

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 August 2005 (18.08.2005)

PCT

(10) International Publication Number
WO 2005/074792 A1

(51) International Patent Classification⁷: **A61B 5/00**

(21) International Application Number:
PCT/US2005/004834

(22) International Filing Date: 28 January 2005 (28.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/539,972 30 January 2004 (30.01.2004) US

(71) Applicants (for all designated States except US): **BROWN UNIVERSITY** [US/US]; 1 Prospect Street, Providence, RI (US). **RHODE ISLAND HOSPITAL** [US/US]; 593 Eddy Street, Providence, RI 02903 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CRAWFORD, Gregory, P.** [US/US]; 517 Lloyd Street, Providence, RI 02916 (US). **JAY, Gregory, D.** [US/US]; 3 Crossbow Road, Norfolk, MA 02056 (US).

(74) Agent: **CSERR, Luann**; Brown University, Brown Technology Partnerships, 47-49 George Street, Providence, RI 02912 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

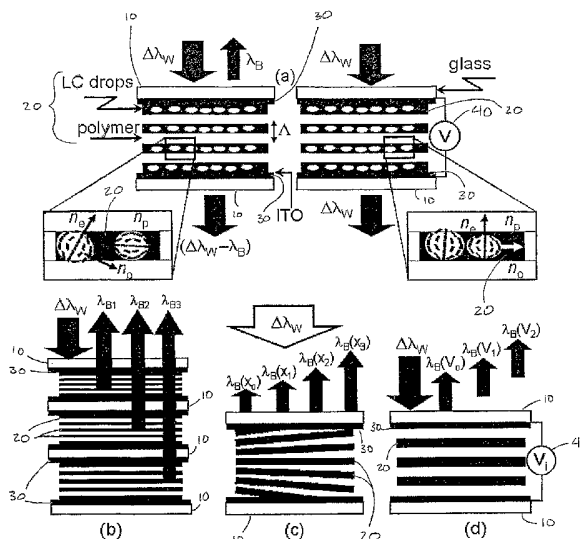
— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report

[Continued on next page]

(54) Title: NON-INVASIVE SPECTROSCOPY OF MAMMALIAN TISSUES



(57) Abstract: In the spectrometric device of this invention the objective lens and diffraction grating are replaced with a spectral imaging apparatus on electrically switchable color filter technology. The spectrometric device comprises wavelength filter means as the spectral imaging apparatus for transmitting or reflecting wavelengths of light, light intensity sensor means arranged and disposed to measure the intensity of the wavelengths transmitted or reflected by the wavelength filter means and generate an electrical signal from the wavelengths transmitted or reflected, output processing means connected to the light intensity sensor means to receive and process the output from the light intensity sensor means, and display means connected to the output processing means to display the output.



-
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

3 NON-INVASIVE SPECTROSCOPY OF MAMMALIAN TISSUES

4

5

6 FIELD OF THE INVENTION

7 This invention relates to the non-invasive, spectrometric,
8 assessment of hemoglobin in the blood of mammalian tissues.

9

10 BACKGROUND

11 The assessment of blood in mammalian tissues is important in
12 different scientific disciplines. In medicine, the assessment of blood,
13 and in particular, the assessment of hemoglobin concentration in the
14 blood, is important in the diagnosis and treatment of many diseases
15 and dysfunctions. In forensic science, the assessment of blood is an
16 indication of contusions or bruises of the skin, which are typical
17 consequences of blunt impact trauma. The invention concerns the
18 non-invasive, spectrometric, assessment of hemoglobin concentration
19 in blood in mammals. Two significant applications of this technology
20 are in the diagnosis of anemia, in which hemoglobin concentration is
21 assessed, and in the determination of blunt force trauma, in which
22 hemoglobin degradation and aging is assessed. These two
23 applications are discussed below.

24 A. Anemia

25 Anemia is often perceived by the general population to be a
26 minor medical condition. However, according to the World Health
27 Organization (WHO), anemia is the single, largest global illness

1 adversely affecting mortality and worker capacity. The United States
2 Department of Health & Human Services deems it a significant public
3 health concern. Of the 16 million people estimated to have anemia in
4 the United States, 78% go undiagnosed. In developing countries where
5 nutritional inadequacies and infectious diseases are more prevalent,
6 the situation is estimated to be even worse.

7 Anemia is a deficiency in the number of healthy red blood cells
8 in an individual's body. This deficiency results in oxygen deficiency in
9 the body's tissues and organ systems. Medically, anemia is defined by
10 the WHO as a hemoglobin concentration below 12 g/dL for females
11 and below 13 g/dL for males. Anemia is well known to the general
12 public to influence physical function by causing fatigue and weakness.
13 It also decreases myocardial function and increases peripheral arterial
14 vasodilation and activation of the sympathetic and reninangiotensin-
15 aldosterone system, which strongly influences the initiation or
16 progression of diseases such as heart failure and renal failure. In
17 addition, anemia affects individuals with other diseases; at least 33%
18 of cancer patients, 65-95% of HIV/AIDS patients, and 70% of
19 rheumatoid arthritis patients also have anemia.

20 Age-related disability and loss in physical function are mounting
21 public health concerns. Loss of physical function endangers the
22 quality of life and independence of many older adults and has
23 significant social and economic repercussions. The prevalence of
24 anemia increases with age and averages about 13% in persons' over 70
25 years of age. A majority of the anemia in aging adults signifies

1 diseases such as cancer and infectious ailments or are due to iron
2 deficiency or malnutrition. Recent studies indicate that anemia in
3 aging adults ins an independent risk factor for decline in physical
4 performance and is associated with higher mortality risks.

5 Yet anemia is severely under-diagnosed. The reasons are two-
6 fold. To determine if a patient is anemic, the physician can either
7 make a visual inspection of the palpebral conjunctiva of the eye socket
8 or take a blood sample and have a cell blood count (CBC) test run.
9 Visual inspection, dependent on the physician's experience and
10 training, is at best only 70% accurate and it has been shown that
11 physicians today are less accurate in diagnosing anemia by visual
12 inspection that in the past. Hung, et al., Evaluation of the Physician's
13 Ability to Recognize the Presence or Absence of Anemia, Fever, and
14 Jaundice, *Academic Emergency Medicine* 7: 146-56 (2000). The CBC
15 test is very accurate, but painful and expensive to perform, time-
16 consuming and often not included in a routine examination.

17 Because of the need to assess hemoglobin concentration in a
18 more accurate and effective manner, a number of devices and methods
19 have been proposed. Exemplary are (i) retinal imaging, see United
20 States Patent No. 6, 305,804 entitled Non-Invasive Measurement of
21 Blood Component Using Retinal Imaging, (ii) blood oxygenation
22 monitoring, see United States Patent No. 6,456,862 entitled Method
23 for Non-Invasive Spectrophotometric Blood Oxygenation Monitoring
24 and United States Patent No. 6,149,589 entitled On-Line and Real-
25 Time Spectroreflectometry Measurement of Oxygenation in Patients

1 Eye, (iii) in-vivo imaging of blood, see United States Patent No.
2 6,104,939 entitled Method and Apparatus for Reflected Imaging
3 Analysis, (iv) blood analyzer technology, see United States patent
4 5,791,345 entitled Non-Invasive Blood Analyzer, and (v) image
5 processing of blood vessels, see United States Patent No. 4,998,533
6 entitled Apparatus and Method for In Vivo Analysis of Red and White
7 Blood Cell Indices. None of these proposed solutions has been
8 embraced by health care professionals, predominately because of
9 inconvenience and inaccuracies in the results.

10 United States Patent Application Publication No. 2003/0002772,
11 published January 2, 2003 and entitled Non-Invasive Determination of
12 Blood Components discloses a method for estimating an amount of
13 hemoglobin in bodily fluids from the color of a tissue surface of a
14 subject by taking a digital color image of the surface of the subject
15 and a color reference object, decomposing the images into sub-
16 images of component colors having values corresponding to the pixels
17 of the images, selecting a window of each of the images, and
18 calculating an estimated level of hemoglobin using values associated
19 with the component values corresponding to the windows. Although
20 this approach is rapid, due to the inherent noise in this approach, the
21 accuracy of this method is limited.

22 Accordingly, there is still a significant need in the art for a
23 device that can quickly, accurately and non-invasively measure or
24 assess hemoglobin concentration. Such a device would have many
25 health care applications, such as in routine physical examinations, in

1 emergency rooms, for emergency rescue professionals, during surgery
2 for in-situ measurement of bleeding, for home health care for the
3 chronically ill and aging population, in developing countries lacking
4 medical facilities, in military medical units and in mass casualty
5 situations and triage units, and by oncology, pediatric, obstetric and
6 gynecology, anesthesiology, infectious disease, gastroenterology,
7 cardiology, nephrology, geriatric and urology specialists who deal with
8 anemia on a regular basis.

