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(54) **Noninvasive measurements of chemical substances**

Nichtinvasive Messungen von chemischen Substanzen

Mesures non-invasives de substances chimiques

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(56) References cited:
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Description

FIELD OF THE INVENTION

[0001] The present invention includes a contact device for mounting on a part of the body to measure bodily functions and to treat abnormal conditions indicated by the measurements.

BACKGROUND OF THE INTENTION

[0002] In relation to an embodiment of the present invention, blood is responsible not only for the transport of oxygen, food, vitamins, water, enzymes, white and red blood cells, and genetic markers, but also provides an enormous amount of information in regards to the overall health status of an individual. The prior art related to analysis of blood relies primarily on invasive methods such as with the use of needles to draw blood for further analysis and processing. Very few and extremely limited methods for non-invasive evaluating blood components are available.

[0003] In the prior art for example, oxygenated hemoglobin has been measured non-invasively. The so called pulse oximeter is based on traditional near infrared absorption spectroscopy and indirectly measures arterial blood oxygen with sensors placed over the skin utilizing LEDs emitting at two wave lengths around 940 and 660 nanometers. As the blood oxygenation changes, the ratio of the light transmitted by the two frequencies changes iridicating the amount of oxygenated hemoglobin in the arterial blood of the finger tip. The present systems are not accurate and provide only the amount of oxygenated hemoglobin in the finger tip.

[0004] The skin is a thick layer of tissue with a thick epithelium. The epithelium is the superficial layers of tissue and vary according to the organ or location in the body. The skin is thick because it is in direct contact with the environment and it is the barrier between the internal organs and the external environment. The skin is exposed and subject to all kind of noxious external agents on a daily basis. Stratified squamous keratinizing epithelium layers of the skin have a strong, virtually impermeable layer called the stratum corneum and keratin. The keratin that covers the skin is a thick layer of a hard and dead tissue which creates another strong barrier of protection against pathogenic organisms but also creates a barrier to the proper evaluation of bodily functions such as non-invasive blood analysis and cell analysis.

[0005] Another drawback in using the skin is due to the fact that the superficial layer of tissue covering the skin does not allow acquisition of important information, only present in living tissue. In addition, the other main drawback in using the skin is because the blood vessels are not easily accessible. The main vascular supply to the skin is located deep and distant from the superficial and still keratinized impermeable skin layer.

[0006] Prior art attempts to use the skin and other areas of the body to perform non-invasive blood analysis, diagnostics and evaluations of bodily functions such as oral, nasal and ear mucosa. These areas have been found to be unsuitable for such tasks. Moreover, placement of an object in oral or nasal mucosa can put the user at risk of aspiration and obstructing the airway which is a fatal event.

[0007] Another drawback in using the skin is the presence of various appendages and glands which prevent adequate measurements from being acquired such as hair, sweat glands, and sebaceous glands with continuous outflowing of sebum. Moreover, the layers of the skin vary in thickness in a random fashion. Furthermore, the layers of the skin are strongly attached to each other, making the surgical implantation of any device extremely difficult. Furthermore the skin is a highly innervated area which is highly sensitive to painful stimuli.

[0008] In order to surgically implant a device under the skin there is need for invasive application of anesthetic by injection around the area to be incised and the obvious risk of infection. Moreover, the structure of the skin creates electrical resistance and makes acquisition of electrical signals a much more difficult procedure.

[0009] Attempts to use electroosmosis as a flux enhancement by iontophoresis with increased passage of fluid through the skin with application of electrical energy, do not provide accurate or consistent signals and measurements due to the skin characteristics described above. Furthermore there is a significant delay in the signal acquisition when electroosmosis-based systems are used on the skin because of the anatomy and physiology of the skin which is thick and has low permeability.

[0010] Previously, a watch with sensing elements in apposition to the skin has been used in order to acquire a signal to measure glucose. Because of the unsuitable characteristics of the skin the watch has to actually shock the patient in order to move fluid. The fluid measured provides inconsistent, inaccurate and delayed results because of the unsuitable characteristics of the skin as described above. It is easy to see how unstable the watch is if one were to observe how much their own watch moves up and down and around one=s pulse during normal use. There is no natural stable nor consistent correct apposition of the sensor surface to the tissue, in this case the dead keratin layer of the thick skin.

[0011] Previously invasive means were used with tearing of the skin in the tip of the fingers to acquire whole blood, instead of plasma, for glucose measurement. Besides being invasive, whole blood from the fingers is used which has to be corrected for plasma levels. Plasma levels provide the most accurate evaluation of blood glucose.

[0012] The conventional way for blood analysis includes intense labor and many expenses using many steps including cumbersome, expensive and bulky laboratory equipment. A qualified medical professional is required to remove blood and this labor is certainly costly. The professionals expose themselves to the risk of ac-

quiring infections and fatal diseases such as AIDS, hepatitis, and other viral and prion diseases. In order to prevent that possible contamination a variety of expensive measures and tools are taken, but still only providing partial protection to the medical professional and the patient. A variety of materials are used such as alcohol swabs, syringes, needles, sterile vials, gloves as well as time and effort. Moreover, effort, time and money must be spent with the disposal of biohazard materials such as the disposal of the sharps and related biohazard material used to remove blood. These practices negatively affect the environment as those biohazard materials are non-degradable and obviously made of non-recycled material.

[0013] In addition, these practices comprise a painful procedure with puncturing the skin and putting the patient and nurse at risk for infection, fatal diseases, contamination, and blood borne diseases. After all of this cumbersome, costly, time-consuming and hazardous procedure, the vials with blood have to be transported by a human attendant to the laboratory which is also costly. At the laboratory the blood is placed in other machines by a trained human operator with all of the risks and costs associated with the procedure of dealing with blood.

[0014] The conventional laboratory instruments then have to separate the blood using special and expensive machines and then materials are sent for further processing and analysis by a trained human operator. Subsequent to that the result is printed and sent to the patient and/or doctor, most frequently by regular mail. All of this process in laboratories is risky, complex, cumbersome, and expensive; and this is only for one test.

[0015] If a patient is admitted to a hospital, this very laborious and expensive process could happen several times a day. Only one simple blood test result can be over $100 dollars and this cost is easily explained by the labor and materials associated with the cost related to manipulation of blood and protection against infections as described above. If four tests are needed over 24 hours, as may occur with admitted patients, the cost then can increase to $400 dollars.

[0016] The world and in particular the United States face challenging health care costs with a grim picture of rapidly rising health care expenditures with a rapid increase in the number and frequency of testing. Today, the worldwide diabetic population alone is over 125 million and is expected to reach 250 million by the year 2008. The United States spent over $140 billion dollars on diabetes alone in 1998. More frequent control of blood glucose is known to prevent complications and would substantially reduce the costs of the disease.

[0017] According to the projections by the Health Care Financing Administration of the United States Department of Health and Human Services, health care spending as a share of U.S. gross domestic product (GDP) is estimated to increase from 13 percent to potentially and amazingly close to 20% of the United States GDP in the near future, reaching over $2 trillion dollars a year, which clearly demonstrates how unwise health care spending can affect the overall economy of a nation.

[0018] The World Health Organization reported in 1995, the percentage of total spending on health by various governments clearly indicating health care costs as a serous global problem and important factor concerning the overall utilization of public money. Public spending on health by the United States government was 47%, while United Kingdom was 84%, France was 81%, Japan was 78%, Canada was 71%. Italy was 70% and Mexico was 56%.

[0019] Infrared spectroscopy is a technique based on the absorption of infrared radiation by substances with the identification of said substances according to its unique molecular oscillatory pattern depicted as specific resonance absorption peaks in the infrared region of the electromagnetic spectrum. Each chemical substance absorbs infrared radiation in a unique manner and has its own unique absorption spectra depending on its atomic and molecular arrangement and vibrational and rotational oscillatory pattern. This unique absorption spectra allows each chemical substance to basically have its own infrared spectrum, also referred as fingerprint or signature which can be used to identify each of such substances.

[0020] Radiation containing various infrared wavelengths is emitted at the substance or constituent to be measured, referred to herein as "substance of interest", in order to identify and quantify said substance according to its absorption spectra. The amount of absorption of radiation is dependent upon the concentration of said chemical substance being measured according to Beer-Lambert's Law.

[0021] When electromagnetic energy is emitted an enormous amount of interfering constituents, besides the substance of interest, are also irradiated such as skin, fat, wall of blood vessels, bone, cartilage, water, blood, hemoglobin, albumin, total protein, melanin, and various other interfering substances. Those interfering constituents and background noise such as changes in pressure and temperature of the sample irradiated drastically reduce the accuracy and precision of the measurements when using infrared spectroscopy. Those many constituents and variables including the substance of interest form then an absorption spectrum for each wavelength. The sum of the absorption for each wavelength of radiation by all of the constituents and variables generates the total absorption with said total absorption spectrum being measured at two or more wavelengths of emission.

[0022] In order then to achieve the concentration of the substance of interest, a procedure must be performed to subtract the statistical absorption spectra for each of the various intervening tissues and interfering constituents, with the exception of the substance of interest being measured. It is then assumed that all of the interfering constituents were accounted for and completely eliminated and that the remainder is the real spectra of the substance of interest. It has been very difficult to prove

this assumption in vivo as no devices or methods in the prior art have yet shown to be clinically useful.

[0023] In the prior art the interfering constituents and variables introduce significant source of errors which are particularly critical since the background noise as found in the prior art tremendously exceeds the signal of the substance of interest which is found in minimal concentrations relative to the whole sample irradiated. Furthermore, in the prior art, the absorption of a solute such as glucose is very small compared to the other various interfering constituents which leads to many statistical errors preventing the accurate statistical measurement of glucose concentration. A variety of other techniques using infrared devices and methods have been described but all of them suffer from the same limitation due to the great amount of interference and noise.

[0024] Other techniques based on comparison with a known reference signal as with phase sensitive techniques have also the same limitations and drawbacks due to the great number of interfering constituents and generation of only a very weak signal. The interfering constituents are source of many artifacts, errors, and variability which leads to inadequate signal and severe reduction of the signal to noise ratio. Besides, calculation errors are common because of the many interfering substances and because the spectra of interfering constituents can overlap with the spectra of the substance of the interest being measured. If adequate signal to noise can be achieved, infrared spectroscopy should be able to provide a clinically useful device and determine the concentration of the substance of interest precisely and accurately.

[0025] Attempts in the prior art using infrared spectroscopy for noninvasive measurement of chemical substances have failed to accurately and precisely measure chemical substances such as for example glucose. The prior art have used transcutaneous optical means, primarily using the skin non-invasively, to determine the concentration of chemical substances. The prior art has also used invasive means with implant of sensors inside blood vessels or around the blood vessels. The prior art used polarized light directed at the aqueous humor of the eye, which is located inside the eye, in an attempt to measure glucose in said aqueous humor. However, precise measurements are very difficult to achieve particularly when there is substantial background noise and minimal concentration of the substance of interest as it occurs in the aqueous humor of the eye. Besides, polarized light techniques as used in the aqueous humor of the eye can only generate a very weak signal and there is low concentration of the solute in the aqueous sample. The combination of those factors and presence of interfering constituents and variables prevent accurate measurements to be achieved when using the aqueous humor of the eye.

[0026] The most frequent optical approaches in the prior art were based on measuring chemical substances using the skin. Other techniques include measuring substances in whole blood in the blood vessel (either non-invasively transcutaneously or invasively around or inside the blood vessel). Yet attempts were made to measure substances present in interstitial fluid with devices implanted under the skin. Attempts were also made by the prior art using the oral mucosa and tongue.

[0027] Mucosal surfaces such as the oral mucosa are made to stand long wear and tear as occurs during mastication. If the oral mucosa or tongue lining were thin with exposed vessels, one would easily bleed during chewing. Thus, those areas have rather thick lining and without plasma leakage. Furthermore these mucosal areas have no natural means for apposition of a sensor such as a natural pocket formation.

[0028] Since there is still a low signal with an enormous amount of interfering constituents, useful devices using the oral mucosal, tongue, and other mucosa such as genito-urinary and gastrointestinal have not been developed. The prior art also attempted to measure glucose using far infrared thermal emission from the body, but a clinically useful device has not been developed due to the presence of interfering elements and great thermal instability of the sample. Near infrared spectroscopy and far-infrared techniques have been tried by the prior art as means to non-invasively measure glucose, but accuracy and precision for clinical application has not been achieved.

[0029] Therefore remains a need to provide a method and apparatus capable of delivering a higher signal to noise by reducing or eliminating interfering constituents, noise, and other variables, which will ultimately provide the accuracy and precision needed for useful clinical application.

[0030] WO 9307801 discloses method and apparatus for determining non-invasively the presence and/or concentration of blood analytes such as glucose in an animal, particularly a human animal. The apparatus comprises a light source for producing a polychromatic light beam and means for modulating the polychromatic light beam such that the modulation frequency is dependent upon the wavelength of light within the beam. The modulated light beam is caused to impinge upon a body part, preferably the front surface of the eye of the animal so that blood analytes interact with the light beam and perturb the spectral distribution of light within the beam. Spectral information is extracted from the resulting light beam by detecting the beam at a plurality of modulation frequencies. The measurements may be linked to pulse measurements in a manner similar to pulse oximetry. The light beam may also be used to heat the body part to a desired temperature. A moulding locates the light source and detector in a fixed location with respect to facial features of the animal. Various methods, including the use of polarisers and CCD detector arrays, are proposed to minimise the effect of specular reflection.

[0031] US5,313,941 discloses a method and apparatus for monitoring glucose, ethyl alcohol and other blood constituents in a noninvasive manner. The measure-

ments are made by monitoring infrared absorption of the desired blood constituent in the long infrared wavelength range where the blood constituent has a strong and distinguishable absorption spectrum. The long wavelength infrared energy is passed through a finger or other vascularized appendage and the measurement made. To prevent the high energy source from burning or causing patient discomfort, only short bursts or pulses of energy are sent through the finger with a very low duty cycle and low optical bandwidth. The bursts are further synchronized with systole and diastole of the cardiac cycle so that only two pulses are sent per heart beat, one during diastole and one during systole. The detection signals measured during application of these bursts of energy are then used to calculate the concentration of the blood constituents in accordance with a polynomial equation.

SUMMARY OF THE INVENTION

[0032] The invention provides apparatus and method as set out in the independent claims, with preferred aspects set out in dependent claims.

[0033] The tear fluid proves to be the most reliable location and indicator of the concentration of chemicals, both organic and inorganic, but other areas of the eye can be utilized to measure the concentration of chemicals. The tear fluid and surface of the eye are the preferred location for these measurements because the tear film and aqueous humor (which can be transmitted through the intact cornea) can be considered an ultrafiltrate of the plasma.

[0034] The apparatus and method of the present invention allows the least traumatic way of measuring chemicals in the body without the need of needle stick and the manipulation of blood. For instance, this may be particularly important as compared to drawing blood from infants because the results provided by the drawn blood sample may not be accurate. There is a dramatic change in oxygen and carbon dioxide levels because of crying, breath holding and even apnea spells that occur during the process of restraining the baby and drawing blood. Naturally, the ability to painlessly measure blood components without puncturing the vessel is beneficial also to any adult who needs a blood work-up, patients with diabetes who need to check their glucose level on a daily basis, and health care workers who would be less exposed to severe diseases such as AIDS and hepatitis when manipulating blood. Patients in intensive care units would benefit by having a continuous painless monitoring of electrolytes, gases, and so on by non-invasive means using the intelligent contact lens system. Moreover, there is no time wasted transporting the blood sample to the laboratory, the data is available immediately and continuously.

[0035] The different amounts of eye fluid encountered in the eye can be easily quantified and the concentration of substances calibrated according to the amount of fluid in the eye. The relationship between the concentration of chemical substances and molecules in the blood and the amount of said chemical substances in the tear fluid can be described mathematically and programmed in a computer since the tear film can be considered an ultrafiltrate ofthe plasma and diffusion of chemicals from capillaries on the surface of the eye have a direct correspondence to the concentration in the blood stream.

[0036] Furthermore, when the eyes are closed there is an equilibrium between the aqueous humor and the tear fluid allowing measurement of glucose in a steady state and since the device can send signals through the intervening eyelid, the glucose can be continuously monitored in this steady state condition. Optical sensors mounted in the contact device can evaluate oxygen and other gases in tissues and can be used to detect the concentration of compounds in the surface of the eye and thus not necessarily have to use the tear film to measure the concentration of said substances. In all instances, the signals can be preferably radio transmitted to a monitoring station. Optical, acoustic, electromagnetic, microelectromechanical systems and the like can be mounted in the contact device and allow the measurement of blood components in the tear film, surface of the eye, conjunctival vessels, aqueous humor, vitreous, and other intraocular and extraocular structures.

[0037] The contact device preferably includes a rigid or flexible annular member in which a transensor is mounted in the device. The transensor is positioned in a way to allow passage of light through the visual axis. The annular member preferably includes an inner concave surface shaped to match an outer surface of the eye and having one or more holes defined therein in which transensors are mounted. It is understood that the contact device conforms in general shape to the surface of the eye with its dimensions and size chosen to achieve optimal comfort level and tolerance. It is also understood that the curvature and shape of the contact device is chosen to intimately and accurately fit the contact device to the surface of the eye for optimization of sensor function. The surface of the contact device can be porous or microporous as well as with mircro-protuberances on the surface. It is also understood that fenestrations can be made in the contact device in order to allow better oxygenation of the cornea when the device is worn for a long period of time. It is also understood that the shape of the contact device may include a ring-like or band-like shape without any material covering the cornea. It is also understood that the contact device may have a base down prism or truncated edge for better centration. It is also understood that the contact device preferably has a myoflange or a minus carrier when a conventional contact lens configuration is used. It is also understood that an eliptical, half moon shape or the like can be used for placement under the eyelid. It is understood that the contact device can be made with soft of hard material according to the application needed. It is also understood that an oversized corneal scleral lens covering the whole anterior surface of the eye can be used as well as hour-

glass shaped lenses and the like. It is understood also that the external surface of the contact device can be made with polymers which increases adherence to tissues or coating which increases friction and adherence to tissues in order to optimize fluid passage to sensors when measuring chemical components. It is understood that the different embodiments which are used under the eyelids are shaped to fit beneath the upper and/or eyelids as well as to fit the upper or lower cul-de-sac.

