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- (71) Applicant: GEORGETOWN UNIVERSITY [US/US];
37th and O Streets, N.W., Washington, DC 20057 (US).
- (72) Inventor: MAKARAND, Paranjape; 16508 Harbour
Twon Drive, Silver Spring, MD 20905 (US).
- (74) Agent: BEY, Dawn-Marie; Bey & Cotropia PLLC, 213
Bayly Court, Richmond, VA 23229 (US).
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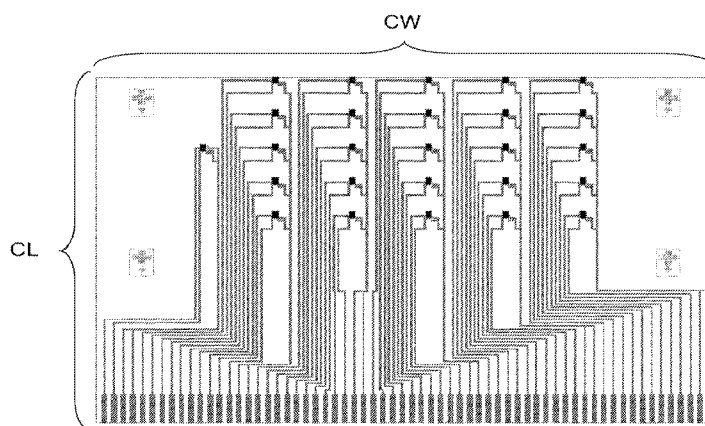


FIG. 1A

(57) **Abstract:** A sensing device comprising a paper-based or other wicking substrate contains detection sites for electrochemically monitoring an analyte in interstitial fluid of a user. Each site includes a heating element, for receiving a first predetermined voltage applied thereto, in order to thermally ablate a stratum corneum of a user's skin to access the interstitial fluid of the user, which is imbibed into a hydrophilic region at the detection site. In one embodiment, the heating element is a serpentine conductive pattern at-
tached at first and second ends thereof to electrode material. In this embodiment, the first voltage preferably creates an open-circuit configuration, including first and second portions of the electrode material that are electrically isolated from each other. The sensing device further comprises a sensing area incorporated into one such electrode that is in contact with the hydrophilic region at the de-
tection site.



MICROFLUIDIC SYSTEMS FOR ELECTROCHEMICAL TRANSDERMAL GLUCOSE SENSING USING A PAPER-BASED OR OTHER WICKING SUBSTRATE

Field of Embodiments

[0001] The present embodiments relate generally to non-invasive or minimally invasive transdermal measurement systems. More specifically, the embodiments relate to paper-based or other wicking microfluidic transdermal glucose measurement systems and processes for their production and use. Other substrates having wicking properties similar to paper are also described.

Background

[0002] Minimally invasive transdermal systems are described in, for example, co-owned U.S. Patents 6,887,202 and 7,931,592, both entitled “Systems and Methods for Monitoring Health and Delivering Drugs Transdermally,” as well as co-owned U.S. Appn. No. 13/459,392, each of which is incorporated herein by reference in its entirety.

[0003] These systems, like the embodiments described herein, provide for a minimally invasive sampling technique and device suitable for rapid, inexpensive, unobtrusive, and pain-free monitoring of important biomedical markers, such as glucose. Existing systems remain open to improvement, particularly with respect to size or footprint, as the systems may be intended to be worn by a person under their clothing. Obviously this application would benefit from a device having a small footprint so as to remain inconspicuous. Similarly, the ability to fit multiple sampling sites on a single device is also desired, facilitating continuous and timely monitoring and reducing the need for user to take affirmative action until the all sampling sites on the device are exhausted. The use of low-cost, flexible, biocompatible and environmentally benign materials is also a desired feature.

Summary

[0004] In a general aspect, a device containing a plurality of individually controllable sites for electrochemically monitoring an analyte in interstitial fluid of a user includes:

a paper-based or other wicking substrate comprising a plurality of isolated

hydrophilic subregions, each surrounded by a hydrophobic region;

and having formed thereon, at each said subregion, a conductive microheater configuration, connectable to a voltage source, effective to heat said subregion when a voltage is applied thereto;

and a system of electrodes effective to measure the level of the analyte in a fluid within said hydrophilic subregion.

[0005] Preferably, at least a portion of the electrodes, including a sensing material on at least one electrode, is within the hydrophilic subregion.

[0006] In one embodiment, the conductive microheater configuration and a system of electrodes are on the same surface of the substrate. In a preferred embodiment, the conductive microheater configuration and a system of electrodes are on opposite surfaces of the substrate.

[0007] Different embodiments of the device can be generally described as follows. These and other embodiments are described more fully below and in the detailed description which follows.

[0008] In a first “single-sided, serpentine” embodiment, sensing elements and heating elements are on the same side of the substrate; a serpentine microheater circuit is connected to sensing electrode elements, one containing sensing material (e.g. glucose oxidase), and the microheater circuit is converted to an open circuit upon heating, thus producing two electrode elements for measuring purposes.

[0009] In a second “single-sided, serpentine” embodiment, sensing elements and heating elements are still on the same side of the substrate, but sensing electrode elements, one containing sensing material (e.g. glucose oxidase), are provided separate from, but adjacent to, the microheater circuit. The microheater circuit may or may not be converted to an open circuit upon heating.

[0010] In a “double-sided, serpentine” embodiment, sensing elements (one containing sensing material, e.g. glucose oxidase) and a serpentine heating element are on opposite sides of the substrate, but associated with the same hydrophilic region. The serpentine microheater circuit may or may not be converted to an open circuit upon heating.

[0011] In a “double sided, circular” embodiment, sensing elements (one containing sensing material, e.g. glucose oxidase) and heating elements (microheaters) are on opposite sides of the

substrate, but associated with the same hydrophilic region, which is enclosed by the microheater, which may be circular in shape.

[0012] In a “single sided, circular” embodiment, sensing elements (one containing sensing material, e.g. glucose oxidase) and heating elements (microheaters) are on the same side of the substrate, and associated with the same hydrophilic region, which is enclosed by the microheater, which may be circular in shape.

[0013] These and other embodiments are described more fully as follows, and in the detailed description below.

[0014] In a first device embodiment, the conductive microheater configuration comprises a serpentine conductive pattern attached at first and second ends thereof to electrode material in said electrode system, in a closed-circuit configuration, for receiving a first predetermined voltage applied thereto, in order to: (i) thermally ablate a stratum corneum of a user's skin to access the interstitial fluid of the user and (ii) form an open-circuit configuration including first and second portions of the electrode material that are electrically isolated from each other; wherein a sensing area is deposited on at least one of the first and second portions of the electrode material. In this embodiment, the conductive microheater configuration and the system of electrodes are typically on the same surface of the substrate.

[0015] A related process for electrochemically monitoring an analyte in interstitial fluid of a user includes:

applying a first predetermined voltage to said conductive microheater configuration provided within a hydrophilic subregion within a paper-based or other wicking device located proximate to a portion of skin of the user, the conductive microheater configuration including a serpentine conductive pattern attached at first and second ends thereof to electrode material, also provided within said hydrophilic subregion, in order to: (i) thermally ablate a stratum corneum of a user's skin to access the interstitial fluid of the user; and (ii) separate the electrode material to form an open-circuit configuration including first and second portions of the electrode material that are electrically isolated from each other;

applying a second predetermined voltage to the formed open-circuit configuration which is electrically contacted with the interstitial fluid;

measuring an electrochemical response resulting from an interaction of the analyte

with a sensing layer on a portion of the electrode material; and

receiving at a measuring component from a sensing area located on at least one of the first and second portions of the electrode material, measurement data indicative of an amount of the analyte in the interstitial fluid of the user;

wherein said conductive microheater configuration and such electrode material are contained within an isolated hydrophilic subregion on said paper-based or other wicking substrate, and said substrate comprises a plurality of said isolated hydrophilic subregions, each surrounded by a hydrophobic region.

[0016] In a second device embodiment, the conductive microheater configuration comprises a serpentine conductive pattern, for receiving a predetermined voltage applied thereto, in order to thermally ablate a stratum corneum of a user's skin to access the interstitial fluid of the user; and the electrode system comprises first and second measuring electrodes, at least one of which contains a sensing area.

[0017] In one embodiment of this aspect, the serpentine conductive pattern is attached at first and second ends thereof to electrode material, and a sensing area is located on at least a portion of the electrode material. The measuring component may receive measurement data from said electrode material, or, in another embodiment, from said first and second measuring electrodes above.

