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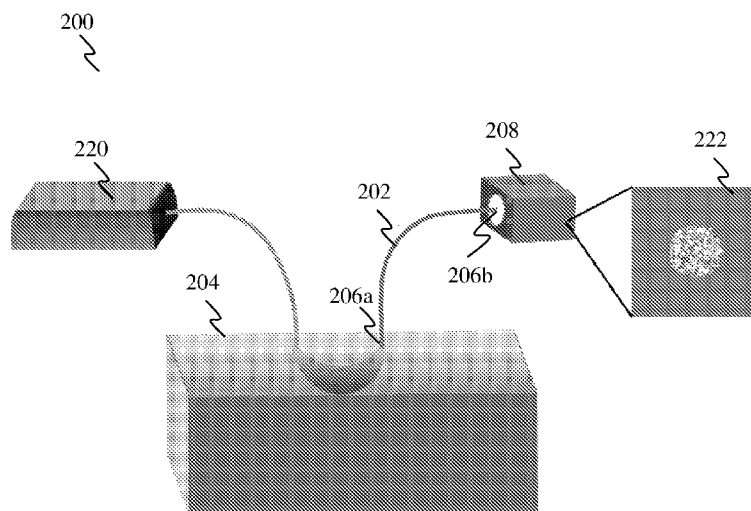


FIG. 2

(57) **Abstract:** According to embodiments of the present invention, an apparatus for non-invasively measuring blood flow in a deep tissue is provided. The apparatus includes a multi-mode optical fiber having a sensing end and a distal end opposite to the sensing end, wherein the multi-mode optical fiber is configured to receive at the sensing end an optical signal emitted from the deep tissue and transmit the received optical signal towards the distal end; an imaging device configured to capture an image of the transmitted optical signal at the distal end; a filtering processor configured to remove a pre-determined background image from the captured image to generate a de-background image; and a processor configured to determine a blood perfusion index from the generated de-background image. According to further embodiments of the present invention, a method of non-invasively measuring blood flow in a deep tissue is also provided.



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## APPARATUS AND METHOD FOR NON-INVASIVELY MEASURING BLOOD FLOW IN A DEEP TISSUE

### Cross-Reference To Related Application

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[0001] This application claims the benefit of priority of Singapore patent application No. 10201902817R, filed 28 March 2019, the content of it being hereby incorporated by reference in its entirety for all purposes.

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### Technical Field

[0002] Various embodiments relate to an apparatus and a method for non-invasively measuring blood flow in a deep tissue, more specifically, using optical means.

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### Background

[0003] Diffuse optical imaging techniques are used to provide non-invasive imaging for various biomedical and healthcare applications. One such application relates to blood flow measurements in deep tissues.

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[0004] Blood flow measurement is important as it plays a vital role in understanding the functionality of the heart. Measurement of blood flow and changes in blood volume provide essential information for the diagnosis of diseases with impaired blood flow.

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[0005] Optical-fiber-based methods for deep blood flow measurement modalities may include diffuse correlation spectroscopy (DCS) and diffuse speckle contrast analysis (DSCA)

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[0006] DCS came about around the year of 2005 for deep tissue blood flow measurement. For DCS, a hardware correlator and an ultra-sensitive photon detector are required to quantify autocorrelation function. In 2013, DSCA emerged as a popular alternative with the use of much more cost-effective hardware to achieve similar deep tissue blood flow measurement. Furthermore, the data analysis algorithm involved when

using DSCA is simplified. Both methods use single-mode fiber for detection and can reach sampling rates of less than 100 Hz.

[0007] Experts in diffuse optical blood flow methods teach away from using multi-mode fiber as detection fiber because of the loss of sensitivity to autocorrelation function due to a larger fiber core of the multi-mode fiber. This subsequently leads to a lower sensitivity of blood flow measurement.

[0008] These teachings are in line with various studies made. For example, in one publication, comparisons were made between single-mode fibers and multi-mode fibers used in improving signal-to-noise ratio of dual wavelength DCS. This study found that multi-mode fibers may be used to increase the detected light intensities and improve signal-to-noise ratio for tissue oxygenation measurements. However, multi-mode fibers were not suitable or useable for the purpose of extracting flow information due to the significantly low value of the coherence factor. This resulted in the reduced sensitivity of the DCS flow measurement.

[0009] Meanwhile, in another publication, a multi-mode detection fiber resulted in low signal-to-noise ratio and loss of the characteristic decay of the DCS correlation curve.

[0010] While noting the existing challenges in using multi-mode fiber for diffuse optical blood flow detection, there remain attractiveness and benefits in exploring the possible use of multi-mode fibers due to inherent advantages such as having lower cost for operation and maintenance, and higher bandwidth capability. Thus, there is a need to seek a solution for an apparatus and method for measuring blood flow in deep tissue with the use of multi-mode fibers, while addressing at least the problems mentioned herein.

## Summary

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[0011] According to an embodiment, an apparatus for non-invasively measuring blood flow in a deep tissue is provided. The apparatus may include a multi-mode optical fiber having a sensing end and a distal end opposite to the sensing end, wherein the multi-mode optical fiber is configured to receive at the sensing end an optical signal emitted from the deep tissue and transmit the received optical signal towards the distal end; an imaging device configured to capture an image of the transmitted optical signal at the

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distal end of the multi-mode optical fiber; a filtering processor configured to remove a pre-determined background image from the captured image to generate a de-background image; and a processor configured to determine a blood perfusion index from the generated de-background image. The blood perfusion index is indicative of an instantaneous blood flow measurement in the deep tissue.

[0012] According to an embodiment, a method for non-invasively measuring blood flow in a deep tissue is provided. The method may include receiving an optical signal emitted from the deep tissue at a sensing end of a multi-mode optical fiber; wherein the received optical signal is transmitted to a distal end of the multi-mode optical fiber, the distal end being opposite to the sensing end; capturing an image of the transmitted optical signal at the distal end of the multi-mode optical fiber; removing a pre-determined background image from the captured image to generate a de-background image; and determining a blood perfusion index from the generated de-background image.

### Brief Description of the Drawings

[0013] In the drawings, like reference characters generally refer to like parts throughout the different views. The drawings are not necessarily to scale, emphasis instead generally being placed upon illustrating the principles of the invention. In the following description, various embodiments of the invention are described with reference to the following drawings, in which:

[0014] FIG. 1A shows a schematic view of an apparatus for measuring blood flow in a deep tissue, according to various embodiments.

[0015] FIG. 1B shows a flow chart illustrating a method for measuring blood flow in a deep tissue, according to various embodiments.

