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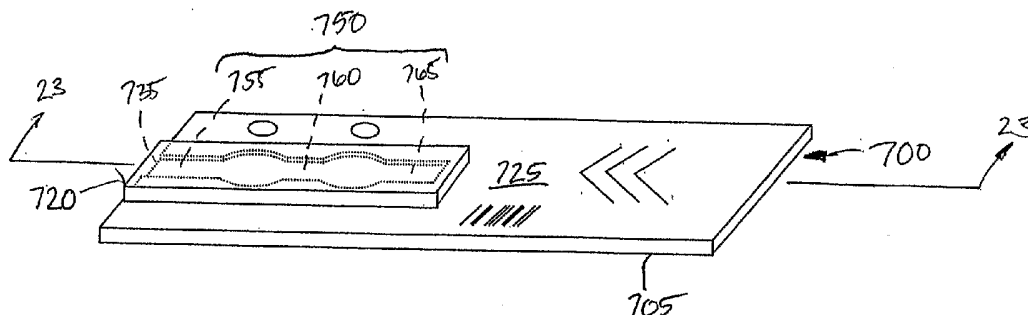
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(54) Title: SAMPLE ELEMENT FOR REAGENTLESS WHOLE BLOOD GLUCOSE METER



(57) Abstract: A reagentless whole-blood analyte detection system includes an infrared radiation source, a detector, and a sample element (700, 800). The sample element (700, 800) includes an elongate member (705, 802), a first sample cell wall (716), a second sample cell wall (715), a cover (720), and a sample supply passage (750, 815). The first sample cell wall in part defines a first sample cell (740). The first and second sample cell walls comprise materials that transmit a substantial portion of radiation in a range of wavelengths between about 6 μm and about 12 μm. The cover (720) at least partially defines at least one of the first sample cell (740) and the second sample cell (745). The sample supply passage comprises a first branch (755) and a second branch (760). The first branch of the sample supply passage extends from the opening (735) to the first sample cell. The second branch of the sample supply passage extends from the first sample cell to the second sample cell.

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**SAMPLE ELEMENT FOR REAGENTLESS
WHOLE BLOOD GLUCOSE METER**

Background of the Invention

5 Field of the Invention

This invention relates generally to systems and components for analyzing whole-blood samples.

Description of the Related Art

Millions of diabetics draw samples of bodily fluid such as blood on a daily basis to
10 monitor the level of glucose in their bloodstream. This practice is called self-monitoring,
and is commonly performed using one of a number of reagent-based glucose monitors.
These monitors measure glucose concentration by observing some aspect of a chemical
reaction between a reagent and the glucose in the fluid sample. The reagent is a chemical
compound that is known to react with glucose in a predictable manner, enabling the
15 monitor to determine the concentration of glucose in the sample. For example, the monitor
may be configured to measure a voltage or a current generated by the reaction between the
glucose and the reagent. A small test strip is often employed to hold the reagent and to host
the reaction between the glucose and the reagent. Reagent-based monitors and test strips
suffer from a variety of problems and also have limited performance.

20 Other techniques for analyzing a sample to determine the presence of a chemical
include spectroscopy. Spectroscopy has been used in laboratory settings in a qualitative
manner, to determine the presence of a chemical compound in a sample. Sometimes more
precise measurements are made to determine the quantity of a compound in a sample.
These measurements require very complicated and expensive laboratory equipment. Also,
25 highly skilled laboratory technicians are generally required to prepare samples for analysis,
to perform the analysis, and to process the results. Each of these stages requires careful
control. For example, the preparation stage in some cases requires very careful measuring,
referred to as micro-pipetting, of a small amount of sample, which is applied to a laboratory
slide. This careful measuring requires very precisely manufactured equipment, extensive
30 training, and a great deal of care.

The cost of purchasing laboratory spectroscopy equipment is prohibitive for most
diabetics. Even if such equipment were more affordable, the skill level required to handle

samples and to prepare such samples for analysis is not possessed by most diabetics. Accordingly, current techniques for analyzing blood without using reagent-based test strips are inadequate.

Summary of the Invention

5 This application describes and claims various sample elements having sample cells that can be used in one or more of a variety of detectors to detect one or more analytes in a sample. The sample elements can be used in connection with invasive and with non-invasive analyte detectors. One such detector detects radiation directed at and transmitted through one or more sample cells of the sample element and a sample contained therein. In
10 one aspect, the sample cell of the sample element is bounded by a sample cell wall that is constructed of a material that has properties that enable it to be made very thin. Reducing the thickness of the sample cell wall tends to reduce the amount of radiation that is absorbed by the sample cell wall. By reducing the absorption of the sample cell wall, the absorption (and, therefore, the properties) of the sample can be more accurately determined.
15 In another aspect, at least two different materials are used as sample cell walls in at least one sample cell. Where two different sample cells bounded by sample cell walls of two different materials are provided, the absorption of the materials can be assessed, and the analyte can be more accurately determined. Also, by providing multiple sample cell wall materials, various corrections can be made, e.g., for differences in the quantity of sample in
20 each sample cell, for variation in the thickness(es) of the sample cell wall(s), etc.

In one embodiment, a reagentless whole-blood analyte detection system that is capable of being deployed near a patient is provided. The reagentless whole-blood detection system includes an infrared radiation source, a detector, and a sample element. The infrared radiation source emits radiation along an optical path. The detector is
25 positioned in the optical path of the radiation. The sample element is configured to be positioned in the optical path of the radiation. The sample element includes an elongate member, a first sample cell wall, a second sample cell wall, a cover, and a sample supply passage. The elongate member has a planar side and an opening located on a peripheral edge thereof. The opening spans at least a portion of the thickness of the elongate member.
30 The first sample cell wall in part defines a first sample cell. The first sample cell wall comprises a first material that transmits a substantial portion of radiation in a range of wavelengths between about 6 μm and about 12 μm . The second sample cell wall in part

defines a second sample cell. The second sample cell wall comprises a second material that transmits a substantial portion of radiation in a range of wavelengths between about 6 μm and about 12 μm . The cover is coupled with the planar side of the elongate member. The cover at least partially defines at least one of the first sample cell and the second sample cell. The sample supply passage comprises a first branch and a second branch. The first branch of the sample supply passage extends from the opening to the first sample cell. The second branch of the sample supply passage extends from the first sample cell to the second sample cell.

In another embodiment, a reagentless whole-blood analyte detection system that is capable of being deployed near a patient is provided. The whole-blood analyte detection system includes an infrared radiation source, a detector, and a sample element. The infrared radiation source emits radiation along an optical path. The detector is positioned in the optical path of the radiation. The sample element is configured to be positioned in the optical path of the radiation. The sample element includes an elongate member, a sample cell wall, a cover, and a sample supply passage. The elongate member has a planar side and an opening located on a peripheral edge of the elongate member. The opening spans at least a portion of the thickness of the peripheral edge. The sample cell wall comprises an inner side, an outer side, and a sample cell wall thickness defined between the inner side of the sample cell wall and the outer side of the sample cell wall. The inner side of the sample cell wall in part defines a sample cell. The sample cell wall comprises a material selected from the group consisting of mylar, polyethylene, deuterized polyethylene. The cover is coupled with the planar side of the elongate member. The cover at least partially defines the sample cell. The sample supply passage extends between the opening and the sample cell.

In another embodiment, a method for performing reagentless whole-blood analyte detection is provided. A sample element is provided that has an opening, a first sample analysis region, a second sample analysis region, a cover, and a sample supply passage. The cover at least partially defines the first sample analysis region and the second sample analysis region. The sample supply passage extends between the opening and at least one of the first sample analysis region and the second sample analysis region. The opening of the sample element is positioned in contact with a sample. The sample is transported from the opening to at least one of the first sample analysis region and the second sample

analysis region via the sample supply passage. The sample is exposed to infrared radiation in a suitable wavelength range directed generally perpendicularly to the first sample analysis region and the second sample analysis region. Radiation transmitted through the sample in the first sample analysis region and through the sample in the second sample analysis region is detected. The quantity of at least one analyte present in the sample is calculating based on the radiation that was transmitted through the sample in the first sample analysis region and through the sample in the second sample analysis region and that was detected.

In another embodiment, a sample element is provided that comprises an opening, a first sample analysis region, a second sample analysis region, a cover member, and a sample supply passage. A first material is associated with the first sample analysis region. A second material is associated with the second sample analysis region. The cover member at least partially defines the first sample analysis region and the second sample analysis region. The sample supply passage extends between the opening and at least one of the first sample analysis region and the second sample analysis region.

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 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.

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.

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.

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

5 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.

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

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

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.

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

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.

20 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.

FIGURE 18 is a perspective view of one embodiment of a sample element.

FIGURE 19 is a cross-sectional view of one arrangement of the embodiment shown in FIGURE 18 taken along section 19-19.

25 FIGURE 20 is a cross-sectional view of another arrangement of the embodiment shown in FIGURE 18 taken along section 19-19.

FIGURE 21 is a cross-sectional view of another arrangement of the embodiment shown in FIGURE 18 taken along section 19-19.

FIGURE 22 is a perspective view of another embodiment of a sample element.

30 FIGURE 23 is a cross-sectional view of one arrangement of the embodiment shown in FIGURE 22 taken along section 23-23.

FIGURE 24 is a cross-sectional view of another arrangement of the embodiment shown in FIGURE 22 taken along section 23-23.

FIGURE 25 is a perspective view of one embodiment of a sample element having an integrated sample extractor.

5 Detailed Description of the Preferred Embodiment

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

This application is directed at a variety of sample elements that can be used in one or more of a variety of detectors to detect one or more analytes in a sample. In the discussion that follows a non-invasive system, a whole-blood system, and various
15 embodiments of sample elements usable therewith are described. Of course, one skilled in the art will recognized that the sample elements described and claimed herein can be used with a wide variety of analyte detectors.

The sample elements generally include one or more sample cells. In one aspect, the sample cell of the sample element is bounded by a sample cell wall that is constructed of a
20 material that has properties that enable it to be made very thin. By reducing the absorption of the sample cell wall, the absorption (and, therefore, the properties) of the sample can be more accurately determined. In another aspect, at least two different materials are used as sample cell walls in at least one sample cell. By providing two different sample cells bounded by sample cell walls of two different materials, various corrections can be made,
25 e.g., for the absorption of the sample cell wall material, and the analyte can be more accurately determined. Also, by providing multiple sample cell wall materials, various corrections can be made, e.g., for the effect of different quantities of sample in each sample cell, for the absorption of the sample cell wall(s), for the variation in the thickness(es) of the sample cell wall(s), etc.

30 **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 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 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.

10 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 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.

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, 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.

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

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 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
5 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
10 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 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
15 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 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
20 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 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
25 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
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
30 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 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 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 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 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 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 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

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 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 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 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 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 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

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.

5 In the embodiment of FIGURE 2A, the heater elements 38 are typically provided 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
10 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
15 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
20 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
25 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
30 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
5 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
10 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
15 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
20 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
25 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.

30 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

5 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.

15 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.

20 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.

25 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

30

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 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 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 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.

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 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 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.

10 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.

20 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.

25 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
30 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.

5 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
10 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 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.

15 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 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
20 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 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.

25 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 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
30 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 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 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 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. 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 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.

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 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".

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 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 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 to 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. 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 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 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 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 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

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 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 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 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.

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 wavelengths, preferably a polished gold coating. The concentrators 26 themselves may be
5 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
10 alternative embodiments. The inner walls of the concentrators converge as they extend 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
15 the detectors 28.

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
20 dimensions or incidence angles may be employed in constructing the concentrators 26.

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
25 positioned above a 3 × 4 array of detectors 28 and concentrators 26. As employed in this 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 μm ± 0.03 μm, 8.40 μm ± 0.03 μm, 9.48 μm ± 0.04 μm, and 11.10 μm ± 0.04 μm, respectively, which correspond to wavelengths around which water and glucose absorb electromagnetic
30 radiation. Typical bandwidths for these filters range from 0.20 μm to 0.50 μm.

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 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. 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

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 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 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 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 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
5 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
10 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
15 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
20 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
25 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
30 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 5 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 10 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 15 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 20 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 25 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. Noninvasive 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 30 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 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

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 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 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 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 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 5 150 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 $F(?)$. Additionally, a phase difference may be measured between the analytical signal Q and either or both reference signals P, R. 10

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 concentration, the phase difference $F(?)$ decreases relative to the first (surface) reference signal P and increases relative to the second (deep tissue) reference signal R. The phase difference(s) $F(?)$ are directly related to analyte concentration and can be used to make accurate determinations of analyte concentration. 15

The phase difference $F(?)$ between the first (surface) reference signal P and the analytical signal Q is represented by the equation: 20

$$F(?) = |t_P - t_Q|$$

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

The phase difference $F(?)$ between the second (deep tissue) reference signal R and the analytical signal Q signal is represented by the equation: 25

$$F(?) = |t_Q - t_R|$$

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) 30 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 induced heat, friction and vibration.

5 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
10 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, 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
15 of additional chemical analytes, including but not 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,
20 hormones, as well as other chemical compounds. To detect a given analyte, one needs only 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
25 virtually any kind.

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.

