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(54) METHOD AND APPARATUS FOR IMPROVING THE ACCURACY OF ALTERNATIVE SITE ANALYTE CONCENTRATION MEASUREMENTS

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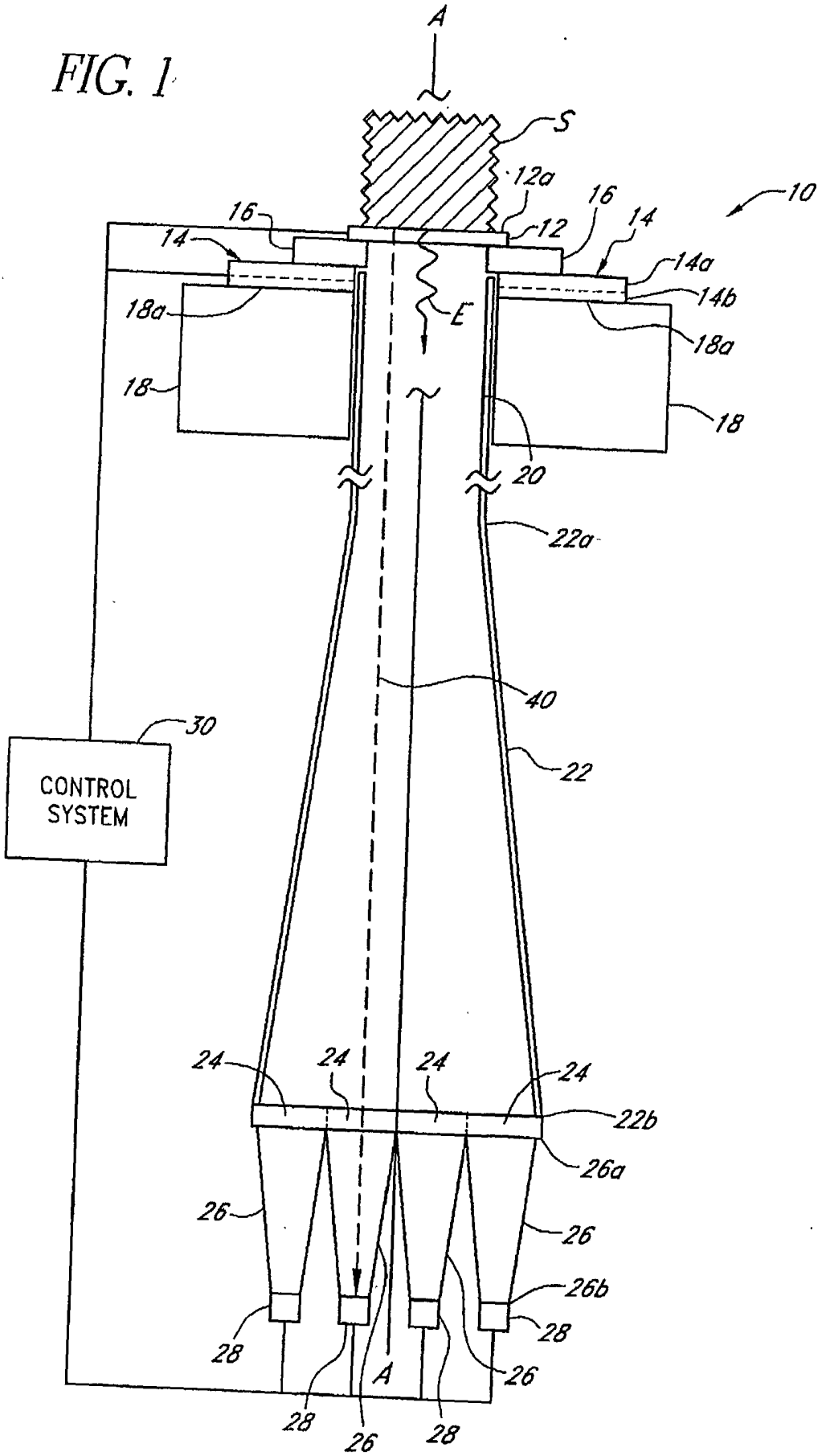
(52) **U.S. Cl.** **435/7.1**; 702/19

(57) **ABSTRACT**

Methods and apparatuses for improving the accuracy of analyte concentration measurements at alternative sites and information provided to the user. The present invention advantageously utilizes information relating to the rate of change of analyte concentrations to adjust analyte concentrations measurements and/or information provided to the user. Therefore, the present invention provides new and improved methods and apparatuses for obtaining analyte concentration information at physiological sites other than the fingertips while ensuring that the analyte concentration information accurately reflects systemic analyte concentration values.

FIG. 1


A
S
12a
16
10
16
12
14
14
14a
14b
18a
E
18a
18
18
20
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40
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CONTROL SYSTEM
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26b
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A
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26
28

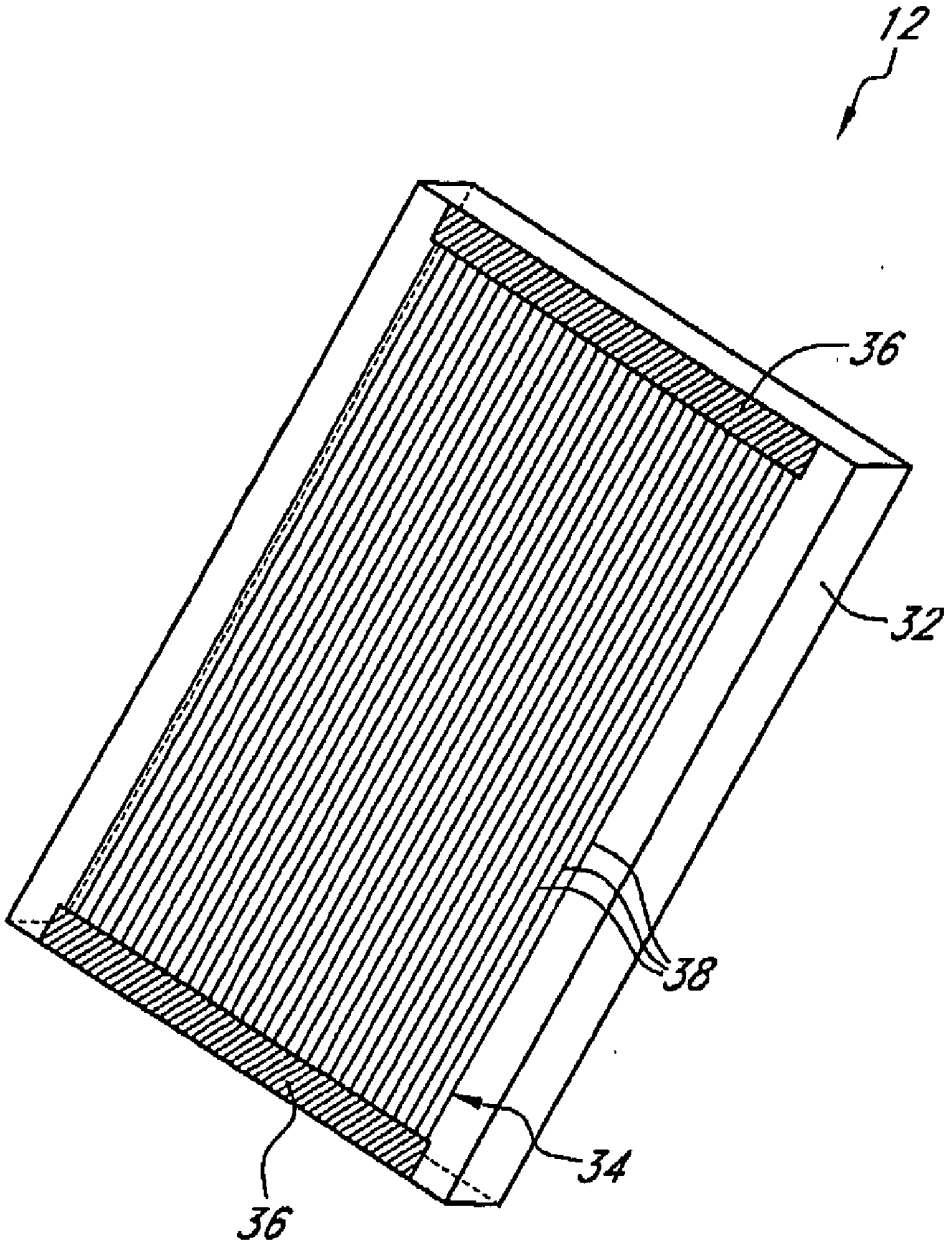

FIG. 2

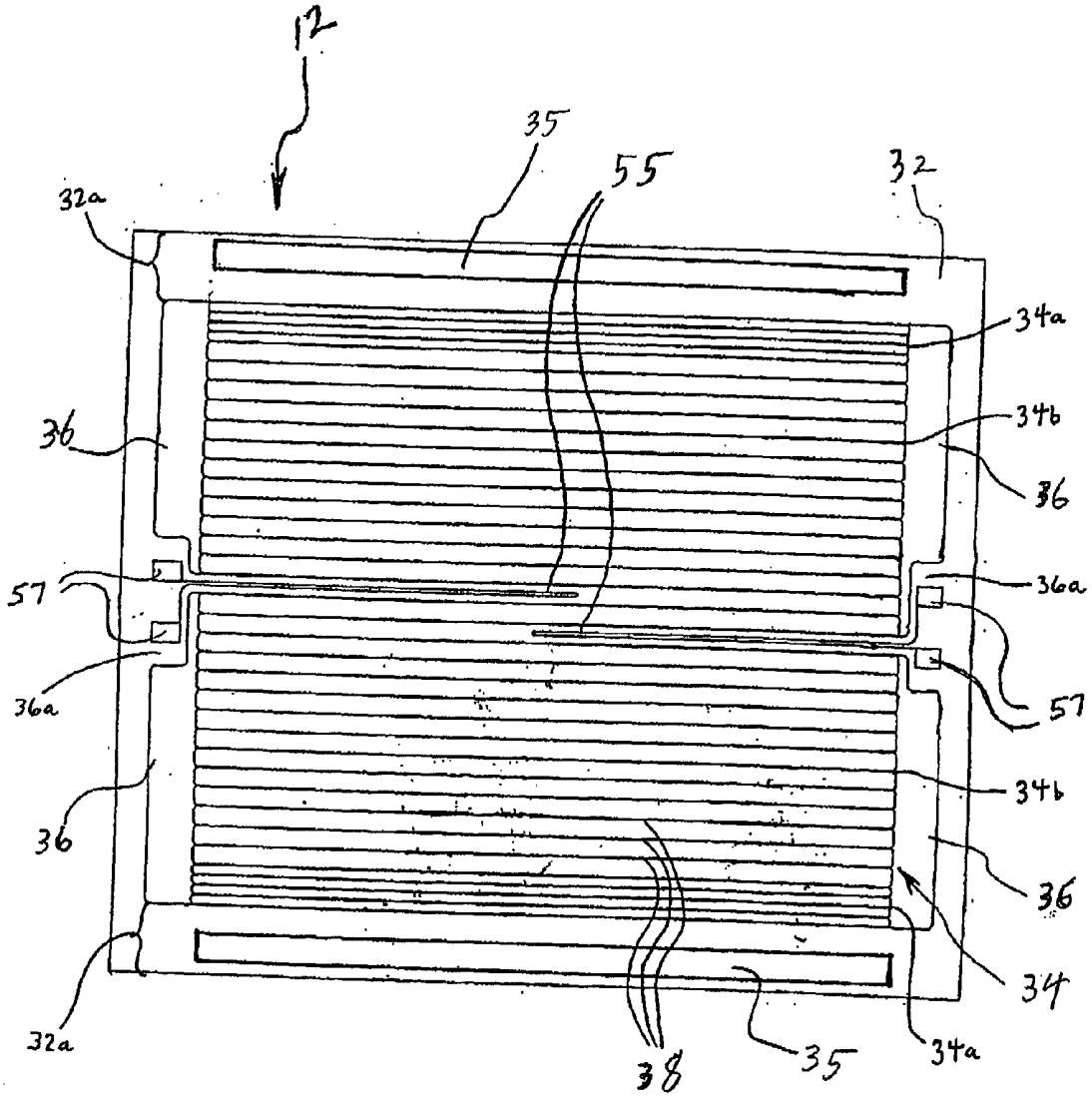
12
35
55
32
32a
34a
34b
36
36
57
36a
57
36a
34b
36
36
34
32a
38
35
34a

