric with the wheel body 52. The body 52 itself is circular, with an outside diameter of 2.00 inches.

[0058] Each of the secondary filter(s) 60 is preferably configured to operate as a narrow band filter, allowing only a selected energy wavelength or wavelength band (i.e., a filtered energy beam (Ef) to pass therethrough. As the filter wheel 50 rotates about its rotational center RC, each of the secondary filter(s) 60 is, in turn, disposed along the major axis X for a selected dwell time corresponding to each of the secondary filter(s) 60.

[0059] The "dwell time" for a given secondary filter 60 is the time interval, in an individual measurement run of the system 10, during which both of the following conditions are true: (i) the filter is disposed on the major axis X; and (ii) the source 20 is energized. The dwell time for a given filter may be greater than or equal to the time during which the filter is disposed on the major axis X during an individual measurement run. In one embodiment of the analyte detection system 10, the dwell time corresponding to each of the secondary filter(s) 60 is less than about 1 second. However, the secondary filter(s) 60 can have other dwell times, and each of the filter(s) 60 may have a different dwell time during a given measurement run.

[0060] Referring again to Figure 2, a stepper motor 70 is connected to the filter wheel 50 and is configured to generate a force to rotate the filter wheel 50. Additionally, the position sensor 80 is disposed over a portion of the circumference of the filter wheel 50 and may be configured to detect the angular position of the filter wheel 50 and to generate a corresponding filter wheel position signal, thereby indicating which filter is in position on the major axis X. Alternatively, the stepper motor 70 may be configured to track or count its own rotation(s), thereby tracking the angular position of the filter wheel, and pass a corresponding position signal to the processor 180. Two suitable position sensors are models EE-SPX302-W2A and EE-SPX402-W2A available from Omron Corporation of Kyoto, Japan.

[0061] From the secondary filter 60, the filtered energy beam (Ef) passes through a beam splitter 100 disposed along the major axis X and having a face 100a

disposed at an included angle θ relative to the major axis X. The splitter 100 preferably separates the filtered energy beam (Ef) into a sample beam (Es) and a reference beam (Er).

[0062] With further reference to Figure 2, the sample beam (Es) passes next through a first lens 110 aligned with the splitter 100 along the major axis X. The first lens 110 is configured to focus the sample beam (Es) generally along the axis X onto the material sample S. The sample S is preferably disposed in a sample element 120 between a first window 122 and a second window 124 of the sample element 120. The sample element 120 is further preferably removably disposed in a holder 130, and the holder 130 has a first opening 132 and a second opening 134 configured for alignment with the first window 122 and second window 124, respectively. Alternatively, the sample element 120 and sample S may be disposed on the major axis X without use of the holder 130.

[0063] At least a fraction of the sample beam (Es) is transmitted through the sample S and continues onto a second lens 140 disposed along the major axis X. The second lens 140 is configured to focus the sample beam (Es) onto a sample detector 150, thus increasing the flux density of the sample beam (Es) incident upon the sample detector 150. The sample detector 150 is configured to generate a signal corresponding to the detected sample beam (Es) and to pass the signal to a processor 180, as discussed in more detail below.

[0064] The reference beam (Er) is directed from the beam splitter 100 to a third lens 160 disposed along a minor axis Y generally orthogonal to the major axis X. The third lens 160 is configured to focus the reference beam (Er) onto a reference detector 170, thus increasing the flux density of the reference beam (Er) incident upon the reference detector 170. In one embodiment, the lenses 110, 140, 160 may be formed from a material which is highly transmissive of infrared radiation, for example germanium or silicon. In addition, any of the lenses 110, 140 and 160 may be implemented as a system of lenses, depending on the desired optical performance. The reference detector 170 is also configured to generate a signal corresponding to the detected reference beam (Er) and to pass the signal to the processor 180, as discussed in more detail below. Except as noted below, the sample and reference detectors 150, 170 may be generally similar to the detector 145 illustrated in Figure 1. Based on signals received from the sample and reference detectors 150, 170, the processor 180 computes the concentration(s), absorbance(s), transmittance(s), etc. relating

to the sample S by executing a data processing algorithm or program instructions residing within the memory 185 accessible by the processor 180.

[0065] In further variations of the detection system 10 depicted in Figure 2, the beam splitter 100, reference detector 170 and other structures on the minor axis Y may be omitted, especially where the output intensity of the source 20 is sufficiently stable to obviate any need to reference the source intensity in operation of the detection system 10. Furthermore, in any of the embodiments of the analyte detection system 10 disclosed herein, the processor 180 and/or memory 185 may reside partially or wholly in a standard personal computer ("PC") coupled to the detection system 10.

[0066] Figure 4 depicts a partial cross-sectional view of another embodiment of an analyte detection system 10, which may be generally similar to any of the embodiments illustrated in Figures 1-3, except as further detailed below. Where possible, similar elements are identified with identical reference numerals in the depiction of the embodiments of Figures 1-4.

[0067] The energy source 20 of the embodiment of Figure 4 preferably comprises an emitter area 22 which is substantially centered on the major axis X. In one embodiment, the emitter area 22 may be square in shape. However the emitter area 22 can have other suitable shapes, such as rectangular, circular, elliptical, etc. One suitable emitter area 22 is a square of about 1.5 mm on a side; of course, any other suitable shape or dimensions may be employed.

[0068] The energy source 20 is preferably configured to selectably operate at a modulation frequency between about 1 Hz and 30 Hz and have a peak operating temperature of between about 1070 degrees Kelvin and 1170 degrees Kelvin. Additionally, the source 20 preferably operates with a modulation depth greater than about 80% at all modulation frequencies. The energy source 20 preferably emits electromagnetic radiation in any of a number of spectral ranges, e.g., within infrared wavelengths; in the mid-infrared wavelengths; above about 0.8 μm ; between about 5.0 μm and about 20.0 μm ; and/or between about 5.25 μm and about 12.0 μm . However, in other embodiments, the detection system 10 may employ an energy source 20 which is unmodulated and/or which emits in wavelengths found anywhere from the visible spectrum through the microwave spectrum, for example anywhere from about 0.4 μm to greater than about 100 μm . In still other embodiments, the energy source 20 can emit electromagnetic radiation in wavelengths

between about 3.5 μm and about 14 μm , or between about 0.8 μm and about 2.5 μm , or between about 2.5 μm and 20 μm , or between about 20 μm and about 100 μm , or between about 6.85 μm and about 10.10 μm . In yet other embodiments, the energy source 20 can emit electromagnetic radiation within the radio frequency (RF) range or the terahertz range. All of the above-recited operating characteristics are merely exemplary, and the source 20 may have any operating characteristics suitable for use with the analyte detection system 10.

[0069] A power supply (not shown) for the energy source 20 is preferably configured to selectably operate with a duty cycle of between about 30% and about 70%. Additionally, the power supply is preferably configured to selectably operate at a modulation frequency of about 10Hz, or between about 1 Hz and about 30 Hz. The operation of the power supply can be in the form of a square wave, a sine wave, or any other waveform defined by a user.

[0070] With further reference to Figure 4, the collimator 30 comprises a tube 30a with one or more highly-reflective inner surfaces 32 which diverge from a relatively narrow upstream end 34 to a relatively wide downstream end 36 as they extend downstream, away from the energy source 20. The narrow end 34 defines an upstream aperture 34a which is situated adjacent the emitter area 22 and permits radiation generated by the emitter area to propagate downstream into the collimator. The wide end 36 defines a downstream aperture 36a. Like the emitter area 22, each of the inner surface(s) 32, upstream aperture 34a and downstream aperture 36a is preferably substantially centered on the major axis X.

[0071] As illustrated in Figure 4, the inner surface(s) 32 of the collimator may have a generally curved shape, such as a parabolic, hyperbolic, elliptical or spherical shape. One suitable collimator 30 is a compound parabolic concentrator (CPC). In one embodiment, the collimator 30 can be up to about 20 mm in length. In another embodiment, the collimator 30 can be up to about 30 mm in length. However, the collimator 30 can have any length, and the inner surface(s) 32 may have any shape, suitable for use with the analyte detection system 10.

[0072] The inner surfaces 32 of the collimator 30 cause the rays making up the energy beam E to straighten (i.e., propagate at angles increasingly parallel to the major axis X) as the beam E advances downstream, so that the energy beam E becomes increasingly or

substantially cylindrical and oriented substantially parallel to the major axis X. Accordingly, the inner surfaces 32 are highly reflective and minimally absorptive in the wavelengths of interest, such as infrared wavelengths.

[0073] The tube 30a itself may be fabricated from a rigid material such as aluminum, steel, or any other suitable material, as long as the inner surfaces 32 are coated or otherwise treated to be highly reflective in the wavelengths of interest. For example, a polished gold coating may be employed. Preferably, the inner surface(s) 32 of the collimator 30 define a circular cross-section when viewed orthogonal to the major axis X; however, other cross-sectional shapes, such as a square or other polygonal shapes, parabolic or elliptical shapes may be employed in alternative embodiments.

[0074] As noted above, the filter wheel 50 shown in Figure 4 comprises a plurality of secondary filters 60 which preferably operate as narrow band filters, each filter allowing only energy of a certain wavelength or wavelength band to pass therethrough. In one configuration suitable for detection of glucose in a sample S, the filter wheel 50 comprises twenty or twenty-two secondary filters 60, each of which is configured to allow a filtered energy beam (Ef) to travel therethrough with a nominal wavelength approximately equal to one of the following: 3 μm , 4.06 μm , 4.6 μm , 4.9 μm , 5.25 μm , 6.12 μm , 6.47 μm , 7.98 μm , 8.35 μm , 9.65 μm , and 12.2 μm . (Moreover, this set of wavelengths may be employed with or in any of the embodiments of the analyte detection system 10 disclosed herein.) Each secondary filter's 60 center wavelength is preferably equal to the desired nominal wavelength plus or minus about 2%. Additionally, the secondary filters 60 are preferably configured to have a bandwidth of about 0.2 μm , or alternatively equal to the nominal wavelength plus or minus about 2%-10%.

[0075] In another embodiment, the filter wheel 50 comprises twenty secondary filters 60, each of which is configured to allow a filtered energy beam (Ef) to travel therethrough with a nominal center wavelengths of: 4.275 μm , 4.5 μm , 4.7 μm , 5.0 μm , 5.3 μm , 6.056 μm , 7.15 μm , 7.3 μm , 7.55 μm , 7.67 μm , 8.06 μm , 8.4 μm , 8.56 μm , 8.87 μm , 9.15 μm , 9.27 μm , 9.48 μm , 9.68 μm , 9.82 μm , and 10.06 μm . (This set of wavelengths may also be employed with or in any of the embodiments of the analyte detection system 10 disclosed herein.) In still another embodiment, the secondary filters 60 may conform to any one or combination of the following specifications: center wavelength tolerance of ± 0.01

μm ; half-power bandwidth tolerance of $\pm 0.01 \mu\text{m}$; peak transmission greater than or equal to 75%; cut-on/cut-off slope less than 2%; center-wavelength temperature coefficient less than .01% per degree Celsius; out of band attenuation greater than OD 5 from $3 \mu\text{m}$ to $12 \mu\text{m}$; flatness less than 1.0 waves at $0.6328 \mu\text{m}$; surface quality of E-E per Mil-F-48616; and overall thickness of about 1 mm.

[0076] In still another embodiment, the secondary filters mentioned above may conform to any one or combination of the following half-power bandwidth ("HPBW") specifications:

Center Wavelength (μm)	HPBW (μm)	Center Wavelength (μm)	HPBW (μm)
4.275	0.05	8.06	0.3
4.5	0.18	8.4	0.2
4.7	0.13	8.56	0.18
5.0	0.1	8.87	0.2
5.3	0.13	9.15	0.15
6.056	0.135	9.27	0.14
7.15	0.19	9.48	0.23
7.3	0.19	9.68	0.3
7.55	0.18	9.82	0.34
7.67	0.197	10.06	0.2

[0077] In still further embodiments, the secondary filters may have a center wavelength tolerance of $\pm 0.5 \%$ and a half-power bandwidth tolerance of $\pm 0.02 \mu\text{m}$.

[0078] Of course, the number of secondary filters employed, and the center wavelengths and other characteristics thereof, may vary in further embodiments of the system 10, whether such further embodiments are employed to detect glucose, or other analytes instead of or in addition to glucose. For example, in another embodiment, the filter wheel 50 can have fewer than fifty secondary filters 60. In still another embodiment, the filter wheel 50 can have fewer than twenty secondary filters 60. In yet another embodiment, the filter wheel 50 can have fewer than ten secondary filters 60.

[0079] In one embodiment, the secondary filters 60 each measure about 10 mm long by 10 mm wide in a plane orthogonal to the major axis X, with a thickness of about 1 mm. However, the secondary filters 60 can have any other (e.g., smaller) dimensions suitable for operation of the analyte detection system 10. Additionally, the secondary filters 60 are preferably configured to operate at a temperature of between about 5°C and about

35 °C and to allow transmission of more than about 75% of the energy beam E therethrough in the wavelength(s) which the filter is configured to pass.

[0080] According to the embodiment illustrated in Figure 4, the primary filter 40 operates as a broadband filter and the secondary filters 60 disposed on the filter wheel 50 operate as narrow band filters. However, one of ordinary skill in the art will realize that other structures can be used to filter energy wavelengths according to the embodiments described herein. For example, the primary filter 40 may be omitted and/or an electronically tunable filter or Fabry-Perot interferometer (not shown) can be used in place of the filter wheel 50 and secondary filters 60. Such a tunable filter or interferometer can be configured to permit, in a sequential, "one-at-a-time" fashion, each of a set of wavelengths or wavelength bands of electromagnetic radiation to pass therethrough for use in analyzing the material sample S.

[0081] A reflector tube 98 is preferably positioned to receive the filtered energy beam (Ef) as it advances from the secondary filter(s) 60. The reflector tube 98 is preferably secured with respect to the secondary filter(s) 60 to substantially prevent introduction of stray electromagnetic radiation, such as stray light, into the reflector tube 98 from outside of the detection system 10. The inner surfaces of the reflector tube 98 are highly reflective in the relevant wavelengths and preferably have a cylindrical shape with a generally circular cross-section orthogonal to the major and/or minor axis X, Y. However, the inner surface of the tube 98 can have a cross-section of any suitable shape, such as oval, square, rectangular, etc. Like the collimator 30, the reflector tube 98 may be formed from a rigid material such as aluminum, steel, etc., as long as the inner surfaces are coated or otherwise treated to be highly reflective in the wavelengths of interest. For example, a polished gold coating may be employed.

[0082] According to the embodiment illustrated in Figure 4, the reflector tube 98 preferably comprises a major section 98a and a minor section 98b. As depicted, the reflector tube 98 can be T-shaped with the major section 98a having a greater length than the minor section 98b. In another example, the major section 98a and the minor section 98b can have the same length. The major section 98a extends between a first end 98c and a second end 98d along the major axis X. The minor section 98b extends between the major section 98a and a third end 98e along the minor axis Y.

[0083] The major section 98a conducts the filtered energy beam (Ef) from the first end 98c to the beam splitter 100, which is housed in the major section 98a at the intersection of the major and minor axes X, Y. The major section 98a also conducts the sample beam (Es) from the beam splitter 100, through the first lens 110 and to the second end 98d. From the second end 98d the sample beam (Es) proceeds through the sample element 120, holder 130 and second lens 140, and to the sample detector 150. Similarly, the minor section 98b conducts the reference beam (Er) from the beam splitter 100, through the third lens 160 and to the third end 98e. From the third end 98e the reference beam (Er) proceeds to the reference detector 170.

[0084] The sample beam (Es) preferably comprises from about 75% to about 85% of the energy of the filtered energy beam (Ef). More preferably, the sample beam (Es) comprises about 80% of the energy of the filtered energy beam (Es). The reference beam (Er) preferably comprises from about 15% and about 25% of the energy of the filtered energy beam (Es). More preferably, the reference beam (Er) comprises about 20% of the energy of the filtered energy beam (Ef). Of course, the sample and reference beams may take on any suitable proportions of the energy beam E.

[0085] The reflector tube 98 also houses the first lens 110 and the third lens 160. As illustrated in Figure 4, the reflector tube 98 houses the first lens 110 between the beam splitter 100 and the second end 98d. The first lens 110 is preferably disposed so that a plane 112 of the lens 110 is generally orthogonal to the major axis X. Similarly, the tube 98 houses the third lens 160 between the beam splitter 100 and the third end 98e. The third lens 160 is preferably disposed so that a plane 162 of the third lens 160 is generally orthogonal to the minor axis Y. The first lens 110 and the third lens 160 each has a focal length configured to substantially focus the sample beam (Es) and reference beam (Er), respectively, as the beams (Es, Er) pass through the lenses 110, 160. In particular, the first lens 110 is configured, and disposed relative to the holder 130, to focus the sample beam (Es) so that substantially the entire sample beam (Es) passes through the material sample S, residing in the sample element 120. Likewise, the third lens 160 is configured to focus the reference beam (Er) so that substantially the entire reference beam (Er) impinges onto the reference detector 170.

[0086] The sample element 120 is retained within the holder 130, which is preferably oriented along a plane generally orthogonal to the major axis X. The holder 130

is configured to be slidably displaced between a loading position and a measurement position within the analyte detection system 10. In the measurement position, the holder 130 contacts a stop edge 136 which is located to orient the sample element 120 and the sample S contained therein on the major axis X.

[0087] The structural details of the holder 130 depicted in Figure 4 are unimportant, so long as the holder positions the sample element 120 and sample S on and substantially orthogonal to the major axis X, while permitting the energy beam E to pass through the sample element and sample. As with the embodiment depicted in Figure 2, the holder 130 may be omitted and the sample element 120 positioned alone in the depicted location on the major axis X. However, the holder 130 is useful where the sample element 120 (discussed in further detail below) is constructed from a highly brittle or fragile material, such as barium fluoride, or is manufactured to be extremely thin.

[0088] As with the embodiment depicted in Figure 2, the sample and reference detectors 150, 170 shown in Figure 4 respond to radiation incident thereon by generating signals and passing them to the processor 180. Based these signals received from the sample and reference detectors 150, 170, the processor 180 computes the concentration(s), absorbance(s), transmittance(s), etc. relating to the sample S by executing a data processing algorithm or program instructions residing within the memory 185 accessible by the processor 180. In further variations of the detection system 10 depicted in Figure 4, the beam splitter 100, reference detector 170 and other structures on the minor axis Y may be omitted, especially where the output intensity of the source 20 is sufficiently stable to obviate any need to reference the source intensity in operation of the detection system 10.

[0089] Figure 5 depicts a sectional view of the sample detector 150 in accordance with one embodiment. The sample detector 150 is mounted in a detector housing 152 having a receiving portion 152a and a cover 152b. However, any suitable structure may be used as the sample detector 150 and housing 152. The receiving portion 152a preferably defines an aperture 152c and a lens chamber 152d, which are generally aligned with the major axis X when the housing 152 is mounted in the analyte detection system 10. The aperture 152c is configured to allow at least a fraction of the sample beam (Es) passing through the sample S and the sample element 120 to advance through the aperture 152c and into the lens chamber 152d.

[0090] The receiving portion 152a houses the second lens 140 in the lens chamber 152d proximal to the aperture 152c. The sample detector 150 is also disposed in the lens chamber 152d downstream of the second lens 140 such that a detection plane 154 of the detector 150 is substantially orthogonal to the major axis X. The second lens 140 is positioned such that a plane 142 of the lens 140 is substantially orthogonal to the major axis X. The second lens 140 is configured, and is preferably disposed relative to the holder 130 and the sample detector 150, to focus substantially all of the sample beam (Es) onto the detection plane 154, thereby increasing the flux density of the sample beam (Es) incident upon the detection plane 154.

[0091] With further reference to Figure 5, a support member 156 preferably holds the sample detector 150 in place in the receiving portion 152a. In the illustrated embodiment, the support member 156 is a spring 156 disposed between the sample detector 150 and the cover 152b. The spring 156 is configured to maintain the detection plane 154 of the sample detector 150 substantially orthogonal to the major axis X. A gasket 157 is preferably disposed between the cover 152b and the receiving portion 152a and surrounds the support member 156.

[0092] The receiving portion 152a preferably also houses a printed circuit board 158 disposed between the gasket 157 and the sample detector 150. The board 158 connects to the sample detector 150 through at least one connecting member 150a. The sample detector 150 is configured to generate a detection signal corresponding to the sample beam (Es) incident on the detection plane 154. The sample detector 150 communicates the detection signal to the circuit board 158 through the connecting member 150a, and the board 158 transmits the detection signal to the processor 180.

[0093] In one embodiment, the sample detector 150 comprises a generally cylindrical housing 150a, e.g. a type TO-39 “metal can” package, which defines a generally circular housing aperture 150b at its “upstream” end. In one embodiment, the housing 150a has a diameter of about 0.323 inches and a depth of about 0.248 inches, and the aperture 150b may have a diameter of about 0.197 inches.

[0094] A detector window 150c is disposed adjacent the aperture 150b, with its upstream surface preferably about 0.078 inches (+/- 0.004 inches) from the detection plane 154. (The detection plane 154 is located about 0.088 inches (+/- 0.004 inches) from the upstream edge of the housing 150a, where the housing has a thickness of about 0.010

inches.) The detector window 150c is preferably transmissive of infrared energy in at least a 3-12 micron passband; accordingly, one suitable material for the window 150c is germanium. The endpoints of the passband may be "spread" further to less than 2.5 microns, and/or greater than 12.5 microns, to avoid unnecessary absorbance in the wavelengths of interest. Preferably, the transmittance of the detector window 150c does not vary by more than 2% across its passband. The window 150c is preferably about 0.020 inches in thickness. The sample detector 150 preferably substantially retains its operating characteristics across a temperature range of -20 to +60 degrees Celsius.

[0095] Figure 6 depicts a sectional view of the reference detector 170 in accordance with one embodiment. The reference detector 170 is mounted in a detector housing 172 having a receiving portion 172a and a cover 172b. However, any suitable structure may be used as the sample detector 150 and housing 152. The receiving portion 172a preferably defines an aperture 172c and a chamber 172d which are generally aligned with the minor axis Y, when the housing 172 is mounted in the analyte detection system 10. The aperture 172c is configured to allow the reference beam (Er) to advance through the aperture 172c and into the chamber 172d.

[0096] The receiving portion 172a houses the reference detector 170 in the chamber 172d proximal to the aperture 172c. The reference detector 170 is disposed in the chamber 172d such that a detection plane 174 of the reference detector 170 is substantially orthogonal to the minor axis Y. The third lens 160 is configured to substantially focus the reference beam (Er) so that substantially the entire reference beam (Er) impinges onto the detection plane 174, thus increasing the flux density of the reference beam (Er) incident upon the detection plane 174.

[0097] With further reference to Figure 6, a support member 176 preferably holds the reference detector 170 in place in the receiving portion 172a. In the illustrated embodiment, the support member 176 is a spring 176 disposed between the reference detector 170 and the cover 172b. The spring 176 is configured to maintain the detection plane 174 of the reference detector 170 substantially orthogonal to the minor axis Y. A gasket 177 is preferably disposed between the cover 172b and the receiving portion 172a and surrounds the support member 176.

[0098] The receiving portion 172a preferably also houses a printed circuit board 178 disposed between the gasket 177 and the reference detector 170. The board 178

connects to the reference detector 170 through at least one connecting member 170a. The reference detector 170 is configured to generate a detection signal corresponding to the reference beam (Er) incident on the detection plane 174. The reference detector 170 communicates the detection signal to the circuit board 178 through the connecting member 170a, and the board 178 transmits the detection signal to the processor 180.

[0099] In one embodiment, the construction of the reference detector 170 is generally similar to that described above with regard to the sample detector 150.

[0100] In one embodiment, the sample and reference detectors 150, 170 are both configured to detect electromagnetic radiation in a spectral wavelength range of between about 0.8 μm and about 25 μm . However, any suitable subset of the foregoing set of wavelengths can be selected. In another embodiment, the detectors 150, 170 are configured to detect electromagnetic radiation in the wavelength range of between about 4 μm and about 12 μm . The detection planes 154, 174 of the detectors 150, 170 may each define an active area about 2 mm by 2 mm or from about 1 mm by 1 mm to about 5 mm by 5 mm; of course, any other suitable dimensions and proportions may be employed. Additionally, the detectors 150, 170 may be configured to detect electromagnetic radiation directed thereto within a cone angle of about 45 degrees from the major axis X.

[0101] In one embodiment, the sample and reference detector subsystems 150, 170 may further comprise a system (not shown) for regulating the temperature of the detectors. Such a temperature-regulation system may comprise a suitable electrical heat source, thermistor, and a proportional-plus-integral-plus-derivative (PID) control. These components may be used to regulate the temperature of the detectors 150, 170 at about 35 °C. The detectors 150, 170 can also optionally be operated at other desired temperatures. Additionally, the PID control preferably has a control rate of about 60 Hz and, along with the heat source and thermistor, maintains the temperature of the detectors 150, 170 within about 0.1 °C of the desired temperature.

[0102] The detectors 150, 170 can operate in either a voltage mode or a current mode, wherein either mode of operation preferably includes the use of a pre-amp module. Suitable voltage mode detectors for use with the analyte detection system 10 disclosed herein include: models LIE 302 and 312 by InfraTec of Dresden, Germany; model L2002 by BAE Systems of Rockville, Maryland; and model LTS-1 by Dias of Dresden, Germany.

Suitable current mode detectors include: InfraTec models LIE 301, 315, 345 and 355; and 2x2 current-mode detectors available from Dias.

[0103] In one embodiment, one or both of the detectors 150, 170 may meet the following specifications, when assuming an incident radiation intensity of about 9.26×10^{-4} watts (rms) per cm^2 , at 10 Hz modulation and within a cone angle of about 15 degrees: detector area of 0.040 cm^2 (2 mm x 2 mm square); detector input of 3.70×10^{-5} watts (rms) at 10 Hz; detector sensitivity of 360 volts per watt at 10 Hz; detector output of 1.333×10^{-2} volts (rms) at 10 Hz; noise of 8.00×10^{-8} volts/sqrtHz at 10 Hz; and signal-to-noise ratios of 1.67×10^5 rms/sqrtHz and 104.4 dB/sqrtHz; and detectivity of 1.00×10^9 cm sqrtHz/watt.

[0104] In alternative embodiments, the detectors 150, 170 may comprise microphones and/or other sensors suitable for operation of the detection system 10 in a photoacoustic mode.

[0105] Any of the disclosed embodiments of the analyte detection system 10 may comprise a near-patient testing system. As used herein, "near-patient testing system" is used in its ordinary sense and includes, without limitation, test systems that are configured to be used where the patient is rather than exclusively in a laboratory, e.g., systems that can be used at a patient's home, in a clinic, in a hospital, or even in a mobile environment. Users of near-patient testing systems can include patients, family members of patients, clinicians, nurses, or doctors. A "near-patient testing system" could also include a "point-of-care" system.

[0106] The components of any of the embodiments of the analyte detection system 10 may be partially or completely contained in an enclosure or casing (not shown) to prevent stray electromagnetic radiation, such as stray light, from contaminating the energy beam E. Any suitable casing may be used. Similarly, the components of the detection system 10 may be mounted on any suitable frame or chassis (not shown) to maintain their operative alignment as depicted in Figures 1-2 and 4. The frame and the casing may be formed together as a single unit, member or collection of members.

[0107] Any of the disclosed embodiments of the analyte detection system 10 may in one embodiment be configured to be operated easily by the patient or user. As such, the system 10 is may comprise a portable device. As used herein, "portable" is used in its ordinary sense and means, without limitation, that the system 10 can be easily transported by the patient and used where convenient. For example, the system 10 is advantageously

small. In one preferred embodiment, the system 10 is small enough to fit into a purse or backpack. In another embodiment, the system 10 is small enough to fit into a pants pocket. In still another embodiment, the system 10 is small enough to be held in the palm of a hand of the user.

