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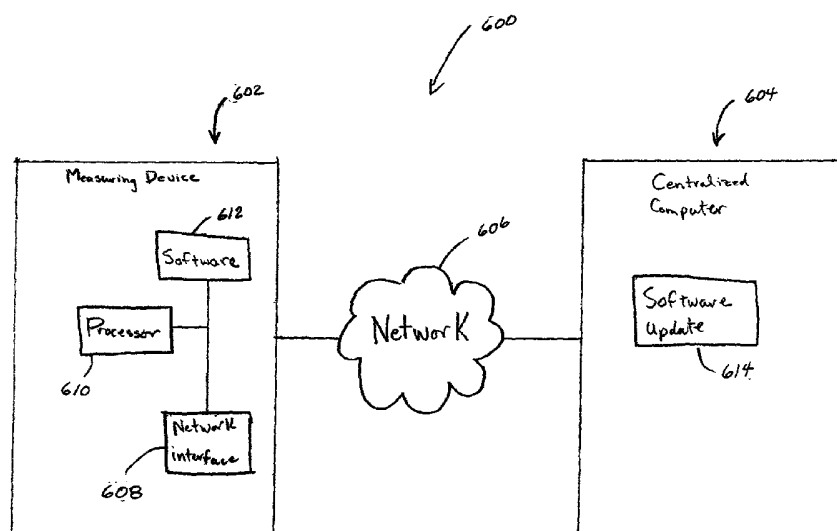
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(54) Title: ANALYTE DETECTION SYSTEM WITH SOFTWARE DOWNLOAD CAPABILITIES



(57) Abstract: An analyte concentration monitoring system having network-based communication features (600) which provide a link between an analyte detection system (602) and a centralized computer (604). The analyte detection system has a processor (610) that calculates analyte concentration in accordance with software (612) executable by the processor. Under certain conditions, the software (612) needs to be updated. Accordingly, when the analyte detection system is connected to the centralized computer, the centralized computer determines whether a software update (614) is needed. If a software update is needed, then the centralized computer conveniently provides the software update to the analyte detection system without intervention from a user.



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ANALYTE DETECTION SYSTEM WITH SOFTWARE DOWNLOAD CAPABILITIES

Background of the Invention

5 Field of the Invention

This invention pertains, in certain embodiments, to medical equipment for measuring blood analyte levels, and more particularly to a blood analyte measuring instrument having internet-based communication features.

Description of the Related Art

10 A patient, having been taught how to use an existing portable analyte monitor is generally required thereafter to independently conduct and record his or her own measurements. Furthermore, the patient typically is required to both record and assess the measurements without benefit from a practitioner or supervising authority. Numerous errors can arise from these unsupervised procedures that may result in serious health risks
15 for patients which knowingly, or inadvertently, are not in compliance with medical directives.

Typically, patients using an analyte monitor are given a schedule of measurements they are required to take and a notebook in which to record the measurements. Patients often forget, or in some instances forego, conducting and correctly recording their analyte
20 levels as measured by the instrument. If patients skip a measurement they may even elect to write down a "likely" number in the notebook as if such a measurement had been taken. Patient interaction with such a manual analyte monitoring instrument therefore provides no assurance of correct measurement and recordation. Furthermore, patients in a myriad of situations may require additional information and assistance with regard to the use and
25 maintenance of their analyte measurement instrument.

In addition, to assure analyte measurement accuracy, a measuring instrument may require periodic calibration or software updates. Assuring calibration compliance on instruments or updating the instrument's software in the field is burdensome.

30

Summary of the Invention

Therefore, a need exists for an analyte monitoring system that encourages patient compliance and facilitates equipment calibration and software updates. The present

invention, in certain embodiments, satisfies those needs, as well as others, and overcomes deficiencies in current monitoring systems and procedures.

The present invention, in certain embodiments, is an analyte measuring device with remote communications capabilities. According to an aspect of the invention, a data link is provided between the equipment and a centralized station, or server. The centralized station can monitor important information, such as: equipment calibration, the diligence of a patient taking and recording measurements according to a schedule, whether a software update is needed and the actual measurements taken by the patient. The centralized station is preferably capable of forwarding information to the patient's physician for evaluation. In addition, the centralized station can have optional capability of locking out the patient if the patient has not paid his or her bills. According to another aspect of the invention, the information is communicated from the analyte measuring device directly to the physician. Accordingly to another aspect, the centralized station can determine an update status of the analyte measuring device's software and automatically send a software update to the analyte measuring device. As can be seen, therefore, the preferred embodiments link the monitoring activities performed by the patient and the assessment of those activities by the physician while reducing the chance of human error introduced into the long-term monitoring and treatment process.

By way of example, and not of limitation, a non-invasive subsurface spectrophotometer instrument equipped with a communications link according to the invention takes the analyte measurements and communicates them over a network, such as the internet. The spectrophotometer instrument comprises data communication circuitry, such as dial-up circuitry, and additional session control protocols which integrate a number of the functions within the instrument for communication over a network connection. A destination site, or sites, on the network are configured to receive information from the instrument and to transmit information and services.

In accordance with yet another embodiment, an analyte concentration monitoring system comprises an analyte detection system having a processor that calculates analyte concentration in accordance with software executable by the processor. The monitoring system further comprises a network interface that is configured to provide connectivity to a computer. The analyte detection system is configured to receive an update to the software from the computer.

In accordance with yet another embodiment, a method of automatically updating software on an analyte detection system, comprises connecting an analyte detection system to a computer via a network, and checking, in the computer, an update status of software included in the analyte detection system. The method further comprises sending, when the
5 update status indicates that a software update is needed, the software update to the analyte detection system via the network without intervention from a user. The method further comprises updating, in the analyte detection system, the software with the software update.

In accordance with yet another embodiment, an analyte concentration monitoring system comprises an analyte detection system comprising a processor, a software, and a
10 network interface. The processor is configured to calculate analyte concentration in accordance to the software, and the network interface is configured to provide connectivity to a computer. The analyte detection system is configured to update the software according to instructions from the computer.

In accordance with yet another embodiment, a method of automatically updating
15 software on an analyte detection system comprises connecting an analyte detection system to a computer via a network. The method further comprises checking, in the computer, an update status of software included in the analyte detection system. The method further comprises encrypting, when the update status indicates that a software update is needed, the software update and sending the software update to the analyte detection system via the
20 network. The method further comprises updating, in the analyte detection system, the software with the software update.

Brief Description of the Drawings

FIGURE 1 is a schematic view of a noninvasive optical detection system.

FIGURE 2 is a perspective view of a window assembly for use with the noninvasive
25 detection system.

FIGURE 2A is a plan view of another embodiment of a window assembly for use with the noninvasive detection system.

FIGURE 3 is an exploded schematic view of another embodiment of a window assembly for use with the noninvasive detection system.

30 FIGURE 4 is a plan view of the window assembly connected to a cooling system.

FIGURE 5 is a plan view of the window assembly connected to a cold-reservoir.

FIGURE 6 is a cutaway view of a heat sink for use with the noninvasive detection system.

FIGURE 6A is a cutaway perspective view of a lower portion of the noninvasive detection system of FIGURE 1.

5 FIGURE 6B is an exploded perspective view of a window mounting system for use with the noninvasive optical detection system.

FIGURE 6C is a partial plan view of the window mounting system of FIGURE 6B.

FIGURE 6D is a sectional view of the window mounting system of FIGURE 6C.

10 FIGURE 7 is a schematic view of a control system for use with the noninvasive optical detection system.

FIGURE 8 depicts a first methodology for determining the concentration of an analyte of interest.

FIGURE 9 depicts a second methodology for determining the concentration of an analyte of interest.

15 FIGURE 10 depicts a third methodology for determining the concentration of an analyte of interest.

FIGURE 11 depicts a fourth methodology for determining the concentration of an analyte of interest.

20 FIGURE 12 depicts a fifth methodology for determining the concentration of an analyte of interest.

FIGURE 13 is a schematic view of a reagentless whole-blood detection system.

FIGURE 14 is a perspective view of one embodiment of a cuvette for use with the reagentless whole-blood detection system.

25 FIGURE 15 is a plan view of another embodiment of a cuvette for use with the reagentless whole-blood detection system.

FIGURE 16 is a disassembled plan view of the cuvette shown in FIGURE 15.

FIGURE 16A is an exploded perspective view of the cuvette of FIGURE 15.

FIGURE 17 is a side view of the cuvette of FIGURE 15.

30 FIGURE 18 is a functional block diagram showing an analyte monitoring system with network connectivity.

FIGURE 19 is a block diagram of the electronic circuits within the analyte monitoring system of FIGURE 18.

FIGURE 20 is a flowchart exemplifying calibration lockout according to one embodiment disclosed herein.

FIGURE 21 is a block diagram of components of an analyte monitoring system having software update capabilities.

5 FIGURE 22 is a flowchart exemplifying updating a analyte monitoring device's software according to another embodiment disclosed herein.

Detailed Description of the Preferred Embodiments

The devices and methods summarized above are described in greater detail below. Part I contains a description of a number of analyte detection systems, including a
10 noninvasive system and a whole-blood system, as well as associated methods of analyte detection. Parts II and III includes a discussion of further systems and methods for, inter alia, updating software executed by analyte detection systems such as (but not limited to) those described in Part I. Accordingly, the systems and methods described in Parts II and III may (but need not) be employed by, within and/or in connection with those described in
15 Part I.

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
20 invention herein disclosed should not be limited by the particular disclosed embodiments described below.

I. OVERVIEW OF ANALYTE DETECTION SYSTEMS

Disclosed herein are analyte detection systems, including a noninvasive system discussed largely in part A below and a whole-blood system discussed largely in part B
25 below. Also disclosed are various methods, including methods for detecting the concentration of an analyte in a material sample. Both the noninvasive system/method and the whole-blood system/method can employ optical measurement. As used herein with reference to measurement apparatus and methods, "optical" is a broad term and is used in its ordinary sense and refers, without limitation, to identification of the presence or
30 concentration of an analyte in a material sample without requiring a chemical reaction to take place. As discussed in more detail below, the two approaches each can operate independently to perform an optical analysis of a material sample. The two approaches can

also be combined in an apparatus, or the two approaches can be used together to perform different steps of a method.

In one embodiment, the two approaches are combined to perform calibration of an apparatus, e.g., of an apparatus that employs a noninvasive approach. In another
5 embodiment, an advantageous combination of the two approaches performs an invasive measurement to achieve greater accuracy and a whole-blood measurement to minimize discomfort to the patient. For example, the whole-blood technique may be more accurate than the noninvasive technique at certain times of the day, e.g., at certain times after a meal has been consumed, or after a drug has been administered.

10 It should be understood, however, that any of the disclosed devices may be operated in accordance with any suitable detection methodology, and that any disclosed method may be employed in the operation of any suitable device. Furthermore, the disclosed devices and methods are applicable in a wide variety of situations or modes of operation, including but not limited to invasive, noninvasive, intermittent or continuous measurement,
15 subcutaneous implantation, wearable detection systems, or any combination thereof.

Any method which is described and illustrated herein is not limited to the exact sequence of acts described, nor is it necessarily limited to the practice of all of the acts set forth. Other sequences of events or acts, or less than all of the events, or simultaneous occurrence of the events, may be utilized in practicing the method(s) in question.

20 A. Noninvasive System

1. Monitor Structure

FIGURE 1 depicts a noninvasive optical detection system (hereinafter “noninvasive system”) 10 in a presently preferred configuration. The depicted noninvasive system 10 is particularly suited for noninvasively detecting the concentration of an analyte in a material
25 sample S, by observing the infrared energy emitted by the sample, as will be discussed in further detail below.

As used herein, the term “noninvasive” is a broad term and is used in its ordinary sense and refers, without limitation, to analyte detection devices and methods which have the capability to determine the concentration of an analyte in in-vivo tissue samples or
30 bodily fluids. It should be understood, however, that the noninvasive system 10 disclosed herein is not limited to noninvasive use, as the noninvasive system 10 may be employed to analyze an in-vitro fluid or tissue sample which has been obtained invasively or

noninvasively. As used herein, the term “invasive” (or, alternatively, “traditional”) is a broad term and is used in its ordinary sense and refers, without limitation, to analyte detection methods which involve the removal of fluid samples through the skin. As used herein, the term “material sample” is a broad term and is used in its ordinary sense and refers, without limitation, to any collection of material which is suitable for analysis by the noninvasive system 10. For example, the material sample S may comprise a tissue sample, such as a human forearm, placed against the noninvasive system 10. The material sample S may also comprise a volume of a bodily fluid, such as whole blood, blood component(s), interstitial fluid or intercellular fluid obtained invasively, or saliva or urine obtained noninvasively, or any collection of organic or inorganic material. As used herein, the term “analyte” is a broad term and is used in its ordinary sense and refers, without limitation, to any chemical species the presence or concentration of which is sought in the material sample S by the noninvasive system 10. For example, the analyte(s) which may be detected by the noninvasive 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. As used herein to describe measurement techniques, the term “continuous” is a broad term and is used in its ordinary sense and refers, without limitation, to the taking of discrete measurements more frequently than about once every 10 minutes, and/or the taking of a stream or series of measurements or other data over any suitable time interval, for example, over an interval of one to several seconds, minutes, hours, days, or longer. As used herein to describe measurement techniques, the term “intermittent” is a broad term and is used in its ordinary sense and refers, without limitation, to the taking of measurements less frequently than about once every 10 minutes.

The noninvasive system 10 preferably comprises a window assembly 12, although in some embodiments the window assembly 12 may be omitted. One function of the window assembly 12 is to permit infrared energy E to enter the noninvasive system 10 from the sample S when it is placed against an upper surface 12a of the window assembly 12. The window assembly 12 includes a heater layer (see discussion below) which is employed

to heat the material sample S and stimulate emission of infrared energy therefrom. A cooling system 14, preferably comprising a Peltier-type thermoelectric device, is in thermally conductive relation to the window assembly 12 so that the temperature of the window assembly 12 and the material sample S can be manipulated in accordance with a
5 detection methodology discussed in greater detail below. The cooling system 14 includes a cold surface 14a which is in thermally conductive relation to a cold reservoir 16 and the window assembly 12, and a hot surface 14b which is in thermally conductive relation to a heat sink 18.

As the infrared energy E enters the noninvasive system 10, it first passes through the
10 window assembly 12, then through an optical mixer 20, and then through a collimator 22. The optical mixer 20 preferably comprises a light pipe having highly reflective inner surfaces which randomize the directionality of the infrared energy E as it passes therethrough and reflects against the mixer walls. The collimator 22 also comprises a light
15 pipe having highly-reflective inner walls, but the walls diverge as they extend away from the mixer 20. The divergent walls cause the infrared energy E to tend to straighten as it advances toward the wider end of the collimator 22, due to the angle of incidence of the infrared energy when reflecting against the collimator walls.

From the collimator 22 the infrared energy E passes through an array of filters 24, each of which allows only a selected wavelength or band of wavelengths to pass
20 therethrough. These wavelengths/bands are selected to highlight or isolate the absorptive effects of the analyte of interest in the detection methodology discussed in greater detail below. Each filter 24 is preferably in optical communication with a concentrator 26 and an infrared detector 28. The concentrators 26 have highly reflective, converging inner walls which concentrate the infrared energy as it advances toward the detectors 28, increasing the
25 density of the energy incident upon the detectors 28.

The detectors 28 are in electrical communication with a control system 30 which receives electrical signals from the detectors 28 and computes the concentration of the analyte in the sample S. The control system 30 is also in electrical communication with the window 12 and cooling system 14, so as to monitor the temperature of the window 12
30 and/or cooling system 14 and control the delivery of electrical power to the window 12 and cooling system 14.

a. **Window Assembly**

A preferred configuration of the window assembly 12 is shown in perspective, as viewed from its underside (in other words, the side of the window assembly 12 opposite the sample S), in FIGURE 2. The window assembly 12 generally comprises a main layer 32
5 formed of a highly infrared-transmissive material and a heater layer 34 affixed to the underside of the main layer 32. The main layer 32 is preferably formed from diamond, most preferably from chemical-vapor-deposited ("CVD") diamond, with a preferred thickness of about 0.25 millimeters. In other embodiments alternative materials which are highly infrared-transmissive, such as silicon or germanium, may be used in forming the
10 main layer 32.

The heater layer 34 preferably comprises bus bars 36 located at opposing ends of an array of heater elements 38. The bus bars 36 are in electrical communication with the elements 38 so that, upon connection of the bus bars 36 to a suitable electrical power source (not shown) a current may be passed through the elements 38 to generate heat in the
15 window assembly 12. The heater layer 34 may also include one or more temperature sensors (not shown), such as thermistors or resistance temperature devices (RTDs), to measure the temperature of the window assembly 12 and provide temperature feedback to the control system 30 (see FIGURE 1).

Still referring to FIGURE 2, the heater layer 34 preferably comprises a first
20 adhesion layer of gold or platinum (hereinafter referred to as the "gold" layer) deposited over an alloy layer which is applied to the main layer 32. The alloy layer comprises a material suitable for implementation of the heater layer 34, such as, by way of example, 10/90 titanium/tungsten, titanium/platinum, nickel/chromium, or other similar material. The gold layer preferably has a thickness of about 4000 Å, and the alloy layer preferably
25 has a thickness ranging between about 300 Å and about 500 Å. The gold layer and/or the alloy layer may be deposited onto the main layer 32 by chemical deposition including, but not necessarily limited to, vapor deposition, liquid deposition, plating, laminating, casting, sintering, or other forming or deposition methodologies well known to those of ordinary skill in the art. If desired, the heater layer 34 may be covered with an electrically insulating
30 coating which also enhances adhesion to the main layer 32. One preferred coating material is aluminum oxide. Other acceptable materials include, but are not limited to, titanium dioxide or zinc selenide.

The heater layer 34 may incorporate a variable pitch distance between centerlines of adjacent heater elements 38 to maintain a constant power density, and promote a uniform temperature, across the entire layer 34. Where a constant pitch distance is employed, the preferred distance is at least about 50-100 microns. Although the heater elements 38
5 generally have a preferred width of about 25 microns, their width may also be varied as needed for the same reasons stated above.

Alternative structures suitable for use as the heater layer 34 include, but are not limited to, thermoelectric heaters, radiofrequency (RF) heaters, infrared radiation heaters, optical heaters, heat exchangers, electrical resistance heating grids, wire bridge heating
10 grids, or laser heaters. Whichever type of heater layer is employed, it is preferred that the heater layer obscures about 10% or less of the window assembly 12.

In a preferred embodiment, the window assembly 12 comprises substantially only the main layer 32 and the heater layer 34. Thus, when installed in an optical detection system such as the noninvasive system 10 shown in FIGURE 1, the window assembly 12
15 will facilitate a minimally obstructed optical path between a (preferably flat) upper surface 12a of the window assembly 12 and the infrared detectors 28 of the noninvasive system 10. The optical path 32 in the preferred noninvasive system 10 proceeds only through the main layer 32 and heater layer 34 of the window assembly 12 (including any antireflective, index-matching, electrical insulating or protective coatings applied thereto or placed
20 therein), through the optical mixer 20 and collimator 22 and to the detectors 28.

FIGURE 2A shows another embodiment of the window assembly 12, that may be used in place of the window assembly 12 depicted in FIGURE 2. The window assembly 12 shown in FIGURE 2A may be similar to that shown in FIGURE 2, except as described below. In the embodiment of FIGURE 2A the main layer 32 has a preferred thickness of up
25 to about 0.012" and more preferably about 0.010" or less. The heater layer 34 may also include one or more resistance temperature devices (RTD's) 55 to measure the temperature of the window assembly 12 and provide temperature feedback to a control system 30. The RTDs 55 terminate in RTD connection pads 57.

In the embodiment of FIGURE 2A, the heater elements 38 are typically provided
30 with a width of about 25 microns. The pitch distance separating centerlines of adjacent heater elements 38 may be reduced, and/or the width of the heater elements 38 may be increased, in the regions of the window assembly 12 near the point(s) of contact with the

thermal diffuser 410 (see FIGURES 6B-6D and discussion below). This arrangement advantageously promotes an isothermal temperature profile at the upper surface of the main layer 32 despite thermal contact with the thermal diffuser.

The embodiment shown in FIGURE 2A includes a plurality of heater elements 38 of substantially equal width which are variably spaced across the width of the main layer 32. In the embodiment of FIGURE 2A, the centerlines of the heater elements 38 are spaced at a first pitch distance of about 0.0070" at peripheral portions 34a of the heater layer 34, and at a second pitch distance of about 0.015" at a central portion 34b of the main layer 32. The heater elements 38 closest to the center are preferably sufficiently spaced to allow the RTDs 55 to extend therebetween. In the embodiment of FIGURE 2A, the main layer 32 includes peripheral regions 32a which extend about 0.053" from the outermost heater element on each side of the heater layer 34 to the adjacent edge of the main layer 32. As shown, the bus bars 36 are preferably configured and segmented to allow space for the RTDs 55 and the RTD connection pads 57, in intermediate gaps 36a. The RTDs 55 preferably extend into the array of heater elements 38 by distance that is slightly longer than half of the length of an individual heater element 38. In alternative embodiments, the RTDs 55 may be located at the edges of the main layer 32, or at other locations as desired for a particular noninvasive system.

With continued reference to FIGURE 2A, the peripheral regions of the main layer 32 may include metallized edge portions 35 for facilitating connection to the diffuser 410 (discussed below in connection with FIGURES 6B-6D). The metallized edge portions 35 may be formed by the same or similar processes used in forming the heater elements 38 and RTDs 55. In the embodiment of FIGURE 2A, the edge portions 35 are typically between about 0.040" and about 0.060" wide by about 0.450" and about 0.650" long, and in one embodiment, they are about 0.050" by about 0.550". Other dimensions may be appropriately used so long as the window assembly 12 may be joined in thermal communication with the diffuser 410 as needed.

In the embodiment shown in FIGURE 2A, the main layer 32 is about 0.690" long by about 0.571" wide, and the heater layer (excluding the metallized edge portions 35) is about 0.640" long by about 0.465" wide. The main layer 32 is about 0.010"-0.012" thick, and is advantageously thinner than about 0.010" where possible. Each heater element 38 is about

0.570" long, and each peripheral region 34a is about 0.280" wide. These dimensions are merely exemplary; of course, other dimensions may be used as desired.

