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(54) LUMINESCENCE BASED NONINVASIVE
REMOTE PARAMETER SENSOR AND
SENSING METHOD

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CPC *A61B 5/01* (2013.01); *A61B 5/0071*
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(58) **Field of Classification Search**
CPC A61B 5/01; A61B 5/015; G01K 13/002
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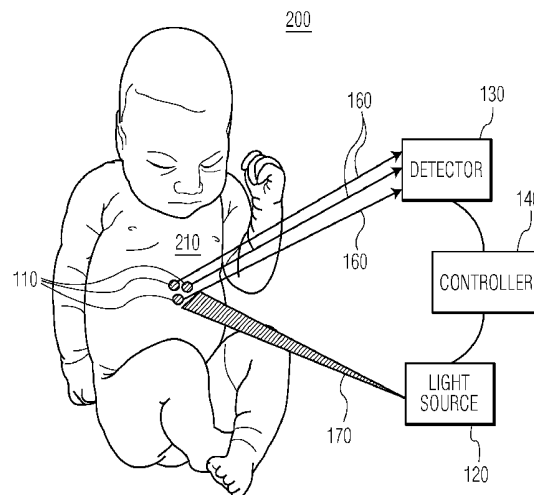
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(57) **ABSTRACT**

A noninvasive remote parameter sensor and sensing method is provided that is particularly suited for the remote monitoring of skin temperature. The sensor and sensing method utilize luminescence-based sensors that are non-toxic and non-irritating to the skin. The sensor preferably utilizes one or more types of fluorophores that are embedded in a soft hydrogel. The sensor is illuminated with excitation light, and temperature is monitored by detecting and analyzing the emission light from the fluorophores. Because a soft hydrogel is used, the sensor can be gently wiped off the skin at the conclusion of temperature measurements.

18 Claims, 10 Drawing Sheets



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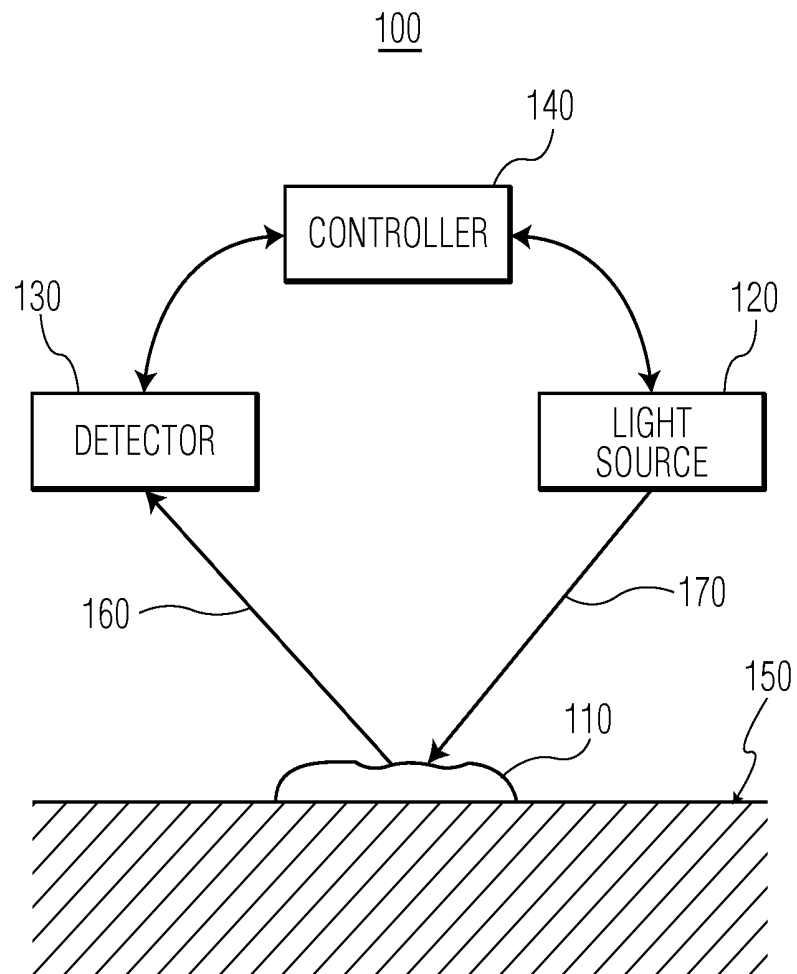


