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**(54) CLASSIFICATION AND CHARACTERIZATION OF TISSUE THROUGH FEATURES RELATED TO ADIPOSE TISSUE**

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CLASSIFICATION ET CARACTERISATION DE TISSUS UTILISANT LES PARTICULARITES DE TISSUS ADIPEUX

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**US-A- 5 348 003 US-A- 5 945 676**

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- **BURMEISTER JASON J ET AL.: "Evaluation of Measurement Sites for Noninvasive Blood Glucose Sensing with Near-Infrared Transmission Spectroscopy" CLINICAL CHEMISTRY, vol. 45, no. 9, September 1999 (1999-09), pages 1621-1627, XP002163585**
- **THODBERG HANS HENRIK: "A Review of Bayesian Neural Networks with an Application to Near Infrared Spectroscopy" IEEE TRANSACTIONS ON NEURAL NETWORKS, vol. 7, no. 1, January 1996 (1996-01), pages 56-72, XP002163586**

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**Description****BACKGROUND OF THE INVENTION**5 **TECHNICAL FIELD**

[0001] This invention relates to the classification of individuals by features related to tissue properties. More particularly, the invention relates to methods of characterizing the tissue by features related to the absorbance spectrum of fat in adipose tissue, based on Near IR spectral measurements.

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**DISCUSSION OF THE PRIOR ART**

[0002] Near infrared (NIR) tissue spectroscopy is a promising noninvasive technology that bases measurements on the irradiation of a tissue site with NIR energy in the 700-2500 nm wavelength range. The energy is focused onto an area of the skin and propagates according to the scattering and absorbance properties of the skin tissue. Thus, energy that is reflected by the skin or that is transmitted through the skin is detected provides information about the tissue volume encountered. Specifically, the attenuation of the light energy at each wavelength is a function of the structural properties and chemical composition of the tissue. Tissue layers, each containing a unique heterogeneous particulate distribution, affect light absorbance through scattering. Chemical components such as water, protein, fat and blood analytes absorb light proportionally to their concentration through unique absorbance profiles or signatures. The measurement of tissue properties, characteristics or composition is based on the technique of detecting the magnitude of light attenuation resulting from its respective scattering and/or absorbance properties.

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*.1 Blood Analyte Prediction*

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[0003] While noninvasive prediction of blood analytes, such as blood glucose concentration, has been pursued through NIR spectroscopy, the reported success and product viability has been limited by the lack of a system for compensating for variations between individuals that produce dramatic changes in the optical properties of the tissue sample. [For example, see Khalil OS. Spectroscopic and clinical aspects of non-invasive glucose measurements. Clin Chem 1999; 45:165-77; or Roe, JN and BR Smoller. "Bloodless Glucose Measurements," Critical Reviews in Therapeutic Drug Carrier Systems, vol. 15, no. 3, pp. 199-241, 1998]. These variations are related to structural differences in the irradiated tissue sample between individuals and include, for example, the thickness of the dermis, distribution and density of skin collagen and percent body fat. While the absorbance features caused by structural variation are repeatable by subject, over a population of subjects they produce confounding nonlinear spectral variation. [See Tan, CY, B. Statham, R. Marks and P.A. Payne. Skin thickness measurement by pulsed ultrasound: its reproducibility, validation and variability. British Journal of Dermatology, vol. 106, pp. 657-667, 1982. Also see Shuster, S., M.M. Black and E. McVitie. The influence of age and sex on skin thickness, skin collagen and density. British Journal of Dermatology, vol. 93, 1975. See also Durnin, J.V.G.A. and M.M. Rahaman. The assessment of the amount of fat in the human body from measurements of skin fold thickness. British Journal of Nutrition, vol. 21, 1967.]

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[0004] Additionally, variations in the subject's physiological state affect the optical properties of tissue layers and compartments over a relatively short period of time. Such variations, for example, may be related to hydration levels, changes in the volume fraction of blood in the tissue, hormonal stimulation, temperature fluctuations and blood hemoglobin levels.

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[0005] While these structural and state variations are the largest sources of variation in the measured near-infrared absorbance spectra, they are not indicative of blood analyte concentrations. Instead, they cause significant nonlinear spectral variation that limits the noninvasive measurement of blood analytes through optically based methods. For example, several reported methods of noninvasive glucose measurement develop calibration models that are specific to an individual over a short period of time. [See Hazen, K. H., "Glucose determination in biological matrices using near-infrared spectroscopy," Doctoral Dissertation, University of Iowa, Aug. 1995. Also see Robinson, M. R., R. P. Eaton, D. M. Haaland, G. W. Koepp, E. V. Thomas, B. R. Stallard and P. L. Robinson, "Noninvasive glucose monitoring in diabetic patients: a preliminary evaluation," Clin. Chem, 38/9, pp 1618-1622, 1992. Also see Malin, S., T. Ruchti, T. Blank, S. Thennadil and S. Monfre. Noninvasive prediction of glucose by near-infrared diffuse reflectance spectroscopy," Clin. Chem, 45 : 9, pp. 1651-1658, 1999.]

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[0006] A related application, "An Intelligent System For Noninvasive Blood Analyte Prediction," United States Patent Application No 09/359,191; filed July 22, 1999 by Malin, S. and T. Ruchti, now United States patent no. 6,280,381, disclosed an apparatus and procedure for substantially reducing this problem by classifying subjects according to spectral features that are related to the tissue characteristics prior to blood analyte prediction. The extracted features are representative of the actual tissue volume irradiated. The groups or classes are defined on the basis of tissue similarity

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such that the spectral variation within a class is small compared to the variation between classes. These internally consistent classes are more suitable for multivariate analysis of blood analytes since the largest source of spectral interference is substantially reduced. In this manner, by grouping individuals according to the similarity of spectral characteristics that represents the tissue state and structure, the confounding nonlinear variation described above is reduced and prediction of blood analytes is made more accurate.

**[0007]** The general method of classification relies on the determination of spectral features most indicative of the sampled tissue volume. The magnitude of such features represents an underlying variable, such as the thickness of tissue or level of hydration.

**[0008]** The absorbance of light by adipose tissue in the sub-dermis, consisting primarily of cells rich in triglycerides, a class of fatty substance, is among the most significant source of spectral variation in noninvasive near-infrared measurements. While adipose tissue profoundly influences overall measurement, the volume fraction of fluid rich in blood analytes is relatively small compared to that present in other layers of the skin.

**[0009]** The dermis, for example, is richly supplied with a vascular network. At the interface between the dermis and subcutaneous fat is the deep vascular plexus, a collection of vessels that runs parallel to the skin surface. From the deep vascular plexus, blood vessels rise toward the skin surface to another dense parallel collection of vessels called the superficial vascular plexus, located 0.3 mm to 0.6 mm from the skin surface.

**[0010]** Consequently, the capillary beds of the dermis are targeted for irradiation and measurement of blood analytes, since they have a high volume fraction of analytes, such as glucose, that vary in accordance with actual blood concentration, compared to other layers of the skin. On the other hand, the absorbance of light by the constituents of adipose tissue contributes only confounding effects to the measurement of the targeted analyte, yet it represents, second only to the absorbance of water, the largest source of spectral variation. For example, Figure 1 shows a near-infrared absorbance spectrum measured on a human subject with large absorbance bands 101, 102, 103, marked by arrows, due to fat stored in adipose tissue. The relative absorbance due to the presence of a typical blood analyte in the sampled tissue volume, such as glucose, is approximately three orders of magnitude smaller than the designated fat absorbance bands.

**[0011]** Thus, the absorbance of light by adipose tissue creates two major obstacles to accurate blood analyte determination. First, the total absorbance related to adipose tissue is a large interference and is not indicative of blood analyte concentrations. Compounding this interference is the fact that the varied attenuation of light by adipose tissue is difficult to model due to the complex nature of the diffusely reflected light in layered systems. Second, the measured absorbance of fat by adipose tissue changes in a manner related to the optical properties of the preceding tissue layers, namely, the dermis, epidermis and stratum corneum. For a given light intensity level, the absorbance due to fat in adipose tissue tends to be constant. However, the light incident on the adipose tissue varies as the surrounding tissue changes according to its physiological state. Thus, the magnitude of fat absorbance in the tissue volume sampled is indirectly related to these changes due to physiological state fluctuations.

**[0012]** Therefore, features related to the absorbance of fat in adipose tissue can be used to classify the nature of the tissue volume sampled with a near-infrared measurement device. The classification of subjects according to the similarity of such features leads to a greater homogeneity of the sampled tissue volume and a reduction in interference related to the skin tissue. This inevitably produces a superior measurement of the concentration of biological compounds in skin, such a blood analytes, among the sub-groups.

## *.2 Body Composition Estimation*

**[0013]** Body composition is an important indicator of health status, and body composition determination plays an important role in health risk assessment and diagnosis, and in monitoring of physical training programs. [See Heyward, V.H. and L.M. Stolarczyk. Applied Body Composition Assessment. Champaign, IL: Human Kinetics, 1996.] Obesity, for example, is a serious health problem that reduces life expectancy by increasing one's risk of developing coronary artery disease, hypertension, Type 11 diabetes, obstructive pulmonary disease, osteoarthritis and certain types of cancer. The increased health risks associated with obesity are related to the total amount of body fat. Not surprisingly, a large number of methods for estimating body composition exist, many of them based on indirect measurements; for example, hydrostatic weighing, bioelectrical impedance, skin fold measurements and others [See Heyward, et al., op. cit.]. In addition, near-infrared analysis in the wavelength range 700-1100 nm has been applied to the noninvasive measurement of body fat [See Conway, J. M., Norris, K.H. and Bodwell, C.E. "A new approach for the estimation of body composition: infrared interactance." The American Journal of Clinical Nutrition, Dec. 1985, pp. 1123-1130].

**[0014]** R.D. Rosenthal in "Near infrared apparatus and method for determining percent fat in a body," United States Patent No. 4,850,365, issued July 25, 1989 and again in "Near-infrared apparatus and method for determining percent fat in a body," United States Patent No. 4,928,014 issued May 22, 1990; and A. Roper and K.O. Johnson, in "Method and apparatus for measuring thickness of fat using infrared light," United States Patent No. 5,014,713, issued May 14, 1991,

disclose methods of performing near-infrared analysis in the 700-1100 nm wavelength regions for the purpose of body composition analysis including the determination of the percent fat and the thickness of fat.

[0015] The use of near-infrared analysis has the advantage of being strictly noninvasive, convenient and affordable. The reported methods are similar and generally involve the irradiation of the tissue with near-infrared light at several wavelengths in the 740-1100 nm range and detecting the light absorbed at a multiplicity of wavelengths. A model is constructed for predicting the percent body fat or the thickness of the subcutaneous fat layer on the basis of the measurement, given reference values from an alternate technique of body composition assessment. Conway, for example, used the second derivative of the absorbance spectrum at 916 nm and 1026 nm to estimate the percent fat of several individuals.

[0016] Rosenthal reports two similar methods for determining percent fat in a body through the use of the measured absorbance at one wavelength and one bandwidth, respectively, and a mathematical model relating the percent body fat to the absorbance measurement. In addition, data on a plurality of physical parameters of the body, such as height, weight, exercise level, sex, race, waste-to-hip measurement and arm circumference, are proposed for use along with the measured near-infrared absorbance in the quantitative determine of body fat content.

[0017] Roper et al. determine the fat thickness in the body through a measuring device involving a pair of infrared emitting diodes and a detector array. A variety of wavelengths in the 700-1100 nm range are detected by the array and produce signals proportional to the light intensity transmitted from the body. These signals are summed and amplified forming a composite signal. The amplitude of this composite signal is claimed to be indicative of the thickness of the layer of fat.

[0018] While the reported methods of near-infrared analysis offer some advantage, their utility is significantly compromised due to the wavelength region selected for analysis. It is especially well understood that melanin is a significant absorber of light below 1100 nm [See Anderson, R. R and J. A. Parrish. "The optics of human skin," J. of Investigative Dermatology, vol. 77 (1), pp. 13-19, 1981]. Therefore, skin color causes large spectral variation at wavelengths below 1100 nm and represents a major confounding effect and source of bias. Furthermore, the depth of penetration in this wavelength region far exceeds the depth of subcutaneously stored fat. In addition, the potential interference due to visible light in this wavelength region is well known and requires special measurement equipment and requirements for blocking it. A method for determining the thickness of subcutaneous fat and percent body fat through the use of near-infrared energy at higher wavelengths (1100- 2500) nm would clearly be advantageous. In this range the depth of penetration is limited to subcutaneous tissue. The optical properties of the adipose cells, as manifested in the measured absorbance spectrum, can be used to estimate the thickness of the subcutaneous tissue and overall level of fatness of the individual.

[0019] United States patent no. 5,945,676 describes an apparatus for determining the concentration of analyte present in a sample using multi-spectral analysis in the near-infrared range.

## SUMMARY OF THE INVENTION

[0020] The invention provides a novel apparatus and related procedures for determination of features related to the absorbance of fat in adipose tissue and subsequent classification of subjects prior to blood analyte estimation. A method is provided for determining the thickness of subcutaneous fat and percent body fat through the use of near-infrared energy at higher wavelengths in the spectral region of 1100-2500nm. In this range the depth of penetration is limited to subcutaneous tissue. The optical properties of the adipose cells, as manifested in the measured absorbance spectrum, can be used to estimate the thickness of the subcutaneous tissue and overall level of fatness of the individual without interference from deeper tissue layers or skin pigmentation.

[0021] In general, the apparatus includes an energy source, a wavelength separator, an optical interface to the subject, a sensor element, and an analyzer. The general method of the invention includes the steps of measuring the NIR absorbance spectra of an *in vivo* tissue sample; detecting outliers, invalid measurements related to various sources of error; subjecting the measured spectrum to various pre-processing techniques; feature extraction, in which the spectral features specifically related to absorbance of fat in adipose tissue are identified and isolated; and calibration, in which the extracted features are compared to a calibration set of exemplary measurements to characterize the spectrum for further blood analyte prediction. A skin fold thickness estimate may be made, and a subsequent estimate of percent body fat.

[0022] These and other features, aspects and advantages of the invention will be better understood with reference to the following description, drawings and appended claims.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0023]

Figure 1 is a plot of a near IR absorbance spectrum measured on a human subject showing absorbance bands due to fat stored in adipose tissue;

5 Figure 2 is a block diagram of a system for classifying tissue according to features related to absorbance spectra of body fat, according to the invention;

Figure 3 shows a normalized NIR absorbance spectrum of water;

10 Figure 4 shows a NIR absorbance spectrum of an excised sample of animal fat.

Figure 5 provides a block diagram of a procedure for extracting spectral features related to the dermis and adipose tissue, according to the invention;

15 Figure 6 shows the NIR absorbance spectra of 19 subjects normalized according to the procedure of Figure 5, according to the invention;

Figure 7 shows a plot of a single wavelength calibration for body fat, according to the invention;

20 Figure 8 provides a block diagram of a procedure for measuring body fat via three wavelengths, according to the invention;

Figure 9 shows a plot of actual body fat versus the extracted feature of Figure 7, according to the invention;

25 Figure 10 shows a block diagram of a method of abstract feature extraction and subject classification, according to the invention;

Figure 11 shows a plot of the first three eigenvectors of a principle component analysis of a dataset following the feature extraction procedure of Figure 10, according to the invention;

30 Figure 12 is a comparison of the third loading (eigenvector) of Figure 11 with the animal fat spectrum of figure 4, according to the invention;

35 Figure 13 provides a pair of block diagrams showing generalized procedures for body fat prediction and classification of subjects according to spectral features associated with body fat, respectively, according to the invention;

Figure 14 shows a plot of predicted skin fold thickness versus actual skin fold thickness, according to the invention.

## **DETAILED DESCRIPTION**

40 **[0024]** A system for non-invasively determining features related to the absorbance of adipose tissue provides an apparatus for measuring the infrared absorbance by tissue irradiated with near-infrared energy and procedures for extracting and classifying the tissue characteristics. Alternately, the absorbance spectrum measured is processed and subjected to an estimation procedure for determining the skin fold thickness and/or the percent body fat.

## **APPARATUS**

45 **[0025]** The apparatus includes an energy source 21, a sensor element 26, an optical interface to the subject 25, a wavelength selection device 22 and an analyzer 33. The energy source 21 generates near-infrared energy in the wavelength range 1100-2500 nm and may consist of a device such as an LED array or a quartz halogen lamp. The sensing elements 26 are detectors that are responsive to the targeted wavelengths. The wavelength separation device 22 may be a monochromator, or an interferometer. Wavelength separation may also be achieved through successive illumination of the elements of the previously described LED array. The optical interface 25 to the subject 20 includes a means for transmitting energy 23 from the source 21 to the target skin tissue measurement site and may be, for example, a light pipe, fiber-optic probes, a lens system or a light directing mirror system. The optical interface 25 to the subject also includes a means for collecting energy 24 from the surrounding tissue areas in reflectance mode at an optimally determined distance(s) and may be composed of staring detectors or fiber optic probes. The collected light is converted to a voltage 26 and sampled through an analog-to-digital converter 27 for analysis on a microprocessor based system 33.

55 **[0026]** In the preferred embodiment, the instrument employs a quartz halogen lamp 21, a monochromator 22 and

InGAs detectors 26. The detected intensity from the sample is converted to a voltage through analog electronics 26 and digitized through a 16-bit A/D converter 27. The spectrum is passed to a processor 33 for processing through the classification procedure. First, the absorbance is calculated 28 on the basis of the detected light through  $-\log(R/R_o)$  where  $R$  is the reflected light and  $R_o$  is the light incident on the sample determined by scanning a reference standard. Subsequent processing steps, described below, result in either a classification 32 or a message indicating an invalid measurement. A block diagram of the integrated system is shown in Figure 2.

