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[Continued on next page]

(54) Title: IMPLANTABLE BIOMEDICAL DEVICES ON BIORESORBABLE SUBSTRATES

(57) Abstract: Provided herein are implantable biomedical devices and methods of administering implantable biomedical devices, making implantable biomedical devices, and using implantable biomedical devices to actuate a target tissue or sense a parameter associated with the target tissue in a biological environment.

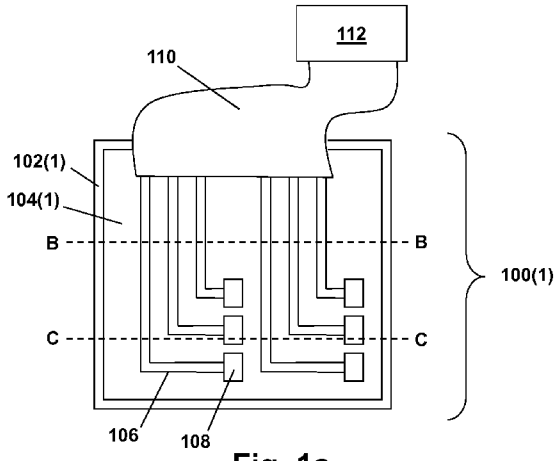


Fig. 1a

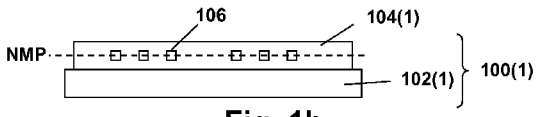


Fig. 1b

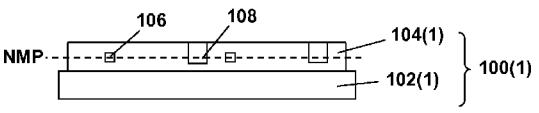


Fig. 1c

Figure 1

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IMPLANTABLE BIOMEDICAL DEVICES ON BIORESORBABLE SUBSTRATES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 61/314,739, filed March 17, 2010, which is hereby incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with United States governmental support under Award Nos. DE-FG02-07ER46471 and DE-FG02-91ER45439 awarded by The U.S. Department of Energy, and by Contract No. W911 NF-07-1-0618 awarded by the U.S. Army Research Laboratory. The U.S. government has certain rights in the invention.

BACKGROUND

[0003] This invention is in the field of biomedical devices, and relates generally to implantable devices for sensing parameters associated with a target tissue and/or for actuating a target tissue. Methods for making, implanting, and using the implantable biomedical devices are provided.

[0004] Implantable biomedical devices have potential for a range of important clinical applications, such as treatment and/or monitoring of neurological disorders (e.g., epilepsy and Parkinson's disease), heart disorders (e.g., arrhythmias), vascular disorders, muscular and/or nerve disorders (e.g., as brain-computer interfaces for controlling prosthetics). Efficacious use of implantable biomedical devices, however, is dependent in part upon design strategies that provide compatibility between the hard, planar surfaces of conventional integrated circuits and medical devices and the soft, curvilinear tissues of biological systems. Overcoming this physical mismatch is important because differences in form traditionally lead to low fidelity coupling at the biotic/abiotic interface and limited long-term tissue health in connection with some conventional implantable devices.

[0005] Attempts to improve device-tissue coupling have in some cases sacrificed electronic performance by moving away from conventional silicon-based electronic

components to amorphous silicon, organic or hybrid organic-inorganic semiconductors, which exhibit electronic properties, such as field effect mobilities, on/off ratios, etc., significantly inferior to corresponding single crystalline silicon-based devices. While such amorphous silicon and organic-based materials may be electronically inferior to singe crystalline silicon, they do have certain properties useful for biomedical applications, such as flexibility, chemically biocompatibility and, in some cases, biodegradability.

[0006] Recently, a number of patents and publications have disclosed implantable, biodegradable devices. For example, International Patent Application Publication WO 2008/085904 discloses biodegradable electronic devices that may include a biodegradable semiconducting material and a biodegradable substrate. International Patent Application Publication WO 2008/108838 discloses biodegradable devices for delivering fluids and/or biological material to tissue. International Patent Application Publication WO 2008/127402 discloses biodegradable sensors containing embedded biological materials. International Patent Application Publication WO 2008/103464 discloses medical devices having nanostructured surfaces, which are optionally coated with a biodegradable polymer. Similarly, International Patent Application Publication WO 99/45860 discloses devices having biocompatible, and optionally resorbable, substrates with projections that, depending on their spacing, either promote or discourage cell adhesion.

[0007] Other patents and publications have disclosed implantable electronic devices. For example, U.S. Patent No. 5,403,700 discloses devices having polyimide substrates supporting patterned metal conductors. U.S. Patent No. 7,190,051 discloses hermetically packaged and implantable electronics fabricated using silicon-on-insulator technology. International Patent Application Publications WO 2009/111641 and WO 2009/114689 disclose stretchable and flexible electronic devices and sensor arrays.

SUMMARY OF THE INVENTION

[0008] The invention provides devices and methods for implantable systems for biomedical applications, including *in vivo* sensing and/or actuating of tissue in a range of biological environments. In some embodiments, for example, implantable devices of the invention combine high performance single crystalline inorganic electronic materials and/or thin electrode arrays with bioresorbable substrates capable of at least partially

resorbing upon contact with a target biological tissue. Incorporation of nanostructured single crystalline inorganic electronic materials and/or thin electrode arrays in some embodiments provides biocompatibility with a range of biological environments and provides mechanical properties (e.g., bending stiffness, Young's modulus, radius of curvature, etc.) and device attributes (e.g., flexibility, stretchability, etc.) useful for establishing conformal contact between the device and a target biological tissue. Incorporation of a bioresorbable substrate having a controllable and/or selectable resorption rate in some embodiments provides a biocompatible means of effectively deploying and interfacing the implantable device with a biological tissue of interest. In some embodiments, for example, at least partial resorption of the resorbable substrate establishes an interface providing for physical contact, electronic contact, thermal contact and/or optical communication between the device and a target biological tissue. In some embodiments, for example, devices of the present invention incorporate a highly biocompatible silk substrate providing useful and controllable resorption rates when provided in contact with a broad class of target tissues.

[0009] The invention enables a versatile tissue sensing and actuation platform supporting a class of implantable biomedical systems, materials and methods suitable for a broad range of biomedical applications, including sensing, electrochemical actuation, drug delivery and the treatment of disease. The combination of nanostructured single crystalline inorganic electronic materials or thin electrode arrays and bioresorbable substrates provides implantable systems that suppress, or entirely avoid, undesirable inflammation and/or immune responses upon implantation. Embodiments combining nanostructured single crystalline silicon or thin electrode arrays and silk resorbable substrates, and optionally a barrier layer having a mesh structure, provide implantable systems compatible with a broad class of tissue types, such as heart tissue, brain tissue, muscle tissue, nerve tissue, epithelial tissue or vascular tissue. In addition, the combination of nanostructured single crystalline inorganic electronic materials or thin electrode arrays and bioresorbable substrates provide implantable systems supporting a wide range of advanced device functionalities, including optical, electronic, electrochemical and chemical sensing and/or actuation.

[0010] Provided herein are implantable biomedical devices and methods of making and using implantable biomedical devices. For example, devices of the invention are useful for *in vivo* sensing of a parameter associated with a target tissue and/or biological

environment, such as a chemical composition (e.g., pH, ionic strength, presence or concentration of a biomarker, protein, carbohydrate, etc.), an electrochemical parameter (e.g., current or voltage), temperature, and/or an optical parameter (e.g., absorption, scattering, etc.). For example, devices of the invention are useful for *in vivo* actuation of a target tissue in a biological environment such as electrochemical actuation, drug delivery, optical actuation etc. Also disclosed are methods of making an implantable biomedical device and methods of administering an implantable biomedical device onto a target tissue in a biological environment. When the implantable biomedical device is administered onto target tissue, a bioresorbable substrate of the implantable biomedical device at least partially resorbs into surrounding tissue of the biological environment, thereby allowing conformational changes to establish conformal contact and/or electrical contact and/or optical contact between the implantable biomedical device and the target tissue.

[0011] An implantable device of this aspect comprises a bioresorbable substrate; an electronic device comprising a plurality of inorganic semiconductor components or electrodes of an electrode array supported, directly or indirectly, by the bioresorbable substrate, where at least one of the inorganic semiconductor components has at least one physical dimension less than or equal to 100 microns, and a thin (e.g. thickness less than or equal to 100 microns) barrier layer having a mesh structure encapsulating at least a portion of the inorganic semiconductor components or electrodes of an electrode array, optionally entirely encapsulating the inorganic semiconductor components or electrodes of an electrode array. Optionally, the implantable device further comprises one or more additional substrate layers, such as one or more additional barrier layer or biocompatible layers, provided between the bioresorbable substrate and the inorganic semiconductor components to further provide encapsulation and/or selective electrical and/or chemical isolation of at least some of the inorganic semiconductor components.

[0012] In an embodiment, for example, provided is an implantable biomedical device for actuating a target tissue or sensing a parameter associated with the target tissue in a biological environment, the device comprising: (1) a bioresorbable substrate; (2) an electronic device comprising a plurality of inorganic semiconductor components supported by the bioresorbable substrate, wherein at least one of the inorganic semiconductor components has at least one physical dimension less than or equal to

100 microns; and (3) a barrier layer encapsulating at least a portion of the inorganic semiconductor components; wherein upon contact with the biological environment the bioresorbable substrate is at least partially resorbed, thereby establishing conformal contact between the implantable biomedical device and the target tissue in the biological environment. The implantable device of an aspect further comprises a biocompatible layer provided on the bioresorbable substrate, for example, provided between the bioresorbable substrate and at least a portion of the electronic device or components thereof. In an embodiment, the barrier layer and/or the biocompatible layer has mesh structure supporting and/or in physical contact with at least a portion of the inorganic semiconductor components of the device. In some embodiments, the electronic device is supported by, and in physical contact with, the bioresorbable substrate. In some embodiments, the electronic device is encapsulated by, and in physical contact with, the biocompatible layer and/or the barrier layer. In an embodiment, all of the inorganic semiconductor components have at least one physical dimension less than or equal to 100 microns.

[0013] In some embodiments, for example, the barrier layer, and optionally the biocompatible layer, function to encapsulate portions of, or all of, the electronic device, thereby preventing current leakage to the local biological environment and/or electrical shorting of the device. In an embodiment, the barrier layer and/or biocompatible layer encapsulates at least 50% of the inorganic semiconductor components of the device, optionally at least 90% of the inorganic semiconductor components of the device, and optionally all of the inorganic semiconductor components of the device. Optionally, the implantable device further comprises one or more electrodes in electrical contact with at least a portion of the semiconductor components, for example electrodes comprising a biocompatible or bioresorbable metal and/or electrodes at least partially, and optionally entirely, encapsulated by the barrier layer, bioresorbable substrate and/or the biocompatible layer.

[0014] In an embodiment, for example, provided is an implantable biomedical device for actuating a target tissue or sensing a parameter associated with the target tissue in a biological environment, the device comprising: an electrode array comprising a plurality of individually addressable metal electrodes, wherein each metal electrode has at least one physical dimension less than or equal to 100 microns; a barrier layer having a mesh structure, wherein the barrier layer at least partially supports the electrode array; and a

bioresorbable substrate supporting the electrode array, the barrier layer or both of the electrode array and the barrier layer; wherein upon contact with the biological environment the bioresorbable substrate is at least partially resorbed, thereby establishing conformal contact between the electrode array and the target tissue in the biological environment. In an embodiment, at least a portion, and optionally all of, the electrodes of the electrode array are physically separated from each other. In an embodiment, the barrier layer is in physical contact with at least a portion of the electrode array, and optionally in physical contact with each of the electrodes of the array. In an embodiment, the bioresorbable substrate is in physical contact with at least a portion of the electrode array and/or in physical contact with at least a portion of the barrier layer. In an embodiment, each of the electrodes of the array is in electrical contact with at least one electronic interconnect, optionally configured for receiving and/or transmitting electronic signals to/from the individually addressable electrodes of the array.

[0015] Devices of this aspect are useful generally for in vivo biomedical applications including sensing, actuating, imaging and/or delivery of therapeutic agents to a local biological environment. In an embodiment, for example, devices of the invention are useful for making electrophysiology measurements of a target tissue in a biological environment or for electrophysically actuating a target tissue in a biological environment, where the biological environment may be an *in-vivo* biological environment, and where the target tissue may be selected from, but not limited to, heart tissue, brain tissue, muscle tissue, nerve tissue, epithelial tissue and vascular tissue.

[0016] Resorption of the bioresorbable substrate is useful for deploying, or otherwise positioning, manipulating and/or interfacing, the electronic device (e.g., a surface, a portion and/or component thereof) in a given biological environment. In some embodiments, for example, the electronic device is brought into conformal contact with a target tissue by a process involving resorption of the resorbable substrate, for example, wherein the resorption process brings the electronic device in contact (e.g., physical, electrical, thermal, etc.) with the target tissue, and optionally wherein the resorption process causes conformal and/or morphological changes to the electronic device that assists in interfacing the device with the target tissue. In some embodiments, the device is deployed in, or otherwise positioned, manipulated and/or interfaced with, a biological environment via a process involving complete resorption of the bioresorbable

substrate, for example, so as to provide the electronic device in physical contact, electrical contact or optical communication with a target tissue. In some embodiments of this aspect, therefore, the resorbable layer functions as a sacrificial layer during deployment so as to facilitate interfacing the electronic device with the target tissue. Alternatively, in other embodiments, the device is deployed in, or otherwise positioned, manipulated and/or interfaced with, a biological environment via a process involving partial, but not complete, resorption of the bioresorbable substrate, for example, so as to provide the electronic device in physical contact, electrical contact or optical communication with a target tissue. In some embodiments of this aspect, therefore, the resorbable layer functions as a partial sacrificial layer during deployment but remains as a structural and/or functional component of the device during use. In the present devices and methods, resorption of the bioresorbable substrate provides a minimally invasive and/or biocompatible approach to establishing conformal contact, and optionally physical contact, conformal contact, thermal contact and/or electrical contact, between the electronic device and the target tissue. In some embodiments, for example, partial or complete resorption of the bioresorbable substrate provides a means of selectively adjusting and/or manipulating the physical dimensions, conformation, morphology and/or shape of the electronic device so as to facilitate establishing conformal contact with a target tissue. In some embodiments, partial or complete resorption of the bioresorbable substrate provides a means of selectively adjusting the chemical composition of the implantable device so as to establish conformal contact with a target tissue in a biocompatible manner, such as in a manner suppressing undesirable immune response and/or inflammation.

[0017] Incorporation of resorbable materials in the present invention may also be implemented in a manner to facilitate removal, biological degradation and/or clearance of the present implantable devices and components thereof. In an embodiment, a device of the invention has a composition, geometry and/or physical dimensions such that upon at least partial resorption of the bioresorbable substrate the device is broken up into fragments that are efficiently processed and cleared by a subject. In an embodiment, for example, the device is configured such that upon at least partial resorption of the bioresorbable substrate the device is broken up into fragments having lateral and thickness dimensions less than 100 microns, optionally less than 10 microns and optionally less than 1 micron, so as to facilitate processing and clearance of the device by a subject. Alternatively, the invention includes implantable devices having

electronic device components that remain essentially intact (e.g., at least 70% intact or optionally at least 90% intact) upon at least partial resorption of the bioresorbable substrate, and optionally upon complete resorption. Embodiments of this aspect of the invention are useful for biomedical applications wherein the device is designed so as to be removable via a surgical procedure. In an aspect, for example, the electronic device component exhibits physical dimensions and/or mechanical properties (e.g., rigidity, hardness, Young's modulus, etc.) after at least partial resorption of the bioresorbable substrate such that the device may be physically removed after implantation (e.g., by a surgeon).

[0018] A variety of materials are useful for the bioresorbable substrate of the present devices, including materials that are efficiently processed and/or remodeled without formation of biologically active, toxic and/or harmful byproducts upon contact with a biological environment. Useful materials for the bioresorbable substrate include, for example, a biopolymer (e.g., protein, peptide, carbohydrate, polynucleotide, etc.), a synthetic polymer, a protein, a polysaccharide, silk, poly(glycerol-sebacate) (PGS), polydioxanone, poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), collagen, chitosan, fibroin, and combinations of these. Useful silk materials for bioresorbable substrates include, for example, silkworm fibroin, modified silkworm fibroin, spider silk, insect silk, recombinant silk, and any combination of these. As used herein, modified silkworm fibroin refers to a polymer composition that is derived via chemical modification of silkworm fibroin.

[0019] The physical dimensions and physical properties of the bioresorbable substrate are important parameters for supporting a range of device functionalities and compatibility with different tissue types. In some embodiments, the bioresorbable substrate has a thickness less than or equal to 10,000 μm, and optionally in some embodiments less than or equal to 1000 μm, and optionally in some embodiments less than or equal to 100 μm, and optionally in some embodiments less than or equal to 10 μm; and optionally in some embodiments less than or equal to 1 μm. Use of a thin bioresorbable substrate (e.g., thickness less than or equal to 100 microns, optionally less than or equal to 10 microns and optionally less than or equal to 1 micron) is useful for providing a flexible, or otherwise deformable, implantable device capable of establishing conformal contact with a wide range of tissue types, including tissues having complex, highly contoured surfaces. In some embodiments, the bioresorbable

substrate has a thickness selected over the range of 100 nanometers and 10000 μm, optionally for some applications selected over the range of 1 μm and 1000 μm, and optionally for some embodiments selected over the range of 1 μm and 10 μm. In some embodiments, the composition and physical properties (e.g., Young's modulus, net bending stiffness, toughness, etc.) of the bioresorbable substrate are selected to provide sufficient structural support for the electronic device component, while also providing an ability to achieve a high degree of conformal contact upon deployment. In some embodiments, the bioresorbable substrate is a low modulus layer. Alternatively, the invention includes devices having a bioresorbable substrate that is a high modulus layer. In some embodiments, for example, the bioresorbable substrate has a Young's modulus less than or equal to 10 GPa, preferably for some applications a Young's modulus less than or equal to 100 MPa, optionally for some applications less than or equal to 10 MPa. In some embodiments, for example, the bioresorbable substrate has a Young's modulus selected over the range of 0.5 MPa and 10 GPa, and optionally for some applications selected over the range of 0.5 MPa and 100 MPa, and optionally for some applications selected over the range of 0.5 MPa and 10 MPa. In some embodiments, for example, the bioresorbable substrate has a net bending stiffness less than or equal to 1×10^9 GPa μm^4, optionally for some applications less than or equal to 1×10^7 GPa μm^4 and optionally for some applications less than or equal to 1×10^6 GPa μm^4. In some embodiments, for example, the bioresorbable substrate has a net bending stiffness selected over the range of 0.1×10^4 GPa μm^4 and 1×10^9 GPa μm^4, and optionally for some applications between 0.1×10^4 GPa μm^4 and 5×10^5 GPa μm^4.

[0020] In some embodiments, the device includes a bioresobable substrate having a controllable and/or selectable *in vivo* resorption rate when provided in contact with a target tissue in a biological environment. The invention includes implantable devices having bioresorbable substrates exhibiting a range of resorption rates that are selected on the basis of an intended biological application, device functionality, tissue type, etc. In some embodiments, for example, the bioresorbable substrate exhibits a large resorption rate *in vivo* so as to provide rapid and complete resorption upon administration, for example, to facilitate interfacing the device with a target tissue and/or to facilitate conformational and/or morphological changes useful for deploying the device in a particular tissue environment. In other embodiments, for example, the bioresorbable substrate exhibits a small resorption rate *in vivo* so as to provide slow and incomplete resorption upon administration, for example, to provide encapsulation of the

electronic components of the device and/or to provide structural properties useful for deploying or removing the device.

[0021] In some biological environments, such as an *in vivo* biological environment, the degradation of the bioresorbable substrate occurs via enzymatic degradation, for example, via protease mediated degradation. In addition, degradation occurs in some embodiments from the surfaces of the bioresorbable substrate that are exposed to the biological environment having degradation enzymes present, such as at the interface with a tissue and/or biological fluid. Accordingly, certain parameters of the bioresorbable substrate may be selected to effectively control the resorption rate. In an embodiment, the chemical composition, physical state and/or thickness of the bioresorbable substrate is selected so as to control the resorption rate. In an embodiment, for example, the bioresorbable substrate comprises a biopolymer exhibiting a useful resorption rate for a selected biological environment, such as a silk biopolymer exhibiting a useful resorption rate. The invention includes bioresorbable substrates comprising amorphous materials, crystalline materials, partially amorphous materials and partially crystalline materials. In an embodiment, the implantable device of the invention includes an at least partially crystalline material, wherein the extent of crystallinity of the bioresorbable substrate is selected to provide a useful and/or preselected resorption rate for a selected biological environment and device application. In some embodiments, the larger the degree of crystallinity of the bioresorbable substrate the slower the resorption rate when provided in contact with the target tissue. For example, the invention includes implantable devices having a bioresorbable substrate with a degree of crystallinity less than or equal to 55%, and optionally a degree of crystallinity less than or equal to 30% and optionally a degree of crystallinity less than or equal to 20%, and optionally a degree of crystallinity less than or equal to 5%. For example, the invention includes implantable devices having a bioresorbable substrate with a degree of crystallinity selected over the range of 0 to 55%, and optionally for some embodiments a degree of crystallinity selected over the range of 1 to 30%, and optionally for some embodiments a degree of crystallinity selected over the range of 5 to 20%. As used herein, 0% crystallinity refers to an entirely amorphous material and the given degree of crystallinity corresponds to the amount of a material provided in a crystalline state relative to the total amount of material. In some embodiments, for example those having a silk bioresorbable substrate, the degree of crystallinity refers to the beta sheet content of the silk bioresorbable substrate.

[0022] Bioresorbable substrates for some applications are biocompatible materials that are processed and/or remodeled upon contact with a target tissue without formation of biologically active, toxic and/or harmful byproducts.

[0023] The geometry and/or morphology of the bioresorbable substrate are other characteristics important to establishing the functional capabilities of the present implantable devices. In an embodiment, the bioresorbable substrate is a continuous layer having approximately uniform thickness (e.g., thicknesses within 10% of average thickness of the layer). Alternatively, the invention includes devices having a bioresobable substrate comprising a discontinuous layer and/or a layer having a nonuniform thickness profile. The invention includes implantable devices having additional bioresorbable substrates and/or layers, for example, for partial or full encapsulation and/or electronic isolation of electronic device components (e.g., semiconductors, electrodes, dielectrics, etc.).

[0024] In some embodiments, the bioresorbable substrate and/or barrier layer and/or second dielectric layer has a planar or non-planar (e.g., curved, concave, convex, etc.) contact surface for physically contacting the surface of a target tissue. Such embodiments are useful, for example, for providing sensing and/or actuation at the surface of a target tissue. In other embodiments, the bioresorbable substrate and/or barrier layer and/or second dielectric layer has a nanostructured or microstructured contact surface for physically contacting the target tissue. Nanostructured or microstructured contact surfaces for some applications comprise a plurality of relief features that physically contact and/or penetrate the surface of a target tissue. In some embodiments, the relief features extend from a surface of the bioresorbable substrate and/or barrier layer and/or second dielectric layer a length selected from the range of 10 nanometers to 1000 nanometers and preferably for some applications selected from the range of 10 nanometers to 500 nanometers. Useful relief features include, but are not limited to, barbs, spikes, columns, protrusions and any combination of these. Devices having a nanostructured bioresobable layer are useful in some embodiments for providing sensing and/or actuation below the surface of a target tissue and/or within the target tissue.

[0025] In some embodiments, at least a portion, and optionally all, of the plurality of inorganic semiconductor components of the electronic device is bonded to the bioresorbable substrate, barrier layer and/or the biocompatible layer. Bonding between

the electronic device and the bioresorbable substrate, barrier layer and/or the biocompatible layer may be achieved directly involving covalent and noncovalent bonding (e.g., Van der Waals forces, hydrogen bonding, London dispersion forces, etc.) between layers and materials. Alternatively, bonding may be achieved by incorporation of an adhesive layer provided between the electronic device and the bioresorbable substrate, barrier layer and/or the biocompatible layer. Useful adhesive layers for bonding comprise a polymer, an elastomer (e.g. PDMS), a prepolymer, a thin metal layer, a silk layer, etc.

[0026] The implantable biomedical device has a neutral mechanical plane and, in some embodiments, at least a portion, and optionally all, of the plurality of semiconductor components or electrodes of the electrode array is positioned proximate (e.g., within 10 microns, and optionally within 1 micron) to the neutral mechanical plane. A thickness of the barrier layer and a thickness of the bioresorbable substrate may be selected so as to position at least a portion of the plurality of semiconductor components or electrodes of the electrode array proximate to the neutral mechanical plane. Embodiments having semiconductor components or electrodes of the electrode array positioned proximate to the neutral mechanical plane are useful for applications wherein the device undergoes a significant change in conformation upon deployment, for example, by enhancing the structural integrity of the device when provided in a non-planar (e.g., bent, curved, convex, concave, etc.) conformation and/or in a stretched conformation.

[0027] Useful inorganic semiconductor components include, but are not limited to, flexible semiconductor structures, stretchable semiconductor structures and/or semiconductor structures capable of undergoing a change in shape so as to conform to the surface of a target tissue. In an embodiment, for example, the inorganic semiconductor components comprises a microstructured material or a nanostructured material such as a nanoribbon, a nanomembrane, or a nanowire. As used herein, the term "microstructured" refers to a structure having at least one physical dimension selected over the range of 1 micron to 1000 microns and the term "nanostructured" refers to a structure having at least one physical dimension selected over the range of 10 nanometers to 1000 nanometers. In an embodiment, the inorganic semiconductor elements comprise a semiconductor device such as a transistor, a transistor channel, a

diode, a p-n junction, a photodiode, a light emitting diode, a laser, an electrode, an integrated electronic device or combinations and/or arrays of these.

[0028] The physical dimensions and shape of the electronic device, and components thereof, and of the implantable device are important parameters for establishing adequate conformal contact between the implantable biomedical device and the target tissue and for minimizing immunological responses to the device, such as minimizing inflammation upon contact with a target tissue. Use of thin inorganic semiconductor components (e.g., thickness less than or equal to 100 microns, optionally less than or equal to 10 microns and optionally less than or equal to 1 micron) is useful for providing a flexible, or otherwise deformable, implantable device capable of establishing conformal contact with a wide range of tissue types, including tissues having complex, highly contoured surfaces. In some embodiments, at least some of, and optionally all of, the inorganic semiconductor components of the electronic device have a thickness less than or equal to 100 microns, and for some applications have a thickness less than or equal to 10 microns, and for some applications have a thickness less than or equal to 1 micron, and for some applications have a thickness less than or equal to 500 nanometers, and for some applications have a thickness less than or equal to 100 nanometers. In some embodiments, at least some of, and optionally all of, the inorganic semiconductor components of the electronic device have a thickness selected from a range of 50 nm to 100 μm, optionally for some applications selected from a range of 50 nm to 10 μm, and optionally for some applications selected from a range of 100 nm to 1000 nm. In some embodiments, at least some of, and optionally all of, the inorganic semiconductor components of the electronic device have lateral physical dimensions (e.g., length, width, diameter, etc.) less than or equal to 10000 μm, and for some applications have lateral physical dimensions less than or equal to 1000 μm, and for some applications have lateral physical dimensions less than or equal to 100 μm, and for some applications have lateral physical dimensions less than or equal to 1 μm. In some embodiments, at least some of, and optionally all of, the inorganic semiconductor components of the electronic device have lateral physical dimensions selected from the range of 100 nm to 10000 μm, optionally for some applications selected from a range of 500 nm to 1000 μm, optionally for some applications selected from a range of 500 nm to 100 μm, and optionally for some applications selected from a range of 500 nm to 10 μm.

[0029] As with other components of the implantable biomedical device, the physical properties of the inorganic semiconductor components (e.g., Young's modulus, net bending stiffness, toughness, etc.) allow the implantable biomedical device to achieve a high degree of conformal contact with a target tissue. In some embodiments, for example, at least a portion, and optionally all, of the inorganic semiconductor components of the electronic device have a Young's modulus less than or equal to 10 GPa, optionally for some applications less than or equal to 100 MPa, optionally for some applications less than or equal to 10 MPa. In some embodiments, for example, at least a portion, and optionally all, of the inorganic semiconductor components of the electronic device have a Young's modulus selected over the range of 0.5 MPa and 10 GPa, and optionally for some applications selected over the range of 0.5 MPa and 100 MPa, and optionally for some applications selected over the range of 0.5 MPa and 10 MPa. In some embodiments, at least a portion, and optionally all, of the inorganic semiconductor components of the electronic device have a net bending stiffness less than or equal to 1×10^8 GPa μm^4, optionally for some applications less than or equal to 5×10^5 GPa μm^4 and optionally for some applications less than or equal to 1×10^5 GPa μm^4. In some embodiments, at least a portion, and optionally all, of the inorganic semiconductor components of the electronic device have a net bending stiffness selected over the range of 0.1×10^4 GPa $\mu m^4$and 1×10^8 GPa μm^4, and optionally for some applications between 0.1×10 GPa $\mu m^4$and 5×10^5 GPa μm^4.

