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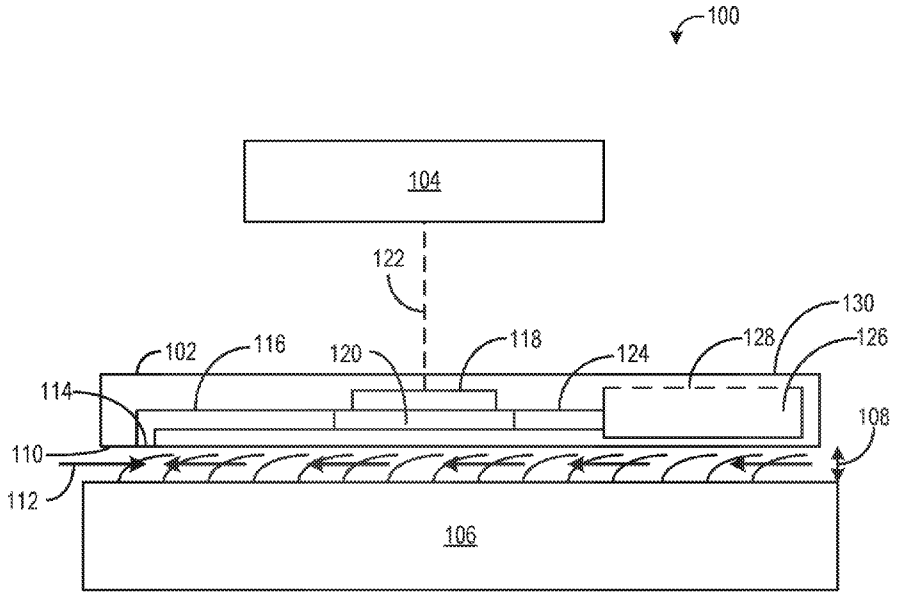


FIG. 1

(57) Abstract: Various methods and systems are provided for monitoring body fluid biomarkers with a wearable device. In one example, the wearable devices includes a sensor adapted to sense the body fluid biomarkers; a microfluidics module including a fluid collector adapted to collect fluid from a subject to which the wearable device is attached, a sensor volume in fluid communication with the sensor, and a wick adapted to wick collected fluid away from the sensor volume, the sensor volume arranged downstream of the fluid collector and upstream of the wick; and an electronics module electrically coupled with the sensor and including a wireless device adapted to wirelessly transfer sensor data received from the sensor.

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METHOD AND SYSTEMS FOR A SENSOR PATCH WITH EMBEDDED MICROFLUIDICS FOR MONITORING OF FLUID BIOMARKERS

GOVERNMENT RIGHTS

[0001] This invention was made with government support under FA8650-13-2-7311 awarded by the US Air Force Research Labs, Nano-Bio-Manufacturing Consortium. The government has certain rights in the invention.

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] The present application claims priority to U.S. Provisional Application No. 62/401,219, entitled "SENSOR PATCH WITH EMBEDDED MICROFLUIDICS FOR MONITORING OF FLUID BIOMARKERS," and filed on September 29, 2016, the entire contents of which are hereby incorporated by reference for all purposes.

FIELD

[0003] Embodiments of the subject matter disclosed herein relate to systems and methods for monitoring fluid biomarkers via a wearable device embedded with microfluidics and sensing elements.

BACKGROUND

[0004] The human body contains a variety of fluid sources that contain biomarkers indicative of a person's health and metabolic state. For example, sweat, saliva, blood, interstitial fluid, etc. may all contain biomarkers such as electrolytes, metabolites, small molecules, hormones, and proteins. The presence and concentrations of these biomarkers (in real-time and over time) may provide diagnostic information as to a person's cognitive state, stress and fatigue levels, electrolyte imbalances and hydration levels and general health. Monitoring these biomarkers may also be used in diagnostic applications for diabetes, drug companion and drug use compliance applications, chronic disease management, infection and sepsis prediction, elderly and pregnancy care, high performance and high exertion applications, etc. By monitoring and analyzing these biomarkers in real-time, a patient's health may be better monitored and medical diagnoses may be more easily

and continuously made. In one example, wearable and minimally invasive systems may be used to collect and/or analyze various biomarkers within fluid sources of a patient to monitor and/or diagnose the patient's health. One example fluid source includes sweat which contains a multitude of electrolytes and metabolites which are the final products of the body's biological processes and may be analyzed for patient health monitoring.

BRIEF DESCRIPTION

[0005] In one embodiment, a wearable device for monitoring body fluid biomarkers comprises: a sensor adapted to sense the body fluid biomarkers; a microfluidics module including a fluid collector adapted to collect fluid from a subject to which the wearable device is attached, a sensor volume in fluid communication with the sensor, and a wick adapted to wick collected fluid away from the sensor volume, the sensor volume arranged downstream of the fluid collector and upstream of the wick; and an electronics module electrically coupled with the sensor and including a wireless device adapted to wirelessly transfer sensor data received from the sensor.

[0006] It should be understood that the brief description above is provided to introduce in simplified form a selection of concepts that are further described in the detailed description. It is not meant to identify key or essential features of the claimed subject matter, the scope of which is defined uniquely by the claims that follow the detailed description. Furthermore, the claimed subject matter is not limited to implementations that solve any disadvantages noted above or in any part of this disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The present invention will be better understood from reading the following description of non-limiting embodiments, with reference to the attached drawings, wherein below:

[0008] FIG. 1 shows a schematic of a system for non-obtrusive and continuous monitoring of body fluid biomarkers, according to an embodiment of the disclosure.

[0009] FIG. 2 shows an embodiment of the system of FIG. 1 where the sensor is a resonance RF sensor, according to an embodiment of the disclosure.

[0010] FIG. 3 shows a schematic of an embodiment of a wearable, microfluidic device prototype, according to an embodiment of the disclosure.

[0011] FIG. 4 shows different embodiments of a sweat collector of a wearable device and corresponding graphs showing the performance of each sweat collector shape, according to an embodiment of the disclosure.

[0012] FIG. 5 shows a first embodiment of sensor and wick portions of a fluidics system of a wearable device, including a sweat inlet from a sweat collector, according to an embodiment of the disclosure.

[0013] FIG. 6 shows an embodiment of a complete wearable device which includes the system of FIG. 5 for a three-sensor design, according to an embodiment of the disclosure.

[0014] FIG. 7 shows an exploded view of an embodiment of a wearable device including a fluidics system and sensor assembly built up via a plurality of layers, according to an embodiment of the disclosure.

[0015] FIG. 8 shows different assembly layers of a second embodiment of the wearable device built in layers, according to an embodiment of the disclosure.

[0016] FIG. 9 shows an exploded view of the different layers of the wearable device of FIG. 8, according to an embodiment of the disclosure.

[0017] FIG. 10 shows an assembled wearable device including an electronics module, according to an embodiment of the disclosure.

[0018] FIG. 11 shows a graph of fluid transport across a wearable device, according to an embodiment of the disclosure.

[0019] FIG. 12 shows a flow chart of a method for monitoring body fluid biomarkers via a wearable device, according to an embodiment of the disclosure.

[0020] FIGS. 8-10 are shown approximately to scale.

DETAILED DESCRIPTION

[0021] The following description relates to various embodiments of systems and methods for monitoring body fluid biomarkers via a wearable device embedded with microfluidics and one or more sensing elements. The device described herein works

by wicking sweat away from an enclosed area of the skin, and uses self-priming microfluidic channels to guide the fluid over a sensor element and into a wicking or absorptive material. Integrated valves, electrodes, and optical feedback systems allow control of the analysis process, and provide information regarding flow-speed and wetting of the absorptive material. Alternate embodiments may be envisioned for the analysis of other biological fluids (such as interstitial fluid, blood, or the like) through the use of alternative or additional input fluid handling hardware including microneedles. The entire device (which, in one embodiment, may be a sweat patch) is made from flexible materials, allowing increased conformity to the body.

[0022] While the embodiments of the wearable device for monitoring of body fluid biomarkers described herein may be described with reference to sweat sensing applications in particular, it should be noted that the devices described herein may also be used for monitoring of biomarkers in alternative body fluids such as interstitial fluid, saliva, blood, and the like with appropriate modifications to the fluid path (such as inclusion of needles or other fluid collection/delivery devices coupled with the microfluidics of the device).

[0023] Previous sweat sensors used for monitoring biomarkers in sweat may rely on the contact of a sensor element directly with the skin of a subject. However, this can cause several problems, such as a change in the analyte concentration due to evaporation, and problems adapting to high and low flow rates. In some examples, sweat monitoring devices themselves may significantly alter an individual's sweat physiology (both sweat rate and sweat solute composition). For instance, in many sweat monitoring devices, the sensing elements are brought in direct or quasi-direct contact with the skin surface for response and signal enhancement purposes. However, direct contact between the device and skin may also cause swelling of the epidermis with consequent blockage of the sweat ducts due to prolonged exposure to water. Such a scenario may lead to artificially reduced sweat rates. Sweat monitoring devices also require adhesives for their attachment to the skin. However, abnormally high sweat rates may result from sweat patches where adhesives blocking sweat glands may lead to compensatory sweating of adjacent glands in the sweat harvesting area.

[0024] In one example, the issues described above may be solved by a wearable device, such as the wearable device shown in FIG. 1, that integrates fluidics (e.g., microfluidics) with fluid biomarker sensors (e.g., ion-selective sensors) and electronics with wireless communication capabilities. The wearable device may be fully integrated and flexible and may be adapted to provide non-obtrusive and continuous monitoring of body fluid biomarkers (such as electrolytes in sweat). Different embodiments of such a device are shown in FIGS. 1-10. As shown in FIGS. 1-10, the wearable device may include three main modules including a sensor module, a microfluidics module, and an electronics module. In one embodiment, the sensor module may include a passive RF sensor adapted to transmit biomarker body fluid data to an external device, as shown in FIG. 2. The microfluidics module may include a collection portion (e.g., sweat collector), a sensor channel or volume in communication with the sensor, and wicking portion, as shown in FIG. 3. In this way, the microfluidics module may collect sweat from the surface of the skin of a subject, flow the sweat to the sensor where it may be sensed, and then wick the sensed sweat away from the sensor and into a wicking apparatus in order to maintain a desired fluid flow rate through the device. Different embodiments of a sweat collector design of the device are shown in FIG. 4. The wearable device may consist of and be built up via a plurality of layers. Different embodiments of a layered, wearable device including embedded microfluidics and sensors are shown in FIGS. 7-9. FIG. 10 shows an embodiment of a fully assembled, layered, wearable device, including an electronics module coupled to an outer side of the layered device. Additionally, FIG. 11 shows an example of fluid flow through the entire wearable device and FIG. 12 shows a flow chart of a method for flowing fluid and sensing biomarkers within the collected fluid, via the wearable device.

[0025] In this way, the fluidics of the wearable device may be designed to effectively collect sweat (or alternate body fluid) from the subject while also minimizing sensor lag (e.g., a time from fluid collection to fluid sensing via the sensor or sensing element of the device). The fluidics may further be designed for the rapid removal of sweat from the sensing site while minimally affecting the sweat physiology of the subject (for example, reduction of the likelihood of hidromeiosis and compensatory sweating).

[0026] Turning first to FIG. 1, a schematic of a system 100 for non-obtrusive and continuous monitoring of body fluid biomarkers is shown. The system 100 includes a wearable device 102 for the uptake of body fluid and sensing of biomarkers within the body fluid. In one embodiment, the device 102 may be a sweat electrolyte monitoring device. As shown in FIG. 1, the device 102 is attached to an outer surface of the skin 106 of a subject. There may be a gap 108 between the outer surface of the skin 106 and an underside (skin side) 110 of the device 102. Sweat 112 (or alternate body fluid) may flow laterally through the gap 108 and to one or more inlets 114 of collection microchannels (part of the device's microfluidics, which may also be referred to herein as a sweat collector) 116 of the device 102. By minimizing the size of the gap 108, the lag time between collecting the sweat, filling the collection microchannels 116, and sensing biomarkers within the collected sweat via the sensor 118 may be reduced. The collection microchannels 116 are fluidly and directly coupled with a sensor compartment 120. The sensor compartment 120 may be the fluid compartment that holds a sensing volume of the fluid (e.g., sweat) to be sensed by the sensor 118 which may include one or more sensing elements and electronics adapted to sense and/or measure various components of the fluid. Together, the sensor 118 and sensor compartment 120 may be referred to herein as the sensor module of the device 102. The sensor 118 may be in wireless communication with an external and remotely located (e.g., remote and separate from the wearable device 102) analysis device 104. The analysis device may be a remote computer, network, or alternate analysis device including a controller having memory with instructions stored thereon for analyzing data acquired by the sensor 118. In this way, there may be a wireless connection 122 between the sensor 118 and analysis device 104. The sensor 118 may include, or be coupled to, an electronic device (e.g., electronics module) capable of wireless communication with the analysis device 104, such as an RF module and/or Bluetooth capable device.