FIG. 1

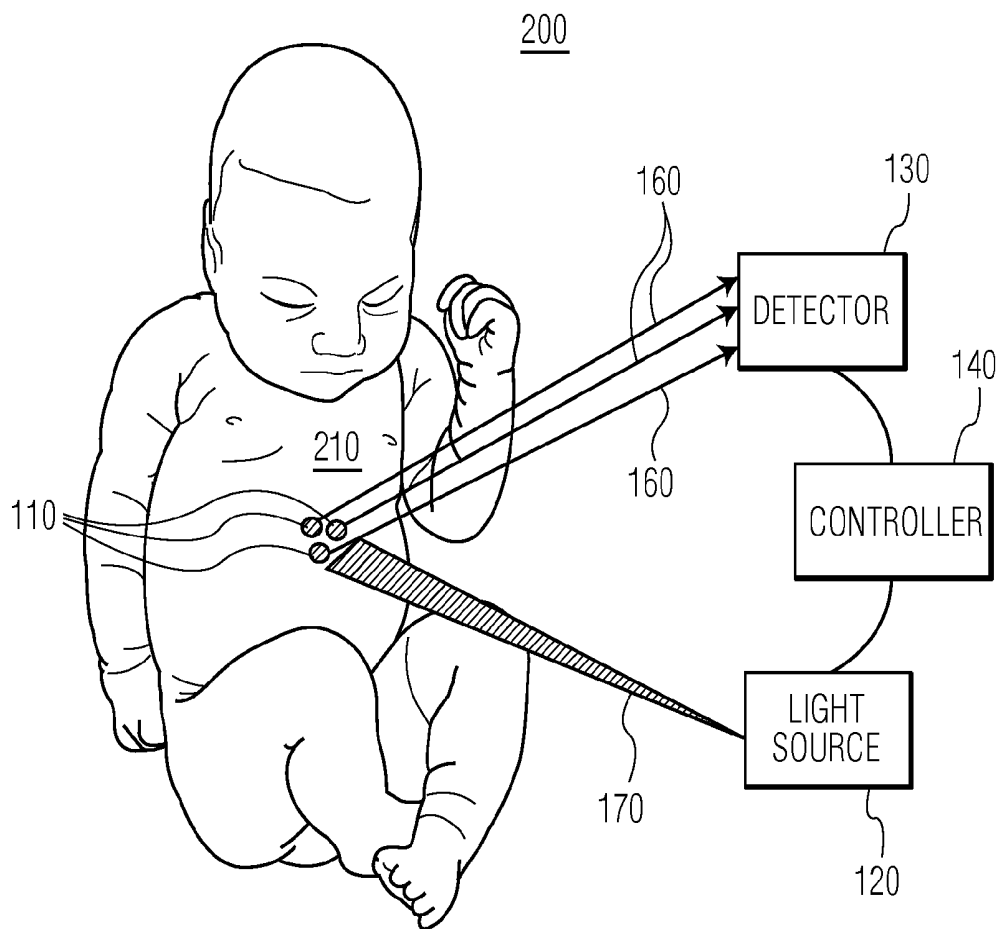


FIG. 2

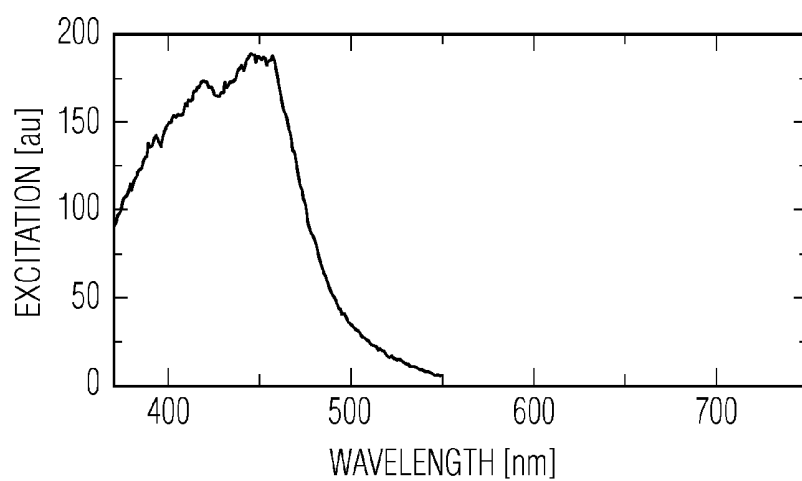


FIG. 3A

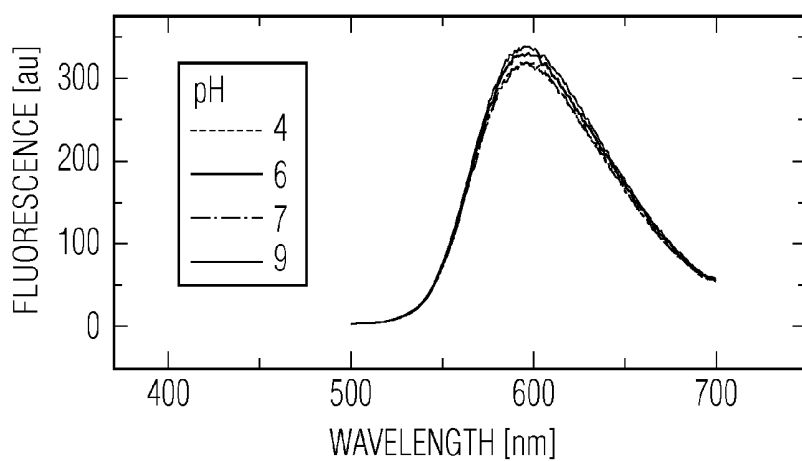


FIG. 3B

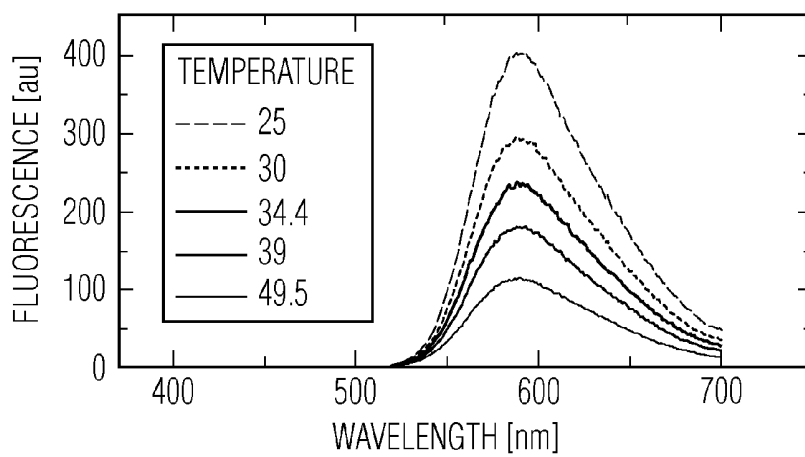


FIG. 3C

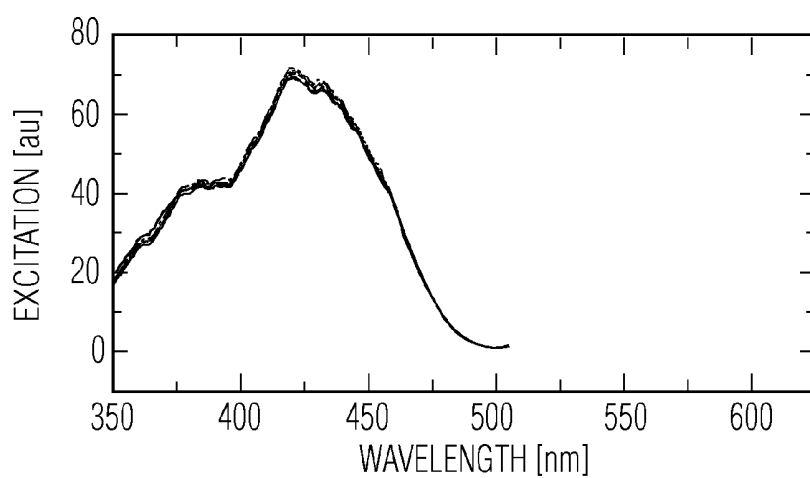


