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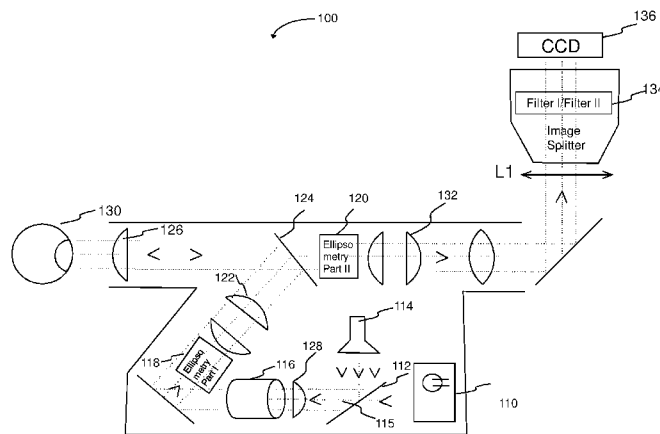


FIG. 1

(57) Abstract: An apparatus and method of measuring oxygenation of tissue in a non-invasive manner are provided. The apparatus comprises a light source configured to emit a light pattern to be projected onto the tissue, in which the light pattern comprises superimposed patterns having different patterns. A detector captures an image of a reflected light pattern which is reflected from the tissue as a result of the projected light pattern. A processor coupled to the detector can be configured to perform a transform on the image of the reflected light pattern and determine oxygenation of each of a plurality of layers of the tissue in response to the transform of the image. Polarimetry can be used in determining a change in polarization angle of light beam. Tissue oxygenation can be determined at a plurality of layers from one snapshot, for example oxygenation of retinal layers.

**METHODS AND APPARATUS FOR MEASURING BLOOD OXYGENATION OF TISSUE****CROSS-REFERENCE**

[001] This application claims priority from US provisional Application No. 62/265,959, filed on December 10, 2015. The above-referenced applications are hereby incorporated by reference.

**BACKGROUND OF THE INVENTION**

[002] Tissue oxygenation is an important physiological parameter in at least some instances. Abnormal oxygenation of tissues and blood is implicated in a number of diseases preceding tissue damage, including infectious processes, diabetic retinopathy, choroidal disorders, stroke and cancer. For instance, the retinal vasculature's oxygen saturation (SO<sub>2</sub>) is a valuable indicator of disease, in particular for patients with diabetic retinopathy (DR) who may experience changes in retinal oxygen saturation during their lifetime. A broad range of studies have shown that the earliest detectable sign of DR is an increase of ~4% in the SO<sub>2</sub> in the retinal veins. Once DR is detected, there are treatment options available to slow or stop DR progression and prevent retinal structural damage. The Early Treatment Diabetic Retinopathy Study (ETDRS), a multicenter clinical trial funded by the NEI, aims to determine whether the progress of DR could be slowed or stopped using either argon laser photocoagulation or aspirin treatment. Although a number of experimental systems aimed at measuring retinal SO<sub>2</sub> have been developed, a reliable, robust model for *in vivo* monitoring is still lacking.

[003] Prior methods and apparatus of measuring oxygenation of the tissue can be less than ideal. The prior methods and apparatus can be more complex and less accurate than would be ideal, and may not be well suited for tissue oxygenation mapping. For example, tissue can move and degrade measurements and the prior methods and apparatus can be less than ideally suited to measure tissue quickly. Measurements of retinal tissue of the eye can be subject to movement when the eye moves, and ocular measurements of the retina can be more difficult and less accurate than would be ideal.

[004] In light of the above it would be desirable to have improved measurements to measure oxygenation of tissue.

**SUMMARY OF THE INVENTION**

[005] The methods and apparatus disclosed herein provide improved measurements of tissue oxygenation with decreased measurement times and improved measurement accuracy. The

methods and apparatus disclosed herein are capable of measuring oxygenation of the tissue with a reduced number of image frames captured by a detector comprising a plurality of pixels, which substantially prevents a degrading in measurement caused by a movement of the tissue during the measurement and improves the accuracy. In some embodiments, single snapshot of the tissue can be used to determine and map blood oxygenation. The methods and apparatus disclosed herein are particularly advantageous in measuring oxygenation of tissue such as retinal tissue of the eye.

**[006]** A light pattern having superimposed patterns can be projected onto the tissue, and a reflected light pattern can be imaged by a detector (e.g., a CCD). The light pattern imaged by the detector can be transformed with a transform function to generate a transform data, and the transform data can be used to determine the oxygenation of the tissue. A map of tissue oxygenation can be determined in response to the transform data from a single measurement frame (e.g., a single snapshot of the tissue) from the detector and displayed to a user.

**[007]** The methods and apparatus disclosed herein can determine oxygenation of the tissue at a plurality of layers. In some instances, the apparatus can comprise an ellipsometer to determine oxygenation of the tissue at each of a plurality of layers of the tissue. The projected light pattern can comprise modulated polarized light. The reflectance and polarization change through different retinal layers can be measured. The information on absorption can be obtained from the change of reflectance for different spatial frequencies. The optical information on different layers can be obtained from the shift of polarization angle. In contrary to a conventional ellipsometry where one would need to scan a range of incidence angles to reconstruct the polarization angle changes, with the methods and apparatus disclosed herein, each spatial frequency corresponds to a unique incidence angle, thus, in one snapshot, all the information needed to map the multilayer retinal structure can be captured.

**[008]** In the methods and apparatus disclosed herein, modulated light can be used, which provides at least two independent radiations in one snapshot. This empowers ellipsometer to capture reflectance at different angles in one snapshot, and allows to determine the optical properties of different layers up to the choroid.

**[009]** In the methods and apparatus disclosed herein, oxygenation of the tissue can be calculated in one snapshot by using an image splitter, which also eliminating the need for eye dilation by using near-infrared (NIR) radiation or laser. In some instances, in case light beam of visible wavelengths is used, eye dilation may be required.

**[0010]** An aspect of the disclosure may provide a method of measuring oxygenation of tissue. The method can comprise projecting a light pattern onto the tissue, said light pattern comprising a superimposed patterns having two or more different patterns; imaging a reflected light pattern which is reflected from the tissue as a result of the projected light pattern; performing a transform on the reflected light pattern; and determining oxygenation of each of a plurality of layers of the tissue in response to the transform of the reflected light pattern.

**[0011]** Aspects of the disclosure may also provide an apparatus to measure oxygenation of tissue. The apparatus can comprise: a light source configured to emit a light pattern to be projected onto the tissue, said light pattern comprising a superimposed patterns having two or more different patterns; a detector for capturing an image of a reflected light pattern which is reflected from the tissue as a result of the projected light pattern; and one or more processors coupled to the detector, the one or more processors being configured to perform a transform on the image of the reflected light pattern and determine oxygenation of each of a plurality of layers of the tissue in response to the transform of the image.

**[0012]** In an aspect, a method of measuring oxygenation of tissue comprises projecting a pattern onto the tissue with two or more wavelengths of light. The pattern is projected onto the tissue. A transform of the pattern is generated, and oxygenation of the tissue is determined in response to the transform of the projected pattern. While the projected pattern can be projected in many ways, in many instances the projected pattern comprises a one dimensional pattern such as a one dimensional sine wave. The projected pattern may comprise two superimposed sine waves in order to determine oxygenation of each of a plurality of layers of the tissue, such as a plurality of layers of retinal tissue. Alternatively, the projected pattern may comprise a two dimensional pattern such as a two dimensional sine wave.