30 As previously shown in FIGURE 8, once a thermal gradient is induced in the sample, the reference and analytical signals P, Q, R fall out of phase with respect to each other. This phase difference $F(?)$ 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.

An oscillating thermal gradient is illustrated using a sinusoidally modulated
5 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
10 event (e.g., cooling) is induced at the sample surface. This causes a decline in the detector 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
15 rise as the sample temperature rises. At some later time t_{C2} , another cooling event is 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.

20 As previously explained in the discussions relating to FIGURE 8, the phase difference $F(?)$ 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
25 delay dependent on the analyte concentration. With increasing concentration, the analytical signal K shifts to the left in FIGURE 9. As with FIGURE 8, the phase difference $F(?)$ may be measured. For example, a phase difference $F(?)$ 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
30 sample.

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 from analysis of wide variety of standards of known analyte concentration. In one
5 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 $F(?)$ may be measured continuously
10 throughout the test period. The phase-difference measurements may be integrated over the entire test period for an extremely accurate measure of phase difference $F(?)$. 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
15 amplitude between the analytical and reference signal(s) may be measured and employed to 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
20 measure the concentration of one or more analytes. By choosing reference and analyte 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
25 using signal processing with Fourier transforms or other techniques allows accurate determinations of phase difference $F(?)$ 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
30 the "zero crossings" (the point at which the signal amplitude changes from positive to 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 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.

10 It has been found that when analyzing a sample of human skin, a temperature event 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 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 $F(?)$ 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 driving frequency may continue for an arbitrarily chosen number of cycles (in region SL_1), for example, two full cycles. Then the fast driving frequency is employed for a selected duration, in region F_1 . 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 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 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 are hereby incorporated by reference herein and made a part of this specification.

B. Whole-Blood Detection System

1. 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.

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-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 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.

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

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
5 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
10 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 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
15 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 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
20 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 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 ;
25 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 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
30 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 .

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 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.

2. Sample Elements

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 entire contents of which 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 entire contents of which 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 entire contents of which 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 contents of which is hereby incorporated by reference herein 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.)

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.

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.

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 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 0.327 μL . Of course, the volume of the sample cell 242 and the cuvette 240 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 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 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 - 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 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 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 Serial No. 10/200,384, filed July 19, 2002, titled REAGENT-LESS WHOLE-BLOOD GLUCOSE METER, the entire contents of which is hereby incorporated by reference herein and made a part of this specification.

3. Further Sample Element Arrangements

Additional embodiments of sample elements enable additional and more accurate analysis methodologies. As discussed more fully below, one embodiment provides a sample element that has a sample cell wall constructed of a material with advantageous physical and radiation transmission properties. These properties enable the sample cell wall to be made thin, reducing the absorption of the sample cell wall. By reducing the absorption of the sample cell wall, the level of the analyte can be more accurately determined. In another embodiment, at least two different materials are used as sample cell walls in at least one sample cell. By providing multiple sample cell wall materials, the absorption of the sample cell wall(s) can be corrected for and the analyte level can be more accurately determined. Providing multiple sample cell wall materials also enables correction for other sources of error, e.g., the effect of different quantities of sample in each sample cell, the effect of sample cell wall thickness variations, etc.

FIGURE 18 illustrates another embodiment of a sample element, indicated by the reference numeral 600, that can be used in a reagentless whole-blood analyte detection

system, such as those described herein. For example, the detection system preferably includes an infrared radiation source and a detector. The detection system preferably is capable of being deployed near a patient and may incorporate other elements, such as those described above in connection with the whole-blood analyte detection systems.

5 As discussed above in connection with the cuvette 240, the sample element 600 is configured to be positioned in the optical path of radiation emitted by a source. The sample element 600 includes an elongate member 605, a sample cell wall 610, a cover 615, and a sample supply passage 620. The elongate member 605 can be constructed of plastic, cardboard, metal, glass, or any other suitable material. The elongate member 605 has a
10 planar side 625 and at least one peripheral edge 630. In various embodiments, the elongate member 605 includes features to aid in the handling of and the placement of the sample element 600.

 In one embodiment an opening 635 is located on the peripheral edge 630 of the elongate member 605. The opening 635 need not be located on the peripheral edge 630. It
15 can be located on any peripheral edge, on the planar side 625, on any surface of the sample element 600. In the illustrated embodiment, the opening 635 spans at least a portion of the thickness of the peripheral edge 630.

 In one embodiment, the sample cell wall 610 has an inner side 640, an outer side 645, and a sample cell wall thickness T defined between the inner side 640 of the sample
20 cell wall 610 and the outer side 645 of the sample cell wall 610. In one embodiment, the sample cell wall 610 is circular in shape and is formed as a thin plate. The inner side 640 of the sample cell wall 610 in part defines a sample cell 650. The sample cell wall 610 can be constructed of any suitable material. As discussed above, the material preferably transmits sufficient radiation in a range of interest for a detection system to perform whole-
25 blood analyte detection. For example, the material can be chosen to transmit a substantial portion of radiation in a range of wavelengths between about $6\ \mu\text{m}$ and about $12\ \mu\text{m}$. Preferably, the sample cell wall 610 does not absorb more than about ten percent of the radiation that is incident upon it. In one embodiment, the sample cell wall 610 is constructed of mylar. The sample cell wall 610 advantageously can be constructed of
30 polyethylene and deuterized polyethylene. Other materials that could be used for the sample cell wall 610 include silicon, germanium, diamond, semiconductor materials, and various other plastics.

Also, the thickness of the sample cell wall 610 can be any suitable thickness. Preferably the thickness of the sample cell wall 610 is such that absorption by the material chosen is relatively small. In one embodiment, the sample cell wall 610 is less than about 1 μm thick. In addition to being very thin, the sample cell wall 610 is preferably constructed
5 to have a consistent thickness. A sample cell wall 610 that is thin and that has a consistent thickness can be manufactured by carefully stretching a film of the chosen material.

The cover 615 is coupled with the planar side 625 of the elongate member 605. In the illustrated embodiment, the cover 615 at least partially defines the sample cell 650. The cover 615 preferably has properties similar to the properties of the sample cell wall 610.
10 However, the cover 615 may absorb less or more radiation than does the sample cell wall 610 in some embodiments. In some embodiments, the cover 615 is constructed of a material that absorbs radiation at wavelengths that differ from those of the sample cell wall 610.

The sample supply passage 620 extends from the opening 635 to the sample cell
15 650. In one embodiment, the sample supply passage 620 includes a sample cell passage 655 and a vent passage 660. The sample cell passage 655 extends between the opening 635 and the sample cell 650. The vent passage 660 communicates with the sample cell 650 and provides a region into which air located in the sample cell 650 can be forced when a sample moves into the sample cell 650. The sample supply passage 620 advantageously provides a
20 mechanism to deliver a sample to the sample cell 650 without using complex techniques used in a laboratory setting, such as pipetting or micro-pipetting.

The movement of a sample to the sample cell 650 preferably is achieved through capillary action, but may also be achieved through wicking, or a combination of wicking and capillary action. One or more flow enhancers may be incorporated into a sample
25 element, such as the sample element 600 to improve the flow of blood into the sample cell 650. A flow enhancer can result from any of a number of physical treatments, chemical treatments, or any topological features on one or more surface of the sample supply passage 620 that improves the flow of the sample into the sample cell 650 compared to a sample supply passage without a flow enhancer. In one embodiment of the sample supply passage
30 620 a flow enhancer is provided by forming one very smooth surface and an opposing surface that has small pores or dimples. These features can be formed by a process where granulated detergent is spread on one surface. The detergent is then washed away to create

the pores or dimples. Another flow enhancer can be formed in the sample supply passage 620 by depositing a surfactant in the passage. Other processes by which flow enhancers can be incorporated into the sample supply passage 620 include a discharge of an electrical voltage, an application of an electrical current, or a corona discharge. These flow enhancers advantageously lower the surface tension of one or more of the surfaces that define the sample supply passage 620, thereby improving flow of a sample in the sample supply passage 620 to the sample cell 650.

By incorporating one or more flow enhancers into the sample element 600, the volume of the sample supply passage 620 can be reduced, the filling time of the sample element 600 can be reduced, or both the volume and the filling time of the sample element 600 can be reduced. Further details concerning flow enhancers and sample elements that incorporate them are disclosed in U.S. Patent Application Serial No. 10/200,384, filed July 19, 2002, titled REAGENT-LESS WHOLE-BLOOD GLUCOSE METER, incorporated by reference above.

The embodiment illustrated in FIGURES 18-19 is a three-layer sample element design. In the illustrated embodiment, the three layers comprise the elongate member 605, the sample cell wall 610, and the cover 615. These layers can be manufactured by any suitable process. In one manufacturing method, the three layers are made of one or more polymeric material, i.e., plastic, and are formed by a stamping process wherein they are stamped out of a larger sheet of plastic. The three layers are joined together by a laminating process. For example, after the elongate member 605, the sample cell wall 610, and the cover 615 are formed via a stamping process, they are laminated together by interposing an adhesive between adjacent layers. For example, an adhesive (not shown) can be interposed between the sample cell wall 610 and the elongate member 605 and an adhesive (not shown) can be interposed between the cover 615 and the elongate member 605. The adhesive is then cured to form the laminated three-layer structure. This manufacturing process has the advantage of being relatively inexpensive and capable of producing large quantities of sample elements in parallel.

FIGURE 20 illustrates a sample element 600A that is substantially the same as the sample element 600, except as discussed below. The sample element 600A includes an elongate member 605A and a sample cell wall 610A. As can be seen, the elongate member 605A and the sample cell wall 610A comprise a unitary construction, i.e., are integrated

into a single layer. The embodiment illustrated by FIGURES 18 and 20 is, therefore, a two-layer sample element design. In the illustrated embodiment, the sample cell wall 610A is shown as a distinct component that is received by a recess formed on one side of the elongate member 605A. In another embodiment, the sample cell wall 610A is the portion of the elongate member 605A adjacent to the sample cell 650 that is parallel to the planar side 625.

The embodiments illustrated by FIGURES 18 - 20 can be constructed using the stamping and laminating processes discussed above. These embodiments can also be constructed using an injection molding process. For example, the elongate member 605A and the sample cell wall 610A can be formed as a single piece using an injection molding process. The cover 615 can then be attached by any suitable fastening technique, e.g., using an adhesive, as discussed above. Alternatively, the cover 615 and the elongate member 605A could be formed as a single piece using an injection molding process. The sample cell wall 610A could then be attached using any suitable fastening technique, e.g., using an adhesive, as discussed above. Like stamping, injection molding provides the advantages of cost savings and large scale production.

FIGURE 21 illustrates a sample element 600B that is substantially the same as the sample element 600, except as discussed below. The sample element 600B includes a sample cell wall 610B that includes a first portion 665 and a second portion 670. The first portion 665 bounds, i.e., forms a boundary of, a portion of a first region 675 of the sample cell 650B. The second portion 670 bounds a portion of a second region 680 of the sample cell 650B. The dashed line shown in FIGURE 21 indicates that the first region 675 and the second region 680 are not necessarily separated by a physical structure. Rather, they preferably are regions of a single volume. Of course, the regions 675, 680 could be separated by an internal structure, such as a septum, so long as the sample can flow into both regions.

The first portion 665 and the second portion 670 preferably are formed such that transmission of radiation through the first region 675 and the first portion 665 of the sample cell wall 610B is different from the transmission of radiation through the second region 680 and the second portion 670 of the sample cell wall 610B. In one embodiment, this is accomplished by forming the first portion 665 and the second portion 670 of different materials. In one embodiment, one of the first portion 665 and the second portion 670 is

formed of mylar, while the other of the first portion 665 and the second portion 670 is formed of a material other than mylar. In another embodiment, the first portion 665 is formed of polyethylene and the second portion 670 is formed of deuterized polyethylene. In another embodiment, the first portion 665 and the second portion 670 are formed of
5 mylar.

As discussed more fully below, by incorporating the first portion 665 and the second portion 670 having different transmission characteristics into the sample element 600B, various useful analysis techniques are made possible.

FIGURES 22 – 24 illustrate another embodiment of sample element, indicated by
10 the reference numeral 700, that can be used in a reagentless whole-blood analyte detection systems hereinbefore described. The sample element 700 includes an elongate member 705, a first sample cell wall 710, a second sample cell wall 715, and a cover 720. The elongate member 705 has a planar side 725 and at least one peripheral edge 730. In one embodiment, an opening 735 is located on the peripheral edge 730 of the elongate member
15 705. As discussed above in connection the sample element 600, the opening 735 need not be located on any particular peripheral edge. In the illustrated embodiment, the opening 735 spans at least a portion of the thickness of the peripheral edge 730. The cover 720 is coupled with the planar side 725 of the elongate member 705. The elongate member 705 and the cover 720 at least partially define a first sample cell 740 and a second sample cell
20 745.