FIGURE 3 depicts an exploded side view of an alternative configuration for the window assembly 12, which may be used in place of the configuration shown in FIGURE 2. The window assembly 12 depicted in FIGURE 3 includes near its upper surface (the surface intended for contact with the sample S) a highly infrared-transmissive, thermally conductive spreader layer 42. Underlying the spreader layer 42 is a heater layer 44. A thin electrically insulating layer (not shown), such as layer of aluminum oxide, titanium dioxide or zinc selenide, may be disposed between the heater layer 44 and the spreader layer 42. (An aluminum oxide layer also increases adhesion of the heater layer 44 to the spreader layer 42.) Adjacent to the heater layer 44 is a thermal insulating and impedance matching layer 46. Adjacent to the thermal insulating layer 46 is a thermally conductive inner layer 48. The spreader layer 42 is coated on its top surface with a thin layer of protective coating 50. The bottom surface of the inner layer 48 is coated with a thin overcoat layer 52. Preferably, the protective coating 50 and the overcoat layer 52 have antireflective properties.

The spreader layer 42 is preferably formed of a highly infrared-transmissive material having a high thermal conductivity sufficient to facilitate heat transfer from the heater layer 44 uniformly into the material sample S when it is placed against the window assembly 12. Other effective materials include, but are not limited to, CVD diamond, diamondlike carbon, gallium arsenide, germanium, and other infrared-transmissive materials having sufficiently high thermal conductivity. Preferred dimensions for the spreader layer 42 are about one inch in diameter and about 0.010 inch thick. As shown in FIGURE 3, a preferred embodiment of the spreader layer 42 incorporates a beveled edge. Although not required, an approximate 45-degree bevel is preferred.

The protective layer 50 is intended to protect the top surface of the spreader layer 42 from damage. Ideally, the protective layer is highly infrared-transmissive and highly resistant to mechanical damage, such as scratching or abrasion. It is also preferred that the protective layer 50 and the overcoat layer 52 have high thermal conductivity and antireflective and/or index-matching properties. A satisfactory material for use as the protective layer 50 and the overcoat layer 52 is the multi-layer Broad Band Anti-Reflective

Coating produced by Deposition Research Laboratories, Inc. of St. Charles, Missouri. Diamondlike carbon coatings are also suitable.

Except as noted below, the heater layer 44 is generally similar to the heater layer 34 employed in the window assembly shown in FIGURE 2. Alternatively, the heater layer 44 may comprise a doped infrared-transmissive material, such as a doped silicon layer, with regions of higher and lower resistivity. The heater layer 44 preferably has a resistance of about 2 ohms and has a preferred thickness of about 1,500 angstroms. A preferred material for forming the heater layer 44 is a gold alloy, but other acceptable materials include, but are not limited to, platinum, titanium, tungsten, copper, and nickel.

The thermal insulating layer 46 prevents the dissipation of heat from the heater element 44 while allowing the cooling system 14 to effectively cool the material sample S (see FIGURE 1). This layer 46 comprises a material having thermally insulative (e.g., lower thermal conductivity than the spreader layer 42) and infrared transmissive qualities. A preferred material is a germanium-arsenic-selenium compound of the calcogenide glass family known as AMTIR-1 produced by Amorphous Materials, Inc. of Garland, Texas. The pictured embodiment has a diameter of about 0.85 inches and a preferred thickness in the range of about 0.005 to about 0.010 inches. As heat generated by the heater layer 44 passes through the spreader layer 42 into the material sample S, the thermal insulating layer 46 insulates this heat.

The inner layer 48 is formed of thermally conductive material, preferably crystalline silicon formed using a conventional floatzone crystal growth method. The purpose of the inner layer 48 is to serve as a cold-conducting mechanical base for the entire layered window assembly.

The overall optical transmission of the window assembly 12 shown in FIGURE 3 is preferably at least 70%. The window assembly 12 of FIGURE 3 is preferably held together and secured to the noninvasive system 10 by a holding bracket (not shown). The bracket is preferably formed of a glass-filled plastic, for example Ultem 2300, manufactured by General Electric. Ultem 2300 has low thermal conductivity which prevents heat transfer from the layered window assembly 12.

b. Cooling System

The cooling system 14 (see FIGURE 1) preferably comprises a Peltier-type thermoelectric device. Thus, the application of an electrical current to the preferred cooling

system 14 causes the cold surface 14a to cool and causes the opposing hot surface 14b to heat up. The cooling system 14 cools the window assembly 12 via the situation of the window assembly 12 in thermally conductive relation to the cold surface 14a of the cooling system 14. It is contemplated that the cooling system 14, the heater layer 34, or both, can be operated to induce a desired time-varying temperature in the window assembly 12 to create an oscillating thermal gradient in the sample S, in accordance with various analyte-detection methodologies discussed herein.

Preferably, the cold reservoir 16 is positioned between the cooling system 14 and the window assembly 12, and functions as a thermal conductor between the system 14 and the window assembly 12. The cold reservoir 16 is formed from a suitable thermally conductive material, preferably brass. Alternatively, the window assembly 12 can be situated in direct contact with the cold surface 14a of the cooling system 14.

In alternative embodiments, the cooling system 14 may comprise a heat exchanger through which a coolant, such as air, nitrogen or chilled water, is pumped, or a passive conduction cooler such as a heat sink. As a further alternative, a gas coolant such as nitrogen may be circulated through the interior of the noninvasive system 10 so as to contact the underside of the window assembly 12 (see FIGURE 1) and conduct heat therefrom.

FIGURE 4 is a top schematic view of a preferred arrangement of the window assembly 12 (of the types shown in FIGURE 2 or 2A) and the cold reservoir 16, and FIGURE 5 is a top schematic view of an alternative arrangement in which the window assembly 12 directly contacts the cooling system 14. The cold reservoir 16/cooling system 14 preferably contacts the underside of the window assembly 12 along opposing edges thereof, on either side of the heater layer 34. With thermal conductivity thus established between the window assembly 12 and the cooling system 14, the window assembly can be cooled as needed during operation of the noninvasive system 10. In order to promote a substantially uniform or isothermal temperature profile over the upper surface of the window assembly 12, the pitch distance between centerlines of adjacent heater elements 38 may be made smaller (thereby increasing the density of heater elements 38) near the region(s) of contact between the window assembly 12 and the cold reservoir 16/cooling system 14. As a supplement or alternative, the heater elements 38 themselves may be made wider near these regions of contact. As used herein, "isothermal" is a broad term and

is used in its ordinary sense and refers, without limitation, to a condition in which, at a given point in time, the temperature of the window assembly 12 or other structure is substantially uniform across a surface intended for placement in thermally conductive relation to the material sample S. Thus, although the temperature of the structure or surface
5 may fluctuate over time, at any given point in time the structure or surface may nonetheless be isothermal.

The heat sink 18 drains waste heat from the hot surface 14b of the cooling system 16 and stabilizes the operational temperature of the noninvasive system 10. The preferred heat sink 18 (see FIGURE 6) comprises a hollow structure formed from brass or any other
10 suitable material having a relatively high specific heat and high heat conductivity. The heat sink 18 has a conduction surface 18a which, when the heat sink 18 is installed in the noninvasive system 18, is in thermally conductive relation to the hot surface 14b of the cooling system 14 (see FIGURE 1). A cavity 54 is formed in the heat sink 18 and preferably contains a phase-change material (not shown) to increase the capacity of the sink
15 18. A preferred phase change material is a hydrated salt, such as calciumchloride hexahydrate, available under the name TH29 from PCM Thermal Solutions, Inc., of Naperville, Illinois. Alternatively, the cavity 54 may be omitted to create a heat sink 18 comprising a solid, unitary mass. The heat sink 18 also forms a number of fins 56 to further increase the conduction of heat from the sink 18 to surrounding air.

20 Alternatively, the heat sink 18 may be formed integrally with the optical mixer 20 and/or the collimator 22 as a unitary mass of rigid, heat-conductive material such as brass or aluminum. In such a heat sink, the mixer 20 and/or collimator 22 extend axially through the heat sink 18, and the heat sink defines the inner walls of the mixer 20 and/or collimator 22. These inner walls are coated and/or polished to have appropriate reflectivity and
25 nonabsorbance in infrared wavelengths as will be further described below. Where such a unitary heat sink-mixer-collimator is employed, it is desirable to thermally insulate the detector array from the heat sink.

It should be understood that any suitable structure may be employed to heat and/or cool the material sample S, instead of or in addition to the window assembly 12/cooling
30 system 14 disclosed above, so long a proper degree of cycled heating and/or cooling are imparted to the material sample S. In addition other forms of energy, such as but not limited to light, radiation, chemically induced heat, friction and vibration, may be employed

to heat the material sample S. It will be further appreciated that heating of the sample can be achieved by any suitable method, such as convection, conduction, radiation, etc.

c. Window Mounting System

FIGURE 6B illustrates an exploded view of a window mounting system 400 which, in one embodiment, is employed as part of the noninvasive system 10 disclosed above. Where employed in connection with the noninvasive system 10, the window mounting system 400 supplements or, where appropriate, replaces any of the window assembly 12, cooling system 14, cold reservoir 16 and heat sink 18 shown in FIGURE 1. In one embodiment, the window mounting system 400 is employed in conjunction with the window assembly 12 depicted in FIGURE 2A; in alternative embodiments, the window assemblies shown in FIGURES 2 and 3 and described above may also be used in conjunction with the window mounting system 400 illustrated in FIGURE 6B.

In the window mounting system 400, the window assembly 12 is physically and electrically connected (typically by soldering) to a first printed circuit board ("first PCB") 402. The window assembly 12 is also in thermally conductive relation (typically by contact) to a thermal diffuser 410. The window assembly may also be fixed to the diffuser 410 by soldering.

The thermal diffuser 410 generally comprises a heat spreader layer 412 which, as mentioned, preferably contacts the window assembly 12, and a conductive layer 414 which is typically soldered to the heat spreader layer 412. The conductive layer 414 may then be placed in direct contact with a cold side 418a of a thermoelectric cooler (TEC) 418 or other cooling device. The TEC 418, which in one embodiment comprises a 25 W TEC manufactured by MELCOR, is in electrical communication with a second PCB 403, which includes TEC power leads 409 and TEC power terminals 411 for connection of the TEC 418 to an appropriate power source (not shown). The second PCB 403 also includes contacts 408 for connection with RTD terminals 407 (see FIGURE 6C) of the first PCB 402. A heat sink 419, which may take the form of the illustrated water jacket, the heat sink 18 shown in FIGURE 6, any other heat sink structures mentioned herein, or any other appropriate device, is in thermal communication with a hot side 418b of the TEC 418 (or other cooling device), in order to remove any excess heat created by the TEC 418.

FIGURE 6C illustrates a plan view of the interconnection of the window assembly 12, the first PCB 402, the diffuser 410 and the thermoelectric cooler 418. The first PCB includes RTD bonding leads 406 and heater bonding pads 404 which permit attachment of

the RTDs 55 and bus bars 36, respectively, of the window assembly 12 to the first PCB 402 via soldering or other conventional techniques. Electrical communication is thus established between the heater elements 38 of the heater layer 34, and heater terminals 405 formed in the heater bonding pads 404. Similarly, electrical communication is established
5 between the RTDs 55 and RTD terminals 407 formed at the ends of the RTD bonding leads 406. Electrical connections can be established with the heater elements 38 and the RTDs 55 via simple connection to the terminals 405, 407 of the first PCB 402.

With further reference to FIGURES 2A and 6B-6C, the heat spreader layer 412 of the thermal diffuser 410 contacts the underside of the main layer 32 of the window
10 assembly 12 via a pair of rails 416. The rails 416 may contact the main layer 32 at the metallized edge portions 35, or at any other appropriate location. The physical and thermal connection between the rails 416 and the window main layer 32 may be achieved by soldering, as indicated above. Alternatively, the connection may be achieved by an adhesive such as epoxy, or any other appropriate method. The material chosen for the
15 window main layer 32 is preferably sufficiently thermally conductive that heat may be quickly removed from the main layer 32 through the rails 416, the diffuser 410, and the TEC 128.

FIGURE 6D shows a cross-sectional view of the assembly of FIGURE 6C through line 22-22. As can be seen in FIGURE 6D, the window assembly 12 contacts the rails 416
20 of the heat spreader layer 412. The conductive layer 414 underlies the spreader layer 412 and may comprise protrusions 426 configured to extend through openings 424 formed in the spreader layer 412. The openings 424 and protrusions 426 are sized to leave sufficient expansion space therebetween, to allow expansion and contraction of the conductive layer 414 without interference with, or causing deformation of, the window assembly 12 or the
25 heat spreader layer 412. Moreover, the protrusions 426 and openings 424 coact to prevent displacement of the spreader layer 412 with respect to the conductive layer 414 as the conductive layer 414 expands and contracts.

The thermal diffuser 410 provides a thermal impedance between the TEC 418 and the window assembly 12, which impedance is selected to drain heat from the window
30 assembly at a rate proportional to the power output of the heater layer 34. In this way, the temperature of the main layer 32 can be rapidly cycled between a "hot" and a "cold"

temperatures, thereby allowing a time-varying thermal gradient to be induced in a sample S placed against the window assembly 12.

The heat spreader layer 412 is preferably made of a material which has substantially the same coefficient of thermal expansion as the material used to form the window assembly main layer 32, within the expected operating temperature range. Preferably, both
5 the material used to form the main layer 32 and the material used to form the heat spreader layer 412 have substantially the same, extremely low, coefficient of thermal expansion. For this reason, CVD diamond is preferred for the main layer 32 (as mentioned above); with a CVD diamond main layer 32 the preferred material for the heat spreader layer 412 is Invar.
10 Invar advantageously has an extremely low coefficient of thermal expansion and a relatively high thermal conductivity. Because Invar is a metal, the main layer 32 and the heat spreader layer 412 can be thermally bonded to one another with little difficulty. Alternatively, other materials may be used for the heat spreader layer 412; for example, any of a number of glass and ceramic materials with low coefficients of thermal expansion may
15 be employed.

The conductive layer 414 of the thermal diffuser 410 is typically a highly thermally conductive material such as copper (or, alternatively, other metals or non-metals exhibiting comparable thermal conductivities). The conductive layer 414 is typically soldered or otherwise bonded to the underside of the heat spreader layer 412.

20 In the illustrated embodiment, the heat spreader layer 412 may be constructed according to the following dimensions, which are to be understood as exemplary; accordingly the dimensions may be varied as desired. The heat spreader layer 412 has an overall length and width of about 1.170", with a central opening of about 0.590" long by 0.470" wide. Generally, the heat spreader layer 412 is about 0.030" thick; however, the
25 rails 416 extend a further 0.045" above the basic thickness of the heat spreader layer 412. Each rail 416 has an overall length of about 0.710"; over the central 0.525" of this length each rail 416 is about 0.053" wide. On either side of the central width each rail 416 tapers, at a radius of about 0.6", down to a width of about 0.023". Each opening 424 is about 0.360" long by about 0.085" wide, with corners rounded at a radius of about 0.033".

30 In the illustrated embodiment, conductive layer 414 may be constructed according to the following dimensions, which are to be understood as exemplary; accordingly the dimensions may be varied as desired. The conductive layer 414 has an overall length and

width of about 1.170", with a central opening of about 0.590" long by 0.470" wide. Generally, the conductive layer 412 is about 0.035" thick; however, the protrusions 426 extend a further 0.075" - 0.085" above the basic thickness of the conductive layer 414. Each protrusion 426 is about 0.343" long by about 0.076" wide, with corners rounded at a
5 radius of about 0.035".

As shown in FIGURE 6B, first and second clamping plates 450 and 452 may be used to clamp the portions of the window mounting system 400 to one another. For example, the second clamping plate 452 is configured to clamp the window assembly 12 and the first PCB 402 to the diffuser 410 with screws or other fasteners extending through
10 the openings shown in the second clamping plate 452, the heat spreader layer 412 and the conductive layer 414. Similarly, the first clamping plate 450 is configured overlie the second clamping plate 452 and clamp the rest of the window mounting system 400 to the heat sink 419, thus sandwiching the second clamping plate 452, the window assembly 12, the first PCB 402, the diffuser 410, the second PCB 403, and the TEC 418 therebetween.
15 The first clamping plate 450 prevents undesired contact between the sample S and any portion of the window mounting system 400, other than the window assembly 12 itself. Other mounting plates and mechanisms may also be used as desired.

d. Optics

As shown in FIGURE 1, the optical mixer 20 comprises a light pipe with an inner
20 surface coating which is highly reflective and minimally absorptive in infrared wavelengths, preferably a polished gold coating, although other suitable coatings may be used where other wavelengths of electromagnetic radiation are employed. The pipe itself may be fabricated from a another rigid material such as aluminum or stainless steel, as long as the inner surfaces are coated or otherwise treated to be highly reflective. Preferably, the
25 optical mixer 20 has a rectangular cross-section (as taken orthogonal to the longitudinal axis A-A of the mixer 20 and the collimator 22), although other cross-sectional shapes, such as other polygonal shapes or circular or elliptical shapes, may be employed in alternative embodiments. The inner walls of the optical mixer 20 are substantially parallel to the longitudinal axis A-A of the mixer 20 and the collimator 22. The highly reflective
30 and substantially parallel inner walls of the mixer 20 maximize the number of times the infrared energy E will be reflected between the walls of the mixer 20, thoroughly mixing the infrared energy E as it propagates through the mixer 20. In a presently preferred

embodiment, the mixer 20 is about 1.2 inches to 2.4 inches in length and its cross-section is a rectangle of about 0.4 inches by about 0.6 inches. Of course, other dimensions may be employed in constructing the mixer 20. In particular it is be advantageous to miniaturize the mixer or otherwise make it as small as possible

5 Still referring to FIGURE 1, the collimator 22 comprises a tube with an inner surface coating which is highly reflective and minimally absorptive in infrared wavelengths, preferably a polished gold coating. The tube itself may be fabricated from a another rigid material such as aluminum, nickel or stainless steel, as long as the inner surfaces are coated or otherwise treated to be highly reflective. Preferably, the collimator
10 22 has a rectangular cross-section, although other cross-sectional shapes, such as other polygonal shapes or circular, parabolic or elliptical shapes, may be employed in alternative embodiments. The inner walls of the collimator 22 diverge as they extend away from the mixer 20. Preferably, the inner walls of the collimator 22 are substantially straight and form an angle of about 7 degrees with respect to the longitudinal axis A-A. The collimator
15 22 aligns the infrared energy E to propagate in a direction that is generally parallel to the longitudinal axis A-A of the mixer 20 and the collimator 22, so that the infrared energy E will strike the surface of the filters 24 at an angle as close to 90 degrees as possible.

In a presently preferred embodiment, the collimator is about 7.5 inches in length. At its narrow end 22a, the cross-section of the collimator 22 is a rectangle of about 0.4
20 inches by 0.6 inches. At its wide end 22b, the collimator 22 has a rectangular cross-section of about 1.8 inches by 2.6 inches. Preferably, the collimator 22 aligns the infrared energy E to an angle of incidence (with respect to the longitudinal axis A-A) of about 0-15 degrees before the energy E impinges upon the filters 24. Of course, other dimensions or incidence angles may be employed in constructing and operating the collimator 22.

25 With further reference to FIGURES 1 and 6A, each concentrator 26 comprises a tapered surface oriented such that its wide end 26a is adapted to receive the infrared energy exiting the corresponding filter 24, and such that its narrow end 26b is adjacent to the corresponding detector 28. The inward-facing surfaces of the concentrators 26 have an inner surface coating which is highly reflective and minimally absorptive in infrared
30 wavelengths, preferably a polished gold coating. The concentrators 26 themselves may be fabricated from a another rigid material such as aluminum, nickel or stainless steel, so long as their inner surfaces are coated or otherwise treated to be highly reflective.

Preferably, the concentrators 26 have a rectangular cross-section (as taken orthogonal to the longitudinal axis A-A), although other cross-sectional shapes, such as other polygonal shapes or circular, parabolic or elliptical shapes, may be employed in alternative embodiments. The inner walls of the concentrators converge as they extend
5 toward the narrow end 26b. Preferably, the inner walls of the collimators 26 are substantially straight and form an angle of about 8 degrees with respect to the longitudinal axis A-A. Such a configuration is adapted to concentrate infrared energy as it passes through the concentrators 26 from the wide end 26a to the narrow end 26b, before reaching the detectors 28.

10 In a presently preferred embodiment, each concentrator 26 is about 1.5 inches in length. At the wide end 26a, the cross-section of each concentrator 26 is a rectangle of about 0.6 inches by 0.57 inches. At the narrow end 26b, each concentrator 26 has a rectangular cross-section of about 0.177 inches by 0.177 inches. Of course, other dimensions or incidence angles may be employed in constructing the concentrators 26.

15 **e. Filters**

The filters 24 preferably comprise standard interference-type infrared filters, widely available from manufacturers such as Optical Coating Laboratory, Inc. ("OCLI") of Santa Rosa, CA. In the embodiment illustrated in FIGURE 1, a 3×4 array of filters 24 is positioned above a 3×4 array of detectors 28 and concentrators 26. As employed in this
20 embodiment, the filters 24 are arranged in four groups of three filters having the same wavelength sensitivity. These four groups have bandpass center wavelengths of $7.15 \mu\text{m} \pm 0.03 \mu\text{m}$, $8.40 \mu\text{m} \pm 0.03 \mu\text{m}$, $9.48 \mu\text{m} \pm 0.04 \mu\text{m}$, and $11.10 \mu\text{m} \pm 0.04 \mu\text{m}$, respectively, which correspond to wavelengths around which water and glucose absorb electromagnetic radiation. Typical bandwidths for these filters range from $0.20 \mu\text{m}$ to $0.50 \mu\text{m}$.

25 In an alternative embodiment, the array of wavelength-specific filters 24 may be replaced with a single Fabry-Perot interferometer, which can provide wavelength sensitivity which varies as a sample of infrared energy is taken from the material sample S. Thus, this embodiment permits the use of only one detector 28, the output signal of which varies in wavelength specificity over time. The output signal can be de-multiplexed based on the
30 wavelength sensitivities induced by the Fabry-Perot interferometer, to provide a multiple-wavelength profile of the infrared energy emitted by the material sample S. In this

embodiment, the optical mixer 20 may be omitted, as only one detector 28 need be employed.

In still other embodiments, the array of filters 24 may comprise a filter wheel that rotates different filters with varying wavelength sensitivities over a single detector 24.

- 5 Alternatively, an electronically tunable infrared filter may be employed in a manner similar to the Fabry-Perot interferometer discussed above, to provide wavelength sensitivity which varies during the detection process. In either of these embodiments, the optical mixer 20 may be omitted, as only one detector 28 need be employed.

f. Detectors

- 10 The detectors 28 may comprise any detector type suitable for sensing infrared energy, preferably in the mid-infrared wavelengths. For example, the detectors 28 may comprise mercury-cadmium-telluride (MCT) detectors. A detector such as a Fermionics (Simi Valley, Calif.) model PV-9.1 with a PVA481-1 pre-amplifier is acceptable. Similar units from other manufacturers such as Graseby (Tampa, Fla.) can be substituted. Other
15 suitable components for use as the detectors 28 include pyroelectric detectors, thermopiles, bolometers, silicon microbolometers and lead-salt focal plane arrays.

g. Control System

- FIGURE 7 depicts the control system 30 in greater detail, as well as the interconnections between the control system and other relevant portions of the noninvasive
20 system. The control system includes a temperature control subsystem and a data acquisition subsystem.

