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Biosensor system with integrated microneedle

Abstract

A biosensor system package includes: a transistor structure in a semiconductor layer having a front side and a back side, the transistor structure comprising a channel region; a buried oxide (BOX) layer on the back side of the semiconductor layer, wherein the buried oxide layer has an opening on the back side of the channel region, and an interface layer covers the back side over the channel region; a multi-layer interconnect (MLI) structure on the front side of the semiconductor layer, the transistor structure being electrically connected to the MLI structure; and a cap structure attached to the buried oxide layer, the cap structure comprising a microneedle.

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References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
8506529	12/2012	Yang	N/A	N/A
8871549	12/2013	Ellis-Monaghan	257/253	H01L 29/66477
9080969	12/2014	Liu et al.	N/A	N/A
9299640	12/2015	Lin	N/A	N/A
10131540	12/2017	Yu et al.	N/A	N/A
10509008	12/2018	Liao et al.	N/A	N/A
10556792	12/2019	Lee et al.	N/A	N/A
10852271	12/2019	Chen et al.	N/A	N/A
11747298	12/2022	Chang et al.	N/A	N/A
12123846	12/2023	Chang et al.	N/A	N/A
12123871	12/2023	Chang et al.	N/A	N/A
2010/0164117	12/2009	Chen	N/A	N/A
2011/0244676	12/2010	Chen et al.	N/A	N/A
2012/0211885	12/2011	Choi et al.	N/A	N/A
2013/0168740	12/2012	Chen	N/A	N/A
2013/0200438	12/2012	Liu et al.	N/A	N/A
2014/0264467	12/2013	Cheng et al.	N/A	N/A
2016/0320337	12/2015	Cheng et al.	N/A	N/A
2017/0067890	12/2016	Lin et al.	N/A	N/A
2017/0158500	12/2016	Chang	N/A	H01L 24/11
2017/0365587	12/2016	Hung et al.	N/A	N/A
2018/0019187	12/2017	Lagouge et al.	N/A	N/A
2018/0172627	12/2017	Chang et al.	N/A	N/A

2018/0238827	12/2017	Cheng et al.	N/A	N/A
2018/0313783	12/2017	Cheng et al.	N/A	N/A
2018/0338713	12/2017	Polsky et al.	N/A	N/A
2019/0145927	12/2018	Huang et al.	N/A	N/A
2024/0410855	12/2023	Chang et al.	N/A	N/A
2025/0035623	12/2024	Chang et al.	N/A	N/A

FOREIGN PATENT DOCUMENTS

Patent No.	Application Date	Country	CPC
103180240	12/2012	CN	N/A
104051512	12/2013	CN	N/A
105977282	12/2015	CN	N/A
108226257	12/2017	CN	N/A
109307701	12/2018	CN	N/A
10 2016 125 295	12/2017	DE	N/A
10 2018 124 826	12/2018	DE	N/A
2 421 596	12/2014	EP	N/A
1 967 581	12/2015	EP	N/A
10-2018-0018287	12/2017	KR	N/A
201638814	12/2015	TW	N/A
2008/008845	12/2007	WO	N/A
WO-2018026830	12/2017	WO	G01N 27/4145

OTHER PUBLICATIONS

Translation of Description of CN 108226257A from Espacenet, 2018, 15 pages (Year: 2018). cited by applicant
Chinese Office Action for Application No. 202110129817.9 mailed Jun. 26, 2024. cited by applicant
Notice of Allowance for Korean Application No. 10-2021-0002574 mailed Jul. 24, 2023. cited by applicant

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Background/Summary

PRIORITY CLAIM AND CROSS-REFERENCE (1) This application is a divisional of U.S. patent application Ser. No. 17/104,059, filed Nov. 25, 2020, which claims the benefit of U.S. Provisional Application No. 62/967,850, filed Jan. 30, 2020, the disclosure of which is hereby incorporated by reference in its entirety.

BACKGROUND
(1) Biosensors are devices for sensing and detecting biomolecules and operate on the basis of electronic, electrochemical, optical, and mechanical detection principles. Biosensors that include transistors are sensors that electrically sense charges, photons, and mechanical properties of bio-

entities or biomolecules. The detection can be performed by detecting the bio-entities or biomolecules themselves, or through interaction and reaction between specified reactants and bio-entities/biomolecules. Such biosensors can be manufactured using semiconductor processes, can quickly convert electric signals, and can be easily applied to integrated circuits (ICs) and microelectromechanical systems (MEMS).

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) Aspects of the present disclosure are best understood from the following detailed description when read with the accompanying figures. It is noted that, in accordance with the standard practice in the industry, various features are not drawn to scale. In fact, the dimensions of the various features may be arbitrarily increased or reduced for clarity of discussion.

(2) FIG. **1**A is a block diagram of an example biosensor system in accordance with some embodiments.

(3) FIG. **1**B is a schematic diagram of an example biosensor used in the biosensor system of FIG. **1**A in accordance with some embodiments.

(4) FIG. **2**A is a cross-sectional diagram illustrating a biosensor system package in accordance with some embodiments.

(5) FIG. **2**B is a cross-sectional diagram illustrating another biosensor system package **200***b* in accordance with some embodiments.

(6) FIG. **3**A is a top view of an integrated continuous biomarker monitoring and treatment chip in accordance with some embodiments.

(7) FIG. **3**B is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip along a line A-A′ of FIG. **3**A in accordance with some embodiments.

(8) FIG. **3**C is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip along a line B-B′ of FIG. **3**A in accordance with some embodiments.

(9) FIG. **3**D is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip along a line C-C′ of FIG. **3**A in accordance with some embodiments.

(10) FIG. **3**E is a diagram illustrating the use of the integrated continuous biomarker monitoring and treatment chip of FIG. **3**A in accordance with some embodiments.

(11) FIG. **3**F is a flowchart illustrating a method of operating the integrated continuous biomarker monitoring and treatment chip of FIG. **3**A in accordance with some embodiments.

(12) FIG. **4**A is a top view of a simultaneously biomarker monitoring and drug releasing treatment chip and the application thereof in accordance with some embodiments.

(13) FIG. **4**B is a flowchart illustrating a method for simultaneous biomarker monitoring and drug releasing treatment chip of FIG. **4**A in accordance with some embodiments.

(14) FIG. **5**A is a top view of another integrated continuous biomarker monitoring and treatment chip in accordance with some embodiments.

(15) FIG. **5**B is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip along a line A-A′ of FIG. **5**A in accordance with some embodiments.

(16) FIG. **5**C is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip along a line B-B′ of FIG. **5**A in accordance with some embodiments.

(17) FIG. **5**D is a cross-sectional diagram illustrating the cross section of the integrated continuous

biomarker monitoring and treatment chip along a line C-C′ of FIG. **5**A in accordance with some embodiments.
(18) FIG. **5**E is a diagram illustrating the use of the integrated continuous biomarker monitoring and treatment chip of FIG. **5**A in accordance with some embodiments.
(19) FIG. **5**F is a flowchart illustrating a method for continuous biomarker monitoring in accordance with some embodiments.
(20) FIG. **5**G is a diagram illustrating the use of the integrated continuous biomarker monitoring and treatment chip of FIG. **5**A in accordance with some embodiments.
(21) FIG. **5**H is a flowchart illustrating a method for continuous biomarker monitoring with closed-loop drug releasing treatment in accordance with some embodiments.
(22) FIG. **6**A and FIG. **6**B are flowcharts illustrating a method of fabricating the biosensor system packages of FIG. **2**A and FIG. **2**B, respectively, in accordance with some embodiments.
(23) FIG. **6**C is a flowchart illustrating the step **624** of the method of FIG. **6**A and FIG. **6**B in accordance with some embodiments.
(24) FIG. **6**D is a flowchart illustrating the step **636** of the method of FIG. **6**A and FIG. **6**B in accordance with some embodiments.
(25) FIG. **6**E is another flowchart illustrating the step **636** of the method of FIG. **6**A and FIG. **6**B in accordance with some embodiments.
(26) FIGS. **7-38** are cross-sectional diagrams illustrating the biosensor system package constructed according to one or more steps of the method of FIG. **6**A and FIG. **6**B in accordance with some embodiments.

DETAILED DESCRIPTION

(27) The following disclosure provides many different embodiments, or examples, for implementing different features of the provided subject matter. Specific examples of components and arrangements are described below to simplify the present disclosure. These are, of course, merely examples and are not intended to be limiting. For example, the formation of a first feature over or on a second feature in the description that follows may include embodiments in which the first and second features are formed in direct contact, and may also include embodiments in which additional features may be formed between the first and second features, such that the first and second features may not be in direct contact. In addition, the present disclosure may repeat reference numerals and/or letters in the various examples. This repetition is for the purpose of simplicity and clarity and does not in itself dictate a relationship between the various embodiments and/or configurations discussed.
(28) Further, spatially relative terms, such as “beneath,” “below,” “lower,” “above,” “upper” and the like, may be used herein for ease of description to describe one element or feature's relationship to another element(s) or feature(s) as illustrated in the figures. The spatially relative terms are intended to encompass different orientations of the device in use or operation in addition to the orientation depicted in the figures. The apparatus may be otherwise oriented (rotated 90 degrees or at other orientations) and the spatially relative descriptors used herein may likewise be interpreted accordingly.
(29) In general, the term “bioFET” as used herein refers to a field-effect transistor (FET) that includes a layer of immobilized capture reagents that act as surface receptors to detect the presence of a target analyte of biological origin. A bioFET is a field-effect sensor with a semiconductor transducer, according to some embodiments. One advantage of bioFETs is the prospect of label-free operation. Specifically, bioFETs enable the avoidance of costly and time-consuming labeling operations such as the labeling of an analyte with, for instance, fluorescent or radioactive probes. The analytes for detection by a bioFET will normally be of biological origin, such as—without limitation—proteins, carbohydrates, lipids, tissue fragments, or portions thereof. A BioFET can be part of a broader genus of FET sensors that may also detect any chemical compound (known in the art as a “ChemFET”) or any other element, including ions such as protons or metallic ions (known