[0027] From the sensor compartment 120, the sensed fluid (e.g., sweat) travels downstream in the device 102 via one or more outlet microchannels (also referred to herein as a capillary network and/or pre-wick channels) 124. The one or more outlet microchannels are directly and fluidly coupled to each of the sensor compartment 120 and a wick 126 which may include a plurality or network of wicking elements or

chambers, as described further below. Sweat flows from the sensor compartment 120, through the outlet microchannels 124, and into the wick 128. In this way, sweat is wicked away from the sensor compartment 120 so that new sweat may be continuously monitored and analyzed via the sensor 118. The wick 128 may include one or more vents (e.g., perforations) 128. In one example, the vents 128 may be located on an outer (e.g., exposed to air) surface 130 of the device 102. As described further below, the underside 110 of the device may be removably coupled (e.g., adhered) to the skin 106 via an adhesive. However, an area of the underside 110 containing the adhesive may be reduced in order to reduce (e.g., limited to edges of the device 102) the impact on normal sweating physiology of the subject.

[0028] FIG. 2 shows an embodiment of the system 100 of FIG. 1 where the sensor 118 is a resonance RF sensor. The system 200 shown in FIG. 2 is composed of three main components: microfluidics 202 for collection, transport and delivery of sweat; passive RF sensors 204 consisting of functionalized inter-digitated electrodes (IDEs) on a flexible RFID tag; and a pick up coil and network analyzer 206 for signal readout, analysis and data communications. System 200 illustrates an embodiment of a wearable device 208 which includes the microfluidics 202 and the passive RF sensors 204. The device 208 is attached to an outer surface of a subject's skin 210. The device 208 includes an absorptive pad 212 for absorbing and collecting fluid (e.g., sweat) from the surface of the skin 210. Collected fluid travels from the absorptive pad into a capillary channel 214 (part of the microfluidics 202). Flow of collected fluid through the capillary channel 214 is shown by arrow 216. The functionalized IDE sensor 218 of the passive RF sensors 204 sits on top of the capillary channel 214 such that the capillary channel directs the sweat to the IDE sensor 218 for sensing. An RFID tag 220 is coupled to the IDE sensor 218. Flow (such as an amount or flow rate) of fluid through the capillary channel 214 may be controlled by a valve 222 positioned upstream of the IDE sensor 218. However, in alternate embodiments, there may additionally or alternatively be a valve positioned in the capillary channel 214, downstream of the IDE sensor 218. A wick 224 including one or more wick vent perforations 226 is coupled to the capillary channel 214, downstream of the IDE sensor 218. A barrier film 228 may cover an outside (exposed outer surface) of the device 208 and serve to protect the internal components

of the device 208. Additionally, an adhesive 230 may be used to adhere the device 208 to the skin 210. In one example, the adhesive 230 may be limited to only the outer edges (e.g., outer perimeter) of the device (as opposed to underneath an entirety of the device) so that the interaction between the skin and adhesive is reduced, thereby reducing the effect on the subject's sweat physiology.

[0029] Impedance spectral analysis may be performed by measuring the inductance coupling between the RFID sensor 204 and a reader pickup coil 232 using a network analyzer 234. The network analyzer may include hardware including analysis and communications hardware and memory with instructions for receiving sensed fluid data from the RFID sensor 204 (upon activation or excitation of the RFID sensor 204) and processing and analyzing the received fluid data. The electric field generated in the RFID sensor 204, upon excitation by the reader pickup coil 232, will extend out of the sensor plane and will be affected by the dielectric properties of the ambient environment, in this instance the sweat, providing the opportunity for measurement of parameters, including bulk sweat conductivity. A conformal protective coating, such as a thin SiO_2 layer deposited on the Au IDE surface, provides a layer of separation of the conducting species from the IDEs.

[0030] Alternate sensor systems, ranging from ion selective electrodes (ISEs, as described further herein) to electrochemical to field effect transistors may be integrated with the microfluidics system shown in FIG. 2. As such, the systems described above provide for multiple flexible microfluidics options that include both paper based and polymer based microfluidics as well as combinations of these systems.

[0031] An example schematic of a microfluidic device prototype is shown in FIG. 3. This microfluidic device 300 is composed of four main parts: a sweat collecting paper based membrane 302 (which, in some embodiments, may alternatively be a polymeric based microfluidics system, as described further below), a capillary fluidic microchannel 304 that directly sits on the surface sensor 306, an electrowetting valve 308 for on-demand analyte flow control across the sensor 306, and a wicking membrane 310 for flow rate control. The direction of sweat through the device 300 is illustrated by arrow 312. The flow of sweat through the capillary fluidic microchannel is independent of gravity. In an alternate embodiment, the

electrowetting valve 308 may be positioned upstream of the sensor 306. In yet another embodiment, an electrowetting valve 308 may be positioned both upstream and downstream of the sensor 306. In one embodiment, the electrowetting valve 308 is connected via conductive traces to an electronics module (such as electronics module 1004 shown in FIG. 10, as described further below) for controlled actuation by application of a low voltage from the electronics module.

[0032] The sweat collecting paper based membrane 202 (or absorptive pad 212 shown in FIG. 2) may be a material that minimizes loss of analyte (e.g., biomarkers within the fluid or sweat) due to nonspecific binding. One example material may include Standard 17 bound glass fiber. In alternate examples, pre-blocking with synthetic or natural adsorptive blocking agents (surfactants, BSA, etc.) may be performed prior to introduction of sweat to the collecting paper based membrane, or modifications may be made to the membrane or absorptive pad materials themselves to change their adsorptive properties. Alternately, a capillary fluidic network may be designed to wick sweat into the test capillary without the use of an absorbent pad on the upstream side of the sensor, as described further herein. This approach offers two potential benefits: first being a much lower surface area to volume ratio than fibrous materials, and the second being a range of materials and surface treatments (plasma treatment, PEGylation, etc.) that may be applied.

[0033] The sweat sensing device described herein may be used for bulk sweat conductivity measurements. Sensor response occurs quickly (e.g., around 40 seconds, in one example) after the initial uptake of fluid at the collection end of the device, due to the small dead volume (which may be on the order of 5-10μL) of the entire microfluidics system. Additionally, the capillary material may be flexible and conform to the body, while being robust enough to prevent liquid movement due to bending or application of pressure.

[0034] The design of the microfluidics system of the wearable device described herein is based on multiple parameters, including a sweat rate of the individual wearing the device. Sweat rate varies dramatically with physical activity, temperature, gender, skin location, physiologic status, among other variables. Since one of the target applications for an embodiment of the wearable device described herein is to monitor hydration status (to prevent dehydration events in training,

aerobic sports or combat), the device was adapted (shaped and sized, as described further below) to function in the middle to upper range of sweat rates. An example of two physiologically relevant sweat rates include a relatively low rate if 13μL/cm^2/hr and a relatively high rate of 96μL/cm^2/hr. Based on these sweat rate values, and the known geometry of the sensor itself (electrode volume is a stadium oval - two semicircles separated by a rectangle - of total length 7mm and width 3mm and a height of 50μm, in one example) the rate of fluid transfer through the sensing volume can be calculated, and used to determine the skin surface area required to collect sufficient sweat to exchange the contents of the sensor volume in an appropriate amount of time (e.g., one volume exchange per minute) for a given sweat rate. These values further enable the calculation of the total sweat volume expected to pass through the device for specific use duration (e.g., 6hrs) and thus the amount of wicking material required to absorb the measured sweat.

[0035] The fluid-handling portion of the wearable device (e.g., the fluidic or microfluidic system) may be broken down into three sections: 1) the skin interface (e.g., sweat collector) 2) the sensor interface and 3) the reservoir/wick. To enable wicking of fluid into the channels, laminated microfluidics formed from one or more hydrophilically-treated plastic films which are held together with patterned adhesives may be used in the wearable device. In this additively based manufacturing technique, a cutting plotter is used to pattern each layer, followed by lamination. This technique allows for rapid prototyping and implementation of channel geometry changes without the need for pattern-dedicated tooling (e.g., masks, stamps) or curing. Furthermore, this method is scalable to manufacturing with dedicated punches.

[0036] FIG. 4 shows a schematic 400 of different embodiments of a sweat collector of the wearable device (which may be used at the inlets 114 of the microchannels shown in FIG. 1, in one example) and corresponding graphs showing the performance of each sweat collector shape. The sweat collector (e.g., skin interface of the device) may be sized and shaped to collect the required (e.g., desired) amounts of sweat. The sweat collector (e.g., fluid collector) includes a fluid collection volume supported by separated adhesive areas. The sweat collector is adapted to interface with the skin of a subject and the fluid collector may include a hydrophilic film arranged adjacent to the fluid collection volume. As one example,

the sweat collector may include a plurality of channels arranged adjacent to one another but spaced apart from one another via an adhesive support structure. Several shapes of the sweat collector are possible, including a circular contour with a central aperture (as shown in (a) of FIG. 4) to channel the sweat from the whole area to the sensor. From testing, it was determined that a sweat collector covering a surface area of $0.9cm^2$ (1.07cm diameter) would be sufficient to pass one volume of sweat per minute through the sensor at the $96\mu L/cm^2/hr.$ sweat rate, and a $6.6cm^2$ area (2.9cm diameter) would be required at the lower $13\mu L/cm^2/hr.$ sweat rate. One potential drawback of a large diameter circle is that it is difficult to control the gap between skin and the collection film over such a large area. An increase in skin-film gap height requires larger amounts of sweat to fill the collection area and can cause variation in filling time. A second, alternative spoked design of the sweat collector, of equivalent area as the circular design, consisting of rectangles running radially out from the collection point, overlapping in a central circle is shown in (b) of FIG. 4. A model of each of these sweat collector designs was used to understand the dynamics of sweat in both devices and specifically to understand the relative velocities and ages of the sweat in the device. The circular design was modeled homogeneously and the spoked design was modeled as a hybrid of linear (blue, (b) of FIG. 4) and circular (dashed red circle, (b) of FIG. 4) flows using the output of the linear model as the boundary conditions for the circular model. The output of this modeling showed that while the sweat velocity (radially inwards) increased for the circular design (see (d) of FIG. 4)), the net effect on the average time excreted sweat took to reach the sensor was minimally changed by altering the design (see (e) of FIG. 4). Based on these results, a hybrid design (shown in (c) of FIG. 4)) was designed which uses minimal adhesive area (at the spokes 402) to maintain the skin-device gap constant while limiting the overall device size. This hybrid design includes collection wedges (also referred to herein as channels) 404 arranged around a circumference of the outer circle 406 of the sweat collector, where the sweat channels from each of the collection wedges 404 into a central outlet aperture 408. As shown in FIG. 4, the collection wedges include a wider, inlet end adapted to uptake sweat, and a narrower, outlet end in fluidic communication with the central outlet aperture 408. In alternate embodiments, the sweat collector may be comprised of channels, free-floating bars,

and/or independent areas of adhesive. In still other embodiments, the spokes 402 shown in FIG. 4 may instead be partial spokes or smaller circles of adhesive.

[0037] There may be a relatively long lag time between filling the device with sweat (or alternate body fluid) and the beginning of sensing (e.g., 46 minutes at the lower sweat rate for a circular collection area), thus it is desirable to minimize the dead volume of the device, both by minimizing the fluidic volume in the device, as well as by minimizing the skin-to-sweat collector gap (e.g., gap 108 shown in FIG. 1). Even with adhesives of minimal thickness (e.g., 25μm), the inherent roughness of skin makes it difficult to reliably achieve gap heights of less than 100μm (assuming shaved skin). However, the structure of the hybrid design shown in (c) of FIG. 4 may minimize the skin-to-sweat collector gap while also reducing device dead volume (sweat channels funnel directly to central outlet aperture 408 which interfaces with the sensor interface, as described further below).

