(54) Title: APPARATUS AND METHOD FOR MEASURING A TISSUE ANALYTE SUCH AS BILIRUBIN USING THE BREWSTER'S ANGLE
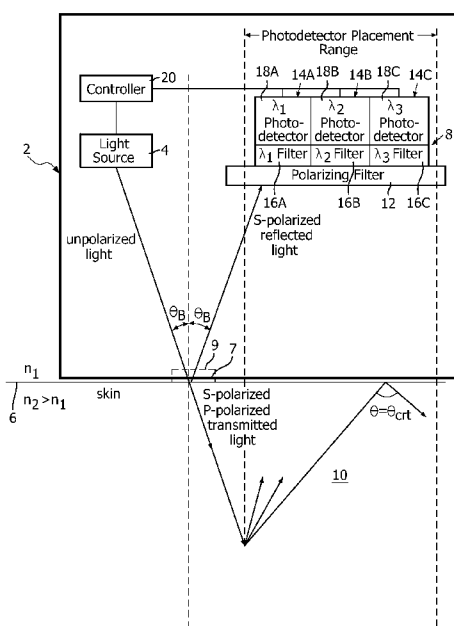
FIG. 1

(57) Abstract: A tissue analyte measuring device (2) includes a light source (4) structured to emit unpolarized light toward the skin surface of a subject, and a detector assembly (8) configured to receive light reflected from the skin surface of the subject and the transcutaneous tissues of the subject, the detector assembly including a polarizing filter (12) and a number of light detector subassemblies (14). The polarizing filter is structured to filter out s-polarized light and pass only p-polarized light to light detector subassemblies. The light source is structured and positioned to emit the unpolarized light in a manner wherein the unpolarized light will exit the measuring device at a predetermined angle with respect to a normal to a light emitting plane of the measuring device, wherein the predetermined angle is an angle (the Brewster's angle) at which only s-polarized light will be reflected by the skin surface when the unpolarized light is incident thereon.

—   *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

—   *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

—   *with international search report (Art. 21(3))*

APPARATUS AND METHOD FOR MEASURING A TISSUE
ANALYTE SUCH AS BILIRUBIN USING THE BREWSTER'S ANGLE

[0001]   The present invention relates to measuring a tissue analyte, such as
bilirubin, in individuals, such as neonates, and more specifically, to an apparatus and
method of measuring a tissue analyte using the Brewster's angle. In one particular
embodiment, the invention relates to an apparatus and method of determining
transcutaneous bilirubin (TcB) and estimating total serum bilirubin (TSB) based
thereon using the Brewster's angle.

[0002]   Neonatal jaundice is a yellowing of the skin and other tissues of a
newborn infant. Typically, a bilirubin level of more than 5 mg/dL manifests clinical
jaundice in neonates. Management of jaundiced neonates typically requires the
measurement and monitoring of total serum bilirubin (TSB), which is most commonly
determined by analyzing a plasma or serum sample from the infant. However, as will
be appreciated, the drawing of blood from infants for such an analysis causes pain and
trauma. This fact has lead to the development of a number of non-invasive techniques
for estimation of TSB.

[0003]   One particular non-invasive method for estimation of TSB, known
as Transcutaneous Bilirubinometry, involves measurement of transcutaneous bilirubin
(TcB). The method relies on the high correlation between TcB and TSB.
Transcutaneous Bilirubinometry devices work by directing light into the skin of the
neonate and detecting specific wavelengths that are reflected back from the neonate's
subcutaneous tissues. The number of wavelengths used varies among different
devices. The detected optical signals are converted to electrical signals by a
photodetector, such as a photodiode, and the electrical signals are analyzed by a
controller to generate a TSB value based on the intensity of the reflected signals.

[0004]   One problem with current Transcutaneous Bilirubinometry devices
is the fact that they have no mechanism for overcoming the impact of reflections
emanating from the surface of the skin. More specifically, as noted above, during
transcutaneous estimation of bilirubin, a device needs to capture and analyze the light
which penetrates the skin and is reflected back by the transcutaneous tissues of the
subject. However, the incident light also undergoes a certain degree of reflection at

1

015067WO1

the skin surface (without penetrating the skin). That reflected light is problematic because it often causes saturation of the detection device and/or adds bias to the intensity measurements. Similar problems exist for devices that use light to measure other tissue analytes, such as other blood or skin analytes.