FIG. 3D

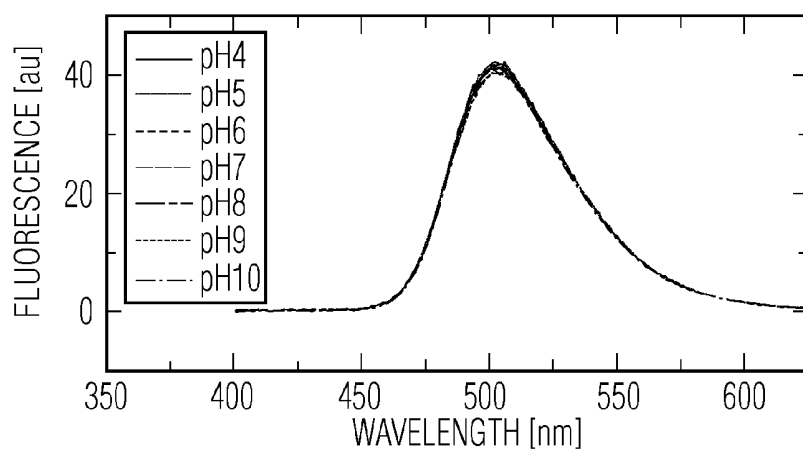


FIG. 3E

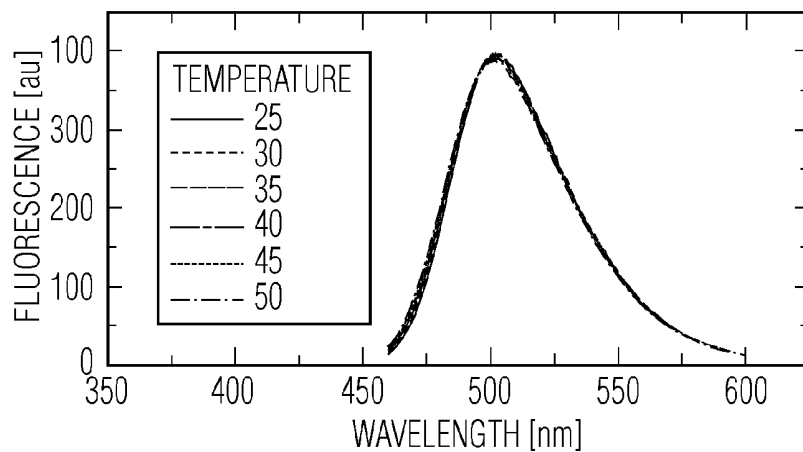


FIG. 3F

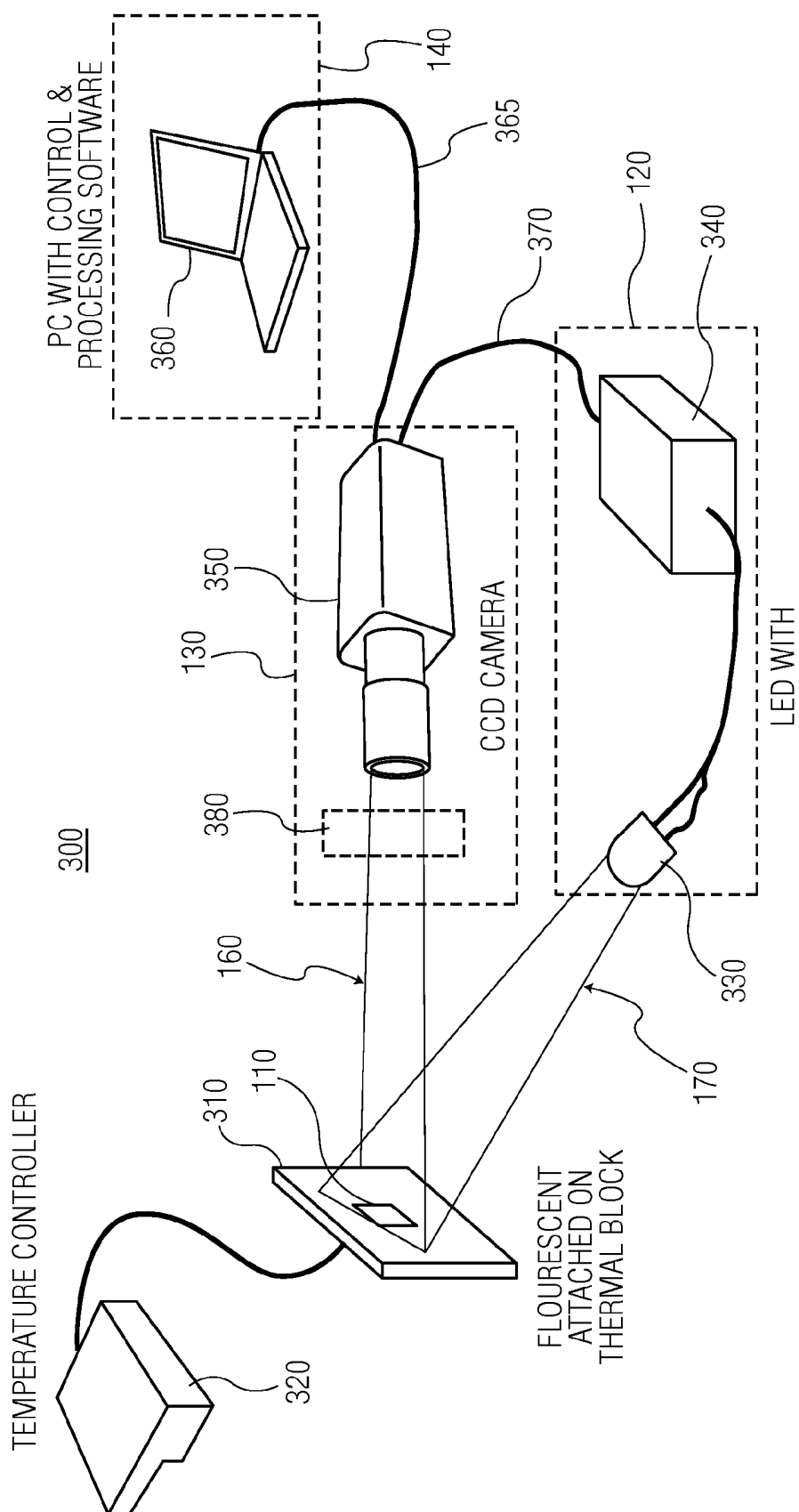


FIG. 4

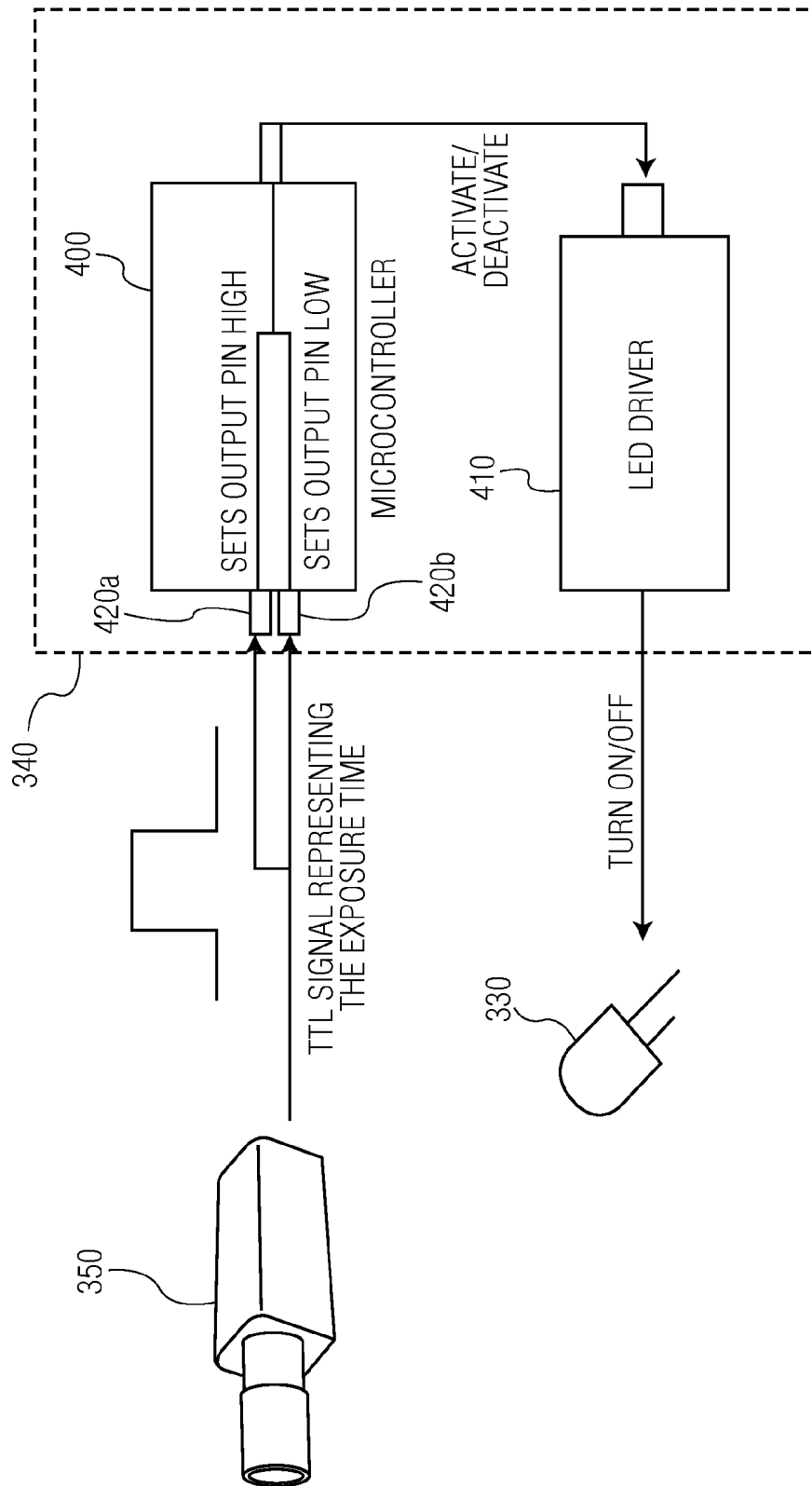
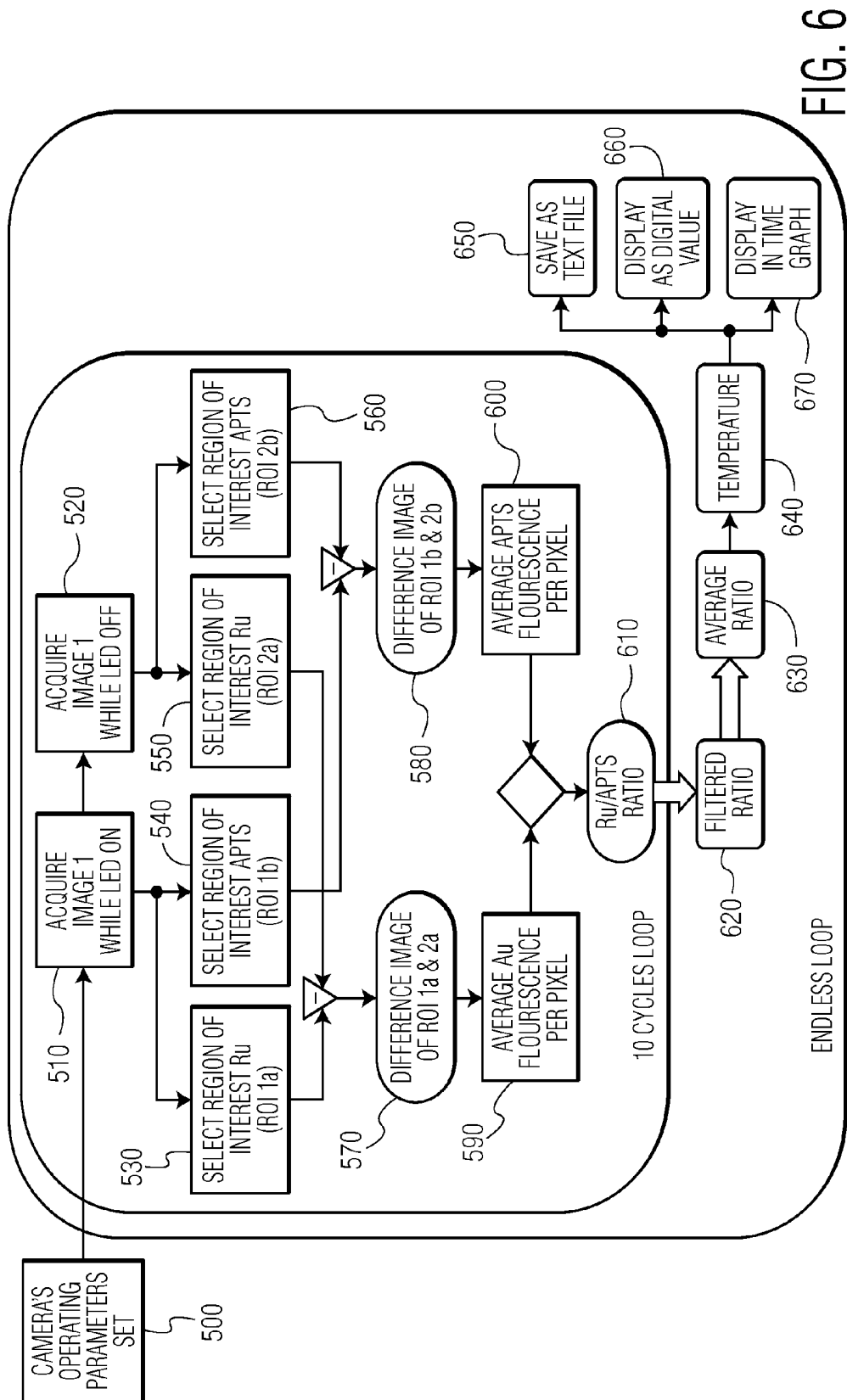


