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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
06 March 2025 (06.03.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/049385 A1

(51) International Patent Classification:
G01N 27/26 (2006.01) *G01N 27/403* (2006.01) *G01N 27/30* (2006.01) *A61B 5/1468* (2006.01) *G01N 27/327* (2006.01) *G01N 27/333* (2006.01)

(21) International Application Number: PCT/US2024/043847

(22) International Filing Date: 26 August 2024 (26.08.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/535,751 31 August 2023 (31.08.2023) US

(71) Applicant: **OHIO STATE INNOVATION FOUNDATION** [US/US]; Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US).

(72) Inventors: **LI, Jinghua**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). **LIU, Tzu-Li**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). **CHEN, Shulin**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). **JIA, Yizhen**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US). **WANG, Qi**; c/o Ohio State Innovation Foundation, Mount Hall, 1st Floor, 1050 Carmack Rd, Columbus, Ohio 43210 (US).

(74) Agent: **AARONSON, Lawrence A.** et al.; MEUNIER CARLIN & CURFMAN LLC, 999 Peachtree St. NE, Suite 1300, Atlanta, Georgia 30309 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY,

(54) Title: FLEXIBLE LIGHT-ADDRESSABLE POTENTIOMETRIC SENSORS

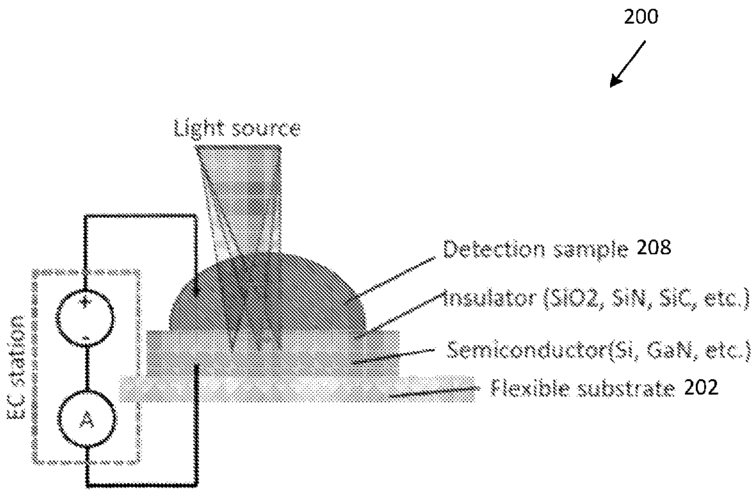

FIG. 2A

(57) Abstract: A flexible, light-addressable potentiometric sensor and related fabrication techniques using a thin-film manufacturing technique that streamlines the sensor's form, resulting in a flexible and adaptable design for various applications. The flexible, light-addressable potentiometric sensor leverages a focused light beam to pinpoint an exact sensing location. By controlling this light beam, the flexible, light-addressable potentiometric sensor can provide high precision light resolution mapping, ensuring accuracy and detail in its operations. The design of the disclosed flexible, light-addressable potentiometric sensor simplifies the manufacturing process, eliminating the need for advanced lithography and thereby increasing the practicality and efficiency of device fabrication for real world applications.

WO 2025/049385 A1

[Continued on next page]

MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

FLEXIBLE LIGHT-ADDRESSABLE POTENTIOMETRIC SENSORS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/535,751, filed August 31, 2023, entitled "FLEXIBLE LIGHT-ADDRESSABLE SENSORS," which is expressly incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under grant no. 2223387 awarded by the National Science Foundation. The government has certain rights in the invention.

BACKGROUND

[0003] For the comprehensive mapping of potential gradients in biological tissue (e.g., brain), which requires detailed and precise data, it is common to use a high-density electrode arrangement (e.g., positioned on the surface of the brain). Using current technologies, the density of electrodes in an arrangement is dependent on the microfabrication process of the electrode arrange. Existing microfabrication techniques come with substantial financial implications, posing a balancing act between achieving high yield and managing production costs.

SUMMARY

[0004] A flexible, light-addressable potentiometric sensor and related fabrication techniques using a thin-film manufacturing technique that streamlines the sensor's form, resulting in a flexible and adaptable design for various applications. The flexible, light-addressable potentiometric sensor leverages a focused light beam to pinpoint an exact sensing location. By controlling this light beam, the flexible, light-addressable potentiometric sensor can provide high precision light resolution mapping, ensuring accuracy and detail in its operations. The design of the disclosed flexible, light-addressable potentiometric sensor simplifies the manufacturing process, eliminating the need for advanced lithography and thereby increasing the practicality and efficiency of device fabrication for real world applications.

[0005] In an aspect, the present disclosure is directed to a light-addressable potentiometric sensor that includes a base substrate formed of a flexible material, a semiconductor layer formed on the base substrate, an electrical contact disposed between the base substrate and the semiconductor layer, and an insulating layer formed on the semiconductor layer. The semiconductor layer may be a photoresponsive material for signal transduction responsive to application of a beam of light. The electrical contact may be formed as an electrical connection between the semiconductor layer and a reference electrode.

[0006] In another aspect, a method of fabricating a light-addressable potentiometric sensor is disclosed. The method may include providing a silicon-on-insulator (SOI) substrate comprising a base layer, an insulating layer, and a semiconductor layer; depositing an electrical contact on the semiconductor layer; depositing a flexible polymer on the electrical contact; and removing the base layer via reactive etching.

[0007] This summary is provided to introduce a selection of concepts in a simplified form that is further described below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] The foregoing summary, as well as the following detailed description of illustrative implementations, is better understood when read in conjunction with the appended drawings. To illustrate the implementations, there are shown in the drawings example constructions; however, the implementations are not limited to the specific methods and instrumentalities disclosed. In the drawings:

[0009] FIGS. 1A-1E illustrate example working principles of the light-addressable potentiometric sensor in accordance with aspects of the disclosure;

[0010] FIGS. 2A-2B illustrate example schematic diagrams light-addressable potentiometric sensors (LAPS) in accordance with aspects of the disclosure;

[0011] FIG. 3 illustrates an alternate configuration of a light-addressable potentiometric sensor in accordance with aspects of the disclosure;

[0012] FIGS. 4A-4D illustrate an example method of fabricating the light-addressable potentiometric sensors in accordance with aspects of the disclosure;

[0013] FIG. 5 illustrates and example setup wherein the light source is generally a controllable a laser, LED array, or the like;

[0014] FIGS. 6A, 6B, 7A and 7B illustrate various graphs illustrating test results for an experimental light-addressable potentiometric sensor; and

[0015] FIG. 8 shows the use of the light-addressable potentiometric sensor to record sine waves.