[0030] In some embodiments, the electronic device, or components thereof, are assembled on the bioresorbable substrate via a printing-based or molding-based process, for example, by transfer printing, dry contact transfer printing, solution-based printing, soft lithography printing, replica molding, imprint lithography, etc. In some of these embodiments, therefore, the electronic device, or components thereof, comprise printable semiconductor materials and/or devices. Integration of the electronic device and bioresorbable substrate components via a printing-based technique is beneficial in some embodiments, as it allows for independent processing of semiconductor devices/materials and processing for the bioresorbable substrate. For example, the printing-based assembly approach allows semiconductor devices/materials to be processed via techniques that would not be compatible with some bioresorbable substrates. In some embodiments, for example, the semiconductor device/materials are first processed via high temperature processing, physical and chemical deposition processing, etching and/or aqueous processing (e.g. developing, etc.), and then

subsequently assembled on the bioresorbable substrate via a printing-based technique. An advantage of this approach is that it avoids processing of the semiconductor device/materials on the bioresorbable substrate in a manner that could negatively impact the chemical and/or physical properties of the bioresorbable substrate, for example, by negatively impacting biocompatibility, toxicity and/or the resorption properties (e.g., resorption rate, etc.) of the bioresorbable substrate. In some embodiments, for example, this approach allows for effective fabrication of the electronic device without exposing the bioresorbable substrate to aqueous processing, for example, processing involving exposure of the bioresorbable substrate to an etchant, a stripper or a developer.

[0031] Useful materials for the inorganic semiconductor components include high quality semiconductor materials such as single crystalline semiconductor materials including pure and doped single crystalline semiconductor materials. Integration of single crystalline semiconductor materials into an implantable biomedical device is particularly beneficial for providing implantable devices exhibiting very good electronic properties. In an embodiment, the semiconductor components comprise a material selected from the group consisting of Si, Ge, Se, diamond, fullerenes, SiC, SiGe, SiO, SiO_2, SiN, AlSb, AlAs, AlIn, AlN, AlP, AlS, BN, BP, BAs, As_2S_3, GaSb, GaAs, GaN, GaP, GaSe, InSb, InAs, InN, InP, CsSe, CdS, CdSe, CdTe, Cd_3P_2, Cd_3As_2, Cd_3Sb_2, ZnO, ZnSe, ZnS, ZnTe, Zn_3P_2, Zn_3As_2, Zn_3Sb_2, $ZnSiP_2$, CuCl, PbS, PbSe, PbTe, FeO, FeS_2, NiO, EuO, EuS, PtSi, TlBr, $CrBr_3$, SnS, SnTe, PbI_2, MoS_2, GaSe, CuO, Cu_2O, HgS, HgSe, HgTe, HgI_2, MgS, MgSe, MgTe, CaS, CaSe, SrS, SrTe, BaS, BaSe, BaTe, SnO_2, TiO, TiO_2, Bi_2S_3, Bi_2O_3, Bi_2Te_3, BiI_3, UO_2, UO_3, $AgGaS_2$, PbMnTe, $BaTiO_3$, $SrTiO_3$, $LiNbO_3$, La_2CuO_4, $La_{0.7}Ca_{0.3}MnO_3$, CdZnTe, CdMnTe, $CuInSe_2$, copper indium gallium selenide (CIGS), HgCdTe, HgZnTe, HgZnSe, PbSnTe, Tl_2SnTe_5, Tl_2GeTe_5, AlGaAs, AlGaN, AlGaP, AlInAs, AlInSb, AlInP, AlInAsP, AlGaAsN, GaAsP, GaAsN, GaMnAs, GaAsSbN, GaInAs, GaInP, AlGaAsSb, AlGaAsP, AlGaInP, GaInAsP, InGaAs, InGaP, InGaN, InAsSb, InGaSb, InMnAs, InGaAsP, InGaAsN, InAlAsN, GaInNAsSb, GaInAsSbP, and any combination of these. In some embodiments, the inorganic semiconductor components include a material selected from the group consisting of Si, SiC, SiGe, SiO, SiO_2, SiN, and any combination of these. In some embodiments, the inorganic semiconductor components comprise single crystalline silicon, porous silicon and/or polycrystalline silicon. In some embodiments, the inorganic semiconductor component comprises a single crystal inorganic semiconductor material. In some

embodiments, the inorganic semiconductor component is a bioresorbable material or a bioinert material. Useful materials for a bioresorbable, inorganic semiconductor component include, but are not limited to, porous silicon, polycrystalline silicon, and any combination of these.

[0032] In some embodiments, electronic devices of this aspect comprise one or more interconnected island and bridge structures. For example, an island structure may comprise one or more semiconductor circuit components of the electronic device. A bridge structure may comprise one or more flexible and/or stretchable electrical interconnections providing electrical communication between elements, for example between different island structures. In this manner, electronic devices of the present invention may comprise stretchable electronic devices having a plurality of electrically interconnected inorganic semiconductor components comprising one or more island structures and one or more flexible and/or stretchable bridge structures providing electrical interconnection; e.g., stretchable electronic interconnects.

[0033] In some embodiments, the electronic device may include one or more additional device components selected from the group consisting of an electrode, a dielectric layer, a chemical or biological sensor element, a pH sensor, an optical sensor, an optical source, a temperature sensor, and a capacitive sensor. The additional device component may comprise a bioinert material or a bioresorbable material. Useful bioinert materials include, but are not limited to, titanium, gold, silver, platinum, and any combination of these. Useful bioresorbable materials include, but are not limited to, iron, magnesium, and any combination of these.

[0034] In some embodiments, at least a portion of the plurality of inorganic semiconductor components comprise one or more of an amplifier circuit, a multiplexing circuit, a current limiting circuit, an integrated circuit, a transistor or a transistor array. Useful multiplexing circuits include those configured to individually address each of a plurality of electrodes spatially arranged over the bioresorbable substrate.

[0035] The physical dimensions, composition and geometry of electrodes are important parameters of implantable electrode arrays and electronic devices of the invention. In an embodiment, the electrodes of the electrode array are metal films, for example thin (e.g., thickness < 100 microns) metal films. Use of thin electrodes (e.g., thickness less than or equal to 100 microns, optionally less than or equal to 10 microns

and optionally less than or equal to 1 micron) is useful for providing a flexible, or otherwise deformable, implantable device capable of establishing conformal contact with a wide range of tissue types, including tissues having complex, highly contoured surfaces. In an embodiment, at least a portion, and optionally all of, the electrodes comprise a biocompatible metal, such as titanium, gold, silver, platinum, and any combination of these. In an embodiment, at least a portion, and optionally all of, the electrodes comprise a bioresorbable metal, such as of iron, magnesium, and any combination of these. In an embodiment, the array comprises at least 10 electrodes and optionally comprises 10 to 10000 electrodes, optionally for some embodiments 10 to 1000 electrodes, and optionally for some embodiments 20 to 100 electrodes . In an embodiment, each of the electrodes has a thickness less than or equal to 10 microns, and optionally each of the electrodes has a thickness less than or equal to 1 micron, and optionally each of the electrodes has a thickness less than or equal to 500 nanometers. In an embodiment, each of the electrodes has a thickness selected over the range of 100 nanometers to 10 microns, and optionally a thickness selected over the range of 100 nanometers to 1 micron, and optionally a thickness selected over the range of 100 nanometers to 500 nanometers. In an embodiment, each of the electrodes has lateral dimensions less than or equal to 10000 microns, and optionally lateral dimensions less than or equal to 1000 microns, and optionally lateral dimensions less than or equal to 100 microns, and optionally lateral dimensions less than or equal to 10 microns. In an embodiment, electrodes in the electrode array are separated from adjacent electrodes by a distance greater than or equal to 10 microns, and optionally a distance greater than 100 microns. In an embodiment, adjacent electrodes are separated from each other by a distance selected from the range of 10 microns to 10 millimeters, and optionally the range of 10 microns to 1000 microns, and optionally the range of 10 to 100 microns.

[0036] In an embodiment, at least a portion of, and optionally all of, the electrodes and/or inorganic semiconductor components of the device are supported by a barrier layer having a mesh structure. Use of a barrier layer having a mesh structure is beneficial in the invention for providing a supporting layer allowing for efficient handling and administration of the implantable device, while at the same time providing mechanical properties (e.g., flexibility, deformability, bendability, etc.) useful for establishing conformal contact with the target tissue. In an embodiment, for example, a mesh structure refers to a layer or other structural component that occupies a portion of, but not all, the foot print area of the device, for example, occupying a portion of, but not

all of, the area of the device that interfaces the target tissue. In an embodiment, for example, the foot print area of the device is an area corresponding to the perimeter of the device that establishes the interface with a target tissue, and the mesh structure of the barrier layer occupies a portion, but not all of the, foot print area. Mesh structures in some embodiments, occupy 75% or less than the foot print area and/or tissue interface area of the device, and optionally 50 % or less than the foot print area and/or tissue interface area; and optionally 25 % or less than the foot print area and/or tissue interface area of the device. In an embodiment, for example, the barrier layer has a mesh structure that is a lattice structure, a perforated structure or a tentacle structure. In an embodiment, for example, the barrier layer is a mesh structure having structural regions at least partially supporting, or optionally in physical contact with, the inorganic semiconductor components or electrodes, wherein structural regions of the barrier layer are separated from each other by voids where the barrier layer is not present. In such embodiments, therefore, the presence of the void regions provides a mesh structured barrier layer occupying less than the foot print area of the device. In an embodiment, for example, the barrier layer having a mesh structure is a discontinuous layer, as opposed to a continuous layer, such as a continuous film or sheet.

[0037] The composition and physical dimensions of the barrier layer are also parameters useful for providing an implantable device useful for establishing conformal contact with a target tissue. Use of a thin barrier layer (e.g., thickness less than or equal to 100 microns, optionally less than or equal to 10 microns, and optionally less than or equal to 1 micron) is useful for providing a flexible, or otherwise deformable, implantable device capable of establishing conformal contact with a wide range of tissue types, including tissues having complex, highly contoured surfaces. In an embodiment, the barrier layer comprises a polymer material, such as an elastomer, a thermoset, a thermoplastic, or a composite polymer material. In an embodiment, for example, the barrier layer is polyimide. The invention includes barrier layers comprising other materials, for example, SU-8, an insulator, a polyimide, a dielectric, and an inorganic dielectric, Si_3N_4. In an embodiment, the barrier layer has a thickness less than or equal to 10000 μm, and optionally a thickness less than or equal to 1000 μm, and optionally a thickness less than or equal to 100 μm, and optionally a thickness less than or equal to 10 μm. In an embodiment, the barrier layer has a thickness selected from the range of 500 nanometers to 1000 μm, and optionally a thickness selected from the range of 500 nanometers to 100 μm, and optionally a thickness selected from the range of 500

nanometers to 10 μm. In some embodiments, the barrier layer is a low modulus layer. Alternatively, the invention includes devices having a barrier layer that is a high modulus layer.

[0038] "Spatially arranged over the bioresorbable substrate" as used herein, refers to a distribution of elements (e.g. device components) over the surface area of a bioresorbable substrate such that each element is located at a different position. Inter-element spacing can be uniform or variable. In some embodiments, the elements are spatially arranged in a regular array pattern with equal inter-element spacing, for example in a 2D array. In some embodiments, the elements are spatially arranged in a line (e.g., a 1D array). Useful spatial arrangements include regular and irregular distributions of elements.

[0039] In some embodiments, the barrier layer and/or bioresorbable substrate encapsulates all of the inorganic semiconductor components and/or electrodes of the electronic device. In other embodiments, the barrier layer and/or bioresorbable substrate completely encapsulates the electronic device itself. In some embodiments, for example, the barrier layer, biocompatible layer, first dielectric layer, second dielectric layer and/or bioresorbable substrate has a thickness less than or equal to 10000 μm, optionally for some embodiments, a thickness less than or equal to 1000 μm, and optionally for some embodiments, a thickness less than or equal to 100 μm, and optionally for some embodiments, a thickness less than or equal to 10 μm. In some embodiments, for example, the barrier layer, biocompatible layer, first dielectric layer, second dielectric layer and/or bioresorbable substrate has a thickness selected from a range of 1 μm to 10000 μm, optionally for some applications selected from a range of 1 μm to 1000 μm, and optionally for some applications selected from a range of 1 μm to 100 μm. In some embodiments, the barrier layer and/or bioresorbable substrate limits net leakage current from the electronic device upon deployment in an *in vivo* biological environment to 10 $\mu A/\mu m^2$ or less.

[0040] Useful materials for the barrier layer and/or biocompatible layer and/or first dielectric layer and/or second dielectric layer include, for example, a polymer, an organic polymer, SU-8, an insulator, a polyimide, a dielectric, an inorganic dielectric, Si_3N_4, and any combination of these. In a specific embodiment, the barrier layer and/or biocompatible layer comprises an electrical insulator. In some embodiments, the barrier

layer and/or biocompatible layer comprises a bioresorbable material or a bioinert material.

[0041] In an embodiment, the physical properties of the implantable biomedical device and/or electrode array (e.g., Young's modulus, net bending stiffness, toughness, etc.) provide rigidity for the device to be self-supporting, while also being capable of achieving a high degree of conformal contact with a target tissue. In an embodiment, the bioresorbable substrate, the electronic device having a plurality of inorganic semiconductor elements, and the barrier layer provide a net bending stiffness of the implantable biomedical device of less than 1×10^9 GPa μm^4, or a net bending stiffness selected from a range of 0.1×10^4 GPa μm^4 to 1×10^8 GPa μm^4, optionally 1×10^5 GPa μm^4 to 1×10^8 GPa μm^4. In some embodiments, the bioresorbable substrate, the electronic device, and the barrier layer each independently comprise a bioresorbable material. In an embodiment, the bioresorbable substrate, the biocompatible layer, the electrode array comprising a plurality of electrodes, and the barrier layer provide a net bending stiffness of the implantable biomedical device of less than 1×10^9 GPa μm^4, or a net bending stiffness selected from a range of 0.1×10^4 GPa μm^4 to 1×10^9 GPa μm^4, optionally 0.1×10^4 GPa μm^4 to 1×10^6 GPa μm^4.

[0042] In an embodiment, the electronic device and barrier layer have a mesh structure, which is formed by removing at least a portion of one or more supporting or encapsulating layers located proximate to an electronic device component (e.g., inorganic semiconductor element, electrode, etc.) to provide a perforated structure, having one or more holes, or a tentacle structure, where semiconductor components are physically connected at a proximal end but physically separated at a distal end.

[0043] In an embodiment, the implantable device, and/or components thereof, are at least partially optically transparent with respect to visible and/or infrared electromagnetic radiation. In an embodiment, for example, the electronic device, bioresorbable substrate, electrode array and/or barrier layer components exhibit a percentage transmission for light in the visible region of the electromagnetic spectrum equal to or greater than 70% and equal to or greater than 90% for some applications. At least partially optically transparent implantable devices are useful for visualizing and/or imaging the device during administration, use and/or removal. In addition, devices of the invention that are at least partially optically transparent are useful for coupling electromagnetic radiation into and/or out of the device. The invention includes, for

example, implantable devices having an LED or laser array component for illuminating a target tissue or optical sensing, wherein the device is capable of transmitting light from the electronic device component through other components of the device, such as the bioresorbable substrate.

[0044] In another aspect, provided are methods for administering and using an implantable biomedical device. A method of this aspect comprises the steps of providing an implantable biomedical device comprising a bioresorbable substrate, an electronic device comprising a plurality of inorganic semiconductor components supported by the bioresorbable substrate, wherein at least one of the inorganic semiconductor components has at least one physical dimension less than or equal to 100 microns, and a barrier layer encapsulating at least a portion of the inorganic semiconductor components; contacting the implantable biomedical device with a target tissue of a subject in a biological environment, and at least partially resorbing the bioresorbable substrate in the biological environment, thereby establishing conformal contact between the implantable biomedical device and the target tissue in the biological environment.

[0045] Methods of this aspect are useful for administering an implantable biomedical device onto target tissue in a biological environment, where the biological environment is an *in-vivo* biological environment and where the target tissue may be selected from, but not limited to, heart tissue, brain tissue, muscle tissue, nerve tissue, epithelial tissue and vascular tissue.

[0046] In some embodiments, the Young's modulus of the implantable biomedical device decreases by at least 20%, or optionally by at least 50%, or optionally by at least 70%, upon complete or partial resorption of the bioresorbable substrate. The net bending stiffness of the implantable biomedical device, in some embodiments, decreases by at least 20%, or optionally by at least 50%, or optionally by at least 70%, upon complete or partial resorption of the bioresorbable substrate.

[0047] In another aspect, provided are methods of actuating a target tissue or sensing a parameter associated with the target tissue of a subject. A method of this aspect comprises the steps of providing an implantable biomedical device comprising a bioresorbable substrate, an electronic device comprising a plurality of inorganic semiconductor components supported by the bioresorbable substrate, wherein at least

one of the inorganic semiconductor components has at least one physical dimension less than or equal to 100 microns, and a barrier layer encapsulating at least a portion of the inorganic semiconductor components; contacting the implantable biomedical device with the target tissue in the biological environment; at least partially resorbing the bioresorbable substrate in the biological environment, thereby establishing conformal contact between the implantable biomedical device and the target tissue in the biological environment; and actuating the target tissue or sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device.

[0048] In another aspect, the invention provides methods for actuating a target tissue or sensing a parameter associated with the target tissue of a subject in a biological environment, the method comprising: (1) providing an implantable biomedical device comprising: an electrode array comprising a plurality of individually addressable metal electrodes, wherein each metal electrode has at least one physical dimension less than or equal to 100 microns; a barrier layer having a mesh structure, wherein the barrier layer at least partially supports the electrode array; and a bioresorbable substrate supporting the electrode array, the barrier layer or both of the electrode array and the barrier layer; contacting the implantable biomedical device with the target tissue in a biological environment; wherein upon contact with the biological environment the bioresorbable substrate is at least partially resorbed, thereby establishing conformal contact between the electrode array and the target tissue in the biological environment; and actuating the target tissue or sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device.

[0049] In an embodiment, the method of this aspect further comprises measuring a voltage at a surface of the target tissue and/or generating a voltage at a surface of the target tissue. In some embodiments, the voltage generated at the surface of the target tissue is sufficient to electrophysically actuate the target tissue. In an embodiment, the method of this aspect further comprises measuring electromagnetic radiation at a surface of the target tissue and/or generating electromagnetic radiation at a surface of the target tissue. In some embodiments, the electromagnetic radiation generated at the surface of the target tissue has a power sufficient to optically actuate the target tissue. In an embodiment, the method of this aspect further comprises measuring a current at a surface of the target tissue and/or generating a current at a surface of the target tissue.

In some embodiments, the current generated at the surface of the target tissue has a value sufficient to electrophysically actuate the target tissue.

[0050] In another aspect, provided are methods for making an implantable biomedical device, for example using a printing-based technique, such as transfer printing. In an embodiment, a method of the invention comprises the steps of: (1) providing a bioresorbable substrate having a receiving surface; and (2) assembling a plurality of inorganic semiconductor components or electrodes of an electrode array on the receiving surface of the bioresorbable substrate by transfer printing. In an embodiment, the step of assembling the plurality of inorganic semiconductor components or electrodes of the electrode array on the receiving surface of the bioresorbable substrate by transfer printing is carried out using dry contact transfer printing, for example, using an elastomeric stamp or a composite stamp. In an embodiment, the method further comprises providing a barrier layer encapsulating at least a portion of, and optionally all of, the inorganic semiconductor components or electrodes of the electrode array on the receiving surface of the bioresorbable substrate, for example, a barrier layer having a mesh structure. The barrier layer in these aspects may completely or partially encapsulate the inorganic semiconductor components or electrodes of the electrode array. In a method of this aspect, the inorganic semiconductor components or electrodes of the electrode array have thicknesses less than or equal to 100 microns, optionally less than or equal to 10 microns, and optionally less than or equal to 1 microns. In an embodiment, the step of encapsulating at least a portion of, and optionally all of, the inorganic semiconductor components or electrodes of the electrode array is carried out before the step of assembling the plurality of inorganic semiconductor components or electrodes of the electrode array on the receiving surface of the bioresorbable substrate by transfer printing. In an embodiment, the method further comprises providing an adhesive layer on the receiving surface of the bioresorbable substrate prior to the step of assembling the plurality of inorganic semiconductor components or electrodes of the electrode array on the receiving surface of the bioresorbable substrate by transfer printing.

[0051] In an embodiment, the invention provides a method of making an implantable electronic device, the method comprising the steps of: (1) providing a bioresorbable substrate having a receiving surface; (2) providing a handle substrate having a sacrificial layer; (3) generating a plurality of semiconductor elements or electrodes of an electrode

array on the sacrificial layer of the substrate; (4) providing a barrier layer on the plurality of semiconductor elements or electrodes of the electrode array; (5) removing the sacrificial layer on the handle substrate, thereby releasing the plurality of semiconductor elements or electrodes of the electrode array; (6) assembling the plurality of inorganic semiconductor components or electrodes of an electrode array on the receiving surface of the bioresorbable substrate by transfer printing. The barrier layer in these aspects may completely or partially encapsulate the inorganic semiconductor components or electrodes of the electrode array. In an embodiment, the step of assembling the plurality of inorganic semiconductor components or electrodes of the electrode array on the receiving surface of the bioresorbable substrate by transfer printing is carried out using dry contact transfer printing, for example, using an elastomeric stamp or a composite stamp. In an embodiment, the method further comprises removing material from selected regions of the barrier layer to generate a mesh structure, for example, via wet or dry etching (e.g., reactive oxygen etching). In a method of this aspect, the inorganic semiconductor components or electrodes of the electrode array have thicknesses less than or equal to 100 microns, optionally less than or equal to 10 microns, and optionally less than or equal to 1 microns. In an embodiment, the method further comprises providing an adhesive layer on the receiving surface of the bioresorbable substrate prior to the step of assembling the plurality of inorganic semiconductor components or electrodes of an electrode array on the receiving surface of the bioresorbable substrate by transfer printing.

[0052] A range of transfer printing methods are useful in the present invention, including those using a conformable transfer device. In an embodiment, the step of assembling the plurality of inorganic semiconductor components or electrodes of the electrode array on the receiving surface of the bioresorbable substrate by transfer printing comprises the steps of: (1) contacting one or more contact surfaces of the semiconductor components or electrodes of the electrode array with a transfer surface of a conformable transfer device, thereby generating a conformable transfer device having the semiconductor components or electrodes of the electrode array disposed on a transfer surface; (2) contacting the transfer surface of the conformable transfer device having the semiconductor components or electrodes of the electrode array with the receiving surface of the bioresorbable substrate in a manner to establish conformal contact between the transfer surface of the conformal transfer device and the receiving surface of the bioresorbable substrate; and (3) separating the conformable transfer

device and the semiconductor components or electrodes of the electrode array, thereby transferring the semiconductor components or electrodes of the electrode array to the receiving surface of the bioresorbable substrate. In an embodiment, the semiconductor components or electrodes of the electrode array are at least partially encapsulated by barrier layer and the transfer surface of the conformable transfer device contacts the barrier layer provided on the contact surfaces of the semiconductor components or electrodes of the electrode array. In an embodiment, the conformal transfer device is a stamp, such as an elastomer stamp or a composite elastomer stamp.

[0053] The invention provides a method of making an implantable device, the method comprising the steps of (1) providing a substrate having a sacrificial layer; applying a first dielectric layer on the sacrificial layer of the substrate; (2) providing at least one inorganic semiconductor component on the first dielectric layer; (3) covering a portion of the at least one inorganic semiconductor component with a second dielectric layer, thereby generating a covered inorganic semiconductor component having an exposed distal end; (4) providing an electrode that physically contacts the exposed distal end of the inorganic semiconductor component; (5) removing at least a portion of the first dielectric layer, the second dielectric layer or both, thereby generating a mesh structure; (6) removing the sacrificial layer on the substrate to leave a mesh structure; and (7) transferring the mesh structure to a receiving surface of a bioresorbable substrate. In an embodiment, the step of removing at least a portion of the first dielectric layer and the second dielectric layer to generate the mesh structure comprises etching, for example, oxygen reactive ion etching. In an embodiment, the step of providing at least one inorganic semiconductor component on the first dielectric layer is carried out via transfer printing, for example, via dry contact transfer printing. In an embodiment, the step of transferring the mesh structure to a receiving surface of a bioresorbable substrate is carried out via transfer printing, for example, via dry contact transfer printing. In embodiments, implantable biomedical devices described above are made according to methods of this aspect. In an embodiment, the inorganic semiconductor component has on dimension less than or equal to 100 microns, optionally for some embodiment less than or equal to 10 microns and optionally for some embodiment less than or equal to 1 micron.

[0054] In another aspect, provided are methods for making an implantable biomedical device. A method of this aspect comprises the steps of: (1) providing a

sacrificial layer on a substrate; (2) applying a first polymer layer on the sacrificial layer on the substrate; (3) providing an electrode array on the first polymer layer, wherein the electrode array comprises a plurality of electrodes; (4) removing at least a portion of the first polymer layer, thereby generating a mesh structure; (5) removing the sacrificial layer on the substrate; and (6) transferring the mesh structure and electrode array to a receiving surface of a bioresorbable substrate. In an embodiment, the step of removing at least a portion of the first polymer comprises dissolving or etching, for example, oxygen reactive ion etching. In an embodiment, the step of providing an electrode array on the first polymer layer, is carried out via transfer printing, for example, via dry contact transfer printing. In an embodiment, the step of transferring the mesh structure and electrode array to a receiving surface of a bioresorbable substrate, is carried out via transfer printing, for example, via dry contact transfer printing.

[0055] In embodiments, implantable biomedical devices described above are made according to methods of this aspect.

[0056] Useful materials for the sacrificial layer on the substrate include, but are not limited to, a polymer, polymethylmethacrylate (PMMA), polyimide, polyethylene terepthalate (PET), polystyrene, polycarbonate, polyvinyl alcohol (PVA), polybenzimidazole, tetrafluoroethylene, SU-8, parylene, polyester, poly-dimethyl-siloxane (PDMS), and any combination of these.

[0057] The implantable biomedical devices described above may be used in the disclosed methods.

[0058] In some embodiments, the geometry of electronic devices may be used to provide stretchability, flexibility, conformability and/or compressibility. In an embodiment, the devices may exploit inorganic semiconductor materials configured into structural shapes that can geometrically accommodate large mechanical deformations without imparting significant strain in the materials themselves. For example, bridges connecting rigid device islands may be wavy, buckled, serpentine or meandering as further described in U.S. Pat. App. No. 11/851,182 (U.S. Pub. No. 2008/0157235); U.S. Pat. App. No. 12/405,475 (U.S. Pub. No. 2010/059863); and U.S. Pat. App. No. 12/398,811 (U.S. Pub. No. 2010/0002402), each of which is hereby incorporated by reference.

[0059] In an aspect, devices disclosed herein comprise one or more stretchable components, such as disclosed in U.S. Pat. App. No. 11/851,182 and/or U.S. Pat. App. No. 12/405,475 and/or U.S. Pat. App. No. 12/398,811, and are made by one or more of the processes disclosed therein. U.S. Pat. App. No. 11/851,182; U.S. Pat. App. No. 12/405,475; and U.S. Pat. App. No. 12/398,811 are hereby incorporated by reference.

[0060] Without wishing to be bound by any particular theory, there may be discussion herein of beliefs or understandings of underlying principles relating to the devices and methods disclosed herein. It is recognized that regardless of the ultimate correctness of any mechanistic explanation or hypothesis, an embodiment of the invention can nonetheless be operative and useful.

BRIEF DESCRIPTION OF THE DRAWINGS

[0061] Figures 1a, 1b and 1c provide top plan and cross-sectional views of an implantable biomedical device, according to an exemplary embodiment.

[0062] Figure 2 provides a top perspective view of the implantable biomedical device of Figure 1.

[0063] Figure 3 provides a top plan view of an implantable biomedical device having islands and bridges, according to an exemplary embodiment.

[0064] Figure 4 provides a side plan view of an implantable biomedical device having a biocompatible layer, according to an exemplary embodiment.

[0065] Figures 5a and 5b provide a process flow schematic for making implantable biomedical devices having mesh structures, according to multiple embodiments.

[0066] Figure 6 provides a flowchart illustrating exemplary steps for making implantable biomedical devices having mesh structures.

[0067] Figure 7 provides a flowchart illustrating exemplary steps for implanting a biomedical device, and optionally using the implanted biomedical device to actuate a target tissue and/or sense a parameter associated with the target tissue.

[0068] Figures 8a and 8b provide side plan views of implantable biomedical devices showing planar contact surfaces and nanostructured or microstructured contact surfaces, respectively.

[0069] Figures 9a, 9b, 9c and 9d provide schematic diagrams and images of implantable biomedical devices having single crystalline silicon electronics. Schematic diagram (left) corresponding high resolution image (right) and microscope image (inset) of (a) ultrathin devices on a carrier wafer, (b) devices lifted onto the surface of a PDMS stamp, and (c) process for transfer printing onto a silk film cast on a silicon wafer. (d) Schematic diagram of transfer printing onto a freestanding silk film (left) and dissolution (right).

[0070] Figures 10a and 10b provide images and data showing bending and electronic properties of the implantable biomedical devices of Figure 9. (a) Ultrathin devices on a flexible silk substrate, in flat (left) and bent (center and right) configurations. (b) Transfer curves (left) and IV curves (right) before (solid curve) and after (dotted curve) dissolution, where I_d, V_g, and V_d represent the drain current, gate voltage, and drain voltage, respectively. The voltage for each IV curve in the right frame denotes the gate bias voltage.

[0071] Figures 11a, 11b and 11c show images of *in-vitro* bioresorbable substrate dissolution. Images of the water dissolution of a system of silicon electronics on silk, at various time stages (left) with magnified views (right): (a) start and (b) after 3 min. (c) Image of devices recovered on filter paper after complete dissolution of the silk (left) with magnified view (right).