FIG. 5



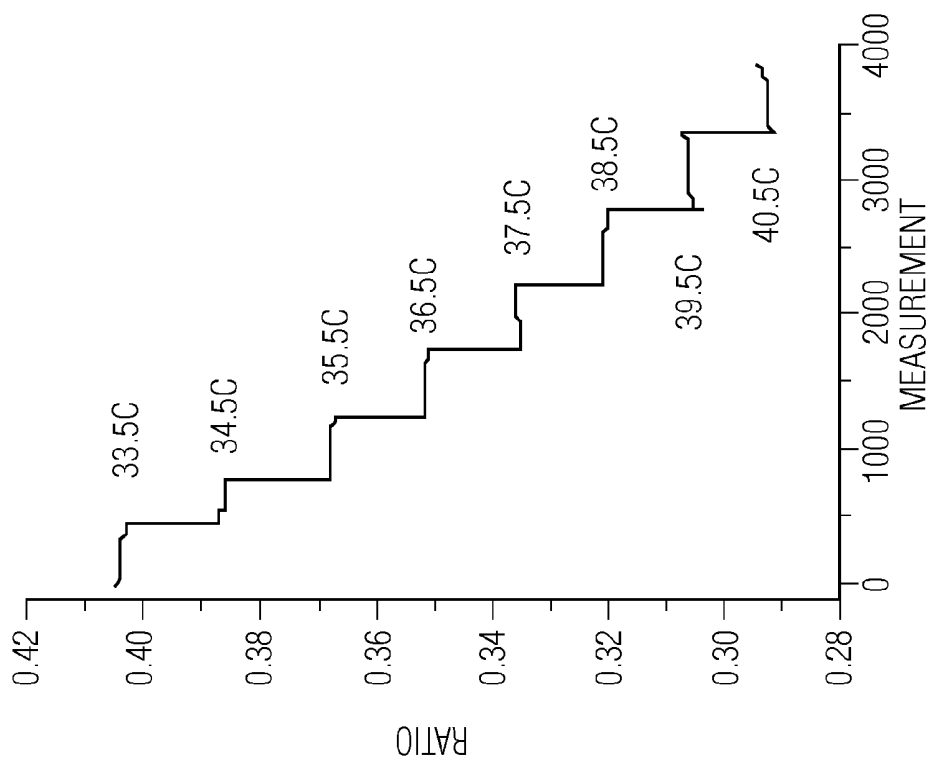


FIG. 7A

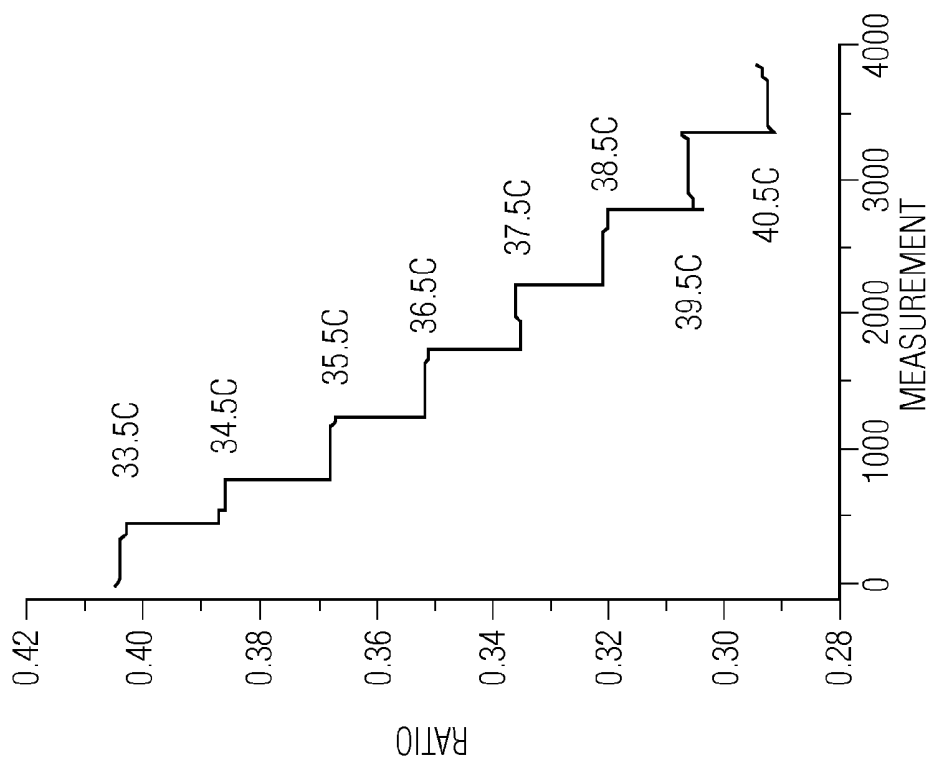


FIG. 7B

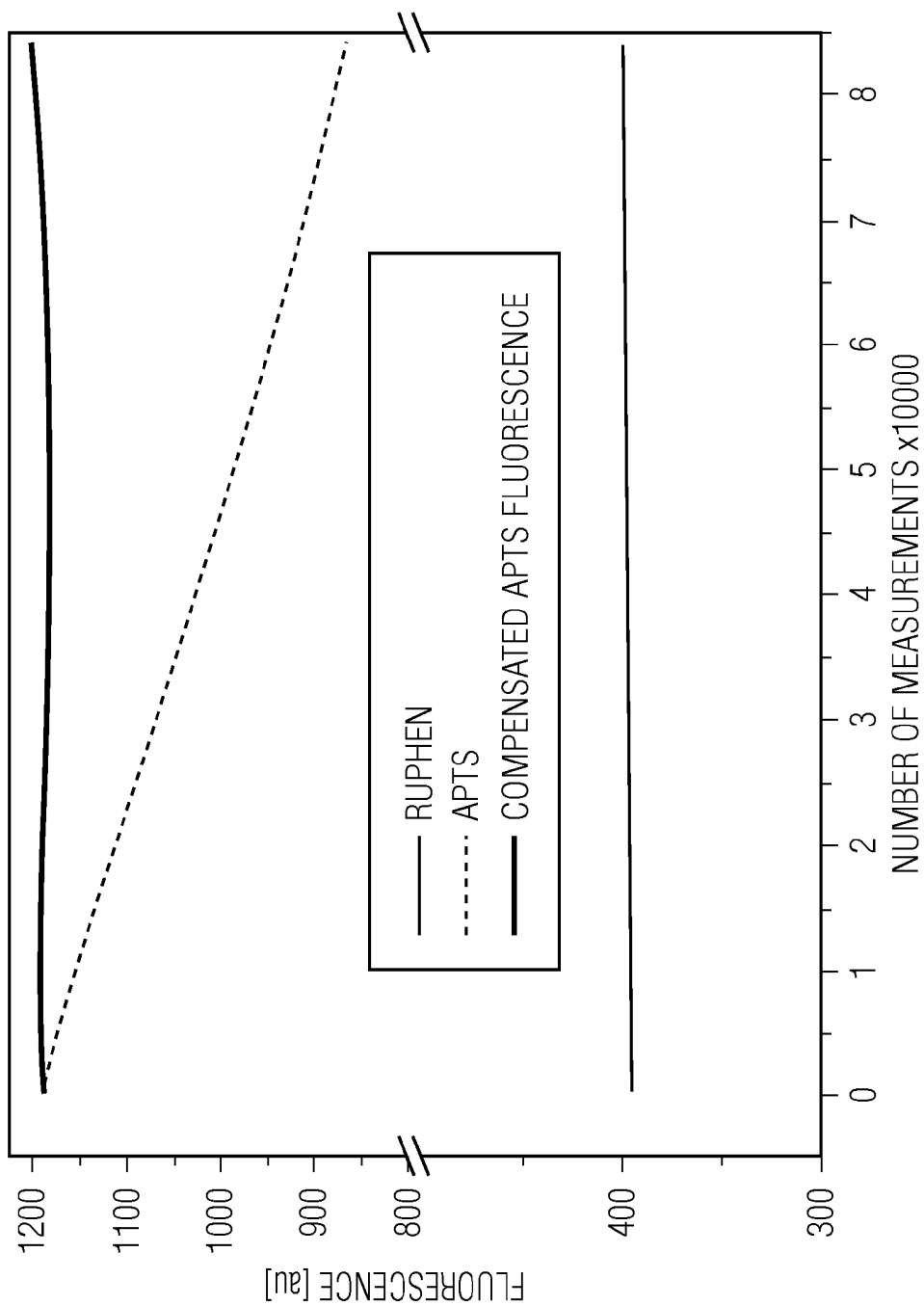


FIG. 8

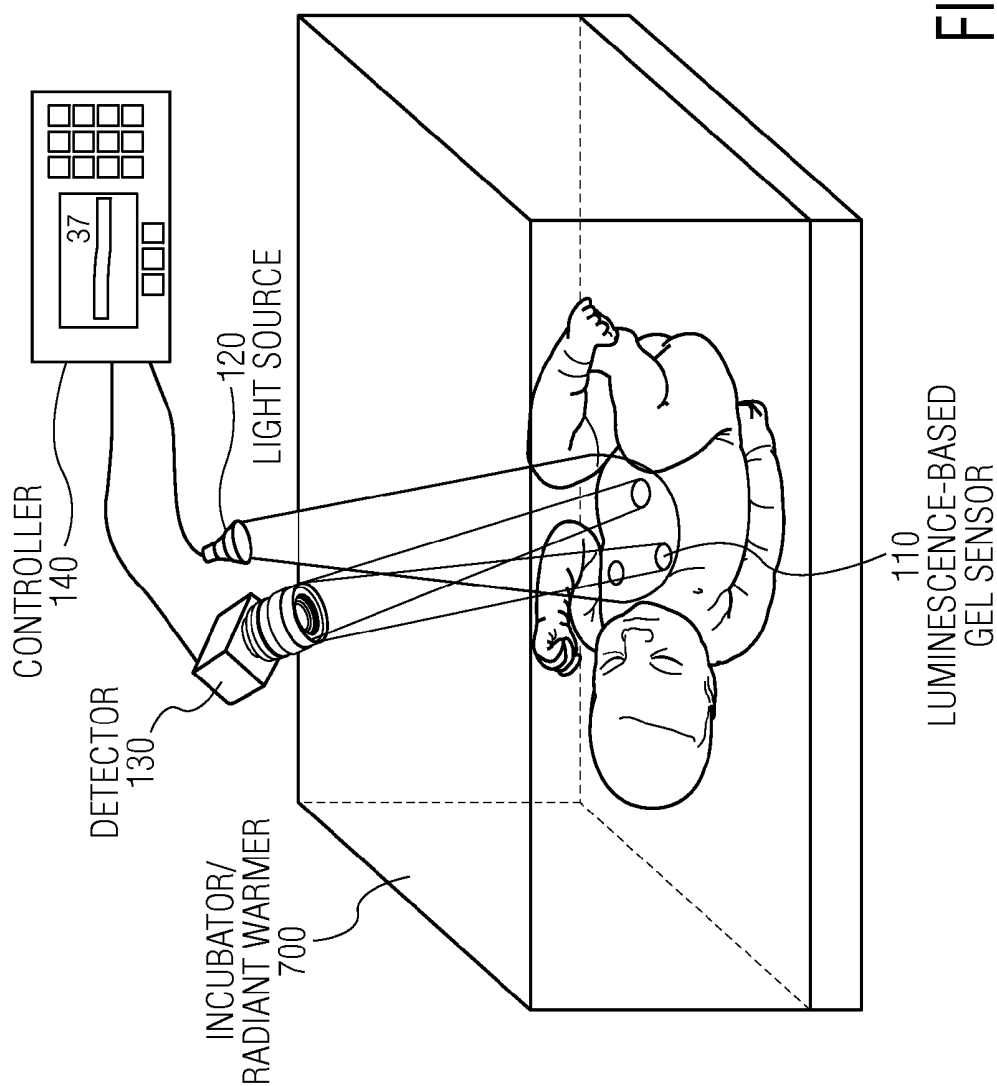


FIG. 9

LUMINESCENCE BASED NONINVASIVE REMOTE PARAMETER SENSOR AND SENSING METHOD

This application is a continuation-in-part of U.S. patent application Ser. No. 13/501,081, filed Apr. 9, 2012. This application also claims priority to U.S. Provisional Application Ser. No. 61/502,542, filed Jun. 29, 2011, whose entire disclosure is incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the noninvasive, remote sensing of predetermined parameters such as, for example, remote sensing of human body temperature.

