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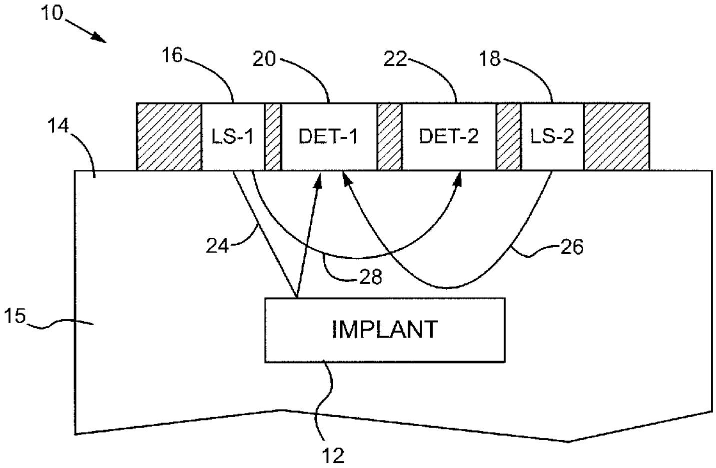

Fig. 1

(57) Abstract: An optical device is used to monitor an implant embedded in the tissue of a mammal (e.g., under the skin). The implant receives excitation light from the optical device and emits light that is detected by the optical device, including an analyte-dependent optical signal. Scatter and absorption properties of tissue change over time due to changes in hydration, blood perfusion and oxygenation. The optical device has an arrangement of light sources, filters and detectors to transmit excitation light within excitation wavelength ranges and to measure emitted light within detection wavelengths. Changes in scattering and absorption of light in the tissue, such as diffuse reflectance, are monitored. The light sources, filters and detectors may also be used to monitor autofluorescence in the tissue to correct autofluorescence background.

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METHOD AND DEVICE FOR CORRECTING OPTICAL SIGNALS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of US provisional patent application 61/785,087 filed on March 14, 2013, titled "Method and Device for Correcting Optical Signals", which application is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] The invention relates to a method and device for monitoring an implant, and in particular to a method and device for correcting luminescent signals emitted from the implant.

[0003] The monitoring of the level of analyte, such as glucose, lactate or oxygen, in certain individuals is important to their health. High or low levels of glucose, or other analytes, may have detrimental effects or be indicative of specific health states. The monitoring of glucose is particularly important to individuals with diabetes, a subset of whom must determine when insulin is needed to reduce glucose levels in their bodies or when additional glucose is needed to raise the level of glucose in their bodies.

[0004] A conventional technique used by many individuals with diabetes for personally monitoring their blood glucose level includes the periodic drawing of blood, the application of that blood to a test strip, and the determination of the blood glucose level using calorimetric, electrochemical, or photometric detection. This technique does not permit continuous or automatic monitoring of glucose levels in the body, but typically must be performed manually on a periodic basis. Unfortunately, the consistency with which the level of glucose is checked varies widely among individuals. Many people with diabetes find the periodic testing inconvenient, and they sometimes forget to test their glucose level or do not have time for a proper test. In addition, some individuals wish to avoid the pain associated with the test. Unmonitored glucose may result in hyperglycemic or hypoglycemic episodes.

An implanted sensor that monitors the individual's analyte levels would enable individuals to monitor their glucose, or other analyte levels, more easily.

[0005] A variety of devices have been developed for monitoring of analytes (e.g., glucose) in the blood stream or interstitial fluid of various tissues. A number of these devices use sensors that are inserted into a blood vessel or under the skin of a patient. These implanted sensors are often difficult to read or to monitor optically, because of low levels of florescence in the presence of high scatter due to dynamic changes in skin conditions (e.g., blood level and hydration). The skin is highly scattering, and the scattering may dominate the optical propagation. Scatter is caused by index of refraction changes in the tissue, and the main components of scatter in the skin are due to lipids, collagen, and other biological components. The main absorption is caused by blood, melanin, water, and other components.

[0006] One device, disclosed in published US patent application 20090221891 to Yu, includes components of an assay for glucose. An optical signal is read out transcutaneously by external optics when the sensor is implanted in vivo. A fluorimeter separately measures, for a donor chromophore and an acceptor chromophore, an excitation light intensity, an ambient light intensity, and an intensity of combined luminescent and ambient light. Measurements are taken by holding the fluorimeter close to the skin and in alignment with the sensor. The final output provided is the normalized ratio between the luminescent intensity from the two fluorophores, which may be converted to analyte concentration using calibration data. A calibration curve is established empirically by measuring response versus glucose concentration. Although this device provides some light signal correction, it may still be difficult to obtain accurate readings due to dynamic skin changes that cause optical scattering and absorption of light emitted from the implant.

[0007] US patent application 20110028806 to Merritt discloses another procedure and system for measuring blood glucose levels. A set of photodiodes detects the luminescence and reflectance of light energy emitted from one or more emitters, such as LEDs, into a patient's skin. Small molecule metabolite reporters (SMMRs) that bind to glucose are introduced to tissue of the stratum corneum and the epidermis to provide more easily detected luminescence. The test results are calibrated with a reflectance intensity measurement taken at approximately the excitation wavelength. In addition, the method includes measuring a second luminescence and reflectance intensity to normalize data from the first set of measurements. First luminescence and reflectance intensity measurements are taken at a site treated with an SMMR. Second luminescence and reflectance intensity measurements are taken at an untreated, background site. The background measurement is then used to correct for the background tissue luminescence and absorption through a wavelength normalization. Although this method provides some light signal correction for background luminescence and reflectance, it may still be difficult to obtain accurate and/or consistent glucose readings from glucose-binding molecules in the epidermis.

[0008] There is still a need for a small, compact device that can accurately and consistently monitor an implanted sensor and provide signals to an analyzer without substantially restricting the movements and activities of a patient. Continuous and/or automatic monitoring of the analyte can provide a warning to the patient when the level of the analyte is at or near a threshold level. For example, if glucose is the analyte, then the monitoring device might be configured to warn the patient of current or impending hyperglycemia or hypoglycemia. The patient can then take appropriate actions.

SUMMARY

[0009] According to one aspect, a method is provided for correcting at least one analyte-dependent optical signal emitted from an implant. The implant is typically embedded in tissue of a mammalian body. The implant is capable of emitting, in response to excitation light within an excitation wavelength range, the analyte-dependent optical signal within an emission wavelength range. The method comprises transmitting first excitation light within the excitation wavelength range through the tissue to the implant and measuring a first optical signal emitted from the tissue, within the emission wavelength range, in response to the first excitation light. The method also comprises transmitting second excitation light within the emission wavelength range into the tissue and measuring a second optical signal emitted from the tissue, within the emission wavelength range, in response to the second excitation light. At least one corrected signal value is calculated in dependence upon the measured signals.

[0010] According to another aspect, an optical detection device is provided for monitoring an implant embedded in tissue of a mammalian body. The implant is capable of emitting, in response to excitation light within an excitation wavelength range, at least one analyte-dependent optical signal within an emission wavelength range. The device comprises a first light source arranged to transmit first excitation light within the excitation wavelength range through the tissue to the implant. A second light source is arranged to transmit second excitation light within the emission wavelength range into the tissue. At least one detector is arranged to measure, in response to the first excitation light, a first optical signal emitted from the tissue in the emission wavelength range and arranged to measure, in response to the second excitation light, a second optical signal emitted from the tissue in the emission wavelength range.

[0011] According to another aspect, a method is provided for correcting at least one analyte-dependent optical signal emitted from an implant embedded in tissue of a mammalian body. The implant is capable of emitting, in response to excitation light within an excitation wavelength range, the analyte-dependent optical signal within an emission wavelength range. The method comprises transmitting first excitation light within the excitation wavelength range through the tissue to the implant and measuring a first optical signal emitted from the tissue, within the emission wavelength range, in response to the first excitation light. The method also comprises transmitting second excitation light within the excitation wavelength range into the tissue and measuring a second optical signal emitted from the tissue, within the emission wavelength range, in response to the second excitation light. The second excitation light and the light emitted in response to the second excitation light form a light path that is spaced laterally from the implant a sufficient distance to avoid significant contribution from implant reporters (e.g., luminescent, luminescent, bioluminescent, or phosphorescent reporters). At least one corrected signal value is calculated in dependence upon the measured optical signals.

[0012] According to another aspect, an optical detection device is provided for monitoring an implant embedded in tissue of a mammalian body. The implant is capable of emitting, in response to excitation light within an excitation wavelength range, at least one analyte-dependent optical signal within an emission wavelength range. The device comprises a first light source arranged to transmit first excitation light in the excitation wavelength range through the tissue to the implant. A first detector is arranged to measure, in response to the first excitation light, a first optical signal emitted from the tissue in the emission wavelength range. A second light source is arranged to transmit second excitation light within the excitation wavelength range into the tissue. A second detector is arranged to measure, in response to the second excitation light, a second optical emitted from the tissue in the emission wavelength range. The second light source and the second detector are positioned with respect to each other such that the second excitation light and the light emitted in response to the second excitation light form a light path that is spaced laterally from the implant a sufficient distance to avoid significant contribution from implant reporters.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The foregoing aspects and advantages of the present invention will become better understood upon reading the following detailed description and upon reference to the drawings where:

[0014] Fig. 1 shows a schematic side view of an optical detection device for monitoring an implant according to one embodiment of the invention.

[0015] Fig. 2 shows a schematic side view of an optical detection device for monitoring an implant according to another embodiment of the invention.

[0016] Fig. 3 shows a schematic side view of aspects of an optical detection device according to another embodiment of the invention.

[0017] Fig. 4 shows a schematic plan view of an optical detection device according to another embodiment of the invention.

[0018] Fig. 5 shows a schematic cross-sectional view of the device of Fig. 4.

[0019] Fig. 6 shows a schematic side view of an optical detection device according to some embodiments of the invention.

[0020] Fig. 7 shows a schematic plan view of an optical detection device according to some embodiments of the invention.

[0021] Fig. 8 shows a schematic cross-sectional view of the device of Fig. 7.

[0022] Fig. 9 shows a schematic plan view of an optical detection device according to some embodiments of the invention.

[0023] Fig. 10 shows a schematic cross-sectional view of the device of Fig. 9.

[0024] Fig. 11 shows a schematic plan view of an optical detection device according to some embodiments of the invention.