**[0013]** The apparatus may comprise an ellipsometer to determine oxygenation of the retina at each of a plurality of layers of the retina. The projected pattern may comprise a plurality of superimposed patterns having different spatial frequencies, for example a first pattern having first spatial frequencies and a second pattern having second spatial frequencies. The first pattern may comprise a first wavelength of light and the second pattern may comprise a second wavelength of light. Each of the plurality of layers of the tissue can be mapped in response to the single frame. A splitter can be used to separate the first wavelength of light from the second wavelength of light imaged onto the detector comprising pixels in order to provide the measurement from a single frame from the detector.

## INCORPORATION BY REFERENCE

[0014] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0016] **FIG. 1** illustrates a system for measuring oxygenation of retinal vasculature, in accordance with embodiments;

[0017] **FIG. 2** illustrates a method of measuring blood oxygenation in a retina, in accordance with embodiments;

[0018] **FIG. 3A** illustrates a sinusoidal pattern, which can be applied to light emitted from LEDs to impart a spatial frequency in a light beam, in accordance with embodiments; and

[0019] **FIG. 3B** illustrates a Fourier transform of a sinusoidal pattern, in which AC and DC components correspond to different Fourier peaks, in accordance with embodiments.

[0020] **FIG. 4** illustrates a system for measuring oxygenation of retinal vasculature, in accordance with embodiments.

## DETAILED DESCRIPTION OF THE INVENTION

[0021] The methods and apparatus disclosed herein are well suited for measurements of many tissues, and can be configured in many ways. The methods and apparatus disclosed herein can be combined with prior methods and apparatus to provide improved measurement of tissue oxygenation, such ellipsometry as known to one of ordinary skill in the art.

[0022] Polarimetry is the measurement of the polarization of transverse waves, such as radio or light waves. Polarimetry is performed on electromagnetic waves that have traveled through or have been reflected, refracted, or diffracted by an object in order to characterize the object. Polarimetry of thin materials and surfaces is also known as ellipsometry. The measured signal is

the change in polarization as the incident radiation (such as light waves) interacts with the material structure of interest (reflected, absorbed, scattered, or transmitted). The polarization change is quantified by the amplitude ratio and the phase difference. Because the signal depends on the thickness as well as the material properties, ellipsometry can be a useful tool for contact free determination of thickness and optical parameters of the material of interest. Upon the analysis of the change of polarization of light, ellipsometry can yield information about the material of interest. Ellipsometry can probe the complex refractive index or dielectric function tensor, which gives access to fundamental physical parameters. In this disclosure, ellipsometer can be used in calculating tissue oxygenation. In some embodiments, the ellipsometer can comprise a first portion and a second portion. The first portion of the ellipsometer can apply polarization to a light beam. The first portion of the ellipsometer can apply different polarizations to different components of a light beam, each component corresponding to a different spatial frequency. The second portion of the ellipsometer can enable a detection of a differential signal based on the different polarizations. Alternatively, a rotating polarizer can be used to polarize the light beam to be directed to the tissue. Information on different layers of the tissue can be distinguished by the changes in polarization angle of the reflected light beam over the incident light beam of the tissue

**[0023]** Biological tissues are composed of a variety of chromophores, which are molecules that absorb light of characteristic wavelengths. If the amount of light that a tissue absorbs can be measured, then concentrations of the chromophores in the tissue can be calculated. This can be useful in clinical applications because some of chromophores in body tissue are markers of important clinical parameters, such as oxygenation. The attenuation of light in tissue is a function of both its absorption and scattering properties. Spatial frequency domain imaging (SFDI) can be used to separate the effects of scattering and absorption, and consequently, to quantify a set of chromophores. SFDI works by shining different patterns light on the tissue, capturing images of the remitted light, and processing the captured images. In this disclosure, SFDI is used in calculating tissue oxygenation. However, in conventional SFDI approach, a sinusoidal light pattern at different phases ( $0$ ,  $2\pi/3$ ,  $4\pi/3$ ) is projected and three sample images are acquired. A reference with known optical properties is used to extract the AC/DC components of the reflectance. From these components, a steady-state diffusion equation can calculate the absorption and reduced scattering. Requiring three snapshots is problematic if the tissue has motion artifacts, such as with retinal imaging.

**[0024]** The present disclosure provides an improved optical method and apparatus for non-invasive measurement of tissue oxygenation. The method and apparatus disclosed herein are

capable of measuring tissue oxygenation with a single snapshot of the tissue, thus can be advantageous in measuring oxygenation of a moving tissue such as retinal tissue of the eye. The method and apparatus disclosed herein enables measurement of oxygenation at each of a plurality of tissue by combining Dimensional Spatial Frequency Domain Imaging (SFDI) algorithm with ellipsometry to benefit from the best of each in a unified technique.

**[0025]** FIG. 1 illustrates a system 100 for measuring oxygenation of tissue. In some embodiments, the tissue can be retinal vasculature of an eye. A main light source 110 can be provided to illuminate a patient's tissue. The main light source can be an optical source emitting visible light and/or infrared light. In some instances, the main light source can be a laser source, such as a laser diode. In some embodiments, the main light source can be an infrared laser diode such as a near-infrared (NIR) diode. Alternatively, the main light source can be a LED.

**[0026]** In some embodiments, a secondary illumination source 114 can be provided in addition to the main light source. The light beam from the secondary illumination source can be mixed with the light beam from the main light source. In some instances, a reflecting surface 112 can be provided to mix the light beam from the main light source and the light beam from the secondary illumination source. For instance, the reflecting surface can be a beam splitter, such as a polarizing beam splitter, to allow the light beam mixture. The secondary illumination source can provide additional lighting as can be needed to more completely illuminate the tissue. The resulting beam 115 from the reflecting surface can comprise a plurality of light wavelengths. The light wavelengths can be preferentially chosen to be distributed about an isosbestic point of oxygenated blood. In some embodiments, the light beam can comprise two wavelengths of light. For example, the resulting beam can comprise wavelengths of 780 nm and 710 nm. Alternatively, the light beam can comprise more than two wavelengths of light. The resulting beam can be polarized, and can comprise a plurality of polarization components.

**[0027]** In some embodiments, the main light source can comprise an array of light emitting diodes, arranged to generate a sinusoidal pattern of light. In some instances, the main light source can generate light beam comprising a plurality of sinusoidal spatial modulations. In some embodiments, the main light source can comprise a first array of LEDs with a first spatial modulation frequency and a first polarization, and the secondary illumination source can comprise a second array of LEDs with a second spatial modulation frequency and a second polarization. The light beam from the main light source and the light beam from the secondary illumination source can be combined by the reflecting surface (for example, a polarizing beam splitter) while maintaining their separate polarizations for use in ellipsometry.

[0028] A diffuser **128** can be positioned in the path of the resulting beam from the reflecting surface, to eliminate high-order components. The diffuser can also generate a smooth sinusoidal pattern of light. The smooth sinusoidal pattern can be generated for each wavelength of light in the resulting beam. In such cases, a first polarization optics **118** and a second polarization optics **120**, which will be described hereinafter, can be omitted.