[0027] In an alternative embodiment, a group of LED's is employed as an energy source 21 to produce energy at pre-selected wavelengths, which is subsequently transmitted 23 toward the skin. The LED's, which surround a single detection element 26 radially, are alternately energized, and the detected energy from each LED that is reflected by or transmitted through the skin is used to form one spectrum. The edge-to-edge distance between each of the LED's and the detector element, or the distance between the point of illumination and the point of detection, is specific to the wavelength of the energy being emitted from the respective LED's. The preferred distance from the point of illumination, comprising the light-emitting surface of the LED's, and the point of detection is a minimum of 1 mm and maximum of 3 mm. The 1 mm distance is used for wavelengths above 1380 nm and the 3 mm distance for wavelengths in the region 1100-1380 nm. The set of wavelengths includes but is not limited to 1100, 1208, 1210, 1275, 1350, 1650, 1720, 1760 nm. The illumination and detection elements 21, 26 are coupled to the target site through staring optics and a lens system 23, 24. One skilled in the art will appreciate that other coupling methods are also applicable, including fiber optics, with the particular configuration being dictated by the desired distance between the points of illumination and detection.

[0028] Alternatively, the measurement can be accomplished with existing commercially available NIR spectrometers, including a Perstorp Analytical NIRS 5000 spectrometer or a Nicolet Magna-IR 760 spectrometer. In addition, the measurement can be made by collecting reflected light off the surface of the skin or light transmitted through a portion of the skin, such as the finger or the ear lobe. Further, the use of reflectance or transmittance can replace the preferred absorbance measurement.

## GENERAL PROCESSING PROCEDURE

[0029] The general procedure for determination of features related to absorbance of triglycerides in adipose tissue is implemented in a microprocessor 33 that automatically receives the measurement information from the ADC 27 as depicted in Figure 2. Subsequent to the calculation of an absorbance spectrum 28, the main components of the feature extraction and classification and/or estimation procedures include outlier detection 29, preprocessing 30, feature extraction 31 and classification and/or estimation 32. The design of each procedure is performed on the basis of a calibration set of exemplary measurements. In this section we summarize the general steps that are described in detail in the subsequent Implementation Section.

### Measurement

[0030] The measurement 28 is a spectrum denoted by the vector  $m \in \mathcal{R}^N$  of absorbance values pertaining to a set of  $N$  wavelengths  $\lambda \in \mathcal{R}^N$  that span the near infrared (1100 to 2500nm). The spectrum is calculated thusly: the detected light is used to create a graph of  $-\log R/R_s$ , where  $R$  is the reflectance spectrum of the skin and  $R_s$  is the reflectance of the instrument standard. In infrared spectroscopy, this graph is analogous to an absorbance spectrum containing quantitative information that is based on the known interaction of the incident light with components of the body tissue and will be henceforth referred to in this manner. A plot of  $m$  versus  $\lambda$  is shown in Figure 1. More particularly, however, the measurement can consist of a specific selection of wavelengths in the near infrared that have been optimized for the extraction of features related to the absorbance of fat as described further below.

### Outlier Detection

[0031] The outlier detection procedure 29 is a method of detecting invalid measurements through spectral variations that result from problems in the instrument, poor sampling of the subject or a subject outside the calibration set. The preferred method for the detection of spectral outliers is through a principal component analysis and an analysis of the residuals. First, the spectrum,  $m$ , is projected onto five eigenvectors, contained in the matrix  $o$ , that were previously developed through a principal component analysis on a calibration set of exemplary absorbance spectra and are stored by the computer system that houses the processor 33. The calculation is given by

$$xpc_o = \sum_{k=1}^7 mo_k \tag{1}$$

5 and produces the 1 by 5 vector of scores,  $xpc_o$  where  $o_k$  is the  $k^{th}$  column of the matrix  $o$ . The residual,  $q$ , is determined according to

$$10 \quad q = m - xpc_o o^T \tag{2}$$

and compared to three times the standard deviation of the expected residual of the calibration set. If greater, the sample is reported to be an outlier and the procedure is terminated.

15 *Preprocessing*

[0032] Preprocessing 30 includes operations such as wavelength selection, scaling, normalization, smoothing, derivatives, filtering and other transformations that attenuate noise and instrumental variation without affecting the signal of interest. The preprocessed measurement,  $x \in \mathcal{R}^N$ , is determined according to

$$25 \quad x = h(\lambda, m) \tag{3}$$

30 where  $h: \mathcal{R}^{Nx2} \rightarrow \mathcal{R}^N$  is the preprocessing function. Wavelength selection is performed on the data to eliminate extraneous variables that may bias the calibration or portions of the measured spectrum with a low signal-to-noise ratio. The specific methods used for feature extraction and estimation of skin fold thickness, described in more detail in the Implementation Section, include wavelength selection, multiplicative scatter correction and derivatives. [See Geladi, P. and D. McDougall and H. Martens. "Linearization and Scatter-Correction for Near-Infrared Reflectance Spectra of Meat," Applied Spectroscopy, 1985: 39: 491-500. Also see Savitzky, A. and M. J. E. Golay, "Smoothing and Differentiation of Data by Simplified Least Squares Procedures," Anal. Chem., vol. 36, no. 8, pp. 1627-1639, 1964.]

**Feature Extraction**

40 [0033] Feature extraction 31 determines the salient characteristics of measurements that are related to the absorbance of triglycerides in adipose tissue. The magnitude of a particular feature is specific to the volume of adipose tissue irradiated by the light. The measured characteristics of this tissue volume are dependent upon the optical properties of the preceding tissue layers and the optical properties of the adipose tissue. Examination of features from different wavelength regions can be used to provide information about the characteristics of the dermis and properties of the adipose tissue.

45 [0034] In general, feature extraction is any mathematical transformation that enhances a quality or aspect of the sample measurement for interpretation. The purpose of feature extraction is to represent concisely and to enhance the properties and characteristics of the tissue measurement site for skin fold thickness estimates, classification and body fat percent prediction. In addition, the features provide significant information about the tissue properties they represent and can be used for alternate purposes such as system diagnostics or optimization.

50 [0035] The features are represented in a vector,  $z \in \mathcal{R}^M$  that is determined from the preprocessed measurement through

$$55 \quad z = f(\lambda, x) \tag{4}$$

where  $f: \mathcal{R}^N \rightarrow \mathcal{R}^M$  is a mapping from the measurement space to the feature space. Decomposing  $f(\bullet)$  will yield specific transformations,  $f_i(\bullet): \mathcal{R}^N \rightarrow \mathcal{R}^M_i$  for determining a specific feature. The dimension,  $M_i$ , indicates whether the  $i^{th}$  feature is a scalar or a vector and the aggregation of all features is the vector  $z$ . When a feature is represented as a vector or a pattern, it exhibits a certain structure indicative of an underlying physical phenomenon.

**[0036]** The individual features are divided into two categories:

1. abstract, and
2. simple.

Abstract features do not necessarily have a specific interpretation related to the physical system. Specifically, the scores of a principal component analysis are useful features although their physical interpretation is not always known. For example, the principal component analysis provides information regarding the nature of the tissue absorbance spectrum. The most significant tissue variation is generally related to its structure, and the absorbance of adipose tissue is an indicator of variation in the structure of the preceding tissue layers. Therefore, the scores of the principal component analysis provide useful information for classification on the basis of the optical properties of the adipose tissue and constitute a valuable set of features.

**[0037]** Simple features are derived from an *a priori* understanding of the sample and can be related directly to a physical phenomenon. For example, the thickness of the dermis or subcutaneous layer results in specific spectral manifestations. These spectral variations are extracted and enhanced and serve as both a feature for subject classification and a measurement of their respective tissue properties.

**[0038]** In the general case the full spectrum can be passed to the classification system. However, the following three specific methods of feature extraction, which have been shown to provide superior classification performance and measurement of other relevant tissue properties are described further below:

1. The scores from factor analysis, specifically principal component analysis.
2. Relative absorbance of water and fat.
3. Normalized magnitude of the absorbance bands of triglycerides in adipose tissue

The detailed implementation of these approaches for extracting features on the basis of a calibration set is provided in the next section.

### **Calibration**

**[0039]** The preprocessed spectra and/or the extracted features are subjected to one of two further processing steps. First, decisions may be made regarding the extracted features for the purpose of subject classification. The determination of a change in the state of the dermis may be made on the basis of the extracted feature through a method of classification 32, for example the degree of tissue hydration. Alternately, the subject may be classified as "fat" because the sampled tissue volume produced a significant feature related to the absorbance of fat. Conversely, the subject may be classified as "thin" because the feature related to the absorbance of fat has a small magnitude. In either case, the classification is based on an assessment of the tissue volume sampled and not the overall body composition of the individual.

**[0040]** The preprocessed spectrum may be subjected to an estimation 32 algorithm that estimates the thickness of the adipose layer or the percent body fat of the subject. In the case of skin fold thickness estimation, the estimation procedure is relatively simple and can operate on the basis of a preprocessed spectrum or extracted features.

**[0041]** In the case of the body composition determination, the procedure relies on the implementation of a model that maps the absorbance spectrum to a percent body fat determination. Although salient features may be used in this algorithm the overall body composition is dependent upon other characteristics, in addition to the local thickness of the adipose tissue. Demographics, such as age and sex, play an important role in the determination of body fat [See Heyward, et al., op. cit.]. Both age and sex can be estimated from the same measured spectrum as previously disclosed in two related applications, "A system for the non-invasive determination of age," United States Patent Application Ser. No. 09/487,231 filed by T. Ruchti, S. Thennadil, S. Malin and J. Rennert on January 19, 2000, now United States patent no. 6,501,982 and "A system for the non-invasive determination of sex," United States Patent Application Ser. No. 09/487,733, filed by T. Ruchti, S. Thennadil, S. Malin and J. Rennert on January 19, 2000, now United States patent no. 6,493,566. Therefore, the method for body composition assessment utilizes both the age and sex determination procedures previously described and the skin fold thickness estimation method disclosed herein.



## 3. Crisp Classification

[0042] The classification of the subject on the basis of the extracted features is performed through a classification step that involves a mapping and a decision. The mapping step is given by

$$L = f(z) \quad (5)$$

where  $L$  is a scalar that can be used to measure the distance from the predefined body composition categories. For example, two values,  $L_{lean}$  and  $L_{fat}$ , associated with the representative or mean value of  $L$  for a "lean" and a "fat" category respectively are predefined and the class assignment is based on the closeness of  $L$  to  $L_{lean}$  and  $L_{fat}$ . For example, the distance of  $L$  to a previously established class means that classes can be measured by

$$\begin{aligned} d_{lean} &= |L_{lean} - L| \\ d_{fat} &= |L_{fat} - L| \end{aligned} \quad (6)$$

The decision is made as follows:

1. if  $d_{lean} < d_{fat}$  then the tissue volume sampled is classified as "lean" or containing relatively low percentage amount of triglycerides.
2. if  $d_{lean} \geq d_{fat}$  then the tissue volume sampled contains a relatively high amount of triglycerides and is classified as "fat."

The mapping and decision limits are determined from a calibration set of exemplary features and corresponding assessments of reference values, i.e. "lean" or "fat," through a classification calibration procedure. Existing methods include linear discriminant analysis, SIMCA, k nearest-neighbor, fuzzy classification and various forms of artificial neural networks. Furthermore, one skilled in the art will appreciate that more than two distinct classes for age can be defined with an upper limit based on the accuracy of the measurement device. [See Duda, R.O. and P.E. Hart, Pattern Classification and Scene Analysis, John Wiley and Sons, New York, 1973. Also see Wold, S. and M. Sjostrom. "SIMCA: A method for analyzing chemical data in terms of similarity and analogy," Chemometrics: Theory and Application, ed. B.R. Kowalski, ACS Symposium Series, 52, 1977. Also see Bezdek, J.C. and S.K. Pal, eds. Fuzzy Models for Pattern Recognition. IEEE Press, Piscataway, NJ, 1992. also see Keller, J., M. Gray and J. Givens. "A Fuzzy K nearest Neighbor Algorithm," IEEE Transactions on Systems, Man, and Cybernetics, Vol. SMC-15, No. 4, pp. 580-585, July/August, 1985. also see Pao, Y.H. Adaptive Pattern Recognition and Neural Networks. Addison-Wesley Publishing Company, Inc., Reading, MA, 1989.]

## .4 Fuzzy Classification

[0043] While statistically based class definitions provide a set of mutually exclusive classes, the appropriate classification of a tissue sample and the resulting spectral variation change over a continuum of values. For example, the level of "leanness" of a sampled tissue volume varies within a population of individuals in a continuous rather than discrete manner. Therefore, the natural variation in the spectra results in significant class overlap. Distinct class boundaries based on the absorbance of fat in adipose tissue do not exist and many measurements are likely to fall between classes and have a statistically equal chance of membership in any of several classes.

Therefore, "hard" class boundaries and mutually exclusive membership functions may be inadequate to model the variation encountered in the target population.

[0044] A more versatile method of class assignment is based on fuzzy set theory [See Bezdek, J.C., et al., op. cit. Also see Chen, C.H., ed., Fuzzy Logic and Neural Network Handbook, Piscataway, NJ: IEEE Press, 1996. Also see Zadeh, L.A. "Fuzzy Sets," Inform. Control, vol. 8, pp. 338-353, 1965.]. Generally, membership in fuzzy sets is defined by a continuum of grades and a set of membership functions that map the feature space into the interval [0,1] for each class. The assigned membership grade represents the degree of class membership with "1" corresponding to the highest degree. Therefore, a sample can simultaneously be a member of more than one class.

[0045] The mapping from feature space to a vector of class memberships is given by

$$c_k = f_k(z) \quad (7)$$

where  $k=1,2,\dots,P$ ,  $f_k(\bullet)$  is the membership function of the  $k^{\text{th}}$  class,  $c_k \in [0,1]$  for all  $k$  and the vector  $c \in \mathfrak{R}^P$  is the set of class memberships. An example of the general equation employed to represent a membership function is

$$y = e^{-\frac{1}{2\sigma^2}(z-\bar{z})^2} \quad (8)$$

where  $y$  is the degree of membership in a sub-set,  $z$  is the feature used to determine membership,  $\bar{z}$  is the mean or center of the fuzzy sub-set and  $\sigma$  is the standard deviation. However, one skilled in the art will appreciate that the suitable membership function is specific to the application.

**[0046]** The membership vector provides the degree of membership in each of the predefined classes and can be used for blood analyte prediction as disclosed by Malin, et. al. in a related application, U. S. Patent Application Ser. No. 09/359,191, now U.S. patent no. 6,280,381, previously cited. Alternately, the degree of class membership can be used to calculate the thickness of adipose tissue and the body composition of the individual through a suitable defuzzification function. The defuzzification function can be determined as described by Malin et al. in a related application, U. S. Patent Application Ser. No. 09/359,191, now U.S. patent no. 6,280,381 previously cited. Alternately, a calibration set of exemplary spectral measurements and associated reference values can be used to determine a calibration model for mapping the class membership to an estimate of the selected variable, skin fold thickness or body composition, for example.

#### .5 Estimation

**[0047]** The method of estimation relies on the employment of a calibration model that maps the preprocessed spectrum through a linear or nonlinear mapping to an estimate of a target variable, such as skin fold thickness or percent body fat. In the linear case, given the processed spectrum,  $x$ , and the calibration model coefficients  $w_c$  the estimate is determined according to

$$\hat{y} = \sum_{k=1}^N w_{c,k} x_k \quad (9)$$

where  $w_{c,k}$  is the  $k^{\text{th}}$  element of  $w_c$  and  $\hat{y}$  is the estimated variable. One skilled in the art will appreciate that a nonlinear mapping from  $x$  to  $\hat{y}$  can also be easily specified through artificial neural networks, nonlinear partial-least squares regression or other nonlinear method of calibration [See Geladi, P. and B.R. Kowalski, "Partial least-squares regression: a tutorial," *Analytica Chimica Acta*, 185, pp. 1-17, 1986. Also see Pao, op. cit.].

**[0048]** The preferred model is linear and is constructed through a factor analysis to decompose the high dimensional, or redundant, data consisting of absorbance, intensity or reflectance measurements at several hundred wavelengths to a few significant factors that represent the majority of the variation within the data set. The factors that capture variation in the spectra correlated to the target variable are used in the calibration model and the samples are projected into the resulting factor space to produce a set of scores for each sample. Finally, multiple linear regression is applied to model the relationship between the scores of the significant factors and the target variable.

**[0049]** In the case of body composition determination, the near-IR age estimate and the near-IR sex estimate for the subject are used with the near-IR estimate of skin fold thickness. Two procedures for body composition determination are disclosed herein. The first employs different calibrations for mapping skin fold thickness to percent body fat for each age group and each sex. The second and preferred implementation is a model that maps the three variables skin fold thickness, age and sex to an estimate of the percent body fat of the individual. This mapping is of the form

$$y = f(x_1, x_2, x_3) \quad (10)$$

where  $y$  is the estimate of the percent body fat,  $x_1$  is the near-IR estimate of skin fold thickness,  $x_2$  is the near-IR estimate of the sex and  $x_3$  is the near-IR estimate of the age as previously disclosed in the two related applications, 09/487,239 and 09/487,733, now United States patents no. 6,501,982 and 6,493,566, respectively. The model  $f()$  is determined by applying an analytical technique such as artificial neural networks to a calibration set of exemplary measurements. One skilled in the art will appreciate that other methods of nonlinear regression can be applied to determine alternate forms for  $f()$ .

## IMPLEMENTATION DETAILS

### Basis Set

[0050] For the purpose of feature extraction and classification, a two-component basis set was provided 40, shown in Figure 3, was calculated through  $-\log(T/T_0)$  where  $T$  is the reflected light and  $T_0$  is the light incident on the sample determined by scanning a blank. A pure component absorbance spectrum of fat 50 was measured by scanning excised bovine adipose tissue with a spectrometer according to the preferred embodiment. The resulting spectrum is shown in Figure 4.

### Experimental Data Set

[0051] The Experimental Data Set for calibrating the models described subsequently was realized through a study of 19 volunteers (16 male and 3 female) with ages ranging from 21 to 55 years. One absorbance spectrum was measured on each subject's forearm on two successive days with a spectrometer according to the preferred embodiment. The percent body fat of the participants was estimated through the Siri equation for body composition [See Siri, W. E. "The gross composition of the body," Adv. Biol. Med. Phys., 4, 1956, pp. 239-280.]. Skin fold thickness was measured on the biceps, triceps, subscapular and suprailliac regions of each subject with a pair of research grade calipers of the type known as HARPENDEN, manufactured by British Indicators, LTD.