The first sample cell wall 710 is similar in construction to the sample cell wall 610. For example, the first sample cell wall 710 comprises a first material that transmits a substantial portion of radiation in a range of wavelengths between about 6 μm and about 12 μm . The first sample cell wall 710 has an inner side that partially defines the first sample
25 cell 740. The second sample cell wall 715 is similar in construction to the sample cell wall 610. For example, the second sample cell wall 715 has an inner side that partially defines the second sample cell 745. The second sample cell wall 715 comprises a second material that transmits a substantial portion of radiation in a range of wavelengths between about 6 μm and about 12 μm . The second material can, but need not be, different from the material
30 used to form the first sample cell wall 710. In one embodiment, the first sample cell wall 710 comprises mylar, and the second sample cell wall 715 comprises a material other than mylar. In another embodiment, the first sample cell wall 710 comprises mylar and the

second sample cell wall 715 comprises mylar. In another embodiment, the first sample cell wall 710 comprises polyethylene and the second material comprises deuterized polyethylene. A sample carrier having two sample zones is disclosed in U.S. Patent No. 5,977,545, incorporated by reference herein above.

5 The sample element 700 also has a sample supply passage 750 that comprises a first branch 755, a second branch 760, and a third branch 765. The first branch 755 of the sample supply passage 750 extends from the opening 735 to the first sample cell 740. The second branch 760 of the sample supply passage 750 extends from the first sample cell 740 to the second sample cell 745. The third branch 765 of the sample supply passage 750
10 communicates with the second sample cell 745 and, in one embodiment communicates with the ambient environment. The third branch 765 of the sample supply passage 750 provides a volume into which air in the second sample cell 745 can be vented, i.e., into which air in the second sample cell 745 can move when it is displaced by a sample that moves into the second sample cell 745.

15 FIGURE 24 illustrates a sample element 700A that is substantially the same as the sample element 700, except as discussed below. The sample element 700A includes an elongate member 705A, a first sample cell wall 710A, and a second sample cell wall 715A. As can be seen, the elongate member 705A, the first sample cell wall 710A, and the second
20 sample cell wall 715A comprises a unitary construction, i.e., are integrated into a single layer. Thus, the embodiment illustrated by FIGURES 22 and 24 is a two-layer sample element design. As discussed above in connection with the sample element 600A, the elongate member 705A and the sample cell walls 710A, 715A can be constructed as a single piece or the elongate member 705A can be formed with two recesses configured to receive the sample cell walls 710A, 715A. In another embodiment, the elongate member
25 705A can be formed as a single piece with the cover 720, with the sample cell walls 710A, 715A being attached to the opposite side of the elongate member 705A via any suitable process, e.g., an adhesive.

 FIGURE 25 illustrates a further embodiment of a sample element 800. The sample element 800 includes an elongate member 802 and a single motion sample extractor 805
30 that is at least partially housed within the elongate member 802. The single motion sample extractor 805 is constructed in any suitable manner. In one embodiment, the single motion sample extractor 805 comprises an elongate piercing member that extends from the

elongate member 802 of the sample element 800. The single motion sample extractor 805 can include a metal lance, a lance made of sharpened plastic, or any other suitable rigid material. The sample extractor 805 works like a miniature razor-blade to create a slice, which can be very small, or a microlaceration into an appendage, such as a finger, forearm, or any other appendage. In this embodiment, the single motion sample extractor 805 is positioned adjacent an opening 810 of a sample supply passage 815. The opening 810 of the sample supply passage 815 is located such that the sample element 800 can be placed adjacent an appendage, moved laterally to create a slice in the appendage, and aligned with the opening 810. As may be seen, the width of the single motion sample extractor 805 is small compared to the width of the sample supply passage 815. This assures that the movement of the sample element 800 that creates the slice in the appendage also positions the opening 810 of the sample supply passage 815 at the slice. Thus, the sample element 800 eliminates the need to separately create a slice and to align the opening 810 of the sample element 800. Although the single motion sample extractor 805 is shown in connection with the sample element 800, it can be incorporated many different sample element configurations, including those illustrated herein.

4. Further Whole Blood Analysis Methodologies

Two measurements are performed to investigate a sample using the embodiments of sample elements illustrated by FIGURES 21 and 22-25. For this purpose, the openings 635 or 735 are brought into contact with a sample, e.g., whole-blood. As discussed above, the sample is transported to the first sample analysis region 675 and to the second sample analysis region 680 of the sample element 600B via the sample supply passage 620 or to the first sample cell 740 and the second sample cell 745 of the sample element 700 via the sample supply passage 750. Infrared radiation is directed through the sample regions 675, 680 or through the sample cells 740, 745. Two infrared spectra are obtained and are combined a whole-blood analyte detection system in such a way that one spectrum of the sample material is obtained that is not overlapped by absorption bands from materials within the sample cell walls 610B, 710. Wavelength ranges for the measurements can be selected by determining the spectra of the first portion 665 of the sample cell wall 610B, the second portion 670 of the sample cell walls 610B before introducing a sample into the sample cell 650B, or by determining the spectra of the sample cell wall 710 and the sample cell wall 715 before introducing a sample into the sample cells 740, 745. The ranges in

which absorption bands from materials in the first portion 665 of the sample cell wall 610B, the second portion 670 of the sample cell walls 610B, the sample cell wall 710, or the sample cell wall 715 are present are stored in the whole-blood analyte detection system. These ranges can then be disregarded in further analysis, e.g., when a combination spectrum is created from the spectra recorded individually. If ranges are present in which none of the materials in the sample cell wall 610B or in which none of the materials in the sample cell walls 710, 715 have any absorption bands, these ranges can be used to match the spectra with each other, i.e. to perform baseline corrections and define a scale of the spectra obtained. Moreover, these ranges can be used to determine the relative quantities of sample in the two sample cells 740, 745.

The sample elements disclosed herein can be used to create qualitative infrared spectra, but they are especially advantageous for use in quantitative infrared spectroscopy. To perform quantitative infrared spectroscopy to determine the concentration of an analyte in the sample, it is preferable that defined quantities of sample be introduced into the sample cells. By providing enclosed sample cells, the sample elements disclosed herein consistently provide about the same sample size, so long as they fill completely. If the sample cells do not fill completely, spectral ranges that are measured through the two sample cells 740, 745 can be used in order to determine the quantity in each of the sample cells 740, 745. Similarly, spectral ranges that are measured through the two portions of the sample cell wall 610B can be used to determine the quantity in each of the first and second analysis regions of the sample element 600B.

In addition to the embodiment of the method described above for infrared spectroscopy in which blank spectra of the sample cell walls 610B, 710, 715 are recorded, it is also possible to store the information on the materials of the sample cell walls 610B, 710, 715 in the whole-blood analyte detection system, or to read them in, preferably directly from a bar code on the sample element. In this case, the evaluating unit can select each of the ranges that are used in the evaluation without recording blank spectra.

The spectra of the sample cell walls 610B, 710, 715 without sample can be used to determine the actual characteristics, i.e. especially the thickness, of the sample cell walls 610B, 710, 715 because these parameters can fluctuate depending on manufacture. When the materials in the sample cell walls 610B, 710, 715 is known, the absorption bands can be used to deduce the thickness of the sample cell walls 610B, 710, 715. These data can be

used to correct the sample spectra, e.g. to take the absorption of the sample cell walls 610B, 710, 715 into account and if necessary, subtract them from the spectra obtained with the sample.

5 An opening of a sample element is brought into contact with a sample. The sample is transported to the sample cell(s), as discussed above, through a sample supply passage. To perform a spectroscopy using sample elements, sample cell volumes usually are provided in the range of a few microliters.

10 To perform a measurement, the sample element 600, 600A, 600B, 700, 700A is placed in a whole-blood analyte detection system, which may be an infrared spectrometer, using the elongate member 605, 605A, 605B, 705, 705A to position the sample element 600, 600A, 600B, 700, 700A so that the sample is in the optical path of a beam of radiation generated by a source. The infrared spectrometer can also be equipped with a bar code reader, a magnetic strip reader or another type of data acquisition device that enters data on the sample element 600, 600A, 600B, 700, 700A and, if necessary, information for spectral
15 analysis.

If the sample element has numerous sample cells, e.g. for evaluating a number of different samples, or if a sample element illustrated in FIGURES 21 and 22-24 is used, it is advantageous for the whole blood analyte detection system (e.g., a infrared spectrometer) to also be equipped with a transport device that makes it possible to position the sample
20 element in the spectrometer in such a way that each of the sample cells is positioned in succession in the optical path of the radiation emitted by the source of radiation.

When a sample cell is located in the optical path of the beam of radiation, the radiation will be incident upon it and will at least partially pass through it. Preferably, the measurement is performed in such a way that the entire sample is measured integrally, i.e.
25 the radiation is incident on the entire quantity of the sample. In this case, a quantitative measurement can be performed even if the sample is not distributed evenly in the sample cell.

The quantity of one or more analytes in the sample is determined based on the transmission spectrum (or spectra) of the sample, as discussed above. The quantity of
30 analyte in the sample can also be determined in a known manner, as disclosed in "Applied Spectroscopy, Vol. 47, pages 1519 to 1521 (1993)" with regard for procedures for

evaluating spectra, and as disclosed in patent application EP-A-0 644 413 with regard for performing quantitative spectroscopy.

One skilled in the art will appreciate that the analysis methodologies and sample elements described herein can incorporate, without being limited by, well known
5 techniques for sample element use and construction, such as some of those set forth in U.S. Patent No. 5,977,545, issued November 2, 1999, titled SAMPLE CARRIER FOR USE IN INFRARED TRANSMISSION SPECTROSCOPY, the entire contents of which is hereby incorporated by reference herein and made a part of this specification.

Although the present invention has been described in terms of certain preferred
10 embodiments, other embodiments apparent to those of ordinary skill in the art also are within the scope of this invention. Thus, various changes and modifications may be made without departing from the spirit and scope of the invention. Moreover, not all of the features, aspects and advantages are necessarily required to practice the present invention. Accordingly, the scope of the present invention is intended to be defined only by the claims
15 that follow.

WHAT IS CLAIMED IS:

1. A reagentless whole-blood analyte detection system capable of being deployed near a patient, comprising:

an infrared radiation source that emits radiation along an optical path;

5 a detector positioned in the optical path of the radiation; and

a sample element configured to be positioned in the optical path of the radiation, the sample element comprising:

10 an elongate member having a planar side and an opening located on a peripheral edge of the elongate member, the opening spanning at least a portion of the thickness of the elongate member;

a first sample cell wall in part defining a first sample cell, the first sample cell wall comprises a first material that transmits a substantial portion of radiation in a range of wavelengths between about 6 μm and about 12 μm ;

15 a second sample cell wall in part defining a second sample cell, the second sample cell wall comprises a second material that transmits a substantial portion of radiation in a range of wavelengths between about 6 μm and about 12 μm ;

20 a cover coupled with to the planar side of the elongate member, the cover at least partially defining at least one of the first sample cell and the second sample cell; and

25 a sample supply passage comprising a first branch and a second branch, the first branch of the sample supply passage extending from the opening to the first sample cell, the second branch of the sample supply passage extending from the first sample cell to the second sample cell.

2. The reagentless whole-blood analyte detection system of Claim 1, wherein the first material comprises mylar.

3. The reagentless whole-blood analyte detection system of Claim 1, wherein the second material comprises mylar.
4. The reagentless whole-blood analyte detection system of Claim 3, wherein the first material comprises mylar.
- 5 5. The reagentless whole-blood analyte detection system of Claim 1, wherein the first material comprises polyethylene.
6. The reagentless whole-blood analyte detection system of Claim 1, wherein the second material comprises deuterized polyethylene.
7. The reagentless whole-blood analyte detection system of Claim 6, wherein
10 the first material comprises polyethylene.
8. The reagentless whole-blood analyte detection system of Claim 1, wherein at least one of the first sample cell wall and the second sample cell wall is attached to the elongate member.
9. The reagentless whole-blood analyte detection system of Claim 1, wherein
15 the elongate member and at least one of the first sample cell wall and the second sample cell wall comprise a unitary construction.
10. The reagentless whole-blood analyte detection system of Claim 1, further comprising an air vent and an air vent passage extending from the air vent to at least one of the first sample cell, the second sample cell, and the sample supply passage.
- 20 11. A reagentless whole-blood analyte detection system capable of being deployed near a patient, comprising:
- an infrared radiation source that emits radiation along an optical path;
 - a detector positioned in the optical path of the radiation; and
 - a sample element configured to be positioned in the optical path of the
25 radiation, the sample element comprising:

an elongate member having a planar side and an opening located on a peripheral edge of the elongate member, the opening spanning a portion of the thickness of the elongate member;

5 a sample cell wall comprising an inner side, an outer side, and a sample cell wall thickness defined between the inner side of the sample cell wall and the outer side of the sample cell wall, the inner side of the sample cell wall in part defining a sample cell, the sample cell wall comprising a material selected from the group consisting of mylar, polyethylene, deuterized polyethylene;

10 a cover attached to the planar side of the elongate member, the cover at least partially defining the sample cell; and

a sample supply passage extending between the opening and the sample cell.

12. The reagentless whole-blood analyte detection system of Claim 11, wherein
15 the thickness of the sample cell is less than about 1 μm .

13. The reagentless whole-blood analyte detection system of Claim 11, wherein the sample cell wall comprises a first portion bounding a portion of a first region of the sample cell and a second portion bounding a portion of a second region of the sample cell.

14. The reagentless whole-blood analyte detection system of Claim 13, wherein
20 one of the first portion and the second portion of the sample cell wall comprises mylar.

