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(54) **MINIATURIZED NONINVASIVE GLUCOSE SENSOR AND CONTINUOUS GLUCOSE MONITORING SYSTEM**

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(71) Applicant: **MEDTRONIC MINIMED, INC.**,  
Northridge, CA (US)

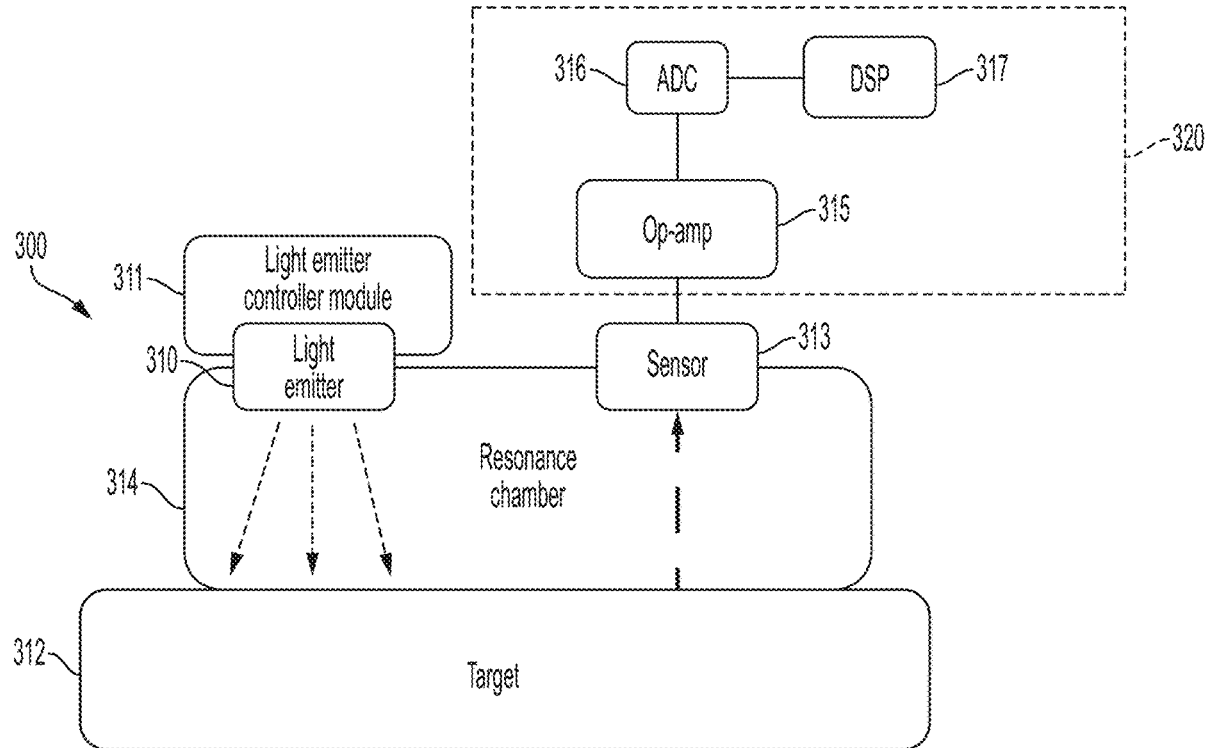
(72) Inventors: **Li Zhou**, Pasadena, CA (US);  
**Raymond M. Russell**, Arcadia, CA (US);  
**Peter Schultz**, Chatsworth, CA (US)

(57) **ABSTRACT**

Systems and methods are described herein for utilizing a photoacoustic sensor for estimating analyte concentration levels. Also described here are training methods for training an analyte sensor to more accurately estimate an analyte concentration level on the basis of a received acoustic signal.

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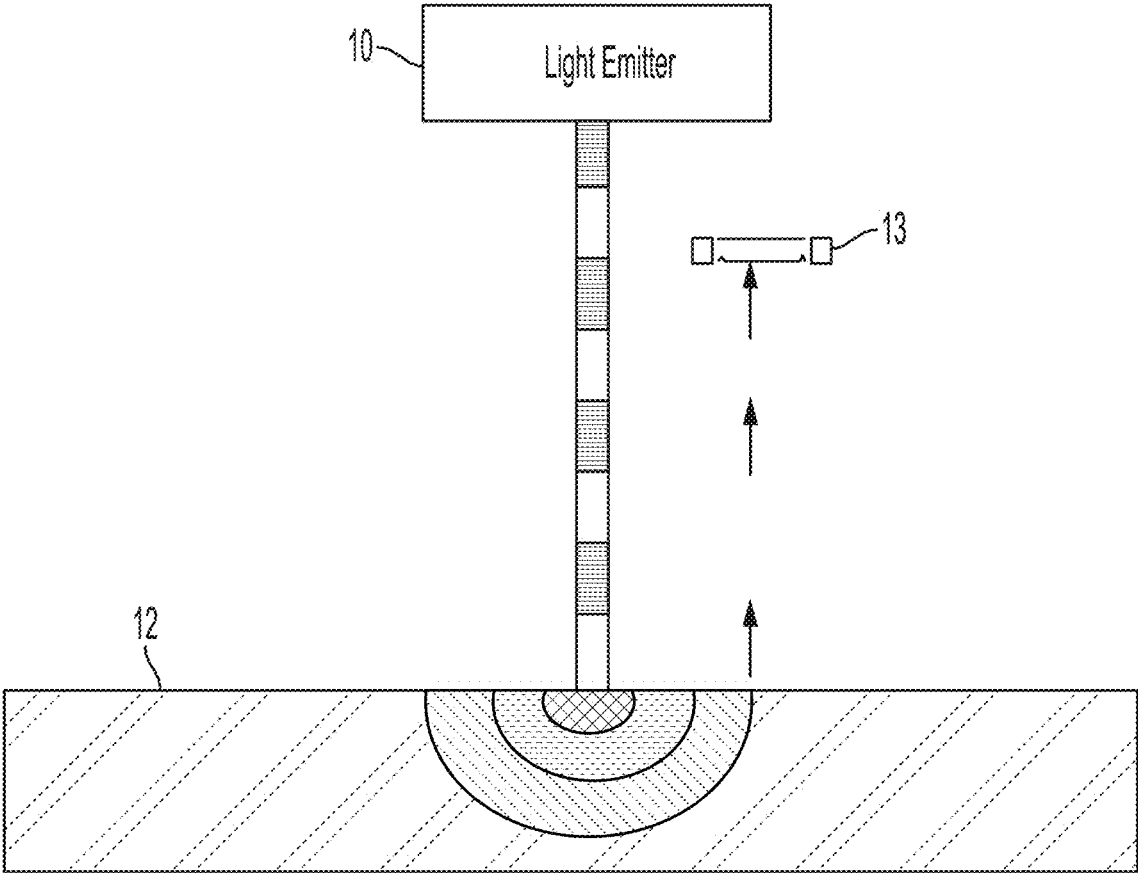


