Nanowired Bioelectric Interfaces

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Abstract

Biological systems have evolved biochemical, electrical, mechanical, and genetic networks to perform essential functions across various length and time scales. High-aspect-ratio biological nanowires, such as bacterial pili and neurites, mediate many of the interactions and homeostasis in and between these networks. Synthetic materials designed to mimic the structure of biological nanowires could also incorporate similar functional properties, and exploiting this structure-function relationship has already proved fruitful in designing biointerfaces. Semiconductor nanowires are a particularly promising class of synthetic nanowires for biointerfaces, given (1) their unique optical and electronic properties and (2) high degree of synthetic control and versatility. These characteristics enable fabrication of a variety of electronic and photonic nanowire devices, allowing for the formation of well-defined, functional bioelectric interfaces at the biomolecular level to the whole-organ level. In this *Focus Review*, we first discuss the history of bioelectric interfaces with semiconductor nanowires. We next highlight several important, endogenous biological nanowires and use these as a framework to categorize semiconductor nanowire-based biointerfaces. Within this framework we then review the fundamentals of bioelectric interfaces with semiconductor nanowires, and comment on both material choice and device design to form biointerfaces spanning multiple length scales. We conclude with a discussion of areas with the potential for greatest impact using semiconductor nanowire-enabled biointerfaces in the future.

Graphical Abstract

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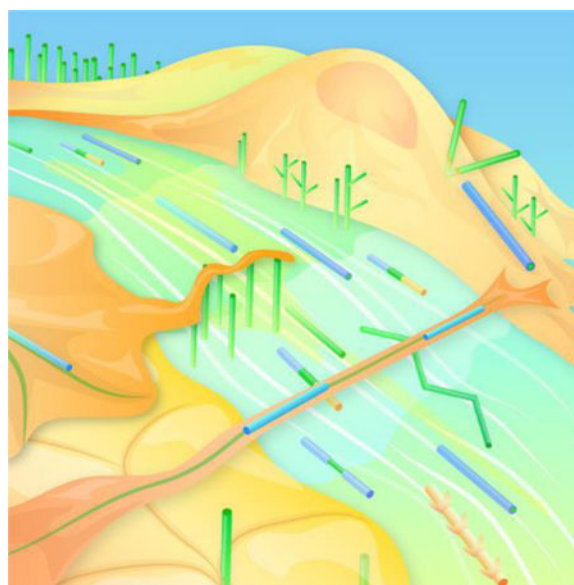
1. Introduction

Biological systems have complex chemical, physical and genetic networks, which cover multiple length and time scales.[1,2] Many of these interactions and synergies are made possible through biological nanowire structures, such as extracellular matrix fibers,[3–5] bacterial pili,[6–9] neurites,[10,11] and cytoskeletal filaments.[12–14] Aberrant transport or signal propagation along these biological nanowires can lead to cell death, tissue or organ malfunction, or diseases that are detrimental to human health.

Synthetic analogs[4,15–22] of the biological nanowires can mimic the structure and function of naturally occurring ones, and have yielded innovations in fields such as tissue engineering,[4,19] synthetic biology[17,19] and artificial machines.[17,18,20] Most synthetic analogs[4,19] display functions of topographical guidance, mechanical support or biochemical affinities. However, active functions such as sensing and modulation have been achieved with specialized materials, such as semiconductors.[21,23–25] These active properties[23–27] are uniquely suited for achieving minimally invasive bioelectronic or biophotonic devices for implants, new tools for biophysical studies, and hybrid cellular materials that are environmentally adaptable. Therefore, synthetic nanowires, particularly those of semiconductor compositions, have been extensively studied as functional biomaterials or components for biophysical signaling at the biointerfaces.[21,23–26]

