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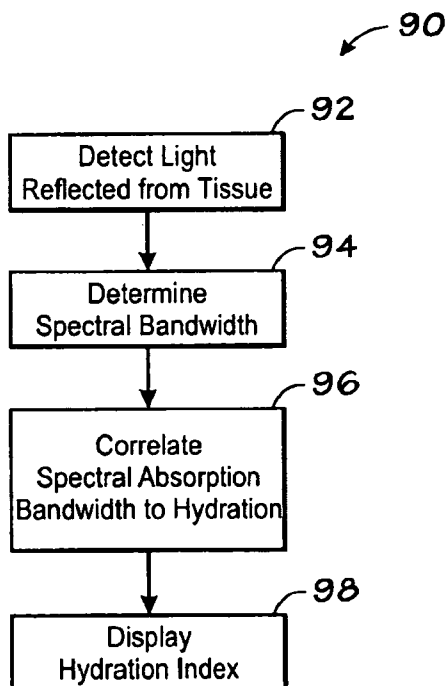
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(54) Title: TISSUE HYDRATION ESTIMATION BY SPECTRAL ABSORPTION BANDWIDTH MEASUREMENT



(57) Abstract: A system and method are provided for determining tissue hydration. Specifically, in accordance with one aspect of the present invention there is provided a method for determining tissue hydration (90). The method (90) includes detecting electromagnetic radiation scattered and reflected from the living tissue (92) and using the detected electromagnetic radiation to determine spectral absorption bandwidth (94). The method (90) also includes correlating the spectral absorption bandwidth to a tissue hydration index (96).

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TISSUE HYDRATION ESTIMATION BY SPECTRAL ABSORPTION BANDWIDTH MEASUREMENT

1. Technical Field

5 The present invention relates generally to determining physiological parameters and, more particularly, to determining tissue hydration.

2. Background Art

10 This section is intended to introduce the reader to various aspects of art that may be related to various aspects of the present invention, which are described and/or claimed below. This discussion is believed to be helpful in providing the reader with background information to facilitate a better understanding of the various aspects of the present invention. Accordingly, it should be understood that these statements are to be read in this light, and not as admissions of prior art.

15 In healthy individuals, homeostatic control mechanisms ensure that a balance between fluid gain and fluid loss is maintained. Therefore, maintaining fluid balance is typically not an issue requiring attention. In ill individuals, however, the maintenance of body fluid balance may be cause for great concern. For example, dehydration or edema may occur if fluid balance is not properly maintained. Dehydration of infants
20 and children suffering from diarrhea and/or vomiting can be life threatening if not recognized and treated promptly. Additionally, individuals with congestive heart failure frequently suffer from edema which must be controlled in order to ensure adequate tissue perfusion and to prevent electrolyte disturbances. Also, over-

administration of intravenous fluids in critically ill or surgical patients may result in lung edema, with resulting impairment of gas exchange.

Tissue hydration estimation using a hydration index, such as a ratio of water to the sum of water and protein, provides an accurate, objective and non-invasive way to measure fluid balance. Methods for measuring water in tissue by near-infrared (NIR) spectrophotometry have been described in the art. Previous attempts at using a hydration index, however, have been focused on measuring absorption features of the various tissue constituents. Additionally, the previous attempts have required a minimum of two wavelengths to measure the absorbance contributions of water and protein, and at least a third wavelength to compensate for the effect of tissue scattering. If measurements are made at wavelengths where lipids or other constituents, such as hemoglobin, contribute substantially to the absorption spectrum, a fourth or more wavelengths may be used to measure the hydration index accurately. Each additional wavelength increases cost and complexity of the system.

DISCLOSURE OF INVENTION

Certain aspects commensurate in scope with the originally claimed invention are set forth below. It should be understood that these aspects are presented merely to provide the reader with a brief summary of certain forms the invention might take and that these aspects are not intended to limit the scope of the invention. Indeed, the invention may encompass a variety of aspects that may not be set forth below.

In accordance with one aspect of the present invention, there is provided a method for determining tissue hydration. The method includes detecting electromagnetic radiation scattered and reflected from the living tissue and using the detected electromagnetic radiation to determine the bandwidth of a spectral absorption feature. The method also includes correlating the absorption bandwidth to a tissue hydration index.

In accordance with another aspect of the present invention there, is provided a system for measurement of living tissue. The system includes a sensor unit configured to emit and detect electromagnetic radiation. The system also includes a hydration index unit coupled to the sensor unit. The hydration index unit is configured to determine absorption bandwidth and correlate the absorption bandwidth to living tissue hydration.

BRIEF DESCRIPTION OF DRAWINGS

Certain exemplary embodiments are described in the following detailed description and in reference to the drawings in which:

FIG. 1 illustrates plots of the absorbance spectra of the principal components in tissue;

FIG. 2 illustrates plots of the averaged reflectance spectrum before and after over-hydration of piglets *in vivo*;

FIG. 3 illustrates a graph of the averaged spectral change induced by hydration change of piglets *in vivo*;

FIG. 4 illustrates a graph of the averaged spectral change induced by hydration of tissue phantoms;

FIG. 5 illustrates a graph of the reflectance spectra of muscle and fat sides of a pork chop;

FIG. 6a illustrates the top side of a handheld system for measuring tissue hydration in accordance with an exemplary embodiment of the present invention;

FIG. 6b illustrates the under side of the system of FIG. 6 in accordance with an exemplary embodiment of the present invention;

FIG. 7 illustrates using the system of FIG. 6a to estimate tissue hydration in accordance with an exemplary embodiment of the present invention;

FIG. 8 illustrates a system for tissue hydration estimation in accordance with an alternative exemplary embodiment of the present invention; and

FIG. 9 is a flowchart illustrating a technique for measuring tissue hydration.

5

MODES FOR CARRYING OUT THE INVENTION

One or more specific embodiments of the present invention will be described below. In an effort to provide a concise description of these embodiments, not all features of an actual implementation are described in the specification. It should be appreciated that in the development of any such actual implementation, as in any engineering or design project, numerous implementation-specific decisions must be made to achieve the developers' specific goals, such as compliance with system-related and business-related constraints, which may vary from one implementation to another. Moreover, it should be appreciated that such a development effort might be complex and time consuming, but would nevertheless be a routine undertaking of design, fabrication, and manufacture for those of ordinary skill having the benefit of this disclosure.

10

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Near Infrared (NIR) absorbance spectra of three major constituents of tissue are shown overlaid in FIG. 1. Specifically, the absorbance spectra of water 10, protein 12 and lipid 14 are shown. As can be seen, the absorbance spectra plots of water 10 and protein 12 have spikes near 1450 nm, while the lipid plot 14 is relatively flat.

20

Referring to FIG. 2, spectra acquired before and after over-hydration on the torso of a piglet is illustrated. Specifically, the plot 16 is the average spectrum before over-hydration and plot 18 shows the spectrum after over-hydration of five piglets. The piglets were over-hydrated using Lactated Ringer's Solution over the course of six hours by approximately 25% of initial body weight. Given the similarity of the features in FIGS. 1 and 2, it may be possible to determine the relative concentrations of each of the tissue constituents *in vivo* by matching a linear combination of the constituent spectra to the *in vivo* spectrum. This simple approach, however, is complicated by the fact that tissue strongly scatters light. The scattering causes a change in the offset as well as the effective path length of light through the tissue as a function of wavelength. In addition, the interaction between the water and the other tissue constituents leads to perturbation of the water spectrum, that cannot be modeled by simply summing the absorbance spectra of pure water with that of the other pure tissue constituents.

A number of theoretical scattering models have been applied to tissue spectra in order to allow the estimation of constituent spectra. Methods for measuring water in tissue by NIR spectroscopy are described in U.S. Pat. No. 6,591,122, U.S. Pub. No. 2003-0220548, and U.S. Pub. No. 2004-0230106, all of which are incorporated herein by reference. However, these techniques are directed to measuring the absorption features of the various tissue constituents and require at least three wavelengths to compensate for the effects of tissue scattering.