FIG. 2A

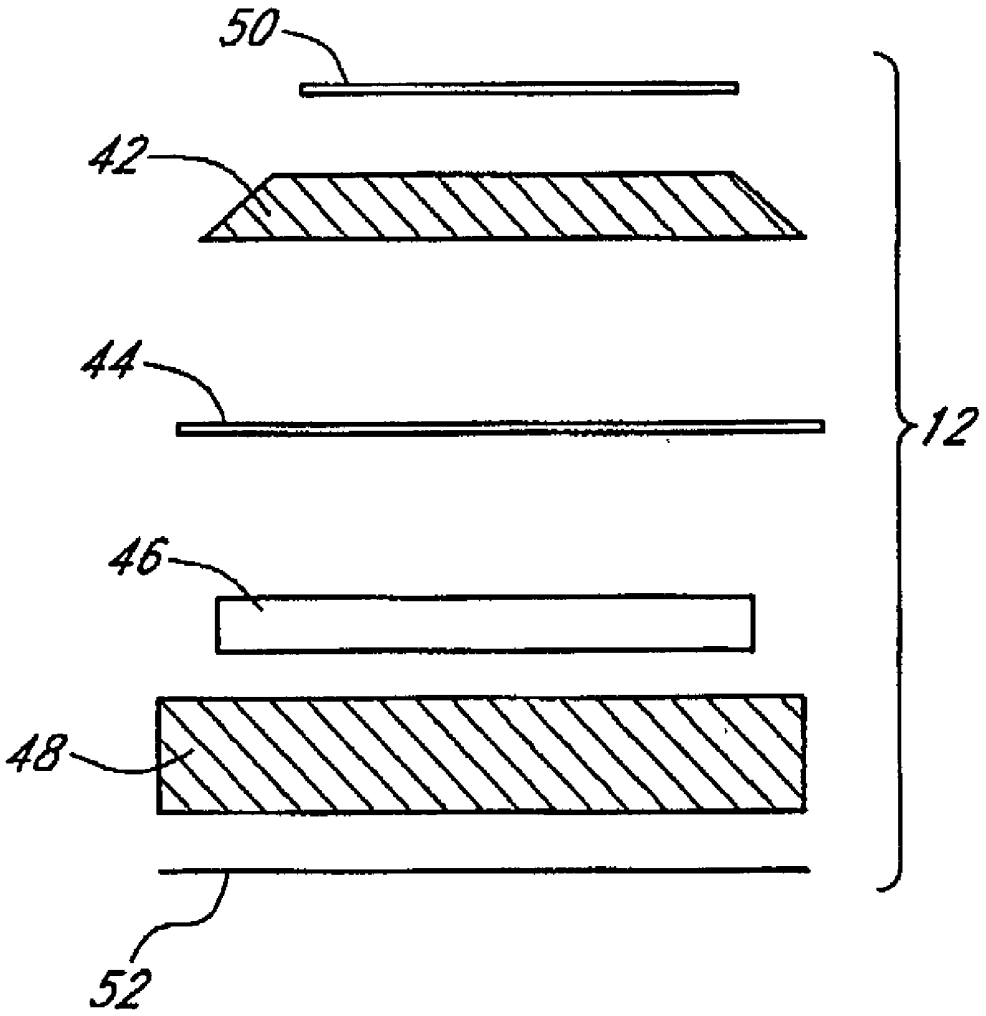

FIG. 3

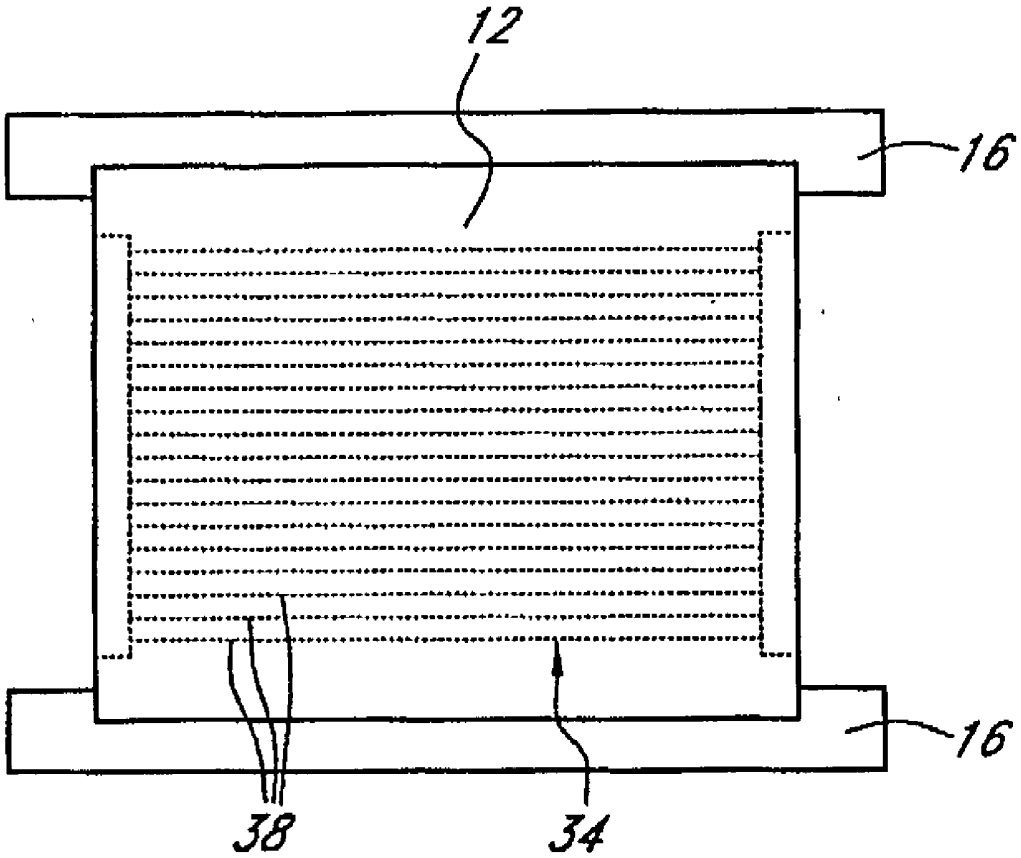

FIG. 4

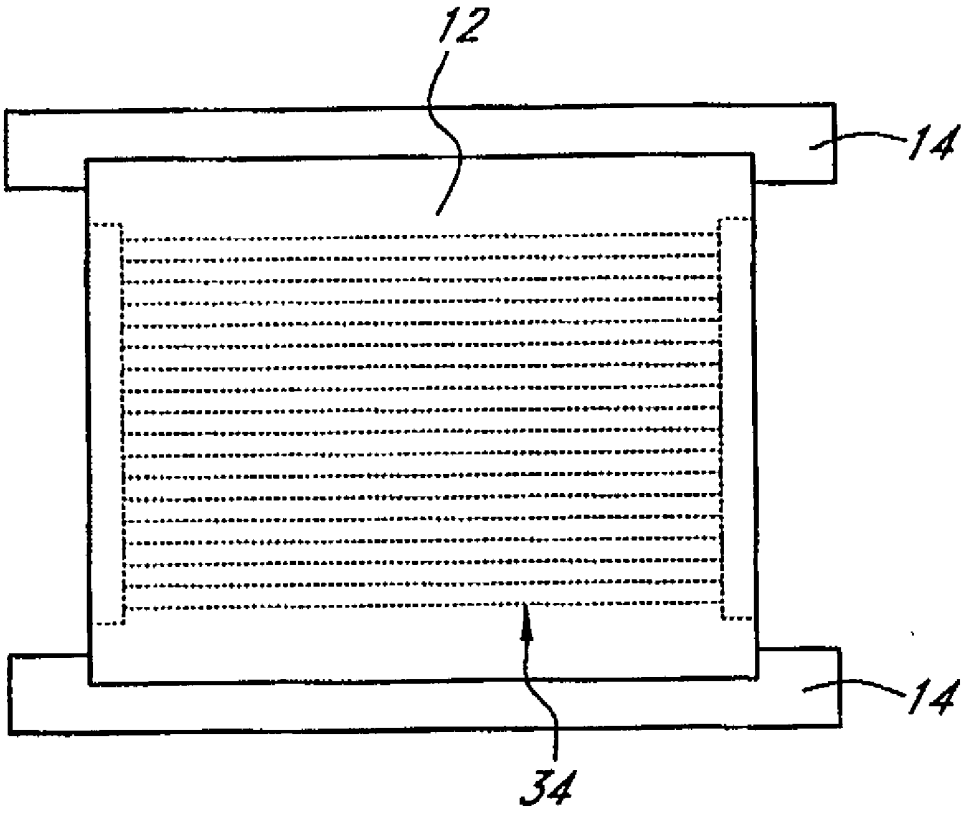

FIG. 5

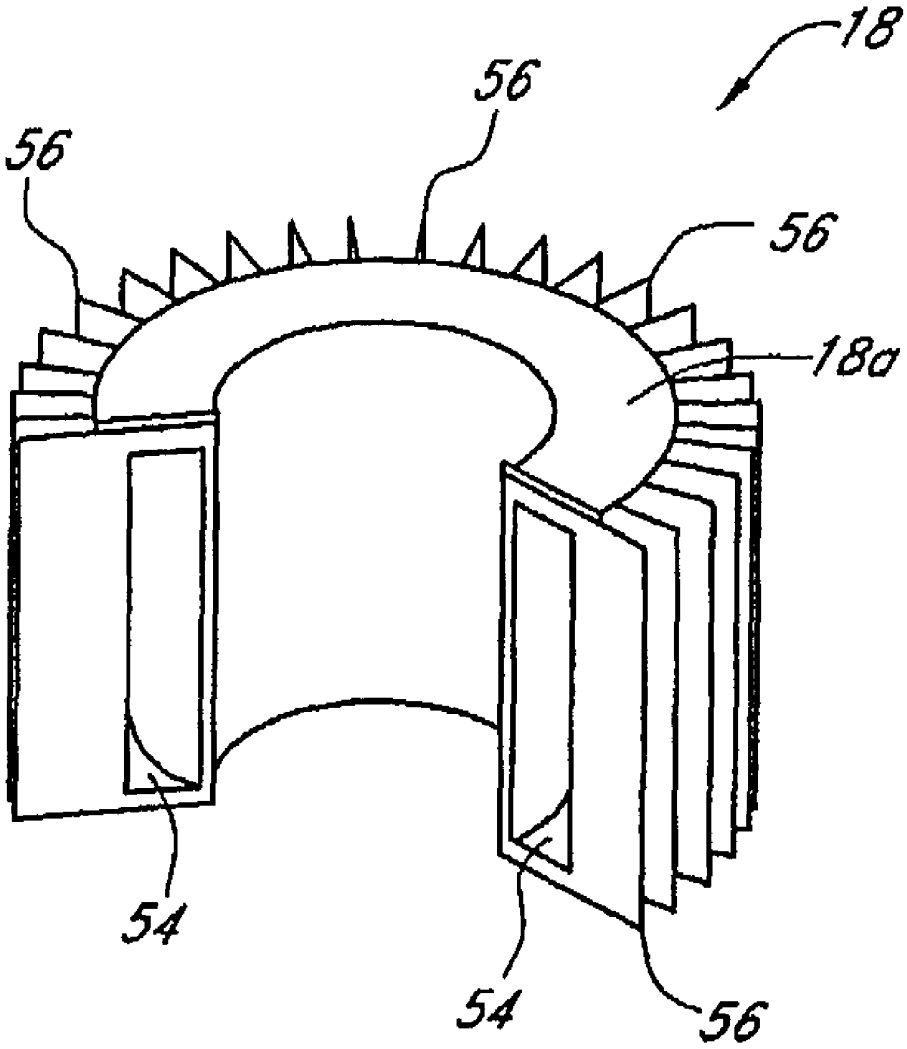

FIG. 6

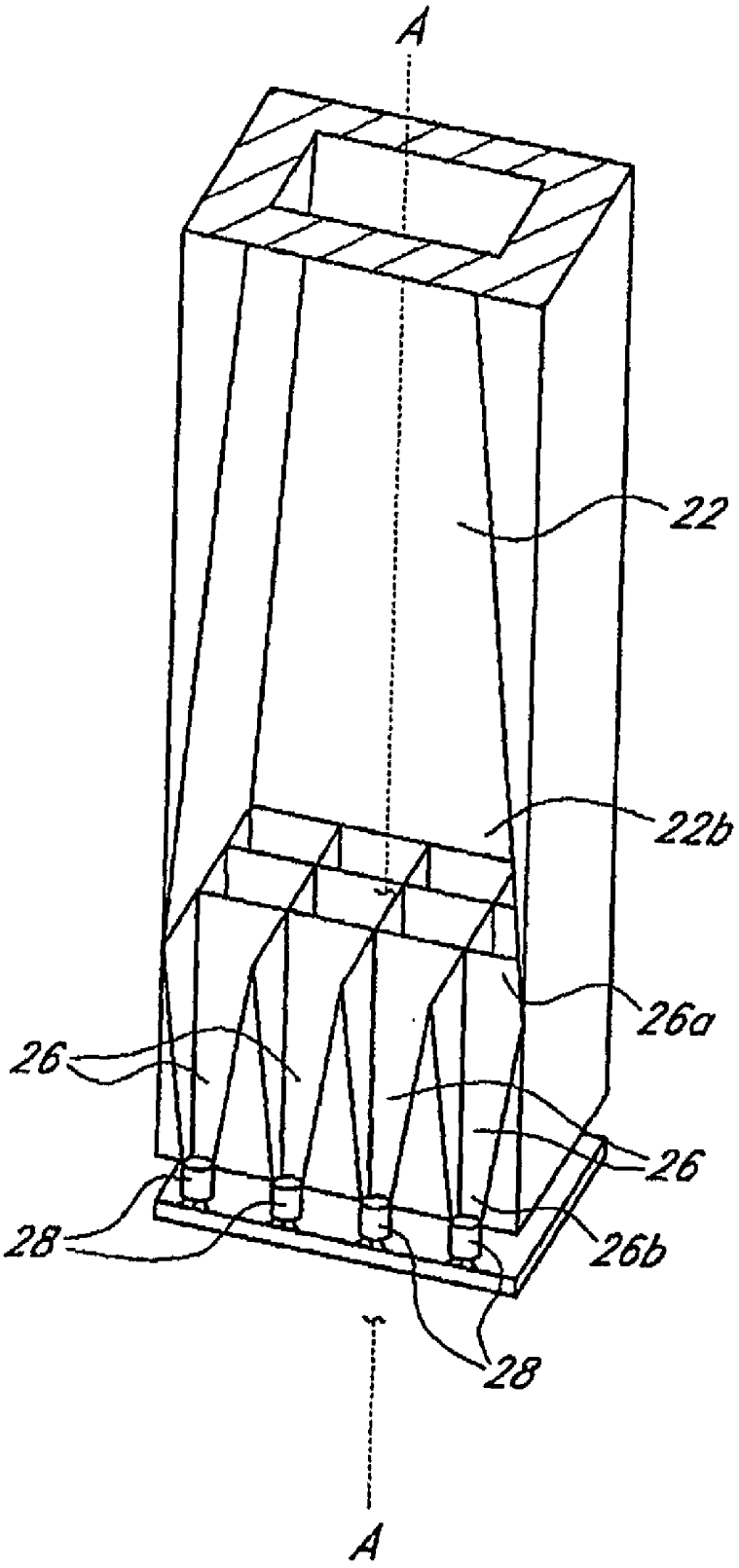

FIG. 6A

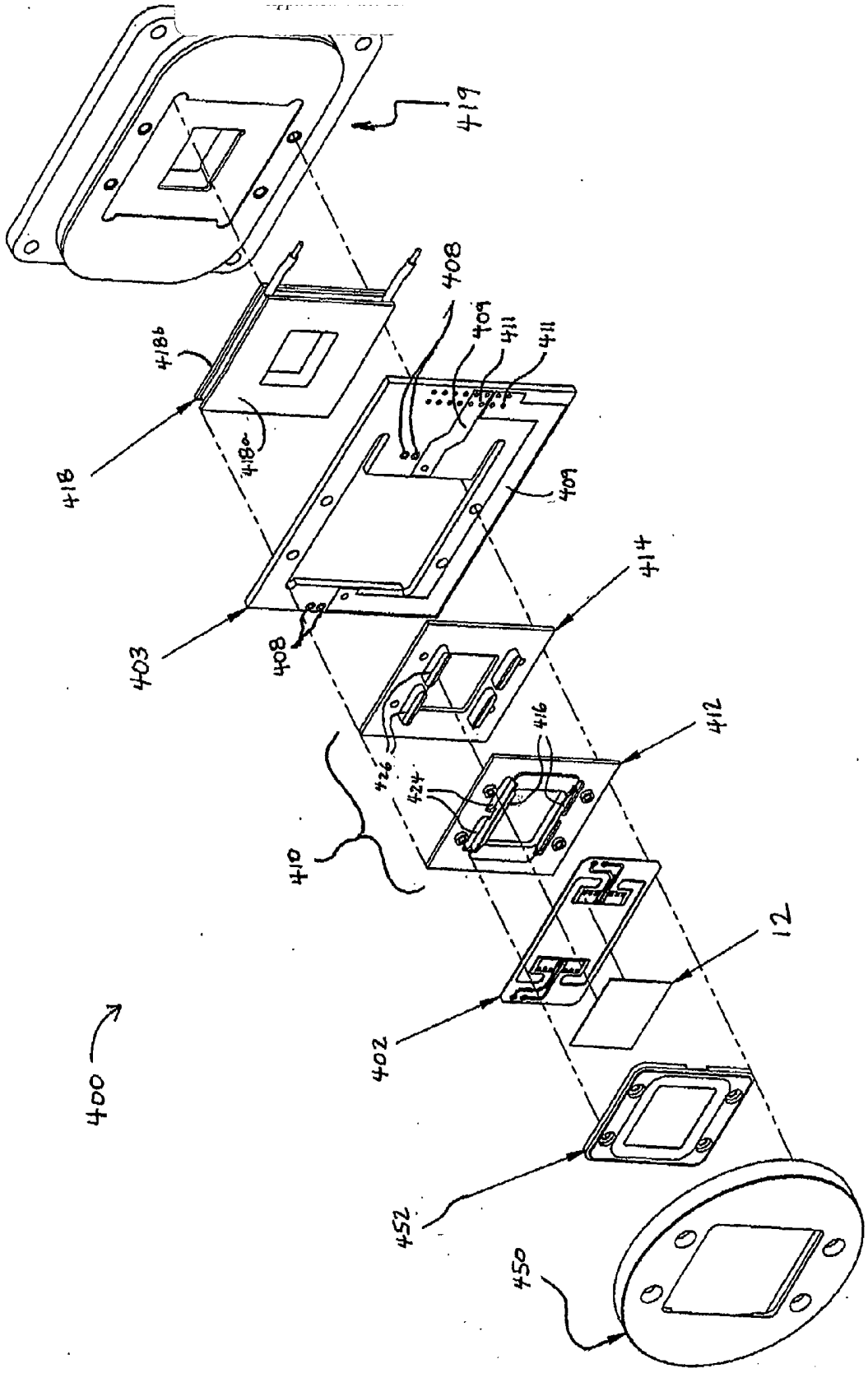
419
408
409
411
411
418a
418
418a
409
414
403
408
416
412
426
424
410
12
402
400
452
450

FIG. 6B

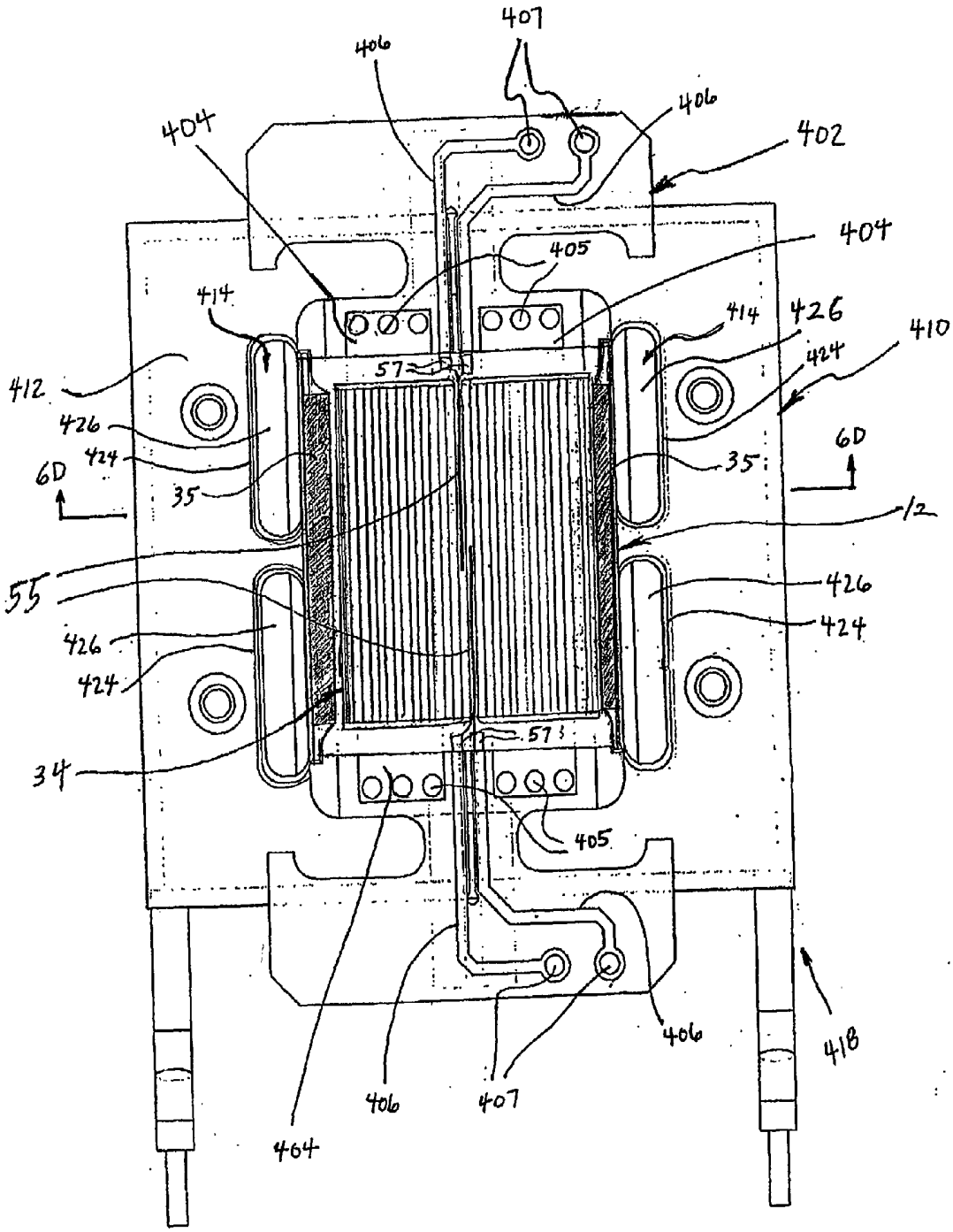
407
406
404
406
402
404
405
414
414
426
410
424
412
57
426
6D
424
35
35
6D
12
55
426
426
424
424
34
57
405
406
418
406
407
464

FIG. 6C

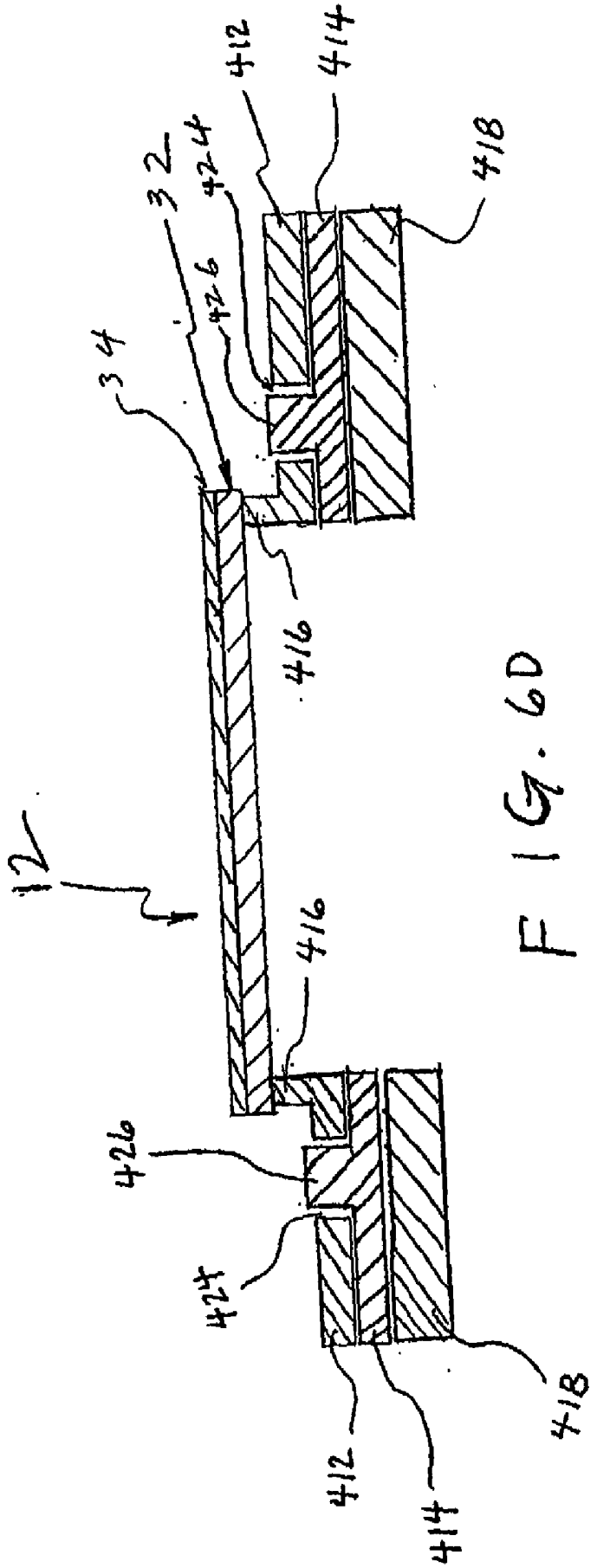

FIG. 6D

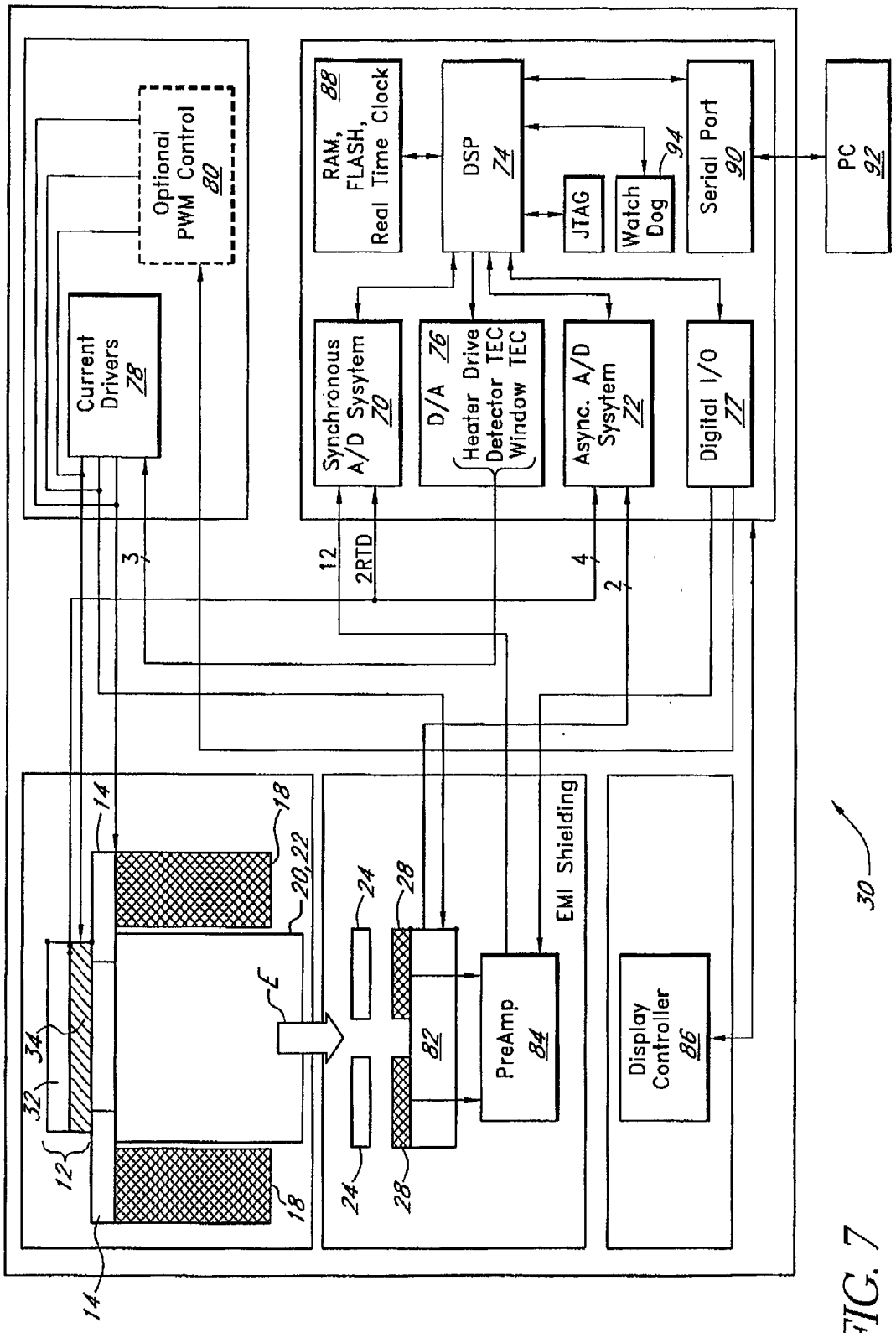
Optional PWM Control 80
Current Drivers 78
RAM, FLASH, Real Time Clock 88
DSP 74
JTAG
Watch Dog 94
Serial Port 90
PC 92
Synchronous A/D Sysytem 70
D/A 76
Heater Drive
Detector TEC
Window TEC
Async. A/D Sysytem 72
Digital I/O 77
12
2RTD
3
4
2
EMI Shielding
PreAmp 84
Display Controller 86
82
14
18
20,22
24
28
34
32
12
30