in the art as an “ISFET”). This disclosure applies to all types of FET-based sensors (“FET sensor”).
(30) “Capture reagent,” as used herein, is a molecule or compound capable of binding the target analyte or target reagent, which can be directly or indirectly attached to a substantially solid material. The capture reagent can be a chemical, and specifically any substance for which there exists a naturally occurring target analyte (e.g., an antibody, polypeptide, DNA, RNA, cell, virus, etc.) or for which a target analyte can be prepared, and the capture reagent can bind to one or more target analytes in an assay.
(31) “Target analyte,” as used herein, is the substance to be detected in the test sample using the present disclosure. The target analyte can be a chemical, and specifically any substance for which there exists a naturally occurring capture reagent (e.g., an antibody, polypeptide, DNA, RNA, cell, virus, etc.) or for which a capture reagent can be prepared, and the target analyte can bind to one or more capture reagents in an assay. “Target analyte” also includes any antigenic substances, antibodies, or combinations thereof. The target analyte can include a protein, a peptide, an amino acid, a carbohydrate, a hormone, a steroid, a vitamin, a drug including those administered for therapeutic purposes as well as those administered for illicit purposes, a bacterium, a virus, and metabolites of or antibodies to any of the above substances.
(32) “Biomarker,” as used herein, means a measurable indicator of the severity or presence of some disease state. More generally a biomarker is anything that can be used as an indicator of a particular disease state or some other physiological state of an organism. A biomarker can be a substance that is introduced into an organism as a means to examine organ function or other aspects of health. For example, rubidium chloride is used in isotopic labeling to evaluate perfusion of heart muscle. It can also be a substance whose detection indicates a particular disease state, for example, the presence of an antibody may indicate an infection. More specifically, a biomarker indicates a change in expression or state of a protein that correlates with the risk or progression of a disease, or with the susceptibility of the disease to a given treatment. Biomarkers can be characteristic biological properties or molecules that can be detected and measured in parts of the body like the blood or tissue. They may indicate either normal or diseased processes in the body. Biomarkers can be specific cells, molecules, or genes, gene products, enzymes, or hormones. Complex organ functions or general characteristic changes in biological structures can also serve as biomarkers.
(33) “Test sample,” as used herein, means the composition, solution, substance, gas, or liquid containing the target analyte to be detected and assayed using the present disclosure. The test sample can contain other components besides the target analyte, can have the physical attributes of a liquid, or a gas, and can be of any size or volume, including for example, a moving stream of liquid or gas. The test sample can contain any substances other than the target analyte as long as the other substances do not interfere with the binding of the target analyte with the capture reagent or the specific binding of the first binding member to the second binding member. Examples of test samples include, but are not limited to, naturally-occurring and non-naturally occurring samples or combinations thereof. Naturally-occurring test samples can be synthetic or synthesized. Naturally-occurring test samples include body or bodily fluids isolated from anywhere in or on the body of a subject, including, but not limited to, blood, plasma, serum, urine, saliva or sputum, spinal fluid, cerebrospinal fluid, pleural fluid, nipple aspirates, lymph fluid, fluid of the respiratory, intestinal, and genitourinary tracts, tear fluid, saliva, breast milk, fluid from the lymphatic system, semen, cerebrospinal fluid, intra-organ system fluid, ascitic fluid, tumor cyst fluid, amniotic fluid and combinations thereof, and environmental samples such as ground water or waste water, soil extracts, air, and pesticide residues or food-related samples.
(34) Detected substances can include, for example, nucleic acids (including DNA and RNA), hormones, different pathogens (including a biological agent that causes disease or illness to its host, such as a virus (e.g., H7N9 or HIV), a protozoan (e.g., *Plasmodium*-causing malaria), or a bacteria (e.g., *E. coli* or *Mycobacterium tuberculosis*)), proteins, antibodies, various drugs or therapeutics or other chemical or biological substances, including hydrogen or other ions, non-ionic molecules or

compounds, polysaccharides, small chemical compounds such as chemical combinatorial library members, and the like. Detected or determined parameters may include, but are not limited to, pH changes, lactose changes, changing concentration, particles per unit time where a fluid flows over the device for a period of time to detect particles (e.g., particles that are sparse), and other parameters.

(35) As used herein, the term "immobilized," when used with respect to, for example, a capture reagent, includes substantially attaching the capture reagent at a molecular level to a surface. For example, a capture reagent may be immobilized to a surface of the substrate material using adsorption techniques including non-covalent interactions (e.g., electrostatic forces, van der Waals, and dehydration of hydrophobic interfaces) and covalent binding techniques where functional groups or linkers facilitate attaching the capture reagent to the surface. Immobilizing a capture reagent to a surface of a substrate material may be based on the properties of the substrate surface, the medium carrying the capture reagent, and the properties of the capture reagent. In some cases, a substrate surface may be first modified to have functional groups bound to the surface. The functional groups may then bind to biomolecules or biological or chemical substances to immobilize them thereon.

(36) A biosensor system includes, among other things, a sensing chip and a microneedle. The microneedle and the sensing chip often are fabricated separately and later assembled manually, which is not a scalable manufacturing solution.

(37) In accordance with some embodiments, a wafer-level packaging solution to fabricate sensing chips and cap structures with microneedles together is provided. The solution may be used for biomarker monitoring and/or drug delivery. Since microneedles and sensing chips are fabricated together, there is no need to assemble the microneedles and the sensing chips manually. It is a more scalable manufacturing solution and may lower manufacturing costs. The increased integration further makes it possible to construct a biomarker monitoring and drug delivery feedback system. When providing therapy to a patient, such a feedback system may prevent delivery of too much drug which could become toxic to the patient. The feedback system is a closed-loop feedback system where the drug delivery is dependent on the biomarker levels. A large number of biosensors may be employed as an array for each microfluidic chamber of the cap structure served by microneedle(s). This provides better statistical analysis of the sensing results and reduces the signal to noise ratio (SNR) of the results. In accordance with some embodiments, the biosensor system package may be connected to a separate chip/die through wire bonding. In accordance with some embodiments, the biosensor system package may be connected to a separate chip/die through a through-substrate via (TSV) structure.

(38) FIG. **1**A is a block diagram of an example biosensor system **100** in accordance with some embodiments. FIG. **1**B is a schematic diagram of an example biosensor **103** used in the biosensor system **100** of FIG. **1**A in accordance with some embodiments. As shown in FIG. **1**A, the example biosensor system **100** may include, among other things, a biosensor array **102**, a control sensor array **104**, temperature sensors **106**, a reference electrode **108**, a sensor interface **130**, an amplifier **132**, a power regulator **134**, an analog-to-digital converter (ADC) **136**, a digital control module **138**, a wireless transceiver (TRX) **140**, a heater **142**, and bonding pads **144**.

(39) The biosensor array **102** may have at least one sensing element for detecting a biological or chemical analyte. The biosensor array **102** may include an array of biosensors (e.g., a biosensor **103** shown in FIG. **1**B), where one or more of the biosensors in the array are functionalized to detect a particular target analyte. Different ones of the biosensors may be functionalized using different capture reagents for detecting different target analytes. The biosensors may be arranged in a plurality of rows and columns, forming a 2-dimensional array of biosensors. In some embodiments, each row of biosensors is functionalized using a different capture reagent. In some embodiments, each column of biosensors is functionalized using a different capture reagent. In some embodiments, a certain range of rows and columns of biosensors are functionalized using a

different capture reagent. Further details regarding an example biosensor **103** is provided below with reference to FIG. **1**B.

(40) The control sensor array **104** has similar structures with the biosensor array **102**. The control sensor array **104** provides reference signals to be compared with the signals generated at the biosensor array **102**, to generate differential signals. The sensor interface **130** interfaces with the biosensor array **102** and the control sensor array **104**. The resultant differential signals are further amplified by the amplifier **132**. The reference electrode **108** provides a reference potential. The reference electrode **108** may be made of one of the following materials: Ag/AgCl, Cu/CuSO.sub.4, AgCl, Au, and P. For Ag/AgCl, a chemical treatment may be required on the deposited and patterned Ag layer to create the AgCl. For Cu/CuSO.sub.4, a chemical treatment may be required on the deposited and patterned Cu layer to create the CuSO.sub.4. For applications where the sensing has to be done at certain temperatures, the heater **142** can adjust the temperature of the biosensor array **102** and the control sensor array **104** based on feedback signals detected by the temperature sensors **106**. The ADC **136** may convert analog signals amplified by the amplifier to digital signals. The digital control module **138** may act as a controller for the biosensor system **100**. The bonding pads **144** are used for bonding the biosensor system to other chips or printed circuit board (PCB). Alternatively, the wireless transceiver **140** may transmit and receive data via wireless communication.

(41) As shown in FIG. **1**B, the example biosensor **103** may include, among other things, a fluid gate **112**, a source region **114**, a drain region **116**, a sensing film **118**, a channel region **120**. A fluid **122** is over the sensing film **118**. The fluid **122** may contain analyte not shown. The sensing film **118** may be an electrically and chemically insulating layer that separates the fluid **122** from the channel region **120**. The sensing film **118** may include, among other things, a layer of a capture reagent. The capture reagent is specific to an analyte and capable of binding the target analyte or target reagent. Upon binding of the analyte, changes in the electrostatic potential at the surface of the sensing film **118** occur, which in turn results in an electrostatic gating effect of the biosensor **103**, and a measurable change in a current I.sub.ds **126** between the source and drain electrodes. A voltage applied to the fluid gate **112** may also change the I.sub.ds **126**.

(42) FIG. **2**A is a cross-sectional diagram illustrating a biosensor system package **200***a* in accordance with some embodiments. FIG. **2**B is a cross-sectional diagram illustrating another biosensor system package **200***b* in accordance with some embodiments. FIG. **6**A and FIG. **6**B are flowcharts illustrating a method of fabricating the biosensor system package **200***a* and **200***b* (collectively **200**) of FIG. **2**A and FIG. **2**B, respectively, in accordance with some embodiments. FIG. **6**C is a flowchart illustrating the step **624** of the method **600** in accordance with some embodiments. FIG. **6**D is a flowchart illustrating the step **636** of the method **600** in accordance with some embodiments. FIG. **6**E is another flowchart illustrating the step **636** of the method **600** in accordance with some embodiments. It should be noted that additional steps can be provided before, during, and after the method **600**, and some of the steps described below can be replaced or eliminated, for additional embodiments of the method. Further, it should be noted that the method **600** is a CMOS-compatible process flow. FIGS. **7**-**38** are cross-sectional diagrams illustrating the biosensor system package constructed according to one or more steps of the method of FIG. **6**A and FIG. **6**B in accordance with some embodiments. It should be noted that FIGS. **2**A-**2**B and **7**-**38** are schematic and are not drawn to scale.

