US 20050203356A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2005/0203356 A1

Samsoondar (43) Pub. Date: Sep. 15, 2005

(54) JOINT-DIAGNOSTIC IN VIVO & IN VITRO APPARATUS

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(21) Appl. No.: **11/071,247**

(22) Filed: **Mar. 4, 2005**

(30) **Foreign Application Priority Data**

Mar. 9, 2004 (CA) 2,460,898

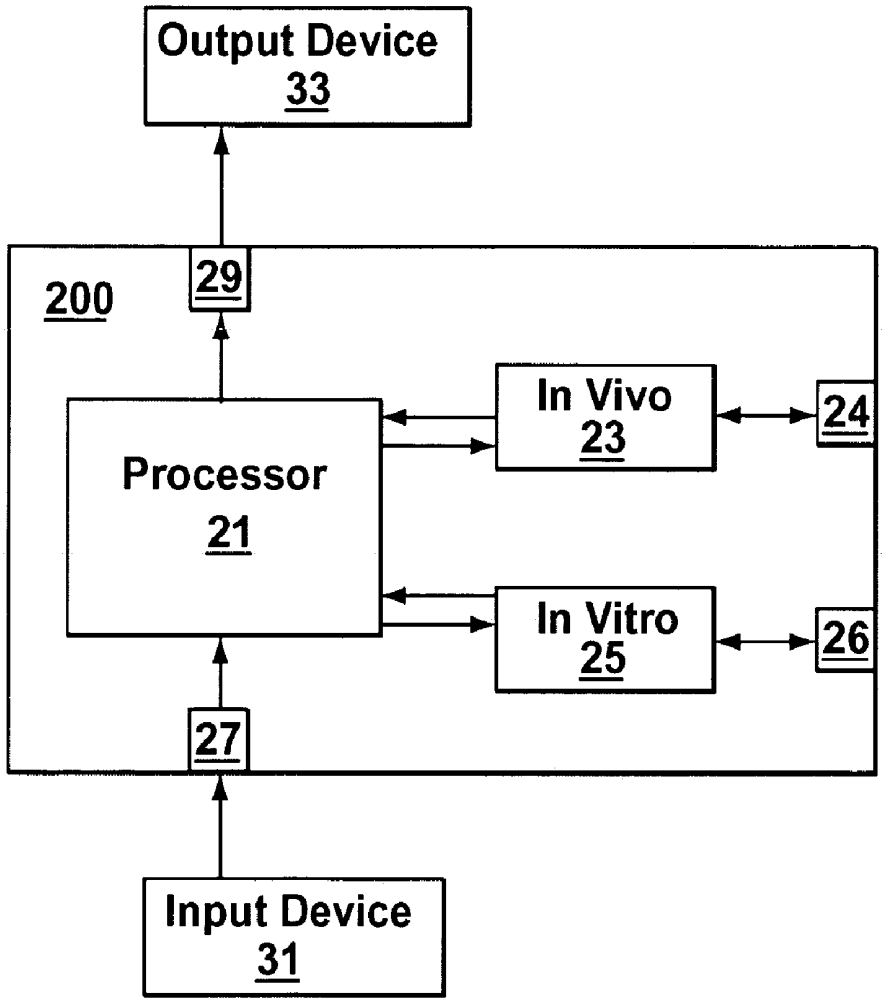
Publication Classification

(51) **Int. Cl.**[7] **A61B 5/00**; B65D 81/00

(52) **U.S. Cl.** **600/322**; 600/573; 600/584; 128/903

(57) **ABSTRACT**

In vivo testing for analytes in a life-form is an attractive concept because a biological sample does not have to be removed from the life-form. However, in vivo testing alone is unable to provide information that is accurate, complete and/or reliable enough to safely replace in vitro testing. In contrast to performing either in vivo or in vitro testing independently and alone, some embodiments of the present invention provide a joint-diagnostic apparatus for combined in vivo and in vitro testing. In some specific embodiments results from an in vitro measurement module are used in combination with subsequent in vivo measurements/observations obtained at a later time, and/or vice versa. Accordingly, in some embodiments in vitro measurements are used to compliment and/or partially compensate for some of the limitations of in vivo testing, and at the same time enabling some of the benefits of in vivo testing by reducing the number of biological samples taken.



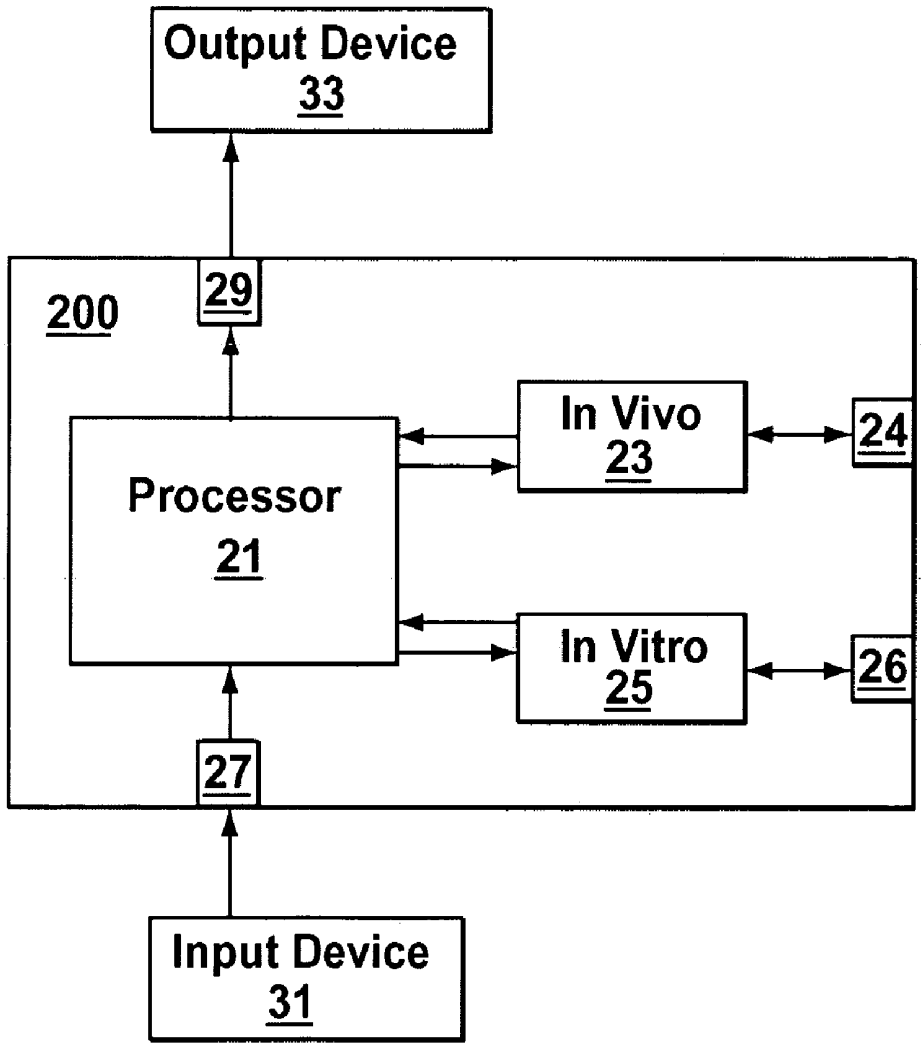

Output Device
33
200
29
Processor
21
In Vivo
23
24
In Vitro
25
26
27
Input Device
31

FIG. 1

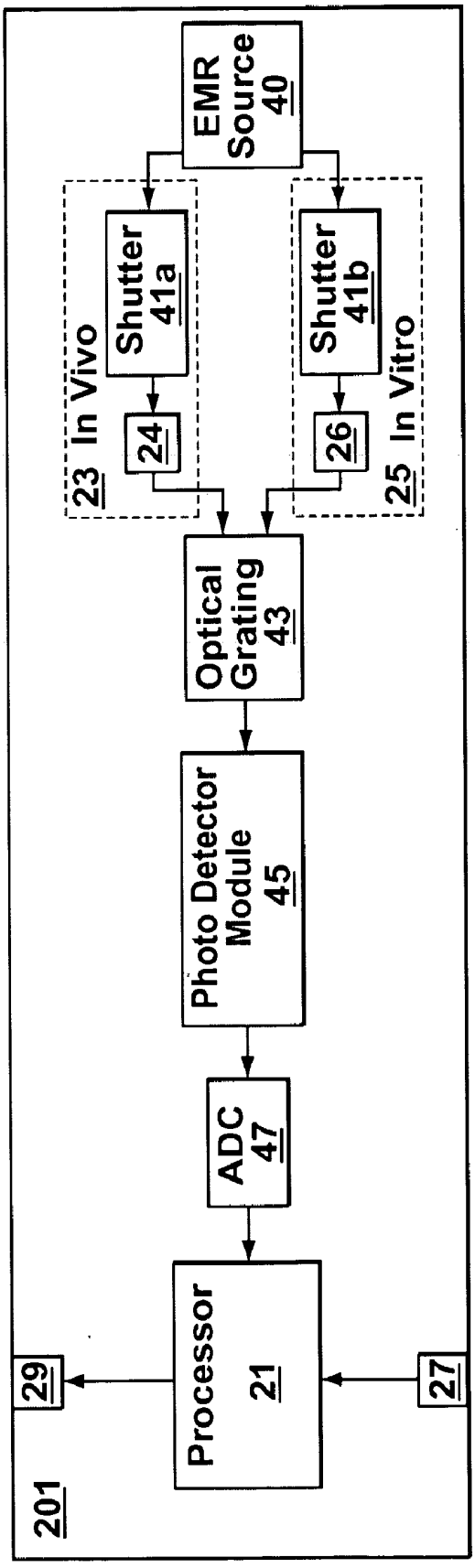

EMR Source 40
Shutter 41a
Shutter 41b
23 In Vivo
24
26
25 In Vitro
Optical Grating 43
Photo Detector Module 45
ADC 47
Processor 21
29
27
201

FIG. 2

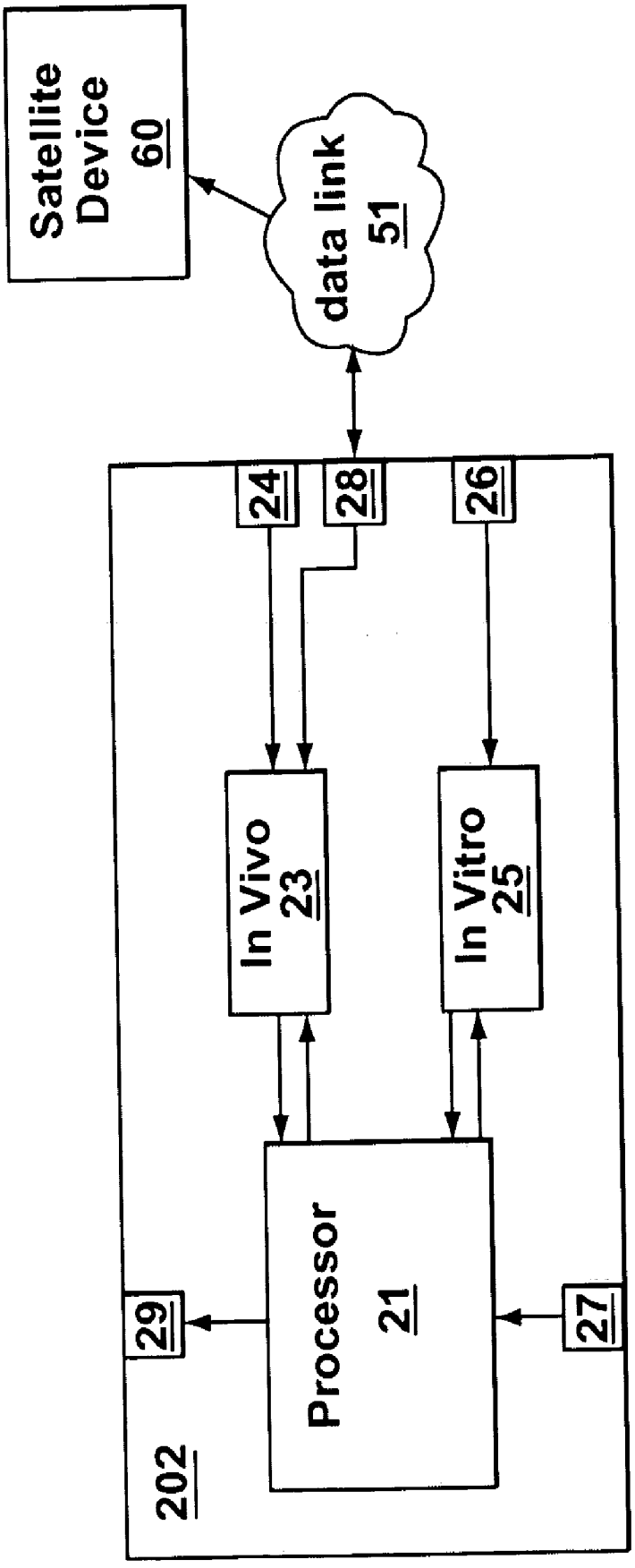

Satellite Device 60
data link 51
24
28
26
In Vivo 23
In Vitro 25
Processor 21
29
27
202