2. Background of the Related Art

Internal body temperature is a physiologic variable that is precisely controlled by the body. Chemical processes and enzymes required to catalyze the associated chemical reactions, thereby regulating cellular function, optimally operate within this narrow thermal bandwidth. Thermoregulation encompasses all physiological processes and responses that balance heat production and heat loss to maintain body temperature within this normal range. Compared to the adult or older pediatric model, thermoregulation is even more critical to neonatal care.

Compared to adults, newborns are particularly vulnerable to temperature extremes. If heat loss is not preempted, newborns could suffer the ill effects of cold stress or hypothermia. Depending on the gestational age, mortality may increase by 10% for each degree Celsius ($^{\circ}$ C.) that a baby's body temperature is below 36° C. Conversely, at relatively high temperatures, infants may be subjected to the dangers of heat stress or hyperthermia. Both types of thermal stresses, hypo- and hyperthermia can be a significant cause of morbidity and mortality in this vulnerable population. Thus, in the hospital setting, infant incubators are designed to keep the infant in an environment of constant temperature.

Nonetheless, providing optimal thermal conditions to the newborn require the body temperature to be measured. To date, wired thermistors are conventionally employed that are attached to a neonate's skin using a strong adhesive to keep them in place. However, adhesive use on the thermistor probe cover is not an innocuous intervention. Investigations have shown increased microbial growth beneath probe covers, some of which have proved to be pathogenic. Others have found skin impairment ranging from chemical sensitivities to prolonged mechanical force on the skin from some adhesives. Adhesives can irritate the skin by occlusion or by altering the skin morphology via epidermal stripping. The removal of adhesively-attached skin temperature probes can result in "skin tears" in which shear or frictional forces separate the dermis from the epidermis.

These tears can compromise skin barrier function, cause a marked increase in transepidermal water loss and, in many cases, disrupt the skin's ability to protect against microorganism invasion. Especially for extremely premature neonates, the adhesive poses a high potential risk of injury due to their immature skin. Studies have shown that at 24 weeks gestation, premature neonates have little stratum corneum and attenuated rete ridges. Their skin is red, wrinkled, translucent, and gelatinous in appearance. They lack subcutaneous tissue, therefore, their dermis is lying directly over the muscle. Consequently, skin stripping secondary to adhesive dressing and/or tape removals can result in full-thickness tissue loss.

Even at 36 weeks (full term), the epidermal and dermal layers of neonates, although structurally similar to an adult, are just up to 60% as thick as those in an adult. As a result, epidermal stripping secondary to tape and adhesive dressing removal is most common in neonates born before 27 weeks gestation and is the primary cause of skin breakdown in the Neonatal Intensive Care Unit (NICU). Given the neonate's attenuated rete ridges, adhesive products typically bond more aggressively to the epidermis than the epidermis does to the dermis. Consequently, epidermal stripping is not only a source of discomfort, but can also lead to other morbidity in very low birth weight neonates and those who are immune-compromised.

Skin friendly adhesives that can hold the wired probe in place while minimizing trauma to the skin have not yet been developed. Alternative temperature probes that can eliminate adhesives also are nonexistent. In addition, remote thermal-imaging systems that may offer non-adhesive, non-contact features and a resolution of 0.3° C. are still too expensive for general use in the NICU.

SUMMARY OF THE INVENTION

An object of the invention is to solve at least the above problems and/or disadvantages and to provide at least the advantages described hereinafter.

Therefore, an object of the present invention is to provide a system and method for the remote sensing of a parameter, such as temperature, in a non-invasive and/or non-contact manner.

Therefore, an object of the present invention is to provide a system and method for the remote sensing of a parameter, such as temperature, in a non-invasive and/or non-contact manner.

Another object of the present invention is to provide a system and method for remotely measuring body temperature in a non-invasive and/or non-contact manner.

Another object of the present invention is to provide a system and method for remotely measuring the body temperature of an infant in a non-invasive and/or non-contact manner.

Another object of the invention is to provide a luminescence-based temperature sensor and sensing method;

Another object of the invention is to provide a luminescence-based gel sensor that can be gently applied to and removed from human skin;

To achieve at least the above objects, in whole or in part, there is provided a noninvasive remote sensor for measuring a parameter of a system, comprising a gel, and a first type of fluorophore embedded in the gel, wherein the first type of fluorophore emits first emission light in response to excitation light, and wherein a chemical property of the type of fluorophores is such that at least one characteristic of the first emission light varies as a function of changes in the parameter being measured.

To achieve at least the above objects, in whole or in part, there is also provided a sensor for remotely monitoring the temperature of an object, comprising a gel adapted to be applied to the object, and a first type of fluorophore embedded in the gel, wherein the first type of fluorophore emits first emission light in response to excitation light, and wherein a chemical property of the first type of fluorophore is such that at least one characteristic of the first emission light varies as a function of temperature.

To achieve at least the above objects, in whole or in part, there is also provided a method of monitoring skin temperature, comprising applying a luminescence-based gel sensor

to skin, wherein the luminescence-based gel sensor comprises a first type of fluorophore embedded in a gel, illuminating the luminescence-based gel sensor with excitation light, detecting emission light from the first type of fluorophore, and determining the skin temperature based on the detected emission light.

Additional advantages, objects, and features of the invention will be set forth in part in the description which follows and in part will become apparent to those having ordinary skill in the art upon examination of the following or may be learned from practice of the invention. The objects and advantages of the invention may be realized and attained as particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described in detail with reference to the following drawings in which like reference numerals refer to like elements wherein:

FIG. 1 is a schematic diagram of a noninvasive remote parameter sensing system that utilizes a luminescence-based sensor, in accordance with one embodiment the present invention;

FIG. 2 is a system for remotely monitoring body temperature that utilizes a luminescence-based gel sensor, in accordance with one embodiment the present invention;

FIG. 3A is a plot of the excitation spectrum of Ruphen;

FIG. 3B is a plot of the emission spectrum of Ruphen at different pH values;

FIG. 3C is a plot of the emission spectrum of Ruphen at different temperatures;

FIG. 3D is a plot of the excitation spectrum of APTS;

FIG. 3E is a plot of the emission spectrum of APTS at different pH values;

FIG. 3F is a plot of the emission spectrum of APTS at different temperatures;

FIG. 4 is a schematic diagram of a system used to measure the effect of temperature on a luminescence-based gel sensor made up of a Ruphen containing hydrogel and an APTS containing hydrogel, in accordance with one embodiment of the present invention;

FIG. 5 is a schematic diagram of one preferred embodiment of the LED controller shown in FIG. 4;

FIG. 6 is a flowchart showing preferred key functional steps executed by the controller 140 for a scenario where the Ruphen containing hydrogel and APTS containing hydrogel that make up the luminescence-based gel sensor are positioned adjacent to each other or otherwise spatially separated from each other, such their emission signals are spatially separated when they reach the detector;

FIG. 7 are plots showing the ratio of fluorescence intensity of Ruphen to APTS as a function of temperature;

FIG. 8 is a plot showing the decrease in fluorescence of Ruphen and APTS due to bleaching effects; and

FIG. 9 is a schematic diagram of an incubator/radiant warmer that incorporates a remote body temperature sensing system, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

By way of example, the present invention will be described in connection with a noninvasive remote temperature sensor and sensing method that is particularly suited for the remote sensing of skin temperature in infants. However, it should be appreciated that the present invention can be

used as a remote sensor for other types of parameters such as, for example, CO₂, pH, ammonia, oxygen, sodium, calcium and potassium.

Throughout the specification, the terms luminophore and fluorophore are used interchangeably and both refer to a chemical compound that re-emits light upon light excitation.

The present invention utilizes luminescence-based sensing. In a preferred embodiment for temperature sensing, a temperature sensing luminophore is incorporated in a soft hydrogel that can then be applied gently on human skin. The adhesion on the skin is strong enough that it does not fall off, but can also be gently wiped off at the conclusion of temperature measurements.

A variety of luminophores have been found to show high sensitivity to temperature. The luminescence intensities and decay times of these compounds decrease with increasing temperatures and can be measured with a high degree of accuracy. Thus, many luminophores have been previously utilized as luminescent temperature probes. However, most of these are not suitable for healthcare applications, particularly neonatal healthcare applications. As an example, alexandrite crystals have been found to be sensitive between 15°-45° C., and the phosphorescence decay time decreases from 300 to 220 microseconds within this range. The long decay time is easy to precisely measure with low cost instrumentation. While these properties may seem appropriate for healthcare applications, alexandrite crystals cannot be ground to a fine powder for application on human skin. Additionally, the grinding process creates defects on the crystal structure which render alexandrite non-luminescent.

