



(51) International Patent Classification:

A61B 5/00 (2006.01) G01N 21/62 (2006.01)
G01N 21/17 (2006.01)

(21) International Application Number:

PCT/IL2009/000675

(22) International Filing Date:

6 July 2009 (06.07.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/078,412 6 July 2008 (06.07.2008) US
61/078,410 6 July 2008 (06.07.2008) US

(71) Applicant (for all designated States except US): **OR-NIM MEDICAL LTD.** [IL/IL]; 1 Yodfat Street, 71291 Lod (IL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ROKNI, Michal** [IL/IL]; 1 Inbar Street, 30900 Zichron Ya'akov (IL). **SCHECHTER REVITAL, Pery** [IL/IL]; 52 Hatizmoret Street, 75573 Rishon Lezion (IL). **BRESKIN, Ilan** [IL/IL]; 10 Toledano Street, 62334 Tel-Aviv (IL). **BALBERG, Michal** [IL/IL]; 19 Nof Harim, 96190 Jerusalem (IL). **METZGER, Yaakov** [IL/IL]; 8 Bareket Street, 45046 Hod Hasharon (IL).

(74) Agent: **REINHOLD COHN AND PARTNERS**; P.o.b. 4060, 61040 Tel-Aviv (IL).

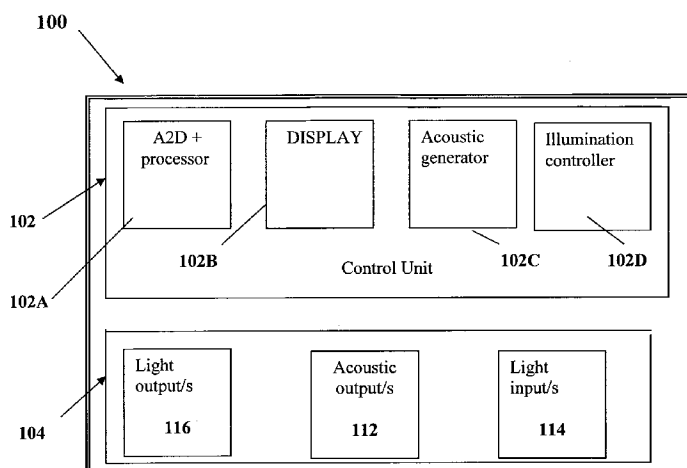
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: METHOD AND SYSTEM FOR NON-INVASIVELY MONITORING FLUID FLOW IN A SUBJECT



(57) Abstract: A monitoring system is presented for monitoring fluid flow in turbid medium. The fluid flow monitoring system comprises a processor utility which is connectable to an acoustic generator associated with one or more acoustic ports and is operable for generating signals S to activate said one or more acoustic ports for irradiating a region of interest with acoustic radiation of a certain frequency range centered at a frequency F and is connectable to at least one light output port associated with one or more light detectors for receiving light of at least one wavelength λ from the region of interest including light tagged by said acoustic radiation. In some embodiments, the processor utility is configured and operable for analyzing the generated signals S and data indicative of the received light including light tagged by the corresponding acoustic radiation and determining correlation between said acoustic signals S and said data indicative of the received light, said correlation being informative of a measure of fluid flow in the medium.

- 1 -

METHOD AND SYSTEM FOR NON-INVASIVELY MONITORING FLUID FLOW IN A SUBJECT

FIELD OF THE INVENTION

The invention is generally in the field of fluid flow measurements, and relates to a method and system for monitoring fluid flow through turbid media. The invention is particularly useful for medical applications such as measuring blood flow in a subject,
5 as well as measurement of some other blood related parameters.

BACKGROUND OF THE INVENTION

Remote monitoring of fluid flow provides utility across a wide range of industrial and healthcare applications. In medical diagnosis, treatment and monitoring, there is frequent need to measure blood flow in order to monitor tissue perfusion,
10 metabolism and general health. This need stems from the biological requirement for transport of oxygen and nutrients to tissues and the removal of waste products (M. E. Raichle and M. A. Mintun, "Brain work and brain imaging", *Annu Rev Neurosci* 2006; 29:449-476).

Existing methods for measuring biological flow include laser Doppler measures
15 of reflected energy changes (as disclosed for example in U.S. Pat. 4,1096,47), variation in impedance on the scalp surface (e.g. US 2008/0200787), or the use of invasive flowmeters implanted directly into the tissue (e.g. U.S. Pat. 5,579,774).

Various techniques for non-invasive measurements of blood related parameters have been developed. Such techniques include frequency-domain spectroscopy, and
20 photoacoustic spectroscopy [D M Hueber *et al* *Phys. Med. Biol.* 46 (2001) 41–62].

A productive approach to non-invasive monitoring in healthcare settings is the use of ultrasound tagged light. (U.S. Pat. 7,541,602, WO 06/097910, WO 05/025399, all

- 2 -

assigned to the assignee of the present application). In this method, the intersection of electromagnetic and acoustic signals has been used to monitor tissue optical properties.

GENERAL DESCRIPTION

5 There is a need in the art for a novel technique enabling the fluid flow measurement, such as blood flow, in a non-invasive, non-ionizing manner to limit discomfort and possible hazards to a patient.

 The present invention utilizes the principles of *ultrasound tagging of light* to monitor flow within a turbid medium. More specifically, the tagging of light by
10 acoustic radiation is used to determine the optical response of a region of interest in the medium, enabling determination of the flow within the region of interest from said optical response. More specifically, according to this technique, a region of interest in a subject (e.g. human body) is illuminated with light of at least one wavelength, and is irradiated with acoustic radiation (preferably ultrasound) such that the acoustic radiation
15 overlaps the illuminated region in at least a part of the region of interest (this overlapping volume is termed "*tagged volume*"). Light scattered from the subject's body, including photons that are tagged by the acoustic radiation and those that are not, is appropriately detected.

 The main idea of some aspects of the invention is to extract information about
20 the blood flow in a subject (generally fluid flow in turbid media) from acousto-optic measurements based on the ultrasound tagging of light. The inventors have found that correlation between light tagged by acoustic radiation and the signal which generates the corresponding acoustic radiation is indicative of a measure of fluid flow in the medium. Also, the inventors have found that a measure of blood flow can be obtained
25 from data indicative of a power spectrum of the received light, including light tagged by the acoustic radiation, namely from the parameters of at least one peak in said power spectrum.

 The following examples can be used to determine parameters of the signal that correspond to measures of flow. According to one not limiting example, for the case of
30 blood flow in tissue, a measure of flow can be defined as: blood flow velocity (measured in cm/sec), blood perfusion (measured in mL(blood)/100mg(tissue)/min),

- 3 -

hemoglobin concentration (C_{tot}) as a function of time, oxygenated hemoglobin or oxygen saturation as a function of time.

According to one broad aspect of the invention, there is provided a monitoring system for monitoring fluid flow in a turbid medium. The system comprises a processor utility which is connectable to an acoustic generator associated with one or more acoustic ports and is operable for generating signals S_0 to activate said one or more acoustic ports for generating acoustic radiation of a certain frequency range centered at a frequency F_0 to irradiate a region of interest, and is connectable to at least one light output port associated with one or more light detectors for receiving light of at least one wavelength λ from the region of interest including light tagged by said acoustic radiation. The processor utility is configured and operable for analyzing the generated signals S_0 and data indicative of the received light including light tagged by the corresponding acoustic radiation and determining correlation between said signals S_0 and said data indicative of the received light, said correlation being informative of a measure of fluid flow in the medium.

The acoustic signal has one of the following profiles: a continuous wave (CW); a modulated continuous wave (e.g. coded signal, e.g. coded signal with narrow autocorrelation); and/or a pulse or sequence of pulses.

In some embodiments of the invention, the processor utility is configured and operable to determine said correlation by carrying out the following:

determining cross correlation, $CCA(\tau, \lambda, T)$, between said signals S_0 and said data indicative of the received light, said cross correlation being calculated for each wavelength λ of light and at a time delay τ from onset of the acoustic signal, and

determining autocorrelation $UTLA$ of said cross correlation $CCA(\tau, \lambda, T)$ at different times T , being time stamps of different measurement times, said autocorrelation $UTLA$ being indicative of a measure of fluid flow within the medium as a function of depth z in the medium.

The autocorrelation $UTLA$ for a predetermined τ , being a function of ΔT , τ and λ , can be determined as follows:

$$UTLA(\Delta T, \tau, \lambda) = \int dT \cdot CCA(T, \tau, \lambda) \cdot CCA(T + \Delta T, \tau, \lambda).$$

- 4 -

A measure of flow can be determined from a decay coefficient of $UTLA(\Delta T, \tau, \lambda)$.

The processor utility may be configured for measuring a decay time T_{decay} , thus providing information indicative of the measure of flow within the monitored medium.

- 5 For example, the processor utility calculates the decay time T_{decay} from a single $UTLA$ signal or from a sum/average over such signals.

The monitoring system preferably includes a control panel associated with a measurement unit. This control panel includes said at least one light output, said one or more acoustic ports, and also at least one light input for illumination of the region of
10 interest with light of one or more wavelengths. The light input(s) is/are associated with one or more light sources (e.g. lasers) producing light of different wavelengths, or with at least one tunable light source.

Preferably, the monitoring system includes an illumination controller. The latter may be configured and operable to enable appropriate selection of wavelength(s) to
15 enable measurement of oxygen saturation. To this end, the illumination controller and a light source system are configured to enable selection of at least three different wavelengths for the illumination during measurements, in accordance with a predetermined clinically relevant range of oxygen saturation values. For example, the wavelengths are selected as those corresponding to a minimal difference between
20 attenuation coefficients of the medium over said saturation range.

According to another broad aspect of the invention, there is provided a monitoring system for use in non-invasive measurements of oxygen saturation in a subject, the system comprising a light source system associated with one or more light sources, and an illumination controller configured and operable to enable selection of at
25 least three wavelengths for the illumination during measurements in accordance with a predetermined clinically relevant range of oxygen saturation values.