[0018] In this embodiment, the conductive microheater configuration and the entire system of electrodes may be on the same surface of the substrate. Alternatively, the serpentine conductive pattern is provided on one surface of the substrate, and the first and second measuring electrodes, which are used for measuring, are provided on an opposite surface of the substrate.

[0019] A related process for electrochemically monitoring an analyte in interstitial fluid of a user includes:

applying a first predetermined voltage to a conductive microheater configuration within a paper-based or other wicking device located proximate to a portion of skin of the user, the conductive microheater configuration including a serpentine conductive pattern, in order to thermally ablate a stratum corneum of a user's skin to access the interstitial fluid of the user;

applying a second predetermined voltage to an open-circuit configuration containing

first and second electrode regions which are in electrical contact with said interstitial fluid, at least one of which contains a sensing area;

measuring an electrochemical response resulting from an interaction of the analyte with said sensing area; and

receiving at a measuring component from the open circuit device, measurement data indicative of an amount of the analyte in the interstitial fluid of the user;

wherein said conductive microheater configuration and such electrode material are contained within an isolated hydrophilic subregion on said paper-based or other wicking substrate, and said substrate comprises a plurality of said isolated hydrophilic subregions, each surrounded by a hydrophobic region.

[0020] In one embodiment of this process, the serpentine conductive pattern is attached at first and second ends thereof to electrode material, a sensing area is located on at least a portion of the electrode material, and said first and second electrode regions are formed upon application of said first voltage, which opens the closed circuit formed by the microheater and electrode material.

[0021] In another embodiment of this process, the first and second electrode regions are first and second measuring electrodes further provided on said substrate. In this embodiment, the serpentine conductive pattern may be provided on one surface of the paper-based or other wicking substrate, and the first and second measuring electrodes may be provided on an opposite surface of the paper-based or other wicking substrate.

[0022] In a third device embodiment, the conductive microheater configuration comprises a circular or otherwise closed element which encloses the hydrophilic subregion of the substrate. In this embodiment, the system of electrodes and conductive microheater configuration are preferably on opposite side of the substrate, but they may be on the same side.

[0023] A related process for electrochemically monitoring an analyte in interstitial fluid of a user includes:

applying a first predetermined voltage to a plurality of conductive microheater configurations on a first surface of a paper-based or other wicking substrate located proximate to a portion of skin of the user, each said configuration enclosing a hydrophilic subregion of the substrate, in order to thermally ablate a stratum corneum of a user's skin, to access the

interstitial fluid of the user within said hydrophilic subregion;

applying a second predetermined voltage to a system of electrodes situated on an opposing surface of the paper-based or other wicking device, one of said electrodes containing a sensing material and being in fluid contact with the hydrophilic subregion; and

measuring an electrochemical response resulting from interaction of the analyte with said sensing material; and

receiving at a measuring component, measurement data derived from said electrochemical response that is indicative of an amount of the analyte in the interstitial fluid of the user.

[0024] A process for forming a paper-based or other wicking device containing a plurality of individually controllable sites for electrochemically monitoring glucose in interstitial fluid of a user includes:

treating a paper-based or other wicking substrate to form a plurality of isolated hydrophilic subregions, each surrounded by a hydrophobic region;

applying to the substrate a pattern of electrodes and conductive channels, to form a plurality of conductive microheater configurations, each including a serpentine conductive pattern and first and second electrode regions contained within one of said hydrophilic subregions; and

depositing a sensing material within one of said electrode regions within each said hydrophilic subregion.

[0025] In one embodiment, the serpentine conductive pattern is attached at first and second ends thereof to said electrode regions. In another embodiment, the first and second electrode regions are first and second measuring electrodes further provided on said substrate. In the latter embodiment, the serpentine conductive pattern may be provided on one surface of the paper-based or other wicking substrate, and the first and second measuring electrodes on an opposite surface of the paper-based or other wicking substrate.

[0026] A further process for forming a paper-based or other wicking device containing a plurality of individually controllable sites for electrochemically monitoring glucose in interstitial fluid of a user includes:

treating a paper-based or other wicking substrate to form a plurality of isolated

hydrophilic subregions, each surrounded by a hydrophobic region;

applying to one surface of the substrate, a pattern of conductive channels, to form a plurality of conductive microheater configurations, each surrounding one such subregion, and conductive channels for connecting each said conductive microheater configuration to a voltage source;

applying to an opposing surface of the substrate, a pattern of electrodes, such that at least one electrode containing a sensing material is in contact with each said hydrophilic subregion, and conductive channels for connecting said electrodes to a measuring source.

[0027] In a fourth device embodiment, a device for electrochemically monitoring an analyte in interstitial fluid of a user includes:

a handle region attached to an end region having an open tip, said end region having a storage region adjacent the open tip,

wherein the periphery of said open tip comprises a conductive microheater element connectable to a voltage source within said device,

and the storage region contains a plurality of electrochemical sensing elements, each comprising a paper-based or other wicking substrate having a system of conductive elements connectable to a voltage source within said device, and each containing an electrode modified with a sensing material for measuring the level of the analyte in a fluid which contacts said sensing elements,

and the device includes a dispensing mechanism effective to move a single sensing element from said storage region to a location within the periphery of said open tip.

[0028] A related process for electrochemically monitoring an analyte in interstitial fluid of a user includes:

providing a device having a handle region attached to an end region having an open tip, said end region having a storage region adjacent the open tip,

wherein the periphery of said open tip comprises a conductive microheater element connectable to a voltage source within said device,

and the storage region contains a plurality of electrochemical sensing elements, each comprising a paper-based or other wicking substrate having a system of conductive elements connectable to a voltage source within said device, and each comprising an electrode

containing a sensing material for measuring the level of the analyte in a fluid which contacts said sensing element,

and wherein the device includes a dispensing mechanism effective to move a single sensing element from said storage region to a location within the periphery of said open tip;

dispensing a single sensing element from said storage region to a location within the periphery of said open tip;

applying the open tip of said device to the skin of the user, such that the conductive element at said tip, and the paper-based or other wicking substrate of the sensing element, both contact the skin of the user;

applying a first predetermined voltage to said conductive microheater element, in order to thermally ablate a stratum corneum of the user's skin, to access the interstitial fluid of the user within the periphery of said open tip, such that said fluid contacts said sensing element;

applying a second predetermined voltage to said electrode containing a sensing material within said sensing element;

measuring an electrochemical response resulting from interaction of the analyte with said sensing material; and

receiving at a measuring component, measurement data derived from said electrochemical response that is indicative of an amount of the analyte in the interstitial fluid of the user.

Brief Description of the Figures

[0029] The following Figures are intended to exemplify the various embodiments described herein and are in no way intended to be limiting.

[0030] Figs. 1A-1D illustrate various dimensions of representative serpentine-microheater devices in accordance with a preferred embodiment herein;

[0031] Figs. 2A and 2B illustrate features of representative circular-microheater devices in accordance with a further preferred embodiment herein;

[0032] Fig. 3 is representative of a normal mask used in preparation of representative devices of Figs. 1A-D in accordance with a preferred embodiment herein; and

[0033] Fig. 4 illustrates features of an exemplary hand-held device for electrochemically

monitoring an analyte in interstitial fluid of a user.

Detailed Description

I. Materials and Fabrication Methods

[0034] The processes described herein can be used to prepare a sensor device based on a paper-based or other wicking substrate, comprising, in selected embodiments, a plurality, typically an array, of individual monitoring sites, each associated with a heating element for use in promoting flow of interstitial fluid to the monitoring site. The device containing the array may be applied to a person's skin, e.g., in the form of an adhered patch, and each individual monitoring site may be controlled to collect interstitial fluid at different times. Such a monitoring system is useful for people who live with a condition, such as diabetes, wherein frequent glucose measurements are required in order to maintain health.

[0035] Micro and nano-fabrication processes are utilized to form a macro device, e.g., on the order of a centimeters in total size, that is comprised of numerous micro and nano-sized layers and components.

[0036] The devices disclosed herein employ a paper-based or other wicking substrate. (The substrate may be so described herein even after it has been treated, as described further below, to render substantial portions of it hydrophobic and/or non-wicking.) The "paper-based" substrate material can be any of a wide variety of paper-based products, including, for example, writing or copy paper, tissue paper, filter paper, chromatography paper, cardboard, or any other paper-based or cellulose-based product having sufficient hydrophilic and bibulous character to promote wicking of aqueous fluid. The material is preferably of sufficient smoothness and uniformity to allow accurate fabrication of the conducting and electrode elements described herein.