(43) As shown in FIGS. **2**A and **2**B, each of the biosensor system package **200***a* and **200***b* (collectively **200**) has a front side (F) and a back side (B). In the example shown in FIG. **2**A and FIG. **2**B, each of the biosensor system package **200***a* and **200***b* includes, among other things, a buried oxide (BOX) layer **206**, a semiconductor layer **208**, a transistor structure (i.e., a FET) **210**, a temperature sensor **211**, a multilevel-interconnect (MLI) structure **212**, a carrier substrate **220**, a separate chip/die (e.g., a RAM and data processing chip) **250**, a trench **222**, an interface layer (e.g., a high-k material layer) **224**, a reference electrode **227**, and a cap structure **228**. The separate chip

250 is connected to the biosensor system package **200***a* of FIG. **2**A by wire bonding, while the separate chip **250** is connected to the biosensor system package **200***b* of FIG. **2**B by a through-substrate via (TSV) structure **246** and a solder bump **248**. The TSV structure **246** is at the front side (F). The cap structure **228** is attached to the back side (B). The cap structure **228** includes, among other things, a cap structure substrate **230**, chamber(s) **244**, a microneedle **241**, an inlet **274**, and optionally a high-k dielectric material layer **242**. The chamber **244** can accommodate fluid samples to be tested. Details of the components of the biosensor system package **200** will be described below with reference to FIGS. **6**A-**6**E and **7**-**38**.

(44) FIG. **3**A is a top view of an integrated continuous biomarker monitoring and treatment chip **300** in accordance with some embodiments. FIG. **3**B is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip **300** along a line A-A′ of FIG. **3**A in accordance with some embodiments. FIG. **3**C is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip **300** along a line B-B′ of FIG. **3**A in accordance with some embodiments. FIG. **3**D is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip **300** along a line C-C′ of FIG. **3**A in accordance with some embodiments. FIG. **3**E is a diagram illustrating the use of the integrated continuous biomarker monitoring and treatment chip **300** of FIG. **3**A in accordance with some embodiments. FIG. **3**F is a flowchart illustrating a method **390** of operating the integrated continuous biomarker monitoring and treatment chip **300** of FIG. **3**A in accordance with some embodiments.

(45) As shown in FIGS. **3**A-**3**D, the integrated continuous biomarker monitoring and treatment chip **300** may include, among other things, a complementary metal-oxide-semiconductor (CMOS) application-specific integrated circuit (ASIC) **348**, a cap structure **362** attached to the back side of the CMOS ASIC **348**, and a gas-liquid separation membrane **358**. In the example shown in FIGS. **3**A-**3**D, the cap structure **362** is attached to the CMOS ASIC **348** via wafer bonding structures **364**, though other means of bonding may be employed. The example CMOS ASIC **348** has, among other things, a biosensor array **302** and a control sensor array **304** at the back side of the CMOS ASIC **348**. The example cap structure **362** has, among other things, a fluid chamber **354** and multiple microneedles **350**. The fluid chamber **354** may accommodate fluid which may contain biomarker molecules (e.g., glucose molecules) **360**. The biosensor array **302** and the control sensor array **304** may detect the existence and density of the biomarker molecules **360** as explained above. The fluid enters the fluid chamber **354** via the multiple microneedles **350**. The number of microneedles **350** may vary as needed. For each microneedle **350**, there is a (silicon) microneedle channel **352** that connects the fluid chamber **354** with outside. The gas-liquid separation membrane **358** is configured to eliminate air bubbles in the fluid chamber **354** since only gas can pass the gas-liquid separation membrane **358**.

(46) Referring to FIGS. **3**E and **3**F, the integrated continuous biomarker monitoring and treatment chip **300** is used for continuous biomarker monitoring, and the method **390** of operating the integrated continuous biomarker monitoring and treatment chip **300** starts at step **391**. At step **391**, the microneedles **350** are inserted into a skin **368**. Specifically, the microneedles **350** penetrate the skin **368** of a body (e.g., human body) **366**. Biomarker molecules (e.g., glucose molecules) **360** may exist in the body **366** (beneath the skin **368**, inside and around the blood vessel **370**). At step **392**, interstitial fluid may naturally flow into the fluid chamber **354** via the microneedle channels **352** of the microneedles **350** due to pressure. As a result, the biomarker molecules **360** enter the fluid chamber **354** as well. At step **393**, the CMOS ASIC **348** with the biosensor array **302** and the control sensor array **304** continuously senses the biomarker molecules **360** and transmits data. Specifically, the biosensor array **302**, along with the control sensor array **304**, may detect the existence and density of the biomarker molecules **360**. The detected signal is further processed (e.g., amplified, converted, etc.) by the CMOS ASIC **348**. The result data may be transmitted via either the bonding pads **344** shown in FIG. **3**A or alternatively the wireless transceiver module **140**

shown in FIG. **1**A. As such, the integrated continuous biomarker monitoring and treatment chip **300** may continuously sense the biomarker molecules **360**, which in turn may be used for diagnose or treatment of certain diseases (e.g., diabetes) related to the biomarker molecules **360**.

(47) FIG. **4**A is a top view of a simultaneously biomarker monitoring and drug releasing treatment chip **400** and the application thereof in accordance with some embodiments. FIG. **4**B is a flowchart illustrating a method **490** for simultaneous biomarker monitoring and drug releasing treatment chip **400** of FIG. **4**A in accordance with some embodiments.

(48) As shown in FIG. **4**A, the simultaneously biomarker monitoring and drug releasing treatment chip **400** may include, among other things, a CMOS ASIC **448**, a cap structure **462** attached to the back of the CMOS ASIC **448**, and two gas-liquid separation membranes **458***a* and **458***b*. In the example shown in FIG. **4**A, the cap structure **462** is attached to the CMOS ASIC **448** via wafer bonding structures not shown, though other means of bonding may be employed. The example CMOS ASIC **448** has, among other things, a biosensor array **402** and a control sensor array **404** at the back of the CMOS ASIC **448**. The example cap structure **462** has, among other things, a fluid chamber **454**, a drug channel **455**, and multiple microneedles **450**. The fluid chamber **454** may accommodate fluid which may contain biomarker molecules (e.g., glucose molecules) not shown. The biosensor array **402** and the control sensor array **404** may detect the existence and density of the biomarker molecules as explained above. The fluid enters the fluid chamber **454** via the multiple microneedles **450**. The number of microneedles **450** may vary as needed. On the other hand, the drug channel may accommodate drug solution **474** which is originally outside the simultaneously biomarker monitoring and drug releasing treatment chip **400**. The drug solution **474**, outside the simultaneously biomarker monitoring and drug releasing treatment chip **400**, is connected to the drug channel **455** through a fluidics valve **476** and a pump **472**. The fluidics valve **476** can be turned on and off based on control signals. When the fluidics valve **476** is turned on, the drug solution **474** can be pumped into the drug channel **455** for delivery via the microneedles **450**. The gas-liquid separation membranes **458***a* and **458***b* are configured to eliminate air bubbles in the fluid chamber **454** and the drug channel **455**, respectively.

(49) Referring to FIG. **4**B and FIG. **4**A, the simultaneously biomarker monitoring and drug releasing treatment chip **400** is used for simultaneously biomarker monitoring and drug releasing treatment, and the method **490** for simultaneous biomarker monitoring and drug releasing treatment chip starts at step **491**. At step **491**, the microneedles **450** are inserted into a skin not shown. Specifically, the microneedles **450** penetrate the skin of a body (e.g., human body) not shown. Biomarker molecules (e.g., glucose molecules) not shown may exist in the body. Interstitial fluid not shown may naturally flow into the fluid chamber **454** via the microneedles **450** due to pressure. As a result, the biomarker molecules not shown may enter the fluid chamber **454** as well. At step **492**, the fluidics valve **476** is turned off. As such, the drug solution **474** cannot flow into the drug channel **455**. At step **493**, the CMOS ASIC **448** with the biosensor array **402** and the control sensor array **404** continuously senses the biomarker molecules and transmits data. Specifically, the biosensor array **402**, along with the control sensor array **404**, may detect the existence and density of the biomarker molecules. The detected signal is further processed (e.g., amplified, converted, etc.) by the CMOS ASIC **448**. At step **494**, the CMOS ASIC **448** determines that the biomarker concentration reaches an abnormal value (e.g., above a threshold concentration). Then at step **495**, the fluidics valve **476** is turned on. As a result, at step **496**, the drug solution **474** flows into the drug channel **455** (e.g., pumped by the pump **472**) and subsequently flows into the skin/body through the microneedles **450**. As such, the drug solution **474** is delivered and the drug releasing treatment begins. On the other hand, the CMOS ASIC **448** still continuously senses the biomarker molecules and transmits data as at step **493**. Due to the drug releasing treatment, the biomarker concentration becomes lower over time. At step **497**, the CMOS ASIC **448** determines that the biomarker concentration turns normal (e.g., below the threshold concentration) again. As a result, the fluidics valve **476** is turned off again such that the drug solution **474** cannot flow into the drug

channel **455**. Accordingly, the method **490** can achieve simultaneous biomarker monitoring and drug releasing treatment with one integrated chip. In other words, the biomarker concentration is being constantly monitored and the drug releasing treatment is triggered automatically based on the real-time biomarker concentration.