DETAILED DESCRIPTION

[0016] One existing strategy for localized mapping of designated areas in biological tissue is through the use of light-addressable potentiometric semiconductors. This technique allows for significantly enhanced resolution, e.g., of approximately 100 nm per pixel. Despite its high-resolution advantages, current designs are rigid and lack adaptability to fit surfaces with complex geometries. The disclosed implementations are directed to, for example, a flexible, light-addressable potentiometric sensor and related fabrication techniques that address various shortcomings of current devices.

[0017] In particular, the disclosed flexible, light-addressable potentiometric sensor can be fabricated using a thin-film manufacturing technique that streamlines the sensor's form, resulting in a flexible and adaptable design for various applications. The disclosed flexible, light-addressable potentiometric sensor leverages a focused light beam to pinpoint an exact sensing location. By controlling this light beam, the disclosed flexible, light-addressable potentiometric sensor can provide high precision light resolution mapping, ensuring accuracy and detail in its operations. Compared to traditional fabrication methods, the design of the disclosed flexible, light-addressable potentiometric sensor simplifies the manufacturing process, eliminating the need for advanced lithography and thereby increasing the practicality and efficiency of device fabrication for real world applications.

[0018] Referring first to FIGS. 1A-1E, there are illustrated various diagrams showing working principles of the disclosed light-addressable potentiometric sensor, which is also referred to herein as a light-addressable potentiometric sensor (LAPS), are shown. In general, a LAPS system includes an unstructured insulator-semiconductor interface 102 (see, FIGS. 1B and 1D). Applying a DC voltage biases the LAPS system towards depletion (see, FIGS. 1A, 1C, 1D and 1E). In this regard, a modification in surface potential can be quantified by measuring change in the photocurrent when the semiconductor is illuminated with a pulsed, focused laser beam, as shown in FIG. 1E. In an example implementation of the principals shown, a solid–liquid interface is formed on the surface of the sensitive film which is potentially proportional to the concentration of the measured species in the solution. This potential is superimposed on the external bias voltage, which changes the thickness of the space charge region between the LAPS insulating layer and the silicon substrate.

[0019] Referring now to FIGS. 2A-2B, there is illustrated schematic diagrams of example light-addressable potentiometric sensors (LAPS). As noted above, a light-addressable potentiometric sensor is configured to be activated using light, offering potential improvements in spatial resolution and/or selective sensing over existing electrode arrays. Generally, the light-addressable potentiometric sensor(s) 200 disclosed herein includes a four-layer structure defined by a flexible substrate 202, a conductive layer 205 or conductive contact, a semiconductor layer 204, and an insulating layer 206. Additional or fewer layers may be used. The flexible substrate 202 provides a backing layer for supporting the semiconductor layer 204, as well as the conductive layer 205 and insulating layer 206. In some implementations, the flexible substrate 202 is formed of a polymer, such as PDMS, PMMA, or Polyimide; however, the present disclosure is not intended to be limiting in this regard. Utilizing a flexible substrate (e.g., a polymer substrate) allows the sensor to be placed on curved or irregular surfaces (e.g., the brain), making it more versatile than sensors built on rigid substrates. It should also be appreciated that the flexible substrate is generally formed of a transparent or at least partially transparent material (e.g., a transparent polymer) to allow light to pass through, e.g., to the semiconductor layer.

[0020] The conductive layer 205 or "contact" provides an electrical interface for the semiconductor nanomembrane. In some implementations, the conductive layer or conductive contact is formed of Cr or indium-tin-oxide (ITO); however, the present disclosure is not intended to be limiting in this regard. For example, the conductive layer may, more generally, be any conductive material (e.g., a suitable metal or alloy, such as copper, gold, aluminum, etc.). Generally, the conductive layer or conductive contact is highly conductive and durable. In some implementations, the conductive layer or conductive contact is transparent or at least partially transparent to allow light to pass through, e.g., to the semiconductor layer.

[0021] The semiconductor layer 204 serves as the photoresponsive material for signal transduction. Generally, the semiconductor layer 204 is a thin-film inorganic or organic semiconductor. More specifically, this may be a semiconductive nanomembrane that in some implementations is formed of silicon (Si), gallium arsenide (GaAs), gallium nitride (GaN), polysilicon, or the like; however, the present disclosure is not intended to be limiting in this regard. Notably, the semiconductor layer is ultrathin and flexible.

[0022] The insulating layer 206 serves as the biofluid barrier and a dielectric. In some implementations, the insulating layer is formed of silicon nitride (Si3N4), silicon dioxide (SiO2), aluminum oxide (Al2O3), and/or hafnium oxide (HfO2); however, the present disclosure is not intended to be limiting in this regard. Notably, the insulating layer 206 is selected to have a high sensitivity (e.g., high k) and stability (e.g., low defect).

[0023] As shown in FIG. 2B, the flexible substrate 202 ranges from 10 to 200 μm in thickness; the conductive layer 205 or contact ranges from 10 to 300 nm in thickness; the semiconductor layer 204 ranges from 50 nm to 2 μm in thickness; and/or the insulating layer 206 ranges from 50 to 200 nm in thickness. In an example implementation, the flexible substrate 202 is 20 μm thick; the conductive layer 205 or contact is less than 1 μm thick; the semiconductor layer 206 is 1 to 2 μm thick; and/or the insulating layer is 100 nm thick.

[0024] FIG. 3 is a diagram of an alternate configuration of a light-addressable potentiometric sensor 300, as described herein, that includes an ion-sensing membrane (ISM) 302 disposed on the insulator 304. An ISM is a membrane that can detect or interact with specific ions. Depending on its composition, the ISM 302 may be selective to certain ions, such as potassium, sodium, hydrogen ions (e.g., for pH sensing), or others. When these ions interact with the ISM 302, they can change its surface potential, which can then be detected by the underlying layers of the sensor. In this regard, the ISM 302 serves as a sensing target for specific materials, which transfers biomarkers concentrations into an electrical surface potential. However, it should be understood that the disclosed light-addressable potentiometric sensor may include an interface material other than ISM, such as aptamers, antibody, molecularly imprinted polymers (MIPs), etc.

