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(54) **ELECTROPHYSIOLOGY USING CONFORMAL ELECTRONICS**

ELEKTROPHYSIOLOGIE UNTER VERWENDUNG KONFORMER ELEKTRONISCHER VORRICHTUNGEN

ÉLECTROPHYSIOLOGIE FAISANT INTERVENIR DES ÉQUIPEMENTS ÉLECTRONIQUES CONFORMES

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Description

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 61/286,921, 61/313,397 and 61/388,529 filed December 16, 2009, March 12, 2010 and September 30, 2010, respectively.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with United States governmental support from The U.S. Department of Energy under Award No. DEFG02-91 ER45439, the National Science Foundation under grant DMI-0328162, the U.S. Department of Energy under Award No. DE-FG02-07ER46471, the U.S. Army Research Laboratory and the U.S. Army Research Office under contract number W911 NF-07-1-0618, the National Institute of Neurological Disorders and Stroke (NINDS) under Award Nos. RO1-NS041811-04 and RO1-NS48598-01 and by the DARPA-DSO and the National Institutes of Health P41 Tissue Engineering Resource Center under award number P41 EB002520. The U.S. Government has certain rights in the invention.

BACKGROUND

[0003] This invention is in the field of medical devices. This invention relates generally to flexible and conformable electronic devices for biomedical applications including sensing and actuation of tissue.

[0004] Sudden cardiac arrest is the leading cause of death in developed countries. Many patients at risk for arrhythmic death have advanced structural heart disease, and preexisting non-lethal ventricular arrhythmias. In these and other cases, cardiac electrophysiologic (EP) studies are used to aid diagnosis and guide therapy. Conventional devices for this purpose use sparse arrays of electrodes that probe potentials at the surface of cardiac tissue. During mapping, sensors are continuously maneuvered to record from discrete sites on the heart. These sequential local recordings are "stitched" together with software to render a complete representation of cardiac electrical activity over a region of interest. The iterative nature of this approach prolongs EP procedures and impedes real time mapping of transient abnormal rhythms. Despite explosive growth and innovation in the broader electronics industry, the key limitation of EP devices is that they have retained the simple electronics-tissue interface of their earliest predecessors of ~40 years ago. Sensing and stimulating electrodes are purely passive metallic contacts individually wired to separate, remote processing units that use traditional semiconductor wafer-based electronics. Rapid, high resolution EP mapping might be most effectively accomplished by embedding modern silicon-based integrated circuit (IC) technology directly at the tissue-electrode interface. Unfortunately the planar shapes and rigid, brittle mechanical properties associated with conventional ICs strictly preclude their non-destructive, intimate integration with the curvilinear, soft surfaces of biological tissues.

[0005] Recently, a number of patents and publications have disclosed flexible, resilient and implantable electrode arrays. For example, U.S. Patent Application Publication US 2007/0043416 discloses an implantable flexible elastic support with a plurality of electrodes held in contact with a target tissue. Similarly, International Patent Application Publication WO 98/49936 discloses a resilient electrode array for sensing signals associated (mapping) and ablating heart tissue. U.S. Patent 5,678,737 discloses an electrophysiology mapping system for displaying a 3D model of epicardial and endocardial surfaces with dynamic display of potential distribution data.

[0006] U.S. Patent Application Publication US 2003/0149456 discloses a multi-electrode cardiac lead adapter which incorporates a multiplexing circuit allowing for control by a conventional single lead cardiac pacing pulse generator. Similarly, U.S. Patent Application Publication US 2006/0173364 discloses a multichannel electrophysiology acquisition system which utilizes a digital multiplexing circuit build on a conventional integrated circuit. U.S. Patent No. 6,666,821 discloses an implantable sensor array system with an associated protective member which prevents the sensors from interacting with the surrounding environment until it is disabled.

[0007] International Application Publication WO 2009/114689 discloses flexible and scalable sensor arrays for recording and modulating physiologic activity. US Patent Application Publication Nos. US 2008/0157235, US 2008/0108171, US 2010/0002402 and U.S. Patent 7,557,367 issued July 7, 2009 disclose multilayer stretchable, foldable and printable semiconductor devices. Document US-A-2009/294803 discloses the most relevant prior art.

SUMMARY OF THE INVENTION

[0008] The invention is defined in the independent claims. Any embodiment which is contradiction to the subject-matter of the independent claims is not part of the invention.

[0009] Provided herein are biomedical devices and methods of making and using biomedical devices for tissue sensing and actuation applications. For example, flexible and/or stretchable biomedical devices are provided including electronic

devices useful for establishing in situ conformal contact with a tissue in a biological environment. The invention includes implantable electronic devices and devices administered to the surfaces(s) of a target tissue, for example, for obtaining electrophysiology data from a tissue such as cardiac tissue, brain tissue or skin. Also disclosed are methods of sensing and making measurements in a biological environment, including methods of making *in vivo* electrophysiology measurements.

[0010] In one aspect, the invention provides devices for interfacing with a tissue in a biological environment including conformable devices. Devices of this aspect are useful, for example, for sensing and/or actuating a tissue in a biological environment. When placed in a biological environment, devices of an aspect of the invention optionally establish conformal contact with a target tissue(s), thereby providing contact useful for sensing or actuation of the tissue. Further, devices of this aspect optionally maintain conformal contact and/or electrical contact and/or optical communication with the surface of a tissue as the tissue moves and/or as the device is moved across a surface of the tissue.

[0011] In an embodiment, the invention provides a device for interfacing with a tissue in a biological environment comprising: (1) a flexible or stretchable substrate; (2) a flexible or stretchable electronic circuit comprising one or more inorganic semiconductor circuit elements supported by the flexible or stretchable substrate; and (3) a barrier layer encapsulating at least a portion of the flexible or stretchable electronic circuit. The materials, physical dimensions and mechanical properties of the device, and components thereof, are selected in some embodiments to provide device attributes useful for a range of biomedical applications, including sensing and actuation of tissue. In an embodiment, for example, the flexible or stretchable substrate, the flexible or stretchable electronic circuit and the barrier layer have compositions, physical dimensions and/or geometries providing a net bending stiffness and/or flexural rigidity of the device low enough that the device establishes conformal contact with the tissue in the biological environment. In certain embodiments, the barrier layer is a moisture barrier, a thermal barrier, an electromagnetic radiation barrier, an electrical barrier, an optical barrier, a magnetic barrier, a selectively permeable or impermeable barrier or any combination of these. In an embodiment, for example, the substrate is a flexible substrate and the electronic circuit is a flexible electronic circuit. In an embodiment, for example, the substrate is a stretchable substrate and the electronic circuit is a stretchable electronic circuit.

[0012] In an embodiment, the invention provides a device for interfacing with a tissue in a biological environment, the device comprising: a flexible or stretchable substrate; a flexible or stretchable electronic circuit supported by the flexible or stretchable substrate, wherein the flexible or stretchable electronic circuit comprises a plurality of sensors, actuators or both sensors and actuators provided in an array and one or more inorganic semiconductor circuit elements; a controller in communication with the flexible or stretchable electronic circuit, the controller configured to receive input signals from the flexible or stretchable electronic circuit and provide output signals to the flexible or stretchable electronic circuit, wherein the controller receives and analyzes input signals corresponding to one or more measurements from the sensors and generates output signals that control or provide one or more sensing or actuation parameter to the flexible or stretchable electronic circuit; and a barrier layer encapsulating at least a portion of the flexible or stretchable electronic circuit; wherein the substrate, the electronic circuit and the barrier layer provide a net bending stiffness of the device low enough that the device establishes conformal contact with the tissue in the biological environment. In an embodiment, the controller receives input signals corresponding to measurements by the sensors of tissue properties, such as composition, structure and physiological properties, and uses the input signals to control sensing and/or actuation of the tissue, for example, via a closed-loop feedback algorithm. In an embodiment, the controller receives input signals corresponding to measurements by the sensors of tissue properties, such as composition, structure and physiological properties, as a function of time and uses the input signals as a function of time to adjust and/or optimize sensing and/or actuation of the tissue. In an embodiment, the controller receives input signals corresponding to measurements by the sensors of tissue properties, such as composition, structure and physiological properties, and uses the input signals to control removal of at least a portion of the tissue, for example, via tissue ablation methods.

[0013] The materials, physical dimensions and mechanical properties of the device, and components thereof, are selected in some embodiments to provide complete or partial electronic, optical, chemical and/or thermal isolation of the device from the tissue and/or biological environment useful for avoiding damage of the tissue during use. In an embodiment, for example, the barrier layer and the flexible or stretchable substrate limit a net leakage current from the electronic circuit to an amount which does not adversely affect the tissue. In an embodiment, for example, the barrier layer and the flexible or stretchable substrate limits heat transfer from the electronic circuit to the tissue in the biological environment to an amount that does not adversely affect the tissue in the biological environment.

[0014] The materials, physical dimensions and mechanical properties of the device, and components thereof, are selected in some embodiments to provide access of the device to the tissue and/or biological environment useful for biomedical applications, including sensing and/or actuation of tissue. In an embodiment, for example, the barrier layer is patterned so as to selectively modulate physical contact, thermal contact, optical communication or electrical communication between the electronic circuit and the tissue in the biological environment. In an embodiment, for example, the barrier layer is patterned so as to provide one or more permeable regions that are selectively permeable to one or more target molecules to allow transport of the target molecules from the biological environment to the electronic circuit

or from the electronic circuit to the biological environment. In an embodiment, for example, the barrier layer is patterned so as to provide one or more impermeable regions that are impermeable to one or more target molecules to prevent transport of the target molecules from the biological environment to the electronic circuit or from the electronic circuit to the biological environment. In an embodiment, for example, the barrier layer is patterned to provide one or more transparent regions, wherein the transparent regions transmit to or from the electronic circuit ultraviolet, visible or near-infrared electromagnetic radiation having a preselected wavelength distribution. In an embodiment, for example, the barrier layer is patterned to provide one or more opaque regions that substantially prevent transmission to or from the electronic circuit of electromagnetic radiation having a preselected distribution of wavelengths in the ultraviolet, visible or near-infrared regions of the electromagnetic spectrum.

[0015] As used in this context, the term "patterned" refers to selective variation of the physical properties, chemical composition, physical dimensions and/or geometry of a device or component thereof, for example via openings, channels, pores, contact regions, permeable regions, impermeable regions, transmissive regions, conductive regions and/or opaque regions. In an embodiment, the barrier layer is patterned to have one or more contact regions, such as openings or passages allowing physical contact between components of the electronic circuit (e.g., electrodes or sensors) and the tissue. In an embodiment, the barrier layer is patterned to have one or more transmissive regions, such as windows allowing optical communication between components (e.g., sensors, optical sources, LEDs, laser, photodiodes, etc.) of the electronic circuit and the tissue. In an embodiment, the barrier layer is patterned to have one or more chemically permeable regions, such as pores or channels allowing selective transport of target molecules between with electronic circuit and the tissue. Patterned in this context may refer to a device component, such as a barrier layer, that is patterned via a microprocessing technique such as optical lithography, soft lithography, etching, e-beam writing and/or laser ablation.

[0016] Devices of the present invention are applicable to a wide range of tissues and biological environments, including implant environments and exposed tissue environments. In an embodiment, for example, the biological environment is an *in-vivo* biological environment. In an embodiment, for example, the biological environment comprises a conductive ionic solution, such as a biological fluid including blood, a component of blood, pericardial fluid, peritoneal fluid, cerumen, and cerebrospinal fluid. In an embodiment, for example, the tissue in the biological environment comprises heart tissue, brain tissue, muscle tissue, skin, nervous system tissue, epithelial tissue, retina tissue, ear drum, tumor tissue, digestive system structures, circulatory system structures and/or vascular tissue. In an embodiment, the device establishes conformal contact with the tissue *in situ* when the device is placed in physical contact with the tissue in the biological environment, and wherein the conformal contact with the tissue in the biological environment is maintained as the tissue or the device moves. In an embodiment, the device is in electrical contact with the tissue in the biological environment, wherein the electrical contact with the tissue in the biological environment is maintained as the tissue or the device moves. In some embodiments, the device of the invention is applied via establishing physical contact with the tissue and/or biological environment, for example by implanting the device or contacting a surface of the tissue with the device.

[0017] The invention provides devices having physical and chemical properties useful for a wide range of biomedical applications including cardiac monitoring, sensing and actuation of brain tissue, vascular therapies and skin mounted sensing. In an embodiment, for example, the substrate, the electronic circuit and the barrier layer provide a net bending stiffness of the device less than or equal to 1×10^8 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 an embodiment, for example, the substrate, the electronic circuit and the barrier layer provide a net bending stiffness of the device selected over the range of 1×10^8 GPa μm^4 - 1×10^5 GPa μm^4, and optionally for some applications selected over the range of 1×10^7 GPa μm^4 - 1×10^5 GPa μm^4, and optionally for some applications selected over the range of 1×10^6 GPa μm^4 - 1×10^5 GPa μm^4. In an embodiment, for example, the substrate, the electronic circuit and the barrier layer provide a net flexural rigidity of the device less than or equal to 1×10^{-4} Nm, and optionally for some embodiments less than or equal to 1×10^{-5} Nm. In an embodiment, for example, the substrate, the electronic circuit and the barrier layer provide a net flexural rigidity of the device selected from the range of 1×10^{-4} Nm to 1×10^{-7} Nm, and optionally for some applications device selected from the range of 1×10^{-5} Nm to 1×10^{-7} Nm. For certain embodiments, devices of this aspect have and/or are capable of having a bending radius for all and/or portions of the device of 100 μm. For example, devices of this aspect can adopt a radius of curvature of 100 μm without undergoing damage to the device or device components, such as mechanical fracture, device failure or interruption of electrical interconnections.

[0018] The invention includes devices having a multilayer geometry, including a geometry wherein the substrate, electronic circuit and barrier layer components (and/or components of these) are provided in a series of stacked layers, including layers and/or thin films that a provided in direct contact with each other in the series of layers or in a series having one or more intermediate layers (e.g., adhesive layers, spacer layers, NMP layers, etc.) provided between device layers of the series. The positioning of device components in multilayer geometries of the present devices may be selected to provide enhanced mechanical attributes or device functionality. In an embodiment, for example, the device has a neutral mechanical plane and at least a portion of the inorganic semiconductor circuit elements are positioned proximate to the neutral mechanical plane. In an embodiment, for example, a thickness of the barrier layer and a thickness

of the flexible or stretchable substrate are selected so as to position at least a portion, or optionally all, of the inorganic semiconductor circuit elements proximate to the neutral mechanical plane. In some embodiments, proximate to the neutral mechanical plane refers to device geometries wherein a device component, such as an electronic circuit component is positioned within 10 microns, and optionally for some applications, within 1 micron, to the overall neutral mechanical plane at a specific position of the device.

[0019] The barrier layer of the present devices may function to completely or partially encapsulate one or more other device components such as flexible or stretchable electronic circuit components and or the flexible or stretchable substrate. In some embodiments, the electronic circuit component is completely encapsulated by, and in physical contact with, the barrier layer and/or flexible or stretchable substrate. In an embodiment, for example, the barrier layer and/or flexible or stretchable substrate encapsulates at least 50% of the electronic circuit component of the device, optionally at least 90% of the electronic circuit component of the device, and optionally all of the electronic circuit component of the device. In an embodiment, the barrier layer partially or completely encapsulates the flexible or stretchable substrate. In an embodiment, for example, the barrier layer encapsulates at least 50% of the flexible or stretchable substrate of the device, optionally at least 90% of the flexible or stretchable substrate of the device, and optionally all of the flexible or stretchable substrate of the device.

[0020] Selection of the composition and physical properties of the barrier layer is an important aspect of the invention for controlling and/or selectively modulating the interface of the device and the tissue and/or biological environment. In an embodiment, for example, the barrier layer has an average thickness over at least a portion of the electronic circuit less than or equal to 1000 μm, optionally for some applications less than or equal to 100 μm, optionally for some applications less than or equal to 10 μm, and optionally for some embodiments applications less than or equal to 1 μm In an embodiment, for example, the barrier layer has a thickness over at least a portion of the electronic circuit selected over the range of 0.25 μm to 1000 μm, and optionally for some applications selected over the range of 0.5 μm to 500 μm, and optionally for some applications selected over the range of 1 μm to 25 μm. In an embodiment, the ratio of the average thickness of the barrier layer to the average thickness of the flexible or stretchable substrate is selected over the range of 0.1 to 10, and optionally for some applications 0.5 to 2.

[0021] In some embodiments, the barrier layer comprises a low modulus material. The invention includes, for example, devices wherein the barrier layer has an average modulus less than or equal to 10 GPa, an average modulus less than or equal to 1 GPa optionally for some embodiments less than or equal to 100 MPa, optionally for some embodiments less than or equal to 10 MPa, and optionally for some embodiments less than or equal to 1 MPa. In an embodiment, for example, the barrier layer has an average modulus selected over the range of 0.5 KPa to 10 GPa, optionally for some application selected over the range of 1 KPa to 1 GPa, and optionally for some application selected over the range of 1 KPa to 100 MPa. In an embodiment, for example, the barrier layer has an average modulus equal to or less than 50 times the average modulus of the skin of the subject at the tissue interface. As will be generally understood by one skilled in the art, use of a barrier layer with a relatively high modulus (e.g., greater than 1 GPa) in some embodiments may require a small thickness (e.g., less than 100 microns or optionally less than 10 microns) to provide net device mechanical properties (e.g., bending stiffness or flexural rigidity) useful for establishing conformal contact with the tissue.

[0022] A range of materials are useful for barrier layers of the devices of the invention. In an embodiment, for example, the barrier layer comprises a material selected from the group consisting of: a polymer, an inorganic polymer, an organic polymer, an elastomer, a biopolymer (e.g., polypeptide, protein, polynucleotide, oligonucleotide, carbohydrate, etc.), a ceramic, and any combination of these. Barrier layers of the invention include composite materials. In an embodiment, for example, the barrier layer comprises an elastomer. In an embodiment, for example, the barrier layer comprises PDMS, SU-8, Si_3N_4, SiO_2, polyurethane, polyimide, parylene, parylene C, silicon carbide (SiC), BCB, NOA, and any combination of these. In an embodiment, for example, the barrier layer is a biocompatible material and/or a bioinert material.

[0023] In an embodiment, for example, the barrier layer is patterned to have one or more nanostructured or microstructured optically transmissive regions, optically opaque regions or selectively permeable regions that are permeable to one or more target molecules, for example, to provide 1 to 1000 of such nanostructured or microstructured regions, and optionally 10-50 of such nanostructured or microstructured regions. 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, such as one or more lateral dimensions (e.g., length or width) selected over the range of 1 micron to 1000 microns. The term "nanostructured" refers to a structure having at least one physical dimension selected over the range of 10 nanometers to 1000 nanometers, such as one or more lateral dimensions (e.g., length or width) selected over the range of 10 nanometers to 1000 nanometers. Microstructured and/or nanostructured regions of the barrier layer include a variety of structures including channels, pores, openings, windows, electrodes, permeable regions, recessed features, relief features (e.g., raised features), transparent regions, opaque regions and the like. In an embodiment, the microstructured or nanostructured region(s) of the barrier layer is one or more openings, pores or channels in the barrier layer so as to provide physical contact between selected regions of the electronic circuit and the tissue or biological environment. In an embodiment, the microstructured or nanostructured region(s) of the barrier layer is one or more optically transparent

windows in the barrier layer so as to provide optical communication between selected regions of the electronic circuit and the tissue and/or biological environment, for example, to allow transmission of electromagnetic radiation having a preselected wavelength distribution, such as light in the visible, ultra violet and/or near infrared regions of the electromagnetic spectrum. In an embodiment, the microstructured or nanostructured region(s) of the barrier layer is one or more electrodes in the barrier layer so as to provide electrical contact between selected regions of the electronic circuit and the tissue and/or biological environment.

[0024] In an embodiment, the barrier layer comprises a multilayer structure, for example, comprising 2 to 50 individual layers and optionally 2 - 20 individual layers. In some embodiments, for example, a barrier layer of the invention comprises a sequence of layers, wherein layers in the sequence are selected from the group consisting of metal layers, inorganic layers (e.g., inorganic dielectrics such as oxides, carbides or nitrides, etc.) and polymer layers. In an embodiment, the layers of the sequence are thin film layers having thicknesses ranging from 10 nanometers to 10 microns. This aspect of the invention is beneficial for providing barrier layers having useful chemical, electronic or thermal properties, such as providing low leakage currents for long periods of time. In an embodiment, for example, the barrier layer is a multilayer structure comprising one or more metal layers separated by one or more inorganic layers or polymer layers. In an embodiment, for example, the barrier layer is a multilayer structure comprising one or more inorganic layers separated by one or more metal layers or polymer layers. In an embodiment, for example, the barrier layer is a multilayer structure comprising one or more polymer layers separated by one or more metal layers or inorganic layers. Use of polymer layers in barrier layers comprising multilayer structures is useful in some embodiments for filling in cracks and/or pinholes in metal and/or inorganic layers. In an embodiment, a barrier layer of the invention comprises a multilayer structure having a total thickness less than 500 microns, optionally for some applications less than 100 microns, and optionally for some applications less than 10 microns.

[0025] Selection of the composition and physical properties of the flexible or stretchable substrate is an important aspect of the invention for providing useful device properties. In an embodiment, for example, the flexible or stretchable substrate has an average thickness less than or equal to 1000 μm, optionally for some applications less than or equal to 100 μm, and optionally for some applications less than or equal to 10 μm. In an embodiment, for example, the flexible or stretchable substrate has an average thickness selected over the range of 0.25 μm to 1000 μm, optionally for some embodiments selected over the range of 10 μm to 500 μm and optionally for some embodiments selected over the range of 10 μm to 100 μm. Substrates of certain devices of the invention have a substantially uniform thickness (e.g., deviations from an average thickness less than 10% and optionally less than 5% and optionally less than 1 %). Alternatively, the invention includes substrates having a thickness that varies selectively along one or more lateral dimension (e.g. length or width) over the electronic circuit. In some embodiments, for example, the substrate is thicker in certain regions, such as regions supporting or in physical contact with components of the electronic circuit, than in other regions of the substrate that are not supporting or in physical contact with components of the electronic circuit. In some embodiments, for example, the substrate is absent in certain regions, such as regions of the substrate that are not supporting or in physical contact with components of the electronic circuit.

[0026] In some embodiments, the device of the invention comprises a substrate having one or more microstructured and/or nanostructured features, including recessed features, relief (e.g.. raised) features, openings, passages and/or channels. In an embodiment, at least a portion of, and optionally all of, the electronic circuit component of the device is supported by a flexible or stretchable substrate having a mesh structure. Use of a substrate having a mesh structure is beneficial in the invention for providing a structurally supporting layer allowing for efficient handling and administration of the device, while at the same time providing mechanical properties (e.g., flexibility, deformability, bendability, stretchability, 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 substrate 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 substrate has a mesh structure that is a lattice structure, a perforated structure or a tentacle structure. In an embodiment, for example, the substrate is a mesh structure having structural regions at least partially supporting, or optionally in physical contact with, one or more of the components of the electronic circuit, such as inorganic semiconductor components or electrodes, wherein structural regions of the substrate are separated from each other by voids, cut outs or other openings where the substrate is not present. In such embodiments, therefore, the presence of the void regions, cut outs or other openings provides a mesh structured substrate occupying less than the foot print area of the device. In an embodiment, for example, the substrate having a mesh structure is a discontinuous layer, as opposed to a continuous layer, such as a continuous film or sheet.

[0027] In an embodiment, for example, the flexible or stretchable substrate comprises a low modulus material. For

example, the invention includes devices having a flexible or stretchable substrate with an average modulus less than or equal to 10 GPa, optionally for some embodiments less than or equal to 100 MPa, optionally for some embodiments less than or equal to 10 MPa, and optionally for some embodiments less than or equal to 1 MPa and optionally less than 0.1 MPa. In an embodiment, for example, the flexible or stretchable substrate has an average modulus selected over the range of 0.5 KPa to 5 GPa, optionally for some application selected over the range of 1K to 1 GPa, and optionally for some application selected over the range of 1 KPa to 100 MPa. In an embodiment, for example, the flexible or stretchable substrate has an average modulus equal to or less than 50 times the average modulus of the skin of the subject at the tissue interface. As will be generally understood by one skilled in the art, use of a flexible or stretchable substrate layer with a relatively high modulus (e.g., greater than 1 GPa) in some embodiments may require a small thickness (e.g., less than 100 microns or optionally less than 10 microns) to provide net device mechanical properties (e.g., bending stiffness or flexural rigidity) useful for establishing conformal contact with the tissue.

[0028] A range of materials are useful for flexible or stretchable substrates of the devices of the invention. In an embodiment, for example, the flexible or stretchable substrate comprises a material selected from the group consisting of: a polymer, an inorganic polymer, an organic polymer, a biopolymer (e.g., polypeptide, protein, polynucleotide, oligonucleotide, carbohydrate, etc.), a plastic, an elastomer, a thermoset, rubber, fabric, paper, a composite material and any combination of these. In an embodiment, for example, the flexible or stretchable substrate comprises PDMS, parylene or polyimide. In an embodiment, for example, the flexible or stretchable substrate comprises a low modulus rubber or a low modulus silicone material, such as Ecoflex ®. In an embodiment, for example, the flexible or stretchable substrate is a biocompatible material or a bioinert material. In an embodiment, for example, the flexible or stretchable substrate and the barrier each comprise the same material, such as the same polymer or elastomer material

[0029] Flexible or stretchable electronic circuit components of the invention include a range of electronic devices, or components thereof, including semiconductor devices, active electronic devices, passive electronic devices, opto-electronic devices, optical devices, and electronic device arrays. Electronic circuits of the invention include, for example, an inorganic semiconductor component, such as a single crystalline inorganic semiconductor structure, doped single crystalline inorganic semiconductor structure, high purity single crystalline inorganic semiconductor structure. This aspect of the invention is particularly useful for accessing devices exhibiting very high electronic device performance, such as devices having transistor components exhibiting useful field effect mobilities and/or on/off ratios.

[0030] In an embodiment, for example, the flexible or stretchable electronic circuit comprises one or more flexible or stretchable inorganic semiconductor structures. In an embodiment, for example, the flexible or stretchable inorganic semiconductor structures of the electronic circuit component comprise a single crystalline inorganic semiconductor, such as single crystalline silicon or a single crystalline iii-v semiconductor structure. To provide useful flexibility in some embodiments, the semiconductor structures of the electronic circuit of the invention are thin semiconductor structures. In an embodiment, for example, the flexible or stretchable inorganic semiconductor structures have an average thickness less than or equal to 500 microns, optionally for some applications less than or equal to 100 microns, optionally for some applications less than or equal to 10 microns, optionally for some applications less than or equal to 1 micron, and optionally for some applications less than or equal to 500 nanometers. In an embodiment, for example, the flexible or stretchable inorganic semiconductor structures have an average thickness selected from the range of 100 nanometers to 1000 microns, optionally for some embodiments selected from the range of 500 nm to 500 microns, optionally for some embodiments selected from the range of 1 micron to 100 microns. In an embodiment, for example, the flexible or stretchable inorganic semiconductor structures have an average thickness selected from the range of 250 nanometers to 100 microns. In an embodiment, for example, the flexible or stretchable inorganic semiconductor structures are ultrathin structures. In an embodiment, for example, each of the flexible or stretchable inorganic semiconductor structures has a net flexural rigidity less than or equal to less than or equal to 1×10^{-4} Nm.. In an embodiment, for example, each of the flexible or stretchable inorganic semiconductor structures has a net bending stiffness less than or equal to 1×10^{8} 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 an embodiment, for example, each of the flexible or stretchable inorganic semiconductor structures is independently a flexible or stretchable semiconductor nanoribbon, semiconductor membrane, semiconductor nanowire or any combination of these. In an embodiment, for example, the flexible or stretchable inorganic semiconductor structures are assembled on the flexible or stretchable substrate via a transfer printing technique, such as dry transfer contact printing and/or transfer printing process using an elastomeric transfer device.

[0031] In an embodiment, the flexible or stretchable electronic circuit further comprises one or more additional device components in physical or electronic contact with the inorganic semiconductor structures. In an embodiment, for example, the flexible or stretchable electronic circuit further comprises one or more flexible or stretchable dielectric structures, wherein at least a portion of the flexible or stretchable inorganic semiconductor structures is in physical contact with one or more of the dielectric structures. A range of dielectric structures are useful in this aspect of the invention including flexible or stretchable dielectric structures having a thickness equal to or less than 100 microns. In an embodiment, for example, the flexible or stretchable electronic circuit further comprises one or more flexible or stretchable electrodes, wherein at least a portion of the flexible or stretchable inorganic semiconductor structures or a portion of the dielectric

structures is in electrical contact with one or more of the electrodes. A range of electrodes are useful in this aspect of the invention including flexible or stretchable electrodes having a thickness equal to or less than 500 microns.

[0032] The invention includes devices wherein the flexible or stretchable electronic circuit comprises a plurality of electronically interconnected island and bridge structures. This aspect of the invention is useful for providing highly conformal and optionally stretchable devices. In an embodiment, for example, the island structures comprise one or more semiconductors, including flexible or rigid semiconductor structures and/or semiconductor electronic devices, semiconductor and dielectric structures, semiconductor and electrode structures, transistors, photodiodes, light emitting diodes, lasers, diodes, integrated circuits, multiplexer circuits, and amplifier circuits. In an embodiment, for example, the bridge structures comprise one or more flexible or stretchable electrical interconnections, such as electrical interconnections having a serpentine, buckled, or bent geometry. In an embodiment, for example, the flexible or stretchable electrical interconnections are encapsulated structures (e.g. encapsulated in polymer or elastomer). In some embodiments, at least a portion of the island structures comprising semiconductor structures are in electrical contact with one or more flexible or stretchable interconnects.

[0033] The invention includes devices wherein the flexible or stretchable electronic circuit is selected from the group consisting of: a flexible or stretchable transistor, a flexible or stretchable diode, a flexible or stretchable amplifier, a flexible or stretchable multiplexer, a flexible or stretchable light emitting diode, a flexible or stretchable laser, a flexible or stretchable photodiode, a flexible or stretchable integrated circuit and any combination of these. In some embodiments, for example, the flexible or stretchable electronic circuit is a CMOS integrated circuit or a logic gate circuit. In an embodiment, the flexible or stretchable electronic circuit further comprises a plurality of sensing or actuating elements spatially arranged over the flexible or stretchable substrate, wherein each sensing or actuating element is in electrical communication with at least one of the plurality of flexible semiconductor circuit elements, for example, wherein at least one of the plurality of sensing or actuating elements is in electrical communication with the tissue when the device is in conformal contact with the tissue in the biological environment. In an embodiment, for example, the actuating elements comprise circuit elements selected from the group consisting of: electrode elements, electromagnetic radiation emitting elements, heating elements, ablation elements and any combination of these. In an embodiment, for example, the flexible or stretchable electronic circuit includes one or more sensing electrode elements, chemical or biological sensor elements, pH sensors, optical sensors, temperature sensors, capacitive sensors, strain sensors, acceleration sensors, movement sensors, displacement sensors and any combination of these. In an embodiment, for example, the flexible or stretchable electronic circuit comprises one or more sensors using a capacitance type circuit. In an embodiment, for example, at least a portion of the sensing or actuating elements is encapsulated by the barrier layer and/or the flexible or stretchable substrate. In some embodiments, at least one sensing element is positioned at the surface of the barrier layer, in electrical communication with a tissue in a biological environment, optical communication with a tissue in a biological environment and/or in physical contact with a tissue in a biological environment.

[0034] In an embodiment, the flexible or stretchable electronic circuit comprises an active circuit, such as an amplifier circuit, multiplexing circuit or a logic gate. In an embodiment, for example, the multiplexing circuit of the flexible or stretchable electronic device is configured to individually address each of a plurality of sensing or actuating circuit elements spatially arranged over the flexible or stretchable substrate, such as a plurality of electrodes in an array. In an embodiment, the flexible or stretchable electronic circuit comprises a current limiting circuit, for example, a current limiting circuit that limits net leakage current from the electronic device to 10 μA or less, optionally for some applications 5 μA or less or optionally for some applications 1 μA or less.

[0035] Devices of this aspect optionally have a neutral mechanical plane wherein at least a portion of the flexible or stretchable electronic circuit, or components thereof, are positioned proximate to the neutral mechanical plane, or wherein optionally all of the components of the flexible or stretchable electronic circuit are positioned proximate to the neutral mechanical plane. In some embodiments, device components, such as flexible semiconductor circuit components, provided proximate to the neutral mechanical plane are within 100 microns of the neutral mechanical plane, optionally for some embodiments within 10 microns of the neutral mechanical plane, optionally for some embodiments within 5 microns of the neutral mechanical plane, and optionally for some embodiments within 1 micron of the neutral mechanical plane. Thicknesses of the device components, such as the flexible substrate and the barrier layer are optionally be selected in some embodiments so as to position the neutral mechanical plane of the device proximate to one or more flexible semiconductor circuit elements.

[0036] In an aspect, the invention provides a conformable device for biomedical sensing applications. In a device of this aspect, the flexible or stretchable electronic circuit is a stretchable or flexible electrode array comprising a plurality of individually addressable electrodes, multiplex circuitry and amplification circuitry. Devices of this aspect include conformable high density electrode arrays for making high-speed and high resolution electrophysiology measurements, for example in cardiac tissue, brain tissue and skin environments. In an embodiment, the stretchable or flexible electrode array comprises 2 to 500,000 electrodes, optionally for some applications 2 to 50,000 electrodes and optionally for some applications 2 to 5,000 electrodes, wherein the electrodes of the array are each optionally individually addressable electrodes.

[0037] In an embodiment, for example, the stretchable or flexible electrode array comprises 20 or more electrode unit cells, optionally 50 or more electrode unit cells, and optionally 100 or more electrode unit cells. In an embodiment, for example, adjacent electrodes of the electrode array are separated from each other by a distance less than or equal to 50 μm, optionally for some applications a distance less than or equal to 500 μm, and optionally for some applications a distance less than or equal to 2000 μm. In an embodiment, for example, the electrode unit cells of the electrode array are disposed on an area of the flexible or stretchable substrate ranging from 10 mm^2 to 10000 mm^2, optionally for some applications 10 mm^2 to 1000 mm^2, and optionally for some applications 100 mm^2 to 1000 mm^2. In some embodiments, the density of electrodes in the stretchable or flexible electrode array is selected over the range of 0.1 electrode mm^{-2} to 50 electrodes mm^{-2}, and optionally for some application selected over the range of 1 electrode mm^{-2} to 20 electrodes mm^{-2}.

[0038] In an embodiment, for example, the stretchable or flexible electrode array comprises a plurality of electrode unit cells, for example, a plurality of electrode unit cells comprising a contact pad, amplifier and multiplexer, wherein the contact pad provides an electrical interface to the tissue and is in electrical communication with the amplifier and multiplexer. In an embodiment, for example, the amplifier and multiplexer of the unit cell comprises a plurality of transistors, for example, 2 to 50 transistors, and optionally for some applications 2 to 10 transistors. In an embodiment, for example, each of the unit cells of the flexible or stretchable electrode array comprises a multilayer structure comprising one or more semiconductor layers, one or more dielectric layers and one or more metal layers provided in a multilayer stacked geometry, for example, a stacked geometry wherein the semiconductor layers, dielectric layers and metal layers are provided in series, wherein adjacent layers are in physical contact with each other or separated by intermediate layers, such as adhesive, spacer and/or boundary layers. In an embodiment, for example, the semiconductor layers of the multilayer structure are positioned proximate to the neutral mechanical plane of the flexible or stretchable electronic circuit.

[0039] In an aspect, the invention provides a device for optical applications, including sensing and providing a local source of electromagnetic radiation at the tissue site. In a device of this aspect, the flexible or stretchable electronic circuit is a stretchable or flexible array of light emitting diodes comprising a plurality of light emitting diodes in electrical communication with a plurality of stretchable or flexible electrical interconnects. Devices of this aspect include high density LED arrays, including implantable LED arrays, stretchable LED arrays and LED arrays for interfacing with tissue including epithelial tissue. Devices of this aspect include large area light emitting diode arrays, for example wherein LEDs of the array are disposed on an area of the flexible or stretchable substrate ranging from 100 mm^2 to 10,000 mm^2, and optionally for some embodiments ranging from 1000 mm^2 to 10,000 mm^2.

[0040] In an embodiment of this aspect, the stretchable or flexible array of light emitting diodes is an island-bridge structure, wherein the light emitting diodes provide islands of the island-bridge structure and the stretchable or flexible electrical interconnects provide bridge structures of the island-bridge structure. In an embodiment, the electrical interconnects and the light emitting diodes are entirely encapsulated by the barrier layer, the flexible or stretchable substrate or both the barrier layer and the flexible or stretchable substrate. In an embodiment, for example, the light emitting diodes comprise the one or more inorganic semiconductor circuit elements of the flexible or stretchable electronic circuit. In an embodiment, for example, each of the stretchable or flexible electrical interconnects comprise a metal film encapsulated in a polymer layer, for example a thin metal film (e.g. , thickness equal to or less than 500 microns) encapsulated in PDMS. In an embodiment, for example, the metal film is positioned proximate to the neutral mechanical plane of the stretchable interconnect. In an embodiment, for example, the device further comprises additional bridge structures physically connecting light emitting diodes of the array, wherein the additional bridge structures comprise a polymer layer. In an embodiment, for example, at least a portion of the stretchable or flexible electrical interconnects have a serpentine, bent or buckled geometry. In an embodiment, electrical interconnects or electrodes of the invention comprise a conductive metal such as copper, silver, gold, aluminum and the like, and alloys thereof.

[0041] In a device of this aspect, the stretchable or flexible array of light emitting diodes of this aspect comprises a multilayer structure comprising a plurality of individually encapsulated LED array layers provided in a multilayer stacked geometry. In an embodiment, for example, the stretchable or flexible array of light emitting diodes comprises 2 to 1000 individually encapsulated LED array layers provided in a multilayer stacked geometry, an optionally 10 to 1000 individually encapsulated LED array layers provided in a multilayer stacked geometry. The multilayer geometry of this aspect of the invention is beneficial for providing high LED densities and fill factors which maintaining a useful degree of conformability and stretchability. In an embodiment, for example, the individually encapsulated LED array layers are combined to provide a density equal to or greater than1 LED mm^{-2}, and optionally equal to or greater than 100 LEDs mm^{-2}. In an embodiment, for example, the individually encapsulated LED array layers provide a density selected from the range of 1 LEDs mm^{-2} to 1000 LEDs mm^{-2}. In an embodiment, for example, the individually encapsulated LED array layers are laterally offset so as to provide a fill factor greater than or equal to 1×10^{-6}, or optionally provide a fill factor selected over the range of 1×10^{-6} to 1×10^{-3}. As used herein, the expression "laterally offset" refers to a multilayer geometry wherein at least a portion of the LEDs in different layers of the device are positioned such that they do not reside on top of each other. As used in this context, the term "fill factor" refers to the fraction of the area of the footprint of the device that is occupied by the LED structures.

[0042] In some embodiments, barrier layers and flexible or stretchable substrates limit a net leakage current from the electronic device to an amount which does not adversely affect a tissue in a biological environment. Barrier layers of the invention include moisture barriers. In one embodiment, the barrier layer is configured to limit a net leakage current from the electronic device to the biological environment to less than 10 μA, optionally for some applications less than 5 μA and optionally for some applications less than 1 μA, and optionally for some applications less than 0.1 μA. In some embodiments, the barrier layer prevents leakage current from being concentrated to small areas so to prevent tissue damage caused by current leakage from the device. In an embodiment, for example, the barrier layer is configured to limit leakage current from the device to the biological environment to 0.1 $\mu A/cm^2$; less, and for some applications 0.01 $\mu A/cm^2$ or less, and for some applications 0.001 $\mu A/cm^2$ or less. In some embodiments, barrier layers of the invention have an electrical resistivity of 10^{14} Ω·m or greater, for example an electrical resistivity selected over the range of 10^{15} to 10^{17} Ω·m. In some embodiments, the barrier layer prevents the rate at which charge is leaked from the electronic device; for example, one barrier layer embodiment limits electrical discharge from a device to 10 μC or less over a period of 1 second. In some embodiments, the barrier layer limits leakage current or average leakage current from the device to 10 μA or less or 5 μA or less over a long period of time, such as 3 hours or more or 5 hours or more.

[0043] In some embodiments, a barrier layer is configured to prevent moisture from reaching the flexible or stretchable electronic circuit and limit leakage current therefrom, for example to less than 10 μA optionally for some applications less than 5 μA and optionally for some applications less than 1 μA. Useful moisture barriers, for example, include those configured for protecting tissue in contact with electronic device embodiments from damage due to leakage current. Further, useful moisture barriers include those configured for protecting electronic devices from damage due to leakage current.

[0044] In an embodiment, the barrier layer is patterned so as to selectively modulate physical, thermal, optical, electromagnetic and/or electrical contact and/or communication between flexible semiconductor circuit elements and the tissue in the biological environment. Optionally, a barrier layer comprises multiple layers. For example, a barrier layer comprises at least one organic polymer layer and at least one inorganic dielectric layer. In specific embodiments, the net thickness of a barrier layer comprising multiple layers is selected over the range of 1 μm to 25 μm or over the range of 1 μm to 100 μm.

[0045] In some embodiments, the barrier layer includes one or more via structures. As used herein, a via structure refers to a recessed region which is at least partially filled with a conducting material. Via structures are useful in a barrier layer for providing electrical communication between electronic circuit components encapsulated by a barrier layer (e.g., semiconductor device such as a transistor, amplifier or multiplexer) and electronic circuit components not encapsulated by a barrier layer and in contact with the tissue or fluid in contact with the tissue (e.g., an electrode). In a specific embodiment, the barrier layer comprises multiple layers and includes multiple offset via structures; for example, one via structure in a lower barrier layer and one via structure in an upper barrier layer in electrical communication with the first via structure. In embodiments, barrier layers including multiple layers with offset via structures are useful as moisture barriers.

[0046] Depending on the application, the barrier layer can have a variable thickness; that is, for certain applications, the barrier layer has a thickness that is spatially variable (i.e., relatively thicker in some regions and relatively thinner in other regions). In embodiments where a sensing element does not need to be exposed and/or in direct contact with or electrical communication with a tissue in a biological environment, barrier layers of spatially varying thickness are useful; for example, when a sensing element is positioned close to the surface (e.g., within 5 μm or less) of the barrier layer but still encapsulated by the barrier layer.

[0047] In embodiments, an electronic device of this aspect further comprises a plurality of actuating elements spatially arranged over the flexible substrate. Optionally, each actuating element is positioned in electrical communication with at least one flexible semiconductor circuit element. Optionally, one or more via structures are configured to and/or positioned in the barrier layer to provide electrical communication between an actuating element and a flexible semiconductor circuit element. In some embodiments, one or more actuating elements are encapsulated by the barrier layer. Useful actuating elements include, but are not limited to, electrode elements, electromagnetic radiation emitting elements, light emitting diodes, lasers, and heating elements. In some embodiments, at least one actuating element is positioned at the surface of the barrier layer, in electrical communication with a tissue in a biological environment, in optical communication with a tissue in a biological environment and/or in physical contact with a tissue in a biological environment. In some embodiments an actuating element is a sensing element.

[0048] "Spatially arranged over the flexible substrate" as used herein, refers to a distribution of elements over the surface area of a flexible 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 or 3D 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.

[0049] Modulation of physical, optical, thermal and/or electrical contact and/or communication is achieved in some embodiments by selective variation of the physical dimensions (e.g., thickness, etc.), shape, and/or composition of the

barrier layer. In some embodiments, for example, the physical dimensions and/or shape of the barrier layer provides a preselected pattern of openings in the barrier layer that expose preselected circuit elements to the tissue and/or biological environment, particularly when the device is provided in conformal contact with the tissue. In some embodiments, for example, the physical dimensions, shape or composition of the barrier layer provide a preselected pattern of electrically conductive and/or optically or electromagnetically transparent regions of the barrier, particularly when the device is provided in conformal contact with the tissue. Barrier layers include, but are not limited to, barrier layers having a plurality of contact regions that expose a components of the electronic circuit (e.g., electrodes, sensors, etc.) to the tissue and/or biological environment. Barrier layers of some embodiments of this aspect provide patterned physical contact between preselected circuit elements, such as electrode and/or sensor components, and the tissue and/or biological environment. Barrier layers include, but are not limited to, barrier layers having a plurality of contact regions that electronically couple a preselected subset of flexible semiconductor circuit elements and the tissue and/or biological environment. Barrier layers of some embodiments of this aspect provide patterned electrical contact between preselected circuit elements, such as electrode and/or sensor components, and the tissue and/or biological environment. Barrier layers include, but are not limited to, barrier layers having a plurality of contact regions that optically couple a preselected subset of flexible semiconductor circuit elements and the tissue and/or biological environment. Barrier layers of some embodiments of this aspect provide patterned optical communication (e.g., a pattern of optically transmissive regions and optically opaque regions) between preselected circuit elements, such as optical source (e.g., laser, LED, fiber optic, etc.) components and photodetector (e.g., photodiode, diode array. etc.) components, and the tissue and/or biological environment. In an embodiment, for example, at least a portion of the barrier layer is opaque or substantially blocks electromagnetic radiation having a preselected range of wavelengths.

[0050] In an embodiment, a barrier layer limits heat transfer from the electronic device to the tissue in the biological environment to an amount that does not adversely affect the tissue. In an embodiment, the barrier layer, or components thereof, have a thermal conductivity of 0.3 W/m·K or less, 0.1 W/m·K or less, 0.01 W/m·K or less, 0.001 W/m·K or less or selected over the range of 0.001 W/m·K to 0.3 W/m·K and/or portions having a thermal resistivity of 3 m·K/W or more, 10 m·K/W or more, 100 m·K/W or more, 1000 m·K/W or more selected over the range of 1 to 1000 m·K/W. In an embodiment, a barrier layer comprises a thermal insulator and/or a heat spreader. Certain device embodiments further include active cooling components; for example active cooling components positioned in thermal communication with the barrier layer and/or in thermal communication with one or more flexible semiconductor circuit elements. In some embodiments, the barrier layer comprises active cooling components, such as thermoelectric cooling devices.

[0051] In an embodiment, a barrier layer includes portions which are at least partially transparent to electromagnetic radiation. In an embodiment, a device comprises a barrier layer patterned to provide one or more transparent regions and one or more non-transparent regions, wherein the transparent regions transmit electromagnetic radiation have wavelengths in the ultraviolet, visible or near-infrared regions of the electromagnetic spectrum having a preselected wavelength distribution, wherein the non-transparent regions substantially prevent transmission of electromagnetic radiation in the in the ultraviolet, visible or near-infrared regions of the electromagnetic spectrum. In an embodiment, a barrier layer includes portions which are opaque or block electromagnetic radiation. In another embodiment, a barrier layer includes portions which are at least partially transparent to electromagnetic radiation and portions which are opaque or block electromagnetic radiation. For example, portions of the barrier layer can be partially or fully transparent to electromagnetic radiation of a selected wavelength or over a selected region of the electromagnetic spectrum. For example, selected over the range of 100 nm to 2000 nm, 1 μm to 2000 μm, 400 nm to 2000 nm or in the UV, visible, IR, near IR, or microwave portions of the spectrum. In embodiments, a barrier layer is selectively patterned to provide one or more transparent regions and one or more opaque regions. In embodiments, a barrier layer is selectively patterned to provide one or more optical components or structures, such as lenses, microlenses, lens arrays, optical filters, reflectors, reflective coatings, and antireflective coatings.

[0052] Transparent or partially transparent barrier layers are useful, for example, when an optical sensor, such as a photodiode, is encapsulated within the barrier layer and/or it is desired to detect electromagnetic radiation. A transparent or partially transparent can also be useful, for example, when a source of electromagnetic radiation, such as a light emitting diode and/or a laser, is encapsulated within the barrier layer and/or it is desired to permit electromagnetic radiation to pass through the barrier layer.

[0053] In an embodiment, a barrier layer includes portions which serve as an electrical, electrostatic and/or magnetic barrier. In specific embodiments, a barrier layer blocks electric fields and/or magnetic fields, for example, blocking fields external to the electronic circuit from interacting with the electronic circuit or blocking fields generated by the electronic circuit from interacting with the tissue and/or biological environment. In various embodiments of this aspect, the barrier layer comprises a Faraday cage, an electrical insulator and/or magnetic shielding. In a specific embodiment, a barrier layer comprises material having an electrical resistivity of $10^{14}\ \Omega\cdot m$ or larger or selected over the range of 10^{15} to $10^{17}\ \Omega\cdot m$.

[0054] In an embodiment, a barrier layer is patterned so as to provide one or more selectively permeable regions that are selectively permeable to one or more target molecules. In some embodiments, the barrier layer provides a plurality of spatially patterned regions which are selectively permeable to one or more target molecules comprising biomolecules,

analytes, liquids or gases. In another aspect, a barrier layer comprises a plurality of spatially patterned impermeable regions which are selectively impermeable to one or more target molecules, such as one or more biomolecules, analytes, liquids or gases. For example, portions of the barrier layer can be selectively permeable to one or more target chemicals, molecules or biomolecules while being impermeable to other chemicals, molecules or biomolecules, such as solvents or aqueous solutions. Optionally, the barrier layer is impermeable to water and salts dissolved therein and is selectively permeable to one or more proteins, organic compounds or biomolecules (e.g., nucleic acids). A selectively permeable barrier layer is useful, for example, when a chemical or biochemical sensor is encapsulated within the barrier layer and it is desired to detect and/or collect a target chemical, molecule or biomolecule. Target molecules useful in the embodiments of the present devices and methods include, but are not limited to: polypeptides, polynucleotides, carbohydrates, proteins, steroids, glycopeptides, lipids, metabolites, drugs or drug precursors.

[0055] In an embodiment, a device of the present invention further comprises a controller in communication with the flexible or stretchable electronic circuit. Controllers of this aspect of the invention are useful for providing device control, signal processing and measurement analysis functionality. In an embodiment, the controller receives input signals from the flexible or stretchable electronic circuit that serves the basis of closed-loop control of the electronic device, for example, providing real-time adjustment of sensing and actuation of the tissue. In an embodiment, for example, the controller provides closed-loop control of sensing and/or actuation based on signals received from the electronic circuit corresponding to measurements of tissue properties.

[0056] For example, the invention includes a controller configured to provide an output signal to the flexible or stretchable electronic circuit, receive an input signal from the flexible or stretchable electronic circuit, or to provide an output signal to the flexible or stretchable electronic circuit and receive an input signal to the flexible or stretchable electronic circuit. As used in this context, the expression "in communication" refers to a configuration of devices or device components such that a signal can be exchanged, and includes one way communication and two way communication between the controller and the flexible or stretchable electronic circuit. In an embodiment, for example, the controller is in electrical communication or wireless communication with the flexible or stretchable electronic circuit. In an embodiment, for example, the output signal provides an input to the flexible or stretchable electronic circuit so as to control actuation or sensing of the tissue in the biological environment. In an embodiment, for example, the output signal provides a sensing or actuation parameter from the controller to the flexible or stretchable electronic circuit, for example, a parameter relating to the timing of a measurement or actuation, the magnitude of a sensing or actuation variable (e.g., voltage, current, power, intensity, temperature, etc.). In an embodiment, for example, the input signal provides a measurement parameter from the flexible or stretchable electronic circuit to the controller, for example a measurement parameter correspondence to a time, voltage, current, intensity, power, or temperature. In an embodiment, for example, the input signal provides a measurement parameter corresponding to a plurality of voltage measurements, current measurements, electromagnetic radiation intensity or power measurements, temperature measurements, pressure measurements, tissue acceleration measurements, tissue movement measurements, target molecule concentration measurements, time measurements, position measurements, acoustic measurements or any combination of these. In an embodiment, for example, the controller receives and analyzes the input signal from the flexible or stretchable electronic circuit and generates an output signal that controls or provides a sensing or actuation parameter(s) to the flexible or stretchable electronic circuit, for example via a closed-loop control algorithm that adjusts the sensing or actuation parameter(s) based on one or more tissue measurements. A wide range of controllers are useful in the present devices and methods, including a microprocessor, microcontroller, digital signal processor, computer or fixed logic device. Controllers of this aspect include implantable controllers, controllers that are administered to the tissue site along with the flexible or stretchable electronic circuit and controllers that are ex vivo.

[0057] In an aspect, a device of the invention further comprises a transfer substrate supporting the flexible or stretchable substrate, the flexible or stretchable electronic circuit or both. Transfer substrates of some devices of the invention function to facilitate administration of the device to a tissue site, for example, by providing net mechanical properties and/or physical dimensions of the device to allow effective handling, transfer and/or deployment to the tissue interface in a manner that does not damage or modify the properties of the other components of the device (e.g., substrate, barrier layer or electronic circuit components). Transfer layers of some embodiments also function as sacrificial layers that are at least partially removed upon administration to the tissue, for example, via dissolution or delamination (e.g., peel back) processes. In an embodiment, the invention provides a method of administrating, or otherwise using, a device of the invention having a transfer layer, the method further comprising the step of at least partially removing the transfer substrate, for example, via dissolving the transfer substrate or separating the transfer substrate from the flexible or stretchable substrate (e.g., via a delamination process). In a method of the invention, for example, partial or complete removal of the transfer substrate results in the device establishing conformal contact with the tissue in the biological environment.

[0058] In some embodiments, the transfer substrate is in physical contact with, and/or optionally bonded to, the flexible or stretchable substrate. In an embodiment, the transfer substrate is bound to the flexible or stretchable substrate via one or more adhesive layers. In an embodiment, the transfer substrate is a removable substrate, wherein the transfer

substrate is partially or completely removed after the device establishes conformal contact with the tissue in the biological environment. In an embodiment, for example, the removable substrate is a dissolvable substrate, wherein the removable substrate is partially or completely dissolved after the device is provided in contact with the tissue in the biological environment, for example via washing or rinsing with one or more solvents (e.g., water). In an embodiment, for example, the removable substrate is configured so as to be able to be separated from the flexible or stretchable substrate after administration, for example, via a delamination process.

[0059] In some embodiments, the transfer substrate comprises a bioinert or biocompatible material, for example, to minimize or avoid inflammation or unwanted immune responses upon administration of the device to a tissue in a biological environment. In an embodiment, for example, the transfer substrate is a polymer layer such as a polyvinyl acetate layer. In an embodiment, for example, the transfer substrate has a thickness selected from the range of 100 μm to 100 mm. in an embodiment, for example, the transfer substrate has a composition and physical dimensions that allowed the device to be handled and/or administered by hand, for example, during a surgical procedure.

[0060] In an aspect, the invention provides a device for collecting electrophysiology data from a tissue in a biological environment, the device comprising: (1) a flexible or stretchable substrate; (2) a flexible or stretchable electrode array comprising one or more inorganic semiconductor circuit elements and a plurality of electrode elements positioned in electrical communication with at least a portion of the semiconductor circuit elements, wherein the one or more inorganic semiconductor circuit elements include multiplex circuitry and amplification circuitry, and wherein the electrode array is supported by the flexible or stretchable substrate; (3) a barrier layer encapsulating at least a portion of the flexible or stretchable electrode array to limit a net leakage current from the flexible or stretchable electrode array to an amount that does not adversely affect the tissue; wherein the flexible or stretchable substrate, the flexible or stretchable electrode array and the barrier layer provide a net bending stiffness of the device low enough that the device establishes conformal contact with the tissue in the biological environment, thereby, positioning at least one of the plurality of electrode elements in electrical communication with the tissue in the biological environment. In an embodiment, for example, the electrode array comprises a plurality of electrode unit cells, wherein each unit cell comprises a contact pad, amplifier and multiplexer. In some embodiments, the contact pad provides an electrical interface to the tissue and is in electrical contact with the amplifier and multiplexer. In an embodiment, for example, each of the unit cells of the flexible or stretchable electrode array comprises a multilayer structure comprising one or more semiconductor layers, one or more dielectric layers and one or more metal layers provided in a multilayer stacked geometry. In an embodiment, for example, the semiconductor layers of the multilayer structure are positioned proximate to the neutral mechanical plane of the flexible or stretchable electronic circuit.

[0061] In an aspect, the invention provides a method of collecting electrophysiology data from a tissue in a biological environment, the method comprising the steps of: (1) providing a conformable electronic device comprising: (i) a flexible or stretchable substrate; (ii) a flexible or stretchable electrode array comprising one or more inorganic semiconductor circuit elements and a plurality of electrode elements positioned in electrical communication with at least a portion of the semiconductor circuit elements, wherein the one or more inorganic semiconductor circuit elements include multiplex circuitry and amplification circuitry, and wherein the electrode array is supported by the flexible or stretchable substrate; (iii) a barrier layer encapsulating at least a portion of the flexible or stretchable electrode array to limit a net leakage current from the flexible or stretchable electrode array to an amount that does not adversely affect the tissue; wherein the flexible or stretchable substrate, the flexible or stretchable electrode array and the barrier layer provide a net bending stiffness of the device low enough that the device establishes conformal contact with the tissue in the biological environment; (2) contacting the tissue with the conformable electronic device, thereby establishing the conformal contact such that at least one of the plurality of electrode elements is positioned in electrical communication with the tissue in the biological environment; and (3) measuring one or more voltages associated with the tissue in the biological environment on at least a portion of the plurality of electrode elements. In an embodiment, for example, the voltages associated with the tissue have a spatial arrangement corresponding to a spatial arrangement of the electrode elements. Methods of the invention may include the steps of administering the conformable device to a subject (e.g., a patient), and/or removal of the conformable device from the subject (e.g., a patient). In an embodiment, the step of contacting the conformable device with the tissue of the subject is carried out by physically contacting one or more surfaces of the tissue with a contact surface of the conformable device.

[0062] In an aspect, the invention provides a device for interfacing with a tissue in a biological environment, the device comprising: (1) a flexible or stretchable substrate; (2) a stretchable or flexible array of light emitting diodes comprising a plurality of light emitting diodes in electrical communication with a plurality of stretchable or flexible electrical interconnects, the stretchable or flexible array of light emitting diodes supported by the flexible or stretchable substrate; and (3) a barrier layer encapsulating at least a portion of the stretchable or flexible array of light emitting diodes to limit a net leakage current from the stretchable or flexible array of light emitting diodes to the tissue to an amount that does not adversely affect the tissue; wherein the flexible or stretchable substrate, stretchable or flexible array of light emitting diodes and the barrier layer provide a net bending stiffness of the device low enough that the device establishes conformal contact with the tissue in the biological environment. In an embodiment, the device of this aspect is an implantable or

skin mounted array of light emitting diodes. In an embodiment, for example, the stretchable or flexible array of light emitting diodes comprises a multilayer structure comprising a plurality of individually encapsulated LED array layers provided in a multilayer stacked geometry, for example, wherein 2 to 50 individually encapsulated LED array layers provided in a multilayer stacked geometry.

[0063] In an embodiment, the invention provides a method of interfacing an array of light emitting diodes with a tissue of a subject, the method comprising the steps of: (1) providing a conformable device for interfacing with a tissue in a biological environment, the device comprising: (i) a flexible or stretchable substrate; (ii) a stretchable or flexible array of light emitting diodes comprising a plurality of light emitting diodes in electrical communication with a plurality of stretchable or flexible electrical interconnects, the stretchable or flexible array of light emitting diodes supported by the flexible or stretchable substrate; and (iii) a barrier layer encapsulating at least a portion of the stretchable or flexible array of light emitting diodes to limit a net leakage current from the stretchable or flexible array of light emitting diodes to the tissue to an amount that does not adversely affect the tissue, wherein the flexible or stretchable substrate, stretchable or flexible array of light emitting diodes and the barrier layer provide a net bending stiffness of the device low enough that the device establishes conformal contact with the tissue in the biological environment; and (2) contacting the conformable device with the tissue of the subject, thereby establishing the conformal contact with the tissue in the biological environment. Methods of the invention may include the steps of administering the conformable device to a subject (e.g., a patient), and/or removal of the conformable device from the subject (e.g., a patient). In an embodiment, the step of contacting the conformable device with the tissue of the subject is carried out by physically contacting one or more surfaces of the tissue with a contact surface of the conformable device.

[0064] The invention provides a range of bioanalytical and therapeutic methods including diagnostic and therapeutic methods. As will be appreciated by one of skill in the art, methods of the invention may utilize any of the device configurations disclosed herein. Devices of this aspect are useful, for example, for making electrophysiology measurements of a tissue in a biological environment. In embodiments, the biological environment is an *in-vivo* biological environment. In certain embodiments, the biological environment comprises an ionic solution, such as saline. Devices of this aspect are useful for making measurements and/or actuating tissues including, but not limited to, heart tissue, brain tissue, muscle tissue, skin, nervous system tissue, vascular tissue, epithelial tissue, retina tissue, ear drum, tumor tissue, digestive system structures and any combination of these.

[0065] In an embodiment, the invention provides a method of sensing or actuating a tissue in a biological environment; the method comprising: (1) providing a subject having the tissue in the biological environment; (2) providing a conformable device, the device comprising: (i) a flexible or stretchable substrate; (ii) a flexible or stretchable electronic circuit supported by the flexible or stretchable substrate, wherein the flexible or stretchable electronic circuit comprises an plurality of sensors, actuators or both sensors and actuators provided in an array, wherein said sensors or actuators comprise one or more inorganic semiconductor circuit elements; and (iii) a barrier layer encapsulating at least a portion of the flexible or stretchable electronic circuit; wherein the barrier layer and the flexible or stretchable substrate limit a net leakage current from the flexible or stretchable electronic circuit to an amount which does not adversely affect the tissue or the barrier layer is patterned so as to selectively modulate physical contact, thermal contact, optical communication or electrical communication between the flexible or stretchable electronic circuit and the tissue in the biological environment; wherein the flexible or stretchable substrate, the flexible or stretchable electronic circuit and the barrier layer provide a net bending stiffness of the device low enough that the conformable device establishes conformal contact with the tissue in the biological environment; (3) contacting the tissue with the conformable device, thereby establishing the conformal contact such that at least a portion of the plurality of sensors, actuators or both sensors and actuators of the array is provided in physical contact, electrical communication, optical communication, fluid communication or thermal communication with the tissue in the biological environment; and (4) sensing or actuating the tissue in contact with the conformable device. In an embodiment, for example, the biological environment is an *in-vivo* biological environment. In an embodiment, for example, the tissue in the biological environment comprises heart tissue, brain tissue, muscle tissue, skin, nervous system tissue, vascular tissue, epithelial tissue, retina tissue, ear drum, tumor tissue, a digestive system structure or any combination of these. In an embodiment, for example, the step of contacting the tissue with the conformable device establishes conformal contact between one or more contact surfaces of the conformable device and an area of the tissue selected from the range of from 10 mm^2 to 10,000 mm^2. In an embodiment, for example, the method further comprising the step of moving the conformable device along a surface of the tissue in the biological environment.

[0066] In an embodiment, the step of sensing or actuating the tissue in contact with the conformable device comprises: generating one or more voltages at a plurality of different regions on a surface of the tissue; sensing one or more voltages at a plurality of different regions on a surface of the tissue; or sensing one or more voltages at a plurality of different regions on a surface of the tissue and generating one or more voltages at a plurality of different regions on the surface of the tissue. In a method, for example for sensing applications, the voltages are selected from the range of -100 mV to 100 mV, optionally for some applications from the range of -50 mV to 50 mV, and optionally for some applications from the range of -20 mV to 20 mV. In a method, for example for stimulation and actuation applications, the voltages are selected from the range of -100 V to 100 V, optionally for some applications from the range of -5 V to 5 V, and optionally

for some applications from the range of -1 V to 1 V.

[0067] In an embodiment, the step of sensing or actuating the tissue in contact with the conformable device comprises: generating one or more currents at a plurality of different regions on a surface of the tissue; sensing one or more currents at a plurality of different regions on a surface of the tissue; or sensing one or more currents at a plurality of different regions on a surface of the tissue and generating one or more currents at a plurality of different regions on the surface of the tissue.

[0068] In an embodiment, the step of sensing or actuating the tissue in contact with the conformable device comprises: sensing electromagnetic radiation at a surface of the tissue; generating electromagnetic radiation at a surface of the tissue; or sensing electromagnetic radiation at a surface of the tissue and generating electromagnetic radiation at the surface of the tissue. In a method, for example, the electromagnetic radiation has a distribution of wavelengths in the ultraviolet, visible, near infrared, microwave and/or radiowave regions of the electromagnetic spectrum. In a method, for example, the step of sensing or actuating the tissue in contact with the conformable device comprises ablating at least a portion of the tissue, such as a portion of the tissue comprising a lesion or tumor.

[0069] In an embodiment, the step of sensing or actuating the tissue in contact with the conformable device comprises: transporting a target molecule from a surface of the tissue to the flexible or stretchable electronic circuit; transporting a target molecule from the flexible or stretchable electronic circuit to a surface of the tissue; or transporting a target molecule from a surface of the tissue to the flexible or stretchable electronic circuit and transporting a target molecule from the flexible or stretchable electronic circuit to a surface of the tissue. In a methods, for example, the target molecule is selected from the group consisting of polypeptides, polynucleotides, carbohydrates, proteins, steroids, glycopeptides, lipids, metabolites and drugs, including photoactive drugs such as Type 1 or Type 2 phototherapy agents.

[0070] In an embodiment, the step of sensing or actuating the tissue in contact with the conformable device comprises: sensing or changing a temperature of a region of the tissue; sensing or changing a pressure of a region of the tissue; sensing or changing a position of the tissue; sensing or generating an electrical field at a region of the tissue; or sensing or generating a magnetic field at a region of the tissue.

[0071] In an embodiment, a method of this aspect further comprises administering to the subject a therapeutic agent, wherein the therapeutic agent localizes at the tissue, wherein the step of sensing or actuating the tissue in contact with the conformable device comprises activating the therapeutic agent at the tissue or specific region thereof (e.g., a tumor or lesion). Methods and devices of the invention are capable of a range of activation techniques, including optical activation, electronic activation, acoustic activation or thermal activation.

[0072] In an embodiment, the step of sensing or actuating the tissue in contact with the conformable device comprises measuring an electrophysiological signal from the tissue, measuring an intensity of electromagnetic radiation from the tissue, measuring a change in the concentration of a target molecule at the target tissue, measuring an acceleration of the tissue, measuring a movement of the tissue, measuring a position of the tissue or region thereof or measuring a temperature of the tissue. In a method, for example, the tissue is heart tissue, and wherein the step of sensing or actuating the tissue in contact with the conformable device comprises simultaneously applying multiple pacing stimuli to the heart tissue, such as applying a plurality of voltages to different areas of the tissue at the same or different times. In an embodiment of this aspect, the tissue is epicardium tissue.

[0073] In an embodiment, the step of contacting the tissue with the conformable device is carried out via a surgical technique. In a method, for example, the step of contacting the tissue with the conformable device is carried out using a catheter. In a method, for example, the conformable device is collapsed, rolled or wrapped on itself and inserted into the catheter, and wherein the catheter is subsequently positioned at the tissue and the conformable device is released from the catheter, thereby delivering the conformable device to a surface of the tissue. In a method, for example, the conformable device changes conformation upon release from the catheter so as to establish conformal contact with one or more surfaces of the tissue, for example by unrolling or unwrapping.

[0074] In an embodiment, a method of the invention comprises a diagnostic or therapeutic procedure, for example a surgical diagnostic or therapeutic procedure. In a method, for example, the diagnostic or therapeutic procedure is selected from the group consisting of anatomic mapping, physiologic mapping and resynchronization therapy. In a method, for example, the diagnostic or therapeutic procedure comprises measuring cardiac contractility, myocardial wall displacement, myocardial wall stress, myocardial movement or ischemic changes. In a method, for example, the diagnostic or therapeutic procedure comprises cardiac mapping or cardiac resynchronization therapy. In a method, for example, the diagnostic or therapeutic procedure comprises cardiac ablation therapy.

[0075] In an embodiment, for example, the flexible or stretchable electronic circuit comprises a plurality of sensors for determination and/or discrimination of tissue properties and one or more actuators that is an ablation source for ablating one or more regions of the tissue. In a method, for example, the sensors for determination and/or discrimination of tissue properties distinguish one or more components of the tissue selected from the group consisting of a lesion, a tumor, epicardial muscle, myocardial tissue, epicardial fat, a coronary artery, and a nerve. In a method, for example, the ablation source selectively ablates the lesion or tumor component of the tissue.

[0076] Without wishing to be bound by any particular theory, there can be discussion herein of beliefs or understandings

of underlying principles relating to the invention. 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

[0077]

Figures 1a, 1b, 1c, 1d and 1e provide schematic illustrations and images corresponding to steps for fabricating a device.

Figures 2a and 2b provide designs of multiplexing circuits for conformable devices; Figures 2c, 2d, 2e and 2f provide data showing electrical properties of conformable devices; Figure 2g shows an image of a conformable device submerged in saline solution and Figure 2h shows a sine wave response before and after saline immersion.

Figures 3a, 3b and 3c show photographs of a conformable device in vivo. Figure 3c also provides a spatial map of electrophysiology data measured by a conformable device showing individual layers of a multilayer device geometry.

Figures 4a, 4b, 4c, 4d, 4e and 4f provide representative electrophysiology data recorded by a conformable device in vivo.

Figures 5a, 5b, 5c and 5d provide schematic illustration corresponding to steps for fabricating conformable devices.

Figure 6 provides a magnified photograph showing a conformable device in a flexed configuration.

Figure 7 shows the physical layout of a single unit cell of a conformable device embodiment.

Figure 8 shows processing steps for forming the unit cell of Figure 7.

Figure 9 shows an optical microscope image of a single unit cell of a conformable device embodiment.

Figure 10a shows a flow diagram for wiring a conformable device to an external circuit. Figures 10b and 10c show photographs of a flexible device and external wiring components.

Figures 11a and 11b show images of the acquisition system.

Figure 12 provides data showing a measured signal to noise ratio dependence on multiplexing frequency.

Figures 13a and b respectively show a schematic diagram of wrapping a conformable device on a curved surface and a cross sectional view of a conformable device embodiment.

Figures 14a and 14b show sine wave measurements on conformable devices before and after immersion in a saline solution at frequencies of 4 and 40 Hz, respectively.

Figures 15a and 15b show images of an animal experiment where a conformable device is place on the surface of cardiac tissue.

Figure 16 shows a color map illustrating the average amplitude of electrophysiology data measured over a cardiac activation cycle.

Figures 17a and 17b show isochronal activation maps without and with external pacing, respectively.

Figure 18 shows representative voltage data for cardiac electrophysiology measurements at four points in time during a cardiac activation cycle.

Figure 19 shows the design of an adapter circuit board embodiment for connecting a conformable device to external circuitry through a 40 pin ribbon cable.

Figure 20 shows the design of an interface circuit board embodiment.

Figure 21 shows an image obtained from an animal experiment.

Figure 22 shows a frame from an electrophysiology data map movie for an unpaced heart.

Figure 23 shows a frame from an electrophysiology data map movie for a paced heart.

Figure 24 shows a frame from an electrophysiology data map movie for a paced heart.

Figure 25a shows a cross sectional image of a single layer barrier layer embodiment. Figure 25b shows a cross sectional image of a dual layer barrier layer embodiment.

Figure 26A provides a schematic illustration of a cross sectional view of a conformal electronic device embodiment. Figure 26B provides a schematic illustration of a cross sectional view of a conformal electronic device having a barrier layer comprising a multilayer structure.

Figure 27. Device layouts of μ-ILED arrays and their responses to uniaxial and balloon-shape biaxial stretching. Figure 27a, Optical image of a 6×6 array of μ-ILEDs (100 μm × 100 μm, and 2.5 μm thick, in an interconnected array with a pitch of ~830 μm) with non-coplanar serpentine bridges on a thin (~400 μm) PDMS substrate (left frame). Schematic illustration (right) and corresponding photograph (inset) of a representative device, with encapsulation. Figure 27b, Optical images of a stretchable 6x6 array of μ-ILEDs, showing uniform emission characteristics under different uniaxial applied strains (top left: 0%, bottom left: 48% along horizontal direction, top right: 0%, bottom right: 46% along diagonal direction). Figure 27c, Current-voltage (I-V) characteristics of this array measured in the strained configurations shown in b (left) and voltage at 20 μA current for different cycles of stretching to 75% along the horizontal direction (right). Figure 27d, Tilted (left) view optical images of a stretchable array (6×6) of μ-ILEDs on a thin (~500 μm) PDMS membrane in a flat configuration (top) and in a hemispherical, balloon state (bottom) induced by pneumatic pressure. Figure 27e, The magnified view of Figure 27d from the top. The yellow dashed boxes highlight the dimensional changes associated with the biaxial strain. Figure 27f, I-V characteristics of the array in its flat and inflated state. Figure 27g, Distribution of meridional and circumferential strains determined by 3D-FEM.

Figure 28. Responses of μ-ILED arrays to twisting and stretching on sharp tips. Figure 28a, Optical images of an array of μ-ILEDs (3×8) on a band of PDMS twisted to different angles (0° (flat), 360°, and 720° from top to bottom), collected with (left) and without (right) external illumination. Figure 28b, SEM image of the array when twisted to 360°. The serpentine interconnects move out of the plane (red box) to accommodate the induced strains. Figure 28c, I-V characteristics of the array twisted by various amounts (0 (flat), 360 and 720°). Figure 28d, Distributions of axial (left), width (center) and shear (right) strain determined by 3D-FEM for twisting to 720°. Figure 28e, Optical images of an array of μ-ILEDs (6×6), tightly stretched on the sharp tip of a pencil, collected with (left) and without (right) external illumination. The white arrows indicate the direction of stretching. The inset image was obtained without external illumination. Figure 28f, I-V characteristics of the array in Figure 28e, before (initial), during (deformed) and after (released) deformation. The inset provides a graph of the voltage needed to generate a current of 20 μA, measured after different numbers of cycles of deformation.

Figure 29. Multilayer laminated configurations of arrays of μ-ILEDs for high effective area coverage and integration on various unusual substrates. Figure 29a, Schematic, exploded view illustration for a stacked device formed by multilayer lamination. Figure 29b, Optical images of a four layer stack of 4×4 arrays with layer-to-layer offsets designed to minimize overlap of interconnect lines with positions of the μ-ILEDs. The images show emission with different numbers of layers in operation (1st layer on, 1 st and 2nd layers on, 1 st, 2nd and 3rd layers on, and 1 st, 2nd, 3rd and 4th layers on). Figure 29c, Optical images of a two layer stack of 8×8 arrays, with different layers in operation. The inset shows the device in a bent state (bending radius ~2 mm) with both layers on. Figure 29d, Optical image of an array of μ-ILEDs (8×8) on a piece of paper, in a folded state (bending radius -400 μm) during operation. The inset shows the device in its flat state. Figure 29e, Image of a 6x6 array on a sheet of aluminum foil under crumpled state. The inset shows the device in its flat state. Figure 29f, Images of a thin (~8 μm), narrow (820 μm) strip of μ-ILEDs (1×8) with serpentine interconnects on a rigid plastic tube (diameter ~2.0 mm, left). Inset shows the magnified view of a single pixel. Figure 29g, A thin strip LED device consisting of an isolated μ-ILED with straight interconnects wrapped around a glass tube (diameter ~5.0 mm, right).

Figure 30a, Schematic exploded view illustration of an array of μ-ILEDs (5×5) on a thin PET film (50 μm thick) coated with an adhesive. Layers of PDMS on the top and bottom provide a soft, elastomeric encapsulation that

offers biocompatibility and an excellent barrier to biofluids and surrounding tissue. Figure 30b, Image of an animal model with this array implanted under the skin, and on top of the muscle tissue. The inset shows the device before implantation.

Figure 31. Schematic illustration of epitaxial layer (a) and fabrication processes for μ-ILEDs arrays on a carrier glass substrate after transfer printing (b).

Figure 32. (a) Schematic illustration (left frame) and corresponding microscope (top right frame) and SEM (bottom right frame) images of a 6×6 μ-ILEDs on a handle glass substrate coated with layers of polymers (epoxy / PI/ PMMA). (b) Schematic illustration (left frame) and corresponding microscope (top right frame) and optical (bottom right frame) images of a 6×6 μ-ILEDs array which is picked up with a PDMS stamp for transfer printing. A shadow mask for selective deposition of Cr/SiO2 (thickness: 3nm/30nm) covers the retrieved array on a soft elastomeric PDMS stamp. (c) Schematic illustration of transfer printing to a pre-strained thin (thickness: ~400 μm) PDMS substrate (left frame) and microscope (top right frame) and SEM (bottom right frame) images of the transferred μ-ILEDs array on a prestrained thin PDMS substrate. Prestrain value was ~20%.