15. The reagentless whole-blood analyte detection system of Claim 13, wherein the first portion of the sample cell wall comprises polyethylene.

16. The reagentless whole-blood analyte detection system of Claim 15, wherein the second portion of the sample cell wall comprises deuterized polyethylene.

25 17. The reagentless whole-blood analyte detection system of Claim 11, wherein the first sample cell wall is attached to the elongate member.

18. The reagentless whole-blood analyte detection system of Claim 11, wherein the elongate member and the first sample cell wall comprise a unitary construction.

19. A method for performing reagentless whole-blood analyte detection comprising:

5 providing a sample element having an opening, a first sample analysis region, a second sample analysis region, a cover at least partially defining the first sample analysis region and the second sample analysis region, and a sample supply passage extending between the opening and at least one of the first sample analysis region and the second sample analysis region;

10 positioning the opening of the sample element in contact with a sample, the sample being transported from the opening to at least one of the first sample analysis region and the second sample analysis region via the sample supply passage;

exposing the sample to infrared radiation in a suitable wavelength range directed generally perpendicularly to the first sample analysis region and the second sample analysis region;

15 detecting radiation transmitted through the sample in the first sample analysis region and through the sample in the second sample analysis region;

calculating the quantity of at least one analyte present in the sample based on the detecting of radiation transmitted through the sample in the first sample analysis region and through the sample in the second sample analysis region.

20 20. A sample element comprising:

an opening,

a first sample analysis region;

a first material associated with the first sample analysis region;

a second sample analysis region;

25 a second material associated with the second sample analysis region;

a cover at least partially defining the first sample analysis region and the second sample analysis region, and

a sample supply passage extending between the opening and at least one of the first sample analysis region and the second sample analysis region.

21. The sample element of Claim 20, further comprising a sample cell and a sample cell wall, the sample cell defining the first sample analysis region and the second
5 sample analysis region, the sample cell wall comprising the first material and the second material.

22. The sample element of Claim 20, further comprising a first sample cell, a first sample cell wall, a second sample cell, and a second sample cell wall, the first sample cell wall comprising the first material and at least partially defining the first sample analysis
10 region, the second sample cell wall comprising the second material and at least partially defining the second analysis region.

23. The sample element of Claim 20, wherein at least one surface of the sample supply passage has a surface tension, the surface tension being reduced by at least one of: a deposition of a granulated detergent, a deposition of a surfactant, dipping the sample supply
15 passage in a surfactant, a discharge of an electrical voltage, an application of an electrical current, or a corona discharge.

24. The sample element of Claim 20, wherein at least one surface of the sample supply passage has a low surface tension.

25. The sample element of Claim 20, further comprising a flow enhancer to
20 increase the flow of the sample in the sample supply passage to the sample cell.

26. The sample element of Claim 25, wherein the flow enhancer comprises a surfactant.

27. The sample element of Claim 25, wherein the flow enhancer comprises a physical treatment of at least a portion of the sample element.

28. The sample element of Claim 25, wherein the flow enhancer comprises a
25 chemical treatment of at least a portion of the sample element.

29. The sample element of Claim 25, wherein the flow enhancer comprises a topological feature on at least one surface of the sample element.

30. The sample element of Claim 20, further comprising a sample extractor.

31. The sample element of Claim 30, wherein the sample extractor is at least
5 partially housed by the sample element.

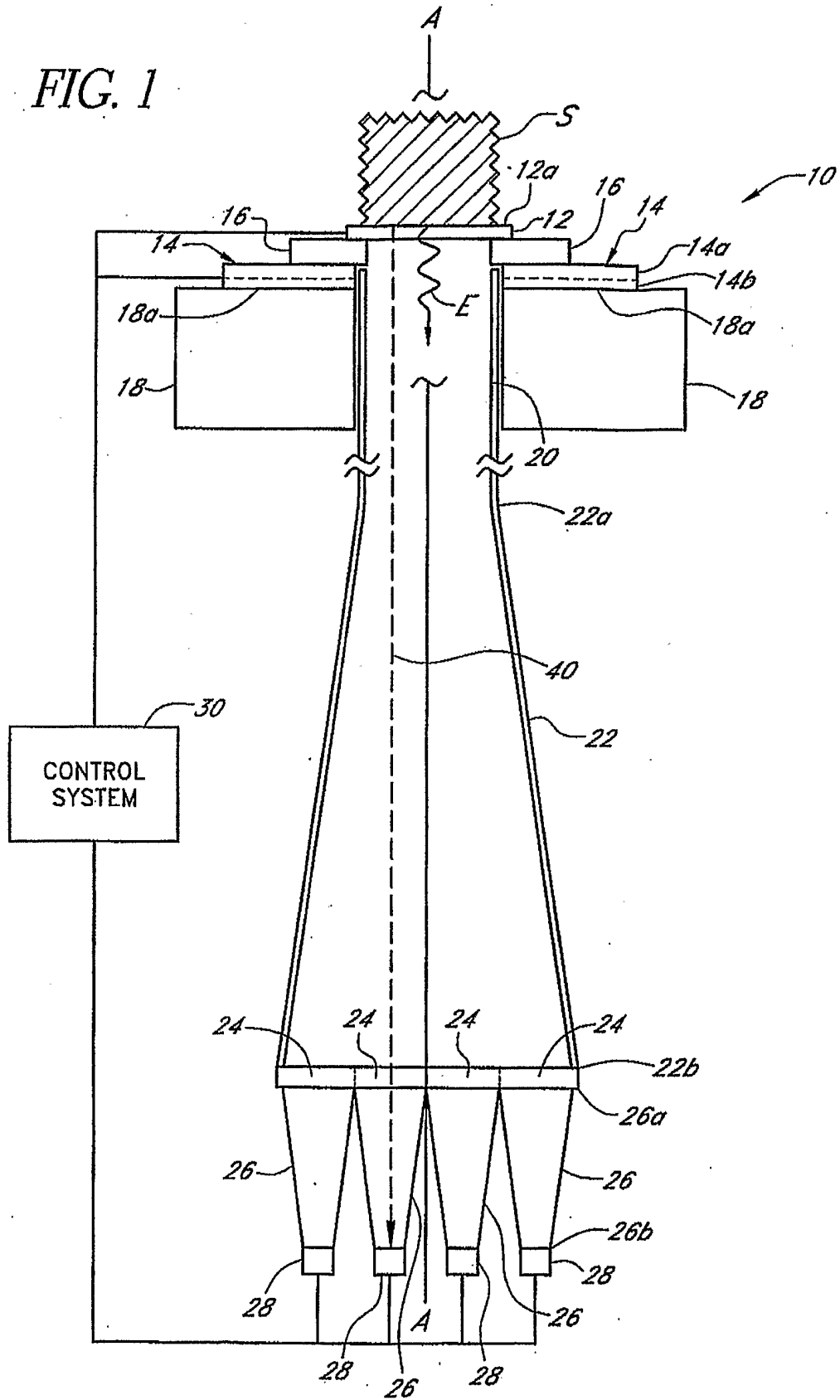
32. The sample element of Claim 30, wherein the sample extractor comprises a lance made of a material selected from the group consisting of: metal, plastic, or any other suitable rigid material.

33. The sample element of Claim 20, further comprising a single-motion sample
10 extractor, wherein a single motion of the sample element creates a laceration in an appendage and places the opening at the laceration so that the sample can be drawn into the sample element.

34. The sample element of Claim 33, wherein the sample extractor comprises a lance made of a material selected from the group consisting of: metal, plastic, or any other
15 suitable rigid material.

35. The sample element of Claim 33, wherein the sample extractor comprises an elongate piercing member that extends from a side of the sample element that has the opening, the longitudinal axis of the sample extractor being laterally offset from but generally parallel to the longitudinal axis of the sample supply passage, the elongate
20 piercing member being small compared to the size of the opening.