[0025] Fig. 12 shows a schematic, exploded view of the device of Fig. 11.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0026] In the following description, it is understood that all recited connections between structures can be direct operative connections or indirect operative connections through intermediary structures. A set of elements includes one or more elements. Any recitation of an element is understood to refer to at least one element. A plurality of elements includes at least two elements. Unless otherwise required, any described method steps need not be necessarily performed in a particular illustrated order. A first element (e.g. data) derived from a second element encompasses a first element equal to the second element, as well as a first element generated by processing the second element and optionally other data. Making a determination or decision according to a parameter encompasses making the determination or decision according to the parameter and optionally according to other data. Unless otherwise specified, an indicator of some quantity/data may be the quantity/data itself, or an indicator different from the quantity/data itself. Computer programs described in some embodiments of the present invention may be stand-alone software entities or sub-entities (e.g., subroutines, code objects) of other computer programs. Computer readable media encompass non-transitory media such as magnetic, optic, and semiconductor storage media (e.g. hard drives, optical disks, flash memory, DRAM), as well as communications links such as conductive cables and fiber optic links. According to some embodiments, the present invention provides, *inter alia*, computer systems comprising hardware (e.g. one or more processors and associated memory) programmed to perform the methods described herein, as well as computer-readable media encoding instructions to perform the methods described herein.

[0027] The following description illustrates embodiments of the invention by way of example and not necessarily by way of limitation.

[0028] Fig. **1** shows a schematic side view of an optical detection device **10** for monitoring an implanted sensor or implant **12**, according to a first embodiment of the invention. The implant **12** is embedded in tissue of a mammalian body (which may be a portion of tissue that is attached or unattached to the rest of the body in various embodiments). The implant **12** is typically embedded under a surface of skin **14**. The implant **12** is embedded at a first depth under the surface of the skin **14**, which is preferably a sufficient depth to position the implant in the subcutaneous tissue (e.g., in the range of 1 to 5 mm under the surface of the skin **14**). In some embodiments, the implant **12** is embedded in the tissue at a depth greater than or equal to 2 mm under the surface of the skin **14**, and in other embodiments the implant **12** is embedded in the tissue at a depth greater than or equal to 4 mm under the surface of the skin.

[0029] The implant **12** is capable of emitting, in response to excitation light within an excitation wavelength range, at least one analyte-dependent optical signal within an emission wavelength range. The analyte may comprise, for example, glucose or other analytes in the body of the individual. Suitable optical signals include, but are not limited, to luminescent, luminescent, bioluminescent, phosphorescent, autoluminescence, and diffuse reflectance signals. In preferred embodiments, the implant **12** contains one or more luminescent dyes whose luminescence emission intensity varies in dependence upon the amount or presence of target analyte in the body of the individual.

[0030] A first light source **16** is arranged to transmit first excitation light within the excitation wavelength range from the surface of the skin **14** to the implant **12**. A second light source **18** is arranged to transmit second excitation light from the surface of the skin **14** into the tissue **15**. The second excitation light is preferably within the emission wavelength range of the analyte-dependent luminescent signal (e.g., the emission peak). Suitable light sources include, without limitation, lasers, semi-conductor lasers, light emitting diodes (LEDs), organic LEDs.

[0031] At least one detector, and more preferably at least two detectors **20**, **22** are arranged with the light sources **16, 18**. The first detector **20** is positioned to measure, in response to the first excitation light from the first light source **16**, a first optical signal (e.g., the intensity of light) emitted at the surface of the skin **14** within the emission wavelength range. The detector **20** is also arranged to measure, in response to the second excitation light, a second optical signal emitted from the tissue **15** through the surface of the skin **14** within the emission wavelength range. Suitable detectors include, without limitation, photodiodes or CCDs. Although multiple detectors are preferred for some embodiments, one could use a single universal detector. The detectors **20**, **22** are preferably filtered (e.g., dichroic filters or other suitable filters) to measure the optical signals emitted within respective wavelength ranges. In this example, a suitable luminescent dye sensitive to glucose concentration is Alexa 647 responsive to excitation light (absorption) in the range of about 600 to 650 nm (absorption peak 647 nm) and within an emission wavelength range of about 670 to 750 nm with an emission peak of about 680 nm.

[0032] In the operation of device **10**, an analyte-dependent luminescent signal emitted from the implant **12** is corrected for diffuse reflectance and/or autofluorescence. The light source **16** is activated to transmit first excitation light within the excitation wavelength range from the surface of the skin **14** to the implant **12**. The first detector **20** measures, in response to the first excitation light, a first optical signal emitted from the tissue **15** at the surface of the skin **14** within the emission wavelength range, as represented by a first light path **24** from the light source **16** to the implant **12** to the first detector **20**. The light path **24** provides the primary analyte-dependent optical signal. The second light source **18** is activated to transmit second excitation light from the surface of the skin **14** to a second depth in the tissue **15** under the surface of the skin **14**. The second excitation light is substantially within the emission wavelength range (e.g., the emission peak) of the analyte-dependent luminescent signal. The first detector **20** measures, in response to the second excitation light, a second optical signal emitted from the tissue **15** through the surface of the skin **14** within the emission wavelength range, as represented by a second light path **26**.

[0033] The second optical signal may be used as a reference signal to correct the primary analyte-dependent optical signal for diffuse reflectance or scattering of light in the tissue **15**. In some embodiments, the second depth to which the light path **26** extends below the surface of the skin **14** may be substantially equal to the first depth at which the implant **12** is embedded (e.g., in the subcutaneous tissue at a depth of 1 to 5 mm under the surface of the skin **14**). In some embodiments, the light path **26** for the second optical signal extends to a depth greater than or equal to 2 mm under the surface of the skin **14**, and in other embodiments the light path **26** for the second optical signal extends to a depth greater than or equal to 4 mm under the surface of the skin.

[0034] An additional correction factor may optionally be obtained by activating the first light source **16** to transmit third excitation light, within the excitation wavelength range, from the surface of the skin **14** to a third depth in the tissue **15**. In some embodiments, the third depth may differ from the first and second depths, and the third depth may be in the range of 1 to 5 mm under the surface of the skin **14**. The second detector **22** measures a third optical signal emitted from the tissue **15** through the surface of the skin **14** within the excitation wavelength range in response to the third excitation light, as represented by a third light path **28**. At least one corrected signal value is calculated in dependence upon the measured optical signals. In one example, the primary analyte-dependent signal from the implant may be corrected as:

[0035] Corrected Signal = S(LS1, D1)*C(LS2, D1)*C(LS1, D2) (1)

[0036] In equation (1) above, the term S(LS1, D1) represents the first optical signal, which is the primary analyte-dependent optical signal measured from the first light path **24** from the first light source **16** to the implant **12** to the first detector **20**. The term C(LS2, D1) represents the second optical signal, which is a correction factor signal measured from the second light path **26** from the second light source **18** to the first detector **20**. The term C(LS1, D2) represents an optional third optical signal, which is an additional correction factor signal measured from the third light path **28** from the first light source **16** to the second detector **22**.

[0037] Thus, the primary analyte-dependent optical signal emitted from the implant **12** may be corrected for diffuse reflectance or scattering within the emission wavelength range of the analyte-dependent optical signal, to account for optical scattering or absorption of the signal in the tissue **15**. The analyte-dependent optical signal may optionally be corrected for scattering, reflectance or attenuation in the excitation wavelength range to account for dynamic changes in skin properties. One advantage of correcting the analyte-dependent signal by one or more reference signals is that accurate and/or consistent glucose values may be determined from measurements of light emitted from an implant located relatively deep in the tissue, such as in the subcutaneous region. Light emitted from the implant **12** may be strongly modulated by the tissue **15** between the implant and the surface of the skin **14**. Embodiments of the present invention provide means to correct for modulation of light emitted from the tissue **15**, in addition to correction for excitation light and background or ambient light, if desired.

[0038] Another advantage is that measurements of the reference optical signals used for correction factors (such as diffuse reflectance, autofluorescence, and/or background light) are taken in the same region of tissue **15** in which the implant **12** is embedded in a few seconds of time or less, so that dynamic skin or tissue properties, that may vary within different regions of the body, are substantially the same for the correction signals as they are for the primary analyte-dependent signal at the time of measurement. Prior to executing optical reads for the analyte-dependent signal, the diffuse reflectance correction signal and/or the autofluorescence correction signal, a dark reading may be taken to account for background or ambient light, and this reading may be used to further correct the signals, e.g., by background subtraction. A preferred order of optical readings for the correction factors is background subtraction, autofluorescence correction, and diffuse reflectance correction, although no particular order is required.

[0039] In some embodiments, an analyte concentration (e.g., glucose level) is determined from the corrected signal value. Preferably a look-up table or calibration curve is used to determine the analyte concentration in dependence upon the corrected signal value. The look-up table or calibration curve may be in a microprocessor included with the optics. In some embodiments, the microprocessor is programmed to store measured signal values and/or to calculate corrected signal values. Alternatively, these functions may be performed in a separate processor or external computer in communication with the optical device. The external processor or computer receives data representative of the measured optical signals and calculates the corrected signal value and analyte concentration. Alternatively, multiple processors may be provided, e.g., providing one or more processors in the optical device that communicate (wirelessly or with wires) with one or more external processors or computers.

[0040] Fig. 2 shows another embodiment of an optical detection device **30** for monitoring an implant **12**. In this embodiment, the implant **12** is further capable of emitting, in response to excitation light within a second excitation wavelength range (that may share or overlap the first emission wavelength range) at least one analyte-independent optical signal within a second emission wavelength range. The implant **12** preferably contains an analyte-independent luminescence dye that functions to control for non-analyte physical or chemical effects on a reporter dye (e.g., photo bleaching or pH). Multiple dyes may used. The analyte-independent optical signal is not modulated by analyte present in the tissue **15** and provides data for normalization, offset corrections, or internal calibration. The analyte-independent signal may compensate for non-analyte affects that are chemical or physiological (e.g., oxygen, pH, redox conditions) or optical (e.g., water, light absorbing/scattering compounds, hemoglobin). Alternatively, the analyte-independent signal may be provided by a stable reference dye in the implant **12**. Suitable stable reference materials include, but are not limited to, lanthanide doped crystals, lanthanide doped nanoparticles, quantum dots, chelated lanthanide dyes, and metal (e.g., gold or silver) nanoparticles. The stable reference dye may provide a reference signal for other signals (e.g., to determine photo bleaching).