FIG. 3

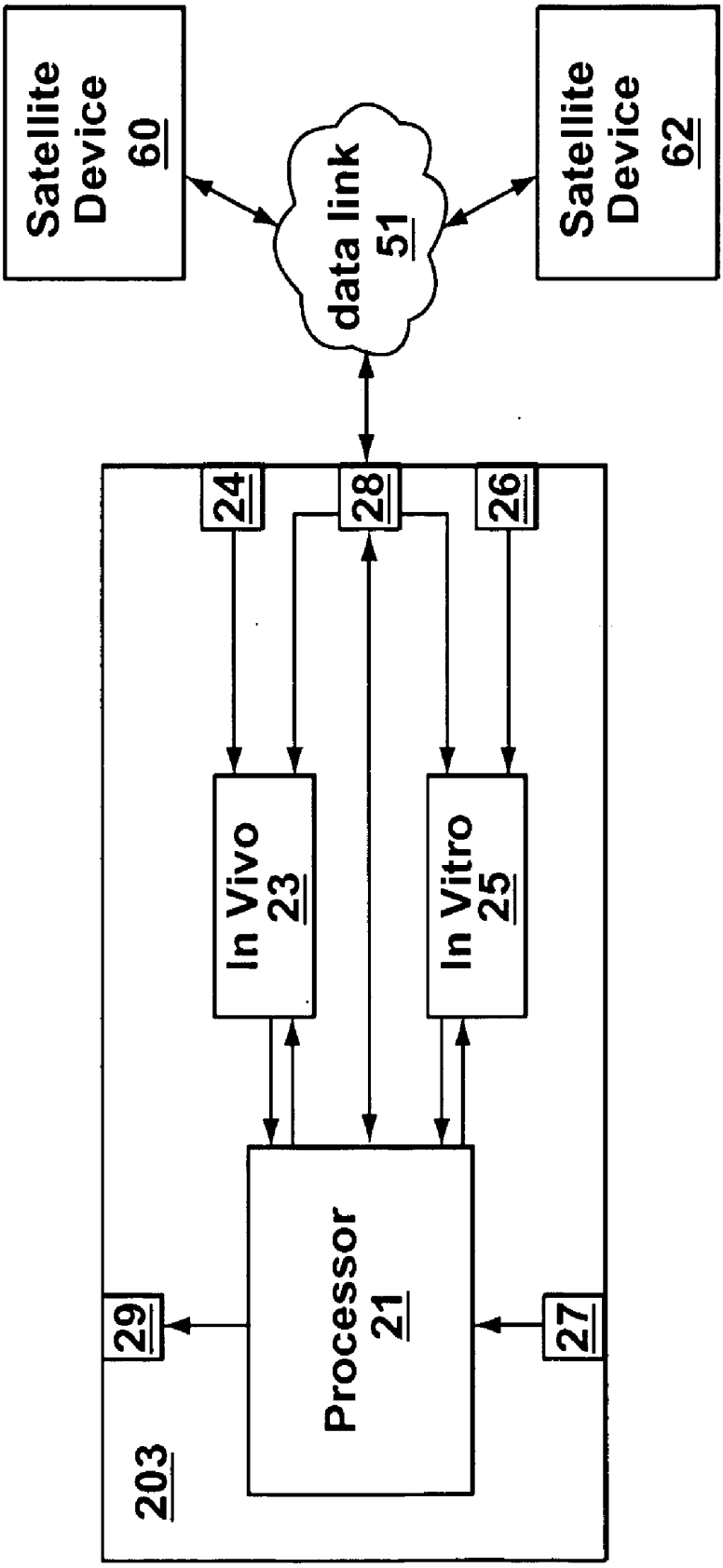

Satellite Device 60
data link 51
Satellite Device 62
24
28
26
In Vivo 23
In Vitro 25
Processor 21
29
27
203

FIG. 4

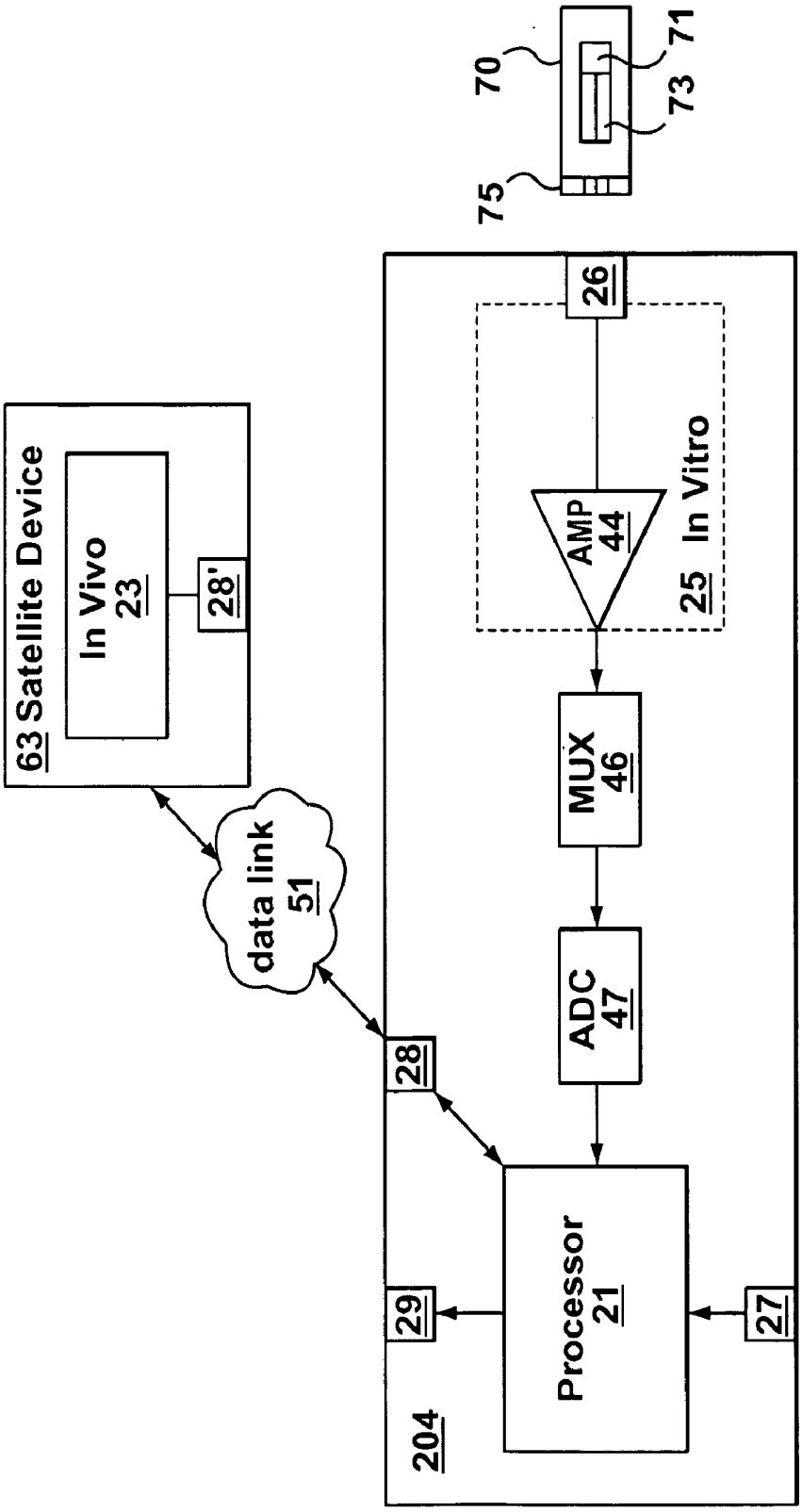

70
71
73
75
26
25 In Vitro
AMP
44
MUX
46
ADC
47
Processor
21
29
27
28
204
data link
51
63 Satellite Device
In Vivo
23
28'