[0038] The transensor may consist of a passive or active radio frequency emitter, or a miniature sonic resonator, and the like which can be coupled with miniature microprocessor mounted in the contact device. The transensors mounted in the contact device can be remotely driven by ultrasonic waves or alternatively remotely powered by electromagnetic waves or by incident light. They can also be powered by microminiature low voltage batteries which are inserted into the contact device.

[0039] As mentioned, preferably the data is transmitted utilizing radio waves, sound waves, light waves, by wire, or by telephone lines. The described techniques can be easily extrapolated to other transmission systems. The transmitter mounted in the contact device can use the transmission links to interconnect to remote monitoring sites. The changes in voltage or voltage level are proportional to the values of the biological variables and this amplified physiologic data signal from the transducers may be frequency modulated and then transmitted to a remote external reception unit which demodulates and reconstitutes the transmitted frequency modulated data signal preferably followed by a low pass filter with the regeneration of an analog data signal with subsequent tracing on a strip-chart recorder.

[0040] The apparatus of the invention can also utilize a retransmiter in order to minimize electronic components and size of the circuit housed in the contact device. The signal from a weak transmitter can be retransmitted to a greater distance by an external booster transmitter carried by the subject or placed nearby. It is understood that a variety of noise destruction methods can be used in the apparatus of the invention.

[0041] Since the apparatus of the invention utilizes externally placed elements on the surface of the eye that can be easily retrieved, there is no tissue damage due to long term implantation and if drift occurs it is possible to recalibrate the device. There are a variety of formats that can be used in the apparatus of the invention in which biologic data can be encoded and transmitted. The type of format for a given application is done according to power requirement, circuit complexity, dimensions and the type of biologic data to be transmitted. The general layout of the apparatus preferably includes an information source with a variety of biological variables, a transducer, a multiplexer, a transmitter, a transmission path and a transmission medium through which the data is transmitted preferably as a coded and modulated signal.

[0042] The apparatus of the invention preferably includes a receiver which receives the coded and modulated signal, an amplifier and low pass filter, a demultiplexer, a data processing device, a display and recording equipment, and preferably an information receiver, a CPU, a modem, and telephone connection. A microprocessor unit containing an autodialing telephone modem which automatically transmits the data over the public telephone network to a hospital based computer system can be used. It is understood that the system may accept digitally coded information or analog data.

[0043] When a radio link is used, the contact device houses a radio frequency transmitter which sends the biosignals to a receiver located nearby with the signals being processed and digitized for storage and analysis by microcomputer systems. When the apparatus of the invention transmits data using a radio link, a frequency carrier can be modulated by a subcarrier in a variety of ways: amplitude modulation (AM), frequency modulation (FM), and code modulation (CM). The subcarriers can be modulated in a variety of ways which includes AM, FM, pulse amplitude modulation (PAM), pulse duration modulation (PDM), pulse position modulation (PPM), pulse code moduation (PCM), delta modulation (DM), and the like.

[0044] It is understood that the ICL structure and the transducer/transmitter housing are made of material preferably transparent to radio waves and the electronic components coated with materials impermeable to fluids and salts and the whole unit encased in a biocompatable material. The electronics, sensors, and battery (whenever an active system is used), are housed in the contact device and are hermetically sealed against fluid penetration. It is understood that sensors and suitable electrodes such as for sensing chemicals, pH and the like, will be in direct contact with the tear fluid or the surface of the eye. It is also understood that said sensors, electrodes and the like may be covered with suitable permeable membranes according to the application needed. The circuitry and electronics may be encased in wax such as beeswax or paraffin which is not permeable to body fluid. It is understood that other materials can be used as a moisture barrier. It is also understood that various methods and materials can be used as long as there is minimal frequency attenuation, insulation, and biocompatibility. The components are further encased by biocompatible materials as the ones used in conventional contact lenses such as Hydrogel, silicone, flexible acrylic, sylastic, or the like.

[0045] The transmitter, sensors, and other components can be mounted and/or attached to the contact device using any known attachment techniques, such as gluing, heat-bonding, and the like. The intelligent contact lens can use a modular construction in its assembly as to allow tailoring the number of components by simply adding previously constructed systems to the contact device.

[0046] It is understood that the transmission of data can be accomplished using preferably radio link, but oth-

er means can also be used. The choice of which energy form to be used by the ICL depends on the transmission medium and distance, channel requirement, size of transmitter equipment and the like. It is understood that the transmission of data from the contact device by wire can be used but has the disadvantage of incomplete freedom from attached wires. However, the connection of sensors by wires to externally placed electronics, amplifiers, and the like allows housing of larger sensors in the contact device when the application requires as well as the reduction of mechanical and electrical connections in the contact device. The transmission of data by wire can be an important alternative when there is congested space due to sensors and electronics in the contact device. It is understood that the transmission of data in water from the contact device can be preferably accomplished using sound energy with a receiver preferably using a hydrophone crystal followed by conventional audio frequency FM decoding.

[0047] It is also understood that the transmission of data from the contact device can be accomplished by light energy as an alternative to radio frequency radiation. Optical transmission of signals using all sorts of light such as visible, infrared, and ultraviolet can be used as a carrier for the transmission of data preferably using infrared light as the carrier for the transmission system. An LED can be mounted in the contact device and transmit modulated signals to remotely placed receivers with the light emitted from the LED being modulated by the signal. When using this embodiment, the contact device in the receiver unit has the following components: a built in infrared light emitter (950 nm), an infrared detector, decoder, display, and CPU. Prior to transmission, the physiologic variables found on the eye or tear fluid are multiplexed and encoded by pulse interval modulation, pulse frequency modulation, or the like. The infrared transmitter then emits short duration pulses which are sensed by a remotely placed photodiode in the infrared detector which is subsequently decoded, processed, and recorded. The light transmitted from the LED is received at the optical receiver and transformed into electrical signals with subsequent regeneration of the biosignals. Infrared light is reflected quite well including surfaces that do not reflect visible light and can be used in the transmission of physiological variables and position/motion measurement. This embodiment is particularly useful when there is limitations in bandwidth as in radio transmission. Furthermore, this embodiment may be quite useful with closed eyes since the light can be transmitted through the skin of the eyelid.

[0048] It is also understood that the transmission of data from the contact device can be accomplished by the use of sound and ultrasound being the preferred way of transmission underwater since sound is less strongly attenuated by water than radio waves. The information is transmitted using modulated sound signals with the sound waves being transmitted to a remote receiver. There is a relatively high absorption of ultrasonic energy by living tissues, but since the eye even when closed has a rather thin intervening tissue the frequency of the ultrasonic energy is not restricted. However, soundwaves are not the preferred embodiment since they can take different paths from their source to a receiver with multiple reflections that can alter the final signal. Furthermore, it is difficult to transmit rapidly changing biological variables because of the relatively low velocity of sound as compared to electromagnetic radiation. It is possible though to easily mount an ultrasonic endoradiosonde in the contact device such as for transmitting pH values or temperature. An ultrasonic booster transmitter located nearby or carried by the subject can be used to transmit the signal at a higher power level. An acoustic tag with a magnetic compass sensor can be used with the information acoustically telemetered to a sector scanning sonar.

[0049] A preferred embodiment of the invention consists of electrodes, FM transmitter, and a power supply mounted in the contact device. Stainless steel micro cables are used to connect the electronics to the transducers to the battery power supply. A variety of amplifiers and FM transmitters including Colpitts oscillator, crystal oscillators and other oscillators preferably utilizing a custom integrated circuit approach with ultra density circuitry can be used in the apparatus of the invention.

[0050] Several variables can be simultaneously transmitted using different frequencies using several transmitters housed in the contact device. Alternatively, a single transmitter (3 channel transmitter) can transmit combined voltages to a receiver, with the signal being subsequently decoded, separated into three parts, filtered and regenerated as the three original voltages (different variables such as glucose level, pressure and temperature). A multiple channel system incorporating all signal processing on a single integrated circuit minimizes interconnections and can be preferably mounted in the apparatus of the invention when multiple simultaneous signal transmission is needed such as transmitting the level of glucose, temperature, bioelectrical, and pressure. A single-chip processor can be combined with a logic chip to also form a multichannel system for the apparatus of the invention allowing measurement of several parameters as well as activation of transducers.

[0051] It is understood that a variety of passive, active, and inductive power sources can be used in the apparatus of the invention. The power supply may consist of micro batteries, inductive power link, energy from biological sources, nuclear cells, micro power units, fuel cells which use glucose and oxygen as energy sources, and the like. The type of power source is chosen according to the biological or biophysical event to be transmitted.

[0052] A variety of signal receivers can be used such a frame aerial connected to a conventional FM receiver from which the signal is amplified decoded and processed. Custom integrated circuits will provide the signal processing needed to evaluate the parameters transmitted such as temperature, pressure flow dimensions, bioelectrical activity, concentration of chemical species and

the like. The micro transducers, signal processing electronics, transmitters and power source can be built in the contact device.

[0053] Power for the system may be supplied from a power cell activated by a micropower control switch contained in the contact device or can be remotely activated by radio frequency means, magnetic means and the like. Inductive radio frequency powered telemetry in which the same coil system used to transfer energy is used for the transmission of data signal can be used in the apparatus of the invention. The size of the system relates primarily to the size of the batteries and the transmitter. The size ofconventional telemetry systems are proportional to the size of the batteries because most of the volume is occupied by batteries. The size of the transmitter is related to the operating frequency with low frequencies requiring larger components than higher frequency circuits. Radiation at high frequencies are more attenuated than lower frequencies by body tissues. Thus a variety of systems implanted inside the body requires lower frequency devices and consequently larger size components in order for the signal to be less atenuated. Since the apparatus of the invention is placed on the surface of the eye there is little to no attenuation of signals and thus higher frequency small devices can be used. Furthermore, very small batteries can be used since the contact device can be easily retrieved and easily replaced. The large volume occupied by batteries and power sources in conventional radio telemetry implantable devices can be extremely reduced since the apparatus of the invention is placed externally on the eye and is of easy access and retrieval, and thus a very small battery can be utilized and replaced whenever needed.

[0054] A variety of system assemblies can be used but the densest system assembly is preferred such as a hybrid assembly of custom integrated circuits which permits realization of the signal processing needed for the applications. The typical resolution of such circuits are in the order of a few microns and can be easily mounted in the contact device. A variety of parameters can be measured with one integrated circuit which translates the signals preferably into a transmission bandwidth. Furthermore, a variety of additional electronics and a complementary metal oxide semiconductor (CMOS) chip can be mounted in the apparatus of the invention for further signal processing and transmission.

[0055] The micropower integrated circuits can be utilized with a variety of transmitter modalities mounted in the intelligent contact lens including radio links, ultrasonic link and the like. A variety of other integrated circuits can be mounted in the contact device such as signal processors for pressure and temperature, power switches for external control of implanted electronics and the like. Pressure transducers such as a capacitive pressure transducer with integral electronics for signal processing can be incorporated in the same silicon structure and can be mounted in the contact device. Evolving semiconductor technology and more sophisticated encoding methods as well as microminiature integrated circuits amplifiers and receivers are expected to occur and can be housed in the contact device. It is understood that a variety of transmitters, receivers, and antennas for transmitting and receiving signals in telemetry can be used in the apparatus of the invention, and housed in the contact device and/or placed remotely for receiving, processing, and analyzing the signal.

[0056] The fluid present on the front surface of the eye covering the conjunctiva and cornea is referred as the tear film or tear fluid. Close to 100% of the tear film is produced by the lacrimal gland and secreted at a rate of 2 μl/min. The volume of the tear fluid is approximately 10 μl. The layer of tear fluid covering the cornea is about 8-10 μm in thickness and the tear fluid covering the conjunctiva is about 15μm thick. The pre-corneal tear film consists of three layers: a thin lipid layer measuring about 0.1μm consisting of the air tear interface, a mucin layer measuring 0.03μm which is in direct contact with the corneal epithelium, and finally the remaining layer is the thick aqueous layer which is located between the lipid and mucin layer. The aqueous layer is primarily derived from the secretions of the lacrimal gland and its chemical composition is very similar to diluted blood with a reduced protein content and slightly greater osmotic pressure. The secretion and flow of tear fluid from the lacrimal gland located in the supero-temporal quadrant with the subsequent exit through the lacrimal puncta located in the infero-medial quadrant creates a continuous flow of tear fluid providing the ideal situation by furnishing a continuous supply of substrate for one of the stoichiometric reactions which is the subject of a preferred embodiment for evaluation of glucose levels. The main component of the tear fluid is the aqueous layer which is an ultrafiltrate of blood containing electrolytes such as sodium, potassium, chloride, bicarbonate, calcium, and magnesium as well as amino acids, proteins, enzymes, DNA, lipids, cholesterol, glycoproteins, immunoglobulins, vitamins, minerals and hormones. Moreover, the aqueous layer also holds critical metabolites such as glucose, urea, catecholamines, and lactate, as well as gases such as oxygen and carbon dioxide. Furthermore, any exogenous substances found in the blood stream such as drugs, radioactive compounds and the like are present in the tear fluid.

[0057] It is also understood that the sensors can be placed on any location on the surface of the eye to measure glucose and other chemical compounds. Besides the conventional circular shape of contact lenses, the shape of the contact device also includes a flat rectangular configuration, ring like or half moon like which are used for applications that require placement under the palpebral conjunctiva or cul-de-sac of the eye.

[0058] It is understood that any electrochemical sensor, thermoelectric sensors, acoustic sensors, piezoelectric sensors, optical sensors, and the like can be mounted in the contact device and placed on the surface of the eye for detection and measurement of blood com-

ponents and physical parameters found in the eye with signals preferably transmitted to a remote station. It is understood that electrochemical sensors using amperometric, potentiometric, conductometric, gravimetric, impedimetric, systems, and the like can be used in the apparatus of the invention for detection and measurement of blood components and physical parameters found in the eye with signals preferably transmitted to a remote station.

[0059] Some preferable ways have been described; however, any other miniature radio transmitters can be used and mounted in the contact device and any microminiature sensor that modulates a radio transmitter and send the signal to a nearby radio receiver can be used. Other microminiature devices capable of modulating an ultrasound device, or infrared and laser emitters, and the like can be mounted in the contact device and used for signal detection and transmission to a remote station. A variety of methods and techniques and devices for gaining and transmitting information from the eye to a remote receiver can be used in the apparatus of the invention.

[0060] It is an object of the present invention to provide an apparatus and method for the non-invasive measurement and evaluation of blood components.

[0061] It is also an object of the present invention to provide an intelligent contact lens system capable of receiving, processing, and transmitting signals such as electromagnetic waves, radio waves, infrared and the like being preferably transmitted to a remote station for signal processing and analysis, with transensors and biossensors mounted in the contact device.

[0062] It is a further object of the present invention to detect physical changes that occur in the eye, preferably using optical emitters and sensors.

[0063] It is a further object of the present invention to provide a novel drug delivery system for the treatment of eye and systemic diseases.

[0064] The above and other objects and advantages will become more readily apparent when reference is made to the following description taken in conjunction with the accompanying drawings.

[0065] The preferred way for evaluation of bodily functions such as diagnostics and non-invasive blood analysis according to the present invention includes placing an intelligent contact lens on the highly vascularized conjunctiva. By the present invention it has been discovered that the surface of the eye and surrounding tissues, in particular the conjunctiva, is the ideal place for diagnostic studies, non-invasive blood analysis, and health status evaluation. This area provides all of the requirements needed for such diagnostics and evaluations including the presence of superficially located fenestrated blood vessels. This is the only area in the body which allows the undisturbed direct view of blood vessels in their natural state. The present invention allows fluid and cell evaluation and diagnostics to be naturally done using the normal physiology of the eye and conjunctiva.

[0066] The fenestrated blood vessels in the conjunctiva are superficially located and leak plasma. Fenestrated blood vessels have pores and/or openings in the vessel wall allowing free flow of fluid through its vessel walls.

[0067] According to the principles of the invention, the surface of the eye and the conjunctiva and surrounding tissues provides the ideal location in the human body for non-invasive analysis and other fluid and cellular diagnostics and the preferred way for evaluation of bodily functions and non-invasive blood analysis. The conjunctiva is the extremely thin continuous membrane which covers the anterior portion of the eye and eye lid and ends in the limbus at the junction with the cornea and at the junction ofthe akin ofthe eye lid The conjunctiva is a thin transparent membrane that covers the white of the eye as the bulbar conjunctiva and lines the eye lids as the palpebral conjunctiva. The conjunctiva has a vast network of blood vessels and lies on a second network of blood vessels on the episclera. The episcleral network is much less voluminous than the conjunctival vessel network.

[0068] The epithelium of the conjunctiva is a stratified columnar epithelium made up of only three or less layers of cells, and the middle layer (polygonal cells) is absent in most of the palpebral conjunctiva. Physiologic, anatomic and *in-vitro* studies by the inventor demonstrated that the blood vessels in the conjunctiva are fenestrated, meaninghave pores, and leak plasma to the surface of the eye and that this plasma can be evaluated when a device is placed in contact with the conjunctiva. The sensing device can be held by any part of the eye lids, partially when the device is not placed in the cul-de-sac or totally when the sensing device is placed in the conjunctival pocket under the eye lid (lower or upper cul-de-sac).