[0016] FIG. 2 shows a schematic perspective view of a diffuse optical cardiogram (DOC) system in part, according to one embodiment.

[0017] FIG. 3 shows a flow chart illustrating an image process flow for background removing and blood perfusion index calculation, according to one embodiment.

[0018] FIG. 4 shows images illustrating an image process for background removing, according to one embodiment.

[0019] FIG. 5A shows a distribution plot representing a raw speckle image of a multi-mode optical fiber tip, as shown in FIG. 4.

[0020] FIG. 5B shows a distribution plot representing the background obtained from averaging about 6000 frames, as shown in FIG. 4.

5 [0021] FIG. 5C shows a distribution plot representing a normalized speckle image without the background of FIG. 5B.

[0022] FIG. 6 shows a plot illustrating a comparison between a photoplethysmogram (PPG) waveform obtained from a pulse oximeter and a cardiogram-like waveform obtained from the apparatus/method according to one embodiment.

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### Detailed Description

[0023] The following detailed description refers to the accompanying drawings that show, by way of illustration, specific details and embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention. Other embodiments may be utilized and structural, logical, and electrical changes may be made without departing from the scope of the invention. The various embodiments are not necessarily mutually exclusive, as some embodiments can be combined with one or more other embodiments to form new  
15  
20 embodiments.

[0024] Embodiments described in the context of one of the methods or devices are analogously valid for the other methods or devices. Similarly, embodiments described in the context of a method are analogously valid for a device, and vice versa.

[0025] Features that are described in the context of an embodiment may correspondingly  
25 be applicable to the same or similar features in the other embodiments. Features that are described in the context of an embodiment may correspondingly be applicable to the other embodiments, even if not explicitly described in these other embodiments. Furthermore, additions and/or combinations and/or alternatives as described for a feature in the context of an embodiment may correspondingly be applicable to the same or  
30 similar feature in the other embodiments.

[0026] In the context of various embodiments, the articles “a”, “an” and “the” as used with regard to a feature or element include a reference to one or more of the features or elements.

5 [0027] In the context of various embodiments, the term “about” or “approximately” as applied to a numeric value encompasses the exact value and a reasonable variance.

[0028] As used herein, the term “and/or” includes any and all combinations of one or more of the associated listed items.

10 [0029] FIG. 1A shows a schematic view of an apparatus 100 for measuring blood flow in a deep tissue, according to various embodiments. The apparatus 100 may include a multi-mode optical fiber 102 having a sensing end 106a and a distal end 106b opposite to the sensing end 106a, wherein the multi-mode optical fiber 102 is configured to receive at the sensing end 106a an optical signal emitted from the deep tissue through a target surface 104 and transmit the received optical signal towards the distal end 106b. The apparatus 100 may also include an imaging device 108 configured to capture an image of the transmitted optical signal at the distal end 106b of the multi-mode optical fiber 102; a filtering processor 112 configured to remove a pre-determined background image from the captured image to generate a de-background image; and a processor 116 configured to determine a blood perfusion index from the generated de-background image. The blood perfusion index is indicative of an instantaneous blood flow measurement in the deep tissue. The imaging device 108 may be in communication with or coupled with the filtering processor 112 as shown by a connection line 110, while the filtering processor 112 may be in communication with or coupled with the processor 116 as shown by a connection line 114.

25 [0030] In the context of various embodiments, the phrase “multi-mode optical fiber” may be interchangeably referred as multi-mode fiber and may refer to a type of optical fiber that has a large core diameter, typically 50  $\mu\text{m}$  to 600  $\mu\text{m}$ , and enables multiple light modes to be propagated.

[0031] The expression “optical signal emitted from the deep tissue” may mean the optical signal being reflected or scattered by the deep tissue.

30 [0032] The term “transmit” used in relation to “transmit the received optical signal towards the distal end” and its associating term “transmitted” may refer to the received

optical signal being propagated to the distal end, and the propagated optical signal at the distal end, respectively.

[0033] In various embodiments, the apparatus 100 may further include a light source configured to emit a beam of light transmissible to the deep tissue to be reflected or scattered as the optical signal emitted from the deep tissue. For example, the light source may include a laser. A continuous wave laser may be used as the light source. The laser power may range from 0.1 mW to 200 mW, depending on the required penetration depth. The wavelength may be in the near infrared (NIR) range, from 700 nm to 1000 nm.

[0034] In other words, various embodiments may provide an optical fiber based device for deep blood flow measurement including a source of excitatory light and a multi-mode fiber with, for example, a charge-coupled device (CCD) for detection. Background fitting and noise removal may be employed for the purpose of processing signals received from the multimode fibers. With the device in combination with the background fitting and noise removal, measurement blood flow may be achieved to provide information on blood flow, cardiac function, vascular system function and blood pressure.

[0035] In various embodiments, the apparatus 100 may further include a calibration processor. The imaging device may be configured to capture a series of images of transmitted optical signals at the distal end 106b, and the calibration processor may be configured to apply an averaging process to the series of images to generate the pre-determined background image. The averaging process may include a Gaussian process, for example, Gaussian averaging. The Gaussian process may be used as the light pattern output from the fiber tip may be similar to a Gaussian distribution. The pre-determined background image may be a Gaussian background. It should be appreciated and understood that in other embodiments, the averaging process may alternatively include other averaging methods, for example, running average and median filtering.

[0036] The calibration processor may at least part of the filtering processor 112 or the processor 116. For example, the calibration processor may be integrated into the filtering processor 112, or integrated into the processor 116. In other words, either the filtering processor 112 or the processor 116 may capable of performing the functions of the calibration processor.

[0037] In some embodiments, the filtering processor 112 may be at least part of the processor 116. For example, the filtering processor 112 may be integrated into the processor 116. In other words, the processor 116 may be capable of performing the functions of the filtering processor 112.

5 [0038] In one embodiment, the imaging device 108 may be configured to capture the series of about 6000 images of the transmitted optical signals at the distal end 106b over a time period ranging between about 6 seconds and about 20 seconds. For example, the imaging device 108 may be a high-speed charge-coupled device (CCD) camera with a frame rate ranging between about 300 frames per second and 1000 frames per second.

10 [0039] In various embodiments, the processor 116 may be further configured to determine a plurality of blood perfusion indexes from a plurality of de-background images obtained and processed from a plurality of images captured by the imaging device 108 over a period of time, and display a cardiogram-like plot depicting a relationship between the plurality of blood perfusion indexes and time.