FIG. 5

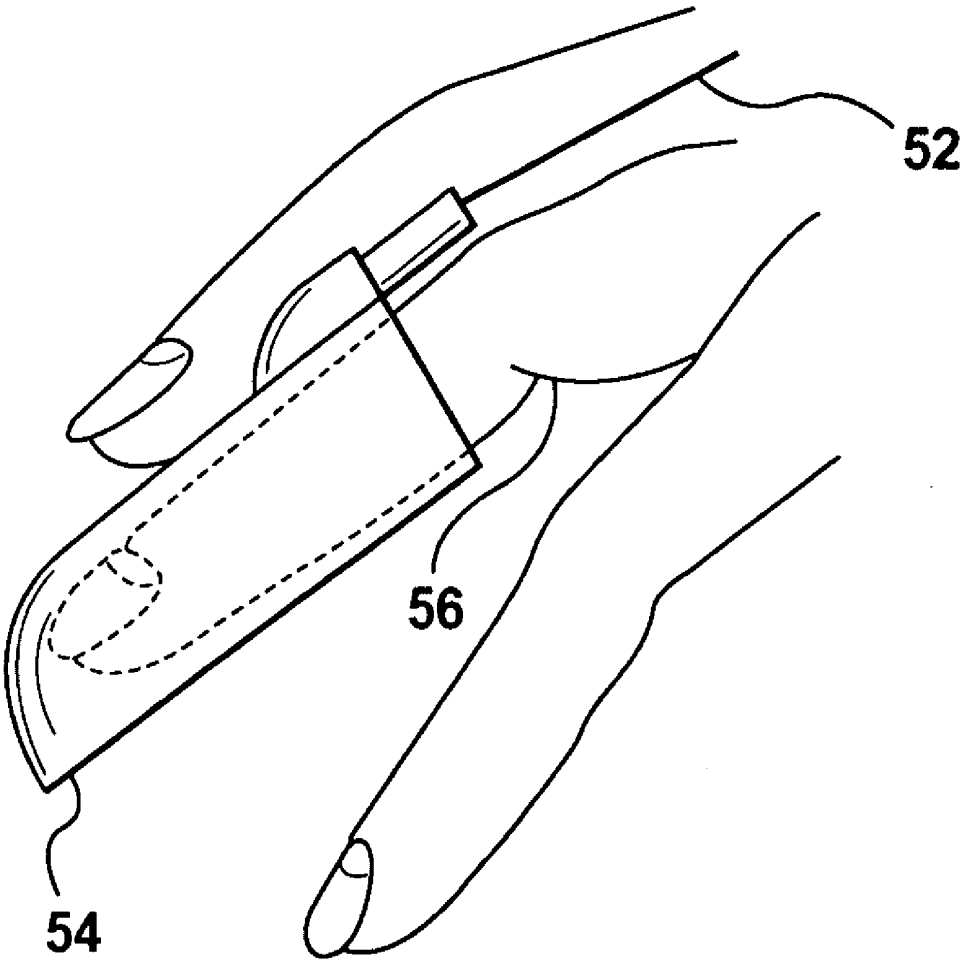


FIG. 6

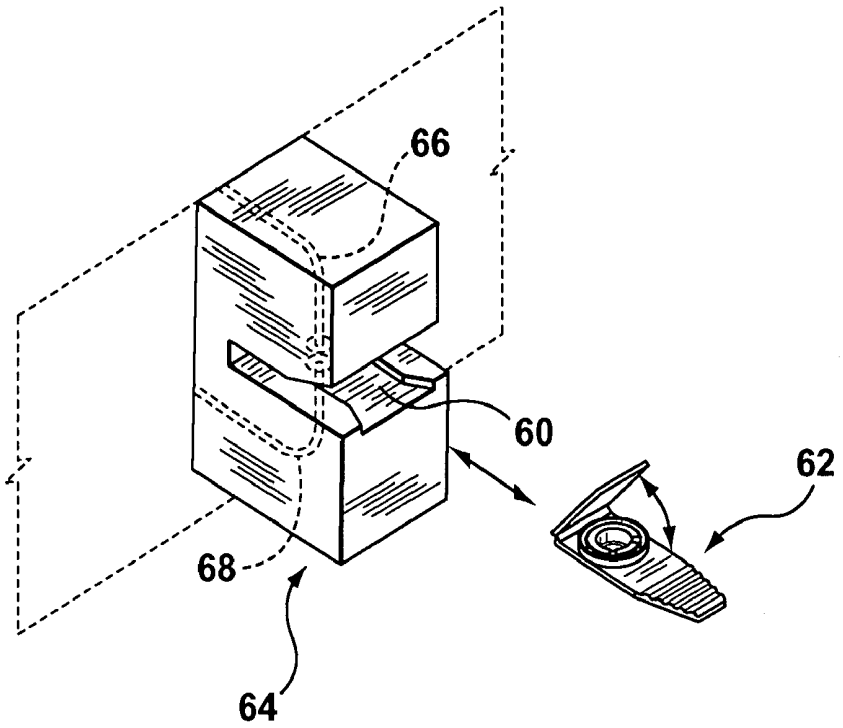


FIG. 7

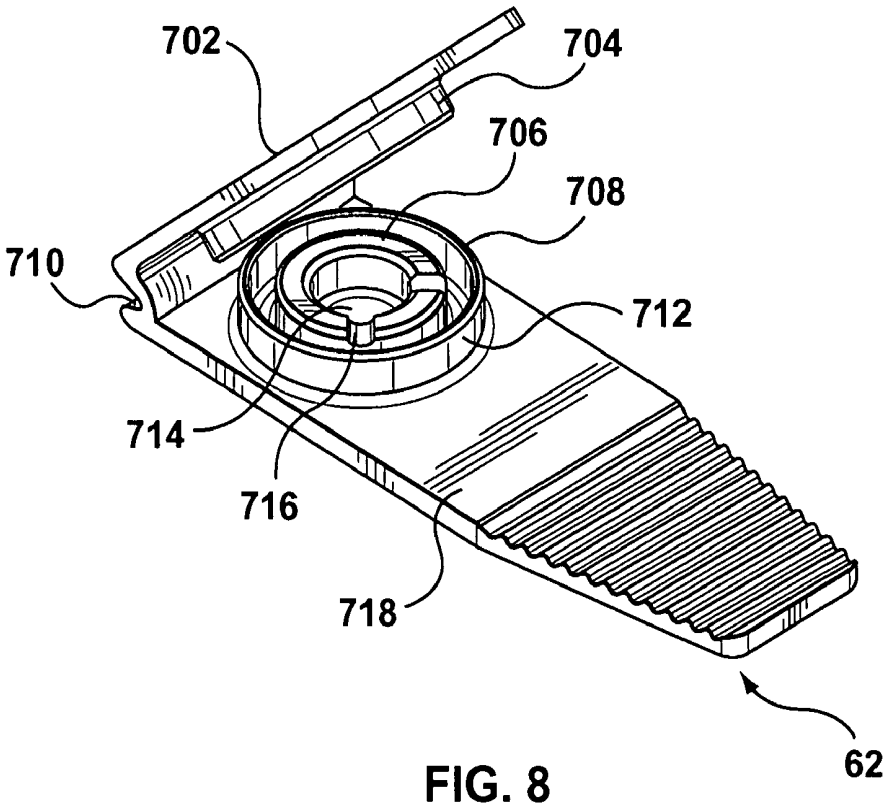


FIG. 8

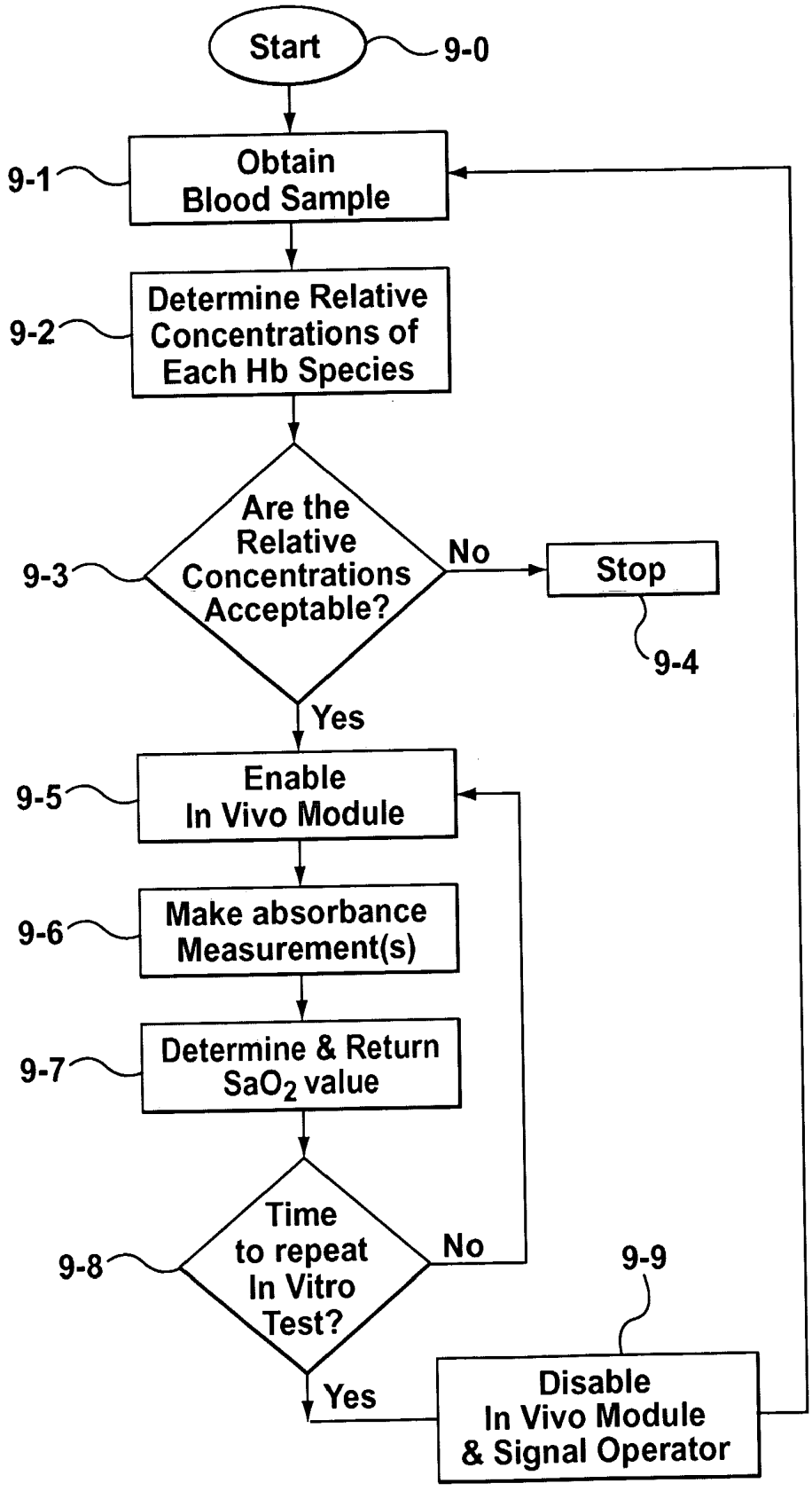

Start
9-0
Obtain Blood Sample
9-1
Determine Relative Concentrations of Each Hb Species
9-2
Are the Relative Concentrations Acceptable?
9-3
No
Stop
9-4
Yes
Enable In Vivo Module
9-5
Make absorbance Measurement(s)
9-6
Determine & Return SaO_2 value
9-7
Time to repeat In Vitro Test?
9-8
No
Yes
9-9
Disable In Vivo Module & Signal Operator

FIG. 9

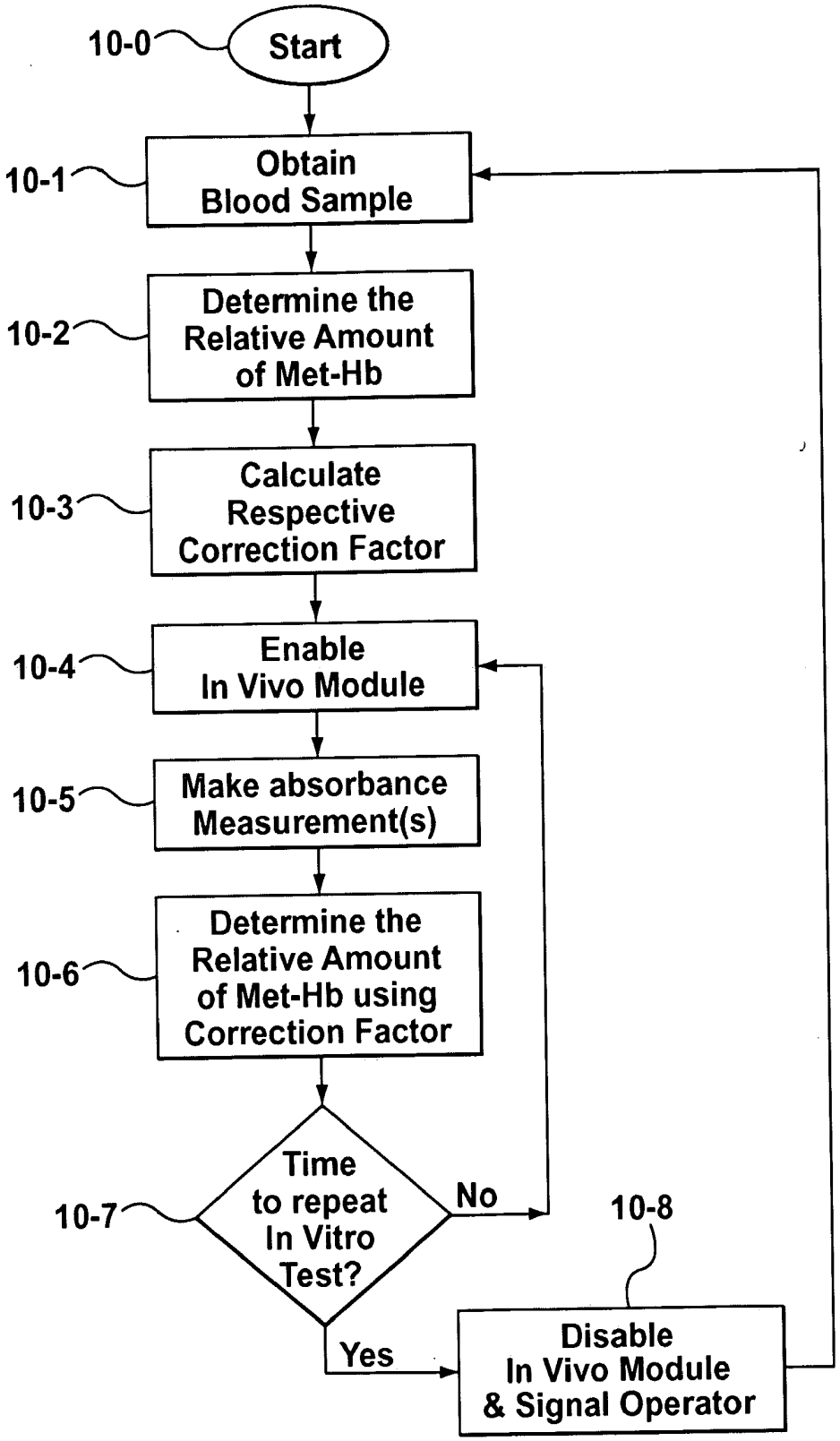

10-0
Start
10-1
Obtain Blood Sample
10-2
Determine the Relative Amount of Met-Hb
10-3
Calculate Respective Correction Factor
10-4
Enable In Vivo Module
10-5
Make absorbance Measurement(s)
10-6
Determine the Relative Amount of Met-Hb using Correction Factor
10-7
Time to repeat In Vitro Test?
No
Yes
10-8
Disable In Vivo Module & Signal Operator

FIG. 10

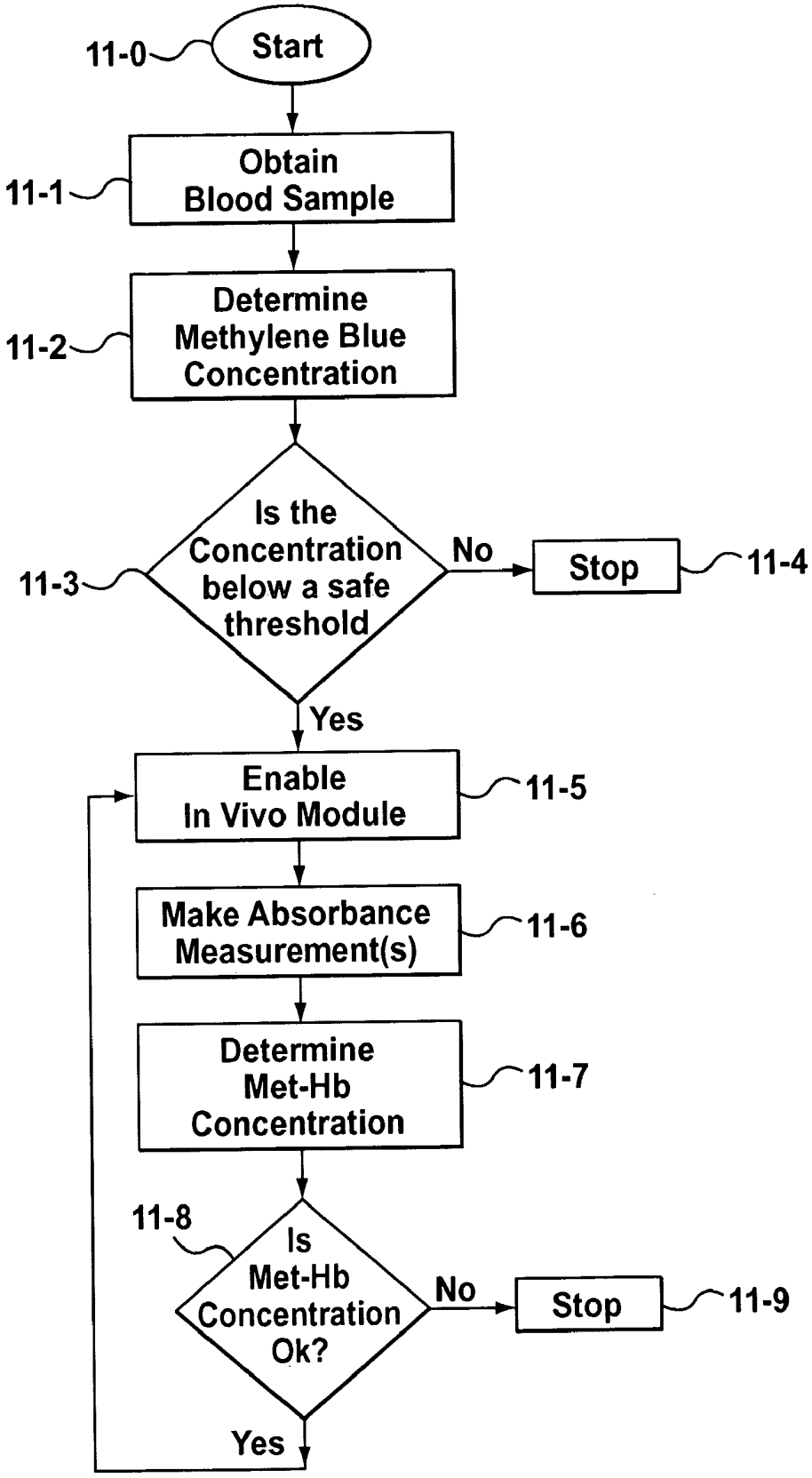

11-0
Start
Obtain Blood Sample
11-1
Determine Methylene Blue Concentration
11-2
Is the Concentration below a safe threshold
11-3
No
Stop
11-4
Yes
Enable In Vivo Module
11-5
Make Absorbance Measurement(s)
11-6
Determine Met-Hb Concentration
11-7
11-8
Is Met-Hb Concentration Ok?
No
Stop
11-9
Yes

FIG. 11

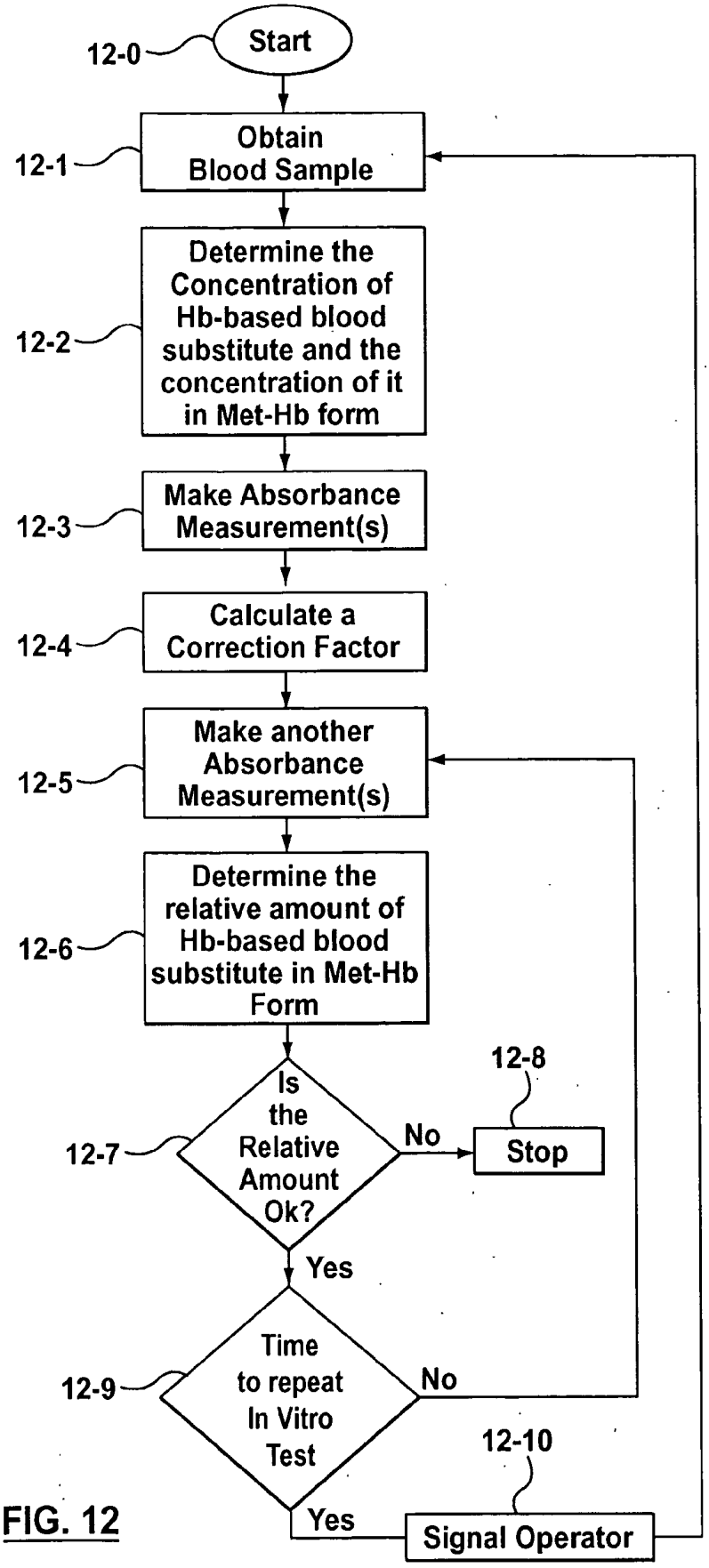

12-0
Start
12-1
Obtain Blood Sample
12-2
Determine the Concentration of Hb-based blood substitute and the concentration of it in Met-Hb form
12-3
Make Absorbance Measurement(s)
12-4
Calculate a Correction Factor
12-5
Make another Absorbance Measurement(s)
12-6
Determine the relative amount of Hb-based blood substitute in Met-Hb Form
12-7
Is the Relative Amount Ok?
No
12-8
Stop
Yes
12-9
Time to repeat In Vitro Test
No
Yes
12-10
Signal Operator