(50) FIG. **5**A is a top view of another integrated continuous biomarker monitoring and treatment chip **500** in accordance with some embodiments. FIG. **5**B is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip **500** along a line A-A′ of FIG. **5**A in accordance with some embodiments. FIG. **5**C is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip **500** along a line B-B′ of FIG. **5**A in accordance with some embodiments. FIG. **5**D is a cross-sectional diagram illustrating the cross section of the integrated continuous biomarker monitoring and treatment chip **500** along a line C-C′ of FIG. **5**A in accordance with some embodiments. FIG. **5**E is a diagram illustrating the use of the integrated continuous biomarker monitoring and treatment chip **500** of FIG. **5**A in accordance with some embodiments. FIG. **5**F is a flowchart illustrating a method **580** for continuous biomarker monitoring in accordance with some embodiments. FIG. **5**G is a diagram illustrating the use of the integrated continuous biomarker monitoring and treatment chip **500** of FIG. **5**A in accordance with some embodiments. FIG. **5**H is a flowchart illustrating a method **590** for continuous biomarker monitoring with closed-loop drug releasing treatment in accordance with some embodiments.

(51) As shown in FIGS. **5**A-**5**D, the integrated continuous biomarker monitoring and treatment chip **500** may include, among other things, a CMOS ASIC **548**, a cap structure **562** attached to the back of the CMOS ASIC **548**, an inlet **578**, and a gas-liquid separation membrane **558**. In the example shown in FIGS. **5**A-**5**D, the cap structure **562** is attached to the CMOS ASIC **548** via wafer bonding structures **564**, though other means of bonding may be employed. The example CMOS ASIC **548** has, among other things, a biosensor array **502** and a control sensor array **504** at the back of the CMOS ASIC **548**. The example cap structure **562** has, among other things, a fluid chamber **554** and multiple microneedles **550**. The fluid chamber **554** may accommodate fluid which may contain biomarker molecules (e.g., glucose molecules) **560**. The biosensor array **502** and the control sensor array **504** may detect the existence and density of the biomarker molecules **560** as explained above. The fluid may enter the fluid chamber **554** via the inlet **578** and/or the multiple microneedles **550**. The number of microneedles **550** may vary as needed. For each microneedle **550**, there is a (silicon) microneedle channel **552** that connects the fluid chamber **554** with outside. The gas-liquid separation membrane **558** is configured to eliminate air bubbles in the fluid chamber **554** since only gas can pass the gas-liquid separation membrane **558**.

(52) Referring to FIGS. **5**E and **5**F, the integrated continuous biomarker monitoring and treatment chip **500** is used for continuous biomarker monitoring. As shown in FIG. **5**E, the fluid chamber **554** is connected to buffer solution **575** through a fluidics valve **576** and a pump **572**. A buffer solution is an aqueous solution consisting of a mixture of a weak acid and its conjugate base, or vice versa. In one example, the buffer solution **575** is 1×PBS (1× Physiological Saline Solution) or PBS with lower concentrations such as 0.1×PBS or 0.01×PBS. In another example, the buffer solution **575** is HEPES [(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)]. In yet another example, the buffer solution **575** is TRIS [tris(hydroxymethyl) aminomethane]. At step **581**, the fluidics valve **576** is turned on and the buffer solution **575** is filled in the fluid chamber **554**. At step **582**, the microneedles **550** are inserted into a skin **568**. Specifically, the microneedles **550** penetrate the skin **568** of a body (e.g., human body) **566**. Biomarker molecules (e.g., glucose molecules) **560** may exist in the body **566** (beneath the skin **568**, inside and around the blood vessel **570**). Interstitial fluid may naturally flow into the fluid chamber **554** via the microneedle channels **552** of the microneedles **550** due to pressure. As a result, the biomarker molecules **560** enter the fluid chamber **554** as well. At step **583**, the fluidics valve **576** is turned off. At step **584**, the CMOS ASIC **548** with the biosensor array **502** and the control sensor array **504** continuously senses the biomarker

molecules **560** and transmits data. Specifically, the biosensor array **502**, along with the control sensor array **504**, may detect the existence and density of the biomarker molecules **560**. The detected signal is further processed (e.g., amplified, converted, etc.) by the CMOS ASIC **548**. The result data may be transmitted via either the bonding pads **544** shown in FIG. **5**A or alternatively the wireless transceiver module **140** shown in FIG. **1**A. As such, the integrated continuous biomarker monitoring and treatment chip **500** may continuously sense the biomarker molecules **560**, which in turn may be used for diagnose or treatment of certain diseases (e.g., diabetes) related to the biomarker molecules **560**.

(53) On the other hand, referring to FIGS. **5**G and **5**H, the integrated continuous biomarker monitoring and treatment chip **500** is used for continuous biomarker monitoring with closed-loop drug releasing treatment. As shown in FIG. **5**G, the fluid chamber **554** is connected to a pump **572** via the inlet **578**, which is further connected to both buffer solution **575** and drug solution **574** through a fluidics valve **576***a* ("V1") and another fluidics valve **576***b* ("V2"), respectively. At step **591**, the fluidics valve **576***a* is turned on and the fluidics valve **576***b* is turned off. As a result, the buffer solution **575** is filled into the fluid chamber **554**. At step **592**, the microneedles **550** are inserted into a skin **568**. Specifically, the microneedles **550** penetrate the skin **568** of a body (e.g., human body) **566**. Biomarker molecules (e.g., glucose molecules) **560** may exist in the body **566** (beneath the skin **568**, inside and around the blood vessel **570**). Interstitial fluid may naturally flow into the fluid chamber **554** via the microneedle channels **552** of the microneedles **550** due to pressure. As a result, the biomarker molecules **560** enter the fluid chamber **554** as well. At step **593**, both the fluidics valve **576***a* and the fluidics valve **576***b* are turned off. At step **594**, the CMOS ASIC **548** with the biosensor array **502** and the control sensor array **504** continuously senses the biomarker molecules **560** and transmits data. Specifically, the biosensor array **502**, along with the control sensor array **504**, may detect the existence and density of the biomarker molecules **560**. The detected signal is further processed (e.g., amplified, converted, etc.) by the CMOS ASIC **548**. The result data may be transmitted via either the bonding pads **544** shown in FIG. **5**A or alternatively the wireless transceiver module **140** shown in FIG. **1**A. At step **595**, the CMOS ASIC **548** determines that the biomarker concentration reaches an abnormal value (e.g., above a threshold concentration). Then at step **596**, the fluidics valve **576***b* is turned on and the fluidics valve **576***a* keeps off for a certain period of time. As a result, at step **597**, the drug solution **574** flows into the drug channel fluid chamber **554** (e.g., pumped by the pump **572**) and subsequently flows into the skin/body through the microneedles **550**. As such, the drug solution **474** is delivered and the drug releasing treatment begins. On the other hand, the CMOS ASIC **448** still continuously senses the biomarker molecules and transmits data as at step **594**. Due to the drug releasing treatment, the biomarker concentration becomes lower over time. After the certain period of time, at step **598**, the fluidics valve **576***b* is turned off while the fluidics valve **576***a* is turned on. As a result, the buffer solution **575** can flow into the fluid chamber **554**. Then at step **599**, both the fluidics valve **576***a* and the fluidics valve **576***b* are turned off. The method **590** then loops back to step **594**. Accordingly, the method **590** can achieve simultaneous biomarker monitoring with closed-loop drug releasing treatment. In other words, the biomarker concentration is being constantly monitored and the drug releasing treatment is triggered automatically based on the real-time biomarker concentration. The buffer solution **575** is added to the fluid chamber **554** every time the drug solution **574** is delivered.

(54) As mentioned above, the biosensor system package **200***a* of FIG. **2**A and the biosensor system package **200***b* of FIG. **2**B are fabricated by the method **600** of FIGS. **6**A-**6**B.

(55) The method **600** begins at step **602** where a substrate is provided. The substrate may be a semiconductor substrate (e.g., wafer). The semiconductor substrate may be a silicon substrate. Alternatively, the substrate may comprise another elementary semiconductor, such as germanium; a compound semiconductor including silicon carbide, gallium arsenic, gallium phosphide, indium phosphide, indium arsenide, and/or indium antimonide; an alloy semiconductor including SiGe,

GaAsP, AlInAs, AlGaAs, GaInAs, GaInP, and/or GaInAsP; or combinations thereof. In embodiments shown in FIGS. **6**A-**6**E and FIGS. **7**-**38**, the substrate is a semiconductor on insulator (SOI) substrate **202**. The SOI substrate **202** shown in FIG. **7** includes a bulk silicon layer **204**, a buried oxide (BOX) layer **206**, and a semiconductor layer **208** (i.e., an active layer **208**). The buried oxide layer **206** may be formed by a process such as separation by implanted oxygen (SIMOX), and/or other suitable processes. The semiconductor layer **208** may include doped regions, such as p-wells and n-wells.

(56) The method then proceeds to step **604** where a transistor structure and a temperature sensor are formed on the substrate. The transistor structure (i.e., the FET) may include a gate structure, a source region, a drain region, and a channel region interposing the source and drain regions. It should be noted that in some embodiments, the transistor structure (i.e., the FET) may be an array of transistor structures. For simplicity, only one transistor structure is used as an example in the description below. As shown in the example in FIG. **7**, the source, drain, and/or channel region of the FET **210** may be formed on an active region in the semiconductor layer **208**. The FET **210** may be an n-type FET (nFET) or a p-type FET (pFET). For example, the source/drain regions may comprise n-type dopants or p-type dopants depending on the FET configuration. The gate structure may include a gate dielectric layer, a gate electrode layer, and/or other suitable layers. In an embodiment, the gate electrode is polysilicon. Other exemplary gate electrodes include metal gate electrodes including material such as, Cu, W, Ti, Ta, Cr, Pt, Ag, Au; suitable metallic compounds like TiN, TaN, NiSi, CoSi; combinations thereof; and/or other suitable conductive materials. In an embodiment, the gate dielectric is silicon oxide. Other exemplary gate dielectrics include silicon nitride, silicon oxynitride, a dielectric with a high dielectric constant (high-k), and/or combinations thereof. Examples of high-k materials include hafnium silicate, hafnium oxide, zirconium oxide, aluminum oxide, tantalum pentoxide, hafnium dioxide-alumina (HfO.sub.2—Al.sub.2O.sub.3) alloy, or combinations thereof. The FET **210** may be formed using typical CMOS processes such as, photolithography; ion implantation; diffusion; deposition including physical vapor deposition (PVD), metal evaporation or sputtering, chemical vapor deposition (CVD), plasma-enhanced chemical vapor deposition (PECVD), atmospheric pressure chemical vapor deposition (APCVD), low-pressure CVD (LPCVD), high density plasma CVD (HDPCVD), atomic layer deposition (ALD), spin on coating; etching including wet etching, dry etching, and plasma etching; and/or other suitable CMOS processes.