- In the temperature control subsystem, temperature sensors (such as RTDs and/or thermistors) located in the window assembly 12 provide a window temperature signal to a synchronous analog-to-digital conversion system 70 and an asynchronous analog-to-digital
25 conversion system 72. The A/D systems 70, 72 in turn provide a digital window temperature signal to a digital signal processor (DSP) 74. The processor 74 executes a window temperature control algorithm and determines appropriate control inputs for the heater layer 34 of the window assembly 12 and/or for the cooling system 14, based on the information contained in the window temperature signal. The processor 74 outputs one or
30 more digital control signals to a digital-to-analog conversion system 76 which in turn provides one or more analog control signals to current drivers 78. In response to the control signal(s), the current drivers 78 regulate the power supplied to the heater layer 34 and/or to

the cooling system 14. In one embodiment, the processor 74 provides a control signal through a digital I/O device 77 to a pulse-width modulator (PWM) control 80, which provides a signal that controls the operation of the current drivers 78. Alternatively, a low-pass filter (not shown) at the output of the PWM provides for continuous operation of the current drivers 78.

In another embodiment, temperature sensors may be located at the cooling system 14 and appropriately connected to the A/D system(s) and processor to provide closed-loop control of the cooling system as well.

In yet another embodiment, a detector cooling system 82 is located in thermally conductive relation to one or more of the detectors 28. The detector cooling system 82 may comprise any of the devices disclosed above as comprising the cooling system 14, and preferably comprises a Peltier-type thermoelectric device. The temperature control subsystem may also include temperature sensors, such as RTDs and/or thermistors, located in or adjacent to the detector cooling system 82, and electrical connections between these sensors and the asynchronous A/D system 72. The temperature sensors of the detector cooling system 82 provide detector temperature signals to the processor 74. In one embodiment, the detector cooling system 82 operates independently of the window temperature control system, and the detector cooling system temperature signals are sampled using the asynchronous A/D system 72. In accordance with the temperature control algorithm, the processor 74 determines appropriate control inputs for the detector cooling system 82, based on the information contained in the detector temperature signal. The processor 74 outputs digital control signals to the D/A system 76 which in turn provides analog control signals to the current drivers 78. In response to the control signals, the current drivers 78 regulate the power supplied to the detector cooling system 14. In one embodiment, the processor 74 also provides a control signal through the digital I/O device 77 and the PWM control 80, to control the operation of the detector cooling system 82 by the current drivers 78. Alternatively, a low-pass filter (not shown) at the output of the PWM provides for continuous operation of the current drivers 78.

In the data acquisition subsystem, the detectors 28 respond to the infrared energy E incident thereon by passing one or more analog detector signals to a preamp 84. The preamp 84 amplifies the detector signals and passes them to the synchronous A/D system 70, which converts the detector signals to digital form and passes them to the processor 74.

The processor 74 determines the concentrations of the analyte(s) of interest, based on the detector signals and a concentration-analysis algorithm and/or phase/concentration regression model stored in a memory module 88. The concentration-analysis algorithm and/or phase/concentration regression model may be developed according to any of the analysis methodologies discussed herein. The processor may communicate the concentration results and/or other information to a display controller 86, which operates a display (not shown), such as an LCD display, to present the information to the user.

A watchdog timer 94 may be employed to ensure that the processor 74 is operating correctly. If the watchdog timer 94 does not receive a signal from the processor 74 within a specified time, the watchdog timer 94 resets the processor 74. The control system may also include a JTAG interface 96 to enable testing of the noninvasive system 10.

In one embodiment, the synchronous A/D system 70 comprises a 20-bit, 14 channel system, and the asynchronous A/D system 72 comprises a 16-bit, 16 channel system. The preamp may comprise a 12-channel preamp corresponding to an array of 12 detectors 28.

The control system may also include a serial port 90 or other conventional data port to permit connection to a personal computer 92. The personal computer can be employed to update the algorithm(s) and/or phase/concentration regression model(s) stored in the memory module 88, or to download a compilation of analyte-concentration data from the noninvasive system. A real-time clock or other timing device may be accessible by the processor 74 to make any time-dependent calculations which may be desirable to a user.

2. Analysis Methodology

The detector(s) 28 of the noninvasive system 10 are used to detect the infrared energy emitted by the material sample S in various desired wavelengths. At each measured wavelength, the material sample S emits infrared energy at an intensity which varies over time. The time-varying intensities arise largely in response to the use of the window assembly 12 (including its heater layer 34) and the cooling system 14 to induce a thermal gradient in the material sample S. As used herein, "thermal gradient" is a broad term and is used in its ordinary sense and refers, without limitation, to a difference in temperature and/or thermal energy between different locations, such as different depths, of a material sample, which can be induced by any suitable method of increasing or decreasing the temperature and/or thermal energy in one or more locations of the sample. As will be discussed in detail below, the concentration of an analyte of interest (such as glucose) in the

material sample S can be determined with a device such as the noninvasive system 10, by comparing the time-varying intensity profiles of the various measured wavelengths.

Analysis methodologies are discussed herein within the context of detecting the concentration of glucose within a material sample, such as a tissue sample, which includes a large proportion of water. However, it will be evident that these methodologies are not limited to this context and may be applied to the detection of a wide variety of analytes within a wide variety of sample types. It should also be understood that other suitable analysis methodologies and suitable variations of the disclosed methodologies may be employed in operating an analyte detection system, such as the noninvasive system 10.

As shown in FIGURE 8, a first reference signal P may be measured at a first reference wavelength. The first reference signal P is measured at a wavelength where water strongly absorbs (e.g., 2.9 μm or 6.1 μm). Because water strongly absorbs radiation at these wavelengths, the detector signal intensity is reduced at those wavelengths. Moreover, at these wavelengths water absorbs the photon emissions emanating from deep inside the sample. The net effect is that a signal emitted at these wavelengths from deep inside the sample is not easily detected. The first reference signal P is thus a good indicator of thermal-gradient effects near the sample surface and may be known as a surface reference signal. This signal may be calibrated and normalized, in the absence of heating or cooling applied to the sample, to a baseline value of 1. For greater accuracy, more than one first reference wavelength may be measured. For example, both 2.9 μm and 6.1 μm may be chosen as first reference wavelengths.

As further shown in FIGURE 8, a second reference signal R may also be measured. The second signal R may be measured at a wavelength where water has very low absorbance (e.g., 3.6 μm or 4.2 μm). This second reference signal R thus provides the analyst with information concerning the deeper regions of the sample, whereas the first signal P provides information concerning the sample surface. This signal may also be calibrated and normalized, in the absence of heating or cooling applied to the sample, to a baseline value of 1. As with the first (surface) reference signal P, greater accuracy may be obtained by using more than one second (deep) reference signal R.

In order to determine analyte concentration, a third (analytical) signal Q is also measured. This signal is measured at an IR absorbance peak of the selected analyte. The IR absorbance peaks for glucose are in the range of about 6.5 μm to 11.0 μm . This detector

signal may also be calibrated and normalized, in the absence of heating or cooling applied to the material sample S, to a baseline value of 1. As with the reference signals P, R, the analytical signal Q may be measured at more than one absorbance peak.

Optionally, or additionally, reference signals may be measured at wavelengths that
5 bracket the analyte absorbance peak. These signals may be advantageously monitored at reference wavelengths which do not overlap the analyte absorbance peaks. Further, it is advantageous to measure reference wavelengths at absorbance peaks which do not overlap the absorbance peaks of other possible constituents contained in the sample.

a. Basic Thermal Gradient

10 As further shown in FIGURE 8, the signal intensities P, Q, R are shown initially at the normalized baseline signal intensity of 1. This of course reflects the baseline radiative behavior of a test sample in the absence of applied heating or cooling. At a time t_C , the surface of the sample is subjected to a temperature event which induces a thermal gradient in the sample. The gradient can be induced by heating or cooling the sample surface. The
15 example shown in FIGURE 8 uses cooling, for example, using a 10° C cooling event. In response to the cooling event, the intensities of the detector signals P, Q, R decrease over time.

Since the cooling of the sample is neither uniform nor instantaneous, the surface cools before the deeper regions of the sample cool. As each of the signals P, Q, R drop in
20 intensity, a pattern emerges. Signal intensity declines as expected, but as the signals P, Q, R reach a given amplitude value (or series of amplitude values: 150, 152, 154, 156, 158), certain temporal effects are noted. After the cooling event is induced at t_C , the first (surface) reference signal P declines in amplitude most rapidly, reaching a checkpoint 150 first, at time t_P . This is due to the fact that the first reference signal P mirrors the sample's
25 radiative characteristics near the surface of the sample. Since the sample surface cools before the underlying regions, the surface (first) reference signal P drops in intensity first.

Simultaneously, the second reference signal R is monitored. Since the second reference signal R corresponds to the radiation characteristics of deeper regions of the sample, which do not cool as rapidly as the surface (due to the time needed for the surface
30 cooling to propagate into the deeper regions of the sample), the intensity of signal R does not decline until slightly later. Consequently, the signal R does not reach the magnitude 150 until some later time t_R . In other words, there exists a time delay between the time t_P at

which the amplitude of the first reference signal P reaches the checkpoint 150 and the time t_R at which the second reference signal R reaches the same checkpoint 150. This time delay can be expressed as a phase difference $\Phi(\lambda)$. Additionally, a phase difference may be measured between the analytical signal Q and either or both reference signals P, R.

5 As the concentration of analyte increases, the amount of absorbance at the analytical wavelength increases. This reduces the intensity of the analytical signal Q in a concentration-dependent way. Consequently, the analytical signal Q reaches intensity 150 at some intermediate time t_Q . The higher the concentration of analyte, the more the analytical signal Q shifts to the left in FIGURE 8. As a result, with increasing analyte
10 concentration, the phase difference $\Phi(\lambda)$ decreases relative to the first (surface) reference signal P and increases relative to the second (deep tissue) reference signal R. The phase difference(s) $\Phi(\lambda)$ are directly related to analyte concentration and can be used to make accurate determinations of analyte concentration.

The phase difference $\Phi(\lambda)$ between the first (surface) reference signal P and the
15 analytical signal Q is represented by the equation:

$$\Phi(\lambda) = |t_P - t_Q|$$

The magnitude of this phase difference decreases with increasing analyte concentration.

The phase difference $\Phi(\lambda)$ between the second (deep tissue) reference signal R and the analytical signal Q signal is represented by the equation:

20
$$\Phi(\lambda) = |t_Q - t_R|$$

The magnitude of this phase difference increases with increasing analyte concentration.

Accuracy may be enhanced by choosing several checkpoints, for example, 150, 152, 154, 156, and 158 and averaging the phase differences observed at each checkpoint. The accuracy of this method may be further enhanced by integrating the phase difference(s)
25 continuously over the entire test period. Because in this example only a single temperature event (here, a cooling event) has been induced, the sample reaches a new lower equilibrium temperature and the signals stabilize at a new constant level I_F . Of course, the method works equally well with thermal gradients induced by heating or by the application or introduction of other forms of energy, such as but not limited to light, radiation, chemically
30 induced heat, friction and vibration.

This methodology is not limited to the determination of phase difference. At any given time (for example, at a time t_X) the amplitude of the analytical signal Q may be

compared to the amplitude of either or both of the reference signals P, R. The difference in amplitude may be observed and processed to determine analyte concentration.

This method, the variants disclosed herein, and the apparatus disclosed as suitable for application of the method(s), are not limited to the detection of in-vivo glucose concentration. The method and disclosed variants and apparatus may be used on human,
5 animal, or even plant subjects, or on organic or inorganic compositions in a non-medical setting. The method may be used to take measurements of in-vivo or in-vitro samples of virtually any kind. The method is useful for measuring the concentration of a wide range of additional chemical analytes, including but not limited to, glucose, ethanol, insulin,
10 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, hormones, as well as other chemical compounds. To detect a given analyte, one needs only
15 to select appropriate analytical and reference wavelengths.

The method is adaptable and may be used to determine chemical concentrations in samples of body fluids (e.g., blood, urine or saliva) once they have been extracted from a patient. In fact, the method may be used for the measurement of in-vitro samples of virtually any kind.

20 **b. Modulated Thermal Gradient**

In some embodiments of the methodology described above, a periodically modulated thermal gradient can be employed to make accurate determinations of analyte concentration.

As previously shown in FIGURE 8, once a thermal gradient is induced in the
25 sample, the reference and analytical signals P, Q, R fall out of phase with respect to each other. This phase difference $\Phi(\lambda)$ is present whether the thermal gradient is induced through heating or cooling. By alternatively subjecting the test sample to cyclic pattern of heating, cooling, or alternately heating and cooling, an oscillating thermal gradient may be induced in a sample for an extended period of time.

30 An oscillating thermal gradient is illustrated using a sinusoidally modulated gradient. FIGURE 9 depicts detector signals emanating from a test sample. As with the methodology shown in FIGURE 8, one or more reference signals J, L are measured. One or

more analytical signals K are also monitored. These signals may be calibrated and normalized, in the absence of heating or cooling applied to the sample, to a baseline value of 1. FIGURE 9 shows the signals after normalization. At some time t_C , a temperature event (e.g., cooling) is induced at the sample surface. This causes a decline in the detector
5 signal. As shown in FIGURE 8, the signals (P, Q, R) decline until the thermal gradient disappears and a new equilibrium detector signal I_F is reached. In the method shown in FIGURE 9, as the gradient begins to disappear at a signal intensity 160, a heating event, at a time t_W , is induced in the sample surface. As a result the detector output signals J, K, L will rise as the sample temperature rises. At some later time t_{C2} , another cooling event is
10 induced, causing the temperature and detector signals to decline. This cycle of cooling and heating may be repeated over a time interval of arbitrary length. Moreover, if the cooling and heating events are timed properly, a periodically modulated thermal gradient may be induced in the test sample.

As previously explained in the discussions relating to FIGURE 8, the phase
15 difference $\Phi(\lambda)$ may be measured and used to determine analyte concentration. FIGURE 9 shows that the first (surface) reference signal J declines and rises in intensity first. The second (deep tissue) reference signal L declines and rises in a time-delayed manner relative to the first reference signal J. The analytical signal K exhibits a time/phase delay dependent on the analyte concentration. With increasing concentration, the analytical
20 signal K shifts to the left in FIGURE 9. As with FIGURE 8, the phase difference $\Phi(\lambda)$ may be measured. For example, a phase difference $\Phi(\lambda)$ between the second reference signal L and the analytical signal K, may be measured at a set amplitude 162 as shown in FIGURE 9. Again, the magnitude of the phase signal reflects the analyte concentration of the sample.

25 The phase-difference information compiled by any of the methodologies disclosed herein can correlated by the control system 30 (see FIGURE 1) with previously determined phase-difference information to determine the analyte concentration in the sample. This correlation could involve comparison of the phase-difference information received from analysis of the sample, with a data set containing the phase-difference profiles observed
30 from analysis of wide variety of standards of known analyte concentration. In one embodiment, a phase/concentration curve or regression model is established by applying regression techniques to a set of phase-difference data observed in standards of known

analyte concentration. This curve is used to estimate the analyte concentration in a sample based on the phase-difference information received from the sample.

Advantageously, the phase difference $\Phi(\lambda)$ may be measured continuously throughout the test period. The phase-difference measurements may be integrated over the
5 entire test period for an extremely accurate measure of phase difference $\Phi(\lambda)$. Accuracy may also be improved by using more than one reference signal and/or more than one analytical signal.

As an alternative or as a supplement to measuring phase difference(s), differences in amplitude between the analytical and reference signal(s) may be measured and employed to
10 determine analyte concentration. Additional details relating to this technique and not necessary to repeat here may be found in the Assignee's U.S. patent application serial no. 09/538,164, incorporated by reference below.

Additionally, these methods may be advantageously employed to simultaneously measure the concentration of one or more analytes. By choosing reference and analyte
15 wavelengths that do not overlap, phase differences can be simultaneously measured and processed to determine analyte concentrations. Although FIGURE 9 illustrates the method used in conjunction with a sinusoidally modulated thermal gradient, the principle applies to thermal gradients conforming to any periodic function. In more complex cases, analysis using signal processing with Fourier transforms or other techniques allows accurate
20 determinations of phase difference $\Phi(\lambda)$ and analyte concentration.

As shown in FIGURE 10, the magnitude of the phase differences may be determined by measuring the time intervals between the amplitude peaks (or troughs) of the reference signals J, L and the analytical signal K. Alternatively, the time intervals between the "zero crossings" (the point at which the signal amplitude changes from positive to
25 negative, or negative to positive) may be used to determine the phase difference between the analytical signal K and the reference signals J, L. This information is subsequently processed and a determination of analyte concentration may then be made. This particular method has the advantage of not requiring normalized signals.

As a further alternative, two or more driving frequencies may be employed to
30 determine analyte concentrations at selected depths within the sample. A slow (e.g., 1 Hz) driving frequency creates a thermal gradient which penetrates deeper into the sample than the gradient created by a fast (e.g., 3 Hz) driving frequency. This is because the individual

heating and/or cooling events are longer in duration where the driving frequency is lower. Thus, the use of a slow driving frequency provides analyte-concentration information from a deeper "slice" of the sample than does the use of a fast driving frequency.

It has been found that when analyzing a sample of human skin, a temperature event
5 of 10° C creates a thermal gradient which penetrates to a depth of about 150 μm , after about 500 ms of exposure. Consequently, a cooling/heating cycle or driving frequency of 1 Hz provides information to a depth of about 150 μm . It has also been determined that exposure to a temperature event of 10° C for about 167 ms creates a thermal gradient that penetrates to a depth of about 50 μm . Therefore, a cooling/heating cycle of 3 Hz provides information
10 to a depth of about 50 μm . By subtracting the detector signal information measured at a 3 Hz driving frequency from the detector signal information measured at a 1 Hz driving frequency, one can determine the analyte concentration(s) in the region of skin between 50 and 150 μm . Of course, a similar approach can be used to determine analyte concentrations at any desired depth range within any suitable type of sample.

As shown in FIGURE 11, alternating deep and shallow thermal gradients may be induced by alternating slow and fast driving frequencies. As with the methods described above, this variation also involves the detection and measurement of phase differences $\Phi(\lambda)$ between reference signals G, G' and analytical signals H, H'. Phase differences are measured at both fast (e.g., 3 Hz) and slow (e.g., 1 Hz) driving frequencies. The slow
20 driving frequency may continue for an arbitrarily chosen number of cycles (in region SL₁), for example, two full cycles. Then the fast driving frequency is employed for a selected duration, in region F₁. The phase difference data is compiled in the same manner as disclosed above. In addition, the fast frequency (shallow sample) phase difference data may be subtracted from the slow frequency (deep sample) data to provide an accurate
25 determination of analyte concentration in the region of the sample between the gradient penetration depth associated with the fast driving frequency and that associated with the slow driving frequency.

The driving frequencies (e.g., 1 Hz and 3 Hz) can be multiplexed as shown in FIGURE 12. The fast (3 Hz) and slow (1 Hz) driving frequencies can be superimposed
30 rather than sequentially implemented. During analysis, the data can be separated by frequency (using Fourier transform or other techniques) and independent measurements of

phase delay at each of the driving frequencies may be calculated. Once resolved, the two sets of phase delay data are processed to determine absorbance and analyte concentration.

Additional details not necessary to repeat here may be found in U.S. Patent No. 6,198,949, titled SOLID-STATE NON-INVASIVE INFRARED ABSORPTION SPECTROMETER FOR THE GENERATION AND CAPTURE OF THERMAL GRADIENT SPECTRA FROM LIVING TISSUE, issued March 6, 2001; U.S. Patent No. 6,161,028, titled METHOD FOR DETERMINING ANALYTE CONCENTRATION USING PERIODIC TEMPERATURE MODULATION AND PHASE DETECTION, issued December 12, 2000; U.S. Patent No. 5,877,500, titled MULTICHANNEL INFRARED DETECTOR WITH OPTICAL CONCENTRATORS FOR EACH CHANNEL, issued on March 2, 1999; U.S. Patent Application Serial No. 09/538,164, filed March 30, 2000 and titled METHOD AND APPARATUS FOR DETERMINING ANALYTE CONCENTRATION USING PHASE AND MAGNITUDE DETECTION OF A RADIATION TRANSFER FUNCTION; U.S. Provisional Patent Application No. 60/336,404, filed October 29, 2001, titled WINDOW ASSEMBLY; U.S. Provisional Patent Application No. 60/340,435, filed December 12, 2001, titled CONTROL SYSTEM FOR BLOOD CONSTITUENT MONITOR; U.S. Provisional Patent Application No. 60/340,654, filed December 12, 2001, titled SYSTEM AND METHOD FOR CONDUCTING AND DETECTING INFRARED RADIATION; U.S. Provisional Patent Application No. 60/336,294, filed October 29, 2001, titled METHOD AND DEVICE FOR INCREASING ACCURACY OF BLOOD CONSTITUENT MEASUREMENT; and U.S. Provisional Patent Application No. 60/339,116, filed November 7, 2001, titled METHOD AND APPARATUS FOR IMPROVING CLINICALLY SIGNIFICANT ACCURACY OF ANALYTE MEASUREMENTS. The entire disclosure of all of the above-mentioned patents, patent applications and publications is hereby incorporated by reference herein and made a part of this specification.

B. Whole-Blood Detection System

FIGURE 13 is a schematic view of a reagentless whole-blood analyte detection system 200 (hereinafter "whole-blood system") in a preferred configuration. The whole-blood system 200 may comprise a radiation source 220, a filter 230, a cuvette 240 that includes a sample cell 242, and a radiation detector 250. The whole-blood system 200 preferably also comprises a signal processor 260 and a display 270. Although a cuvette 240

is shown here, other sample elements, as described below, could also be used in the system 200. The whole-blood system 200 can also comprise a sample extractor 280, which can be used to access bodily fluid from an appendage, such as the finger 290, forearm, or any other suitable location.

5 As used herein, the terms “whole-blood analyte detection system” and “whole-blood system” are broad, synonymous terms and are used in their ordinary sense and refer, without limitation, to analyte detection devices which can determine the concentration of an analyte in a material sample by passing electromagnetic radiation into the sample and detecting the absorbance of the radiation by the sample. As used herein, the term “whole-
10 blood” is a broad term and is used in its ordinary sense and refers, without limitation, to blood that has been withdrawn from a patient but that has not been otherwise processed, e.g., it has not been hemolysed, lyophilized, centrifuged, or separated in any other manner, after being removed from the patient. Whole-blood may contain amounts of other fluids, such as interstitial fluid or intracellular fluid, which may enter the sample during the
15 withdrawal process or are naturally present in the blood. It should be understood, however, that the whole-blood system 200 disclosed herein is not limited to analysis of whole-blood, as the whole-blood system 10 may be employed to analyze other substances, such as saliva, urine, sweat, interstitial fluid, intracellular fluid, hemolysed, lyophilized, or centrifuged blood or any other organic or inorganic materials.