[0072] Figure 12 provides photographs of a biomedical device implanted in a mouse model. Procedure and result of the animal toxicity test: image before (left) and shortly after (center) and two weeks after (right) implantation.

[0073] Figures 13a, 13b and 13c provide schematic illustrations and images corresponding to steps for fabricating silk-supported implantable biomedical devices. Schematic illustration and images corresponding to steps for fabricating conformal silk-supported PI electrode arrays. a, Casting and drying of silk fibroin solution on a temporary substrate of PDMS; 5-15 μm thick silk film after drying for 12 hours at room temperature. b, Steps for fabricating the electrode arrays, transfer printing them onto silk, and connecting to ACF cable. c, Schematic illustration of clinical usage of a representative device in an ultrathin mesh geometry with dissolvable silk support.

[0074] Figures 14a, 14b and 14c provide images of an implantable biomedical device fabrication process using a thick polyimide film. Electrode array fabrication process using thick PI film (Kapton, Dupont, USA). a, attach PI film to PDMS coated glass. b, electrode array fabrication. c, ACF connection.

[0075] Figures 15a and 15b provide images of implantable biomedical devices on silk and polyimide, respectively, after connection of anisotropic conductive film cables and circuit boards. Images of electrode array after connection of ACF and circuit board. a,electrode array with thin (< 10 μm) substrate thickness. b, electrode array with thick (> 10 μm) substrate thickness.

[0076] Figures 16a, 16b, 16c show time-dependent changes as a silk substrate dissolves. Time dependent changes as the silk substrate dissolves. a, Dissolution of the silk via submersion in warm water. b, Total bending stiffness of 7 μm and 2.5 μm electrode arrays on supporting silk films as a function of thickness of the supporting silk film; inset shows the ratio of bending stiffness between 7 μm and 2.5 μm. c, Time dependent change in volume of a silk film during dissolution (left frame) and bending stiffness calculated for silk treated in 70% ethanol for 5 seconds for two different array thicknesses (right frame). The 5 second ethanol treatment increases the dissolution time from minutes to about 1 hour. Figure 16d shows The bending stiffness of the neural sensor of thickness 7 μm and 2.5 μm on a silk backing substrate.

[0077] Figure 17 shows time-dependent bending stiffness changes for 7 μm and 2.5 μm implantable biomedical devices.

[0078] Figures 18a, 18b, 18c and 18d show photographs of neural implantable biomedical devices of varying thickness on simulated brain models. Neural electrode arrays of varying thickness on simulated brain models to illustrate flexibility. a, Schematic illustration of trends in thickness and structure that improve conformal contact. b, Series of pictures illustrating how the thickness of the electrode array contributes to conformal contact on a brain model. c, Magnified view of these pictures. d, Image of an electrode array with a mesh design on dissolvable silk substrate. Arrows indicate struts in the mesh that help to stabilize the Au interconnects after dissolution of the silk. The inset illustrates the high degree of conformal contact that can be achieved on the brain model once the silk substrate has been dissolved.

[0079] Figure 19 shows design parameters for a mesh electrode array.

[0080] Figures 20a and 20b provide images of mesh implantable biomedical devices on a glass cylinder and a human brain model, respectively, after dissolution of a silk substrate.

[0081] Figures 21a, 21b, 21c, 21d and 21e provide images and graphs of mechanically modeled, theoretically predicted, and measured properties of implantable biomedical devices. Mechanical modeling, theoretical predictions and measured properties. a, A thin film wrapped around a cylinder of radius R. The unwrapped and wrapped states appear in the top and center frames, respectively. The bottom frame compares the mechanics model and experiments. b, A thin film wrapped around two overlapped cylinders. The top and center frames show the unwrapped and wrapped states, respectively. The bottom frame shows a comparison between the mechanics model and experiments. c, Images of electrode arrays (76 μm sheet in left top, 2.5 μm sheet in right top and 2.5 μm mesh in bottom panel) wrapped onto a glass hemisphere. d, Mechanics models for sheet (left frame) and mesh (right frame) designs. e, The critical adhesion energy (left frame) and the normal (peeling) stress between the film and sphere surface (right frame) for sheet and mesh designs.

[0082] Figures 22a, 22b, 22c and 22d provide images of wrapping experiments on glass cylinders of different diameters (diameter is a, 3.5cm, b,1.3cm, c, 0.4cm and d, 0.1cm.)

[0083] Figures 23a and 23b provide images of wrapping experiments on overlapped cylinders (a, angled view. b, side view).

[0084] Figures 24a and 24b provide modeling results for the critical adhesion energy and normal (peeling) stress, respectively. a, The critical adhesion energy for sheet and mesh designs. b, The normal (peeling) stress between the film and sphere surface for sheet and mesh designs.

[0085] Figures 25a, 25b, 25c and 25d provide photographs and data from animal validation experiments. Photographs and data from animal validation experiments. Image of electrode array on cat brain (left) and average evoked response from each electrode with the color showing the extent of cross-correlation between the evoked response on each electrode and an average of all the responses (right) for 75 μm a, 2.5

μm b and 2.5 μm mesh c electrode array. d, Representative voltage data from a single electrode in a 2.5 μm mesh electrode array showing a sleep spindle.

[0086] Figures 26a and 26b provide schematic diagrams of implantable biomedical devices. Schematic diagram for analytical model and its modeling result. a, Cross section of the neural sensor, with geometrical parameters illustrated. b, Cross section of the neural sensor on a silk backing substrate.

[0087] Figure 27 shows the design of a circuit board.

DETAILED DESCRIPTION OF THE INVENTION

[0088] In general, the terms and phrases used herein have their art-recognized meaning, which can be found by reference to standard texts, journal references and contexts known to those skilled in the art. The following definitions are provided to clarify their specific use in the context of the invention.

[0089] "Functional layer" refers to a layer that imparts some functionality to the device. For example, the functional layer may contain semiconductor components. Alternatively, the functional layer may comprise multiple layers, such as multiple semiconductor layers separated by support layers. The functional layer may comprise a plurality of patterned elements, such as interconnects running between electrodes or islands. The functional layer may be heterogeneous or may have one or more properties that are inhomogeneous. "Inhomogeneous property" refers to a physical parameter that can spatially vary, thereby effecting the position of the neutral mechanical plane within a multilayer device.

[0090] "Structural layer" refers to a layer that imparts structural functionality, for example by supporting and/or encapsulating device components.

[0091] "Semiconductor" refers to any material that is an insulator at a very low temperature, but which has an appreciable electrical conductivity at a temperature of about 300 Kelvin. In the present description, use of the term semiconductor is intended to be consistent with use of this term in the art of microelectronics and electronic devices. Useful semiconductors include those comprising elemental semiconductors, such as silicon, germanium and diamond, and compound semiconductors, such as group IV compound semiconductors such as SiC and SiGe, group III-V semiconductors

such as AlSb, AlAs, AlN, AlP, BN, BP, BAs, GaSb, GaAs, GaN, GaP, InSb, InAs, InN, and InP, group III-V ternary semiconductors alloys such as $Al_xGa_{1-x}As$, group II-VI semiconductors such as CsSe, CdS, CdTe, ZnO, ZnSe, ZnS, and ZnTe, group I-VII semiconductors such as CuCl, group IV – VI semiconductors such as PbS, PbTe, and SnS, layer semiconductors such as PbI_2, MoS_2, and GaSe, oxide semiconductors such as CuO and Cu_2O. The term semiconductor includes intrinsic semiconductors and extrinsic semiconductors that are doped with one or more selected materials, including semiconductors having p-type doping materials and n-type doping materials, to provide beneficial electronic properties useful for a given application or device. The term semiconductor includes composite materials comprising a mixture of semiconductors and/or dopants. Specific semiconductor materials useful for some embodiments include, but are not limited to, Si, Ge, Se, diamond, fullerenes, SiC, SiGe, SiO, SiO_2, SiN, AlSb, AlAs, AlIn, AlN, AlP, AlS, BN, BP, BAs, As_2S_3, GaSb, GaAs, GaN, GaP, GaSe, InSb, InAs, InN, InP, CsSe, CdS, CdSe, CdTe, Cd_3P_2, Cd_3As_2, Cd_3Sb_2, ZnO, ZnSe, ZnS, ZnTe, Zn_3P_2, Zn_3As_2, Zn_3Sb_2, $ZnSiP_2$, CuCl, PbS, PbSe, PbTe, FeO, FeS_2, NiO, EuO, EuS, PtSi, TlBr, $CrBr_3$, SnS, SnTe, PbI_2, MoS_2, GaSe, CuO, Cu_2O, HgS, HgSe, HgTe, HgI_2, MgS, MgSe, MgTe, CaS, CaSe, SrS, SrTe, BaS, BaSe, BaTe, SnO_2, TiO, TiO_2, Bi_2S_3, Bi_2O_3, Bi_2Te_3, BiI_3, UO_2, UO_3, $AgGaS_2$, PbMnTe, $BaTiO_3$, $SrTiO_3$, $LiNbO_3$, La_2CuO_4, $La_{0.7}Ca_{0.3}MnO_3$, CdZnTe, CdMnTe, $CuInSe_2$, copper indium gallium selenide (CIGS), HgCdTe, HgZnTe, HgZnSe, PbSnTe, Tl_2SnTe_5, Tl_2GeTe_5, AlGaAs, AlGaN, AlGaP, AlInAs, AlInSb, AlInP, AlInAsP, AlGaAsN, GaAsP, GaAsN, GaMnAs, GaAsSbN, GaInAs, GaInP, AlGaAsSb, AlGaAsP, AlGaInP, GaInAsP, InGaAs, InGaP, InGaN, InAsSb, InGaSb, InMnAs, InGaAsP, InGaAsN, InAlAsN, GaInNAsSb, GaInAsSbP, and any combination of these. Porous silicon semiconductor materials are useful for aspects described herein. Impurities of semiconductor materials are atoms, elements, ions and/or molecules other than the semiconductor material(s) themselves or any dopants provided to the semiconductor material. Impurities are undesirable materials present in semiconductor materials which may negatively impact the electronic properties of semiconductor materials, and include but are not limited to oxygen, carbon, and metals including heavy metals. Heavy metal impurities include, but are not limited to, the group of elements between copper and lead on the periodic table, calcium, sodium, and all ions, compounds and/or complexes thereof.

[0092] A "semiconductor component" broadly refers to any semiconductor material, composition or structure, and expressly includes high quality single crystalline and

polycrystalline semiconductors, semiconductor materials fabricated via high temperature processing, doped semiconductor materials, inorganic semiconductors, and composite semiconductor materials.

[0093] A "component" is used broadly to refer to an individual part of a device. An "interconnect" is one example of a component, and refers to an electrically conducting structure capable of establishing an electrical connection with another component or between components. In particular, an interconnect may establish electrical contact between components that are separate. Depending on the desired device specifications, operation, and application, an interconnect is made from a suitable material. Suitable conductive materials include semiconductors.

[0094] Other components include, but are not limited to, thin film transistors (TFTs), transistors, electrodes, integrated circuits, circuit elements, control elements, microprocessors, transducers, islands, bridges and combinations thereof. Components may be connected to one or more contact pads as known in the art, such as by metal evaporation, wire bonding, and application of solids or conductive pastes, for example.

[0095] "Neutral mechanical plane" (NMP) refers to an imaginary plane existing in the lateral, *b*, and longitudinal, *l*, directions of a device. The NMP is less susceptible to bending stress than other planes of the device that lie at more extreme positions along the vertical, *h*, axis of the device and/or within more bendable layers of the device. Thus, the position of the NMP is determined by both the thickness of the device and the materials forming the layer(s) of the device.

[0096] "Coincident" refers to the relative position of two or more objects, planes or surfaces, for example a surface such as a neutral mechanical plane that is positioned within or is adjacent to a layer, such as a functional layer, substrate layer, or other layer. In an embodiment, a neutral mechanical plane is positioned to correspond to the most strain-sensitive layer or material within the layer.

[0097] "Proximate" refers to the relative position of two or more objects, planes or surfaces, for example a neutral mechanical plane that closely follows the position of a layer, such as a functional layer, substrate layer, or other layer while still providing desired conformability without an adverse impact on the strain-sensitive material physical properties. "Strain-sensitive" refers to a material that fractures or is otherwise

impaired in response to a relatively low level of strain. In general, a layer having a high strain sensitivity, and consequently being prone to being the first layer to fracture, is located in the functional layer, such as a functional layer containing a relatively brittle semiconductor or other strain-sensitive device element. A neutral mechanical plane that is proximate to a layer need not be constrained within that layer, but may be positioned proximate or sufficiently near to provide a functional benefit of reducing the strain on the strain-sensitive device element when the device is conformed to a tissue surface.

[0098] "Electronic device" generally refers to a device incorporating a plurality of components, and includes large area electronics, printed wire boards, integrated circuits, component arrays, biological and/or chemical sensors, and physical sensors (e.g., temperature, etc.).

[0099] "Sensing" refers to detecting the presence, absence, amount, magnitude or intensity of a physical and/or chemical property. Useful electronic device components for sensing include, but are not limited to electrode elements, chemical or biological sensor elements, pH sensors, temperature sensors and capacitive sensors.

[00100] "Actuating" refers to stimulating, controlling, or otherwise affecting an external structure, material or fluid, for example a biological tissue. Useful electronic device components for actuating include, but are not limited to, electrode elements, electromagnetic radiation emitting elements, light emitting diodes, lasers, and heating elements.

[00101] "Island" refers to a relatively rigid component of an electronic device comprising a plurality of semiconductor components. "Bridge" refers to structures interconnecting two or more islands or one island to another component. Specific bridge structures include semiconductor interconnects.

[00102] "Encapsulate" refers to the orientation of one structure such that it is at least partially, and in some cases completely, surrounded by one or more other structures. "Partially encapsulated" refers to the orientation of one structure such that it is partially surrounded by one or more other structures. "Completely encapsulated" refers to the orientation of one structure such that it is completely surrounded by one or more other structures. The invention includes implantable devices having partially or completely encapsulated inorganic semiconductor components and/or electrodes.

[00103] "Barrier layer" refers to a component spatially separating two or more other components or spatially separating a component from a structure, material or fluid external to the device. In one embodiment, a barrier layer encapsulates one or more components. In some embodiments, a barrier layer separates one or more components from an aqueous solution, a biological tissue or both.

[00104] A barrier layer(s), and optionally a sacrificial layer on a substrate, may be etched to produce a "mesh structure", where at least a portion of the barrier layer(s), and optionally the sacrificial layer on a substrate , is removed. For example a portion of the barrier layer(s) disposed approximately 10 nanometers or more from an inorganic semiconductor component or additional component is removed. Removal of at least a portion of the barrier layer(s), and optionally the sacrificial layer on the substrate, may produce (i) one or more holes within the barrier layer(s) and/or (ii) electrical components, which are physically joined by a barrier layer(s) at a proximal end and physically separated at a distal end. In one embodiment, a mesh structure may be disposed upon a contiguous bioresorbable substrate, which provides structural support for the device during deployment into a biological environment.

[00105] "Contiguous" refers to materials or layers that are touching or connected throughout in an unbroken sequence. In one embodiment, a contiguous layer of an implantable biomedical device has not been etched to remove a substantial portion (e.g., 10% or more) of the originally provided material or layer.

[00106] "Active circuit" and "active circuitry" refer to one or more components configured for performing a specific function. Useful active circuits include, but are not limited to, amplifier circuits, multiplexing circuits, current limiting circuits, integrated circuits, transistors and transistor arrays.

[00107] "Substrate" refers to a material, layer or other structure having a surface, such as a receiving surface, that is capable of supporting one or more components or electronic devices. A component that is "bonded" to the substrate refers to a component that is in physical contact with the substrate and unable to substantially move relative to the substrate surface to which it is bonded. Unbonded components or portions of a component, in contrast, are capable of substantial movement relative to the substrate.

[00108] "Bioresorbable" refers to a material that is susceptible to being chemically broken down into lower molecular weight chemical moieties by reagents that are naturally present in a biological environment. In an *in-vivo* application, the chemical moieties may be assimilated into human or animal tissue. A bioresorbable material that is "substantially completely" resorbed is highly resorbed (e.g., 95% resorbed, or 98% resorbed, or 99% resorbed, or 99.9% resorbed, or 99.99% resorbed), but not completely (i.e., 100%) resorbed.

[00109] "Biocompatible" refers to a material that does not elicit an immunological rejection or detrimental effect when it is disposed within an *in-vivo* biological environment. For example, a biological marker indicative of an immune response changes less than 10%, or less than 20%, or less than 25%, or less than 40%, or less than 50% from a baseline value when a biocompatible material is implanted into a human or animal.

[00110] "Bioinert" refers to a material that does not elicit an immune response from a human or animal when it is disposed within an *in-vivo* biological environment. For example, a biological marker indicative of an immune response remains substantially constant (plus or minus 5% of a baseline value) when a bioinert material is implanted into a human or animal.

[00111] "Nanostructured contact surface" and "microstructured contact surface" refer to device surfaces having nanometer-sized and micrometer-sized relief features, respectively, for contacting and penetrating a target tissue and improving adhesion between the implantable biomedical device and the target tissue. The relief features extend a length, *x*, from a substantially contiguous plane of the device surface. Quantitative descriptors of a structured contact surface include surface roughness parameters, such as R_{max}, R_a, and normalized roughness (R_a/R_{max}), all of which may be measured by atomic force microscopy (AFM). R_{max} is the maximum height between a highest peak to a lowest valley. R_a is the center-line-mean roughness, which is the average of an absolute value of a deviation from a center line of a roughness curve to the roughness curve. The surface of a substrate or barrier layer is "substantially smooth", for the purposes of this disclosure, if the surface has an R_a value of 100 nm or less. If the surface has an R_a value greater than 100 nm, the surface is considered to be a "structured surface" for purposes of this disclosure. A structured surface may

contain at least one feature selected from the group consisting of barbs, spikes, protrusions and any combination of these.

[00112] "Dielectric" refers to a non-conducting or insulating material. In an embodiment, an inorganic dielectric comprises a dielectric material substantially free of carbon. Specific examples of inorganic dielectric materials include, but are not limited to, silicon nitride, silicon dioxide and polymers.

[00113] "Polymer" refers to a macromolecule composed of repeating structural units connected by covalent chemical bonds or the polymerization product of one or more monomers, often characterized by a high molecular weight. The term polymer includes homopolymers, or polymers consisting essentially of a single repeating monomer subunit. The term polymer also includes copolymers, or polymers consisting essentially of two or more monomer subunits, such as random, block, alternating, segmented, grafted, tapered and other copolymers. Useful polymers include organic polymers or inorganic polymers that may be in amorphous, semi-amorphous, crystalline or partially crystalline states. Crosslinked polymers having linked monomer chains are particularly useful for some applications. Polymers useable in the methods, devices and components include, but are not limited to, plastics, elastomers, thermoplastic elastomers, elastoplastics, thermoplastics and acrylates. Exemplary polymers include, but are not limited to, acetal polymers, biodegradable polymers, cellulosic polymers, fluoropolymers, nylons, polyacrylonitrile polymers, polyamide-imide polymers, polyimides, polyarylates, polybenzimidazole, polybutylene, polycarbonate, polyesters, polyetherimide, polyethylene, polyethylene copolymers and modified polyethylenes, polyketones, poly(methyl methacrylate), polymethylpentene, polyphenylene oxides and polyphenylene sulfides, polyphthalamide, polypropylene, polyurethanes, styrenic resins, sulfone-based resins, vinyl-based resins, rubber (including natural rubber, styrene-butadiene, polybutadiene, neoprene, ethylene-propylene, butyl, nitrile, silicones), acrylic, nylon, polycarbonate, polyester, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polyolefin or any combinations of these.

[00114] "Elastomeric stamp" and "elastomeric transfer device" are used interchangeably and refer to an elastomeric material having a surface that can receive as well as transfer a material. Exemplary elastomeric transfer devices include stamps, molds and masks. The transfer device affects and/or facilitates material transfer from a donor material to a receiver material.

[00115] "Elastomer" refers to a polymeric material which can be stretched or deformed and returned to its original shape without substantial permanent deformation. Elastomers commonly undergo substantially elastic deformations. Useful elastomers include those comprising polymers, copolymers, composite materials or mixtures of polymers and copolymers. Elastomeric layer refers to a layer comprising at least one elastomer. Elastomeric layers may also include dopants and other non-elastomeric materials. Useful elastomers include, but are not limited to, thermoplastic elastomers, styrenic materials, olefinic materials, polyolefin, polyurethane thermoplastic elastomers, polyamides, synthetic rubbers, PDMS, polybutadiene, polyisobutylene, poly(styrene-butadiene-styrene), polyurethanes, polychloroprene and silicones. In some embodiments, an elastomeric stamp comprises an elastomer. Exemplary elastomers include, but are not limited to silicon containing polymers such as polysiloxanes including poly(dimethyl siloxane) (i.e. PDMS and h-PDMS), poly(methyl siloxane), partially alkylated poly(methyl siloxane), poly(alkyl methyl siloxane) and poly(phenyl methyl siloxane), silicon modified elastomers, thermoplastic elastomers, styrenic materials, olefinic materials, polyolefin, polyurethane thermoplastic elastomers, polyamides, synthetic rubbers, polyisobutylene, poly(styrene-butadiene-styrene), polyurethanes, polychloroprene and silicones. In an embodiment, a polymer is an elastomer.

[00116] "Conformable" refers to a device, material or substrate which has a bending stiffness that is sufficiently low to allow the device, material or substrate to adopt any desired contour profile, for example a contour profile allowing for conformal contact with a surface having a pattern of relief features. In certain embodiments, a desired contour profile is that of a tissue in a biological environment.

[00117] "Conformal contact" refers to contact established between a device and a receiving surface, which may for example be a target tissue in a biological environment. In one aspect, conformal contact involves a macroscopic adaptation of one or more surfaces (e.g., contact surfaces) of an implantable device to the overall shape of a tissue surface. In another aspect, conformal contact involves a microscopic adaptation of one or more surfaces (e.g., contact surfaces) of an implantable device to a tissue surface resulting in an intimate contact substantially free of voids. In an embodiment, conformal contact involves adaptation of a contact surface(s) of the implantable device to a receiving surface(s) of a tissue such that intimate contact is achieved, for example,

wherein less than 20% of the surface area of a contact surface of the implantable device does not physically contact the receiving surface, or optionally less than 10% of a contact surface of the implantable device does not physically contact the receiving surface, or optionally less than 5% of a contact surface of the implantable device does not physically contact the receiving surface.

[00118] "Young's modulus" is a mechanical property of a material, device or layer which refers to the ratio of stress to strain for a given substance. Young's modulus may be provided by the expression:

$$E = \frac{(\text{stress})}{(\text{strain})} = \left(\frac{L_0}{\Delta L}\right)\left(\frac{F}{A}\right), \qquad \text{(I)}$$

where E is Young's modulus, L_0 is the equilibrium length, ΔL is the length change under the applied stress, F is the force applied, and A is the area over which the force is applied. Young's modulus may also be expressed in terms of Lame constants via the equation:

$$E = \frac{\mu(3\lambda + 2\mu)}{\lambda + \mu}, \qquad \text{(II)}$$

where λ and μ are Lame constants. High Young's modulus (or "high modulus") and low Young's modulus (or "low modulus") are relative descriptors of the magnitude of Young's modulus in a given material, layer or device. In some embodiments, a high Young's modulus is larger than a low Young's modulus, preferably about 10 times larger for some applications, more preferably about 100 times larger for other applications, and even more preferably about 1000 times larger for yet other applications. In an embodiment, a low modulus layer has a Young's modulus less than 100 MPa, optionally less than 10 MPa, and optionally a Young's modulus selected from the range of 0.1 MPa to 50 MPa. . In an embodiment, a high modulus layer has a Young's modulus greater than 100 MPa, optionally greater than 10 GPa, and optionally a Young's modulus selected from the range of 1 GPa to 100 GPa.

[00119] "Inhomogeneous Young's modulus" refers to a material having a Young's modulus that spatially varies (e.g., changes with surface location). A material having an inhomogeneous Young's modulus may optionally be described in terms of a "bulk" or "average" Young's modulus for the entire material.

[00120] "Low modulus" refers to materials having a Young's modulus less than or equal to 10 MPa, less than or equal to 5 MPa or less than or equal to 1 MPa.

[00121] "Bending stiffness" is a mechanical property of a material, device or layer describing the resistance of the material, device or layer to an applied bending moment. Generally, bending stiffness is defined as the product of the modulus and area moment of inertia of the material, device or layer. A material having an inhomogeneous bending stiffness may optionally be described in terms of a "bulk" or "average" bending stiffness for the entire layer of material.

[00122] Described herein are implantable biomedical devices for sensing a parameter associated with a target tissue and/or actuating a target tissue in a biological environment, as well as methods for making and using the implantable biomedical devices. These devices are capable of intimate integration on the soft, curvilinear surfaces of biological tissues and are useful for monitoring and/or treating medical conditions in real time and with high spatial precision. The disclosed devices and methods also include those specially suited for monitoring and/or actuating tissues *in-vivo*. The approaches rely on dissolvable, biocompatible, and bioresorbable substrates, where dissolution and capillary forces drive a wrapping process. Purely passive electrode systems serve to demonstrate the advantages and underlying aspects of these systems, but the same approaches are compatible with fully active electronics and optoelectronics.

[00123] Implantable biomedical devices and methods of making and using the devices will now be described with reference to the figures. For clarity, multiple items within a figure may not be labeled and the figures may not be drawn to scale. Like numerals in multiple figures represent like items, and items numbered with parentheses, e.g., implantable biomedical devices **100(1)-100(7)**, represent species within a genus, which may be broadly referred to without parentheses, e.g., implantable biomedical device **100**.

[00124] Figure 1a shows a top plan view of an implantable biomedical device **100(1)** having a plurality of electronic interconnects **106** and electrodes **108**, which form part of an electronic device, disposed upon or encapsulated within a barrier layer **104(1)** that is supported by a bioresorbable substrate **102(1)**. Connection of an anisotropic conductive film (ACF) cable **110** to implantable biomedical device **100(1)** allows for communication

with a circuit board **112**, which may be used in conjunction with known software, memory devices, user interfaces, and power sources (not shown) to analyze data obtained from device **100(1)** and/or to deliver electromagnetic radiation to device **100(1)**. Figure 1b shows a cross-sectional view of implantable biomedical device **100(1)** taken through a plane defined by line **B-B**. Interconnects **106** are shown as encapsulated within barrier layer **104(1)** and coincident to a neutral mechanical plane (**NMP**) of the device. Figure 1c shows a cross-sectional view of implantable biomedical device **100(1)** taken through a plane defined by line **C-C**. Interconnects **106** remain disposed within barrier layer **104(1)**, but electrodes **108** are shown as exposed to ambient conditions. In other embodiments (not shown), the entire electronic device including electrodes **108** may be encapsulated within a barrier layer.

[00125] Figure 2 provides a top perspective view of implantable biomedical device **100(1)** having physical dimensions including a vertical dimension or height, *h*, a lateral dimension or width, *b*, and a longitudinal dimension or length, *L*. Implantable biomedical device **100(1)** may have any regular or irregular shape, but will often be in the form of a square or rectangular parallelogram.

[00126] Figure 3 shows a top plan view of an implantable biomedical device **100(2)** having islands **302** and bridges **304**, which form part of an electronic device. Islands **302** and bridges **304** are at least partially encapsulated by a barrier layer **104(2)** and supported by a bioresorbable substrate **102(2)**. Islands **302** may, for example, be rigid semiconductor components linked by bridges **304**, which may have a wavy, serpentine or meandering configuration that allows for a high degree of flexibility, bendability, conformability or compressibility. Bridges **304** may be disposed completely within the plane of the islands or at least a portion of bridges **304** may extend vertically above the plane of the islands, such that a void space exists beneath at least part of each bridge **304**.

[00127] Figure 4 shows a side plan view of an implantable biomedical device **100(3)** having a biocompatible layer **402** in addition to a bioresorbable substrate **102(3)**, a barrier layer **104(3)** and electronic device components **404**, such as interconnects, electrodes, islands, bridges, etc.

[00128] Figures 5a and 5b provide schematic illustrations of implantable biomedical devices **100(4)** and **100(5)** having mesh structures. Figure 5a shows an electronic

device having a tentacle mesh structure, where semiconductor components **502** are at least partially encapsulated by a barrier layer and/or biocompatible layer **508**. Layer **508** physically joins proximal ends **504** of semiconductor components **502**, but distal ends **506** of semiconductor components **502** are physically separated. In some embodiments, each semiconductor component **502** is separated from every other semiconductor component at its distal end **506**. In other embodiments, groups of two or more semiconductor components **502** may be physically separated from other groups of neighboring semiconductor components **502**. A bioresorbable substrate **102(4)** provides support for the mesh electronic device.

[00129] Figure 5b shows an electronic device having a perforated mesh structure, where semiconductor components in the form of islands **302** and bridges **304** are at least partially encapsulated by a barrier layer and/or biocompatible layer **510**. Layer **510** contains holes **512** where the material of layer **510** has been removed, e.g., by reactive ion etching. A bioresorbable substrate **102(5)** provides support for the mesh electronic device. Perforated mesh structures are not limited to electronic devices comprising islands and bridges. Barrier and/or biocompatible layer material may be removed to form holes in any of the electronic devices described herein. For example, etching of implantable biomedical device **100(4)** (Fig. 5a) that removes material between semiconductor components **502** but leaves both proximal **504** and distal **506** ends joined will create a perforated mesh structure.