FIG. 1

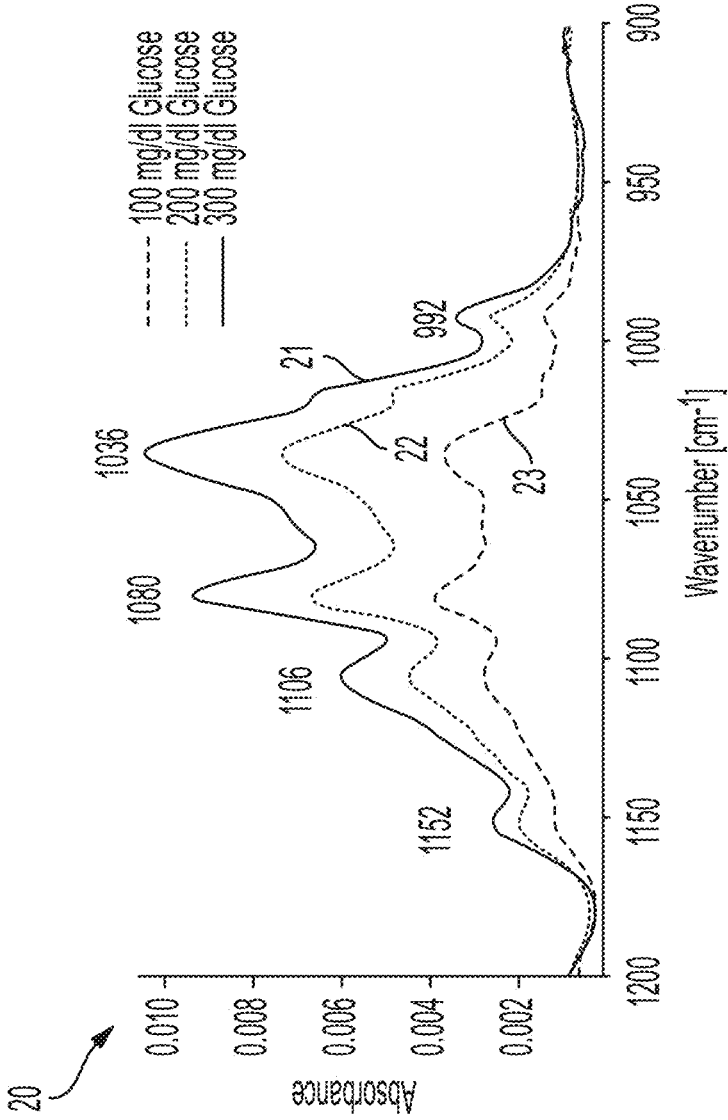


FIG. 2

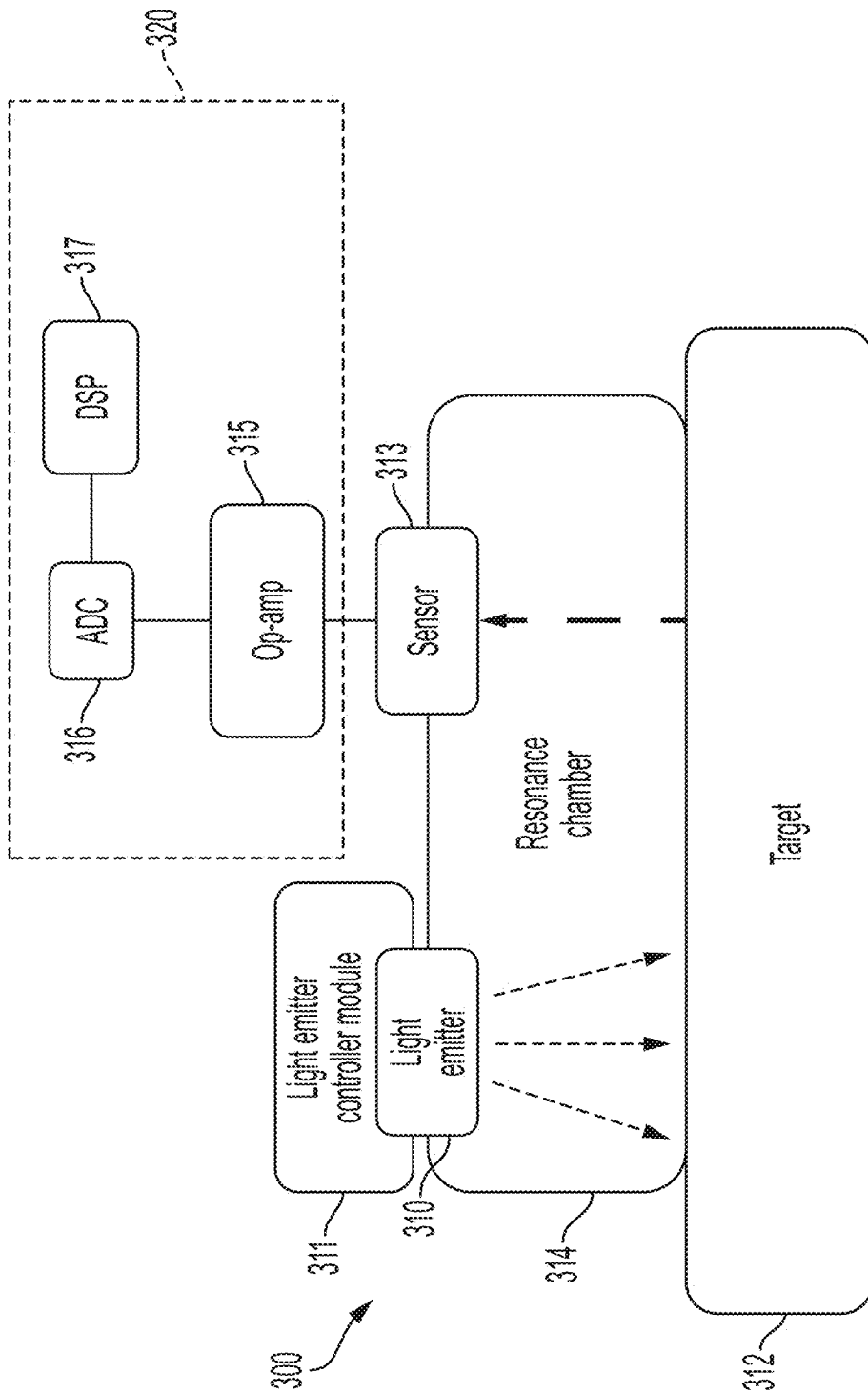


FIG. 3

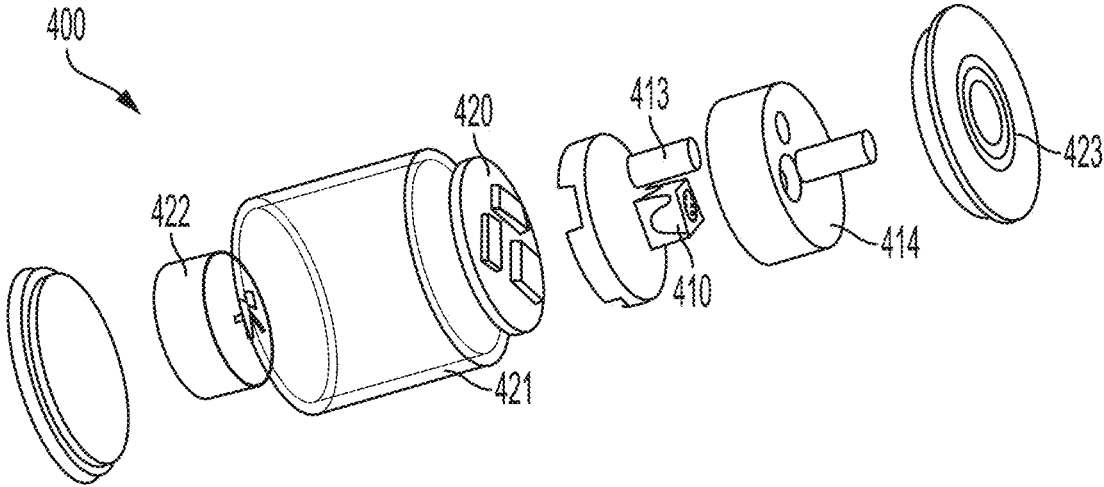


FIG. 4

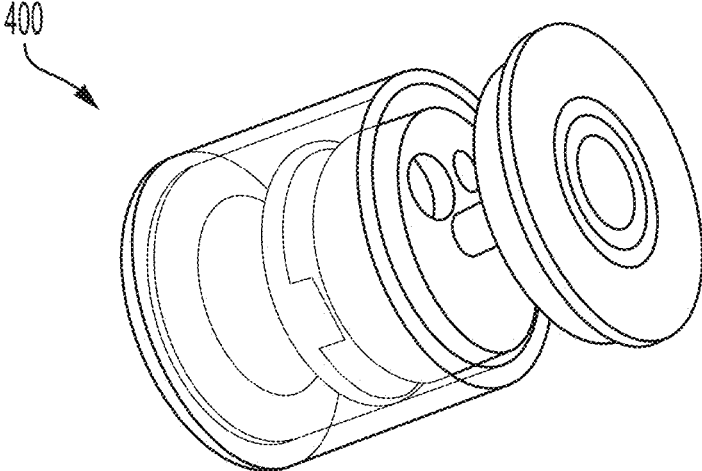


FIG. 5

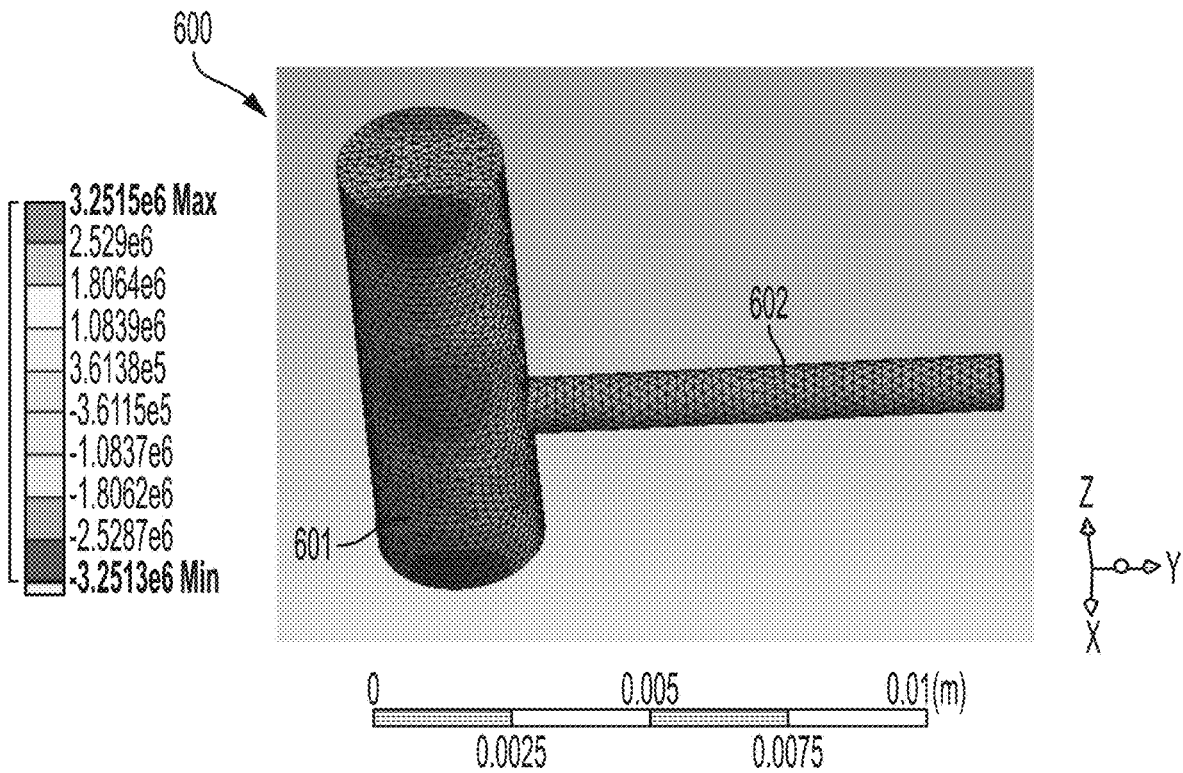
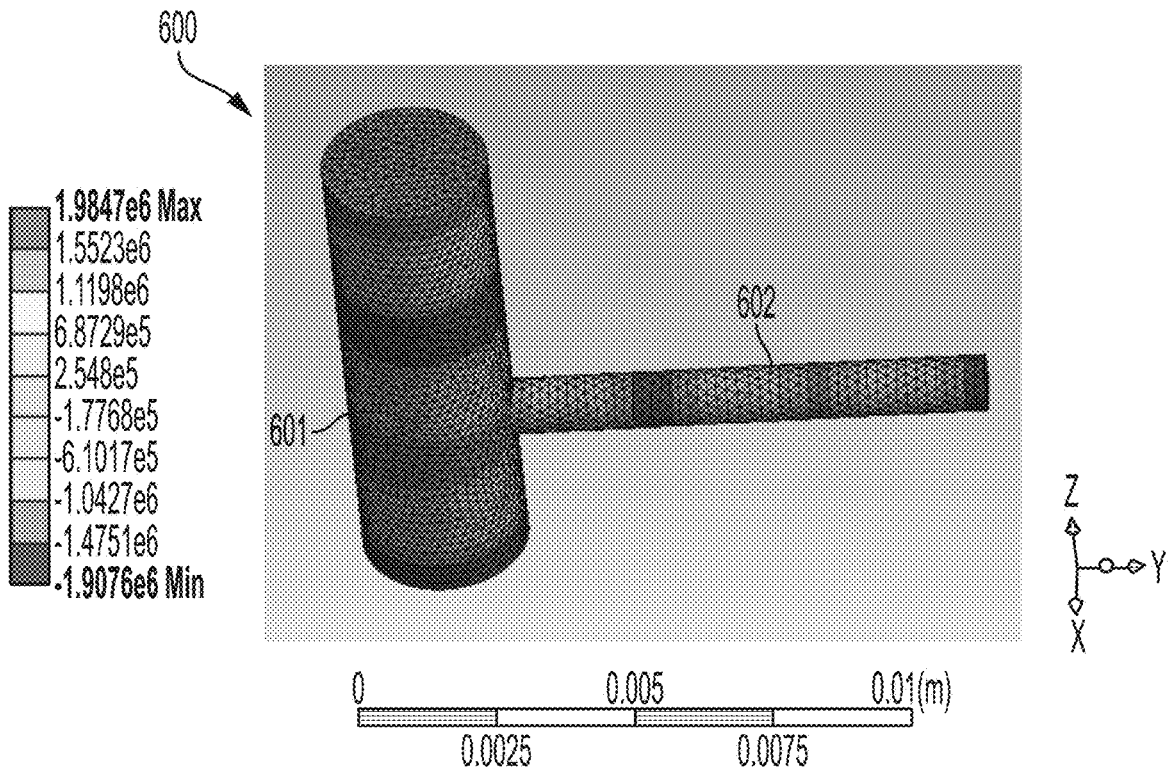