FIG. 1



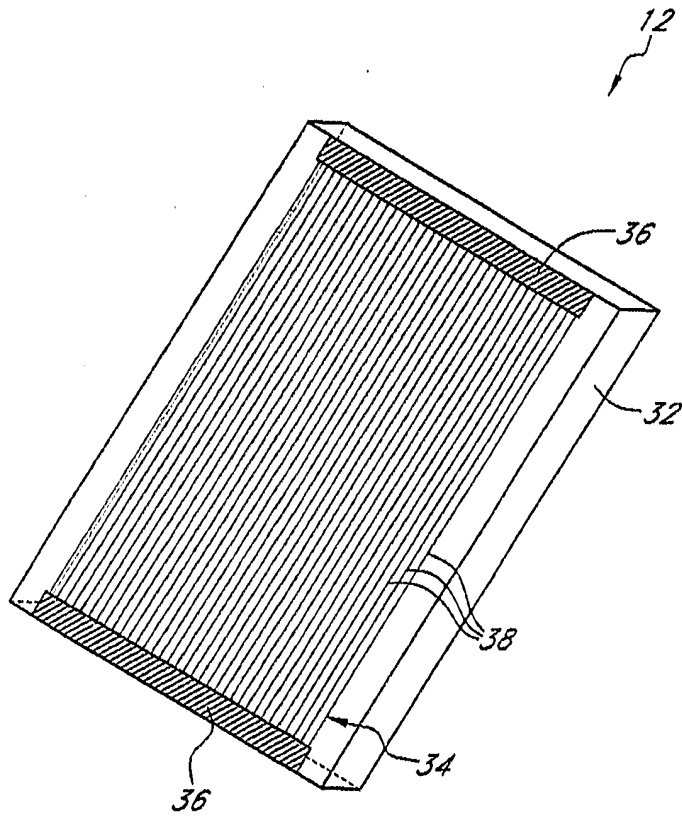


FIG. 2

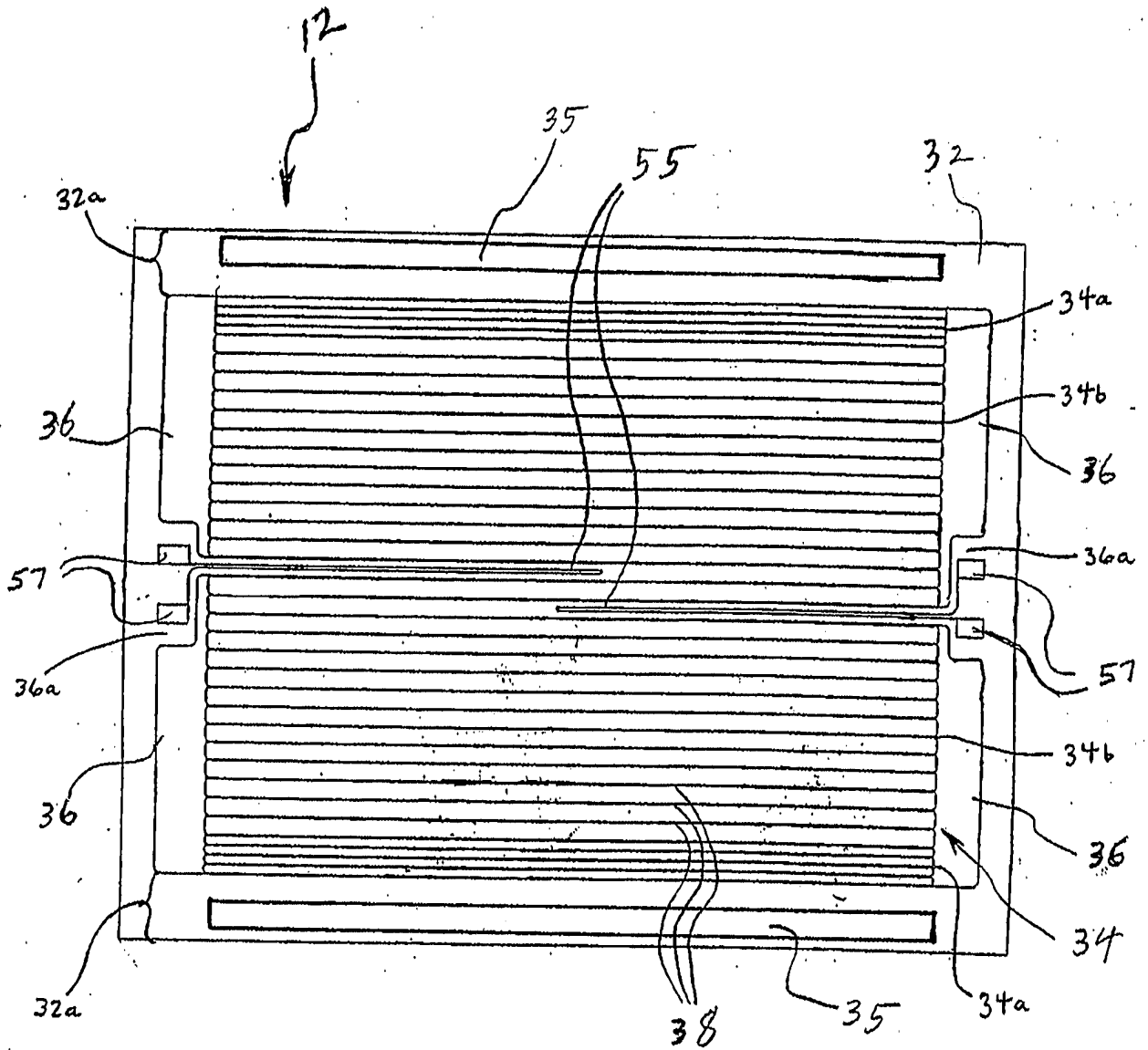


FIG. 2A

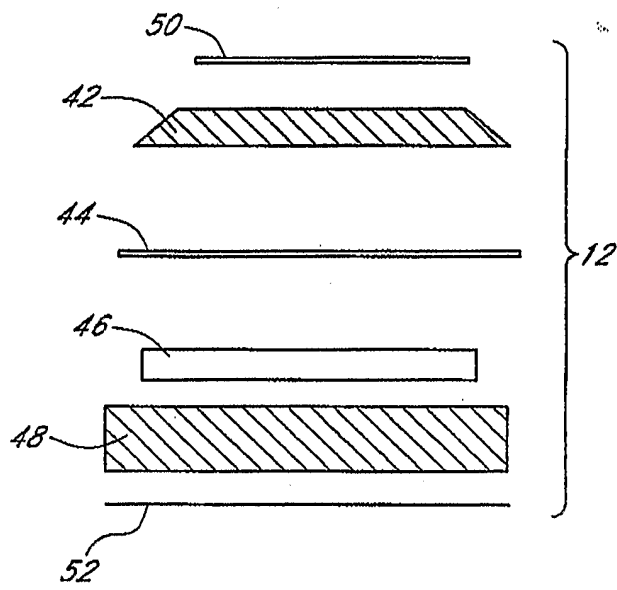


FIG. 3

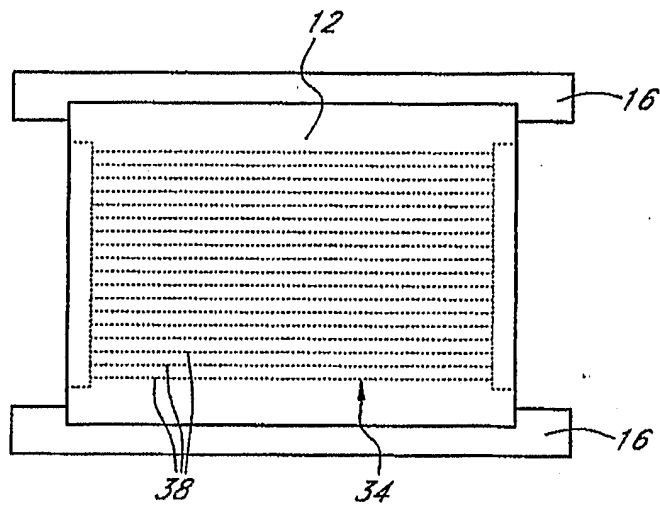


FIG. 4

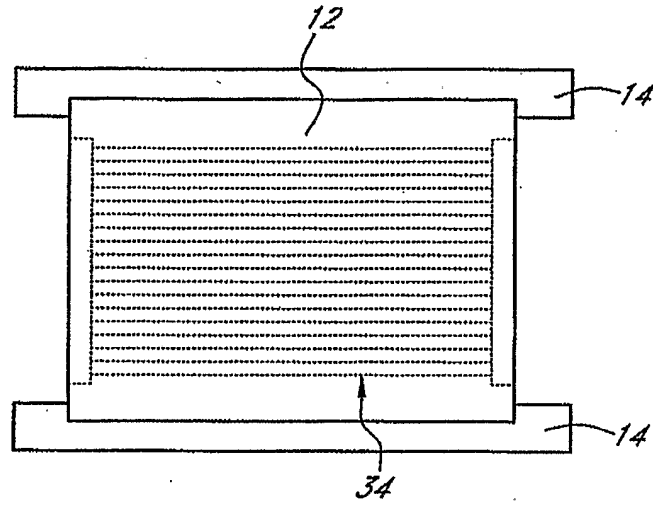


FIG. 5