20 The whole-blood system 200 may comprise a near-patient testing system. As used herein, “near-patient testing system” is a broad term and 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
25 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.

 The whole-blood system 200 may in one embodiment be configured to be operated easily by the patient or user. As such, the system 200 is preferably a portable device. As used herein, “portable” is a broad term and is used in its ordinary sense and means, without
30 limitation, that the system 200 can be easily transported by the patient and used where convenient. For example, the system 200 is advantageously small. In one preferred embodiment, the system 200 is small enough to fit into a purse or backpack. In another

embodiment, the system 200 is small enough to fit into a pants pocket. In still another embodiment, the system 200 is small enough to be held in the palm of a hand of the user.

Some of the embodiments described herein employ a sample element to hold a material sample, such as a sample of biological fluid. As used herein, "sample element" is
5 a broad term and is used in its ordinary sense and includes, without limitation, structures that have a sample cell and at least one sample cell 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. As used herein, the term "disposable" when applied to a
10 component, such as a sample element, is a broad term and is used in its ordinary sense and means, without limitation, that the component in question is used a finite number of times and then discarded. Some disposable components are used only once and then discarded. Other disposable components are used more than once and then discarded.

The radiation source 220 of the whole-blood system 200 emits electro-magnetic
15 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 whole-blood system 200 may employ a radiation source 220 which emits in wavelengths found anywhere from the visible spectrum through the microwave spectrum, for example
20 anywhere from about 0.4 μm to greater than about 100 μm . In still further embodiments the radiation source emits 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 about 20 μm , or between about 20 μm and about 100 μm , or between about 6.85 μm and about 10.10 μm .

25 The radiation emitted from the source 220 is in one embodiment modulated at a frequency between about one-half hertz and about one hundred hertz, in another embodiment between about 2.5 hertz and about 7.5 hertz, in still another embodiment at about 50 hertz, and in yet another embodiment at about 5 hertz. With a modulated radiation source, ambient light sources, such as a flickering fluorescent lamp, can be more easily
30 identified and rejected when analyzing the radiation incident on the detector 250. One source that is suitable for this application is produced by ION OPTICS, INC. and sold under the part number NL5LNC.

The filter 230 permits electromagnetic radiation of selected wavelengths to pass through and impinge upon the cuvette/sample element 240. Preferably, the filter 230 permits radiation at least at about the following wavelengths to pass through to the cuvette/sample element: 3.9, 4.0 μm , 4.05 μm , 4.2 μm , 4.75, 4.95 μm , 5.25 μm , 6.12 μm , 7.4 μm , 8.0 μm , 8.45 μm , 9.25 μm , 9.5 μm , 9.65 μm , 10.4 μm , 12.2 μm . In another embodiment, the filter 230 permits radiation at least at about the following wavelengths to pass through to the cuvette/sample element: 5.25 μm , 6.12 μm , 6.8 μm , 8.03 μm , 8.45 μm , 9.25 μm , 9.65 μm , 10.4 μm , 12 μm . In still another embodiment, the filter 230 permits radiation at least at about the following wavelengths to pass through to the cuvette/sample element: 6.85 μm , 6.97 μm , 7.39 μm , 8.23 μm , 8.62 μm , 9.02 μm , 9.22 μm , 9.43 μm , 9.62 μm , and 10.10 μm . The sets of wavelengths recited above correspond to specific embodiments within the scope of this disclosure. Furthermore, other subsets of the foregoing sets or other combinations of wavelengths can be selected. Finally, other sets of wavelengths can be selected within the scope of this disclosure based on cost of production, development time, availability, and other factors relating to cost, manufacturability, and time to market of the filters used to generate the selected wavelengths, and/or to reduce the total number of filters needed.

In one embodiment, the filter 230 is capable of cycling its passband among a variety of narrow spectral bands or a variety of selected wavelengths. The filter 230 may thus comprise a solid-state tunable infrared filter, such as that available from ION OPTICS INC. The filter 230 could also be implemented as a filter wheel with a plurality of fixed-passband filters mounted on the wheel, generally perpendicular to the direction of the radiation emitted by the source 220. Rotation of the filter wheel alternately presents filters that pass radiation at wavelengths that vary in accordance with the filters as they pass through the field of view of the detector 250.

The detector 250 preferably comprises a 3 mm long by 3 mm wide pyroelectric detector. Suitable examples are produced by DIAS Angewandte Sensorik GmbH of Dresden, Germany, or by BAE Systems (such as its TGS model detector). The detector 250 could alternatively comprise a thermopile, a bolometer, a silicon microbolometer, a lead-salt focal plane array, or a mercury-cadmium-telluride (MCT) detector. Whichever structure is used as the detector 250, it is desirably configured to respond to the radiation

incident upon its active surface 254 to produce electrical signals that correspond to the incident radiation.

In one embodiment, the sample element comprises a cuvette 240 which in turn comprises a sample cell 242 configured to hold a sample of tissue and/or fluid (such as whole-blood, blood components, interstitial fluid, intercellular fluid, saliva, urine, sweat and/or other organic or inorganic materials) from a patient within its sample cell. The cuvette 240 is installed in the whole-blood system 200 with the sample cell 242 located at least partially in the optical path 243 between the radiation source 220 and the detector 250. Thus, when radiation is emitted from the source 220 through the filter 230 and the sample cell 242 of the cuvette 240, the detector 250 detects the radiation signal strength at the wavelength(s) of interest. Based on this signal strength, the signal processor 260 determines the degree to which the sample in the cell 242 absorbs radiation at the detected wavelength(s). The concentration of the analyte of interest is then determined from the absorption data via any suitable spectroscopic technique.

As shown in FIGURE 13, the whole-blood system 200 can also comprise a sample extractor 280. As used herein, the term "sample extractor" is a broad term and is used in its ordinary sense and refers, without limitation, to any device which is suitable for drawing a sample material, such as whole-blood, other bodily fluids, or any other sample material, through the skin of a patient. In various embodiments, the sample extractor may comprise a lance, laser lance, iontophoretic sampler, gas-jet, fluid-jet or particle-jet perforator, ultrasonic enhancer (used with or without a chemical enhancer), or any other suitable device.

As shown in FIGURE 13, the sample extractor 280 could form an opening in an appendage, such as the finger 290, to make whole-blood available to the cuvette 240. It should be understood that other appendages could be used to draw the sample, including but not limited to the forearm. With some embodiments of the sample extractor 280, the user forms a tiny hole or slice through the skin, through which flows a sample of bodily fluid such as whole-blood. Where the sample extractor 280 comprises a lance (see FIGURE 14), the sample extractor 280 may comprise a sharp cutting implement made of metal or other rigid materials. One suitable laser lance is the Lasette Plus® produced by Cell Robotics International, Inc. of Albuquerque, New Mexico. If a laser lance, iontophoretic sampler, gas-jet or fluid-jet perforator is used as the sample extractor 280, it

could be incorporated into the whole-blood system 200 (see FIGURE 13), or it could be a separate device.

Additional information on laser lances can be found in U.S. Patent No. 5,908,416, issued June 1, 1999, titled LASER DERMAL PERFORATOR; the entirety of this patent is hereby incorporated by reference herein and made a part of this specification. One suitable gas-jet, fluid-jet or particle-jet perforator is disclosed in U.S. Patent No. 6,207,400, issued March 27, 2001, titled NON- OR MINIMALLY INVASIVE MONITORING METHODS USING PARTICLE DELIVERY METHODS; the entirety of this patent is hereby incorporated by reference herein and made a part of this specification. One suitable iontophoretic sampler is disclosed in U.S. Patent No. 6,298,254, issued October 2, 2001, titled DEVICE FOR SAMPLING SUBSTANCES USING ALTERNATING POLARITY OF IONTOPHORETIC CURRENT; the entirety of this patent is hereby incorporated by reference herein and made a part of this specification. One suitable ultrasonic enhancer, and chemical enhancers suitable for use therewith, are disclosed in U.S. Patent No. 5,458,140, titled ENHANCEMENT OF TRANSDERMAL MONITORING APPLICATIONS WITH ULTRASOUND AND CHEMICAL ENHANCERS, issued October 17, 1995, the entire disclosure of which is hereby incorporated by reference and made a part of this specification.

FIGURE 14 shows one embodiment of a sample element, in the form of a cuvette 240, in greater detail. The cuvette 240 further comprises a sample supply passage 248, a pierceable portion 249, a first window 244, and a second window 246, with the sample cell 242 extending between the windows 244, 246. In one embodiment, the cuvette 240 does not have a second window 246. The first window 244 (or second window 246) is one form of a sample cell wall; in other embodiments of the sample elements and cuvettes disclosed herein, any sample cell wall may be used that at least partially contains, holds or supports a material sample, such as a biological fluid sample, and which is transmissive of at least some bands of electromagnetic radiation, and which may but need not be transmissive of electromagnetic radiation in the visible range. The pierceable portion 249 is an area of the sample supply passage 248 that can be pierced by suitable embodiments of the sample extractor 280. Suitable embodiments of the sample extractor 280 can pierce the portion 249 and the appendage 290 to create a wound in the appendage 290 and to provide an inlet for the blood or other fluid from the wound to enter the cuvette 240. (The sample extractor

280 is shown on the opposite side of the sample element in FIGURE 14, as compared to FIGURE 13, as it may pierce the portion 249 from either side.)

5 The windows 244, 246 are preferably optically transmissive in the range of electromagnetic radiation that is emitted by the source 220, or that is permitted to pass through the filter 230. In one embodiment, the material that makes up the windows 244, 246 is completely transmissive, i.e., it does not absorb any of the electromagnetic radiation from the source 220 and filter 230 that is incident upon it. In another embodiment, the material of the windows 244, 246 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 windows 244, 246 is not negligible, but it is known and stable for a relatively long period of time. In another embodiment, the absorption of the windows 244, 246 is stable for only a relatively short period of time, but the whole-blood system 200 is configured to observe the absorption of the material and eliminate it from the analyte measurement before the material properties can change measurably.

15 The windows 244, 246 are made of polypropylene in one embodiment. In another embodiment, the windows 244, 246 are made of polyethylene. Polyethylene and polypropylene are materials having particularly advantageous properties for handling and manufacturing, as is known in the art. Also, polypropylene can be arranged in a number of structures, e.g., isotactic, atactic and syndiotactic, which may enhance the flow characteristics of the sample in the sample element. Preferably the windows 244, 246 are made of durable and easily manufactureable materials, such as the above-mentioned polypropylene or polyethylene, or silicon or any other suitable material. The windows 244, 246 can be made of any suitable polymer, which can be isotactic, atactic or syndiotactic in structure.

25 The distance between the windows 244, 246 comprises an optical pathlength and can be between about 1 μm and about 100 μm . In one embodiment, the optical pathlength is between about 10 μm and about 40 μm , or between about 25 μm and about 60 μm , or between about 30 μm and about 50 μm . In still another embodiment, the optical pathlength is about 25 μm . The transverse size of each of the windows 244, 246 is preferably about equal to the size of the detector 250. In one embodiment, the windows are round with a diameter of about 3 mm. In this embodiment, where the optical pathlength is about 25 μm the volume of the sample cell 242 is about 0.177 μL . In one embodiment, the length of the

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sample supply passage 248 is about 6 mm, the height of the sample supply passage 248 is about 1 mm, and the thickness of the sample supply passage 248 is about equal to the thickness of the sample cell, e.g., 25 μm . The volume of the sample supply passage is about 0.150 μL . Thus, the total volume of the cuvette 240 in one embodiment is about
5 0.327 μL . Of course, the volume of the cuvette 240/sample cell 242/etc. can vary, depending on many variables, such as the size and sensitivity of the detectors 250, the intensity of the radiation emitted by the source 220, the expected flow properties of the sample, and whether flow enhancers (discussed below) are incorporated into the cuvette 240. The transport of fluid to the sample cell 242 is achieved preferably through capillary
10 action, but may also be achieved through wicking, or a combination of wicking and capillary action.

FIGURES 15-17 depict another embodiment of a cuvette 305 that could be used in connection with the whole-blood system 200. The cuvette 305 comprises a sample cell 310, a sample supply passage 315, an air vent passage 320, and a vent 325. As best seen in
15 FIGURES 16,16A and 17, the cuvette also comprises a first sample cell window 330 having an inner side 332, and a second sample cell window 335 having an inner side 337. As discussed above, the window(s) 330/335 in some embodiments also comprise sample cell wall(s). The cuvette 305 also comprises an opening 317 at the end of the sample supply passage 315 opposite the sample cell 310. The cuvette 305 is preferably about 1/4 -
20 1/8 inch wide and about 3/4 inch long; however, other dimensions are possible while still achieving the advantages of the cuvette 305.

The sample cell 310 is defined between the inner side 332 of the first sample cell window 330 and the inner side 337 of the second sample cell window 335. The perpendicular distance T between the two inner sides 332, 337 comprises an optical
25 pathlength that can be between about 1 μm and about 1.22 mm. The optical pathlength can alternatively be between about 1 μm and about 100 μm . The optical pathlength could still alternatively be about 80 μm , but is preferably between about 10 μm and about 50 μm . In another embodiment, the optical pathlength is about 25 μm . The windows 330, 335 are preferably formed from any of the materials discussed above as possessing sufficient
30 radiation transmissivity. The thickness of each window is preferably as small as possible without overly weakening the sample cell 310 or cuvette 305.

Once a wound is made in the appendage 290, the opening 317 of the sample supply passage 315 of the cuvette 305 is placed in contact with the fluid that flows from the wound. In another embodiment, the sample is obtained without creating a wound, e.g. as is done with a saliva sample. In that case, the opening 317 of the sample supply passage 315 of the cuvette 305 is placed in contact with the fluid obtained without creating a wound. The fluid is then transported through the sample supply passage 315 and into the sample cell 310 via capillary action. The air vent passage 320 improves the capillary action by preventing the buildup of air pressure within the cuvette and allowing the blood to displace the air as the blood flows therein.

Other mechanisms may be employed to transport the sample to the sample cell 310. For example, wicking could be used by providing a wicking material in at least a portion of the sample supply passage 315. In another variation, wicking and capillary action could be used together to transport the sample to the sample cell 310. Membranes could also be positioned within the sample supply passage 315 to move the blood while at the same time filtering out components that might complicate the optical measurement performed by the whole-blood system 200.

FIGURES 16 and 16A depict one approach to constructing the cuvette 305. In this approach, the cuvette 305 comprises a first layer 350, a second layer 355, and a third layer 360. The second layer 355 is positioned between the first layer 350 and the third layer 360. The first layer 350 forms the first sample cell window 330 and the vent 325. As mentioned above, the vent 325 provides an escape for the air that is in the sample cell 310. While the vent 325 is shown on the first layer 350, it could also be positioned on the third layer 360, or could be a cutout in the second layer, and would then be located between the first layer 360 and the third layer 360. The third layer 360 forms the second sample cell window 335.

The second layer 355 may be formed entirely of an adhesive that joins the first and third layers 350, 360. In other embodiments, the second layer may be formed from similar materials as the first and third layers, or any other suitable material. The second layer 355 may also be formed as a carrier with an adhesive deposited on both sides thereof. The second layer 355 forms the sample supply passage 315, the air vent passage 320, and the sample cell 310. The thickness of the second layer 355 can be between about 1 μm and about 1.22 mm. This thickness can alternatively be between about 1 μm and about 100 μm .

This thickness could alternatively be about 80 μm , but is preferably between about 10 μm and about 50 μm . In another embodiment, the second layer thickness is about 25 μm .

In other embodiments, the second layer 355 can be constructed as an adhesive film having a cutout portion to define the passages 315, 320, or as a cutout surrounded by adhesive.

Further information can be found in U.S. Patent Application No. 10/055,875, filed January 21, 2002, titled REAGENT-LESS WHOLE-BLOOD GLUCOSE METER. The entire contents of this patent application are hereby incorporated by reference herein and made a part of this specification.

II. ANALYTE MONITORING INSTRUMENT HAVING NETWORK CONNECTIVITY

Referring to FIGURE 18, an analyte detection system 500 is shown connected to remote stations 524, 528 over a network 520, which may comprise one or more wireless or hardwired links, or a combination of wireless and hardwired links, and/or the Internet. In the illustrated embodiment, the analyte detection system 500 comprises the noninvasive system 10 described above. In other embodiments, the analyte detection system may comprise any other suitable noninvasive system such as (but not limited to) those described in U.S. Patents Nos. 5,900,632 to Sterling et al. and 5,615,972 to Braig et al., the entirety of each of which is hereby incorporated by reference herein and made a part of this specification. In still other embodiments, the analyte detection system 500 may comprise any suitable invasive system such as (but not limited to) the whole-blood system 200 disclosed above.

Because the noninvasive system 10 is depicted in the embodiment of FIGURE 18, the hand and forearm 512 of a patient is shown positioned to allow a measurement to be performed by an analyte detector element 514 of the analyte detection system 500. The analyte detection system 500 includes a signal processing system 516 which collects the measurements and/or other suitable information from the detector element 514 and processes the data into a set of results. In the illustrated embodiment, the analyte detection system 500 includes input and output devices, such as a display and a set of control inputs (not shown) for communicating information directly to and from the patient. The signal processing system 516 is equipped with a network interface 517 along with one or more

processing elements 519 for processing the measurement signals and for control of network communications.

Data is communicated over the network 520 as determined by the configuration of the system 500 and the state and condition of the measurement being performed.

5 Measurement data may accordingly be communicated to the remote station(s) 524, 528 at the time the measurement is performed, or it may be retained within the system 500 and sent to the remote station(s) according to a schedule or other selection criterion. The system 500 and/or remote station(s) 524, 284 may be capable of comparing each measurement with a set of limits and providing alerts to a supervisory authority regarding
10 excursions therefrom.

In FIGURE 18 the measurement data is shown passing through a connection 518 to the network 520, and from there through another connection 522 to a centralized monitoring computer 524 or to a server. The centralized computer 524 may be capable of checking the data for emergency conditions and logging the data for later use. In addition,
15 the centralized computer 524 may monitor the status of the system(s) 500 for proper operation and calibration. It will be appreciated that multiple centralized computers 524 or servers can be provided for communicating with the system(s) 500. In one embodiment, the network interface 517 is a wireless interface (and the connection 518 is a wireless connection), such as but not limited to a Bluetooth interface, an IEEE 802.11(b) interface or
20 a cellular interface, implemented through appropriate hardware built into the system 500.

Furthermore, the centralized computer 524 may simultaneously transfer or route the data (e.g., measurements, system status, etc.) via connection 526 to a computer 528 in the office of a medical practitioner over the network 520. Instead of or in addition to the medical practitioner computer 528, the network may include connections to a computer
25 528' located at the manufacturer of the analyte detection system 500, to a computer 528'' located at the patient's home, and/or to a computer 528''' located at the home or place of business of a parent of the patient. Alternatively, the data may be directly sent over the network 520 to the medical practitioner 528/manufacturur 528'/patient's home 528''/patient's parent 528''' from the signal processing system 516; in this instance the
30 centralized computer 524 is not necessary and may be omitted from the network 520. Where the centralized computer 524 is omitted, any of the computer(s) 528/528'/528''/528''' (hereinafter, collectively "528") may be capable of checking the data

received from the system 500 for emergency conditions, logging the data for later use, and/or monitoring the status of the system 500 for proper operation and calibration. It will be appreciated that the foregoing data routing is provided as an example, and not as a limitation, of the data routing utilized to provide the network services in support of a patient's use of the system 500.

In one embodiment, the system 500 includes a panic button 530 which permits the patient to alert a medical practitioner should an important concern arise. In addition, sound and/or visual output may be provided by the system 500 for signaling the patient when the time arrives to perform a measurement, or of a directive from a supervisory authority as received over the network 520.

In another embodiment, the system 500 includes a location button 531 which permits the patient to signal his or her location (as well as the location of the system 500) to any of the remote station(s) 524, 528. When so signaled, a remote user at a remote station 524/528 can direct emergency assistance to the location of the patient/system, should the remote user discover that the patient's condition merits immediate medical attention. In one embodiment, the location information is generated via GPS (Global Positioning System) equipment built into the system 500 and accessible by the processing element(s) 519. In another embodiment, the system 500 continually, intermittently or otherwise automatically transmits its location to any or all of the remote station(s) 524, 528, and the location button 531 may be omitted. In still another embodiment, the system 500 is configured to transmit its location to remote station(s) 524, 528 in response to a query sent from the remote station(s) to the system 500.

In another embodiment, the GPS equipment is supplemented by storage, within appropriate memory accessible by the processing element(s) 519 and/or the GPS equipment, of favorite locations frequented by the patient. Examples of favorite locations include Home, Work, School, etc. and/or a widely recognizable expression thereof, such as the associated street address, nearest cross streets, ZIP or postal code, and/or longitude and latitude. The purpose of such storage is to counteract the tendency of GPS equipment to lose contact with the GPS satellite(s) when the GPS device in question is located inside of a building or other large structure.

Accordingly, when the system 500 loses contact with the GPS satellite(s) and a need arises, under any of the circumstances discussed herein, to transmit the location of the

patient/system to a remote user, the system 500 recognizes the loss of contact with the GPS satellite(s) and selects for transmission one of the patient's favorite locations based on the last GPS-computed position of the user/system prior to loss of contact with the GPS satellite(s). In one embodiment, the system 500 selects and transmits whichever favorite
5 location is nearest the last GPS-computed position of the system 500. In another embodiment, the system 500 selects and transmits this nearest favorite location only when the nearest favorite location is within a given minimum distance (e.g., 10 miles, 5 miles, 1 mile, 0.5 miles) from the last GPS-computed position of the system 500. In still another embodiment, the system 500 displays a list of the patient's stored favorite locations on a
10 suitable display, and the patient can select, using an appropriate input device (keypad, button, touchscreen, mouse, voice recognition system, etc.) built into or connected to the system 500, his or her present location from a list of favorites and prompt the system 500 to transmit the selected location.

Any of the location-transmission processes discussed above may be implemented in
15 an algorithm or program instructions executable by, and residing within memory accessible by, the processing element(s) 519 of the system 500 (in particular, by the signal processor 74/260 where the system 500 comprises the noninvasive system 10 or the whole-blood system 200, respectively).