FIG. 12

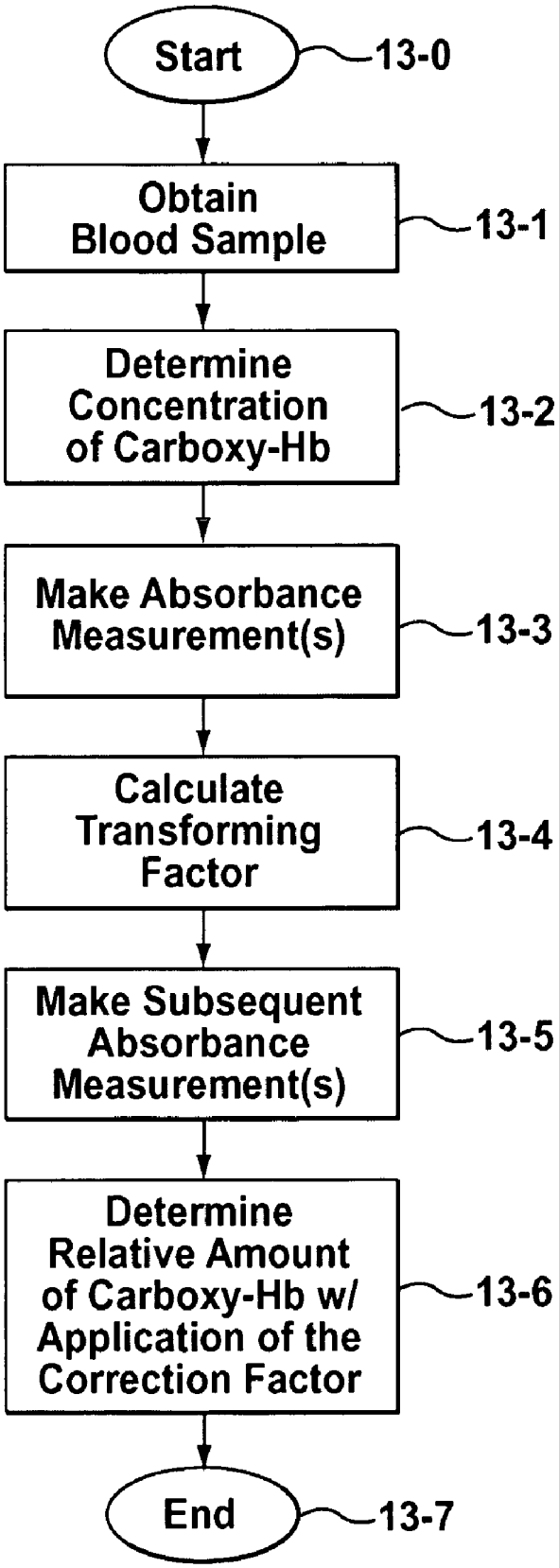

Start
13-0
Obtain Blood Sample
13-1
Determine Concentration of Carboxy-Hb
13-2
Make Absorbance Measurement(s)
13-3
Calculate Transforming Factor
13-4
Make Subsequent Absorbance Measurement(s)
13-5
Determine Relative Amount of Carboxy-Hb w/ Application of the Correction Factor
13-6
End
13-7

FIG. 13

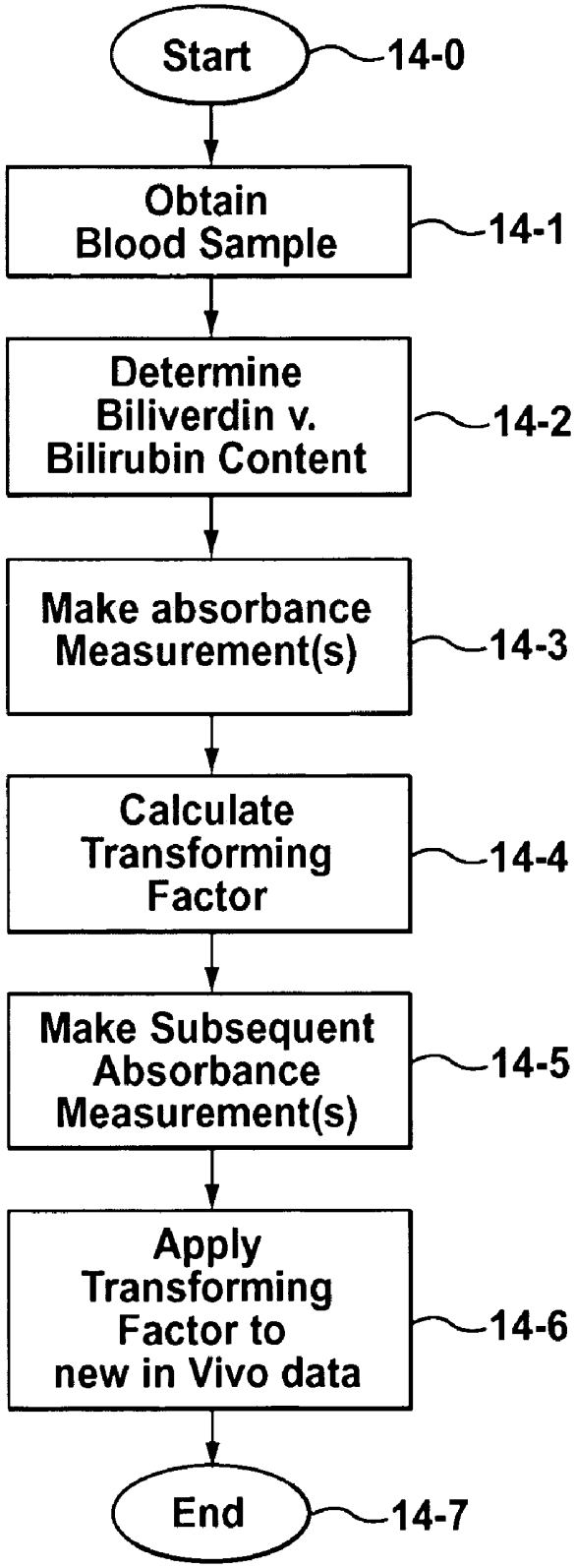

Start
14-0
Obtain Blood Sample
14-1
Determine Biliverdin v. Bilirubin Content
14-2
Make absorbance Measurement(s)
14-3
Calculate Transforming Factor
14-4
Make Subsequent Absorbance Measurement(s)
14-5
Apply Transforming Factor to new in Vivo data
14-6
End
14-7

FIG. 14

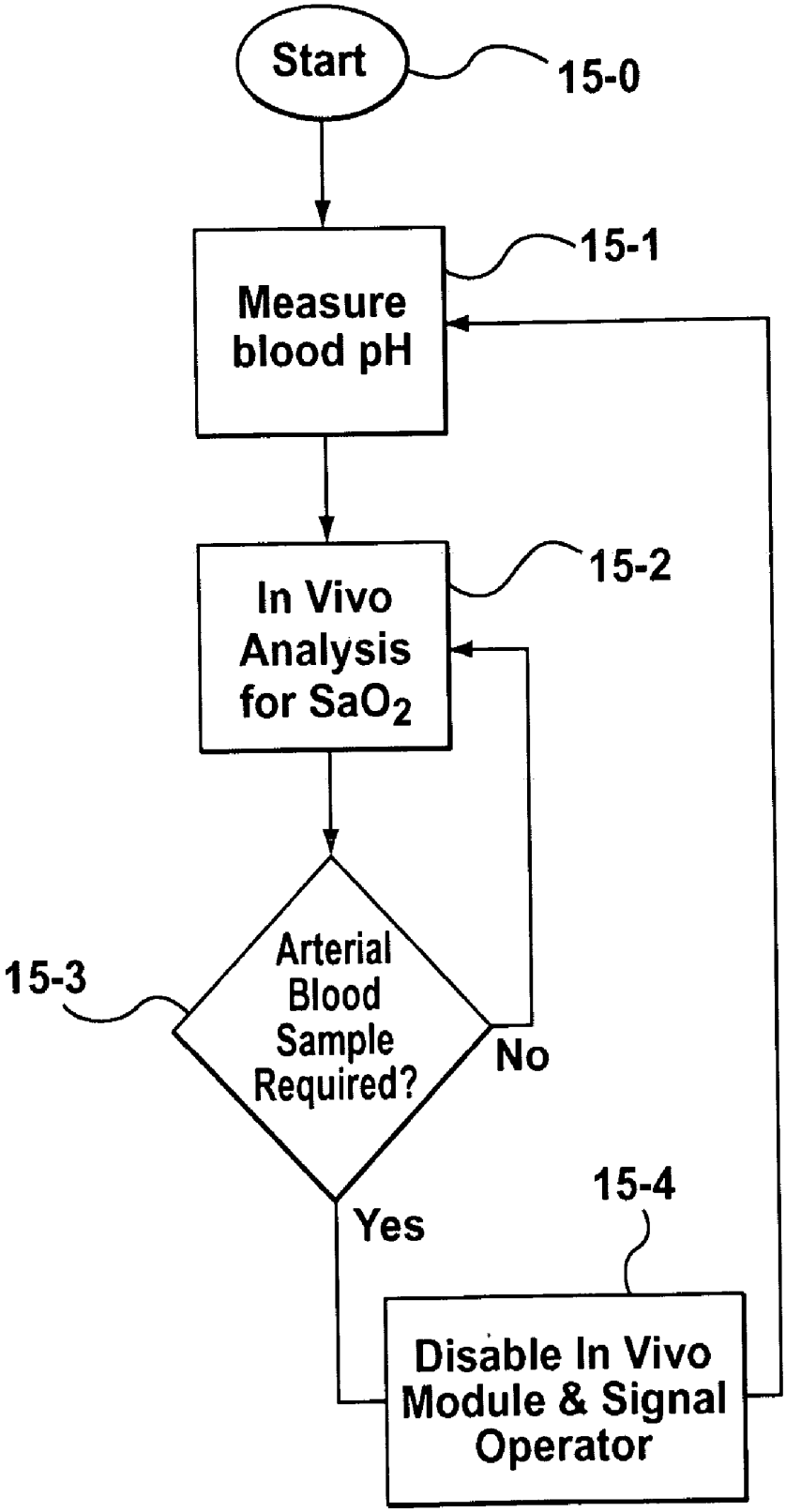

Start
15-0
Measure blood pH
15-1
In Vivo Analysis for SaO_2
15-2
Arterial Blood Sample Required?
15-3
No
Yes
15-4
Disable In Vivo Module & Signal Operator

FIG. 15

JOINT-DIAGNOSTIC IN VIVO & IN VITRO APPARATUS

PRIORITY CLAIM

[0001] This application claims the benefit of Canadian Patent Application No. 2,460,898 under the Paris Convention. The Canadian Patent Application No. 2,460,898 was filed on Mar. 9, 2004, and is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention relates to diagnostic testing for analytes in a life-form, and, in particular to apparatus for cooperative in vivo and in vitro testing.

BACKGROUND OF THE INVENTION

[0003] In vitro testing for a particular analyte in a life-form (e.g. humans, wild and domestic animals, etc.) requires a biological sample to be taken from the life-form. That is, in vitro testing is an invasive procedure that involves removing something (e.g. blood, skin, organ tissue, etc.) from the life-form, thereby damaging the life-form. In addition to damaging the life-form, in vitro testing techniques have a number of inherent risks that cannot easily be avoided. For example, such risks include sample mix-up, infection of the life-form and those handling the biological samples, and loss of critical fluids and/or tissue. Pain is also sometimes an issue. Despite the risks, in vitro testing is often the only suitable way to accurately obtain diagnostic information about an analyte in a life-form.

[0004] By contrast, in vivo testing techniques are considered non-invasive because biological samples are not required. Generally, in vivo testing involves measuring things outside of a life-form without breaking the epidermis of the life-form and/or handling biological samples. A drawback to almost all of the known in vivo testing methods is that in vivo testing methods do not provide information that is either accurate or complete enough to enable reliable interpretation of the information actually gathered. Consequently, in vitro testing is often reverted to as a failsafe diagnostic tool, which negates the benefits provided by performing in vivo testing.

[0005] An example of a known in vivo testing method is disclosed in U.S. Pat. No. 6,654,622. Specifically, U.S. Pat. No. 6,654,622 discloses the measurement of carbon dioxide that has diffused through skin, and can be sensed by electrochemical detectors, in order to provide an assessment of the arterial oxygen saturation and the transcutaneous carbon dioxide partial pressure on an ear lobe. The system disclosed is incapable of determining blood pH, which is required to accurately interpret in vivo data when considering metabolic acidosis with respiratory compensation. As a result, blood must be drawn, which negates any benefit provided by the in vivo test, since all of the necessary information can be obtained from the blood sample.

[0006] Another example of an in vivo testing method is Near Infrared (NIR) spectroscopic analysis. The compartmentalization of body fluids presents currently unresolved complications for measuring a particular concentration of analytes in a life-form using NIR spectroscopic analysis. In particular, a NIR system cannot discriminate between analyte concentrations in different types of tissue/fluid, which means that a NIR system can only determine a tissue analyte concentration and not a blood (or another specific fluid) analyte concentration. The correlation between a particular blood (or another specific fluid) analyte concentration and a corresponding tissue analyte concentration is typically unreliable and has little predictive value. The errors produced from such data are referred to as "random inaccuracies". Repetitive testing will not significantly reduce the magnitude of total error caused by random inaccuracies.

[0007] One specific example of an applied spectroscopic method is known as Pulse Oximetry. Pulse Oximetry can be used to monitor hemoglobin oxygen saturation or blood oxygen saturation (SaO_2) in a patient by measuring the light attenuated by a body part at two wavelengths—one wavelength selected from the visible spectrum and a second wavelength selected from the NIR spectrum. Successful Pulse Oximetry relies on the assumption that the Total-Hemoglobin (Tot-Hb) in a human is primarily composed of Oxy-hemoglobin (Oxy-Hb) and Deoxy-hemoglobin (Deoxy-Hb). However, this is not always a safe assumption, as there may be elevated levels of dyshemoglobins—such as, for example, Methemoglobin (Met-Hb), Carboxy-Hemoglobin (Carboxy-Hb) and Sulf-Hemoglobin (Su-Hb)—that are related to the condition of a patient. Increasing concentrations of dyshemoglobins cause Pulse Oximetry measurement errors to increase dramatically, leading to highly inaccurate measurements.

[0008] Another specific example of an applied spectroscopic method is described in U.S. Pat. No. 4,267,844. The U.S. Pat. No. 4,267,844 discloses a spectroscopic instrument for characterizing jaundice. Jaundice is caused by high levels of bilirubin and can lead to permanent brain damage in newborn babies (i.e. neonates). A reliable non-invasive method would be preferred to drawing blood from the neonates. However, spectroscopic measurement of bilirubin is complicated by the presence of bilirubin in more than one type of fluid/tissue and the unreliable correlation between bilirubin levels in blood (i.e., vascular tissue) and bilirubin levels in extra-vascular tissue.