A range of semiconductor nanowires has been synthesized over the past 25 years, covering group IV, group III-V, group II-VI, and metal oxide semiconductors.[25,26] These synthetic advances have led to new opportunities in biomaterial functions, bio-interfacing device configurations, and physicochemical interactions with biological components. First, nanowires with controlled variations in doping, geometry, defect distribution, and their corresponding physical properties (*e.g.*, persistence length, thermal or electrical transport), can be rationally designed and chemically produced. In particular, some of the physical

properties in nanowire structures can be qualitatively different from those found in their bulk counterparts, which allows for unique biomaterial functions in nanowires not otherwise possible in planar systems. For example, kinked silicon (Si) nanowires can be internalized into endothelial cells[28] for intracellular force dynamics recording,[29] a tool not derivable from planar Si system. Second, when combined with existing top-down micro-fabrications, these nanowire building blocks can be assembled into novel device layouts,[30,33,31–33] such as a high density array of U-shaped Si nanowire field effect transistors (FETs) where the radii of curvature can be arbitrarily controlled by the substrate topography.[33] Third, the nanowire geometries have enabled highly localized and dynamic biointerface structures, and physicochemical interactions between the semiconductor surfaces and the surfaces of the cellular components such as phospholipids and organelles.[26,34]

In this *Focus Review*, we highlight the sciences and engineering practices that are pertinent to nanowire-enabled biointerfaces. While most examples and illustrations are focused on silicon nanowires and their devices, these same concepts have also been implemented in or could be adapted in other nanowire systems for bioelectric studies. Specifically, we start with a timeline summarizing key semiconductor nanowire-enabled bioelectric interface contributions that covers diverse disciplines including recent photosynthesis[35–37] and neural engineering.[38–43] Next, we briefly discuss the important structures and roles of naturally occurring nanowires in biology. Guided by these natural nanowire examples and biomimetic concepts, we then categorize the semiconductor nanowire devices based on their functions at the biointerfaces, where the fundamentals for bioelectric interfaces will be highlighted. Additionally, we review approaches and challenges to achieving multiscale biointerfaces with semiconductor nanowire components, highlighting specialized material designs and novel device structures. Finally, we outline areas with potential for the most significant impact in this broad field in the future.

2. Historical timeline

Although the first field effect transistor (FET) was invented in the late 1940s,[44] nanowire FETs for chemical and biological sensing were only first described in 2001.[45] The subsequent implementation of nanowire-based extracellular sensors,[46,47] intracellular delivery tools,[48–50] and intracellular electrical recording tools[51–53] are all major milestones in semiconductor nanowire-enabled bioelectric tools for single cell studies, where fundamentals and applications regarding nanowire integration, bioelectric signal transduction and cellular entrance were developed (Fig. 1). Starting in the early 2010s, other important aspects of semiconductor nanowired bioelectric interfaces have been explored. [23,26,27,31,32,38–43] These include 3D electronic interfaces with synthetic tissues,[31,32] injectable devices,[27,38–40,54] minimally invasive interfaces with brains,[27,38–40,54] semiconductor-enabled photoelectrochemical synthesis from microbes,[35,41,55] and non-genetic and optically controlled neuromodulation (Fig.1).[23,26,41–43] Among these milestones, several examples are directly relevant to the advancement of the chemical synthesis of nanowires. For example, using pressure modulation,[56] kinked Si nanowires were synthesized with 120°, 60° and 0° junction angles.[51,53,56] Together with a phospholipid bilayer coating, the kinked Si nanowire-based FETs became the first solid state tools for intracellular electrophysiology, such as recording the natural beating patterns of

cardiomyocytes.[51] On the other hand, new device fabrication approaches have also enabled significant progress in biointegration. One notable example is the injectable nano-bioelectronics,[27] where the fabrication of a freestanding, macroporous and ultraflexible nanoelectronics mesh[31] is the key to achieving device delivery through capillary needle injection to yield scar-free implantation and neural integration.