[0005] Thus, there is room for improvement in the field of tissue analyte analysis using light, such as Transcutaneous Bilirubinometry. In particular, there is a need for a method and device that overcomes the adverse impact of light reflections emanating from the surface of the skin.

[0006] In one embodiment, a tissue analyte (such as bilirubin) measuring device is provided that includes a light source structured and positioned to emit unpolarized light toward a skin surface of a subject when the measuring device is positioned adjacent to the skin surface, and a detector assembly configured to receive light reflected from the subject including light reflected by the skin surface of the subject and by transcutaneous tissues of the subject, the detector assembly including a polarizing filter and a number of light detector subassemblies, the polarizing filter being structured to filter out s-polarized light and pass only p-polarized light to the number of light detector subassemblies. In the exemplary embodiment, the light source is structured and positioned to emit the unpolarized light in a manner wherein the unpolarized light will exit the measuring device at a predetermined angle with respect to a normal to a light emitting plane of the measuring device, the light emitting plane being configured to be positioned adjacent to a skin surface of a subject, wherein the predetermined angle is an angle (the Brewster's angle) at which only s-polarized light will be reflected by the skin surface when the unpolarized light is incident thereon.

[0007] In another embodiment, a method of measuring a tissue analyte of a subject, such as bilirubin, is provided that includes directing unpolarized light at the skin surface of a subject at a predetermined angle with respect to a normal to the skin surface, wherein in response to the unpolarized light being incident on the skin surface, reflected light is reflected by the skin surface and by transcutaneous tissues of the subject, filtering out s-polarized light from the reflected light and passing only p-polarized light from the reflected, and determining a measurement relating to the analyte based on the p-polarized light. In the exemplary embodiment, the

2

015067WO1

predetermined angle is an angle at which only s-polarized light will be reflected by the skin surface (the Brewster's angle).

[0008]   These and other objects, features, and characteristics of the present invention, as well as the methods of operation and functions of the related elements of structure and the combination of parts and economies of manufacture, will become more apparent upon consideration of the following description and the appended claims with reference to the accompanying drawings, all of which form a part of this specification, wherein like reference numerals designate corresponding parts in the various figures. It is to be expressly understood, however, that the drawings are for the purpose of illustration and description only and are not intended as a definition of the limits of the invention. As used in the specification and in the claims, the singular form of "a", "an", and "the" include plural referents unless the context clearly dictates otherwise.

[0009]   FIG. 1 is a schematic diagram of a bilirubin measuring device according to an exemplary embodiment of the present invention.

[0010]   Directional phrases used herein, such as, for example and without limitation, top, bottom, left, right, upper, lower, front, back, and derivatives thereof, relate to the orientation of the elements shown in the drawings and are not limiting upon the claims unless expressly recited therein.

[0011]   As employed, herein, the statement that two or more parts or components are "coupled" together shall mean that the parts are joined or operate together either directly or through one or more intermediate parts or components.

[0012]   As employed herein, the statement that two or more parts or components "engage" one another shall mean that the parts exert a force against one another either directly or through one or more intermediate parts or components.

[0013]   As employed herein, the term "number" shall mean one or an integer greater than one (i.e., a plurality).

[0014]   The present invention relates the measurement of tissue analytes using light analysis, and in particular to an apparatus and method for measuring such tissue analytes. One such tissue analyte is bilirubin. For illustrative purposes, the present invention is described in connection with a device for measuring (e.g., estimating) bilirubin levels that is able to estimate bilirubin levels using

015067WO1

Transcutaneous Bilirubinometry. It will be understood that that is meant to be exemplary, and that the present invention may be used to measure other tissue analytes, such as, without limitation, oxygen saturation (Sp0$_2$), V0$_2$, melanin, and hemoglobin and hemoglobin components like methemoglobin, oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, etc.

