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(54) **Title**: SYSTEM FOR NONINVASIVE DETERMINATION OF ALCOHOL IN TISSUE

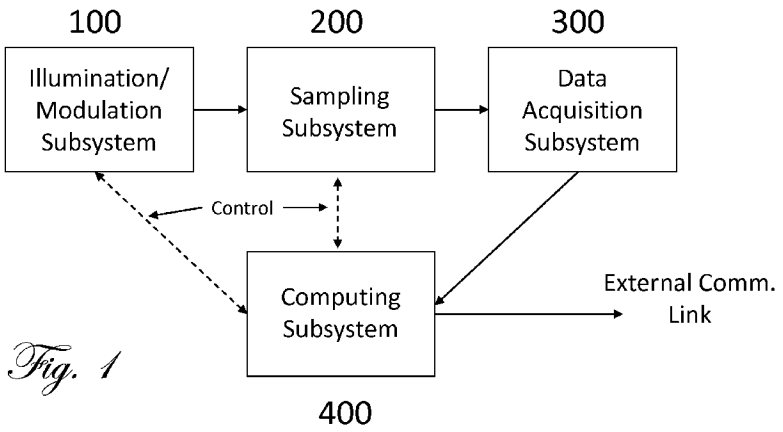

Fig. 1

(57) **Abstract**: An apparatus and method for non-invasive determination of attributes of human tissue by quantitative infrared spectroscopy to clinically relevant levels of precision and accuracy. The system includes subsystems optimized to contend with the complexities of the tissue spectrum, high signal- to-noise ratio and photometric accuracy requirements, tissue sampling errors, calibration maintenance problems, and calibration transfer problems. The subsystems include an illumination/modulation subsystem, a tissue sampling subsystem, a calibration maintenance subsystem, an FTIR spectrometer subsystem, a data acquisition subsystem, and a computing subsystem.

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SYSTEM FOR NONINVASIVE DETERMINATION OF ALCOHOL IN TISSUE

FIELD OF THE INVENTION

[0001] The present invention generally relates to a quantitative spectroscopy system for measuring the presence or concentration of alcohol, alcohol byproducts, alcohol adducts, or substances of abuse utilizing non-invasive techniques in combination with multivariate analysis.

BACKGROUND OF THE INVENTION

[0002] Current practice for alcohol measurements is based upon either blood measurements or breath testing. Blood measurements define the gold standard for determining alcohol intoxication levels. However, blood measurements require either a venous or capillary sample and involve significant handling precautions in order to minimize health risks. Once extracted, the blood sample must be properly labeled and transported to a clinical laboratory or other suitable location where a clinical gas chromatograph is typically used to measure the blood alcohol level. Due to the invasiveness of the procedure and the amount of sample handling involved, blood alcohol measurements are usually limited to critical situations such as for traffic accidents, violations where the suspect requests this type of test, and accidents where injuries are involved.

[0003] Because it is less invasive, breath testing is more commonly encountered in the field. In breath testing, the subject must expire air into the instrument for a sufficient time and volume to achieve a stable breath flow that originates from the alveoli deep within the lungs. The device then measures the alcohol content in the air, which is related to blood alcohol through a breath-blood partition coefficient. The blood-breath partition coefficient used in the United States is 2100 (implied units of mg EtOH/dL blood per mg EtOH/dL air) and varies between 1900 and 2400 in other nations. The variability in the partition coefficient is due to the fact that it is highly subject dependent. In other words, each subject will have a partition coefficient in the 1900 to 2400 range that depends on his or her physiology. Since knowledge of each subject's partition coefficient is unavailable in field applications, each nation assumes a single partition coefficient value that is globally applied to all measurements. In the U.S., defendants in DUI cases often use the globally applied partition coefficient as an argument to impede prosecution.

[0004] Breath measurements have additional limitations. First, the presence of "mouth alcohol" can falsely elevate the breath alcohol measurement. This necessitates a 15-minute waiting period prior to making a measurement in order to ensure that no mouth alcohol is present. For a similar reason, a 15 minute delay is required for individuals who are observed to burp or vomit. A delay of 10 minutes or more is often required between breath measurements to allow the instrument to return to equilibrium with the ambient air and zero alcohol levels. In addition, the accuracy of breath alcohol measurements is sensitive to numerous physiological and environmental factors.

[0005] Multiple government agencies, and society in general, seek non-invasive alternatives to blood and breath alcohol measurements. Quantitative spectroscopy offers the potential for a completely non-invasive alcohol measurement that is not sensitive to the limitations of the current measurement methodologies. While non-invasive determination of biological attributes by quantitative spectroscopy has been found to be highly desirable, it has been very difficult to accomplish. Attributes of interest include, as examples, analyte presence, analyte concentration (e.g., alcohol concentration), direction of change of an analyte concentration, rate of change of an analyte concentration, disease presence (e.g., alcoholism), disease state, and combinations and subsets thereof. Non-invasive measurements via quantitative spectroscopy are desirable because they are painless, do not require a fluid draw from the body, carry little risk of contamination or infection, do not generate any hazardous waste, and can have short measurement times.

[0006] Several systems have been proposed for the non-invasive determination of attributes of biological tissue. These systems have included technologies incorporating polarimetry, mid-infrared spectroscopy, Raman spectroscopy, Kromoscopy, fluorescence spectroscopy, nuclear magnetic resonance spectroscopy, radio-frequency spectroscopy, ultrasound, transdermal measurements, photo-acoustic spectroscopy, and near-infrared spectroscopy. However, these systems have not replaced direct and invasive measurements.

[0007] As an example, Robinson et al. in U.S. Patent No. 4,975,581 disclose a method and apparatus for measuring a characteristic of unknown value in a biological sample using infrared spectroscopy in conjunction with a multivariate model that is empirically derived from a set of spectra of biological samples of known characteristic values. The above-mentioned characteristic is generally the concentration of an analyte, such as alcohol, but also can be any chemical or physical property of the sample. The method of Robinson et al. involves a two-step process that includes both calibration and prediction steps.

[0008] In the calibration step, the infrared light is coupled to calibration samples of known characteristic values so that there is attenuation of at least several wavelengths of the infrared radiation as a function of the various components and analytes comprising the sample with known characteristic value. The infrared light is coupled to the sample by passing the light through the sample or by reflecting the light off the sample. Absorption of the infrared light by the sample causes intensity variations of the light that are a function of the wavelength of the light. The resulting intensity variations at a minimum of several wavelengths are measured for the set of calibration samples of known characteristic values. Original or transformed intensity variations are then empirically related to the known characteristics of the calibration samples using multivariate

algorithms to obtain a multivariate calibration model. The model preferably accounts for subject variability, instrument variability, and environment variability.

[0009] In the prediction step, the infrared light is coupled to a sample of unknown characteristic value, and a multivariate calibration model is applied to the original or transformed intensity variations of the appropriate wavelengths of light measured from this unknown sample. The result of the prediction step is the estimated value of the characteristic of the unknown sample. The disclosure of Robinson et al. is incorporated herein by reference.

[0010] A further method of building a calibration model and using such model for prediction of analytes and/or attributes of tissue is disclosed in commonly assigned U.S. Patent No. 6,157,041 to Thomas et al., entitled "Method and Apparatus for Tailoring Spectrographic Calibration Models," the disclosure of which is incorporated herein by reference.

[0011] In U.S. Patent No. 5,830,112, Robinson describes a general method of robust sampling of tissue for non-invasive analyte measurement. The sampling method utilizes a tissue-sampling accessory that is pathlength optimized by spectral region for measuring an analyte such as alcohol. The patent discloses several types of spectrometers for measuring the spectrum of the tissue from 400 to 2500 nm, including acousto-optical tunable filters, discrete wavelength spectrometers, filters, grating spectrometers and FTIR spectrometers. The disclosure of Robinson is incorporated hereby reference.

[0012] Although there has been substantial work conducted in attempting to produce commercially viable non-invasive near-infrared spectroscopy-based systems for determination of biological attributes, no such device is presently available. It is believed that prior art systems discussed above have failed for one or more reasons to fully meet the challenges imposed by the spectral characteristics of tissue which make the design of a non-invasive measurement system a formidable task. Thus, there is a substantial need for a commercially viable device which incorporates subsystems and methods with sufficient accuracy and precision to make clinically relevant determinations of biological attributes in human tissue.

SUMMARY OF THE INVENTION

[0013] The present invention generally relates to a quantitative spectroscopy system for measuring the presence or concentration of alcohol, alcohol byproducts, alcohol adducts, or substances of abuse utilizing non-invasive techniques in combination with multivariate analysis.

[0014] The present system overcomes the challenges posed by the spectral characteristics of tissue by incorporating a design that includes, in some embodiments, five optimized subsystems. The design contends with the complexities of the tissue spectrum, high signal-to-noise ratio and photometric accuracy requirements, tissue sampling errors, calibration maintenance problems,

calibration transfer problems plus a host of other issues. The five subsystems include an illumination/modulation subsystem, a tissue sampling subsystem, a data acquisition subsystem, a computing subsystem, and a calibration subsystem.

[0015] The present invention further includes apparatus and methods that allow for implementation and integration of each of these subsystems in order to maximize the net attribute signal-to-noise ratio. The net attribute signal is the portion of the near-infrared spectrum that is specific for the attribute of interest because it is orthogonal to all other sources of spectral variance. The orthogonal nature of the net attribute signal makes it perpendicular to the space defined by any interfering species and as a result, the net attribute signal is uncorrelated to these sources of variance. The net attribute signal-to-noise ratio is directly related to the accuracy and precision of the present invention for non-invasive determination of the attribute by quantitative near-infrared spectroscopy.

[0016] The present invention can use near-infrared radiation for analysis. Radiation in the wavelength range of 1.0 to 2.5 microns (or wavenumber range of 10,000 to 4,000 cm^{-1}) can be suitable for making some non-invasive measurements because such radiation has acceptable specificity for a number of analytes, including alcohol, along with tissue optical penetration depths of up to 5 millimeters with acceptable absorbance characteristics. In the 1.0 to 2.5 micron spectral region, the large number of optically active substances that make up the tissue complicate the measurement of any given substance due to the overlapped nature of their absorbance spectra. Multivariate analysis techniques can be used to resolve these overlapped spectra such that accurate measurements of the substance of interest can be achieved. Multivariate analysis techniques, however, can require that multivariate calibrations remain robust over time (calibration maintenance) and be applicable to multiple instruments (calibration transfer). Other wavelength regions, such as the visible and infrared, can also be suitable for the present invention.

[0017] The present invention documents a multidisciplinary approach to the design of a spectroscopic instrument that incorporates an understanding of the instrument subsystems, tissue physiology, multivariate analysis, near-infrared spectroscopy and overall system operation. Further, the interactions between the subsystems have been analyzed so that the behavior and requirements for the entire non-invasive measurement device are well understood and result in a design for a commercial instrument that will make non-invasive measurements with sufficient accuracy and precision at a price and size that is commercially viable.

[0018] The subsystems of the non-invasive monitor are highly optimized to provide reproducible and, preferably, uniform radiance of the tissue, low tissue sampling error, depth targeting of the tissue layers that contain the property of interest, efficient collection of diffuse reflectance spectra

from the tissue, high optical throughput, high photometric accuracy, large dynamic range, excellent thermal stability, effective calibration maintenance, effective calibration transfer, built-in quality control, and ease-of-use.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1 is a schematic depiction of a non-invasive spectrometer system incorporating the subsystems of the present invention;

Figure 2 is a graphical depiction of the concept of net attribute signal in a three-component system;

Figure 3 is a diagramed view of a system of the present invention using a means for spatially and angularly homogenizing emitted radiation;

Figure 4 is a schematic of an embodiment of the present invention incorporating a semiconductor light source with Hadamard encoding;

Figure 5 is a schematic of an embodiment of the present invention incorporating a semiconductor light source with Hadamard encoding, where the encoding is performed after the light has interacted with the sample;

Figure 6 is an embodiment of an electronic circuit designed to monitor and control the temperature of a solid state light source;

Figure 7 is an embodiment of an electronic circuit designed to control the drive current of a solid state light source including means for turning the light source on and off;

Figure 8 is an embodiment of an electronic circuit designed to monitor and control the temperature of a solid state light source including means for altering the desired control temperature;

Figure 9 is an embodiment of an electronic circuit designed to control the drive current of a solid state light source including means for turning the light source on and off and altering the desired drive current;

Figure 10 is a perspective view of elements of an example tissue sampling subsystem;

[0020] Figure 11 is a perspective view of an ergonomic apparatus for holding the sampling surface and positioning a tissue surface thereon;

Figure 12 is a plan view of the sampling surface of the tissue sampling subsystem, showing an example arrangement of illumination and collection optical fibers;

Figure 13 is an alternative embodiment of the sampling surface of the tissue sampling subsystem;

Figure 14 is an alternative embodiment of the sampling surface of the tissue sampling subsystem;

Figure 15 is a depicts various aspects of a sampler orientation;

Figure 16 is a diagramed view of a two-channel sampling subsystem;

Figure 17 is a graphical representation showing the benefits of a two-channel sampling subsystem;

Figure 18 is a diagramed view of the interface between the sampling surface and the tissue when topical interferents are present on the tissue;

Figure 19 is a diagramed view of an alternative positioning device for the tissue relative to the sampling surface;

Figure 20 is a schematic representation of an example data acquisition subsystem;

[0021] Figure 21 is a schematic representation that shows various aspects of an example computing subsystem;

Figure 22 is the spectrum of water before and after path length correction to account for photon propagation through tissue;

Figure 23 is a diagram of a hybrid calibration formation process;

Figure 24 is a schematic representation of a decision process that combines three topical interferent mitigation strategies;

Figure 25 demonstrates the effectiveness of multivariate calibration outlier metrics for detecting the presence of topical interferents;

Figure 26 shows normalized NIR spectra of 1300 and 3000 K blackbody radiators over the 100-33000 cm^{-1} (100-0.3 microm) range;

Figure 27 shows the measured intensity over time observed for a demonstrative ceramic blackbody light source;

Figure 28 shows the spectral emission profiles of several demonstrative NIR LED's;

Figure 29 is a perspective end view and a detail plan view of a light pipe suitable for use with the present invention;

Figure 30 is an illustration of internal reflection and the resulting channeling;

[0022] Figure 31 shows a schematic of the components of an example embodiment of the present invention;

Figure 32 is a schematic of the arrangement of illumination and collection fibers at the sample interface for an example embodiment of an optical probe of the present invention;

Figure 33 depicts noninvasive tissue spectra acquired using 22 wavelengths;

Figure 34 compares noninvasive tissue alcohol concentrations obtained from the spectra in figure 33 to contemporaneous capillary blood alcohol concentration;

Figure 35 is an illustration of the optical combination of multiple semiconductor light sources.

DETAILED DESCRIPTION OF THE INVENTION

[0023] For the purposes of the present invention, the term "**analyte concentration**" generally refers to the concentration of an analyte, such as alcohol. The term "**analyte property**" includes analyte concentration and other properties, such as the presence or absence of the analyte or the direction

or rate of change of the analyte concentration, or a biometric, which can be measured in conjunction with or instead of the analyte concentration. While the disclosure generally references alcohol as the "**analyte**" of interest, other analytes, including but not limited to substances of abuse, alcohol biomarkers, and alcohol byproducts, can also benefit from the present invention. The term "**alcohol**" is used as an example analyte of interest; the term is intended to include ethanol, methanol, ethyl glycol or any other chemical commonly referred to as alcohol. For the purposes of this invention, the term "**alcohol byproducts**" includes the adducts and byproducts of the metabolism of alcohol by the body including, but not limited to, acetone, acetaldehyde, and acetic acid. The term "**alcohol biomarkers**" includes, but is not limited to, Gamma Glutamyl Transferase (GGT), Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), Mean Corpuscular Volume (MCV), Carbohydrate-Deficient Transferrin (CDT), Ethyl Glucuronide (EtG), Ethyl Sulfate (EtS), and Phosphatidyl Ethanol (PEth). The term "**substances of abuse**" refers to, but is not limited to, THC (Tetrahydrocannabinol or marijuana), cocaine, M-AMP (methamphetamine), OPI (morphine and heroin), OxyContin, Oxycodone, and PCP (phencyclidine). The term "**biometric**" refers to an analyte or biological characteristic that can be used to identify or verify the identity of a specific person or subject. The present invention addresses the need for analyte measurements of samples utilizing spectroscopy where the term "**sample**" generally refers to biological tissue. The term **"subject"** generally refers to a person from whom a sample measurement was acquired.

[0024] The terms **"solid state light source"** or **"semiconductor light source"** refer to all sources of light, whether spectrally narrow (e.g. a laser) or broad (e.g. an LED) that are based upon semiconductors which include, but are not limited to, light emitting diodes (LED's), vertical cavity surface emitting lasers (VCSEL's), horizontal cavity surface emitting lasers (HCSEL's), quantum cascade lasers, quantum dot lasers, diode lasers, or other semiconductor diodes or lasers. Furthermore, plasma light sources and organic LED's, while not strictly based on semiconductors, are also contemplated in the embodiments of the present invention and are thus included under the solid state light source and semiconductor light source definitions for the purposes of this disclosure.

[0025] For the purposes of this invention the term "**dispersive spectrometer**" indicates a spectrometer based upon any device, component, or group of components that spatially separate one or more wavelengths of light from other wavelengths. Examples include, but are not limited to, spectrometers that use one or more diffraction gratings, prisms, holographic gratings. For the purposes of this invention the term "**interferometric/modulating spectrometer**" indicates a class of spectrometers based upon the optical modulation of different wavelengths of light to different frequencies in time or selectively transmits or reflects certain wavelengths of light based upon the properties of light interference. Examples include, but are not limited to, Fourier transform

interferometers, Sagnac interferometers, mock interferometers, Michelson interferometers, one or more etalons, or acousto-optical tunable filters (AOTF's). One skilled in the art recognizes that spectrometers based on combinations of dispersive and interferometric/modulating properties, such as those based on lamellar gratings, are also contemplated with respect to the present invention.

[0026] The invention makes use of "**signals**", described in some of the examples as absorbance or other spectroscopic measurements. Signals can comprise any measurement obtained concerning the spectroscopic measurement of a sample or change in a sample, e.g., absorbance, reflectance, intensity of light returned, fluorescence, transmission, Raman spectra, or various combinations of measurements, at one or more wavelengths. Some embodiments make use of one or more models, where such a model can be anything that relates a signal to the desired property. Some examples of models include those derived from multivariate analysis methods, such as partial least squares regression (PLS), linear regression, multiple linear regression (MLR), classical least squares regression (CLS), neural networks, discriminant analysis, principal components analysis (PCA), principal components regression (PCR), discriminant analysis, neural networks, cluster analysis, and K-nearest neighbors. Single or multi-wavelength models based on the Beer-Lambert law are special cases of classical least squares and are thus included in the term multivariate analysis for the purposes of the present invention.

[0027] The following detailed description should be read with reference to the drawings. The drawings, which are not necessarily to scale, depict illustrative embodiments that are not intended to limit the scope of the invention. For the purposes of the application, the term "**about**" applies to all numeric values, whether or not explicitly indicated. The term "**about**" generally refers to a range of numbers that one of skill in the art would consider equivalent to the recited value (i.e., having the same function or result). In some instances, the term "**about**" can include numbers that are rounded to the nearest significant figure.

[0028] Spectroscopic measurement systems typically require some means for resolving and measuring different wavelengths of light in order to obtain a spectrum. Some common approaches achieve the desired spectrum include dispersive (e.g. grating and prism based) spectrometers and interferometric (e.g. Michelson, Sagnac, or other interferometer) spectrometers. Noninvasive measurement systems that incorporate such approaches are often limited by the expensive nature of dispersive and interferometric devices as well as their inherent size, fragility, and sensitivity to environmental effects. The present invention can provide an alternative approach for resolving and recording the intensities of different wavelengths using solid state light sources such as light emitting diodes (LED's), vertical cavity surface emitting lasers (VCSEL's), horizontal cavity surface emitting lasers (VCSEL's), diode lasers, quantum cascade lasers, or other solid state light sources.

[0029] Referring now to Figure 1, a non-invasive monitor that is able to achieve acceptable levels of accuracy and precision for analyte property measurements is depicted in schematic view. The overall systems of the present invention can be viewed for discussion purposes as comprising five subsystems; those skilled in the art will appreciate other subdivisions of the functionality disclosed. The subsystems include an illumination/modulation subsystem 100, a tissue sampling subsystem 200, a data acquisition subsystem 300, a processing subsystem 400, and a calibration subsystem (not shown).

[0030] The subsystems can be designed and integrated in order to achieve a desirable net attribute signal-to-noise ratio. The net attribute signal is the portion of the near-infrared spectrum that is specific for the attribute of interest because it is orthogonal to other sources of spectral variance. Figure 2 is a graphical representation of the net attribute signal in a three dimensional system. The net attribute signal-to-noise ratio is directly related to the accuracy and precision of the non-invasive attribute determination by quantitative near-infrared spectroscopy with the present invention.

[0031] The subsystems provide reproducible and preferably spatially uniform radiance of the tissue, low tissue sampling error, depth targeting of appropriate layers of the tissue, efficient collection of diffuse reflectance spectra from the tissue, high optical throughput, high photometric accuracy, large dynamic range, excellent thermal stability, effective calibration maintenance, effective calibration transfer, built-in quality control and ease-of-use. Each of the subsystems is discussed below in more detail.

ILLUMINATION/MODULATION SUBSYSTEM (100)

[0032] The illumination/modulation subsystem 100 generates the light used to interrogate the sample (e.g. skin tissue of a human). In classical spectroscopy using dispersive or interferometric spectrometers, the spectrum of a polychromatic light source (or sample of interest) is measured either by dispersing the different wavelengths of light spatially (e.g. using a prism or a diffraction grating) or by modulating different wavelengths of light to different frequencies (e.g. using a Michelson interferometer). In these cases, a spectrometer (a subsystem distinct from the light source) is required to perform the function of "encoding" different wavelengths either spatially or in time such that each can be measured substantially independently of other wavelengths. While dispersive and interferometric spectrometers are known in the art and can adequately serve their function in some environments and applications, they can be limited by their cost, size, fragility, and complexity in other applications and environments.

[0033] An advantage of solid-state light sources incorporated in the systems disclosed in the present invention is that they can be modulated in intensity. Thus, multiple light sources that emit different wavelengths of light can be used with each light source modulated at a different frequency.

The independently modulated light sources can be optically combined into a single beam and introduced to the sample. A portion of the light can be collected from the sample and measured by a single photodetector. The result is the effective combination of the light source and the spectrometer into a single illumination/modulation subsystem that can offer significant benefits in size, cost, energy consumption, and overall system stability since the spectrometer, as an independent subsystem, is eliminated from the measurement system.

[0034] Several parameters of systems for measuring analyte properties incorporating solid state light sources must be considered including, but not limited to, the number of solid-state light sources required to perform the desired measurement, the emission profile of the light sources (e.g. spectral width, intensity), light source stability and control, and their optical combination. As each light source is a discrete element, it can be advantageous to combine the output of multiple light sources into a single beam such that they are consistently introduced and collected from the sample.

[0035] Furthermore, the modulation scheme for the light sources must also be considered as some types of sources can be amenable to sinusoidal modulations in intensity where others can be amenable to being switched on and off or square wave modulated. In the case of sinusoidal modulation, multiple light sources can be modulated at different frequencies based on the electronics design of the system. The light emitted by the multiple sources can be optically combined, for example using a light pipe or other homogenizer, introduced and collected from the sample of interest, and then measured by a single detector. The resulting signal can be converted into an intensity versus wavelength spectrum via a Fourier, or similar, transform.

[0036] Alternatively, some light sources are switched between the on and off state or square wave modulated which are amenable to a Hadamard transform approach. However, in some embodiments, rather than a traditional Hadamard mask that blocks or passes different wavelengths at different times during a measurement, the Hadamard scheme can be implemented in electronics as solid state light sources can be cycled at high frequencies. A Hadamard or similar transform can be used to determine the intensity versus wavelength spectrum.

[0037] Another advantage of solid state light sources is that many types (e.g. VCSELs) emit a narrow range of wavelengths (which in part determines the effective resolution of the measurement). Consequently, in some example embodiments, shaping or narrowing the emission profile of light sources with optical filters or other approaches is not required as they are already sufficiently narrow. This can be advantageous due to decreased system complexity and cost. Furthermore, the emission wavelengths of some solid state light sources, such as VCSEL's, are tunable over a range of wavelengths via either the supplied drive current, drive voltage, or by changing the temperature of the light source. The advantage of this approach is that if a given measurement requires a specific

number of wavelengths, the system can achieve the requirement with fewer discrete light sources by tuning them over their feasible ranges. For example, if measurement of a noninvasive property required 20 wavelengths, 10 discrete VCSEL's might be used with each of the 10 being tuned to 2 different wavelengths during the course of a measurement. In this type of scheme, a Fourier or Hadamard approach remains appropriate by changing the modulation frequency for each tuning point of a light source or by combining the modulation scheme with a scanning scheme.

[0038] It is important to note that the present invention also envisions several embodiments of blackbody light sources rather than solid-state light sources. In these embodiments, the broad blackbody source is converted to multiple, narrow light sources using optical filters such as, but not limited to, linearly variable filters (LVF's), dielectric stacks, distributed Bragg gratings, photonic crystal lattice filters, polymer films, absorption filters, reflection filters, etelons, dispersive elements such as prisms and gratings, and quantum dot filters. The resulting multiple bands of wavelengths can be modulated by a Fourier scheme or Hadamard mask. Similar to the solid-state concepts, the spectrometer system is combined with the light source which can offer substantial benefits in terms of size, cost, and the robustness of the system.

[0039] In other embodiments, a dispersive element such as a grating or prism is used to spatially separate the wavelengths of light from a broad band source (either a blackbody, LED, or other broad emitting light source). The dispersive element separates the different wavelengths which can be independently modulated at their locations on a focal plane using a Hadamard mask or mechanical chopper (e.g. for a Fourier scheme). Similar to the embodiments previously described, the resulting light can be homogenized and introduced to the optical probe. Figures 4 and 5 show schematics of embodiments of the present invention that incorporate a blackbody light source with Hadamard encoding.

[0040] In mechanically modulated embodiments incorporating a Hadamard mask or mechanical chopper, in some cases it can be advantageous to perform the modulating step after the light has been collected from the sample by the optical probe (200). Figure 5 shows a schematic of an embodiment of such a system.

[0041] Analyte properties can be measured at a variety of wavelengths spanning the ultraviolet and infrared regions of the electromagnetic spectrum. For *in vivo* measurements in skin, such as alcohol or substances of abuse, the near infrared (NIR) region of 1,000 nm to 2,500 nm region can be important due to the sensitivity and specificity of the spectroscopic signals for the analyte of interest as well as other chemical species (e.g. water) that are present in human skin. Furthermore, the absorptivities of the analytes are low enough that the near infrared light can penetrate a few millimeters into the skin where the analytes of interest reside. The 2,000 nm to 2,500 nm

wavelength range can be of particular utility as it contains combination bands rather than the weaker, less distinct overtones encountered in the 1,000 to 2,000 nm portion of the NIR.

[0042] In addition to the commonly available LEDs, VCSELs, diode lasers in the visible region of the spectrum, there are solid state light sources available with emission wavelengths throughout the NIR region (1,000 to 2,500 nm). These light sources are suitable for the analyte and biometric property measurement systems of the present invention. Some examples of available NIR solid state light sources that are VCSELs produced by Vertilas GmbH, and the VCSEL's, quantum cascade lasers, laser diodes available from Laser Components GmbH, or lasers and diodes available from Roithner Laser, Epitex, Dora Texas Corporation, Microsensor Tech, SciTech Instruments, Laser 2000, Redwave Labs, and Deep Red Tech. These examples are included for demonstrative purposes and are not intended to be limiting of the types of solid state light sources suitable for use with the present invention.