[0069] Unlike other tissues covering the body the conjunctiva has a vast network of blood vessels which are superficially located and easily accessible. This can be seen by pulling down the lower eye lid and looking at the red tissue with the actual blood vessels being visualized. Those blood vessels and thin membrane are protected by the eye lid and the palpebral conjunctiva is normally hidden behind the eye lids. The blood vessels are in close proximity to the surface and the redness in the tissue is due to the presence of the vast network of superficial blood vessels. This area of the body allows the undisturbed direct view of the blood vessels. Besides the fact that the blood vessels have thin walls and are superficially located, those vessels have a very important and peculiar feature - fenestration with continuous leakage of plasma to the surface of the eye. The plasma continuously leaks from the conjunctival blood vessels, and since they are superficially located, only a few micrometers have to be traveled by this fluid to reach the surface of the eye, with the fluid being then acquired by the diagnostic system of the intelligent contact lens of the present invention in apposition to the tissue surface.

[0070] Besides the presence of such superficial and fenestrated vessels, the conjunctiva, contrary to the skin, has a thin epithelium with no keratin which makes acqui-

sition of signals a much easier process. Moreover, the conjunctiva has little electrical resistance due to the lack of a significant lipid layer as found in the skin such as the stratum corneum with a good rate of permeation of substances.

[0071] It is important to note that the acquisition of the signal as disclosed by the invention involves a natural occurrence in which the eye lid and surrounding ocular structures hold the sensing device in direct apposition to the conjunctiva. The simple apposition of the intelligent contact lens to the conjunctiva can create a stimuli for flow toward the sensor and the eye lid; muscular function works as a natural pump. Furthermore, the lack of keratin in the conjunctiva also eliminates a critical barrier creating the most suitable place for evaluation of bodily functions and non-invasive cell analysis with epithelial, white blood cells, and the like being naturally or artificially pumped into the intelligent contact lens for analysis.

[0072] The contact lens according to the principles of the present invention provides the ideal structure which is stable, continuous and correctly positioned against the tissue, in this case the living thin superficial layer of the thin conjunctiva of the eye. The eye lids provide the only natural and superficial means in the body for sensor apposition to the tissues being evaluated without the need for other supporting systems creating a perfect, continuous and undisturbed natural and physiologic contact between the sensing devices and tissues due to the natural anatomy and tension present in the cul-de-sac of the eye lids.

[0073] The natural pocket that is formed by the eye lids provides the ideal location for the undisturbed placement of sensing devices such as the intelligent contact lens of the present invention. Besides providing an undisturbed place for sensor placement and apposition, the natural eye lid pocket provides a place that is out of sight allowing a more desirable cosmetic appearance in which no hardware is exposed or visible to another person.

[0074] The eye lids are completely internally covered by the conjunctiva allowing a vast double surface, both anterior and posterior surface, to be used as an area to acquire signals for chemicals, protein and cell evaluation. Furthermore and of vital importance is the fact that the eye lid is also the only place in the body that work as a natural pump of fluid to sensing devices.

[0075] The eye lid creates a natural pump effect with a force of 25,000 dynes. The force generated by the eye lids is used by the present invention to move fluids and cells toward sensing devices and works as the only natural enhancer to increase fluid transport and cell motion toward a sensing device. The pumping and/or tension effect by the eye lid allows the fluid or cells to more rapidly reach and permeate the sensor surface.

[0076] The presence of the intelligent contact lens against the conjunctiva in the conjunctival pocket creates physiologic changes which increases flow and permeation of fluid flux towards the sensor. The lens can be made irregular which creates friction against the thin and loosely arranged cell layers of the conjunctiva providing a further increase of flow of fluid and cells to the sensor. Since the blood vessels in the conjunctiva are fenestrated and superficial the fluid flows freely from the vessels to the surface. This rate of flow can be enhanced by the presence of the lens and the friction that is created between lens surface and conjunctiva due to the tension and muscular activity present in the eye lid. The free flow of fluid associated with the natural pump action of the eye lid moves fluid toward the intelligent contact lens which can be used to store such fluid and cells for immediate or later processing.

[0077] When the later processing method is used, the partial or complete intelligent contact lens is removed from the eye for further evaluation. A variety of ionization storage areas can be housed in the intelligent contact lens with the flow of fluid being continuously carried out by the eye lid pumping action. Furthermore, the conjunctiva provides a large area for housing the diagnostic systems of the intelligent contact lens with its microchips, microsensors, and hardware for signal acquisition, evaluation, processing and transmission. There is a surprising amount of space in the conjunctiva and its natural pockets under the eye lid in each eye. An average of 16 square centimeters of conjunctival area in the human eye allows enough area for housing the necessary lens hardware including two natural large pocket formations under the lower and upper eye lid. Since the superficial layer of the conjunctiva is a living tissue, contrary to the skin which is dead tissue, a variety of materials can be used in the lens to create the apposition needed by combining hydrophilic and hydrophobic biocompatible material lens surfaces such as hydroxyethylmethacrylate and silicone which allow precise balance of material to create the apposition and isolation from contaminants while even creating a suction cup effect to increase fluid flow.

[0078] An exemplary housing of the intelligent contact lens can consist of a surrounding silicone surface which creates adherence around the sensor surface and thus prevents contaminants to reach the sensor. The fluid or cells to be evaluated are then kept isolated from the remaining environment of the eye and any potential contaminant The remaining portion of the contact lens can be made with hydrogel such as hydroxyethylmethacrylate which is physiologic for the eye. It is understood that a variety of lens materials presently used for or later developed for contact lenses can be used as housing material. Any other new materials used in conventional contact lenses or intraocular lenses can be used as the housing for the diagnostic systems of the intelligent contact lens of the present invention. Moreover since the diagnostic intelligent contact lens is preferably placed in the cul-de-sac or conjunctival pocket, there is no problem with oxygen transmissibility and corneal swelling as occurs with contact lenses placed on the cornea.

[0079] Contact lenses placed on the cornea generally cause hypoxic stress leading to corneal swelling when said contact lenses are worn for extended periods of time.

The conjunctiva is highly vascularized with internal supply of oxygen allowing extended wear of the contact lenses placed in the conjunctival pocket. Contrary to that, the cornea is avascular and requires external supply of oxygen to meet its metabolic needs.

[0080] Therefore, preferably, by utilizing a natural physiologic action in which there is continuous free flow of fluid through blood vessels associated with the continuous tension effect by the lid and a thin permeable tissue layer such as the conjunctival epithelium, the system of the invention is capable of providing continuous measurement of fluids allowing the creation of a continuous feed-back system. The intelligent contact lens as described can have magnetic and/or electric elements which are actuated by electrical force or external magnetic forces in order to enhance the performance and/or augment the functions of the system. The dimensions and design for the lens are made in order to optimize function, comfort, and cosmesis. For example, a length of less than 4 mm and a height of less than 7mm for the lower pocket and less than 10 mm for the upper pocket may be used. A thickness of less than 2.5 mm, and preferably less than 1.0 mm, would be used. The diagnostic systems of the intelligent contact lens of the present invention is referred to herein as any ICL which is primarily used for fluid, chemicals, proteins, molecular or cell diagnosis and the like.

[0081] It is important to note that previously, after removing blood from a patient, major laboratory analysis was required consisting of the separation of blood components to acquire plasma. In the case of the conjunctiva and the eye, according to the principles of the invention, the body itself deliver the plasma already separated for measurement and freely flowing to the ICL sensing device externally or infernally (surgically) placed. To further create the perfect location for evaluation of bodily functions, the conjunctival area is poorly innervated which allows placement of the ICL in the conjunctival sac for long periods of time with no sensation of discomfort by the user. There are only few pain fibers, but no pressure fibers in the conjunctiva. Furthermore, as mentioned, there is a vast amount of space under the lids allowing multiple sensing devices and other hardware to be placed in the conjunctival area.

[0082] To further provide the perfect location for measurements of fluid and cells, the sensing device can be held in place by the eye lid creating the perfect apposition between the surface of the eye and the ICL sensor. Since the blood vessels are superficially located, only a few micrometers have to be traveled by the fluid to reach the surface of the eye, with the fluid being then acquired by the ICL in apposition to the tissue surface. No other organ has the advantage of the natural pocket of the eye lid to secure a sensor in position and apposition naturally without need of other devices or external forces. A combination of a hydrophobic and a hydrophilic surface of the ICL housing creates the stability that is needed for the ICL to remain in any type of apposition to the conjunctival surface, meaning more tightly adherent or less adherent to the conjunctival surface according to the evaluation being carried out. To further create the prefect environment for evaluation of blood components, the eye lid during blinking or closure, creates a pump effect which is an adjunctive in directing the plasma components toward the sensor.

[0083] The present invention uses plasma, but non-invasively. Furthermore, contrary to the finger, the ocular surface evaluated by the system of the present invention is irrigated by a direct branch from the carotid artery allowing the direct evaluation of brain analyte level. The brain analyte level is the most important value for the evaluation of the metabolic state of a patient.

[0084] The cells of the epithelium of the conjunctiva are alive and loosely adherent allowing cell analysis to be performed using the ICL, contrary to the skin surface which is dead. The ICL can naturally remove the cells from the surface during the action of the eye lid or by mechanical pumping means or electrical means and then living cells can then be extracted for further evaluation within the ICL or outside the ICL. Appropriate membrane surfaces are used to separate cells components and fluid components. Different permeabilities of membranes in apposition to the conjunctiva are used according to the function that is carried out or the function of a particular ICL.

[0085] The present invention brings not only innovation but also a cost-effective system allowing diagnostic and blood evaluation to be done in a way never possible before. The current invention allows unbelievable savings for the patient, government and society in general. An ICL can be disposable and provide continuous measurement over 24 hours and costs to the user around $5 to $8 dollars for one single or multiple testing ICL (meaning more than one analyte is evaluated). The material used in the ICL includes an inexpensive polymer. The reagents and/or enzymatic membranes are used in very small quantities and are also thus inexpensive, and the electronics, integrated circuits and transmitter are common and fairly inexpensive when mass produced as is done with conventional chips.

[0086] The current invention provides means to better control health care expenditure by delivering systems that are astonishingly 20 times cheaper than the prior art using a variety of means ranging from low-cost amperometric systems to disposable micro fluidic chips and integration of biochemical and disposable silicon chip technologies into the ICLs. The ICLs can perform numerous analysis per lens and if just one more test is performed the cost of ICL remains about the same since the new reagents are used in minute quantities and the similar electronics can be used in the same ICL. In this case, with dual testing (two tests per lens, four times a day) the ICL is a staggering 100 times cheaper.

[0087] The system of the invention allows a life-saving technological innovation to help contain health care costs and thus enhance the overall economy of the nation, as

well as to not only provide a technological innovation that can be used in industrialized nations but also in economically challenged countries, ultimately allowing life-saving diagnostic and monitoring biological data to be accessible in a cost-effective and wide-spread manner. Moreover, this affordable system allows not only individual measurements but also continuous 24 hour non-invasive measurement of analysts including during sleeping, allowing thus the creation of an artificial organ with precisely tailored delivery of medications according to the analyte levels.

[0088] Furthermore, it is understood that a small rod with sensing devices housed in the tip can be used. In that embodiment the patient places the sensor against the conjunctiva after pulling the eye lid down and exposing the red part and then applying the sensing device against it for measurement. Alternatively, the tip of the rod is lightly rubbed against the conjunctiva to create microdisruption as naturally caused by the eyelid tension, and then the sensing device is applied and the sensor activated for measurement. It is understood that any other means to promote or increase transudation of plasma in the conjunctiva can be used with the ICL, including, but not limited to heating systems, creating a reverse electroosmotic flow, electrophoresis, application of current, ultrasonic waves as well as chemical enhancers of flow, electroporation and other means to increase permeation.

[0089] The ICL biomicrochips can be produced using photolithography, chemical etching techniques and silicon chip technologies similar to those used in the manufacture of computer chips. The ICL system thus achieve the miniaturization needed for the ICL dimensions with microchannels etched into the chip substrate measuring up to 100 micrometers, and preferably up to10 micrometers in depth, by 1 to 500 micrometers, and preferably 10 to 100 micrometers wide.

[0090] The microchannels carry the fluid and cells from the eye and have reservoirs and chambers with the reagents and sample solutions needed for analysis. The ICL radio frequency transceivers comprise microelectronic systems with radio frequency integrated circuits allowing the small dimensions to be achieved for incorporation into the ICL.

[0091] A variety of power sources have been described, but in order to minimize hardware and cost of the ICL, an ultra-capacitor charged externally through electromagnetic induction coupling can be used instead of the polymer microbatteries or rechargeable batteries. Although there is an enormous amount of space in the conjunctival area, with two large pockets in each eye as described, allowing much larger systems to be used, it is preferable that the most miniaturized system be used which then allows multiple tests to be simultaneously performed.

[0092] A variety of processes and apparatus can be used for manufacturing ICLs including casting, molding, spin-cast, lathing and the like. An exemplary embodiment for low-cost mass production of the ICL consists of production of the detection and transmission hardware (chemical microchips, processor, transmitter, power supply) as one unit (sheet-like) for instance mounted in polyamide or other suitable material. The sheet then, which can have different shapes, but preferably a rectangular or ring-like configuration, is placed inside a cavity defined between moulding surfaces of conventional contact lens manufacturing apparatus. The moulding surfaces and cavity determine the shape and thickness of the ICL to be produced according to the function needed.

[0093] However, an ICL placed in an eye lid pocket or an annular ring contact lens will have a maximum thickness of 2.5 mm, preferably less than 1.0 mm. An oversized round or regular round contact lens configuration having a diameter of less than 3 cm for an oversize contact lens and a diameter less than 12 mm for a regular contact lens, will have a maximum thickness of 1.0 mm, and preferably less than 0.5 mm.

[0094] After the hardware above is in the cavity, the lens polymer is dispensed into the cavity with subsequent polymerization of the lens material as for instance with the use of heat, ultraviolet light, or by using two materials which in contact trigger polymerization. Accordingly, the

[0095] It is an object of the present invention to provide methods and apparatus for measuring a substance of interest using natural body far-infrared emissions which occur in a thermally stable environment such as in the eyelid pocket.

[0096] Still a further object of the invention is to provide an apparatus and method that allows direct application of Beer-Lambert's law in-vivo.

[0097] Yet a further object is to provide a method and apparatus for continuous measurement of core temperature in a thermally stable environment.

[0098] By the present invention, the discovery of plasma present in and on the surface of the conjunctiva can be used for a complete analysis of blood components. Plasma corresponds to the circulating chemistry of the body and it is the standard used in laboratories for sample testing. Interstitial fluid for instance is tested in labs only from corpses but never from a living person.

[0099] Laboratories also do not use whole blood for measuring compounds such as for example, glucose. Laboratories separate the plasma and then measure the glucose present in plasma.

[0100] Measurement of glucose in whole blood is subject to many errors and inaccuracies. For example changes in hematocrit that occur particularly in women, certain metabolic states, and in many diseases can have an important effect on the true value of glucose levels. Moreover, the cellular component of blood alters the value of glucose levels.

[0101] Many of the machines which use whole blood (invasive means using finger prick) give a fictitious value which attempts to indicate the plasma value. Measurements in interstitial fluid also give fictitious values which tries to estimate what the plasma values of glucose would

be if measured in plasma.

[0102] Measurement of substances in the plasma gives the most accurate and precise identification and concentration of said substances and reflects the true metabolic state of the body. In addition, the optical properties of plasma are stable and homogeneous in equivalent sample population.

[0103] Evaluations have been made of the external surfaces and mucosal areas of the human body and only one area has been identified with superficial vessels and leakage of plasma. This area with fenestrations and plasma leakage showed to be suitable for noninvasive measurements. This preferred area is the conjunctival lining of the eye including the tear punctum lining.

[0104] Another area identified but with leakage of lymphatic fluid is in the oral mucosa between teeth, but leakage is of only a small amount, not constant, and not coming from superficial vessels with fenestrations and plasma leakage as it occurs in the conjunctiva.

[0105] The methods and apparatus using superficially flowing plasma adjacent to the conjunctiva as disclosed in the present invention provides an optimal point for diagnostics and a point of maximum detected value and maximum signal for determination of concentration or identification of substances independent of the type of electromagnetic radiation being directed at or through the substance of interest in the sample.

[0106] These areas in the eye provide plasma already separated from the cellular component of blood with said plasma available superficially on the surface of the eye and near the surface of the eye. The plasma fills the conjunctival interface in areas with blood vessels and without blood vessels. Plasma flowing through fenestrations rapidly leaks and permeates the whole conjunctival area, including areas denuded from blood vessels.

[0107] The plasma can be used for non-invasive or minimally invasive analysis, for instance, using chemical, electrochemical, or microfluidic systems. The conjunctiva and plasma can also be used for evaluation and identification of substances using electromagnetic means such as with the optical techniques of the present invention. The measurement provided by the present invention can determine the concentration of any constituent in the eye fluid located adjacent to the conjunctiva. A variety of optical approaches such as infrared spectroscopy can be used in the present invention to perform the measurements in the eye including transmission, reflectance, scattering measurement, frequency domain, or for example phase shift of modulated light transmitted through the substance of interest, or a combination of these.

[0108] The methods, apparatus, and systems of the present invention can use spectroscopic analysis of the eye fluid including plasma present on, in, or preferably under the conjunctiva to determine the concentration of chemical species present in such eye fluid while removing or reducing all actual or potential sources of errors, sources of interference, variability, and artifacts.

[0109] The method and apparatus of the present invention overcomes all of the issues and problems associated with previous techniques and devices. In accordance with the present invention, plasma containing the substance to be measured is already separated and can be used for measurement including simultaneous and continuous measurement of multiple substances present in said plasma or eye fluid. One of the approaches includes non-invasive and minimally invasive means to optically measure the substance of interest located in the eye fluid adjacent to the conjunctiva.

