(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 June 2017 (29.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/107921 A1

(51) International Patent Classification:
A61B 5/0205 (2006.01) *A61B 5/0295* (2006.01)

(21) International Application Number:
PCT/CN2016/111298

(22) International Filing Date:
21 December 2016 (21.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/270,971 22 December 2015 (22.12.2015) US

(71) Applicant: **THE CHINESE UNIVERSITY OF HONG KONG** [CN/CN]; Shatin, New Territories, Hong Kong (CN).

(72) Inventors: **ZHAO, Ni**; Apt 302, Building 12, Shenda Xincun, Shenzhen, Guangdong (CN). **ZHANG, Yuanting**; 9D, Block 7, Monte, Vista, Ma On Shan, Hong Kong (CN). **LIU, Jing**; 153# Xi Men Community, Xihuan Road, Jingzhou District, Jingzhou, Hubei (CN). **DING, Xiaorong**; Room 502, Unit 1, Building 2 of Ming Yuan, Jincheng Garden, No. 289 Shuhan Rd, Jinniu District, Chengdu, Sichuan (CN). **DAI, Wenxuan**; Rm 102, No. 300 Huxili Road, Jiangshan, Zhejiang (CN). **LI, Yao**; Room 201, Apt 1, Building 7, Qianhui Community, Dawukou, Shizuishan, Ningxia (CN). **YUAN, Shanshan**; 3-304, Cuiyuan Garden, North District of XilingXia, Liantang, Luohu District, Shenzhen, Guangdong (CN).

(74) Agent: **INSIGHT INTELLECTUAL PROPERTY LIMITED**; 19 A, Tower A, InDo Building, No. 48A Zhichun Road, Haidian District, Beijing 100098 (CN).

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

[Continued on next page]

(54) Title: METHOD FOR MEASURING CARDIOVASCULAR AND RESPIRATORY PARAMETERS BASED ON MULTI-WAVELENGTH PHOTOPLETHYSMOGRAPHY

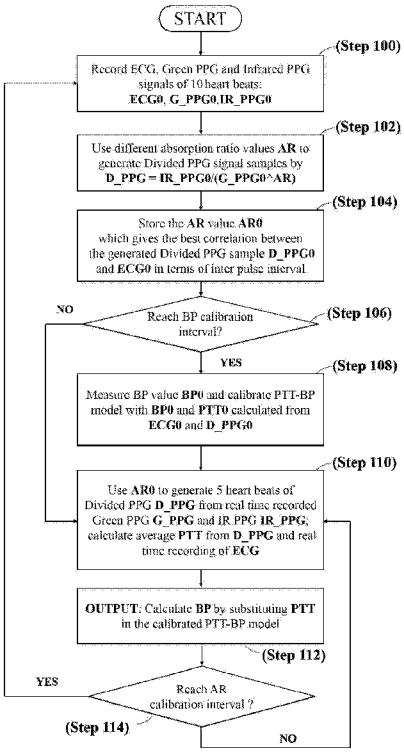

FIG. 6

(57) Abstract: Accurate and effective methods for measuring cardiovascular and respiratory parameters are provided. The method for deriving a depth-specific photoplethysmography (PPG) signal from multi-wavelength PPG signals includes choosing light wavelength combinations, calibrating a multi-layer light-tissue interaction model referring to a physiological signal, and generating the depth-specific PPG signal from the multi-wavelength PPG signals based on the calibrated light-tissue interaction model. The disclosed method for cuff-less blood pressure measurement includes recording a physiological signal and multi-wavelength PPG signals of a predetermined body part, deriving the depth-specific PPG signal reflecting the arterial blood volume with the physiological signal as a reference, calculating the pulse transit time (PTT) from the physiological signal and the derived arterial blood PPG signal, and calculating the blood pressure from the calibrated PTT and blood pressure relationship.

WO 2017/107921 A1

TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

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

METHOD FOR MEASURING CARDIOVASCULAR AND RESPIRATORY PARAMETERS BASED ON MULTI-WAVELENGTH PHOTOPLETHYSMOGRAPHY

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No. 62/270,971, filed December 22, 2015, the disclosure of which is hereby incorporated by reference in its entirety, including all figures, tables and drawings.

FIELD OF THE INVENTION

This invention relates to methods for measuring cardiovascular and respiratory parameters using a depth-specific photoplethysmography (PPG) signal derived from multi-wavelength PPG.

BACKGROUND

Photoplethysmography (PPG) is a simple and low-cost optical technique that can be used to detect blood volume changes in the microvascular bed of tissue and estimate cardiovascular and respiratory parameters. A PPG sensor system typically includes a light source and a light detector, and infrared (IR) light emitting diodes (LEDs) are usually used as the light emitting component. PPG is often used to make non-invasive measurements at the skin surface. The accuracy of extracting cardiovascular- and respiratory-related information from the PPG signals, however, is usually not satisfactory due the PPG signal being generated from a single-wavelength light that can only provide the overall blood volume changes along the light penetration path, but not the blood volume changes of a specific layer. For example, IR PPG measures the sum total of volume changes in any and all blood vessels (*e.g.*, large and small arteries, arterioles, capillaries, venules, and veins) throughout the skin, while the blood pulsation

signal of a specific layer like pure arterial blood volume changes cannot be separated out from the IR PPG signal. The inability to distinguish depth of single-wavelength PPG measurements intrinsically degrades the performance for estimating cardiovascular and respiratory parameters, which requires the physiological information of the blood vessels in certain depths.

Pulse Transit Time (PTT) is the time it takes the pulse pressure waveform to propagate through a length of the arterial tree, which is a promising method to measure blood pressure (BP) in a continuous and cuff-less manner. In PTT measurement, PPG is commonly used to mark the arrival of the pulse wave at a peripheral site. Because arteries and capillaries are different in blood vessel wall components and blood circulation paths, arterial blood volume waveform and capillary blood volume waveform have different morphologies, as well as a phase shift. In this sense, IR PPG or any other single-wavelength PPG signal is a superposition of various pulse wave functions of blood vessels in different types and depths, thus unable to reflect the pure arterial blood change in the deep layer of the skin. Therefore, PTT cannot be precisely measured with a single wavelength PPG in which the capillary blood pulsations fundamentally weaken PTT's BP tracking ability.

BRIEF SUMMARY OF THE INVENTION

Generating a depth-specific PPG signal that can reflect blood pulsation information within a specific tissue has great importance for measuring cardiovascular and respiratory parameters.

The instant invention provides accurate and effective methods for measuring cardiovascular and respiratory parameters, which can include deriving a depth-specific photoplethysmography (PPG) signal from multi-wavelength PPG signals. Deriving the depth-specific PPG signal can include choosing light wavelength combinations, calibrating a multi-layer light-tissue interaction model referring to a physiological signal like electrocardiography (ECG), and generating the depth-specific PPG signal from the multi-wavelength PPG signals based on the calibrated light-tissue interaction model. The

generated depth-specific PPG signal can replace traditional single-wavelength PPG in various cardiovascular and respiratory applications with fundamentally improved performance. In addition, the instant invention also provides methods for measuring blood pressure using a depth-specific PPG signal, which is generated from infrared PPG (IR_PPG) and green PPG (G_PPG) to reflect the arterial blood volume pulsation.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will hereafter be described with reference to the accompanying drawings, wherein like reference numerals denote like elements.

Figure 1A shows a diagram of an element arrangement of a sensor with multiple LEDs and one light detector, according to an embodiment of the subject invention.

Figure 1B shows a diagram of an element arrangement of a sensor with multiple LEDs and multiple light detectors, according to an embodiment of the subject invention.

Figure 2 shows the skin structure and the propagation of multi-wavelength light in the skin.

Figure 3A shows a two-layer light-tissue interaction model.

Figure 3B shows a three-layer light-tissue interaction model.

Figure 4 shows feature extraction for a two-layer model based on ECG, infrared (IR) PPG and Green (G) PPG signals, according to an embodiment of the subject invention.

Figure 5 shows an example result of blood pressure (BP) and Heart Rate (HR) tacking performance of a two-layer model with varying absorption ratio.