[0041] The second embodiment differs from the first embodiment described above in that the device **30** includes a third light source **40** for transmitting excitation light into the tissue **15** through the surface of the skin **14**. In the operation of device **30**, an analyte-dependent luminescent signal emitted from the implant **12** is corrected using three reference signals. The first light source **32** is activated to transmit excitation light within a first excitation wavelength range from the surface of the skin **14**, through the tissue **15**, to the implant **12**. The first detector **34** measures, in response to the first excitation light, a first optical signal emitted from the tissue **15** at the surface of the skin **14** within a first emission wavelength range, as represented by a first light path **42** from the first light source **32**, to the implant **12**, and to the first detector **34**. This first optical signal is the primary analyte-dependent optical signal.

[0042] The second light source **38** is activated to transmit second excitation light from the surface of the skin **14** to a second depth in the tissue **15**. The second excitation light is preferably within the first emission wavelength range (e.g., the emission peak) of the primary analyte-dependent optical signal. The first detector **34** measures, in response to the second excitation light, a second optical signal emitted from the tissue **15** at the surface of the skin **14** within the emission wavelength range, as represented by a second light path **44**. The second optical signal may be used to correct for diffuse reflectance or scattering of light in the tissue **15** between the implant **12** and the surface of the skin **14**. In some embodiments, the depth of the second light path **44** may be substantially equal to the first depth at which the implant **12**

is embedded (preferably in the subcutaneous tissue 1 to 5 mm under the surface of the skin **14**). In some embodiments, the light path **44** for the second optical signal extends to a depth greater than or equal to 2 mm under the surface of the skin **14**, and in other embodiments the light path **44** for the second optical signal extends to a depth greater than or equal to 4 mm under the surface of the skin.

[0043] Next, the light source **38** is activated to transmit third excitation light in the second excitation wavelength range from the surface of the skin **14** to the implant **12**. The second detector **36** measures, in response to the third excitation light, a third optical signal emitted from the tissue **15** at the surface of the skin **14** within the second emission wavelength range, as represented by a third light path **46**. In this embodiment, the third optical signal is the analyte-independent luminescent signal. Next, the third light source **40** is activated to transmit fourth excitation light from the surface of the skin **14** into the tissue **15**. The fourth excitation light is preferably within the emission wavelength range of the analyte-independent luminescent signal. The detector **36** measures, in response to the fourth excitation light, a fourth optical signal emitted from the tissue **15** at the surface of the skin **14** within this emission wavelength range, as represented by a fourth light path **48**. At least one corrected signal value is calculated in dependence upon the measured optical signals. In one example, the primary analyte-dependent signal from the implant **12** may be corrected as:

[0044] Corrected Signal = S(LS1, D1)*C(LS2, D1)/[S(LS2, D2)*C(LS3, D2)] (2)

[0045] In equation (2) above, the term S(LS1, D1) represents the first optical signal which is the primary analyte-dependent signal measured from the first light path **42** from the first light source **32** to the implant **12** to the first detector **34**. The term C(LS2, D1) represents the second optical signal, which is a correction factor signal measured from the second light path **44** from the second light source **38** to the first detector **34**. The term S(LS2, D2) represents the third optical signal, which is the analyte-independent signal measured from the third light path **46** extending from the second light source **38** to the implant **12** to the second detector **36**. The term C(LS3, D2) represents the fourth optical signal, which is a correction factor signal measured from the fourth light path **48** extending from the third light source **40** to the second detector **36**.

[0046] In some embodiments in which two implant reporters (e.g., luminescent dyes) are utilized, it is possible that the implant reporters may share or overlap excitation (absorption) or emission wavelength ranges. For example, in the embodiment of Fig. 2, the emission wavelength range of the first dye, which provides the analyte-dependent luminescence signal, shares or overlaps the excitation wavelength range of the second dye, which provides the analyte-independent luminescence signal. In another embodiment, the first and second dyes may share or overlap excitation wavelength ranges (so that a common light source may be used) and emit optical signals within different emission wavelength ranges. In another embodiment, the first and second dyes may be excited by light within different excitation wavelength ranges and emit optical signals within the same or overlapping emission wavelength range(s).

[0047] Fig. 3 shows optical interrogation at different depths **D2**, **D3**, **D4** in the tissue **15** relative to the first depth **D1** of the implant **12** under the surface of the skin **14**. The spacing distances **S1**, **S2**, **S3** between the arrangement of detectors **52**, **54**, **56** and the light source **50** determines the depths **D2**, **D3**, **D4** of the respective light paths. In some embodiments, readings for optical signal corrections are performed at multiple depths, as represented by the respective light paths, and the measured values of the reference optical signals used for correction are averaged for the correction factor. In some embodiments, the light path for the reference optical signal extends to a depth **D2** in the tissue **15** that is greater than the depth **D1** at which the implant **12** is embedded. The light path for the reference optical signal may also extend to a depth **D3** in the tissue **15** such that the light path passes through the implant **12**.

[0048] When the optical device has multiple possible combinations of spacing distances between the light sources and detectors as shown in Figs. 3-9, implementation may be more flexible, because the depth of the implant **12** may be application-specific. In one embodiment, at least one analyte-independent signal, which may be emitted by the stable reference dye, is used to determine the appropriate depth for the light path(s) and resulting optical signal(s) measured to correct the analyte-dependent signal for diffuse reflectance and/or autofluorescence. Preferably a look-up table is used to determine, based on the measured intensity of the analyte-independent luminescent signal emitted from the implant, which of the possible depth(s) for normalization optical signals should be used, or more specifically which light source/detector pairing(s). The look-up table may be in a microprocessor included with the optical device, or in a separate processor or external computer in communication with the optical device that receives data representative of the measured optical signals (e.g., intensities of light measured within selected wavelengths).

[0049] In some embodiments, the processor is programmed to determine (e.g., by calculation or a look-up table) a quantity or weight assigned to measurements of one or more diffuse reflectance signals. The quantity or weight assigned to the measured diffuse reflectance signal may then be used in correcting or normalizing one or more implant reporter signals (e.g., the primary analyte-dependent signal emitted from the implant) to calculate the corrected signal value. The quantity or weight is preferably determined in dependence upon the intensity of an analyte-independent optical signal (e.g., from the stable reference dye). The intensity of the analyte-independent optical signal may vary with the depth of the implant in the tissue. For example, if the implant is embedded in tissue at a depth of 2 mm under the surface of the skin, the amount of light attenuation in the tissue will likely be less than if the implant were embedded at a depth of 4mm. Reporter optical signals emitted from a shallower implant may require less of a correction factor for diffuse reflectance and/or autofluoresence than those signals emitted from an implant embedded at a greater depth. In some embodiments, the diffuse reflectance correction factor used to correct or normalize the analyte-dependent signal is proportional to depth, and the quantity or weight assigned to the diffuse reflectance measurement is determined in dependence upon the measurement of the analyte-independent signal.

[0050] Fig. 4 shows another embodiment of an optical device **60** having additional light sources and detectors with multiple possible combinations of spacing distances between the light sources and detectors. The light sources and detectors are arranged in a sensor patch **62** adapted to be placed on the surface of the skin, and described in greater detail below. At least one, and more preferably three central exciter light sources **64A**, **64B**, and **64C** are positioned to transmit excitation light through a central via **66** in the patch **62**. The central via **66** may contain one or more optical waveguide(s). At least one detector, and more preferably an inner ring of three central detectors **68A**, **68B**, and **68C** are arranged around the central via **66**. There is also preferably an outer ring **70** having multiple outer-ring exciter light sources and outer-ring detectors (in this example twenty-five outer-ring light sources and detectors) arranged in a substantially ring-shaped pattern, providing many permutations of possible optical channels. The combination of an excitation light source and a detection band is an optical channel. An example of one possible implementation of the optical device **60** will now be given with reference to Figs. 4-11 and Table 1, describing twelve optical channels.

TABLE 1

Optical Channel	*Function*	*Excitation*	*Emissions Detected*	*Exciter*	*Detector*	*Comments*
1	Implant Reporter 1	Excitation Peak Reporter 1	Emission Peak Reporter 1	Central Exciter 1	Central Detector 1	Analyte-dependent 1
2	Implant Reporter 2	Excitation Peak Reporter 2	Emission Peak Reporter 2	Central Exciter 2	Central Detector 2	Analyte-independent 1
3	Implant Reporter 3	Excitation Peak Reporter 3	Emission Peak Reporter 3	Central Exciter 3	Central Detector 3	Stable Reference dye
4	Exciter Power Normalization	Excitation Peak Reporter 1	Excitation Peak Reporter 1	Central Exciter 1	Outer Detector 6	Power Normalization 1
5	Exciter Power Normalization	Excitation Peak Reporter 2	Excitation Peak Reporter 2	Central Exciter 2	Outer Detector 6	Power Normalization 2
6	Exciter Power Normalization	Excitation Peak Reporter 3	Excitation Peak Reporter 3	Central Exciter 3	Outer Detector 6	Power Normalization 3
7	Diffuse Reflectance 1	Emission Peak Reporter 1	Emission Peak Reporter 1	Outer Exciter 6	Outer Detector 6	Diffuse Reflectance Data
8	Diffuse Reflectance 2	Emission Peak Reporter 2	Emission Peak Reporter 1	Outer Exciter 7	Outer Detector 6	Diffuse Reflectance Data
9	Diffuse Reflectance 3	Emission Peak Reporter 3	Emission Peak Reporter 1	Outer Exciter 8	Outer Detector 6	Diffuse Reflectance Data
10	Autofluorescence 1	Excitation Peak Reporter 1	Emission Peak Reporter 1	Outer Exciter 1	Outer Detector 1	Autofluorescence and ambient light
11	Autofluorescence2	Excitation Peak Reporter 2	Emission Peak Reporter 2	Outer Exciter 2	Outer Detector 2	Autofluorescence and ambient light
12	Autofluorescence3	Excitation Peak Reporter 3	Emission Peak Reporter 3	Outer Exciter 3	Outer Detector 3	Autofluorescence and ambient light

[0051] As shown in Table 1, optical channels 1-3 function to measure three reporter dye signals from the implant, including an analyte-specific signal, an analyte-independent signal, and a stable reference dye signal. Optical channel 1 functions to measure an analyte-specific luminescent signal from the implant, such as a light signal whose intensity varies with glucose level. Other embodiments may include multiple analyte-dependent signals from the implant. Optical channel 2 functions to measure an analyte-independent control for non-analyte physical or chemical effects on the reporter dyes (e.g., photo bleaching, pH,). Optical channel 3 functions to measure a stable reference dye (e.g., lanthanide).

