

Interfacing Biomolecules, Cells and Tissues with Nanowire-based Electrical Devices

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I. INTRODUCTION

Detection and qualification of biological and chemical species are critical to many areas of health care and the life sciences, from diagnostic disease to the discovery and screening of new drug molecules. Central to detection is the transduction of a signal associated with the selective recognition of a species of interest. Several approaches have been reported for the detection of biological molecules, including ELISA,¹ surface plasmon resonance,² nanoparticles,³ chemically sensitive field-effect transistors⁴ and micro-cantilevers.⁵ Although all have shown feasibility and promising progress applicability, none has yet demonstrated the combination of features required for rapid, highly sensitive multiplexed detection of biomolecules.

Nano-science and technology, whose unifying theme is the control of matter in this size range, allows revolutionary changes of the fundamental properties of matter and phenomena that are often drastically different compared to those they exhibit on the

bulk phase. Since dimensionality plays a critical role in determining the qualities of matters, the realization of the great potential of nanoscale science and technology has opened the door to other disciplines such as life sciences and medicine, where the interface between them offers exciting new applications along with basic science research. The application of nanotechnology in life sciences, nanobiotechnology, is already having an impact on sensing, diagnostics and drug delivery. Several nanostructures have been reported for this task, including nanoparticles,³ carbon nanotubes⁶ and nanowires.⁷ Inorganic nanowires, nanocrystals and carbon nanotubes exhibit unique electrical, optical and magnetic properties that can be exploited for sensing and imaging.⁷ Advances in nanoscale materials have enabled to construct electronic circuits in which the component parts are comparable in size to the biological and chemical entities being sensed, therefore represent excellent primary transducers for producing signals that ultimately interface to macroscopic instruments. The ability to transduce chemical/biological binding events into electronic/digital signals suggests the potential for highly sophisticated interface between nano-electronic and biological information processing systems.

Specifically, semiconducting nanowires are emerging as remarkably powerful building blocks in nanoscience, with the potential to have a significant impact on numerous areas of science and technology. Critical to the advances now being made worldwide with nanowires has been the well-developed understanding of nanowires growth mechanism, which has enabled the reproducible synthesis of nanowires of homogenous composition and diameter with controllable electronic and optical properties. Nowadays, semiconductor nanowires can be rationally and predictably controlled with all key parameters, including diameter, length, chemical composition and doping/electronic properties^{8,9} with the ability to integrate arrays of discrete elements. Significantly, these characteristics make semiconductor nanowires one of the best defined and most versatile nanomaterial systems available today, thus enabling scientists to move beyond device proof-of-concept studies to the exploration of new areas of science and technology.

During the last decade nanowire-based electronic devices emerged as a powerful and universal platform, demonstrating key advantages such as rapid, direct, highly sensitive multiplexed de-

tection, for a wide-range of biological and chemical species from single molecules up to ultimate level of living cells.

In this manuscript we present representative examples in which these novel electrical devices have been used for living cells and tissues. Recording electrical signals from cells and tissues is a substantial tool for interrogating areas ranging from the fundamental biophysical studies of function in, for example, the heart and brain, through medical monitoring and intervention. NW-FET devices have the potential to form strongly coupled interfaces with cell membranes due to their inherent intrinsic characteristics, thus they can be used as highly sensitive local probes for extracellular and intracellular recordings, as recently demonstrated. As basic research, the direction is most stimulating and fruitful; however, it is important to realize that these powerful tools, if integrated with fundamental biology, can provide essential breakthroughs. Pulling down the barriers between very different sciences and technologies leads to surprising and new insights. The field is certainly most inter-disciplinary.

II. NANOWIRE FIELD-EFFECT DEVICES AS SENSORS

Detectors based on semiconductor nanowires are configured as field-effect-transistors (FETs), which exhibit a conductance change in response to variations in the electric field or potential at the surface of the channel region.^{7,10a} In a standard FET, a semiconductor is connected to metal source and drain electrodes, through which a current is injected and collected, respectively. The conductance of the semiconductor is switched on and off or modulated by a third gate electrode capacitively coupled through a thin dielectric layer,^{10b} Fig. 1A. In the case of a p-Si or other p-type semiconductor, applying a positive gate voltage depletes carriers and reduces the conductance, whereas applying a negative gate voltage leads to an accumulation of carriers and increases the conductance. Conductance modulations are dependent on the thickness of the oxide dielectric layer of the gate.¹¹ The dependence of the conductance on gate voltage makes FETs natural candidates for electrically based sensing, because the electric field resulting from the binding of a charged species to the gate dielectric is ana-

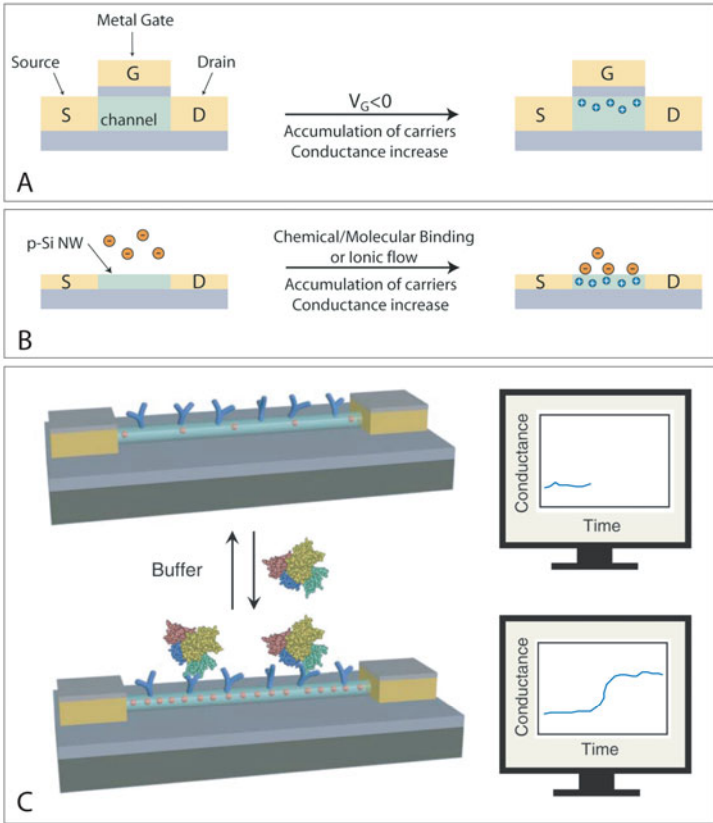


Figure 1. (A) Schematic of a p-type planar FET device, where S, D and G correspond to source, drain and gate electrodes, respectively. (B) Schematic of electrically based sensing using a p-type NWFET, where binding of a charged biological or chemical species to the chemically modified gate dielectric is analogous to applying a voltage using a gate electrode. (C) (left) Schematic illustration of a nanowire field-effect transistor configured as a sensor with antibody receptors (blue). (right) Binding of a protein with a net negative charge to a p-type nanowire yields an increase in conductance.

logues to the effect of applying a voltage with a gate electrode. The idea for sensing with FETs was introduced several decades ago,¹² but with planar FET sensors of previous planar devices which precluded their application due to their limited sensitivity.

Semiconductor nanowires and carbon nanotubes can also be configured as FETs. These devices overcome limitations of planar CHEMFETs by the use of their 1D nanoscale morphology, because the extremely high surface-to-volume ratios associated with these nanostructures make their electrical properties extremely sensitive to species adsorbed on their surfaces.¹³

The diameter of single wall carbon nanotubes, naturally occurring as hollow cylinders, is in the 1-nm range, the diameter of a DNA duplex. Because of the tubular structure of the nanotube, all the current flows at the surface of the channel, in direct contact with the environment.¹⁴ In the case of nanowire device, an analyte binding to the surface of the nanowire leads to a change through the entire cross section of the device versus only a thin region near the surface of a planar device, resulting in a much greater change in device conductance for the NW versus a planar FET,¹⁵ increasing the sensitivity to a point that single molecule detection is possible.¹³

Specifically, Si-nanowires configured as FETs exhibit performance characteristics comparable to or better than the best reported in the microelectronics industry for planar silicon devices¹⁶. Silicon-based nanotechnology is particularly promising since it is compatible with the conventional silicon microtechnology; silicon has been without doubt the basic building material for the semiconductor industry and the workhorse for micro-and nanotechnologies. SiNWs can be prepared as single crystal structures with diameters as small as 2–3 nm,¹⁷ with complementary n- and p-type doping. Their electronic characteristics are well controlled during growth in contrast to carbon nanotubes and are also achieved with high reproducibility.^{16b} The fabrication of SiNW-FET devices is relatively straightforward compared to conventional planar silicon FET devices, and combines bottom-up assembly of the nanowires on the device chip together with a single step of photolithography to make the metal contacts. Furthermore, SiNWs can be assembled on nearly any type of surface, including those that are typically not compatible with standard CMOS processing, such as flexible plastic substrates.¹⁸ Lastly, their native oxide surfaces allow to chemi-

cally modify them and to bind them specific receptors groups to their surfaces.