[0052] While this is a specific experiment aimed at the determination of a suitable set for classification and estimation of features and attributes associated with the thickness of adipose tissue, one skilled in the art will readily appreciate that, for different subjects and for different target performance levels, other experiments with more or fewer subjects would be performed.

### Projection algorithm

[0053] A first method of feature extraction characterizes tissue based on an absorbance spectrum measured with a near-IR spectrometer in the wavelength region of 1100-1350nm. Referring now to Figure 5, the measured spectrum 61 is normalized by projecting 62 a water absorbance spectrum 60 onto the measured spectrum 61 and calculating the difference 65. The peak 66 of the resulting fat absorbance band near 1210 nm is used to determine the percent body fat or thickness of adipose tissue at the measurement site using a simple univariate mapping.

[0054] Given the measured spectrum 61,  $x$ , and the pure component spectrum of water 60,  $p$ , the projection 62 of the water spectrum onto the measured spectrum is determined according to

$$m = \left[ p_w p_w^T \right]^{-1} p_w x_w \quad (11)$$

where  $m$  is a scalar representing the magnitude of water absorbance and the subscript  $w$  represents a subset of wavelengths (1100-1150 nm and 1300-1350 nm). Since water is predominantly concentrated in the dermal layer, the magnitude of  $m$  represents an extracted feature 63 related to the characteristics of the dermis that may be subsequently used in the classification 64 of subjects through linear Discriminant analysis as described below.

[0055] The water spectrum 60 is projected 62 and subtracted 65 from the measurement 61 according to

$$z = x - mp \quad (12)$$

where  $z$  is the final spectrum. The method summarized in equations 11 and 12, above was applied to the Experimental Data Set and plots of  $z$  for all subjects in the Experimental Data Set are shown in Figure 6. As the figure clearly shows, the magnitude of the absorbance peak at 1210nm correlates with percent body fat, so that individuals with the highest percent body fat have the most pronounced absorbance peak at or around 1210 nm. Furthermore, the magnitude of this peak is a feature 67 related to the thickness of the adipose tissue in the subcutaneous layer that is used in a further classification 68 of subjects.

[0056] While this procedure was explained through example in the 1100-1350 nm range, one skilled in the art will appreciate that this method is easily extendable to the 1650-1800 nm wavelength range where additional features related to the absorbance of adipose tissue exist at 1720 and 1760 nm as shown in Figure 1. Furthermore, the basis set could include other components that could then be used in the projection to extract features related to other characteristics of the tissue including hydration, protein concentrations, skin cholesterol, and others.

[0057] For classification, a Discriminant function is applied to classify the subjects based on the two features 63, 67, either in two separate steps 64, 68 as indicated in Figure 5, or through a single step. For example, given the vector  $f$  containing both features 63,67 of Figure 5, the subject is classified into one of two categories to produce the scalar,  $L$ :

$$L = fw \quad (13)$$

where  $w$  is a vector of weights. This result is compared to  $\bar{L}$ , the center between the two classes. If  $L > \bar{L}$  then the subject is classified into Group 1. If not, the spectrum is classified as belonging to Group 2. The two resulting groups contain a greater degree of homogeneity in the sampled tissue volume than the original population.

[0058] In addition, an arbitrary number of groups can be defined, depending upon the desired level of homogeneity in each group. Furthermore, a fuzzy classification system can be developed by defining a set of membership functions for the set of predefined classes. For example, given  $z$ , the peak magnitude of the spectra in Figure 6, the group of subjects may be denoted as thin, medium and fat corresponding to the absorbance related to fat in adipose tissue. For each class the mean feature,  $\bar{z}$ , and standard deviation,  $\sigma$ , are calculated. The membership function defining the degree of membership in a particular class is given by

$$y = e^{\frac{-1}{2\sigma^2}(z-\bar{z})^2} \quad (14)$$

where  $y$  is the degree of membership. While this membership function is Gaussian, one skilled in the art will appreciate that the suitable membership function is specific to the application. The mean and standard deviation associated with each of the three categories were determined based on the target population in the Experimental Data Set.

[0059] Values for the feature inputs to the membership functions that are unusually high or low fall outside the expected range of the sub-sets and are assigned low membership values. This information is used to indicate that the subject's tissue characteristics are outside of the previously examined population and is used for outlier analysis. For the current implementation when  $y < 0.1$  for all sub-sets the prediction is assigned a low confidence level.

[0060] The resulting class memberships are suitable for use in categorization for blood analyte prediction as described by Malin, et al in a related application 09/359,191, now United States patent no. 6,280,381. The membership functions described have been designed for a specific population of subjects and cannot be generalized to all potential individuals. The invention, however, is directed to the arbitrary use of membership functions to assign a degree of membership in a given class to a subject for blood analyte prediction.

### Estimation of Body Composition

[0061] The procedure for extracting features related to the fat in adipose tissue shown in Figure 5 can be used to estimate the percent body fat of the individual. For example, the extracted feature,  $z$ , at 1210 nm was plotted versus percent body fat in Figure 7. The percent body fat is estimated via

$$fat\% = az_{1210nm} + b \quad (25)$$

where  $a$  is the slope of the line in Figure 7 and  $b$  is the corresponding intercept, and  $z_{1210nm}$  is the magnitude of  $z$  at 1210 nm. In this particular example, one calibration was developed for all subjects regardless of age or sex. Improved accuracy can be obtained through a larger data set and the use of age and sex estimates as indicated by Equation 10.

### 5 **Feature Extraction with Two or Three Wavelengths**

[0062] The method of feature extraction and body fat estimation described above can be performed with an entire spectrum as previously described or with 2-3 wavelengths, depending on the desired level of accuracy. For example, the procedure of Figure 5 was modified as shown in Figure 8 and involves the measurement of body fat using spectra 81 measured at three wavelengths. The feature  $z$ , is calculated by projecting the water spectrum 80 on the measurement at only two wavelengths 82 and determining the difference 83 at a third wavelength. Therefore, the procedure can be implemented in a system with three LED's equally spaced

[0063] The selected wavelengths are preferably 1124, 1210 and 1276 nm and the corresponding absorbances of water are 0.4781, 0.184148 and 0.164745 respectively. The percent body fat is estimated 84 via

$$fat\% = az_{1210nm} + b$$

(16)

where  $a$  is the slope,  $b$  is the intercept, and  $z_{1210nm}$  is the magnitude of  $z$  at 1210nm (the extracted feature). In the current embodiment  $a=388.18$  and  $b=9.177$ .

[0064] This procedure was applied to the Experimental Data Set and the extracted feature,  $z_{1210nm}$ , was calculated for each absorbance spectrum 81. The actual percent body fat of each subject versus the extracted feature is shown in Figure 9. The correlation coefficient ( $r$ ) of 0.81 indicates that the same method can be generalized to involve two or more wavelengths.

### 30 **Abstract Feature Extraction**

[0065] Abstract feature extraction is utilized as an alternate method for feature extraction and subject classification as depicted in Figure 10. For this implementation, a separate data set of 266 arm scans on subjects of diverse sex, age and ethnicity were used to determine the parameters. A principal component analysis was performed on the 266 sample data set and the scores of the first three eigenvectors are plotted in Figure 11. Figure 12 compares the third eigenvector from figure 11 with the absorbance spectrum of the animal fat sample of figure 4. As shown, the third eigenvector closely matches the absorbance spectrum of fat. Therefore, the first three scores,  $xpc_{1-3}$ , are utilized as features for subject classification.

[0066] The determination of the subject class occurs as follows. First, the absorbance spectrum,  $m$  28, is provided from the outlier detection system. Wavelength selection 100 is applied to truncate the spectral range to regions with significant absorbance due to fat in adipose tissue (1100 to 2500 nm). The spectrum is projected 101 onto the eigenvectors,  $p_k$ , previously developed through a principal component analysis on the 266 sample calibration set. The calculation, shown in Figure 10, produces the 1 by  $N$  vector of scores,  $xpc$ .

[0067] A Discriminant function is applied to classify the subjects on the basis of the first  $M$  scores ( $M=3$  in this application). The scores are rotated 102 through a cross product with the discriminant  $w$ , as depicted in Figure 10 to produce the scalar,  $L$ . This result is compared 103 to  $\bar{L}$ , the center between the two classes. If  $L > \bar{L}$  then the sampled tissue volume is classified as having significant absorbance due to fat 104. If not, the tissue volume is classified as having low absorbance due to fat 105. As discussed previously, one skilled in the art will recognize that this system can be generalized to an arbitrary number of classes or employ a fuzzy classification system.

### 50 **General Estimation and Classification Methods**

[0068] The general estimation implementation, shown in Figures 13a, uses a general calibration model 131 to predict a variable related to the absorbance of fat in adipose tissue at one or more wavelength regions from 1100-2500 nm. An absorbance spectrum 28 is provided. Specific wavelength ranges, such as 1550 to 1800 nm and 2050 to 2350 nm, are selected and preprocessed 30 using windowed multiplicative scatter correction or other appropriate methods. The processed data are mapped to a body fat prediction 32 using a calibration model 131 that is realized using known methods, including principal component regression [Martens, H. and T. Naes. *Multivariate Calibration*, New York: John Wiley and Sons, 1989.], partial least squares regression and artificial neural networks. For example, a five-factor partial-

least squares model was developed for estimating the skin fold thickness using spectra from the Experimental Data Set. The test set predictions through cross validation are shown in Figure 14. As shown in the figure the standard error of prediction (SEP) was 1.42, resulting in a prediction accuracy of approximately seventy percent. While the experimental results demonstrate the validity and benefit of the estimation procedure, accuracy of the results is directly dependent on the accuracy of the spectral measurements. Further improvement to results accuracy will be achieved through improvements in the noise level and the resolution of the spectrometer.

[0069] The general classification procedure for grouping subjects according to features related to the absorbance of fat in adipose tissue is shown in Figure 13b. Again an absorbance spectrum 28 is provided. Specific wavelength ranges, such as 1100-1350 nm and 1550 to 1800 nm, are selected and preprocessed 30 using windowed multiplicative scatter correction or other appropriate methods. The processed data are subjected to feature extraction through a factor-based method, such as principal component analysis. Finally, the subject is classified into a body fat category 32 through a classification procedure 132, such as linear Discriminant analysis, SIMCA, k nearest-neighbor and various forms of artificial neural networks.

**Claims**

1. A non-invasive method of characterizing and classifying the state and structure of tissue on the basis of spectral absorbance features related to fat in the subcutaneous tissue comprising the steps of:

- providing a calibration set of exemplary measurements;
- measuring NIR absorbance spectrum of a skin tissue sample;
- detecting outliers, wherein said outliers are invalid measurements caused by spectral variation due to any of instrument malfunction, poor sampling and subjects outside of said calibration set;
- providing a basis set, wherein said basis set comprises a pure component spectrum of water and one of animal fat, for feature extraction and preprocessing;
- preprocessing said NIR spectrum, wherein said preprocessing step includes one or more transformations that attenuate noise and instrumental variation without affecting signal of interest, including any of wavelength selection, scaling, normalization, smoothing, derivatives, and filtering; and
- extracting features, whereby features of measurements relevant to classification are determined.

2. The method of claim 1, wherein said spectrum is denoted by a vector  $m \in \mathfrak{R}^N$  of absorbance values pertaining to a set of  $N$  wavelengths  $\lambda \in \mathfrak{R}^N$ .

3. The method of Claim 1, wherein said NIR spectral measurements are in the wavelength region of approximately 1100 to 2500nm.

4. The method of Claim 1, wherein said outlier detection step employs principal components analysis and residual analysis to detect spectral outliers.

5. The method of Claim 4, wherein said outlier detection step further comprises the steps of:

projecting a spectrum  $m$  onto a plurality of eigenvectors, contained in a matrix  $\mathbf{o}$ , said matrix  $\mathbf{o}$  being previously developed through principal components analysis of said calibration set, where

$$xpc_o = \sum_{k=1}^7 m o_k ,$$

and where  $\mathbf{o}_k$  is the  $k^{th}$  column of the matrix  $\mathbf{o}$ ; determining residual  $q$ , according to

$$q = m - xpc_o o^T ;$$

comparing said residual  $q$  to three times the standard deviation of the residual of said calibration set; and

reporting said sample as an outlier if  $q$  is greater.

6. The method of Claim 1, wherein said features are represented in a vector  $z \in \mathbb{R}^M$  that is determined from a pre-processed measurement through:

$$z = f(\lambda, x),$$

where  $f: \mathbb{R}^N \rightarrow \mathbb{R}^M$  is a mapping from a measurement space to a feature space, wherein decomposing  $f(\bullet)$  yields specific transformations,  $f_i(\bullet): \mathbb{R}^N \rightarrow \mathbb{R}^{M_i}$  for determining a specific feature, wherein the dimension  $M_i$  indicates whether an  $i^{\text{th}}$  feature is a scalar or vector and an aggregation of all features is the vector  $z$ , wherein said transformations enhance a quality or aspect of sample measurement for interpretation to represent concisely properties and characteristics of the tissue measurement site and wherein a feature exhibits a certain structure indicative of an underlying physical phenomenon when said feature is represented as a vector or a pattern.

7. The method of Claim 6, wherein individual features are divided into two categories comprising:

abstract features that do not necessarily have a specific interpretation related to a physical system; and simple features that are derived from an *a priori* understanding of a sample and that can be related directly to a physical phenomenon.

8. The method of Claim 4, wherein said feature extraction step comprises principal component analysis.
9. The method of Claim 6, wherein said feature extraction step comprises normalizing the magnitude of absorbance bands of fat in adipose tissue.
10. The method of Claim 6, wherein said feature extraction step comprises comparing water and fat absorbance spectra of said sample to water and fat absorbance spectra of said calibration set.

11. The method of Claim 8, wherein said feature extraction step comprises the steps of:

truncating said spectrum  $m$  at the wavelength region of approximately 1100 - 2500nm; projecting said truncated spectrum onto a plurality,  $p_k$ , of eigenvectors, where said eigenvectors were previously calculated through principal component analysis of said calibration set;

wherein said projection produces a 1 by  $N$  vector of scores,  $x_{pc}$ ; and

applying a Discriminant function whereby said samples are classified on the basis of the first  $M$  scores, wherein said scores are rotated through a cross product with a Discriminant,  $w$ , to produce a scalar,  $L$ .

12. The method of Claim 11, wherein  $M = 3$ .

13. The method of Claim 1, further comprising the step of:

classifying said sample according to predefined categories of fatness and leanness.

14. The method of Claim 13, wherein said spectrum is limited to any of the wavelength regions of approximately 1100-1350nm and approximately 1650 - 1800nm.

15. The method of Claim 14, wherein said feature extraction step comprises the step of:

normalizing said limited spectrum.

16. The method of Claim 15, wherein said normalizing step comprises the steps of:

projecting said spectrum of water on said limited spectrum according to

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$$m = [P_w P_w^T]^{-1} P_w x_w,$$

where m is a scalar representing the magnitude of water absorbance and the subscript w represents a subset of wavelengths; and

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subtracting said pure water spectrum from said limited spectrum according to

$$z = x - mp,$$

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where z is a final spectrum.

17. The method of Claim 13, wherein said classification step comprises the steps of:

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measuring similarity of at least one feature to said predefined categories; and  
assigning membership in said predefined categories.

18. The method of Claim 17, wherein said assigning step uses mutually exclusive classes and assigns each sample to one class.

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19. The method of Claim 17, wherein said assigning step uses a fuzzy classification system that allows class membership in more than one class simultaneously.

20. The method of Claim 18, wherein said assigning step further comprises the steps of:

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mapping said sample to one of said predefined classes; and  
applying a decision rule to assign class membership.

21. The method of Claim 20, wherein said mapping step is given by:

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$$L = f(z),$$

where L is a scalar that measures distance of a sample from the predefined categories.

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22. The method of Claim 18, wherein said categories are "fat" and "lean" and where  $L_{fat}$  corresponds to a representative value for said "fat" class and  $L_{lean}$  corresponds to a representative value for said "lean" class; and wherein said class assignment is based on the closeness of L to  $L_{fat}$  and  $L_{lean}$ .

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23. The method of Claim 22, wherein a distance  $d_{fat}$  of L to  $L_{fat}$  is measured by

$$d_{fat} = |L_{fat} - L|,$$

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and wherein a distance  $d_{lean}$  of L to  $L_{lean}$  is measured by

$$d_{lean} = |L_{lean} - L|.$$

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24. The method of Claim 23, wherein said decision rule is:



If  $d_{lean} < d_{fat}$  said sample is classified as "lean;"

If  $d_{lean} \geq d_{fat}$  said sample is classified as "fat."

5 25. The method of Claim 20, wherein limits for said mapping and said decision rule are determined from a calibration set of exemplary measurements and corresponding reference values of fat and lean through a classification calibration procedure.

10 26. The method of Claim 25, wherein said classification calibration comprises any of linear Discriminant Analysis, SIMCA, k nearest neighbor, fuzzy classification artificial neural networks.

27. The method of Claim 26, wherein said mapping step is given by

$$L = fw,$$

15 where  $w$  is a vector of weights, and wherein  $L$  is compared with  $\bar{L}$ , where  $\bar{L}$  is a center between two of said mutually exclusive classes.

20 28. The method of Claim 27, wherein said assigning step employs a decision rule, wherein said decision rule is

If  $L > \bar{L}$ , said sample is assigned to a first of said two classes;

If  $L \leq \bar{L}$ , said sample is assigned to a second of said two classes.

25 29. The method of Claim 16, wherein class membership is defined by a continuum of grades, and wherein a set of membership functions map a feature space into an interval  $[0,1]$  for each class and wherein an assigned grade of "1" represents a highest degree of class membership.

30 30. The method of Claim 29, wherein the mapping from the feature space to a vector of class memberships is given by:

$$c_k = f_k(z),$$

35 where  $k=1, 2, \dots, P$ , and where  $f_k(\cdot)$  is the membership of the  $K^{th}$  class, and where  $c_k \in [0,1]$  for all  $k$  and where a vector  $c \in \mathfrak{R}^P$  is the set of all class memberships.