15 [0040] The apparatus 100 may be capable of measuring blood flow in the deep tissue at a rate of more than 300 Hz.

[0041] FIG. 1B shows a flow chart illustrating a method 120 for measuring blood flow in a deep tissue, according to various embodiments.

[0042] In the method 120, at 122, an optical signal emitted from the deep tissue may be received at a sensing end 106a of a multi-mode optical fiber 102. The received optical signal may be transmitted (or may propagate) to a distal end 106b of the multi-mode optical fiber 102, the distal end 106b being opposite to the sensing end 106a. At 124, an image of the transmitted optical signal may be captured at the distal end 106b of the multi-mode optical fiber 102. At 126, a pre-determined background image may be removed from the captured image to generate a de-background image. At 128, a blood perfusion index may be determined from the generated de-background image. The blood perfusion index is indicative of an instantaneous blood flow measurement in the deep tissue.

20 [0043] In various embodiments, the method 120 may further include emitting a beam of light transmissible to the deep tissue that is reflected or scattered as the optical signal emitted from the deep tissue.

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[0044] The step of capturing the image at 124 may include capturing the image using a charge-coupled device (CCD) camera with a frame rate ranging between about 300 frames per second and 1000 frames per second.

[0045] In various embodiments, the pre-determined background image is obtainable from capturing a series of images of transmitted optical signals at the distal end 106b, and applying an averaging process to the series of images. In other words, prior to the step of capturing the image at 124, a series of images of the transmitted optical signals may be captured at the distal end 106b, and an averaging process, for example, a Gaussian process, may be applied to the series of images to generate the pre-determined background image (not shown in FIG. 3). For example, the step of capturing the series of images at 124 may include capturing about 6000 images of the transmitted optical signals at the distal end 106b over a time period ranging between about 6 seconds and about 20 seconds. As discussed above, the pre-determined background image may be a Gaussian background.

[0046] At 126, with the pre-determined background image removed, the de-background image may have a signal-to-noise ratio (SNR) of more than 20 dB, where SNR is given by  $10 \times \log(I_M/N_{std})$ ,  $I_M$  being the mean intensity of signal and  $N_{std}$  being the standard deviation of the CCD area with no light signal. The high SNR of the de-background image causes higher sensitivity to the blood flow. The coherence factor of the de-background image may also be significantly improved, thereby enabling the multi-mode optical fiber 102 to be used for the purpose of extracting flow information. For example, the de-background image may be generated by dividing the captured image at 124 by the pre-determined background image. The generation of the de-background image may be performed by the filtering processor 112.

[0047] In various embodiments, the step of determining the blood perfusion index at 128 may include calculating the blood perfusion index with a formulae,  $\left(\frac{I}{std}\right)^2$ , where  $I$  represents a mean intensity of pixels of the de-background image, and  $std$  represents a standard deviation of the pixels of the de-background image.

[0048] The method 120 may further include determining a plurality of blood perfusion indexes from a plurality of de-background images obtained and processed from a

plurality of images of optical signals received by the multi-mode optical fiber 102 captured over a period of time, and displaying a cardiogram-like plot depicting a relationship between the plurality of blood perfusion indexes and time. Each of the plurality of de-background images may be obtained from removing the pre-determined background image from each corresponding image of the plurality of images.

[0049] In various embodiments, the step of determining the plurality of blood perfusion indexes may be performed in a manner to allow a measurement of blood flow in the deep tissue at a rate of more than 300 Hz.

[0050] While the method described above is illustrated and described as a series of steps or events, it will be appreciated that any ordering of such steps or events are not to be interpreted in a limiting sense. For example, some steps may occur in different orders and/or concurrently with other steps or events apart from those illustrated and/or described herein. In addition, not all illustrated steps may be required to implement one or more aspects or embodiments described herein. Also, one or more of the steps depicted herein may be carried out in one or more separate acts and/or phases.

[0051] Various embodiments provide the apparatus 100 and the method 120 of non-invasively measuring blood flow in the deep tissue.

[0052] More specifically, the apparatus 100 and the method 120 for in vivo non-invasive measurement of deep blood flow, may take the form of a diffuse optical cardiogram (DOC) through pulsatile flowmetry, which will be discussed in more details below.

[0053] The DOC may be derived from a non-invasive optical method using multi-mode optical fiber for fast ( $> 300$  Hz) deep tissue pulsatile blood flow measurement. Due to the fast sampling rate, every detail of blood flow changes in a single cardiac cycle may be resolved clearly. For the first time, the blood flow in arteries and capillary network may be measured at significantly high speed that the flow waveform resembles a cardiogram, as the name DOC suggests. DOC provides more information than electrocardiogram (ECG) because blood flow is a reflection of both cardio function and vascular system status. DOC benefits fast diagnosis of cardio and vascular diseases.

[0054] FIG. 2 shows a schematic perspective view of a DOC system 200 in part, performing an in vivo non-invasive deep blood flow measurement. The DOC system 200 may include the same or like elements or components as those of the apparatus 100 of

FIG. 1A, and as such, the same ending numerals are assigned and the like elements may be as described in the context of the apparatus 100 of FIG. 1A, and therefore the corresponding descriptions are omitted here.

[0055] In FIG. 2, a beam of light from a light source (e.g. a laser) 220 is transmitted to a target surface 204 through to the deep tissue (underneath or below the target surface 204) where blood flow is measured. Due to the environmental influences of the blood flow and/or the deep tissue, the light may be absorbed, reflected or scattered. The reflected or scattered light is emitted from the deep tissue to be received at a sensing end 206a of a multi-mode fiber 202. The received light is then transferred to (or propagates to) a distal end 206b of the multi-mode fiber 202. A speckle image 222 of the light at the distal end 206b is captured by a CCD camera 208. As the multi-mode fiber 202 carries information of numerous speckles, the spatial contrast of these speckles may be used to extract blood perfusion index (or interchangeably referred to as blood flow index) within one shot of the CCD camera 208.

[0056] In the DOC system 200, an auto background fitting method may be implemented to compensate the sensitivity loss, which enables the use of multi-mode fiber 202 as a detection fiber for blood flow measurement. This was not possible in existing DCS due to the reduced sensitivity when using multi-mode fiber.