Figure 33. (a) Schematic illustration of top encapsulation layers indicating some of the key dimensions. (b) Schematic illustration of the cross sectional structure at an island, with approximate thicknesses for each layer. The inset corresponds to an SEM image of a μ-ILEDs array after transfer printing to a thin PDMS substrate with prestrain of ~20%. (c) Schematic illustration of the cross sectional structure at metal interconnection bridges, with approximate thicknesses of each layer.

Figure 34. (a) Tilted view SEM images of adjacent μ-ILEDs (yellow dashed boxes) before (left, formed with ~20% pre-strain) and after (right) stretching along the horizontal direction (red arrows). (b) Strain distributions determined by 3D-FEM for the cases corresponding to frames in (a). The black outlines indicate the positions of the devices and the serpentines before relaxing the pre-strain.

Figure 35. (a) Optical microscope images of two pixels in a μ-ILEDs array with a serpentine bridge design before (left frame) and after (right frame) external stretching along the horizontal direction. The upper and lower images show optical micrographs in emission light off (upper) and on (lower) states. The distance between adjacent pixels appears in the lower images and used for calculation of applied strains. The lower images were obtained without external illumination. (b) Optical micrograph images of two pixels in a μ-ILEDs array before (left frame) and after (right frame) external stretching along the diagonal direction. (c) FEM simulation under external stretching along the diagonal direction (left frame), and strain contours in the GaAs active island (top right frame) and the metal bridge (bottom right frame).

Figure 36. Optical images of a 6×6 μ-ILEDs array with a serpentine mesh design with external illumination under the same strain circumstances as Figure 27b.

Figure 37. (a) Optical image of an 8x8 μ-ILEDs array on a thin PDMS substrate in its on state, which is under the same kind of deformed condition as bottom left frame of Figure 27d. (b) Top view optical images of same array as Figure 27d in its 'flat' (left frame) and 'inflated' state (right frame) without external illumination. (c) Spatial distribution of FEM results of the right frame of Figure 27d and analytical solutions calculated from Equations (S1) and (S2).

Figure 38. (a) Schematic illustrations of a 3×8 μ-ILEDs array integrated on a thin PDMS substrate with detailed dimensions (upper frame: registrations of the μ-ILEDs on a PDMS donor substrate, lower frame: entire view of the printed 3×8 μ-ILEDs array). The inset on top represents an optical microscope image of this μ-ILEDs array on a handle glass substrate before transfer printing. (b) Magnified view of the SEM image in Figure 28b. The white dotted rectangle highlights the non-coplanar bridge structures. (c) Voltage at 20 μA current for each twisting cycle of 360°.

Figure 39. FEM strain contours of axial (top), width (center), and shear (bottom) strains for 360° twisted PDMS substrate.

Figure 40. Fatigue test result of a 6×6 μ-ILEDs array as shown in Figure 28e. (a) Plot of I-V characteristics of a 6×6 μ-ILEDs array as a function of deformation cycles. (b) Plot of voltage needed to generate a current of 20 μA measured after deformation cycles up to 1000 times. Each deformed state is approximately same as shown in Figure 28e.

Figure 41. (a) Schematic illustration of stacked devices describing states of Figure 29b. (b) Optical images of stacked devices as shown in Figure 29b, collected without external illumination.

Figure 42. (a) The strain distribution of the two-layer system in the stacked array bent to a radius of curvature 2 mm, as shown in Figure 29c. The black dashed rectangles demonstrate the positions of μ-ILEDs. (b) The strain distribution in GaAs layers in the μ-ILEDs island.

Figure 43. (a) Optical image of a 6×6 μ-ILEDs array with serpentine metal interconnects, integrated on fabrics, in its bent and on state (bending radius ~4.0 mm). The inset shows the device in its flat and off state. (b) Plot of I-V characteristics of this array in its bent state. Inset provides a graph of the voltage needed to generate a current of 20 μA, measured after different numbers of cycles of bending deformation. (c) Optical image of an 8×8 μ-ILEDs array with a human pattern, integrated on a fallen leaf, in its bent and on state. The inset image was collected with external illumination. (d) Plot of I-V characteristics in the bent state as shown in Figure 43c. (e) Optical image of a μ-ILEDs array integrated on a paper in its folded and on state. (f) Optical image of the same μ-ILEDs array as shown in Figure 29e in its mildly crumbled state. Inset represents microscope image of adjacent four pixels in their on states.

Figure 44. (a) Plot of I-V characteristics of a 6×6 μ-ILEDs array integrated on paper in its flat (Figure 29d inset) and folded (Figure 29d) state. (b) Plot of I-V characteristics of a 6×6 μ-ILEDs array integrated on aluminum foil in its flat (Figure 29e inset) and crumbled (the center frame of Figure 29e) state. (c) Fatigue tests of arrays of 6×6 μ-ILEDs as shown in Figure 43e. Plot of I-V characteristics of a μ-ILEDs array integrated on paper as a function of deformation cycles (left frame). Plot of voltage needed to generate a current of 20 μA measured after deformation cycles up to 1000 times (right frame). (d) Fatigue tests of arrays of 6×6 μ-ILEDs as shown in Figure 43f. Plot of I-V characteristics of a μ-ILEDs array integrated on aluminum foil as a function of deformation cycles (left frame). Plot of voltage needed to generate a current of 20 μA measured after deformation cycles up to 1000 times (right frame).

Figure 45. SEM images of various substrate such as fabrics (a), Al foils (b), paper (c), and fallen leaves (d) before (left frame) and after (right frame) coating of thin layer of PDMS.

Figure 46. Schematic illustration of the encapsulation of an implantable array of μ-ILEDs as described in Figures 30a and 30b.

Figure 47. (a) Result of Luminance (L) - Current (I) - Voltage (V) measurement of an individual pixel with and without applied ohmic contacts. (b) Applied voltage to generate a current of 20 μA, measured after different operation time. The inset provides I-V characteristics with different operation time.

Figure 48. (a) Schematic illustration of analytical model for the inflation and printing-down of PDMS film. (b) FEM contours of meridional (upper left) and circumferential (lower left) strains of the inflated state and its comparison with analytical solutions calculated from Equations (S1) and (S2). (c) FEM contours of meridional (upper left) and circumferential (lower left) strains of the as-printed state and its comparison with analytical solutions Equations (S3) and (S4) (right frame).

Figure 49. Schematic illustration of the cross section of μ-ILEDs on a substrate.

Figure 50 provides: (a) Four frames of the electrode array transfer printed onto thin, low modulus ecoflex. On skin (left top), partially peeled off state (right top), magnified view of each top frame (bottom). Blue dotted boxes correspond to the magnified images at the bottom frame. The modulus and thickness of ecoflex substrate is ~50kPa and ~30um, respectively. The electrode array is facing down to skin, sandwiched by the skin and ecoflex substrate. (b) Schematic view of application procedures of skin patch to the skin. The electrode array is transfer printed onto ecoflex, coated on the PVA film, and water dissolvable and biocompatible film. The transferred electrode array is positioned onto the right location of skin. Some water can be applied to the backside of PVA film to dissolve it away. Thin, low modulus skin patch conforms very well to skin, like a tattoo. (c) Deformed images of skin patch on skin to four different directions and their magnified views. The highly conformal skin patch follows the wrinkles on skin very well. (d) Electrode array transfer printed at the backside of the commercial temporary tattoo. It is applied to the skin. Instead of ecoflex thin film, a temporary tattoo can be used for the purpose of camouflage or cover-up. (e) A schematic diagram illustrating a cross-sectional view of a skin-mounted conformal device of the invention having a polyimide encapsulating barrier layer.

Figure 51 provides (a) Mechanically optimized fully serpentine electrode array (left). The right frame shows the

stress-strain relationship from which the modulus in the plot was calculated. The optimized design shows comparable modulus with the bare skin. (b) Debonding experiment results under tension (left) and compression (right). As the modulus and thickness decrease, the debonding happens at larger strain. (c) Cross-sectional image (X-ray) of skin electronic devices located on the pig skin.

Figure 52 provides (a) Serpentine shape active EMG/EKG sensor. Left top frame shows source, drain and gate of nmos transistor and silicon drain to gate feedback resistor. Inset shows conventional shape active EMG/EKG sensor. Left bottom image shows the final device image for serpentine shape device and its magnified view (inset). Right top and bottom frame shows transfer and IV curve for the transistor. (b) Circuit diagram for active EMG/EKG sensor and the frequency response of active sensor (common source amplifier). (c) Microscope image of temperature sensor using platinum resistor and gold serpentine wires. Right frame shows the calibration curve, showing different resistances of temperature sensor at different temperatures. (d) Microscope image of strain gauge using conductive PDMS (CPDMS). Right frame shows the calibration curve of the strain gauge. (e) Microscope images of proximity sensor using forward and reverse biased LED array. Forward biased LED array radiates light and reverse biased LED array detects the reflected light from the object. As the distance between the object and LED array decreases, the reflectance increases and thereby the photocurrent increases, as shown in the right frame. (f) A single LED pixel powered by wireless power transmission coil. Right frame shows the IV curve of LED pixel. (g) Microscope image of PN diodes (left) and it S21 value measured at different frequencies in radio frequency range. (h) Microscope image of inductor and capacitor pair (left top). Right top plot shows S21 value of capacitor at various RF frequencies and left bottom plot shows S21 and S11 values of inductor at RF frequencies. Right bottom plot shows the estimated oscillation frequencies for different capacitors.

Figure 53 provides (a) Passive electrode array on forehead for undeformed (left top) and deformed (right top and bottom) state. Left bottom image shows the partially peeled off state. (b) EEG measurement results for Stroop test. When the target letter matches with the highlighted letter (congruent case) the response speed is faster than unmatched (incongruent case) case. (c) EEG measurement results for eye open and eye close case. Left plot shows raw EEG and right plot shows results after Fourier transformation.

Figure 54 provides (a) EKG measurement result measured with active EKG sensor (left) and magnified view of single heartbeat (right). (b) EMG measurement result from a right leg during walking (from 0 sec to 10 sec) and standing (from 10 sec to 20 sec) measured with active EMG sensor (left) and conventional passive EMG sensor with conductive gel (right). (c) Magnified view of EMG signal of (b). (d) Corresponding spectrogram for each electrode. (e) EMG measurement result from neck for four different words, "up", "down", "left" and "right". (f) Corresponding spectrogram for four words. (g) Video game control using recorded EMG signal.

FIG. 55 is block diagram of a system for a wide range of biological sensing and therapeutic treatment applications.

FIG. 56 is a diagram depicting the collapsible nature of a flexible high-density micro-array device that can be deployed to a tissue site.

FIG. 57 is a diagram depicting insertion of the array device into a sheath for introduction into a patient.

FIG. 58 is a diagram depicting deployment of the array device from a sheath to a tissue surface.

FIG. 59 is a diagram of the array device deployed on the surface of the heart.

FIGs. 60 and 61 are diagrams showing connection of the array device to an implantable electronics unit.

FIG. 62 is a diagram showing a specific example of elements on the array device.

FIG. 63 is a timing diagram showing examples of stimulation timing schemes to groups of elements on the array device.

FIG. 64 is a flow chart of a continuously adjustable stimulation process using the array device.

FIG. 65 is a diagram showing a configuration of the array device suitable for providing mechanical support to a portion of the heart.

FIG. 66 is a block diagram showing the array device used in a cardiac mapping and ablation system configuration.

FIGs. 67A and 67B are diagrams showing photos of actual deployment of the array device on the surface of a heart. FIG. 67C is a diagram depicting the mapping data that can be obtained from the array device in the environment shown in FIGs. 67A and 67B.

FIG. 68 illustrates an example of the array device 100.

FIG. 69 is a schematic diagram that illustrates how unit cells connect to other unit cells to create a multiplexed signal output, for example for sensing from one of the elements 110 that is configured to operate as a sensor electrode.

FIG. 70 is similar to FIG. 69, but adds stimulation control capability. In this example, the stimulation input lines STIM0, STIM1, etc., are provided.

FIG. 71 illustrates a schematic diagram that is similar to FIG. 70, but uses independent stimulation row select signals.

FIG. 72 shows an example transistor level schematic for an element 110 in a sensing configuration. There is a constant current source 112, a current mirror 114 and a multiplexer 116.

FIG. 73 shows an example transistor level layout for an element 110 with stimulation control according to that described above in connection with FIG. 70.

FIG. 74 shows an example transistor level layout for an element 110 with row independent selectable stimulation control according to that described above in connection with FIG. 71.

DETAILED DESCRIPTION OF THE INVENTION

[0078] 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.

[0079] The terms "flexible" and "bendable" are used synonymously in the present description and refer to the ability of a material, structure, device or device component to be deformed into a curved or bent shape without undergoing a transformation that introduces significant strain, such as strain characterizing the failure point of a material, structure, device or device component. In an exemplary embodiment, a flexible material, structure, device or device component may be deformed into a curved shape without introducing strain larger than or equal to 5%, for some applications larger than or equal to 1%, and for yet other applications larger than or equal to 0.5% in strain-sensitive regions. A used herein, some, but not necessarily all, flexible structures are also stretchable. A variety of properties provide flexible structures (e.g., device components) of the invention, including materials properties such as a low modulus, bending stiffness and flexural rigidity; physical dimensions such as small average thickness (e.g., less than 100 microns, optionally less than 10 microns and optionally less than 1 micron) and device geometries such as thin film and mesh geometries.

[0080] "Stretchable" refers to the ability of a material, structure, device or device component to be strained without undergoing fracture. In an exemplary embodiment, a stretchable material, structure, device or device component may undergo strain larger than 0.5% without fracturing, for some applications strain larger than 1% without fracturing and for yet other applications strain larger than 3% without fracturing. A used herein, many stretchable structures are also flexible. Some stretchable structures (e.g., device components) are engineered to be able to undergo compression, elongation and/or twisting so as to be able to deform without fracturing. Stretchable structures include thin film structures comprising stretchable materials, such as elastomers; bent structures capable of elongation, compression and/or twisting motion; and structures having an island - bridge geometry. Stretchable device components include structures having stretchable interconnects, such as stretchable electrical interconnects.

[0081] "Functional layer" refers to a device-containing layer that imparts some functionality to the device. For example, the functional layer may be a thin film such as a semiconductor layer. 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 device-receiving pads 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 surface (NMS) within the multilayer device.

[0082] "Semiconductor" refers to any material that is an insulator at a low temperature, but which has an appreciable electrical conductivity at a temperatures 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 element 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, 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 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 semiconductor 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 in some embodiments include, but are not limited to, Si, Ge, SiC, AlP, AlAs, AlSb, GaN, GaP, GaAs, GaSb, InP, InAs, GaSb, InP, InAs, InSb, ZnO, ZnSe, ZnTe, CdS, CdSe, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, PbS, PbSe, PbTe, AlGaAs, AlInAs, AlInP, GaAsP, GaInAs, GaInP, AlGaAsSb, AlGaInP, and GaInAsP. Porous silicon semiconductor materials are useful for applications of aspects described herein in the field of sensors and light emitting materials, such as light emitting diodes (LEDs) and solid state lasers. 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.

[0083] "Semiconductor element", "semiconductor structure" and "semiconductor circuit element" are used synonymously in the present description and broadly refer 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, organic and inorganic semiconductors and composite semiconductor materials and structures having one or more additional semiconductor components and/or non-semiconductor components, such as dielectric layers or materials, electrodes and/or conducting layers or materials.

[0084] "Coincident" refers to refers to the relative position of two or more objects, planes or surfaces, for example a surface such as a NMS or NMP that is positioned within or is adjacent to a layer, such as a functional layer, substrate layer, or other layer. In an embodiment, a NMS or NMP is positioned to correspond to the most strain-sensitive layer or material within the layer.

[0085] "Proximate" refers to the relative position of two or more objects, planes or surfaces, for example a NMS or NMP that closely follows the position of a layer, such as a functional layer, substrate layer, or other layer while still providing desired flexibility or stretchability without an adverse impact on the strain-sensitive material physical properties. 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 NMS or NMP 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 folded.

[0086] "Electronic device" is used broadly herein to refer to devices such as integrated circuits, imagers or other optoelectronic devices. Electronic device may also refer to a component of an electronic device such as passive or active components such as a semiconductor, interconnect, contact pad, transistors, diodes, LEDs, circuits, etc. Devices disclosed herein may relate to the following fields: collecting optics, diffusing optics, displays, pick and place assembly, vertical cavity surface-emitting lasers (VCSELS) and arrays thereof, LEDs and arrays thereof, transparent electronics, photovoltaic arrays, solar cells and arrays thereof, flexible electronics, micromanipulation, plastic electronics, displays, pick and place assembly, transfer printing, LEDs, transparent electronics, stretchable electronics, and flexible electronics.

[0087] A "component" is used broadly to refer to a material or individual component used in a device. An "interconnect" is one example of a component and refers to an electrically conducting material capable of establishing an electrical connection with a component or between components. In particular, an interconnect may establish electrical contact between components that are separate and/or can move with respect to each other. Depending on the desired device specifications, operation, and application, an interconnect is made from a suitable material. For applications where a high conductivity is required, typical interconnect metals may be used, including but not limited to copper, silver, gold, aluminum and the like, and alloys. Suitable conductive materials further include semiconductors, such as silicon and GaAs and other conducting materials such as indium tin oxide.

[0088] An interconnect that is "stretchable" or "flexible" is used herein to broadly refer to an interconnect capable of undergoing a variety of forces and strains such as stretching, bending and/or compression in one or more directions without adversely impacting electrical connection to, or electrical conduction from, a device component. Accordingly, a stretchable interconnect may be formed of a relatively brittle material, such as GaAs, yet remain capable of continued

function even when exposed to a significant deformatory force (e.g., stretching, bending, compression) due to the interconnect's geometrical configuration. In an exemplary embodiment, a stretchable interconnect may undergo strain larger than 1%, optionally 10% or optionally 30% or optionally up to 100% without fracturing. In an example, the strain is generated by stretching an underlying elastomeric substrate to which at least a portion of the interconnect is bonded. For certain embodiments, flexible or stretchable interconnects include interconnects having wavy, meandering or serpentine shapes.

[0089] A "device component" is used to broadly refer to an individual component within an electrical, optical, mechanical or thermal device. Components include, but are not limited to, a photodiode, LED, TFT, electrode, semiconductor, other light-collecting/detecting components, transistor, integrated circuit, contact pad capable of receiving a device component, thin film devices, circuit elements, control elements, microprocessors, transducers and combinations thereof. A device component can be connected to one or more contact pads as known in the art, such as metal evaporation, wire bonding, application of solids or conductive pastes, for example. Electrical device generally refers to a device incorporating a plurality of device components, and includes large area electronics, printed wire boards, integrated circuits, device components arrays, biological and/or chemical sensors, physical sensors (e.g., temperature, light, radiation, etc.), solar cell or photovoltaic arrays, display arrays, optical collectors, systems and displays.

[0090] "Sensing element" and "sensor" are used synonymously and refers to a device component useful as a sensor and/or useful for detecting the presence, absence, amount, magnitude or intensity of a physical property, object, radiation and/or chemical. Sensors in some embodiments function to transduce a biological signal into an electrical signal, optical signal, wireless signal, acoustic signal, etc. Useful sensing elements include, but are not limited to electrode elements, chemical or biological sensor elements, pH sensors, optical sensors, photodiodes, temperature sensors, capacitive sensors strain sensors, acceleration sensors, movement sensors, displacement sensors, pressure sensors, acoustic sensors or combinations of these.

[0091] "Actuating element" and "actuator" are used synonymously and refers to a device component useful for interacting with, stimulating, controlling, or otherwise affecting an external structure, material or fluid, for example a biological tissue. Useful actuating elements include, but are not limited to, electrode elements, electromagnetic radiation emitting elements, light emitting diodes, lasers and heating elements. Actuating elements include electrodes for providing a voltage or current to a tissue. Actuating elements include sources of electromagnetic radiation for providing electromagnetic radiation to a tissue. Actuating elements include ablation sources for ablating tissue. Actuating elements include thermal sources for heating tissue. Actuating elements include displacement sources for displacing or otherwise moving a tissue.

[0092] "Island" or "device island" refers to a relatively rigid device element or component of an electronic device comprising multiple semiconductor elements or active semiconductor structures. "Bridge" or "bridge structure" refers to stretchable or flexible structures interconnecting two or more device islands or one device island to another device component. Specific bridge structures include flexible semiconductor interconnects.

[0093] "Barrier layer" refers to a device component spatially separating two or more other device components or spatially separating a device component from a structure, material or fluid external to the device. In one embodiment, a barrier layer encapsulates one or more device components. In embodiments, a barrier layer separates one or more device components from an aqueous solution, a biological tissue and/or a biological environment. In some embodiments, a barrier layer is a passive device component. In some embodiments, a barrier layer is a functional, but non-active, device component. In a specific embodiment, a barrier layer is a moisture barrier. As used herein, the term "moisture barrier" refers to a barrier layer which provides protection to other device components from bodily fluids, ionic solutions, water or other solvents. In one embodiment, a moisture barrier provides protection to an external structure, material or fluid, for example, by preventing leakage current from escaping an encapsulated device component and reaching the external structure, material or fluid. In a specific embodiment, a barrier layer is a thermal barrier. As used herein, the term "thermal barrier" refers to a barrier layer which acts as a thermal insulator, preventing, reducing or otherwise limiting the transfer of heat from one device component to another or from a device component to an external structure, fluid or material. Useful thermal barriers include those comprising materials having a thermal conductivity of 0.3 W/m·K or less, such as selected over the range of 0.001 to 0.3 W/m·K. In some embodiments, a thermal barrier comprises active cooling components, such as components known in the art of thermal management, such as thermoelectric cooling devices and systems. Thermal barriers also include those barriers comprising thermal management structures, such as structures useful for transporting heat away from a portion of a device or tissue; in these and other embodiments, a thermal barrier comprises thermally conductive material, for example material having a high thermal conductivity, such as a thermal conductivity characteristic of a metal.

[0094] "Leakage current" or "leakage" refers to electric current which flows from an electronic device along an unintended path. Under certain conditions, leakage of sufficient current from an electronic device can damage the device and/or components thereof. In certain circumstances, leakage current can also or alternatively damage the material into which it flows.

[0095] "Active circuit" and "active circuitry" refers to one or more device components configured for performing a

specific function. Useful active circuits include, but are not limited to, amplifier circuits, multiplexing circuits, logic circuits, CMOS circuits, processors, and current limiting circuits. Useful active circuit elements include, but are not limited to, transistor elements and diode elements.

[0096] "Selectively permeable" refers to a property of a material to allow certain substances to pass through the material while preventing other substances from being passed through. In one embodiment, a selectively permeable material allows one or more target chemicals, molecules and/or biomolecules to be passed through the material while preventing water, ionic solutions, bodily fluids, salts, proteins and other substances from being passed through the material. In an embodiment, the barrier layer of a device has spatially patterned permeable regions, impermeable regions or a combination of both permeable regions and impermeable regions.

[0097] "Substrate" refers to a material having a surface that is capable of supporting a structure, including an electronic device or electronic device component. An structure that is "bonded" to the substrate refers to a portion of the structure in physical contact with the substrate and unable to substantially move relative to the substrate surface to which it is bonded. Unbonded portions, in contrast, are capable of substantial movement relative to the substrate.

[0098] A "NMS adjusting layer" refers to a layer whose primary function is adjusting the position of the NMS in the device. For example, the NMS adjusting layer may be an encapsulating layer or an add layer such as an elastomeric material.

[0099] In the context of this description, a "bent configuration" refers to a structure having a curved conformation resulting from the application of a force. Bent structures may have one or more folded regions, convex regions, concave regions, and any combinations thereof. Useful bent structures, for example, may be provided in a coiled conformation, a wrinkled conformation, a buckled conformation and/or a wavy (i.e., wave-shaped) configuration. Bent structures, such as stretchable bent interconnects, may be bonded to a flexible substrate, such as a polymer and/or elastic substrate, in a conformation wherein the bent structure is under strain. In some embodiments, the bent structure, such as a bent ribbon structure, is under a strain equal to or less than 30%, optionally a strain equal to or less than 10%, optionally a strain equal to or less than 5% and optionally a strain equal to or less than 1% in embodiments preferred for some applications. In some embodiments, the bent structure, such as a bent ribbon structure, is under a strain selected from the range of 0.5% to 30%, optionally a strain selected from the range of 0.5% to 10%, and optionally a strain selected from the range of 0.5 % to 5%. Alternatively, the stretchable bent interconnects may be bonded to a substrate that is a substrate of a device component, including a substrate that is itself not flexible. The substrate itself may be planar, substantially planar, curved, have sharp edges, or any combination thereof. Stretchable bent interconnects are available for transferring to any one or more of these complex substrate surface shapes.

[0100] "Thermal contact" refers to the ability of two or more materials and/or structures that are capable of substantial heat transfer from the higher temperature material to the lower temperature material, such as by conduction. Thermal communication refers to a configuration of two or more components such that heat can be directly or indirectly transferred from one component to another. In some embodiments, components in thermal communication are in direct thermal communication wherein heat is directly transferred from one component to another.. In some embodiments, components in thermal communication are in indirect thermal communication wherein heat is indirectly transferred from one component to another via one or more intermediate structures separating the components.

[0101] "Fluid communication" refers to the configuration of two or more components such that a fluid (e.g., a gas or a liquid) is capable of transport, flowing and/or diffusing from one component to another component. Elements may be in fluid communication via one or more additional elements such as tubes, containment structures, channels, valves, pumps or any combinations of these.. In some embodiments, components in fluid communication are in direct fluid communication wherein fluid is capable of transport directly from one component to another.. In some embodiments, components in fluid communication are in indirect fluid communication wherein fluid is capable of transport indirectly from one component to another via one or more intermediate structures separating the components.

[0102] "Electrical contact" refers to the ability of two or more materials and/or structures that are capable of transferring charge between them, such as in the form of the transfer of electrons or ions. Electrical communication refers to a configuration of two or more components such that an electronic signal or charge carrier can be directly or indirectly transferred from one component to another. As used herein, electrical communication includes one way and two way electrical communication. In some embodiments, components in electrical communication are in direct electrical communication wherein an electronic signal or charge carrier is directly transferred from one component to another.. In some embodiments, components in electrical communication are in indirect electrical communication wherein an electronic signal or charge carrier is indirectly transferred from one component to another via one or more intermediate structures, such as circuit elements, separating the components.

[0103] "Optical communication refers to a configuration of two or more components such that electromagnetic radiation can be directly or indirectly transferred from one component to another. As used herein, optical communication includes one way and two way optical communication. In some embodiments, components in optical communication are in direct optical communication wherein electromagnetic radiation is directly transferred from one component to another.. In some embodiments, components in optical communication are in indirect optical communication wherein an electromagnetic

radiation is indirectly transferred from one component to another via one or more intermediate structures, such as reflectors, lenses, or prisms, separating the components.

[0104] "Ultrathin" refers to devices of thin geometries that exhibit extreme levels of bendability. In an embodiment, ultrathin refers to circuits having a thickness less than 1 μm, less than 600 nm or less than 500 nm. In an embodiment, a multilayer device that is ultrathin has a thickness less than 200 μm, less than 50 μm, or less than 10 μm.

[0105] "Thin layer" refers to a material that at least partially covers an underlying substrate, wherein the thickness is less than or equal to 300 μm, less than or equal to 200 μm, or less than or equal to 50 μm. Alternatively, the layer is described in terms of a functional parameter, such as a thickness that is sufficient to isolate or substantially reduce the strain on the electronic device, and more particularly a functional layer in the electronic device that is sensitive to strain.

[0106] "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 and silicon dioxide.

[0107] "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, graft, tapered and other copolymers. Useful polymers include organic polymers or inorganic polymers and may be in amorphous, semi-amorphous, crystalline or partially crystalline states. Cross linked polymers having linked monomer chains are particularly useful for some applications. Polymers useable in the methods, devices and device components include, but are not limited to, plastics, elastomers, thermoplastic elastomers, elastoplastics, thermostats, 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, ethylenepropylene, butyl, nitrile, silicones), acrylic, nylon, polycarbonate, polyester, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polyolefin or any combinations of these.

[0108] "Elastomer" refers to a polymeric material which can be stretched or deformed and return 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 useful include, but are not limited to, thermoplastic elastomers, styrenic materials, olefenic 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, olefenic materials, polyolefin, polyurethane thermoplastic elastomers, polyamides, synthetic rubbers, polyisobutylene, poly(styrene-butadiene-styrene), polyurethanes, polychloroprene and silicones. In an embodiment, a flexible polymer is a flexible elastomer.

[0109] "Elastomeric stamp" or "elastomeric transfer device" are used interchangeably and refer to.an elastomeric material having a surface that can receive as well as transfer a component, such as an electronic device or component thereof. Exemplary elastomeric transfer devices include stamps, molds and masks. The transfer device affects and/or facilitates feature transfer from a donor material to a receiver material. Stamps and transfer device may be used for assembling components via transfer printing, such as dry contact transfer printing.

[0110] "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. Conformal contact includes large area conformal contact, for example, wherein conformal contact between a tissue and device component is over an area greater than or equal to 1000 mm^2, and optionally greater than or equal to 10,000 mm^2.

[0111] "Conformable" refers to a device, material or substrate which has a bending stiffness sufficiently low to allow the device, material or substrate to adopt a desired contour profile, for example a contour profile allowing for conformal contact with a surface having a pattern of relief or recessed features. In certain embodiments, a desired contour profile is that of a tissue in a biological environment, for example heart tissue.

[0112] "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 optionally less than or equal to 1 MPa and optionally for some applications less than or equal to 0.1 MPa.

[0113] "Young's modulus" and "modulus" are used interchangeably and refer to 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 10 times larger for some applications, more preferably 100 times larger for other applications and even more preferably 1000 times larger for yet other applications. "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 layer of material.

[0114] "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.

[0115] "Adversely affect" in the context of a tissue and/or biological environment, refers to a stimulus, such as voltage, current, temperature, electric field, electromagnetic radiation or combination thereof, capable of damaging, disrupting, reducing viability and/or killing cells of the tissue in the biological environment. As will be understood by a skilled artisan, conditions that adversely affect a tissue in a biological environment depend on the specific type and composition of the tissue and biological environment of the tissue. In an embodiment, for example, a barrier layer limits the leakage current from the electronic device to the tissue to a specific amount, such as a value equal to or less than 0.1 $\mu A/cm^2$, optionally for some applications equal to or less than 0.01 $\mu A/cm^2$; and optionally for some applications equal to or less than 0.001 $\mu A/cm^2$, so as to not adversely affect the tissue. In an embodiment, for example, a barrier layer limits the thermal transfer from the electronic device to the tissue so as to provide in situ increase in temperature of the tissue equal to or less than 0.5, optionally 1, optionally 2, or optionally 5 degrees Celsius so as to not adversely affect the tissue.

[0116] "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 electronic devices, device components and/or inorganic semiconductor components and/or electrodes.

[0117] "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.

[0118] "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.

[0119] Described herein are conformable electrophysiology data acquisition devices and methods for acquiring electrophysiology data at high-speed and high-resolution. The conformable devices disclosed herein include devices incorporating a moisture barrier; moisture barriers, for example, are useful for preventing conductive solutions from penetrating into electronic devices and thereby producing leakage current from components thereof. The conformable devices disclosed herein include devices useful for diagnosing and treating medical conditions in real time and with high spatial precision. The disclosed devices and methods also include those suited for monitoring electrical, optical, thermal and tissue characteristics of tissues *in-vivo* as they undergo motion, for example the tissue of a beating heart. The disclosed devices and methods further include those especially suited for monitoring electrical characteristics of tissues having nonplanar surfaces.

[0120] The invention may be further understood by the following non-limiting examples.

EXAMPLE 1: High-Speed, High-Resolution Cardiac Electrophysiology In-Vivo Using Conformal Electronics

[0121] Mapping cardiac arrhythmias with standard, clinical electrophysiology (EP) devices can be a tedious, lengthy process, particularly over the epicardial surface. Probes with small numbers (4-10) of widely spaced (2-5 mm) passive electrodes sequentially record electrical activity from small areas of heart muscle as they are moved manually, point to point, across regions of interest. Because each electrode requires a separate connection to external processors, spatial resolution and mapping speed are limited by practical constraints on the number and configuration of electrodes and wires that can fit in the device. This example describes a high resolution, high speed system that eliminates these constraints. The device uses fully integrated, conformal electronic circuits (built with >2,000 single crystal silicon nanoribbon transistors) to simultaneously record from 288 multiplexed (16:1) channels, each with its own on-board amplifier. The low bending stiffness of the device allows it to adhere to the dynamic, three dimensional (3D) surface of the beating heart via physical lamination, without pins or adhesives. This integrated system maps activity at high spatial (sub-mm) and temporal (sub-ms) resolutions over large areas in a single pass, without human intervention. This functionality is demonstrated by mapping the spread of ventricular depolarization from spontaneous and paced activation wavefronts in-vivo in a porcine animal model, thereby introducing a platform for a new generation of intelligent, implantable medical devices.

[0122] Sudden cardiac arrest is the leading cause of death in developed countries. Many patients at risk for arrhythmic death have advanced structural heart disease, and preexisting non-lethal ventricular arrhythmias. In these and other cases, cardiac electrophysiologic (EP) studies are used to aid diagnosis and guide therapy. Conventional devices for this purpose use sparse arrays of electrodes that probe potentials at the surface of cardiac tissue. During mapping, sensors are continuously maneuvered to record from discrete sites on the heart. These sequential local recordings are "stitched" together with software to render a complete representation of cardiac electrical activity over a region of interest. The iterative nature of this approach prolongs EP procedures and impedes real time mapping of transient abnormal rhythms. Despite explosive growth and innovation in the broader electronics industry, the key limitation of EP devices is that they have retained the simple electronics-tissue interface of their earliest predecessors of ~40 years ago. Sensing and stimulating electrodes are purely passive metallic contacts individually wired to separate, remote processing units that use traditional semiconductor wafer-based electronics. Rapid, high resolution EP mapping might be most effectively accomplished by embedding modern silicon-based integrated circuit (IC) technology directly at the tissue-electrode interface. Unfortunately the planar shapes and rigid, brittle mechanical properties associated with conventional ICs strictly preclude their non-destructive, intimate integration with the curvilinear, soft surfaces of biological tissues.

[0123] Recent advances in material science provide a solution to this problem through scalable routes to ICs that offer the performance of similarly designed devices on semiconductor wafers, but with the mechanical properties of thin sheets of plastic or rubber. This technology relies on established, inorganic semiconductors (e.g. Si) configured into structural forms that provide the desired mechanical properties. For example, single crystal silicon in the form of nanoscale ribbons, membranes or wires are flexible by virtue of their small thicknesses. Multilayer circuit structures that exploit such materials in neutral mechanical plane designs can accommodate bending to radii of curvature of ~50 μm without fracture or degradation in their electrical properties. These and related strategies enable high-performance, active electrode arrays that can stretch, fold, and conform to complex, 3D dynamic surfaces, such as the epicardial surface of the beating heart. The ability to incorporate active, powered components on flexible substrates, including amplifiers and transistor-based multiplexing circuitry, enables a high density of active electrodes on an EP device, without the need for a connecting wire between each element, or for an implanted or external control unit. Below, this example further describes the successful implementation of a system of this type, at levels of integration (i.e. >2000 transistors) that significantly exceed previous reports of active biomedical or other classes of flexible devices, and in clinically relevant modes of use (i.e. high speed, high resolution EP mapping in-vivo) that provide clear advantages over existing technologies. The results are important not only to cardiac EP applications but more generally to new classes of active electronic systems that can be integrated intimately with the human body for diagnostic or therapeutic benefit.

[0124] Figure 1 shows a set of images and illustrations that detail the fabrication sequence at a single unit cell (Figures 1a-d), and a completed device (Figure 1e). Each cell consists of a contact pad that serves as an electrical interface to the tissue and an associated amplifier and multiplexer. The device includes an 18 by 16 array of such amplified electrodes to provide a total of 288 measurement points, spaced by 800 μm and covering a total area of 14.4 mm by 12.8 mm. See Figure 1. Each unit cell comprises 7 transistors for a total of 2016, representing the highest level of integration achieved in any non-display flexible electronic system. With integrated multiplexing circuitry, only 36 wires are required to connect all 288 measurement points to external data acquisition and control units.

[0125] The fabrication involves formation of transistors and interconnects in four metal layers. In the first step, transfer printing delivers to a flexible plastic substrate (polyimide; ~25 μm) an organized collection of single crystalline, semiconductor grade silicon nanomembranes (260 nm) with patterned regions of doping for ohmic contacts (Figure 1a). Plasma enhanced chemical vapor deposition of SiO2 (~100 nm) at reduced temperatures yields a gate dielectric through which source/drain contact openings are formed by photolithography and etching in buffered oxide etchant. Electron beam evaporation, photolithography and wet etching define the first layer of metal interconnect, including source, drain and gate contacts, as shown in Figure 1 b. Similarly fabricated second and third metal layers form the column and row addressing electrodes (Figure 1c, d) where a thin layer of spin cast polyimide (1.4 μm) with etched via holes provides the interlayer dielectric between the first and second metal layers, a trilayer organic/inorganic stack (polyimide/Si_3N_4/epoxy; 1.4 μm/80 nm/9 μm) and a single layer of epoxy (9 μm) forms a similar interlayer for the second and third and third and fourth metal layers, respectively. Details appear in Figures 5 through 9, described below. These different layers locate the circuit at the neutral mechanical plane and ensure reliable operation when immersed in saline solution, as described subsequently. The top metal layer defines surface electrodes (Au pads, 250 × 250 μm) that contact the cardiac tissue and connect to the underlying circuits through via holes. These electrodes, which we refer to as inputs, have impedances of 100 KOhm + 10% at 1 KHz, as measured using a similarly designed passive electrode array immersed in normal saline (0.9%) solution. The entire device connects to a data acquisition system through an anisotropic conductive film (ACF) connector with 36 contacts. See the methods and Figure 10 for details of the fabrication procedures, and dimensions of devices.

[0126] The right frames of Figure 1c and Figure 2a provide annotated images and circuit diagrams, respectively, of the amplifier and the multiplexing transistor. The amplifier uses a source-follower configuration with significant current gain. The multiplexing transistor enables readout of all inputs via programmed, sequential addressing of each row of electrodes, thereby providing a 16× reduction in the required number of output wires compared to a non-multiplexed electrode array. The schematic in Figure 2b illustrates how the unit cell in Figure 2a can be connected to other unit cells to create the multiplexed signal output. During multiplexed sampling, one row of electrodes is selected at a time by driving one of the row select signals, such as R_0 (highlighted in blue in Figure 2b), high and all of the others low (R_1 ... R_n, where R_1 is highlighted in green). This allows the unit cells in that row to drive the column output lines (C_0 ... C_n, where C_0 is highlighted in red), which are connected to a high-speed analog to digital converter (see Figure 11, National Instruments, USA). Row select signals are rapidly cycled to sample all electrodes on the array. Figure 2c presents electrical characteristics of a representative multiplexing transistor. The transistor exhibits an on/off ratio and electron mobility of ~10^5 and ~490 cm^2/Vs, respectively. The high mobility, compared to organics or other materials for flexible electronics, enables the amplifier to have a high bandwidth, as shown in Figure 2d, and the multiplexer to switch quickly, as shown in Figure 2e, even for the relatively coarse dimensions of the devices reported here (i.e. channel lengths of ~40 μm). Figure 2d shows the measured and simulated bandwidth of a single amplifier with the multiplexing disabled. The amplifier shows performance properties consistent with design targets and simulations, i.e. -3 db cutoff frequency of ~200 kHz. Simulations were obtained using commercial software (Cadence, Cadence Design Systems, USA). See methods for more details about the simulations. As shown in Figure 2e, the multiplexer switching time was about 5 μs. The switching time was limited, however, by the slew rate of the external row select signals provided to the array, as shown in blue and green. Figure 2f shows the percentage of the final voltage value attained during the allotted settling time, averaged across all of the electrodes, for increasing multiplexing frequency. These results demonstrate that multiplexing rates up to 200 kHz are possible, yielding sampling rates up to 12.5 kHz per electrode. Figure 12 further shows that the signal to noise ratio (SNR) for the system remains constant up to 200 kHz multiplexing frequency. If the slew rate of the row select signals is increased, the multiplexing rate can be further increased. In experiments described below, the 16 row select signals were cycled at 10 kHz, yielding a sampling rate of 625 Hz per active electrode, with all 16 electrodes in a given row thus sampled simultaneously. The multiplexed analog signals were synchronously sampled at 50 kHz, 5 times oversampling per switch interval, to improve the signal-to-noise ratio: Data were acquired, demultiplexed, stored, and displayed using custom MATLAB software (The MathWorks™, Natick, MA).

[0127] In addition to the electrical properties, mechanical flexibility and capacity to operate while immersed in a saline environment are critically important for this application. Analytical mechanics modeling elucidates the bend-induced strains in all layers of the devices used in animal experiments. The thicknesses of the layers of epoxy and the substrate were chosen to place the active circuit components near the neutral mechanical plane. As a result, for bend radii of ~5 cm, typical of those encountered in human cardiac EP studies, maximum strains in the Si and SiO_2 are calculated to be

0.001% and 0.0001%, respectively. These values are orders of magnitude below the fracture strains for our devices, and they are also significantly less than those expected to alter their electrical performance. Another feature of the device design is that the bending stiffness of the circuit is sufficiently low to allow conformal wrapping on the moist surface of the cardiac tissue. These mechanics can also be modeled by comparing the system energy for a circuit in a flat configuration to one in a wrapped state (see Figure 13). The result is that wrapping is energetically favored when $\gamma > B/2R^2$, where γ is the adhesion energy between the circuit and the tissue, R is the radius of curvature, and B is the bending stiffness of the circuit. Using R~2.5 cm and a computed value of B, one finds that wrapping is the preferred configuration for cases where $\gamma > 34.7$ mJ/m^2. The reported value of adhesion energy between two wet surfaces is ~75-150 mJ/m^2. Based upon these models and measurements from the fabricated devices, the conclusion is that the circuits will naturally wrap around the cardiac tissue without any separate mechanism to ensure adhesion. The partially wet surface of the tissue, in-vivo, facilitates this outcome. To accommodate this aspect and to enable device use in realistic clinical settings, the circuit must provide sustained operation when immersed in the body's fluids. It was found that the inorganic/organic encapsulation scheme described previously serves as an effective water barrier for this purpose. Figure 2g shows a circuit immersed in a saline bath, to test for leakage currents by creating a conduction path from the device to a separate ground electrode in the bath. A cutoff value of 10 μA was selected, consistent with the International Electrotechnical Commission standards for medical electronic equipment (IEC 60601-1). Roughly 75% of the fabricated devices passed this test. Randomly selected samples were tested for long term reliability in the saline bath and found to operate for greater than 3 hours while maintaining a leakage current less than 10 μA. Figure 2h presents 20 Hz sine wave response before and after saline immersion for 10 minutes, verifying negligible changes in circuit properties. 4 Hz and 40Hz results are also displayed in Figure 14.

[0128] *In-vivo* experiments were performed in normal 80-90 pound male Yorkshire pigs. The heart was surgically exposed via a median sternotomy and a subsequent pericardiotomy. The flexible EP circuit was then placed on the epicardial surface while under direct visualization (Figure 3a). See methodology details in Figure 15 and Figure 21. The device remained adhered to the curvilinear surface of the heart, even during vigorous cardiac motion. Figure 3b shows motion snapshots at various stages of the cardiac cycle; the blue lines highlight the dynamic variations in the surface shape associated with maintaining conformal contact. Given the average heart rate of ~77 beats per minute (BPM) during *in-vivo* experiments and a recording duration of ~137 minutes, the device provided reliable data over the course of >10,000 bending cycles during the experiments. Unipolar voltage data were recorded from all 288 electrode elements using the sampling and multiplexing strategy described above. Baseline electrogram data were collected in sinus rhythm with the array in multiple positions and orientations on the epicardial surface. Data were also recorded while pacing the heart from multiple locations relative to the array via a standard, non-steerable decapolar electrode EP catheter (Boston Scientific, San Jose, CA) held in contact with the epicardial surface. Figure 3c shows the array positioned over the left anterior descending (LAD) coronary artery, with the pacing catheter positioned just inferior to the array. The color coded map in this frame shows a visual representation of the data collected from the device, using procedures described below.

[0129] Data from all channels were filtered and processed using custom MATLAB software to determine the relative activation time at each contact by comparing the time of the maximum negative slope (dV/dt) of the unipolar electrogram to the maximum negative slope of the average electrogram of all 288 channels. These activation times were then used to generate isochronal maps showing propagation of paced and unpaced cardiac depolarization wavefronts spreading across the array for a variety of recording sites and pacing conditions (see Figure 22 for more details). Sample voltage trace data from a single channel without remote pacing are shown in Figure 4a. The inset at right highlights the very low noise level of the recording. The signal to noise ratio (SNR) is approximately 50. Note that negative is plotted up by convention. Figure 4b shows voltage data for all channels taken at 4 points in time. Figure 22 shows some of the voltage data presented in Figure 4b. Figure 16 illustrates the uniformity of all of the electrodes by plotting the average peak amplitude of the cardiac activation. Figure 17a shows an isochronal activation map made from this voltage data, illustrating the natural activation pattern of the heart. Data from 5 of the 18 columns have been removed due to failures in the metal interconnections. All of the remaining channels and all rows functioned properly. Figure 4c shows an average voltage trace collected from all of the electrodes. Dashed lines have been plotted on the trace to illustrate the instant in time that each frame in Figure 4b was taken. Sample voltage trace data from a single channel with remote pacing are shown in Figure 4d. Figures 4e and 17b show isochronal maps generated by pacing from three different locations relative to the array. Based on relative activation times, conduction velocity across the array (transverse to fiber axis) was 0.9 mm/msec (Figure 4e); the velocity in the longitudinal direction (approximately parallel to the orientation of the LAD) was faster by a factor of 3 (Figure 17b). These results are consistent with anisotropic conduction properties measured in previous studies. Figure 18 shows the same paced voltage data as in the right panel of Figure 4e for all channels taken at 4 instants in time. Figure 23 and Figure 24 show sample voltage data used to generate the isochronal map in the left and right panels of Figure 4e, respectively. Figure 4f shows sample distance vs. activation plots for selected rows of the electrode array following the arrows in Figure 4e.

[0130] Collectively, these results represent mapping of electrical activity in the heart at unprecedented rates and levels of spatial and temporal resolution. This approach of conformal, integrated circuits for a new form of biointerfaced elec-

tronics provides a fundamentally new way to measure electrical processes in or on the body, with many clinically important implications. Specifically for the system introduced here, the high temporal and spatial resolution should improve accuracy and reduce mapping time for many cardiac arrhythmias. The more general benefit of these technologies, in the broadest sense, is the capacity to integrate the full power of silicon-based electronics technology for multiple modalities of sensing and energy delivery on a single conformable device. For example, multi-site cardiac pacing with closed-loop feedback of local ventricular contractility or cardiac output measurements via distributed arrays of active sensory and stimulation electrodes could form the basis of an entirely new class of assistive synchronization devices in cardiology. Furthermore, the mechanical properties of the circuits permit packaging in catheter-based delivery systems, with the ability to deploy on and conform to large, irregular curvilinear surfaces of the body. Pursuing these and related ideas using the materials and electronics strategies reported here has great potential to yield technologies with important benefits to human health.

[0131] METHODS. Circuit design. Each unit cell incorporates an nMOS based source-follower amplifier configuration. This circuit provides significant current gain to enable fast switching of the multiplexers by supplying the current needed to charge the parasitic output capacitances. These parasitics come from several sources, including the inactive multiplexing transistors in a given column, the ~2 foot long cables that connect the electrode array to the interface circuit board, the circuit board itself and the input capacitance of its buffer amplifiers.

[0132] Circuit fabrication. The fabrication starts with the preparation of the polyimide substrate (25 μm; Kapton, Dupont, USA). For ease of handling, a sheet of this material was attached to a glass slide coated with a thin layer of poly(dimethylsiloxane) as a soft adhesive. Separately doped silicon nanoribbons were prepared through a high temperature diffusion process using a p-type silicon-on-insulator (SOI) wafer (Si(260 nm)/SiO_2(1000 nm)/Si; SOITEC, France) and phosphorous spin-on-dopant (SOD) (P509, Filmtronics, USA). A 300 nm thick layer of SiO_2 deposited by plasma enhanced chemical vapor deposition (PECVD) served as the diffusion barrier mask. Doping regions were defined through conventional photolithography and CF_4/O_2 reactive ion etching (RIE). The diffusion was performed at 950~1000 °C in a rapid thermal annealing (RTA) system. A series of wet etching steps with HF and piranha solution (H_2O_2 and H_2SO_4 mixture) removed the SOD and SiO_2.

[0133] Doped nanomembranes derived by patterned etching of the top silicon layer of the SOI wafer were transfer printed onto the polyimide substrate using a thin, spin cast layer of a precursor to polyimide as an adhesive. To prepare the structures for transfer, the buried SiO_2 layer was etched away with concentrated HF solution to yield freestanding nanomembranes. The polyimide precursor was cured at 300 °C for 1 h immediately after printing. Further isolation of the active Si components, such as source, drain and channel regions, was accomplished by photolithography and reactive ion etching with SF_6. A thin gate oxide of SiO_2 (~100 nm) was then deposited by PECVD. The source/drain contact regions were opened with buffered oxide etchant through a photolithographically patterned mask. The gate electrodes and metal interconnects were deposited by electron evaporation of Cr/Au (~5 nm/~145 nm) and patterned through wet etching. Each unit cell contains 7 transistors, interconnected by wiring as described in the main text. Isolation of the metal layers was accomplished with a polyimide interlayer dielectric with thickness of 1.4 μm. Connections between layers were established through holes defined by patterned reactive ion etching with O_2. A stack of organic/inorganic insulation layers followed by encapsulation with a photocurable epoxy (SU8, Microchem Corp) formed a water-tight seal, as described above. The flexible heat seal connector was used to connect the electrodes with the data acquisition system. After aligning the connector to gold pads at the periphery of the circuit, the application of heat (~170 °C) and pressure (applied with clips) for 15 min. formed low resistance and strong connection between the conductive film and the electrode array. The other side of flexible conductive film was connected to an adapter circuit board. The design of this adapter board is shown in Figure 19.

[0134] Acquisition system. The adapter circuit board was connected via a standard 40 pin ribbon cable to the main interface circuit board shown in Figure 20. This custom circuit board provided the row select signals from to the electrode array and provided buffering of the analog output signals from the array. The buffering was accomplished by TLC2274 op-amps (Texas Instruments). This stage of buffering further reduced the output impedance to allow for longer cable runs and improved switching speed. The outputs of this circuit board were connected to National Instruments PXI-6281 and USB-6259 high-speed M Series multifunction data acquisition (DAQ) modules via standard BNC cables. The National Instruments DAQ modules were used to generate the row select signals and to sample the multiplexed analog output signals from the electrode array. In total, 18 analog input channels were used.

[0135] Circuit Simulation. Simulations were performed using Cadence's "spectreS" simulator. The "NCSU_TechLib_ami06" tech library was used for all of the transistors.

[0136] Animal experiments. The array was placed on the heart of an adult pig and conformed to the epicardial surface, including epicardial coronary vessels (Figure 3). Initially, the array was positioned between the epicardium and parietal pericardium, where it was demonstrated to slide easily across the surface of the heart. Subsequently, the parietal pericardium was removed, and the array was left to stay in position via surface tension alone.

[0137] **Supplementary Methods.** Nearly all of the materials and methods relied on specialized setups specifically designed for this project, including many of the planar processing steps and transfer printing processes, the encapsulation strategies, the circuit designs and acquisition system, the methods for interconnection and readout and the mechanics

analysis. The following describes additional details on certain aspects.

[0138] Fabrication sequence. The steps, outlined above, were implemented using a mask set illustrated in Figures 5 and 6. In Figure 5, the green boxes correspond to the isolated silicon active regions that are connected by pink color first metal layer. After spin coating of PI interlayer dielectric and following dry etching for via, first metal layers are connected to yellow color second metal layer through purple color first via, which finishes the device fabrication process, as shown in Figure 5.

[0139] Since the measurement environment is wet and contains large amount of ions due to the saline solution, a multilayer insulation strategy is required to prevent the leakage current that may cause electrical shock to the test animal. The inorganic/organic multilayer and additional thick organic insulation layer were used for this passivation, as shown in Figures 7 and 8. Figure 7 shows the overall design and Figure 8 describes step by step encapsulation process. Another aspect of the encapsulation design is the misaligned via structure, between via 2 and via 3. By the intentional misalignment of the vias, the first via can be completely covered by the final epoxy layer.

[0140] Interconnection scheme. After the device fabrication, the flexible sensor can be interconnected to the circuit board through a flexible ACF film. For this connection, heat and pressure should be applied. After alignment between ACF film and the sample, clipping with conventional metal clips provide enough pressure for the connection. To prevent mechanical failure in samples during clipping and to spread pressure over the whole connection area, a piece of PDMS and glass can be added, as shown in Figure 10a. After clipping, heating at 180 °C for 15 min. results in a good connection between the metal and ACF film. The image before and after the heal seal connection is shown in Figures 10b and 10c.

[0141] Data processing. Data from all channels were high pass filtered at 1 Hz and 20 times up-sampled to 12.5 kHz sampling rate before processing. After up-sampling the data were smoothed and demeaned to remove the DC bias. An average signal was constructed and the derivative was taken to identify the relative activation times using an automatic peak search algorithm.

[0142] Mechanics of the circuit wrapping on a curved surface. For a thin film of length L and bending stiffness B wrapping on a cylinder of radius R, as shown in Figure 13a, the total energy of the wrapped state is composed of two parts, the bending energy in the thin film U_b and the adhesion energy U_a between the thin film and the cylinder. The bending energy in the thin film is

$$\frac{1}{2}U_b = \frac{1}{2}B\kappa^2 L = \frac{B}{2R^2}L. \quad \text{(III)}$$

[0143] The adhesion energy is

$$\frac{1}{2}U_a = -\gamma L, \quad \text{(IV)}$$

[0144] where γ is the adhesion energy (per unit area) between the thin film and the cylinder. If $U_b + U_a < 0$ (the unwrapped state has energy of 0), the wrapped state is energetically favorable, and thus the thin film wraps around the cylinder. This gives

$$\gamma > \frac{B}{2R^2}. \quad \text{(V)}$$

[0145] The cross sectional layout of the circuit, which will be used to determine the bending stiffness B, is shown in Figure 13b. The top SU8 layer has a thickness h_1 = 18 μm, Young's modulus E_{SU8} = 5.6 GPa and Poisson's ratio v_{SU8} = 0.22. The bottom PI layer has a thickness h_2 = 25 μm, Young's modulus E_{PI} = 3.4 GPa and Poisson's ratio v_{PI} = 0.34. The middle layer, of thickness ~ 5 μm, is composed of several different components. The material and thickness of each component is shown in Figure 13b, and their Young's moduli are: E_{Si} = 150 GPa, E_{SiO2} = 72 GPa, E_{Au} = 78 GPa, E_{Si3N4} = 194 GPa. Since each of these components only occupies a small portion of each layer of material, the position of the mechanical neutral axis can be approximately obtained as (within a few percent error)

$$y_0 = \frac{1}{2}\frac{\bar{E}_{PI}h_2^2 + \bar{E}_{SU8}h_1(2h_2 + h_1)}{\bar{E}_{PI}h_2 + \bar{E}_{SU8}h_1}, \quad \text{(VI)}$$

where $\overline{E}_{PI} = E_{PI}/(1-\nu_{PI}^2)$ and $\overline{E}_{SU8} = E_{SU8}/(1-\nu_{SU8}^2)$ are the plain strain moduli of PI and SU8, respectively. The bending stiffness of the circuit is

$$B = \overline{E}_{PI} h_2 \left(\frac{1}{3} h_2^2 - h_2 y_0 + y_0^2 \right) + \overline{E}_{SU8} h_1 \left[\frac{1}{3} h_1^2 + h_1 (h_2 - y_0) + (h_2 - y_0)^2 \right]. \quad \text{(VII)}$$

[0146] The strain at a point of coordinate *y* is given by

$$\varepsilon = \frac{y - y_0}{R_b}, \quad \text{(VIII)}$$

where *Rb* is the bending radius of curvature of the circuit. The position of the mechanical neutral axis is calculated as y_0 = 26.5 μm. With the bending stiffness given by Eq. (VII), Eq. (VIII) gives γ > 8.7 mJ/m^2. For a bending radius R_b = 5 cm, the maximum strain in the Si and SiO_2 is ~0.001% and ~0.0001%, respectively; the strains in the four Au layers are ~0.001%, 0.004%, 0.03% and 0.05%, respectively.

FIGURE CAPTIONS

[0147] Figure 1. Schematic illustration and images corresponding to steps for fabricating active, conformal electronics for cardiac electrophysiology mapping, and photograph of a completed device. Figure 1a, Schematic illustration (left) and optical micrograph (right) of a collection of doped silicon nanomembranes at a unit cell. Figure 1b, Configuration after fabrication of the source, drain and gate contacts, with suitable interconnects and row electrodes for multiplexed addressing. Figure 1c, Configuration after fabrication of the second metal layer, including the column output electrodes. Annotations in the image on the right indicate the multiplexing transistor and the various components of the amplifier. Figure 1d, Final layout after deposition of encapsulation layers and fabrication of the contact electrode that provides the interface to the cardiac tissue. Figure 1e, Photograph of a completed device, in a slightly bent state. The inset at the bottom provides a magnified view of a pair of unit cells.

[0148] Figure 2. Design and electrical properties of an active, flexible device for cardiac electrophysiology mapping. Figure 2a, Circuit diagram for a unit cell, with annotations corresponding to those in Figure 1 c. Figure 2b, Circuit diagram of four unit cells, indicating the scheme for multiplexed addressing. Figure 2c, Current-voltage characteristics of a representative multiplexing transistor. Figure 2d, Frequency response of a representative amplifier. Figure 2e, Representative multiplexer switching response, showing the row select signals, column output and simulated column output. The response time is limited by the external row select signal slew rate. Figure 2f, Average percentage settled to final value for increasing single electrode sampling rate, indicating the maximum useable multiplexing rate is approximately 200 kHz. Figure 2g, Photograph of a completed device with ACF interconnect, immersed in a saline solution. Figure 2h, Sine wave response (at 20 Hz) before and after saline immersion for 10 minutes.

[0149] Figure 3. Photographs of a flexible EP mapping device in use on a porcine animal model. Figure 3a, Photograph of flexible device conforming to the cardiac tissue via surface tension. The inset provides a magnified image at a different viewing angle. Figure 3b, Sequence of movie frames collected at different times during the contraction cycle of the heart, illustrating the ability of the device to bend in a way that maintains intimate, conformal contact with the tissue during cardiac rhythm. Blue lines pasted on image highlights the degree of bending along the device. A conventional pacing electrode is indicated in the left frame (white arrow). Figure 3c, Photograph of a device on the left anterior descending (LAD) coronary artery, with overlaid color map of the relative time of depolarization from paced activation. The white arrow in the lower left indicates the source of the pacing and the red colors in the activation map indicate the areas of earliest response.

[0150] Figure 4. Representative data recorded from a porcine animal model using a flexible EP mapping device. Figure 4a, Representative single voltage trace without external pacing. (Inset) Magnified view of the system noise. The black arrow indicates the source of the inset data. The signal to noise ratio (SNR) of the recorded signal was approximately 50. Figure 4b, Representative voltage data for all electrodes at 4 points in time showing un-paced cardiac wave front propagation. Voltage is plotted using the colour scale in the right corner. Figure 4c, Average voltage from all electrodes illustrating the point in time that each frame in Figure 4b was taken. The colour of the dotted lines corresponds to the colour of the time label in Figure 4b. Figure 4d, Representative single voltage trace with external pacing from a standard clinical electrode. The black arrow and box highlight the pacing artifact. Note that negative is plotted up by convention in Figures 4a, 4c and 4d. Figure 4e, Color map of relative activation times for two different external pacing sites. The

activation times are plotted using the color bar shown at the right. Asterisks (*) indicate the relative location of the external pacing electrode. The scale bar illustrates the spacing between electrode locations. The data from the activation map at the locations marked by lines i - iii are plotted below in Figure 4f. Figure 4f, Distance vs. activation delay plots for selected rows of the electrode array following the arrows in Figure 4e.

[0151] Figure 5. Schematic illustration corresponding to steps for fabricating active, conformal electronics for cardiac electrophysiology mapping. Nine unit cells are shown to illustrate their interconnection at each metal level.

[0152] Figure 6. Magnified view of a completed device, in a slightly bent state to illustrate detail.

[0153] Figure 7. Physical layout of a single unit cell showing the additional insulation layers added to prevent leakage current in saline solution.

[0154] Figure 8. Sequential process of trilayer organic/inorganic stack fabrication.

[0155] Figure 9. Optical microscope image of a single unit cell with completed insulation layers.

[0156] Figure 10. a) Schematic diagram of ACF connection process. Image of flexible electrode array, ACF film and the circuit board before b) and after c) heat seal connection.

[0157] Figure 11. Image of acquisition system during the animal experiment: a) front view, b) side view.

[0158] Figure 12. Signal to noise ratio dependence on multiplexing frequency for a 20 Hz test signal.

[0159] Figure 13. Schematic diagram of wrapping model a) and cross-sectional view of sensor b).

[0160] Figure 14. Sine wave measurement before and after immersion into the saline solution: 4Hz a) and 40Hz b).

[0161] Figure 15. Image of experiment with porcine animal model a) and photograph of flexible device conforming to the cardiac tissue via surface tension b).

[0162] Figure 16. Colour map illustrating the amplitude uniformity of all of the channels by plotting the average peak amplitude of the cardiac activation cycle.

[0163] Figure 17. Isochronal activation map without a) and with b) pacing. The relative pacing electrode location is indicated by an asterisk (*).

[0164] Figure 18. Representative voltage data for all electrodes at 4 points in time showing paced cardiac wave front propagation. The relative pacing electrode location is indicated by an asterisk (*). Voltage is plotted using the colour scale in the right corner. The bottom frame shows the average voltage from all electrodes. The dashed colour lines illustrate the points in time that each frame was taken. Note that negative is plotted up by convention.

[0165] Figure 19. Design of the adapter circuit board which adapts the ACF ribbon to a 40 pin connector.

[0166] Figure 20. Design of the main interface circuit board which connects the 40 pin ribbon cable to the acquisition system.

[0167] Figure 21. Animal experiment.

[0168] Figure 22. Unpaced voltage data from all electrodes illustrating the natural activation pattern of the heart. The bottom frame shows an average ECG signal composed of all of the above channels along with a guide bar to show the current position in the voltage trace. Four frames from this movie are presented in Figure 4b.

[0169] Figure 23. Voltage data from all electrodes illustrating the paced activation pattern of the heart. The asterisk (*) indicates the relative position of the pacing electrode. The bottom frame shows an average ECG signal composed of all of the above channels along with a guide bar to show the current position in the voltage trace. Data from this interval in the recording were processed to create the isochronal map shown in the left frame of Figure 4e.

[0170] Figure 24. Voltage data from all electrodes illustrating the paced activation pattern of the heart. The asterisk (*) indicates the relative position of the pacing electrode. The bottom frame shows an average ECG signal composed of all of the above channels along with a guide bar to show the current position in the voltage trace. Data from this interval in the recording were processed to create the isochronal map shown in the right frame of Figure 4e. Four frames from this movie are presented in Figure 18.

EXAMPLE 2: Multilayer Encapsulation for Enhanced Moisture Barrier

[0171] One advantage achieved by encapsulation is prevention of leakage current from electronic circuitry to a surrounding conductive solution, such as saline solution, while the contact type metal electrode that is connected to the gate of load transistor is exposed to the surface to make a conformal and intimate contact to the curvilinear, soft cardiac tissue. This example describes a multilayer encapsulation structure to enhance prevention of leakage current.

[0172] Multiple Layer Structure with Mis-aligned Via Structure. The encapsulation can be a single polymer layer or in can be a multilayer structure. If a single polymer layer (e.g., ~20 μm) is used, pinholes can form following a dry etching process for via interconnect due to incomplete masking. Such pinholes can be prevented, for example, if a photo-definable thick polymer, such as SU8, is used, since the etching process is not needed. For a one layer structure, a mis-aligned via structure is not typically use. Use of a single via structure for some device applications may increase the chance of leakage through the contact region where the metal electrode and the gate of the transistor are connected. Therefore, even though a very thick polymer layer is used, this contact region may not be thoroughly protected with a single polymer layer/via structure. Figure 25a illustrates a single encapsulation layer with an electrode element connected

to the gate of a transistor with a single via structure.

[0173] To solve this problem, a multilayer encapsulation with a mis-aligned via structure can be used, as illustrated in Figure 25b. In this structure, the contact region is encapsulated with another layer of polymer, leading to a reduced chance of leakage. For example, instead of thick one polymer layer (-20 μm), two layers of polymer (~10 μm each) can be used and the second layer can fill the first via and protect the contact region between the electrode and load transistor.

[0174] Even with the two layer structure described above, however, it is possible that delamination between two layers, especially between a metal and a polymer layer, can induce leakage current to flow along the interface between these two layers. To minimize this possibility, multiple mis-aligned via structure can be used. For example, three 7 μm polymer layers or four 5 μm polymer layers can be used. For any multilayer structure such as these, all vias for each layer should be misaligned.

[0175] Thickness of Encapsulation Layer (Neutral Mechanical Plane (NMP) Design. Thicker encapsulation layers generally provide better leakage prevention. However, a deformable (e.g., flexible, bendable) system needs to consider the induced strain during deformation. To reduce unwanted mechanical fracture of inorganic materials, such as silicon, the device layer should be located near the neutral mechanical plane. Therefore, the top encapsulation layer thickness can be determined depending on the substrate thickness and material property, such as modulus.

[0176] Material of Encapsulant - Inorganic/Organic multilayer. To enhance flexibility, a thinner substrate is used in some embodiments; to place the device layer at the NMP, and optionally a thinner encapsulation layer is also used. However, the thinner the polymer layer, the higher the risk for pinholes or defects and, therefore, the potential for increased leakage current. In addition, since the micro structure certain polymers is composed of fibers, the penetration of ionic fluid through gaps between each polymer fiber, in the case of a thin polymer layer, can result in increased leakage current. To prevent this kind of leakage, while maintaining thin thickness, very thin (~50nm) inorganic layers, such as silicon nitride, can be inserted between each organic layer. This inorganic/organic multilayer effectively prevents the leakage current caused by ionic fluid penetrating through the organic polymer layers.

[0177] A further method for reducing pinholes or defects in an organic or polymer material includes reflowing during curing of the polymer.

[0178] Table 1 summarizes encapsulation considerations for some embodiments.

Table 1.

Factor	Exemplary Configuration or Considerations
Electrical leakage	<10 μA
Total encapsulant thickness	Encapsulation thickness/substrate thickness : 0.5 - 2 (0.5 - 2 thickness ratio in the case of the same material with the substrate.) (If different material, modulus of both materials may be considered to locate NMP near device layers.)
Substrate thickness	- Active electronics: 5 μm - 30 μm - Passive electronics: 1 μm - 30 μm
Bending stiffness	$<10^8$ GPa μm^4
Number of misaligned vias	>1
Organic/inorganic thickness	Organic: 1 μm - 20 μm, Inorganic: 10 nm - 500nm
Modulus of organic material	0.5 MPa ~ 5 GPa

[0179] Flexible vs. Stretchable. The above descriptions of this example are generally useful for flexible systems, though they can also apply to stretchable systems. An alternative approach for stretchable systems utilizes, for example, island and bridge structures, such as serpentine bridges. The encapsulation, however, should be similar, since the encapsulation layer for an island should parallel the flexible system. One additional aspect of the stretchable system is the passivation of a serpentine bridge sidewall. After dry etching to make a serpentine structure, for example, the sidewalls of serpentine metal interconnects are exposed. Even with a small amount of delamination between multilayers of a serpentine bridge during stretching deformation, large leakage currents can be generated from the metal interconnects. To prevent leakage, the margin from the edge of the metal interconnect can be increased. Additionally, the side wall can be passivated with another layer of polymer after etching.

EXAMPLE 3: Schematic of a Conformal Electronic Device for Sensing or Actuation

[0180] Figure 26A provides a schematic illustration of a cross sectional view of a conformal electronic device embod-

iment for sensing or actuation of a tissue in a biological environment. Conformable device **100** comprises flexible or stretchable substrate **110** supporting a flexible or stretchable electronic circuit comprising plurality of inorganic semiconductor circuit elements **120,** such as electronic device components including sensors, actuators, electrode arrays, LED arrays, optical sources, integrated circuits, multiplexing circuits and/or amplifiers. Barrier layer **130** encapsulating at least a portion of the flexible or stretchable electronic circuit may provide a moisture barrier, a thermal barrier, an electromagnetic barrier, an electrical barrier, a magnetic barrier, a selectively permeable or impermeable barrier or any combination of these. In some embodiments, the flexible substrate, the flexible or stretchable electronic circuit and the barrier layer provide a net bending stiffness or flexural rigidity of the device low enough that the device establishes conformal contact with the tissue in the biological environment. In some embodiments, conformal contact is established between external surface **135** of the device **100** and a tissue in a biological environment.

[0181] Optionally, the conformal device **100** further comprises a controller **155** in communication with the flexible or stretchable electronic circuit comprising plurality of inorganic semiconductor circuit elements **120,** for example one way or two way communication as shown by the arrows indicated in Figure 26A and 26B. In an embodiment, controller **155** is provided in electrical communication or wireless communication, and optionally is positioned away from the tissue interface. In some embodiments, controller **155** is configured to receive input signals **156** from the electronic circuit that correspond to measurements of one or more sensed parameters, such as time information, tissue properties (e.g., position, composition, movement, electronic, chemical, optical, temperature, etc.), or other properties of the biological environment. Input signals **156** may represent raw data or processed data, optionally in the form of a measurement. In some embodiments, controller **155** is configured to provide output signals **157** to the electronic circuit that correspond to one or more control parameters, such as control signals for controlling the sensing and or actuation of the tissue, including one or more time parameter, electronic parameter, optical parameter, etc. In an embodiment, controller **155** is a processor that receives and analyzes input signals **156** and generates output signals **157** based at least in part on the input signals **156.** In an embodiment, controller uses input signals **156** and output signals **157** to provide close-loop control of sensing or actuation of the tissue.

[0182] In some embodiments, the physical dimensions and material properties of flexible substrate **110** and barrier layer **130** are selected such that the semiconductor circuit elements **120** of the flexible or stretchable electronic circuit are provide proximate to the neutral mechanical plane of the device (illustrated by thick dotted line, drawing element **150).** Optionally, device **100** further comprises one or more additional electronic device components **140** not encapsulated by barrier layer **130,** optionally provided in physical and/or electrical contact with the target tissue in the biological environment. Additional electronic device components **140** useful in some embodiments, include sensors and actuators such as electrodes, voltage sensing or actuating elements, current sensing or actuating elements, optical sensors or actuators, temperature sensors or actuators, pH sensors, chemical or biological sensors, capacitive sensors, electrode elements, photodiodes, thermistors strain sensors, acceleration sensors, movement sensors, and displacement sensors or actuators.

[0183] Figure 26B provides a schematic illustration of a cross sectional view of a conformal electronic device having a barrier layer comprising a multilayer structure. As shown in Figure 26B, barrier layer **130** comprises a sequence of individual layers **130a - 130e.** In some embodiments, individual layers **130a -130e** comprise a sequence of layer selected from the group consisting of polymer layers, inorganic layers (e.g., inorganic dielectric materials such as an oxide, carbide or nitride, etc.) and metal layers. In some embodiments, individual layers **130a - 130e** comprise a sequence of thin film structures, for example, thin film structures fabricated by deposition (e.g., evaporative, sputtering, etc.) or coating techniques. In some embodiments, individual layers **130a - 130e** comprise a sequence of thin film structures including at least one metal thin film and at least one dielectric thin film, and optionally at least one polymer thin film.

EXAMPLE 4: Waterproof AlInGaP Optoelectronics with Application Examples in Biomedicine and Robotics

[0184] This example explores new areas and implements mechanically optimized layouts to achieve arrays of inorganic LEDs and PDs in systems that can accommodate extreme modes of mechanical deformation, for integration on substrates of diverse materials and formats. Additionally, materials and design strategies allow operation even upon complete immersion in saline solutions, biofluids, solutions of relevance to clinical medicine and soapy water, thereby opening new and unconventional opportunities for seamless integration of opotelectronics with biomedical and robotic systems. Thin implantable sheets (i.e. LED tattoos provide an example). Specifically, this example describes advances, in the following order: (1) experimental and theoretical aspects of mechanical designs that enable freely deformable, interconnected collections of LEDs and PDs on soft, elastomeric membranes, bands and coatings, (2) strategies for achieving high effective fill factors in these systems, using laminated multilayer constructs, (3) device examples on diverse substrates and in varied geometrical forms, (4) low modulus, biocompatible encapsulation materials that preserve key mechanical properties and, at the same time, enable robust operation when integrated on or implanted in living systems, (5) flexible optoelectronic components for biomedicine, with in vivo demonstrations on animal models.

[0185] For active materials, thin epitaxial semiconductor layers grown on GaAs wafers are prepared, and then vertically

etched to define lateral dimensions of devices built with them. Release from the wafer via selective elimination of an underlying layer of AlAs, followed by transfer printing accomplishes integration on substrates of interest. The fabrication scheme described here uses a dual transfer process that involves first printing the semiconductor materials to a temporary substrate (glass plate coated with a trilayer of epoxy / polyimide (PI) / poly(methylmethacrylate) (PMMA)) for forming contacts, interconnections and structural bridges, and encapsulation layers. Dissolving the PMMA releases fully formed, interconnected collections of devices. A second transfer printing step achieves integration on elastomeric sheets (e.g. poly(dimethylsiloxane), PDMS) or other substrates coated with thin layers of PDMS, with strong bonding only at the locations of the devices. For all examples described in this example, the LEDs (referred to herein as μ-ILEDs to highlight the small sizes and the distinction over organic devices), and the PDs (i.e. μ-IPDs) have lateral dimensions of 100×100 μm and thicknesses of 2.5 μm, corresponding to volumes that are orders of magnitude smaller than those of commercially available devices. The thin geometries are important because they allow the use of thin film metallization for interconnect and optimized mechanical designs, described next. Details of the processing and layouts appear in Figures 33-35.

[0186] Figures 27a and 36 present optical images, schematic illustrations, scanning electron microscope (SEM) images, and finite element modeling of the mechanics of arrays of μ-ILEDs connected by serpentine shaped ribbons that serve as either structural bridges or electrical interconnects, transferred to a thin, pre-strained sheet of PDMS (~400 μm thick). Here, and as described below, the devices are connected in series (Figure 32a), such that all of them turn on and off together; a single failed device leads to failure of the entire array. The interconnects consist of thin films of metal with photodefined layers of epoxy on top and bottom to locate the metal at the neutral mechanical plane. The bridges are similar, but without the metal. Detailed geometries appear in Figure 33. Releasing the pre-strain yields non-coplanar layouts in the serpentines via a controlled, non-linear buckling response, as shown in the left frame of Figure 27a (~20% pre-strain). The right frame and inset of Figure 27a present a schematic illustration and magnified optical image of a representative μ-ILED, respectively. These design choices are informed by careful studies of the mechanics through three dimensional finite element modeling (3D-FEM) of the complete systems; they represent highly optimized, versions of those used for silicon circuits and μ-ILEDs. The results enable stable and robust operation during large scale uniaxial, biaxial, shear and other mixed modes of deformation, as described in the following.

[0187] Figures 34a and 35a show tilted view scanning electron microscope (SEM) images and corresponding optical microscope images of adjacent μ-ILEDs and non-coplanar serpentine interconnects formed with ~20% biaxial pre-strain before (left) and after (right) uniaxial stretching (~60%), respectively. The separations between adjacent pixels change by an amount expected from the pre-strain and the applied strain, where a combination of in- and out-of-plane conformational changes in the serpentines accommodate the resulting deformations in a way that avoids any significant strains at the positions of the μ-ILEDs. In particular, 3D-FEM modeling results (Figure 34b) reveal peak strains in the metal interconnect and the μ-ILEDs that are >300 times smaller than the applied strain (Figure 35c shows similar results for ~59% stretching along the diagonal direction, corresponding to Figure 35b). Figures 27b and 36 present two dimensional, in-plane stretching of a 6×6 array of μ-ILEDs along horizontal (left) and diagonal (right) directions. The uniform and constant operating characteristics of all devices are clearly apparent in the dark and bright (without and with external illumination) images of Figure 27b and Figure 36 as well as in the current-voltage (I-V) characteristics (left frame of Figure 27c). The applied strains, calculated from the separations of inner edges of adjacent pixels before and after stretching, reach ~48% and ~46% along the horizontal and diagonal directions, respectively. The I-V characteristics are invariant even after 100000 cycles of 75% stretching along the horizontal direction (right frame of Figure 27c).