[0025] As shown, the light-addressable potentiometric sensor can, in some implementations, further include an encapsulation layer 306 that at least partially encapsulates one of more layers of the sensor. Encapsulation can serve as a protective layer that isolates the sensor (or its components) from the environment, thereby protecting sensitive parts of the sensor from contamination, physical damage, or unwanted chemical reactions. Generally, the encapsulation layer is formed of a material that is inert and chemically stable.

[0026] Referring now to FIGS. 4A-4D, there are illustrated diagrams the demonstrate a method of fabricating the light-addressable potentiometric sensor(s). Generally, a light-addressable potentiometric sensor starts as a silicon-on-insulator (SOI) substrate that includes a "handling" or base substrate – shown as a silicon wafer – on which a thermal SiO_2 layer (e.g., the insulating layer) and a device Si layer (e.g., the semiconductor layer) are disposed (FIG. 4A). An electrical contact (e.g., the conductive layer) is then formed on the semiconductor layer (FIG. 4B). In some implementations, the electrical contact is transparent (e.g., ITO). A polymer (e.g., the flexible substate) is then deposited on top of the electrical contact. Subsequently, the "handling" or base substrate can be removed, e.g., via reactive ion etching. The device can then be flipped, as necessary, and the electrical contact wired to a voltage source and/or current meter for measuring a response to illumination via a light source, as discussed above (FIG. 4C).

[0027] It is noted that plasma-enhanced chemical vapor deposition (PECVD) is one existing technique to deposit the SiO_2 layer (FIG. 4D). However, as a low-temperature process, PECVD can introduce a number of defects into structure during deposition, which leads to subpar insulation quality and density. As a consequence, devices fabricated using this method tend to exhibit a higher susceptibility to electrical leakage, raising concerns about long-term reliability and performance. To address these shortcomings and enhance the overall quality, the disclosed fabrication strategy utilizes back-etched Silicon-On-Insulator (SOI) wafers. These SOI wafers are fabricated under high-temperature conditions, specifically at around 1200°C, resulting in a structure that is significantly denser and exhibits superior insulating properties to other materials.

[0028] FIG. 5 shows an example experimental setup for the light-addressable potentiometric sensor(s) described herein. In this example, a light-addressable potentiometric sensor 502 is positioned on a biological tissue 504 (e.g., the surface of the brain) to monitor neural activity or other biochemical processes occurring on the contact surface. The platform can be used for sparse sampling across large areas to identify focal point of interest, and dense sampling with high spatial resolution in local areas. In sparse or single-point sampling, the sensor can be used to scan or sample a single point (focal points) of interest. This can be likened to a high temporal monitoring. Specifically, once the sensor is positioned on the biological tissue, a light source can be used to illuminate a point or multiple points (e.g., by scanning). When a region of interest is defined, the sensor can then perform dense sampling, offering high spatial resolution in that local area. This provides detailed, "high-resolution" data about the specific region.

[0029] As shown in the setup of FIG. 5, the light source 506 is generally a controllable a laser, LED array, or the like. The light source may be configured to be modulated (adjusted in intensity, on-off frequency, or position) to target specific regions of the sensor. When light interacts with the sensor 502 (particularly the regions interfacing with the tissue), a transient photocurrent is generated at a specific location on the sensor. Depending on the bioelectric activity or biomarkers present at the interface, e.g., between the sensor and the tissue, the photocurrent properties are altered correspondingly. In some implementations, an output signal from the sensor is transmitted to or otherwise obtained by a process device that can interpret the signal. The processing device may be, for example, a microcontroller, a digital signal processor (DSP), an amplifier, a lock-in amplifier, a data acquisition system, a general-purpose computer, or the like.

[0030] In some implementations, before beginning measurements, the sensor may be calibrated. First, a baseline may be established by measuring a "dark" current (i.e., the non-illuminated condition). The output in this state would represent baseline or zero point. In some implementations, a calibration curve (surface potential vs photocurrent) is obtained in a controlled condition. For instance, when measuring ion concentrations, a standard solution may be used to calibrate the sensor response. In some implementations, response to reference modulated light is determined by exposing the sensor to a modulated light and recording the sensor's output. In this manner, the sensor's signal can be sperate form noise, e.g., using a lock-in amplifier. Once the discrepancies between the sensor's output and the true values or reference measurements is determined, software can be used to automatically adjust or compensate for the readings in real-time.

[0031] FIGS. 6A, 6B, 7A and 7B include various graphs illustrating test results for an experimental light-addressable potentiometric sensor. FIGS. 6A and 6B show results of raw data and light stimulation, as well as bias sweeping and photocurrent correlation. Illuminating the sensor at a frequency of 100Hz resulted in a "transient spike." As shown, a distinct response both when the light is turned on and when the light turned off indicates that the sensor can rapidly detect changes in illumination. As mentioned above, in some implementations, the output of the sensor can be connected to a lock-in amplifier for extracting signals from noisy backgrounds. By locking onto a specific reference frequency (in this case, twice the illumination frequency at 200Hz), the sensor's true response can be distinguished from background noise or interference.

[0032] In some implementations, by varying the potential difference (bias) between the solution and the semiconductor layer of the sensor, the internal electric field is effectively modulated. This can impact charge separation and hence the photocurrent. The results shown indicate a direct relationship between the photocurrent observed when the light is on, and the potential applied to the sensor. This suggests that the sensor's response can be modulated and controlled, which can be useful for calibration or tuning the sensor for specific applications.

[0033] FIGS. 7A-7B shows testing results for a light-addressable potentiometric sensor configured with an ISM for sodium specificity. In particular, the results in FIGS. 7A-7B were obtained by integrating an ISM tailored to be sensitive to sodium ions. This specificity is important, as it allows the sensor to target sodium concentrations while possibly ignoring or minimizing responses to other ions. With sodium ions binding or interacting with the ISM, a surface potential (or voltage) is generated on the sensor. This potential is directly correlated to the concentration of sodium ions in the solution, turning the sensor into a quantitative device for measuring sodium levels. A calibration curve is shown that illustrates the relationship between the observed photocurrent (output of the sensor) and the known sodium ion concentrations (input). If the photocurrent is directly tuned or influenced by the sodium ion concentration in the solution, the calibration curve will show a clear trend (either linear or non-linear) indicating this relationship.