FIG. 7

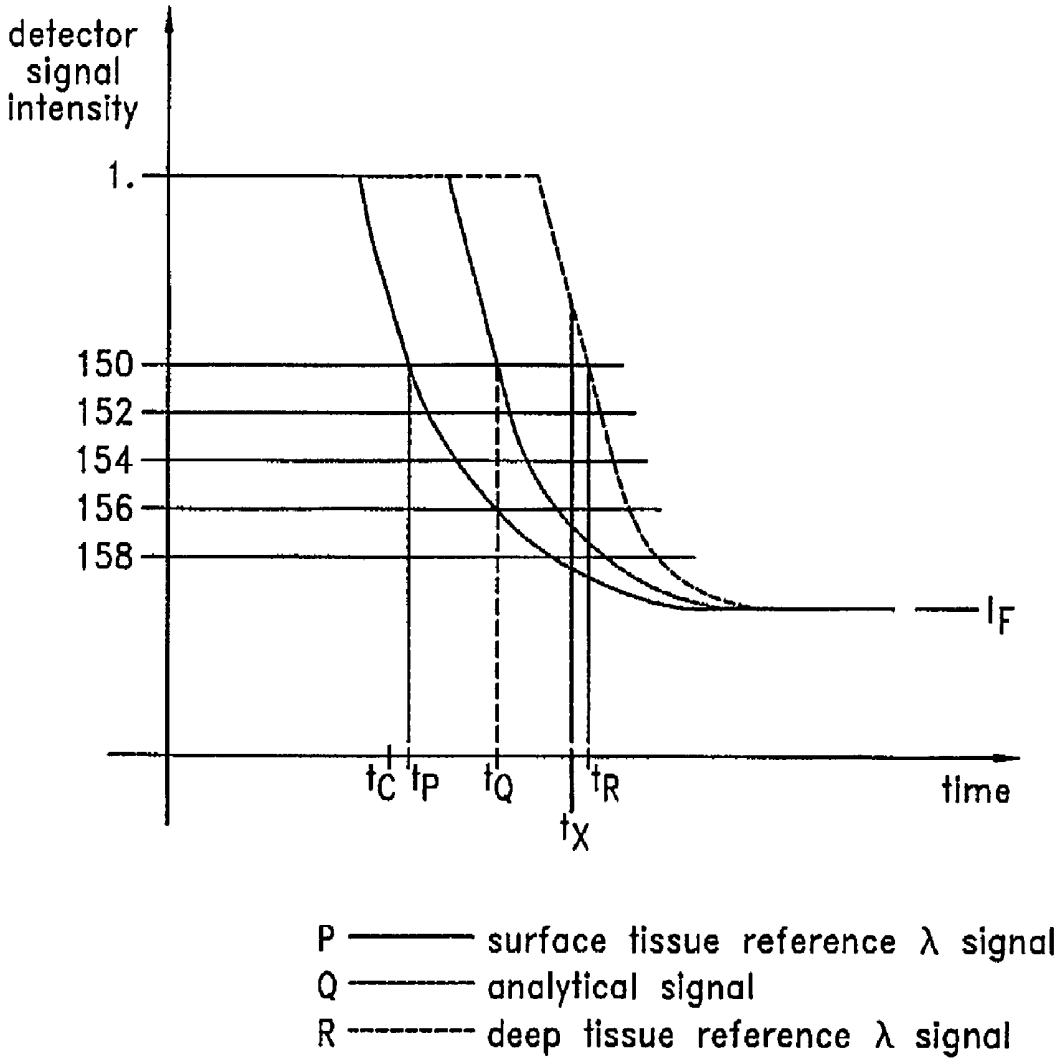
detector
signal
intensity
1.
150
152
154
156
158
I_F
t_C
t_P
t_Q
t_R
t_X
time
P ——— surface tissue reference λ signal
Q ——— analytical signal
R ---------- deep tissue reference λ signal

FIG. 8

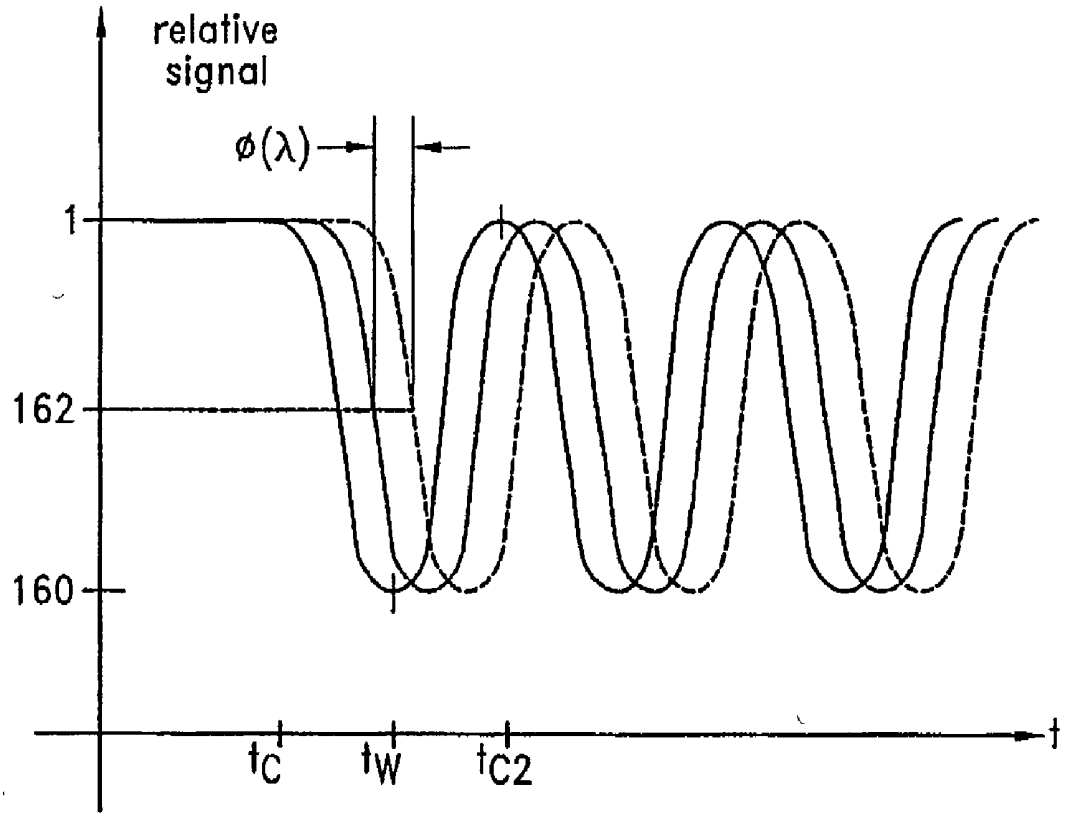
relative
signal
ø(λ)
1
162
160
t
tC
tW
tC2
J surface tissue reference signal
K analytical signal
L deep tissue reference signal

FIG. 9

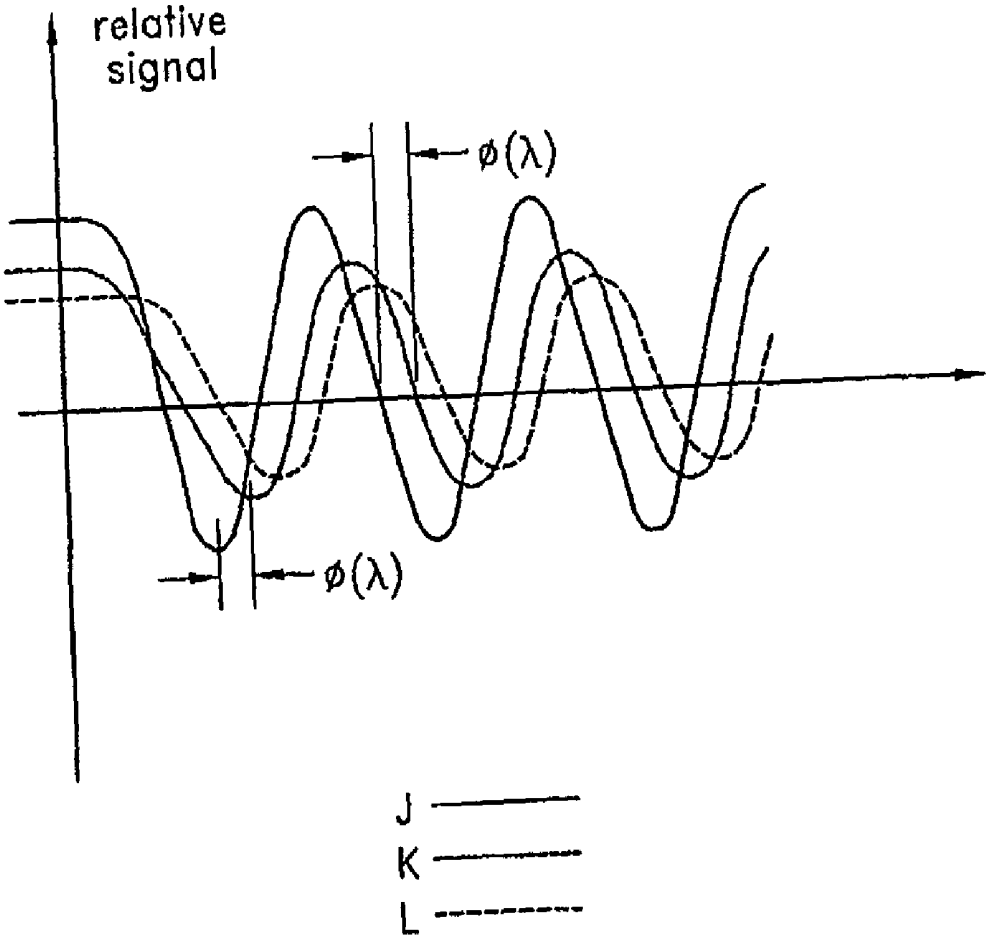

FIG. 10

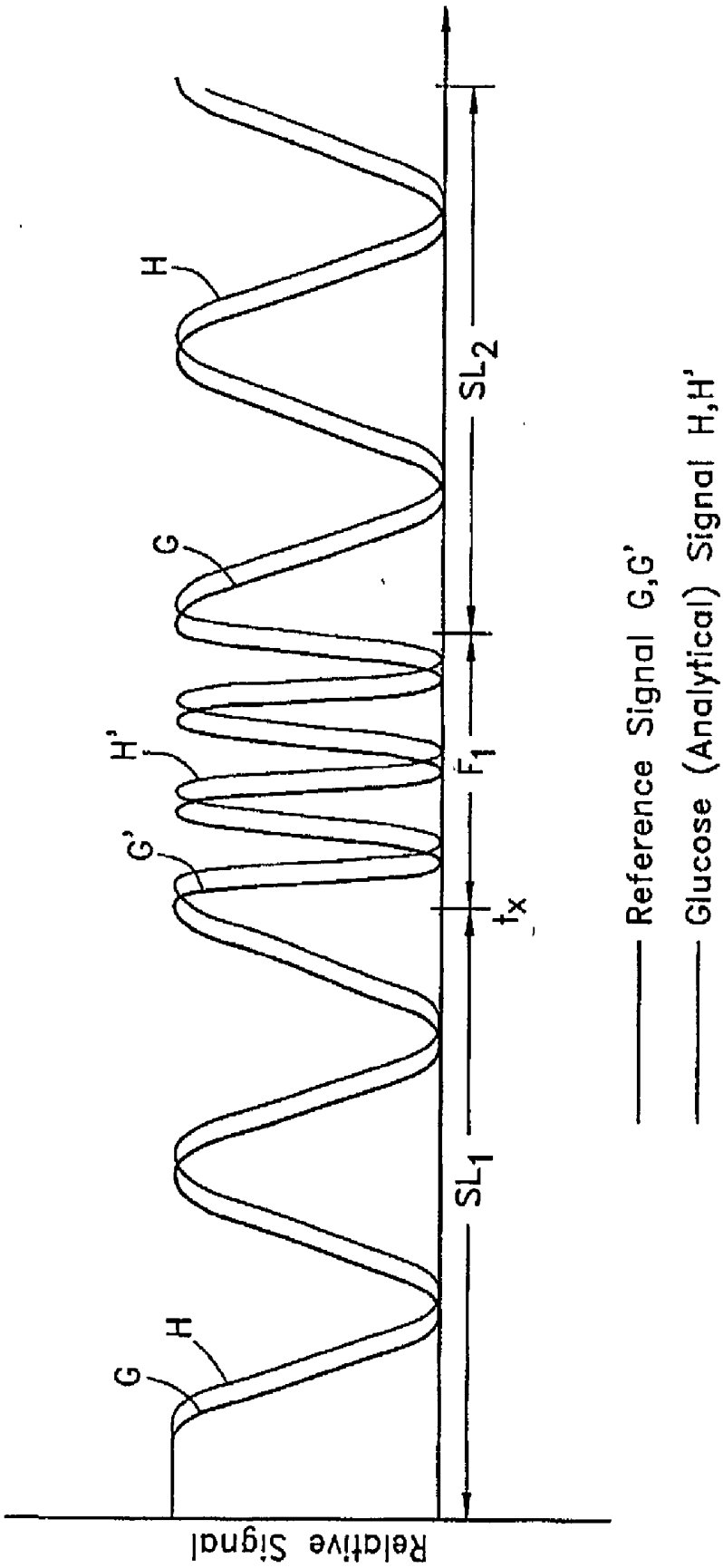
Relative Signal
G
H
G'
H'
G
H
SL_1
t_x
F_1
SL_2
Reference Signal G,G'
Glucose (Analytical) Signal H,H'

FIG. 11

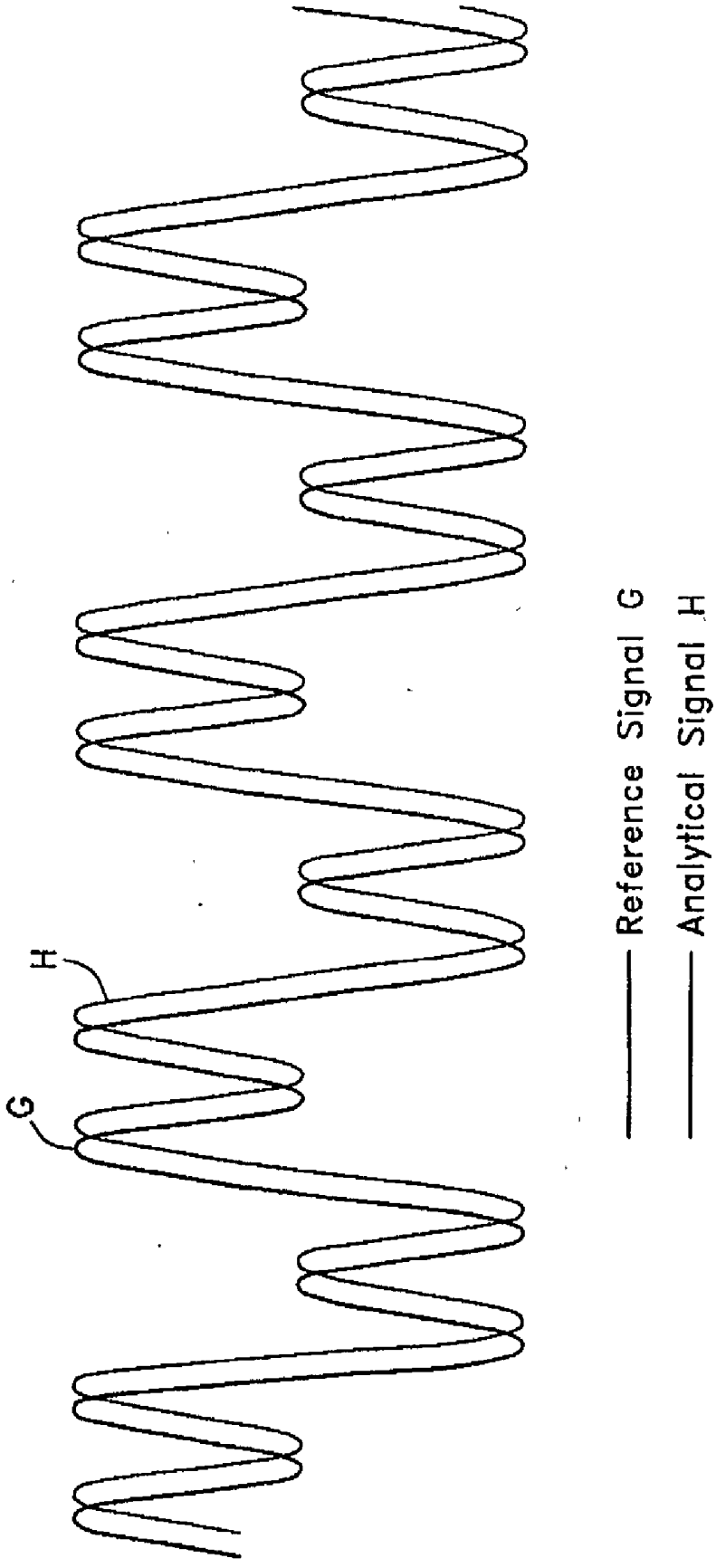

FIG. 12

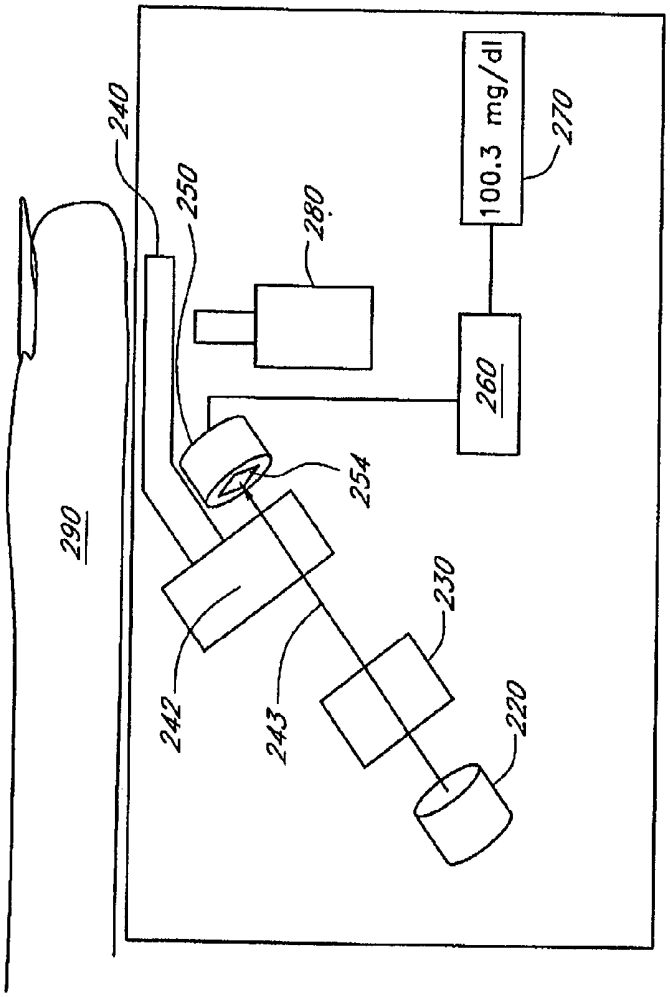
240
250
280
100.3 mg/dl
270
260
254
290
230
242
243
220

