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Flexible biosensors based on field-effect transistors and multi-electrode arrays: a review

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ABSTRACT

As biosensors are widely used in the medical field, flexible devices compatible with live animals have aroused great interest. Especially, significant research has been carried out to develop implantable or skin-attachable devices for real-time bio-signal sensing. From the device point of view, various biosensor types such as field-effect transistors (FETs) and multi-electrode arrays (MEAs) have been reported as diverse sensing strategies. In particular, the flexible FETs and MEAs allow semiconductor engineering to expand its application, which had been impossible with stiff devices and materials. This review summarizes the state-of-the-art research on flexible FET and MEA biosensors focusing on their materials, structures, sensing targets, and methods.

KEY WORDS

Bio-transistor, brain-machine interface, field-effect transistor, flexible biosensor, multi-electrode array, neural probe, semiconductor.

1. INTRODUCTION

Bio-application of semiconductors has emerged as a great interest both in the academic and industry [1]-[7]. In particular, wearable or implantable biosensors are closely related to the miniaturized flexible electronics that can be created with the help of semiconductor design and fabrication processes. In general, flexible biosensors can be used to detect electrical signals such as brainwaves or electromyography (EMG), or chemical signals such as glucose and pH through both inside (in-vivo) or outside (ex-vivo) of live animals. These biosensors and systems can be utilized as diagnostic and/or treatment tools for various diseases, or as a front-end device of a brain-machine interface (BMI), which can control external devices combining robots and artificial intelligence (AI).

For successful biomedical systems, the functionality and performance of the flexible biosensor are the critical points. To this end, biosensors in the form of a field-effect transistor (FET) are attracting attention due to their utilities for the current amplification and circuit integration. Besides, biosensors in the form of a multi-electrode array are also being actively studied because it can measure multiple signals with high spatial resolution.

In this paper, we review a multitude of flexible biosensors based on the field-effect transistor (FET) and multi-electrode arrays. Specifically, the structure of the FET biosensor, flexible substrate materials, active materials, sensing targets, and detection methods will be introduced. Besides, multi-electrode array type biosensors will be discussed focusing on the design, electrode materials, sensing target, etc. This review will be of great help for semiconductor engineers and researchers who want to transform their technologies into bio-applications.

2. FET-TYPE FLEXIBLE BIOSENSORS

Various FET structures, flexible substrates, and active materials have been utilized for specific sensing targets. Some representative FET-type flexible biosensors are summarized in Table 1. Different FET structures such back gate, top gate, dual gate, side gate, and ion-gated FET biosensors have been demonstrated on a variety of flexible substrates such as polyethylene terephthalate (PET), polyimide (PI), and polyethylene naphthalate (PEN).

Table 1. Field-effect transistor type flexible biosensors

Structure	Flexible substrate material	Active material	Sensing target	Detecting method	Channel dimension (W/L)	Notes	Ref
Back gate FET	Polyimide	β-Bi_2O_3 nanofibers	Serotonin detecting	Conductance modulation	200 μm/ 300 μm	Real-time sensing serotonin with linear detecting range of 10 nM - 1 μM	[8]
Back gate FET	PET	graphene	K+ ions	Dirac point shift	2.8 mm/ 1.5 mm	Detected target ions over the range of 1 μM – 20 mM	[9]
Bottom gate TFT	PEN	IGZO	pH	Threshold voltage drift	200 μm/ 9 μm	Extended gate sensor was connected to the gate terminal of TFT	[10]
Multilayer structure	PET	SWCNTs	pH/Glucose	Conductance modulation	10 μm/ 1 mm	Glucose was detected by the local pH change.	[6]
Top gate FET	Polyimide	ZnO	Sweat	Electrochemical impedance spectroscopy	-	The linear detection range was from 10ng/mL to 200ng/mL while the limit of detection was 1ng/mL	[19]
Dual-gate FET	PEN	FS0027	Immunoglobulin G	Conductance modulation	40 mm/ 40 μm	Label-Free Protein Detection	[11]
Bottom gate FET	Polyimide	Graphene	Virus	Voltage gain from source to drain change	-	Showed linear response in the 0.1 μg/ml – 100 μg/ml range with the limit of detection around 0.1 μg/ml	[20]
Ion-gated FET	PEN	Graphene	VEGF	Conductance modulation	100 μm/ 5 μm	10 fM – 10 nM of VEGF was detectable	[21]
Side gate FET	PET	In_2O_3	Glucose	Conductance modulation	500 μm/ 25 μm	Detected 1 μM -1 mM of glucose with a detection limit of about 10 nM	[22]
Side gate FET	Polyimide	CNT	Organophosphorus pesticides	Conductance modulation	50 μm/ 55 nm	The enzyme was immobilized to detect a target in the range of 1 pM-1 mM	[23]
Bottom gate FET	PEN	DNTT	Biosignal	Signal amplification	6000 μm/ 20 μm	Gel composite used as the electrode to the heart for detection	[24]