MEASUREMENT RESOLUTION AND RESOLUTION ENHANCEMENT

[0043] In a dispersive spectrometer the effective resolution of a spectroscopic measurement is often determined by the width of an aperture in the system. The resolution limiting aperture is often the width of the entrance slit. At the focal plane where light within the spectrometer is detected, multiple images of the slit are formed, with different wavelengths located at different spatial locations on the focal plane. Thus, the ability to detect one wavelength independent of its neighbors is dependent on the width of the slit. Narrower widths allow better resolution between wavelengths at the expense of the amount of light that can be passed through the spectrometer. Consequently, resolution and signal to noise ratio generally trade against each other. Interferometric spectrometers have a similar trade between resolution and signal to noise ratio. In the case of a Michelson interferometer the resolution of the spectrum is in part determined by the distance over which a moving mirror is translated with longer distances resulting in greater resolution. The consequence is that the greater the distance, the more time is required to complete a scan.

[0044] In the case of the measurement systems of the present invention, the resolution of the spectrum is determined by the spectral width of each of the discrete light sources (whether a different light source, one tuned to multiple wavelengths, or a combination thereof). For measurements of analyte properties requiring high resolution, a VCSEL or other suitable solid state laser can be used. The widths of the laser's emission can be very narrow, which translates into high resolution. In measurement applications where moderate to low resolution are required, LED's can be suitable as they typically have wider emission profiles (the output intensity is distributed across a wider range of wavelengths) than solid state laser alternatives.

[0045] The effective resolution of light sources can be enhanced through the use, or combination of, different types of optical filters. The spectral width of a light source can be narrowed or attenuated using one or more optical filters in order to achieve higher resolution (e.g. a tighter range of emitted wavelengths). Examples of optical filters that are contemplated in embodiments of the present invention include, but are not limited to: linearly variable filters (LVF's), dielectric stacks, distributed Bragg gratings, photonic crystal lattice filters, polymer films, absorption filters, reflection filters, etelons, dispersive elements such as prisms and gratings, and quantum dot filters.

[0046] Another means for improving the resolution of measurements obtained from embodiments of the present invention is deconvolution. Deconvolution, and other similar approaches, can be used to isolate the signal difference that is present between two or more overlapping broad light sources. For example, two light sources with partially overlapping emission profiles can be incorporated into a measurement system. A measurement can be acquired from a sample and a spectrum generated (via a Hadamard, Fourier transform, or other suitable transform). With knowledge of the emission profiles of the light sources, the profiles can be deconvolved from the spectrum in order to enhance the resolution of the spectrum.

STABILIZATION AND CONTROL OF LIGHT SOURCE WAVELENGTH AND INTENSITY

[0047] The peak emission wavelength of solid state light sources, particularly lasers, can be influenced by changing the thermal state or electrical properties (e.g. drive current or voltage) of the light source. In the case of semi conductor lasers, changing the thermal state and electrical properties alters the optical properties or physical dimensions of the lattice structure of the semiconductor. The result is a change in the cavity spacing within the device, which alters the peak wavelength emitted. Since solid state light sources exhibit these effects, when they are used in spectroscopic measurement systems the stability of the peak wavelength of emission and its associated intensity can be important parameters. Consequently, during a measurement control of both the thermal state and electrical properties of each light source can be advantageous in terms of overall system robustness and performance. Furthermore, the change in optical properties caused by thermal state and electrical conditions can be leveraged to allow a single light source to be tuned to multiple peak wavelength locations. This can result in analyte property measurement systems that can measure more wavelength locations than the number of discrete light sources which can reduce system cost and complexity.

[0048] Temperature stabilization can be achieved using multiple approaches. In some embodiments, a light source or light sources can be stabilized by raising the temperature above (or cooling below) ambient conditions with no additional control of the temperature. In other embodiments, the light source or light sources can be actively controlled to a set temperature

(either cooled or heated) using a control loop. A diagram of a temperature control loop circuit suitable for the present invention is shown in Figure 6.

[0049] The electrical properties of light sources also influence the emission profile (e.g. wavelength locations of emission) of solid state light sources. It can be advantageous to stabilize the current and/or voltage supplied to the light source or light sources. For example, the peak emission of VCSELs depends on drive current. For embodiments where the stability of the peak wavelength is important, the stability of the drive current becomes an important figure of merit. In such cases, an electronic circuit can be designed to supply a stable drive current to the VCSEL. The complexity and cost of the circuit can depend on the required stability of the drive current. Figure 7 shows a current drive circuit suitable for use with the present invention. One skilled in the art recognizes that alternative embodiments of current control circuits are known in the art and can also be suitable for the present invention. Furthermore, some solid state light sources require control of the drive voltage, rather than drive current; one skilled in the art recognizes that electronics circuits designed to control voltage rather than current are readily available.

[0050] In some embodiments, a single solid state light source, such as a VCSEL, is tuned to multiple wavelengths during the course of a measurement. In order to achieve the tuning of the light sources, the circuits shown in Figures 6 and 7 can be modified to include the control of the temperature set point and current, respectively. Figures 8 and 9 depict embodiments of temperature and current control circuits, respectively, that allow tuning of the emission wavelength. In some embodiments, either tuning temperature or drive current/voltage can be sufficient to realize the desired tuning of the peak emission wavelength. In other embodiments, control of both the temperature and drive current/voltage can be required to achieve the desired tuning range.

[0051] Furthermore, optical means for measuring and stabilizing the peak emission wavelength can also be incorporated into the systems described in connection with the present invention. A Fabry-Perot etalon can be used to provide a relative wavelength standard. The free spectral range and finesse of the etalon can be specified to provide an optical passband that allows active measurement and control of the VCSEL peak wavelength. An example embodiment of this etalon uses a thermally stabilized, flat fused-silica plate with partially mirrored surfaces. For systems where each VCSEL is required to provide multiple wavelengths, the free spectral range of the etalon can be chosen such that its transmission peaks coincide with the desired wavelength spacing for tuning. One skilled in the art will recognize that there are many optical configurations and electronic control circuits that are viable for this application. One example control circuit is showing in Figure 9. An alternate wavelength encoding scheme uses a dispersive grating and a secondary array detector to encode the VCSEL wavelength into a spatial location on the array. For either the dispersive or the etalon based

schemes, a secondary optical detector that has less stringent performance requirements than the main optical detector can be used. Active control can reduce the stability requirements of the VCSEL temperature and current control circuits by allowing real time correction for any drift.

[0052] Light homogenizers such as optical diffusers, light pipes, and other scramblers can be incorporated into some embodiments of the illumination/modulation subsystem 100 in order to provide reproducible and, preferably, uniform radiance at the input of the tissue sampling subsystem 200. Uniform radiance can ensure good photometric accuracy and even illumination of the tissue. Uniform radiance can also reduce errors associated with manufacturing differences between light sources. Uniform radiance can be utilized in the present invention for achieving accurate and precise measurements. *See, e.g.*, U.S. Patent 6,684,099, incorporated herein by reference.

[0053] A ground glass plate is an example of an optical diffuser. The ground surface of the plate effectively scrambles the angle of the radiation emanating from the light source and its transfer optics. A light pipe can be used to homogenize the intensity of the radiation such that it is spatially uniform at the output of the light pipe. In addition, light pipes with a double bend will scramble the angles of the radiation. For creation of uniform spatial intensity and angular distribution, the cross section of the light pipe should not be circular. Square, hexagonal and octagonal cross sections are effective scrambling geometries. The output of the light pipe can directly couple to the input of the tissue sampler or can be used in conjunction with additional transfer optics before the light is sent to the tissue sampler. *See, e.g.*, U.S. Patent application 09/832,586, "Illumination Device and Method for Spectroscopic Analysis," incorporated herein by reference.

SAMPLING SUBSYSTEM 200

[0054] Figure 1 indicates that the orientation of the tissue sampling subsystem 200 is between the illumination/modulation (100) and data acquisition (300) subsystems. Referring to Figure 1, the tissue sampling subsystem 200 introduces radiation generated by the illumination/modulation subsystem 100 into the tissue of the subject, collects a portion of the radiation that is not absorbed by the tissue and sends that radiation to optical detector in the data acquisition subsystem 300 for measurement. Figures 10 through 20 depict elements of an example tissue sampling subsystem 200. Referring to Figure 10, the tissue sampling subsystem 200 has an optical input 202, a sampling surface 204 which forms a tissue interface 206 that interrogates the tissue and an optical output 207. The subsystem further includes an ergonomic apparatus 210, depicted in Figure 11, which holds the sampling surface 204 and positions the tissue at the interface 206. In an example subsystem, a device that thermostats the tissue interface is included and, in some embodiments, an apparatus that repositions the tissue on the tissue interface in a repetitive fashion is included. In

other embodiments, an index matching fluid can be used to improve the optical interface between the tissue and sampling surface. The improved interface can reduce error and increase the efficiency, thereby improving the net attribute signal. See, e.g. U.S. patents 6,622,032, 6,152,876, 5,823,951, and 5,655,530, incorporated herein by reference.

[0055] The optical input 202 of the tissue sampling subsystem 200 receives radiation from the illumination/modulation subsystem 100 (e.g., light exiting a light pipe) and transfers that radiation to the tissue interface 206. As an example, the optical input can comprise a bundle of optical fibers that are arranged in a geometric pattern that collects an appropriate amount of light from the illumination/modulation subsystem. Figure 12 depicts one example arrangement. The plan view depicts the ends of the input and output fibers in a geometry at the sampling surface including six clusters 208 arranged in a circular pattern. Each cluster includes four central output fibers 212 which collect diffusely reflected light from the tissue. Around each grouping of four central output fibers 212 is a cylinder of material 215 which ensures about a 100 μm gap between the edges of the central output fibers 212 and the inner ring of input fibers 214. The 100 μm gap can be important to measuring ethanol in the dermis. As shown in Figure 12, two concentric rings of input fibers 214 are arranged around the cylinder of material 215. As shown in one example embodiment, 32 input fibers surround four output fibers.

[0056] Figure 13 demonstrates an alternative to cluster geometries for the sampling subsystem. In this embodiment, the illumination and collection fiber optics are arranged in a linear geometry. Each row can be either for illumination or light collection and can be of any length suitable to achieve sufficient signal to noise. In addition, the number of rows can be 2 or more in order to alter the physical area covered by the sampling subsystem. The total number of potential illumination fibers is dependent on the physical size of emissive area of the light source and the diameter of each fiber. Multiple light sources can be used to increase the number of illumination fibers. The number of collection fibers depends upon the area of the interface to the interferometer subsystem. If the number of collection fibers results in an area larger than the interferometer subsystem interface allows, a light pipe or other homogenizer followed by an aperture can be used to reduce the size of the output area of the sampling subsystem. The purpose of the light pipe or other homogenizer is to ensure that each collection fiber contributes substantially equally to the light that passes through the aperture.

[0057] In some embodiments the sampling subsystem of the present invention, the portion of the optical probe that interacts with the sample can be comprised of a stack of two or more linear ribbons of optical fibers. These arrangements allow the size and shape of the optical probe interface to be designed appropriately for the sample and measurement location (e.g. hand, finger) of

interest. Figure 14 shows an example embodiment of a sampling subsystem based on a linear stack off ribbons. Additional details regarding suitable embodiments for use in the present invention can be found in co-pending U.S. applications 12/185,217 and 12/185,224, each of which is incorporated herein by reference.

[0058] The sampling subsystems can also use one or more channels, where a channel refers to a specific orientation of the illumination and collection fibers. An orientation is comprised of the angle of the illumination fiber or fibers, the angle of the collection fiber or fibers, the numerical aperture of the illumination fiber or fibers, the numerical aperture of the collection fiber or fibers, and the separation distance between the illumination and collection fiber or fibers. Figure 15 is a diagram of parameters that form an orientation. Multiple channels can be used in conjunction, either simultaneously or serially, to improve the accuracy of the noninvasive measurements. Figure 16 is a diagram of a two channel sampling subsystem. In this example, the two channels are measuring the same tissue structure. Therefore each channel provides a measurement of the same tissue from a different perspective. The second perspective helps to provide additional spectroscopic information that helps to decouple the signals due to scattering and absorption. Referring to Figure 16, the group of fibers (1 source, 1 receiver #1, and 1 receiver #2 in this example) can be replicated 1 to N times in order to increase the sampler area and improve optical efficiency. Each of the fibers can have a different numerical aperture and angle (θ). The distances between fibers, X and Y, determine the source-receiver separation. Furthermore, an additional source channel can be added that creates a 4-channel sampling subsystem. One skilled in the art recognizes the large number of possible variants on the number and relationship between channels.

[0059] Figure 17 is a bar chart of example of the benefits of a multiple channel sampler that was used for noninvasive glucose measurements. It is clear from the figure that the combination of the two channels provides superior measurement accuracy when compared to either channel individually. While this example uses two channels, additional channels can provide additional information that can further improve the measurement.

[0060] Another aspect of a multiple channel sampling subsystem is the ability to improve detection and mitigation of topical interferents, such as sweat or lotion, present on the sample. Figure 18 is a diagram of a multiple channel sampling subsystem in the presence of a topical interferent. The figure shows the sampling subsystem at the tissue interface, a layer of topical interferent, and the tissue. In this example the contribution to each channel's measurement due to the topical interferent is identical. The path through interferent is similar for both channels, while path through tissue is different. This allows the potential to decouple the common topical interferent signal present in both channels from the tissue signal that will be different for the two channels.

[0061] The clustered input and output fibers are mounted into a cluster ferrule that is mounted into a sampling head 216. The sampling head 216 includes the sampling surface 204 that is polished flat to allow formation of a good tissue interface. Likewise, the input fibers are clustered into a ferrule 218 connected at the input ends to interface with the illumination/modulation subsystem 100. The output ends of the output fibers are clustered into a ferrule 220 for interface with the data acquisition subsystem 300.

[0062] The optical input can use a combination of light pipes, refractive and/or reflective optics to transfer input light to the tissue interface. It can be important that the input optics of the tissue sampling subsystem collect sufficient light from the illumination/modulation subsystem 100 in order to achieve an acceptable net attribute signal.

[0063] The tissue interface irradiates the tissue in a manner that targets the compartments of the tissue pertinent to the attribute of interest, and can discriminate against light that does not travel a significant distance through those compartments. As an example, a 100-μm gap discriminates against light that contains little attribute information. In addition, the tissue interface can average over a certain area of the tissue to reduce errors due to the heterogeneous nature of the tissue. The tissue sampling interface can reject specular and short pathlength rays and it can collect the portion of the light that travels the desired pathlength through the tissue with high efficiency in order to maximize the net attribute signal of the system. The tissue sampling interface can employ optical fibers to channel the light from the input to the tissue in a predetermined geometry as discussed above. The optical fibers can be arranged in pattern that targets certain layers of the tissue that contain good attribute information.

[0064] The spacing, angle, numerical aperture, and placement of the input and output fibers can be arranged in a manner to achieve effective depth targeting. In addition to the use of optical fibers, the tissue sampling interface can use a non-fiber based arrangement that places a pattern of input and output areas on the surface of the tissue. Proper masking of the non-fiber based tissue sampling interface ensures that the input light travels a minimum distance in the tissue and contains valid attribute information. Finally, the tissue sampling interface can be thermostatted to control the temperature of the tissue in a predetermined fashion. The temperature of the tissue sampling interface can be set such that the invention reduces prediction errors due to temperature variation. Further, reference errors are reduced when building a calibration model. These methods are disclosed in U.S. Patent Application Serial No. 09/343,800, entitled "Method and Apparatus for Non-Invasive Blood Analyte Measurement with Fluid Compartment Equilibration," which is incorporated herein by reference.

[0065] The tissue sampling subsystem can employ an ergonomic apparatus or cradle 210 that positions the tissue over the sampling interface 206 in a reproducible manner. An example ergonomic apparatus 210 is depicted in Figure 11. In the case of sampling the underside of the forearm, an ergonomic cradle design is essential to ensure good contact with the sampling interface. The ergonomic cradle 210 includes a base 221 having an opening 223 therethrough. The opening is sized for receiving the sample head 216 therein to position the sampling surface 204 generally coplanar with an upper surface 225 of the base 221. The ergonomic cradle 210 references the elbow and upper arm of the subject via a bracket 222 in conjunction with a float-to-fit handgrip 224 to accurately position the forearm on the tissue sampling interface. Careful attention must be given to the ergonomics of the tissue sampling interface or significant sampling error can result.

[0066] The example ergonomic cradle 210 is designed such that the forearm of the subject is reliably located over the sampling head 216. The bracket 222 forms an elbow rest that sets the proper angle between the upper arm and the sampling head 216, and also serves as a registration point for the arm. The adjustable hand rest 224 is designed to hold the fingers in a relaxed manner. The hand rest position is adjusted for each subject to accommodate different forearm lengths. In some embodiments, a lifting mechanism is included which raises and lowers the cradle periodically during sampling to break and reform the tissue interface. Reformation of the interface facilitates reduction of sampling errors due to the rough nature and heterogeneity of the skin. Alternate sites, for example fingertips, can also be accommodated using variations of the systems described herein.

[0067] An alternative to the ergonomic cradle is diagramed in Figure 19. Instead of a cradle located on the measurement system, the positioning device is located on the tissue. The positioning device can either be reusable or disposable and can be adhered to the tissue with medical adhesive. The positioning device can also include an optically transparent film or other material that prevents physical contact with the sampling subsystem while preserving the desired optical characteristics of the measurement. The positioning device interfaces to the sampling subsystem in a pre-determined manner, such as alignment pins, in order to reproducibly locate the tissue to the sampling subsystem. The positioning device also prevents movement of the tissue relative to the sampling subsystem during the measurement process.

[0068] The output of the tissue sampling subsystem 200 transfers the portion of the light not absorbed by the tissue that has traveled an acceptable path through the tissue to the optical detector in the data acquisition subsystem 300. The output of the tissue sampling subsystem 200 can use any combination of refractive and/or reflective optics to focus the output light onto the optical detector. In some embodiments, the collected light is homogenized (see US 6,684,099, Apparatus and Methods for Reducing Spectral Complexity in Optical Sampling, incorporated herein

by reference) in order to mitigate for spatial and angular effects that might be sample dependent (see Figure 3).

[0069] As an example application, the non-invasive measurement of alcohol in humans places extreme requirements on the performance of the instrumentation due to the small size of the alcohol absorption spectrum relative to the water absorption of the body. In addition, interferences due to absorption of other spectroscopically active compounds such as collagen, lipids, protein, etc. reduce the useful portions of the alcohol absorption spectrum, yielding a net attribute signal that is small. To first order approximation, 1 mg/dl of alcohol concentration change is equivalent to 7 Au of spectral variance for the effective pathlength light travels through tissue using the present invention. Therefore, in order to measure alcohol non-invasively with clinically acceptable accuracy, the spectrometer portion of the non-invasive alcohol monitor must have a large signal-to-noise ratio (SNR) and excellent photometric accuracy.

DATA ACQUISITION SUBSYSTEM 300

[0070] The data acquisition subsystem 300 converts the optical signal from the sampling subsystem into a digital representation. Figure 20 is a schematic representation of the data acquisition subsystem. An important aspect of the present invention is that, similar to an interferometric spectrometer, only a single element detector is required to measure all desired wavelengths. Array detectors and their supporting electronics are a significant drawback due to their expensive nature.

[0071] The optical detector converts the incident light into an electrical signal as a function of time. Examples of detectors that are sensitive in the spectral range of 1.0 to 2.5 microm include InGaAs, InAs, InSb, Ge, PbS, and PbSe. An example embodiment of the present invention can utilize a 1-mm, thermo-electrically cooled, extended range InGaAs detector that is sensitive to light in the 1.0 to 2.5 microm range. The 2.5 microm, extended range InGaAs detector has low Johnson noise and, as a result, allows Shot noise limited performance for the photon flux emanating from the tissue sampling subsystem. The extended InGaAs detector has peak sensitivity in the 2.0 to 2.5 microm spectral region where three very important alcohol absorption features are located. In comparison with the liquid nitrogen cooled InSb detector, the thermo-electrically cooled, extended range InGaAs can be more practical for a commercial product. Also, this detector exhibits over 120 dbc of linearity in the 1.0 to 2.5 microm spectral region. Alternative detectors can be suitable if the alcohol measurement system utilizes alternative wavelength regions. For example, a silicon detector can be suitable if the wavelength range of interest were within the 300 – 1100 nm range.

[0072] Any photodetector can be used with the present invention as long as the given photodetector satisfies basic sensitivity, noise and speed requirements. A suitable photodetector can have a shunt resistance greater than 6000 ohms, a terminal capacitance less than 6 nano farads

and a minimum photosensitivity of 0.15 amps per watt over the 1.0 to 2.5 micron spectral region. In addition, the photodetector can have a cut-off frequency greater than or equal to 1000 hertz. The shunt resistance of the photodetector defines the Johnson or thermal noise of the detector. The Johnson noise of the detector must be low relative to the photon flux at the detector to ensure Shot noise limited performance by the detector. The terminal capacitance governs the cut-off frequency of the photodetector and may also be a factor in the high frequency noise gain of the photodetector amplifier. The photo sensitivity is an important factor in the conversion of light to an electrical current and directly impacts the signal portion of the SNR equation.

[0073] The remainder of the data acquisition subsystem 300 amplifies and filters the electrical signal from the detector and then converts the resulting analog electrical signal to its digital representation with an analog to digital converter, digital filtering, and re-sampling of the digital signal from equal time spacing to equal position spacing. The analog electronics and ADC must support the high SNR and linearity inherent in the signal. To preserve the SNR and linearity of the signal, the data acquisition subsystem 300 can support at least 100 dbc of SNR plus distortion. The data acquisition subsystem 300 can produce a digitized representation of the signal. In some embodiments, a 24-bit delta-sigma ADC can be operated at 96 or 192 kilohertz. If system performance requirements permit, alternate analog to digital converters can be used in which the sample acquisition is synchronized with the light source modulation rather than captured at equal time intervals. The digitized signal can be passed to an embedded computer subsystem 600 for further processing, as discussed below.

[0074] Further, the data acquisition subsystem 300 can utilize a constant time sampling, dual channel, delta-sigma analog-to-digital converter (ADC) to support the SNR and photometric accuracy requirements of the present non-invasive glucose measurement. In some embodiments, the delta-sigma ADC utilized supports sampling rates of over 100 kHz per channel, has a dynamic range in excess of 117 dbc and has total harmonic distortion less than -105 dbc. In a system that has only one channel of signal to digitize (instead of the two more common in delta-sigma ADC's), the signal can be passed into both inputs of the ADC and averaged following digitization. This operation can help to reduce any uncorrelated noise introduced by the ADC.

[0075] The constant time sampling data acquisition subsystem 300 has several distinct advantages over other methods of digitizing signals. These advantages include greater dynamic range, lower noise, reduced spectral artifacts; detector noise limited operation and simpler and less expensive analog electronics. In addition, the constant time sampling technique allows digital compensation for frequency response distortions introduced by the analog electronics prior to the ADC. This includes non-linear phase error in amplification and filtering circuits as well as the non-ideal

frequency response of the optical detector. The uniformly sampled digital signal allows for the application of one or more digital filters whose cumulative frequency response is the inverse of the analog electronics' transfer function (see, e.g., US 7,446,878, incorporated herein by reference).

COMPUTING SUBSYSTEM 400

[0076] The computing subsystem 400 performs multiple functions such converting the digitized data obtained from the data acquisition subsystem 300 to single beam spectra, performing spectral outlier checks on the single beam spectra, spectral preprocessing in preparation for prediction of the attribute of interest, prediction of the attribute of interest, system status checks, all display and processing requirements associated with the user interface, and data transfer and storage. Figure 21 is a schematic representation that shows the various aspects of a suitable computing subsystem. In some embodiments, the computing subsystem is contained in a dedicated personal computer or laptop computer that is connected to the other subsystems of the invention. In other embodiments, the computing subsystem is a dedicated, embedded computer.

[0077] After converting the digitized data from the detector to single beam spectra, the computer system can check the single beam spectra for outliers or bad scans. An outlier sample or bad scan is one that violates the hypothesized relationship between the measured signal and the properties of interest. Examples of outlier conditions include conditions where the calibrated instrument is operated outside of the specified operating ranges for ambient temperature, ambient humidity, vibration tolerance, component tolerance, power levels, etc. In addition, an outlier can occur if the composition or concentration of the sample is different than the composition or concentration range of the samples used to build the calibration model. The calibration model will be discussed as part of the calibration subsystem later in this disclosure. Any outliers or bad scans can be deleted and the remaining good spectra can be averaged together to produce an average single beam spectrum for the measurement. The average single beam spectrum can be converted to absorbance by taking the negative base 10 logarithm (log10) of the spectrum. The absorbance spectrum can be scaled by a single beam spectrum to renormalize the noise.

[0078] The scaled absorbance spectrum can be used to determine the attribute of interest in conjunction with a calibration model that is obtained from the calibration subsystem 500. After determination of the attribute of interest, the computing subsystem 400 can report the result 830, e.g., to the subject, to an operator or administrator, to a recording system, or to a remote monitor. The computing subsystem 400 can also report the level of confidence in the goodness of the result. If the confidence level is low, the computing subsystem 400 can withhold the result and ask the subject to retest. If required, additional information can be conveyed that directs the user to perform a corrective action. See, e.g., US Application 20040204868, incorporated herein by

reference. The results can be reported visually on a display, by audio and/or by printed means. Additionally, the results can be stored to form a historical record of the attribute. In other embodiments, the results can be stored and transferred to a remote monitoring or storage facility via the internet, phone line, or cell phone service.

[0079] The computing subsystem 400 includes a central processing unit (CPU), memory, storage, a display and preferably a communication link. An example of a CPU is the Intel Pentium microprocessor. The memory can be, e.g., static random access memory (RAM) and/or dynamic random access memory. The storage can be accomplished with non-volatile RAM or a disk drive. A liquid crystal display can be suitable. The communication link can be, as examples, a high speed serial link, an Ethernet link, or a wireless communication link. The computer subsystem can, for example, produce attribute measurements from the received and processed interferograms, perform calibration maintenance, perform calibration transfer, run instrument diagnostics, store a history of measured alcohol concentrations and other pertinent information, and in some embodiments, communicate with remote hosts to send and receive data and new software updates.

[0080] The computing system 400 can also contain a communication link that allows transfer of a subject's alcohol measurement records and the corresponding spectra to an external database. In addition, the communication link can be used to download new software to the computer and update the multivariate calibration model. The computer system can be viewed as an information appliance. Examples of information appliances include personal digital assistants, web-enabled cellular phones and handheld computers.

CALIBRATION SUBSYSTEM 500

[0081] A calibration model is used in connection with the spectral information in order to obtain alcohol measurements. In some embodiments, the calibration model is formed by acquiring blood reference measurements and contemporaneous spectroscopic data on multiple subjects in a wide variety of environmental conditions. In these embodiments, spectroscopic data can be acquired from each subject over a range of blood alcohol concentrations. In other embodiments, a hybrid calibration model can be to measure the alcohol concentrations of subject spectra. In this case, the term hybrid model denotes that a partial least squares (PLS) calibration model was developed using a combination of *in vitro* and *in vivo* spectral data. The *in vitro* portion of the data was a 0.1 mm pathlength transmission spectrum of 500 mg/dL alcohol in water measured using the non-invasive measurement system configured for transmission measurements. The transmission spectrum was ratioed to a 0.1 mm pathlength transmission spectrum of water, converted to absorbance, and normalized to unit pathlength and concentration.