In accordance with the present technique, a method and apparatus are provided to estimate analyte concentration through a spectral absorption bandwidth measurement. Specifically, a method and apparatus for determining a whole body hydration index using spectral absorption bandwidth is disclosed. The technique
5 correlates the spectral absorption bandwidth of the water absorption band centered at 1450 nm with whole body hydration and is capable of estimating a hydration index with less than one percent error using only two narrow-band light sources, such as light emitting diodes (LEDs).

10 Near-infrared (NIR) spectroscopic studies of *in vivo* piglets undergoing hydration changes indicate that the spectral bandwidth of the water absorption band centered at 1450 nm is strongly correlated with whole body hydration. The studies have shown that perturbations of the absorption bandwidth of water occur according to the relative concentration of tissue constituents. For example, lipid concentration has
15 been shown to have a strong effect on the absorption bandwidth. As the concentration of lipid-to-water increases, the absorption bandwidth becomes narrower and the peak is blue-shifted, indicating a decrease in hydration. Additionally, as described above, the plots 16 and 18 illustrate the opposite effect caused by over-hydration. As can be seen, over-hydration causes a broadening and red-shifting of the peak centered at 1450.
20 Accordingly, the absorption bandwidth of water can be correlated to a hydration index indicative of the relative concentrations of constituents of tissue. For example, a hydration index derived from the spectral bandwidth measurement relating to the ratio

of water-to-water and other constituents based on the spectral bandwidth of the water absorption band.

Difference spectra from 15 piglet hydration change experiments are shown in FIG. 3. The difference spectra are generated by subtracting the initial spectrum from the spectrum measured after a hydration change. The difference spectra are averaged according to the type of hydration change that was performed. Plot 20 illustrates the averaged spectra for five piglets which experienced over-hydration, plot 22 illustrates the averaged spectra of eight piglets which experienced dehydration, and plot 24 illustrates the averaged spectra of two piglets which served as control. Dehydration was accomplished by ultrafiltration of the blood over the course of six hours by approximately 9% of initial body weight.

A spectral broadening effect with over-hydration is manifested in the difference spectra as an increase in the tails of the 1450 nm water band relative to the center of the band. The difference spectra measured during dehydration experiments are remarkably symmetrical with the over-hydration difference spectra, showing a narrowing of the same absorbance band with dehydration. The control experiments, where no hydration change was performed, showed little variation in the spectra between the beginning and end of the experiment. Although only the averaged changes are shown in FIG. 3, the same bandwidth trend was observed in all individual piglet experimentations. The high reproducibility of the bandwidth trend observed

across multiple piglets suggests that a simple measurement of absorption bandwidth may be useful as a hydration estimate.

Table 1 shows various possible combinations of wavelengths between 800 and 1600 nm which may be selected and used for correlating to the hydration index. Using only two wavelength bands, centered at 1450 and 1500 nm, with a 75 nm full-width half-max bandwidth, the hydration index can be predicted with a high correlation coefficient (R^2) and calibration error of approximately one percent. Therefore, using only these two wavelengths, the width of the 1450 nm water band on the long wavelength side can effectively be measured.

Table 1

Effect of Increasing number of wavelengths on prediction error.						
# λ 's	R^2	Err. (%)	λ_1 (nm)	λ_2 (nm)	λ_3 (nm)	λ_4 (nm)
1	0.354	1.79	1650			
2	0.809	0.98	1500	1450		
3	0.838	0.91	1550	1430	850	
4	0.887	0.76	1500	1450	1100	1070

The source of the water bandwidth variation due to hydration changes was investigated using tissue "phantoms." The phantoms were artificially constructed to mimic real tissue by selecting materials with similar constituents and optical properties to real tissue. The phantoms were constructed from varying proportions of water, protein, lipid, and scatterers, such as silicon oxide beads. FIG. 4 shows the average effect of increasing either the protein or lipid concentrations relative to the water concentration. The protein plot 26, illustrating the effect of increasing the

concentration of protein relative to the water content, shows a much smaller effect on a percent weight basis relative to the lipid plot 28. The largest effect of increasing lipid concentration relative to water is a narrowing of the water band centered at 1450 nm. Importantly, it appears that the interaction effect between lipid and water effects both the long and short wavelength sides of the water band, whereas the interaction effect between protein and water effects primarily only the short wavelength side of the water band. On this basis, it should thereby be possible to separate the interaction effects due to protein and lipid on the water spectrum. For example, it may be possible to directly measure lean water fraction (or Hydration Index) by making 2 separate bandwidth measurements, one on the long wavelength side and another on the short wavelength side of the 1450 nm water absorption peak.

The tissue phantom results suggest that a major cause of the water band shift effect is interaction between water and lipid. In order to confirm this in real tissue, diffuse reflectance spectra of a pork chop were measured on a fatty portion and on a lean portion. The results, shown in FIG. 5, demonstrate that the interaction between lipid and water has the effect of narrowing and blue-shifting the water absorption peak at 1450 nm. Plot 30 illustrates the transmission spectrum of lean pork chop, while plot 32 illustrates the transmission spectrum of fatty pork chop. Plot 32 shows the spectrum of the fatty pork chop is narrower and blue-shifted as compared to plot 30 of the lean pork chop. Thus, the results shown in FIG. 5 confirm the "phantom" tests by demonstrating the narrowing of the water band centered at 1450 when lipid concentration is increased.

The hypothesized mechanism for the water bandwidth change with tissue hydration is interaction between water and surrounding tissue constituents (principally lipid and protein) leading to disruption of the hydrogen bonding network of liquid water. The broad width of the NIR absorbance bands of water at room temperature have previously been suggested to be due to the wide variety of hydrogen bonding interactions available to water. Evidence for this includes the observed narrowing and blue-shifting of the NIR water absorption peaks with increasing temperature. Various solutes and solvents have been classified as having either an ordering or disordering affect on water based on the width and peak position of NIR water bands. From the results discussed above, it is clear that both protein and lipid have a disordering effect on the hydrogen bonding in water, but with distinctive spectral signatures. Increasing the protein or lipid concentration relative to water will have a similar effect to increasing temperature of a pure water solution causing the width of NIR water bands to become narrower and the peak to shift to the blue.

In an exemplary embodiment, two light emitting diodes (LEDs) operating in the 1350-1650 nm spectral region, such as the 1450 and 1500 nm LEDs described above, are implemented with a detector, such as an InGaAs detector. The LEDs are selected to have a spectral bandwidth of approximately 75 nm or less. The LEDs are configured to transmit light into blood perfused tissue and the detector is configured to detect the light that is scattered and reflected by the tissue constituents and may be

separated from the detector by 1-5 mm. For example, the LEDs may be positioned 2.5 mm from the detector.

In an alternative exemplary embodiment, a third LED emitting at about 1400 nm is used to provide a separate measurement of the absorption bandwidth on the short wavelength side of the 1450 nm peak. The short and long bandwidth measurements are then combined to provide an estimate of the lean water fraction in the tissue. For example, the logarithm of the reflectance measured from the three LEDs may be linearly combined to produce a quantity related to the ratio of water to protein (r) in the tissue. This ratio can then be related to the lean water fraction (f_w^d) by: $f_w^d = r / (1+r)$.

The amount of pressure applied to the blood perfused tissue should be limited to avoid exclusion of water from the sampled area. In an alternative embodiment, however, the pressure applied to the tissue may be varied and used as a means of separating “free” water from “bound” water, as disclosed in *Method for Evaluating Extracellular Water Concentration in Tissue*, by Clark R. Baker, Jr., et al., U.S. Ser. No. 11/283,506, which is incorporated herein by reference.