[0110] An electromagnetic measurement, such as optical, is based on eye fluid including plasma flowing in a living being on the surface of the eye. The method and apparatus involves directing electromagnetic radiation at or through the conjunctiva with said radiation interacting with the substance of interest and being collected by a detector. The data collected is then processed for obtaining a value indicative of the concentration of the substance of interest.

[0111] It is very important to note that measurements using the electromagnetic technique as described in the present invention do not require any flow of fluid to reach the sensor in order to determine the concentration of the substance of interest. The system is reagentless and determination of the concentration of the substance of interest is accomplished simply by detecting and analyzing radiation that interacts with the substance of interest present adjacent to the conjunctiva

[0112] The present invention reduces variability due to tissue structure, interfering constituents, and noise contribution to the signal of the substance of interest, ultimately substantially reducing the number of variables and the complexity of data analysis, either by empirical or physical methods. The empirical methods including Partial Least squares (PLS), principal component analysis, artificial neural networks, and the like while physical methods include chemometric techniques, mathematical models, and the like. Furthermore, algorithms were developed using *in-vitro* data which does not have extraneous tissue and interfering substances completely accounted for as occurs with measurement in deep tissues or with excess background noise such as in the skin and with blood *in vivo.* Conversely, standard algorithms for *in-vitro* testing correlates to the *in vivo* testing of the present invention since the structures of the eye approximates a Lambertian surface and the conjunctiva is a transparent and homogeneous structure that can fit with the light-transmission and light-scattering condition characterized by Beer-Lambert's law.

[0113] The enormous amount of interfering constituents, source of errors, and variables in the sample which are eliminated or reduced with the present invention include:

- Sample with various layers of tissue
- Sample with scattering tissue
- Sample with random thickness
- Sample with unknown thickness

- Sample with different thickness among different individuals
- Sample that changes in thickness with aging
- Sample that changes in texture with aging
- Sample with keratin
- Sample that changes according to exposure to the environment
- Sample with barriers to penetration of radiation
- Sample that changes according to the local ambient
- Sample with fat
- Sample with cartilage
- Sample with bone
- Sample with muscle
- Sample with high water content
- Sample with walls of vessels
- Sample with non-visible medium that is the source of the signal
- Sample with opaque interface
- Sample interface made out of dead tissue
- Sample with interface that scars
- Sample highly sensitive to pain and touch
- Sample with melanin
- Sample interface with different hue
- Sample with hemoglobin
- Sample medium which is in motion
- Sample medium with cellular components
- Sample with red blood cells
- Sample with uneven distribution of the substance being measured
- Sample with unsteady supply of the substance being measured
- Non-homogeneous sample
- Sample with low concentration of the substance being measured
- Sample surrounded by structures with high-water content
- Sample surrounded by irregular structures
- Sample medium that pulsates
- Sample with various and unknown thickness of vessel walls
- Sample with unstable pressure
- Sample with variable location
- Sample filled with debris
- Sample located deep in the body
- Sample with unstable temperature
- Sample with thermal gradient
- Sample in no.direct contact with thermal energy
- Sample with no active heat transfer
- Sample with heat loss
- Sample influenced by external temperature
- Sample with no-isothermic conditions
- Sample with self-absorption of thermal energy

[0114] An exemplary representation of some of the interfering constituents present in the sample irradiated that are reduced or eliminated by the present invention.

a) Radiation directed at a target tissue can be absorbed by the various constituents including several layers of the skin, various blood cellular components, fat, bone, walls of the blood vessel, and the like. This drastically reduces the signal and processing requires subtracting all of those intervening elements. All of the named interfering constituents in the sample irradiated are eliminated with the present invention.

b) Skin alone as the target tissue creates reduction of signal to noise because skin by itself is an additional scattering tissue. The present invention eliminates interfering scattering structures in the sample irradiated.

c) Thickness of the skin (which includes the surface of the tongue) is random within the same individual even in an extremely small area with changes in thickness depending on location. It is very difficult to know the exact thickness of the skin from point to point without histologic (tissue removal) studies. There is great variability in signal due to skin thickness. All of those sources of errors and variability such as random thickness and unknown thickness of the structure in the sample irradiated are eliminated.

d) Thickness of the skin also varies from individual to individual at the exact same location in the skin and thus the signal has to be individually considered for each living being. Individual variation in thickness of the structure in the sample irradiated is also eliminated.

e) Changes in texture and thickness in the skin that occurs with aging have a dramatic effect in acquiring accurate measurements. Changes in texture and thickness due to aging of the structure in the sample irradiated are also eliminated.

f) Changes in the amount of keratin in the skin and tongue lining which occurs in different metabolic and environmental conditions also prevent accurate signal acquisition. Keratin and variability in the sample irradiated are both also eliminated.

g) Skin structure such as amount of elastin also varies greatly from person to person, according to the amount of sun exposure, pollution, changes in the ozone layer, and other environmental factors which lead to great variability in signal acquisition. There is elimination of the sample irradiated being susceptible to most of the environmental factors by being naturally shielded from said environmental factors.

h) Due to the structure and thickness of the skin the radiation can fail to penetrate and reach the location in which the substance of interest is present. There is elimination of a structure in the sample irradiated that can work as a barrier to radiation.

i) Measurements are also affected by the day-to-day variations in skin surface temperature and hydration in the same individual according to ambient conditions and metabolic status of said individual. There is elimination of structures in the sample irradiated

that is susceptible to changes in temperature and hydration according to ambient conditions.

j) The intensity of the reflected or transmitted signal can vary drastically from patient to patient depending on the individual physical characteristics such as the amount of fat. A thin and obese person will vary greatly in the amount of fat and thus will vary greatly in the radiation signal for the same concentration of the substance of interest. There is elimination of fat in the sample area being irradiated.

k) The amount of protein such as muscle mass also varies greatly from person to person. There is elimination of muscle mass variability in the sample area being irradiated.

1) The level of water content and hydration of skin and surrounding structures varies from individual to individual and in the same individual over time with evaporation. There is elimination of variability from person to person and over time due to changes in water evaporation in the sample area being irradiated.

m) Thickness and texture of walls of blood vessels also change substantially with aging and greatly vary from location to location. There is elimination in the sample being irradiated of signal variability due to presence of walls which change substantially with aging and location.

n) The deep blood vessels location and structure within the same age group still varies greatly from person to person and anatomic variation is fairly constant with different depth and location of blood vessel in each individual. Since those blood vessels are located deep and covered by an opaque structure like the skin it is impossible to precisely determine the position of said blood vessels. There is elimination of source medium for the signal which is not visible during irradiation of the sample.

[0115] The use of conjunctiva and plasma present adjacent to said conjunctiva and the eyelid pocket provides an optimum location for measurement by electromagnetic means in a stable environment which is undisturbed by internal or external conditions.

[0116] Signal to noise is greatly improved since the thin transparent conjunctiva is the only intervening tissue in the optical path to be traversed from source to detector.

[0117] The conjunctiva does not age like the skin or blood vessels. Both the thickness and texture of the conjunctiva remain without major changes throughout the lifespan of a person. That can be easily noted by looking at the conjunctiva of a normal person but with different ages, such as a 25 year old and a 65 year old person.

[0118] The conjunctiva is a well vascularized tissue, but still leaves most of its area free from blood vessels which allows measurement of plasma to be performed without interference by blood components. Those areas free of vessels are easily identified and the eyeball of a normal person is white with few blood vessels. Furthermore, the conjunctiva in the cul-de-sac rim is free of blood vessels and plasma is collected there due to gravity, and measurement of substance of interest in the cul-de-sac is one of the preferred embodiments of the present invention.

[0119] Moreover, the conjunctiva is capable of complete regeneration without scarring. Furthermore, the conjunctiva can provide easy coupling with the surface of the sensing means since the conjunctiva surface is a living tissue contrary to the skin surface and tongue lining which is made out of dead tissue (keratin). In addition, the conjunctiva is easily accessible manually or surgically. Besides, the conjunctiva has only a few pain fibers and no tactile fibers creating minimal sensation to touch and to any hardware in contact with the conjunctival tissue.

[0120] Skin has various layers with random and inconstant thickness. The skin has several layers including: the epidermis which varies in thickness depending on the location from approximately 80 to 250μ, the dermis with thickness between approximately 1 to 2 mm, and the subcutaneous tissue which varies substantially in thickness according to area and physical constitution of the subject and which falls in the centimeter range reaching various centimeters in an obese person. The conjunctiva is a few micrometers thick mono-layer structure with constant thickness along its entire structure. The thickness of the conjunctiva remains the same regardless of the amount of body fat. Normal conjunctiva does not have fat tissue.

[0121] In the present invention the superficial and the only interface radiated, involves the conjunctiva, a very thin layer of transparent homogenous epithelial tissue. Wavelengths of less than 2000 nm do not penetrate well through skin. Contrary to that, due to the structure and thickness of the conjunctiva, a broad range of wavelengths can be used and will penetrate said conjunctiva.

[0122] Melanin is a cromophore and there is some amount of melanin in the skin of all normal individuals, with the exception of pathologic status as in complete albinos. The skin with melanin absorbs near-infrared light which is the spectral region of interest in near-infrared spectroscopy and the region, for example, where glucose absorbs light. The present invention eliminates surface barriers and sources of error and variability such as melanin present in the skin and which varies from site to site and from individual to individual. Normal conjunctiva does not have melanin.

[0123] There are variations from person to person in thickness and color of skin and texture of skin. Normal conjunctiva is transparent in all normal individuals and has the equivalent thickness and texture.

[0124] The present invention eliminates enormous sample variability due to location as occur in the skin with different thickness and structure according to the area measured in said skin. The conjunctiva is a thin and homogeneous tissue across its entire surface area.

[0125] There is elimination of variability due to changes

in texture and structure as occur in the skin due to aging. The conjunctiva is homogeneous and does not age like the skin. There is also elimination of variability found in the skin surface due to the random presence of various glands such as sweat glands, hair follicles, and the like.

[0126] There is elimination of an optically-opaque structure like the skin. It is very difficult to apply Beer-Lambert's law when using the skin. The law describes the relationship between light absorption and concentration and according to Beer-Lambert's law the absorbance of a constituent is proportional to its concentration in solution. The conjunctiva is a transparent and homogeneous structure which can fit with the light-transmission and light-scattering phenomena characterized by Beer-Lambert's law.

[0127] There is elimination of interfering constitutes and light scattering elements such as fat, bone, cartilage and the like. The conjunctiva does not have a fat layer and radiation does not have to go through cartilage or bone to reach the substance of interest.

[0128] In the present invention the conjunctiva, which is a thin mono-layer transparent homogeneous structure, is the only interfering tissue before radiation reaches the substance of interest already separated and collected in the plasma adjacent to said conjunctiva. Since the conjunctiva does not absorb the near-infrared light there is no surface barrier as an interfering constituent and since the conjunctiva is very thin and homogeneous there is minimal scattering after penetration.

[0129] In addition, the temperature in the eye is fairly constant and the pocket in the eyelid offers a natural and thermally sealed pocket for placement of sensing means.

[0130] Presence of whole blood and other tissues such as skin scatters light and further reduces the signal. The present invention eliminates absorption interference by cromophores such as hemoglobin such as present in whole blood. Radiation can be directed at the conjunctival area free of blood and hemoglobin, but with plasma collected underneath. Thus another source of error is eliminated as caused by confusion of hemoglobin spectra with glucose spectra.

[0131] The reflective or transmissive measurements of the present invention involve eye fluid and plasma adjacent to the conjunctiva which creates the most homogeneous medium and provides signal to noise useful for clinical applications. The present invention provides plasma which is the most accurate and precise medium for measuring and identifying substances. The present invention provides said plasma covered only by the conjunctiva which is a structure which does not absorb near-infrared light.

[0132] The plasma is virtually static or in very slow motion as under the conjunctiva which creates a stable environment for measurement.

[0133] The plasma present in the eye provides a sample free of blood constituents which are source of errors and scattering. The plasma being irradiated is free of major cellular components and it is homogeneous with minimal scattering.

[0134] The background where the plasma is collected includes the sclera which is a homogeneous and white reflective structure with virtually no water contained in its layers. Thus, there is also elimination of surrounding tissue composed by large amounts of water.

[0135] The present invention eliminates light being radiated through a tissue with varying amounts of glucose depending on the location such as the skin with the epidermis, dermis and subcutaneous having different concentrations of glucose. In the present invention glucose is evenly distributed in the plasma adjacent to the conjunctiva.

[0136] The plasma present in the eye is a great source of undisturbed and stable signal for glucose as the eye requires a stable supply of glucose since glucose is the only source of energy that can be used by the retina. The retina requires a steady supply of glucose for proper functioning and to process visual information. The eye has a stable supply of glucose and a relative increase in the amount of the substance of interest such as for example glucose which increases the signal to noise ratio and allows fewer wavelengths to be used in order to obtain measurements.

[0137] The eye also has the highest amount of blood per gram of tissue in the whole body and thus provide a continuous supply of blood at high rate which is delivered as plasma through the conjunctival vessels.

[0138] The concentration of chemical substances in the plasma are high in relation to the whole sample allowing a high signal to noise ratio to be acquired. Glucose is found in very dilute quantities in whole blood and interstitial fluid but it is relatively concentrated in the plasma providing a higher signal as found in the surface of the eye. In complex media such as the blood where there is a great number of overlapping substances, the number of required wavelengths increases substantially. In a homogenous sample such as the plasma adjacent to the conjunctiva, the reduction in the number of wavelengths does not affect accuracy. In addition, it is difficult for a detector to identify the glucose absorption peak due to the variability in scatter as occurs with blood. The present invention can rely on more cost-effective detectors as the absorption peak in the plasma sample can be more easily identified.

[0139] Due to the presence of minimal interfering components and high signal to noise ratio, the present invention can detect lower glucose levels (hypoglycemia). The strength of signal for the substance of interest is a function of the concentration and the homogeneity of the sample. Blood and other tissues are highly non-homogeneous. Contrary to that the plasma is highly homogeneous and with higher concentration of the substance of interest in relation to the total sample.

[0140] There is elimination of a very low signal source with great background noise as it occurs in the aqueous humor of the eye. Plasma generates a high signal due to the relative high concentration of the substance of in-

terest already naturally separated from cellular components and with minimal background noise.

[0141] There is reduction in the amount of interfering elements such as water. The present invention includes water displacement both passively and actively. Passive displacement is observed when the concentration of the substance of interest increases as found in the plasma adjacent to the conjunctiva which decreases water interference and the sample is surrounded by the sclera which is a structure which does not contain water. Active displacement is observed when artificially using a hydrophobic surface for the contact device which displaces water from the surface of the tissue creating a dry interface.

[0142] There is elimination of structural and absorption background irregularities as occur in the skin, inside of the eye, blood vessels, and the like. The conjunctiva is positioned against a smooth white homogeneous water-free surface, the sclera.

[0143] There is elimination of variability due to the direct pulsation of the wall of blood vessel. Blood by nature is constantly in rapid motion and such rapid motion can create significant variability in the measurements. The present invention eliminates error and variability due rapid motion of the sample as occurs in blood vessels. Plasma flows continuously through fenestrations but not in a pulsatile manner. The plasma collected adjacent to the conjunctiva has insignificant pulsating content.

[0144] There is elimination of an important source of variability as occur in moving blood with cellular components in a blood vessel which is not homogeneous and creates further scattering. Plasma flows continuously through fenestrations but without cellular components.

[0145] Many and rapid changes occur in flowing blood inside a blood vessel. Due to this phenomena the resulting spectra has to be acquired in an extremely short period of time which is done in an attempt to decrease the number of artifacts and source of errors. Due to the poor signal created by the various and rapid changes in flow, measurements have to be repeated several times within a very short period of time and the total averaged. This leads to complicated construction of devices and controlling systems, but still only delivering a poor signal to noise. The present invention allows the spectra to be acquired over longer periods of time and without the need for such repeat measurements since there is minimal background noise and interfering constituents. This, therefore, allows lower cost and more efficient systems to be made and used.

[0146] There are variations from person to person in thickness and texture of blood vessel walls. There is also variability due to changes in texture and structure that occur in the vessel wall due to aging. The apparatus and methods of the present invention include directing radiation that does not need to penetrate through the wall of blood vessels to acquire the signal for the substance of interest. Therefore, the above source of errors and variability are eliminated.

[0147] There is reduction or elimination of variability and error due to changes in pressure between the sensor interface and the tissue. Many errors occur when techniques require placement of a body part against the sensor in which the subject or the operator is artificially applying the pressure. An example is when a subject applies his/her skin against the sensor or an operator grasps the tongue or finger of a subject. The pressure applied by either the subject or the operator varies substantially over time and from measurement to measurement and from subject to subject and from operator to operator. The interface between the tissue and sensor changes continuously with contact pressure and manipulation by the subject or operator since those structures such as skin and tongue have several layers that change and yield in reaction to applied pressure. Even if pressure controlled systems are used, there is significant variation because of the different texture and thickness from individual to individual, from location to location, and in the same individual over time which prevents precise measurements from being acquired.

[0148] One of the preferred embodiments of the present invention which uses a contact device in the eyelid pocket eliminates this variation in pressure. The pressure applied by the eyelid in the resting state is fairly constant and equal in normal subjects with a horizontal force of 25,000 dynes and a tangential force of 50 dynes.

[0149] Body temperature such as is found in the surface of the skin is variable according to the environment and shift of spectra can occur with changes in temperature. The eyelid pocket provides an optimum location for temperature measurement which has a stable temperature and which is undisturbed by the ambient conditions. The conjunctival area radiated has a stable temperature derived from the carotid artery. Moreover, when the embodiment uses a contact device which is located in the eyelid pocket, there is a natural, complete thermal seal and stable core temperature. Good control of the temperature also provides increased accuracy and if desired, reduction of the number of wavelengths. Besides, the stable temperature environment allows use of the natural body infrared radiation emission as means to identify and measure the substance of interest.