[0082] Light propagation through tissue is a complex function of the diffuse reflectance optical tissue sampler design, physiological variables, and wavenumber. Consequently, the pathlength of light through tissue has a wavenumber dependence that is not encountered in scatter-free transmission measurements. In order to account for the wavenumber dependence, the interaction of the optical tissue sampler with the scattering properties of human tissue was modeled via Monte-Carlo simulation using a commercial optical ray-tracing software package (TracePro). Using the resulting model of the photon-tissue interactions, an estimate of the effective pathlength of light through the dermis and subcutaneous tissue layers as a function of wavenumber was generated. The effective pathlength (l_{eff}) is defined as

$$l_{eff}(\nu) = \frac{\sum_{i=1}^{N} l_i \exp(-\mu_a(\nu) l_i)}{\sum_{i=1}^{N} l_i},$$

where ν is wavenumber, l_i is the pathlength traversed by the i^{th} ray in the Monte Carlo simulation [mm], N is the total number of rays in the simulation, and $_a$ is the (wavenumber-dependent) absorption coefficient [mm^{-1}]. Due to its large absorption in vivo, water is the only analyte that has a significant effect on the effective pathlength. Therefore, for the purposes of the effective pathlength calculation, the absorption coefficients used were those of water at physiological concentrations. The alcohol absorbance spectrum (as measured in transmission) was then scaled by the computed path function to form a corrected alcohol spectrum representative of the wavenumber dependent pathlength measured by the diffuse reflectance optical sampler. Figure 22 shows the alcohol absorbance spectrum before and after correction by the path function. The solid line is before correction; the dotted line is after correction. This corrected spectrum formed the base spectrum for the mathematical addition of alcohol to the calibration spectra.

[0083] The *in vivo* data comprised noninvasive tissue spectra collected from persons who had not consumed alcohol. A hybrid model was formed by adding the alcohol pure component spectrum, weighted by various alcohol "concentrations" (ranging from 0 to 160 mg/dL), to the noninvasive tissue spectral data. The PLS calibration model was built by regressing the synthetic alcohol concentrations on the hybrid spectral data. Figure 23 is a schematic representation of a hybrid calibration formation process. The hybrid calibration in this work used approximately 1500 non-invasive tissue spectra that were collected from 133 subjects over three months.

[0084] The use of hybrid calibration models, rather than calibration models built from spectra acquired from subjects who have consumed alcohol, can provide significant advantages. The hybrid modeling process makes it possible to generate calibration spectra that contain higher concentrations (up to 160 mg/dL in this work) of alcohol than would be considered safe for

consumption in a human subject study (120 mg/dL is considered a safe upper limit). This can result in a stronger calibration with a wider range of analyte concentrations that is able to predict higher alcohol concentrations more accurately. This can be important because alcohol concentrations observed in the field can be more than double the maximum safe dosage in a clinical research setting. The hybrid calibration process also allows the prevention of correlations between alcohol and the spectral interferents in tissue. For example, the random addition of alcohol signal to the calibration spectra prevents alcohol concentration from being correlated with water concentration. Thus, the hybrid approach prevents the possibility that the measurement could spuriously track changes in tissue water content instead of alcohol concentration.

[0085] Once formed, it is desirable that a calibration remain stable and produce accurate attribute predictions over an extended period of time. This process is referred to as calibration maintenance and can be comprised of multiple methods that can be used individually or in conjunction. The first method is to create the calibration in a manner that inherently makes it robust. Several different types of instrumental and environmental variation can affect the prediction capability of a calibration model. It is possible and desirable to reduce the magnitude of the effect of instrumental and environmental variation by incorporating this variation into the calibration model.

[0086] It is difficult, however, to span the entire possible range of instrument states during the calibration period. System perturbations can result in the instrument being operated outside the space of the calibration model. Measurements made while the instrument is in an inadequately modeled state can exhibit prediction errors. In the case of *in vivo* optical measurements of medically significant attributes, these types of errors can result in erroneous measurements that degrade the utility of the system. Therefore it is often advantageous to use additional calibration maintenance techniques during the life of the instrument in order to continually verify and correct for the instrument's status.

[0087] Examples of problematic instrument and environmental variation include, but are not limited to: changes in the levels of environmental interferents such as water vapor or CO_2 gas, changes in the alignment of the instrument's optical components, fluctuations in the output power of the instrument's illumination system, and changes in the spatial and angular distribution of the light output by the instrument's illumination system.

[0088] Calibration maintenance techniques are discussed in U.S. Patent 6,983,176, "Optically Similar Reference Samples and Related Methods for Multivariate Calibration Models Used in Optical Spectroscopy"; U.S. Patent 7,092,832, "Adaptive Compensation for Measurement Distortions in Spectroscopy"; US Patent 7,098,037, "Accommodating Subject and Instrument Variations in Spectroscopic Determinations", and US Patent 7,202,091, "Optically Similar Reference Samples",

each of which is incorporated herein by reference. In some of the disclosed methods, an environmentally inert non-tissue sample, such as an integrating sphere, that may or may not contain the attribute of interest is used in order to monitor the instrument over time. The sample can be incorporated into the optical path of the instrument or interface with the sampling subsystem in a manner similar to that of tissue measurements. The sample can be used in transmission or in reflectance and can contain stable spectral features or contribute no spectral features of its own. The material can be a solid, liquid, or gel material as long as its spectrum is stable or predicable over time. Any unexplained change in the spectra acquired from the sample over time indicate that the instrument has undergone a perturbation or drift due to environmental effects. The spectral change can then be used to correct subsequent tissue measurements in humans in order to ensure and accurate attribute measurement.

[0089] Another means for achieving successful calibration maintenance is to update the calibration using measurements acquired on the instrument over time. Usually, knowledge of the reference value of the analyte property of interest is required in order to perform such an update. However, in some applications, it is known that the reference value is usually, but not always, a specific value. In this case, this knowledge can be used to update the calibration even though the specific value of the analyte property is not known for each measurement. For example, in alcohol screening in residential treatment centers, the vast majority of measurements are performed on individuals that have complied with their alcohol consumption restrictions and therefore have an alcohol concentration of zero. In this case, the alcohol concentration measurement or the associated spectrum obtained from the device of the present invention can be used in conjunction with a presumed zero as a reference value. Thus, the calibration can be updated to include new information as it is acquired in the field. This approach can also be used to perform calibration transfer as measurements with presumed zeros can be used at the time of system manufacture or installation in order to remove any system-specific bias in the analyte property measurements of interest. The calibration maintenance update or calibration transfer implementation can be accomplished by a variety of means such as, but not limited to, orthogonal signal correction (OSV), orthogonal modeling techniques, neural networks, inverse regression methods (PLS, PCR, MLR), direct regression methods (CLS), classification schemes, simple median or moving windows, principal components analysis, or combinations thereof.

[0090] Once a calibration is formed, it is often desirable to transfer the calibration to all existing and future units. This process is commonly referred to as calibration transfer. While not required, calibration transfer prevents the need for a calibration to be determined on each system that is manufactured. This represents a significant time and cost savings that can affect the difference

between success or failure of a commercial product. Calibration transfer arises from the fact that optical and electronic components vary from unit to unit which, in aggregate, can result in a significant difference in spectra obtained from multiple instruments. For example, two light sources can have different color temperatures thereby resulting in a different light distribution for the two sources. The responsivity of two detectors can also differ significantly, which can result in additional spectral differences.

[0091] Similar to calibration maintenance, multiple methods can be used in order to effectively achieve calibration transfer. The first method is to build the calibration with multiple instruments. The presence of multiple instruments allows the spectral variation associated with instrument differences to be determined and made orthogonal to the attribute signal during the calibration formation process. While this does approach reduces the net attribute signal, it can be an effective means of calibration transfer.

[0092] Additional calibration transfer methods involve explicitly determining the difference in the spectral signature of a system relative to those used to build the calibration. In this case, the spectral difference can then be used to correct a spectral measurement prior to attribute prediction on a system or it can be used to correct the predicted attribute value directly. The spectral signature specific to an instrument can be determined from the relative difference in spectra of a stable sample acquired from the system of interest and those used to build the calibration. The samples described in the calibration maintenance section are also applicable to calibration transfer. See, e.g. U.S. Patent 6,441,388, "Method and Apparatus for Spectroscopic Calibration Transfer", incorporated herein by reference.

ADDITIONAL ASPECTS OF THE PRESENT INVENTION

ALCOHOL MEASUREMENT MODALITIES

[0093] Depending on the application of interest, the measurement of an analyte property can be considered in terms of two modalities. The first modality is "**walk up**" or "**universal**" and represents an analyte property determination wherein prior measurements of the sample (e.g. subject) are not used in determining the analyte property from the current measurement of interest. In the case of measuring *in vivo* alcohol, driving under the influence enforcement would fall into this modality as in most cases the person being tested will not have been previously measured on the alcohol measurement device. Thus, no prior knowledge of that person is available for use in the current determination of the analyte property.

[0094] The second modality is termed "**enrolled**" or "**tailored**" and represents situations where prior measurements from the sample or subject are available for use in determining the analyte property of the current measurement. An example of an environment where this modality can be

applied is vehicle interlocks where a limited number of people are permitted to drive or operate a vehicle or machine. Additional information regarding embodiments of enrolled and tailored applications can be found in US Patents 6,157,041 and 6,528,809, titled "Method and Apparatus for Tailoring Spectroscopic Calibration Models", each of which is incorporated herein by reference. In enrolled applications, the combination of the analyte property measurement with a biometric measurement can be particularly advantageous as the same spectroscopic measurement can assess if a prospective operator is authorized to use the equipment or vehicle via the biometric while the analyte property can access their fitness level(e.g. sobriety).

METHODS FOR DETERMINING BIOMETRIC VERIFICATION OR IDENTIFICATION FROM SPECTROSCOPIC SIGNALS

[0095] Biometric identification describes the process of using one or more physical or behavioral features to identify a person or other biological entity. There are two common biometric modes: identification and verification. Biometric identification attempts to answer the question of, "do I know you?" The biometric measurement device collects a set of biometric data from a target individual. From this information alone it assesses whether the person was previously enrolled in the biometric system. Systems that perform the biometric identification task, such as the FBI's Automatic Fingerprint Identification System (AFIS), are generally very expensive (several million dollars or more) and require many minutes to detect a match between an unknown sample and a large database containing hundreds of thousands or millions of entries. In biometric verification the relevant question is, "are you who you say you are?" This mode is used in cases where an individual makes a claim of identity using a code, magnetic card, or other means, and the device uses the biometric data to confirm the identity of the person by comparing the target biometric data with the enrolled data that corresponds with the purported identity. The present apparatus and methods for monitoring the presence or concentration of alcohol or substances of abuse in controlled environments can use either biometric mode.

[0096] There also exists at least one variant between these two modes that is also suitable for use in the present invention. This variant occurs in the case where a small number of individuals are contained in the enrolled database and the biometric application requires the determination of only whether a target individual is among the enrolled set. In this case, the exact identity of the individual is not required and thus the task is somewhat different (and often easier) than the identification task described above. This variant might be useful in applications where the biometric system is used in methods where the tested individual must be both part of the authorized group and sober but their specific identity is not required. The term "identity characteristic" includes all of the above modes, variants, and combinations or variations thereof.

[0097] There are three major data elements associated with a biometric measurement: calibration, enrollment, and target spectral data. The calibration data are used to establish spectral features that are important for biometric determinations. This set of data consists of series of spectroscopic tissue measurements that are collected from an individual or individuals of known identity. Preferably, these data are collected over a period of time and a set of conditions such that multiple spectra are collected on each individual while they span nearly the full range of physiological states that a person is expected to go through. In addition, the instrument or instruments used for spectral collection generally should also span the full range of instrumental and environmental effects that it or sister instruments are likely to see in actual use. These calibration data are then analyzed in such a way as to establish spectral wavelengths or "factors" (i.e. linear combinations of wavelengths or spectral shapes) that are sensitive to between-person spectral differences while minimizing sensitivity to within-person, instrumental (both within- and between-instruments), and environmental effects. These wavelengths or factors are then used subsequently to perform the biometric determination tasks.

[0098] The second major set of spectral data used for biometric determinations is the enrollment spectral data. The purpose of the enrollment spectra for a given subject or individual is to generate a "representation" of that subject's unique spectroscopic characteristics. Enrollment spectra are collected from individuals who are authorized or otherwise required to be recognized by the biometric system. Each enrollment spectrum can be collected over a period of seconds or minutes. Two or more enrollment measurements can be collected from the individual to ensure similarity between the measurements and rule out one or more measurements if artifacts are detected. If one or more measurements are discarded, additional enrollment spectra can be collected. The enrollment measurements for a given subject can be averaged together, otherwise combined, or stored separately. In any case, the data are stored in an enrollment database. In some cases, each set of enrollment data are linked with an identifier (e.g. a password or key code) for the persons on whom the spectra were measured. In the case of an identification task, the identifier can be used for record keeping purposes of who accessed the biometric system at which times. For a verification task, the identifier is used to extract the proper set of enrollment data against which verification is performed.

[0099] The third and final major set of data used for the biometric system is the spectral data collected when a person attempts to use the biometric system for identification or verification. These data are referred to as target spectra. They are compared to the measurements stored in the enrollment database (or subset of the database in the case of identity verification) using the classification wavelengths or factors obtained from the calibration set. In the case of biometric

identification, the system compares the target spectrum to all of the enrollment spectra and reports a match if one or more of the enrolled individual's data is sufficiently similar to the target spectrum. If more than one enrolled individual matches the target, then either all of the matching individuals can be reported, or the best match can be reported as the identified person. In the case of biometric verification, the target spectrum is accompanied by an asserted identity that is collected using a magnetic card, a typed user name or identifier, a transponder, a signal from another biometric system, or other means. The asserted identity is then used to retrieve the corresponding set of spectral data from the enrollment database, against which the biometric similarity determination is made and the identity verified or denied. If the similarity is inadequate, then the biometric determination is cancelled and a new target measurement may be attempted.

[0100] In one method of verification, principle component analysis is applied to the calibration data to generate spectral factors. These factors are then applied to the spectral difference taken between a target spectrum and an enrollment spectrum to generate Mahalanobis distance and spectral residual magnitude values as similarity metrics. Identify is verified only if the aforementioned distance and magnitude are less than a predetermined threshold set for each. Similarly, in an example method for biometric identification, the Mahalanobis distance and spectral residual magnitude are calculated for the target spectrum relative each of the database spectra. The identity of the person providing the test spectrum is established as the person or persons associated with the database measurement that gave the smallest Mahalanobis distance and spectral residual magnitude that is less than a predetermined threshold set for each.

[0101] In an example method, the identification or verification task is implemented when a person seeks to perform an operation for which there are a limited number of people authorized (e.g., perform a spectroscopic measurement, enter a controlled facility, pass through an immigration checkpoint, etc.). The person's spectral data is used for identification or verification of the person's identity. In this example method, the person initially enrolls in the system by collecting one or more representative tissue spectra. If two or more spectra are collected during the enrollment, then these spectra can be checked for consistency and recorded only if they are sufficiently similar, limiting the possibility of a sample artifact corrupting the enrollment data. For a verification implementation, an identifier such as a PIN code, magnetic card number, username, badge, voice pattern, other biometric, or some other identifier can also be collected and associated with the confirmed enrollment spectrum or spectra.

[0102] In subsequent use, biometric identification can take place by collecting a spectrum from a person attempting to gain authorization. This spectrum can then be compared to the spectra in the enrolled authorization database and an identification made if the match to an authorized database

entry was better than a predetermined threshold. The verification task is similar, but can require that the person present the identifier in addition to a collected spectrum. The identifier can then be used to select a particular enrollment database spectrum and authorization can be granted if the current spectrum is sufficiently similar to the selected enrollment spectrum. If the biometric task is associated with an operation for which only a single person is authorized, then the verification task and identification task are the same and both simplify to an assurance that the sole authorized individual is attempting the operation without the need for a separate identifier.

[0103] The biometric measurement, regardless of mode, can be performed in a variety of ways including linear discriminant analysis, quadratic discriminant analysis, K-nearest neighbors, neural networks, and other multivariate analysis techniques or classification techniques. Some of these methods rely upon establishing the underlying spectral shapes (factors, loading vectors, eigenvectors, latent variables, etc.) in the intra-person calibration database, and then using standard outlier methodologies (spectral F ratios, Mahalanobis distances, Euclidean distances, etc.) to determine the consistency of an incoming measurement with the enrollment database. The underlying spectral shapes can be generated by multiple means as disclosed herein.

[0104] First, the underlying spectral shapes can be generated based upon simple spectral decompositions (eigen analysis, Fourier analysis, etc.) of the calibration data. The second method of generating underlying spectral shapes relates to the development of a generic model as described in U.S. Patent No. 6,157,041, entitled "Methods and Apparatus for Tailoring Spectroscopic Calibration Models," which is incorporated by reference. In this application, the underlying spectral shapes are generated through a calibration procedure performed on intra-person spectral features. The underlying spectral shapes can be generated by the development of a calibration based upon simulated constituent variation. The simulated constituent variation can model the variation introduced by real physiological or environmental or instrumental variation or can be simply be an artificial spectroscopic variation. It is recognized that other means of determining underlying shapes would be applicable to the identification and verification methods of the present invention. These methods can be used either in conjunction with, or in lieu of the aforementioned techniques.

CALIBRATION CHECK SAMPLES

[0105] In addition to disposables to ensure subject safety, disposable calibration check samples can be used to verify that the instrument is in proper working condition. In many commercial applications of alcohol measurements, the status of the instrument must be verified to ensure that subsequent measurements will provide accurate alcohol concentrations or attribute estimates. The instrument status is often checked immediately prior to a subject measurement. In some embodiments, the calibration check sample can include alcohol. In other embodiments, the check

sample can be an environmentally stable and spectrally inert sample, such as an integrating sphere. The check sample can be a gas or liquid that is injected or flowed through a spectroscopic sampling chamber. The check sample can also be a solid, such as a gel, that may contain alcohol. The check sample can be constructed to interface with the sampling subsystem or it can be incorporated into another area of the optical path of the system. These examples are meant to be illustrative and are not limiting to the various possible calibration check samples.

DIRECTION OF CHANGE (DOC) AND RATE OF CHANGE (ROC)

[0106] The present invention also comprises methods for measurement of the direction and magnitude of concentration changes of tissue constituents, such as alcohol, using spectroscopy. The non-invasive measurement obtained from the current invention is inherently semi-time resolved. This allows attributes, such as alcohol concentration, to be determined as a function of time. The time resolved alcohol concentrations can then be used to determine the rate and direction of change of the alcohol concentration. In addition, the direction of change information can be used to partially compensate for any difference in blood and non-invasive alcohol concentration that is caused by physiological kinetics. *See* US 7,016,713, "Determination of Direction and Rate of Change of an Analyte", and US Application 20060167349, "Apparatus for Noninvasive Determination of Rate of Change of an Analyte", each of which is incorporated herein by reference. A variety of techniques for enhancing the rate and direction signal have been uncovered. Some of these techniques include heating elements, rubrifractants, and index-matching media. They should not be interpreted as limiting the present invention to these particular forms of enhancement or equilibration. These enhancements are not required to practice the present invention, but are included for illustrative purposes only.

SUBJECT SAFETY

[0107] Another aspect of non-invasive alcohol measurements is the safety of the subjects during the measurements. In order to prevent measurement contamination or transfer of pathogens between subjects it can be desirable, but it is not necessary, to use disposable cleaning agents and/or protective surfaces in order to protect each subject and prevent fluid or pathogen transfer between subjects. For example, in some embodiments an isopropyl wipe can be used to clean each subject's sampling site and/or the sampling subsystem surface prior to measurement. In other embodiments, a disposable thin film of material such as ACLAR can be placed between the sampling subsystem and the subject prior to each measurement in order to prevent physical contact between the subject and the instrument. In other embodiments, both cleaning and a film can be used simultaneously. As mentioned in the sampling subsystem portion of this disclosure, the film can also be attached to a positioning device and then applied to the subject's sampling site. In this

embodiment, the positioning device can interface with the sampling subsystem and prevent the subject from moving during the measurement while the film serves its protective role.

TOPICAL INTERFERENTS

[0108] In subject measurements the presence of topical interferents on the sampling site is a significant concern. Many topical interferents have spectral signatures in the near infrared region and can therefore contribute significant measurement error when present. The present invention deals with the potential for topical interferents in three ways that can be used individually or in conjunction. Figure 24 shows a flow diagram that describes a method for combining the three topical interferent mitigation approaches into one combined process. First, a disposable cleaning agent similar to that described in the subject safety section can be used. The use of the cleaning agent can either be at the discretion of the system operator or a mandatory step in the measurement process. Multiple cleaning agents can also be used that individually target different types of topical interferents. For example, one cleaning agent can be used to remove grease and oils, while another could be used to remove consumer goods such as cologne or perfume. The cleaning agents can remove topical interferents prior to the attribute measurement in order to prevent them from influencing the accuracy of the system.

[0109] A second method for mitigating the presence of topical interferents is to determine if one or more interferents is present on the sampling site. The multivariate calibration models used in the calibration subsystem offer inherent outlier metrics that yield important information regarding the presence of un-modeled interferents (topical or otherwise). As a result, they provide insight into the trustworthiness of the attribute measurement. Figure 25 shows example outlier metric values from noninvasive measurements using the present invention acquired during the clinical studies. All of the large metric values (clearly separated from the majority of the points) correspond to measurements where grease had been intentionally applied to the subject's sampling site. These metrics do not specifically identify the cause of the outlier, but they do indicate that the associated attribute measurement is suspect. An inflated outlier metric value (a value beyond a fixed threshold, for example) can be used to trigger a fixed response such as a repeat of the measurement, application of an alternative calibration model, or a sampling site cleaning procedure. This is represented in Figure 24 as the "Spectral Check OK" decision point.

[0110] The final topical interferent mitigation method involves adapting the calibration model to include the spectral signature of the topical interferent. The adapted calibration model can either be created on demand or selected from an existing library of calibration models. Each calibration in the library can be targeted at mitigating a different interferent or class of interferents such as oils. In some embodiments, the appropriate calibration model can be chosen based on the portion of an

acquired spectrum that is unexplained by the original calibration model. This portion of the spectrum is referred to as the calibration model residual. Because each topical interferent or class of interferents has a unique near infrared spectrum, the calibration model residual can be used to identify the topical interferent.

[0111] The model residual or the pure spectrum (obtained from a stored library) of the interferents can then be incorporated into the spectra used to form the calibration. The multivariate calibration is then reformed with the new spectra such that the portion of the attribute signal that is orthogonal to the interferent can be determined. The new calibration model is then used to measure the attribute of interest and thereby reduce the effects of the topical interferent on attribute measurement accuracy. The resulting model will reduce the effect of the interferent on the alcohol measurement at the expense of measurement precision when no interferents are present. This process is referred to as calibration immunization. The immunization process is similar to the hybrid calibration formation process shown in Figure 24, but includes the additional step of the mathematical addition of the interferent's spectral variation. It should be noted that, due to the impact of the immunization process on measurement precision, it can be desirable to identify possible interferents for each measurement and immunize specifically against them rather than attempt to develop a calibration that is immunized against all possible interferents. Additional details can be found in US 20070142720, "Apparatus and methods for mitigating the effects of foreign interferents on analyte measurements in spectroscopy", incorporated herein by reference.

NOVEL BLACKBODY LIGHT SOURCES

[0112] It is important to note that the present invention also envisions several embodiments of alcohol measurement systems incorporating broadband light sources rather than narrowband solid state light sources. An example light source is a ceramic element such as those commonly used as igniters for furnaces and stoves. These light sources have a lower color temperature than standard filament lamps and are therefore more efficient in the near-infrared spectral region. These sources also have comparatively large emissive surfaces that are less sensitive to spatial effects that are encountered throughout the lifetime of the light source. An additional advantage of igniter-based light sources is a substantially longer lifetime when compared to filament lamps. In these embodiments, the broad blackbody source can be converted to multiple, narrow light sources using optical filters such as, but not limited to, linearly variable filters (LVF's), dielectric stacks, distributed Bragg gratings, photonic crystal lattice filters, polymer films, absorption filters, reflection filters, etalons, dispersive elements such as prisms and gratings, and quantum dot filters. The resulting multiple bands of wavelengths can be modulated by a Fourier scheme or Hadamard mask.

[0113] Some embodiments of the present invention eliminate the drawbacks of filament-based light sources by replacing them with alternative sources of IR and NIR light. Ceramic-based blackbody light sources and semiconductor-based light sources offer several advantages including elimination of the glass envelope, higher efficiency (less light in unwanted spectral regions), and more stable spatial emission. Consequently, the ceramic and semiconductor light sources offer an improved foundation for subsequent spatial and angular homogenization. Furthermore, due to the improved optical efficiency, these light sources do not require undesired wavelengths to be optically filtered prior to sample illumination. The reduction of the illumination source as an instrument variance or interferent has been found to improve the ability to build an optical system and model which can accurately predict analyte concentrations in turbid media such as tissue. Some embodiments of the present invention provide this illumination stability by collecting and modifying the output emitted by a light source prior to illuminating the sample under investigation.

[0114] Some embodiments of the present invention relate to methods for minimizing spectroscopic variances due to radiation emitters of angular and/or spatial homogenization. Angular homogenization is any process that takes an arbitrary angular distribution, or intensity (W/sr), of emitted radiation, and creates a more uniform angular distribution. Spatial homogenization is the process of creating a more uniform distribution of irradiance (W/m^2) across an output or exit face.

[0115] All practical light sources produce a non-uniform irradiance distribution due to their physical structure. Thus, radiation emitter differences (e.g., a different source) will result in different non-uniform irradiance distributions. These differences in irradiance distribution can translate into spectroscopic differences between light sources. Thus, it can be useful to take different irradiance distributions due to emitter differences and create similar or ideally the same irradiance distribution. An example method of creating similar irradiance distributions is to create a uniform irradiance distribution.

[0116] Differences in the radiation emitter can also result in differences in angular distribution. As above, it can be useful to create an illumination system where radiation emitter differences do not affect the angular distribution observed by the sample or at the input to the spectrometer. One mechanism is to create a uniform angular distribution. An ideal angular homogenizer would uniformly distribute the light over a sphere (4 pi sr) regardless of the angular distribution from the emitter. An ideal reflective angular homogenizer would uniformly distribute light over a hemisphere (2 pi sr). Due to the fact that other optical components in the system must collect light within a defined numerical aperture, ideal homogenizers are typically very inefficient. Thus, the instrument designer must weigh the benefits of angular homogenization with loss in optical efficiency.

Regardless of the specific embodiment, angular homogenization can be a critical component in the realization of an illumination system that has reduced sensitivity to emitter differences.

[0117] The present invention provides a system for producing spatially and angularly homogenized light from an irregular emitter and using the homogenized light for spectral analysis. The resulting homogenized radiation illuminates the sample or sampler in a consistent and reproducible form, thus allowing for accurate and dependable spectroscopic measurements.

[0118] An additional benefit of the current invention is spatial homogenization. The color temperature of filament and ceramic light sources is not spatially uniform across the entire emissive area of the source. Thus, color temperature variations across the filament will result in spectral differences across the filament length. These spectral differences due to color temperature variations or other filament differences can be different between emitters and can change over time. Thus, it can also be important to take the different spectral distribution due to spatial heterogeneity of the emitter and create a preferably uniform spectral distribution at all spatial locations at the output of the illumination system.

[0119] Advantages of the present invention can be illustrated by the familiar occurrence of routine maintenance to a spectrometer. It is common for radiant light sources to burn out. Although application dependent, the replacement of the light source can result in analyte measurement errors and can necessitate recalibration of the spectrometer following the light source replacement. In systems intended for commercial use by unskilled operators, recalibration is not desired. With the present invention, however, differences in the light source are irrelevant and proper performance of the optical measurement system is maintained. Regardless of the spatial and angular characteristics of the radiation emitted by the light source, the use of the illumination systems of the present invention will result in radiation incident on the sample which remains substantially spatially and angularly homogenized. Thus, a light source change will not detract from the accuracy and dependability of molecular absorbance measurements using the present invention.

[0120] The present invention further specifies a system for providing illumination to biological tissue samples. More specifically, the system is particularly suited for spectroscopic illumination of biological tissues for determining and quantifying the concentration of specific analytes within or other characteristics of the tissue. The present invention enables a practitioner to construct and operate an illumination device that permits measurements with a high signal-to-noise ratio (SNR) while minimizing thermal damage to biological tissue. With a high SNR, chemometric models can be developed for differentiating between a particular analyte and interferents similar to that analyte. The present invention allows for spectroscopic analysis of turbid media by satisfying the following conditions:

(1) The radiation emitted by the present invention contains wavelengths useful for measuring the analyte of interest. The radiation can be continuous versus wavelength, in locally continuous bands, or selected to particular wavelengths. The result is radiation that encompasses the wavelength regions that contain the NIR or IR spectral "fingerprint" for the analyte of interest. For the noninvasive measurement of ethanol using NIR spectroscopy, this wavelength region spans approximately from 1.0 to 2.5 μm.