SUMMARY OF THE INVENTION

[0009] According to an aspect of an embodiment of the invention there is provided a joint-diagnostic apparatus including: an in vivo measurement module for analysis of a first analyte in a life-form; an in vitro measurement module for analysis of a second analyte in the life-form; and, a processor module having computer readable program code means embodied thereon for producing (i) a first parameter having a first value derived from the analysis of the first analyte, (ii) a second parameter having a second value derived from the analysis of the second analyte; and (iii) a combined result based on the first value and the second value.

[0010] In some embodiments the processor module comprises a Boolean operator for determining (i) if the first value meets an in vivo value threshold, (ii) the combined result to be the second value if the first value meets the in vivo value threshold, and (iii) the combined result to be a Boolean flag when the first value does not meet the in vivo value threshold.

[0011] In some embodiments, the processor module comprises a Boolean operator for determining (i) if the second

value meets an in vitro value threshold, (ii) the combined result to be the first value if the second value meets the in vitro value threshold, and (iii) the combined result to be a Boolean flag when the second value does not meet the in vitro value threshold.

[0012] In some embodiments the first value is obtained by measuring a first measurable characteristic related to the first analyte, and the second value is obtained by measuring a second measurable characteristic related to the second analyte, and wherein the first observable characteristic differs from second observable characteristic.

[0013] In some embodiments the processor module comprises a computer readable program code means embodied therein for jointly analyzing the values of the first and second parameters, the computer readable program code means having computer readable instructions for determining a relationship between the first and second values.

[0014] In some embodiments the combined result includes a third parameter having a value related to the relationship between the first and second values. Alternatively, in other embodiments the first and second parameters do represent measurements of the same observable characteristic. Alternatively and/or additionally, a third value for the third parameter represents a measurement of the same observable characteristic as at least one of the first and second parameters. Alternatively and/or additionally, a third value for the third parameter represents a measurement of an observable characteristic different from both the first and second parameters.

[0015] In some embodiments the joint-diagnostic apparatus also includes: a remotely operable satellite device for collecting data; and a data-communication link for connecting the remotely operable satellite device to at least one of the in vivo measurement module, the in vitro measurement module, and the processor.

[0016] In some embodiments, the in vitro measurement module includes an electromagnetic radiation (EMR) source and detector for spectroscopic analysis. In some specific embodiments, the joint diagnostic apparatus also then includes a remotely operable satellite device defining a slot, and housing the EMR source and detector; and a data-communication link for connecting the remotely operable satellite device to at least one of the in vivo measurement module, the in vitro measurement module, and the processor.

[0017] According to some aspects of the invention, the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a measure of hemoglobin oxygen saturation (SaO_2) derived from the first parameter, and the computer readable program code means includes computer readable instructions for: determining respective relative amounts of different hemoglobin species present in the blood sample from the in vitro absorbance measurement of the blood sample; comparing each of the relative amounts of the different hemoglobin species present in the blood sample to a corresponding threshold value; and returning an indication about the measure of hemoglobin oxygen saturation (SaO_2) derived from the first parameter as a result of the comparison of each relative amount of hemoglobin species to its corresponding threshold value.

[0018] According to some other aspects of the invention the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a relative amount of Met-hemoglobin present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for: determining a fourth parameter that is a relative amount of Met-hemoglobin present in the blood sample from the in vitro absorbance measurement of the blood sample; calculating a correction factor which is a ratio of the fourth parameter to the third parameter; and applying the correction factor to subsequent in vivo measurements of the third parameter.

[0019] According to yet other aspects of the invention the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a relative amount of Met-hemoglobin present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for: determining a concentration of Methylene Blue in the blood sample from the in vitro absorbance measurement of the blood sample; comparing the concentration of Methylene Blue in the blood sample to a corresponding threshold value; and returning an indication about the concentration of Methylene Blue in the blood sample as a result of the comparison.

[0020] According to even other aspects of the invention the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a relative amount of hemoglobin-based blood substitute in Met-hemoglobin form present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for: determining a fourth parameter that is a relative amount hemoglobin-based blood substitute in Met-hemoglobin form present in the blood sample from the in vitro absorbance measurement of the blood sample; calculating a correction factor which is a ratio of the fourth parameter to the third parameter; and applying the correction factor to subsequent in vivo measurements of the third parameter.

[0021] According to yet another aspect of the invention the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a relative amount of Carboxy-hemoglobin form present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for: determining a fourth param-

eter that is a relative amount of Carboxy-hemoglobin present in the blood sample from the in vitro absorbance measurement of the blood sample; calculating a transforming factor which is a ratio of the fourth parameter to the third parameter; and applying the correction factor to subsequent in vivo measurements of the third parameter.

[0022] According to even yet another aspect of the invention the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a ratio of biliverdin and bilirubin present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for: determining a fourth parameter that is a ratio of biliverdin and bilirubin present in the blood sample from the in vitro absorbance measurement of the blood sample; calculating a transforming factor which is a ratio of the fourth parameter to the third parameter; and applying the transforming factor to subsequent in vivo measurements of the third parameter.

[0023] According to another embodiment of the invention there is provided a joint-diagnostic in vivo and in vitro spectroscopic apparatus including: an in vivo spectroscopic measurement module for producing a first plurality of parameters, each having a value related to the spectroscopic analysis of a first plurality of analytes; an in vitro measurement module for producing a second plurality of parameters, each having a value related to the analysis of a second plurality of analytes; and a computer usable medium having computer readable program code means embodied therein for jointly analyzing some of each of the first and second pluralities of parameters thereby producing a third plurality of parameters from values of some of the first and second parameters, the third plurality of parameters being indicative of a clinical-relationship between some of the first and second pluralities of parameters.

[0024] Other aspects and features of the present invention will become apparent, to those ordinarily skilled in the art, upon review of the following description of the specific embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] For a better understanding of the present invention, and to show more clearly how it may be carried into effect, reference will now be made, by way of example, to the accompanying drawings, which illustrate aspects of embodiments of the present invention and in which:

[0026] **FIG. 1** is a schematic drawing of a first joint-diagnostic apparatus according to an embodiment of the invention;

[0027] **FIG. 2** is a schematic drawing of a second joint-diagnostic apparatus according to an embodiment of the invention;

[0028] **FIG. 3** is a schematic drawing of a third joint-diagnostic apparatus according to an embodiment of the invention;

[0029] **FIG. 4** is a schematic drawing of a fourth joint-diagnostic apparatus according to an embodiment of the invention;

[0030] **FIG. 5** is a schematic drawing of a fifth joint-diagnostic apparatus according to an embodiment of the invention;

[0031] **FIG. 6** is a schematic drawing of a specific example of a remotely operable satellite device for use with a joint-diagnostic apparatus according to an embodiment of the invention;

[0032] **FIG. 7** is a perspective view of an in vitro sample receptor suitable for use with a joint-diagnostic apparatus according to an embodiment of the invention;

[0033] **FIG. 8** is an enlarged perspective view of a biological sample vessel shown in **FIG. 7**;

[0034] **FIG. 9** is a flow chart illustrating a method of operating a joint-diagnostic apparatus, according to an aspect of the invention, to monitor hemoglobin oxygen saturation (SaO_2);

[0035] **FIG. 10** is a flow chart illustrating a method of operating a joint-diagnostic apparatus, according to an aspect of the invention, to monitor oxidation of hemoglobin;

[0036] **FIG. 11** is a flow chart illustrating a method of operating a joint-diagnostic apparatus, according to an aspect of the invention, to monitor methylene blue treatment of methemoglobinemia;

[0037] **FIG. 12** is a flow chart illustrating a method of operating a joint-diagnostic apparatus, according to an aspect of the invention, to monitor oxidation of hemoglobin-based blood substitutes;

[0038] **FIG. 13** is a flow chart illustrating a method of operating a joint-diagnostic apparatus, according to an aspect of the invention, to monitor fluctuating levels of Carboxy-hemoglobin;

[0039] **FIG. 14** is a flow chart illustrating a method of operating a joint-diagnostic apparatus, according to an aspect of the invention, to monitor a ratio of biliverdin to bilirubin; and

[0040] **FIG. 15** is a flow chart illustrating a method of operating a joint-diagnostic apparatus, according to an aspect of the invention, to monitor metabolic acidosis with respiratory compensation.

DETAILED DESCRIPTION OF THE INVENTION

[0041] In vivo testing for analytes in a life-form is an attractive concept because a biological sample does not have to be removed from the life-form. However, in vivo testing alone is unable to provide information that is accurate, complete and/or reliable enough to safely replace in vitro testing in all circumstances. In contrast to performing either in vivo or in vitro testing independently and alone, some embodiments of the present invention provide a joint-diagnostic apparatus for cooperative in vivo and in vitro testing. In some specific embodiments results from an in vitro measurement module are used in combination with subsequent in vivo measurements/observations obtained at a later time to provide a combined result, and/or vice versa. Accordingly, in some embodiments in vitro measurements are used to compliment and/or partially compensate for some of the limitations of in vivo testing, and at the same

time provide some of the benefits of in vivo testing by reducing the number of biological samples taken.

[0042] Referring to **FIG. 1**, shown is a schematic drawing of a joint-diagnostic apparatus **200** according to an embodiment of the invention. Those skilled in the art will appreciate that the joint-diagnostic apparatus **200** includes a suitable combination of structural elements, mechanical systems, hardware, firmware and software arranged to support the function and operation of the joint-diagnostic apparatus **200**, and, for the sake of simplicity, portions of the joint-diagnostic apparatus **200** have been divided into functional units in order to conveniently describe aspects of this specific embodiment. To that end, the joint-diagnostic apparatus **200** includes a processor (i.e. processor module) **21**, an in vivo measurement module **23** and an in vitro measurement module **25**. The processor **21** is coupled to each of the in vivo and in vitro measurement modules **23**, **25**. Those skilled in the art will also appreciate that these functional blocks are not necessarily discrete elements in all embodiments of the invention.

[0043] The joint diagnostic apparatus **200** also includes a number of data ports and receptors. The data ports provide data pathways to and from the processor **21**, whereas the receptors provide measurement interfaces (i.e. sensing sites) for the in vivo and in vitro measurement modules **23**, **25**. Specifically, an input port **27** and an output port **29** are each coupled to the processor **21** to provide respective data paths to and from the processor **21**. Respective in vivo and in vitro receptors **24** and **26** are provided as measurement interfaces for the corresponding in vivo and in vitro measurement modules **23** and **25**. Examples of specific arrangements for the in vivo and in vitro receptors **24** and **26** are described in more detail further below with reference to **FIGS. 2 and 5-8**.

[0044] In some embodiments the input port **27** is coupled to receive instructions, input by a user, from an external input device **31**. The external input device **31** may include, without limitation, a keyboard, a touch-pad/screen, a mouse, a digital-pen and a voice-command sensing system. Similarly, in some embodiments the output port **29** is coupled to deliver results, status-flags, printouts, warnings and the like to an external output device **33**. The external output device **33** may include, without limitation, a display module, a printer, a hard-drive, another software program and an audible-signal generator. Additionally and/or alternatively, the input and output devices **31**, **33** may be integrated into the joint-diagnostic apparatus **200**.

[0045] In some embodiments the in vivo measurement module **23** includes, without limitation, electrochemical sensors, biosensors, spectroscopic devices and other types of transcutaneous sensors for non-invasively analyzing an analyte in a life form.

[0046] In some embodiments the in vitro measurement module **25** includes, without limitation, electrochemical sensors, biosensors, spectroscopic devices, chemical reagent delivery devices and other known devices used in in vitro testing to analyze an analyte in a biological sample taken from a life-form.

[0047] In operation the in vivo and in vitro measurement modules **23** and **25** are employed to analyze respective first and second analytes. The processor **21** has two alternative modes of operation. In both modes of operation the processor **21** generates a combined result from the analysis data/observations provided by the in vivo measurement module **23** and the in vitro measurement module **25**. Accordingly, in some embodiments the processor **21** includes computer readable program code means embodied thereon for producing (i) a first parameter having a first value derived from the analysis of the first analyte, (ii) a second parameter having a second value derived from the analysis of the second analyte; and (iii) a combined result based on the first value and the second value. In the first mode of operation the combined result may serve as a Boolean flag, an agreement, a confirmation, a correction-factor, a transforming-factor and/or an integrity-assessment for the first value of the first parameter in light of the second value of the second parameter. In the second mode of operation the combined result may serve as a Boolean flag, an agreement, a confirmation, a correction-factor, a transforming-factor and/or an integrity-assessment for the second value of the second parameter in light of the first value of the first parameter. Specific examples of the two modes of operation, the parameters and analytes considered are described in detail below with reference to the flow-charts shown in **FIGS. 9-15**.

[0048] Referring now to **FIG. 2**, shown is a schematic drawing of a joint-diagnostic apparatus **201** arranged to perform spectroscopic analysis on a portion of a life-form and on a biological sample taken from the same life-form. Again, for the sake of simplicity, portions of the joint-diagnostic apparatus **201**, shown in **FIG. 2**, have been divided into functional units in order to conveniently describe aspects of this specific embodiment of the invention. However, those skilled in the art will appreciate that the joint-diagnostic apparatus **201** also includes a suitable combination of associated structural elements, electrical systems, mechanical systems, hardware, firmware and software arranged to support the function and operation of the joint-diagnostic apparatus **201**.

[0049] The joint-diagnostic apparatus **201** illustrated in **FIG. 2** is similar to the joint-diagnostic apparatus **200** illustrated in **FIG. 1**, and accordingly, elements common to each are designated using the same reference numerals. For brevity, the description of **FIG. 1** will not be repeated with respect to **FIG. 2**. Moreover, in addition to the features described with reference to **FIG. 1**, the joint-diagnostic apparatus **201** also includes an electromagnetic radiation (EMR) source **40**, an optional optical grating **43**, a photo-detector module **45** and an analog-to-digital converter (ADC) **47**, that are provided so as to be shared by the in vivo and in vitro measurement modules **23**, **25**.

[0050] The optical grating **43**, the photo-detector module **45** and the analog-to-digital converter (ADC) **47** are connected in series between the processor **21** and the in vivo and in vitro measurement modules **23**, **25**. In some embodiments the optical grating **43** includes a transmission grating and in other embodiments the optical grating **43** includes a reflection grating. In some embodiments, the photo-detector module **45** includes one or more photo-diodes arranged optionally into an array. However, other detectors, such as for example, Charged Coupled Detectors (CCD), may also be used.