FIG. 6

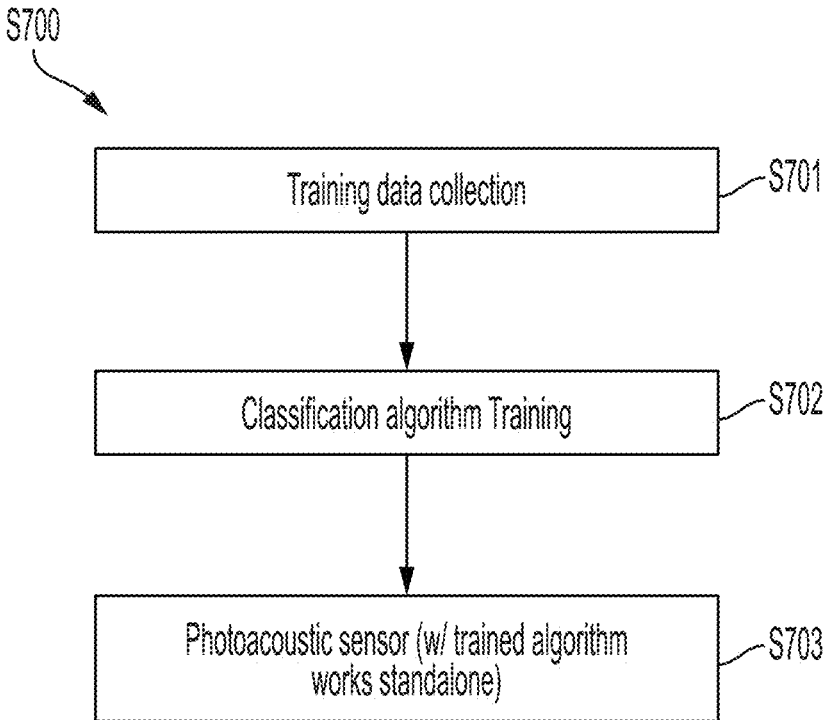


FIG. 7



S800

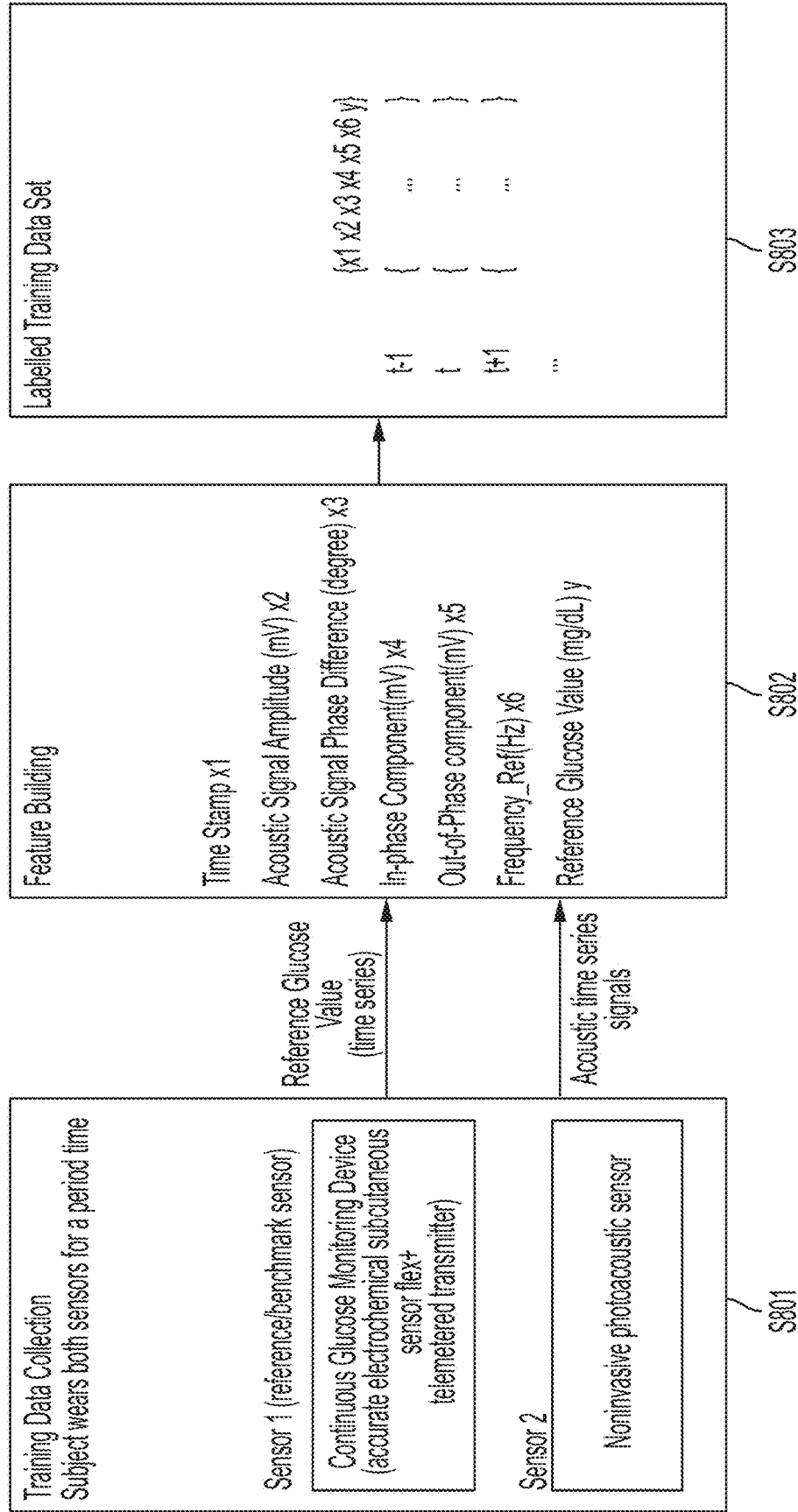


FIG. 8

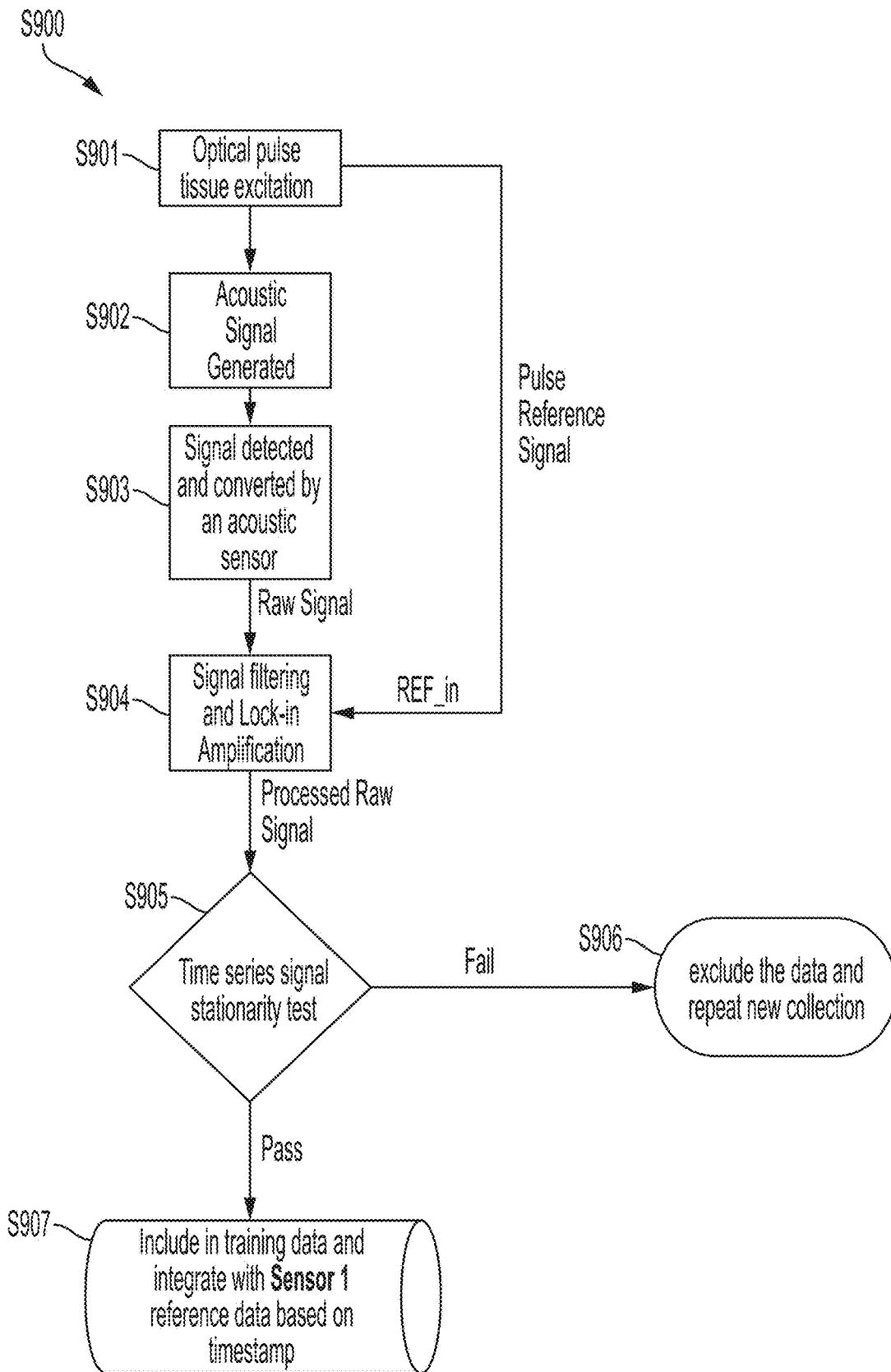


FIG. 9

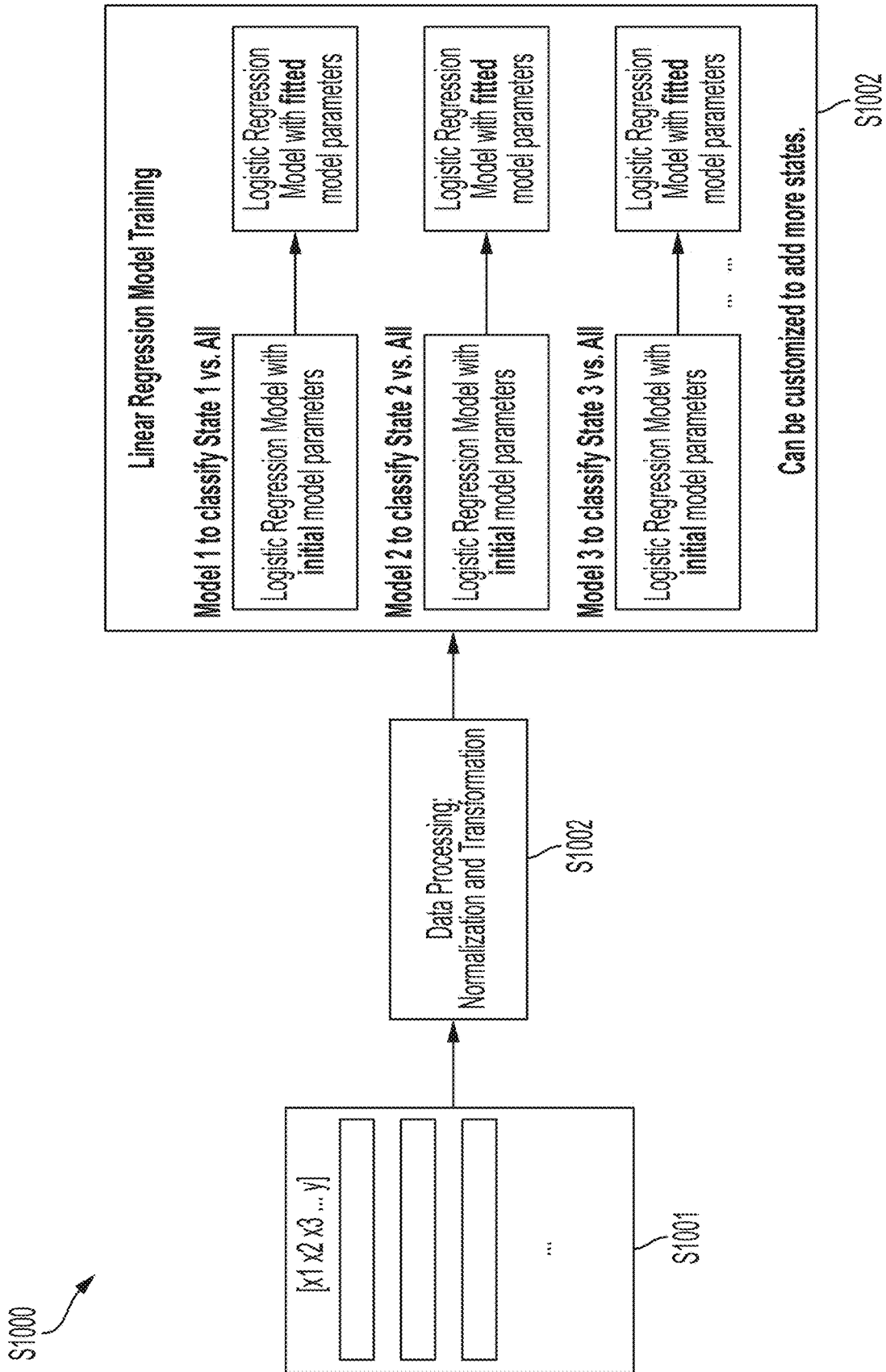


FIG. 10

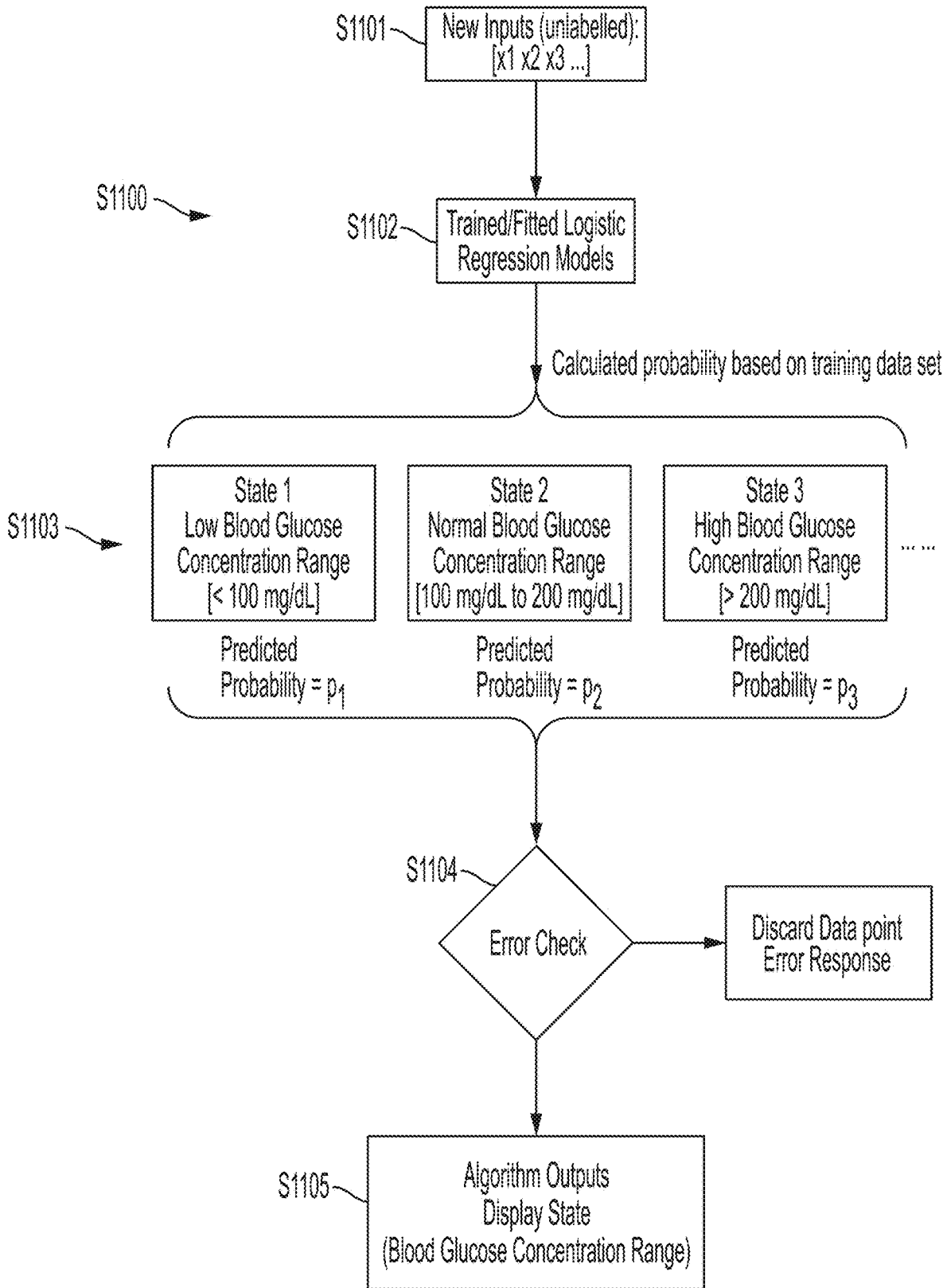


FIG. 11

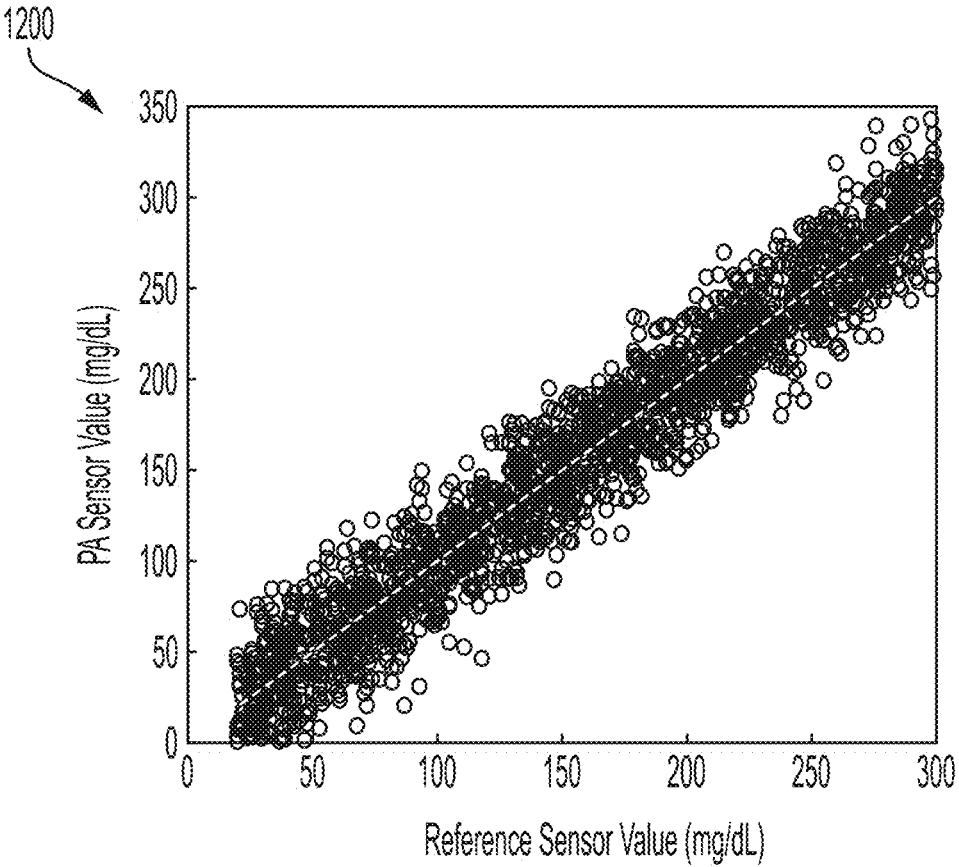


FIG. 12

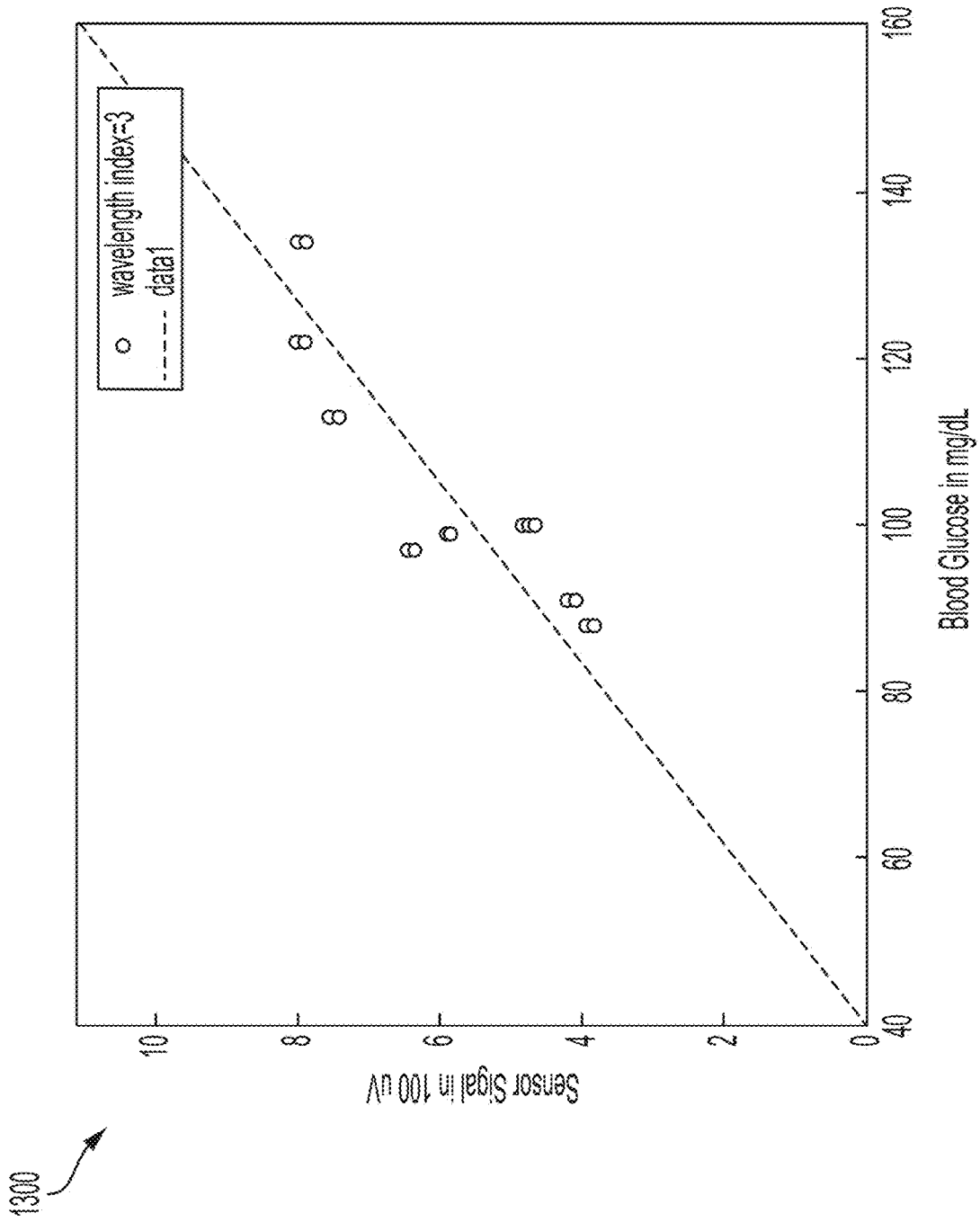


FIG. 13

## MINIATURIZED NONINVASIVE GLUCOSE SENSOR AND CONTINUOUS GLUCOSE MONITORING SYSTEM

### TECHNICAL FIELD

[0001] Embodiments of the subject matter described herein relate generally to photoacoustic techniques for monitoring analyte concentration levels. More particularly, embodiments of the subject matter described herein relate to photoacoustic techniques for monitoring blood glucose concentration levels of a user.

### BACKGROUND

[0002] There are approximately 450 million people suffering from diabetes worldwide. As is known, diabetes is a result of the body's inefficient production or use of insulin, which leads to medical complications of hyper- or hypoglycemia in the short term, and micro- or macro-vascular problems in the long term if left untreated. The control of blood glucose concentration levels to within a desired range, for example through the administration of insulin, is therefore necessary to prevent the development of such complications.

[0003] In order to determine when blood glucose concentration levels need to be controlled, it is necessary to measure the blood-glucose concentration levels of a diabetic person.

[0004] Photoacoustic techniques for monitoring glucose concentration levels are desirable for several reasons. In particular, photoacoustic techniques do not require an invasive component, such as a transdermal sensor probe or a "finger prick" puncture, in order to monitor the glucose concentration levels of a user. Due to the non-invasive nature of photoacoustic techniques, it is possible to increase user comfort whilst wearing the device and also to improve the ease and comfort of installation of the device. Furthermore, it is possible to continuously measure the blood glucose concentration level with photoacoustic methods, in contrast to the less-useful intermittent monitoring realized by "finger-prick" monitoring techniques.

[0005] Photoacoustic techniques rely upon the irradiation of a target with light, such as light provided by a laser beam. The light produces thermal effects, such as a volumetric expansion, in the target and the thin layer of air contacting the target due to thermal diffusion, which causes a pressure oscillation that generates an acoustic wave. The characteristics of this acoustic wave depend upon several factors, such as the target's absorption co-efficient to the wavelength of light used, the density of the medium through which the acoustic wave propagates, the thermal expansion co-efficient of the target, the velocity of the acoustic wave, and so on.

[0006] If skin is used as a target, the light may penetrate a distance into the skin and excite molecules, such as glucose molecules, beneath the skin. The acoustic wave generated by the thermal excitation (and subsequent volumetric expansion) of these glucose molecules can be used to estimate the concentration of the glucose molecules.