Figure 6 shows a flowchart of an operation of measuring BP based on ECG and multi-wavelength PPG, according to an embodiment of the subject invention.

DETAILED DESCRIPTION OF THE INVENTION

The instant invention provides accurate and effective methods for measuring cardiovascular and respiratory parameters by deriving depth-specific photoplethysmography (PPG) signals from multi-wavelength PPG signals, as well as methods of measuring blood pressure using depth-specific PPG signals that are generated from infrared PPG (IR_PPG) and green PPG (G_PPG) to reflect arterial blood volume pulsation.

In preferred embodiments, the methods of the instant invention provide accurate blood pressure measurements for clinical applications in bedside monitors and ambulatory health monitors. Advantageously, the methods of the instant invention provide more accurate measurements of PTT along the arteries as compared to conventional single-wavelength PPG methods.

The foregoing and other advantages of the invention will appear from the following description. In the description, reference is made to the accompanying drawings which form a part hereof, and in which there is shown by way of illustration a preferred embodiment of the invention. Such embodiment does not necessarily represent the full scope of the invention, however, and reference is made therefore to the claims and herein for interpreting the scope of the invention.

In an embodiment, depth-specific PPG signal generation can include one or more of the following steps:

1. Determination of the range of target measuring depth or layer of the tissue based on the parameter to estimate;

2. Selection of wavelength combinations of PPG signals for deriving the depth-specific PPG signal; and/or

3. Extraction of the derived depth-specific PPG signals from the multi-wavelength PPG signals, wherein the depth-specific signals are proportional to the blood volume within a depth range beneath the measured site of the predetermined body part.

In many embodiments, the multi-wavelength PPG sensor can include a light source that emits light of two or more wavelengths, and a light detector. The light of different wavelengths penetrates the tissue to different depths depending on the absorption characteristics of the tissue layers, and different amounts of light of each wavelength come out of the tissue and are detected by the light detector. In some embodiments, the light source is one LED that can emit light in different wavelengths. In other embodiments, the light source is comprised of multiple small-sized LEDs that are packed closely, each LED emitting light at a different wavelength.

In some embodiments, the light detector comprises one photodetector with a wide wavelength response range whereby a multiplexer is used to separate the PPG signal of each wavelength. In other embodiments, the light detector comprises multiple detectors with high wavelength selectivity whereby multi-wavelength light can illuminate at the same time.

In preferred embodiments, the multi-wavelength PPG sensor emits multi-wavelength light to the peripheral vasculature in a predetermined body part and measures the intensity of the reflected light of each wavelength. The predetermined body part for measurement includes but is not limited to finger, thumb, hand, arm, abdomen, foot, or any body part directly associated with the peripheral vasculature.

Embodiments of the instant invention provide an algorithm for extracting the depth-specific PPG signals from multi-wavelength PPG signals. In some embodiments, multi-wavelength light is emitted from the light source, and light of different wavelengths penetrates the tissue to different depths. For example, PPG signals generated from the short penetrating light are considered to reflect the blood volume pulsation of the superficial layer of the tissue, while PPG signals generated from deep penetrating light are considered to reflect the blood volume pulsation at a deeper layer of the tissue. Advantageously, green or blue light is short penetrating light and red or infrared light is deep penetrating light.

In preferred embodiments, the methods of the instant invention measure the blood volume pulsation in the deep tissue layers only by removing the superficial blood pulsation from the deep penetration PPG signal. The methods are based on the Beer-Lambert's Law and

provide that the depth-specific PPG is derived by dividing the deep-penetrating PPG signal amplitude by the short-penetrating PPG signal amplitude to the power of the absorption ratio (AR) of the two wavelengths.

In further embodiments, methods of the instant invention provide that the AR between different light wavelengths in the algorithm is determined within the value range that generates depth-specific PPG signals with a constant time offset to a preassigned reference physiological signal. In many embodiments, the reference physiological signal is an electrocardiography (ECG) signal. In other embodiments, the reference physiological signal is the same short wavelength PPG signal that is used to generate the depth-specific PPG signal. In yet other embodiments, the reference physiological signal is a ballistocardiography (BCG) signal or an impedance cardiography (ICG) signal.

In many embodiments, a method for cuff-less blood pressure (BP) measurement based on multi-wavelength PPG can include one or more of the following steps:

1. Recording an ECG signal and multi-wavelength PPG signals of a predetermined body part simultaneously;

2. Choosing the wavelength combination for deriving arterial blood PPG signals, wherein the wavelength combination includes short penetrating light that is considered to reflect the blood volume pulsation of the superficial layer of the tissue and deep penetrating light that is considered to reflect the blood volume pulsation at a deeper layer of the tissue;

3. Determining the light ARs for deriving an arterial blood PPG signal with the recorded ECG signal as a reference, wherein the AR selected from a value range that provides an inter beat interval (IBI) of the derived arterial blood PPG (D_PPG) that stably correlates with the IBI signal of the ECG is chosen;

4. Calculating the PTT using the ECG signal and arterial blood PPG signal derived from the multi-wavelength PPG; and

5. Calculating the BP by the calibrated BP-PTT model.

In preferred embodiments, the method for cuff-less BP measurement of the instant invention provides an arterial blood PPG signal for PTT calculation that improves PTT's tracking ability of BP.

In some embodiments, the arterial blood pressure is derived from two wavelengths PPG or three wavelengths PPG according to the accuracy requirement and computing ability of the system. Advantageously, the methods of the instant invention have no limitation in the BP estimation model from PTT. The relationship between PTT and BP can be linear, nonlinear, or adopt other complicated forms. In some embodiments, the ECG signal is replaced by other signals (including, but not limited to, short wavelength PPG, BCG signals and ICG signals) as the reference signal in determining AR values and calculating PTT.

In many embodiments, the methods of the instant invention are implemented in various physiological monitoring applications, such as smartwatches, fitness bands, and other wearable devices and bedside monitors. In some embodiments, a method can be implemented in wearable platforms, including but not limited to an Apple watch, LG Watch Urbane, and/or Motorola Moto 360 smart watch, by adding one light source to the wearable platform. Advantageously, the methods of the instant invention provide wider user acceptance compared to other wearable platforms due to improved accuracy based on the use of multi-wavelength PPG signals. Furthermore, the realization of the algorithm of the instant invention is more feasible to be implemented in smart wearable devices because it requires less computing power.

Multi-Wavelength PPG Sensor Probes.

Referring to Figure 1, in one embodiment, a multi-wavelength PPG sensor probe **10** of the instant invention has a multi-wavelength light emitter **12** and a light detector **22**. Preferably, the multi-wavelength light emitter **12** and the light detector **22** are small in size and/or flexible so as to improve the conformity to the skin and comfort for the user. Advantageously, as the sensor measures PPG signals in reflection mode, it can be placed on various body surfaces, such as a fingertip, wrist, thumb, hand, arm, abdomen, foot, earlobe, or any other body part directly associated with the peripheral vasculature.

In some embodiments, the multi-wavelength light emitter **12** of the instant invention includes multiple LEDs, for example, a blue LED **14**, an infrared LED **16**, a green LED **18**, and a yellow LED **20** (Figure 1). In preferred embodiments, the LEDs are closely packed, thus ensuring they illuminate the same tissue.

In some embodiments, the light detector **22** is a photodiode **24** with a wide spectral responsivity range (Figure 1A). In one non-limiting example, a method of the instant invention provides sensors to acquire the multi-wavelength PPG signals, wherein the sensors' blue LED **14**, infrared LED **16**, green LED **18**, and yellow LED **20** are turned on such that the mixed signals from the photodiode **24** that contains the reflected light information of different wavelengths are separated into four channels by a demultiplexer. In preferred embodiments, the distance D between the light emitter **12** and the light detector **22** is set appropriately to achieve good signal-to-noise ratio.