FIG. 13

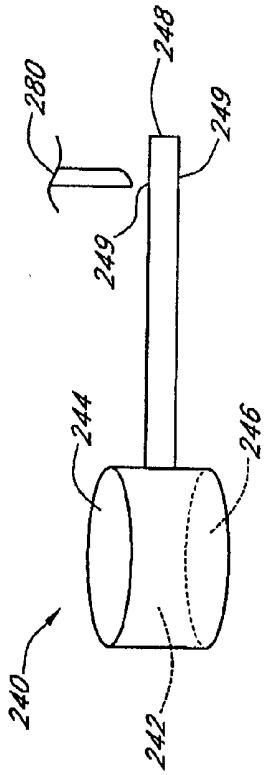
280
248
249
249
244
246
240
242

FIG. 14

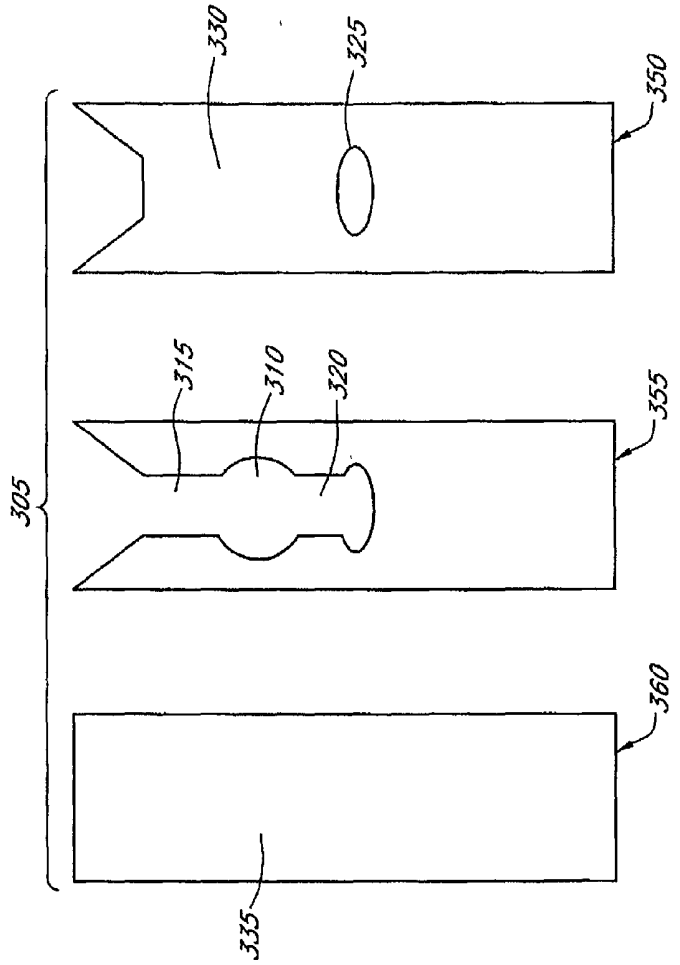

FIG. 16

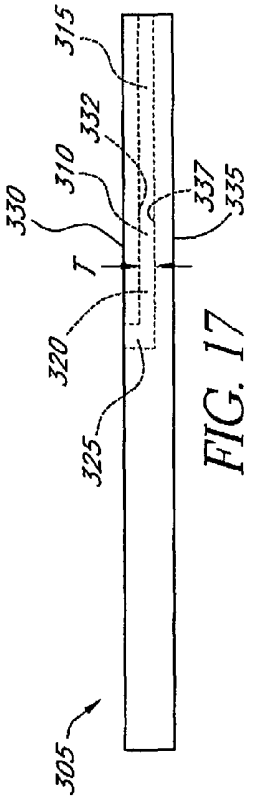

FIG. 17

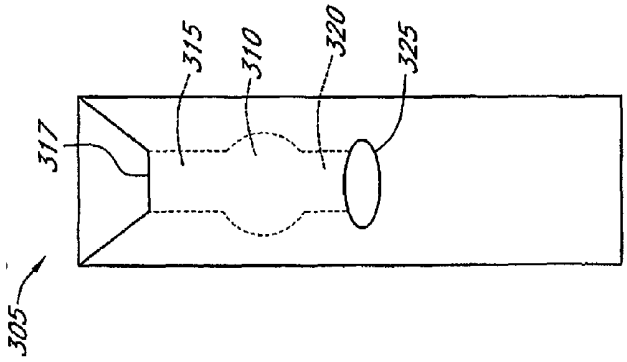

FIG. 15

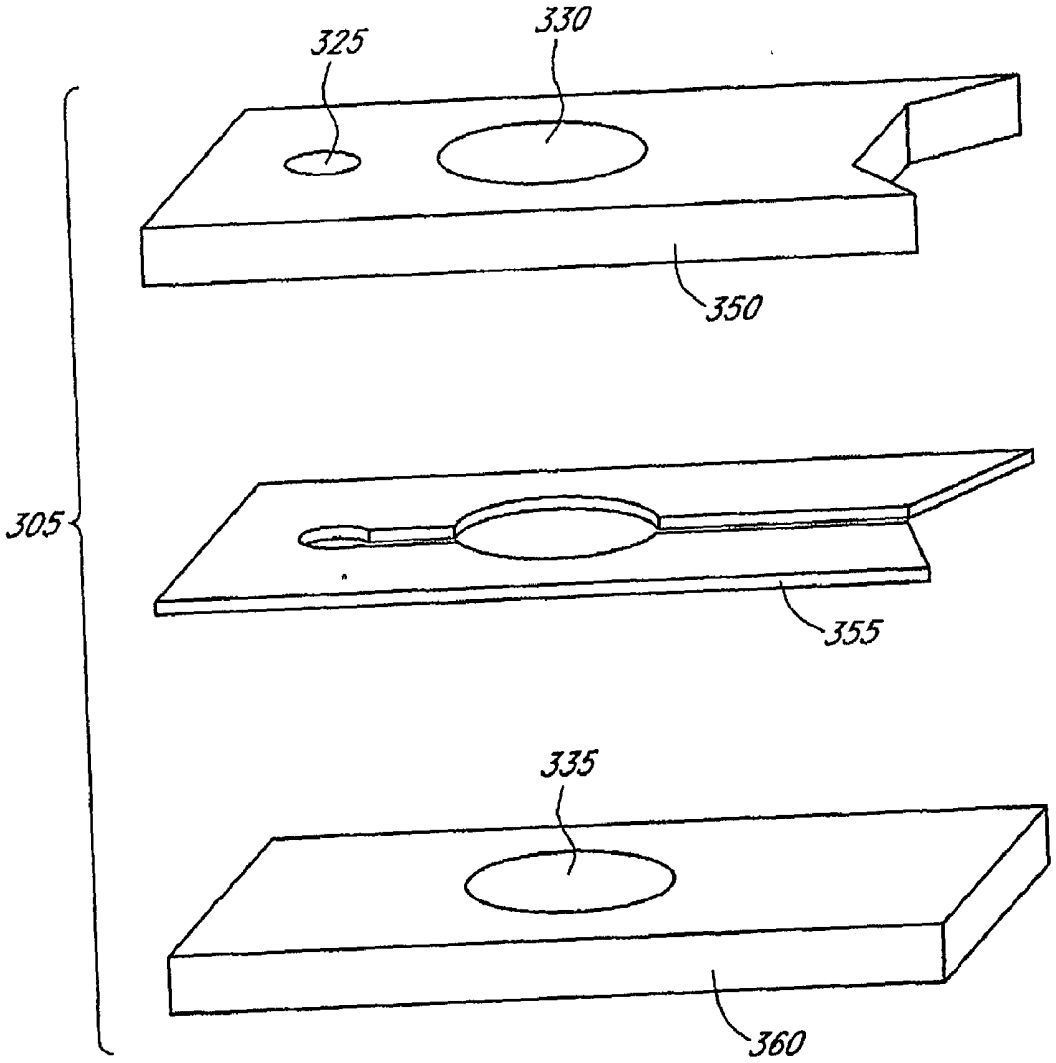

FIG. 16A

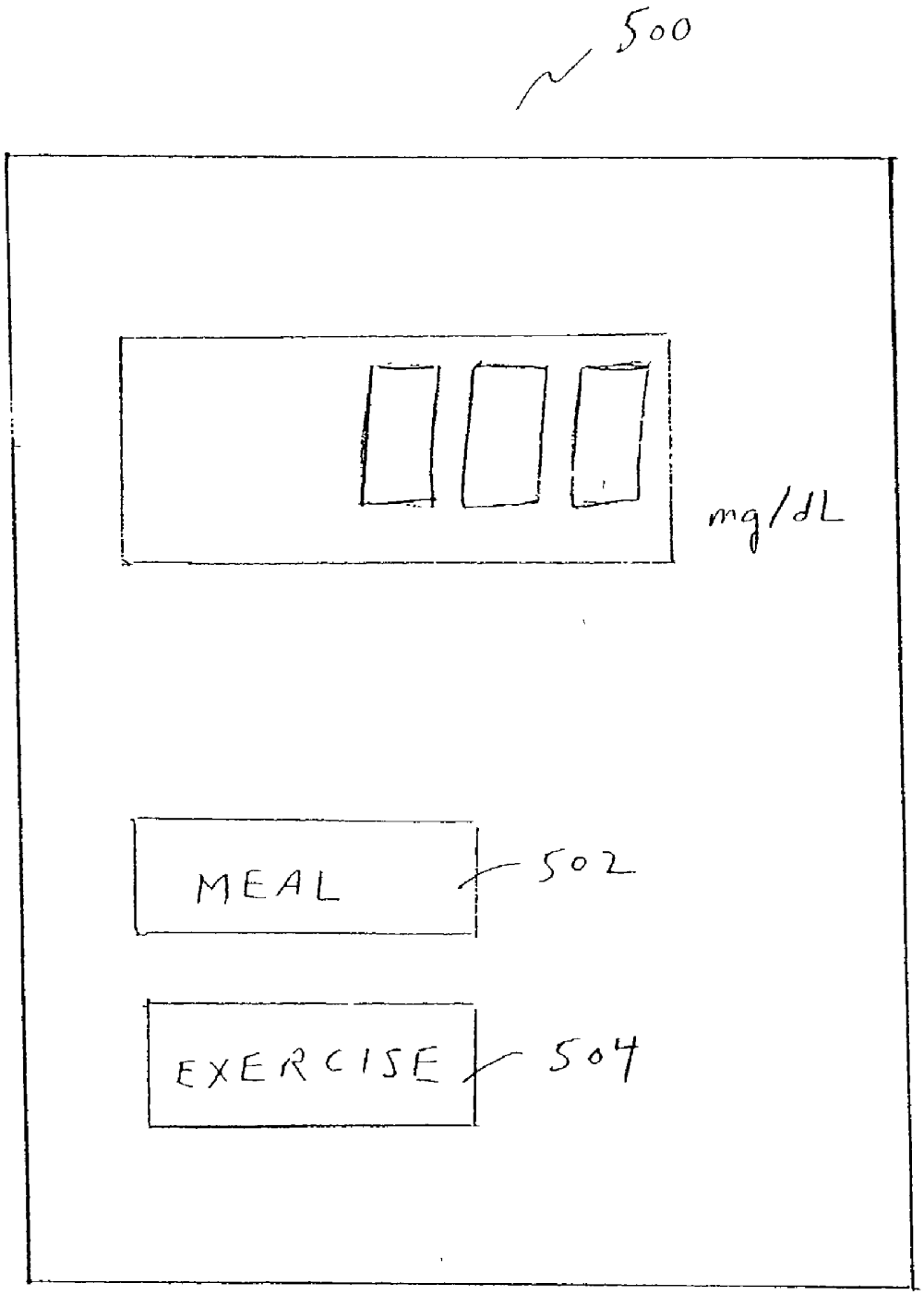

FIGURE 18

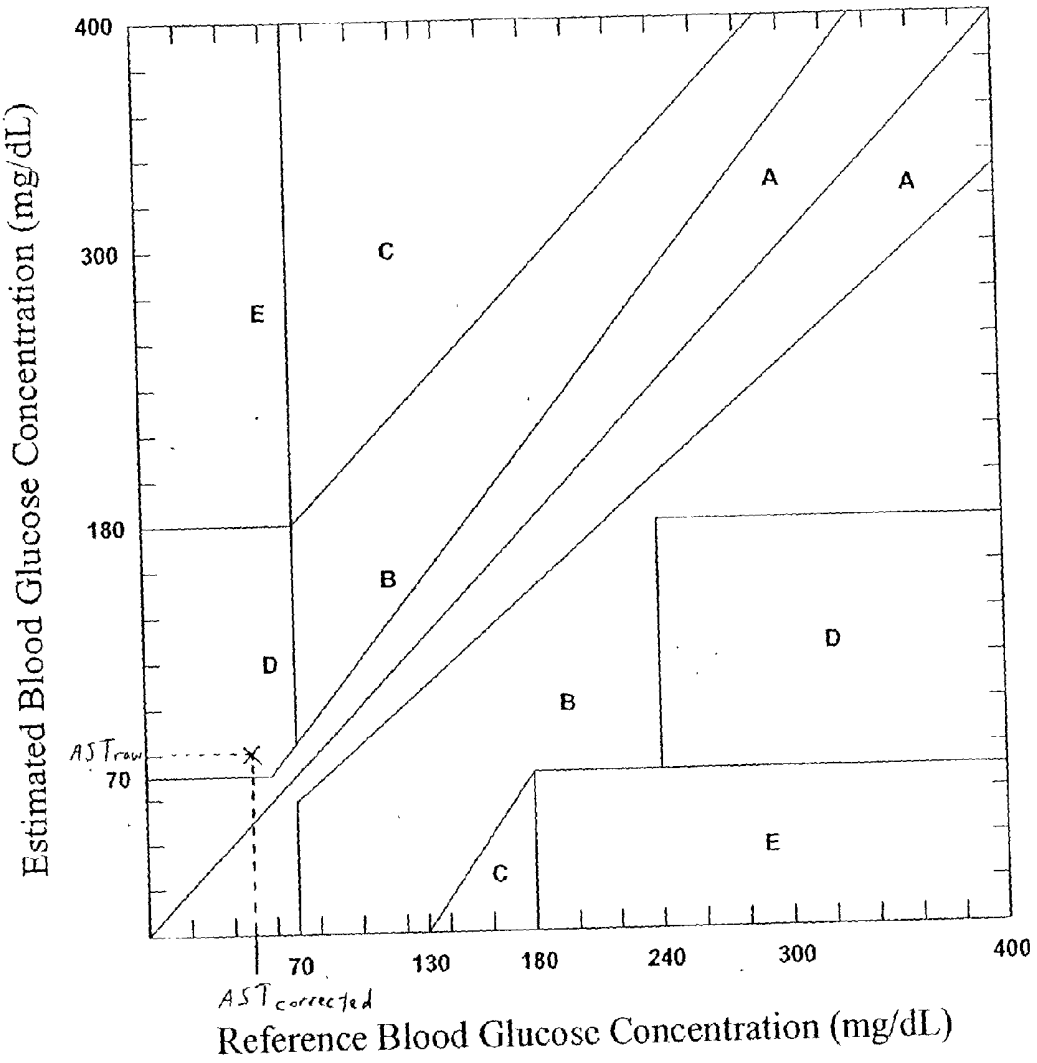
Estimated Blood Glucose Concentration (mg/dL)
400
300
180
70
AST raw
AST corrected
70
130
180
240
300
400
A
A
C
E
B
D
D
B
E
C
Reference Blood Glucose Concentration (mg/dL)

FIGURE 19

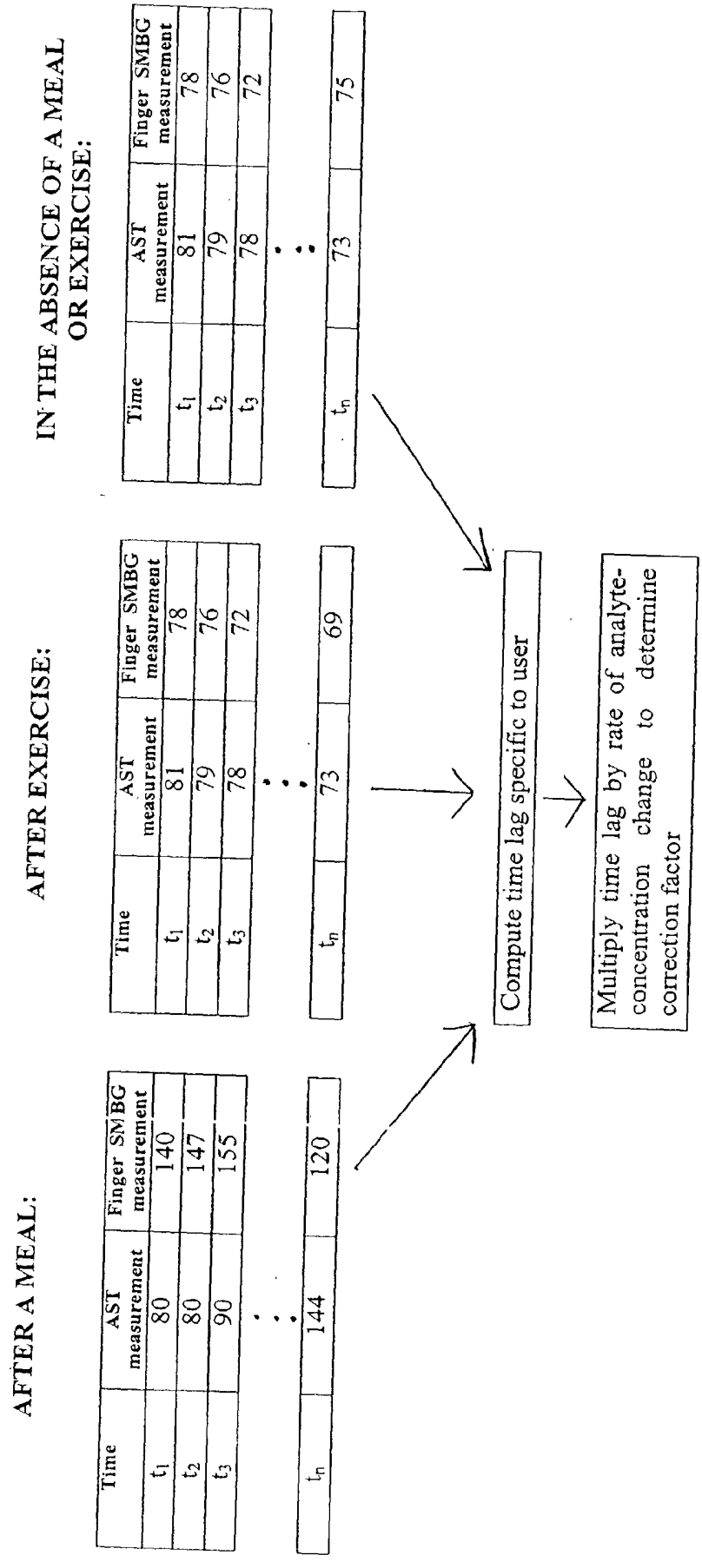
AFTER A MEAL:
Time
AST measurement
Finger SMBG measurement
t_1 80 140
t_2 80 147
t_3 90 155
t_n 144 120
AFTER EXERCISE:
Time
AST measurement
Finger SMBG measurement
t_1 81 78
t_2 79 76
t_3 78 72
t_n 73 69
IN THE ABSENCE OF A MEAL OR EXERCISE:
Time
AST measurement
Finger SMBG measurement
t_1 81 78
t_2 79 76
t_3 78 72
t_n 73 75
Compute time lag specific to user
Multiply time lag by rate of analyte-concentration change to determine correction factor