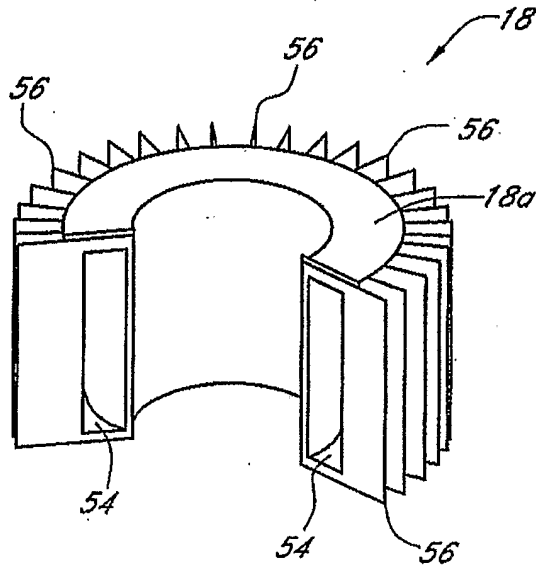


FIG. 6

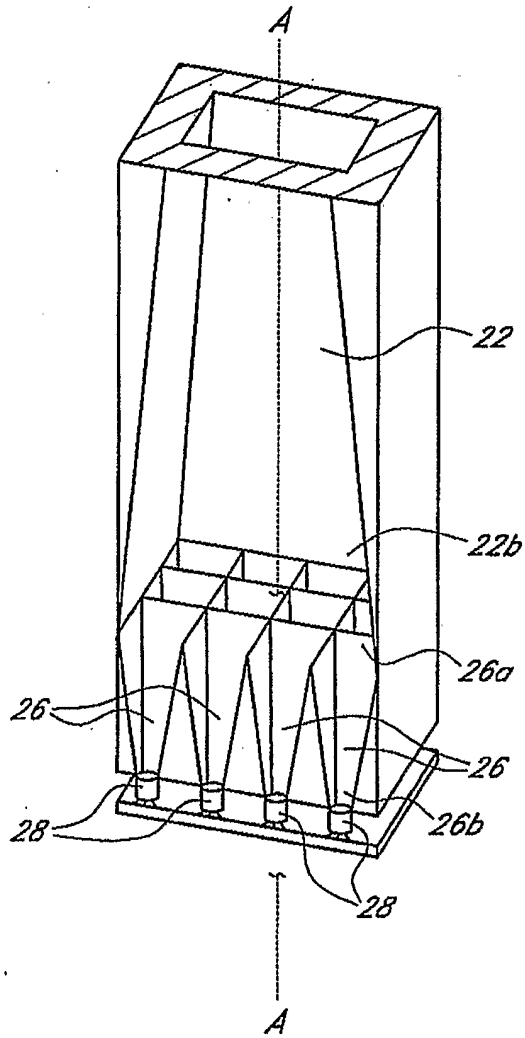


FIG. 6A

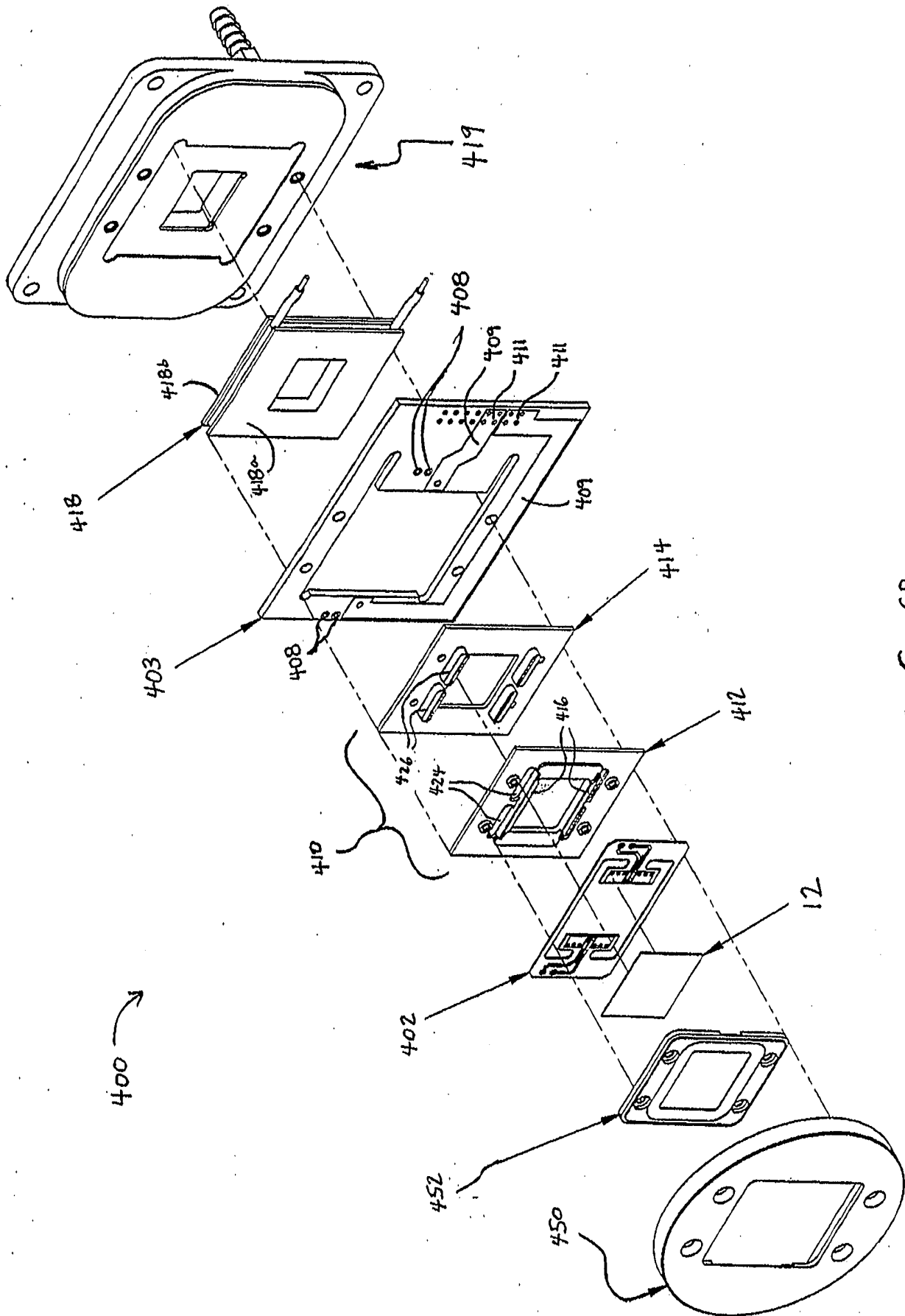


FIG. 6B

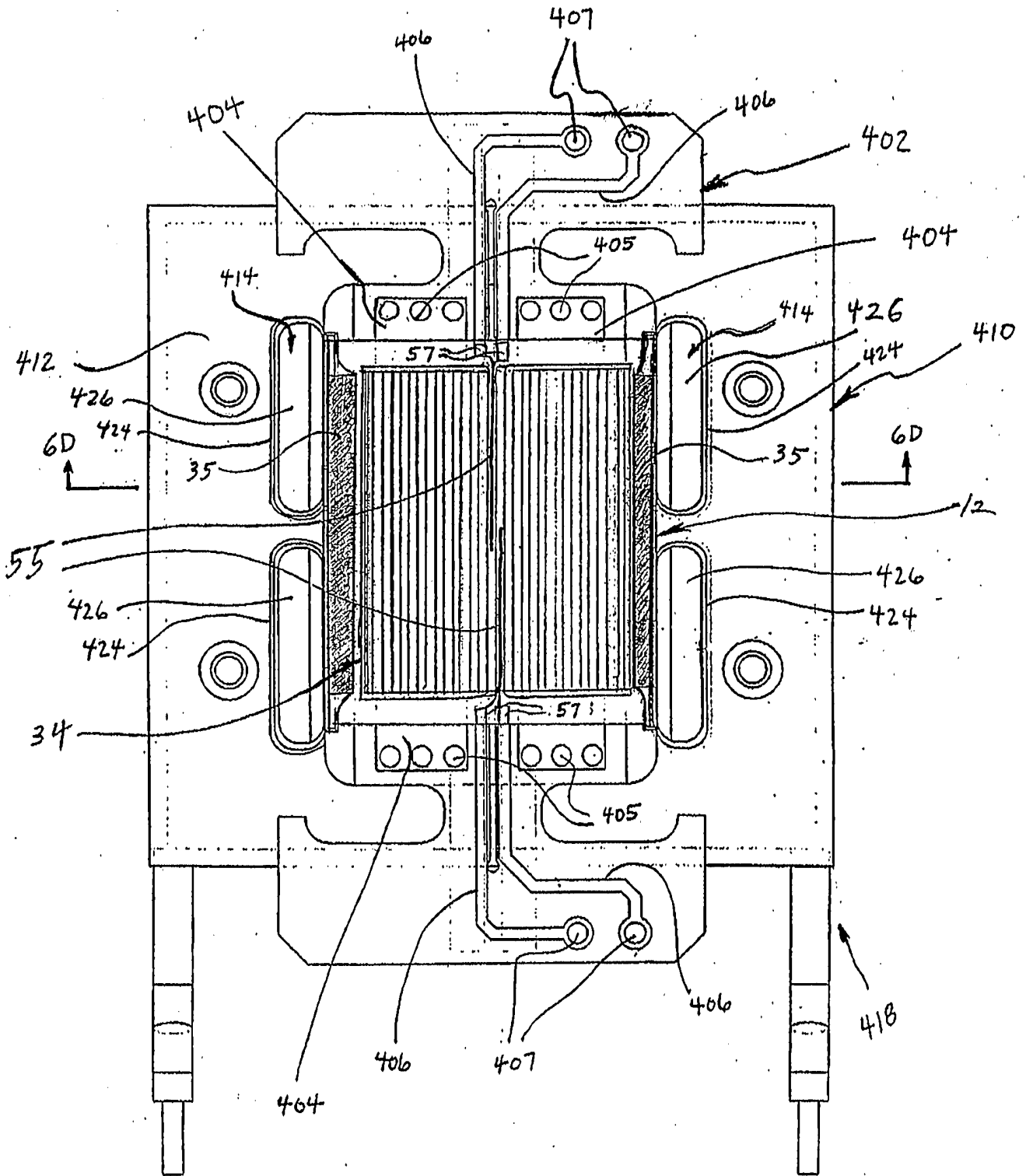


FIG. 6C

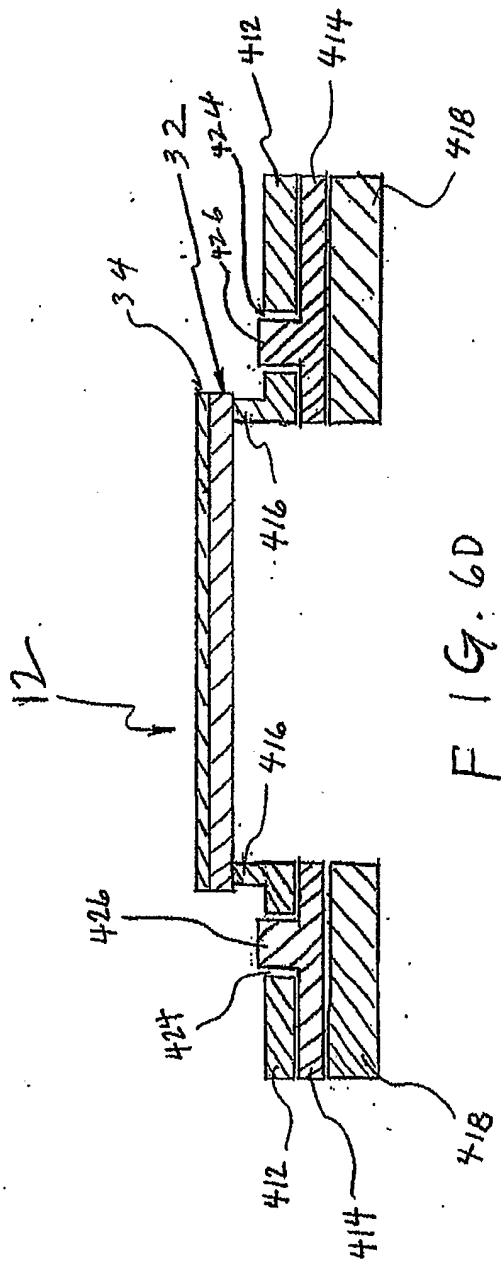
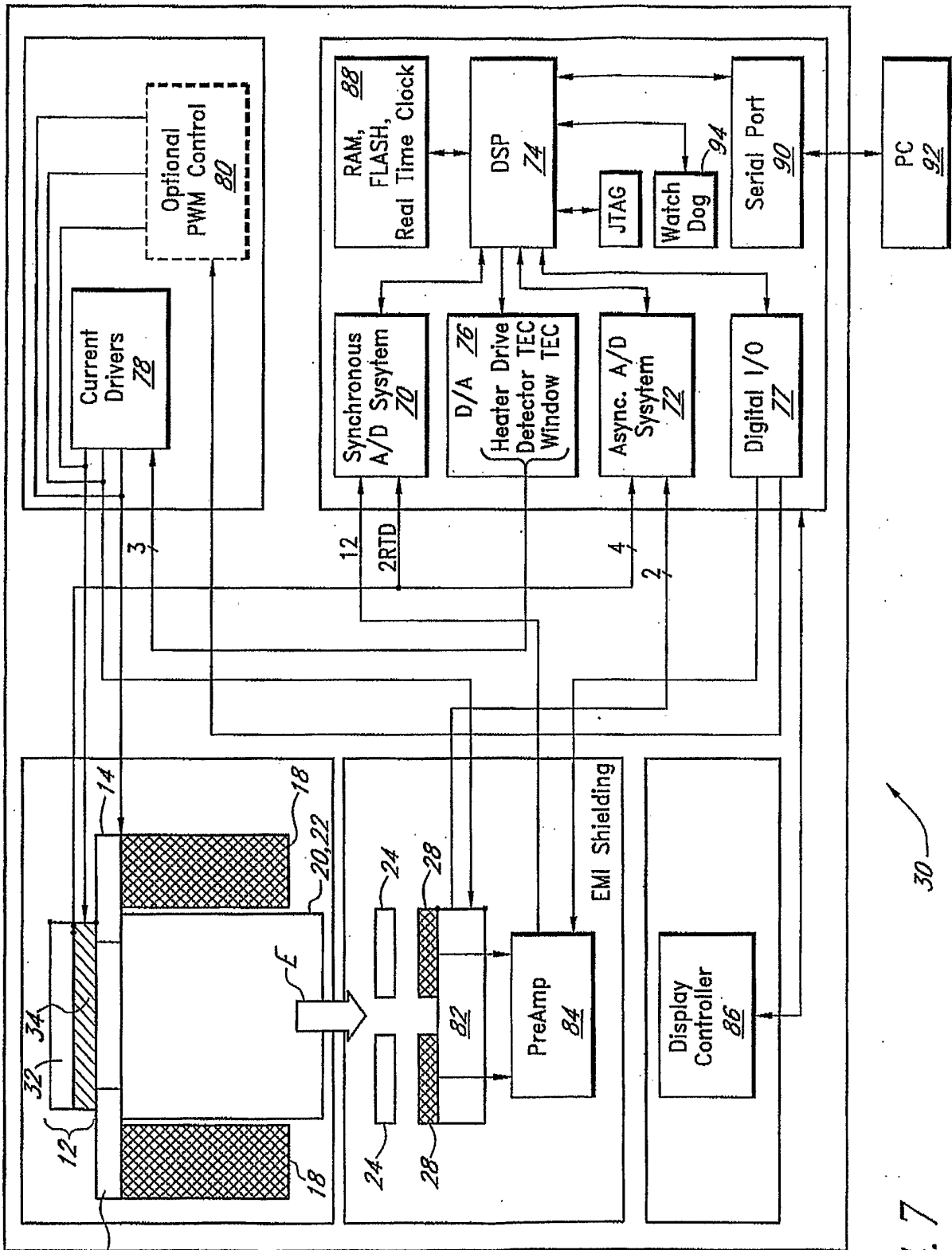