3.   Naturally occurring biological nanowires

Certain microorganisms can produce protein-based microbial nanowires,[6,7,9] that have been implicated in facilitating extracellular electron transport for bioenergy utilization and the global cycling of carbon and metals (Fig. 2A). For example, the pili nanowires in *Geobacter sulfurreducens* are anchored in the cell envelope and can extend for multiple cell lengths (Fig. 2A). While more studies are still needed to improve our understanding of the electron transport facilitated by microbial nanowires, a few hypotheses such as the metallic-like conductivity model and the electron hopping model have been proposed to explain experimental observations.[6,7,8,9] These microbes either alone or in conjunction with associated nanowires can also transfer electrons to electron acceptors in minerals and yield changes in their redox states.[6,7] This has enabled electrical coupling between many species within a heterogeneous microbial system thereby promoting the exchange of energy and information. The study of microbial nanowires has broad implications in biogeochemistry, bioenergy, and bioremediation.

Other biological nanowires that facilitate bioelectric signal transduction includes axonal and dendritic projections (i.e., neurites), as well as the filopodia near their ends. A neurite is a membrane protrusion from a neuron soma, which plays critical roles in establishing excitatory and inhibitory synaptic connections among neurons in a network. At the ends of the axons and dendrites, the filopodia from the growth cones serve as the 'antennae' to probe the local bioelectric and biochemical microenvironment, and guide the neurites to their targets.

Membrane-based nanotubes[57,58] are distinct from filopodia or microbial nanowires, and they can form intercellular connections and conduits in multiple cell types, including those in the nervous[57] and immune systems[58] (Fig. 2B). These intercellular nanotubes permit chemical (*e.g.*, calcium-mediated) or particle (*e.g.*, viral particles, Fig. 2B) transmission among connected populations, and may constitute a conserved means of intercellular communication. For example, it has been shown that intercellular nanotubes allow the transfer of exogenous and endogenous prions (*i.e.*, misfolded protein particles) between infected and naïve neuronal cells[57] (Fig. 2B). This specialized intercellular connection has also been suggested as one pathway for the transmission of the human immunodeficiency virus (HIV)[58].

Cytoskeletal systems contain 3D nanowire ultrastructures (Fig. 2C).[12–14, 59] Their role is not merely a passive one where they provide structural support for cells, but instead they are dynamic and active components involved in cell migration and intracellular signaling.[12–14] Specifically, actin filaments[59] (Fig. 2C) and microtubules are structurally and functionally polarized nanowire tracks for myosin, kinesin or dynein motor proteins. Cells rely on these

intracellular transport systems to sort and shuttle molecular or nanoscopic cargo along nanowire 'highways' to targeted destinations, yielding highly organized and compartmentalized intracellular domains.[60,61] Any alteration of such cargo transport (either bidirectional or unidirectional) would cause cellular malfunction; for example, blockage of axonal transport may give rise to disorders of the central nervous system.[62,63] These cytoskeletal filaments represent a rich substrate for biological or biophysical activities within a cell, as the filaments have a large total surface area that is comparable to the area of a cell membrane.

Finally, most extracellular matrix (ECM) contains nanowire components,[3–5] such as the collagen fibers seen in connective tissues (Fig. 2D). Cells produce ECM during development, and ECM in turn plays multiple fundamental roles for cells and tissues, such as the control of cell migration, growth and survival. The ECM's chemical composition, hierarchical structures, and mechanical behaviors are all central to its interactions with cells. To achieve biochemical and mechanical homeostasis, cells constantly sense and regulate ECM components (including the nanowires and other associated molecules). Such a dynamic and closed-loop interaction is used to maintain the structural integrity and biological functionality across multiple length scales.

4. Semiconductor analogs of biological nanowires

The structures and functions of naturally occurring biological nanowires suggest multiple ways to interface biology with semiconductor nanowires, which include but are not limited to, bioelectric sensing and modulation,[25,26,35] intracellular delivery,[48–50] and biomechanical regulation of cells and tissues.[64–66] While biological materials are typically much softer and more flexible than their inorganic counterparts, the mechanical properties of semiconductor nanowires can be readily tailored to match certain aspects of biological studies.[26] For instance, Si, when made in a ~100 nm diameter nanowire form, can be stretched to ~ 16% tensile strain,[67] approaching the maximum cytoskeletal tensile strain of ~10%. Taking a different example, a Si nanowire with a ~ 5 nm diameter has an estimated persistence length (a parameter used to describe the rigidity of an elastic rod) of ~ 2 mm, which falls within the range for that of microtubule filaments (~ 1–5 mm).[26] The elasticity and bendability of the Si nanowires support the existing studies on nanowire-based electronic interfaces with biological systems.[25,68,69]