Figure 1 shows a structure of FET-type flexible biosensors based on PET substrate. As a sensing mechanism, for instance, a shift of the I-V curve in accordance with the pH value of the solution on the gate can be utilized as a pH sensor. Even the neuromorphic transistor with multiple gates can be integrated for the feasibility of a neuromorphic device with high performance and enhanced functionality.

A. ION-SENSITIVE FET (ISFET) BIOSENSORS

ISFET is a widely used FET-type biosensor used for measuring ion concentrations in solution. In the ISFET, the solution is used as the gate electrode and other device parts follow the conventional FET devices. When the ion concentration (such as H+) changes, the current through the FET will change accordingly. The ISFET biosensors have advantages such as good scalability, ultra-sensitivity, rapid real-time detection, inherent amplification, lower power requirements, and direct electrical readout in comparison to microcantilever sensors, fluorescence devices, and other types of biosensors. In particular, compared to more complex measurements such as cyclic voltammetry, the simple direct electrical readout is possible and has the advantage of being compatible with the CMOS process [1]-[7].

Badhulika et al. (2020) demonstrated a flexible polyimide (PI) substrate-based ISFET biosensor on Al functionalized β-Bi_2O_3 nanofibers for highly selective

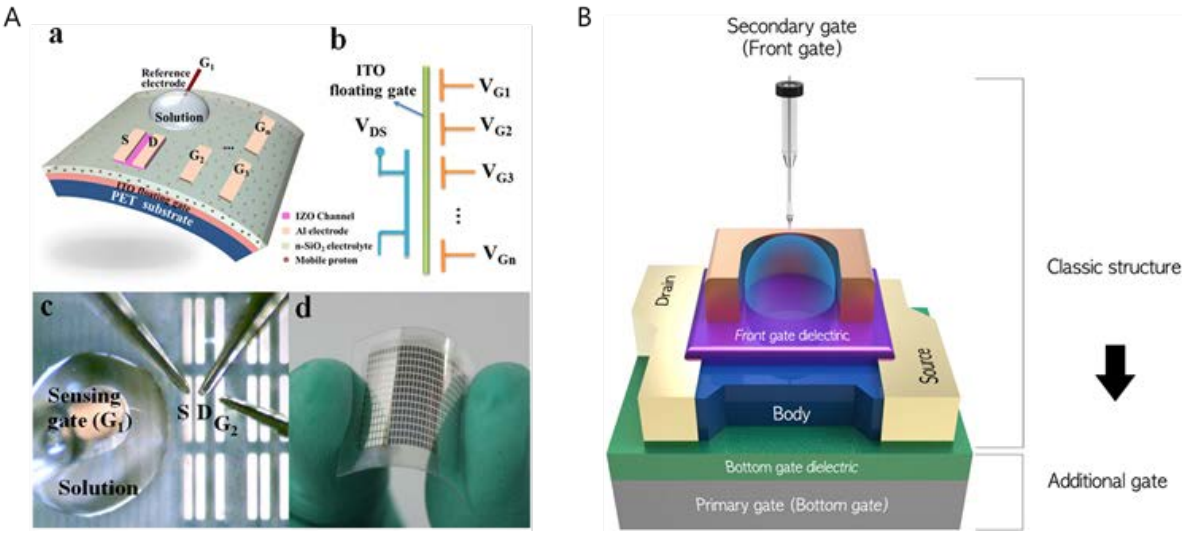

Figure 1 Neuromorphic FET-based flexible biosensor on PET substrate and its flexibility exhibition. (A) Schematic of the flexible pH sensor based on a neuromorphic transistor with multiple gate electrodes. [18] An Ag/AgCl reference electrode immersed in the solution droplet acts as the sensing gate. In-plane Al electrodes are used as the control gates. The schematic image of the capacitive network of the flexible neuromorphic transistor and an optical microscope image of the system. (B) A cross-sectional schematic image of the double gate (DG) ion-sensitive FET (ISFET). [15]