According to yet another broad aspect of the invention, there is provided a monitoring system for monitoring fluid flow in a turbid medium, the system comprising: a processor utility which is connectable to an acoustic generator associated
30 with one or more acoustic ports and is operable for generating signals (S_0) to activate said one or more acoustic ports for irradiating a region of interest with acoustic

- 5 -

radiation of a certain frequency range centered at a frequency F_0 and is connectable to at least one light output port associated with one or more light detectors for receiving light of at least one wavelength λ from the region of interest including light tagged by said acoustic radiation, the processor utility being configured and operable for analyzing
5 data indicative of a power spectrum of the received light including light tagged by the acoustic radiation; identifying in said data at least one of the following light intensity peaks: a peak around said frequency F_0 , a peak around a harmonic of said frequency F_0 ; and determining a measure of the fluid flow according to parameters of said at least one peak.

10 In some embodiments, the processor utility may also analyze the data indicative of the received light to identify in said data a DC intensity peak and use the parameters of such at least two peaks for the fluid flow measure. The acoustic radiation in this case may be in the form of a continuous wave or modulated continuous wave.

More specifically, the invention is useful for blood flow measurements and is
15 therefore described below with respect to this specific application.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, embodiments will now be described, by way of non-limiting examples only,
20 with reference to the accompanying drawings, in which:

Fig. 1 is a block diagram of an example of a monitoring system of the present invention suitable for non-invasively measuring blood flow in a subject;

Fig. 2 shows an example of a $CCA(\lambda, \tau)$ signal as a function of delay time τ ;

Fig. 3 exemplifies the $CCA(T, \lambda, \tau)$ for different time stamps T ;

25 **Fig. 4** shows a flow diagram of a method of the invention for calculating a flow parameter from the autocorrelation of $CCA(\lambda, \tau)$;

Fig. 5 shows the light intensity power spectrum in the vicinity of the ultrasound frequency (marked as "0");

- 6 -

Fig. 6 shows a flow index defined according to the width of the power spectrum, as a function of time, during a measurement on a human arm that includes two cuff occlusions marked by two straight bold lines;

Fig. 7 illustrates influence of flow on the amplitude of the $CCA(\lambda, \tau)$ signal during a session of cuff occlusion when the light and ultrasound are emitted into the patient's arm;

Fig. 8 shows absorption coefficients spectra for Hb and HbO₂;

Fig. 9 shows $1/\Delta\mu^{12}$; $1/\Delta\mu^{23}$; $1/\Delta\mu^{31}$ as a function of saturation s for three different wavelength $\lambda_1=666\text{nm}$; $\lambda_2=778\text{nm}$; $\lambda_3=872\text{nm}$;

Fig. 10 illustrates an example of selection of wavelengths according to the present invention for optimal measurements of oxygen saturation;

Fig. 11 shows an example of angle $\theta(s)$ between experimental and theoretical vectors as a function of saturation; and

Fig. 12 shows a block diagram of an illumination controller system of the present invention for selection of optimal wavelengths for measurements in accordance with a desired saturation range.

DESCRIPTION OF EMBODIMENTS

Reference is made to **Fig. 1** showing schematically an example of a monitoring system, generally designated **100**, configured and operable according to the invention for non-invasive monitoring of one or more blood related parameters including a blood flow parameter. System **100** is configured as a control station and includes a control unit **102** and a control panel **104** which is associated with a measurement unit. Control panel **104** is in communication with utilities of control unit **102** and with those of the measurement unit. At least a part of the control panel **104** may be integral with control unit **102** and configured to connect respective ports of the control panel to those of the to external measurement unit, or may be part of the measurement unit and connected to the control unit via wires or via wireless signal transmission.

Control panel **104** includes one or more light output ports **116**, one or more light input ports **114**, and one or more acoustic ports **112**. Light output port(s) **116** is/are

- 7 -

associated with one or more photodetectors either directly or via guiding element(s), e.g. optical fiber(s). Light input port(s) **114** is/are associated with one or more light sources (lasers) either directly or via guiding element(s), e.g. optical fiber(s). Control unit **102** includes *inter alia* a data processing utility **102A** (including also an analog-to-digital converter), an acoustic generator **102C** and a data presentation utility **102B** such as display, as well as user interface (not shown).

Also preferably provided in the control unit **102** is an illumination controller **102D**. Illumination controller **102D** may be used for selecting one or more light inputs and/or one or more light outputs for the illumination and light collection from multiple ports. In some embodiments of the invention, monitoring system is configured for optical measurements of blood parameters, such as oxygen saturation. In this case, illumination controller **102D** operates to select optimal wavelengths to be used in the measurements in accordance with a desired oxygen saturation range, e.g. as defined by user. This will be described more specifically further below.

Data processing utility **102A** includes appropriate hardware and/or software modules. As will be described more specifically further below, the data processing utility includes *inter alia* a module capable of processing measured optical data coming from photodetector(s) (light output(s) **116**) and signal S_0 from acoustic generator **102C** and determining cross correlation, $(CCA(\lambda, \tau))$, between signal S_0 indicative of acoustic (ultrasound) radiation (e.g. coded signal or continuous signal) and the corresponding measured data indicative of detected light including ultrasound tagged light signals. The data indicative of the detected light may be the amplitude of such signal or its absolute value, or another function corresponding to this signal. The output of such cross-correlator module includes for example amplitude or phase of the cross correlation at different delays of the acoustic signal, as will be described below.

Light input port(s) **114** is/are operated (e.g. via illumination controller **102D** or manually by user) to deliver coherent laser light into the media (including a region of interest), and light scattered back from the tissue within the illuminated region (including at least a part of the region of interest) is collected by at least one light output port **116** that is associated with (coupled to) a photodetector. Acoustic generator **102C** generates signals S_0 of certain frequency range, centered at frequency (F_0) and operates an ultrasound transducer (constituted by acoustic port **112**) to emit ultrasound waves of

- 8 -

said frequency (F_0) into the monitored medium that is simultaneously illuminated by the laser light, and when interacting with light in the media "tags" the light that travels through the medium. Therefore, some of the light detected at the light output **116** is modulated at the ultrasound frequency (F_0), or at the vicinity of the ultrasound
5 frequency.

The generation of acoustic waves can be in one of the following modes: a continuous wave (CW), a modulated continuous wave (coded), or a single pulse or sequence of pulses (burst).

In some embodiments of the invention, the ultrasound is generated by a coded
10 signal with a narrow autocorrelation. The principles of this technique are described in U.S. Pat. 7,541,602, assigned to the assignee of the present application and incorporated herein by reference with respect to this specific but not limiting example. The acoustic radiation generated into the turbid medium has a pressure profile $PA(\tau)$ within the medium; here τ is the time delay within a single ultrasound tagged signal $CCA(\lambda, \tau)$
15 from the onset of the acoustic wave. The "*narrow autocorrelation function*" refers to an autocorrelation which is negligible for any delay time τ larger than the determined time resolution of the system. The latter may for example be determined as the time resolution of detection of the electromagnetic radiation response, or as the temporal bandwidth of the acoustic excitation of the ultrasound transducer, or as the required
20 spatial resolution divided by the speed of sound in the media.

Light of wavelength λ is irradiated into the medium (e.g. using illumination controller **102D** and light input ports **114**), and detected by at least one light output element **116**. The cross correlation, $CCA(\tau, \lambda)$, of the detected light intensity (I) at each wavelength λ with signals S_0 at delay τ (constituting the data indicative of the detected
25 light including ultrasound tagged light signals) has contributions from the ultrasound pressure amplitude as a function of delay τ , $PA(\tau)$, and from the light distribution $LD(\lambda)$ in the monitored medium at depth z , where z is a function of τ as will be shown below. In other words, $CCA(\tau, \lambda)$ represents the light distribution at wavelength λ at depth z multiplied by the acoustic power distribution or pressure amplitude, or a function of the
30 acoustic pressure amplitude ($PA(\tau)$) at a distance z from the acoustic transducer.

- 9 -

As indicated above, the time parameter τ is the time delay within a single $CCA(\lambda, \tau)$ signal from the onset of the signal generated by acoustic generator. **Fig. 2** shows an example of a $CCA(\lambda, \tau)$ signal as a function of delay time τ ; this graph is actually indicative of the signal dependence on the z -coordinate in the medium where the signal has been generated (where the "tagging" occurred). The time parameter τ signifies the depth coordinate (z) along the path of the acoustic signal within the monitored region according to the following:

$$z = \int_0^{\tau} v_{US}(\tau') d\tau',$$

where $v_{US}(\tau)$ is the ultrasound velocity within the region of the monitored medium reached by the ultrasound at a delay τ .

Each $CCA(\lambda, \tau)$ signal carries its own time stamp T which signifies the time of the onset of the acoustic signal. An example of such signals, calculated for different times T and different time delays τ is shown in **Fig. 3** and is therefore marked $CCA(\lambda, \tau, T)$.

Referring to **Fig. 4**, there is exemplified a flow diagram **200** of a method of the invention for calculation of function $UTLA$, being the autocorrelation of the $CCA(\tau, \lambda, T)$ at different times T . More specifically, $CCA(\lambda, \tau, T)$ for at least one wavelength λ is calculated by the correlator module of the processing utility (step **202**), and a certain value of τ is set (step **204**). For a predetermined τ , $UTLA(\Delta T, \tau, \lambda)$ is calculated as autocorrelation of $CCA(\lambda, \tau, T)$ as follows (step **206**):

$$UTLA(\Delta T, \tau, \lambda) = \int dT \cdot CCA(T, \tau, \lambda) \cdot CCA(T + \Delta T, \tau, \lambda) \quad (1)$$

Then, a flow measure can be calculated from the decay coefficient of $UTLA(\Delta T, \tau, \lambda)$ – step **208**. This is associated with the following:

$UTLA$ decays with increasing ΔT , the decay being characterized by a decay constant T_{decay} , which depends on the tissue properties. For example, the decay can be exponential:

$$UTLA(\Delta T, \tau, \lambda) \propto \exp(-\Delta T / T_{decay}). \quad (2)$$

The CCA signal and thus the $UTLA$ signal are affected by the movement of scattering centers within the monitored medium. Variations in the distribution of

- 10 -

scattering centers lead to a decorrelation of the *UTLA* signal. Thus, T_{decay} is indicative of variations and rate of variations in the scattering centers' distribution within the monitored medium. More specifically, a flow within the monitored medium leads to a variation of the scattering centers within the medium and therefore to changes in the decay constant T_{decay} . An increase in flow within the monitored medium leads to a shorter correlation time between *CCA* signals, and a smaller T_{decay} , while a decrease in flow leads to a larger T_{decay} .