[0052] As listed in Table 1 and shown in Fig. 4, each of the optical channels 1-3 comprises a respective pairing of one of the three central exciter light sources **64A**, **64B**, and **64C** with a corresponding one of the three central detectors **68A**, **68B**, and **68C**. Fig. 6 shows a schematic side view of the light paths for optical detection of the implant reporters. Excitation light is transmitted through the central via **66** (which preferably contains a monolithic waveguide) from the surface of the skin **14**, through the tissue **15**, and to the implant **12**. Central detectors **68A**, **68B**, and **68C** measure, in response to the excitation light, optical signals emitted from the tissue **15** at the surface of the skin **14** in respective emission wavelength ranges.

[0053] A suitable dye for the analyte-dependent signal is Alexa 647 which is responsive to excitation light within an excitation wavelength range of about 600 to 650 nm (excitation peak 647 nm) and within an emission wavelength range of about 670 to 750 nm with an emission peak of about 680 nm. A suitable dye for the analyte-independent signal is Alexa 750 which is responsive to excitation light within an excitation wavelength range of about 700 to 760 nm (excitation peak 750 nm) and within an emission wavelength range of about 770 to 850 nm with an emission peak of about 780 nm. A suitable stable reference dye is erbium with a first excitation light wavelength range of about 650 to 670 nm (excitation peak about 650 nm), a second excitation wavelength range of about 800 to 815 nm (with an excitation peak of about 805 nm), and an emission wavelength range of about 980 to 1050 nm (emission peak of about 1020 nm). In another embodiment, erbium an Alexa 647 may be excited from the same light source, which has the advantage that an optional step of power normalization between multiple light sources is reduced or eliminated.

[0054] Referring again to Table 1, optical channels 4-6 provide exciter power normalization signals, which are preferred in embodiments where more than one light source is used. The exciter power normalization signals are used to normalize differences in the power of excitation light output by each light source, which output power may vary slightly for each light source. As shown in Figs. 4-5, the attenuation of excitation light traveling from central via **66** to outer ring **70** is measured, reducing or eliminating contribution by reporters (e.g., fluorophores) of the implant **12**. The optical channels 4-6 comprise three combinations of pairings of the three central exciter light sources **64A**, **64B**, and **64C** with outer-ring detector **6**. Alternatively, multiple detectors may be used to detect the intensity of exciter power normalization signals, preferably outer-ring detectors. For exciter power normalization signals, excitation light within the excitation wavelength range of an implant reporter is transmitted into the tissue **15**. An optical signal emitted from the tissue **15** within the excitation wavelength range is measured by the detector **6**. The corrected signal value for an implant reporter may be normalized for exciter power of a respective light source, e.g., by dividing the optical signal measured for the reporter by the measured intensity of the excitation light within the excitation wavelength range.

[0055] Optical channels 7-9 (Table 1) provide diffuse reflectance measurements to correct the luminescent dye reporter signals from the implant. As shown in Figs. 7-8, outer detector **6** measures attenuation by tissue **15** of light signals in the emission wavelength ranges of the luminescent reporter dyes of the implant **12**. Optical channels 7-9 comprise three of the outer exciter light sources **71A**, **71B**, and **71C** arranged in outside ring **70**, each paired with the detector **6** in this example, and preferably positioned to provide a range of distances between each light source/detector combination, to compute diffuse reflectance correction values for each luminescent reporter dye of the implant **12**. Rather than employing the detector **6** to measure all three optical signals, multiple detectors may be used in alternative embodiments.

[0056] Optical channels 10-12 (Table 1) provide measurements of autofluorescence and ambient light to correct the luminescent dye reporter signals from the implant. As shown in Figs. 9-10, optical channels 10-12 comprise three pairs **73A**, **73B**, and **73C** of the outer exciter light sources and outer-ring detectors arranged in the outside ring **70**. The three pairs **73A**, **73B**, and **73C** of the outer exciter light sources and outer detectors provide the same excitation and emission spectra of the three reporter luminescent dyes of the implant **12**, and are located on outer ring **70** away from implant **12**. In particular, each pair of outer exciter light source/detector for the autofluorescence measurement(s) are positioned with respect to each other such that the excitation light and the light emitted in response to the excitation light form a light path **78** that is spaced laterally from the implant **12** a sufficient distance to avoid significant contribution from implant fluorophores.

[0057] It is preferred that the lateral spacing **S4** be greater than or equal to 0.25 cm, more preferably greater than 0.5 cm, and most preferably greater than 1 cm. It is also preferred that the depth of the light path **78** extend about 1 to 5 mm into the tissue 15 under the surface of the skin 14. When multiple pairs are used, each light path may have substantially the same depth or different depths, and the measured intensities of the autofluorescence optical signals may be averaged to obtain a correction factor. It is preferred that the contribution from the implant reporter(s) (e.g., fluorophores) to the autofluorescence measurement be less than 30% of the measured intensity, more preferably less than 20%, an most preferably less than 10%.

[0058] Fig. 11 shows a plan view of the sensor patch **62** having central via **66** for excitation light. Preferred dimensions of patch **62** may be, for example, a diameter of about 16 mm and a thickness **T** of about 1.6 mm. Fig. 12 shows a schematic, exploded view of the patch **62** comprising multiple layers in a stack. In some embodiments, the layers may comprise a plastic cover **80** having a preferred thickness of about 200 um, a light control film **82** having a preferred thickness of about 100 um, a filter **84** having a preferred thickness of about 200 um, another light control film **86** having a preferred thickness of about 100 um, a silicon layer **88** having a preferred thickness of about 200 um, a printed circuit board (PCB) **90** having a preferred thickness of about 400 um, a battery **92** having a preferred thickness of about 300 um, and a case **94** having a thickness of about 200 um. The PCB **90** may include a microprocessor that is programmed to store measured values and/or to calculate the corrected signal values as previously described. The light control film is a lens array with an aperture array on its back side.

[0059] It should be clear to one skilled in the art that embodiments of the described invention may include cabled or wireless hand-held readers, wireless skin patch readers, bench-top instruments, imaging systems, handheld devices (e.g., cell phones or mobile communication devices), smartphone attachments and applications, or any other configuration that utilizes the disclosed optics and algorithms.

[0060] Tissue optical heterogeneity in some cases may be significant. Thus, it may be advantageous to utilize a single light source and a single detector to assure that every color passes through the same optical pathway through the tissue. In one embodiment, a light source can be positioned with a set of moveable filters between the light source and the surface of the skin. Similarly a single photodetector can be utilized in place of separate discrete detector elements. The detector may be used to detect different colors by using moveable or changeable filters to enable multiple wavelengths to be measured. Changing or moving filters may be accomplished by a mechanical actuator controlling a rotating disc, filter strip or other means. Alternatively, optical filters may be coated with a material that when subjected to current, potential, temperature or another controllable influence, will change optical filtering properties, so that a single photodetector can serve to detect multiple colors.

[0061] It will be clear to one skilled in the art that the above embodiments may be altered in many ways without departing from the scope of the invention. For example, many different permutations or arrangements of one or more light sources, one or more detectors, filters, and/or fibers connecting the optical components may be used to realize the device and method of the invention. For example, in some embodiments the light sources and detectors are arranged with optical fibers or cables to transmit excitation light into the skin and measure optical signals emitted from the skin, without having to position the light sources and detectors directly on the skin of an individual. Presently preferred values for dimensions of the device and/or wavelength ranges may differ in alternative embodiments. Accordingly, the scope of the invention should be determined by the following claims and their legal equivalents.

CLAIMS

What is claimed is:

1. A method for correcting at least one analyte-dependent optical signal emitted from an implant embedded in tissue of a mammalian body, the implant being capable of emitting, in response to being excited by light within an excitation wavelength range, the analyte-dependent optical signal within an emission wavelength range, the method comprising:
   a) transmitting a first generated light within the excitation wavelength range through the tissue to the implant;
   b) measuring, in response to the first excitation light, a first optical signal emitted from the tissue within the emission wavelength range;
   c) transmitting a second generated light into the tissue, wherein the second generated light is substantially within the emission wavelength range of the analyte-dependent optical signal;
   d) measuring, in response to the second generated light, a second optical signal emitted from the tissue within the emission wavelength range; and
   e) calculating at least one corrected signal value in dependence upon the measured signals.

2. The method of claim 1, wherein the second optical signal travels a light path that extends to a depth in the tissue that is substantially equal to the depth at which the implant is embedded.

3. The method of claim 2, wherein the depths are in the range of 1 to 5 mm under a surface of skin.

4. The method of claim 1, wherein the second optical signal travels a light path that extends to a depth in the tissue that is greater than the depth at which the implant is embedded.

5. The method of claim 1, further comprising the steps of:
transmitting third generated light into the tissue, wherein the third generated light is within the excitation wavelength range; and
measuring, in response to the third generated light, a third optical signal emitted from the tissue in the emission wavelength range, wherein the third optical signal travels a light path that is spaced laterally from the implant a sufficient distance to avoid significant contribution from implant reporters, and wherein the corrected signal value is calculated in further dependence upon the measured third optical signal.

6. The method of claim 1, wherein the implant is embedded in subcutaneous tissue, and wherein the second optical signal travels a light path that extends to a depth in the tissue that is greater than or equal to 2 mm under a surface of skin.

7. The method of claim 1, further comprising the steps of transmitting third generated light into the tissue and measuring a third optical signal emitted from the tissue, wherein the implant is embedded at a first depth in the tissue, the second optical signal travels a light path that extends to a second depth in the tissue, the third optical signal travels another light path that extends to a third depth in the tissue, the third depth differs from the first and second depths, and the corrected signal value is calculated in further dependence upon the third optical signal.

8. The method of claim 1, wherein:
the excitation wavelength range is a first excitation wavelength range;
the implant is embedded at a first depth in the tissue; and
the second optical signal travels a first light path that extends to a second depth in the tissue, the method further comprising:
transmitting a third generated light within a second excitation wavelength range through the tissue to the implant;
measuring, in response to the third generated light,at least one analyte-independent optical signal emitted from the tissue; and
determining the second depth in dependence upon the analyte-independent optical signal.

9. The method of claim 1, wherein the step of calculating at least one corrected signal value includes the steps of measuring at least one analyte-independent optical signal emitted from the implant and assigning a quantity or weight to the measurement of the second optical signal in dependence upon the measurement of the analyte-independent signal.

10. The method of claim 1, wherein the excitation wavelength range is a first excitation wavelength range and the emission wavelength range is a first emission wavelength range, the method further comprising the steps of:

transmitting third generated light within a second excitation wavelength range through the tissue to the implant;

measuring, in response to the third generated light, a third optical signal emitted from the tissue within a second emission wavelength range;

transmitting fourth generated light into the tissue, wherein the fourth generated light is within the second emission wavelength range; and

measuring, in response to the fourth generated light, a fourth optical signal emitted from the tissue, wherein the corrected signal value is calculated in further dependence upon the measured third and fourth optical signals.