[0108] When enclosed in the external casing (not shown), the analyte detection system 10 is advantageously no larger than 5.4 inches long by 3.5 inches wide by 1.5 inches deep. In further embodiments, the enclosed system 10 may be no more than about 80% or 90% of this size. In still further embodiments, the enclosed analyte detection system 10 takes up less than about one-half, or less than about one-tenth the volume of a laboratory-grade Fourier Transform Infrared Spectrometer (FTIR), which typically measures about 2 feet wide by one foot high by one foot deep. Accordingly, in these embodiments the enclosed analyte detection system 10 has a volume of less than about 1750 cubic inches, or less than about 350 cubic inches. In still another embodiment, the analyte detection system 10 measures about 3.5 inches by 2.5 inches by 2.0 inches, and/or has a volume of about 10 cubic inches. Despite its relatively small size as disclosed above, the analyte detection system 10 achieves very good performance in a variety of measures. However, the analyte detection system 10 is not limited to these sizes and can be manufactured to other suitable dimensions as may be needed for particular applications.

[0109] In one method of operation, the analyte detection system 10 shown in Figures 2 or 4 measures the concentration of one or more analytes in the material sample S, in part, by comparing the electromagnetic radiation detected by the sample and reference detectors 150, 170. During operation of the detection system 10, each of the secondary filter(s) 60 is sequentially aligned with the major axis X for a dwell time corresponding to the secondary filter 60. (Of course, where an electronically tunable filter or Fabry-Perot interferometer is used in place of the filter wheel 50, the tunable filter or interferometer is sequentially tuned to each of a set of desired wavelengths or wavelength bands in lieu of the sequential alignment of each of the secondary filters with the major axis X.) The energy source 20 is then operated at (any) modulation frequency, as discussed above, during the dwell time period. The dwell time may be different for each secondary filter 60 (or each wavelength or band to which the tunable filter or interferometer is tuned). In one embodiment of the detection system 10, the dwell time for each secondary filter 60 is less than about 1 second. Use of a dwell time specific to each secondary filter 60

advantageously allows the detection system 10 to operate for a longer period of time at wavelengths where errors can have a greater effect on the computation of the analyte concentration in the material sample S. Correspondingly, the detection system 10 can operate for a shorter period of time at wavelengths where errors have less effect on the computed analyte concentration. The dwell times may otherwise be nonuniform among the filters/wavelengths/bands employed in the detection system.

[0110] For each secondary filter 60 selectively aligned with the major axis X, the sample detector 150 detects the portion of the sample beam (Es), at the wavelength or wavelength band corresponding to the secondary filter 60, that is transmitted through the material sample S. The sample detector 150 generates a detection signal corresponding to the detected electromagnetic radiation and passes the signal to the processor 180. Simultaneously, the reference detector 170 detects the reference beam (Er) transmitted at the wavelength or wavelength band corresponding to the secondary filter 60. The reference detector 170 generates a detection signal corresponding to the detected electromagnetic radiation and passes the signal to the processor 180. Based on the signals passed to it by the detectors 150, 170, the processor 180 computes the concentration of the analyte(s) of interest in the sample S, and/or the absorbance/transmittance characteristics of the sample S at one or more wavelengths or wavelength bands employed to analyze the sample. The processor 180 computes the concentration(s), absorbance(s), transmittance(s), etc. by executing a data processing algorithm or program instructions residing within the memory 185 accessible by the processor 180.

[0111] The signal generated by the reference detector may be used to monitor fluctuations in the intensity of the energy beam emitted by the source 20, which fluctuations often arise due to drift effects, aging, wear or other imperfections in the source itself. This enables the processor 180 to identify changes in intensity of the sample beam (Es) that are attributable to changes in the emission intensity of the source 20, and not to the composition of the sample S. By so doing, a potential source of error in computations of concentration, absorbance, etc. is minimized or eliminated.

[0112] In one embodiment, the detection system 10 computes an analyte concentration reading by first measuring the electromagnetic radiation detected by the detectors 150, 170 at each center wavelength, or wavelength band, without the sample element 120 present on the major axis X (this is known as an "air" reading). Second, the

system 10 measures the electromagnetic radiation detected by the detectors 150, 170 for each center wavelength, or wavelength band, with the sample element 120 present on the major axis X, but without the material sample S (i.e., a “dry” reading). Third, the system 10 measures the electromagnetic radiation detected by the detectors 150, 170 with an opaque element or mask (such as a secondary filter 60 which is substantially opaque in the wavelength(s) of interest) disposed on the major axis X between the source 20 and beam splitter 100, and/or with the source 20 switched off (i.e., a “dark” reading). Fourth, the system 10 measures the electromagnetic radiation detected by the detectors 150, 170 for each center wavelength, or wavelength band, with the material sample S present in the sample element 120, and the sample element 120 and sample S in position on the major axis X (i.e., a “wet” reading). Finally, the processor 10 computes the concentration(s), absorbance(s) and/or transmittances relating to the sample S based on these compiled readings.

[0113] Figure 7 depicts a further embodiment of a method 190 of operating either of the analyte detection systems 10 depicted in Figure 2 or Figure 4 (or, alternatively, any suitable detection system). In the following description, the method 190 is conducted in the transmittance domain; however, it may alternatively be performed in the absorbance domain with the relevant measures adjusted accordingly for working with absorbance measures rather than transmittance measures.

[0114] In an operational block 190a, a “dark” reading is taken as discussed above, wherein the processor 180 computes a dark transmittance reading TD, which is stored in memory. Next, an “air” reading is taken, as discussed above, in an operational block 190b. This operation may comprise computing and storing an air transmittance reading TA, and a gain factor GF which equals $100\%/TA$ (see operational block 190c), as well as a simultaneous air reference intensity RIA (operational block 190d), based on the output of the reference detector 170 during the air reading. In one embodiment, any or all of the air transmittance reading TA, gain factor GF and air reference intensity RIA are computed at each of the wavelengths or wavelength bands of interest, yielding, for example, $TA_{\lambda 1}$, $TA_{\lambda 2}$, ... $TA_{\lambda n}$; $GF_{\lambda 1}$, $GF_{\lambda 2}$, ... $GF_{\lambda n}$; etc.

[0115] In operational block 190e, a “wet” reading is taken as described above, with the sample element and sample S therein positioned on the major axis X. The wet reading yields a series of wavelength-specific transmittance values $T_{\lambda 1}$, $T_{\lambda 2}$, ... $T_{\lambda n}$ in each

of the wavelengths or bands of interest, which values are stored in memory, along with simultaneously-recorded corresponding wet reference intensities $RIW_{\lambda 1}$, $RIW_{\lambda 2}$, ... $RIW_{\lambda n}$ which arise from the output of the reference detector 170 at each wavelength/band of interest while the wet reading is taken. The wet reading is then shifted (see block 190f) by subtracting the dark transmittance reading(s) from each of the wavelength-specific transmittance values $T_{\lambda 1}$, $T_{\lambda 2}$, ... $T_{\lambda n}$, yielding shifted transmittance values $TS_{\lambda 1}$, $TS_{\lambda 2}$, ... $TS_{\lambda n}$. In block 190g, the shifted transmittance values are scaled by multiplying each of the values $TS_{\lambda 1}$, $TS_{\lambda 2}$, ... $TS_{\lambda n}$ by the previously-computed gain factor (s) GF. Where wavelength-specific gain factors $GF_{\lambda 1}$, $GF_{\lambda 2}$, ... $GF_{\lambda n}$ have been computed, each shifted transmittance value $TS_{\lambda i}$ is multiplied by its corresponding gain factor $GF_{\lambda i}$. Either option yields shifted, scaled transmittance values $TSS_{\lambda 1}$, $TSS_{\lambda 2}$, ... $TSS_{\lambda n}$.

[0116] In operational block 190h, each of the shifted, scaled transmittance values $TSS_{\lambda 1}$, $TSS_{\lambda 2}$, ... $TSS_{\lambda n}$ is source-referenced. First, a series of reference factors $RF_{\lambda 1}$, $RF_{\lambda 2}$, ... $RF_{\lambda n}$ are computed by dividing the air reference intensity RIA by each of the wet reference intensities $RIW_{\lambda 1}$, $RIW_{\lambda 2}$, ... $RIW_{\lambda n}$. Where a series of air reference intensities $RIA_{\lambda 1}$, $RIA_{\lambda 2}$, ... $RIA_{\lambda n}$ have been compiled, each air reference intensity $RIA_{\lambda i}$ is divided by its corresponding wet reference intensity $RIW_{\lambda i}$ to generate the reference factors $RF_{\lambda 1}$, $RF_{\lambda 2}$, ... $RF_{\lambda n}$. Each of the shifted, scaled transmittance values $TSS_{\lambda 1}$, $TSS_{\lambda 2}$, ... $TSS_{\lambda n}$ is source-referenced by multiplying it by the corresponding reference factor $RF_{\lambda 1}$, $RF_{\lambda 2}$, ... $RF_{\lambda n}$ to generate shifted, scaled, source-referenced transmittance values $TSSR_{\lambda 1}$, $TSSR_{\lambda 2}$, ... $TSSR_{\lambda n}$.

[0117] Each of the shifted, scaled, source-referenced transmittance values $TSSR_{\lambda 1}$, $TSSR_{\lambda 2}$, ... $TSSR_{\lambda n}$ is sample-element referenced in operational block 190i, to yield final transmittance values $TF_{\lambda 1}$, $TF_{\lambda 2}$, ... $TF_{\lambda n}$. Any of the sample-element referencing methods disclosed herein may be employed. While the sample-element referencing operation 190i is depicted at the end of the illustrated method 190, this referencing 190i may in practice comprise a number of sub-operations that are intermingled with the other operations of the method 190, as will become apparent from the discussion herein of the various sample-element referencing methods. Regardless of the nature of the sample-element referencing operation, the final transmittance values $TF_{\lambda 1}$, $TF_{\lambda 2}$, ... $TF_{\lambda n}$ may then be employed to compute the concentration of the analyte(s) of interest in the sample S.

[0118] In further embodiments, any suitable variation of the method 190 may be employed. Any one or combination of the operations 190a-190i may be omitted, depending on the desired level of measurement precision. For example, the dark reading 190a and subsequent shift 190f may be omitted. Instead of or in addition to omission of these operations 190a, 190f, the air reading 190b may be omitted, in whole or in part. Where measurement/computation of the air transmittance reading TA and gain factor GF (block 190c) are omitted, the scaling operation 190g may also be omitted; likewise, where measurement/computation of the air reference intensity RIA (block 190d) is omitted, the source referencing operation 190h may also be omitted. Finally, instead or in addition to the foregoing omissions, the sample element referencing operation 190i may be omitted.

[0119] In any variation of the method 190, the operations may be performed in any suitable sequence, and the method 190 is by no means limited to the sequence depicted in Figure 7 and described above. Although, in the foregoing discussion of the method 190, a number of measurements and computations are performed in the transmittance domain, in further embodiments any or all of these measurements and computations may be performed in the absorbance or optical density domain. Under the foregoing discussion, the method 190 includes “live” computation/measurement of the dark transmittance reading TD, air transmittance reading TA, gain factor GF and air reference intensity RIA, during a measurement run of the detection system 10. In further embodiments of the method 190, any or all of these values may be predetermined or computed in a previous measurement, then stored in memory for use in a number of subsequent measurement runs, during which the value in question is recalled from memory for use as described above, rather than measured/computed anew.

[0120] In still further embodiments, any of the computational algorithms or methods discussed below may be employed to compute the concentration of the analyte(s) of interest in the sample S from (any) final transmittance values $TF_{\lambda 1}$, $TF_{\lambda 2}$, ... $TF_{\lambda n}$ output by any of the embodiments of the method 190 discussed herein. Any of the disclosed embodiments of the method 190 may reside as program instructions in the memory 185 so as to be accessible for execution by the processor 180 of the analyte detection system 10.

[0121] In one embodiment, the processor 180 is configured to communicate the analyte concentration results and/or other information to a display controller (not shown), which operates a display (not shown), such as an LCD display, to present the information to

the user. In one embodiment, the processor 180 can communicate to the display controller only the concentration of glucose in the material sample S. In another embodiment, the processor 180 can communicate to the display controller the concentration of ketone in addition to the concentration of glucose in the material sample S. In still another embodiment, the processor 180 can communicate to the display controller the concentration of multiple analytes in the material sample S. In yet another embodiment, the display outputs the glucose concentration with a resolution of 1 mg/dL.

II. SAMPLE ELEMENT

[0122] In view of the foregoing disclosure of certain embodiments of the analyte detection system 10, the following section discusses various embodiments of a cuvette or sample element for use with the analyte detection system 10. As used herein, “sample element” is a broad term and is used in its ordinary sense and includes, without limitation, structures that have a sample chamber and at least one sample chamber wall, but more generally includes any of a number of structures that can hold, support or contain a material sample and that allow electromagnetic radiation to pass through a sample held, supported or contained thereby; e.g., a cuvette, test strip, etc.

[0123] Figures 8 and 9 depict a cuvette or sample element 120 for use with any of the various embodiments of the analyte detection system 10 disclosed herein. Alternatively, the sample element 120 may be employed with any suitable analyte detection system. The sample element 120 comprises a sample chamber 200 defined by sample chamber walls 202. The sample chamber 200 is configured to hold a material sample which may be drawn from a patient, for analysis by the detection system with which the sample element 120 is employed. Alternatively, the sample chamber 200 may be employed to hold other organic or inorganic materials for such analysis.

[0124] In the embodiment illustrated in Figures 8-9, the sample chamber 200 is defined by first and second lateral chamber walls 202a, 202b and upper and lower chamber walls 202c, 202d; however, any suitable number and configuration of chamber walls may be employed. At least one of the upper and lower chamber walls 202c, 202d is formed from a material which is sufficiently transmissive of the wavelength(s) of electromagnetic radiation that are employed by the analyte detection system 10 (or any other system with which the sample element is to be used). A chamber wall which is so transmissive may

thus be termed a “window;” in one embodiment, the upper and lower chamber walls 202c, 202d comprise first and second windows so as to permit the relevant wavelength(s) of electromagnetic radiation to pass through the sample chamber 200. In another embodiment, these first and second windows are similar to the first and second windows 122, 124 discussed above. In yet another embodiment, only one of the upper and lower chamber walls 202c, 202d comprises a window; in such an embodiment, the other of the upper and lower chamber walls may comprise a reflective surface configured to back-reflect any electromagnetic energy emitted into the sample chamber 200 by the analyte detection system with which the sample element 120 is employed. Accordingly, this embodiment is well suited for used with an analyte detection system in which a source and a detector of electromagnetic energy are located on the same side as the sample element.

[0125] In various embodiments, the material that makes up the window(s) of the sample element 120 is completely transmissive, i.e., it does not absorb any of the electromagnetic radiation from the source 20 and first and second filters 40, 60 that is incident upon it. In another embodiment, the material of the window(s) has some absorption in the electromagnetic range of interest, but its absorption is negligible. In yet another embodiment, the absorption of the material of the window(s) is not negligible, but it is stable for a relatively long period of time. In another embodiment, the absorption of the window(s) is stable for only a relatively short period of time, but the analyte detection system 10 is configured to observe the absorption of the material and eliminate it from the analyte measurement before the material properties can change measurably. Materials suitable for forming the window(s) of the sample element 120 include barium fluoride, silicon, polypropylene, polyethylene, or any polymer with suitable transmissivity (i.e., transmittance per unit thickness) in the relevant wavelength(s). Where the window(s) are formed from a polymer, the selected polymer can be isotactic, atactic or syndiotactic in structure, so as to enhance the flow of the sample between the window(s). One type of polyethylene suitable for constructing the sample element 120 is type 220, as extruded, available from KUBE Ltd. of Staefa, Switzerland.

[0126] In one embodiment, the sample element 120 is configured to allow sufficient transmission of electromagnetic energy having a wavelength of between about 4 μm and about 10.5 μm through the window(s) thereof. However, the sample element 120 can be configured to allow transmission of wavelengths in any spectral range emitted by the

energy source 20. In another embodiment, the sample element 120 is configured to receive an optical power of more than about 1.0 MW/cm^2 from the sample beam (Es) incident thereon for any electromagnetic radiation wavelength transmitted through the secondary filter(s) 60. In still another embodiment, the sample element 120 is configured to allow transmission of about 75% of the electromagnetic energy incident upon the sample chamber 200 therethrough. Preferably, the sample chamber 200 of the sample element 120 is configured to allow a sample beam (Es) advancing toward the material sample S within a cone angle of 45 degrees from the major axis X (see Figures 1, 2) to pass therethrough.

[0127] In the embodiment illustrated in Figures 8-9, the sample element further comprises a supply passage 204 extending from the sample chamber 200 to a supply opening 206 and a vent passage 208 extending from the sample chamber 200 to a vent opening 210. While the vent opening 210 is shown at one end of the sample element 120, in other embodiments the vent opening 210 may be positioned on either side of the sample element 120, so long as it is in fluid communication with the vent passage 208.

[0128] In operation, the supply opening 206 of the sample element 120 is placed in contact with the material sample S, such as a fluid flowing from a wound on a patient. The fluid is then transported through the sample supply passage 204 and into the sample chamber 200 via capillary action. The vent passage 208 and vent opening 210 improve the sample transport by preventing the buildup of air pressure within the sample element and allowing the sample to displace the air as the sample flows to the sample chamber 200.

[0129] Where the upper and lower chamber walls 202c, 202d comprise windows, the distance T (measured along an axis substantially orthogonal to the sample chamber 200 and/or windows 202a, 202b, or, alternatively, measured along an axis of an energy beam (such as but not limited to the energy beam E discussed above) passed through the sample chamber 200) between them comprises an optical pathlength (see Figure 9). In various embodiments, the pathlength is between about $1 \mu\text{m}$ and about $300 \mu\text{m}$, between about $1 \mu\text{m}$ and about $100 \mu\text{m}$, between about $25 \mu\text{m}$ and about $40 \mu\text{m}$, between about $10 \mu\text{m}$ and about $40 \mu\text{m}$, between about $25 \mu\text{m}$ and about $60 \mu\text{m}$, or between about $30 \mu\text{m}$ and about $50 \mu\text{m}$. In still another embodiment, the optical pathlength is about $25 \mu\text{m}$. In some instances, it is desirable to hold the pathlength T to within about plus or minus $1 \mu\text{m}$ from any pathlength specified by the analyte detection system with which the sample element 120 is to be employed. Likewise, it may be desirable to orient the walls 202c, 202d with

respect to each other within plus or minus 1 μm of parallel, and/or to maintain each of the walls 202c, 202d to within plus or minus 1 μm of planar (flat), depending on the analyte detection system with which the sample element 120 is to be used.

[0130] In one embodiment, the transverse size of the sample chamber 200 (i.e., the size defined by the lateral chamber walls 202a, 202b) is about equal to the size of the active surface of the sample detector 150. Accordingly, in a further embodiment the sample chamber 200 is round with a diameter of about 4 mm.

[0131] The sample element 120 shown in Figures 8-9 has, in one embodiment, sizes and dimensions specified as follows. The supply passage 204 preferably has a length of about 17.7 mm, a width of about 0.7 mm, and a height equal to the pathlength T. Additionally, the supply opening 206 is preferably about 3 mm wide and smoothly transitions to the width of the sample supply passage 204. The sample element 120 is about 0.375 inches wide and about one inch long with an overall thickness of between about 1.025 mm and about 1.140 mm. The vent passage 208 preferably has a length of about 1.8 mm to 2 mm and a width of about 3.8 mm to 4 mm, with a thickness substantially equal to the pathlength between the walls 202c, 202d. The vent aperture 210 is of substantially the same height and width as the vent passage 208. Of course, other dimensions may be employed in other embodiments while still achieving the advantages of the sample element 120.

[0132] The sample element 120 is preferably sized to receive a material sample S having a volume less than or equal to about 3 μL (or less than or equal to about 2 μL , or less than or equal to about 1 μL) and more preferably a material sample S having a volume less than or equal to about 0.85 μL . Of course, the volume of the sample element 120, the volume of the sample chamber 200, etc. can vary, depending on many variables, such as the size and sensitivity of the sample detector 150, the intensity of the radiation emitted by the energy source 20, the expected flow properties of the sample, and whether flow enhancers are incorporated into the sample element 120. The transport of fluid to the sample chamber 200 is achieved preferably through capillary action, but may also be achieved through wicking or vacuum action, or a combination of wicking, capillary action, and/or vacuum action.

[0133] Figure 10 depicts one approach to constructing the sample element 120. In this approach, the sample element 120 comprises a first layer 220, a second layer 230, and a third layer 240. The second layer 230 is preferably positioned between the first layer 220 and the third layer 240. The first layer 220 forms the upper chamber wall 202c, and the third layer 240 forms the lower chamber wall 202d. Where either of the chamber walls 202c, 202d comprises a window, the window(s)/wall(s) 202c/202d in question may be formed from a different material as is employed to form the balance of the layer(s) 220/240 in which the wall(s) are located. Alternatively, the entirety of the layer(s) 220/240 may be formed of the material selected to form the window(s)/wall(s) 202c, 202d. In this case, the window(s)/wall(s) 202c, 202d are integrally formed with the layer(s) 220, 240 and simply comprise the regions of the respective layer(s) 220, 240 which overlie the sample chamber 200.

[0134] With further reference to Figure 10, the second layer 230 may be formed entirely of an adhesive that joins the first and third layers 220, 240. In other embodiments, the second layer 230 may be formed from similar materials as the first and third layers, or any other suitable material. The second layer 230 may also be formed as a carrier with an adhesive deposited on both sides thereof. The second layer 230 includes voids which at least partially form the sample chamber 200, sample supply passage 204, supply opening 206, vent passage 208, and vent opening 210. The thickness of the second layer 230 can be the same as any of the pathlengths disclosed above as suitable for the sample element 120. The first and third layers can be formed from any of the materials disclosed above as suitable for forming the window(s) of the sample element 120.

[0135] The sample chamber 200 preferably comprises a reagentless chamber. In other words, the internal volume of the sample chamber 200 and/or the wall(s) 202 defining the chamber 200 are preferably inert with respect to the sample to be drawn into the chamber for analysis. As used herein, "inert" is a broad term and is used in its ordinary sense and includes, without limitation, substances which will not react with the sample in a manner which will significantly affect any measurement made of the concentration of analyte(s) in the sample with the analyte detection system 10 or any other suitable system, for a sufficient time (e.g., about 1-30 minutes) following entry of the sample into the chamber 200, to permit measurement of the concentration of such analyte(s). Alternatively,

the sample chamber 200 may contain one or more reagents to facilitate use of the sample element in sample assay techniques which involve reaction of the sample with a reagent.

[0136] In one embodiment, the sample element may be configured to separate plasma from a whole-blood or other similar sample, via employment of an appropriate filter or membrane, between the entry point of the sample into the sample element, and the sample chamber(s). In a sample element so configured, the plasma flows downstream from the filter/membrane, to the sample chamber(s). The balance of the sample (e.g., blood cells) remains at the filter/membrane. In various embodiments, the filter/membrane may be constructed from microporous polyethylene or microporous polytetrafluoroethylene. In another embodiment, the filter/membrane may be constructed from BTS-SP media available from Pall Corporation of East Hills, NY.

III. SAMPLE ELEMENT REFERENCING

[0137] In this section, there are disclosed a number of methods for sample-element referencing, which generally comprises compensating for the effects of the sample element on the measurement of analyte concentration. Any one or combination of the methods disclosed in this section may reside as program instructions in the memory 185 so as to be accessible for execution by the processor 180 of the analyte detection system 10. In addition, any one or combination of the methods disclosed in this section may be employed as the sample-element referencing operation 190i of various embodiments of the method 190 depicted in Figure 7 and discussed above.

[0138] Where employed as the sample-element referencing operation 190i of the method 190 (or where otherwise employed), any of the methods disclosed in this section may be performed in a wavelength-specific fashion, i.e. by computing a sample-element referenced transmittance, absorbance or optical density at each wavelength/band analyzed by the analyte detection system in question.

[0139] As discussed above, materials having some electromagnetic radiation absorption in the spectral range employed by the analyte detection system 10 can be used to construct some or all of the sample element 120. The accuracy of an analyte detection system, such as the system 10 disclosed herein, may be improved by accounting for any scattering or absorption phenomena attributable to the sample element when computing the concentration of the analyte(s) of interest. Such scattering or absorption due to imperfect transmission properties of the materials of the sample element may be overcome by

determining at least one reference level of absorbance of the sample element and then removing the reference level from a subsequent measurement performed with the sample element. Devices and methods for overcoming imperfect transmission properties of materials employed in sample elements are now discussed with reference to Figures 11-21.

[0140] In one embodiment, an empty, unused sample element, such as the sample element 120, can be referenced by determining the reference level of absorbance/transmittance (and scattering) of the sample element 120. In certain embodiments, the method comprises positioning the sample chamber 200 of the sample element 120 within the sample beam E_s which passes through the windows 202c, 202d. The analyte detection system 10 then determines a reference level of absorbance or transmittance by the windows 202c, 202d. A sample material is then drawn into the sample chamber 200. The sample beam E_s is then passed through the windows 202c, 202d of the sample chamber 200 as well as the sample itself. The analyte detection system 10 determines an analytical level of absorbance or transmittance by the combination of the sample and the windows 202c, 202d. Upon determining the reference and analytical levels of absorbance or transmittance, the analyte detection system 10 can account for absorption/transmission effects of the material comprising the windows 202c, 202d when determining the concentration of the analyte(s) of interest. Analyzing the reference and analytical levels of absorbance or transmittance (in other words, accounting for the absorbance/transmittance effects of the material comprising the windows 202c, 202d) can comprise calculating a difference in optical density between the two. Alternatively, analyzing the levels can comprise calculating a ratio of the analytical level of transmission to the reference level of transmission.

[0141] The difference-calculation alternative is employed where the sample element referencing method is performed in the absorbance or optical density domain, and the ratio-calculation alternative is employed where the method is performed in the transmittance domain. The resulting data set (typically, an absorbance or transmittance spectrum assembled from sample-element referenced absorbance/transmittance measurements taken at each wavelength/band analyzed by the detection system 10) can then be analyzed to compute the concentration of the analyte(s) of interest in the sample. This concentration analysis may be performed by employing any suitable method, including but not limited to any of the various computational algorithms discussed in further detail in Section IV below. For example, any of the methods disclosed below for determining

analyte concentration(s) independent of the optical pathlength through the sample, may be employed.

[0142] Figure 11 is a schematic illustration of a sample element 302 configured to be referenced by an analyte detection system, such as but not limited to the analyte detection system 10 disclosed above, in accordance with methods described in detail below. Except as further described herein, the sample element 302 may in one embodiment be similar to any of the embodiments of the sample element 120 discussed above. As depicted in Figure 11, the sample element 302 comprises a referencing chamber 304 situated between first and second referencing windows 304a, 304b; and a sample chamber 306 situated between first and second sample windows 306a, 306b. In one embodiment, the separation (i.e., pathlength) between the inner surfaces of the referencing windows 304a, 304b is different than the separation (i.e., pathlength) between the inner surfaces of the sample windows 306a, 306b. In certain embodiments, the pathlength of the referencing chamber 304 is smaller than that of the sample chamber 306, while in other embodiments the pathlength of the sample chamber 306 is smaller than that of the referencing chamber 304. In still other embodiments, the pathlength of the referencing chamber 304 is substantially zero. In one embodiment, one of the chambers 304, 306 has a pathlength of about 10 microns, and the other of the chambers has a pathlength of about 30 microns.