UTLA is a function of τ , and therefore a function of the depth coordinate z along the ultrasound path into the monitored medium. Hence, *UTLA* provides information indicative of a measure of flow within the medium as a function of depth.

In the above-described example, generation of an acoustic wave by a coded signal with narrow autocorrelation was considered. The invention is not limited to this specific example.

In some other embodiments of the invention, the acoustic radiation is generated by signal S_0 in the form of a pulse or a series of pulses ($PU(T)$), i.e., not necessarily a coded signal. Light of wavelength λ is irradiated into the medium, and detected by at least one light output element. The cross correlation $CCA(\tau, \lambda)$ is that of the detected light intensity at wavelength λ with the pulse or series of pulses that generate the acoustic signal, the time parameter τ being the time within a single *CCA* signal. Each *CCA* signal carries its own time stamp T which signifies the time the acoustic signal was generated. Using short pulses allows for probing variations on shorter time scales.

The *UTLA* signal, being an autocorrelation of the $CCA(\tau, \lambda)$ at different times T , is calculated according to equation (1) above, and the decay time T_{decay} is measured, thus providing information indicative of a measure of flow within the monitored medium. Depending on the time resolution requirement, T_{decay} can be calculated from a single *UTLA* signal or from a sum/average over such signals.

In yet other embodiments of the invention, the generated acoustic signal is a continuous wave (CW), or a series of phase synchronized pulses (i.e. modulated CW). Light of wavelength λ is irradiated into the medium, and detected by at least one light output element. The spectral width of the power spectrum of the detected light intensity ($|I(\Omega)|^2$) is peaked around at least two frequencies: 0 Hz (i.e. DC) and at the ultrasound

- 11 -

frequency (F_0) and its harmonics (multiples of F_0). A measure of flow in the monitored medium is defined according to parameters of at least the peak at F_0 . Furthermore, a measure of flow in the monitored medium can be characterized by a combination of parameters from the peak at F_0 and/or the peaks at its harmonics, and/or the DC peak.

5 An example for the power spectrum around F_0 is shown in **Fig. 5**. In this example a CW ultrasound wave of $F_0=1\text{MHz}$ was transmitted into the tissue by an ultrasound transducer (acoustic output **112**) positioned between two optical fibers (light input **114** and light output **112**). The signal output of the photodetector was digitized and the power spectrum of the collected light was calculated for two flow conditions,
10 Flow 1 and Flow 2 where $\text{Flow1} > \text{Flow2}$. As can be seen, the width of the power spectrum during Flow 1 is wider than that during Flow 2 and its peak is lower.

 The width of the power spectrum peaks is affected by frequency broadening effects, such as Doppler broadening due to Brownian motion of scattering centers within the monitored medium. When there is an increase in flow, the spectral width
15 increases, while a decrease in flow results in a narrower power spectrum. The power spectrum width is therefore indicative of a measure of flow.

 For example, the spectral width can be determined as the width of a Lorentzian fit to the power spectrum. As another example, one can measure the full width at half maximum amplitude of the power spectrum at F_0 . Other methods can be used to
20 correlate a parameter of the power spectrum (e.g. width, standard deviation, peak amplitude, or any other fitting function) to the flow in the underlying monitored medium. In addition, comparisons to matching parameter measures for the DC power spectrum can be made. These can contribute to an increase in the measurement accuracy, reduce error and improve stability of the measurement.

25 An example of a measurement of flow during a cuff occlusion performed on a human arm is shown in **Fig. 6**. The cuff is inflated two times, with a reflow in between the two inflations. A flow index was defined according to spectral width (i.e. the width of the distribution according to a Lorentzian shape was correlated to the flow, and is defined as the flow index). The flow index is plotted as a function of time. As clearly
30 seen in the figure, during the cuff occlusions (marked by dark bold straight lines below the curve), the flow index decreased significantly, while an expected increase in flow due to hyperemia can clearly be seen between the cuffing episodes. A calibration curve

- 12 -

can thus be calculated, based on simultaneous measurement of different flow conditions (for example, different flow velocities, or different volume/min) to provide a scaled measurement of flow.

Turning back to **Fig. 2**, the amplitude of the $CCA(\lambda, \tau)$ signal at a predetermined delay time τ is affected by flow in the underlying monitored medium. An increase in flow results in a decrease in the $CCA(\lambda, \tau)$ signal amplitude, while a decrease in flow results in an increase in the $CCA(\lambda, \tau)$ signal amplitude. In particular, flow in the underlying monitored medium affects the peak $CCA(\lambda, \tau)$ amplitude. Such an example is shown in **Fig. 7**, depicting the influence of blood flow in a patient's arm on the peak amplitude of the $CCA(\lambda, \tau)$ signal during a session of cuff occlusion when the light and ultrasound were emitted into the patient's arm. The flow index was taken to be a function of the inverse $CCA(\lambda, \tau)$ peak height. During the cuff occlusion, the blood flow decreased.

In another aspect, the present invention provides optimization of optical measurements of oxygen saturation in oximetry. Generally, this can be implemented in the same monitoring system **100** exemplified in **Fig. 1**, either associated with the same measurement unit or a separate optical measurement unit, such as pulse oximeter or a tissue oximeter. Construction and operation of an oximeter are known *per se* and therefore need not be described in details except to note that it includes light input(s) and light output(s) for illuminating a region of interest with at least two different wavelengths and detecting light reflected and/or transmitted through said region. Generally, systems where this invention can be used include, but are not limited to: Near infrared spectroscopy with frequency domain spectroscopy, optical coherence tomography (OCT), photoacoustics, ultrasound-tagged-light (UTL), and oximetry.

Considering the system of **Fig. 1** for measuring both the fluid (blood) flow and the oxygen saturation, the system is shiftable between two measurement modes, one utilizing ultrasound tagging of light for blood flow measurement as described above (the acoustic generator and port being active) and the other being either pure optical mode or ultrasound tagging of light mode for measuring oxygen saturation (the acoustic generator and acoustic port being passive or active).

- 13 -

This aspect of the invention is based on the understanding of the following: Oxygen saturation is defined as the ratio between the concentration of oxygenated hemoglobin and the total hemoglobin concentration. If the saturation is s , then the attenuation coefficient of light at wavelength λ_i is given by

$$5 \quad \gamma_i = \sqrt{3\mu^i(\mu_s^i + \mu^i)},$$

wherein μ_s^i and μ^i are the scattering coefficient and the absorption coefficient for light of wavelength λ_i , respectively. The absorption coefficient in the medium is given by:

$$\begin{aligned} \mu^i &= \varepsilon_{Hb}^i C_{Hb} + \varepsilon_{HbO}^i C_{HbO} \\ &= C_{tot} (\varepsilon_{Hb}^i + (\varepsilon_{HbO}^i - \varepsilon_{Hb}^i) s), \end{aligned} \quad (2)$$

wherein $\varepsilon_{Hb, HbO}^i$ are the extinction coefficients of oxy- and deoxyhemoglobin, $C_{Hb, HbO}$ are their concentrations, and C_{tot} is the total hemoglobin concentration.

Thus, for a given saturation s

$$\alpha^{ijk} = \frac{\Delta\gamma^{ij}}{\Delta\gamma^{ik}}, \quad (3)$$

where $\Delta\gamma^{ij} = \gamma^i - \gamma^j$, is the attenuation difference between two wavelengths.

Thus, by measuring α^{ijk} , and using known values for the extinction coefficients of oxy- and deoxyhemoglobin, the saturation s can be calculated.

Pulse oximetry has traditionally been used on patient populations where arterial blood oxygen saturation is typically greater than 90%. Arterial oxygen saturation in general patient population rarely drops below 70%. When it does drop to such a low value, an unhealthy clinical condition is indicated, and intervention is generally called for. In this situation, a high degree of accuracy in the estimate of saturation is not clinically relevant, as much as is the trend over time. There is a need in the art to provide oxygen saturation measurements in a predetermined range of saturation levels, with a predetermined sensitivity.

The present invention provides a novel tissue oximeter sensor and system, which enables more accurate estimation of arterial and venous oxygen saturation at predetermined saturation ranges. This technique is particularly useful for estimating arterial saturation of a living fetus during labor where the saturation range of principal importance and interest is generally between 15% and 70%, and is particularly useful

- 14 -

for estimating venous saturation of cerebral tissue in patients who experience significant shunting of blood flow into their brain because of interruption in the blood flow to the brain due to impaired vascular condition, or during surgery or any other procedure requiring general anesthesia. The range of principal importance and interest in venous saturation is roughly between 50% and 70%. By contrast, a typical healthy human has an arterial saturation greater than 90% and venous saturation in the brain of about 50% to 70%.

Thus, light of at least three wavelengths is generated. Provided the attenuation differences $\Delta\gamma^{12}$, $\Delta\gamma^{23}$ and $\Delta\gamma^{31}$ can be determined, then the oxygen saturation of blood in the monitored regions can be calculated according to equation (3) above.

Reference is made to **Figs. 8 and 9**, where **Fig. 8** shows the absorption spectra for Hb and HbO, and **Fig. 9** plots $1/\Delta\mu^{12}$; $1/\Delta\mu^{23}$; $1/\Delta\mu^{31}$, where $\Delta\mu^{ij} = \mu^i - \mu^j$, as a function of the saturation s for $\lambda_1=666\text{nm}$; $\lambda_2=778\text{nm}$; $\lambda_3=872\text{nm}$. The absorption coefficients are based on data compiled by Scott Prahl from measurements performed by W. B. Gratzner, Med. Res. Council Labs, Holly Hill, London, and N. Kollias, Wellman Laboratories, Harvard Medical School, Boston (<http://omlc.ogi.edu/spectra/hemoglobin/>).

From **Fig. 9** it can be understood that the denominator of the right term in equation (3) above is zero at specific saturations (s_0). At saturations s_0 , where the denominator is zero, there is a discontinuity in the dependence of $1/\Delta\mu$ on saturation levels. For the above selection of wavelengths, the points of singularity are $s_0^{12} \sim 86.5\%$; $s_0^{23} \sim 47.5\%$; $s_0^{31} \sim 75.5\%$ (for the resolution plotted in these graphs). For this specific example, the scattering coefficients for these wavelengths and saturations are similar, therefore as the saturation of the measured region approaches these singularity values, small changes in the oxygen saturation level result in a significant change in the inverse of the attenuation difference ($1/\Delta\gamma$). This enables creation of an oximeter with increased sensitivity for these regions.