Many other alternative embodiments, besides the combinations of LEDs shown in table 1, are also envisioned. One highly accurate method of determining the water bandwidth employs a tunable laser to scan across the water bands, for example. This method is disclosed in greater detail in *Tunable Laser-based Spectroscopy System for*

Non-invasively Measuring Body Water Content, by Seungug Koh, et al., U.S. Ser. No. 11/716,394, which is incorporated herein by reference. Other alternative light sources include vertical-cavity surface-emitting lasers (VCSELs) and broadband sources coupled with narrowband optical filters. Other methods for determining bandwidth,
5 generally known to those skilled in the art of NIR spectroscopy, including scanning-grating spectroscopy, diode array spectroscopy, Fourier transform spectroscopy, and Hadamard transform spectroscopy may also be implemented.

Although measurement of the bandwidth of the water spectrum at 1450 nm has
10 been discussed in detail herein, it will be appreciated that other water absorption bands may be used to achieve similar results. Specifically, measuring the spectral width of the water bands having peaks at 980, 1190, 1900, or 2350 nm may also be useful in determining a hydration index.

15 Referring to FIG. 6a, an illustration of a system configured to measure tissue hydration in accordance with an exemplary embodiment of the present invention is shown and generally designated by the reference numeral 50. The system 50 may be configured as a single unit that can be carried with a user, nurse or doctor. The system 50 has a top side 52 with a display 54 configured to indicate the percent hydration of
20 the tissue that is being probed. The top side 52 of the system 50 may have a keypad 55 that can allow a user to communicate with the system 50. For example the keypad 55 can be used to turn on and off the system 50, or to enter baseline values or other

pertinent parameters. For example, baseline hydration values indicative of a certain condition such as dehydration or over-hydration may be entered.

The underside 56 of the system 50 is illustrated in FIG. 6b. The underside 56
5 has an emitter 58 and a detector 60. The emitter 58 may be at least one device capable
of emitting electromagnetic radiation in the 980 to 2350 nm spectral region. For
example, the emitter 58 may be one or more LEDs operating at wavelengths indicated
in Table 1 above. Alternatively, the emitter 58 may be a source capable of emitting
across a broad range of wavelengths, such as a tunable laser. Light transmitted into the
10 tissue of a patient is reflected and/or scattered by the various constituents of the tissue
before arriving at a photoelectric detector 60. The detector 60 may be an InGaAS
detector, or any other suitable photodetector capable of detecting at the wavelengths of
light emitted by the emitter 58. The underside 56 may be opaque except for where the
emitter 58 and detector 60 are located, since the opaque colorization helps to limit
15 reflections as well as interference from light sources other than the emitter 58.

The system 50 may take measurements from a single location on a patient's
body and correlate the measurement to a whole body hydration index. Specifically, the
system 50 may be placed along the centerline of the torso of a patient 70, as shown in
20 FIG. 7 and a hydration index indicative of whole body hydration may be determined.
In alternative applications, the system 50 may be configured to be placed on multiple
locations of a patient's body to test for other conditions, such as edema, for example.

A system showing an alternative exemplary embodiment is shown in FIG. 8, and is generally designated by the reference numeral 72. The system 72 has similar features to the system 50, but is intended to be placed on a desktop, shelf, or cart. The housing 74 of the system 72 is larger than that of the handheld embodiment and may be configured with additional features, such as increased memory space and/or expansion, for example. The system 72 has a display 76, a keypad 78 and a connector 80. The display 76 may be configured to indicate a hydration index measurement or other measured parameters. The keypad 78 may allow for users to input pertinent data, as discussed above. The connector 80 allows for a sensor 82 to communicate with the system 72 via a cable 84 or other means. The sensor 82 houses emitters and detectors, as described above, for taking spectral measurements. The spectral measurements are passed to the system 72 via the cable 84 for analysis and determination of hydration.

Turning to FIG. 9, a flowchart of an exemplary technique for determining fluid balance is illustrated and generally designated by the reference numeral 90. The technique begins by detecting light reflected from tissue, as indicated at block 92. As explained previously, a sensor can be placed along the centerline of the torso of the individual and transmit light into tissue. The tissue constituents of the tissue absorb, scatter and reflect the light. Light scattered and reflected by the tissue may be detected by a photodetector.

The spectral bandwidth of a water absorption band is determined by the detected light, as indicated at block 94. The spectral absorption bandwidth is correlated to the

hydration of the tissue, as indicated at block 96. As discussed in detail above, the absorption bandwidth of water varies according to the relative concentration of tissue constituents. Specifically, over-hydration is indicated by a red shift and a broadening of the absorption bandwidth of water, while dehydration is indicated by a blue shift and a narrowing of the absorption bandwidth of water. Therefore, the measurement of the spectral absorption bandwidth allows for the determination of the hydration index.

The correlation between the spectral absorption bandwidth and the hydration index of the tissue is a direct correlation. Specifically, the absorption bandwidth in nanometers indicates a particular hydration index of the tissue. For example, an absorption bandwidth of 15 nm may indicate hydration level of 80%. In alternative embodiments, the correlation between the absorption bandwidth and hydration may be more complex. For example, in an alternative embodiment, the peak shift may be considered in combination with absorption bandwidth. In another embodiment, the absorption bandwidth may be measured separately on the short and long wavelength sides of the absorption peak. Additionally, in yet another alternative embodiment, patient specific parameters may be taken into consideration when determining the hydration level. For example, a patient's body fat percentage or body temperature may be entered and used to calibrate the correlation of between absorption bandwidth and the hydration level. The calibration may, for example, cause the correlation of absorption bandwidth to hydration to be scaled in accordance with the body fat percentage.

The hydration index, once determined, may be displayed, as indicated at block 98. The hydration index displayed may be used in determining whether or not an individual has a proper fluid balance. Specifically, the hydration index can indicate a dehydration or over-hydration state. The technique 90 may be repeated and a series of measurements may be made over time. The measurements may then be compared to determine if hydration trends are occurring such that there may be cause for alarm or to indicate a change in treatment may be necessary. Accordingly, the observed trend data can be used to determine if a patient is becoming dehydrated, for example.

The spectroscopic studies on piglets, discussed above, were conducted using a reflectance sensor with low-OH optical fibers to collect NIR spectra. A ring of 36 illumination fibers (400 μm core diameter, 0.37 NA) were arranged in a 5 mm diameter circle around 6 detection fibers (200 μm diameter, 0.22 NA). The sensor was attached to the tissue via an oval-shaped adhesive. The sensor was placed in contact with the tissue, but without applying pressure. Light was supplied to the illumination fibers by two 0.5 W tungsten filament bulbs. The detection fibers were arranged in a line for input into the NIR spectrometer. The NIR spectrometer consisted of a grating and a 256-element cooled InGaAs diode array and allowed the NIR spectrum to be measured with 18 nm resolution between 800 and 1600 nm.

In the studies, pre-anesthetic medication (telazol/atropine) was given intramuscularly 30 minutes prior to the induction of anesthesia. Each piglet was intubated and general anesthesia was induced using 2% isoflurane in oxygen. After induction,

catheters were inserted into a central artery and vein, and a Foley catheter was surgically inserted into the bladder. General anesthesia was maintained by volume-controlled ventilation with isoflurane (2.0 vol%) delivered in 100% oxygen via veterinary anesthesia ventilator. The protocol allowed adjustments of inspired
5 isoflurane concentration in the order of 1-2 vol% according to reactions to standardized noxious stimuli or changes in blood pressure and heart rate. Ventilation (volume-controlled) was adjusted to produce normo-capnia (arterial carbon dioxide level about 40 mmHg) based on repeated arterial blood gas analysis and end-tidal carbon dioxide monitoring.

10 The over-hydration experiments consisted of administration of 1L of LRS in 20 minutes followed by 40 minutes of equilibration time. Additionally, a supplemental volume of LRS was given to compensate for the fluid lost from urine and blood sampling during the 40 minute equilibration period. This was repeated five times on each piglet so that a total of five liters of fluid was added over a five hour period. The
15 under-hydration experiments consisted of removing 350 ml of body fluid from the piglets at hourly intervals over a four- or five-hour period via ultrafiltration.