9 B. Forensics

10 Visible contusions or bruises of the skin, the typical
11 consequence of blunt impact trauma, develop after the rupture of
12 blood vessels due to compressive or shearing forces imposed on the
13 body. Bruises are characterized as either subcutaneous or
14 intracutaneous, depending on the tissue layer that is affected. See
15 Bohnert, et al., Spectrophotometric Evaluation of the Colour of Intra-
16 and Subcutaneous Bruises, *Int'l Journal of Legal Medicine* 113(6): 343-
17 8 (2000). A subcutaneous bruise appears at the site of impact or
18 indirectly by local expansion or shifting of a hemorrhage. After a time
19 interval of hours to days, hemorrhages that are originally localized
20 deep in the tissue layers can extend toward the surface of the skin.
21 The bruise can change color over the course of time from blue to
22 green to yellow during the passing days as a result of the breakdown
23 and diffusion of hemoglobin. When the skin is forced by the
24 application of pressure into channel or profile, the blood is forced into
25 those sections of skin not exposed to the pressure, with hemorrhages

1 occurring as a result of vascular ruptures in the dermis. There have
2 been many studies on how to date bruising and how to distinguish
3 abusive bruising from accidental bruising. See for example, Bariciak,
4 et al., Dating Bruises in Children: an Assessment of Physician
5 Accuracy, *Pediatrics* 112(4), 804-7 (2003); Dunstan, et al., A Scoring
6 System for Bruise Patterns: A Tool for Identifying Abuse", *Archives of*
7 *Disease in Childhood* 86(5): 330-33 (2002) and Carpenter, The
8 Prevalence and distribution of Bruising in Babies, *Archives of Disease*
9 *in Childhood* 80: 363-66 (1999). The color impression of a bruise, its
10 spectral signature and the extent of hemoglobin degradation are all
11 indicators of bruise age. Although a few recent studies of
12 spectrometric assessment of skin have been undertaken to diagnose
13 various skin diseases, we are aware of no studies relating to
14 spectrometric assessment of skin to assess bruise condition and age.
15 Assessments are routinely made by physicians without evidence-
16 based, scientific, support and there is currently no objective standard
17 or device for assessing bruises in mammals, especially humans.

18 Accordingly, there is also a compelling need in the art for a non-
19 invasive device and method to accurately age and assess the condition
20 of bruised tissue.

21

22 INVENTION SUMMARY

23 In one aspect, the invention provides a non-invasive
24 spectrometric device and method for assessing or detecting
25 hemoglobin concentration in mammalian tissues. More specifically,

1 the invention provides a non-invasive spectrometric device and
2 method for assessing or detecting hemoglobin concentration in
3 dermal and epidermal tissues of the skin in mammals. The device can
4 be used to detect hemoglobin concentration in an area of the skin that
5 has been subjected to bruising, in the palpebral conjunctiva area of
6 the eye socket, in the earlobe or in any other tissue surface.

7 Spectrometers are well know in the art. In operation, light
8 energy from a light source enters the spectrometer via an entrance slit,
9 passes through an objective lens, a diffraction grating and an exit slit.
10 The diffraction grating diffracts the light into its component
11 wavelengths and the wavelengths then strikes a detector that
12 generates a voltage in proportion to the intensity of the light hitting it.
13 The voltage drives a read-out device designed to provide the data on
14 the light's intensity. In early spectrometers, only one wavelength
15 could be detected and its intensity measured at a time. More recently,
16 the exit slit and detector have been replaced by an array of charge
17 coupled devices (CCDs), which has enabled measurement of more than
18 one wavelength at a time. (The number of wavelengths that can be
19 simultaneously measured is determined by the number of elements in
20 the CCD array.) The array generates an output that is used to
21 reconstruct the intensity of the light striking each element of the array.
22 This output is sent to a output device such as a monitor, a laptop
23 computer, a PDA (portable digital assistant) device, a printer or the
24 like.

1 In the spectrometric device of this invention the objective lens
2 and diffraction grating are replaced with a spectral imaging apparatus
3 based on electrically switchable color filter technology. The
4 spectrometric device of the invention comprises wavelength filter
5 means as the spectral imaging apparatus for transmitting or reflecting
6 wavelengths of light, light intensity sensor means arranged and
7 disposed to measure the intensity of the wavelengths transmitted or
8 reflected by the wavelength filter means and generate an electrical
9 signal from the wavelengths transmitted or reflected, output
10 processing means connected to the light intensity sensor means to
11 receive and process the output from the light intensity sensor means,
12 and display means connected to the output processing means to
13 display the output.

14 In one aspect, the light intensity sensor means is arranged and
15 disposed in stacked relation to the wavelength filter means such that
16 wavelengths of light are transmitted through the wavelength filter
17 means into the light intensity sensor means. In another aspect, the
18 light intensity sensor means is arranged and disposed in angular
19 relation to the wavelength filter means such that wavelengths of light
20 are reflected from the wavelength filter means into the light intensity
21 sensor means. In both of these aspects the light intensity sensor
22 means may be provided by an array of charged coupled devices (CCD)
23 or by a photodiode. The currently preferred embodiment employs a
24 CCD array.

1 The wavelength filter means comprises at least one pair of
2 planer substrates in parallel-opposed relation, at least one layer of
3 light-wavelength modulating material disposed between the pair of
4 planer substrates to achieve spectral coverage in the visible light
5 spectrum, and a power source in power-providing communication with
6 the substrate. The substrates will typically be composed of ITO-
7 coated glass or plastic such that electricity may be employed as the
8 source of power, but in one aspect of the invention described in detail
9 below, electrically conducting substrates are unnecessary because the
10 source of power is thermal. Three different types of known light-
11 wavelength modulating materials may be employed in the wavelength
12 filter means: deformed helix ferroelectric liquid crystals, holographic
13 polymer dispersed liquid crystals, and cholesteric liquid crystals.

14 The light-wavelength modulating material, in one aspect,
15 comprises deformed helix ferroelectric liquid crystals (DH-FLC),
16 electrically tuned to exhibit pre-determined wavelength selection
17 properties. By "electrically tuned" we mean that when a voltage is
18 applied across the DH-FLC, the pitch of molecules elongates, which
19 correspondingly lengthens the wavelength of light exhibited. As in
20 understood in the art, the voltage applied to DH-FLC crystals varies
21 the pitch, which lengthens the wavelength of light transmitted or
22 reflected. Due to this fact, varying voltages can be applied to the DH-
23 FLC materials to set the materials to transmit or reflect at pre-
24 determined wavelengths. Typically DH-FLC have been employed in
25 display applications. In such applications, parallel boundary

1 conditions are employed. In the DH-FLC of this inventions, the
2 molecules in the layers of the DH-FLC employed are aligned
3 perpendicular to the surfaces of the planer substrates, i.e.
4 homeotropic alignment. This modification achieves the reflective
5 capacity of the material.

6 The power source employed to modulate the DH-FLC can be
7 either electrical power or thermal power. For thermal power
8 applications, a transparent resistive heater or other thermal power
9 source is positioned on the planer, exterior, surface of one of the
10 substrates, which are not ITO coated. For electrical power
11 applications, the electrical power source is connected to the
12 conducting elements, the ITO coating, of the substrate to create an in-
13 plane electric field using well-know techniques in the art.

14 In another aspect, the spectrometric device of the invention
15 includes light-wavelength modulating material composed of
16 holographic polymer dispersed liquid crystals (H-PDLC) disposed
17 between electrically conducting substrates. In this aspect, the light
18 wavelength modulating material and electrically conducting substrates
19 are arranged in a stack. The stack is composed of a plurality of layers
20 of H-PDLC arranged in alternating, superposed, relation to a plurality
21 of substrate layers. The number of substrate layers equals the number
22 of layers of H-PDLC, plus one. In other words, the wavelength
23 modulating material includes alternating layers of, from bottom to top,
24 substrate and H-PDLC in a stack with the top layer being a layer of the
25 substrate. Each side of the substrate layer adjacent to H-PDLC will

1 have an electrical conducting coating, for example indium–tin–oxide
2 (ITO) in order to complete the circuit. Consequently, the top and
3 bottom layers of substrate may have an electrical conducting coating
4 on only the side, the side disposed interiorly and adjacent to the H–
5 PDLC. The stack may be composed of as many alternating layers of
6 electrically conducting substrate and H–PDLC as is desired but
7 preferably the stack will be composed of between two and ten layers of
8 H–PDLC (and therefore between three and eleven layers of substrate).