[0015]   When light moves between two media of differing refractive indices, generally some of the light is reflected at the boundary and some of the light is transmitted through the boundary. At one particular angle of incidence, called the Brewster's angle (θ_B), light with a particular polarization, identified below, cannot be reflected at the boundary, and instead is perfectly transmitted through the boundary. The Brewster's angle (θ_B) is also known as the polarization angle. When traversing from a first medium with a refractive index n$_1$ to a second medium with a refractive index n$_2$, with n$_2$ > n$_1$, the Brewster's angle is given by: θ_B = arctan(n$_2$ /n$_1$).

[0016]   The particular light polarization that cannot be reflected at the Brewster's angle is the polarization for which the electric field of the light waves lies in the same plane as the incident rays and the surface normal (i.e., the plane of incidence). This polarization is called p-polarization because it is parallel to the plane. On the other hand, light with perpendicular polarization is called s-polarized light. At the Brewster's angle, some s-polarized light will be transmitted through the boundary and some will be reflected. Thus, for light incident at the Brewster's angle on a boundary between two media where n$_2$ > n$_1$, any light that is reflected will be only s-polarized light.

[0017]   As described in greater detail below, the present invention employs the properties of the Brewster's angle to provide a mechanism for overcoming the adverse impact of reflections emanating from the surface of the skin during the transcutaneous estimation of bilirubin levels.

[0018]   FIG. 1 is a schematic diagram of a bilirubin measuring device 2 according to an exemplary embodiment of the present invention. Bilirubin measuring device 2 includes light source 4 which is structured to emit unpolarized light. Light source 4 may be a single light emitting device or a plurality of light emitting devices. Light source 4 may be, for example and without limitation, an LED (or LEDs) which emits/emit unpolarized light, such as unpolarized white light or unpolarized light of

015067WO1

one or more particular wavelengths, or an incandescent light source (or sources) that emits/emit unpolarized light, such as unpolarized white light or unpolarized light of one or more particular wavelengths. In addition, as illustrated in FIG. 1, light source 4 is structured to direct the emitted unpolarized light toward skin surface 6 of a subject through light emitting plane 7 defined by light emitting portion 9 of bilirubin measuring device 2 so that it is incident against skin surface 6 at the Brewster's angle (θ_B). The unpolarized light will thus be transmitted to/through a boundary between a first media through which the unpolarized light is originally transmitted, such as air **[Is this correct?]**, having a refractive index n_1, and a second media comprising skin surface 6 having a refractive index n_2. As noted above, the Brewster's angle (θ_B) may be determined using the equation $\theta_B = \arctan(n_2/n_1)$ (the refractive index of the skin is known in the literature). Alternatively, the Brewster's angle (θ_B) may be determined empirically by adjusting the angular position of light source 4 and finding the angle at which p-polarized light disappears from the reflected light. Light source 4 may be structured to direct the emitted unpolarized light so that it is incident on skin surface 6 at the Brewster's angle (θ_B) in a number of ways, such as by coupling a transmission optical fiber or fibers to light source 4 which directs the light at that angle (a collimating lens system may also be coupled to the fiber or fibers), or directing the light through a collimating lens system to direct the light at that angle . In addition, light emitting portion 9 may be a portion of a housing of bilirubin measuring device 2 that is structured to allow light to escape, and may be, for example, a hole or window (e.g., glass or plastic) in the housing that allows light to escape.

[0019]   Bilirubin measuring device 2 further includes detector assembly 8 that is structured and configured to receive light reflected from the subcutaneous tissue 10 of a subject, such as a neonate. For example, one or more optical fibers may be coupled to detector assembly 8 to collect and direct the reflected light toward detector assembly 8. Detector assembly 8 is, in the exemplary embodiment, shielded from all light except the light that is reflected.

