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(54) Title: METHODS FOR POSITIONING AN ANALYTE SENSING DEVICE

(57) Abstract: Aspects of the present disclosure include methods for determining an analyte concentration. In practicing methods according to certain embodiments, an analyte sensing unit is positioned at a location on the body of a subject, such that localized movement is applied to the location and the applied movement is sufficient to provide for mixing of interstitial fluid and determining an analyte concentration in the interstitial fluid. Devices and systems for practicing methods of the invention are also described.

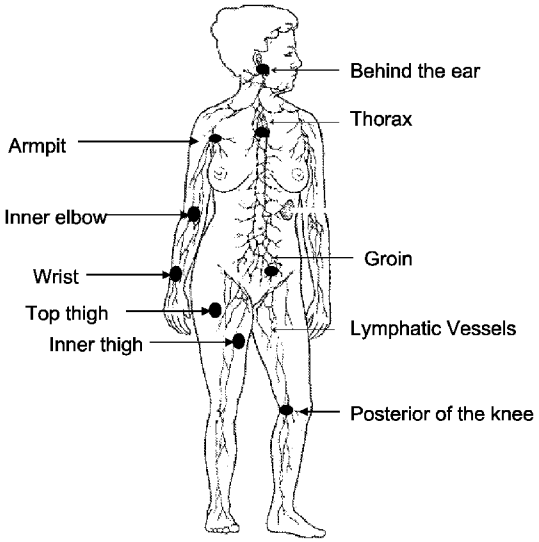

FIG. 1

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METHODS FOR POSITIONING AN ANALYTE SENSING DEVICE

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 61/529,141 filed August 30, 2011, the disclosure of which is incorporated by reference herein in its entirety.

INTRODUCTION

[002] Management of diabetes requires knowledge of the glycemia of patients. In general, health care professionals and diabetic patients base their decisions of injection and dosage of insulin or ingestion of food on blood glycemia, meaning the glucose concentration in blood. In hospitals or clinics, venous blood is withdrawn and sent to a laboratory for analysis or is analyzed at the bedside or in the office of the health care professional. Many times, however, the skin is lanced by the diabetic patient to obtain a droplet of blood which is used for the assay. Systems for frequently or continuously and automatically monitoring glycemia in the subcutaneous ISF, known as continuous glucose monitoring (CGM) devices, are also available. Sensors of CGM systems may be implanted in the subcutaneous tissue in a variety of places on the body.

[003] While continuous glucose monitoring is desirable, there are several challenges associated with obtaining accurate and stable glucose concentrations from continuous glucose monitors in interstitial fluid. Accordingly, further development of methods for obtaining accurate glucose concentrations from interstitial fluid as well as analyte-monitoring devices and systems is desirable.

SUMMARY

[004] Aspects of the present disclosure include methods for determining the presence and/or concentration of an analyte. In practicing methods according to certain embodiments, an analyte sensing unit is positioned at a location on the body of a subject, localized movement is applied to the location that is sufficient to provide for mixing of interstitial fluid, and the presence and/or concentration of an analyte concentration in the interstitial fluid is determined using the applied sensor. Devices and systems for practicing methods of the invention are also described.

BRIEF DESCRIPTION OF THE DRAWINGS

[005] A detailed description of various embodiments of the present disclosure is provided herein with reference to the accompanying drawings, which are briefly described below. The drawings are illustrative and are not necessarily drawn to scale. The drawings illustrate various embodiments of the present disclosure and may illustrate one or more embodiment(s) or example(s) of the present disclosure in whole or in part. A reference numeral, letter, and/or symbol that is used in one drawing to refer to a particular element may be used in another drawing to refer to a like element.

[006] **FIG. 1** shows a schematic of suitable positions on the body of a human according to certain embodiments of the present disclosure.

[007] **FIG. 2** shows a schematic of suitable positions on the wrist of a human according to certain embodiments of the present disclosure.

[008] **FIG. 3A** depicts the time course of the ratio of normalized signals from paired sensors. **FIGS. 3B-3C** show histograms from sensors positioned according to certain embodiments of the present disclosure.

[009] **FIG. 4A** depicts the time course of the percentage difference of normalized signals from paired sensors. **FIGS. 4B-4C** show histograms from sensors positioned according to certain embodiments of the present disclosure.

[0010] **FIGS. 5A-5F** show correlation data and histograms from sensors positioned according to certain embodiments of the present disclosure.

[0011] **FIGS. 6A-6B** show correlation data and histograms from sensors positioned according to certain embodiments.

[0012] **FIGS. 7A-7B** show correlation data between continuous glucose monitoring sensors in the interstitial fluid and blood glucose values from sensors positioned according to certain embodiments.

DETAILED DESCRIPTION

[0013] Aspects of the present disclosure include methods for determining an analyte concentration. In practicing methods according to certain embodiments, an analyte sensing unit is positioned at a location on the body of a subject, and applying movement to the location such that the applied movement is sufficient to provide for mixing of interstitial fluid and determining an analyte concentration in the interstitial fluid. Devices and systems for practicing methods of the invention are also described.

[0014] Before the embodiments of the present disclosure are described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course,

vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the embodiments of the invention will be embodied by the appended claims.

[0015] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0016] In the description of the invention herein, it will be understood that a word appearing in the singular encompasses its plural counterpart, and a word appearing in the plural encompasses its singular counterpart, unless implicitly or explicitly understood or stated otherwise. Merely by way of example, reference to "an" or "the" "analyte" encompasses a single analyte, as well as a combination and/or mixture of two or more different analytes, reference to "a" or "the" "concentration value" encompasses a single concentration value, as well as two or more concentration values, and the like, unless implicitly or explicitly understood or stated otherwise. Further, it will be understood that for any given component described herein, any of the possible candidates or alternatives listed for that component, may generally be used individually or in combination with one another, unless implicitly or explicitly understood or stated otherwise. Additionally, it will be understood that any list of such candidates or alternatives, is merely illustrative, not limiting, unless implicitly or explicitly understood or stated otherwise.

[0017] Various terms are described below to facilitate an understanding of the invention. It will be understood that a corresponding description of these various terms applies to corresponding linguistic or grammatical variations or forms of these various terms. It will also be understood that the invention is not limited to the terminology used herein, or the descriptions thereof, for the description of particular embodiments. Merely by way of example, the invention is not limited to particular analytes, bodily or tissue fluids, blood or capillary blood, or sensor constructs or usages, unless implicitly or explicitly understood or stated otherwise, as such may vary.

[0018] The publications discussed herein are provided solely for their disclosure prior to the filing date of the application. Nothing herein is to be construed as an admission that the

embodiments of the invention are not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

[0019] In further describing the present disclosure, methods for determining an analyte concentration in a subject are described first in greater detail. Next, devices and systems practicing methods of the present disclosure are also described.

METHODS FOR MONITORING AN ANALYTE USING A SENSOR UNIT POSITIONED ON A SUBJECT

[0020] As summarized above, aspects of the disclosure include methods for determining the presence and/or concentration of an analyte concentration in a subject by positioning an analyte sensing device at a location on the body of the subject, applying movement to the location such that the applied localized movement is sufficient to provide for mixing of interstitial fluid and determining an analyte concentration in the interstitial fluid.

[0021] Interstitial flow is the movement of fluid through a three dimensional extracellular matrix of a tissue and is present in all tissues where convection is needed to transport solutes through the interstitial space. Incoming interstitial fluid originates in the arterioles and is rapidly cleared primarily by the venules. However, in some cases, interstitial fluid which is not cleared by venules is cleared more slowly by the lymphatic system. As a result, interstitial fluid not rapidly cleared by the venules often remains stagnant (i.e., experiences little to no movement) in certain parts of the body resulting in spatially and temporally heterogenous concentration of analytes. As an alternative, the stagnant interstitial fluid can be equilibrated back with the arteriole-venule interstitial fluid by applied muscle movement around the interstitial space before the stagnant interstitial fluid is cleared by the lymphatic system.

[0022] For example, the glycemia of interstitial fluid at a location where interstitial fluid is rapidly cleared by the venules or is equilibrated with the arteriole-venule interstitial fluid by applied movement at the location correlates strongly with instantaneous blood glycemia. On the other hand, the glycemia of interstitial fluid at a location where the interstitial fluid is not rapidly cleared by the venules or is not equilibrated with the arteriole-venule interstitial fluid by movement at the location (i.e., is stagnant) can result in a poor correlation between glycemia in interstitial fluid and instantaneous blood glycemia.

[0023] Aspects of the present disclosure include methods for determining an analyte concentration in the interstitial fluid of a subject such that the analyte concentration in the interstitial fluid correlates strongly with the concentration of the analyte in the blood. In some instances, methods include positioning an analyte sensor at a location on the body of a subject and applying movement, e.g., provided by a source other than normal or inherent body

movement or function, to the location sufficient to provide for mixing of the interstitial fluid such that analyte concentration in the interstitial fluid strongly correlates with the analyte concentration in the blood.