 At the completion of the experiment, the animals were euthanized and then frozen at -20°C. The entire carcass was then homogenized by grinding. To determine Hydration Index, several representative samples (approximately 1 g) of the
20 homogenized carcass were accurately weighed to within 0.001 g. Samples were then lyophilized for at least three days and re-weighed. Lyophilization and weighing were repeated until no further weight change was observed. The fat content was then

determined using a modification of the Folch method which excluded water from the extraction process. Briefly, an organic solvent was used to extract lipids from lyophilized tissue samples. The lipid-containing organic solvent was removed, washed with a solvent, and evaporated until only the lipid remained. Samples were re-weighed and the final weight was the fat-free, dry tissue weight. The hydration index was computed as the ratio of weight of water-to-the sum of the fat-free, dry tissue weight and the water weight. By combining the final whole carcass composition with continuous body weights, the hydration index could be determined throughout the experiment.

The solid tissue phantoms were created by mixing gelatin ("protein" component), corn oil ("lipid" component), scatterer (silicon oxide beads in water, 0.6-1.6 μm diameter, 2% solids content), and buffered water (deionized water 25 mM sodium carbonate, 50 mM sodium phosphate, 0.45% sodium chloride, pH 7.4). A two-level factorial design was constructed using lipid (5%, 15%), protein (15%, 20%), and scatterer (1%, 2%) as the variables. Temperature was treated as a fourth variable that was varied between two levels (25°C, 30°C). A total of 16 optical measurements were made on the phantoms. Due to the factorial design of the experiment, the effect of each variable could be isolated simply by subtracting the average of all 8 samples at the low level of a given variable from the high level of the same variable.

While the invention may be susceptible to various modifications and alternative forms, specific embodiments have been shown by way of example in the drawings and have been described in detail herein. However, it should be understood that the

invention is not intended to be limited to the particular forms disclosed. Indeed, the present techniques may not only be applied to measurements of tissue hydration, but these techniques may also be utilized for the measurement and/or analysis of other analytes. The invention, therefore, is to cover all modifications, equivalents, and
5 alternatives falling within the spirit and scope of the invention as defined by the following appended claims.

CLAIMS

1. A method for determining tissue hydration comprising:
detecting electromagnetic radiation scattered and reflected from the living tissue;
using the detected electromagnetic radiation to determine spectral absorption bandwidth;
5 and
correlating the spectral absorption bandwidth to a tissue hydration index.

2. The method of claim 1, comprising determining peak shift and correlating peak
shift and the spectral absorption bandwidth to the tissue hydration index.
10

3. The method of claim 1, wherein emitting electromagnetic radiation comprises
using light emitting diodes (LEDs) operating in the near-infrared spectrum having a
spectral bandwidth of less than approximately 75 nm.

- 15 4. The method of claim 3, comprising using LEDs having emission peaks at 1500
nm and 1450 nm.

5. The method of claim 4 comprising using an additional LED having an emission
peak at 1400 nm, the method comprising combining the measurements at the three
20 wavelengths to provide an estimate of a lean water fraction in the tissue.

6. The method of claim 5, comprising:
linearly combining the logarithm of the measurements at the three wavelengths to produce
a quantity related to the ratio of water-to-protein, (r), in the tissue; and
correlating the ratio to the lean water fraction, (f_w^l), by: $f_w^l = r / (1+r)$.
- 5
7. The method of claim 3, comprising using LEDs having emission peaks at 1550
nm, 1450 nm and 1400 nm.
8. The method of claim 3, comprising using LEDs having emission peaks at 1550
10 nm, 1430 nm and 850 nm.
9. The method of claim 3, comprising using LEDs having emission peaks at 1500
nm, 1450 nm, 1100 nm, and 1070 nm.
- 15
10. The method of claim 1, wherein emitting electromagnetic radiation comprises
using at least one tunable laser.
11. The method of claim 1, wherein emitting electromagnetic radiation comprises
using vertical-cavity surface-emitting lasers.
- 20
12. The method of claim 1, wherein emitting electromagnetic radiation comprises
using a broadband source coupled with narrowband optical filters.

13. The method of claim 1, wherein emitting electromagnetic radiation comprises implementing NIR spectroscopy.
14. The method of claim 13, comprising using scanning-grating spectroscopy.
- 5
15. The method of claim 13, comprising using diode array spectroscopy.
- ;
16. The method of claim 13, comprising Fourier transform spectroscopy.
- 10
17. The method of claim 13, comprising Hadamard transform spectroscopy.
18. The method of claim 1, wherein detecting electromagnetic radiation comprises using an InGaAs detector.
- 15
19. The method of claim 3, comprising using at least two LEDs having emission peaks spaced 25 to 250 nm apart in the 1800 to 2100 nm region of the spectrum.
20. A system for measurement of living tissue comprising:
a sensor unit configured to emit and detect electromagnetic radiation; and
20 an hydration index unit coupled to the sensor unit and configured to determine spectral absorption bandwidth and correlate the spectral absorption bandwidth to living tissue hydration.

21. The system of claim 20, comprising a display configured to output a tissue hydration estimation.
22. The system of claim 20, wherein the sensor unit comprises at least one emitter and
5 at least one detector.
23. The system of claim 20, wherein the at least one emitter operates in the 1300 nm to 1650 nm spectral region.
- 10 24. The system of claim 20, wherein the at least one emitter comprises a first LED operating at 1500 nm having a spectral bandwidth of less than 75 nm and a second LED operating at 1450 nm having a spectral bandwidth of less than 75 nm.
25. The system of claim 24, wherein the at least one emitter comprises a third LED
15 operating at 1400 nm having a spectral bandwidth of 75 nm or less.
26. The system of claim 22, wherein the at least one detector comprises an InGaAs photodetector.
- 20 27. The system of claim 20, wherein the hydration index unit is configured to determine peak shift and correlate peak shift and spectral absorption bandwidth to hydration.

28. The system of claim 20, wherein the hydration index unit and the sensor unit are integrated into the same housing.
29. The system of claim 20, wherein the sensor unit comprises a tunable laser.
- 5 30. The system of claim 20, wherein the sensor comprises a broadband source coupled with narrowband optical filters.
31. The system of claim 20, wherein the sensor comprises a vertical-cavity surface-emitting laser.
- 10 32. The system of claim 20, wherein the sensor comprises a scanning-grating spectroscope.
- 15 33. The system of claim 20, wherein the sensor comprises a diode array spectroscope.
34. The system of claim 20, wherein the sensor comprises a Fourier transform spectroscope.
- 20 35. The system of claim 20, wherein the sensor comprises a Hadamard transform spectroscope.

36. A method for estimating analyte concentration comprising:
measuring the spectral absorption bandwidth of an analyte near an absorption band of the
analyte, wherein measuring the spectral absorption bandwidth of the analyte
comprises transmitting electromagnetic radiation into living tissue and using a
5 photo sensitive detector to generate a photo electrical signal representative of the
electromagnetic radiation detected; and
correlating the spectral absorption bandwidth of the analyte to a relative concentration
level of the analyte.
- 10 37. The method of claim 36 comprising determining peak shift of the absorption band
of the analyte and correlating the peak shift to the concentration of the analyte.
38. The method of claim 36 comprising calibrating the correlation of the spectral
absorption bandwidth to the analyte concentration based on a determination of body fat or
15 local fat.
39. The method of claim 36 comprising calibrating the correlation of the spectral
absorption bandwidth to the analyte concentration based on a determination of body
temperature.