In other embodiments, the light detector **22** can include multiple light detectors with high selectivity to a certain band of light wavelength. In one non-limiting example, the light detector **22** includes a blue light sensitive light detector **24**, a red light sensitive light **detector** 26, a green light sensitive light detector **28**, and a yellow light sensitive light detector **30**. Advantageously, light detectors **24**, **26**, **28**, and **30** generate the PPG signals corresponding to the blue LED **14**, red LED **16**, green LED **18**, and yellow LED **20**, respectively, without a multiplexer. In preferred embodiments, the light detectors are packed closely to ensure that the PPG signals are measured from the same body part.

Multi-Wavelength Light Interaction with Tissue.

Referring to Figure 2, skin has three layers: the epidermis **32**, the outmost layer; the dermis **34**, the layer under the epidermis **32** that is the connective tissue layer of skin; and the hypodermis **36**, the layer underneath the dermis that merges with it and mainly contains adipose tissue. The arteries **40** supplying the skin are located deep in the hypodermis **36**. Branches of the arteries **40**, called arterioles **51**, pass upwards to form a deep and a superficial plexus.

Capillaries **38** are found beneath the epidermis **32**, and are linked to the arterioles **51** and venules **52**.

When light reaches the tissue, it is reflected, absorbed, scattered, and transmitted. As the light scattering and absorption coefficient of the tissue varies with the wavelength, the penetration ability of different light wavelengths is also different.

In a non-limiting example of a method of the instant invention, blue light **44**, green light **46**, yellow light **48**, and infrared light **50** emitted from the light emitter **12** propagate within different tissue layers, and the light coming out of the tissue is detected by the light detector **22**. As most of the blue light **44** and green light **46** are scattered by the epidermal layer **32**, the penetration depth of blue light **44** may be only about 1.2 mm, while green light **46** penetrates a little deeper than blue light **44**. The thickness of the epidermis can be about 0.8 mm to about 1.5 mm. Therefore, blue light **44** can only reach the capillaries, and green light **44** can penetrate through the epidermis **32** and reach some of the arterioles **51** in the dermis **34**. Longer wavelength light like yellow light **48**, can penetrate deep into the dermis and reach a large portion of the arterioles **51**. In contrast, red light or infrared light **50** with strong penetration ability can go through the whole skin and reach the deep arteries **40** in the hypodermis **36**.

Establishment of a Multi-Layer Models for Extraction of Pure Arterial Blood Volume.

Referring to Figure 3A, in some embodiments, a method of the instant invention provides a two-layer model that extracts pure arterial blood volume, based on the physiological facts of the light-tissue interaction. In the two-layer model, the first layer **54** represents the epidermis as a homogenous layer highly perfused by capillary blood, and the second layer **53** represents the dermis **34** and hypodermis **36** (Figure 2) as a homogenous layer highly perfused by arterial blood (Figure 3A). In the two-layer model of the instant invention, light of wavelength **λ2** penetrates the first layer **54** and reaches a portion of the second layer **53**, while light of wavelength **λ1** propagates through both layer **54** and layer **53**. The following parameters in the model are provided:

V_c: Volume of capillary blood in the capillary blood layer **54**

V_a: Volume of arterial blood in the arterial blood layer **53**

ε_{c1}: Molar extinction coefficient of capillary blood in light wavelength **λ1**

ε_{c2}: Molar extinction coefficient of capillary blood in light wavelength **λ2**

ε_{a1}: Molar extinction coefficient of arterial blood in light wavelength **λ1**

ε_{a2}: Molar extinction coefficient of arterial blood in light wavelength **λ2**

k_1: The portion of arterial blood in layer 52 reached by light **λ2**

$I_{\lambda 1}$: Intensity of the incident light **λ1**

$I'_{\lambda 1}$: Intensity of light **λ1** coming out from the surface

$I_{\lambda 2}$: Intensity of the incident light **λ2**

$I'_{\lambda 2}$: Intensity of light **λ2** coming out from the surface

The two-layer model, based on Beer-Lambert's Law that relates the attenuation of light to the properties of the material through which the light is traveling, can provide pure arterial blood volume information that is extracted by removing the capillary blood volume information registered by **λ2** PPG from the **λ1** PPG signal. The light intensity of light **λ1** and **λ2** coming out from the surface, namely the **λ1** PPG amplitude and **λ2** PPG amplitude, are described in Equation 1 and Equation 2.

$$I'_{\lambda 1} = I_{\lambda 1} e^{-\varepsilon_{c1} V_c} e^{-\varepsilon_{a1} V_a} \quad \text{(Eq. 1)}$$

$$I'_{\lambda 2} = I_{\lambda 2} e^{-\varepsilon_{c2} V_c} e^{-\varepsilon_{a2} k_1 V_a} \quad \text{(Eq. 2)}$$

The arterial blood volume can be expressed by Equation 3.

$$\frac{I'_{\lambda 1}}{\left(I'_{\lambda 2}\right)^{\varepsilon_{c1}/\varepsilon_{c2}}} = \frac{I_{\lambda 1}}{\left(I_{\lambda 2}\right)^{\varepsilon_{c1}/\varepsilon_{c2}}} e^{-(\varepsilon_{a1} - k_1 \varepsilon_{a2} \varepsilon_{c1}/\varepsilon_{c2}) V_a} \quad \text{(Eq. 3)}$$

In Equation 3, as the terms $\frac{I_{\lambda 1}}{\left(I_{\lambda 2}\right)^{\varepsilon_{c1}/\varepsilon_{c2}}}$ and $-(\varepsilon_{a1} - k_1 \varepsilon_{a2} \varepsilon_{c1} / \varepsilon_{c2})$ can be treated as constants, the D_PPG signal with amplitude $\frac{I_{\lambda 1}}{\left(I_{\lambda 2}\right)^{\varepsilon_{c1}/\varepsilon_{c2}}} e^{-(\varepsilon_{a1} - k_1 \varepsilon_{a2} \varepsilon_{c1}/\varepsilon_{c2}) V_a}$ can reflect the pure arterial blood information.

Referring to Figure 3B, in some embodiments, methods of the instant invention can provide a three-layer model for a more accurate estimation of the arterial blood volume. Compared to the two-layer model in Figure 3A, the three-layer model provides an additional homogenous layer representing the superficial tissue **56**. Light of wavelength **λ3** can penetrate through the tissue layer **56** and a portion of the capillary blood layer **54**. Other parameters additional to those included in the two-layer model are:

V_t: Volume of tissue in the first layer **56**

ε_{c3}: Molar extinction coefficient of capillary blood in light wavelength **λ3**

ε_{t1}: Molar extinction coefficient of tissue in light wavelength **λ1**

ε_{t2}: Molar extinction coefficient of tissue in light wavelength **λ2**

ε_{t3}: Molar extinction coefficient of tissue in light wavelength **λ3**

k_2: The portion of capillary blood layer 54 reached by light **λ2**

$I_{\lambda 3}$: Intensity of the incident light **λ3**

$I'_{\lambda 3}$: Intensity of light **λ3** coming out from the surface

Similarly, **λ1** PPG, **λ2** PPG, and **λ3** PPG signals measured at the skin surface can be expressed by Equation 4, Equation 5, and Equation 6, respectively.

$$I'_{\lambda 1} = I_{\lambda 1} e^{-\varepsilon_{t1} V_t} e^{-\varepsilon_{c1} V_c} e^{-\varepsilon_{a1} V_a} \quad \text{(Eq. 4)}$$

$$I'_{\lambda 2} = I_{\lambda 2} e^{-\varepsilon_{t2} V_t} e^{-\varepsilon_{c2} V_c} e^{-\varepsilon_{a2} k_1 V_a} \quad \text{(Eq. 5)}$$

$$I'_{\lambda 3} = I_{\lambda 3} e^{-\varepsilon_{t3} V_t} e^{-\varepsilon_{c3} k_2 V_c} \quad \text{(Eq. 6)}$$

By eliminating the tissue volume information registered in λ3 PPG and the capillary blood volume information registered in λ2 PPG from the λ1 PPG that contains the volume information of all the layers, the arterial blood information can be calculated in Equation 7.

$$\frac{I'_{\lambda 1}}{\left(I'_{\lambda 3}\right)^{\alpha_1 - \alpha_2 \alpha_3} \left(I'_{\lambda 2}\right)^{\alpha_3}} = \frac{I_{\lambda 1}}{\left(I_{\lambda 3}\right)^{\alpha_1 - \alpha_2 \alpha_3} \left(I_{\lambda 2}\right)^{\alpha_3}} e^{-\left(\varepsilon_{a3} - \varepsilon_{a2} k_2 \cdot \alpha_3\right) \cdot V_a} \quad \text{(Eq. 7)}$$

where $\alpha_1 = \frac{\varepsilon_{t1}}{\varepsilon_{t3}}$, $\alpha_2 = \frac{\varepsilon_{t2}}{\varepsilon_{t3}}$ and $\alpha_3 = \frac{\varepsilon_{c1} - \varepsilon_{c3} k_2 \alpha_1}{\varepsilon_{c2} - \varepsilon_{c3} k_2 \alpha_2}$.