[0024] In embodiments of the present disclosure, mixing of interstitial fluid at the location where the analyte sensor unit is positioned may be sufficient when the concentration of the analyte in the interstitial fluid at the location on the body corresponds closely with the concentration of the analyte as determined in the blood. By "corresponds closely" is meant that at least 80% or more of the concentration values determined from the interstitial fluid are within 20% or more of the concentration values as determined in blood. For example, at least 85% or more, such as 88% or more, such as 90% or more, such as 95% or more, such as 98% or more, and including 99% or more of the concentration values determined from the interstitial fluid are within 20% or more, such as within 15% or more, such as within 10% or more, including within 5% or more of the concentration values as determined by blood. In certain embodiments, at least 95% of the concentration values of the analyte determined in the interstitial fluid are within 20% of the concentration values as determined in blood.

[0025] In some embodiments, applied movement at the location on the body of the subject is sufficient to provide for mixing of stagnant interstitial fluid with the arteriole-venule interstitial fluid at the location. In these embodiments, an analyte sensor device may be positioned at a location on the subject and movement is applied to the location such that the applied movement sufficiently mixes stagnant interstitial fluid with the arteriole-venule interstitial fluid. In this way, interstitial fluid not rapidly cleared by the venules does not remain stagnant (i.e., experiences little to no movement, in other words remains in motion or is dynamic) and therefore provides an accurate analyte concentration. As such, in these embodiments, the interstitial fluid remains stagnant in the interstitial space for 10 minutes or less, such as 8 minutes or less, such as 6 minutes or less, such as 5 minutes or less, such as 4 minutes or less, such as 3 minutes or less, such as 2 minutes or less including 1 minute or less. In some embodiments, a sufficient mixing of the stagnant interstitial fluid with the arteriole-venule interstitial fluid may be provided by a correspondingly sufficient amount of applied movement to the location.

[0026] As described above, aspects of the present disclosure include positioning an analyte sensor device at a location on the body of a subject such that localized movement is applied manually or mechanically to the location sufficient to provide for mixing of interstitial fluid at the location. The term "localized" is used in its conventional sense to refer to movement which is applied within 100 mm or less from the location of the positioned sensor. For example, movement as provided by embodiments of the disclosure may include movement which is 90

mm or less, such as 80 mm or less, such as 70 mm or less, such as 60 mm or less, such as 50 mm or less, such as 40 mm or less, such as 30 mm or less, such as 20 mm or less, including 10 mm or less from the location of the analyte sensor device.

[0027] In certain embodiments, prior to positioning the analyte sensor device at a location on the body, the location is identified and selected as a suitable location for positioning the analyte sensor device. Depending on the physiology of the subject, suitable locations may include the legs, the arms, the wrist, the groin, the chest, among other locations. Any convenient location on the body may be suitable for positioning the analyte sensor device according to the present disclosure so long as the applied movement at the selected location or locations is sufficient to provide for mixing of interstitial fluid at the location. In identifying and selecting a suitable location for positioning the analyte sensor device, methods may further include determining the amplitude (e.g., rate of displacement) of applied muscle movement at the desired location. For example, the amplitude of applied movement such as exercise or massage may be predetermined or may be determined by mechanical, manual or electronic measurement as the movement is applied. Depending on the physiology of the subject, the amplitude of displacement during the applied movement (e.g., exercise, massage, etc.) may range, such as from about 10 to 75 mm, such as from about 15 to 65 mm, such as from about 20 to 60 mm, such as from about 25 to 55 mm, such as from about 25 to 50 mm, including from about 25 to 45 mm. Movement of the location of the positioned sensor during applied movement may also vary depending on the rate of movement by the subject. For example, the rate of applied movement may range, such as for example from about 8 to 100 cycles of movement (e.g., moving of the legs back and forth or the hand back and forth) per minute, such as about 10 to 90 cycles per minute, such as about 20 to 75 cycles per minute, such as about 20 to 50 cycles per minute, including about 25 cycles per minute. As such, the total applied localized movement may be from about 50 to about 1000 mm per minute, such as from about 75 to 750 mm per minute, such as from about 100 to 500 mm per minute, such as from about 150 to 400 mm per minute, including about 250 mm per minute.

[0028] In other instances, identifying and selecting a suitable location for positioning the analyte sensor unit may include determining the amount interstitial mixing at the desired location as a result of the applied movement.

[0029] As summarized above, aspects of the disclosure include methods for determining an analyte concentration in a subject by positioning an analyte sensing device at a location on the body of the subject, such that localized movement is applied to the location and the applied localized movement is sufficient to provide for mixing of interstitial fluid and determining an analyte concentration in the interstitial fluid. Figure 1 depicts certain locations for placing an analyte sensor device on the body of a subject according to methods of the present disclosure. In

certain embodiments, methods for determining an analyte concentration in a subject include positioning an analyte sensing unit at a location on the body of the subject, applying movement to the location such that the location experiences movement sufficient to provide for mixing of interstitial fluid at the location and determining an analyte concentration in the interstitial fluid after a predetermined amount of time after the applied movement. By "applied movement" is meant intentionally (i.e., consciously) moving the location in a manner suitable to facilitate increased circulation of interstitial fluid at the location. Sufficient movement can be applied using any convenient protocol. For example, movement may be applied by contracting or flexing a joint, such as for example through bending of the knee or elbow during exercise (e.g., walking, jogging, running, jumping, etc.) or the rotation, bending or shaking of the wrist such as during exercise or hand-waving. Alternatively or in addition, sufficient movement may be applied to the location by massaging the area around the analyte sensor device. For example, the analyte sensor device may be positioned on the upper deltoid, the wrist, the upper chest, the groin, the inner armpit, or behind the ear. Where the analyte sensor device is positioned on the upper deltoid, the wrist, the upper chest, the groin, the inner armpit, or behind the ear, these areas may be massaged in order to apply a movement to the location sufficient to provide mixing of interstitial fluid at the location prior to determining the analyte concentration. The amount of applied movement at the location on the body may vary, in some instances, ranging from 1 to 30 minutes of applied movement, such as 5 to 30 minutes, such as 5 to 25 minutes, such as 5 to 20 minutes, including 10 to 15 minutes of applied movement. In certain instances, a sufficient amount of applied movement may be provided in terms of the rate of displacement of the muscle (e.g., forearm, calf, bicep, quadriceps, etc.), such as from about 50 to about 1000 mm per minute, such as from about 75 to 750 mm per minute, such as from about 100 to 500 mm per minute, such as from about 150 to 400 mm per minute, including about 250 mm per minute.

[0030] In certain embodiments, where movement sufficient to provide for mixing of interstitial fluid is applied, the analyte sensor device may be positioned behind the knee (i.e., posterior portion of the knee joint). By "behind the knee" is meant the posterior portion of the leg which is located above the calf. As such, movement sufficient to provide for mixing of interstitial fluid at the posterior of the knee may include movement which is applied within about 50 mm or less from the posterior portion of the knee, such as within about 45 mm or less, such as within about 40 mm or less, such as within about 35 mm or less, such as within about 30 mm or less, such as within about 25 mm or less, such as within 20 mm or less, such as within about 15 mm or less, such as within about 10 mm or less, including within about 5 mm or less of the posterior portion of the knee. Movement applied to the posterior portion of the knee may vary, in some instances,

repeatedly bending and relaxing the knee for a predetermined amount of time or through exercise (e.g., walking, jumping, running, etc.).

[0031] In other embodiments, where movement sufficient to provide for mixing of interstitial fluid is applied, the analyte sensor device may be positioned on the calf. As such, movement sufficient to provide for mixing of interstitial fluid at the calf may include movement which is applied within about 50 mm or less from the calf, such as within about 45 mm or less, such as within about 40 mm or less, such as within about 35 mm or less, such as within about 30 mm or less, such as within about 25 mm or less, such as within 20 mm or less, such as within about 15 mm or less, such as within about 10 mm or less, including within about 5 mm or less of the calf. Movement applied to the calf may vary, such as for example through exercise (e.g., walking, jumping, running, etc.).

[0032] In yet other embodiments, where movement sufficient to provide for mixing of interstitial fluid is applied, the analyte sensor device may be positioned on the inner elbow (i.e., anterior portion of the elbow joint). By "inner elbow" is meant the anterior portion of the arm which is located between the biceps and the forearm. As such, movement sufficient to provide for mixing of interstitial fluid at the inner elbow may include movement which is applied within about 50 mm or less from the inner elbow, such as within about 45 mm or less, such as within about 40 mm or less, such as within about 35 mm or less, such as within about 30 mm or less, such as within about 25 mm or less, such as within 20 mm or less, such as within about 15 mm or less, such as within about 10 mm or less, including within about 5 mm or less of the inner elbow. Movement applied to the inner elbow may vary, in some instances, repeatedly bending and relaxing the elbow for a predetermined amount of time or through exercise (e.g., walking, jumping, running, etc.).