[0188] Uniaxial stretching and compressing are among the simplest modes of deformation. Others of interest include biaxial, shear and related. The results of Figures 27d-g, and 37 demonstrate the ability of the reported designs to allow these sorts of motions, through large strains induced by pneumatic pressure, achieved by inflation of a thin (500 μm) membrane of PDMS that supports an array similar to that of Figure 27b. Injecting air through a syringe in a specially designed cylinder that serves as a mount for the device deforms the initially flat array (top frame of Figure 27d) into a balloon shape (bottom frame of Figure 27d). Figure 27e shows four pixels in the 'flat' (top) and 'inflated' states (bottom) during operation, with external illumination. The area expansion induced in this manner can reach ~85% without any device failures. The I-V characteristics also show no appreciable differences between the flat and inflated states (Figure 27f). 3D-FEM is used to model the inflation induced deformation of a circular elastomeric membrane, with the same thickness (500 μm) and diameter (20 mm) as in experiment, but without a mounted μ-ILED array. As illustrated in Figures 27g and 37c, both the circumferential and meridional strains reach ~37.3% when inflated to a height of 8.3 mm, the same as in the bottom frame of Figure 27d. Measured displacements of devices in the system of the bottom frame of Figure 27e indicate strains of ~36%, which are comparable to values calculated by 3D-FEM. This observation suggests an important conclusion: with the designs reported here, the arrays provide negligible mechanical loading of the soft, elastomeric membrane support, consistent with the very low effective modulus provided by the optimized, non-coplanar serpentines.

[0189] Corkscrew twisting (Figure 28a) provides another well-defined mode of deformation that is of interest. Here, large shear strains occur in addition to stretching / compressing in the axial and width directions. The device test structure in this case consists of a 3x8 array of μ-ILEDs transferred to a band of PDMS without pre-strain (see Figure 38a for

details). Optical images of flat, 360°, and 720° twisting deformations with (left) and without (right) external illumination (Figure 28a) reveal uniform and invariant emission. These strains lead to out-of-plane motions of the serpentines, as shown in Figures 28b and 34b. The μ-ILEDs remain attached to the PDMS substrate due to their strong bonding. Electrical measurements indicate similar I-V characteristics with different twisting angles (Figure 28c) and at different stages of fatigue tests, as shown in Figure 38c. Figure 28d presents distributions of various strain components, evaluated at the surface of a band of PDMS with thickness 0.7 mm by 3D-FEM: axial stretching (left frame), width stretching (middle frame) and shear (right frame). (For 360° twisting, see Figure 39). The results demonstrate that the PDMS surface undergoes both extreme axial/width stretching and shear deformations, with shear dominating, and reaching values of ~40% for the 720° twist. As for the case of Figures 27d and 27g, the distributions of strain for the bare PDMS substrate can provide reasonably good estimates for the system. These controlled uniaxial (Figure 27b), biaxial (Figure 27d) and twisting (Figure 28a) modes suggest an ability to accommodate arbitrary deformations. As two examples, Figures 28e and 28f show cases of stretching onto the sharp tip of a pencil and wrapped onto a cotton swab. The array of 6×6 μ-ILEDs pulled onto the pencil (red arrows indicate stretching directions) experiences local, peak strains of up to ~100%, estimated from distances between adjacent devices in this region. Similar but milder and more spatially distributed deformations occur on the cotton swab, with an 8×8 array. In both cases, observation and measurement indicate invariant characteristics, without failures, even in fatigue tests.

[0190] A feature of the layouts that enable these responses is the relatively small area coverage of active devices, such that the serpentine structures can absorb most of the motions associated with applied strain. An associated disadvantage, for certain applications, is that only a small part of the overall system emits light. This limitation can be circumvented with layouts that consist of multilayer stacks of devices, in laminated configurations, with suitable spatial offsets between layers. The exploded view schematic illustration in Figure 29a shows this concept with four layers. Figure 41 provides details. Integration is accomplished with thin coatings of PDMS (~300 μm) that serve simultaneously as elastomeric interlayer dielectrics, encapsulants and adhesives. Here, each layer consists of a substrate of PDMS (300 μm thick) and an array of LEDs (total thickness with interconnect, ~8 μm). The total thickness of the four layer system, including interlayers of PDMS, is ~1.3 mm. Optical images of emission from a four layer system appear in Figure 29b (with external illumination) and Figure 41b (without external illumination). Figure 29c shows a two layer case, where each layer lights up in a different pattern. The inset on the right illustrates the same system in a bent state (bending radius = 2 mm), where the maximum strain in top and bottom GaAs layers is only 0.006% and 0.007%, respectively as shown by 3D-FEM simulation (Figure 42). The PDMS interlayers restrict the motion of the serpentines, but by an amount that reduces only slightly the overall deformability. The extent of free movement can be maximized by minimizing the modulus of the encapsulant. Here, PDMS was mixed in a ratio to yield a Young's modulus of ~0.1 MPa, to retain nearly ~90% of the stretchability of the unencapsulated case.

[0191] The favorable mechanical characteristics enable integration onto a variety of substrates that are incompatible with conventional optoelectronics. As demonstrations, μ-ILED devices were built on swatches of fabric (Figure 43a), tree leaves (Figure 43c), sheets of paper (Figure 29d), and pieces of aluminum foil (Figure 29e). In all cases, transfer printing successfully delivers the devices to these substrates with thin (-50 μm) coatings of PDMS that serve as planarizing and strain isolating layers, and as adhesives. Bending and folding tests for each case indicate robust operation under deformed states. The smallest bending radii explored experimentally were 4 mm, 2.5 mm, and 400 μm for the fabric, leaf, and paper, respectively. Theoretical modeling, using Young's moduli and thicknesses 1.2 MPa, 800 μm, 23.5 MPa, 500 μm, 600 MPa and 200 μm for the fabric, leaf and paper, respectively, shows that the fabric, leaf and paper can be completely folded, in the sense that the strain in the GaAs remains much smaller than its failure strain (~1%) even when the bend radius equals the substrate thickness. Without the strain isolation provided by the PDMS, the fabric can still be folded, but the leaf and paper can only be bent to minimal radii of 1.3 mm and 3.5 mm, respectively. This result occurs because the Young's modulus of PDMS (0.4 MPa) is much smaller than those of leaf and paper (i.e., strain isolation), while the Young's moduli of PDMS and fabric are more similar. Random wrinkling, including multi-directional folding with inward and outward bending can be accommodated, as is apparent in the devices on paper and aluminum foil (~30 μm). In images of the latter case (Figure 29e), the number density of wrinkles reaches ~200 per cm^2 with approximate radii of curvature as small as 150 μm (See Figures 43-45 for additional images, plots of I-V characteristics, results of fatigue tests, and surface topography of these substrates).

[0192] Figures 29f and 29g present images of an array of μ-ILEDs (1×8) with serpentine metal bridges and a single μ-ILED device with long (1.25 cm × 185 μm) metal interconnects, both on flexible, thin (~8 μm) ribbons mounted onto cylindrical supports. Alternatively, for longer term implantable applications, subdermal μ-ILEDs can overcome scattering limitations and bring in-vivo illumination to deep layers of tissue. This approach could yield capabilities complementary to those of fiber-optic probe-based medical spectroscopic methods, by enabling real-time evaluation of deep-tissue pathology while allowing precise delivery of radiation in programmable arrays. Such devices can be formed in geometries of strips or threads, or of sheets. As an example of the latter, the left frame of Figures 30a and 46 show a schematic exploded view and an illustration of fabrication procedures, respectively, for a 5×5 array of μ-ILEDs on a thin sheet of polyethylene terephthalate (PET; Grafix DURA-RAR, 50 μm thickness) film coated with an adhesive layer (epoxy) and

encapsulated on top and bottom with PDMS. Thin (~500 μm) ceramic insulated gold wires that connect to metal pads at the periphery of the array provide access to external power supplies. Figure 30b presents a picture of an animal model with the device implanted subdermally in direct contact with the underlying musculature (See methods section for details). The inset shows the same device before implantation. For continuous operation at the current levels reported here, peak increases in temperature at the tissue of a couple of degrees C are estimated. Short pulsed mode operation could further minimize the possibility of adverse thermal effects and also, at the same time, allow the use of phase-sensitive detection techniques for increasingly sophisticated diagnostics, imaging and physiological monitoring.

[0193] In summary, the advances described here in mechanics, high fill factor multilayer layouts and biocompatible designs provide important, unusual capabilities in inorganic optoelectronics, as demonstrated by successful integration onto various classes of substrate and by use in representative devices for biomedical and robotics applications.

[0194] **Methods.** Delineating Epitaxial Semiconductor Material for μ-ILEDs and μ-IPDs. For fabrication of the μ-ILEDs and μ-IPDs, the process began with epitaxial films that included a quantum well structure (4 x (6-nm-thick $Al_{0.25}Ga_{0.25}In_{0.5}P$ barriers / 6-nm-thick $In_{0.56}Ga_{0.44}P$ wells) / 6-nm-thick $Al_{0.25}Ga_{0.25}In_{0.5}P$ barriers) and an underlying sacrificial layer of $Al_{0.96}G_{0.04}As$ on a GaAs wafer. Details appear in Figure 31 a. Inductively coupled plasma reactive ion etching (ICP-RIE; Unaxis SLR 770 system) with Cl_2/H_2 through a hard mask of SiO_2 formed trenches down to the $Al_{0.96}G_{0.04}As$, to delineate active materials in 6x6 or 8x8 or 3x8 or 1x4 arrays of squares with sizes of 100 μm x 100 μm. Next, photolithography defined photoresist structures at the four corners of each square to hold the epitaxial layers to the underlying GaAs wafer during removal of the $Al_{0.96}G_{0.04}As$ with diluted hydrofluoric (HF, Transene, USA) acid (deionized water (DI): 49% HF acid = 1:100).

[0195] Fabricating Arrays of μ-ILEDs and μ-IPDs in Mesh Designs with Serpentine Interconnects on Glass Substrates. The released squares of epitaxial material formed according to procedures described above were transfer printed onto a glass substrate coated with layers of a photodefinable epoxy (SU8-2; Microchem.; 1.2 μm thick), polyimide (PI; Sigma-Aldrich; 1.2 μm thick), and poly(methylmethacrylate) (PMMA A2; Microchem.; 100 nm thick) from top to bottom. Next, another layer of epoxy (SU8-2, 2.0 μm) was spin-cast and then removed everywhere except from the sidewalls of the squares by reactive ion etching (RIE; PlasmaTherm 790 Series) to reduce the possibility of partial removal of the bottom n-GaAs layer during the 1 st step of an etching process (1st step: $H_3PO_4 : H_2O_2 : DI = 1 : 13 : 12$ for 25 seconds / 2nd step: $HCl : DI = 2 : 1$ for 15 seconds / 3rd step: $H_3PO_4 : H_2O_2 : DI = 1 : 13 : 12$ for 24 seconds) that exposed the bottom n-GaAs layer for n-contacts. Next, another layer of epoxy (1.2 μm thick) spin-cast and photopatterned to expose only certain regions of the top p-GaAs and bottom n-GaAs, provided access for metal contacts (non-Ohmic contacts) and interconnect lines (Cr / Au, 30 nm / 300 nm) deposited by electron beam evaporation and patterned by photolithography and etching. These lines connected devices in a given row in series, and adjacent rows in parallel. A final layer of spin cast epoxy (2.5 μm) placed the devices and metal interconnects near the neutral mechanical plane. Next, the underlying polymer layers (epoxy / PI / PMMA) were removed in regions not protected by a masking layer of SiO_2 (150 nm thick) by RIE (oxygen plasma, 20 sccm, 150 mtorr, 150 W, 40 min). Wet etching the remaining SiO_2 with buffered oxide etchant exposed the metal pads for electrical probing, thereby completing the processing of arrays of μ-ILEDs (and/or μ-IPDs) with serpentine interconnects.

[0196] Transfer Printing of Stretchable Arrays of Devices to Substrates of Interest. Dissolving the PMMA layer of the structure described above with acetone at 75 °C for 10 minutes released the interconnected array of devices from the glass substrate. Lifting the array onto a flat elastomeric stamp and then evaporating layers of Cr / SiO_2 (3 nm / 30 nm) selectively onto the backsides of the devices enabled strong adhesion to sheets or strips of PDMS or to other substrates coated with PDMS. For the PDMS balloon of Figure 27d, prestrain was applied by partially inflating the balloon, followed by transfer printing the μ-ILEDs and then releasing (deflating) the balloon. For small substrates, roller printing techniques were used. See below for details.

[0197] Stretching Tests and Electrical Characterization. Stretching tests were performed using custom assemblies of manually controlled mechanical stages, capable of applying strains along x, y, and diagonal directions. For fatigue testing, one cycle corresponds to deformation to a certain level and then return to the undeformed state. Each fatigue test was performed up to 1000 cycles to levels of strains similar to those shown in the various figures. Electrical measurements were conducted using a probe station (4155C; Agilent), by directly contacting metal pads while stretched, bent, or twisted. The measurement was performed using a lead-out conductor line, bonded to metal pads of the arrays of μ-ILEDs. Typical voltage scan ranges for measurement of the 6x6, 8x8, and 3x8 arrays was 0 ~ 60 V, 0 ~ 80V, and 0 ~ 90V, respectively.

[0198] Animal Experiments. All procedures were performed under approved animal protocols. A female Balb/c mouse was anesthetized with an intraperitoneal injection of a mix of ketamine/xylazine. The depth of anesthesia was monitored by palpebral and withdrawal reflexes to confirm that the animal had reached "stage 3" of anesthesia. Once the animal was lightly anesthetized, the back was shaved and cleaned at the incision site with 70% ethanol, followed by a betadine surgical scrub. Previous implants were removed from the mouse and the animal was euthanized according to approved protocols. For the implants, the incision was performed on the dorsal side of the mouse and the suturing was carried out across the dermal layers (outer layers and subcutaneous tissues) above the muscle tissue.

[0199] Photographs. Images in Figures 27a and 29e were combined images to eliminate out-focused regions. Tens of pictures were captured at different focal depths using a Canon 1Ds Mark III with a Canon MP-E 1-5x Macro lens, and those captured pictures are merged in the software "helicon focus" to create completely focused image from several partially focused images.

[0200] Figure Captions. Figure 27. Device layouts of μ-ILED arrays and their responses to uniaxial and balloon-shape biaxial stretching. Figure 27a, Optical image of a 6×6 array of μ-ILEDs (100 μm × 100 μm, and 2.5 μm thick, in an interconnected array with a pitch of ~830 μm) with non-coplanar serpentine bridges on a thin (~400 μm) PDMS substrate (left frame). Schematic illustration (right) and corresponding photograph (inset) of a representative device, with encapsulation. Figure 27b, Optical images of a stretchable 6x6 array of μ-ILEDs, showing uniform emission characteristics under different uniaxial applied strains (top left: 0%, bottom left: 48% along horizontal direction, top right: 0%, bottom right: 46% along diagonal direction). Figure 27c, Current-voltage (I-V) characteristics of this array measured in the strained configurations shown in b (left) and voltage at 20 μA current for different cycles of stretching to 75% along the horizontal direction (right). Figure 27d, Tilted (left) view optical images of a stretchable array (6×6) of μ-ILEDs on a thin (-500 μm) PDMS membrane in a flat configuration (top) and in a hemispherical, balloon state (bottom) induced by pneumatic pressure. Figure 27e, The magnified view of Figure 27d from the top. The yellow dashed boxes highlight the dimensional changes associated with the biaxial strain. Figure 27f, I-V characteristics of the array in its flat and inflated state. Figure 27g, Distribution of meridional and circumferential strains determined by 3D-FEM.

[0201] Figure 28. Responses of μ-ILED arrays to twisting and stretching on sharp tips. Figure 28a, Optical images of an array of μ-ILEDs (3×8) on a band of PDMS twisted to different angles (0° (flat), 360°, and 720° from top to bottom), collected with (left) and without (right) external illumination. Figure 28b, SEM image of the array when twisted to 360°. The serpentine interconnects move out of the plane (red box) to accommodate the induced strains. Figure 28c, I-V characteristics of the array twisted by various amounts (0 (flat), 360 and 720°). Figure 28d, Distributions of axial (left), width (center) and shear (right) strain determined by 3D-FEM for twisting to 720°. Figure 28e, Optical images of an array of μ-ILEDs (6×6), tightly stretched on the sharp tip of a pencil, collected with (left) and without (right) external illumination. The white arrows indicate the direction of stretching. Figure 28f, Optical images of a stretchable 8×8 array wrapped and stretched downward on the head of a cotton swab. The inset image was obtained without external illumination. Figure 28g, I-V characteristics of the array in Figure 28e, before (initial), during (deformed) and after (released) deformation. The inset provides a graph of the voltage needed to generate a current of 20 μA, measured after different numbers of cycles of deformation.

[0202] Figure 29. Multilayer laminated configurations of arrays of μ-ILEDs for high effective area coverage and integration on various unusual substrates. Figure 29a, Schematic, exploded view illustration for a stacked device formed by multilayer lamination. Figure 29b, Optical images of a four layer stack of 4x4 arrays with layer-to-layer offsets designed to minimize overlap of interconnect lines with positions of the μ-ILEDs. The images show emission with different numbers of layers in operation (1 st layer on, 1 st and 2nd layers on, 1 st, 2nd and 3rd layers on, and 1 st, 2nd, 3rd and 4th layers on). Figure 29c, Optical images of a two layer stack of 8×8 arrays, with different layers in operation. The inset shows the device in a bent state (bending radius ~2 mm) with both layers on. Figure 29d, Optical image of an array of μ-ILEDs (8×8) on a piece of paper, in a folded state (bending radius ~400 μm) during operation. The inset shows the device in its flat state. Figure 29e, Image of a 6×6 array on a sheet of aluminum foil under crumpled state. The inset shows the device in its flat state. Figure 29f, Images of a thin (~8 μm), narrow (820 μm) strip of μ-ILEDs (1~8) with serpentine interconnects on a rigid plastic tube (diameter ~2.0 mm, left). Inset shows the magnified view of a single pixel. Figure 29g, A thin strip LED device consisting of an isolated μ-ILED with straight interconnects wrapped around a glass tube (diameter ~5.0 mm, right). The insets provide a magnified view. Figure 29i, Image of a 1~8 array with serpentine metal bridges on a ~700 μm diameter fiber, wrapped around a glass tube (diameter ~1.4 mm, left frame) and, in a knotted state (inset), respectively, resting on coins (pennies) to set the scale.

[0203] Figure 30a, Schematic exploded view illustration of an array of μ-ILEDs (5~5) on a thin PET film (50 μm thick) coated with an adhesive. Layers of PDMS on the top and bottom provide a soft, elastomeric encapsulation that offers biocompatibility and an excellent barrier to biofluids and surrounding tissue. Figure 30b, Image of an animal model with this array implanted under the skin, and on top of the muscle tissue. The inset shows the device before implantation. Contact Scheme. Here, simple metal (Cr/Au) to doped GaAs contacts are used instead of ohmic contacts. For improved electrical characteristics, conventional ohmic contacts of metal interconnects to GaAs can be implemented. To form the ohmic contact, a series of metal stacks followed by appropriate annealing (n ohmic contact metals: Pd/Ge/Au followed by anneal at 175 °C for 1 hour, p ohmic contact metal: Pt/Ti/Pt/Au in this paper) can be used, which results in lower take-off voltage can be obtained as shown in Figure 47a.

[0204] Long-term operation. Long-term operation was tested using two LED devices, connected in series, on a thin slab of PDMS was performed under the constant current mode (0.75 mA). Both devices showed robust and reliable performance during the continuous operation for 100 hours without affecting I-V characteristics as shown in Figure 47b.

[0205] FEM Simulation of Balloon Deformation. Figure 48a illustrates the mechanics model for inflating and transfer printing onto the PDMS balloon of Figure 27. The initially flat, circular thin film (initial state, upper left frame of Figure

38a) of radius r is fixed at its outer boundary, and is inflated by air to a spherical cap of height h (inflated state, right frame of Figure 48a). The radius of the sphere is $R = (h^2 + r^2)/(2h)$. The spherical cap is pressed down and flattened during transfer printing, as shown in the lower left frame of Figure 48a (as-print state). The deformation is uniform along the meridional direction during inflation, while all material points move vertically downward during printing. Therefore, for a point of distance x_0 to the film center at the initial state, its position changes to x_1 in the inflated state with an arc distance s_1 to the film center, and then changes to x_2 in the state during printing, where $s_1 = (R_{x0}/r) \arcsin(r/R)$ and $x_1 = x_2 = R \sin[(x_0/r) \sin^{-1}(r/R)]$. These give the meridional and circumferential strains of the inflated state as:

$$\varepsilon_{\theta 1} = \frac{R}{r}\arcsin\frac{r}{R} - 1. \tag{S1}$$

$$\varepsilon_{\varphi 1} = \frac{R}{x_0}\sin\left(\frac{x_0}{r}\arcsin\frac{r}{R}\right) - 1. \tag{S2}$$

[0206] The meridional and circumferential strains at the state during printing are given by:

$$\varepsilon_{\theta 2} = \frac{R}{r}\cos\left(\frac{x_0}{r}\sin^{-1}\frac{r}{R}\right)\sin^{-1}\frac{r}{R} - 1, \tag{S3}$$

$$\varepsilon_{\varphi 2} = \frac{R}{x_0}\sin\left(\frac{x_0}{r}\sin^{-1}\frac{r}{R}\right) - 1. \tag{S4}$$

Finite element method (FEM) was used to study this process in order to validate the analytical model above. The contours of meridional and circumferential strains of the inflated state appear in the upper and lower left frames of Figure 48b, respectively. The results are compared with analytical solutions, Equations (S1) and (S2), in the right frame of Figure 48b, and show good agreement. Therefore, the analytical formulae, Equations (S1) and (S2), can be used to predict the PDMS strain under different inflation, and further to estimate the strain in devices on the balloon surface. Figure 48c shows the contours of meridional (upper left frame) and circumferential (lower left frame) strains of the asprint state, and the comparison with analytical solutions from Equations (S3) and (S4) (right frame). The analytical solutions, once again, agree well with FEM simulations without any parameter fitting.

[0207] Bending of LEDs on Various Substrates. The LED, as illustrated in Figure 49, consists of multiple layers with thicknesses $h_1 = 3.5$ μm, $h_2 = 2.5$ μm, $h_3 = 1.2$ μm and $h_4 = 1.2$ μm, and Young's moduli are $E_{SU8} = 5.6$ GPa, $E_{GaAs} = 85.5$ GPa and $E_{PI} = 3.2$ GPa. These layers are modeled as a composite beam with equivalent tensile and bending stiffnesses. The PDMS strain isolation layer has thickness $h_5 = 50$ um and Young's modulus E_{PDMS}=0.4 MPa. The Young's modulus E_{sub} and thickness H of the substrate are 1.2 MPa and 0.8 mm for the fabric, 23.5 MPa and 0.5 mm for the fallen leaf, and 600 MPa and 0.2 mm for the paper. The strain isolation model then gives very small maximum strains in GaAs, 0.043%, 0.082% and 0.23% for the completely folded fabric, leaf and paper, respectively. The minimal bend radii are the same as the corresponding substrate thicknesses H, i.e., 800 μm, 500 μm and 200 μm for the fabric, leaf and paper, respectively. For the Al foil substrate, the minimum bend radius is obtained as 139 μm when the strain in GaAs reaches 1%.

[0208] Without the PDMS strain isolation layer, the LED and substrate are modeled as a composite beam. The position of neutral axis (measured from the top surface) is given by:

$$y_0 = \frac{\left\{\begin{array}{l} E_{SU8}\left[(h_1+h_3)^2+2h_2h_3\right]+E_{PI}h_4(2h_1+2h_2+2h_3+h_4) \\ +E_{GaAs}h_2(2h_1+h_2)+E_{sub}H(2h_1+2h_2+2h_3+2h_4+H) \end{array}\right\}}{2\left[E_{SU8}(h_1+h_3)+E_{GaAs}h_2+E_{PI}h_4+E_{sub}H\right]}.$$

The maximum strain in GaAs is $\varepsilon_{GaAs} = \frac{1}{R_b}\max\left(\left|y_0-h_1\right|,\left|h_1+h_2-y_0\right|\right)$ where R_b is the bending radius. Therefore, the minimum bending radius of LED array on the substrate is $R_b = \frac{1}{\varepsilon_{failure}}\min\left(\left|y_0-h_1\right|,\left|h_1+h_2-y_0\right|\right)$, where $\varepsilon_{failure}$ = 1% is the failure strain of GaAs. For the fabric substrate, the maximum strain in GaAs is only 0.34% even when it is completely folded, which gives the minimum bending radius the same as the thickness 0.8 mm. For the fallen leaf and the paper, the minimum bending radii are 1.3 mm and 3.5 mm.

[0209] Figure Captions. Figure 33. Schematic illustration of epitaxial layer (a) and fabrication processes for μ-ILEDs arrays on a carrier glass substrate after transfer printing (b).

[0210] Figure 32. (a) Schematic illustration (left frame) and corresponding microscope (top right frame) and SEM (bottom right frame) images of a 6×6 μ-ILEDs on a handle glass substrate coated with layers of polymers (epoxy / PI / PMMA). (b) Schematic illustration (left frame) and corresponding microscope (top right frame) and optical (bottom right frame) images of a 6×6 μ-ILEDs array which is picked up with a PDMS stamp for transfer printing. A shadow mask for selective deposition of Cr/SiO_2 (thickness: 3nm/30nm) covers the retrieved array on a soft elastomeric PDMS stamp. (c) Schematic illustration of transfer printing to a pre-strained thin (thickness: ~400 μm) PDMS substrate (left frame) and microscope (top right frame) and SEM (bottom right frame) images of the transferred μ-ILEDs array on a prestrained thin PDMS substrate. Prestrain value was ~20%.

[0211] Figure 33. (a) Schematic illustration of top encapsulation layers indicating some of the key dimensions. (b) Schematic illustration of the cross sectional structure at an island, with approximate thicknesses for each layer. The inset corresponds to an SEM image of a μ-ILEDs array after transfer printing to a thin PDMS substrate with prestrain of ~20%. (c) Schematic illustration of the cross sectional structure at metal interconnection bridges, with approximate thicknesses of each layer.

[0212] Figure 34. (a) Tilted view SEM images of adjacent μ-ILEDs (yellow dashed boxes) before (left, formed with ~20% pre-strain) and after (right) stretching along the horizontal direction (red arrows). (b) Strain distributions determined by 3D-FEM for the cases corresponding to frames in (a). The black outlines indicate the positions of the devices and the serpentines before relaxing the pre-strain.

[0213] Figure 35. (a) Optical microscope images of two pixels in a μ-ILEDs array with a serpentine bridge design before (left frame) and after (right frame) external stretching along the horizontal direction. The upper and lower images show optical micrographs in emission light off (upper) and on (lower) states. The distance between adjacent pixels appears in the lower images and used for calculation of applied strains. The lower images were obtained without external illumination. (b) Optical micrograph images of two pixels in a μ-ILEDs array before (left frame) and after (right frame) external stretching along the diagonal direction. (c) FEM simulation under external stretching along the diagonal direction (left frame), and strain contours in the GaAs active island (top right frame) and the metal bridge (bottom right frame).

[0214] Figure 36. Optical images of a 6×6 μ-ILEDs array with a serpentine mesh design with external illumination under the same strain circumstances as Figure 27b.

[0215] Figure 37. (a) Optical image of an 8×8 μ-ILEDs array on a thin PDMS substrate in its on state, which is under the same kind of deformed condition as bottom left frame of Figure 27d. (b) Top view optical images of same array as Figure 27d in its 'flat' (left frame) and 'inflated' state (right frame) without external illumination. (c) Spatial distribution of FEM results of the right frame of Figure 27d and analytical solutions calculated from Equations (S1) and (S2).

[0216] Figure 38. (a) Schematic illustrations of a 3×8 μ-ILEDs array integrated on a thin PDMS substrate with detailed dimensions (upper frame: registrations of the μ-ILEDs on a PDMS donor substrate, lower frame: entire view of the printed 3×8 μ-ILEDs array). The inset on top represents an optical microscope image of this μ-ILEDs array on a handle glass substrate before transfer printing. (b) Magnified view of the SEM image in Figure 28b. The white dotted rectangle highlights the non-coplanar bridge structures. (c) Voltage at 20 μA current for each twisting cycle of 360°.

[0217] Figure 39. FEM strain contours of axial (top), width (center), and shear (bottom) strains for 360° twisted PDMS substrate.

[0218] Figure 40. Fatigue test result of a 6×6 μ-ILEDs array as shown in Figure 28e. (a) Plot of I-V characteristics of a 6×6 μ-ILEDs array as a function of deformation cycles. (b) Plot of voltage needed to generate a current of 20 μA measured after deformation cycles up to 1000 times. Each deformed state is approximately same as shown in Figure 28e.

[0219] Figure 41. (a) Schematic illustration of stacked devices describing states of Figure 29b. (b) Optical images of stacked devices as shown in Figure 29b, collected without external illumination.

[0220] Figure 42. (a) The strain distribution of the two-layer system in the stacked array bent to a radius of curvature 2 mm, as shown in Figure 29c. The black dashed rectangles demonstrate the positions of μ-ILEDs. (b) The strain distribution in GaAs layers in the μ-ILEDs island.

[0221] Figure 43. (a) Optical image of a 6×6 μ-ILEDs array with serpentine metal interconnects, integrated on fabrics, in its bent and on state (bending radius ~4.0 mm). The inset shows the device in its flat and off state. (b) Plot of I-V characteristics of this array in its bent state. Inset provides a graph of the voltage needed to generate a current of 20 μA, measured after different numbers of cycles of bending deformation. (c) Optical image of an 8x8 μ-ILEDs array with a human pattern, integrated on a fallen leaf, in its bent and on state. The inset image was collected with external illumination. (d) Plot of I-V characteristics in the bent state as shown in Figure 43c. (e) Optical image of a μ-ILEDs array integrated on a paper in its folded and on state. (f) Optical image of the same μ-ILEDs array as shown in Figure 29e in its mildly crumbled state. Inset represents microscope image of adjacent four pixels in their on states.

[0222] Figure 44. (a) Plot of I-V characteristics of a 6x6 μ-ILEDs array integrated on paper in its flat (Figure 29d inset) and folded (Figure 29d) state. (b) Plot of I-V characteristics of a 6×6 μ-ILEDs array integrated on aluminum foil in its flat (Figure 29e inset) and crumbled (the center frame of Figure 29e) state. (c) Fatigue tests of arrays of 6×6 μ-ILEDs as shown in Figure 43e. Plot of I-V characteristics of a μ-ILEDs array integrated on paper as a function of deformation cycles (left frame). Plot of voltage needed to generate a current of 20 μA measured after deformation cycles up to 1000 times (right frame). (d) Fatigue tests of arrays of 6×6 μ-ILEDs as shown in Figure 43f. Plot of I-V characteristics of a μ-ILEDs array integrated on aluminum foil as a function of deformation cycles (left frame). Plot of voltage needed to generate a current of 20 μA measured after deformation cycles up to 1000 times (right frame).

[0223] Figure 45. SEM images of various substrate such as fabrics (a), Al foils (b), paper (c), and fallen leaves (d) before (left frame) and after (right frame) coating of thin layer of PDMS.

[0224] Figure 46. Schematic illustration of the encapsulation of an implantable array of μ-ILEDs as described in Figures 30a and 30b.

[0225] Figure 47. (a) Result of Luminance (L) - Current (I) - Voltage (V) measurement of an individual pixel with and without applied ohmic contacts. (b) Applied voltage to generate a current of 20 μA, measured after different operation time. The inset provides I-V characteristics with different operation time.

[0226] Figure 48. (a) Schematic illustration of analytical model for the inflation and printing-down of PDMS film. (b) FEM contours of meridional (upper left) and circumferential (lower left) strains of the inflated state and its comparison with analytical solutions calculated from Equations (S1) and (S2). (c) FEM contours of meridional (upper left) and circumferential (lower left) strains of the as-printed state and its comparison with analytical solutions Equations (S3) and (S4) (right frame).

[0227] Figure 49. Schematic illustration of the cross section of μ-ILEDs on a substrate.

Example 5: System for Biological Sensing and Stimulating Applications Using high Density Array Devices

[0228] The capacity to intimately integrate the full power of modern semiconductor technology with the soft, fluid-bathed, curvilinear and moving surfaces of an animal, e.g., a human, has major implications for human health, for diagnostic, therapeutic and surgical applications. In general, current forms of high performance electronic devices are built on the hard, rigid and brittle surfaces of semiconductor wafers, in formats that are inherently incompatible with establishing intimate, large area interfaces with a biological tissue. Electronic platforms that are flexible and stretchable have the potential to avoid these limitations. An example of a flexible high-density active electrode array fabricated particularly for biological applications is disclosed in commonly assigned International Patent Application Publication No. WO 2009/114689, published on September 17, 2009, and entitled "Flexible and Scalable Sensor Arrays for Recording and Modulating Physiologic Activity".

[0229] One example of a biological therapeutic application is cardiac resynchronization therapy (CRT). CRT refers to the simultaneous application of multiple pacing stimuli to different areas of a failing heart in order to improve cardiac function. In patients with heart failure due to myocardial infarction or other causes, the ability of the ventricle to pump blood is compromised by dyssynchronous activity in various walls of the ventricle. By promoting more organized mechanical contraction via two or more electrical stimuli that are carefully timed and positioned on or in the heart, more synchronous and thus more efficient ventricular function can be restored. Unlike basic pacemaker therapy, in which a single electrical stimulus is applied to the ventricle for each heartbeat purely to treat abnormally slow heart rhythms, CRT is designed to effectively replace the electrical system of the failing heart and improve the organization of ventricular contraction at all heart rates.

[0230] Another application is to map conditions across the surface of a biological tissue, e.g., the heart, to determine an appropriate stimulation scheme to be applied, e.g., pacing or ablating. Cardiac mapping is useful to isolate failing areas and to use that information to determine where to focus treatment, such as ablation treatment. There are numerous biological sensing and stimulating applications that would benefit from a highly flexible and yet miniaturized device that supports an array of elements useful for sensing a variety of conditions from the tissue and/or for applying different types of energy to the tissue.

[0231] In an embodiment, the invention provides a thin and highly flexible device having an array of elements that can be used for sensing or stimulating is used as a platform from which numerous biological sensing, mapping and stimulating applications are provided. There are numerous applications described herein that exploit the spatial arrangement of elements on the device, and in so doing, provide a mechanism to deliver treatments that would not otherwise be possible without more invasive procedures, such as surgery.

[0232] Referring first to FIG. 55, a system 10 is shown that is designed for biological sensing and therapeutic treatment applications. The system 10 comprises a flexible high-density micro-array device (array device) 100 that connects or interfaces with a control system 200. The array device 100 is configured to be placed in operational contact or communication with a biological tissue shown at reference numeral 20 for monitoring and/or therapeutic treatment of the biological tissue. Examples of biological tissue for which the array device 100 may be used include heart tissue, brain or other nervous system organs, muscles, retinas, ear drums, circulatory system structures, tumor tissues, and digestive system structures.

[0233] Examples of specific structures and fabrication techniques for the array device 100 are described in the aforementioned co-pending application. FIGs. 68-74, described hereinafter, illustrate additional electrical circuit configurations for the array device 100. The array device 100 comprises an array of elements 110 that may be sensors and/or effectors on a thin and highly flexible substrate 115. The array device 100 is fabricated using silicon-based circuit fabrication techniques. It is highly flexible and stretchable and well suited to flex with the natural movement of a biological tissue.

[0234] The elements 110 on the array device 100 may serve as sensors and/or effectors. As used herein, an effector is any device that takes a signal and introduces an intervention to modulate biological (e.g., brain or heart) activity. Examples of effectors include electrical stimulators, photo/light-emitters (e.g., for activating brain tissues impregnated with a light responsive compound), chemical releasing/infusion devices, devices that change temperature, pressure, and/or acceleration, and devices that introduce electrical, magnetic or other fields, etc. Illumination sources such as a light source or other source that can activate tissue for diagnostic or monitoring purposes may also be used. For example, such illumination sources may be used to activate brain tissue to interrogate its function but not necessarily to modulate its activity.

[0235] Similarly, a sensor is any element that can be used to transduce a biological signal into an electrical or other signal. Examples of sensors include: electrical contacts for recording electrophysiological signals, optical detectors for recording light correlates of biological activity, chemical sensors for detecting changes in chemical concentrations or PH (e.g., chloride, neurotransmitters, lactate, glucose, other metabolites, neuro-active compounds, medications, biological substances such as tumor-secreted factors, etc.), devices for measuring temperature, force, acceleration, movement, pressure, etc.

[0236] A sensor may also include functionality of the effector as defined above.

[0237] The control system 200 interfaces with the electrode array device 100 through one or more direct wired connections, or optionally though a wireless connection. The control system 200 comprises a signal analysis subsystem 300 and a treatment application subsystem 400. One or both of these subsystems may be employed for a particular application. Some of the functions of these subsystems may be incorporated on-board the array device 100. The signal analysis subsystem analyzes signals obtained from individual elements 110 of the array device 100 for those elements configured as sensor elements. An example of an application of the signal analysis subsystem is to analyze local ventricular contraction parameters derived from sensor elements 110 in the form of strain gauge micro-sensors. The treatment application subsystem 400 takes input from the signal analysis subsystem or some other source in order to determine parameters for a therapy to be applied, via the array device 100, or some other device. For example, the treatment application subsystem 400 may determine pacing parameters to be employed when the array device 100 is configured to apply multiple spatially diverse pacing stimuli. These are only examples of the possible functions of the signal analysis subsystem 300 and treatment application subsystem 400. Other examples are described hereinafter. In addition, while signal analysis subsystem 300 and therapy application subsystem 400 are shown as separate blocks, they be implemented within a single block, i.e., by a microprocessor, microcontroller, digital signal processor, or other programmable or fixed logic device.

[0238] Turning to FIG. 56, a diagram is provided to show that the array device 100 can be collapsed (wrapped or rolled on itself) for introduction into a body of an animal for deployment at the biological tissue site of interest. To this end, as shown in FIG. 57, the array device 100, when collapsed, rolled or wrapped on itself, may be inserted into a catheter or other introducer sheath device 30 for guidance and delivery to the biological tissue site.

Example Application: Cardiac Resynchronization

[0239] One application described herein relates to cardiac resynchronization.

[0240] Referring to FIGs. 58 and 59, an example application is shown in which the array device 100 is introduced inside the pericardium of the heart of an animal using the introducer sheath 30. Once the introducer sheath 30 reaches into the pericardium, the array device 100 is allowed to unroll or unwrap by being pushed outward from the sheath 30, such as by a guide wire, in order to make contact with an area of the heart of interest as shown in FIG. 59. Suitable electrical (and/or physical) contact between the array elements 110 of the array device and the heart tissue is enhanced by the pericardial fluid around the surface of the heart inside the pericardial sac.

[0241] Thus, FIGs. 58 and 59 show that the array device 100 is a thin, ultra-flexible device platform supporting an array of active electronics that can be introduced into or around the heart via standard catheter delivery techniques in a traditional electrophysiology laboratory. It is collapsed (e.g., retracted, rolling, or folded), moved to within or around the heart and related structures (with the assistance of a combination of fluid and air injected in the pericardial space), and re-deployed at a separate location.

[0242] In one form, the device 100 is initially introduced into the body on a biodegradable backing platform (e.g. silk). This biodegradable platform will provide additional support for implantation and initial manipulation, then dissolve and facilitate close adherence of the device 100 to cardiac and heart-related tissues.

[0243] In an alternative form, the array device 100 may be directly placed on the epicardium via surgical techniques.

[0244] Turning to FIGs. 60 and 61, an example of a closed-loop application of the array device 100 is now described. In this example, the array device 100 is secured to the epicardium and connected to an implantable electronics unit 500 within which the control system 200 resides. The electronics unit 500 connects to the array device via a tunneled lead 510 and also connects to transvenous right atrial and right ventricular pacing electrodes 530 and 535 via leads 520 and 525.

[0245] In the configuration shown in FIG. 61, pacing stimuli can be delivered in a programmable fashion with high spatial and temporal adaptability that is well suited for cardiac resynchronization therapy (CRT). As explained herein, CRT involves the simultaneous application of multiple pacing stimuli to different areas of the heart. Since the array device 100 has numerous spatially arranged elements 110, which can be configured as active effector elements, the array device 100 is well suited to provide a fully implantable system that is capable of delivering CRT.

[0246] In particular, the array device 100 provides for the ability to pace the heart from essentially any location, sequence of locations, or combination of locations on the ventricles. This allows for customization and optimization of pacing for each individual patient, with the goal of increasing both the number of patients for whom CRT will be indicated and the proportion of patients that experience a positive response.

[0247] FIGs. 62 and 63 illustrate the flexibility in spatially controlling pacing stimuli to the heart. FIG. 62 is a simplified diagram of the active area of the array device, showing effector elements 110 of the array device 100 arranged in rows A-D and columns 1-4. FIG. 63 illustrates a variety of spatial and timing schemes that may be employed with respect to the effector elements on the array device. In addition to the schemes depicted in FIG. 63, individual effector elements 110 may be addressed for delivering a stimulus at a particular time instant. Thus, there are numerous spatial and timing schemes that can be employed in connection with the array device 100 for delivering pacing stimuli to the heart. Furthermore, the array device 100 makes feasible a multitude of additional applications and advantages over existing resynchronization devices and systems. Incorporation of sensors such as strain gauges at select array elements 110 can provide information on local ventricular contraction parameters that enable a closed-loop system in which the control system 200 can adjust and optimize pacing parameters in real-time. Such a system may be crucial in improving the response rate to resynchronization therapy, as current optimization techniques focus on adjusting parameters at one point in time and maintaining those parameters as the "permanent" settings.

[0248] Further still, using appropriate sensors (described above) for the elements of the array device 100, the array device 100 may be employed with integrated active circuitry for measuring cardiac contractility, myocardial wall displacement, myocardial wall stress, and movement in real-time, with high spatial and temporal resolution. Similarly, the array device 100 may be employed with integrated active circuitry for modulating, that is, actively controlling, cardiac contractility, myocardial wall displacement, myocardial wall stress, and movement in real-time, with high spatial and temporal resolution, through appropriate stimuli. As described above, the array device 100 may be employed with integrated active circuitry for measuring and improving myocardial contractile function in a real-time, closed-loop system.

[0249] FIG. 64 illustrates a flow chart for a continuously adjustable stimulation process 600 that may be performed by the control system 200: At 610, local ventricular contraction is sensed from suitably configured sensor elements on the array device 100. At 620, the contraction data obtained from the sensor elements on the array device 100 is analyzed to continuously characterize (e.g., on a beat-by-beat basis) the ventricular contraction behavior of the heart. At 630, pacing parameters associated with CRT or other pacing schemes for pacing stimuli delivered via effector elements of the array device 100 (or via other pacing electrodes positioned in or on the heart) are continuously adjusted based on the ventricular contraction behavior of the heart.

[0250] Some real-time adjustment in heart rate and atrioventricular timing can be effected by incorporation of various activity sensors in current devices. However, these changes are based on preset algorithms rather than concurrently measured individual patient data. It is likely that ideal atrioventricular and interventricular timing varies significantly with changing hemodynamic conditions. Consequently, the ability to integrate instantaneous feedback on a beat-by-beat basis may improve a patient's response to CRT.

[0251] In addition, an implanted electrode array can be used to record information about spontaneous arrhythmias that may develop. Heart failure with diminished left ventricular ejection fraction (EF) is associated with an increased risk of sudden cardiac death, and large randomized trials have demonstrated mortality benefit from prophylactic ICD implant in patients both with and without prior myocardial infarction (MI). As such, many patients for whom CRT is indicated also qualify for implantable cardioverter-defibrillator (ICD) implantation. A significant portion of patients with an ICD will eventually develop a life-threatening tachyarrhythmia that will require an ICD shock; a subgroup of those patients may have multiple episodes requiring multiple shocks, a painful and psychologically stressful therapy. Catheter ablation procedures for eliminating ventricular tachycardia are becoming increasingly common to prevent further arrhythmias and ICD shocks in such patients, and localization of the clinically important arrhythmia can at times be difficult. The more extensive and detailed spatial information recorded by an implanted array of electrodes during an arrhythmia prior to hospitalization, compared with the limited information recorded by the two or three leads in conventional devices, will help in planning a more efficient and effective ablation procedure. It will also provide more data with which to compare arrhythmias induced during an EP study, facilitating more rapid identification of those arrhythmias that are clinically relevant.

[0252] Another scheme that may be employed with the use of the device 100 is to electrically silence regions of the heart that are responsible for generating life threatening arrhythmias through timed depolarization. Using correctly timed stimulations from the array device 100 to the heart, arrhythmogenic foci or areas of myocardium can be maintained in a constant state of depolarization, and thus be unable to participate in arrhythmogenesis. The array device 100 can be configured, functionally, in size, to act on regions of the heart (e.g. the entirety of a myocardial infarction) that are too large to be treated with conventional ablation techniques. Similar concepts may apply to treatment of epilepsy, with brain stimulation to prevent the development of seizure activity. A different but related technique is use of the array device 100 for "electrical silencing" through stimulation of neural inputs to the heart, i.e., the sympathetic trunk or ganglionated plexi that innervate the heart. A closed-loop mechanism may be employed to modify the spatial and temporal pattern of stimulation in real-time based on the effectiveness of arrhythmia suppression.

[0253] It is possible that the array device 100, once implanted, could additionally provide mechanical support to the failing heart. Passive constraint of the ventricles against chronic dilation via an implanted synthetic mesh-like device was previously studied in randomized trials of the CorCap™ Cardiac Support Device (CSD) (Acorn Cardiovascular, Inc., St. Paul, Minnesota).

[0254] FIG. 65 illustrates a configuration of the array device 100 that may be suitable to provide mechanical support to a failing heart. The array device 100, equipped to operate as both a pacing device and a recording device, can provide active, mechanical systolic support analogous to cardiomyoplasty. The array device 100 is constructed of a size suitable to be wrapped around a region of the heart to provide passive mechanical support for facilitating ventricular diastole or active mechanical support to augment systolic function.

[0255] The device serves as a flexible, active, multi-scale array with adjustable spatial and temporal resolution capable of high-density recording and stimulation from the epicardium or endocardium. The pacing configurations and schemes that are available through the use of the array device 100 are numerous, from single-site pacing to multiple-site pacing. In addition, the array device 100 can be used in a system to treat arrhythmias that cannot be safely or effectively ablated. Moreover, the array device 100 can be used to detect the early stages of a cardiac event and to treat it with a suitable stimulation scheme to stop it.

Example Application: Anatomic and Physiologic Mapping and Ablation

[0256] Anatomic and physiologic mapping of the surface of a biological tissue has important applications. For example, mapping the epicardial surface via percutaneous pericardial puncture, as first demonstrated in patients with Chagas' disease and ventricular tachycardia (VT), has proven useful in ablation of VT circuits with crucial portions of the reentrant circuits located in subepicardial muscle. Surgical data suggests that at least 15% of post-myocardial infarction VT is dependent on such subepicardial circuits, a proportion that is likely much higher in patients with non-ischemic cardiomyopathy and VT.

[0257] One advantage to the aforementioned percutaneous procedure is the ability to access the epicardium without the need for surgical exposure. However, the lack of surgical exposure creates several obstacles, including inability to easily visualize the location and course of epicardial coronary arteries and the phrenic nerve, as well as difficulties distinguishing epicardial fat from scarred myocardium. The appearance of multi-component and late electrograms has been primarily used to distinguish an area of scar from fat. A method for direct visualization of epicardial landmarks

using real-time video pericardioscopy has been described in the literature. Multiple fluoroscopic techniques have also been used to localize the coronary arteries at the time of epicardial mapping, including simultaneous catheter-based coronary angiography and fusion of a 3D electroanatomical map with previously acquired computed tomography (CT) angiograms. Both methods require exposure to intravenous (IV) contrast material, and both are limited by the precision of merging two sets of images, whether by eye or using a computer-assisted technique. In contrast, during traditional epicardial mapping via a surgical approach, both coronary arteries and epicardial fat are easily distinguished visually by the operator.

[0258] The availability of a single instrument that can be used to reliably map both the structures and electrical properties of the heart with exquisite spatial resolution, despite the absence of direct visualization, is very desirable. Such an instrument would ideally take advantage of traditional endovascular approaches or a percutaneous pericardial approach.

[0259] Reference is now made to FIG. 66 for an application of the system 10 (FIG. 55) adapted for a simultaneous anatomic and physiologic mapping and ablation application. In this application, the body organ to be mapped and treated is the heart, but this is only by way of example. The array device 100 is delivered to the endocardium or epicardium via traditional endovascular techniques or by a modified version of the nonsurgical transthoracic approach now commonly used, e.g., as depicted and described above in connection with FIGs. 58 and 59. The array device 100 is configured to have a large number of electrodes over an array of spatial locations that are configured as sensors for recording electrograms and also elements that are configured as effectors for delivering radiofrequency (RF) or other ablation energy. In addition, some of array elements may be configured as one or more of a variety of sensors (optical, chemical or other) for detection of epicardial coronary artery blood flow and discrimination of tissue properties.

[0260] The array device 100 is connected via a suitable lead 540 to a control system shown at reference numeral 200' that is external to the patient. The control system 200' comprises a signal generator 310, a controller 320, a display 330 and a signal processor 410. The signal processor 410 analyzes output of the sensor array elements on the array device 100 and generates data suitable for displaying mapping images on the display 330, such as shown at the mapping image 335. In one example, the mapping image 335 may be a three-dimensional (3D) map of electrophysiologic properties (e.g., voltage activation), anatomic properties (e.g., muscle, epicardial vessels, or fat), and ablation sites. In the mapping image 335, there is a region 335a (dark purple) that represents healthy muscle, a region 335b (rainbow range of colors) that represents varying degrees of scared myocardium a region 335c (light purple) that represents an area of epicardial fat. The bold dashed lines shown at 337 represent epicardial coronary arteries and the dots (red in color) 339 represent ablation sites. The mapping image 335 thus illustrates, through color or other visual indications, all of these anatomic and physiologic properties identified by a single multimodal array device 100 employing the techniques described herein.

[0261] Technologies that may be integrated on the flexible array and adapted for sensing conditions of coronary arteries include optical sensors, pressure or strain measurements, acoustic sensors, and chemical sensors. These sensors may also be used to detect ischemic changes and other abnormalities associated with tissue compromise and disease. Relatively simple measurements of tissue conductivity and impedance may be sufficient for distinguishing epicardial fat from muscle.

[0262] The signal processor 410 may also generate data that is useful to the controller 320 to control the signal generator 310. The controller 320 may be an automated controller, e.g., microprocessor suitably programmed with control logic, or a manual control apparatus. In either case, the controller 320 is configured to modify the ablation energy produced by the signal generator 310 for application via any combination of effector elements on array device 100.

[0263] The ability to include active circuitry on the array device 100 enables minimization of electrical connections between the array and the operator, thereby promoting the primary goal of an adaptable yet small device that can be delivered percutaneously or endovascularly. Moreover, the ability to record and store localized cardiac electrograms from multiple spatially diverse sites simultaneously during ventricular arrhythmias enables faster and more accurate localization of those arrhythmias in the electrophysiology laboratory.

[0264] The spatial arrangement of sensors on the array device 100 allows for creation of a 3D electroanatomic map-analogous to the functionality of the CARTO XP (BiosenseWebster) and EnSite NavX™ (St. Jude Medical) mapping systems. Depending upon the array size and density of the array device 100, all electrodes could be localized in 3D space using only a select subset of elements (electrodes) on the array device, with interpolation of the remaining point locations. More specifically, the array device 100 is placed in or on the heart (only) during a mapping and/or ablation procedure, and it may be moved around in or on the heart in order to map as large an area as possible of the heart. This is indicated by the arrows in FIG. 66. The select subset of electrodes is used as select points on the array device that are localized (relative to other structures or catheters in the heart) using, for example, magnetic-based 3D localization techniques such as those of the CARTO XP or impedance-based 3D localization NavX systems. Using interpolation of the localization data for the select subset of elements, the exact position of every element on the array device 100 is localized.

[0265] This position tracking technique is useful to create a virtual 3D map of where the array device 100 has been on or in the heart and some representation of the data collected at those locations on or in the heart. One example is a voltage map. A 3D "shell" of the surface is generated from the voltage measurements made at elements of the array

device and the voltage levels at every measurement point may be color-coded. With numerous sensor modalities on the array device 100, the array device 100 may be used to superimpose multiple 3D maps at the same time, such as for voltage measurements, blood flow measurements and strain (pressure) measurements. Alternatively, given the 3D deformability of the array device 100, emitters of different types can be linked to each electrode contact to compute the location of all the elements of the array device with higher resolution.

[0266] Thus, the array device 100 serves as a flexible, active, multi-scale device with adjustable spatial and temporal resolution capable of high-density recording from and stimulation to the heart, delivered both through standard endovascular techniques to the endocardium and minimally invasively to the epicardium.

[0267] The device 100 is an implantable flexible electronic device with integrated active circuitry useful for both anatomic and electrical mapping of the heart surface and surrounding structures with high spatial and temporal resolution. Information gathered from a variety of sensor modalities integrated on the device can be used to distinguish myocardial tissue, epicardial fat, coronary arteries, large nerves, and other structures underlying the device.

[0268] The device 100 can deliver ablation energy via RF or other modality and effect a clinically significant lesion with high spatial resolution. Ablation can be spatially tuned in closed-loop fashion at the resolution of individual electrodes on the array.

[0269] In addition to mapping and ablating arrhythmias directly, the cardiac applications for such a device are wide-ranging. Mapping other cardiac and mediastinal structures, including ganglionated plexi and other components of the cardiac autonomic nervous system, are examples of such future direction in the treatment of arrhythmias. The highly adaptable nature of the array device 100 in terms of size, shape, and the type of electronic components included also lends itself to incorporation with existing long-term monitoring devices, such as the Chronicle® implantable hemodynamic monitor or long-term arrhythmia event monitors.

[0270] The foregoing concepts related to cardiac mapping have been demonstrated in live animal experiments, together with the ability to record useful electrical signals and reliably pace the heart from an array device with passive circuitry placed on the epicardial surface of the ventricle under direct visualization. In addition, an array device with active circuitry has been used to record electrograms from 288 array sensor elements of the array device 100 covering a 2.2 square centimeter area of the left ventricular epicardium using only 36 separate connecting wires between the array and the recording apparatus. A much higher degree of multiplexing is envisioned to allow for the use of a single USB 2.0, Firewire™ or similar connector providing input and output access to and from the array device.

Example In-Vivo Experiments

[0271] With reference to FIGs. 67A, 67B and 67C, data from in-vivo experiments are now described. In-vivo experiments were performed in two normal 80-90 pound male Yorkshire pigs. The heart was surgically exposed via a median sternotomy and subsequent pericardiotomy. An array device 100 was placed on the epicardial surface while under direct visualization as shown in FIG. 67A. The device adhered to the curvilinear surface of the heart, even during vigorous cardiac motion and during rapid pacing. FIG. 67B shows motion snapshots at various stages of the cardiac cycle and it is seen that the array device adapts to the dynamic variations in the surface shape of the heart in order to maintain conformal contact. Given the average heart rate of approximately 77 beats per minute (BPM) during in-vivo experiments and a recording duration of approximately 137 minutes, the device provided reliable data over the course of more than 10,000 bending cycles during our experiments.

[0272] Unipolar voltage data were recorded from all 288 sensors on the array device 100 using a multiplexing and sampling scheme. Baseline electrogram data were collected in sinus rhythm with the array in multiple positions and orientations on the epicardial surface. Data were also recorded while pacing the heart from multiple locations relative to the array device via a standard, non-steerable decapolar electrode EP catheter held in contact with the epicardial surface. FIG. 67C shows the array device 100 positioned over the left anterior descending (LAD) coronary artery, with the pacing catheter shown at 32 positioned just inferior to the array. The color coded map 340 in this frame shows a visual representation of the data collected from the array device 100, using procedures described below.

[0273] Data from all 288 sensors on the array device 100 were filtered and processed using custom MATLAB software to determine the relative activation time at each contact by comparing the time of the maximum negative slope (dV/dt) of the unipolar electrogram to the maximum negative slope of the average electrogram of all 288 sensor channels. These activation times were then used to generate isochronal maps showing propagation of paced and unpaced cardiac depolarization wavefronts spreading across the array for a variety of sensor sites and pacing conditions.

[0274] Sample voltage trace data from a single channel without remote pacing are shown in FIG. 4a. The inset at right highlights the very low noise level of the recording, with a signal-to-noise ratio (SNR) of approximately 50. Note that negative is plotted up in the figure, by convention.

[0275] FIG. 4b shows voltage data for all channels taken at 4 points in time and showing paced cardiac wavefront propagation. Voltage is plotted using the color scale in the right corner. FIG. 4c illustrates a plot of average voltage from sensing elements and illustrating the point in time that each frame in FIG. 4b was taken. The color of the dotted lines

corresponds to the color of the time label in FIG. 4b.

[0276] FIG. 4d illustrates a representative single voltage trace with external pacing from a standard clinical electrode. The black arrow and box highlight the pacing artifact. Note that negative is plotted up by convention in FIG. 4a, 4c, and 4d.

[0277] FIG. 4e illustrates isochronal color maps of relative activation times for two different external pacing sites. The activation times are plotted using the color bar shown at the right. Asterisks (*) indicate the relative location of the external pacing electrode. The scale bar illustrates the spacing between electrode locations. The data from the activation map at the locations marked by lines i - iii are plotted in FIG. 4f in distance vs. activation delay plots for selected rows of the sensor array following the arrows in FIG. 4e.

[0278] These results clearly establish this technology as the basis for devices with advanced capabilities. With straightforward additions to the circuits and external control, the same systems could provide multi-site cardiac pacing with closed-loop feedback of local ventricular contractility or cardiac output measurements via distributed arrays of active sensory and stimulation electrodes. Furthermore, the mechanical properties of the circuits permit packaging in catheter-based delivery systems, with the ability to deploy on and conform to large and small, irregular curvilinear surfaces of the body. Pursuing these possibilities and other biomedical devices with other functionality using the materials and electronics strategies reported here has great potential to yield technologies with important benefits to human health.

Example Array Device and Circuit Configurations

[0279] FIG. 68 illustrates an example of the array device 100. The array device comprises an array of elements 110 that, in the example shown in FIG. 68, are electrodes, each of which is coupled to an associated preamplifier 120. The output of each preamplifier is coupled to a column line 130 through an analog switch 140. By activating a specific row signal 145 and de-activating the other (N-1) row signals, the output of the selected row amplifier will be allowed to drive the column line 130. In this manner, any one of the N rows can be selected to drive the column amplifier 150. This column amplifier 150 provides additional gain to match the range of the signal to the input range of the column analog to digital converter 160. The column analog to digital converter 160 converts the analog signals from the electrode channels to digital values. The digital output of the column analog to digital converter 160 is connected to a digital buffer 170, and the outputs of all N digital buffers 170 (one for each column) are connected together. Each column signal 120 can be individually selected via the N column select signals 180. In this way, the data from the N column analog to digital converters 160 can be combined down to one digital input on the integrated microprocessor 190.

[0280] With reference to FIGs. 69-70, schematic diagrams are shown for various configurations of sensing and stimulation selection control of elements in the array device 100. These configurations are useful in connection with various sensing and stimulation applications, examples of which are described above.

[0281] Turning to FIG. 69, a schematic diagram is shown that illustrates how unit cells connect to other unit cells to create a multiplexed signal output, for example for sensing from one of the elements 110 that is configured to operate as a sensor electrode. During multiplexed sampling, one row of electrodes is selected at a time by driving one of the row select signals (such as R_0) high, and all of the other row select signals low. This allows the elements in that row to drive the column output lines labeled C0, C1, ..., to a high-speed analog-to-digital converter. The row select signals are rapidly cycled to sample all elements 110 on the array device 100.

[0282] FIG. 70 is similar to FIG. 69, but adds stimulation control capability. In this example, the stimulation input lines STIM0, STIM1, etc., are provided. When a stimulation voltage is driven onto one of the stimulation input lines while any or all of the row select lines are enabled, the elements 110 (electrodes) will deliver stimulation energy to the local tissue area. The configuration shown in FIG. 70 adds a minimal amount of extra wiring and complexity, but is tied to the recording multiplexing rate due to the sharing of the row select signals.

[0283] FIG. 71 illustrates a schematic diagram that is similar to FIG. 70, but uses independent stimulation row select signals. Like the configuration of FIG. 69, when a stimulation voltage is driven onto one of the stimulation input lines while any or all of the row select lines are enabled, the elements 110 (electrodes) will deliver a stimulation energy to the local tissue area. However, stimulation row selection signals STIM R0, STIM R1, ..., are provided. These signals are used to selectively enable stimulation at any or all of the rows. This configuration adds more external wires but provides for a stimulation capability that is time independent of sensing multiplexing.

[0284] FIG. 72 shows an example transistor level schematic for an element 110 in a sensing configuration. There is a constant current source 112, a current mirror 114 and a multiplexer 116.

[0285] FIG. 73 shows an example transistor level layout for an element 110 with stimulation control according to that described above in connection with FIG. 70. In this configuration, there is a stimulation control demultiplexing transistor 118 that is connected to the stimulation control line, e.g., STIM0. FIG. 74 shows an example transistor level layout for an element 110 with row independent selectable stimulation control according to that described above in connection with FIG. 71. In the configuration of FIG. 74, there is a demultiplexing transistor 118 that is connected to both the stimulation control line, STIM0, and to the stimulation row select control line STIM R0.

[0286] The devices, configurations and techniques described herein are meant to be by way of example only. Other

applications for the array device 100 include ablation for treatment of neurological maladies and pain treatment in muscle and other tissues. In addition, ablation techniques may be performed with different types of energies and modalities. Ablation modalities that could be applied include: RF energy (whether single frequency or phased), cryoablation (freezing), laser energy, and high-intensity focused ultrasound (HIFU). Additionally, high voltage electrical stimulation can be used as an ablation technique. In this application, the cells are destroyed through electroporation, which is a mechanism by which high voltage electrical fields create pores or the breakdown of the cell membrane. With enough energy, this causes irreversible damage and cell death, achieving the goal of ablation.

Example 6: Conformable Skin -Mounted Electronic Devices for Interfacing with Tissue

[0287] The invention provides skin-mounted electronic devices for electrophysiological mapping and sensing various other characteristics from the body and/or tissue of a subject. A major difference, however, from other implantable devices, such as a conventional cardiac sensor, is that this skin-mounted electronic device of the invention is non-invasive. For example, even though it positioned on skin, i.e. non-invasive, the device of this apsect is capable of making electrocardiography, electromyography, electroencephalography (EKG, EMG and EEG) measurements, from the heart, muscle and brain tissue, respectively.

[0288] An important issue of invasiveness with respect to medical devices is post-surgery recovery. For example, many surgical procedures require large incision that causes post-surgery trauma. The present skin-mounted non-invasive device does not require recovery since it is attached to skin, like a bandage, rather than implanted or surgically administered as in some conventional medical device. Another important advantage of the present skin-mounted devices is that they can be used for long periods of time, which is not feasible with conventional implantable and even non-invasive devices. For example, many invasive medical devices have issues of long time biocompatibility in the human body. Also some conventional non-invasive sensors, such as commercial EEG electrodes, require use of conductive gel to reduce impedance and provide higher signal to noise ratios. Such conventional devices, however, cannot be used for long periods of time as the conductive gel is prone to drying out. In addition, the conductive gel can be uncomfortable and cause skin irritation. The present skin-mounted electronic devices do not require a conductive gel, for example because it is capable of using active capacitance coupled devices for electrophysiological mapping.

[0289] In an embodiment, the invention provides a device for establishing an interface with a skin of a subject, the device comprising: (1) a flexible or stretchable substrate having an average modulus less than or equal to 1 MPa; (2) a flexible or stretchable electronic circuit comprising one or more inorganic semiconductor circuit elements, said flexible or stretchable electronic circuit supported by the flexible or stretchable substrate; and (3) a barrier layer encapsulating at least a portion of the flexible or stretchable electronic circuit, the flexible or stretchable substrate or both flexible or stretchable electronic circuit and the substrate; wherein the substrate, barrier layer and the electronic circuit provide a net bending stiffness of the device low enough that the device establishes conformal contact with the skin of the subject. Devices of this aspect of the invention include skin mounted tissue sensors, tissue actuators and arrays of tissue sensors and actuators. In come embodiments, for example, matching of the modulii of components of the device (e.g., substrate, electronic circuit or barrier layer) and the skin is useful for establishing robust conformal contact at the interface with the skin. In an embodiment, the device does not include an adhesive layer between the skin and the electronic circuit component.

[0290] The composition, physical dimensions and properties of the flexible or stretchable substrate is important in devices of this aspect of the invention. In an embodiment, for example, flexible or stretchable substrate has an average modulus less than or equal to 500 KPa, optionally for some applications less than or equal to 100 KPa, and optionally for some applications less than or equal to 50 KPa. In an embodiment, for example, the flexible or stretchable substrate has an average modulus selected over the range of 0.5 KPa to 100 KPa. In an embodiment, for example, the flexible or stretchable substrate has an average modulus equal to or less than 50 times the average modulus of the skin of the subject at the interface. In an embodiment, for example, the flexible or stretchable substrate has a thickness less than or equal to 500 microns, optionally for some applications less than or equal to 100 microns and optionally for some applications less than or equal to 50 microns. In an embodiment, for example, the flexible or stretchable substrate has a thickness selected over the range of 1 to 500 microns, and optionally selected over the range of 1 to 100 microns, and selected over the range of 1 to 50 microns. In an embodiment, for example, the flexible or stretchable substrate is a low modulus polymer, such as a low modulus rubber or a low modulus silicone material. In an embodiment, for example, the flexible or stretchable substrate is Ecoflex ®. In an embodiment, for example, the flexible or stretchable substrate is a bioinert or biocompatible material.

[0291] The composition, physical dimensions and properties of the flexible or stretchable substrate is important in devices of this aspect of the invention. In an embodiment, the flexible or stretchable electronic circuit comprises one or more sensors or actuators and/or one or more amplifiers or multiplex circuits. For example, devices of this aspect include a flexible or stretchable electronic circuit comprising one or more electrodes, transistors, light emitting diodes, photodiodes, temperature sensors, electrocardiography sensors, electromyography sensors, electroencephalography sensors,

thermistors, diodes, capacitive sensors, or any combinations of these. In an embodiment, the flexible or stretchable electronic circuit comprises one or more single crystalline inorganic semiconductor structures. In an embodiment, the flexible or stretchable electronic circuit is assembled on the flexible or stretchable substrate via contact printing.

[0292] In an embodiment, a device of this aspect further comprises a transfer substrate supporting the flexible or stretchable substrate, the flexible or stretchable electronic circuit or both, for example a transfer substrate in physical contact with the flexible or stretchable substrate. In an embodiment, for example, the transfer substrate is a removable substrate, wherein the transfer substrate is partially or completely removed upon providing the device in contact with the skin of the subject. In an embodiment, for example, the removable substrate is a dissolvable substrate, wherein the removable substrate is partially or completely dissolved after the device is provided in contact with the skin of the subject. In an embodiment, the transfer substrate is a polymer such as polyvinyl acetate.

[0293] In an aspect, the invention provides a method of interfacing an electronic device with skin of a subject, the method comprising: (1) providing the skin of the subject; (2) providing a conformable electronic device, the device comprising: (i) a flexible or stretchable substrate having an average modulus less than or equal to 1 MPa; (ii) a flexible or stretchable electronic circuit comprising one or more inorganic semiconductor circuit elements, said flexible or stretchable electronic circuit supported by the flexible or stretchable substrate; (iii) a barrier layer encapsulating at least a portion of the flexible or stretchable electronic circuit; and (iv) a transfer substrate supporting said flexible or stretchable substrate, said flexible or stretchable electronic circuit or both; (3) contacting the conformable electronic device to a receiving surface of the skin, wherein upon contact the flexible or stretchable electronic circuit is positioned between the skin and the a flexible or stretchable substrate; and (4) at least partially removing the transfer substrate, wherein the flexible or stretchable substrate, barrier layer and the flexible or stretchable electronic circuit provide a net bending stiffness of the device low enough that the device establishes conformal contact with the skin of the subject upon at least partial removal of the transfer substrate, thereby interfacing the electronic device with the skin of the subject. In an embodiment, the step of at least partially removing the transfer substrate comprises entirely removing the transfer substrate. In an embodiment, the step of at least partially removing the transfer substrate comprises dissolving the transfer substrate after the step of contacting the conformable electronic device to a receiving surface of the skin.

[0294] Methods of this aspect of the invention may further comprising sensing and/or actuating a tissue of the subject, for example wherein the tissue of the subject is a heart, muscle or brain of the subject. In an embodiment, for example, the method further comprises making electrocardiography measurements, electromyography measurements or electroencephalography measurements of the subject. In an embodiment, for example, the method further comprises providing electromagnetic radiation to the tissue of the subject. In an embodiment, for example, the method further comprises measuring the temperature of the tissue of the subject. In an embodiment, for example, the method further comprises making one or more voltage measurements, current measurements, electromagnetic radiation intensity or power measurements, temperature measurements, pressure measurements, tissue acceleration measurements, or tissue movement measurements of the tissue of the subject.

[0295] In some embodiments, a transfer substrate is a PVA backing layer that is able to be dissolved with water. Benefits of the use of a PVA backing layer include that it is biocompatible and does not result in problems with the skin. Use of a low modulus flexible or stretchable substrate is beneficial for providing very good conformal contact to the skin, which is important in some sensing applications for providing a low impedance and high signal to noise ratio. Also good conformal contact enables very strong lamination for long periods of time without the need for additional chemical adhesive.

[0296] In the case of active skin electronic device, for example, active EKG/EMG sensors, the electronic circuit component may comprise an electrode. The electrode of this aspect may be in physical contact with the skin or may not be in physical contact with the skin at the interface. Embodiments of this aspect include, for example, use of capacitance type circuit that do not require physical contact. In some embodiments, for example, the device is passivated with one or more thin layer of polyimide.

[0297] Figure 50e provides a schematic diagram illustrating a cross-sectional view of a skin-mounted conformal device of the invention having an encapsulating barrier layer. As illustrated in figure 50e the device comprises a flexible or stretchable Ecoflex® substrate supporting a flexible or stretchable electronic circuit having a multilayer device geometry. The electronic circuit component comprises a series of layers including encapsulating polyimide layers (PI), and functional silicon (Si) layer, silicon oxide layer (SiO_2) and gold layers (AU1, AU2, and AU3). The invention includes, however, skin-mounted devices having one or more electrodes directly exposed and/or in physical contact with the skin, for example, without polyimide encapsulation.

[0298] To demonstrate the applicability of this aspect of the invention for a range of biomedical applications, the skin-mounted electronic devices were fabricated and interfaced with skin in the context of tissue sensing and actuation applications. Figures 50 - 54 provide device schematics, images and experimental results describing this aspect of the invention.

[0299] Figure 50 provides: (a) Four frames of the electrode array transfer printed onto thin, low modulus ecoflex. On skin (left top), partially peeled off state (right top), magnified view of each top frame (bottom). Blue dotted boxes correspond

to the magnified images at the bottom frame. The modulus and thickness of ecoflex substrate is ~50kPa and ~30um, respectively. The electrode array is facing down to skin, sandwiched by the skin and ecoflex substrate, (b) Schematic view of application procedures of skin patch to the skin. The electrode array is transfer printed onto ecoflex, coated on the PVA film, an water dissolvable and biocompatible film. The transferred electrode array is positioned onto the right location of skin. Some water can be applied to the backside of PVA film to dissolve it away. Thin, low modulus skin patch conforms very well to skin, like a tattoo. (c) Deformed images of skin patch on skin to four different directions and their magnified views. The highly conformal skin patch follows the wrinkles on skin very well. (d) Electrode array transfer printed at the backside of the commercial temporary tattoo. It is applied to the skin. Instead of ecoflex thin film, a temporary tattoo can be used for the purpose of camouflage or cover-up.

[0300] Figure 51 provides (a) Mechanically optimized fully serpentine electrode array (left). The right frame shows the stress-strain relationship from which the modulus in the plot was calculated. The optimized design shows comparable modulus with the bare skin. (b) Debonding experiment results under tension (left) and compression (right). As the modulus and thickness decrease, the debonding happens at larger strain. (c) Cross-sectional image (X-ray) of skin electronic devices located on the pig skin.

[0301] Figure 52 provides (a) Serpentine shape active EMG/EKG sensor. Left top frame shows source, drain and gate of nmos transistor and silicon drain to gate feedback resistor. Inset shows conventional shape active EMG/EKG sensor. Left bottom image shows the final device image for serpentine shape device and its magnified view (inset). Right top and bottom frame shows transfer and IV curve for the transistor. (b) Circuit diagram for active EMG/EKG sensor and the frequency response of active sensor (common source amplifier). (c) Microscope image of temperature sensor using platinum resistor and gold serpentine wires. Right frame shows the calibration curve, showing different resistances of temperature sensor at different temperatures. (d) Microscope image of strain gauge using conductive PDMS (CPDMS). Right frame shows the calibration curve of the strain gauge. (e) Microscope images of proximity sensor using forward and reverse biased LED array. Forward biased LED array radiates light and reverse biased LED array detects the reflected light from the object. As the distance between the object and LED array decreases, the reflectance increases and thereby the photocurrent increases, as shown in the right frame. (f) A single LED pixel powered by wireless power transmission coil. Right frame shows the IV curve of LED pixel. (g) Microscope image of PN diodes (left) and it S21 value measured at different frequencies in radio frequency range. (h) Microscope image of inductor and capacitor pair (left top). Right top plot shows S21 value of capacitor at various RF frequencies and left bottom plot shows S21 and S11 values of inductor at RF frequencies. Right bottom plot shows the estimated oscillation frequencies for different capacitors.

[0302] Figure 53 provides (a) Passive electrode array on forehead for undeformed (left top) and deformed (right top and bottom) state. Left bottom image shows the partially peeled off state. (b) EEG measurement results for Stroop test. When the target letter matches with the highlighted letter (congruent case) the response speed is faster than unmatched (incongruent case) case. (c) EEG measurement results for eye open and eye close case. Left plot shows raw EEG and right plot shows results after Fourier transformation.

[0303] Figure 54 provides (a) EKG measurement result measured with active EKG sensor (left) and magnified view of single heartbeat (right). (b) EMG measurement result from a right leg during walking (from 0 sec to 10 sec) and standing (from 10 sec to 20 sec) measured with active EMG sensor (left) and conventional passive EMG sensor with conductive gel (right). (c) Magnified view of EMG signal of (b). (d) Corresponding spectrogram for each electrode. (e) EMG measurement result from neck for four different words, "up", "down", "left" and "right". (f) Corresponding spectrogram for four words. (g) Video game control using recorded EMG signal.

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STATEMENTS REGARDING VARIATIONS

[0305] 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 present invention has been specifically disclosed by preferred embodiments, exemplary embodiments and optional features, modification and variation of the concepts herein disclosed may 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 present invention and it will be apparent to one skilled in the art that the present invention may 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 obvious 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.

[0306] 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.

[0307] 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."

[0308] 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.

[0309] Whenever a range is given in the specification, for example, a temperature range, a time range, or a composition 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. 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.

[0310] As used herein, "comprising" is synonymous 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" may be replaced with either of the other two terms. The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein.

[0311] 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 present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may 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

1. A device (100) for interfacing with a tissue in a biological environment, the device (100) comprising:

a flexible or stretchable substrate (110);
a flexible or stretchable electronic circuit comprising one or more sensors and one or more inorganic semiconductor circuit elements (120) supported by the flexible or stretchable substrate (110); and

a barrier layer (130) encapsulating at least a portion of the flexible or stretchable electronic circuit, wherein the barrier layer has a thickness over at least a portion of the electronic circuit selected over the range of 0.25 μm to 1000 μm and an average Young's modulus less
than or equal to 10 GPa,
wherein the barrier layer (130) and the flexible or stretchable substrate (110) limit a net leakage current from the device to the biological environment to an amount which does not adversely affect the tissue and is less than 0.1 $\mu A/cm^2$; and
wherein the flexible or stretchable substrate (110), the flexible or stretchable electronic circuit and the barrier layer (130) provide a net bending stiffness of the device (100) low enough that the device (100) establishes conformal contact with the tissue in the biological environment.