For a given selection of three wavelengths, the location of the singularity points and therefore the sensitivity for changes in saturation is dependent on $\Delta\mu^{12}$; $\Delta\mu^{23}$ and $\Delta\mu^{31}$, which in turn depend on λ_1 , λ_2 and λ_3 . Therefore, the selection of wavelengths for

performing oxygen saturation measurements can be based on the clinical use of the monitoring system.

The present invention provides selection criteria for wavelengths to be used in monitoring tissue or blood oxygenation. The selection criteria can be used in two
5 different embodiments described below.

In the first embodiment, clinical cases requiring maximal sensitivity for measurements of oxygen saturation levels in a particular range are used. For example, when monitoring the oxygen saturation of a fetus, where normal arterial saturation values are within 30-70%, it is particularly important to provide a high sensitivity
10 measurement for $s \sim 30\%$. Therefore, wavelength selection according to the present invention, should include two wavelengths, at which the absorption at $s_0 = 30\%$ is equal. In this connection, reference is made to **Fig. 10** illustrating a possible selection of wavelengths according to the present invention. For example two of the wavelengths marked λ^{30}_1 ; λ^{30}_2 ; λ^{30}_3 can be selected or two of the wavelengths marked λ^{*30}_1 ;
15 λ^{*30}_2 ; λ^{*30}_3 . Such a selection will result in an oximeter with an improved sensitivity for measuring oxygen saturation in the vicinity of 30%.

The second embodiment relates to clinical cases requiring a constant sensitivity over a predetermined range of oxygen saturation levels. In such cases the wavelength selection should include at least three wavelengths that provide singular values spanning
20 the widest clinically relevant saturation range. For example, if $\lambda_1 = 760\text{nm}$; $\lambda_2 = 785\text{nm}$; $\lambda_3 = 852\text{nm}$, then $s_0^{12} = 83\%$; $s_0^{23} = 40\%$; and $s_0^{31} = 66\%$ span the saturation range of 40%-80%. In this case for all saturations between 40% and 80%, the measurement sensitivity is optimized. Using this selection, the signal-to-noise ratio of the measurement system should be sufficient, so that small changes in $1/\Delta\gamma$ can be
25 detected to allow for changes in the saturation to be monitored.

The invention provides two methods for determining the oxygen saturation level in the measured region are provided. Any of these methods can be used for any selection of three wavelengths, and is not limited to the selection criteria above.

The first method can be described as follows: To find the saturation s for a given
30 set of experimental data, all the experimental $\alpha_{ex}^{ijk}(s)$ were calculated. Then, they were compared to theoretical values $\alpha_{th}^{ijk}(s)$ derived from literature, or measured empirically.

- 16 -

In order to compare them to these theoretical $\alpha_{th}^{ijk}(s)$, which are dependent on the saturation s , the following function was defined:

$$d(s) = \sqrt{\frac{(\alpha_{ex}^{123} - \alpha_{th}^{123}(s))^2}{|\alpha_{th}^{123}(s)|^2} + \frac{(\alpha_{ex}^{231} - \alpha_{th}^{231}(s))^2}{|\alpha_{th}^{231}(s)|^2} + \frac{(\alpha_{ex}^{312} - \alpha_{th}^{312}(s))^2}{|\alpha_{th}^{312}(s)|^2}} \quad (4)$$

5 Then, the minima of $d(s)$ was found. The calculated value of s is the value which corresponds to the minimal $d(s)$.

The second method consists of the following: First, the two dimensional space is considered that is spanned by any two out of the three attenuation differences $\Delta\gamma^{12}$; $\Delta\gamma^{23}$ and $\Delta\gamma^{31}$ (if measurement errors are neglected the third absorption
10 difference depends on the other two). As an example, $\Delta\gamma^{12}$; $\Delta\gamma^{23}$ were chosen.

The theoretical vector, $\Delta\vec{\gamma}_{th} = (\Delta\gamma^{12}_{th}, \Delta\gamma^{23}_{th})$, and the experimental vector, $\Delta\vec{\gamma}_{ex} = (\Delta\gamma^{12}_{ex}, \Delta\gamma^{23}_{ex})$, were then drawn in this space.

The next step included comparison between the resulting experimental vector and the theoretical vector, known from the literature, for each saturation s . For all
15 possible saturations (s), the angle $\theta(s)$ between the two vectors in this space was calculated as:

$$\cos\theta(s) = \frac{\Delta\vec{\gamma}_{th}(s) \cdot \Delta\vec{\gamma}_{ex}}{|\Delta\vec{\gamma}_{th}(s)| |\Delta\vec{\gamma}_{ex}|} \quad (5)$$

20 Then, the minimum of $\theta(s)$ was found. The value of s which corresponds to the minimal $\theta(s)$ is the calculated saturation.

Adding the third absorption difference so that three dimensional space is considered spanned by $\Delta\gamma^{12}$; $\Delta\gamma^{23}$, and $\Delta\gamma^{31}$ increases the accuracy of the measurement, and enables to estimate the measurement error.

25 An example of the angle $\theta(s)$ as a function of saturation is given in **Fig. 11**. In this example the three wavelengths are $\lambda_1 = 730\text{nm}$; $\lambda_2 = 760\text{nm}$; $\lambda_3 = 830\text{nm}$. For a given measurement of $\Delta\vec{\gamma}_{ex} = (X1, Y1)$, $\theta(s)$ is plotted versus saturation s . The minimum of θ

- 17 -

as a function of saturation is at $s \sim 58\%$. Thus, the saturation in this tissue volume is $\sim 58\%$. This measurement is independent of optical pathlength and blood concentration in the measured tissue, and provides an absolute measure for the saturation.

Theoretical values that are used to either select the preferred wavelengths and/or
5 to determine the oxygen saturation level may include the following: values calculated from extinction coefficients in the literature (for example S. Takatani and M. D. Graham, "Theoretical analysis of diffuse reflectance from a two-layer tissue model," IEEE Trans. Biomed. Eng., BME-26, 656--664, (1987)); values measured *in-vivo* using known spectroscopic methods, and calibrated to oxygen saturation levels; values
10 measured *in-vitro* using known spectroscopic methods, and calibrated to oxygen saturation levels; values calculated from *in-vivo* measurements of one tissue type and used on a different tissue type; a look-up table determined according to any known extrapolation algorithm, based on empirical or theoretical data corresponding to different oxygen saturation levels.

15 Reference is made to **Fig. 12** illustrating by way of a block diagram a monitoring system **300** configured as a multiple wavelength oximeter, enabling selection of at least three wavelengths according to a desired saturation range. System **300** is generally configured as an illumination controller which can be a stand alone system associated with a light source system in an optical measurement unit (oximeter),
20 for example being integral with the oximeter, or as a part of the above described system **100** (illumination controller **102D**). System **300** includes an illumination controller **302** and a control panel **304**, where the light input port(s) is/are associated with a light source system comprising light of different wavelengths or at least one tunable light source. Illumination controller **302** is configured as an electronic unit including *inter*
25 *alia* a processor utility **302A**, user interface **302C** and a display **302B**. Control panel **304** includes one or more light input ports **314** associated with one or more light sources, and one or more light output ports **316** associated with one or more photodetectors. User selects the desired saturation range and enters the respective data through user interface **302C**. Processor utility **302A** analyses the user input and selects
30 optimal wavelengths to activate. The light input ports **314** may be associated with a plurality of light sources (more than three), and processor utility **302A** controls the activation of each light source, or may be associated with a tunable light source, where

- 18 -

the processor utility **302A** controls the tuned wavelength. The use of lasers is preferred since they have a narrow line width, that provides improved accuracy over broad-band LEDs or lamps with filters. According to the wavelengths of the light sources in the system, the available "singular points", i.e. the saturation levels that provide a desired sensitivity, are calculated by processor utility **302A** and presented on display **302B** for the user (for example high sensitivity at low saturation, or equal sensitivity for a broad range of saturation levels). The user selects the desired saturation range according to the clinical application. The control unit activates at least three corresponding light sources that provide the desired sensitivity in the selected saturation range.

10 The light source choice can be automated by a dynamic algorithm which first estimates the oxygen saturation using a selection of light sources which provide a wide accuracy range, and then according to the results chooses a different light source selection to focus on that specific saturation range. Assuming that the physiological oxygen saturation level varies only slightly between consecutive measurements, one can
15 use the last saturation measurement to optimize the light source choice for the next measurement. Another option is to use all the light sources for the same measurement, and average the resulting oxygen saturation levels according to weights determined by the accuracy of each wavelength selection.

Those skilled in the art will appreciate that various modifications and changes
20 can be applied to the embodiments of the invention described hereinabove without departing from its scope defined in and by the appended claims.

CLAIMS:

1. A monitoring system for monitoring fluid flow in turbid medium, the system comprising: a processor utility which is connectable to an acoustic generator associated with one or more acoustic ports and is operable for generating signals S_0 to activate said one or more acoustic ports for generating acoustic radiation of a certain frequency range centered at a frequency F_0 to irradiate a region of interest and is connectable to at least one light output port associated with one or more light detectors for receiving light of at least one wavelength λ from the region of interest including light tagged by said acoustic radiation, the processor utility being configured and operable for analyzing the signals S_0 and data indicative of the received light including light tagged by the corresponding acoustic radiation and determining correlation between said signals S_0 and said data indicative of the received light, said correlation being informative of a measure of fluid flow in the medium.
2. A monitoring system according to Claim 1, wherein the acoustic radiation has one of the following profiles: a continuous wave (CW); a modulated continuous wave; and a pulse or sequence of pulses.
3. A monitoring system according to Claim 1 or 2, wherein the processor utility is configured and operable to determine said correlation by carrying out the following:
 - determining cross correlation, $CCA(\tau, \lambda, T)$, between said signal S_0 generated by acoustic generator and said data indicative of the received light, said cross correlation being calculated for each wavelength λ of light and at a time delay τ from onset of signal S , and
 - determining auto correlation $UTLA$ of said cross correlation $CCA(\tau, \lambda, T)$ at different times T being time stamps of different measurement times, said autocorrelation $UTLA$ being indicative of a measure of fluid flow within the medium as a function of depth z in the medium.
4. A monitoring system according to Claim 3, wherein the processor utility is configured for determination of said autocorrelation $UTLA$ for a predetermined τ , being a function of ΔT , τ and λ , as follows:

$$UTLA(\Delta T, \tau, \lambda) = \int dT \cdot CCA(T, \tau, \lambda) \cdot CCA(T + \Delta T, \tau, \lambda),$$
 and determining the flow measure from a decay coefficient of $UTLA(\Delta T, \tau, \lambda)$.