[0057] To make use of a multi-mode detection fiber (e.g. 202), an auto background fitting and removal process has to be performed before data acquisition. On the CCD camera 208, the image of the output from the multi-mode fiber 202 is a mix of the Gaussian background and the speckle pattern (more specifically, diffuse laser speckle). The background needs to be removed before the speckle pattern may be used. Several methods may be explored, for example, numerical simulation, averaging over a large number of actual multi-mode fiber images, or numerical simulation based on the actual measurements. However, the pure numerical simulation method may cause significant errors if the required parameters are not sufficiently accurate. The latter two methods may be more practical, where the method of averaging over a large number of actual multi-mode fiber images may involve approximately 6000 images as described below, with reference to FIGS. 4 and 5, while the method of numerical simulation based on the actual

measurements (no examples being shown) may allow for fewer (e.g. about 600) images to be used.

[0058] FIG. 3 shows a flow chart illustrating an image process flow 300 for background removing and blood perfusion index calculation using the DOC system 200. At 302, the sensor, more specifically the sensing end 206a of the multi-mode fiber 202 is placed to the measurement location (e.g. the target surface 204). At 304, approximately 6000 CCD images of the multi-mode fiber tip (i.e. at the distal end 206b) are collected. The approximate 6000 CCD images are averaged at 306 to generate a Gaussian background of the fiber tip (i.e., at the distal end 206b). The Gaussian background is denoted as BG. From now (or rather thereafter), at 308, every raw CCD image, IM, removes the background by using Equation 1 to obtain a de-background image,  $IM_{de-BG}$ :

$$IM_{de-BG} = IM / BG \quad \text{- Equation 1}$$

[0059] In other words, the raw CCD image, IM undergoes pre-processing prior to data acquisition.

[0060] From  $IM_{de-BG}$ , the blood perfusion index (BPI) is calculated at 310 by using Equation 2 shown at 312:

$$BPI = (I / std)^2 \quad \text{- Equation 2}$$

where  $I$  is the mean intensity of the pixels, and  $std$  is the standard deviation of the pixels.

[0061] FIG. 4 shows images illustrating an image process for background removing. The image 400 depicts an example of a raw CCD image of the multi-mode fiber tip. At 402, by taking and collecting approximately 6000 images at the frame rate of 300 frames per second, as described in Step 304 of FIG. 3, and averaging these 6000 images, as described in Step 306 of FIG. 3, a Gaussian background (BG) 404 averaged from these 6000 images may be obtained. At 406, a new image, IM, is dividing by BG to remove the Gaussian background (BG) 404 so as to obtain the de-background image 408,  $IM_{de-BG}$ , as described in Step 308 of FIG. 3. The BPI may be calculated from the de-background image 408,  $IM_{de-BG}$ , as described in Steps 310 and 312 of FIG. 3.

[0062] FIG. 5A corresponds to the image 400, showing a three-dimensional distribution plot 500 representing the raw speckle image of the multi-mode optical fiber tip (i.e. at the distal end 206b), while FIG. 5B corresponds to the image 404, showing a three-dimensional distribution plot 502 representing the background obtained from averaging about 6000 frames, as shown in FIG. 4. FIG. 5C corresponds to the image 408, showing a three-dimensional distribution plot 504 representing a normalized speckle image without the background of FIG. 5B. This way, the speckle information may be extracted.

[0063] After the background removal as described in FIGS. 4 and 5, every CCD frame generates one blood perfusion index, as described in Steps 310 and 312 of FIG. 3.

[0064] The sampling rate may be determined by the imaging frame rate. An industrial camera may easily reach 300 to 1000 frames per second (fps). Therefore, the blood flow measurement may reach this level of high speed from the DOC system 200.

[0065] When the blood flow is measured at such high speed, several interesting results may be observed as shown in FIG. 6 where a conventional photoplethysmogram (PPG) waveform 602 acquired by a pulse oximeter on human fingers to provide measurement of temporal blood volume changes is simultaneously compared against a measurement of DOC 604 on a in vivo human thumb. As can be seen from the plot 600 of FIG. 6, more significant details of one cardiac cycle may be observed from the DOC waveform as compared to that of the PPG waveform. It should be understood and appreciated that the flow peak always precedes (i.e. in front of) the volume peak. The DOC waveform carries information of cardio system, vascular system and blood pressure. The DOC system may be developed employed into a new routine medical checkup method as ECG, PPG and blood pressure monitoring.

[0066] In conclusion, the DOC is the first deep tissue blood flow measurement method using multi-mode fiber. An auto background fitting and removal algorithm (i.e. a de-background method) is developed to enable the use of multi-mode fiber as detection fiber. To the best of the inventors' knowledge, this is also the fastest blood flow measurement method (practically  $> 300$  Hz), as the theoretical speed limit becomes the frame rate of the camera used. This enables the DOC system to resolve every detail of a cardiac cycle. Furthermore, cardiogram-like waveforms may be generated from the fast blood flow measurement, which cannot be measured by any other existing device.

[0067] While the invention has been particularly shown and described with reference to specific embodiments, it should be understood by those skilled in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the invention as defined by the appended claims. The scope of the invention is  
5 thus indicated by the appended claims and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced.

**CLAIMS**

1. An apparatus for non-invasively measuring blood flow in a deep tissue, comprising:

5 a multi-mode optical fiber having a sensing end and a distal end opposite to the sensing end, wherein the multi-mode optical fiber is configured to receive at the sensing end an optical signal emitted from the deep tissue and transmit the received optical signal towards the distal end;

an imaging device configured to capture an image of the transmitted optical signal  
10 at the distal end of the multi-mode optical fiber;

a filtering processor configured to remove a pre-determined background image from the captured image to generate a de-background image; and

a processor configured to determine a blood perfusion index from the generated de-background image, the blood perfusion index being indicative of an instantaneous  
15 blood flow measurement in the deep tissue.

2. The apparatus of claim 1, further comprising a light source configured to emit a beam of light transmissible to the deep tissue to be reflected or scattered as the optical signal emitted from the deep tissue.

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3. The apparatus of claim 1, wherein the imaging device comprises a charge-coupled device (CCD) camera with a frame rate ranging between about 300 frames per second and 1000 frames per second.

25 4. The apparatus of claim 1, further comprising a calibration processor, wherein the imaging device is configured to capture a series of images of transmitted optical signals at the distal end, and wherein the calibration processor is configured to apply an averaging process to the series of images to generate the pre-determined background image.

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5. The apparatus of claim 4, wherein the averaging process comprises a Gaussian process.

6. The apparatus of claim 4, wherein the calibration processor is at least part of the  
5 filtering processor or the processor.

7. The apparatus of claim 4, wherein the imaging device is configured to capture the series of about 6000 images of the transmitted optical signals at the distal end over a time period ranging between about 6 seconds and about 20 seconds.

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8. The apparatus of claim 1, wherein the filtering processor is at least part of the processor.