[0037] Other fibrous materials may be used as well, such as textiles, including nanofibrous meshes or mats formed from polymeric fibers, preferably nanospun fibers, more preferably electrospun fibers. Electrospun fibers may be prepared having diameters in the sub-micrometer range, e.g. in the hundreds or even tens of nanometers, and are characterized by high specific surface area. The process of electrospinning is well known in the art and has been applied to biocompatible polymers for use in biomedical applications; see e.g. Zhang *et al.*, *J. Matl. Sci.*

Matls. in Medicine 16 (2005) 933-946. Examples of biocompatible polymers that may be used include, but are not limited to, polylactic acid, polyglycolic acid, polyacrylic acid, polyalkylene oxides, and derivatives and copolymers thereof, as well as naturally occurring polymers, such as cellulose, collagen, and silk, and derivatives and copolymers thereof. Also contemplated for use is “bucky paper”, i.e. sheets formed from networks of carbon nanotubes. Again, any biocompatible material may be used as long as it is inert to materials used in preparation and has sufficient hydrophilic and bibulous character to promote wicking of aqueous fluid. As above, the material is preferably of sufficient smoothness and uniformity to allow accurate fabrication of the conducting and electrode elements described herein.

[0038] Methods of fabricating paper-based microfluidic systems are known in the art; see, for example, Martinez *et al.*, *PNAS* 105(50):19606-19611 (2008) and Martinez *et al.*, *Anal. Chem.* 82:3-10 (2010). Typically, a first step in preparing a paper-based or other wicking microfluidic sensing device, as disclosed herein, comprises treatment of a paper-based or other wicking substrate to render selected regions of the substrate hydrophobic and resistant to entry of body fluids (i.e. non-wicking). The hydrophobic material used may be, for example, a photoresist, such as SU-8, which is uniformly applied, cured through a mask, and then selectively removed in uncured areas, using standard masking and photolithography techniques. Other means of selectively removing regions of a hydrophobic coating from a paper-based or other wicking substrate include, for example, removal of a polymer such as polystyrene by inkjet etching (see e.g. Abe *et al.*, *Analyt. Chem.* 80 (2008) 6928-6934) or plasma oxidation of a hydrophobic coating through a metal mask (see e.g. Li *et al.*, *Analyt. Chem.* 80 (2008) 9131-9134).

[0039] In one rapid and convenient method, a pattern of wax is printed onto the paper-based or other wicking substrate, which is subsequently heated, such that the wax penetrates through the paper-based or other wicking substrate in accordance with the pattern. This technique is not generally preferred for forming very narrow hydrophilic regions, since the melting wax spreads in a planar direction as well.

[0040] The hydrophilic regions of the paper-based or other wicking substrate which remain untreated, or which are re-exposed after selective removal of a hydrophobic material, will be accessible to flow of hydrophilic fluids (typically body fluid, such as interstitial fluid, or other

aqueous or hydrophilic fluids), and may comprise channels and/or spots on the substrate.

[0041] As described above, the hydrophilic subregions of the substrate are typically hydrophilic/ wicking by virtue of the nature of the untreated substrate, which is itself hydrophilic/wicking. However, a substrate with hydrophilic subregions, for use in the devices described herein, could also be formed by starting with a hydrophobic substrate material and treating subregions of the hydrophobic substrate to render them hydrophilic/wicking.

[0042] Fluids that contact the hydrophilic subregions of the substrates as described herein are typically drawn into and through them by capillary action. In the instant devices, as described further below, interstitial fluid released by heat ablation is wicked into the hydrophilic subregions and contacts electrodes associated with these regions. In selected embodiments, the electrodes are on an opposite surface of the substrate from the heating element(s).

[0043] In the sensing devices described herein, the paper-based or other wicking substrate may be treated over its entire surface to render it hydrophobic, and a plurality or array of detection sites is then formed by selectively removing the hydrophobic material and thus restoring the hydrophilic surface in the selected subregions. Alternatively, the hydrophilic material may be selectively applied everywhere except the selected subregions.

[0044] Although it is generally most convenient to incorporate the hydrophobic material uniformly and continuously, with the exception of the hydrophilic subregions, it is only necessarily that the hydrophobic material surround each hydrophilic subregion, in array-based devices, such that diffusion of the wickable fluid is restricted to the hydrophilic subregions.

[0045] Generally, both surfaces of the substrate are treated, and the pattern of hydrophilic subregions extends through the substrate. However, in some cases, as described further below, hydrophilic subregions and/or channels may be provided which do not traverse the entire thickness of the device. This could be accomplished, for example, by employing a multilayer substrate having a top layer with hydrophilic subregions in a hydrophobic field, as described herein, attached to a fully hydrophobic sublayer. Means of multilayer fabrication are also described in the Martinez *et al.* references cited above. In the instant devices, the fully hydrophobic sublayer would face away from the skin in use.

[0046] The hydrophilic subregions, which are typically isolated subregions, and are

usually, but not necessarily, generally circular in shape, and are the regions at which fluid will be imbibed and analyzed, as described further below. For example, in Fig. 2A, subregions 14, each encircled by a conducting element 18, are hydrophilic subregions. In Fig. 1D, the circled region 32, which surrounds the serpentine element 30 and portions of the surrounding electrode elements E1-E4, is a hydrophilic subregion.

[0047] After formation of the pattern of hydrophilic subregions on the paper-based or other wicking substrate, the desired pattern of conducting elements is applied, on one or both surfaces of the substrate, in accordance with the particular embodiment. See, for example, the network of electrodes, conducting traces and contacts illustrated for a serpentine-microheater embodiment in Fig. 5A. Metals, such as, for example, gold or platinum, or conducting polymers, such as, for example, polypyrrole (PPy) or polyaniline (PANI), may be used for the conducting elements.

[0048] The sensing electrode (of which at least one is associated with each hydrophilic subregion) is modified with a sensing material specific for the analyte of choice, e.g. glucose oxidase (GOx) for analysis of glucose in interstitial fluid. The electrode itself may comprise a conducting polymer, such as PPy, modified with GOx. The conducting polymer may be fabricated as a mesh of electrospun conducting polymer, typically PPy or PANI (see e.g. Chronakis *et al.*, *Polymer* 47(5):1597-1603 (2006); Miao *et al.*, *J. Nanosci. Nanotech.* 10:5507-5519 (2010).

[0049] The sensing, GOx-modified electrode is typically paired with a metal (platinum or gold) electrode, as shown, for example, in Fig. 2B. Such a system is known in the art for electrochemical detection of glucose.

[0050] For application of metals to the paper-based or other wicking substrate, sputtering or vapor deposition techniques known in the art may be used, using known masking technologies. A metal mask, such as a copper mask, may be used to produce the desired pattern (see e.g. Shiroma *et al.*, *Analytica Chimica Acta* 725 (2012) 44-50). In one procedure, gold is sputtered using a standard plasma deposition machine. As an alternative to gold, platinum may be used. A layer of gold or platinum approximately 5000 Å (500 nm) in thickness, for example, may be applied.

[0051] Alternatively, conducting traces and/or electrodes may be applied to the paper-based

or other wicking substrate via screen printing, employing solutions or suspensions of conductive polymers, such as described above, metal particles, or conducting inks, such as carbon/Prussian Blue or Ag/AgCl, as known in the art. See e.g. Dungchai *et al.*, *Analyt. Chem.* 81 (2009) 5821-5826) and references cited therein.

[0052] The sensing material, for detection of glucose, is glucose oxidase (GOx), and it is preferably applied in combination with the conducting polymer PPy. The PPy/GOx electrode material is typically applied to the appropriately masked substrate by electrodeposition, as known in the art. See e.g. Liu *et al.*, *Matl. Sci. Eng. C* 27(1):47-60 (Jan 2007); Yamada *et al.*, *Chem. Lett.* 26(3):201-202 (1997); Fortier *et al.*, *Biosens. Bioelectronics* 5:473-490 (1990).

[0053] In selected embodiments, the amount of polypyrrole in the matrix is in accordance with one-step chronoamperometric deposition at 0.6 volts for 60 seconds, and the amount of glucose oxidase in the matrix is in accordance with one-step chronoamperometric deposition at 0.4 volts for 10 minutes.

[0054] A CV scan may then be then run, e.g. from -1 V to +1 V, to verify deposition and indicate the reduction potential of the applied PPy/GOx matrix. A polarization step may be used to eliminate built-in charges between the sensor's metal layer and the conducting PPy matrix. The steady state signal obtained serves as baseline for future measurements.