and rapid detection of serotonin. The sensor of Badhulika has a sensitivity of 51.64 μA/nM in the wide linear range of 10 nM to 1 μM of serotonin with a low limit of detection (LOD) of 0.29 nM [8].

Li et al. (2017) demonstrated flexible PET-based graphene ion-sensitive field-effect transistors (GISFETs) for K+ ion detection in various media over a wide ionic concentration range of 1 μM–20 mM. The sensor has a sensitivity of 61 ± 4.6 mV/decade over two months [9].

Shah et al. reported indium gallium zinc oxide (IGZO)-ISFET, using indium tin oxide (ITO) as a sensing layer and gold as a reference electrode, on a flexible PEN substrate. The IGZO-ISFET shows a methodology by which biosensors could be directly integrated into a flexible electronics process. Also, they engineer a complete system with the integrated sensor, flexible electronics, and CMOS readout chip [10].

Merkoci et al. (2014) demonstrated a flexible PEN-based organic thin-film transistor (OTFT) fabricated mainly by inkjet printing and subsequently functionalized with antibodies for protein recognition [11]. The sensor is capable of detecting 100 ng mL^{-1}(1.5 nM) with a relative standard deviation of 9% for bovine serum albumin detection. They reported an important starting point for the design and fabrication of flexible, organic biosensing devices by inkjet printing.

Amer and Zhou (2018) demonstrated the In_2O_3 FET-based wearable biosensors with on-chip gold side gate electrodes can be used for highly sensitive detection of glucose over a range of 1 μM–1 mM of glucose with a detection limit of about 10 nM [12]. The non-invasive glucose detection in human body fluids, such as tears and sweat, was also demonstrated. The capture method includes antigen-antibody, ion detection using a membrane, DNA-DNA detection, and enzyme reaction. Various target analytes are captured in the channel area according to the method of functionalization [13].

ISFET has the disadvantage of being vulnerable to temperature variation. Takei et al. (2017) demonstrate a flexible sweat pH sensor using an IGZO-based ISFET, integrated with a printed flexible temperature sensor for compensating for the ISFET temperature effect [14].

B. RESEARCH DIRECTIONS OF FET-TYPE BIOSENSORS

Although FET-type flexible biosensor has been actively studied, more research on device structure, materials, and sensing targets are required for wider utility. We introduce a few research directions about technology computer-aided design (TCAD) simulation, inorganic and organic sensor materials, and sensing targets including brain signals.

Body thickness effect on the double gate ISFET was studied for the optimization of biosensors [15]. Although the overall test was carried out by TCAD simulation, this research proposed a meaningful conclusion. Evaluation of the electrical characteristics of the ISFET with various body thickness proved that ultra-thin body (UTB) FET performed better gate controllability and restraint to the uncontrolled phenomenon. The sensing ability of ISFET was found to be surpassed by UTB compared to a thicker body.

A water-gated organic field-effect transistor sensor for detecting weak reaction was reported [16]. The sensor was fabricated on a flexible substrate with a gold