[0051] The EMR source **40** is coupled to provide EMR to the in vivo and in vitro measurement modules **23**, **25**. In some embodiments the EMR source **40** is a tungsten lamp,

a laser, a Light Emitting Diode (LED) or any combination thereof producing EMR at various desired wavelengths. The amount of EMR directed to each of the in vivo and in vitro measurement modules **23** and **25** can be fixed or variable as desired. In some embodiments the EMR **40** source is operable to produce EMR at at least one wavelength in the approximate range of 300 nm to 2500 nm.

[**0052**] Within the in vivo measurement module **23**, a first shutter **41***a* is provided to control the flow of EMR into the in vivo receptor **24**. Similarly, within the in vitro measurement module **25**, a second shutter **41***b* is provided to control the flow of EMR into the in vitro receptor **26**. The first and second shutters **41***a* and **41***b* are preferably independently controlled between open and closed positions, thereby adjusting the amount of EMR reaching the corresponding in vivo and in vitro receptors **24** and **26**, respectively. In one specific mode of operation, the first shutter **41***a* is open and the second shutter **41***b* is fully closed, in order to perform in vivo analysis. In another specific mode of operation, the first shutter **41***a* is fully closed and the second shutter **41***b* is open, in order to perform in vitro analysis. As such, the control of the shutters **41***a,b* provides a multiplexing and/or toggle-control for the operation of the in vivo and in vitro measurement modules **23**, **25**.

[**0053**] Also in operation, the optical grating **43** receives a respective EMR output from one of the in vivo and in vitro measurement modules **23**, **25** and the ADC **47** delivers electronic data derived from the spectroscopic outputs to the processor **21**. The electronic data derived by the ADC **47** from the raw electrical output of the photo-detector module **45** is proportional to the time that the photo-detector module **45** integrates the spectroscopic signal received from the grating **43**. Optionally, the electrical signal produced by the photo-detector module **45** may be amplified, attenuated, level shifted, and/or hard-limited. The electronic data derived by the ADC **47** is then processed by the processor **21** to produce absorbance data.

[**0054**] Provided for illustrative purposes only, equation (1), given below, has been derived as a very specific example of a quantitative approach to determining a numerical value for absorbance when conducting spectroscopic analysis.

$$A_i=\log\{(RL_i-RD_i)/(SL_i-SD_i)\}+\log(ITS/ITR) \quad (1)$$

[**0055**] Specifically, with respect to equation (1) the term A_i is a measure of the absorbance by a pixel i, the terms RL_i and RD_i are the respective light and dark reference pixel readings for pixel i, the terms SL_i and SD_i are the respective light and dark sample pixel readings for pixel i, the term ITS is the integration time for the sample measurement, and the term ITR is the integration time for the reference measurement. A light sample reading refers to a pixel reading after exposure of the pixel to the EMR for a specific integration time. A dark reading refers to a pixel reading over the same integration time, with the pixel shielded from the EMR. It should be understood that the SL_i reading could be the EMR transmitted through the sample, the EMR reflected from the sample, or both. In some embodiments a form of absorbance pre-processing, for example, without limitation, taking the first derivative of absorbance, could be used in a calibration algorithm.

[**0056**] In alternative embodiments, the in vivo and in vitro measurement modules **23**, **25** may be arranged to independently provide absorbance data that the processor **21** can use to produce a combined result. In such embodiments, each measurement module **23**, **25** includes an optical grating, photo-detector, ADC and sub-processor.

[**0057**] Also, although the joint-diagnostic apparatus **201** illustrated in **FIG. 2** appears to be a dual beam system, it is not because EMR in each module **23**, **25** is ultimately directed through one of the respective receptors **24** and **26**. That is, at any particular time the EMR from the EMR source **40** is directed only through in vivo or in vitro measurement receptors and not through a reference path that is independent of the state of each measurement receptor. Additionally and/or alternatively, one or both of the measurement modules **23**, **25** may also include an EMR reference path (not shown), in which EMR does not travel through a receptor, but instead is used as a reference measurement, which provides compensation for fluctuations in the EMR, as shown in equation (1).

[**0058**] Referring now to **FIG. 3**, shown is a schematic drawing of another joint-diagnostic apparatus **202**. Again, for the sake of simplicity, portions of the joint-diagnostic apparatus **202**, shown in **FIG. 3**, have been divided into functional units in order to conveniently describe aspects of this specific embodiment of the invention. However, those skilled in the art will appreciate that the joint-diagnostic apparatus **202** also includes a suitable combination of associated structural elements, electrical systems, mechanical systems, hardware, firmware and software arranged to support the function and operation of the joint-diagnostic apparatus **202**.

[**0059**] The joint-diagnostic apparatus **202** illustrated in **FIG. 3** is similar to the joint-diagnostic apparatus **200** illustrated in **FIG. 1**, and accordingly, elements common to both share common reference numerals. For brevity, the description of **FIG. 1** will not be repeated with respect to **FIG. 3**. In addition to those features described with reference to **FIG. 1**, the joint-diagnostic apparatus **202** includes a remotely operable satellite device **60** for collecting data relevant to the in vivo measurement module **23**. In some embodiments, the satellite device **60** includes, without limitation, electrochemical sensors, biosensors and spectroscopic devices. Those skilled in the art will also appreciate that the satellite device **60** also includes a suitable combination of associated structural elements, electrical systems, mechanical systems, hardware, firmware and software arranged to support the function and operation of the satellite device **60**.

[**0060**] The joint-diagnostic apparatus **202** also includes a communication port **28** that is internally coupled to the in vivo measurement module **23**. In some embodiments, the communication port **28** and the satellite device **60** include, without limitation, simple wire connections, respective optical fiber modems, wireless modems, Universal Serial Bus (USB) ports, Ethernet modems or the like, in order to establish a data link **51**. Accordingly, in operation, the communication port **28** is employed to establish the data link **51** between the in vivo measurement module **23** and the remotely operable satellite device **60**.

[**0061**] More generally, with continued reference to **FIG. 3** and with now added reference to a joint-diagnostic apparatus **203** shown in **FIG. 4**, the communication port **28** may also be internally coupled to the in vitro measurement module **25**

and the processor **21**. Additionally and/or alternatively, the communication port **28** may be connected to any number of functional units within a joint-diagnostic apparatus according to an embodiment of the invention.

[**0062**] The joint-diagnostic apparatus **203**, shown in **FIG. 4**, also includes a second remotely operable satellite device **62**, which may or may not be similar to the satellite device **60**. In some embodiments, the communication port **28** and the satellite devices **60** and **62** include, without limitation, simple wire connections, respective optical fiber modems, wireless modems, USB ports, Ethernet modems or the like, in order to establish the data link **51**. In some embodiments the satellite devices **60**, **62** include sensors (and optionally related elements) for collecting data relevant to the in vivo measurement module **23** and/or the in vitro measurement module **25**. For example, the satellite device **62** can be used to remotely analyze a blood sample from within a quarantine testing-room, while the satellite device **60** is used to collect absorbance data for the in vivo measurement module **23**. In some embodiments, the processor **21** and the in vivo and in vitro measurement modules **23**, **25** share data collected from the satellite devices.

[**0063**] Referring to **FIG. 5**, shown is a schematic drawing of another joint-diagnostic apparatus **204** according to an embodiment of the invention. Again, for the sake of simplicity, portions of the joint-diagnostic apparatus **204**, shown in **FIG. 5**, have been divided into functional units in order to conveniently describe aspects of this specific embodiment of the invention. However, those skilled in the art will appreciate that the joint-diagnostic apparatus **204** also includes a suitable combination of associated structural elements, electrical systems, mechanical systems, hardware, firmware and software arranged to support the function and operation of the joint-diagnostic apparatus **204**.

[**0064**] The joint-diagnostic apparatus **204** illustrated in **FIG. 5** is similar to the joint-diagnostic apparatus **200** illustrated in **FIG. 1**, and accordingly, elements common to both share common reference numerals. However, most of the in vivo measurement module **23** is now located in a remotely operable satellite device **63**. Accordingly, in some embodiments, the satellite device **63** includes, without limitation, electrochemical sensors, biosensors and spectroscopic devices, in addition to a suitable combination of structural elements, electrical systems, mechanical systems, hardware, firmware and software arranged to support the function and operation of the satellite device **63**.

[**0065**] The joint-diagnostic apparatus **204** includes a communication port **28** that is coupled to a multiplexer **46** (MUX **46**, which is described in further detail below), and the satellite device **63** has a corresponding communication port **28'**. In some embodiments, the communication ports **28**, **28'** include, without limitation, simple wire connections, respective optical fiber modems, wireless modems, USB ports, Ethernet modems and the like, in order to establish the data link **51**.

[**0066**] The in vitro measurement module **25** includes an amplifier **44** connected to the in vitro receptor **26** and a cartridge **70** that can be inserted into the in vitro receptor **26**. The cartridge **70** includes a biological sample reservoir **71**, one or more sensors **73** (two shown), and electrical contacts **75** (two shown). The sensors **73** may include, without limitation, electrochemical sensors, biosensors, chemically sensitive membranes, and the like, for analyzing a biological sample in the reservoir **71**. The sensors **73** are coupled to electrical contacts **75** that are used to relay electrical signals from the sensors **73** to the in vitro receptor **26**. In some embodiments, the in vitro receptor **26** includes at least one spectroscopic device.

[**0067**] Within the joint-diagnostic apparatus **204**, the in vivo and in vitro measurement modules **23**, **25** share common elements through the use of the multiplexer (MUX) **46**. The communication port **28'**, for the in vivo measurement module **23**, and the amplifier **44**, of the in vitro measurement module **25**, are coupled to the multiplexer **46**. The multiplexer **46** toggles access to the ADC **47**, and ultimately the processor **21**, between the in vivo and in vitro measurement modules **23**, **25**. In alternative embodiments, the in vivo and in vitro measurement modules **23**, **25** may each include respective sub-processors and ADCs.

[**0068**] A schematic drawing of a finger receptor **54**, according to an embodiment of the invention, is illustrated in **FIG. 6**. The finger receptor **54** is adapted to fit around a finger **56**. The finger receptor **54** is a very specific example of a remotely operable satellite device that is suitable for use in various embodiments of the invention. The finger receptor **54** includes a data port **52** and at least one sensor (not shown). Optionally an EMR source, such as for example, one or more light emitting diodes (LEDs), may also be included in the finger receptor **54**. The sensor may be, without limitation one of an electrochemical sensor, a biosensor, a spectroscopic sensor, a heat sensor, a pulse sensor, etc. More generally, a satellite device, such as the finger receptor **54**, may include other elements included in one of or both of the in vivo and in vitro measurement modules **23**, **25**. In alternative embodiments, a satellite device, like the finger receptor **54**, is adapted to fit around or be placed next to another body part.

[**0069**] Referring now to **FIGS. 7 and 8**, shown are respective perspective views of an in vitro receptor **64** and a biological sample vessel **62** suitable for use with various embodiments of the invention. The in vitro receptor **64**, shown in **FIG. 7**, is specifically provided to perform spectroscopic analysis on a biological sample contained in the biological sample vessel **62**. The in vitro receptor **64** includes an input slot **60** into which the biological sample vessel **62** can be placed. Incident EMR is delivered into the slot **60** by an optical fiber **68**. The EMR having passed through a biological sample is received by a receiving optical fiber **66**. In alternative embodiments, an EMR source and detector can be arranged around the slot **60**. In such embodiments, the optical fibers **66**, **68** would not necessarily be required.

[**0070**] With specific reference to **FIG. 8**, the biological sample vessel **62** is a very specific example of a vessel that is suitable for use with various embodiments of the invention. The biological sample vessel **62** includes a base plate **718**, a cover plate **702** and sample well **714** defined by closed wall **706**. In some embodiments, a hinge **710** connects the cover plate **702** to the base plate **718** by a hinge **710**. Alternatively, a non-hinged cover plate may also be used. In some such embodiments the cover plate **702** may be snapped on to the base plate **718**. Overflow openings or grooves **716** in closed wall **706** allow excess sample to flow out of sample well **714** when cover plate **702** is closed over

sample well **714** and base plate **718**. A second containment wall **712** may be employed to retain the sample that overflows the sample well **714**, into an overflow ring (circular groove between wall **706** and wall **712**) to prevent leakage of fluid from the sample tab, while permitting a sample of sufficient volume to fill the well.

[**0071**] The biological sample vessel may be manufactured from a number of different materials, such as for example, but not limited to, a transparent, translucent or reflective material, such as glass, plastic or a combination thereof, or a reflective material. If the base plate **718** and cover plate **702** are transparent or translucent, then it is preferred that the base plate **718** and cover plate **702** is made from a transparent or translucent plastic, such as but not limited to polypropylene, polycarbonate, polyethylene, or polystyrene, however, a glass plate may also be used. If either of the base plate **718** or cover plate **702** is reflective, then a reflective material, for example but not limited to a ceramic coating, barium sulfate, Spectralon™, Spectraflect™, or Duraflect™ may be used for one of the base or cover plates **702**, **718**.

[**0072**] In alternative embodiments, items such as cuvettes, cartridges, test tubes, pipette tips, Petri dishes, beakers, flasks and the like could also be used to hold a biological sample.

[**0073**] Flow-charts are provided in **FIGS. 9-15** that illustrate very specific examples of how a joint-diagnostic apparatus according to an embodiment of the invention can be applied to provide co-operative in vitro and in vivo testing using a single apparatus provided by an embodiment of the invention.

[**0074**] Specifically, referring to **FIG. 9**, shown is a flow chart depicting a method for monitoring hemoglobin (Hb) oxygen saturation (SaO_2) employing a joint-diagnostic apparatus according to an embodiment of the invention. At step **9-1**, a blood sample is obtained from a patient. The blood sample is analyzed at step **9-2** in an in vitro measurement module to determine relative concentrations of different hemoglobin species present in the blood sample. In some embodiments, the in vitro analysis of the blood sample includes at least one of spectroscopic analysis, mechanical analysis, electrochemical analysis, biosensor analysis, chemical analysis with the aid of a reagent, and analysis without the aid of a reagent.

[**0075**] At step **9-3**, at least one of the hemoglobin species is compared to a respective threshold value to determine whether or not valid and/or relatively accurate data can be obtained from subsequent in vivo measurements. If the at least one of the hemoglobin species violates a respective threshold (e.g. there is either too much or too little of the species present), then the joint-diagnostic apparatus disables an in vivo measurement module and signals the operator at step **9-4** (no path, step **9-3**). On the other hand, if none of the thresholds is violated (yes path, step **9-3**), the in vivo measurement module is enabled at step **9-5**. Subsequently, at step **9-6** in vivo spectroscopic measurements are made, and a measurement of oxygen saturation is ultimately provided in step **9-7**, using for example, without limitation, a pulse oximeter.

[**0076**] At step **9-8**, it is determined whether or not an in vitro test should be repeated. Criteria for making such a determination include, without limitation, an amount of time elapsed since the last in vitro test, an upper limit for a number of in vivo tests that can be performed between in vitro testing, anomalous data provided by the in vivo testing, a lower threshold for hemoglobin oxygen saturation as determined by in vivo testing. If further in vitro testing is not required (no path, step **9-8**), subsequent in vivo testing may be repeated starting from step **9-5**. On the other hand, if further in vitro testing is deemed to be required (yes path, step **9-8**), then the in vivo measurement module is disabled and the operator is signaled accordingly at step **9-9**. As such, the method is repeated starting at step **9-1**.