[0034] FIG. 8 shows the use of the SiO2-Si nanomembranes to record sine waves, which can be up to 100 Hz at an amplitude of 0.2 V. This gives the light-addressable sensor(s) of the present disclosure the ability to record electrophysiological signals. This system can reach an amplitude of several millivolts and 250 Hz, which is the scale of common ECG and Ecog.

[0035] From these results, the following attributes of the disclosed light-addressable sensor can be obtained:

Rapid Responsiveness: The sensor's ability to quickly generate a transient response to light changes indicates that it has a fast response time, which can be crucial for real-time monitoring or high-frequency applications.

Noise Reduction Capabilities: The successful use of a lock-in amplifier to extract the desired signal underscores the sensor's potential to operate in noisy environments or situations with a lot of background interference.

Tunability: The direct correlation between the applied potential and the light-on photocurrent signifies the tunability of the sensor. By adjusting the bias, the sensor's response may be optimized for specific applications or conditions.

Comparison to Other Sensors: The specifics of how this sensor compares to others would depend on the metrics of interest (e.g., sensitivity, speed, noise resilience). However, the features highlighted above, e.g., rapid response, tunability, and noise reduction capability, suggest it possesses some advantages over conventional sensors that lack these traits.

Quantitative Analysis: With a clear calibration curve, the sensor not only detects the presence of sodium ions but also quantifies their concentration. This ability transforms the sensor into a precise analytical tool.

Versatility of the Sensor: The integration of the ISM on generic platform demonstrates the sensor's adaptability. By changing the ISM or tailoring its properties, the sensor can potentially be adapted for other specific ions or molecules, making it a versatile platform for various sensing applications.

Potential for Real-time Monitoring: Given the sensor's rapid response as indicated in the previous figures, this sodium-specific configuration might be suitable for real-time monitoring of sodium ion fluctuations in various environments.

[0036] Configuration of Certain Implementations

[0037] The construction and arrangement of the systems and methods as shown in the various implementations are illustrative only. Although only a few implementations have been described in detail in this disclosure, many modifications are possible (e.g., variations in sizes, dimensions, structures, shapes, and proportions of the various elements, values of parameters, mounting arrangements, use of materials, colors, orientations, etc.). For example, the position of elements may be reversed or otherwise varied, and the nature or number of discrete elements or positions may be altered or varied. Accordingly, all such modifications are intended to be included within the scope of the present disclosure. The order or sequence of any process or method steps may be varied or re-sequenced according to alternative implementations. Other substitutions, modifications, changes, and omissions may be made in the design, operating conditions, and arrangement of the implementations without departing from the scope of the present disclosure.

[0038] The present disclosure contemplates methods, systems, and program products on any machine-readable media for accomplishing various operations. The implementations of the present disclosure may be implemented using existing computer processors, or by a special purpose computer processor for an appropriate system, incorporated for this or another purpose, or by a hardwired system. Implementations within the scope of the present disclosure include program products including machine-readable media for carrying or having machine-executable instructions or data structures stored thereon. Such machine-readable media can be any available media that can be accessed by a general purpose or special purpose computer or other machine with a processor. By way of example, such machine-readable media can comprise RAM, ROM, EPROM, EEPROM, CD-ROM or other optical disk storage, magnetic disk storage or other magnetic storage devices, or any other medium which can be used to carry or store desired program code in the form of machine-executable instructions or data structures, and which can be accessed by a general purpose or special purpose computer or other machine with a processor.

[0039] When information is transferred or provided over a network or another communications connection (either hardwired, wireless, or a combination of hardwired or wireless) to a machine, the machine properly views the connection as a machine-readable medium. Thus, any such connection is properly termed a machine-readable medium. Combinations of the above are also included within the scope of machine-readable media. Machine-executable instructions include, for example, instructions and data which cause a general-purpose computer, special purpose computer, or special purpose processing machines to perform a certain function or group of functions.

[0040] Although the figures show a specific order of method steps, the order of the steps may differ from what is depicted. Also, two or more steps may be performed concurrently or with partial concurrence. Such variation will depend on the software and hardware systems chosen and on designer choice. All such variations are within the scope of the disclosure. Likewise, software implementations could be accomplished with standard programming techniques with rule-based logic and other logic to accomplish the various connection steps, processing steps, comparison steps and decision steps.

[0041] It is to be understood that the methods and systems are not limited to specific synthetic methods, specific components, or to particular compositions. It is also to be understood that the terminology used herein is for the purpose of describing particular implementations only and is not intended to be limiting.

[0042] As used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another implementation includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another implementation. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

[0043] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0044] Throughout the description and claims of this specification, the word “comprise” and variations of the word, such as “comprising” and “comprises,” means “including but not limited to,” and is not intended to exclude, for example, other additives, components, integers or steps. “Exemplary” means “an example of” and is not intended to convey an indication of a preferred or ideal implementation. “Such as” is not used in a restrictive sense, but for explanatory purposes.

[0045] Disclosed are components that can be used to perform the disclosed methods and systems. These and other components are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these components are disclosed that while specific reference of each various individual and collective combinations and permutation of these may not be explicitly disclosed, each is specifically contemplated and described herein, for all methods and systems. This applies to all aspects of this application including, but not limited to, steps in disclosed methods. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific implementation or combination of implementations of the disclosed methods.

WHAT IS CLAIMED IS:

1. A light-addressable potentiometric sensor comprising:

a base substrate formed of a flexible material;

a semiconductor layer formed on the base substrate, the semiconductor layer comprising a photoresponsive material for signal transduction responsive to application of a beam of light;

an electrical contact disposed between the base substrate and the semiconductor layer, the electrical contact forming an electrical connection between the semiconductor layer and a reference electrode; and

an insulating layer formed on the semiconductor layer.

2. The light-addressable potentiometric sensor of claim 1, wherein the flexible material is a polymer.

3. The light-addressable potentiometric sensor of claim 2, wherein the polymer is one of PDMS, PMMA, or Polyimide.

4. The light-addressable potentiometric sensor of claim 1, wherein the base substrate is at least partially transparent.

5. The light-addressable potentiometric sensor of claim 1, wherein the electrical contact is formed of Cr or indium-tin-oxide (ITO).