FIGURE 20

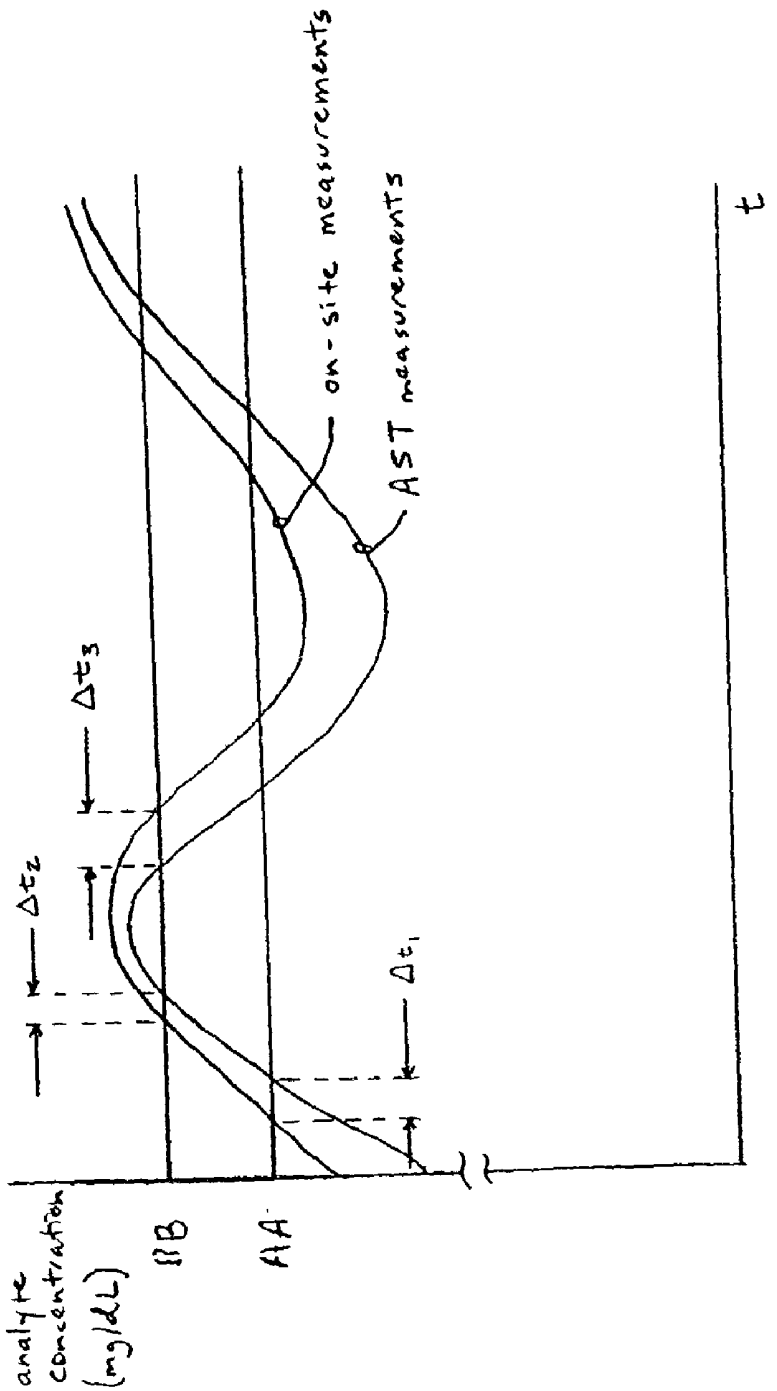
analyte concentration (mg/dL)
BB
AA
on-site measurements
AST measurements
Δt_3
Δt_2
Δt_1
t

FIGURE 21

METHOD AND APPARATUS FOR IMPROVING THE ACCURACY OF ALTERNATIVE SITE ANALYTE CONCENTRATION MEASUREMENTS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/332,093, filed Nov. 21, 2001, and of U.S. Provisional Application No. 60/354,436, filed Feb. 4, 2002; the disclosures of the aforementioned applications are hereby incorporated in their entirety herein by reference.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This present invention relates generally to determining analyte concentrations in material samples. More specifically, the present invention relates to methods and apparatuses for improving the accuracy of blood-constituent measurements and/or blood-constituent measurement devices.

[0004] 2. Description of the Related Art

[0005] The analysis of materials and the determination of the presence or concentration of chemical species contained therein is a common and important process in chemistry, biology, and the medical sciences. Particularly important is the analysis of biological fluids, such as, for example, blood, urine, or saliva, to determine the concentration of various constituents. Also of great importance is the measurement of the concentration of various chemical constituents embedded within biological materials, such as, for example, tissue. Chemical analysis of blood, urine, and other biological fluids is crucial to the diagnosis, management, treatment, and care of a wide variety of diseases and medical conditions.

[0006] Analysis of various blood components is of importance in both the diagnosis and treatment of diseases of the circulatory system. For example, the level of various types of cholesterol in the blood has a strong correlation with the onset of heart disease. Urine analysis provides valuable information relating to kidney function and kidney disease. The concentration of alcohol in the blood is known to be related to a subject's physical response time and coordination and can provide information related to, for example, the individual's fitness to drive a motor vehicle. In the case of diabetes, accurate monitoring of blood glucose levels is necessary for efficient management of this disease.

[0007] Millions of diabetics draw samples of bodily fluid such as blood on a daily basis to monitor the level of glucose in their bloodstream. Traditional blood samples for Self Monitoring of Blood Glucose ("SMBG") are taken from a finger with a lance. Tests have shown that finger blood glucose levels correlate highly to systemic blood glucose values. Fingertips are highly vaseularized and therefore offer an ideal site from which to draw relatively large (1-3 uL) drops of blood for SMBG analysis. Fingertips are also highly innervated, providing good tactile sense which unfortunately makes lancing to obtain the blood sample painful. What is needed is a method and apparatus for obtaining accurate blood glucose measurements at an alternative site (i.e. a site other than at the fingertips).

SUMMARY OF THE INVENTION

[0008] In accordance with one embodiment, there is provided a method of improving the accuracy of analyte concentration measurements at alternative sites. The method disclosed herein involves: determining a rate of change of analyte concentration; measuring an analyte concentration at an alternative site; and adjusting the measured analyte concentration based on the rate of change to generate an adjusted analyte concentration value which is a more accurate estimate of the systemic analyte concentration value.

[0009] In accordance with another embodiment, there is provided a method for improving the accuracy of information provided to a user by an analyte detection system. This method involves determining a rate of change of analyte concentration and adjusting the information provided to the user based on the rate of change.

[0010] In accordance with yet another embodiment, there is provided a system for measuring the concentration of an analyte at an alternative site which has a processing circuit and a module executable by the processing circuit whereby the processing circuit receives an analyte concentration measurement taken at the alternative site, determines a rate of change of the concentration of the analyte, and provides information to the user based on the rate of change.

[0011] In accordance with a further embodiment, there is provided a system for measuring the concentration of an analyte at an alternative site which has a processing circuit and a module executable by the processing circuit whereby the processing circuit receives an analyte concentration measurement taken at the alternative site, determines a rate of change of the concentration of the analyte, and adjusts said analyte concentration measurement based on said rate of change.

[0012] Another embodiment involves determining the clinical significance of an error in the measured analyte concentration.

[0013] Another embodiment involves adjusting the measured analyte concentration by: determining a time lag between analyte concentrations measured on-site and at an alternative site; determining a correction factor based on the time lag and the rate of change of analyte concentration; and adjusting the measured analyte concentration value by the correction factor.

[0014] Another embodiment involves correcting the measured analyte concentration based on the rate of change of the analyte concentration. Here, correction of the measured analyte concentration involves determining the time lag between analyte concentrations measured on-site and at an alternative site. Correction also involves taking a follow-up analyte concentration measurement at a time that falls between the time of previous analyte concentration measurement and the sum of the time lag and the time of the previous analyte concentration measurement. Correction also involves determining the rate of analyte concentration change during the time period between the previous analyte concentration measurement and the follow-up analyte concentration measurement. Correction also involves extrapolating the analyte concentration value to a time after the sum of the time lag and the time of the previous analyte concentration measurement by using the rate of analyte concentration change in between the previous analyte concentration measurement and the follow-up analyte concentration measurement.

[0015] Another embodiment involves screening measured analyte concentration values to remove outlier concentration

values and/or rate of concentration change values based on statistical analysis, data history, and/or data forecasts or trends.

[0016] Another embodiment relates to the determination of the rate of change of analyte concentration by: estimating that the absolute value of the rate of change is relatively high; estimating that the absolute value of the rate of change will remain relatively high for about 1-2 hours; and/or receiving data input from the user and estimating, based on the data, that the absolute value of the rate of change is relatively high.

[0017] Another embodiment relates to the determination of the rate of change of analyte concentration by: measuring a first analyte concentration at a first measurement time; measuring a second analyte concentration at a second measurement time; and computing the rate of change based on the first and second analyte concentrations and the first and second measurement times.

[0018] Another embodiment relates to adjusting information provided to the user by: measuring a raw analyte concentration; calculating a corrected analyte concentration based on the rate of change and the raw analyte concentration; assessing the clinical significance of a measurement error based on the raw analyte concentration and the corrected, analyte concentration; and/or warning the user to take an on-site analyte concentration measurement based on the clinical significance of the measurement error.

[0019] Another embodiment relates to providing information to the user by: warning the user that the absolute value of the rate of change is high; prompting the user to take an on-site analyte concentration measurement; warning the user, when the absolute value of said rate of change is relatively high, that alternative-site measurements are likely to be inaccurate; prompting the user to take an on-site analyte concentration measurement; and/or warning the user that the concentration of the analyte is increasing or decreasing.

[0020] Another embodiment involves a timing circuit accessible by the processing circuit of the system that measures the concentration of an analyte at an alternative site.

[0021] Another embodiment involves a system with a user-interface whereby the user is able to input data into the analyte detection system, wherein the processing circuit considers said data in adjusting the analyte concentration to generate an adjusted analyte concentration value.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] **FIG. 1** is a schematic view of a noninvasive optical detection system.

[0023] **FIG. 2** is a perspective view of a window assembly for use with the noninvasive detection system.

[0024] **FIG. 2A** is a plan view of another embodiment of a window assembly for use with the noninvasive detection system.

[0025] **FIG. 3** is an exploded schematic view of another embodiment of a window assembly for use with the noninvasive detection system.

[0026] **FIG. 4** is a plan view of the window assembly connected to a cooling system.

[0027] **FIG. 5** is a plan view of the window assembly connected to a cold reservoir.

[0028] **FIG. 6** is a cutaway view of a heat sink for use with the noninvasive detection system.

[0029] **FIG. 6A** is a cutaway perspective view of a lower portion of the noninvasive detection system of **FIG. 1**.

[0030] **FIG. 6B** is an exploded perspective view of a window mounting system for use with the noninvasive optical detection system.

[0031] **FIG. 6C** is a partial plan view of the window mounting system of **FIG. 6B**.

[0032] **FIG. 6D** is a sectional view of the window mounting system of **FIG. 6C**.

[0033] **FIG. 7** is a schematic view of a control system for use with the noninvasive optical detection system.

[0034] **FIG. 8** depicts a first methodology for determining the concentration of an analyte of interest.

[0035] **FIG. 9** depicts a second methodology for determining the concentration of an analyte of interest.

[0036] **FIG. 10** depicts a third methodology for determining the concentration of an analyte of interest.

[0037] **FIG. 11** depicts a fourth methodology for determining the concentration of an analyte of interest.

[0038] **FIG. 12** depicts a fifth methodology for determining the concentration of an analyte of interest.

[0039] **FIG. 13** is a schematic view of a reagentless whole-blood detection system.

[0040] **FIG. 14** is a perspective view of one embodiment of a cuvette for use with the reagentless whole-blood detection system.

[0041] **FIG. 15** is a plan view of another embodiment of a cuvette for use with the reagentless whole-blood detection system.

[0042] **FIG. 16** is a disassembled plan view of the cuvette shown in **FIG. 15**.

[0043] **FIG. 16A** is an exploded perspective view of the cuvette of **FIG. 15**.

[0044] **FIG. 17** is a side view of the cuvette of **FIG. 15**.

[0045] **FIG. 18** is a perspective view of an AST device with meal and exercise buttons.

[0046] **FIG. 19** depicts the classification of erroneous measurements by their clinical implications.

[0047] **FIG. 20** depicts a methodology for determining the corrector factor for an AST device user.

[0048] **FIG. 21** depicts the determination of AST time lag specific to an individual.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0049] The highly innervated nature of the fingertips makes it desirable patients to take blood glucose measure-

ments at an alternative site. Alternative site ("AST") testing can be conducted at sites less highly innervated. One of the most popular alternative sites is the forearm. However, the concentrations of blood constituents such as glucose measured at alternative sites, particularly the forearm, can exhibit a time lag relative to simultaneous concentration measurements taken at the finger.

[0050] The time lag associated with certain alternative site measurements can be minimized or corrected for by utilizing the rate of change of analyte concentration in the measurement device and/or the time lag between analyte concentrations measured on-site and at an alternative site. Disclosed here are methods and apparatus for methods and apparatuses for improving the accuracy of an AST blood-constituent measurement device. Part I describes the measurement of an analyte by using systems such as a non-invasive analyte detection system or a whole blood analyte detection system. In a presently preferred embodiment, the analyte concentration measurement system measures the concentration of glucose in blood. An analyte concentration measurement is clinically accurate when the measurement results in correct treatment of a patient. However, an instrument may erroneously report a measurement that causes a patient to receive the wrong treatment. Part II describes a method and apparatus for improving the accuracy of alternative site analyte concentration measurements. In a presently preferred embodiment, the rate of analyte concentration change and/or the time lag associated with the patient are utilized to provide accurate analyte concentration measurements at the AST.

[0051] Although certain preferred embodiments and examples are disclosed below, it will be understood by those skilled in the art that the invention extends beyond the specifically disclosed embodiments to other alternative embodiments and/or uses of the invention and obvious modifications and equivalents thereof. Thus, it is intended that the scope of the invention herein disclosed should not be limited by the particular disclosed embodiments described below.

Overview of Analyte Detection Systems

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] A. Noninvasive System

[0057] 1. Monitor Structure

[0058] **FIG. 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.

[0059] 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.

[**0060**] The noninvasive system **10** preferably comprises a window assembly **12**, although in some embodiments the window assembly **12** may be omitted. One function of the window assembly **12** is to permit infrared energy E to enter the noninvasive system **10** from the sample S when it is placed against an upper surface **12***a* of the window assembly **12**. The window assembly **12** includes a heater layer (see discussion below) which is employed to heat the material sample S and stimulate emission of infrared energy therefrom. A cooling system **14**, preferably comprising a Peltier-type thermoelectric device, is in thermally conductive relation to the window assembly **12** so that the temperature of the window assembly **12** and the material sample S can be manipulated in accordance with a detection methodology discussed in greater detail below. The cooling system **14** includes a cold surface **14***a* which is in thermally conductive relation to a cold reservoir **16** and the window assembly **12**, and a hot surface **14***b* which is in thermally conductive relation to a heat sink **18**.

[**0061**] 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 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 infrared energy when reflecting against the collimator walls.

[**0062**] 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 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**.

[**0063**] 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**.

[**0064**] 2. Window Assembly

[**0065**] 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 **FIG. 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**.

[**0066**] 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 **FIG. 1**).

[**0067**] Still referring to **FIG. 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 or 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.

[**0068**] 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.

[**0069**] 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**.

[**0070**] 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 **FIG. 1**, the window assembly **12** will facilitate a minimally obstructed optical path between a (preferably flat) upper surface **12***a* 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**.

[**0071**] **FIG. 2***a* shows another embodiment of the window assembly **12**, that may be used in place of the window assembly **12** depicted in **FIG. 2**. The window assembly **12** shown in **FIG. 2A** may be similar to that shown in **FIG. 2**, except as described below. In the embodiment of **FIG. 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**.

[**0072**] In the embodiment of **FIG. 2**A, 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 FIGS. **6**B-**6**D and discussion below). This arrangement advantageously promotes an isothermal temperature profile at the upper surface of the main layer **32** despite thermal contact with the thermal diffuser.

[**0073**] The embodiment shown in **FIG. 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 **FIG. 2**A, the centerlines of the heater elements **38** are spaced at a first pitch distance of about 0.0070" at peripheral portions **34***a* of the heater layer **34**, and at a second pitch distance of about 0.015" at a central portion **34***b* 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 **FIG. 2**A, the main layer **32** includes peripheral regions **32***a* which extend about 0.053" from the outermost heater element on each side of the heater layer **34** to the adjacent edge of the main layer **32**. As shown, the bus bars **36** are preferably configured and segmented to allow space for the RTDs **55** and the RTD connection pads **57**, in intermediate gaps **36***a*. The RTDs **55** preferably extend into the array of heater elements **38** by distance that is slightly longer than half of the length of an individual heater element **38**. In alternative embodiments, the RTDs **55** may be located at the edges of the main layer **32**, or at other locations as desired for a particular noninvasive system.

[**0074**] With continued reference to **FIG. 2**A, 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 FIGS. **6**B-**6**D). The metallized edge portions **35** may be formed by the same or similar processes used in forming the heater elements **38** and RTDs **55**. In the embodiment of **FIG. 2**A, 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.

[**0075**] In the embodiment shown in **FIG. 2**A, 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 **34***a* is about 0.280" wide. These dimensions are merely exemplary; of course, other dimensions may be used as desired.

[**0076**] **FIG. 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 **FIG. 2**. The window assembly **12** depicted in **FIG. 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.

[**0077**] 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 **FIG. 3, a** preferred embodi-

ment of the spreader layer **42** incorporates a beveled edge. Although not required, an approximate 45-degree bevel is preferred.

[**0078**] The protective layer **50** is intended to protect the top surface of the spreader layer **42** from damage. Ideally, the protective layer is highly infrared-transmissive and highly resistant to mechanical damage, such as scratching or abrasion. It is also preferred that the protective layer **50** and the overcoat layer **52** have high thermal conductivity and antireflective and/or index-matching properties. A satisfactory material for use as the protective layer **50** and the overcoat layer **52** is the multi-layer Broad Band Anti-Reflective Coating produced by Deposition Research Laboratories, Inc. of St. Charles, Mo. Diamondlike carbon coatings are also suitable.

[**0079**] Except as noted below, the heater layer **44** is generally similar to the heater layer **34** employed in the window assembly shown in **FIG. 2**. Alternatively, the heater layer **44** may comprise a doped infrared-transmissive material, such as a doped silicon layer, with regions of higher and lower resistivity. The heater layer **44** preferably has a resistance of about 2 ohms and has a preferred thickness of about 1,500 angstroms. A preferred material for forming the heater layer **44** is a gold alloy, but other acceptable materials include, but are not limited to, platinum, titanium, tungsten, copper, and nickel.

[**0080**] 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 **FIG. 1**). This layer **46** comprises a material having thermally insulative (e.g., lower thermal conductivity than the spreader layer **42**) and infrared transmissive qualities. A preferred material is a germanium-arsenic-selenium compound of the calcogenide glass family known as AMTIR-1 produced by Amorphous Materials, Inc. of Garland, Tex. The pictured embodiment has a diameter of about 0.85 inches and a preferred thickness in the range of about 0.005 to about 0.010 inches. As heat generated by the heater layer **44** passes through the spreader layer **42** into the material sample S, the thermal insulating layer **46** insulates this heat.

[**0081**] 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.

[**0082**] The overall optical transmission of the window assembly **12** shown in **FIG. 3** is preferably at least 70%. The window assembly **12** of **FIG. 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**.

[**0083**] 3. Cooling System

[**0084**] The cooling system **14** (see **FIG. 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 **14***a* to cool and causes the opposing hot surface **14***b* 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 **14***a* 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.

[**0085**] 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 **14***a* of the cooling system **14**.

[**0086**] 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 **FIG. 1**) and conduct heat therefrom.

[**0087**] **FIG. 4** is a top schematic view of a preferred arrangement of the window assembly **12** (of the types shown in **FIG. 2** or **2A**) and the cold reservoir **16**, and **FIG. 5** is a top schematic view of an alternative arrangement in which the window assembly **12** directly contacts the cooling system **14**. The cold reservoir **16**/cooling system **14** preferably contacts the underside of the window assembly **12** along opposing edges thereof, on either side of the heater layer **34**. With thermal conductivity thus established between the window assembly **12** and the cooling system **14**, the window assembly can be cooled as needed during operation of the noninvasive system **10**. In order to promote a substantially uniform or isothermal temperature profile over the upper surface of the window assembly **12**, the pitch distance between centerlines of adjacent heater elements **38** may be made smaller (thereby increasing the density of heater elements **38**) near the region(s) of contact between the window assembly **12** and the cold reservoir **16**/cooling system **14**. As a supplement or alternative, the heater elements **38** themselves may be made wider near these regions of contact. As used herein, "isothermal" is a broad term and is used in its ordinary sense and refers, without limitation, to a condition in which, at a given point in time, the temperature of the window assembly **12** or other structure is substantially uniform across a surface intended for placement in thermally conductive relation to the material sample S. Thus, although the temperature of the structure or surface may fluctuate over time, at any given point in time the structure or surface may nonetheless be isothermal.