9. The apparatus of claim 1, wherein the processor is further configured to determine  
15 a plurality of blood perfusion indexes from a plurality of de-background images obtained and processed from a plurality of images captured by the imaging device over a period of time, and display a cardiogram-like plot depicting a relationship between the plurality of blood perfusion indexes and time.

20 10. The apparatus of claim 1, wherein the apparatus is capable of measuring blood flow in the deep tissue at a rate of more than 300 Hz.

11. A method for non-invasively measuring blood flow in a deep tissue, the method comprising:

25 receiving an optical signal emitted from the deep tissue at a sensing end of a multi-mode optical fiber; wherein the received optical signal is transmitted to a distal end of the multi-mode optical fiber, the distal end being opposite to the sensing end;

capturing an image of the transmitted optical signal at the distal end of the multi-mode optical fiber;

30 removing a pre-determined background image from the captured image to generate a de-background image; and

determining a blood perfusion index from the generated de-background image, the blood perfusion index being indicative of an instantaneous blood flow measurement in the deep tissue.

5 12. The method of claim 11, further comprising emitting a beam of light transmissible to the deep tissue that is reflected or scattered as the optical signal emitted from the deep tissue.

10 13. The method of claim 11, wherein the step of capturing the image comprises capturing the image using a charge-coupled device (CCD) camera with a frame rate ranging between about 300 frames per second and 1000 frames per second.

15 14. The method of claim 11, where the pre-determined background image is obtainable from capturing a series of images of transmitted optical signals at the distal end, and applying an averaging process to the series of images.

15. The method of claim 14, wherein the averaging process comprises a Gaussian process.

20 16. The method of claim 14, wherein capturing the series of images comprises capturing about 6000 images of the transmitted optical signals at the distal end over a time period ranging between about 6 seconds and about 20 seconds.

25 17. The method of claim 11, further comprising determining a plurality of blood perfusion indexes from a plurality of de-background images obtained and processed from a plurality of images of optical signals received by the multi-mode optical fiber captured over a period of time, and displaying a cardiogram-like plot depicting a relationship between the plurality of blood perfusion indexes and time.

18. The method of claim 17, wherein each of the plurality of de-background images is obtained from removing the pre-determined background image from each corresponding image of the plurality of images.

5 19. The method of claim 17, wherein the step of determining the plurality of blood perfusion indexes is performed in a manner to allow a measurement of blood flow in the deep tissue at a rate of more than 300 Hz.

20. The method of claim 11, wherein the step of determining the blood perfusion  
10 index comprises calculating the blood perfusion index with a formulae,  $\left(\frac{I}{std}\right)^2$ , where  $I$  represents a mean intensity of pixels of the de-background image, and  $std$  represents a standard deviation of the pixels of the de-background image.