(57) The temperature sensor may detect the temperature of the chamber **244** in FIGS. **2**A and **2**B. As shown in the example in FIG. **7**, the temperature sensor **211** is formed in the semiconductor layer **208**. In some embodiments, the temperature sensor **211** may include a thermal coupling element (e.g., a platinum thermocouple).

(58) The method **600** then proceeds to step **606** where a multi-layer interconnect (MLI) structure is formed above the transistor structure. The MLI structure may include conductive lines, conductive vertical interconnect accesses (vias), and/or interposing dielectric layers (e.g., interlayer dielectric (ILD) layers). The MLI structure may provide physical and electrical connection to the transistor (i.e., the FET), described above with reference to step **604**. The conductive lines may comprise copper, aluminum, tungsten, tantalum, titanium, nickel, cobalt, metal silicide, metal nitride, poly silicon, combinations thereof, and/or other materials possibly including one or more layers or linings. The interposing dielectric layers (e.g., ILD layers) may comprise silicon dioxide, fluorinated silicon glass (FGS), SILK (a product of Dow Chemical of Michigan), BLACK DIAMOND (a product of Applied Materials of Santa Clara, Calif.), and/or other suitable insulating materials. The MLI structure may be formed by suitable processes typical in CMOS fabrication such as CVD, PVD, ALD, plating, spin-on coating, and/or other processes.

(59) As shown in the example in FIG. **7**, an MLI structure **212** is disposed on the substrate **202** and above the FET **210** and the temperature sensor **211**. The MLI structure **212** includes a plurality of conductive lines **214** connected by conductive vias or plugs **216**. In one embodiment, the

conductive lines **214** include aluminum and/or copper. In one embodiment, the vias or plugs **216** include tungsten. In another embodiment, the vias or plugs **216** include copper. In one embodiment, the interposing dielectric layers **218** are disposed on the substrate **202** including interposing the conductive features of the MLI structure **212**. The interposing dielectric layers **218** may be ILD layers. In another embodiment, the dielectric layer **218** is a single ILD layer. In one embodiment, each of the interposing dielectric layer **218** includes silicon oxide. The MLI structure **212** may provide electrical connection to the gate and/or the source/drain of the FET **210**. As shown in the example in FIG. **7**, the MLI structure **212** is at the front side (F) while the substrate **202** is at the back side (B).

(60) Additionally, conductive line(s) in the first metal layer ("M1 layer") may be used as the heater **142** as shown in FIG. **1**A. In other words, conductive line(s) can be an embedded (electric-resistive) heater used to generate heat. In some embodiments, the heater may have multiple zones that are individually controllable, and/or is made of materials such as Al, Cu, TiAlN, though other material may also be employed. Alternatively, the heater maybe arranged under a semiconductor substrate and made of silicon or polysilicon. By using an embedded heater, temperature control and uniformity may be improved.

(61) The method **600** then proceeds to step **608** where a carrier substrate is attached to the front side (F). In other words, the carrier substrate is attached to the MLI structure. The carrier substrate may protect the front side (F) during subsequent steps. In one embodiment, the carrier substrate is bonded to the MLI structure. In another embodiment, the carrier substrate is bonded to a passivation layer formed on the MLI structure. The carrier substrate may be attached using fusion, diffusion, eutectic, and/or other suitable bonding methods. Exemplary compositions for the carrier substrate include silicon, glass, and quartz. It should be noted that other compositions are possible and within the scope of the present disclosure. As shown in the example in FIG. **8**, a carrier substrate **220** is attached to the MLI structure **212**. In some embodiments, the carrier substrate **220** may include functionalities such as, interconnect features, wafer bonding sites, defined cavities, and/or other suitable features.

(62) The method **600** then proceeds to step **610** where the wafer is flipped. As shown in FIG. **9**, the back side (B) is on the top. In other words, the bulk silicon layer **204** is on the top. The method **600** then proceeds to step **612** where the bulk silicon layer **204** is removed. The removal may be accomplished by mechanical or chemical means. For example, a mechanical means includes polishing or grinding, such as chemical mechanical polishing (CMP). A chemical means includes wet etch, such as HF/nitric/acetic acid (HNA) or tetramethylammonium hydroxide (TMAH) or dry etch including plasma and non-plasma etch. As shown in the example in FIG. **10**, the bulk silicon layer **204** in FIG. **9** is removed. The buried oxide layer **206** is on the top at the back side (B).

(63) The method **600** then proceeds to step **614** where the buried oxide layer is patterned to form an opening at the back side (B). A photoresist pattern is formed on the buried oxide layer. In some embodiments, the photoresist pattern protects some of the buried oxide layer from a subsequent non-plasma etch to expose the backside (B) of the biosensor system package. Specifically, the photoresist pattern protects some of the buried oxide layer from the subsequent non-plasma etch to expose the active region of the transistor structure formed at step **604**. The non-plasma etch may be a wet etch or a dry etch that does not involve plasma. In some embodiments, a two-step etch process may be employed to form the opening at the back side (B). The first etching step contains plasma and the second etching step is a non-plasma etch. As shown in the example in FIG. **11**, the non-plasma etch forms a trench **222** having a bottom exposing the channel region of the FET **210**. A non-plasma etch is used to avoid plasma-induced damage (PID) at the exposed surface of the channel region **219**. In a non-limiting example, the height of the trench **222** may range between 0.3 μm to 1 μm, while the width of the trench **222** may range between 0.5 μm to 200 μm (in some extreme cases). In some embodiments, the sidewall profile of the trench **222** is substantially straight. After the non-plasma etch, the photoresist pattern is removed. A PID-less photoresist

removal process such as stripping and ozone ashing may be used. Because the exposed surface of the trench **222** and the exposed surface of the channel region of the FET **210** are susceptible to plasma-induced damage (PID), some plasma ashing processes may not be used to remove the photoresist pattern.

(64) The method **600** then proceeds to step **616**. At step **616**, an interface layer is deposited. In one embodiment, the interface layer is a high-k material layer. The interface layer is compatible (e.g., friendly) for biomolecules or bio-entities binding. For example, the interface layer may include a capture reagent layer, which is a layer of capture reagent capable of binding a target analyte in the fluid samples. In some embodiments, the interface layer includes a plurality of layers. For instance, the interface layer may include a dielectric material (e.g., a high-k material), a conductive material, and/or other suitable material for holding a receptor. Exemplary interface materials include high-k dielectric films, metals, metal oxides, dielectrics, and/or other suitable materials. As a further example, exemplary interface layer materials include HfO.sub.2, Ta.sub.2O.sub.5, Pt, Au, W, Ti, Al, Cu, oxides of such metals, SiO.sub.2, Si.sub.3N.sub.4, Al.sub.2O.sub.3, TiO.sub.2, TiN, ZrO.sub.2, SnO, SnO.sub.2; and/or other suitable materials. The interface layer may be formed using CMOS processes such as, for example, physical vapor deposition (PVD) (sputtering), chemical vapor deposition (CVD), plasma-enhanced chemical vapor deposition (PECVD), atmospheric pressure chemical vapor deposition (APCVD), low-pressure CVD (LPCVD), high density plasma CVD (HDPCVD), or atomic layer CVD (ALCVD). A photoresist pattern is formed over the interface layer to protect a portion of the interface layer. The portion over the channel region of the FET is protected. Unprotected portions of the interface layer are removed in a subsequent etch process. The etch process may involve any known etch process including plasma etch, since the portion susceptible to PID is protected. The interface layer completely covers the channel region and may partially cover the source region and drain region. The partial coverage of the source and drain region may be adjusted based on the FET design and area requirements for the interface layer. In some embodiments, the interface layer may not be patterned and etched and remains over the respective surfaces of the FET.

(65) As shown in the example in FIG. **11**, an interface layer **224** (e.g., a high-k material layer) is formed on the exposed surface of the trench **222** and the exposed surface of the active region **219** of the FET **210**. Additionally, the interface layer **224** is deposited over the entire surface of the buried oxide layer **206**.

(66) Alternatively at step **618**, an interface layer is deposited while some bonding sites are exposed. The boding sites are used for bonding a microfluidic channel cap structure to the back side (B), which will be described in detail below at step **626**. It should be noted that whether bonding sites are required depends on specific bonding requirements. Similar to step **616**, the interface layer may be formed using CMOS processes such as, for example, PVD (sputtering), CVD, PECVD, APCVD, LPCVD, HDPCVD, or ALCVD. A photoresist pattern is formed over the interface layer to protect a portion of the interface layer, and the bonding sites are not protected. Unprotected portions of the interface layer are removed in a subsequent etch process. The etch process may involve any known etch process including plasma etch, since the portion susceptible to PID is protected. After etching and optionally adding a passivating or blocking agent, the photoresist is removed in a PID-free photoresist removal process.

(67) As shown in the example in FIG. **12**, the interface layer **224** (e.g., a high-k material layer) is formed on the exposed surface of the trench **222** and the exposed surface of the active region **219** of the FET **210**, while two bonding sites **226** are exposed. In other words, the buried oxide layer **206**, except for the two bonding sites **226**, are covered by the interface layer **224**. It should be noted that the shape of the bonding sites may vary depending on the shape of the microfluidic channel cap structure.