[0020]   Detector assembly 8 includes polarizing filter 12. Polarizing filter 12 is a filter that passes only p-polarized light and filters out (i.e., rejects) s-polarized light. Detector assembly 8 also includes a number of detector subassemblies 14, which in the illustrated embodiment are detector subassemblies 14A, 14B, 14C (while

015067WO1

three such detector subassemblies 14 are shown, that is meant to be exemplary only and it will be appreciated that more or less than three detector subassemblies 14 may also be used). Detector subassemblies 14A, 14B, 14C are each structured to receive and detect the light that is passed by polarizing filter 12 (i.e., p-polarized light only).

[0021]   Each detector subassembly 14A, 14B, 14C includes an optical filter 16A, 16B, 16C operatively coupled to an associated photodetector 18A, 18B, 18C. Each photodetector 18A, 18B, 18C is a device, such as, without limitation, a photodiode, that converts light into a current or voltage. Furthermore, in the illustrated embodiment, each optical filter 16A, 16B, 16C is a band pass filter that is centered at a predetermined wavelength of light with a predetermined full-width at half maximum (FWHM). In the exemplary embodiment, the optical filter 16A, 16B, 16C are chosen to pass a plurality of predetermined wavelengths that are required for determining one or both of a TCB level and a TSB level of the subject (e.g., 484 nm, 517 nm, and 563 nm).

[0022]   Bilirubin measuring device 2 also includes controller 20 that is operatively coupled to light source 4 and detector subassemblies 14A, 14B, 14C. Controller 20 includes a processing portion which may be, for example, a microprocessor, a microcontroller or some other suitable processing device, and a memory portion that may internal to the processing portion or operatively coupled to the processing portion and that provides a storage medium for data and software executable by the processing portion for controlling the operation of bilirubin measuring device 2, including calculating TcB and/or estimating TSB based on the intensity levels of the light detected by detector assemblies 14A, 14B, 14C.

[0023]   In operation, bilirubin measuring device 2 is placed against skin surface 6 of a subject, such as a neonate. Controller 20 then causes light source 4 to emit and direct unpolarized light toward skin surface 6. As described elsewhere herein and as shown in FIG. 1, that light will be incident on skin surface 6 at the Brewster's angle (θ_B). This will result in p-polarized light from the transmitted unpolarized light being perfectly transmitted through the boundary at skin surface 6, with no p-polarized light being reflected by skin surface 6. In addition, some s-polarized light from the transmitted unpolarized light will be transmitted through the boundary at skin surface 6 and some will be reflected by skin surface 6. Thus, the

015067WO1

only light that will reflected by skin surface 6 is s-polarized light. That light will be filtered out by polarizing filter 12 and therefore not reach detector subassemblies 14A, 14B, 14C. As a result, no light reflected by skin surface 6 will be detected by detector subassemblies 14A, 14B, 14C and thus will not cause the adverse effects discussed elsewhere herein (e.g., saturation). Instead, only light that has penetrated skin surface 6 and has been reflected back will reach detector subassemblies 14A, 14B, 14C. More specifically, the p-polarized light perfectly transmitted through the boundary at skin surface 6 (along with any s-polarized light that is also transmitted) will undergo multiple scattering and some of it will be reflected by subcutaneous tissue 10 and be directed toward detector assembly 8. P-polarized light that is reflected from subcutaneous tissue 10 will be passed through polarizing filter 12 (any s-polarized light reflected from subcutaneous tissue 10 will be filtered out) and will be filtered by optical filters 16A, 16B, 16C and detected by photodetectors 18A, 18B, 18C, which each convert the detected light into an electrical signal (voltage or current). Those electrical signals are then provided to controller 20. In the exemplary embodiment, the electrical signals are amplified, for example using operational amplifiers, before being provided top controller 20. Controller 20 will then calculate TcB and/or estimate TSB based on those signals using any of a number of known methodologies. Suitable methodologies are described in, for example, one or more of the following, the disclosures of which are incorporated herein by reference: United States Patent Nos. 5,353,790; 6,847,835; 6,882,873; S. L. Jacques et al., "Developing an Optical Fiber reflectance Spectrometer to Monitor Bilirubinemia in Neonates", SPIE Proceedings 2975:115-124, *Laser-Tissue Interactions*, San Jose, CA Feb. 1997; and G. J. Newman, "Bilirubin Measurements in Neonates," SPIE Vol. 3913 (2000), in *In Vitro Diagnostic Instrumentation*.