Many other materials, such as zinc sulfide and lanthanide phosphors (e.g., La₂O₂S:Eu) also show strong temperature sensitivity over the desired range of temperatures. The lanthanide phosphors also show desirable lifetime changes as the temperature changes. Unfortunately, all of these luminophores are only excitable by UV light, which is potentially harmful to human skin, particularly neonatal skin.

In contrast to UV-excited materials, there are classes of luminophores that are excitable by visible light, such as ruthenium(II) tris(1, 10-phenanthroline) (Ruphen) and ruthenium(II) tris(bipyridine) (Rubpy). These dyes are not only highly luminescent, but their luminescence intensity and decay times are also very sensitive to temperature. Moreover, they have been found to be nontoxic and incapable of penetrating human skin.

These dyes that are excitable with visible light have been widely employed as temperature probes in various research fields. Luminescence-based temperature probes have a variety of advantages over thermoelectric probes, including immunity to high electromagnetic fields, the suitability for long distance measurements, and virtually unlimited spatial resolution. For instance, luminophores can be employed in thermal convection studies in both huge bioreactors and micro-sized lab-on-a-chip environments. Furthermore, since light transmission requires no conducting medium, the probe and the photodetector need not to be in direct contact. Accordingly, remote detection can be realized. Due to the advantages of luminescence sensors, a number of luminescence-based temperature probes have been developed.

FIG. 1 is a schematic diagram of a noninvasive remote parameter sensing system 100 that utilizes a luminescence-based sensor 110, in accordance with one embodiment of the present invention. The remote parameter sensing system 100 includes a luminescence-based sensor 110, a light source 120, a detector 130 and a controller 140. The luminescence-based sensor 110 is in contact with a surface 150 where the

parameter, such as temperature, is to be measured, and is preferably a gel that is embedded with a chemical that emits light **160**, via luminescence, when it is excited by excitation light **170** from the light source **120** at an appropriate excitation frequency. The chemical properties of the luminescence-based sensor **110** are such that at least one characteristic of the emission light **160** (such as, for example, emission intensity) varies as a function of variations in the parameter being measured.

The controller **140** controls the measurement process, including control of the light source **120**, receiving detector signals from the detector **130** and processing and analyzing the detector signals to analyze the parameter being measured.

FIG. 2 is a schematic diagram of a system **200** for remotely and noninvasively monitoring body temperature utilizing one or more luminescence-based gel sensors **110**, in accordance with another embodiment of the present invention. The system **200** includes a light source **120**, detector **130**, controller **140**, and at least one luminescence-based gel sensor **110** placed on the skin **210** of the subject whose temperature is being measured.

The luminescence-based gel sensors **110** are preferably applied onto multiple sites on the subject's skin **210**. The luminescence-based gel sensors are illuminated from a distance with excitation light **170** from light source **120**, and the emission light **160** is detected by detector **130**. The detector signals are then analyzed by controller **140**. In one preferred embodiment, the detector **130** is a movable CCD camera and the controller **140** is programmed with shape recognition software for controlling the position of the CCD camera to follow the luminescence-based gel sensors **110** as the subject moves.

The temperature sensing system **200** offers many advantages of over existing systems. First, there is no need for problematic adhesives to keep the luminescence-based gel sensors **110** in place. It is very easy to daub the luminescence-based gel sensors **110** on the skin **210**, and the luminescence-based gel sensors **110** can be removed easily by gentle wiping with a wet tissue. Thus, the skin **210** will not be exposed to any stress associated with applying and removing an adhered probe.

Another advantage is the flexibility of the luminescence-based gel sensors **110**. For example, luminescence-based gel sensors **110** can be smeared anywhere and at multiple points on the subject. In contrast, taking temperature readings at multiple points with wired thermistors can be very cumbersome, and creates the added danger of an infant getting caught in a tangle of wires. Further, as the luminescence-based gel sensors **110** are always in close contact with the skin **210**, optimal heat transfer from the skin **210** to the luminescence-based gel sensors **110** are ensured at all times, thereby increasing the accuracy of the temperature measurement and its correlation to core body temperature.

While temperature sensing luminophores have been used in the art, they require UV light excitation, which is not acceptable for humans (particularly infants), or they emit light in the IR wavelength range where radiant warmers will interfere. The luminescence-based gel sensors **110** in system **200** are preferably designed to be excited with and emit light in the visible wavelength range.

As discussed above, the luminescence-based gel sensors **110** are preferably temperature sensitive nontoxic luminophores in a hydrogel matrix. The preferred properties of the luminophores and hydrogel matrix will now be discussed.

In general, there are three approaches for measuring temperature: (1) steady state luminescence intensity mea-

surements; (2) ratiometric intensity measurements; and (3) decay time measurements. The simplest is approach (1), which measures the steady state luminescence intensity. However, this approach is not suitable for long term measurements, as the intensity can drift due to photobleaching of the luminophore. Methods (2) and (3) offer solutions to this problem.

Approach (2) takes the intensity ratio of two emission bands of the luminophore system to represent the temperature. Assuming the photobleaching effect has the same impact on the emission bands, the ratio is unaffected, thereby making the system less prone to drift.

Approach (3) utilizes the decay time of the luminophore as the temperature sensitive parameter. The decay time is the time span required for the luminophore dye at the excited state to return to the electronic ground state. This transition is temperature dependent. Since it is an intrinsic property of the dye molecule, the temperature measurement based on the decay time technique is entirely independent of the luminophore concentration.

The luminescence process is initiated by the absorption of light by the ground state luminophore, and in the process promoting the molecule to an electronic excited state. The ruthenium luminophores mentioned above (Ruphen and Rubpy) undergo intersystem crossing from the lowest singlet excited state to the triplet state (technically a singlet-triplet hybrid), which is normally at a lower energy. Return of the triplet to the singlet ground state requires intersystem crossing, i.e. a "forbidden" process. This explains both the long decay lifetimes, as well as the red-shifted emission.

In a preferred embodiment, the luminescence-based gel sensor **110** is made up of two different types of fluorophores in a hydrogel matrix. The two fluorophores are preferably Ruphen and 8-aminopyrene-1,3,6-trisulfonic acid ("APTS").

The luminophores Ruphen and APTS are an ideal fluorophore pair for ratiometric temperature measurement. In Ruphen, the ruthenium ion Ru(II) forms an octahedral complex with three phenanthroline molecules. The complex has a strong absorption band at around 450 nm due to the very prominent metal to ligand charge transfer transition (MLCT) to the triplet MLCT state that is energetically slightly lower than the triplet d-d state. The transition from the MLCT state to the ground state results in emission of light (at 590 nm) whereas the promotion to the d-d state by thermal energy leads to the radiationless decay to the ground state. These two processes compete at any given temperature. Hence, less fluorescence emission is observed at higher temperatures and vice versa.

APTS, on the other hand, is a polycyclic aromatic compound consisting of 4 fused benzene rings. The excitation maximum is at around 420 nm in aqueous solution, whereas the emission peak is located at 500 nm. As shown on FIGS. 3A and 3D, both dyes can be excited by visible blue light, which is harmless to human skin and, therefore, acceptable for use on humans. Additionally, an inexpensive but efficient LED can be employed as a single excitation light source **120**.

The emission peaks of Ruphen (FIGS. 3B and 3C) and APTS (FIGS. 3E and 3F) are about 90 nm apart. Accordingly, they can be easily isolated with the appropriate filters. Moreover, the fluorescence of Ruphen and APTS are only slightly affected by pH, as shown in FIGS. 3B and 3E, respectively. This is important, as the skin of neonates at different gestational ages have varying pH levels.

More importantly, ambient temperature has varying impacts on the fluorescence of the two dyes. On the one

hand, as shown in FIG. 3C, the fluorescence intensity of Ruphen drops drastically by 75 percent when the ambient temperature is changed from 25° C. to 50° C. The significant temperature sensitivity in the physiological range makes Ruphen an ideal body temperature sensor. On the other hand, the same temperature change has virtually no impact on the fluorescence of APTS, as shown in FIG. 3F. Thus, APTS makes a very good reference sensor for Ruphen in ratiometric temperature measurements.

As discussed above, there is a need for remote and non-adhesive temperature sensing for infants. To this end, the luminescence-based gel sensor **110** preferably utilizes a skin-friendly vehicle or matrix for the luminophore dyes. The matrix in which the sensing luminophores are incorporated is a replacement for the harmful adhesive currently used to keep thermistors in place.

The matrix provides several important functions. It is the affixing component that enables contact of the luminophore dyes with the skin **210**. It encapsulates the dyes within a semi-solid structure preventing the dyes from being blown off (if powder) or wiped off (if liquid) from the skin **210**. The matrix also provides good heat transfer from the skin/body to the temperature sensing luminophore dyes, allowing for precise body temperature measurements to be carried out.

In order to be used as a temperature sensor on a human subject, the matrix should be biocompatible, should not harbor harmful microorganisms and should be non-irritating to the skin **210**. Also, the matrix should not excessively absorb heat from the radiant warmer in the incubator or other sources, as this can cause a temperature reading higher than the skin temperature. Further, while the matrix should adhere well to the skin **210**, it should be easily removable without irritating or harming the skin **210**.