6. The light-addressable potentiometric sensor of claim 1, wherein the electrical contact is at least partially transparent.

7. The light-addressable potentiometric sensor of claim 1, wherein the semiconductor layer is a nanomembrane formed of silicon or gallium arsenide.

8. The light-addressable potentiometric sensor of claim 1, wherein the insulating layer is formed of silicon nitride (Si_3N_4), silicon dioxide (SiO_2), aluminum oxide (Al_2O_3), or hafnium oxide (HfO_2).

9. The light-addressable potentiometric sensor of claim 1, wherein the base substrate ranges from 10 to 200 μm in thickness.

10. The light-addressable potentiometric sensor of claim 1, wherein the electrical contact substrate ranges from 10 to 300 nm in thickness.

11. The light-addressable potentiometric sensor of claim 1, wherein the semiconductor layer ranges from 50 nm to 2 μm in thickness.

12. The light-addressable potentiometric sensor of claim 1, wherein the insulating layer ranges from 50 to 200 nm in thickness.

13. A method of fabricating a light-addressable potentiometric sensor, the method comprising:

providing a silicon-on-insulator (SOI) substrate comprising a base layer, an insulating layer, and a semiconductor layer;

depositing an electrical contact on the semiconductor layer;

depositing a flexible polymer on the electrical contact; and

removing the base layer via reactive etching.

14. The method of claim 13, wherein the flexible polymer is PDMS, PMMA, or Polyimide.

15. The method of claim 13, wherein the base substrate is at least partially transparent.

16. The method of claim 13, wherein the electrical contact is formed of Cr or indium-tin-oxide (ITO).

17. The method of claim 13, wherein the electrical contact is at least partially transparent.

18. The method of claim 13, wherein the semiconductor layer is a nanomembrane formed of silicon or gallium arsenide.

19. The method of claim 13, wherein the insulating layer is formed of silicon nitride (Si_3N_4), silicon dioxide (SiO_2), aluminum oxide (Al_2O_3), or hafnium oxide (HfO_2).

20. The method of claim 13, wherein at least one of:

the flexible polymer ranges from 10 to 200 μm in thickness;

the electrical contact ranges from 10 to 300 nm in thickness;

the semiconductor layer ranges from 50 nm to 2 μm in thickness; or

the insulating layer ranges from 50 to 200 nm in thickness.