- 20 -

5. A monitoring system according to Claim 4, wherein the acoustic signal is a coded signal with a narrow autocorrelation.
6. A monitoring system according to Claim 4, wherein the processor utility is configured for measuring a decay time T_{decay} , thus providing information indicative of
5 the measure of flow within the monitored medium.
7. A monitoring system according to Claim 6, wherein the processor utility is configured for calculating the decay time T_{decay} from a single *UTLA* signal or from a sum/average over such signals.
8. A monitoring system according to Claim 6 or 7, wherein the acoustic signal is in
10 the form of a pulse or a series of pulses.
9. A monitoring system according to any one of Claims 1 to 8, comprising a control panel associated with a measurement unit, said control panel comprising at least one light input for illumination of the region of interest with light of one or more wavelengths, said at least one light output, and said one or more acoustic ports.
- 15 10. A monitoring system according to Claim 9, wherein the at least one light input is associated with one or more light sources producing light of different wavelengths, or at least one tunable light source.
11. A monitoring system according to any one of Claims 1 to 10, comprising an illumination controller configured and operable to enable selection of at least three
20 different wavelengths for the illumination during measurements, said wavelengths being selected in accordance with a predetermined clinically relevant range of oxygen saturation values.
12. A monitoring system according to Claim 11, wherein said wavelengths are selected as those corresponding to a minimal difference between attenuation
25 coefficients of the medium over said saturation range.
13. A monitoring system for monitoring fluid flow in a turbid medium, the system comprising: a processor utility which is connectable to an acoustic generator associated with one or more acoustic ports and is operable for generating signals S_0 to activate said one or more acoustic ports for irradiating a region of interest with acoustic radiation of a
30 certain frequency range centered at a frequency F_0 and is connectable to at least one light output port associated with one or more light detectors for receiving light of at

- 21 -

least one wavelength λ from the region of interest including light tagged by said acoustic radiation, the processor utility being configured and operable for analyzing data indicative of the received light including light tagged by the acoustic radiation; identifying in said data at least one of the following light intensity peaks: a peak around
5 said frequency F_0 , a peak around a harmonic of said frequency F_0 ; and determining a measure of the fluid flow according to parameters of said at least one peak.

14. A monitoring system according to claim 13, wherein said processor utility is further configured and operable for analyzing said data indicative of the received light including light tagged by the acoustic radiation; identifying in said data a DC intensity
10 peak and using parameters of the at least two peaks for the fluid flow measure.

15. A monitoring system according to Claim 13 or 14, wherein the acoustic signal is in the form of a continuous wave or a modulated continuous wave or pulses or a series pulses.

16. A monitoring system according to any one of Claims 13 to 15, comprising a
15 control panel associated with a measurement unit, said control panel comprising at least one light input for illumination of the region of interest with light of one or more wavelengths, said at least one light output, and said one or more acoustic ports.

17. A monitoring system according to Claim 16, wherein the at least one light input is associated with one or more light sources producing light of different wavelengths, or
20 at least one tunable light source.

18. A monitoring system according to any one of Claims 13 to 17, comprising an illumination controller configured and operable to enable selection of at least three different wavelengths for the illumination during measurements, said wavelengths being selected in accordance with a predetermined clinically relevant range of oxygen
25 saturation values.

19. A monitoring system according to Claim 18, wherein said wavelengths are selected as those corresponding to a minimal difference between attenuation coefficients of the medium over said saturation range.

20. A monitoring system for use in non-invasive measurements of oxygen saturation
30 in a subject, the system comprising a light source system associated with one or more light sources, and an illumination controller configured and operable to enable selection

- 22 -

of at least three wavelengths for the illumination during measurements in accordance with a predetermined clinically relevant range of oxygen saturation values.

21. A monitoring system according to Claim 20, wherein the light source system comprises one or more wavelengths, or at least one tunable light source.

- 5 **22.** A monitoring system according to Claim 20 or 21, wherein said wavelengths are selected as those corresponding to a minimal difference between attenuation coefficients of the medium over said saturation range.