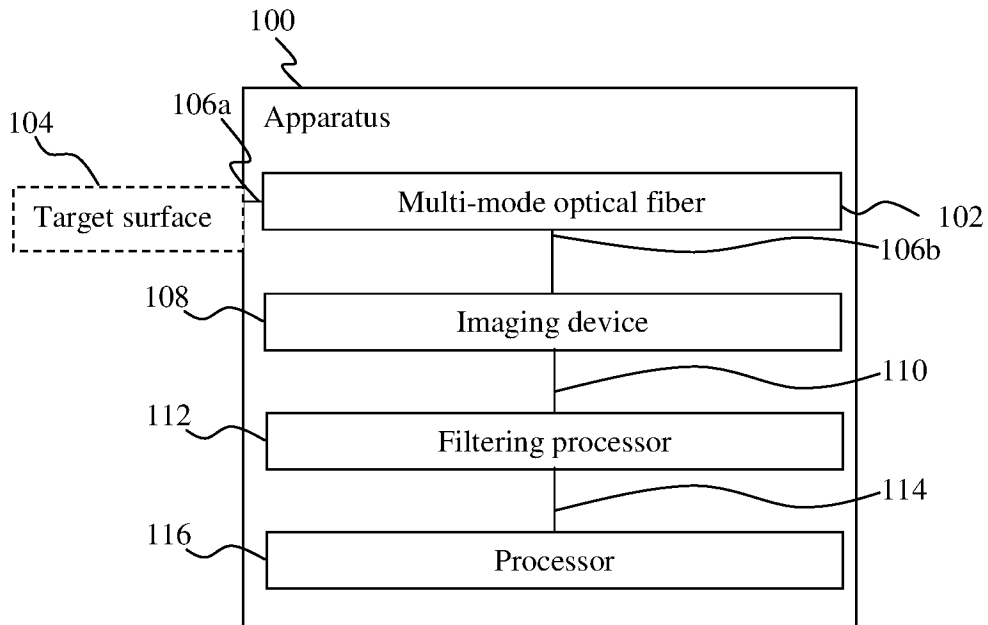


FIG. 1A

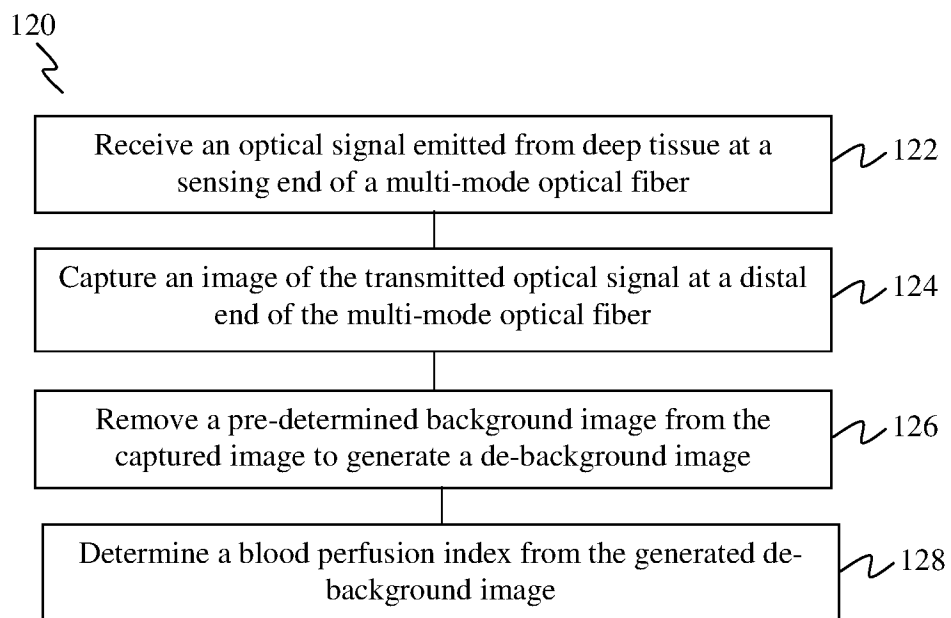


FIG. 1B

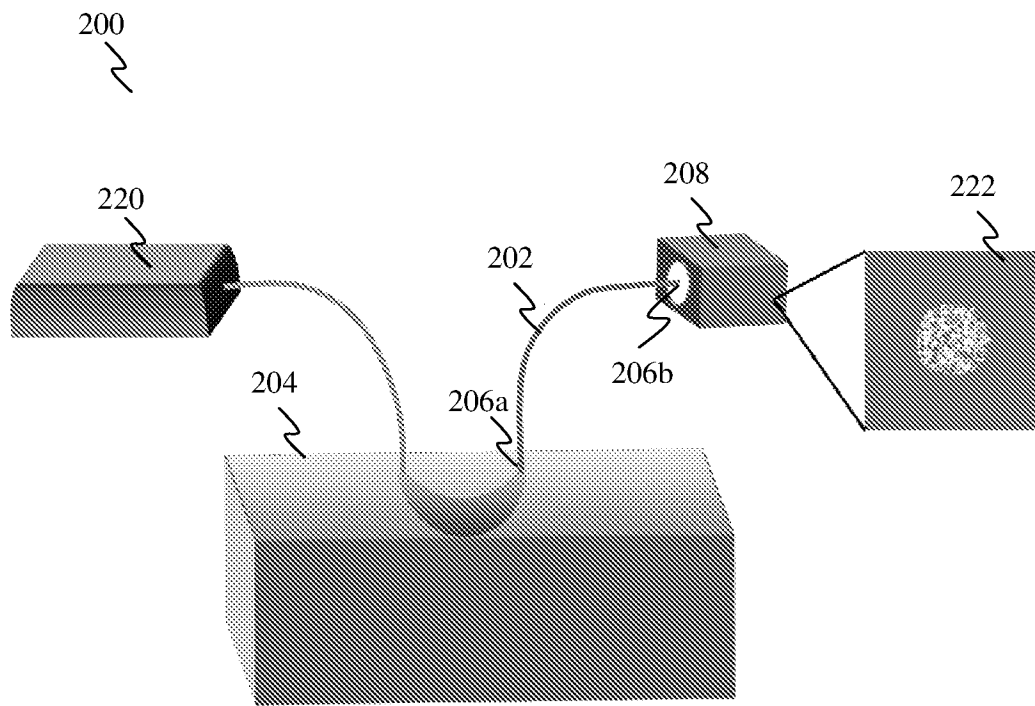


FIG. 2

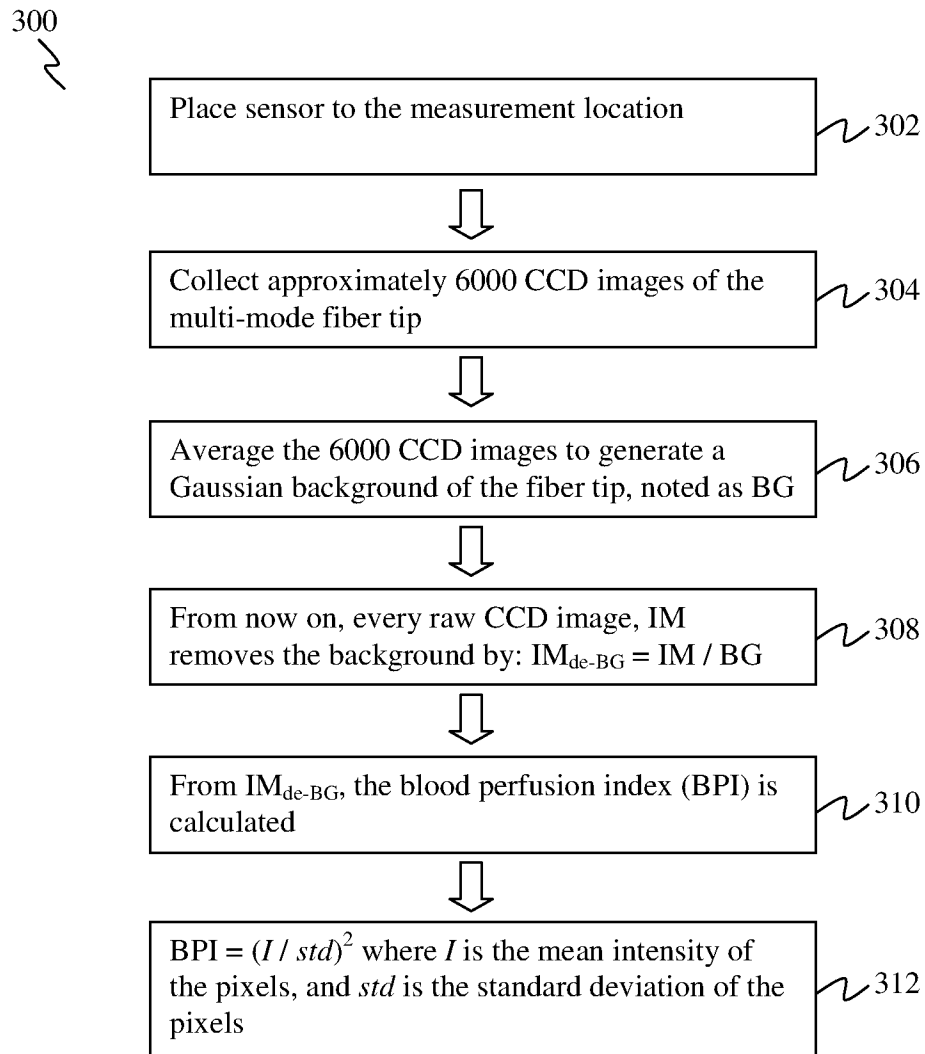


FIG. 3

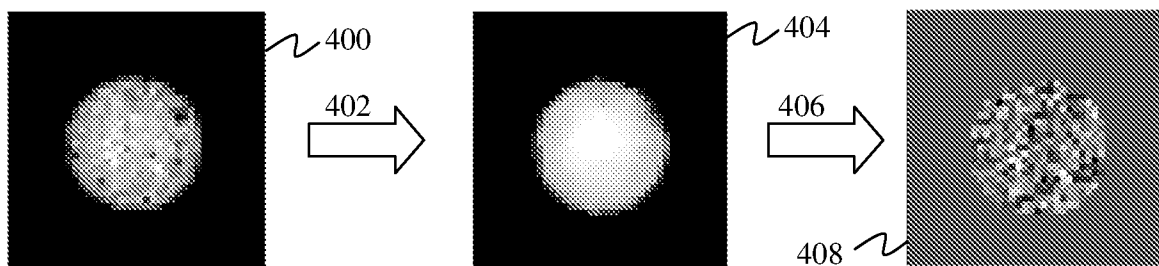


FIG. 4

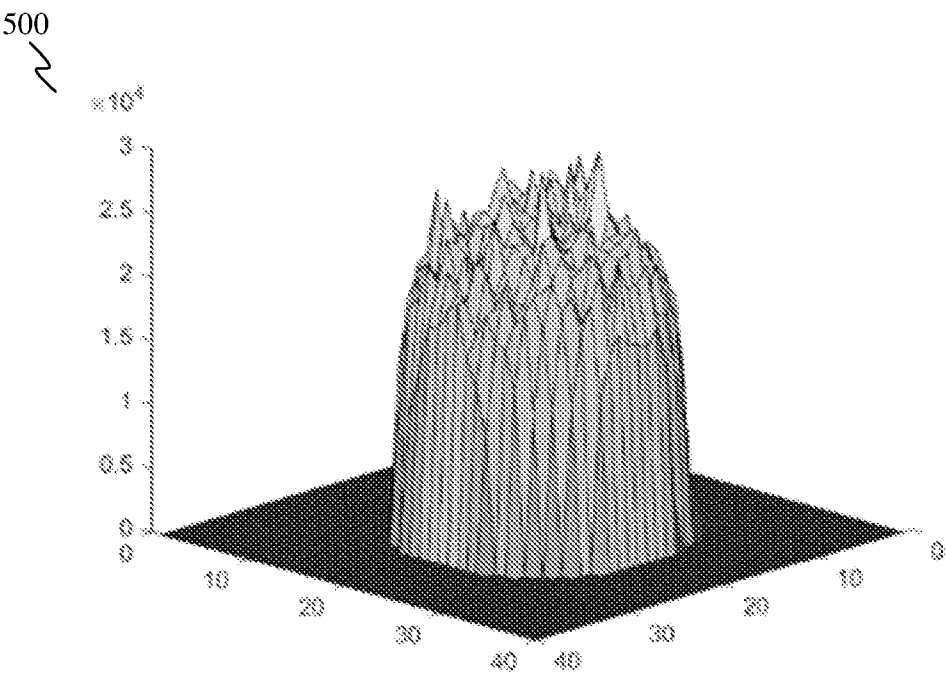


FIG. 5A

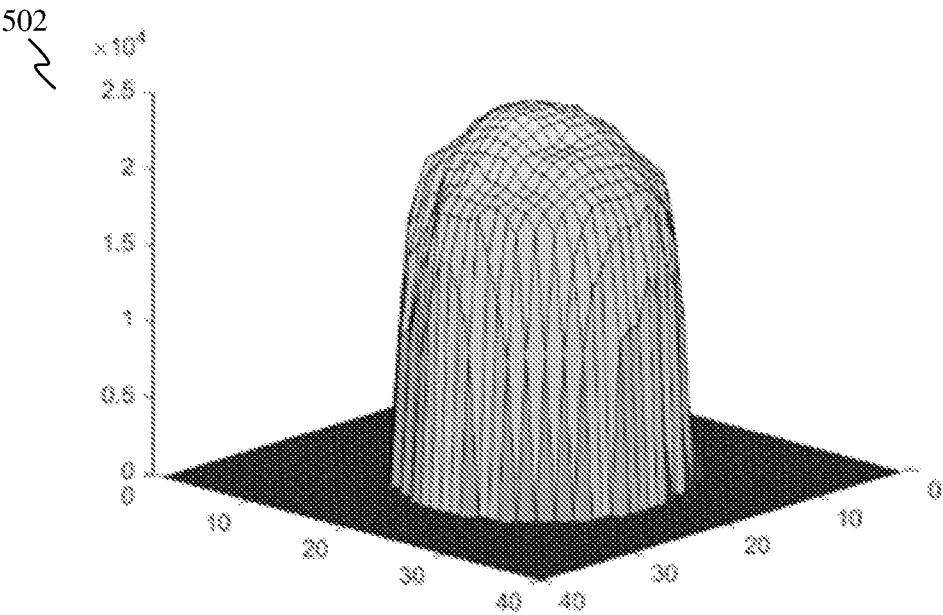


FIG. 5B

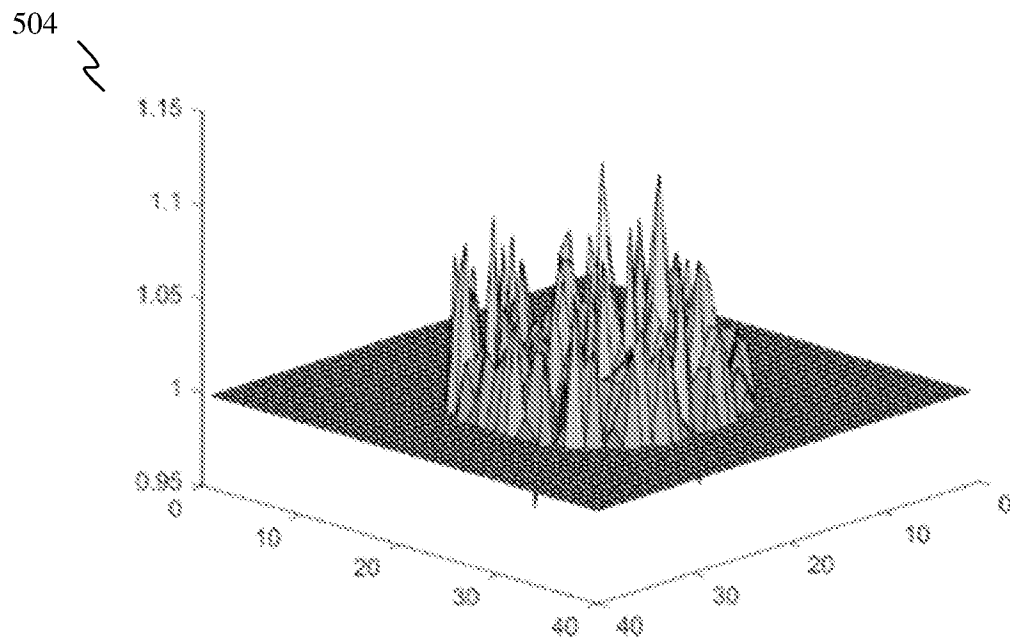


FIG. 5C

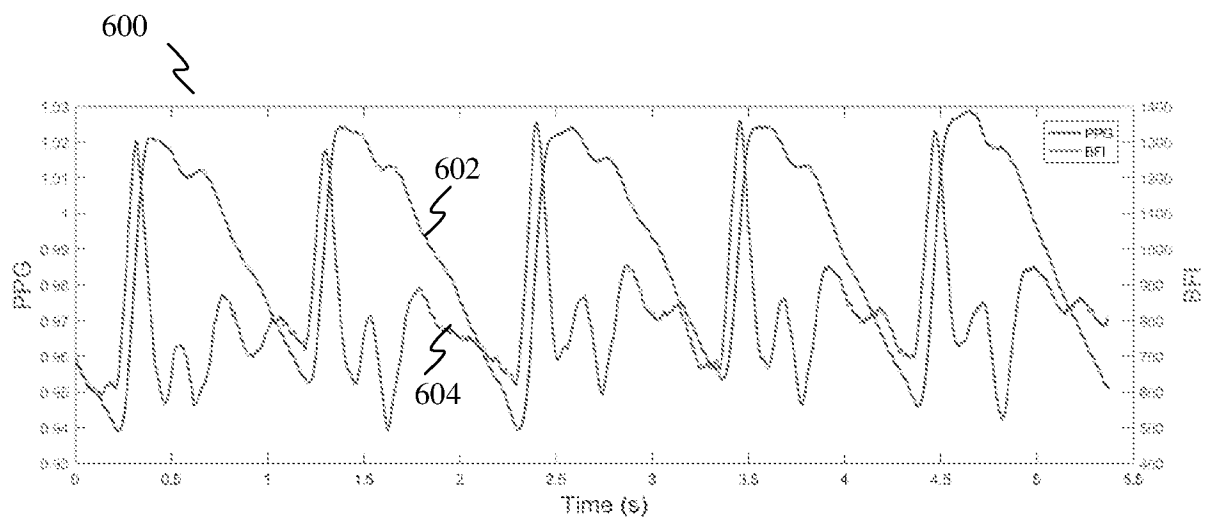


FIG. 6

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2020/050157

## A. CLASSIFICATION OF SUBJECT MATTER

**A61B 5/026 (2006.01)**

According to International Patent Classification (IPC)

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61B

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)

FAMPAT/BIOSIS/COMPENDEX/EMBASE/INSPEC/MEDLINE/EPODOC/WPIA: diffuse; spectroscopy; flowmetry; non-invasive; multimode fiber; blood flow/perfusion index; filter; background; speckle and equivalent terms

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                         | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | WO 2014/116483 A1 (NANYANG TECHNOLOGICAL UNIVERSITY) 31 July 2014<br>Whole document, particularly para. [0005], [0006], [0031], [0034], [0035], [0038], [0040], [0041]; Fig. 3B, 5, 8, 9                                                                                                                                                                   | 1-20                  |
| X         | BI R. ET AL., Multi-channel deep tissue flowmetry based on temporal diffuse speckle contrast analysis. <i>Optics Express</i> , 20 September 2013, Vol. 21, No. 19, pages 22854-22861<br>[Retrieved on 2020-07-24] <DOI: 10.1364/OE.21.022854><br>Whole document                                                                                            | 1-20                  |