2. The device (100) of claim 1 wherein the sensors are configured to measure:

an electrophysiological signal from the tissue, or a movement of the tissue;
wherein the tissue in the biological environment comprises heart tissue, brain tissue, skin, muscle tissue, nervous system tissue, vascular tissue, epithelial tissue, retina tissue, ear drum, tumor tissue, digestive system structures or any combination of these; and
wherein the barrier layer (130) or the flexible or stretchable substrate (110) is a biocompatible material or a bioinert material.

3. The device (100) of any of claims 1 or 2, wherein the device (100) establishes conformal contact or electrical contact with the tissue *in situ* when the device (100) is placed in physical contact with the tissue in the biological environment, and wherein the conformal contact with the tissue in the biological environment is maintained as the tissue moves or when the device (100) moves.

4. The device (100) of any of claims 1-3, wherein the flexible or stretchable electronic circuit comprises a plurality of electronically interconnected island and bridge structures, wherein the bridge structures comprise a flexible or stretchable electrical interconnect in a serpentine geometry.

5. The device (100) of claim 2-4, wherein at least one of the sensors is in electrical communication or optical communication with the tissue when the device (100) is in conformal contact with the tissue in the biological environment.

6. The device (100) of any of claims 1-5, wherein the flexible or stretchable electronic circuit is a stretchable or flexible electrode array comprising a plurality of electrodes, multiplex circuitry and amplification circuitry.

7. The device (100) of claim 6, wherein the stretchable or flexible electrode array comprises a plurality of electrode unit cells; wherein the number of electrode unit cells is 50 or more, adjacent electrode unit cells are separated from each other by a distance less than or equal to 50 μm, and the electrode unit cells are disposed on an area of the flexible or stretchable substrate (110) ranging from 10 mm^2 to 10,000mm^2.

8. The device (100) of claim 7, wherein each electrode unit cell of the electrode array comprises a contact pad, amplifier and multiplexer, wherein the contact pad provides an electrical interface to the tissue and is in electrical communication with the amplifier and multiplexer.

9. The device (100) of any of claims 1-8, wherein the barrier layer (130) is a moisture barrier.

10. The device (100) of any of claims 1-9 further comprising a transfer substrate supporting said flexible or stretchable substrate (110), said flexible or stretchable electronic circuit or both.

11. The device (100) of any of claims 1-5, wherein the flexible or stretchable electronic circuit is a stretchable or flexible array of light emitting diodes comprising a plurality of light emitting diodes in electrical communication with a plurality of stretchable or flexible electrical interconnects, wherein the flexible array of light emitting diodes comprises a multilayer structure comprising between 2 to 1,000 individually encapsulated LED array layers provided in a multilayer stacked geometry.

12. The device (100) of any of claims 1-11, wherein the barrier layer (130) limits net leakage current from the device (100) to 10 μA or less.

13. The device (100) of any of claims 1-12, wherein the electronic circuit and the barrier layer (130) provide:

a net bending stiffness of the device (100) less than or equal to $1x10^8$ GPa μm^4; or
a net flexural rigidity of the device (100) less than or equal to $1x10^{-4}$ Nm.

14. A method of sensing or actuating a tissue in a biological environment; the method comprising:

providing a subject having the tissue in the biological environment;
providing a conformable device (100), the device (100) comprising
a flexible or stretchable substrate (110);

a flexible or stretchable electronic circuit supported by the flexible or stretchable substrate (110), wherein the flexible or stretchable electronic circuit comprises an plurality of sensors, actuators or both sensors and actuators provided in an array, wherein said sensors or actuators comprise one or more inorganic semiconductor circuit elements (120); and
a barrier layer (130) encapsulating at least a portion of the flexible or stretchable electronic circuit; wherein the barrier layer (130) has a thickness over at least a portion of the electronic circuit selected over the range of 0.25 μm to 1000 μm and an average Young's modulus less than or equal to 10 GPa, and the barrier layer (130) and the flexible or stretchable substrate (110) limit a net leakage current from the device to the biological environment to an amount which does not adversely affect the tissue and is less than 0.1 $\mu A/cm^2$; wherein the flexible or stretchable substrate (110), the flexible or stretchable electronic circuit and the barrier layer (130) provide a net bending stiffness of the device (100) low enough that the conformable device (100) establishes conformal contact with the tissue in the biological environment;

contacting the tissue with the conformable device (100), thereby establishing the conformal contact such that at least a portion of the plurality of sensors, actuators or both sensors and actuators of the array is provided in physical contact, electrical communication, optical communication, fluid communication or thermal communication with the tissue in the biological environment; and sensing or actuating the tissue in contact with the conformable device (100);
wherein the aforesaid is not a method for treatment of the human or animal body by surgery or therapy and is not a diagnostic method practised on the human or animal body.

15. The device (100) of claim 1, wherein the flexible or stretchable substrate (110) has an average Young's modulus less than or equal to 1 MPa; and the barrier layer (130) encapsulating both flexible or stretchable electronic circuit and the flexible or stretchable substrate (110).

16. The method of claim 14, wherein the device (100) is skin-mounted and the interfaced tissue is skin having an average Young's modulus, and the flexible or stretchable substrate (110) as well as the barrier layer (130) have a Young's modulus that is matched to the skin Young's modulus and is less than or equal to 50 times the interfaced tissue average Young's modulus; the flexible or stretchable substrate (110) has an average Young's modulus less than or equal to 1 MPa; and the device (100) further comprises:

a transfer substrate supporting said flexible or stretchable substrate (110),
said flexible or stretchable electronic circuit or both; the method further comprising the steps of:

contacting the conformable electronic device (100) to a receiving surface of said skin, wherein upon contact said flexible or stretchable electronic circuit is positioned between said skin and said a flexible or stretchable substrate (110);
and
at least partially removing said transfer substrate, wherein the device (100) establishes conformal contact with the skin of the subject upon at least partial removal of the transfer substrate.

17. The device (100) of claim 1, wherein the device (100) is skin-mounted and the interfaced tissue is skin having an average Young's modulus, and the flexible or stretchable substrate (110) as well as the barrier have a Young's modulus that is matched to the skin Young's modulus and is less than or equal to 50 times the interfaced tissue average Young's modulus.

18. The device (100) of claim 1, configured to: measure an intensity of electromagnetic radiation from the tissue, measure

temperature, or measure a change in a concentration of ta target molecule at the target tissue.

19. The method of claim 14, wherein the step of sensing or actuating the tissue in contact with the conformable device (100) comprises measuring an electrophysiological signal from the tissue, measuring an acceleration of the tissue, measuring a movement of the tissue, measuring an intensity of electromagnetic radiation from the tissue, measuring a temperature, or measuring a change in a concentration of a target molecule at the tissue.

Patentansprüche

1. Vorrichtung (100) zum Verbinden mit einem Gewebe in einer biologischen Umgebung, wobei die Vorrichtung (100) umfasst:

ein flexibles oder dehnbares Substrat (110);
eine flexible oder dehnbare elektrische Schaltung umfassend einen oder mehrere Sensoren und ein oder mehrere anorganische Halbleiterschaltelemente (120), welche durch das flexible oder dehnbare Substrat (110) unterstützt sind; und
eine Barriereschicht (130), welche zumindest einen Anteil der flexiblen oder dehnbaren elektronischen Schaltung ummantelt, wobei die Barriereschicht eine Dicke über zumindest einen Anteil der elektronischen Schaltung, ausgewählt aus einem Bereich von 0,25 μm bis 1000 μm und einem mittleren E-Modul kleiner oder gleich 10 GPa, aufweist,
wobei die Barriereschicht (130) und das flexible oder dehnbare Substrat (110) einen netto-Leckagestrom von der Vorrichtung zu der biologischen Umgebung auf einen Betrag beschränken, der das Gewebe nicht nachteilig beeinflusst und der kleiner ist als 0,1 $\mu A/cm^2$; und
wobei das flexible oder dehnbare Substrat (110), die flexible oder dehnbare elektrische Schaltung und die Barriereschicht (130) eine netto-Biegesteifigkeit der Vorrichtung (100) bereitstellen, die klein genug ist, so dass die Vorrichtung (100) einen konformen Kontakt mit dem Gewebe in der biologischen Umgebung herstellt.

2. Vorrichtung (100) nach Anspruch 1, wobei die Sensoren ausgestaltet sind zum Messen: eines elektrophysiologischen Signals von dem Gewebe, oder einer Bewegung des Gewebes;
wobei das Gewebe in der biologischen Umgebung Herzgewebe, Hirngewebe, Haut, Muskelgewebe, Nervensystemgewebe, vaskuläres Gewebe, Epithelgewebe, Netzhautgewebe, Trommelfell, Tumorgewebe, Verdauungssystemstrukturen oder jede Kombination von diesen umfasst; und
wobei die Barriereschicht (130) oder das flexible oder dehnbare Substrat (110) ein biokompatibles oder bioinertes Material ist.

3. Vorrichtung (100) nach einem der Ansprüche 1 oder 2, wobei die Vorrichtung (100) konformen Kontakt oder elektrischen Kontakt mit dem Gewebe in situ herstellt, wenn die Vorrichtung (100) in physischen Kontakt mit dem Gewebe in der biologischen Umgebung gebracht ist, und wobei der konforme Kontakt mit dem Gewebe in der biologischen Umgebung aufrechterhalten ist, wenn sich das Gewebe oder die Vorrichtung (100) bewegt.

4. Vorrichtung (100) nach einem der Ansprüche 1-3, wobei die flexible oder dehnbare elektronische Schaltung eine Vielzahl von elektronisch verbundenen Insel- oder Brückenstrukturen umfasst, wobei die Brückenstrukturen eine flexible oder dehnbare elektrische Verbindung in einer Serpentinengeometrie umfassen.

5. Vorrichtung (100) nach einem der Ansprüche 2-4, wobei zumindest einer der Sensoren in elektrischer Verbindung oder optischer Verbindung mit dem Gewebe ist, wenn die Vorrichtung (100) in konformen Kontakt mit dem Gewebe in der biologischen Umgebung ist.

6. Vorrichtung (100) nach einem der Ansprüche 1-5, wobei die flexible oder dehnbare elektronische Schaltung eine dehnbare oder flexible Elektrodenanordnung ist, umfassend eine Vielzahl von Elektroden, Multiplex-Schaltkreisen und Verstärkungs-Schaltkreisen.

7. Vorrichtung (100) nach Anspruch 6, wobei die dehnbare oder flexible Elektrodenanordnung eine Vielzahl von Elektrodeneinheitszellen umfasst; wobei die Anzahl der Elektrodeneinheitszellen 50 oder mehr ist, benachbarte Elektrodeneinheitszellen voneinander beabstandet sind durch einen Abstand weniger oder gleich 50 μm, und die Elektrodeneinheitszellen auf einer Fläche, angefangen von 10 mm^2 bis 10000 mm^2, des flexiblen oder dehnbaren Substrats (110) angeordnet sind.

8. Vorrichtung (100) nach Anspruch 7, wobei jede Elektrodeneinheitszelle der Elektrodenanordnung ein Kontaktpad, einen Verstärker und einen Multiplexer umfasst, wobei das Kontaktpad eine elektrische Schnittstelle zu dem Gewebe darstellt und in elektrischer Verbindung mit dem Verstärker und dem Multiplexer ist.

9. Vorrichtung (100) nach einem der Ansprüche 1-8, wobei die Barriereschicht (130) eine Feuchtigkeitsbarriere ist.

10. Vorrichtung (100) nach einem der Ansprüche 1-9 weiter umfassend ein Transfersubstrat, welches das flexible oder dehnbare Substrat (110), die flexible oder elektronische Schaltung oder beides unterstützt.

11. Vorrichtung (100) nach einem der Ansprüche 1-5, wobei die flexible oder dehnbare elektronische Schaltung eine dehnbare oder flexible Anordnung von lichtemittierenden Dioden ist umfassend eine Vielzahl von lichtemittierenden Dioden in elektrischer Verbindung mit einer Vielzahl von dehnbaren oder flexiblen elektrischen Verbindungen, wobei die flexible Anordnung von lichtemittierenden Dioden eine Multischichtstruktur umfasst, welche zwischen 2 und 1000 individuell ummantelte LED-Anordnungsschichten umfasst, welche in einer Multischichtgestapelten Geometrie bereitgestellt sind.

12. Vorrichtung (100) nach einem der Ansprüche 1-11, wobei die Barriereschicht (130) den netto-Leckagestrom von der Vorrichtung (100) auf 10 μA oder weniger beschränkt.

13. Vorrichtung (100) nach einem der Ansprüche 1-12, wobei die elektronische Schaltung und die Barriereschicht (130) bereitstellen:

eine netto-Biegesteifigkeit der Vorrichtung (100) von weniger als oder gleich $1x10^8$ GPa μm^4; oder
eine netto-Biegesteifigkeit der Vorrichtung (100) von weniger als oder gleich $1x10^{-4}$ Nm.

14. Verfahren zum Erfassen oder Ansteuern eines Gewebes in einer biologischen Umgebung; wobei das Verfahren umfasst:

Bereitstellen eines Subjekts, welches das Gewebe in der biologischen Umgebung aufweist;
Bereitstellen einer konformen Vorrichtung (100), wobei die Vorrichtung (100) ein flexibles oder dehnbares Substrat (110) aufweist;
eine flexible oder dehnbare Schaltung, unterstützt durch das flexible oder dehnbare Substrat (110), wobei das flexible oder dehnbare Substrat (110) eine Vielzahl von Sensoren, Aktuatoren oder beides, Sensoren und Aktuatoren, bereitgestellt in einer Anordnung umfasst, wobei die Sensoren oder Aktuatoren eine oder mehrere anorganische Halbleiterschaltelemente (120) aufweisen; und
eine Barriereschicht (130), welche zumindest einen Anteil der flexiblen oder dehnbaren elektronsichen Schaltung ummantelt, wobei die Barriereschicht (130) eine Dicke über zumindest einen Anteil der elektronischen Schaltung, ausgewählt aus einem Bereich von 0,25 μm bis 1000 μm und einem mittleren E-Modul kleiner oder gleich 10 GPa, aufweist, und wobei die Barriereschicht (130) und das flexible oder dehnbare Substrat (110) einen netto-Leckagestrom von der Vorrichtung zu der biologischen Umgebung beschränken auf einen Betrag, der das Gewebe nicht nachteilig beeinflusst und der kleiner ist als 0,1 $\mu A/cm^2$;
wobei das flexible oder dehnbare Substrat (110), die flexible oder dehnbare elektrische Schaltung und die Barriereschicht (130) eine netto-Biegesteifigkeit, die klein genug ist, der Vorrichtung (100) bereitstellen, so dass die konforme Vorrichtung (100) einen konformen Kontakt mit dem Gewebe in der biologischen Umgebung herstellt;
Kontaktieren des Gewebes mit der konformen Vorrichtung (100), dadurch Herstellung des konformen Kontakts, so dass zumindest ein Anteil der Vielzahl von Sensoren, Aktuatoren oder Sensoren und Aktuatoren der Anordnung in physischen Kontakt, elektrischer Verbindung, optischer Verbindung, fluidischer Verbindung oder thermaler Verbindung mit dem Gewebe in der biologischen Umgebung hergestellt ist; und
Erfassen oder Ansteuern des Gewebes, welches in Kontakt mit der konformen Vorrichtung (100) steht;
wobei das obengenannte kein Verfahren zur Behandlung des Menschen- oder Tierkörpers durch Operation oder Therapie ist und nicht ein diagnostisches Verfahren ist, welches am Menschen- oder Tierkörper durchgeführt wird.

15. Vorrichtung (100) nach Anspruch 1, wobei
das flexible oder dehnbare Substrat (110) ein mittleres E-Modul von weniger oder gleich 1 MPa aufweist; und
wobei die Barriereschicht (130) sowohl die flexible oder dehnbare Schaltung als auch das flexible oder dehnbare Substrat (110) ummantelt.

16. Verfahren nach Anspruch 14, wobei die Vorrichtung (100) auf Haut angebracht ist und das verbundene Gewebe Haut ist, welches ein mittleres E-Modul aufweist, und wobei sowohl das flexible oder dehnbare Substrat (110) als auch die Barriereschicht (130) ein E-Modul aufweisen, welches dem E-Modul der Haut angepasst ist und weniger ist als oder gleich 50-mal dem E-Modul des verbundenen Gewebes;
wobei das flexible oder dehnbare Substrat (110) ein mittleres E-Modul von weniger oder gleich 1 MPa aufweist; und wobei die Vorrichtung (100) weiter umfasst:

ein Transfer-Substrat, welches das flexible oder dehnbare Substrat (110), die flexible oder dehnbare elektronische Schaltung oder beides unterstützt; wobei das Verfahren weiter die Schritte umfasst:

Kontaktieren der konformen elektronischen Vorrichtung (100) an eine Empfangsoberfläche der Haut, wobei bei Kontakt die flexible oder dehnbare elektronische Schaltung positioniert wird zwischen der Haut und dem flexiblen oder dehnbaren Substrat (110); und
zumindest teilweises Entfernen des Transfer-Substrats, wobei die Vorrichtung (100) konformen Kontakt mit der Haut des Subjekts bei zumindest teilweiser Entfernung des Transfer-Substrats herstellt.

17. Vorrichtung (100) nach Anspruch 1, wobei die Vorrichtung (100) auf Haut angebracht ist und das verbundene Gewebe Haut ist, welches ein mittleres E-Modul aufweist, und wobei sowohl das flexible oder dehnbare Substrat (110) als auch die Barriereschicht ein E-Modul aufweisen, welches dem E-Modul der Haut angepasst ist und weniger ist als oder gleich 50-mal dem E-Modul des verbundenen Gewebes.

18. Vorrichtung (100) nach Anspruch 1, ausgestaltet um: eine Intensität von elektromagnetischer Strahlung von dem Gewebe zu messen, Temperatur zu messen, oder eine Veränderung einer Konzentration von dem Zielmolekül in dem Zielgewebe zu messen.

19. Verfahren nach Anspruch 14, wobei der Schritt des Erfassens und Ansteuerns des Gewebes, das in Kontakt mit der konformen Vorrichtung (100) steht, die Messung eines elektrophysiologischen Signals von dem Gewebe, Messung einer Beschleunigung des Gewebes, Messung einer Bewegung des Gewebes, Messung einer Intensität von elektromagnetischer Strahlung von dem Gewebe, Messung einer Temperatur, oder Messung einer Veränderung einer Konzentration eines Zielmoleküls in dem Gewebe umfasst.

Revendications

1. Dispositif (100) pour un interfaçage avec un tissu dans un environnement biologique, le dispositif (100) comprenant :

un substrat flexible ou étirable (110) ;
un circuit électronique flexible ou étirable comprenant un ou plusieurs capteurs et un ou plusieurs éléments de circuit semi-conducteurs inorganiques (120) portés par le substrat flexible ou étirable (110) ; et
une couche barrière (130) encapsulant au moins une partie du circuit électronique flexible ou étirable, la couche barrière ayant une épaisseur sur au moins une partie du circuit électronique sélectionnée sur la plage allant de 0,25 μm à 1000 μm et un module de Young moyen inférieur ou égal à 10 GPa,
dans lequel la couche barrière (130) et le substrat flexible ou étirable (110) limitent un courant de fuite net provenant du dispositif vers l'environnement biologique à une quantité qui n'affecte pas défavorablement le tissu et est inférieure à 0,1 $\mu A/cm^2$; et dans lequel le substrat flexible ou étirable (110), le circuit électronique flexible ou étirable et la couche barrière (130) fournissent une résistance à la flexion nette du dispositif (100) assez faible pour que le dispositif (100) établisse un contact conforme avec le tissu dans l'environnement biologique.

2. Dispositif (100) selon la revendication 1, dans lequel les capteurs sont configurés pour mesurer : un signal électrophysiologique provenant du tissu, ou un mouvement du tissu ;
dans lequel le tissu dans l'environnement biologique comprend un tissu de coeur, un tissu de cerveau, une peau, un tissu de muscle, un tissu de système nerveux, un tissu vasculaire, un tissu épithélial, un tissu de rétine, un tympan d'oreille, un tissu de tumeur, des structures de système digestif ou une quelconque combinaison de ceux-ci ; et
dans lequel la couche barrière (130) ou le substrat flexible ou étirable (110) est un matériau biocompatible ou un matériau bio-inerte.

3. Dispositif (100) selon l'une quelconque des revendications 1 ou 2, dans lequel le dispositif (100) établit un contact

conforme ou un contact électrique avec le tissu in situ lorsque le dispositif (100) est placé en contact physique avec le tissu dans l'environnement biologique, et dans lequel le contact conforme avec le tissu dans l'environnement biologique est maintenu lorsque le tissu se déplace ou lorsque le dispositif (100) se déplace.

4. Dispositif (100) selon l'une quelconque des revendications 1 à 3, dans lequel le circuit électronique flexible ou étirable comprend une pluralité de structures d'îlot et de pont interconnectées électroniquement, les structures de pont comprenant une interconnexion électrique flexible ou étirable dans une géométrie de serpentin.

5. Dispositif (100) selon l'une des revendications 2 à 4, dans lequel au moins l'un des capteurs est en communication électrique ou en communication optique avec le tissu lorsque le dispositif (100) est en contact conforme avec le tissu dans l'environnement biologique.

6. Dispositif (100) selon l'une quelconque des revendications 1 à 5, dans lequel le circuit électronique flexible ou étirable est un réseau d'électrodes étirable ou flexible comprenant une pluralité d'électrodes, de circuiterie de multiplexage et de circuiterie d'amplification.

7. Dispositif (100) selon la revendication 6, dans lequel le réseau d'électrodes étirable ou flexible comprend une pluralité de cellules unitaires d'électrode ; le nombre de cellules unitaires d'électrode étant de 50 ou plus, des cellules unitaires d'électrode adjacentes étant séparées les unes des autres d'une distance inférieure ou égale à 50 μm, et les cellules unitaires d'électrode étant disposées sur une surface du substrat flexible ou étirable (110) allant de 10 mm^2 à 10 000 mm^2.

8. Dispositif (100) selon la revendication 7, dans lequel chaque cellule unitaire d'électrode du réseau d'électrodes comprend un plot de contact, un amplificateur et un multiplexeur, le plot de contact fournissant une interface électrique avec le tissu et étant en communication électrique avec l'amplificateur et le multiplexeur.

9. Dispositif (100) selon l'une quelconque des revendications 1 à 8, dans lequel la couche barrière (130) est une barrière contre l'humidité.

10. Dispositif (100) selon l'une quelconque des revendications 1 à 9, comprenant en outre un substrat de transfert portant ledit substrat flexible ou étirable (110), ledit circuit électronique flexible ou étirable ou les deux.

11. Dispositif (100) selon l'une quelconque des revendications 1 à 5, dans lequel le circuit électronique flexible ou étirable est un réseau étirable ou flexible de diodes électroluminescentes comprenant une pluralité de diodes électroluminescentes en communication électrique avec une pluralité d'interconnexions électriques étirables ou flexibles, le réseau flexible de diodes électroluminescentes comprenant une structure multicouche comprenant entre 2 à 1 000 couches de réseau de DEL encapsulées individuellement agencées dans une géométrie empilée multicouche.

12. Dispositif (100) selon l'une quelconque des revendications 1 à 11, dans lequel la couche barrière (130) limite un courant de fuite net provenant du dispositif (100) à 10 μA ou moins.

13. Dispositif (100) selon l'une quelconque des revendications 1 à 12, dans lequel le circuit électronique et la couche barrière (130) fournissent :

une résistance à la flexion nette du dispositif (100) inférieure ou égale à 1×10^8 GPa μm^4 ; ou
une rigidité à la flexion nette du dispositif (100) inférieure ou égale à 1×10^{-4} Nm.

14. Procédé de détection ou d'actionnement d'un tissu dans un environnement biologique ; le procédé comprenant :

la fourniture d'un sujet ayant le tissu dans l'environnement biologique ;
la fourniture d'un dispositif conforme (100), le dispositif (100) comprenant un substrat flexible ou étirable (110) ;
un circuit électronique flexible ou étirable porté par le substrat flexible ou étirable (110), le circuit électronique flexible ou étirable comprenant une pluralité de capteurs, des actionneurs ou à la fois des capteurs et des actionneurs agencés dans un réseau, lesdits capteurs ou actionneurs comprenant un ou plusieurs éléments de circuit semi-conducteurs inorganiques (120) ; et
une couche barrière (130) encapsulant au moins une partie du circuit électronique flexible ou étirable ; la couche barrière (130) ayant une épaisseur sur au moins une partie du circuit électronique sélectionnée sur la plage allant de 0,25 μm à 1000 μm et un module de Young moyen inférieur ou égal à 10 GPa, et la couche barrière

(130) et le substrat flexible ou étirable (110) limitant un courant de fuite net provenant du dispositif vers l'environnement biologique à une quantité qui n'affecte pas défavorablement le tissu et est inférieure à 0,1 $\mu A/cm^2$; dans lequel le substrat flexible ou étirable (110), le circuit électronique flexible ou étirable et la couche barrière (130) fournissent une résistance à la flexion nette du dispositif (100) assez faible pour que le dispositif conforme (100) établisse un contact conforme avec le tissu dans l'environnement biologique ;
la mise en contact du tissu avec le dispositif conforme (100), établissant ainsi le contact conforme de telle sorte qu'au moins une partie de la pluralité de capteurs, d'actionneurs ou à la fois de capteurs et d'actionneurs du réseau est disposée en contact physique, en communication électrique, en communication optique, en communication fluidique ou en communication thermique avec le tissu dans l'environnement biologique ; et
la détection ou l'actionnement du tissu en contact avec le dispositif conforme (100) ; dans lequel ce qui précède n'est pas un procédé pour un traitement du corps humain ou animal par chirurgie ou thérapie et n'est pas une méthode de diagnostic pratiquée sur le corps humain ou animal.

15. Dispositif (100) selon la revendication 1, dans lequel
le substrat flexible ou étirable (110) possède un module de Young moyen inférieur ou égal à 1 MPa ; et
la couche barrière (130) encapsule à la fois le circuit électronique flexible ou étirable et le substrat flexible ou étirable (110).

16. Procédé selon la revendication 14, dans lequel le dispositif (100) est monté sur la peau et le tissu interfacé est une peau ayant un module de Young moyen, et le substrat flexible ou étirable (110) ainsi que la couche barrière (130) ont un module de Young qui est mis en correspondance avec le module de Young de peau et est inférieur ou égal à 50 fois le module de Young moyen de tissu interfacé ;
le substrat flexible ou étirable (110) possède un module de Young moyen inférieur ou égal à 1 MPa ;
et le dispositif (100) comprend en outre :

un substrat de transfert portant ledit substrat flexible ou étirable (110), ledit circuit électronique flexible ou étirable ou les deux ; le procédé comprenant en outre les étapes suivantes :

la mise en contact du dispositif électronique conforme (100) avec une surface de réception de ladite peau, où lors du contact ledit circuit électronique flexible ou étirable est positionné entre ladite peau et ledit substrat flexible ou étirable (110) ; et le retrait au moins partiel dudit substrat de transfert, le dispositif (100) établissant un contact conforme avec la peau du sujet après retrait au moins partiel du substrat de transfert.

17. Dispositif (100) selon la revendication 1, dans lequel le dispositif (100) est monté sur la peau et le tissu interfacé est une peau ayant un module de Young moyen, et le substrat flexible ou étirable (110) ainsi que la barrière ont un module de Young qui est mis en correspondance avec le module de Young de peau et est inférieur ou égal à 50 fois le module de Young moyen de tissu interfacé.

18. Dispositif (100) selon la revendication 1, configuré pour: mesurer une intensité de rayonnement électromagnétique provenant du tissu, mesurer une température, ou mesurer un changement d'une concentration d'une molécule cible au niveau du tissu cible.

19. Procédé selon la revendication 14, dans lequel l'étape consistant à détecter ou actionner le tissu en contact avec le dispositif conforme (100) comprend la mesure d'un signal électro-physiologique provenant du tissu, la mesure d'une accélération du tissu, la mesure d'un mouvement du tissu, la mesure d'une intensité de rayonnement électromagnétique provenant du tissu, la mesure d'une température ou la mesure d'un changement d'une concentration d'une molécule cible au niveau du tissu.

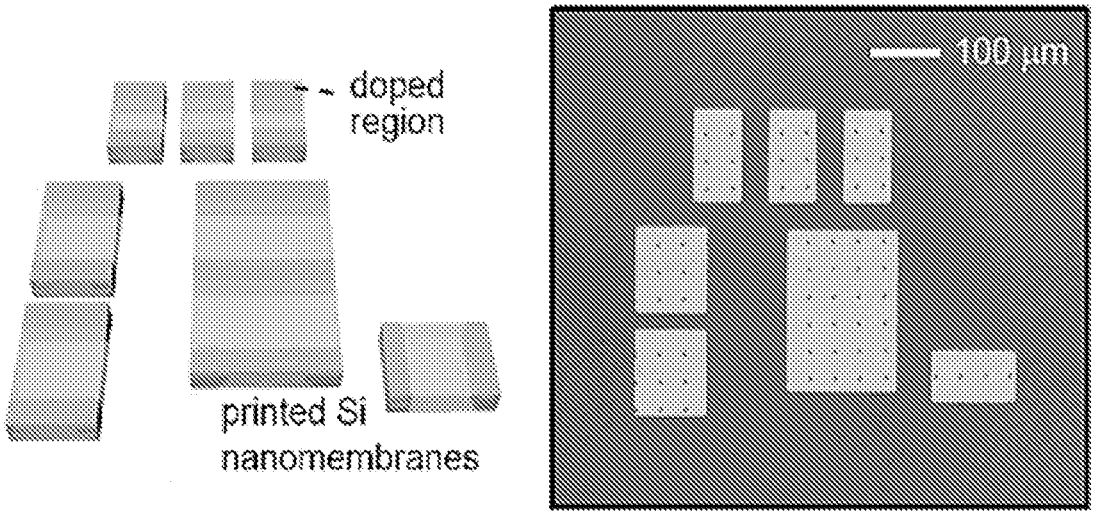


Figure 1a

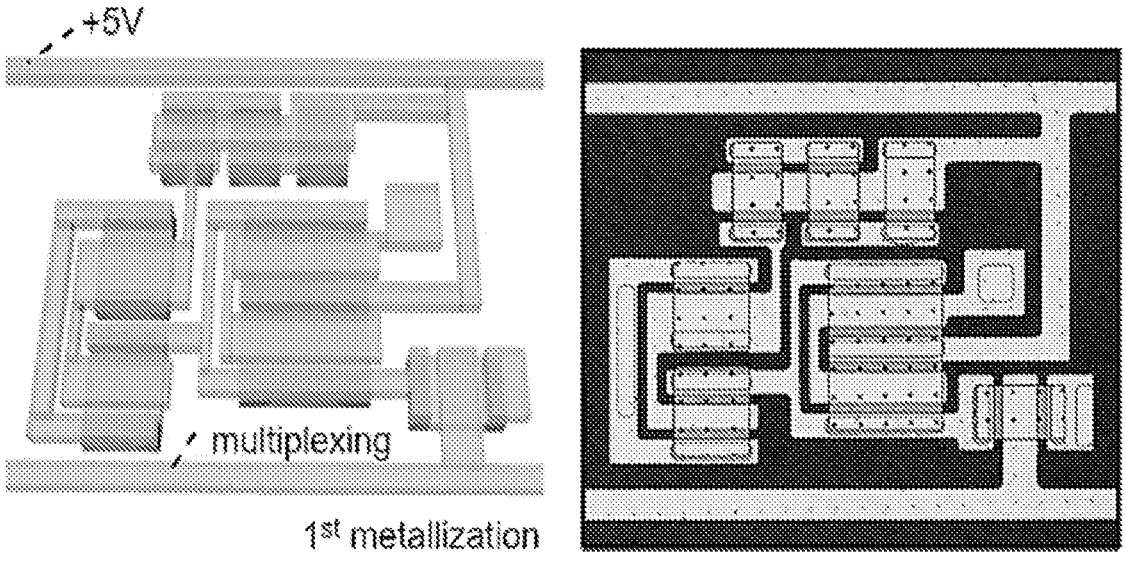


Figure 1b

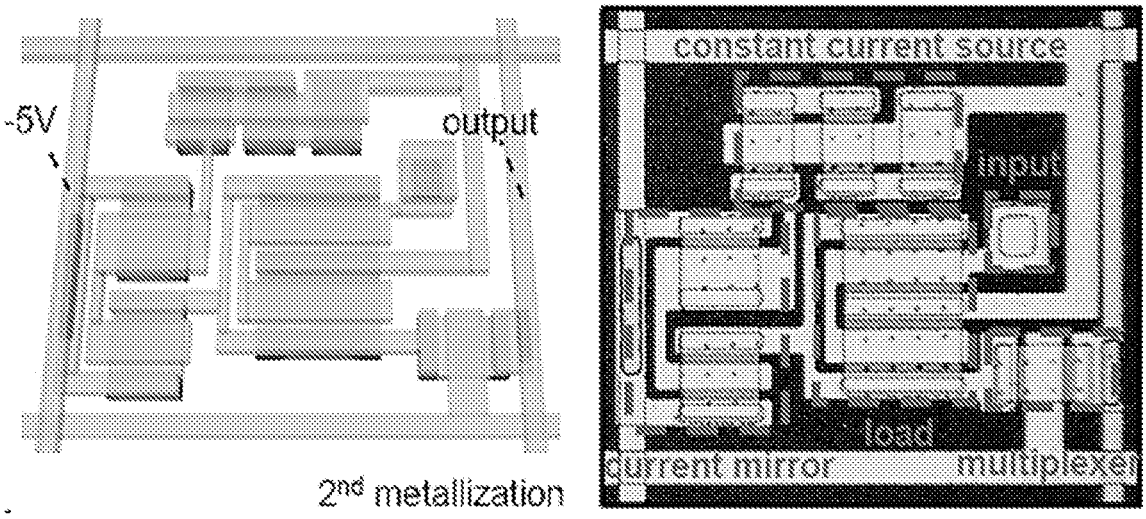


Figure 1c

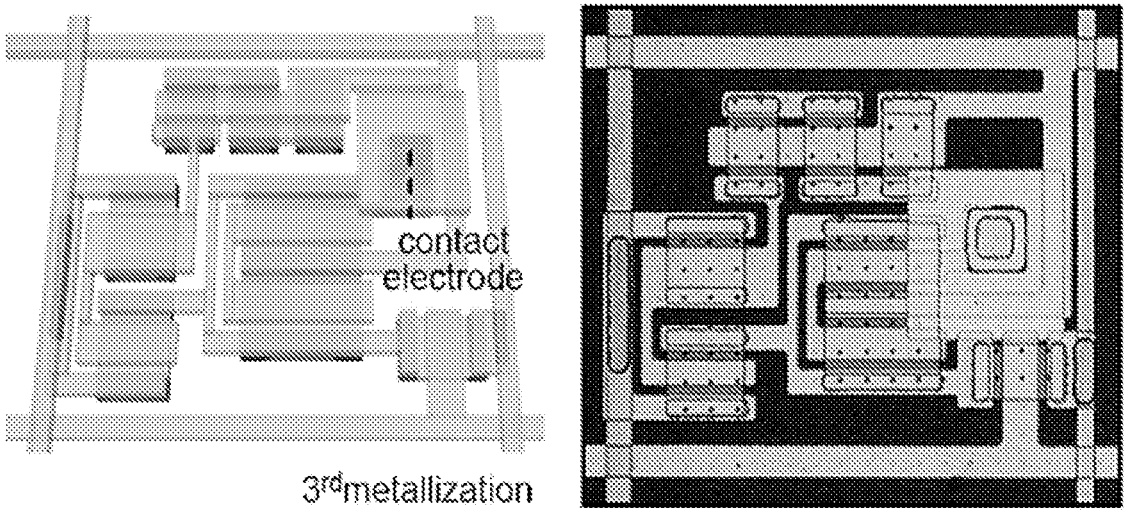


Figure 1d

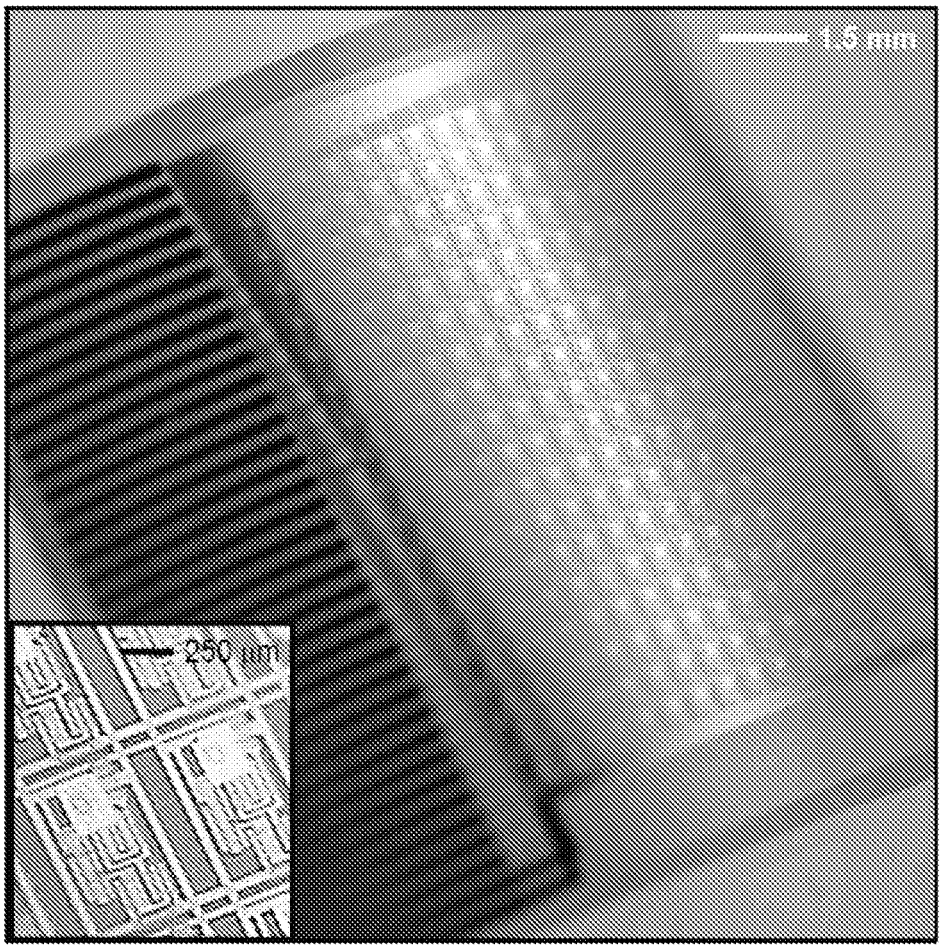


Figure 1e

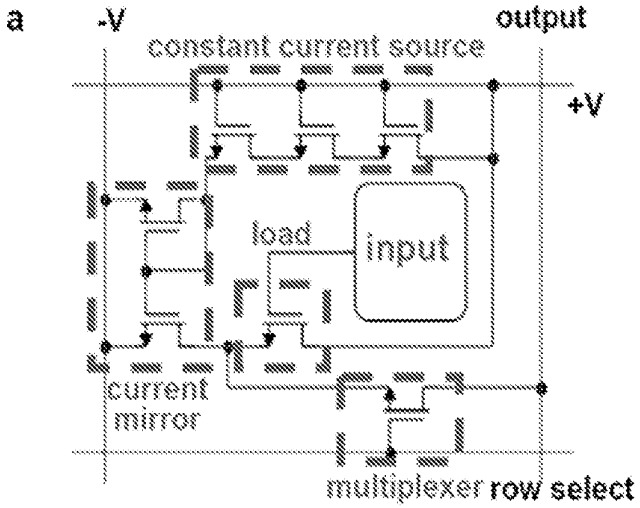


Figure 2a

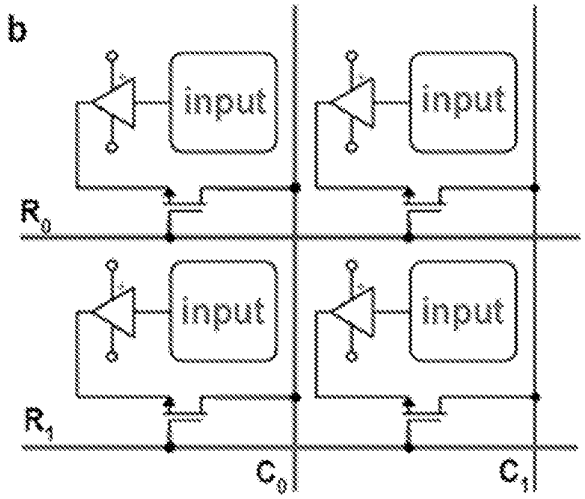
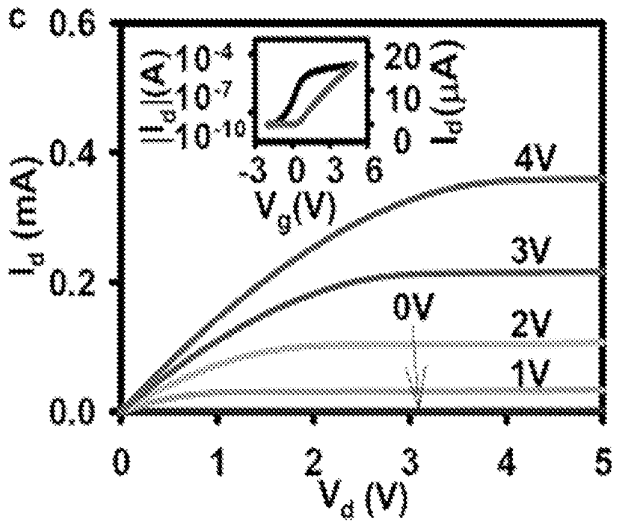


Figure 2b



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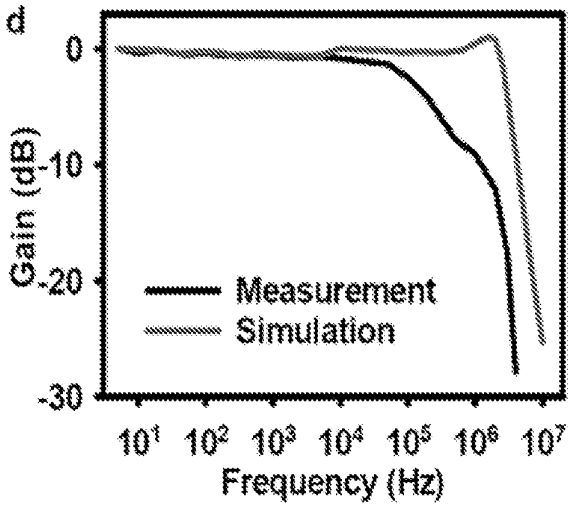


Figure 2d

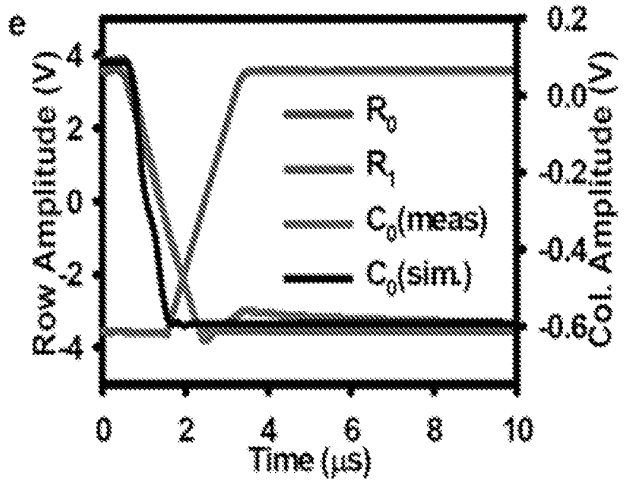


Figure 2e

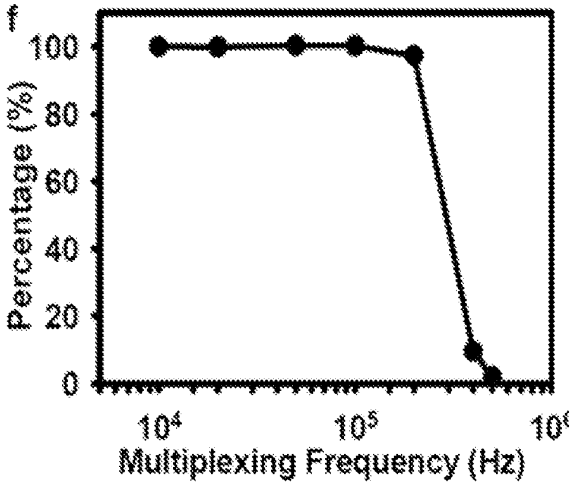


Figure 2f

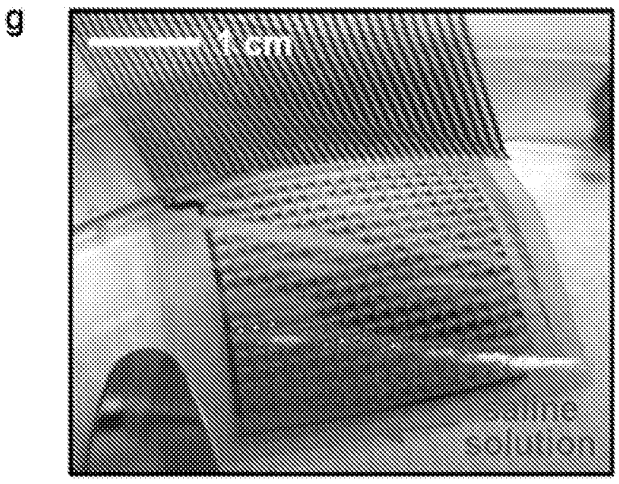


Figure 2g

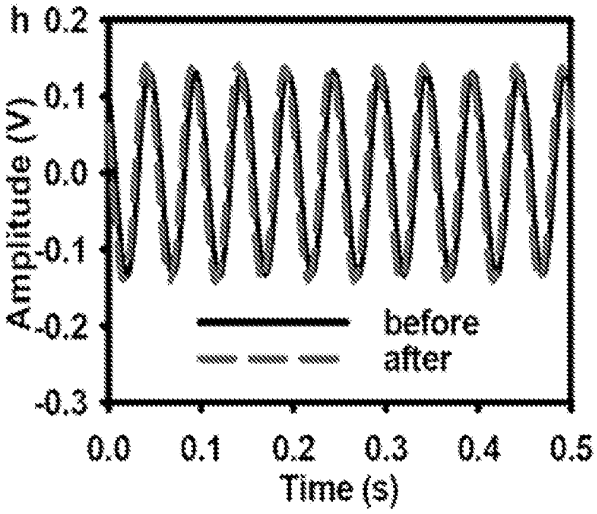


Figure 2h

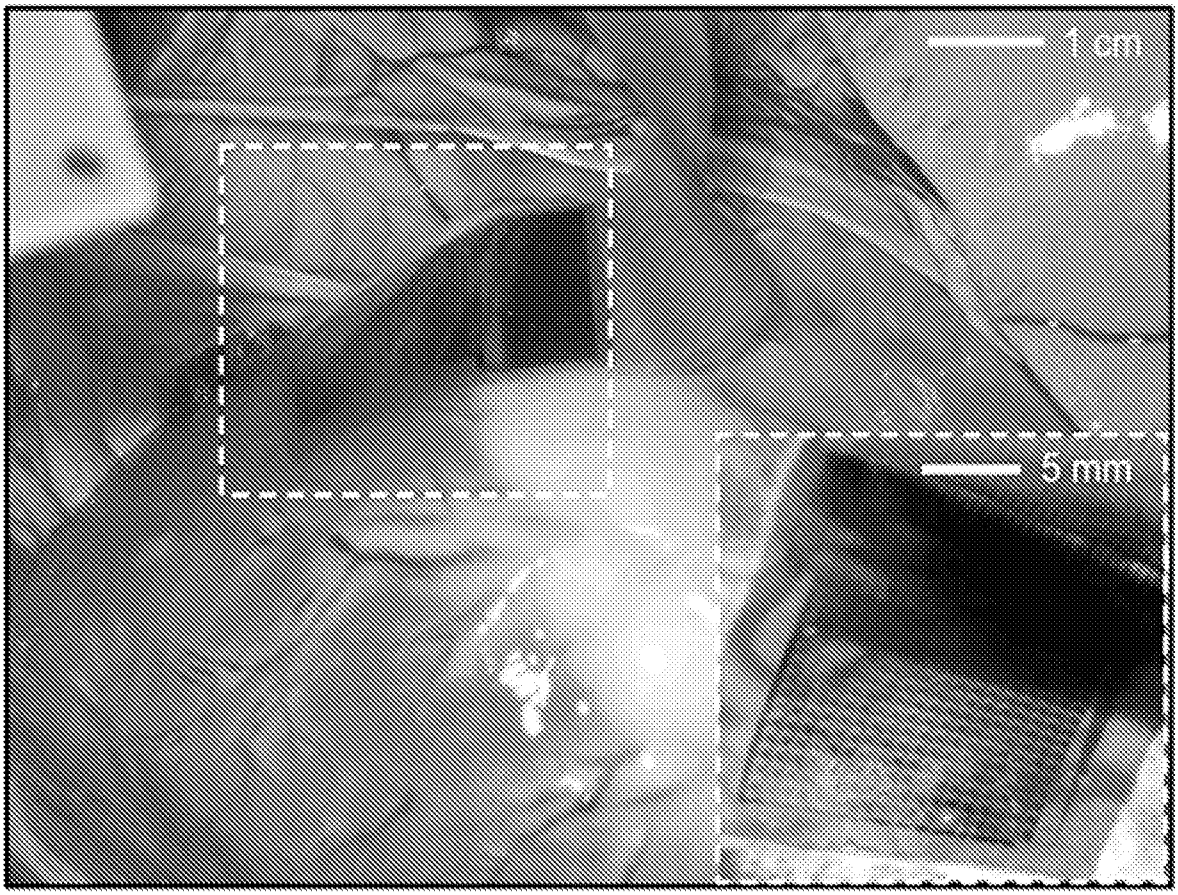


Figure 3a

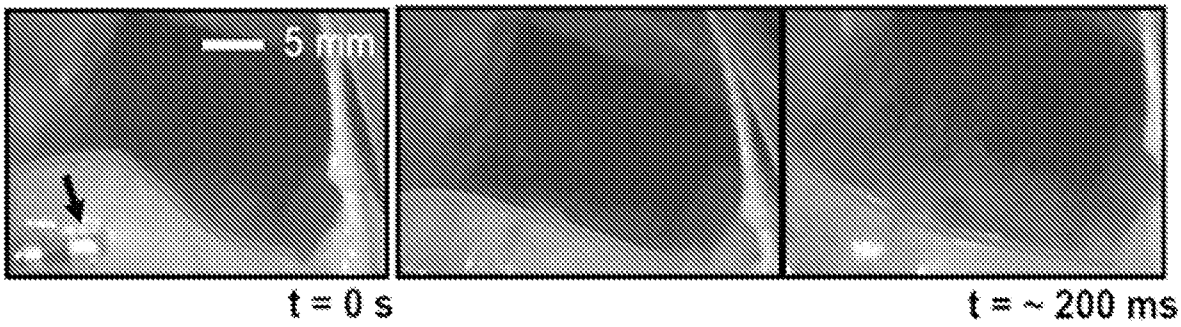


Figure 3b

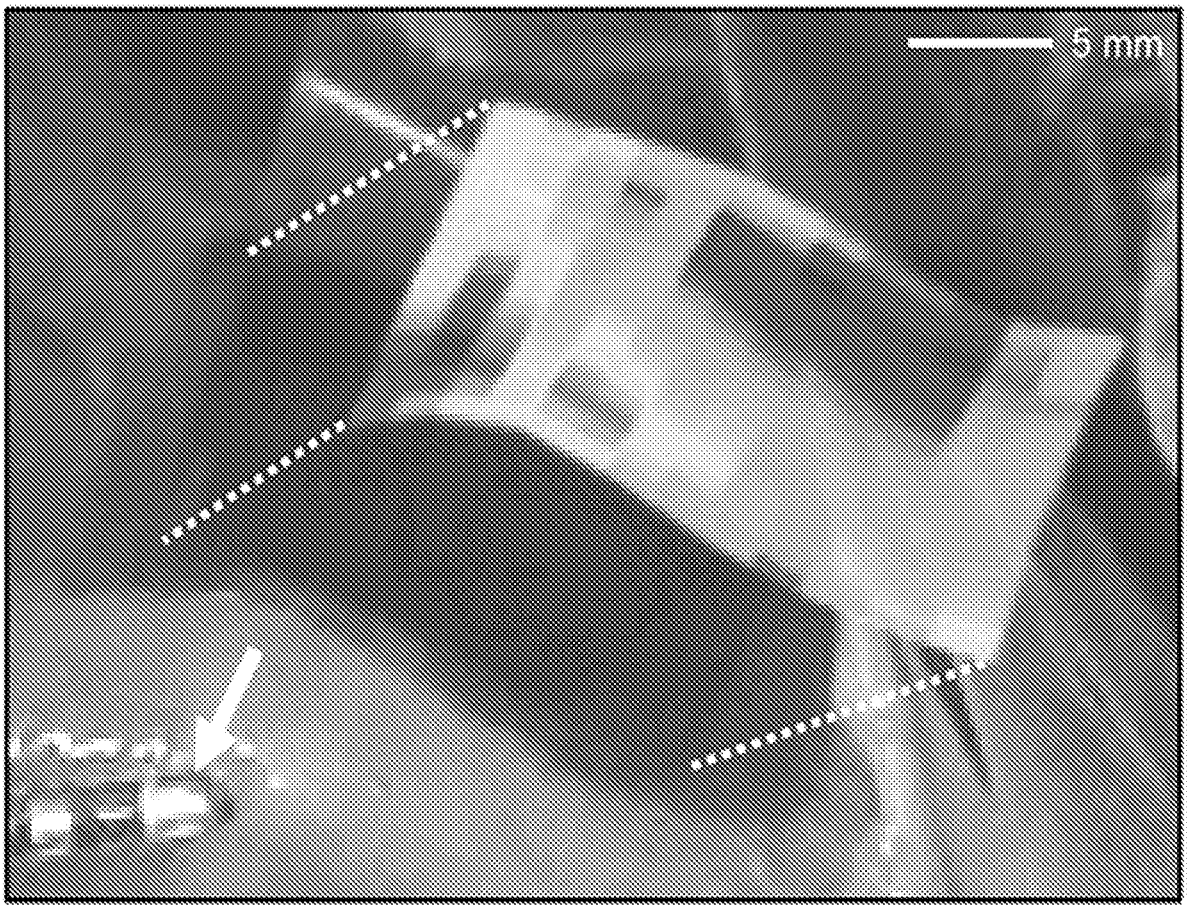


Figure 3c

Figure 4a

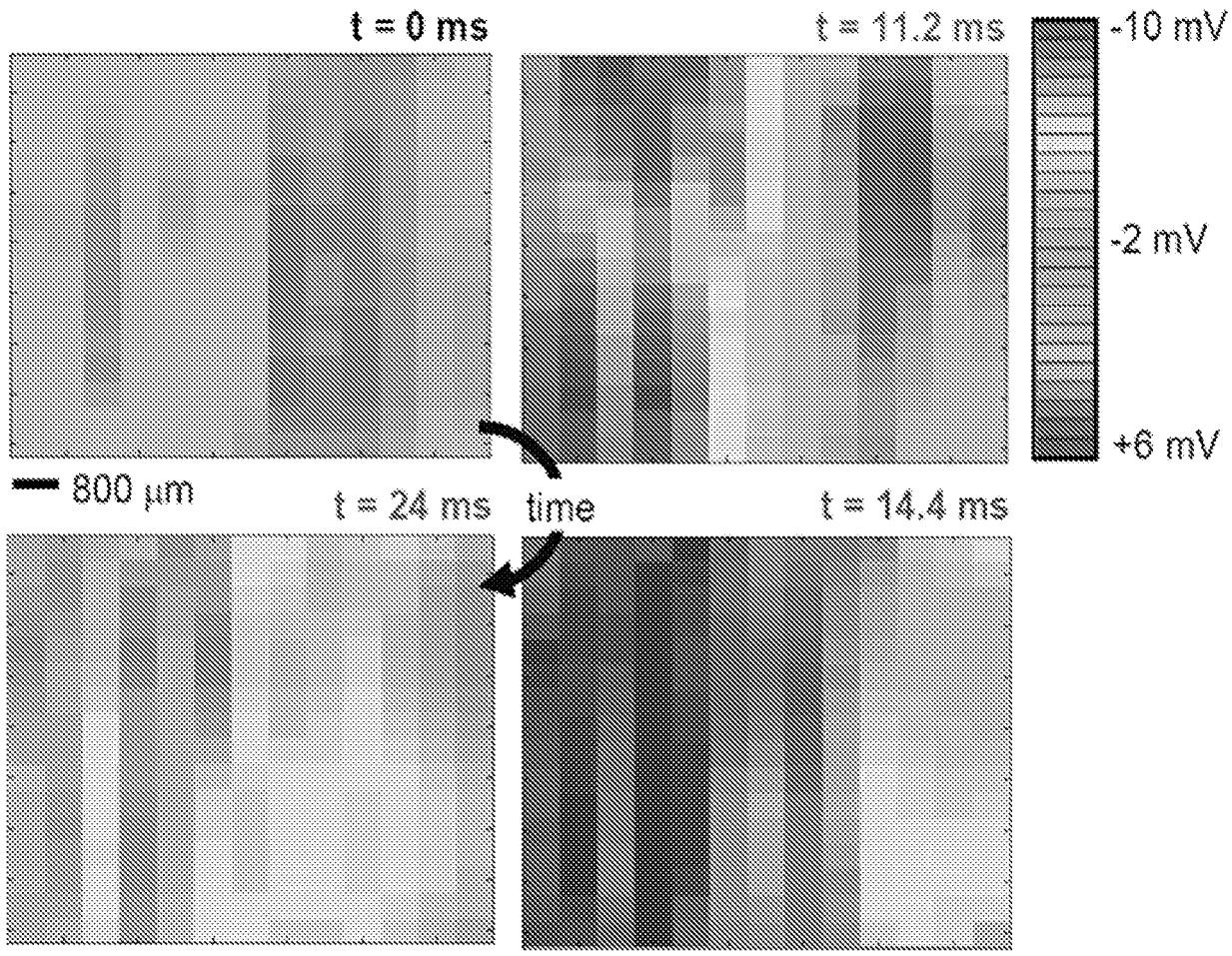


Figure 4b

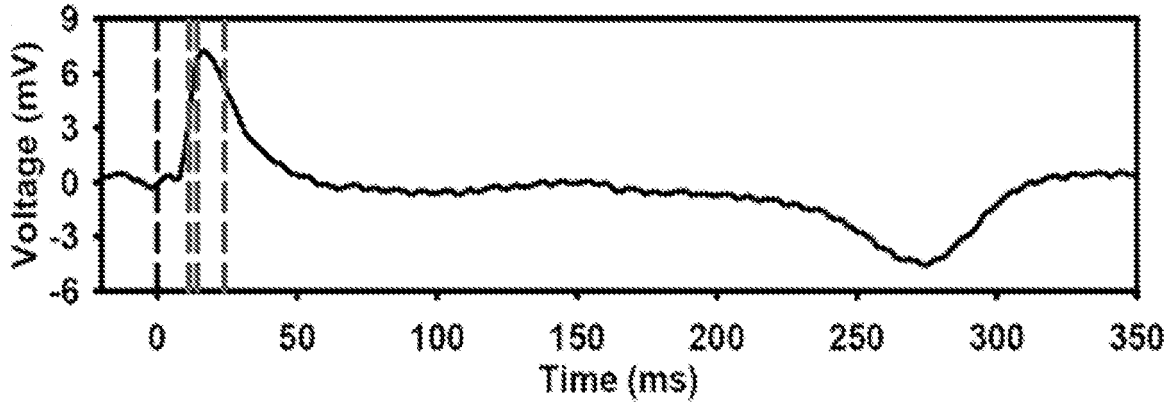


Figure 4c

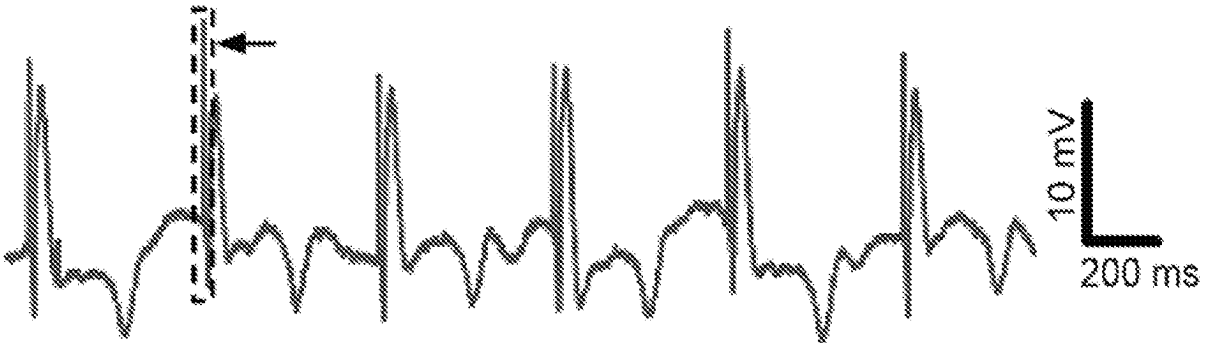


Figure 4d

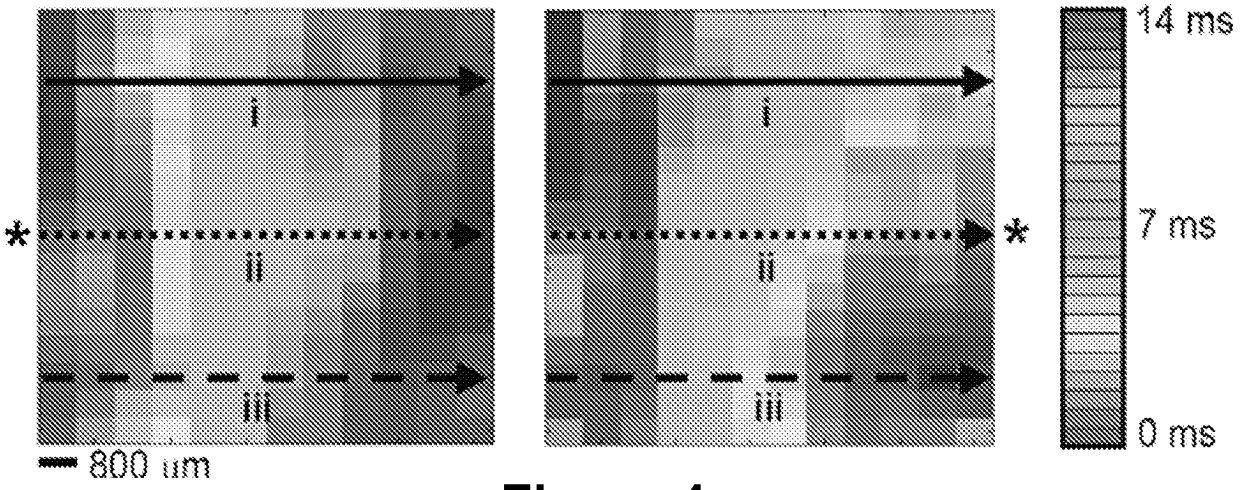


Figure 4e

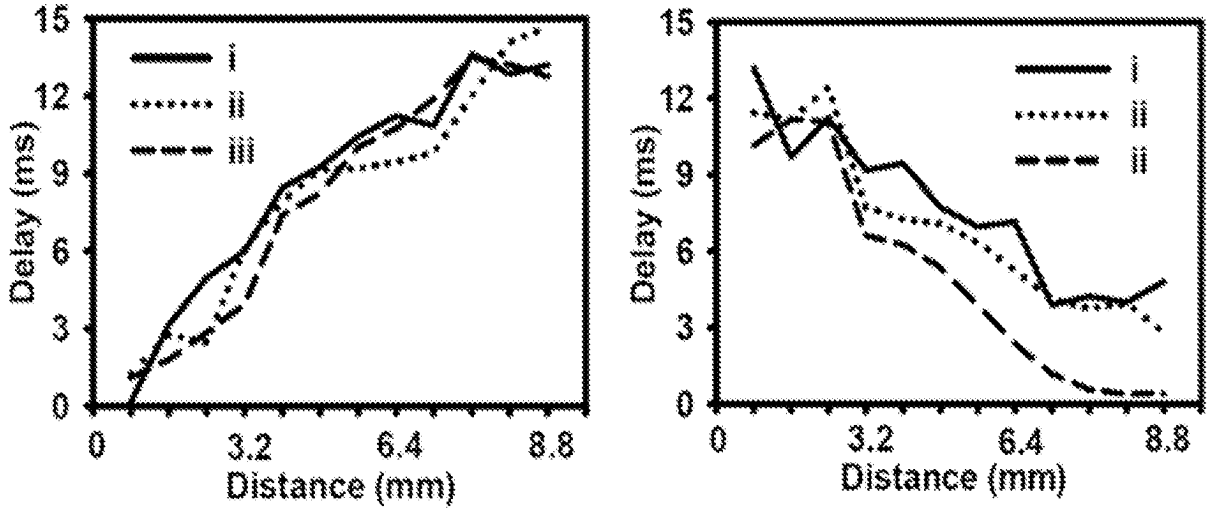


Figure 4f

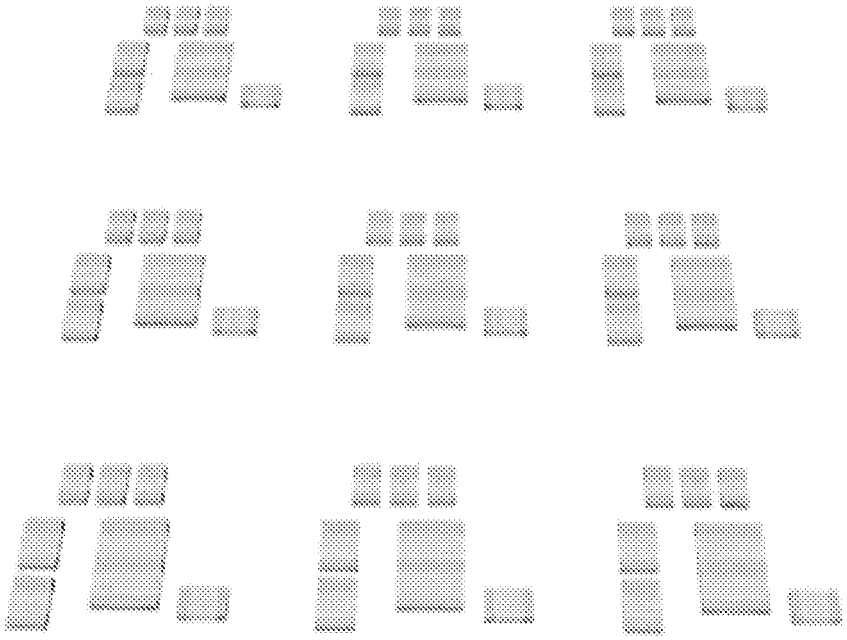


Figure 5a

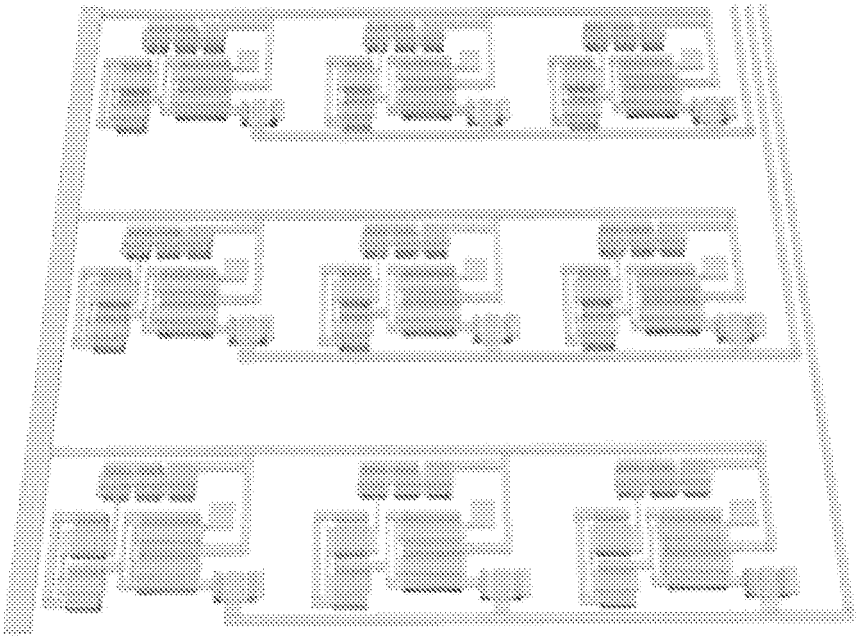


Figure 5b

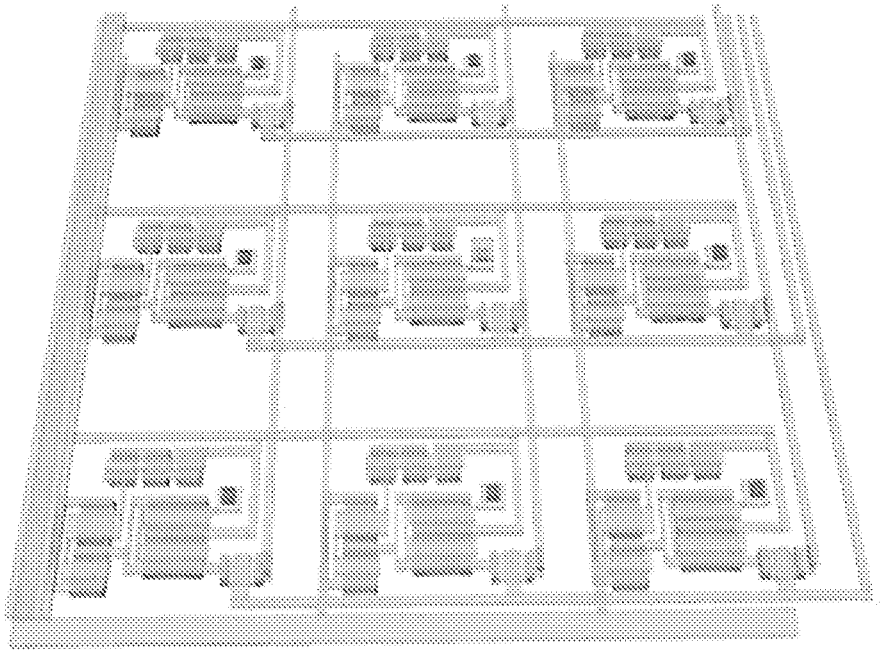


Figure 5c

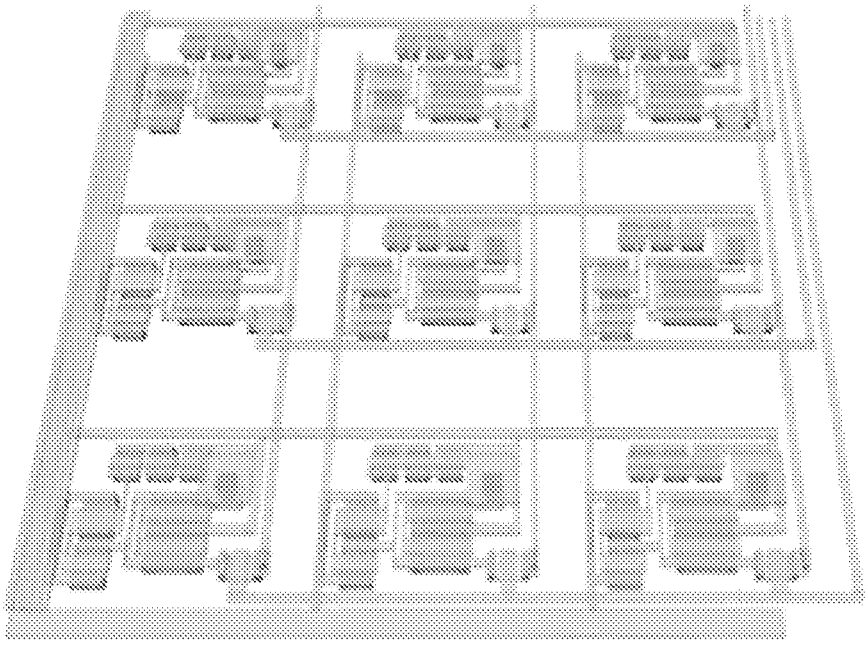


Figure 5d

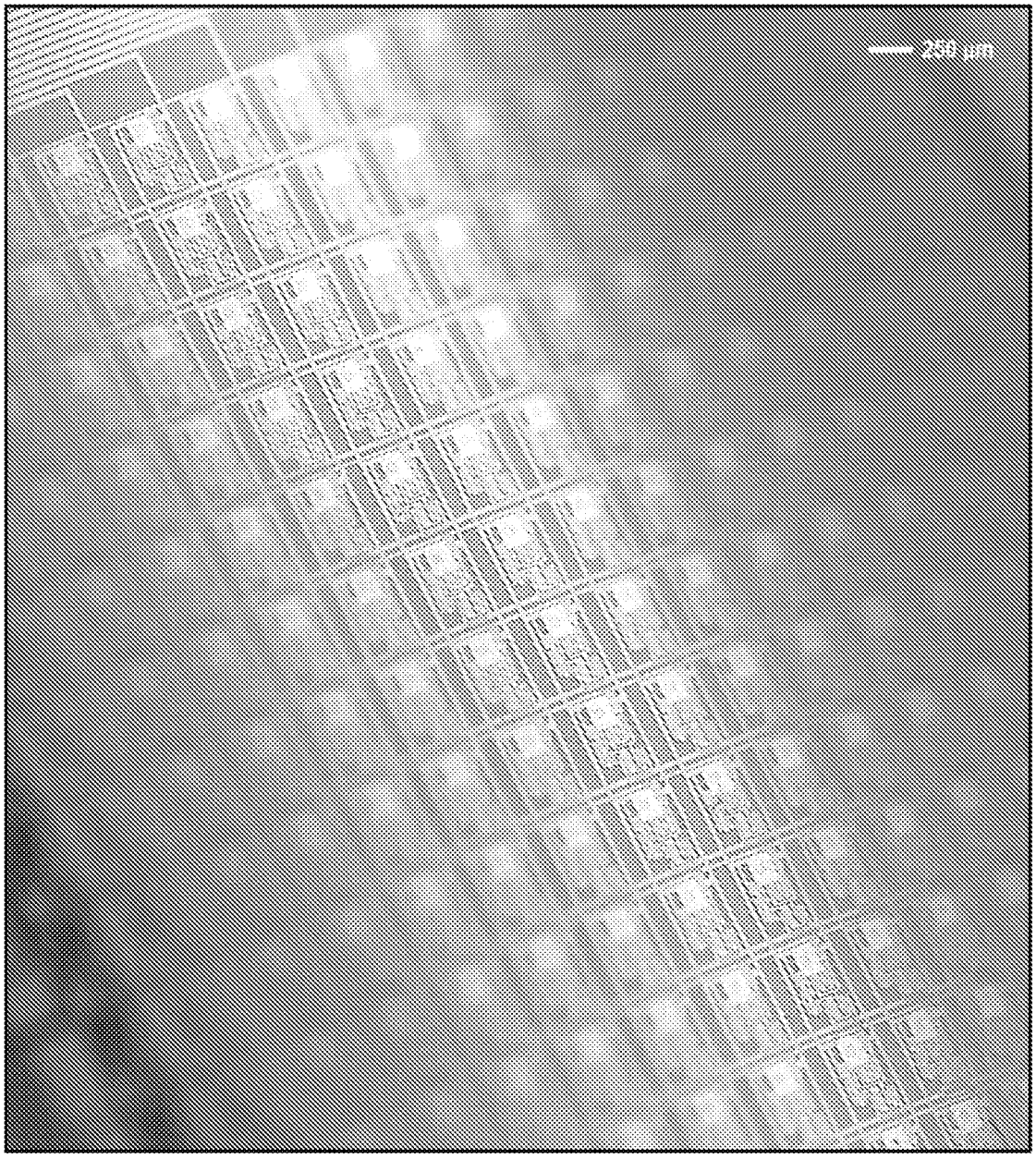


Figure 6

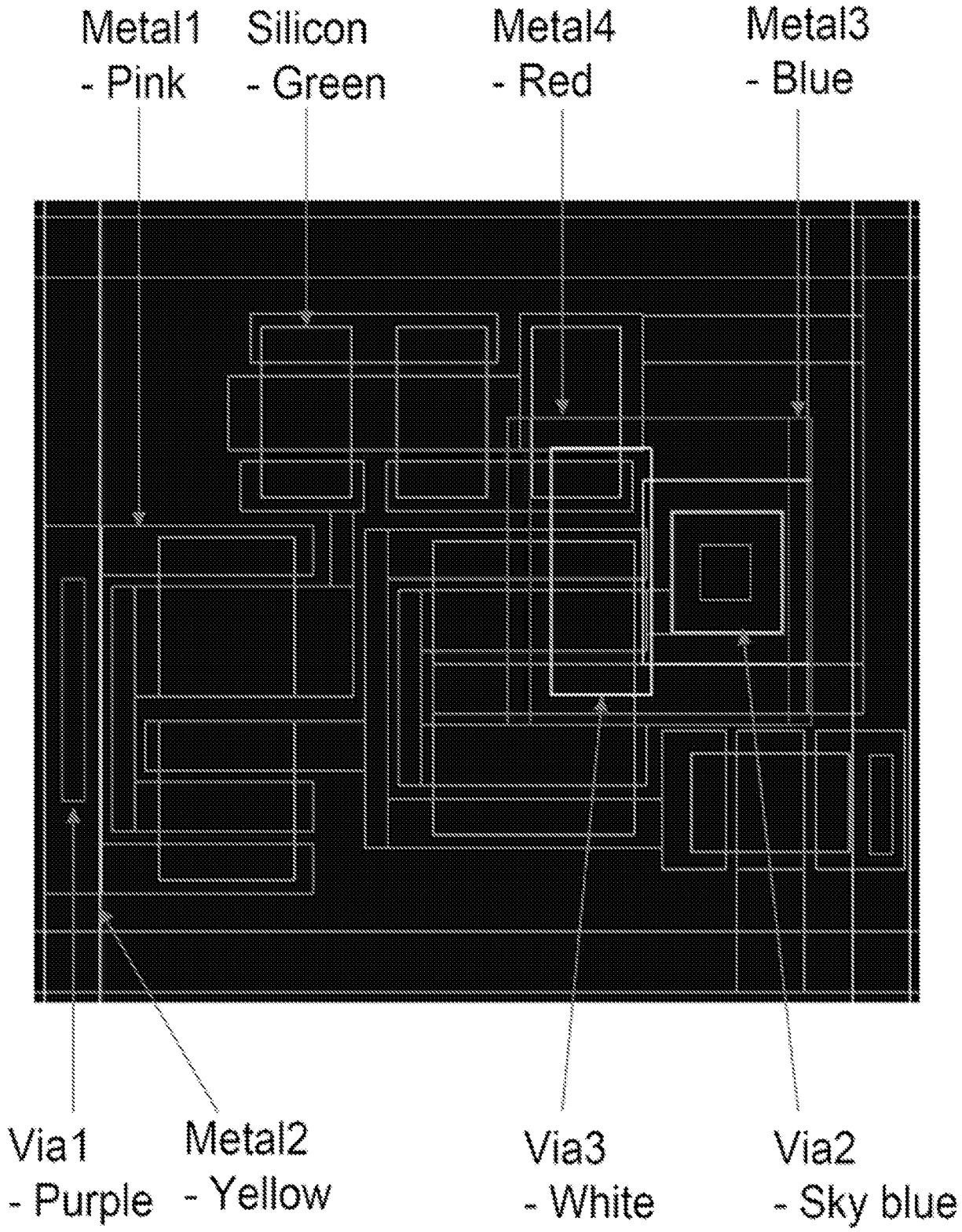

Metal1
- Pink
Silicon
- Green
Metal4
- Red
Metal3
- Blue
Via1
- Purple
Metal2
- Yellow
Via3
- White
Via2
- Sky blue