[0033] In yet other embodiments, where movement sufficient to provide for mixing of interstitial fluid is applied, the analyte sensor device may be positioned on the wrist. By "wrist" is meant either the anterior portion of the arm which is located between the hand and the forearm or posterior portion of the arm which is located between the back of the hand and the posterior forearm. In other words, the word "wrist" refers to the posterior and anterior radiocarpal joint (i.e., the joint between the radius and the carpus) or the anatomical region surrounding the carpus including the distal parts of the bones of the forearm and the proximal parts of the metacarpus. The wrist may be divided into regions, including the lower wrist and the upper wrist. Figure 2 depicts locations for subcutaneously positioning an analyte sensor device on the wrist according to certain methods of the present disclosure. In some instances, locations on the wrist suitable for placing an analyte sensing device include two zones (e.g., Zones A and B in Figure 2). Zone A is defined by a first line (LINE 1) connecting the radiocarpal joint and a

second line (LINE 2) at the midpoint between the radiocarpal joint and the forearm. Zone B extends between LINES 2 and 3 (i.e., from the midpoint between the radiocarpal joint and forearm and the lower edge of the forearm).

[0034] The physiology of subjects employing the methods described herein may vary depending on many factors such as age, gender, height and weight. As such, locations for positioning an analyte sensor device on the wrist according to embodiments of the disclosure may vary. As described above, locations for positioning an analyte sensor device on the wrist may include locations which are located on the lower wrist or the upper wrist (e.g., Zones A and/or B as depicted in Figure 2). As such, the analyte sensor device may be positioned 75 mm or less from the radiocarpal joint, such as within about 60 mm or less, such as within about 50 mm or less, such as within about 40 mm or less, including within about 25 mm or less from the radiocarpal joint. In other embodiments, an analyte sensor device is positioned within about 75 mm or less from the forearm, such as within about 60 cm or less, such as within about 50 cm or less, such as within about 40 cm or less, including within about 25 mm or less from the forearm.

[0035] In embodiments of the present disclosure, movement sufficient to provide for mixing of interstitial fluid at the wrist may include movement which is applied within about 25 mm or less from the wrist, such as within about 20 mm or less, such as within about 15 mm or less, such as within about 10 mm or less, including within about 5 mm or less of the wrist. Movement applied to the wrist may vary, in some instances, repeatedly rotating or bending and relaxing the wrist for a predetermined amount of time or through exercise (e.g., walking, jumping, running, etc.) or hand-waving. In yet other embodiments, where movement sufficient to provide for mixing of interstitial fluid is applied, the analyte sensor unit may be positioned on the groin. As such, movement sufficient to provide for mixing of interstitial fluid at the groin may include movement which is applied within about 50 mm or less from the groin, such as within about 45 mm or less, such as within about 40 mm or less, such as within about 35 mm or less, such as within about 30 mm or less, such as within about 25 mm or less, such as within 20 mm or less, such as within about 15 mm or less, such as within about 10 mm or less, including within about 5 mm or less of the groin. Movement applied to the groin may vary, such as for example, massaging the groin for a predetermined amount of time or through exercise (e.g., walking, jumping, running, etc.).

[0036] In yet other embodiments, the analyte sensor device is positioned on the thorax of the subject. By thorax (i.e., chest) is meant the part of the body located between the abdomen and the neck. The thorax may be divided into regions, including the central thorax and the outer thorax. The outer thorax may include the lower thorax situated near the upper abdomen and the upper thorax situated near the neck. The outer thorax also includes the part of the thorax distal

to the midline of the body on either the right or left side of the body. In some embodiments, the analyte sensor device is positioned at the apex of the thorax. As described above, the apex of the thorax is the central point of the thorax, situated along the midline of the body and equidistant from the neck and the upper abdomen. In certain embodiments, applied movement sufficient to provide for mixing of interstitial fluid at the thorax may include movement which is applied within about 50 mm or less from the thorax, such as within about 45 mm or less, such as within about 40 mm or less, such as within about 35 mm or less, such as within about 30 mm or less, such as within about 25 mm or less, such as within 20 mm or less, such as within about 15 mm or less, such as within about 10 mm or less, including within about 5 mm or less of the thorax. Movement applied to the thorax may vary, such as for example, massaging the thorax for a predetermined amount of time or through exercise (e.g., walking, jumping, running, etc.).

[0037] In certain embodiments, applying movement to the location where the analyte sensor device is positioned includes applying the movement in a regular periodic pattern. By "regular periodic pattern" is meant that the movement is applied according to predetermined time intervals. For example, in some instances, the movement may be applied every 1 second or more, such as 5 seconds or more, such as every 10 seconds or more, such as every 15 seconds or more, such as every 30 seconds or more, such as every 60 seconds or more, such as every 90 seconds or more, such as every 500 seconds or more, including every 1000 seconds or more. Alternatively or in addition, the movement may be applied for predetermined durations. For example, movement applied in a regular periodic pattern may include applying the movement for 2 minutes or more, such as 5 minutes or more, such as 7 minutes or more, such as 10 minutes or more, such as 15 minutes or more, such as 30 minutes or more, such as 60 minutes or more, including 90 minutes or more. In other instances, applying the movement includes repeating the movement in a regular periodic pattern such as repeating the movement every 2 minutes or more, such as every 5 minutes or more, such as every 7 minutes or more, such as every 10 minutes or more, such as every 15 minutes or more, such as every 30 minutes or more, such as every 60 minutes or more, including every 90 minutes or more.

[0038] In some embodiments, applying movement to the location such that the movement is sufficient to provide for mixing of interstitial fluid at the location include externally applied movements. By "externally applied movements" is meant movements that are applied by a device, machine or person other than the subject. For example, in some instances externally applied movement may include mechanically applying movement to the location, such as by a motorized muscle contractor, mechanical stretching contraption or a massaging device. In other instances, externally applied movement may include electrically applying movement to the

location, such as by electrical impulse, or applying an electrical current to leads attached to the body to stimulate or generate movement at the location.

[0039] In certain embodiments of the present disclosure, an analyte concentration is determined after applying movement to the location of the positioned analyte sensor. The amount of time between applying movement at the location and determining the concentration of an analyte at the location may vary. For example, the time may range, such as from 1 to 30 minutes of after the applied movement, such as 5 to 30 minutes, such as 5 to 25 minutes, such as 5 to 20 minutes, including 10 to 15 minutes after the applied movement. In other embodiments, the analyte concentration may be determined both before and after applying movement to the location. In yet other embodiments, the analyte concentration may be determined concurrently while applying movement to the location.

[0040] In embodiments of the present disclosure, an analyte sensor unit is positioned at a location on the body of a subject. In some instances, positioning an analyte sensor unit at a location on the body includes implanting an analyte sensor into the subcutaneous tissue at the location. As described below, force may be applied to an insertion device, either manually or mechanically to implant the sensor beneath the surface of the skin. In certain instances, an insertion gun may be employed to implant the sensor into the subcutaneous tissue. Insertion devices for implanting an analyte sensor into the subcutaneous tissue may include, but are not limited to those described in U.S. Patent No. 6,175,752 filed April 30, 1998, the disclosure of which is incorporated by reference in its entirety. Where an analyte sensor is implanted into the subcutaneous tissue, the depth of implantation varies depending on the physiology of the subject as well as the particular location on the body selected. In some instances, the analyte sensor is implanted to a depth of from about 1.0 to 15.0 mm beneath the surface of the skin, such as about 1.5 to 12.5 mm, such as about 2.0 to 10.0 mm, such as about 2.5 to 9.0 mm, such as 3.0 to 7.5 mm, including 4.0 to 6.0 mm beneath the surface of the skin.

[0041] In certain embodiments, methods of the present disclosure include positioning more than one analyte sensor device at one or more locations on the body of the subject. Where more than one analyte sensor devices are positioned on the body, the analyte sensor devices may be positioned on the thorax, or an extremity (i.e., leg, arm, wrist etc.) or any combination thereof. For example, in certain instances, two or more analyte sensor device may be positioned on the arm, such as for example, a first analyte sensor device on the left arm and a second analyte sensor device on the right arm. In other instances, a first analyte sensor device is position on the lower arm and a second analyte sensor device is positioned on the upper arm. In other instances, a first analyte sensor device is positioned on the wrist on the left arm and a second analyte sensor device is positioned on the wrist of the right arm. In other instances, a first analyte sensor

is positioned on the wrist and a second analyte sensor is positioned on the deltoid of the same arm (e.g., left wrist, left deltoid or right wrist, right deltoid). In other instances, a first analyte sensor is positioned on the wrist and a second analyte sensor is positioned on the deltoid of the opposing arm (e.g., left wrist, right deltoid or right wrist, left deltoid) In yet other instances, two or more analyte sensor devices may be positioned on the leg, such as for example a first analyte sensor device positioned to the left leg and a second analyte sensor device positioned to the right leg or a first analyte sensor device positioned on the upper leg and a second analyte sensor device positioned on the lower leg, or a combination thereof.