[00130] Figure 6 provides a flowchart **600** illustrating exemplary steps for making implantable biomedical devices **100** having a mesh structure, e.g., **100(4)** and **100(5)**. In step **604**, a sacrificial layer is provided on a substrate. A first dielectric layer is applied to the sacrificial layer on a substrate in step **606**, and at least one inorganic semiconductor component is positioned or otherwise assembled on the first dielectric layer in step **608**. A portion of the at least one inorganic semiconductor component is covered with a second dielectric layer, in step **610**, to generate a covered inorganic semiconductor component having an exposed distal end. In step **612**, an electrode is positioned to physically contact the exposed distal end of the inorganic semiconductor component. A portion of the first and second dielectric layers is then removed to generate a mesh structure in step **614**. The sacrificial layer on the substrate is removed (e.g., dissolved or etched), in step **616**, to leave a substantially substrate-free, mesh structure. The substantially substrate-free, mesh structure is transferred to a

bioresorbable substrate in step **618**, for example using transfer printing, such as dry contact transfer printing.

[00131] Figure 7 provides a flowchart **700** illustrating exemplary steps for implanting a biomedical device **100**, and optionally using the implanted biomedical device to actuate a target tissue and/or sense a parameter associated with the target tissue. In step **704**, an implantable biomedical device **100** is provided. The implantable biomedical device is then contacted, in step **706**, with a target tissue in a biological environment and a bioresorbable substrate of the implantable biomedical device is at least partially resorbed to establish conformal contact between the implantable biomedical device and the target tissue, in step **708**. In optional step **710**, the target tissue is actuated. A voltage, electromagnetic radiation or current may be generated at a surface of the target tissue, in optional step **712**. In another optional step, **714**, a parameter associated with the target tissue may be sensed. A voltage, electromagnetic radiation or current may be measured at a surface of the target tissue, in optional step **716**. Steps **710** and **712** for actuating the target tissue and steps **714** and **716** for sensing a parameter associated with the tissue are not mutually exclusive. For example, in one embodiment, a portion of semiconductor components of an implantable biomedical device may actuate the target tissue while another portion senses parameters associated with the target tissue. In another embodiment, all the semiconductor components of an implantable biomedical device may alternately sense and actuate, e.g., in accordance with a feedback loop.

[00132] Figures 8a and 8b show side plan views of implantable biomedical devices **100(6)** and **100(7)** having planar contact surfaces **802** and nanostructured or microstructured contact surfaces **804**, respectively. As shown in Figure 8, barrier layer **104** interfaces with the target tissue. However, in alternate embodiments, bioresorbable substrate **102** may interface with the target tissue, and bioresorbable substrate **102** may be planar or structured. Structured contact surfaces **804**, have nanometer-sized or micrometer-sized relief features **806**, such as barbs **808**, spikes **810**, and protrusions **812**, which may extend a length, *x*, from a surface of implantable biomedical device **100(7)**.

[00133] In some embodiments, implantable biomedical devices advantageously utilize silk as a bioresorbable substrate. Silk is biocompatible, FDA-approved, optically transparent, mechanically robust (high mechanical modulus and toughness), and flexible in thin film form. It is also compatible with aqueous processing, which preserves

sensitive electronic functions, and amenable to chemical and biological functionalization. The presence of diverse amino acid side chains facilitates coupling chemistry for functionalizing silks. Silk is also water soluble with programmable rates of proteolytic biodegradation (yielding non-inflammatory amino acids) over a range from minutes to hours to years.

[00134] Some other natural polymers that exhibit properties similar to or analogous to silk include, but are not limited to, chitosan, collagen, gelatin, agarose, chitin, polyhydroxyalkanoates, pullan, starch (amylose amylopectin), cellulose, hyaluronic acid, or any combination of these.

[00135] Silk may be obtained from various natural sources, for example, from the silkworm *Bombyx mori* or from the spider *Nephila clavipes*. Silk solutions used in accordance with embodiments of the present invention may be obtained, for example, from a solution containing a dissolved silkworm silk (e.g. from *Bombyx mori*), a dissolved spider silk (e.g. from *Nephila clavipes*), or from a solution containing a recombinant silk, such as from bacteria, yeast, mammalian cells, transgenic animals, or transgenic plants.

[00136] In an embodiment, the silk of the bioresorbable substrate may be silk fibroin protein, which consists of layers of antiparallel beta sheets and has a primary structure consisting mainly of the recurrent amino acid sequence $(Gly\text{-}Ser\text{-}Gly\text{-}Ala\text{-}Gly\text{-}Ala)_n$. Fibroin is known to arrange itself in three structures, called silk I, II, and III. Silk I is the natural, amorphous form of fibroin, as emitted from the *Bombyx mori* silk glands. Silk II refers to the crystalline arrangement of fibroin molecules in spun silk, which has greater strength. Silk III is formed principally in solutions of fibroin at an interface (i.e. air-water interface, water-oil interface, etc.). In the disclosed implantable biomedical devices, silk I, II and/or III may be used.

[00137] Silk substrates were typically prepared from material derived from *Bombyx mori* cocoons, according to published procedures. *See,* Sofia, S., McCarthy, M.B., Gronowicz, G. & Kaplan, D.L. Functionalized silk-based biomaterials for bone formation. *J. Biomed. Mater. Res.* **54**, 139-148 (2001); Perry, H., Gopinath, A., Kaplan, D.L., Negro, L.D. & Omenetto, F.G. Nano- and micropatterning of optically transparent, mechanically robust, biocompatible silk fibroin films. *Adv. Mater.* **20**, 3070-3072 (2008); and WO 2008/108838. Briefly, boiling the cocoons in a 0.02 M aqueous solution of

sodium carbonate for 60 minutes removed sericin, a water-soluble glycoprotein that binds fibroin filaments in the cocoon but which can induce undesirable immunological responses. An aqueous solution of lithium bromide at 60°C solubilized the silk fibroin fibers and subsequent dialysis removed the lithium bromide. Centrifugation followed by microfiltration eliminated particulates to yield solutions of 8-10% silk fibroin with minimal contaminants.

[00138] Using an alternate method, silk solutions may be prepared using organic solvents, as described in WO 2008/108838 which is hereby incorporated by reference in its entirety. Use of organic solvents in the preparation of silk materials can alter the biocompatibility and physical properties of silk materials. For example, immersion of silk films in organic solvents, such as methanol, may cause dehydration of the hydrated or swollen structure, leading to crystallization and, thus, loss of solubility in water. Further, the use of organic solvents can render the silk material less degradable.

[00139] As noted above, the presence of organic solvents, as compared to aqueous solvents, in the silk solution, may generate silk substrates with more crystalline structures, as compared to amorphous structures. This phenomenon may be used to control, for example, the rate of bioresorption of the silk. Accordingly, depending on the desired resorption rate, the silk solution may be prepared using any suitable ratio of aqueous:organic solution, for example, 100% aqueous, about 80% aqueous, about 60% aqueous, about 50% aqueous, about 40% aqueous, about 20% aqueous, or about 10% aqueous.

[00140] Additional techniques may be used to control the bioresorption rate of the silk substrate. For example, the rate at which resorption occurs may be tailored by altering: substrate material, substrate thickness, crosslinking, the extent of inter-chain hydrogen bonding or Van der Waals forces, and/or molecular alignment (e.g., via mono-axial or bi-axial stretching, spinning into fiber, and/or weaving). In an embodiment, it may be desirable to rapidly resorb the bioresorbable substrate at the time of device implantation. Bioresorption may be accelerated, for example, by washing the implanted device with water or saline.

[00141] Additional bioresorbable polymers including, but not limited to, a biopolymer, a synthetic polymer, a protein, a polysaccharide, poly(glycerol-sebacate) (PGS), polydioxanone, poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), collagen,

chitosan, or any combination of these, may be used alone as the bioresorbable substrate or may be added to the silk solution to generate composite silk substrates. In one embodiment, a substrate comprises from about 50 to about 99.99 parts by volume (vol%) silk protein solution and from about 0.01 to about 50 vol% additional polymer.

[00142] In some aspects, implantable biomedical devices described herein may be used for drug delivery. In one embodiment, one or more therapeutic agents may be encapsulated within the substrate material as a liquid, a gel, a dispersed solid, or any other appropriate physical form, to be administered to a patient upon resorption of the substrate. To form these therapeutically enhanced substrate materials, the silk or other bioresorbable polymer solution may be mixed with one or more therapeutic agents, and optionally a pharmaceutically acceptable carrier, prior to forming the substrate. Any pharmaceutical carrier that does not dissolve the bioresorbable material may be used.

[00143] In some embodiments, implantable biomedical devices of the invention are used to administer, deliver and/or activate a therapeutic agent provided to a subject. In an embodiment of this aspect, the bioresorbable substrate is a multifunctional component that releases a therapeutic agent upon administration to a biological environment and/or contact with a target tissue. The invention includes, for example, bioresorbable substrates having embedded therapeutic agents, such as drugs (e.g., small molecule therapeutics), nanoparticles and/or biomolecules, such as proteins, peptides, oligonucleotides (e.g., DNA or RNA), etc. This aspect of the present invention may be useful for a range of therapeutic applications including controlled release of therapeutic agents and/or targeted administration of therapeutic agents to a selected tissue type. Release of the therapeutic agent in these embodiments may occur by processes mediated by resorption of the bioresorbable substrate in contact with a target tissue. The invention includes implantable devices and systems wherein the electronic device component mediates release of therapeutic agent from the bioresorbable substrate via thermal means, for example by local heating of components of the implantable device, such as the bioresorbable substrate. The invention includes implantable devices and systems wherein the electronic device component mediates release of therapeutic agent from the bioresorbable substrate via processes driven by generation and control of local electric fields, such as electrophoresis processes for the release of proteins or peptides. The invention includes implantable devices and systems wherein the electronic device component mediates release and/or activation of

a therapeutic agent from the bioresorbable substrate via processes driven by absorption of electromagnetic radiation. In an embodiment, the implantable device includes an electronic device component, such as a laser or LED array, capable of optically activating a therapeutic agent during and/or upon release from the bioresorbable substrate. This aspect of the invention is useful for therapeutic applications including phototherapy.

[00144] Therapeutic agents that may be used in conjunction with the devices described herein include, but are not limited to: small molecules; proteins; peptides; nucleotides; nucleic acids; carbohydrates; simple sugars; cells; genes; anti-thrombotics; anti-metabolics; anticoagulants; antimitotics; fibrinolytics; anti-inflammatory steroids; monoclonal antibodies; vitamins; sedatives; steroids; hypnotics; antiinfectives, such as antibiotics and antiviral agents; chemotherapeutic agents (i.e., anticancer agents); prostaglandins, radiopharmaceuticals, anti-rejection agents; analgesics; anti-inflammatory agents; hormones, such as steroids; growth factors (inhibitors and promoters), such as epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, insulin-like growth factor, transforming growth factors, and vascular endothelial growth factor; anti-angiogenic proteins such as endostatin; polysaccharides; glycoproteins; lipoproteins; and any combination of these.

[00145]

[00146] For example, a therapeutic agent circulating through an *in-vivo* biological environment may be activated when it receives electromagnetic radiation from a biomedical device implanted at a therapeutic site. In particular, energy within the ultraviolet and visible regions of the electromagnetic spectrum may be useful.

[00147] The invention may be further understood by the following non-limiting examples.

EXAMPLE 1: Silicon Electronics on Silk as a Path to Bioresorbable, Implantable Devices

[00148] Many existing and envisioned classes of implantable biomedical devices require high performance electronics/sensors. An approach that avoids some of the longer term challenges in biocompatibility involves a construction in which some parts or all of the system resorbs in the body over time. This example describes strategies for

integrating single crystalline silicon electronics, where the silicon is in the form of nanomembranes, onto water soluble and biocompatible silk substrates. Electrical, bending, water dissolution and animal toxicity studies suggest that this approach might provide many opportunities for future biomedical devices and clinical applications.

[00149] Advanced implantable biomedical devices have great potential in clinical applications. Systems that allow insertion into the body to establish conformal contact with the curvilinear surfaces of various organs must be flexible and biocompatible. The conformal and flexible characteristics could be enabled by recently reported organic, inorganic, and nanomaterial based electronics. Achieving biocompatibility, on the other hand, can be challenging, due to the complex nature of the biological response to many organic and inorganic materials. An ideal solution to this problem that largely avoids the longer term issues involves the construction of the electronics out of materials that are soluble and biodegradable; here the device simply disappears, or resorbs, over time. Alternatively, a large fraction of the device can be designed to resorb, such that a sufficiently small amount of material remains that its induced biological response is negligible. This approach has the advantage that it does not require the development of an entire set of biodegradable electronic materials, but still yields an overall system that dissipates bulk material features at a rate suitable for the application. This example describes the combination of silicon electronics, based on nanomembranes of silicon, with biodegradable thin film substrates of silk protein, to yield a flexible system and device that is largely resorbable in the body. The use of silicon provides high performance, good reliability, and robust operation. Silk is attractive, compared to other biodegradable polymers such as poly(glycolic acid), poly(L-lactic acid), and collagen, because of its robust mechanical properties, the ability to tailor the dissolution, and/or biodegradation rates from hours to years, the formation of noninflammatory amino acid degradation products, and the option to prepare the materials at ambient conditions to preserve sensitive electronic functions

[00150] Figure 9 shows the schematic fabrication process. Single crystalline nanomembranes of silicon (thickness ~260 nm p-type, SOITEC, France) were used to construct transistors on ultrathin sheets of polyimide (PI). Briefly, the doped silicon nanomembranes were transfer printed onto a film of PI (PI, ~1.2 μm, Sigma Aldrich, USA) cast onto a thin sacrificial layer of poly(methylmethacrylate) (PMMA, ~100 nm, A2 PMMA, MicroChem, USA) on a silicon wafer (i.e., carrier wafer for processing). After

printing, a series of fabrication processes, including photolithography, reactive ion etching, plasma enhanced chemical vapor deposition of oxides, and electron beam evaporation of metals, formed silicon metal oxide field effect transistors connected by metal lines. Next, spin coating a layer of PI (~1.2 μm) encapsulated the active devices and located them near the neutral mechanical plane. Dry etching the polymer layers completed the fabrication of an array of isolated devices on PMMA, as shown in Fig. 9(a). Next, dissolving the PMMA with acetone released the devices from the carrier wafer. These devices were lifted onto the surface of a transfer stamp of poly(dimethylsiloxane) (PDMS, Sylgard 184, Dow Corning, USA), as shown in Fig. 9(b). Transfer printing delivered the devices to either a spin cast film of silk on a silicon substrate (Fig. 9(c)) or a freestanding silk membrane (Fig. 9(d)). To accomplish transfer at high yield, a ~7% aqueous silk solution was spin coated on the backsides of the devices while on the PDMS stamp, at spin rates between 2000 and 3000 rpm for 30 s. This layer of silk served as an adhesive for a transfer, which involves first establishing conformal contact with the silk substrate while on a hot plate (~110 °C) and then slowly retrieving the stamp. This process yielded a system in which the substrate is water soluble, and resorbable, but the devices are not, as shown in the schematic diagram in Fig. 9(d). An important point is that the devices can be constructed in very small dimensions (interconnected or not, depending on the application), with very small total amounts of material, thereby offering the possibility to minimize their effects on the biology. Further, the mode of processing the silk can be designed to yield rapid dissolution rates, as is the case here, or to degrade over years.

[00151] Figure 10(a) shows a freestanding silk film with transfer printed silicon devices. The center and right frames of Fig. 10(a) demonstrate the mechanical flexibility of the system. Under bending at these levels (radius of curvature, *R*, as ~5 mm), no mechanical or adhesive failure was observed. It is estimated that the bend induced strains at the top surface of the silk film (~25 μm, ~5 mm bending radius) are in the range of ~0.25%. Electrical measurements of a typical *n* channel device show expected properties (solid line of Fig. 10(b)). Here, the channel length and width was 13 and 100 μm, respectively, and the gate oxide thickness was 50 nm. The electron mobility, threshold voltage, and on/off ratio calculated from the transfer curve in the left frame of Fig. 10(b) are ~500 cm^2/V s, ~0.2 V, and $>10^4$, respectively. The current-voltage characteristics at different gate biases are shown in the right frame of Fig. 10(b). The gate leakage current was less than tens of picoamperes. Also, the *n*MOS transistor was

characterized after dissolving the silk substrate in water and then filtering out the devices onto filter paper (dotted line of Fig. 10(b)). Even after dissolution, the transistors functioned with only modest changes in properties. The electron mobility, threshold voltage, and on/off ratio were estimated from the transfer curves to be ~440 cm^2/V s, ~0.5 V, and $>10^4$.

[00152] This dissolution process relies on the capability of silk to disintegrate in water, leaving proteins as the products that are then degraded by proteolytic activity. The resulting silk fibroin protein is a Food and Drug Administration (FDA) approved biocompatible material that generates noninflammatory amino acid degradation products usable in cell metabolic functions. Further, the mechanical properties of the silk substrate can be tailored, based on the mode of processing, to match the level of toughness required. To illustrate the process, images were collected at various times after dipping a typical device into a petri dish filled with water, at room temperature. With a ~25 μm thick silk substrate, complete dissolution within 3 min was observed, as shown in Figs. 11(a) and 11(b). Figure 11(c) shows devices recovered onto a piece of filter paper. Since the vast majority of this type of implantable device consists of the substrate and because the sizes of the active devices can be reduced even further by using standard microelectronic technology, very tiny or negligible residues of nonresorbable materials can remain after dissolution.

[00153] Similar types of devices were implanted into animals to determine the inflammatory response. Here, the devices consisted of doped silicon, silicon dioxide, and metal layers encapsulated with PI, similar to those described previously. Since PI and gold are known to be biocompatible, the main concerns were for the silicon and silicon dioxide. Recent reports on the biocompatibility of porous nanoparticles of silicon and silicon dioxide suggest the possibility of biocompatibility in the Si/SiO_2 components used in the transistors. To examine this issue directly, samples were implanted subcutaneously in mice (left and center frame of Fig. 12) and retrieved after two weeks. The results show the partial dissolution of the film in this time frame, as well as the lack of any inflammation around the implant site. The mice did not exhibit any sign of abscessing or liquid buildup, and initial integration of the silk carrier into the subcutaneous layers could be observed. The size of the implant is estimated to be between 15% - 20% smaller than the originally implanted device and detachment of a few transistor structures can be observed, as shown in the right frame of Fig. 12.

Although additional studies are required, these initial in vivo tests suggest some promise for this form of biodegradable electronics.

[00154] In conclusion, unconventional material processing and device fabrication procedures have been developed for a class of implantable biomedical device that is largely, but not completely, bioresorbable. The systems combine an FDA approved biomaterial substrate, silk, and with silicon nanomaterial electronic devices. Preliminary in vivo toxicity and inflammatory evaluations showed no harmful effects on a living animal. A technology of this type could open various possible applications for insertion of high performance flexible electronics into implantable biomedical devices. Further, since silk is the toughest known natural biopolymer in fiber form, this substrate provides a suitable base substrate upon which to develop a family of such implantable devices, where *in vivo* lifetime of components can be tailored from short to long term, hours to years.

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EXAMPLE 2: Dissolvable Films of Silk Fibroin for Ultrathin, Conformal Bio-Integrated Electronics

[00168] Electronics that are capable of intimate, non-invasive integration with the soft, curvilinear surfaces of biological tissues offer important opportunities for diagnosing and treating disease and for improving brain-machine interfaces. This example describes a material strategy for a type of bio-interfaced system that relies on ultrathin electronics supported by bioresorbable substrates of silk fibroin. Mounting such devices on tissue and then allowing the silk to dissolve and resorb initiates a spontaneous, conformal wrapping process driven by capillary forces at the biotic / abiotic interface. Specialized mesh designs and ultrathin forms for the electronics ensure minimal stresses on the tissue and highly conformal coverage, even for complex curvilinear surfaces. Combined experimental and theoretical studies of the materials and underlying mechanics reveal the key mechanisms. In vivo, neural mapping experiments on feline animal models illustrate one mode of use for this class of technology. These concepts provide capabilities for implantable or surgical devices that lie outside those of wafer-based technologies or known forms of flexible electronics.

[00169] Strategies for bio-integrated electronics must overcome the challenges associated with the mismatch between the hard, planar surfaces of semiconductor wafers and the soft, curvilinear tissues of biological systems. These differences in

mechanics and form lead, almost invariably, to low fidelity coupling at the biotic/abiotic interface and limited long-term tissue health. The difficulties are most pronounced and the solutions are perhaps most important in systems designed for brain-computer interfaces (BCIs). Penetrating microelectrode arrays consisting of sharp pins (typically, 10 x 10 arrays of pins with base widths ~80 μm, lengths ~1.5 mm and pitch ~400 μm) that connect to flat platforms for conventional wafer-based electronics are valuable for research in BCI, but they damage the tissue and do not offer long-term electrical interface stability. Comparable BCI performance can be achieved with non-penetrating, surface electrode systems that are minimally-invasive and provide greatly improved stability. Standard clinical subdural electrode arrays are useful for BCI but their widely spaced (~1 cm), large contact electrodes (~0.35 cm diameter) spatially undersample the electrical signals present on the surface of the brain. Decreasing the spacing and size of the measurement points can improve BCI performance by providing access to high temporal and spatial frequency signals. Such designs, however, demand excellent conformal coverage over the highly convoluted brain surface to ensure direct coupling between the brain surface and the electrodes.

[00170] Reducing the thickness of the substrate decreases the bending rigidity, thereby improving conformal contact. Unfortunately, clinical arrays and even the thinnest devices designed for research have thicknesses (700 μm and >10 μm, respectively) that are larger than desired. In conventional designs, ultrathin geometries (i.e. < 10 μm; thinner better) are impractical because the films are not sufficiently self-supporting to be manipulated effectively during fabrication or implantation. Another disadvantage is that even extremely thin, flexible systems can only wrap shapes with zero Gaussian curvature (i.e. developable surfaces such as cylinders and cones). Complex surfaces of tissue like the brain are impossible without introducing wrinkles or folds. This example presents solutions to these two problems, via the combined use of ultrathin electronics (down to <3 μm) in highly open, mesh geometries mounted on sacrificial, bioresorbable silk fibroin substrates.

[00171] Silk is an appealing biopolymer for this application because it is optically transparent, mechanically robust and flexible in thin film form, compatible with aqueous processing, amenable to chemical and biological functionalization, and it is biocompatible, bioresorbable, and water soluble with programmable rates of dissolution. In addition, the ability of silk films to serve as a platform for transistors and various

classes of photonic devices has been demonstrated. The process for preparing silk substrates for the purposes reported here began with material derived from *Bombyx mori* cocoons, and followed published procedures. Briefly, boiling the cocoons in a 0.02 M aqueous solution of sodium carbonate for 60 minutes removed sericin, a water-soluble glycoprotein that binds fibroin filaments in the cocoon but can induce undesirable immunological responses. An aqueous solution of lithium bromide at 60 °C solubilized the fibers and subsequent dialysis removed the lithium bromide. Centrifugation followed by micro-filtration eliminated particulates to yield solutions of 8% - 10% silk fibroin with minimal contaminants. Casting a small amount of the solution on a flat piece of poly(dimethylsiloxane) (PDMS) followed by crystallization in air (~12 h) yielded uniform films (thickness of 20-50 μm) (Fig 13a) that were subsequently removed from the PDMS for integration with separately fabricated electronics.

[00172] For the systems described in the following, polyimide (PI) served as a support for arrays of electrodes designed for passive neural recording. Control devices consisted of otherwise similar layouts, but formed using standard photolithographic procedures applied directly on commercial PI films (Kapton, DuPont) with thicknesses of 25 and 75 μm (Fig 14). Anisotropic conductive film (ACF) bonded to electrode pads at one end of the arrays provided electrical connection to the external data acquisition system (Fig 15). Ultrathin PI films, with or without mesh layouts, cannot be manipulated effectively for processing, interconnecting or implanting onto the brain due to their extreme flexibility and mechanical fragility. For these cases, the fabrication process exploited layers of PI spin cast onto silicon wafers coated with sacrificial films of poly(methylmethacrylate) (PMMA) (left frame of Fig 13b). After the electrode fabrication, the mesh structure devices underwent further etching to remove unwanted parts of the PI. The processing was completed by dissolving the PMMA layer with acetone, transfer printing the entire assembly to a film of silk and connecting the ACF, yielding easily manipulated bioresorbable neural recording systems. See schematic illustrations and images of Fig. 13b. In all cases, the electrode arrays consisted of 30 measurement electrodes (Au, 150 nm) in a 6 x 5 configuration, each with dimensions of 500 μm x 500 μm and spaced by 2 mm. Interconnection wires to each electrode were protected by a thin (~1.2 μm) overcoat of PI to prevent contact with the tissue. Details of the fabrication steps appear in the methods section. The electrode arrays were implanted by placing them on the brain and then flushing with saline to dissolve the silk, thereby inducing

spontaneous, conformal wrapping of the device, as illustrated schematically for the mesh design in Fig. 13c.

[00173] The sequence of images in Fig. 16a shows the dissolution process for a representative case (7 μm thick PI film, connected to ACF on a silk substrate with thickness of ~25 μm) inserted into warm water (~35 °C). As the silk substrate disappears, the total bending stiffness, *EI*, diminishes dramatically due to its cubic dependence on thickness. Computed results appear in Fig 16b and Fig 16d for PI thicknesses of 2.5 and 7 μm. To highlight the benefits of reduced thickness, the inset shows the ratio of *EI* for these two cases. Through programmed control of the dissolution rate via modifications of the silk protein secondary structure, these changes in *EI* can be designed to occur over periods of time ranging from seconds to years, depending on requirements. Figure 16c shows, as an example, the dissolution rate of silk film slightly treated with ethanol (left frame) and computed time dependence of *EI* in devices that employ more thorough ethanol treatment (right frame). See below for detailed conditions. This dissolution time can be lengthened even more by extending the treatment time to days or weeks; the corresponding time dependence of *EI* appears in Fig 17.

[00174] To examine the ability of these systems to conform to relevant surfaces, experiments were performed using a human brain model, following the basic steps shown in Fig. 13c. Figure 18 provides images for various cases after washing with saline, including relatively thick control devices that do not incorporate silk. Clearly, the extent of conformal coverage increases with decreasing thickness; the mesh design provides further improvements, as shown in Figs. 18d, 19 and 20. To reveal the underlying mechanics, systematic and quantitative studies were performed on well-defined surfaces that capture certain basic features of the curvature of the brain. The first set of experiments explored wrapping the devices on isolated and overlapped cylindrical surfaces. Figure 21a shows the simplest case of a device with bending stiffness *EI*, thickness *h*, width *b* and length 2*L*, wrapped on a cylinder with radius *R*. Analytical expressions for *EI* can be written for the multilayer structures of Fig. 13 in terms of material properties and geometries, as described below. The unwrapped state (top frame of Fig. 21a) corresponds to zero energy. The energy of the wrapped state (center frame of Fig. 21a) consists of two parts, the bending energy of the thin film $Ub = EIL/R^2$, and the adhesion energy between the thin film and the cylinder $U_a = -2\gamma bL$,

where γ is the adhesion energy per unit area. For the wrapped state to be energetically favorable, $U_b + U_a \leq 0$, which gives

$$\gamma \geq \gamma_c = \frac{EI}{2R^2 b}. \tag{1}$$

The bottom frame of Fig. 21a compares the above relation with a series of experiments (Fig. 22). The data are consistent with an adhesion energy per unit area γ on the order of 10 mJ/m^2, which is comparable to reported values for wet interfaces. Reducing the thickness provides clear benefits, e.g. wrapping cylinders using only capillary adhesion forces is possible for R ~1 cm when h < ~15 μm.

[00175] A pair of overlapped cylinders represents a simple model for a gyrus of the brain. Figure 21b shows cylinders with radii R, a center-to-center separation of $2d$ and connected by a smooth arc of radius r_0, at the angular position $\theta_0 \sin^{-1}[d/(R + r_0)]$. As with the single cylinder, the energy of the unwrapped state (top frame of Fig. 21b) was chosen to be zero. The wrapped configuration involves bending energy of the film and adhesion energy at the interface, according to (see below for details)

$$U_2 = \frac{EI}{R}\left[\frac{R\theta\sin\theta}{d - R\sin\theta} - \left(\frac{\gamma}{\gamma_c} - 1\right)\left(\frac{L}{R} + \theta - \frac{d\theta}{R\sin\theta}\right)\right]. \tag{2}$$

where γ_c is given in Eq. (1), and θ is the contact angle of thin film with one cylinder, which is determined by minimizing U_2 to give

$$\frac{R\sin\theta}{d - R\sin\theta} + \frac{dR\theta\cos\theta}{(d - R\sin\theta)^2} - \left(\frac{\gamma}{\gamma_c} - 1\right)\left(1 - \frac{d}{R\sin\theta} + \frac{d\theta\cos\theta}{R\sin^2\theta}\right) = 0. \tag{3}$$

The solution of Eq. 3 takes the form $\theta = \theta(d/R, \gamma/\gamma_c)$. For $\gamma_c < \gamma_c$, the energy has a minimum at θ = 0, and the film does not wrap around the cylinders. Partial wrapping occurs to a contact angle of θ (i.e. contact for angles between 0 and $\theta < \theta_0$) for $\gamma_c \leq \gamma < \gamma'_c$, where γ'_c is obtained from Eq. (3) with $\theta = \theta_0$ as $\gamma'_c = \gamma_c\left\{1 + (1+\lambda)R^2 / \left[(1-\lambda)r_0^2\right]\right\}$ and $\lambda = r_0 d \Big/ \left\{(R + r_0)\sqrt{(R + r_0)^2 - d^2}\sin^{-1}\left[d/(R + r_0)\right]\right\}$. For $\gamma \geq \gamma'_c$, wrapping is complete (i.e. conformal contact for angles between 0 and θ_0). By comparing Eq. (3) with the experiment in Fig. 23, the extracted adhesion energy per unit area is found to be γ =

10mJ/ m^2. Results appear in the bottom frame of Fig. 21b, where the parameters correspond roughly to features on the brain model: R=6.14 mm, d=5.93 mm and r_0=1.72 mm. (Experimental images appear in Fig. 23.) The critical thickness for conformal contact is h_0 = 4.9 μm, i.e., devices thinner than ~4.9 μm achieve conformal contact on this surface. The experimental results are consistent with this calculation.