Figure 7

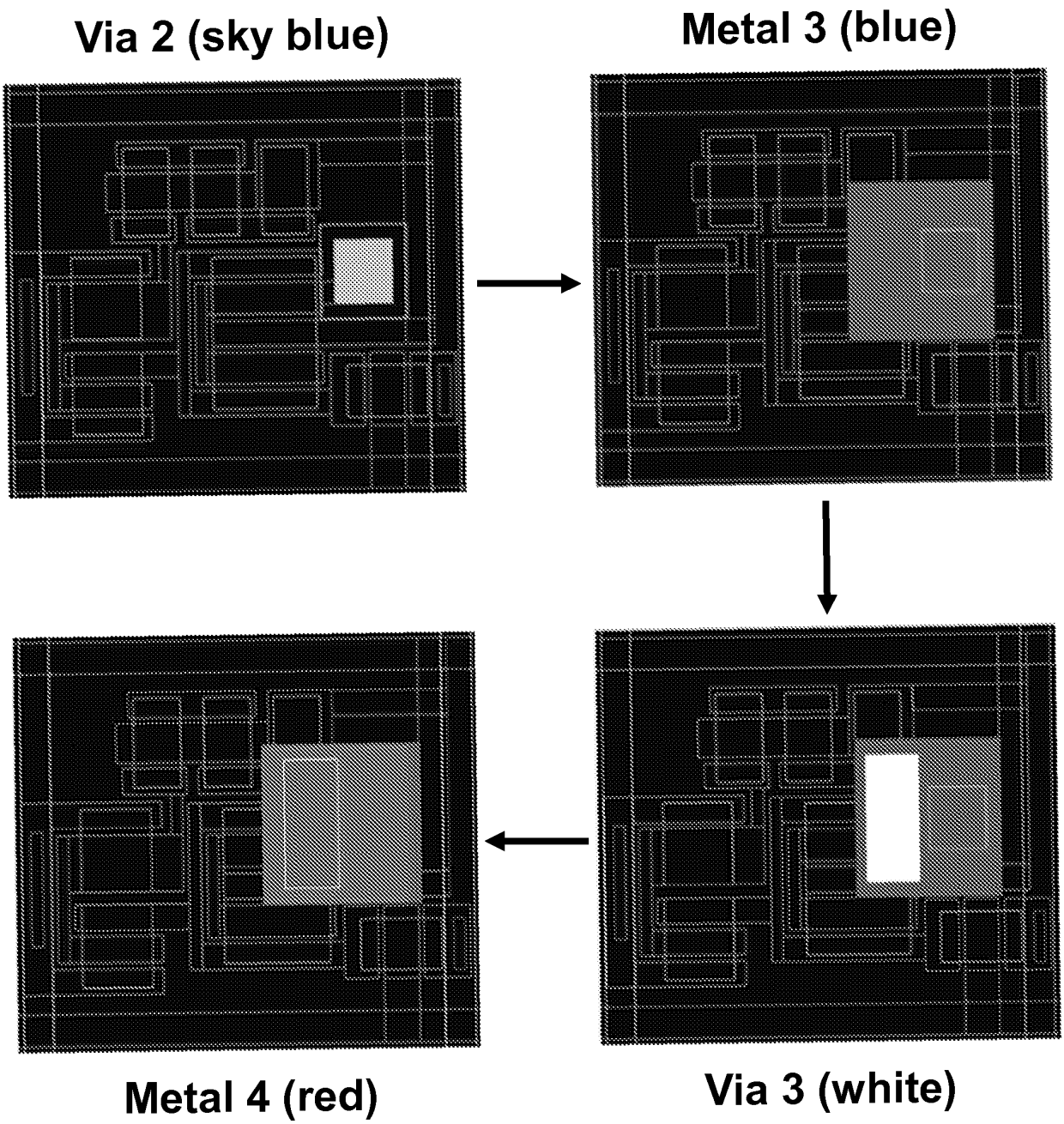


Figure 8

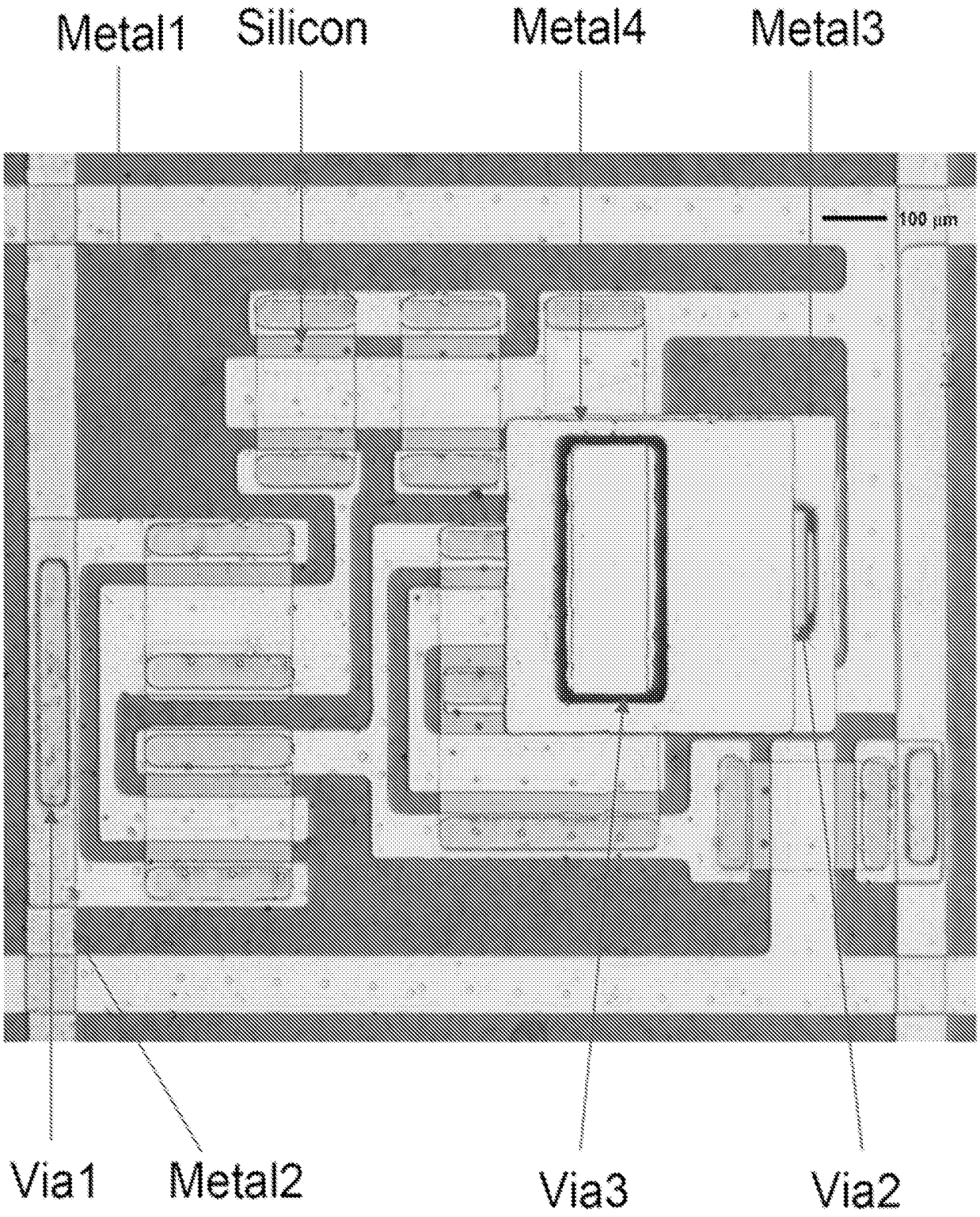


Figure 9

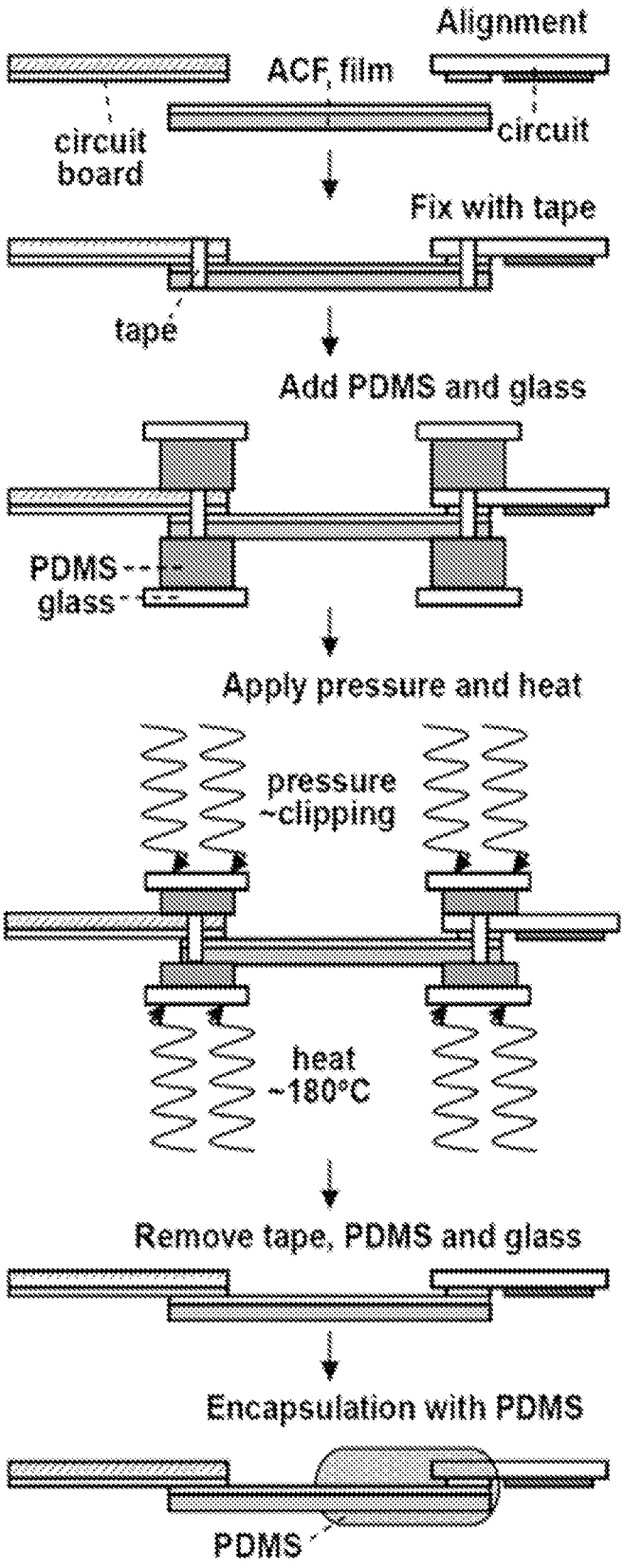

Alignment
ACF film
circuit board
circuit
Fix with tape
tape
Add PDMS and glass
PDMS
glass
Apply pressure and heat
pressure ~clipping
heat ~180°C
Remove tape, PDMS and glass
Encapsulation with PDMS
PDMS

Figure 10a

Figure 10b

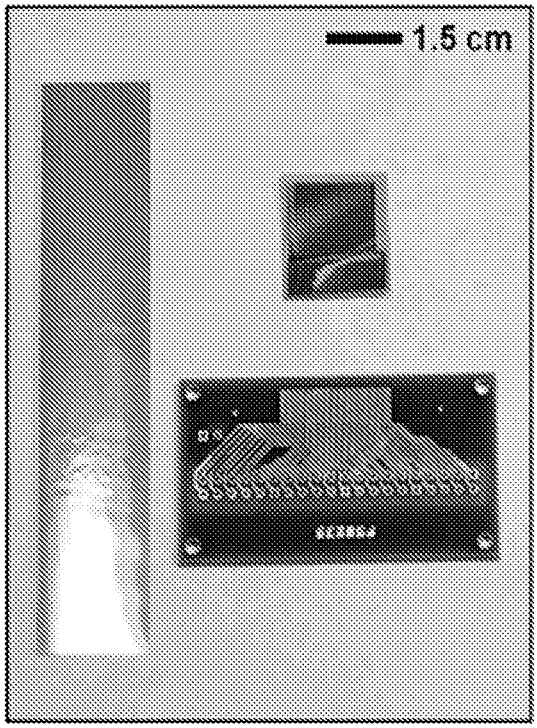


Figure 10c

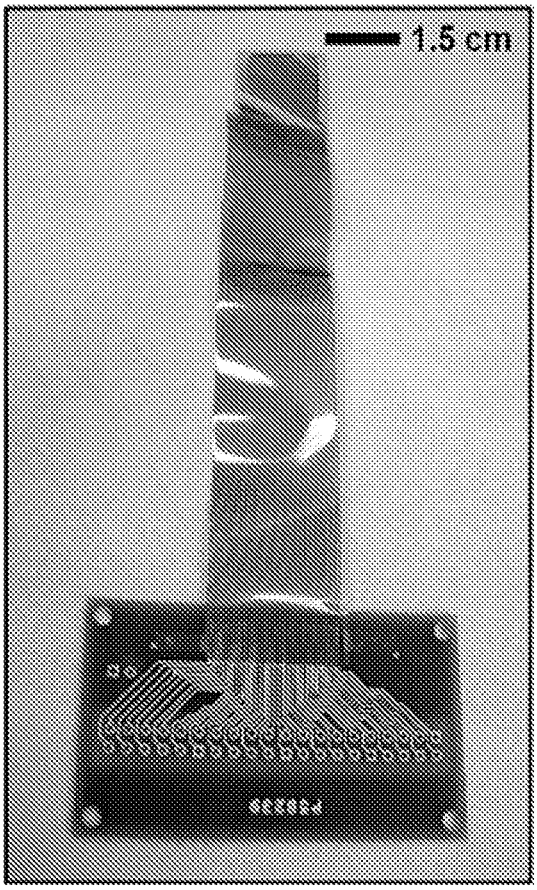


Figure 11a

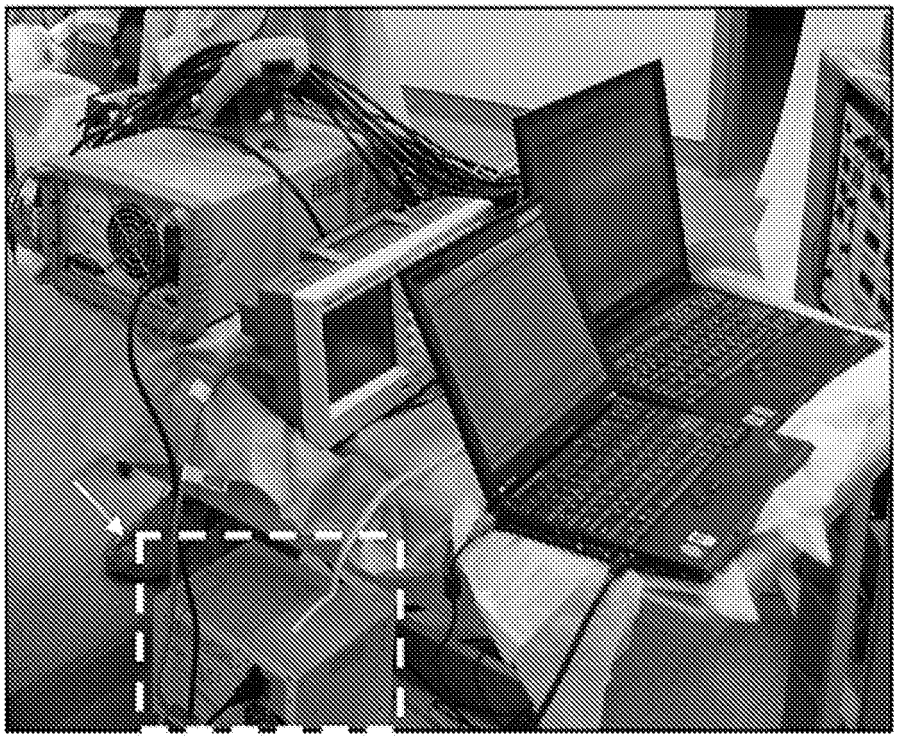


Figure 11b

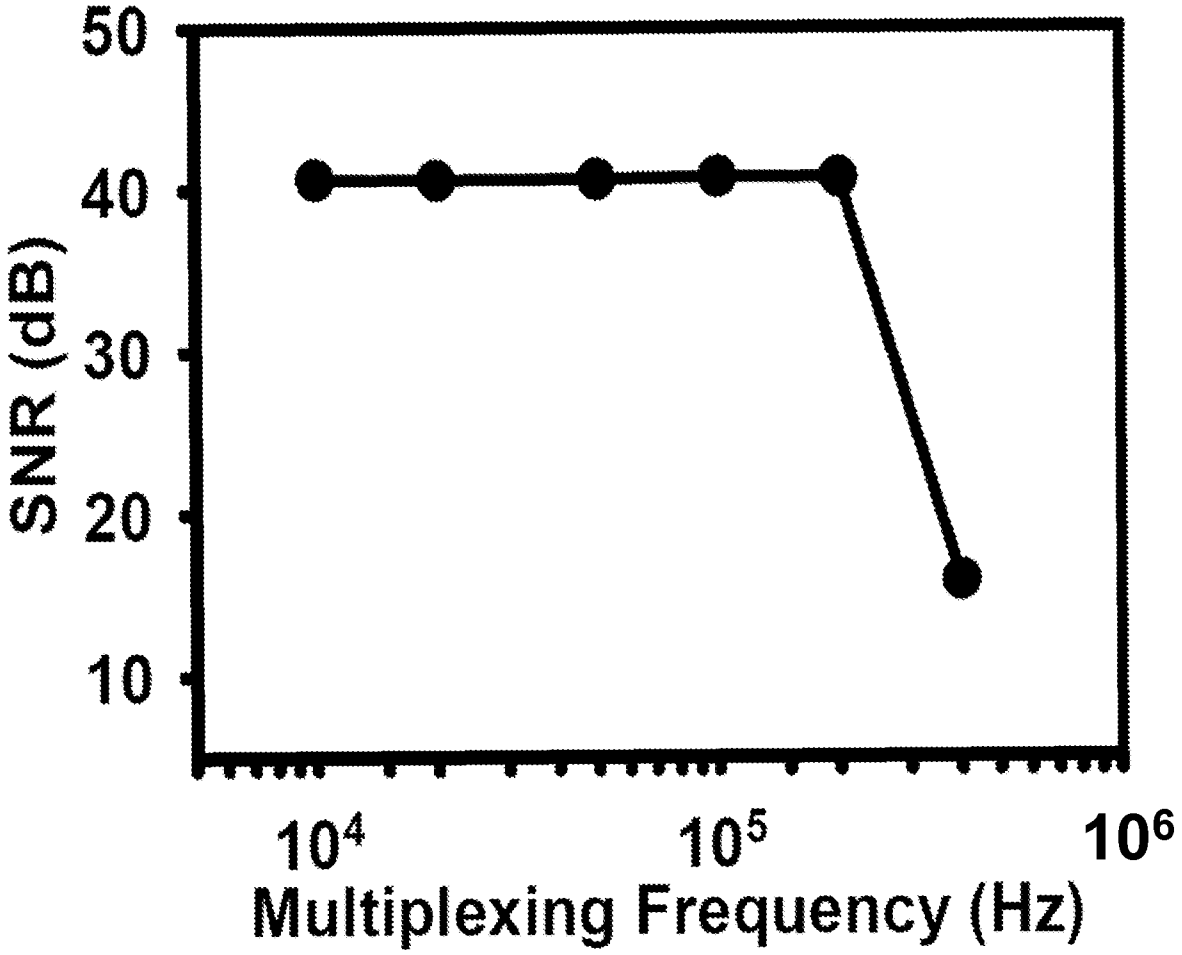


Figure 12

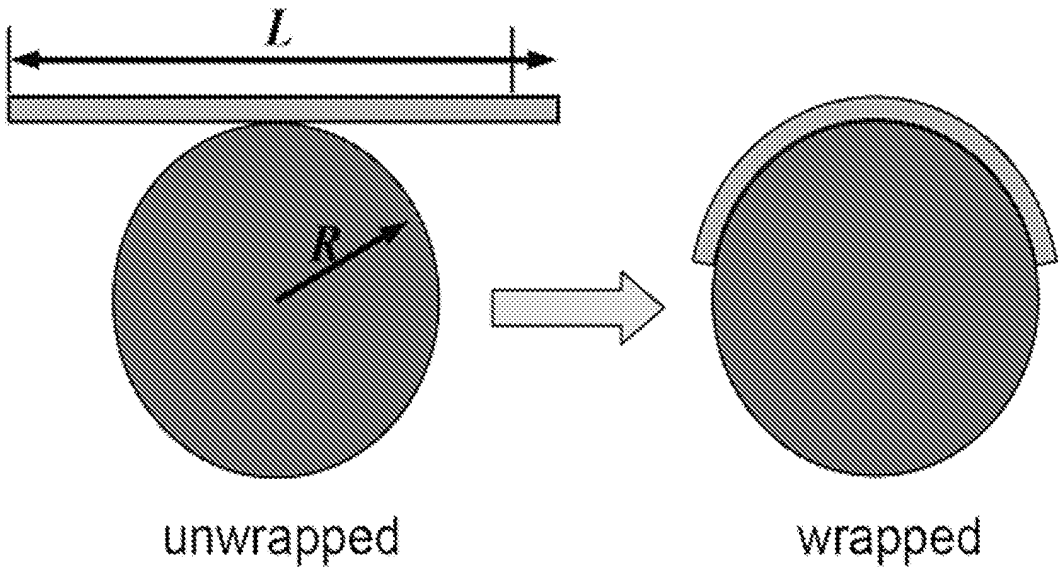


Figure 13a

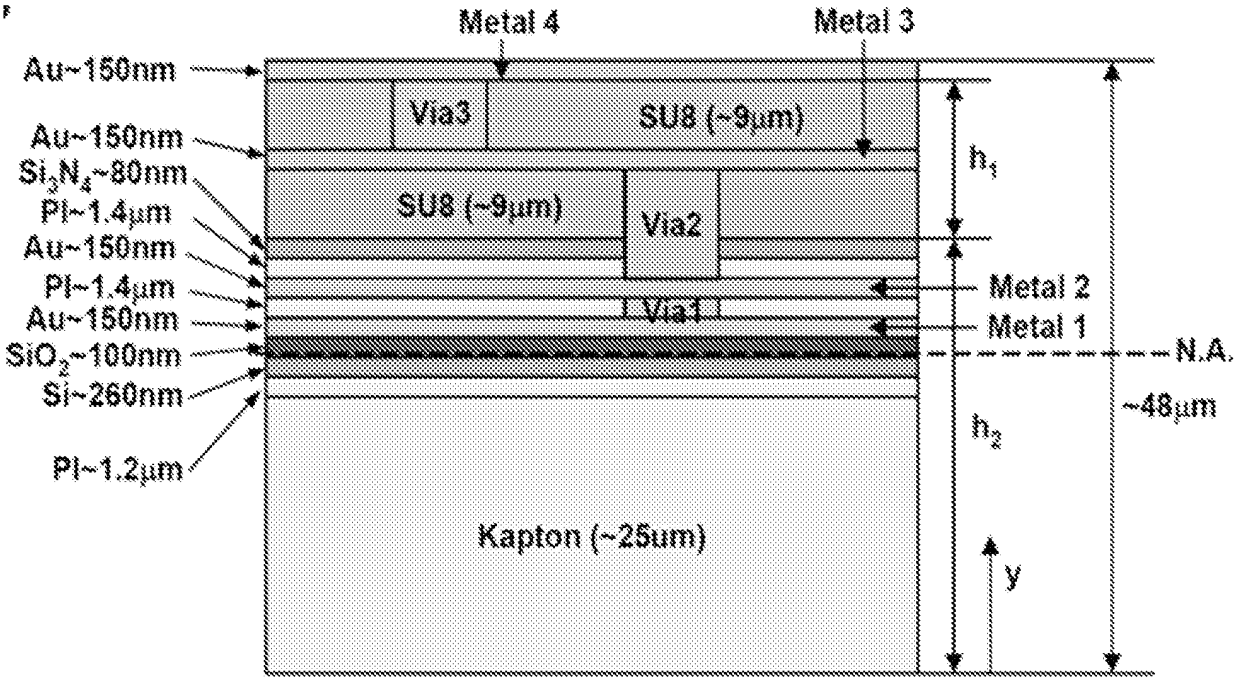


Figure 13b

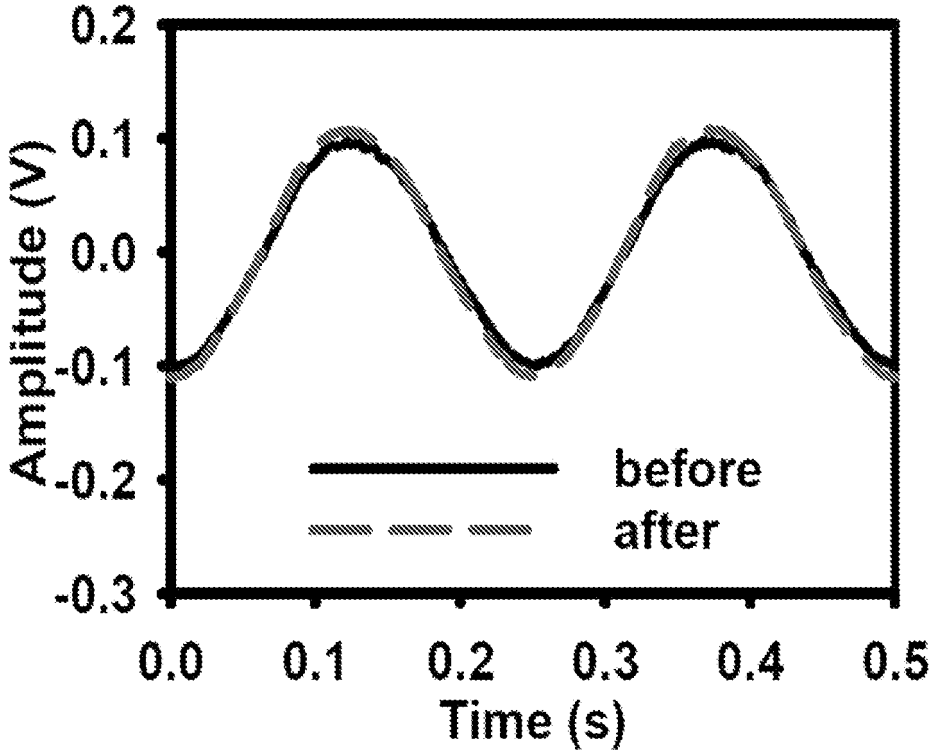


Figure 14a

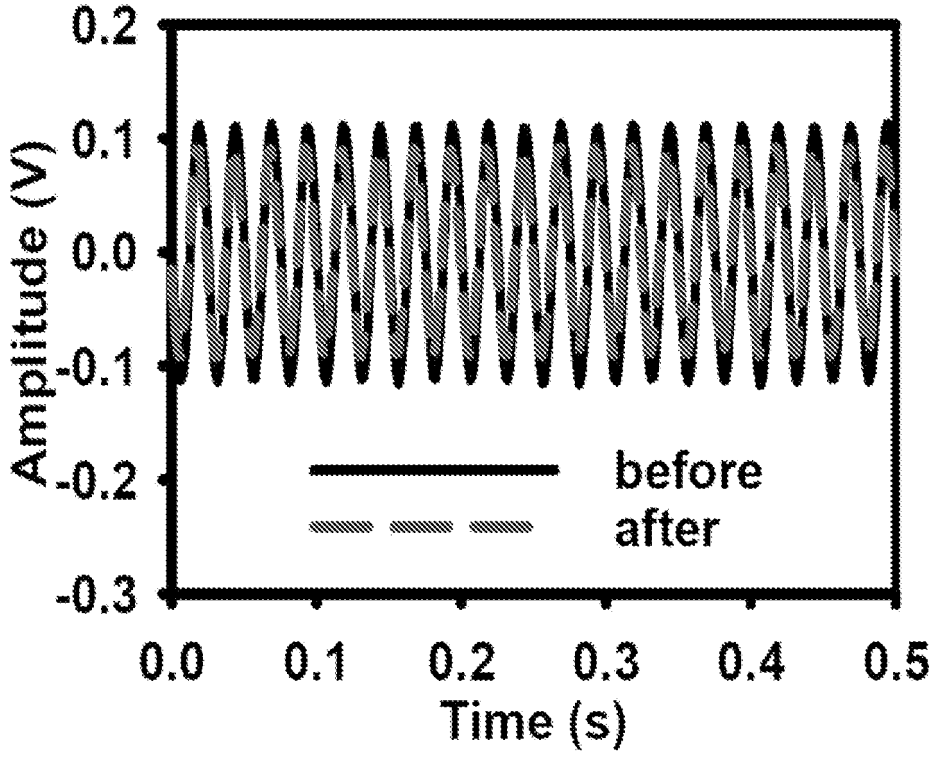


Figure 14b

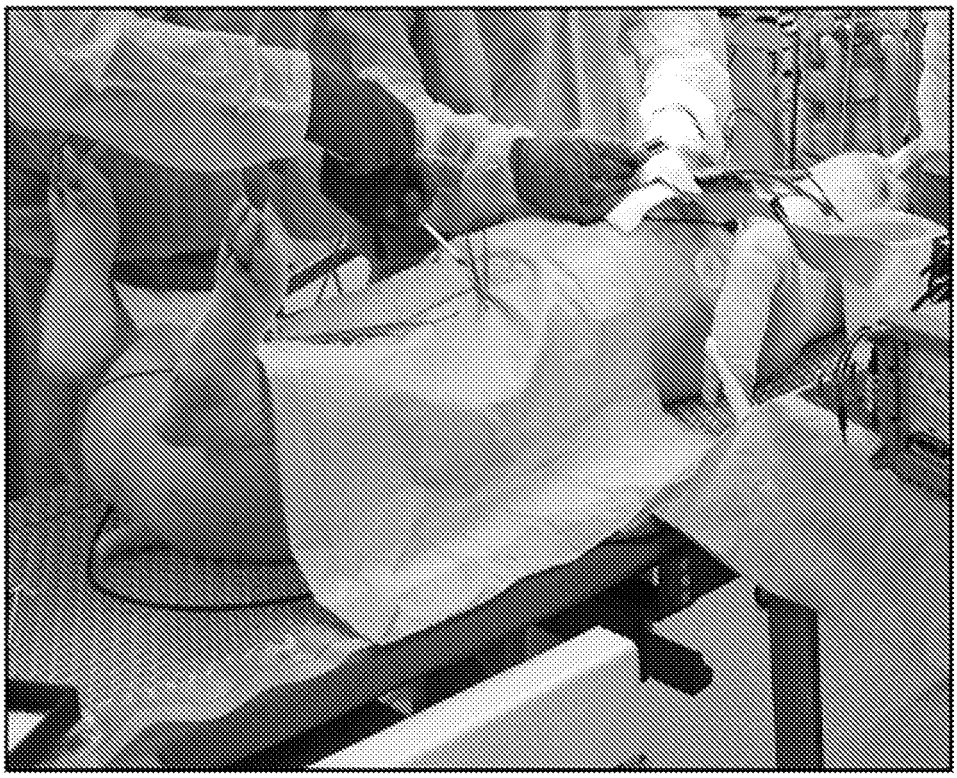


Figure 15a

Figure 15b

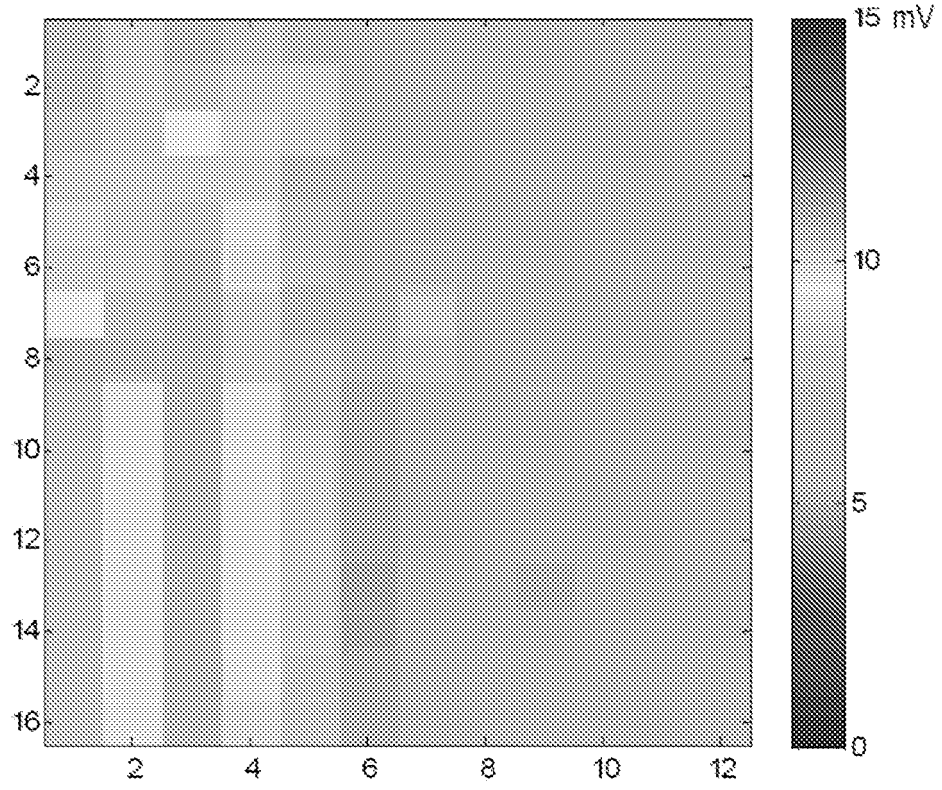


Figure 16

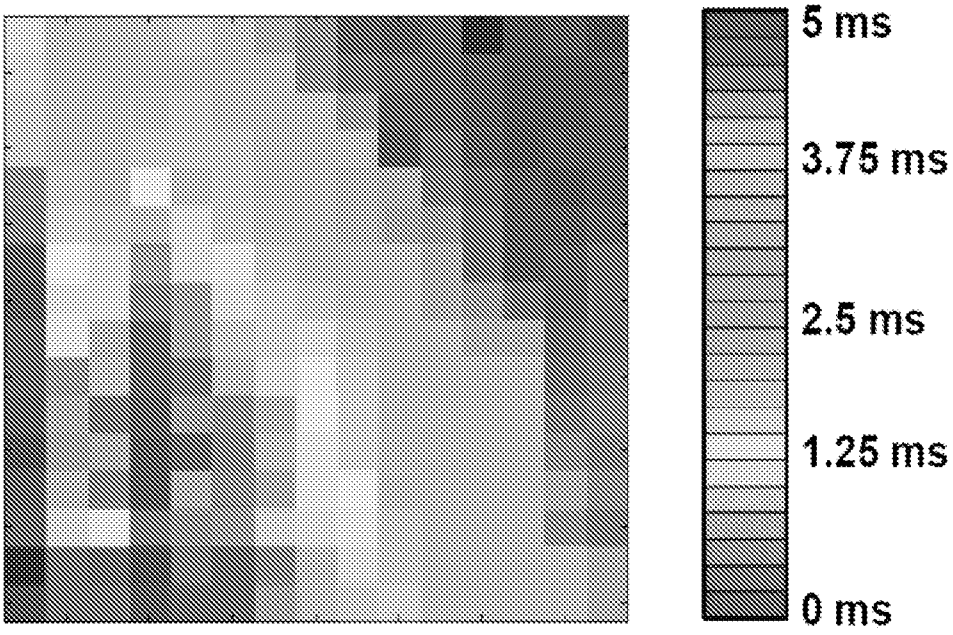
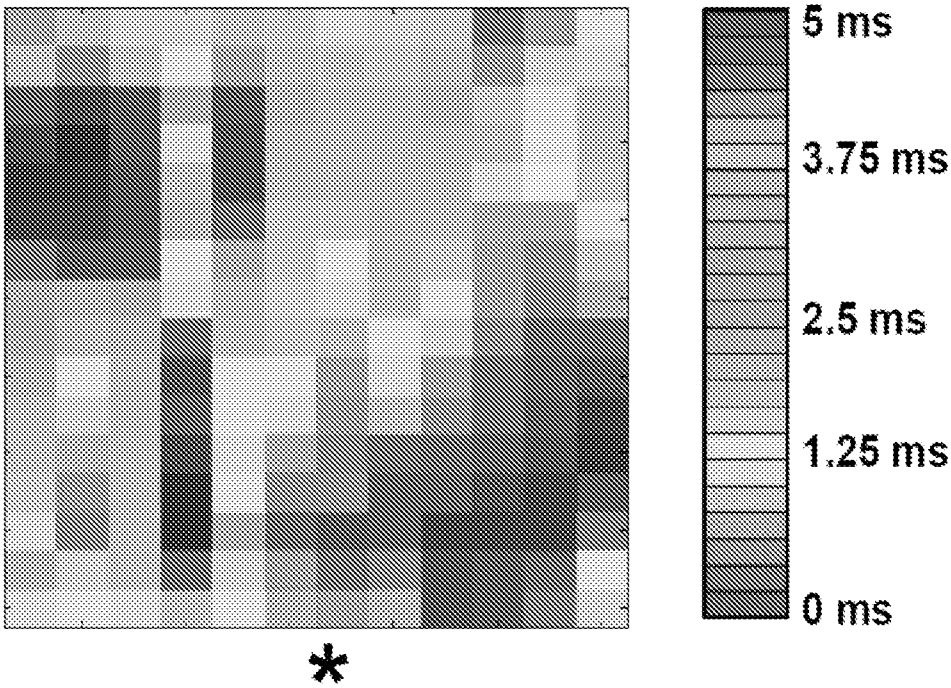


Figure 17a



*

Figure 17b

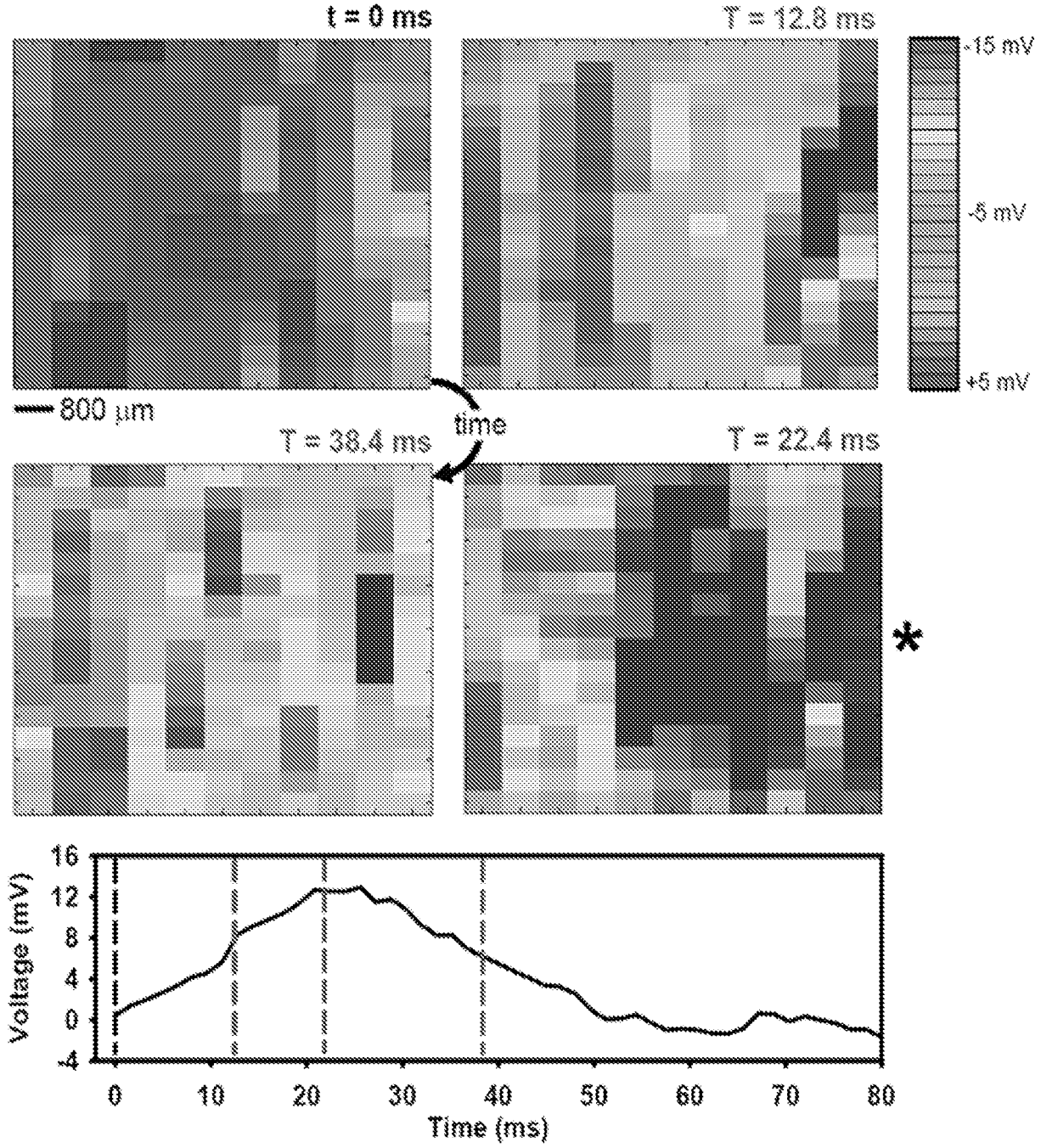

t = 0 ms
T = 12.8 ms
-15 mV
-5 mV
+5 mV
800 µm
time
T = 38.4 ms
T = 22.4 ms
*
Voltage (mV)
16
12
8
4
0
-4
0
10
20
30
40
50
60
70
80
Time (ms)

Figure 18

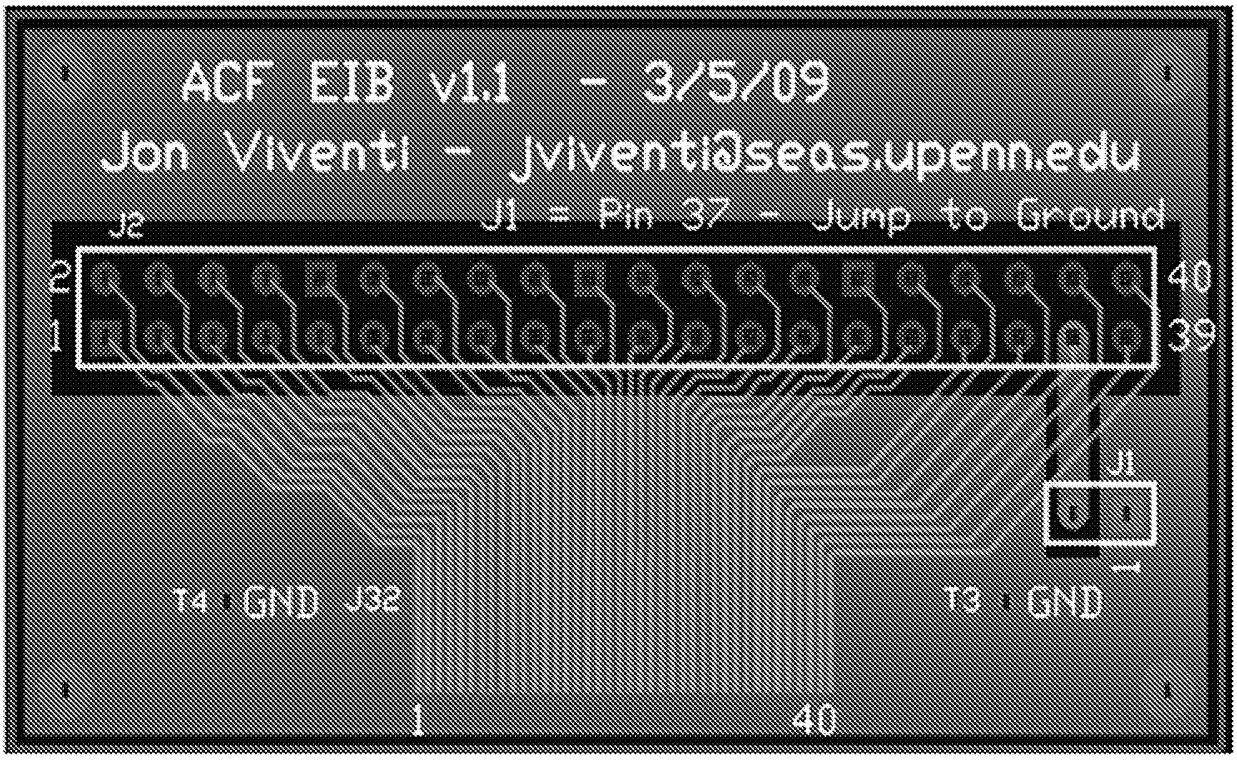

ACF EIB v1.1 - 3/5/09
Jon Viventi - jviventi@seas.upenn.edu
J2
J1 = Pin 37 - Jump to Ground
2
1
40
39
J1
1
T4 - GND J32
T3 - GND
1
40

Figure 19

Figure 20

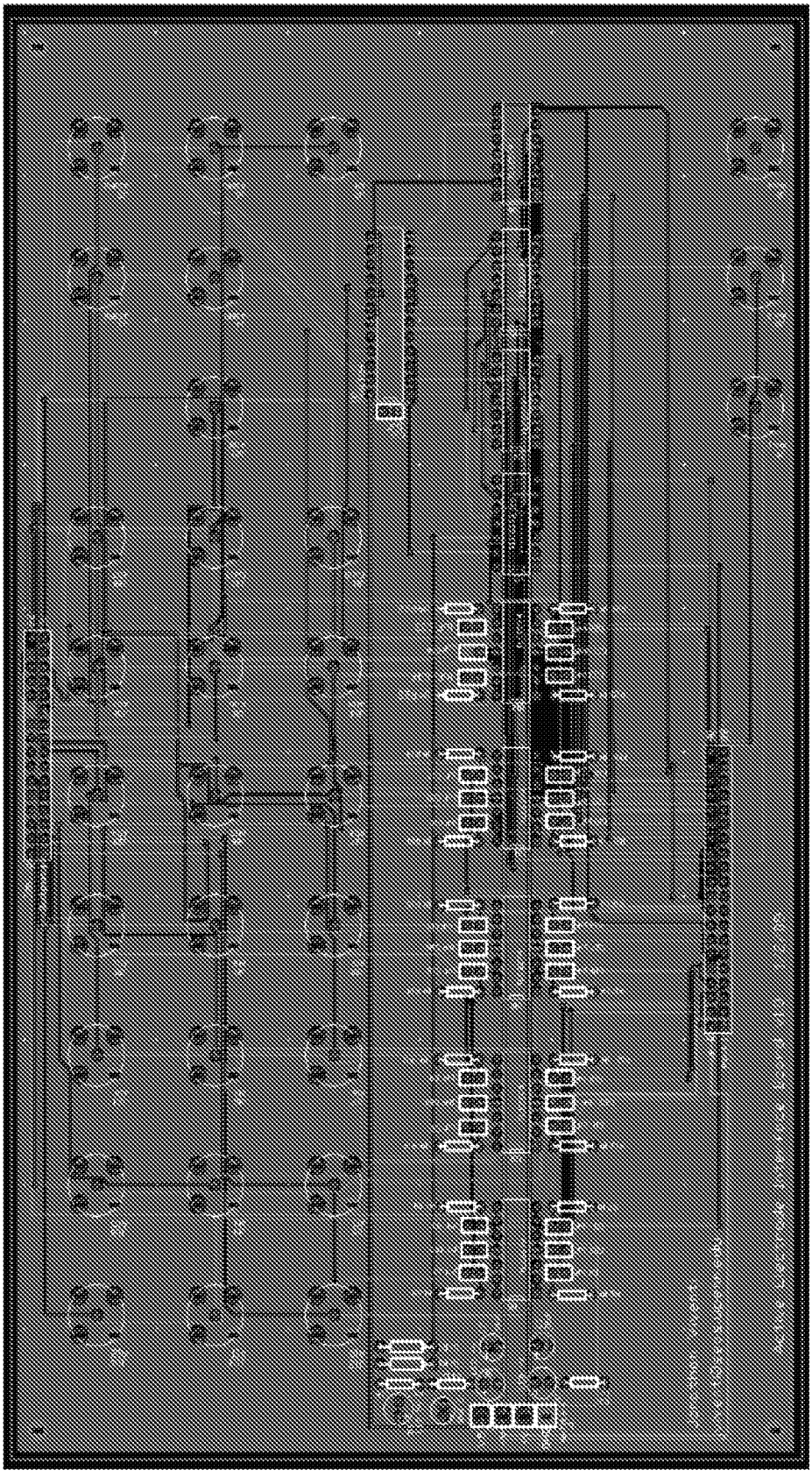
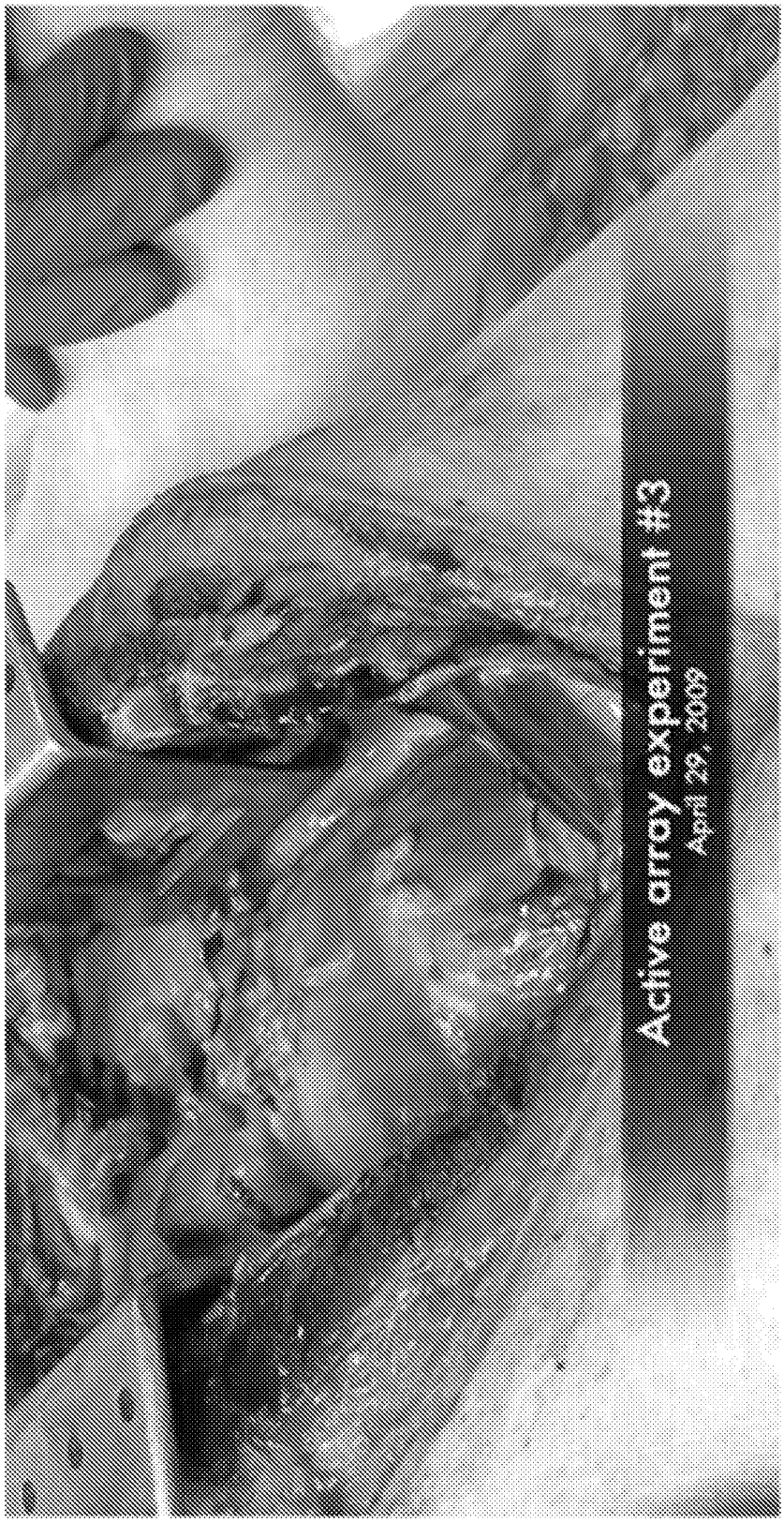


Figure 21



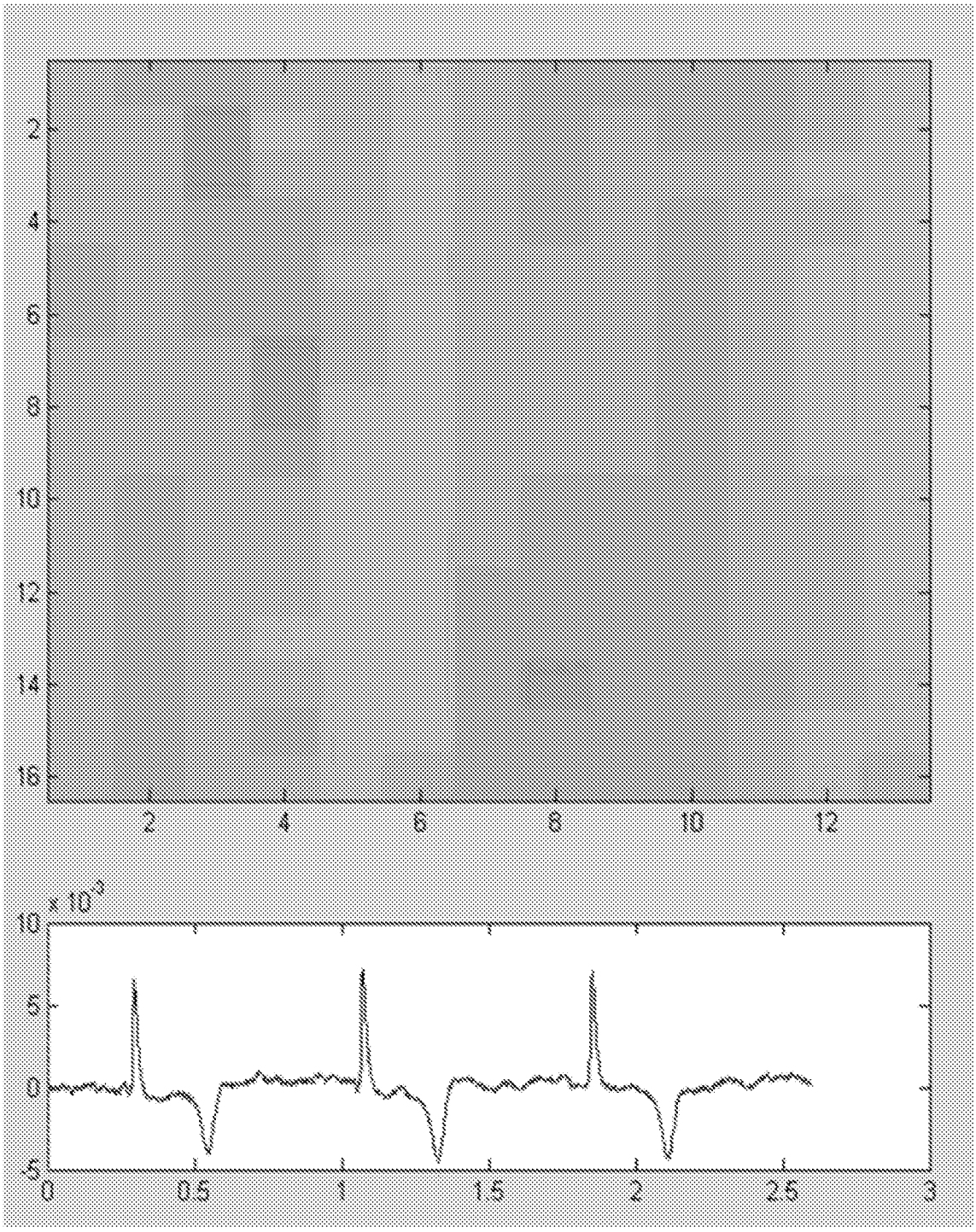


Figure 22

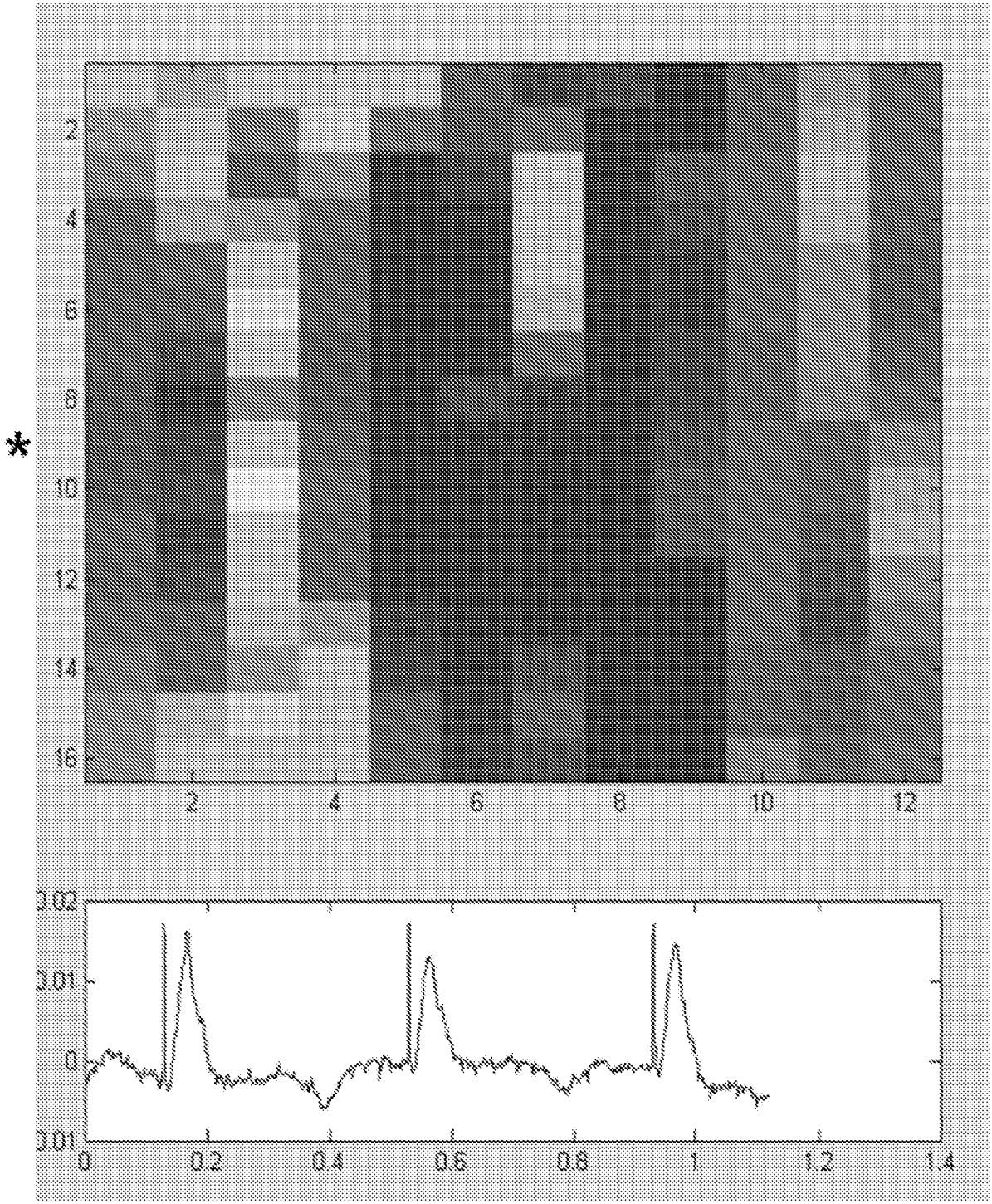
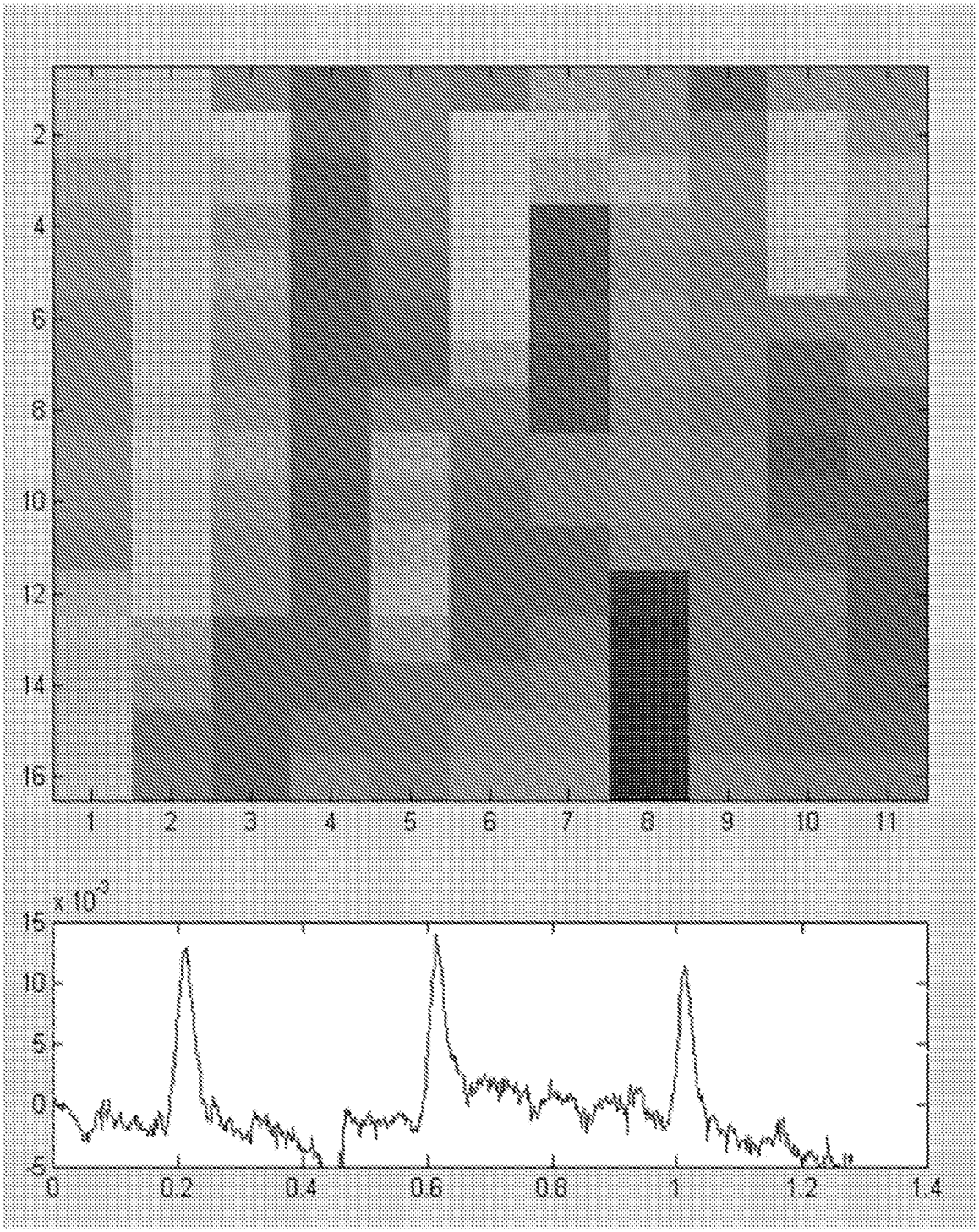


Figure 23


2
4
6
8
10
12
14
16
1
2
3
4
5
6
7
8
9
10
11
x 10^-3
15
10
5
0
-5
0
0.2
0.4
0.6
0.8
1
1.2
1.4