[0143] As illustrated in Figure 11, the first referencing window 304a and first sample window 306a are preferably of substantially similar thickness, and the second referencing window 304b and second sample window 306b are preferably of substantially similar thickness as well. In one embodiment, all of the windows 304a, 304b, 306a, 306b are of substantially similar thickness. However, in other embodiments these thicknesses may differ among the windows.

[0144] In one embodiment, one or more of the outer surfaces of one or more of the windows 304a, 304b, 306a, 306b is textured. This may be done by, for example, sanding the surface(s) in question, and/or molding or otherwise constructing them to have a relatively non-smooth surface finish. Depending on the materials employed to construct the sample element, texturing may improve the optical qualities of the sample element by reducing fringing. This texturing may be employed with any of the embodiments of the sample element disclosed herein by, for example, texturing one or both of the outer surfaces of the windows 202c, 202d of the sample element 120.

[0145] In one method of operation, the sample element 302 is coupled with an analyte detection system 10 which utilizes a single beam of electromagnetic radiation for referencing the sample element 302 and for measuring the concentration of an analyte in the sample. A sample is drawn into the referencing chamber 304 (in those embodiments where the referencing chamber is of sufficient pathlength or volume) and into the sample chamber 306. The sample element 302 is placed in a reference position within the analyte detection system 10 wherein the referencing chamber 304 and referencing windows 304a, 304b reside within an optical path of a reference beam 308 of electromagnetic radiation. The reference beam 308 is then passed through the referencing chamber 304 (and, where applicable, that portion of the sample contained therein), and referencing windows 304a, 304b. The analyte detection system 10 determines a reference level of absorbance or transmittance of the reference beam 308 due to absorbance or transmittance by the combination of (any) sample within the referencing chamber 304 and the referencing windows 304a, 304b. The sample element 302 is placed into an analytical position wherein the sample chamber 306 and sample windows 306a, 306b reside within the optical path of an analytical beam 310. The analytical beam 310 is then passed through the sample-filled sample chamber 306 and sample windows 306a, 306b. The analyte detection system 10 determines an analytical level of absorbance or transmittance of the analytical beam 310 due to absorbance or transmittance by the combination of the sample within the sample chamber 306 and the sample windows 306a, 306b. In one embodiment, reference and analytical levels of absorbance or transmittance are measured at each wavelength/band analyzed by the analyte detection system 10.

[0146] Upon determining the reference and analytical levels of absorbance or transmittance, the analyte detection system 10 can account for absorbance or transmittance effects of the material comprising the sample element 302 when determining the concentration of the analyte(s) of interest in the sample. Analyzing the reference and analytical levels of absorbance or transmittance (in other words, accounting for the absorbance or transmittance effects of the material comprising the sample element 302) can comprise calculating a difference between the two. Alternatively, analyzing the levels can comprise calculating a ratio of the analytical level to the reference level.

[0147] The difference-calculation alternative is employed where the sample element referencing method is performed in the absorbance or optical density domain, and

the ratio-calculation alternative is employed where the method is performed in the transmittance domain. Where reference and analytical levels of absorbance or transmittance have been measured in each of a series of wavelengths/bands, the difference calculation or ratio calculation is performed on the (reference level, analytical level) pair measured at each wavelength/band in the series.

[0143] The resulting data set (for example, an absorbance or transmittance spectrum assembled from sample-element referenced absorbance/transmittance measurements taken at each wavelength/band analyzed by the detection system 10) can then be analyzed to compute the concentration of the analyte(s) of interest in the sample. This concentration analysis may be performed by employing any suitable method, including but not limited to any of the various computational algorithms discussed in further detail in Section IV below. For example, any of the methods disclosed below for determining analyte concentration(s) independent of the optical pathlength through the sample, may be employed.

[0149] Where significant differences arise between the thicknesses of the first referencing window 304a and first sample window 306a, or between the thicknesses of the first referencing window 304a and first sample window 306a, the absorbance/transmittance data output by the ratio-calculation/difference calculation procedure may "include" some of the absorbance/transmittance aspects of the window material. Accordingly, where desired various embodiments of the methods disclosed in Section IV below for removing non-analyte contributions from absorption data, may be employed when analyzing the absorbance/transmittance data to determine analyte concentration.

[0150] In another method of operation depicted in Figure 12, the sample element 302 is coupled with an analyte detection system 10 which utilizes separate beams of electromagnetic radiation for referencing the sample element 302 and for measuring the concentration of an analyte in the sample. A sample is drawn into the referencing chamber 304 (in those embodiments where the referencing chamber is of sufficient volume) and into the sample chamber 306 of the sample element 302. As depicted in Figure 12, the sample element 302 is placed within the analyte detection system 10 so that the referencing chamber 304 and referencing windows 304a, 304b reside within the path of the reference beam 308 and so that the sample chamber 306 and sample windows 306a, 306b reside within the path of an analytical beam 312. The reference beam 308 passes through the

referencing chamber 304 (and, where applicable, any portion of the sample contained therein), and referencing windows 304a, 304b, and the analytical beam 312 passes through the sample chamber 306, that portion of the sample contained therein, and the sample windows 306a, 306b. The analyte detection system 10 determines a reference level of absorbance or transmittance of the reference beam 308 due to absorbance or transmittance by the combination of (any) sample within the referencing chamber 304 and the material comprising the reference windows 304a, 304b, and determines an analytical level of absorbance or transmittance of the analytical beam 312 due to absorbance or transmittance by the combination of the sample and the material comprising the sample windows 306a, 306b.

[0151] Upon determining the reference and analytical levels of absorbance or transmittance, the analyte detection system 10 can account for absorbance or transmittance effects of the material comprising the sample element 302 when determining the concentration of the analyte(s) of interest in the sample. Analyzing the reference and analytical levels of absorbance or transmittance (in other words, accounting for the absorbance or transmittance effects of the material comprising the sample element 302) can comprise calculating a difference between the two. Alternatively, analyzing the levels can comprise calculating a ratio of the analytical level to the reference level.

[0152] The difference-calculation alternative is employed where the sample element referencing method is performed in the absorbance or optical density domain, and the ratio-calculation alternative is employed where the method is performed in the transmittance domain. Where reference and analytical levels of absorbance or transmittance have been measured in each of a series of wavelengths/bands, the difference calculation or ratio calculation is performed on the (reference level, analytical level) pair measured at each wavelength/band in the series.

[0153] The resulting data set (for example, an absorbance or transmittance spectrum assembled from sample-element referenced absorbance/transmittance measurements taken at each wavelength/band analyzed by the detection system 10) can then be analyzed to compute the concentration of the analyte(s) of interest in the sample. This concentration analysis may be performed by employing any suitable method, including but not limited to any of the various computational algorithms discussed in further detail in Section IV below. For example, any of the methods disclosed below for determining

analyte concentration(s) independent of the optical pathlength through the sample, may be employed.

[0154] Where significant differences arise between the thicknesses of the first referencing window 304a and first sample window 306a, or between the thicknesses of the first referencing window 304a and first sample window 306a, the absorbance/transmittance data output by the ratio-calculation/difference calculation procedure may “include” some of the absorbance/transmittance aspects of the window material. Accordingly, where desired various embodiments of the methods disclosed in Section IV below for removing non-analyte contributions from absorption data, may be employed when analyzing the absorbance/transmittance data to determine analyte concentration.

[0155] In certain embodiments, a sample element may be referenced so as to overcome transmission properties of the materials comprising the sample element by drawing a sample into the sample element and then compressing a sample chamber of the sample element, thereby changing the separation (i.e., pathlength) between the inner surfaces of the sample chamber by a predetermined amount. Such embodiments use a deformable sample element and controllably change the pathlength of the beam of electromagnetic radiation passing through the material of, and/or the sample within, the sample chamber. The change in pathlength facilitates distinguishing the absorbance or transmittance by the material of the sample element from the absorbance or transmittance by the sample within the sample chamber, by using any of the analysis methods (i.e., difference-calculation, ratio-calculation) disclosed above.

[0156] Figure 13 is a cross-sectional view of one embodiment of an analyte detection system 406 comprising compressors 408, 409 for deforming a sample element 402 between absorbance or transmittance measurements. In some embodiments, the analyte detection system 406 may be generally similar to the system 10 disclosed above, and the sample element 402 may be generally similar to the sample element 120 disclosed above, except as further described below. In other embodiments, the analyte detection system 406 may comprise any suitable analyte detection system, with additional structure as further described below.

[0157] As shown, the sample element 402 is positionable within the analyte detection system 406 such that a sample chamber 404 of the sample element 402 is positioned between the compressors 408, 409. Each compressor 408, 409 has a hollow

portion 412 aligned with the major axis of the compressor to allow for substantially unimpeded passage of a beam of electromagnetic radiation through the compressors 408, 409 and through the sample chamber 404. In one embodiment, the compressors 408, 409 may have a circular cross-section (i.e., the compressors 408, 409 are formed as cylinders). In other embodiments, the compressors 408, 409 can have other cross-sectional shapes. Preferably, the sample element 402 is made of a material which is sufficiently pliable to allow for compression by the compressors 408, 409.

[0158] As illustrated in Figure 13, the analyte detection system 406 includes a proximity switch 445 which, in certain embodiments, detects the insertion of the sample element 402 into the analyte detection system 406. In response to the proximity switch 445, the analyte detection system 406 can advantageously control the forces exerted on the sample element 402 by the compressors 408, 409. In one embodiment, upon activation of the proximity switch 445 by the inserted sample element 402, the compressors 408, 409 contact the sample element 402 and exert oppositely-directed forces 410, 411, respectively, on the sample element 402. In certain embodiments, the forces 410, 411 are sufficiently small so as to avoid substantially compressing the sample element 402. In one such embodiment, the sample element 402 is optimally positioned within the optical path of the beam 443 of the analyte detection system 406 and gently held in this optimal position by the compressors 408, 409, as shown in Figure 13.

[0159] The beam 443 of electromagnetic radiation is passed through the sample chamber 404 to yield a first measurement of absorbance or transmittance by the combination of the sample and the sample element 402 once the sample is drawn into the sample chamber 404. In certain embodiments, the sample is drawn into the sample chamber 404 of the sample element 402 prior to insertion of the sample element 402 into the analyte detection system 406. In other embodiments, the sample is drawn into the sample chamber 404 after the sample element 402 is positioned in the analyte detection system 406.

[0160] After the first measurement of absorbance or transmittance is taken, the analyte detection system 406 compresses the sample element 402 by increasing the forces 410, 411 exerted by the compressors 408, 409. These increased forces 410, 411 more strongly compress the sample element 402. In response to this stronger compression, the optical pathlength through the sample element 402 is modified. Preferably, the sample

element 402 undergoes plastic deformation due to the compression forces 410, 411, while in other embodiments, the deformation is elastic.

[0161] Once the optical pathlength through the sample element 402 is modified, a second measurement of absorbance or transmittance by the combination of the sample and the sample element 402 is taken. The analyte detection system 406 then computes a sample-element referenced absorbance or transmittance of the sample based on the first measurement of absorbance or transmittance at the first pathlength and the second measurement of absorbance or transmittance at the second pathlength, using any of the analysis methods (i.e., difference-calculation, ratio-calculation) disclosed above. Changing the optical pathlength facilitates distinguishing the absorbance or transmittance by the material comprising the sample element 402 from the absorbance or transmittance by the sample within the sample chamber 404. Thus, the analyte detection system 406 provides a measurement of the absorbance or transmittance by the sample which is substantially free of contributions from the absorbance or transmittance of the material comprising the sample element 402. Such measurements can increase the accuracy of the analyte concentration measurements performed by the system 10 based on the sample-element referenced absorbance or transmittance measurements. These analyte concentration measurements may be performed by employing any suitable method, including but not limited to any of the various computational algorithms discussed in further detail in Section IV below. For example, any of the methods disclosed below for determining analyte concentration(s) independent of the optical pathlength through the sample, may be employed.

[0162] In the embodiment illustrated by Figure 13, the compressors 408, 409 decrease the optical pathlength of the sample chamber 404 by compressing the sample chamber 404. Figure 14 is a cross-sectional view of another embodiment of analyte detection system 506 configured for changing the optical pathlength of the sample element 402. The structure and operation of the analyte detection system 506 are substantially the same as the analyte detection system 406 illustrated in Figure 13, except with regard to the compressors. As shown in Figure 14, the compressor 508 comprises a first compressor window 512, and the compressor 509 comprises a second compressor window 513. The compressor windows 512, 513 contact the sample chamber 404 when the compressors 508, 509 grip the sample element 402. The compressor windows 512, 513 serve to more evenly

distribute the oppositely-directed forces 410, 411, respectively, across an area of the sample chamber 404.

[0163] The compressor windows 512, 513 are preferably at least partially optically transmissive in the range of electromagnetic radiation comprising the beam 443. In one embodiment, one or both of the compressor windows 512, 513 comprises a material that is substantially completely transmissive to the electromagnetic radiation comprising the beam 443. In yet another embodiment, the absorbance of the material of one or both of the compressor windows 512, 513 is not negligible, but it is known and stable for a relatively long period of time, and is stored in memory (not shown) of the analyte detection system 506 so that the system 506 can remove the contributions due to absorbance or transmittance of the material from measurements of the concentration of the analyte(s) of interest. In another embodiment, the absorbance of one or both of the compressor windows 512, 513 is stable for only a relatively short period of time, but the analyte detection system 506 is configured to observe the absorbance of the material and substantially eliminate it from the analyte measurement before the material properties change significantly.

[0164] In various embodiments, the compressor windows 512, 513 may be formed from silicon, germanium, polyethylene, or polypropylene, and/or any other suitable infrared-transmissive material.

[0165] In certain embodiments, a sample element is referenced so as to overcome transmission properties of the material comprising the sample element by drawing a sample such as whole blood into the sample element and then compressing the sample element to cause the sample chamber of the sample element to expand in a controlled manner, thereby controllably increasing the separation between the inner surfaces of the sample chamber. In this way, the compression of the sample element increases the optical pathlength through the sample chamber. The change in the optical pathlength facilitates distinguishing the absorbance or transmittance by the material comprising the sample element from the absorbance or transmittance by the sample within the sample chamber.

[0166] Figures 15-16 illustrate an embodiment of an analyte detection system 606 configured for expanding a sample chamber 604 of a sample element 602. The analyte detection system 606 comprises a first profile 608 adjacent to a first chamber window 612 of the sample chamber 604, and a second profile 609 adjacent to a second chamber window

613 of the sample chamber 604. The profiles 608, 609 are open spaces into which the chamber windows 612, 613 can expand when the sample element 602 is forcibly compressed by the analyte detection system 606. Preferably, the sample element 602 is made of a material which is sufficiently pliable to allow for expansion of the sample chamber 604 into the profiles 608, 609. Preferably, the sample element 602 undergoes plastic deformation, while in other embodiments, the deformation is elastic.

[0167] As illustrated in Figure 16, when the analyte detection system 606 compresses the sample element 602, the analyte detection system 606 exerts oppositely-directed forces 610, 611 on the sample element 602. This causes the chamber windows 612, 613 to respectively expand into the profiles 608, 609, thereby increasing the separation between the inner surfaces of the sample chamber 604 and increasing the optical pathlength of the beam 443 through the sample chamber 604. The change in optical pathlength enables the analyte detection system 606 to compute a sample-element referenced measurement of the absorbance or transmittance of the sample, using any of the analysis methods disclosed above. Thus, the analyte detection system 606 substantially eliminates the contribution of absorbance or transmittance of the material comprising the sample element 602 in order to increase the accuracy of the analyte concentration measurements performed by the system 10 based on the sample-element referenced absorbance or transmittance measurements. These analyte concentration measurements may be performed by employing any suitable method, including but not limited to any of the various computational algorithms discussed in further detail in Section IV below. For example, any of the methods disclosed below for determining analyte concentration(s) independent of the optical pathlength through the sample, may be employed.

[0168] Figures 17-18 depict another embodiment of the sample element 302 discussed above in connection with Figures 11-12. Except as further detailed below, the embodiment of the sample element 302 depicted in Figures 17-18 may be generally similar to the sample element 120 disclosed above, and/or the sample element 302 of Figures 11-12. In addition, the sample element 302 depicted in Figures 17-18 may be employed in practicing any of the sample-element referencing methods disclosed herein, including without limitation those methods discussed in connection with the sample element 302 depicted in Figures 11-12.

[0169] The sample element 302 further comprises a first strut 320 disposed in the referencing chamber 304 and extending from the first referencing window 304a to the second referencing window 304b. In addition, a second strut 322 is disposed in the sample chamber 306 and extends from the first sample window 306a to the second sample window 306b. The struts 320, 322 are preferably oriented in the chambers 304, 306 so that they extend generally parallel to an optical axis of a beam of energy passed through either of the chambers 304, 306, when the sample element 302 is employed in measuring analyte concentrations. For example, when the sample element 302 is placed in the analyte detection system 10, the strut(s) 320, 322 extend generally parallel to the major axis X and/or the energy beam E.

[0170] The struts 320, 322 depicted in Figures 17-18 comprise members having sufficient column and tensile strength to minimize or prevent inward or outward deflection of the referencing windows 304a, 304b and sample windows 306a, 306b, respectively. The struts 320, 322 advantageously assist in preserving the planarity of the windows 304a, 304b, 306a, 306b, thereby enhancing the accuracy of some analyte-concentration measurements taken with the sample element 302. Although various computational algorithms are disclosed below for preserving measurement accuracy despite imperfections in sample-element geometry (e.g., pathlength, window planarity, window parallelism), the struts 320, 322 may be employed instead of or in addition to various combinations of such algorithms when measuring analyte concentrations.

[0171] In the illustrated embodiment, the struts 320, 322 comprise cylindrical members (i.e. having a circular cross-section); however, any other suitable cross-sectional shape (including without limitation oval, square, rectangular, triangular, etc.) may be employed. In the illustrated embodiment, the struts 320, 322 maintain a substantially constant cross-section as they extend from the first window 304a/306a to the second window 304b/306b; however, a varying cross-section may be employed.

[0172] In the embodiment shown in Figures 17-18, the struts 320, 322 are of substantially similar cross-sectional area, and a single strut is employed in each of the chambers 304, 306. However, the number of struts employed in each chamber may vary, as two, three, four or more may be used in each chamber, and the total cross-sectional area of the referencing-chamber struts may either equal (in one embodiment) or differ from (in

another embodiment) that of the sample-chamber struts. Similarly, strut(s) may be employed in only one, or both, of the referencing and sample chambers 304, 306.

[0173] In one embodiment, each of the struts 320, 322 is substantially opaque to the wavelength(s) of energy employed by the analyte detection system (such as the system 10) with which the sample element 302 is employed. For example, the struts 320, 322 may be formed from a material which is substantially opaque to the wavelength(s) of interest, in the source intensity range employed by the detection system, and when formed in a pathlength less than or equal to the shorter of the struts 320, 322. In another example, the struts may be formed from a material which does not meet the above criteria, but a mask layer (not shown) may be positioned in each strut, or in or on one of the windows 304a/304b and one of the windows 306a/306b, in axial alignment with each strut. The mask layers are substantially opaque to the wavelength(s) of interest and are shaped and sized to conform to the (largest) cross-section of the corresponding struts, so as to substantially prevent passage of the energy beam E through the struts 320, 322. In still further embodiments, any suitable structure may be employed to substantially prevent passage of the energy beam E through the struts 320, 322.

[0174] By making the struts 320, 322 substantially opaque to the wavelength(s) of interest, or by otherwise preventing passage of the energy beam E through the struts 320, 322, the absorbance/transmittance of the struts drops out from the absorbance/transmittance data when the difference or ratio is computed of the absorbance/transmittance measured in each chamber 304, 306. In other words, by making the absorbance/transmittance of the struts 320, 322 independent of the length of the struts, their absorbance/transmittance can be accounted for in computing analyte concentrations, despite their difference in length. In another embodiment, a similar result can be obtained by otherwise constructing the struts 320, 322 to have substantially equal absorbance or transmittance, but without making the struts 320, 322 opaque.

[0175] In yet another embodiment, the strut(s) 320, 322 may be formed from a material which is highly transmissive of the wavelength(s) of interest. For example, where infrared wavelengths are employed in the measurement of analyte concentrations, the strut(s) may be formed from silicon, germanium, polyethylene, polypropylene, or a combination thereof.

[0176] Figure 17, as an upper plan view of the sample element 302, also depicts a vent passage 324 and supply passage 326 in fluid communication with the referencing and sample chambers 304, 306, respectively. The vent and supply passages 324, 326 may be generally similar to their counterparts disclosed above in connection with the sample element 120. In addition, the vent passage 324 and supply passage 326 may be employed in any of the embodiments of the sample element 302 discussed herein.

[0177] It is further contemplated that one or more struts of the type presently disclosed may be employed in the sample chamber 200 of the sample element 120, so as to extend from the upper window 202c to the lower window 202d.

[0178] Figures 19 and 20 depict yet another embodiment of the sample element 302 discussed above in connection with Figures 11-12 and 17-18. Except as further detailed below, the embodiment of the sample element 302 depicted in Figures 19-20 may be generally similar to the sample element 120 disclosed above, and/or the sample elements 302 of Figures 11-12 and 17-18. In addition, the sample element 302 depicted in Figures 19-20 may be employed in practicing any of the sample-element referencing methods disclosed herein, including without limitation those methods discussed in connection with the sample elements 302 depicted in Figures 11-12 and 17-18.

[0179] The sample element 302 depicted in Figures 19-20 further comprises a stiffening layer 340 which is secured to the sample element 302, preferably on the underside thereof, by any appropriate means, such as adhesives, heat bonding, ultrasonic bonding, integral formation, etc. The stiffening layer 340 is sized and shaped, and its material chosen, to impart additional stiffness and rigidity to the sample element 302. The stiffening layer 304 may be formed from the materials used to form the balance of the sample element 302, or other suitable materials as desired. The stiffening layer 340 includes an opening 342 which is aligned with the referencing chamber 304 and sample chamber 306 to permit a beam of electromagnetic energy (such as the beam E when the sample element 302 is employed with the system 10) to pass to the windows 304b, 306b. Other than the opening 342, the stiffening layer 340 is preferably coextensive with the underside of the sample element 302.

[0180] In other embodiments, a similar stiffening layer may be secured to the upper side of the sample element 302, instead of or in addition to the stiffening layer 340 depicted in Figures 19-20. Such an upper-side stiffening layer may include a staggered

portion to conform to the difference in thickness between the reference and sample chambers 304, 306 on the upper side of the sample element 302.

[0181] It is further contemplated that one or more stiffening layers similar to the layer 340 may be employed with the sample element 120 disclosed above, secured to one or both of the first and third layers 220, 240.

[0182] Figure 21 depicts another embodiment of the sample element 302 discussed above in connection with Figures 11-12 and 17-20. Except as further detailed below, the embodiment of the sample element 302 depicted in Figure 21 may be generally similar to the sample element 120 disclosed above, and/or the sample elements 302 of Figures 11-12 and 17-20. In addition, the sample element 302 depicted in Figure 21 may be employed in practicing any of the sample-element referencing methods disclosed herein, including without limitation those methods discussed in connection with the sample elements 302 depicted in Figures 11-12 and 17-20.

[0183] The sample element 302 depicted in Figure 21 further comprises stiffening ribs 350 which are integrally formed with one or both of the first and second referencing windows 304a, 304b. The stiffening ribs 350 preferably extend across the entire length of the windows 304a, 304b, and may continue into the balance of the sample element 302. The stiffening ribs 350 depicted in Figure 21 are arranged to extend longitudinally across the windows 304a, 304b so that they extend generally orthogonal to an optical axis of a beam of energy passed through the chamber 304 when the sample element 302 is employed in measuring analyte concentrations. For example, when the sample element 302 is placed in the analyte detection system 10, the ribs 350 extend generally orthogonal to the major axis X and/or the energy beam E. In other embodiments, the ribs 350 may extend in any direction, so long as they are oriented to extend generally orthogonal to such an optical axis. Furthermore, the ribs 350 may be employed in any combination of the windows 304a, 304b, 306a, 306b, or the windows 202c, 202d of the sample element 120.

[0184] In any of these embodiments, any suitable size, shape and number of ribs may be employed, other than those depicted in Figure 21. However, in one embodiment, the configuration of ribs employed on the window 304a substantially matches that of the window 306a, and the configuration of ribs employed on the window 304b substantially

matches that of the window 306b. Such an arrangement may improve the accuracy of the sample-element referencing methods employed with the sample element 302.

[0185] The ribs 350 advantageously assist in preserving the planarity of the windows 304a, 304b, 306a, 306b, thereby enhancing the accuracy of analyte-concentration measurements taken with the sample element 302. Although various computational algorithms are disclosed below for preserving measurement accuracy despite imperfections in sample-element geometry (e.g., pathlength, window planarity, window parallelism), the ribs 350 may be employed instead of or in addition to various combinations of such algorithms when measuring analyte concentrations.

IV. ALGORITHMS

[0186] This section discusses a number of computational methods or algorithms which may be used to calculate the concentration of the analyte(s) of interest in the sample S, and/or to compute other measures that may be used in support of calculations of analyte concentrations. Any one or combination of the algorithms disclosed in this section may reside as program instructions in the memory 185 so as to be accessible for execution by the processor 180 of the analyte detection system 10 to compute the concentration of the analyte(s) of interest in the sample, or other relevant measures. Alternatively, any one or combination of the algorithms disclosed in this section may be executed by or in connection with a Fourier Transform Infrared Spectrometer (FTIR) device, such as the SPECTRUM ONE model available from Perkin-Elmer Inc., of Wellesley, MA, for determining analyte concentrations or other measures. In addition, any one or combination of the algorithms disclosed in this section may be employed in connection with any of the embodiments of the method 190 depicted in Figure 7 and discussed above. For example, the disclosed algorithms may be employed to compute the concentration of the analyte(s) of interest in the sample S from (any) final transmittance values $TF_{\lambda 1}$, $TF_{\lambda 2}$, ... $TF_{\lambda n}$ output by the method 190.

A. Methods for Determining Blood Analyte Concentrations

[0187] In many measurements, the contribution from the analyte of interest (e.g., glucose) to the measured absorption spectrum is often only a small percentage of the contribution from other substances within the sample. For example, blood by volume is typically composed of about 70% water, about 30% solids, mostly protein, and only about 0.1% glucose. Blood also includes other species such as urea, alanine, and in some cases

alcohol or other sugars such as fructose. Therefore, blood glucose measurements are highly sensitive and vulnerable to inaccuracies.

[0188] If an accurate glucose measurement is desired, the characteristics of each of the different blood constituents should be considered. Because the sample absorption at any given wavelength is a sum of the absorptions of each component of the sample at that wavelength, IR absorption measurements are complicated by the presence of these other components. Consequently, to allow effective compensation and adjustments to measured IR absorption for the presence of other blood components, it is helpful to understand which constituents are present in the sample, understand their effects on the analyte that is being measured (such as glucose), and correct for any differences that intrinsic and measuring-device-related variables may cause.

[0189] Advantageously, absorption data in the mid-IR spectral region (for example, about 4 microns to about 11 microns) are used. Although water is the main contributor to the total absorption across this spectral region, the peaks and other structures present in the blood spectrum from about 6.8 microns to 10.5 microns are due to the absorption spectra of other blood components. The 4 to 11 micron region has been found advantageous because glucose has a strong absorption peak structure from about 8.5 to 10 microns, whereas most other blood constituents have a low and flat absorption spectrum in the 8.5 to 10 micron range. The main exceptions are water and hemoglobin, both of which absorb fairly strongly in this region, and which are also the two most significant blood components in terms of concentration. Certain embodiments of the techniques described herein are thus directed to removing the contributions of water and hemoglobin from this spectral region to resolve the contribution, and thus concentration, of glucose in the sample.