40 31. The method of claim 30, wherein a membership function is represented by

$$y = e^{\frac{-1}{2\sigma^2}(z-\bar{z})^2},$$

45 where  $y$  is the degree of membership in a fuzzy subset,  $z$  is the feature used to determine membership,  $\bar{z}$  is the center of a fuzzy subset, and  $\sigma$  is the standard deviation.

50 32. The method of Claim 30, wherein said membership vector provides the degree of class membership in each of said predefined classes.

33. The method of Claim 1, further comprising the step of:

estimating thickness of a skinfold, said skinfold comprising a layer of adipose tissue.

55 34. The method of Claim 33, wherein said estimating step uses any of preprocessed spectra and extracted features.

35. The method of Claim 34, wherein said estimating step further comprises the step of:

providing a calibration model to map said preprocessed spectrum through a mapping to an estimate of skin fold thickness.

36. The method of Claim 35, wherein said mapping is linear.

37. The method of Claim 36, wherein said skin fold thickness estimate is determined according to

$$\hat{y} = \sum_{k=1}^N w_{c,k} x_k ;$$

given the preprocessed spectrum  $x$ , and the calibration model  $w_c$ , where  $w_{c,k}$  is the  $k^{\text{th}}$  element of  $w_c$  and  $y$  is the skin fold thickness estimate.

38. The method of Claim 37, wherein said calibration model employs factor analysis to decompose a high-dimensional (redundant) data set comprising absorbance, intensity or reflectance measurements at a plurality of wavelengths to significant factors representing the majority of variation within said data set; and wherein said calibration model includes factors that capture variation in said spectra correlated with variation in skin fold thickness.

39. The method of Claim 38, further comprising the steps of;

projecting said samples into a resulting factor space to produce a set of scores for each sample; and applying multiple linear regression to model the relationship between said scores and said skin fold thickness.

40. The method of claim 35, wherein said mapping is non-linear.

41. The method of Claim 40, wherein said non-linear mapping is specified through any of artificial neural networks and non-linear partial least squares regression.

42. The method of Claim 33, further comprising the step of:

estimating body composition of a subject.

43. The method of Claim 42, wherein said body composition estimating step comprises the step of;

mapping a skin fold thickness estimate, a sex estimate and an age estimate to an estimate of the percent body fat of said subject according to:

$$y = f(x_1, x_2, x_3),$$

where  $y$  is the estimate of the percent body fat,  $x_1$  is the skin fold thickness estimate,  $x_2$  is the sex estimate, and  $x_3$  is the age estimate and  $f()$  is a calibration model.

44. The method of Claim 43, wherein said model  $f()$  is determined by applying a nonlinear regression method to a calibration set of exemplary measurements.

45. The method of Claim 42, wherein said spectrum is limited to three wavelengths.

46. The method of Claim 45, wherein said three wavelengths are 1124, 1210, and 1276nm.

47. The method of Claim 46, wherein said feature extraction step comprises the step of:

normalizing said limited spectrum.

48. The method of Claim 47, wherein said normalizing step comprises the steps of:

projecting said spectrum of water onto two of said three wavelengths; and  
 subtracting said pure water spectrum from said limited spectrum at the third of said wavelengths according to

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$$z = x - mp ,$$

10 where  $z$  is a final spectrum.

49. The method of Claim 47, further comprising the step of:

estimating the percent bodyfat according to

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$$fat\% = az_{1210nm} + b ,$$

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where  $a$  is the slope,  $b$  is the intercept and  $z_{1210nm}$  is the magnitude of  $z$  at 1210nm, where  $z$  is an extracted feature.

50. The method of Claim 13, or Claim 33, further comprising the step of:

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performing a blood analyte prediction

51. An apparatus for non-invasively characterizing and classifying the state and structure of a skin tissue sample based on spectral absorbance features related to the absorbance of fat in the subcutaneous tissue of a subject comprising:

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means for generating near infrared NIR energy;  
 means for separating said generated NIR energy into a plurality of wavelength regions;  
 an optical interface comprising:

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means for transmitting said NIR energy from said wavelength separating means towards a target measurement site on a subject; and  
 means for collecting NIR energy emanating from said measurement site;

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means for detecting said collected energy and converting said collected energy to a voltage;  
 means for converting said voltage to a digital value; and  
 means for analyzing said digital value, said means for analyzing adapted to carry out the method of claim 1, whereby said analysis results in any of a characterization and a classification of said skin tissue sample.

52. The apparatus of Claim 51, wherein said energy source and said wavelength separating means together comprise an array of LED's surrounding said detecting means in a radial fashion, each of said LED's and said detecting means having a lateral edge and wherein each of said LED's successively emits energy at a specific wavelength in a set of pre-selected wavelengths.

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53. The apparatus of Claim 52, wherein said set of pre-selected wavelengths includes 1100nm, 1208nm, 1210nm, 1275nm, 1350nm, 1650nm, 1720nm, 1760nm.

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54. The apparatus of Claim 52, wherein said lateral edge of any of said LED's comprises a point of illumination and said lateral edge of said detecting means comprises a point of detection, and wherein a distance between said point of illumination and said point of detection is approximately 1-3mm.

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55. The apparatus of Claim 54, wherein said LED array and said detecting means are coupled with said measurement site by means of staring optics and a lens system.

56. The apparatus of Claim 51, wherein said energy source is a quartz halogen lamp wherein said lamp transmits energy

in the wavelength range of approximately 1100 - 2500nm.

57. The apparatus of Claim 56, wherein said wavelength separating means is any of a monochromator and an interferometer.

58. The apparatus of Claim 51 wherein said transmission means is any of a light pipe, a fiber-optic probe, a lens system, and a light-directing mirror system.

59. The apparatus of Claim 51, wherein said energy collecting means comprises any of at least one staring optical detector and at least one fiber-optic probe.

60. The apparatus of Claim 51, wherein said energy detecting means comprises InGAs detectors.

61. The apparatus of Claim 51, wherein said digitizing means comprises a 16-bit A/D converter.

62. The apparatus of Claim 58, wherein a point of illumination is set through any of a focusing lens and a fiber-optic probe.

63. The apparatus of Claim 59, wherein a point of detection is set through any of a staring optical detector or a fiber-optic probe.

### Patentansprüche

1. Nichtinvasives Verfahren zum Charakterisieren und Klassifizieren des Zustands und einer Struktur von Gewebe auf der Basis von spektralen Absorptionsmerkmalen, die auf Fett in dem subkutanen Gewebe bezogen sind, mit folgenden Schritten:

Liefere eines Kalibrierungssatzes von exemplarischen Messungen;  
 Messen eines NIR-Absorptionsspektrums einer Hautgewebeprobe;  
 Erfassen von Ausreißern, wobei die Ausreißer ungültige Messungen sind, die durch eine spektrale Variation aufgrund von entweder einer Gerätefehlfunktion, einer schlechten Probenahme oder von Objekten außerhalb des Kalibrierungssatzes bewirkt werden;  
 Liefere eines Basissatzes, wobei der Basissatz ein reines Komponentenspektrum von Wasser und eines von tierischem Fett aufweist, für eine Merkmalsextraktion und ein Vorverarbeiten ;  
 Vorverarbeiten des NIR-Spektrums, wobei der Schritt des Vorverarbeitens eine oder mehrere Transformationen umfasst, die ein Rauschen und eine Gerätevariation dämpfen, ohne ein interessierendes Signal zu beeinflussen, umfassend eine Wellenlängenauswahl, ein Skalieren, eine Normierung, ein Glätten, Ableitungen und ein Filtern;  
 und  
 Extrahieren von Merkmalen, wodurch Merkmale von Messungen, die für eine Klassifizierung relevant sind, bestimmt werden.

2. Verfahren nach Anspruch 1, bei dem das Spektrum durch einen Vektor  $m \in \mathbb{R}^N$  von Absorptionswerten, die einen Satz von N Wellenlängen  $\lambda \in \mathbb{R}^N$  betreffen, angegeben wird.

3. Verfahren nach Anspruch 1, bei dem die spektralen NIR-Messungen in dem Wellenlängenbereich von etwa 1100 bis 2500 nm liegen.

4. Verfahren nach Anspruch 1, bei dem der Schritt des Erfassens von Ausreißern eine Hauptkomponentenanalyse und eine Residuenanalyse, um spektrale Ausreißer zu erfassen, verwendet.

5. Verfahren nach Anspruch 4, bei dem der Schritt des Erfassens von Ausreißern ferner folgende Schritte aufweist:

Projizieren eines Spektrums  $m$  auf eine Mehrzahl von Eigenvektoren, die in einer Matrix  $o$  enthalten sind, wobei die Matrix  $o$  vorher durch eine Hauptkomponentenanalyse des Kalibrierungssatzes entwickelt wird, wobei

$$xpc_o = \sum_{k=1}^7 mo_k$$

und wobei  $o_k$  die  $k$ -te Spalte der Matrix  $o$  ist; wobei das Residuum  $q$  gemäß

$$q = m - xpc_o o^T$$

bestimmt wird;

Vergleichen des Residuums  $q$  mit der dreifachen Standardabweichung des Residuums des Kalibrierungssatzes;

und

Berichten der Probe als einen Ausreißer, wenn  $q$  größer ist.

6. Verfahren nach Anspruch 1, bei dem die Merkmale in einem Vektor  $z \in \mathfrak{R}^M$  dargestellt sind, der aus einer vorverarbeiteten Messung durch

$$z = f(\lambda, x)$$

bestimmt wird, wobei  $f: \mathfrak{R}^N \rightarrow \mathfrak{R}^M$  eine Abbildung von einem Messungsraum auf einen Merkmalsraum ist, wobei

ein Zerlegen von  $f(\bullet)$  spezifische Transformationen  $f_i(\bullet): \mathfrak{R}^N \rightarrow \mathfrak{R}^{M_i}$  zum Bestimmen eines spezifischen Merkmals ergibt, wobei die Dimension  $M_i$  anzeigt, ob ein  $i$ -tes Merkmal ein Skalar oder ein Vektor ist, und eine Aggregation aller Merkmale der Vektor  $z$  ist, wobei die Transformationen eine Qualität oder einen Aspekt einer Probenmessung für eine Interpretation verbessern, um Eigenschaften und Charakteristika der Gewebemessstelle präzise darzustellen, und wobei ein Merkmal eine bestimmte Struktur zeigt, die ein zugrunde liegendes physikalisches Phänomen anzeigt, wenn das Merkmal als ein Vektor oder ein Muster dargestellt wird.

7. Verfahren nach Anspruch 6, bei dem einzelne Merkmale in zwei Kategorien geteilt werden, die aufweisen:

abstrakte Merkmale, die nicht notwendigerweise eine spezifische Interpretation, die auf ein physikalisches System bezogen ist, haben; und

einfache Merkmale, die aus einem A-priori-Verständnis einer Probe abgeleitet werden, und die direkt auf ein physikalisches Phänomen bezogen sein können.

8. Verfahren nach Anspruch 4, bei dem der Schritt des Extrahierens von Merkmalen eine Hauptkomponentenanalyse aufweist.

9. Verfahren nach Anspruch 6, bei dem der Schritt des Extrahierens von Merkmalen ein Normieren der Größe von Absorptionsbändern von Fett in einem Fettgewebe aufweist.

10. Verfahren nach Anspruch 6, bei dem der Schritt des Extrahierens von Merkmalen ein Vergleichen von Wasser- und Fettabsorptionsspektren der Probe mit Wasser- und Fettabsorptionsspektren des Kalibrierungssatzes aufweist.

11. Verfahren nach Anspruch 8, bei dem der Schritt des Extrahierens von Merkmalen folgende Schritte aufweist:

Beschneiden des Spektrums  $m$  bei dem Wellenlängenbereich von etwa 1100 bis 2500 nm;

Projizieren des beschnittenen Spektrums auf eine Mehrzahl,  $p_k$ , von Eigenvektoren, wobei die Eigenvektoren vorher durch eine Hauptkomponentenanalyse des Kalibrierungssatzes berechnet wurden;

wobei die Projektion einen 1-mal-N-Vektor von Scores,  $xpc$ , erzeugt; und

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Anwenden einer Diskriminantenfunktion, wodurch die Proben auf der Basis der ersten  $M$  Scores klassifiziert werden, wobei die Scores durch ein Kreuzprodukt mit einer Diskriminanten  $w$  rotiert werden, um einen Skalar  $L$  zu erzeugen.

5 **12.** Verfahren nach Anspruch 11, bei dem  $M=3$  ist.

**13.** Verfahren nach Anspruch 1, das ferner folgenden Schritt aufweist:

Klassifizieren der Probe gemäß vordefinierten Kategorien von Fetttheit und Magerkeit.

10 **14.** Verfahren nach Anspruch 13, bei dem das Spektrum auf einen der Wellenlängenbereiche von etwa 1100 bis 1350 nm und etwa 1650 bis 1800 nm begrenzt ist.

15 **15.** Verfahren nach Anspruch 14, bei dem der Schritt des Extrahierens von Merkmalen folgenden Schritt aufweist:

Normieren des begrenzten Spektrums.

**16.** Verfahren nach Anspruch 15, bei dem der Schritt des Normierens folgende Schritte aufweist:

20 Projizieren des Wasserspektrums auf das begrenzte Spektrum gemäß

$$m = [p_w p_w^T]^{-1} p_w x_w,$$

25 wobei  $m$  ein Skalar ist, der die Größe einer Wasserabsorption darstellt, und der Index  $w$  einen Teilsatz von Wellenlängen darstellt; und

30 Subtrahieren des reinen Wasserspektrums von dem begrenzten Spektrum gemäß

$$z = x - mp$$

35 wobei  $z$  ein endgültiges Spektrum ist.

40 **17.** Verfahren nach Anspruch 13, bei dem der Schritt des Klassifizierens folgende Schritte aufweist:

Messen einer Ähnlichkeit von mindestens einem Merkmal zu den vordefinierten Kategorien; und Zuweisen einer Zugehörigkeit zu den vordefinierten Kategorien.

45 **18.** Verfahren nach Anspruch 17, bei dem der Schritt des Zuweisens sich gegenseitig ausschließende Klassen verwendet und jede Probe einer Klasse zuweist.

**19.** Verfahren nach Anspruch 17, bei dem der Schritt des Zuweisens ein Fuzzy-Klassifizierungssystem, das eine Klassenzugehörigkeit zu mehr als einer Klasse gleichzeitig erlaubt, verwendet.

50 **20.** Verfahren nach Anspruch 18, bei dem der Schritt des Zuweisens ferner folgende Schritte aufweist:

Abbilden der Probe auf eine der vordefinierten Klassen; und Anwenden einer Entscheidungsregel, um eine Klassenzugehörigkeit zuzuweisen.

55 **21.** Verfahren nach Anspruch 20, bei dem der Schritt des Abbildens durch

$$L = f(z)$$

5 gegeben ist, wobei  $L$  ein Skalar ist, der einen Abstand einer Probe von den vordefinierten Kategorien misst.

22. Verfahren nach Anspruch 18, bei dem die Kategorien "fett" und "mager" sind, wobei  $L_{fett}$  einem darstellenden Wert für die Klasse "fett" und  $L_{mager}$  einem darstellenden Wert für die Klasse "mager" entspricht; und bei dem die Klassenzuweisung auf der Nähe von  $L$  zu  $L_{fett}$  und  $L_{mager}$  basiert.

23. Verfahren nach Anspruch 22, bei dem ein Abstand  $d_{fett}$  von  $L$  zu  $L_{fett}$  durch

$$15 \quad d_{fett} = |L_{fett} - L|,$$

gemessen wird, und bei dem ein Abstand  $d_{mager}$  von  $L$  zu  $L_{mager}$  durch

$$20 \quad d_{mager} = |L_{mager} - L|$$

25 gemessen wird.

24. Verfahren nach Anspruch 23, bei dem die Entscheidungsregel lautet:

30 wenn  $d_{mager} < d_{fett}$ , wird die Probe als "mager" klassifiziert;  
wenn  $d_{mager} \geq d_{fett}$ , wird die Probe als "fett" klassifiziert.

25. Verfahren nach Anspruch 20, bei dem aus einem Kalibrierungssatz von exemplarischen Messungen und entsprechenden Bezugswerten von fett und mager durch ein Klassifizierungskalibrierungsverfahren Grenzen für das Abbilden und die Entscheidungsregel bestimmt werden.

26. Verfahren nach Anspruch 25, bei dem die Klassifizierungskalibrierung eine lineare Diskriminantenanalyse, eine SIMCA-Analyse, eine k-Nearest-Neighbor-Analyse oder künstliche neuronale Netze mit einer Fuzzy-Klassifizierung aufweist.

27. Verfahren nach Anspruch 26, bei dem der Schritt des Abbildens durch

$$45 \quad L = \bar{f}w$$

gegeben ist, wobei  $w$  ein Vektor von Gewichten ist, und bei dem  $L$  mit  $\bar{L}$  verglichen wird, wobei  $\bar{L}$  eine Mitte zwischen zwei der sich gegenseitig ausschließenden Klassen ist.

28. Verfahren nach Anspruch 27, bei dem der Schritt des Zuweisens eine Entscheidungsregel verwendet, wobei die Entscheidungsregel lautet:

55 wenn  $L > \bar{L}$ , wird die Probe einer ersten der zwei Klassen zugewiesen;  
wenn  $L \leq \bar{L}$ , wird die Probe einer zweiten der zwei Klassen zugewiesen.

29. Verfahren nach Anspruch 16, bei dem eine Klassenzugehörigkeit durch ein Kontinuum von Stufen definiert ist, und bei dem ein Satz von Zugehörigkeitsfunktionen einen Merkmalsraum in ein Intervall  $[0, 1]$  für jede Klasse abbildet,

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und bei dem eine zugewiesene Stufe von "1" einen höchsten Grad einer Klassenzugehörigkeit darstellt.

- 5 **30.** Verfahren nach Anspruch 29, bei dem das Abbilden von dem Merkmalsraum auf einen Vektor von Klassenzugehörigkeiten durch

$$c_k = f_k(z),$$

10 gegeben ist, wobei  $k = 1, 2, \dots, P$  und wobei  $f_k(\cdot)$  die Zugehörigkeit der  $k$ -ten Klasse ist, und wobei  $c_k \in [0, 1]$  für alle  $k$  und wobei ein Vektor  $c \in \mathfrak{R}^P$  der Satz aller Klassenzugehörigkeiten ist.