[**0088**] The heat sink **18** drains waste heat from the hot surface **14***b* of the cooling system **16** and stabilizes the operational temperature of the noninvasive system **10**. The preferred heat sink **18** (see **FIG. 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 **18***a* which, when the heat sink **18** is installed in the noninvasive system **18**, is in thermally conductive relation to the hot surface **14***b* of the cooling system **14** (see **FIG. 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, Ill. 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.

[**0089**] 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.

[**0090**] 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 achieved by any suitable method, such as convection, conduction, radiation, etc.

[**0091**] 4. Window Mounting System

[**0092**] **FIG. 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 **FIG. 1**. In one embodiment, the window mounting system **400** is employed in conjunction with the window assembly **12** depicted in **FIG. 2A**; in alternative embodiments, the window assemblies shown in **FIGS. 2 and 3** and described above may also be used in conjunction with the window mounting system **400** illustrated in **FIG. 6B**.

[**0093**] 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.

[**0094**] 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 **418***a* of a thermoelectric cooler (TEC) **418** or other cooling device. The TEC **418**, which in one embodiment comprises a 25 W TEC manufactured by MELCOR, is in electrical communication with a second PCB **403**, which includes TEC power leads **409** and TEC power terminals **411** for connection of the TEC **418** to an appropriate power source (not shown). The second PCB **403** also includes contacts **408** for connection with RTD terminals **407** (see **FIG. 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 **FIG. 6**, any other heat sink structures mentioned herein, or any other appropriate device, is in thermal communication with a hot side **418***b* of the TEC **418** (or other cooling device), in order to remove any excess heat created by the TEC **418**.

[**0095**] **FIG. 6C** illustrates a plan view of the interconnection of the window assembly **12**, the first PCB **402**, the diffuser **410** and the thermoelectric cooler **418**. The first PCB includes RTD bonding leads **406** and heater bonding pads **404** which permit attachment of the RTDs **55** and bus bars **36**, respectively, of the window assembly **12** to the first PCB **402** via soldering or other conventional techniques. Electrical communication is thus established between the heater elements **38** of the heater layer **34**, and heater terminals **405** formed in the heater bonding pads **404**. Similarly, electrical communication is established 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**.

[**0096**] With further reference to FIGS. **2**A and **6**B-**6**C, 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 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**.

[**0097**] **FIG. 6D** shows a cross-sectional view of the assembly of **FIG. 6**C through line **22-22**. As can be seen in **FIG. 6**D, 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 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.

[**0098**] 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**.

[**0099**] 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.

[**0100**] 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**.

[**0101**] 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".

[**0102**] 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".

[**0103**] As shown in **FIG. 6**B, 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 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.

[**0104**] 5. Optics

[**0105**] As shown in **FIG. 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 a another rigid material such as aluminum or stainless steel, as long as the inner surfaces are coated or otherwise treated to be highly reflective. Preferably, the 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

[**0106**] Still referring to **FIG. 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.

[**0107**] In a presently preferred embodiment, the collimator is about 7.5 inches in length. At its narrow end **22***a*, the cross-section of the collimator **22** is a rectangle of about 0.4

inches by 0.6 inches. At its wide end **22***b*, 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**.

[**0108**] With further reference to **FIGS. 1 and 6**A, each concentrator **26** comprises a tapered surface oriented such that its wide end **26***a* is adapted to receive the infrared energy exiting the corresponding filter **24**, and such that its narrow end **26***b* 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 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.

[**0109**] Preferably, the concentrators **26** have a rectangular cross-section (as taken orthogonal to the longitudinal axis A-A), although other cross-sectional shapes, such as other polygonal shapes or circular, parabolic or elliptical shapes, may be employed in alternative embodiments. The inner walls of the concentrators converge as they extend toward the narrow end **26***b*. 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 **26***a* to the narrow end **26***b*, before reaching the detectors **28**.

[**0110**] In a presently preferred embodiment, each concentrator **26** is about 1.5 inches in length. At the wide end **26***a*, the cross-section of each concentrator **26** is a rectangle of about 0.6 inches by 0.57 inches. At the narrow end **26***b*, each concentrator **26** has a rectangular cross-section of about 0.177 inches by 0.177 inches. Of course, other dimensions or incidence angles may be employed in constructing the concentrators **26**.

[**0111**] 6. Filters

[**0112**] The filters **24** preferably comprise standard interference-type infrared filters, widely available from manufacturers such as Optical Coating Laboratory, Inc. ("OCLI") of Santa Rosa, Calif. In the embodiment illustrated in **FIG. 1, a** 3×4 array of filters **24** is positioned above a 3×4 array of detectors **28** and concentrators **26**. As employed in this 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 radiation. Typical bandwidths for these filters range from 0.20 μm to 0.50 μm.

[**0113**] 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.

[**0114**] 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.

[**0115**] 7. Detectors

[**0116**] 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.

[**0117**] 8. Control System

[**0118**] **FIG. 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.

[**0119**] 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 signal(s), the current drivers **78** regulate the power supplied to the heater layer **34** and/or to the cooling system **14**. In one embodiment, the processor **74** provides a control signal through a digital I/O device **77** to a pulse-width modulator (PWM) control **80**, which provides a signal that controls the operation of the current drivers **78**. Alternatively, a low-pass filter (not shown) at the output of the PWM provides for continuous operation of the current drivers **78**.

[**0120**] 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.

[0121] In yet another embodiment, a detector cooling system **82** is located in thermally conductive relation to one or more of the detectors **28**. The detector cooling system **82** may comprise any of the devices disclosed above as comprising the cooling system **14**, and preferably comprises a Peltier-type thermoelectric device. The temperature control subsystem may also include temperature sensors, such as RTDs and/or thermistors, located in or adjacent to the detector cooling system **82**, and electrical connections between these sensors and the asynchronous A/D system **72**. The temperature sensors of the detector cooling system **82** provide detector temperature signals to the processor **74**. In one embodiment, the detector cooling system **82** operates independently of the window temperature control system, and the detector cooling system temperature signals are sampled using the asynchronous A/D system **72**. In accordance with the temperature control algorithm, the processor **74** determines appropriate control inputs for the detector cooling system **82**, based on the information contained in the detector temperature signal. The processor **74** outputs digital control signals to the D/A system **76** which in turn provides analog control signals to the current drivers **78**. In response to the control signals, the current drivers **78** regulate the power supplied to the detector cooling system **14**. In one embodiment, the processor **74** also provides a control signal through the digital I/O device **77** and the PWM control **80**, to control the operation of the detector cooling system **82** by the current drivers **78**. Alternatively, a low-pass filter (not shown) at the output of the PWM provides for continuous operation of the current drivers **78**.

[0122] In the data acquisition subsystem, the detectors **28** respond to the infrared energy E incident thereon by passing one or more analog detector signals to a preamp **84**. The preamp **84** amplifies the detector signals and passes them to the synchronous A/D system **70**, which converts the detector signals to digital form and passes them to the processor **74**. The processor **74** determines the concentrations of the analyte(s) of interest, based on the detector signals and a concentration-analysis algorithm and/or phase/concentration regression model stored in a memory module **88**. The concentration-analysis algorithm and/or phase/concentration regression model may be developed according to any of the analysis methodologies discussed herein. The processor may communicate the concentration results and/or other information to a display controller **86**, which operates a display (not shown), such as an LCD display, to present the information to the user.

[0123] A watchdog timer **94** may be employed to ensure that the processor **74** is operating correctly. If the watchdog timer **94** does not receive a signal from the processor **74** within a specified time, the watchdog timer **94** resets the processor **74**. The control system may also include a JTAG interface **96** to enable testing of the noninvasive system **10**.

[0124] In one embodiment, the synchronous A/D system **70** comprises a 20-bit, **14** channel system, and the asynchronous A/D system **72** comprises a 16-bit, 16 channel system. The preamp may comprise a 12-channel preamp corresponding to an array of 12 detectors **28**.

[0125] The control system may also include a serial port **90** or other conventional data port to permit connection to a personal computer **92**. The personal computer can be employed to update the algorithm(s) and/or phase/concentration regression model(s) stored in the memory module **88**, or to download a compilation of analyte-concentration data from the noninvasive system. A real-time clock or other timing device may be accessible by the processor **74** to make any time-dependent calculations which may be desirable to a user.

[0126] 9. Analysis Methodology

[0127] The detector(s) **28** of the noninvasive system **10** are used to detect the infrared energy emitted by the material sample S in various desired wavelengths. At each measured wavelength, the material sample S emits infrared energy at an intensity which varies over time. The time-varying intensities arise largely in response to the use of the window assembly **12** (including its heater layer **34**) and the cooling system **14** to induce a thermal gradient in the material sample S. As used herein, "thermal gradient" is a broad term and is used in its ordinary sense and refers, without limitation, to a difference in temperature and/or thermal energy between different locations, such as different depths, of a material sample, which can be induced by any suitable method of increasing or decreasing the temperature and/or thermal energy in one or more locations of the sample. As will be discussed in detail below, the concentration of an analyte of interest (such as glucose) in the material sample S can be determined with a device such as the noninvasive system **10**, by comparing the time-varying intensity profiles of the various measured wavelengths.

[0128] 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 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**.

[0129] As shown in **FIG. 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.

[0130] As further shown in **FIG. 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.

[0131] 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.

[0132] 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.

[0133] 10. Basic Thermal Gradient

[0134] As further shown in **FIG. 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 tC, 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 **FIG. 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.

[0135] 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 tC, the first (surface) reference signal P declines in amplitude most rapidly, reaching a checkpoint **150** first, at time tP. 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.

[0136] 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 **150** until some later time tR. In other words, there exists a time delay between the time tP at which the amplitude of the first reference signal P reaches the checkpoint **150** and the time tR at which the second reference signal R reaches the same checkpoint **150**. This time delay can be expressed as a phase difference $\Phi(\lambda)$. Additionally, a phase difference may be measured between the analytical signal Q and either or both reference signals P, R.

[0137] 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 tQ. The higher the concentration of analyte, the more the analytical signal Q shifts to the left in **FIG. 8**. As a result, with increasing analyte concentration, the phase difference $\Phi(\lambda)$ decreases relative to the first (surface) reference signal P and increases relative to the second (deep tissue) reference signal R. The phase difference(s) $\Phi(\lambda)$ are directly related to analyte concentration and can be used to make accurate determinations of analyte concentration.

[0138] The phase difference $\Phi(\lambda)$ between the first (surface) reference signal P and the analytical signal Q is represented by the equation:

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

[0139] The magnitude of this phase difference decreases with increasing analyte concentration.

[0140] The phase difference $\Phi(\lambda)$ between the second (deep tissue) reference signal R and the analytical signal Q signal is represented by the equation:

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

[0141] The magnitude of this phase difference increases with increasing analyte concentration.

[0142] 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) 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 IF. 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.

[0143] This methodology is not limited to the determination of phase difference. At any given time (for example, at a time tX) 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.

[0144] This method, the variants disclosed herein, and the apparatus disclosed as suitable for application of the method(s), are not limited to the detection of in-vivo glucose concentration. The method and disclosed variants and apparatus may be used on human, animal, or even plant subjects, or on organic or inorganic compositions in a non-medical setting. The method may be used to take measurements of in-vivo or in-vitro samples of virtually any kind. The method is useful for measuring the concentration of a wide range of additional chemical analytes, including but not limited to,

glucose, ethanol, insulin, water, carbon dioxide, blood oxygen, cholesterol, bilirubin, ketones, fatty acids, lipoproteins, albumin, urea, creatinine, white blood cells, red blood cells, hemoglobin, oxygenated hemoglobin, carboxyhemoglobin, organic molecules, inorganic molecules, pharmaceuticals, cytochrome, various proteins and chromophores, microcalcifications, hormones, as well as other chemical compounds. To detect a given analyte, one needs only to select appropriate analytical and reference wavelengths.

[0145] The method is adaptable and may be used to determine chemical concentrations in samples of body fluids (e.g., blood, urine or saliva) once they have been extracted from a patient. In fact, the method may be used for the measurement of in-vitro samples of virtually any kind.

[0146] 11. Modulated Thermal Gradient

[0147] In some embodiments of the methodology described above, a periodically modulated thermal gradient can be employed to make accurate determinations of analyte concentration.

[0148] As previously shown in **FIG. 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 $\Phi(\lambda)$ is present whether the thermal gradient is induced through heating or cooling. By alternatively subjecting the test sample to cyclic pattern of heating, cooling, or alternately heating and cooling, an oscillating thermal gradient may be induced in a sample for an extended period of time.

[0149] An oscillating thermal gradient is illustrated using a sinusoidally modulated gradient. **FIG. 9** depicts detector signals emanating from a test sample. As with the methodology shown in **FIG. 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. **FIG. 9** shows the signals after normalization. At some time tC, a temperature event (e.g., cooling) is induced at the sample surface. This causes a decline in the detector signal. As shown in **FIG. 8**, the signals (P, Q, R) decline until the thermal gradient disappears and a new equilibrium detector signal IF is reached. In the method shown in **FIG. 9**, as the gradient begins to disappear at a signal intensity **160**, a heating event, at a time tW, is induced in the sample surface. As a result the detector output signals J, K, L will rise as the sample temperature rises. At some later time tC2, 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.

[0150] As previously explained in the discussions relating to **FIG. 8**, the phase difference $\Phi(\lambda)$ may be measured and used to determine analyte concentration.

[0151] **FIG. 9** shows that the first (surface) reference signal J declines and rises in intensity first. The second (deep tissue) reference signal L declines and rises in a time-delayed manner relative to the first reference signal J. The analytical signal K exhibits a time/phase delay dependent on the analyte concentration. With increasing concentration, the analytical signal K shifts to the left in **FIG. 9**. As with **FIG. 8**, the phase difference $\Phi(\lambda)$ may be measured. For example, a phase difference $\Phi(\lambda)$ between the second reference signal L and the analytical signal K, may be measured at a set amplitude **162** as shown in **FIG. 9**. Again, the magnitude of the phase signal reflects the analyte concentration of the sample.

[0152] The phase-difference information compiled by any of the methodologies disclosed herein can correlated by the control system **30** (see **FIG. 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 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.

[0153] Advantageously, the phase difference $\Phi(\lambda)$ may be measured continuously throughout the test period. The phase-difference measurements may be integrated over the entire test period for an extremely accurate measure of phase difference $\Phi(\lambda)$. Accuracy may also be improved by using more than one reference signal and/or more than one analytical signal.

[0154] As an alternative or as a supplement to measuring phase difference(s), differences in amplitude between the analytical and reference signal(s) may be measured and employed to 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 Ser. No. 09/538,164, incorporated by reference below.

[0155] Additionally, these methods may be advantageously employed to simultaneously 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 **FIG. 9** illustrates the method used in conjunction with a sinusoidally modulated thermal gradient, the principle applies to thermal gradients conforming to any periodic function. In more complex cases, analysis using signal processing with Fourier transforms or other techniques allows accurate determinations of phase difference $\Phi(\lambda)$ and analyte concentration.

[0156] As shown in **FIG. 10**, the magnitude of the phase differences may be determined by measuring the time intervals between the amplitude peaks (or troughs) of the reference signals J, L and the analytical signal K. Alternatively, the time intervals between the "zero crossings" (the point at which the signal amplitude changes from positive to 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.

[0157] As a further alternative, two or more driving frequencies may be employed to determine analyte concentra-

tions 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.

[0158] 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.

[0159] As shown in **FIG. 11**, alternating deep and shallow thermal gradients may be induced by alternating slow and fast driving frequencies. As with the methods described above, this variation also involves the detection and measurement of phase differences $\Phi(\lambda)$ between reference signals G, G' and analytical signals H, H'. Phase differences are measured at both fast (e.g., 3 Hz) and slow (e.g., 1 Hz) driving frequencies. The slow driving frequency may continue for an arbitrarily chosen number of cycles (in region SL1), for example, two full cycles. Then the fast driving frequency is employed for a selected duration, in region F1. The phase difference data is compiled in the same manner as disclosed above. In addition, the fast frequency (shallow sample) phase difference data may be subtracted from the slow frequency (deep sample) data to provide an accurate 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.

[0160] The driving frequencies (e.g., 1 Hz and 3 Hz) can be multiplexed as shown in **FIG. 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.

[0161] Additional details not necessary to repeat here may be found in U.S. Pat. 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 Mar. 6, 2001; U.S. Pat. No. 6,161,028, titled METHOD FOR DETERMINING ANALYTE CONCENTRATION USING PERIODIC TEMPERATURE MODULATION AND PHASE DETECTION, issued Dec. 12, 2000; U.S. Pat. No. 5,877,500, titled MULTICHANNEL INFRARED DETECTOR WITH OPTICAL CONCENTRATORS FOR EACH CHANNEL, issued on Mar. 2, 1999; U.S. patent application Ser. No. 09/538,164, filed Mar. 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 Oct. 29, 2001, titled WINDOW ASSEMBLY; U.S. Provisional Patent Application No. 60/340,435, filed Dec. 12, 2001, titled CONTROL SYSTEM FOR BLOOD CONSTITUENT MONITOR; U.S. Provisional Patent Application No. 60/340,654, filed Dec. 12, 2001, titled SYSTEM AND METHOD FOR CONDUCTING AND DETECTING INFRARED RADIATION; U.S. Provisional Patent Application No. 60/336,294, filed Oct. 29, 2001, titled METHOD AND DEVICE FOR INCREASING ACCURACY OF BLOOD CONSTITUENT MEASUREMENT; and U.S. Provisional Patent Application No. 60/339,116, filed Nov. 7, 2001, titled METHOD AND APPARATUS FOR IMPROVING CLINICALLY SIGNIFICANT ACCURACY OF ANALYTE MEASUREMENTS. The entire disclosure of all of the above-mentioned patents, patent applications and publications is hereby incorporated by reference herein and made a part of this specification.

[0162] B. Whole-Blood Detection System

[0163] **FIG. 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.

[0164] 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.

[0165] 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.

[0166] 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 limitation, that the system **200** can be easily transported by the patient and used where convenient. For example, the system **200** is advantageously small. In one preferred embodiment, the system **200** is small enough to fit into a purse or backpack. In another embodiment, the system **200** is small enough to fit into a pants pocket. In still another embodiment, the system **200** is small enough to be held in the palm of a hand of the user.

[0167] 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 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 and then discarded. Some disposable components are used only once and then discarded. Other disposable components are used more than once and then discarded.

[0168] The radiation source **220** of the whole-blood system **200** emits electromagnetic radiation in any of a number of spectral ranges, e.g., within infrared wavelengths; in the mid-infrared wavelengths; above about 0.8 μm; between about 5.0 μm and about 20.0 μm; and/or between about 5.25 μm and about 12.0 μm. However, in other embodiments the 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 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.

[0169] 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.

[0170] 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.

[0171] 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**.

[0172] 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.

[0173] 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.

[**0174**] As shown in **FIG. 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.

[**0175**] As shown in-**FIG. 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 **FIG. 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, N. Mex. 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 **FIG. 13**), or it could be a separate device.

[**0176**] Additional information on laser lances can be found in U.S. Pat. No. 5,908,416, issued Jun. 1, 1999, titled LASER DERMAL PERFORATOR; the entirety of this patent is hereby incorporated by reference herein and made a part of this specification. One suitable gas-jet, fluid-jet or particle-jet perforator is disclosed in U.S. Pat. No. 6,207,400, issued Mar. 27, 2001, titled NON- OR MINIMALLY INVASIVE MONITORING METHODS USING PARTICLE DELIVERY METHODS; the entirety of this patent is hereby incorporated by reference herein and made a part of this specification. One suitable iontophoretic sampler is disclosed in U.S. Pat. No. 6,298,254, issued Oct. 2, 2001, titled DEVICE FOR SAMPLING SUBSTANCES USING ALTERNATING POLARITY OF IONTOPHORETIC CURRENT; the entirety of this patent is hereby incorporated by reference herein and made a part of this specification. One suitable ultrasonic enhancer, and chemical enhancers suitable for use therewith, are disclosed in U.S. Pat. No. 5,458,140, titled ENHANCEMENT OF TRANSDERMAL MONITORING APPLICATIONS WITH ULTRASOUND AND CHEMICAL ENHANCERS, issued Oct. 17, 1995, the entire disclosure of which is hereby incorporated by reference and made a part of this specification.

[**0177**] **FIG. 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 **FIG. 14**, as compared to **FIG. 13**, as it may pierce the portion **249** from either side.)

[**0178**] 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.

[**0179**] 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.

[**0180**] 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 cuvette **240**/sample cell **242**/etc. can vary, depending on many variables, such as the size and sensitivity of the detectors **250**, the intensity of the radiation emitted by the source **220**, the expected flow properties of the sample, and whether flow enhancers (discussed below) are incorporated into the cuvette **240**. The transport of fluid to the sample cell **242** is achieved preferably through capillary action, but may also be achieved through wicking, or a combination of wicking and capillary action.