B. Pathlength-Insensitive Determinations of Blood Analyte Concentrations

[0190] In certain embodiments, a method determines an analyte concentration in a sample comprising the analyte and a substance. The method comprises providing an absorption spectrum of the sample, with the absorption spectrum having an absorption baseline. The method further comprises shifting the absorption spectrum so that the absorption baseline approximately equals a selected absorption value in a selected absorption wavelength range. The method further comprises subtracting a substance contribution from the absorption spectrum. Thus, the method provides a corrected absorption spectrum substantially free of a contribution from the substance.

[0191] In certain embodiments, providing the absorption spectrum comprises providing the transmittance spectrum of the sample, with the transmittance spectrum having a transmittance baseline. In certain embodiments, the transmittance spectrum of the sample is provided by transmitting at least a portion of an infrared signal through the sample. The infrared signal comprises a plurality of wavelengths. The portion of the infrared signal transmitted through the sample is measured as a function of wavelength. Various configurations and devices can be used to provide the transmittance spectrum in accordance with embodiments described herein.

[0192] In certain embodiments, the transmittance baseline is defined to be the value of the transmittance spectrum at wavelengths at which transmittance is a minimum. For blood, this value is typically at about 6.1-6.2 microns where water and hemoglobin both are strong absorbers. While the transmittance spectrum from the sample at these wavelengths is expected to be nearly zero, various effects, such as instrumental error and thermal drift, can result in a nonzero contribution to the transmittance baseline. In addition, effects such as instrumental error and thermal drift can result in a wavelength shift of known features in the transmittance spectrum from the expected wavelengths of these features.

[0193] In certain such embodiments, providing the absorption spectrum comprises shifting the transmittance spectrum so that the transmittance baseline approximately equals zero in a selected transmittance wavelength range. In certain embodiments in which the sample comprises blood, the selected transmittance wavelength range comprises wavelengths at which the transmittance is a minimum. In certain such embodiments, the selected transmittance wavelength range comprises wavelengths between approximately 6 microns and approximately 6.15 microns. In other such embodiments, the selected transmittance wavelength range comprises wavelengths between approximately 12 microns and approximately 13 microns. The transmittance spectrum at these wavelengths may be partially affected by contributions from various blood components that are present at low concentration levels. In still other such embodiments, the selected transmittance wavelength range comprises wavelengths approximately equal to 3 microns. Each of these wavelengths corresponds to a strong water absorption peak.

[0194] In embodiments in which there is a nonzero contribution to the transmittance baseline, the transmittance spectrum may be shifted. In certain embodiments,

the transmittance spectrum is shifted so that the transmittance spectrum in the wavelength range of 6 to 6.2 microns is approximately equal to zero. In embodiments in which known features are shifted in wavelength from their expected wavelengths, the transmittance spectrum can be shifted in wavelength. In addition, the shifting of the transmittance spectrum can be performed nonlinearly (e.g., shifting different wavelengths by differing amounts across the transmittance spectrum).

[0195] Providing the absorption spectrum further comprises determining the absorption spectrum from the transmittance spectrum. In certain embodiments, the relation between the transmittance spectrum and the absorption spectrum is expressed as:

$$A(\lambda) = \ln\left(\frac{1}{T(\lambda)}\right),$$

where λ is the wavelength, $A(\lambda)$ is the absorption as a function of wavelength, and $T(\lambda)$ is the transmittance as a function of wavelength.

[0196] In certain embodiments, the method comprises shifting the absorption spectrum so that its absorption baseline approximately equals a selected absorption value (such as 0, 0.5, 1, etc.) in a selected absorption wavelength range. In certain embodiments, the absorption baseline can be selected to be defined by a portion of the absorption spectrum with low absorption. In certain embodiments in which the sample comprises blood, the selected absorption wavelength range comprises wavelengths between approximately 3.8 microns and approximately 4.4 microns. In certain other embodiments, the selected absorption wavelength range comprises wavelengths between 9 microns and approximately 10 microns.

[0197] In certain other embodiments in which the sample comprises blood, the absorption baseline is defined to be the magnitude of the absorption spectrum at an isosbestic wavelength at which water and a whole blood protein have approximately equal absorptions. In such embodiments, the absorption spectrum is shifted to a selected value at the isosbestic wavelength by adding or subtracting a constant offset value across the entire wavelength spectral data set. In addition, the shifting of the absorption spectrum can be performed nonlinearly (e.g., shifting the portions of the absorption spectrum in different wavelength ranges by different amounts). Shifting the absorption spectrum such that the absorption is set to some value (e.g., 0) at a protein-water isosbestic point preferably helps remove the dependence on hemocrit level of the overall spectrum position relative to zero.

[0198] The effective isosbestic point can be expected to be different for different proteins in different solutions. Exemplary whole blood proteins include, but are not limited to, hemoglobin, albumin, globulin, and ferritin. These isosbestic wavelengths can be used to obtain a current measure of the effective optical pathlength in the filled cuvette, either before or during measurements at other wavelength ranges.

[0199] Such information is very useful in subsequent calculations for compensation of instrument-related pathlength non-linearities. Because the measured absorption of the protein and water are identical at the isosbestic wavelength, the measured absorption at the isosbestic wavelength is independent of the ratios of the protein concentration and the water concentration (hemocrit level). At an isosbestic wavelength, for a given sample volume, the same amount of absorption would be observed whether the sample was entirely water, entirely protein, or some combination of the two. The absorption at the isosbestic wavelength is then an indication of the total sample volume, independent of the relative concentrations of water and protein. Therefore, the observed absorption at an isosbestic wavelength is a measure of the pathlength of the sample only. In certain embodiments, the observed absorption at an isosbestic wavelength can be useful for measuring the effective optical pathlength for a sample. As a result, various embodiments of the above-described method may be employed to accurately determine the concentration of analyte(s) of interest in a sample independent of optical pathlength, i.e. without need for prior knowledge of the pathlength and/or without requiring that the sample chamber of the sample element conform closely to a specified or expected pathlength. Additionally, such information can be used in subsequent calculations for compensation of instrument-related pathlength nonlinearities. In certain embodiments, these measurements can be made before or concurrently with absorption measurements in other wavelength ranges.

C. Subtraction of Non-Analyte Contributions From Absorption Data

[0200] One goal of the spectroscopic analysis can be to derive the ratio of the analyte volume (for example, glucose volume) to the total blood volume. The process of measuring a glucose concentration can include subtracting one or more contributions to the absorption spectrum from other substances in the blood that interfere with the detection of the glucose. In certain embodiments, a reference substance absorption spectrum is provided and is scaled by multiplying it by a scaling factor. The scaled reference substance absorption spectrum is subtracted from the measured absorption spectrum. This procedure

thus preferably provides the corrected absorption spectrum which is substantially free of a contribution from the substance. Such procedures can be used to subtract the absorption contributions of water and/or hemoglobin, as well as other constituents of blood. In addition, the scaling factor provides a measure of the absorption due to the substance of the reference substance absorption spectrum. As described more fully below, in embodiments in which multiple scaling factors are determined for multiple substances, ratios of the scaling factors provide information regarding the concentration ratios of the substances in question. These determinations of the concentration ratios are substantially independent of the optical pathlength through the sample. Such concentration ratios can be used to determine the concentration of a selected substance within the sample regardless of the optical path length through the sample.

[0201] In certain embodiments, the measured absorption spectrum can be further corrected for other contributions which are not due to the analyte of interest. For example, alcohol is a potentially interfering substance with the glucose measurement because the absorption of alcohol is similar to that of glucose in the wavelength range of interest. It is observed that the peak height ratio of the absorption peak at about 9.6 microns to the absorption peak at about 9.2 microns for pure glucose is approximately 1.1-1.2, and the ratio for pure alcohol is approximately 3.0-3.2. This ratio of peak heights varies between these two values for absorption spectra for mixtures of glucose and alcohol. Thus, the peak height ratio can be used to determine the relative concentrations of alcohol and glucose. The contribution from alcohol can then be subtracted from the measured absorption spectrum.

[0202] In certain embodiments, the measured absorption spectrum can be corrected for contributions from free protein, which has an absorption peak centered around 7.1 microns. In certain other embodiments, the measured absorption spectrum can be further corrected for contributions from a boundary layer between water and a whole blood protein. Features in the measured absorption spectrum due to components of the boundary layer arise from interactions between the water and whole blood protein. These spectral features are ascribed to "bound" components or hydrated protein. The corresponding contributions across the measured absorption spectrum can be corrected by subtracting the appropriate scaled reference absorption, such that the corrected absorption spectrum is approximately zero for a selected range of wavelengths. In certain embodiments, the range

of wavelengths is between about 7.0 and 7.2 microns, or alternatively between 7.9 and 8.1 microns, or alternatively at a combination of wavelength ranges.

[0203] Temperature also affects the correct subtraction of the water contribution to the total spectrum because the absorption spectrum of water changes with temperature changes. It is therefore advantageous for the system to store several different water reference spectra, with each one applicable to a selected temperature range. The appropriate reference would be selected for scaling and subtraction based on the temperature of the sample. In some embodiments, hardware such as thermocouples, heaters, and the like may be provided to directly measure or control the temperature of the sample. Although this approach may be suitable at times, it can be difficult to accurately measure and control the blood temperature as the sample size is very small, and the actual blood temperature may vary from the cuvette temperature or the ambient temperature surrounding the cuvette.

[0204] The contribution of temperature to the absorption spectra can alternatively be addressed by analyzing the sample spectrum itself, because different parts of the water absorption spectrum are affected by temperature by different amounts. For example, the absorbance difference of the water absorption spectrum between about 4.9 microns and 5.15 microns is not very dependent on temperature, whereas the absorbance difference between 4.65 microns and 4.9 microns is highly temperature dependent. As temperature changes for a given sample with constant water concentration, the absorbance difference between 4.65 and 4.9 microns will change a lot, and the absorbance difference between 4.9 and 5.15 microns will not change much at all. Thus, the ratio of the absorbance difference between two points having high temperature dependence (e.g., 4.65 and 4.9 microns) to the absorbance difference between two points having low temperature dependence (e.g., 4.9 and 5.15 microns) can be used as a measure of temperature. Once this measurement is made, an appropriate selection from several different stored water reference curves can be made.

[0205] In certain embodiments, the reference substance absorption spectrum is provided by correcting a stored spectrum for wavelength nonlinearities. For example, where the substance comprises water, knowledge of the optical pathlength (based on the total sample absorption at one or more isosbestic wavelengths) as well as the measured absorption at one or more wavelengths dominated by water absorption (e.g., between

approximately 4.5 and 5 microns) can be used to correct a stored reference water absorption spectrum for wavelength nonlinearities across the spectrum. Such corrections of the stored reference spectrum are advantageous for reducing distortions in the final results. Similarly, prior knowledge of optical pathlength based on total sample absorption at an isosbestic wavelength, as well as on total protein absorption in a selected wavelength range (e.g., 7.0-7.2 microns, or 7.9-8.1 microns) allows for the modification of a reference protein absorption spectrum that is compensated for nonlinearities.

[0206] In certain embodiments, after correcting the measured absorption spectrum for contributions of one or more substances, the corrected absorption spectrum is fitted with reference analyte spectral data to provide a measure of the analyte concentration. The reference analyte spectral data can include data at a wavelength near an analyte absorption maximum. For example, the absorption spectrum of glucose includes various peaks, with the two largest peaks at wavelengths of approximately 9.25 and 9.65 microns, respectively. The absorption difference of the corrected absorption spectrum between a wavelength of about 8.5 microns and a wavelength of approximately 9.65 microns can provide a measure of the glucose concentration in the blood sample. Following the definition of glucose in blood (i.e., a measure of glucose per volume of the sample), a useful measure for glucose concentration is preferably obtained from algorithmically-derived infrared quantities by dividing the final glucose quantity by total water, total protein, or alternatively a combination of both.

[0207] Although the above discussion focuses on data sets comprising measurements over the entire range of IR wavelengths, it will be appreciated that it is not necessary to obtain data across the entire spectrum, but only at the discrete wavelengths used in the analysis. In certain embodiments where water and hemoglobin contributions are subtracted from a whole blood spectrum to find glucose concentration, as little as ten or fewer total measurements are needed. Additional components to be subtracted may require one or two more measurements each.

[0208] For example, to characterize the water contribution, measurements at about 4.7 microns and 5.3 microns may be obtained. For characterizing hemoglobin, measurements at about 8.0 and 8.4 microns may be obtained. The glucose characterization may involve a measure of the difference between about 8.5 microns and 9.6 microns. This is six values, two for each component. In embodiments where it is desired to zero the

transmittance curve and shift the absorbance values, it may be desirable to further make transmittance measurements at about the 6.1 micron water absorbance peak and the 4.1 micron water/protein isosbestic point. As described above, the addition of another data point at about 4.9 microns allows the determination of temperature. Another measurement at the lower alcohol peak of about 9.25 microns can be used to compensate the glucose measurement for alcohol content as well as is also described above. In certain embodiments, the values of optical density at these six wavelengths can be expressed as six linear equations which can be solved to yield the glucose concentration path length and the ratio of glucose volume to total blood volume.

[0209] In certain embodiments, the method uses the optical density (OD), which can be expressed as:

$$OD_i = (c_w \alpha_{wi} + c_h \alpha_{hi} + c_g \alpha_{gi}) \cdot d$$

where: d = cuvette path length;
 c_w = water volume concentration;
 c_h = hemocrit volume concentration;
 c_g = glucose volume concentration;
 α_{wi} = water absorption at wavelength 'i';
 α_{hi} = hemocrit absorption at wavelength 'i'; and
 α_{gi} = glucose absorption at wavelength 'i'.

The absorption of the various components (e.g., α_{wi} , α_{hi} , α_{gi}) at various wavelengths is a property of the components themselves, and can be known or provided to the system for use in the calculation of the analyte concentrations. In various embodiments described below, the blood sample is modeled as a three-component mixture of water, hemocrit, and glucose (i.e., $c_w + c_h + c_g = 1$). Other embodiments can model the blood sample with more components, fewer components, or different components.

[0210] In certain embodiments, the method uses three two-wavelength sets. The first set is in the wavelength region where water absorption dominates. The second set is in a region where water and hemocrit absorptions dominate, and the third set in a region where absorptions from all three components dominate. In certain embodiments, the calculations are based on OD differences of each wavelength pair to reduce or minimize offsets and baseline drift errors. Absorption values for the three components at each of the six wavelengths are shown in Table 1:

Wavelength	α_{wi}	α_{hi}	α_{gi}
1	α_{w1}	0	0
2	α_{w2}	0	0
3	α_{w3}	α_{h3}	0
4	α_{w4}	α_{h4}	0
5	α_{w5}	α_{h5}	α_{g5}
6	α_{w6}	α_{h6}	α_{g6}

[0211] Substituting these values from Table 1 into the equation for OD yields the following relations:

$$\begin{aligned}
 OD_1 &= c_w \alpha_{w1} d ; \\
 OD_2 &= c_w \alpha_{w2} d ; \\
 OD_3 &= (c_w \alpha_{w3} + c_h \alpha_{h3}) \cdot d ; \\
 OD_4 &= (c_w \alpha_{w4} + c_h \alpha_{h4}) \cdot d ; \\
 OD_5 &= (c_w \alpha_{w5} + c_h \alpha_{h5} + c_g \alpha_{g5}) \cdot d ; \text{ and} \\
 OD_6 &= (c_w \alpha_{w6} + c_h \alpha_{h6} + c_g \alpha_{g6}) \cdot d .
 \end{aligned}$$

[0212] Certain embodiments of the method comprise computing the quantity A which is equal to the product of the water concentration and the path length. The quantity A can be termed the “water scaling factor,” and can be expressed by the following relation:

$$A = \frac{OD_2 - OD_1}{(\alpha_{w2} - \alpha_{w1})} = c_w d .$$

In certain embodiments in which the values of

water absorption at the two wavelengths is known or provided to the system, this ratio of the difference of two measured absorption values with the difference of two reference absorption values at the same wavelengths yields a water scaling factor A indicative of the amount of water in the sample.

[0213] Using A and the water absorptions at each wavelength, the “water free” OD can then be calculated and expressed by the following relation:

$$OD'_i = OD_i - A \alpha_{wi} .$$

In this way, the “water free” OD value equals the measured OD value minus the scaled reference absorption value for water. Combining the above equations yields the following relations:

$$\begin{aligned}
 OD'_3 &= c_h \alpha_{h3} \cdot d ; \\
 OD'_4 &= c_h \alpha_{h4} \cdot d ;
 \end{aligned}$$

$$OD'_5 = (c_h \alpha_{h5} + c_g \alpha_{g5}) \cdot d ; \text{ and}$$

$$OD'_6 = (c_h \alpha_{h6} + c_g \alpha_{g6}) \cdot d .$$

[0214] In certain embodiments, the “water free” absorptions at wavelengths 3 and 4 are used to calculate the quantity B which is proportional to the product of the hemocrit concentration and path length. The quantity B can be termed the “hemocrit scaling factor,” and can be expressed by the following relation:

$$B = \frac{OD'_4 - OD'_3}{\alpha_{h4} - \alpha_{h3}} = c_h d .$$

In certain embodiments in which the values of hemocrit absorption at the two wavelengths is known or provided to the system, this ratio of the difference of two “water free” OD values with the difference of two reference absorption values for hemocrit at the same wavelengths yields a hemocrit scaling factor B indicative of the amount of hemocrit in the sample.

[0215] By using B and the hemocrit absorptions at each wavelength, the “glucose only” OD is calculated in certain embodiments to be expressed by the following relation:

$$OD''_i = OD'_i - B \alpha_{hi} .$$

In this way, the “glucose only” OD value equals the measured OD value minus the scaled reference absorption values for water and for hemocrit.

[0216] From the above equations, the following relations can be calculated:

$$OD''_5 = c_g \alpha_{g5} d ; \text{ and}$$

$$OD''_6 = c_g \alpha_{g6} d .$$

[0217] The glucose concentration path length product, given by the quantity C which can be termed the “glucose scaling factor,” and which can be expressed by the following relation:

$$C = \frac{OD''_6 - OD''_5}{\alpha_{g6} - \alpha_{g5}} = c_g d .$$

In certain embodiments in which the values of glucose absorption at the two wavelengths is known or provided to the system, this ratio of the difference of two “glucose only” OD values with the difference of two reference absorption values for glucose at the same

wavelengths yields a glucose scaling factor C indicative of the amount of glucose in the sample.

[0218] The desired ratio of glucose volume to total blood volume can then be expressed (using the relation: $c_w + c_h + c_g = 1$) by the following relation:

$$c_g = \frac{c_g}{c_w + c_h + c_g} = \frac{C}{A + B + C}.$$

By taking the ratio of the glucose scaling factor to the sum of the water scaling factor, the hemocrit scaling factor, and the glucose scaling factor, the resulting concentration ratio c_g is substantially independent of the path length of the sample. Thus, certain embodiments described herein provide a method of determining the glucose content of a blood sample independent of the path length of the blood sample.

D. System and Temperature Effects on Absorption

[0219] In certain embodiments, the resulting absorption spectrum (e.g., after being corrected for instrumental drift, optical pathlength, distortions, and contributions from major components) can be fitted with a reference glucose absorption spectrum to remove the glucose contribution. This absorption spectrum can be used further for individual determination of residual components. In certain embodiments, the residual components include high molecular weight substances, including but not limited to, other proteins, albumin, hemoglobin, fibrinogen, lipoproteins, and transferrin. In certain embodiments, the residual components include low molecular weight substances, including but not limited to, urea, lactate, and vitamin C. The final glucose measure can be corrected for the presence of such lower level potentially interfering substances by subtracting reference spectra of specific substances, such as urea, from the residual data.

1. Expression of integral optical density as sum of terms

[0220] In certain embodiments, various non-analyte contributions to the measured absorption spectrum can be determined. For a water-filled cuvette irradiated by light transmitted through a filter “ n ”, the optical density can be expressed as being equal to the average water absorption through the filter multiplied by the pathlength, plus a correction term due to the finite filter width and shape, plus a correction term due to the cuvette shape, and a cross-term resulting from finite filter width and cuvette shape by the following relation:

$$OD_n = \langle \alpha_n \rangle d_{avg} - \frac{1}{2} d_{avg}^2 J_{3n} - A \langle \alpha_n \rangle^2 - A J_{3n} \left(1 - 2 \langle \alpha_n \rangle d_{avg} + \frac{1}{2} \langle \alpha_n \rangle^2 d_{avg}^2 \right),$$

where

$$\langle \alpha_n \rangle \equiv \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \alpha(\lambda),$$

$\alpha(\lambda)$ = water absorption spectrum,

$f_n(\lambda)$ = transmission spectrum of filter “n”,

$N_n = \int d\lambda f_n(\lambda)$ = filter normalization,

$2w$ = cuvette width,

$d(x) = d_{avg} + \delta(x)$ = cuvette path length,

d_{avg} = average cuvette path length and the following relation is true: $\int_{-w}^w dx \delta(x) = 0$,

$A \equiv \frac{1}{2} \frac{1}{2w} \int_{-w}^w dx \cdot \delta(x)^2$ = distortion parameter, and

$J_{3n} \equiv \frac{1}{N_n} \int d\lambda f_n(\lambda) \Delta_n^2(\lambda) = \frac{1}{N_n} \int d\lambda \cdot f(\lambda) \cdot (\alpha(\lambda) - \langle \alpha_n \rangle)^2$ = non-linear filter term.

2. Temperature effects on optical density

[0221] In addition, the optical density OD_n can be expressed to include contributions to the measured absorption spectrum from changes in water temperature, changes in filter temperature, and a cross-term resulting from water and filter temperature changes by the following relation:

$$OD_n = \langle \alpha_{on} \rangle d_{avg} + \langle \beta_n \rangle \Delta T_w d_{avg} + \langle \gamma_n \rangle \Delta T_f d_{avg} + \langle \alpha_n \rangle^2 A + T_n,$$

where

$$T_n = \langle \xi_n \rangle \Delta T_w \Delta T_f d_{avg} - \frac{1}{2} d_{avg}^2 J_{3n} - A J_{3n} \left(1 - 2 \langle \alpha_n \rangle d_{avg} + \frac{1}{2} \langle \alpha_n \rangle^2 d_{avg}^2 \right),$$

$\langle \alpha_{on} \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \alpha_o(\lambda)$, where $\alpha_o(\lambda)$ = water absorption at $\Delta T_w = \Delta T_f = 0$,

ΔT_w = water temperature change,

ΔT_f = filter temperature change,

$$\langle \alpha_n \rangle = \langle \alpha_{on} \rangle + \langle \beta_n \rangle \Delta T_w + \langle \gamma_n \rangle \Delta T_f + \langle \xi_n \rangle \Delta T_w \Delta T_f,$$

$$\langle q_n \rangle \equiv \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot q(\lambda),$$

$$\beta(\lambda) = \frac{\delta \alpha_o(\lambda)}{\delta T_w} = \text{absorption water temperature sensitivity},$$

$$\gamma_n(\lambda) = \frac{\delta\alpha_o(\lambda)}{\delta T_f} = \frac{\delta\alpha_o(\lambda)}{\delta\lambda} \cdot \frac{\delta\lambda_n}{\delta T_f} = \text{absorption filter temperature sensitivity,}$$

$$\xi_n(\lambda) = \frac{\delta^2\alpha_o(\lambda)}{\delta T_w \delta T_f} = \frac{\delta\beta(\lambda)}{\delta T_f} = \frac{\delta\beta(\lambda)}{d\lambda} \cdot \frac{d\lambda_n}{\delta T_f} = \text{change in } \beta(\lambda) \text{ with filter}$$

temperature, and

$$\frac{d\lambda_n}{\delta T_f} = \text{filter "n" temperature sensitivity.}$$

E. Subtraction of System and Temperature Effects From Absorption Data

[0222] The analysis of the absorption data preferably uses a finite number of absorption measurements to determine the path length, water temperature, filter temperature and cuvette shape. In certain embodiments, the analysis utilizes four OD measurements which, assuming $T_n = 0$ and $\langle\alpha_n\rangle = \langle\alpha_{on}\rangle$, are expressed as a set of linear equations to be solved expressed by the following relation:

$$\begin{pmatrix} OD_1 \\ OD_2 \\ OD_3 \\ OD_4 \end{pmatrix} = \begin{pmatrix} \langle\alpha_{01}\rangle & \langle\beta_1\rangle & \langle\gamma_1\rangle & \langle\alpha_{01}\rangle^2 \\ \langle\alpha_{02}\rangle & \langle\beta_2\rangle & \langle\gamma_2\rangle & \langle\alpha_{02}\rangle^2 \\ \langle\alpha_{03}\rangle & \langle\beta_3\rangle & \langle\gamma_3\rangle & \langle\alpha_{03}\rangle^2 \\ \langle\alpha_{04}\rangle & \langle\beta_4\rangle & \langle\gamma_4\rangle & \langle\alpha_{04}\rangle^2 \end{pmatrix} \cdot \begin{pmatrix} d_{avg} \\ \Delta T_w d_{avg} \\ \Delta T_f d_{avg} \\ A \end{pmatrix}.$$

The solution of this set of linear equations can provide an initial estimate of the parameters $(d_{avg}, \Delta T_w, \Delta T_f, A)$ which are used to evaluate the non-linear terms $(T_1...T_4)$. The next estimate of $(d_{avg}, \Delta T_w, \Delta T_f, A)$ can be found by solving the following relation:

$$\begin{pmatrix} OD_1 - T_1 \\ OD_2 - T_2 \\ OD_3 - T_3 \\ OD_4 - T_4 \end{pmatrix} = \begin{pmatrix} \langle\alpha_{01}\rangle & \langle\beta_1\rangle & \langle\gamma_1\rangle & \langle\alpha_1\rangle^2 \\ \langle\alpha_{02}\rangle & \langle\beta_2\rangle & \langle\gamma_2\rangle & \langle\alpha_2\rangle^2 \\ \langle\alpha_{03}\rangle & \langle\beta_3\rangle & \langle\gamma_3\rangle & \langle\alpha_3\rangle^2 \\ \langle\alpha_{04}\rangle & \langle\beta_4\rangle & \langle\gamma_4\rangle & \langle\alpha_4\rangle^2 \end{pmatrix} \cdot \begin{pmatrix} d_{avg} \\ \Delta T_w d_{avg} \\ \Delta T_f d_{avg} \\ A \end{pmatrix}.$$

This process can be repeated until estimates of path length, water temperature, filter temperature and cuvette non-parallelism (i.e., the degree to which opposed walls/windows of the sample chamber deviate from parallel) converge.

[0223] Measurements using this approach may not deliver the desired accuracy over the entire range of temperature and cuvette/sample chamber shape. Other approaches may be used to yield more stable results. One such alternative approach is based on rewriting the equations above as follows:

$$OD_n = \langle \alpha_{on} \rangle d_{avg} + \langle \beta_n \rangle \Delta T_w d_{avg} + \langle \gamma_n \rangle \Delta T_f d_{avg} + \langle \alpha_n \rangle^2 A - \frac{1}{2} d_{avg}^2 J_{3n} + S_n,$$

$$S_n = \langle \xi_n \rangle \Delta T_w \Delta T_f d_{avg} - A J_{3n} \left(1 - 2 \langle \alpha_n \rangle d_{avg} + \frac{1}{2} \langle \alpha_n \rangle^2 d_{avg}^2 \right).$$

Rearranging the terms of these relations yields the following relation:

$$OD_n - d_{avg} \langle \alpha_{on} \rangle + \frac{1}{2} d_{avg}^2 J_{3n} - S_n = d_{avg} \langle \beta_n \rangle \Delta T_w + d_{avg} \langle \gamma_n \rangle \Delta T_f + \langle \alpha_n \rangle^2 A.$$

Embodiments in which this relation is used to analyze the absorption data are described below.