II. Serpentine-Microheater Configuration

[0055] In a first device embodiment, as described above, the conductive microheater configuration comprises a serpentine conductive pattern, attached at first and second ends thereof to electrode material in said electrode system, for receiving a first predetermined voltage applied thereto, in order to: (i) thermally ablate a stratum corneum of a user's skin to access the interstitial fluid of the user and (ii) form an open-circuit configuration including first and second portions of the electrode material that are electrically isolated from each other; wherein a sensing area is deposited on at least one of the first and second portions of the electrode material. In this embodiment, the conductive microheater configuration and the system of electrodes are typically on the same surface of the substrate.

[0056] In a second device embodiment, as described above, the conductive microheater configuration comprises a serpentine conductive pattern, for receiving a predetermined voltage

applied thereto, in order to thermally ablate a stratum corneum of a user's skin to access the interstitial fluid of the user; and the electrode system comprises first and second measuring electrodes, at least one of which contains a sensing area.

[0057] In one embodiment of this aspect, the serpentine conductive pattern is attached at first and second ends thereof to electrode material, and a sensing area is located on at least a portion of the electrode material. The measuring component may receive measurement data from said electrode material, or, in another embodiment, from said first and second measuring electrodes above.

[0058] In this embodiment, the conductive microheater configuration and the entire system of electrodes may be on the same surface of the substrate. Alternatively, the serpentine conductive pattern is provided on one surface of the substrate, and the first and second measuring electrodes, which are used for measuring, are provided on an opposite surface of the substrate.

[0059] Details of exemplary serpentine-microheater-containing devices, in which the conductive elements and electrodes are on the same side of the substrate, are set forth below.

[0060] For double-sided devices, electrodes designated E3 and E4 in the description and figures, and associated electrical conduits, are fabricated on the opposite site (away from skin side) of the substrate from the serpentine heaters and electrode regions E1 and E2 attached thereto. In this case, E3 is not attached to E2 as it is in the configuration shown in the figures and described below.

[0061] The device dimensions in the embodiments described here are typically in the micron range. More specifically, and by way of example, various dimensions of an individual device are shown in Figs. 1A-1D. Referring to Fig. 1A, chip width (CW) is approximately 32,000 microns and chip length (CL) is approximately 23,000 microns. Referring to Fig. 1B, chip-to-chip pitch width (CCPW) is approximately 4,000 microns and chip length (CCPL) is approximately 2100 microns. Referring to Fig. 1C, serpentine heater dimensions are as follows: the heater lead width (HLW) is approximately 125 microns; the heater pad to pad (HP2P) is approximately 74 microns; the heater total width (HTW) is approximately 121 microns; the space between elements (S) is approximately 5 microns; the short heater width (HWS) is approximately 8 microns; the long heater width (HWL) is approximately 9 microns;

the short heater length (HLS) is approximately 48 microns; the medium heater length (HLM) is approximately 64 microns; and the long heater length (HLL) is approximately 69 microns.

[0062] Fig. 1D illustrates additional dimensions between various electrodes that are available for use with processes described herein. More particularly, as shown, E1, E2, E3 and E4 illustrate different portions of electrode material; E3, in this embodiment, is an extension of E2. Further, in a preferred configuration, E1 and E2 are initially part of a closed-circuit system along with the serpentine conductor, i.e., heater 30. As shown in Fig. 1C, the distance between E1 and E2 is approximately 74 microns (HP2P). As shown in Fig. 1D, the distance between E3 and E4 is approximately 164 microns.

[0063] Accordingly, taking the specific embodiment of Fig. 1A-1D as an exemplary serpentine-microheater device, the individual monitoring sites (exclusive of electrodes/leads) are at least the size of the heater, i.e., approximately HTW x HP2P, which is 121 microns x 74 microns = 8954 microns². Generally, an active area of approximately 50 x 50 microns = 2500 microns² is sufficient to ablate the stratum corneum and access a sufficient amount of interstitial fluid to perform desired glucose monitoring. The depth of the active (ablated) area is typically approximately 40 microns. One skilled in the art recognizes that these dimensions may vary in accordance with manufacturing tolerances and other considerations. The dimension may be optimized in accordance with intended location of the device on the user's body and other attributes of the user, e.g., skin tone, type, follicle structure and the like. This optimization is within the scope of the invention.

[0064] In a preferred operation, the process for taking a glucose reading requires only two of the four electrode portions, E1 and E2. In this preferred operation, an approximately 3 volt initial pulse is applied to the heater through electrode portions E1 and E2, which initially forms a closed-circuit configuration. This initial pulse (typically about 30 μ sec in duration) causes the serpentine conductive material to heat up, and ultimately said heat transfers to the skin of the subject, which is in thermal contact therewith. This heat thermally ablates a portion of the stratum corneum, allowing interstitial fluid to come into contact with the device. This initial approximately 3 volt pulse also acts to open or "blow" the heater and open the previously closed circuit, thus forming an open-circuit configuration. This results in the formation of two separate and electrically isolated electrodes. A second voltage pulse of approximately 0.3 to

0.4 volts is applied to the open circuit, and measurement of current occurs between E1 and E2, at least one of which has been modified with a sensing material, i.e., GOx/PPy matrix. The sensing layer is in communication with a measurement device, e.g., integrated circuitry including a microprocessor, for receiving measurement data from the sensing layer. This measurement data may be in the form of current readings and is indicative of an amount of analyte, e.g., glucose, in the interstitial fluid of the user. In this embodiment, electrode portions E3 and E4 are not used.

[0065] In an alternative embodiment, the initial 3 volt pulse may not open the circuit. In this case, a second approximately 3 volt pulse may be applied. Once the circuit is opened, the measurement pulse and processes described above are applicable.

[0066] In an alternative embodiment, after the approximately 3 volt pulse is applied to the heater through electrode portions E1 and E2 to cause the heater to ablate the stratum corneum and release the interstitial fluid, electrode portions E3 and E4 are used as the measuring electrodes for measuring current resulting from the electrochemical reaction of the analyte with the sensing layer, in response to a voltage pulse of approximately 0.3 to 0.4 volts applied thereto. Similarly, if for some reason the circuit simply does not open, electrode portions E3 and E4 may be used as the measuring electrodes, in response to a voltage pulse of approximately 0.3 to 0.4 volts applied thereto.

[0067] In one embodiment, the serpentine microheaters and connecting traces are applied to one surface of the paper-based or other wicking substrate, and the measuring electrodes, e.g. electrode portions E3 and E4 and their connecting traces, are applied to the other surface of the substrate, with these elements associated with the hydrophilic wicking regions as above. The surface of the substrate to which the serpentine microheaters and connecting traces are applied is the surface that contacts the user's skin in use. This configuration has the advantage that the sensing material (GOx) on electrode portion E3 or E4 is less exposed to heat in the microablation step. The thickness of the substrate may vary but is sufficient to provide such heat protection.

III. "Circular" Microheater Configuration

[0068] An alternative device configuration, employing circular microheaters, is illustrated

in Fig. 2A. A plurality, in this case an array, of detection sites 16, each comprising a micro-heating element 18, is shown (in part) on one surface 12 of a paper-based or other wicking substrate. The substrate has been treated to render a substantial portion of the surface hydrophobic, as described above, so that the regions interior to the micro-heating elements make up hydrophilic subregions 14. In one embodiment, each subregion has an interior diameter of about 50-100 μ , and the width of the micro-heating element 18 is approximately 10 μ . The micro-heating element 18 is generally circular in shape, but can be any shape that encloses the hydrophilic subregion 14.

[0069] In use of the device, surface 12 is in contact with the skin of the user, and controlled application of a voltage to the micro-heaters is effect to ablate the stratum corneum and thus release interstitial fluid, which is wicked into the hydrophilic subregions 14. The remainder of the substrate (or at least the area immediately surrounding each micro-heating element 18) is preferably hydrophilic, such that flow of interstitial fluid from the ablated skin surface is directed to the subregions 14 interior to the micro-heating elements.

[0070] On the opposing surface 20 of the substrate (which faces away from the user's skin during use), illustrated in Fig. 2B, at least one detecting electrode system (or "electrode pair") 22 is in contact with each hydrophilic subregion, such that analyte (glucose) from the interstitial fluid is able to come into contact with reagent (glucose oxidase, or GOx) on the sensor electrode. Fig. 2B shows an embodiment in which two electrode pairs are provided for a single detection site. Having a multiplicity of electrode pairs at a site allows for multiple readings that can be averaged to increase precision. Each detecting electrode pair (system) comprises a GOx-modified electrode 24, which may be a metal electrode modified with GOx or PPy/GOx, or a PPy electrode modified with GOx, and a metal (gold or platinum) electrode 26. As shown, at least a portion of the electrode, including the portion containing the GOx reagent, comes into contact with interstitial fluid at the hydrophilic subregion 14.