[0007] However, there are disadvantages associated with the use of photoacoustic techniques for monitoring blood glucose concentration levels. In particular, the acoustic wave generated through the excitation of glucose molecules may not be of sufficient magnitude to obtain a strong enough signal for the accurate measurement of the blood glucose

concentration. Furthermore, the characteristics of the acoustic wave may vary from person to person, dependent upon (for example) the user's skin light transmittivity characteristics, skin sweat gland activity, skin composition and structure, and so on.

[0008] Accordingly, it is desirable to overcome the disadvantages associated with photoacoustic techniques for measuring analyte concentrations, such as blood glucose concentration levels. Furthermore, other desirable features and characteristics will become apparent from the subsequent detailed description and the appended claims, taken in conjunction with the accompanying drawings and the foregoing technical field and background.

### BRIEF SUMMARY

[0009] According to a first aspect of the invention, there is provided an analyte monitor. The analyte monitor includes a light emitter configured to emit light at a target. The analyte monitor includes a sensor configured to sense acoustic waves generated by analyte molecules in the target in response to the emitted light. The analyte monitor also includes a resonance chamber sized to form a standing wave with the generated acoustic waves. The analyte monitor includes a signal processing module configured to estimate an analyte concentration level on the basis of the sensed acoustic waves.

[0010] According to a second aspect of the invention, there is provided a method for training an algorithm for estimating analyte concentration levels of a specific target from acoustic signals generated via thermal vibration of analyte molecules in the target in response to irradiation of the target with light. The method includes the step of obtaining acoustic signals with a sensor of a first analyte monitor and simultaneously obtaining analyte concentration levels using a reference analyte monitor to form a training set, the reference analyte monitor and the first analyte monitor being different. The method includes the step of training an algorithm of a signal processing module of the first analyte monitor using features of the obtained acoustic signals and the obtained analyte concentration levels of the training set. The method also includes the step of, after training of the algorithm, using the first analyte monitor to estimate analyte concentration levels from obtained acoustic signals.