[00176] Cylindrical surfaces like those of Fig. 21a and 21b are developable; the brain is not. As a model of non-developable surface, the case of a hemispherical substrate was examined. Figure 21c shows results for electrode arrays with sheet designs at thicknesses of 7 and 2.5 μm and with an open mesh layout at 2.5 μm, each on a glass hemisphere with radius of curvature of 6.3 mm. With only water capillarity as the adhesion force, the mesh electrode array achieves excellent conformal contact. The sheets show comparatively poor contact, with large wrinkles, even for the thinnest case (i.e. 2.5 μm). Mechanical analysis of a simple model reveals the underlying physics. The left frame of Fig. 21d shows the case of a circular film with radius $r+w$ wrapped onto a sphere with radius R. The central green part denotes a PI plate of radius r, tension stiffness $(Eh)_{PI}$ and equi-biaxial bending stiffness $(EI)_{PI}$. The yellow ring corresponds to a multilayer structure of PI and Au, of width w, tension stiffness $(Eh)_{composite}$ and equi-biaxial bending stiffness $(EI)_{composite}$. For the film to wrap around the sphere, the required minimum adhesion energy per unit area is obtained analytically as

$$\gamma_c^{sheet} = \frac{(EI)_{PI}}{R^2} + \frac{(Eh)_{PI}}{r^2}\int_0^r \left(1-\frac{R}{x}\sin\frac{x}{R}\right)^2 x dx + \frac{2w(EI)_{composite}}{rR^2} + \frac{w(Eh)_{composite}}{r}\left(1-\frac{R}{r}\sin\frac{r}{R}\right)^2 . \quad (4)$$

A model for the mesh design that consists of only a circular strip of a corresponding multilayer of PI and Au appears in the right frame of Fig. 21d. In this case, the minimum adhesion energy per unit area is

$$\gamma_c^{mesh} = \frac{(EI)_{composite}}{R^2} + \frac{w^2(Eh)_{composite}}{24r^2}\left(1-\sqrt{1-\frac{r^2}{R^2}}\right)^2 . \quad (5)$$

[00177] For the case that w <<r, γ_c^{sheet} in Eq. (4) is always larger than γ_c^{mesh} in Eq. (5), i.e., $\gamma_c^{sheet} > \gamma_c^{mesh}$. The inference is that the open mesh design requires much lower adhesion energy than the corresponding sheet, thereby leading to greatly improved ability for conformal coverage, as shown in the left frame of Fig. 21e. Figure 24a shows

critical adhesion energies for films with thicknesses up to 80 μm. For a thickness of 2.5 μm and $w/r = 4$, $\gamma_c^{sheet} = 29.1 mJ/m^2$ for the sheet, which is more than 12 times larger than the mesh $\gamma_c^{mesh} = 2.4 mJ/m^2$. In addition, the mesh design involves membrane strains that are smaller, by roughly a factor of w/r, compared to sheets with similar thickness. For the experimental mesh systems, this ratio is on the order of 1/4. As a result, for a representative critical wrinkling strain of 0.1%, nearly two thirds of the sheet will wrinkle. Under the same conditions, the entire mesh gives perfect, conformal contact. Finally, the normal (peeling) interfacial stresses for the mesh is only 1/4 of that for the sheet (right frame of Fig. 21e and Fig. 24b), leading to improved adhesion and reduced forces applied to the substrate. See below for details.

[00178] *In-vivo* neural monitoring experiments on a feline animal model demonstrated the practical implications of these favorable mechanics. The tests involved an anesthetized cat mounted in a sterotaxic apparatus with its eyes focused on a monitor that subtended 28 x 22 degrees of space. An initial craniotomy and durotomy exposed a 2 x 3 cm region of cortex. The electrode arrays covered much of visual cortex, as shown in the left frames of Fig 25a, b and c. Visual stimuli consisted of full-field drifting gratings presented for 1 second at 2 Hz with a spatial frequency of 0.5 cycles/degree. Gratings were presented at 2 different directions over 8 different orientations (16 unique stimuli).

[00179] Three kinds of electrode arrays were used for comparison: 76 μm and 2.5 μm thick sheets and a 2.5 μm thick mesh. The second two included dissolvable silk supports. The left images of Fig 25a, b and c illustrate the progressively improved conformal contact with reduced thickness (i.e. 76 μm to 2.5 μm, in Fig. 25a and b, respectively) and with introduction of the mesh (i.e. Fig. 25c). The right frames of Fig 25a, b and c demonstrate the effectiveness of decreasing the electrode thickness and the mesh structure on physiological measurements of brain activity. In particular, these frames show the average evoked response measured at each electrode, each plotted in a spatial orientation that corresponds to the images in the left frames. The background color of each plot illustrates the zero-lag cross-correlation between the evoked response on that electrode and an average of all the responses from the entire array. The color bar at the bottom of Fig. 25c provides the numerical scale for all of the colors used in Fig 25a, b and c. This measurement serves as a quantitative metric of the electrode performance, because the uniform nature of the stimulation is expected to

evoke similar responses across the entire visual cortex. In each case, 28 of the 30 electrode channels were recorded and evaluated for evoked potential response, as colored in green through red. Two channels, indicated in grey, served as local reference. The channels with high and low correlations to the average response are colored green and red, respectively. The 76 μm (Fig 25a) electrode array exhibited the fewest channels with good response, due to poor contact at many of the electrodes. The 2.5 μm array (Fig 25b) showed better conformal contact and correspondingly more channels with good responses. The 2.5 μm mesh electrode (Fig 25c) showed the best performance, with nearly all channels in good contact and with highly correlated responses. Figure 25d shows representative single channel data from one of the 2.5 μm mesh electrodes. A sleep spindle is observed with good signal amplitude and signal to noise ratio. This collective set of observations is consistent with the systematic mechanics studies described previously.

[00180] In summary, this example introduces a class of conformal electronics capable of intimate integration on the soft, curvilinear surfaces of biological tissues. The approaches rely on dissolvable, biocompatible and bioresorbable substrates, where dissolution and capillary forces drive a wrapping process in a non-invasive manner. Although purely passive electrode systems serve to demonstrate the advantages and underlying aspects of these systems, the same approaches are compatible with fully active electronics and optoelectronics. As a result, these concepts may have the potential to yield important technologies for human health, by providing capabilities that are unavailable with established classes of implantable devices.

[00181] **METHODS**. THICK ELECTRODE ARRAY (> 25 μM) FABRICATION. Commercial PI films (Kapton, Dupont, USA) with thicknesses of 25 and 75 μm were attached to a temporary carrier substrate consisting of a glass slide coated with PDMS. After cleaning the surfaces with acetone, isopropyl alcohol (IPA) and deionized (DI) water, electron beam evaporation formed uniform coatings of metal (Cr/Au, 50/1450 A). Photolithography and patterned etching yielded arrays of interconnect lines. Thin layers of PI (thickness ~1.2 μm) spin cast and patterned by reactive ion etching left only the ends of the lines exposed. Additional deposition and patterning defined square metal electrode pads at these locations. Peeling away from the PDMS coated glass slide and bonding to on ACF cable, using procedures described in a separate section, completed the fabrication. Figure 14 provides a schematic diagram and images of the process.

[00182] THIN ELECTRODE ARRAY (< 10 μM) FABRICATION. The fabrication in this case used a carrier silicon wafer coated with a thin (~1.2 μm) spin cast layer of poly(methylmethacrylate) (PMMA, A2, MicroChem, USA). The device substrate consisted of a film of PI (Sigma Aldrich, USA) spin cast onto the PMMA. Procedures similar to those described for thick devices formed the metal electrodes and PI overcoat. After fabrication, the ultrathin devices were released by dissolving the sacrificial PMMA layer. Transfer printing with a PDMS stamp delivered the devices to dry silk film substrates, coated with ~9% silk solution as an adhesive. The final step involved bonding of an ACF cable.

[00183] MESH ELECTRODE ARRAY (< 10 μM) FABRICATION. The first and last parts of the fabrication sequence were identical to the steps outlined in the previous section. The only difference was the addition of a step to remove certain regions of the polymer layers (i.e. PI and underlying PMMA) by oxygen reactive ion etching through a mask (design in Fig. 26) to define the mesh structure. Detailed dimensions are as follows: thickness ~2.5 μm, contact electrode size 500 μm x 500 μm, mesh width ~250 μm. (See more details in Fig. 19) This etching immediately followed the formation of the electrode pads.

[00184] ACF CONNECTION. The contact pads on the electrode array were first aligned with the ACF cable. Metal clips were used to apply pressure, spread evenly over the contact pad area using a piece of PDMS inserted between the ACF and the clips. Next, the clamped sample and ACF were placed in an oven preheated to ~150 °C for ~15 min. This process formed a strong mechanical bond between the electrode array and the ACF with low electrical resistance.

[00185] ACQUISITION SYSTEM. The electrode arrays were connected to a Neuralynx DigitalLynx data acquisition system via anisotropic conductive film (ACF) and a custom electrode interface board. The board appears in Fig. 27. Fig. 15 shows the connected electrode array, ACF ribbon and circuit board.

[00186] ANIMAL EXPERIMENTS. Animal experiments were conducted according to protocol. Anesthesia was obtained by an intraperitoneal injection of thiopental (25 mg/kg). Subsequent inhalent isofluroane was administered during cannulation of a branch of the femoral vein. Following cannulation, anesthesia was maintained through thiopental infusion (8-12 mg/hr) and supplemented by intermittent thiopental boluses.

The level of anesthesia was constantly monitored through the use of an EEG (presence of "sleep spindles" and slow wave oscillations), a CO_2 Monitor (~4 %), and a blood pressure and heart rate monitor (~180-200 bpm).

[00187] **SUPPLEMENTARY INFORMATION**. Silk dissolution test. By altering the secondary structure of a silk film, one can program the amount of time it takes for the film to dissolve in water. In some embodiments, it is desirable for the film to dissolve within minitues, or within hours. No treatment was required to make the film dissolve in miniutes. Creating some beta sheet structure by exposing to 70% ethanol for approximately 5 seconds increased the dissolution time to approximately 1 hour. To determine a dissolution rate, 51 square inch films were made, exposed to ethanol for 5 seconds, put in a room temperature water bath and their dry weight after a certain time in the water bath was measured. See Fig 16c.

[00188] The bending stiffness of the thin film. The cross sectional geometry of the thin film is illustrated in Fig. 26a. There are n gold bricks (size b_m x h_m, Young's modulus E_{Au} = 78GPa and Poisson's ratio v_{Au} = 0.44) surrounded by PI (size b x h, Young's modulus E_{PI} = 2.5 GPa and Poisson's ratio v_{PI} = 0.34). The distance between the neutral axis and bottom of the thin film is

$$y_0 = \frac{\frac{h}{2}\,1+\frac{2h'+h_m}{h}\left(\frac{E_{Au}}{E_{PI}}-1\right)\frac{nb_m h_m}{bh}}{1+\left(\frac{E_{Au}}{E_{PI}}-1\right)\frac{nb_m h_m}{bh}}, \qquad \text{(S1)}$$

where $h'$is the distance between bottoms of gold bricks and thin film. The bending stiffness of the thin film is

$$EI = E_{PI}bh\left(\frac{1}{3}h^2 - hy_0 + y_0^2\right) + \left(E_{Au}-E_{PI}\right)nb_m h_m\left[\frac{1}{3}h_m^2 + h_m\left(h'-y_0\right)+\left(h'-y_0\right)^2\right]. \qquad \text{(S2)}$$

[00189] The bending stiffness of the thin film on a silk backing substrate. The cross sectional geometry of the thin film on a silk backing substrate is illustrated in Fig. 26b. The silk backing substrate has a thickness H and Young's modulus E_{Silk} = 2.8GPa. The

distance between the neutral axis and bottom of the thin film is

$$y_0 = \frac{\frac{h}{2}\,1+\frac{2h'+h_m}{h}\left(\frac{E_{Au}}{E_{PI}}-1\right)\frac{nb_m h_m}{bh}-\frac{E_{silk}H^2}{E_{PI}h^2}}{1+\left(\frac{E_{Au}}{E_{PI}}-1\right)\frac{nb_m h_m}{bh}+\frac{E_{silk}H}{E_{PI}h}} \quad (S3)$$

[00190] The bending stiffness of the thin film is

$$EI = E_{PI}bh\left(\frac{1}{3}h^2 - hy_0 + y_0^2\right) + E_{silk}bH\left(\frac{1}{3}H^2 + Hy_0 + y_0^2\right) + \left(E_{Au} - E_{PI}\right)nb_m h_m\left[\frac{1}{3}h_m^2 + h_m\left(h' - y_0\right) + \left(h' - y_0\right)^2\right] \quad (S4)$$

[00191] A thin film wrapping around two overlapped cylinders. The beam theory gives the unwrapped part of thin film (above the connecting arc in the center frame of Fig. 21b) is (part of) a circle of radius r given by

$$r = \frac{d}{\sin\theta} - R \quad (S5)$$

[00192] The bending energy in the thin film is obtained as

$$U_b = EI\frac{1}{r^2}r\theta + EI\frac{1}{R^2}\left(L - r\theta\right) = EI\frac{\theta\sin\theta}{d - R\sin\theta} + \frac{EI}{R^2}\left(L + R\theta - \frac{d\theta}{\sin\theta}\right) \quad (S6)$$

[00193] The adhesion energy is

$$U_a = -2\gamma b\left(L + R\theta - \frac{d\theta}{\sin\theta}\right) \quad (S7)$$

[00194] The total energy of the wrapped state is the summation of the above bending energy and adhesion energy,

$$U_2 = \frac{EI}{R}\left[\frac{R\theta\sin\theta}{d - R\sin\theta} - \left(\frac{\gamma}{\gamma_c} - 1\right)\left(\frac{L}{R} + \theta - \frac{d\theta}{R\sin\theta}\right)\right], \quad (S8)$$

where γ_c is given in Eq. (1).

[00195] Mechanics model for mesh design. For the sheet design as shown in the left frame of Fig. 21d, the thin film is modeled as a plate. The central green part denotes the

PI plate of radius *r*, tension stiffness $(Eh)_{PI} = \bar{E}_{PI} h$ and equi-biaxial bending stiffness $(EI)_{PI} = \bar{E}_{PI}(1+\nu_{PI})h^3/12$, where $\bar{E}_{PI} = E_{PI}/(1-\nu_{PI}^2)$ is the plane-strain modulus of PI. The yellow ring is the sandwiched composite of PI and Au of width *w*, tension stiffness $(Eh)_{composite} = \bar{E}_{PI} h + (\bar{E}_{Au} - \bar{E}_{PI}) h_m$ and equi-biaxial bending stiffness

$$(EI)_{composite} = \bar{E}_{PI}(1+\nu_{PI})h\left(\frac{1}{3}h^2 - hy_1 + y_1^2\right) + \left[\bar{E}_{Au}(1+\nu_{Au}) - \bar{E}_{PI}(1+\nu_{PI})\right]\left[\frac{1}{3}h_m^2 + h_m(h'-y_1) + (h'-y_1)^2\right]h_m$$

, where

$$y_1 = \frac{\frac{h}{2}\,1 + \frac{(2h'+h_m)h_m}{h^2}\left[\frac{\bar{E}_{Au}(1+\nu_{Au})}{\bar{E}_{PI}(1+\nu_{PI})} - 1\right]}{1 + \left[\frac{\bar{E}_{Au}(1+\nu_{Au})}{\bar{E}_{PI}(1+\nu_{PI})} - 1\right]\frac{h_m}{h}}$$

is the distance between the neutral axis and bottom of the thin film, and $\bar{E}_{Au} = E_{Au}/(1-\nu_{Au}^2)$ is the plane-strain modulus of Au. The total energy of the wrapped state, which is composed of the bending energy and membrane energy in the thin film and the adhesion energy between the thin film and sphere, is given analytically as

$$U_{sheet} = \frac{\pi r^2}{R^2}(EI)_{PI} + \pi(Eh)_{PI}\int_0^r\left(1 - \frac{R}{x}\sin\frac{x}{R}\right)^2 x\,dx + \frac{2\pi r w}{R^2}(EI)_{composite} + \pi r w(Eh)_{composite}\left(1 - \frac{R}{r}\sin\frac{r}{R}\right)^2 - \pi r^2\gamma \quad . \qquad (S9)$$

[00196] For the thin film to wrap around the sphere, $U_{sheet} \le 0$, which gives the required minimum adhesion energy per unit area γ_c^{sheet} in Eq. (4). The maximum circumferential membrane strain is

$$\varepsilon_m^{sheet} = -\left(1 - \frac{R}{r+w}\sin\frac{r+w}{R}\right) . \qquad (S10)$$

[00197] The maximum interfacial normal (peeling) stress is obtained as

$$\sigma_{normal}^{sheet} = \frac{\bar{E}_{PI}(1+\nu_{PI})(h-h_m) + \bar{E}_{Au}(1+\nu_{Au})h_m}{R}\left(1 - \frac{R}{r+w}\sin\frac{r+w}{R}\right) . \qquad (S11)$$

[00198] For the mesh design as shown in the right frame of Fig. 21d, the total energy of the wrapped state, which is also composed of the bending energy and membrane energy in the yellow composite ring and the adhesion energy between the thin film and the sphere, is given analytically as

$$U_{mesh} = \frac{2\pi rw}{R^2}(EI)_{composite} + \pi(Eh)_{composite}\frac{w^3}{12r}\left(1-\sqrt{1-\frac{r^2}{R^2}}\right)^2 - 2\pi rw\gamma \quad . \qquad \text{(S12)}$$

[00199] From $U_{mesh} \leq 0$ for the thin film to wrap around the sphere, the required minimum adhesion energy per unit area γ_c^{mesh} in Eq. (5) is obtained. The maximum circumferential membrane strain is

$$\varepsilon_m^{mesh} = -\left[1-\frac{R}{r+w}\sin\left(\frac{w}{2R}+\arcsin\frac{2r+w}{2R}\right)\right] . \qquad \text{(S13)}$$

[00200] The maximum interfacial normal (peeling) stress is obtained as

$$\sigma_{normal}^{sheet} = \frac{\bar{E}_{PI}(1+\nu_{PI})(h-h_m)+\bar{E}_{Au}(1+\nu_{Au})h_m}{R}\frac{w}{2r}\left(1-\sqrt{1-\frac{r^2}{R^2}}\right) . \qquad \text{(S14)}$$

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STATEMENTS REGARDING INCORPORATION BY REFERENCE AND VARIATIONS

[00226] All references throughout this application, for example patent documents including issued or granted patents or equivalents; patent application publications; and non-patent literature documents or other source material; are hereby incorporated by reference herein in their entireties, as though individually incorporated by reference, to the extent each reference is at least partially not inconsistent with the disclosure in this application (for example, a reference that is partially inconsistent is incorporated by reference except for the partially inconsistent portion of the reference).

[00227] The following references relate generally to flexible and/or stretchable semiconductor materials and devices and are each hereby incorporated by reference in its entirety: U.S. Patent Application no. 12/778,588, filed on May 12, 2010, PCT International Application No. PCT/US05/19354, filed June 2, 2005 and published under No. WO2005/122285 on December 22, 2005, U.S. Provisional Patent Application No. 61/313,397, filed March 12, 2010, U.S. Patent Application No. 11/851,182, filed September 6, 2007 and published under No. 2008/0157235 on July 3, 2008, and PCT International Application No. PCT/US07/77759, filed September 6, 2007 and published under No. WO2008/030960 on March 13, 2008.

[00228] The following references relate generally to bioresorbable substrates and methods of making bioresorbable substrates and are each hereby incorporated by reference in its entirety: PCT Patent Application PCT/US03/19968 filed 6/24/2003, PCT Patent Application PCT/US04/000255 filed 1/7/2004, PCT Patent Application PCT/US04/11199 filed 4/12/2004, PCT Patent Application PCT/US05/20844 filed 6/13/2005, and PCT Patent Application PCT/US06/029826 filed 7/28/2006.

[00229] The terms and expressions which have been employed herein are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the invention has been specifically disclosed by preferred embodiments, exemplary embodiments and optional features, modification and variation of the concepts herein disclosed can be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims. The specific embodiments provided herein are examples of useful embodiments of the invention and it will be apparent to one skilled in the art that the invention can be carried out using a large number of variations of the devices, device components, methods steps set forth in the present description. As will be apparent to one of skill in the art, methods and devices useful for the present methods can include a large number of optional composition and processing elements and steps.

[00230] When a group of substituents is disclosed herein, it is understood that all individual members of that group and all subgroups, including any isomers, enantiomers, and diastereomers of the group members, are disclosed separately.

When a Markush group or other grouping is used herein, all individual members of the group and all combinations and subcombinations possible of the group are intended to be individually included in the disclosure. When a compound is described herein such that a particular isomer, enantiomer or diastereomer of the compound is not specified, for example, in a formula or in a chemical name, that description is intended to include each isomers and enantiomer of the compound described individual or in any combination. Additionally, unless otherwise specified, all isotopic variants of compounds disclosed herein are intended to be encompassed by the disclosure. For example, it will be understood that any one or more hydrogens in a molecule disclosed can be replaced with deuterium or tritium. Isotopic variants of a molecule are generally useful as standards in assays for the molecule and in chemical and biological research related to the molecule or its use. Methods for making such isotopic variants are known in the art. Specific names of compounds are intended to be exemplary, as it is known that one of ordinary skill in the art can name the same compounds differently.

[00231] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and equivalents thereof known to those skilled in the art, and so forth. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. The expression “of any of claims XX-YY” (wherein XX and YY refer to claim numbers) is intended to provide a multiple dependent claim in the alternative form, and in some embodiments is interchangeable with the expression “as in any one of claims XX-YY.”

[00232] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[00233] Whenever a range is given in the specification, for example, a range of integers, a temperature range, a time range, a composition range, or concentration

range, all intermediate ranges and subranges, as well as all individual values included in the ranges given are intended to be included in the disclosure. As used herein, ranges specifically include the values provided as endpoint values of the range. As used herein, ranges specifically include all the integer values of the range. For example, a range of 1 to 100 specifically includes the end point values of 1 and 100. It will be understood that any subranges or individual values in a range or subrange that are included in the description herein can be excluded from the claims herein.

[00234] As used herein, "comprising" is synonymous and can be used interchangeably with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. As used herein, "consisting of" excludes any element, step, or ingredient not specified in the claim element. As used herein, "consisting essentially of" does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claim. In each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" can be replaced with either of the other two terms. The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein.

[00235] One of ordinary skill in the art will appreciate that starting materials, biological materials, reagents, synthetic methods, purification methods, analytical methods, assay methods, and biological methods other than those specifically exemplified can be employed in the practice of the invention without resort to undue experimentation. All art-known functional equivalents, of any such materials and methods are intended to be included in this invention. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed can be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

CLAIMS

We claim:

1. An implantable biomedical device for actuating a target tissue or sensing a parameter associated with the target tissue in a biological environment, said device comprising:

   a bioresorbable substrate;

   an electronic device comprising a plurality of inorganic semiconductor components supported by said bioresorbable substrate, wherein at least one of said inorganic semiconductor components has at least one physical dimension less than or equal to 100 microns; and

   a barrier layer encapsulating at least a portion of said inorganic semiconductor components,

   wherein upon contact with said biological environment said bioresorbable substrate is at least partially resorbed, thereby establishing conformal contact between said implantable biomedical device and said target tissue in said biological environment.

2. An implantable biomedical device for actuating a target tissue or sensing a parameter associated with the target tissue in a biological environment, said device comprising:

   a bioresorbable substrate;

   a biocompatible layer provided on said bioresorbable substrate;

   an electronic device comprising a plurality of inorganic semiconductor components supported by said biocompatible layer, wherein at least one of said inorganic semiconductor components has at least one physical dimension less than or equal to 100 microns; and

   a barrier layer encapsulating at least a portion of said inorganic semiconductor components,

wherein upon contact with said biological environment said bioresorbable substrate is at least partially resorbed, thereby establishing conformal contact between said implantable biomedical device and said target tissue in said biological environment.

3. The device of any of claims 1-2, wherein said biological environment is an *in-vivo* biological environment.

4. The device of any of claims 1-3, wherein said target tissue in said biological environment comprises heart tissue, brain tissue, muscle tissue, epithelial tissue, nerve tissue, or vascular tissue.

5. The device of any of claims 1-4, wherein said bioresorbable substrate is completely resorbed upon contact with said biological environment.

6. The device of any of claims 1-4, wherein said bioresorbable substrate is not completely resorbed upon contact with said biological environment.

7. The device of any of claim 1-6, wherein resorption of said bioresorbable substrate establishes physical contact between said electronic device and said target tissue.

8. The device of any of claim 1-7, wherein resorption of said bioresorbable substrate establishes conformal contact between said electronic device and said target tissue.

9. The device of any of claim 1-8, wherein resorption of said bioresorbable substrate establishes electrical contact between said electronic device and said target tissue.

10. The device of any of claims 1-9, wherein said bioresorbable substrate comprises a biopolymer, a synthetic polymer, a protein, a polysaccharide, silk or any combination of these.

11. The device of any of claims 1-10, wherein said bioresorbable substrate comprises a poly(glycerol-sebacate) (PGS), polydioxanone, poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), collagen, chitosan, fibroin, or any combination of these.

12. The device of any of claims 1-10, wherein said bioresorbable substrate comprises a silkworm fibroin, modified silkworm fibroin, spider silk, insect silk, recombinant silk, or any combination of these.

13. The device of any of claims 1-12, wherein said bioresorbable substrate has a thickness less than or equal to 10000 μm.

14. The device of any of claims 1-12, wherein said bioresorbable substrate has a thickness selected from the range of 100 nanometers to 10000 μm.

15. The device of any of claims 1-14, wherein said bioresorbable substrate has a Young's modulus selected from the range of 0.5 MPa and 10 GPa.

16. The device of any of claims 1-15, wherein said bioresorbable substrate has a net bending stiffness less than or equal to 1×10^9 GPa μm^4.

17. The device of any of claims 1-15, wherein said bioresorbable substrate has a net bending stiffness selected from the range of 0.1×10^4 GPa $\mu m^4$and 1×10^9 GPa μm^4.

18. The device of any of claims 1-17, wherein the bioresorbable substrate has a degree of crystallinity less than 55%.

19. The device of any of claims 1-17, wherein the bioresorbable substrate has a degree of crystallinity selected over the range of 0 to 55%.

20. The device of any of claims 1-19, wherein the bioresorbable substrate has a planar contact surface for contacting the target tissue.

21. The device of any of claims 1-19, wherein the bioresorbable substrate has a nanostructured or microstructured contact surface for contacting the target tissue.

22. The device of claim 21, wherein the bioresorbable substrate has a plurality of relief features, wherein said relief features penetrate said target tissue upon contact between said implantable biomedical device and said target tissue.

23. The device of claim 22, wherein the relief features extend from a surface of the bioresorbable substrate a length selected from the range of 10 nanometers to 1000 nanometers.

24. The device of any of claims 1-23, wherein at least a portion of the plurality of inorganic semiconductor components of the electronic device is bonded to the barrier layer or the biocompatible layer.

25. The device of any of claims 1-24, wherein said implantable biomedical device has a neutral mechanical plane and at least a portion of said plurality of inorganic semiconductor components is positioned proximate to said neutral mechanical plane.

26. The device of claim 25, wherein a thickness of said barrier layer and a thickness of said bioresorbable substrate are selected so as to position at least a portion of said plurality of semiconductor circuit components proximate to said neutral mechanical plane.

27. The device of any of claims 1-26, wherein at least one of said inorganic semiconductor components is a flexible semiconductor structure or a stretchable semiconductor structure.

28. The device of any of claims 1-27, wherein at least one of said inorganic semiconductor components is a nanoribbon, a nanomembrane, a nanowire, a transistor channel, a diode, a p-n junction, a photodiode, a light emitting diode, a laser or a combination of these.

29. The device of any of claims 1-28, wherein at least one of said inorganic semiconductor components of the electronic device has a thickness less than or equal to 10 microns.

30. The device of any of claims 1-28, wherein at least one of said inorganic semiconductor components of the electronic device has a thickness selected from the range of 50 nanometers to 10 microns.

31. The device of any of claims 1-30, wherein at least one of said inorganic semiconductor components of the electronic device has lateral physical dimensions less than or equal to 10000 microns.

32. The device of any of claims 1-30, wherein at least one of said inorganic semiconductor components of the electronic device has lateral physical dimensions selected from the range of 500 nanometers to 10000 microns.

33. The device of any of claims 1-32, wherein at least one of said inorganic semiconductor components of the electronic device has a Young's modulus selected from the range of 0.5 MPa to 10 GPa.