9 In one embodiment of this aspect of the invention, the stack is
10 composed of one layer of H–PDLC sandwiched between two layers of
11 electrically conducting substrate. In this aspect, there exists in the H–
12 PDLC film a variable index of refraction of the liquid crystal, which is
13 different from the index of refraction of the polymer. This variable
14 index of refraction permits continuous modification of the reflection or
15 transmission peak, thereby eliminating the need for multiple
16 “gratings”, each providing reflection or transmission at a single peak.
17 These variable refraction index H–PDLC and their operation are
18 described in detail in United States Patent Publication No.
19 2002/0130988 herein incorporated by reference.

20 In an alternate embodiment of the invention, the light–
21 wavelength modulating material is composed of cholesteric liquid
22 crystals (CLC) disposed between electrically conducting substrates. In
23 this embodiment the CLC may also be composed a plurality of CLC
24 layers arranged in alternating, superposed, relation to a plurality of
25 substrate layer. In this case, the stack will have a number of substrate

1 layers one greater than the number of CLC layers and the power
2 source will produce electrical energy perpendicular to the pitch axis of
3 the CLC layers.

4 The CLC layers have the capacity to reflect light of different,
5 per-determined wavelengths, but because they are inherently reflect
6 light in a right or left handed manner, the maximum efficiency will be
7 only 50%. Consequently, to increase the efficiency, the device may
8 further include a passive optical element such as a quarter-wave plate
9 disposed in parallel relation between two reflective CLC of opposite-
10 handedness.

11 In another aspect, one CLC layer may be interposed between two
12 electrically conducting substrate layers. In this aspect, there exists in
13 the CLC film a variable index of refraction of the liquid crystal, which is
14 different from the index of refraction of the polymer. Like the variable
15 refraction index H-PDLC, the variable index of refraction in the CLC
16 permits continuous modification of the reflection or transmission
17 peak, thereby eliminating the need for multiple "gratings", each
18 providing reflection or transmission at a single peak.

19 The output processing means connected to the light intensity
20 sensor means to receive and process the output from the light
21 intensity sensor means can be any of the well-known output
22 processing means employed in spectrometers. Likewise, the display
23 means connected to the output processing means to display the
24 output can be configured using well-known techniques in the art to
25 display indicia of the estimated level of hemoglobin detected.

1 In the operation of the device of the invention, light is projected
2 from the area of epidermal tissue of interest into the device and is
3 then filtered by the wavelength filter means and detected by the light
4 sensor means of the device, the latter of which generates an electrical
5 signal from the wavelengths transmitted or reflected and transmits
6 that signal to the output processing means, which processes the
7 output and transmits it to a display readable by a physician or other
8 health care professional. The basics of how spectrometers and other
9 spectroscopic tools (such as, for example, spectrophotometers) work
10 is well known in the art and succinctly described in Steven L. Brown,
11 "Laboratory Techniques for General Chemistry, Ch. 5, Spectroscopy" ,
12 2002, Hayden-McNeil Publishing, Plymouth, Michigan.

13 The invention also includes a method of detecting or assessing
14 the concentration of hemoglobin in a mammalian subject suspected of
15 having an abnormal hemoglobin concentration. The method comprises
16 the steps of (a) exposing an area of tissue of a mammalian subject
17 suspected of having an abnormal hemoglobin concentration to a
18 spectrometer of the invention to receive and analyze light reflected
19 from the area of tissue; (b) reading the output from the spectrometer
20 indicating the hemoglobin concentration in the area of tissue exposed
21 to the spectrometer; and (c) comparing the hemoglobin concentration
22 of the output to the hemoglobin concentration in a control standard
23 for a normal epidermal tissue specimen.

24

25 DESCRIPTION OF THE DRAWINGS

1 Fig. 1 is an illustration of a H-DPLC containing device. In (a) the
2 prior art panel is illustrated in its voltage-off and voltage applied
3 positions. In (b) and (c) two embodiments of the device of the
4 invention are illustrated in which only one layer of H-DPLC is
5 employed.

6 Fig. 2 is a graphic representation of the transmission results (a)
7 and the reflection results (b) for the stack of five H-DPLC layers
8 described in detail below.

9 Fig. 3 illustrates the mode of operation of a prior art CLC panel
10 (a) in planar (left), focal conic (middle) and homeotropic (right) states.
11 In (b) an embodiment of the invention composed of a stack of three
12 CLC panels is illustrated. In (c) an embodiment of the invention
13 composed of one CLC in IPS mode is illustrated.

14 Fig. 4 is a graphic representation of the transmission results (a)
15 and the reflection results (b) for a CLC device composed of three panel
16 pairs to reflect red, green and blue as described in detail below.
17 Results are shown in (c) for a single panel CLC IPS device that nearly
18 covers the entire spectral range as described in detail below.

19 Fig. 5 illustrates the device of the invention comprising DH-FLC
20 crystals subject to in-plane switching to produce a red-shift.

21 Fig. 6 is a graphic representation of the transmission results (a)
22 and reflection results (b) as temperature varies in the DH-FLC
23 containing device of the invention.

24

25 DETAILED DESCRIPTION

1 In the spectrometric device of this invention the objective lens
2 and diffraction grating are replaced with a spectral imaging apparatus
3 based on electrically switchable color filter technology. The
4 spectrometric device of the invention comprises wavelength filter
5 means as the spectral imaging apparatus for transmitting or reflecting
6 wavelengths of light, light intensity sensor means arranged and
7 disposed to measure the intensity of the wavelengths transmitted or
8 reflected by the wavelength filter means and generate an electrical
9 signal from the wavelengths transmitted or reflected, output
10 processing means connected to the light intensity sensor means to
11 receive and process the output from the light intensity sensor means,
12 and display means connected to the output processing means to
13 display the output. The light intensity sensor means may take the
14 form of an array of charge coupled devices (CCDs) or a photodiode.
15 The output processing means and display means are both well-
16 recognized elements of spectrometric devices and need not be
17 described in detail here as the skilled artisan would be able without
18 undue experimentation to arrange, connect and incorporated these
19 elements. Any of the well-known output processing means and
20 display means known in the art may be used.

21 In one aspect, the light intensity sensor means is arranged and
22 disposed in stacked relation to the wavelength filter means such that
23 wavelengths of light are transmitted through the wavelength filter
24 means into the light intensity sensor means. In another aspect, the
25 light intensity sensor means is arranged and disposed in angular

1 relation to the wavelength filter means such that wavelengths of light
2 are reflected from the wavelength filter means into the light intensity
3 sensor means.

4 The wavelength filter means comprises at least one pair of
5 planer substrates in parallel-opposed relation, at least one layer of
6 light-wavelength modulating material disposed between the pair of
7 planer substrates to achieve spectral coverage in the visible light
8 spectrum, and a power source in power-providing communication with
9 the substrate. The substrates will typically be composed of ITO-
10 coated glass or plastic such that electricity may be employed as the
11 source of power, but in one aspect of the invention described in detail
12 below, electrically conducting substrates are unnecessary because the
13 source of power is thermal. Three different types of known light-
14 wavelength modulating materials may be employed in the wavelength
15 filter means: holographic polymer dispersed liquid crystals (H-PDLC),
16 cholesteric liquid crystals (CLC), and deformed helix ferroelectric liquid
17 crystals (DH-FLC). These types of liquid crystals are well-known in the
18 art. Their use, including the modifications necessary or desirable to
19 employ them in the spectrometric device of the invention, is described
20 in detail below.

21 A. H-PDLC containing devices

22 Holographic polymer dispersed liquid crystals are created by a
23 simple one-step fabrication process in which a homogeneous mixture
24 of photosensitive prepolymer and nematic liquid crystal is exposed to
25 an interference pattern process following the method disclosed in

1 Bowley and Crawford, "Diffusion Kinetics of Formation of Holographic
2 Polymer Dispersed Liquid Crystal Display Materials", 2000, *Applied*
3 *Physics Letters* 76. In the bright regions of the interference pattern
4 the polymerization occurs more rapidly than in the dark regions,
5 forcing the non-reactive liquid crystal out of the bright regions and
6 into the dark regions. This diffusion process creates a stratified
7 material composed of liquid crystal droplets and polymer rich layers
8 that is locked-in by the photo-polymerization process. The grating
9 pitch is given by $\Lambda = \lambda_f / 2 \langle n \rangle \sin \theta$, where λ_f is the wavelength of the
10 exposing laser beams, $\langle n \rangle$ is the average index of refraction of the
11 liquid crystal and polymer mixture, and 2θ is the angle between the
12 exposure beams inside the sample. Since the liquid crystal typically
13 has an average index of refraction that is larger than that of the
14 polymer, a spatial perturbation in the index of refraction exists.