The reproducible and tunable conducting properties of semi-conducting nanowires, combined with the ability to bind desired analytes on their surface yields electrical readout that offers revolutionary conception, which has many advantages over conventional organic molecular dyes for labeling and optical-based detection of biological and chemical entities.^{19a}

III. NANOWIRE FIELD EFFECT DEVICES FOR THE DETECTION OF MOLECULAR SPECIES

The unique features of semiconductor nanowires have enabled to produce highly sensitive devices that have been demonstrated for variety of biological and chemical applications. In all reports, key features such as direct, label free, real time, ultrahigh sensitivity, exquisite selectivity and the potential for integration of addressable arrays were shown, which set these devices apart from other sensor technologies available today. In the following Section we discuss representative examples which clearly demonstrate the potential of these devices to significantly impact many areas of biology and medicine.

NW-based FET can be configured as sensing device for biological and chemical molecules by linking receptor groups that recognize specific molecules to the surface of the NWs, [Fig. 1B and C](#). SiNWs have native oxide coating that is naturally formed with their exposure to air. Extensive data exist for the chemical modification of silicon oxide or glass surfaces from planar chemical and biological sensors.^{19b} Practically, the receptor solutions are delivered by a mated microfluidic channel to the chemically modified nanowires and the linkage is straightforward. When the sensor device with surface receptor is exposed to a solution containing a macromolecule like a protein or a chemical agent who has a net charge in the aqueous solution, specific binding will lead to a change in the surface charge that surrounds the nanowire and a change in the conductance respectively.

As a proof of concept, a flexible integrated NW sensor platform was developed, that incorporates SiNWs with well defined p- or n-type doping; source and drain electrodes that are insulated

from the aqueous environment so that only processes occurring at the SiNW surface contribute to the electrical signals; and a mated microfluidic channel (formed between a poly-dimethylsiloxane (PDMS) mold and the sensor chip) for delivery of solution suspensions onto specific locations on the SiNW-FET surface, Fig. 2A.

The detection capability of nanowire devices was first demonstrated in 2001 for pH monitoring, as well as selective detection of streptavidin and calcium ions.^{10a} Notably, biotin-modified NWs were able to detect streptavidin down to the picomolar concentration range. The potential of Si-NW FET devices as a tool for drug discovery was illustrated in 2005 for the identification of molecular inhibitors of tyrosine kinases whose constitutive activity is responsible for chronic myelogenous leukemia.²⁰

For diagnostic purposes of DNA, NW-based devices were demonstrated for detection of the activity and inhibition of telomerase, a ribonucleoprotein that is active in $\geq 80\%$ of known human cancers, from unamplified extracts from as few as ten tumor cells, in solutions with relatively high (mM) ionic strength.^{15b} In addition, the detection of genetic single mutation associated with cystic fibrosis was carried out at concentrations down to the 10-fM level,²¹ which is 2–5 orders of magnitude better than that demonstrated for real-time measurements including SPR,²² nanoparticles enhanced SPR²² and quartz crystal microbalance²³ for DNA detection.

In 2004, the limit of biological detection, single particle sensitivity, was achieved by detecting, in real time, the reversible and selective binding of virus particles to antibody modified NWFETs. Delivery of a highly diluted virus solution on the order of ~ 80 aM or 50 viruses/ml yielded clear conductance changes that were supported by simultaneous optical imaging of fluorescently labeled influenza viruses indicating on the binding and unbinding of a single virus,^{15a} Fig. 2B.

Ultimately, the multiplexed real time detection with ultrahigh sensitivity and exquisite selectivity was demonstrated in 2005 for the detection of cancer biomarkers, at concentrations down to ~ 2 fM,^{15b} Fig. 3A. These results represent a sensitivity limit 10^4 – 10^9 times below that afforded by ion sensitive planar FETs.²⁴ Also, the detection can be carried out on as little as drop of blood instead of the milliliters needed for current analyses. The multiplexed detection of protein biomarkers is especially important in the diagnosis

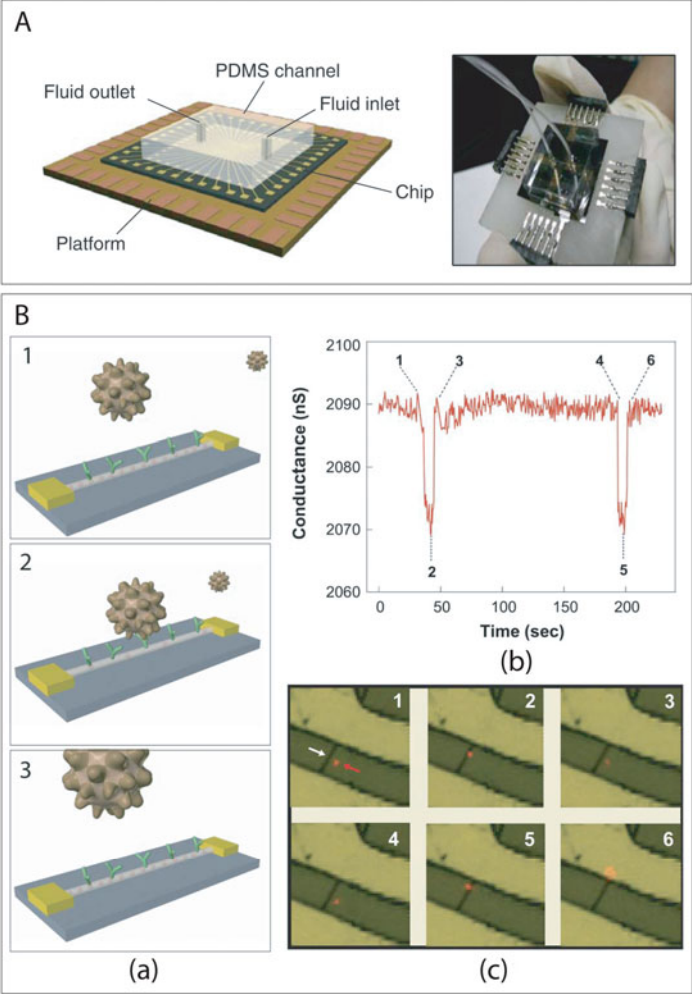


Figure 2. A) (left) Schematic and (right) photograph of a prototype nanowire sensor biochip with integrated microfluidic sample delivery. B) (a) Schematic illustration of a single virus binding and unbinding to the surface of a NWFET modified with antibody receptors. (b) Conductance vs. time data recorded from a single device modified with anti-influenza type A antibody. (c) Optical data recorded simultaneously with conductance data in (b). Combined bright-field and fluorescence images correspond to time points 1-6 indicated in the conductance data; virus appears as a red dot in the images.

of complex diseases like cancer because disease heterogeneity makes single marker tests inadequate. Moreover, detection of markers associated with different stages of disease pathogenesis could facilitate early detection.

The examples described in this Section illustrate the unique capabilities of nanowire-based field-effect sensor device arrays for medicine and life sciences, broadly defined. Throughout these experiments, devices have shown very good device-to-device absolute detection reproducibility and simultaneous false positive signals were discriminated; complementary electrical signals from p- and n-type devices provide a simple yet robust means for detecting false positive signals from either electrical noise or nonspecific binding of protein. It is important to note that these exquisite sensitivities were also verified by Reed's group in 2007 that used top-down fabricated NWs to demonstrate specific label free detection of proteins below 100 fM concentration, as well as real-time monitoring of the cellular immune response.

However, some limitations also exist. An intrinsic limitation of FET devices is that the detection sensitivity depends on solution ionic strength^{25a}. In the case of nanowire FET-sensing, low salt (<1 mM) buffers are required to prevent screening of the charge-based electronic signal. Because blood serum samples have high ionic strength, diagnostic will require means to overcome the deceptive shielding. A simple desalting step before analysis was demonstrated to allow for highly sensitive assays.^{15b} Recently, to overcome these limitations, Reed's group^{25b} has developed an inline microfabricated device that operates upstream of the nanosensors to purify biomarkers of interest prior to the detection step. The microfluidic purification chip captures the protein biomarkers directly from physiological solutions and, after a washing step is performed, the antigens are released into a clean low ionic strength buffer suitable for high-sensitivity sensing, as schematically described in Fig. 3B. First, a blood sample flows through the chip and the chip-bound antibodies bind to the soluble biomarkers, essentially purifying these molecules from whole blood. After this capture step, wash and sensing buffers are perfused through the device. Flow is then halted, and the sensing buffer-filled chip is irradiated with ultraviolet (UV) light, resulting in cleavage of the photolabile group and release of the bound biomarker-antibody complexes. Finally, the released purified antigen molecules, bound