[**0181**] FIGS. **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 **FIGS. 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 ¼-⅛ inch wide and about ¾ inch long; however, other dimensions are possible while still achieving the advantages of the cuvette **305**.

[**0182**] 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**.

[**0183**] 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.

[**0184**] 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**.

[**0185**] **FIGS. 16 and 16**A 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**.

[**0186**] 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.

[**0187**] 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.

[**0188**] Further information can be found in U.S. patent application Ser. No. 10/055,875, filed Jan. 21, 2002, titled REAGENT-LESS WHOLE-BLOOD GLUCOSE METER. The entire contents of this patent application are hereby incorporated by reference herein and made a part of this specification.

Method and Apparatus for Improving the Accuracy of an Alternative Site Analyte Concentration Measurement

[**0189**] The methods and apparatus described in the previous section titled OVERVIEW OF ANALYTE DETECTION SYSTEMS and illustrated in FIGS. **1-17** can generally be used with any number of methods and apparatuses for determining analyte concentrations, and more specifically can be used with the methods and apparatuses for allowing a patient to determine analyte concentrations at less innervated testing sites, such as, for example, at an AST, as

disclosed herein. Traditional blood samples for Self Monitoring of Blood Glucose ("SMBG") are taken from a finger with a lance. Tests have shown that finger blood glucose levels correlate highly to systemic blood glucose values. Fingertips are highly vascularized and therefore offer an ideal site from which to draw relatively large (1-3 uL) drops of blood for SMBG analysis. Fingertips are also highly innervated, providing good tactile sense which unfortunately makes lancing to obtain the blood sample painful.

[0190] Alternative site testing can be conducted at sites less highly innervated. Reduced innervation produces less or in some cases no pain. However, such alternative sites typically are less vascularized and therefore provide smaller blood samples (0.3-1 uL). Recently, SMBG instruments using lower blood volumes have made alternative site testing popular. A new class of SMBG instruments which are capable of measuring glucose levels with no blood withdrawal at all (e.g. noninvasive) can also be employed to make alternative site measurements.

[0191] One of the most popular alternative sites is the forearm. The concentrations of blood constituents such as glucose measured at alternative sites, particularly the forearm, can exhibit a time lag relative to simultaneous concentration measurements taken at the finger. The time lag varies according to the individual; however, 10 minutes is a typical value for this time lag. If a person's blood glucose level is changing rapidly, for instance 3 mg/dL per min., a time lag of 10 minutes will produce an erroneous alternative-site reading of 30 mg/dL.

[0192] Regardless of where glucose measurements are taken, rapid changes in blood glucose concentration do not always exist. Most of the time the glucose level is steady or is changing slowly (i.e. the magnitude of rate of change is less than 1 mg/dL per minute). However, after an individual eats, the blood glucose concentration may rise rapidly. Similarly, blood glucose concentration may fall rapidly after an individual engages in strenuous exercise. The instantaneous value of the blood glucose rate of change almost always falls between −3 and +3 mg/dL per minute, typically between −2.5 and +2.5 mg/dL per minute, depending on the type and level of the individual's activity.

[0193] Disclosed herein are methods and apparatus for improving the accuracy of a blood-constituent measurement and/or of a blood-constituent measurement device. The disclosed methods and apparatus are further suitable for improving the accuracy of an alternative-site ("AST") blood-constituent measurement device. As used herein, the term "alternative-site blood-constituent measurement device" ("AST device") is a broad term and is used in its ordinary sense and refers, without limitation, to analyte detection devices which are capable of (but need not be restricted to) measuring the concentration of one or more blood constituents, such as glucose or any other analyte, at an alternative site. As used herein, the term "alternative site" is a broad term and is used in its ordinary sense and refers, without limitation, to any measurement location on the body other than the fingers, such as the forearm or abdomen.

[0194] Although much of the discussion herein takes place within the exemplary environment of determining the concentration of glucose within a subject's blood, it should be noted that the methods and apparatus disclosed herein are not limited to blood glucose concentration. Rather, the disclosed methods and apparatus may be employed in the measurement of a wide variety of analytes, including but not limited to alcohol, urea, or any other analyte disclosed herein, within a wide variety of bodily fluids or tissues, including but not limited to interstitial fluid, intercellular fluid, saliva, urine, tissue biopsies, or any other fluids or sample types disclosed herein. Therefore, any reference herein to blood, glucose, or blood constituents should be construed as exemplary and not limiting. A blood constituent is one form of analyte, but the methods and apparatus disclosed herein can apply to any analyte.

[0195] As discussed below, various embodiments of an AST correction method generally comprise: (1) calculating or estimating the rate of change of concentration of an analyte or blood constituent, such as glucose; and/or (2) correcting information provided to an AST device user based on the observed rate of change. Apparatuses for carrying out these methods are also disclosed. The various methods described and illustrated herein may be done by device, person, or a combination of device and person.

[0196] In one method, the AST correction method is used to calibrate the AST device. The AST device and correction method may be used in numerous applications, including, but not limited to, monitoring blood glucose levels, detecting and analyzing changes and trends in blood glucose levels, and forecasting blood glucose levels. The AST device and correction method may be used in the context of blood glucose measurements obtained invasively or noninvasively or through a combination of both invasive and noninvasive measures.

[0197] In another method, the AST device utilizes the rate of glucose-concentration change to determine the accuracy of AST blood glucose measurements. In one embodiment, there is provided a method for determining the rate of change of a patient's blood glucose concentration value and for determining whether or not this rate of change is large enough to produce significant errors in AST SMBG measurements. In another embodiment, the rate of change information is used to correct for errors that may be present in AST measurements. In yet another embodiment, an AST device is configured to either warn of possible errors or automatically correct for the errors after determining that there is a large rate of change in the blood glucose concentration which will produce significant errors in AST SMBG measurements.

[0198] 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.

[0199] A. Timing Circuit

[0200] The methods disclosed herein may advantageously utilize or be executed by or with an AST device which incorporates a timing circuit. For example, the AST device may comprise various embodiments of the noninvasive system **10** disclosed above, with a timing circuit accessible by the signal processor **74** (see **FIG. 7**). Alternatively, the AST device may comprise various embodiments of the whole-blood system **200** disclosed above, with a timing circuit accessible by the signal processor **260** (see **FIG. 13**).

In further alternatives, the AST device can comprise any suitable AST device with a timing circuit.

[0201] As used herein, the term "timing circuit" is a broad term and is used in its ordinary sense and refers, without limitation, to any device that is capable of tracking or calculating intervals of time. The presence of a timing circuit allows the AST device to determine time intervals between glucose measurements for rate change calculations. In one embodiment, the timing circuit comprises a real-time clock. As used herein, the term "real-time clock" is a broad term and is used in its ordinary sense and refers, without limitation, to any device that is capable of tracking or calculating intervals of time and keeping the time of day, the day of week, the day of month, the month and/or the year.

[0202] Alternatively, the timing circuit can be any timing system or mechanism either attached or detached from the AST device. In one embodiment, the timing circuit is an internal clock which time-stamps glucose measurements. In another embodiment, the timing circuit comprises a user-interface whereby the user is able to manually enter time information into the AST device. For example, the user may enter time information based on an external clock, such as, for example, a wristwatch or a wall clock. In yet another embodiment, time information is transmitted from external clocks to the AST device via signals, such as, for example, radio signals, infrared signals, etc.

[0203] With continued reference to **FIGS. 7 and 13**, it should be further noted that in executing the methods disclosed herein, computations may be performed by the signal processor **74** on data stored within memory accessible thereby (where the method is executed by the noninvasive system **10**), or by the signal processor **260** on data stored within memory accessible thereby (where the method is executed by the whole-blood system **200**). Any of the methods disclosed herein may reside in memory as a data-processing algorithm or program instructions executable by the processor **74** of the noninvasive system **10**, by the processor **260** of the whole-blood system **200**, or by processing circuit or hardware of any suitable AST device. In one embodiment, the processing circuit works in conjunction with a module that is executable by the processing circuit. In one embodiment, the module can comprise one or more electrical devices, mechanical devices, components thereof, instructions for operation, combinations thereof, etc.

[0204] B. Determination Of Rate Of Analyte-Concentration Change

[0205] Various methods may be employed to determine the rate of analyte-concentration change. In one method, the user inputs information into the AST device. Such information could include "Meal" to indicate that the user is about to eat or has eaten a meal, or "Exercise" to indicate that the user is about to engage in or has engaged in strenuous physical activity. To support this method the AST device **500** could include a Meal button **502** and/or an Exercise button **504** (see **FIG. 18**) for convenient input of relevant information. However, any suitable structure may be employed to facilitate this data entry.

[0206] In one embodiment, the AST device estimates the rate of analyte-concentration change by assigning a predetermined rate of analyte-concentration change to a given type of input information. For example, the AST device may assign a high positive value to the rate of change, such as that often observed after a meal, if the user pushes the Meal button, or a high negative rate of change, such as that often observed after exercise, if the user pushes the Exercise button. The actual numerical value of each predetermined rate of change would preferably be calibrated for the device user.

[0207] The AST device may advantageously be configured to time stamp the input information based on the output of the real-time clock. In response to the input information, the AST device notes or records within its memory that the absolute value of the rate of change of analyte/glucose concentration will be higher than normal for a given duration, for example, 1 hour, 1.5 hours, or 2 hours after eating or after exercise.

[0208] In another method of determining the rate of analyte/glucose-concentration change, the AST device is configured to record and time stamp the analyte-concentration measurements. As one approach, analyte/glucose-concentration measurements may be recorded at two different times (t_1 and t_2, for example), and then rate of change may be computed as (concentration at t_2−concentration at t_1)/(t_2−t_1). It should be noted that (concentration at t_2−concentration at t_1) may comprise samples from a continuously taken measurement.

[0209] In the absence of a real-time clock, t_1 and t_2 may be limited to being two successive times, such as Monday 10:20:00 for t_1 and Monday 10:30:00 for t_2. In contrast, the utilization of a real-time clock also allows one to monitor trends in concentration and trends in rates of change. For example, with a real-time clock the AST device may be operated or configured to take measurements at times t_1, t_2, and t_3, and then compute rates of change between t_1 and t_2, between t_2 and t_3, and/or between t_1 and t_3. Further, rates of change may be computed for the aforementioned times (t_1, t_2, and t_3) on day 1 and the corresponding times (t_1, t_2, and t_3) on day 2, and so on.

[0210] In one embodiment, measurements may be taken every 10 minutes; however, the frequency of such measurements can vary. More frequent measurements are helpful for detecting and correcting for rapid rates of analyte/glucose-concentration change. In addition, more frequent measurements provide a larger number of sample measurements with which to determine if there exists a consistency or trend among the measured values. Similarly, a higher frequency of measurements facilitates the process of determining whether a given computed rate of change is an outlier that should be disregarded.

[0211] It should be noted, however, that a higher frequency of measurements not only requires more measurements that need to be taken in a given period of time, but it also requires more memory to store the measurement values, both of which result in the use of more system resources. Thus, there is a tradeoff between measurement rate and available system resources. In an alternative embodiment, which can be implemented when the availability of system resources is not a limiting factor, the AST device takes continuous measurements.

[0212] C. Correcting Information Provided To User

[0213] Various methods may be employed to correct the information provided to the AST device user by the AST device.

[0214] 1. Display a Warning

[0215] In one method, the AST device displays and/or sounds a warning that the absolute value of the rate of change of analyte/glucose-concentration is high and that AST measurements may be in error. Instead of or in addition to such a warning, the AST device could prompt the user to make a fingertip or on-site measurement, either invasively or noninvasively.

[0216] 2. External Model

[0217] A further method of correcting the information provided to the user involves determining the clinical significance of an error in an AST measurement. Preferably, the AST device uses an external model, such as, for example, a variation of the Clarke Error Grid or the like, to assess the clinical significance of a computed AST error.

[0218] A rate of change of glucose concentration is determined by any of the methods disclosed above. An AST error is computed based on the rate of change and a typical AST time lag, for example 10 minutes. An AST measurement is taken yielding a raw (i.e. uncorrected) AST glucose value AST_{raw}. In addition, a corrected AST glucose value $AST_{corrected}$ is computed using the AST error as discussed above. The significance of the error is assessed by using an external model. With reference to **FIG. 19**, in one embodiment, the significance of the error is determined on a variation of the Clarke error grid by plotting the intersection of the glucose values: AST_{raw} on the Estimated Blood Glucose Concentration (vertical) axis and $AST_{corrected}$ on the Reference Blood Glucose Concentration (horizontal) axis.

[0219] With continued reference to **FIG. 19**, the significance of the error is determined by the zone in which the resulting data point lies. Zones A and B represent values where the errors in AST measurements are considered clinically acceptable. Zone C represents values that would result in an unnecessary correction of acceptable glucose. Zone D represents values that would result in a dangerous failure to detect and treat. Zone E represents values that would lead to treatment opposite of what clinical accuracy would call for. If the variation of the Clarke error grid analysis yields an AST measurement error represented by zones C, D, or E, the AST device warns the user to measure glucose concentration at an on-site location, such as the finger or finger-tip. Alternatively, the AST device could so warn the user if the variation of the Clarke error grid analysis yields a zone B, C, D or E error, or a zone D or E error.

[0220] For example, assume the rate of change is measured or known to be high, such as −3 mg/dL per min due to strenuous exercise. The AST device computes a possible AST error of −30 mg/dL based on a typical 10 minute lag. An AST measurement is made and a value of 80 mg/dL is found. The AST device, referring to a variation of the Clarke error grid, determines that the value of 80 mg/dL less the potential lag error of −30 mg/dL yields a value of 50 mg/dL, which yields a zone D error as shown in **FIG. 19**. In this case the AST device warns the user to make another measurement using an on-site location like the finger or fingertip.

[0221] 3. Automatic Correction

[0222] In another method, the AST device advantageously automatically corrects an AST measurement based on rate of change information. To implement the automatic correction process, the device develops a user specific correction factor via individual calibration. Although it is possible that several users may share the same correction factor, it is preferred to develop a distinct correction factor for each user.

[0223] In one embodiment, illustrated in **FIG. 20**, the correction factor is developed by making repeated AST and on-site analyte concentration measurements under conditions selected to capture a range of analyte change rates. In the embodiment shown in **FIG. 20**, this could be done by using the AST device to measure and record the concentration of an analyte, for example glucose, after a meal, after exercise, and/or in the absence of either of these activities. Methods and conditions under which glucose measurements are taken for individual calibration of the AST device include but are not limited to glucose tolerance tests and/or glucose measurements taken during and/or after strenuous physical activity. In alternative embodiments, repeated AST determinations are made in conjunction with withdrawal of blood samples and/or noninvasive measurements, either with or without traditional finger/fingertip SMBG determinations.

[0224] Once a set of user-specific information relating to analyte concentration, measurement location, and/or measurement time is recorded by or entered into the AST device, the device computes at last one AST time lag specific to that individual. In one embodiment, this is done by plotting the observed analyte concentrations vs. time, for on-site and AST measurements (see **FIG. 21**). At one or more selected analyte concentrations AA, BB, etc., one or more time lags Δt_1, Δt_2, Δt_3 can be calculated from the distance along the time-axis between the respective intercepts of the on-site and AST curves with a horizontal line representing the concentration in question. The computed time lags can be averaged to generate an overall time lag specific to the user. In one embodiment, separate user-specific time lags may be calculated in this manner for "Meal,""Exercise," and/or "No Meal/Exercise" conditions by relying only on the data corresponding to the condition in question. As discussed above with reference to **FIG. 18**, the AST device may advantageously be configured to accept user input of the present condition and select the appropriate time lag based on the selected condition. It is contemplated that the data collection/recording and the time lag calculations described herein may be done manually or by the AST device, or by a combination of manual and device-reliant techniques.

[0225] With the time lag thus determined, the AST device multiplies the lag by the rate of analyte change determined by any of the methods disclosed herein to calculate a correction factor. The correction factor is either added to or subtracted from the AST measurement to correct it and make it consistent with the on-site value. In other embodiments, some or all of these calculations may be performed manually, instead of or in addition to machine calculation.

[0226] For example, suppose that the user or AST device has information from an individual consisting of simultaneous on-site and AST analyte-concentration measurements through a period of rapidly changing analyte concentration, such as after a meal and during exercise. From this infor-

mation the AST device or user computes that the AST vs. on-site lag in that individual is 11 min. An AST measurement is made and a value of 100 mg/dL found. At the time of the AST measurement the user or AST device determines that the analyte rate of change is +1 mg/dL/min. The user or AST device then computes a correction factor (11 min*1 mg/dL per min=11 mg/dL). This factor is added to the measured value of 100 mg/dL and the AST device may advantageously display the corrected value of 111 mg/dL.

[0227] In another embodiment, the AST device increases the accuracy of AST measurements by using time data from a real-time clock to extrapolate AST measurements based on the user's AST time lag. For example, suppose that a user has just eaten a meal and that his/her AST time lag is known or has previously been determined to be 17 minutes. Given that the user's AST time lag is 17 min., an AST measurement at t=17 min. provides an accurate estimate of an on-site measurement at t=0 min. In one embodiment, the AST device takes blood-glucose measurements every 10 minutes. Suppose that the user's AST blood-glucose is 80 mg/dL at t=0 min. and 120 mg/dL at t=10 min. Under one approach, the AST device uses linear extrapolation to determine what AST blood-glucose will be at t=17 min. Here, the rate of AST blood-glucose change can be calculated as (120−80 mg/dL)/(10−0 min.), which yields 4 mg/dL/minute. Knowing the rate of change and time lag, the AST device can extrapolate what the AST blood-glucose level will be at t=17 min. as follows:

> Blood-glucose=[rate of change*(time interval between t=17 min. and initial time)]+(AST glucose level at initial time).

[0228] Here, blood-glucose=[4 mg/dL/minute*(17−0 minutes)]+80 mg/dL, or blood-glucose=[4 mg/dL/minute*(17−10) minutes]+120 mg/dL. Both sets of calculations yield a glucose concentration of 148 mg/dL, as opposed to a value of 80 mg/dL which does not take into account the user's AST time lag. In another embodiment, the AST device uses curve-fitting and/or other non-linear extrapolation techniques to estimate on-site analyte-concentration values based on AST measurements and the AST time lag.

[0229] 4. Outlier Rejection and Forecasting

[0230] In another method, the AST device corrects the information provided to the AST device user by screening the measured concentrations of a blood constituent, such as glucose, and/or the calculated rates of concentration change in order to remove outlier concentration and/or outlier rate values from consideration while monitoring rates of change and/or communicating results to a user. As used herein, the term "outlier value" is a broad term and is used in its ordinary sense and refers, without limitation, to a value that is far removed from other values in a set of data. Consequently, an outlier value may create an extreme deviation from the expected or average value of a set of data. For example, calculating the rate of change using an outlier blood-constituent value will likely result in an erroneous rate of change value, which may in turn decrease the accuracy of alternate site blood-constituent measurements.

[0231] In one embodiment, the AST device rejects outlier values (i.e. measurement values or rate of change calculations based on measurement values) independently of the AST correction methods described above. In another embodiment, the AST device advantageously applies the AST correction methods and rejects outlier values, either before or after applying the AST correction method.

[0232] In the examples illustrated herein, the analyte concentration ("AC_n") measurements and rate of analyte-concentration change ("RC_n") calculations are done on an intermittent basis. In other embodiment, however, the AST device takes continuous AC_n measurements and/or calculates RC_n values on a continuous basis.

[0233] For example, in one embodiment, the AST device stores AC_n values over a period of five hours and time-stamps each AST measurement. The duration of the period-of-time or time-episode during which the AST device measures, time-stamps, and stores AC_n values is determined and/or adjusted by the AST device or user. In another embodiment, the time-episode and/or the AC_n values measured during the time-episode are labeled and/or categorized by the conditions (e.g. "Meal," "Exercise," and/or "No Meal/Exercise") present during the time-episode, as determined by the AST device or user. In the example illustrated herein, the AST device measures, time-stamps, and stores thirty AC_n values (AC_{n-1}, AC_{n-2}, . . . AC_{n-30}) over a period of five hours. Preferably, these AST measurements are taken at equally spaced time intervals. In the present example, the AST device measures AC_n values every 10 minutes.