Microbial nanowires[6,7] suggest semiconductor nanowire-based bioelectric interfaces in which electrons, or more generally, charge carriers, moving through the nanowires are modulated for sensing[25] or injected into the biological systems for control of activity[23] (Fig. 3A, left). These carriers originate either from doping or from the absorption of photons,[26] suggesting the potential of using distinct types of devices, including field effect transistors[25] and photoelectrochemical devices,[26] to create the biointerface as well as sensor and/or modulated biological systems.

Intercellular nanotubes,[57,58] the lipid membrane-based conduits for highly efficient signal transduction across the intracellular domains of different cells (Fig. 2B), suggest direct intracellular delivery of molecules or particles with semiconductor nanowires (Fig. 3A,

middle). In this scenario, a semiconductor nanowire typically represents a sharp nanoscale vehicle that is minimally invasive, but sufficiently robust to penetrate the cellular barrier such as a plasma membrane. For example, bioactive molecules, including proteins and nucleic acids, have been delivered into mammalian cells by vertical nanowire arrays with surface bioconjugation.[48–50,70,71] While most current studies only use the passive roles of nanowires for this application, active properties such as a semiconductor's photoelectrochemical response or electro- or photoluminescence[26] may be leveraged for future studies to promote on-demand and programmed delivery.

The fibrous components in the ECM (Fig. 2D) and their biophysical roles[3,4] define design rules for semiconductor nanowires-based biointerfaces, where the topographical and mechanical features of nanowires alone can result in notable cellular responses[64,66,72–79] (Fig. 3A, right) such as accelerated neuritogenesis.[79] In addition to Si nanowires, many compound semiconductor nanowires[64,66,72–78] have been used for such studies, suggesting their minimal cytotoxicity and future utilities in nanowire-enabled photonic[76] or optoelectronic biointerfaces. Examples include the patterning of neural projections over indium phosphide (InP) nanowire arrays,[64] and differential growth of neurons and glial cells from gallium phosphide (GaP) nanowire arrays.[78] Moreover, studies based on non-semiconductor nanopillars[65,80–82] showed local accumulation of curvature sensing membrane proteins[81] and the deformation of the nucleus,[82] suggesting that secondary structures such as anisotropic grooves[83,84] or crystal facets[84–87] could be incorporated in semiconductor nanowired biointerfaces. Finally, the fibrous and porous ECM architecture[3,4] has also inspired the development of a class of macroporous nanoelectronic scaffolds for synthetic tissues and hybrid cellular systems.[31,32] Despite these advances, more in-depth studies are needed to fully understand the nanowires' geometry for controlling the biophysical dynamics of membrane proteins and their associated intracellular components such as cytoskeletal filaments and endoplasmic reticulum.

5. Semiconductor principles for bioelectric studies

Here we focus on the functional bioelectric interfaces enabled directly by semiconductor device properties. The FET and the diode represent the two most basic semiconductor device configurations,[26] with the former typically used for bioelectric sensing[25] and the latter for both sensing[88] and modulation.[26,37]