11. The method of claim 1, further comprising the steps of transmitting third generated light into the tissue and measuring a third optical signal emitted from the tissue, wherein the third excitation light is within the excitation wavelength range, and wherein the corrected signal value is calculated in further dependence upon the third optical signal.

12. An optical detection device for monitoring an implant embedded in tissue of a mammalian body, the implant being capable of emitting, in response to being excited by light within an excitation wavelength range, at least one analyte-dependent optical signal within an emission wavelength range, the device comprising:

a) a first light source arranged to transmit first generated light within the excitation wavelength range through the tissue to the implant;

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b) a second light source arranged to transmit second generated light into the tissue, wherein the second generated light is substantially within the emission wavelength range;

c) at least one detector arranged to measure, in response to the first generated light, a first optical signal emitted from the tissue in the emission wavelength range and arranged to measure, in response to the second generated light, a second optical signal emitted from the tissue in the emission wavelength range

13. The device of claim 12, further comprising at least one processor arranged to receive data representative of the measured optical signals, wherein the processor is programmed to calculate at least one of a quantity or a concentration of analyte according to the measured optical signals.

14. The device of claim 12, wherein the second light source and at least one detector are arranged such that the second optical signal travels a light path that extends to a depth in the tissue that is substantially equal to the depth at which the implant is embedded.

15. The device of claim 12, wherein the second light source and at least one detector are arranged such that the second optical signal travels a light path that extends to a depth in the tissue that is greater than the depth at which the implant is embedded.

16. The device of claim 15, wherein the depths in the tissue are in a range of 1 to 5 mm under a surface of skin.

17. The device of claim 12, further comprising:

a third light source arranged to transmit third generated light within the excitation wavelength range into the tissue; and

at least a second detector arranged to measure, in response to the third generated light, a third optical signal emitted from the tissue within the emission wavelength range, wherein the third light source and at least second detector are arranged such that the third generated light and the light emitted in response to the third excitation light form a light path that is

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spaced laterally from the implant a sufficient distance to avoid significant contribution from implant reporters.

18. The device of claim 12, wherein the implant is embedded in subcutaneous tissue, and the second light source and at least one detector are arranged such that the second optical signal travels a light path that extends to a depth in the tissue greater than or equal to 3 mm under a surface of skin.

19. The device of claim 12, further comprising:

a third light source arranged to transmit third generated light into the tissue; and

at least a second detector arranged to measure, in response to the third generated light, a third optical signal emitted from the tissue, wherein the implant is embedded at a first depth in the tissue, the light sources and detectors are arranged such that the second optical signal travels a light path that extends to a second depth in the tissue, the third optical signal travels another light path that extends to a third depth in the tissue, and the third depth differs from the first and second depths.

20. The device of claim 13, wherein the implant is embedded at a first depth in the tissue, the second light source and at least one detector are arranged such that the second optical signal travels a light path that extends to a second depth in the tissue, and the processor is further programmed to determine the second depth in dependence upon a measurement of at least one analyte-independent signal emitted from the implant.

21. The device of claim 13, wherein the processor is further programmed to determine the corrected signal value by assigning a quantity or weight to the measurement of the second optical signal in dependence upon a measurement of at least one analyte-independent signal emitted from the implant.

22. The device of claim 12, wherein the excitation wavelength range is a first excitation wavelength range, the implant is further capable of emitting, in response to being excited

by light within a second excitation wavelength range, at least one analyte-independent optical signal within a second emission wavelength range, and the device further comprises:

a third light source arranged to transmit third generated light in the second excitation wavelength range through the tissue to the implant, wherein the at least one detector is arranged with the third light source to measure, in response to the third generated light, a third optical signal emitted from the tissue in the second emission wavelength range; and

a fourth light source arranged to transmit a fourth generated light into the tissue, wherein the fourth generated light is substantially within the second emission wavelength range, and wherein the at least one detector is arranged with the fourth light source to measure, in response to the fourth generated light, a fourth optical signal emitted from the tissue.

23. The device of claim 13, wherein the at least one detector is further arranged to measure, in response to third generated light transmitted into the tissue, a third optical signal emitted from the tissue within the excitation wavelength range, and wherein the processor is further programmed to calculate the quantity or concentration of analyte in dependence upon the third optical signal.

24. The device of claim 12, wherein the light sources and at least one detector are arranged in a sensor patch adapted to be placed on a surface of skin.

25. A method, comprising:

sending a first generated light within an excitation wavelength range from a first light emitting diode (LED) of an optical device disposed on a skin of a mammalian body, the first generated light sent through tissue of the mammalian body to an implant embedded in the tissue, the implant configured to absorb light within the excitation wavelength range and fluoresce to emit an analyte-dependent optical signal within an emission wavelength range in response to absorbing light within the excitation wavelength range;

receiving, with at least one detector of the optical device disposed on the skin of the mammalian body and in response to the first generated light being sent through the tissue, a first optical signal emitted from the implant embedded in the tissue within the emission wavelength range;

calculate, with a processor of the optical device disposed on the skin of the mammalian body, an initial value indicative of a concentration of the analyte based on the first optical signal;

sending, from the optical device disposed on the skin of the mammalian body and into the tissue, a second generated light, the second generated light sent from a second LED pre-configured to emit light within the emission wavelength range;

receiving, with the at least one detector and in response to the second generated light, a second optical signal emitted from the tissue within the emission wavelength range;

calculating, with the processor, a correction factor based on the second optical signal, the correction factor indicative of background within the emission wavelength range; and

calculating, with the processor, the concentration of the analyte by applying the correction factor to the initial value indicative of the concentration of the analyte.

26. The method of claim 25, wherein the second optical signal travels a light path that extends to a depth in the tissue that is substantially equal to a depth at which the implant is embedded.

27. The method of claim 26, wherein the depth at which the implant is embedded is in the range of 1 to 5 mm under a surface of skin.

28. The method of claim 25, wherein the second optical signal travels a light path that extends to a depth in the tissue that is greater than a depth at which the implant is embedded.

29. The method of claim 25, wherein the correction factor is a first correction factor and the first generated light, the implant, and the first optical signal collectively define at least a portion of a first light path, the method further comprising:

sending a third generated light from the optical device into the tissue, the third generated light being within the excitation wavelength range;

receiving, with the at least one detector and in response to the third generated light, a third optical signal emitted from the tissue in the emission wavelength range; and

calculating, with the processor a second correction factor based on the third optical signal light, the second correction factor associated with autofluorescence of the tissue, the third generated light and the third optical signal collectively defining at least a portion of the second light path, at least a portion of the second light path spaced laterally from a corresponding portion of the first light path, the concentration of the analyte calculated by applying the first correction factor and the second correction factor to the initial value indicative of the concentration of the analyte.

30. The method of claim 25, wherein:

the implant is embedded in subcutaneous tissue; and

the second generated light travels a light path that extends to a depth in the tissue that is greater than or equal to 2 mm under a surface of skin.

31. The method of claim 25, wherein the implant is embedded at a first depth in the tissue, the second optical signal travels a first light path that extends to a second depth in the tissue, and the correction factor is a first correction factor, the method further comprising:

sending a third generated light from the optical device into the tissue such that the third generated light travels a second light path that extends to a third depth in the tissue, the third depth being different from the first depth and the second depth;

receiving, with the at least one detector and in response to the third generated light, a third optical signal emitted from the tissue; and

calculating with the processor a second correction factor based on the third optical signal the second correction factor associated with the second light path, the concentration of the analyte calculated by applying the first correction factor and the second correction factor to the initial value indicative of the concentration of the analyte.

32. The method of claim 25, wherein:

the excitation wavelength range is a first excitation wavelength range;

the implant is embedded at a first depth in the tissue; and

the second optical signal travels a first light path that extends to a second depth in the tissue, the method further comprising:

sending a third generated light from the optical device into the tissue, the third generated light sent before the second generated light, the third generated light being within a second excitation wavelength range; and

receiving, with the at least one detector and in response to the third generated light, an analyte-independent optical signal-emitted from the tissue; and

determining the second depth using the analyte-independent optical signal.

33. The method of claim 25, wherein the correction factor is a first correction factor, the method further comprising:

receiving, with the at least one detector, an analyte independent optical signal emitted from the implant; and

calculating, with the processor, a second correction factor based on an analyte-independent optical signal emitted from the implant, the concentration of the analyte calculated by applying the first correction factor and the second correction factor to the initial value indicative of the concentration of the analyte.

34. The method of claim 25, wherein the excitation wavelength range is a first excitation wavelength range, the emission range is a first emission range, the implant is configured to emit a signal having a second emission range in response to receiving an excitation signal within the second excitation wavelength range, the initial value is a first initial value, and the correction factor is a first correction factor, the method further comprising:

sending a third generated light from a third LED of the optical device pre-configured to emit light within the second excitation wavelength range through the tissue to the implant;

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receiving, with the at least one detector and in response to the third generated light, a third optical signal emitted from the implant embedded within the tissue within the second emission wavelength range;

calculating, with the processor a second initial value indicative of excitation of the implant by the third generated light based on the third optical signal;

sending a fourth generated light from a fourth LED of the optical device into the tissue, the fourth LED pre-configured to emit light within the second emission wavelength range; and

receiving, with the at least one detector and in response to the fourth generated light, a fourth optical signal emitted from the tissue; and

calculating, with the processor, a second correction factor based on the fourth optical signal, the concentration of the analyte calculated based on the initial value indicative of the concentration of the analyte, the initial value indicative of excitation of the implant by the third generated light, the first correction factor, and the second correction factor.

35. The method of claim 25, wherein the at least one detector is a first detector, the method further comprising:

sending a third generated light from a third LED of the optical device into the tissue, the third LED pre-configured to emit light within the excitation wavelength range;

receiving, with a second detector and in response to the third generated light, a third optical signal emitted from the tissue within the excitation wavelength range, the third LED and the second detector spaced apart from the first LED and the first detector within a housing of optical device such that when the first LED sends the first generated light to the implant, the third LED is spaced apart from the implant and the third optical signal is not sent to the implant;

calculating with the processor, a second correction factor based on the third optical signal, the second correction factor associated with autofluorescence of the tissue, the concentration of the analyte calculated by applying the first correction factor and the second correction factor to the initial value indicative of the concentration of the analyte.