During the last two decades, significant advances have been made in the development of biocompatible and biodegradable materials for biomedical applications. In the biomedical field, the goal is to develop and characterize artificial materials for use in the human body to measure, restore, and improve physiologic function, and enhance survival and quality of life.

Typically, inorganic (metals, ceramics, and glasses) and polymeric (synthetic and natural) materials have been used for such items as artificial heart-valves, (polymeric or carbon-based) and synthetic blood-vessels. However, the preferred matrix for the luminophores are hydrogels.

Hydrogels are a network of polymer chains that are water-insoluble and are highly absorbent. They can contain over 99% water, which makes them highly flexible like natural tissue. Applications for hydrogels cover a wide range of fields. For example, polylactic acids are used as scaffolds in tissue engineering, 2-hydroxypropyl-methacrylate polymers (HPMA) has been widely employed in drug delivery systems, and polyacrylic acid is used as the super-absorbent in disposable diapers. In addition, contact lenses are made from silicone or polyacrylamide (15).

Of particular interest are hydrogels used for wound dressings, as they have the desired properties suitable for the sensitive skin of neonates. As such, they create or maintain a moist environment so that the skin **210** cannot dry out. They are well permeable to oxygen, so that the skin **210** underneath can breathe. In addition, these hydrogels protect wounds from the entry of microbes. Moreover, they adhere firmly even on the wounds, and can be gently removed without irritation.

Glyceryl polyacrylate (GPA) and chitosan are the subjects of active research as antibacterial wound dressing gels. Chitosan is a linear polysaccharide composed of randomly

distributed β -(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine produced commercially by de-acetylation of chitin, the structural element in the exoskeleton of crustaceans (crabs, shrimp, etc.) and cell walls of fungi. The amino group in chitosan has a pKa value of ~ 6.5 , thus, chitosan is positively charged and soluble in acidic to neutral solution with a charge density dependent on pH and the deacetylation value. This makes chitosan and its derivatives a bio-adhesive which readily binds to negatively charged surfaces, such as mucosal membranes.

Chitosan and its derivatives are approved to be hypoallergenic and antibacterial. Its high tensile and bioadhesive strength are advantageous for forming a tacky sensing layer. Further, it can be gently dissolved by a slightly acidic solution at pH 6.0.

Glyceryl polyacrylate (GP) is a clathrate gel known for its high water retention ability. It does not dry even when exposed to ambient air or subjected to vacuum for 48 hours. This property is particularly useful for inactivating microbes by depriving them of water through osmotic effect. Studies show that by adding a certain amount of glycerol, the viscosity of the gel can be controlled. This results in a product that can adhere well on the skin **210** but that can also be easily peeled off.

For at least the reasons set forth above, chitosan gel is preferably used as the hydrogel matrix in the luminescence-based gel sensor **110**. The chitosan gel is preferably prepared as follows. Chitosan (medium molecular weight, Sigma) is dissolved in 0.1 M acetic acid (Sigma) to make a 2% w/v gel. To each gram of this gel, 0.5 g glycerol is added. To prepare the gels containing the fluorophores, 0.1 g of silica gel adsorbed with either Ruphen or APTS is added to 1 gram of the chitosan. The luminescence-based gel sensor **110** preferably includes both a Ruphen containing gel and an APTS containing gel.

The present invention preferably uses ratiometric measurements to measure temperature using the luminescence-based gel sensor **110**. The ratiometric method has the advantage that the imaging system, as well as the data acquisition and processing system, need not be very sophisticated and fast. However, two luminescence signatures need to be measured to arrive at the ratio.

FIG. 4 is a schematic diagram of a system **300** used to measure the effect of temperature on a luminescence-based gel sensor **110** made up of a Ruphen containing hydrogel and an APTS containing hydrogel. The system **300** includes a thermal block **310** on which the luminescence-based gel sensor **110** is placed. A temperature controller **320** is used to control the temperature of the thermal block **310**. A light source **120** that includes an LED **330** and an LED controller **340** is used to generate excitation light **170**. A detector **130** that includes a CCD camera **350** is used to detect the emission light **160** from the luminescence-based gel sensor **110**. For a luminescence-based gel sensor **110** made up of a Ruphen containing hydrogel and an APTS containing hydrogel, the LED is preferably a blue LED with an excitation peak at 475 nm.

The CCD camera **350** is controlled by controller **140**. Controller **140** includes a computer **360** that is connected to the CCD camera **350** via cable **365**. The CCD camera **350** transmits image data to and receives control commands from the computer **360**. The CCD camera **350** is connected to the LED controller **340** via cable **370**. The CCD camera **350** sends a timing signal to the LED controller **340** representing the time the CCD camera **350** makes an exposure. This timing signal is used to switch the LED **330** on and off.

If the Ruphen containing hydrogel and APTS containing hydrogel that make up the luminescence-based gel sensor **110** are mixed together or are otherwise not spatially separated from each other, then the emission light from the Ruphen and the emission light from the APTS will spatially overlap at the CCD camera **350**. In this scenario, two different band pass filters must be used to isolate the Ruphen and APTS emission light. This can be suitably implemented incorporating a switchable band pass filter **380** in detector **130** that switches between a first band pass filter designed to pass the emission light from the Ruphen and a second band pass filter designed to pass the emission light from the APTS. The switchable filter **380** can be, for example, a filter wheel.

Another approach to discriminate between two spatially overlapping emission signals is a technique based on the decay time difference between two luminophores. When a luminophore is exposed to intensity modulated excitation light, the observed luminescence intensity is dependent on the modulation frequency ω and the luminophore decay time τ . This dependency is described by the following equation: $f = s / (1 + \omega^2 \tau^2)^{-0.5}$, where s is the steady state luminescence intensity of the fluorophore, ω is the angular modulation frequency and τ is the decay time.

According to this equation, the modulated luminescence decreases with increasing modulation frequencies, eventually reaching a certain frequency where the luminescence is completely diminished (i.e., demodulated). The longer the decay time, the lower this boundary frequency is.

Suppose there are two luminophores in a system with a decay time difference of three orders of magnitude. When the system is excited with modulated excitation light at a frequency where the luminescence of the dye with longer decay time is demodulated, only the luminescence of the dye with shorter decay time will be observed.

At a lower frequency, emission from both the luminophores will be observed. Thus, one can calculate the ratio of the emission at the higher and lower excitation frequencies as an alternative to intensity ratios at two wavelengths. This technique has been successfully exploited for the determination of glucose and glutamine using fluorescently labeled periplasmic binding protein sensors.

Decay time measurements usually require sophisticated and fast performing imaging systems. Conventional methods use multi-channel plate (MCP) based image intensifiers. Unfortunately, MCPs are comparatively expensive, prone to photo-damage due to overexposure and require elaborate electronics. Moreover, MCP's spatial resolution is relatively low. Furthermore, MCPs can inject a comparatively high noise level in the measurement.

If the decay time technique is used, the controller **140** of system **300** preferably utilizes lock-in imaging for decay time measurements. This enables decay time measurements for a fraction of the cost and space of an MCP. The decay time can be determined by a phase modulation technique. In this approach, the luminescence modulated with a frequency ω is phase shifted in comparison to the excitation light. The phase shift ϕ is dependent on the decay time τ by the relation $\tau = \tan(\phi) / \omega$.

The phase shift can be determined with images from the CCD camera **350** as follows: Images are taken with phase delays (relative to the modulated excitation light) of $0, 0.5\pi, \pi$ and 1.5π . The phase shift is calculated as $\phi = \arctan[(S_{1.5\pi} - S_{0.5\pi}) / (S_0 - S_\pi)] - \phi'$, where ϕ' is the instrumental phase delay which can be estimated by measuring the reflected exci-

tation light. This technique is immune to interference from ambient light, which ensures precise temperature measurements.

If the Ruphen containing hydrogel and APTS containing hydrogel that make up the luminescence-based gel sensor **110** are positioned adjacent to each other or otherwise spatially separated from each other such their emission signals are spatially separated when they reach the CCD camera **350**, and the CCD camera **350** can simultaneously image the emission light from both the Ruphen and APTS without the need for the switchable band pass filter **380**. In this mode of operation, the LED **330** is switched on and off by the CCD camera **350** as follows.

As shown in FIG. 5, the LED controller **340** preferably includes a microcontroller **400** and an LED driver **410**. The IO-port of the CCD camera **350** is connected to two external interrupt pins **410a** and **420b** on the microcontroller **400**. The first interrupt responds to the rising edge of the camera output signal. The microcontroller **400** activates the current source by setting its PWM input pin at high, which then turns the LED **330** on. The second interrupt is responsive to the falling edge and turns the LED **330** off. Further, the microcontroller **400** is preferably programmed to turn on the LED **330** on every second camera signal. This enables the camera to take alternately one image with LED excitation light and one image with no LED excitation light, which is important for the cancellation of noise caused by ambient light.

The controller **140** in FIGS. 1, 2 and 4 above, as well as FIG. 9, discussed below, preferably includes control and image analysis software. This control and image analysis software can be suitably implemented with the LabVIEW programming platform (LabVIEW 2010+Vision module) sold by National Instruments.

FIG. 6 shows the preferred key functional steps of the control and image analysis software for the scenario where the Ruphen containing hydrogel and APTS containing hydrogel that make up the luminescence-based gel sensor **110** are positioned adjacent to each other or otherwise spatially separated from each other, such their emission signals are spatially separated when they reach the CCD camera **350**. The process starts at step **500**, where the CCD camera **350** is set at continuous acquisition mode (typically 30 frames per second), the CCD camera **350** exposure time is preferably set to 16 ms and the CCD camera **350** resolution is preferably set at 640×480 .