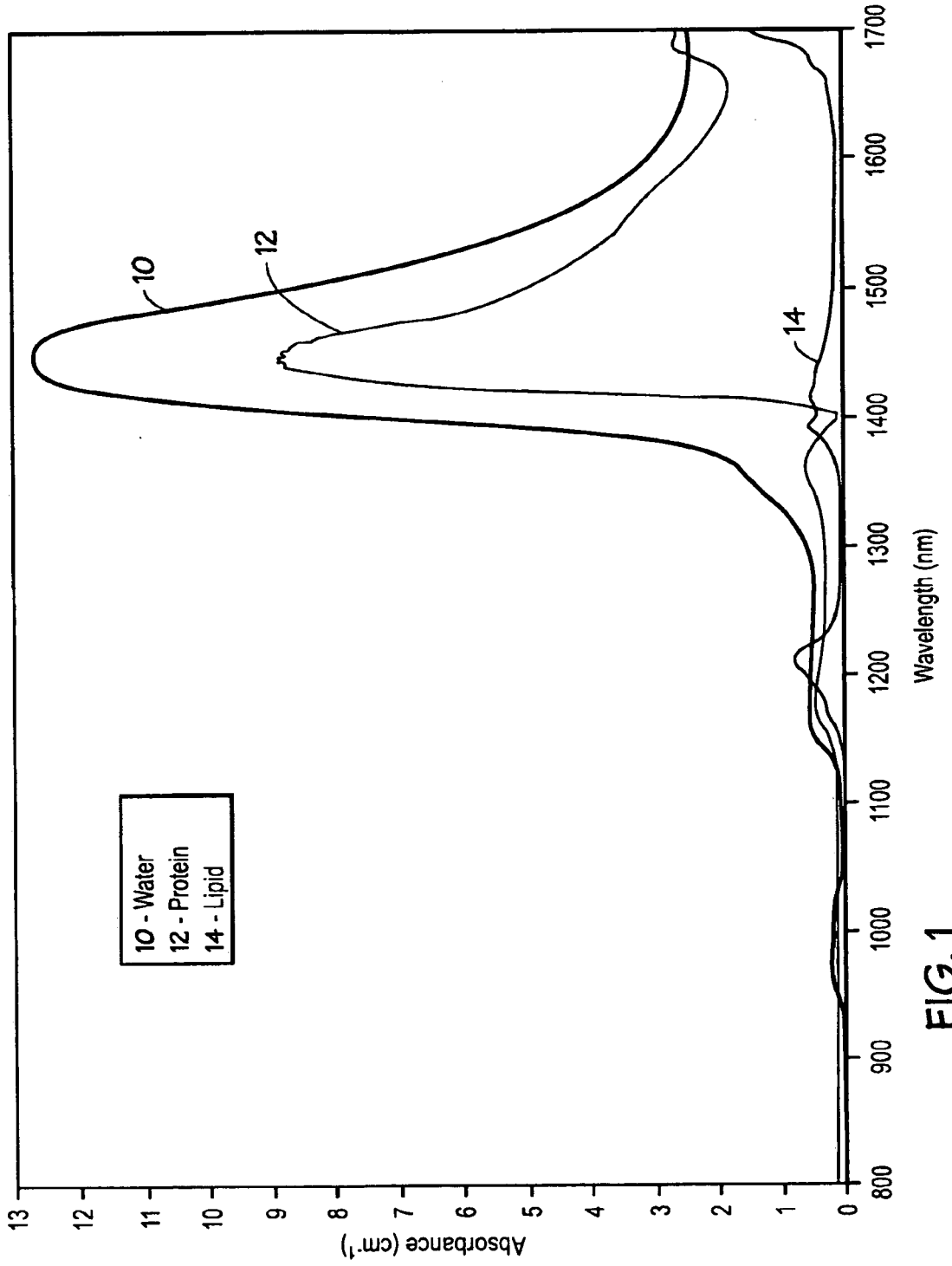


FIG. 1

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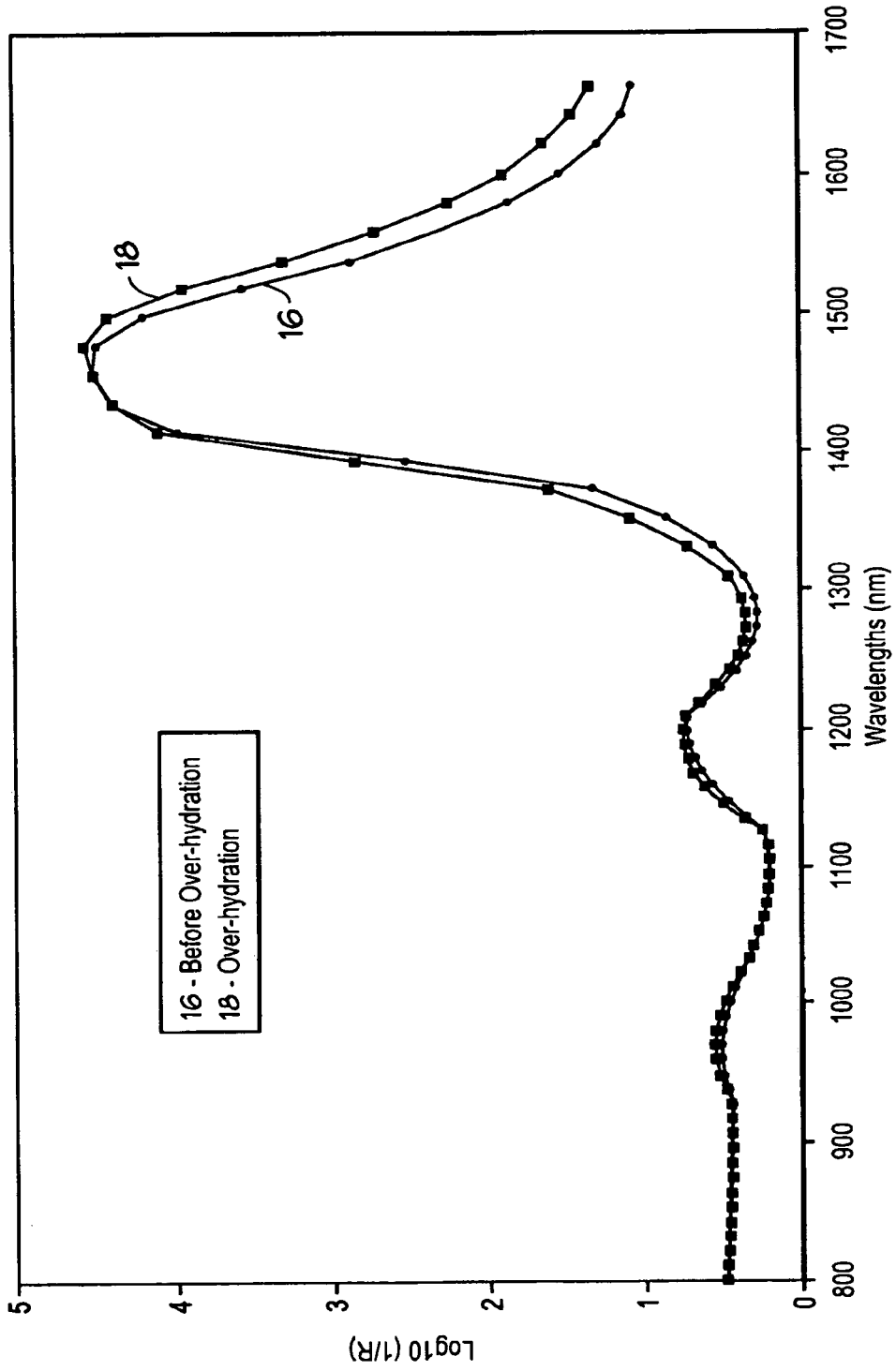