[0024] In one exemplary embodiment, bilirubin measuring device 2 is a fully integrated system, where both light source 4 and detector assembly 8 are positioned on the same measurement board, positioned slightly apart from the skin or measurement surface, to allow the light emitted by light source 4 to be reflected and detected as described herein. Care should be taken to prevent direct light from light source 4 from hitting detector assembly 8. Rather, only reflected light should be permitted to do so.

015067WO1

[0025]   Furthermore, the optimal placement of the detector subassemblies
14A, 14B, 14C (as well as polarizing filter 12) could be estimated/predicted based on
two parameters, the angle of the s-polarized reflected light (which, as shown in FIG. 1
is same as the Brewster's angle (θ_B) of the incident light) and the depth of penetration
within the skin of the incident light. The light which penetrates skin surface 6
depends on the intensity of the incident light which could penetrate till the end of the
epidermis (below skin surface 6, where the bilirubin is deposited). The light which
has penetrated skin surface 6 undergoes multiple scatterings and also total internal
reflection. If the scattered light incident angle is less than θ_{crt} (critical angle), then the
light will be reflected back. So, in the exemplary embodiment, the detector
subassemblies 14A, 14B, 14C should not be placed beyond the θ_{crt} (critical angle),
since no reflected light from the skin is available. In another alternative embodiment,
the detector signal is scanned as a function of angle to estimate the angle range over
which the light is transmitted back from skin so that an outer boundary can be
established where there is determined to be no light transmitted back.

[0026]   Although the invention has been described in detail for the purpose
of illustration based on what is currently considered to be the most practical and
preferred embodiments, it is to be understood that such detail is solely for that
purpose and that the invention is not limited to the disclosed embodiments, but, on the
contrary, is intended to cover modifications and equivalent arrangements that are
within the spirit and scope of the appended claims. For example, it is to be
understood that the present invention contemplates that, to the extent possible, one or
more features of any embodiment can be combined with one or more features of any
other embodiment.

CLAIMS:

1.   A tissue analyte measuring device (2), comprising:

a light source (4) structured and positioned to emit unpolarized light toward a skin surface (6) of a subject when the measuring device is positioned adjacent to the skin surface; and

a detector assembly (8) configured to receive light reflected from the subject including light reflected by the skin surface of the subject and by transcutaneous tissues of the subject, the detector assembly including a polarizing filter (12) and a number of light detector subassemblies (14), the polarizing filter being structured to filter out s-polarized light and pass only p-polarized light to the number of light detector subassemblies.

2   The measuring device according to claim 1, wherein the light source is structured and positioned to emit the unpolarized light in a manner wherein the unpolarized light will exit the measuring device at a predetermined angle with respect to a normal to a light emitting plane (7) of the measuring device, the light emitting plane being configured to be positioned adjacent to a skin surface of a subject, wherein the predetermined angle is an angle at which only s-polarized light will be reflected by the skin surface when the unpolarized light is incident thereon.

3.   The measuring device according to claim 2, wherein the predetermined angle is a Brewster's angle determined using a refractive index of human skin.

4.   The measuring device according to claim 2, wherein the light source is structured and positioned to emit the unpolarized light in a manner wherein the unpolarized light will exit the measuring device and be incident on the skin surface at a predetermined angle with respect to a normal to the skin surface when the measuring device is placed against the skin surface, wherein the predetermined angle is an angle at which only s-polarized light will be reflected by the skin surface when the unpolarized light is incident thereon.

5.   The measuring device according to claim 4, wherein the predetermined angle is a Brewster's angle determined using a refractive index of human skin.

6.   The measuring device according to claim 1, wherein the number of light detector assemblies is a plurality of light detector assemblies.

7.   The measuring device according to claim 6, wherein each of the light detector subassemblies includes a filter (16) and a photodetector (18).