In Equation 7, as the term $\frac{I_{\lambda 1}}{\left(I_{\lambda 3}\right)^{\alpha_2-\alpha_1\alpha_3}\left(I_{\lambda 2}\right)^{\alpha_3}}$ and $-\left(\varepsilon_{a3}-\varepsilon_{a2}k_2\cdot\alpha_3\right)$ can be treated as constants, the D_PPG signal with amplitude $\frac{I_{\lambda 1}}{\left(I_{\lambda 3}\right)^{\alpha_1-\alpha_2\alpha_3}\left(I_{\lambda 2}\right)^{\alpha_3}}e^{-\left(\varepsilon_{a3}-\varepsilon_{a2}k_2\cdot\alpha_3\right)\cdot V_a}$ can reflect the pure arterial blood information. Advantageously, three-layer models of the instant invention consider the influence of three tissue layers, including the superficial tissue, during light propagation, thus providing clearer arterial blood volume information compared to the two-layer models.

In preferred embodiments, the multi-layer models of the instant invention provide volume change information of a certain layer, namely a depth-specific PPG signal, derived from multi-wavelength PPG signals. In some embodiments, the multi-layer models of the instant invention provide volume change information of the capillary blood layer. The multi-layer models can provide volume change information of the arterial blood layer. Advantageously, the depth-specific PPG signals fundamentally improve the performance of PPG-based physiological monitoring applications.

In one non-limiting example, methods of the instant invention provide the D_PPG from IR_PPG and G_PPG, where D_PPG reflects the arterial blood pulsation. Advantageously, the D_PPG shows an improved correlation between PTT and BP. Referring to Figure 4, in many embodiments, the operation of deriving D_PPG from ECG, IR_PPG and G_PPG is based on the two-layer model. In preferred embodiments, the D_PPG is derived as the ratio of the IR_PPG amplitude and the G_PPG amplitude to a power of the AR, that is $\frac{IR\_PPG}{\left(G\_PPG\right)^{AR}}$. In a further preferred embodiment, the ECG signal is used as a reference to decide the optimal value range of AR. Advantageously, because the periodical pulsations of the ECG and PPG signals are all generated by the beating heart, the IBI of the D_PPG signal matches the IBI of the ECG to a certain extent if the D_PPG only contains the arterial blood pulsation. As D_PPG can reflect pure arterial blood pulsation with a range of AR values, the synchrony level between IBI of the ECG and IBI of the D_PPG derived with these AR values will become nearly unchanged. The

ECG_IBI is defined as the time interval between the R peaks of the ECG, while the IR_IBI, G_IBI and D_IBI are defined as peak intervals of the respective waveforms (Figure 4). The PTT is defined as the time interval between the R peak of the ECG waveform and the peak of the PPG waveform during the same heart cycle. Hence, IP_PTT, G_PTT, and D_PTT denote the PTT calculated from IR_PPG, G_PPG, and D_PPG respectively.

Referring to Figure 5, in many embodiments, the correlation coefficients between ECG_IBI and D_IBI can be used to determine a AR value range for deriving a D_PPG signal. The absolute correlation coefficients between D_PTT and DBP (diastolic blood pressure); and D_PTT and SBP (systolic blood pressure) with varying ARs are also shown in Figure 5. When AR equals zero, the D_PPG equals IR_PPG. In further embodiments, the correlation coefficient between ECG_IBI and D_IBI remains nearly unchanged in a certain range of AR value, at the same time, the correlation coefficient between D_PTT and DBP; and D_PTT and SBP will also stay stable in this AR value range. For example, the correlation relationship between ECG_IBI and D_IBI stays stable when AR is larger than 2.8. Meanwhile, strong and improved correlation coefficients are observed between D_PTT and DBP; and D_PTT and SBP, respectively, compared to those between IR_PTT and SBP; and IR_PTT and DBP (Figure 5).

In further preferred embodiments, the methods of the instant invention use the ECG as reference to indicate the optimal AR value range for D_PPG. In other embodiments, the ECG signals are replaced by other physiological signals, including, but not limited to, short wavelength PPG, BCG and ICG.

In a preferred non-limiting example, the BP can be monitored with ECG and multi-wavelength PPG sensors following the operation described in the work flow in Figure 6. ECG, G_PPG, and IR_PPG signals can be recorded for multiple heart beats (*e.g.*, 10 heart beats) as ECG0, G_PPG0, and IR_PPG0 (Step **100**). The recording period in Step **100** can be adjusted according to the specific application. Various D_PPG samples can be generated from IR_PPG0 and G_PPG0 using the relation IR_PPG0/(G_PPG0^AR) with different AR values (Step **102**). The correlation coefficients between D_IBI of the D_PPG samples and ECG_IBI

of ECG0 can be calculated, and the AR value that generates the D_PPG sample D_PPG0 best correlated with ECG0 in terms of IBI, can be stored as AR0 for deriving workable D_PPG signals in later steps (Step **104**). It can be determined whether the D_PPG values obtained using the procedure of the previous steps gives D_PTT values that fall within an interval that is suitable for BP calibration (Step **106**), wherein the calibration time interval and/or changes in physiological parameters, such as the heart rate exceeding a predetermined threshold, are considered. That is, the judgement condition can be whether the calibration time interval is reached, or whether changes in physiological parameters like heart rate exceed the predetermined thresholds.

In some embodiments, in which the BP calibration conditions are met, absolute BP values BP0 can be measured with the aid of certain BP measurement devices, and BP0 together with D_PTT0, which is the average D_PTT value calculated from ECG0 and D_PPG0, can be used to generate a calibrated PTT-BP model (Step **108**).

In other embodiments, in which BP calibration conditions are not met in Step **106**, ECG, IR_PPG, and G_PPG signals can be recorded (*e.g.*, for every 5 heart beats) as ECGn, IR_PPGn and G_PPGn (Step **110**). The recording period can be adjusted according to the specific application. D_PPGn signals can be generated from IR_PPGn and G_PPGn with AR0, and the average D_PTTn can be calculated from D_PPGn and ECGn.

The BP can be estimated as BPn from D_PTTn by substituting D_PTTn in the calibrated PTT-BP model. It can be determined whether the calibration interval for AR is reached, wherein the judgment criteria can be a time interval or the threshold for changes of the parameter such as the estimated BP value BPn. In certain embodiments, if the AR calibration condition is not met, Step **110** will be executed to measure BP with the stored AR value AR0 again. In other embodiments, if the AR calibration condition is met, the series of processing steps starting with Step **100** will be repeated to fine-tune the process.

In certain embodiments, the process of measuring blood pressure of the instant invention (see Figure 6) can be modified to adopt different models, different light wavelength

combinations, and/or different cardiac signals (*e.g.*, signals other than ECG). In some embodiments, the workflow and/or measuring principles can also be modified to measure other cardiovascular and respiratory parameters with multi-wavelength PPG.

"Cardiorespiratory parameters" include, but are not limited to, respiration rate, blood pressure, and cardiac rhythm.

"Cardiac disease states" include, but are not limited to, heart failure, arrhythmia, coronary artery disease, cardiomyopathy and endocarditis.

The methods and processes described herein can be embodied as code and/or data. The software code and data described herein can be stored on one or more computer-readable media, which may include any device or medium that can store code and/or data for use by a computer system. When a computer system reads and executes the code and/or data stored on a computer-readable medium, the computer system performs the methods and processes embodied as data structures and code stored within the computer-readable storage medium.