1. Water temperature, filter temperature, cuvette shape analysis

[0224] In certain embodiments, the water temperature, filter temperature, and cuvette shape are analyzed. In such embodiments, the analysis comprises “step 1” in which transmission measurements, filter parameters and water spectral properties are inputted:

Transmission measurements $(\tau_1, \tau_2, \tau_3, \tau_4)$,

Filter curves $[f_1(\lambda), f_2(\lambda), f_3(\lambda), f_4(\lambda)]$,

Filter temperature sensitivities $\left[\frac{d\lambda_1}{\delta T_f}, \frac{d\lambda_2}{\delta T_f}, \frac{d\lambda_3}{\delta T_f}, \frac{d\lambda_4}{\delta T_f} \right]$, and

Water spectral properties $\left[\alpha_o(\lambda), \beta(\lambda), \frac{\delta \alpha_o(\lambda)}{\delta \lambda}, \frac{\delta \beta(\lambda)}{\delta \lambda} \right]$.

[0225] Certain embodiments of the analysis further comprise “step 2” in which optical densities and filter constants are calculated:

$$OD_n = -\ln(\tau_n),$$

$$\langle \alpha_{on} \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \alpha_o(\lambda),$$

$$\langle \beta_n \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \beta(\lambda),$$

$$\langle \gamma_n \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \frac{\delta \alpha_o(\lambda)}{\delta \lambda} \cdot \frac{d\lambda_n}{\delta T_f}, \text{ and}$$

$$\langle \xi_n \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \frac{\delta \beta(\lambda)}{\delta \lambda} \cdot \frac{d\lambda_n}{\delta T_f}.$$

[0226] In certain embodiments, the analysis further comprises “step 3” in which the non-linear filter terms and cuvette distortion matrix element are estimated using the following relations:

$$J_{3n} = \frac{1}{N_n} \int d\lambda \cdot f(\lambda) \cdot (\alpha(\lambda) - \langle \alpha_o \rangle)^2,$$

$$\langle \alpha_n \rangle^2 = \langle \alpha_{on} \rangle^2, \text{ and}$$

$$S_n = 0.$$

[0227] In certain embodiments, the analysis further comprises “step 4” in which the analysis solves for $(\Delta T_w, \Delta T_f, A)$ as a function of path length d using (OD_1, OD_2, OD_3) and (OD_2, OD_3, OD_4) . The values of $(d_{avg}, \Delta T_w, \Delta T_f, A)$ are estimated by finding value of d where solutions for $(\Delta T_w, \Delta T_f, A)$ are same for both sets of transmission measurements:

$$\begin{pmatrix} OD_1 - d\langle \alpha_{o1} \rangle + \frac{1}{2}d^2J_{31} - S_1 \\ OD_2 - d\langle \alpha_{o2} \rangle + \frac{1}{2}d^2J_{32} - S_2 \\ OD_3 - d\langle \alpha_{o3} \rangle + \frac{1}{2}d^2J_{33} - S_3 \end{pmatrix} = \begin{pmatrix} d\langle \beta_1 \rangle & d\langle \gamma_1 \rangle & \langle \alpha_1 \rangle^2 \\ d\langle \beta_2 \rangle & d\langle \gamma_2 \rangle & \langle \alpha_2 \rangle^2 \\ d\langle \beta_3 \rangle & d\langle \gamma_3 \rangle & \langle \alpha_3 \rangle^2 \end{pmatrix} \cdot \begin{pmatrix} \Delta T_w \\ \Delta T_f \\ A \end{pmatrix}, \text{ and}$$

$$\begin{pmatrix} OD_2 - d\langle \alpha_{o2} \rangle + \frac{1}{2}d^2J_{32} - S_2 \\ OD_3 - d\langle \alpha_{o3} \rangle + \frac{1}{2}d^2J_{33} - S_3 \\ OD_4 - d\langle \alpha_{o4} \rangle + \frac{1}{2}d^2J_{34} - S_4 \end{pmatrix} = \begin{pmatrix} d\langle \beta_2 \rangle & d\langle \gamma_2 \rangle & \langle \alpha_2 \rangle^2 \\ d\langle \beta_3 \rangle & d\langle \gamma_3 \rangle & \langle \alpha_3 \rangle^2 \\ d\langle \beta_4 \rangle & d\langle \gamma_4 \rangle & \langle \alpha_4 \rangle^2 \end{pmatrix} \cdot \begin{pmatrix} \Delta T_w \\ \Delta T_f \\ A \end{pmatrix}.$$

[0228] In certain embodiments, the analysis further comprises “step 5” in which new estimates of absorption and non-linear terms are calculated:

$$\langle \alpha_n \rangle = \langle \alpha_{on} \rangle + \langle \beta_n \rangle \Delta T_w + \langle \gamma_n \rangle \Delta T_f + \langle \xi_n \rangle \Delta T_w \Delta T_f,$$

$$J_{3n} = \frac{1}{N_n} \int d\lambda \cdot f(\lambda) \cdot (\alpha(\lambda) - \langle \alpha_n \rangle)^2, \text{ and}$$

$$S_n = \langle \xi_n \rangle \Delta T_w \Delta T_f d - A J_{3n} \left(1 - 2\langle \alpha_n \rangle d + \frac{1}{2} \langle \alpha_n \rangle^2 d^2 \right).$$

In certain embodiments, the analysis further comprises “step 6” in which “step 4” and “step 5” are repeated until the solution converges to a desired accuracy.

2. Water temperature, filter temperature, parallel cuvette analysis

[0229] In certain other embodiments, the water temperature and filter temperature are analyzed for a parallel cuvette (i.e., one in which opposed walls of the sample chamber are substantially parallel). In such embodiments, the analysis comprises “step 1” in which transmission measurements, filter parameters and water spectral properties are inputted:

Transmission measurements (τ_1, τ_2, τ_3) ,

Filter curves $[f_1(\lambda), f_2(\lambda), f_3(\lambda)]$,

Filter temperature sensitivity $\left[\frac{d\lambda_1}{dT_f}, \frac{d\lambda_2}{dT_f}, \frac{d\lambda_3}{dT_f} \right]$, and

Water spectral properties $\left[\alpha_o(\lambda), \beta(\lambda), \frac{\delta\alpha_o(\lambda)}{\delta\lambda}, \frac{\delta\beta(\lambda)}{\delta\lambda} \right]$.

[0230] Certain embodiments of the analysis further comprise “step 2” in which optical densities and filter constants are calculated:

$$OD_n = -\ln(\tau_n),$$

$$\langle \alpha_{on} \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \alpha_o(\lambda),$$

$$\langle \beta_n \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \beta(\lambda),$$

$$\langle \gamma_n \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \frac{\delta\alpha_o(\lambda)}{\delta\lambda} \cdot \frac{d\lambda_n}{dT_f}, \text{ and}$$

$$\langle \xi_n \rangle = \frac{1}{N_n} \int d\lambda \cdot f_n(\lambda) \cdot \frac{\delta\beta(\lambda)}{\delta\lambda} \cdot \frac{d\lambda_n}{dT_f}.$$

[0231] In certain embodiments, the analysis further comprises “step 3” in which the non-linear filter terms and cuvette distortion matrix element are estimated using the following relations:

$$J_{3n} = \frac{1}{N_n} \int d\lambda \cdot f(\lambda) \cdot (\alpha(\lambda) - \langle \alpha_o \rangle)^2,$$

$$\langle \alpha_n \rangle^2 = \langle \alpha_{on} \rangle^2, \text{ and}$$

$$S_n = 0.$$

[0232] In certain embodiments, the analysis further comprises “step 4” in which the analysis solves for $(\Delta T_w, \Delta T_f)$ as a function of path length d using (OD_1, OD_2) and (OD_2, OD_3) . The values of $(d_{avg}, \Delta T_w, \Delta T_f)$ are estimated by finding values of d where solutions for $(\Delta T_w, \Delta T_f)$ are same for both sets of transmission measurements:

$$\begin{pmatrix} OD_1 - d\langle\alpha_{o1}\rangle + \frac{1}{2}d^2J_{31} - S_1 \\ OD_2 - d\langle\alpha_{o2}\rangle + \frac{1}{2}d^2J_{32} - S_2 \end{pmatrix} = \begin{pmatrix} d\langle\beta_1\rangle & d\langle\gamma_1\rangle \\ d\langle\beta_2\rangle & d\langle\gamma_2\rangle \end{pmatrix} \cdot \begin{pmatrix} \Delta T_w \\ \Delta T_f \end{pmatrix}, \text{ and}$$

$$\begin{pmatrix} OD_2 - d\langle\alpha_{o2}\rangle + \frac{1}{2}d^2J_{32} - S_2 \\ OD_3 - d\langle\alpha_{o3}\rangle + \frac{1}{2}d^2J_{33} - S_3 \end{pmatrix} = \begin{pmatrix} d\langle\beta_2\rangle & d\langle\gamma_2\rangle \\ d\langle\beta_3\rangle & d\langle\gamma_3\rangle \end{pmatrix} \cdot \begin{pmatrix} \Delta T_w \\ \Delta T_f \end{pmatrix}.$$

[0233] In certain embodiments, the analysis further comprises “step 5” in which new estimates of absorption and non-linear terms are calculated:

$$\langle\alpha_n\rangle = \langle\alpha_{on}\rangle + \langle\beta_n\rangle\Delta T_w + \langle\gamma_n\rangle\Delta T_f + \langle\xi_n\rangle\Delta T_w\Delta T_f,$$

$$J_{3n} = \frac{1}{N_n} \int d\lambda \cdot f(\lambda) \cdot (\alpha(\lambda) - \langle\alpha_n\rangle)^2, \text{ and}$$

$$S_n = \langle\xi_n\rangle\Delta T_w\Delta T_f d - AJ_{3n} \left(1 - 2\langle\alpha_n\rangle d + \frac{1}{2}\langle\alpha_n\rangle^2 d^2 \right).$$

In certain embodiments, the analysis further comprises “step 6” in which “step 4” and “step 5” are repeated until the solution converges to a desired accuracy.

F. Contribution to Analyte Concentration Errors by Instrument Factors

[0234] Transmission data measured at each wavelength by certain apparatuses are typically affected by a combination of instrument factors and blood properties. The instrument factors include, but are not limited to, filter temperature, cuvette shape and filter characteristics (e.g., center wavelengths, temperature sensitivity, bandwidth, shape). The blood properties include, but are not limited to, blood temperature, the relative concentrations of the blood components and scattering. Before the transmission data are used to calculate analyte (e.g., glucose) concentration, the instrument factors are preferably determined and corresponding corrections are preferably made for each transmission value. As described above in relation to transmission measurements, each of the instrument factors can influence the transmission of a water-filled cuvette. In certain embodiments, the

analysis can predict the analyte concentration error introduced by the instrument factors over the expected variation range for the apparatus:

[0235] As described above, transmission measurements in the “water region” of wavelengths can be used to determine the blood’s water content without considering other blood constituents. Once the water content is known, in certain embodiments, the water contribution at each of the wavelengths outside the water region can be calculated and removed. As described above, a water reference spectrum can be fitted to approximate the blood spectrum in a wavelength range of approximately 4.7 microns to approximately 5.3 microns. The fitted water spectrum can then be subtracted from the blood spectrum to produce an effectively water-free spectrum.

[0236] In certain transmission measurement systems, the filters have finite width and shape, the cuvettes may or may not be parallel, and the temperatures of the blood and filters may not be controlled. These factors will cause transmission changes that are not due to blood component changes or path length changes. If they are not corrected, the analysis can have corresponding errors in the calculated analyte concentration (e.g., glucose errors). While each of these instrument factors in isolation can result in a corresponding glucose error, in actual systems, the glucose error will be due to a combination of all the instrument factors.

[0237] In certain embodiments, the analysis described above can be used to estimate the magnitude of the glucose error for each instrument factor. The analysis can predict the optical density as a function of cuvette shape, filter shape, water temperature and filter temperature for a water-filled cuvette. The glucose error can be evaluated using four wavelengths, two in the water region, one at a glucose reference wavelength (e.g., 8.45 microns) and one at the peak of the glucose absorption (e.g., 9.65 microns). The effects of each instrument factor can be studied separately.

[0238] In certain embodiments, a method of evaluating the glucose error comprises calculating the transmission and optical density (od_1, od_2, od_3, od_4) at each wavelength for a water-filled cuvette with instrument factor under study. The method further comprises using the optical density of the two water measurements (od_1, od_2) to determine the water content at the glucose reference and measurement wavelengths (λ_3, λ_4). The method further comprises calculating the expected optical density

(OD_{3c}, OD_{4c}) at the glucose reference and measurement wavelengths. The method further comprises calculating residuals $(\Delta OD_3, \Delta OD_4)$, which are the difference between the exact and calculated optical densities at the glucose reference and measurement wavelengths. The method further comprises determining the glucose error by calculating the glucose concentration consistent with residual difference $(\Delta OD_4 - \Delta OD_3)$.

[0239] The optical density corresponding to transmission through a filter for a water-filled non-parallel cuvette with parallel illumination (e.g., exposed to a substantially cylindrical energy beam) can be expressed by the following relation:

$$od_n = -\ln(\tau_n) = -\ln \left[\frac{1}{N_n} \cdot \frac{1}{2w} \int d\lambda f_n(\lambda) \int_{-w}^w dx \exp[-\alpha_n(\lambda)d(x)] \right],$$

where

- $f_n(\lambda)$ = filter transmission,
- N_n = filter normalization,
- $d(x)$ = cuvette path length,
- ΔT_w = water temperature change,
- ΔT_f = filter temperature change, and
- $2w$ = cuvette width.

As used herein, the above relation is referred to as the “exact optical density” because it does not include the various approximations described herein.

[0240] The water absorption adjusted for water and filter temperature can be expressed by the following relation:

$$\alpha_n(\lambda) = \alpha_o(\lambda) + \beta(\lambda)\Delta T_w + \gamma_n(\lambda)\Delta T_f + \xi_n(\lambda)\Delta T_w\Delta T_f.$$

An approximate solution for the optical density can be expressed by the following relations:

$$OD_n = \langle \alpha_{on} \rangle d_{avg} + \Delta OD_n, \text{ and}$$

$$\Delta OD_n = -\frac{1}{2} d_{avg}^2 J_{3n} + \langle \beta_n \rangle \Delta T_w d_{avg} + \langle \gamma_n \rangle \Delta T_f d_{avg} + \langle \alpha_n \rangle^2 A + S_n,$$

where d_{avg} = average cuvette path length and $d(x) = d_{avg} \Rightarrow A = 0$. In these equations, four instrument factors which contribute to the optical density are specified by the following parameters:

- $f_n(\lambda)$ = filter function,
- ΔT_w = water temperature change from nominal,

$$\begin{aligned}\Delta T_f &= \text{filter temperature change from nominal,} \\ d(x) &= \text{cuvette shape.}\end{aligned}$$

In addition, the average absorption through the filter is represented by $\langle \alpha_{on} \rangle$ and ΔOD_n represents the effects due to water temperature, filter temperature, filter shape and cuvette shape.

1. Calculation of the analyte contribution errors

[0241] Considering each instrument factor separately, ΔOD_n becomes a function only of that factor. This allows the calculation of the glucose sensitivity for each factor and the evaluation of the accuracy of the approximate solution for the optical density as compared to the exact optical density. Table 2 shows the values of each of the four instrument factors for various simulations. Each row shows the values of the instrument factors for a particular simulation and the corresponding value of ΔOD_n . The filter shape $\delta(\lambda_n)$ is a delta function representing an infinitely narrow filter at λ_n .

Table 2:

	$f_n(\lambda)$	ΔT_w	ΔT_f	$d(x)$	ΔOD_n
Filter shape	$f_n(\lambda)$	0	0	d_{avg}	$-\frac{1}{2}d_{avg}^2 J_{3n}$
Water temp	$\delta(\lambda_n)$	ΔT_w	0	d_{avg}	$\langle \beta_n \rangle \Delta T_w d_{avg}$
Filter temp	$\delta(\lambda_n)$	0	ΔT_f	d_{avg}	$\langle \gamma_n \rangle \Delta T_f d_{avg}$
Cuvette shape	$\delta(\lambda_n)$	0	0	$d_{avg} + \varepsilon(x)$	$\langle \alpha_n \rangle^2 A$

[0242] Each simulation starts by calculating the set of exact optical densities $[od_1, od_2, od_3, od_4]$ using the relation for the exact optical density and the instrument factors from Table 2. For all simulations, the calibration constants are the set $[\langle \alpha_{01} \rangle, \langle \alpha_{02} \rangle, \langle \alpha_{03} \rangle, \langle \alpha_{04} \rangle]$, and the approximate optical densities $OD_n = \langle \alpha_{on} \rangle d_{avg} + \Delta OD_n$.

[0243] For the uncorrected case, the calculated path length (d_c) can be expressed using the exact optical densities from the water region and the calibration constants in the following relation:

$$d_c = \frac{od_2 - od_1}{\langle \alpha_{02} \rangle - \langle \alpha_{01} \rangle}.$$

The second two calibration constants can be used to predict the optical densities at (λ_3, λ_4) as follows:

$$OD_{3c} = \langle \alpha_{o3} \rangle \cdot d_c, \text{ and}$$

$$OD_{4c} = \langle \alpha_{o4} \rangle \cdot d_c.$$

The residuals can be expressed by the following relations:

$$\Delta OD_3 = OD_{3c} - od_3, \text{ and}$$

$$\Delta OD_4 = OD_{4c} - od_4.$$

The glucose error can be expressed by the following relation:

$$\Delta c_g = \frac{\Delta OD_4 - \Delta OD_3}{\Delta g_4 - \Delta g_3} \cdot \frac{1}{d_c},$$

where $(\Delta g_3, \Delta g_4)$ represents the glucose absorption at (λ_3, λ_4) .

[0244] The glucose error for the corrected case can be determined by making the following transformation:

$$od_n \rightarrow od_n - \Delta OD_n,$$

and repeating the steps outlined above. The corrected glucose error is a measure of how accurately the approximate optical densities equal the exact optical densities. It is an indication of the range over which the instrument parameter (in this case filter width) can vary and still be predicted by the approximate equation.

[0245] In certain embodiments, the cuvette/sample chamber shape can be modeled by introducing a curvature (Δc) and wedge (Δp) to a parallel cuvette/sample chamber having a path length (d_0). The curvature can be modeled as being on one side of the cuvette, but the sensitivity is the same as if the same curvature is distributed between the top and bottom surfaces. The cuvette width is $2w$. Other cuvette shapes may also be modeled.

[0246] Graphs of the uncorrected and corrected glucose error as a function of cuvette shape parameters, path length, water temperature variation from nominal, and filter temperature from nominal can be generated using the method described above. The relative contributions of the various cuvette shape parameters can be compared to determine which parameters have the larger effect on the resultant glucose error. This analysis can demonstrate which sensitivities provide glucose errors which are too large unless corrected

for. This analysis underestimates the corrected errors since it does not include cross terms when two or more factors are present. This analysis can also show whether the approximate optical density expansion agrees with the exact integral solution, that is, whether the higher order terms are needed.

V. SAMPLE ELEMENT WITH BARRIER MATERIAL

A. Sample Element

[0247] Figure 22 is a schematic view of one embodiment of a sample element 1000 which may be employed with the analyte detection system 10 disclosed above. Alternatively, the sample element 1000 may be employed with any suitable analyte detection system. The sample element 1000 generally comprises a sample chamber 1002 and a barrier 1004. The barrier 1004 comprises a first side 1006 configured for contact with the skin PS of a patient at a lancing site LS, and a second side 1008 in fluid communication with the sample chamber 1002. In various embodiments, fluid communication may be established between the second side 1008 and the sample chamber 1002 via one or more passages, such as one or more capillary channels, a wicking material (or a combination of such passage(s)/channel(s) and wicking material), through intervening chamber(s), or simple adjacency between the second side 1008 and the sample chamber 1002.

[0248] The sample chamber may comprise a partially or completely enclosed volume within the sample element 1000 and is configured to hold a sample of bodily fluid, such as but not limited to whole blood, blood components such as plasma, interstitial fluid and/or intercellular fluid, withdrawn from the patient's skin PS at the lancing site LS. In one embodiment, the sample chamber 1002 is at least partially defined by a housing 1020. When the barrier 1004 is placed in contact with the lancing site LS and the barrier 1004 and site are lanced (see below), the barrier 1004 permits the sample to pass from the first side 1006 to the second side 1008 while allowing little or substantially none of the sample to pass in the opposite direction, from the second side 1008 to the first side 1006. Accordingly, once the sample reaches the second side 1008, it tends to flow toward the sample chamber 1002 until the chamber 1002 is substantially filled with the sample. These properties of the barrier 1004 also tend to minimize the amount of sample that remains at the lancing site LS after removal of the sample element 1000 therefrom. For similar

reasons, the barrier also ensures that a large proportion, or even substantially all, of the withdrawn sample is taken into, or made available for being taken into, the sample element 1000.

[0249] The sample chamber 1002 preferably comprises a reagentless chamber. In other words, the internal volume of the sample chamber 1002 and/or the wall(s) defining the chamber 1002 are preferably inert with respect to the sample to be drawn into the chamber for analysis. Alternatively, the sample chamber 1002 may contain one or more reagents to facilitate use of the sample element in sample assay techniques which involve reaction of the sample with a reagent.

[0250] Figures 23-24 depict another embodiment of the sample element 1000 in which the barrier 1004 and an opening 1010 are positioned on one side of the sample element 1000. This arrangement permits a lance 1013 to be driven through the sample element 1000 and barrier 1004 after the barrier has been positioned against the patient's skin PS at the lancing site LS. Once the lance 1013 has pierced the barrier 1004 and skin PS, the sample passes through the barrier 1004 as detailed above, and then into the sample element 1000. The sample element 1000 shown in Figures 23-24 may (but need not) further comprise a pierceable and self-resealing portion 1012 on the side of the sample element, opposite the barrier and within the path of the lance 1013. The portion 1012 may be formed from a relatively soft polymer so that it will tend to re-seal after the lance has been driven through it and withdrawn, thereby preserving the tendency of the sample to flow from the second side 1008 of the barrier into the sample element 1000. Either or both of the pierceable and self-resealing portion 1012 or barrier 1004 may be mounted flush with the surrounding portions of the sample element 1000 (as the portion 1012 is depicted in Figure 24) or in an overlying fashion (as the barrier 1004 is depicted in Figure 24).

[0251] The sample element 1000 shown in Figures 23-24 may further comprise a supply passage 1022 to establish fluid communication between the sample chamber 1002 and the second side 1008. Sidewalls 1022a, 1022b of the supply passage 1022 are formed on either side of the passage by the overlying portions of the sample element 1000. Similarly, windows 1002a, 1002b are formed on either side of the chamber 1002 by the overlying portions of the sample element 1000. One or more vent passages 1024 may be employed to vent the sample chamber 1002 and/or opening 1010 via fluid communication

with vent opening(s) 1026 disposed at one or both ends of the sample element (or formed in the side(s) thereof).

[0252] The supply passage 1022, opening 1010 and/or any other structures located between the sample chamber 1002 and the second side 1008 of the barrier 1004, may be considered a flow path extending from the sample chamber. Where the vent passage 1024 leading from the portion 1012 is omitted, the flow path is enclosed on all sides (except where the flow path joins the sample chamber 1002) until an opening is formed in the barrier 1004 and/or portion 1012.

[0253] In the depicted configuration, the sample chamber 1002 is longitudinally offset from the barrier 1004 and portion 1012, so that a beam of electromagnetic radiation may pass through the chamber 1002 and windows 1002a, 1002b without interference from the material forming the barrier and the portion 1012. This embodiment of the sample element 1000 is suitable for use with the various embodiments of the analyte detection system 10 disclosed herein, or any other system which analyzes a sample by passing a beam of electromagnetic radiation through the sample chamber 1002. Accordingly, the materials and methods disclosed above as suitable for constructing the sample element 120, may be employed likewise in constructing the sample element 1000.

[0254] Suitable materials for the barrier 1004 are discussed in further detail below. In general, the barrier 1004 and/or portion 1012 may be constructed to be more easily pierced by a lance than is the housing 1020, or are the portions of the housing adjacent the barrier 1004 or portion 1012, or are either of the layers of material employed to construct the housing 1020 (where a layered construction technique similar to that shown in Figure 7 is employed in making the sample element 1000, as may be done in various embodiments). More specifically, the barrier 1004 and/or portion 1012 may be constructed to be more easily pierced by a lance than are either of the windows 1002a, 1002b or are either of the sidewalls 1022a, 1022b of the supply passage 1022.

[0255] In another embodiment of the sample element 1000, the sample chamber 1002 may overlap, either partially or completely, the barrier 1004 and/or portion 1012. This embodiment may be useful, for example, where any interference from the barrier 1004 or portion 1012 is negligible or compensated for in the computations and/or measurements performed by the analyte detection system employed with the sample element 1000. The supply passage 1022 may be shortened or eliminated altogether when the chamber 1002 so

overlaps the barrier 1004 and/or portion 1012. Such an “overlapping” chamber 1002 may also be used where the sample element 1000 is constructed for use in an analysis technique that does not necessarily involve passing a beam of electromagnetic energy through the sample chamber (e.g., an electrochemical technique).

[0256] In various embodiments, the sample element 1000 shown in Figures 23-24 may be generally similar to the sample element 120 disclosed above, and/or any other sample element or cuvette disclosed herein, but further configured as shown in Figures 23-24. The sample element 1000 of Figures 23-24 may have a sample chamber which contains a reagent, or is reagentless. The sample element 1000 and sample collection method depicted in Figures 23-24 advantageously minimize or eliminate the blood visible to the patient on his or her skin, thereby minimizing or eliminating the patient’s perceived pain level due to lancing. In various embodiments, the lance 1013 may comprise a conventional sharp lance, laser lance, iontophoretic device, or any suitable sample extractor.

[0257] In still further embodiments, the sample element 1000 may be generally similar to any of the sample elements or cuvettes disclosed herein, but further configured as shown in Figures 23-24.

[0258] Figures 24A-24B depict another embodiment of a sample element 1200, which may be generally similar to any of the sample elements or cuvettes disclosed herein (e.g., the various disclosed embodiments of the sample element 1000), but further configured as shown in Figures 24A-24B. The sample element 1200 generally comprises a sample chamber 1202 and a barrier 1204. The barrier 1204 comprises a first side 1206 configured for contact with the skin PS of a patient at a lancing site LS, and a second side 1208 in fluid communication with the sample chamber 1202. In various embodiments, fluid communication may be established between the second side 1208 and the sample chamber 1202 via one or more passages, such as a sample passage 1222 as shown, one or more capillary channels, a wicking material (or a combination of such passage(s)/channel(s) and wicking material), through intervening chamber(s), or simple adjacency between the second side 1208 and the sample chamber 1202.

[0259] The sample element 1200 may further comprise a pierceable portion 1212 on the side of the sample element, opposite the barrier 1204. The portion 1212 may be formed from a soft polymer so as to impart a self-sealing quality to the portion 1212; alternatively, the portion 1212 may be formed from a similar material as is employed in the

barrier 1204. In the embodiment depicted in Figures 24A-24B, the barrier 1204 and the portion 1212 comprise substantially identical components, being similarly sized and formed from the same barrier material. Both of the barrier 1204 and portion 1212 are depicted as flush with the sides of the sample element 1200; however, either or both may be situated in an overlying fashion as the barrier 1004 is shown in Figure 24. In other embodiments, either or both of the barrier 1204 and portion 1212 may comprise a thinned portion of the sample element housing 1220, which is constructed from the same material as is employed in the balance of the housing 1220.