34. The device of any of claims 1-33, wherein at least one of said inorganic semiconductor components of the electronic device has a net bending stiffness less than or equal to 1×10^8 GPa μm^4.

35. The device of any of claims 1-34, wherein at least one of said inorganic semiconductor components comprises a single crystal inorganic semiconductor material.

36. The device of any of claims 1-34, wherein at least one of said inorganic semiconductor components comprises material selected from the group consisting of single crystalline silicon, porous silicon, and polycrystalline silicon.

37. The device of any of claims 1-36, wherein at least one of said inorganic semiconductor components is a bioresorbable material or bioinert material.

38. The device of any of claims 1-37, wherein said electronic device comprises a plurality of island and bridge structures.

39. The device of claim 38, wherein said island structures comprise one or more semiconductor circuit components of said electronic device.

40. The device of claim 38, wherein said bridge structures comprise one or more flexible electrical interconnects.

41. The device of any of claims 1-40, wherein said electronic device further comprises one or more additional device components selected from the group consisting of an electrode, a dielectric layer, a chemical or biological sensor element, a pH sensor, an optical sensor, an optical source, a temperature sensor, and a capacitive sensor.

42. The device of claim 41, wherein at least one of said additional device components comprises a bioinert material or a bioresorbable material.

43. The device of claim 42, wherein said bioinert material is selected from the group consisting of titanium, gold, silver, platinum, and any combination of these.

44. The device of claim 42, wherein said bioresorbable material is selected from the group consisting of iron, magnesium, and any combination of these.

45. The device of any of claims 1-44, wherein at least a portion of said plurality of inorganic semiconductor components comprise one or more of an amplifier circuit, a multiplexing circuit, a current limiting circuit, an integrated circuit, a transistor or a transistor array.

46. The device of claim 45, wherein said multiplexing circuit is configured to individually address each of a plurality of electrodes spatially arranged over said bioresorbable substrate.

47. The device of any of claims 1-46, wherein said barrier layer encapsulates all of the inorganic semiconductor components of the electronic device.

48. The device of any of claims 1-47, wherein said barrier layer completely encapsulates the electronic device.

49. The device of any of claims 1-48, wherein said barrier layer comprises material selected from the group consisting of a polymer, an organic polymer, SU-8, an insulator, a polyimide, a dielectric, an inorganic dielectric, Si_3N_4, and any combination of these.

50. The device of any of claims 1-49, wherein said barrier layer comprises an electrical insulator.

51. The device of any of claims 1-50, wherein said barrier layer limits net leakage current from said electronic device to 10 $\mu A/\mu m^2$ or less.

52. The device of any of claims 1-51, wherein said barrier layer comprises a bioresorbable material or a bioinert material.

53. The device of any of claims 1-52, wherein said barrier layer has a thickness less than or equal to 100 μm.

54. The device of any of claims 1-52, wherein said barrier layer has a thickness selected from the range of 1 μm to 100 μm.

55. The device of any of claims 1-54, wherein the barrier layer has a planar contact surface for contacting the target tissue.

56. The device of any of claims 1-54, wherein the barrier layer has a nanostructured or microstructured contact surface for contacting the target tissue.

57. The device of claim 56, wherein the barrier layer has a plurality of relief features, wherein said relief features penetrate said target tissue upon contact between said implantable biomedical device and said target tissue.

58. The device of claim 57, wherein said relief features extend from a surface of the barrier layer a length selected from the range of 10 nanometers to 1000 nanometers.

59. The device of any of claims 1-58, wherein said bioresorbable substrate, said electronic device, and said barrier layer provide a net bending stiffness of the implantable biomedical device of less than 1×10^9 GPa μm^4.

60. The device of any of claims 2-59, wherein said bioresorbable substrate, said biocompatible layer, said electronic device, and said barrier layer provide a net bending stiffness of the implantable biomedical device of less than 1×10^9 GPa μm^4.

61. The device of any of claims 1-60, wherein said barrier layer has a mesh structure.

62. The device of any of claims 1-61, wherein said bioresorbable substrate, said electronic device, and said barrier layer each independently comprise a bioresorbable material.

63. The device of claim 2, wherein said biocompatible layer comprises material selected from the group consisting of a polymer, an organic polymer, SU-8, an insulator, a polyimide, a dielectric, an inorganic dielectric, Si_3N_4, and any combination of these.

64. The device of claim 2, wherein said biocompatible layer comprises an electrical insulator.

65. The device of claim 2, wherein said biocompatible layer comprises a resorbable material or a bioinert material.

66. The device of claim 2, wherein said biocompatible layer has a thickness selected from the range of 1 μm to 25 μm.

67. A method for administering an implantable biomedical device, said method comprising:

providing the implantable biomedical device comprising:

a bioresorbable substrate;

an electronic device comprising a plurality of inorganic semiconductor components supported by said bioresorbable substrate, wherein at least one of said inorganic semiconductor components has at least one physical dimension less than or equal to 100 microns; and

a barrier layer encapsulating at least a portion of said inorganic semiconductor components;

contacting said implantable biomedical device with a target tissue in a biological environment; and

at least partially resorbing said bioresorbable substrate in said biological environment, thereby establishing conformal contact between said implantable biomedical device and said target tissue in said biological environment.

68. The method of claim 67, wherein said biological environment is an *in-vivo* biological environment.

69. The method of any of claims 67-68, wherein said target tissue in said biological environment comprises heart tissue, brain tissue, muscle tissue, nerve tissue, epithelial tissue, or vascular tissue.

70. The method of any of claims 67-69, wherein said bioresorbable substrate is completely resorbed upon contact with said biological environment.

71. The method of any of claims 67-69, wherein said bioresorbable substrate is not completely resorbed upon contact with said biological environment.

72. The method of any of claim 67-71, wherein resorption of said bioresorbable substrate establishes physical contact, conformal contact, or electrical contact between said electronic device and said target tissue.

73. The method of any of claims 67-72, wherein the bioresorbable substrate has a degree of crystallinity less than or equal to 55%.

74. The method of any of claims 67-72, wherein the bioresorbable substrate has a degree of crystallinity selected over the range of 0 to 55%.

75. The method of any of claims 67-74, wherein the Young's modulus of said implantable biomedical device decreases by at least 50% upon resorption of the bioresorbable substrate.

76. The method of any of claims 67-75, wherein the net bending stiffness of said implantable biomedical device decreases by at least 50% upon resorption of the bioresorbable substrate.

77. A method of actuating a target tissue or sensing a parameter associated with the target tissue in a biological environment, said method comprising:

providing an implantable biomedical device comprising:

a bioresorbable substrate;

an electronic device comprising a plurality of inorganic semiconductor components supported by said bioresorbable substrate, wherein at least one of said inorganic semiconductor components has at least one physical dimension less than or equal to 100 microns; and

a barrier layer encapsulating at least a portion of said inorganic semiconductor components;

contacting said implantable biomedical device with the target tissue in a biological environment;

at least partially resorbing said bioresorbable substrate in said biological environment, thereby establishing conformal contact between said implantable biomedical device and said target tissue in said biological environment; and

actuating the target tissue or sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device.

78. The method of claim 77, wherein said biological environment is an *in-vivo* biological environment.

79. The method of any of claims 77-78, wherein said target tissue in said biological environment comprises heart tissue, brain tissue, muscle tissue, nerve tissue, epithelial tissue, or vascular tissue.

80. The method of any of claims 78-79, wherein resorption of said bioresorbable substrate establishes physical contact, conformal contact, or electrical contact between said electronic device and said target tissue.

81. The method of any of claims 77-80, wherein said step of sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device comprises measuring voltage at a surface of the target tissue.

82. The method of any of claims 77-80, wherein said step of actuating the target tissue that is in conformal contact with the implantable biomedical device comprises generating voltage at a surface of the target tissue.

83. The method of claim 82, wherein the voltage generated at the surface of the target tissue is sufficient to electrophysically actuate the target tissue.

84. The method of any of claims 77-80, wherein said step of sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device comprises measuring electromagnetic radiation at a surface of the target tissue.

85. The method of any of claims 77-80, wherein said step of actuating the target tissue that is in conformal contact with the implantable biomedical device comprises generating electromagnetic radiation at a surface of the target tissue.

86. The method of claim 85, wherein said electromagnetic radiation generated at the surface of the target tissue has a power sufficient to optically actuate the target tissue.

87. The method of any of claims 77-80, wherein said step of sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device comprises measuring a current at a surface of the target tissue.

88. The method of any of claims 77-80, wherein said step of actuating the target tissue that is in conformal contact with the implantable biomedical device comprises generating a current at a surface of the target tissue.

89. The method of claims 88, wherein said current generated at the surface of the target tissue is sufficient to electrophysically actuate the target tissue.

90. An implantable biomedical device for actuating a target tissue or sensing a parameter associated with the target tissue in a biological environment, said device comprising:

an electrode array comprising a plurality of individually addressable metal electrodes, wherein each metal electrode has at least one physical dimension less than or equal to 100 microns;

a barrier layer having a mesh structure, wherein said barrier layer at least partially supports said electrode array; and

a bioresorbable substrate supporting said electrode array, said barrier layer or both of said electrode array and said barrier layer;

wherein upon contact with said biological environment said bioresorbable substrate is at least partially resorbed, thereby establishing conformal contact between said electrode array and said target tissue in said biological environment.

91. The device of claim 90, wherein said electrodes of said electrode array are physically separated from each other.

92. The device of claim 90, wherein said barrier layer is in physical contact with at least a portion of said electrodes of said electrode array.

93. The device of claim 90, wherein said bioresorbable substrate is in physical contact with at least a portion of said electrode array or in physical contact with at least a portion of said barrier layer.

94. The device of claim 90, wherein each of said electrodes of said array is in electrical contact with at least one electronic interconnect.

95. The device of claim 90, wherein said bioresorbable substrate comprises a poly(glycerol-sebacate) (PGS), polydioxanone, poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), collagen, chitosan, fibroin, or any combination of these.

96. The device of claim 90, wherein said bioresorbable substrate comprises a silkworm fibroin, spider silk, insect silk, recombinant silk, or any combination of these.

97. The device of claim 90, wherein said bioresorbable substrate has a thickness less than or equal to 10000 μm.

98. The device of claim 90, wherein said bioresorbable substrate has a thickness selected from the range of 100 nanometers to 10000 μm.

99. The device of claim 90, wherein resorption of said bioresorbable substrate establishes physical contact, conformal contact, or electrical contact between said electrode array and said target tissue.

100. The device of claim 90, wherein said mesh structure is a perforated mesh structure or a tentacle mesh structure.

101. The device of claim 90, wherein said electrode array comprises 10 to 1000 electrodes.

102. The device of claim 90, wherein each of said metal electrodes has a thickness less than or equal to 10 microns.

103. The device of claim 90, wherein each of said metal electrodes has a thickness selected over the range of 100 nanometers to 10 microns.

104. The device of claim 90, wherein each of said metal electrodes has lateral dimensions less than or equal to 10000 microns.

105. The device of claim 90, wherein each of said metal electrodes has lateral dimensions selected over the range of 1 micron to 10000 microns.

106. The device of claim 90, wherein adjacent metal electrodes in said mesh structure are separated from each other by a distance greater than or equal to 10 microns.

107. The device of claim 90, wherein adjacent metal electrodes in said mesh structure are separated from each other by a distance selected from the range of 10 microns to 10 millimeters.

108. The device of any of claims 90-107, wherein said metal electrodes comprise a bioinert metal or a biocompatible metal.

109. The device of claim 108, wherein said bioinert metal is selected from the group consisting of titanium, gold, silver, platinum, and any combination of these.

110. The device of claim 108, wherein said bioresorbable metal is selected from the group consisting of iron, magnesium, and any combination of these.

111. The device of any of claims 90-110, wherein said barrier layer or said bioresorbable substrate completely encapsulates the electrode array.

112. The device of any of claims 90-111, wherein said barrier layer comprises material selected from the group consisting of a polymer, an organic polymer, SU-8, an insulator, a polyimide, a dielectric, an inorganic dielectric, Si_3N_4, and any combination of these.

113. The device of any of claims 90-112, wherein said barrier layer has thickness less than or equal to 100 μm.

114. The device of any of claims 90-112, wherein said barrier layer has a thickness selected from the range of 1 μm to 100 μm.

115. A method for actuating a target tissue or sensing a parameter associated with the target tissue in a biological environment, the method comprising:

providing an implantable biomedical device comprising:

an electrode array comprising a plurality of individually addressable metal electrodes, wherein each metal electrode has at least one physical dimension less than or equal to 100 microns;

a barrier layer having a mesh structure, wherein said barrier layer at least partially supports said electrode array; and

a bioresorbable substrate supporting said electrode array, said barrier layer or both of said electrode array and said barrier layer;

contacting said implantable biomedical device with the target tissue in a biological environment; wherein upon contact with said biological environment said bioresorbable substrate is at least partially resorbed, thereby establishing conformal contact between said electrode array and said target tissue in said biological environment; and

actuating the target tissue or sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device.

116. The method of claim 115, wherein said biological environment is an *in-vivo* biological environment.

117. The method of any of claims 115-116 wherein said target tissue in said biological environment comprises heart tissue, brain tissue, muscle tissue, nerve tissue, epithelial tissue, or vascular tissue.

118. The method of any of claims 115-117, wherein resorption of said bioresorbable substrate establishes physical contact, conformal contact, or electrical contact between said electronic device and said target tissue.

119. The method of any of claims 115-118, wherein the step of sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device comprises measuring voltage at a surface of the target tissue.

120. The method of any of claims 115-118, wherein the step of actuating the target tissue that is in conformal contact with the implantable biomedical device comprises generating voltage at a surface of the target tissue.

121. The method of claim 120, wherein the voltage generated at the surface of the target tissue is sufficient to electrophysically actuate the target tissue.

122. The method of any of claims 115-118, wherein the step of sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device comprises measuring electromagnetic radiation at a surface of the target tissue.

123. The method of any of claims 115-118, wherein the step of actuating the target tissue that is in conformal contact with the implantable biomedical device

comprises generating electromagnetic radiation at a surface of the target tissue.

124. The method of claim 123, wherein the power generated at the surface of the target tissue is sufficient to optically actuate the target tissue.

125. The method of any of claims 115-118, wherein the step of sensing the parameter associated with the target tissue that is in conformal contact with the implantable biomedical device comprises measuring current at a surface of the target tissue.

126. The method of any of claims 115-118, wherein the step of actuating the target tissue that is in conformal contact with the implantable biomedical device comprises generating current at a surface of the target tissue.

127. The method of claim 126, wherein the current generated at the surface of the target tissue is sufficient to electrophysically actuate the target tissue.

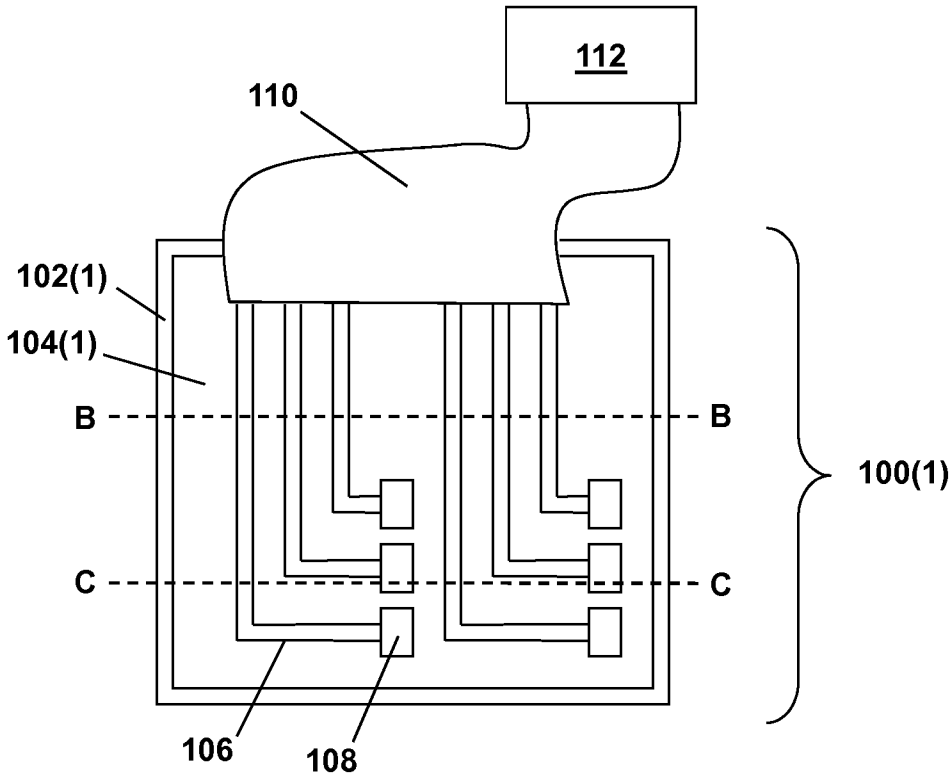


Fig. 1a

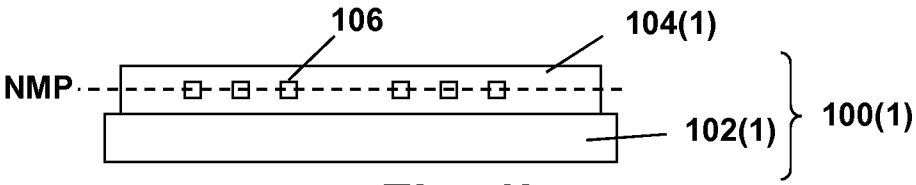


Fig. 1b

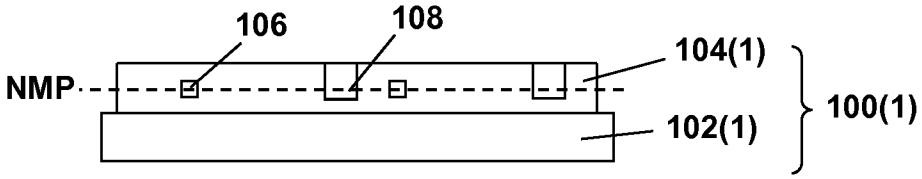


Fig. 1c

Figure 1

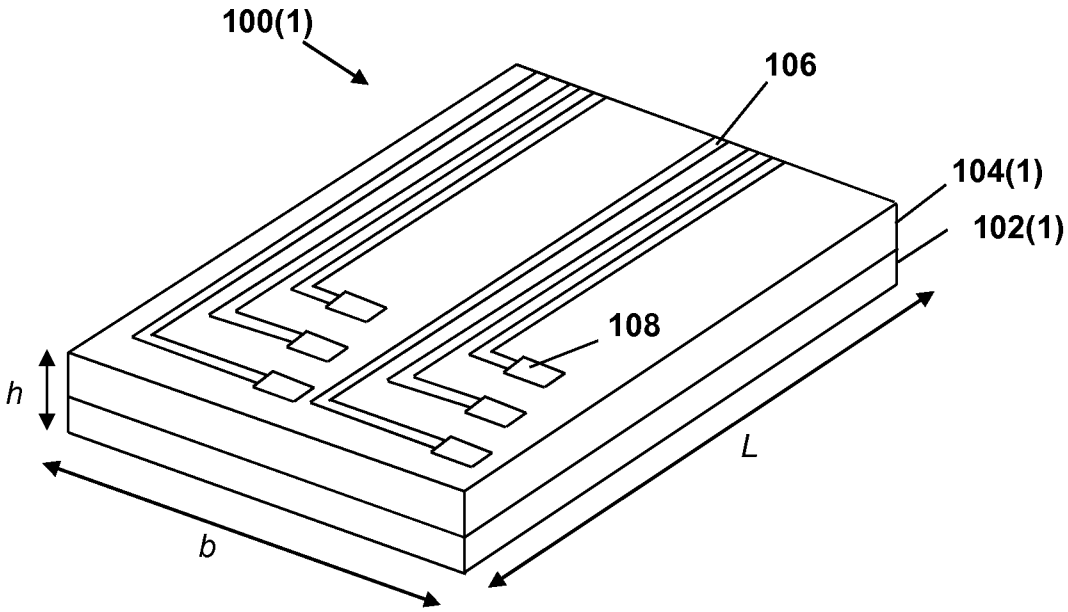


Figure 2

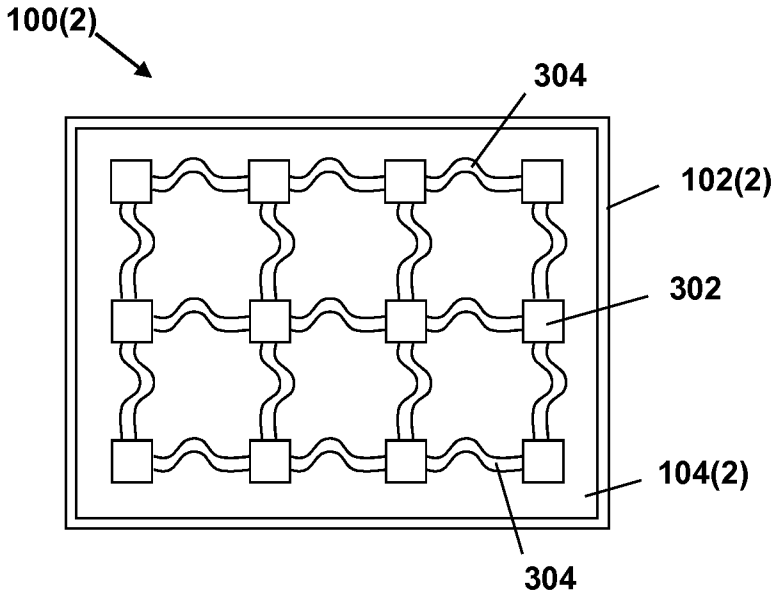


Figure 3

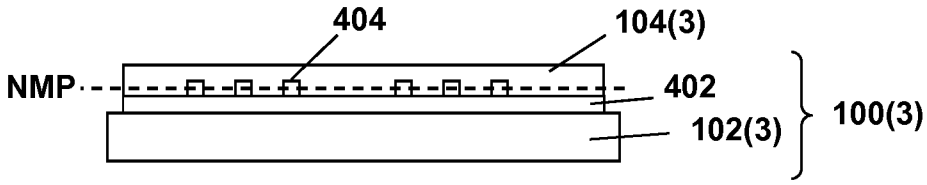


Figure 4

Fig. 5a

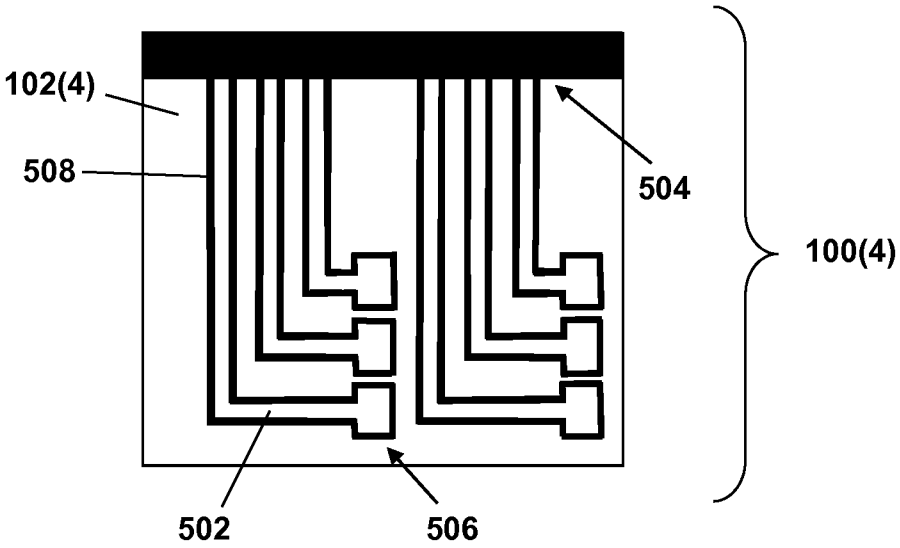


Fig. 5b

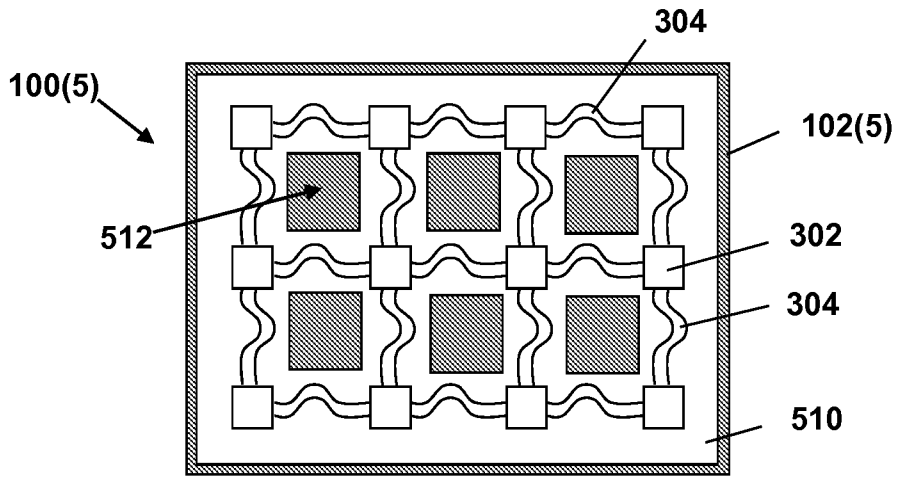


Figure 5

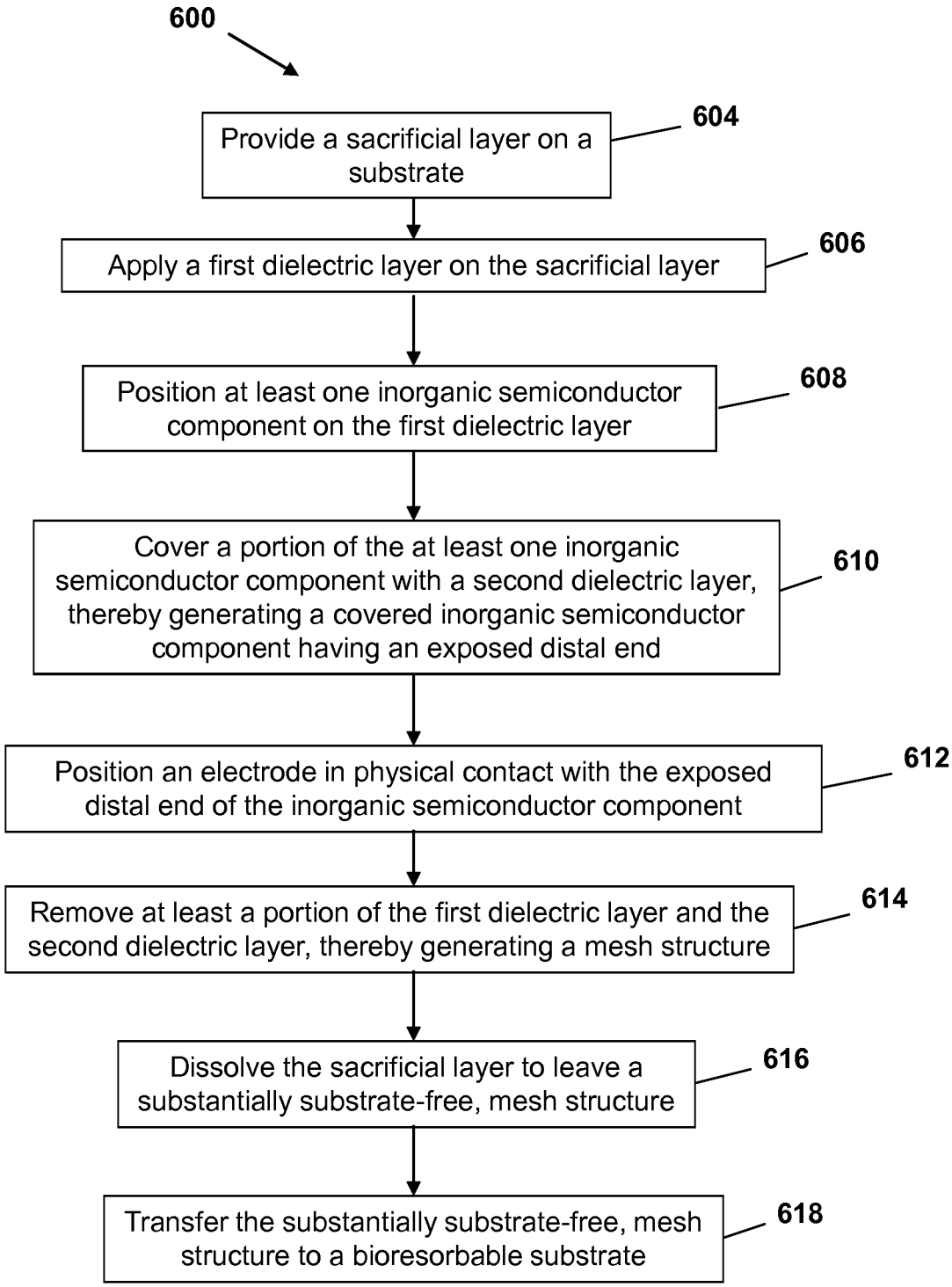

600
Provide a sacrificial layer on a substrate
604
Apply a first dielectric layer on the sacrificial layer
606
Position at least one inorganic semiconductor component on the first dielectric layer
608
Cover a portion of the at least one inorganic semiconductor component with a second dielectric layer, thereby generating a covered inorganic semiconductor component having an exposed distal end
610
Position an electrode in physical contact with the exposed distal end of the inorganic semiconductor component
612
Remove at least a portion of the first dielectric layer and the second dielectric layer, thereby generating a mesh structure
614
Dissolve the sacrificial layer to leave a substantially substrate-free, mesh structure
616
Transfer the substantially substrate-free, mesh structure to a bioresorbable substrate
618