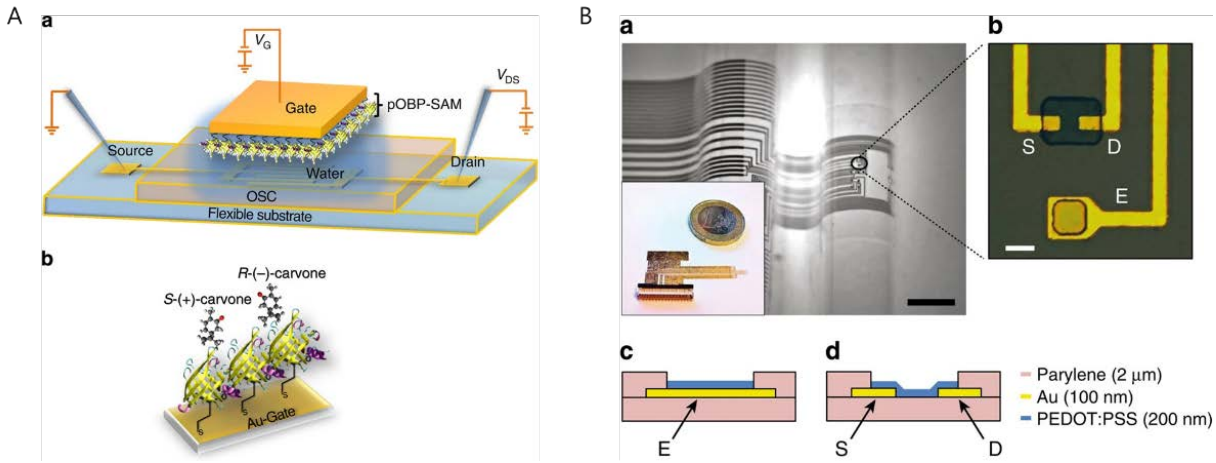

Figure 2. (A) Water-gated bio-organic FET with the source (S) and drain (D) interdigitated structure on a flexible foil. The S–D patterned substrate is covered by the p-type semiconductor, and a bio-functionalized Au-plate hangs in contact with the water droplet, acting as a gate (G). [16] (B) Organic FET-type electrocorticography (ECoG) probe for brainwave detection. Optical micrograph of the flexible biosensor in which the transistor/electrode arrays are integrated. The channel of a transistor and a surface electrode, in which the Au films that act as source (S), drain (D), and electrode pad (E) are identified. A cross-sectional view of the electrode and transistor channel is shown. [17]

source, drain, and gate. PBTTT-C14, a p-type organic semiconductor (OSC) was deposited on the interdigitated source and drain as shown in Figure 2A. A droplet of water was dropped on OSC contacting electrically to the gate. Gate surface exposed to the water was modified with a protein self-assembled monolayer. The response of immobilized protein on the gate surface and target molecule was measured and the result noted high sensitivity despite the low molecule concentration of 100pM. Capacitance modulation of the protein layer by molecule-protein binding enabled detecting weak interaction between protein and target. This work showed sensitive biosensors fabricated with organic material at a low cost.

Generally, brain signal recording has been carried out on the electrode. However, in vivo recording using the organic electrochemical transistor (OECT) was demonstrated [17]. The overall structure is described in Figure 2B. Parylene film was used as a flexible substrate of the transistor, then, Au drain and source were deposited onto the substrate. poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) was coated on the channel area as the active material. To evaluate the capability of epilepsy diagnosis and cortical mapping of the device, OECT was implanted in a rat model of epilepsy along with electrodes for comparison. In-vivo test, OECT performed a higher signal to noise ratio (SNR) than electrodes. Recording time to acquire the same information could be shortened with higher SNR. This work proposes a potential breakthrough for recording small and local brain signals with OECT.

3. MEA-TYPE FLEXIBLE BIOSENSORS

The biosensor using multi-electrode array (MEA) has been widely used for electrical signal sensings, such as brain waves and electromyogram, by taking advantage of the characteristics of the electrodes reading the electrical potential when they contact with the living body. Chemical sensing through a functionalized electrode (e.g. glucose (blood sugar) sensor) has been successful as well. Here, we introduce some representative MEA-type flexible biosensors focusing on electrical signal sensing (e.g. brainwave).

A. SENSING TARGETS AND MATERIALS

MEA-type neural electrodes are used to record signals from nerve cells, or to stimulate them electrically. Specifically, the high-density MEAs for brainwave detection can be integrated using semiconductor processes to record large amounts of signals, enabling the mapping of brain activity [25]. The MEA also can be utilized as a chemical sensor by attaching enzymes or other bio-functional materials to the MEAs [26]. Some representative MEA-type flexible biosensors are summarized in Table 2.