| A         | SEONG M. ET AL., Simultaneous blood flow and blood oxygenation measurements using a combination of diffuse speckle contrast analysis and near-infrared spectroscopy., <i>Journal of Biomedical Optics</i> , 17 February 2016, Vol. 21, No. 2, pages 027001: pages 1-5<br>[Retrieved on 2020-07-24] <DOI: 10.1117/1.JBO.21.2.027001><br>Abstract; Section 2 | -                     |

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\*Special categories of cited documents:

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Date of the actual completion of the international search

24/07/2020

(day/month/year)

Date of mailing of the international search report

11/08/2020

(day/month/year)

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2020/050157

**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                           | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | US 2018/0103861 A1 (SUTIN J. ET AL.) 19 April 2018<br>Whole document, particularly para. [0058], [0062]-[0069], [0072], [0073], [0078], [0086]                                                                                                                                                                                                               | -                     |
| A         | HE L. ET AL., Using optical fibers with different modes to improve the signal-to-noise ratio of diffuse correlation spectroscopy flow-oximeter measurements. <i>J Biomed Opt</i> , 1 March 2013, Vol. 8, No. 3, pages 037001: pages 1-10<br>[Retrieved on 2020-07-24] <DOI: 10.1117/1.JBO.18.3.037001><br>Whole document, particularly Sections 2.1, 2.2 & 4 | -                     |
| A         | WANG D. ET AL., Fast blood flow monitoring in deep tissues with real-time software correlators. <i>Biomedical Optics Express</i> , 3 February 2016, Vol. 7, No. 3, pages 776-797<br>[Retrieved on 2020-07-24] <DOI: 10.1364/BOE.7.000776><br>Whole document                                                                                                  | -                     |