36. A device, comprising:

a sensor patch configured to be placed on a surface of a skin of a mammalian body, the sensor patch including a case;

a first light source disposed within the case and pre-configured to generate a first optical signal within an excitation wavelength range of a luminescent dye to illuminate an implant containing the luminescent dye embedded in tissue of the mammalian body, the luminescent dye configured to emit an analyte-dependent optical signal within an emission wavelength range in response to absorbing light within the excitation wavelength range;

a second light source disposed within the case and pre-configured to generate a second optical signal within the emission wavelength range to illuminate the tissue; and

at least one detector disposed within the case configured to (1) receive a third optical signal emitted from the implant embedded in the tissue, the third optical signal being within the emission wavelength range and emitted by the implant in response to the implant being illuminated with the first optical signal and (2) receive a fourth optical signal in response to the tissue being illuminated by the second optical signal, the fourth optical signal being within the emission wavelength range.

37. The device of claim 36, further comprising at least one processor disposed within the case configured to:

receive data from the at least one detector representative of the third optical signal indicative of a concentration of the analyte and data representative of the fourth optical signal indicative of at least one of diffuse reflectance or scattering of light in the tissue,

calculate a correction factor using the data representative of the third optical signal and the data representative of the fourth optical signal, and

calculate at least one of a quantity or a concentration of analyte by applying the correction factor to the data representative of the third optical signal.

38. The device of claim 36, wherein a distance between the second light source and the at least one detector within the case is substantially equal to a distance between the first light source and the at least one detector within the case such that the first optical signal and the second optical signal each travel a light path that extends to a depth in the tissue that is substantially equal to a depth at which the implant is embedded.

39. The device of claim 36, wherein a distance between the second light source and the at least one detector within the case is greater than a distance between the first light source and the at least one detector within the case such that the second optical signal travels a light path that extends to a depth in the tissue that is greater than a depth at which the implant is embedded.

40. The device of claim 36, wherein the second light source is spaced apart from the at least one detector within the case such that the second optical signal travels a light path that extends to a depth of 1 to 5 mm under a surface of skin.

41. The device of claim 36, wherein the at least one detector includes a first detector, the first detector and the first light source are disposed within a first portion of the case such that the first optical signal and the third optical signal travels a first light path that includes the implant and is associated with the first portion of the case, the device further comprising:

a third light source disposed within a second portion of the case, the third light source pre-configured to generate a fifth optical signal within the excitation wavelength range to illuminate the tissue; and

a second detector disposed within the second portion of the case, the second detector configured to receive a sixth optical signal emitted from the tissue, the sixth optical signal being within the emission wavelength range, the first portion of the case mutually exclusive from the first portion of the case such that the fifth optical signal and the sixth optical signal travel a second light path associated with the second portion of the case that is spaced laterally from the implant when the first light source illuminates the implant such that the sixth optical signal does not include a significant contribution from the implant.

42. The device of claim 36, wherein the implant is embedded in subcutaneous tissue, and the second light source and at least one detector are configured such that the second optical signal travels a light path that extends to a depth in the tissue greater than or equal to 3 mm under a surface of skin.

43. The device of claim 36, wherein the at least one detector includes a first detector, the first detector and the second light source spaced a first distance apart within the case such that the

second optical signal and the fourth optical signal collectively define a first light path that extends to a first depth in the tissue, and the implant is embedded at a second depth in the tissue, the device further comprising:

a third light source disposed within the case and configured to generate a fifth optical signal to illuminate the tissue; and

a second detector disposed within the case and configured to receive a sixth optical signal emitted from the tissue, the third light source and the second detector spaced apart within the case a second distance different from the first distance such that the fifth optical signal and the sixth optical signal collectively define a second light path that extends to a third depth in the tissue, the second depth differing from the first depth and the third depth.

44. The device of claim 36, wherein the implant is embedded at a first depth in the tissue, the second light source and at least one detector are collectively configured such that the second optical signal travels a light path that extends to a second depth in the tissue, the device further comprising:

a processor disposed within the case configured to:

receive data representative of an analyte-independent optical signal emitted from the implant, and

determine the second depth using the data representative of the analyte-independent signal.

45. The device of claim 37, wherein the processor is further configured to:

receive data representative of an analyte-independent optical signal emitted from the implant, and

calculate the correction factor using the data representative of an analyte-independent optical signal.

46. The device of claim 36, wherein:

the analyte-dependent optical signal is a first analyte-dependent optical signal;

the emission wavelength range is a first emission wavelength range;

the excitation wavelength range is a first excitation wavelength range;

the luminescent dye is a first luminescent dye configured to emit the first analyte-dependent optical signal within the first emission wavelength range in response to absorbing light within the first excitation wavelength range;

the implant includes a second luminescent dye configured to emit an analyte-independent optical signal within a second emission wavelength range in response to absorbing light within a second excitation wavelength range, the device further comprising:

a third light source disposed within the case and pre-configured generate a fifth optical signal within the second excitation wavelength range to illuminate the implant, the at least one detector configured to receive a sixth optical signal emitted from the implant, the sixth optical signal being within the second emission wavelength range and emitted from the implant in response to the implant being illuminated with the fifth optical signal; and

a fourth light source disposed within the case and pre-configured to generate a seventh optical signal within the second emission wavelength range to illuminate the tissue, the at least one detector configured to receive an eighth optical signal in response to the tissue being illuminated by the seventh optical signal.

47. The device of claim 37, wherein:

the at least one detector is further configured to receive a fifth optical signal in response to the tissue being illuminated by a sixth optical signal, the sixth optical signal within the excitation wavelength range; and

the processor is further configured to calculate the correction factor using data representative of the fifth optical signal.

48. The device of claim 36, wherein the first light source and the second light source are light emitting diodes.

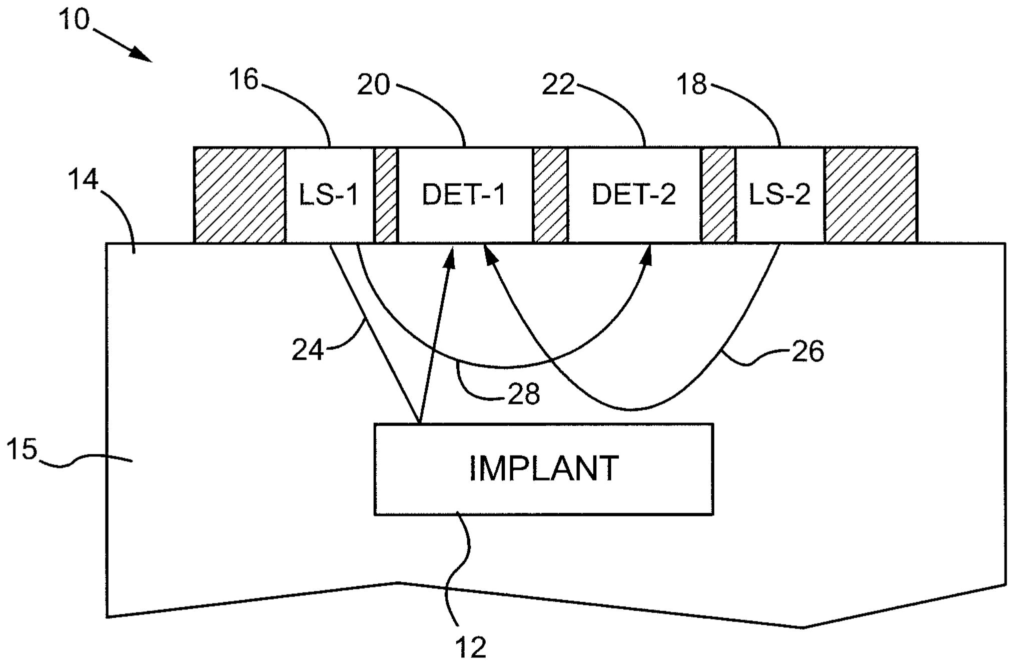
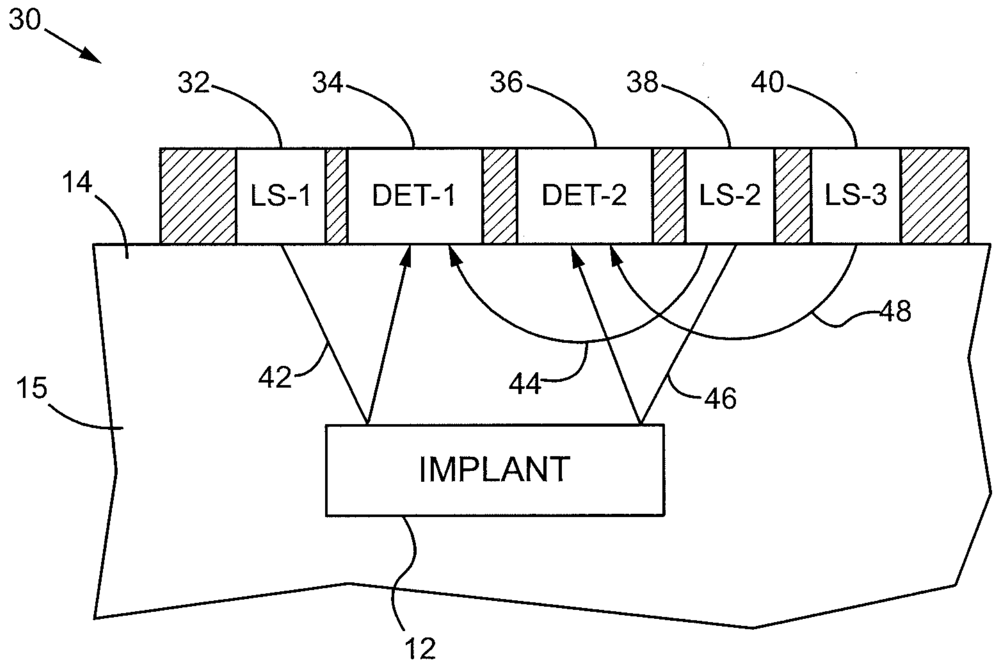


Fig. 1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38
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DET-1
DET-2
LS-2
LS-3
48
42
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46
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IMPLANT
12