- 15 **31.** Verfahren nach Anspruch 30, bei dem eine Zugehörigkeitsfunktion durch

$$y = e^{-\frac{1}{2\sigma^2}(z - \bar{z})^2}$$

20 dargestellt ist, wobei  $y$  der Grad einer Zugehörigkeit zu einem Fuzzy-Teilsatz ist,  $z$  das Merkmal ist, das verwendet wird, um eine Zugehörigkeit zu bestimmen,  $\bar{z}$  die Mitte eines Fuzzy-Teilsatzes ist, und  $\sigma$  die Standardabweichung ist.

- 25 **32.** Verfahren nach Anspruch 30, bei dem der Zugehörigkeitsvektor den Grad einer Klassenzugehörigkeit zu jeder der vordefinierten Klassen liefert.

- 30 **33.** Verfahren nach Anspruch 1, das ferner folgenden Schritt aufweist:

Schätzen einer Dicke einer Hautfalte, wobei die Hautfalte eine Schicht von Fettgewebe aufweist.

- 35 **34.** Verfahren nach Anspruch 33, bei dem der Schritt des Schätzens entweder vorverarbeitete Spektren oder extrahierte Merkmale verwendet.

- 35.** Verfahren nach Anspruch 34, bei dem der Schritt des Schätzens ferner den folgenden Schritt aufweist:

Liefern eines Kalibrierungsmodells, um das vorverarbeitete Spektrum durch ein Abbilden auf eine Schätzung einer Hautfaldendicke abzubilden.

- 40 **36.** Verfahren nach Anspruch 35, bei dem das Abbilden linear ist.

- 37.** Verfahren nach Anspruch 36 bei dem die Hautfaldendickenschätzung gemäß

$$\hat{y} = \sum_{k=1}^N w_{c,k} x_k$$

50 bestimmt wird, wobei das vorverarbeitete Spektrum  $x$  und das Kalibrierungsmodell  $w_c$  gegeben sind, wobei  $w_{c,k}$  das  $k$ -te Element von  $w_c$  und  $y$  die Hautfaldendickenschätzung ist.

- 55 **38.** Verfahren nach Anspruch 37, bei dem das Kalibrierungsmodell eine Faktoranalyse verwendet, um einen hochdimensionalen (redundanten) Datensatz, der Absorptions-, Intensitäts- oder Reflexionsmessungen bei einer Mehrzahl von Wellenlängen aufweist, in signifikante Faktoren, die die Mehrheit einer Variation innerhalb des Datensatzes darstellen, zu zerlegen; und bei dem das Kalibrierungsmodell Faktoren umfasst, die eine Variation in den Spektren, die mit einer Variation einer



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Hautfaldendicke korreliert ist, erfassen.

39. Verfahren nach Anspruch 38, das ferner folgende Schritte aufweist:

- 5 Projizieren der Proben in einen resultierenden Faktorraum, um einen Satz von Scores für jede Probe zu erzeugen; und  
Anwenden einer multiplen linearen Regression, um die Beziehung zwischen den Scores und der Hautfaldendicke zu modellieren.

10 40. Verfahren nach Anspruch 35, bei dem das Abbilden nichtlinear ist.

41. Verfahren nach Anspruch 40, bei dem das nicht lineare Abbilden durch entweder künstliche neuronale Netze oder eine nichtlineare partielle Regression unter Verwendung der Methode der kleinsten Quadrate spezifiziert wird.

15 42. Verfahren nach Anspruch 33, das ferner folgenden Schritt aufweist:

Schätzen einer Körperzusammensetzung eines Objekts.

20 43. Verfahren nach Anspruch 42, bei dem der Schritt des Schätzens der Körperzusammensetzung folgenden Schritt aufweist:

Abbilden einer Hautfaldendickenschätzung, einer Geschlechtsschätzung und einer Altersschätzung auf eine Schätzung des prozentualen Körperfetts des Objekts gemäß

25

$$y = f(x_1, x_2, x_3),$$

30 wobei  $y$  die Schätzung des prozentualen Körperfetts ist,  $x_1$  die Hautfaldendickenschätzung ist,  $x_2$  die Geschlechtsschätzung ist, und  $x_3$  die Altersschätzung und  $f()$  ein Kalibrierungsmodell ist.

44. Verfahren nach Anspruch 43, bei dem das Modell  $f()$  durch Anwenden eines nichtlinearen Regressionsverfahrens auf einen Kalibrierungssatz von exemplarischen Messungen bestimmt wird.

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45. Verfahren nach Anspruch 42, bei dem das Spektrum auf drei Wellenlängen begrenzt ist.

46. Verfahren nach Anspruch 45, bei dem die drei Wellenlängen 1124, 1210 und 1276 nm sind.

40 47. Verfahren nach Anspruch 46, bei dem der Schritt des Extrahierens von Merkmalen folgenden Schritt aufweist:

Normieren des begrenzten Spektrums.

48. Verfahren nach Anspruch 47, bei dem der Schritt des Normierens folgende Schritte aufweist:

45

Projizieren des Wasserspektrums auf zwei der drei Wellenlängen; und  
Subtrahieren des reinen Wasserspektrums von dem begrenzten Spektrum bei der Dritten der Wellenlängen gemäß

50

$$z = x - mp$$

wobei  $z$  ein endgültiges Spektrum ist.

55

49. Verfahren nach Anspruch 47, das ferner folgenden Schritt aufweist:

Schätzen des prozentualen Körperfetts gemäß

$$Fett\% = az_{1210nm} + b,$$

wobei  $a$  die Steigung,  $b$  der Schnitt und  $z_{1210nm}$  die Größe von  $z$  bei 1210 nm ist, wobei  $z$  ein extrahiertes Merkmal ist.

50. Verfahren nach Anspruch 13 oder Anspruch 33, das ferner folgenden Schritt aufweist:

Durchführen einer blutanalytischen Vorhersage.

51. Vorrichtung zum nichtinvasiven Charakterisieren und Klassifizieren des Zustands und einer Struktur einer Hautgewebeprobe basierend auf spektralen Absorptionsmerkmalen, die auf die Absorption von Fett in dem subkutanen Gewebe eines Objekts bezogen sind, mit:

einer Einrichtung zum Erzeugen einer Nahinfrarot-(NIR-) Energie;  
einer Einrichtung zum Trennen der erzeugten NIR-Energie in eine Mehrzahl von Wellenlängenbereichen;  
einer optischen Schnittstelle, mit:

einer Einrichtung zum Senden der NIR-Energie von der Wellenlängentrenneinrichtung hin zu einer Zielmessstelle an einem Objekt; und  
einer Einrichtung zum Sammeln einer NIR-Energie, die von der Messstelle ausstrahlt;

einer Einrichtung zum Erfassen der gesammelten Energie und Umwandeln der gesammelten Energie in eine Spannung;  
einer Einrichtung zum Umwandeln der Spannung in einen digitalen Wert; und  
einer Einrichtung zum Analysieren des digitalen Werts, wobei die Einrichtung zum Analysieren angepasst ist, um das Verfahren nach Anspruch 1 auszuführen, wodurch die Analyse in einer Charakterisierung oder einer Klassifizierung der Hautgewebeprobe resultiert.

52. Vorrichtung nach Anspruch 51, bei der die Energiequelle und die Wellenlängentrenneinrichtung zusammen ein Feld von LEDs, das die Erfassungseinrichtung in einer radialen Weise umgibt, aufweisen, wobei sowohl die LEDs als auch die Erfassungseinrichtung eine Seitenkante haben, und bei der jede der LEDs aufeinanderfolgend eine Energie bei einer spezifischen Wellenlänge in einem Satz von vorausgewählten Wellenlängen emittiert.

53. Vorrichtung nach Anspruch 52, bei der der Satz von vorausgewählten Wellenlängen 1100 nm, 1208 nm, 1210 nm, 1275 nm, 1350 nm, 1650 nm, 1720 nm und 1760 nm umfasst.

54. Vorrichtung nach Anspruch 52, bei der die Seitenkante von jeder der LEDs einen Beleuchtungspunkt aufweist, und die Seitenkante der Erfassungseinrichtung einen Erfassungspunkt aufweist, und bei der ein Abstand zwischen dem Beleuchtungspunkt und dem Erfassungspunkt 1 bis 3 mm ist.

55. Vorrichtung nach Anspruch 54, bei der das LED-Feld und die Erfassungseinrichtung mittels einer Ansichtoptik und eines Linsensystems mit der Messstelle gekoppelt sind.

56. Vorrichtung nach Anspruch 51, bei der die Energiequelle eine Quarzhalogenlampe ist, wobei die Lampe Energie in dem Wellenlängenbereich von etwa 1100 bis 2500 nm sendet.

57. Vorrichtung nach Anspruch 56, bei der die Wellenlängentrenneinrichtung entweder ein Monochromator oder ein Interferometer ist.

58. Vorrichtung nach Anspruch 51, bei der die Sendeeinrichtung entweder ein Lichtleiter, eine faseroptische Sonde, ein Linsensystem oder ein Lichtlenkspiegelsystem ist.

59. Vorrichtung nach Anspruch 51, bei der die Energiesammeleinrichtung entweder mindestens einen Ansichtoptikdetektor oder mindestens eine faseroptische Sonde aufweist.

60. Vorrichtung nach Anspruch 51, bei der die Energieerfassungseinrichtung InGAs-Detektoren aufweist.

61. Vorrichtung nach Anspruch 51, bei der die Digitalisierungseinrichtung einen 16-Bit-A/D-Wandler aufweist.
62. Vorrichtung nach Anspruch 58, bei der ein Beleuchtungspunkt durch entweder eine Fokussierlinse oder eine faser-optische Sonde eingestellt wird.
63. Vorrichtung nach Anspruch 59, bei der ein Erfassungspunkt durch entweder einen Ansichtoptikdetektor oder eine faseroptische Sonde eingestellt wird.

**Revendications**

1. Procédé non invasif de caractérisation et de classement de l'état et de la structure d'un tissu sur la base de caractéristiques d'absorption spectrale associées à la graisse dans le tissu sous-cutané comprenant les étapes consistant à :

procurer un ensemble d'étalonnage de mesures d'exemple,  
 mesurer le spectre d'absorption du proche infrarouge d'un prélèvement de tissu de peau,  
 détecter des observations aberrantes, où lesdites observations aberrantes sont des mesures invalides provo-  
 quées par une variation spectrale due à l'un quelconque d'un mauvais fonctionnement d'un instrument, d'un  
 prélèvement médiocre et de sujets à l'extérieur dudit ensemble d'étalonnage,  
 procurer un ensemble de base, où ledit ensemble de base comprend un spectre de composant pur d'eau et  
 un de graisse animale, en vue d'une extraction et d'un pré-traitement de caractéristique,  
 pré-traiter ledit spectre d'infrarouge proche, où ladite étape de pré-traitement comprend une ou plusieurs trans-  
 formations qui atténuent le bruit et les variations des instruments sans affecter le signal intéressant, y compris  
 l'un quelconque d'une sélection de longueur d'onde, d'une mise à l'échelle, d'une normalisation, d'un lissage,  
 de dérivés et d'un filtrage et,  
 l'extraction de caractéristiques, grâce à quoi des caractéristiques de mesures pertinentes pour le classement  
 sont déterminées.

2. Procédé selon la revendication 1, dans lequel ledit spectre est désigné par un vecteur  $m \in \mathfrak{R}^N$  de valeurs d'absor-  
 bance se rapportant à un ensemble de N longueurs d'onde  $\lambda \in \mathfrak{R}^N$ .
3. Procédé selon la revendication 1, dans lequel lesdites mesures de spectre d'infrarouge proche sont dans la région  
 de longueurs d'onde d'environ 1100 à 2500 nm.
4. Procédé selon la revendication 1, dans lequel ladite étape de détection d'observations aberrantes emploie une  
 analyse de composantes principales et une analyse résiduelle pour détecter des observations aberrantes spectrales.
5. Procédé selon la revendication 4, dans lequel ladite étape de détection d'observations aberrantes comprend en  
 outre les étapes consistant à :

projeter un spectre m sur une pluralité de vecteurs propres, contenus dans une matrice o, ladite matrice o étant  
 précédemment développée par le biais d'une analyse de composantes principales dudit ensemble d'étalonnage,  
 où

$$xpc_o = \sum_{k=1}^7 mo_k,$$

et où  $o_k$  est la  $k^e$  colonne de la matrice o,  
 déterminer le q résiduel, selon

$$q = m - xpc_o^T,$$

comparer ledit q résiduel à trois fois l'écart type du reste dudit ensemble d'étalonnage et,

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signaler ledit prélèvement comme étant une observation aberrante si  $q$  est plus grand.

6. Procédé selon la revendication 1, dans lequel lesdites caractéristiques sont représentées dans un vecteur  $z \in \mathfrak{R}^M$  qui est déterminé à partir d'une mesure pré-traitée, par le biais de :

$$z = \mathbf{f}(\lambda, x),$$

où  $f : \mathfrak{R}^N \rightarrow \mathfrak{R}^M$  est un mappage d'un espace de mesure en un espace de caractéristique, où la décomposition  $f(\bullet)$  donne des transformations spécifiques,  $f_i(\bullet) : \mathfrak{R}^N \rightarrow \mathfrak{R}^{M_i}$  pour déterminer une caractéristique spécifique, où la dimension  $M_i$  indique si une  $i^{\text{e}}$  caractéristique est un scalaire ou un vecteur et un agrégat de toutes les caractéristiques est le vecteur  $z$ , où lesdites transformations renforcent une qualité ou un aspect de la mesure du prélèvement en vue d'une interprétation pour représenter de manière concise les propriétés et les caractéristiques du site de mesure du tissu et où une caractéristique présente une certaine structure indicative d'un phénomène physique sous-jacent, lorsque ladite caractéristique est représentée sous la forme d'un vecteur ou d'un motif.

7. Procédé selon la revendication 6, dans lequel les caractéristiques individuelles sont réparties en deux catégories comprenant :

des caractéristiques abstraites qui n'ont pas nécessairement une interprétation spécifique associée à un système physique et,

des caractéristiques simples qui sont obtenues à partir d'une compréhension a priori d'un prélèvement et qui peuvent être associées directement à un phénomène physique.

8. Procédé selon la revendication 4, dans lequel ladite étape d'extraction de caractéristique comprend une analyse de composante principale.

9. Procédé selon la revendication 6, dans lequel ladite étape d'extraction de caractéristique comprend la normalisation de l'amplitude de bandes d'absorbance de graisse dans un tissu adipeux.

10. Procédé selon la revendication 6, dans lequel ladite étape d'extraction de caractéristique comprend la comparaison des spectres d'absorbance de l'eau et de la graisse dudit prélèvement aux spectres d'absorbance d'eau et de graisse dudit ensemble d'étalonnage.

11. Procédé selon la revendication 8, dans lequel ladite étape d'extraction de caractéristique comprend les étapes consistant à :

tronquer ledit spectre  $m$  à la région de longueur d'onde d'approximativement 1100 à 2500 nm, projeter ledit spectre tronqué sur une pluralité,  $p_k$ , de vecteurs propres, où lesdits vecteurs propres ont été précédemment calculés par le biais d'une analyse de composantes principales dudit ensemble d'étalonnage,

où ladite projection produit un vecteur de notes 1 à  $N$ ,  $x_{pc}$  et,

l'application d'une fonction de discriminant grâce à quoi lesdits prélèvements sont classés sur la base des  $M$  premières notes, où lesdites notes font l'objet d'une permutation circulaire par le biais d'un produit croisé avec un discriminant,  $w$ , pour produire un scalaire,  $L$ .

12. Procédé selon la revendication 11, dans lequel  $M = 3$ .

13. Procédé selon la revendication 1, comprenant en outre l'étape consistant à :

classifier ledit prélèvement conformément à des catégories prédéfinies d'adiposité et de pauvreté en graisse.

14. Procédé selon la revendication 13, dans lequel ledit spectre est limité à l'une quelconque des régions de longueurs d'onde d'approximativement 1100 à 1350 nm et d'approximativement 1650 à 1800 nm.

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15. Procédé selon la revendication 14, dans lequel ladite étape d'extraction de caractéristique comprend l'étape consistant à :

normaliser ledit spectre limité.

16. Procédé selon la revendication 15, dans lequel ladite étape de normalisation comprend les étapes consistant à :

projeter ledit spectre de l'eau sur ledit spectre limité conformément à

$$m = \left[ p_w p_w^T \right]^{-1} p_w x_w,$$

où m est un scalaire représentant l'amplitude de l'absorbance de l'eau et l'indice w représente un sous-ensemble de longueurs d'ondes et,

soustraire ledit spectre d'eau pure dudit spectre limité conformément à

$$z = x - mp,$$

où z est un spectre final.

17. Procédé selon la revendication 13, dans lequel ladite étape de classement comprend les étapes consistant à :

mesurer la similarité d'au moins une caractéristique desdites catégories prédéfinies et affecter une appartenance auxdites catégories prédéfinies.

18. Procédé selon la revendication 17, dans lequel ladite étape d'affectation utilise des classes mutuellement exclusives et affecte chaque prélèvement à une classe.

19. Procédé selon la revendication 17, dans lequel ladite étape d'affectation utilise un système de classement analogique flou qui permet une appartenance de classe dans plus d'une classe simultanément.

20. Procédé selon la revendication 18, dans lequel ladite étape d'affectation comprend en outre les étapes consistant à :

mapper ledit prélèvement sur l'une desdites classes prédéfinies et, appliquer une règle de décision pour affecter une appartenance à une classe.

21. Procédé selon la revendication 20, dans lequel ladite étape de mappage est donnée par:

$$L = f(z),$$

où L est un scalaire qui mesure la distance d'un prélèvement par rapport aux catégories prédéfinies.

22. Procédé selon la revendication 18, dans lequel lesdites catégories sont "gras" et "maigre" et où  $L_{\text{gras}}$  correspond à une valeur représentative pour ladite classe "gras" et  $L_{\text{maigre}}$  correspond à une valeur représentative pour ladite classe "maigre", et où ladite affectation de classe est fondée sur la proximité de L par rapport à  $L_{\text{gras}}$  et  $L_{\text{maigre}}$ .