It should be appreciated by those skilled in the art that computer-readable media include removable and non-removable structures/devices that can be used for storage of information, such as computer-readable instructions, data structures, program modules, and other data used by a computing system/environment. A computer-readable medium includes, but is not limited to, volatile memory such as random access memories (RAM, DRAM, SRAM); and non-volatile memory such as flash memory, various read-only-memories (ROM, PROM, EPROM, EEPROM), magnetic and ferromagnetic/ferroelectric memories (MRAM, FeRAM), and magnetic and optical storage devices (hard drives, magnetic tape, CDs, DVDs); network devices; or other media now known or later developed that is capable of storing computer-readable information/data. Computer-readable media should not be construed or interpreted to include any propagating signals. A computer-readable medium of the subject invention can be, for example, a compact disc (CD), digital video disc (DVD), flash memory device, volatile memory, or a hard disk drive (HDD), such as an external HDD or the HDD of a computing device, though embodiments are not limited thereto. A computing device can be, for example, a laptop

computer, desktop computer, server, cell phone, or tablet, though embodiments are not limited thereto.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

All patents, patent applications, provisional applications, and publications referred to or cited herein (including those in the "References" section, if present) are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

CLAIMS

What is claimed is:

1. A method for deriving a blood volume pulsation signal within a certain depth of a predetermined body part, the method comprising the steps of:

determining a range of target measuring depth or layer of tissue in the predetermined body part;

selecting wavelength combinations of PPG signals to derive a PPG signal specific for the range of target depth or layer of tissue;

emitting light of two or more different wavelengths to the predetermined body part and measuring multi-wavelength photoplethysmograghy (PPG) signals; and

extracting the derived depth-specific PPG signal from the multi-wavelength PPG signals, wherein the derived depth-specific PPG signal is proportional to the blood volume within the range of target depth or layer of tissue in the predetermined body part.

2. The method according to claim 1, wherein the derived depth-specific PPG signal is proportional to the blood volume in the vasculature within the range of target depth or layer of tissue in the predetermined body part.

3. The method according to claim 2, wherein the derived depth-specific PPG signal is proportional to the blood volume in the arteries within the range of target depth or layer of tissue in the predetermined body part.

4. The method according to claim 1, wherein emitting light of two or more different wavelengths to the predetermined body part comprises using a multi-wavelength light emitter including multiple LEDs, and a light detector including a photodiode,

wherein the method further comprises:

detecting the light of multiple wavelengths coming out of the tissue of the predetermined body part in order; and

separating, by a demultiplexer, the mixed signal into light information from different wavelengths.

5. The method according to claim 1, further comprising detecting, by multiple light detectors, light of multiple wavelengths coming out of the tissue of the predetermined body part.

6. The method according to claim 1, wherein deriving the depth-specific PPG signal includes removing the blood volume pulsation profiles in the superficial layer detected by the shallow penetrating light from the blood volume pulsation profiles in the deep layer detected by the deep penetrating light.

7. The method according to claim 6, wherein removing blood volume pulsation profiles detected by the shallow penetrating light comprises the steps of:

building a multiple-tissue layer model based on the measured multi-wavelength PPG signals and the derived depth-specific PPG signal by incorporating parameters comprising light wavelengths, light absorption coefficients, and light penetration depths;

determining the light absorption ratios of different light wavelengths; and

deriving the depth-specific PPG signal that reflects the blood volume pulsation in a specific tissue depth from multi-wavelength PPG signals by substituting the light absorption ratios that reflect the difference of the tissue absorption characteristics of the different light wavelengths.

8. The method according to claim 7, wherein determining the light absorption ratios comprises selecting the absorption ratio value range that gives the constant correlation of the inter beat intervals between the derived depth-specific PPG signal and selected cardiac signals.

9. The method according to claim 7, wherein the multiple-tissue layer model is a two-tissue layer model and the derived depth-specific PPG signal with amplitude $\frac{I_{\lambda 1}}{\left(I_{\lambda 2}\right)^{\varepsilon_{c1}/\varepsilon_{c2}}} e^{-(\varepsilon_{a1}-k_1\varepsilon_{a2}\varepsilon_{c1}/\varepsilon_{c2})V_a}$ is obtained,

where $I'_{\lambda 1}$ is the intensity of light of a first wavelength coming out from the surface; $I'_{\lambda 2}$ is the intensity of light of a second wavelength different from the first wavelength coming out from the surface; V_a is the volume of arterial blood in the arterial blood layer; ε_{c1} is the molar extinction coefficient of capillary blood in the light of the first wavelength; and ε_{c2} is the molar extinction coefficient of capillary blood in the light of the second wavelength.

10. The method according to claim 7, wherein the multiple-tissue layer model is a three-tissue layer model and the derived PPG signal with amplitude $\frac{I_{\lambda 1}}{\left(I_{\lambda 3}\right)^{\alpha_1-\alpha_2\alpha_3}\left(I_{\lambda 2}\right)^{\alpha_3}} e^{-(\varepsilon_{a3}-\varepsilon_{a2}k_2\cdot\alpha_3)\cdot V_a}$ is obtained,

where $I'_{\lambda 1}$ is the intensity of light of a first wavelength coming out from the surface; $I'_{\lambda 2}$ is the intensity of light of a second wavelength different from the first wavelength coming out from the surface; $I'_{\lambda 3}$ is the intensity of light of a third wavelength different from both the first and second wavelengths coming out from the surface; V_a is the volume of arterial blood in the arterial blood layer

where $\alpha_1=\frac{\varepsilon_{t1}}{\varepsilon_{t3}}$, $\alpha_2=\frac{\varepsilon_{t2}}{\varepsilon_{t3}}$ and $\alpha_3=\frac{\varepsilon_{c1}-\varepsilon_{c3}k_2\alpha_1}{\varepsilon_{c2}-\varepsilon_{c3}k_2\alpha_2}$; ε_{t1} is the molar extinction coefficient of tissue in the light of the first wavelength; ε_{t2} is the molar extinction coefficient of tissue in the light of the second wavelength; ε_{t3} is the molar extinction coefficient of tissue in the light of the third wavelength; ε_{c3} is the molar extinction coefficient of capillary blood in the light of the third wavelength; and k_2 is the portion of capillary blood layer reached by the light of the second wavelength.

11. The method according to claim 7, further comprising using the depth-specific PPG signal to estimate at least one cardiorespiratory parameter selected from respiration rate, blood pressure, cardiac rhythm, and different cardiac disease states including heart failure, arrhythmia, coronary artery disease, cardiomyopathy, and endocarditis.

12. A method for cuff-less blood pressure measurement, the method comprising the steps of:

recording a physiological signal and multi-wavelength PPG signals of a predetermined body part;

building a multiple-tissue layer model between the recorded multi-wavelength PPG signals and a derived depth-specific PPG signal by incorporating parameters comprising light wavelengths, the light absorption coefficients of different tissues, and light penetration depths;

selecting the wavelength combination for deriving a depth-specific PPG signal reflecting the deep pure arterial blood volume changes, whereby the blood pulsation profile in the veins and capillaries embedded in the shallow tissue layer are removed;

determining the light absorption ratios of different light wavelengths;

deriving the arterial blood PPG signal with the physiological signal as a reference;

calculating the pulse transit time (PTT) from the physiological signal and the derived arterial blood PPG signal; and

calculating the blood pressure from the calibrated PTT and blood pressure relationship.

13. The method according to claim 12, wherein the physiological signal is an electrocardiogram (ECG) signal.

14. The method according to claim 12, wherein the physiological signal is a ballistocardiography (BCG) signal, an impedance cardiography (ICG) signal, or a short wavelength PPG signal.

15. The method according to claim 12, wherein determining the light absorption ratios comprises selecting the value range that gives a constant correlation of the inter beat intervals between the derived depth-specific PPG signal and the selected reference physiological signal.

16. An apparatus for deriving a blood volume pulsation signal within a certain depth of a predetermined body part, the apparatus comprising:

at least one processor; and

a memory storing instructions, which when executed by the at least one processor, cause the at least one processor to perform the method according to any one of claims 1-11.