(68) The method **600** then proceeds to step **620**. At step **620**, the buried oxide layer, the semiconductor layer, and the first interposing dielectric layer are patterned and etched to form

opening(s) at the back side (B) to expose conductive line(s) at the first metal layer ("M1 layer"). A photoresist pattern is formed on the buried oxide layer and the interface layer deposited at step **616** or **618**. Similar to step **614**, the photoresist pattern protects the interface layer and some of the buried oxide layer from a subsequent etch to expose the backside (B) of the biosensor system package in some embodiments. As shown in the example in FIG. **13**, two openings **225***a* and **225***b* (collectively **225**) are formed at the back side (B). The number of openings **225** may vary as needed. In the example shown in FIG. **13**, the opening **225***a* is used for depositing a reference electrode while the opening **225***b* is used for subsequent wire bonding. In another example, there is only one opening **225** used for depositing a reference electrode. In other words, no opening **225** is formed for wire bonding. As shown in FIG. **13**, the openings **225***a* and **225***b* are formed in the buried oxide layer **206**, the semiconductor layer **208**, and the first interposing dielectric layer **218-1**, and have bottoms exposing the conductive lines **214***a* and **214***b*, respectively, at the M1 layer. In some embodiments, the sidewall profile of the trench **222** is substantially straight. After the etch process, the photoresist pattern is removed.

(69) The method **600** then proceeds to step **622**. At step **622**, a reference electrode is deposited in one of the opening(s). As a result, the reference electrode is connected to one conductive line exposed in the opening at step **620**. As mentioned above, the reference electrode may be made of one of the following materials: Ag/AgCl, Cu/CuSO.sub.4, AgCl, Au, and P. For Ag/AgCl, a chemical treatment may be required on the deposited and patterned Ag layer to create the AgCl. For Cu/CuSO.sub.4, a chemical treatment may be required on the deposited and patterned Cu layer to create the CuSO.sub.4. As shown in FIG. **14**, the reference electrode **227** is deposited in the opening **225***a* formed at step **620**. The electrode **227** is connected to the conductive line **214***a* exposed in the opening **225***a*.

(70) The method **600** then proceeds to step **624**. At step **624**, a cap structure is fabricated. FIG. **6**C is a flowchart diagram illustrating the step **624** of the method **600** of FIG. **6**B in accordance with some embodiments. The step **624** is a CMOS-compatible process flow. At step **652**, a cap structure substrate is provided. The cap structure substrate may be a silicon substrate, though other suitable materials may be employed. As shown in the example in FIG. **15**, a silicon substrate **230** is provided.

(71) At step **654**, the cap structure substrate is patterned and etched to predefine global cavity regions. The global cavity region corresponds to the microfluidic channel. A photoresist pattern is formed on the cap structure substrate. The photoresist pattern protects some of the cap structure substrate from a subsequent etch to predefine the global cavity region. After patterning the cap structure substrate, the global cavity regions are predefined by etching the cap structure substrate. The etching process may be a wet etch, such as HF/nitric/acetic acid (HNA) or tetramethylammonium hydroxide (TMAH) or dry etch including plasma and non-plasma etch. Afterwards, the photoresist is removed. As shown in the example in FIG. **16**, two global cavity regions **232** are predefined at the top surface of the cap structure substrate **230**, and the cap structure substrate **230** has been etched from 0.11 μm to 0.51 μm in this example.

(72) At step **656**, a hard mask is deposited on bonding areas of the cap structure substrate. In some embodiments, the bonding areas of the cap structure substrate correspond to the bonding sites on the buried oxide layer at step **618**. Specifically, the bonding areas of the cap structure substrate interface with the bonding sites on the buried oxide layer, and the cap structure is bonded to the buried oxide layer (or any appropriate intermediate bonding layer deposited and patterned on the buried oxide layer), which will be described in detail below at step **626**. The hard mask can protect the bonding areas from subsequent etching processes. In some embodiments, the hard mask may be formed of oxide. In some embodiments, the hard mask may be formed of poly silicon. The hard mask is formed using suitable processes such as CVD and/or the like. In a non-limiting example, the thickness of the hard mask ranges from 0.3 μm to 1 μm. As shown in the example in FIG. **17**, the hard masks **236** (e.g., oxide hard mask) are deposited on the bonding areas **234** of the cap

structure substrate **230**. The hard masks **236** may protect the bonding areas **234** from subsequent etching processes.

(73) At step **658**, certain regions of the global cavity regions are patterned and etched. A photoresist pattern is formed on the hard mask and portions of the global cavity regions. The photoresist pattern protects the hard mask and portions of the global cavity region from a subsequent etch. Subsequently, the cap structure substrate is etched. The etching process may be a wet etch, such as HF/nitric/acetic acid (HNA) or tetramethylammonium hydroxide (TMAH) or dry etch including plasma and non-plasma etch. Afterwards, the photoresist is removed. As shown in the example in FIG. **18**, the photoresist pattern **238** is on the hard mask **236** and portions of the global cavity regions **232**. The exposed portions of the global cavity region **232** are etched to form deep regions **239**. The photoresist pattern **238** is then removed, and the structure is as shown in the example in FIG. **19**. The entire global cavity regions **232**, including the deep regions **239**, are exposed, while the bonding areas **234** are covered by the hard masks **236**.

(74) At step **660**, the entire global cavity regions are blanket etched. Specifically, the entire global cavity regions, including the deep regions, are etched back evenly by a certain depth, to form the chambers of the cap structure. The chambers of the cap structure may be used as either fluid chambers (e.g., the fluid chamber **454** as shown in FIG. **4**A) or drug channels (e.g., the drug channel **455** as shown in FIG. **4**A). On the other hand, the bonding areas covered by the hard masks are protected during the blanket etch. The blanket etching process may be any suitable etching processes such as wet etch or dry etch including plasma and non-plasma etch. As shown in the example in FIG. **20**, the entire global cavity regions **232** of the cap structure substrate **230**, including the deep regions **239**, are etched by a predefined etch depth ED. The predefined etch depth ED corresponds to the desired height of the chambers **244** of the cap structure **228**.

(75) Optionally at step **662**, a high-k dielectric material layer is deposited on the global cavity regions and the hard masks. Step **662** is optional depending on applications. The high-k dielectric material layer may be formed using CMOS processes such as, for example, PVD (sputtering), CVD, PECVD, APCVD, LPCVD, HDPCVD, or ALCVD. In one non-limiting example, the high-k dielectric material layer has a thickness of 2 nm to 3 nm. As shown in the example in FIG. **21**, the high-k dielectric material layer **242** is deposited on the global cavity regions **232** (thus the chambers **244**) and the hard masks **236**. The high-k dielectric material layer **242** covers the bottom and sidewalls of the chambers **244**, the bottom and sidewalls of the deep regions **239**, and the hard mask **236**.

(76) Optionally at step **664**, the interface layer on the top of the hard mask is removed. In one embodiment, a photoresist spray coater may be sprayed, by a spray coating process, to cover the global cavity region. The photoresist spray coater protects the high-k dielectric material layer when the high-k dielectric material layer on the hard mask is removed. The interface layer on the top of the hard mask is removed by suitable processes such as plasma etching. In an example plasma etching process, a mixture of gasses comprising oxygen, a fluorine-containing material and an inert gas is provided, and a high-speed stream of glow discharge (plasma) of the mixture of gasses is shot (in pulses) at the high-k dielectric material layer. The spray coating process is used to coat photoresist over a region with deep features. In the spray coating process, fine droplets of photoresist are deposited onto the structure. The angle at which the photoresist droplets are sprayed permits the photoresist to make its way into the deep trenches and sidewalls.

(77) At step **666**, the hard mask is removed. The hard mask is removed by any suitable processes. In one embodiment, the hard mask is removed by wet etch. In some embodiments, the wet etch is a fluorine containing etch, such as dilute hydrofluoric acid (HF). In some embodiments, the wet etch is an ammonia hydroxide/hydrogen peroxide etch. The wet etch removes the hard mask without substantially removing or harming the high-k dielectric material layer. As shown in the example in FIG. **22**, the optional high-k dielectric material layer **242** on the hard mask **236** and the hard mask **236** are removed at step **664** and step **666**, respectively. The bonding areas **234** are exposed. The

bottom and sidewalls of the global cavity regions **232** and deep regions **239** are covered with the high-k dielectric material layer **242**. As such, the cap structure **228** is fabricated.

(78) Referring back to FIG. **6**B, the method **600** proceeds to step **626** where the cap structure is bonded to the backside of the biosensor system package. Specifically, the cap structure is bonded to the buried oxide layer. In some embodiments, the bonding sites of the buried oxide layer interface with the bonding areas of the cap structure substrate. In other embodiments, an intermediate bonding layer, that is deposited and patterned on the buried oxide layer, interfaces with the bonding areas of the cap structure substrate. The cap structure may be bonded to the backside of the biosensor system package using fusion bond, eutectic bond, anodic bond, and/or other suitable bonding methods. Fusion bonding utilizes temperature and pressure to join semiconductor materials. In one non-limiting example, in a room-temperature fusion bonding process, a bonder device forces the cap structure and the backside of the biosensor system package together. This is followed by an annealing process to increase the bond strength. In a eutectic bond, an intermediate metal layer that can produce a eutectic system is utilized. The eutectic metals are alloys that transform directly from solid to liquid state, or vice versa from liquid to solid state, at a specific composition and temperature without passing a two-phase equilibrium. As the eutectic temperature can be much lower than the melting temperature of the two or more pure elements, the eutectic bond may have the benefits of low processing temperatures, low resultant stress induced in final assembly, high bonding strength, large fabrication yield and a good reliability. In an anodic bond, glasses are sealed to either silicon or metal without introducing an intermediate layer.

(79) As shown in the example in FIG. **23**, the cap structure **228** is bonded to the backside (B) of the biosensor system package **200**. Specifically, the cap structure **228** is bonded to the buried oxide layer **206**. The bonding sites **226** of the buried oxide layer **206** interface with the boding areas **234** of the cap structure substrate **230**. In the example shown in FIG. **23**, the conductive line **214***b*, as mentioned above with reference to FIG. **14**, may be used for wire bonding later.

(80) Alternatively, as shown in the example in FIG. **24**, the cap structure **228** is bonded to the backside (B) of the biosensor system package **200**. Different from the example shown in FIG. **23**, a through-substrate via (TSV) structure rather than a wire bonding is used for connecting the biosensor system package **200** with a separate chip later. The TSV structure will be described in detail below.