[0042] Where an analyte sensor device is positioned on an extremity, the analyte sensor device may be positioned behind the joint of the extremity, such as behind the knee or the elbow or along the anterior portion of the wrist. In another example, a first analyte sensor device may be positioned on the leg such as behind the knee joint and a second analyte sensor device may be positioned on the arm, such for example on the forearm, the deltoid, along the anterior portion of the wrist or behind the elbow. In other instances, a first analyte sensor device may be positioned on the groin and a second analyte sensor device may be positioned on the leg, such for example on the thigh or on the calf.

[0043] In certain instances, methods of the present disclosure further include determining the concentration of an analyte using two or more analyte sensor devices positioned on different parts of the body and comparing the concentrations from each of the analyte sensor devices. Determining the concentration of an analyte using two or more analyte sensor devices positioned on different parts of the body and comparing concentration values obtained by each analyte sensor device may be used to improve the accuracy or precision of the acquired analyte concentration values or may be used to further calibrate one or more of the analyte sensor devices. By "comparing" is meant the analyte concentration values obtained from each analyte sensor device may be related to each other mathematically (e.g., by an algorithm) or may simply be visually compared by the user. For example, in some instances, values obtained from one of the analyte sensor device may be used to calibrate one or more of the other analyte sensor device. In other instances, values obtained from one of the analyte sensor device may be used to mathematically (e.g., by an algorithm) correct the values obtained by one or more of the other analyte sensor device. Depending on the location of the analyte sensor device (e.g., having involuntary muscle movement or intentionally applied movement), methods for positioning and obtaining an analyte concentration from the two or more sensors may follow the appropriate protocols as described in greater detail above.

[0044] In certain embodiments, the method further includes monitoring or measuring (automatically) the localized movement sufficient to provide for mixing of circulating and non-

circulating interstitial fluid in a subcutaneous space of the location, during the sensor wear period. In such embodiments, a motion sensor may be positioned proximal to the analyte sensor and may measure or monitor the level of localized movement to determine whether the level of movement meets a predetermined level that provides for mixing of circulating and non-circulating interstitial fluid in a subcutaneous space of the location, during the sensor wear period.

SYSTEMS FOR DETERMINING AN ANALYTE CONCENTRATION

[0045] Aspects of the present disclosure also include analyte monitoring systems for practicing the subject methods (e.g., determining the analyte concentration). The particular configuration of a system and other units used in the analyte monitoring system may depend on the use for which the analyte monitoring system is intended and the conditions under which the analyte monitoring system will operate. One embodiment of the analyte monitoring system includes a sensor configured for at least partial insertion into the subject. For example, insertion of the sensor may be made for insertion in subcutaneous tissue for testing analyte levels in interstitial fluid. This level may be correlated and/or converted to analyte levels in blood or other fluids. The site and depth of implantation may affect the particular shape, components, and configuration of the sensor. Examples of suitable sensors for use in the analyte monitoring systems of the invention are described in U.S. Patent No. 6,175,752, the disclosure of which is incorporated herein by reference.

[0046] Additional embodiments of analyte monitoring systems suitable for practicing methods of the present disclosure are described in U.S. Patent Nos., U.S. Pat. No. 6,134,461, U.S. Pat. No. 6,579,690, U.S. Pat. No. 6,605,200, U.S. Pat. No. 6,605,201, U.S. Pat. No. 6,654,625, U.S. Pat. No. 6,746,582, U.S. Pat. No. 6,932,894, U.S. Pat. No. 7,090,756, U.S. Pat. No. 5,356,786; U.S. Pat. No. 6,560,471; U.S. Pat. No. 5,262,035; U.S. Pat. No. 6,881,551; U.S. Pat. No. 6,121,009; U.S. Pat. No. 7,167,818; U.S. Pat. No. 6,270,455; U.S. Pat. No. 6,161,095; U.S. Pat. No. 5,918,603; U.S. Pat. No. 6,144,837; U.S. Pat. No. 5,601,435; U.S. Pat. No. 5,822,715; U.S. Pat. No. 5,899,855; U.S. Pat. No. 6,071,391; U.S. Pat. No. 6,377,894; U.S. Pat. No. 6,600,997; U.S. Pat. No. 6,514,460; U.S. Pat. No. 5,628,890; U.S. Pat. No. 5,820,551; U.S. Pat. No. 6,736,957; U.S. Pat. No. 4,545,382; U.S. Pat. No. 4,711,245; U.S. Pat. No. 5,509,410; U.S. Pat. No. 6,540,891; U.S. Pat. No. 6,730,200; U.S. Pat. No. 6,764,581; U.S. Pat. No. 6,503,381; U.S. Pat. No. 6,676,816; U.S. Pat. No. 6,893,545; U.S. Pat. No. 6,514,718; U.S. Pat. No. 5,262,305; U.S. Pat. No. 5,593,852; U.S. Pat. No. 6,746,582; U.S. Pat. No. 6,284,478; U.S. Pat. No. 7,299,082; U.S. Pat. No. 7,811,231; U.S. Pat. No. 7,822,557; U.S; U.S. Pat. No. 8,106,780; Patent Application Publication No. 2010/0198034; U.S. Patent Application Publication No.

2010/0324392; U.S. Patent Application Publication No. 2010/0326842 U.S. Patent Application Publication No. 2007/0095661; U.S. Patent Application Publication No. 2008/0179187 ; U.S. Patent Application Publication No. 2008/0177164; U.S. Patent Application Publication No. 2011/0120865; U.S. Patent Application Publication No. 2011/0124994; U.S. Patent Application Publication No. 2011/0124993; U.S. Patent Application Publication No. 2010/0213057; U.S. Patent Application Publication No. 2011/0213225; U.S. Patent Application Publication No. 2011/0126188; U.S. Patent Application Publication No. 2011/0256024; U.S. Patent Application Publication No. 2011/0257495; U.S. Patent Application Publication No. 2012/0157801; U.S. Patent Application Serial No. 13/407,617, and U.S. Patent Application Serial No. 13/526,136, the disclosures of each of which are incorporated herein by reference in their entirety. Moreover, methods of the present disclosure may be practiced using battery-powered or self-powered analyte sensors, such as those disclosed in U.S. Patent Application Publication No. 2010/0213057, incorporated herein by reference in its entirety.

EXPERIMENTAL

EXAMPLE 1

[0047] The histograms and best-fit trend line from paired and normalized continuous glucose monitors (FreeStyle Navigator from Abbott Diabetes Care, Alameda CA) positioned at different locations on the body are shown in Figures 3a-c. The current of each sensor was normalized by dividing its instantaneous value by its average value over the entire test. The ratio (normalized instantaneous current of sensor 1)/(normalized instantaneous current of sensor 2) was calculated for each minute, then the calculated current ratios were placed into 0.02 wide bins and their number in each bin was counted.

[0048] Figure 3a depicts the time course of the ratio of normalized signals from paired sensors positioned on the left calf and right calf after localized movement is applied in the form of exercise to the location of the sensor. Figures 3b-c depict histograms of the ratio distribution of the data acquired from paired sensors where both sensors are positioned on the same person and localized movement is applied in the form of exercise to the location of the sensor. Figures 3b: *sensor 1* positioned on the left calf just below the center of the inside of the knee and *sensor 2* positioned on the right calf just below the center of the inside of the knee. Figure 3c: *sensor 1* positioned the outside of the upper arm, on the side opposite to the armpit and *sensor 2* positioned on the calf just below the center of the inside of the knee.

[0049] The deviation from a normal or Gaussian distribution is a measure of the temporal dissimilarity of the interstitial fluid found at each particular location. As such, dissimilarity

between the interstitial fluid found in each location would result in different determined analyte concentrations depending on the location of the positioned analyte sensor device. As depicted in Figures 3a-c, the distribution is close to normal, meaning Gaussian, for paired sensors with both in the back of the knee, but is much broader and is not Gaussian for paired sensors with one on the outside of the arm opposite to the armpit and the other on the inside of the knee. This demonstrates that there is a little dissimilarity between paired sensors with both on the back of the knee when localized movement in the form of exercise is applied to the location, but there is dissimilarity between interstitial fluid found on the outside of the arm opposite the armpit and interstitial fluid found in the inside of the knee.