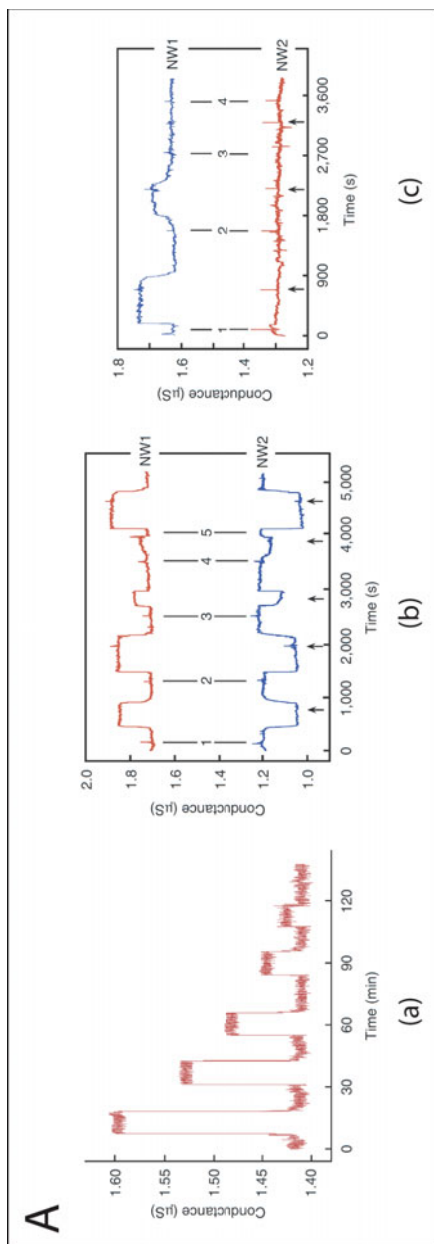


Figure 3. (A) Real-time nanowire sensing results. (a) Conductance versus time data recorded following alternate delivery of PSA and pure buffer solutions; the PSA concentrations were 5 ng/ml, 9 ng/ml, 0.9 pg/ml, and 90 fg/ml, respectively. The buffer solutions used in all measurements were 1 mM phosphate (potassium salt) containing 2 mM KCl, pH 7.4. (b) Complementary sensing of PSA using p-type (NW1) and n-type (NW2) devices. Points 1-5 correspond to the addition of PSA solutions of (1,2) 0.9 ng/ml, (3) 9 pg/ml, (4) 0.9 pg/ml, and (5) 5 ng/ml. (c) Conductance-versus time data recorded simultaneously from 2 p-type silicon nanowire devices in an array, where NW1 was functionalized with PSA Ab1, and NW2 was modified with ethanolamine. Points 1-4 correspond to times when solutions of (1) 9 pg/ml PSA, (2) 1 pg/ml PSA, (3) 10 $\mu\text{g/ml}$ BSA, (4) a mixture of 1 ng/ml PSA and 10 $\mu\text{g/ml}$ PSA Ab1 were delivered.

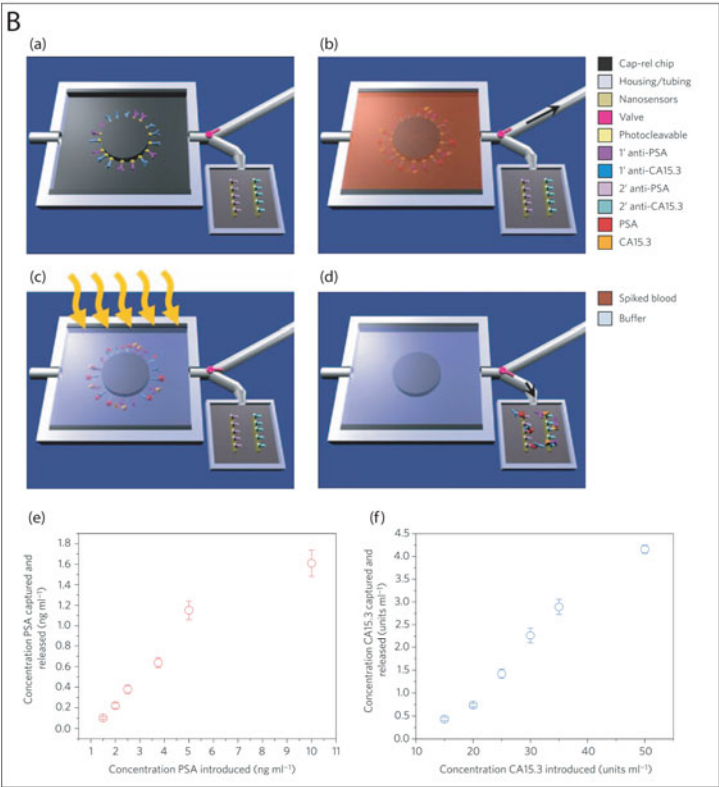


Figure 3. Continuation. (B) Schematic of MPC operation. (a) Primary antibodies to multiple biomarkers, here PSA and carbohydrate antigen 15.3, are bound with a photocleavable crosslinker to the MPC. The chip is placed in a plastic housing and a valve (pink) directs fluid flow exiting the chip to either a waste receptacle or the nanosensor chip. (b) Whole blood is injected into the chip with the valve set to the waste compartment (black arrow shows the direction of fluid flow) and, if present in the sample, biomarkers bind their cognate antibodies. (c) Washing steps follow blood flow, and the chip volume (5 ml) is filled with sensing buffer before UV irradiation (orange arrows). During UV exposure, the photolabile crosslinker cleaves, releasing the antibody–antigen complexes into solution. (d) The valve is set to the nanosensor reservoir (black arrow shows the direction of fluid flow) and the 5 ml volume is transferred, enabling label free sensing to be performed to determine the presence of specific biomarkers. (e, f) Scatter plots showing the concentration of PSA (e) and CA15.3 (f) released from the MPC versus the concentration of PSA and CA15.3 introduced in whole blood, respectively. Each data point represents the average of three separate MPC runs, and error bars represent one standard deviation.

to their specific antibody, are flowed into the sensing compartment where the sensing events occur on the nanoribbon-based devices. However, this sensing platform requires the use of a pair of antibodies against each biomarker of interest, one during the purification capturing step and one during the sensing step. Additionally, the use of silicon *nanoribbons* limited the detection sensitivity of the platform to ~ 1 ng/mL.

IV. NANOWIRE FET ARRAYS FOR THE ELECTRICAL MONITORING OF SINGLE NEURON AND NEURAL CIRCUITS

Previous studies provided strong support that NW and CNT devices have substantially higher sensitivity than planar FETs and thus can offer advantages for cellular recording beyond other technologies available today. Methods for measuring the electrical activity produced by electroactive cells include techniques such as glass micropipette electrodes,²⁶ voltage sensitive dyes,^{26c} multi electrode arrays (MEAs)²⁷ and planar FETs,²⁸ which have and continue to play an important role in understanding the electrical behavior of individual cells and cellular networks.^{29b} Micropipette electrodes can stimulate and record extracellular potentials *in vitro* and *in vivo* but more importantly, it can measure intracellular potentials with relatively good spatial resolution,^{29b,30} capability that the other technologies still cannot reach. Yet, this method is invasive and especially difficult to multiplex where multiple recordings from different neurons are intended. Extracellular recordings are noninvasive and allow recording from multiple sites, from both individual cells and neural networks,^{29,31} but suffer from very low signal-to-noise (S/N) ratio because of the use of relatively large electrodes and their imprecise positioning relative to the cell.³¹

Nanotechnology-based devices are particularly attractive for interfacing with neurons since they are compatible with the size of neuron projections, and are able to detect and stimulate cellular activity at the level of individual axons or dendrites. A unique intrinsic feature of these devices compared with conventional planar devices is that the nanodevices protrude from the plane of the substrate, and hence can increase NW/cell interfacial coupling, forming naturally tighter junctions with the local cell membrane.

Indeed, studies have shown that nanostructured interfaces can enhance neuronal adhesion and activity.^{14,32} It has been demonstrated that CNT networks or etched silica promote cellular adhesion, spreading and guidance, even in the absence of conventional adhesion factors such as polylysine.^{32b,33} Neuronal stimulation through carbon nanotubes was demonstrated for the first time in 2005, by capacitive coupling to micron-scale pads consisting of tightly-packed carbon nanotube pillars.³⁴ Then, in 2006, nanotubes were assembled into mats using a layer-by-layer technique, and stimulation was achieved by passing lateral current pulses through the conductive mat.³⁵ In a follow-up work in 2007, the same technique was used to assemble close-packed films of photoactive HgTe nanoparticles; illumination of the film resulted in photochemistry and charge-transfer that subsequently stimulated an interfaced neuron.³⁶ Two other separate studies demonstrated that neurons cultured on CNT mats exhibit enhanced spiking activity (vs. those cultured on planar control surfaces), and suggest that the conductive, nanostructured surface enhances membrane excitability.³⁷

The first electronic interface between NWs and neurons was reported by Lieber's group in 2006 in which hybrid structures consisting of nanowires FET arrays and patterned neurons were assembled and electrically characterized.³⁸ An important aspect of this work is the surface patterning and the incorporation of cells with respect to the NW-FET-devices with the ability to explore the cellular activity with the nanowires positioned directly at the vicinity of the cell surface. For a FET array to be used to record neuronal signals, the gate dimensions should ideally be on the nanometer scale, and the neurons have to *sit* on the non-metallized gate of the FET, affecting the source-drain current by capacitive coupling when the neuron undergoes a membrane voltage change. Several recent studies provided strong support that neurons growing according to pattern exhibit healthy electrophysiological properties and synaptic connections.³⁹ Nevertheless, this task is intriguing due to the difficulty of culturing cells in well defined orientations over nanoscale devices while maintaining good device characteristics.