In any of the embodiments discussed herein, the system 500 and/or one or more of
20 the remote station(s) 524, 528 may be configured to encrypt any or all of the data that it transmits over the network 520. Where the user of any of the system 500 and the remote station(s) 524, 528 (or the system/remote station itself) is authorized to receive, read and/or otherwise use the encrypted data, the recipient system 500/remote station 524, 528 is configured to decrypt the encrypted data, to make the data available to the device and/or the
25 user thereof. By encrypting the data, physician-patient confidentiality, or any physician-patient privilege may be preserved, preventing unauthorized reading or use of the data. Encryption also permits transmission of data over wireless networks or public networks such as the Internet while preserving confidentiality of the transmitted data.

It is contemplated that the encryption and decryption may be performed in any
30 suitable manner, with any suitable methods, software and/or hardware presently known or hereafter developed. In the system 500, the encryption and/or decryption processes may be implemented in an algorithm or program instructions executable by, and residing within

memory accessible by, the processing element(s) 519 of the system 500 (in particular, by the signal processor 74/260 where the system 500 comprises the noninvasive system 10 or the whole-blood system 200, respectively). In the remote station(s) 524, 528, the encryption and/or decryption processes may be implemented in an algorithm or program
5 instructions executable by, and residing within memory accessible by, processing element(s) (not shown) of the remote station 524/528 in question.

The connection of the system 500 to the network 520, provides either a direct or indirect link from the patient to the practitioner. The practitioner is thereby accorded an ability to monitor the status of the patient and may elect to be alerted should deviations in
10 the measurement values the or timeliness thereof arise. The system may be configured to transmit measurement data at predetermined intervals, or at the time each measurement is performed. The measurements can be transmitted using various network protocols which include standard internet protocols, encrypted protocols, or email protocols.

In one embodiment, the signal processing system 516 is additionally capable of
15 providing visual or audible cues to the patient when the time arrives to conduct a measurement. These alerts may be augmented by requests, transmitted over the network 520 to the instrument, from the practitioner. Errors introduced within measurements and recordation within a manual system can thereby be eliminated with the electronically logged measurements. It will be appreciated that the system provides enhanced utility and
20 measurement credibility in comparison to the use of an instrument that requires manual logging of the measurements and permits no practitioner interaction therewith.

Secretive non-compliance may also be eliminated as the patient is not conferred the responsibility of manually logging measurements. In using the system 500, the measurements collected within the instrument by the patient are capable of being
25 transmitted to a practitioner, or a centralized computer, such that if a patient is not being diligent in conducting measurements, the practitioner may immediately contact the patient to reinforce the need for compliance. In addition, the information provided over the network can be used to warn the practitioner when measurement readings appear abnormal, so that the practitioner may then investigate the situation and verify the status of the patient.

30 It will be appreciated that the invention has particular utility for patients preferring to receive direct guidance from a practitioner. The information that flows between the

patient and the practitioner increases the ability of the practitioner to provide knowledgeable patient guidance.

FIGURE 19 illustrates the functional blocks of an embodiment of circuitry 532 for implementing the signal processing hardware 516 shown in FIGURE 18. A network connection 534 connects to a network processing circuit, exemplified by an Internet Protocol (IP) circuit or processor 536. Numerous circuits are available for providing internet connectivity, such as the SX-Stack™ chip from Scenix Semiconductor, and the iChip™ from Connect One Electronics. These integrated circuit chips and other available chips provide interface layers for supporting a Transmission Control Protocol/Internet Protocol (TCP/IP). The internet protocol chip 536 has an interface 538 with a control processor section 540, which preferably comprises a microcontroller or the like. The control processor section 540 in turn has access to conventional memory 542. To provide security and fault tolerance of the instrument it is preferable for the control processor, or the internet protocol circuit, to encrypt and provide verification strings or tokens within the data being sent across the network, and accordingly to decrypt information being received and verify the received strings or tokens. The control processor 540 has an interface 544 with the instrumentation circuits 546, which is in turn configured with an interface 548 to the analyte detection element 514 shown in FIGURE 18.

The network link provides a mechanism to facilitate performing and recording analyte measurements under supervision, while it additionally provides for periodic instrument calibration, and the ability to assure both measurement and calibration compliance. Calibration data can be communicated from systems 500 in the field to the system manufacturer, or a service organization, so that the systems 500 and their calibrations may be logged. The disclosed network link can be utilized to provide various mechanisms for assuring calibration compliance. Generally the mechanisms are of two categories, those that provide information or a warning about calibration, and those that prevent use of an instrument which is out of calibration. In one embodiment, systems 500 which have exceeded their calibration interval, or schedule, are to be locked out from further use until recalibration is performed. For example, the system 500 may be set to operate for thirteen months for a given calibration interval of twelve months. The system 500 may issue warnings prior to the expiration of calibration, and warnings of increased severity after the expiration of the calibration interval. If the system 500, however, is not

properly calibrated by the end of the thirteen months, normal operation ceases, thereby locking out the user after providing an appropriate error message in regard to the expired calibration. Upon recalibration, the calibrated operation interval is restored to provide for another thirteen month period of calibrated operation.

5 Alternatively, or in addition thereto, a "lockout command" can be sent to the system 500 over the network 520 from the manufacturer, practitioner or system maintenance organization, thereby engaging a lockout mode of the system 500, so that operation may not be continued until the system 500 has been serviced. The lockout command could also be sent in the event that the patient has not paid his or her bills, or be sent under other
10 circumstances warranting lockout of the system 500.

 Another mode is that of locking out normal system use after the expiration of calibration, and allowing limited use thereafter only after a code, or token, has been downloaded from a supervisory site. Although many variations are possible, the code could for instance be provided when a calibration appointment is made for the system 500. To
15 provide continued service and minimize cost, the patient may be allowed to perform calibration checks of the system 500. The patient is supplied with a small set of analyte calibration standards which are read by the system 500 once it is put into a calibration mode and preferably connected to a remote site for supervising the process. Should the calibration check pass, wherein the instrument readings fall within normal levels, or be
20 capable of being automatically adjusted thereto, the calibration interval may be extended. Failure of the calibration check would typically necessitate returning the system 500 for service.

 FIGURE 20 illustrates an embodiment of a process 550 for assuring calibration compliance within the analyte detection system 500 by utilizing a lockout mechanism. The
25 programmed instructions associated with the analyte detection system 500 are started at block 552 and initialized at block 554, and a check is made on a lockout flag at block 556 to determine if it was set during a prior session by a command received via the network 520, or due to being out of calibration. Not having been locked out from a prior session, the real-time clock (RTC) of the system 500 is read at block 558 and a calculation is
30 performed at block 560 comparing the current date with the stored calibration date and calibration interval. If upon checking calibration at block 562 the calibration interval has not yet expired, then a calculation is performed at block 564 comparing the current date

with the stored calibration date and near-calibration interval. Near-calibration is checked at block 566 and, if calibration is to expire soon, then a user warning is issued at block 568, preferably informing the user of the date of the upcoming expiration of the calibration interval. The lockout flag is cleared at block 570 and processing within the system 500 continues with normal instrument functions being accessible at block 572, along with calibration and other limited functions at block 574, until the user shuts down the instrument and processing ends at block 576. If the lockout flag was set from a prior instrument operation, or the calibration interval was exceeded, then a lockout flag would be set at block 578, and the instrument functionality would thereby be restricted to execution of the calibration procedures and other limited functions at block 578 while the normal instrument functionality would not be accessible. The calibration procedure itself may be augmented and improved by providing interaction between the servicing party and the manufacturer, such interaction may include providing guidance information to the servicing party, and the collection of measurement information by the manufacturer.

It will be appreciated that the present invention provides functionality beyond that which can be provided by a stand-alone analyte detection system, as the practitioner, or practitioner's office, is involved in the analyte measurement process to confer a portion of the benefits normally associated with an office visit. The aforesaid description illustrates how these features provide the capability for two-way data flow which facilitates the conducting and recording of correct measurements while encouraging compliance in regard to both measurements and instrument calibration. Furthermore, the data collected by the system may be utilized by others in addition to the practitioner, such as pharmaceutical companies which may be provided data access to alter or administer medication programs, and insurance companies which may require data regarding patient diligence according to the specified treatment program.

III. SOFTWARE DOWNLOAD CAPABILITIES

FIGURE 21 illustrates one embodiment of a software update system 600. The software update system 600 includes an analyte detection system 602 that is connectable to a centralized computer 604 via a network 606. The analyte detection system 602 may comprise a portable, near-patient device that is capable of optically measuring analytes in a material sample. Other examples of the analyte measuring device 602 include, but not limited to, the noninvasive system 10 discussed in this disclosure, the whole-blood system

200 discussed in this disclosure, or any other suitable invasive or noninvasive analyte detection system.

As used herein, the term "computer" is a broad term and is used in its ordinary sense and refers, without limitation, to any programmable electronic device that can store, retrieve and process data. Examples of computers include terminal devices, such as personal computers, workstations, servers, mini computers, main-frame computers, laptop computers, a network of individual computers, mobile computers, palm top computers, hand held computers, set top for a TV, an interactive television, an interactive kiosk, a personal digital assistant ("PDA"), an interactive wireless communications device, or a combination thereof. The computers may further possess storage devices, input devices such as a keyboard, mouse or scanner, and output devices such as a computer screen or a speaker. Furthermore, the computers may serve as clients, servers, or a combination thereof.

As used herein, the term "network" is a broad term and is used in its ordinary sense and refers, without limitation, to a series of points or nodes interconnected by communication paths, such as a group of interconnected computers. Examples of networks are the Internet, storage networks, local area networks and wide area networks.

Further to FIGURE 21, the analyte detection system 602 includes a network interface 608, a processor 610 and software 612. The centralized computer 604 includes at least one software update 614. In one embodiment, when the analyte measuring device 602 is connected to the network 606, the analyte detection system 602 and the centralized computer 604 are in two-way communication. Consequently, the analyte detection system 602 may send information (e.g., analyte measurements) to the centralized computer 604 and the centralized computer 604 may send information (e.g., a software update 614) to the analyte measuring device 602. Other architectures of networked systems, as known by those skilled in the art, may also be used in place of the architecture set forth in FIGURE 21. For example, the architecture shown in FIGURE 18, and/or any of the variants thereof discussed above in connection with FIGURE 18. may be used instead of the system 600 shown in FIGURE 21. For example, one or more of the computers 528/528'/528''/528''' may share the herein-described functions of, or replace entirely, the centralized computer 604, in which case the centralized computer 604 may be omitted.

As used herein, the term “processor” is a broad term and is used in its ordinary sense and refers, without limitation, to the part of a computer that operates on data. Examples of processors are central processing units (“CPU”) and microprocessors.

As used herein, the term “software” is a broad term and is used in its ordinary sense and refers, without limitation, to instructions executable by a computer or related device. Examples of software include computer programs and operating systems.

As used herein, the term “software update” or “update” is a broad term and is used in its ordinary sense and refers, without limitation, to information used by a computer to modify software. A software update may be, for example, data, algorithms or programs.

A process flow diagram of a preferred software update process 700 is shown in FIGURE 22. First, in an act 702, a user performs analyte measurements with the analyte detection system 602. Advantageously, as discussed above, the user may perform analyte measurements using the analyte detection system 602 at a remote location (e.g., the user’s home).

Further to the act 702, the analyte detection system 602 detects analytes in a material sample and calculates an analyte concentration in accordance to the analyte detection system’s software 612. Additionally, the analyte detection system may issue alerts to the user, for example, in response to exceeded tolerances defined in the software 612. The alerts may be visually displayed to the user and/or audibly sounded to the user. For instance, the analyte detection system 602 may issue an alert in response to an elapsed calibration time tolerance defined in the software 612. Other alerts may be issued when the software or analyte-concentration calculation algorithm is out of date, or when the analyte concentration readings made by the detection system 602 are higher or lower than defined safe limits or ranges.

In one embodiment, the software 612 is contained in the analyte detection system 602 internally. In another embodiment, the software 612 is retained external to the analyte detection system 602.

Next, in an act 704, the analyte detection system 602 is connected to the centralized computer 604 via the network 606. Advantageously, the network interface 608 readily connects the analyte detection system 602 to the network 606. Furthermore, once the analyte measuring device 602 is connected to the network 606, the analyte measuring device 602 is, in one embodiment, in two-way communication with the centralized

computer 604. In one embodiment, the communication between the analyte measuring device 602 and the centralized computer 604 is established without any intervention from a user.

The process 700 then proceeds to a decision act 706 where the centralized computer 604 determines an update status for the analyte measuring device's software 612. Various conditions may trigger the centralized computer 604 to update the software 612. In one embodiment, a condition for updating the software 612 is the presence of a new drug in the material sample (e.g., a new drug taken by the user) that alters the analyte calculations. Specifically, the centralized computer 604 determines whether the software 612 currently in use accounts for the use of the new drug. If the current software does not account for the new drug, the centralized computer 604 sends a software update 614 over the network 706 that does account for the new drug, and as a result, corrects future analyte calculations performed by the analyte measuring device 602. In another embodiment, a condition for updating the software 612 is where a new analyte-detection algorithm is developed. For example, the new algorithm may improve the accuracy or speed of the analyte detection system 602 over the software 612 currently in use. In another embodiment, a condition for updating the software 612 is where the analyte detection system 602 should display a new warning or where the monitoring device should display an existing warning in response to new or different events. The existing warning or the new warning may be displayed, for instance, in response to new information learned from a subset of a customer population. Advantageously, other conditions not specifically mentioned herein may also trigger the centralized computer 604 to update the software 612.

If the centralized computer 604 decides that the software 612 does not need to be updated in the decision act 706, then the update process 700 proceeds via the "No" path to an act 708. In the act 708, the user disconnects the analyte detection system 602 from the network and the software 612 is not updated. Thus, the analyte detection system 602 operates in the same manner as the analyte detection system 602 previously operated in the act 702.

If the centralized computer 604 decides that the software 612 needs to be updated in the decision act 706, then the update process 700 proceeds via the "Yes" path to an act 710. In the act 710, the centralized computer 604 sends a software update 614 to the analyte detection system 602. In one embodiment, the centralized computer 604 contains a

database of various software updates 614, and consequently, the centralized computer 604 selects the appropriate software update 614 from the database and then sends the software update 614 to the analyte detection system 602.

5 Next, in an act 712, the analyte detection system 602 receives (e.g. downloads) the software update 614. The analyte detection system 602 then preferably modifies the software 612 to an updated version of the software 612. The process then proceeds to an act 714.

10 In the act 714, the user performs analyte measurements in accordance with the updated software 612. Thus, depending upon the software update 614, the analyte measuring device 602 operates differently than the manner in which the analyte measuring device 602 previously operated in act 702. One example is that the analyte detection system 602 may calculate analyte concentrations differently. Another example is that the analyte detection system 602 may displays new warnings to the user. A further example is that the analyte detection system 602 may display the same warnings, but the warnings are
15 triggered by different events.

In any of the embodiments of the software update system 600 discussed herein, the analyte detection system 602 and/or the centralized computer 604 (or, where applicable, the computer(s) 528) may be configured to encrypt any or all of the data that it transmits over the network 606. Where the user of any of the analyte detection system 602 and the
20 centralized computer 604 (or the analyte detection system/centralized computer itself) is authorized to receive, read and/or otherwise use the encrypted data, the recipient system 602/computer 604 is configured to decrypt the encrypted data, to make the data available to the device and/or the user thereof. By encrypting the data, physician-patient confidentiality, or any physician-patient privilege may be preserved, preventing unauthorized reading or use
25 of the data. Encryption also permits transmission of data over wireless networks or public networks such as the Internet while preserving confidentiality of the transmitted data.

It is contemplated that the encryption and decryption may be performed in any suitable manner, with any suitable methods, software and/or hardware presently known or hereafter developed. In the analyte detection system 602, the encryption and/or decryption
30 processes may be implemented in an algorithm or program instructions executable by, and residing within memory accessible by, the processor 610 of the analyte detection system 602 (in particular, by the signal processor 74/260 where the analyte detection system 602

comprises the noninvasive system 10 or the whole-blood system 200, respectively). In the centralized computer 604 (or, where applicable, the computer(s) 528), the encryption and/or decryption processes may be implemented in an algorithm or program instructions executable by, and residing within memory accessible by, processing element(s) (not
5 shown) of the computer 604/528 in question.

The software update process 700 has many advantages. One advantage is that the software 612 of the analyte measuring device 602 may be updated without requiring significant user participation. Another advantage is that the software 612 may be quickly and conveniently updated at a remote location (e.g., the user's home) rather than requiring
10 the user to travel to, for example, a doctor's office or other administrative center.

Although described above in connection with particular embodiments of the present invention, it should be understood the descriptions of the embodiments are illustrative of the invention and are not intended to be limiting. Various modifications and applications may occur to those skilled in the art without departing from the true spirit and scope of the
15 invention. Furthermore, any method which is described and/or illustrated herein is not limited to the exact sequence of acts described, nor is it necessarily limited to the practice of all of the acts set forth. Other sequences of events or acts, or less than all of the events, or simultaneous occurrence of the events, may be utilized in practicing the method(s) in question.

WHAT IS CLAIMED IS:

1. An analyte concentration monitoring system, comprising:
an analyte detection system having a processor that calculates analyte concentration in accordance with software executable by said processor, and a
5 network interface that is configured to provide connectivity to a computer;
wherein said analyte detection system is configured to receive an update to said software from said computer.
2. The monitoring system of Claim 1, wherein said software comprises an algorithm.
- 10 3. The monitoring system of Claim 1, wherein said software comprises data.
4. The monitoring system of Claim 1, wherein said software comprises instructions.
5. The monitoring system of Claim 1, wherein said software comprises a program.
- 15 6. The monitoring system of Claim 1, wherein said computer is configured to check an update status of said analyte detection system and select said update based on said update status.
7. The monitoring system of Claim 6, wherein said computer automatically checks said update status upon connection of said computer to said analyte detection system
20 via said interface.
8. The monitoring system of Claim 7, wherein said computer sends said update to said analyte detection system without intervention from a user.
9. The monitoring system of Claim 1, wherein said software comprises at least one warning and instructions for communication of said at least one warning to a user of
25 said analyte detection system.
10. The monitoring system of Claim 1, wherein said computer is at a remote location and said network interface connects to said computer via an Internet connection.
11. The monitoring system of Claim 1, wherein said network interface comprises a wireless interface.
- 30 12. The monitoring system of Claim 11, wherein said wireless connection comprises a Bluetooth interface.

13. The monitoring system of Claim 11, wherein said wireless connection comprises an IEEE 802.11(b) interface.

14. The monitoring system of Claim 1, wherein said computer is configured to encrypt said update.

5 15. The monitoring system of Claim 14, wherein said analyte detection system is configured to decrypt said update.

16. A method of automatically updating software on an analyte detection system, comprising:

connecting an analyte detection system to a computer via a network;
10 in said computer, checking an update status of software included in said analyte detection system;

when said update status indicates that a software update is needed, sending said software update to said analyte detection system via said network without intervention from a user; and

15 in said analyte detection system, updating said software with said software update.

17. The method of Claim 16, further comprising sending information from said analyte detection system to said computer via said network.

18. The method of Claim 17, wherein said information includes analyte
20 concentration measurements.

19. The method of Claim 17, further comprising encrypting said information.

20. The method of Claim 19, further comprising decrypting said information.

21. The method of Claim 16, wherein said software update includes at least one warning and instructions for communication of said at least one warning to a user of said
25 analyte detection system.

22. The method of Claim 16, further comprising displaying a warning on said analyte detection system.

23. The method of Claim 16, further comprising calculating the analyte concentration, wherein said software update alters said calculating.

30 24. The method of Claim 16, further comprising encrypting said software update.

25. The method of Claim 24, further comprising decrypting said software update.

26. An analyte concentration monitoring system, comprising:

5 an analyte detection system comprising a processor, a software, and a network interface, wherein the processor is configured to calculate analyte concentration in accordance to said software, and wherein said network interface is configured to provide connectivity to a computer;

wherein said analyte detection system is configured to update said software according to instructions from said computer.

10 27. The monitoring system of Claim 26, wherein said software comprises an algorithm.

28. The monitoring system of Claim 26, wherein said software comprises data.

29. The monitoring system of Claim 26, wherein said software comprises instructions.

15 30. The monitoring system of Claim 26, wherein said software comprises a program.

31. The monitoring system of Claim 26, wherein said computer is configured to check an update status of said analyte detection system and select said update based on said update status.

20 32. The monitoring system of Claim 31, wherein said computer automatically checks said update status upon connection of said computer to said analyte detection system via said interface.

33. The monitoring system of Claim 32, wherein said software comprises at least one warning and instructions for communication of said at least one warning to a user
25 of said analyte detection system.

34. The monitoring system of Claim 26, wherein said computer is at a remote location and said network interface connects to said computer via an Internet connection.

35. The monitoring system of Claim 26, wherein said computer is configured to encrypt said instructions.

30 36. The monitoring system of Claim 26, wherein said analyte detection system is configured to decrypt said instructions.

37. A method of automatically updating software on an analyte detection system, comprising:

connecting an analyte detection system to a computer via a network;

5 in said computer, checking an update status of software included in said analyte detection system;

when said update status indicates that a software update is needed, encrypting said software update and sending said software update to said analyte detection system via said network; and

10 in said analyte detection system, updating said software with said software update.

38. The method of Claim 37, further comprising sending information from said analyte detection system to said computer via said network.

39. The method of Claim 38, wherein said information includes analyte concentration measurements.

15 40. The method of Claim 38, further comprising encrypting said information.