23. Procédé selon la revendication 22, dans lequel une distance  $d_{\text{gras}}$  de L à  $L_{\text{gras}}$  est mesurée par

$$d_{\text{gras}} = | L_{\text{gras}} - L |,$$

et où une distance  $d_{\text{maigre}}$  de L à  $L_{\text{maigre}}$  est mesurée par

$$d_{\text{maigre}} = | L_{\text{maigre}} - L | .$$

5 24. Procédé selon la revendication 23, dans lequel ladite règle de décision est :

si  $d_{\text{maigre}} < d_{\text{gras}}$ , ledit prélèvement est classé comme étant "maigre",  
 si  $d_{\text{maigre}} \geq d_{\text{gras}}$ , ledit prélèvement est classé comme étant "gras".

10 25. Procédé selon la revendication 20, dans lequel les limites pour ledit mappage et ladite règle de décision sont déterminées à partir d'un ensemble d'étalonnage de mesures d'exemple et de valeurs correspondantes de référence d'un caractère gras ou maigre par l'intermédiaire d'une procédure d'étalonnage de classement.

15 26. Procédé selon la revendication 25, dans lequel ledit étalonnage de classement comprend l'un quelconque d'une analyse à discriminant linéaire, d'un procédé SIMCA, du voisin le plus proche k, de réseaux neuronaux artificiels à classement flou.

27. Procédé selon la revendication 26, dans lequel ladite étape de mappage est donnée par

20

$$L = \mathbf{f} \mathbf{w},$$

Où  $\mathbf{w}$  est un vecteur de coefficients de pondération et où  $L$  est comparé à  $\bar{L}$ , où  $\bar{L}$  est un centre entre deux classes desdites classes mutuellement exclusives.

25

28. Procédé selon la revendication 27, dans lequel ladite étape d'affectation emploie une règle de décision, où ladite règle de décision est

30

si  $L > \bar{L}$ , ledit prélèvement est affecté à la première desdites deux classes,  
 si  $L \leq \bar{L}$ , ledit prélèvement est affecté à la seconde desdites deux classes.

35

29. Procédé selon la revendication 16, dans lequel ladite appartenance à une classe est définie par un continuum de notations et dans lequel un ensemble de fonctions d'appartenance mappe un espace de caractéristiques dans l'intervalle [0,1] pour chaque classe et dans lequel une notation affectée de "1" représente le degré le plus élevé d'appartenance à une classe.

30. Procédé selon la revendication 29, dans lequel le mappage à partir de l'espace de caractéristiques en un vecteur d'appartenance à des classes est donné par :

40

$$c_k = \mathbf{f}_k(\mathbf{z}),$$

45

où  $k = 1, 2 \dots P$  et où  $\mathbf{f}_k(\bullet)$  est l'appartenance à la  $k^{\text{e}}$  classe et où  $c_k \in [0, 1]$  pour tous les  $k$  et où un vecteur  $\mathbf{c} \in \mathfrak{R}^P$  est l'ensemble de toutes les appartenances à des classes.

31. Procédé selon la revendication 30, dans lequel une fonction d'appartenance est représentée par

50

$$y = e^{-\frac{1}{2\sigma^2}(x-\bar{x})^2},$$

où  $y$  est le degré d'appartenance dans un sous-ensemble flou,  $z$  est la caractéristique utilisée pour déterminer une appartenance,  $\bar{z}$  est le centre d'un sous-ensemble flou et  $\sigma$  est l'écart type.

55

32. Procédé selon la revendication 30, dans lequel ledit vecteur d'appartenance procure le degré d'appartenance à une classe dans chacune desdites classes prédéfinies.

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33. Procédé selon la revendication 1, comprenant en outre l'étape consistant à :

estimer l'épaisseur d'un pli cutané, ledit pli cutané comprenant une couche de tissu adipeux.

5 34. Procédé selon la revendication 33, dans lequel ladite étape d'estimation utilise l'un quelconque des spectres pré-traités et des caractéristiques extraites.

35. Procédé selon la revendication 34, dans lequel ladite étape d'estimation comprend en outre l'étape consistant à :

10 procurer un modèle d'étalonnage pour mapper ledit spectre prétraité par le biais d'un mappage en une estimation de l'épaisseur de pli cutané.

36. Procédé selon la revendication 35, dans lequel ledit mappage est linéaire.

15 37. Procédé selon la revendication 36, dans lequel ladite estimation d'épaisseur de pli cutané est déterminée conformément à

$$20 \hat{y} = \sum_{k=1}^N w_{c,k} x_k,$$

25 étant donné le spectre prétraité  $x$  et le modèle d'étalonnage  $W_c$ , où  $w_{c,k}$  est le  $k^{\text{e}}$  élément de  $W_c$  et  $y$  est l'estimation d'épaisseur de pli cutané.

30 38. Procédé selon la revendication 37, dans lequel ledit modèle d'étalonnage emploie une analyse factorielle pour décomposer un ensemble de données de grande dimension (redondant) comprenant des mesures d'absorbance, d'intensité ou de réflexion à une pluralité de longueurs d'onde en facteurs significatifs représentant la majorité de la variation à l'intérieur dudit ensemble de données et,

dans lequel ledit modèle d'étalonnage comprend des facteurs qui acquièrent une variation dans lesdits spectres corrélée à la variation de l'épaisseur de pli cutané.

35 39. Procédé selon la revendication 38, comprenant en outre les étapes consistant à :

projeter lesdits prélèvements dans un espace de facteur résultant pour produire un ensemble de notes pour chaque prélèvement et,

40 appliquer une régression linéaire multiple pour modéliser la relation entre lesdites notes et ladite épaisseur de pli cutané.

40. Procédé selon la revendication 35, dans lequel ledit mappage est non linéaire.

45 41. Procédé selon la revendication 40, dans lequel ledit mappage non linéaire est spécifié par le biais de l'un quelconque de réseaux neuronaux artificiels et de régressions partielles linéaires par la méthode des moindres carrés.

42. Procédé selon la revendication 33, comprenant en outre l'étape consistant à :

estimer la composition corporelle d'un sujet.

50 43. Procédé selon la revendication 42, dans lequel ladite étape d'estimation de composition corporelle comprend l'étape consistant à :

55 mapper une estimation de l'épaisseur du pli cutané, une estimation du sexe et une estimation de l'âge en une estimation du pourcentage de graisse du corps dudit sujet conformément à :

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$$y = f(x_1, x_2, x_3),$$

5 où y est l'estimation du pourcentage de graisse du corps,  $x_1$  est l'estimation de l'épaisseur du pli cutané,  $x_2$  est l'estimation du sexe et  $x_3$  est l'estimation de l'âge et f() est un modèle d'étalonnage.

10 **44.** Procédé selon la revendication 43, dans lequel ledit modèle f() est déterminé en appliquant une méthode de régression non linéaire à un ensemble d'étalonnage de mesures d'exemple.

**45.** Procédé selon la revendication 42, dans lequel ledit spectre est limité à trois longueurs d'onde.

**46.** Procédé selon la revendication 45, dans lequel les trois longueurs d'onde sont 1124, 1210 et 1276 nm.

15 **47.** Procédé selon la revendication 46, dans lequel ladite étape d'extraction de caractéristique comprend l'étape consistant à :

normaliser ledit spectre limité.

20 **48.** Procédé selon la revendication 47, dans lequel ladite étape de normalisation comprend les étapes consistant à :

projeter ledit spectre d'eau sur deux desdites trois longueurs d'onde et,  
soustraire ledit spectre d'eau pure dudit spectre limité à la troisième desdites longueurs d'onde conformément à

25

$$z = x - mp,$$

où z est un spectre final.

30 **49.** Procédé selon la revendication 47, comprenant en outre l'étape consistant à :

estimer le pourcentage de graisse du corps conformément à :

35

$$\% \text{ de graisse} = az_{1210\text{nm}} + b,$$

où a est la pente, b est le segment sur l'axe et  $z_{1210\text{nm}}$  est l'amplitude de z à 1210nm, où z est une caractéristique extraite.

40 **50.** Procédé selon la revendication 13 ou la revendication 33, comprenant en outre l'étape consistant à :

exécuter une prédiction d'analyse de sang.

45 **51.** Dispositif de caractérisation et de classement de manière non invasive de l'état et de la structure d'un prélèvement de peau sur la base de caractéristiques d'absorbance spectrale associée à l'absorbance de la graisse dans le tissu sous cutané d'un sujet comprenant :

50 un moyen destiné à générer une énergie dans le proche infrarouge NIR,  
un moyen destiné à séparer ladite énergie dans le proche infrarouge généré en une pluralité de régions de longueurs d'onde,  
une interface optique comprenant :

55 un moyen destiné à transmettre ladite énergie dans le proche infrarouge provenant dudit moyen de séparation de longueur d'onde vers un site de mesure cible sur un sujet et,  
un moyen destiné à recueillir l'énergie dans le proche infrarouge émanant du site de mesure,  
un moyen destiné à détecter ladite énergie recueillie et à convertir ladite énergie collectée en une tension,  
un moyen destiné à convertir ladite tension en une valeur numérique et,



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un moyen destiné à analyser ladite valeur numérique, ledit moyen d'analyse étant conçu pour exécuter le procédé de la revendication 1, grâce à quoi ladite analyse résulte en l'un quelconque d'une caractérisation et d'un classement dudit prélèvement de tissu de peau.

- 5
- 52.** Dispositif selon la revendication 51, dans lequel ladite source d'énergie et ledit moyen de séparation de longueur d'onde constituent ensemble un réseau de diodes LED entourant ledit moyen de détection d'une manière radiale, chacune desdites diodes LED et dudit moyen de détection ayant un bord latéral et dans lequel chacune desdites diodes LED émet successivement de l'énergie à une longueur d'onde spécifique dans un ensemble de longueurs d'onde présélectionnées.
- 10
- 53.** Dispositif selon la revendication 52, où ledit ensemble de longueurs d'onde présélectionnées comprend 1100nm, 1208nm, 1210nm, 1275nm, 1350nm, 1650nm, 1720nm, 1760nm.
- 54.** Dispositif selon la revendication 52, dans lequel ledit bord latéral de l'une quelconque desdites diodes LED comprend un point d'illumination et ledit bord latéral dudit moyen de détection comprend un point de détection, et dans lequel la distance entre ledit point d'illumination et ledit point de détection est d'approximativement 1 à 3 mm.
- 15
- 55.** Dispositif selon la revendication 54, dans lequel ledit réseau de diodes LED et ledit moyen de détection sont couplés avec ledit site de mesures au moyen d'une optique d'observation et d'un système de lentilles.
- 20
- 56.** Dispositif selon la revendication 51, dans lequel ladite source d'énergie est une lampe à halogène à quartz, où ladite lampe transmet l'énergie dans la plage de longueurs d'onde d'approximativement 1100 à 2500nm.
- 57.** Dispositif selon la revendication 56, dans lequel ledit moyen de séparation de longueurs d'onde est l'un quelconque d'un monochromateur ou d'un interféromètre.
- 25
- 58.** Dispositif selon la revendication 51, dans lequel ledit moyen de transmission est l'un quelconque d'un tuyau de lumière, d'une sonde à fibre optique, d'un système de lentilles et d'un système de miroir dirigeant la lumière.
- 59.** Dispositif selon la revendication 51, dans lequel ledit moyen de recueil d'énergie comprend l'un quelconque d'au moins un détecteur optique d'observation et d'au moins une sonde à fibre optique.
- 30
- 60.** Dispositif selon la revendication 51, dans lequel ledit moyen de détection d'énergie comprend des détecteurs du type INGAS.
- 35
- 61.** Dispositif selon la revendication 51, dans lequel ledit moyen de numérisation comprend un convertisseur A/N à 16 bits.
- 62.** Dispositif selon la revendication 58, dans lequel un point d'illumination est établi au travers de l'un quelconque d'une lentille de focalisation et d'une sonde à fibre optique.
- 40
- 63.** Dispositif selon la revendication 59, dans lequel un point de détection est établi par le biais de l'un quelconque d'un détecteur optique d'observation et d'une sonde à fibre optique.
- 45
- 50
- 55

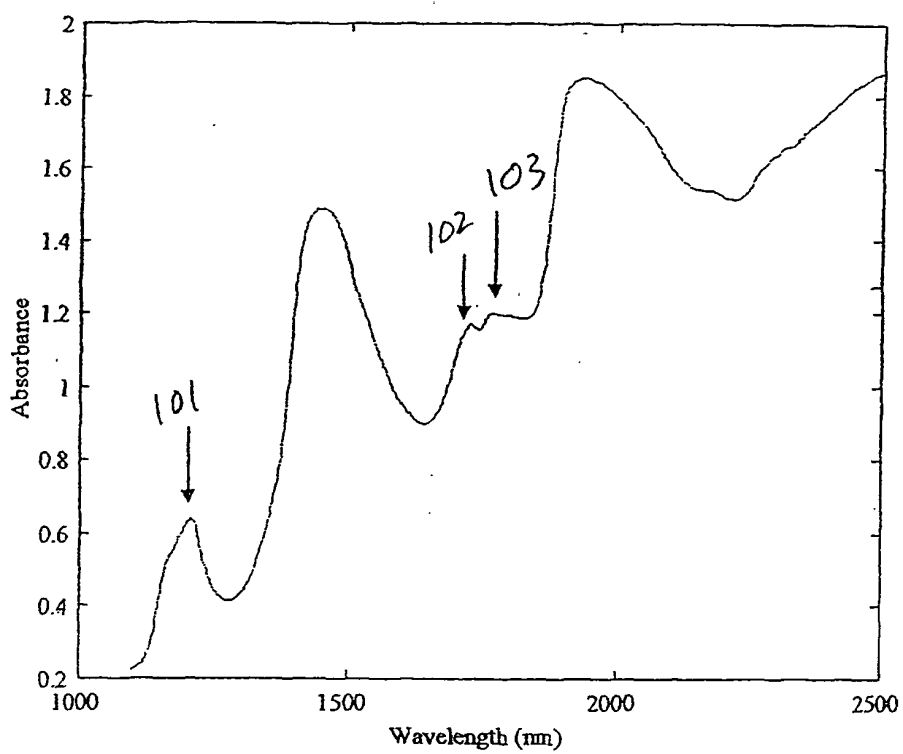


Figure 1.

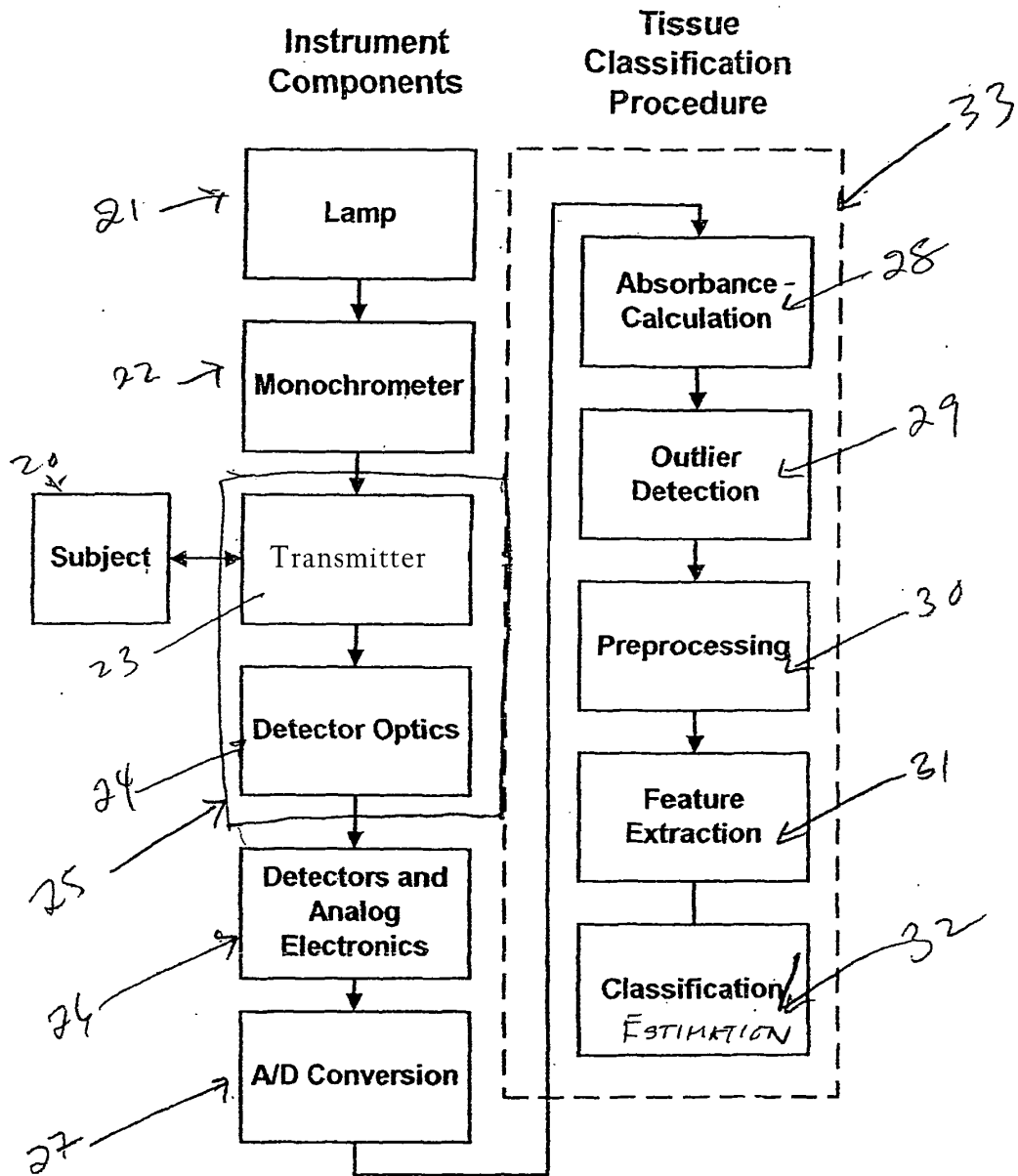


Figure 2.