*

Figure 24

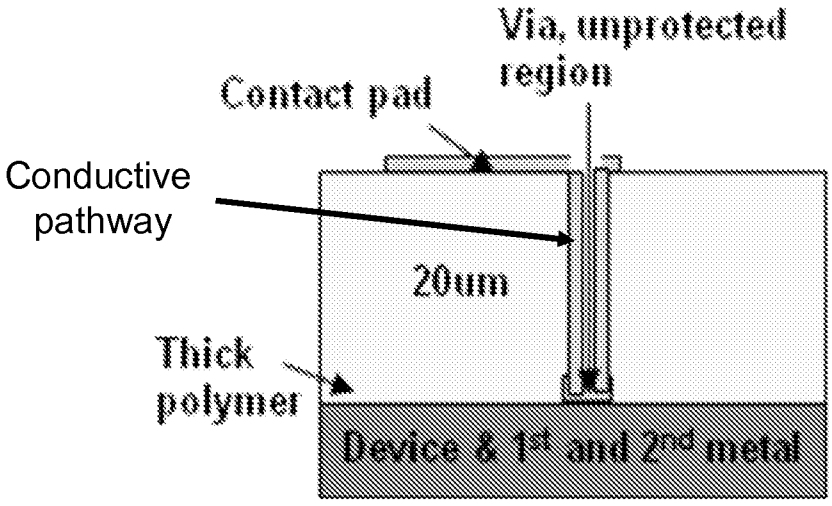


Figure 25a

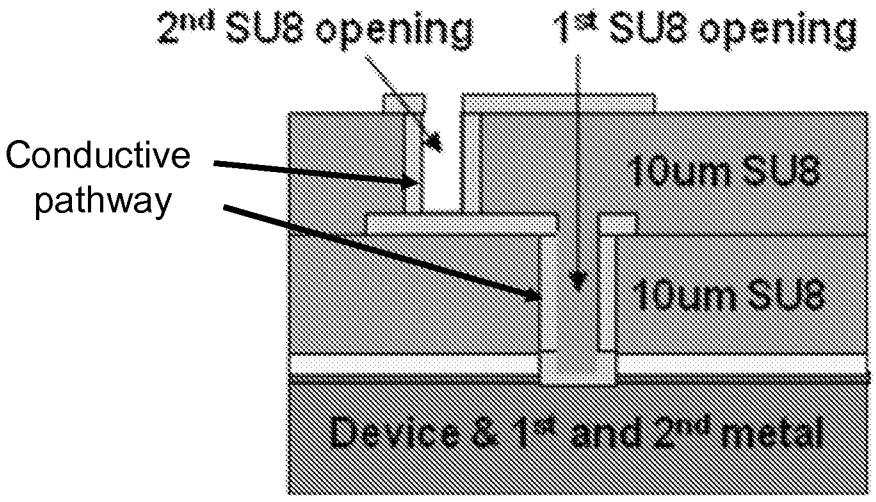


Figure 25b

Figure 26A

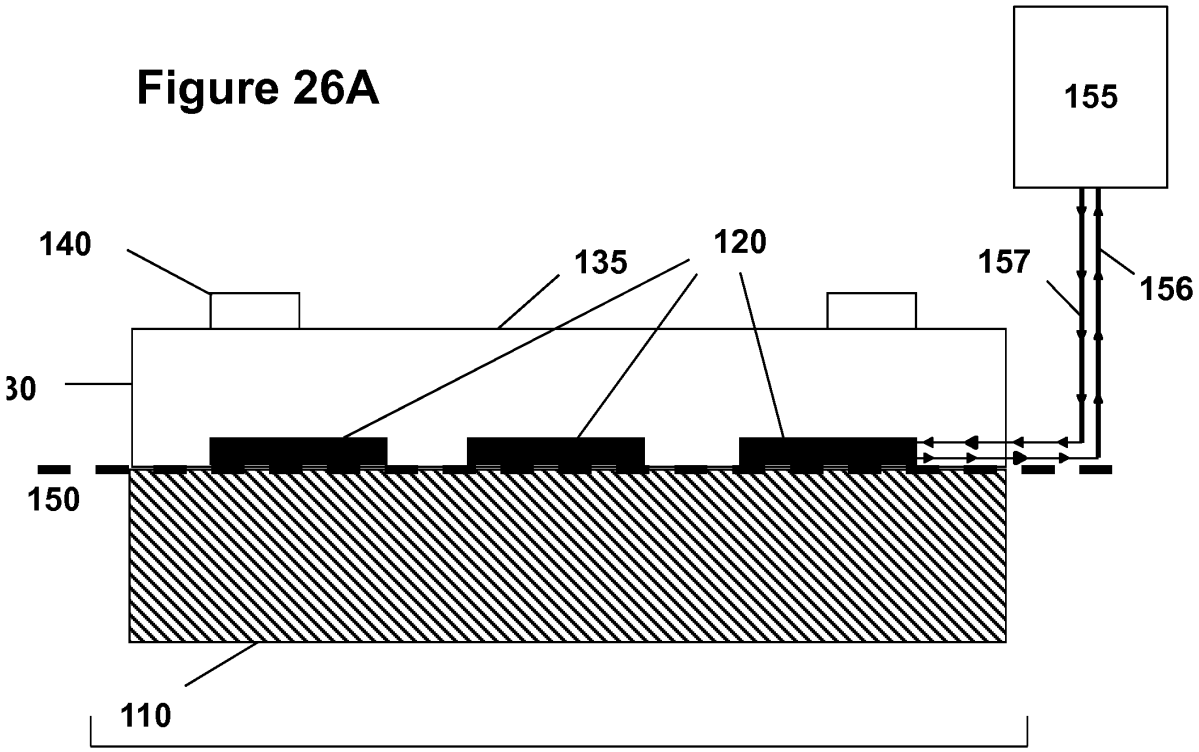


Figure 26B

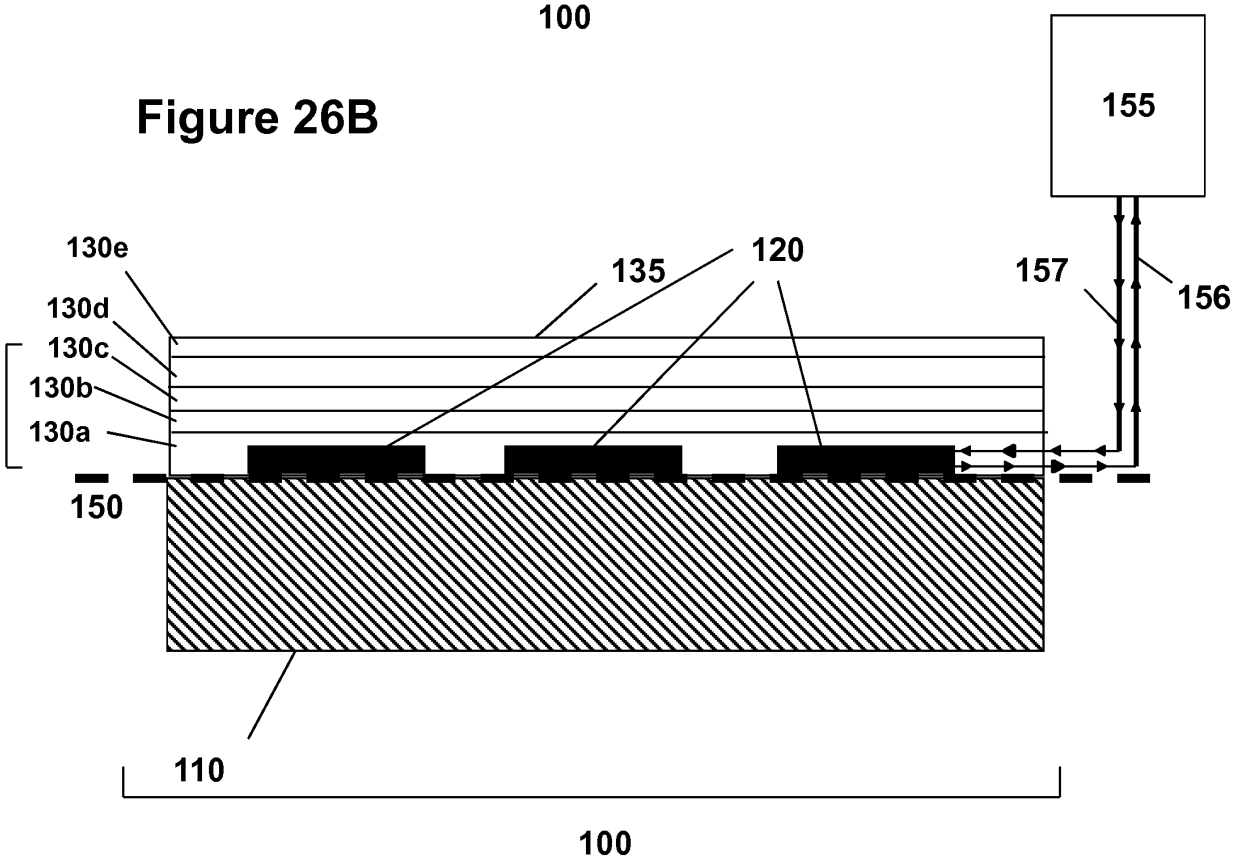


Figure 27a

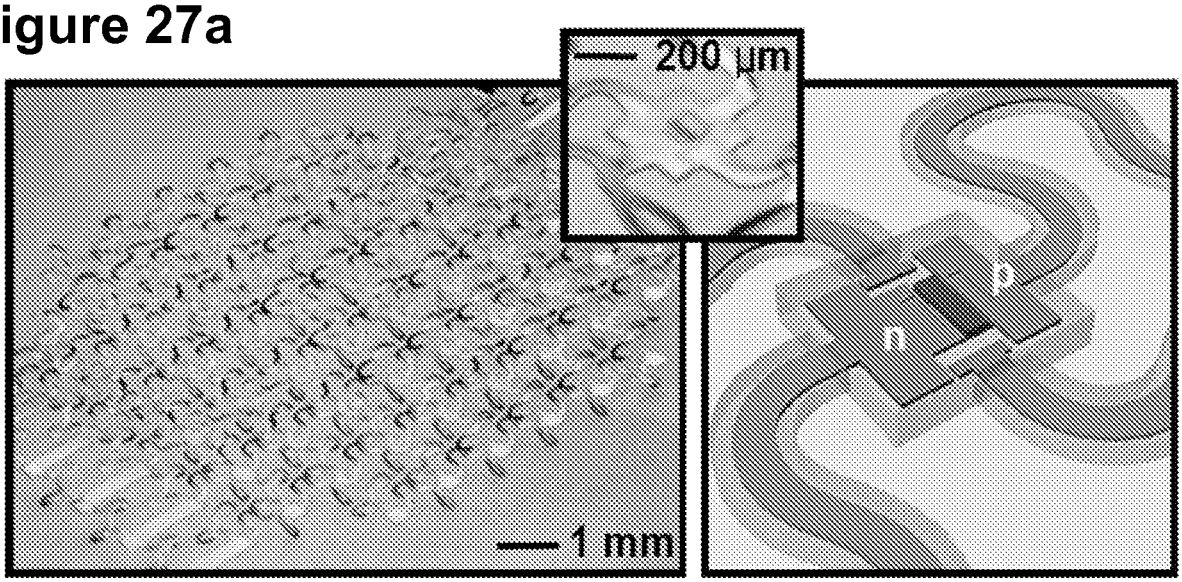


Figure 27b

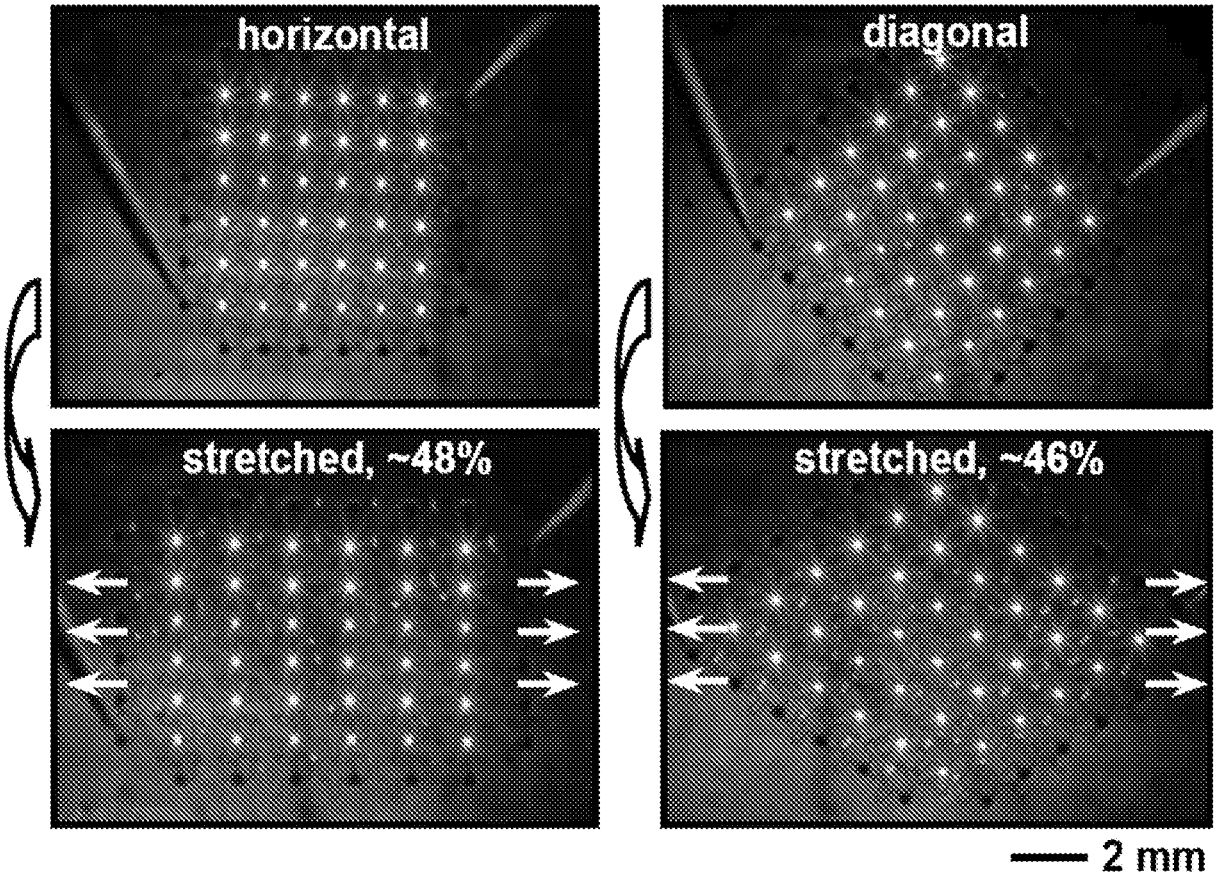


Figure 27c

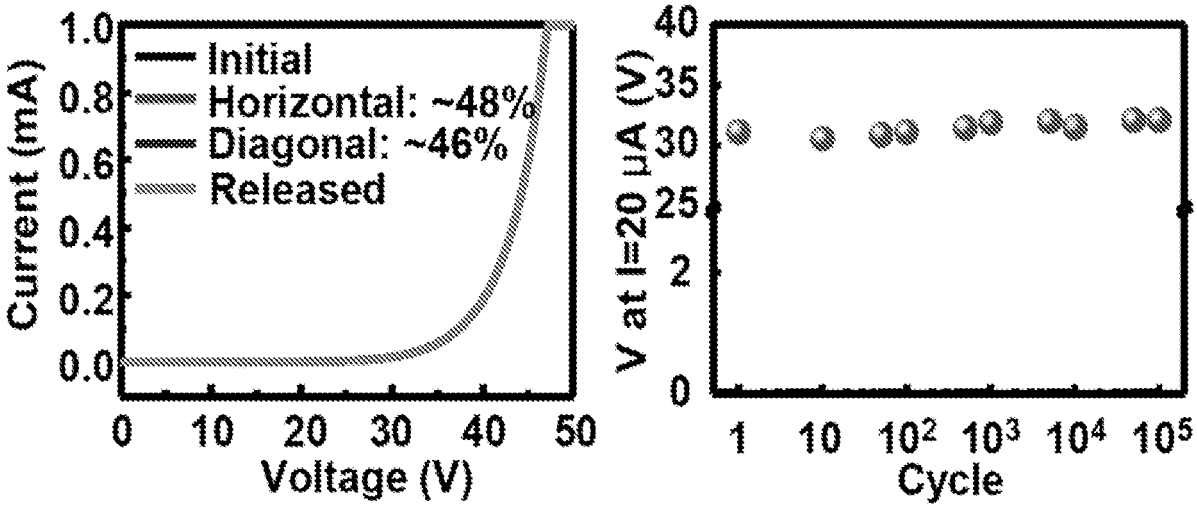


Figure 27d

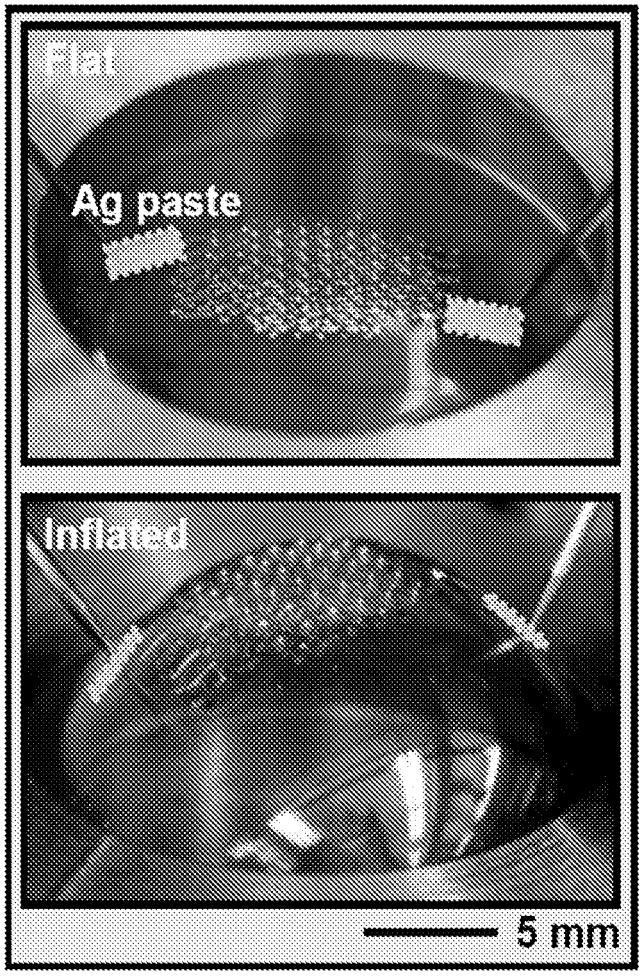


Figure 27e

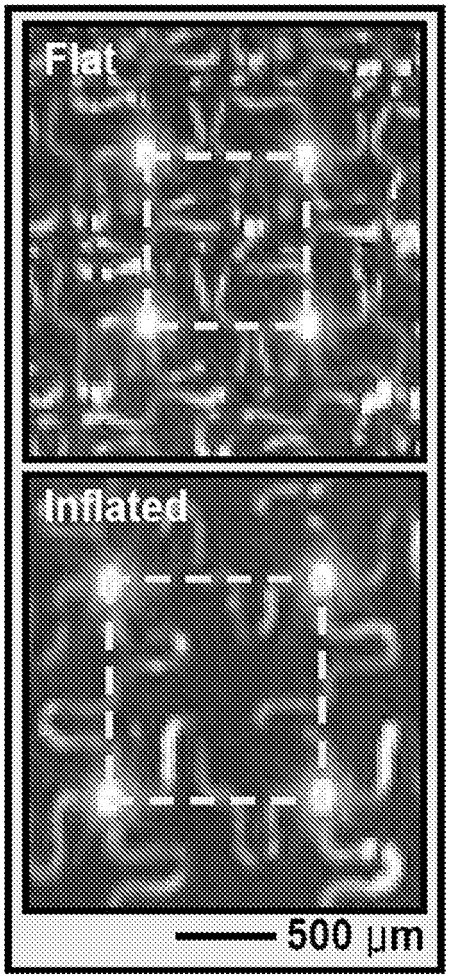


Figure 27f

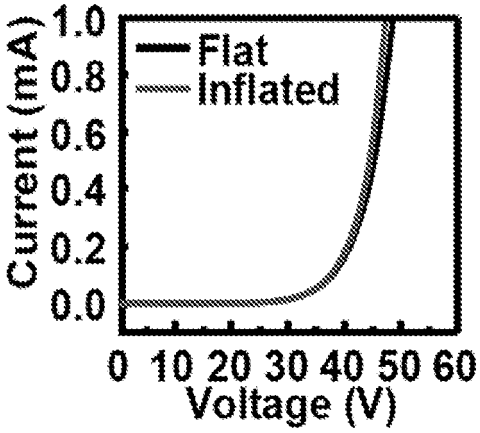


Figure 27g

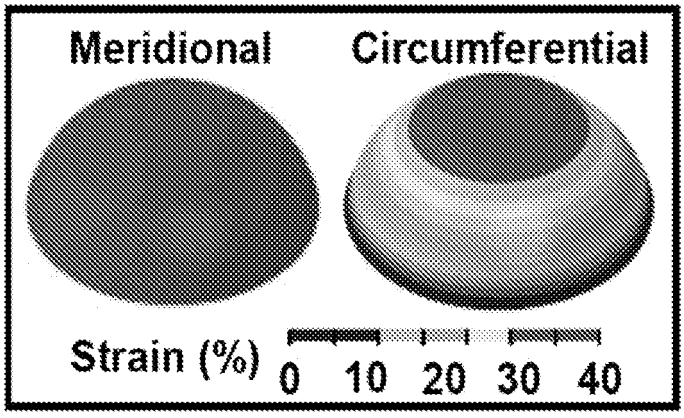


Figure 28a

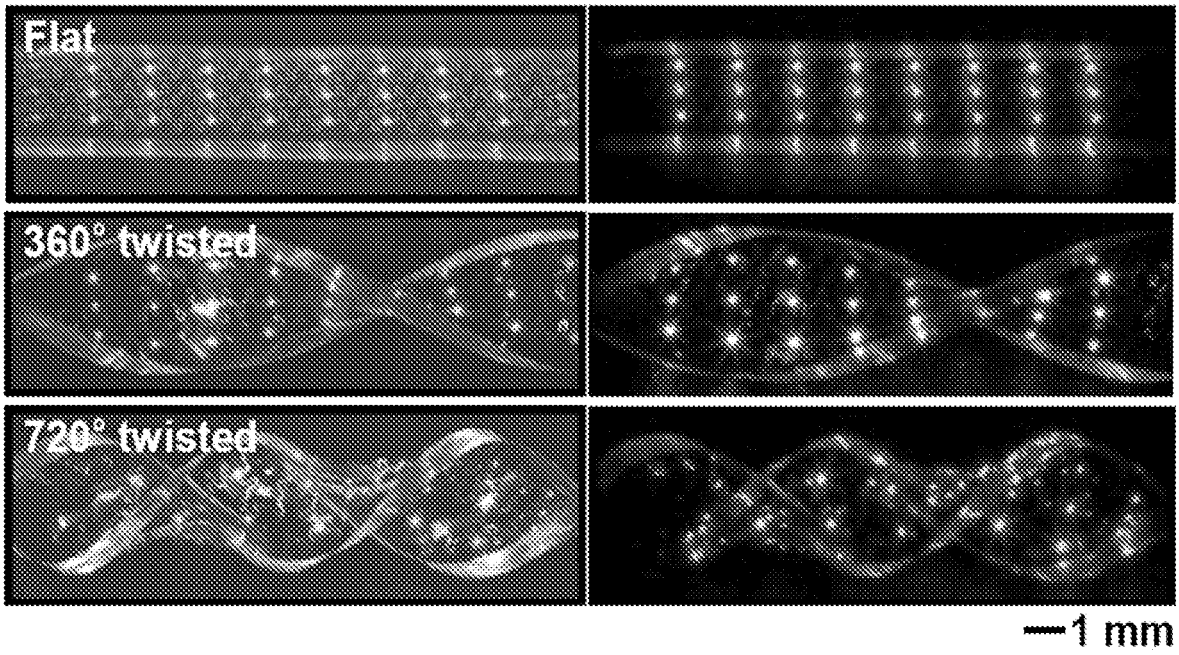


Figure 28b

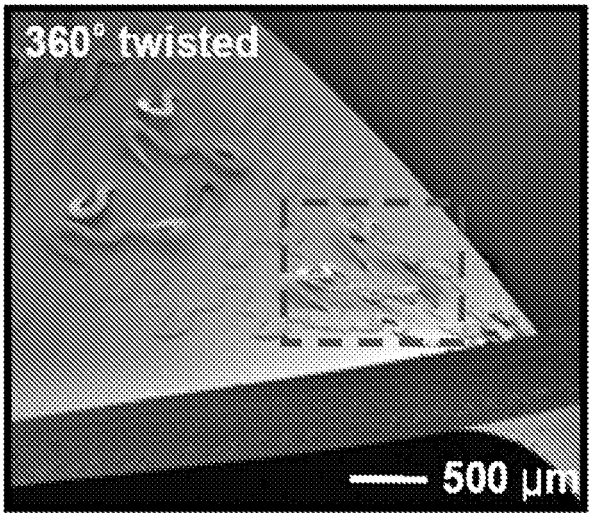


Figure 28c

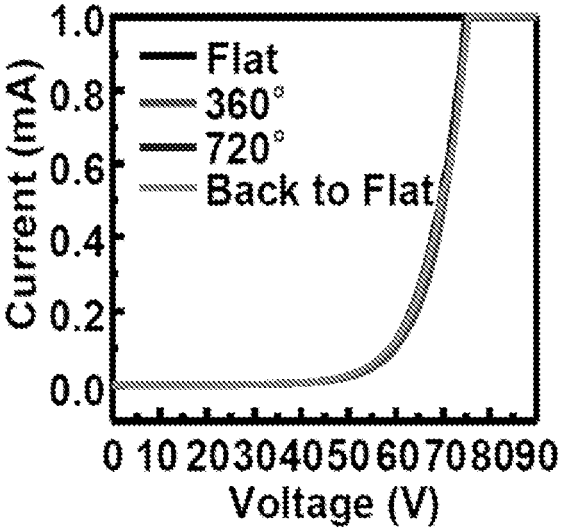
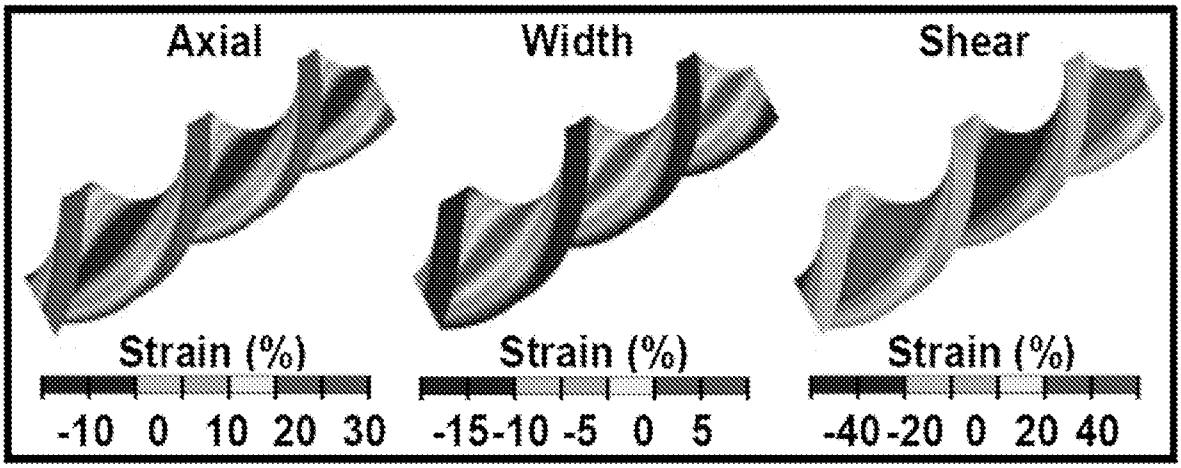


Figure 28d


Axial
Strain (%)
-10 0 10 20 30
Width
Strain (%)
-15 -10 -5 0 5
Shear
Strain (%)
-40 -20 0 20 40

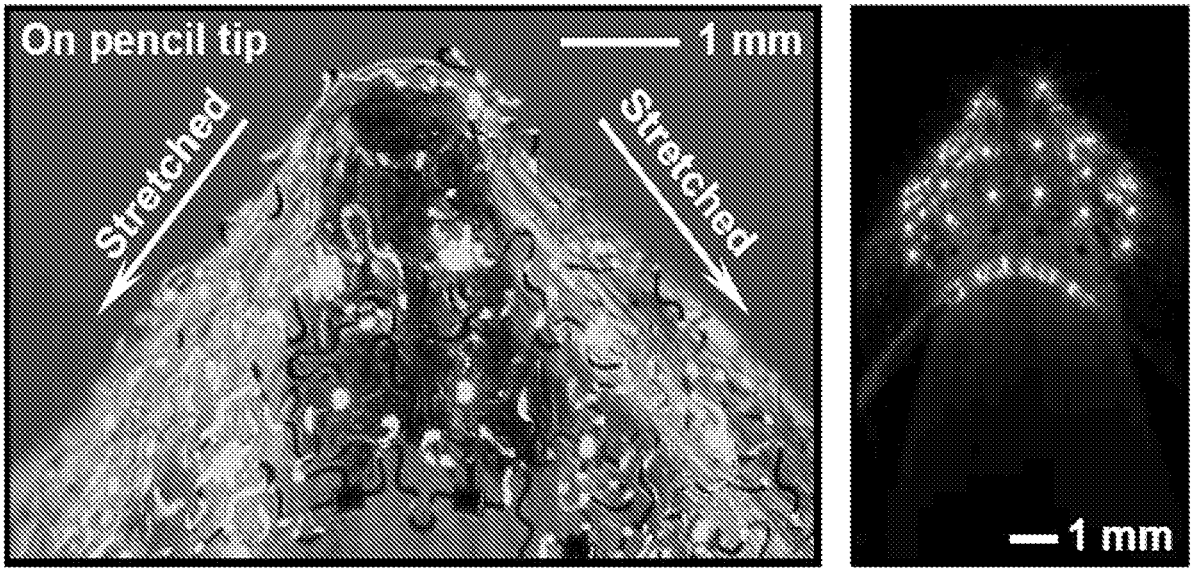


Figure 28e

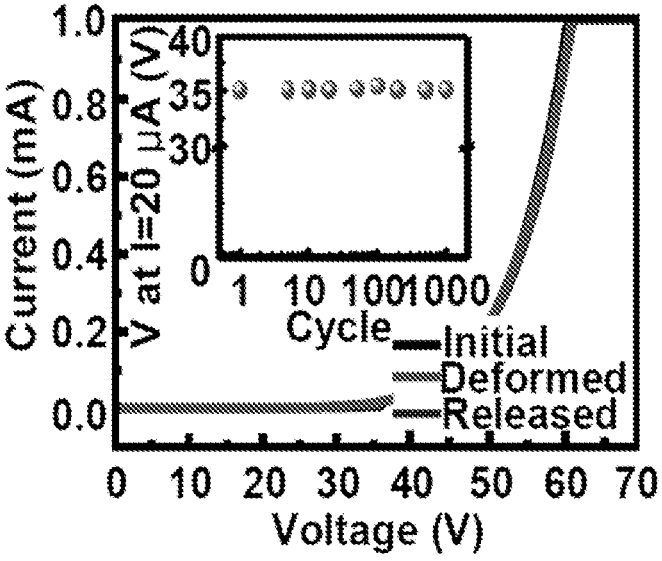


Figure 28f

Figure 29a

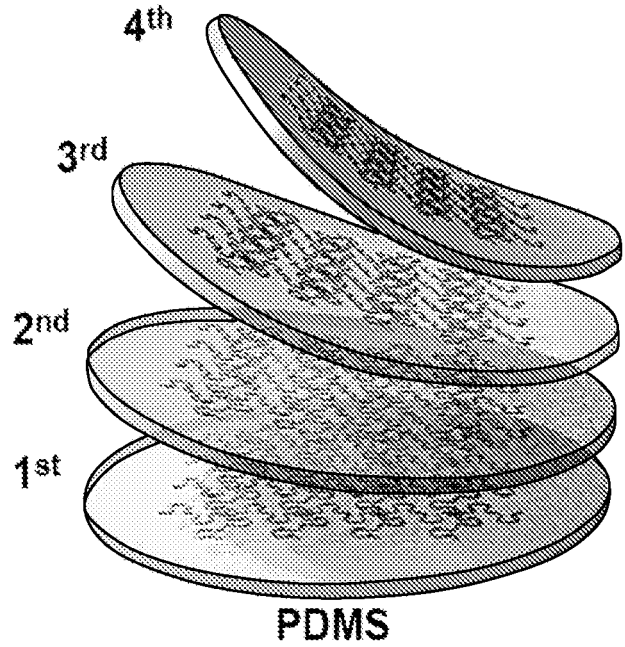


Figure 29b

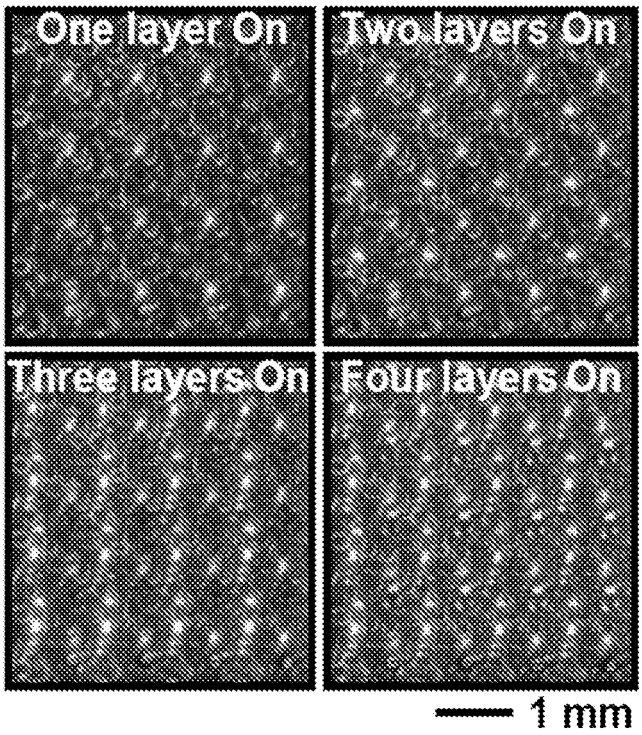


Figure 29c

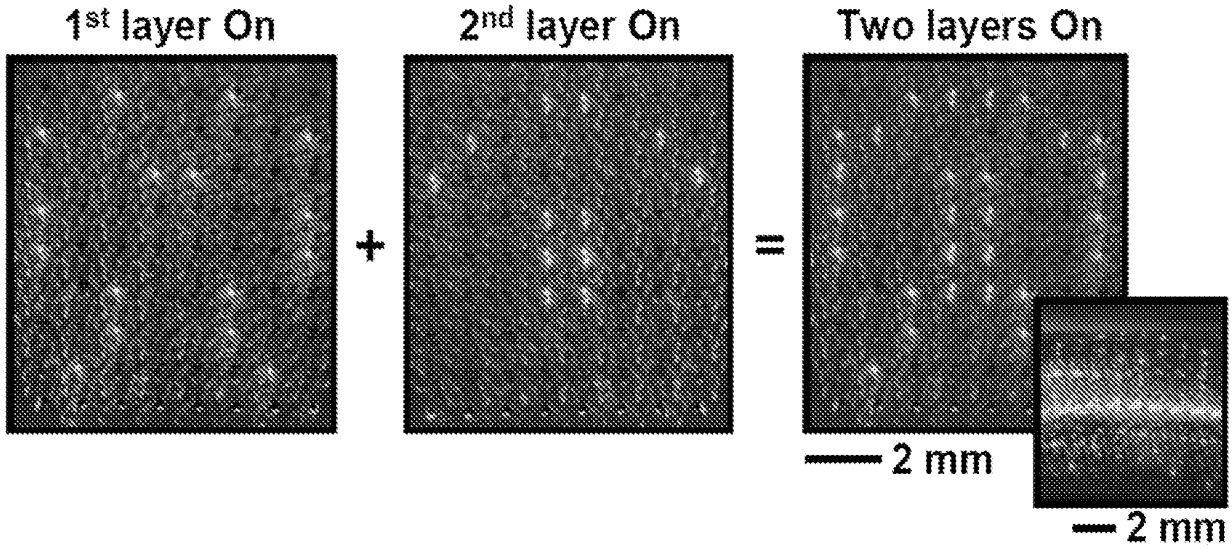


Figure 29d

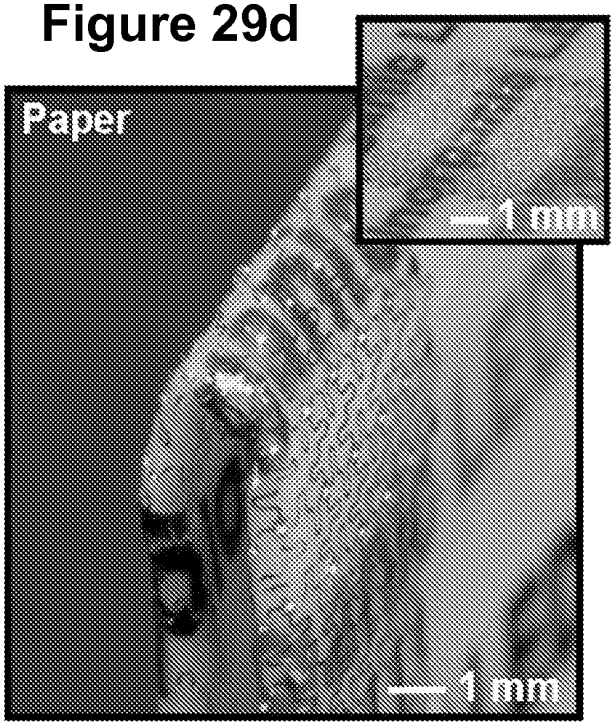


Figure 29e

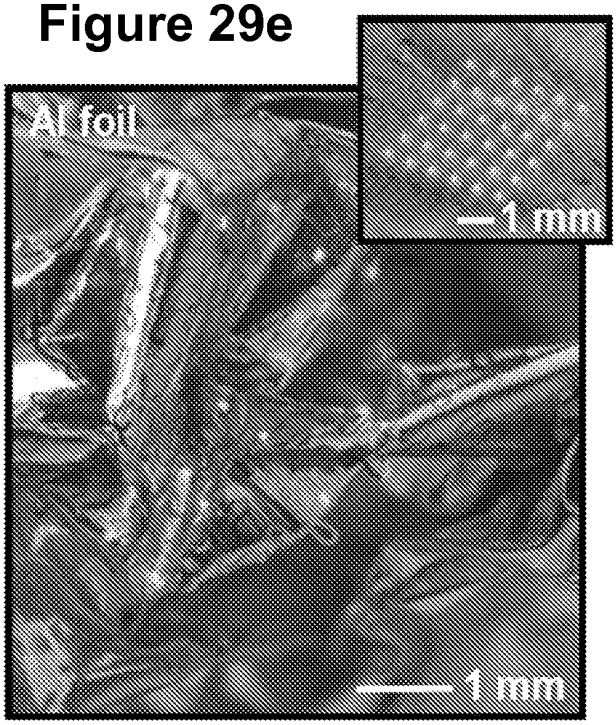


Figure 29f

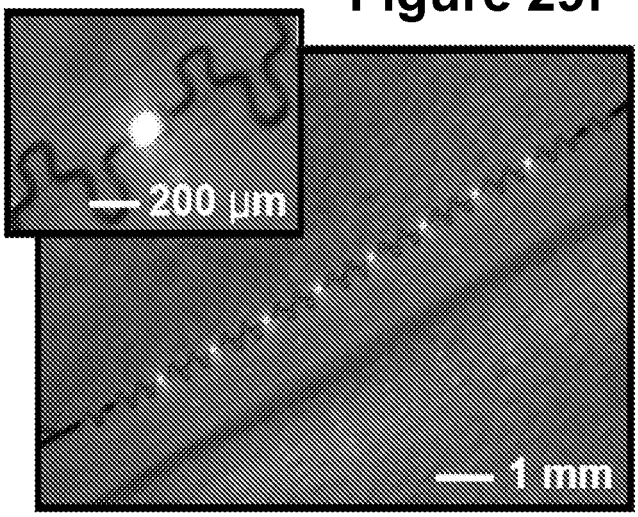
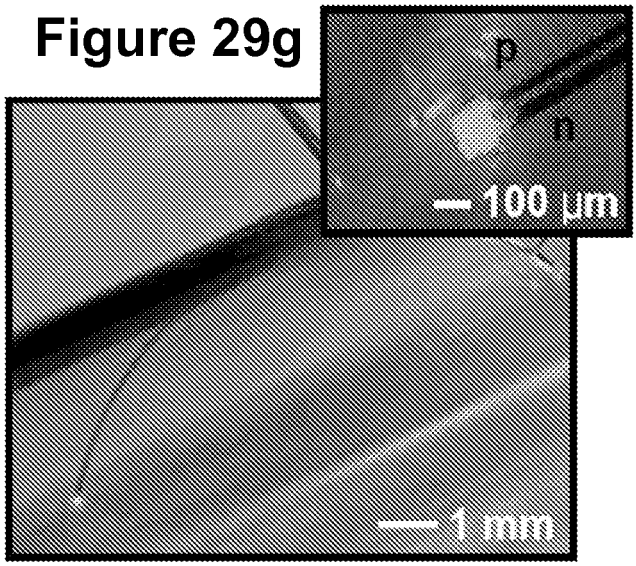


Figure 29g



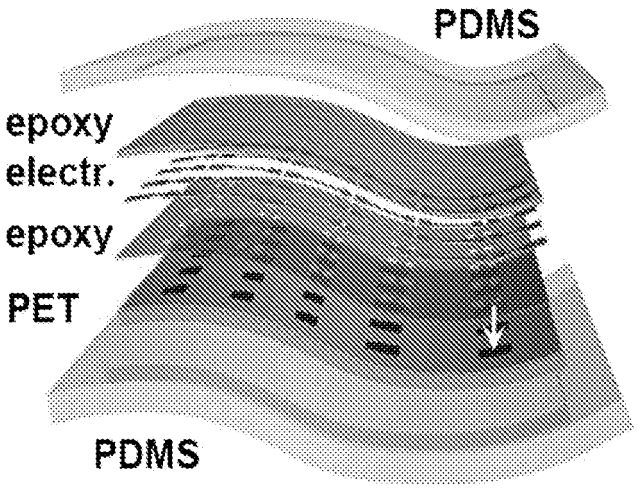


Figure 30a

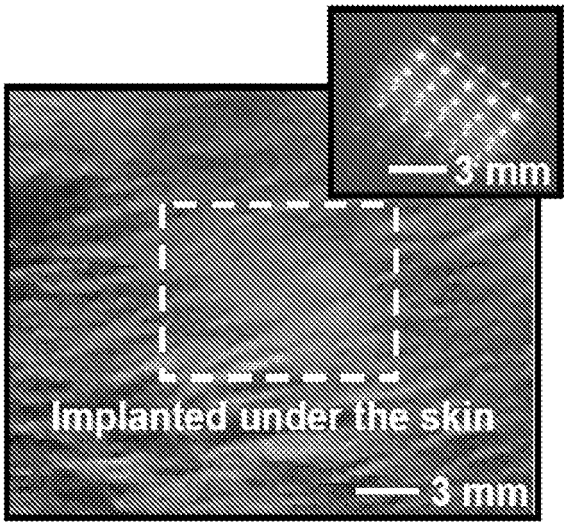
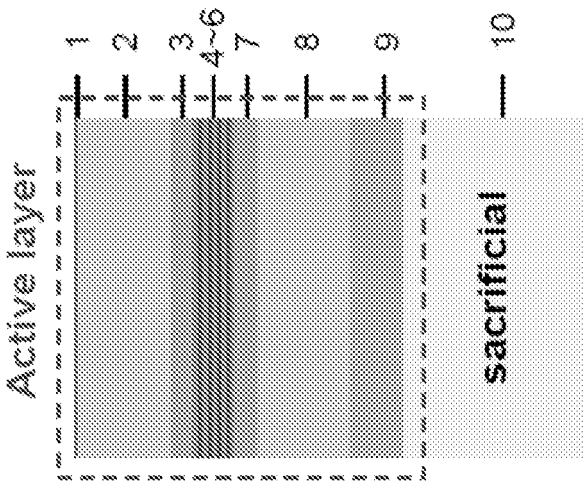


Figure 30b

Figure 31a

	Layer	Composition	Thickness (Å)	Dopant	Doping Concentration
1	p-Contact	GaAs	50	C	1.00E+19
2	p-Spreader	$Al_{0.45}Ga_{0.55}As$	8000	C	1.00E+18
3	p-Cladding	$In_{0.5}Al_{0.5}P$	2000	Zn	3.00E17 ~ 6.00E17
4	Barrier	$Al_{0.25}Ga_{0.25}In_{0.5}P$	60	NA	< 1.00E16
5	4 X Well	$In_{0.56}Ga_{0.44}P$	4 X 60	NA	< 1.00E16
6	4 X Barrier	$Al_{0.25}Ga_{0.25}In_{0.5}P$	4 X 60	NA	< 1.00E16
7	n-Cladding	$In_{0.5}Al_{0.5}P$	2000	Si	1.00E+18
8	n-Spreader	$Al_{0.45}Ga_{0.55}As$	8000	Si	1.00E+18
9	n-Contact	GaAs	5000	Si	4.00E+18
10	Sacrificial	$Al_{0.98}Ga_{0.02}As$	15000	Si	1.00E+17



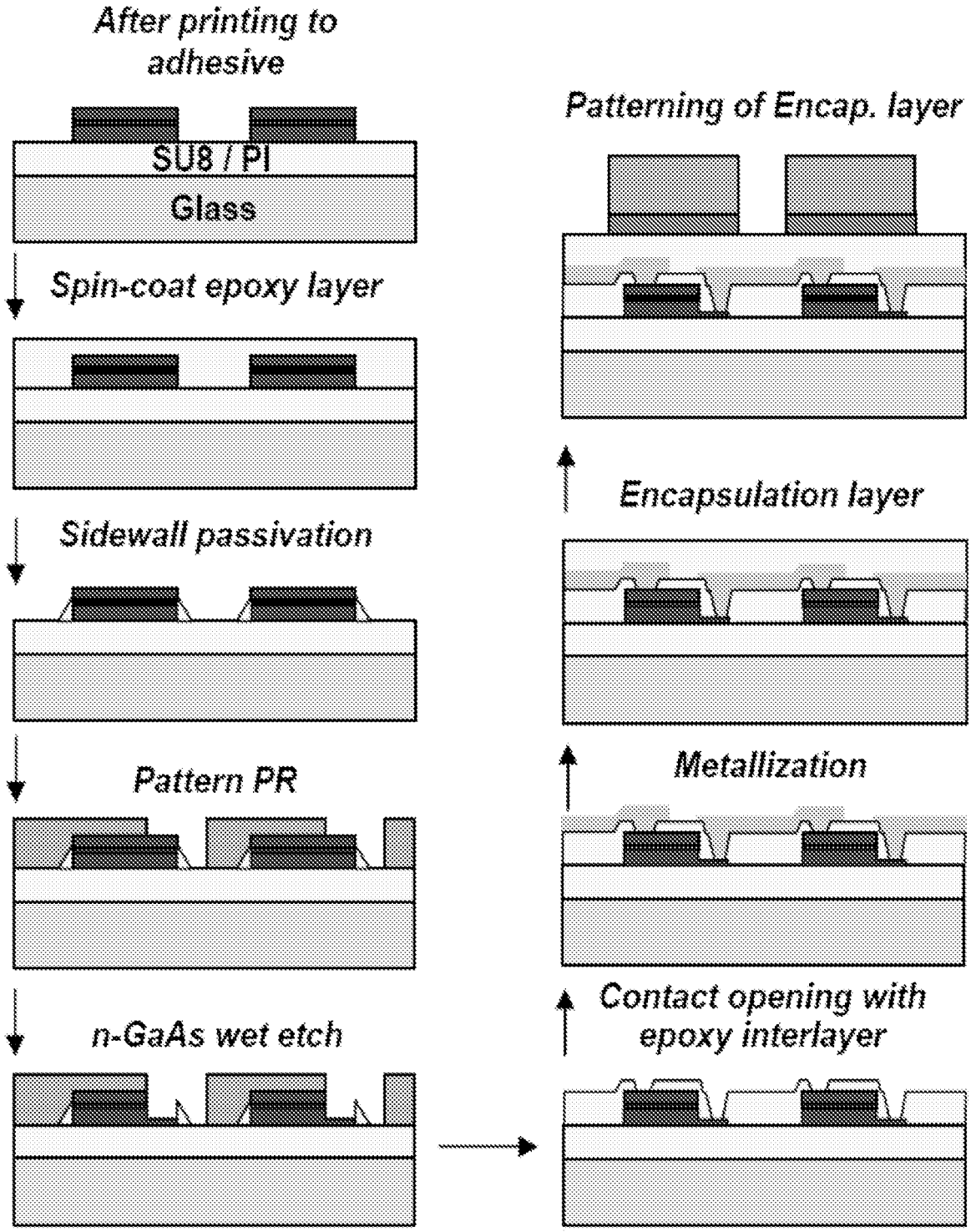

After printing to adhesive
SU8 / PI
Glass
Spin-coat epoxy layer
Sidewall passivation
Pattern PR
n-GaAs wet etch
Contact opening with epoxy interlayer
Metallization
Encapsulation layer
Patterning of Encap. layer

Figure 31b

Figure 32a

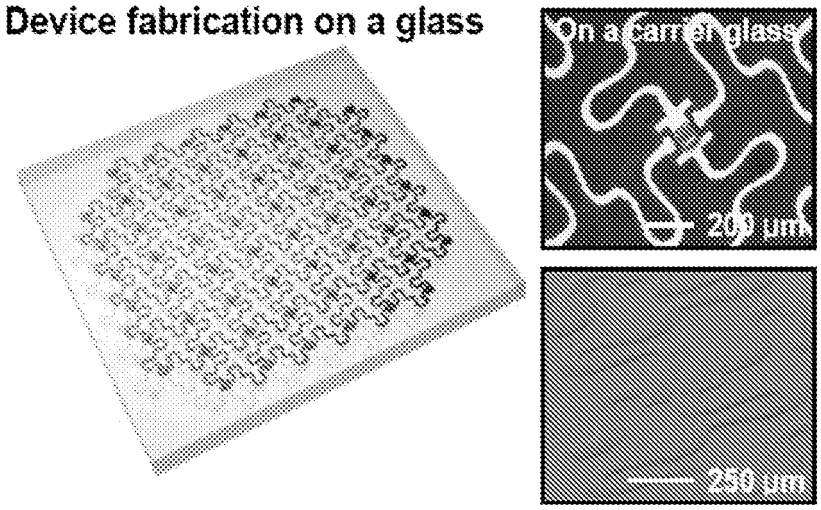


Figure 32b

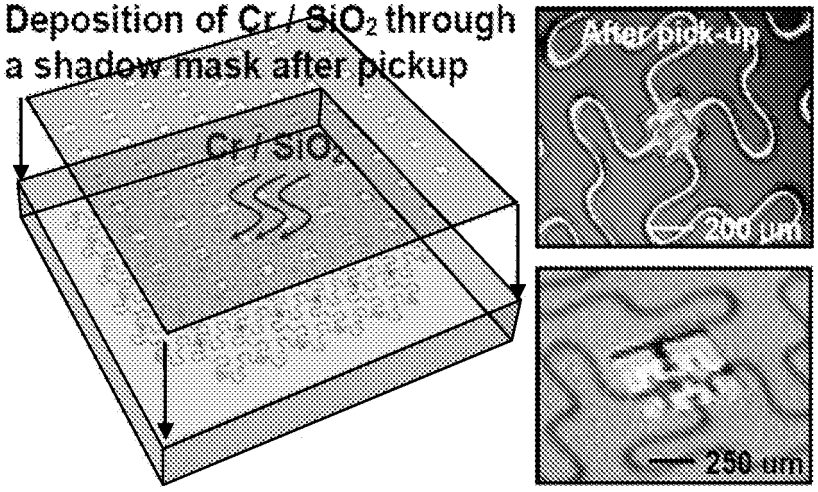


Figure 32c

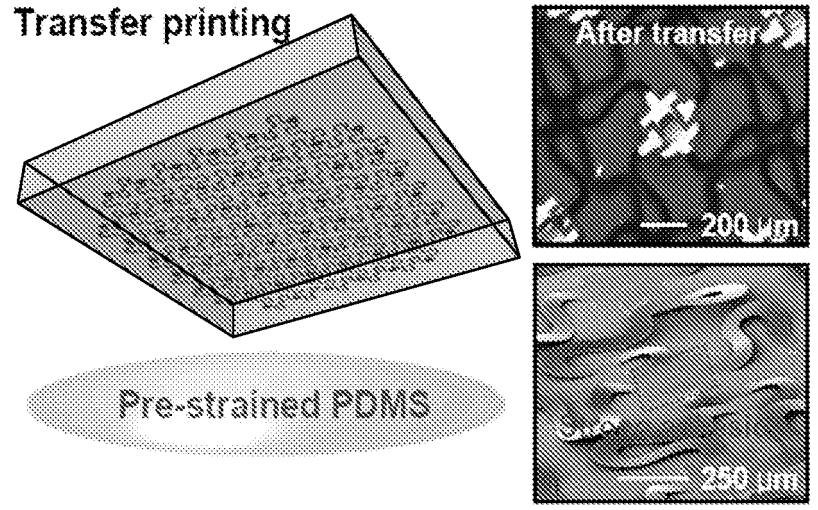


Figure 33a

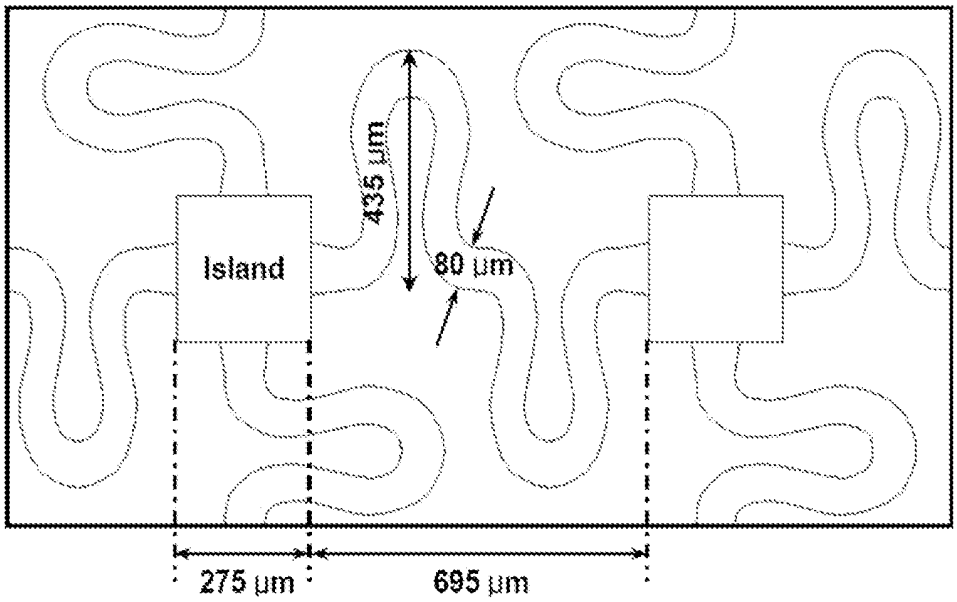


Figure 33b

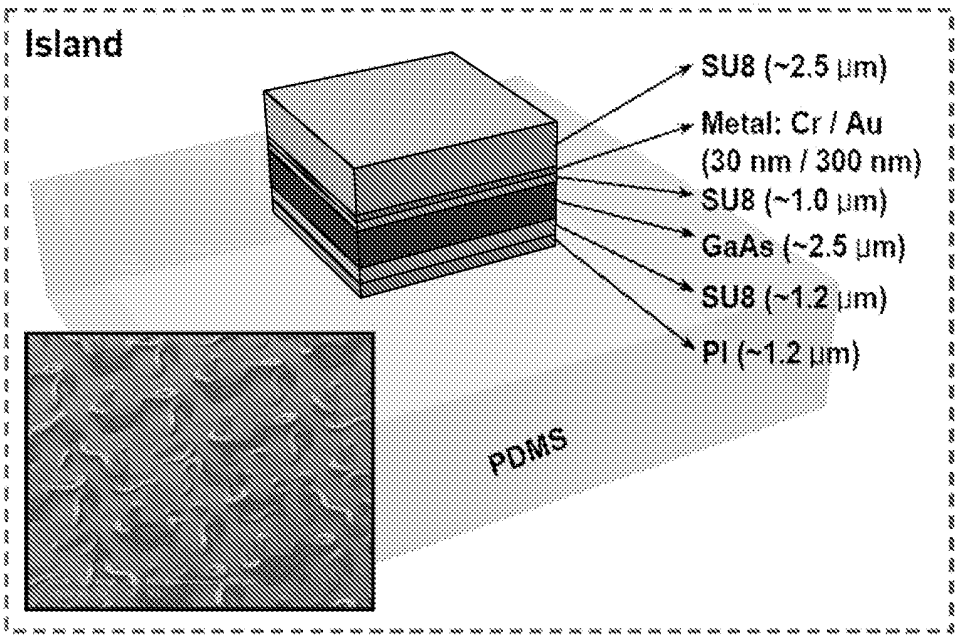


Figure 33c

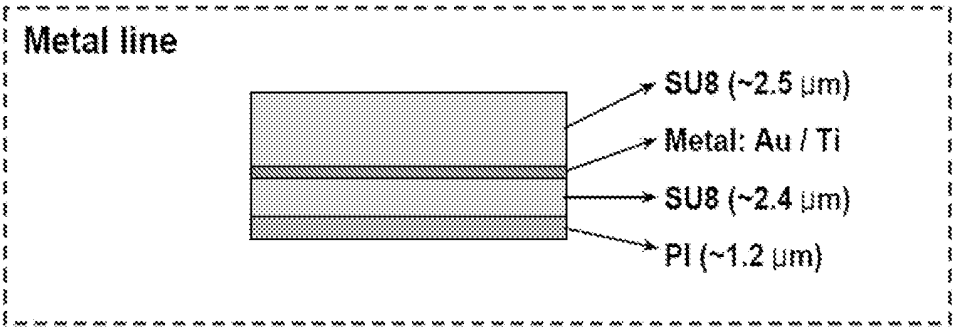
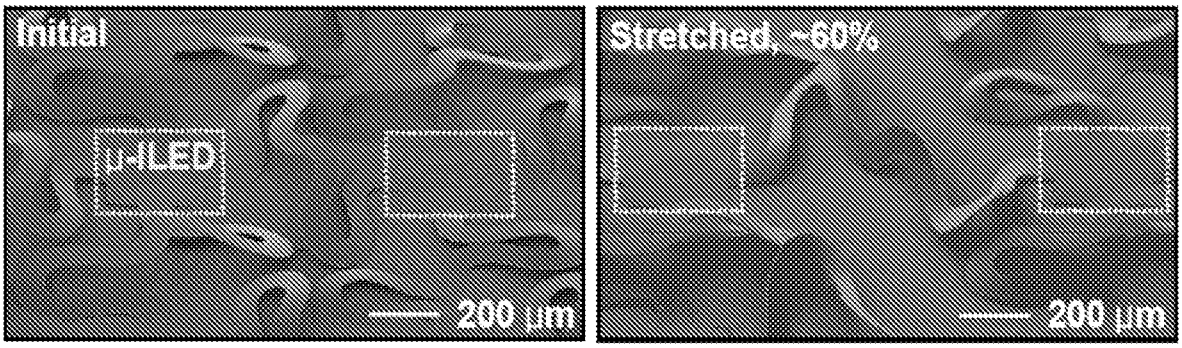


Figure 34a



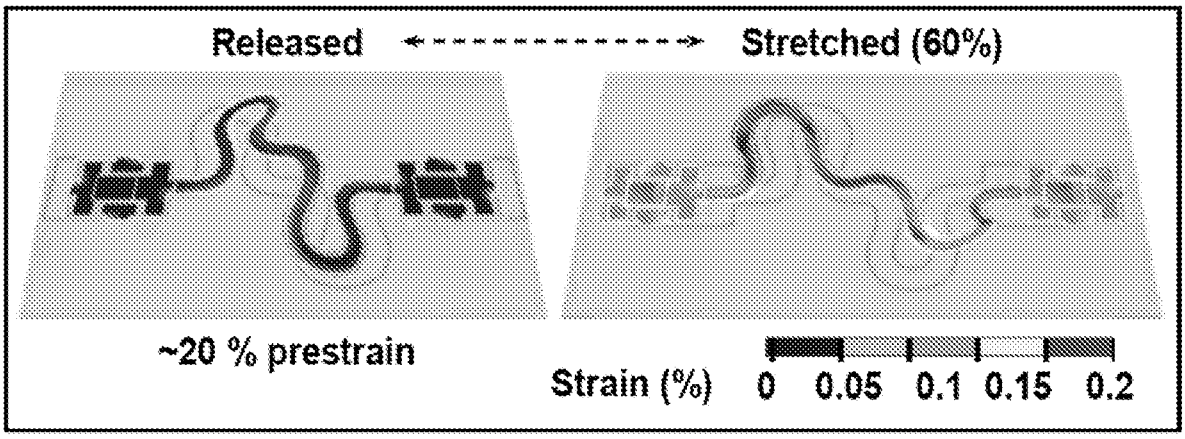


Figure 34b

Figure 35a

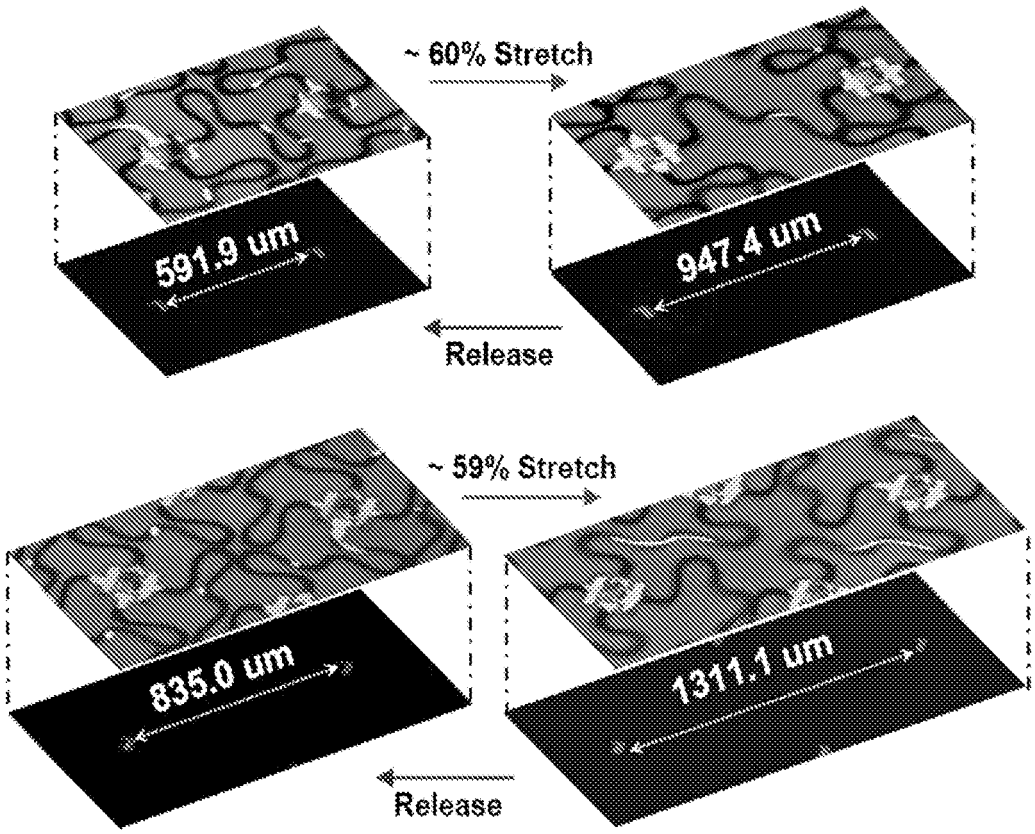


Figure 35b

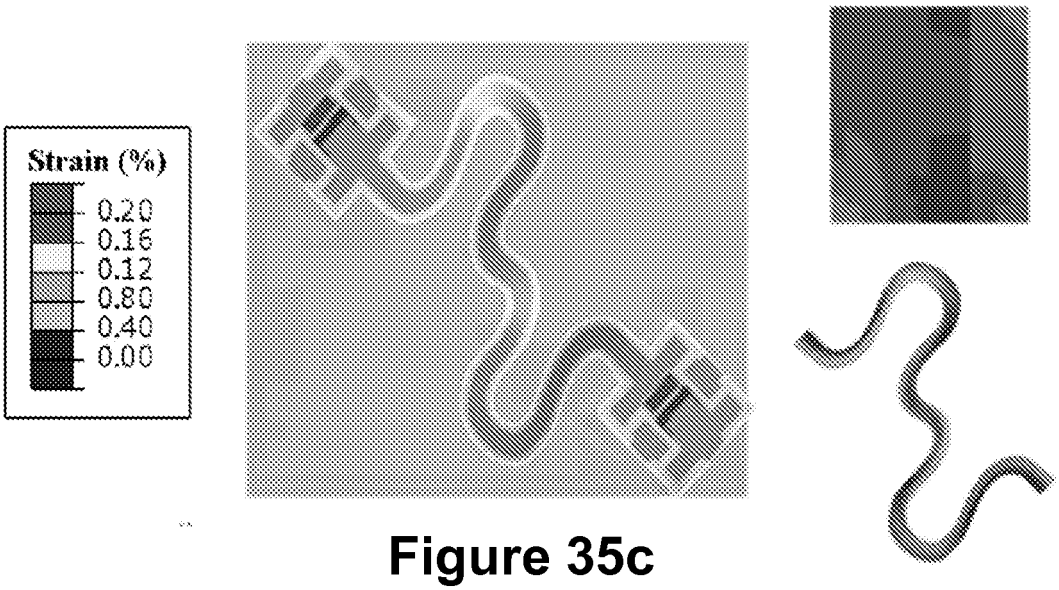
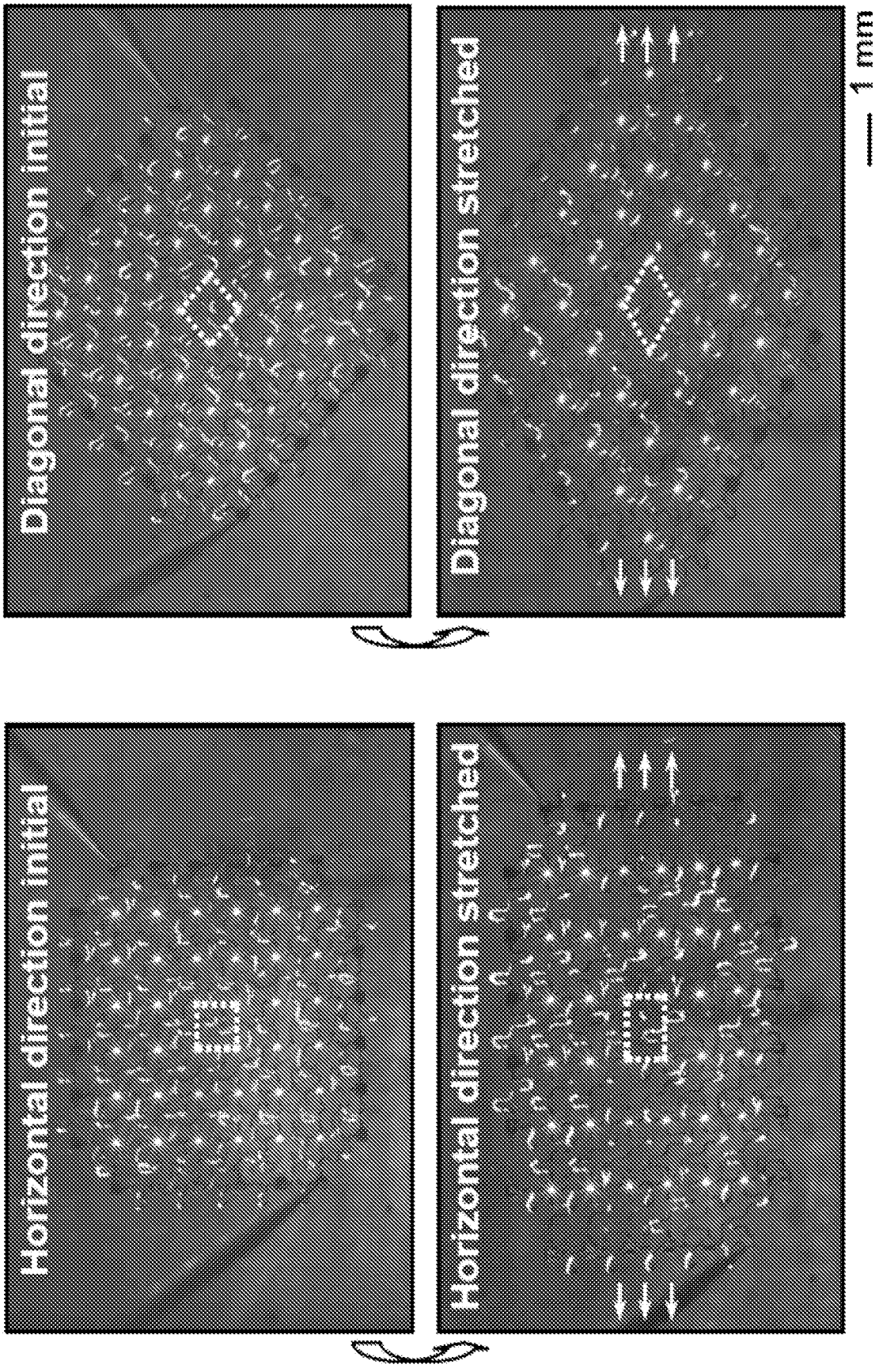


Figure 35c

Figure 36


Diagonal direction initial
Diagonal direction stretched
1 mm
Horizontal direction initial
Horizontal direction stretched

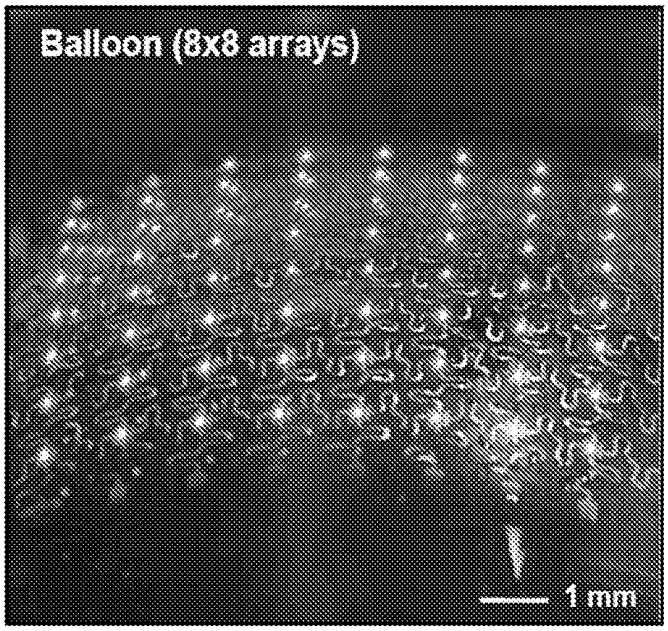
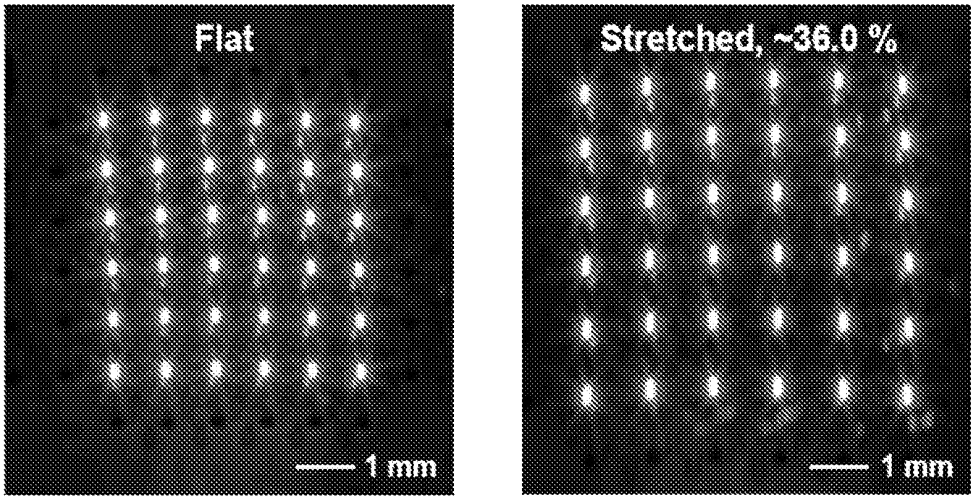


Figure 37a

Figure 37b



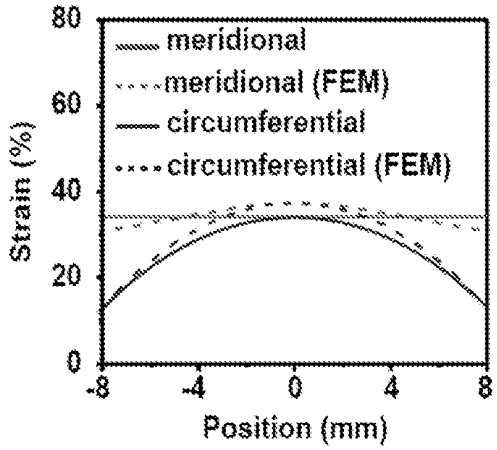
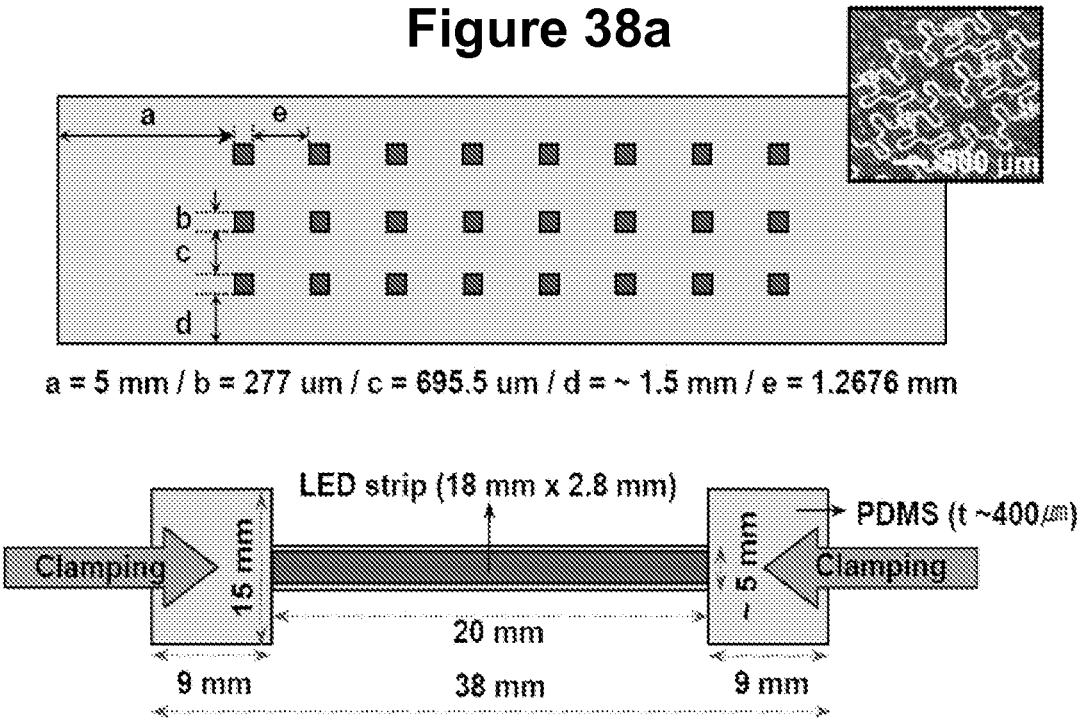


Figure 37c

Figure 38a



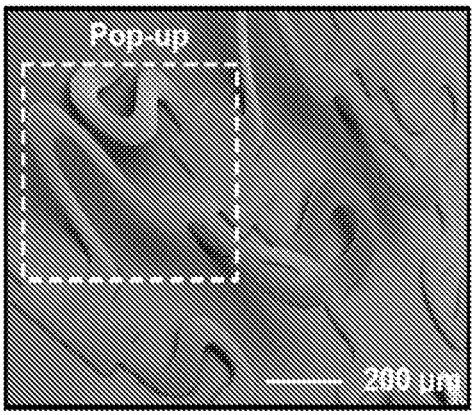


Figure 38b

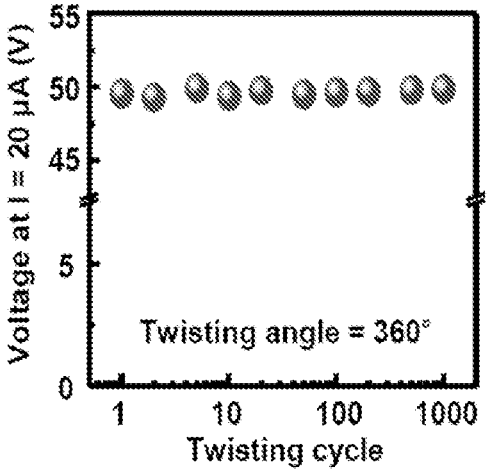


Figure 38c

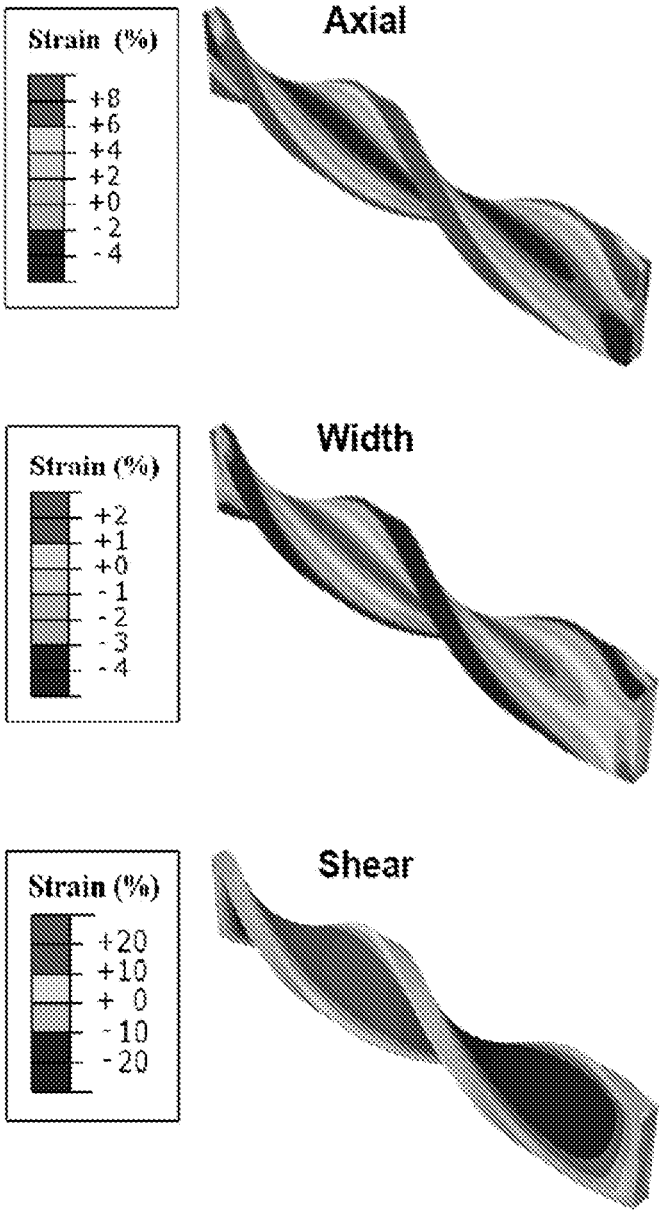
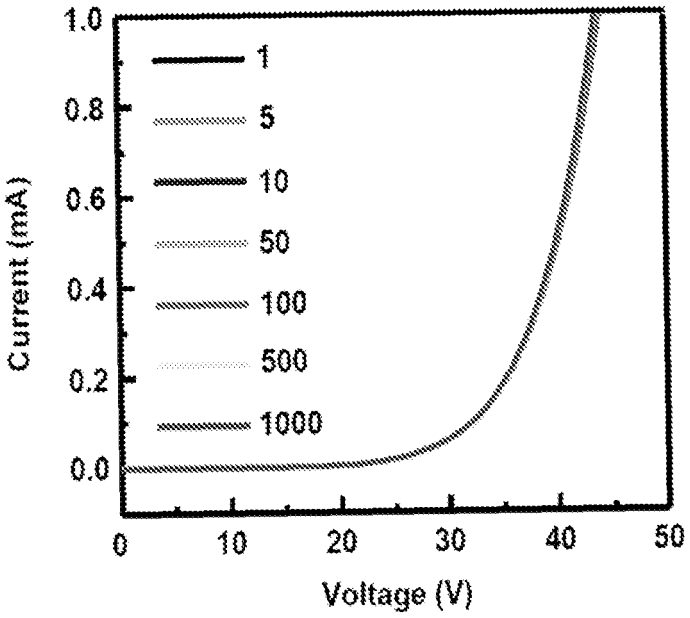

Strain (%)
+8
+6
+4
+2
+0
-2
-4
Axial
Strain (%)
+2
+1
+0
-1
-2
-3
-4
Width
Strain (%)
+20
+10
+ 0
-10
-20
Shear