[0029] The light beam can then then directed through shaping optics **116**, which are configured to shape an incident, which is in a substantially Gaussian beam profile, into a toroidal beam profile. Thereafter, the light beam can be directed into first polarization optics **118**.

[0030] The first polarization optics **118** can comprise a first portion of an ellipsometer, such that a first polarization can be applied to the light beam. A second polarization optics **120** can be provided in a later stage of the beam path, such that changes in polarization can be measured using known methods of ellipsometry. The first polarization optics **118** can apply different polarizations to different components of a light beam, each component corresponding to a different spatial frequency. For example, if a spatial modulation of beam intensity comprises a first and second spatial frequency component, each with different spatial frequencies, then the first polarization optics can be configured to apply a different polarization shift to each component, thereby allowing a differential signal to be detected based on the different polarization shifts measured as the beam passes through the second polarization optics **120** with polarization-based attenuation.

[0031] In some embodiments, the polarized light beam, which is polarized by the first polarization optics **118**, can then be sent through focusing optics **122**, as needed, to shape the light beam to have an appropriately-sized toroidal beam profile. The light beam can be reflected off a beam splitter **124**, which comprises a reflective surface with a hole through which light can pass. The toroidal beam profile can be aligned such that its center coincides with the hole, such that most of the incident light of the beam is reflected toward a target tissue **130**. The target tissue can be retina, which is a non-diffuse multi-layered tissue.

[0032] The light reflected toward the target tissue can be focused by a focusing lens **126** to fall on the target tissue. In some instance, the target tissue can be retina, the incident light can be focused by the focusing lens to fall on the retina, strike the patient's retina and scatter off. A significant portion of the scattered light can be reflected back toward the beam splitter **124**, and can be directed through the hole in the beam splitter **124**. Depending on the propagation depth into the tissue, the polarization angle of the reflected light beam can be rotated. As a result, the reflected light can have a slightly rotated polarization with respect to the polarization of the light

beam incident on the tissue. This change in the polarization can be captured by the second polarization optics **120** and can be manifested as a reduction in the intensity of the captured light. Information on different layers of the tissue can be distinguished by the changes in polarization angle of the reflected light beam. In other words, the information of depth of tissue can be encoded in the angle of polarization of light.

**[0033]** Shaping optics **132** can then be provided in the light path to resize the light beam, and the light beam can be directed through a filter **134** to isolate the correct wavelengths of light. The filter can be an image splitter. For example, the filter can direct light of different wavelengths to different portions of a detector **136**. The detector can be a CCD camera comprising an array of pixels. Each portion of the detector can measure an image of the corresponding wavelength. The light beam can strike the detector, allowing the light beam to be imaged. In some embodiments, the ellipsometer, which comprises the first polarization optics and the second first polarization optics, can provide sensitivity to shifts in polarization of the light beam as it reflects off the target tissue. These detected shifts in polarization, such as rotations in polarization, can be used to calculate depths of light penetration, from which the method and apparatus as disclosed in this disclosure can detect depth dependent properties of blood oxygenation in the tissue.

**[0034]** The detector can be coupled to a processor which can be used to determine blood oxygenation based on measured signals from detector. The processor can further be coupled to a display to show measured results, such as a blood oxygenation map, to the user.

**[0035]** In some instances, if oxygenation as a function of depth is not to be determined, the ellipsometer can be omitted by removing the first polarization optics **118** and the second polarization optics **120**.

**[0036]** **FIG. 2** illustrates a method **200** of measuring blood oxygenation in a tissue. In process or step **210**, a tissue such as retina of the patient can be illuminated with illuminating light. The illuminating light can come from a main light source. The main light source can be an optical source emitting visible light and/or infrared light. In some instances, the main light source can be a laser source, such as an infrared laser diode. In some embodiments, the main light source can comprise an array of light emitting diodes, arranged to generate a sinusoidal pattern of light. The illuminating light can comprise a plurality of wavelengths, and be polarized to provide for ellipsometric imaging. In some embodiments, the illuminating light can comprise two wavelengths of light. Alternatively, the illuminating light can comprise more than two wavelengths of light. The illuminating light can comprise a sinusoidal intensity distribution; for

example, a 1D sinusoid or a 2D sinusoid. In some cases, the illuminating light can comprise a plurality of summed sinusoids, including sinusoids summed with different weighting factors. The illumination can comprise a single imaging pulse, with a single sinusoidal intensity distribution. In some embodiments, the imaging pulse can comprise a plurality of frequencies and a plurality of sinusoidal spatial modulations, with each spatial modulation corresponding to a particular polarization.

**[0037]** The illuminating light can be allowed to reflect from the tissue for collection in an apparatus configured to measure light intensity. In some instances, the apparatus can be configured to determine light intensity as a function of polarization. For example, the light intensity can be determined as a function of polarization by using an ellipsometer.

**[0038]** In process or step **220**, the reflected light from the tissue can be imaged by a detector. The detector can be an array of pixels, for example pixels of a CCD array. The signal of each pixel can correspond to an intensity as a function of polarization angle. This variation of intensity with respect to polarization angle can correspond to a variation of polarization angle with respect to penetration depth of light reflecting from the tissue. For instance, an increasing penetration depth can correspond to an increasing shift in polarization. By using an ellipsometer to detect the polarization shifts, the measurement in process or step **220** can be divided into a plurality of intensities as a function of depth, with each intensity corresponding to a different layer of depth in the tissue. This correlation between depth and polarization can be determined by using known properties of tissue and blood. Based on these properties, a comparison of intensity as a function of polarization can be used to determine oxygenation as a function of depth. Each of a plurality of wavelengths can be measured on corresponding pixels of the detector. For example, different wavelengths can be separated by filter to illuminate corresponding portions of the CCD.

**[0039]** In process or step **230**, a spatial Fourier transform can be performed. Based on this spatial Fourier transform, in process or step **240**, a plurality of frequency components can be extracted, corresponding to AC and DC components. The AC and DC components can correspond to sinusoidal components, and each AC component can correspond to a particular polarization. In some instance, the AC component is the sinusoidal component where frequency is 0, and a DC component may be the sinusoidal component where frequency is an imposed spatial frequency  $f$ . The intensities of each of the DC and AC components can be determined, and a frequency-specific intensity can be determined for each. For example, a general form of

AC and DC components can correspond to the intensity equation  $I = A + B\cos(kx)$ , in which A is the DC component and B is the AC component.

**[0040]** In process or step **250**, AC and DC components can be determined for a plurality of pixels of the detector (for example, the CCD). Specific Fourier components corresponding to each of the AC and DC intensities can be isolated with only a modest decrease in spatial resolution. For example, AC and DC intensities can be determined with a resolution loss factor of 10 to 1. Thus, for example, a 1000x1000 detector can produce an image for each component with an effective resolution of about 100x100.

**[0041]** In process or step **260**, blood oxygenation levels can be determined for a plurality of pixels. The blood oxygenation level of each pixel can be determined by a comparison of the intensities of the AC and DC components of reflected light for the plurality of wavelengths, from which absorption can be determined, using a modified Beer-Lambert absorption model. Known absorption properties of tissue, and especially of oxygenated and deoxygenated blood, can be used to calculate absorption based on the relative intensities of the AC and DC components. The blood oxygenation levels can further be determined as a function of depth, where different polarizations of light corresponding to different depths. This determination can be represented, for example, as a map of blood oxygenation. Measurement sensitivity of 3.5% or better can be achieved. Thus, it can be possible to diagnose small changes in blood oxygenation, where increased oxygenation of about 3% to 5% can be a warning sign of diseases such as diabetic retinopathy. Because this determination can be made from a single image, noise sources such as tissue movement between images can be avoided.