(2) The radiation emitted by the present invention is of sufficiently high spectral radiance to provide a high signal-to-noise ratio in the spectral region of interest. In the measurement of ethanol using NIR spectroscopy, for example, the radiation from a ceramic light source or one or more semiconductor light sources concentrated with one or more optical elements, such as lenses and or mirrors, will provide a spectral radiance that satisfies this condition.

(3) The spectral radiance is generally invariant when subjected to changes in the spectral excitance of the emitter. Reasonably expected changes in the spectral excitance are those due to rotation and/or small translation of the emitter, or replacement of the emitter with another emitter of the same general construction.

[0121] By satisfying the above conditions, the ceramic-based light sources of the present invention eliminate the need for recalibration due to illumination variability (light source changes, source aging, source rotation or movement) or, in some embodiments, development of a chemometric model that compensates for such changes. Simple maintenance such as replacing the light source do not necessitate recalibration or the development of chemometric models sensitive to light source changes. Furthermore, rotations and translations of the light source caused by jolts, bumps, and other similar vibrations can have minimal effects on the accuracy of a test.

ADVANTAGES OF SEMICONDUCTOR LIGHT SOURCE ALTERNATIVES

[0122] Most light sources used in spectroscopy are blackbody radiators. The light emitted by a blackbody radiator is governed by Plank's law which indicates that the intensity of the light emitted is a function of wavelength and the temperature of the blackbody.

[0123] Figure 26 shows normalized NIR spectra of 1300 and 3000 K blackbody radiators over the 100-33000 cm^{-1} (100-0.3 microm) range with the 4000-8000 cm^{-1} (2.5-1.25 microm) range used by the TruTouch device shaded. 1300 K is a reasonable temperature for the ceramic-based blackbody light source the TruTouch technology currently employs and 3000 K is a reasonable temperature for Quartz Tungsten Halogen (QTH) lamps which are often employed in spectroscopic applications. Figure 26 indicates that the optical efficiency of both blackbody light sources is not ideal in that a significant amount of light is emitted at wavelengths outside the TruTouch region of interest with the optical efficiency of the ceramic light source being 58% and the QTH only 18%.

[0124] In addition to optical efficiency, blackbody light sources can have poor electrical efficiency. Practical blackbody light sources require a significant amount of electrical power, not all of which is converted to emitted light. Electrical and optical power measurements on hundreds of ceramic blackbody light sources that show an average of 1.1W of optical power at an average of 24W of electrical power (4.4% electrical efficiency). When combined with the optical efficiency of 58%, the overall efficiency of the ceramic blackbody is approximately 2.5%. In other words, at 24W of electrical power, approximately 0.6W of optical power is emitted in the 4000 to 8000 cm^{-1} region of interest. Further losses are incurred as not all light emitted by the source is collected by the remainder of the optical system.

[0125] As indicated by the low electrical efficiency, most of the applied electrical power is converted to heat which has a detrimental beyond the higher than desired power requirement. The heat generated by the blackbody light source can have an impact on the thermal state and stability of the spectroscopic measurement device. Consequently, in some situations the device must be powered on and allowed to reach thermal equilibrium prior to performing measurements. The equilibration time associated with the blackbody light source can range from minutes to hours which can be disadvantageous in some situations.

[0126] Blackbody light sources exhibit an aging effect as the material resistance changes. From an optical perspective, there are to significant implications associated with the light source aging. First, as the resistance increases the amount of optical power emitted decreases. Figure 27 shows the measured intensity over time observed for a demonstrative ceramic blackbody light source that exhibits a 50% reduction in power over 3500 hours. The intensity degradation over time tends to be exponential in nature and can necessitate replacement of the light source at regular intervals which can be disadvantageous in some deployment environments. Second, the temperature of the light source changes which alters the distribution of the light as a function of wavelength. Depending on the severity of the color temperature change, the stability of the spectroscopic device over time can be impacted.

[0127] LEDs and other solid state light sources, in contrast, are narrower in their emission profiles, which allow the ability to concentrate the emitted light in the 4000 to 8000 cm^{-1} region of interest. Figure 28 shows the spectral emission profiles of several commercially available NIR LEDs that were obtained from their respective product data sheets. The range of available LEDs allows the investigation of their combination to form a light source system that spans the 4000-8000 cm^{-1} region of interest while minimizing light output at lower and higher wavenumber that are not employed by the desired measurement. Thus, the resulting system will exhibit an improved optical efficiency. It is important to note, that in contrast to other embodiments involving modulation

schemes previously discussed, the objective of these embodiments of solid state light sources is to use multiple solid state light sources to collectively mimic the optical properties of a blackbody light source in a more efficient package.

[0128] Figure 28 demonstrates that no single currently available LED can viably replace a blackbody light source as the spectral emission profiles do not span the entire 4000 to 8000 cm^{-1} region of interest. Consequently, multiple LEDs can be optically combined in order to generate a suitable light source subsystem. The number of LED's that can be incorporated into the light source subsystem is ultimately determined by the area and angular acceptance of the optical system and the size and angular divergence of the individual LEDs. While the determination of the optimal combination of LEDs is an extensive effort involving optical and mechanical design and spectroscopic analysis a simplified approach is shown in Figure 35 that does not invoke any optical design or photon collection efficiencies (which are different for blackbody and LED light sources), nor the design required to optically combine the outputs of multiple LEDs. The blackbody line in figure 35 corresponds to a 1300^{O}K blackbody light source, and is the desired target for the LED combination in this example. The dotted lines are the individual profiles of each type of LED and the sum line is the sum of the dotted lines which assumes no losses are encountered in the optical combination. It is further assumed in this example that the magnitude of each dotted line can be practically influenced by either changing the input power to the respective LED or by adding more LEDs of that type. Furthermore, within a given spectral region of interest, some wavelengths can be more important than others to a given application such as alcohol measurements in tissue. The narrow profiles exhibited by the LEDs can allow better fine tuning of the relative intensities of the wavelengths as compared to blackbody light sources.

[0129] LEDs do not critically fail in any manner similar to filament lamps. Instead they exhibit an intensity degradation over time. As a result, the lifetimes of LEDs are measured in terms of the time in hours required for the average LED of a given type to reach 50% of its original intensity (T50). The lifetimes of LEDs, for example, range from 50,000 to 100,000 hours. As a result, LEDs offer the potential for a 10X improvement in light source life and a corresponding reduction in the need for routine maintenance relative to blackbody light sources.

[0130] LEDs and semiconductor lasers such as VCSELs can have small emissive areas when compared to their blackbody counterparts that is driven by the size of the semiconductor die itself. The photon emission cannot occur outside of the area of the die as it is generated within the semiconductor structure. The small size (a common emissive area is a 0.3mm x 0.3mm square or 0.09 mm^2) can be advantageous in that any heterogeneity within that area will be insignificant relative to size of the output of the illumination system (which can be several mm^2 or larger

depending on the application). Thus, as long as the die (or dies if multiple semiconductors are employed) do not physically move, the spatial output will be very stable. Subsequent spatial homogenizers can then uniformly distribute the light emitted by the die across the entire area of the illumination system output.

[0131] Another advantage of semiconductor light sources such as LEDs is the ability to incorporate more than one dye into the same physical package. As the output of an LED is typically spectrally narrower than a blackbody light source, multiple LEDs of different types (e.g. peak wavelength of emission) can be combined to increase the spectral range of the illumination system. Furthermore, additional LEDs of the same type can be included in order to increase the optical power at the corresponding wavelengths. Such approaches allow a high level of control over both the specific wavelengths and relative intensities emitted by an illumination system. This can be used to accentuate wavelengths important to a given analyte of interest such as alcohol, while reducing the output at less-important wavelengths. Whether the set of LEDs is all of the same type or a mixture, up to several hundred LEDs can be incorporated into the same package while retaining an integrated optical area consistent with use in noninvasive analyte measurements such as alcohol.

[0132] Another advantage of semiconductor light sources is the ability to select which light sources are on at a given time as well as tune their output via voltage or current and temperature. Consequently, a single illumination system can be optimized for measurements of multiple analytes. For example, when measuring alcohol in tissue a given set of LEDs can be activated. Likewise, a different set can be activated when measuring a different analyte such as cholesterol or glucose.

METHODS FOR SPATIAL AND ANGULAR HOMOGENIZATION

[0133] Light homogenizers such as optical diffusers, light pipes, and other scramblers can be incorporated into some embodiments of the illumination/modulation subsystem 100 in order to provide reproducible and, preferably, uniform radiance at the input of the tissue sampling subsystem 200. Uniform radiance can ensure good photometric accuracy and even illumination of the tissue. Uniform radiance can also reduce errors associated with manufacturing differences between light sources. Uniform radiance can be utilized in the present invention for achieving accurate and precise measurements. *See, e.g.*, U.S. Patent No. 6,684,099, which is incorporated herein by reference.

[0134] A ground glass plate is an example of an optical diffuser. The ground surface of the plate effectively scrambles the angle of the radiation emanating from the light source and its transfer optics. A light pipe can be used to homogenize the intensity of the radiation such that it is spatially uniform at the output of the light pipe. In addition, light pipes with a double bend will scramble the angles of the radiation. For creation of uniform spatial intensity and angular distribution, the cross

section of the light pipe should not be circular. Square, hexagonal and octagonal cross sections are effective scrambling geometries. The output of the light pipe can directly couple to the input of the tissue sampler or can be used in conjunction with additional transfer optics before the light is sent to the tissue sampler. *See, e.g.*, U.S. Patent Application No. 09/832,586, "Illumination Device and Method for Spectroscopic Analysis," which is incorporated herein by reference.

[0135] In an example embodiment, the radiation homogenizer is a light pipe. Figure 29 shows a perspective end view and a detail plan view of a light pipe of the present invention. Light pipe is generally fabricated from a metallic, glass (amorphous), crystalline, polymeric, or other similar material, or any combination thereof. Physically, the light pipe comprises a proximal end, a distal end, and a length therebetween. The length of a light pipe, for this application, is measured by drawing a straight line from the proximal end to the distal end of the light pipe. Thus, the same segment of light pipe may have varying lengths depending upon the shape the segment forms. The length of the segment readily varies with the light pipe's intended application.

[0136] In an example embodiment as illustrated in Figure 29, the segment forms an S-shaped light pipe. The S-shaped bend in the light pipe provides angular homogenization of the light as it passes through the light pipe. It is, however, recognized that angular homogenization can be achieved in other ways. A plurality of bends or a non-S-shaped bend could be used. Further, a straight light pipe could be used provided the interior surface of the light pipe included a diffusely reflective coating over at least a portion of the length. The coating provides angular homogenization as the light travels through the pipe. Alternatively, the interior surface of the light pipe can be modified to include dimples or "microstructures" such as micro-optical diffusers or lenses to accomplish angular homogenization. Finally, a ground glass diffuser could be used to provide some angular homogenization.

[0137] The cross-section of the light pipe may also form various shapes. In particular, the cross-section of the light pipe is preferably polygonal in shape to provide spatial homogenization. Polygonal cross-sections include all polygonal forms having three to many sides. Certain polygonal cross-sections are proven to improve spatial homogenization of channeled radiation. For example, a light pipe possessing a hexagonal cross-section the entire length thereof provided improved spatial homogenization when compared to a light pipe with a cylindrical cross-section of the same length.

[0138] Additionally, cross-sections throughout the length of the light pipe may vary. As such, the shape and diameter of any cross-section at one point along the length of the light pipe may vary with a second cross-section taken at a second point along the same segment of pipe.

In certain embodiments, the light pipe is of a hollow construction between the two ends. In these embodiments, at least one lumen or conduit may run the length of the light pipe. The lumens of

hollow light pipes generally possess a reflective characteristic. This reflective characteristic aids in channeling radiation through the length of the light pipe so that the radiation may be emitted at the pipe's distal end. The inner diameter of the lumen may further possess either a smooth, diffuse or a textured surface. The surface characteristics of the reflective lumen or conduit aid in spatially and angularly homogenizing radiation as it passes through the length of the light pipe.

[0139] In additional embodiments, the light pipe is of solid construction. The solid core could be cover plated, coated, or clad. Again, a solid construction light pipe generally provides for internal reflection. This internal reflection allows radiation entering the proximal end of the solid light pipe to be channeled through the length of the pipe. The channeled radiation may then be emitted out of the distal end of the pipe without significant loss of radiation intensity. An illustration of internal reflection and the resulting channeling is shown in Figure 30.

[0140] The faceted elliptical reflector is an example of an embodiment of the present invention which produces only part of the desired characteristics in the output radiation. In the case of the faceted reflector, spatial homogenization is achieved but not angular homogenization. In other cases, such as passing the output of the standard system through ground glass, angular homogenization is achieved but not spatial homogenization. In embodiments such as these, where only angular or spatial homogenization is produced (but not both) some improvement in the performance of the spectroscopic system may be expected. However, the degree of improvement would not be expected to be as great as for systems where spatial and angular homogenization of the radiation are simultaneously achieved.

[0141] Another method for creating both angular and spatial homogenization is to use an integrating sphere in the illumination system. Although common to use an integrating sphere for detection of light, especially from samples that scatter light, integrating spheres have not been used as part of the illumination system when seeking to measure analytes noninvasively. In practice, radiation output from the emitter could be coupled into the integrating sphere with subsequent illumination of the tissue through an exit port. The emitter could also be located in the integrating sphere. An integrating sphere will result in exceptional angular and spatial homogenization but the efficiency of this system is significantly less than other embodiments previously specified.

[0142] It is also recognized that other modifications can be made to the present disclosed system to accomplish desired homogenization of light. For example, the light source could be placed inside the light pipe in a sealed arrangement which would eliminate the need for the reflector. Further, the light pipe could be replaced by an integrator, wherein the source is placed within the integrator. Further, the present system could be used in non-infrared applications to achieve similar results in different wavelength regions depending upon the type of analysis to be conducted.

DESCRIPTION OF EXAMPLE EMBODIMENTS

[0143] In an example embodiment of the present invention (schematically depicted in figure 31), a noninvasive alcohol measurement system is comprised of 13 VCSEL's that are used to measure 22 discrete wavelengths. Table 1 shows a list of each VCSEL and the associated target peak wavelengths that will be interrogated during the course of the measurement. In this embodiment, each VCSEL is stabilized to a constant temperature. The peak wavelength of each VCSEL is controlled based on the circuit shown in Figure 7 (each VCSEL having its own circuit), which also enables the VCSEL to be turned On and Off. The specific state (On/Off) of each VCSEL at a given time during a measurement is determined by a predetermined Hadamard matrix. In example embodiments incorporating solid state light sources the Hadamard matrix is a pattern of On/Off states versus time for each VCSEL that is stored in software rather than a physical mask or chopper. This allows the On/Off states stored in software to be conveyed to the electronic control circuits of each VCSEL during the measurement.

Light Source #	Wavelengths measured (cm^{-1})
1	4196.35, 4227.2
2	4288.91, 4304.34
3	4319.77, 4335.20
4	4350.62
5	4381.48, 4412.34
6	4443.19, 4474.05
7	4535.76, 4566.61
8	4597.47, 4612.90
9	4643.75
10	4674.61, 4690.04
11	4764.17
12	4828.88
13	4875.17, 4906.02

Table 1

[0144] As several of the VCSEL's in table 1 are responsible for 2 wavelength locations, a Hadamard scheme that incorporates all wavelengths can be difficult to achieve. In this case, a combination of scanning and Hadamard encoding can allow all target wavelengths to be measured. In the present embodiment, all VCSEL's are tuned to their 1^{st} target wavelength (for those with more than 1 target wavelength) and a Hadamard encoding scheme used to achieve the associated multiplex benefit. The VCSEL's can then be tuned to their second target wavelength and a 2^{nd} Hadamard encoding scheme used. VCSEL's with only 1 target wavelength can be measured in either or both groups or divided among the groups.

[0145] Furthermore, the groups can be interleaved in time. For example, for a 2 second measurement, the first group can be measured for the 1^{st} second and the 2^{nd} group for the 2^{nd}

second. Alternatively, the measurement can alternate at 0.5 second intervals for 2 seconds. The measurement times do not need to be symmetric across the groups. For example, it can be desirable to optimize signal to noise ratio by weighting the measurement time towards one or the other group. One skilled in the art recognizes that many permutations of measurement time, balancing the number of groups, balancing the ratio of scanning to Hadamard, and interleaving are possible and contemplated in the embodiments of the present invention.

[0146] In the example embodiment, the output of each VCSEL is combined and homogenized using a hexagonal cross-sectioned light pipe. In some embodiments, the light pipe can contain one or more bends in order to provide angular homogenization in addition to spatial homogenization. Regardless, at the output of the light pipe, the emission of all VCSEL's is preferably spatially and angularly homogenized such that all wavelengths have substantially equivalent spatial and angular content upon introduction to the input of the sampling subsystem 200.

[0147] The homogenized light is introduced to the input of an optical probe. In the example embodiment, the input is comprised of 225, 0.37NA silica-silica optical fibers (referred to as illumination fibers) arranged in a geometry consistent with the cross section of the light homogenizer. The light is then transferred to the sample interface. The light exits the optical probe and enters the sample, a portion of that light interacts with the sample and is collected by 64 collection fibers. In the present example embodiment, the collection fibers are 0.37 NA silica-silica fibers. Figure 32 shows the spatial relationship between the illumination and collection fibers at the sample interface.

[0148] The optical probe output arranges the collection fibers into a geometry consistent with the introduction to a homogenizer. For the example embodiment, the homogenizer is a hexagonal light pipe. The homogenizer ensures that the content of each collection fiber contributes substantially equally to the measured optical signal. This can be important for samples, such as human tissue, that can be heterogeneous in nature. The output of the homogenizer is then focused onto an optical detector. In the present example embodiment, the optical detector is an extended InGaAs diode whose output current varies based upon the amount of incident light.

[0149] The processing subsystem then filters and processes the current and then converts it to a digital signal using a 2 channel delta-sigma ADC. In the example embodiment, the processed analog detector signal is divided and introduced to both ADC channels. As the example embodiment involves VCSEL's with 2 measurement groups (e.g. 2 target wavelengths), a Hadamard transform is applied to the spectroscopic signal obtained from each group and the subsequent transforms combined to form an intensity spectrum. The intensity spectrum is then base 10 log transformed prior to subsequent alcohol concentration determination.

[0150] The example embodiment is suitable for either "enrolled" or "walk-up/universal" modalities as well as applications combining alcohol with other analyte properties such as substances of abuse. Furthermore, any of the discussed modalities or combinations can be considered independently or combined with the measurement of a biometric property.

[0151] 3,245 alcohol measurements were obtained from 89 people on 5 noninvasive alcohol systems that measured spectra incorporating 22 wavelengths in the "walk-up" modality. The measurements spanned a wide range of demographic and environmental. Figure 33 shows the near-infrared spectroscopic measurements obtained from the study. Figure 34 compares noninvasive alcohol concentrations obtained from the spectroscopic measurements shown in Figure 33 to contemporaneous capillary blood alcohol concentration (BAC) alcohol.

[0152] In another example embodiment, 50 wavelengths are measured using 24 VCSELs. Table 2 shows the VCSEL's and their target wavelengths. As some of the VCSEL's contain 3 target wavelengths, there are 3 groups, each with its own Hadamard encoding scheme. The remainder of the system parameters, including the optical probe design, light homogenizers, detector, and processing is identical to the earlier described example embodiment.

Light Source #	Wavelengths measured (cm^{-1})
1	4150.06
2	4227.20
3	4304.34, 4319.77, 4335.20
4	4350.62, 4366.05, 4381.48
5	4396.91, 4412.34, 4427.76
6	4443.19, 4458.62
7	4535.76
8	4566.61, 4582.04
9	4674.61, 4690.04, 4705.46
10	4751.75, 4767.17
11	4782.60, 4798.03
12	4890.60, 4906.02
13	5291.72, 5322.57
14	5384.28
15	5461.42, 5476.85
16	5708.27, 5723.69
17	5800.83, 5816.26
18	5847.12, 5862.54, 5877.97
19	5893.40, 5908.83
20	5939.68, 5955.11, 5970.54
21	6016.82, 6032.25
22	6063.10
23	6124.82, 6140.24
24	7189.33, 7204.76

Table 2

[0153] In some example embodiments, calibration transfer can be performed using a small number of measurements on samples with known analyte properties. In the case of noninvasive alcohol measurements, each instrument can have a small number of measurements performed on individuals with no alcohol present. Any non-zero alcohol result on the instrument translates into a measurement error that can be used to correct subsequent measurements on that instrument. The number of measurements used to estimate the correction can vary and generally depends on the required accuracy of the correction. In general, this process is analogous to an instrument specific calibration consistent with alcohol devices, such as breath testers, that are calibrated individually.

[0154] A similar approach can be applied to calibration maintenance. In many applications of alcohol testing, the majority of measurements are performed on individuals where alcohol is unlikely to be present. For example in workplace safety where employees are routinely tested for alcohol, it is much more likely that an employee will be alcohol free than intoxicated (e.g. most people enter the workplace alcohol-free). In this case, the true alcohol concentration can be assumed to be zero and a median or other means for excluding the infrequent, true alcohol events could be used to

estimate an instruments correction. This can implemented as a running median filter, a moving window, or more sophisticated multivariate algorithm for determining the appropriate correction at a given time.

[0155] Those skilled in the art will recognize that the present invention can be manifested in a variety of forms other than the specific embodiments described and contemplated herein. Accordingly, departures in form and detail can be made without departing from the scope and spirit of the present invention as described in the appended claims.

CLAIMS

We claim:

1. An apparatus for determining an analyte property of a sample, comprising:

a. An illumination subsystem comprising a semiconductor light source;

b. A sampling subsystem, mounted with the illumination subsystem such that light from the illumination subsystem is directed to a sample by the sampling subsystem;

c. A data acquisition subsystem, mounted with the sampling subsystem such that light from the sample is communicated from the sampling subsystem to the data acquisition subsystem;

d. A computing subsystem, mounted with the data acquisition subsystem such that the computing subsystem can determine the analyte property from information from the data acquisition subsystem.

2. An apparatus as in claim 1, wherein the sampling subsystem comprises an interface to in vivo tissue.

3. An apparatus as in claim 2, wherein the interface to in vivo tissue comprises an interface to tissue of a human hand.

4. An apparatus as in claim 3, wherein the interface to tissue of a human hand comprises an interface to tissue on the top of one or more fingers between the first and second knuckles thereof.

5. An apparatus as in claim 1, wherein the illumination subsystem comprises a plurality of semiconductor light sources.

6. An apparatus as in claim 5, wherein the output of the plurality of semiconductor light sources is optically combined before communication to the sample.

7. An apparatus as in claim 5, wherein the output of the plurality of semiconductor light sources is homogenized spatially, angularly, or both, before communication to the spectrometer.

8. An apparatus as in claim 5, wherein each semiconductor light source is characterized by a center wavelength different from the center wavelengths of other of the plurality of semiconductor light sources.

9. An apparatus as in claim 8, wherein each semiconductor light source is modulated at a modulation frequency different than the modulation frequency of other of the plurality of semiconductor light sources.

10. An apparatus as in claim 9, wherein the modulation is according to one or more of Fourier, Hadamard, Fishers, z transform, sinusoidal, square, and triangular wave modulation.

11. An apparatus as in claim 9, wherein the correspondence of semiconductor light source to modulation frequency is random.

12. An apparatus as in claim 9, wherein the modulation is performed by one or more of controlling drive voltage of the semiconductor light source, controlling drive current of the semiconductor light source, controlling drive power of the semiconductor light source, controlling a mechanical mask mounted with the illumination subsystem, controlling an optical mask mounted with the illumination subsystem, controlling a filter wheel mounted with the illumination subsystem, controlling a chopper wheel mounted with the illumination subsystem, controlling an electrically controlled optical component mounted with the illumination subsystem, controlling a liquid crystal device mounted with the illumination subsystem, controlling a digital mirror device mounted with the illumination subsystem, controlling an acouto-optic tunable filter mounted with the illumination subsystem.

13. An apparatus as in claim 1, wherein the semiconductor light source comprises at least one of VCSEL, diode laser, quantum cascade laser, quantum dot laser, LED, HCSEL, organic LED.

14. An apparatus as in claim 1, wherein at least one of the drive current, drive voltage, drive power, and temperature of the semiconductor light source is stabilized.

15. An apparatus as in claim 1, wherein at least one of the emission wavelength and emission profile of the semiconductor light source is tuned by controlling at least one of drive voltage, drive current, drive power, or temperature of the semiconductor light source.

16. An apparatus as in claim 7, wherein the light is homogenized by at least one of a light pipe and a diffuser.

17. An apparatus as in claim 1, wherein the analyte property is at least one of: concentration of one or more analytes, presence of one or more analytes, direction of change of concentration of one or more analytes, rate of change of concentration of one or more analytes, and presence of one or more interferents that tend to cause errors in the measurement of one or more other analyte properties.

18. An apparatus as in claim 2,wherein the analyte property is at least one of: concentration of one or more analytes, presence of one or more analytes, direction of change of concentration of one or more analytes, rate of change of concentration of one or more analytes, presence of one or more interferents that tend to cause errors in the measurement of one or more other analyte properties, and a biometric property of the tissue.

19. A method of determining an analyte property in a human, comprising

a. Providing an apparatus as in any of claims 2-18;

b. Using the apparatus to determine optical properties of tissue of the human;

c. Using the computing subsystem to determine the analyte property.

20. A method as in claim 19, wherein the computing subsystem uses information from previous interactions with the apparatus in combination with information from the present interaction with the apparatus in the determination of the analyte property.

21. A method as in claim 19, wherein the computing subsystem does not use information from previous interactions with the apparatus in combination with information from the present interaction with the apparatus in the determination of the analyte property.

22. A method as in claim 19, wherein the analyte property is at least one of: concentration of one or more analytes, presence of one or more analytes, direction of change of concentration of one or more analytes, rate of change of concentration of one or more analytes, presence of one or more interferents that tend to cause errors in the measurement of one or more other analyte properties, and a biometric property of the tissue.

23. A method as in claim 22, wherein the analyte property is at least two of concentration of one or more analytes, presence of one or more analytes, direction of change of concentration of one or more analytes, rate of change of concentration of one or more analytes, presence of one or more interferents that tend to cause errors in the measurement of one or more other analyte properties, and a biometric property of the tissue.

24. A method as in claim 22, wherein the analyte is at least one of: alcohol, alcohol byproducts, alcohol markers, and alcohol adducts.

25. A method as in claim 19, wherein the analyte property comprises both determination of an analyte concentration and determination of a biometric property.

26. A method of maintaining calibration of an apparatus as in claim 1, comprising adjusting the calibration of the apparatus using a plurality of measurements with assumed values taken at different times.

27. A method of transferring the calibration of a first apparatus as in claim 1 to a second apparatus as in claim 1, comprising determining a difference in the spectral response between the first and second apparatuses, and transferring the calibration of the first apparatus, adjusted to accommodate the difference, to the second apparatus.

28. A method as in claim 27, wherein determining a difference comprises determining the response of both apparatuses to samples with known analyte properties.

29. An apparatus as in claim 1, wherein the semiconductor light source produces light with at least one wavelength in at least one of the following ranges: 4150 to 4900, 5400 to 6800, 4150 to 7400, 4000 to 8000.

30. An apparatus as in claim 1, wherein the sampling subsystem communicates light to the sample at a plurality of distinct regions of the sample.

31. An apparatus as in claim 1, wherein the sampling subsystem collects light from a plurality of distinct regions of the sample.