15 The principle is illustrated in Fig. 1(a). The H-PDLC includes
16 liquid crystal and matrix polymer layers (20) which form a reflection
17 grating capable of reflecting a wavelength of light disposed between a
18 pair or more than one pair of electrically conducting substrates (10),
19 which may be formed from indium-tin-oxide (ITO)-coated glass or
20 plastic. See for example, PCT Patent Publication WO 01/20406
21 published 22 March 2001, which discloses a multicolored reflection
22 liquid crystal display device in which the liquid crystal film is capable
23 of reflecting two different wavelengths of light. Each electrically
24 conducting substrate layer (10) is connected with a means for

1 providing electrical energy through the electrodes of the conductant
2 (30) and into the H-PDLC (20).

3 In the absence of an applied voltage, a refractive index
4 modulation exists between the liquid crystal rich planes (shown as
5 droplets) and the pure polymer planes of the H-PDLCs. The average
6 index of refraction of the liquid crystal rich layers, n_{LC} , is some
7 combination of the ordinary, n_o , and the extraordinary, n_e , index of
8 refraction of the liquid crystal, which is estimated as $n_{LC}^2 \approx (n_e^2 +$
9 $2n_o^2)/3$. When the material is illuminated with a broadband white-
10 light source, a narrow reflection band is rejected with reflectives
11 greater than 50% and peak widths in the 15–30 nm range depending
12 on the birefringence of the liquid crystal, index of refraction of the
13 polymer, and sample thickness. Since liquid crystal molecules possess
14 a positive dielectric anisotropy they align parallel to the applied
15 electric field when an external voltage (40) is applied. In the aligned
16 state, the ordinary refractive index of the liquid crystal matches that of
17 the polymer and the index modulation vanishes. The H-PDLC (20)
18 becomes transparent to all wavelengths, as shown in Fig. 1(a), right
19 panel. Switching voltages in the range of 50–100 volts are needed,
20 since the liquid crystal is highly constricted by the holographic planes
21 of dimensions 170–200 nm for visible reflections; however, the
22 response times can be very fast, in some cases, less than 100 μ
23 seconds.

24 In one embodiment of the current invention, these HPDLCs are
25 employed as a spectrometric device. This embodiment is illustrated in

1 Fig 3(b), in which the spectrometric device comprises a plurality of
2 planer H-PDLC film layers disposed in alternating, stacking relation
3 with a plurality of planer ITO-coated substrate layers. The H-PDLC
4 stratified films are sandwiched between the ITO coated glass
5 substrates and maintained at a distance of between about 2 to about
6 30 micronmeters. Between 2 and 20 H-PDLC film layers, and therefore
7 between 3 and 21 substrate layers may be employed. Preferably,
8 between 2 and 10 layers of H-PDLC and therefore between 3 and 11
9 substrate layers may be employed. Electrical leads 30 are then
10 connected to the edges of each of the planer ITO glass substrates so
11 the H-PDLC material can be exposed to an applied voltage. When a
12 voltage is applied, an electric field is created within the material and
13 the H-PDLCs can be tuned to a transparent state. By using multiple H-
14 PDLC layers, various wavelengths can be allowed to pass through the
15 stack by applying different voltages to the different substrate layers.
16 In Fig. 1(b), the stack is shown with broad band incident white light,
17 $\Delta\lambda_w$, and three reflection bands λ_{B1} , λ_{B2} , λ_{B3} , whose peak wavelength is
18 dictated by Bragg's law, $\lambda_B = 2d\langle n \rangle$ for normally incident light, where
19 d is the thickness of the holographid plane. In the embodiment
20 illustrated in Fig. 3(b), a stack of three H-PDLC layers is shown but the
21 device may be constructed with more or less than three layers to
22 generate a number of reflection bands corresponding to the number of
23 H-PDLC layers in the stack.

24 In another embodiment, the stack is composed of five H-PDLC
25 film layers interspersed between planer ITO-coated substrates instead

1 of three layers as described above. Fig. 2 is a graphic representation
2 of data for such a stack in transmission, Fig. 2(a) and in reflection, Fig.
3 2(b). In reflection (Fig. 2(b)), the five-layered H-PDLC stack exhibits
4 between 30–40% reflectance in the wavelength range between about
5 600 and 760 λ [nm].

6 Referring again to Fig. 1, parts (c) and (d) illustrate two alternate
7 embodiments of this aspect of the inventions. In the aspect illustrated
8 in (c), only one H-PDLC film is needed and employed because a spatial
9 gradient has been created in the holographic plane sizes from one
10 edge of the sample to the other. The H-PDLC sample can then act as a
11 wavelength modulating material for multiple wavelengths. In order to
12 selected different wavelengths, the ITO coating can be pixilated so that
13 the various wavelengths can be electrically addressed independently.

14 In the alternate embodiment shown in (d), only one H-PDLC film
15 is needed and employed because there exists in the H-PDLC film a
16 variable index of refraction of the liquid crystal, which is different from
17 the polymer. In this way, as the electric field is applied to the two
18 substrates, and the index of refraction changes with respect to the
19 index of the polymer enabling the H-PDLC to be electrically addressed
20 to a pre-determined wavelength. This alternate embodiment is
21 described in detail in PCT Patent Publication WO 01/20406 published
22 22 March 2001, which is herein incorporated by reference.

23 All of these above embodiments of H-PDLC can be used in the
24 non-invasive, spectrometric device of the invention to assess
25 hemoglobin concentration in the blood of mammalian tissues.

1

2 B. CLC containing devices

3 Cholesteric liquid crystals (CLC) are also known in the art. CLC
4 exhibit long-range, orientational order analogous to conventional
5 nematic liquid crystals, except that the molecules are chiral. See
6 Blinoff and Chigrinov, *Electro-Optic Effects in Liquid Crystals*, Springer,
7 New York, (1994). Consequently, the structure acquires a
8 spontaneous right-handed or left-handed twist about a helical axis
9 normal to the average direction of the liquid crystal molecules. The
10 degree of twist of the phase is characterized by the cholesteric pitch,
11 "P". Heretofore, CLC have been used in flat-panel display
12 applications. See Yang, et al., in *Liquid Crystals in Complex*
13 *Geometries Formed by Polymer and Porous Networks*, Crawford, GP
14 and Sumer, S, eds., Taylor & Francis, London (1996); Doane, et al.,
15 *Cholesteric Liquid Crystals for Flexible Display Applications*, John Wiley
16 & Sons, London, (2004). The operation of a CLC device is illustrated in
17 Figure 3(a) left panel. In the zero voltage state illustrated in the left
18 panel, the molecules are aligned in the planar configuration between
19 the substrate layers, and since the structure is periodic, they can
20 reflect a bandwidth centered at λ_B , which is dictated by Bragg's law (λ_B
21 = $\langle n \rangle P$ for normal incidence). Upon application of an applied voltage
22 ($V_1 \sim 10\text{--}15$ volts for a $5\text{ }\mu\text{m}$ sample), a positive dielectric anisotropy
23 material ($\Delta\epsilon > 0$) transforms to a focal conic state, which is
24 characterized by a random distribution of helical pitches, as shown in
25 Fig. 3(a), middle panel. This state is transparent and remains that way

1 even after the voltage is removed. In other words, this device
2 possesses bi-stable memory since the focal conic state can remain
3 indefinitely even after the field is removed. Upon application of a
4 higher voltage ($V_2 \sim 25\text{--}30$ volts), the material transforms to the
5 homeotropic, aligned, state as shown in Fig. 3(a), right panel. When the
6 voltage is abruptly removed, the homeotropic state transforms back to
7 the reflective planar state. Fig. 3(a) right panel. The chiral pitch can be
8 engineered, or set, by mixing in different concentrations the chiral
9 components to reflect in the ultraviolet, visible and near infrared in
10 accordance with art-recognized techniques. The switching time is on
11 the order of 30–50 ms slower, depending on the mode, than other
12 liquid crystal materials.

13 In order for CLC to be used in a non-invasive spectrometer, full
14 spectral coverage in the visible light spectrum is required. This can be
15 achieved by employing a CLC stack, comprising a plurality of layers of
16 cholesteric liquid crystal materials. Fig. 3(b) illustrates a three-stack
17 of CLC panels that reflect red, green and blue. Fig. 4(a) presents the
18 data for this stack in the transmission mode and Fig. 4(b) presents the
19 data for this stack in the reflection mode upon application of the
20 applied voltage. Since CLC are intrinsically right- or left-handed
21 because of their chirality, they can reflect only right-handed or left-
22 handed, circularly polarized, light, ideally with 50% efficiency at the
23 Bragg wavelength. To solve this problem, we disposed and arranged
24 the panels that reflected red, green and blue as panel pairs, each color
25 having a right handed and a left handed panel forming the respective

1 pairs, so that we actually had six panels in the stack, two red, then two
2 green, then two blue. We then integrated a passive optical element
3 between two identically reflecting panels to achieve a much higher
4 efficiency, exceeding 80%, as shown in Fig. 4(a) and (b). In the
5 embodiment illustrated the passive optical element employed was a
6 quarter-wave plate, but the skilled artisan will recognize that any
7 passive optical element could be used. Alternatively, to achieve the
8 same outcome, a left handed panel and a right handed panel with the
9 same λ_B can be stacked.