**[0042]** In process or step **270**, a blood oxygenation map can be generated and stored to a computer-readable medium. The blood oxygenation map can be further displayed to a user. If the blood oxygenation map indicates an increased oxygenation above a threshold, a warning can be provided, indicating that the user can be in danger of diseases such as diabetic retinopathy. The threshold can be a predefined threshold, or can be based on a comparison to prior measurements of blood oxygenation.

**[0043]** Although the above processes and steps show a method of measuring tissue oxygenation in accordance with some embodiments, a person of ordinary skill in the art will recognize many variations based on the teachings described herein. The processes and steps can be completed in a different order. Processes and steps can be added or deleted. Some of the processes and steps can comprise sub-processes and sub-steps of other processes and steps. Many of the processes and steps can be repeated as often as desired by the user.

[0044] In some embodiments, multiple spatial frequencies can be used and each frequency's polarization change can be calculated to average out an error caused by scattering in detecting the polarization angle, although retinal layers are more absorptive. In some instances, green and red wavelengths can be used to increase a contrast if the light beam generated by the main light source (e.g., NIR) does not provide enough contrast. In some instances, if there is insufficient contrast, the output can be limited to the average SO<sub>2</sub> in each section of the ETDRS map.

[0045] FIG. 3A illustrates a sinusoidal pattern, which can be applied to light emitted from the main light source to impart a spatial frequency in a light beam, as disclosed herein. FIG. 3B illustrates a Fourier transform of a sinusoidal pattern, in which AC and DC components correspond to different Fourier peaks. The central peak corresponds to the DC component, and the side peaks correspond to AC components. Each component can individually be extracted to generate a corresponding two-dimensional intensity distribution. For example, unwanted peaks can be masked off and an inverse Fourier transform can be applied to generate a two dimensional image corresponding only to unmasked spatial frequencies.

[0046] FIG. 4 illustrates a system 400 for measuring oxygenation of retinal vasculature, in accordance with embodiments. In some embodiments, the tissue can be retinal vasculature of an eye. The main light source 100 can be a laser source, such as a laser diode or an infrared laser diode such as a near-infrared (NIR) diode. In some embodiments, the main light source can be a LED. A secondary illumination source 114 can be provided in addition to the main light source. The light beam from the secondary illumination source can be mixed with the light beam from the main light source at a reflecting surface 112. In some instances, the reflecting surface can be a beam splitter, such as a polarizing beam splitter, to allow the light beam mixture. The resulting beam 115 from the reflecting surface can comprise a plurality of light wavelengths. The light wavelengths can be preferentially chosen to be distributed about an isosbestic point of oxygenated blood. In some embodiments, the illuminating light can comprise two wavelengths of light. For example, the resulting beam can comprise wavelengths of 780 nm and 710 nm. Alternatively, the illuminating light can comprise more than two wavelengths of light.

[0047] The resulting beam 115 can then pass through a diffuser 128 to eliminate high-order components. The light beam can then then directed through shaping optics 116, which are configured to shape an incident light, which is in a substantially Gaussian beam profile, into a toroidal beam profile. Thereafter, the light beam can be directed into a modulation stage 140.

[0048] At the modulation stage 140, the light beam can be patterned by passing through a structure attached to a motorized stage. The motorized stage can be shifted to create different

phases and frequencies. In some embodiments, the uniform light beam from the main light source can be patterned into a sinusoidal pattern of different phases and frequencies at the modulation stage **140**. The light beam can then be directed through focusing optics **122**, as needed, to shape the light beam to have an appropriately-sized toroidal beam profile.

**[0049]** The light beam can then be directed to a rotating polarizer **142** which polarizes the light beam to be impinged on the tissue. In some instances, the rotating polarizer can be driven by a motor. The polarized light beam can then be reflected off a beam splitter **124**, which comprises a reflective surface with a hole through which light can pass. The light beam can be reflected at the beam splitter toward the target tissue **130**. The target tissue can be retina. The light reflected toward the target tissue can be focused by a focusing lens **126** to fall on the target tissue. In some instance, the target tissue can be retina, the incident light can be focused by the focusing lens to fall on the retina, strike the patient's retina and scatter off. A significant portion of the scattered light can be reflected back toward the beam splitter **124**, and can be directed through the hole in the beam splitter **124**.

**[0050]** Depending on the propagation depth into the tissue, the polarization angle of reflected light beam can be rotated. As a result, the reflected light can have a slightly rotated polarization with respect to the polarization of the light beam incident on the tissue. This change in the polarization can be captured by the polarizer and can be manifested as a reduction in the intensity of the captured light. Information on different layers of the tissue can be distinguished by the changes in polarization angle of the reflected light beam. In other words, the information of depth of tissue can be encoded in the angle of polarization of light.

**[0051]** Shaping optics **132** can then be provided in the light path to resize the light beam, and the light beam can be directed through a filter **134** to isolate the correct wavelengths of light. The filter can be an image splitter. For example, the filter can direct light of different wavelengths to different portions of a detector **136**. The detector can be a CCD camera comprising an array of pixels. Each portion of the detector can measure an image of the corresponding wavelength.

In the method and apparatus as disclosed in present disclosure, the incident polarized light is spatially modulated and the reflectance and polarization change through different retinal layers are measured. The information from absorption is encoded in the change of reflectance for different spatial frequencies. The optical information from different layers is encoded in the shift of polarization angle. In contrary to conventional ellipsometry where one would need to scan a range of incidence angles to reconstruct the polarization angle changes, with the method

and apparatus as disclosed in present disclosure, each spatial frequency corresponds to a unique incidence angle. Thus, in one snapshot, all the information needed to map the multilayer retinal structure can be captured. In some instances, the one snapshot can be selected from a plurality of snapshots of the tissue. For example, a 1-second video can be captured on the tissue which contains 60 frames, and one snapshot having the optimal imaging quality can be selected. The selection of snapshot can be performed manually or automatically by algorithms. In some embodiments, more than one snapshot can be needed if more than two wavelengths of light are used to calculate the oxygenation of tissue such as retina. For example, different spatially modulated light can illuminate in different snapshots.

**[0052]** The method and apparatus as disclosed in present disclosure are based on the physics of retinal layers. No assumptions or a priori knowledge about the structure is needed. The index of reflectance, absorption coefficient, and scattering coefficient can be calculated from Equation 1:

$$n_t = n_i \sin(\theta_i) \left\{ 1 + \tan(\theta_i)^2 \left( \frac{1 - \tan(\psi) e^{i\Delta}}{1 + \tan(\psi) e^{i\Delta}} \right)^2 \right\}^{\frac{1}{2}}$$

where:  $n$  is the index of refraction,  $\theta$  is an angle of radiation,  $\psi$  is ellipsometry angle,  $\Delta$  is ellipsometry phase,  $i$  is incident medium and  $t$  is transmitted radiation. In each snapshot, at least two spatial frequencies can be used to calculate the unknown parameters (e.g., absorption and scattering coefficients).