(81) For embodiments with TSV structures as mentioned above, the method **600** then optionally proceeds to step **628** where the wafer is flipped. Afterwards, the carrier substrate which is at the front side (F) of the biosensor system package is now on the top. The method **600** then optionally proceeds to step **630** where the carrier substrate is thinned. In one example, the carrier substrate is thinned by grinding. The grinding process may include rotating a disk holding the biosensor system package lined with an appropriate grinding material. It should be noted that other processes such as CMP may also be employed. As shown in FIG. **25**, the carrier substrate **220** has been thinned. The thickness of the carrier substrate is selected in accordance with step **632** which will be discussed below.

(82) The method **600** then optionally proceeds to step **632** where a through-substrate via (TSV) structure is created through the carrier substrate and connected to the MLI structure. The TSV is used to provide electrical connections and for heat dissipation for the biosensor system package **200**. As shown in the example in FIG. **26**, a TSV structure **246** is created through the carrier substrate **220** and connected to the MLI structure **212**. Although only one TSV structure **246** is shown in the example in FIG. **26**, more than one TSV structure may be formed to pass through the carrier substrate **220**. The TSV structure **246** includes a liner **246***a*, a diffusion barrier layer **246***b*, and a conductive material **246***c*. In one embodiment, the TSV structure **246** is formed by the following operations. Firstly, a TSV opening is formed extending to a conductive line **214** of the MLI structure **212** by one or more etching processes. After the TSV opening is formed, the liner **246***a* is formed on sidewalls of the TSV opening to act as an isolation layer, such that the

conductive material **246***c* of the TSV structure **246** and the carrier substrate **220** do not directly contact with each other. Afterwards, the diffusion barrier layer **246***b* is conformally formed on the liner **246***a* and on the bottom of the TSV opening. The diffusion barrier layer **246***b* is used to prevent the conductive material **246***c*, which will be formed later, from migrating to undesired regions. After the diffusion barrier layer **246***b* is formed, the conductive material **246***c* is used to fill into the TSV opening. Afterwards, excess liner **246***a*, diffusion barrier layer **246***b*, and conductive material **246***c*, which are on the outside of the TSV opening, are removed by a planarization process, such as a chemical mechanical polishing (CMP) process, although any suitable removal process may be used.

(83) The liner **246***a* is made of an insulating material, such as oxides or nitrides. The liner **246***a* may be formed by using a PECVD process or other applicable processes. The liner **246***a* may be a single layer or multi-layers. In some non-limiting examples, the liner **246***a* has a thickness in a range from about 100 Å to about 5000 Å. The diffusion barrier layer **246***b* is made of Ta, TaN, Ti, TiN or CoW. In some embodiments, the diffusion barrier layer **246***b* is formed by a PVD process. In some embodiments, the diffusion barrier layer **246***b* is formed by plating. In some embodiments, the conductive material **246***c* is made of copper, copper alloy, aluminum, aluminum alloys, or combinations thereof. Alternatively, other applicable materials may be used. The width, depth, and aspect ratio of the TSV structure **246** may be selected under different circumstances. Since the carrier substrate **220** is thinned at step **630**, the TSV structure **246** has a relatively small aspect ratio. As such, the void problems and the extrusion or diffusion problems resulting from a high aspect ratio of the TSV structure are resolved or greatly reduced. In addition, the overall package height of the biosensor system package **200** is reduced to meet advanced packaging requirements. As such, the biosensor system package **200** may achieve a small form factor.

(84) The method **600** then proceeds to optional step **634** where the wafer is flipped for the case where a TSV structure was created. Afterwards, the cap structure is on the top, whereas the TSV structure is at the bottom. The method **600** then proceeds to step **636** where microneedle(s) are created at the back side (B) of the biosensor system package. FIG. **6**D is a flowchart diagram illustrating the step **636** of the method **600** of FIG. **6**B in accordance with some embodiments. FIG. **6**E is another flowchart diagram illustrating the step **636** of the method **600** of FIG. **6**B in accordance with some embodiments. The step **636** is a CMOS-compatible process flow.

(85) Referring to FIG. **6**D, the method **636** starts optionally at step **672** where the cap structure substrate is thinned. Step **672** is optional and depends on microneedle height(s). The cap structure substrate is thinned by any suitable processes such as grinding and CMP. In the example shown in FIG. **27**, the cap structure substrate **230** is thinned by grinding the top part of the cap structure **228**.

(86) The method **636** then proceeds to step **674**. At step **674**, hard mask(s) are deposited at microneedle position(s). For simplicity, the situation of one microneedle is described below. The hard mask at the microneedle position can protect the microneedle position from subsequent etching processes. In some embodiments, the hard mask may be formed of oxide. In some embodiments, the hard mask may be formed of polysilicon. The hard mask is formed using suitable processes such as CVD and/or the like. As shown in the example in FIG. **28**, the hard masks **237** (e.g., oxide hard mask) are deposited on the cap structure substrate **230** at the microneedle position. The hard masks **237** may protect the microneedle position from subsequent etching processes.

(87) In one embodiment, the method **636** then proceeds to step **676** and step **678**. At step **676**, the cap structure substrate is etched using isotropic etching and anisotropic etching in an alternate manner (i.e., multiplexing). In other words, the etching process is switching between isotropic etching and anisotropic etching. Isotropic etching is an etching process that removes a material in multiple directions, and therefore any horizontal components of the etch direction may result in undercutting of patterned areas. Anisotropic etching, on the other hand, is an etching process that aims to preferentially remove a material in specific directions to obtain intricate and often flat shapes. In one embodiment, the anisotropic etching used here is anisotropic deep reactive ion

etching (DRIE) while the isotropic etching used here is sulfur hexafluoride (SF.sub.6) plasma etching. Specifically, the Bosch process (i.e., pulsed or time-multiplexed etching) is used. In some embodiments, after the etching process, the apex of the microneedle is sharpened by a final wet oxidation following by a consecutive oxide strip. The oxidation is made with the hard mask still being on the microneedle, which may result in a sharp apex. In the example shown in FIG. **29**, after step **676**, the deep regions **239** are opened, and the chambers **244** can therefore be connected outside. A microneedle **241** is formed at the microneedle position.

(88) The method **636** then proceeds to step **678**, where the hard mask(s) are removed. The hard mask is removed by any suitable processes. In one embodiment, the hard mask is removed by wet etch. In some embodiments, the wet etch is a fluorine containing etch, such as dilute hydrofluoric acid (HF). In some embodiments, the wet etch is an ammonia hydroxide/hydrogen peroxide etch. As shown in the example in FIG. **30**, the hard mask **237** shown in FIG. **29** is removed at step **678**. The apex of the microneedle **241** is therefore exposed. As such, the microneedle **241** is fabricated.

(89) Alternatively in another embodiment, the method **636** may proceed to steps **680**, **682**, and **684**. At step **680**, the cap structure substrate is etched using anisotropic etching by a predetermined depth. The predetermined depth is approximate to a height of a microneedle. In one embodiment, the anisotropic etching used here is anisotropic deep reactive ion etching (DRIE). At step **682**, the hard mask is removed. The hard mask is removed by any suitable processes. In one embodiment, the hard mask is removed by wet etch. In some embodiments, the wet etch is a fluorine containing etch, such as dilute hydrofluoric acid (HF). In some embodiments, the wet etch is an ammonia hydroxide/hydrogen peroxide etch. Then at step **684**, the cap structure substrate is etched using isotropic etching to form apex(es) of the microneedle(s). In some embodiments, the isotropic etching used here is sulfur hexafluoride (SF.sub.6) plasma etching. The horizontal removal of the cap structure substrate **230** help form apex(es) of the microneedle(s).

(90) In the example shown in FIG. **31**, after step **680**, the deep regions **239**, except the deep region **239** corresponding to the microneedle position, are opened, and the chambers **244** can therefore be connected outside. In the example shown in FIG. **32**, after step **682** and step **684**, the hard mask **237** shown in FIG. **31** is removed at step **682**. The top of the microneedle **241** is therefore exposed. The top of the microneedle **241** is further sharpened to form the apex after step **684**. As such, the microneedle **241** is fabricated.

(91) Referring to FIG. **6**E, the method **636** shown in FIG. **6**E applies to relatively long microneedles. Relatively long microneedles may be desirable in certain applications. As shown in FIG. **6**E, the method **636** starts at step **691** where the cap structure substrate is thinned to open the deep regions. The cap structure substrate is thinned by any suitable processes such as grinding and CMP. In the example shown in FIG. **33**, the cap structure substrate **230** is thinned by grinding the top part of the cap structure **228**. After step **691**, the deep regions **239** are opened, and the chambers **244** can therefore be connected outside.

(92) The method **636** then proceeds to step **692** where a second cap structure is fabricated and bonded to the cap structure. In the example shown in FIG. **34**, a second cap structure **228**′ is fabricated. The fabrication process of the second cap structure **228**′ is similar to method **624** as shown in FIG. **6**C, and therefore is not described in detail. The second cap structure **228**′ has a deep region **239**′ formed in a cap structure substrate **230**′. A high-k dielectric material **242**′ covers the top surface and sidewalls of the deep region **239**′. In the example shown in FIG. **35**, the second cap structure **228**′ is bonded to the cap structure **228**. As mentioned above, the second cap structure **228**′ may be bonded to the cap structure **228** using fusion bond, eutectic bond, anodic bond, and/or other suitable bonding methods. Alignment marks may be employed during the bonding process for alignment. As shown in FIG. **35**, the deep region **239** and the deep region **239**′ are aligned and form a relatively long needle.

(93) The method **636** then proceeds to step **693** where hard mask(s) are deposited at microneedle position(s). In one embodiment, the method **636** proceeds to step **694** and step **695**. Alternatively in

another embodiment, the method **636** may proceed to step **696**, step **697**, and step **698**. Steps **693**-**698** are similar to steps **674**-**684** of FIG. **6**D, respectively, therefore are not described in detail again. After implementing the method **636**, a relatively long microneedle is fabricated.

(94) Referring back to FIG. **6**B, after microneedle(s) are created at the back side of the biosensor system package at step **636**, the method **600** then proceeds to step **638**. At step **638**, the biosensor system package **200** is diced. In the example shown in FIG. **36**, the biosensor system package **200** is diced by a dicing tool or saw, at the dashed lines shown in FIG. **36**, to be separate from other neighboring components. Alignment marks may be employed in the dicing process.