10 The stacked solution illustrated in Fig. 4(b) was experimentally
11 evaluated and the results are shown in Fig. 5(a) and (b). The full
12 spectral width of the reflection peak in Fig. 4(b) is $\Delta\lambda_{FWHM} > 100\text{nm}$.
13 The spectral width is largely dictated by the birefringence of the CLC
14 material, Δn . To decrease the spectral bandwidth, materials with a
15 lower Δn can be employed. For example, for a material with a
16 $\Delta n \sim 0.05$, bandwidths on the order of $\Delta\lambda_{FWHM} \sim 30\text{nm}$ for $\lambda_B = 600\text{nm}$
17 can be achieved. Because CLC materials do not have the scattering
18 losses observed with H-PDLC materials, numerous panels can be
19 stacked to achieve full spectral coverage in the visible range.

20 A CLC in-plane switching (IPS) mode is shown in Fig. 4(c) in
21 which field direction is parallel to the substrates, orthogonal to how it
22 was applied in Fig. 4(a) and (b). As an in-plane voltage is applied
23 perpendicular to the pitch axis of the CLC, the pitch elongates and the
24 reflection red-shifts. This IPS mode permits the use of one panel to
25 span nearly the entire visible spectral range, as is shown in Fig. 4(c).

1 This mode enable electrical tuning of the reflection band from 450 nm
2 to 700nm. Assuming linearity in the transition region, the
3 tunability/resolution metric is $\Delta V/\Delta\lambda \sim 0.15$ V/nm for the peak
4 maximum. The downside of this approach is that overall efficiency
5 may be reduced because the electrodes on the surface of the substrate
6 reduce the optical throughput, as CLC materials do not respond above
7 the electrode. By offsetting a pair of transparent conducting
8 electrodes on the top and bottom substrates and by driving them with
9 voltage signals out of phase, this problem is alleviated. In addition,
10 because the switching voltage is higher in the CLC IPS mode as
11 compared to conventional IPS mode, the electrodes must be arranged
12 closer together so that maximum drive voltages do not exceed 40–50
13 volts. The preferred distance between electrodes is around 5 μm , but
14 the skilled artisan will recognize that distance between electrodes can
15 be optimized for various materials without any undue
16 experimentation.

17 C. DH-FLC

18 The art-known ferroelectric liquid crystal, or chiral smectic C
19 phase (SmC) liquid crystals, consists of layers of molecules. This
20 thickness of the chiral smectic C layers are less than one molecular
21 length. See Yeh and Gu, *Optics of Liquid Crystals*, John Wiley, New
22 York, (1999). As a result, the molecules must tilt at an angle with
23 respect to the layer normal. Because the tilt angle is fixed, the
24 molecular orientation is confined to a cone with a half apex angle of θ .
25 Ferroelectric liquid crystal materials have intrinsic chirality and

1 associated pitch, much like CLC materials, and they have a dipole
2 moment perpendicular to the long molecular axis, rather than parallel
3 to it as in the case of CLCs materials. In ferroelectric switching, the
4 molecules switch on the cone.

5 Art-known, deformed helix ferroelectric liquid crystal materials
6 (DH-FLC) were first used in display applications. See Verhulst, et al., A
7 Wide Viewing Angle Video Display Based on Deformed Helix
8 Ferroelectric LC and Diode Active Matrix, *Proceeding of the*
9 *International Display Research Conference 94: 377-80* (1994). In
10 those applications, parallel boundary conditions were employed, i.e.,
11 the molecules are aligned in parallel to the substrate surfaces In this
12 embodiment of the invention, homeotropic alignment, wherein the
13 molecules are aligned perpendicular to the substrate surfaces, should
14 be employed so that the panel provides a wavelength selection
15 property similar to the CLC panel. Dynamic switching times for panels
16 of DH-FLC materials operated as described above should be less than
17 500 μ s.

18 This embodiment is illustrated in Fig. 5. Pitch is deformable
19 using temperature or an in-plane electric field. If an in-plane electric
20 field is employed, the helix deforms or elongates and the reflection
21 red-shifts. If the in-plane switching (IPS) mode described above for
22 CLC materials is employed, the same disadvantages described will
23 result and accordingly, the IPS electrodes should be located closer
24 together to minimize aperture loss. A preferred range is about 5 μ m,
25 but the skilled artisan will recognize that distance between electrodes

1 can be optimized for various materials without any undue
2 experimentation. If temperature is employed to accomplish switching,
3 a transparent resistive heater may be incorporated into the device and
4 employed in place of electric power in accordance with well-
5 recognized methods. A DH-FLC panel having homeotropic alignment
6 at the surfaces, i.e., in which the molecules are aligned perpendicular
7 to the plane of the layer was prepared and subjected to temperature
8 increases. The data is presented in Fig. 6(a) and (b) for transmission
9 and reflection, respectively. Since the refractive index of the material
10 was small and the cone angle was around 30 degrees, the sample was
11 tilted with respect to the incident light to increase the index
12 perturbation with respect to the incoming light. One DH-FLC panel
13 can cover the entire visible spectral range, as is illustrated in Fig. 6(c).
14 Assuming linearity in the transition region of Fig. 6(c), the
15 tenability/resolution metric is $\Delta V / \Delta \lambda \sim 0.12^\circ/\text{nm}$.

16 The DH-FLC panels of the invention may be switched either
17 electrically or thermally. Electrical switching is currently the preferred
18 mode. Like the CLC-containing devices of the invention, electrical
19 switching may be accomplished by advantageous employment of the
20 herein disclosed IPS mode, in which the field direction is parallel to the
21 substrates. Thermal switching can be accomplished by employing a
22 transparent resistive heater, which is connected to a power supply
23 (typically a current source) employing methods and materials well-
24 known in the art.

1 Other embodiments are within the scope and spirit of the
2 claims. Certain elements and functions of the invention described
3 above can be implemented using software, hardware, firmware,
4 hardwiring, or any combinations of these in art-recognized ways.
5 Features, elements and means of the invention implementing various
6 functions may be physically located at various positions rather than in
7 a single location or apparatus.

8 All references cited in this document are hereby incorporated by
9 reference herein for the substance of their disclosure.