FIG. 6D



30

FIG. 7

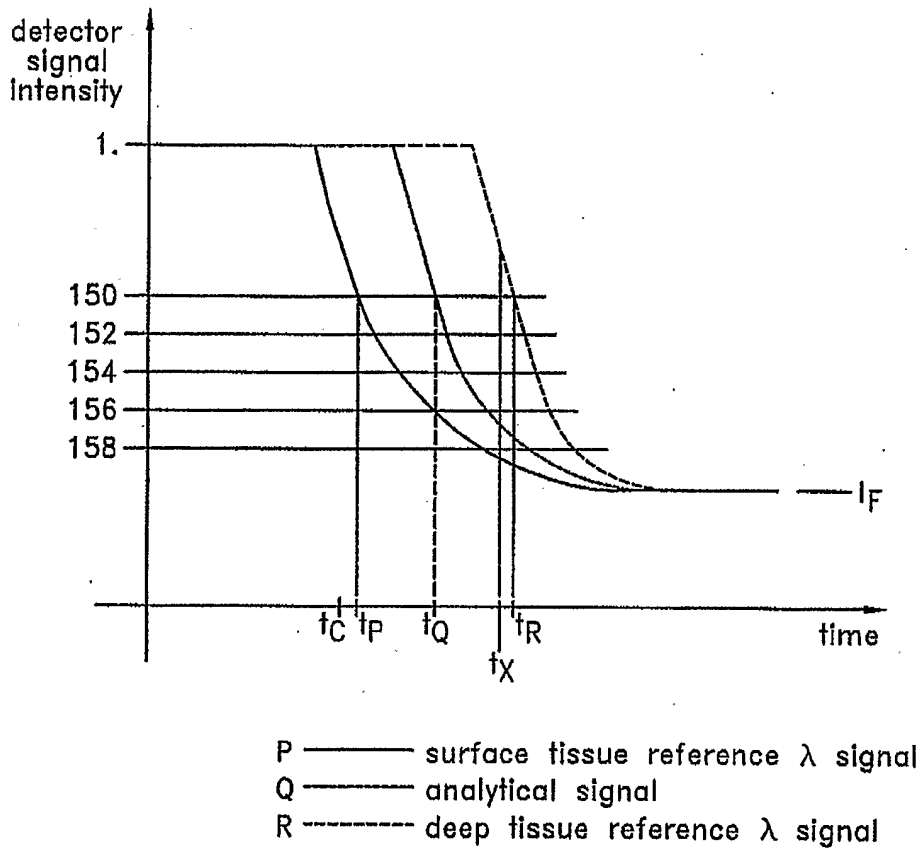


FIG. 8

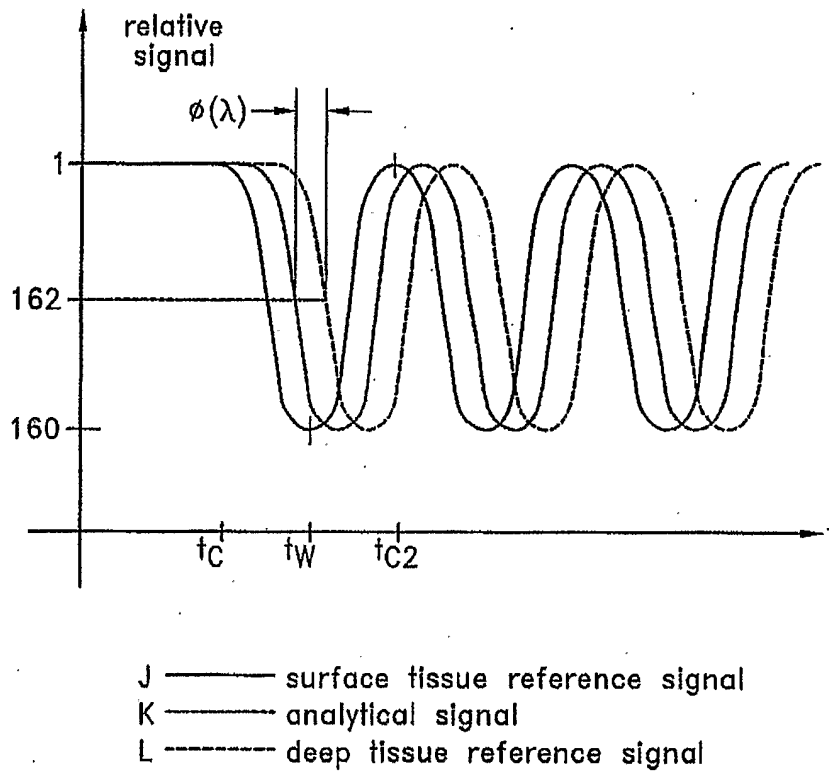


FIG. 9

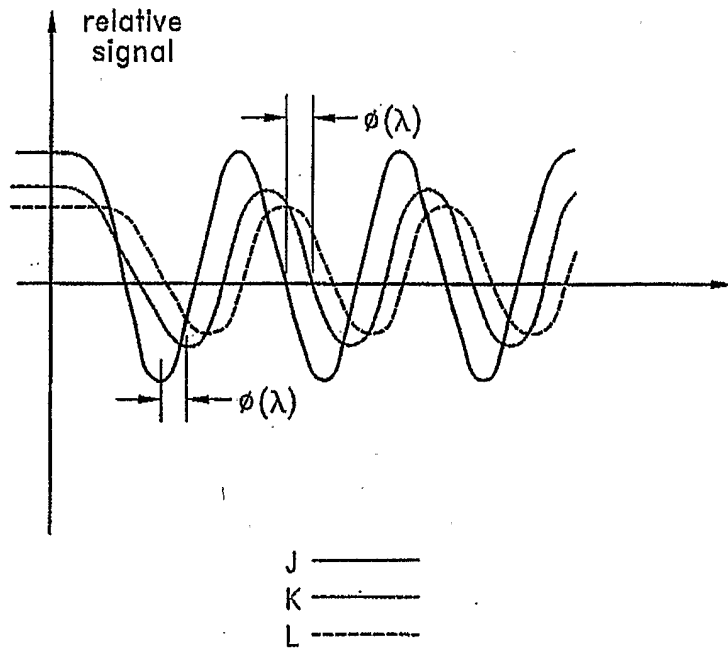


FIG. 10

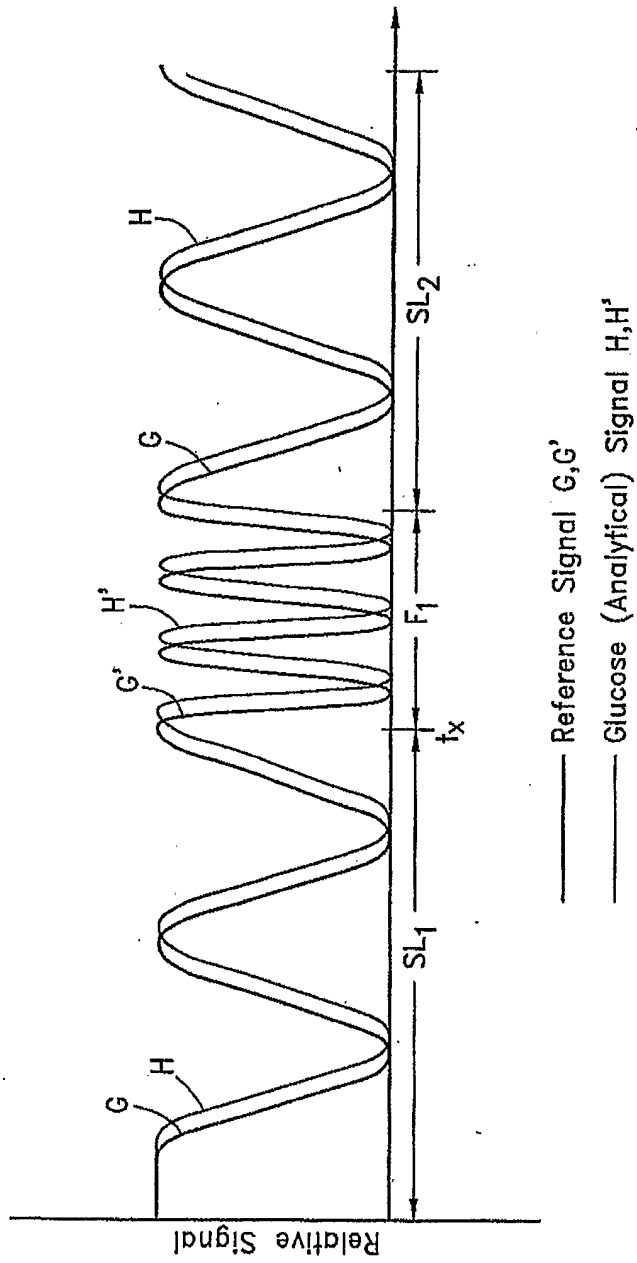


FIG. 11

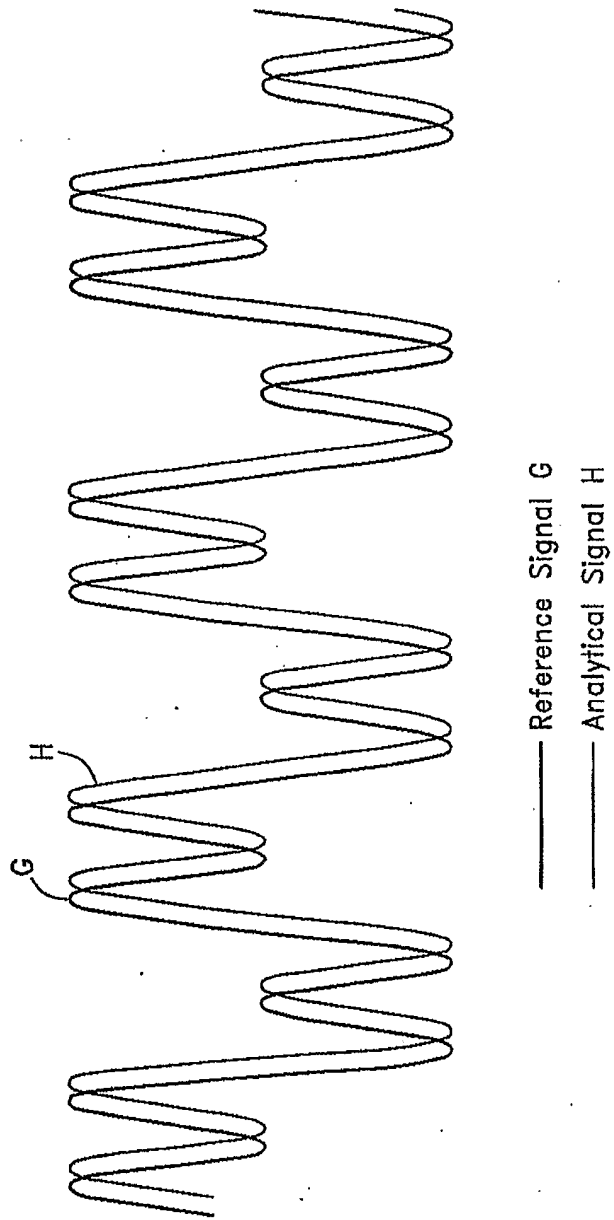


FIG. 12

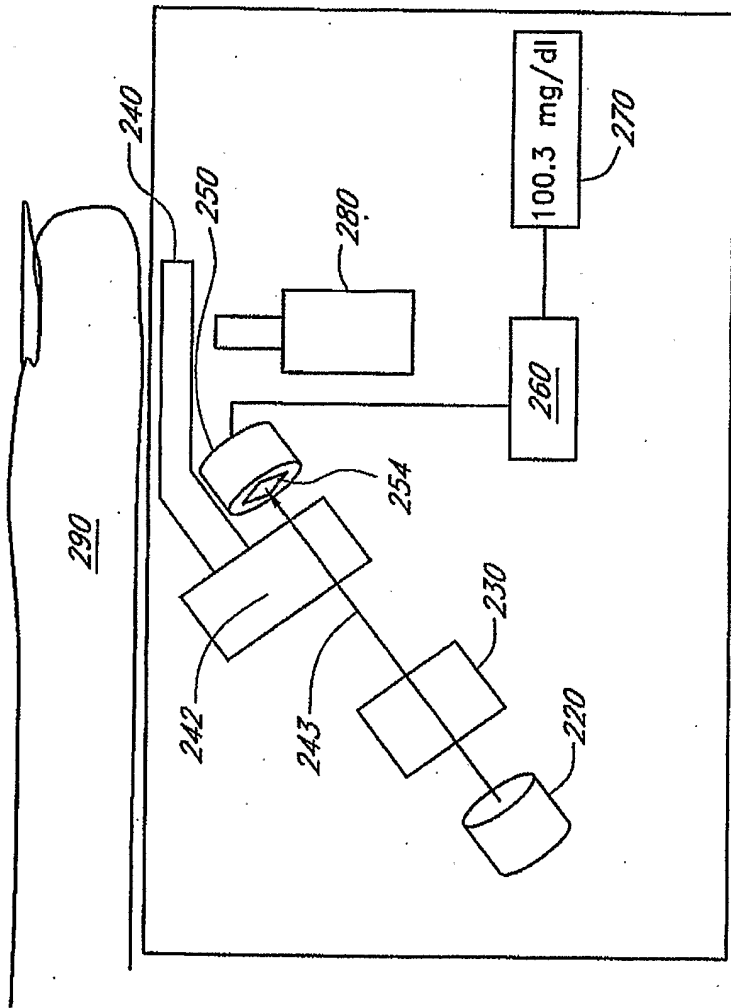


FIG. 13

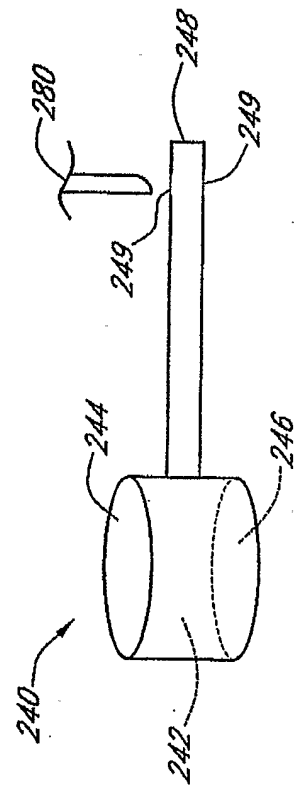


FIG. 14

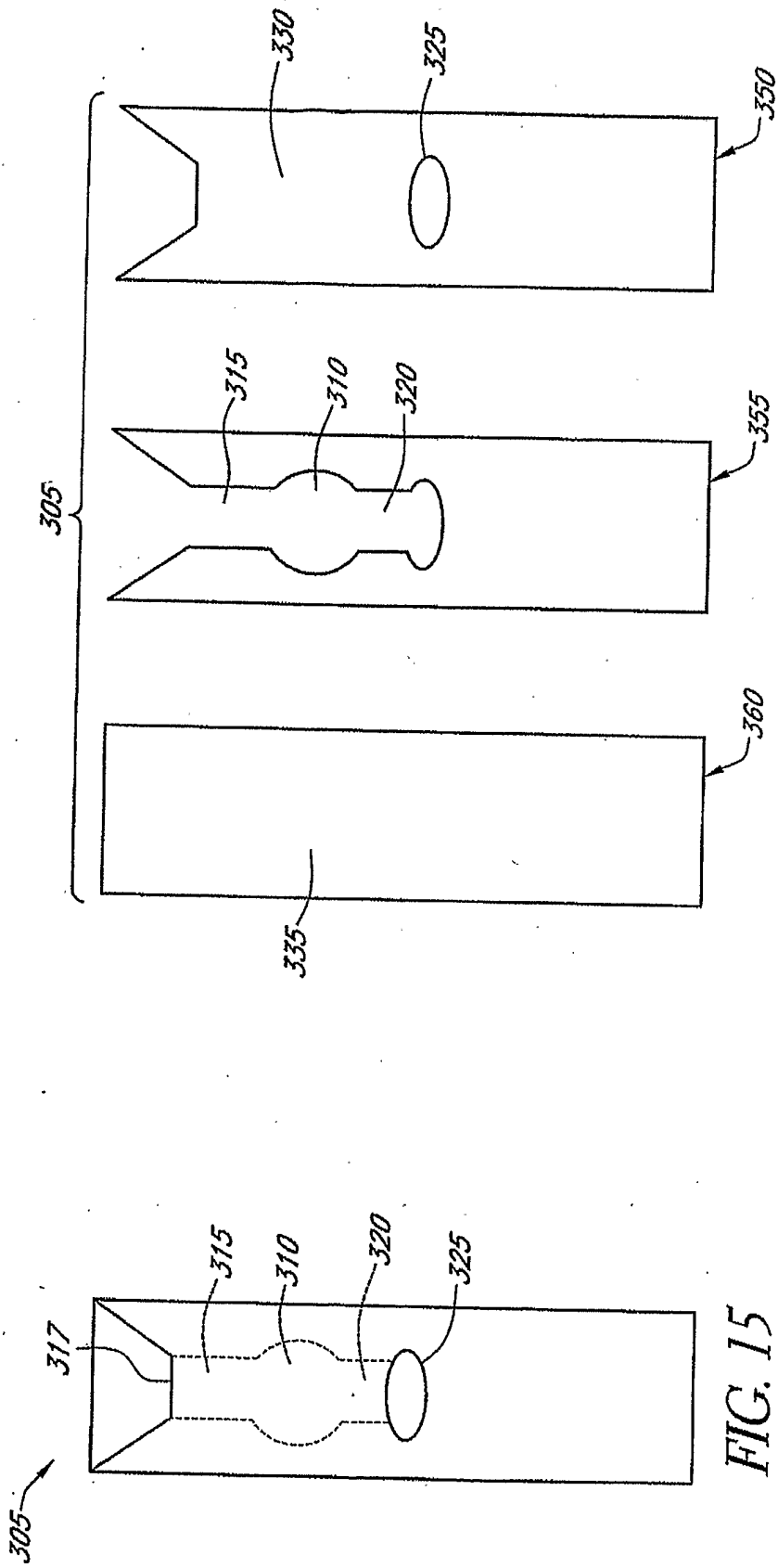


FIG. 16

FIG. 15

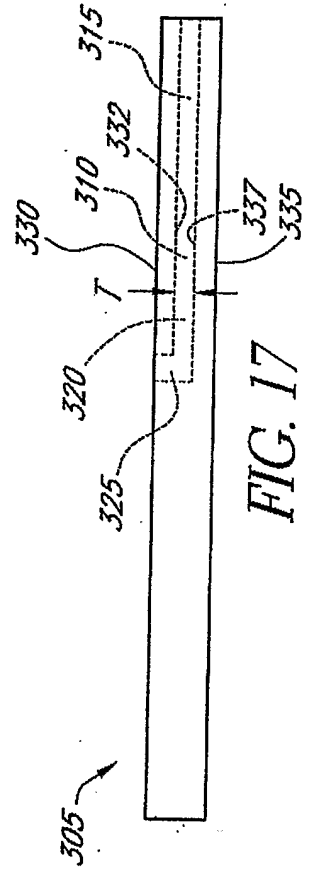


FIG. 17

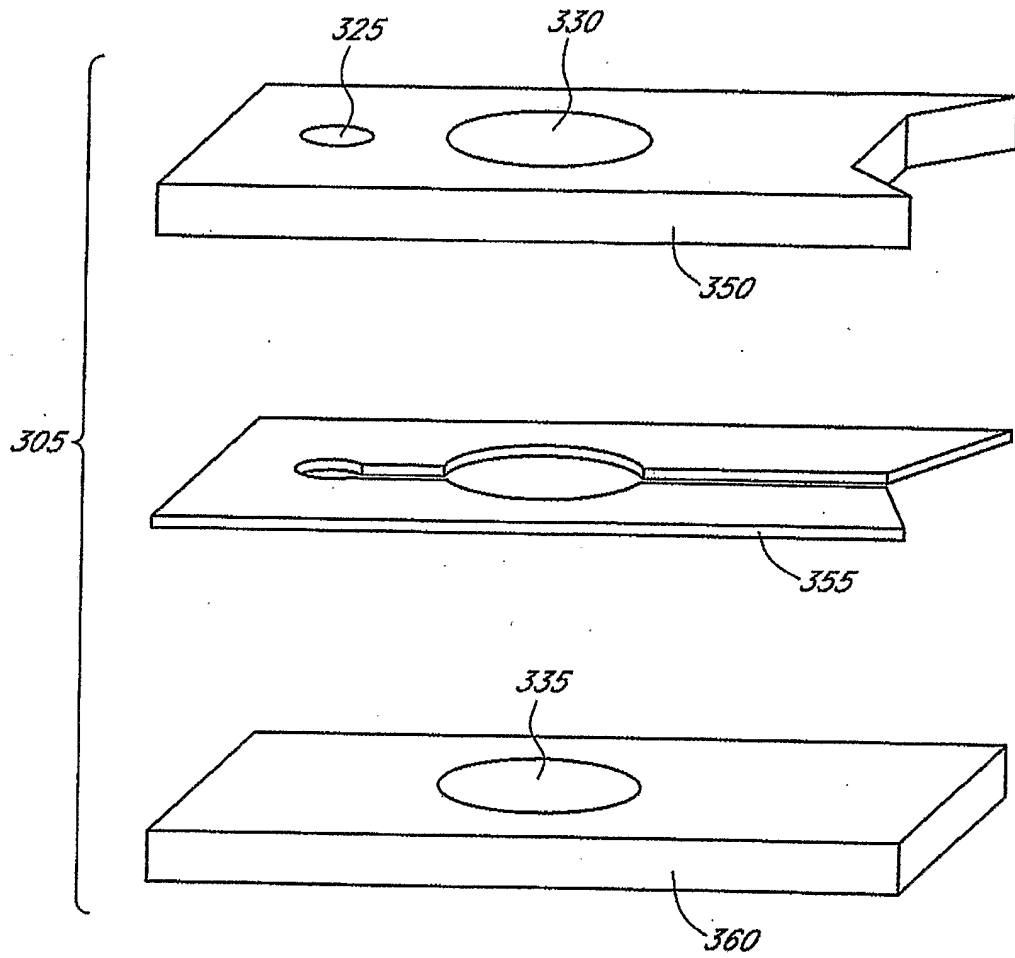


FIG. 16A

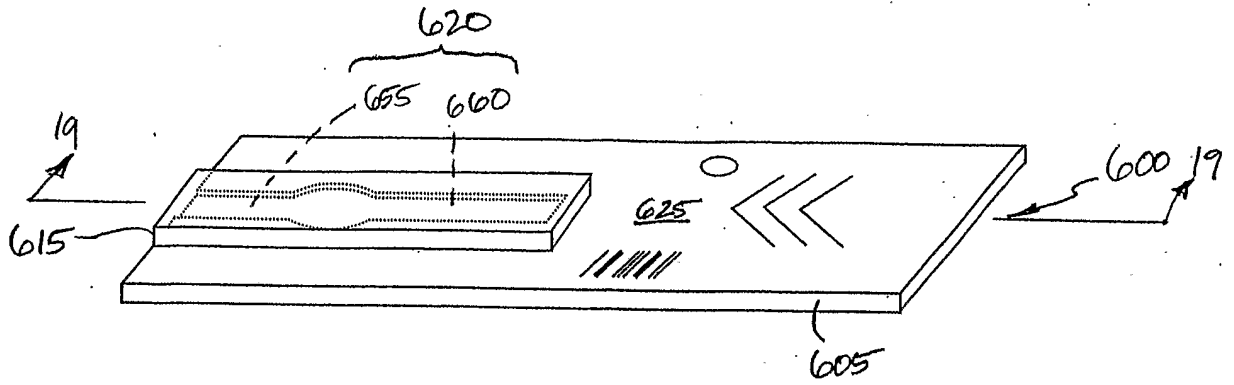


FIGURE 18

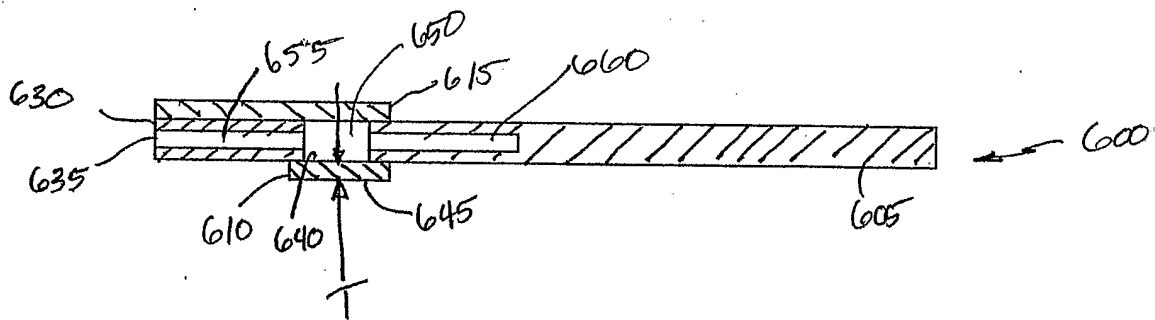


FIGURE 19

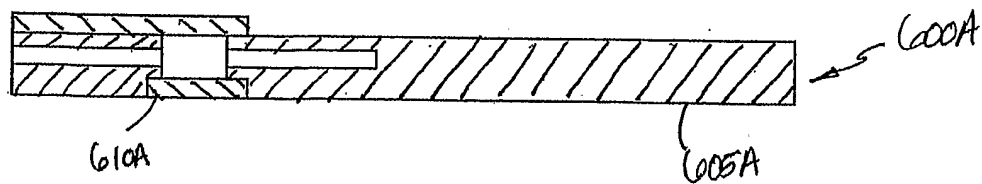


FIGURE 20

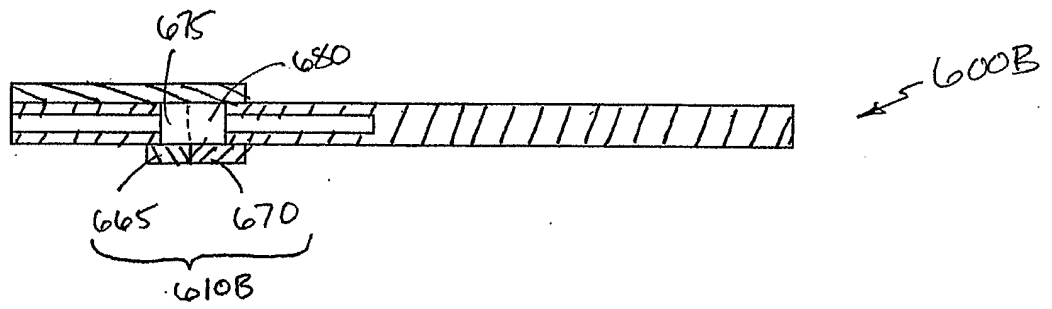


FIGURE 21

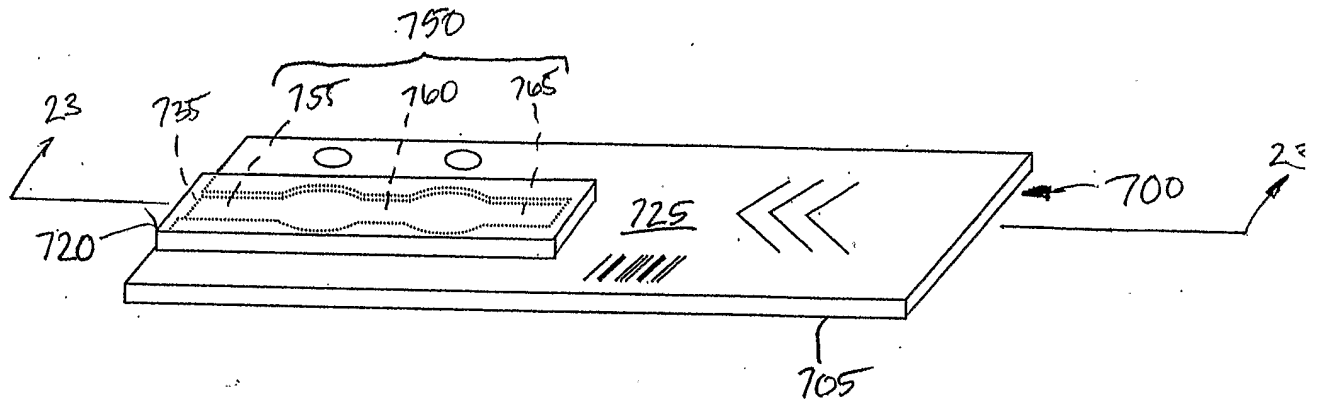


FIGURE 22

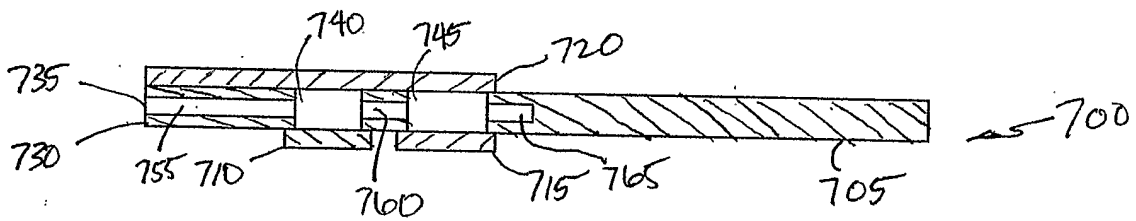


FIGURE 23

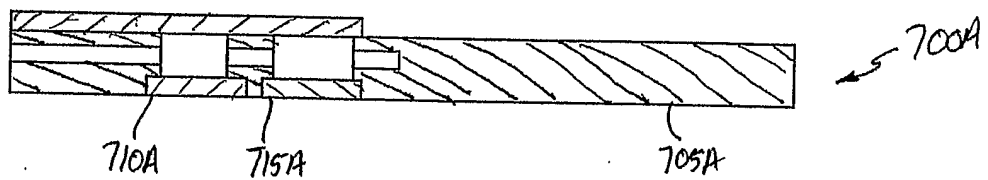


FIGURE 24

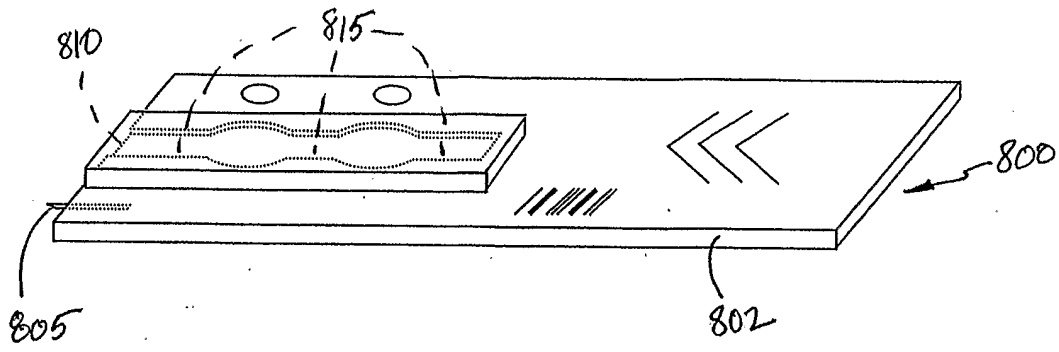


FIGURE 25

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/000145

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00 G01N21/03

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 G01N A61B

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.
A	WO 99/40411 A (DAEDALUS I LLC) 12 August 1999 (1999-08-12) page 6, line 31 -page 9, line 20; figures 3-5	1-35
A	US 5 977 545 A (HAAR HANS-PETER ET AL) 2 November 1999 (1999-11-02) cited in the application the whole document	1-35
A	WO 97/25608 A (MINNESOTA MINING & MFG) 17 July 1997 (1997-07-17) figure 2	20-35
P,X	WO 03/052391 A (STERLING BERNHARD B ;BRAIG JAMES R (US); HARTSTEIN PHILIP C (US);) 26 June 2003 (2003-06-26) figures 15-17	11-18

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
O document referring to an oral disclosure, use, exhibition or other means	*Z* document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 8 June 2004	Date of mailing of the international search report 17/06/2004
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Hooper, M
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Information on patent family members

International Application No
PCT/US2004/000145

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