17. A non-transitory computer storage medium storing a computer program, which when executed by one or more computers, cause the one or more computers to perform the method according to any one of claims 1-11.

18. An apparatus for cuff-less blood pressure measurement, the apparatus comprising:

at least one processor; and

a memory storing instructions, which when executed by the at least one processor, cause the at least one processor to perform the method according to any one of claims 12-15.

19. A non-transitory computer storage medium storing a computer program, which when executed by one or more computers, cause the one or more computers to perform the method according to any one of claims 12-15.

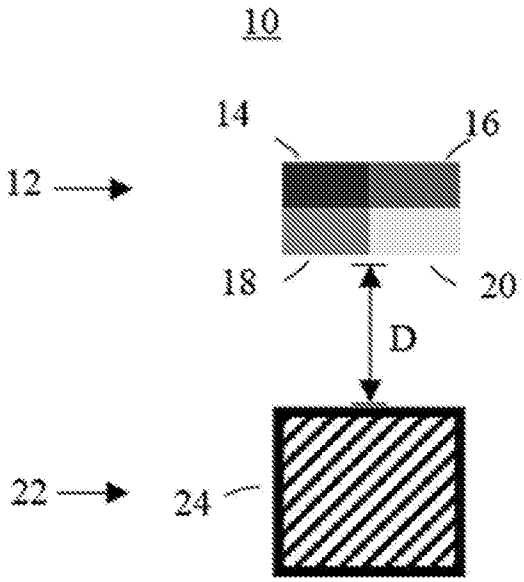

FIG. 1A

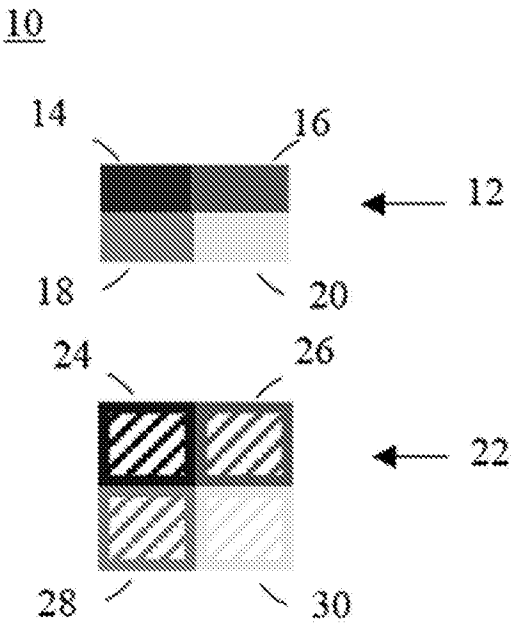

FIG. 1B

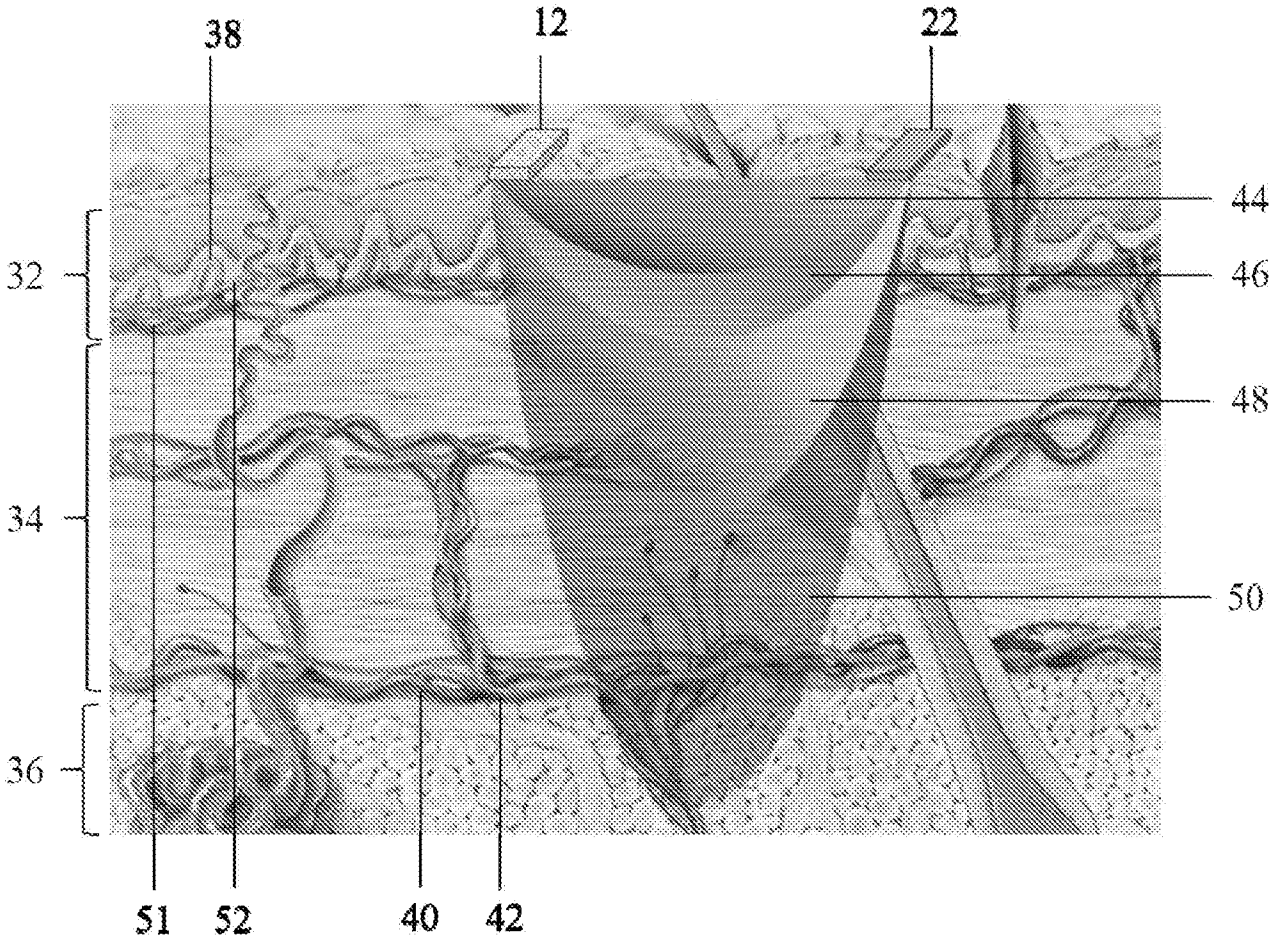

FIG. 2

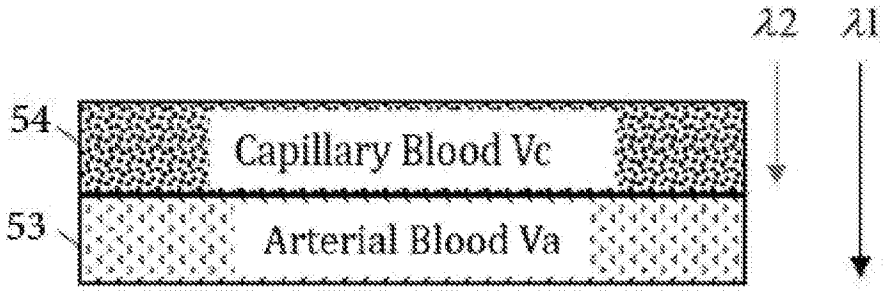
λ2
λ1
54
Capillary Blood Vc
53
Arterial Blood Va