10

1 We claim:

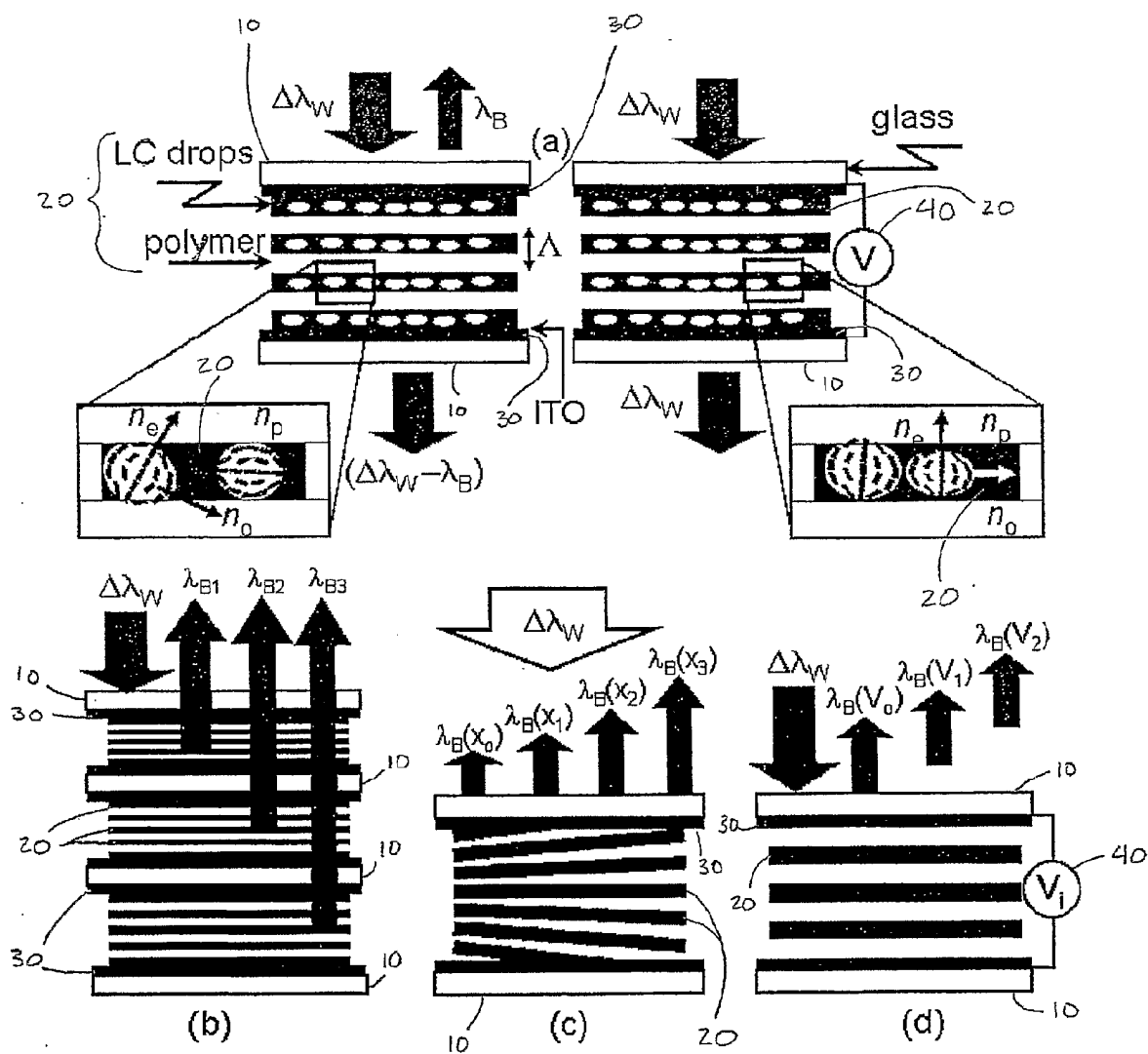
2

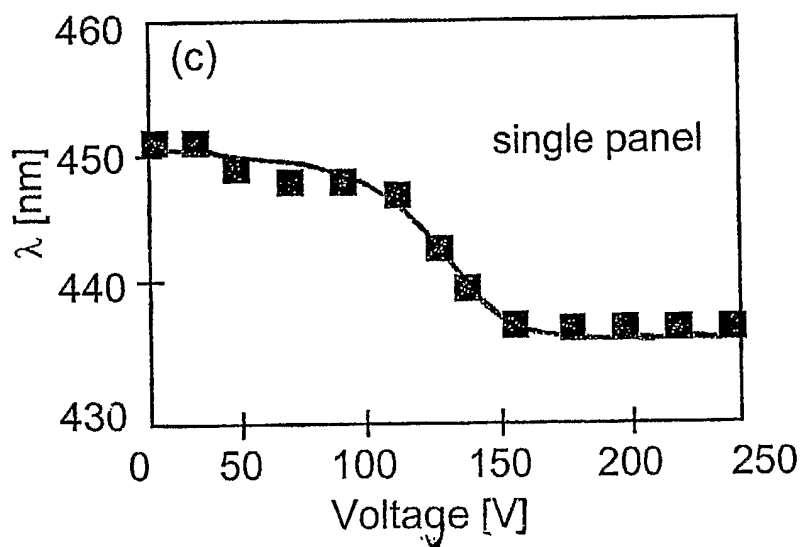
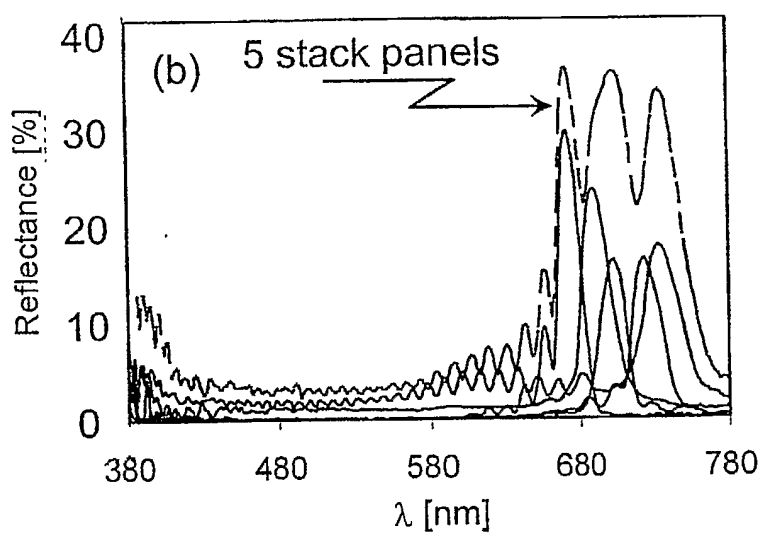
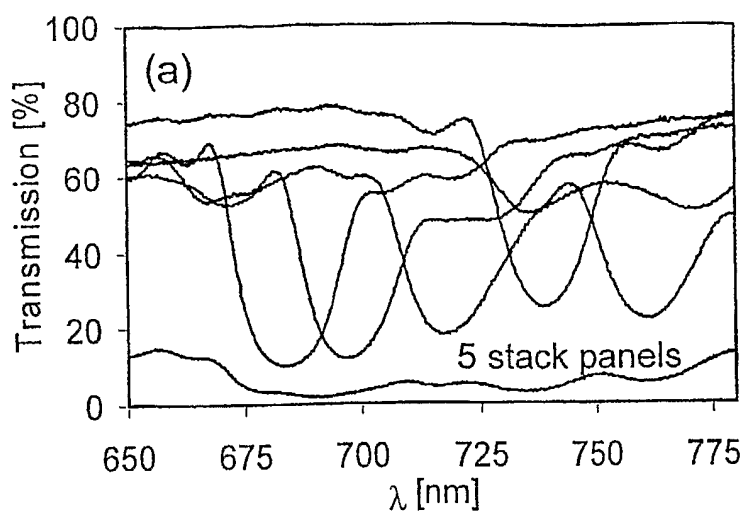
- 3 1. A non-invasive spectrometric device for assessing the level of
4 hemoglobin in mammalian tissues comprising (a) wavelength
5 filter means for transmitting or reflecting wavelengths of
6 light; (b) light intensity sensor means arranged and disposed
7 to measure the intensity of the wavelengths transmitted or
8 reflected by the wavelength filter means and generate an
9 electrical signal therefrom, (c) output processing means
10 connected to the light intensity sensor means to receive and
11 process the output therefrom; and (d) display means
12 connected to the output processing means to display the
13 output.
- 14 2. The device of claim 1 wherein the light intensity sensor
15 means is arranged and disposed in stacked relation to the
16 wavelength filter means such that wavelengths of light are
17 transmitted through the wavelength filter means into the
18 light intensity sensor means.
- 19 3. The device of claim 1 wherein the light intensity sensor
20 means is arranged and disposed in angular relation to the
21 wavelength filter means such that wavelengths of light are
22 reflected from the wavelength filter means into the light
23 intensity sensor means.
- 24 4. The device of claim 1 wherein the wavelength filter means
25 comprises at least one pair of planer substrates in parallel-