[0050] Figure 4a depicts the time course of the percentage difference of normalized signals from paired sensors positioned on the left calf and right calf after localized movement is applied in the form of exercise to the location of the sensor. Figures 4b-c depict the normalized paired sensor output differences defined by equation (1): $(Sens_1 - Sens_2)/1/2(Sens_1 + Sens_2)$ for the sensors positioned as discussed above for Figures 3b-c. For two error-free sensors in two temporally similarly behaving ISFs the distribution would be an infinitesimally narrow line, vertical to the x-axis, at x=0. For two sensors with a finite measurement error, residing in temporally similarly behaving ISFs, the width of the distribution is expected to increase and the height of the distribution is expected to decrease as the measurement error increases; the distribution would remain normal i.e. Gaussian, even for large measurement errors. For two sensors residing in two temporally dissimilar fluids the distribution is not expected to be Gaussian, irrespective of the measurement error. The deviation from Gaussian distribution is a measure of the temporal dissimilarity of the two ISFs.

[0051] As illustrated in Figures 4b-c, the distributions for two sensors in the backs of the left knee and in the back of the right knee are Gaussian; they are, however, much broader and are not Gaussian for two sensors with one residing in the upper arm on the side facing away from the chest and the other in the back of the knee. As such, this demonstrates that there is a temporal dissimilarity of the ISF of different sites on the body, namely the upper arm side facing away from the chest, whereas ISF of the back of the knees show similar glycemia in the ISF.

[0052] Figures 5a-c depict the correlation of normalized signals and the distributions of the ratio of normalized signals for symmetrically positioned sensors on the left calf and right calf. Movement is applied to the muscle at the position in the form of exercise. Figures 5d-f depict histograms of the ratio distribution of the data acquired from the paired sensors as well as its normalized distribution curve. As depicted by Figures 5a-f, when movement is applied to the location where the sensor is positioned, the ISF/lymph mixing is similar to the circulation of

capillary blood. As such, outputs of symmetrically placed left and right sensors show similar data values.

[0053] The data illustrated in Figure 5 is summarized in Table 1 below:

Table 1

Position Location	R^2	Slope	Intercept	n
Calf	0.76	0.95	0.03	3
Outer Arm	0.72	0.98	0.01	1
Inner Arm	0.68	0.98	0.03	1
Upper Chest	0.66	0.95	0.05	1

[0054] Figures 6a-b depict correlation data between a continuous glucose monitoring sensor positioned at the calf where movement was applied in the form of exercise and corresponding glucose values as obtained by blood. Figure 6a depicts a scatter plot with best-fit line demonstrating that positioning a sensor on the calf in combination with applied movement may result in good correlation between CGM glucose concentrations obtained in interstitial fluid and glucose concentrations as obtained by blood. Figure 6b depicts the distribution of residuals from the data obtained by the CGM monitor.

[0055] Table 2 summarizes data obtained by continuous glucose monitoring positioned on the calf. As illustrated, when movement is applied (e.g., walking, running, contracting and flexing of the calf muscle) in combination with positioning the sensor device on the calf, the correlation between values obtained by measurements in the interstitial fluid and measurements obtained in blood is strong. However, in the absence of applied movement (e.g., during sleep) to the calf, there was a weaker correlation between glucose measurements in the interstitial fluid.

Table 2

Awake – Applied Movement (e.g., flexing, contracting calf muscles, walking)		
R^2	Slope	Intercept
0.92	0.99	0
0.69	1	0.03

Asleep – No Applied Movement (e.g., in supine position)		
R^2	Slope	Intercept
0.41	0.4	0.51
0.35	0.78	0.22

[0056] Figures 7a-b illustrate the calculation and correlation between the scaled current from a continuous glucose monitor for glucose measurements obtained in interstitial fluid with glucose values as obtained by blood (FreeStyle, Abbott Diabetes Care, Alameda CA). Figure 7a depicts the correlation between scaled currents obtained by the CGM sensor device positioned on the calf with blood glucose concentration. Blood glucose may be calculated from the scaled current according to Equation (2):

Blood Glucose (BG) = Scaled Current (SC) x (Average BG)/(Average SC).

[0057] Figure 7b depicts the correlation between blood glucose as determined using Equation (2) from the scaled current (from continuous glucose monitor sensors positioned on the calf and applying localized muscle movement in the form of exercise) and blood glucose as determined using a blood glucose meter.

[0058] Figures 7a-b depict the correlation between blood glucose as determined using Equation (2) from scaled current from continuous glucose monitor sensors positioned on the calf and applying localized muscle movement and blood glucose as determined using a blood glucose meter. As illustrated by the data in Figures 7a-b, there is a strong correlation between glucose values determined from scaled currents by continuous glucose monitoring sensors in the interstitial fluid and glucose values determined by a glucose meter from blood when continuous glucose monitoring sensors are positioned on the calf and movement is applied to the calf.

EXAMPLE 2

[0059] Glucose concentration values obtained from continuous glucose monitor sensors positioned at various locations on the body were tested and compared with blood glucose values obtained by in vitro test strips (FreeStyle Navigator from Abbott Diabetes Care, Alameda CA). Continuous glucose values were calculated from sensor data with the NEAT program. The subject was a non-diabetic woman who was 55 years old having a medium build (BMI 23) and was determined to be physically active. Continuous sensors were implanted using a standard mounting plate. Sensors were placed on the upper arm, wrist, top of the thigh and the inner thigh (see Table 3). For the sensors positioned on the upper arm, the top of the thigh as well as the inner thigh, sensors were positioned to two different depths (3.4 mm and 5 mm). For sensors

positioned on the wrist, the sensor was placed 1 inch up from the wrist bone, (such as, e.g., where a watch might be worn). Band aids were added to the mounting tape to secure the mounting plate and transmitter. No pain and little blood was observed during insertion of the continuous glucose sensors.

[0060] Blood samples for in vitro blood glucose values were taken from multiple areas for comparison: finger, forearm, thigh, etc. The absolute relative deviation (ARD) between values from the implanted continuous glucose monitor and values obtained by in vitro blood glucose (i.e., test strip) were calculated (|cgm - bgl/bg) for all blood samples.

[0061] The mean and standard deviation of ARD values for continuous glucose monitor sensors positioned at each location on the body are summarized in Table 3. For sensors positioned on the arm and thigh locations, the mean ARD ranged from about 0.11 to 0.18 with an average value of 0.14, and the standard deviation of the ARD ranged from 0.08 to 0.20 with an average value of 0.11. The 3.4 mm sensor tested at the wrist showed a mean ARD of 0.133. Analysis of variance for the systematic variation of mean ARD with location, for the four locations with both short and standard sensors, gave p = 0.13.

Table 3

Sensor Depth (mm)	Position on Body	ARD Mean	ARD StdDev	N
3.4	Arm Upper	0.147	0.108	78
5	Arm Upper	0.114	0.078	67
3.4	Wrist	0.133	0.119	515
3.4	Thigh (Top)	0.114	0.084	65
5	Thigh (Top)	0.125	0.089	66
3.4	Thigh (Inner)	0.117	0.104	389
5	Thigh (Inner)	0.103	0.079	140

[0062] The present description should not be considered limited to the particular examples described above, but rather should be understood to cover all aspects as fairly set out in the attached claims. Various modifications, equivalent processes, as well as numerous structures to which the transition metal complexes may be applicable will be readily apparent to those of skill in the art upon review of the instant specification.

THAT WHICH IS CLAIMED IS:

1. A method of determining a concentration of an analyte, the method comprising:

positioning an analyte sensor device at a location on the body of a subject;

applying movement to the location, wherein the movement is sufficient to provide for mixing of interstitial fluid at the location; and

determining an analyte concentration in the interstitial fluid.

2. The method according to Claim 1, wherein the movement is applied in a regular periodic pattern.

3. The method according to Claim 2, wherein the regular periodic pattern comprises repeating the movement for 5 minutes or more and wherein the movement is applied 5 minutes or more before determining the analyte concentration in the interstitial fluid.

4. The method according to Claim 1, wherein the movement is an externally applied movement.

5. The method according to Claim 4, wherein the externally applied movement is electrically applied.

6. The method according to Claim 2, wherein the externally applied movement is mechanically applied.

7. The method according to Claim 1, wherein the applied movement comprises contracting or flexing a muscle.

8. The method according to Claim 1, wherein the location is on the wrist.

9. The method according to Claim 1, wherein the location is behind the knee.

10. The method according to Claim 1, wherein the location is the inner elbow.

11. The method according to Claim 1, wherein the applied movement comprises massaging the location.

12. The method according to Claim 1, wherein the location is the inner armpit.

13. The method according to Claim 1, wherein the location is the groin.

14. The method according to Claim 1, wherein at least 95% of the analyte concentration values determined in the interstitial fluid is within 5% of an analyte concentration determined in blood.

15. The method according to Claim 1, further comprising measuring a level of the movement applied to the location during the sensor wear period.

16. The method according to Claim 1, wherein the analyte sensor device comprises:

a housing adapted for placement on the surface of skin having a bottom surface for contacting with the skin and wherein the housing comprises:

an electrochemical sensor having a portion within the housing and a portion exterior to the housing and having a length to permit insertion of the second portion beneath the surface of the skin; and

an adhesive disposed on the bottom surface of the housing to attach the housing to the surface of the skin.