[0234] In a preferred embodiment, the AST device uses statistical analysis to calculate a mean and standard deviation for the set of AC_n data for a given time-episode. Typically, for a normal or Gaussian distribution of data, one standard deviation away from the mean accounts for approximately 68 percent of the values in the data set. Two standard deviations away from the mean account for approximately 95 percent of the values in the data set. Three standard deviations account for approximately 99 percent of the values in the data set. For each time-episode, the user and/or AST device uses the mean AC_n and standard deviation values to define a permissible range of values to be included in the measurement history (AC_{n-1}, AC_{n-2}, etc.). In other embodiments, different statistical approach methods and/or user-specific parameters, including but not limited to maximum and/or minimum analyte concentrations and/or rates of analyte-concentration change, as determined, for example, by glucose tolerance tests, may be used to define a permissible range of values to be included in the measurement history.

[0235] In the example illustrated herein, the AST device defines the permissible range of AC_n values as two standard deviations away from the mean AC_n value. For each AC_n measurement, the AST device determines whether the AC_n value falls within two standard deviations of the mean AC_n value. If the AC_n value falls within the permissible range, the AST device stores this AC_n value and/or uses it for other determinations, such as calculation of the rate of analyte-concentration change. If the AC_n value falls outside of the permissible range, the AST device: does not record the AC_n value in the measurement history; does not report the outlier measurement to the user; takes another AC_n measurement; warns the user to make another measurement using an on-site location like the finger or fingertip; and/or rejects any rate of change calculations done based on the outlier measurement.

[0236] Similarly, in another embodiment, the AST device calculates and RC_n data for periods of time defined and/or

categorized by the AST device and/or user. For example, in one embodiment, the AST device calculates and stores RC_{HOUR} data for one-hour time-episodes throughout a twenty-four time period. More specifically, for a given one-hour time-episode, the AST device uses the corresponding AC_n data (i.e. AC_{n-1}, AC_{n-2}, etc.) to calculate a RC_n for each pair of successive AC_n values (RC_{n-1}, RC_{n-2}, etc.). The AST device then calculates the mean value (RC_{hour}) for the RC_n data set. The AST device performs this calculation twenty-four times in a day with each of the twenty-four RC_{hour} values corresponding to a one-hour time-episode. Next, the AST device calculates the mean and standard deviation for the data set containing these twenty-four RC_{hour} values.

[0237] In the example illustrated herein, the AST device defines the permissible range of RC_{hour} values as being within two standard deviations away from the mean RC_{hour} value. Analogous to the example above which illustrates the rejection of outlier AC_n values, if the RC_n value falls within the permissible range (i.e. two standard deviations from the mean RC_{hour} value), the AST device stores this RC_n value and/or uses it for calculations based on RC_n values, including but not limited to the correction factor for an AST measurement. If the RC_n value falls outside of the permissible range, the AST device: does not record the RC_n value in the measurement history; does not report the outlier RC_n value to the user; takes another AC_n measurement with which to calculate another RC_n value; warns the user to make another AC_n measurement using an on-site location like the finger or fingertip; and/or rejects any calculations based on the outlier RC_n value.

[0238] In another method, the AST device is advantageously configured to forecast future AC_n values (AC_{n+1}, AC_{n+2}, etc.) and/or RC_n values (RC_{n+1}, RC_{n+2}, etc.). The AST device extrapolates future AC_n and/or RC_n values by analyzing past values of AC_n (i.e. AC_{n-1}, AC_{n-2}, etc.) and RC_n (i.e. RC_{n-1}, RC_{n-2}, etc.) in the measurement history. The AST device creates or maintains sets of data based on: time of day; day of the week; and/or conditions present during a time-episode.

[0239] In a preferred embodiment, the AST device uses statistical analysis to calculate the mean and standard deviation for sets of data in the measurement histories of AC_n and RC_n. For example, in one illustrative embodiment, the AST device forecasts the rate of glucose-concentration change for Thursday 8:00:00 by first creating a subset (i.e. AC_{n-1}, AC_{n-2}, and AC_{n-3}) of the measurement history corresponding to AST glucose concentration measurements taken on Monday 8:00:00, Tuesday 8:00:00, and Wednesday 8:00:00 during the same week. The AST device then calculates past rates of glucose-concentration change (i.e. RC_{n-1}, RC_{n-2}, and RC_{n-3}) based on the value of AC_{n-1}, AC_{n-2}, and AC_{n-3}. Next, the AST device calculates a mean value ("RC_{mean}") and standard deviation for the subset of data consisting of RC_{n-1}, RC_{n-2}, and RC_{n-3}. In the example illustrated herein, the AST device's forecasted RC_n value for Thursday 8:00:00 is equal to RC_{mean}.

[0240] In the embodiment illustrated above, the AST device forecasts the future value of RC_n by calculating the average and standard deviation of past values of RC_n. In other embodiments, different statistical methods and/or curve-fitting techniques may be implemented on subsets and/or entire sets of past AC_n and/or RC_n values to extrapolate future AC_n and/or RC_n values.

[0241] D. Adjustment Factor and Discrete Time Analyte Measurements

[0242] In one aspect of the present invention, various methods may be employed to ensure that a user's blood-analyte concentration level returns to or is maintained at basal or normal levels. These methods generally involve: (1) having a physician or clinical practitioner determine at least one adjustment factor for the patient; and (2) utilizing an AST device that advises the patient to take the appropriate dose of treatment/medicine at certain times of the day. In one embodiment, the AST device utilizes the clinically determined adjustment factor to perform the user/patient advisory function described herein. As used herein, treatment/medicine generally refers to anything that the patient consumes or injects into him or herself in order to control his/her blood-analyte concentration. For example, in the context of controlling a patient's blood-glucose concentration, the treatment/medicine can comprise one or more of insulin, glucose, food, or any other medicine or consumable that affects the patient's blood-glucose levels.

[0243] In one embodiment, a physician, clinical practitioner, or other qualified healthcare professional (hereinafter collectively referred to as "physician") determines the adjustment factor for a certain treatment/medicine, such as, for example, insulin, that is needed to return the patient's blood-glucose concentration to basal or normal levels. For example, the adjustment factor can be expressed as units of insulin needed per gram of carbohydrate consumed by the user. In one embodiment, in the context of using insulin to regulate blood-glucose levels, the adjustment factor comprises the Insulin Adjustment Factor ("IAF"). It should be noted that the adjustment factor is not determined by the AST device, but is instead determined by a physician. It should also be noted that the adjustment factor can vary from individual to individual.

[0244] In one embodiment, the present method of having the AST device advise the user to take a certain dose of treatment/medicine in order to return the user's blood-analyte levels to the target level (i.e. the normal or basal level) is incorporated into the AST device. However, the present method is not central to or required for the operation of the AST device. In one embodiment, the AST device has an on/off switch with which to activate/deactivate the user advisory function. It will generally be up to the user's physician to determine whether or not to activate the user advisory function of the AST device. If the physician decides that it would be desirable to activate the user advisory function, then the physician will determine the user's adjustment factor and enter this number into the AST device via a data-input or user-interface.

[0245] In one embodiment, the AST device includes a data-input interface with which the physician can input the target analyte level. Here, the AST device calculates the appropriate dose of treatment/medicine that the user should take based on the user's current, corrected AST blood-analyte measurement, the user's target analyte level, and the user's adjustment factor. The AST device then advises the user to take the calculated dose of treatment/medicine. For example, in the context of managing blood-glucose levels where the user is undergoing a hyperglycemic episode, the AST device will advise the user to take a certain dosage of insulin in order to return the blood-glucose to a basal or resting levels.

[0246] In one embodiment, the AST device calculates the appropriate dose of treatment/medicine by utilizing a computer-based algorithm, such as, for example, a neural network system. AST device training signals that include variables, such as, for example, the current analyte concentration, the target analyte concentration, the adjustment factor, the treatment/medicine dosage, etc., are fed into the neural network. In one embodiment, the neural network system provides or estimates appropriate doses of treatment/medicine for each measured blood-analyte measurement based on current input information and historical data values. It should be noted that any computer-based algorithm or training system known in the art may be implemented to program the AST device to notify the user of the appropriate treatment/medicine dosage.

[0247] In another aspect of the present invention, the AST device, which includes a real-time clock, reminds the user to take blood-analyte measurements several times throughout the day. In one preferred embodiment, the AST device reminds the user to take measurements during wake hours only. The real-time clock allows for time data and time interval data to be stored automatically. In one embodiment, in the exemplary context of blood-glucose management, the user can take a finger-stick glucose measurement in response to the reminder by the AST device. Here, the user can enter glucose measurement data into the AST device via a data-input interface or via any other appropriate data storage means. Glucose measurements can be done on the meter (i.e. the AST device) as well as manually. In another embodiment, the user can simply utilize the AST device itself to measure blood-glucose.

[0248] Over time, through repeated measurements, the AST device allows the physician to compile trends in the user's blood-analyte levels during the user's wake hours. In one embodiment, the AST device will remind the user to take analyte measurements 6-8 times during the user's wake hours. For example, in one embodiment, the device reminds the user to take analyte measurements when he/she: wakes up; eats breakfast; before lunch; after lunch; before dinner; after dinner; and before bed. It should be noted that the actual times or events during/before/after which the device reminds the user to take measurements can vary depending on various factors, such as, for example, the user's habits and lifestyle. It should be noted that the measurement of analyte levels is not continuous and is not automatic. Rather, the device instructs the user to take measurements at several selected discrete times throughout the user's wake hours. As such, this aspect of the present invention allows for a more efficient method of monitoring a user's analyte levels. It should be noted that measurements can be taken more frequently (i.e. more than 6-8 times per day) when more intensive management is required. In one embodiment, in the context of intensive blood-glucose management, blood-glucose is measured frequently at regular time intervals. In another embodiment, the blood-glucose is measured more is measured frequently at non-regular time intervals. For example, more measurements can be taken during wake hours than during other hours in the day.

[0249] In yet another aspect of the present invention, the AST device determines when to remind the user to take analyte measurements by taking into consideration the current analyte level, the targeted analyte level, the measured analyte highs and lows, etc. The AST device builds a case history about the user's analyte levels during his/her wake hours and adjusts the times at which it reminds the user to take an analyte measurement. In one embodiment, the AST device utilizes fuzzy logic and/or other predictive analysis methods known in the art to determine when it should remind the user to take analyte measurements. This can require storing and processing large amounts of data. As such, in one embodiment, the data is transmitted to an outside processing circuit, unit, computer, storage device, etc. The processed information is then transmitted back to the AST device. In another embodiment, the AST device also utilizes fuzzy logic and/or other predictive analysis methods known in the art to determine what the target analyte level should be. This target value is then provided to the physician who can consider the suggested target value when making the decision as to what the user's target analyte concentration should be.

[0250] In addition to suggesting target values to the physician, the AST device measurements assist physicians in treating patients in any number of ways. In one embodiment, the blood-glucose measurements provided by the AST device can be used to expedite and/or supplement hospital protocols for monitoring and/or treating patients. For example, in a situation where a patient at a hospital is experiencing a hyperglycemic episode, such as, for example a blood-glucose level equal to or exceeding 520 mg/dL, it is common hospital protocol to send draw blood from the patient and send the blood sample out to a laboratory for blood work. One reason for this is that typical methods of blood-glucose measurement, such as, for example, finger-stick measurements, do not provide accurate measurements when the blood-glucose is as high as 520 mg/dL. In one embodiment, the AST device blood-glucose measurements are used by physicians to obtain an accurate and timely blood-glucose value, thereby providing an alternative to typical methods of measuring blood-glucose, and thereby alleviating the need to send blood samples for lab work or to wait for results. In another embodiment, the AST device essentially serves as a portable medical record providing information, including but not limited to analyte and time data values, with which physicians and hospitals can provide improved treatments for patients.

[0251] It is to be understood that the patent rights arising hereunder are not to be limited to the specific embodiments or methods described in this specification or illustrated in the drawings, but extend to other arrangements, technology, and methods, now existing or hereinafter arising, which are suitable or sufficient for achieving the purposes and advantages hereof.

What is claimed is:

1. A method for improving the accuracy of analyte concentration measurements, the method comprising:

determining a rate of change of analyte concentration;

measuring an analyte concentration at an alternative site; and

adjusting the measured analyte concentration based on said rate of change to generate an adjusted analyte concentration value which is a more accurate estimate of the systemic analyte concentration value.

2. The method of claim 1, further comprising:

determining the clinical significance of an error in the measured analyte concentration.

3. The method of claim 1, wherein adjusting the measured analyte concentration comprises:

determining a time lag between analyte concentrations measured on-site and at an alternative site;

determining a correction factor based on the time lag and said rate of change of analyte concentration; and

adjusting the measured analyte concentration value by said correction factor.

4. The method of claim 1, further comprising:

correcting the measured analyte concentration based on the rate of change of the analyte concentration, further comprising:

determining the time lag between analyte concentrations measured onsite and at an alternative site;

taking a follow-up analyte concentration measurement at a time that falls between the time of previous analyte concentration measurement and the sum of the time lag and the time of the previous analyte concentration measurement;

determining the rate of analyte concentration change during the time period between the previous analyte concentration measurement and the follow-up analyte concentration measurement; and

extrapolating the analyte concentration value to a time after the sum of the time lag and the time of the previous analyte concentration measurement by using the rate of analyte concentration change in between the previous analyte concentration measurement and the follow-up analyte concentration measurement.

5. The method of claim 1, further comprising:

screening measured analyte concentration values to remove outlier concentration values and/or rate of concentration change values based on statistical analysis, data history, and/or data forecasts or trends.

6. A method for improving the accuracy of information provided to a user by an analyte detection system, said method comprising:

determining a rate of change of analyte concentration; and

adjusting said information provided to said user based on said rate of change.

7. The method of claim 6, wherein determining said rate of change comprises estimating that the absolute value of said rate of change is relatively high.

8. The method of claim 6, wherein determining said rate of change comprises estimating that the absolute value of said rate of change will remain relatively high for about 1-2 hours.

9. The method of claim 6, wherein determining said rate of change comprises receiving data input from the user and estimating, based on said data, that the absolute value of said rate of change is relatively high.

10. The method of claim 9, wherein said data comprises at least one of (i) that the user is about to eat or has just eaten a meal and (ii) that the user is about to engage in or has just engaged in physical exercise.

11. The method of claim 6, wherein determining said rate of change comprises:

measuring a first analyte concentration at a first measurement time;

measuring a second analyte concentration at a second measurement time; and

computing said rate of change based on said first and second analyte concentrations and said first and second measurement times.

12. The method of claim 11, wherein determining said rate of change further comprises continuously computing said rate of change.

13. The method of claim 6, wherein adjusting said information comprises warning the user that the absolute value of said rate of change is relatively high.

14. The method of claim 13, wherein adjusting said information further comprises prompting the user to take an on-site analyte concentration measurement.

15. The method of claim 6, wherein adjusting said information comprises warning the user, when the absolute value of said rate of change is relatively high, that alternative-site measurements are likely to be inaccurate.

16. The method of claim 15, wherein adjusting said information further comprises prompting the user to take an on-site analyte concentration measurement.

17. The method of claim 6, wherein adjusting said information comprises at least one of (i) warning the user that said analyte concentration is increasing and (ii) warning the user that said analyte concentration is decreasing.

18. The method of claim 6, wherein adjusting said information comprises adjusting an analyte concentration measurement based on said rate of change.

19. The method of claim 6, wherein adjusting said information comprises:

measuring a raw analyte concentration;

calculating a corrected analyte concentration based on said rate of change and said raw analyte concentration;

assessing the clinical significance of a measurement error based on said raw analyte concentration and said corrected analyte concentration; and

warning the user to take an on-site analyte concentration measurement based on the clinical significance of said measurement error.

20. The method of claim 19, wherein assessing the clinical significance comprises using an external model.

21. The method of claim 20, wherein the external model comprises a variation of the Clarke error grid.

22. The method of claim 6, wherein determining said rate of change comprises rejecting outlier analyte-concentration measurements.

23. A system for measuring the concentration of an analyte at an alternative site, said system comprising:

a processing circuit; and

a module executable by the processing circuit whereby the processing circuit receives an analyte concentration measurement taken at the alternative site, determines a

rate of change of the concentration of said analyte, and provides information to the user based on said rate of change.

24. The system of claim 23, wherein providing information comprises warning the user that the absolute value of the rate of change is high.

25. The system of claim 23, wherein providing information comprises prompting the user to take an on-site analyte concentration measurement.

26. The system of claim 23, wherein providing information comprises warning the user, when the absolute value of said rate of change is relatively high, that alternative-site measurements are likely to be inaccurate.

27. The system of claim 26, wherein providing information further comprises prompting the user to take an on-site analyte concentration measurement.

28. The system of claim 23, wherein providing information comprises at least one of (i) warning the user that the concentration of said analyte is increasing and (ii) warning the user that the concentration of said analyte is decreasing.

29. The system of claim 23, wherein the analyte concentration measurement is a measurement of the concentration of glucose within blood.

30. The system of claim 23, further comprising a timing circuit accessible by said processing circuit.

31. The system of claim 30, wherein the timing circuit comprises a real-time clock.

32. The system of claim 31, wherein the real-time clock is capable of keeping the time of day, the day of week, the day of month, the month, and/or the year.

33. The system of claim 23, further comprising a user-interface whereby the user is able to input data into the analyte detection system, wherein the processing circuit considers said data in adjusting the analyte concentration to generate an adjusted analyte concentration value.

34. The system of claim 33, wherein said data comprises at least one of (i) that the user is about to eat or has just eaten a meal and (ii) that the user is about to engage in or has just engaged in physical exercise.

35. The system of claim 23, wherein the processing circuit assesses the clinical significance of a possible error in said analyte concentration measurement.

36. The system of claim 35, wherein assessing the clinical significance comprises using an external model.

37. The system of claim 36, wherein the external model comprises a variation of the Clarke error grid.

38. The system of claim 23, wherein the processing circuit screens measured analyte concentration values to remove outlier concentration values and/or rate of concentration change values based on statistical analysis, data history, and/or data forecasts or trends.

39. A system for measuring the concentration of an analyte at an alternative site, said system comprising:

a processing circuit; and

a module executable by the processing circuit whereby the processing circuit receives an analyte concentration measurement taken at the alternative site, determines a rate of change of the concentration of said analyte, and adjusts said analyte concentration measurement based on said rate of change.

40. The system of claim 39, wherein the analyte concentration measurement is a measurement of the concentration of glucose within blood.

41. The system of claim 39, further comprising a timing circuit accessible by said processing circuit.

42. The system of claim 41, wherein the timing circuit comprises a real-time clock.

43. The system of claim 42, wherein the real-time clock is capable of keeping the time of day, the day of week, the day of month, the month, and/or the year.

44. The system of claim 39, further comprising a user-interface whereby the user is able to input data into the analyte detection system, wherein the processing circuit considers said data in adjusting the analyte concentration to generate an adjusted analyte concentration value.

45. The system of claim 44, wherein said data comprises at least one of (i) that the user is about to eat or has just eaten a meal and (ii) that the user is about to engage in or has just engaged in physical exercise.

46. The system of claim 39, wherein the processing circuit assesses the clinical significance of a possible error in said analyte concentration measurement.

47. The system of claim 46, wherein assessing the clinical significance comprises using an external model.

48. The system of claim 47, wherein the external model comprises a variation of the Clarke error grid.

49. The system of claim 39, wherein the processing circuit screens measured analyte concentration values to remove outlier concentration values and/or rate of concentration change values based on statistical analysis, data history, and/or data forecasts or trends.

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专利名称(译)	用于提高替代位点分析物浓度测量的准确度的方法和装置		
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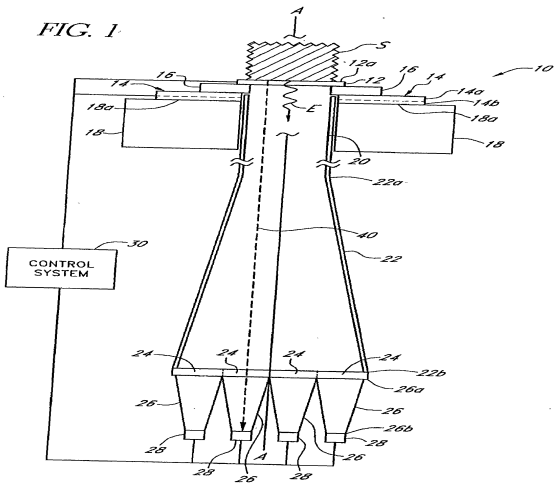
摘要(译)

用于提高在替代位置处的分析物浓度测量的准确度的方法和装置以及提供给用户的信息。本发明有利地利用与分析物浓度变化率有关的信息来调节分析物浓度测量值和/或提供给用户的信息。因此，本发明提供了新的和改进的方法和装置，用于在指尖以外的生理位置获得分析物浓度信息，同时确保分析物浓度信息准确地反映全身分析物浓度值。

FIG. 1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22a
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CONTROL SYSTEM
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22b
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