1/10

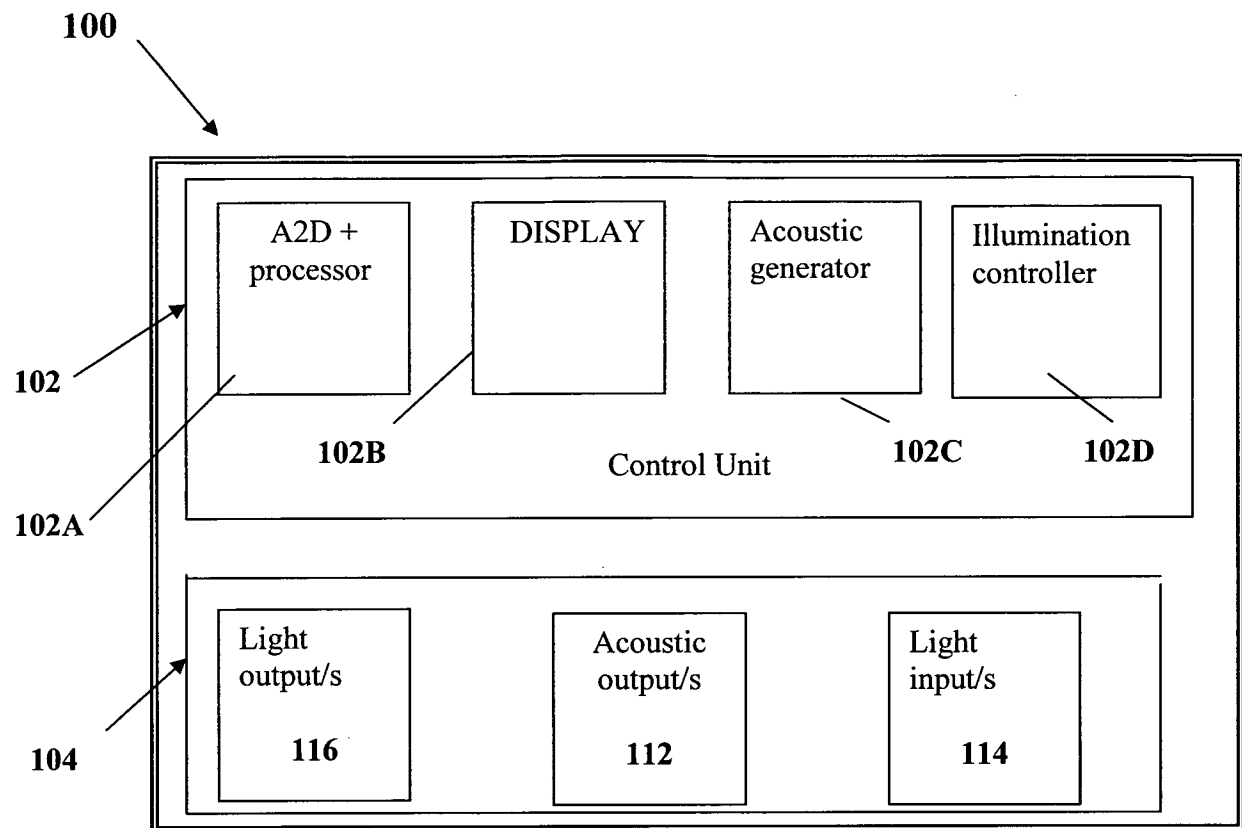


FIG. 1

2/10

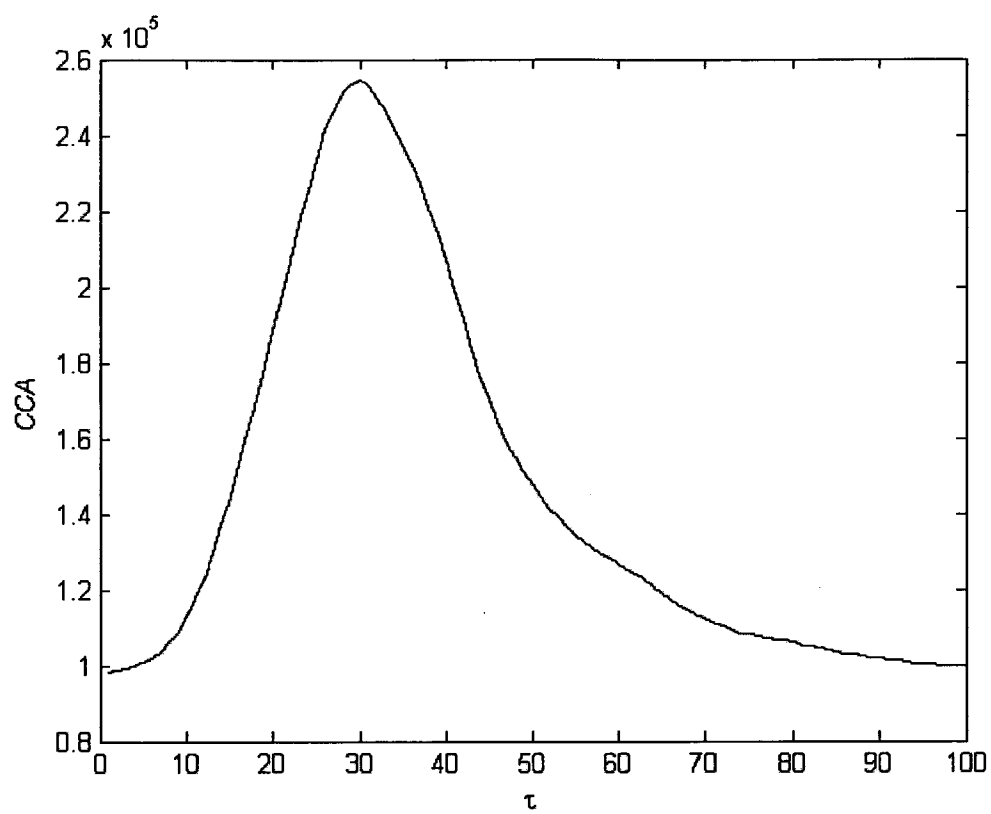


FIG. 2

3/10

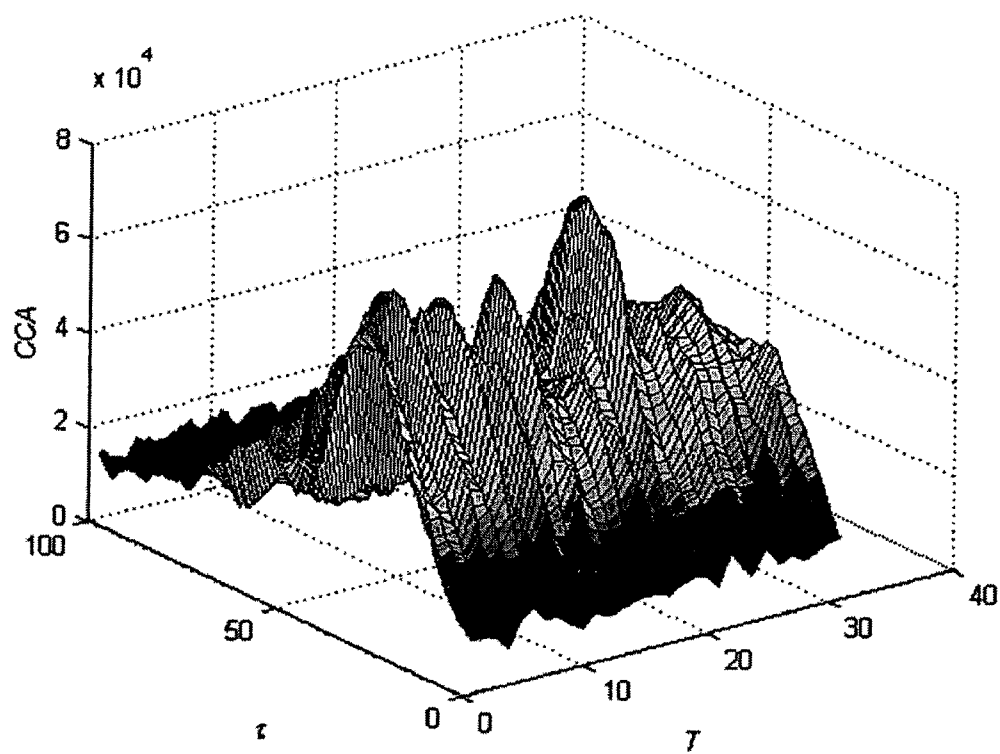


FIG. 3

4/10

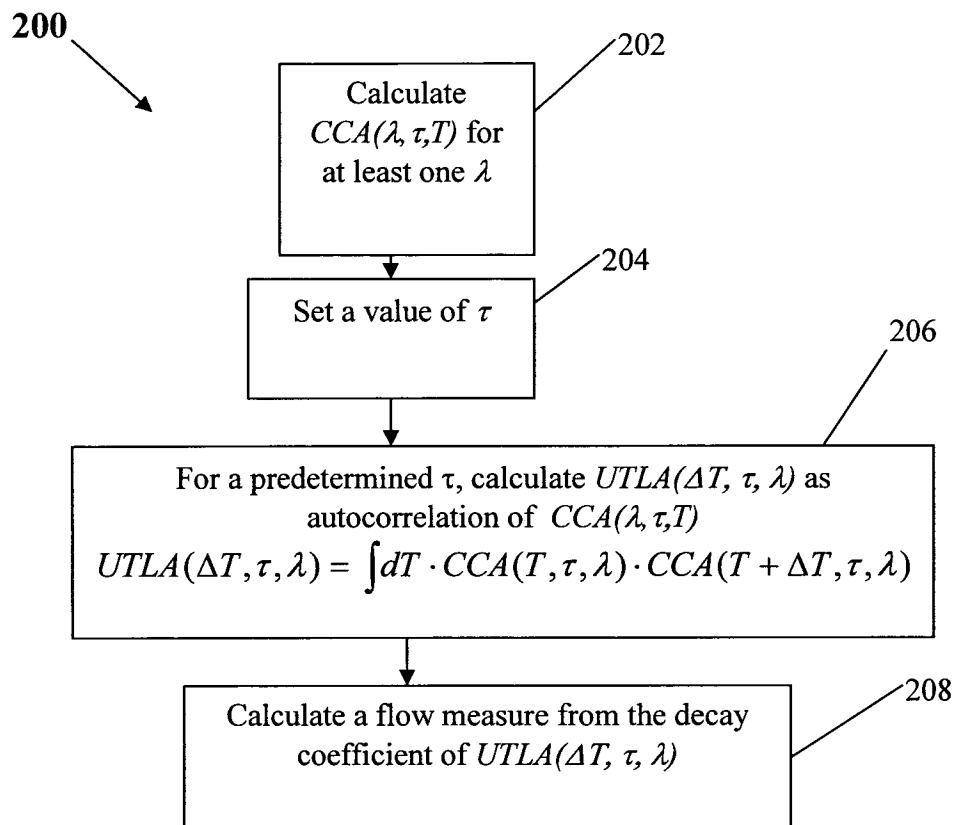


FIG. 4

5/10

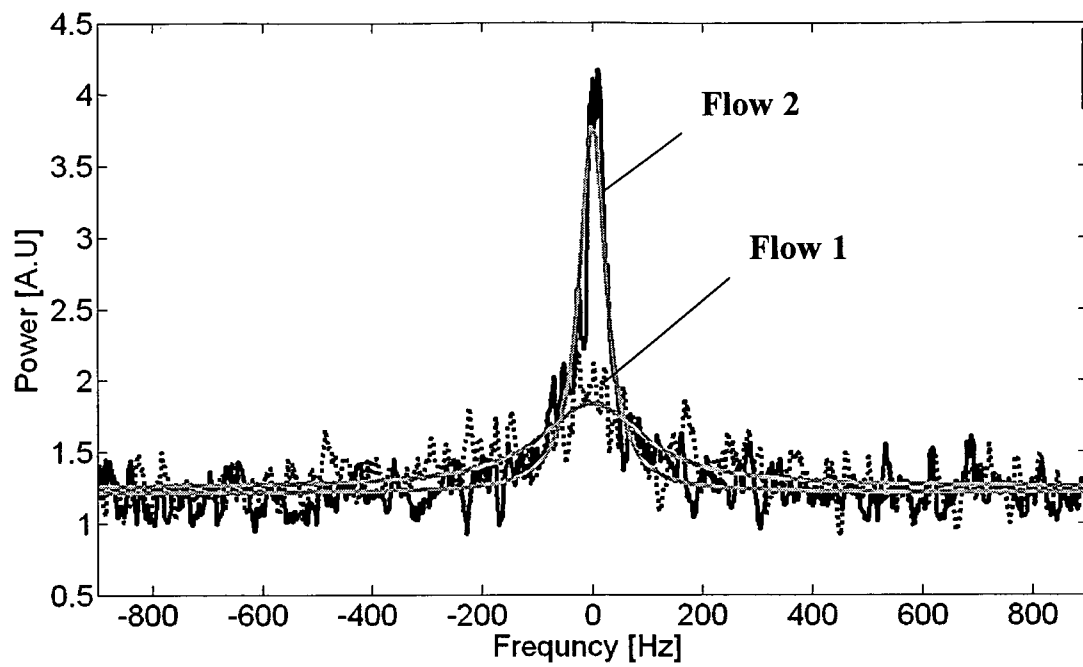


FIG. 5

6/10

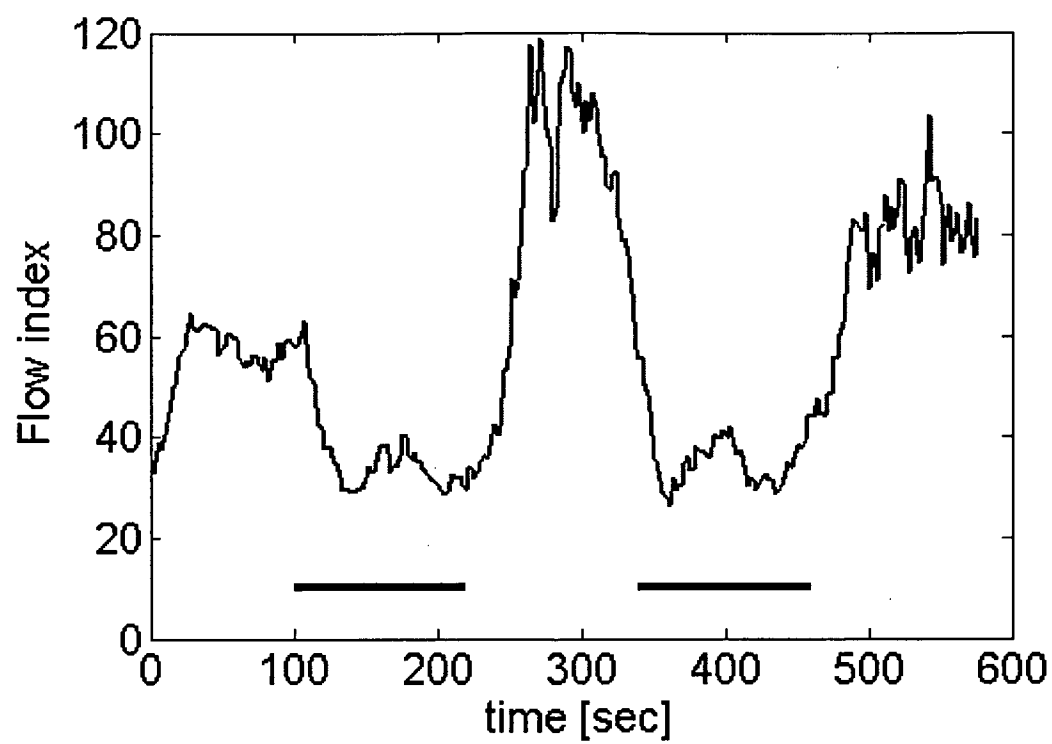


FIG. 6

7/10

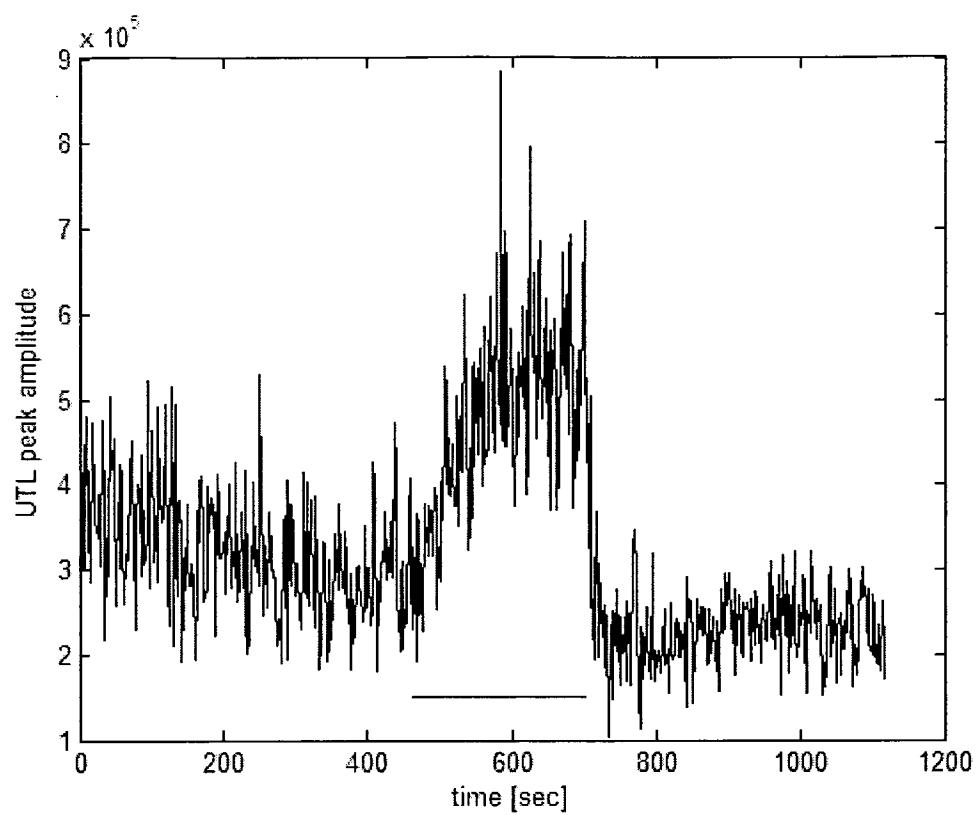


FIG. 7

8/10

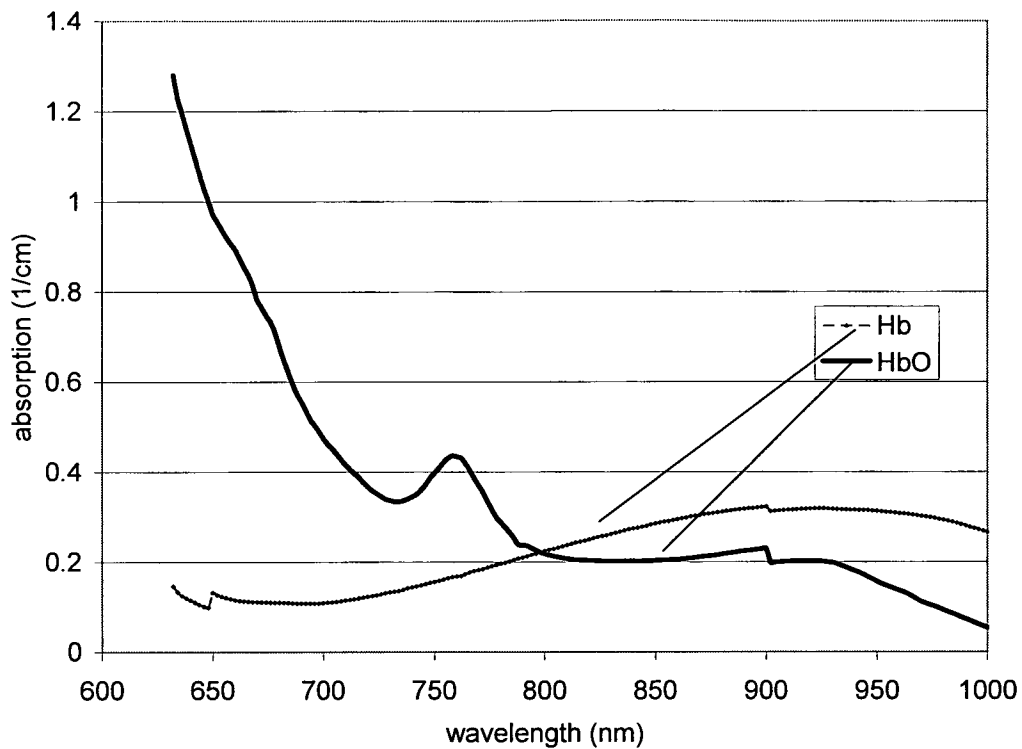


FIG. 8

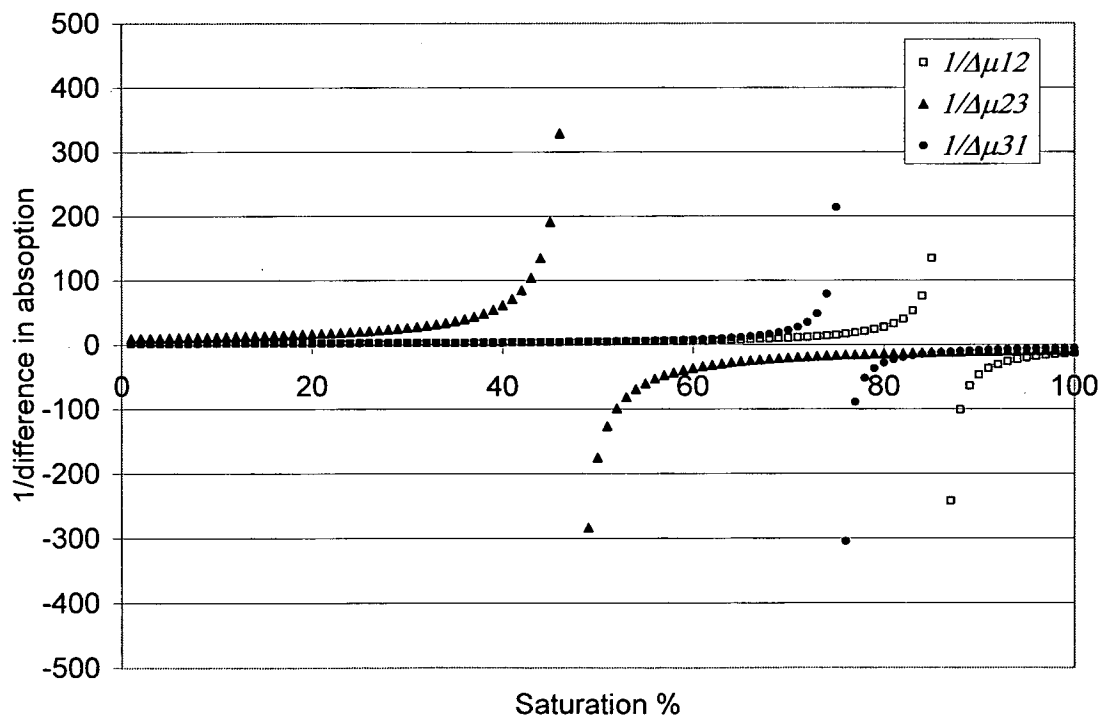


FIG. 9

9/10

Saturation = 30%

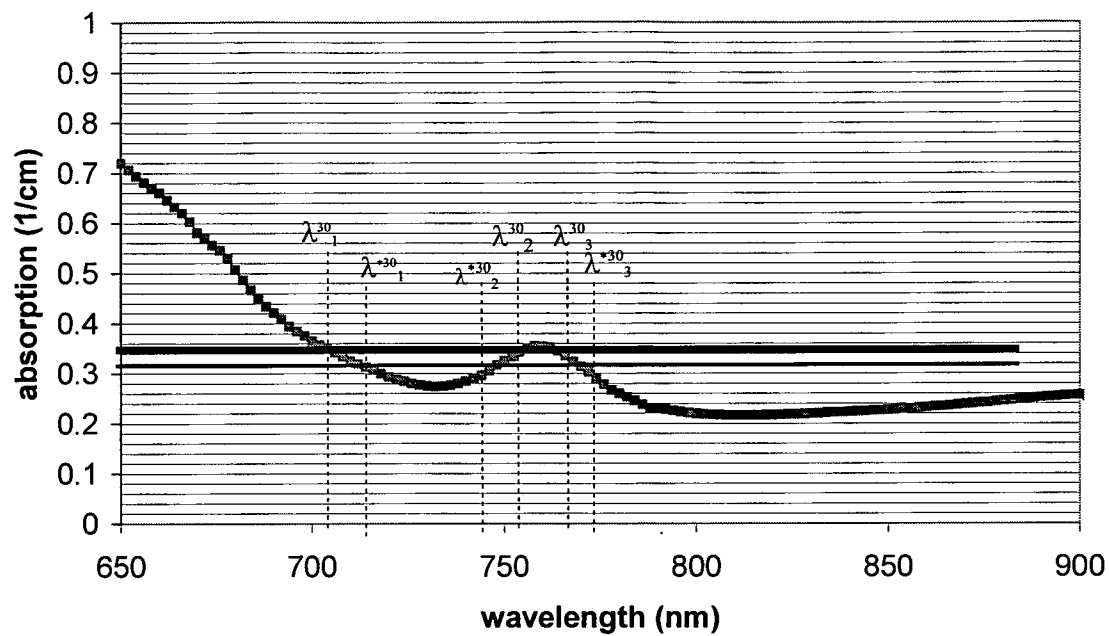


FIG. 10

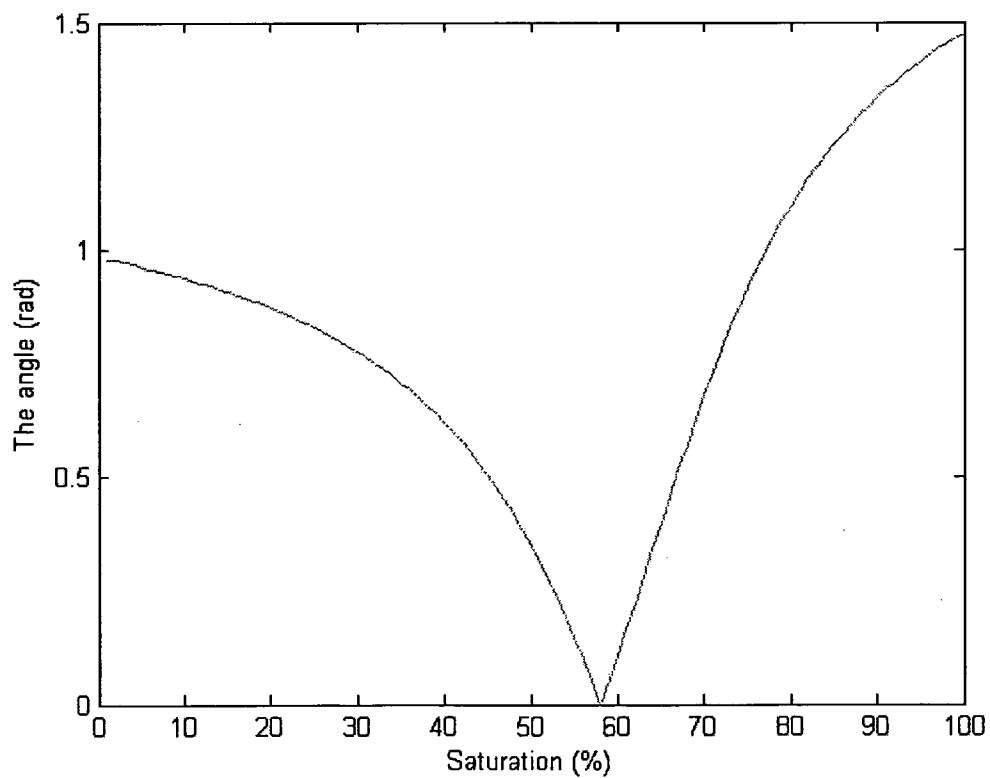


FIG. 11

10/10

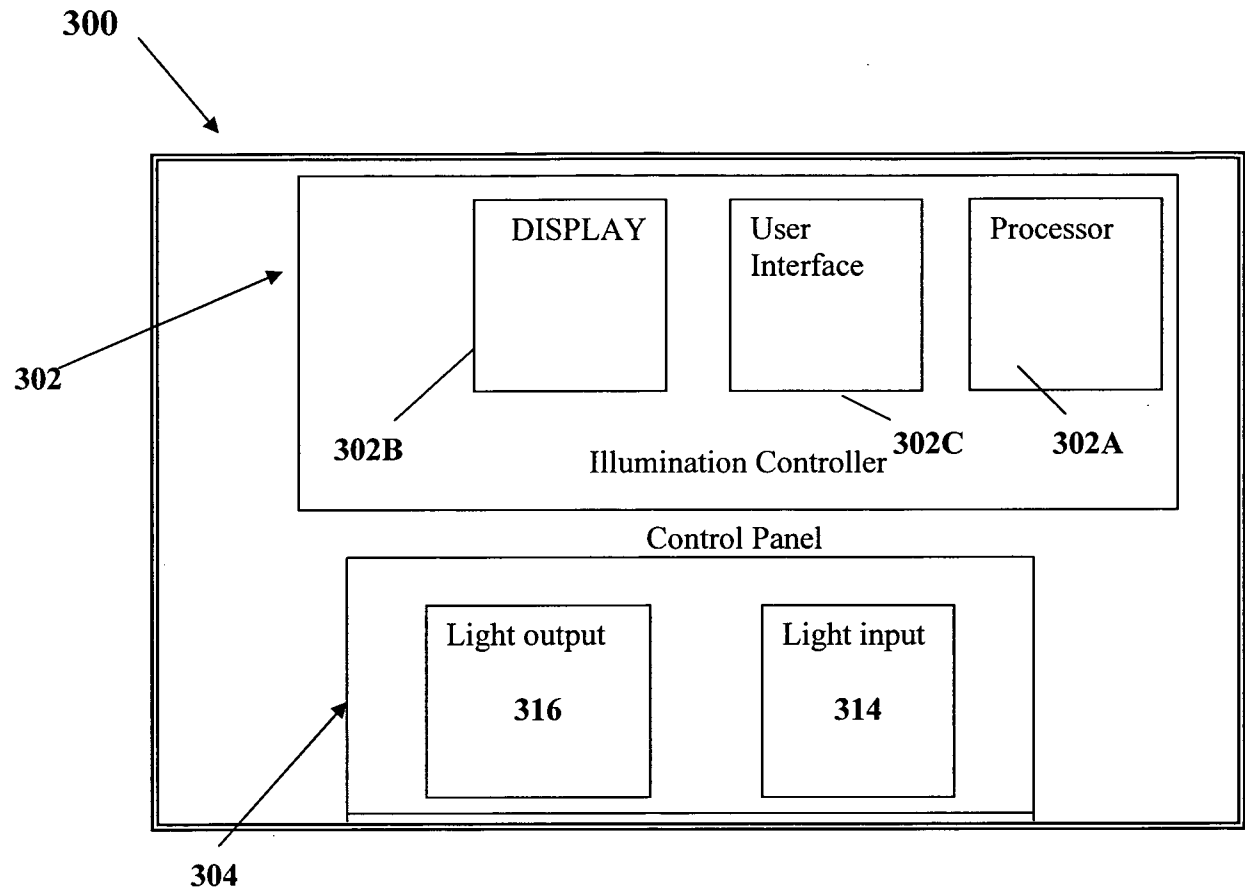


FIG. 12

INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2009/000675

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61B5/00 G01N21/17 G01N21/62

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61B G01N

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/247506 A1 (BALBERG MICHAL [IL] ET AL) 2 November 2006 (2006-11-02)	20-22
A	paragraphs [0001], [0012], [0013], [0015], [0016], [0018] - [0022], [0028], [0031], [0035], [0063] - [0066], [0068], [0069], [0080], [0081], [0083]; figures	1-19
X	WO 2006/097910 A (OR NIM MEDICAL LTD [IL]; BALBERG MICHAL [IL]; PERY-SHECHTER REVITAL [I]) 21 September 2006 (2006-09-21)	20-22