Figure 39

Figure 40a



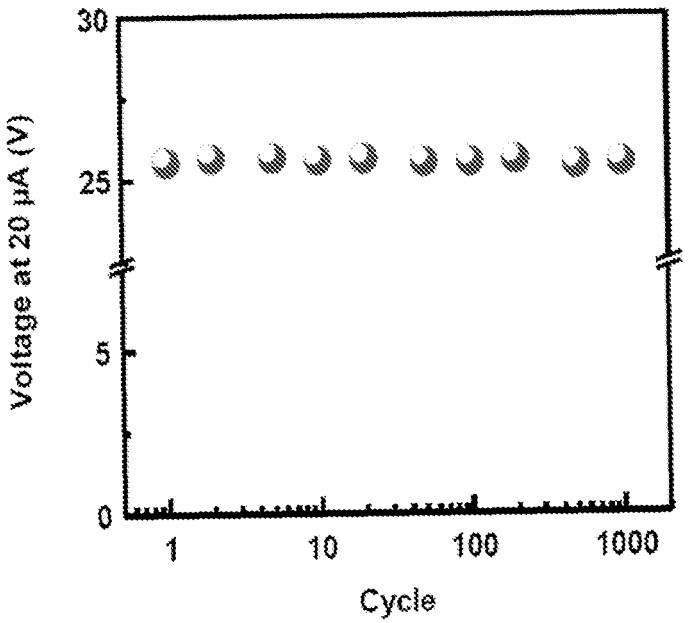


Figure 40b

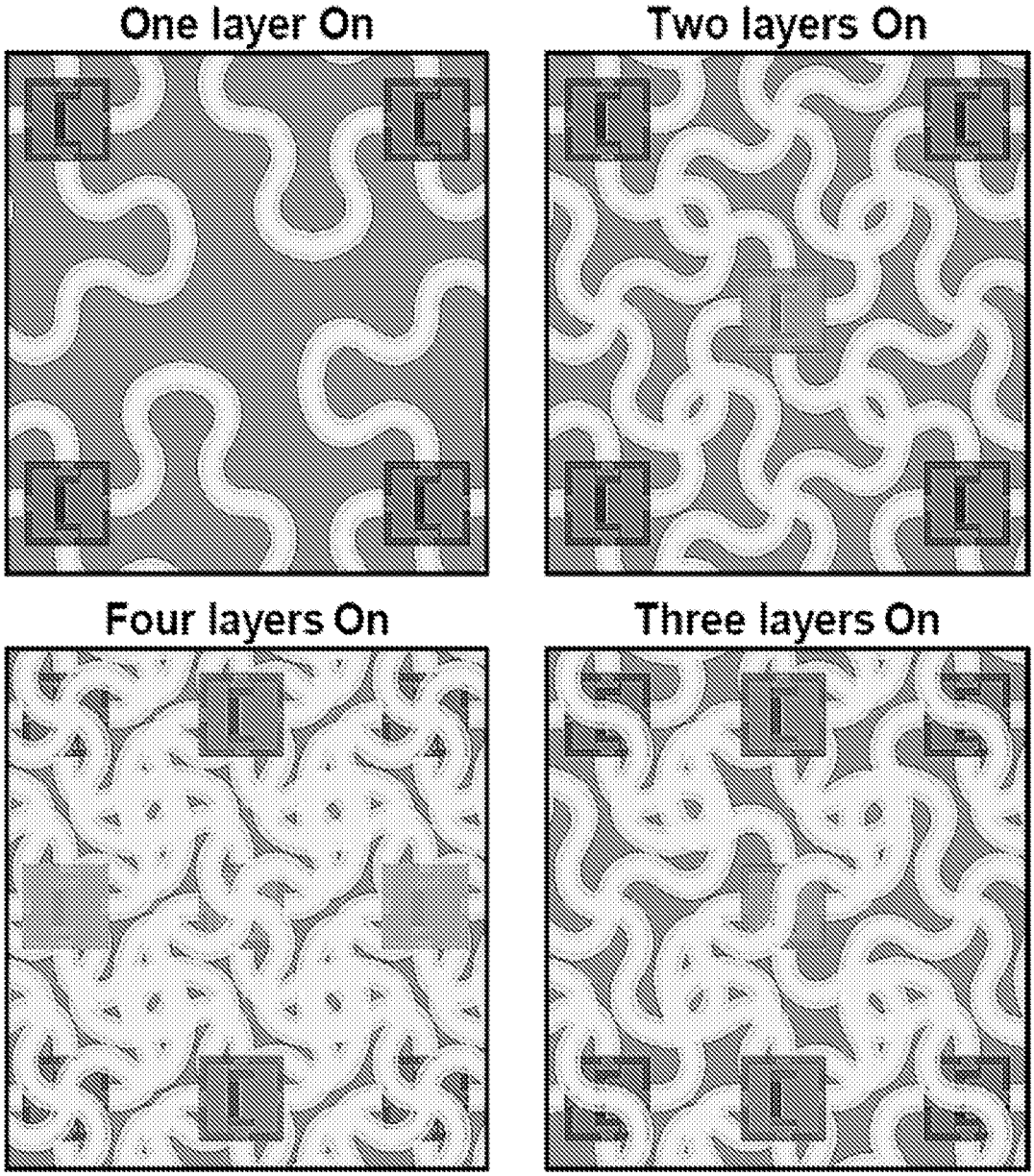


Figure 41a

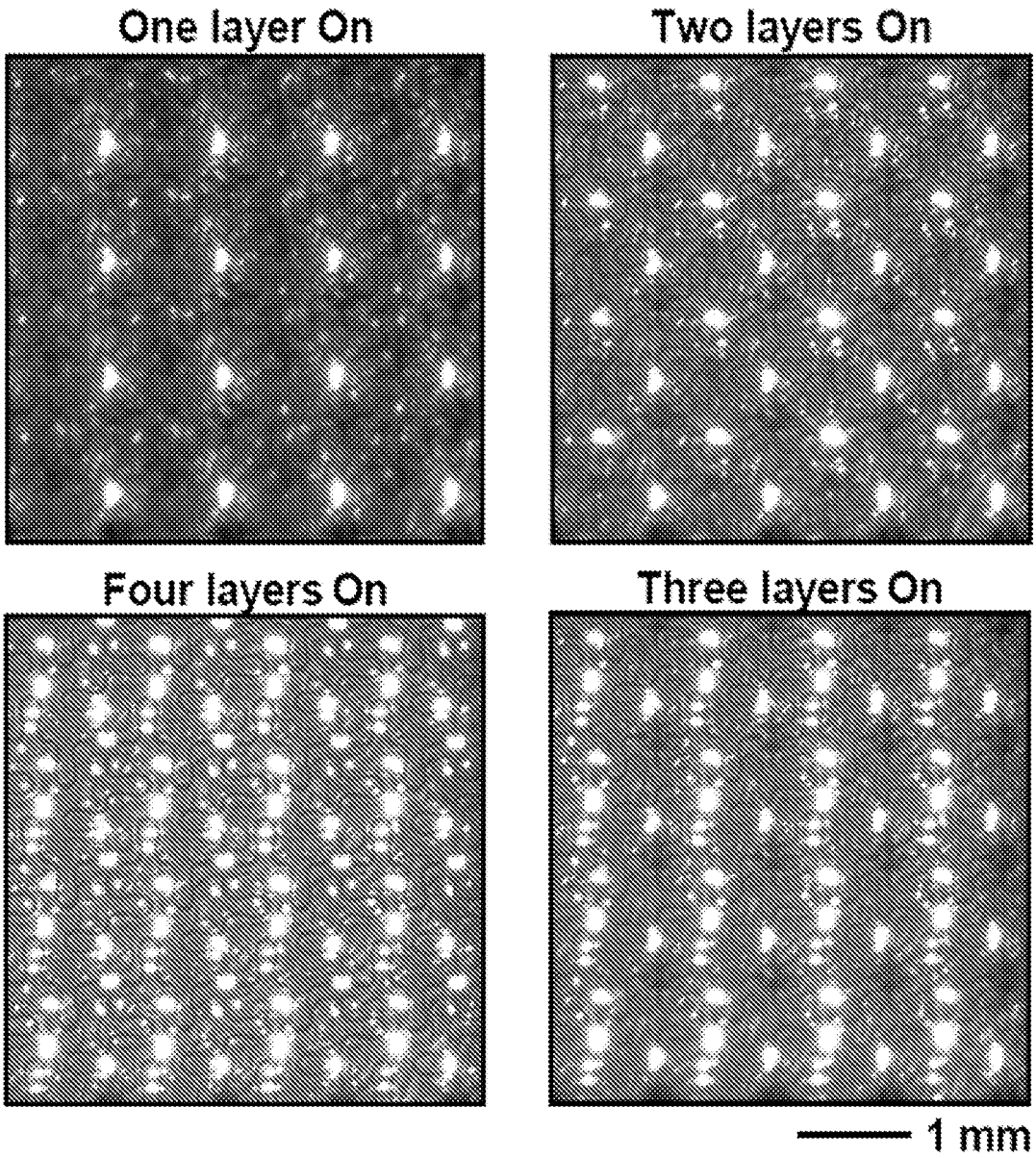


Figure 41b

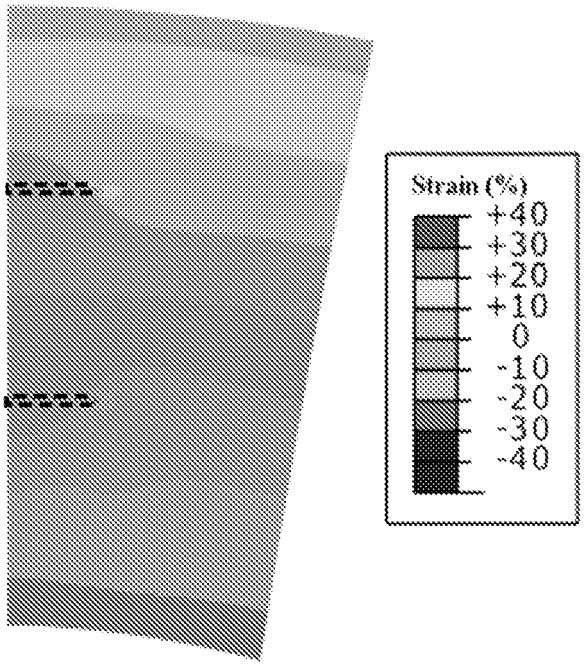


Figure 42a

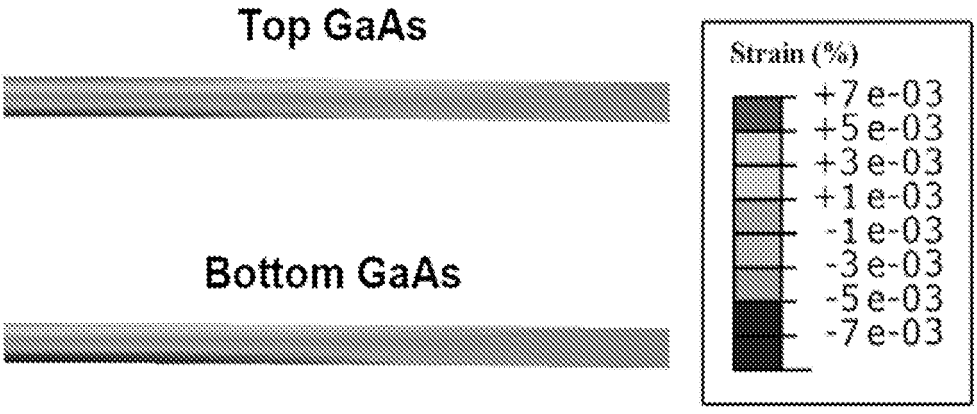


Figure 42b

Figure 43b

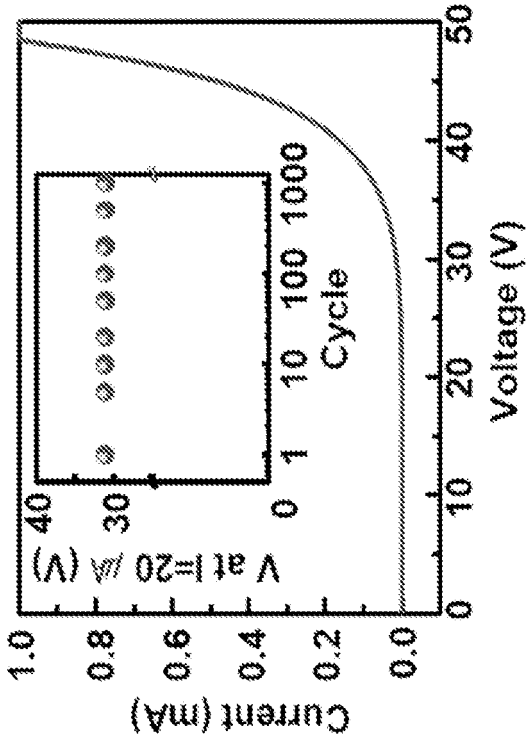


Figure 43a

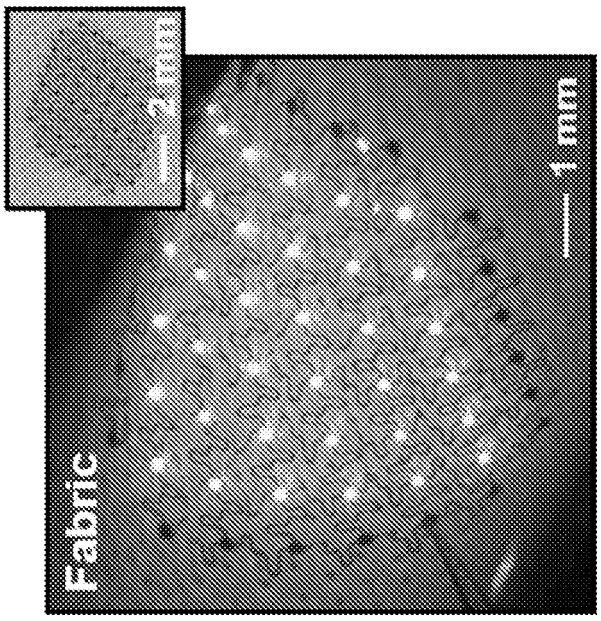


Figure 43d

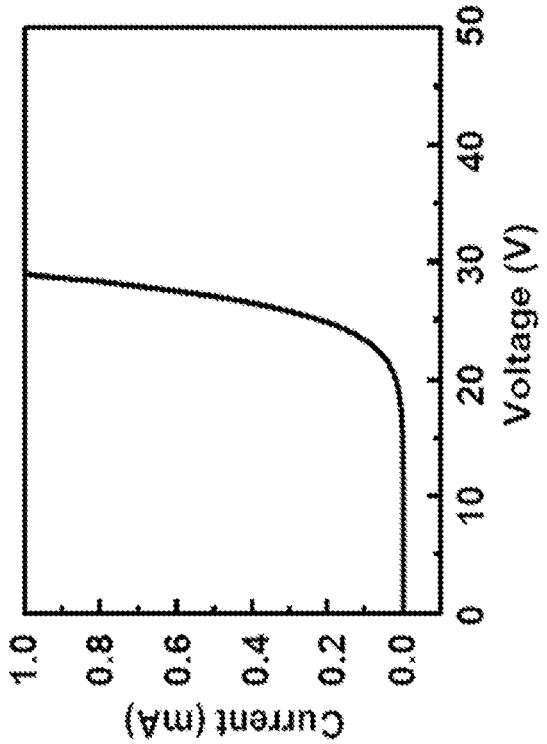


Figure 43c

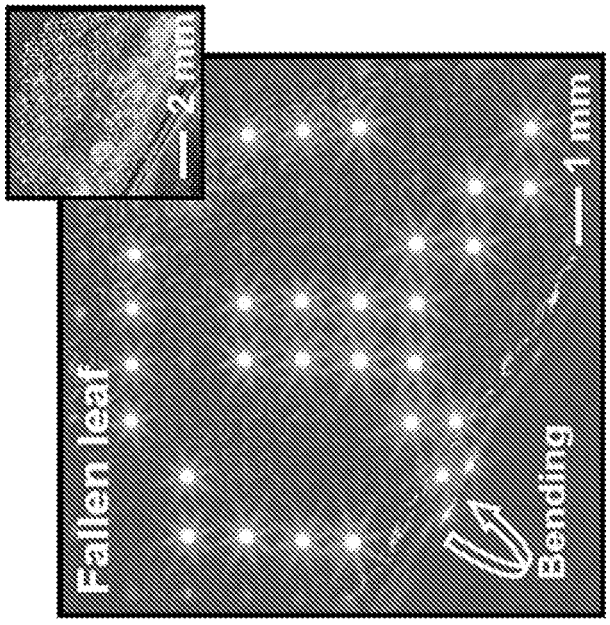


Figure 43f

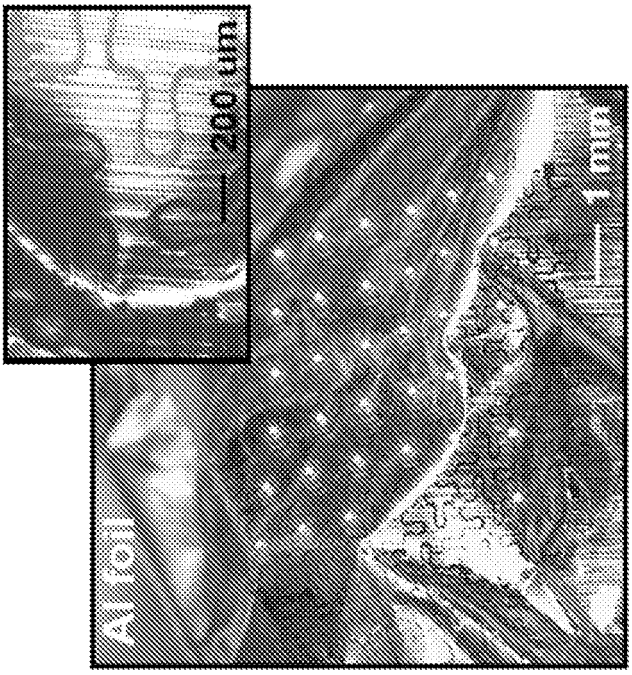


Figure 43e

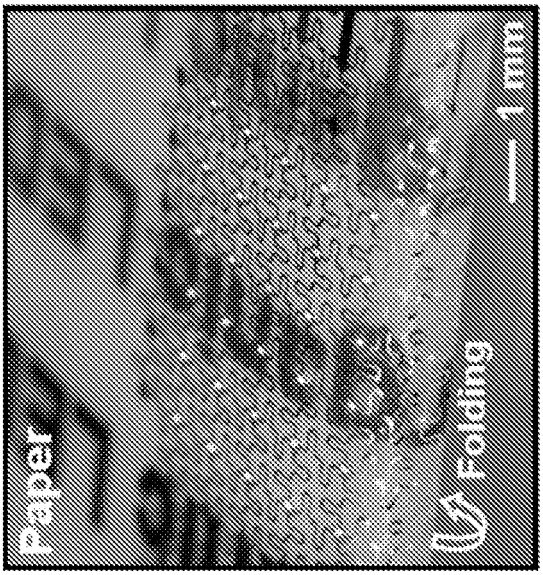


Figure 44a

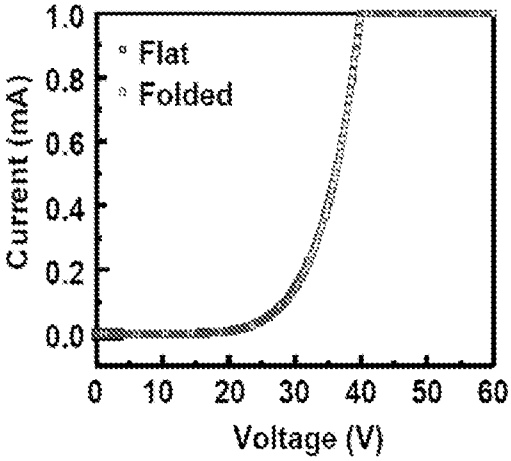


Figure 44b

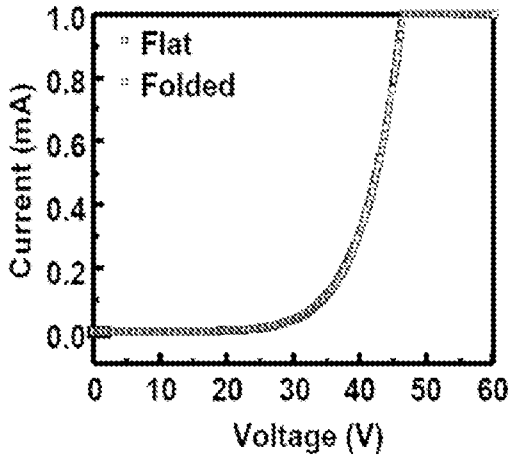
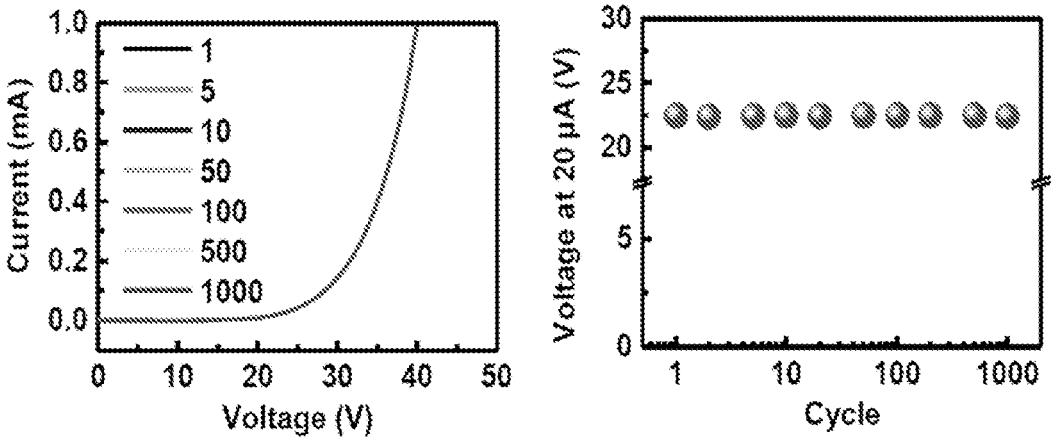


Figure 44c



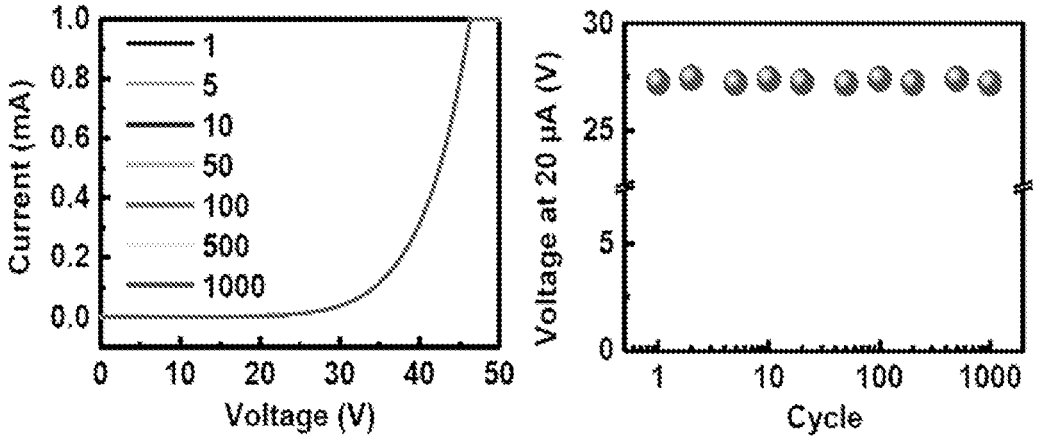


Figure 44d

Figure 45a

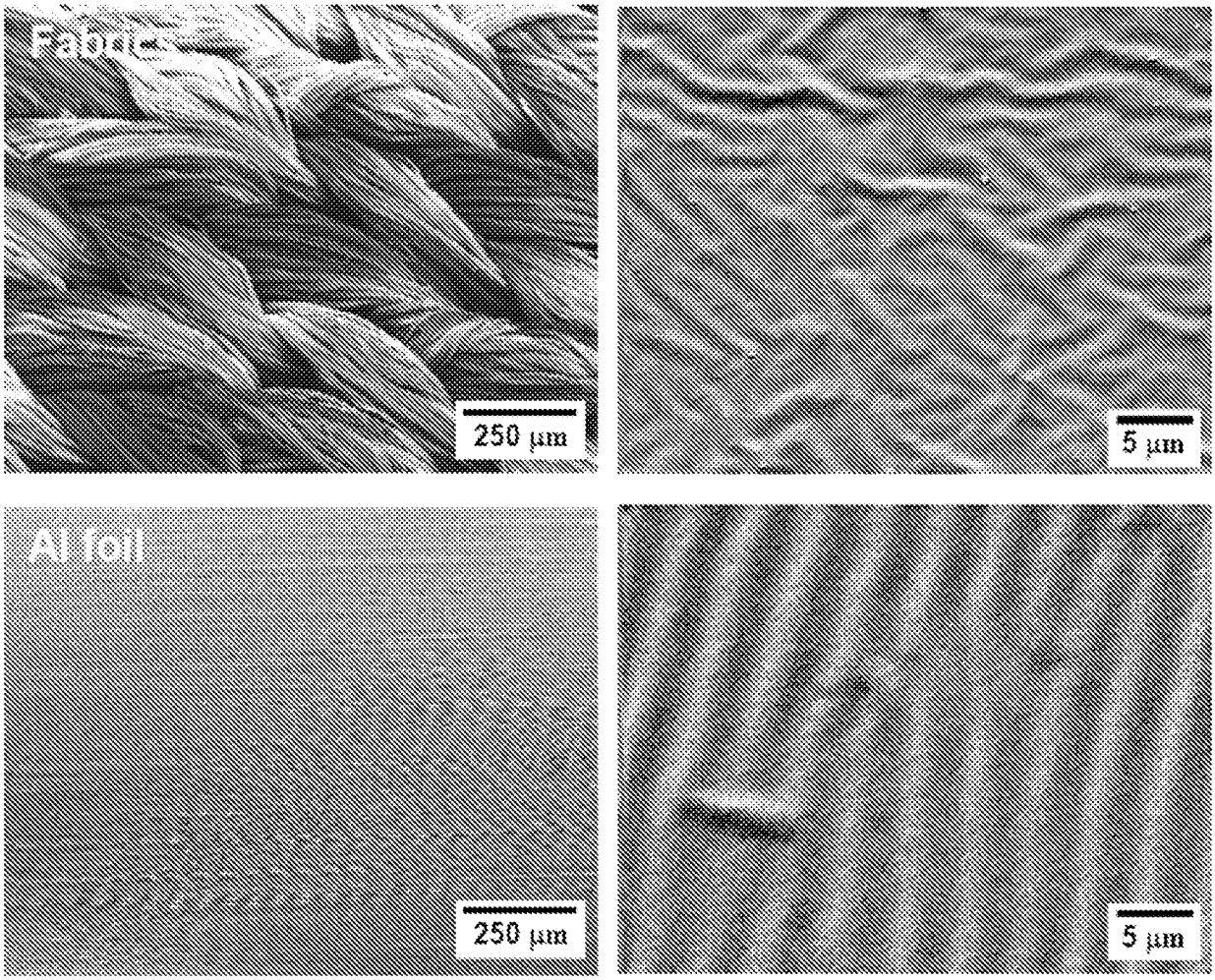


Figure 45b

Figure 45c

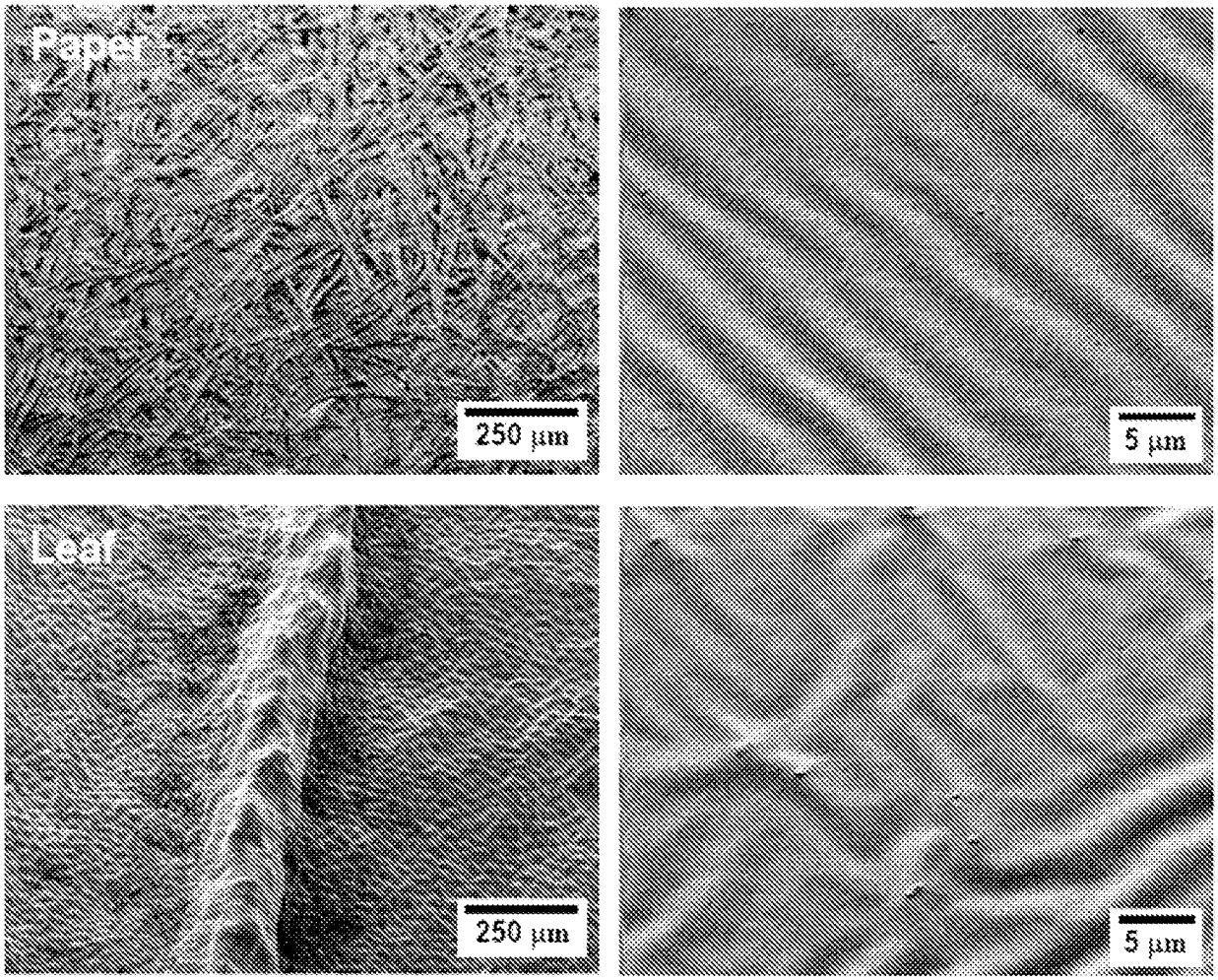


Figure 45d

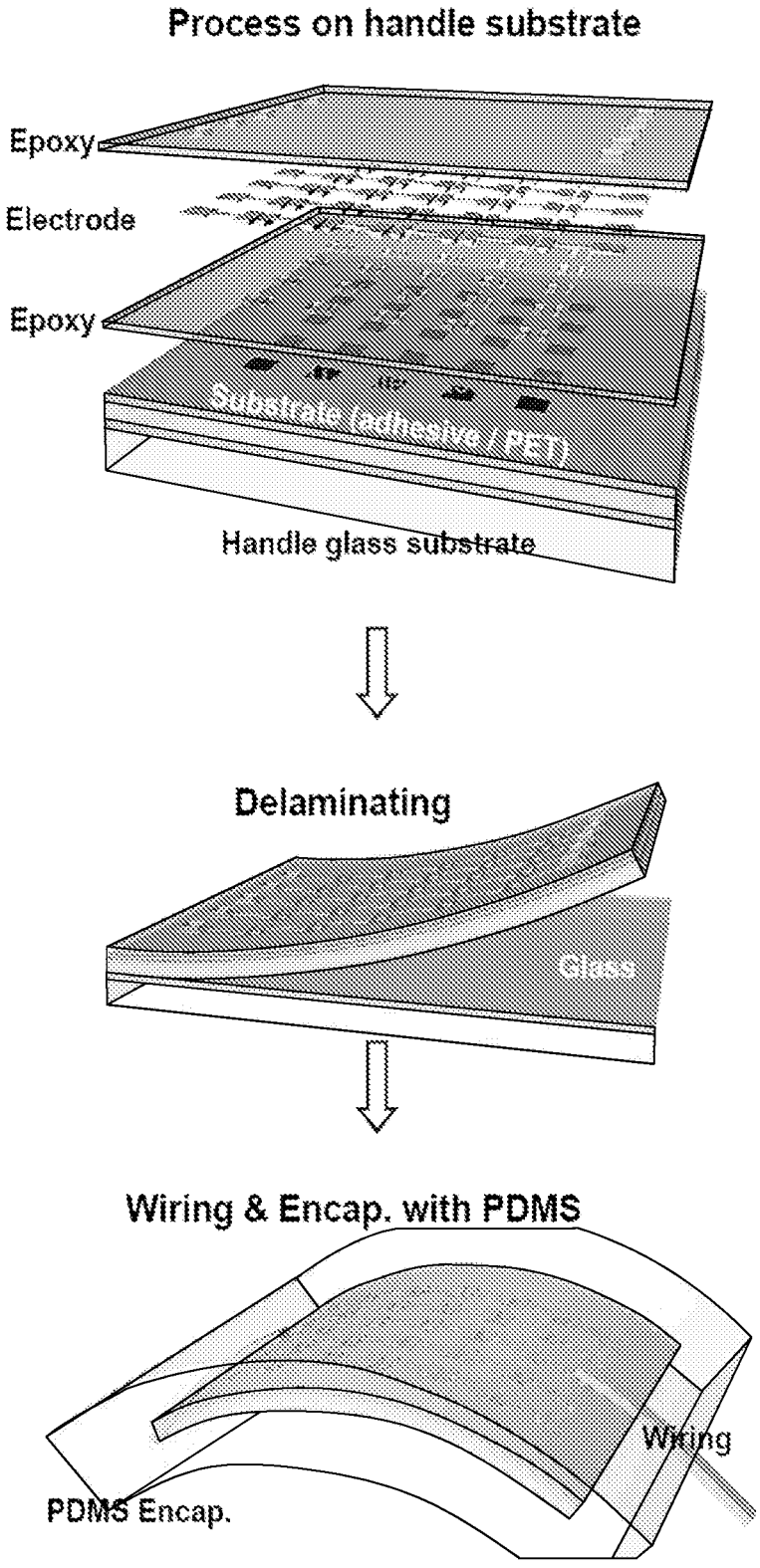

Process on handle substrate
Epoxy
Electrode
Epoxy
Substrate (adhesive / PET)
Handle glass substrate
Delaminating
Glass
Wiring & Encap. with PDMS
Wiring
PDMS Encap.

Figure 46

Figure 47a

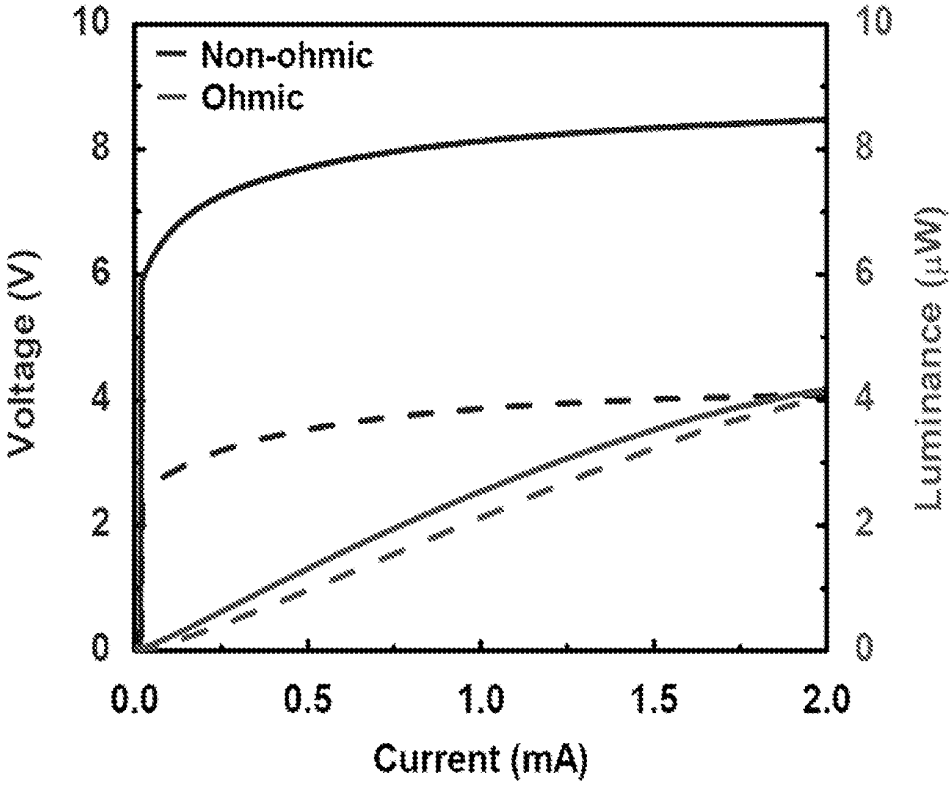


Figure 47b

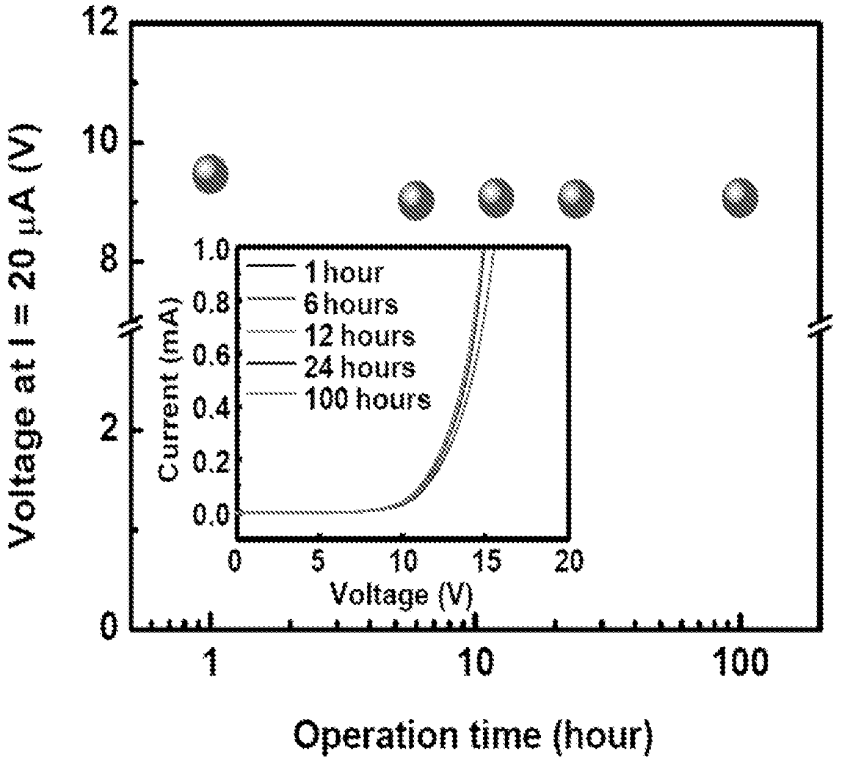


Figure 48a

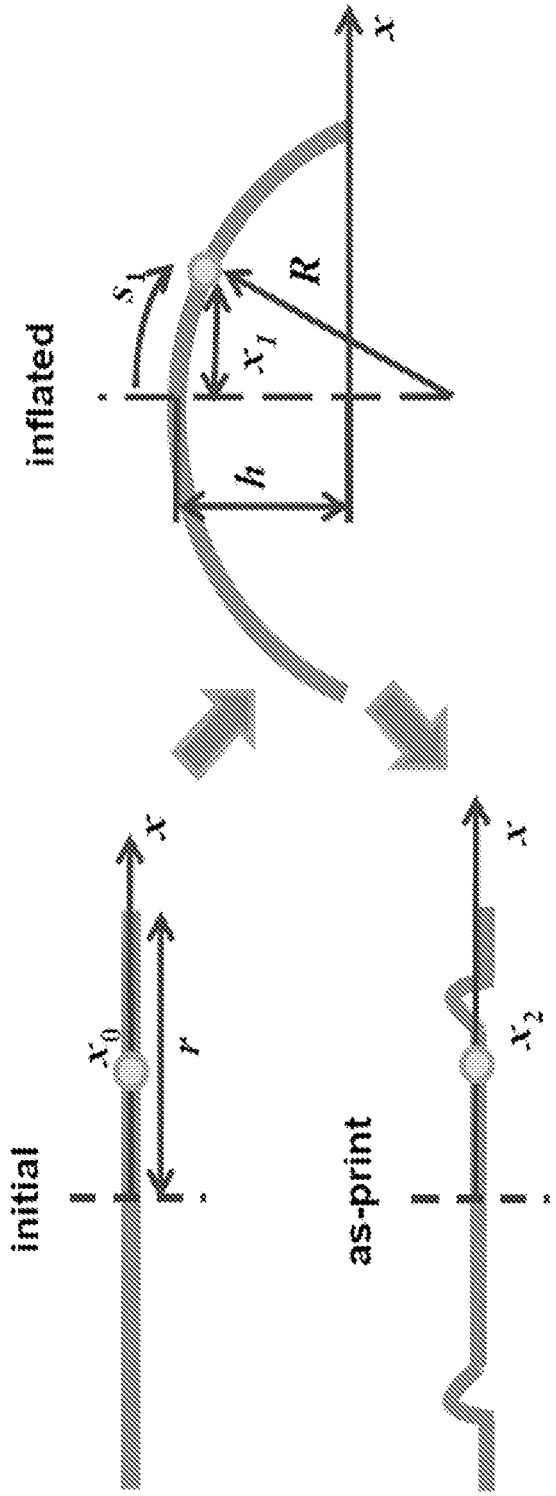


Figure 48b

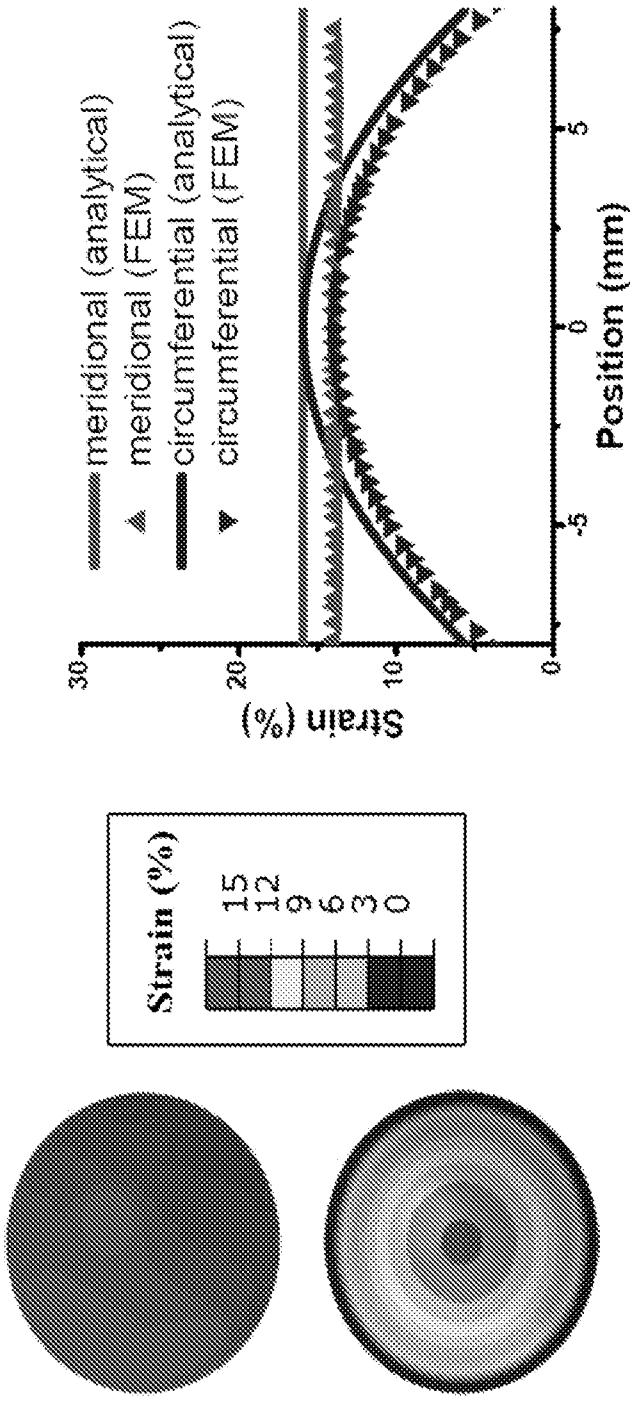

meridional (analytical)
meridional (FEM)
circumferential (analytical)
circumferential (FEM)
Strain (%)
30
20
10
0
-5
0
5
Position (mm)
Strain (%)
15
12
9
6
3
0

Figure 48c

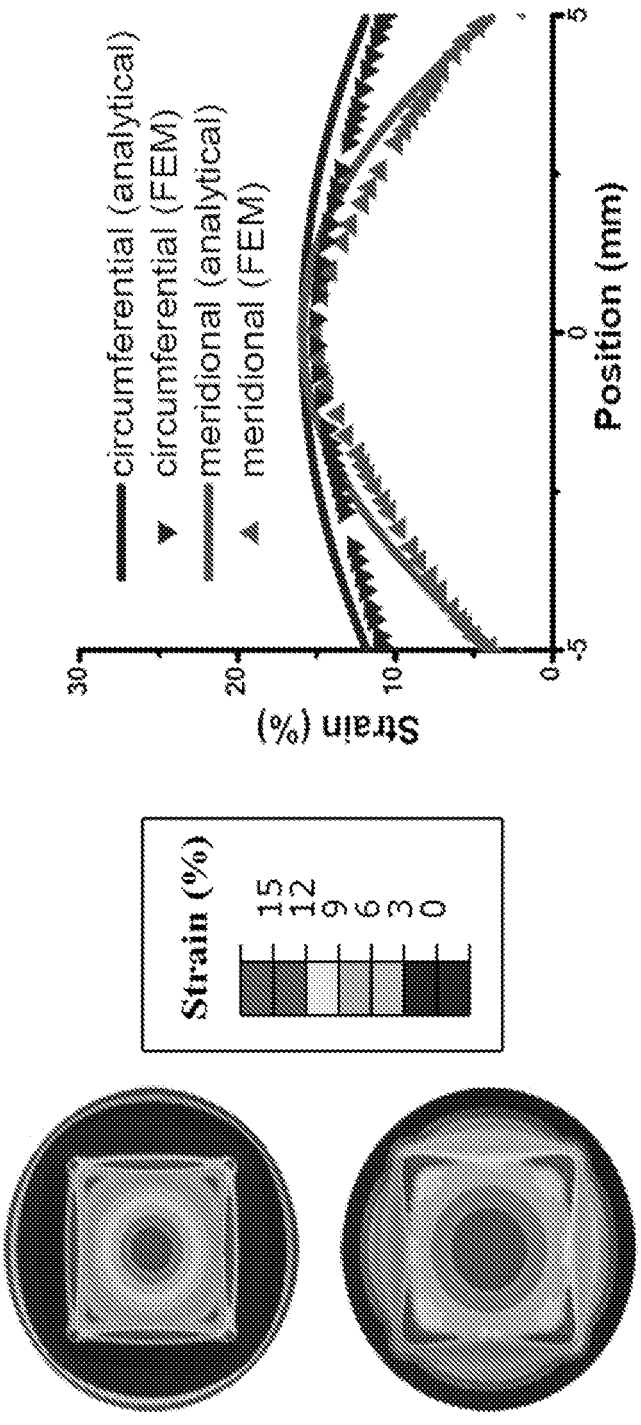

circumferential (analytical)
circumferential (FEM)
meridional (analytical)
meridional (FEM)
Strain (%)
30
20
10
0
-5
0
5
Position (mm)
Strain (%)
15
12
9
6
3
0

Figure 49

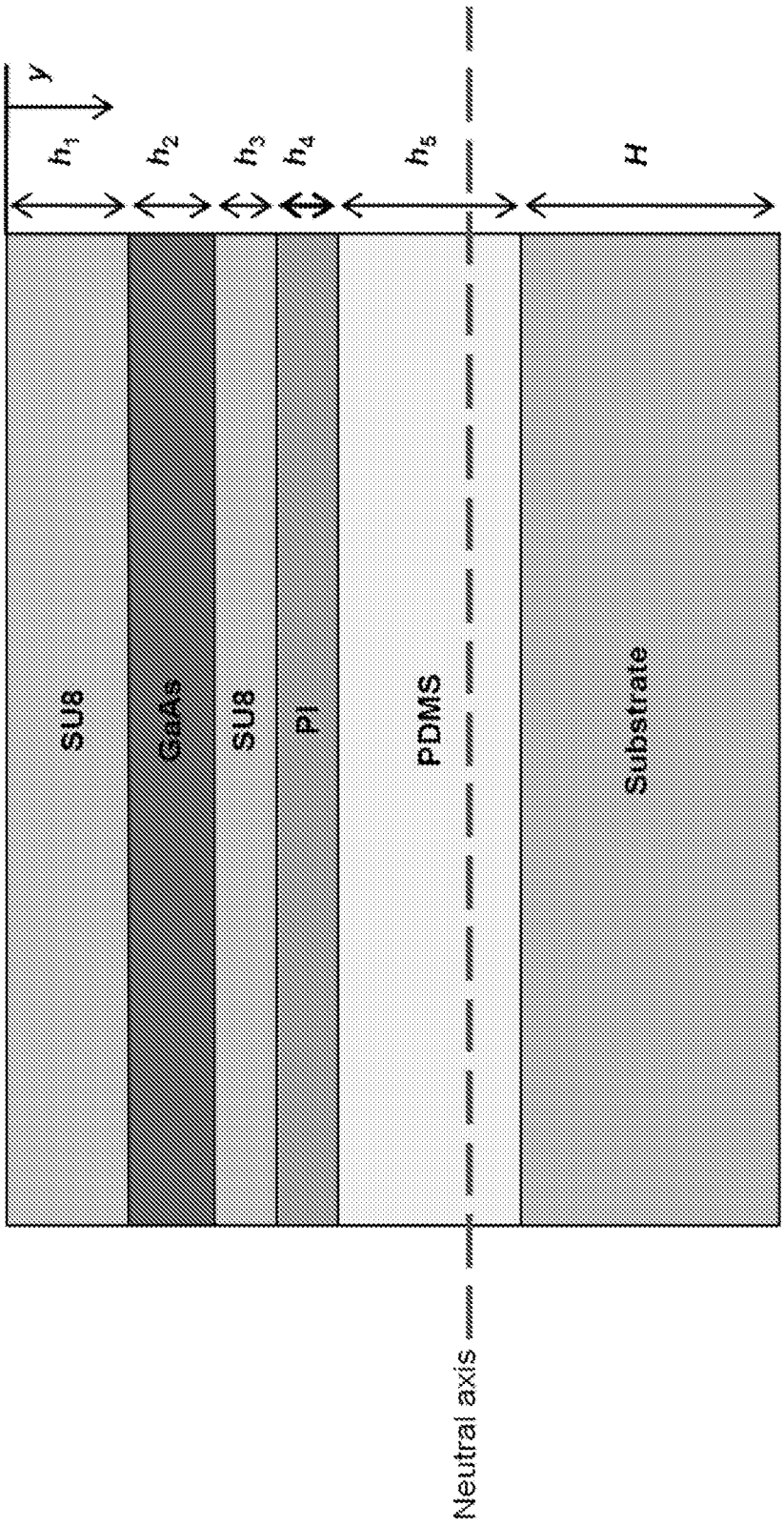


Figure 50a

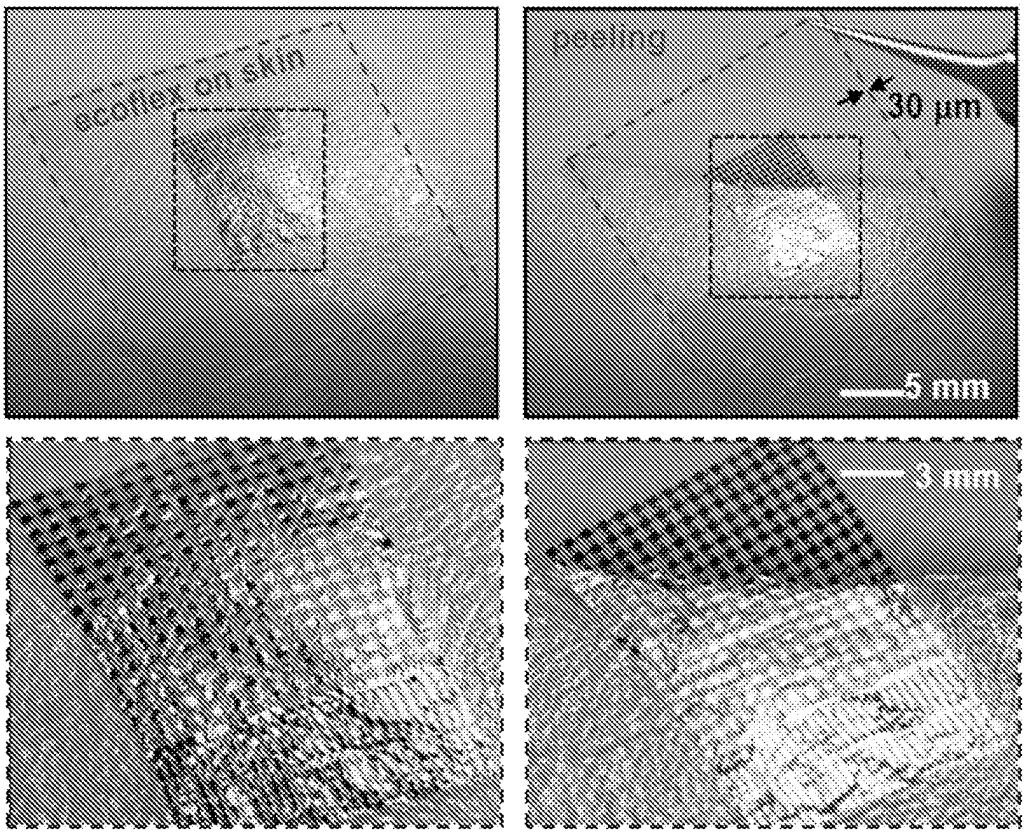


Figure 50b

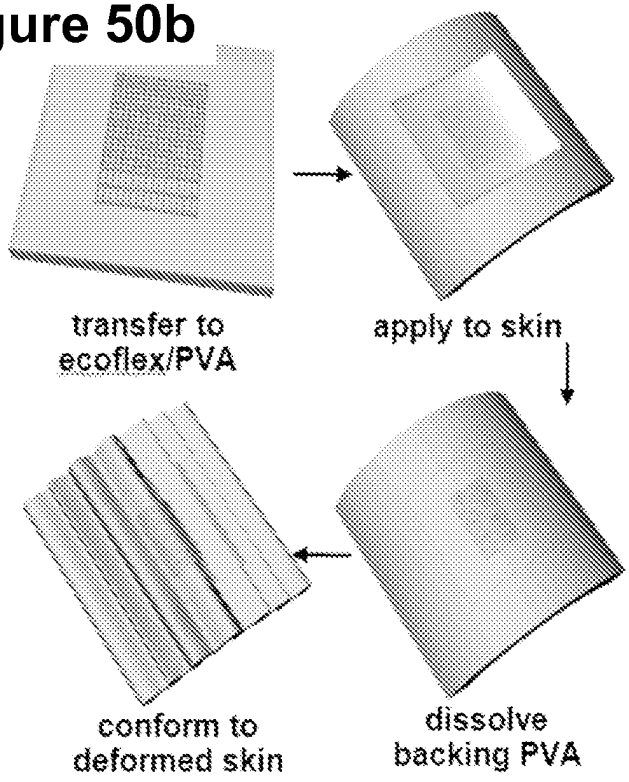


Figure 50c

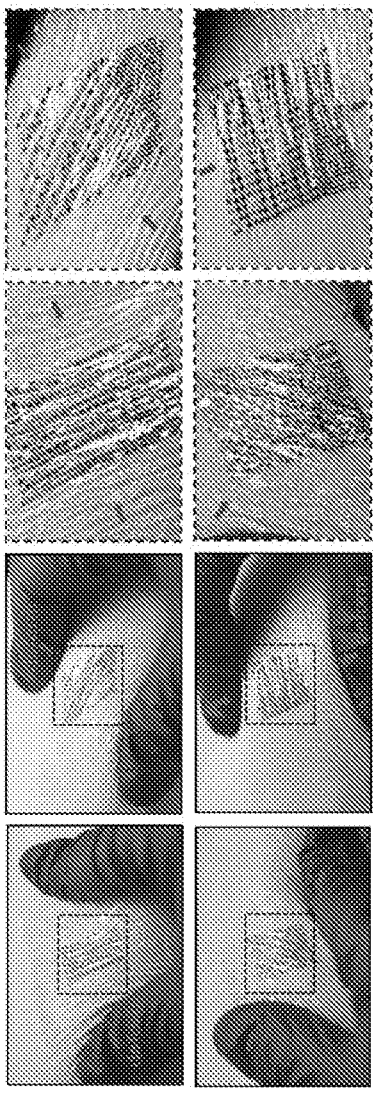
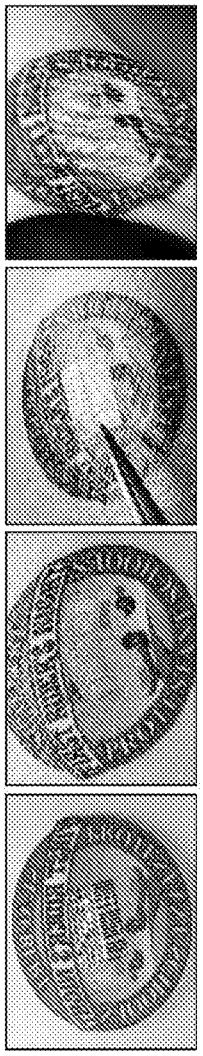


Figure 50d



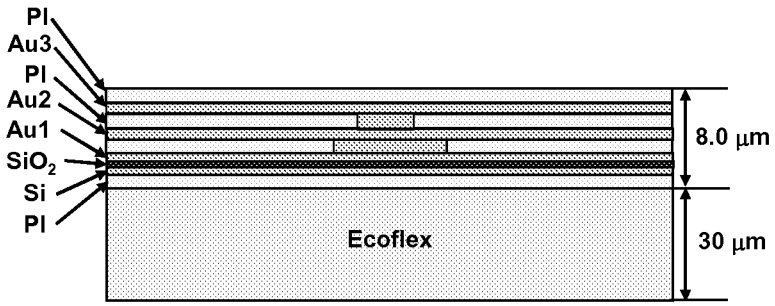


Figure 50e

Figure 51a

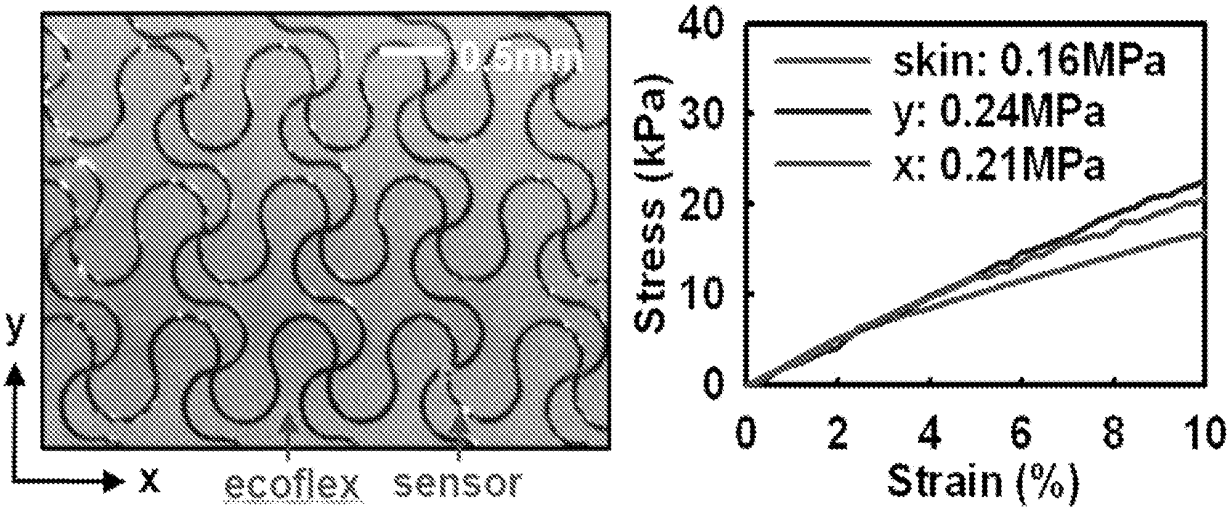


Figure 51b

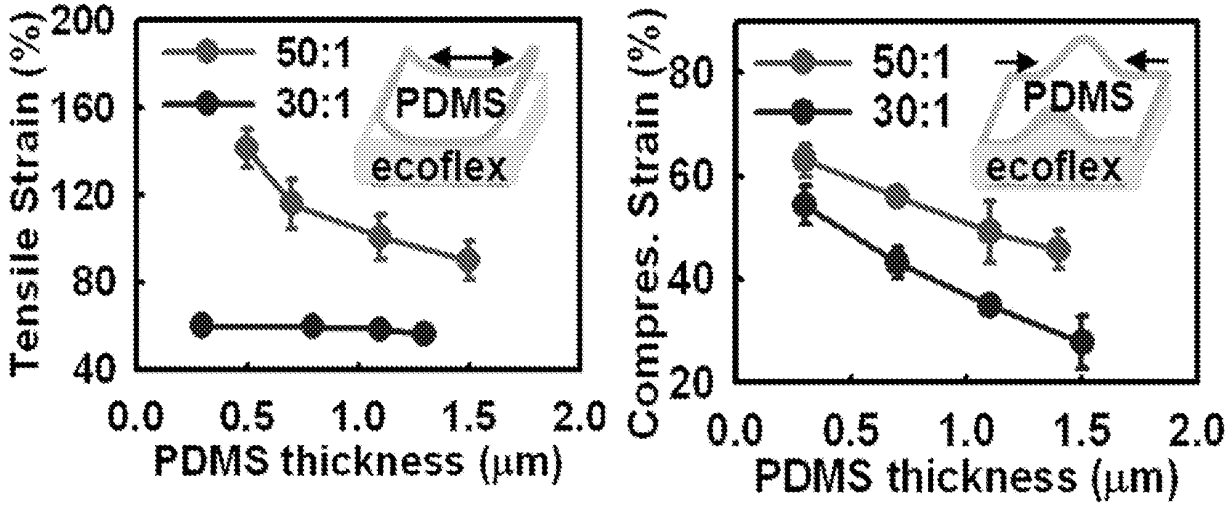


Figure 51c

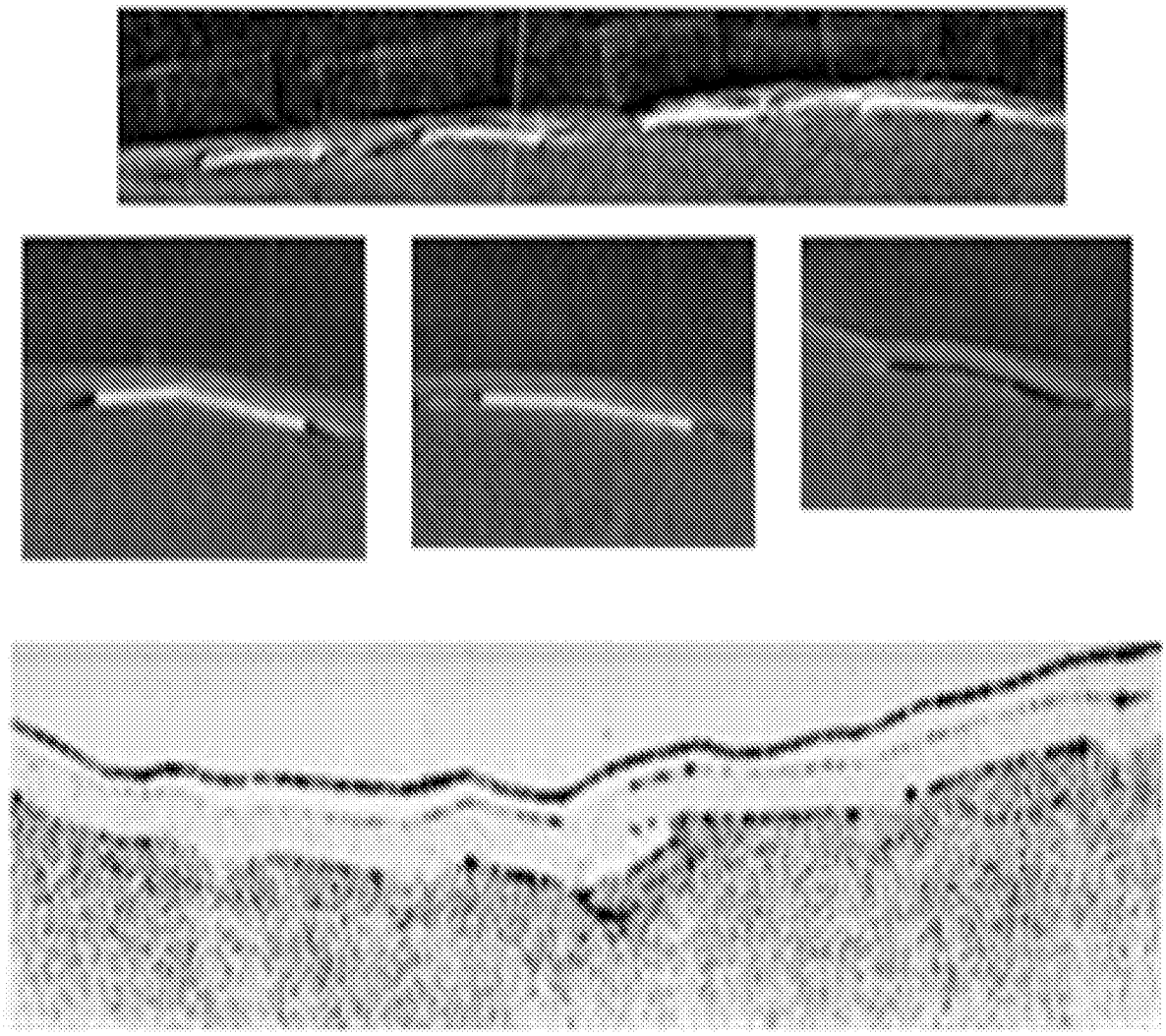


Figure 52a

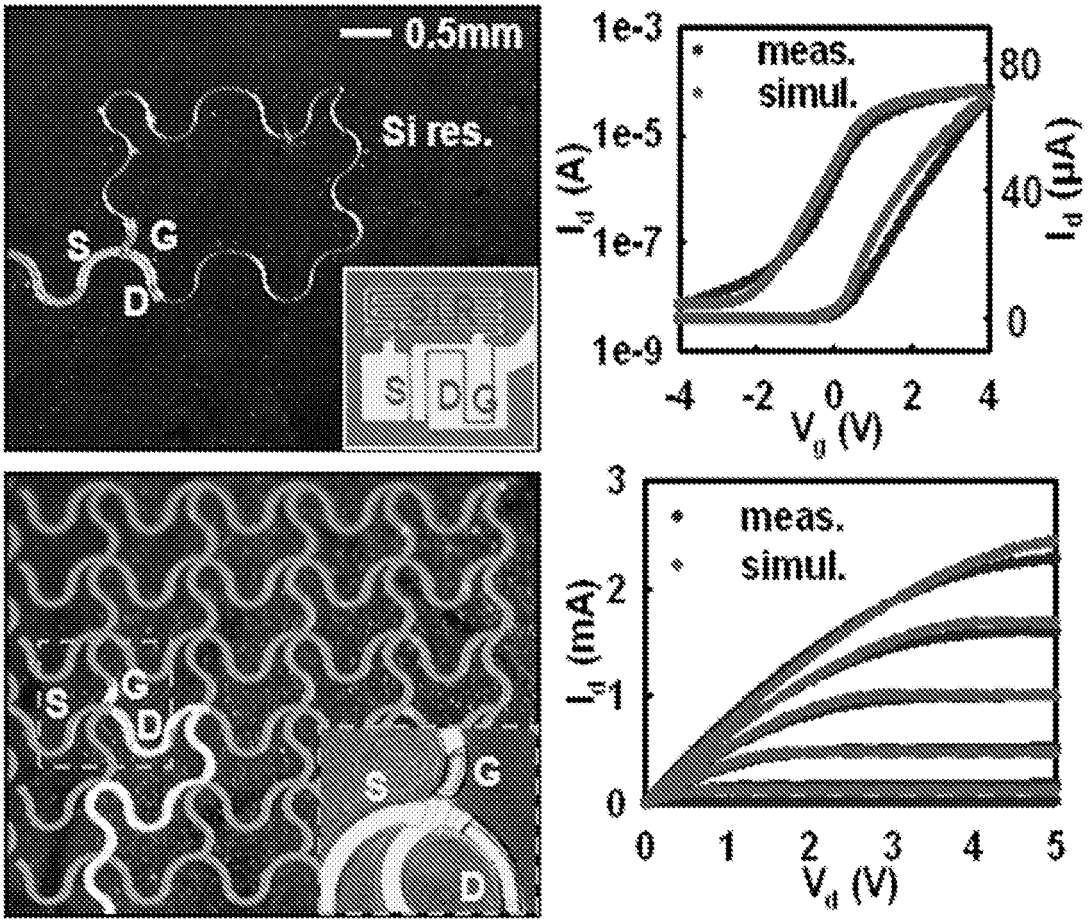


Figure 52b

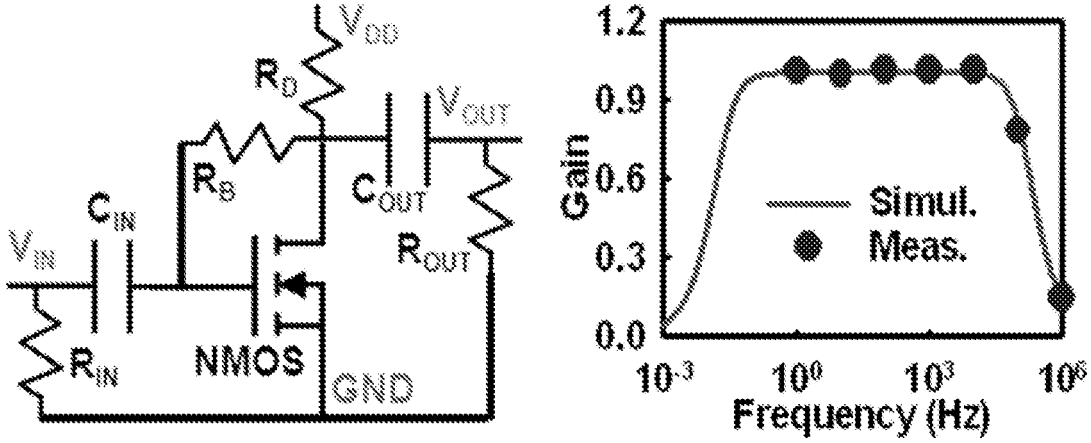


Figure 52c

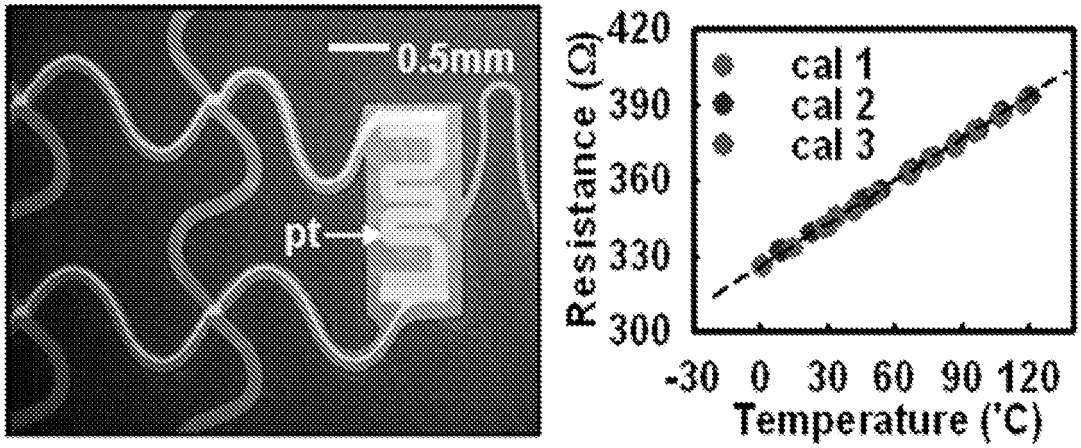


Figure 52d

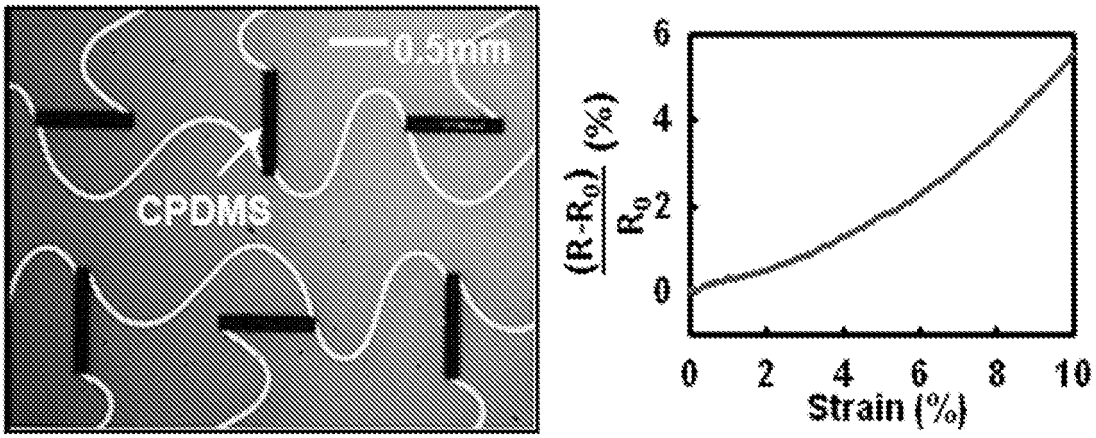


Figure 52e

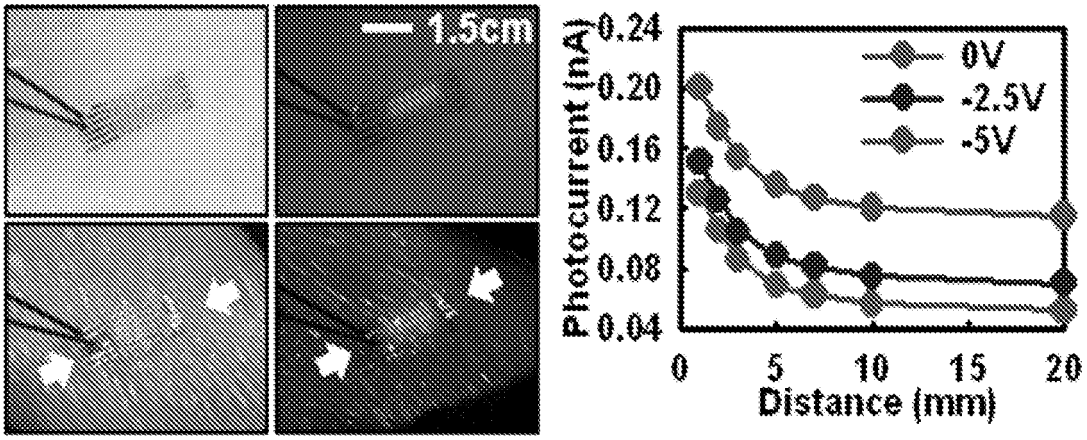


Figure 52f

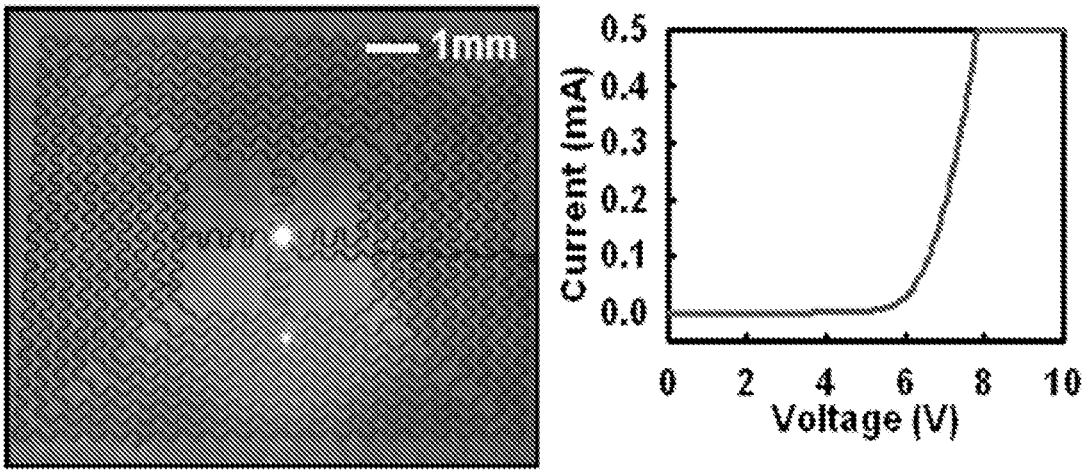


Figure 52g

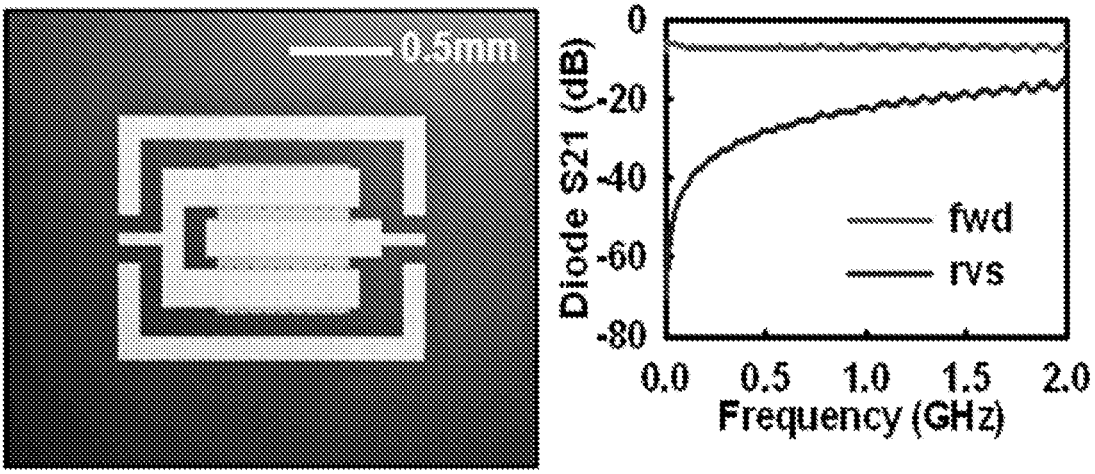


Figure 52h

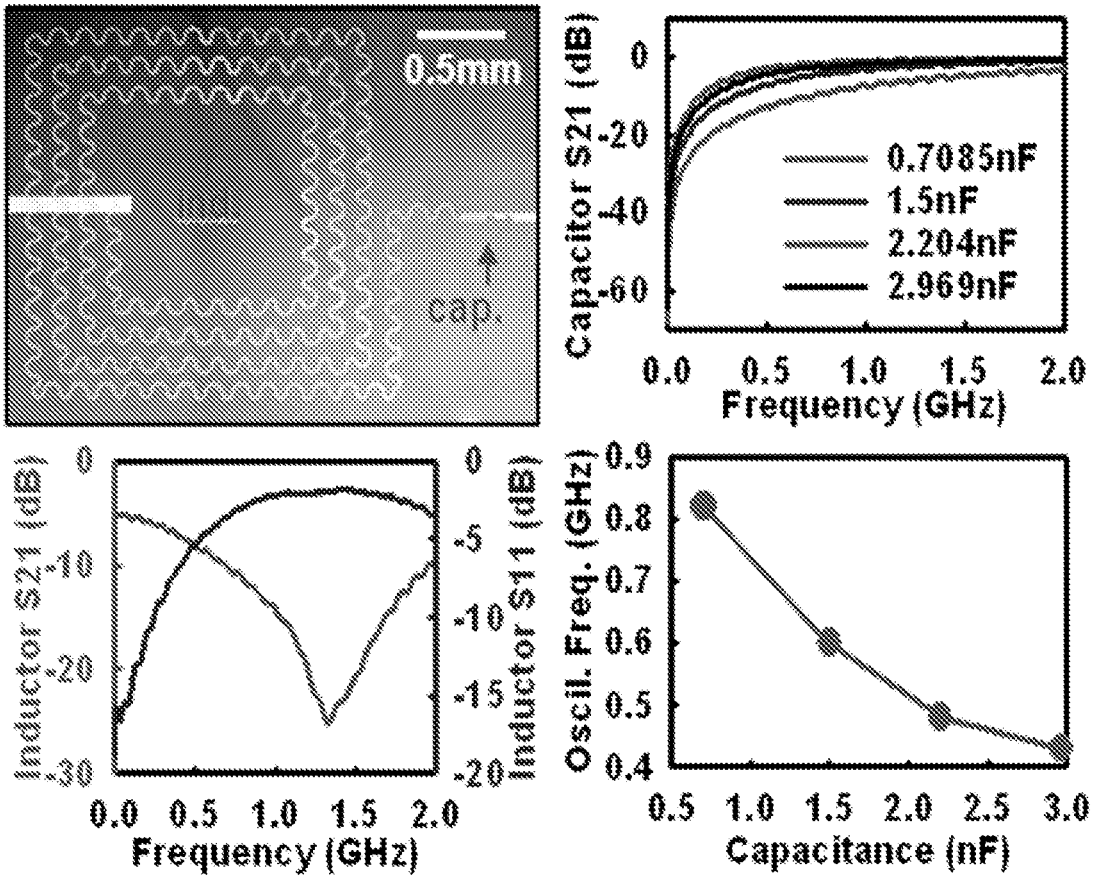

0.5mm
cap.
Capacitor S21 (dB)
0
-20
-40
-60
0.7085nF
1.5nF
2.204nF
2.969nF
0.0 0.5 1.0 1.5 2.0
Frequency (GHz)
Inductor S21 (dB)
0
-10
-20
-30
Inductor S11 (dB)
0
-5
-10
-15
-20
0.0 0.5 1.0 1.5 2.0
Frequency (GHz)
Oscil. Freq. (GHz)
0.9
0.8
0.7
0.6
0.5
0.4
0.5 1.0 1.5 2.0 2.5 3.0
Capacitance (nF)