In this work, p- and n-type Si-NWs were incorporated into FET device array structures in well defined positions in which they were spatially located along the axon and dendrites or at the junc-

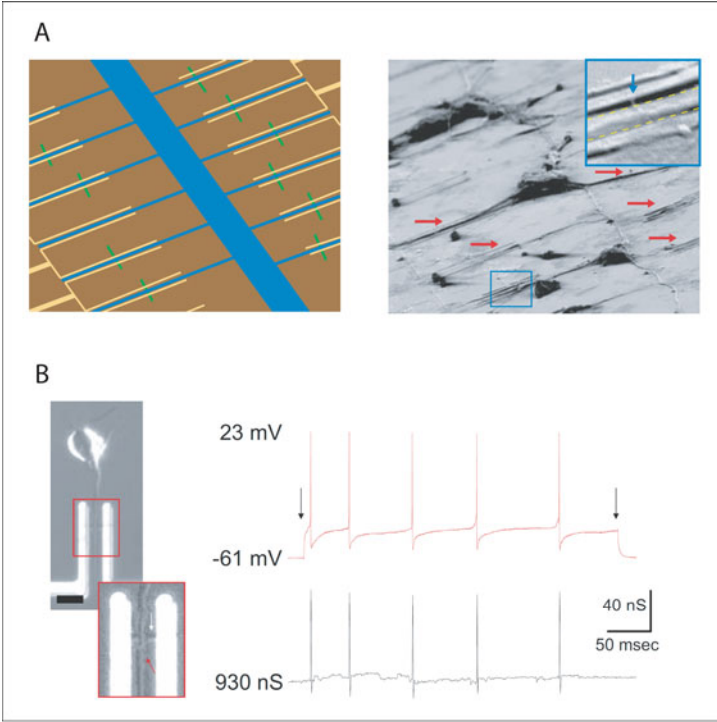


Figure 4. (A) NW/neuron interfaces. Schematic of interconnected neuron motif and SEM image of fixed neurons exhibiting a neural network where multiple neurites are interfaced with NW devices (red arrows). Inset: Zoom depicting an axon (denoted by yellow dotted lines) guided between source and drain electrodes across a NWFET (highlighted by blue arrow). (B) (left) Optical image of a cortical neuron aligned across a NWFET; (inset) High resolution image of region where axon (red arrow) crosses a NW (yellow arrow). (right) red trace- Intracellular potential of an aligned cortex neuron (after 6 days in culture) during stimulation with a 500 msec long current injection step of 0.1 nA; black trace- time-correlated signal from axon measured using a p-type NWFET.

tion with the cell body, creating *small* hybrid junctions with a typical junction area of $0.01\text{--}0.02\text{ }\mu\text{m}^2$ which is at least two orders of magnitude smaller than microfabricated electrodes and planar FETs. Neuron cell growth was guided with respect to the device element by using chemically adhesive and repelling factors of poly-D-lysine and fluorosilane, respectively, Fig. 4A. Action po-

tential signals were elicited and recorded either by a conventional glass microelectrode impaled in the soma or by NW electrodes interfaced with an axon or dendrite.

Various set-ups of device structures were designed, for instance, a repeating 1-neuron/1-nanowire motif with the soma and the axon directed across the respective nanowire element. The results show the direct temporal correlation between the intracellular spikes initiated and recorded in the soma and the corresponding conductance peaks measured by the nanowire at the axon nanowire junction, Fig. 4B. For a p-type NW, an action potential will result in enhanced conductance followed by reduced conductance (the relative potential at the outer membrane becomes more negative and then more positive). Also, stimulation with the NW at the NW/axon junction resulted in somatic action potential spikes, which were detected with the intracellular electrode.

In this work it was shown that nanowire devices can be used to stimulate, inhibit, or reversibly block signal propagation along specific pathways while simultaneously following the signal flow throughout the network, capabilities that current techniques are not able to.

Following this work, other groups reported on the effective electrical interfacing between nanowire-based devices and bioelectrical cells.⁴⁰

In a later work, reported in 2010, Si NWFET arrays were used for mapping neural circuits in the brain,^{40a} Fig. 5A. Neural circuits are organized into hierarchical networks operating on spatial and temporal scales that span multiple orders of magnitude.^{40d} It is highly desirable to map the activities in large populations of neurons with high position accuracy and precise timing. Revealing the functional connectivity in natural neuronal networks is central to understanding circuits in the brain. It was shown that silicon nanowire field-effect transistor (Si NWFET) arrays fabricated on transparent substrates can be reliably interfaced to acute brain slices. Devices were readily designed to record across a wide-range of length scales. Simultaneous NWFET and patch clamp studies enabled unambiguous identification of action potential signals, with signal amplitudes of 0.3 to 3 mV, Fig. 5B.

These results demonstrate that the NWFET arrays detect local activity of the pyramidal cell layer and lateral olfactory tract on at least the 10- μ m scale, and thus can be used to understand the func-

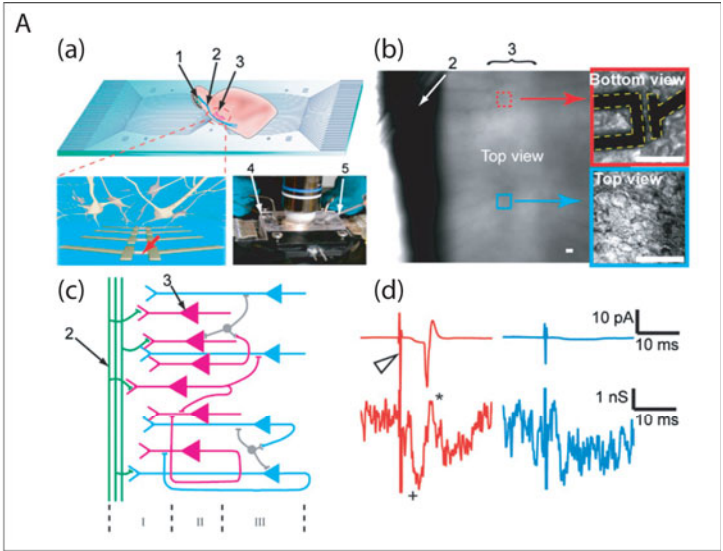


Figure 5. (A) NW-arrays for mapping neural circuits in the brain. (a) Measurement schematics. (Top) Overview of a NWFET array fabricated on a transparent substrate with slice oriented with pyramidal cell layer over the devices. (Bottom Left) Zoom-in of device region illustrating interconnected neurons and NWFETs. (Bottom Right) Photograph of the assembled sample chamber. 1, 2, and 3 indicate the mitral cells in the olfactory bulb, the lateral olfactory tract, and the pyramidal cells, resp. 4 and 5 mark the stimulation electrode and the patch clamp pipette, resp. (b) Top view of the NWFET array/brain slice region in fully assembled chamber with medium. Red Box shows a higher resolution image of a single device in contact with the neurons at the bottom of the slice. Blue Box shows the outermost neurons of the slice through an immersed lens from the top. (c) Laminar organization and input circuitry of the piriform cortex (Layer I–III). (d) Conductance recording from a NWFET (Lower Traces) in the same region as neuron used to record cell-attached patch clamp results (Upper Traces). Stimulation in the LOT was performed with strong (200 μ A, Red Traces) and weak (50 μ A, Blue Traces) 200 μ s current pulses. The open triangle marks the stimulation pulse. (B) Localized detection with NWFET arrays. (a) (left) Optical image of brain slice over Si NWFET arrays defined by electron beam lithography. The dashed frames mark the positions of devices 1–4 and 5–6. (right) Schematics of the devices. (b) Signals obtained from devices 1–6 with 200 μ s stimulation of 2.5 (left) and 1 mA (right); $n=21$. The dashed oval marks the region where signals of opposite polarity were recorded from devices 30 μ m apart.

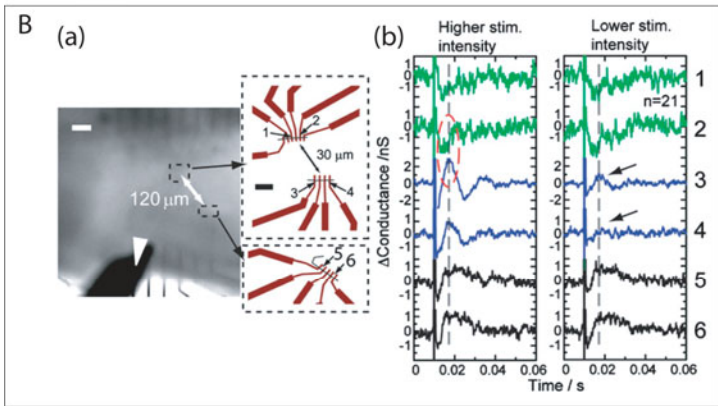


Figure 5. Continuation.

tional connectivity of this region. Furthermore, the plasticity of olfactory system suggests that the network is highly dynamic. Thus, highly localized direct recording of ensembles of neurons in the context of spatially resolved stimulation could serve as a powerful tool to visualize the dynamic, functional connection map and provide information necessary to understand the circuits and plasticity in this and other neural systems.

We believe that in the future this novel approaches would enable to study experimentally the complete dynamics not just of individual cells, but of a complete neuronal network or neural circuits in the brain. These integrated *living* electronic circuits will clearly provide meaningful information about the real mechanisms involved in electrical signal transduction in neuronal arrays, simulating the activity in the brain.