8.   The measuring device according to claim 7, wherein each filter is centered at a predetermined wavelength.

9.   The measuring device according to claim 8, wherein the tissue analyte is bilirubin, wherein the filters are structured to pass a plurality of predetermined wavelengths required for determining one or both of a TCB level and a TSB level of the subject.

10.   The measuring device according to claim 9, further comprising a controller (20) operatively coupled to the light source and the number of light detector subassemblies, wherein each photodetector is structured to convert light received thereby to an electrical signal, and wherein the controller is adapted to determine one or both of a TCB level and a TSB level of the subject based on the electrical signal received from each photodetector.

11.   The measuring device according to claim 7, wherein each photodetector is a photodiode.

12.   A method of measuring a tissue analyte of a subject, comprising:

directing unpolarized light at a skin surface of a subject at a predetermined angle with respect to a normal to the skin surface, wherein in response to the unpolarized light being incident on the skin surface, reflected light is reflected by the skin surface and by transcutaneous tissues of the subject;

filtering out s-polarized light from the reflected light and passing only p-polarized light from the reflected; and

determining a measurement relating to the analyte based on the p-polarized light.

13.   The method according to claim 12, wherein the predetermined angle is an angle at which only s-polarized light will be reflected by the skin surface.

14.   The method according to claim 12, wherein the predetermined angle is a Brewster's angle determined using a refractive index of human skin.

15.   The method according to claim 12, wherein the determining includes filtering the p-polarized light to produce one or more filtered lights, detecting the one or more filtered lights and determining the measurement using the detected one or more filtered lights.

16.   the method according to claim 15, wherein the one or more filtered lights is a plurality of filtered lights each including a predetermined wavelength.

17.   The method according to claim 16, wherein the tissue analyte is bilirubin, and wherein each predetermined wavelength is required for determining one or both of a TCB level and a TSB level of the subject.
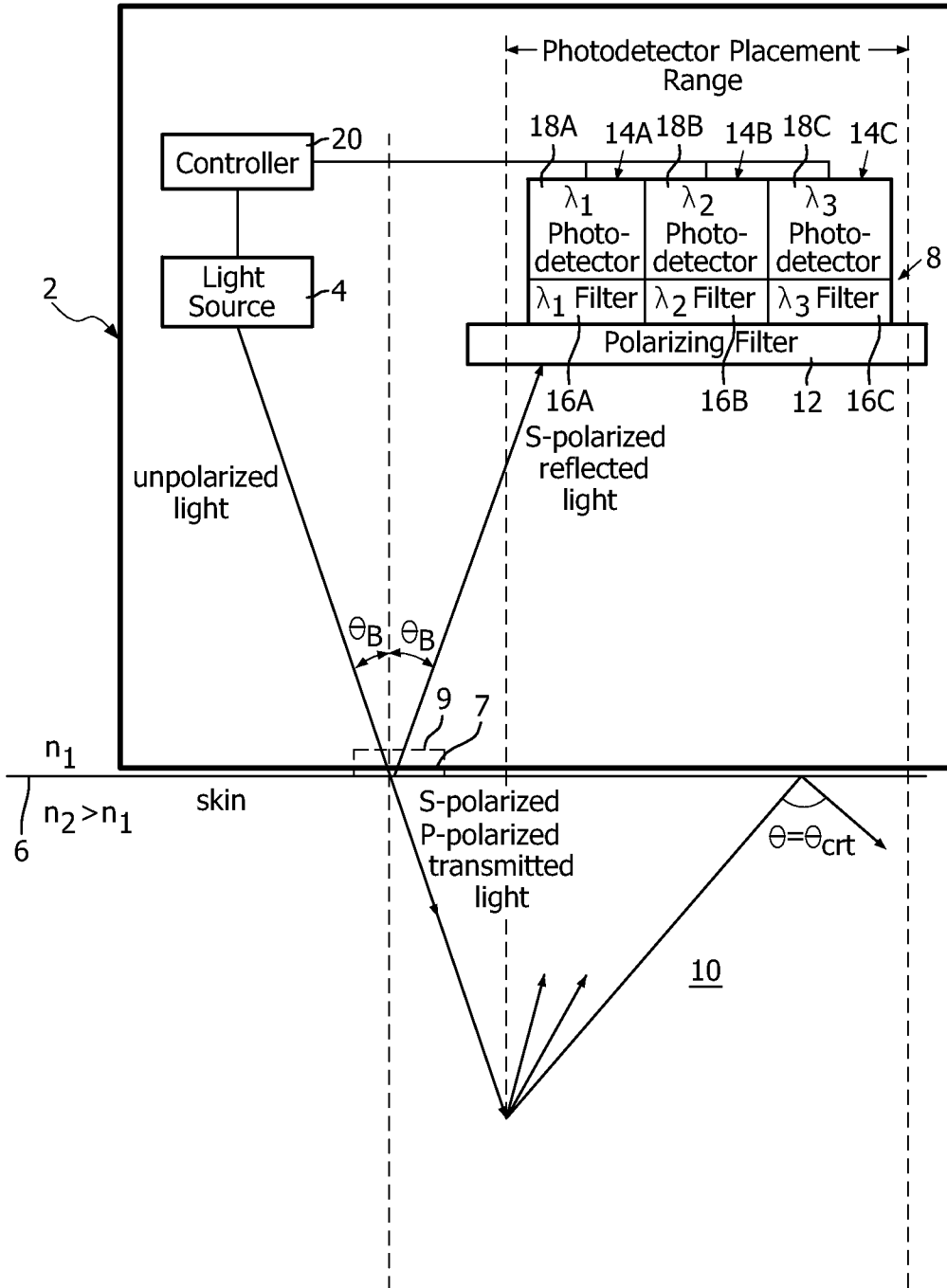
1/1