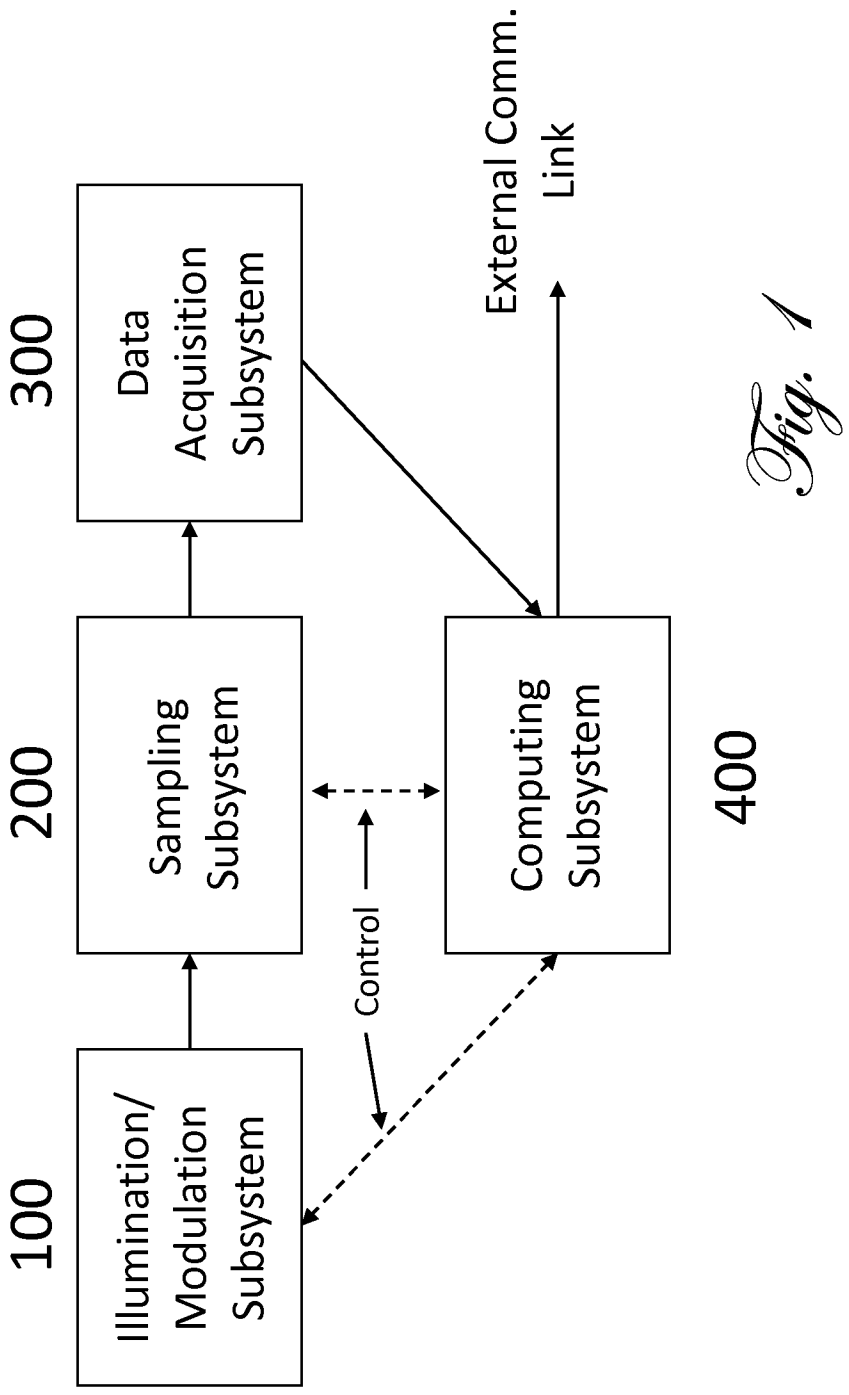

100
Illumination/ Modulation Subsystem
200
Sampling Subsystem
300
Data Acquisition Subsystem
Control
Computing Subsystem
400
External Comm. Link

Fig. 1

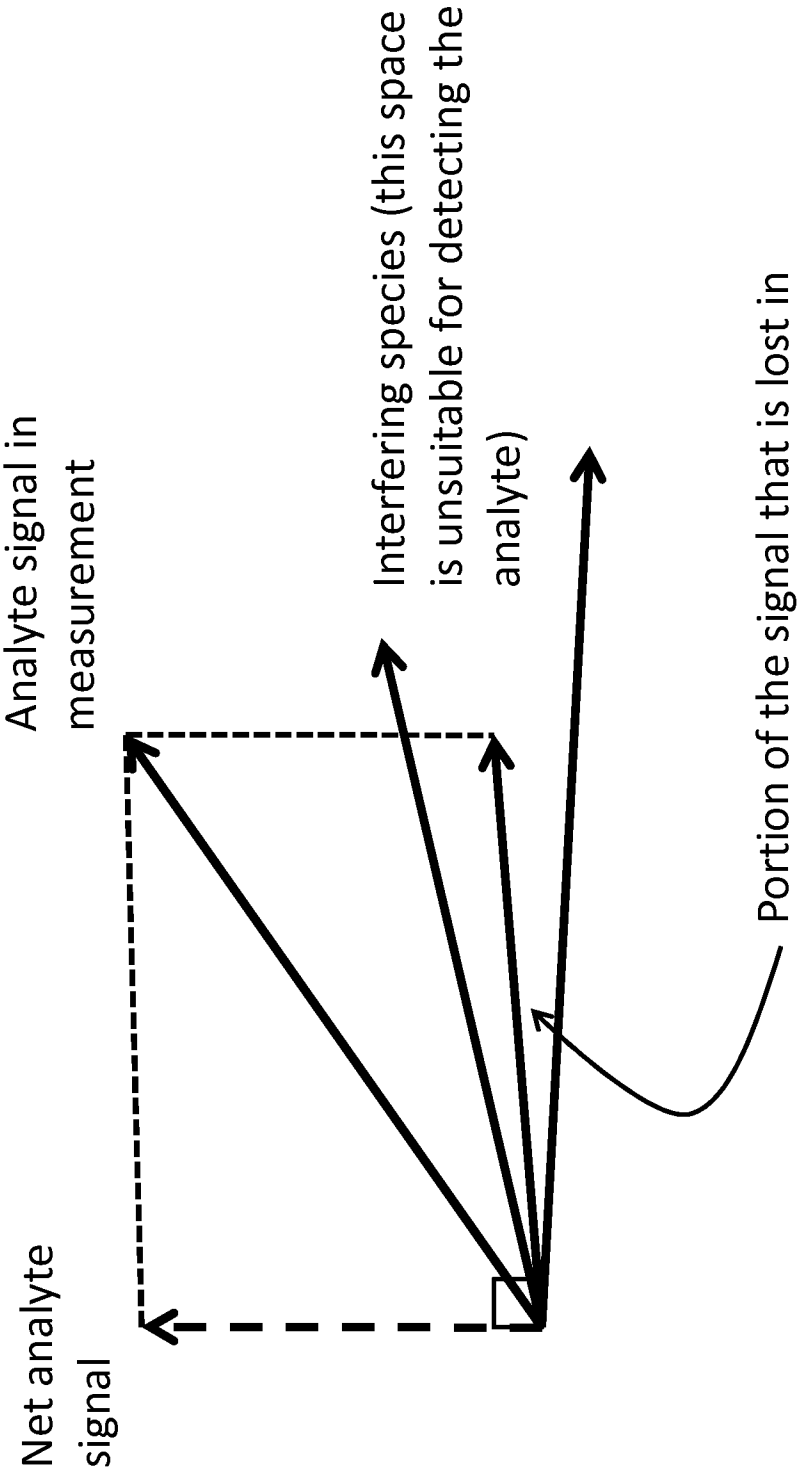

Analyte signal in measurement
Interfering species (this space is unsuitable for detecting the analyte)
Portion of the signal that is lost in the interfering signals
Net analyte signal

Fig. 2

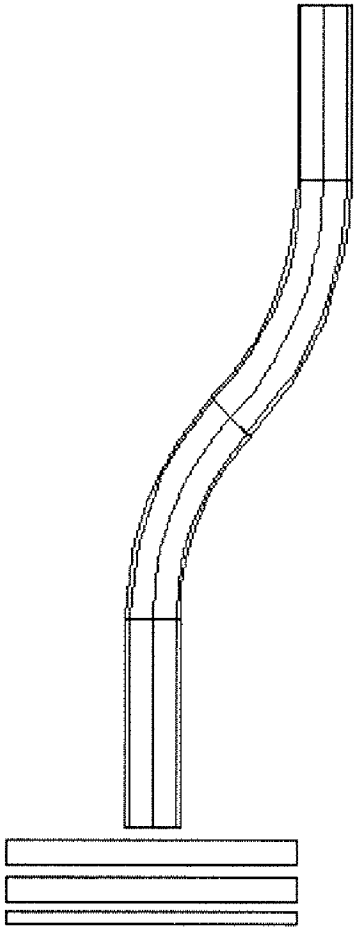


Fig. 3

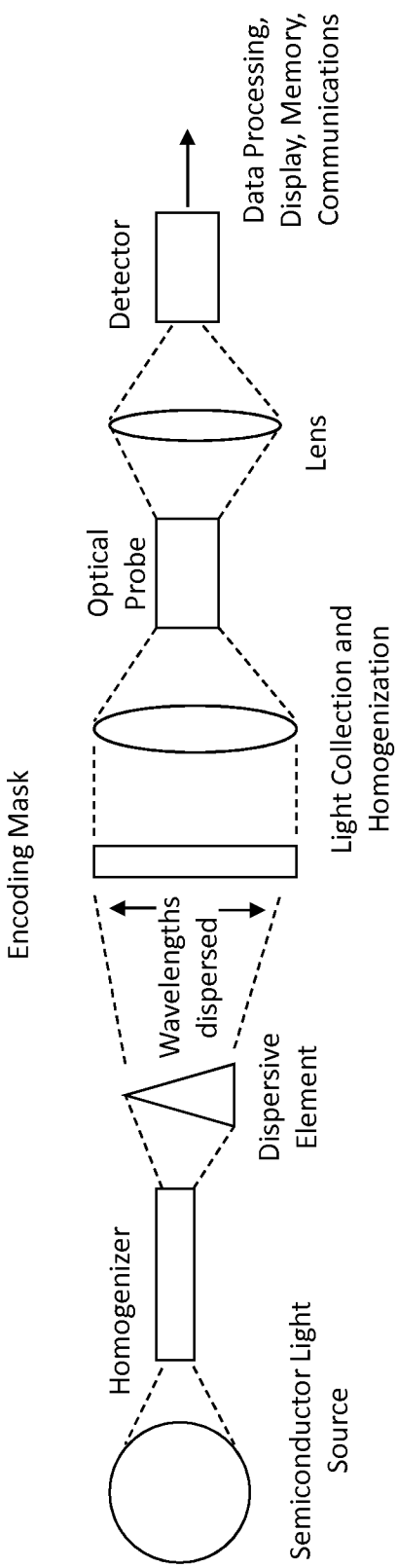

Semiconductor Light Source
Homogenizer
Dispersive Element
Wavelengths dispersed
Encoding Mask
Light Collection and Homogenization
Optical Probe
Lens
Detector
Data Processing, Display, Memory, Communications

Fig. 4

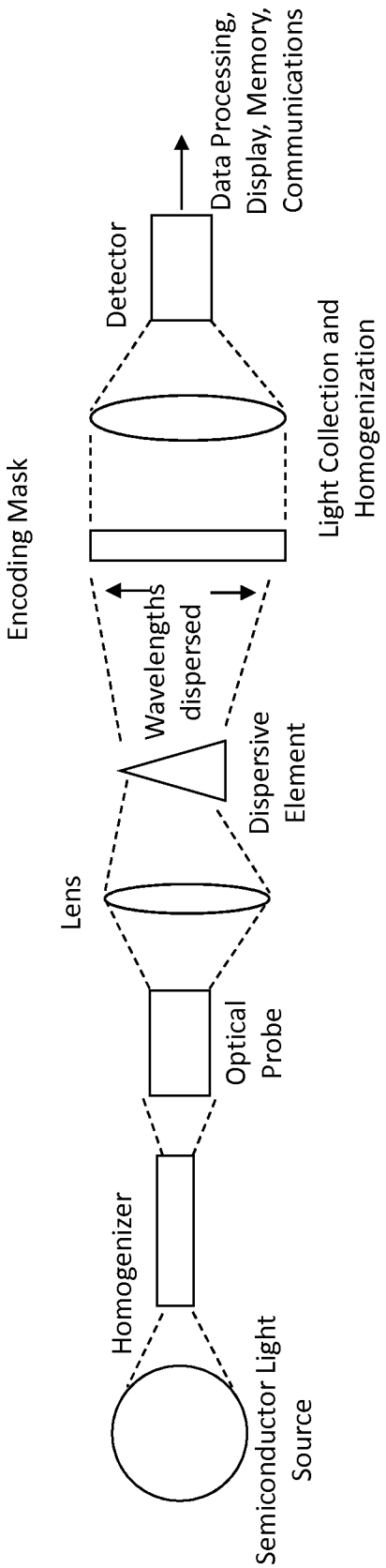

Semiconductor Light Source
Homogenizer
Optical Probe
Lens
Dispersive Element
Wavelengths dispersed
Encoding Mask
Light Collection and Homogenization
Detector
Data Processing, Display, Memory, Communications

Fig. 5

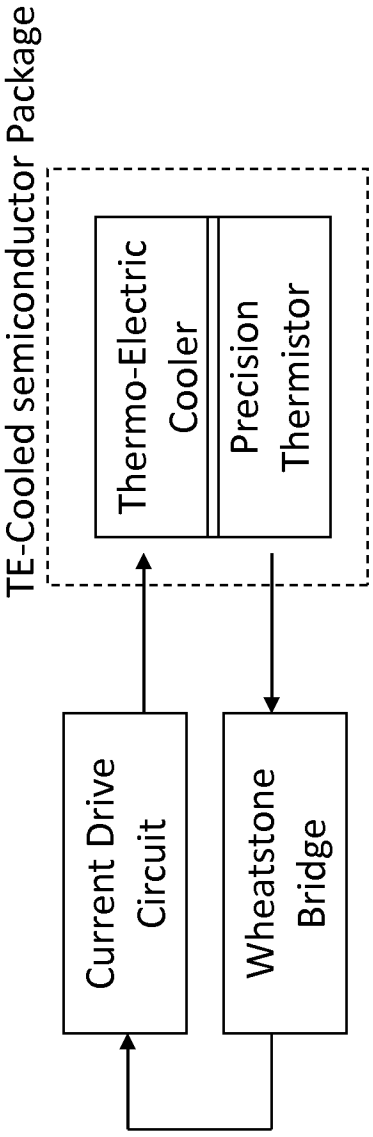

TE-Cooled semiconductor Package
Thermo-Electric Cooler
Precision Thermistor
Current Drive Circuit
Wheatstone Bridge

Fig. 6

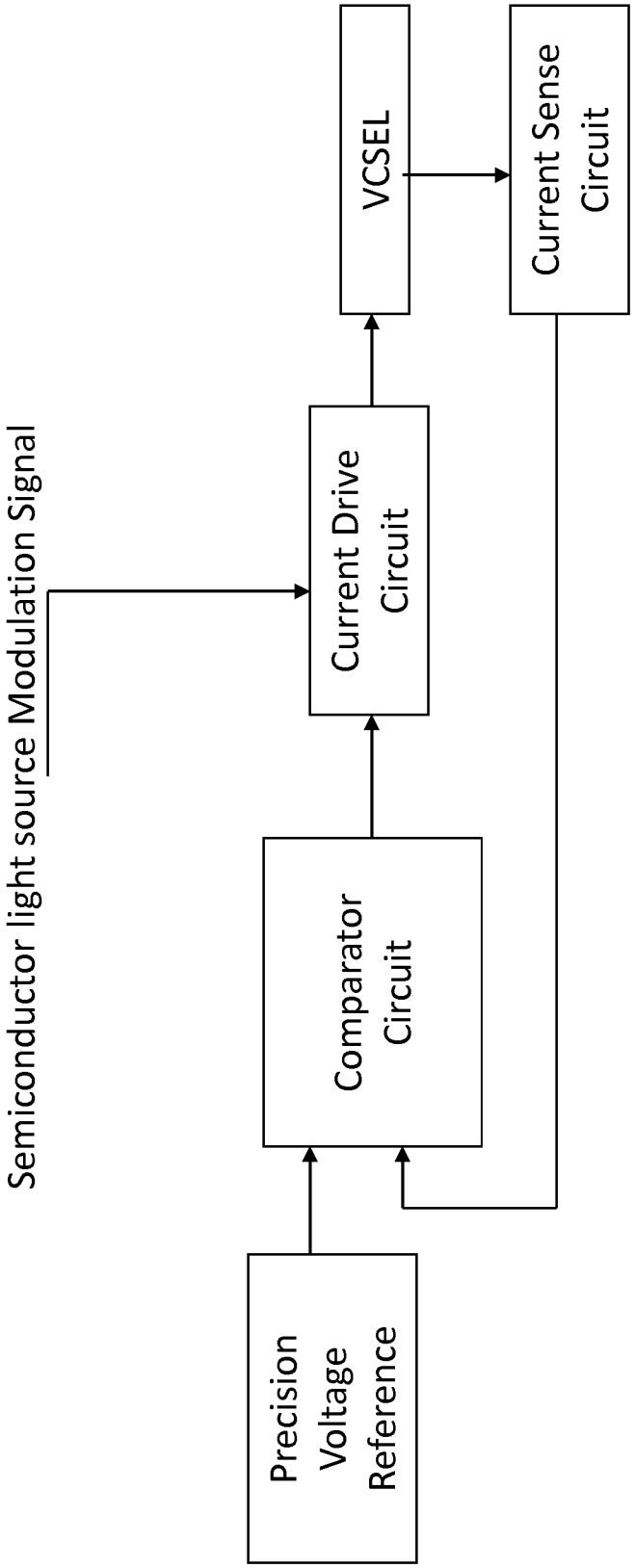

Semiconductor light source Modulation Signal
Precision Voltage Reference
Comparator Circuit
Current Drive Circuit
VCSEL
Current Sense Circuit

Fig. 7

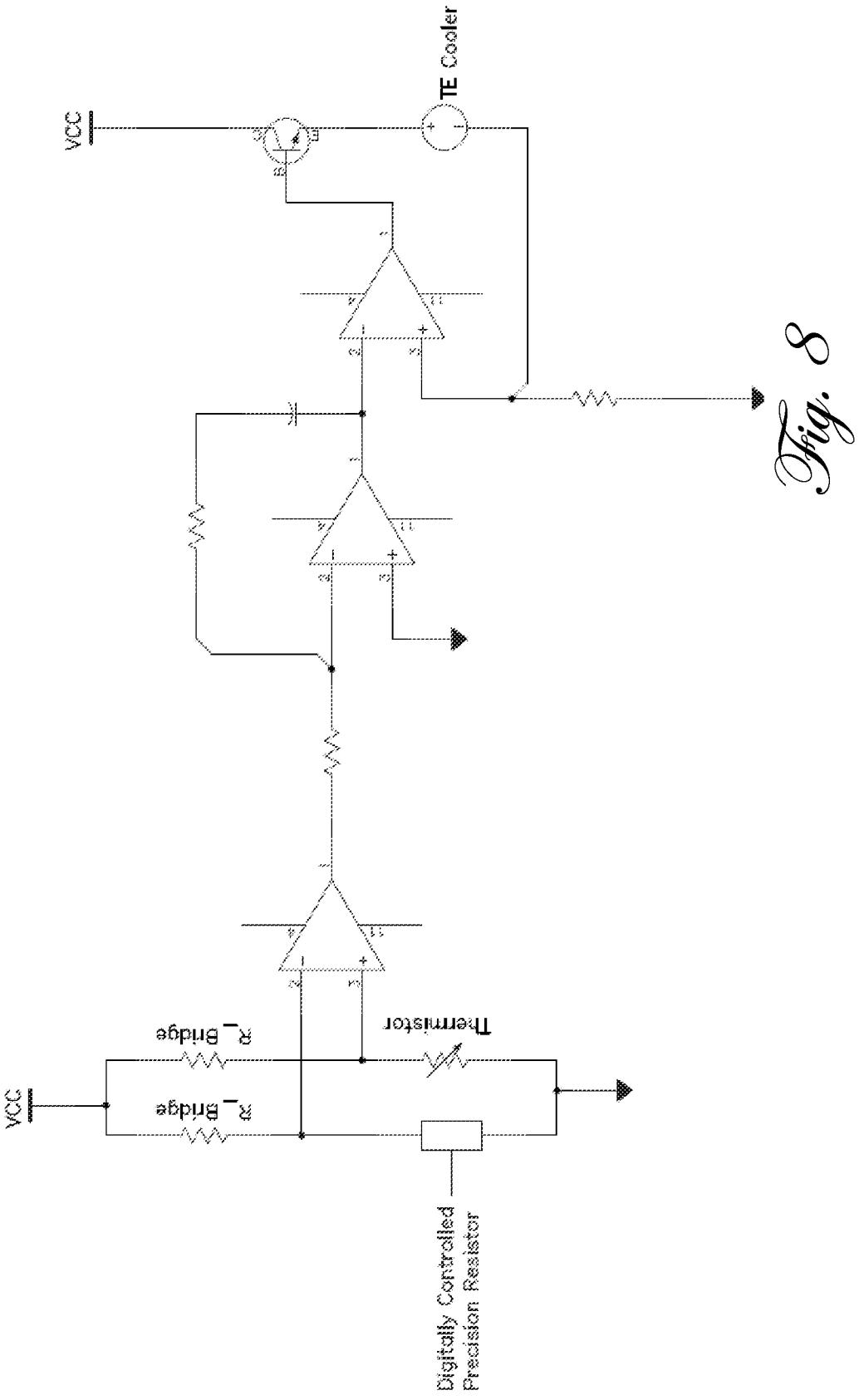

TE Cooler
VCC
R_Bridge
R_Bridge
Thermistor
VCC
Digitally Controlled
Precision Resistor

Fig. 8

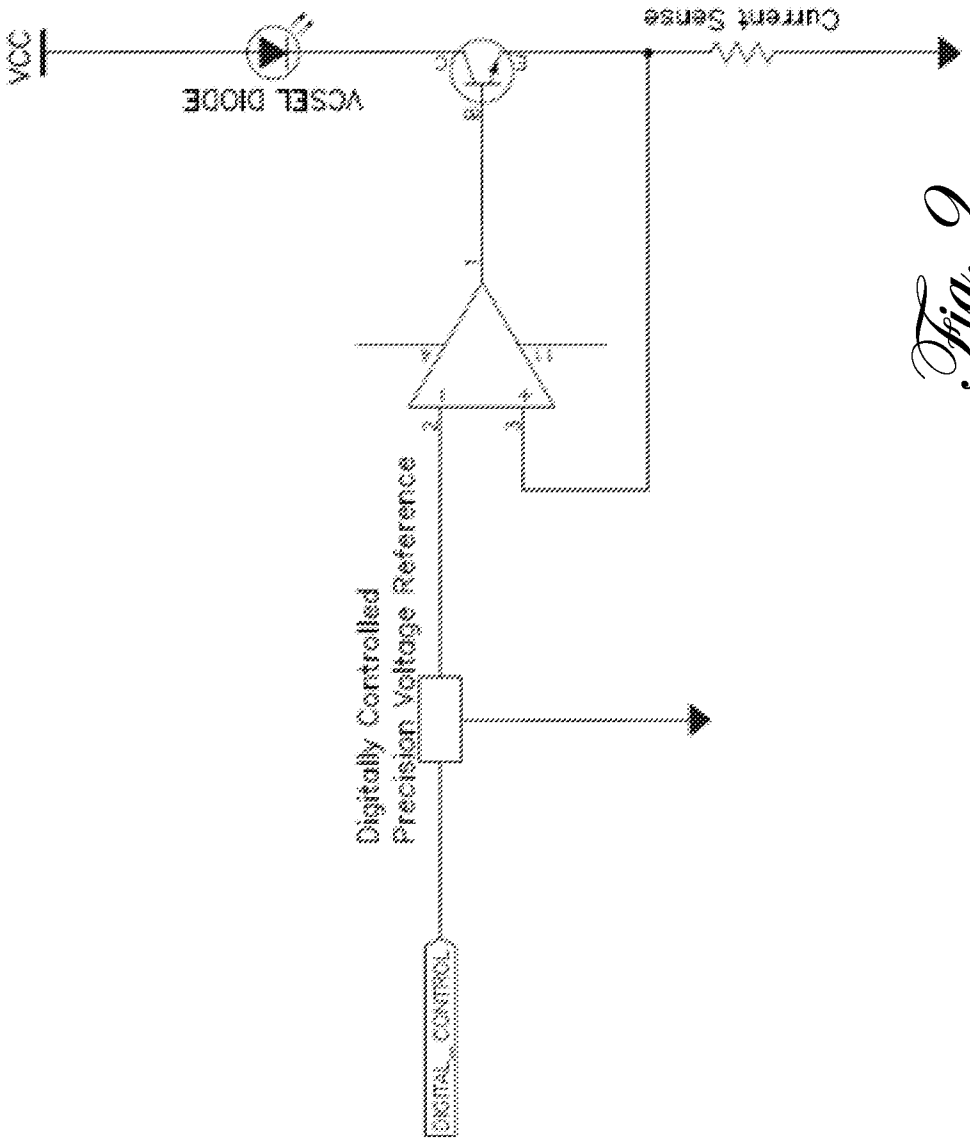

VCC
VCSEL DIODE
Current Sense
Digitally Controlled
Precision Voltage Reference
DIGITAL CONTROL