**[0053]** With the method and apparatus as disclosed in present disclosure, the absorption of Layer 2 with  $\geq 95\%$  accuracy can be accurately detected *in vivo* in a patient and similar accuracy can be obtained in a model. The oxygenation throughout the retinal layers can be measured non-invasively with  $\sim 4\%$  sensitivity (e.g., being sensitive to  $4\%$  changes in  $\text{SO}_2$ ), which is powerful enough to detect the onset of DR prior to structural damage *in vivo* in patients. Therefore, the method and apparatus as disclosed in present disclosure can be capable of detecting a change in oxy-hemoglobin  $\leq 0.3$  g/dL and achieving  $\leq 2\%$  error in hemoglobin compared with spectroscopy.

**[0054]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein can be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that

methods and structures within the scope of these claims and their equivalents be covered thereby.

**CLAIMS**

## WHAT IS CLAIMED IS:

1. A method of measuring oxygenation of tissue, said method comprising:  
  
projecting a light pattern onto the tissue, said light pattern comprising a superimposed patterns having two or more different patterns;  
  
imaging a reflected light pattern which is reflected from the tissue;  
  
performing a transform on the reflected light pattern; and  
  
determining oxygenation of each of a plurality of layers of the tissue in response to the transform of the reflected light pattern.
2. The method of claim 1, wherein the transform comprises a spatial Fourier transform, and wherein the oxygenation is determined in response to frequency components of the spatial Fourier transform of the reflected light pattern.
3. The method of claim 2, wherein the frequency components of the spatial Fourier transform comprises an AC component where frequency is 0 and a DC component where frequency is an imposed spatial frequency.
4. The method of claim 1, further comprising generating an oxygenation map of the tissue in response to the transform of the reflected light pattern.
5. The method of claim 1, further comprising generating a two dimensional oxygenation map of the tissue in response to the transform of the reflected light pattern.
6. The method of claim 1, wherein the projected light pattern comprises a one dimensional light pattern, and said method further comprising generating a two dimensional oxygenation map of the tissue in response to the transform of the projected one dimensional light pattern.
7. The method of claim 1, wherein the projected light pattern is imaged with a detector comprising a plurality of pixels, and wherein said method further comprising determining an amount of light scattering and an amount of light reflection for each pixel of the plurality.
8. The method of claim 1, further comprising determining a two dimensional oxygenation map for each layer of a plurality of layers of the tissue.

9. The method of claim 1, wherein determining oxygenation of each of a plurality of layers of the tissue comprises applying different polarizations to different components of the projected light pattern with an ellipsometer.

10. The method of claim 1, wherein tissue comprises retina of an eye.

11. The method of claim 1, wherein the different patterns comprises a first pattern and a second pattern, the first pattern comprising a first spatial frequency, and the second pattern comprising a second spatial frequency, and determining oxygenation of each of a plurality of layers of the tissue comprises determining the oxygenation at each of the plurality of layers in response to a first polarization of the first spatial frequency of light and a second polarization of the second spatial frequency of light.

12. The method of claim 1, wherein the different patterns comprises a first pattern and a second pattern, the first pattern comprising a first wavelength of light, and the second pattern comprising a second wavelength of light, and determining oxygenation of each of a plurality of layers of the tissue comprises determining the oxygenation at each of the plurality of layers in response to a first polarization of the first wavelength of light and a second polarization of the second wavelength of light.

13. The method of claim 1, wherein determining oxygenation of each of a plurality of layers of the tissue comprising determining the oxygenation of each of the plurality of layers in response to a single frame of image of the reflected light pattern.

14. The method of claim 11, further comprising splitting the image, with a splitter, into a first image of the first pattern having the first spatial frequency of light and a second image of the second pattern having the second spatial frequency of light.

15. The method of claim 12, further comprising splitting the image, with a splitter, into a first image of the first pattern having the first wavelength of light and a second image of the second pattern having the second wavelength of light.

16. The method of claim 1, wherein the projected light pattern comprises a one dimensional pattern.

17. The method of claim 16, wherein the one dimensional pattern is a one dimensional sine wave.

18. The method of claim 1, wherein the projected light pattern comprises a two dimensional pattern.

19. The method of claim 18, wherein the two dimensional pattern is a two dimensional sine wave.
20. An apparatus to measure oxygenation of tissue, said apparatus comprising:  
a light source configured to emit a light pattern to be projected onto the tissue, said light pattern comprising a superimposed pattern having two or more different patterns;  
a detector for capturing an image of a reflected light pattern which is reflected from the tissue; and  
one or more processors coupled to the detector, the one or more processors being configured to perform a transform on the image of the reflected light pattern and determine oxygenation of each of a plurality of layers of the tissue in response to the transform of the image.
21. The apparatus of claim 20, wherein the transform comprises a spatial Fourier transform, and wherein the oxygenation is determined in response to frequency components of the spatial Fourier transform of the reflected light pattern.
22. The apparatus of claim 21, wherein the frequency components of the spatial Fourier transform comprises an AC component where frequency is 0 and a DC component where frequency is an imposed spatial frequency.
23. The apparatus of claim 20, wherein the one or more processors are configured to generate an oxygenation map of the tissue in response to the transform of the reflected light pattern.
24. The apparatus of claim 20, wherein the one or more processors are configured to generate a two dimensional oxygenation map of the tissue in response to the transform of the reflected light pattern.
25. The apparatus of claim 20, wherein the projected light pattern comprises a one dimensional light pattern, and wherein the one or more processors are configured to generate a two dimensional oxygenation map of the tissue in response to the transform of the reflected one dimensional light pattern.
26. The apparatus of claim 20, wherein the projected light pattern is imaged with a detector comprising a plurality of pixels, and wherein the one or more processors are configured

to determine an amount of light scattering and an amount of light reflection for each pixel of the plurality.

27. The apparatus of claim 20, wherein the one or more processors are configured to determine a two dimensional oxygenation map for each layer of a plurality of layers of the tissue.

28. The apparatus of claim 20, further comprising an ellipsometer which applies different polarizations to different components of the projected light pattern so as to determine oxygenation at each of a plurality of layers of the tissue.

29. The apparatus of claim 20, wherein tissue comprises retinal tissue of an eye.

30. The apparatus of claim 20, wherein the different patterns comprises a first pattern and a second pattern, the first pattern comprising a first spatial frequency, and the second pattern comprising a second spatial frequency, and

wherein the one or more processors are configured to determine the oxygenation at each of the plurality of layers in response to a first polarization of the first spatial frequency of light and a second polarization of the second spatial frequency of light.

31. The apparatus of claim 20, wherein the different patterns comprises a first pattern and a second pattern, the first pattern comprising a first wavelength of light, and the second pattern comprising a second wavelength of light, and

wherein the one or more processors are configured to determine the oxygenation at each of the plurality of layers in response to a first polarization of the first wavelength of light and a second polarization of the second wavelength of light.

32. The apparatus of claim 20, wherein the one or more processors are configured to determine the oxygenation of each of the plurality of layers in response to a single frame of the image from the detector.

33. The apparatus of claim 30, further comprising a splitter to split the image into a first image of the first pattern having the first spatial frequency of light and a second image of the second pattern having the second spatial frequency of light.