[0011] According to a third aspect of the invention, there is provided a computer-readable medium containing instructions which, when executed by a processor, performs a method for training an algorithm for estimating analyte concentration levels of a specific target from acoustic signals generated via thermal vibration of analyte molecules in the target in response to irradiation of the target with light. The method includes the step of obtaining acoustic signals with a sensor of a first analyte monitor and simultaneously obtaining analyte concentration levels using a reference analyte monitor to form a training set, the reference analyte monitor and the first analyte monitor being different. The method includes the step of training an algorithm of a signal processing module of the first analyte monitor using features of the obtained acoustic signals and the obtained analyte concentration levels of the training set; and after training of the algorithm, using the first analyte monitor to estimate analyte concentration levels from obtained acoustic signals.

[0012] This summary is provided to introduce a selection of concepts in a simplified form that are further described

below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0013] A more complete understanding of the subject matter may be derived by referring to the detailed description and claims when considered in conjunction with the following figures, wherein like reference numbers refer to similar elements throughout the figures.

[0014] FIG. 1 shows a schematic of a photoacoustic technique for measuring an analyte concentration of a target;

[0015] FIG. 2 shows a graph of wavelengths of light that strongly interact with glucose molecules;

[0016] FIG. 3 shows a schematic of an analyte monitor in accordance with exemplary embodiments;

[0017] FIG. 4 shows an exploded view of an analyte monitor in accordance with exemplary embodiments;

[0018] FIG. 5 shows an angled partially transparent perspective view of an analyte monitor in accordance with exemplary embodiments;

[0019] FIG. 6 shows computer simulations of a resonance chamber in accordance with exemplary embodiments;

[0020] FIG. 7 shows a flowchart of a method in accordance with exemplary embodiments;

[0021] FIG. 8 shows a flowchart of another method in accordance with exemplary embodiments;

[0022] FIG. 9 shows a flowchart of another method in accordance with exemplary embodiments;

[0023] FIG. 10 shows a flowchart of another method in accordance with exemplary embodiments;

[0024] FIG. 11 shows a flowchart of another method in accordance with exemplary embodiments;

[0025] FIG. 12 shows a graph comparing results obtained from an analyte monitor in accordance with exemplary embodiments to a conventional analyte monitor; and

[0026] FIG. 13 shows another graph comparing results obtained from an analyte monitor in accordance with exemplary embodiments to a conventional analyte monitor.

#### DETAILED DESCRIPTION

[0027] The following detailed description is merely illustrative in nature and is not intended to limit the embodiments of the subject matter or the application and uses of such embodiments. As used herein, the word “exemplary” means “serving as an example, instance, or illustration.” Any implementation described herein as exemplary is not necessarily to be construed as preferred or advantageous over other implementations. Furthermore, there is no intention to be bound by any expressed or implied theory presented in the preceding technical field, background, brief summary or the following detailed description.