[0038] The second section of the device (the sensor interface) interfaces the sensor chip with the collection fluidics on the upstream side and the wick on the downstream side. A first embodiment of the sensor and wick portions of the fluidics system of the device, including a sweat inlet from the sweat collector portion is shown in FIG. 5. Specifically, FIG. 5 shows a schematic 500 of a portion of the fluidics system of the wearable device including a sweat inlet 502 from the collector portion, a sensor 504, a plurality of valves 506 disposed in channels (e.g., capillary channels), and a plurality of wicks (or wick compartments) 508. In order to minimize the overall device dead volume, the sensor 504 is placed as close to the inlet 502 as possible to minimize sensor lag. In one example, an adhesive gasket is used to attach the sensor 504 (patterned on a solid glass substrate, in one embodiment) to the device. In alternate embodiments, the interdigitated electrode and associated contacts of the sensor 504 may be printed directly on the film comprising the fluidic, or onto another flexible substrate joined to the device, as described further below.

[0039] The third section of the device (the reservoir/wick 508) provides an outlet for the collected sweat and attempts to maintain a relatively consistent efflux of sweat. In one embodiment, fiber-based materials (cellulosic and similar materials) using capillary force to wick the incoming sweat into pores may be used, though alternatives including hydrogels and highly absorbent polymers such as sodium salts

of polyacrylic acid may be considered for high sweat rate applications. One of the critical characteristics of a wick for this application is the flow rate, specifically having a very low flow rate compared to traditional cellulosic materials to avoid outpacing the flow rate of the sweat released by the body. Several materials may be used such as, but not limited to; regenerated cellulose, cellulose acetate and mixed ester materials having very high water capillary rise times (>1000 sec to climb 4 cm) compared to traditional materials (tens of seconds) indicating the ability to control flow.

[0040] Because of the large net volumes of sweat that may flow through this sensor 504 (e.g., ~250μL in 6hrs), the wick may be broken up into multiple gated wicks, as shown in FIG. 5, which can be separately triggered (via opening and closing the valves 506) to maintain a reasonably consistent capillary driving force throughout the use of the device. A wick will lose its capillary driving force as it becomes full of fluid (e.g., sweat), and thus the ability to divert flow into a fresh wick as the driving force plateaus and/or drops in the initial wick allows for more consistent flow rates over the test duration. As will be discussed below, one embodiment includes printing electrowetting-based valves directly onto the hydrophilic film used to generate the capillary channel. Each valve may be triggered by monitoring the conductivity across each wick (such that the filling of one wick triggers the opening of the next valve). For example, conductivity measurements across each wick may provide feedback to electrowetting (e.g., electrokinetic) valves arranged at the inlet of each wick. Thus, when a conductivity measurement across a first wick indicates a full or nearly full wick, the valve coupled to the first wick may close and a second valve coupled to an empty, second wick may open, thereby allowing the second wick to begin filling. In this way, the wicks may be sequentially filled via the valves and wick level feedback system (referred to herein as adaptive flow control). By monitoring a filling rate of the different wicks (e.g., based on when each valve opens and closes), a sweat rate may be estimated. The sweat rate may then be used for diagnostic or additional analytic purposes. In an alternate embodiment, dyes may be incorporated into the microfluidics and/or wicks of the device in order to provide a visual indication and estimation of the sweat rate. For example, the device may include multiple dye caches for obtaining sweat rate data for the device.

[0041] Combining the initial concepts described above for each section, an embodiment of a complete device (e.g., a wearable patch) which combines all components for a three-sensor design (e.g., Na+, K+, and conductivity) is shown in FIG. 6. Specifically, FIG. 6 shows an embodiment of a wearable device 600 that includes three sections where each section includes a fluid (e.g., sweat) collector (or a sweat uptake area) 602 which may be similar in design to the sweat collector shown in (c) of FIG. 4. Each of the three sections further includes an inlet 604 to a sensor 606. Each sensor 606 is coupled to a plurality of branching capillary (microfluidic) channels 608 which each may include an adjustable valve 610 disposed therein. Each of the capillary channels in one of the sections is directly and fluidly coupled to a separate wick 612 for that section. In this way, each section includes a plurality of wicks 612, where each wick 612 is spaced apart from adjacent wicks. The components of the device 600 are coupled to a flexible/adhesive backing 614. The wearable device 600 may be modified to include alternate sensor modalities (e.g., ion selective electrodes) and alternate or additional electronic components (e.g., electrowetting valves, fill sensors, sensor leads, and the like). In certain embodiments, the three parallel sensor (Na+, K+, conductivity) design described above may be split into a single channel, multi-wick design to decrease build time and complexity, but may be combined with multiple sensors/sensor sections as needed in a final patch design.

[0042] The sensor patch assembly of the device may be built up from multiple layers of flexible adhesive and non-adhesive materials, as shown in FIG. 7. Specifically, FIG. 7 shows an exploded view of an embodiment of a wearable device 700 including a fluidics system similar to that shown in FIG. 4 (c) and FIG. 5. The device 700 includes a first layer 702 including the fluid collector (e.g., the fluid collector shown in (c) of FIG. 4) which may be formed from PSA, in one example; a second layer 704 which may be formed from a hydrophilic PET material; a third layer 706 which may be formed from Tegaderm; a fourth layer 708 which may be formed from PSA and include the microfluidics system including the inlet, sensor, capillaries, and wick channels (fluid spaces adapted to interface with the wicks or wicking material) described above with reference to FIGS. 5 and 6; a fifth layer 710 including the wicks; a sixth layer 712 formed from a hydrophilic PET material, in one example,

and including a covering for the wicks, capillaries, and sensor; and a seventh layer 714 formed from Tegaderm.

[0043] In one embodiment, the materials forming the layers of the device 700 shown in FIG. 7 are cut with a xurography plotter system and assembled manually, but at scale could be manufactured by a combination of ballistic punch/rotary die cutting and roll-to-roll processes. The materials in use in this device pose some unique challenges, specifically the use of very low modulus materials such as thermoplastic polyurethane (TPU)/Tegaderm. Because of the low modulus of the TPU/Tegaderm, order-of-operations is important in device assembly and the generation of multiple sub-assemblies (on rigid supports where possible). Thus, PSA formulations with backing layers of appropriate adhesion to enable peel-off from different substrates may be used.

[0044] Materials for the different layers of the device may be selected to generate the functional (e.g., electronic, fluidic) and structural (e.g., adhesive) layers of the device. For example, the core of the device is the self-priming sensor chamber/fluidics where all of the device capabilities must come together in order to allow sweat flow past the sensor, with control via electrowetting valves or other valves such as optically activated valves (or passive means, as described further below). In particular, the fluidics of the device should be "self-priming" (e.g., not needing gravity or pumps) to enable uptake of sweat as soon as it comes into contact with the fluidic.

[0045] In some embodiments, PET-based ion specific electrode sensors may be incorporated into the sensor design of the device. Thus, the sensor volume (e.g., sensor compartment 120 shown in FIG. 1) may be modified (size and shape) to accommodate this type of sensor. For example, instead of the diamond-shaped RF sensor chamber shown in FIGS. 5-7, the sensor compartment may be oblong, as described further below.

[0046] A second embodiment of the wearable device built in layers is shown in FIGS 8-9. Specifically, FIG. 8 shows the different assembly layers of a wearable device 800 while FIG. 9 shows an exploded view of the different layers of the wearable device 800. Turning first to FIG. 8, a first layer 802 of the assembly of the device 800 is shown. The first assembly layer 802 is the skin interface (e.g., the

portion of the device which interfaces directly with a subject's skin) and includes an adhesive gasket 810, collection volume 812, and hydrophilic film 813, which make up the fluid collector 815, attached to a patch substrate 814 of the device 800. The second assembly layer 804 is the sensor interface and includes a sensor gasket 816, a sensor volume 818 (e.g., the compartment that holds the sample fluid and interfaces with the sensing elements of the sensor), an inlet 820 to the sensor volume, and an outlet 822 from the sensor volume (which is fluidly coupled to the pre-wick, as described further below). The third assembly layer 806 is the sweat reservoir/wick layer and includes the sensor 824, the pre-wick 826 (which is fluidly coupled to the outlet 822), and the wick (e.g., wick assembly) 828 (which is fluidly coupled to the pre-wick 826). The pre-wick 826 includes an inlet end coupled to the outlet 822 and an outlet end coupled to a central reservoir 829 of the wick 828, the outlet end wider than the inlet end. As shown in FIG. 8, the wick 828 is shaped as a fan with a plurality of triangular sections (e.g., digits 827) stemming off a common, central portion (e.g., reservoir) 829 of the wick arranged closest to the pre-wick 826. In this way, the wick 828 is one continuous wick with a plurality of separated wick sections at a distal end of the wick 828. A liquid front 830 of the fluid traveling from the pre-wick 826 into the reservoir 829 of the wick 828 is also shown in FIG. 8.

[0047] In one embodiment, the sensor 824 may be an ion selective electrode (ISE) sensor adapted to determine positive and/or negative ions in aqueous environments. These ISE sensors may be used to measure electrolyte composition and ion concentration in physiological situations, such as blood plasma and sweat. The sensor 824 may include solid-state ISEs (such as solid state Na+ and K+ ISEs) paired with a solid-state reference electrode. In alternate embodiments, the sensor 824 may include non-solid-state ISEs (such as a non-solid state polymeric ISE).

[0048] Returning to FIG. 8, the fully assembled device (e.g., sweat patch) 800 is shown at 808. The top layer shown at 808 includes vents 832 in the wick 828 (e.g., at the end of each separate triangular portion of the wick 828), copper conductors 834 extending from the sensor 824, and mechanical, button contacts 836 positioned at the end of each of the copper conductors 834. The button contacts 836 may interface with electronics of the device 800, as described further below. In alternate embodiments, the copper conductors 834 may not be copper, but may instead be

magnetic contacts. Further, in one example, the button contacts 836 may instead be magnetic connectors or snaps.

[0049] As shown by the second assembly layer 804, the second section of the device 800 interfaces the sensor (e.g., sensor chip) 824 with the collection fluidics (fluid collector 815) on the upstream side and the wick 828 on the downstream side. The geometry of this section is defined by the geometry of the ion-specific electrode sensor 824 which is made up of two circular electrodes separated by a small gap, as shown in the third assembly layer 806. Thus, the minimum volume of the sensor volume 818 is two semicircles with a rectangular region in-between (known as a stadium oval). In this volume, a glass fiber wick is placed to both ensure rapid and even distribution of liquid across the two electrodes, filter any debris such as dead skin particles, as well as to decrease the hold-up volume.

[0050] The third and final section of the device, as shown by third assembly layer 806, provides an outlet for the collected sweat and attempts to maintain a consistent efflux of sweat. As explained above, one of the important characteristics of a wick for this application is the flow rate, specifically having a very low flow rate compared to traditional cellulosic materials to avoid outpacing the flow rate of the sweat released by the body. As shown in the third assembly layer 806, a fan-shaped wick design was chosen to allow motion of the separate "digits" 827 of the wick 828 during use, while maintaining a large fluid reservoir area. Because of the thickness of the wick (0.625mm, in one example), a small pre-wick 826 is incorporated to transfer fluid from the sensor volume 818 to the reservoir 829. The design of the wick 828, with the multiple digits 827 may allow the device 800 to operate for an extended period of time without getting filled up. As such, continuous and prolonged monitoring of the subject may be accomplished with the device.

[0051] FIG. 9 shows an exploded view of the device 800 with the fluid collector 815 which may include an adhesive material for adhering to the skin of a subject. The fluid collector 815 is covered by the hydrophilic film 813 which is attached to the patch substrate 814 (which may be Tegaderm, in one embodiment). The inlet 820 from the fluid collector 815 to the sensor volume extends through the hydrophilic film 813, patch substrate 814, and to a layer 902 (which may be an adhesive material layer) including the sensor volume 818 and outlet 822. The pre-wick 826 is

positioned between the adhesive layer 902 and the wick 828. An additional hydrophilic film 904 is positioned over the layer 902, pre-wick 826, and edge of wick 828. The hydrophilic film 904 is positioned underneath the sensor 834 which is part of layer 906 including the sensor, copper conductors 834, and button contacts 834 (which in alternate embodiments may be an alternate type of connectors such as magnetic connectors). The assembly of device 800 further includes a top sheet 908 which may be made of Tegaderm, in one example.

[0052] In this way, the microfluidics patch is built up from multiple layers of flexible adhesive and non-adhesive materials, as shown in FIGS. 8-9. At the shown prototype scale, these materials may be cut with a xurography plotter system and assembled manually, but at scale could be manufactured by a combination of ballistic punch/rotary die cutting and roll-to-roll processes. The core of the device is the self-priming chamber that allows for sweat uptake, as soon as it comes into contact with the fluidics, and sweat transport past the ISE sensor. A highly hydrophilic PET film may provide the required self-priming behavior. As introduced above, the materials in use in this work pose some unique challenges, specifically the use of very low modulus materials such as thermoplastic polyurethane (TPU). Because of the low modulus of the TPU, it is challenging to affix a pressure sensitive adhesive (PSA) and remove its backing for adhesion to another layer without irreparably wrinkling/deforming/self-adhering the low modulus layer. Thus, order-of-operations is critical in device assembly and the generation of multiple sub-assemblies (on rigid supports where possible) is helpful, as shown in FIGS. 8-9.