34. The apparatus of claim 31, further comprising a splitter to split the image into a first image of the first pattern having the first wavelength of light and a second image of the second pattern having the second wavelength of light.

35. The apparatus of claim 20, wherein the projected light pattern comprises a one dimensional pattern.
36. The apparatus of claim 35, wherein the one dimensional pattern is a one dimensional sine wave.
37. The apparatus of claim 30, wherein the projected light pattern comprises a two dimensional pattern.
38. The apparatus of claim 37, wherein the two dimensional pattern is a two dimensional sine wave.
39. A method of measuring oxygenation of tissue, the method comprising:  
projecting a pattern onto the tissue with two or more wavelengths of light;  
imaging the pattern projected onto the tissue;  
generating a transform of the pattern; and  
determining oxygenation of each of a plurality of layers of the tissue in response to the transform of the projected pattern.
40. The method of claim 39, wherein the transform comprises a Fourier transform and wherein the oxygenation is determined in response to frequencies of the Fourier transform of the projected pattern.
41. The method of claim 39, further comprising generating an oxygenation map of the tissue in response to the Fourier Transform of the projected pattern.
42. The method of claim 39, further comprising generating a two dimensional oxygenation map of the tissue in response to the Fourier Transform of the projected pattern.
43. The method of claim 39, wherein the pattern comprises a one dimensional pattern and further comprising generating a two dimensional oxygenation map of the tissue in response to the Fourier Transform of the projected one dimensional pattern.
44. The method of claim 39, wherein the projected pattern is imaged with a detector comprising a plurality of pixels and wherein an amount of scattering and an amount of reflection is determined for each pixel of the plurality.

45. The method of claim 39, further comprising determining oxygenation of a plurality of layers of the tissue.
46. The method of claim 39, further comprising determining a two dimensional oxygenation map for each layer of a plurality of layers of the tissue.
47. The method of claim 39, further comprising illuminating the tissue with an ellipsometer to determine oxygenation at a plurality of layers of the tissue.
48. The method of claim 39, wherein tissue comprises retinal tissue of an eye, the wherein a funduscope projects the pattern onto the retina of the eye and images the pattern onto the detector.
49. The method of claim 39, wherein the pattern comprises a superimposed pattern having first a frequency comprising a first wavelength of light and a second frequency comprising a second wavelength of light.
50. The method of claim 39, wherein the pattern comprises a superimposed pattern having first a frequency comprising a first wavelength of light and a second frequency comprising a second wavelength of light and wherein a processor comprises instructions to determine the oxygenation at each of the plurality of layers in response to first polarization of the first wavelength of light and second polarization of the second wavelength of light.
51. The method of claim 39, wherein the processor comprises instructions to determine the oxygenation of said each of the plurality of layers in response to a single frame of the image from the detector
52. The method of claim 39, wherein a splitter to splits the image into a first image of a first pattern having a first wavelength of light and a second image of a second pattern having a second wavelength of light.
53. An apparatus to measure oxygenation of tissue, comprising:
- a light source configured to emit two or more wavelengths of light to project a pattern on to the tissue;
  - a detector to receive the image of the pattern projected onto the tissue; and
  - a processor coupled to the detector, the processor configured with instructions to determine a transform of the image projected onto the tissue and determine oxygenation of each of a plurality of layers of the tissue in response to the transform of the image.

54. The apparatus of claim 53, wherein the transform comprises a Fourier transform and wherein the wherein the oxygenation is determined in response to frequencies of the Fourier transform of the projected pattern.

55. The apparatus of claim 53, wherein the processor is configured to generate an oxygenation map of the tissue in response to the Fourier Transform of the projected pattern.

56. The apparatus of claim 53, further comprising generating a two dimensional oxygenation map of the tissue in response to the Fourier Transform of the projected pattern.

57. The apparatus of claim 53, wherein the pattern comprises a one dimensional pattern and further comprising generating a two dimensional oxygenation map of the tissue in response to the Fourier Transform of the projected one dimensional pattern.

58. The apparatus of claim 53, wherein the projected pattern is imaged with a detector comprising a plurality of pixels and wherein the processor is configured to determine an amount of scattering and an amount of reflection for each pixel of the plurality.

59. The apparatus of claim 53, wherein the processor is configured with instructions to determining oxygenation of a plurality of layers of the tissue.

60. The apparatus of claim 53, wherein the processor is configured with instructions to determine a two dimensional oxygenation map for each layer of a plurality of layers of the tissue.

61. The apparatus of claim 53, further comprising an ellipsometer to illuminate the tissue and determine oxygenation at a plurality of layers of the tissue.

62. The apparatus of claim 53, wherein tissue comprises retinal tissue of an eye, the apparatus further comprising a funduscope to image the retina of the eye and the pattern onto the detector.

63. The apparatus of claim 53, wherein the pattern comprises a superimposed pattern having first a frequency comprising a first wavelength of light and a second frequency comprising a second wavelength of light.

64. The apparatus of claim 53, wherein the pattern comprises a superimposed pattern having first a frequency comprising a first wavelength of light and a second frequency comprising a second wavelength of light and wherein the processor comprises instructions to

determine the oxygenation at each of the plurality of layers in response to first polarization of the first wavelength of light and second polarization of the second wavelength of light.

65. The apparatus of claim 53, wherein the processor comprises instructions to determine the oxygenation of said each of the plurality of layers in response to a single frame of the image from the detector.

66. The apparatus of claim 53, further comprising a splitter to split the image into a first image of a first pattern having a first wavelength of light and a second image of a second pattern having a second wavelength of light.

67. A method of measuring oxygenation of tissue, the method comprising:  
projecting a one dimensional pattern onto the tissue with two or more wavelengths of light;  
imaging the one dimensional pattern projected onto the tissue onto a detector;  
generating a transform of the one dimensional pattern; and  
determining oxygenation of the tissue in response to the transform of the projected one dimensional pattern.

68. An apparatus to measure oxygenation of tissue, comprising:  
a light source configured to emit two or more wavelengths of light to project a one dimensional pattern on to the tissue;  
a detector to receive the image of the one dimensional pattern projected onto the tissue;  
and  
a processor coupled to the detector, the processor configured with instructions to determine a transform of the one dimensional pattern projected onto the tissue and determine oxygenation of the tissue in response to the transform of the one dimensional pattern.