FIG. 1

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00   G01N21/21   G01N21/47
ADD.

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	WO 96/39925 A1 (UNIV ARKANSAS [US]) 19 December 1996 (1996-12-19) page 7, line 34 - page 8, line 11 page 11, line 22 - page 12, line 11 figure 1 -----	1-6, 12-17
X	US 2008/219522 A1 (HOOK JAROSLAV [US]) 11 September 2008 (2008-09-11) paragraph [0047] - paragraph [0049] figure 1 -----	1,6-17
X	US 4 398 541 A (PUGLIESE PETER [US]) 16 August 1983 (1983-08-16) column 3, line 3 - line 35 column 4, line 20 - line 62 figure 1 -----	1-5
	-/--	

[X] Further documents are listed in the continuation of Box C.   [X] 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	Date of mailing of the international search report
30 August 2011	07/09/2011

| 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 Bengtsson, Johan |

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

C(Continuation).   DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/073450 A2 (UNIV PENNSYLVANIA [US]; ENGHETA NADER [US]; PUGH EDWARD [US]; LIN SHIH) 13 July 2006 (2006-07-13) paragraph [0034] - paragraph [0035] paragraph [0049] - paragraph [0050] figures 1(B), 1(D) -----	1-6

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9639925	A1	19-12-1996	AT	282985 T	15-12-2004
			AT	200020 T	15-04-2001
			AU	706419 B2	17-06-1999
			AU	5929696 A	30-12-1996
			CA	2223089 A1	19-12-1996
			DE	69612283 D1	03-05-2001
			DE	69612283 T2	08-11-2001
			DE	69633946 D1	30-12-2004
			DE	69633946 T2	02-03-2006
			DK	830077 T3	18-06-2001
			EP	1066791 A2	10-01-2001
			EP	1514510 A1	16-03-2005
			EP	0830077 A1	25-03-1998
			ES	2156280 T3	16-06-2001
			HK	1032520 A1	20-05-2005
			JP	3734508 B2	11-01-2006
			JP	11509748 T	31-08-1999
			US	6272374 B1	07-08-2001
			US	6032070 A	29-02-2000
			US	2001027273 A1	04-10-2001
US 2008219522	A1	11-09-2008	NONE		
US 4398541	A	16-08-1983	NONE		
WO 2006073450	A2	13-07-2006	US	2007280513 A1	06-12-2007