A	page 1, line 2 - line 5; figures page 2, line 12 - page 6, line 20 page 7, line 7 - line 27 page 9, line 28 - page 13, line 19 page 15, line 17 - line 25 page 18, line 1 - page 19, line 22 page 27, line 5 - line 18	1-19
	----- -/-	

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

29 October 2009

Date of mailing of the international search report

06/11/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040;
Fax: (+31-70) 340-3016

Authorized officer

Mundakapadam, S

INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2009/000675

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/039195 A (WOOLSTHORPE TECHNOLOGIES LLC [US]; STERLING BERNHARD B [US]) 3 April 2008 (2008-04-03) page 1, line 6 - line 8 page 3, line 1 - page 4, line 15 -----	20-22
P,X	US 2008/296514 A1 (METZGER YAACOV [IL] ET AL METZGER YAACOV [IL] ET AL) 4 December 2008 (2008-12-04) paragraphs [0001], [0005], [0006], [0008], [0009], [0013] - [0019], [0022] - [0025], [0027], [0038], [0039], [0043], [0045], [0046], [0049] - [0053]; figures -----	1,9,10
A	DE 196 54 053 A1 (SCHWEIGER GUSTAV PROF DR TECHN [DE]) 25 June 1998 (1998-06-25) the whole document -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2009/000675

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-19

directed to a monitoring system suitable for monitoring fluid flow in a turbid medium.

2. claims: 20-22