17. The method according to Claim 16, wherein positioning comprises:

contacting an insertion device coupled with the analyte sensor device to the skin of the subject;

inserting at least a portion of the electrochemical sensor subcutaneously beneath the surface of the skin at the location on the body of the subject using the insertion device; and

decoupling the insertion device from the analyte sensor unit.

18. The method according to Claim 17, wherein the electrochemical sensor is inserted to a depth of about 2.0 to about 8.0 mm beneath the surface of the skin.

19. The method according to Claim 16, wherein the electrochemical sensor comprises:

a working electrode comprising an analyte responsive enzyme and a mediator; and

a counter electrode.

20. The method according to Claim 19, wherein the analyte is glucose and wherein the analyte responsive enzyme is glucose oxidase or glucose dehydrogenase.

21. The method according to Claim 1, wherein the method further comprises displaying the analyte concentration.

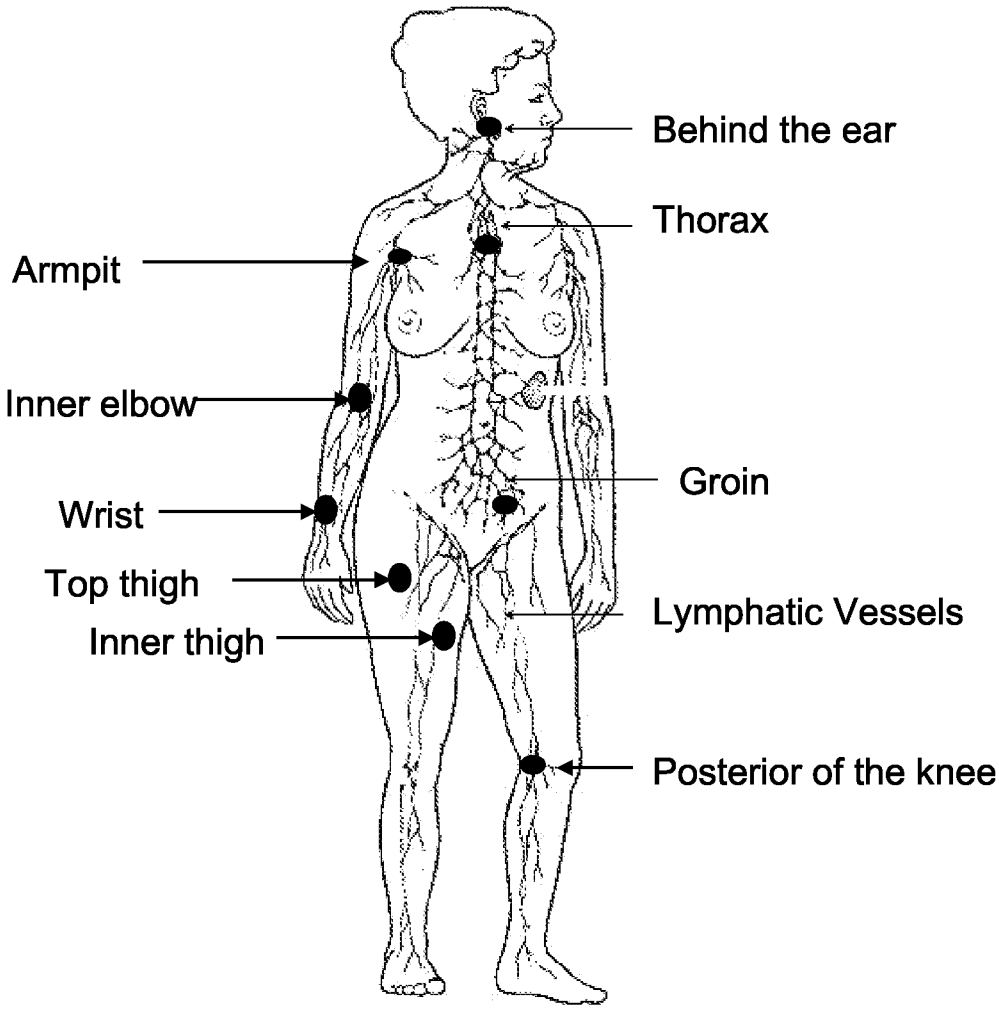

Behind the ear
Thorax
Armpit
Inner elbow
Groin
Wrist
Top thigh
Lymphatic Vessels
Inner thigh
Posterior of the knee