41. The method of Claim 40, further comprising decrypting said information.

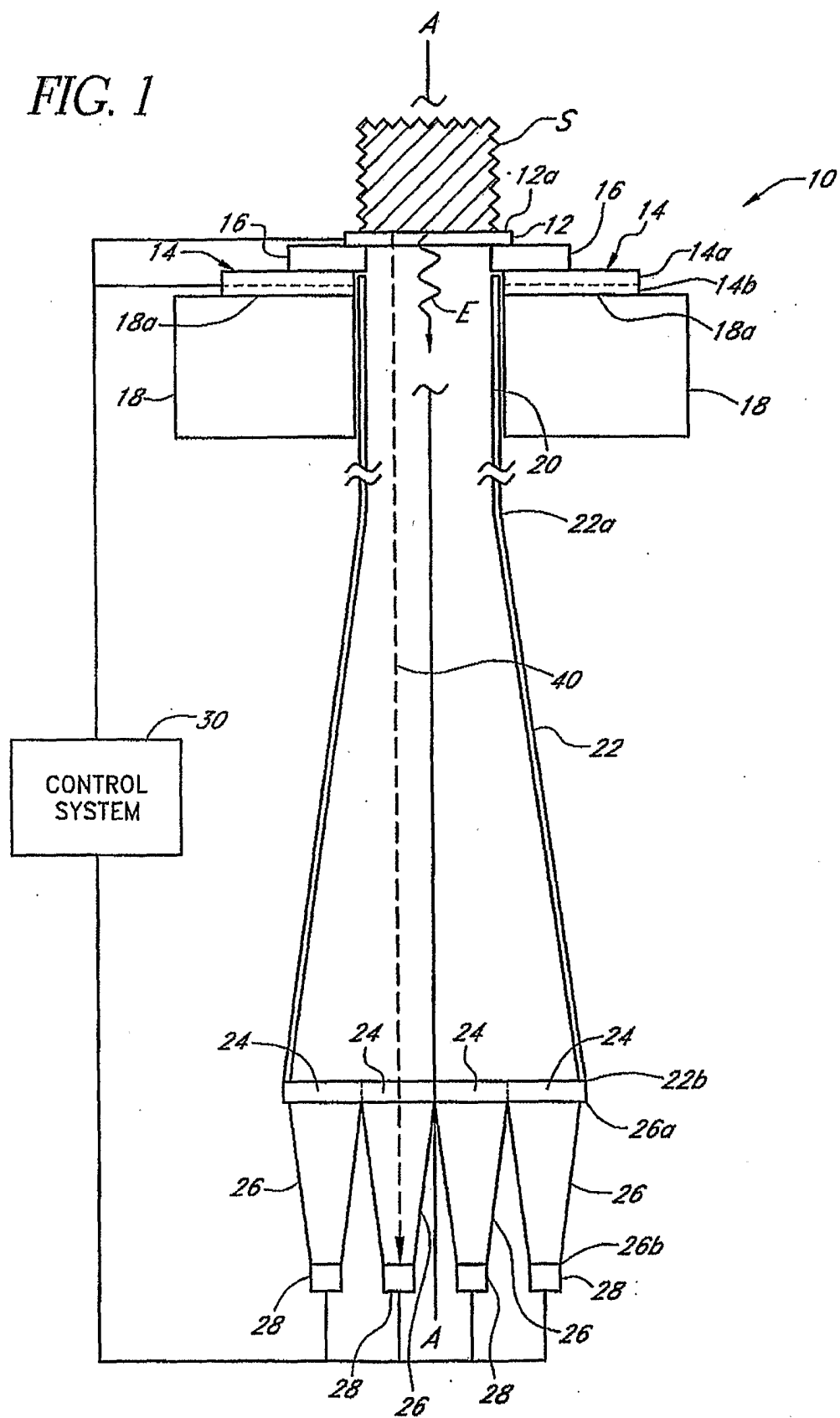
42. The method of Claim 37, wherein said software update includes at least one warning and instructions for communication of said at least one warning to a user of said analyte detection system.

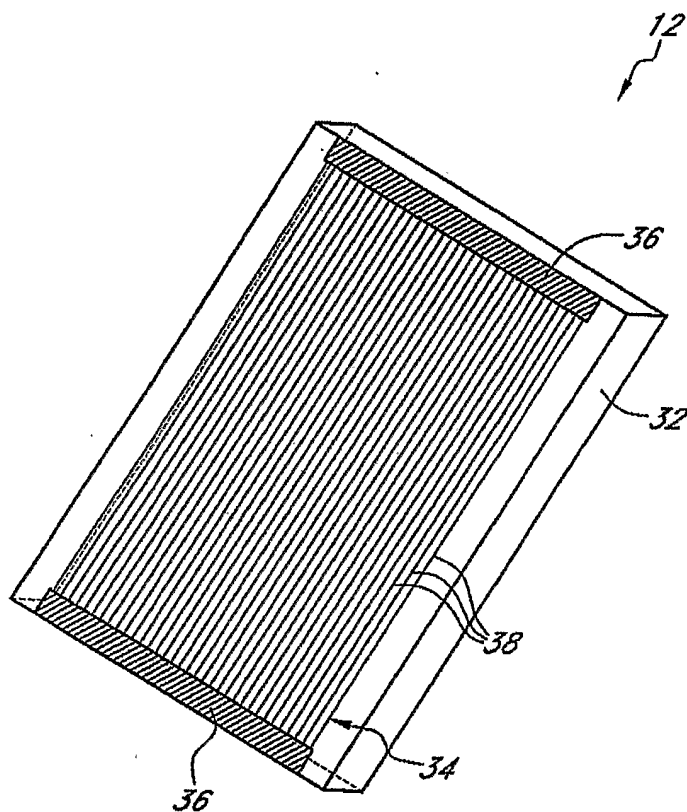
20 43. The method of Claim 37, further comprising displaying a warning on said analyte detection system.

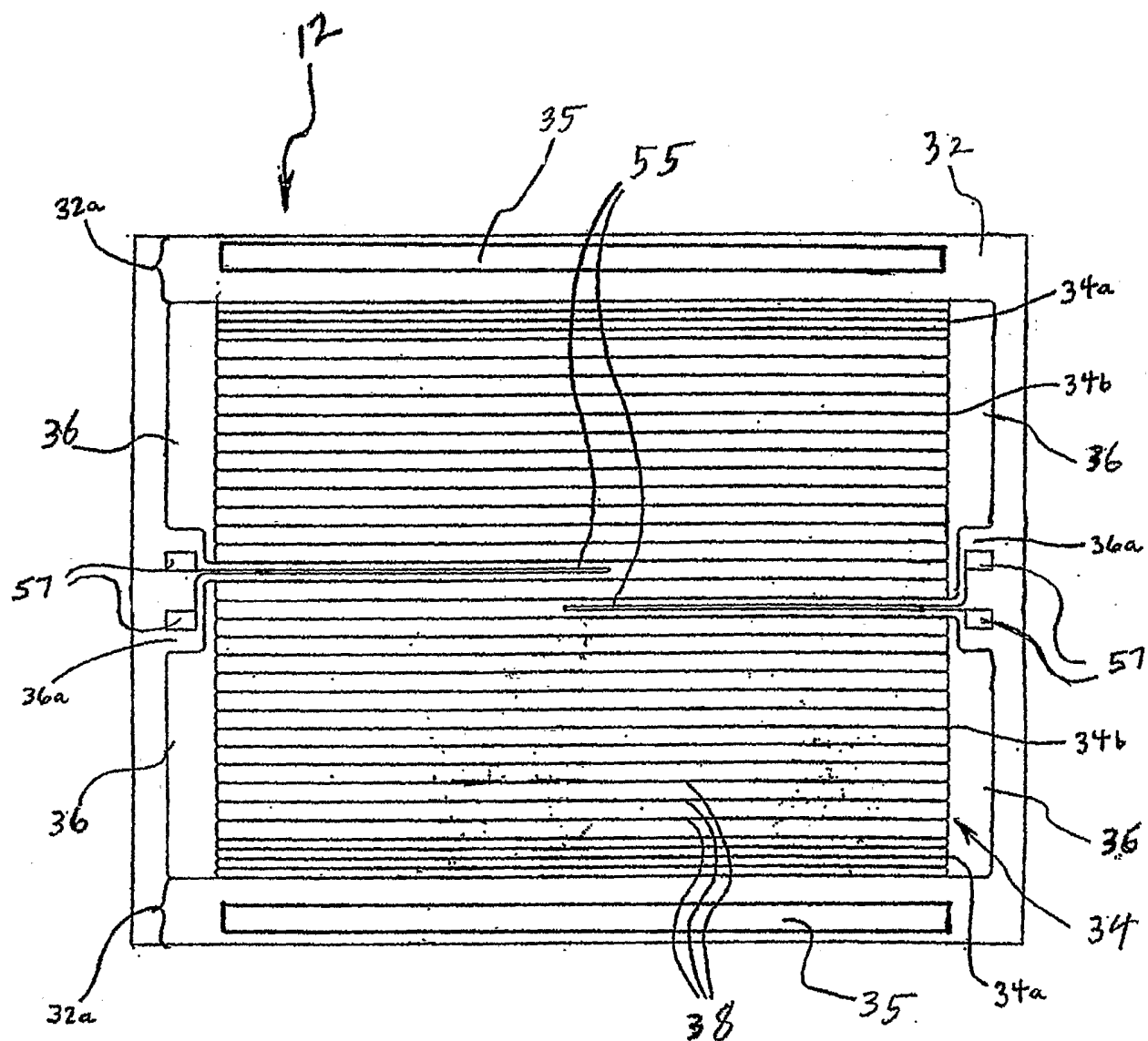
44. The method of Claim 37, further comprising calculating the analyte concentration, wherein said software update alters said calculating.

25 45. The method of Claim 37, wherein sending said software update to said analyte detection system comprises sending said software update without intervention from a user.

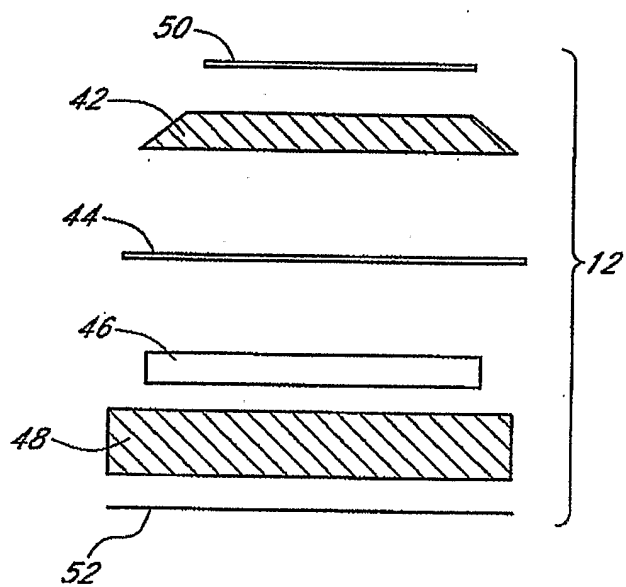
FIG. 1

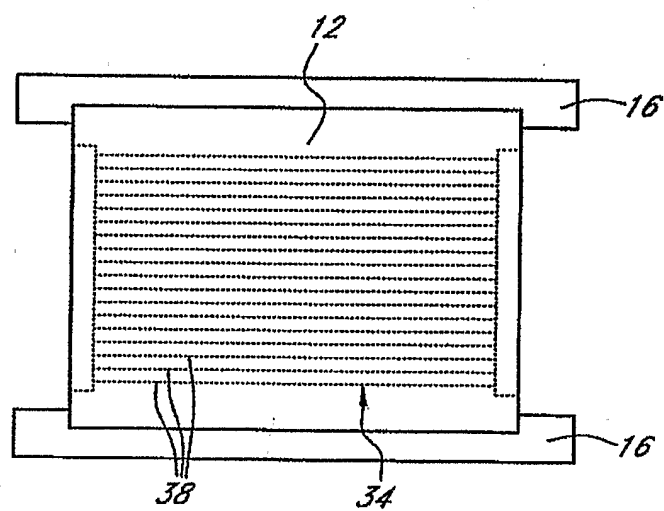


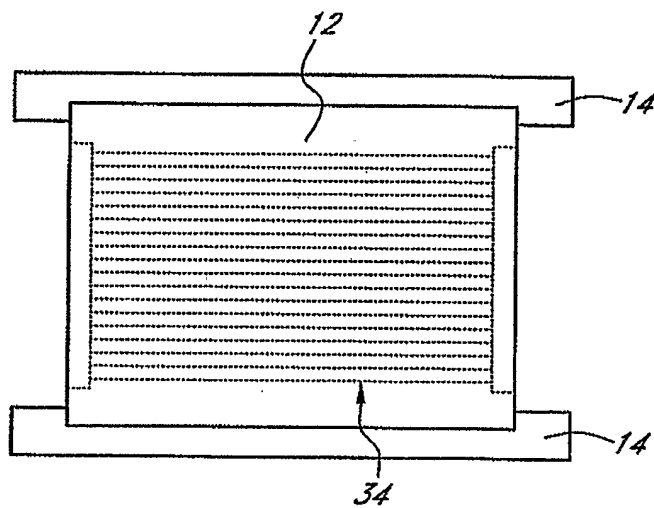
*FIG. 2*

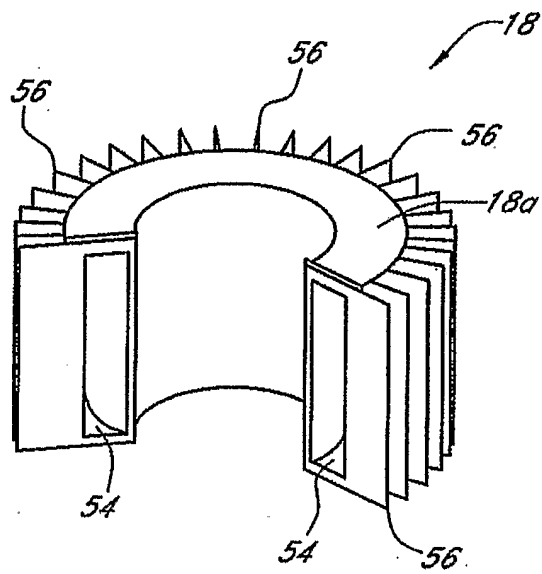


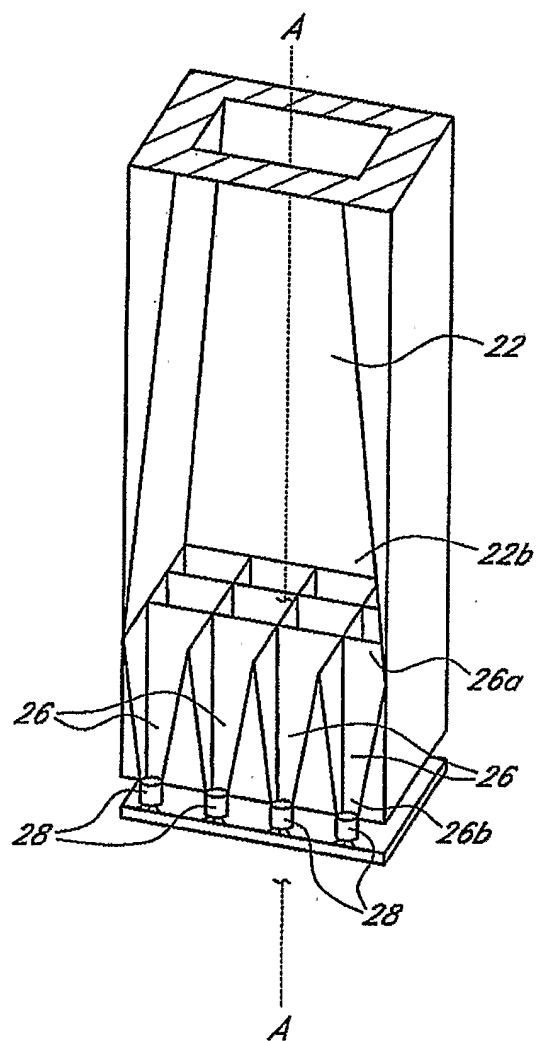
F / G. 2A

*FIG. 3*

*FIG. 4*

*FIG. 5*

*FIG. 6*

*FIG. 6A*

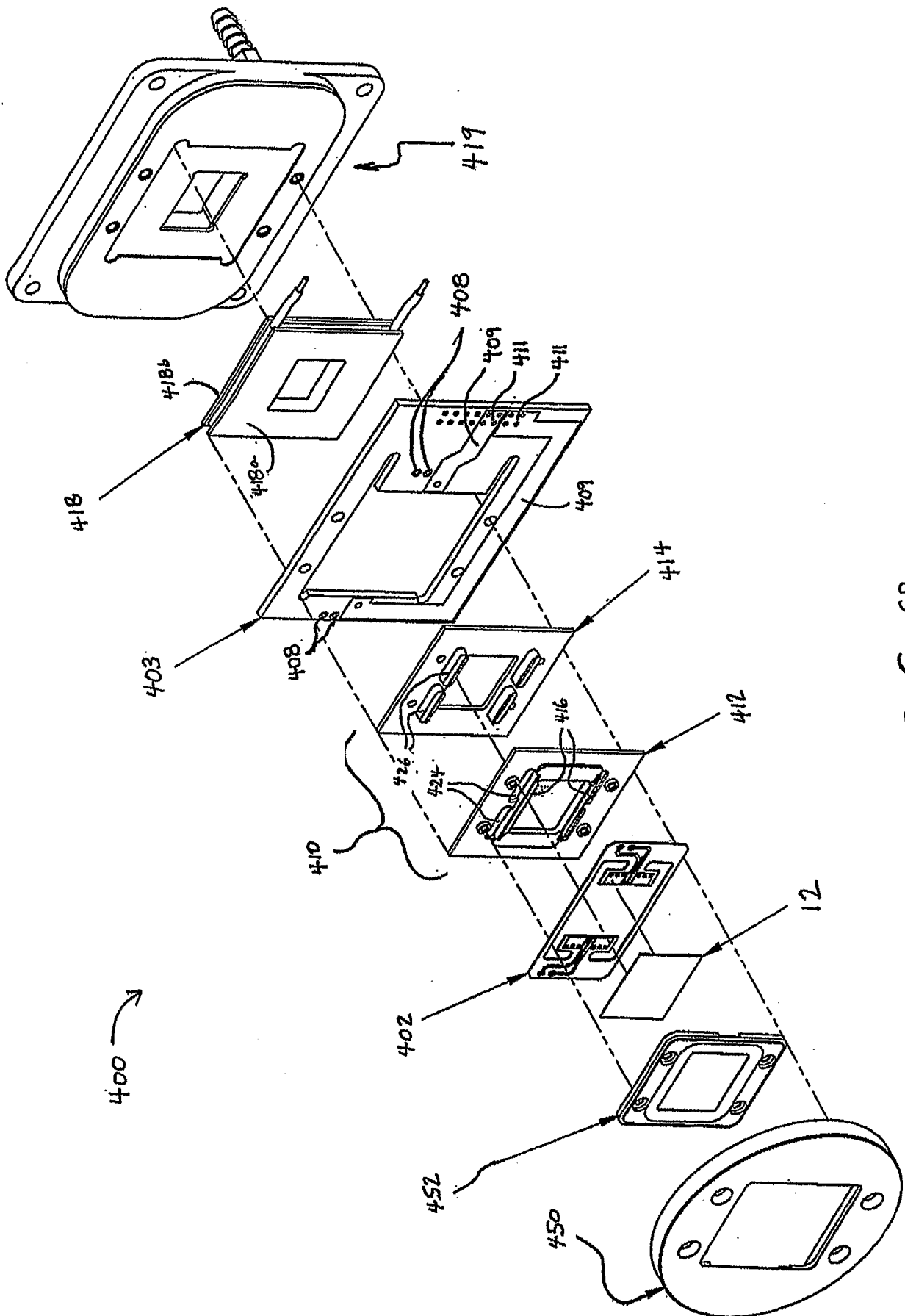
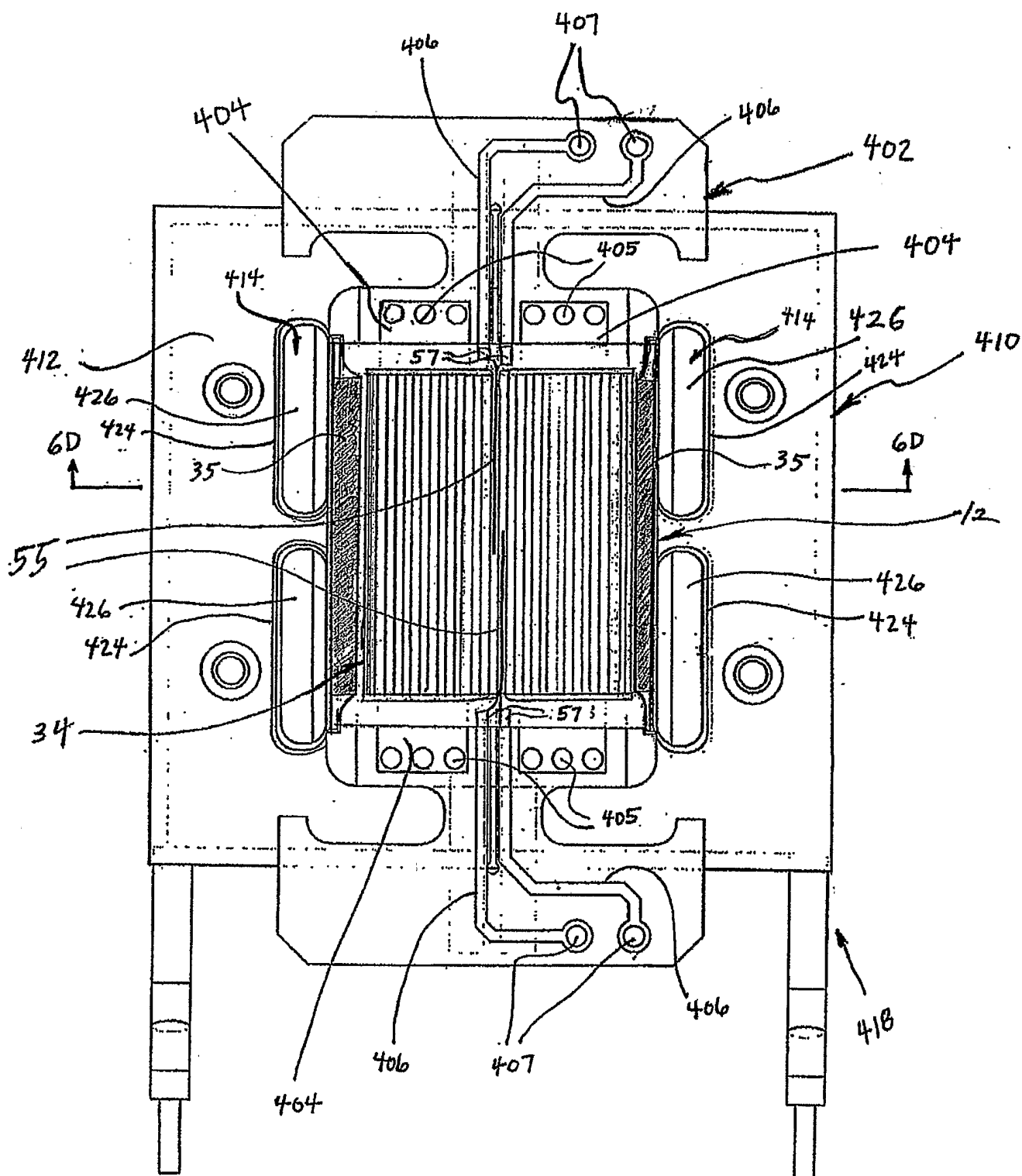
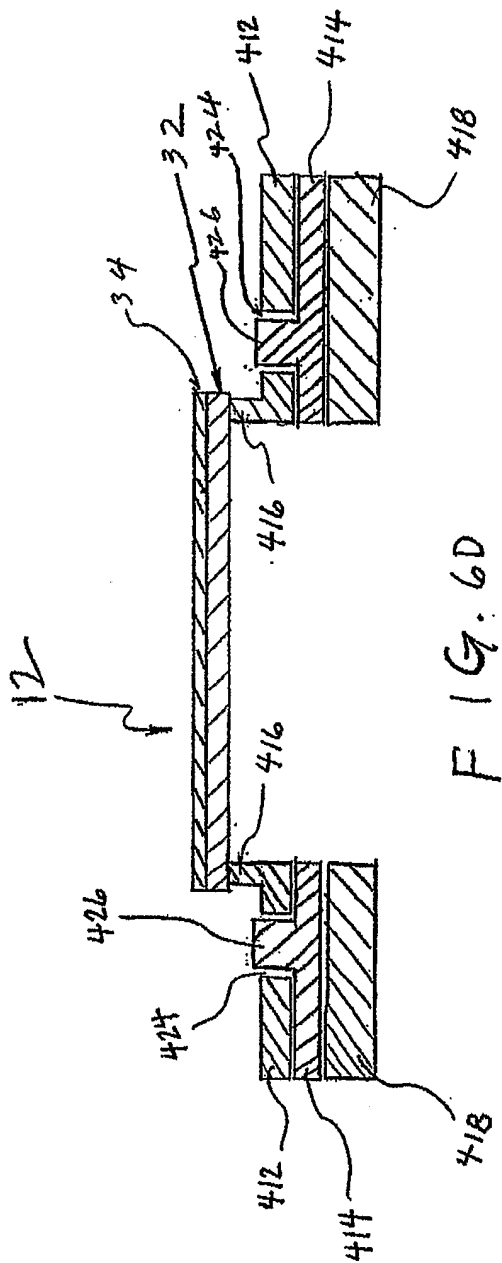