(95) The method **600** then proceeds to step **640** where a separate chip is connected to the biosensor system package through either wire bonding or the TSV structure. The separate chip may be any chips that function as a portion of the biosensor system. In one embodiment, the separate chip is a RAM chip. In one embodiment, the separate chip is a data processing chip. In one embodiment, the separate chip is a RAM and data processing chip.

(96) As shown in FIG. **37**, the biosensor system package **200** is connected to a separate chip **250** through wire bonding. Wire bonding is a method of making interconnections and is cost-effective and flexible. A metal (e.g., Al, Cu, Ag, or Au) wire **251** connects the separate chip **250** and the conductive line **214***b* in this example. As such, the biosensor system package **200** is fabricated using the method **600**.

(97) Alternatively as shown in FIG. **38**, the biosensor system package **200** is connected to the separate chip **250** through the TSV structure formed at step **632** above. The separate chip may be bonded to the TSV structure by any suitable processes. Compared with the wire bonding mentioned above, the connection through the TSV structure is a more compact solution and has less resistance, capacitance, and inductance, which can achieve faster chip-to-chip data transmission with less noise, distortion, and power consumption. In one embodiment, the separate chip is bonded to the TSV structure by solder bump bonding. Solder Bumps are the small spheres of solder (solder balls) that are bonded to contact areas or pads of semiconductor devices. In one example, the solder bump bonding includes the following operations: placing solder bump(s) on the TSV structures; flipping the wafer; aligning the solder bump(s) with contact pad(s) of the separate chip; and reflowing the solder bump(s) in a furnace to establish the bonding between the TSV structure and the separate chip. In other embodiments, the separate chip may be bonded to the TSV structure by wire bonding. As shown in the example in FIG. **38**, the separate chip **250** is bonded to the TSV structure **246** by solder bumps bonding (using a solder bump **248**). As such, the biosensor system package **200** is fabricated using the method **600**.

(98) Embodiments in accordance with the disclosure include a biosensor system package. The biosensor system package includes: a transistor structure in a semiconductor layer having a front side and a back side, the transistor structure comprising a channel region; a buried oxide (BOX) layer on the back side of the semiconductor layer, wherein the buried oxide layer has an opening on the back side of the channel region, and an interface layer covers the back side over the channel region; a multi-layer interconnect (MLI) structure on the front side of the semiconductor layer, the transistor structure being electrically connected to the MLI structure; and a cap structure attached to the buried oxide layer, the cap structure comprising a microneedle.

(99) Further embodiments include a biosensor system package. The biosensor system package includes: a biosensor structure in a semiconductor layer having a front side and a back side, the biosensor structure comprising a channel region and an interface layer covering the back side over the channel region; a buried oxide (BOX) layer on the back side of the semiconductor layer, wherein the buried oxide layer has an opening on the back side of the channel region, and the interface layer is exposed in the opening; a multi-layer interconnect (MLI) structure on the front side of the semiconductor layer, the biosensor structure being electrically connected to the MLI structure; a reference electrode connected to the MLI structure and configured to provide a reference potential; and a cap structure attached to the buried oxide layer, the cap structure

comprising a microneedle.
(100) Further embodiments include a method of fabricating a biosensor system package. The method includes: providing a substrate, the substrate comprising a semiconductor layer having a front side and a back side, a buried oxide (BOX) layer at the back side, and a bulk silicon layer at the back side; forming a transistor structure on the substrate, wherein a channel region of the transistor structure is in the semiconductor layer; forming a multi-layer interconnect (MLI) structure on the front side of the semiconductor layer, wherein the MLI structure is electrically connected to the transistor structure; attaching a carrier substrate to the MLI structure; removing the bulk silicon layer; etching the buried oxide layer to form an opening at the back side over the channel region; depositing an interface layer on the back side over the channel region; fabricating a cap structure using a complementary metal-oxide-semiconductor (CMOS) compatible process flow; bonding the cap structure to the BOX layer; and creating a microneedle on the cap structure.
(101) The foregoing outlines features of several embodiments so that those skilled in the art may better understand the aspects of the present disclosure. Those skilled in the art should appreciate that they may readily use the present disclosure as a basis for designing or modifying other processes and structures for carrying out the same purposes and/or achieving the same advantages of the embodiments introduced herein. Those skilled in the art should also realize that such equivalent constructions do not depart from the spirit and scope of the present disclosure, and that they may make various changes, substitutions, and alterations herein without departing from the spirit and scope of the present disclosure.

Claims

1. A biosensor system package comprising: a transistor structure in a semiconductor layer having a front side and a back side, the transistor structure comprising a channel region; a buried oxide (BOX) layer on the back side of the semiconductor layer, wherein the buried oxide layer has an opening over the channel region, and an interface layer covers the channel region; a multi-layer interconnect (MLI) structure on the front side of the semiconductor layer, the transistor structure being electrically connected to the MLI structure; a carrier substrate on the MLI structure; a through substrate via (TSV) structure extending though the carrier substrate and configured to provide an electrical connection between the MLI structure and a separate die; and a cap structure attached to the buried oxide layer, the cap structure comprising a silicon substrate attached to the buried oxide layer and a dielectric layer on the silicon substrate, the silicon substrate and the dielectric layer define a wall of a fluid chamber that has the dielectric layer lining at least part of the fluid chamber and the silicon substrate and the dielectric layer define a microneedle connected to the wall of the fluid chamber and that extends away from the wall of the fluid chamber, wherein the dielectric layer lines a microneedle channel of the microneedle that extends from the fluid chamber, through the wall of the fluid chamber and through the microneedle.
2. The biosensor system package of claim 1, wherein the TSV structure comprises: a conductive material; a liner isolating the conductive material from the carrier substrate; and a diffusion barrier layer between the conductive material and the liner.
3. The biosensor system package of claim 1, wherein the separate die is electrically connected to the TSV structure through a solder bump.
4. The biosensor system package of claim 1, wherein the fluid chamber is configured to accommodate fluid samples to be tested, and wherein the microneedle channel is fluidically coupled to the fluid chamber for inflow and outflow of the fluid samples.
5. The biosensor system package of claim 4, wherein the dielectric layer comprises: a high-k dielectric material layer covering a bottom and sidewalls of the fluid chamber.
6. The biosensor system package of claim 4, wherein the silicon substrate has bonding areas interfacing with bonding sites of the buried oxide layer.

7. The biosensor system package of claim 4, wherein the interface layer comprises a layer of capture reagent capable of binding a target analyte in the fluid samples.
8. The biosensor system package of claim 1, further comprising: a reference electrode connected to the MLI structure and configured to provide a reference potential.
9. The biosensor system package of claim 1, wherein the interface layer is a high-k material layer.
10. A biosensor system package comprising: a transistor structure in a semiconductor layer having a front side and a back side, the transistor structure comprising a channel region; a buried oxide (BOX) layer on the back side of the semiconductor layer, wherein the buried oxide layer has an opening over the channel region, and an interface layer covers the channel region; a multi-layer interconnect (MLI) structure on the front side of the semiconductor layer, the transistor structure being electrically connected to the MLI structure; a carrier substrate on the MLI structure; a through substrate via (TSV) structure extending though the carrier substrate and configured to provide an electrical connection between the MLI structure and a separate die; and a cap structure attached to the buried oxide layer, the cap structure comprising a silicon substrate attached to the buried oxide layer and a dielectric layer on the silicon substrate, the silicon substrate and the dielectric layer define a wall of a fluid chamber that has the dielectric layer lining at least part of the fluid chamber, the dielectric layer includes a high-k dielectric material layer covering a bottom and sidewalls of the fluid chamber, and the silicon substrate and the dielectric layer define a microneedle connected to the wall of the fluid chamber and that extends away from the wall of the fluid chamber, wherein the dielectric layer lines a microneedle channel of the microneedle that extends from the fluid chamber, through the wall of the fluid chamber and through the microneedle.
11. The biosensor system package of claim 10, wherein the TSV structure comprises: a conductive material; a liner isolating the conductive material from the carrier substrate; and a diffusion barrier layer between the conductive material and the liner.
12. The biosensor system package of claim 10, wherein the separate die is electrically connected to the TSV structure through a solder bump.
13. The biosensor system package of claim 10, wherein the silicon substrate has bonding areas interfacing with bonding sites of the buried oxide layer.
14. The biosensor system package of claim 10, wherein the interface layer comprises a layer of capture reagent capable of binding a target analyte in fluid samples.
15. The biosensor system package of claim 10, wherein the interface layer is a high-k material layer.
16. A biosensor system package comprising: a transistor structure in a semiconductor layer having a front side and a back side, the transistor structure comprising a channel region; a buried oxide (BOX) layer on the back side of the semiconductor layer, wherein the buried oxide layer has an opening over the channel region, and an interface layer covers the channel region; a multi-layer interconnect (MLI) structure on the front side of the semiconductor layer, the transistor structure being electrically connected to the MLI structure; a carrier substrate on the MLI structure; a through substrate via (TSV) structure extending though the carrier substrate and configured to provide an electrical connection between the MLI structure and a separate die; and a cap structure attached to the buried oxide layer, the cap structure comprising a silicon substrate attached to the buried oxide layer and a dielectric layer on the silicon substrate that has bonding areas interfacing with bonding sites of the buried oxide layer, the silicon substrate and the dielectric layer define a wall of a fluid chamber that has the dielectric layer lining at least part of the fluid chamber and the silicon substrate and the dielectric layer define a microneedle connected to the wall of the fluid chamber and that extends away from the wall of the fluid chamber, wherein the dielectric layer lines a microneedle channel of the microneedle that extends from the fluid chamber, through the wall of the fluid chamber and through the microneedle.
17. The biosensor system package of claim 16, wherein the TSV structure comprises: a conductive material; a liner isolating the conductive material from the carrier substrate; and a diffusion barrier

layer between the conductive material and the liner.
18. The biosensor system package of claim 16, wherein the separate die is electrically connected to the TSV structure through a solder bump.
19. The biosensor system package of claim 16, wherein the interface layer comprises a layer of capture reagent capable of binding a target analyte in fluid samples.
20. The biosensor system package of claim 16, wherein the interface layer is a high-k material layer.