[0071] Connector traces 28 are connectable to a voltage source (via contacts not shown), and electrodes 24, 26 are connectable to a means of detection (as is shown in more detail for the serpentine microheater embodiment), via appropriate connectors and contacts.

[0072] In preferred operation, an approximately 3 volt initial pulse is applied to one or more micro-heating elements 18 via connector traces 28. This initial pulse (typically about 30

μsec in duration) causes the micro-heating element(s) to heat up, and ultimately said heat transfers to the skin of the subject, which is in thermal contact therewith. This heat thermally ablates a portion of the stratum corneum, allowing interstitial fluid to come into contact with the substrate, in particular at hydrophilic subregions 14, where the fluid is wicked to the opposing surface 20 of the substrate, where it contacts at least GOx-modified electrode 24. The depth of the active (ablated) area is typically approximately 40 microns.

[0073] A second voltage pulse of approximately 0.3 to 0.4 volts is applied to the electrode pair, and measurement of current occurs between the electrodes, which are in communication with a measurement device, e.g., integrated circuitry including a microprocessor, for receiving the measurement data. This measurement data may be in the form of current readings and is indicative of an amount of analyte, e.g., glucose, in the interstitial fluid of the user.

[0074] The above-described configuration has the advantage that the sensing material (GOx) on the electrodes is protected from heat produced in the microablation step. A thickness of the substrate of about 100 μ is typical; however, the thickness may vary depending on the nature of the substrate (e.g. its porosity and wicking ability). However, the thickness of the substrate is preferably sufficient to provide such heat protection for the sensing material.

[0075] Although the double-sided device has the above-noted advantages, a single-sided device may be provided and still provide the advantages of convenience, cost, flexibility, and disposability. In a “single-sided, circular” microheater device, each microheater is flanked by, but not contacting, one or more pairs of sensing electrodes. In one embodiment, these elements are contained within a hydrophilic subregion of the corresponding surface of the substrate; that is, the hydrophilic subregion extends beyond the borders of the microheater to include at least a portion of the sensing electrode that includes the sensing material. Alternatively, hydrophilic channels could be provided in the corresponding surface of the substrate, from the interior of the microheater to the electrode(s). In both instances, the hydrophilic regions are provided on only the first surface of the substrate; the opposite surface (which would be away from the skin in use) is rendered fully hydrophobic, to restrict fluid flow to the skin-facing surface.

IV. Pen-Based Device

[0076] Also provided is a convenient, typically hand-held device for electrochemically

monitoring an analyte in interstitial fluid of a user. Components of an exemplary device 34 are illustrated in Fig. 4. The device includes a plurality of sensing elements 36, each comprising a system of electrodes, as described above, on an individual portion of a paper-based or other wicking substrate. Each individual sensing element has a system of conductive elements 37 connectable to a controllable voltage source 38 within the device, and each comprises at least one electrode 39 modified with a sensing material, such as glucose oxidase (GOx), for measuring the level of the analyte in a fluid which contacts the sensing element.

[0077] Although not shown, connective elements located e.g. in the inner wall of device 34 can serve to place elements 37, 39, and/or 50 (as described below) in contact with the controllable voltage source 38.

[0078] For measurement of glucose, each sensing element 36 typically includes a pair of electrodes, such as described for the array-based devices above, where one is a GOx-modified electrode and the other is a metal electrode, such as platinum or gold. Materials for use as the paper-based or other wicking substrate, and for the electrodes and other conductive elements, include those described for the array-based embodiments above.

[0079] With further reference to Fig. 8, the device preferably includes a handle region 40 attached to an end region 42 having an open tip 44. (In practice, the tip could be a closed tip which is openable prior to use.) The end region includes a storage region 46, for containing the sensing elements 36, adjacent the open tip. The periphery 48 of the open tip comprises a conductive microheater element 50, which is connectable to the voltage source 38 within the device.

[0080] Preferably, the conductive element 50 is in permanent contact with the voltage source, while each sensing element 36 is placed into contact with the voltage source only when it is dispensed into an operating position within the periphery 48 of the tip. Typically, conductive elements within the sensing element 36 are able to be placed in contact with conductive element 50 when the sensing element 36 is dispensed into operating position.

[0081] Preferably, the device includes a dispensing mechanism 52, operable by the user, which is effective to move a single sensing element 36 from storage region 46 to a location within the periphery 48 of the open tip 44. More preferably, the dispensing mechanism is also effective to eject a used sensing element from its location within the periphery of the open tip.

[0082] In use, a single sensing element 36 is dispensed from the storage region 46 to a location within the periphery 48 of the open tip 44 (if there is not a sensing element in place already), and the open tip 44 is applied to the skin of the user, such that the conductive element 50 and the paper-based or other wicking substrate of the sensing element 36 each contact the skin of the user.

[0083] A first predetermined voltage, e.g. about 3V, as described above, is then applied from the voltage source 38 to the conductive microheater element 50, sufficient to heat element 50 to thermally ablate a stratum corneum of the user's skin, to access the interstitial fluid of the user within the periphery 48 of said open tip, such that the fluid contacts the sensing element 36 and is drawn into the paper-based or other wicking substrate of the sensing element 36.

[0084] In one embodiment, the conductive element 50 and the electrodes on the sensing elements 36 are fabricated on a single side of the paper-based or other wicking substrate, that being the side that faces the skin of the user when in use. In another embodiment, the conductive element 50 is fabricated on the side facing the skin of the user, and the electrodes are on the other side, to reduce exposure of the sensing material within the electrodes to heat during skin ablation. The fluid produced upon ablation is wicked through the substrate to contact the sensing material.

[0085] Following the dispersal of interstitial fluid into the sensing element 36, a second predetermined voltage (e.g. about 0.3-0.4 V) is applied to the system of conductive elements on the sensing element, which comprises, as noted above, an electrode modified with GOx, and preferably a gold or platinum electrode. The electrochemical response resulting from interaction of the analyte with the sensing material (GOx) is measured, and measurement data derived from the electrochemical response, indicative of an amount of the analyte (glucose) in the interstitial fluid of the user, is received at a measuring component. Preferably, a readout would be presented on the hand-held device.

[0086] Preferably, the dispensing mechanism 52 can also be used to eject the used, disposable sensing element 36 from the device, or into a further storage compartment, and to advance a further sensing element into position, either concurrently or at a later time.

V. Additional Components

[0087] Integrated circuitry (IC), including radio frequency (RF) communication capability,

may be included as part of any device in order to transmit data readings to a remote location. By way of example, this transmission may be facilitated as part of a home area network (HAN) in a first instance, e.g., using protocols such as those described as part of the Zigbee standards. Further still, the data readings may be further transmitted outside of the HAN in accordance with a home health or telehealth communications system using existing wide area networks (WANs) such as the Internet.

[0088] The present embodiments provide for other advantages over the existing art in addition to non-invasive features. For example, the devices do not require a separate reservoir for collecting interstitial fluid, an additional perfusion liquid to mix with the interstitial fluid, or any additional means for affirmatively suctioning or pulling in the interstitial fluid. The devices are structured such that the natural dispersion of the interstitial fluid from the heated area is sufficient to trigger an electrochemical response with the GOx reagent. The paper-based or other wicking devices also employ low-cost, biocompatible and environmentally benign materials, and the porosity of the substrate allows, in some embodiments, both surfaces to be used, thus reducing the overall dimensions of the device. Finally, the use of double-sided devices reduces exposure of the sensing material (enzyme) to heat during the ablation process.

[0089] One skilled in the art recognizes the other areas of application for the devices described herein. While the examples specifically described herein are directed to glucose monitoring, adaptations could be made to ascertain other information from the biomolecules and biomarkers in the interstitial fluid. For example, the individual sites could monitor for infectious disease (microbial, fungal, viral); hazardous compounds; heart or stroke indicators (troponin, C-reactive protein); chemical or biological toxins; cancer markers (PSA, estrogen); drug efficacy and dosing (metabolites); and the like. Such applications of the device as described are considered to be within the scope of the present invention.