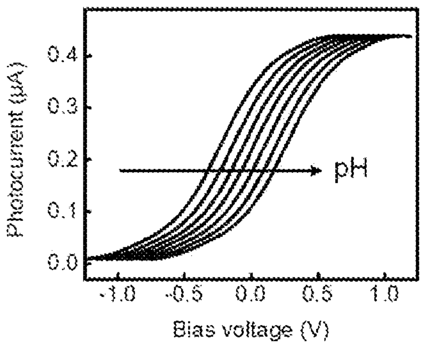

FIG. 1A

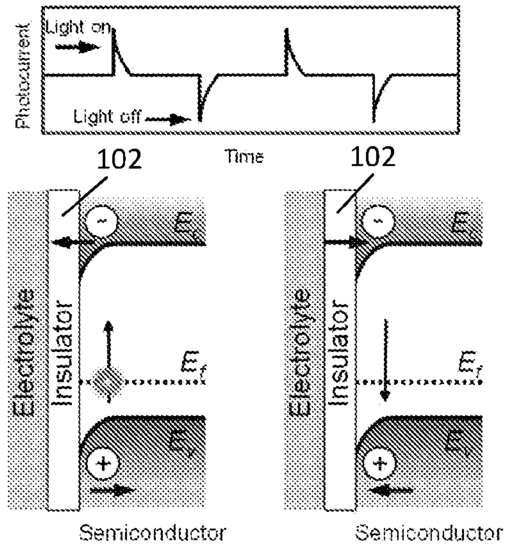

FIG. 1B

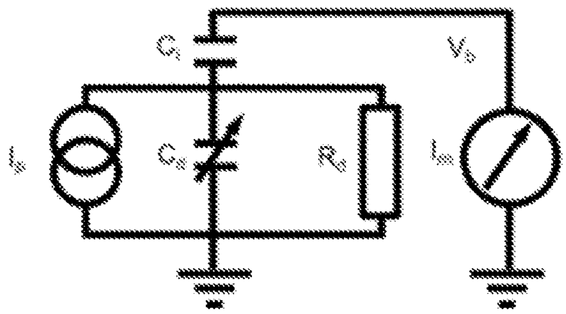

FIG. 1C

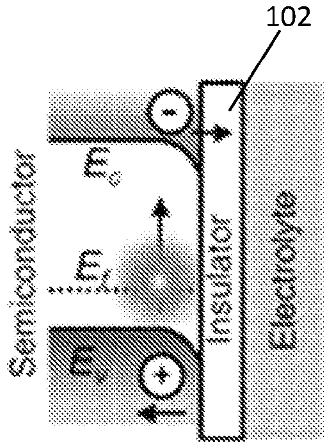

FIG. 1D

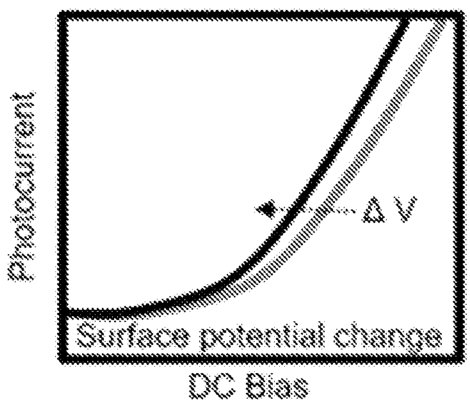

FIG. 1E

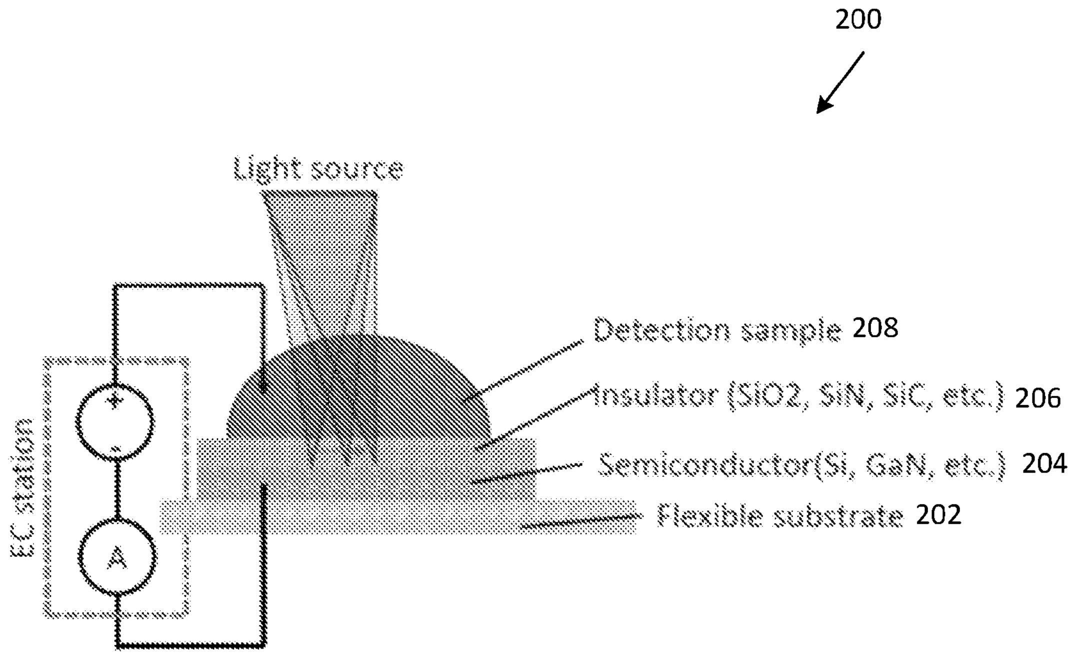
200
Light source
Detection sample 208
Insulator (SiO2, SiN, SiC, etc.) 206
Semiconductor(Si, GaN, etc.) 204
Flexible substrate 202
EC station
+
-
A

FIG. 2A

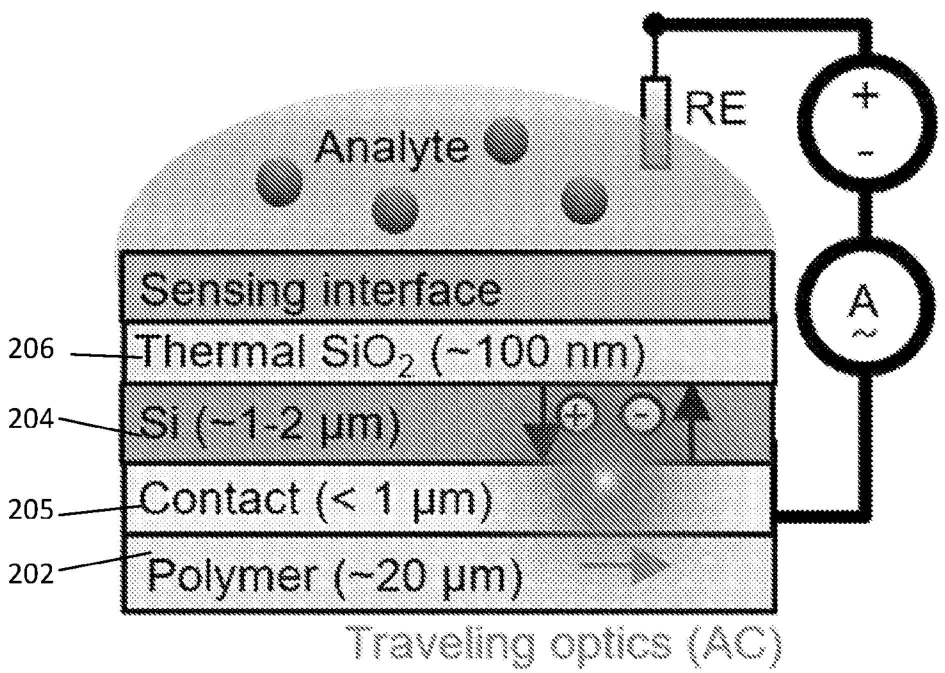
RE
+
-
A
Analyte
Sensing interface
206
Thermal SiO2 (~100 nm)
204
Si (~1-2 µm)
205
Contact (< 1 µm)
202
Polymer (~20 µm)
Traveling optics (AC)