FIG. 2

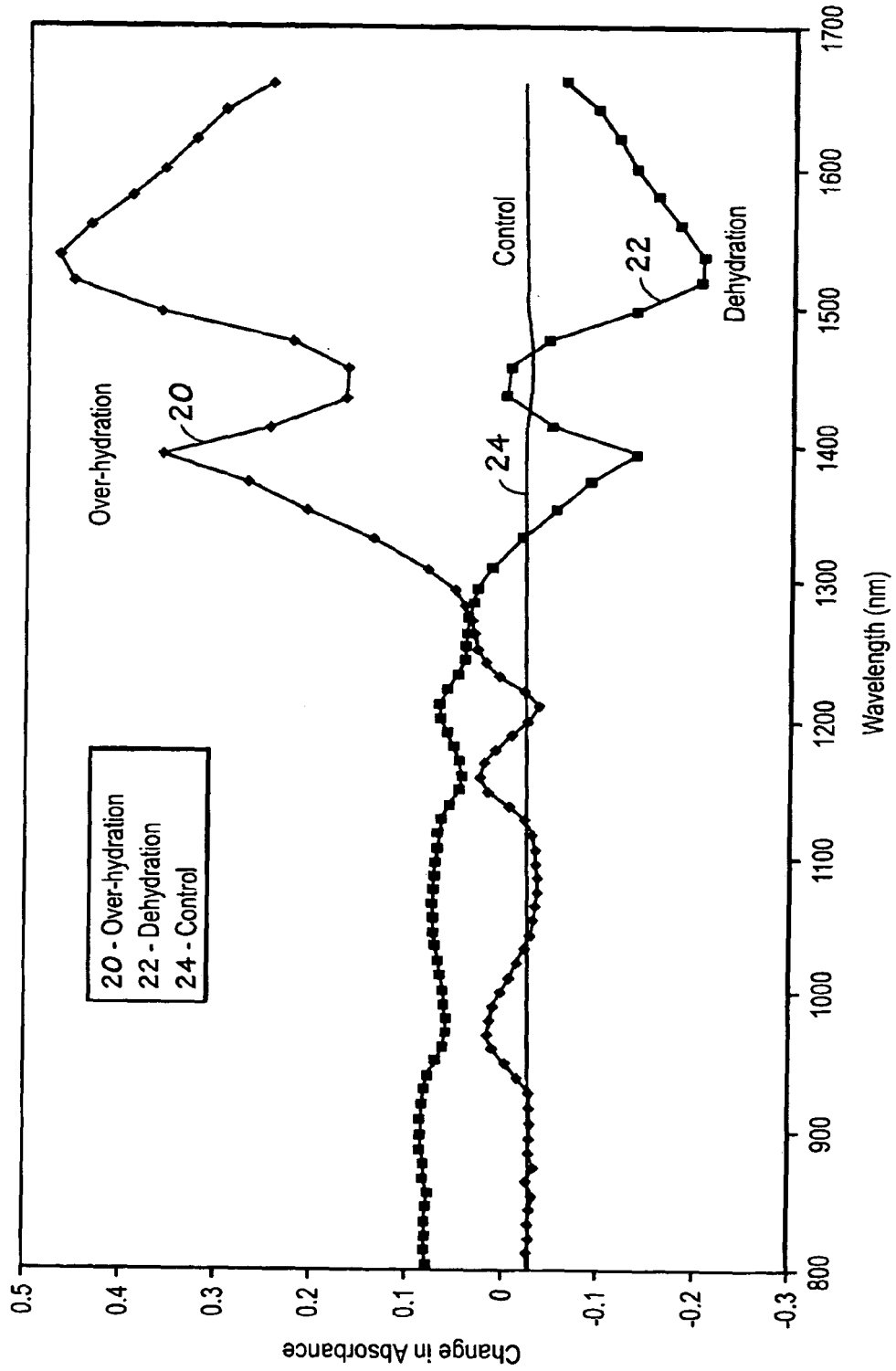


FIG. 3

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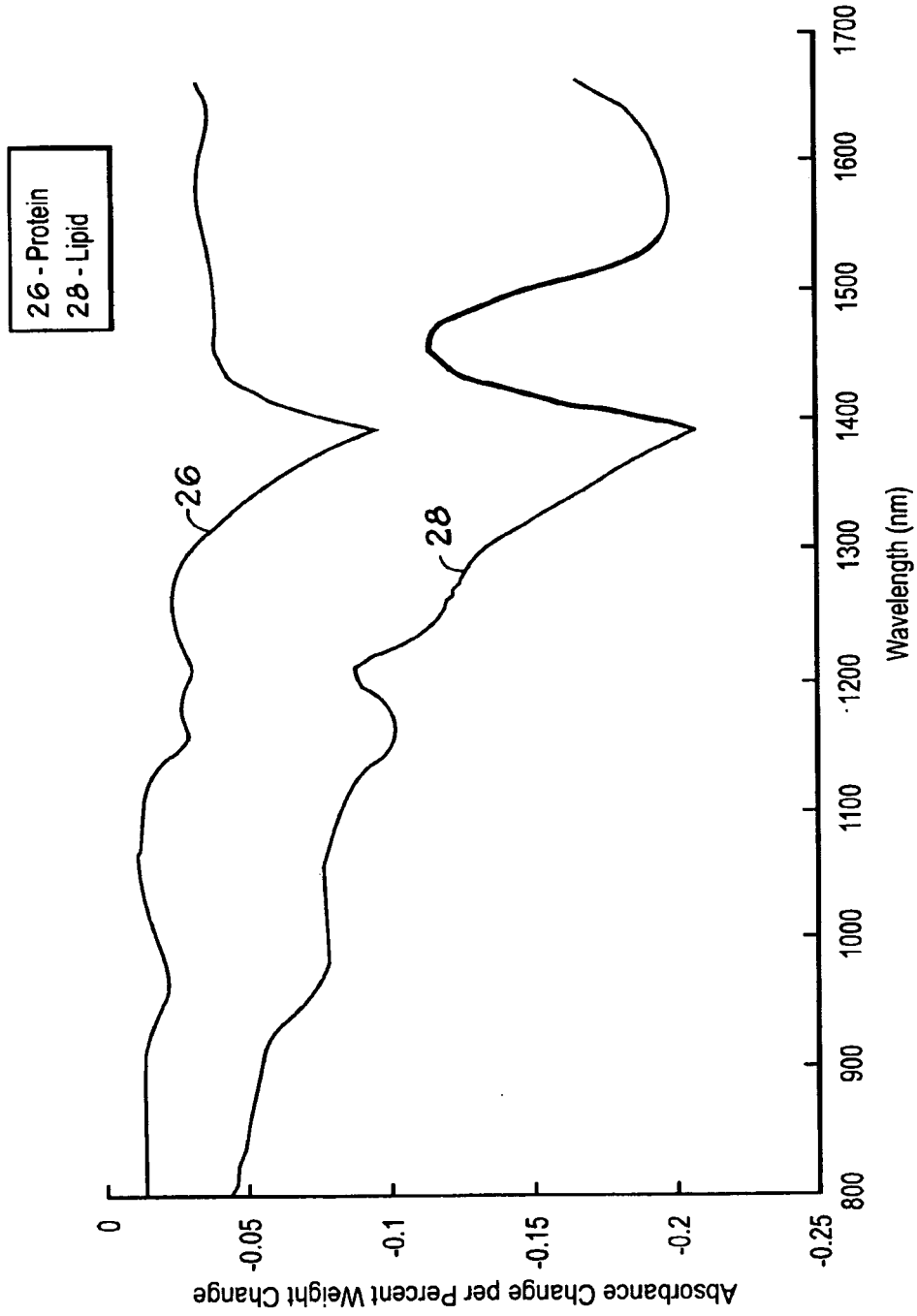