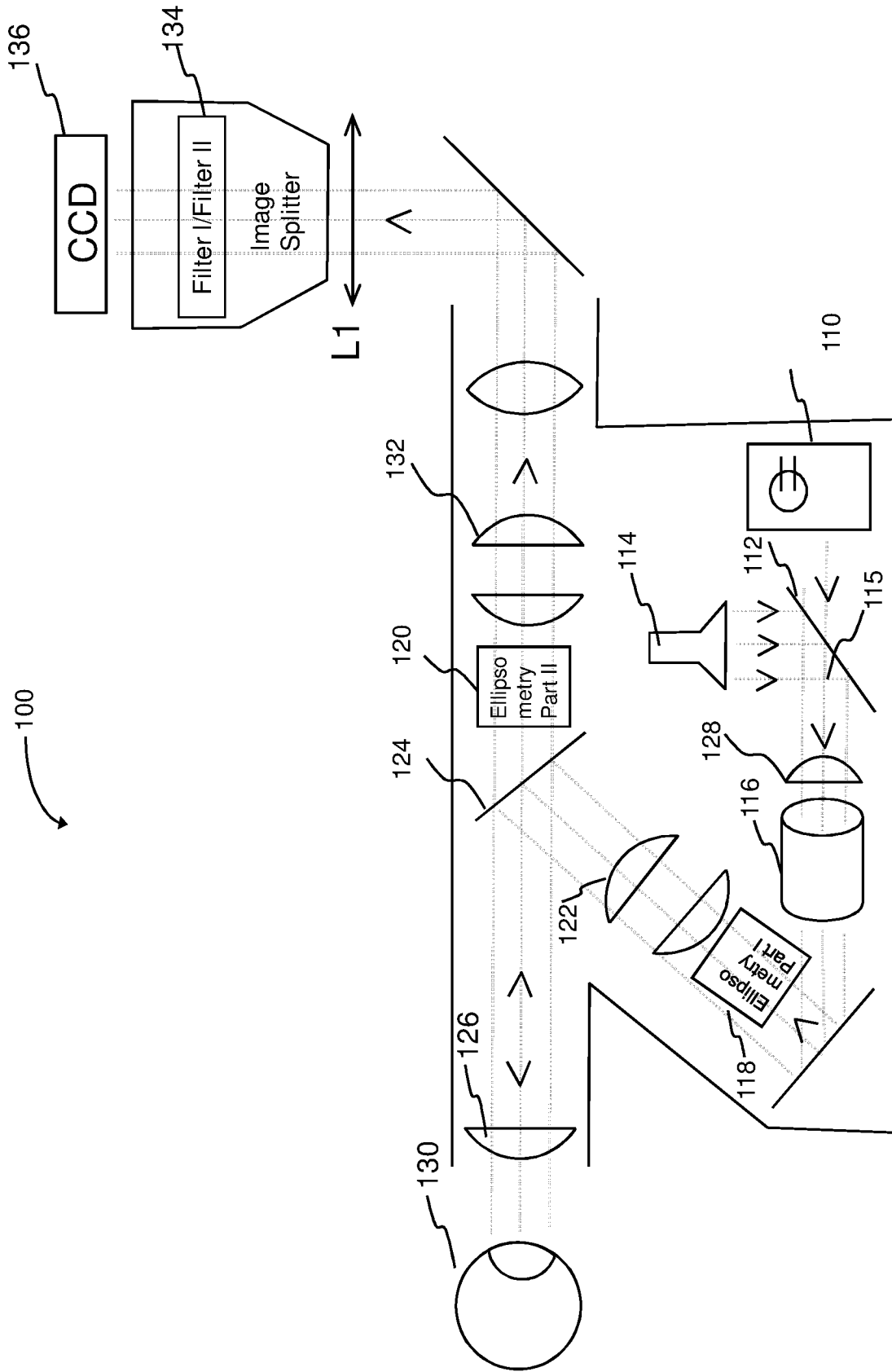


FIG. 1

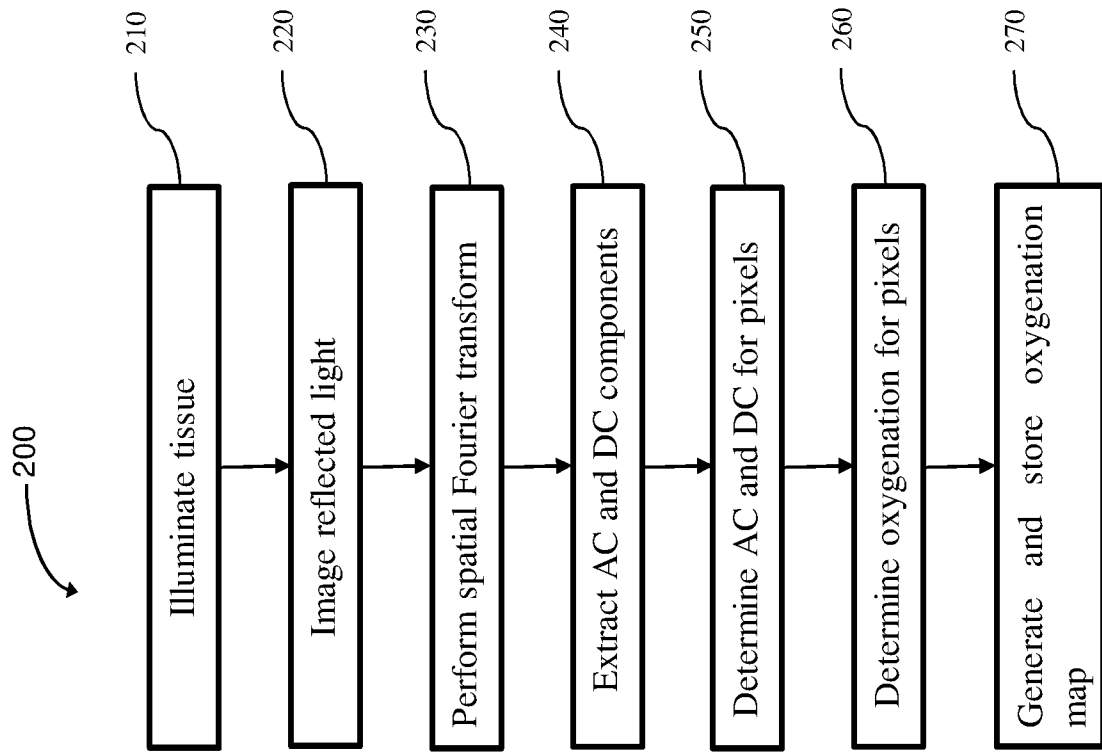


FIG. 2

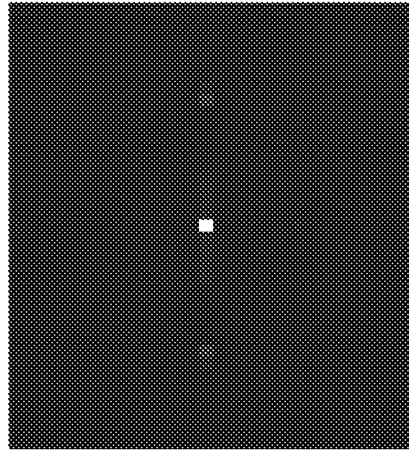


FIG. 3B

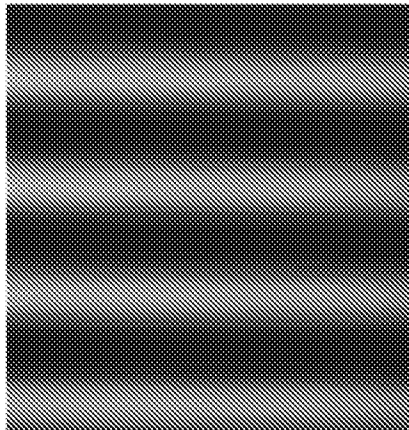


FIG. 3A

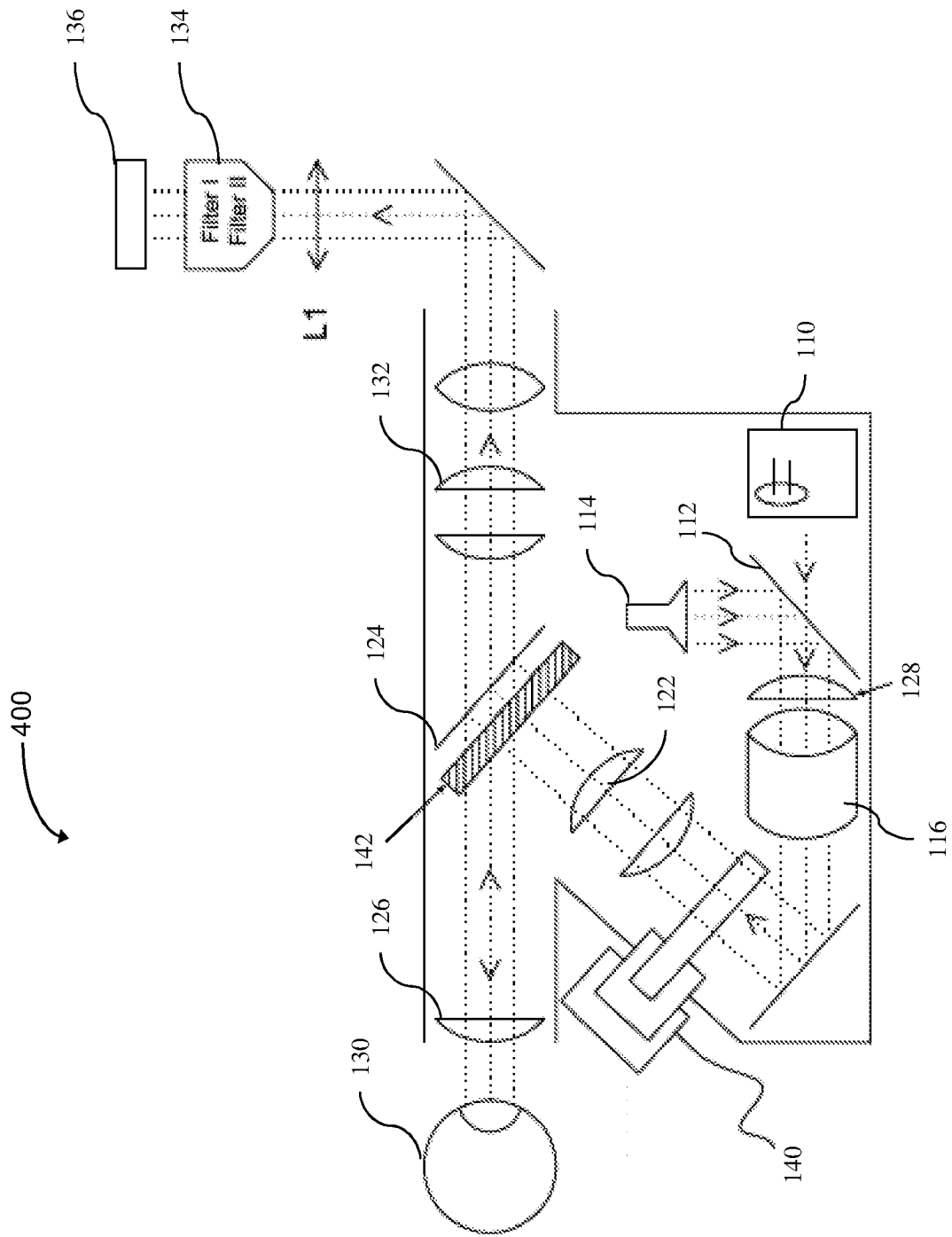


FIG. 4

## INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/US2016/065990****A. CLASSIFICATION OF SUBJECT MATTER****A61B 5/00(2006.01)i, A61B 5/1455(2006.01)i**

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 5/00; A61B 3/113; A61B 3/12; A61B 3/10; A61B 6/00; G06T 7/00; G01B 9/02; A61B 3/14; A61B 5/1455

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) &amp; Keywords: tissue, oxygenation, light, pattern, reflect

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005-0288565 A1 (KERR) 29 December 2005 See paragraphs [24],[86]-[92], claims 1,33 and figure 1.	39-46,48-60,62-68
Y		1-38,47,61
Y	WO 2015-105689 A1 (MICROSOFT TECHNOLOGY LICENSING, LLC) 16 July 2015 See claim 1 and figure 2.	1-38
Y	US 5822035 A (BILLE) 13 October 1998 See column 4, line 67 - column 5, line 1.	9,28,47,61
Y	US 2010-0094135 A1 (FANG-YEN et al.) 15 April 2010 See claim 38.	11,14,30,33
A	US 2009-0153798 A1 (DICK et al.) 18 June 2009 See claim 67 and figure 1.	1-68

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

\* Special categories of cited documents:

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"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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

10 March 2017 (10.03.2017)

Date of mailing of the international search report

**15 March 2017 (15.03.2017)**

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2016/065990**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005-0288565 A1	29/12/2005	EP 1611840 A1	04/01/2006