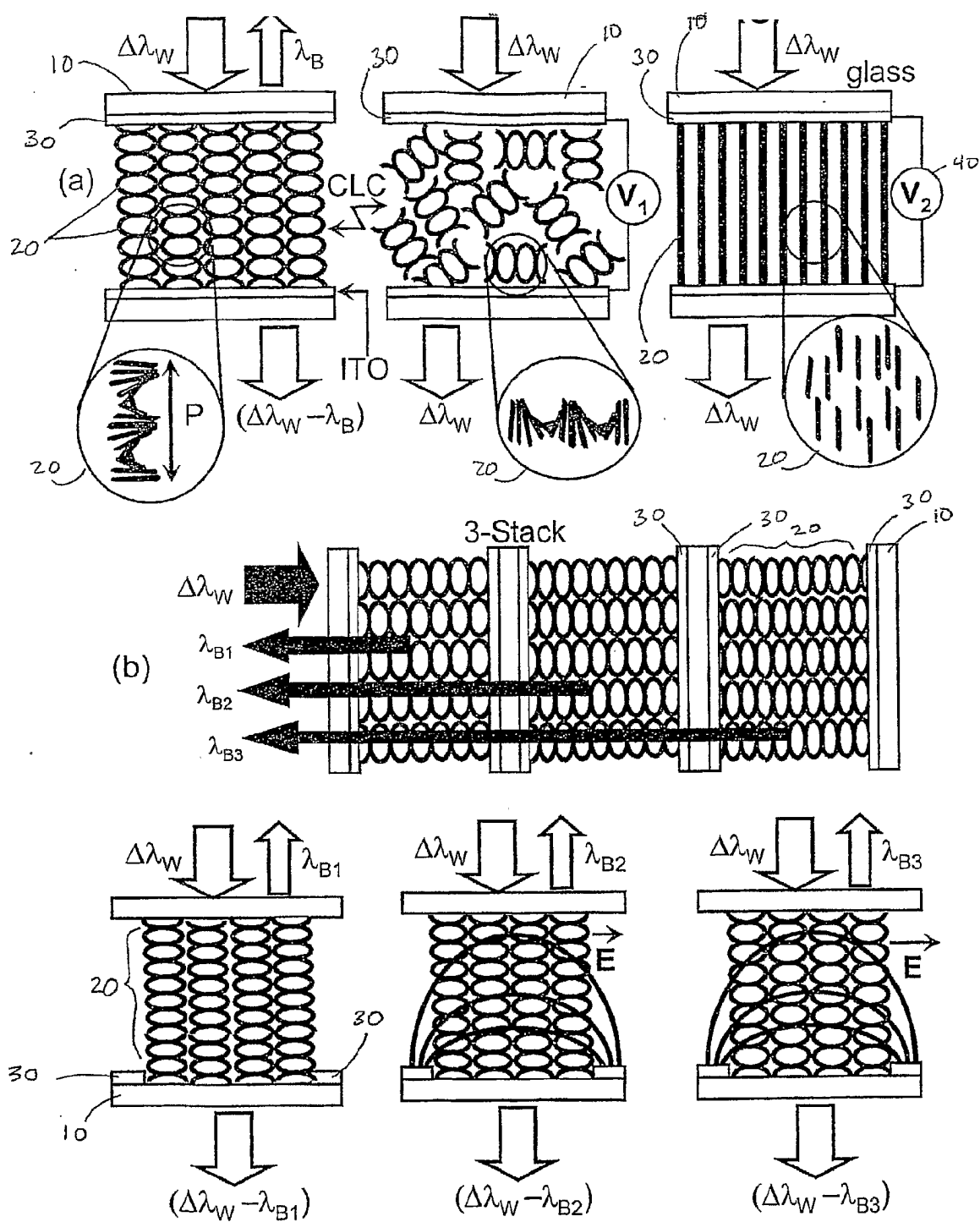
- 1 opposed relation, at least one layer of light-wavelength
2 modulating material disposed between the pair of planer
3 substrates to achieve spectral coverage in the visible light
4 spectrum, and a power source in power-providing
5 communication with the substrate.
- 6 5. The device of claim 4 wherein the substrates are electrically
7 conducting substrates.
- 8 6. The device of claim 4 wherein the light-wavelength
9 modulating material comprises deformed helix ferroelectric
10 liquid crystals (DH-FLC), electrically tuned to exhibit pre-
11 determined wavelength selection properties.
- 12 7. The device of claim 6 wherein the molecules in the layers of
13 the DH-FLC are aligned perpendicular to the surfaces of the
14 planer substrates.
- 15 8. The device of claim 5 wherein the power source is in
16 electrical communication with the substrates to create an in-
17 plane electric field.
- 18 9. The device of claim 4 wherein the power source is in thermal
19 communication with one of the pair of substrates to create a
20 temperature change in the wavelength modulating material.
- 21 10. The device of claim 9 wherein the power source is a
22 transparent resistive heater positioned on the planer exterior
23 surface of one of the pair of substrates.

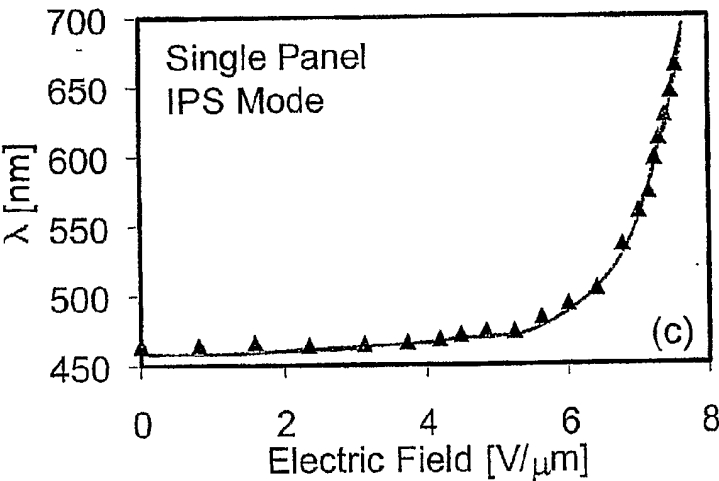
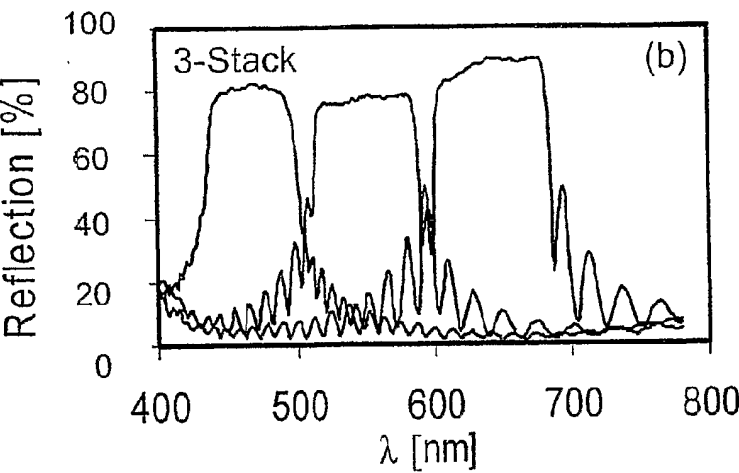
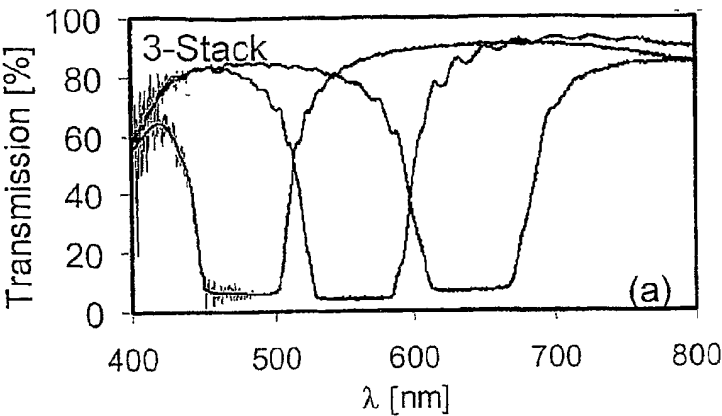
- 1 11. The device of claim 5 wherein the light-wavelength
2 modulating material comprises a layer of holographic
3 polymer dispersed liquid crystals (H-PDLC).
- 4 12. The device of claim 11 wherein one layer of H-PDLC is
5 arranged between two parallel-opposed electrically
6 conducting substrate layers so as to form a spatial gradient
7 in the H-PDLC from one edge of the substrate layers to the
8 opposing edge of the substrate layers.
- 9 13. The device of claim 11 wherein one layer of H-PDLC is
10 arranged between two parallel-opposed electrically
11 conducting substrate layers and wherein the H-PDLC has an
12 index of refraction variable in response to an applied electric
13 field.
- 14 14. The device of claim 11 comprising a stack composed of a
15 plurality of layers of H-PDLC arranged in alternating,
16 superposed, relation to a plurality of substrate layers,
17 wherein the number of substrate layers equals the number of
18 layers of H-PDLC plus one.
- 19 15. The device of claim 12 wherein the stack is composed of
20 between two and twenty layers of H-PDLC layers.
- 21 16. The device of claim 5 wherein the light-wavelength
22 modulating material comprises at least on layer of cholesteric
23 liquid crystals (CLC).
- 24 17. The device of claim 14 forming a stack composed a plurality
25 of CLC layers arranged in alternating, superposed, relation to