[0150] Far-infrared radiation spectroscopy measures natural thermal emissions after said emissions interact and are absorbed by the substance of interest at the conjunctival surface. The present invention provides a thermally stable medium, insignificant number of interfering constituents, and the thin conjunctival lining is the only structure to be traversed by the thermal emissions from the eye before reaching the detector. Thus there is higher accuracy and precision when converting the thermal energy emitted as heat by the eye into concentration of the substance of interest.

[0151] The ideal thermal environment provided by the conjunctiva in the eyelid pocket can be used for non-invasive evaluation of blood components besides the measurement of temperature. Far-infrared spectroscopy

can measure absorption of far-infrared radiation contained in the natural thermal emissions present in the eyelid pocket. Natural spectral emissions of infrared radiation by the conjunctiva and vessels include spectral information ofblood components. The long wavelength emitted by the surface of the eye as heat can be used as the source of infrared energy that can be correlated with the identification and measurement of the concentration of the substance of interest. Infrared emission traverses only an extremely small distance from the eye surface to the sensor which means no attenuation by interfering constituents.

[0152] Spectral radiation of infrared energy from the surface of the eye can correspond to spectral information of the substance of interest. These thermal emissions irradiated as heat at 38 degrees Celsius can include the 4,000 to 14,000 nm wavelength range. For example, glucose strongly absorbs light around the 9,400 nm band. When far-infrared heat radiation is emitted by the eye, glucose will absorb part of the radiation corresponding to its band of absorption. Absorption of the thermal energy by glucose bands is related in a linear fashion to blood glucose concentration in the thermally sealed and thermally stable environment present in the eyelid pocket.

[0153] The natural spectral emission by the eye changes according to the presence and concentration of a substance of interest. The far-infrared thermal radiation emitted follow Planck's Law and the predicted amount of thermal radiation can be calculated. Reference intensity is calculated by measuring thermal energy absorption outside the substance of interest band. The thermal energy absorption in the band of substance of interest can be determined via spectroscopic means by comparing the measured and predicted values at the conjunctiva/plasma interface. The signal is then converted to concentration of the substance of interest according to the amount of thermal energy absorbed.

[0154] The Intelligent Contact Lens in the eyelid pocket provides optimal means for non-invasive measurement of the substance of interest using natural heat emission by the eye. Below is an exemplary representation of various unique advantages and features provided by the present invention.

- higher signal as found in the plasma/conjunctiva interface due to less background interference
- undisturbed signal since the heat source is in direct apposition to the sensing means
- stable temperature since the eyelid pocket is thermally sealed
- the eyelid pocket functions as a cavity since the eyelid edge is tightly opposed to the surface of the eyeball easily observed in the eye. To see the inside of the eyelid pocket it is necessary to actively pull the eyelid.
- there is no heat loss inside the cavity
- there is active heat transfer from the vessels caused by local blood flow in direct contact with the sensor
- the temperature of the eye, by being supplied directly from the central nervous system circulation, is in direct equilibrium with core temperature.

[0155] Temperature is proportional to blood perfusion. The conjunctiva is extremely vascularized and the eye is the organ in the whole body with the highest amount of blood per gram of tissue. The conjunctiva is a thin homogeneous layer of equal composition and the eyelid pocket is a sealed thermal environment without cooling of surface layers. The blood vessels in the conjunctiva are branches of the carotid artery coming directly from the central nervous system which allows measuring the precise core temperature of the body.

[0156] The eyelid pocket provides a sealed and homogeneous thermal environment. When the eyelids are closed (during blinking or with eyes closed) or at any time inside the eyelid pockets, the thermal environment of the eye exclusively corresponds to the core temperature of the body. In the eyelid pocket there is prevention of passive heat loss in addition to associated active heat transfer since the conjunctiva is a thin lining of tissue free of keratin and with capillary level on the surface.

[0157] Skin present throughout the body, including the tongue, is covered with keratin, a dead layer of thick tissue that alters transmission of infrared energy emitted as heat. The conjunctiva does not have a keratin layer and the sensor can be placed in intimate thermal contact with the blood vessels.

[0158] Skin with its various layers and other constituents selectively absorb infrared energy emitted by deeper layers before said energy reaches the surface of said skin. Contrary to that, the conjunctiva is homogeneous with no absorption of infrared energy and the blood vessels are located on the surface. This allows undisturbed delivery of infrared energy to the surface of the conjunctiva and to a temperature detector such as an infrared detector placed in apposition to said surface of the conjunctiva.

[0159] In the skin and other superficial parts of the body there is a thermal gradient with the deeper layers being warmer than the superficial layers. In the conjunctiva there is no thermal gradient since there is only a monolayer of tissue with vessels directly underneath. The thermal energy generated by the conjunctival blood vessels exiting to the surface corresponds to the undisturbed core temperature of the body.

[0160] The surface temperature of the skin and other body parts does not correspond to the blood temperature. The surface temperature in the eye corresponds to the core temperature of the body.

[0161] Thus, skin is not suitable for creating a thermally sealed and stable environment for measuring temperature and the concentration of the substance of interest. Most important, no other part of the body, but the eye provides a natural pocket structure for direct apposition

of the temperature sensor in direct contact with the surface of the blood vessel. The conjunctiva and eyelid pocket provides a thermally sealed environment in which the temperature sensor is in direct apposition to the heat source. Moreover, in the eyelid pocket thermal equilibrium is achieved immediately as soon as the sensor is placed in said eyelid pocket and in contact with the tissue surface.

[0162] The method and apparatus of the present invention provides optimal means for measurement of the concentration of the substance of interest from the infrared energy emissions by the conjunctival surface as well as evaluation of temperature with measurement of core temperature.

[0163] The temperature sensor, preferably a contact thermosensor, is positioned in the sealed environment provided by the eyelid pocket, which eliminates spurious readings which can occur by accidental reading of ambient temperature.

[0164] The apparatus uses the steps of sensing the level of temperature, producing output electrical signals representative of the intensity of the radiation, converting the resulting input, and sending the converted input to a processor. The processor is adapted to provide the necessary analysis of the signal to determine the temperature and concentration of the substance of interest and displaying the temperature level and the concentration of the substance of interest.

[0165] The apparatus can provide core temperature, undisturbed by the environment, and continuos measurement in addition to far-infrared spectroscopy analysis for determining the concentration of the substance of interest with both single or continuous measurement.

[0166] The present invention yet includes means for collecting natural far-infrared radiation emitted as heat from the eye, means for positioning a radiation collector to receive said radiation, and means for converting the collected radiation from the eye into the concentration of the Substance of interest. The present invention also provides methods for determining the concentration of the substance of interest with said methods including the steps of using the natural far-infrared emission from the eye as the resulting radiation for measuring the substance of interest, collecting the resulting radiation spectra in a thermally stable environment, providing an electrical signal upon detection, processing the signal and reporting the concentration of the substance of interest according to said signal. A thermally stable environment includes open eye or closed eye. The thermal emission collection means are in contact with the conjunctiva in the eyelid pocket with eyes open or closed.

[0167] With closed eye, the collection means can also be in contact with the cornea. With closed eyes the cornea is in equilibrium with the aqueous humor inside the eye with transudation of fluid to the surface of the cornea. The cornea during closed eyes or blinking is in thermal equilibrium with core body temperature. When the eyes are closed the equilibrium created allows the evaluation of substances of interest using a contact lens with optical or electrochemical sensors placed on the surface of the cornea. The invention also includes means and methods for positioning the thermal emission collection means in a stable position and with stable pressure and with eyes open or closed.

[0168] The present invention further includes measuring the core temperature of the body, both single and continuous measurements. The present invention includes means for collecting thermal radiation from the eye, means for positioning temperature sensitive devices to receive thermal radiation from the eye in a thermally stable environment, and means for converting said thermal radiation into the core temperature of the body. The present invention also provides methods for determining core temperature of the body with said methods including the steps of using thermal emissions from the eye in a thermally stable environment, collecting the thermal emission by the eye, providing an electrical signal upon detection, processing the signal and reporting the temperature level. The invention also includes means and methods for proper positioning of the temperature sensor in a stable position and with stable pressure as achieved in the eyelid pocket. The invention yet includes means to monitor a bodily function and dispense medications or activate devices according to the signal acquired. The invention further includes apparatus and methods for treating vascular abnormalities and cancer. The invention further includes means to dispense medications.

[0169] Substances of interest can include any substance present adjacent to the conjunctiva or surface of the eye which is capable of being analyzed by electromagnetic means. For example but not by way of limitation such substances can include any substance present in plasma such as molecular, chemical or cellular, and for example exogenous chemicals such as drugs and alcohol as well as endogenous chemicals such as glucose, oxygen, bicarbonate, cardiac markers, cancer markers, hormones, glutamate, urea, fatty acids, cholesterol, triglycerides, proteins, creatinine, aminoacids and the like and cellular constituents such as cancer cells, and the like. Values such as pH can also be calculated as pH can be related to light absorption using reflectance spectroscopy.

[0170] Substances of interest can also include hemoglobin, cytochromes, cellular elements and metabolic changes corresponding to light interaction with said substances of interest when directing electromagnetic radiation at said substances of interest. All of those constituents and values can be optimally detected in the conjunctiva or surface of the eye using electromagnetic means and in accordance with their optical, physical, and chemical characteristics.

[0171] For the purpose of the description herein, the sclera is considered as one structure. It is understood however, that the sclera has several layers and surrounding structures including the episclera and Tenon's capsule.

[0172] For the purpose of the description herein, light and radiation are used interchangeably and refers to a form of energy contained within the electromagnetic spectrum.

[0173] The eye fluid, conjunctival area, methods and apparatus as disclosed by the present invention provides ideal means and sources of signals for measurement of any substance of interest allowing optimal and maximum signals to be obtained. The present invention allows analytical calibration since the structure and physiology of the conjunctiva is stable and the amount of plasma collected adjacent to the conjunctiva is also stable. This type of analytical calibration can be universal which avoids clinical calibration that requires blood sampling individually as a reference.

[0174] The foregoing a nd other objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of the present invention when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0175]

FIG. 1 schematically illustrates the position of sensor in accordance with a preferred embodiment of the present invention.

FIG. 2 shows an enlarged view of the sensor shown in FIG. 100A.

FIG. 3 is a schematic block diagram of an apparatus according to one preferred embodiment of the present invention and shown schematically in FIGS. 100A-B.

FIG. 4 schematically illustrates a sensor arrangement in accordance with a preferred embodiment of the present invention.

FIG. 5-6 shows a cross-sectional view of one preferred embodiment of the present invention.

FIG. 7 shows a cross-sectional view of an alternative embodiment of the present invention.

FIG. 8 schematically illustrates a preferred embodiment of the present invention.

FIG. 9-11 schematically illustrate various positions for directing the probe arrangement in accordance with a preferred embodiment of the present invention.

FIG. 12 is a schematic block diagram for continuous monitoring of chemical substances in accordance with a preferred embodiment of the present invention.

FIG. 13 is a schematic block diagram of a probe arrangement

FIG. 14 schematically illustrates a probe arrangement in accordance with a preferred embodiment of the present invention.

FIG. 15-16 shows cross-sectional views of the probe arrangement in two different positions in relation to the tissue being evaluated.

FIG. 17-19 shows a frontal view of different arrangements for the sensor and filter used in the measuring probe.

FIG. 21 shows a cross-sectional view of the probe arrangement using a rotatable filter system in accordance with a preferred embodiment of the present invention.

FIG. 20 shows a frontal view of the rotatable filter of FIG. 104K-1.

FIG. 22-24 schematically illustrates various measuring arrangements in accordance with an alternative embodiment of the present invention.

FIG. 25 schematically illustrates a probe arrangement with a supporting arm.

FIG. 26 schematically illustrates a probe arrangement for simultaneous non-contact evaluation of both eyes for detection of abnormalities due to asymmetric measurements.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0176] Now with reference to FIG. 1, the temperature and far-infrared detection ICL 2650 includes a housing 2652 having the shape of a contact device to engage the surface ofthe eye and an infrared sensor 2654 which detects infrared radiation from the eye. The far-infrared detection ICL 2650 is preferably placed in the eyelid pocket 2420 which allows intimate and stable contact with the tissue in the eye.

[0177] Referring to FIG. 2, an infrared sensor 2654 is placed in apposition to the conjunctiva 2656 bulbar or palpebral, but preferably the bulbar conjunctiva in apposition to the sclera. Alternatively the face of the sensor 2654 can be placed in apposition to the red palpebral conjunctiva 2656, with said conjunctiva containing blood vessels superficially and being in apposition to the eyelid. The heat radiation 2660 emitted by the plasma 2658 in apposition to the sclera 2659 travels directly to the infrared sensor 2654. The heat radiation 2660 passes only through the thin conjunctiva 2656 with said infrared emission 2660 not being absorbed by the conjunctiva 2656.

[0178] The infrared emission 2660 from the blood/plasma 2658 in the conjunctival vessels is collected by the sensor 2654 which can include an infrared sensor or other conventional means to detect temperature on contact. The temperature sensor 2654, preferably a contact thermosensor, is positioned in the sealed environment provided by the eyelid pocket 2420, which eliminates spurious readings which can occur by accidental reading of ambient temperature. The sensor 2654 can measure the intensity of the infrared radiation 2660.

[0179] For example, a thermopile sensor which converts the infrared radiation 2660 into an electrical signal can be used or a temperature sensor as a thermistor-like element. The sensor 2654 coupled with a filter that correlates with the substance of interest converts said infra-

red energy 2660 into an electrical signal. The signal is then transmitted by wireless or wired transmission to a processor (not shown) which calculates the concentration of the substance of interest.

[0180] FIG. 3 shows a schematic block diagram of one preferred far-infrared spectroscopy measuring apparatus of the present invention. The apparatus includes a thermal infrared detector 2654 which has a filter 2662 and a sensing element 2664 with said sensing element 2664 being preferably a thermopile and responding to thermal infrared radiation 2660 naturally emitted by the eye. A variety of infrared sensors responsive to thermal radiation can be used as sensor 2664 besides a thermopile, such as for example, optoelectronic sensors including thermistor-based infrared sensor, temperature sensitive resistor, pyroelectric sensors, and the like, and preferably thin membrane sensors. The detector 2654 faces the conjunctiva 2656 and if the face of the detector 2654 is encased by the housing 2652 material, said material is preferably transparent to infrared radiation.

[0181] The far-infrared radiation 2660 emitted by the conjunctival blood/plasma 2658 (within the spectrum corresponding to thermal radiation from the body; from 4,000 to 14,000 nm) is partially absorbed by the substance of interest 2350 according to its band of spectral absorption and which is related in a linear fashion to the concentration of said substance of interest 2350. For example in the thermally sealed and thermally stable environment in the eyelid pocket 2420 (FIG. 5), at 38 degrees Celsius spectral radiation 2660 emitted as heat by the eye in the 9,400 nm band is absorbed by glucose in a linear fashion according to the amount of the concentration of glucose. The resulting radiation from conjunctiva/plasma 2658 is the thermal emission 2660 minus the absorbed radiation by the substance or interest 2350.

[0182] This resulting radiation enters the infrared detector 2654 which generates an electrical signal corresponding to the spectral characteristic and intensity of said resulting radiation. The resulting radiation is then converted into digital information by converter 2666. The signal 2671 is then transmitted by RF transceiver 2668 to a remotely placed receiver 2670 connected to a processor 2672.

[0183] The processor 2672 then calculates the concentration of the substance of interest 2350 according to the amount of thermal energy absorbed in relation to the reference intensity absorption outside the substance of interest band. The output can be adapted to report the value on a display 2674, activate an audio transmitter 2676, and control dispensing means 2678 for the delivery of medications.

[0184] A variety of filters can be used to include the spectral region of correlation to the substance of interest. The apparatus can also include a heating induction element and cooling element as well as light radiation and collection means (not shown) to create an integrated far-infrared and near-infrared system. The front surface of contact device can have a coating to increase energy transfer in the spectral region of interest.

[0185] In reference to FIG. 4, the temperature and far-infrared detection ICL 2651 includes a housing 2653 having the shape of a contact device to engage the surface of the eye and a dual infrared detector arrangement 2654 which is selected to detect far-infrared radiation corresponding to the substance of interest, and sensor 2655 which is used as a reference and detects radiation outside the wavelength corresponding to the substance of interest. Filters are used to select a wavelength of interest and a reference wavelength to calculate the concentration of the substance of interest. The far-infrared detection ICL 2651 is preferably placed in the eyelid pocket 2420 which allows intimate and stable contact with the tissue and source of heat as found in the eye surface.

[0186] A contact device with a germanium coated selective filter coupled to a thermopile detector was constructed and used to non-invasively measure conjunctival plasma glucose emitted as thermal emission from the eye. The preferred embodiment comprised an arrangement which included the thermopile coupled to the germanium coated selective filter for passing a wavelength corresponding to a wavelength of high correlation with the substance of interest.

[0187] For this exemplary measurement of glucose, wavelength centered around 9,400 nm (glucose band) was used. There is a prominent absorption peak of glucose around 9,400 nm due to the carbon-oxygen-carbon bond in its pyrane ring present in the glucose molecule. The contact device filter system allowed passage of the glucose band which is used as a reference measuring point while simultaneously measuring thermal energy absorption outside the glucose band. The thermal energy absorption in the glucose band by plasma glucose is spectroscopically determined by comparing the measured and predicted radiation at the conjunctival surface.

[0188] The predicted amount of thermal energy radiated can be calculated by the Planck distribution function. The absorption of the thermal energy in the plasma glucose band is related in a linear fashion to glucose concentration and the percentage of thermal energy absorption is arithmetically converted to plasma glucose concentration. One preferred embodiment includes a dual detector arrangement in the same contact device. One detector has a filter for reference and the other has a narrow band pass filter for the substance of interest. The ratio of the two wavelengths is used to determine the concentration of the substance of interest.