Fig. 9

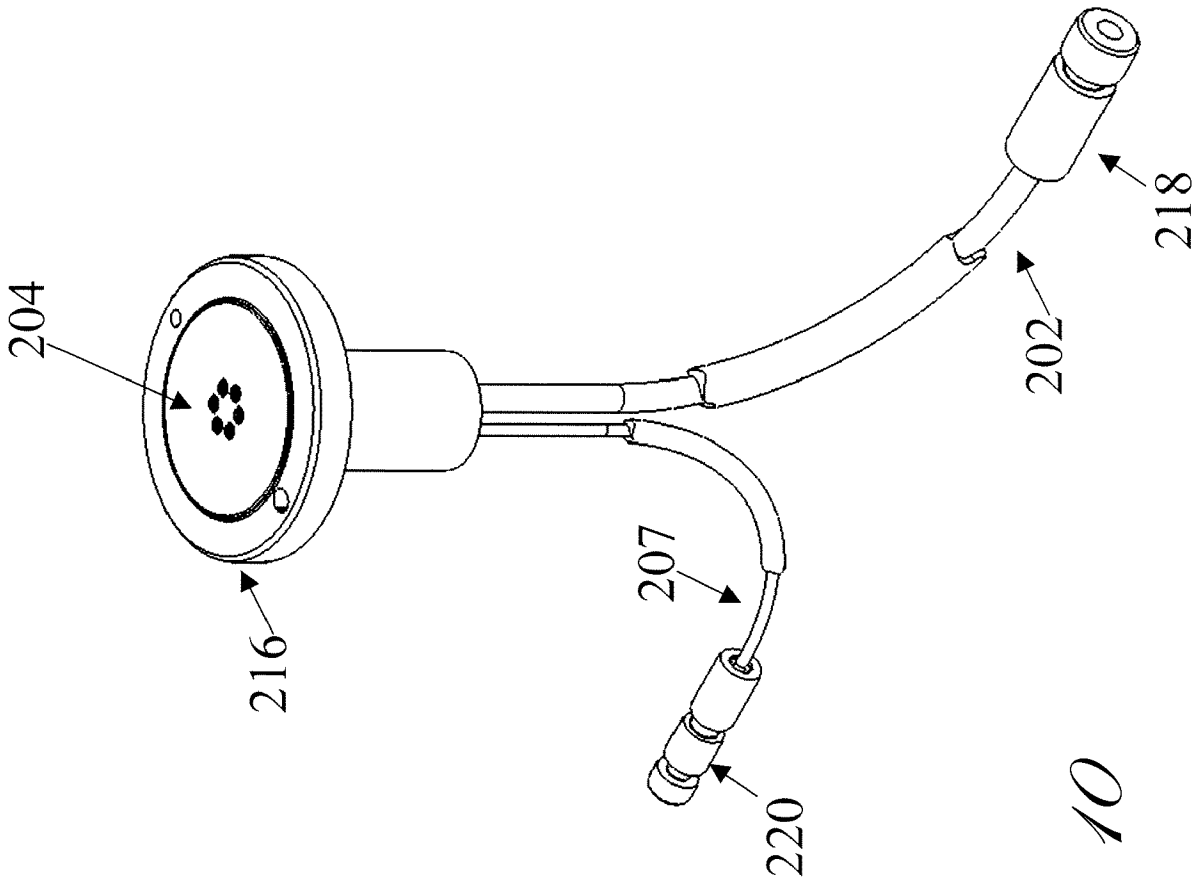


Fig. 10

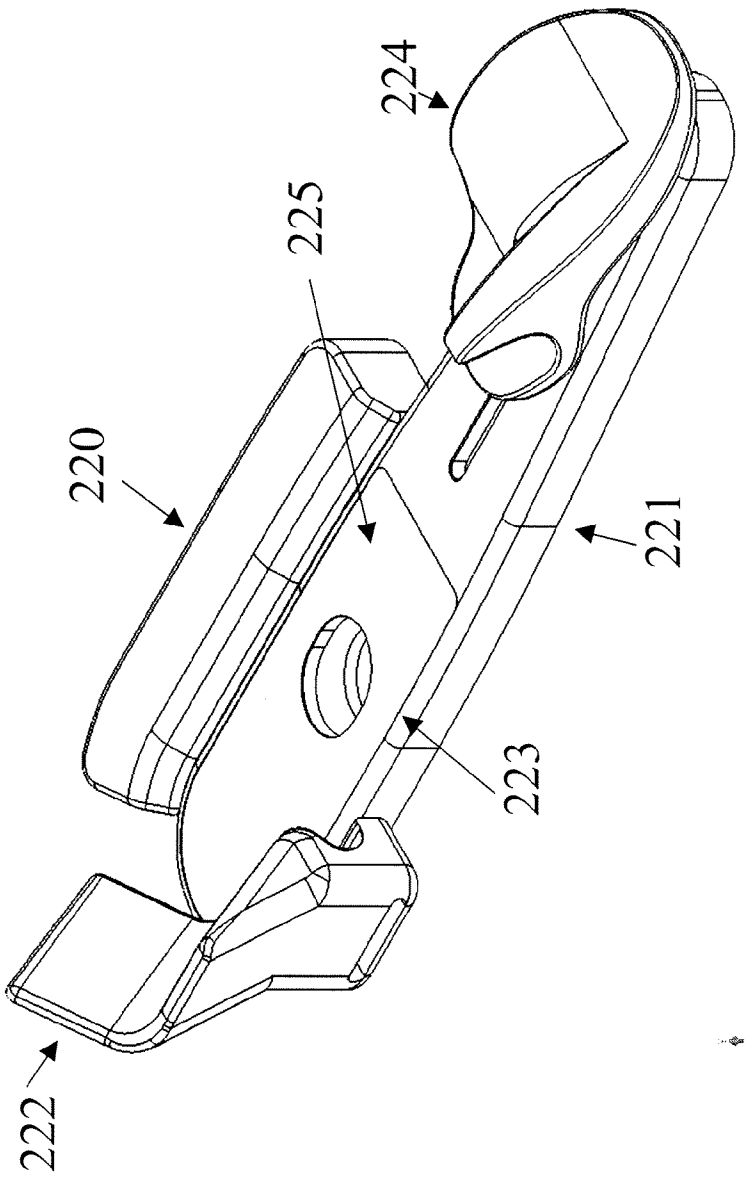


Fig. 11

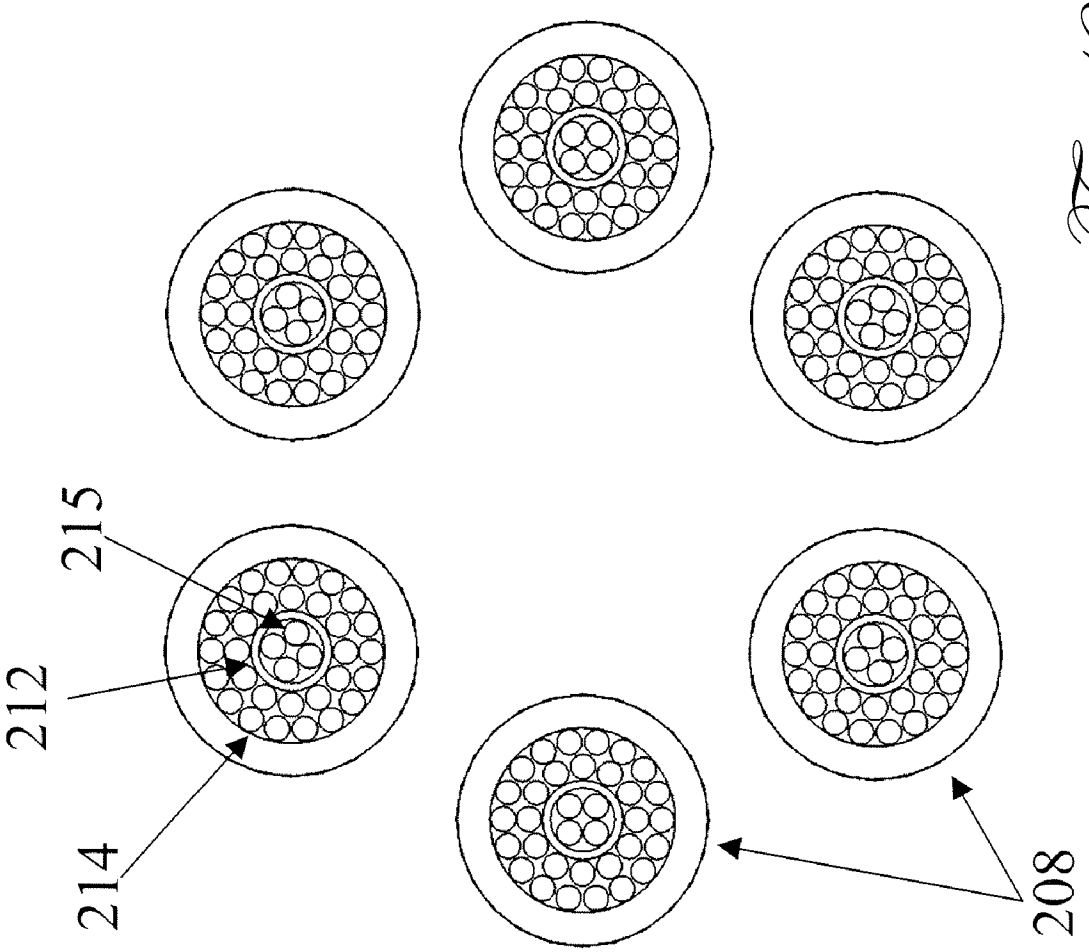


Fig. 12

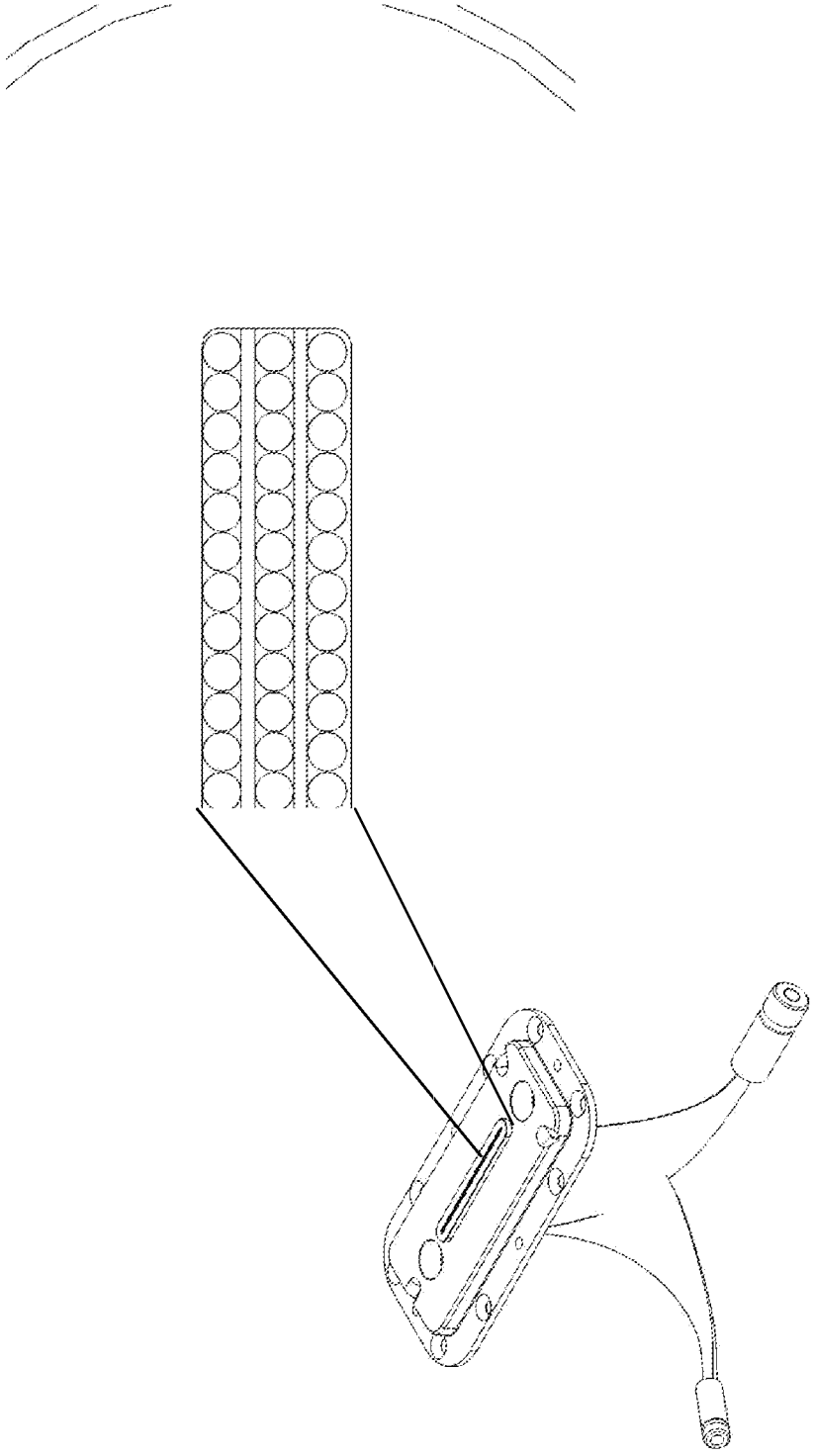


Fig. 13

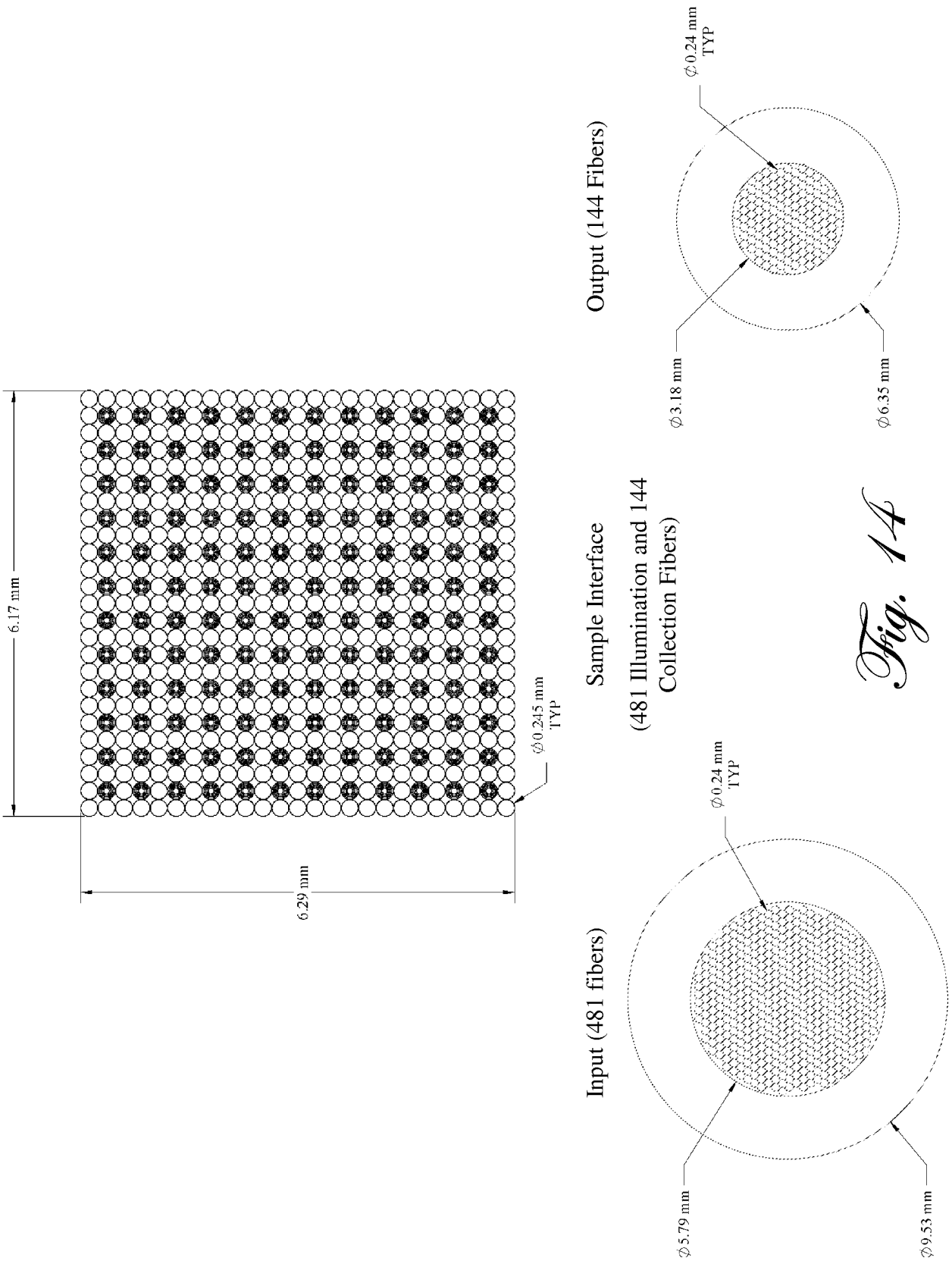

Sample Interface
(481 Illumination and 144
Collection Fibers)
6.17 mm
6.29 mm
Ø0.245 mm
TYP
Input (481 fibers)
Ø0.24 mm
TYP
Ø5.79 mm
Ø9.53 mm
Output (144 Fibers)
Ø0.24 mm
TYP
Ø3.18 mm
Ø6.35 mm

Fig. 14

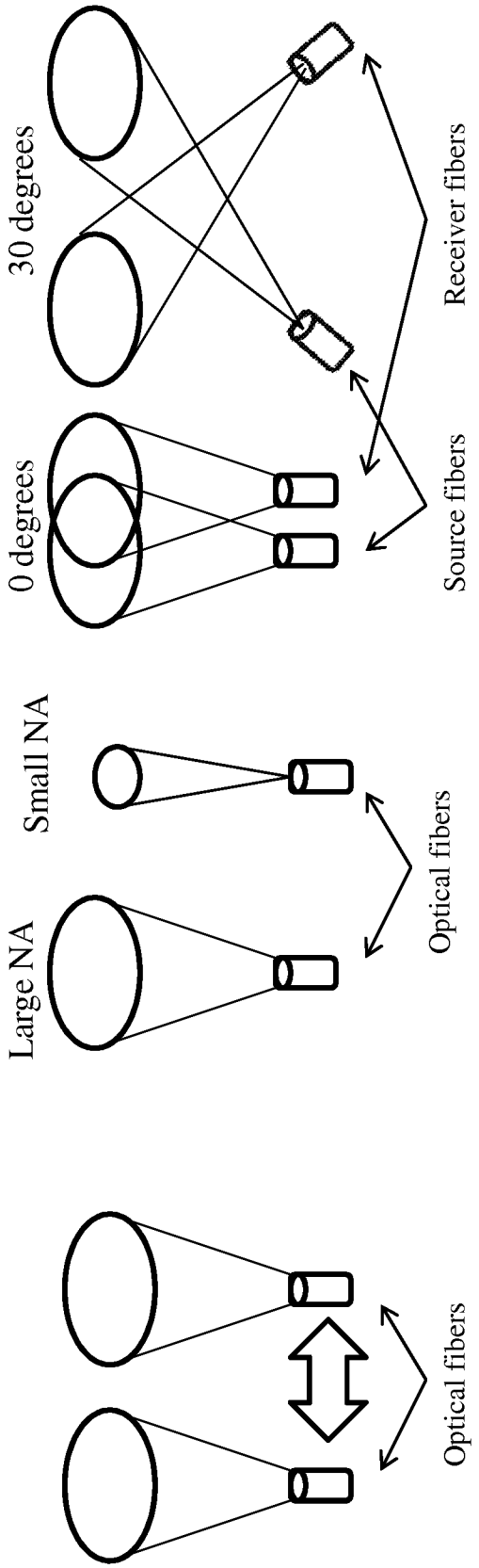

Illumination-collection separation
Optical fibers
Large NA
Small NA
Optical fibers
Numerical aperture
0 degrees
30 degrees
Source fibers
Receiver fibers
Illumination-collection angle

Fig. 15

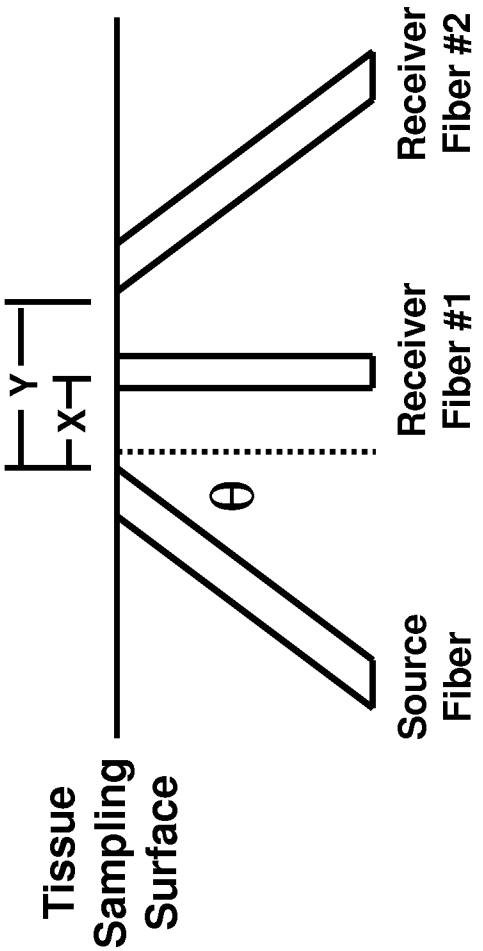

Tissue Sampling Surface
Source Fiber
Receiver Fiber #1
Receiver Fiber #2
θ
X
Y

Fig. 16

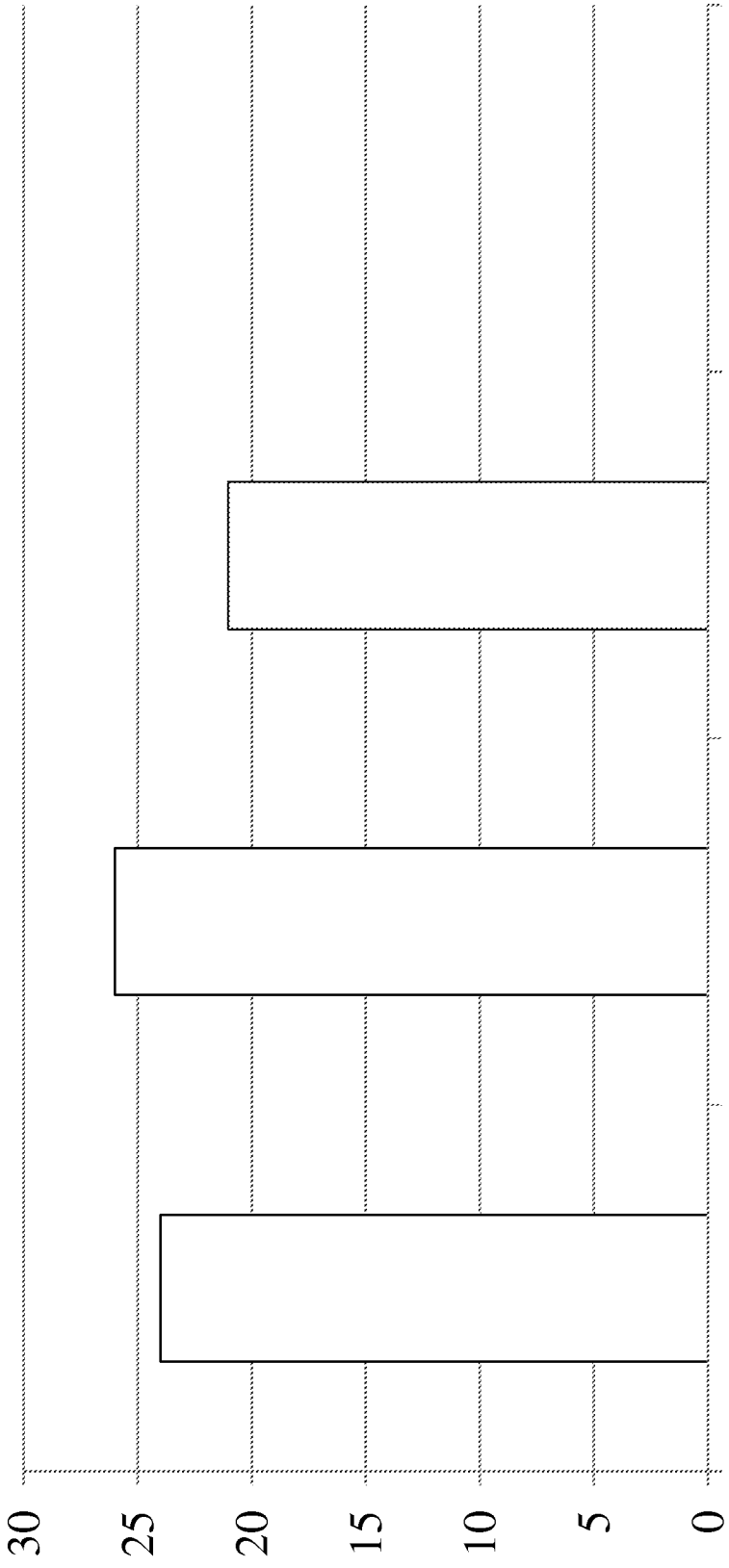


Fig. 17

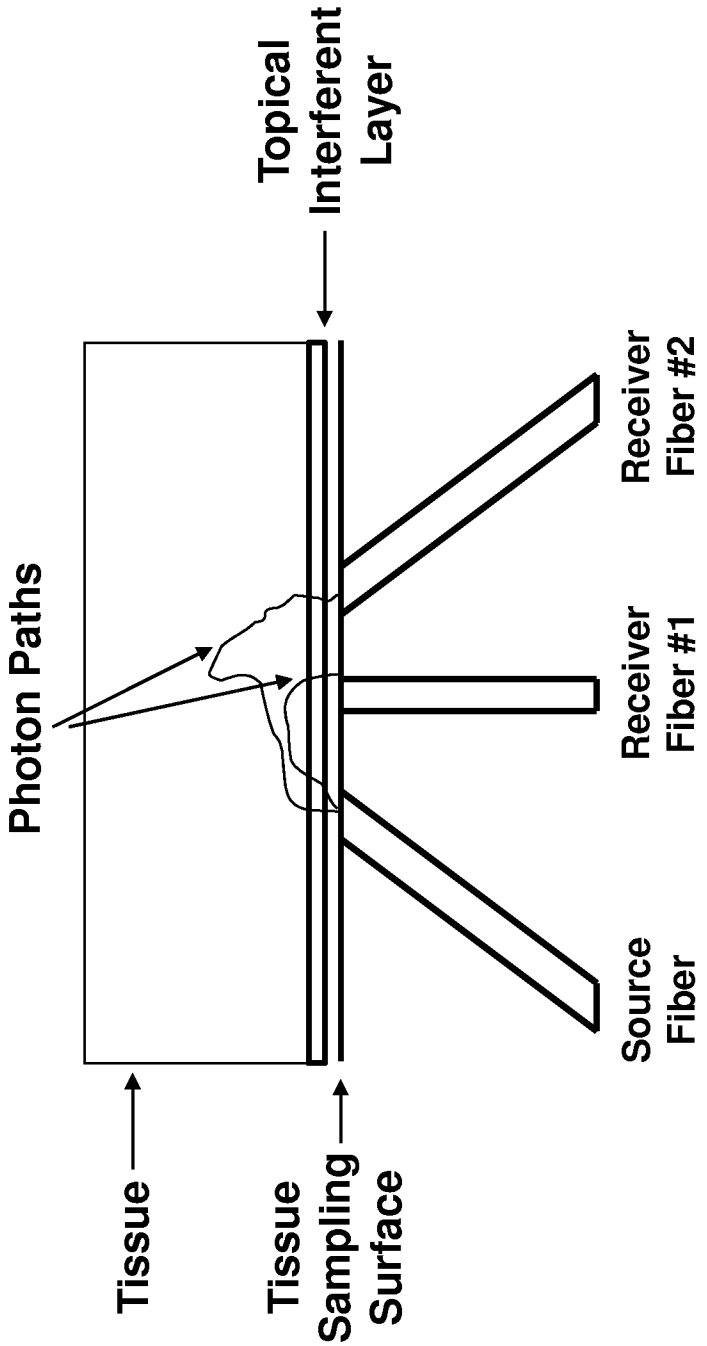

Topical Interferent Layer
Photon Paths
Receiver Fiber #2
Receiver Fiber #1
Source Fiber
Tissue
Tissue Sampling Surface