[0260] The barrier 1204 and portion 1212, together with adjoining portions of the sample element 1200, may define an entry chamber 1230 into which fluid initially flows upon passing the barrier 1204. As shown in Figures 24A-24B, the entry chamber 1230 may have a perimeter which is smaller than that of the barrier 1204 and/or portion 1212, so as to minimize the volume of blood or other fluid needed to fill the entry chamber 1230. Alternatively the perimeter of the entry chamber 1230 may be coextensive with, or larger than, that of the barrier 1204 and/or portion 1212, or the entry chamber 1230 may simply comprise a longitudinal extension of the supply passage 1222 into the area between the barrier 1204 and portion 1212.

[0261] In the depicted embodiment, a vent passage 1224 extends from the sample chamber 1202, to a vent opening 1226 formed in the side of the sample element 1200. In addition, a separator 1240, which may comprise any suitable membrane, filter, etc., may be disposed in the supply passage 1222 (or otherwise upstream of the sample chamber 1202), and employed to separate plasma from a whole-blood sample, or liquid and finer solid components from other heterogeneous samples. In a sample element 1200 so configured, a whole-blood or other heterogeneous sample may flow downstream in the supply passage 1222 until it reaches the separator 1240. The separator 1240 allows substantially only the plasma of a whole-blood sample, or substantially only the liquid and finer solid components of other heterogeneous samples, to flow downstream, past the separator, toward the sample chamber 1202. The balance of the sample (e.g., blood cells and/or coarse solids) remains at the separator. In some embodiments, the separator may be constructed from microporous polyethylene or microporous polytetrafluoroethylene. In another embodiment, the separator may be constructed from BTS-SP media available from Pall Corporation of East Hills, NY.

[0262] As with the embodiment of Figures 23-24, the sample element 1200 may be placed against a patient's skin PS so that the barrier 1204 contacts the skin PS at a lancing site LS. With the sample element 1200 so positioned, a lance 1213 may be driven through the barrier 1204 and portion 1212, into the patient's skin PS. After the lance 1213 is withdrawn, blood and/or other fluids flow from the wound formed at the lancing site LS, through an opening formed in the barrier 1204 by the lance, and into the sample element. By maintaining moderate pressure on the sample element 1200/barrier 1204 against the lancing site LS (and/or employing an adhesive to affix the barrier 1204 temporarily to the patient's skin PS), substantially all of the blood/fluids that flow from the wound in the skin PS will flow through the barrier 1204 and into the sample element 1200. Thus, less of the blood/fluid is left at the lancing site, reducing waste and perceived pain.

[0263] The supply passage 1222, entry chamber 1230, and/or any other structures located between the sample chamber 1202 and the second side 1208 of the barrier 1204, may be considered a flow path extending from the sample chamber. In the depicted embodiment, the flow path is enclosed on all sides (except where the flow path joins the sample chamber 1202) until an opening is formed in the barrier 1204 and/or portion 1212.

[0264] As discussed above with respect to the sample element 1000 and the barrier 1004, the barrier 1204 and/or portion 1212 may be constructed to be more easily pierced by a lance than is the housing 1220, or are the portions of the housing adjacent the barrier 1204 or portion 1212, or are either of the layers of material employed to construct the housing 1220 (where a layered construction technique similar to that shown in Figure 7 is employed in making the sample element 1200, as may be done in various embodiments). More specifically, the barrier 1204 and/or portion 1212 may be constructed to be more easily pierced by a lance than are either of the windows 1202a, 1202b or are either of the sidewalls 1222a, 1222b of the supply passage 1222.

[0265] Figure 25 depicts a sample extractor 1100 which may be employed with a sample element such as those shown in Figures 23-24 or 24A-24B. The sample extractor has a sample element holder 1102 which is configured to hold the sample element 1000/1200, and an extractor drive 1104 which is depicted schematically and may comprise a spring-loaded lance drive, a laser, or other components suitable for the lancing technology employed in the sample extractor 1100. When loaded into the sample element holder 1102,

the sample element 1000/1200 is aligned with the extractor drive 1104 so that the sample extractor 1100 will pierce the barrier 1004/1204 when actuated.

[0266] Accordingly, the user can draw a sample in an easy, one-handed manner by pressing the barrier 1004/1204 of the loaded sample element 1000/1200 against a finger F (or any other suitable lancing site) before actuating the lance, thereby drawing a sample into the sample element 1000/1200 while exploiting the benefits of the barrier 1004/1204 as discussed herein. In the depicted embodiment, the sample element holder 1102 comprises clips 1106, 1108 with a slot 1110 therebetween to permit contact between the barrier 1004/1204 and the finger F (or other lancing site), as well as visual confirmation of the presence of a sample in the sample element 1000/1200. However, any suitable structure may be employed as the sample element holder 1102. In a further embodiment, the sample extractor 1100 may form an integral portion of (i.e., be built into) an analyte detection system such as the analyte detection system 10 described above.

[0267] In some embodiments, the extractor drive 1104 is adjustable to permit the user to select a lance driving force. Any suitable mechanism, of which many are presently known, may be employed to achieve this adjustability. An adjustable extractor drive permits the user to select an appropriate driving force to suit the thickness and material of the barrier 1004/1204 employed in the sample element (or otherwise), the desired penetration depth of the lance, and the type and/or quantity of bodily fluid sought when lancing.

[0268] Figure 26 depicts another embodiment of a sample extractor 1300 which may be employed with a sample element such as those shown in Figures 23-24 or 24A-24B, or any other suitable sample element. The sample extractor 1300 may be generally similar to the sample extractor 1100 except as further detailed below. The sample extractor 1300 generally comprises a reusable extractor drive 1304 and a disposable lance cartridge 1350, which is configured for removable attachment to the extractor drive 1304.

[0269] The lance cartridge 1350 includes a sample element holder 1302 which is configured to removably hold the sample element 1000/1200 so that a portion of the barrier 1004/1204 is exposed, via a slot 1310 or other suitable opening, for contact with a finger F, or other suitable lancing site on a patient. In the depicted embodiment, the sample element holder 1302 comprises clips 1306, 1308; however, any suitable structure may be employed to hold the sample element as needed.

[0270] The lance cartridge 1350 further comprises a lance guide 1320, inside of which a lance assembly 1322 is slidably disposed. The lance assembly 1322 includes a lance 1324, handle portion 1326, and guide flanges 1328. When the lance cartridge 1350 is assembled to the extractor drive 1304 (these items are shown in close proximity in Figure 26, but not in the assembled state), a lance actuator 1330 of the drive 1304 grips the handle portion 1326. Thus, movement of the lance actuator 1330 downward (i.e. along the line of action A-A toward the finger F), under the urging of a drive mechanism 1332, causes the lance assembly 1324 to move downward as well, driving the lance 1324 through the sample element 1000/1200 and the barrier 1004/1204, and into the finger F. Once the lance 1324 reaches the endpoint of its downward movement, the drive mechanism 1332 draws the actuator 1330 and lance assembly 1322 upward along the line of action A-A, toward the home position shown in Figure 26. Upon retraction of the lance 1324, blood and/or other fluids may flow from the wound formed in the finger F, through the barrier 1004/1204 and into the sample element 1000/1200 in the manner discussed above.

[0271] Once the sample of blood/fluids has flowed into the sample chamber 1002/1202, the user may withdraw the sample element 1000/1200 from the holder 1302 of the cartridge 1350 and load it into the analyte detection system for analysis of the sample in the usual manner. The remainder of the cartridge 1350, including the (now soiled) lance assembly 1322, may be removed from the extractor drive 1304 and discarded.

[0272] In the embodiment shown in Figure 26, the drive mechanism 1332 is depicted schematically as a spring system. It is contemplated that any drive mechanism suitable for use with a conventional sharp lance, such as the lance 1324, may be employed in the extractor drive 1304.

[0273] The depicted embodiment of the lance cartridge is configured for removable attachment to the extractor drive 1304 via interlockable lips or ridges 1360, 1362. However, any suitable attachment apparatus may be employed, e.g., threads, etc.

[0274] It is further contemplated that the extractor drive 1304 may be built-into an analyte detection system (e.g., any of the embodiments of the analyte detection system 10 disclosed herein, or any other suitable analyte detection system) so as to form an integral part thereof. Such an analyte detection system may be further configured to measure analyte concentration(s) within the sample drawn into the sample element 1000/1200 by, for example, advancing the sample element 1000/1200 from the lancing position shown in

Figure 26, to a measurement position in which the sample chamber(s) of the sample element are situated within an optical path defined by a source and detector of the analyte detection system (see, e.g., Figs. 1-2, 4). This may be done by advancing the sample element 1000/1200 longitudinally, generally orthogonal to the section plane employed in Figure 26, until the sample chamber is disposed across or within the optical path. The sample element 1000/1200 may be so advanced by powered rollers, manual pressure (e.g. on an exposed end of the sample element), or a combination of the two.

[0275] With such an “integrated” analyte detection system, a measurement may be taken by simply attaching the lance cartridge 1350 to the extractor drive 1304, placing the barrier 1004/1204 against the lancing site, actuating the lance 1324, holding the barrier against the lancing site until a sufficient sample has flowed into the sample element, and causing the sample element 1004/1204 to advance to the measurement position. Accordingly, handling of the sample element 1004/1204 is minimized, and any need to carry, handle and operate a separate lance, extractor drive, sample element, and detection system is eliminated.

B. Barrier

[0276] As used herein, “barrier” is a broad term and is used in its ordinary sense and refers, without limitation, to a membrane, sheet, layer, etc. which, when a first side thereof is placed against a lancing site on a patient’s skin, permits at least a portion of a bodily fluid sample emerging from the lancing site to pass from the first side to a second side opposite the first side while allowing substantially none of the sample to pass in the opposite direction, from the second side to the first side. These properties may arise from the configuration of the barrier itself, or the application of pressure upon the barrier against the lancing site, or a combination of the two.

[0277] In one embodiment, the barrier 1004/1204 (see Figures 22-24B) may comprise a nonporous polymer membrane which permits a sample fluid to flow into the sample element 1000/1200 through a hole formed in the membrane when the membrane and the patient’s skin are lanced. Alternatively, the barrier may comprise a membrane, such as a polymer membrane, in which a number of pores or capillaries are formed to permit a sample fluid to flow therethrough; the pores/capillaries may also serve to collect any residual blood from the lancing site. Medical plastics such as polyurethane, polyethylene, and the like may be employed to form barriers in accordance with these embodiments. In

still further embodiments, the barrier may be formed from a mesh (such as a finely woven nylon mesh), or a fibrous material (such as an absorbent fibrous fleece), or a semi-permeable membrane. The barrier may be a perforated or non-perforated plastic film dressing, a non-woven fabric made from hydrophobic fibers, a silicone-coated knitted fabric, or a porous polyamide net coated with silicone, such as MEPITEL(TM) available from Molnlycke Health Care AB of Goteborg, Sweden.

[0278] In one embodiment, the barrier 1004/1204 comprises a membrane, sheet, layer, etc. formed from sintered, porous PTFE (polytetrafluoroethylene) or PE (polyethylene); the first side 1006/1206 and/or second side 1008/1208 may also be treated to become hydrophilic. In various embodiments, the barrier may have a thickness of about 30-100 microns; however, any suitable thickness may be employed. In yet another embodiment, the barrier 1004/1204 comprises a membrane, sheet, layer, etc. formed from LATERAL-FLO(TM) available from Porex Corporation of Fairburn, Georgia; the first side 1006 and/or second side 1008 may also be treated to become hydrophilic. Further information on suitable barrier materials may be found in U.S. Patent No. 6,399,188, issued on June 4, 2002, titled SINTERED POROUS PLASTIC MATERIAL.

[0279] Alternatively, the barrier 1004/1204 may comprise a membrane, sheet, layer, etc. or other portion of a sample element, which membrane, sheet, layer, portion, etc. is pierceable by ordinary lancing equipment or sample extraction equipment when such lancing/sample-extraction equipment is used in an ordinary manner.

[0280] Regardless of the specific material employed, the barrier 1004/1204 may generally comprise a layer, sheet, membrane, etc. of hydrophobic material. Any of the various barriers discussed herein may also include a clotting agent on the second side thereof. Any of the various barriers discussed herein may also include an antibacterial or antimicrobial coating on either side thereof, and/or be (at least partially) formed from an antibacterial or antimicrobial material.

[0281] In other embodiments, the barrier 1004/1204 may comprise a surgical drape, particularly an incise drape, or a portion of surgical-drape or incise-drape material, employed with or without an adhesive layer for affixing the barrier to the lancing site LS. Such drapes may comprise, for example, a polyurethane film. In one embodiment, the barrier 1004/1204 comprises a sterile surgical drape.

[0282] Figures 27-28 depict the function of the barrier 1004/1204 in greater detail. Although only the barrier itself is depicted, Figures 27-28 illustrate the function of the barrier in the various uses contemplated herein: as a part of a sample element (e.g., as in Figs. 22-24, 24A-24B), or as a “stand-alone” material applied or affixed to the lancing site and/or sample element before lancing. In Figures 27-28, the barrier 1004/1204 has been affixed to the patient’s skin PS with an adhesive 1400; however, the adhesive 1400 may be omitted in various other implementations of the barrier 1004/1204.

[0283] Upon lancing through the barrier 1004/1204 (and any adhesive) and into the patient’s skin PS, an opening 1410 is formed in the barrier 1004/1204 and a wound W is formed in the skin PS. Bodily fluid F, such as whole blood, interstitial fluid, intercellular fluid or mixtures thereof, flows from the wound W, through the opening 1410 in the barrier 1004/1204, and collects at the second side 1008/1208 of the barrier. Where the barrier 1004/1204 is part of a sample element, the collected fluid F will flow towards the sample chamber(s). Where the barrier 1004/1204 comprises a “stand-alone” material applied to the skin before lancing, a sample element may be placed in contact with the collected fluid F to cause the fluid F to flow into the sample element in the usual manner.

[0284] Various measures are contemplated for creating a tight seal or firm, intimate contact between the barrier 1004/1204 and the skin PS around the wound W. Such a tight seal or firm contact encourages the fluid F to flow from the wound W through the opening 1410, rather than laterally between the skin PS and the first side 1006/1206 of the barrier 1004/1204. In various embodiments, any one or combination of the following measures may be employed: (1) an adhesive on the first side of the barrier (as shown in Figs. 27-28); (2) urging, with moderate pressure, the barrier against the lancing site and/or the lancing site against the barrier; and (3) applying a lateral tension (i.e. along the plane of the barrier) to the barrier, or otherwise maintaining the barrier taut, during use.

[0285] Where an adhesive is employed (see, e.g., Figures 27-28), a layer of suitable adhesive may overlie the entire first surface 1006/1206 of the barrier 1004/1204, or only those portions of the first surface where lance-through is expected. An adhesive may be employed with any of the barriers disclosed herein, whether the barrier forms a part of a sample element or is employed as a stand-alone material applied to the lancing site prior to lancing. A removable, “peel-off” backing may be used to cover the adhesive until the barrier or sample element is to be used.

[0286] Where the barrier 1004/1204 comprises a stand-alone material applied to the lancing site prior to lancing, the barrier 1004/1204 may be urged against the lancing site LS (and/or the lancing site urged against the barrier) by holding a section of the barrier material by its edges and pressing it against the lancing site such that the barrier material conforms closely to the skin near the lancing site. Such close conformance is illustrated in use with a relatively flat lancing site (Figure 27) and a curved lancing site (Figure 28). Where the barrier 1004/1204 forms part of a sample element, the sample element itself may be grasped in a manner that allows the barrier to be pressed against the lancing site to ensure intimate contact between the two. With moderate pressure, the barrier may deflect slightly inward, into the sample element housing, and conform closely to any curvature of the lancing site (see Figure 28).

[0287] Tension may be applied to a stand-alone barrier by manually stretching the barrier before or while applying it against the lancing site or sample element. Alternatively, a stand-alone barrier may be slightly stretched and mounted on a generally rigid hoop or perimeter frame having an opening therein for lancing through the barrier after it has been placed against the skin. A barrier that forms part of a sample element may also be placed under tension by slightly stretching it before mounting it to the sample element, and mounting it in the tensioned state.

[0288] When implemented as shown in Figures 27-28, the barrier 1004 advantageously shields the wound W and the fluid F from contaminants located on the surface of the patient's skin PS around the lancing site LS. Various embodiments of the barrier disclosed herein achieve this functional advantage; however, the surgical drape embodiment (especially a sterile surgical drape) is particularly suited for achieving this advantage.

[0289] In various embodiments, the barrier 1004/1204 may have a hemostatic coating on its first side 1006/1206 to minimize after-bleed at the lancing site. A conformal adhesive may alternatively be employed on the first side 1006/1206 to adhere the barrier to the lancing site while the sample is being drawn; a removable seal or cover may be employed over the adhesive until the sample element 1000/1200 is ready for use. In certain embodiments, the barrier 1004/1204 is adhesively attached or otherwise bonded to the sample element 1000/1200. Alternatively, the barrier 1004/1204 may be a separate element

which may be attached to the sample element 1000/1200 by the user or placed at the lancing site without attachment to the sample element 1000/1200.

[0290] Where the barrier 1004/1204 is implemented as a “stand-alone” material applied or affixed to the lancing site before lancing, the bodily fluid that collects on the second side of the barrier after lancing may be taken into a sample element by placing the sample element in fluid communication with the collected fluid. This may be done by, for example, placing an appropriate portion of the sample element in contact with the collected fluid. The fluid then flows into the sample element until the sample chamber is full. In various embodiments, either all or only a portion of the collected fluid is taken into the sample element. Where only a portion is taken, the remaining collected fluid (still present on the second side of the barrier) may be easily removed from the lancing site by removing the barrier itself.

[0291] Although this invention has been disclosed in the context of certain preferred embodiments and examples, it will be understood by those skilled in the art that the present invention extends beyond the specifically disclosed embodiments to other alternative embodiments and/or uses of the invention and obvious modifications and equivalents thereof. Thus, it is intended that the scope of the present invention herein disclosed should not be limited by the particular embodiments described above, but should be determined only by a fair reading of the claims that follow.

WHAT IS CLAIMED IS:

1. A sample element for holding a volume of bodily fluid drawn from the skin of a patient at a withdrawal site, said sample element comprising:
a housing defining a sample chamber therein; and
a barrier having a first side configured to contact the skin of the patient at said withdrawal site, and a second side in fluid communication with said sample chamber, said barrier being configured to be pierced by a lance, to permit said bodily fluid to pass from said first side to said second side.
2. The sample element of Claim 1, wherein said barrier is formed from a substantially nonporous material.
3. The sample element of Claim 2, wherein said barrier, in the absence of an opening pierced therein, is configured to permit substantially none of said bodily fluid to pass from said first side to said second side.
4. The sample element of Claim 1, wherein said barrier, when placed against the skin of a patient and pierced, is configured to permit substantially none of said bodily fluid to pass from said second side to said first side.
5. The sample element of Claim 1, further comprising an adhesive disposed on said first side of said barrier.
6. The sample element of Claim 1, wherein said sample chamber is reagentless.
7. The sample element of Claim 1, wherein said sample chamber is at least partially defined by a window.
8. The sample element of Claim 7, wherein said window is transmissive of infrared radiation.
9. The sample element of Claim 7, wherein said barrier is more easily pierced by a lance than is said window.

10. The sample element of Claim 1, wherein said barrier is more easily pierced by a lance than is an adjacent portion of said housing.

11. The sample element of Claim 1, further comprising a supply passage extending from said sample chamber, said supply passage having a first sidewall adjacent said barrier, said barrier being more easily pierced by a lance than is said first sidewall.

12. The sample element of Claim 1, further comprising a separator located between said second side of said barrier and said sample chamber.

13. A sample element for holding a volume of bodily fluid, said sample element comprising:

- a housing having a sample chamber therein, and a flow path extending from said sample chamber; and

- a barrier disposed across said flow path, said barrier having a first side configured to contact the skin of a patient at a lancing site;

- said flow path being enclosed on all sides except where said flow path joins said sample chamber such that, upon formation of an opening in said barrier, fluid may flow from said first side, through said flow path and into said sample chamber.

14. The sample element of Claim 13, wherein said barrier has a second side in fluid communication with said sample chamber.

15. The sample element of Claim 13, wherein said barrier is pierceable to permit bodily fluid to pass through said barrier.

16. The sample element of Claim 13, wherein said sample chamber is reagentless.

17. The sample element of Claim 13, wherein said sample chamber is at least partially defined by a window.

18. The sample element of Claim 17, wherein said window is transmissive of infrared radiation.

19. The sample element of Claim 17, wherein said barrier is more easily pierced by a lance than is said window.

20. The sample element of Claim 13, wherein said barrier is more easily pierced by a lance than is an adjacent portion of said housing.

21. The sample element of Claim 13, further comprising a supply passage extending from said sample chamber, said supply passage having a first sidewall adjacent said barrier, said barrier being more easily pierced by a lance than is said first sidewall.

22. The sample element of Claim 13, wherein said flow path comprises a supply passage.

23. The sample element of Claim 22, wherein said flow path comprises a supply passage and an entry chamber in fluid communication with said supply passage.

24. The sample element of Claim 13, further comprising a separator located in said flow path.

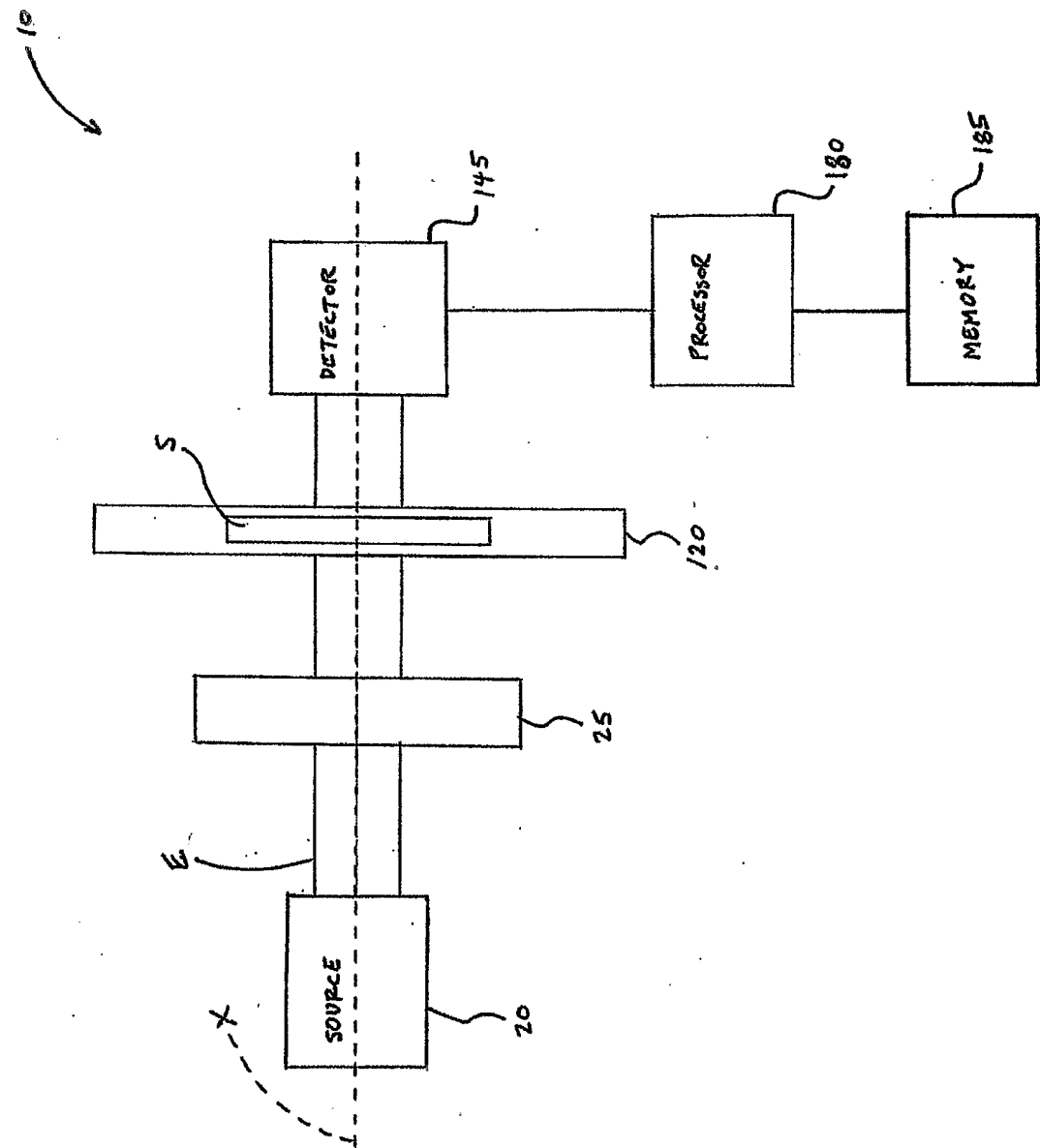
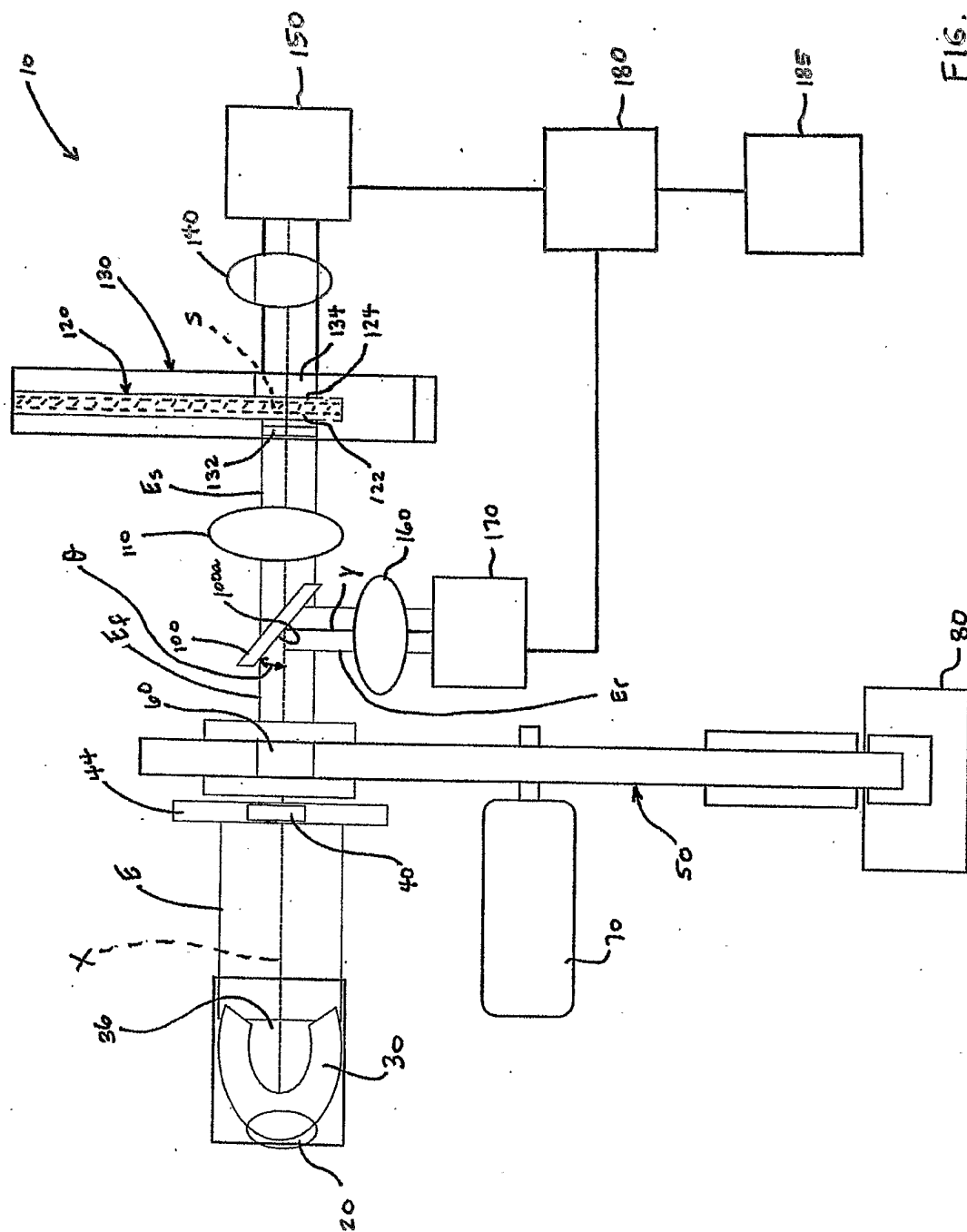