Fig. 2

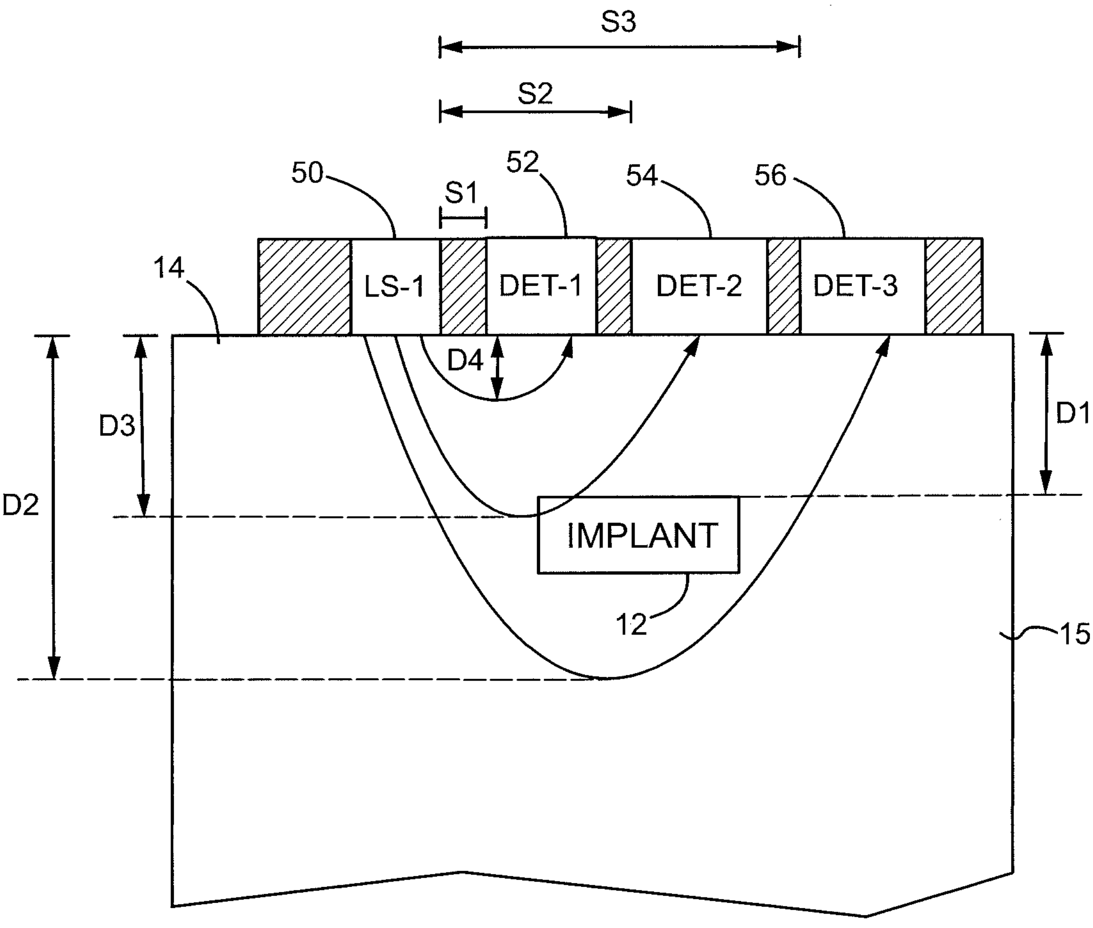
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Fig. 3