Fig. 18

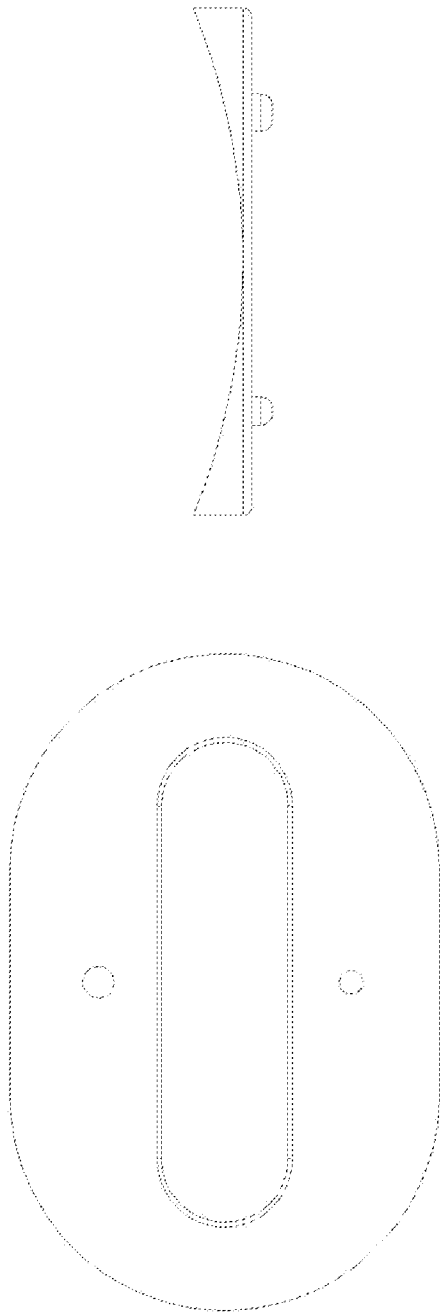


Fig. 19

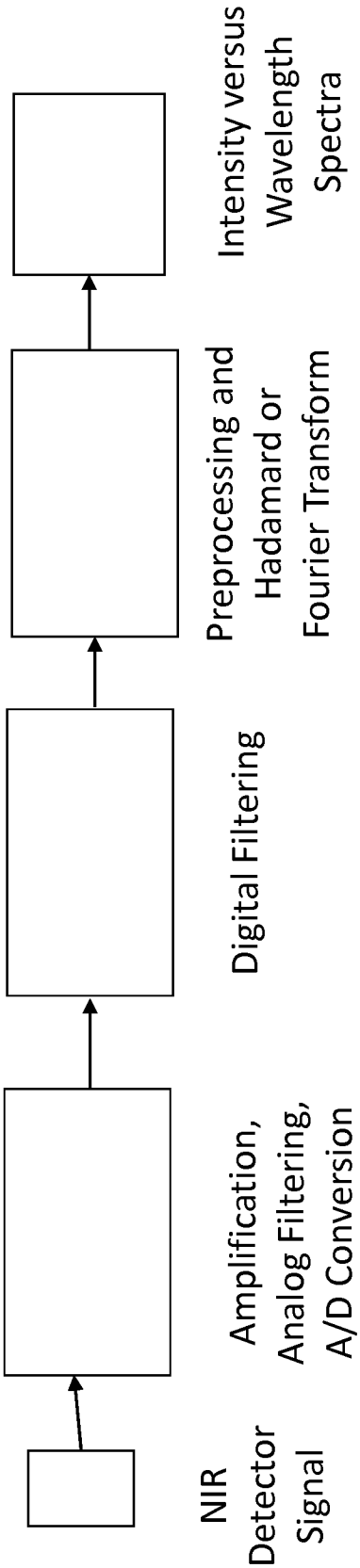
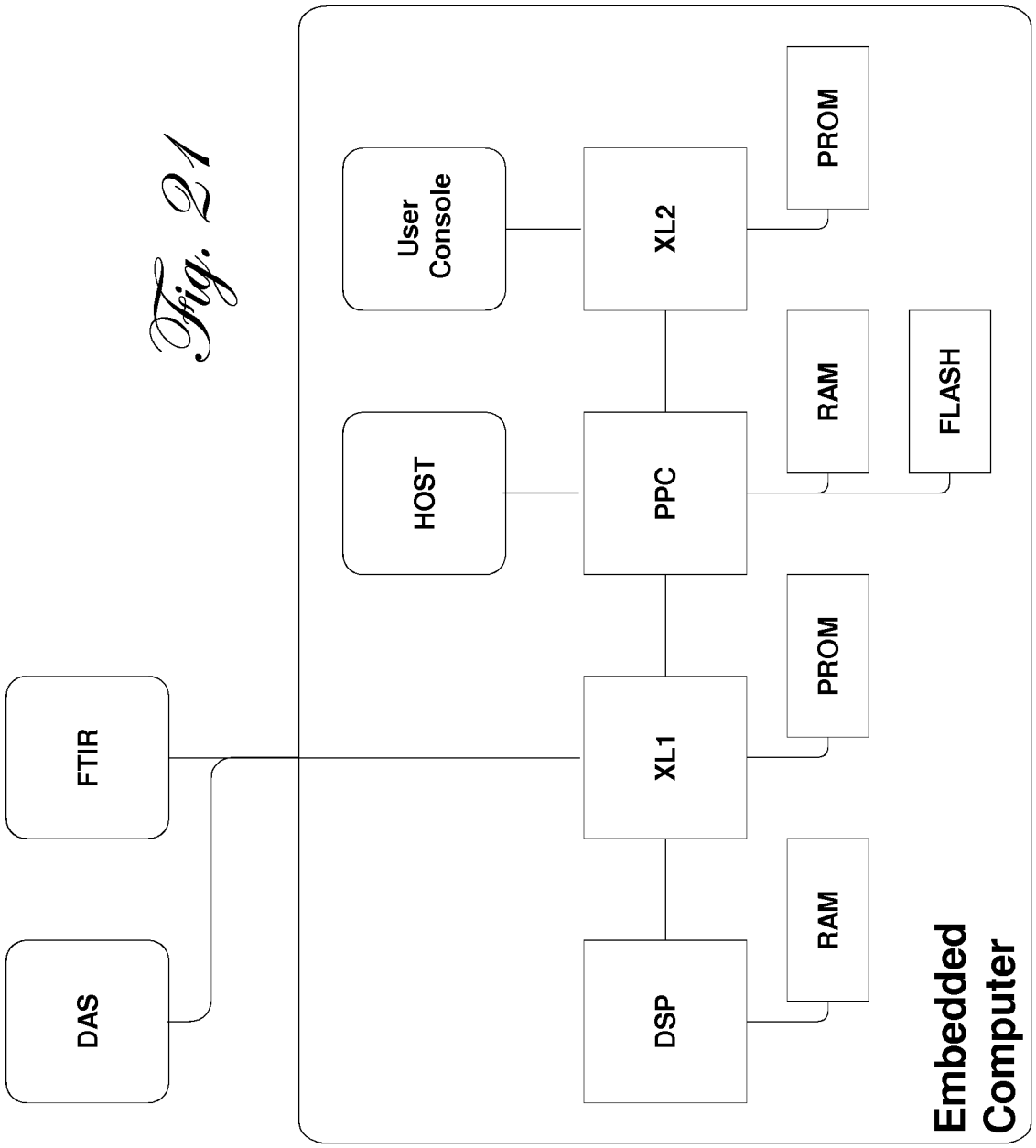

NIR Detector Signal
Amplification, Analog Filtering, A/D Conversion
Digital Filtering
Preprocessing and Hadamard or Fourier Transform
Intensity versus Wavelength Spectra

Fig. 20

Fig. 21


FTIR
DAS
User Console
HOST
XL2
PPC
XL1
DSP
PROM
RAM
FLASH
PROM
RAM
Embedded Computer

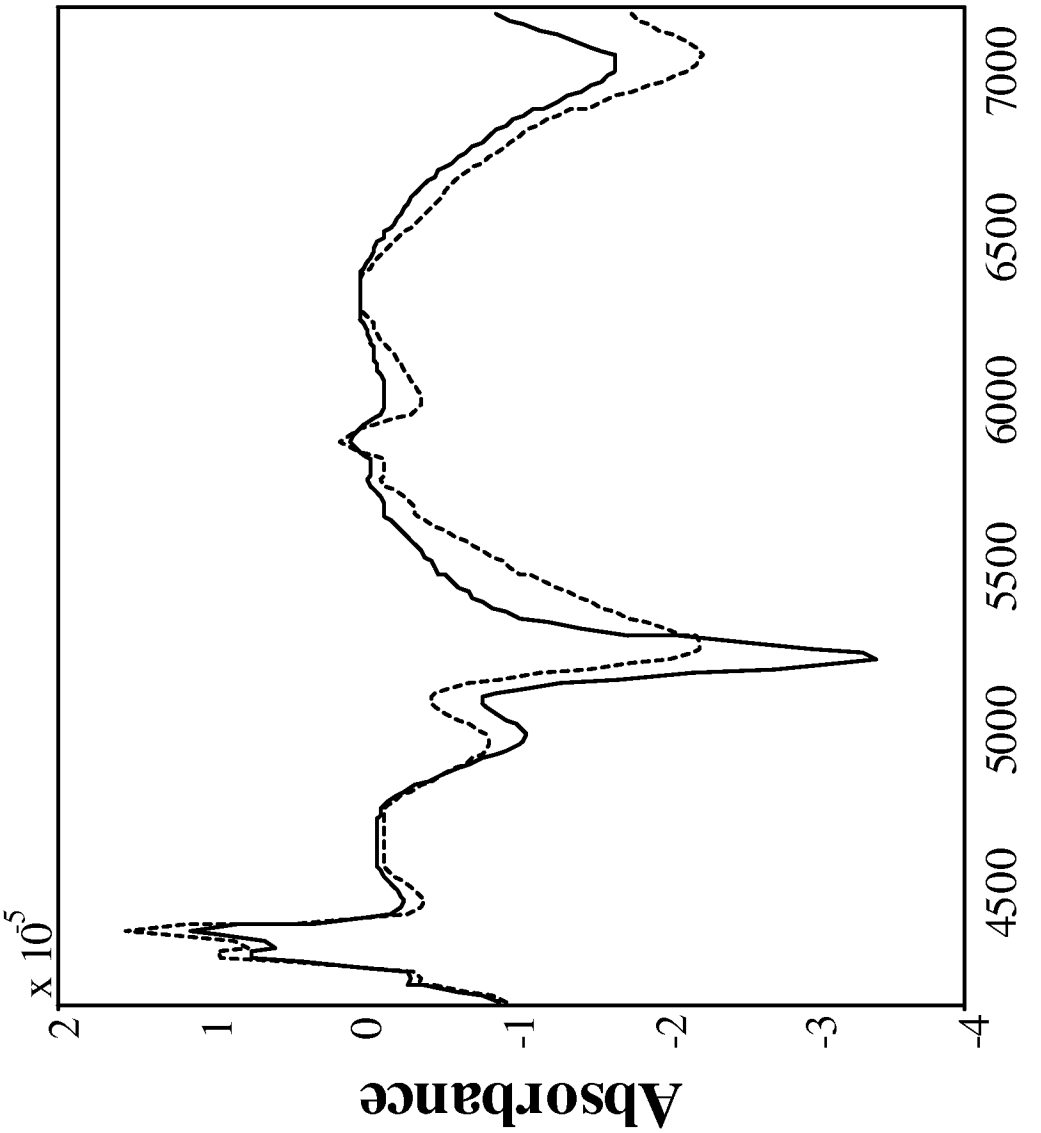

x 10^-5
2
1
0
-1
-2
-3
-4
Absorbance
4500
5000
5500
6000
6500
7000
Wavenumber

Fig. 22

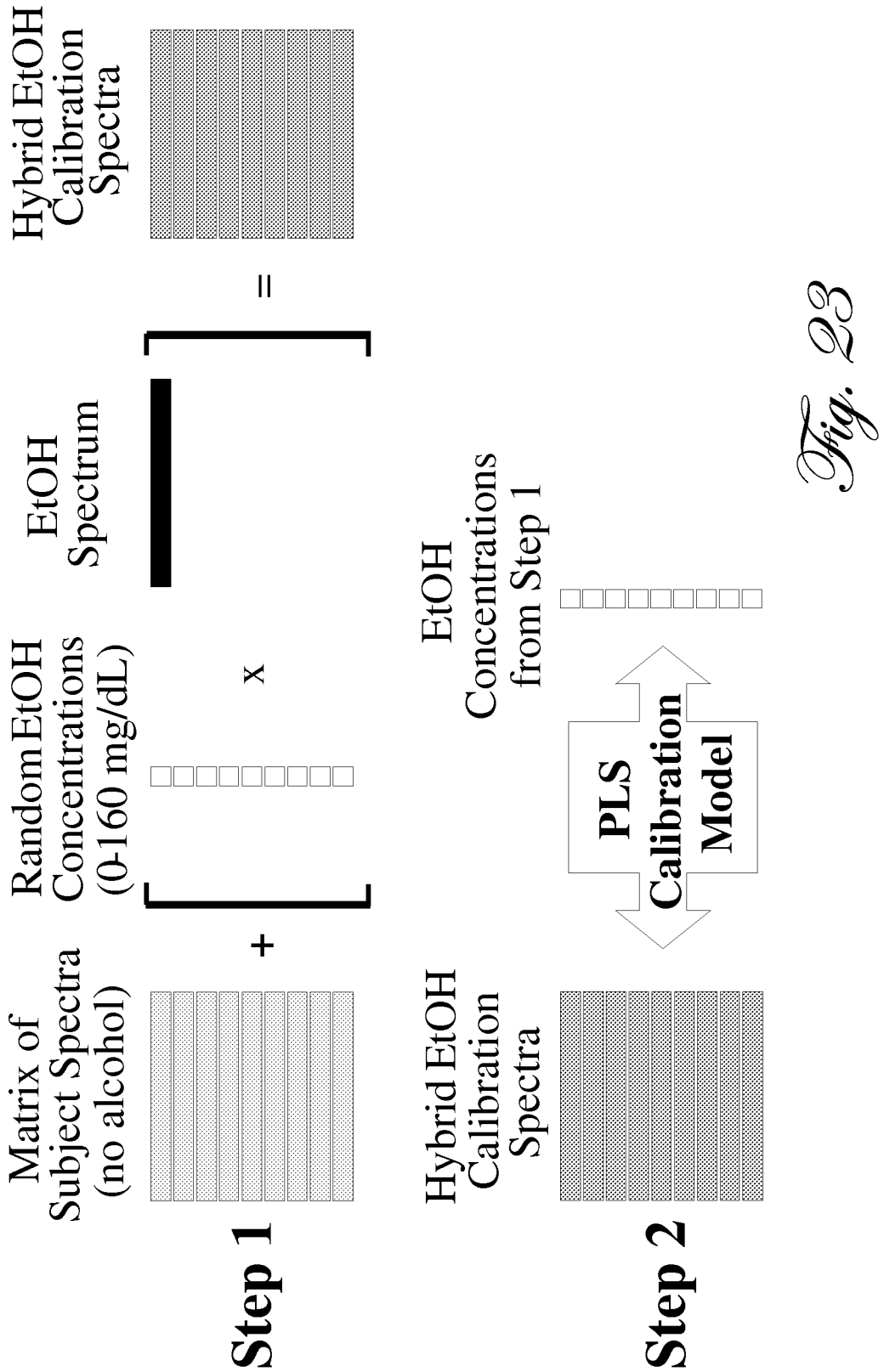

Step 1
Matrix of Subject Spectra (no alcohol)
+
Random EtOH Concentrations (0-160 mg/dL)
x
EtOH Spectrum
=
Hybrid EtOH Calibration Spectra
Step 2
Hybrid EtOH Calibration Spectra
PLS Calibration Model
EtOH Concentrations from Step 1

Fig. 23

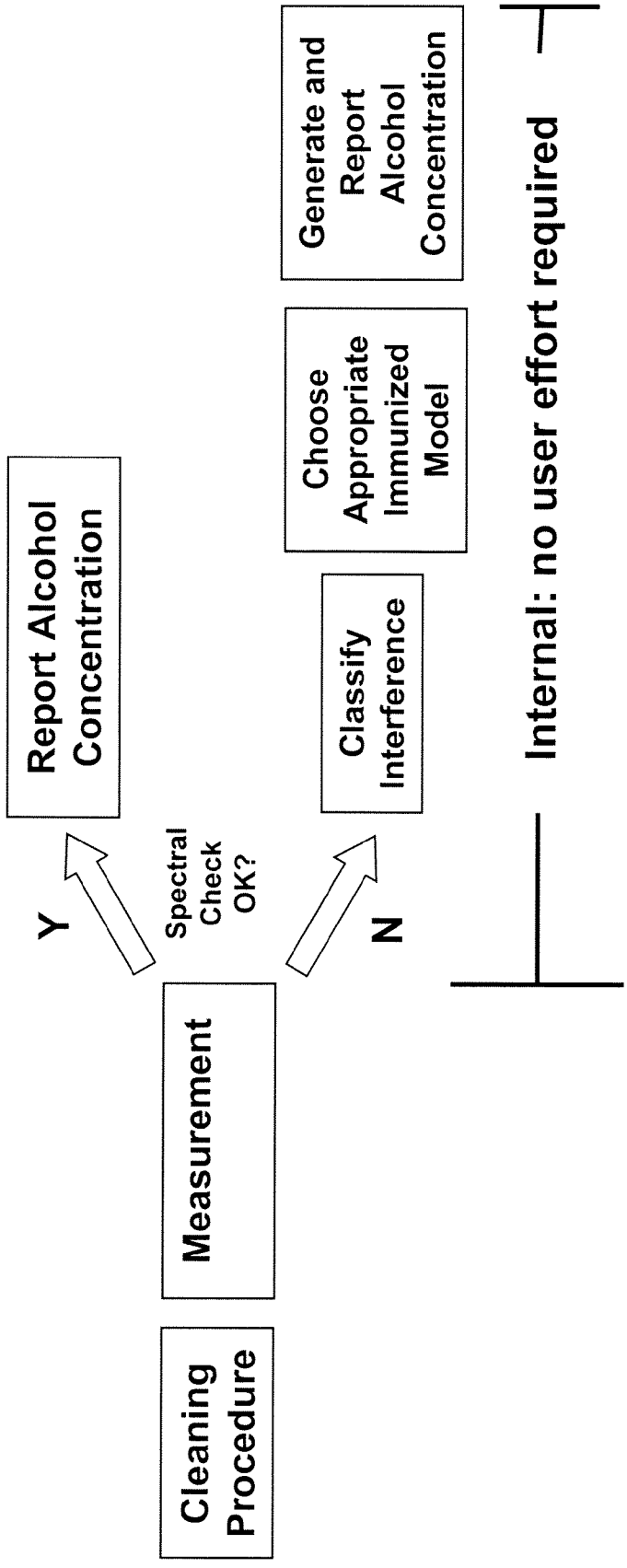

Cleaning Procedure
Measurement
Spectral Check OK?
Y
N
Report Alcohol Concentration
Classify Interference
Choose Appropriate Immunized Model
Generate and Report Alcohol Concentration
Internal: no user effort required

Fig. 2A

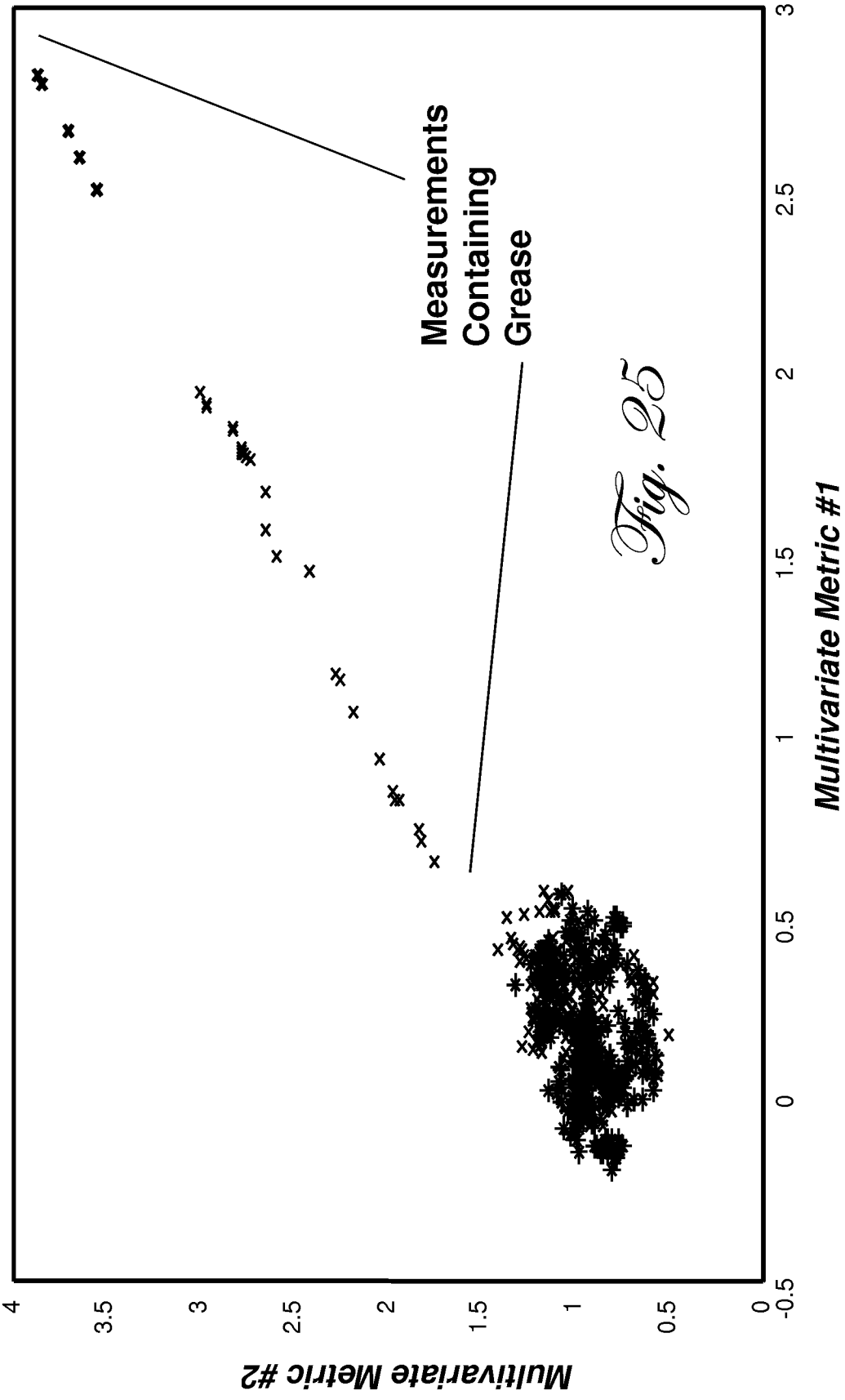

Measurements Containing Grease
Multivariate Metric #2
Multivariate Metric #1
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
0
0.5
1
1.5
2
2.5
3

Fig. 25

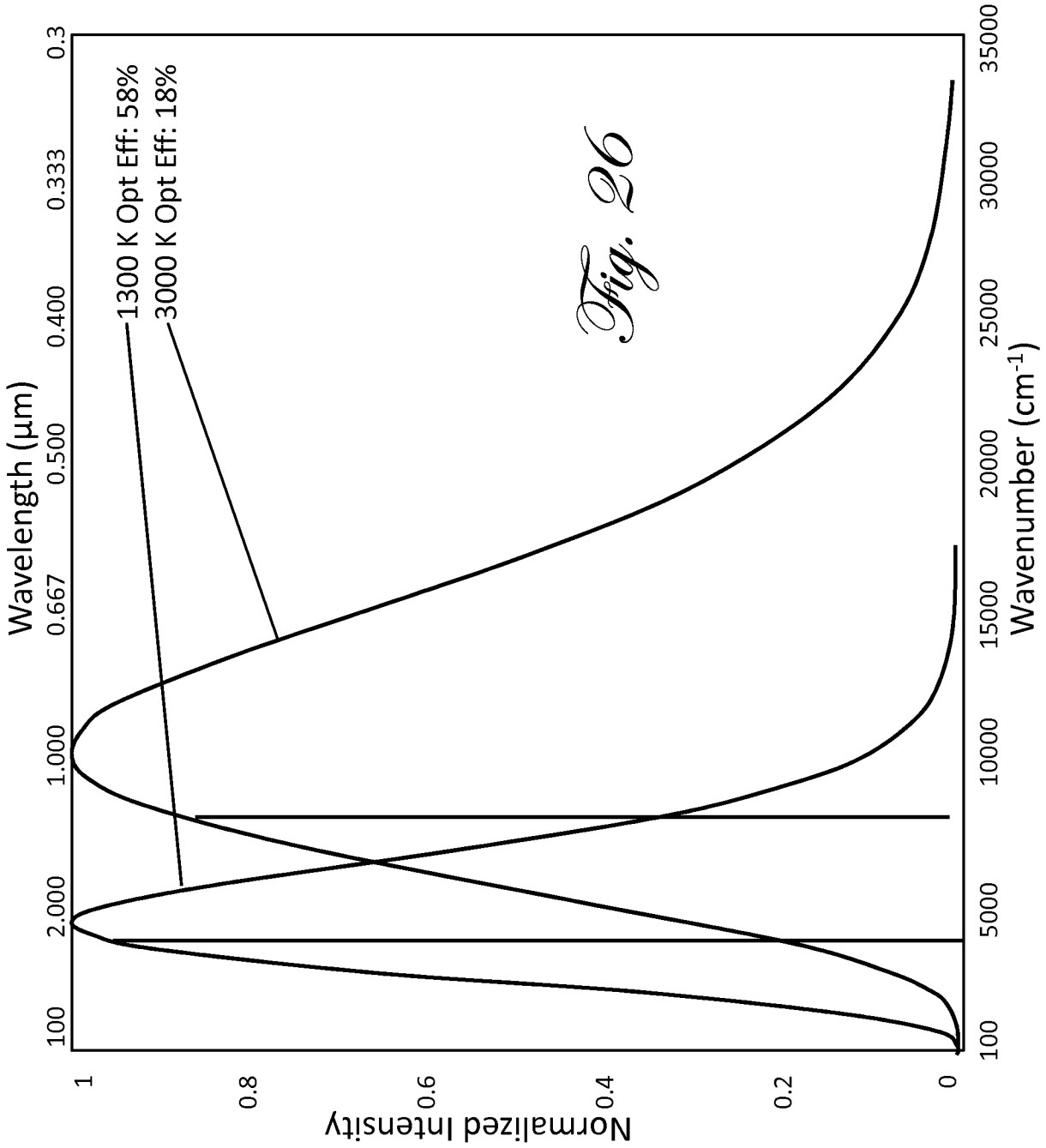

Wavelength (μm)
100
2.000
1.000
0.667
0.500
0.400
0.333
0.3
1300 K Opt Eff: 58%
3000 K Opt Eff: 18%
Normalized Intensity
1
0.8
0.6
0.4
0.2
0
100
5000
10000
15000
20000
25000
30000
35000
Wavenumber (cm-1)

Fig. 26

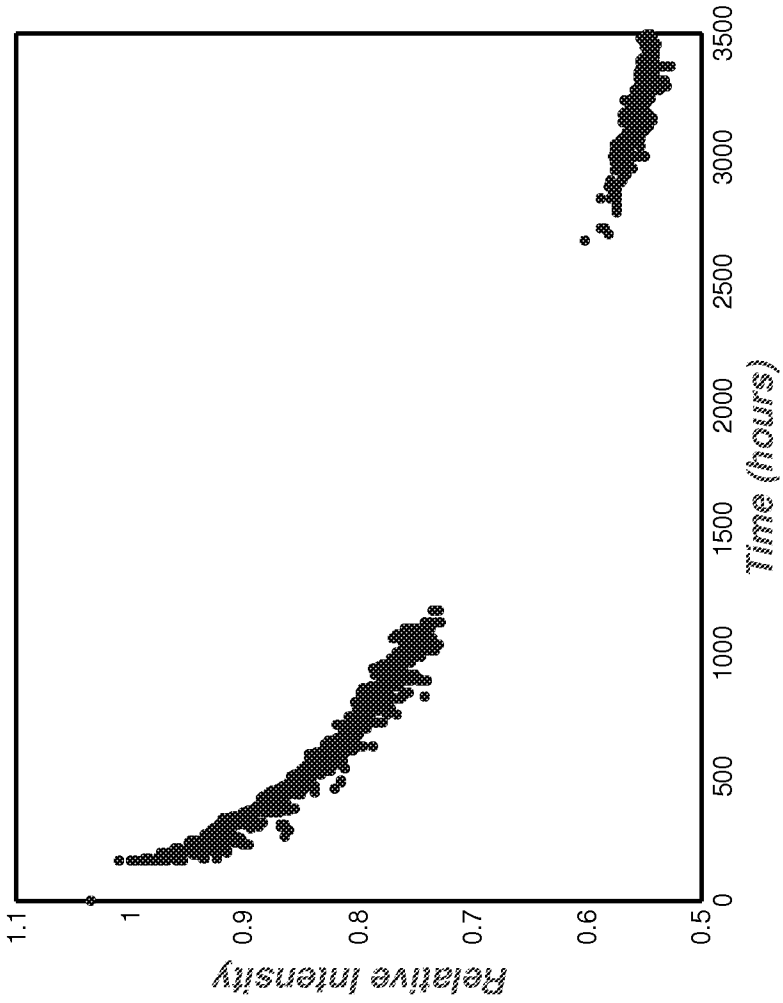

Relative Intensity
1.1
1
0.9
0.8
0.7
0.6
0.5
0
500
1000
1500
2000
2500
3000
3500
Time (hours)