Figure 53a

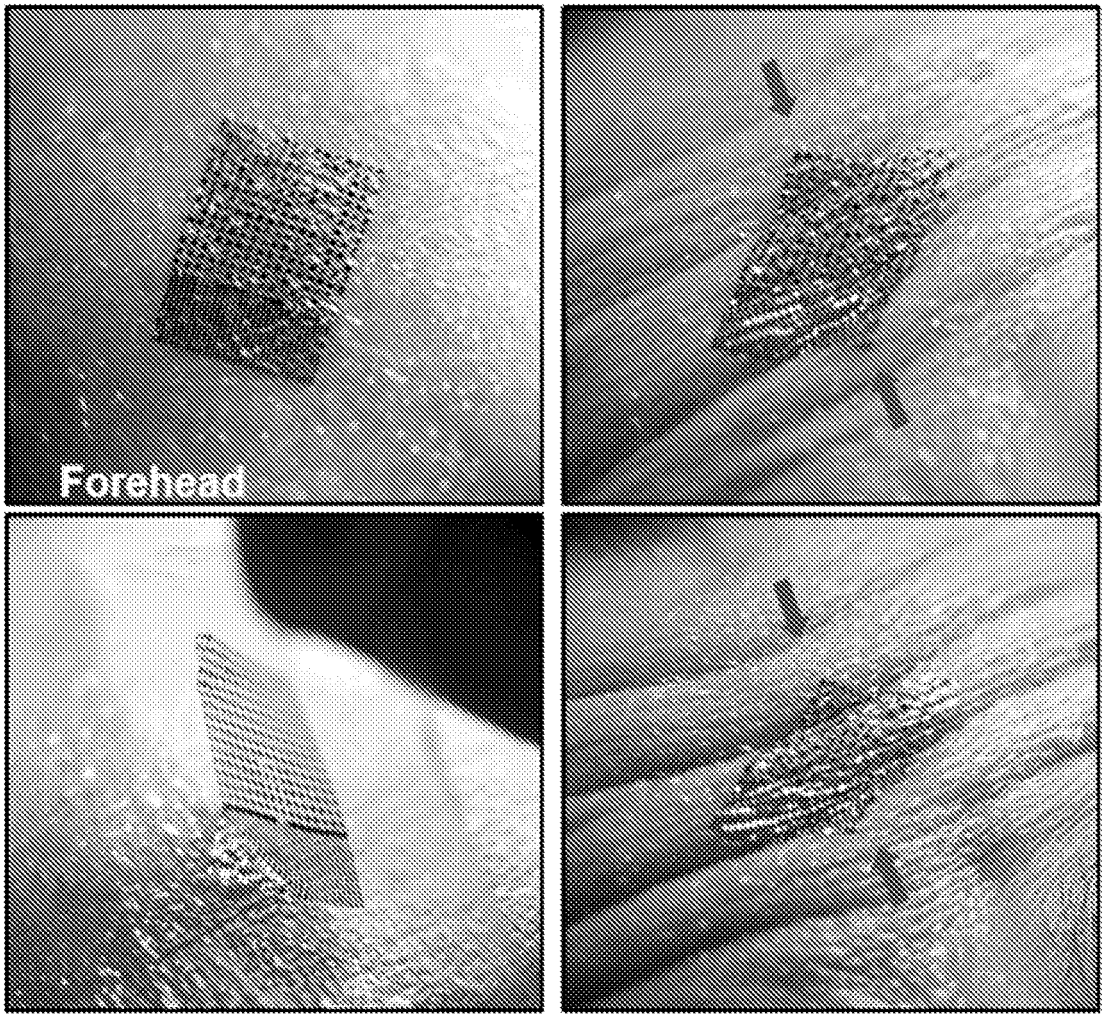


Figure 53b

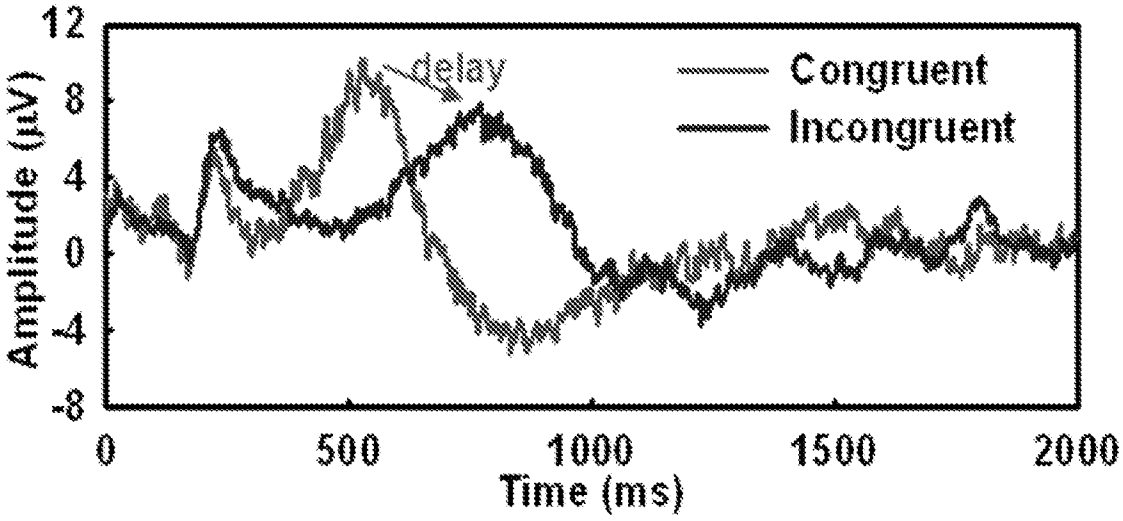


Figure 53c

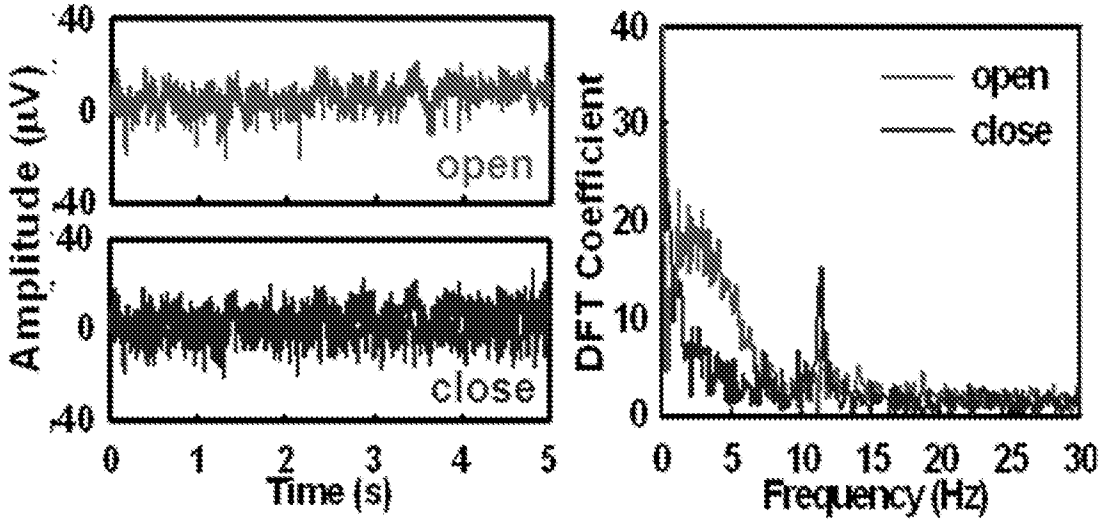


Figure 54a

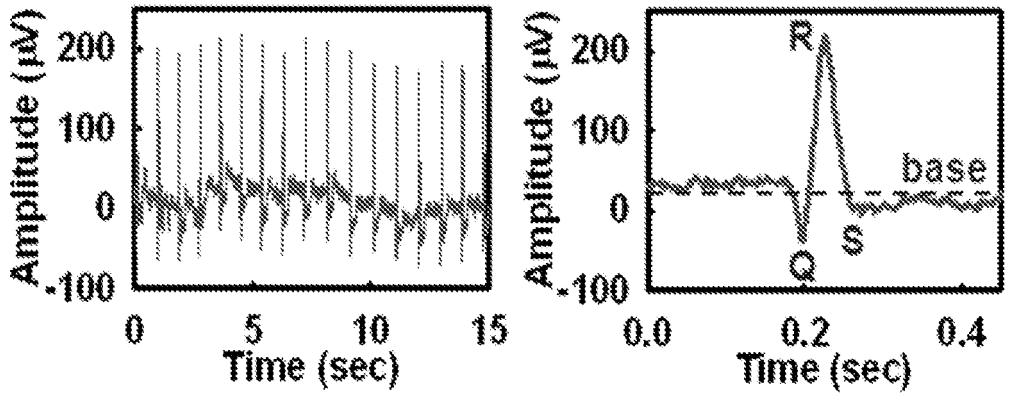


Figure 54b

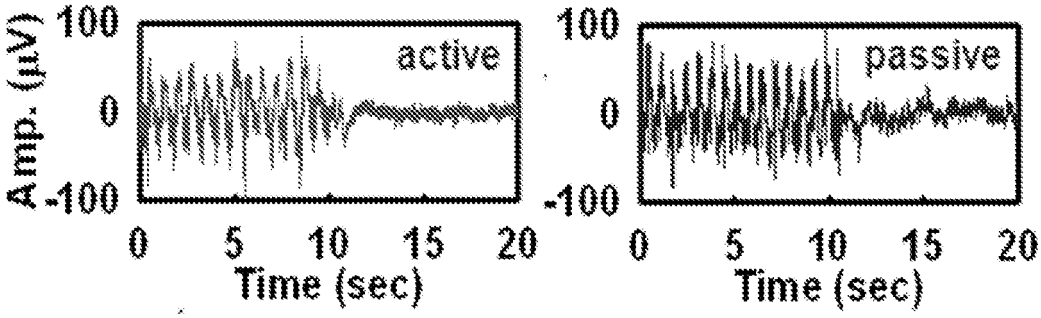


Figure 54c

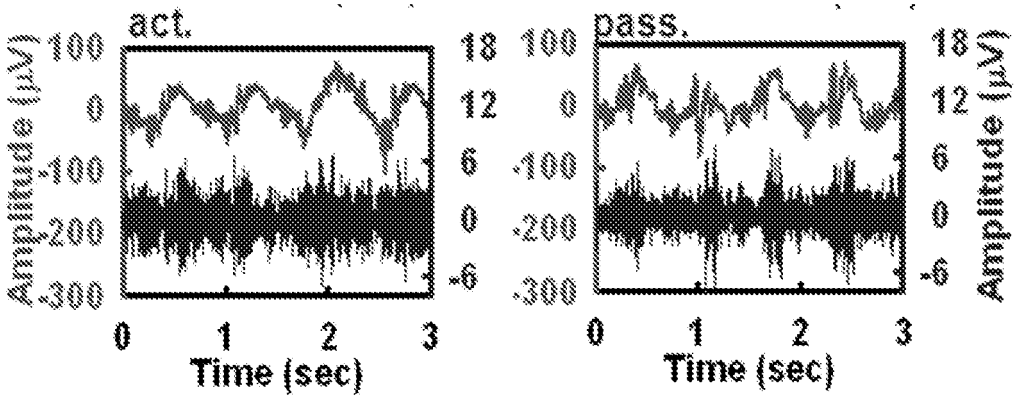


Figure 54d

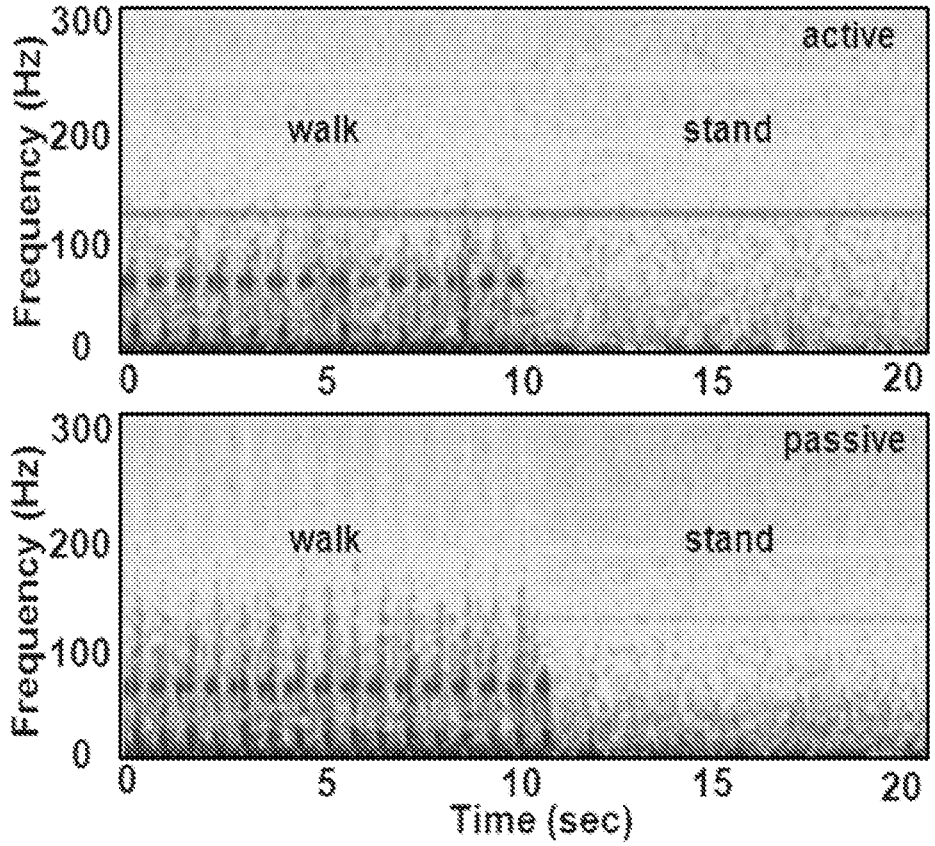


Figure 54e

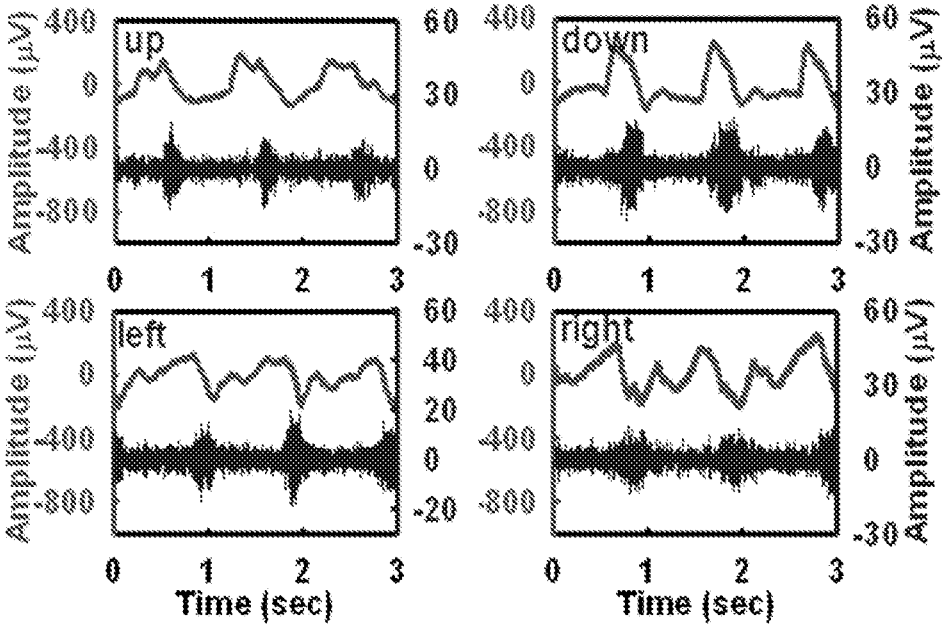


Figure 54f

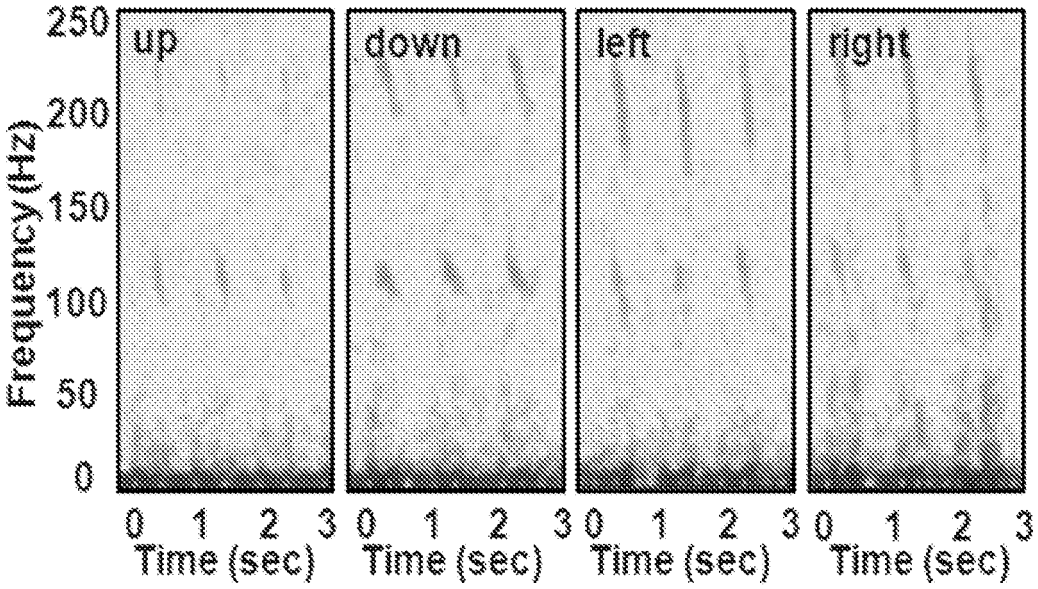


Figure 54g

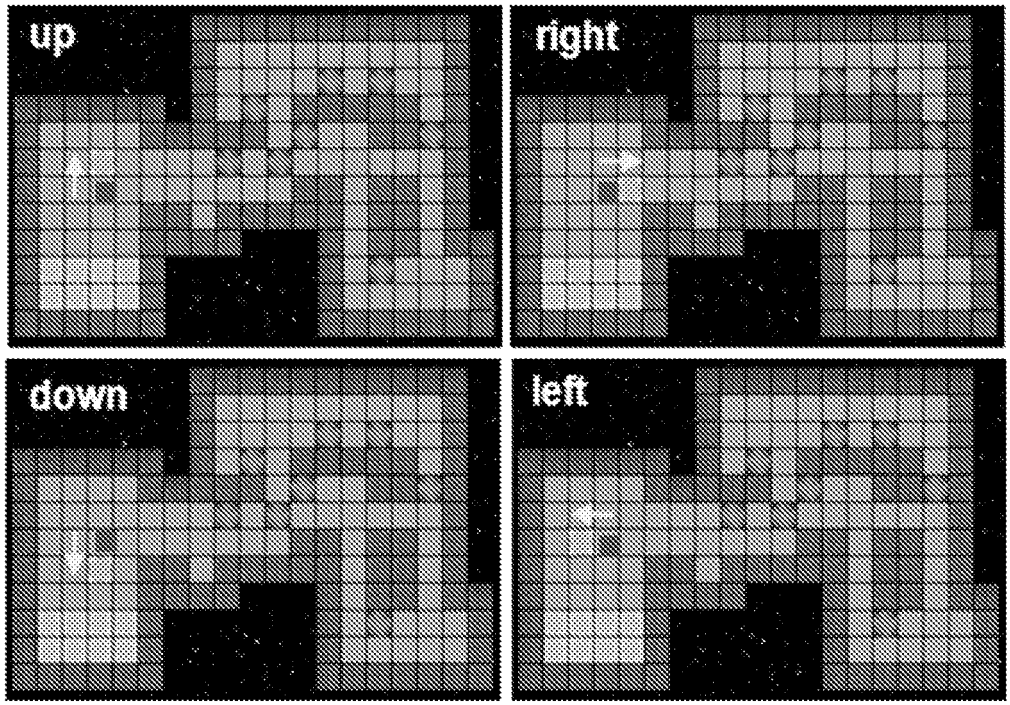
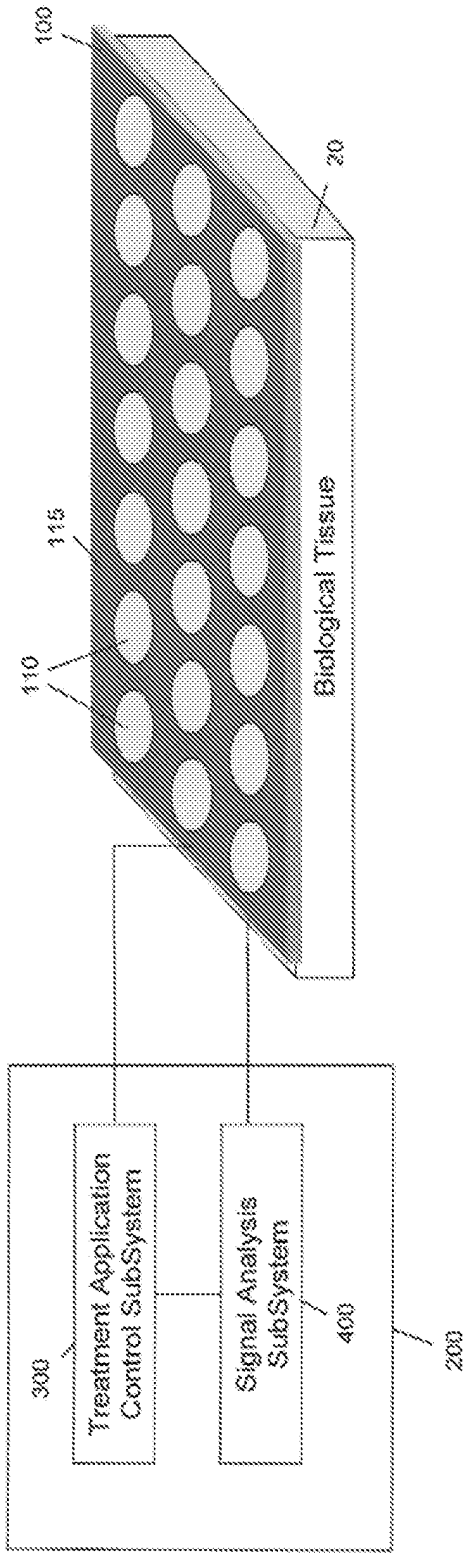


Figure 55



10

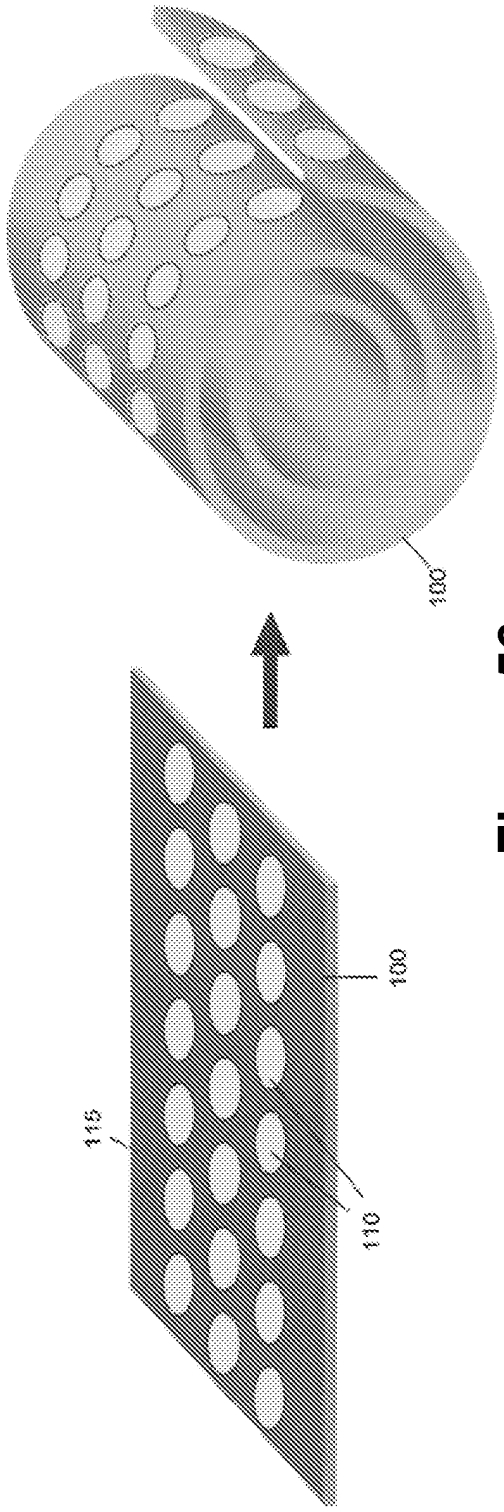


Figure 56

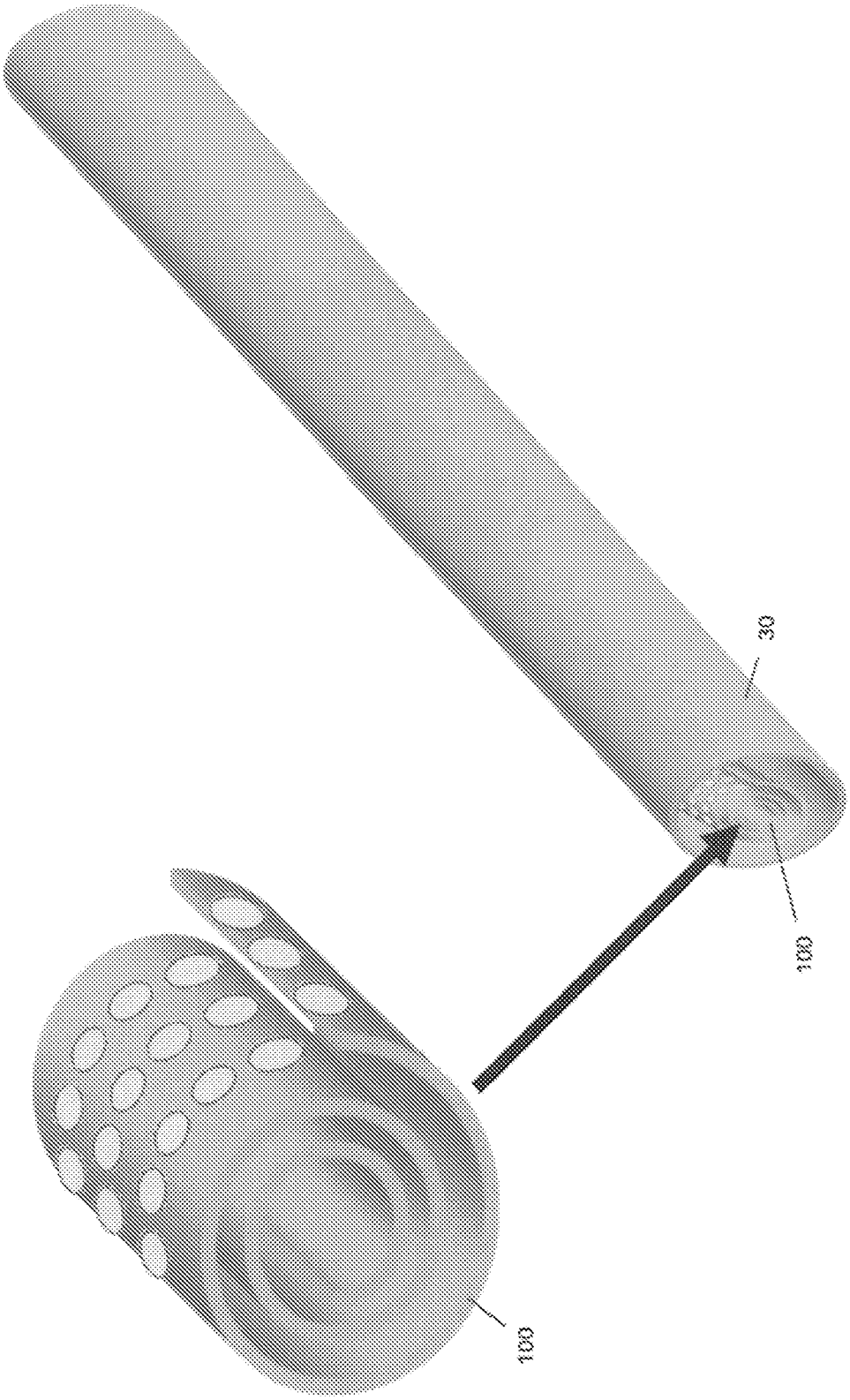


Figure 57

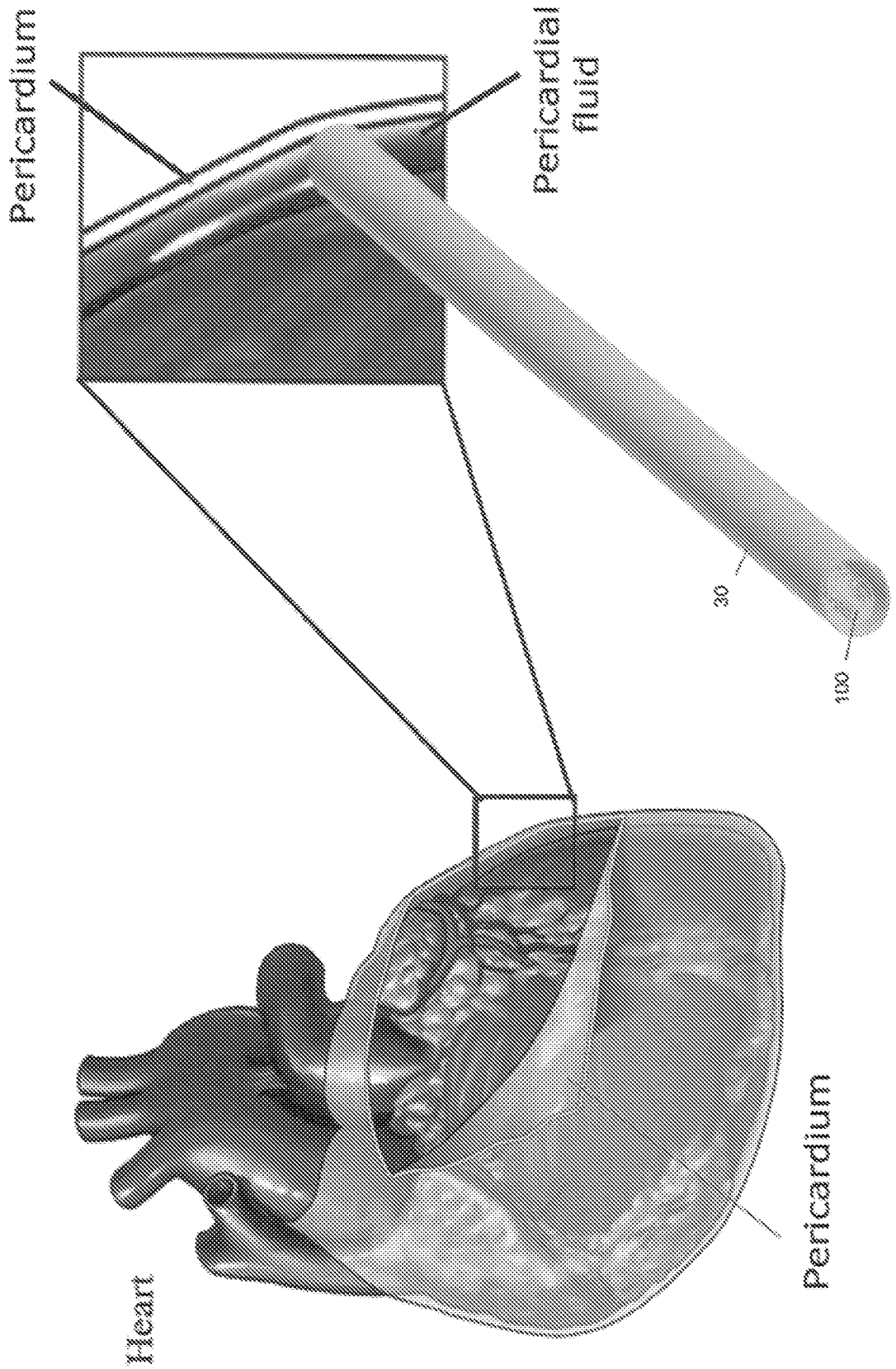


Figure 58

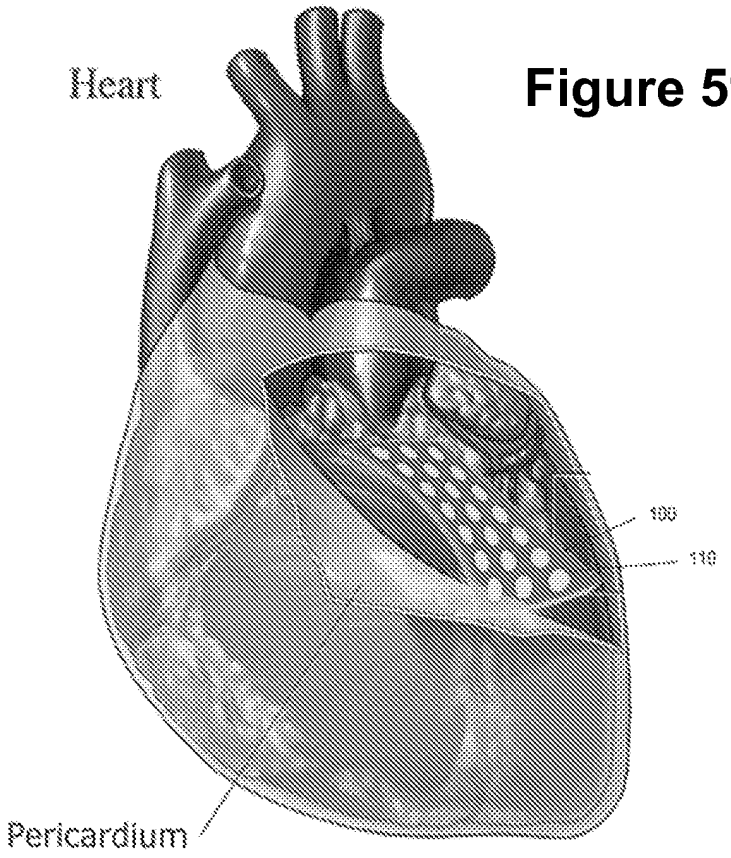


Figure 59

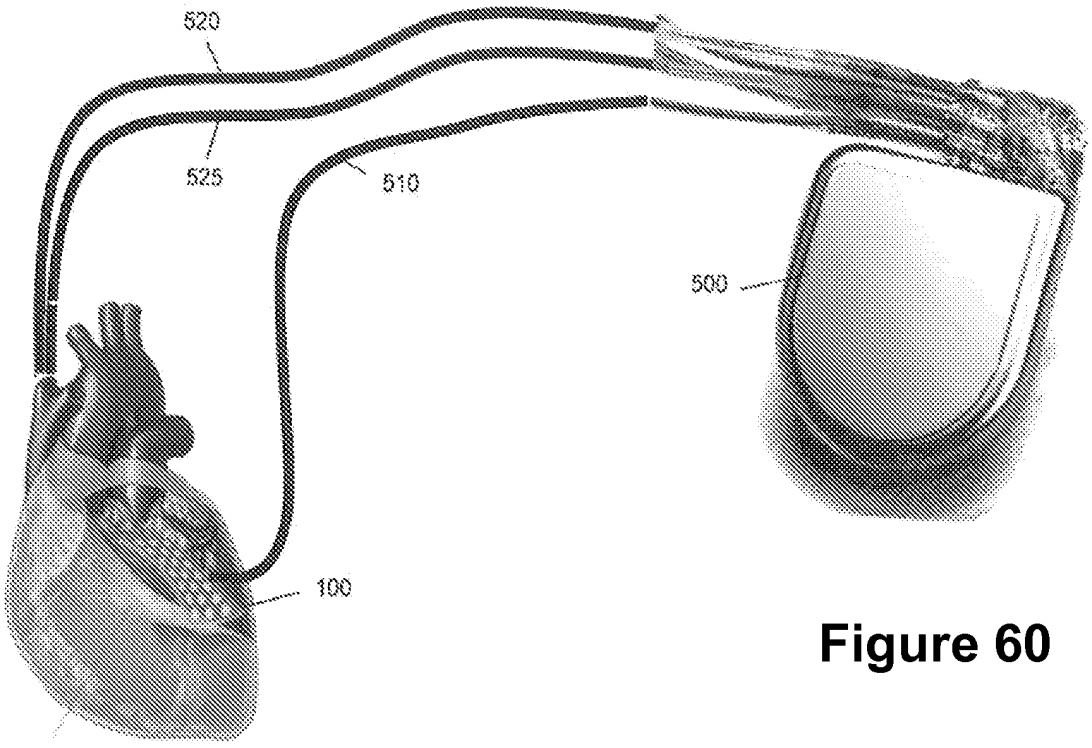


Figure 60

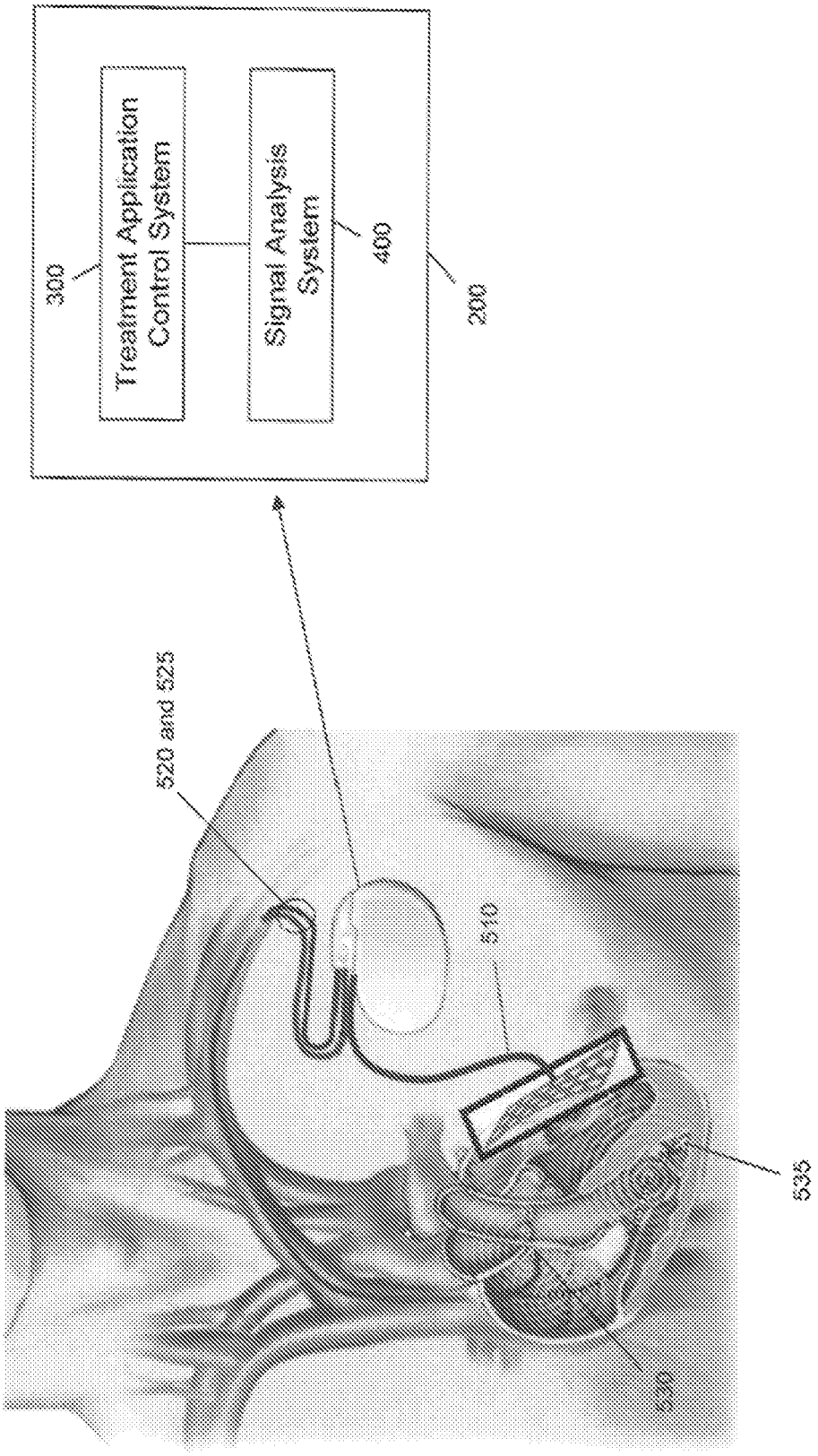

300
Treatment Application Control System
Signal Analysis System
400
200
520 and 525
510
535
530

Figure 61

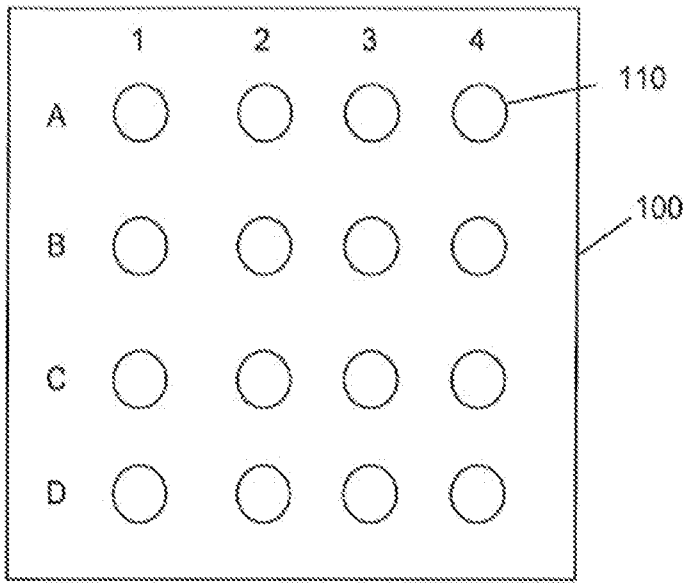


Figure 62

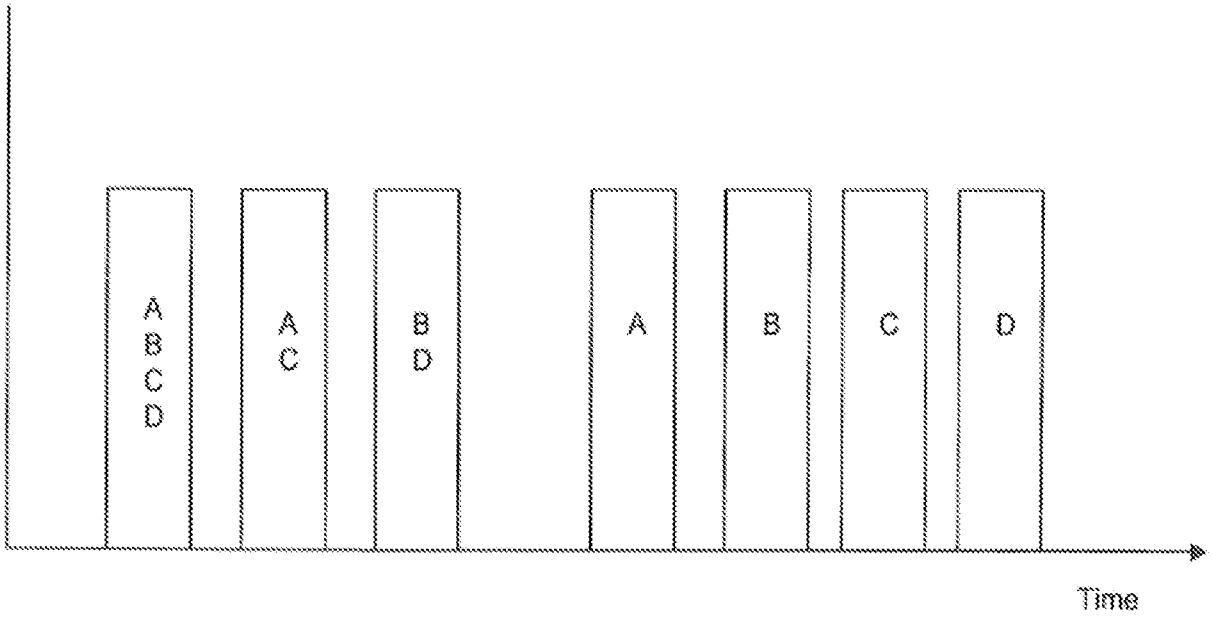


Figure 63

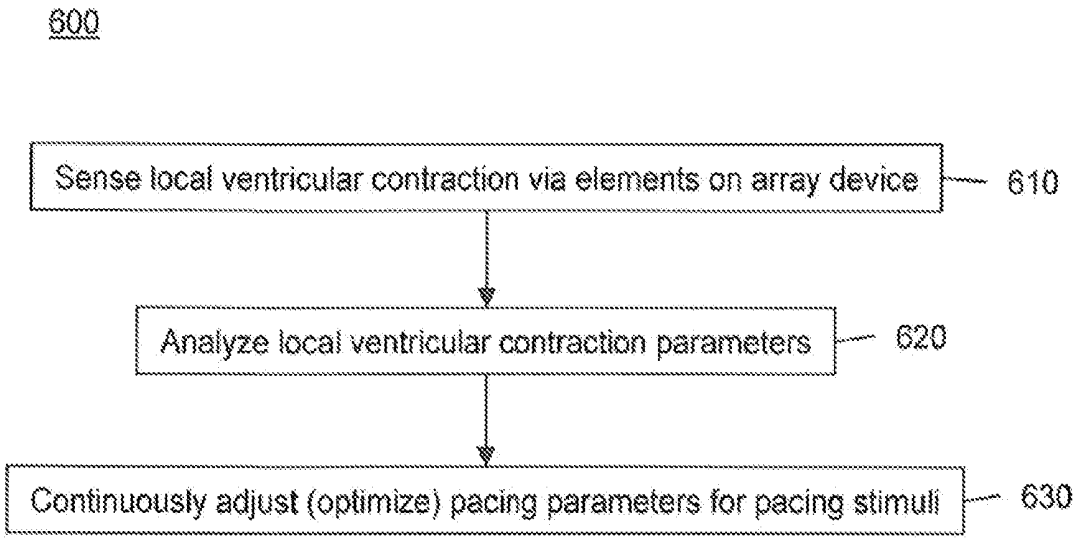


Figure 64

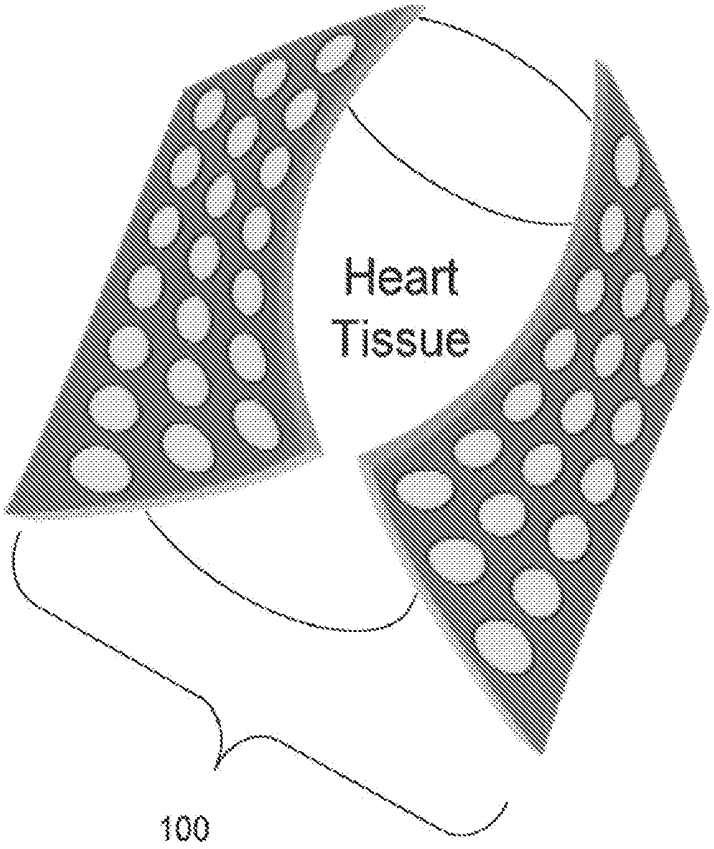


Figure 65

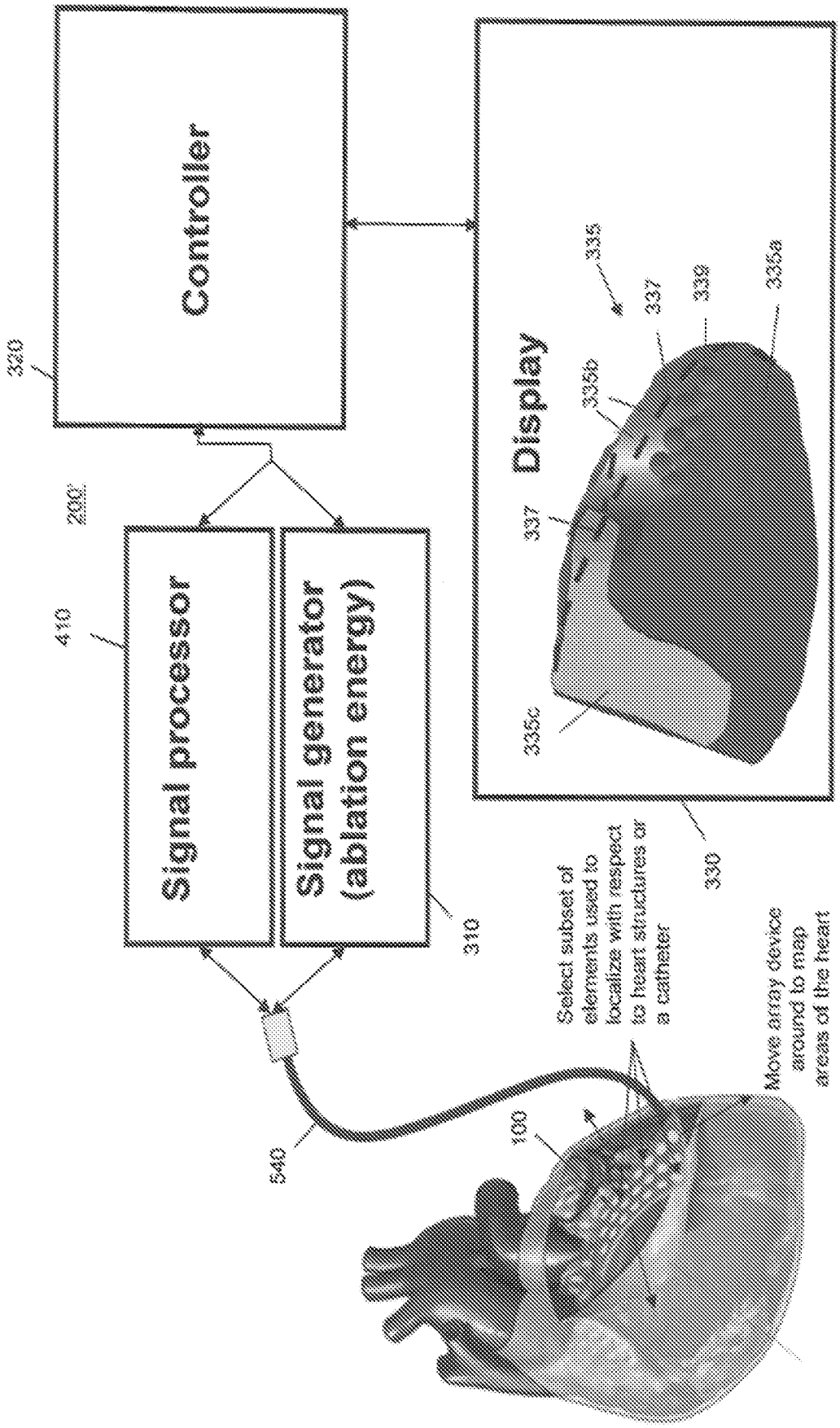

Controller
320
200'
Signal processor
410
Signal generator (ablation energy)
310
Display
337
335c
335b
335
337
339
335a
330
Select subset of elements used to localize with respect to heart structures or a catheter
Move array device around to map areas of the heart
100
540

Figure 66

Figure 67A

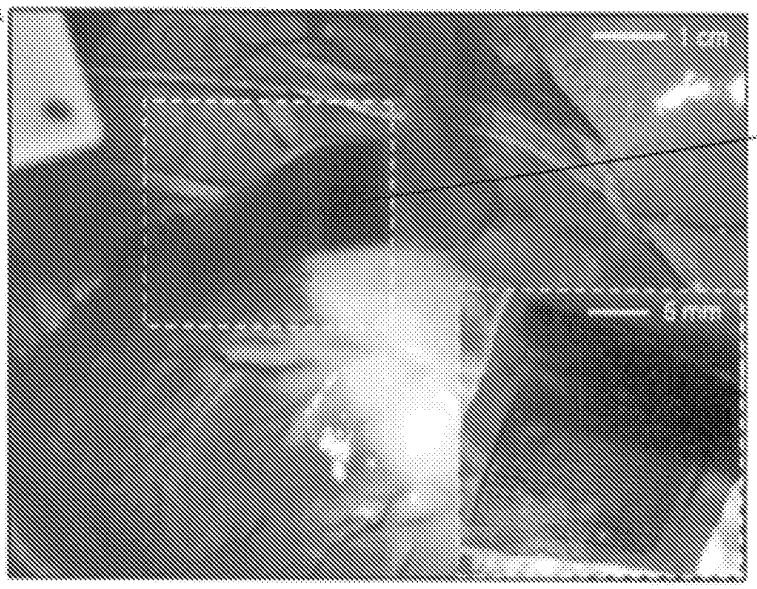


Figure 67B

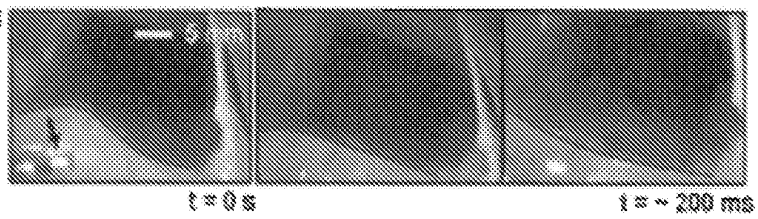
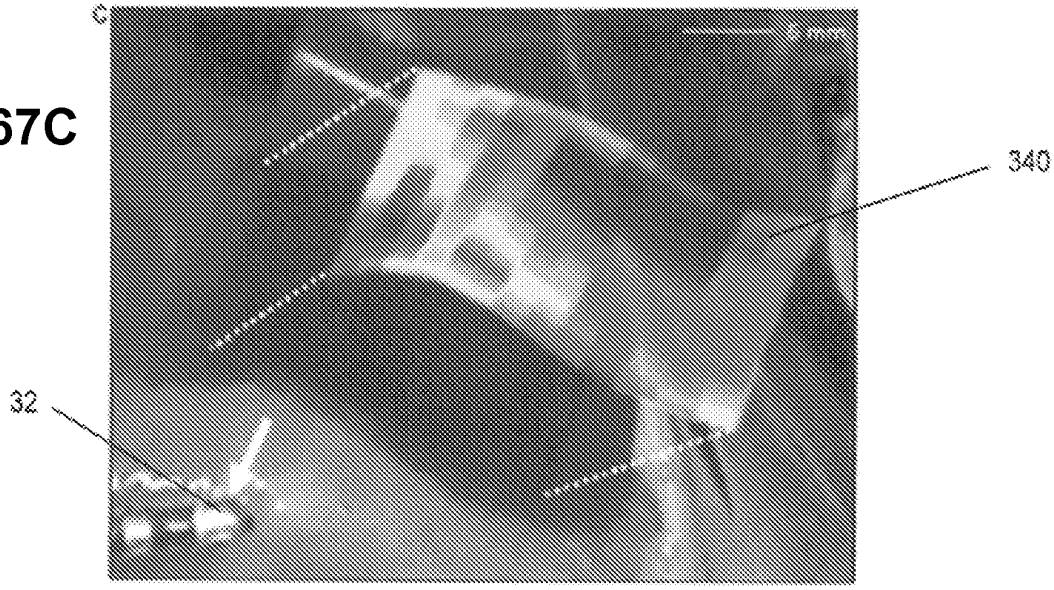


Figure 67C



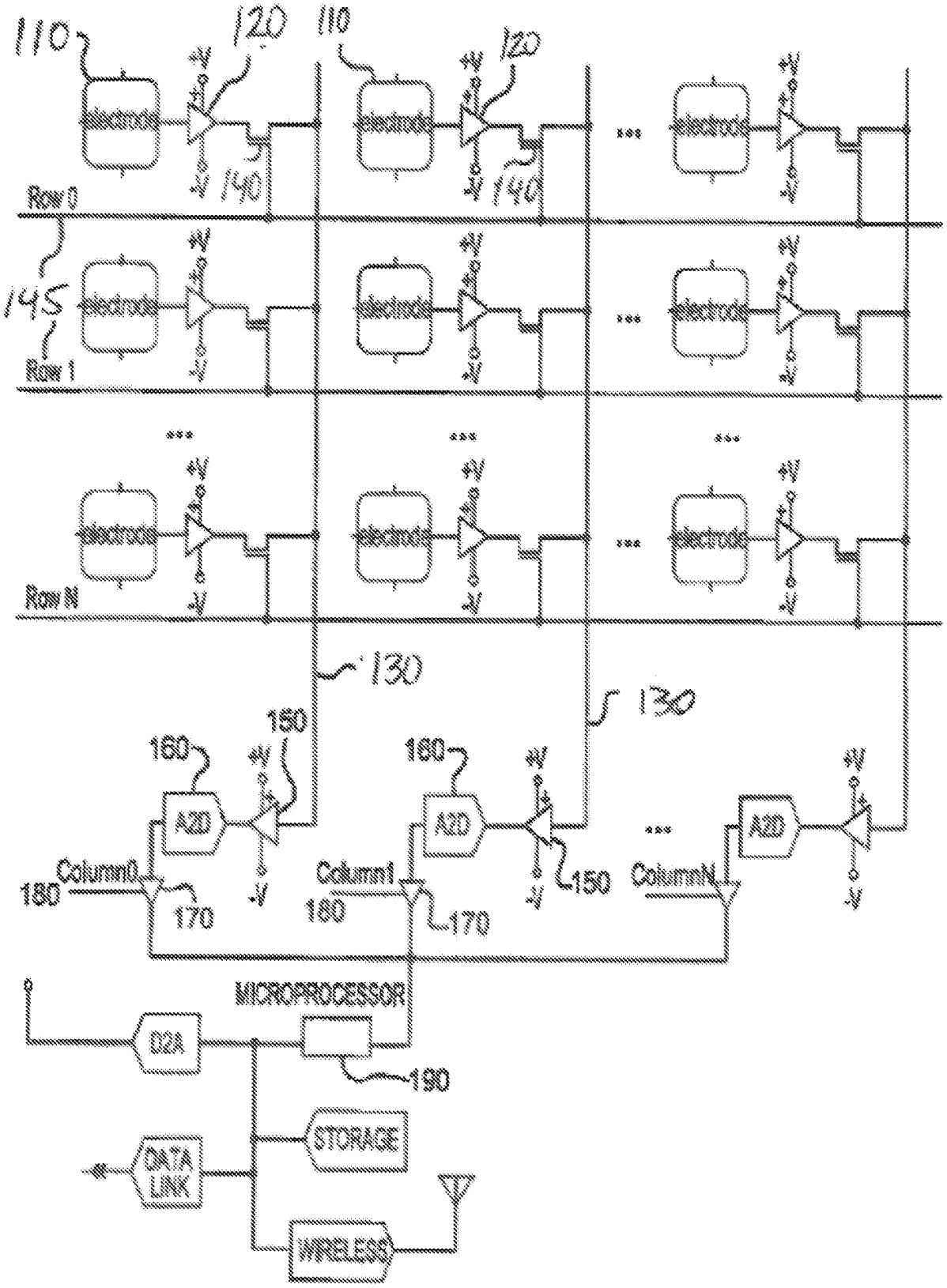

110
120
110
120
Electrode
+V
-V
140
140
Row 0
145
Row 1
Row N
130
130
150
160
160
A2D
150
Column0
Column1
ColumnN
180
170
180
170
MICROPROCESSOR
D2A
190
STORAGE
DATA LINK
WIRELESS

Figure 68

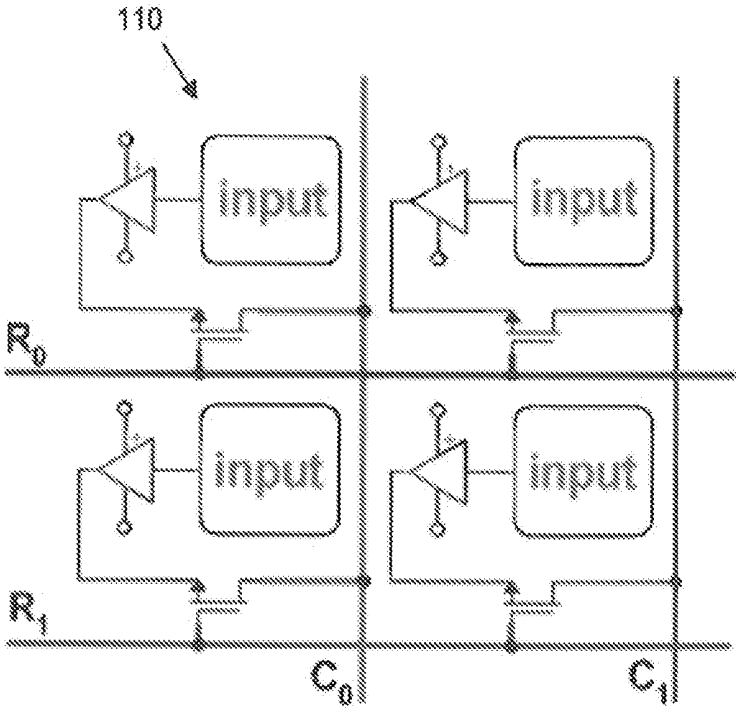


Figure 69

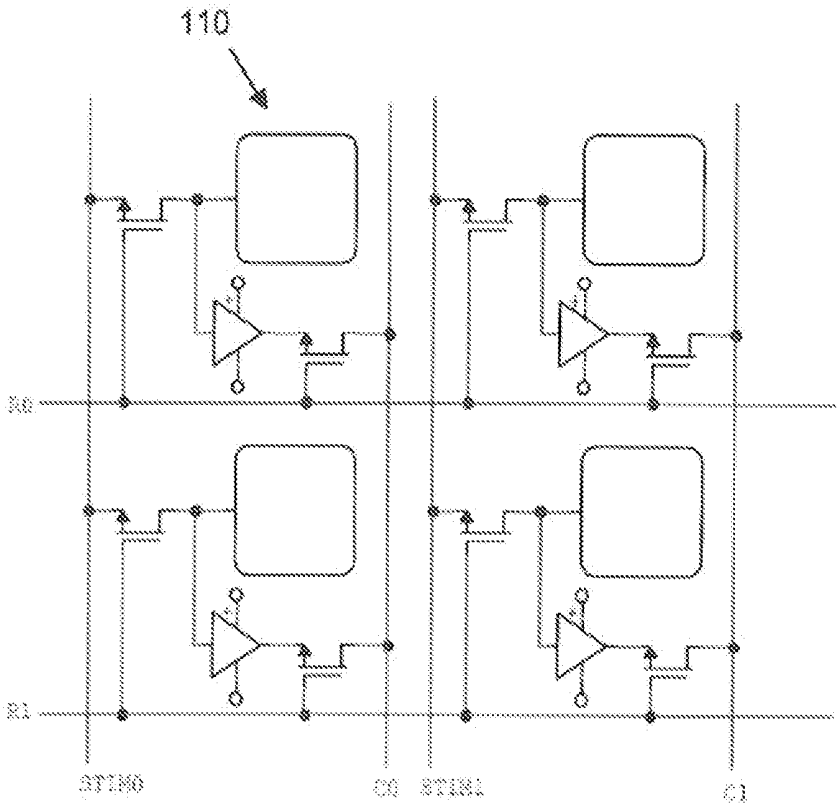


Figure 70

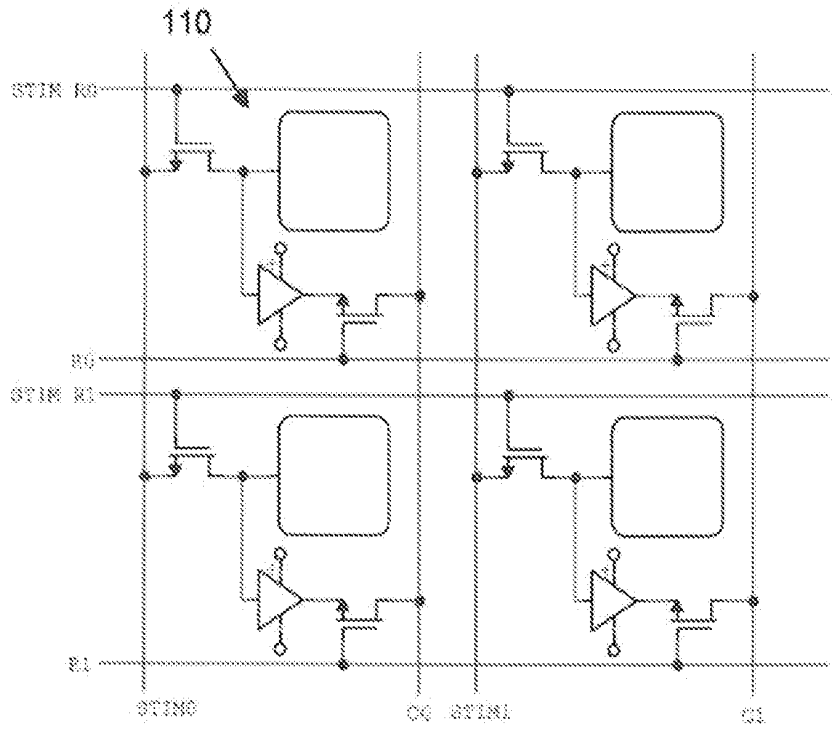


Figure 71

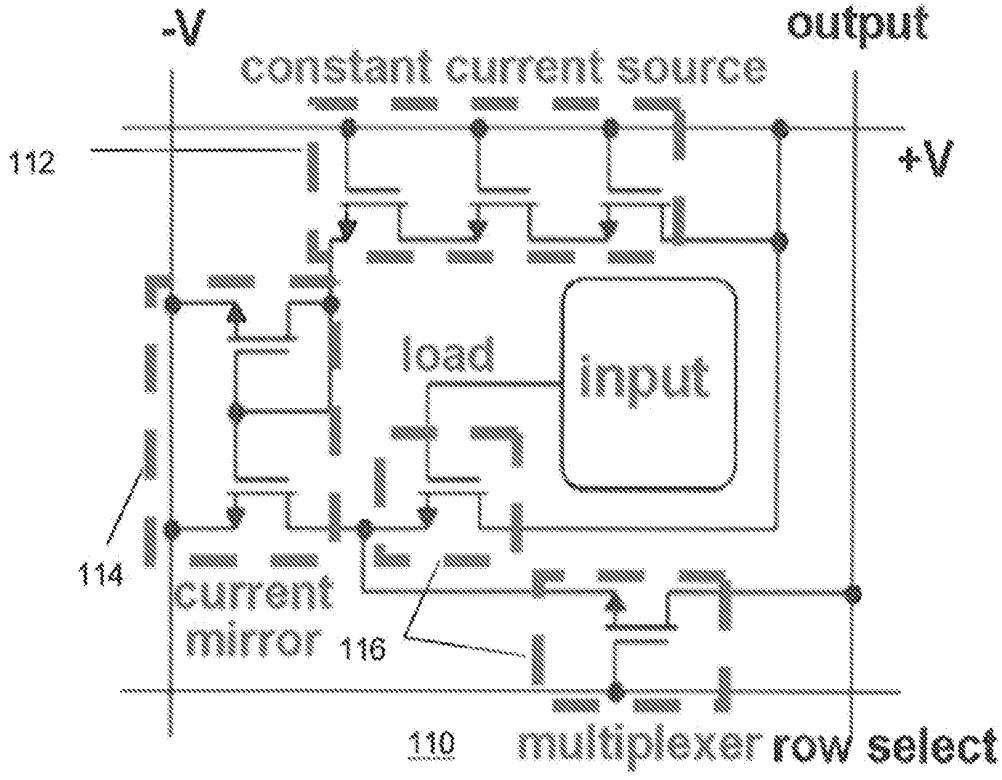


Figure 72

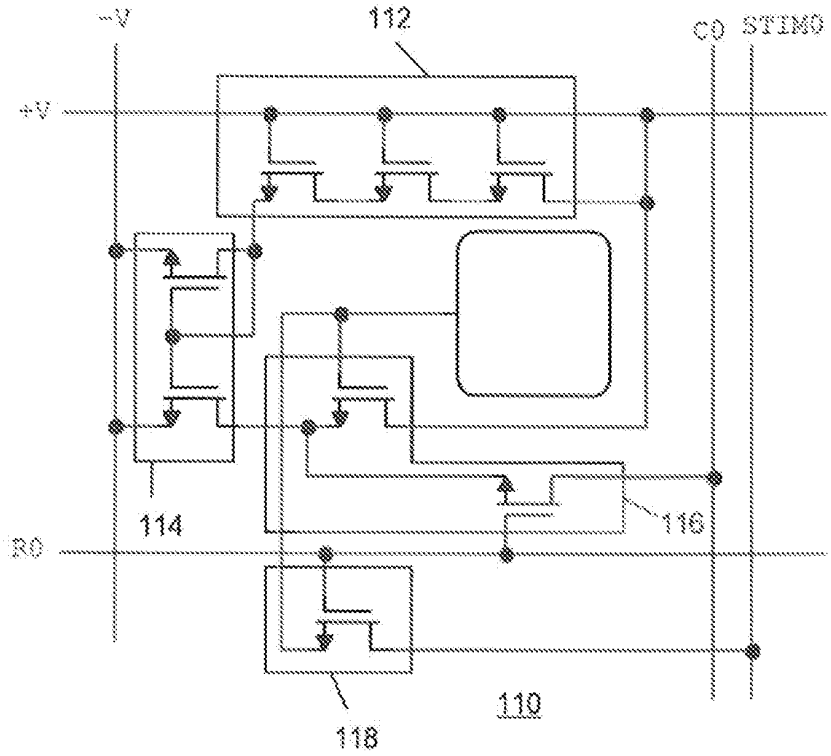


Figure 73

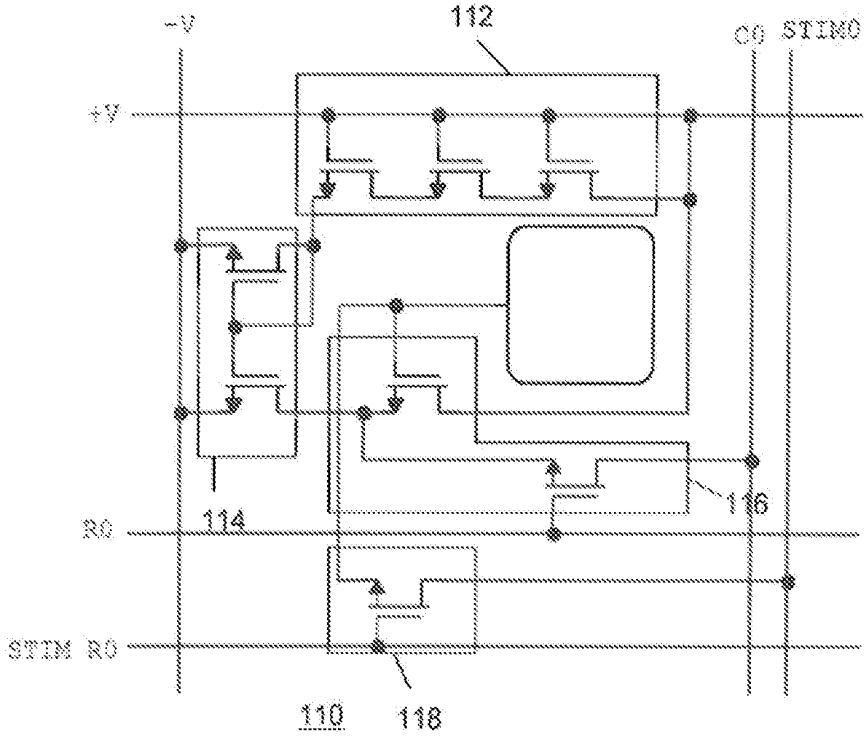


Figure 74

REFERENCES CITED IN THE DESCRIPTION

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摘要(译)

本文提供了生物医学装置以及制造和使用用于感测和致动应用的生物医学装置的方法。例如，提供了柔性和/或可拉伸的生物医学装置，包括可用于建立与生物环境中的组织的原位保形接触的电子装置。本发明包括可植入电子装置和施用于靶组织表面的装置，例如，用于从诸如心脏，脑组织或皮肤的组织获得电生理学数据。