CLAIMS

1. A device containing a plurality of individually controllable sites for electrochemically monitoring an analyte in interstitial fluid of a user, the device comprising:
 - a paper-based or other wicking substrate comprising a plurality of isolated hydrophilic subregions, each surrounded by a hydrophobic region;
 - and having formed thereon, at each said subregion, a conductive microheater configuration, connectable to a voltage source, effective to heat said subregion when a voltage is applied thereto;
 - and a system of electrodes effective to measure the level of the analyte in a fluid within said hydrophilic subregion.
2. The device of claim 1, wherein at least a portion of the system of electrodes, including a sensing material on at least one electrode, is within the hydrophilic subregion.
3. The device of claim 1, wherein the conductive microheater configuration and a system of electrodes are on opposite surfaces of the substrate.
4. The device of claim 1, wherein the conductive microheater configuration and a system of electrodes are on the same surface of the substrate.

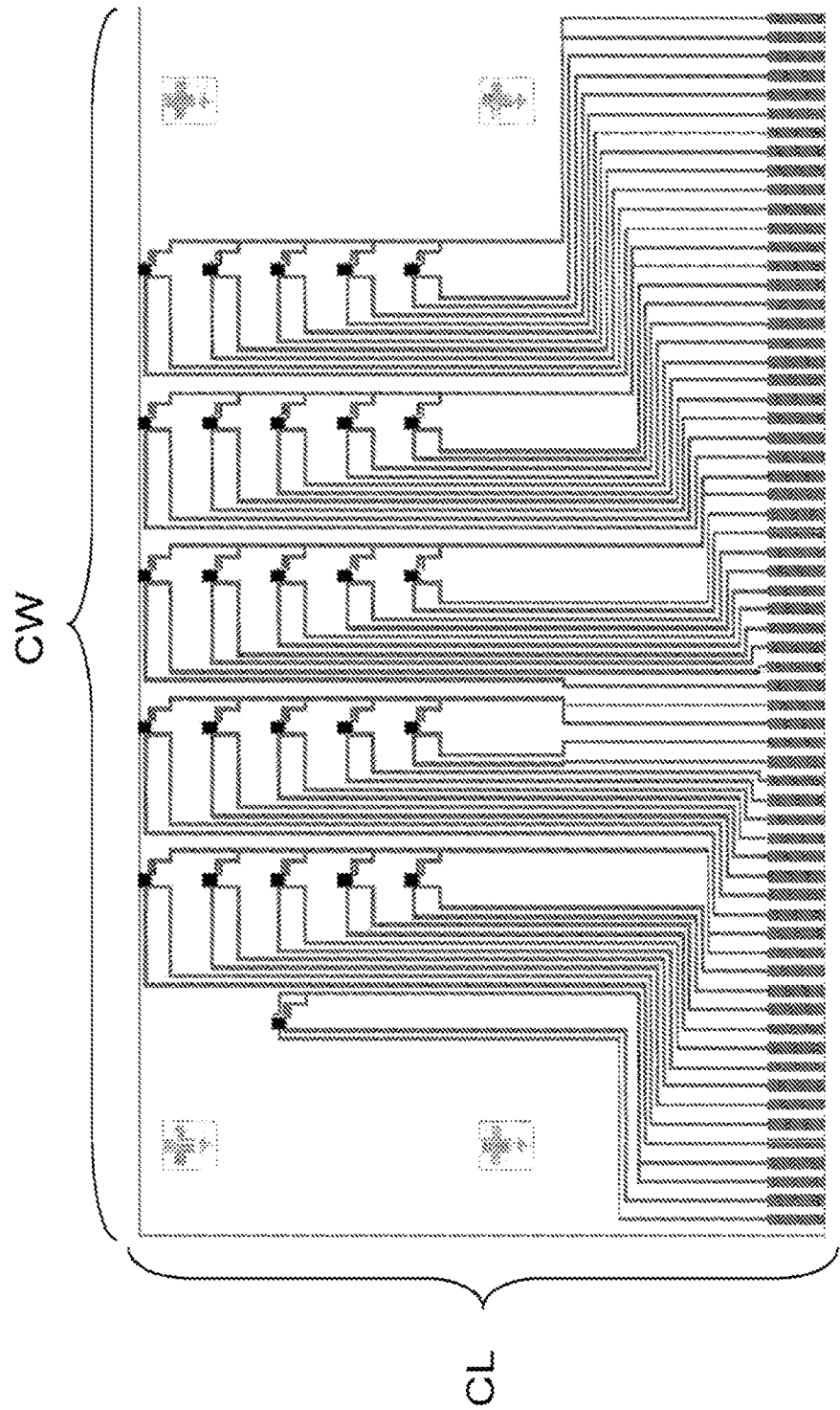


FIG. 1A

FIG. 1B

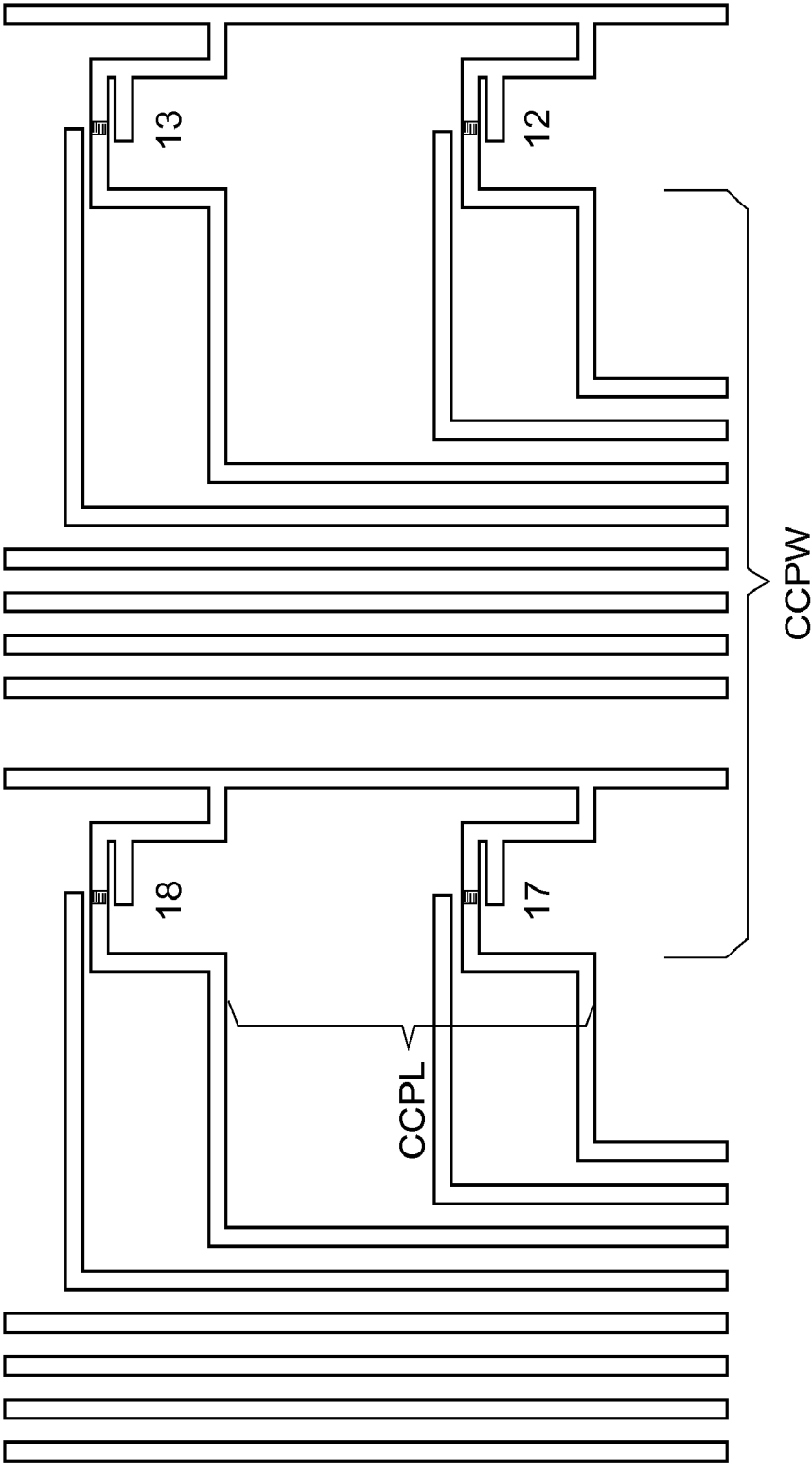


FIG. 1C

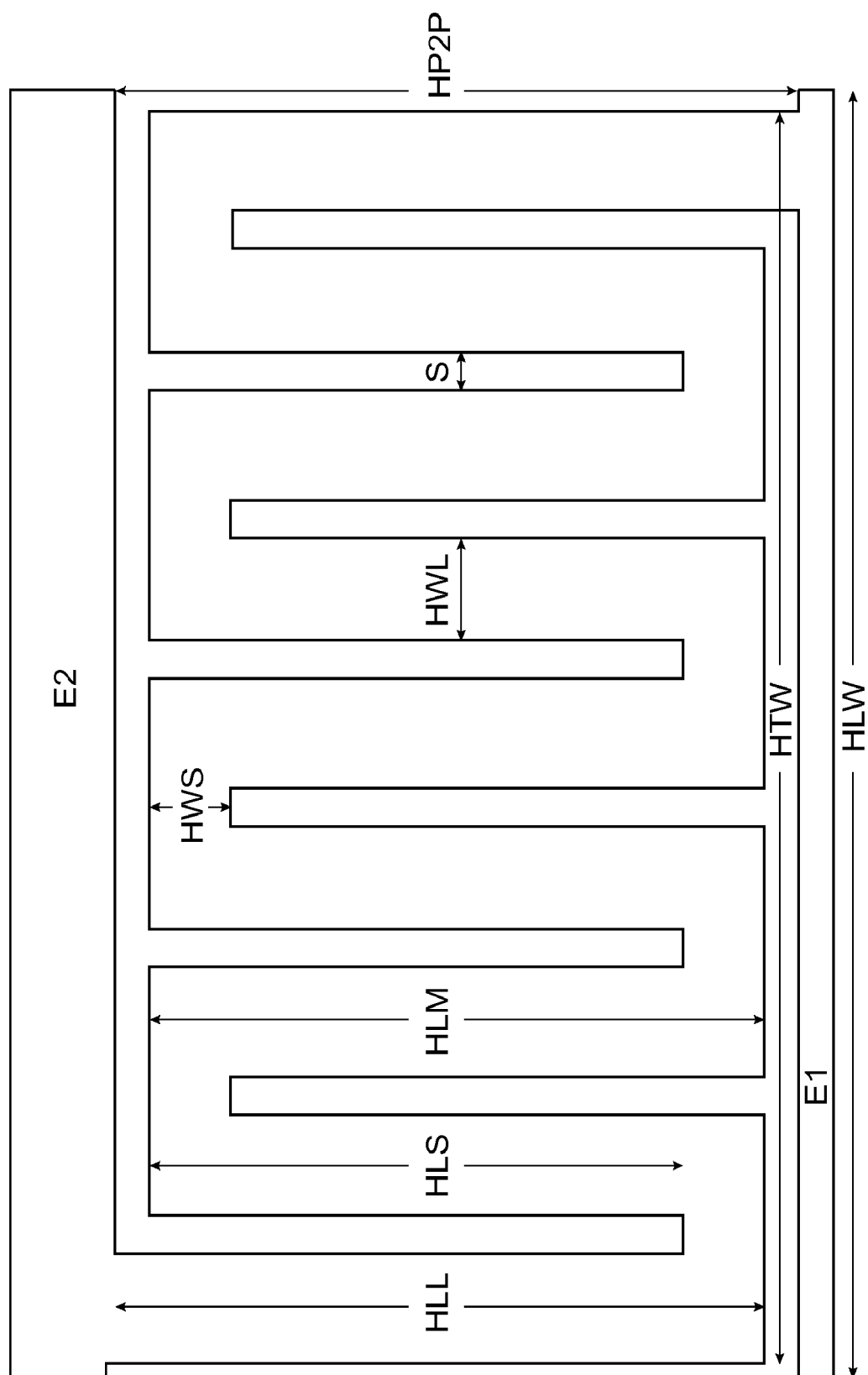
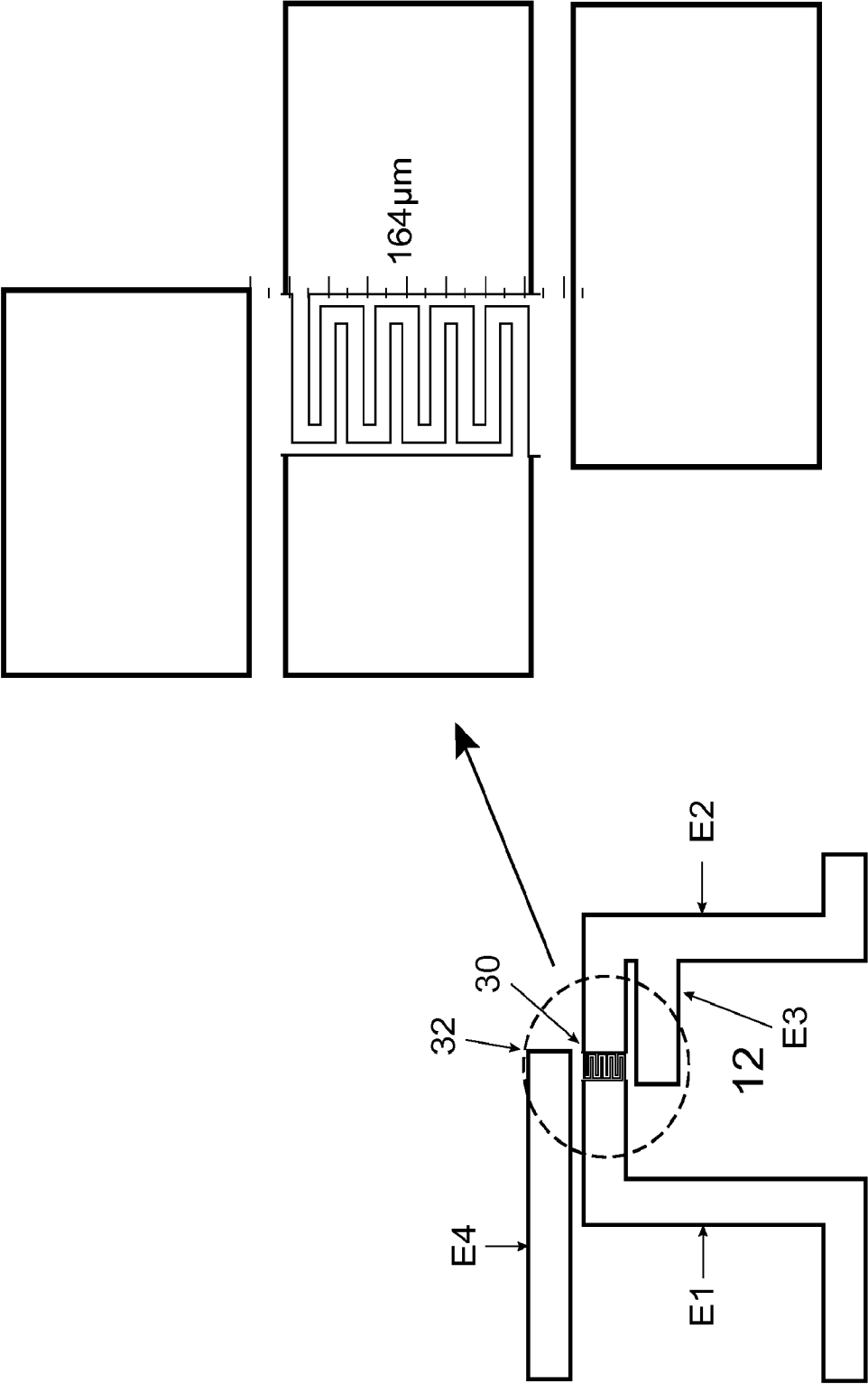