[0053] In the embodiments of the wearable device described herein, a triangular pattern (either as separate triangular sections, as shown in FIGS. 5-7 or a fan/bird's tail design with separated triangular sections extending from a common reservoir base, as shown in FIGS. 8-9) is used for the wicking membrane; however, a variety of patterns such as circular, square or serpentine may be used. It should be noted that the choice of the wicking membrane pattern, as well as its porosity, thickness and composition together with the length of the capillary channels may have a bearing on the order in which the channels will be filled. Thus, these parameters may be adapted to determine and direct the sweat flow path into the wicks of the wicking membrane.

[0054] As one embodiment, passive sequential filling of multiple wicks (or wick sections, as shown in FIGS. 8-9) offers an option for maintaining a desired sweat flow rate through the device without the complexity of sensing and feedback-controlled valving. Ensuring that the same sequence of filling occurs each time can be accomplished by placing sequential impediments to fluid flow (hydrophobic patches, circuitous fluid paths, variations in capillary length, width, etc.) causing the incoming fluid to fill certain wicks prior to others (ensuring consistent fluid flow rates). Thus, the different digits 827 of the wick 828 shown in FIG. 8 may have a different capillary length and/or width and/or different fluid flow impediments adapted to sequentially fill the digits 827. Specifically, in one example, an end of each digit 827 coupled to the reservoir 829 may have a different shape or size or include a different flow impediment that allows one digit to fill before or after an adjacent digit. For example, the sequential filling of wicks may include filling a first wick (e.g., a first of digits 827 shown in FIG. 8) and then upon complete or near complete filling of the first wick, a second, adjacent wick (e.g., a second of digits 827 shown in FIG. 8) will begin filling, and so on, until all wicks of the wicking assembly are full. This may maintain a near constant fluid flow rate through the device, thereby ensuring constant and accurate sensing via the sensor of the device. In alternate embodiments, the separate wicks or digits 827 of the wick 828 may be filled non-sequentially. For example, a single wick or wick digit may be filled at once, but the order of filling may not be sequential (e.g., one wick to the next adjacent wick). In one example, the path and order of filling the separate wicks or wick digits may be random. In another example, multiple wicks or digits of the wick may fill at the same time while still maintaining a desired fluid flow rate through the device.

[0055] The wearable device described herein also includes an electronics module including electronics adapted to receive signals/outputs from the sensor (e.g., the RFID, IDE, and/or ISE sensor(s) of the wearable device, as described above). The electronics module may also be adapted for data readout to an external electronic device, computer, or network and providing energy to the components of the electronics module and the sensor(s) of the wearable device. The electronics module may also control electrowetting valves of the device (as described above) by applying a low voltage (e.g., less than 12V, in one example) for actuation of the electrowetting

valves. An example of an electronics module, coupled with an embodiment of the assembled wearable device (including the microfluidics and sensor modules) is shown in FIG. 10. Specifically, FIG. 10 shows an embodiment of an assembled wearable device 1000 that may have similar components to the wearable devices described herein. In one example, the wearable device 1000 may include a base 1002 including the microfluidics module and sensor module of the wearable device, which may include the same or similar components as device 800 shown in FIGS. 8 and 9. The wearable device 1000 further includes the electronics module 1004. The electronics module 1004 includes internal electronics housed within an outer casing (e.g., case or housing) 1006. The outer casing 1006 may be relatively flexible and constructed from various methods, one of which may include 3D printing. For example, the outer casing 1006 may be adapted to support a relatively non-flexible PCB of the electronics module 1004, while also coupling with a relatively flexible interface to the flexible microfluidics module (e.g., included in base 1002) to allow the full device to move comfortably with the user. In one example, the material of the outer casing 1006 may be a flexible additive resin. Additionally, in some embodiments, antistatic coatings may be used on the outer casing 1006 to shield the device and improve the signal to noise ratio. In a further embodiment, a further rigid skeleton may be disposed around the PCB material inside the soft outer casing to further protect the internal electronics.

[0056] The outer casing 1006 sits on top of and couples to an outer surface of the base 1002 via one or more fasteners 1008 (two shown in FIG. 10). The fasteners 1008 may be complementary to and adapted to mate with fasteners on the base 1002. In one example, fasteners 1008 may be removably coupled with the button contacts 836 shown in FIG. 8. In this example, fasteners 1008 may be mechanical or magnetic buttons or snaps which snap to corresponding buttons or snaps on the base 1002. In alternate embodiments, the button contacts may instead be magnetic connectors (such as self-aligning magnetic snaps). Thus, the fasteners 1008 may be magnetic connectors adapted to couple with corresponding magnetic connectors on the base 1002. In one example, the magnetic connectors may allow for easier connections and increased ease of assembling of the device. In this way, the electronics within the electronics module 1004 may be electrically coupled with the sensor (e.g., sensor 824

shown in FIGS. 8-9) through the fasteners 1008 and corresponding fasteners on the base 1002, which may be electrically conductive.

[0057] The electronics of the electronics module 1004 may include a microcontroller unit (MCU), one or more switches (such as a power switch and/or reset switch or button), various electronic connectors, battery connections, charging connections, signal amplifiers such as a high-impedance amplifier required for ISEs, a wireless communication module, a built-in memory, a power management unit, a battery, a communications management unit, an antenna, and the like. In one embodiment, the electronics of the electronics module 1004 may include a data acquisition and communications transfer board (such as a Bluetooth transfer board that is adapted to transfer data output from the sensor of the device, wirelessly, to an external electronics device or network). Together, the electronics module 1004 and base (including the microfluidics module and sensor module) form an integrated wearable device (e.g., patch). In one embodiment, this may be an integrated sweat patch.

[0058] The devices described herein may include a combination of disposable and non-disposable (e.g., re-usable) parts, all disposable parts, or all non-disposable parts. As one example, the microfluidics module and sensor module may be disposable while the electronics module is non-disposable. In another example, each and all of the microfluidics module, the sensor module, and the electronics module may be disposable.

[0059] FIGS. 5-10 show example configurations with relative positioning of the various components. If shown directly contacting each other, or directly coupled, then such elements may be referred to as directly contacting or directly coupled, respectively, at least in one example. Similarly, elements shown contiguous or adjacent to one another may be contiguous or adjacent to each other, respectively, at least in one example. As an example, components laying in face-sharing contact with each other may be referred to as in face-sharing contact. As another example, elements positioned apart from each other with only a space there-between and no other components may be referred to as such, in at least one example. As yet another example, elements shown above/below one another, at opposite sides to one another, or to the left/right of one another may be referred to as such, relative to one another.

Further, as shown in the figures, a topmost element or point of element may be referred to as a "top" of the component and a bottommost element or point of the element may be referred to as a "bottom" of the component, in at least one example. As used herein, top/bottom, upper/lower, above/below, may be relative to a vertical axis of the figures and used to describe positioning of elements of the figures relative to one another. As such, elements shown above other elements are positioned vertically above the other elements, in one example. As yet another example, shapes of the elements depicted within the figures may be referred to as having those shapes (e.g., such as being circular, straight, planar, curved, rounded, chamfered, angled, or the like). Further, elements shown intersecting one another may be referred to as intersecting elements or intersecting one another, in at least one example. Further still, an element shown within another element or shown outside of another element may be referred as such, in one example.

[0060] FIG. 11 shows a graph 1100 of fluid transport across the wearable device (within the microfluidics) where sodium concentration is on the y-axis and time (in seconds) is on the x-axis. Graph 1100 shows the events of fluid (e.g., sweat) delivery to the patch at 1102, fluid sensing between 1104 and 1106, and fluid removal to the reservoir (of the wick) after 1106. As mentioned earlier, the design (e.g., shape, size, and arrangement) of the fluidics module, and more specifically the wicking reservoir, allow for rapid removal of the analyte from the sensing site, minimizing new and old sweat mixing.

[0061] FIG. 12 shows a flow chart of a method for monitoring body fluid biomarkers via a wearable device, such as one of the wearable devices described herein and shown in FIGS. 1-10. FIG. 12 begins at 1202 by collecting a body fluid from a subject via a fluid collector (e.g., sweat collector) which may be part of a collection portion of a microfluidics module of the wearable device. In one example, fluid (e.g., sweat) from a subject's skin may enter the device via the fluid collector (such as the fluid collector 815 shown in FIG. 8). For example, the sweat from the subject's skin may enter the fluid collector at a rate of at least $10\mu L/cm^2/hr$. In this way, the fluid collector and additional microfluidic channels and wicks of the device may be sized and oriented, as explained herein, to perform at and handle sweat rates of at least $10\mu L/cm^2/hr$. In applications where the subject's local sweat rate is low

(e.g., <10μL/cm^2/hr), a sweat stimulant (such as a pilocarpine nitrate) may be used to stimulate sweat production to a sufficient rate for analysis and/or electrophoresis may be used to accelerate the movement of ions into and through the device. At 1204, the method includes transporting (e.g., flowing) collected fluid via microfluidics of the device to a sensor compartment or volume in fluid communication with a sensor (such as sensor volume 818 shown in FIG. 8). In one embodiment, transporting the collected fluid may include flowing fluid through the fluid collector, to a central aperture of the fluid collector, and to an inlet (such as inlet 820 shown in FIG. 8) to the sensor volume. Transporting the collected fluid via the microfluidics of the device may include flowing fluid through the microfluidic channels of the device without the aid of gravity or pumps. At 1206, the method includes sensing biomarkers (such as electrolytes) within the fluid in the sensor volume via a sensor fluidly coupled to the sensor volume (such as sensor 824 shown in FIG. 8). In one example, sensing the biomarkers may include measuring a concentration of sodium or potassium within a sweat sample in the sensor volume using the sensor. At 1208, the method includes continuously obtaining (e.g., receiving) sensor outputs from the sensor at an electronics module of the device that is electrically coupled with the sensor. In one example, the method at 1208 may include the sensor sending sensor outputs to the electronics module as collected fluid passes through the sensor volume. The electronics module may then wireless transfer the obtained sensor data (outputs) to an external device (e.g., a computer, network, or alternate device located remote from the wearable device and subject) at 1210. In one example, this may be done via RF pairing technology (as shown in FIG. 2). In another example, the data may be transferred wireless via Bluetooth technology or an alternate wireless communication device. In one example, the obtaining of sensor data and wireless communication of the obtained sensor data may happen continuously and in real-time, thereby providing real-time monitoring of bio-fluids of a subject via the wearable device. Thus, in one example, as a subject is moving or exercising, sensor data may be obtained and communicated to an external device for analysis.

[0062] At 1212, the method includes wicking sensed fluid away from the sensor volume and into one or more wicks fluidly coupled to the sensor volume. In one embodiment, the method at 1212 may include flowing fluid from the sensor volume to

a wick or network of wicks via one or more microfluidic channels coupled between the wick and sensor volume. In another embodiment, the method at 1212 may including flowing fluid from the sensor volume to an upstream reservoir of a wick (such as wick 828 shown in FIG. 8) via a pre-wick channel (such as pre-wick 826 shown in FIG. 8). From the reservoir of the wick, the fluid may then flow into the individual wicks, wick compartments, or wick digits (such digits 827 shown in FIG. 8). The method at 1214 includes sequentially filling the separate wick compartments (or wick digits) and maintaining a continuous, desired flow rate of fluid through the device (e.g., a relatively constant flow rate without the flow rate decreasing due to a wick compartment becoming filled with fluid). Sequentially filling the separate wick compartments may include filling a first wick compartment first and then filling an adjacent, second wick compartment after the first wick compartment is full or mostly full, and so on, until all wick compartments are full. This may maintain a relatively constant flow rate of fluid from the sensor volume to the wick and thus a relatively constant flow rate through the device, thereby enabling continuous measurement of fluid (e.g., sweat). In one example, the method at 1214 may include sequentially filling the wick compartments via passive means (e.g., using the structure of the wicks and capillary tubes leading up to the individual wick compartments, as described herein). In another example, the method at 1214 may include actively, sequentially filling the wick compartment via one or more valves (such as electrowetting valve disclosed herein) arranged in the capillary tubes fluidly coupled to each separate wick or wick compartment (such as the valves shown in FIG. 3 and FIGS. 5-6).