V. NANOWIRE BASED ELECTRICAL DEVICES AS TISSUE MONITORING ELEMENTS

The ability of NW-FETs devices to measure cellular and sub-cellular activity gave the motivation to step forward to the next level of complexity with biological interfaces and to use these nanoelectronic devices for the recording from a whole organ, from

a beating heart.⁴¹ Recording electrical signals *in vitro* and *in vivo* from whole hearts is applied in areas ranging from basic studies of cardiac function to patient healthcare.⁴² Different techniques are used across the surface of the heart to examine cardiac dysfunction such as arrhythmia,^{42,26c} including macroscale metallic electrodes,⁴² optical microscopy of dyed tissue,^{26c} or multielectrode arrays (MEAs), but all suffer from relatively low resolution signals that in part is related to their being planar rigid structures that cannot conform to organs, such as the heart, which are intrinsically three-dimensional (3D) soft objects.

NW and nanotube device arrays, besides being exquisite sensors, can be fabricated on flexible and transparent polymer substrates,^{18a, 18b} allowing the chip to bent and conform to 3D curved surfaces.

In this work, electrical recordings from whole embryonic chicken hearts were recorded using p-type NWFET arrays in both planar and bent conformations, Fig. 6A. Initially, planar NWFET chip configuration was used to record a freshly isolated heart. After a brief period of equilibration with medium, hearts beat spontaneously at a typical frequency of 1–3 Hz. Signals were recorded simultaneously from the NWFET and from a conventional glass pipette inserted into the heart, showing close temporal correlation between peaks, with ca. 100 ms consistent time difference between pipette and NW peaks since the pipette was inserted into a spatially remote region with respect to the NWFET devices, Fig. 6Ba. Examination of individual NW signals revealed a peak shape with a fast initial phase (full width at half maximum, FWHM = 6.8 ± 0.7 ms) followed by a slower phase (FWHM = 31 ± 9 ms), corresponding to transient ion channel current and mechanical motion, respectively. NW-FET signals were reproducible, with the chips being stable for multiple experiments, exhibiting excellent S/N. However, the voltage calibrated for these peaks depend on the device transconductance, that is, the water gate potential being applied which determines the sensitivity of the device, G/v_g . While the conductance of the fast transient decreased from ca. 55 to 11 nS with the water gate varied from -0.4 to 0.4 V (Fig. 6Bc) in correlation with the decrease in device sensitivity, the voltage-calibrated signal determined using the device transconductance was essentially constant at 5.1 ± 0.4 mV for this same variation of water gate voltage. These results confirm the stability of the inter-

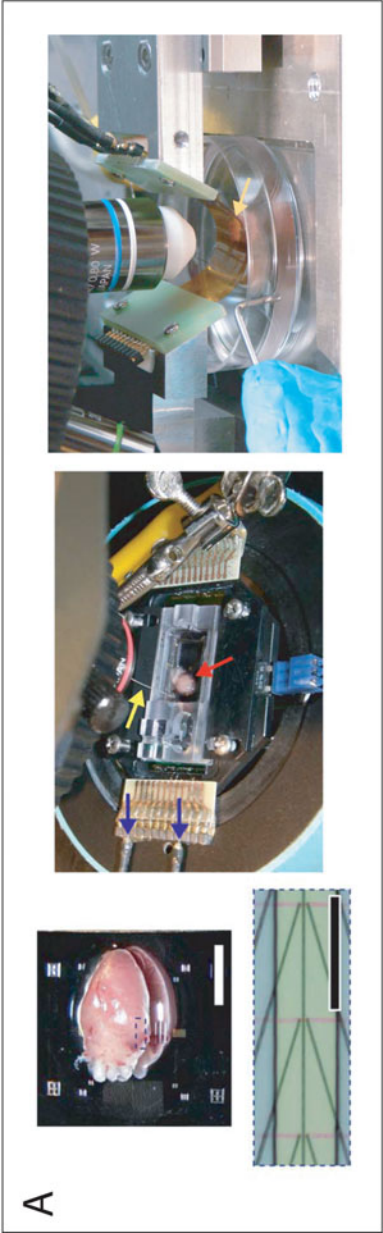


Figure 6. (A) NW/heart interfaces. (top left) Magnified image of heart on surface of planar chip; (bottom left) Zoom of dotted region in upper image showing three pairs of NW devices; (middle) Photograph of experimental setup showing heart on NWFET chip in temperature regulated cell. Arrows show position of heart (red), Ag/AgCl reference electrode (yellow) and source/drain interconnect wires (blue); (right) Photograph of heart (yellow arrow) located underneath bent substrate with NWFETs on the lower concave face of the substrate.

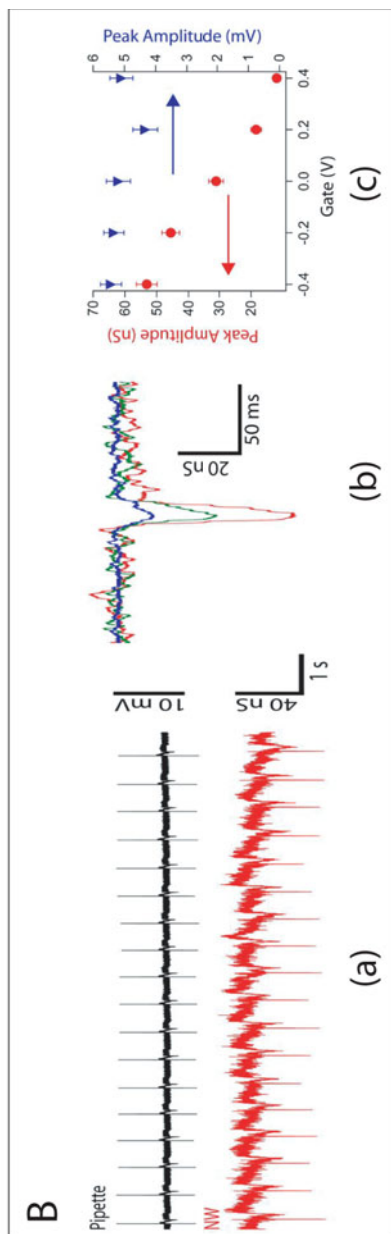


Figure 6. Continuation. (B) (a) Simultaneous recordings from a glass pipette (black trace) and a NW device (red trace). (b) Expansion of single fast transients measured from a heart for $V_g = -0.3$ (red), 0 (green) and 0.3 V (blue). (c) Plots of peak conductance amplitude (red) and calibrated peak voltage amplitude (blue) vs. V_g for same experiment shown in (b).

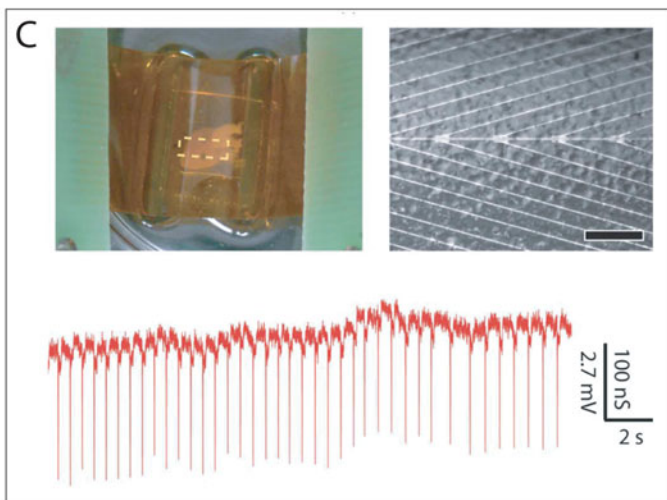


Figure 6. Continuation. (C) (left) Top-down photograph of a heart located underneath bent substrate with NW-FETs on the lower concave face of the substrate, which enables overall registration between heart and lithographically-defined markers on the substrate. (right) Optical image taken with the same system showing features on the heart surface versus position of individual NW devices, which are located along the central horizontal axis. (bottom) Recorded conductance data from a NW-FET in this configuration.

face between the NW-FETs and the beating heart, and highlight the necessity of recording explicit device sensitivity to interpret corresponding voltages.⁴¹

As mentioned, the fabrication of NWs and CNT FETs on flexible plastic substrates allows the entire chip to wrap the tissue and increase the contact area with the recording elements (Fig. 6A, right panel). Furthermore, it can be used for *in vivo* studies as demonstrated in the case of polymer-based MEAs.⁴³ NW-FETs were assembled on 50- μm thick flexible and transparent Kapton substrates. To confirm the robustness of the measurements, the heart was rotated 180° and a consistent inversion of signal was observed. Secondly, the deformed conformation was investigated by a bent device chip with concave surface facing a beating heart immersed in medium, Fig. 6C. The Kapton is a flexible and trans-

parent substrate allowing simultaneous optical imaging and electronic recording in configurations that are not readily accessible with traditional planar device chips, yet advantageous for producing diverse, functional tissue-device interfaces. It allows for both visual inspection, which enables rough orientation of the device array to the heart, and higher-resolution imaging through the transparent substrate while recording from NWFET devices. Notably, recording from a representative NWFET device in this inverted configuration demonstrated excellent S/N fast component peaks correlated with the spontaneously-beating heart. Still, the average magnitude of the conductance peaks and calibrated voltage are similar to that recorded in more traditional planar configuration. In addition, similar recording were achieved on beating hearts in which bent chips were oriented with convex NWFET surface wrapped partially around the heart.