FIG. 1D



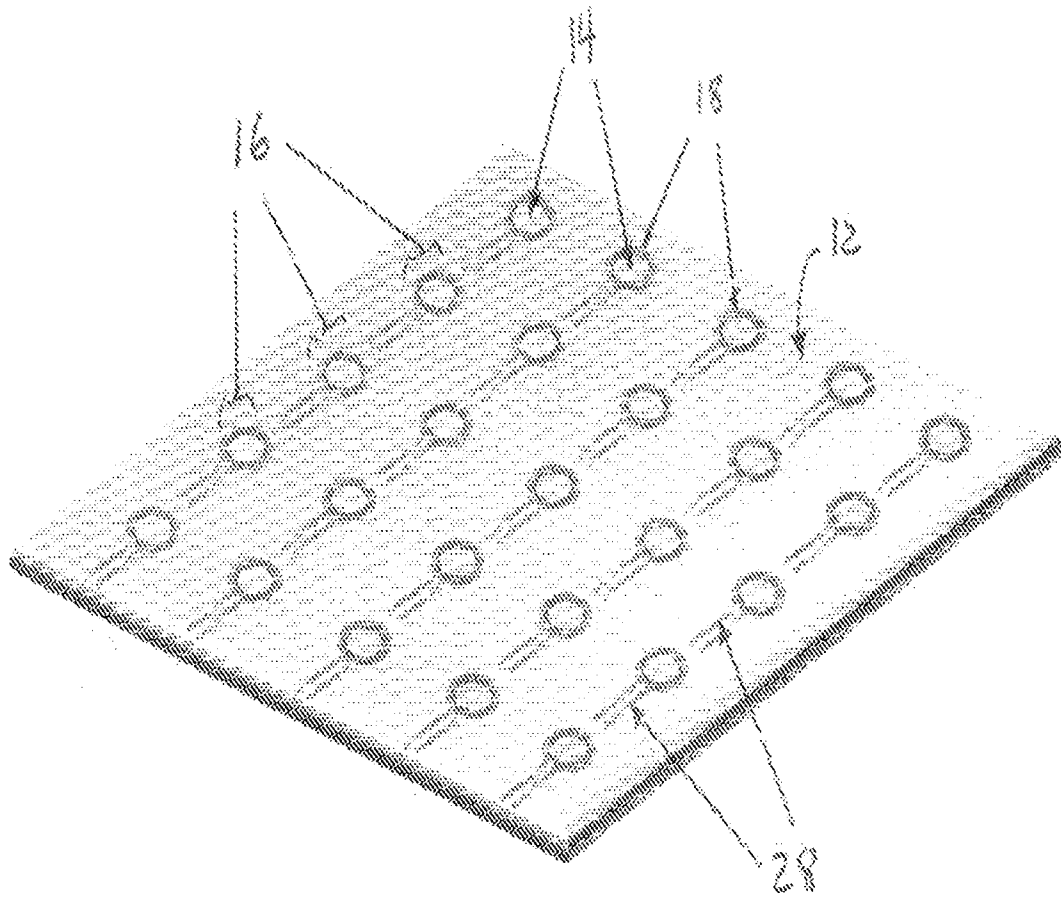


Fig. 2A

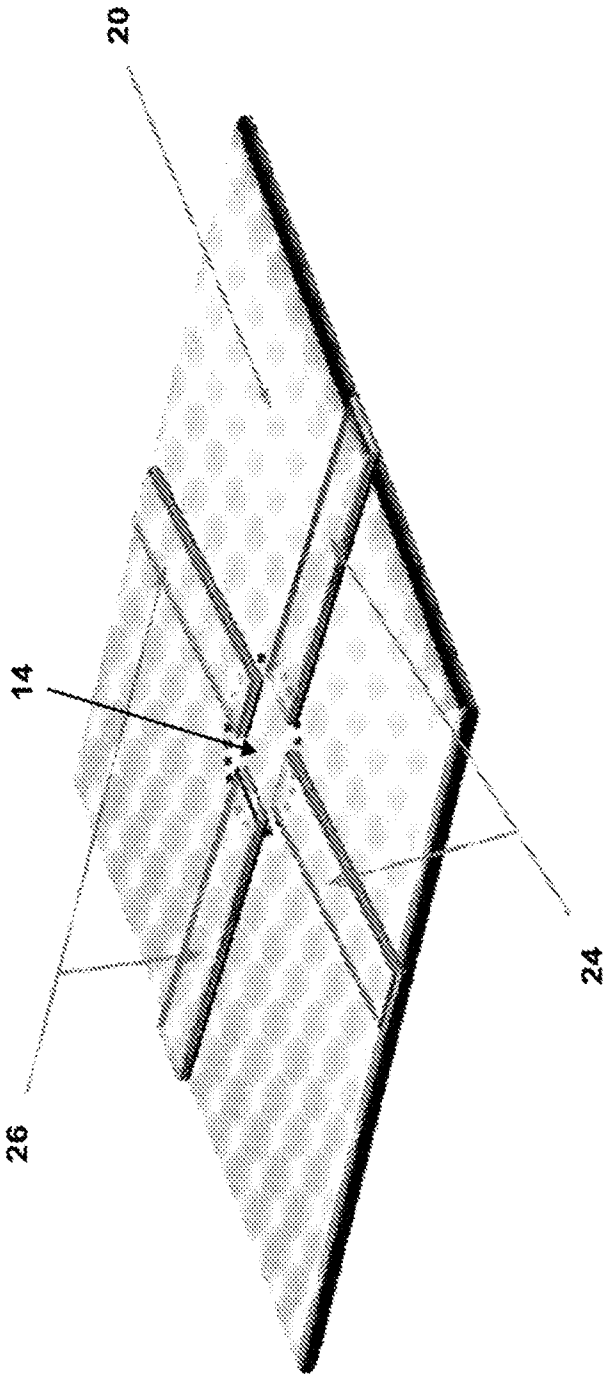


Fig. 2B

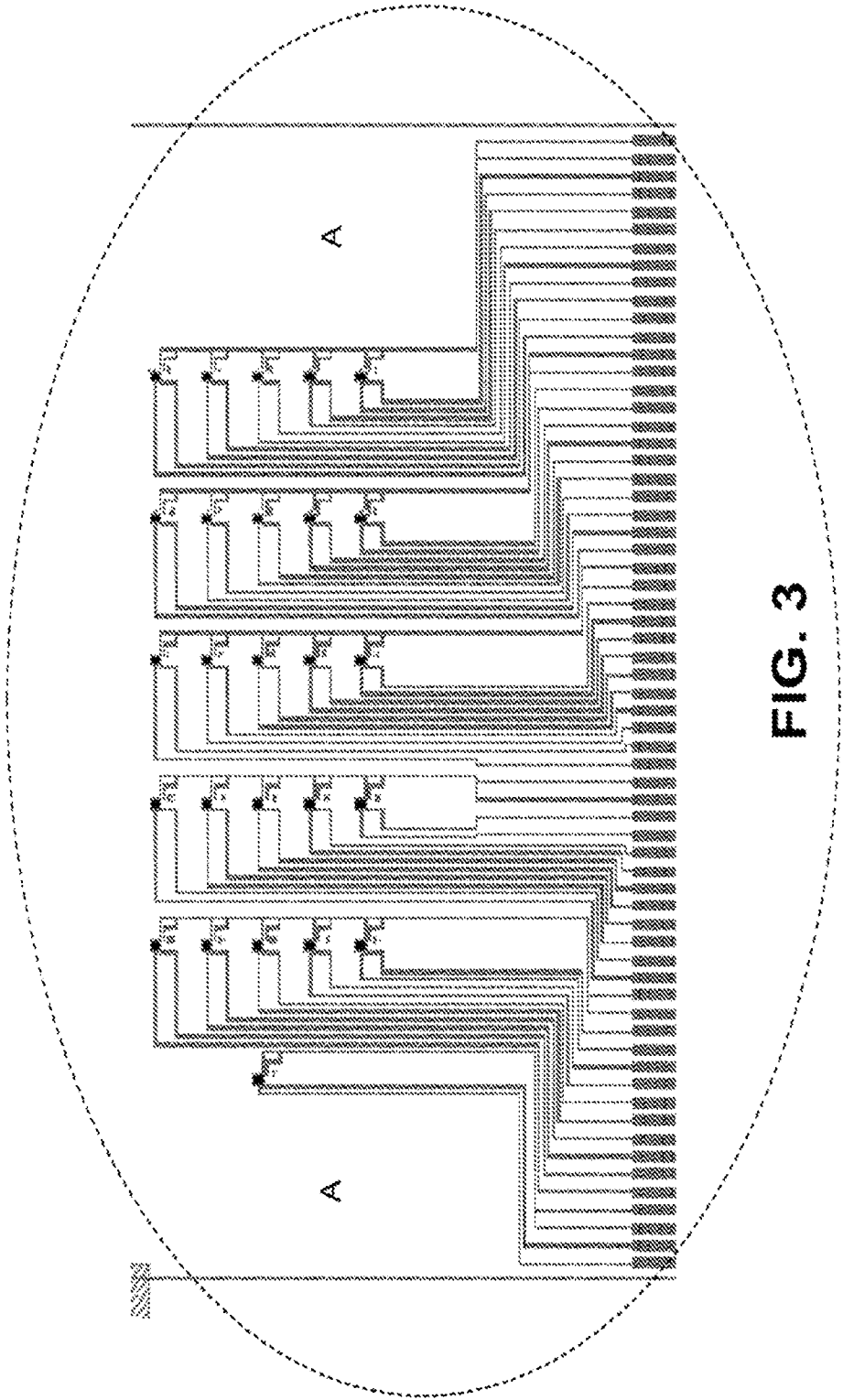


FIG. 4