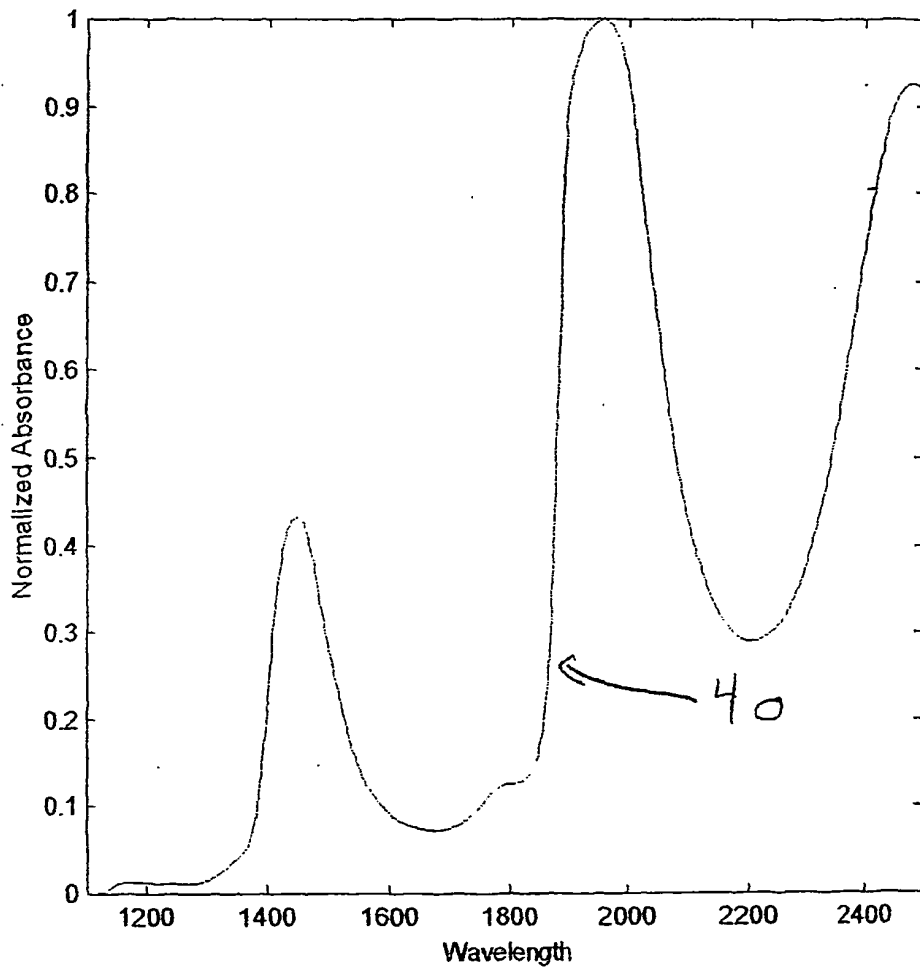


Figure 3.

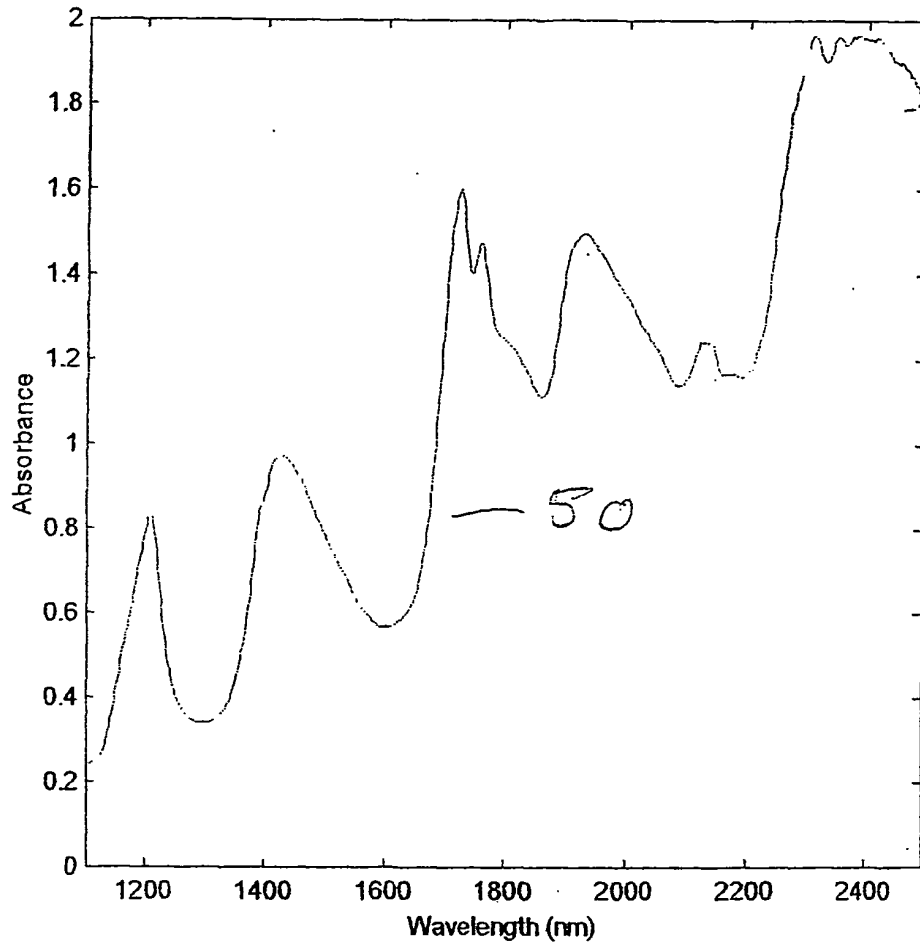


Figure 4 .

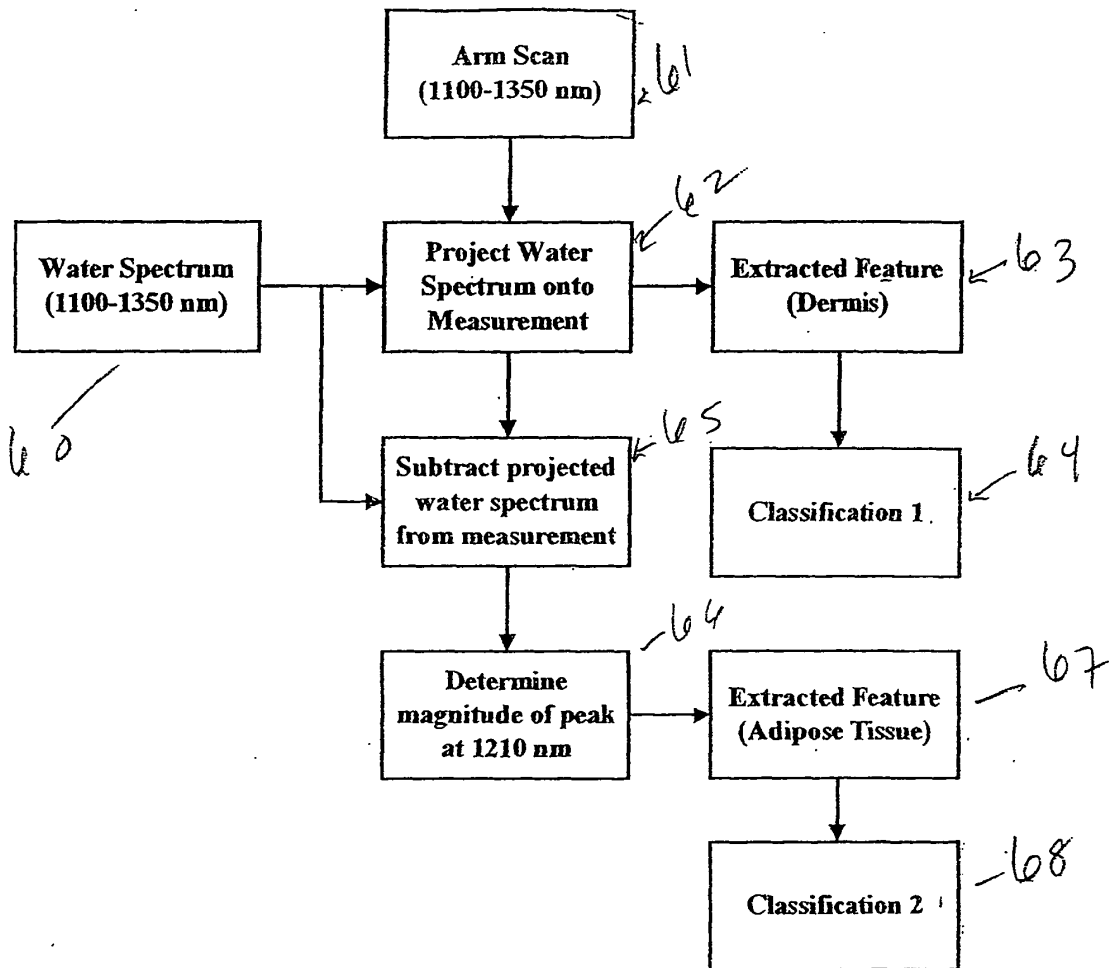


Figure 5.

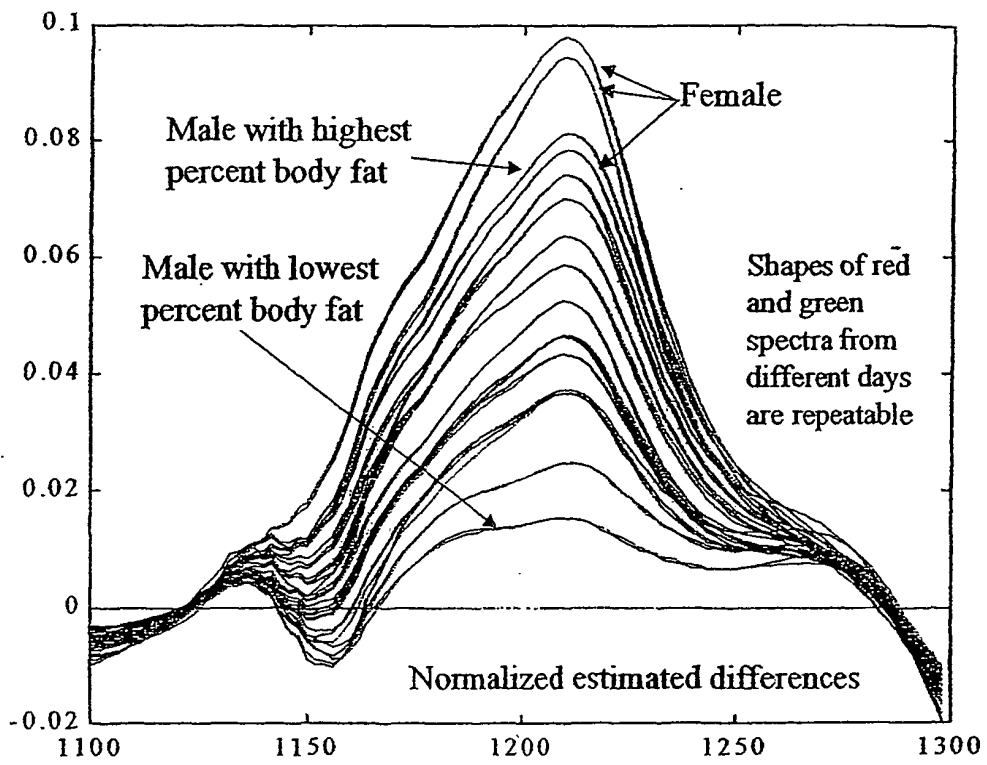


Figure.6.

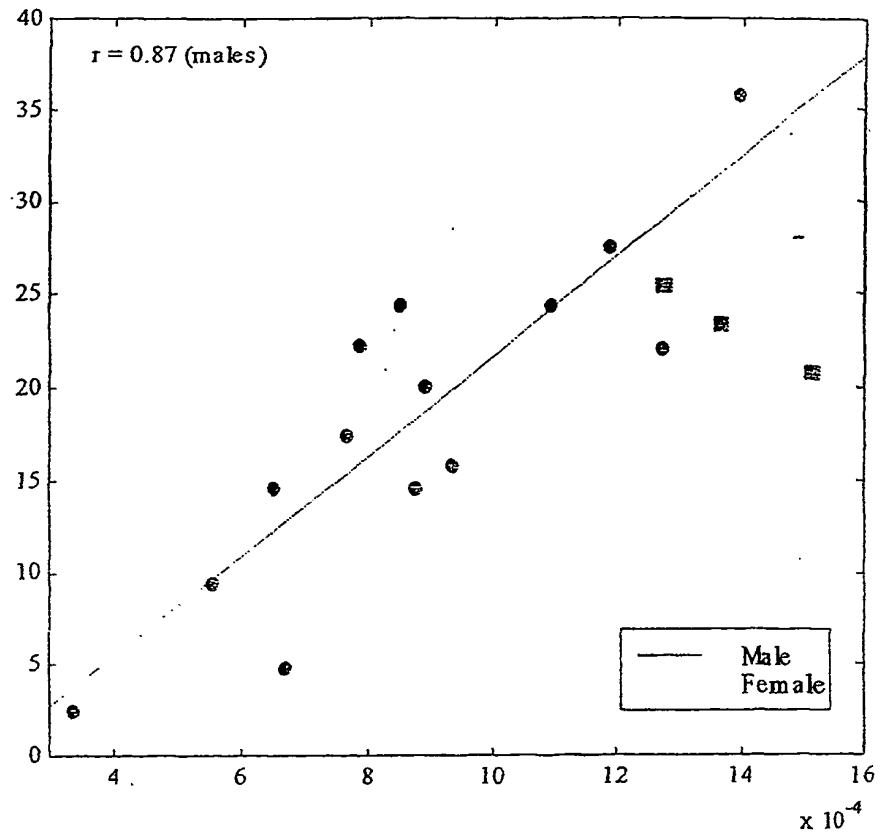


Figure 7



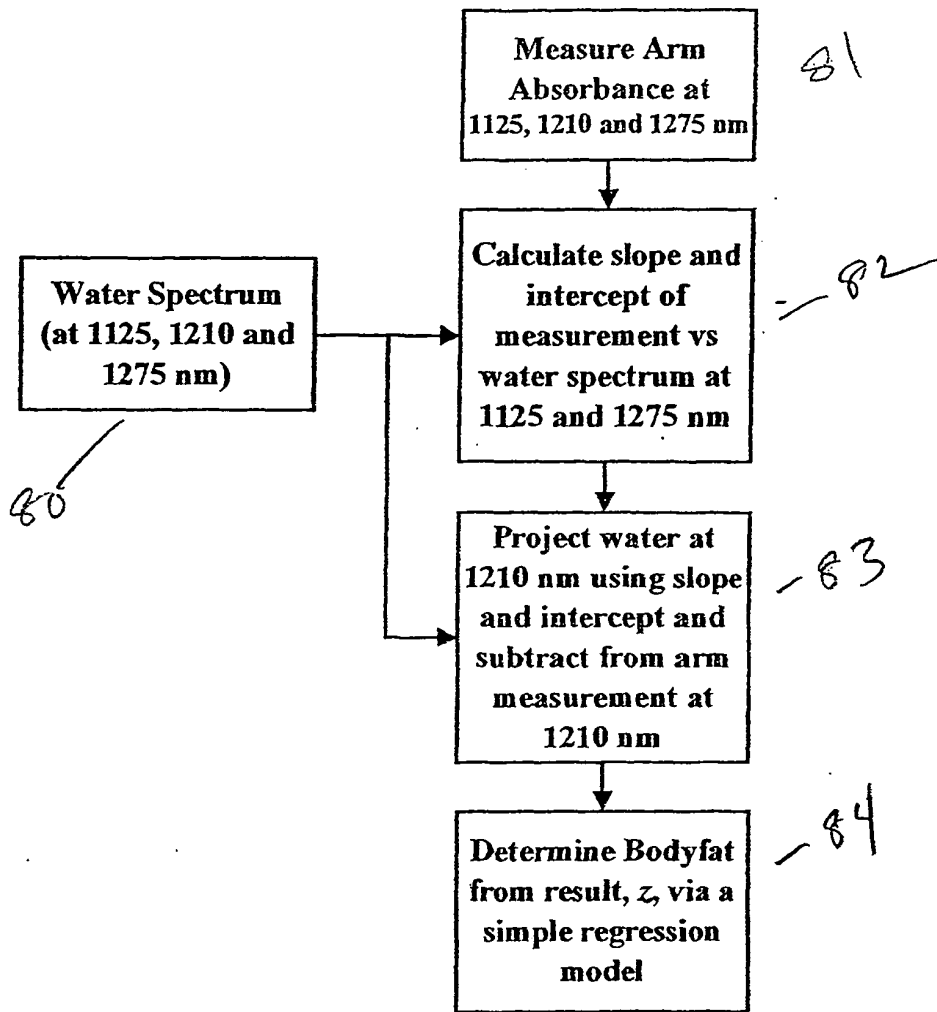


Figure.8.

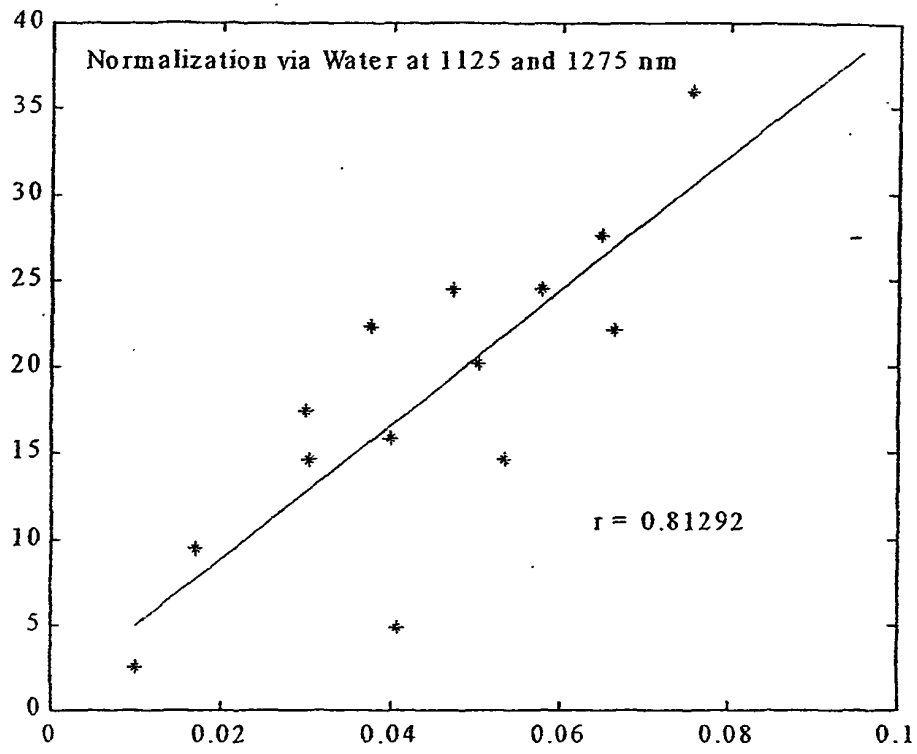


Figure 9.