Fig. 27

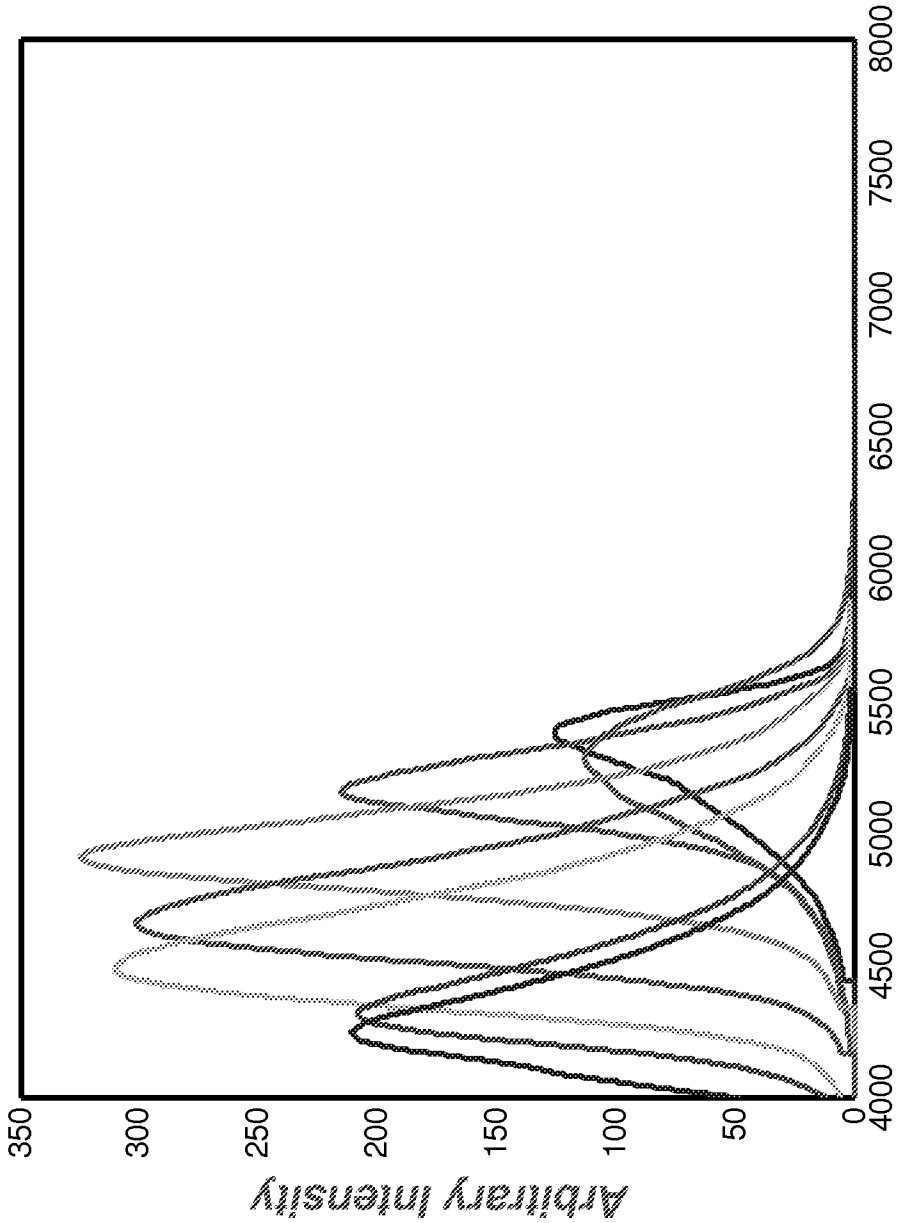
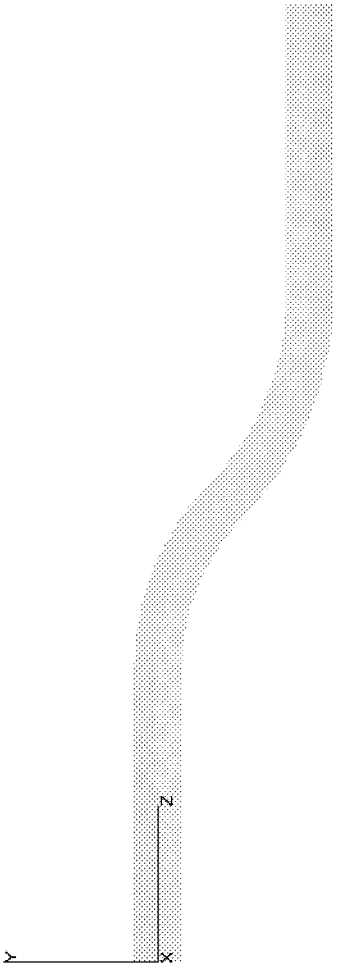
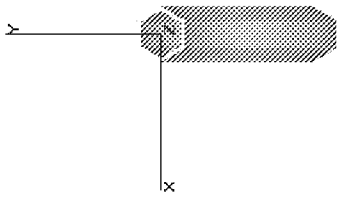

Arbitrary Intensity
350
300
250
200
150
100
50
0
4000
4500
5000
5500
6000
6500
7000
7500
8000
Wavenumber

Fig. 28



Side View



End View

Fig. 29

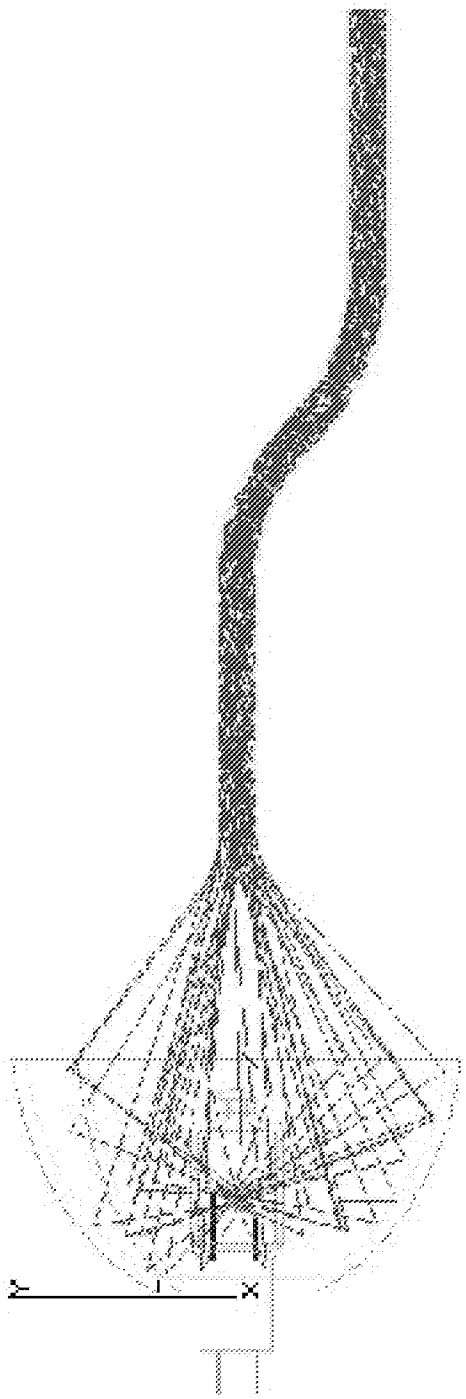


Fig. 30

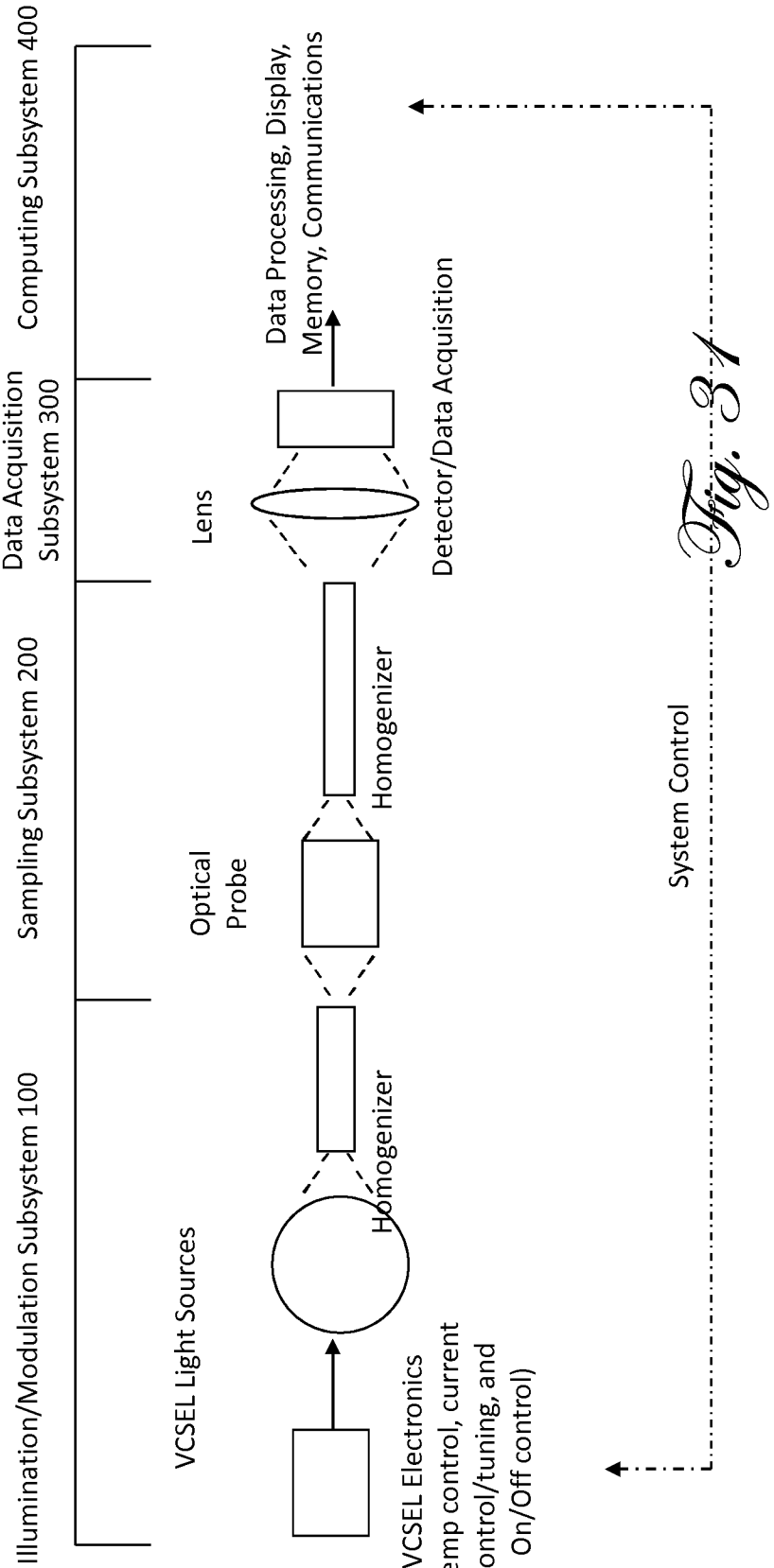

Illumination/Modulation Subsystem 100
Sampling Subsystem 200
Data Acquisition Subsystem 300
Computing Subsystem 400
VCSEL Light Sources
VCSEL Electronics (temp control, current control/tuning, and On/Off control)
Homogenizer
Optical Probe
Homogenizer
Lens
Detector/Data Acquisition
Data Processing, Display, Memory, Communications
System Control

Fig. 31

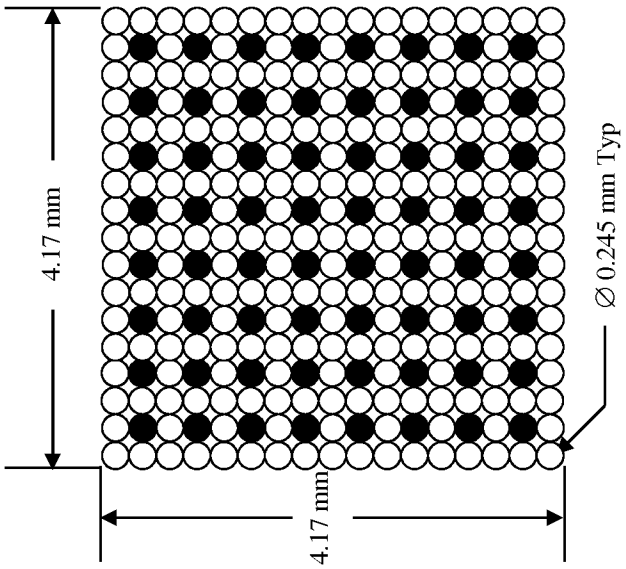
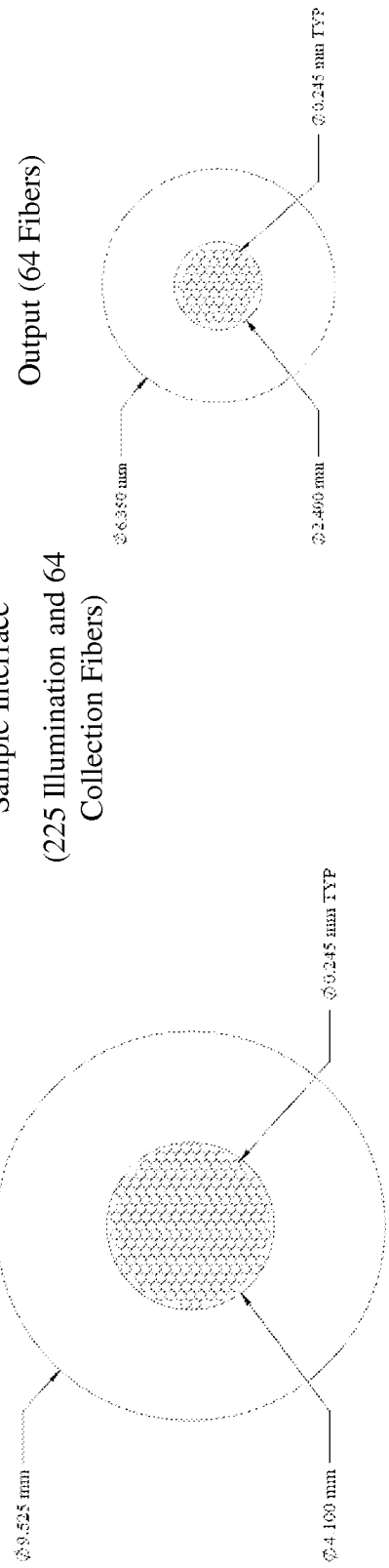

4.17 mm
4.17 mm
Ø 0.245 mm Typ

Fig. 32


Input (225 fibers)
Sample Interface
(225 Illumination and 64
Collection Fibers)
Output (64 Fibers)
Ø9.525 mm
Ø4.100 mm
Ø0.245 mm TYP
Ø6.350 mm
Ø2.460 mm
Ø0.245 mm TYP

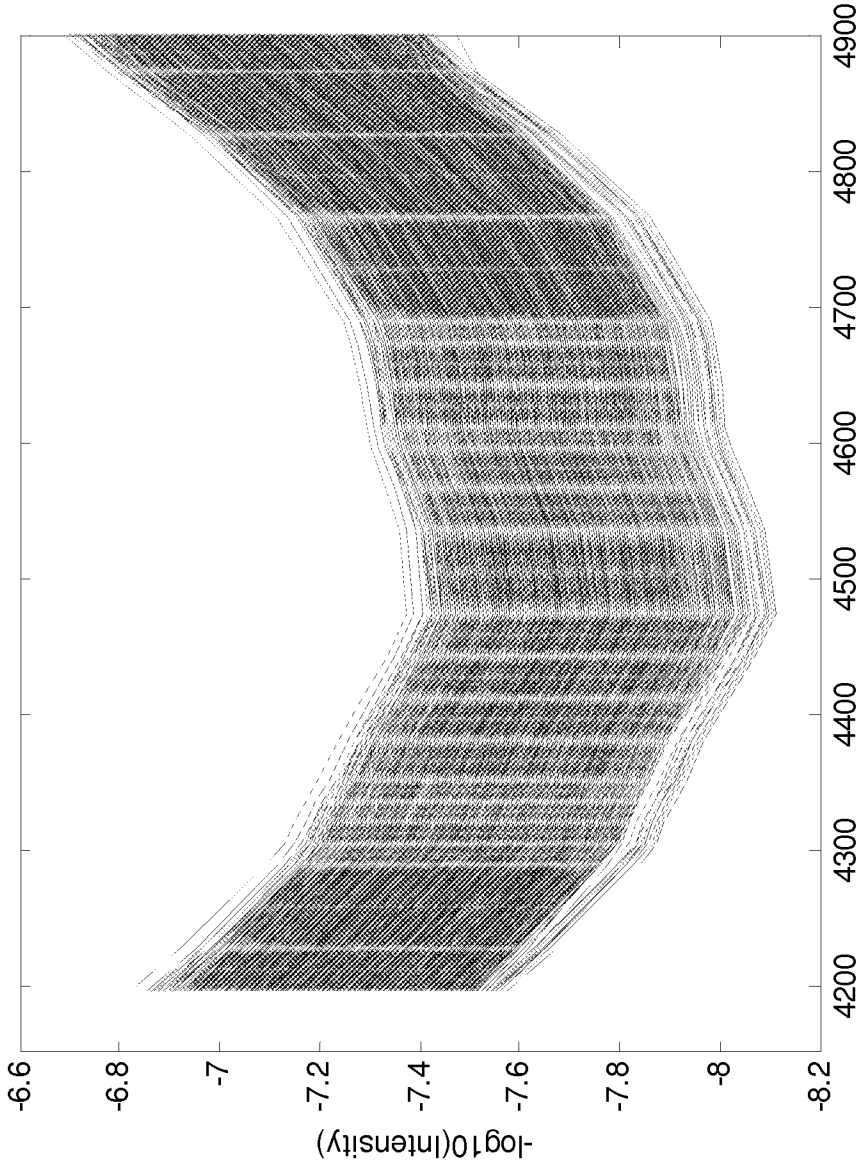

-log10(Intensity)
-6.6
-6.8
-7
-7.2
-7.4
-7.6
-7.8
-8
-8.2
4200
4300
4400
4500
4600
4700
4800
4900
Wavenumber (cm-1)

Fig. 33

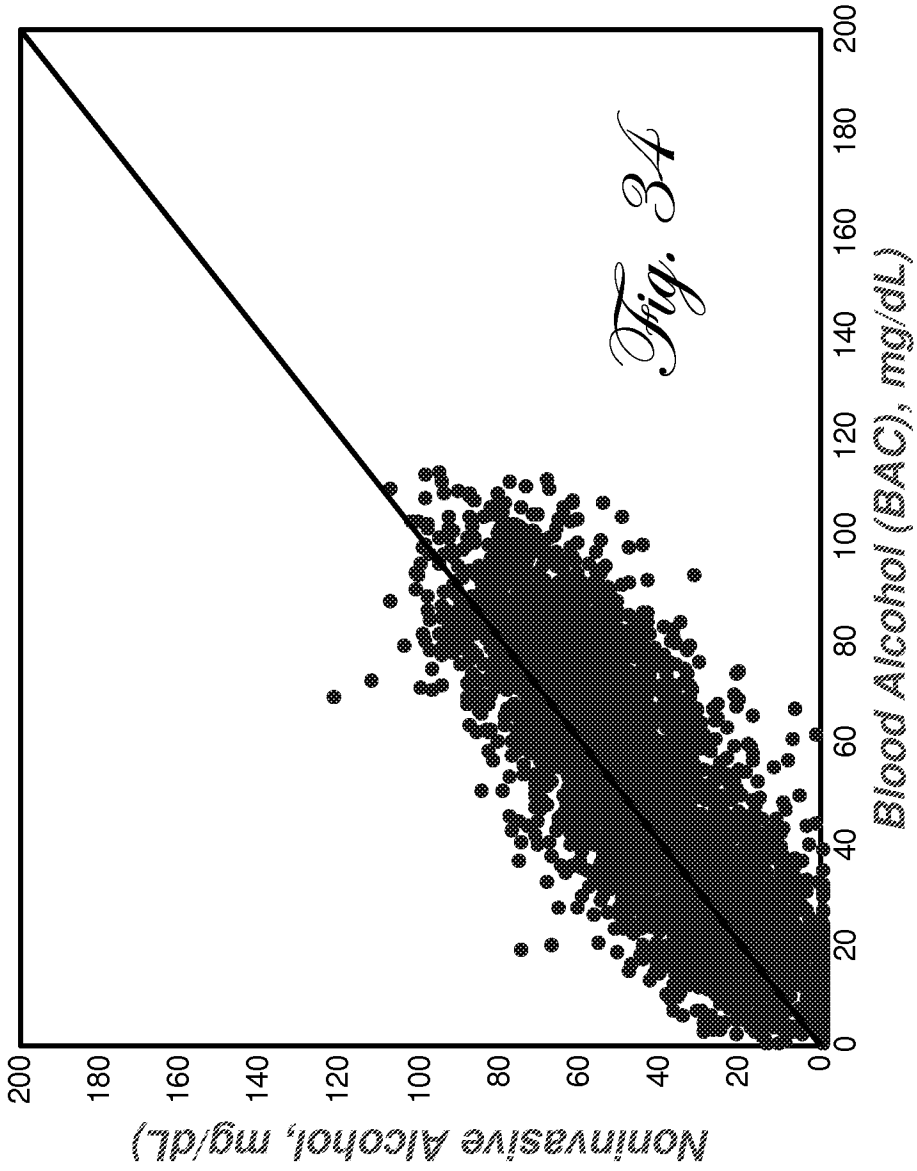

Nonintrusive Alcohol, mg/dL)
0
20
40
60
80
100
120
140
160
180
200
Blood Alcohol (BAC), mg/dL)
0
20
40
60
80
100
120
140
160
180
200

Fig. 34

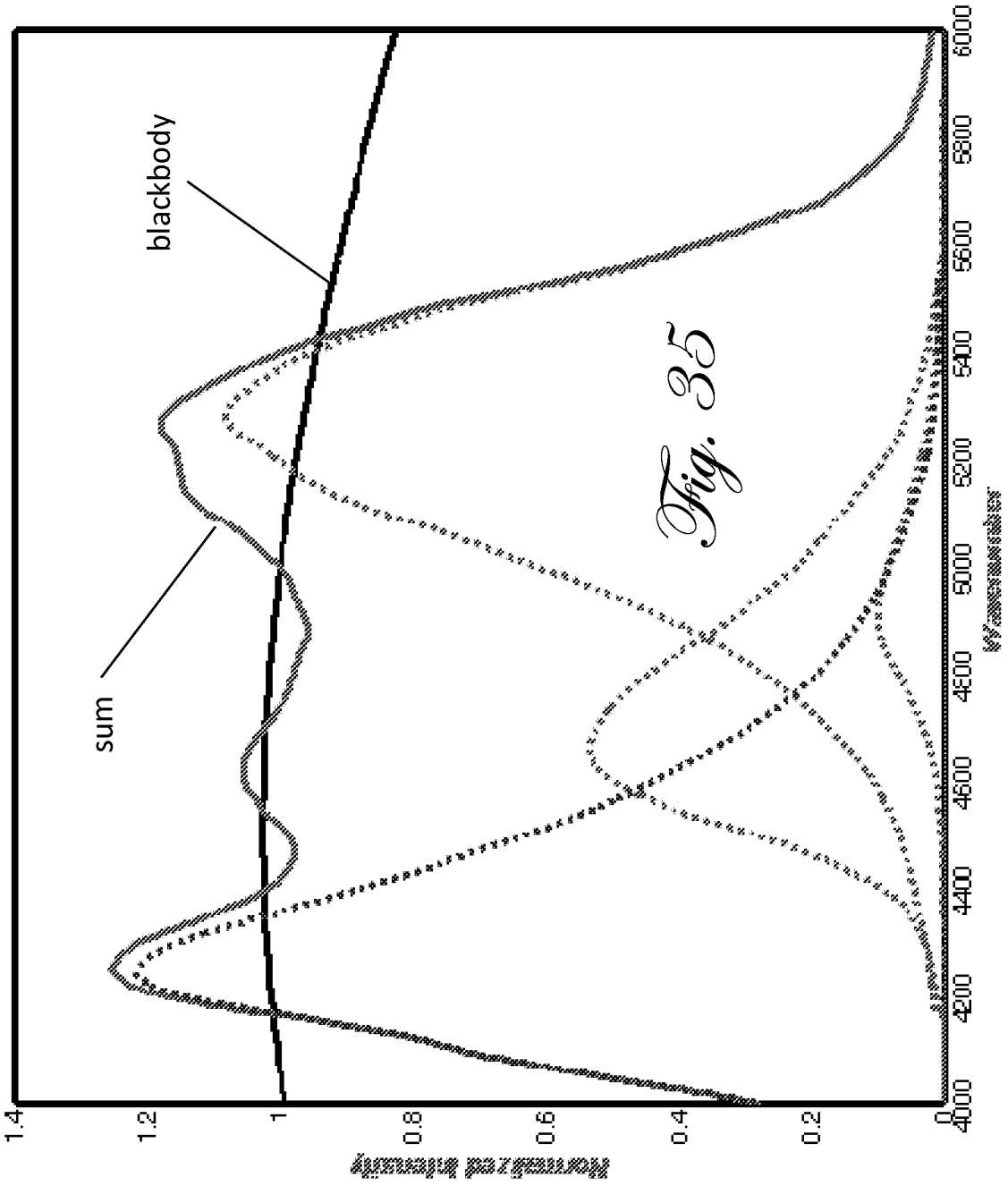

blackbody
sum
Normalized Intensity
Wavenumber
1.4
1.2
1
0.8
0.6
0.4
0.2
0
4000
4200
4400
4600
4800
5000
5200
5400
5600
5800
6000

Fig. 35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/021898

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/00 (2010.01)
USPC - 600/310
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61B 5/00 (2010.01)
USPC - 600/300, 301, 306, 309, 310, 323, 334, 336, 363

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent, Google Patent, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2007/0073118 A1 (RIDDER et al) 29 March 2007 (29.03.2007) entire document	1-10, 12-13, 16-31 ---------- 11, 14-15
Y	US 4,703,474 A (FOSCHINI et al) 27 October 1987 (27.10.1987) entire document	11
Y	US 2005/0261560 A1 (RIDDER et al) 24 November 2005 (24.11.2005) entire document	14-15

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 March 2010	23 MAR 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

专利名称(译)	用于无创测定组织中酒精的系统		
公开(公告)号	EP2389100A1	公开(公告)日	2011-11-30
申请号	EP2010733950	申请日	2010-01-23
[标]申请(专利权)人(译)	特鲁塔奇科技公司		
申请(专利权)人(译)	TRUTOUCH TECHNOLOGIES，INC.		
当前申请(专利权)人(译)	TRUTOUCH TECHNOLOGIES，INC.		
[标]发明人	RIDDER TRENT VER STEEG BEN MILLS MIKE LAAKSONEN BENTLEY		
发明人	RIDDER, TRENT VER STEEG, BEN MILLS, MIKE LAAKSONEN, BENTLEY		
IPC分类号	A61B5/00		
CPC分类号	A61B5/4845 A61B5/0075 A61B5/0088 A61B5/14546 A61B5/1455 A61B5/1495 A61B5/6826 G01J3/02 G01J3/0205 G01J3/0218 G01J3/0229 G01J3/0291 G01J3/14 G01J2003/1286 G01N21/274 G01N21/359 G01N21/474 G01N2201/129		
代理机构(译)	HART，DEBORAH MARY		
优先权	61/147107 2009-01-25 US		
其他公开文献	EP2389100A4		
外部链接	Espacenet		

摘要(译)

一种用于通过定量红外光谱法无创地确定人体组织属性的装置和方法，以达到临床相关的精确度和准确度。该系统包括经过优化的子系统，可以应对组织光谱的复杂性，高信噪比和光度精度要求，组织采样误差，校准维护问题和校准转移问题。子系统包括照明/调制子系统，组织采样子系统，校准维护子系统，FTIR光谱仪子系统，数据采集子系统和计算子系统。