The flexibility of multi-electrodes facilitates contact with the brain surface to observe high-quality signals. Conventional metal MEAs can also be developed as flexible electrodes using flexible substrates but using novel conductors such as carbon nanotube (CNT) makes it easier to maintain flexibility [27]. Recently, graphene electrode arrays with special features including transparency have been utilized to develop flexible and transparent biosensors, which can further enhance their application [28]. The detailed device structure and fabrication methods are described in Figure 3. Although the device is used for bio-application, the semiconductor technologies used in the work indicates that the flexible biosensors are closely related to semiconductor engineering.

The nerve cells also exist in the retina of the eye, thus MEAs can be used to observe the activity of nerve cells in the retina [29]. Because the retina has a

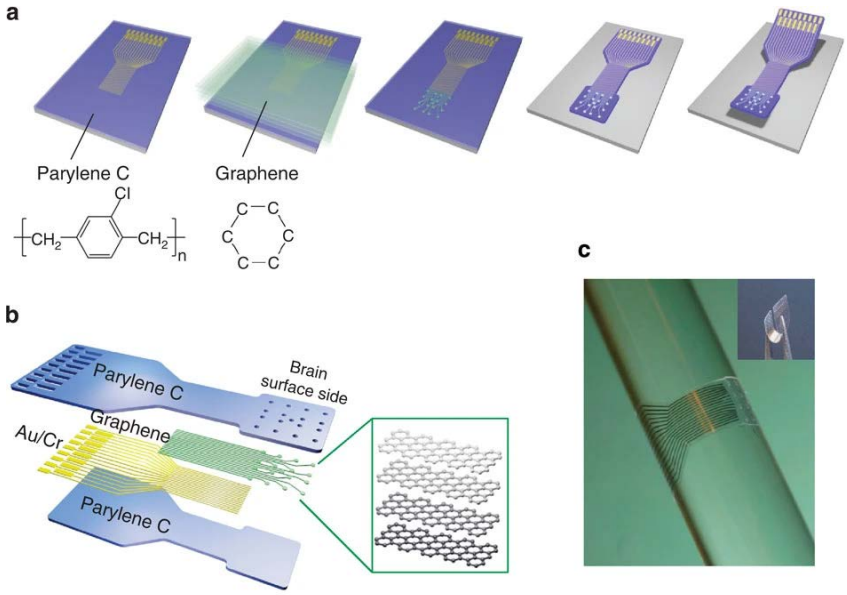

Figure 3. Flexible multi-electrode arrays based on graphene and Parylene C substrate for brain signal recording (a) Basic fabrication process: metal patterning of traces and connection pads on Parylene C/silicon wafer. The silicon wafer can be used as a handling substrate. Graphene transfer and patterning to form electrode sites. Second Parylene C deposition and patterning to form device outline. Removal of the device from the silicon wafer. (b) Diagram of graphene electrode arrays and (c) demonstration of device flexibility. [28]

distribution of nerve cells that function differently depending on the area, MEAs makes it easier to record area-specific signals, which can be applied appropriately to give electrically necessary stimulation. The flexible MEAs is also easy to observe the activity of frequently moving neurons, such as the spinal nervous system [30].

Recording neural signals from muscles (i.e. electromyogram, EMG) is another interesting area. The signals from muscles can be observed on the skin surface through temporary electrical signals generated by the combined electrical activity of individual cells in the muscular tissue [31]. These myocardial signals also allow local observation of the distribution of electrical signals at the measurement location. If observed through MEA, meaningful results such as signal differences at different locations can be identified [32].

MEAs can integrate with other sensors and become more multifunctional biosensors. One biosensor may contain not only electrical signal recording via MEA, but also another measuring device such as heat