These results demonstrate that these flexible and transparent NW chips can be used to record electronic signals from organs in configurations not achievable by conventional electronics. We believe that NWFET arrays fabricated on flexible plastic and/or biopolymer substrates can become unique tools for electrical recording from other tissue/organ samples or as powerful implants.

VI. NANOWIRES-BASED TRANSISTOR FLEXIBLE ARRAYS FOR THE ELECTRICAL RECORDING OF CARDIOMYOCYTES

One of the difficulties of culturing live cells over electrical devices is maintaining good device characteristics. Devices can suffer from destructive effects such as corrosion, solution drift, electrical shorts, etc. To address these key issues, a flexible approach was developed to interface NW FET arrays with cultures of cardiomyocyte monolayers cultured on optically-transparent PDMS sheets that were brought into contact with the devices.⁴⁴ It allowed to grow the cells separately, identify desired specific cell regions and place them over the NWFET devices, and more importantly, to investigate the relationship between the interface and signal magnitude which is critical to understand in relation to cells and nanoscale structures. Rat cardiomyocytes were shown to grow on

top-down NW FETs by another group with high S/N and millivolts amplitudes,^{45a} but not on bottom-up NW or CNT FETs.

Embryonic chicken cardiomyocytes were cultured on 100–500 μm thick rectangular pieces of PDMS to form cell monolayers, and then the PDMS/cardiomyocyte substrate was transferred into a well, which contains extracellular medium, over a NWFET chip fabricated on a standard substrate (Fig. 7a-d). PDMS/cardiomyocyte cell substrates were positioned using a x-y-z manipulator under an optical microscope to bring spontaneously beating cells into direct contact with the NWFETs (Fig. 7e). This approach enabled to manipulate the PDMS/ cells substrate independently of the NWFET chip and to contact specific monolayer regions with specific devices, and subsequently change the region that is being monitored with the NWFETs. Notably, the ability to identify and register specific cellular regions over NWFET elements has not been demonstrated previously for either planar or nanoscale FET where cells have been cultured directly over device chips.

Measurement of the conductance versus time from a Si NWFET in contact with a spontaneously beating cardiomyocyte cell monolayer (Fig. 7f) yields regularly spaced peaks with a frequency of ca. 1.5 Hz and $S/N \geq 4$. Signal amplitudes that were tuned by varying device sensitivity through changes in water gate-voltage potential, V_g , showed an average calibrated voltage of 2.8 ± 0.5 mV. The calibration was further illustrated by data recorded with V_g values from -0.5 to 0.1 V (Fig. 7g), where the conductance signal amplitudes decrease from 31 to 7 nS, respectively, but the calibrated voltage, 2.9 ± 0.3 mV, remained unchanged, indicating a robust NWFET/cell interface.

Signal amplitude was further increased by using a micropipette to displace the PDMS/cells substrate at a fixed distance towards the device, Figs. 7h and 7i. A direct comparison of single peaks recorded for different ΔZ values shows a consistent monotonic increase in peak amplitudes without any observable change in peak shape or peak width over $>2\times$ change in amplitude, and that the peak width is consistent with time-scales for ion fluxes associated with ion-channel opening/closing^{28a}. A plot of the experimental results (Fig. 7j) summarizes the systematic 2.3-fold increase in conductance and calibrated voltage peak amplitude, and moreover, demonstrates that these amplitude changes are reversible for increasing and decreasing PDMS/cells displacement.

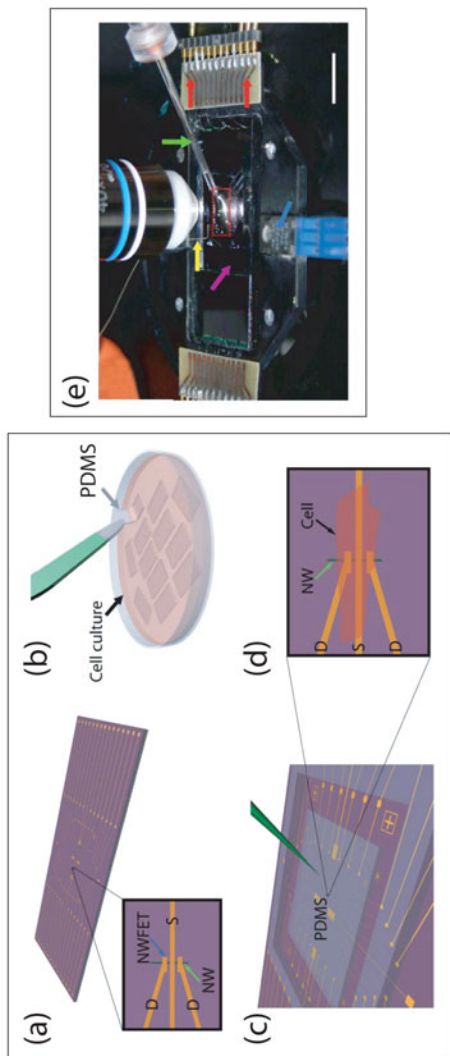


Figure 7. (A) Schematic of the experimental approach. (a) NW-FET chip, where NW devices are located at the central region of the chip. The visible linear features (gold) correspond to NW contacts and interconnect metal. Zoom-in showing a source (S) and 2 drain (D) electrodes connected to a vertically oriented NW (blue arrow) define 2 NW-FETs. (b) Cardiomyocytes cultured on thin flexible pieces of PDMS, where one piece is being removed with tweezers (green). (c) PDMS substrate with cultured cells oriented over the device region of the NW-FET chip. The green needle-like structure indicates the probe used to both manipulate the PDMS/cell substrate to specific NW device locations. (d) Schematic of a cardiomyocyte (black arrow) oriented over a NW (green arrow) device. (e) Photograph of the experimental setup showing the PDMS piece (red dashed box) on top of a NW-FET chip within a solution well that is temperature-regulated with an integrated heater (blue arrow). Additional yellow, purple, green, and red arrows highlight positions of the Ag/AgCl reference electrode, solution medium well, glass manipulator/force pipette connected to x-y-z manipulator, and plug-in connectors between NW-FET interconnect wires and measurement electronics, respectively.

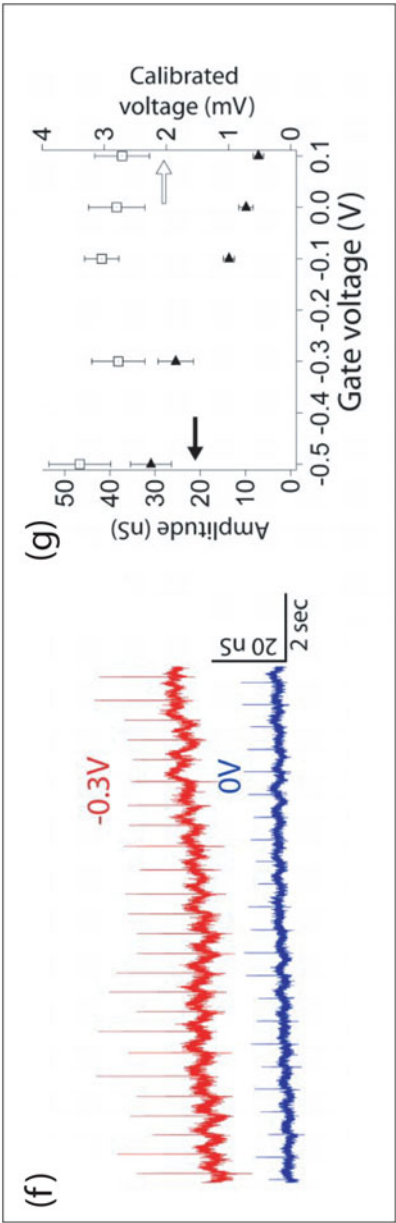


Figure 7. Continuation. (f) Conductance vs. time traces recorded at $V_g = -0.3$ V (red) and 0 V (blue) for the same NW-FET–cardiomyocyte interface; the device sensitivities at -0.3 and 0 V were 9.2 and 3.5 nS/mV, respectively. (g) Plots of peak conductance amplitude (open squares) and calibrated peak voltage amplitude (filled triangles) vs. V_g ; data were obtained from the same experiments shown in f. Error bars correspond to ± 1 SD.

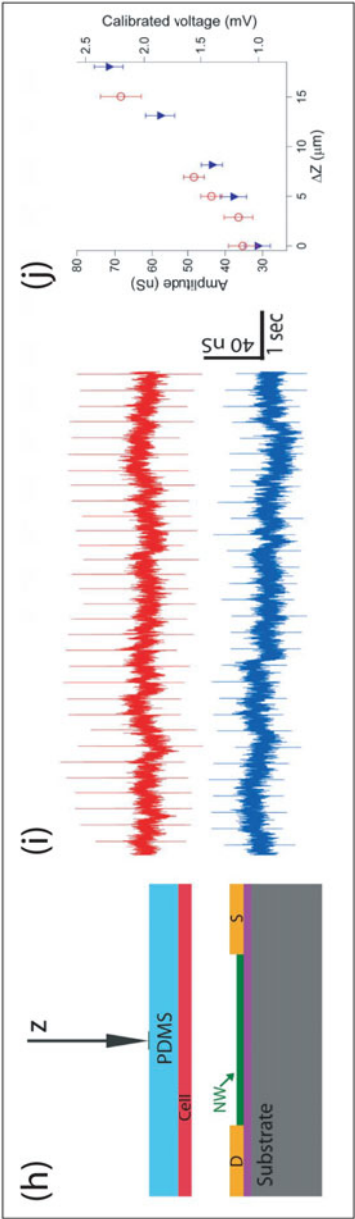


Figure 7. Continuation. Effect of applied force on recorded signals. (h) Schematic illustrating displacement (Z) of the PDMS/cell substrate with respect to a NW/FET device. (i) Two representative traces recorded with the same device for ΔZ values of 8.2 μm (blue) and 18.0 μm (red). (j) Summary of the recorded conductance signals and calibrated voltages vs. ΔZ , where the open red circles (filled blue triangles) were recorded for increasing (decreasing) ΔZ .