At steps **510** and **520**, two sequential image frames are acquired from the CCD camera **350**. As discussed above, the LED controller **340** ensures the first image frame is with the LED **330** off and the second image frame is with the LED **330** on. In this way, the first image frame corresponds to the intensity of the ambient light only, while second image frame corresponds to the intensity of the ambient light plus the fluorescence from the luminescence-based gel sensor **110**.

At steps **530** and **540**, the process identifies the regions in the first image frame that correspond to the Ruphen emission (ROI **1a**) and the APTS emission (ROI **1b**), respectively. At steps **550** and **560**, the process identifies the regions in the second image frame that correspond to the Ruphen emission (ROI **2a**) and the APTS emission (ROI **2b**), respectively.

At step **570**, pixel values for ROI **1a** are subtracted from pixel values for ROI **2a**. At step **580**, pixel values for ROI **1b** are subtracted from pixel values for ROI **2b**. This effectively reduces or eliminates the contribution of ambient light to the pixel values, such that only the contribution from the Ruphen and APTS fluorescence emission remain.

Then, at steps 590 and 600 the average Ruphen fluorescence and APTS fluorescence per pixel, respectively, is calculated. This is suitably done by extracting the images of the Ruphen and APTS fluorescent gels, and then manually setting the spatial coordinates of the Ruphen and APTS fluorescent gel images.

At step 610, the ratio of the average Ruphen fluorescence per pixel to the average APTS fluorescence per pixel is calculated. At step 620, the ratio is preferably subjected to a 90 point moving average filter, which minimizes possible influence of rapid changes in illumination (e.g., people walking close the luminescence-based gel sensor 110). This moving average filtering yields an average ratio 630.

This average ratio is then linearly scaled to temperature at step 640. The temperature value can then be saved as a text file (step 650), displayed as a digital value on a digital display (step 660) and/or displayed as a time graph (step 670). The user has the option to change various parameters including, but not limited to, the exposure time of the CCD camera 350 (frame rate), the resolution of the CCD camera 350, the parameters of the digital filtering step 620.

The system 300 of FIG. 4 was used to determine the effect of temperature changes on the luminescence-based gel sensor 110. As shown in FIG. 7, within a physiologically relevant temperature range, the ratio of the fluorescence intensity of Ruphen and APTS correlates linearly to the temperature of the thermal block 310. Based on this data, the luminescence-based gel sensor 110 has a resolution of 0.0032° C.

Photobleaching is an intrinsic property of the luminophores and is influenced by the presence of oxidants, such as oxygen. Since the luminescence-based gel sensor 110 employs two different luminophores, their bleaching rates will differ from one another. As shown in FIG. 8, the fluorescence of APTS drops almost linearly by 25% from its original value after 8 hours of illumination, while the fluorescence of Ruphen remains virtually unchanged. This divergence could lead to a significant drift of the measurement signal if no compensation measures are undertaken. To correct this discrepancy, a compensation loop is preferably implemented in the control and image analysis software. The compensation algorithm takes into consideration the exposure time of the luminophore to the blue LED excitation light and compensates for the drop of the APTS fluorescence. It is also assumed that the ambient oxygen concentrations are constant within the duration of the measurements. As can be seen in FIG. 8, the software compensated for the decrease in fluorescence of APTS over an 8-hour period to a satisfactory extent. The average compensated value is 1189.9 and its standard deviation is ± 4.21 .

The luminescence-based gel sensor 110 of the present invention is particularly suitable as a remote body temperature sensing system in incubators and radiant warmers 700 for infant and neonatal care, as shown in FIG. 9. Temperature measurements can be taken remotely without the need for the standard adhesive thermistors that can irritate or damage the baby's skin. The luminescence-based gel sensors 110 are easy to apply and remove without the risk of damaging the baby's skin. Further, the luminescence-based gel sensors 110 do not require a wired connection, thereby eliminating the risk of the baby getting tangled in wires. In addition, because the remote body temperature system can operate in the visible spectrum, there is no detector interference from the radiant warmers used in incubators and radiant warmers.

The foregoing embodiments and advantages are merely exemplary, and are not to be construed as limiting the

present invention. The present teaching can be readily applied to other types of apparatuses. The description of the present invention is intended to be illustrative, and not to limit the scope of the claims. Many alternatives, modifications, and variations will be apparent to those skilled in the art. Various changes may be made without departing from the spirit and scope of the invention, as defined in the following claims. For example, although the luminescence-based gel sensors have been described in connection with a remote body temperature sensing system, it can be adapted for the remote sensing of other parameters by choosing the appropriate light sources and luminescence-based gel sensors.

What is claimed is:

1. A noninvasive remote sensor for measuring temperature, comprising:

at least a first gel;

a first type of fluorophore embedded in at least the first gel, wherein the first type of fluorophore emits first emission light via luminescence in response to first excitation light, wherein the luminescence of the first type of fluorophore varies as a function of temperature;

a second type of fluorophore embedded in at least the first gel that also contains the first type of fluorophore, wherein the second type of fluorophore emits second emission light via luminescence in response to second excitation light, wherein the luminescence of the second type of fluorophore varies as a function of temperature;

a light detector positioned to detect the first and second emission light, wherein the light detector generates at least one detector signal corresponding to the first and second emission light, wherein at least one characteristic of the at least one detector signal represents both at least one parameter of the first emission light of the first emission light and at least one parameter of the first emission light; and

a process controller in communication with the light detector, wherein the process controller determines a temperature value of an object in contact with at least the first gel based on the at least one characteristic of the at least one detector signal, wherein the temperature value is dependent on the at least one characteristic of the at least one detector signal such that a change in the at least one characteristic of the at least one detector signal will result in a change in the determined temperature value.

2. The sensor of claim 1, wherein the at least one characteristic comprises a ratio $F1/F2$, where $F1$ corresponds to an intensity of light emitted from the first type of fluorophore and $F2$ corresponds to an intensity of light emitted from the second type of fluorophore.

3. The sensor of claim 1, wherein the at least one characteristic corresponds to a decay time difference between the first and second emission light when the first and second excitation light is intensity modulated.

4. The sensor of claim 1, wherein the first and second types of fluorophores comprise fluorophores that are excitable by visible light.

5. The sensor of claim 4, wherein the first type of fluorophore comprises ruthenium(II) tris(1, 10-phenanthroline).

6. The sensor of claim 4, wherein the second type of fluorophore comprises 8-aminopyrene-1,3,6-trisulfonic acid.

7. The sensor of claim 1, wherein at least the first gel is non-toxic and hypoallergenic.

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8. The sensor of claim 1, wherein at least the first gel has anti-bacterial properties.

9. The sensor of claim 1, wherein at least the first gel comprises a hydrogel matrix.

10. The sensor of claim 9, wherein at least the first gel 5 comprises chitosan or glyceryl polyacrylate.

11. The sensor of claim 3, wherein the light detector comprises a CCD camera.

12. The sensor of claim 11, wherein the process controller 10 utilizes lock-in imaging to measure the decay time difference.

13. A noninvasive remote sensor for measuring temperature, comprising:

a first;

a first type of fluorophore embedded in the first hydrogel, 15 wherein the first type of fluorophore emits first emission light via luminescence in response to first excitation light, wherein the luminescence of the hydrogel first type of fluorophore varies as a function of temperature;

a second hydrogel;

a second type of fluorophore embedded in the second hydrogel, wherein the second type of fluorophore emits 20 second emission light via luminescence in response to second excitation light, wherein the luminescence of the second type of fluorophore varies as a function of temperature;

at least one light detector positioned to detect the first and second emission light, wherein the light detector generates 25 at least one detector signal corresponding to the first and second emission light, wherein at least one

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characteristic of the at least one detector signal represents both at least one parameter of the first emission light and at least one parameter of the second emission light; and

a process controller in communication with the at least one light detector, wherein the process controller determines a temperature value of an object in contact with both the first and second hydrogels based on the at least one characteristic of the at least one detector signal, wherein the determined temperature value is dependent 30 on the at least one characteristic of the at least one detector signal such that a change in the at least one characteristic of the at least one detector signal will result in a change in the determined temperature value.

14. The sensor of claim 13, wherein the at least one characteristic comprises a ratio $F1/F2$, where F1 corresponds to an intensity of light emitted from the first type of fluorophore and F2 corresponds to an intensity of light emitted from the second type of fluorophore.

15. The sensor of claim 13, wherein the first and second types of fluorophores comprise fluorophores that are excitable by visible light.

16. The sensor of claim 15, wherein the first type of fluorophore comprises ruthenium(II) tris(1, 10-phenanthroline).

17. The sensor of claim 15, wherein the second type of fluorophore comprises 8-aminopyrene-1,3,6-trisulfonic acid.

18. The sensor of claim 13, wherein the first and second 30 hydrogels each comprise chitosan or glyceryl polyacrylate.

* * * * *

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摘要(译)

提供了一种非侵入式远程参数传感器和传感方法，其特别适用于皮肤温度的远程监测。传感器和传感方法利用基于发光的传感器，其对皮肤无毒且无刺激性。传感器优选使用嵌入软水凝胶中的一种或多种类型的荧光团。用激发光照射传感器，并通过检测和分析来自荧光团的发射光来监测温度。由于使用了柔软的水凝胶，因此在温度测量结束时可以轻轻擦去皮肤上的传感器。