FIG. 3A

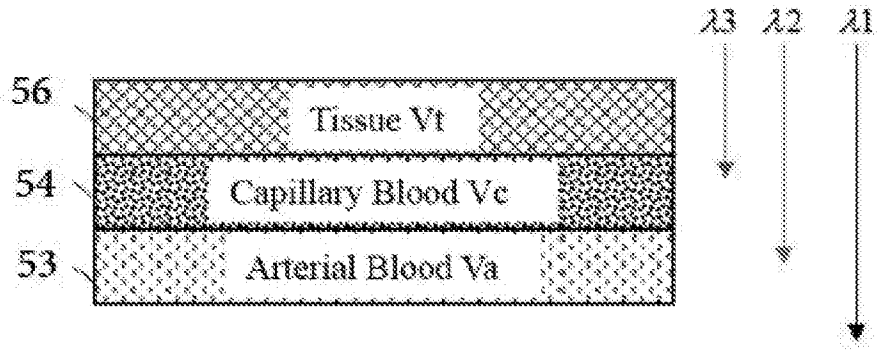
λ3
λ2
λ1
56
Tissue Vt
54
Capillary Blood Vc
53
Arterial Blood Va

FIG. 3B

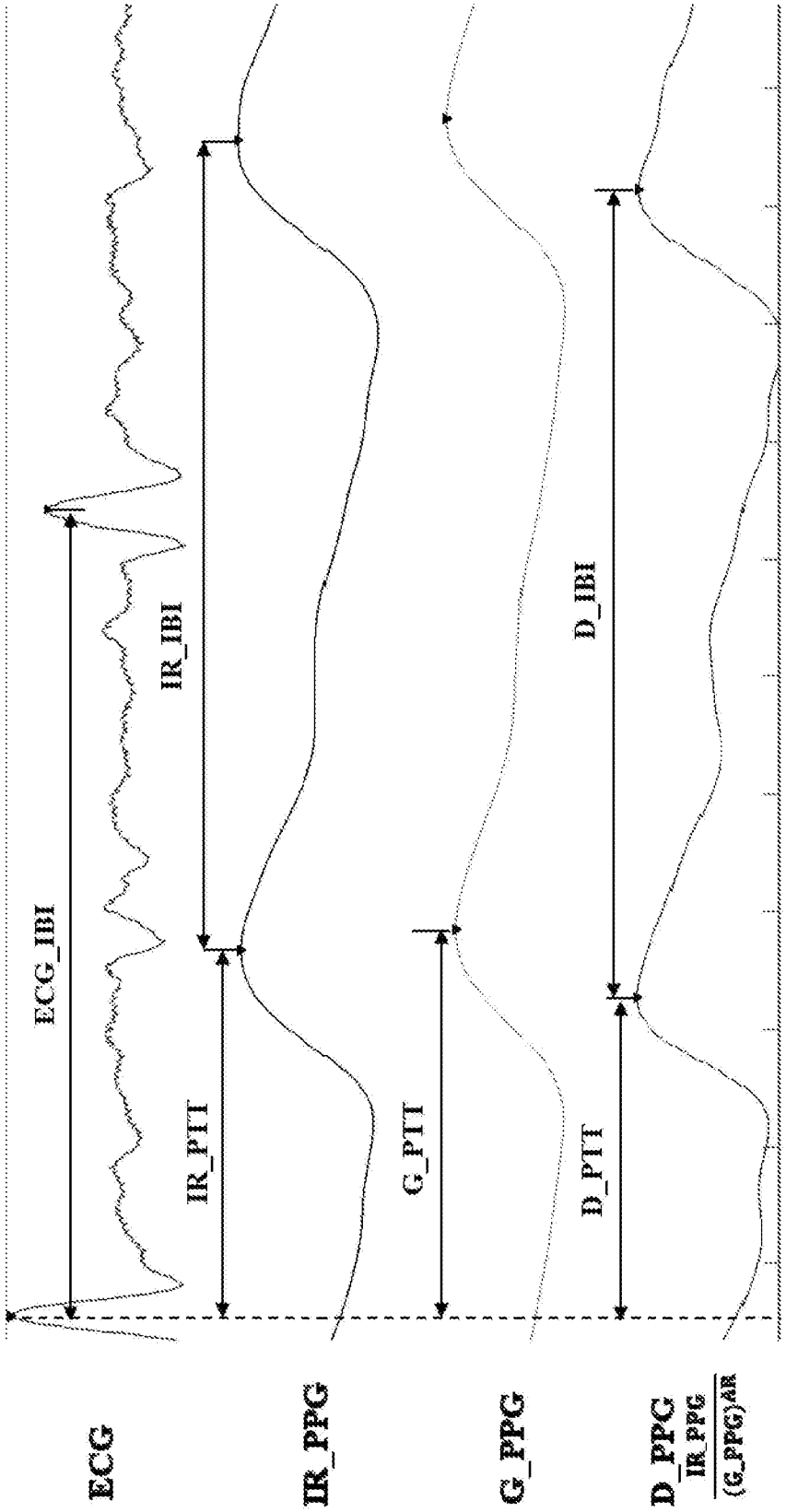
ECG_IBI
IR_IBI
IR_PTT
G_PTT
D_IBI
D_PTT
ECG
IR_PPG
G_PPG
D_PPG
IR_PPG / (G_PPG)^AR

FIG. 4

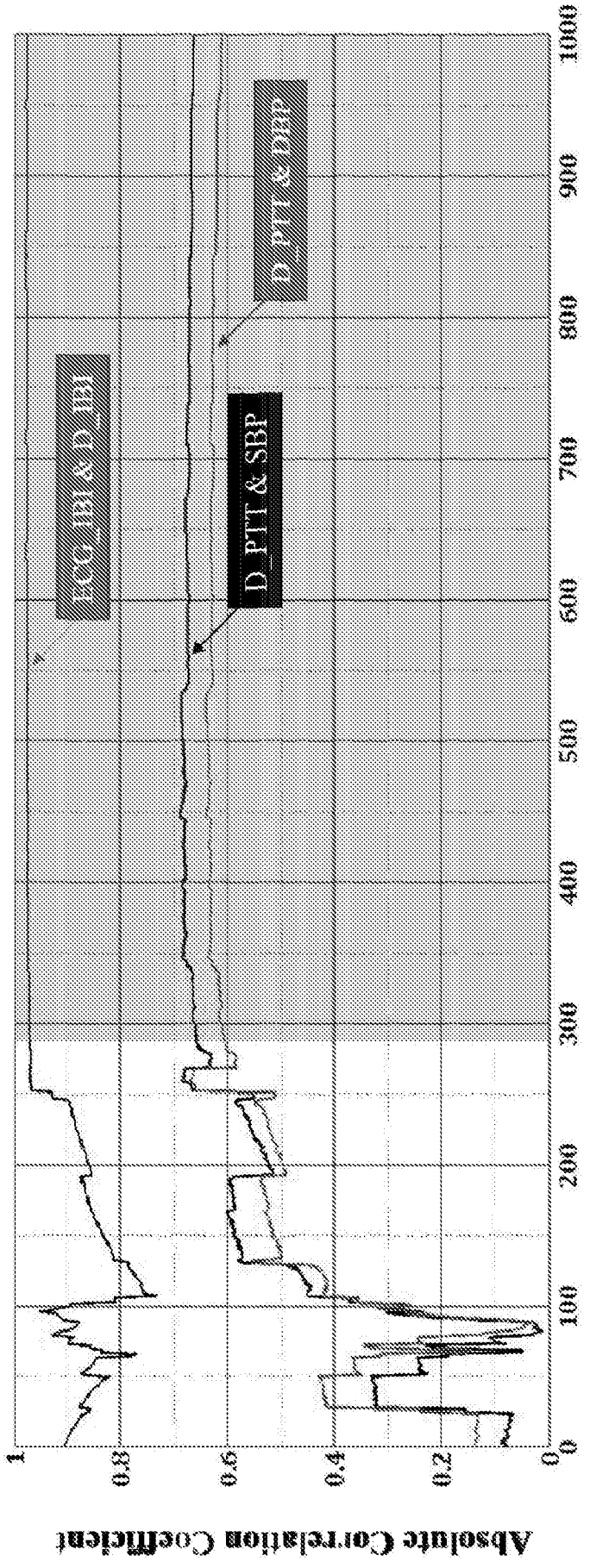
ECG_III & D_PTT
D_PTT & SBP
D_PTT & DBP
Absolute Correlation Coefficient
Absorption Ratio(×10-2)
1
0.8
0.6
0.4
0.2
0
0
100
200
300
400
500
600
700
800
900
1000