[0028] Techniques and technologies may be described herein in terms of functional and/or logical block components, and with reference to symbolic representations of operations, processing tasks, and functions that may be performed by various computing components or devices. Such operations, tasks, and functions are sometimes referred to as being computer-executed, computerized, software-implemented, or computer-implemented. It should be appreciated that the various block components shown in the figures may be realized by any number of hardware, soft-

ware, and/or firmware components configured to perform the specified functions. For example, an embodiment of a system or a component may employ various integrated circuit components, e.g., memory elements, digital signal processing elements, logic elements, look-up tables, or the like, which may carry out a variety of functions under the control of one or more microprocessors or other control devices.

[0029] When implemented in software or firmware, various elements of the systems described herein are essentially the code segments or instructions that perform the various tasks. In certain embodiments, the program or code segments are stored in a tangible processor-readable medium, which may include any medium that can store or transfer information. Examples of a non-transitory and processor-readable medium include an electronic circuit, a semiconductor memory device, a ROM, a flash memory, an erasable ROM (EROM), a floppy diskette, a CD-ROM, an optical disk, a hard disk, or the like.

[0030] “Connected/Coupled”—The following description refers to elements or features being “connected” or “coupled” together. As used herein, unless expressly stated otherwise, “coupled” or “connected” means that one element/feature is directly or indirectly joined to (or directly or indirectly communicates with) another element/feature, and not necessarily mechanically.

[0031] In addition, certain terminology may also be used in the following description for the purpose of reference only, and thus are not intended to be limiting. For example, terms such as “upper”, “lower”, “above”, and “below” refer to directions in the drawings to which reference is made. Terms such as “front”, “back”, “rear”, “side”, “outboard”, and “inboard” describe the orientation and/or location of portions of the component within a consistent but arbitrary frame of reference which is made clear by reference to the text and the associated drawings describing the component under discussion. Such terminology may include the words specifically mentioned above, derivatives thereof, and words of similar import. Similarly, the terms “first”, “second”, and other such numerical terms referring to structures do not imply a sequence or order unless clearly indicated by the context.

[0032] For the sake of brevity, conventional techniques related to signal processing, data transmission, signaling, network control, and other functional aspects of the systems (and the individual operating components of the systems) may not be described in detail herein. Furthermore, the connecting lines shown in the various figures contained herein are intended to represent exemplary functional relationships and/or physical couplings between the various elements. It should be noted that many alternative or additional functional relationships or physical connections may be present in an embodiment of the subject matter.

[0033] It should be appreciated that the later-described digital signal processor, and any corresponding logical elements, individually or in combination, are exemplary means for performing a claimed function.

[0034] FIG. 1 shows a schematic illustrating how photoacoustic measurement techniques may be used to obtain a sensor signal representative of an analyte concentration, for example a blood glucose concentration level of a user. As can be seen in FIG. 1, a light emitter 10 is configured to emit light towards a target 12, which may be tissue of a user, for example skin. The light incident on the target 12 penetrates



a distance into the target **12** and interacts with analyte molecules, for example glucose molecules, present in the target **12**. The analyte molecules are thermally excited and vibrate, and the medium surrounding these molecules undergoes a volumetric expansion, thereby generating an acoustic wave. This acoustic wave propagates out of the target **12** and into the medium surrounding the target, for example air. The propagation of the acoustic wave is illustrated in FIG. **1** through the use of bold arrows. The acoustic wave is then detected by a sensor **13** configured to convert the pressure of the acoustic wave into an electrical signal. In an exemplary embodiment, the sensor **13** comprises a microphone. In an alternative exemplary embodiment, the sensor **13** comprises a transducer, for example a piezoelectric transducer.

[0035] In an exemplary embodiment, the wavelength of the light emitted by the light emitter **10** is selected so as to strongly interact with the analyte of interest. As can be seen in the graph **20** shown in FIG. **2**, if the analyte of interest is glucose, the wavelength of the light emitted by the light emitter can be selected to correspond to wavelengths which interact strongly with glucose molecules for thermal excitation of the glucose molecules. The graph **20** of FIG. **2** shows that wavenumbers (the reciprocal of wavelength) of between about **1150** and **1000** interact strongly with glucose molecules. This range of wavenumbers corresponds to wavelengths of light in the mid-infrared region.

[0036] As can also be seen in FIG. **2**, the absorbance of light by glucose molecules in this wavenumber region generally increases as the glucose concentration level increases. The three spectra **21**, **22** and **23** shown in the graph **20** relate to the absorbance of light at blood glucose concentration levels of 300 mg/dl, 200 mg/dl and 100 mg/dl, respectively.

[0037] In general, the higher the level of absorbance of light by the analyte, the greater the acoustic response signal that will be generated by that analyte. As such, the magnitude of the acoustic response signal after irradiation of the target with light can be correlated to the analyte concentration level.

[0038] The present inventors recognized that at certain analyte concentration levels, the magnitude of the acoustic response is not large enough to accurately distinguish between differences in analyte concentrations without the use of highly-sensitive, expensive sensors. These types of highly-sensitive sensor may be prohibitively expensive when attempting to commercialize an analyte monitor based on photoacoustic techniques.

[0039] In order to circumvent the need for these kinds of expensive sensors to accurately detect the magnitude of the acoustic response from the target, the inventors recognized that the acoustic signal response may be improved through the use of a resonance chamber. A resonance chamber uses the physical principle of resonance to enhance the acoustic response. More specifically, when an acoustic wave enters the resonance chamber, the acoustic wave reflects back and forth within the chamber with minimal energy loss so as to form a standing wave. As additional acoustic waves enter the resonance chamber, the intensity of the standing wave increases.

[0040] As such, by pulsing the light emitted from the light emitter **10** and then measuring the intensity of the acoustic standing wave formed in reaction to these light pulses, it is

possible to more accurately correlate the acoustic response to an analyte concentration value for a given quality of sensor.

[0041] The inventors additionally found that, through the use of a resonance chamber, a certain amount of noise-filtering of the acoustic response was achievable. More specifically, since the resonance chamber is sized so as to form a standing wave with acoustic waves having a specific wavelength of interest, “noise” (acoustic waves of different wavelengths/frequencies) are not amplified by the standing wave in the same manner as the acoustic waves having the wavelength of interest. As such, the resonance chamber not only amplifies the wavelengths of the acoustic waves of interest, but also advantageously acts as a mechanical bandwidth-filter for the acoustic waves of the acoustic response.

[0042] A schematic analyte monitor **300** in accordance with an exemplary embodiment is shown in FIG. **3**. As can be seen in FIG. **3**, the analyte monitor **300** includes a light emitter **310** for emitting light shown with thin dashed lines) towards a target **312**. In an exemplary embodiment, the light emitter **310** comprises a light-emitting diode (LED). In an alternative embodiment, the light emitter **310** comprises a laser chip. A light emitter controller module **311** includes circuitry associated with the lighter emitter **310**. In exemplary embodiments, the light emitter controller module **311** is configured to control the light emitter **10** such that the pulses of light emitted by the light emitter **10** have a pre-determined or a variable pulse repetition frequency (PRF). In other words, the light emitter controller module **311** is suitable for modulating the frequency of the light pulses emitted by the light emitter **310**. Preferably, the light emitter controller module **311** is configured to control the light emitter **310** so as to emit light pulses having a duration of about 500 ns per pulse at a frequency of about 50 kHz or more. This pulse duration and frequency has been found to achieve a good acoustic response for certain analytes of interest, such as glucose.

[0043] In an embodiment, the light emitter **310** may include a heat conduction element (not shown) configured to conduct heat away from the light emitter **310** so as to reduce the likelihood that the light emitter **310** is heated to an undesirable temperature. In an additional or alternative embodiment, the light emitter **310** may include an anti-reflection surface (not shown) to reduce acoustic signal response noise caused by reflections of the emitted light.

[0044] The analyte monitor **300** further includes a sensor **313**, for example a microphone or a transducer, such as a piezoelectric transducer. The sensor **313** is configured to detect acoustic waves (shown with a bold dashed line) emitted from the thermal excitation of analyte molecules and volumetric expansion in the target **312** by the light emitted from the light emitter **310** and generate an electrical signal based on these acoustic waves.

[0045] The analyte monitor **300** further includes a resonance chamber **314**. The resonance chamber **314** is sized and dimensioned so as to form a standing wave for acoustic waves having a wavelength corresponding to the wavelength of acoustic waves generated through the volumetric expansion of the analyte-containing medium of interest after irradiation with light, which is controlled by pulse repetition frequency (PRF). For example, if the analyte of interest was glucose, and the wavelength of the acoustic wave generated through the irradiation of glucose with light at the pulse repetition frequency around 55 KHz was on the order of

about 6 mm, then the resonance chamber would be sized and dimensioned to as to support a standing wave having a length on the order of 6 mm. In an embodiment, the resonance chamber has a length that is a scalar multiple of the length of the acoustic wave generated through the thermal excitation and subsequent volumetric expansion of a glucose molecule, for example 6 mm, 12 mm, 18 mm, and so on. It will be appreciated that if the standing wave were to have a different wavelength, the dimensions of the resonance chamber may be changed accordingly. Although the embodiment in FIG. 3 shows the light emitter being inside the resonance chamber, in various embodiments the light emitter is located outside of the resonance chamber.

[0046] The present inventors found that, through the use of such a resonance chamber, acoustic wave amplification of up to about three times can be achieved, in comparison to the base acoustic signal. Furthermore, as explained above, the resonance chamber may perform a noise-filtering function.

[0047] In exemplary embodiments, the sensor 313 is operably connected to a signal processing module 320. In the embodiment shown in FIG. 3, the signal processing module 320 includes an operational amplifier (“op-amp”) 315 configured to further amplify the electronic signal derived from the acoustic response of the target 312. In exemplary embodiments, the op-amp 315 is operably connected to an analog-to-digital converter 316 configured to convert the analog electrical signal from the sensor 313 to a digital signal. In exemplary embodiments, the analog-to-digital converter 316 is operably connected to a digital signal processor (“DSP”) 317 for processing of the digital signal.

[0048] Converting the analog signal from the sensor 313 into a digital signal allows for the accurate separation of different magnitudes of acoustic response into “bins” corresponding to different glucose concentration levels, these “bins” being separated by pre-determined threshold values. For example, an acoustic response of a first magnitude or less could be determined to correlate to a glucose concentration level of about 100 mg/dl or below, which could be determined by the signal processing module 320 as corresponding to a “hypoglycemic” glucose level. An acoustic response having a magnitude between the first magnitude and a second magnitude could be determined to correlate to a glucose concentration of between about 100 mg/dl and about 200 mg/dl, which could be determined by the signal processing module 320 as corresponding to a “normal” glucose level. Still further, an acoustic response having a magnitude greater than the second magnitude could be determined to correlate to a glucose concentration of over about 200 mg/dl, which could be determined by the signal processing module 320 as corresponding to a “hyperglycemic” glucose level.