FIG. 2B

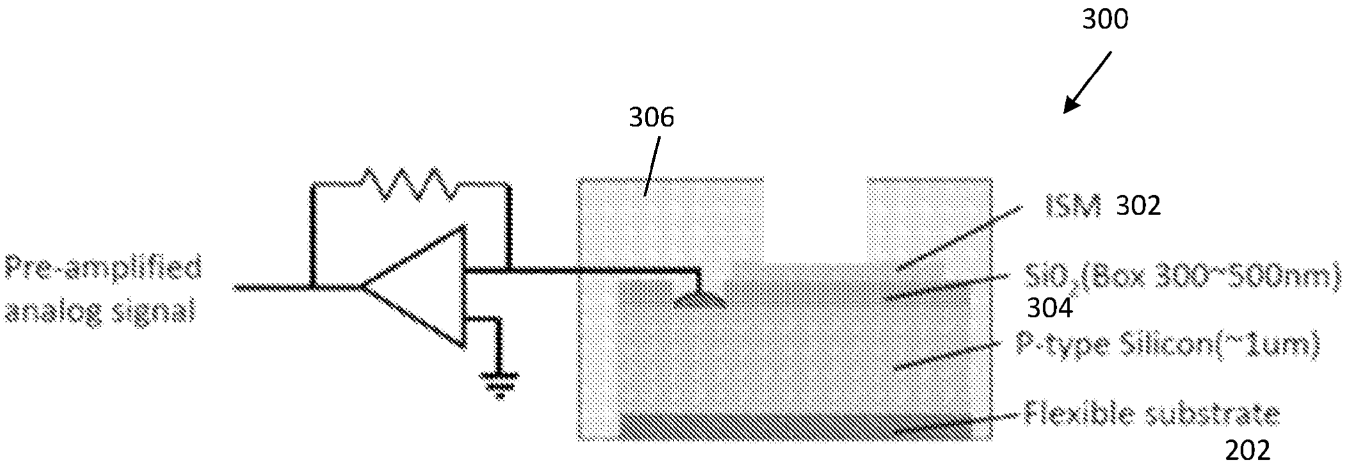

FIG. 3

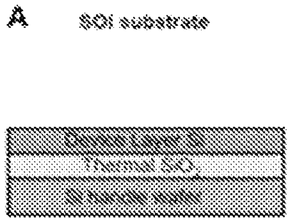

FIG. 4A

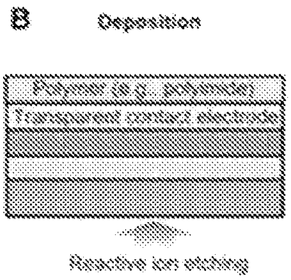

FIG. 4B

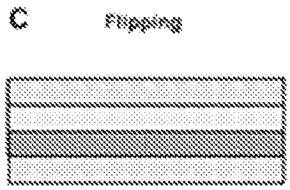

FIG. 4C

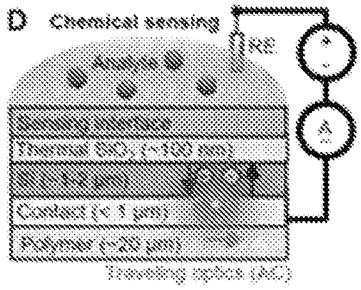

FIG. 4D

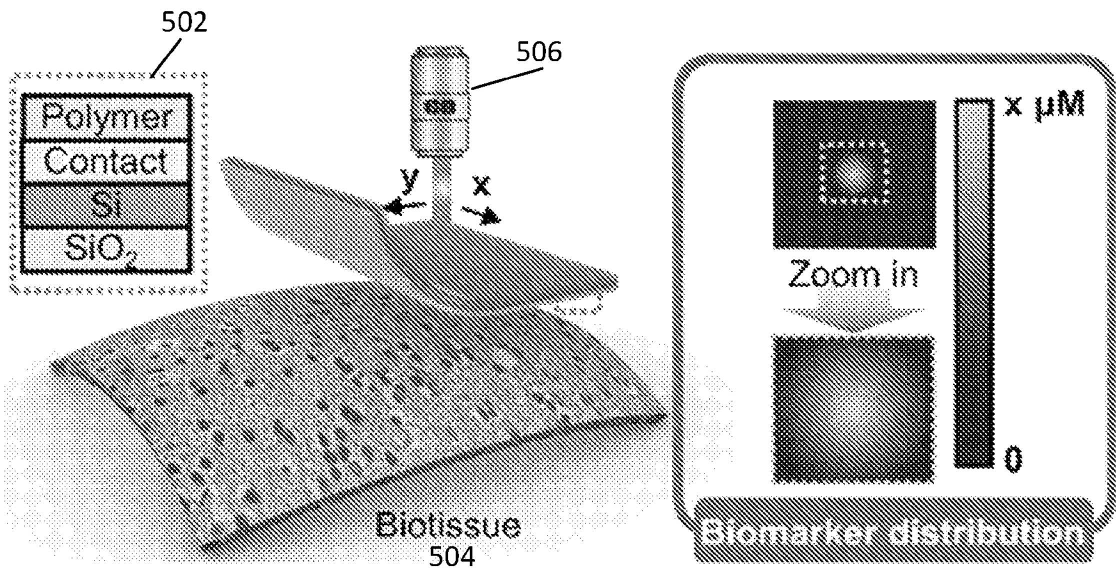
502
Polymer
Contact
Si
SiO2
506
y
x
Biotissue
504
x μM
Zoom in
0
Biomarker distribution