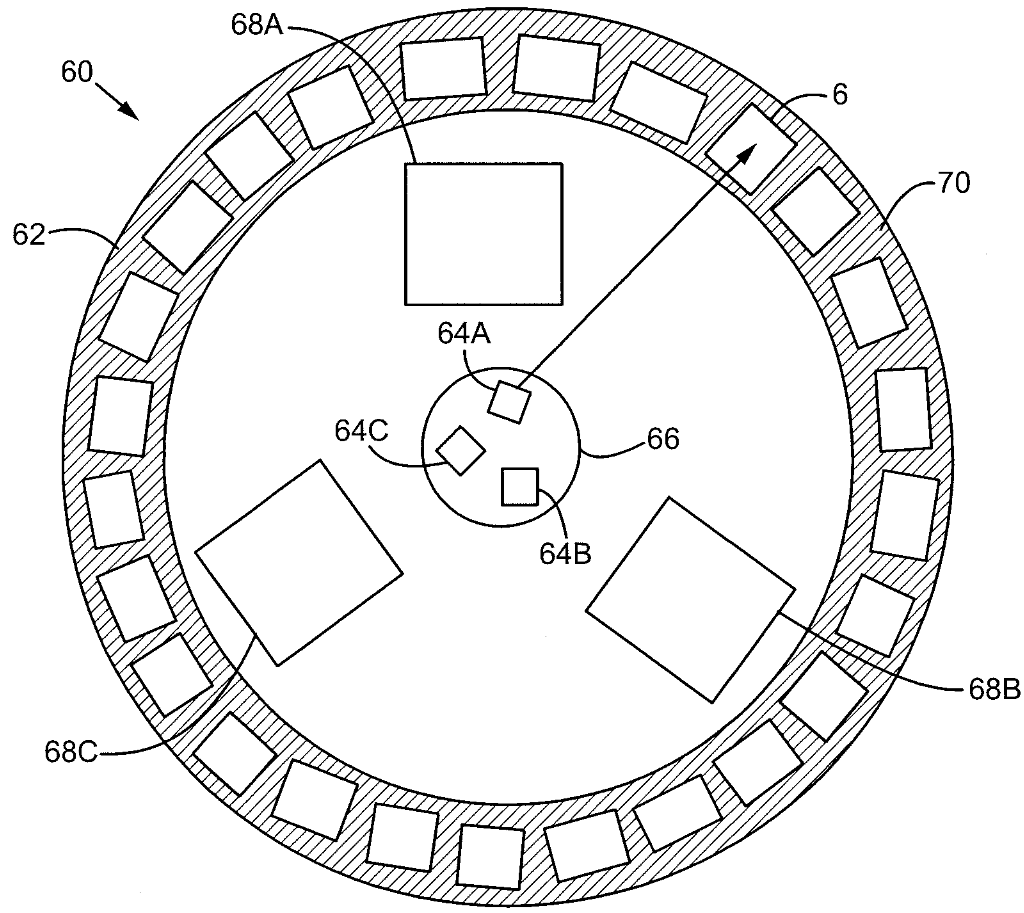

Fig. 4

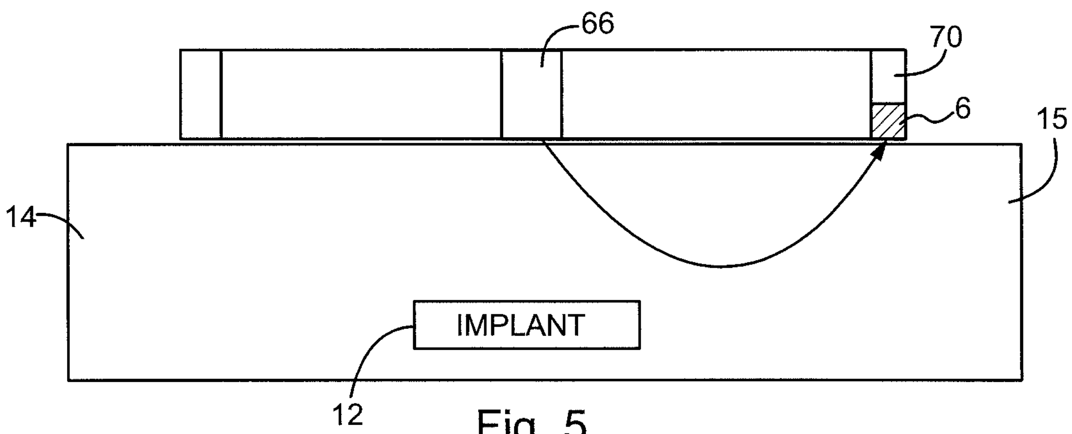

Fig. 5

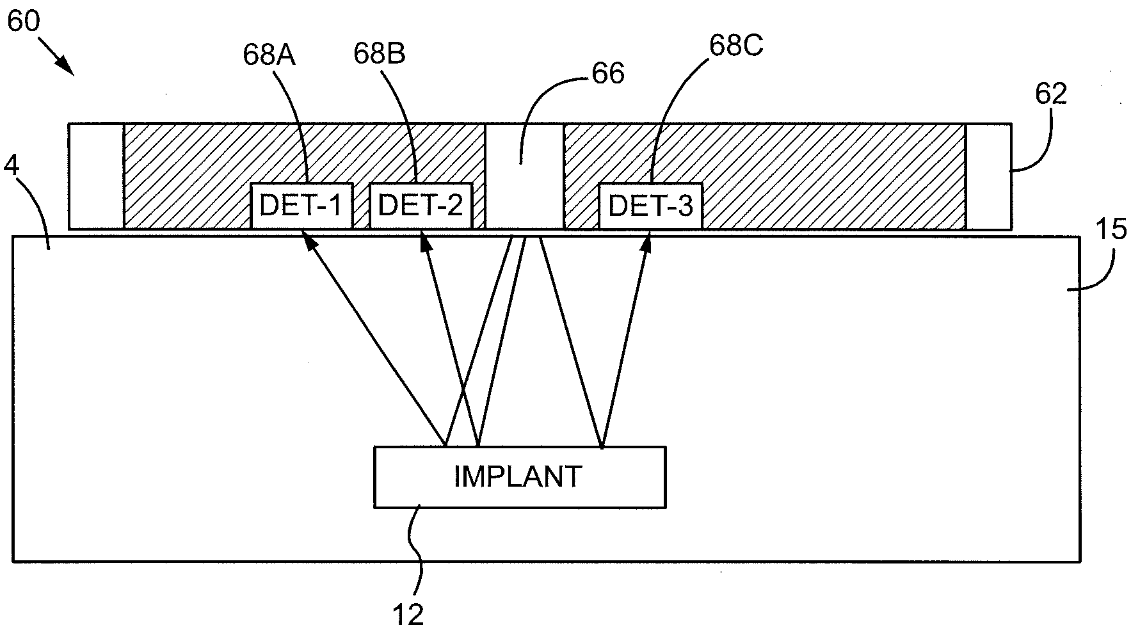

Fig. 6

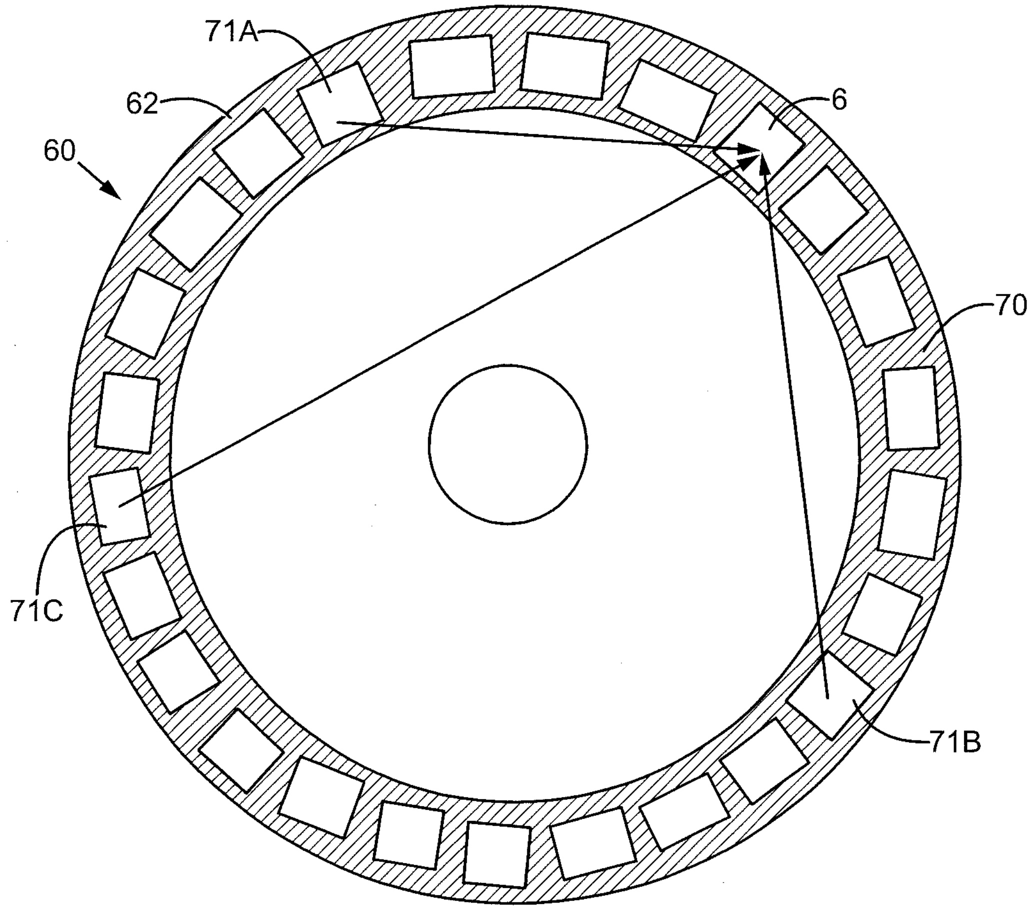

Fig. 7

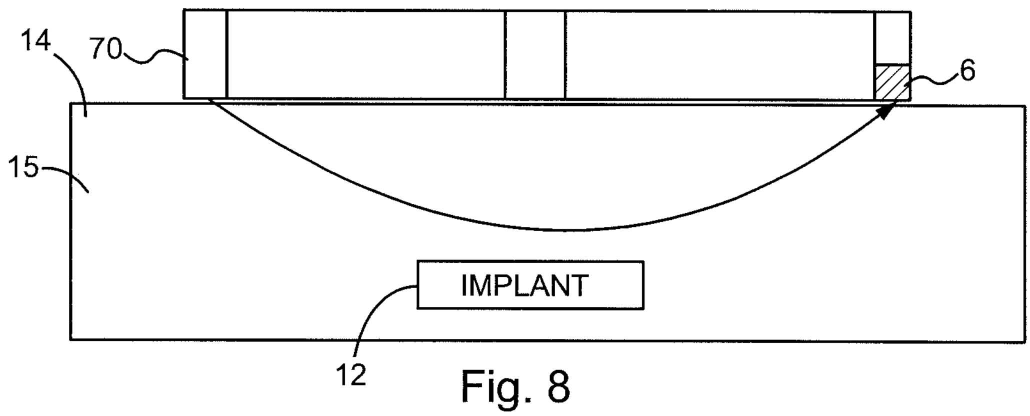

Fig. 8

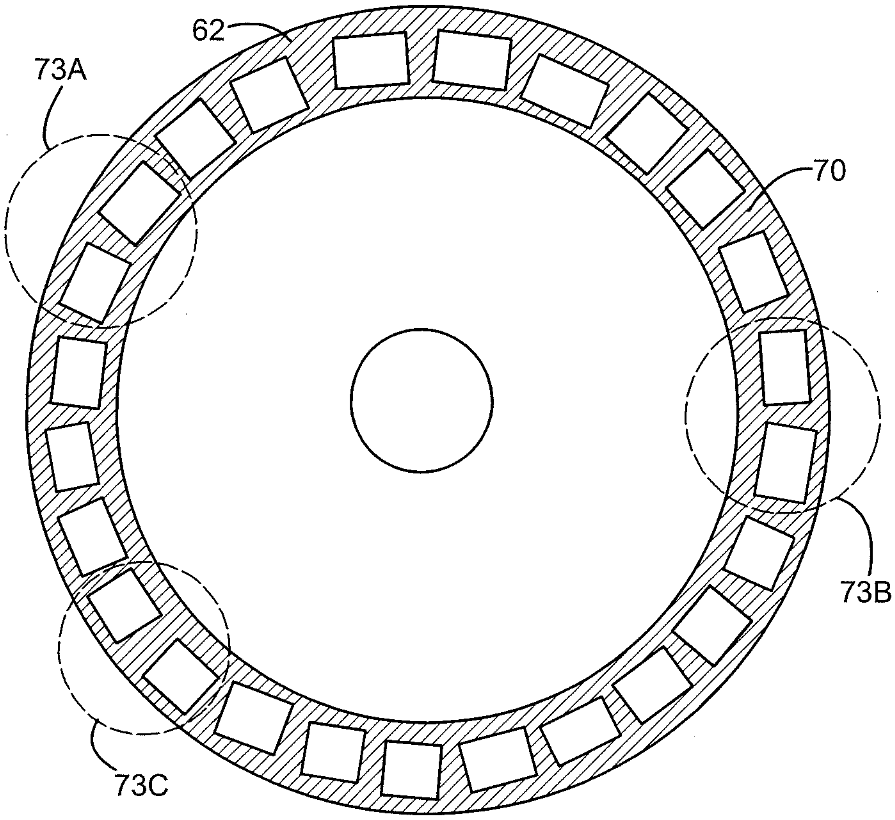

Fig. 9

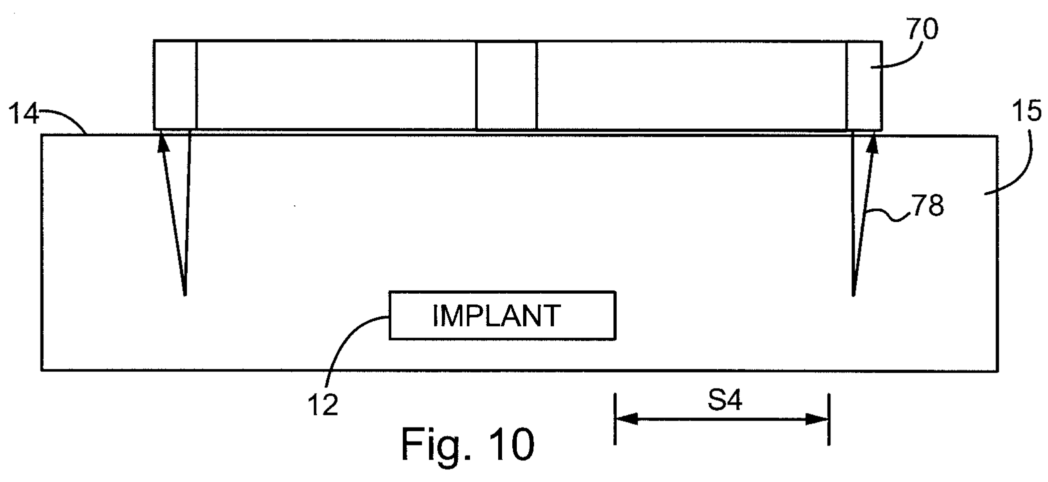

Fig. 10

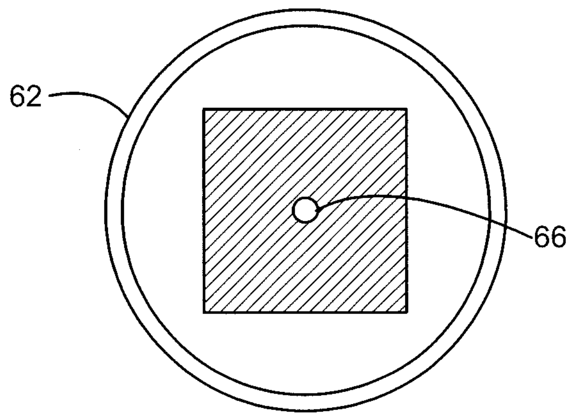

Fig. 11

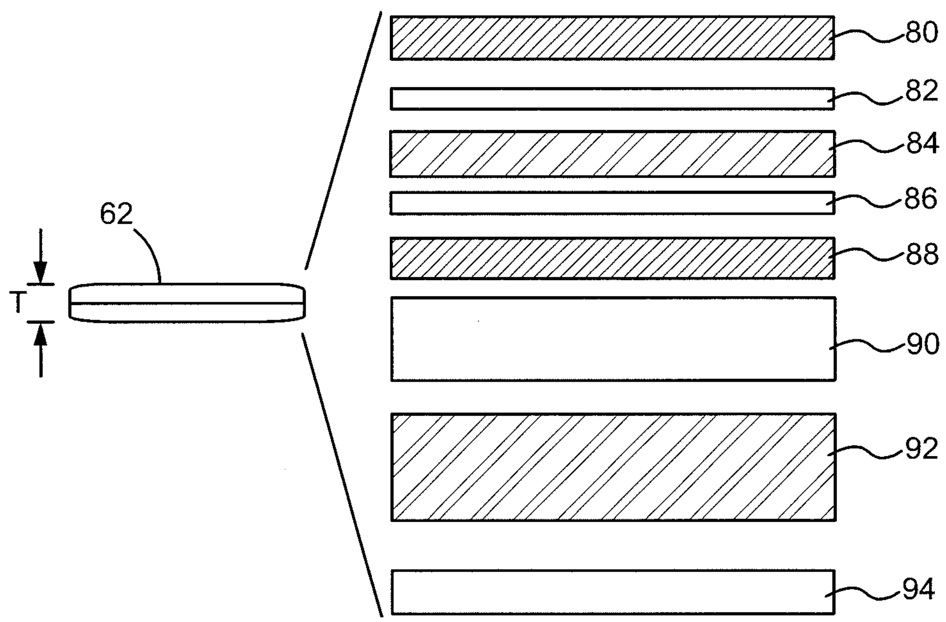

Fig. 12