[0189] The system and method of the invention using the conjunctiva/plasma interface solves all of the critical problems with the technique of using thermal emissions by the body for non-invasive analysis. One of the critical issues is related to the fact that the signal size of human thermal emissions is very small as occurs in the skin, mucosal areas, tympanic membrane and other surface areas in the body. This inability of acquiring a useful signal is in addition to the other drawbacks and interfering constituents previously mentioned. The present inven-

tion using its preferred embodiments achieves a high signal and correlation by providing a unique place in the body that combines a thermally sealed and stable environment as in the eyelid pocket with a contact device that provides direct contact of detector to the source of heat (blood and plasma) associated with measurement of core temperature, large area of the contact sensor to detector, no interfering constituents, and with active heat transfer from the tissue to the detector.

[0190] In addition, due to the characteristics of the conjunctiva/ plasma interface as described and high signal obtained, other novel techniques can be easily achieved. One of them includes the use of a calibration line as another preferred embodiment. The concentration of plasma glucose can be obtained by invasive means and analyzed in the laboratory setting. The range of glucose levels of usual interest in clinical practice (40 to 400 mg/dl) obtained invasively creates a reference database to be correlated to the intensity of radiation obtained using the contact device in the eyelid pocket of the present invention. Planck's function can be used to convert temperature to intensities. This invasive reference is done for each clinically useful level of temperature, for example 35 to 41 degrees Celsius. For example, at 37 degrees Celsius, the concentration of glucose (e.g. 100 mg/dl was the glucose level) measured invasively correlated to the spectral intensity value detected at 9,400 nm by the contact device. The concentration of the substance of interest is then determined by correlating the predicted value with the acquired (unknown) value using the predetermined calibration line.

[0191] Alternatively, a temperature sensor can be included in the contact device and provide a correction factor according to the level of temperature thus avoiding a calibration table that requires different levels of reference temperature. Processing applies automatically the real time value of the temperature to determine the concentration of the substance of interest. Yet in another alternative embodiment, input means can be provided that allows the user to input the temperature value manually with processing applying that value when calculating the concentration.

[0192] Alternatively, a heating element is incorporated in the contact device. The increase in temperature creates a reference measurement which is correlated with the measurement achieved using the natural thermal emission. Moreover, a bandpass filter can be used to select one particular wavelength such as 11,000 nm that is used as a reference and compared to the wavelength of the substance of interest creating a dual detector system with narrow bandpass interference filter. One detector/filter passing a narrow range of radiation centered at 9400 nm and a second detector/filter passing radiation centered at 11000 nm. Selective filters are used to adjust passage of radiation related to the spectrum region of interest, in the case of glucose from 9,000 to 11,000 nm. For detection of ethanol levels the 3,200 to 3,400 nm region of the spectrum is selected. Alternatively, a heating and cooling of the surface of the conjunctiva can be used and the thermal gradient used to determine the concentration of the substance of interest.

[0193] Another preferred embodiment includes the use of Beer-Lambert's law in-vivo to determine the concentration of the substance of interest using thermal emissions. In otherparts of the body, with the exception of the eyelid pocket and surface of the eye, various natural phenomena and structural characteristics occur that prevent the direct in-vivo use of Beer's law for the determination of the concentration of the substance of interest:

1. The optical path length cannot be determined. In standard spectroscopic calibration and in-vitro measurement, the optical path length comprises the length traversed by light in the sample being evaluated such as for example contained in a cuvette. In any part of the body the thermal emission travels an unknown path from the origin of heat deep in the body until it reaches the surface.
2. Self-absorption. This relates to the phenomena that deep layers of tissue selectively absorb wavelengths of infrared energy prior to emission at the surface. The amount and type of infrared energy self-absorbed is unknown. At the surface those preferred emissions are weak due to self-absorption by the other layers deriving insignificant spectral characteristic of the substance being analyzed. Self-absorption by the body thus naturally prevents useful thermal emission for measurement to be delivered at the surface.
3. Thermal gradient. The deeper layers inside the body are warmer than the superficial layers. The path length increases as the thermal gradient is produced. This third factor in addition to the two described above to further prevent undisturbed natural body heat to be used for determination of concentration of substances. Moreover, there is excessive and highly variable scattering of photons when passing through various layers such in the skin and other solid organs. This scattering voids the Beer-Lambert law due to radiation that is lost and not accounted for in the measurement associated to an unknown extension of the optical path length and other thermal loss.

[0194] The characteristics of the conjunctiva/plasma interface as described fits with and obeys Beer-Lambert's law. The conjunctiva is a transparent surface covering a clear solution (plasma is clear which prevents multiple scattering) which contain a substance to be measured such as glucose. Due to the unique geometry of the conjunctiva/plasma interface, the method and apparatus of this preferred embodiment provide for a key variable in-vivo that allows direct use of Beer-Lambert's law, which is the optical path length. The embodiment provides the equivalent of an in-vivo "cuvette" since the conjunctiva/ plasma interface thickness (d) is stable for each location

in the eye. The mid to inferior third of the undisturbed bulbar conjunctiva/plasma interface measures 100 μm. Dimensions (d) are similar for each area but can vary greatly from area to area reaching a few millimeters in the lower parts and 20 micrometers in the upper third of the conjunctiva/plasma interface.

[0195] One face of the cuvette is the conjunctiva surface and the other face is the sclera with clear plasma in between. The sclera has tissue insulation characteristics that make this surface of the cuvette as the origin of the thermal radiation. The sclera accomplish that because it is a tissue completely avascular, white and cold in relation to the conjunctiva /plasma interface which has the heat source coming from the blood and plasma, The efficiency with which glucose absorbs light is called extinction coefficient (E). E is measured as the amount of absorption produced over 1cm optical path length by 1 molar solution. Then, the radiation absorbed or Absorbance ($A=\log I_o/I$) by the dissolved material (e.g., glucose) equals the molar extinction coefficient (E) of the substance of interest for the particular wavelength employed times the concentration (c) times the optical path length (d). The equation can be written as:

$$A = \log(I_o/I) = E \cdot c \cdot d \quad (1)$$

[0196] And rewritten to determine the unknown concentration (c)

$$c = A/E \cdot d \quad (2)$$

where Io can be measured as the original intensity of the incident radiation, I is the transmitted intensity through the sample corresponding to the substance of interest according to the wavelength selected and can be detected with a photodetector,

[0197] The other two interfering problems above, self-absorption and thermal gradient, are also eliminated providing the accuracy and precision needed for clinical application. There is no self-absorption by tissues. The radiation (heat) is generated by the local blood/plasma flow and the only tissue traversed is the conjunctival lining which does not absorb the radiation. There is no other tissue interposed in the path from source (heat in the eye surface) to detector. In addition, there are no deep or superficial layers interposed and since the source of heat (blood/plasma) is in direct apposition to the detector, thermal gradient is insignificant.

[0198] Filters can limit the wavelength (thermal radiation) to the desired range. It is understood that multiple filters with different wavelength selectivity can be used for the simultaneous measurement of various substances of interest For example a selective filter allows passage of 9,400 nm band when the substance of interest is glucose. The incident thermal energy traversing the detector, for example a thermopile detector, is proportional to the glucose concentration according to a calibration reference. Alternatively filters can be used to select a wavelength of interest and a reference wavelength to calculate the concentration of the substance of interest as previously described. Yet alternatively the ratio of the concentration of water to the substance of interest can be used to determine the concentration since the concentration of water is known (molecular weight of water is 18 forming a 55.6 molar solution with water band at 11000 nm).

[0199] FIG. 5 shows the far-infrared detection Intelligent Contact Lens 2650 in the eyelid pocket 2420 which provides non-invasive measurement of the substance of interest using natural eye emission as heat in addition to providing measurement of core temperature of the body. The sensor 2654, in contact with the conjunctiva 2656 and substance of interest 2350, draws thermal energy (heat) from said conjunctiva/plasma 2658 and maximizes the temperature detection function. There is no interference since the heat source which is the blood/plasma flow in the surface of the conjunctiva 2656 is in direct apposition to the sensor 2654. The eyelid pocket 2420 functions as a cavity since the eyelid edge 2693 is tightly opposed to the surface of the eyeball 2692. The eyelid pocket 2420 provides a sealed and homogeneous thermal environment. There is active heat transfer from the conjunctiva/plasma 2658 to the sensor 2654 caused by local blood/plasma flow which is in direct contact with said sensor 2654. The opposing surface, the sclera 2659, serves as an insulating element. The increasing surface-to-surface contact as occur naturally in the eyelid pocket 2420 (conjunctiva surface-to-sensor surface contact) increases the rate of heat energy 2660 transfer from conjunctiva 2656 to temperature sensor 2654.

[0200] FIG. 6 shows the far-infrared detection Intelligent Contact Lens 2651 in the eyelid pocket 2420 which provides non-invasive measurement of the substance of interest using natural eye emission as heat in addition to providing measurement of core temperature of the body. The sensor 2654 in contact with the red palpebral conjunctiva 2657 and substance of interest 2350 draws energy from said conjunctiva 2657 and blood vessels 2661 to maximize temperature detection function. The heat source which is the blood/plasma flow in the surface of the conjunctiva 2657 is in direct apposition to the sensor 2654. The eyelid pocket 2420 functions as a cavity since the eyelid edge 2693 is tightly opposed to the surface of the eyeball 2692.

[0201] The eyelid pocket 2420 provides a sealed and homogeneous thermal environment with capillary level 2661 present in the surface. There is active heat transfer from the vessels 2661 to the sensor 2654 caused by local blood/plasma flow which is in direct contact with said sensor 2654. The increasing surface-to-surface contact as occur naturally in the eyelid pocket 2420 (conjunctiva surface-to-sensor surface contact) increases the rate of heat energy 2660 transfer from conjunctiva 2657 to tempera-

ture sensor 2654.

[0202] FIG. 7 shows an alternative embodiment illustrating a cross-section view of the eye with cornea 2694, upper and lower eyelids 2410, 2411, anterior segment of the eye 2696 with aqueous humor 2588 and substance of interest 2350 in said anterior chamber 2696 of the eye. FIG. 7 also shows the eyes closed with the thermal sensor 2654 located on the surface of the cornea 2694 and the substance of interest 2350 and thermal emission 2660 coming through the cornea 2694. When the eyelids are closed (during blinking or during sleeping), the thermal environment of the eye is exclusively internal corresponding to the core temperature of the body. This alternative embodiment can be preferably used for measurement of temperature or substance of interest 2350 during sleeping.

[0203] FIG. 8 shows a schematic illustration of another preferred embodiment using non-contact infrared detection of thermal radiation from the conjunctiva/plasma interface 2310. A penlight 2731 measuring device receives radiation 2660 which passes through filter 2733 corresponding to high correlation with the substance of interest 2350 and filter 2732 that works as a reference filter outside of the range corresponding to the substance of interest 2350. The pen 2731 contains the electronics and processing (not shown) needed to calculate and display the data. Display 2737 shows the concentration of the substance of interest, for example the glucose value and display 2735 shows the temperature value. FIG 9-11 shows illustratively the different locations in the eye that measurement canbe done, in the conjunctiva 2739, in the inner canthal area and tear punctum 2741, and in the cornea 2742.

[0204] FIG. 12 is a block diagram of a continuous measurement system of the invention in which the infrared detector is mounted preferably in the frame of eye glasses. A head-band and the like can also be used. The field of view of the infrared sensor is directed at the exposed conjunctival area when the eyes are open. The continuous signal of the infrared sensor is delivered to a RF transmitter which transmits the signal to an external receiver for subsequent processing and display.

[0205] FIG. 13 shows the measuring pen 2731 coupled with a telescope or lighting system which are in line with the area from which radiation is being emitted from the surface of the eye. This allows precise aim and indicates the area being measured for consistency.

[0206] FIGS. 14 is a schematic view of the probe of pen 2731. The tip rests against the conjunctiva 2320 with a sensor arrangement located in a recess inside the tip of the probe. The sensor arrangement includes filter 2662a for the substance of interest and 2662b that is used as a reference and infrared detector 2664.

[0207] FIGS. 15-16 show a cross-sectional view for various positions of the probe of pen 2731 in relation to the conjunctiva. FIG. 15 show the probe resting on the conjunctiva 2320 and covered by disposable cover 2665 while FIG. 16 shows the probe receiving thermal radiation 2660 away from the conjunctiva 2320.

[0208] FIGS 17-19 show in more detail some arrangements for selecting substance of interest according to the wavelength. FIG. 18 shows filter 2662a corresponding to the substance of interest and filter 2662b used as a reference. FIG 19 shows a similar arrangement as in FIG. 18 with an additional temperature sensor 2667. FIG 17 shows a preferred embodiment with a selection arrangement consisting of infrared sensor 2662e receiving thermal radiation 2660 from conjunctiva 2320 at the body temperature. Infrared sensor 2662e has two junctions, a cold junction 2662d and a hot junction 2662c. The cold junction is covered with a membrane (not shown) to reduce the amount of heat reaching said cold junction 2662d. In addition, the cold junction 2662d is artificially cooled and thus receives the radiation from the conjunctiva 2320 at a lower temperature. The increased temperature gradient created increases the voltage signal of detector 2662e facilitating determination of the concentration of the substance of interest. Alternatively, the cold junction 2662d is mounted surrounding the hot junction 2662c (not shown) and an aperture is created to direct the heat toward the hot junction 2662c while avoiding the cold junction 2662d. The above arrangements which increase the temperature gradient in the infrared sensor helps said sensor 2662e to remain with a high signal since when the narrow band pass filter is placed in front of the infrared detector the signal is decreased. Narrow band pass filters such as found in rotatable filter 2673 are placed preferably in front of the hot junction and centered at the wavelength corresponding to the substance of interest. The signal can also be increased by increasing the number of junctions in the detector and increasing the resistance. A thermistor can be incorporated to measure the temperature in the cold junction in order to accurately measure the temperature of the conjunctiva. The probe head 2731a a of pen 2731 can include a wall (not shown) positioned between sensor 2662c and sensor 2662d.

[0209] A variety of means can be used to increase the temperature gradient between the hot and cold junctions of a thermopile and increase the signal including using a power source to bring the cold junction to a lower temperature. Besides using thermoelectric means, contact cooling with cold crystals or cold bodies can be used to decrease the temperature of the sensor. When using the contact device 2400 the cooling of the cold junction cools the conjunctiva in a very efficient manner since the conjunctiva is very thin and has a small thermal mass. When using the pen 2731 the cooling of the infrared sensor is carried from the surface of the sensor to the conjunctival surface with cooling of said conjunctival surface.

[0210] Due to the characteristics of the conjunctiva/plasma interface as described, with direct application of Beer-Lambert's law and determination of a precise calibration line, a reference filter may be eliminated. This simple and cost-effective arrangement is only possible in a place like the conjunctiva/plasma interface. The in-

tensity of the received radiation is evaluated against a predetermined calibration line and corrected according to the temperature detected.

[0211] The characteristics of the plasma-conjunctiva interface allows a variety of hardware arrangements and techniques to be used in order to determine the concentration of the substance of interest as has been described. One preferred embodiment is shown as a cross-sectional view in FIGS. 21. The arrangement of probe head of pen 2731 includes a rotatable filter 2763 for measurement of various substances according to selection of the appropriate filter corresponding to the substance of interest. FIG. 20 shows a planar view ofrotatable filter 2673 including three narrow bandpass filters. The rotatable filter 2673 contains filters 2663, 2669, 2671 corresponding to the wavelength of three different substances.

[0212] For example filter 2663 is centered at 9400 nm for measuring glucose, filter 2669 is centered at 8300 nm for measuring cholesterol and filter 2671 is centered at 9900 nm for measuring ethanol. Filter 2667 is centered at between 10.5 m and 11 m and is used as a reference filter. The filter being used is in apposition with detector 2664. The filters not being used, for example filter 2663 rests against a solid part 2773 of the probe not permeable to infrared radiation. Although only one reference filter is shown it is understood that a similar rotatable system with different reference filters can be used according to the substance being measured. Infrared detector 2664 can consist of passive detectors such as thermopile detectors. The electrical signal generated by detector 2664 is fed into the processor (not shown) for determination of the concentration of the substance of interest. A variety of focusing lens and collimating means known in the art including polyethylene lens or calcium fluoride lens can be used for better focusing radiation into infrared detector 2664.

[0213] By applying Beer-Lambert's law, the ratio of the reference and measured values is used to calculate the concentration of the substance of interest independent of the temperature value. One preferred method for determining the concentration of the substance of interest is to direct the field of view of the detector to capture radiation coming from the medial canthal area of the eye (comer of the eye), which is the hottest spot on the surface of the human body. The field of view of an infrared detector can also be directed at the eyelid pocket lining after the eyelid is pulled away.

[0214] FIG. 22 shows another preferred temperature measuring system 2675 in which the temperature detector 2677 rests against the canthal area (inner corner of the eye) and tear duct of the eye and the body 2679 of the contact device rests in the eyelid pocket. FIG. 23 shows an alternative embodiment for measurement of concentration of substances using far infrared thermal emission from the eye and a temperature gradient. The contact device 2703 includes infrared sensor 2704. Infrared sensor 2704 has a superior half 2704a exposed to ambient temperature above the eyelid pocket and the inferior half2704b remains inside the eyelid pocket measuring core temperature. Alternatively, one sensor can be placed against the skin and another one in the eyelid pocket.

[0215] FIG. 24 shows a device 2705 for measuring substances of interest or temperature using a band or ring-like arrangement including both the upper and lower eyelid pockets.