FIG. 5

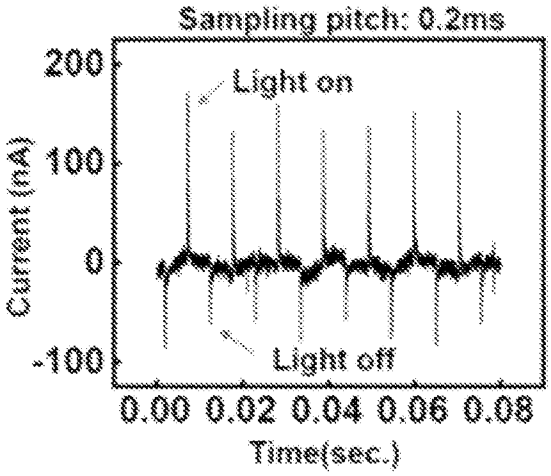

FIG. 6A

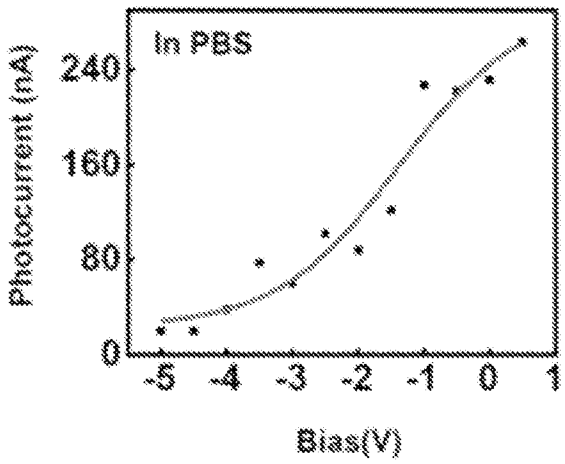

FIG. 6B

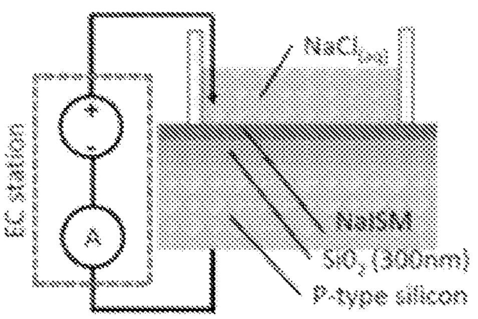

FIG. 7A

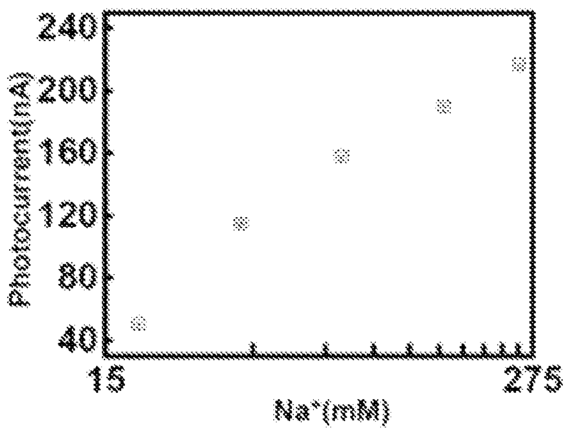

FIG. 7B

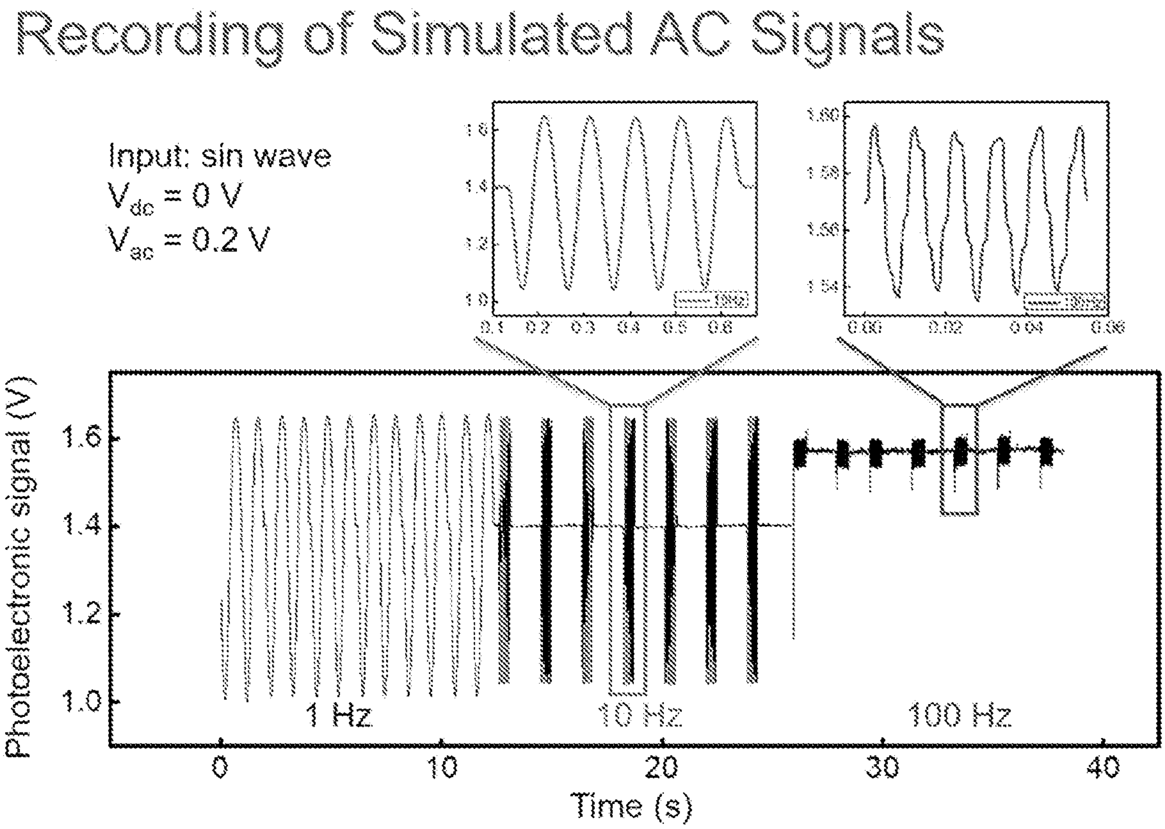
Recording of Simulated AC Signals
Input: sin wave
V_{dc} = 0 V
V_{ac} = 0.2 V
Photoelectronic signal (V)
1.6
1.4
1.2
1.0
1 Hz
10 Hz
100 Hz
0
10
20
30
40
Time (s)

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/043847

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. G01N 27/26; G01N 27/30; G01N 27/327; G01N 27/403 (2024.01)

ADD. A61B 5/1468; G01N 27/333 (2024.01)

CPC - INV. G01N 27/26; G01N 27/305; G01N 27/3275; G01N 27/4035

ADD. A61B 5/1468; A61B 5/6868; A61B 2562/12; A61B 2562/164; G01N 27/3335

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	GUO, Y. ET AL. "Miniature multiplexed label-free pH probe in vivo" Biosensors and Bioelectronics. 2020; <Abstract; Pages 2-4, 9; Figure 1>; <DOI: 10.1016/j.bios.2020.112870>	1-4, 7-8, 12 --- 5-6, 9-11, 13-20
Y	WO 2018/098417 A1 (ELWHA LLC (US)) 31 May 2018; Pages 5, 6, 12, 15, 19, 41, 69, 80, 87, 96	5-6, 11
Y	US 2004/0014240 A1 (TAKEGUCHI KEIGO (JP)) 22 January 2004; Paragraphs [0002], [0007], [0049], [0174], [0175]	9
Y	US 8,519,447 B2 (ZEUN HENDRIK (CHEMNITZ DE)) 27 August 2013; Abstract; Columns 3, 6; Claim 14	10
Y	US 2002/0031854 A1 (WALKER HOWARD W (US)) 14 March 2002; Paragraphs [0010], [0016], [0017], [0020]; Claims 1-2, 8; Figure 3	13-20
Y	YANG, C. ET AL. "Spatial resolution and 2D chemical image of light-addressable potentiometric sensor improved by inductively coupled-plasma reactive-ion etching" 1295-1301. Sensors and Actuators B: Chemical. 2018; <Abstract; pages 2, 4, 5>; <DOI: 10.1016/j.snb.2017.12.151>	13-20
A	CN 102288655 B (ZHEJIANG UNIV (HANGZHOU CITY CN)) 24 July 2013; Entire Document	13-20
P,X	WO 2024/010976 A1 (OHIO STATE INNOVATION FOUNDATION (US)) 11 January 2024; Entire Document	1-20

☐ 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

"D" document cited by the applicant in the international application

"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
24 October 2024 (24.10.2024)	JAN 16 2025

Name and mailing address of the ISA/	Authorized officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300