FIG. 1

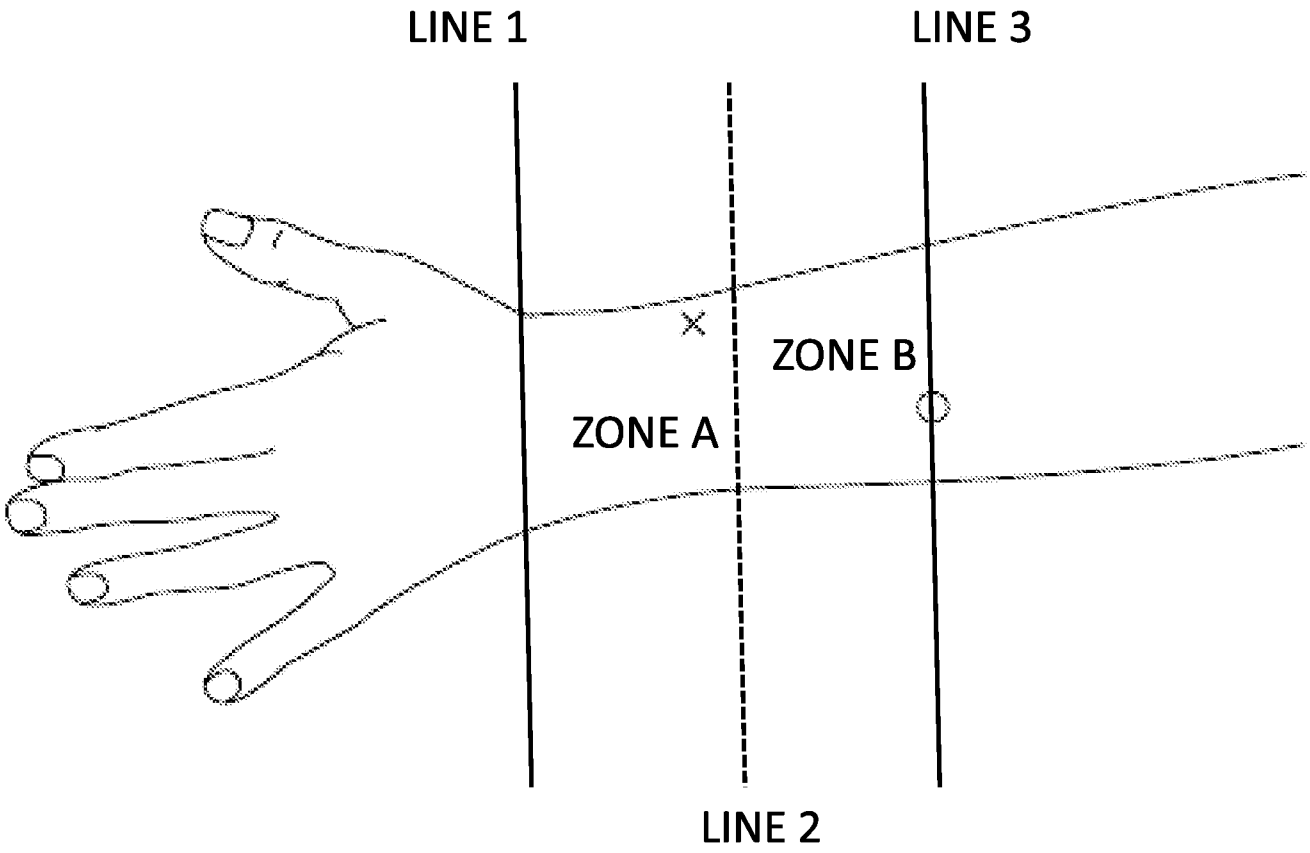


FIG. 2

FIG. 3A

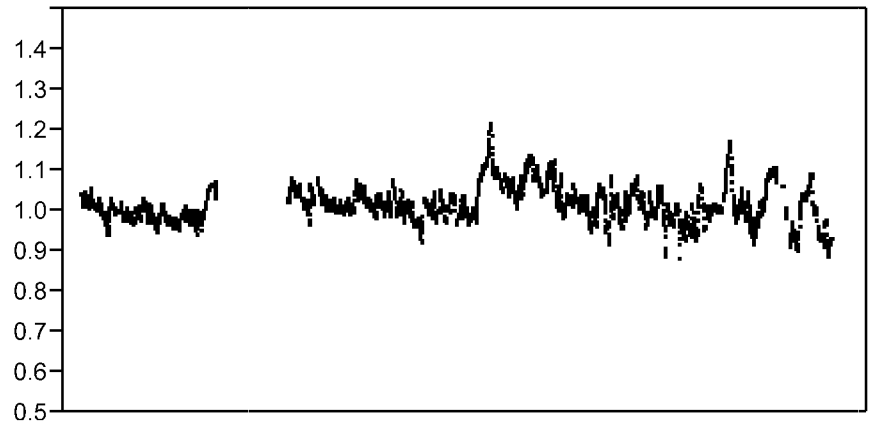


FIG. 3B

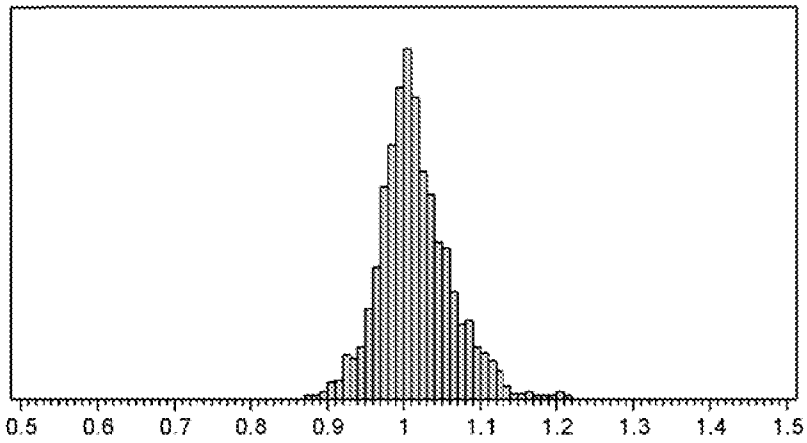


FIG. 3C

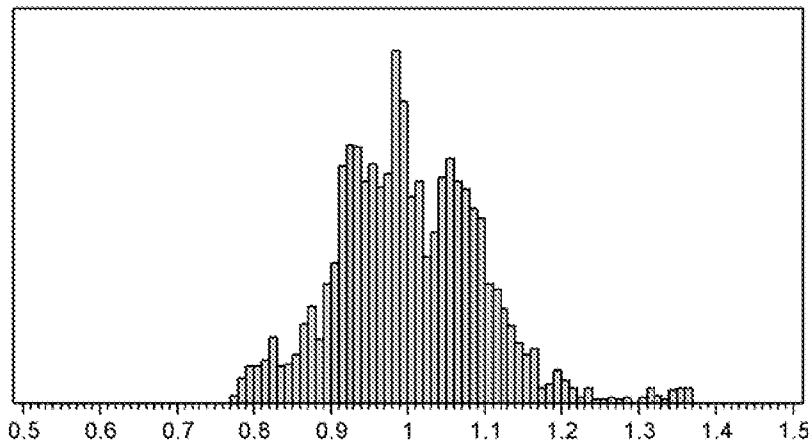


FIG. 4A

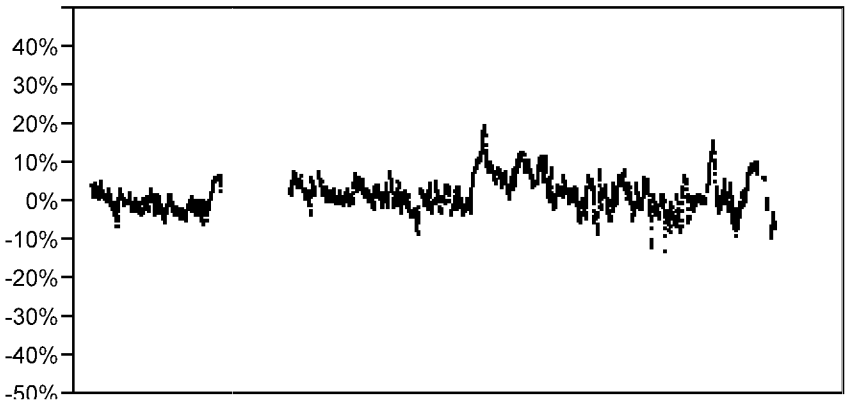


FIG. 4B

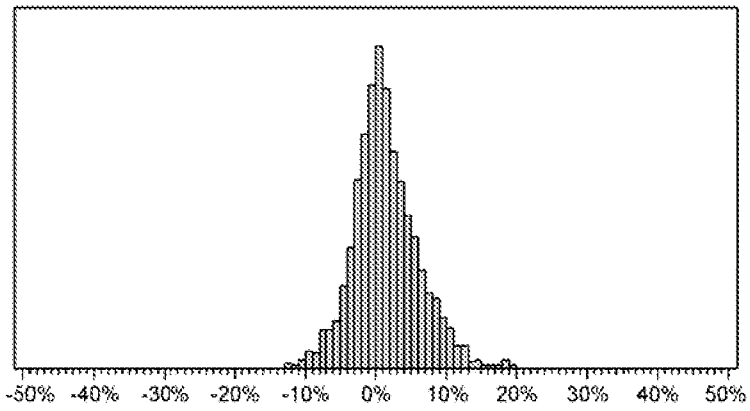


FIG. 4C

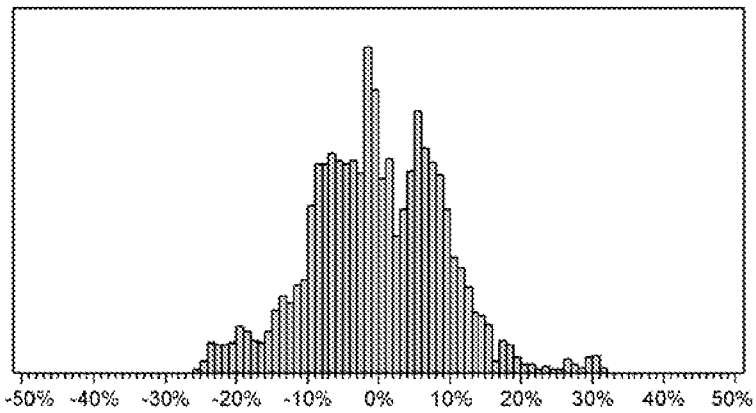


FIG. 5A

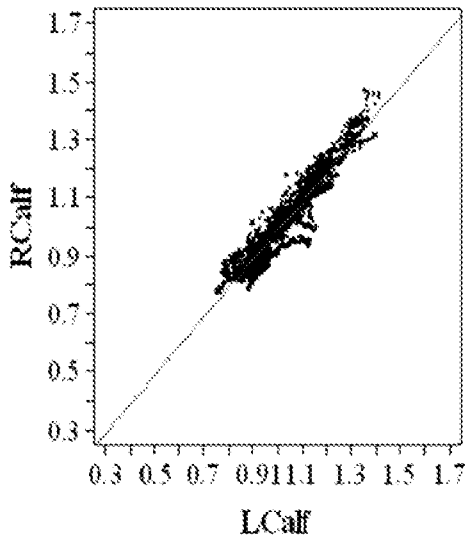


FIG. 5B

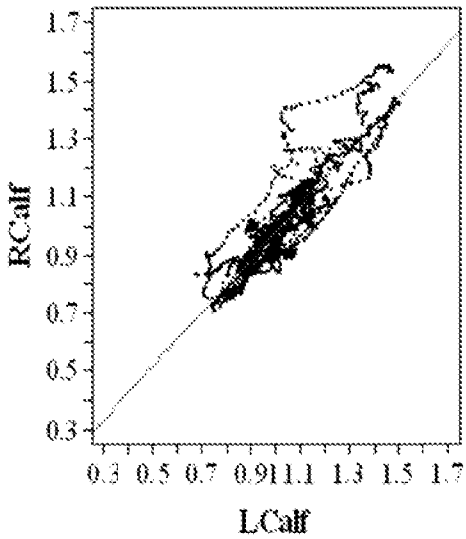


FIG. 5C

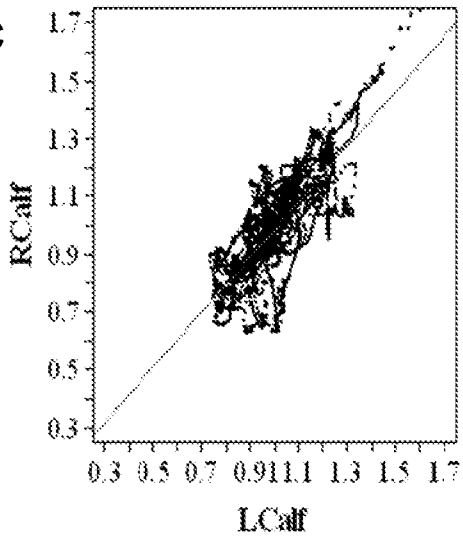


FIG. 5D

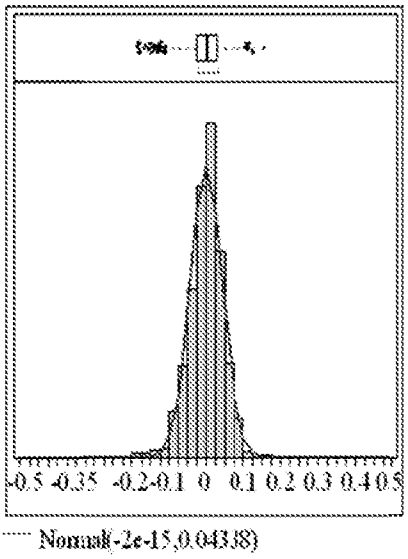


FIG. 5E

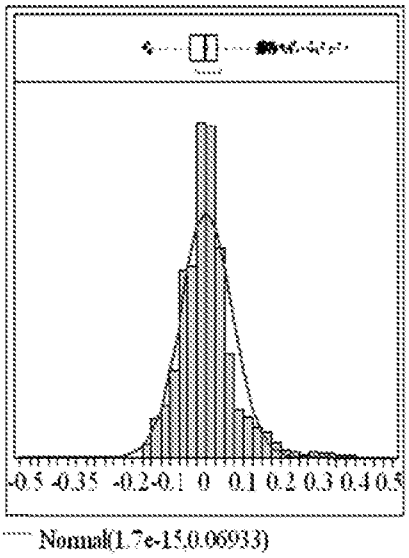


FIG. 5F

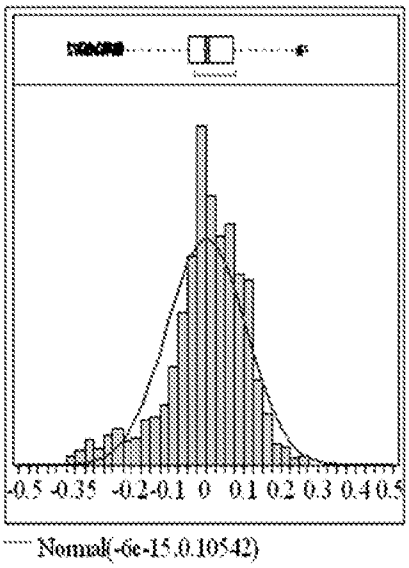


FIG. 6A

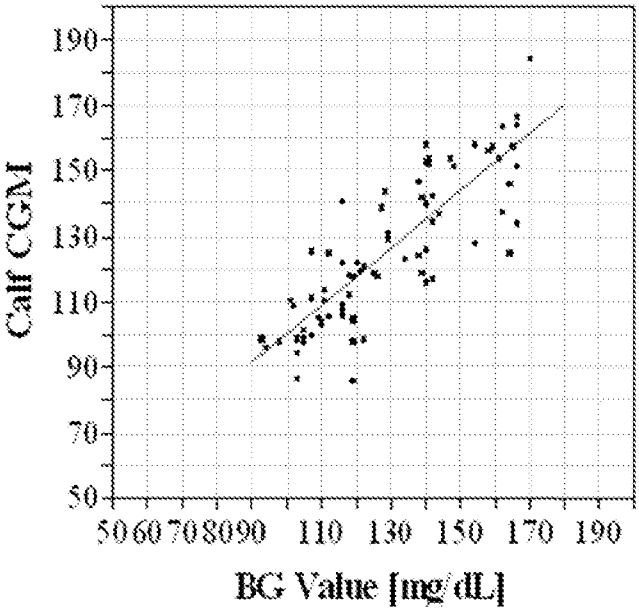

Calf CGM
190
170
150
130
110
90
70
50
50 60 70 80 90 110 130 150 170 190
BG Value [mg/dL]

FIG. 6B

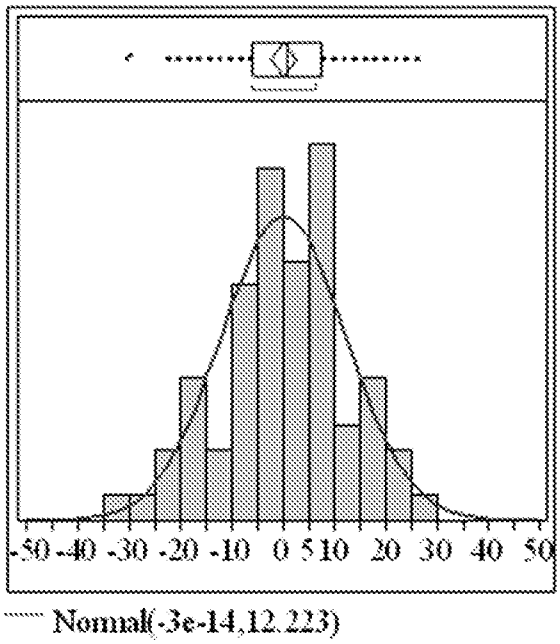

-50 -40 -30 -20 -10 0 5 10 20 30 40 50
Normal(-3e-14,12.223)

FIG. 7A

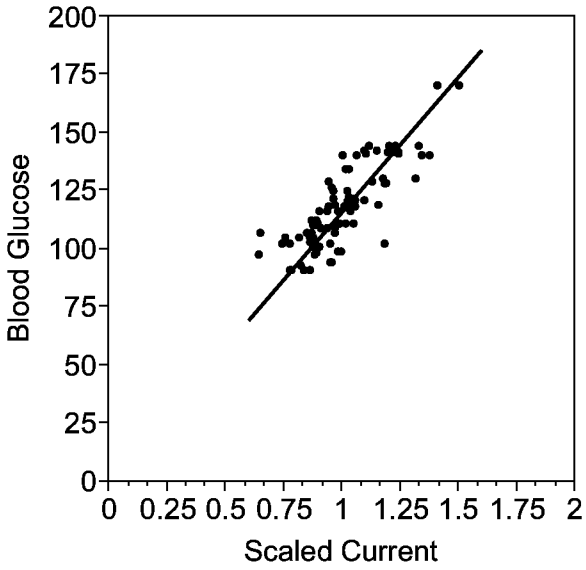
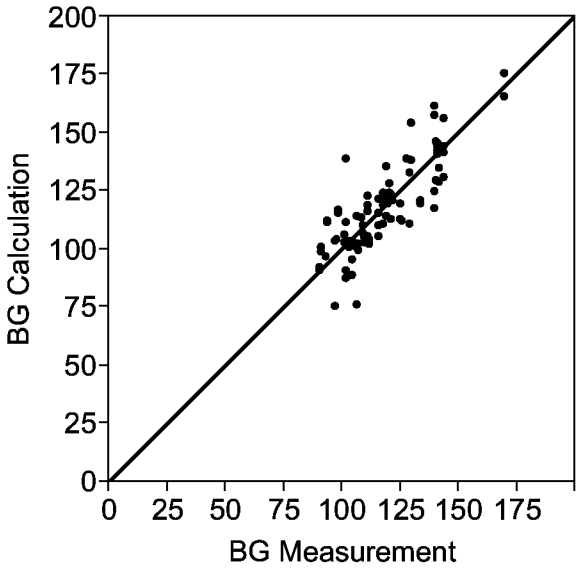

Blood Glucose
200
175
150
125
100
75
50
25
0
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2
Scaled Current

FIG. 7B


BG Calculation
200
175
150
125
100
75
50
25
0
0 25 50 75 100 125 150 175
BG Measurement

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US12/53083

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/05, 5/00 (2012.01)
USPC - 600/345, 347, 365