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/SG2020/050157**

*Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.*

| Patent document cited in search report | Publication date | Patent family member(s)                                                                                                                                                                                                                                                    | Publication date                                                                                                                                                                                 |
|----------------------------------------|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| WO 2014/116483 A1                      | 31/07/2014       | HK 1218849 A1<br>CN 105188523 A<br>BR 112015017456 A2<br>SG 11201505620Y A<br>AU 2014209741 A1<br>JP 2019217352 A<br>MX 2015009381 A<br>US 2014/0206980 A1<br>AU 2018260946 A1<br>RU 2015133309 A<br>KR 20150135241 A<br>JP 2016509509 A<br>CA 2898708 A1<br>EP 2948052 A1 | 17/03/2017<br>23/12/2015<br>11/07/2017<br>28/08/2015<br>27/08/2015<br>26/12/2019<br>25/01/2016<br>24/07/2014<br>29/11/2018<br>03/03/2017<br>02/12/2015<br>31/03/2016<br>31/07/2014<br>02/12/2015 |
| US 2018/0103861 A1                     | 19/04/2018       | CN 107613851 A<br>JP 2018510726 A<br>US 2018/0070831 A1<br>WO 2016/164891 A1<br>CN 107613858 A<br>WO 2016/164894 A1<br>JP 2018517443 A                                                                                                                                     | 19/01/2018<br>19/04/2018<br>15/03/2018<br>13/10/2016<br>19/01/2018<br>13/10/2016<br>05/07/2018                                                                                                   |