[**0077**] Referring now to **FIG. 10**, shown is a flow chart depicting a method for monitoring oxidation of hemoglobin (Hb) during treatment for methemoglobinemia, employing a joint-diagnostic apparatus according to an embodiment of the invention.

[**0078**] Oxidation of the iron in the heme moiety of Hb molecules is a normal process. Enzymes are continually at work reversing the oxidation process and thus preventing the accumulation of Met-Hb. Methemoglobinemia is a condition in people that lack enzymes required to reverse the oxidation process. In a specific example, the Met-Hb reductase system may be underdeveloped in infants, making methemoglobinemia more prevalent among infants. One specific reason for the higher incidence of methemoglobinemia among infants and neonates is an underdeveloped gastrointestinal system. In an underdeveloped gastrointestinal system, the bacteria level could rise due to a decreased secretion of gastric acid. Nitrates are usually converted into nitrites by bacteria of the gastrointestinal system, and the nitrites in turn react with the Hb to produce Met-Hb. Blood loss is critical in neonates, and even a heel-prick blood sample from a pre-matured neonate is considered critical blood loss. In these neonates, the decreased frequency of blood sampling due to the use of an in vivo apparatus that monitors % Met-Hb would be especially useful.

[**0079**] At step **10-1**, a blood sample is obtained from a patient. The blood sample is analyzed at step **10-2** in an in vitro measurement module to determine a relative concentration of Met-Hemoglobin (Met-Hb) present in the blood sample. In some embodiments, the in vitro analysis of the blood sample includes at least one of spectroscopic analysis, mechanical analysis, electrochemical analysis, biosensor analysis, chemical analysis with the aid of a reagent, and analysis without the aid of a reagent.

[**0080**] At step **10-3**, a correction factor, which can be used in combination with subsequent in vivo measurements, is calculated using the results of the in vitro analysis. Briefly, the correction factor is used to adjust subsequent in vivo measurements in view of the initial in vitro measurement. In some embodiments, the correction factor is calculated as a ratio of the relative amount of Met-Hb determined using in vitro analysis to a relative amount of Met-Hb determined using a preliminary in vivo spectroscopic measurement. The in vivo measurement module is then enabled at step **10-4**, and further in vivo spectroscopic measurements are made at step **10-5**. In alternative embodiments the relative amount of Met-Hb determined using in vitro analysis is employed in a regressive algorithm in which the correction factor is updated between each subsequent in vivo test. Subsequently, at step **10-6** the relative amount of Met-Hb can be derived using the correction factor previously determined.

[0081] At step **10-7**, it is determined whether or not an in vitro test should be repeated. Criteria for making such a determination include, without limitation, an amount of time elapsed since the last in vitro test, an upper limit for a number of in vivo tests that can be performed between in vitro testing, anomalous data provided by the in vivo testing, and an upper or lower threshold for Met-Hb concentration as determined by in vivo testing. If further in vitro testing is not required (no path, step **10-7**), subsequent in vivo testing may be repeated starting from step **10-4**. On the other hand, if further in vitro testing is deemed to be required (yes path, step **10-7**), then the in vivo measurement module is disabled and the operator is signaled accordingly at step **10-8**. As such, the method is repeated starting at step **10-1**.

[0082] **FIG. 11** is a flow chart illustrating a method for monitoring levels of methylene blue, in the treatment of methemoglobinemia, employing a joint-diagnostic apparatus according to an embodiment of the invention. Although methylene blue is used to treat methemoglobinemia, high doses have a paradox affect that in turn induces methemoglobinemia as opposed to reducing it. Therefore, it is important to maintain the blood concentration of methylene blue between an upper limit and a lower limit. The upper and lower limits together define a therapeutic window for the dosage of methylene blue. At step **11-1**, a blood sample is obtained from a patient. The blood sample is analyzed at step **11-2** in an in vitro measurement module to determine a relative concentration of methylene blue. In some embodiments, the in vitro analysis of the blood sample includes at least one of spectroscopic analysis, mechanical analysis, electrochemical analysis, biosensor analysis, chemical analysis with the aid of a reagent, and analysis without the aid of a reagent.

[0083] At step **11-3**, it is determined whether or not the amount of methylene blue violates a threshold (e.g. a therapeutic window). If the amount of methylene blue present in the blood sample violates the threshold, then the joint-diagnostic apparatus disables an in vivo measurement module and signals the operator at step **11-4** (no path, step **11-4**). The signal to the operator may specifically indicate that the methylene blue level has reached a toxic level and/or that the in vitro measurement of Met-Hb level is abnormally high. On the other hand, if the threshold is not violated (yes path, step **11-3**), the method proceeds to step **11-5**, in which the in vivo measurement module is enabled. Subsequent in vivo absorbance measurements are made at step **11-6** from which a relative amount of Met-Hb can be derived at step **11-7**.

[0084] At step **11-8**, it is determined whether or not the Met-Hb level is within an acceptable range. If the Met-Hb level is not within an acceptable range (no path, step **11-8**), in vivo testing is stopped and an operator is signaled accordingly at step **11-9**. On the other hand, if the Met-Hb level is within an acceptable range further in vivo testing continues from step **11-5** (yes path, step **11-8**).

[0085] Referring to **FIG. 12**, shown is a flow chart depicting a method monitoring oxidation of hemoglobin-based blood substitutes. At step **12-1**, a blood sample is obtained from a patient. The blood sample is analyzed at step **12-2** in an in vitro measurement module to determine concentrations of the Hb-based blood substitute and the amount of the Hb-based blood substitute in Met-Hb form. In some embodiments, the in vitro analysis of the blood sample includes at least one of spectroscopic analysis, mechanical analysis, electrochemical analysis, biosensor analysis, chemical analysis with the aid of a reagent, and analysis without the aid of a reagent.

[0086] A preliminary in vivo spectroscopic measurement is made at step **12-3**. Then, at step **12-4**, a correction factor, which can be used in combination with subsequent in vivo measurements, is calculated using the results of the in vitro analysis. In some embodiments, the correction factor is calculated as a ratio of the relative amount of Met-Hb determined using in vitro analysis to a relative amount of Met-Hb determined using the preliminary in vivo absorbance measurement. The in vivo measurement module is then enabled and further in vivo spectroscopic measurements are made at step **12-5**. In alternative embodiments the relative amount of Met-Hb determined using in vitro analysis is employed in a regressive algorithm in which the correction factor is updated between each subsequent in vivo test. Subsequently, at step **12-6** the relative amount of Met-Hb can be derived using the correction factor previously determined.

[0087] At step **12-7**, it is determined whether or not the amount of Met-Hb present violates a threshold (e.g. a safety threshold and/or upper or lower limit concentration). If the amount of Met-Hb violates the threshold, then the joint-diagnostic apparatus disables an in vivo measurement module and signals the operator at step **12-8** (no path, step **12-7**). On the other hand, if the threshold is not violated (yes path, step **12-7**), the method proceeds to step **12-9**.

[0088] At step **12-9**, it is determined whether or not an in vitro test should be repeated. Criteria for making such a determination include, without limitation, an amount of time elapsed since the last in vitro test, an upper limit for a number of in vivo tests that can be performed between in vitro testing, anomalous data provided by the in vivo testing, an upper or lower threshold for Met-Hb as determined by in vivo testing. The amount of Met-Hb may be quantified either as a concentration or as a fraction of total hemoglobin. If further in vitro testing is not required (no path, step **12-9**), subsequent in vivo testing may be repeated starting from step **12-5**. On the other hand, if further in vitro testing is deemed to be required (yes path, step **12-9**), then the in vivo measurement module is disabled and the operator is signaled accordingly at step **12-10**. As such, the method is repeated starting at step **12-1**.

[0089] Yet another method of operating a joint-diagnostic apparatus is illustrated in **FIG. 13**. Specifically, **FIG. 13** is a flow chart depicting a method of monitoring fluctuating levels of Carboxy-Hemoglobin (Carboxy-Hb).

[0090] A measurement of the ratio of Carboxy-Hb to Total-Hb could be used for monitoring the accumulation of Carboxy-Hb after exposure to carbon monoxide, and could also be used for monitoring the re-conversion of Carboxy-Hb into Oxy-Hb, after optional treatment with oxygen. Unlike Oxy-Hb, which exists in significantly different levels in arterial and venous blood, Carboxy-Hb exists in approximately the same levels in all blood compartments. Hence, the in vivo Carboxy-Hb measurement does not have to be synchronized with the pulse as in pulse oximetry. On the other hand, whereas a calibration algorithm for hemoglobin

oxygen saturation can be developed empirically by administering oxygen to human subjects, it is unethical to do the same with carbon monoxide.

[0091] At step **13-1**, a blood sample is obtained from a patient. The blood sample is analyzed at step **13-2** in an in vitro measurement module to determine a relative concentration of Carboxy-Hb in the blood sample. In some embodiments, the in vitro analysis of the blood sample includes at least one of spectroscopic analysis, mechanical analysis, electrochemical analysis, biosensor analysis, chemical analysis with the aid of a reagent, and analysis without the aid of a reagent. A preliminary in vivo spectroscopic measurement is made at step **13-3**.

[0092] At step **13-4**, a transforming factor, which can be used in combination with subsequent in vivo measurements, is calculated using the results of the in vitro analysis. In some embodiments, the transforming factor is determined from a ratio of the relative amount of Carboxy-Hb determined using in vitro analysis to a preliminary in vivo spectroscopic measurement. The transforming factor is used to convert the absorbance measurement into a measurement of Carboxy-HB. The in vivo measurement module is then enabled and further in vivo spectroscopic measurements are made at step **13-5**. Subsequently, at step **13-6** the relative amount of Carboxy-Hb can be derived using a correction factor previously determined as described below for a alternative embodiment. Those skilled in the art will appreciate that steps **13-4** to **13-6** can be repeated a number of times between subsequent blood samples and in vitro testing as described above.

[0093] In an alternative embodiment a preliminary in vivo calibration algorithm for the relative amount of Carboxy-Hb is developed using spectroscopic data and corresponding blood Carboxy-Hb data, previously collected from other patients and/or the present patient being monitored. A correction factor is determined from the ratio of the Carboxy-Hb determined by the preliminary in vivo calibration algorithm and the Carboxy-Hb determined by the in vitro.

[0094] Referring to **FIG. 14**, shown is a flow chart depicting a method of monitoring relative amounts of biliverdin to bilirubin. At step **14-1**, a blood sample is obtained from a patient. The blood sample is analyzed at step **14-2** in an in vitro measurement module to determine a ratio of biliverdin to bilirubin in the blood sample. In some embodiments, the in vitro analysis of the blood sample includes at least one of spectroscopic analysis, mechanical analysis, electrochemical analysis, biosensor analysis, chemical analysis with the aid of a reagent, and analysis without the aid of a reagent. A preliminary in vivo absorbance measurement is made at step **14-3**. Then, at step **14-4**, a transforming factor, which can be used in combination with subsequent in vivo measurements, is calculated using the results of the in vitro analysis. In some embodiments, the transforming factor is calculated as a ratio of the ratio of biliverdin to bilirubin determined using in vitro analysis to that same ratio determined using the preliminary in vivo absorbance measurement. The in vivo measurement module is then enabled and further in vivo EMR absorbance measurements are made at step **14-5**.

[0095] In alternative embodiments the ratio of biliverdin to bilirubin determined using in vitro analysis is employed in a regressive algorithm in which a correction factor is determined and updated between each subsequent in vivo test. Subsequently, at step **14-6** the ratio of biliverdin to bilirubin can be derived using the correction factor previously determined. Those skilled in the art will appreciate that steps **14-4** to **14-6** can be repeated a number of times between subsequent blood samples and in vitro testing as described above.

[0096] Lastly, referring to **FIG. 15** shown is a flow chart illustrating a method for conducting diagnostic measurements related to blood gas measurement, which usually includes partial pressures of oxygen and carbon dioxide in blood, and blood pH. At step **15-1**, an in vitro measurement module is employed to measure the blood pH in a pin-prick blood sample (capillary blood). Following the determination of blood pH, at step **15-2** an assessment of the arterial oxygen saturation and the transcutaneous carbon dioxide partial pressure is made. This may be accomplished in the same manner as described in U.S. Pat. No. 6,654,622. Transcutaneous carbon dioxide partial pressure measurement is considered non-invasive since the skin does not have to be broken in order to obtain a result.

[0097] At step **15-3**, it is determined whether or not an arterial blood sample must be obtained for blood gas measurement. Criteria for making such a determination include, without limitation, discordance between the pH in the capillary blood sample and the transcutaneous carbon dioxide partial pressure. In one specific example, a discordance between blood pH and the transcutaneous carbon dioxide partial pressure can lead to a false-diagnosis of alkalosis, which occurs when the blood pH is too high. By contrast acidosis (respiratory or metabolic) is a condition manifested by low blood pH. High transcutaneous partial pressure of carbon dioxide is also indicative of acidosis, in particular, respiratory acidosis. However, when a person has metabolic acidosis, the body's mechanism to counteract the acidosis is respiratory compensation (i.e. hyperventilation). This condition is called metabolic acidosis with respiratory compensation, and in such a condition, the transcutaneous carbon dioxide partial pressure may be low and can be interpreted as alkalosis.

[0098] If an arterial blood sample is not required (no path, step **15-3**), subsequent in vivo testing may be repeated starting from step **15-2**. On the other hand, if an arterial blood sample is required (yes path, step **15-3**), then the in vivo measurement module is disabled and the operator is signaled accordingly at step **15-4**. As such, the method is repeated from step **15-1**.

[0099] While the above description provides example embodiments, it will be appreciated that the present invention is susceptible to modification and change without departing from the fair meaning and scope of the accompanying claims. Accordingly, what has been described is merely illustrative of the application of aspects of embodiments of the invention. Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

I claim:

1. A joint-diagnostic apparatus comprising:

an in vivo measurement module for analysis of a first analyte in a life-form;

an in vitro measurement module for analysis of a second analyte in the life-form; and,

a processor module having computer readable program code means embodied thereon for producing (i) a first parameter having a first value derived from the analysis of the first analyte, (ii) a second parameter so having a second value derived from the analysis of the second analyte; and

(iii) a combined result based on the first value and the second value.

2. An apparatus according to claim 1 further comprising a display module for displaying the combined result.

3. An apparatus according to claim 1 wherein the processor module comprises a Boolean operator for determining (i) if the first value meets an in vivo value threshold, (ii) the combined result to be the second value if the first value meets the in vivo value threshold, and (iii) the combined result to be a Boolean flag when the first value does not meet the in vivo value threshold.

4. An apparatus according to claim 1 wherein the processor module comprises a Boolean operator for determining (i) if the second value meets an in vitro value threshold, (ii) the combined result to be the first value if the second value meets the in vitro value threshold, and (iii) the combined result to be a Boolean flag when the second value does not meet the in vitro value threshold.