[0049] As will later be explained in more detail with respect to FIG. 11 in an embodiment, upon determination of a “hypoglycemic” or “hyperglycemic” glucose level, the signal processing module 320 is configured to transmit a warning signal to the user of the analyte monitor, or to take some other form of action (such as automatically activating an insulin pump).

[0050] Furthermore, by “binning” the acoustic responses using pre-determined thresholds, a more computationally efficient and accurate monitoring of glucose concentration level results. In particular, by comparing the magnitude of the acoustic response to pre-determined thresholds, hypo-

glycemic and hyperglycemic events may be detected more quickly and more accurately by the signal processing module 320.

[0051] Turning to FIG. 4, an exploded-view diagram of an analyte monitor 400 in accordance with an embodiment is shown. The analyte monitor 400 includes a light emitter 410 configured to emit light of a pre-determined wavelength. The analyte monitor 400 further includes a sensor 413 configured to detect acoustic waves generated from the volumetric expansion of an analyte of interest after irradiation of that analyte of interest with light generated by the light emitter 410. The analyte monitor 400 further includes a resonance chamber 414 sized and configured to form a standing wave from the acoustic waves so as to amplify the magnitude of the acoustic waves. The analyte monitor 400 further includes a signal processing module 420 configured to estimate an analyte concentration level based on the magnitude of the sensed acoustic response.

[0052] In exemplary embodiments, the analyte monitor 400 further includes a power source 422 configured to supply power to one or more of the light emitter 410, the sensor 413 and the signal processing module 420, or other components of the analyte monitor 400.

[0053] In exemplary embodiments, the analyte monitor 400 further includes a case 421 configured to surround one or more of the above-described components. In exemplary embodiments, the case 421 may comprise a case cover having a transmitter 423 incorporated into the case cover. In other exemplary embodiments, the transmitter 423 is located elsewhere in the analyte monitor, for example proximate to the signal processing module 420. Incorporation of the transmitter 423 into the case cover allows for the transmitter 423 to have a larger size than if the transmitter 423 were to be located inside the case 421 of the analyte monitor 400 and also to reduce the overall size of the analyte monitor. For example, in instances where the transmitter 423 comprises an antenna (for example a RF antenna), the increased size of the transmitter 423 allows for a more powerful signal to be generated by the transmitter 423.

[0054] The transmitter 423 is operably connected to the signal processing module 420. When a measured analyte concentration is determined to be outside of a “normal” range, the transmitter 423 is configured to transmit a signal responsive to this determination. For example, in an embodiment, the transmitter 423 is configured to transmit a signal to a remote device (not shown), such as a smartphone or smartwatch, in order to warn the user of the analyte device of the high or low analyte concentration level. Additionally or alternatively, the transmitter 423 is configured to transmit a signal to a remote device (not shown) for application of an additional substance to the user of the analyte monitoring device, such as an insulin pump for delivering insulin to the patient.

[0055] FIG. 5 shows an angled phantom view of a partially-assembled analyte monitor 400. As can be seen in FIG. 5, the assembled analyte monitor 400 may have a length of around below about 50 mm, for example below about 40 mm, such as below about 30 mm, preferably below about 20 mm, most preferably about 15 mm. The assembled analyte monitor 400 may have a width of below about 50 mm, for example below about 40 mm, such as below about 30 mm, preferably below about 20 mm, most preferably about 18 mm. As such, the assembled analyte monitor 400 may be worn discretely by a user, or even incorporated into jewelry

or clothing of the user, for example incorporated into an earring, a watch or a bracelet.

[0056] Another view of a resonance chamber in accordance with exemplary embodiments is shown in FIG. 6. In FIG. 6, two computer models of a resonance chamber 600 are shown. The resonance chamber 600 includes a resonance branch 601 and a measurement branch 602. The resonance branch 601 is sized and dimensioned so as to form a standing wave, in the manner as described above. The measurement branch 602 connects the resonance branch 601 to the sensor.

[0057] As can be seen in the two figures of FIG. 6, the length of the resonance branch 601 and the placement of the measurement branch 602 along the resonance branch are important for obtaining a clear signal of the acoustic response. In particular, as can be seen in the bottom figure of FIG. 6, the measurement branch 602 is positioned adjacent to a node of the standing wave formed in the resonance branch 601. As such, minimal propagation of the acoustic wave down the measurement branch 602 occurs, and a lower magnitude acoustic response is measured by the sensor. Further, as can be seen in the top figure of FIG. 6, the measurement branch 602 is positioned close to an antinode of the standing wave formed in the resonance branch 601. As such, a good propagation of the acoustic wave down the measurement branch 602 occurs, and an acceptable magnitude acoustic response signal is measured by the sensor. As such, in an exemplary embodiment, the measurement branch 602 is positioned proximate to an anti-node of the standing wave to be formed in the resonance chamber 601.

[0058] When developing the analyte monitor described above, the inventors recognized that the acoustic responses of each user to the light emitted from the light emitter are individual. In other words, a variety of variables may affect the acoustic response of a user, such as skin transmittivity, skin composition, sweat gland activity and so on. As such, the inventors found that a training procedure to personalize the analyte monitor to an individual user increased the accuracy of the analyte monitor in detecting raised or lowered analyte concentrations.

[0059] FIG. 7 shows an overview of a general method S700 for training an analyte monitor for a specific user. The individual steps of this general method will be explained in more detail with reference to FIGS. 8, 9, 10 and 11. At step S701, training data for training a signal processing module of the analyte monitor is collected from a specific user. In an embodiment, the training data is collected by obtaining analyte concentration levels of the user from a conventional analyte monitor, such as a commercially-available continuous glucose monitor having an invasive component (such as a transdermal probe), in combination with measuring acoustic responses from the analyte monitor in accordance with various embodiments as described herein. After sufficient training data has been collected from the user, the method progresses to step S702.

[0060] At step S702, the algorithm used by the signal processing module to correlate certain acoustic signal responses to the obtained analyte concentration levels is trained using the training data collected from the user. In an embodiment, the training of the signal processing module is a supervised machine learning process, where training data is first labelled and then used in training. In an embodiment, after the signal processing module is trained using the training data, the signal processing module may be tested against validation data to determine the accuracy of the

signal processing module in determining analyte concentration levels. After training of the signal processing module to an acceptable accuracy, the method progresses to step S703.

[0061] At step S703, the analyte monitor has been adapted to the individual characteristics of the user and is used to monitor an analyte concentration level of the use without the concurrent use of another analyte monitor.

[0062] Each of the steps S701, S702 and S703 of the method S700 will now be described in more detail.

[0063] FIG. 8 shows a more detailed flowchart S800 illustrating exemplary steps involved in the collection of a training data set of step S701. At Step S801, data is collected from a specific user via two or more analyte monitors. One of these analyte monitors is an analyte monitor in accordance with exemplary embodiments as described herein, and at least one other of these analyte monitors comprises a conventional analyte monitor, such as a continuous glucose monitor comprising a transdermal probe. The conventional analyte monitor collects data related to the user's blood analyte concentration levels to be used as reference data. The analyte monitor in accordance with various embodiments obtains acoustic responses in parallel with obtaining the reference data.

[0064] As the reference data is obtained in parallel with the acoustic responses, it is possible to correlate features of the acoustic responses to the reference data. In Step S802, features (x1, x2, x3, x4, x5 and x6) of the acoustic response signals detected by the sensor of the analyte monitor in accordance with exemplary embodiments are associated with the simultaneously-obtained analyte reference values (y) obtained by the conventional analyte monitor.

[0065] For example, if the analyte of interest is glucose, reference glucose concentration values (y) obtained from the conventional analyte sensor can be associated with the time stamp (x1), amplitude (x2), phase difference (x3), in-phase component (x4), out-of-phase component (x5) and frequency (x6) of the acoustic signal response obtained via the analyte monitor in accordance with exemplary embodiments. It is to be noted that the above list of features is not an exhaustive list, and other features of the acoustic signal response may additionally or alternatively be associated with the reference glucose concentration values (y) obtained from the conventional analyte monitor.

[0066] After association of the features (x1, x2, x3, x4, x5 and x6) of the acoustic response to the reference data (y), the method progresses to step S803, where a labelled training data set is constructed, using conventional techniques, with this data.

[0067] In FIG. 9, a further flowchart 5900 shows how training data is collected by the analyte monitor in accordance with exemplary embodiments as described herein. At Step S901, tissue of a user is excited via an optical pulse from a light emitter. The method then progresses to step S902.

[0068] At Step S902, an acoustic signal is generated by analytes in the tissue in response to the optical pulse. At Step S903, this acoustic signal is detected by a sensor and converted into an electrical signal, in the manner described previously.

[0069] At Step S904, the electrical signal is filtered to reduce the amount of noise in the signal. In an embodiment, this filtering is achieved through the use of a bandwidth filter. In an embodiment, this filtering is achieved via a time-based filtering technique, where a pulse reference sig-

nal generated at the same time as the emission of the optical pulse in Step S901, and wherein only acoustic signals received a pre-determined time after the pulse reference signal has been generated are allowed through the signal filter. Additionally or alternatively, this signal filtering may utilize timestamps associated with the pulse frequency of light to filter out noise through a comparison of the timestamps of the emitted light and the timestamps of acoustic signal responses to the light. Also at Step S904, the filtered electrical signal is amplified, for example through the use of an operational amplifier. The method then progresses to Step S905.

[0070] At Step S905, a time series stationarity test is applied to the filtered, amplified electrical signal in order to test for noise in the signal caused by, for example, contact pressure and/or motion of the user. If the signal fails this time series stationarity test, the method progresses to Step S906, where the collected data is excluded from the training data set. If the signal passes this time series stationarity test, the method progresses to Step S907, where the collected data is included in the training data set for training the analyte monitor according to various embodiments as described herein.

[0071] The method S900 is repeated until sufficient data has been collected to form a training data set large enough for training the algorithm used by the signal processing module.

[0072] FIG. 10 shows a detailed flowchart S1000 illustrating exemplary steps involved in the training of the algorithm used in the digital signal processor as per step S702 in method S700. At Step S1001, the labelled training data set is completed. The method then progresses to Step S1002.