[0063] In this way, a wearable device including integrated fluidics, bio-fluid biomarker sensing sensors, and electronics adapted for wireless communication may be used to non-obtrusively and continuously monitor biomarkers in bio-fluid (such as sweat) of a subject. The wearable device may include microfluidics, a sensor module (which may be an ion-selective sensor, in one example), and an electronics module. As described herein, the design (e.g., size and arrangement) of the microfluidics may allow for the effective collection of fluid while minimizing lag time between fluid collection and sensing via the sensor. The design of the fluidics, including the hydrophilic materials, channel design, and wick design, may allow for an increased

rate of fluid removal from a sensor volume while minimally affecting sweat physiology of the subject. Further, the flexible materials of the microfluidics, electronics module, and sensor module may allow for a flexible device that allows for accurate sensing, even under stress and/or bending (due to subject movement or motion). Further, due to the branched or multiple wick compartment structure of the wick of the device, as well as the reduced adhesive area (contacting the subject's skin) of the fluid collection portion of the microfluidics, the device may be used for an extended period of time without disrupting the sweat physiology of the subject and without filling up the device (and thus requiring change-out with an empty device). As a result, a subject's body fluid may be monitored continuously for an extended period of time, thereby providing data of increased accuracy for subject diagnosis and treatment. The technical effect of collecting fluid from an outer surface of skin of a subject via a fluid collector of a wearable device; transporting the collected fluid to a sensor volume in fluidic communication with a bio-fluid sensor via microfluidics; wirelessly transferring sensor data output from the bio-fluid sensor to an external device; and wicking fluid away from the sensor volume and into one or more wick chambers of a wick of the wearable device at a continuous flow rate is the real-time, continuous measurement and analysis of biomarkers in a fluid while reducing an influence of the device on regular subject physiology.

[0064] As one embodiment, a wearable device for monitoring biomarkers in body fluid, comprises: a sensor adapted to sense the biomarkers in body fluid; a microfluidics module including a fluid collector adapted to collect fluid from a subject to which the wearable device is attached, a sensor volume in fluid communication with the sensor, and a wick adapted to wick collected fluid away from the sensor volume, the sensor volume arranged downstream of the fluid collector and upstream of the wick; and an electronics module electrically coupled with the sensor and including a wireless device adapted to wirelessly transfer sensor data received from the sensor. In a first example of the wearable device, the collected fluid is sweat. In a second example of the wearable device, each of the sensor, microfluidics, and electronics module are coupled to a flexible substrate of the wearable device and the wearable device is constructed from a plurality of layers, where the sensor, fluid collector, sensor volume, and wick are all arranged in different layers of the plurality

of layers. In a third example of the wearable device, the fluid collector includes a fluid collection volume supported by separated adhesive areas, the fluid collector adapted to interface with a skin of a subject to which the wearable device is attached, and the fluid collector includes a hydrophilic film arranged adjacent to the fluid collection volume. In a fourth example of the wearable device, the fluid collector includes a plurality of collection channels arranged in a circle, each channel of the plurality of collection channels including an inlet end adapted to interface with the skin and an outlet end arranged proximate to a common, central aperture, the central aperture fluidly coupled to an inlet of the sensor volume and each channel of the plurality of collection channels is separated from an adjacent channel of the plurality of channels via a narrow spoke, where a portion of the narrow spoke includes an adhesive adapted to adhere the fluid collector to the skin of the subject. In a fifth example of the wearable device, the sensor volume includes an outlet fluidly and directly coupled to a pre-wick channel adapted to direct fluid to the wick, the pre-wick including an inlet end coupled to the outlet and an outlet end coupled to a central reservoir of the wick, the outlet end wider than the inlet end. In a sixth example of the wearable device, the sweat collector, sensor volume and wick are adapted to perform at a sweat rate of at least $10\mu L/cm^2/hr$. In a seventh example of the wearable device, the wick is fan-shaped and includes a plurality of separate digits stemming off a common, central reservoir of the wick, where each digit of the plurality of separate digits is a fluid compartment adapted to hold a volume of collected and sensed fluid. In an eighth example of the wearable device, the wick is separated into a plurality of separate wick compartments and wherein each wick compartment of the plurality of separate wick compartments is fluidly coupled to an adjustable valve adapted to adjust a flow of fluid from the sensor volume to the wick compartment to which it is coupled. In a ninth example of the wearable device, the wick is separated into a plurality of separate wick compartments and wherein each wick compartment of the plurality of separate wick compartments is fluidly coupled to a microfluidic channel, where each microfluidic channel is adapted such that the plurality of separate wick compartments are filled in a sequential progression. In a tenth example of the wearable device, the sensor is an ion selective electrode sensor including an ion selective electrode paired with a reference electrode. In an eleventh example of the

wearable device, the electronics module is electrically coupled to the sensor and directly coupled to a base of the wearable device via complementary magnetic connectors arranged on the electronics module and the base, the microfluidics module and sensor incorporated into the base. In a twelfth example of the wearable device, the electronics module includes a flexible outer casing surrounding electronics including a microcontroller unit, a high impedance amplifier, a power management unit, a battery, a communications management unit, a built-in memory, and an antenna in electronic communication with the sensor.

[0065] As another embodiment, a method for monitoring biomarkers in body fluid , comprises: collecting fluid from an outer surface of skin of a subject via a fluid collector of a wearable device; transporting the collected fluid to a sensor volume in fluidic communication with a bio-fluid sensor via microfluidics; wirelessly transferring sensor data output from the bio-fluid sensor to an external device; and wicking fluid away from the sensor volume and into one or more wick chambers of a wick of the wearable device at a continuous flow rate. In a first example of the method, the method further comprises continuously obtaining outputs from the bio-fluid sensor at an electronics module of the wearable device and wirelessly transferring sensor data, including the obtained outputs, from the electronics module to the external device. In a second example of the method, collecting fluid includes collecting sweat at a sweat rate of at least $10\mu L/cm^2/hr$, where the sweat rate is one of a natural sweat rate or a sweat rate produced from local application of a sweat stimulant to a sweat collection site on the skin to induce sweat production under conditions where the natural sweat rate is less than $10\mu L/cm^2/hr$. In a third example of the method, transporting the collected fluid to the sensor volume includes flowing collected fluid directly from the fluid collector to an inlet of the sensor volume, the sensor volume arranged adjacent to a central outlet aperture of the fluid collector and further comprising sequentially filling the one or more wick chambers and maintaining the continuous flow rate from the sensor volume to the wick.

[0066] As yet another embodiment, a wearable device for monitoring biomarkers in body fluid, comprises: a sensor module including a sensor adapted to sense biomarkers in a body fluid; a microfluidics module including a fluid collector adapted to collect the body fluid from a subject via a plurality of narrowing channels arranged

in a circle, a sensor volume fluidly coupled to the sensor module and the fluid collector, and a wick fluidly coupled downstream of the sensor volume, the wick including a plurality of continuous but separate wick compartments; and an electronics module electrically coupled to the sensor and including a wireless device adapted to transmit sensor data received from the sensor to an external device. In a first example of the wearable device, the wearable device is comprised of a plurality of stacked layers, the plurality of stacked layers including a first layer including the fluid collector, a second layer including the sensor volume and a pre-wick channel fluidly coupling an outlet of the sensor volume to the wick, and a third layer including the wick, where the second layer is positioned between the first layer and third layer. In a second example of the wearable device, the electronics module is removably coupled to a base of the wearable device via electrically conductive magnetic connectors, the base including the microfluidics module and sensor module.

[0067] As used herein, an element or step recited in the singular and proceeded with the word "a" or "an" should be understood as not excluding plural of said elements or steps, unless such exclusion is explicitly stated. Furthermore, references to "one embodiment" of the present invention are not intended to be interpreted as excluding the existence of additional embodiments that also incorporate the recited features. Moreover, unless explicitly stated to the contrary, embodiments "comprising," "including," or "having" an element or a plurality of elements having a particular property may include additional such elements not having that property. The terms "including" and "in which" are used as the plain-language equivalents of the respective terms "comprising" and "wherein." Moreover, the terms "first," "second," and "third," etc. are used merely as labels, and are not intended to impose numerical requirements or a particular positional order on their objects.

[0068] This written description uses examples to disclose the invention, including the best mode, and also to enable a person of ordinary skill in the relevant art to practice the invention, including making and using any devices or systems and performing any incorporated methods. The patentable scope of the invention is defined by the claims, and may include other examples that occur to those of ordinary skill in the art. Such other examples are intended to be within the scope of the claims if they have structural elements that do not differ from the literal language of the

claims, or if they include equivalent structural elements with insubstantial differences from the literal languages of the claims.

CLAIMS:

1. A wearable device for monitoring biomarkers in body fluid, comprising:

a sensor adapted to sense the biomarkers in body fluid;

a microfluidics module including a fluid collector adapted to collect fluid from a subject to which the wearable device is attached, a sensor volume in fluid communication with the sensor, and a wick adapted to wick collected fluid away from the sensor volume, the sensor volume arranged downstream of the fluid collector and upstream of the wick; and

an electronics module electrically coupled with the sensor and including a wireless device adapted to wirelessly transfer sensor data received from the sensor.

2. The wearable device of claim 1, wherein the collected fluid is sweat.

3. The wearable device of claim 1, wherein each of the sensor, microfluidics, and electronics module are coupled to a flexible substrate of the wearable device and wherein the wearable device is constructed from a plurality of layers, where the sensor, fluid collector, sensor volume, and wick are all arranged in different layers of the plurality of layers.

4. The wearable device of claim 1, wherein the fluid collector includes a fluid collection volume supported by separated adhesive areas, the fluid collector adapted to interface with a skin of a subject to which the wearable device is attached, and wherein the fluid collector includes a hydrophilic film arranged adjacent to the fluid collection volume.

5. The wearable device of claim 4, wherein the fluid collector includes a plurality of collection channels arranged in a circle, each channel of the plurality of collection channels including an inlet end adapted to interface with the skin and an outlet end arranged proximate to a common, central aperture, the central aperture fluidly coupled to an inlet of the sensor volume and wherein each channel of the plurality of collection channels is separated from an adjacent channel of the plurality of channels

via a narrow spoke, where a portion of the narrow spoke includes an adhesive adapted to adhere the fluid collector to the skin of the subject.

6. The wearable device of claim 1, wherein the sensor volume includes an outlet fluidically and directly coupled to a pre-wick channel adapted to direct fluid to the wick, the pre-wick including an inlet end coupled to the outlet and an outlet end coupled to a central reservoir of the wick, the outlet end wider than the inlet end.

7. The wearable device of claim 1, wherein the sweat collector, sensor volume and wick are adapted to perform at a sweat rate of at least 10μL/cm^2/hr.

8. The wearable device of claim 1, wherein the wick is fan-shaped and includes a plurality of separate digits stemming off a common, central reservoir of the wick, where each digit of the plurality of separate digits is a fluid compartment adapted to hold a volume of collected and sensed fluid.

9. The wearable device of claim 1, wherein the wick is separated into a plurality of separate wick compartments and wherein each wick compartment of the plurality of separate wick compartments is fluidly coupled to an adjustable valve adapted to adjust a flow of fluid from the sensor volume to the wick compartment to which it is coupled.

10. The wearable device of claim 1, wherein the wick is separated into a plurality of separate wick compartments and wherein each wick compartment of the plurality of separate wick compartments is fluidly coupled to a microfluidic channel, where each microfluidic channel is adapted such that the plurality of separate wick compartments are filled in a sequential progression.

11. The wearable device of claim 1, wherein the sensor is an ion selective electrode sensor including an ion selective electrode paired with a reference electrode.

12. The wearable device of claim 1, wherein the electronics module is electrically coupled to the sensor and directly coupled to a base of the wearable device via complementary magnetic connectors arranged on the electronics module and the base, the microfluidics module and sensor incorporated into the base.

13. The wearable device of claim 1, wherein the electronics module includes a flexible outer casing surrounding electronics including a microcontroller unit, a high impedance amplifier, a power management unit, a battery, a communications management unit, a built-in memory, and an antenna in electronic communication with the sensor.

14. A method for monitoring biomarkers in body fluid, comprising:

collecting fluid from an outer surface of skin of a subject via a fluid collector of a wearable device;

transporting the collected fluid to a sensor volume in fluidic communication with a bio-fluid sensor via microfluidics;

wirelessly transferring sensor data output from the bio-fluid sensor to an external device; and

wicking fluid away from the sensor volume and into one or more wick chambers of a wick of the wearable device at a continuous flow rate.

15. The method of claim 14, further comprising continuously obtaining outputs from the bio-fluid sensor at an electronics module of the wearable device and wirelessly transferring sensor data, including the obtained outputs, from the electronics module to the external device.