[0216] FIG. 25 shows the pen 2706 connected to an arm 2707 at a fixed distance. The tip of the pen or probe 2706 has an angled tip to fit with the curvature of the sclera with a radius of approximately 11.5 mm. The filed of view of the pen 2706 is in accordance with the distance of the eye surface to the sensor. The arm 2707 can be used to push the lower lid down and expose the conjunctival area to be measured. This facilitates exposing the conjunctiva and provides measurement of the same location and same distance. Fresnell lenses can be added to measure temperature at a longer distances. An articulated ann or flexible shaft can also be used to facilitate reaching the area of interest.

[0217] Other alternative means to determine the concentration of the substance of interest using the conjunctiva/plasma interface includes using an actual reference cell with a known amount of the substance being measured incorporated in the pen 2731 which is used as a reference. In addition, stimulating an enzymatic reaction to process glucose can be used. Since processing of glucose can cause an exothermic reaction, the amount of heat generated can be correlated with the amount of glucose.

[0218] FIG. 26 shows simultaneous measurement of temperature of the right and left eye with a non-contact infrared system 2693. Arm 2695 carries a sensor measuring temperature for the right eye which is displayed on display 2701. Arm 2697 carries a sensor measuring temperature for the left eye which is displayed on display 2669. The difference in temperature (left eye is 38.3°C (101°F), and right eye 36.1°C (97°F) can be indicative of a disorder. An asymmetric eye temperature also can corresponds with carotid disease and nervous system abnormalities. Although temperature was used as an illustration, the device can also be used for detecting asymmetry in the concentration of chemical substances.

[0219] The invention includes the following aspects:

22. An apparatus for noninvasive measurement of a concentration of at least one substance in the eye, said apparatus comprising: a detecting device for receiving infrared energy from the eye and for measuring infrared absorption of at least one substance present in said eye based upon the infrared energy generated by the eye, and a processing device for determining the concentration of the at least one substance based upon the infrared absorption.

23. The apparatus of aspect 22, wherein said at least one substance includes at least one of glucose, eth-

anol and cholesterol.

24. The apparatus of aspect 22, further comprising two narrow band pass filters disposed between the eye and said detecting device, one of the narrow bandpass filters passing infrared energy in a wavelength corresponding to absorption of said infrared energy by the substance being measured and the other of the narrow bandpass filters passing infrared energy outside the wavelength of absorption of the substance being measured.

25. The apparatus of aspect 24, wherein said one filter has a bandwidth centered on about 9,400 nm and the other filter has a band width centered at between 10,500 and 11, 000 nm.

26. The apparatus of aspect 24, wherein said one filter has a bandwidth centered on about 9,900 nm and the other filter has a band width centered at between 10,500 and 11,000 nm.

27. The apparatus of aspect 24, wherein said one filter has a bandwidth centered on about 8,300 nm and the other filter has a band width centered at between 10,500 and 11,000 nm.

28. The apparatus of aspect 21, wherein a cooling device is used to increase a temperature gradient between a cold junction and a hot junction of an infrared sensor of said detecting device.

29. An apparatus for noninvasive measurement of a concentration of at least one substance in the eye, said apparatus comprising: a detecting device for detecting radiation intensity of two wavelengths of light in an infrared region emitted by said eye with said detecting device detecting radiation intensity of the two wavelengths with one of said wavelengths having a high absorption correlation with the substance being measured and the other of said wavelengths having a lower absorption correlation with the substance being measured and providing an output signal, and a processing device for processing the output signal obtained from the detecting device for determining the concentration of the at least one substance according to the absorption of infrared energy by said substance.

30. A method for noninvasive measuring at least one substance in the eye, said method comprising the steps of: receiving and detecting infrared energy from said eye, determining infrared absorption of at least one substance present in said eye from said infrared energy from said eye, and processing and determining the concentration of said at least one substance from the infrared absorption.

31. A method for noninvasive measurement of at least one substance in the eye, said method comprising the steps of : detecting two wavelengths in the infrared region emitted by said eye with one of said wavelengths having a high absorption correlation with the substance being measured and the other of said wavelengths having a lower absorption correlation with the substance being measured, and processing the detected wavelengths for determining a concentration of at least one substance according to the absorption of infrared energy by said substance.

32. An apparatus for noninvasive measurement of at least one substance in the eye, said apparatus comprising: a receiving device for receiving infrared energy from said eye, a detecting device for determining infrared absorption of at least one substance present in said eye from the infrared energy generated by said eye, a sensor for measuring temperature of said eye, a processing device for determining temperature of the eye and the concentration of at least one substance based upon the infrared absorption and the measured temperature.

33. A method for noninvasive measurement of at least one substance in the eye, said method comprising the steps of: receiving infrared energy from said eye, determining an amount of infrared absorption of at least one substance present in said eye from the infrared energy generated by said eye, measuring temperature of said eye, and determining the amount of the concentration of at least one substance based upon the infrared absorption and temperature of the eye.

Claims

1. An apparatus (2650, 2651, 2731) for noninvasive measurement of a concentration of at least one substance (2350) in or on a conjunctiva of an eye, the apparatus comprising
a detecting device (2654) arranged for detecting infrared radiation (2660) generated as natural thermal emission from said conjunctiva of said eye and for measuring infrared absorption by said substance, wherein the infrared radiation has a wavelength from 4,000 nanometers to 14,000 nanometers, and
a processor arranged for determining the concentration of the at least one substance based upon the absorption of infrared radiation, generated as natural thermal emission by said eye, by the at least one substance.

2. The apparatus of claim 1, wherein said at least one substance includes at least one of glucose, ethanol and cholesterol.

3. The apparatus of claim 1 or claim 2, further comprising at least one filter (2262, 2733) for selecting an infrared radiation wavelength.

4. The apparatus of claim 3, wherein the at least one filter has a bandwidth centered on about 9,400 nm corresponding to the radiation signature of glucose.

5. The apparatus of claim 3, wherein the at least one filter has a bandwidth centered on about 9,900 nm corresponding to the radiation signature of ethanol.

6. The apparatus of claim 3, wherein the at least one filter has a bandwidth centered on about 8,300 nm corresponding to the radiation signature of cholesterol.

7. The apparatus of claim 3, wherein the at least one filter passes radiation having wavelengths from 9,000 nanometers to 11,000 nanometers.

8. The apparatus of any preceding claim, wherein the apparatus is a pen device (2731) adapted to be held by a hand of a subject.

9. The apparatus of claims 1 to 7, further comprising a housing (2652, 2653) adapted for placement in an eyelid pocket, the housing comprising the detecting device.

10. A method for noninvasive measurement of at least one substance in or on the conjunctiva of an eye, the method comprising the steps of:

receiving and detecting infrared radiation generated as natural thermal emission by an eye,
determining infrared absorption of at least one substance present in or on the conjunctiva of the eye from the infrared radiation generated as natural thermal emission from the eye, and
determining the concentration of the at least one substance from the infrared absorption,
wherein, the infrared radiation has a wavelength from 4,000 nanometers to 14,000 nanometers.

11. The method of claim 10 further comprising measuring the temperature of the eye and determining the concentration of the at least one substance from the infrared absorption and from the temperature of the eye.

12. The method of claim 10 or claim 11, further comprising a step of selecting a desired wavelength of the infrared radiation.

13. The method of claim 12, wherein the infrared radiation comprises infrared radiation having wavelengths from 9,000 nanometers to 11,000 nanometers.

14. The method of any one of claims 10 to 13, wherein the at least one substance includes at least one of glucose, ethanol and cholesterol.

15. The method of any one of claims 10 to 14, wherein determining infrared absorption of the at least one substance is carried out within the eyelid pocket.

Patentansprüche

1. Gerät (2650, 2651, 2731) zur nichtinvasiven Messung einer Konzentration mindestens einer Substanz (2350) in oder an einer Augenbindehaut, wobei das Gerät aufweist:

eine Nachweisvvzxielxtung (2654), die für den Nachweis von Infrarotstrahlung (2660), die als natürliche Wärmeausstrahlung von der Augenbindehaut erzeugt wird, und zur Messung der Infrarotabsorption durch die Substanz eingerichtet ist, wobei die Infrarotstrahlung eine Wellenlänge von 4000 Nanometer bis 14000 Nanometer aufweist, und
einen Prozessor, der für die Konzentrationsbestimmung der mindestens einen Substanz auf der Basis der Absorption von als natürliche Wärmeausstrahlung des Auges erzeugter Infrarotstrahlung durch die mindestens eine Substanz eingerichtet ist.

2. Gerät nach Anspruch 1, wobei die mindestens eine Substanz mindestens eine der Komponenten Glucose, Ethanol und Cholesterin enthält.

3. Gerät nach Anspruch 1 oder Anspruch 2, das ferner mindestens einen Filter (2662, 2733) zur Auswahl der Wellenlänge der Infrarotstrahlung aufweist.

4. Gerät nach Anspruch 3, wobei der mindestens eine Filter eine auf etwa 9400 nm zentrierte Bandbreite aufweist, die der Strahlungssignatux von Glucose entspricht.

5. Gerät nach Anspruch 3, wobei der mindestens eine Filter eine auf etwa 9900 nm zentrierte Bandbreite aufweist, die der Strahlungssignatur von Ethanol entspricht.

6. Gerät nach Anspruch 3, wobei der mindestens eine Filter eine auf etwa 8300 nm zentrierte Bandbreite aufweist, die der Strahlungssignatur von Cholesterin entspricht.

7. Gerät nach Anspruch 3, wobei der mindestens eine Filter Strahlung mit Wellenlängen von 9000 Nano-

meter bis 11000 Nanometer durchlässt.

8. Gerät nach einem der vorstehenden Ansprüche, wobei das Gerät ein Stiftgerät (2731) ist, das so angepasst ist, das es von einer Person in der Hand gehalten werden kann.

9. Gerät nach einem der Ansprüche 1 bis 7, das ferner ein Gehäuse (2652, 2653) aufweist, das zum Einsetzen in eine Augenlidtasche eingerichtet ist, wobei das Gehäuse die Nachweisvorrichtung aufweist.

10. Verfahren zur nichtinvasiven Messung mindestens einer Substanz in oder an einer Augenbindehaut, wobei das Verfahren die folgenden Schritte aufweist:

Empfang und Nachweis von Infrarotstrahlung, die als natürliche Wärmeausstrahlung durch ein Auge erzeugt wird,
Bestimmen der Infrarotabsorption der in oder an der Augenbindehaut vorhandenen mindestens einen Substanz aus der als natürliche Wärmeausstrahlung des Auges erzeugten Infrarotstrahlung, und
Bestimmen der Konzentration der mindestens einen Substanz aus der Infrarotabsorption,
wobei die Infrarotstrahlung eine Wellenlänge von 4000 Nanometer bis 14000 Nanometer aufweist.

11. Verfahren nach Anspruch 10, das ferner eine Temperaturmessung des Auges und die Konzentrationsbestimmung der mindestens einen Substanz aus der Infrarotabsorption und aus der Temperatur des Auges aufweist.

12. Verfahren nach Anspruch 10 oder Anspruch 11, das ferner einen Schritt zur Auswahl einer gewünschten Wellenlänge der Infrarotstrahlung aufweist.

13. Verfahren nach Anspruch 12. wobei die Infrarotstrahlung eine Infrarotstrahlung mit Wellenlängen von 9000 Nanometer bis 11000 Nanometer aufweist.

14. Verfahren nach einem der Ansprüche 10 bis 13, wobei die mindestens eine Substanz mindestens eine der Komponenten Glucose, Ethanol und Cholesterin enthält.

15. Verfahren nach einem der Ansprüche 10 bis 14, wobei die Bestimmung der Infrarotabsorption der mindestens einen Substanz innerhalb der Augenlidtasche ausgeführt wird.

Revendications

1. Appareil (2650, 2651, 2731) pour une mesure non invasive d'une concentration d'au moins une substance (2350) dans ou sur une conjonctive d'un oeil, l'appareil comprenant:

un dispositif de détection (2654) agencé pour détecter un rayonnement infrarouge (2660) généré comme une émission thermique naturelle provenant de ladite conjonctive dudit oeil et pour mesurer l'absorption infrarouge par ladite substance, dans lequel le rayonnement infrarouge possède une longueur d'onde de 4.000 nanomètres à 14.000 nanomètres, et
un processeur agencé pour déterminer la concentration de la au moins une substance sur la base de l'absorption du rayonnement infrarouge, généré comme une émission thermique naturelle par ledit oeil, par la au moins une substance.

2. Appareil selon la revendication 1, dans lequel ladite au moins une substance inclut au moins un parmi le glucose, l'éthanol et le cholestérol.

3. Appareil selon la revendication 1 ou la revendication 2, comprenant en outre au moins un filtre (2662, 2733) pour sélectionner une longueur d'onde de rayonnement infrarouge.

4. Appareil selon la revendication 3, dans lequel le au moins un filtre possède une largeur de bande centrée sur environ 9.400 nm correspondant à la signature de rayonnement du glucose.

5. Appareil selon la revendication 3, dans lequel le au moins un filtre possède une largeur de bande centrée sur environ 9.900 nm correspondant à la signature de rayonnement de l'éthanol.

6. Appareil selon la revendication 3, dans lequel le au moins un filtre possède une largeur de bande centrée sur environ 8.300 nm correspondant à la signature de rayonnement du cholestérol.

7. Appareil selon la revendication 3, dans lequel le au moins un filtre laisse passer un rayonnement possédant des longueurs d'onde de 9.000 nanomètres à 11.000 nanomètres.

8. Appareil selon l'une quelconque des revendications précédentes, où l'appareil est un dispositif de type stylo (2731) adapté pour être tenu par la main d'un sujet.

9. Appareil selon les revendications 1 à 7, comprenant en outre un boîtier (2652, 2653) adapté pour un pla-

cement dans une poche de paupière, le boîtier comprenant le dispositif de détection.

10. Procédé pour une mesure non invasive d'au moins une substance dans ou sur la conjonctive d'un oeil, le procédé comprenant les étapes de:

réception et détection d'un rayonnement infrarouge généré comme une émission thermique normale par un oeil,
détermination de l'absorption infrarouge d'au moins une substance présente dans ou sur la conjonctive de l'oeil à partir du rayonnement infrarouge généré comme une émission thermique normale à partir de l'oeil, et
détermination de la concentration de la au moins une substance à partir de l'absorption infrarouge,
dans lequel le rayonnement infrarouge possède une longueur d'onde de 4.000 nanomètres à 14.000 nanomètres.

11. Procédé selon la revendication 10, comprenant en outre la mesure de la température de l'oeil et la détermination de la concentration de la au moins une substance à partir de l'absorption infrarouge et à partir de la température de l'oeil.

12. Procédé selon la revendication 10 ou la revendication 11, comprenant en outre une étape de sélection d'une longueur d'onde désirée du rayonnement infrarouge.

13. Procédé selon la revendication 12, dans lequel le rayonnement infrarouge comprend un rayonnement infrarouge possédant des longueurs d'onde de 9.000 nanomètres à 11.000 nanomètres.

14. Procédé selon l'une quelconque des revendications 10 à 13, dans lequel la au moins une substance inclut au moins un parmi le glucose, l'éthanol et le cholestérol.

15. Procédé selon l'une quelconque des revendications 10 à 14, dans lequel la détermination de l'absorption infrarouge de la au moins une substance est réalisée dans la poche de la paupière.