Figure 6

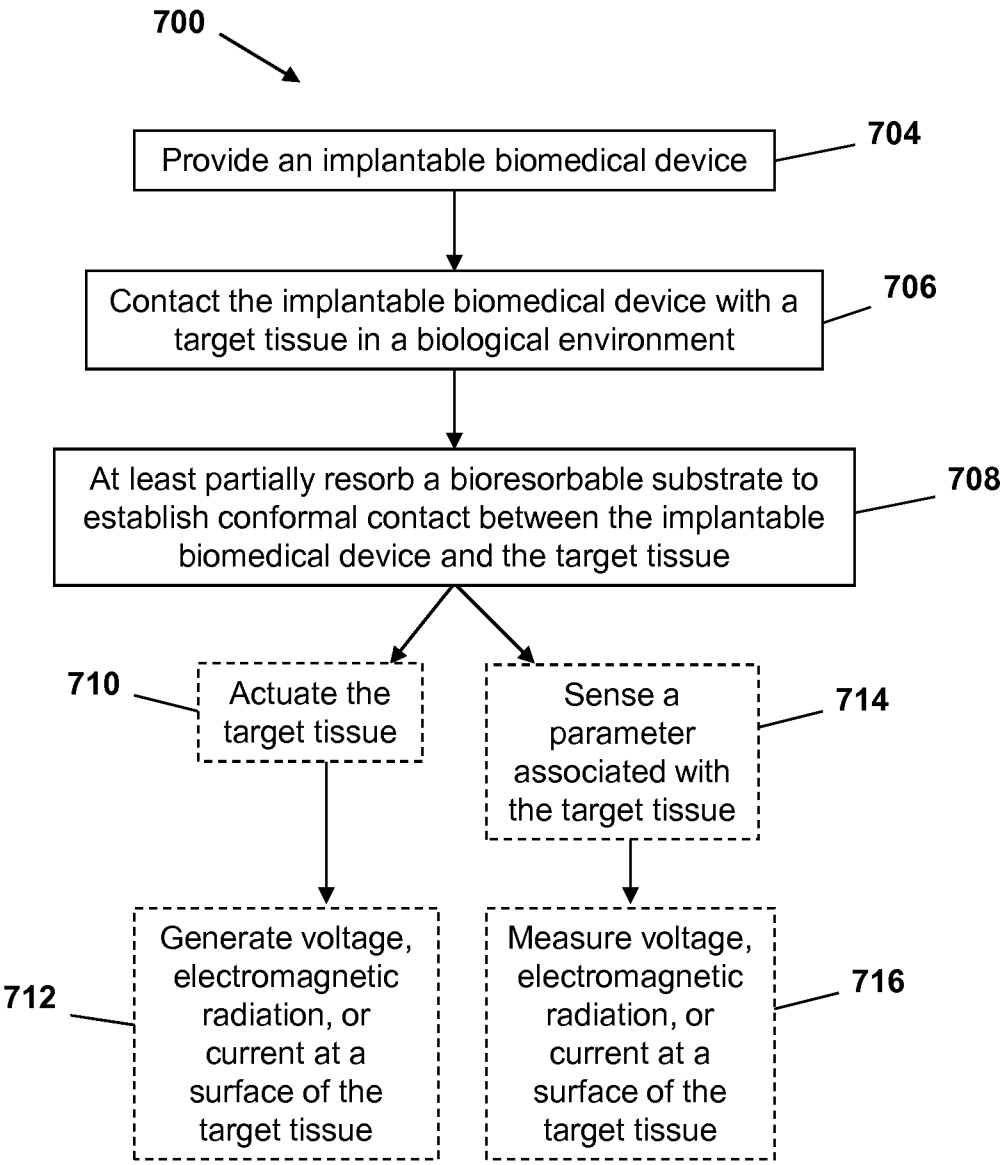

700
Provide an implantable biomedical device
704
Contact the implantable biomedical device with a target tissue in a biological environment
706
At least partially resorb a bioresorbable substrate to establish conformal contact between the implantable biomedical device and the target tissue
708
710
Actuate the target tissue
Sense a parameter associated with the target tissue
714
712
Generate voltage, electromagnetic radiation, or current at a surface of the target tissue
Measure voltage, electromagnetic radiation, or current at a surface of the target tissue
716

Figure 7

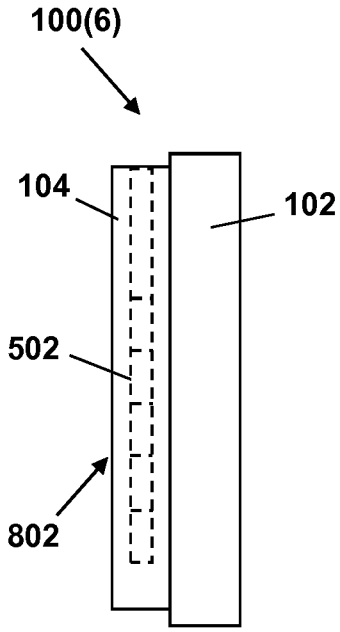


Fig. 8a

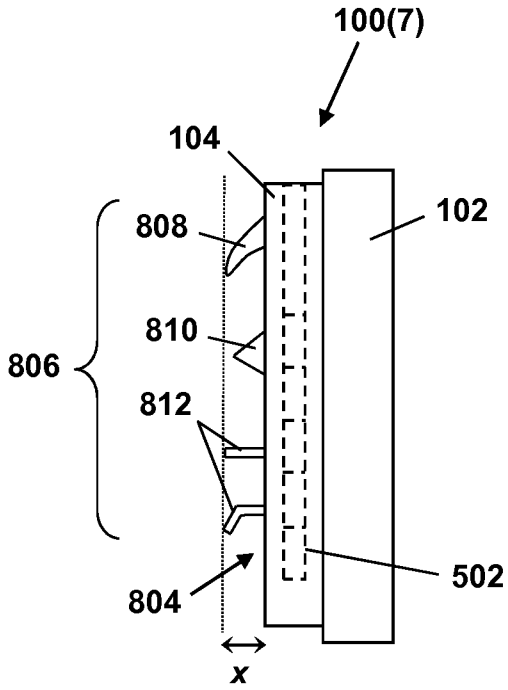


Fig. 8b

Figure 8

Fig. 9a

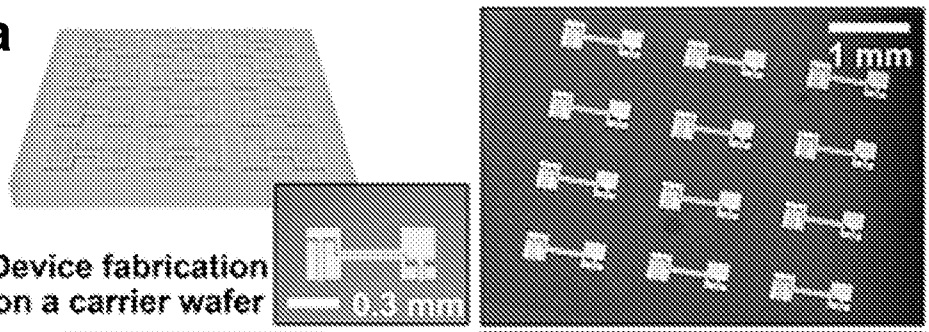


Fig. 9b

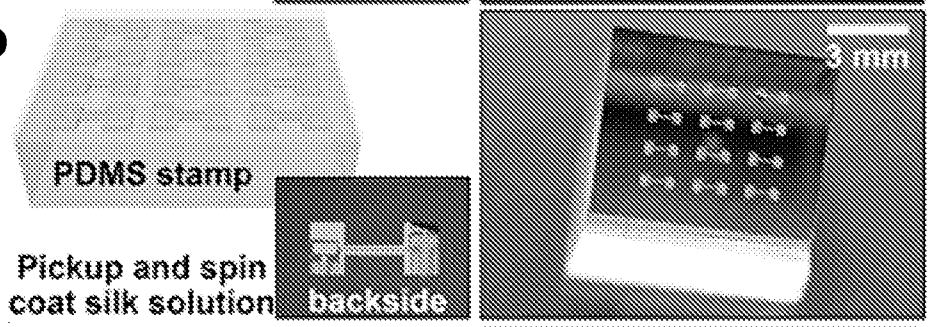


Fig. 9c

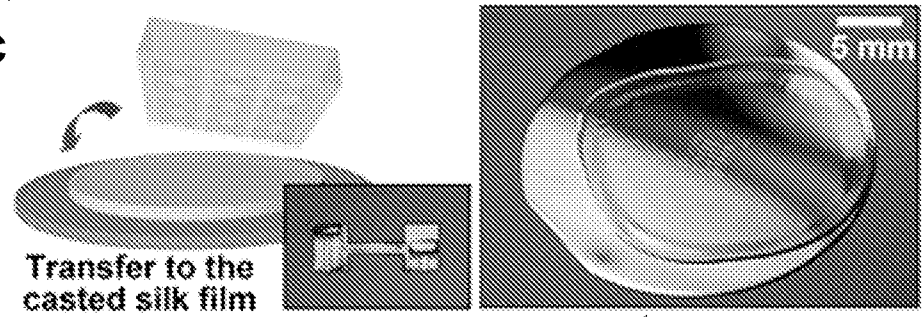


Fig. 9d

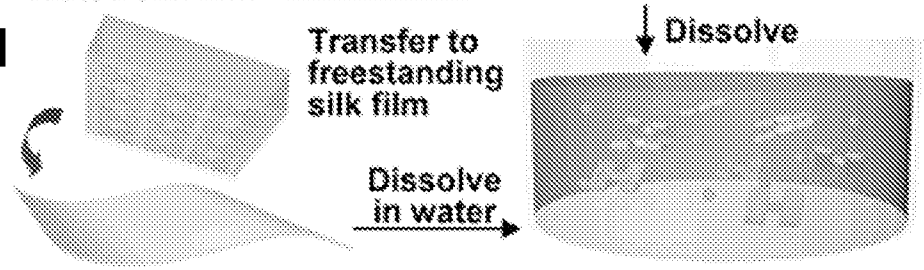


Figure 9

Fig. 10a

Fig. 10b

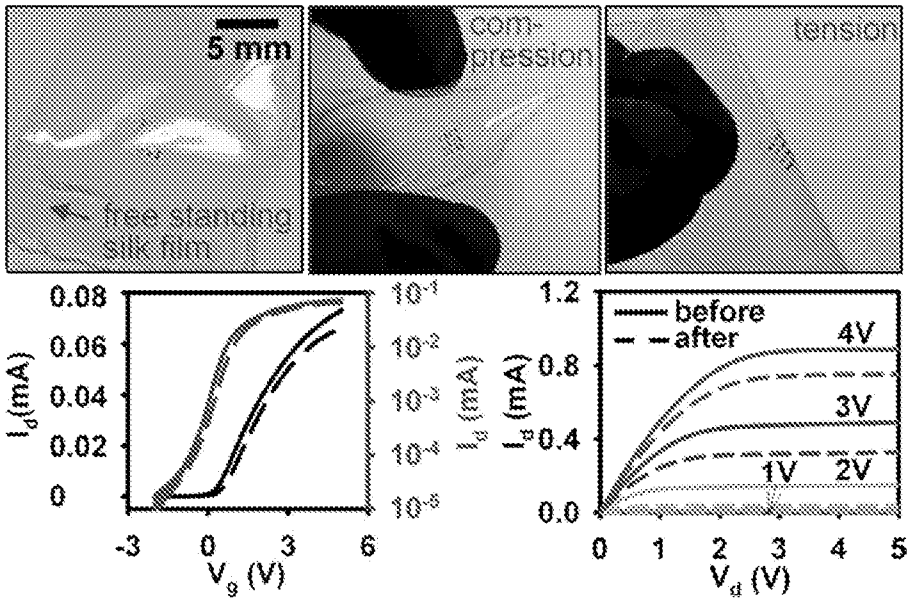


Figure 10

Fig. 11a

Fig. 11b

Fig. 11c

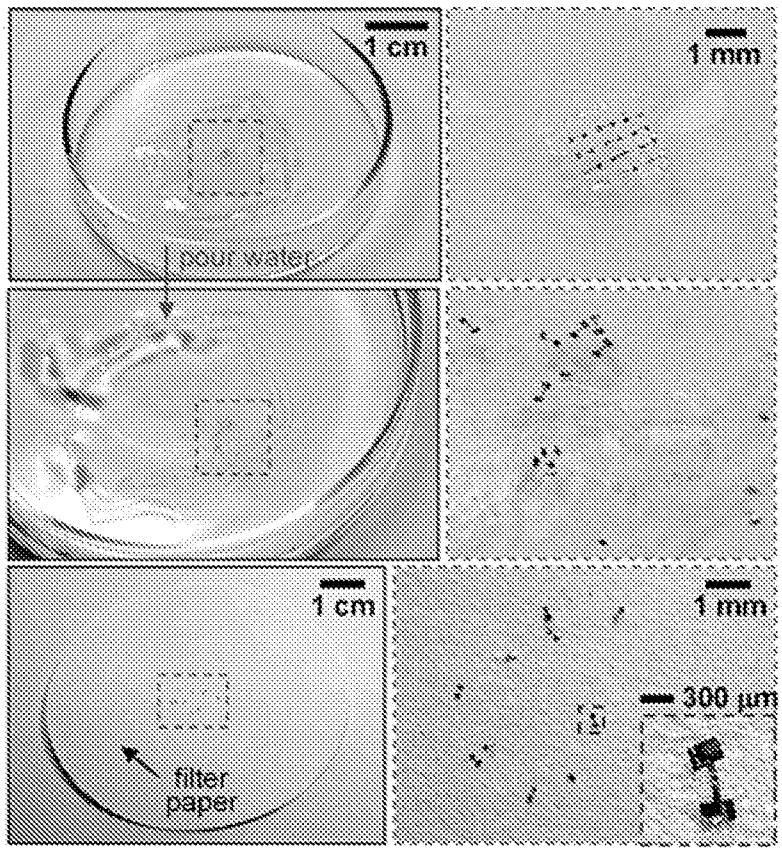


Figure 11



Figure 12

Fig. 13a

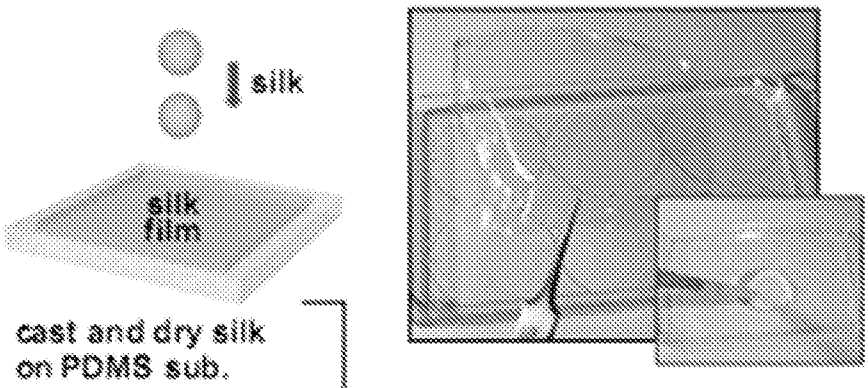


Fig. 13b

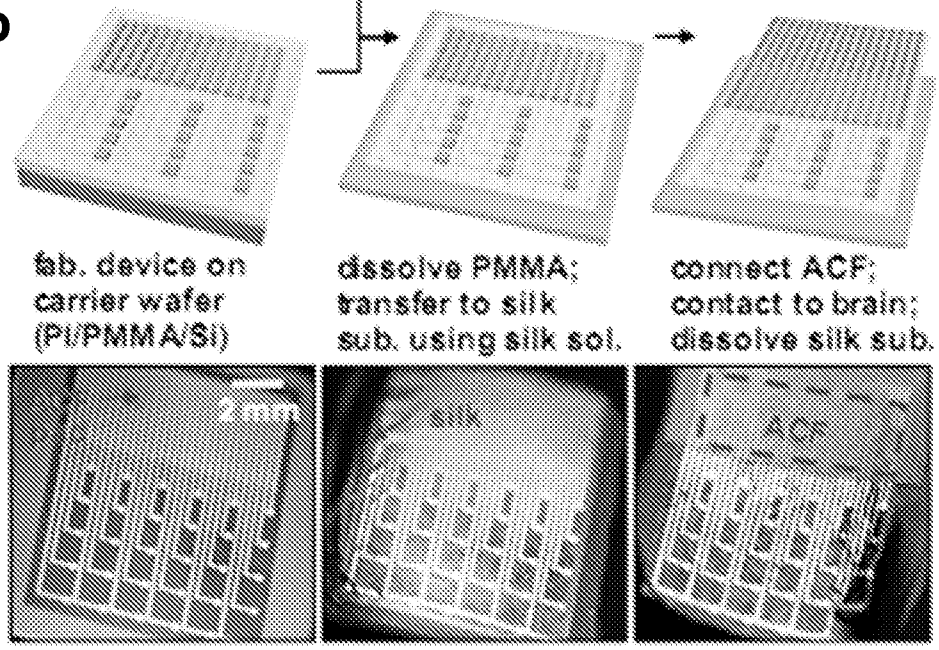


Fig. 13c

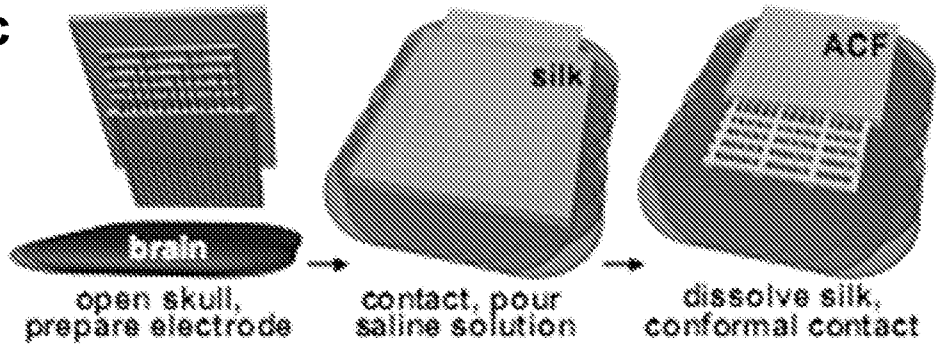


Figure 13

Fig. 14a

Fig. 14b

Fig. 14c

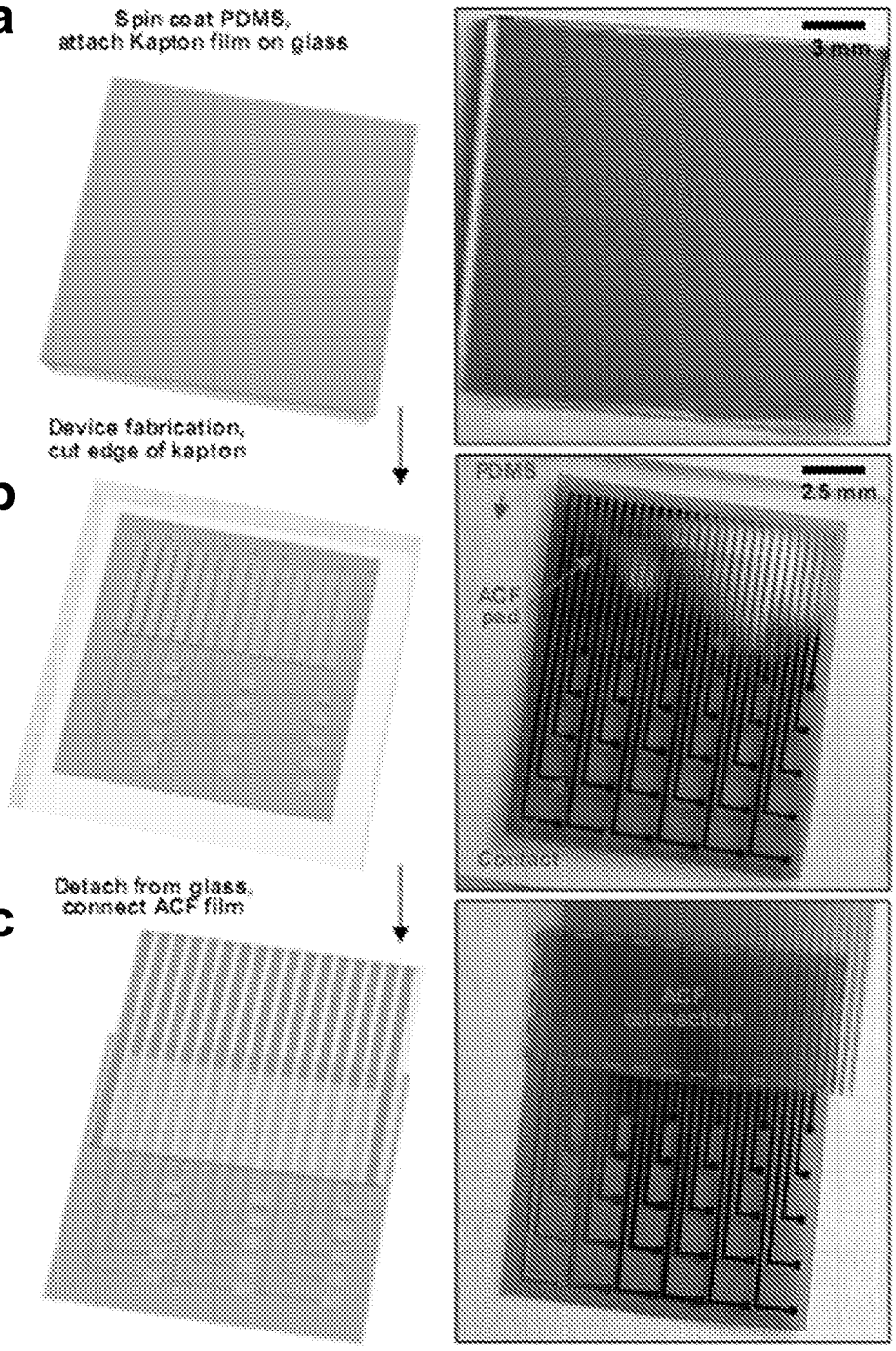


Figure 14

Fig. 15a

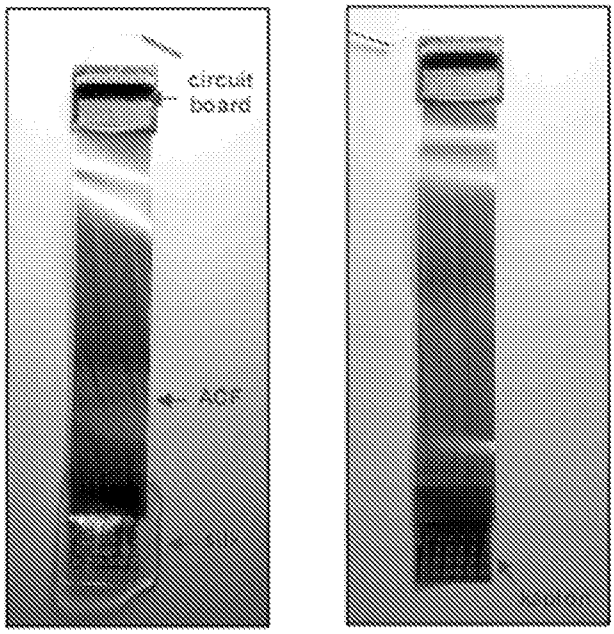


Fig. 15b

Figure 15

Fig. 16a

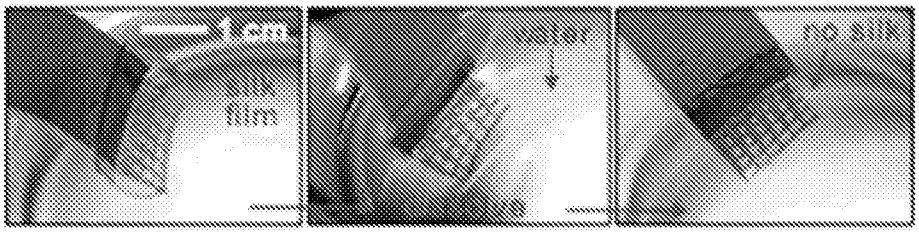


Fig. 16b

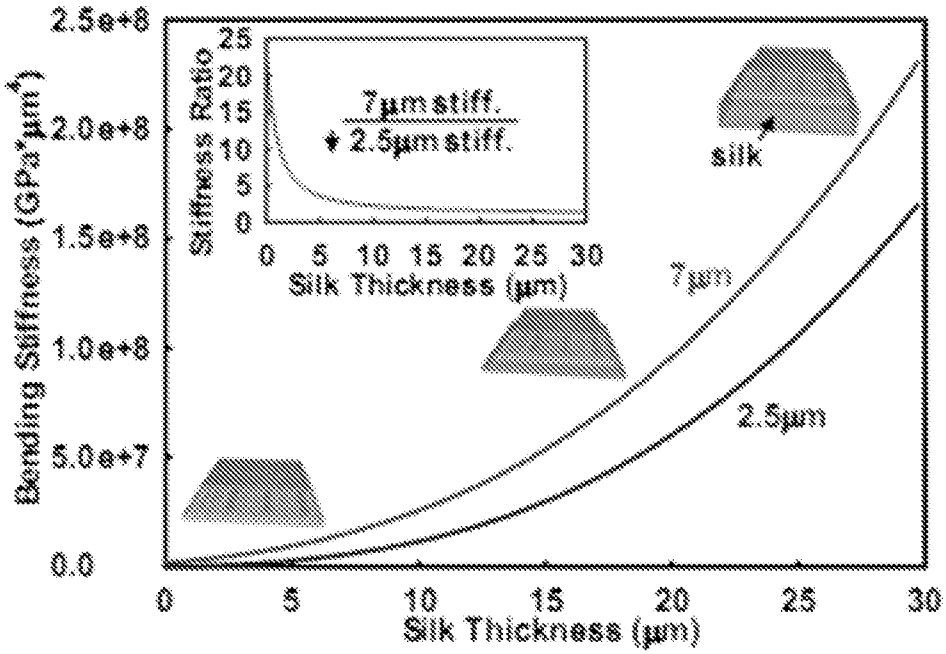


Fig. 16c

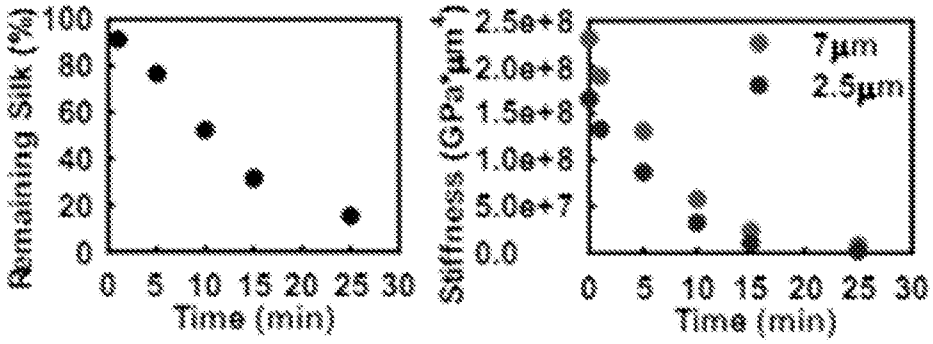


Fig. 16d

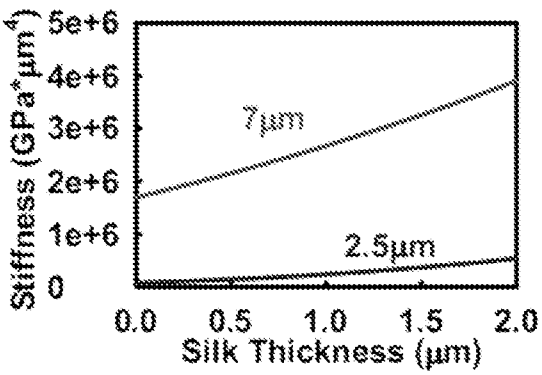


Figure 16

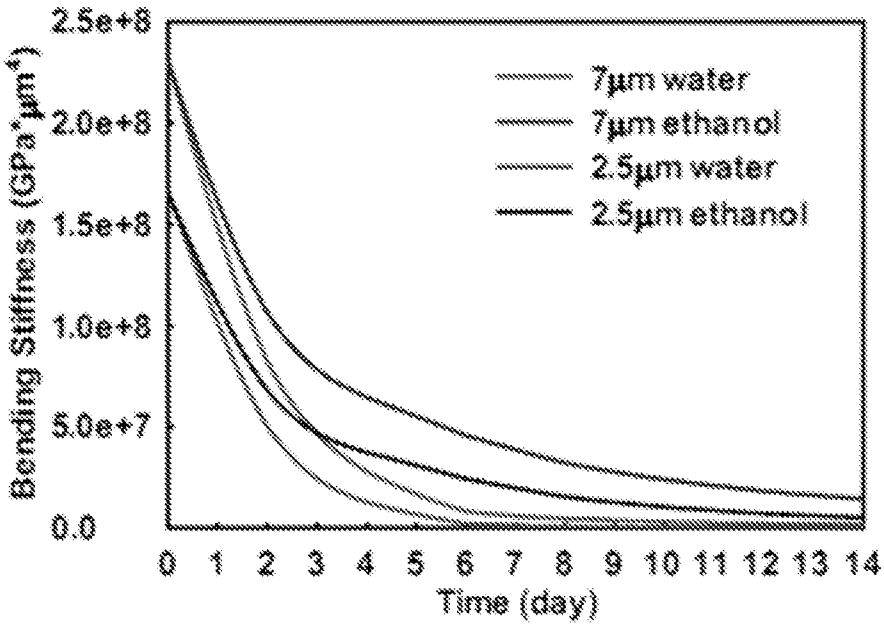

Bending Stiffness (GPa*μm⁴)
2.5e+8
2.0e+8
1.5e+8
1.0e+8
5.0e+7
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (day)
7μm water
7μm ethanol
2.5μm water
2.5μm ethanol