directed to a monitoring system suitable for monitoring oxygen saturation in a subject.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IL2009/000675

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006247506 A1	02-11-2006	NONE	
WO 2006097910 A	21-09-2006	EP 1863387 A1 US 2008312533 A1	12-12-2007 18-12-2008
WO 2008039195 A	03-04-2008	EP 2073694 A1	01-07-2009
US 2008296514 A1	04-12-2008	WO 2008149342 A2 US 2009264722 A1	11-12-2008 22-10-2009
DE 19654053 A1	25-06-1998	NONE	

专利名称(译)	用于非侵入地监测受试者中的流体流动的方法和系统		
公开(公告)号	EP2339957A1	公开(公告)日	2011-07-06
申请号	EP2009787456	申请日	2009-07-06
[标]申请(专利权)人(译)	OR-NIM医疗有限公司		
申请(专利权)人(译)	OR-NIM MEDICAL LTD.		
当前申请(专利权)人(译)	OR-NIM MEDICAL LTD.		
[标]发明人	ROKNI MICHAL SCHECHTER REVITAL PERY BRESKIN ILAN BALBERG MICHAL METZGER YAAKOV		
发明人	ROKNI, MICHAL SCHECHTER REVITAL, PERY BRESKIN, ILAN BALBERG, MICHAL METZGER, YAAKOV		
IPC分类号	A61B5/00 G01N21/17 G01N21/62		
CPC分类号	G01N21/1717 A61B5/0261 A61B5/14551 G01N21/1702		
优先权	61/078410 2008-07-06 US 61/078412 2008-07-06 US		
外部链接	Espacenet		

摘要(译)

提出了一种监测系统，用于监测混浊介质中的流体流动。流体流动监测系统包括处理器实用程序，该处理器实用程序可连接到与一个或多个声学端口相关联的声学发生器，并且可操作于产生信号S₀以激活所述一个或多个声学端口，用于利用声辐射照射感兴趣的区域。某个频率范围以频率F₀为中心，并且可连接到与一个或多个光检测器相关的至少一个光输出端口，用于接收至少一个波长的光？来自感兴趣的区域，包括由所述声辐射标记的光。在一些实施例中，处理器实用程序被配置并可操作于分析所生成的信号S₀和指示所接收的光的数据，包括由相应的声辐射标记的光，并确定所述声信号S₀和指示所接收的光的所述数据之间的相关性。，所述相关性是介质中流体流量测量的信息。