16. The method of claim 14, wherein collecting fluid includes collecting sweat at a sweat rate of at least $10\mu L/cm^2/hr$, where the sweat rate is one of a natural sweat rate or a sweat rate produced from local application of a sweat stimulant to a sweat collection site on the skin to induce sweat production under conditions where the natural sweat rate is less than $10\mu L/cm^2/hr$.

17. The method of claim 14, wherein transporting the collected fluid to the sensor volume includes flowing collected fluid directly from the fluid collector to an inlet of the sensor volume, the sensor volume arranged adjacent to a central outlet aperture of the fluid collector and further comprising sequentially filling the one or more wick chambers and maintaining the continuous flow rate from the sensor volume to the wick.

18. A wearable device for monitoring biomarkers in body fluid, comprising:

a sensor module including a sensor adapted to sense biomarkers in a body fluid;

a microfluidics module including a fluid collector adapted to collect the body fluid from a subject via a plurality of narrowing channels arranged in a circle, a sensor volume fluidly coupled to the sensor module and the fluid collector, and a wick fluidly coupled downstream of the sensor volume, the wick including a plurality of continuous but separate wick compartments; and

an electronics module electrically coupled to the sensor and including a wireless device adapted to transmit sensor data received from the sensor to an external device.

19. The wearable device of claim 18, wherein the wearable device is comprised of a plurality of stacked layers, the plurality of stacked layers including a first layer including the fluid collector, a second layer including the sensor volume and a pre-wick channel fluidly coupling an outlet of the sensor volume to the wick, and a third layer including the wick, where the second layer is positioned between the first layer and third layer.

20. The wearable device of claim 18, wherein the electronics module is removably coupled to a base of the wearable device via electrically conductive magnetic connectors, the base including the microfluidics module and sensor module.

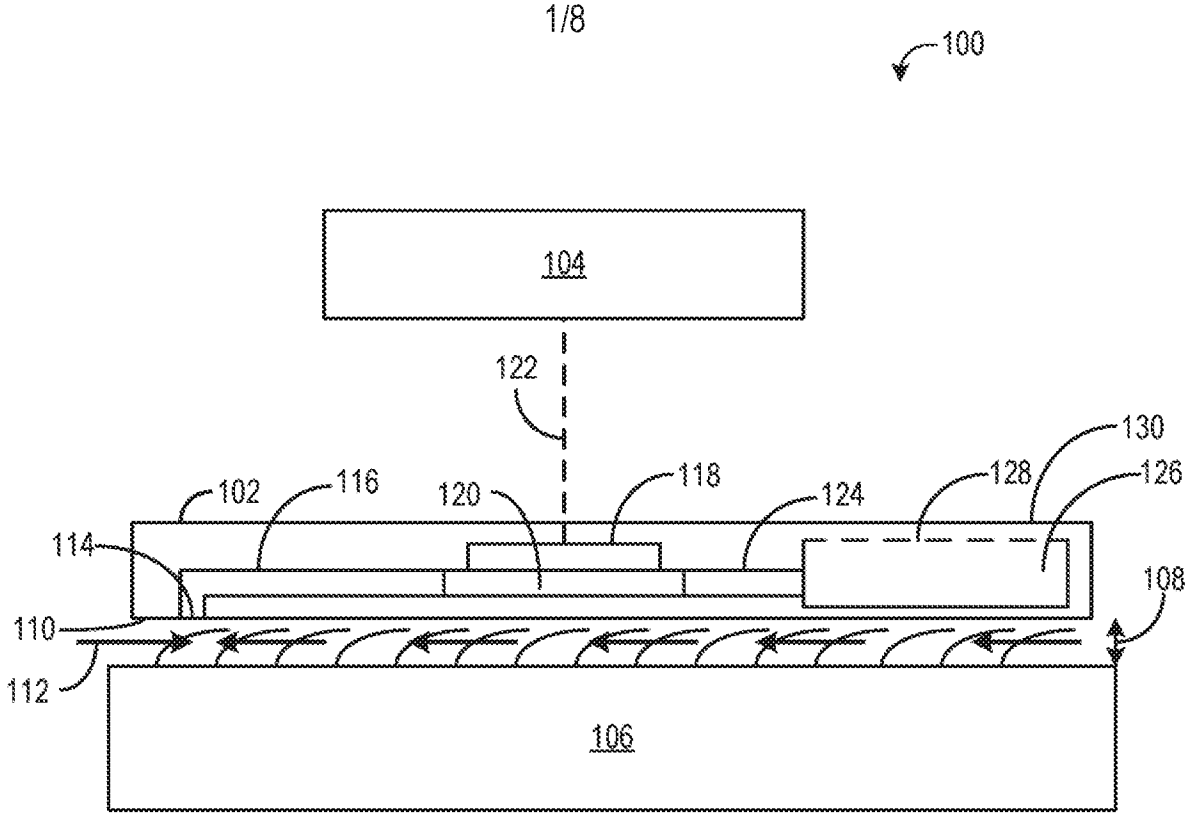

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FIG. 1

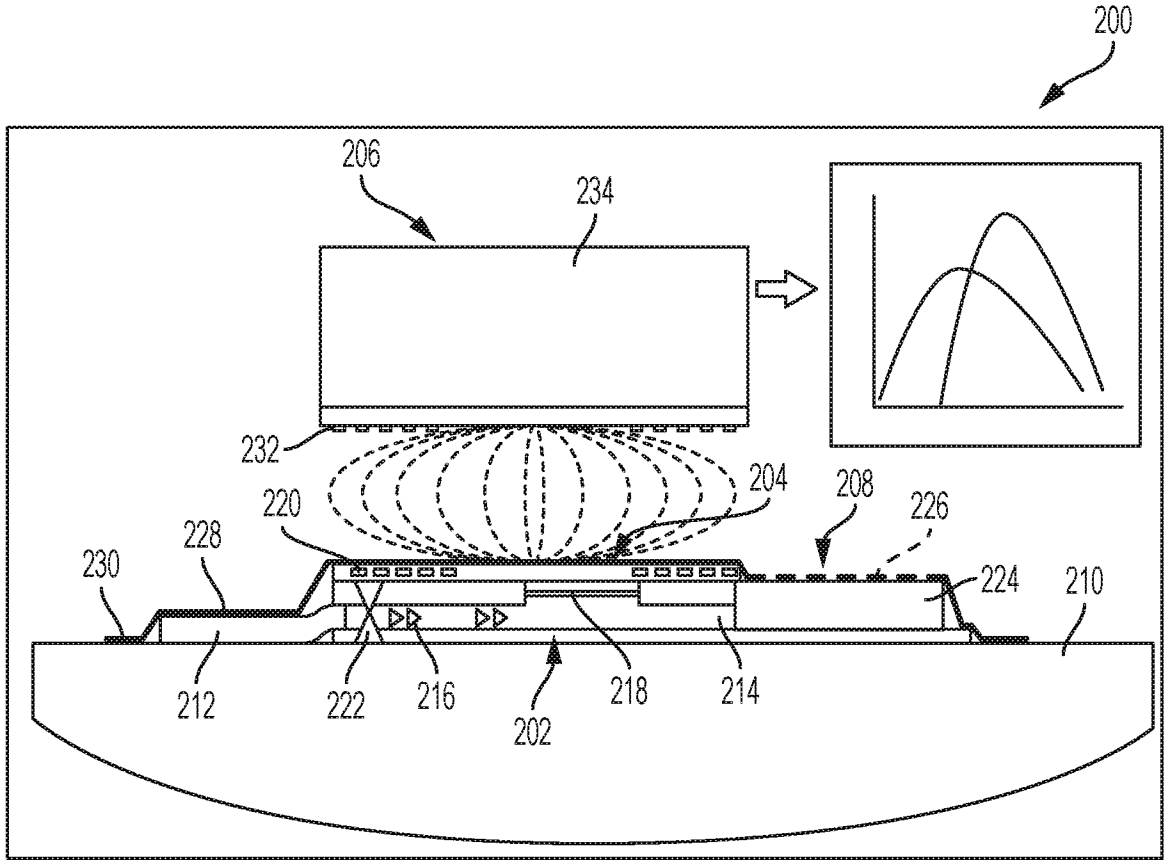

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FIG. 2

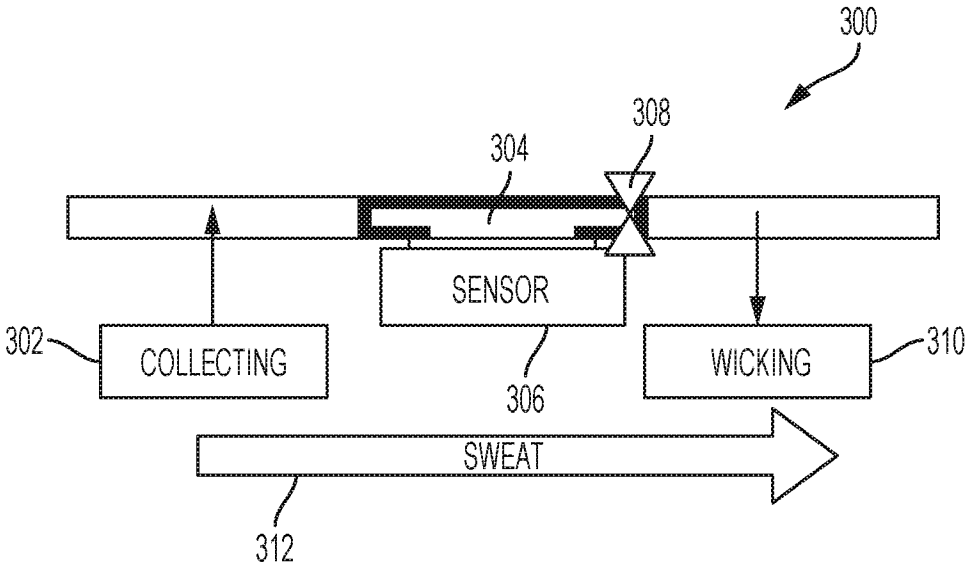

300
308
304
SENSOR
302
COLLECTING
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WICKING
310
SWEAT
312

FIG. 3

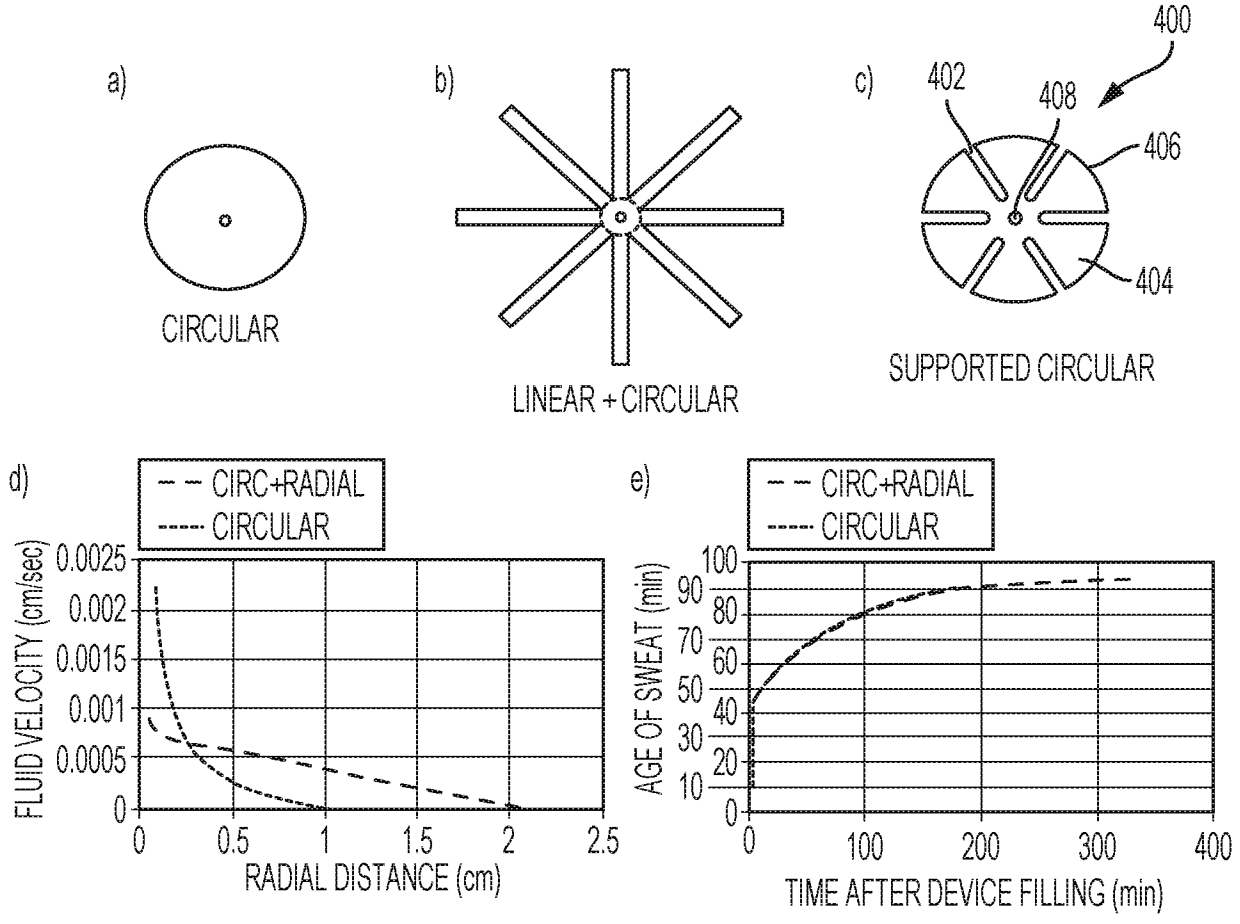

a)
CIRCULAR
b)
LINEAR + CIRCULAR
c)
400
402
408
406
404
SUPPORTED CIRCULAR
d)
CIRC+RADIAL
CIRCULAR
FLUID VELOCITY (cm/sec)
0.0025
0.002
0.0015
0.001
0.0005
0
0
0.5
1
1.5
2
2.5
RADIAL DISTANCE (cm)
e)
CIRC+RADIAL
CIRCULAR
AGE OF SWEAT (min)
100
90
80
70
60
50
40
30
20
10
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0
100
200
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400
TIME AFTER DEVICE FILLING (min)