FIG. 6B



F I G. 6C



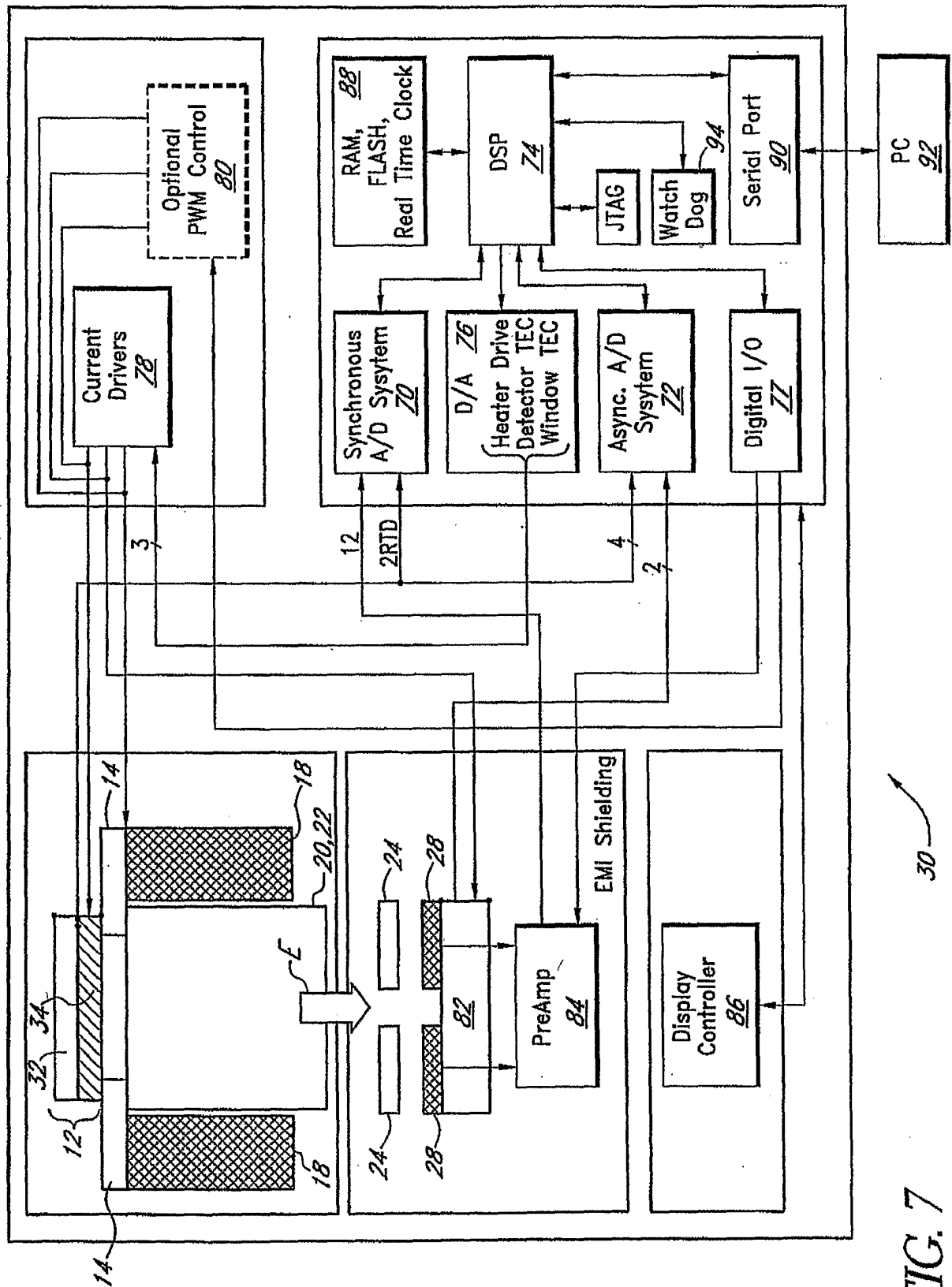
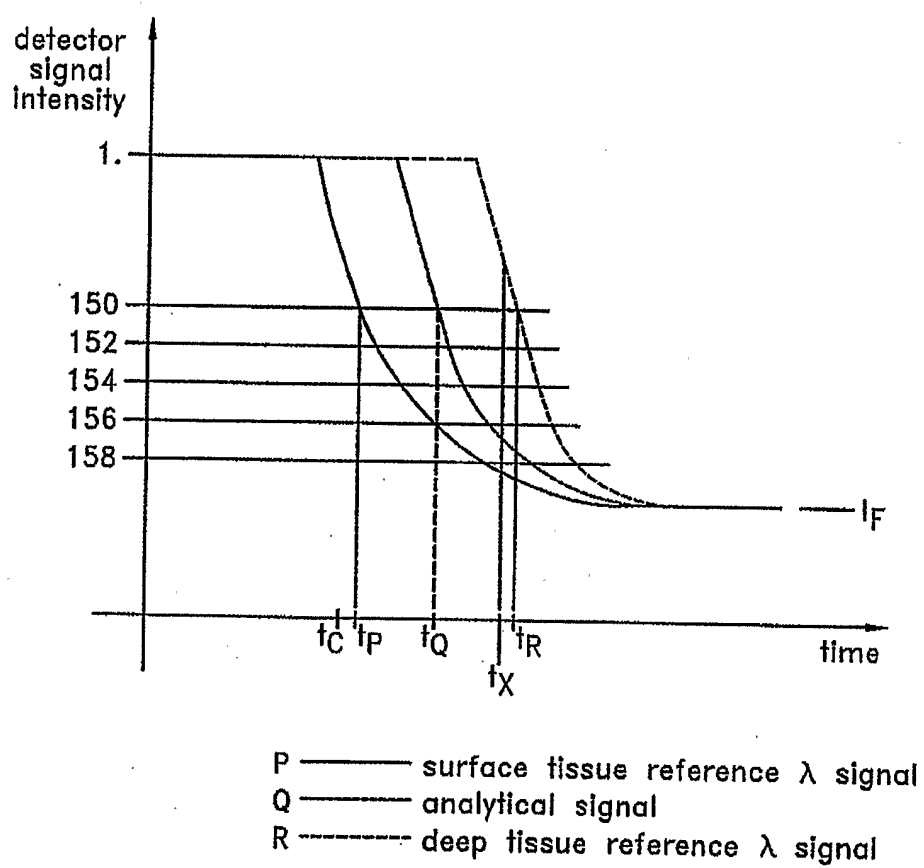
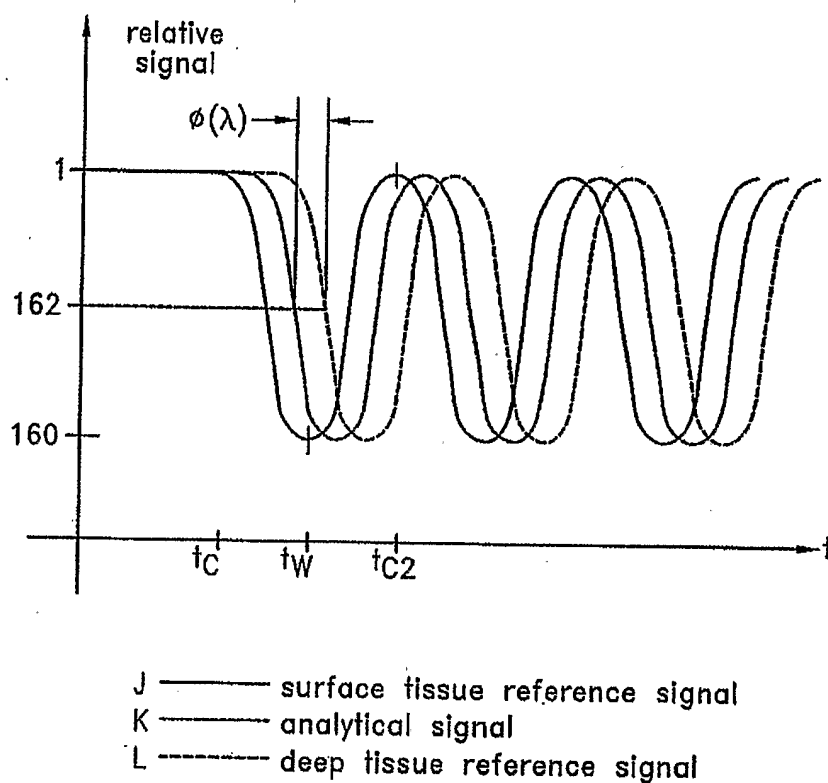
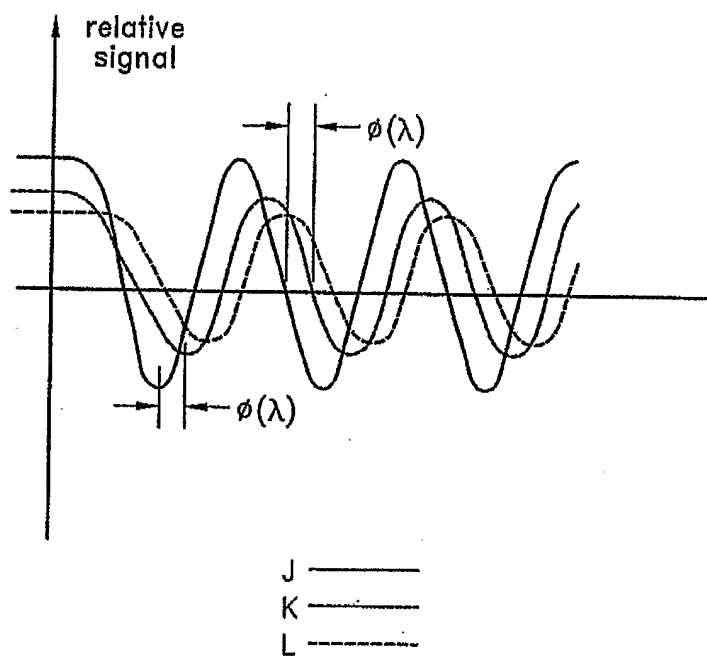