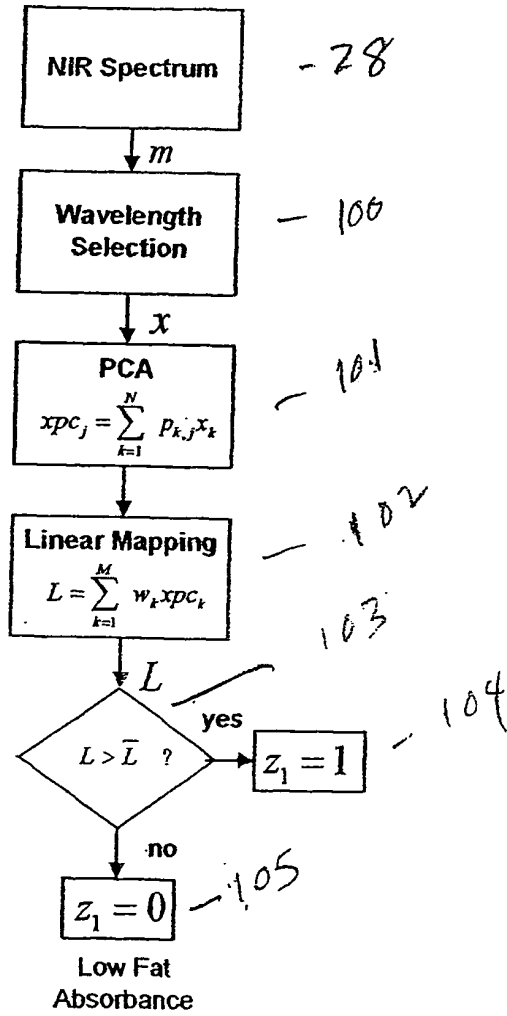


Figure 10.

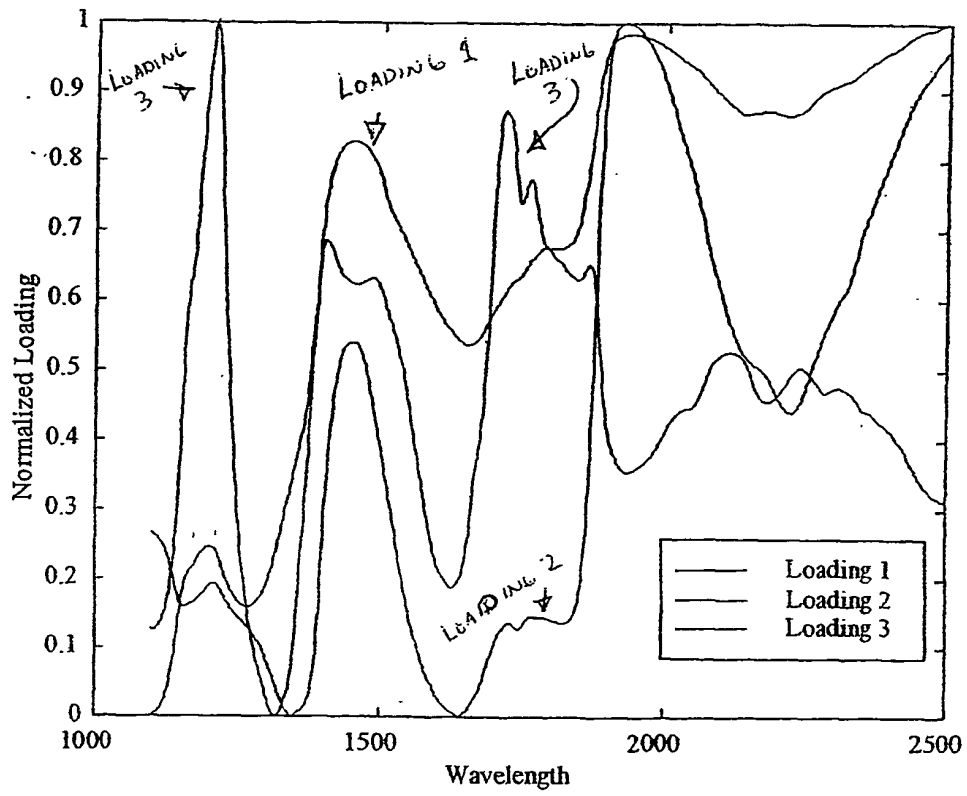


Figure 11.

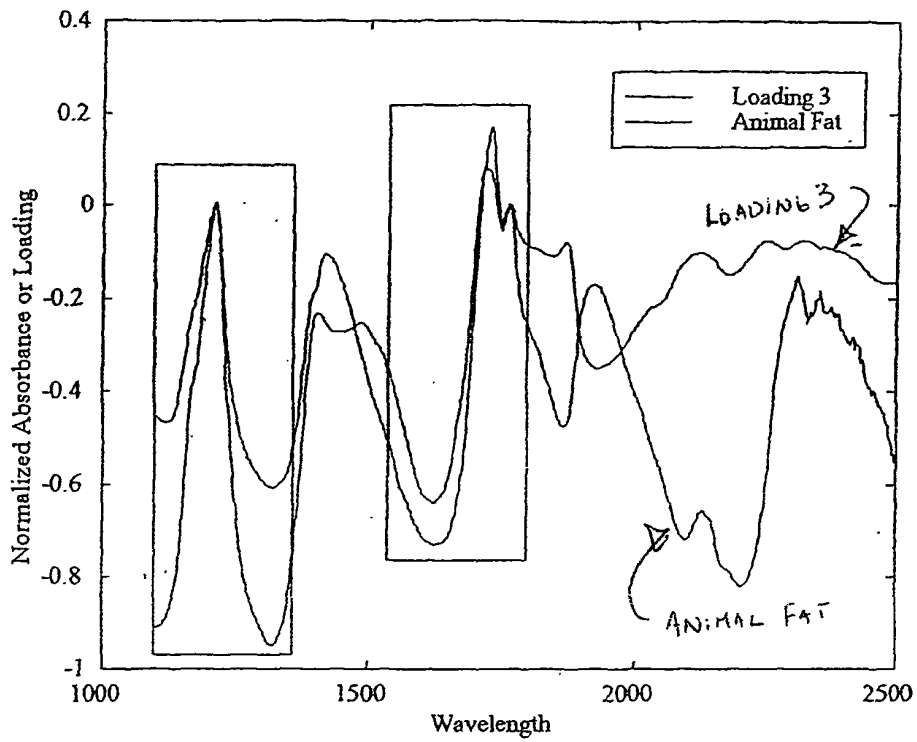


Figure 12.

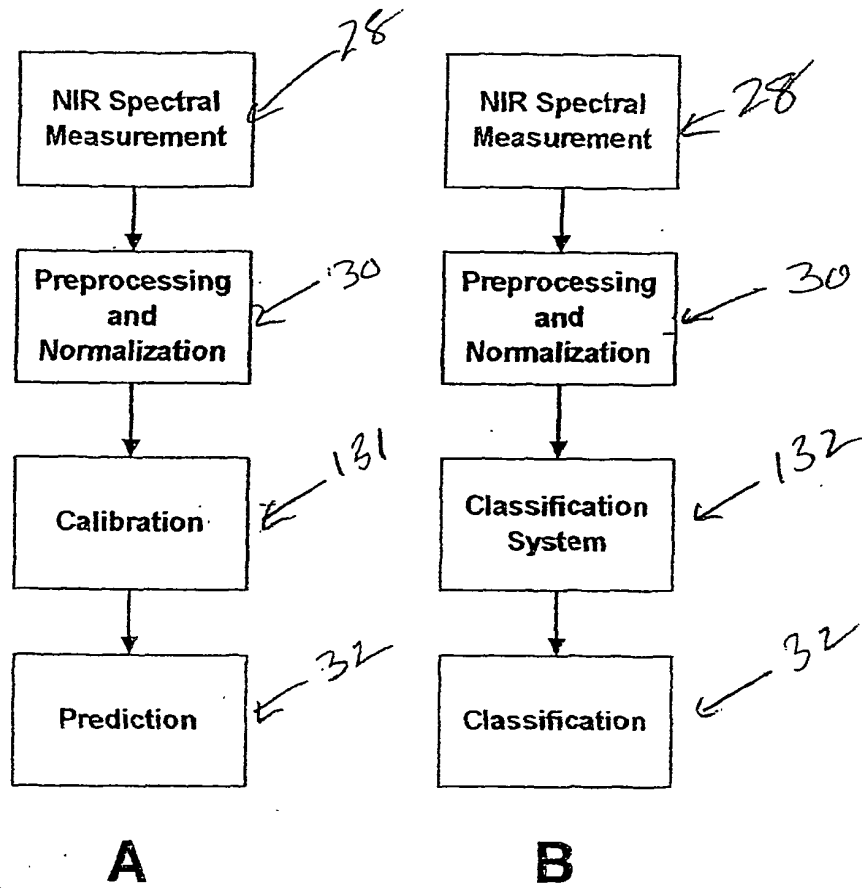


Figure 13.

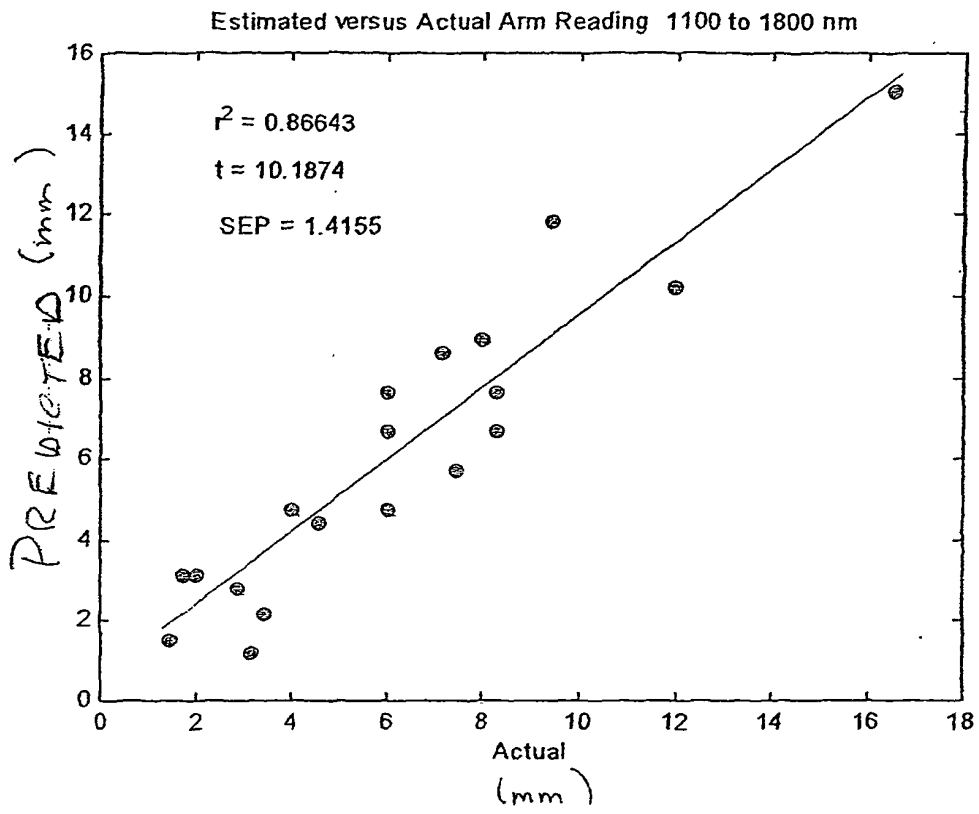


Figure 14

## REFERENCES CITED IN THE DESCRIPTION

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## Patent documents cited in the description

- US 35919199 B, Malin, S. and T. Ruchti [0006]
- US 6280381 B [0006] [0046] [0046] [0060]
- US 4850365 A [0014]
- US 4928014 A [0014]
- US 5014713 A [0014]
- US 5945676 A [0019]
- US 487 A [0041]
- US 231 A, T. Ruchti, S. Thennadil, S. Malin and J. Rennert [0041]
- US 6501982 B [0041] [0049]
- US 48773300 A, T. Ruchti, S. Thennadil, S. Malin and J. Rennert [0041]
- US 6493566 B [0041] [0049]
- US 359191 A [0046] [0046]
- US 09359191 B, Malin [0060]

## Non-patent literature cited in the description

- *Clin Chem*, 1999, vol. 45, 165-77 [0003]
- **ROE, JN ; BR SMOLLER.** Bloodless Glucose Measurements. *Critical Reviews in Therapeutic Drug Carrier Systems*, 1998, vol. 15 (3), 199-241 [0003]
- **TAN, CY ; B. STATHAM ; R. MARKS ; P.A. PAYNE.** Skin thickness measurement by pulsed ultrasound: its reproducibility, validation and variability. *British Journal of Dermatology*, 1982, vol. 106, 657-667 [0003]
- **SHUSTER, S ; M.M. BLACK ; E. MCVITIE.** The influence of age and sex on skin thickness, skin collagen and density. *British Journal of Dermatology*, 1975, vol. 93 [0003]
- **DURNIN, J.V.G.A ; M.M. RAHAMAN.** The assessment of the amount of fat in the human body from measurements of skin fold thickness. *British Journal of Nutrition*, 1967, vol. 21 [0003]
- **HAZEN, K. H.** Glucose determination in biological matrices using near-infrared spectroscopy. *Doctoral Dissertation*, August 1995 [0005]
- **ROBINSON, M. R ; R. P. EATON ; D. M. HAALAND ; G. W. KOEPP ; E. V. THOMAS ; B. R. STALLARD ; P. L. ROBINSON.** Noninvasive glucose monitoring in diabetic patients: a preliminary evaluation. *Clin. Chem*, 1992, vol. 38 (9), 1618-1622 [0005]
- **MALIN, S ; T. RUCHTI ; T. BLANK ; S. THENNADIL ; S. MONFRE.** Noninvasive prediction of glucose by near-infrared diffuse reflectance spectroscopy. *Clin. Chem*, 1999, vol. 45 (9), 1651-1658 [0005]
- **HEYWARD, V.H ; L.M. STOLARCZYK.** Applied Body Composition Assessment. *Human Kinetics*, 1996 [0013]
- **CONWAY, J. M ; NORRIS, K.H ; BODWELL, C.E.** A new approach for the estimation of body composition: infrared interactance. *The American Journal of Clinical Nutrition*, December 1985, 1123-1130 [0013]
- **ANDERSON, R. R ; J. A. PARRISH.** The optics of human skin. *J. of Investigative Dermatology*, 1981, vol. 77 (1), 13-19 [0018]
- **GELADI, P ; D. MCDOUGALL ; H. MARTENS.** Linearization and Scatter-Correction for Near-Infrared Reflectance Spectra of Meat. *Applied Spectroscopy*, 1985, vol. 39, 491-500 [0032]
- **SAVITZKY, A ; M. J. E. GOLAY.** Smoothing and Differentiation of Data by Simplified Least Squares Procedures. *Anal. Chem.*, 1964, vol. 36 (8), 1627-1639 [0032]
- **DUDA, R.O ; P.E. HART.** Pattern Classification and Scene Analysis. John Wiley and Sons, 1973 [0042]
- SIMCA: A method for analyzing chemical data in terms of similarity and analogy. **WOLD, S ; M. SJOSTROM.** Chemometrics: Theory and Application. 1977, vol. 52 [0042]
- Fuzzy Models for Pattern Recognition. IEEE Press, 1992 [0042]
- A Fuzzy K nearest Neighbor Algorithm. **KELLER, J ; M. GRAY ; J. GIVENS.** IEEE Transactions on Systems, Man, and Cybernetics. July 1985, vol. 15, 580-585 [0042]
- **PAO, Y.H.** Adaptive Pattern Recognition and Neural Networks. Publishing Company, Inc, 1989 [0042]
- **BEZDEK, J.C et al.** Fuzzy Logic and Neural Network Handbook. IEEE Press, 1996 [0044]
- **ZADEH, L.A.** Fuzzy Sets. *Inform. Control*, 1965, vol. 8, 338-353 [0044]
- **GELADI, P ; B.R. KOWALSKI.** Partial least-squares regression: a tutorial. *Analytica Chimica Acta*, 1986, vol. 185, 1-17 [0047]



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- **SIRI, W. E.** The gross composition of the body. *Adv. Biol. Med. Phys.*, 1956, vol. 4, 239-280 **[0051]**
- **MARTENS, H ; T. NAES.** *Multivariate Calibration.* John Wiley and Sons, 1989 **[0068]**

专利名称(译)	通过与脂肪组织相关的特征对组织进行分类和表征		
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摘要(译)

用于表征和分类组织样本的状态和结构的非侵入性系统在体内组织的近红外吸收光谱上操作。提供了一种方法，该方法使用近红外光谱测量来基于与脂肪组织中的脂肪相关的吸收特征来表征和分类采样的组织的状态和结构。还提供了一种估计皮肤褶皱厚度的方法。该方法提供了关于组织可变性来源的信息，因此可用于建立组织结构的一般类别。基于该测定的受试者分类适合于进一步的光谱分析和生物和化学化合物（例如血液分析物）的测量。本发明还提供了一种基于皮肤褶皱厚度估计来估计体脂百分比的方法。本发明还提供了一种用于测量与数字处理器耦合的吸收光谱的装置，用于执行所需的分析。