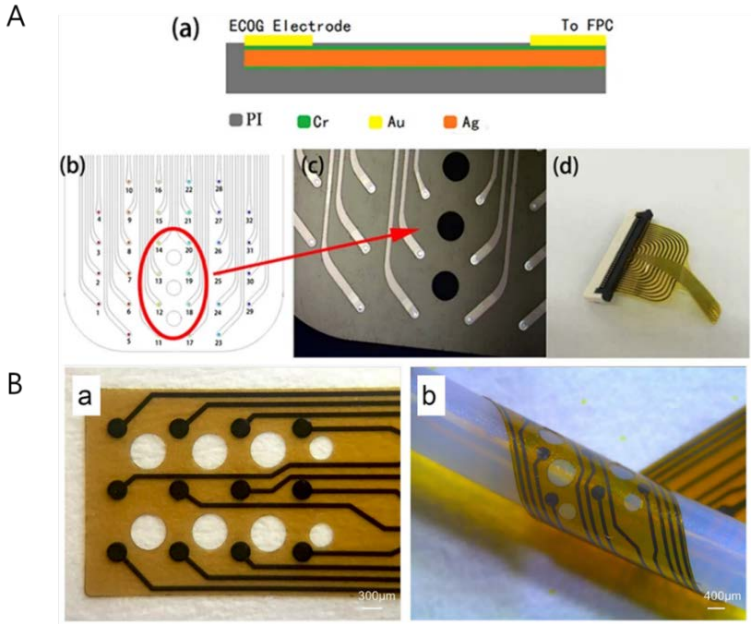

Figure 4. (A) Flexible microelectrodes array for brain signal sensing. A cross-sectional view of a microelectrode and images of ECoG type electrode device with 32 microelectrodes are shown. Drug delivery through the flexible multi-electrode array is also an important research area. (The three large holes in the image are for drug injection.) [34] (B) Representative images of glassy carbon (GC) and platinum (Pt) thin-film electrode arrays. GC 12 electrode array images and the flexibility of the device are shown.[35]

detection, or a device for treatment such as drug delivery (Figure 4). Even, there is an example of an optogenetic sensor that analyzes brain activity by stimulating the brain with light [33]. Through the highly integrated biosensors with the aid of semiconductor engineering, the MEAs can be one of the most powerful tools for bio-signal sensing.

Table 2. Multi-electrode array type flexible biosensors

Design	Flexible substrate material	Electrode material	Purpose	Size (μm)	Notes	Ref
2D 16-channel electrode array	Parylene-C	Graphene	μECoG	500×500×25 (Channel)	Transparency enabled applying optogenetics	[36]
Microwire	Fluorosilicone	PEDOT-PEG and PDMS	DBS	125 (diameter)	Inflammatory tissue response is mitigated by implant softness and flexibility	[41]
2D 9-channel electrode array	Off-stoichiometry thiol-ene-epoxy	Au	Neural recording		The electrode is rigid at room temperature.	[42]
Multi-shank Michigan probe	Silicone	Iridium	Neural recording, Neural circuit modulation and drug infusion	128×7000×40	Multifunctional neural probe integrated with microfluidic channels optical waveguides for optical stimulation and microelectrode arrays for recording	[43]
2D multi-channel electrode array	PDMS	Multi-walled CNT	Recording and stimulation with retinas	100 (diameter)	A new fabrication technique to realize non-Faradaic CNT based electrodes was used	[27]
3D sheath multi-channel electrode	Parylene-C	Pt	Neural recordings and integration	45 (diameter)	Opening between the substrate and 3d electrode array for ingrowth of neurons	[44]
Michigan probe	Parylene-C	Boron-doped polycrystalline diamond (BDD)	ECoG	8100×6700 (Device)	BDD patterns from the silicon substrate were transferred onto the flexible Parylene substrate	[45]
Tube shaped electrode	Polyimide	Au	Motor cortex recording and optical stimulation	360 (diameter)	Optical fiber was integrated into the electrode for optical stimulation.	[46]
3D Microneedle electrode array	Parylene	Au	Neural recording	-	Electrode was formed on mesh structure to increase the flexibility.	[47]
Nanowire-coated fiber probes	PDMS	AgNW	Stimulation and recording in the spinal cord.	105-135 (diameter)	AgNW was coated on the fiber as the electrode material	[48]
32-channel electrode array	Parylene	Au	ECoG	50×50	Simultaneous recordings of ECoG and intracortical spike/LFP within the same region was developed.	[49]
Michigan probe	SU-8	Au	Neural recording	Sub 1um-thickness	Electron-beam lithography was applied to reduce the physical dimensions of the electrode	[50]
64-channel electrode array	SU-8	Porous graphene	Recording and stimulation on motor cortex	-	Evoked knee flexion through neural stimulation.	[51]
9 Channel electrode arrays	Polyimide	Polyimide, PEDOT and ZnO	ECoG	800 × 800	Combined ZnO nanowire electrode with Au/Graphene hybrid structure	[52]
Mesh Serpentine structure	Shape memory polymer	Au	Vagus nerve		Shape memory polymer helped electrode to Maintain contact on the target nerve in the body temperature	[39]
Multi-electrode array	Parylene-C	Pt/Ir	ECoG	700 μm (diameter)	Altered Insulation layer to the active site by laser pyrolysis.	[53]