FIG. 4

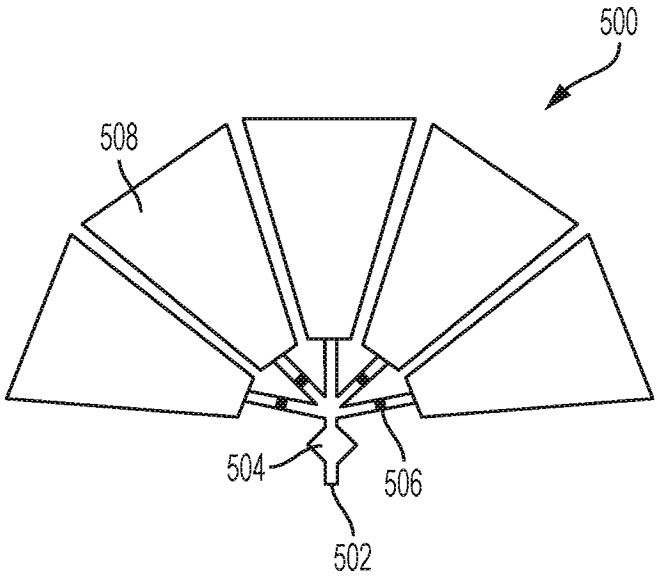


FIG. 5

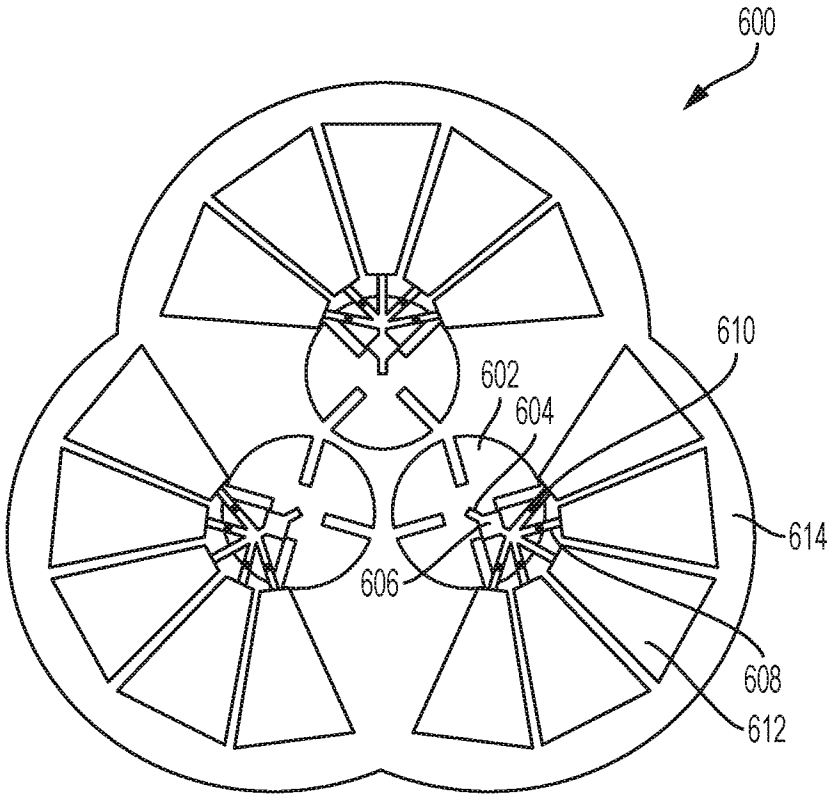


FIG. 6

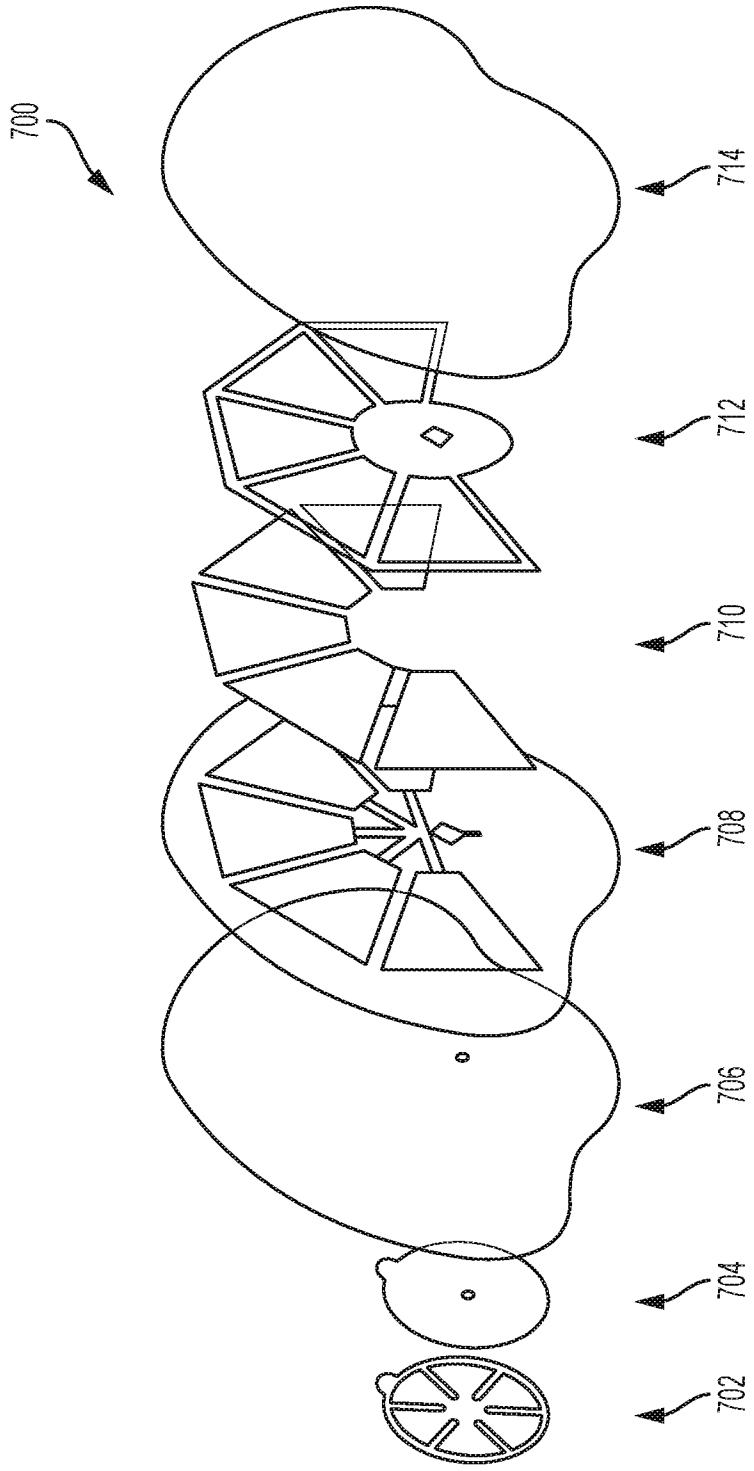


FIG. 7

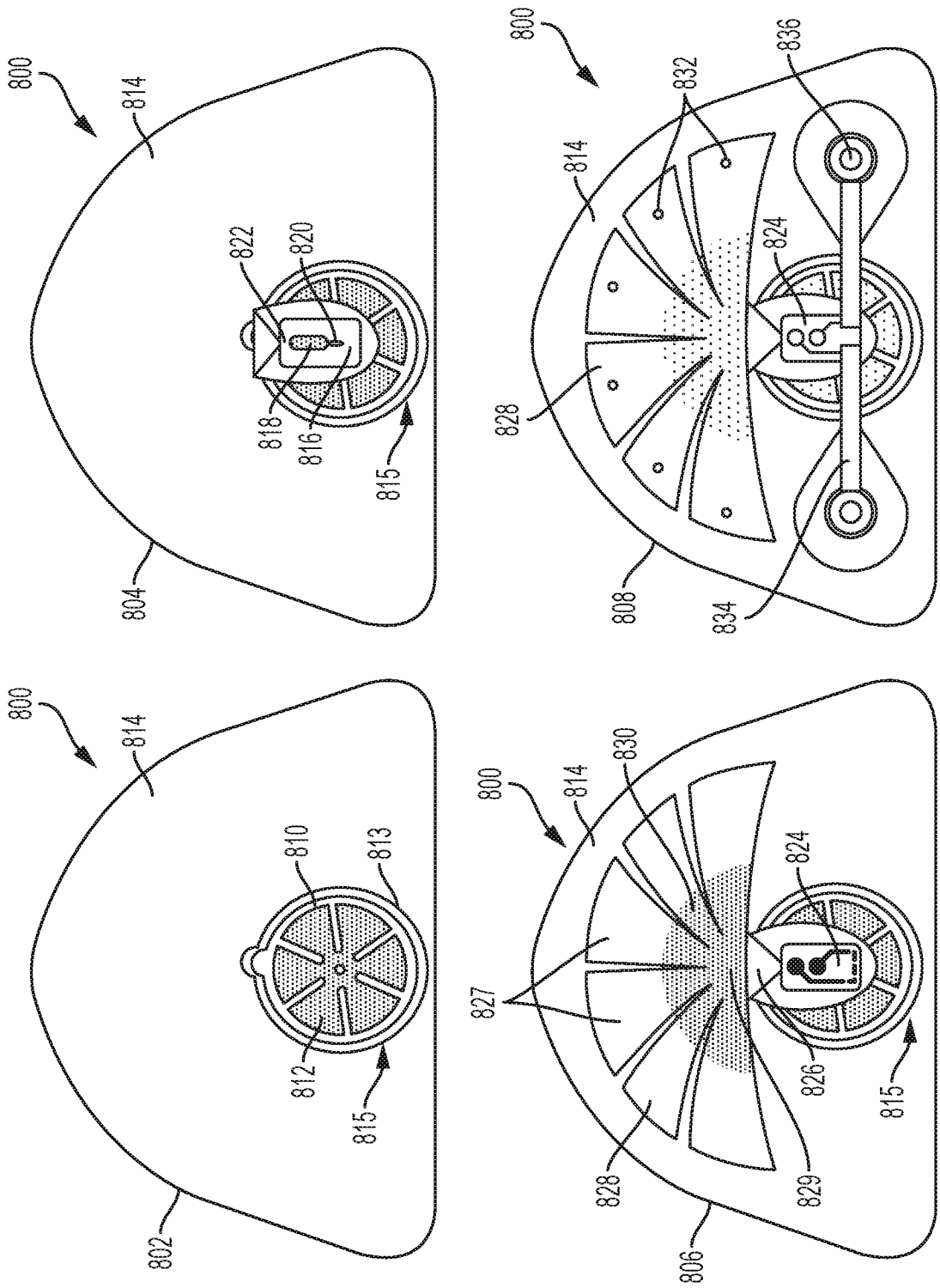

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FIG. 8

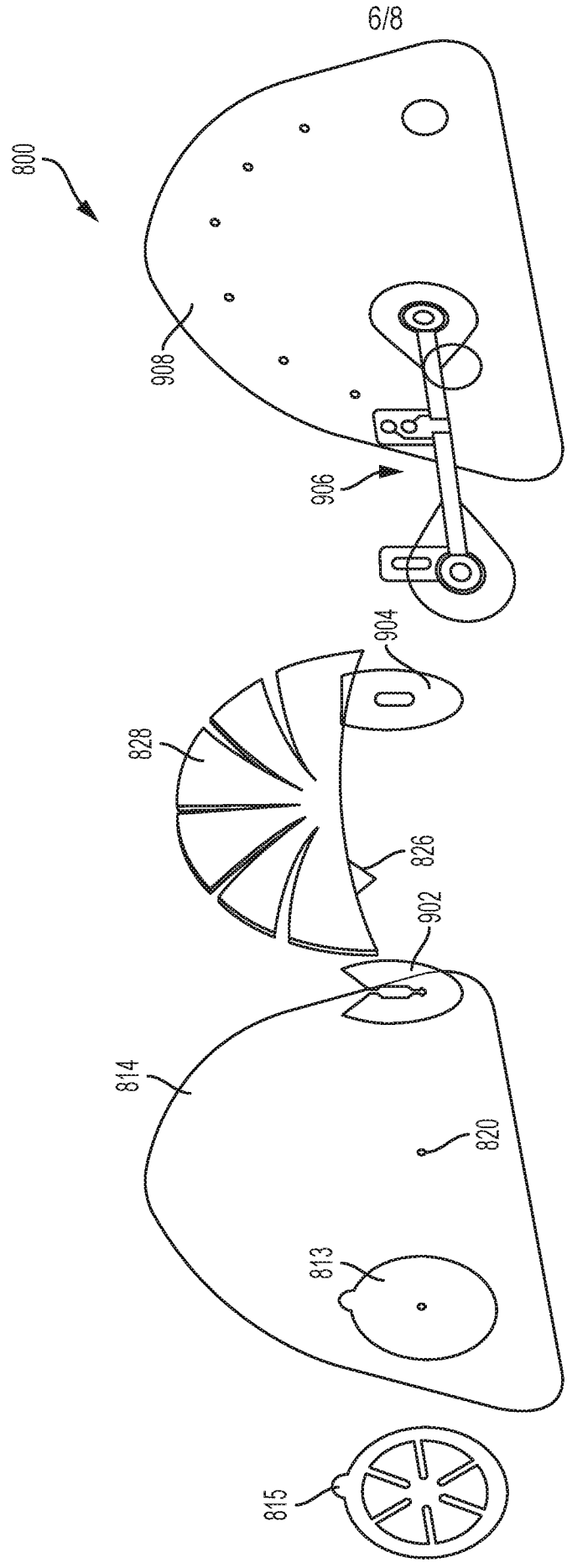


FIG. 9

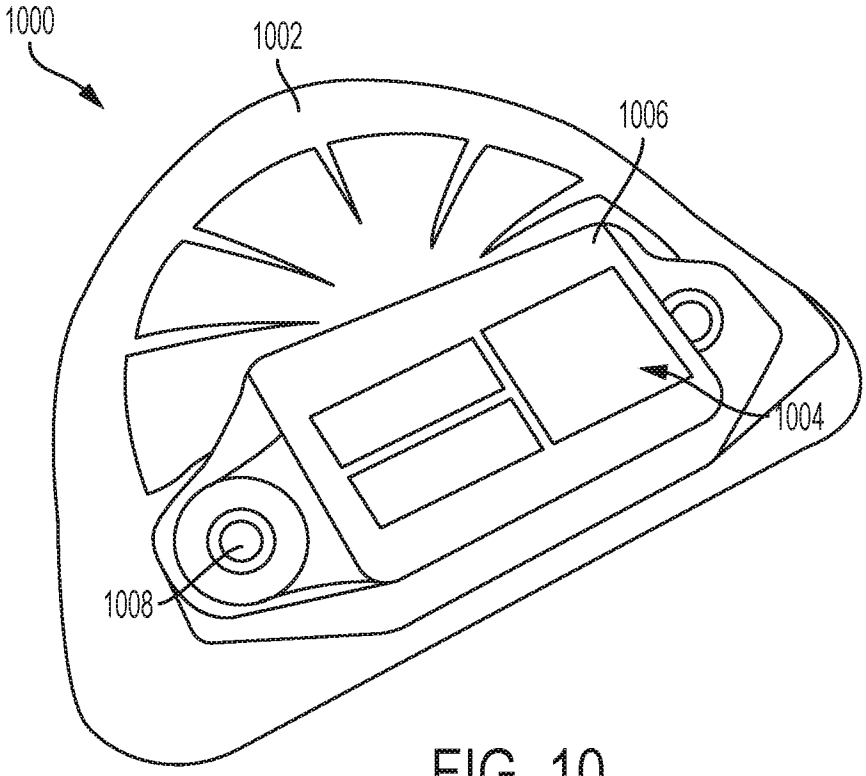

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FIG. 10

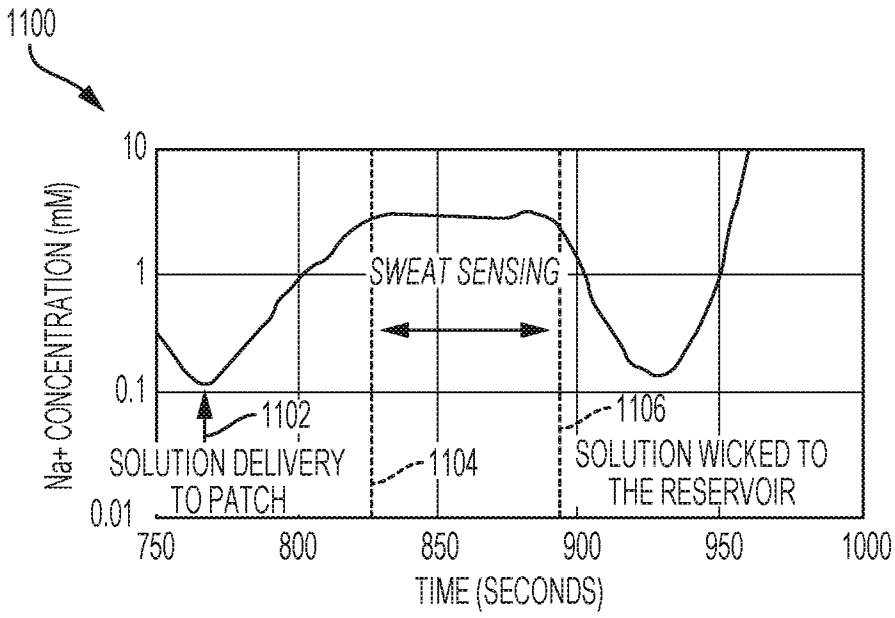

1100
10
1
0.1
0.01
Na+ CONCENTRATION (mM)
SWEAT SENSING
1102
SOLUTION DELIVERY TO PATCH
1104
1106
SOLUTION WICKED TO THE RESERVOIR
750
800
850
900
950
1000
TIME (SECONDS)

FIG. 11

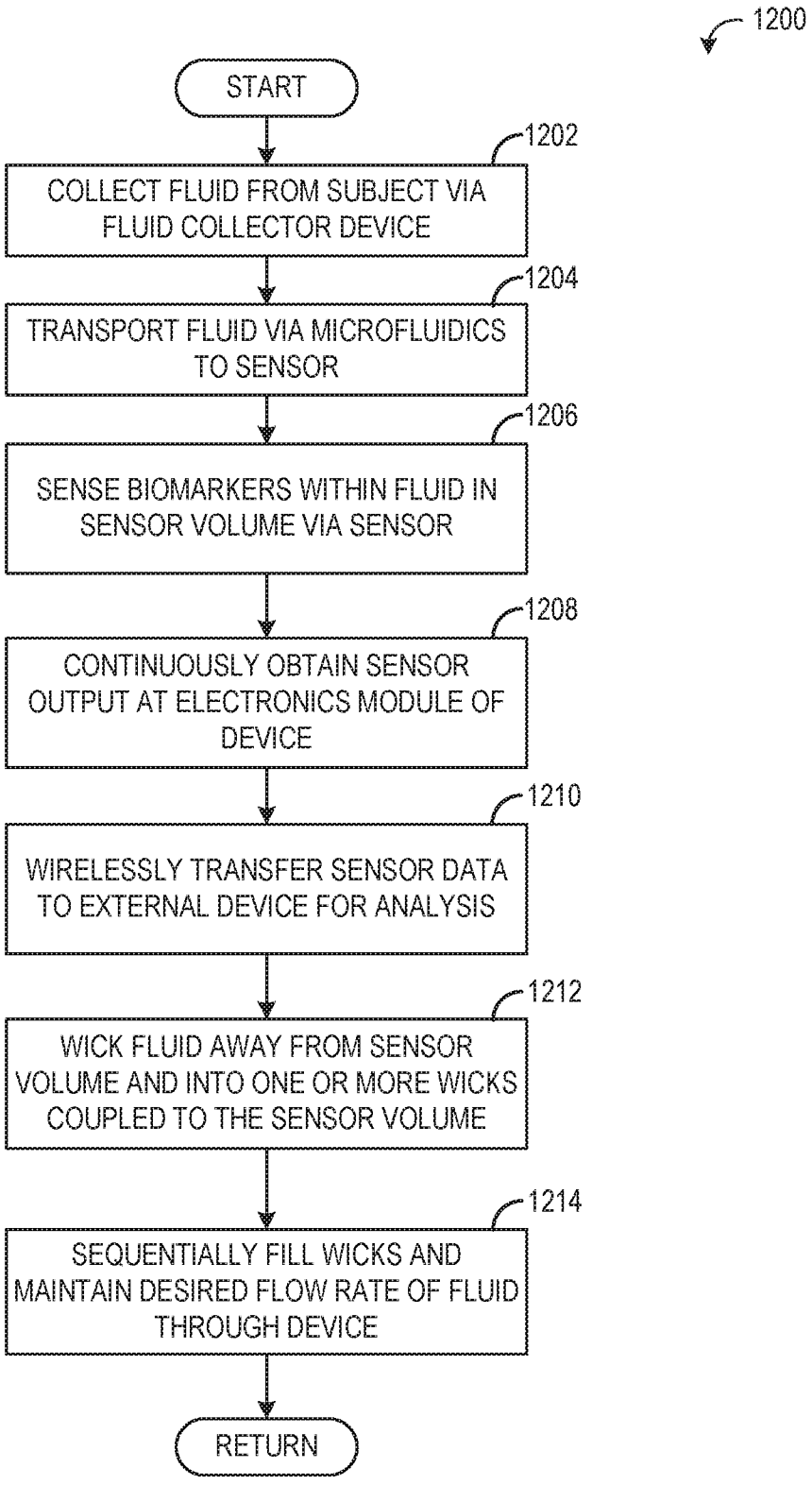

1200
START
1202
COLLECT FLUID FROM SUBJECT VIA FLUID COLLECTOR DEVICE
1204
TRANSPORT FLUID VIA MICROFLUIDICS TO SENSOR
1206
SENSE BIOMARKERS WITHIN FLUID IN SENSOR VOLUME VIA SENSOR
1208
CONTINUOUSLY OBTAIN SENSOR OUTPUT AT ELECTRONICS MODULE OF DEVICE
1210
WIRELESSLY TRANSFER SENSOR DATA TO EXTERNAL DEVICE FOR ANALYSIS
1212
WICK FLUID AWAY FROM SENSOR VOLUME AND INTO ONE OR MORE WICKS COUPLED TO THE SENSOR VOLUME
1214
SEQUENTIALLY FILL WICKS AND MAINTAIN DESIRED FLOW RATE OF FLUID THROUGH DEVICE
RETURN

FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/054599

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/145 B01L3/00
ADD.

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)
A61B B01L

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)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/112165 A1 (HEIKENFELD JASON C [US]) 23 April 2015 (2015-04-23)	1-8, 11-16, 18-20
A	abstract paragraph [0057] - paragraph [0058]	9,10,17

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2018	21/03/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Van Dop, Erik

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/054599

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015112165 A1	23-04-2015	AU 2014337151 A1	05-05-2016
		CA 2927213 A1	23-04-2015
		CN 105916433 A	31-08-2016
		EP 3057491 A1	24-08-2016
		JP 2016533227 A	27-10-2016
		US 2015112165 A1	23-04-2015
		WO 2015058064 A1	23-04-2015