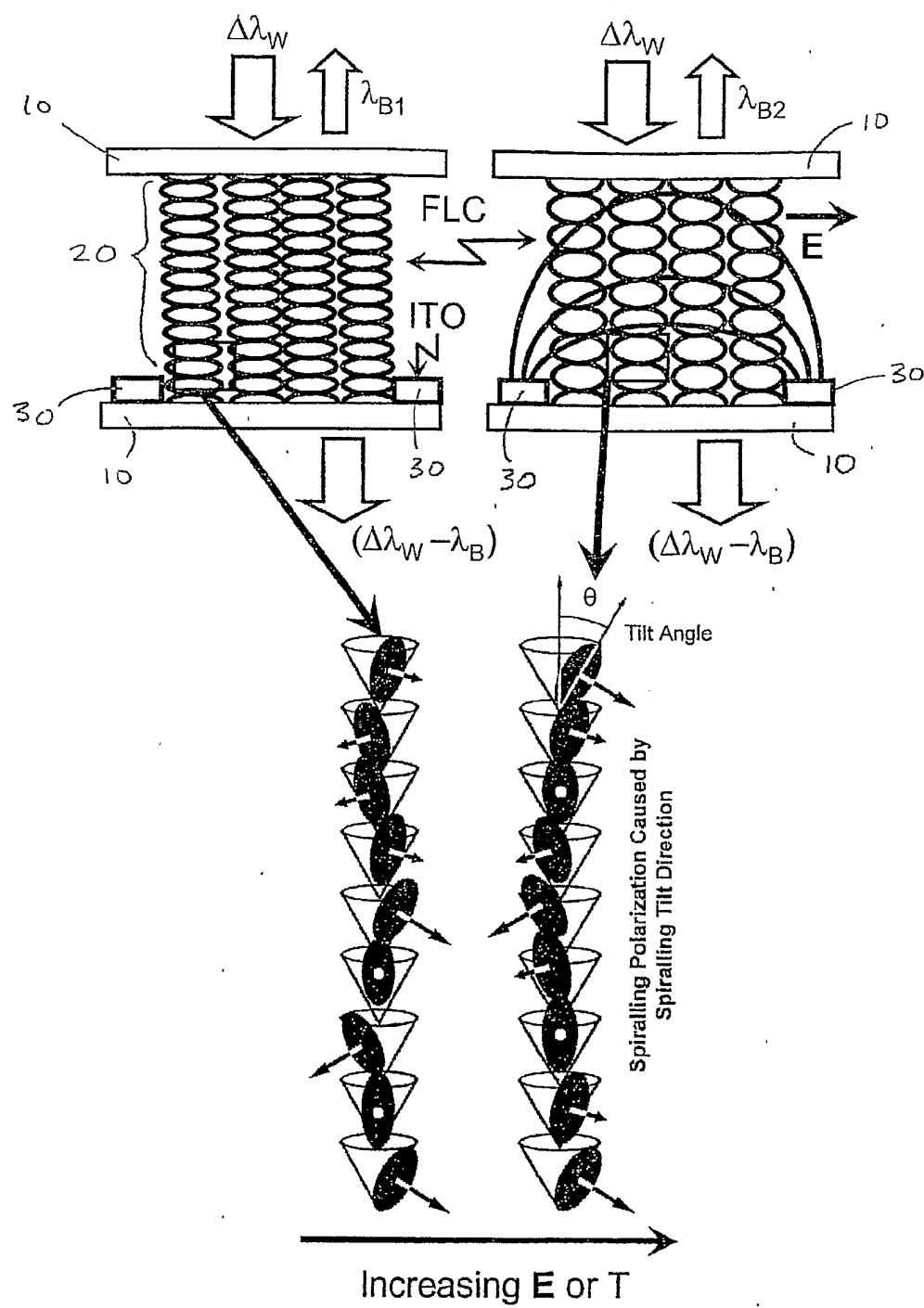
- 1 a plurality of substrate layers, the plurality of CLC layers
2 having the capacity to reflect light of different, per-
3 determined wavelengths, the stack having a number of
4 substrate layers one greater than the number of CLC layers
5 and wherein the power source produces electrical energy
6 perpendicular to the pitch axis of the CLC layers.
- 7 18. The device of claim 15 further comprising a passive optical
8 element disposed in parallel relation between two reflective
9 CLC of opposite-handedness.
- 10 19. The device of claim 16, composed of one layer of CLC
11 disposed between two layers of electrically conducting
12 substrate, wherein the one layer of CLC is subjected to a in-
13 plane electric field to produce different pitch sizes as the
14 electric field is increased.
- 15 20. The device of claim wherein the light intensity sensor means
16 is selected from the group consisting of an array of CCD and
17 a photodiode.
18

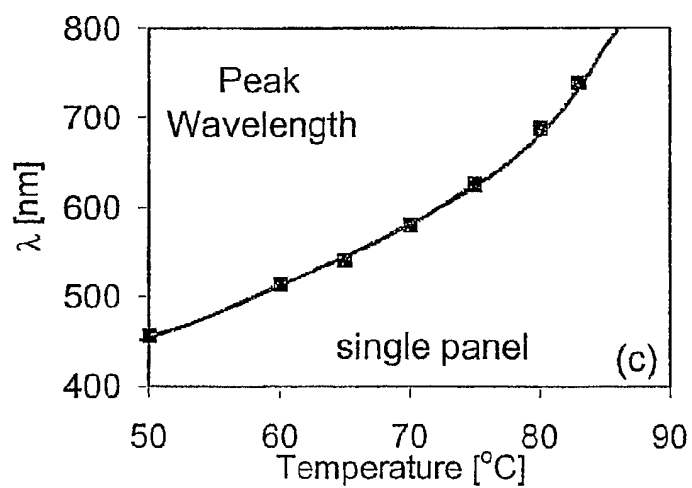
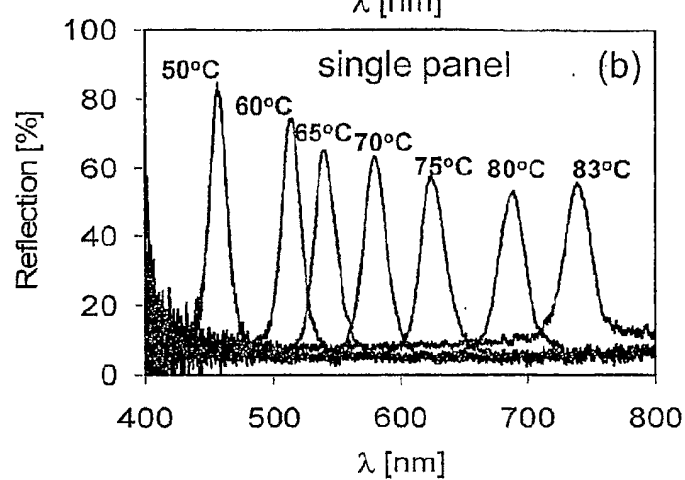
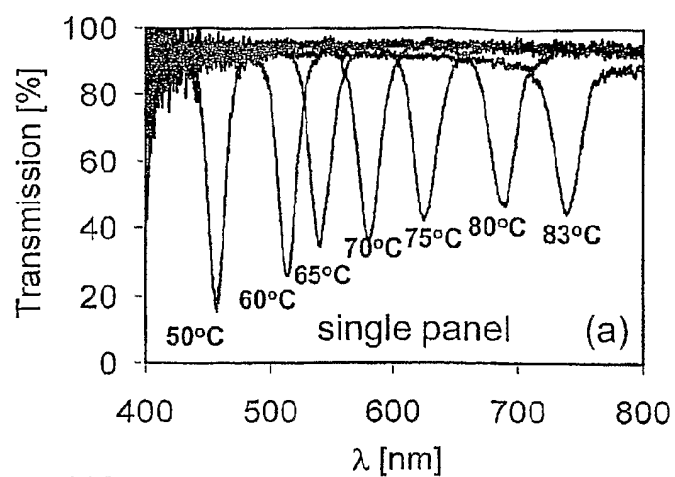












6/6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/04834

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61B 5/00 US CL : 600/322,323,310 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 600/322,323,310 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,348,003 A (Caro) 20 September 1994 (20.09.1994), Abstract, Fig. 5, column 5, lines 45-50.	1-3, and 20
---		-----
Y		4-19
Y	US 5,132,826 A (Johnson et al.) 21 July 1992 (21.07.1992), column 4, line 61 to column 5, line 8.	4-8
Y	US 2003/0048970 A1 (Cole et al.) 13 March 2003 (13.03.2003), Abstract and Fig. 2.	4 and 9-10
Y	US 6,567,573 B1 (Domash et al.) 20 May 2003 (20.05.2003), Abstract and Figs. 1-2.	4-5 and 11-15
Y	US 2002/0131694 A1 (So et al.) 19 September 2002 (19.09.2002), Abstract and Fig. 7.	4-5 and 16-19
☐ 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	"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
"E"	earlier application or patent published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 23 June 2005 (23.06.2005)		Date of mailing of the international search report 20 JUL 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230		Authorized officer Matthew Kremer <i>Anne Neal</i> Telephone No. 571-272-3700

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/04834

Continuation of B. FIELDS SEARCHED Item 3:

DERWENT, JPO,EPO - search terms: hemoglobin, helix ferroelectric, DHF, holographic polymer dispersed, HPD, cholesteric, CLC