FIG. 7

*FIG. 8*

*FIG. 9*

*FIG. 10*

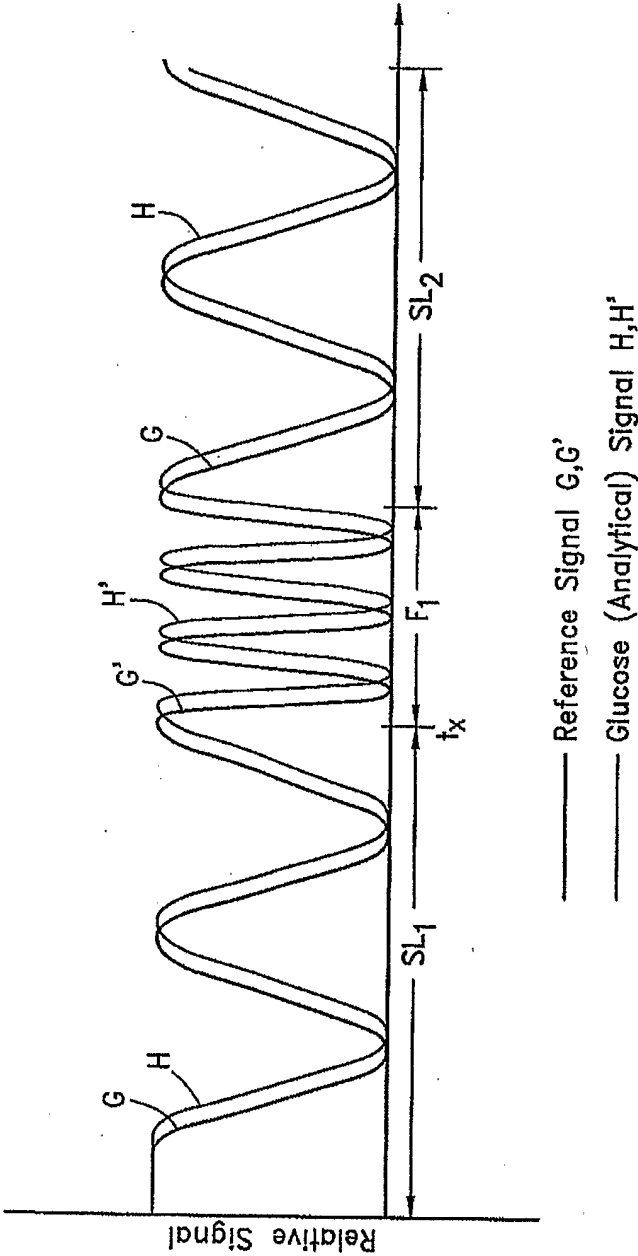


FIG. 11

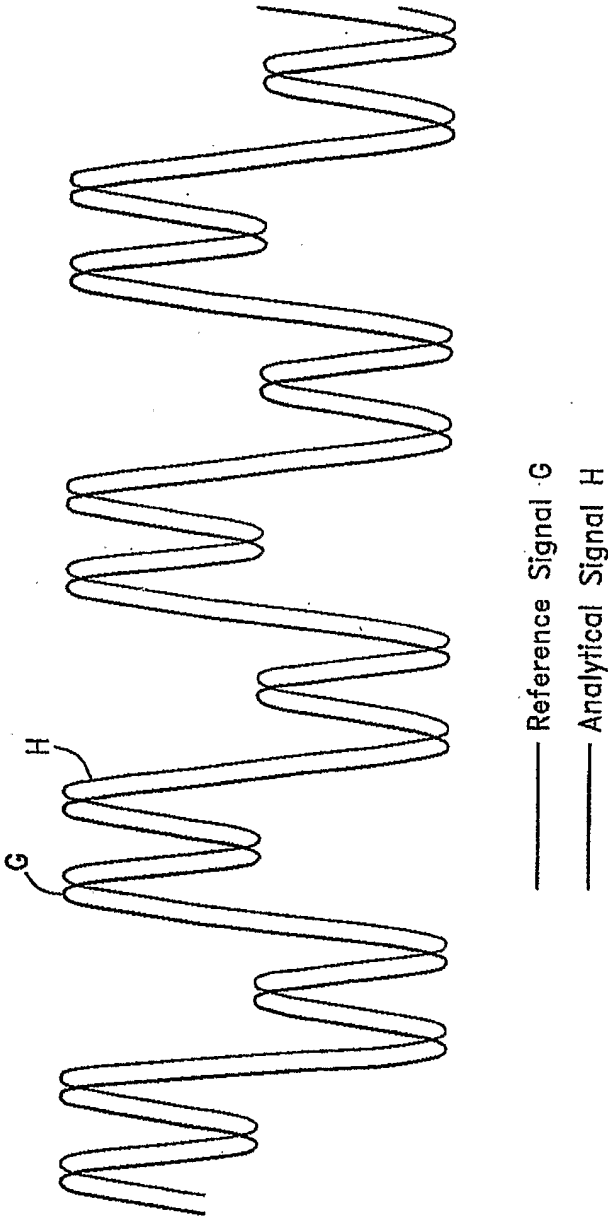


FIG. 12

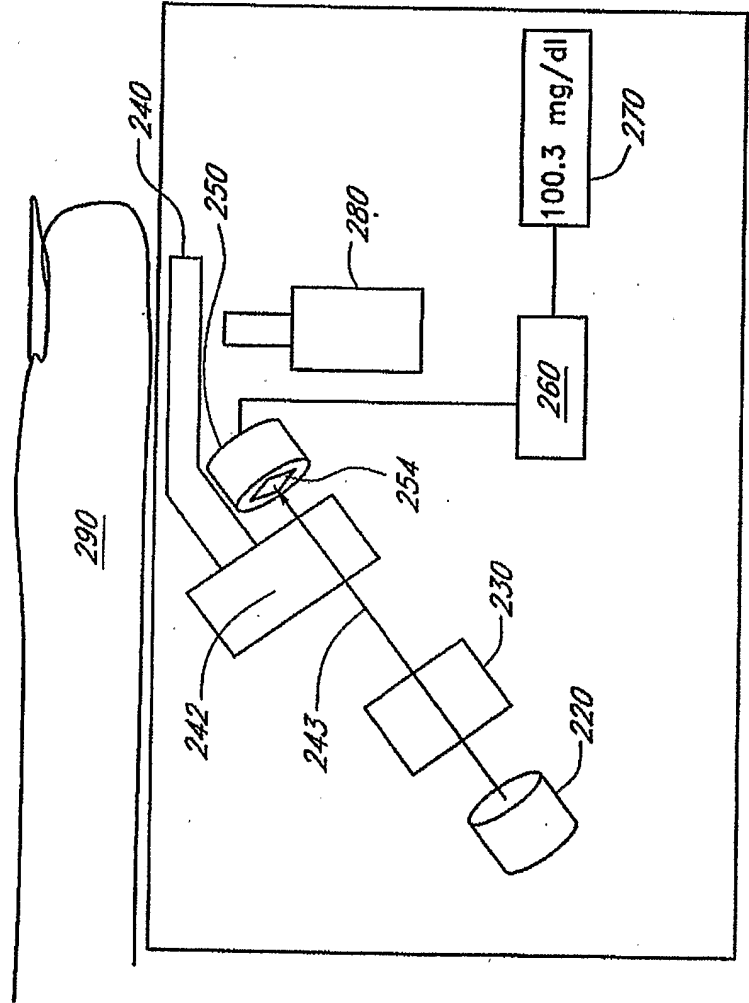


FIG. 13

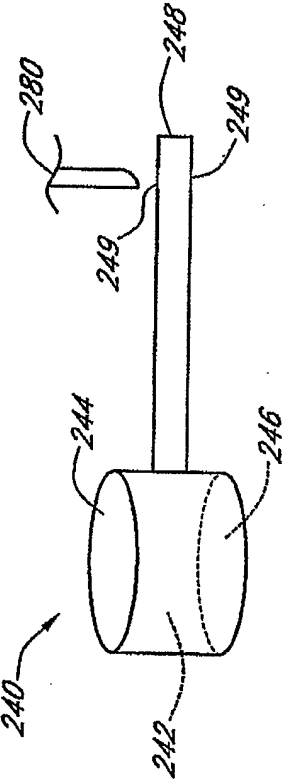
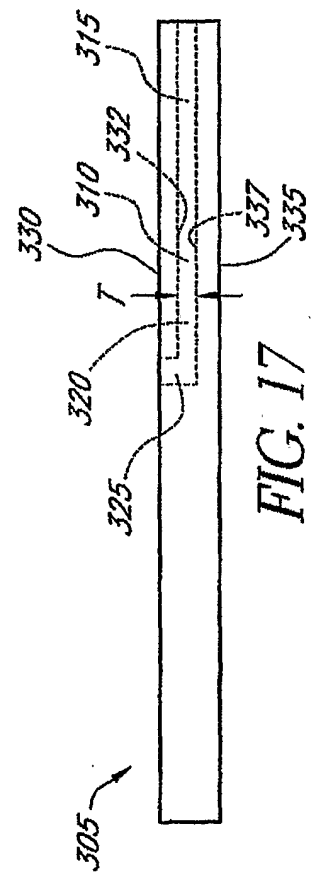
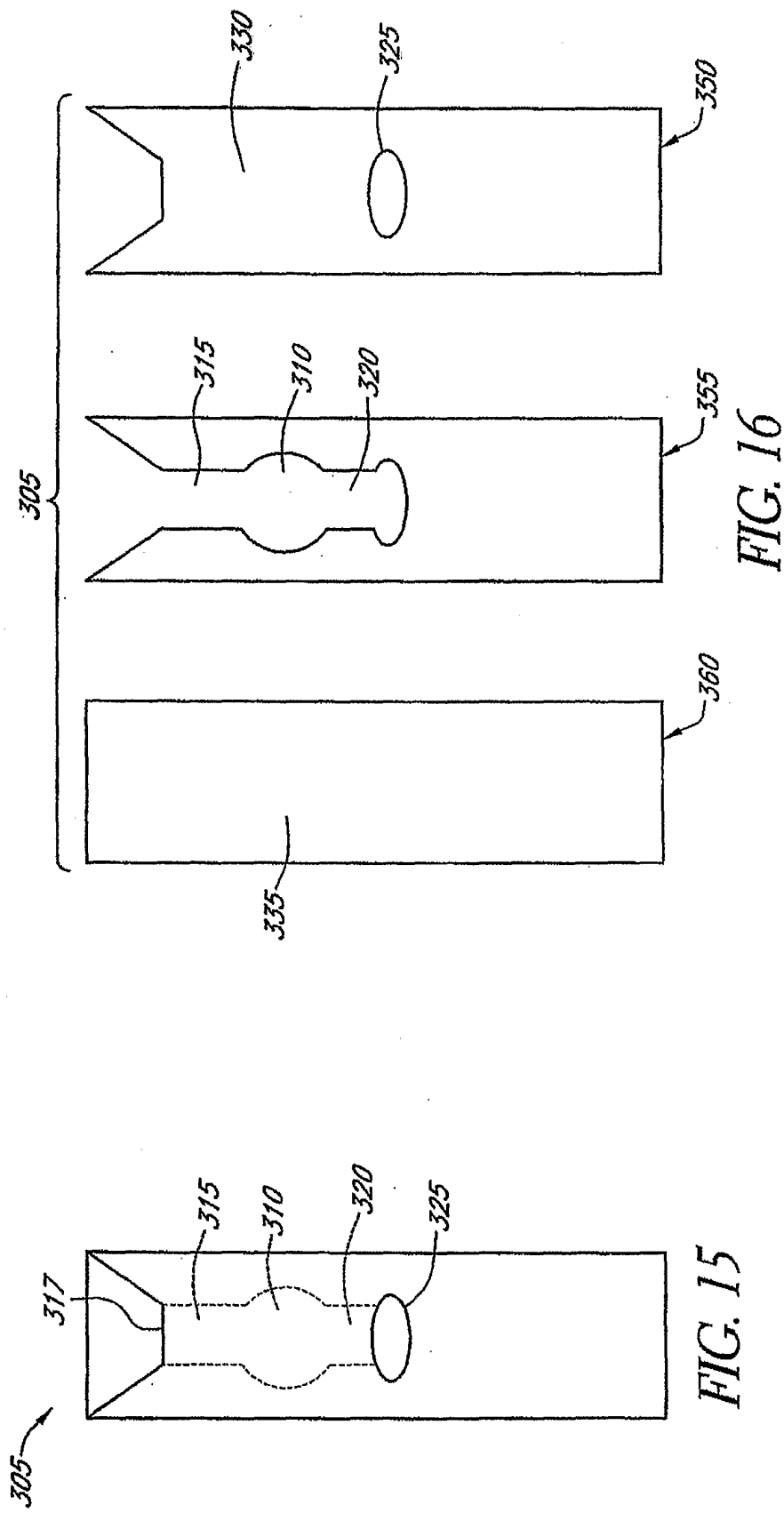
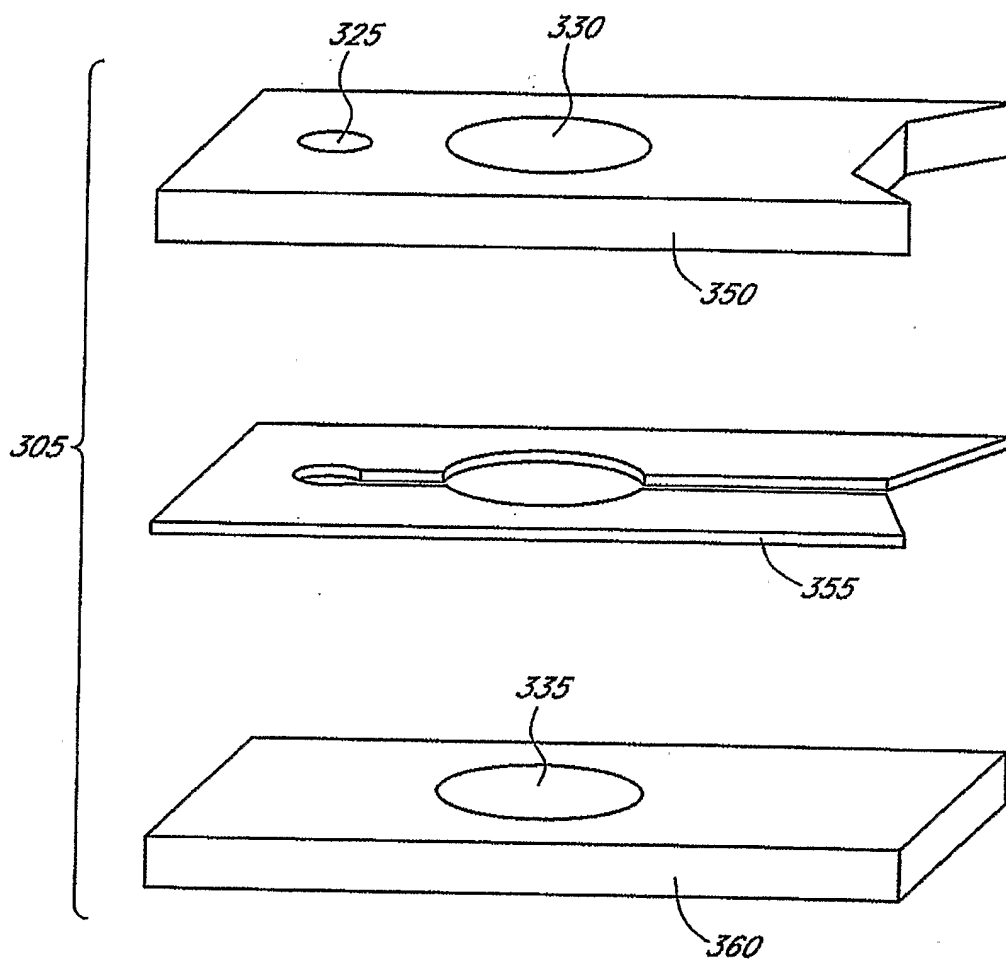
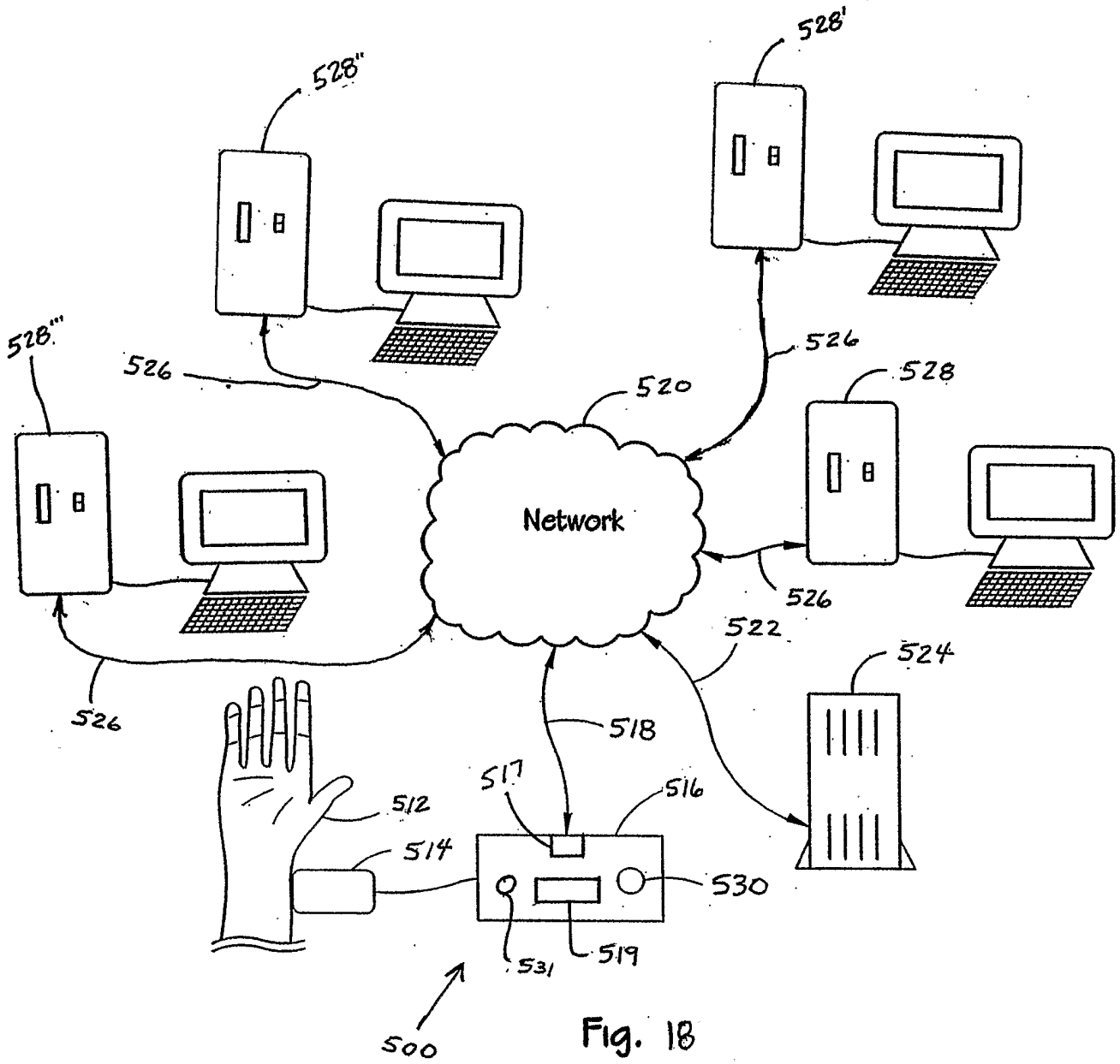


FIG. 14



*FIG. 16A*



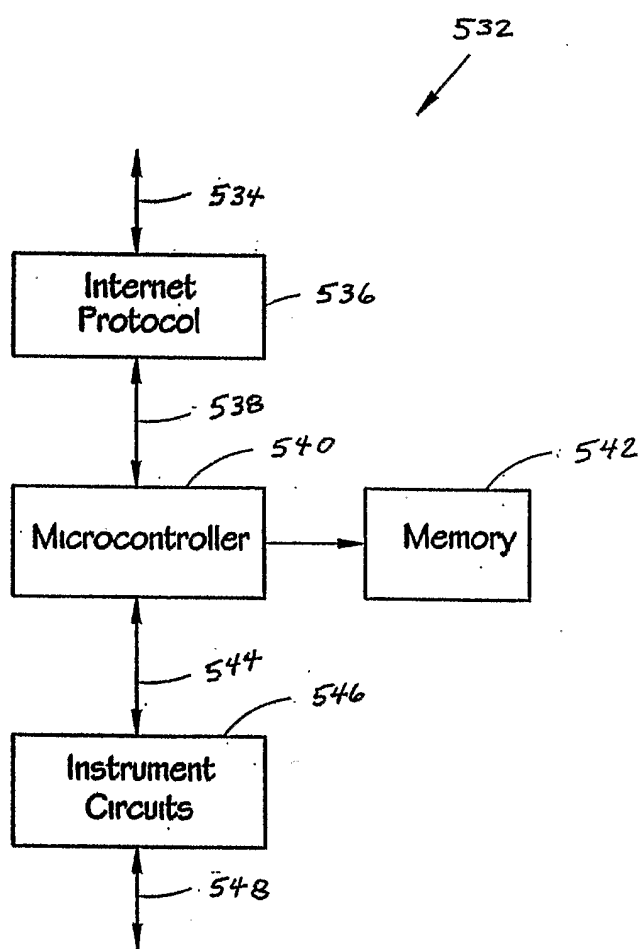


Fig. 19

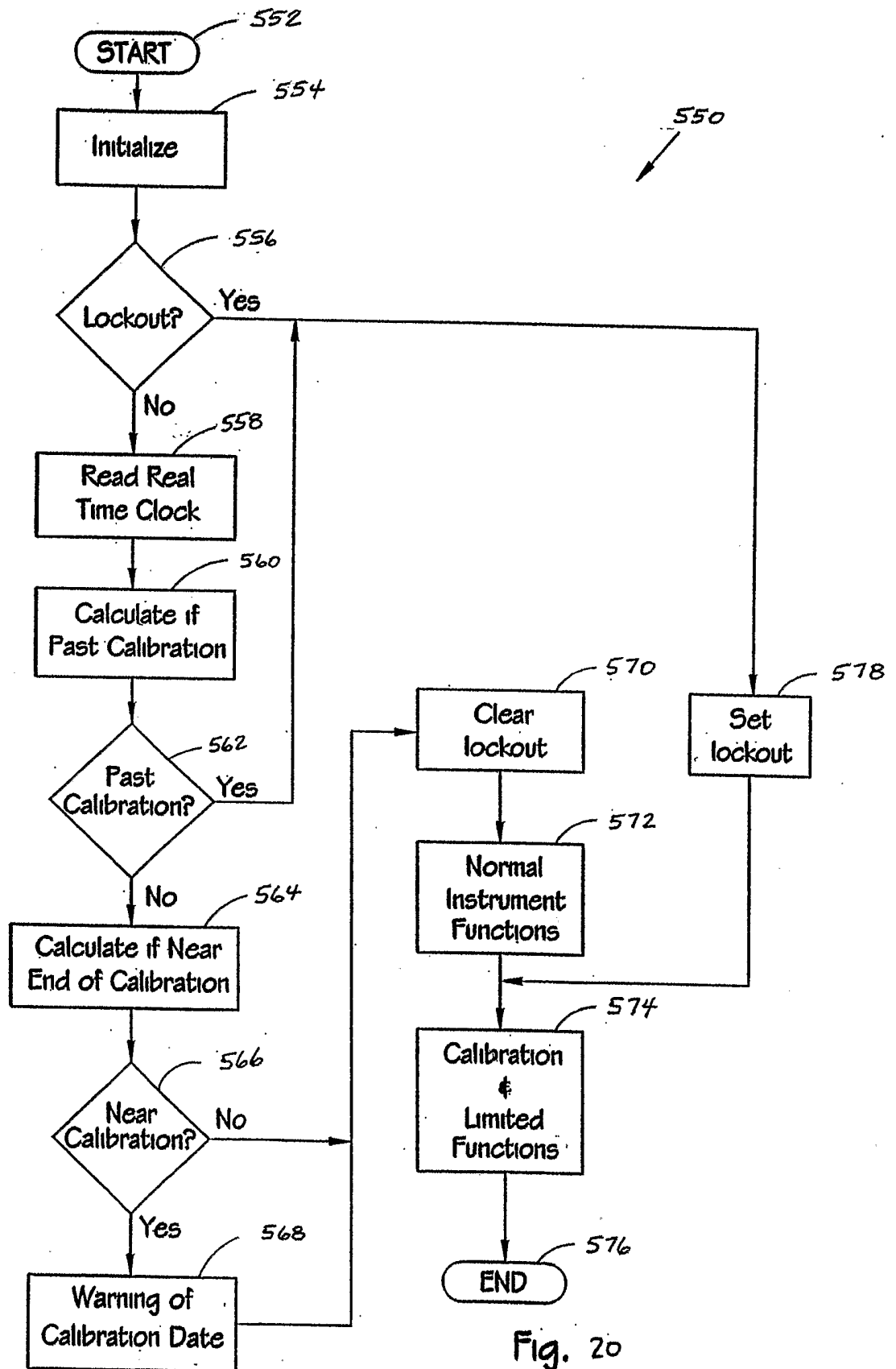


Fig. 20

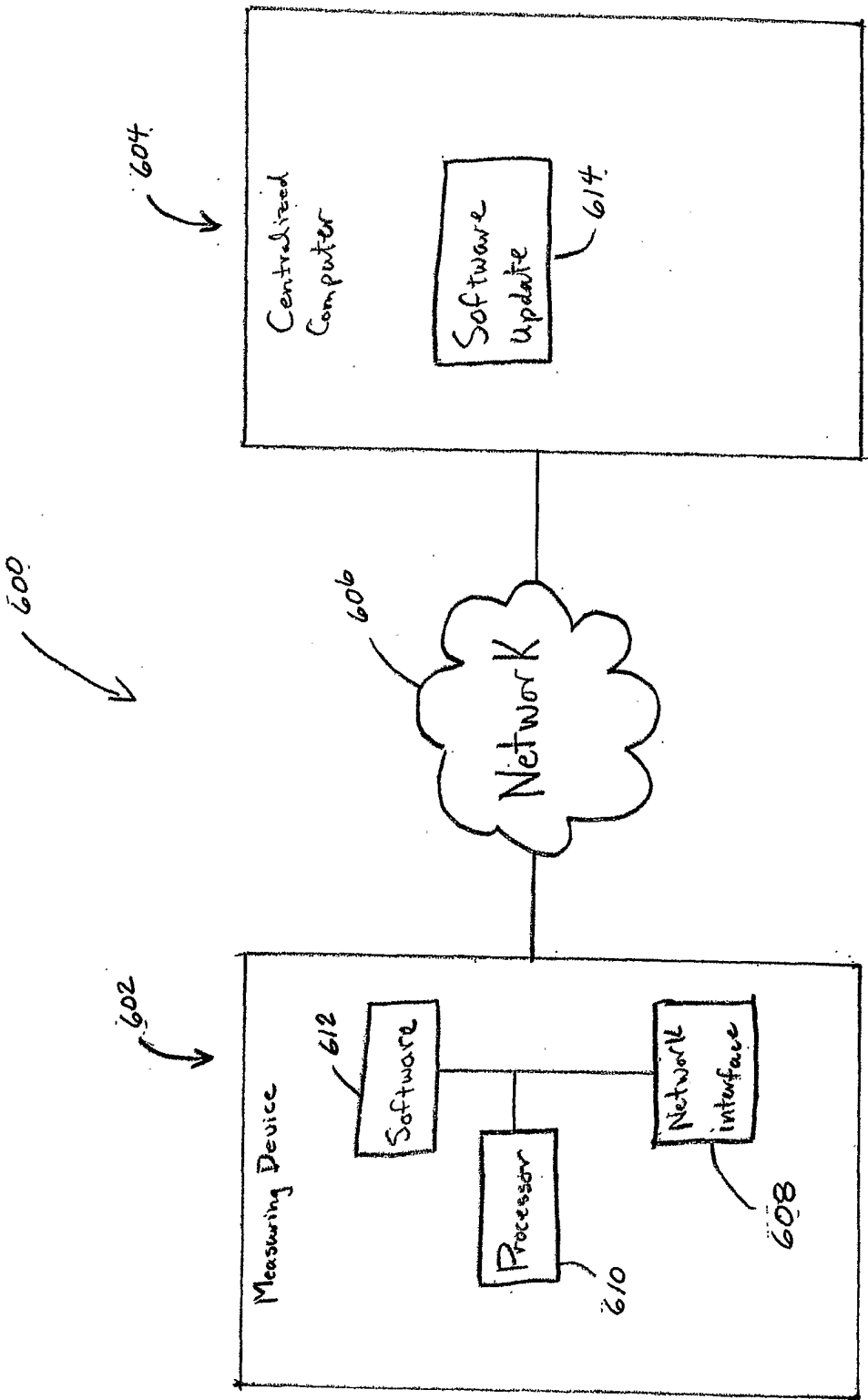


FIGURE 21

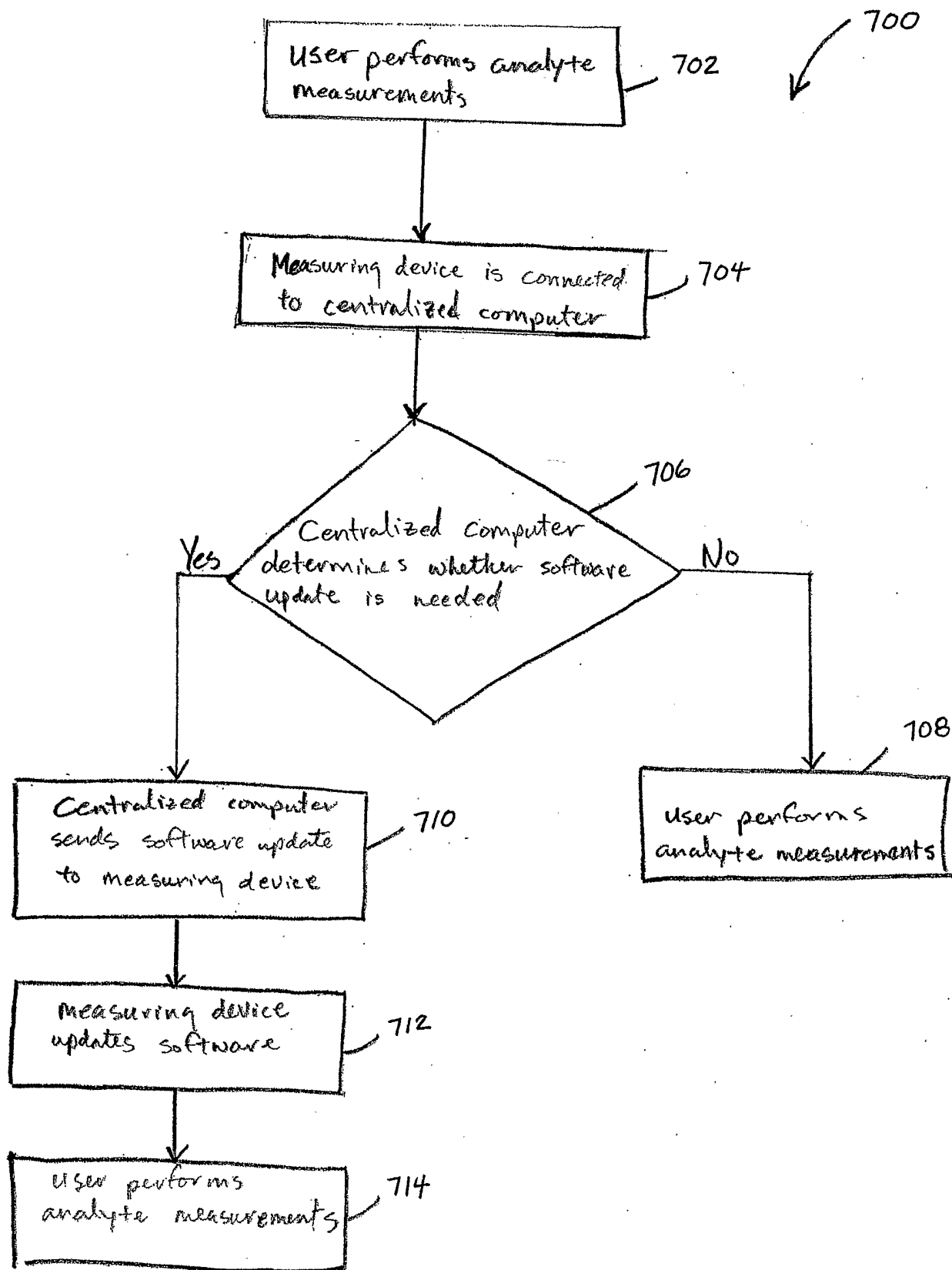


FIGURE 22

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/35200

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00 G06F19/00

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 G06F

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, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/045808 A1 (TIERNEY MICHAEL J ET AL) 18 April 2002 (2002-04-18) paragraph '0153! - paragraph '0162! ---	1-45
X	WO 02 082990 A (RIO GRANDE MEDICAL TECHNOLOGIE) 24 October 2002 (2002-10-24) page 74, line 26 -page 75, line 12 -----	1-45

☐ 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

12 March 2004

Date of mailing of the international search report

23/03/2004

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Hooper, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/35200

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002045808 A1	18-04-2002	US 2003225319 A1 WO 0217210 A2	04-12-2003 28-02-2002
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