FIG. 4

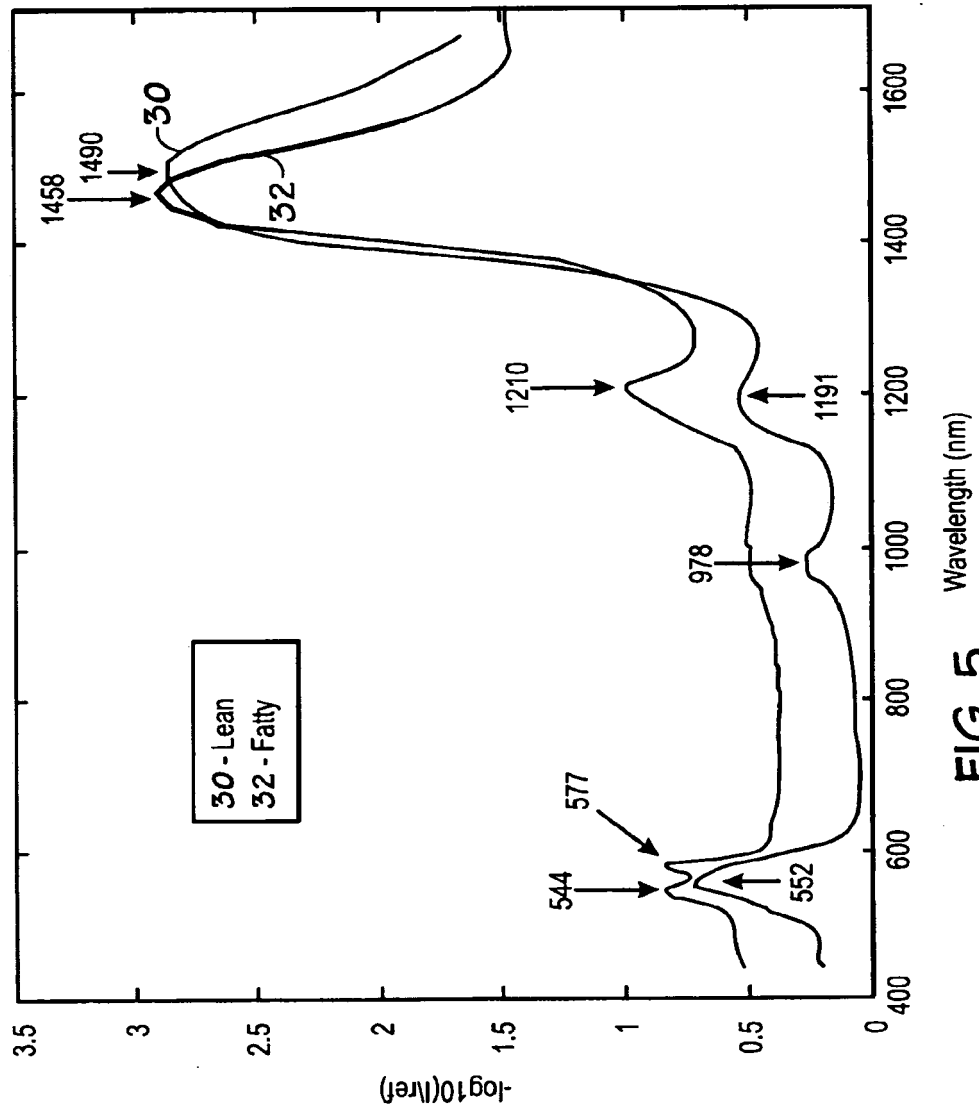


FIG. 5

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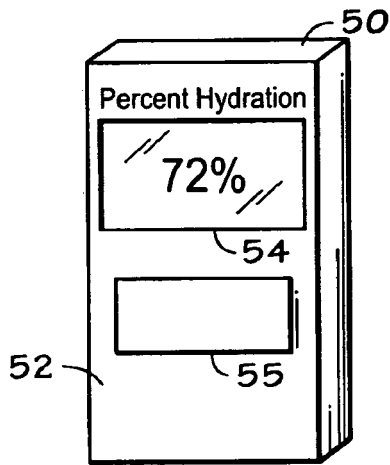


FIG. 6A

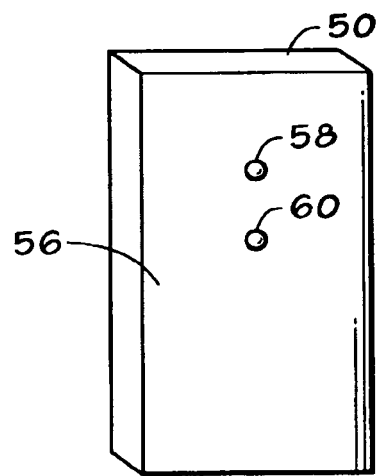


FIG. 6B

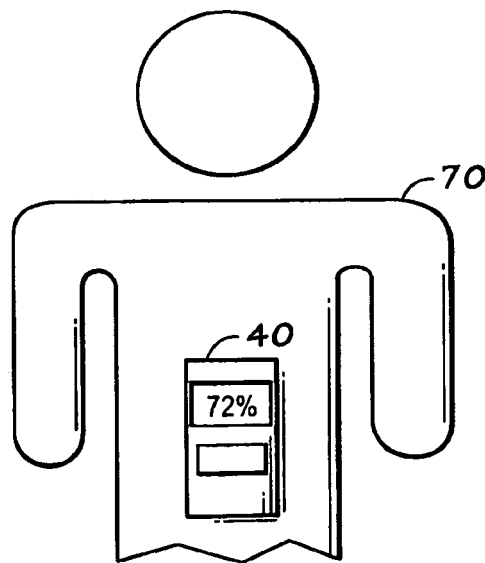


FIG. 7

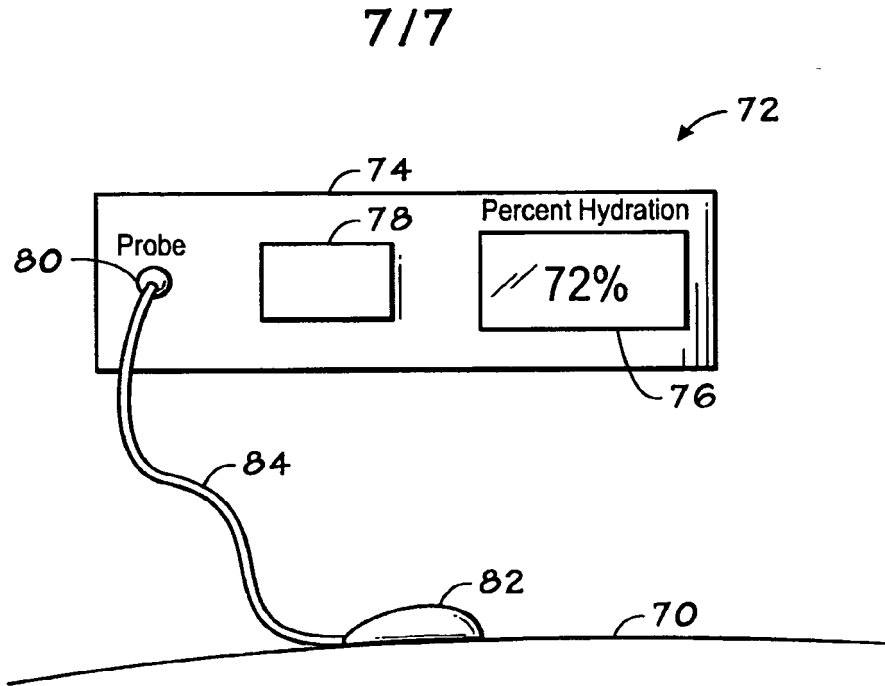


FIG. 8

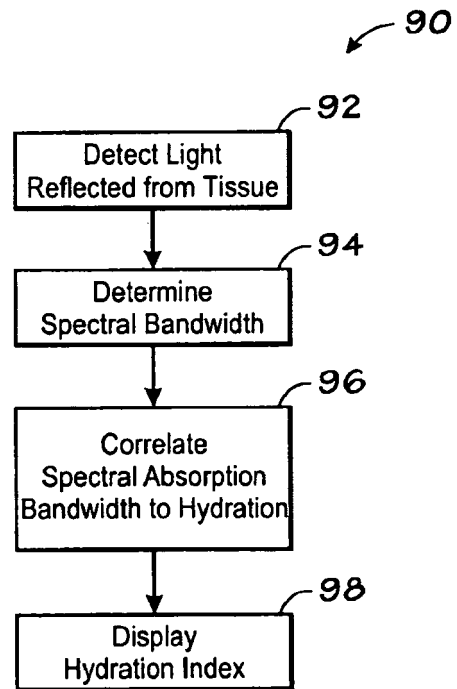


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/020239

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N21/35 A61B5/00 G01N21/25

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 2006/276696 A1 (SCHURMAN MATTHEW J [US] ET AL) 7 December 2006 (2006-12-07) paragraphs [0029], [0046]	36
A	J H ALI, WANG W B, ZEVALLOS M, ALFANO R R.: "Near Infrared Spectroscopy and Imaging to Probe Differences in Water Content in Normal and Cancer Human Prostate Tissues" TECHNOLOGY IN CANCER RESEARCH & TREATMENT, vol. 3, no. 5, October 2004 (2004-10), pages 491-497, XP009094805 the whole document	20-39
A	WO 95/19562 A (BLOCK MYRON J [US]) 20 July 1995 (1995-07-20) the whole document	20-39
	-/--	