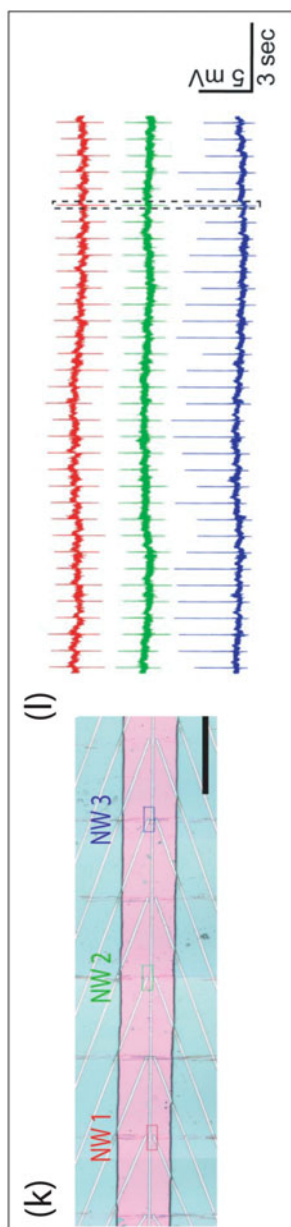


Figure 7. Continuation. Multiplexed NWFET recording. (k) Optical micrograph showing 3 NWFET devices (NW1, NW2, NW3) in a linear array, where pink indicates the area with exposed NW devices. (l) Representative conductance vs. time signals recorded simultaneously from NW1, NW2, and NW3.

Pushing the limits of PDMS/cell displacement experiments close to but below the point of cell disruption yielded peaks with average conductance amplitude of 299 ± 7 nS and corresponding calibrated signal amplitudes as large as 10.5 ± 0.2 mV. In comparison to previous studies, cardiomyocytes cultured on conventional planar FET devices have yielded peaks with S/N of 2–6 and amplitudes from 0.2–2.5 mV, which highlight this approach and the high performance of the Si-NWFET devices used.

Lastly, multiplexed measurements of NWFET devices were carried out and configured in a linear array with an average spacing of 300 μm so that signal propagation within the cardiomyocyte monolayers could be characterized. Simultaneous recordings from three NW devices in contact with spontaneously beating monolayer (Fig. 7k-l) yielded very stable and high S/N (~ 10) peaks. Using the individually characterized sensitivities for each NW, calibrated voltages with relative large magnitude of 4.6 ± 0.4 , 4.0 ± 0.3 and 5.9 ± 0.9 mV were obtained, indicating that a good junction is formed between each of the NWFETs and PDMS/cell substrate in the experiment. These results and device separations yield approximate propagation speeds of 0.07–0.21 m/s that are consistent with measurements on monolayers of neonatal rat cardiomyocytes.^{45b}

VII. NANOSCALE 3D-FLEXIBLE FET BIOPROBES

The studies reviewed here demonstrate that NW electrical devices, fabricated on rigid or flexible planar substrates, can be used for ultrasensitive detection of biological markers and high-resolution extracellular recording from cells and tissues with relevance to healthcare and medicine. However, localized and tunable 3D intracellular recording using nanoscale field-effect transistor devices, in a similar manner to glass micropipette, has never been demonstrated before.⁴⁶ The design of minimally-invasive nanoFET probe for intracellular recording applications is a significant fabrication challenge because the S (source) and D (Drain) typically dominate the overall device size and define a planar and rigid structure regardless of whether the nanoFET is on or suspended above a substrate.⁴⁷ Nevertheless, this kind of nanoFET could function as mechanically non-invasive probe capable of entering cells through endocytic pathways in a similar manner to nanoparticles.⁴⁸ Moreo-

ver, when interfacing with cells, the FETs process input/output information without the need for direct exchange with cellular ions, thus interfacial impedance and biochemical invasiveness to cells can be minimized. Lastly, it could be integrated for multiplexed intracellular measurements.

Recently, it was demonstrated that variation of reactant partial pressures during the VLS silicon nanowire (SiNW) growth could introduce reproducible 120° kinks,⁴⁹ and that the junction regions could be doped to create p-n diodes and FETs. This methodology was used to create a two-terminal FET probe in a *cis* crystal conformation that could be inserted into single cells by selective *in-situ* doping during synthesis to localize the nanoscale FET element (Figure 8a, magenta segments), and simultaneously *wire-up* the FET channel with nanowire S/D components (Fig. 8a, blue segments). The authors used heavy n^{++} -type doping for the nanowire S/D arms, and reduced the concentration to light n-type doping to introduce a short ~ 200 nm region serving as the FET detector of the overall probe.

In the next step, an unconventional nanoelectronic device fabrication approach was developed to allow these probes to be free standing. Remote electrical interconnects were made to the S/D nanowire arms on ultrathin SU-8 polymer ribbons above a sacrificial layer (Fig. 8c, upper panel). The interfacial stress between materials⁵⁰ was used to bend the probe upward after a final lift-off process (Fig. 8c, lower panel). The acute-angle kinked nanowire geometry and the extended S/D arms spatially separate the functional nanoscale FET from the bulky interconnects for a minimum interference by a distance up to ~ 30 μm , comparable to the size of single cells. The sensitivity of the 3D nanoscale FET probes was characterized and found to yield similar sensitivities to kinked nanowire devices fabricated on planar substrates.

In order to use the 3D nanoFET probes in cells (Fig. 8e, f), the negatively charged SiO_2 surface of the SiNWs was modified with unilamellar vesicles of phospholipid bilayers, which can fuse with cell membranes.⁵¹ Examination of the dye-labeled modified probes revealed a continuous shell on the acute-angle nanoprobe, and $< 1\%$ changes in both the nanoFET conductance and sensitivity.

Initially, phospholipid-modified nanoFET probe was used to monitor the calibrated potential change of an isolated HL-1 cell (Fig. 8g), clamped by a micropipette to intracellular potential of

−50 mV, showing a sharp ~52 mV drop within 250 ms after cell/tip contact. During recording, the potential maintained at a relatively constant value of ca. −46 mV, and returned to baseline when the cell was detached. Interestingly, nanoFET probes of sim-

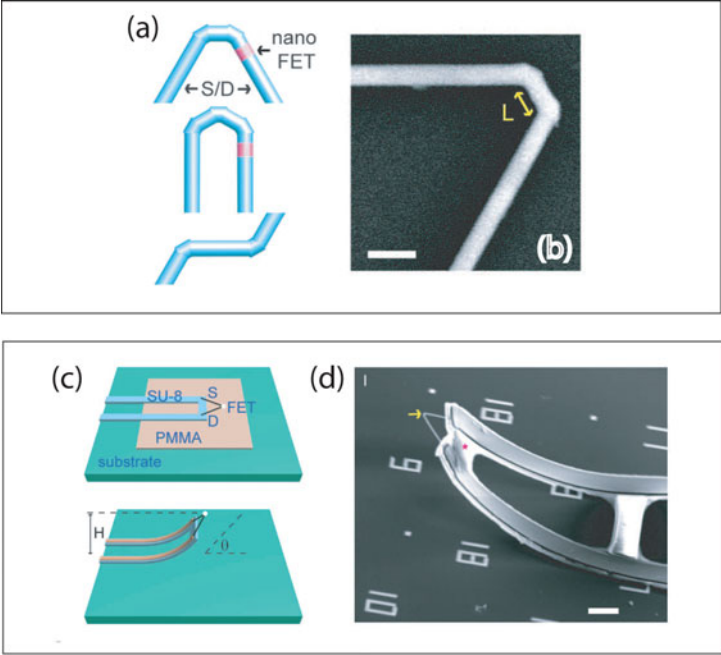


Figure 8. 3D kinked nanowire probes. (a) Schematics of 60° (top) and 0° (middle) multiply kinked nanowires and cis (top) and trans (bottom) configurations in nanowire structures. The blue and pink regions designate the source/drain (S/D) and nanoscale FET channel, respectively. (b) SEM image of a doubly kinked nanowire with a cis configuration. (c) Schematics of device fabrication. Patterned poly (methylmethacrylate) and SU-8 microribbons serve as a sacrificial layer and flexible device support, respectively. The dimensions of the lightly doped n-type silicon segment (white dots) are ~80 by 80 by 200 nm³. H and q are the tip height and orientation, respectively, and S and D designate the built-in source and drain connections to the nanoscale FET. (d) SEM image of an as-made device. The yellow arrow and pink star mark the nanoscale FET and SU-8, respectively.