FIG. 1

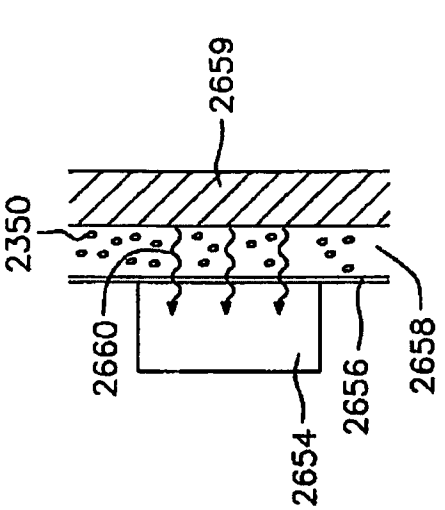


FIG. 2

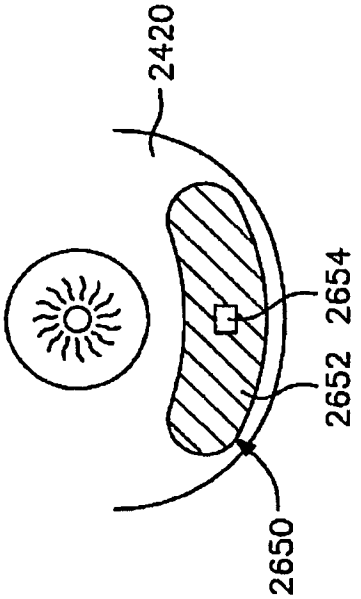


FIG. 3

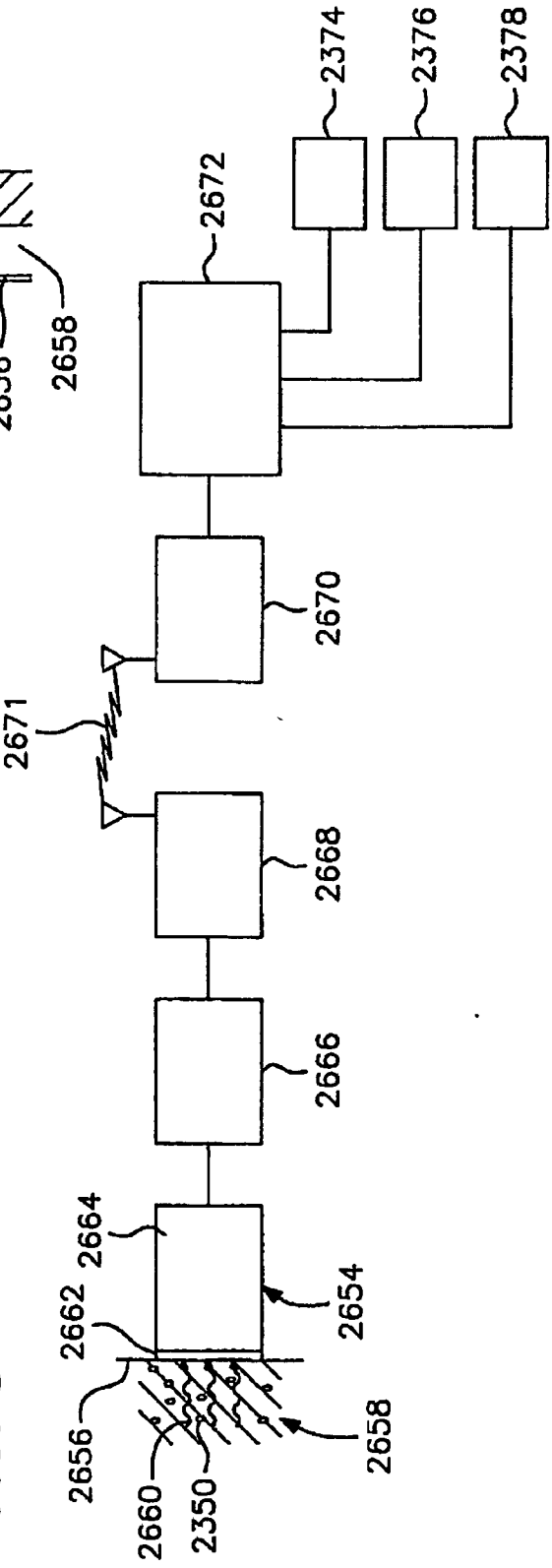
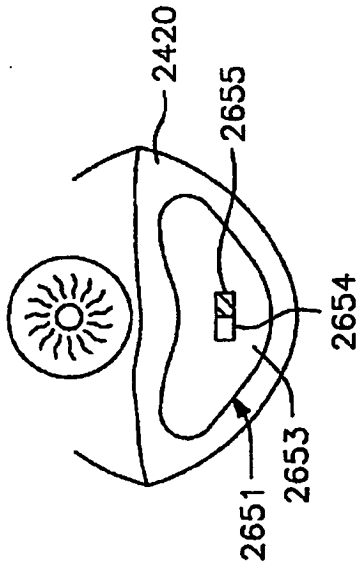


FIG. 4



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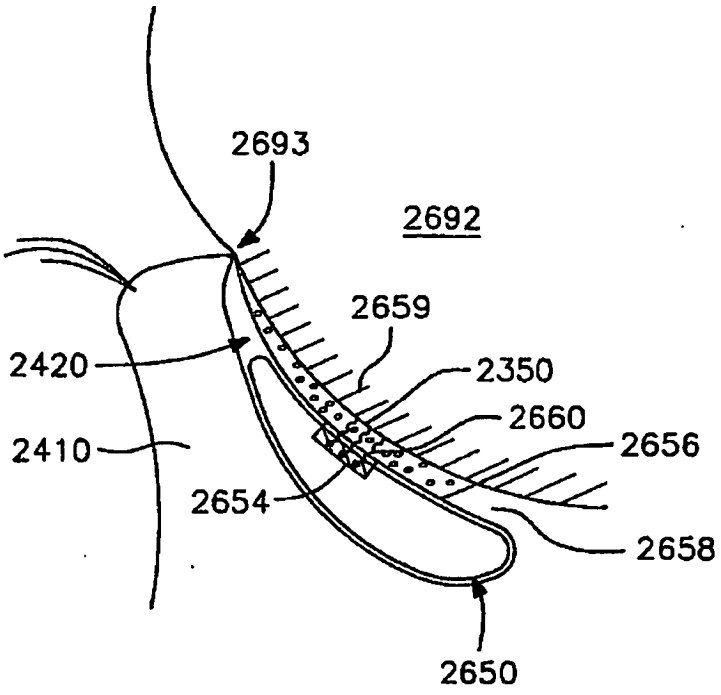

FIG. 6

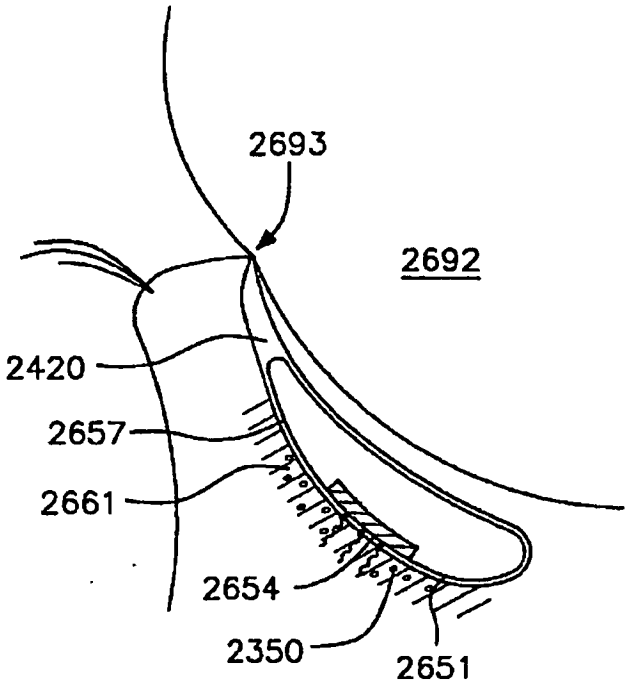
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FIG. 7

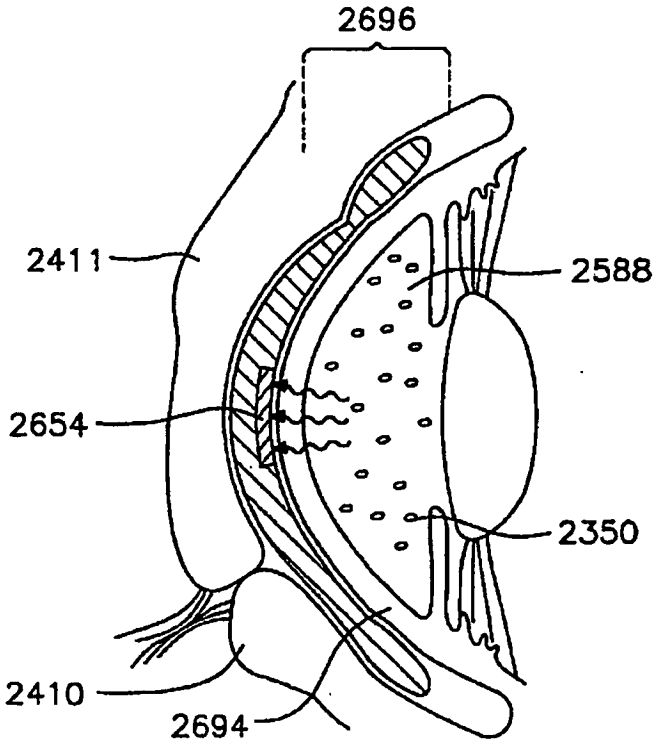
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FIG. 8

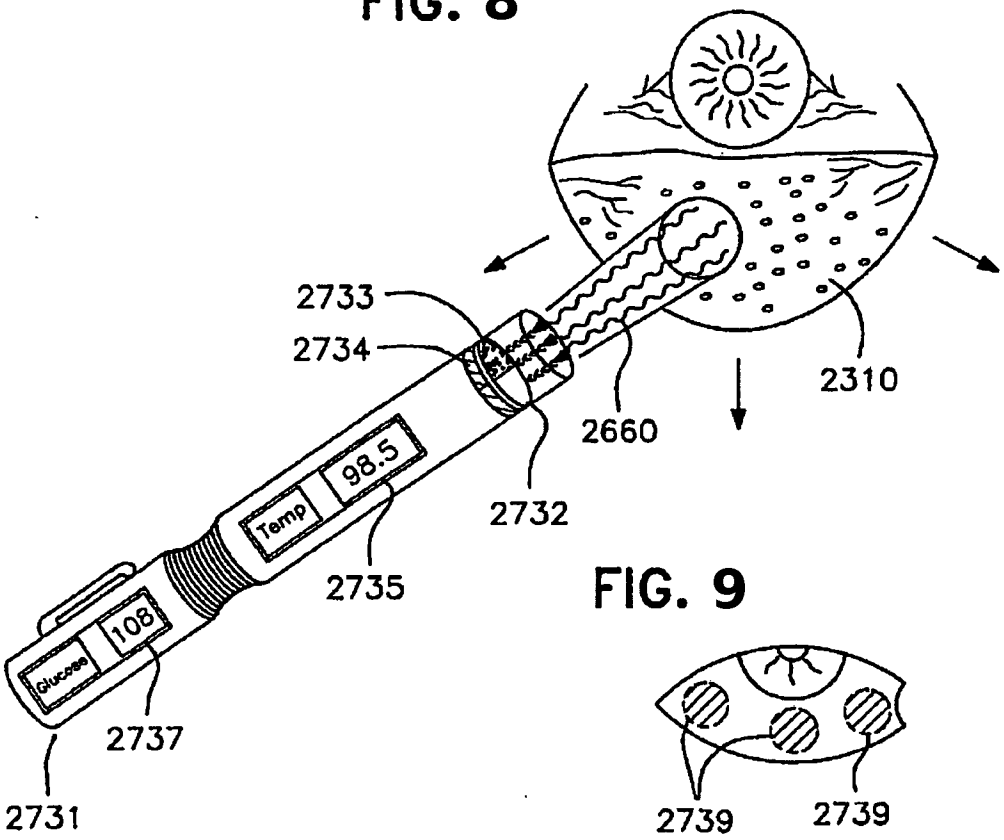
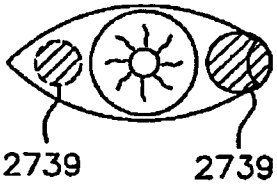


FIG. 9

FIG. 10

FIG. 11



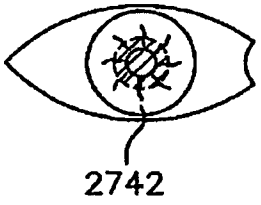


FIG. 12

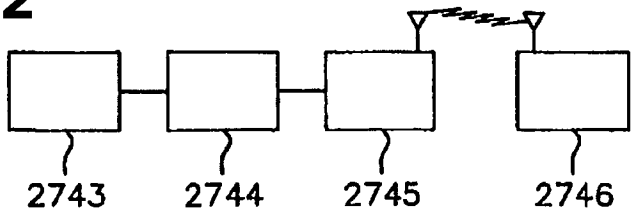


FIG. 13

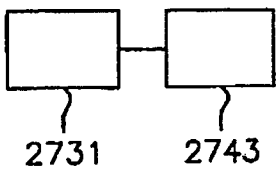


FIG. 14

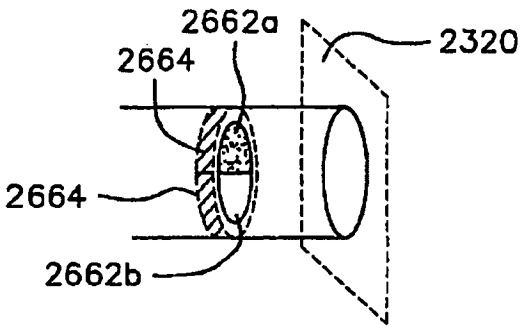


FIG. 15

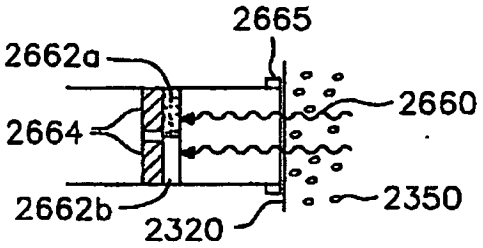


FIG. 16

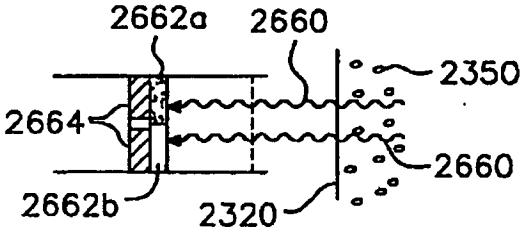


FIG. 17

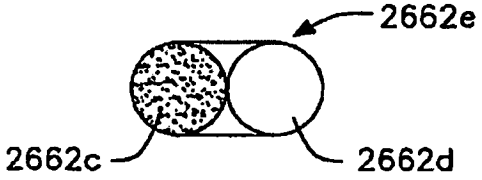


FIG. 18

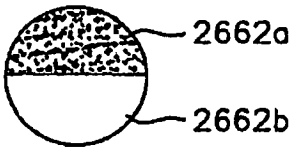


FIG. 19

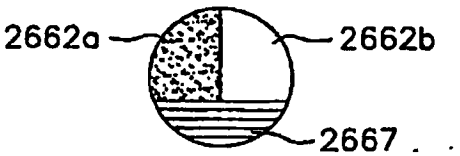


FIG. 20

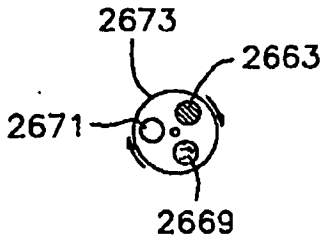


FIG. 21

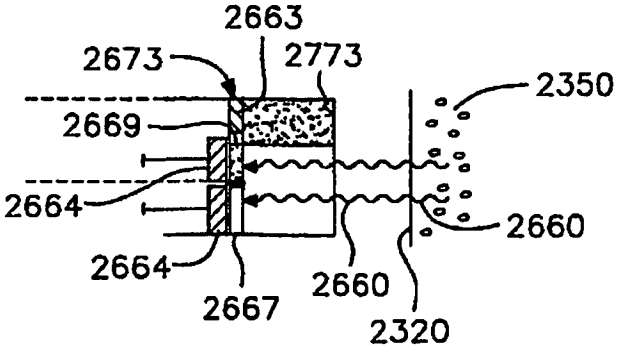


FIG. 22

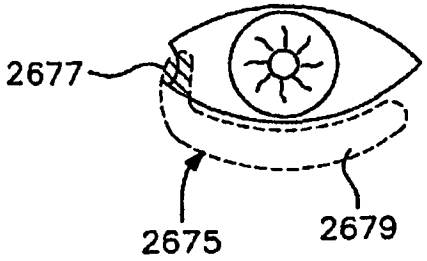


FIG. 23

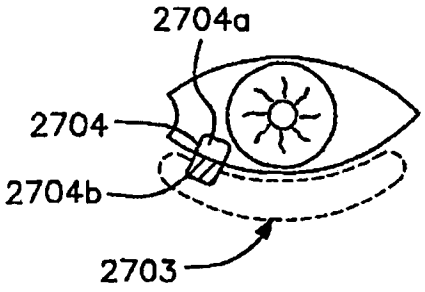


FIG. 24

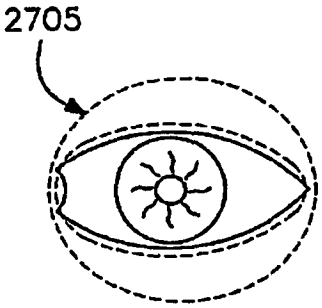


FIG. 25

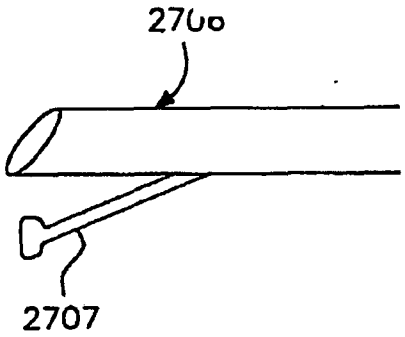
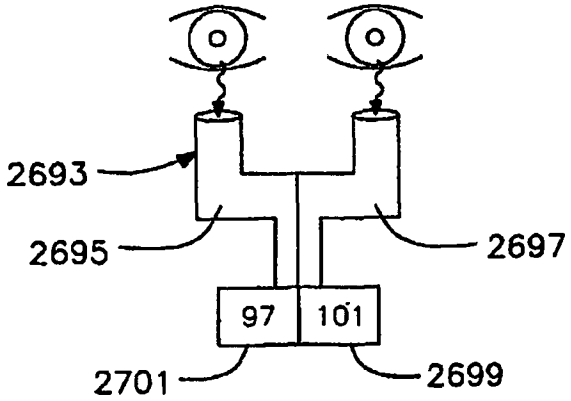


FIG. 26



REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 9307801 A **[0030]**
- US 5313941 A **[0031]**

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公开(公告)号	EP1818008B1	公开(公告)日	2011-11-02
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IPC分类号	A61B5/1455 G01N27/327 A61B3/10 A61B3/117 A61B3/12 A61B3/16 A61B5/00 A61B5/01 A61B5/02 A61B5/022 A61B5/025 A61B5/03 A61B5/11 A61B5/145 A61B5/18 A61B8/06 A61F9/00 A61F9/007 A61K31/409 A61K45/00 A61N1/365 A61N1/39 A61N5/06 A61N5/10 A61P9/00 A61P27/02 A61P27/06 A61P35/00 G01N21/35 G01N27/416		
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代理机构(译)	INSTONE，TERRY		
优先权	09/790653 2001-02-23 US		
其他公开文献	EP1818008A1		
外部链接	Espacenet		

摘要(译)

一种用于非侵入式测量眼睛中至少一种物质的浓度的装置，包括检测装置，用于接收来自眼睛的红外能量，并用于基于由所产生的红外能量测量所述眼睛中存在的至少一种物质的红外吸收。眼睛和用于基于红外吸收确定至少一种物质的浓度的处理装置。