Figure 17

Fig. 18a

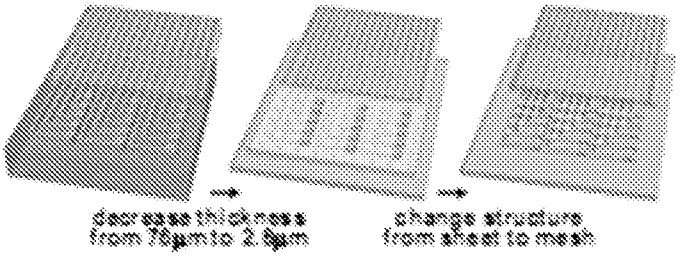


Fig. 18b

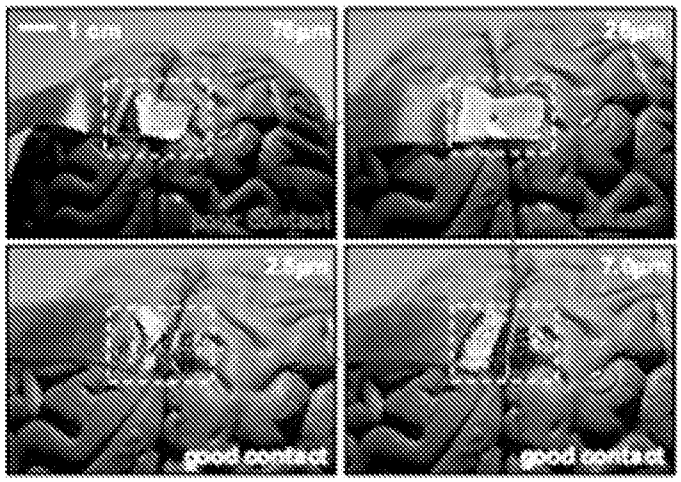


Fig. 18c

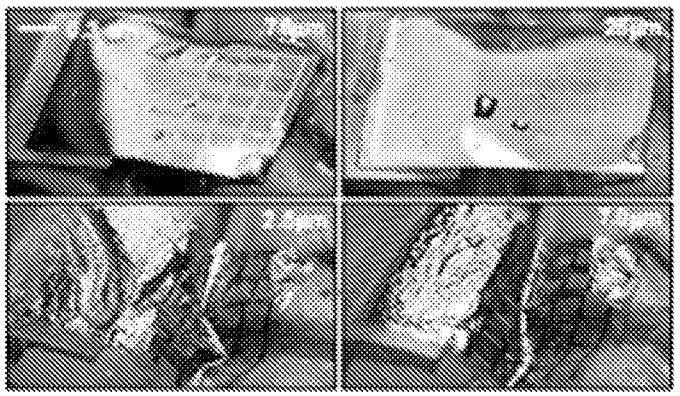


Fig. 18d

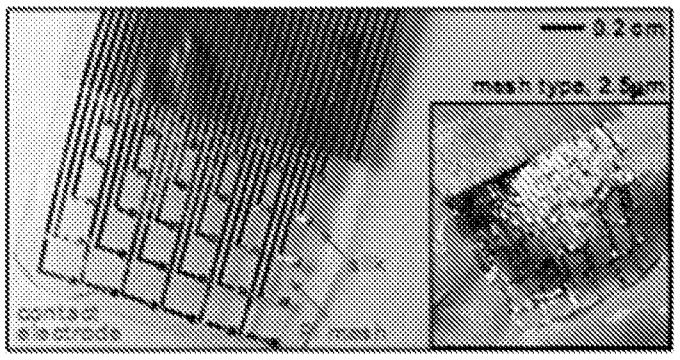


Figure 18

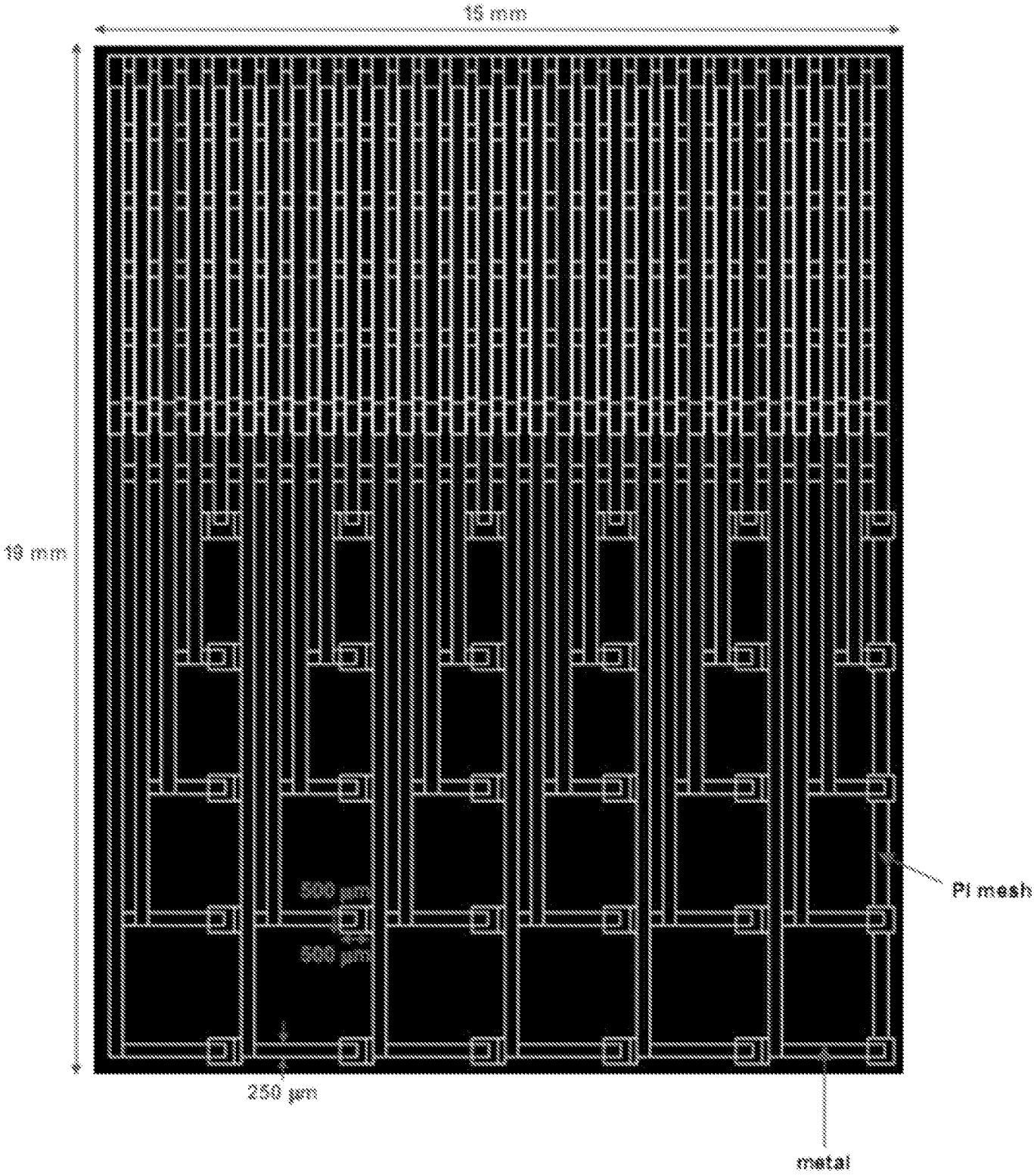


Figure 19

Fig. 20a

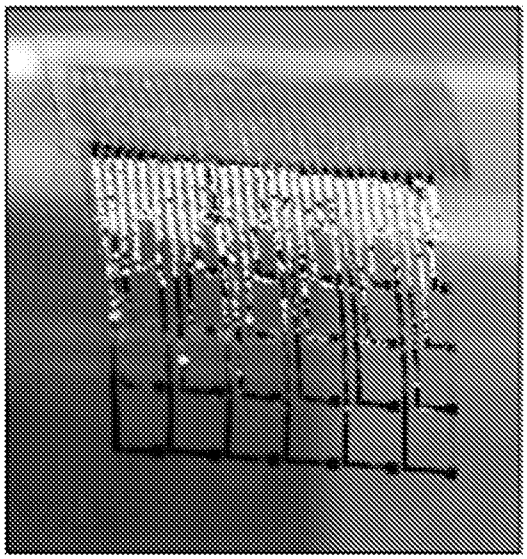


Fig. 20b

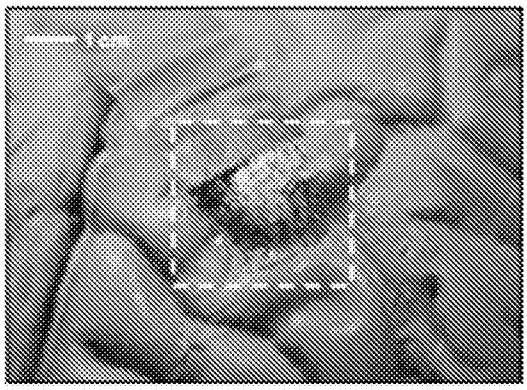


Figure 20

Fig. 21a

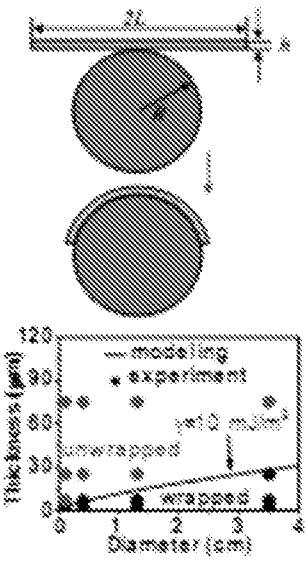


Fig. 21b

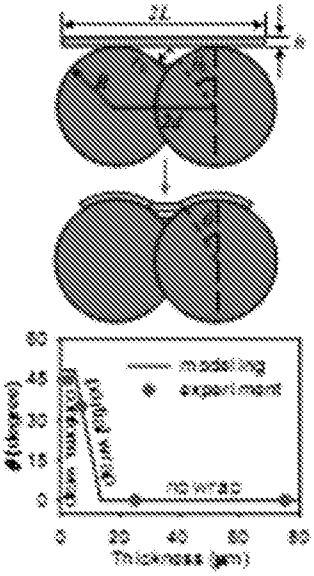


Fig. 21c

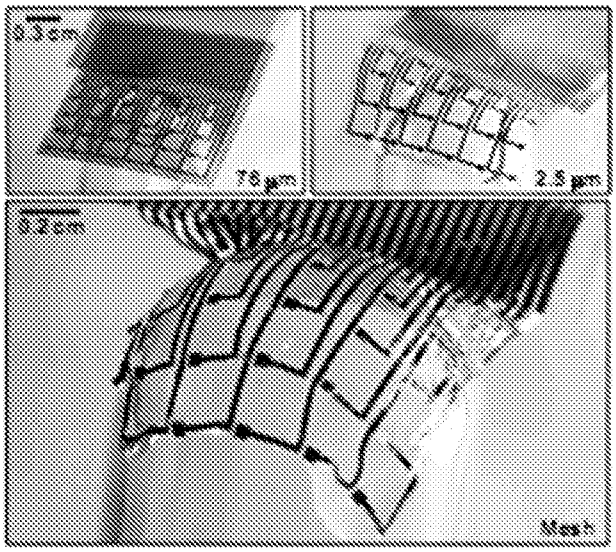


Fig. 21d

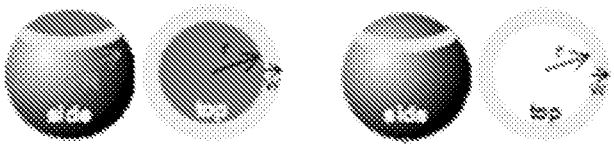


Fig. 21e

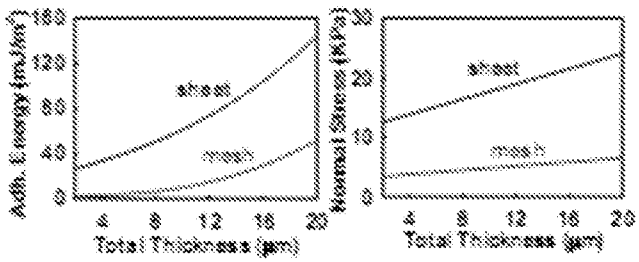


Figure 21

Fig. 22a

Fig. 22b

Fig. 22c

Fig. 22d

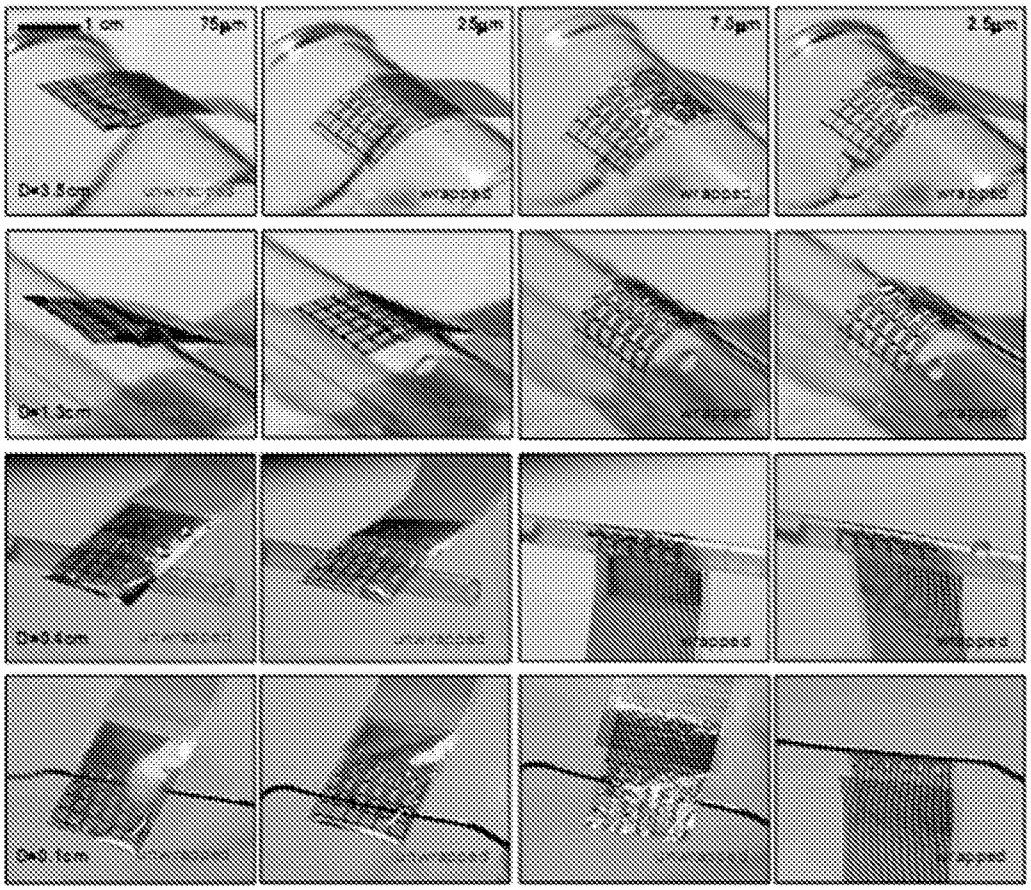


Figure 22

Fig. 23a

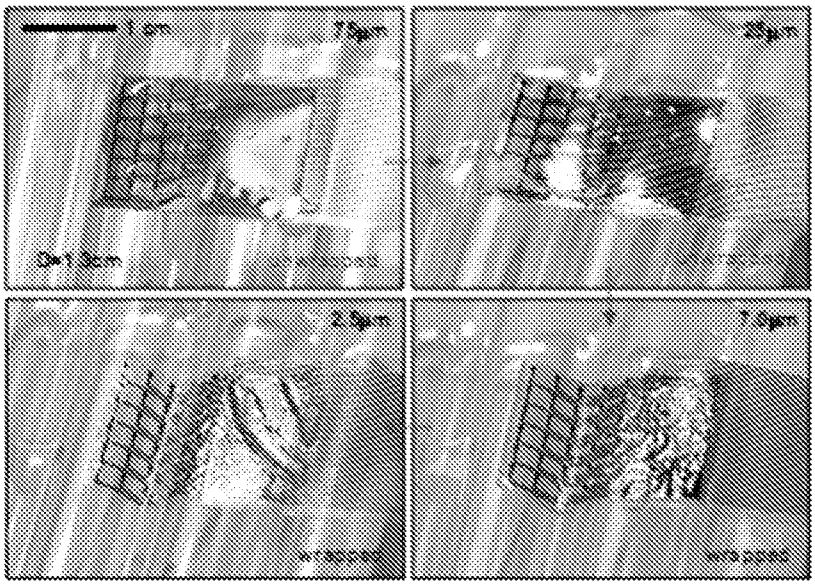


Fig. 23b

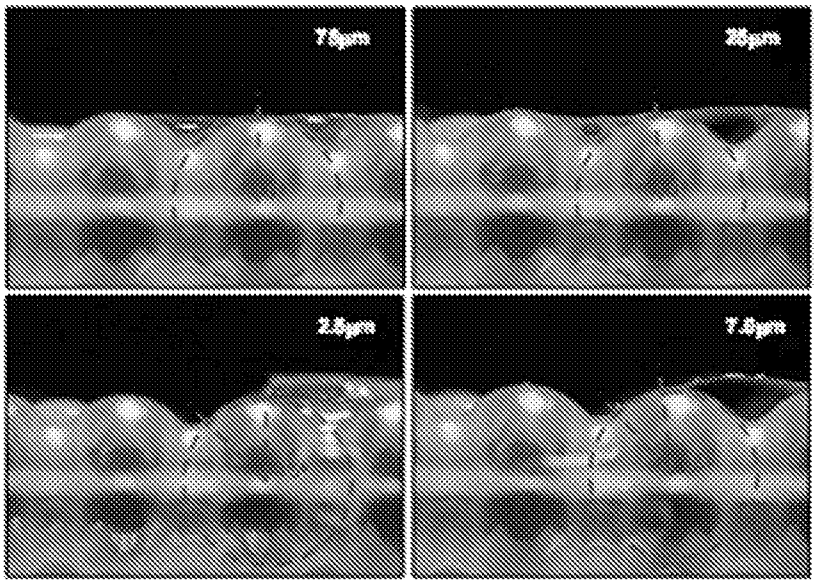


Figure 23

Fig. 24a

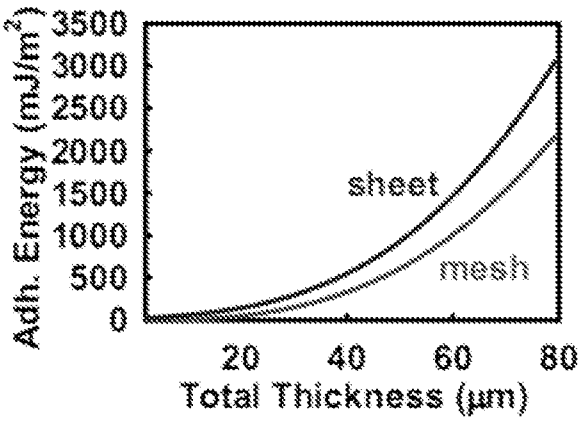


Fig. 24b

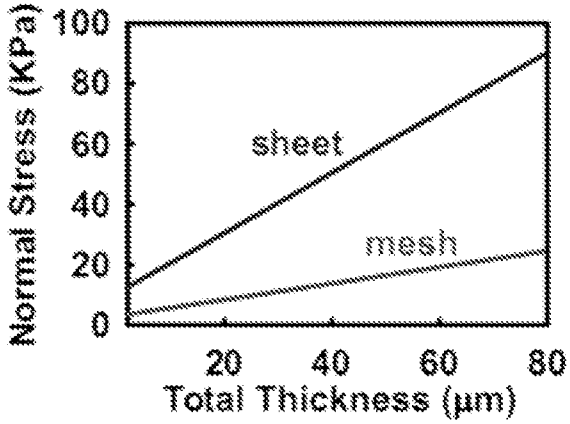


Figure 24

Fig. 25a

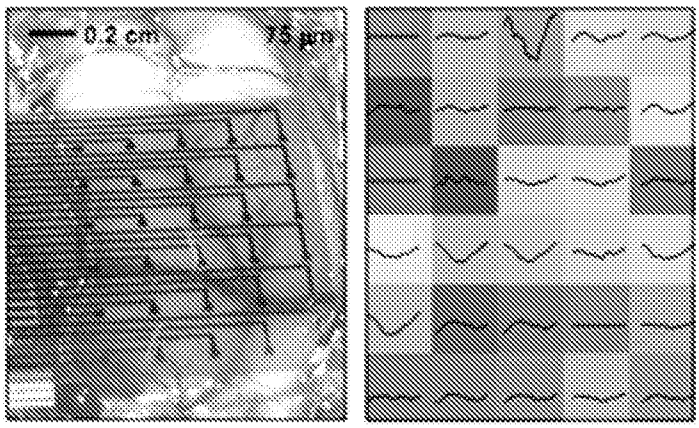


Fig. 25b

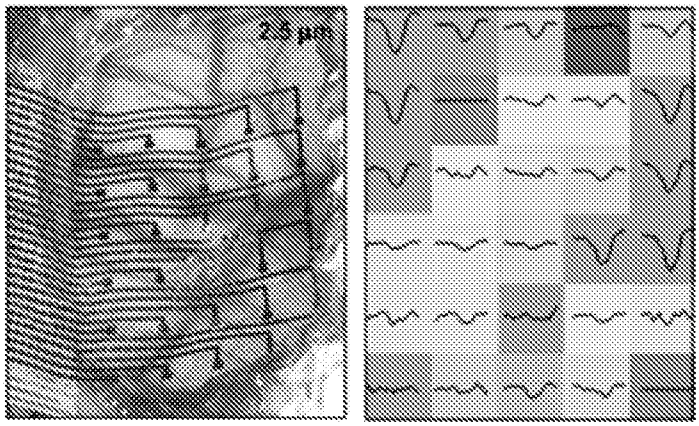


Fig. 25c

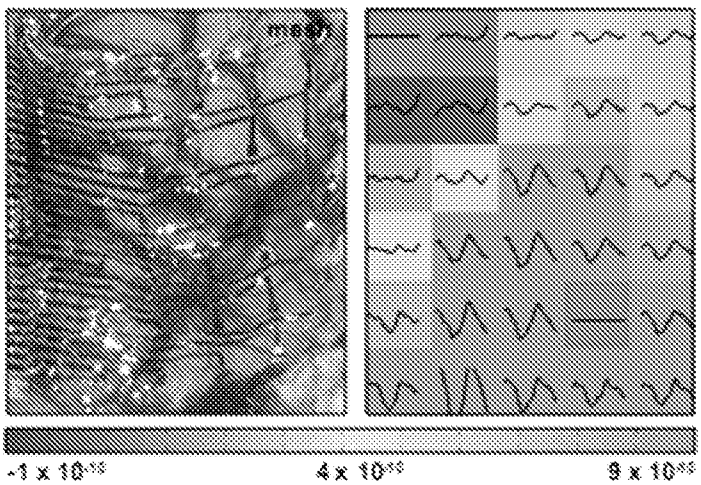


Fig. 25d

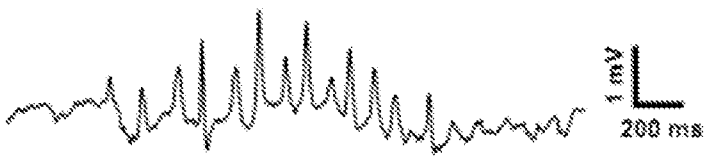


Figure 25

Fig. 26a

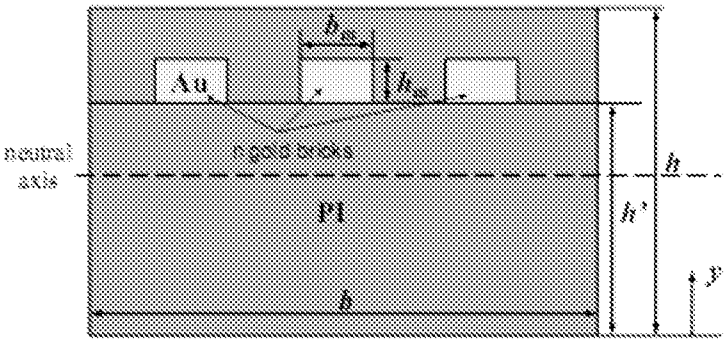


Fig. 26b

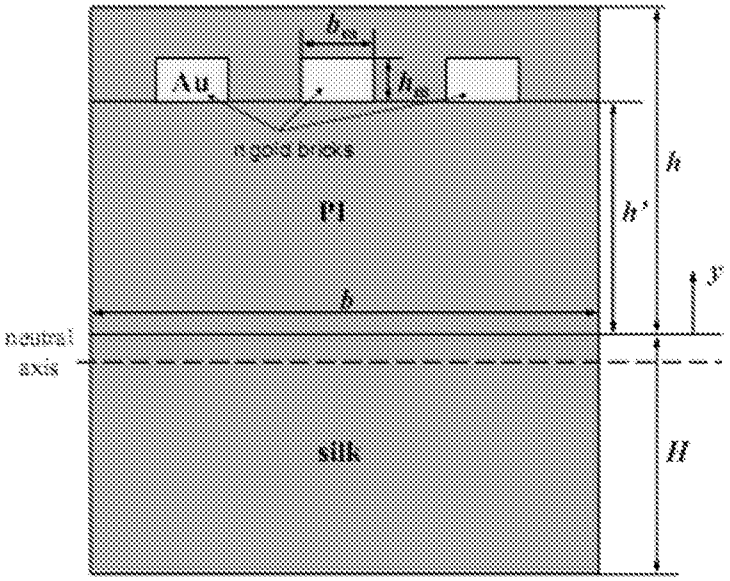


Figure 26

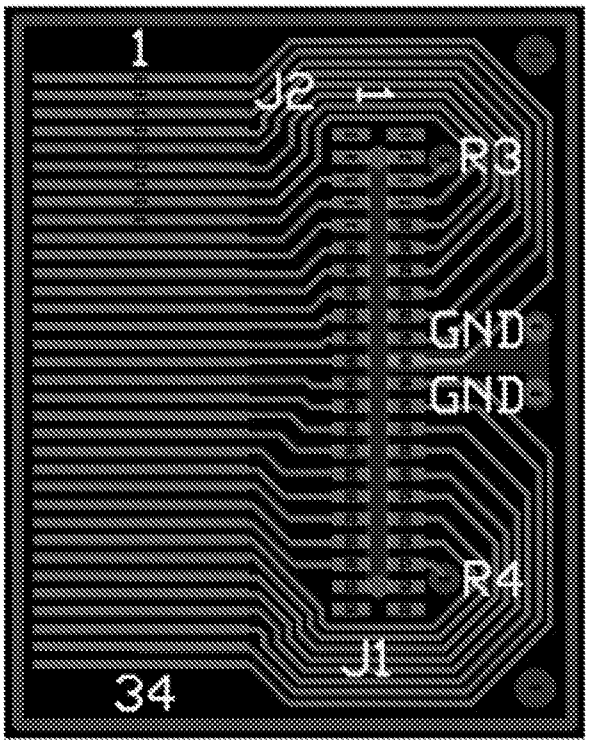


Figure 27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/50468

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/1473 (2010.01)
USPC - 600/377
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61B 5/1473 (2010.01)
USPC - 600/377

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
A61B5/00, 5/04, 5/05, 5/145, 5/1468
600/300, 309, 345, 372, 373, 386, 393, 395

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB, USPT, EPAB, JPAB); Google
Search Terms: electrode, sensor, cover, substrate, layer, coating, resorb$, bioresorb$, dissolv$, bioabsorb$, absorb$, degra$, biodegra$, establish, contact, communicationn

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0073130 A1 (FINCH et al.) 29 March 2007 (29.03.2007) Entire document, especially Abstract, para[0002], para[0024] - para[0032], para[0096] - para[0099] and para[0103].	1-3, 63-69, 77-79, 90-95, 97-107, 108-109/(90-95, 97-107) and 115-117
Y		96, 108-109/(96), 110
Y	US 2007/0031607 A1 (DUBSON et al.) 08 February 2007 (08.02.2007) Abstract, para[0005] and para[0304].	96, 108-110/(96)
Y	US 2009/0208555 A1 (KUTTLER et al.) 20 August 2009 (20.08.2009) Abstract, para[0014] - para[0015].	110
A	US 5,427,096 A (BOGUSIEWICZ et al.) 27 June 1995 (27.06.1995) Entire document.	1-3, 63-69, 77-79, 90-95, 97-109 and 115-117

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 2010 (22.12.2010)	06 JAN 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/50468

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-62, 70-76, 80-89, 111-114, 118-127
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.