B. ELECTROCORTICOGRAPHY (ECOG) TYPE BIOSENSOR

Electrocorticography (ECoG) is a methodology developing brain-machine interface directly on the cerebral cortex. Availability of recording signal or stimulating the cortex has been demonstrated for a wide application. ECoG electrode also has been developed in several areas and especially, flexibility

has been one of the main elements of the device for better contact on the cortex. Also, as biocompatibility, chemical stability, and good dielectric property are required for the insulation layer of the neural electrode, polymers such as Parylene or PDMS have been introduced in the electrode fabrication continuously.

Wireless ECoG electrode-external device system with a high spatial resolution was reported [34]. Implanted microelectrode detected brain signal then, integrated circuit processed signal and interacted with the cellphone. Cellphones provided information through the app on the display. A subject could be identified whether suffering from epilepsy by a pre-trained detecting model. Based on recording, precise epilepsy lesions could be located. Also, it has demonstrated ECoG device could electrically stimulate the lesions, which showed a potential method to treat the disorders. This study exhibits the application of wireless communication between the electrode and the phone for diagnostic and treatment.

Glassy carbon (GC) based electrode deposited on the polyimide substrate was proposed [35] (Figure 4). To assess the stability of GC based electrode on the current stimulation compared to Pt, the biphasic current was repeatedly applied, and the result indicated the better reliability of GC. To enhance electrical characteristics, PEDOT:PSS was electrodeposited on GC and Pt for comparison. Adhesion of polymer coating was also more stable on GC in the test. In neural signal recordings, a combination of GC and PEDOT: PSS exhibited higher SNR suggesting GC was appropriate material for polymer coating.

Graphene is an excellent active material with fine conductivity, biocompatibility, flexibility, and stretchability. Research on utilizing graphene as the electrode has been reported considerably. Research on the fabrication of graphene electrode array for neural imaging and optogenetics was reported [28], [36]. Stimulating light was delivered to the brain passing a transparent graphene layer and the activated signal was recorded successfully. Another example was a graphene electrode implanted in a genetically modified mouse [36]. Neurons of the transgenic mouse emit the fluorescence light when the neurons are activated. Applied stimulation, evoked light could be observed via fluorescence microscopy without interference due to the transparency of graphene.

C. DEEP BRAIN STIMULATION ELECTRODE

Therapeutic effect of deep brain stimulation on neurological disorder has been abundantly studied. However, Young's modulus of brain tissue is much lower than the insulator of the neural probe and this mechanical mismatch between the tissue and the electrode induces foreign body response which causes inflammation and degrades the electrical performance of the device. Thus, flexibility has been the main concern in the fabrication of the neural probe for long-term stability.

A wireless flexible probe for optogenetic stimulation and dopamine detection was reported [37] (Figure 5). PEDOT:PSS was deposited on a flexible polyimide-based substrate as the working electrode. Before the in-vivo test, a linear relationship between the dopamine concentration and the response current was observed in the range of 0.1–10 μM. Through the animal test, the promotion of dopamine release by optical stimulation was proved. Optical stimulation from the integrated LED was found to be effective more than two weeks from implantation. However, electrical sensitivity degraded within several hours due to the in-vivo environment.

Another research aiming at long-term recordings of ultra-thin cluster electrode was reported [38] (Figure 5). A bundle of deep brain electrodes was coated with gelatin to facilitate implantation without a support shuttle. After implantation, gelatin-coating dissolved and the electrical performance of the electrode did not degrade during 8 weeks showing stable recording quality.