		EP 1611840 B1	13/08/2008
		GB 2415778 A	04/01/2006
		GB 2415778 B	14/05/2008
		US 7502639 B2	10/03/2009
WO 2015-105689 A1	16/07/2015	CN 105900141 A	24/08/2016
		EP 3092616 A1	16/11/2016
		KR 10-2016-0108394 A	19/09/2016
		US 2015-0193920 A1	09/07/2015
		US 9292765 B2	22/03/2016
US 5822035 A	13/10/1998	EP 0832597 A1	01/04/1998
		EP 0832597 B1	23/05/2007
		JP 10-213483 A	11/08/1998
		JP 3554663 B2	18/08/2004
US 2010-0094135 A1	15/04/2010	AU 2002-357307 A1	30/06/2003
		CA 2469817 A1	26/06/2003
		CA 2469817 C	14/02/2012
		CA 2529942 A1	06/01/2005
		CN 1826518 A	30/08/2006
		EP 1456600 A1	15/09/2004
		EP 1456600 B1	12/02/2014
		EP 1644720 A2	12/04/2006
		JP 2005-513429 A	12/05/2005
		JP 2005-513429 A6	12/05/2005
		JP 2007-524075 A	23/08/2007
		JP 2013-152243 A	08/08/2013
		JP 4550423 B2	22/09/2010
		JP 5416883 B2	12/02/2014
		US 2003-0112444 A1	19/06/2003
		US 2005-0057756 A1	17/03/2005
		US 2005-0105097 A1	19/05/2005
		US 2013-0265585 A1	10/10/2013
		US 6934035 B2	23/08/2005
		US 7365858 B2	29/04/2008
US 7557929 B2	07/07/2009		
US 8334982 B2	18/12/2012		
US 9528817 B2	27/12/2016		
WO 03-052345 A1	26/06/2003		
WO 2005-001445 A2	06/01/2005		
WO 2005-001445 A3	15/12/2005		
US 2009-0153798 A1	18/06/2009	DE 102005034332 A1	25/01/2007
		EP 1906811 A2	09/04/2008
		EP 1906811 B1	20/04/2016
		EP 1910710 A1	16/04/2008
		EP 1910710 B1	19/10/2011

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2016/065990**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 2009-502220 A	29/01/2009
		JP 5016598 B2	05/09/2012
		US 7926945 B2	19/04/2011
		WO 2007-009631 A1	25/01/2007
		WO 2007-009761 A2	25/01/2007
		WO 2007-009761 A3	25/10/2007