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REVIEW

Nanoelectronics-biology frontier: From nanoscopic probes for action potential recording in live cells to three-dimensional cyborg tissues

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Summary Semiconductor nanowires configured as the active channels of field-effect transistors (FETs) have been used as detectors for high-resolution electrical recording from single live cells, cell networks, tissues and organs. Extracellular measurements with substrate supported silicon nanowire (SiNW) FETs, which have projected active areas orders of magnitude smaller than conventional microfabricated multielectrode arrays (MEAs) and planar FETs, recorded action potential and field potential signals with high signal-to-noise ratio and temporal resolution from cultured neurons, cultured cardiomyocytes, acute brain slices and whole animal hearts. Measurements made with modulation-doped nanoscale active channel SiNW FETs demonstrate that signals recorded from cardiomyocytes are highly localized and have improved time resolution compared to larger planar detectors. In addition, several novel three-dimensional (3D) transistor probes, which were realized using advanced nanowire synthesis methods, have been implemented for intracellular recording. These novel probes include (i) flexible 3D kinked nanowire FETs, (ii) branched intracellular nanotube SiNW FETs, and (iii) active silicon nanotube FETs. Following phospholipid modification of the probes to mimic the cell membrane, the kinked nanowire, branched intracellular nanotube and active silicon nanotube FET probes recorded full-amplitude intracellular action potentials from spontaneously firing cardiomyocytes. Moreover, these probes demonstrated the capability of reversible, stable, and long-term intracellular recording, thus indicating the minimal invasiveness of the new nanoscale structures and suggesting biomimetic internalization via the phospholipid modification. Simultaneous, multi-site intracellular recording from both single cells and cell networks were also readily achieved by interfacing independently addressable nanoprobe devices with cells. Finally, electronic and biological systems have been seamlessly merged in 3D for the first time using macroporous

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nanoelectronic scaffolds that are analogous to synthetic tissue scaffold and the extracellular matrix in tissue. Free-standing 3D nanoelectronic scaffolds were cultured with neurons, cardiomyocytes and smooth muscle cells to yield electronically-innervated synthetic or 'cyborg' tissues. Measurements demonstrate that innervated tissues exhibit similar cell viability as with conventional tissue scaffolds, and importantly, demonstrate that the real-time response to drugs and pH changes can be mapped in 3D through the tissues. These results open up a new field of research, wherein nanoelectronics are merged with biological systems in 3D thereby providing broad opportunities, ranging from a nanoelectronic/tissue platform for real-time pharmacological screening in 3D to implantable 'cyborg' tissues enabling closed-loop monitoring and treatment of diseases. Furthermore, the capability of high density scale-up of the above extra- and intracellular nanoscopic probes for action potential recording provide important tools for large-scale high spatio-temporal resolution electrical neural activity mapping in both 2D and 3D, which promises to have a profound impact on many research areas, including the mapping of activity within the brain.

Introduction

Large-scale and high spatial resolution cellular and subcellular-level interfaces between electrical sensors and biological systems are crucial for both fundamental biophysical studies and medical monitoring and intervention [1—5]. For example, the exploration of the brain function depends largely on the development of new tools that can simultaneously measure and manipulate the electrical activity of thousands or even millions of neurons with high spatial and temporal resolution. Over the past several decades, a variety of electrical probes including glass micropipette intracellular and patch-clamp electrodes [1,4,5], multielectrode arrays (MEAs) [2,4,6—8], and planar field-effect transistors (FETs) [9—12] were developed and widely used to record action potentials and transmembrane potential changes from electroactive cells and tissues, as well as to probe chemical events at the surface of tissues or individual cells. These probes, which are normally micrometer in size, can readily interface with cellular level resolution and provide valuable information on cell network function. However, the size of these probes poses a challenge to record from small subcellular structures or to carryout simultaneous, large-scale multi-site recording with subcellular-level resolution [10,13—16].

The intense interest placed in recent years on chemically-synthesized semiconductor nanowires has led to the development of a broad range of structures with rationally controlled geometry, composition, and electronic properties [17—21]. As predictable and synthetically well-controlled structures, semiconductor nanowires have been used as powerful building blacks for the bottom-up assembly of functional devices such as FETs, photodetectors, and photodiodes [18,19,22,23]. Nanoscale functional devices such as nanoFETs can be used as voltage and chemical sensors thereby enabling new classes of molecular scale electronic interfaces with biological systems [24—29]. Compared to conventional glass micropipettes, sharp metal electrodes, or microfabricated MEAs and planar FETs, there are two major advantages of these new nanoFET based sensors. First, the small size of these probes (Fig. 1a) allows for simultaneous multi-site recording with increased number and density of recording sites, which enables larger scale and higher spatial resolution, and also intracellular measurements that are much less invasive to cells [27—29,32,33]. In addition, the small size also enables more localized, higher spatial precision measurements, which is necessary for subcellular level interfacing, for example, in measurements from neurites [27,30,31]. Second, the intrinsic strength of bottom-up assembly (Fig. 1b) allows semiconducting nanowire functional elements to be assembled on nearly any type of surface, including those that are typically not compatible with standard CMOS processing, such as flexible plastic substrates [23,34—38]. Moreover, sequential patterning and assembly steps further enable fabrication of distinct nanowire nanodevices on a substrate (Fig. 1b) to incorporate multi-function in measurement chips [37]. Last, bottom-up assembly of nanowires enables the fabrication of flexible, free-standing devices [28,39]. Three-dimensional (3D), free-standing, macroporous device array can be utilized as the scaffolding for synthetic tissue constructs and used to monitor cellular activity throughout 3D cellular networks [39], capabilities that are not accessible with conventional electrode probes or even recently developed flexible electronics [36,40,41].

In this review, we will describe the development of new biological sensing devices using semiconducting nanowires as the probe structure and detector or nanowire based structures as the functional detector element, as well as their application in extracellular and intracellular measurements. Specific emphasis will be placed on transmembrane and action potential recording from living biological systems ranging from cultured cells, acute tissue slices, and whole organs through synthetic nanoelectronic/tissue constructs. The uniqueness enabled by the use of nanometer scale functional semiconducting nanowires will be highlighted, and exciting future applications of these new probes in biophysical and electrophysiological studies will be discussed.

Extracellular electrical recording

The potential change outside the cells associated with the transmembrane change of excited cells can be recorded by metal or glass micropipette electrodes to monitor the electric activity of the cells [2,6,7,11]. Compared to intracellular recording, which normally places the tip of the probe structure inside the cells, extracellular recording is less invasive and provides ready access to simultaneous