D. SENSOR TARGETING PERIPHERAL NERVOUS SYSTEM

Neural electrodes are capable of operation in the peripheral nervous system (PNS). Some research reported PNS electrodes using shape memory polymer as the substrate [39]. Shape memory polymers were optimized to respond at body temperature. Therefore, when electrodes are attached to the nerve, electrodes change the shape and maintain contact with the nerve. Stimulation ability also has been demonstrated showing that the heart rate of the subject decreased with the electrical neuromodulation on the vagus nerve. Another example of PNS electrodes was described in Ref. [40] (Figure 5). An optical nerve cuff electrode was developed for coincident signal monitoring and optical stimulation. The test was carried out to show that signal recordings with the optical stimulation were not affected by stimulation artifact while neural signals were affected by electrical stimulation that induces the neural signal recording. Further, optical stimulation successfully evoked neural activity in an animal test. Test results have suggested that ankle joint contraction was elicited stimulation.

6. CONCLUSION

In this paper, flexible biosensors with diverse methods and targets were reviewed focusing on FET and MEA type biosensors. As aforementioned, flexible materials have many advantages over stiff materials, though stiff metals have good conductivity and processability. Thus, the usage of polymers, which have conductivity, biocompatibility, and flexibility, has been increased in

biosensor research.

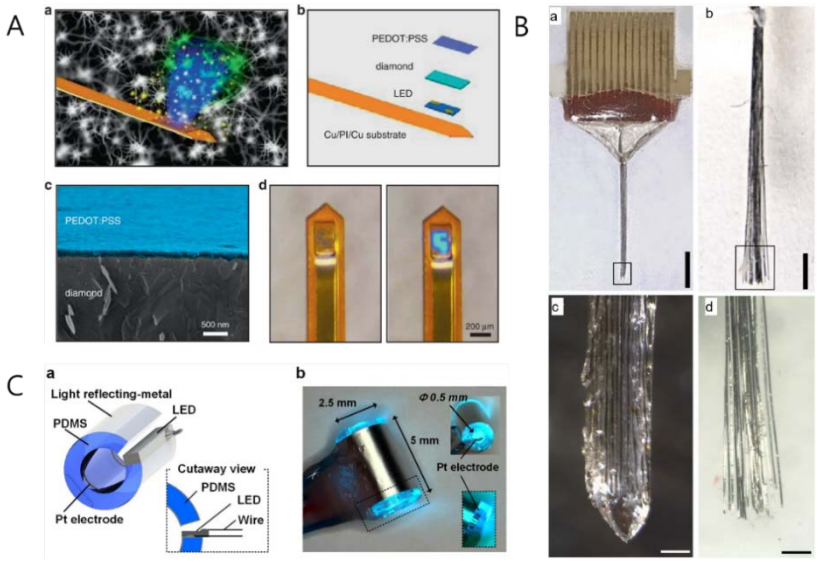

Figure 5. (A) Illustration of the structure of the microprobe system for optogenetic stimulation and dopamine detection. [37] (B) Light field images visualizing the cluster electrode before and after in vitro implantation. Close up of the probe and its conical tip and the electrode tip after insertion into 37°C agarose are exhibited. [38] (C) Optical nerve cuff electrode for optogenetic stimulation with simultaneous neural signal recording and picture of an active device in light illumination. [40]

Numerical interpretation of diagnostic or treatment is a big advantage of biosensors. For example, real-time sensing of blood sugar, which is one of the competitive research objects, helps the treatment of diabetes. Noninvasive glucose sensor has already been commercialized in fierce market competition. In FET biosensors, most of the reviewed devices employ current as the detecting method. Provided proper linearity, sensibility, and limit of detection, conductance modulation induced by gate potential change could be a proper method for target sensing. The development of wearable or implantable devices with integrated multi-electrodes could be used for not only the diagnosis/treatment of disease but also the construction of a stable brain-machine interface. Adoption in the clinical application including neuro-prosthetics would require a long-term stable and multifunctional connection between body and machine. Finally, continuous progress on semiconductor technology and flexible biosensors are expected to make high-quality medical devices.

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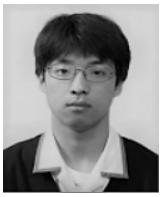

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