Fig. 4



25E

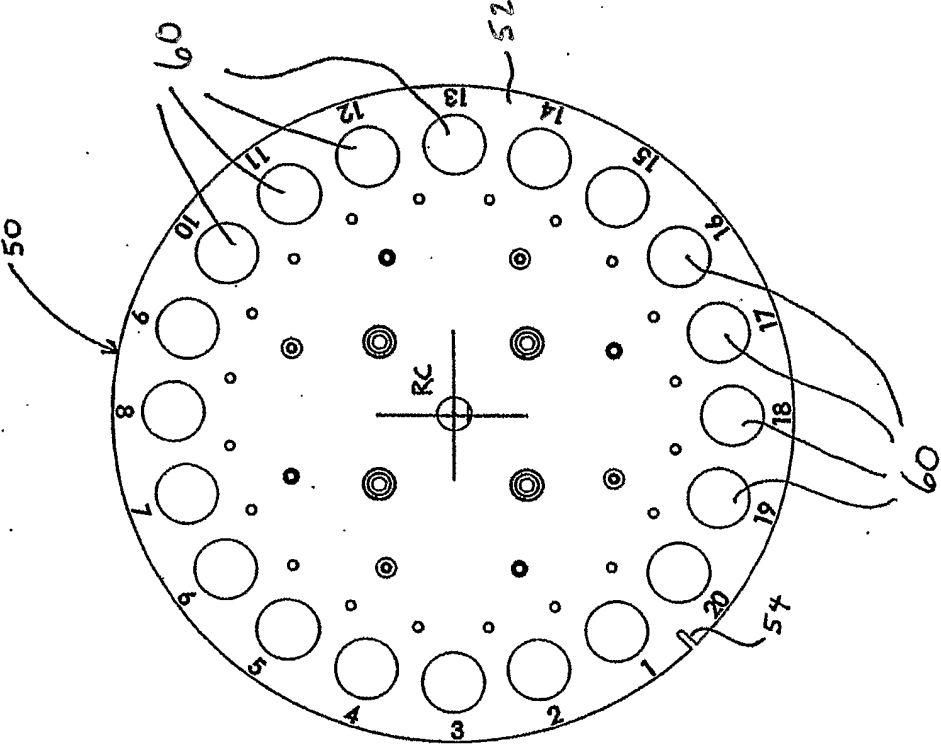


FIG. 3

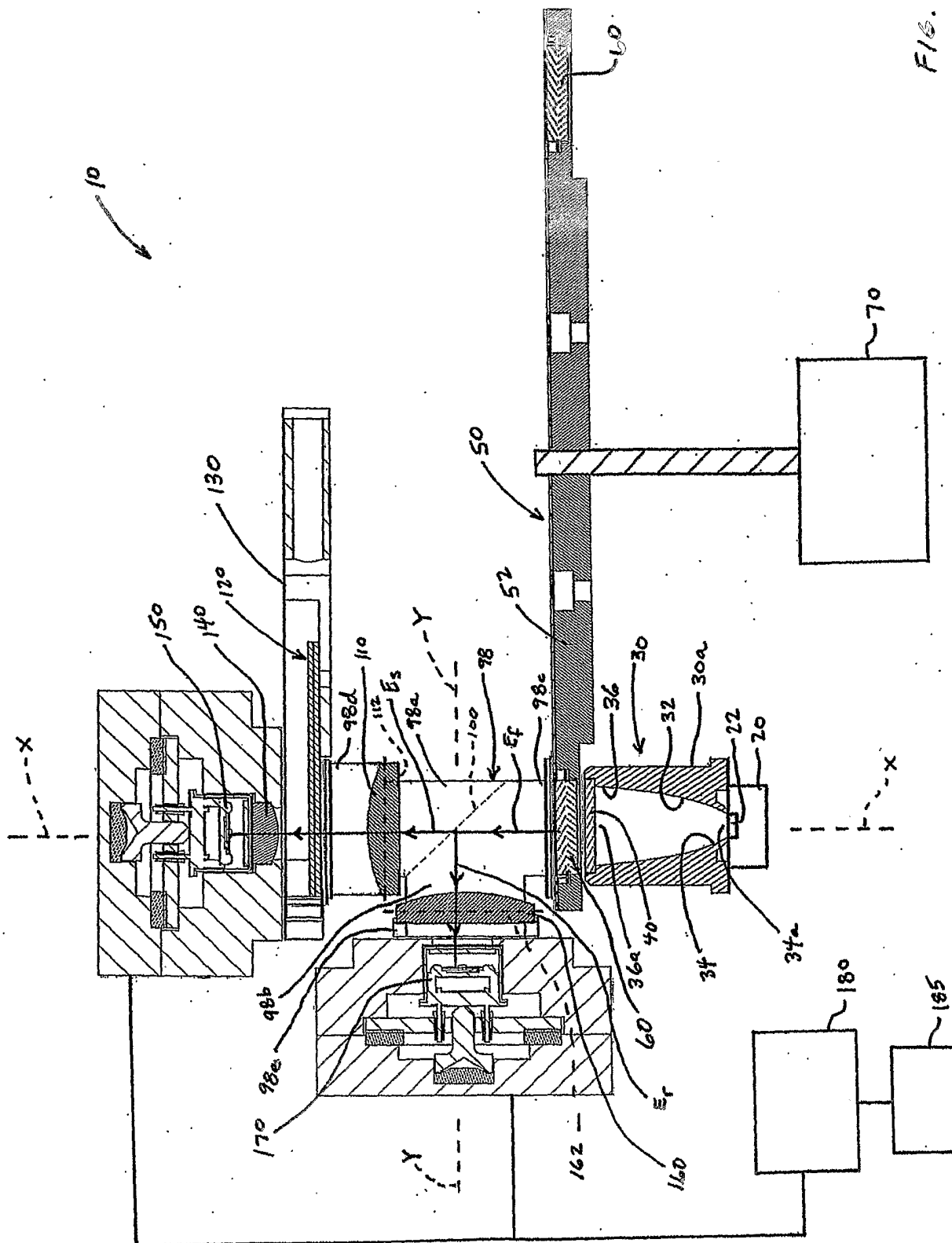
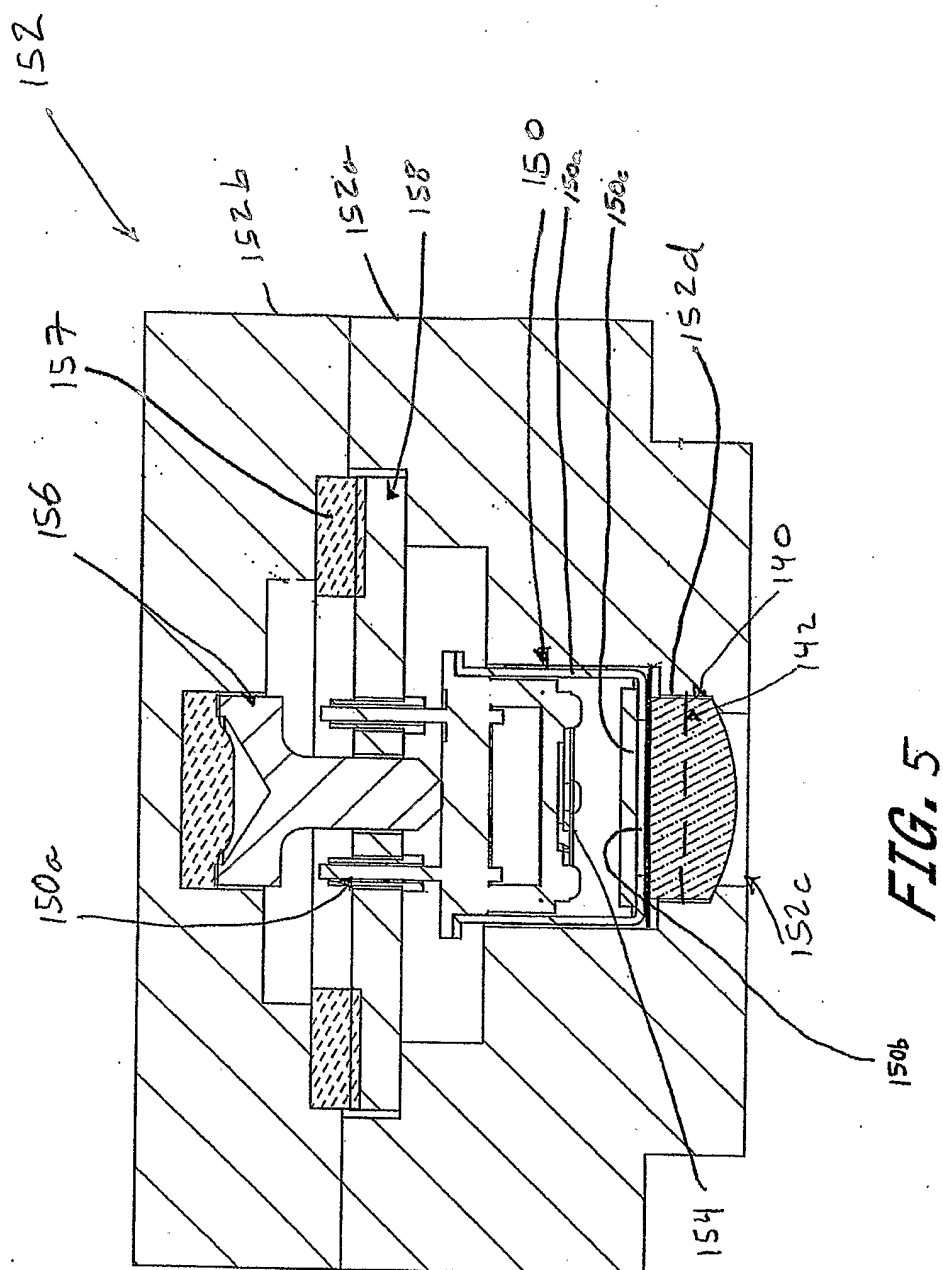