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

6 February 2008

Date of mailing of the international search report

12/02/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Anscombe, Marcel

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/020239

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	POTTS R O ET AL: "A NONINVASIVE, IN VIVO TECHNIQUE TO QUANTITATIVELY MEASURE WATER CONCENTRATION OF THE STRATUM CORNEUM USING ATTENUATED TOTAL-REFELCTANCE INFRARED SPECTROSCOPY" ARCHIVES OF DERMATOLOGICAL RESEARCH, SPRINGER, INTERNATIONAL, BERLIN, DE, vol. 277, 1985, pages 489-495, XP008000238 ISSN: 0340-3696 the whole document	20-39
A	US 2006/167350 A1 (MONFRE STEPHEN L [US] ET AL) 27 July 2006 (2006-07-27) the whole document	20-39
A	US 2004/147034 A1 (GORE JAY PRABHAKAR [US] ET AL) 29 July 2004 (2004-07-29) the whole document	20-39
A	LIANGYUN LIU ET AL: "Estimating winter wheat plant water content using red edge width" IGARSS 2003. IEEE 2003 INTERNATIONAL GEOSCIENCE AND REMOTE SENSING SYMPOSIUM. PROCEEDINGS. TOULOUSE, FRANCE, JULY 21 - 25, 2003, IEEE INTERNATIONAL GEOSCIENCE AND REMOTE SENSING SYMPOSIUM, NEW YORK, NY : IEEE, US, vol. VOL 7 OF 7, 21 July 2003 (2003-07-21), pages 1688-1691, XP010703163 ISBN: 0-7803-7929-2 the whole document	20,36
A	WO 03/010510 A (ARGOSE INC [US]; MESSERSCHMIDT ROBERT G [US]; MANSFIELD JAMES [US]; BR) 6 February 2003 (2003-02-06) the whole document	20-39

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-19

The subject-matter of claim 1 comprises subject-matter relating to the following steps:

- (i) "detecting from the living tissue; using the detected to determine bandwidth" - which is an examination by acquiring and processing data and where "using" comprises the sense of determining trends in the absorption bandwidth to provide indication for changes to treatment (description, page 17, line 6-7);
- (ii) "correlating to a tissue hydration index" - which includes "index can indicate a dehydration" which implicitly comprises comparison with a standard or normal hydration (description, page 17, line 3 & 5);
- (iii) "correlating to a tissue hydration index" which includes "index can indicate a dehydration" which implicitly comprises comparison with a standard or normal hydration which corresponds to the step of finding a significant deviation (description, page 17, line 3);
- (iv) "for determining tissue hydration" - which includes indicating dehydration or over hydration which is the attribution of a clinical picture of dehydration or over hydration (description, page 17, line 4 & 7).

The only explicitly technical step is step (i), since technical means are implicit; whereas steps (ii-iv) is not necessarily technical as claimed e.g. could refer to thought processes. The only technical step, step (i), is claimed as being performed on "a living tissue" which comprises human and animal living tissue and therefore the technical step of claim 1 is claimed as being performed on the human or animal body - rendering the subject-matter of claim 1 a method of diagnosis of the human or animal body.

Claim 2 further defines the step (i). Claims 3 & 4 refer to technical details of step (i). Claims 5 & 6 refers to an intermediate processing step. Claims 7-12, 18 & 19 are further device specifications concerning step (i). Claims 13-17 are intermediate processing steps. Therefore, using the same argument as for claim 1 mutatis mutandis, claims 2-19 are also method of diagnosis of the human or animal body.

Claims 1-19 are therefore not searched (Art. 17(2)(a)(i) PCT and Rule 39.1(iv) PCT).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/020239

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1. Claims Nos.: 1-19
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

- 2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

- 2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

- 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

- 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2007/020239

Patent document cited in search report	Publication date	Patent family member(s)	Publication date																												
US 2006276696	A1	07-12-2006	NONE																												
WO 9519562	A	20-07-1995	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 15%;">CA</td> <td style="width: 25%;">2180128</td> <td style="width: 15%;">A1</td> <td style="width: 45%;">20-07-1995</td> </tr> <tr> <td>DE</td> <td>69530284</td> <td>D1</td> <td>15-05-2003</td> </tr> <tr> <td>DE</td> <td>69530284</td> <td>T2</td> <td>29-01-2004</td> </tr> <tr> <td>EP</td> <td>0742897</td> <td>A1</td> <td>20-11-1996</td> </tr> <tr> <td>ES</td> <td>2194048</td> <td>T3</td> <td>16-11-2003</td> </tr> <tr> <td>JP</td> <td>3649732</td> <td>B2</td> <td>18-05-2005</td> </tr> <tr> <td>JP</td> <td>9510884</td> <td>T</td> <td>04-11-1997</td> </tr> </table>	CA	2180128	A1	20-07-1995	DE	69530284	D1	15-05-2003	DE	69530284	T2	29-01-2004	EP	0742897	A1	20-11-1996	ES	2194048	T3	16-11-2003	JP	3649732	B2	18-05-2005	JP	9510884	T	04-11-1997
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JP	9510884	T	04-11-1997																												
US 2006167350	A1	27-07-2006	NONE																												
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WO 03010510	A	06-02-2003	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 15%;">AU</td> <td style="width: 25%;">2002355272</td> <td style="width: 15%;">A1</td> <td style="width: 45%;">17-02-2003</td> </tr> </table>	AU	2002355272	A1	17-02-2003																								
AU	2002355272	A1	17-02-2003																												

专利名称(译)	通过光谱吸收带宽测量估计组织水合作用		
公开(公告)号	EP2074407A1	公开(公告)日	2009-07-01
申请号	EP2007838450	申请日	2007-09-18
[标]申请(专利权)人(译)	内尔科尔普里坦贝内特公司		
申请(专利权)人(译)	NELLCOR PURITAN BENNETT LLC		
当前申请(专利权)人(译)	COVIDIEN LP		
[标]发明人	DEBRECZENY MARTIN P BAKER JR CLARK R		
发明人	DEBRECZENY, MARTIN, P. BAKER JR., CLARK, R.		
IPC分类号	G01N21/35 A61B5/00 G01N21/25		
CPC分类号	A61B5/0059 A61B5/4869 G01N21/3554 G01N21/3563 G01N21/359		
优先权	11/528154 2006-09-27 US		
外部链接	Espacenet		

摘要(译)

提供了一种用于确定组织水合作用的系统和方法。具体地，根据本发明的一个方面，提供了一种用于确定组织水合作用的方法(90)。方法(90)包括检测从活组织(92)散射和反射的电磁辐射，并使用检测到的电磁辐射来确定光谱吸收带宽(94)。方法(90)还包括将光谱吸收带宽与组织水合指数相关联(96)。