FIG. 5

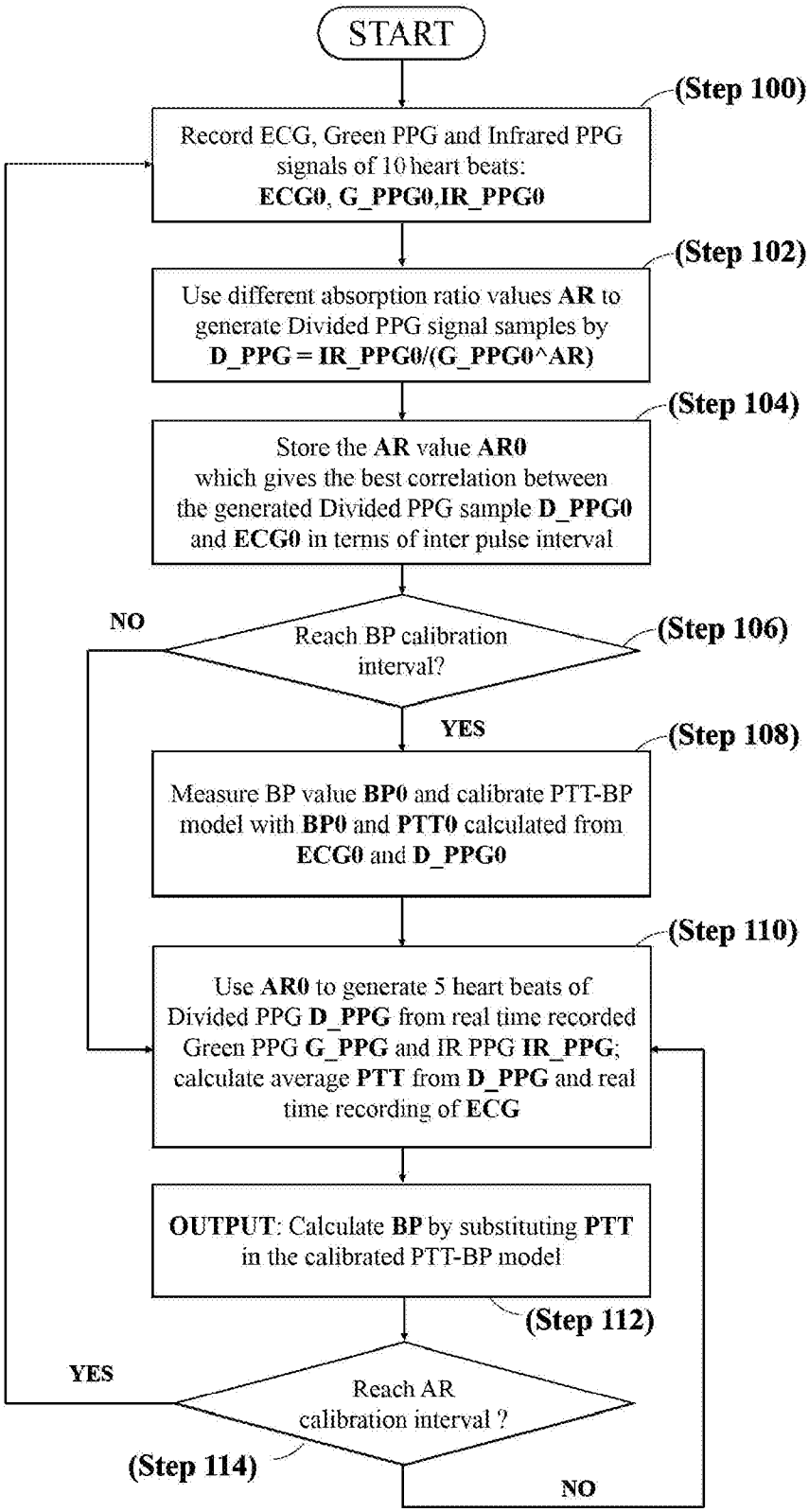
START
(Step 100)
Record ECG, Green PPG and Infrared PPG signals of 10 heart beats: ECG0, G_PPG0,IR_PPG0
(Step 102)
Use different absorption ratio values AR to generate Divided PPG signal samples by D_PPG = IR_PPG0/(G_PPG0^AR)
(Step 104)
Store the AR value AR0 which gives the best correlation between the generated Divided PPG sample D_PPG0 and ECG0 in terms of inter pulse interval
NO
Reach BP calibration interval?
(Step 106)
YES
(Step 108)
Measure BP value BP0 and calibrate PTT-BP model with BP0 and PTT0 calculated from ECG0 and D_PPG0
(Step 110)
Use AR0 to generate 5 heart beats of Divided PPG D_PPG from real time recorded Green PPG G_PPG and IR PPG IR_PPG; calculate average PTT from D_PPG and real time recording of ECG
OUTPUT: Calculate BP by substituting PTT in the calibrated PTT-BP model
(Step 112)
YES
Reach AR calibration interval ?
(Step 114)
NO

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/111298

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/0205(2006.01)i; A61B 5/0295(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)

A61B5/-

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)

CNPAT,CNKI,WPI,EPODOC: BLOOD, VOLUME, PULS+, SIGNAL, DEPTH, PPG, MULTIPLE, WAVELENGTH?, PHOTOPLETHYSMOGRAGHY, PRESSURE, LAYER?, DERIV+, MODEL, PTT, TRANSIT+, TIME

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 101484065 A (THE UNIVERSITY OF NOTTINGHAM) 15 July 2009 (2009-07-15) description, pages 13-14, 18-20, figures 3-7 and claims 19-30	1-5, 16-17
A	CN 103347439 A (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 09 October 2013 (2013-10-09) the whole document	1-11, 16-19
A	CN 101002673 A (TSINGHUA UNIVERSITY) 25 July 2007 (2007-07-25) the whole document	1-11, 16-19
A	CN 101564290 B (HUAZHONG UNIVERSITY OF SCIENCE & TECHNOLOGY) 25 May 2011 (2011-05-25) the whole document	1-11, 16-19
A	US 2009234245 A1 (O2 MEDTECH, INC.) 17 September 2009 (2009-09-17) the whole document	1-11, 16-19

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

* Special categories of cited documents:

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

"E" earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2017	**16 March 2017**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	**WEN,Bo**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)61648419**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/111298

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

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

1. ☑ Claims Nos.: **12-15**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] The subject-matter of claims 12-15 refers to a method of blood pressure measurement. Therefore, the subject-matter of claims 12-15 refers to a method of performing a diagnostic action in a person, and is excluded from international search according to PCT Rule 39.1 (iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/111298

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	101484065	A	15 July 2009	AU	2007242649	A1	01 November 2007
				CN	101484065	B	09 November 2011
				US	2009306487	A1	10 December 2009
				JP	2009533121	A	17 September 2009
				CA	2649187	A1	01 November 2007
				CA	2649187	C	23 June 2015
				EP	2004038	B1	21 October 2015
				ES	2556648	T3	19 January 2016
				US	2014243622	A1	28 August 2014
				JP	5270533	B2	21 August 2013
				ZA	200809559	A	25 November 2009
				ZA	200809559	B	25 November 2009
				GB	0607270	D0	17 May 2006
				AU	2007242649	B2	18 July 2013
				US	8768424	B2	01 July 2014
				EP	2004038	A2	24 December 2008
				WO	2007122375	A2	01 November 2007
				IN	9363DELNP2008	A	19 June 2009
CN	103347439	A	09 October 2013	US	9492089	B2	15 November 2016
				US	2013289394	A1	31 October 2013
				WO	2012065140	A2	18 May 2012
				EP	2637557	B1	14 October 2015
				JP	2013545543	A	26 December 2013
				EP	2637557	A2	18 September 2013
				KR	20140014079	A	05 February 2014
				CN	103347439	B	17 February 2016
CN	101002673	A	25 July 2007	CN	100482154	C	29 April 2009
CN	101564290	B	25 May 2011	CN	101564290	A	28 October 2009
US	2009234245	A1	17 September 2009		None		