Fig. 4



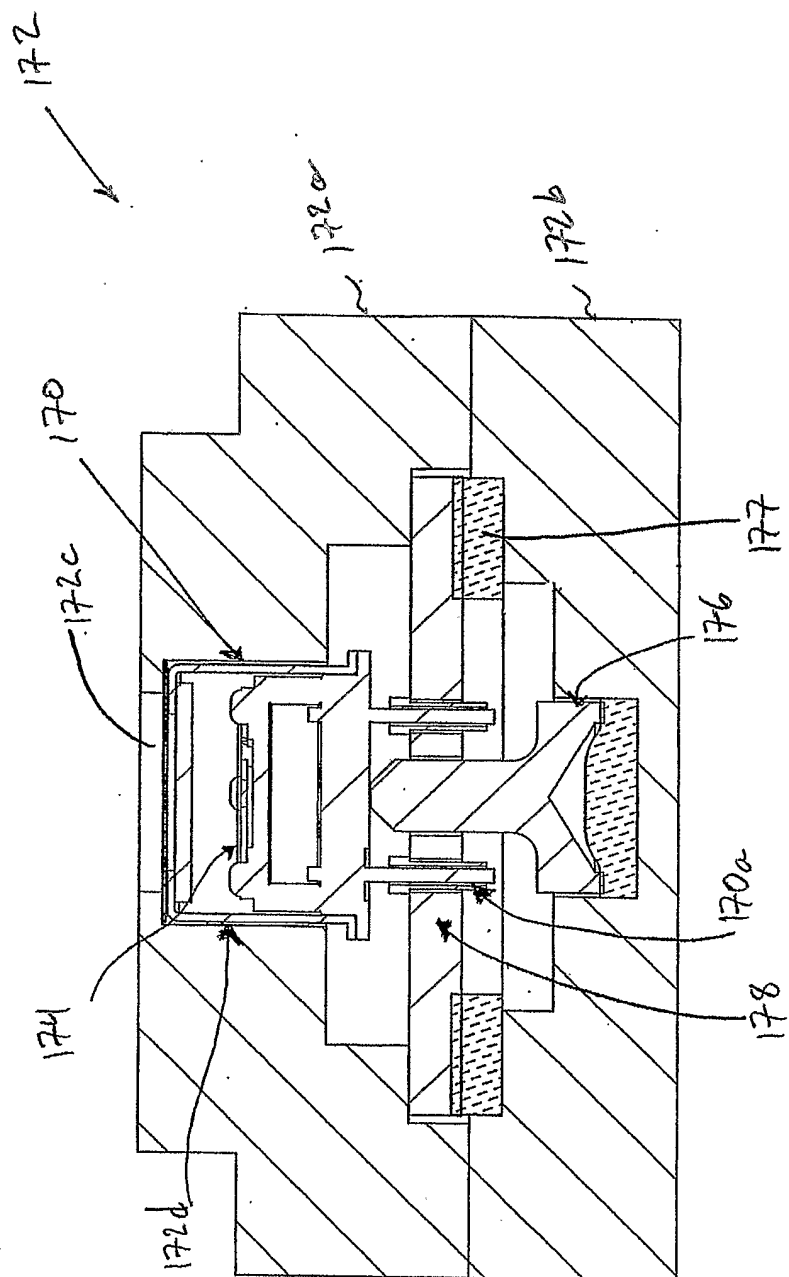


FIG. 6

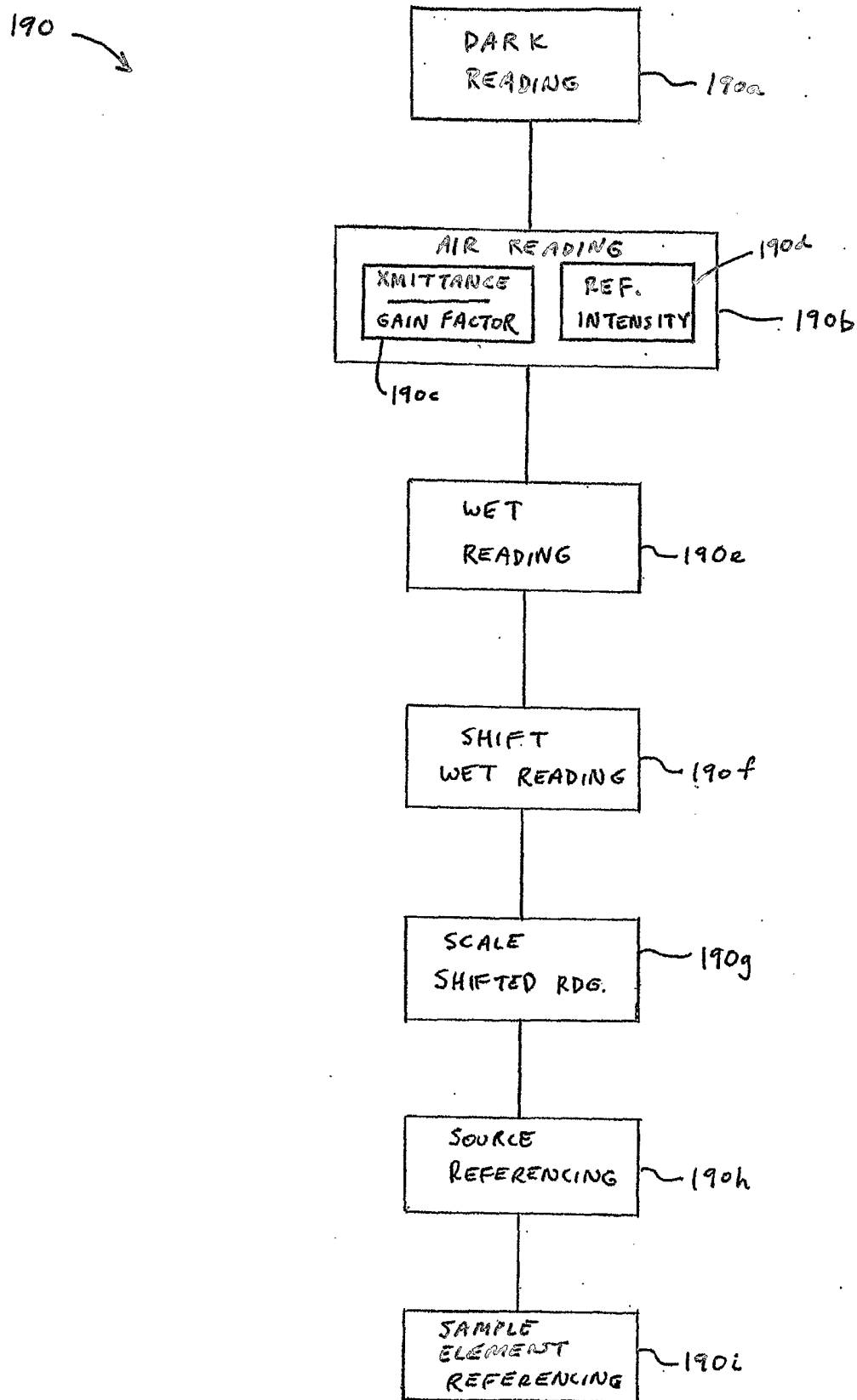


FIG. 7

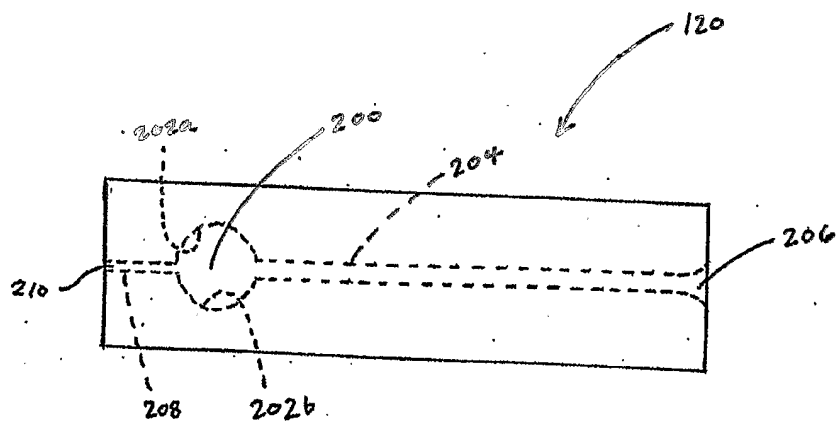


FIG. 8

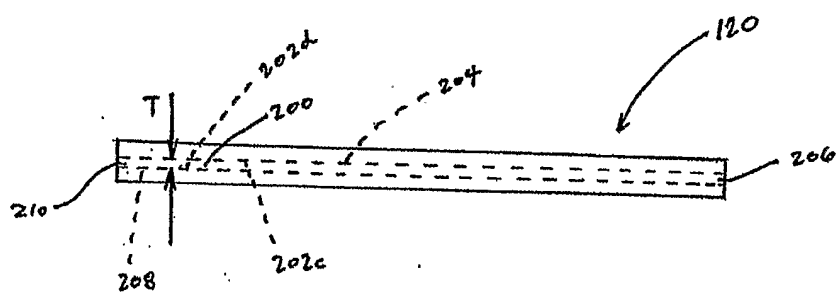


FIG. 9

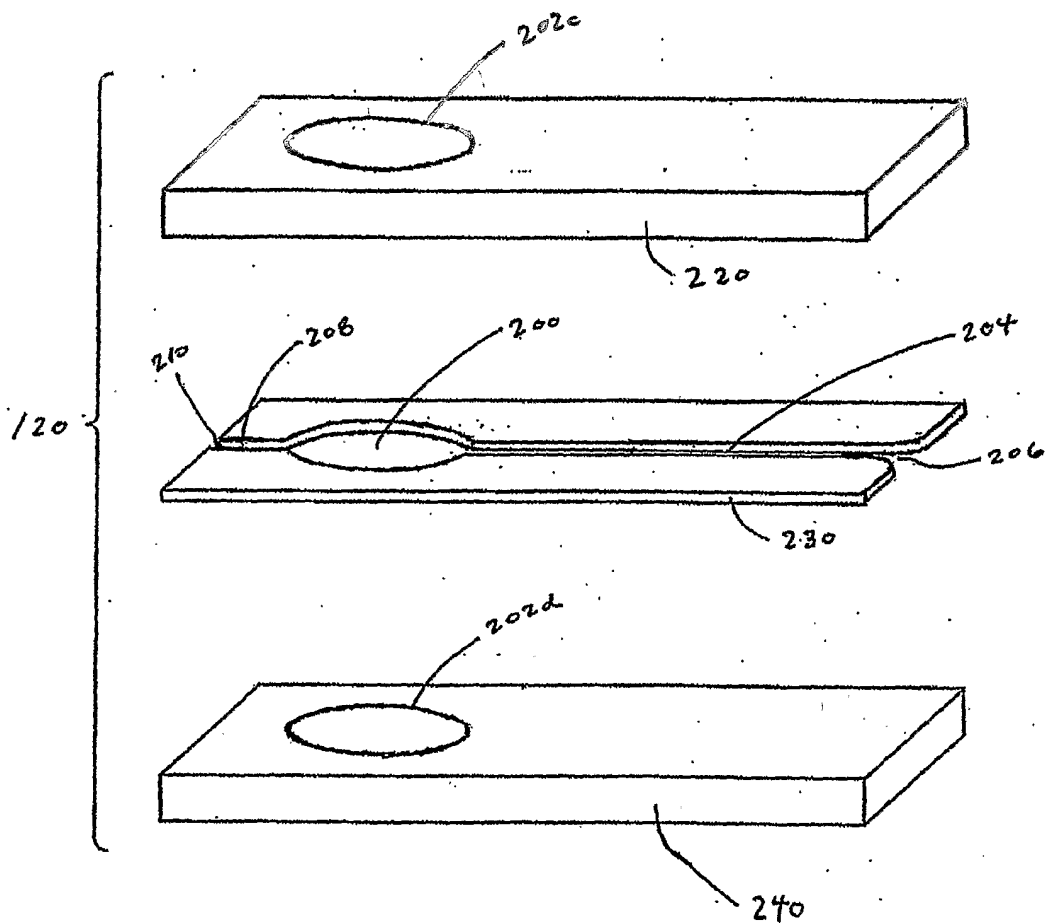


FIG. 10

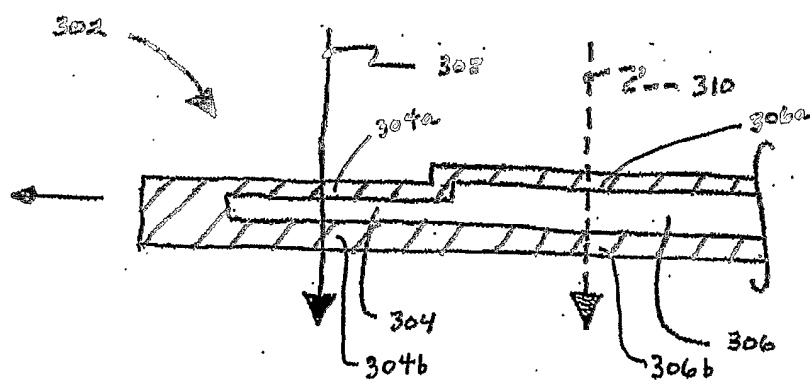


Figure 11

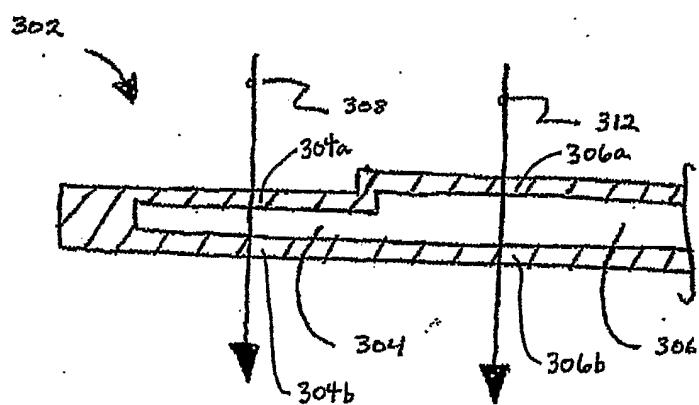


Figure 12

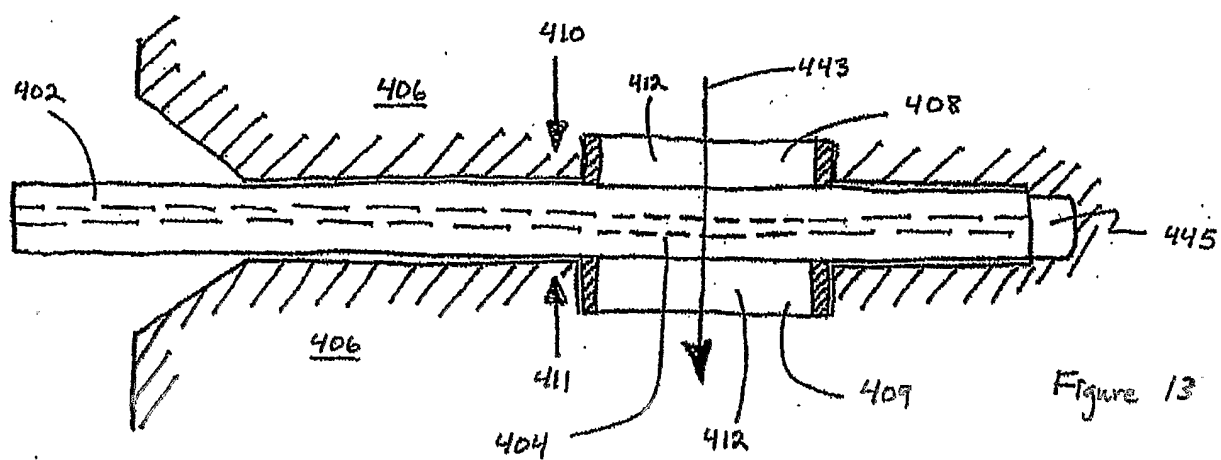


Figure 13

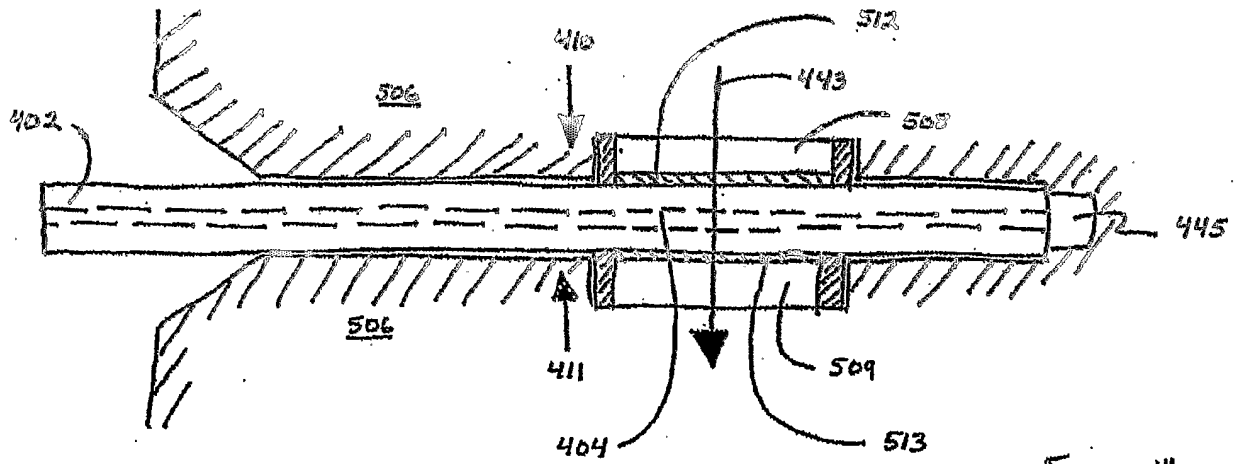


Figure 14

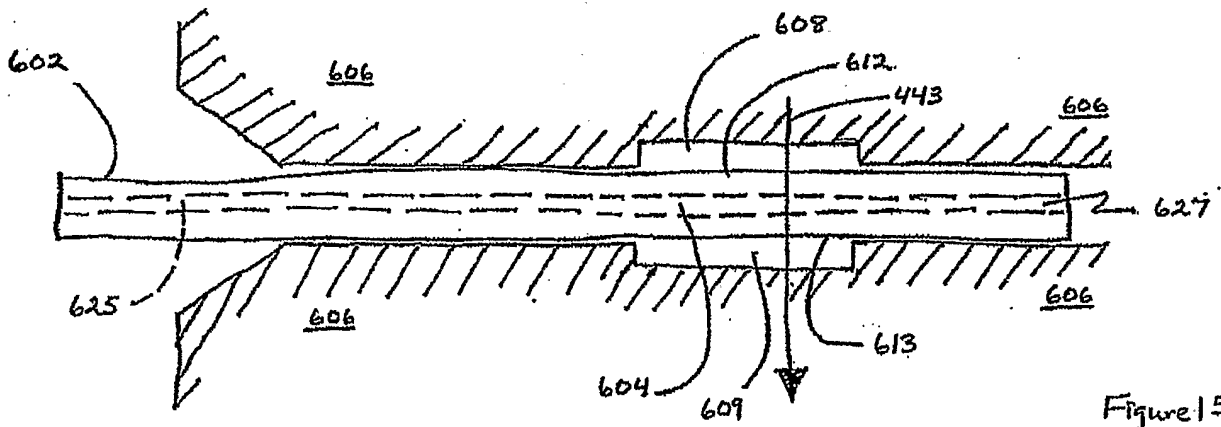


Figure 15

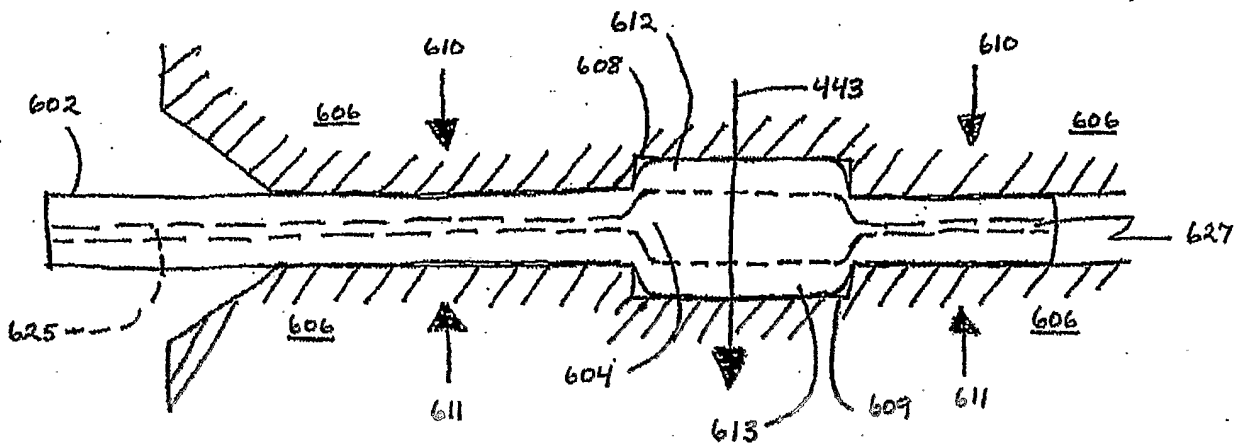
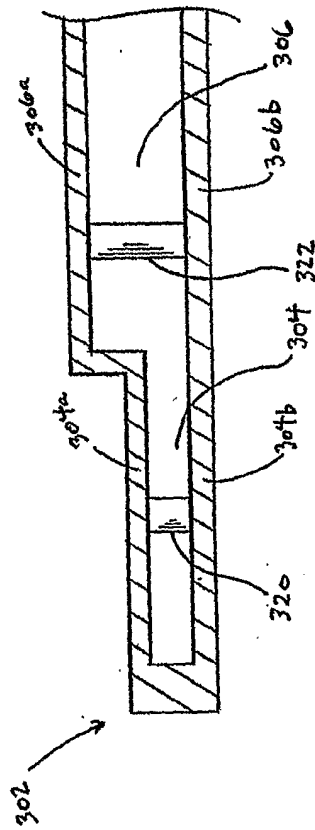
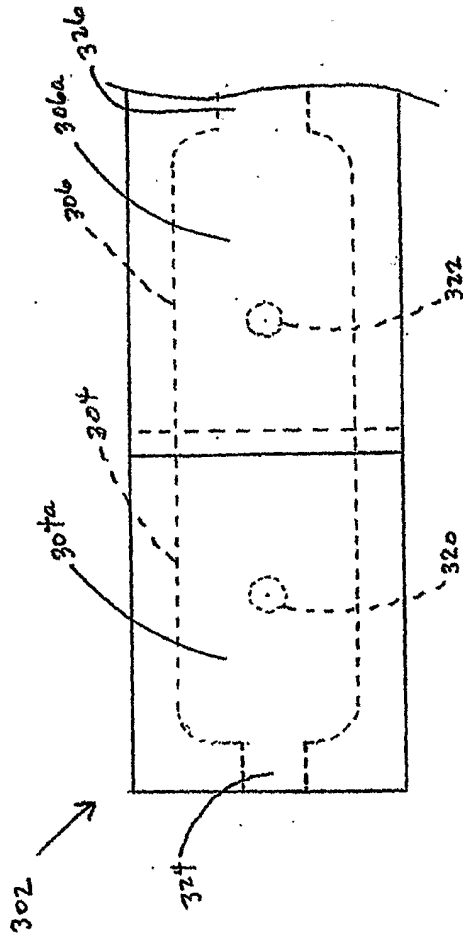
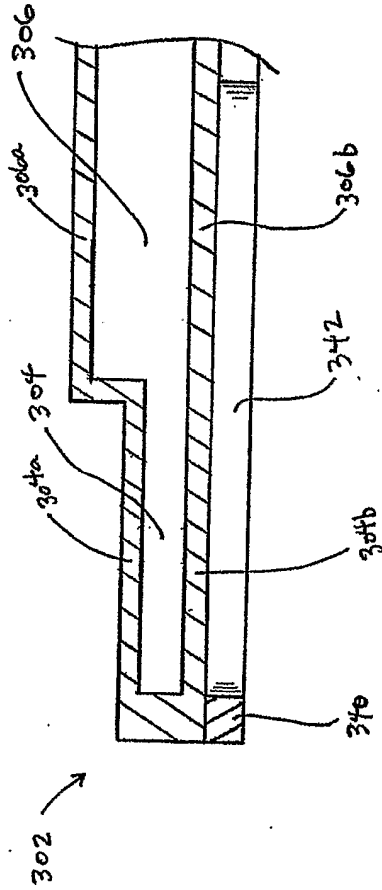
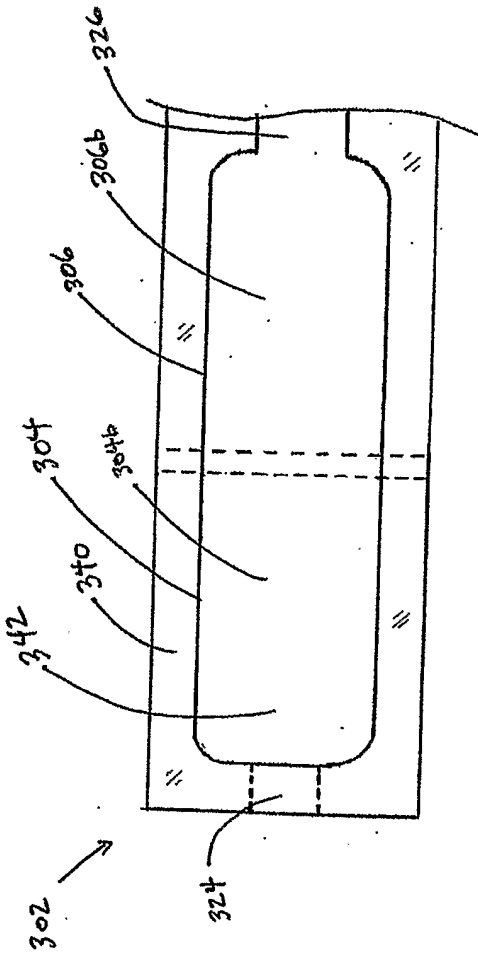


Figure 16





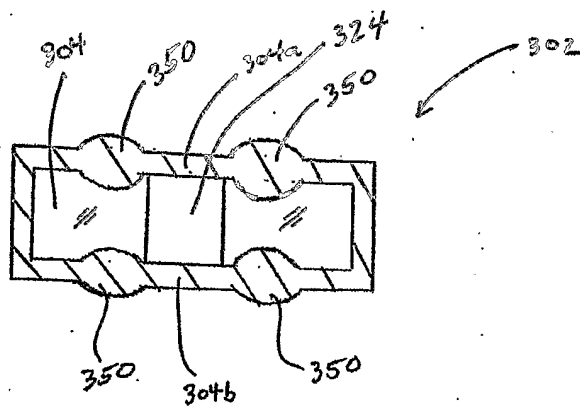


FIG. 21

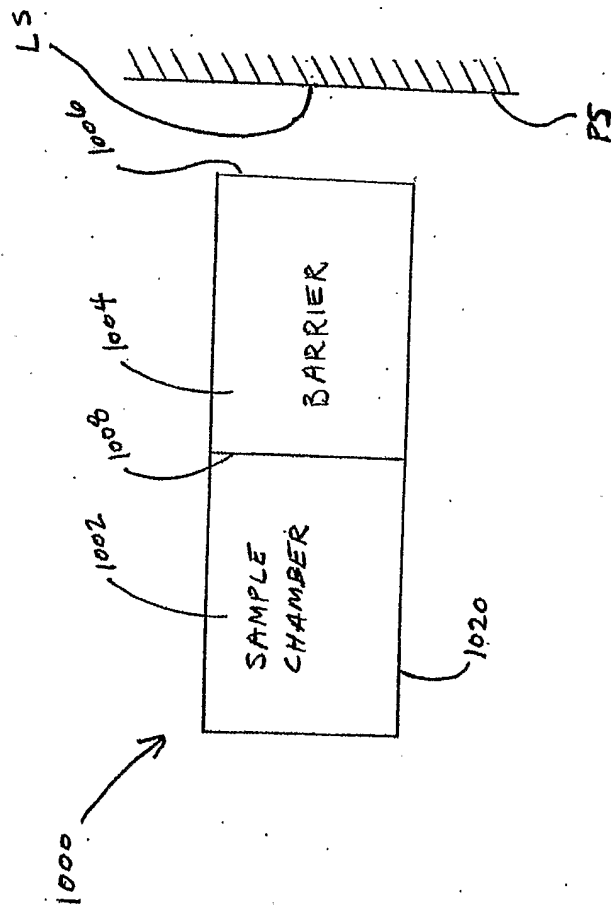


FIG. 22

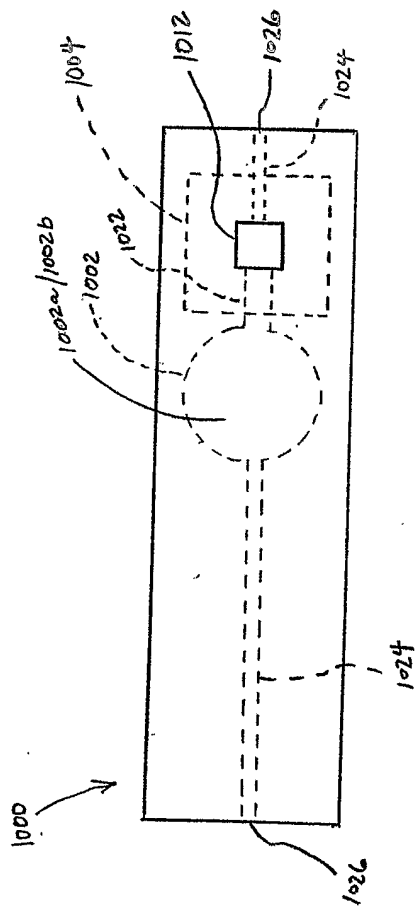


FIG. 23

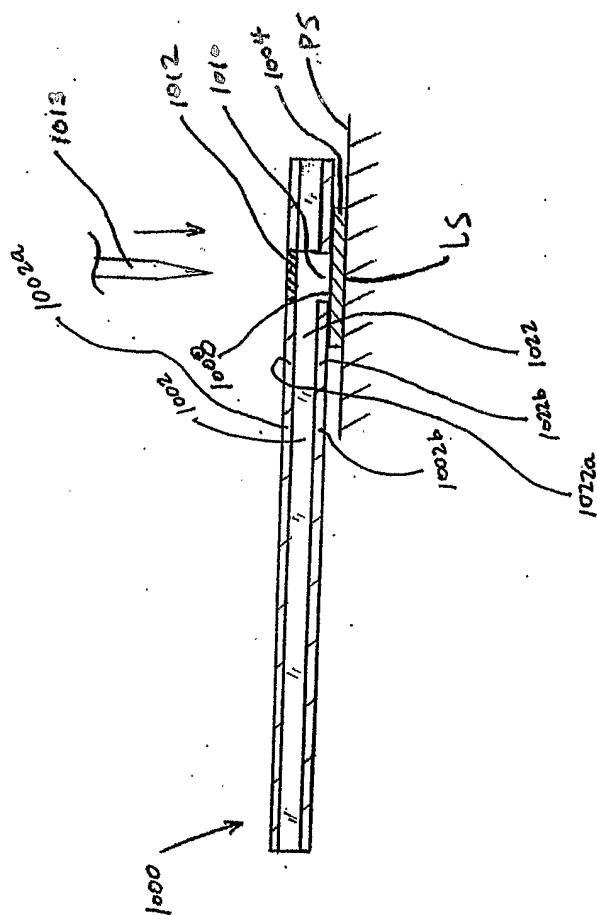


Fig. 24

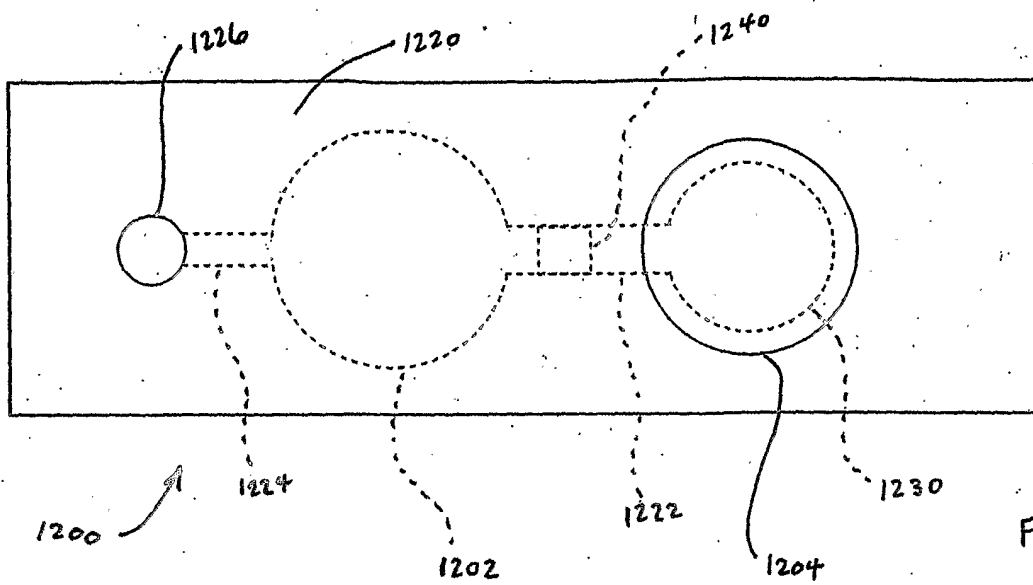


FIG. 24A

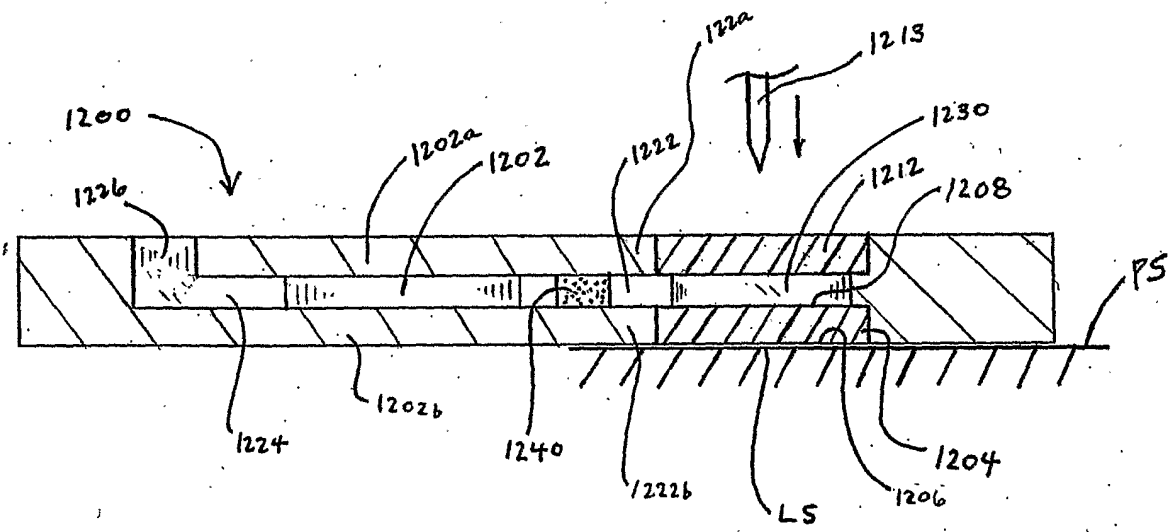


FIG. 24B

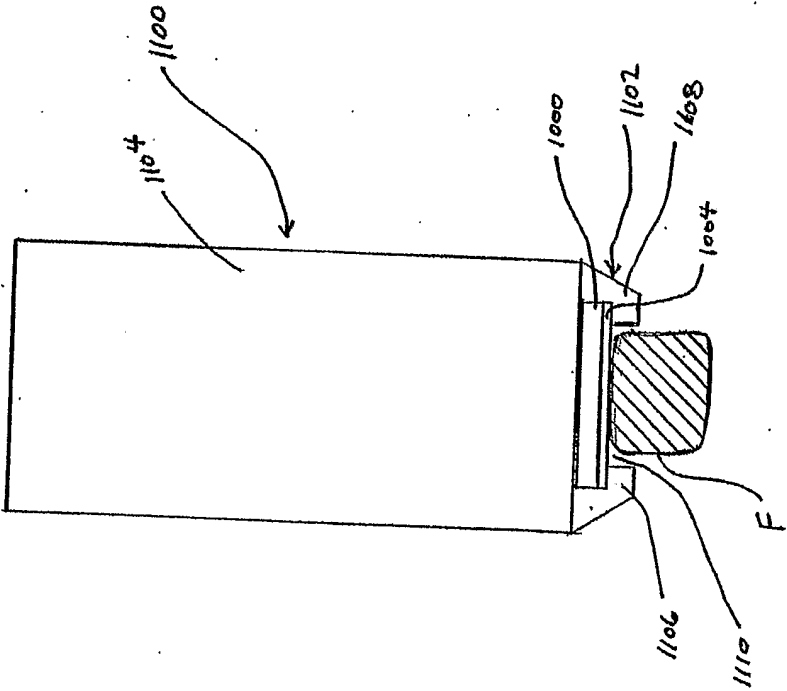
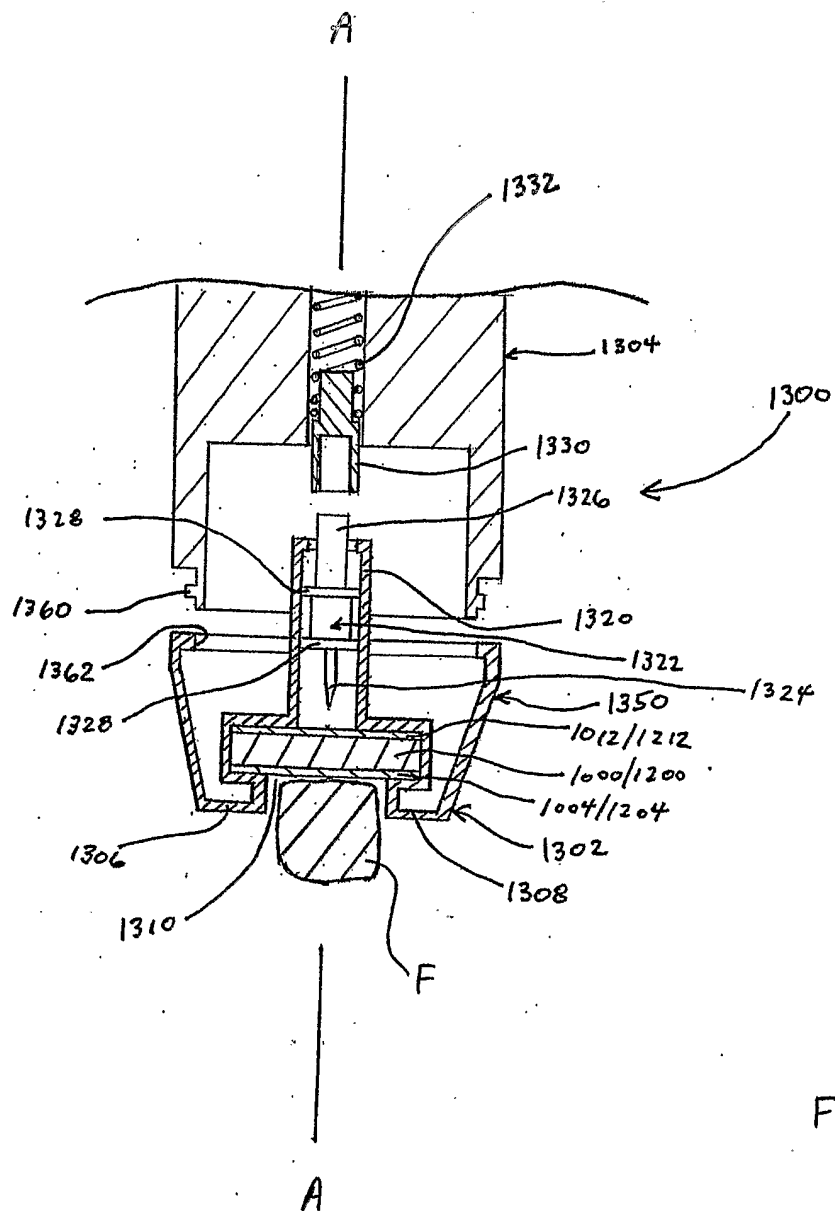
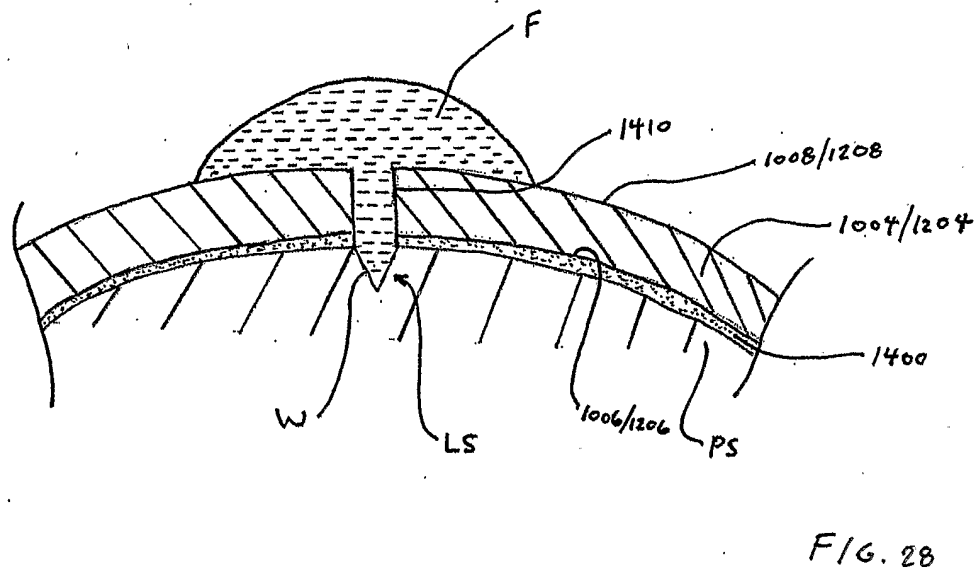
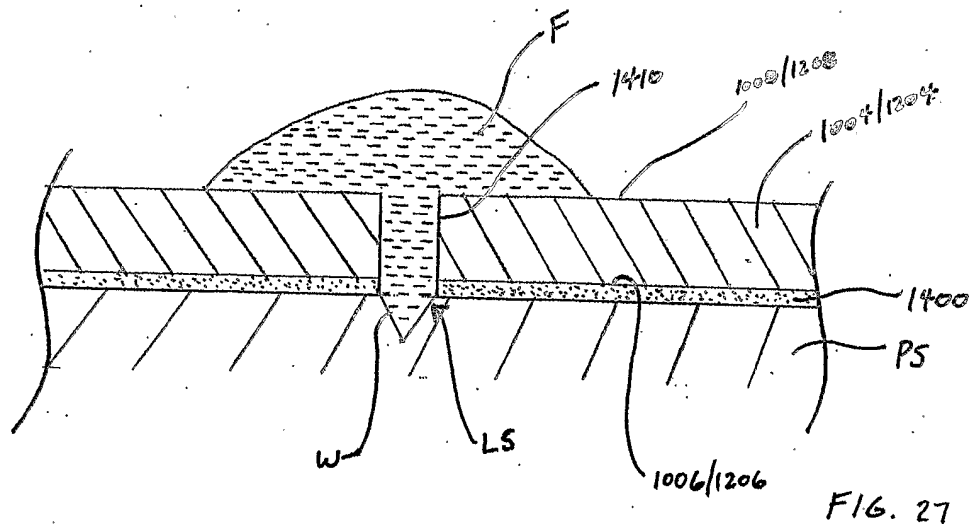


Fig. 25





INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US2004/011430

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61B5/15 B01L3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61B B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 636 640 A (STAEHLIN JOHN H) 10 June 1997 (1997-06-10) column 1, lines 55-60 column 3, lines 21-65 column 4, line 60 - column 5, line 40 column 6, line 45 - column 7, line 20; figures 1,2,6a,9,11	1-24
X	US 2002/099308 A1 (EPPSTEIN JONATHAN A ET AL) 25 July 2002 (2002-07-25) paragraphs '0038! - '0040!, '0046!, '0047!, '0058! - '0060!, '0066!, '0067!; figures 1,3	1-5,10, 11, 13-15, 20-23
X	US 4 787 398 A (GARCIA FERNANDO S ET AL) 29 November 1988 (1988-11-29) column 7, lines 10-56; figure 3	1,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

19 August 2004

Date of mailing of the international search report

30/08/2004

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Pohjamo, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/011430

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