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)
IPC(8): A61B 5/05, 5/00, 5/06 (2012.01)
USPC: 600/300, 309, 345, 347, 365; 422/50, 68.1; 436/63

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)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); DialogPRO; ACS; Google/Google Scholar; sensor*, biosensor*, interstitial*, mixing, localiz*, glucose*, diabet*, implant*, subcutaneous*, analyte, concentration

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2011/0144463 A1 (PESACH, B et al.), June 16, 2011, abstract; figure 10; paragraphs [0002], [0068], [0102], [0127], [0131], [0135], [0184], [0203]; Claim 102	1-6, 11, 15, 21 ---- 7-10, 12-14, 16-20
Y	US 7069078 B2 (HOUBEN, R), June 27, 2006, abstract; column 2, lines 39-46; column 3, lines 20-33	7
Y	US 7775975 B2 (BRISTER, M et al.), August 17, 2010, abstract; column 22, lines 54-67 to column 23, lines 1-3; column 29, lines 1-25; column 81, lines 58-67 to column 2, lines 1-11	8-10, 12, 13
Y	US 2010/0174166 A1 (BRISTER, M et al.), July 8, 2010, abstract; figures 1, 5; paragraphs [0011], [0053], [0057], [0087], [0090]-[0093], [0107], [0110], [0112], [0139], [0263], [0297], [0298]	14, 16-20

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

* 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
06 November 2012 (06.11.2012)	27 NOV 2012

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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