5. An apparatus according to claim 1, wherein the first and second analytes are the same.

6. An apparatus according to claim 1, wherein the first value is obtained by measuring a first measurable characteristic related to the first analyte, and the second value is obtained by measuring a second measurable characteristic related to the second analyte, and wherein the first observable characteristic differs from second observable characteristic.

7. An apparatus according to claim 1, wherein the processor module comprises a computer readable program code means embodied therein for jointly analyzing the values of the first and second parameters, the computer readable program code means having computer readable instructions for determining a relationship between the first and second values.

8. An apparatus according to claim 7, wherein the combined result includes a third parameter having a value related to the relationship between the first and second values.

9. An apparatus according to claim 1, wherein the first and second parameters do represent measurements of the same observable characteristic.

10. An apparatus according to claim 8, wherein a third value for the third parameter represents a measurement of the same observable characteristic as at least one of the first and second parameters.

11. An apparatus according to claim 8, wherein a third value for the third parameter represents a measurement of an observable characteristic different from both the first and second parameters.

12. An apparatus according to claim 8, wherein the value of the third parameter is indicative of one of an agreement, a confirmation, a correction-factor and an integrity-assessment of the first value in view of the second value.

13. An apparatus according to claim 8, wherein the value of the third parameter is indicative of one of an agreement, a confirmation, a correction-factor and an integrity-assessment of the second value in view of the first value.

14. An apparatus according to claim 7 further comprising:

a remotely operable satellite device for collecting data; and

a data-communication link for connecting the remotely operable satellite device to at least one of the in vivo measurement module, the in vitro measurement module, and the processor.

15. An apparatus according to claim 14, wherein the data-communication link includes at least one of a wireless modem, a USB port, an Ethernet modem, a fiber-optic modem, a twisted-pair modem and a wire connection.

16. An apparatus according to claim 15, wherein the data-communication link is also operable to transmit data to the remotely operable satellite device.

17. An apparatus according to claim 14, wherein a portion of the in vivo spectroscopic measurement module is included within the remotely operable satellite device.

18. An apparatus according to claim 14, wherein a portion of the in vitro measurement module is included within the remotely operable satellite device.

19. An apparatus according to claim 14, wherein a portion of the processor is included within the remotely operable satellite device.

20. An apparatus according to claim 7, wherein the in vivo measurement module includes a receptor for accepting a portion of the life-form for spectroscopic analysis.

21. An apparatus according to claim 20, wherein the in vivo measurement module includes an electromagnetic radiation (EMR) source and detector arranged within the receptor.

22. An apparatus according to claim 21, wherein the detector is arranged to detect EMR that has travelled through the portion of the life-form accepted into the receptor.

23. An apparatus according to claim 21, wherein the detector is arranged to detect EMR that has reflected from the portion of the life-form accepted into the receptor.

24. An apparatus according to claim 21 further comprising:

a remotely operable satellite device housing the receptor, the EMR source and detector; and

a data-communication link for connecting the remotely operable satellite device to at least one of the in vivo measurement module, the in vitro measurement module, and the processor.

25. An apparatus according to claim 21, wherein the EMR source is operable to produce EMR at at least one wavelength in the approximate range of 300 nm to 2500 nm.

26. An apparatus according to claim 21, wherein the EMR source includes at least one of a tungsten lamp, a laser and a Light Emitting Diode (LED).

27. An apparatus according to claim 7, wherein the in vitro measurement module includes a receptor for accepting a biological sample from the life-form for analysis.

28. An apparatus according to claim 27, wherein the receptor is arranged to accept a vessel containing a biological sample.

29. An apparatus according to claim 28, wherein the vessel contains at least one reagent in combination with the biological sample.

30. An apparatus according to claim 29, wherein the biological sample includes at least one of whole blood, a portion of whole blood, interstitial fluid, serum, plasma, urine, cerebrospinal fluid, sputum, synovial fluid, lymphatic fluid and feces.

31. An apparatus according to claim 7, wherein the in vitro measurement module includes an electromagnetic radiation (EMR) source and detector for spectroscopic analysis.

32. An apparatus according to claim 31, wherein the detector is arranged to detect EMR that has travelled through the biological sample.

33. An apparatus according to claim 31, wherein the detector is arranged to detect EMR that has reflected from the biological sample.

34. An apparatus according to claim 31 further comprising:

a remotely operable satellite device defining a slot, and housing the EMR source and detector; and

a data-communication link for connecting the remotely operable satellite device to at least one of the in vivo measurement module, the in vitro measurement module, and the processor.

35. An apparatus according to claim 31, wherein the EMR source is operable to produce EMR at at least one wavelength in the approximate range of 300 nm to 2500 nm.

36. An apparatus according to claim 31, wherein the EMR source includes at least one of a tungsten lamp, a laser and a Light Emitting Diode (LED).

37. An apparatus according to claim 8, wherein the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a measure of hemoglobin oxygen saturation (SaO_2) derived from the first parameter, and the computer readable program code means includes computer readable instructions for:

determining respective relative amounts of different hemoglobin species present in the blood sample from the in vitro absorbance measurement of the blood sample;

comparing each of the relative amounts of the different hemoglobin species present in the blood sample to a corresponding threshold value; and

returning an indication about the measure of hemoglobin oxygen saturation (SaO_2) derived from the first parameter as a result of the comparison of each relative amount of hemoglobin species to its corresponding threshold value.

38. An apparatus according to claim 37, wherein the indication is at least one of an error message, a confirmation message, and a signal that disables the in vivo measurement module.

39. An apparatus according to claim 37, wherein the computer readable program code means also includes computer readable instructions for disabling the in vivo measurement module until an in vitro measurement is repeated.

40. An apparatus according to claim 39, wherein the instructions for disabling the in vivo measurement module, until an in vitro measurement is repeated, occurs after at least one of a predetermined number of in vivo measurements, a predetermined amount of time and if the measure of hemoglobin oxygen saturation (SaO_2) derived from the first parameter breaches a corresponding threshold value.

41. An apparatus according to claim 37, wherein the computer readable program code means also includes computer readable instructions for deriving the measure of hemoglobin oxygen saturation (SaO_2) from the first parameter according to a Pulse Oximetry technique that employs the use of at least two wavelengths of EMR.

42. An apparatus according to claim 8, wherein the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a relative amount of Met-hemoglobin present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for:

determining a fourth parameter that is a relative amount of Met-hemoglobin present in the blood sample from the in vitro absorbance measurement of the blood sample;

calculating a correction factor which is a ratio of the fourth parameter to the third parameter; and

applying the correction factor to subsequent in vivo measurements of the third parameter.

43. An apparatus according to claim 42, wherein the relative amounts of Met-hemoglobin are calculated as a ratio of the amount of Met-hemoglobin to the total-hemoglobin.

44. An apparatus according to claim 42, wherein the computer readable program code means also includes computer readable instructions for disabling the in vivo measurement module until an in vitro measurement is repeated.

45. An apparatus according to claim 44, wherein the instructions for disabling the in vivo measurement module, until an in vitro measurement is repeated, occurs after at least one of a predetermined number of in vivo measurements, a predetermined amount of time and if the relative amount Met-hemoglobin derived from the first parameter breaches a corresponding threshold value in subsequent in vivo measurements.

46. An apparatus according to claim 42, wherein the computer readable program code means also includes computer readable instructions for deriving the relative amount of Met-hemoglobin from a ratio of absorbance measurements at two wavelengths.

47. An apparatus according to claim 8, wherein the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a relative amount of Met-hemoglobin present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for:

determining a concentration of Methylene Blue in the blood sample from the in vitro absorbance measurement of the blood sample;

comparing the concentration of Methylene Blue in the blood sample to a corresponding threshold value; and

returning an indication about the concentration of Methylene Blue in the blood sample as a result of the comparison.

48. An apparatus according to claim 47, wherein the indication is at least one of an error message, a confirmation message, a toxicity measurement, the concentration of Methylene Blue, the time the in vitro measurement was made and a signal that disables the in vivo measurement module.

49. An apparatus according to claim 47, wherein the computer readable program code means also includes computer readable instructions for disabling the in vivo measurement module until an in vitro measurement is repeated.

50. An apparatus according to claim 49, wherein the instructions for disabling the in vivo measurement module, until an in vitro measurement is repeated, occurs after at least one of a predetermined number of in vivo measurements, a predetermined amount of time, and if the relative amount Met-hemoglobin derived from the first parameter breaches a corresponding threshold value in subsequent in vivo measurements.

51. An apparatus according to claim 47, wherein the computer readable program code means also includes computer readable instructions for deriving the relative amount of Met-hemoglobin from a ratio of absorbance measurements at two wavelengths.

52. An apparatus according to claim 8, wherein the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a relative amount of hemoglobin-based blood substitute in Met-hemoglobin form present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for:

determining a fourth parameter that is a relative amount hemoglobin-based blood substitute in Met-hemoglobin form present in the blood sample from the in vitro absorbance measurement of the blood sample;

calculating a correction factor which is a ratio of the fourth parameter to the third parameter; and

applying the correction factor to subsequent in vivo measurements of the third parameter.

53. An apparatus according to claim 52, wherein the relative amounts of hemoglobin-based blood substitute in Met-hemoglobin form are calculated as a ratio of a concentration of hemoglobin-based blood substitute and a concentration of hemoglobin-based blood substitute in Met-hemoglobin form.

54. An apparatus according to claim 52, wherein the computer readable program code means also includes computer readable instructions for disabling the in vivo measurement module until an in vitro measurement is repeated.

55. An apparatus according to claim 54, wherein the instructions for disabling the in vivo measurement module, until an in vitro measurement is repeated, occurs after at least one of a predetermined number of in vivo measurements, a predetermined amount of time, and if the relative amount hemoglobin-based blood substitute in Met-hemoglobin form derived from the first parameter breaches a corresponding threshold value in subsequent in vivo measurements.

56. An apparatus according to claim 52, wherein the computer readable program code means also includes computer readable instructions for deriving the relative amount of hemoglobin-based blood substitute in Met-hemoglobin form from a ratio of absorbance measurements at two wavelengths.

57. An apparatus according to claim 8, wherein the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a relative amount of Carboxy-hemoglobin form present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for:

determining a fourth parameter that is a relative amount of Carboxy-hemoglobin present in the blood sample from the in vitro absorbance measurement of the blood sample;

calculating a transforming factor which is a ratio of the fourth parameter to the third parameter; and

applying the correction factor to subsequent in vivo measurements of the third parameter.

58. An apparatus according to claim 57, wherein the relative amounts of Carboxy-hemoglobin are calculated as a ratio of a concentration of total-hemoglobin and a concentration of Carboxy-hemoglobin.

59. An apparatus according to claim 57, wherein the computer readable program code means also includes computer readable instructions for disabling the in vivo measurement module until an in vitro measurement is repeated.

60. An apparatus according to claim 59, wherein the instructions for disabling the in vivo measurement module, until an in vitro measurement is repeated, occurs after at least one of a predetermined number of in vivo measurements, a predetermined amount of time, and if the relative amount Carboxy-hemoglobin derived from the first parameter breaches a corresponding threshold value in subsequent in vivo measurements.

61. An apparatus according to claim 57, wherein the computer readable program code means also includes computer readable instructions for deriving the relative amount of Carboxy-hemoglobin from a ratio of absorbance measurements at two wavelengths.

62. An apparatus according to claim 8, wherein the first parameter is an in vivo absorbance measurement of a body part of the life-form taken at at least one wavelength of electromagnetic radiation (EMR), the second parameter is an in vitro absorbance measurement of a blood sample of the life form taken at at least one wavelength of EMR, the third parameter is a ratio of biliverdin and bilirubin present in the life-form derived from the first parameter, and the computer readable program code means includes computer readable instructions for:

determining a fourth parameter that is a ratio of biliverdin and bilirubin present in the blood sample from the in vitro absorbance measurement of the blood sample;

calculating a transforming factor which is a ratio of the fourth parameter to the third parameter; and

applying the transforming factor to subsequent in vivo measurements of the third parameter.

63. An apparatus according to claim 62, wherein the ratios of biliverdin and bilirubin are calculated from a concentration of biliverdin and a concentration of bilirubin.

64. An apparatus according to claim 62, wherein the computer readable program code means also includes computer readable instructions for disabling the in vivo measurement module until an in vitro measurement is repeated.

65. An apparatus according to claim 64, wherein the instructions for disabling the in vivo measurement module, until an in vitro measurement is repeated, occurs after at least one of a predetermined number of in vivo measurements, a predetermined amount of time, and if the third parameter breaches a corresponding threshold value in subsequent in vivo measurements.

66. An apparatus according to claim 62, wherein the computer readable program code means also includes computer readable instructions for deriving the ratio of biliverdin and bilirubin from a ratio of absorbance measurements at two wavelengths.

67. A joint-diagnostic in vivo and in vitro spectroscopic apparatus comprising:

an in vivo spectroscopic measurement module for producing a first plurality of parameters, each having a value related to the spectroscopic analysis of a first plurality of analytes;

an in vitro measurement module for producing a second plurality of parameters, each having a value related to the analysis of a second plurality of analytes; and,

a computer usable medium having computer readable program code means embodied therein for jointly analyzing some of each of the first and second pluralities of parameters thereby producing a third plurality of parameters from values of some of the first and second parameters, the third plurality of parameters being indicative of a clinical-relationship between some of the first and second pluralities of parameters.

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专利名称(译)	联合诊断体内和体外装置		
公开(公告)号	US20050203356A1	公开(公告)日	2005-09-15
申请号	US11/071247	申请日	2005-03-04
[标]申请(专利权)人(译)	CHROMEDX		
申请(专利权)人(译)	CHROMEDX INC.		
当前申请(专利权)人(译)	COVIDIEN LP		
[标]发明人	SAMSOONDAR JAMES		
发明人	SAMSOONDAR, JAMES		
IPC分类号	A61B5/055 A61B5/145 A61K49/00 G01N21/17 G01N21/25 G01N21/77 G01N21/78 G01N33/483 G01N33/487 G01N33/49 G06F19/00 A61B5/00 B65D81/00		
CPC分类号	A61B5/00		
优先权	2460898 2004-03-09 CA		
外部链接	Espacenet USPTO		

摘要(译)

对生命形式的分析物进行体内测试是一个有吸引力的概念，因为生物样本不必从生命形式中去除。然而，单独的体内测试不能提供足够准确，完整和/或可靠的信息以安全地替换体外测试。与独立和单独进行体内或体外测试相反，本发明的一些实施方案提供了用于组合体内和体外测试的联合诊断装置。在一些具体实施方案中，来自体外测量模块的结果与随后在稍后获得的体内测量/观察结合使用，和/或反之亦然。因此，在一些实施方案中，体外测量用于补充和/或部分补偿体内测试的一些限制，并且同时通过减少所采集的生物样品的数量来实现体内测试的一些益处。