[0073] At Step S1002, a supervised learning method is used to train the algorithm used by the digital signal processor on the labelled training data set. More specifically, the algorithm used by the digital signal processor uses the features (x1), (x2), (x3), (x4), (x5) and (x6) of the electric signal derived from received acoustic responses and estimates a glucose concentration level based on these features. The estimated glucose concentration level is then compared to the obtained glucose concentration level (y) corresponding to those features as obtained from the conventional analyte monitor. Based on the accuracy of the comparison, parameters of the algorithm are adjusted. Statistical normalization and transformation techniques, such as linear regression techniques, may be used in this adjusting of parameters.

[0074] After the parameters have been adjusted, the glucose concentration level is again estimated and compared to the obtained glucose concentration level (y) corresponding to those features as obtained from the conventional analyte monitor. In this manner, the algorithm is iteratively trained to more accurately estimate the glucose concentration level of the user based on the features of the acoustic response signal obtained from the analyte monitor in accordance with various embodiments. When the algorithm is fully trained, a more accurate personalized calibration for a specific user is achieved. In particular, the analyte monitor according to embodiments as described herein is better able to account for variations in the skin conditions and characteristics of a specific user.

[0075] FIG. 11 shows a more detailed flowchart S1100 of the use of a trained analyte monitor in monitoring analyte concentration levels of a user, as per step S703 in FIG. 7.

[0076] At step S1101, the trained analyte monitor obtains acoustic responses that are converted into electrical signals having features (x1, x2, x3, etc.) that can be used to estimate an analyte concentration of a user. The method then progresses to step S1102.

[0077] At Step S1102, the features of the electrical signal are used, using the algorithms of the trained digital signal processor module, to estimate an analyte concentration level. After estimation of the analyte concentration level, the method progresses to step S1103.

[0078] At Step S1103, the estimated analyte concentration level is sorted into a "bin", each bin corresponding to analyte concentration levels of a particular user state. For example, the estimated analyte concentration level is a blood glucose concentration level, and the estimated glucose concentration level is sorted into one of three bins, the first bin having a range of below about 100 mg/dl and corresponding to a hypoglycemic state, the second bin having a range of between about 100 mg/dl and 200 mg/dl and corresponding to a "normal" state, and the third bin having a range of above about 200 mg/dl and corresponding to a hyperglycemic state. In an exemplary embodiment, the end-points of the ranges of the bins are variable and can be varied on the basis of a particular user's blood glucose characteristics.

[0079] In an exemplary embodiment, a probability of the estimated blood glucose level falling within a certain bin is estimated by the trained algorithm of the digital signal processor, based on the features of the electrical signal derived from the acoustic response. In this manner, a probabilistic confidence level of the "binning" step can be determined. In exemplary embodiments, multiple estimations of the blood glucose level can be performed, and the confidence level can be iteratively re-evaluated on the basis of each subsequent estimation. In this manner, a high confidence level of the binning of the blood glucose concentration estimation can be achieved.

[0080] After the analyte concentration estimation is binned, the method progresses to Step S1104. At step S1104, the algorithm of the digital signal processor outputs the "state" corresponding to the estimated analyte concentration level. For example, if the estimated blood glucose concentration level was above 200 mg/dl, the algorithm would output a "hyperglycemic" state. After outputting of this state, the method progresses to Step S1105.

[0081] At Step S1105, action is performed in response to the output of the state, if required. For example, if a "hyperglycemic" state is output by the analyte monitor, an alert may be transmitted to a remote device so as to warn the user of this state. Additionally or alternatively, a signal may be transmitted to an insulin pump so as to administer an amount of insulin in response to the output of the state. Additionally or alternatively, a signal is transmitted to a display device to display the blood glucose concentration state.

[0082] In order to test the accuracy of glucose concentrations estimated with the analyte monitor of embodiments as described herein and a conventional continuous glucose monitor having a transdermal probe, glucose concentration measurements were tested simultaneously in-silico using a trained analyte monitor according to an embodiment and a transdermal continuous glucose monitor and then compared to each other. The results of these comparisons are shown in the graph 1200 of FIG. 12. As shown in FIG. 12, the glucose concentrations estimated by the trained analyte monitor in

accordance with embodiments as described herein closely matched the glucose concentrations measured using a conventional, commercially-available continuous glucose monitor having a transdermal probe.

**[0083]** Glucose concentration estimations were also obtained with an in-silico simulation of untrained analyte monitor in accordance with embodiments as described herein and compared to the glucose concentrations estimations obtained with a trained algorithm prototype analyte monitor in accordance with embodiments as described herein. It was determined that the prototype untrained analyte monitor had a success rate of about 60% in determining hypoglycemic events, whereas the prototype trained analyte monitor had a success rate in excess of about 85% in determining hypoglycemic events, thereby demonstrating the effect of the machine learning training algorithm in improving the accuracy of glucose concentration estimations.

**[0084]** Further, in-vivo, experiments were also performed, as shown in the graph 1300 of FIG. 13. As can be seen in FIG. 13, there is a strong correlation between the sensor signal obtained from the analyte monitor in accordance with embodiments having a trained algorithm and a known blood glucose concentration level obtained from a reference sensor, thereby indicating the accuracy of this method in detecting blood glucose concentration levels.

**[0085]** The various tasks performed in connection with the processes described herein may be performed by software, hardware, firmware, or any combination thereof. For illustrative purposes, the following description of process S700 may refer to elements mentioned in connection with FIGS. 1 to 6. In practice, portions of process S700 may be performed by different elements of the described system, e.g., the digital signal processor module or a different controller module. It should be appreciated that process S700 may include any number of additional or alternative tasks, the tasks shown in FIG. 7 need not be performed in the illustrated order, and process S700 may be incorporated into a more comprehensive procedure or process having additional functionality not described in detail herein. Moreover, one or more of the tasks shown in FIG. 7 could be omitted from an embodiment of the process S700 as long as the intended overall functionality remains intact.

**[0086]** While at least one exemplary embodiment has been presented in the foregoing detailed description, it should be appreciated that a vast number of variations exist. It should also be appreciated that the exemplary embodiment or embodiments described herein are not intended to limit the scope, applicability, or configuration of the claimed subject matter in any way. Rather, the foregoing detailed description will provide those skilled in the art with a convenient road map for implementing the described embodiment or embodiments. It should be understood that various changes can be made in the function and arrangement of elements without departing from the scope defined by the claims, which includes known equivalents and foreseeable equivalents at the time of filing this patent application.

What is claimed is:

1. An analyte monitor, the analyte monitor comprising:
  - a light emitter configured to emit light toward a target,
  - a sensor configured to sense acoustic waves generated by analyte molecules in the target in response to the light emitted by the light emitter,

- a resonance chamber sized to form a standing wave from generated acoustic waves, and

- a signal processing module configured to estimate an analyte concentration level on the basis of acoustic waves sensed by the sensor.

2. The analyte monitor of claim 1, wherein the light emitter is configured to emit light having a wavelength in the mid-infrared region.

3. The analyte monitor of claim 1, wherein the sensor is positioned proximate to an anti-node of the standing wave to be formed in the resonance chamber.

4. The analyte monitor of claim 1, wherein the signal processing module is configured to determine whether the estimated analyte concentration level falls within one of two or more pre-determined ranges.

5. The analyte monitor of claim 4, further comprising a transmitter configured to transmit a signal when the estimated analyte concentration level falls within one of the two or more pre-determined ranges.

6. The analyte monitor of claim 1, wherein the sensor comprises a microphone.

7. The analyte monitor of claim 1, wherein the sensor comprises a transducer.

8. The analyte monitor of claim 1, wherein the resonance chamber comprises a resonance branch for formation of the standing wave and a measurement branch connecting the resonance branch to the sensor, the measurement branch being positioned proximate to an anti-node of the standing wave to be formed in the resonance branch.

9. A method for estimating analyte concentration levels of a specific target from acoustic signals generated by volumetric expansion of the target due to thermal vibration of analyte molecules in the target in response to irradiation of the target with light, the method comprising:

- obtaining acoustic signals with a sensor of a first analyte monitor and simultaneously obtaining analyte concentration levels using a reference analyte monitor to form a training set, the reference analyte monitor and the first analyte monitor being different monitors;

- training an algorithm of a signal processing module of the first analyte monitor using features of the obtained acoustic signals and the obtained analyte concentration levels of the training set; and

- after training of the algorithm, using the first analyte monitor to estimate analyte concentration levels from obtained acoustic signals.

10. The method of claim 9, wherein the reference analyte monitor is a continuous glucose monitor having an invasive component and wherein the first analyte monitor is non-invasive.

11. The method of claim 9, wherein the features of the obtained acoustic signals are selected from the group comprising: a timestamp of the recording acoustic signal; an amplitude of the acoustic signals, an in-phase component of the acoustic signals; and out-of-phase component of the acoustic signals; and a frequency of the acoustic signals.

12. The method of claim 9, wherein the step of using the first analyte monitor to estimate analyte concentration levels from obtained acoustic signals comprises determining whether an estimated value of the analyte concentration level falls within two or more pre-determined ranges.

**13.** The method of claim **12**, further comprising determining a confidence level that the analyte concentration level falls within one of the two or more pre-determined ranges.

**14.** The method of claim **12**, wherein the method further comprises transmitting, using a transmitter, a signal in response to a determination that the estimated value of the analyte concentration level falls within one or more of the two or more pre-determined ranges.

**15.** The method of claim **14**, wherein the signal is a blood glucose concentration pre-determined range value or an alert signal.

**16.** The method of claim **9**, wherein the analyte molecules are glucose molecules.

**17.** The method of claim **9**, wherein the step of using the first analyte monitor to estimate concentration levels from obtained acoustic signals comprises amplifying and filtering of the obtained acoustic signal.

**18.** The method of claim **17**, wherein at least part of the amplifying and filtering of the obtained acoustic signal is performed using a resonance chamber.

**19.** The method of claim **9**, further comprising the steps of:

converting the obtained acoustic signals into an analog electrical signal using a sensor; and  
converting the analog electrical signal into a digital electrical signal using an analog-to-digital converter.

**20.** A computer readable storage medium comprising instructions which, when executed by a processor, perform a method for estimating analyte concentration levels of a specific target from acoustic signals generated by thermal vibration of analyte molecules in the target in response to irradiation of the target with light, the method comprising:  
obtaining acoustic signals with a sensor of a first analyte monitor and simultaneously obtaining analyte concentration levels using a reference analyte monitor to form a training set, the reference analyte monitor and the first analyte monitor being different;  
training an algorithm of a signal processing module of the first analyte monitor using features of the obtained acoustic signals and the obtained analyte concentration levels of the training set; and  
after training of the algorithm, using the first analyte monitor to estimate analyte concentration levels from obtained acoustic signals.

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