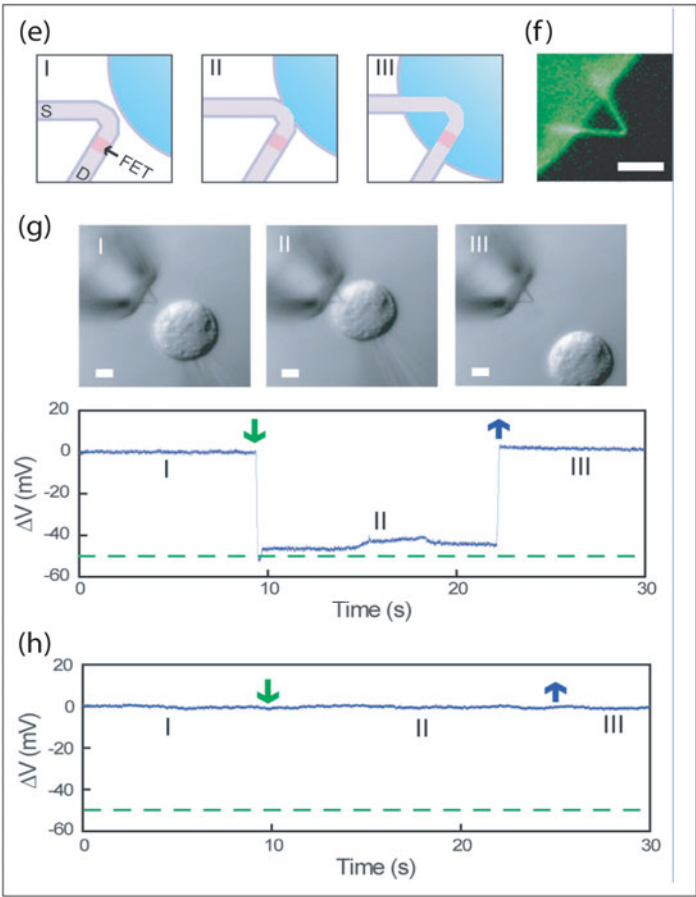
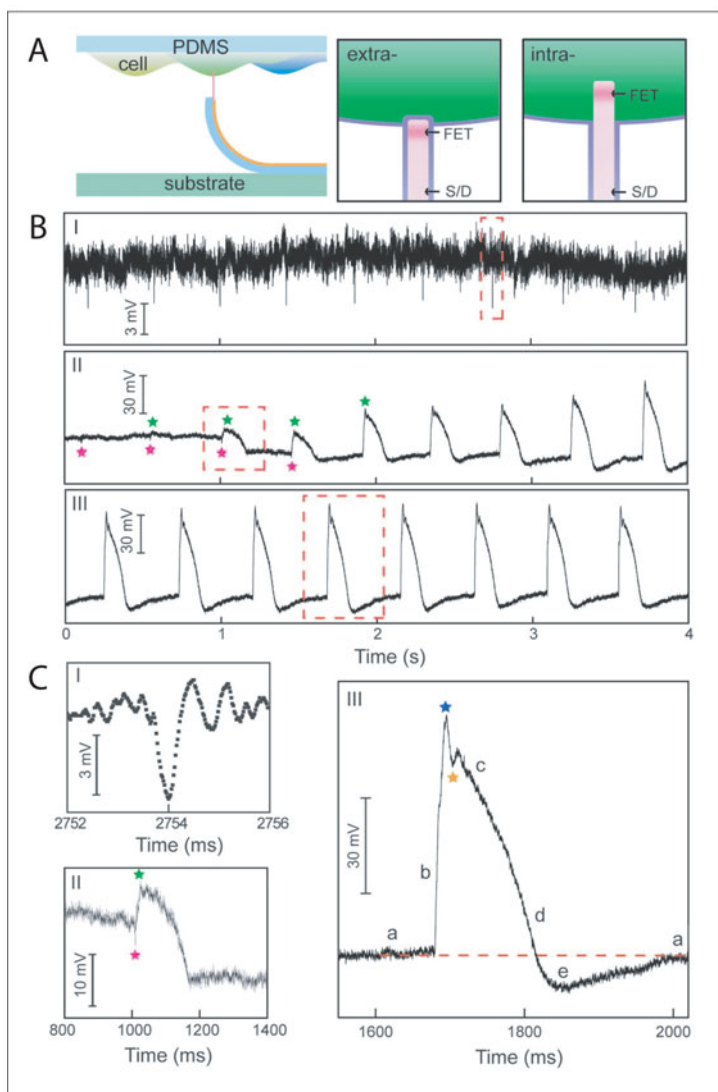


Figure 8. Continuation. (e) Schematics of nanowire probe entrance into a cell. Dark purple, light purple, pink, and blue colors denote the phospholipid bilayers, heavily doped nanowire segments, active sensor segment, and cytosol, respectively. (f) False-color fluorescence image of a lipidcoated nanowire probe. (g) Differential interference contrast microscopy images (upper panels) and electrical recording (lower panel) of an HL-1 cell and 60° kinked nanowire probe as the cell approaches (I), contacts and internalizes (II), and is retracted from (III) the nanoprobe. A pulled-glass micropipette (inner tip diameter ~ 5 mm) was used to manipulate and voltage clamp the HL-1 cell. The dashed green line corresponds to the micropipette potential. Scale bars, 5 mm. (h) Electrical recording with a 60° kinked nanowire probe without phospholipids surface modification. Green and blue arrows in (g) and (h) mark the beginnings of cell penetration and withdrawal, respectively.

when the cell was detached. Interestingly, nanoFET probes of similar sensitivity that were not coated with a phospholipid bilayer exhibited only baseline fluctuations ($< \pm 1$ mV) (Fig. 8h), suggesting that the biochemical modification is crucial for assisting access to the intracellular region, possibly through membrane fusion.

Next, the formation of intracellular interface between the 3D nanoFET probes and spontaneously beating cardiomyocytes was investigated. Embryonic chicken cardiomyocytes were cultured on PDMS substrates⁴⁴ and then positioned to place individual cells over the phospholipid bilayer-modified vertical ($\theta = 90^\circ$) nano-probes^{44,52} (Fig. 9A). Representative conductance versus time data recorded from a 3D nanoFET probed in gentle contact with a beating cell showed regularly spaced spikes with a frequency of ca. 2.3 Hz consistent with beating cardiomyocyte (Fig. 9B, I). The peaks have a potential change of ~ 3 –5 mV, $S/N \geq 2$, and a sub-millisecond width (Fig. 9C, I). The peak amplitude, shape and width have characteristics of extracellular recordings made with nanowire devices on substrates,⁴⁴ supported by optical images recorded at the same time. After a relatively brief (~ 40 s) period of extracellular signals, several pronounced changes in recorded signals were observed (Figs. 9B and C, II and III) without application of external force to the PDMS/cell support. Specifically, the initial extracellular signals gradually disappeared (Figs. 9B and B, II, magenta stars). There was a concomitant decrease in baseline potential and new peaks emerged that had an opposite sign, similar

Figure 9. Electrical recording from beating cardiomyocytes. (A) Schematics of cellular recording from the cardiomyocyte monolayer on PDMS (left) and highlight of extracellular (middle) and intracellular (right) nanowire/cell interfaces. The cell membrane and nanowire lipid coatings are marked with purple lines. (B) Electrical recording from beating cardiomyocytes: (i) extracellular recording, (ii) transition from extracellular to intracellular recordings during cellular entrance, and (iii) steady-state intracellular recording. Green and pink stars denote the peak positions of intracellular and extracellular signal components, respectively. The red-dashed boxes indicate regions selected for (C). (C) Zoom-in signals from the corresponding red-dashed square regions in (B). Blue and orange stars designate features that are possibly associated with inward sodium and outward potassium currents, respectively. The red-dashed line is the baseline corresponding to intracellular resting state.



frequency, much greater amplitude, and longer duration (Fig. 9C, II, green stars). These new peaks, which are coincident with cell beating, rapidly reached a steady state (Fig. 9C, III) with an average calibrated peak amplitude of ~ 80 mV and duration of ~ 200 ms. The amplitude, sign, and duration are near those reported for whole-cell patch clamp recordings from cardiomyocytes,^{42,53} and thus it was concluded that these data represent a transition to steady-state intracellular recording with the 3D nanowire probe. When the PDMS/cell substrate was mechanically-retracted from the 3D kinked nanowire devices, the intracellular peaks disappeared, but reappeared when the cell substrate was brought back into gentle contact with the device.

Additional work remains in order to develop this new synthetic nanoprobe as routine tool like the patch-clamp micropipette,⁵⁴ although we believe that there are already clear advantages: Electrical recording with kinked nanowire probes is relatively simple without the need for resistance or capacitance compensation,⁵⁵ the nanoprobe is chemically less invasive than pipettes as there is no solution exchange, the small size and biomimetic coating minimizes mechanical invasiveness, and the nanoFETs have high spatial and temporal resolution for recording.

VIII. CONCLUSIONS

We have shown that NW-based field-effect sensor devices represent a powerful detection platform for a broad range of biological and chemical species in solution. The examples described in this chapter show clearly the potential of NW-based field-effect sensor devices to significantly impact disease diagnosis, drug discovery, neurosciences, as well as serve as powerful new tools for research in many areas of biology and medicine. We believe that these advances could be developed at the commercial level in simple NW sensor devices and probes that would represent a clear application of nanotechnology, and, more importantly, a substantial benefit to humankind.

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