5.1. Nanowire FETs

A FET device (Fig. 3B) contains a semiconductor channel, source/drain/gate electrical terminals, and a gate dielectric layer.[21,26] In a nanowire FET, the semiconductor channel comes directly from the nanowire backbone, and thus the entire device fabrication involves minimum top-down lithography. For a FET, a small change in the gate-source voltage (V_{GS}) produces a significant drain-source current (I_{DS}) variation, due to either the accumulation or depletion of charge carriers near the dielectric/semiconductor interface. In a conventional FET, the gate voltage is usually applied by the gate metal electrode. However, for nanowire FETs used in chemical and biological sensing,[47] the gate metal element is unnecessary and the gate signal arises from changes in the local electrochemical potential at the nanowire

surface (Fig. 3B, upper). Three biologically relevant events can yield changes in the local electrochemical potential, including (1) a change in nanowire FET surface charges due to binding of a charged or polar molecule or biomolecule, (2) the flow of ions in cells and tissues, and (3) the change of ion gradients established across a membrane. Depending on the biological events that yield the gate potential variation, we can achieve, for example, extracellular recording of the field potentials from brain tissues[27,89] associated with ion flow, electrical monitoring of the intracellular entrance of a nanoscale object[51] due to transmembrane ion gradient, and antibody-antigen binding or molecular conformation changes,[32,90,91] which change the surface charge density.

5.1.1.   Surface charge variation—Perhaps the most obvious origin for varying the local electrochemical potential and 'gating' a nanowire FET is associated with the binding of charged ions, biomolecules or particles. In this general scenario, the electrical sensing amplitude is affected by the characteristic charge screening length as defined by the Debye-Hückel equation:

$$\lambda_{D} = \frac{1}{\sqrt{4\pi l_{B} \sum_{i} \rho_{i} z_{i}^{2}}},$$

where l_{B} is the Bjerrum length, ρ_{i} is the mean concentration of i-th ion, and z_{i} is the integer charge number for the same ion. The Debye-Hückel length defines a limit within which the electrical recording of charged species with an FET is effective due to incomplete electrostatic screening by other ions. Under physiological conditions, the screening by the surface-absorbed counterions is ~ 0.7 nm. Given the intrinsic diffusion kinetics of the analytes, as well as the finite size of the surface modification layer, researchers have adopted several approaches to enhance the nanowire FET-based biomolecular sensing in ionic aqueous solutions.[32,90–94] For example, aqueous solutions with low ion concentrations, which are not typical of physiological conditions, have been used for the real-time sensing of proteins[92,93] and virus[94] particles such that the Debye length is larger than size of the species being detected. Alternatively, specialized FET surface functionalizations[32,90,91] that can yield local increase of effective screening length,[90] have enabled sufficient electrical gating effect for detection even under physiological conditions.

5.1.2.   Dynamic ion flow—Ion flows can yield endogenous bioelectric fields and a heterogeneous electrochemical potential distribution in the extracellular space, and moreover, these field variation can occur on multiple biological length scales such as at a larger scale of interstitial tissue spaces or much smaller scale of intercellular junctions.[26] The extracellular bioelectric potential can be quantified using Poisson's equation:[95]

$$\varphi(x', y', z') = \frac{1}{4\pi\sigma} \int \frac{I_{v}(x, y, z)}{r(x, y, z, x', y', z')} dxdydz,$$

where $\varphi(x',y',z')$ denotes the bioelectric potential at (x',y',z') location, σ is the electrical conductivity of the saline, I_{v} is the ionic current at (x,y,z), and $r(x,y,z,x',y',z')$ is the distance between two points in the space, (x,y,z) and (x',y',z').[26] With Poisson's equation, also it is

possible to define design and experimental methods for nanowire-based FET sensing. For instance, to maximize the amplitude of φ, the conductivity σ could be reduced by decreasing the mobility of the ions contributing to conduction and/or by increasing the local current I_v. These goals can achieved by reducing the distance between a FET sensor device and the ionic current sources, such as an excitable cell membrane or tissue wound site, by mechanical manipulation[96,97] or design of the nanowire surface topography.[51,88]

5.1.3.   Ion concentration gradient—Ion concentration differences yield trans-membrane or Nernst potentials, given by the Goldman-Hodgkin-Katz equation for the limit of a total current density of zero:

$$V_m = \frac{RT}{F} \ln \frac{\displaystyle\sum_i^N P_{M_i^+}\left[M_i^+\right]_{\text{out}} + \sum_j^M P_{A_j^-}\left[A_j^-\right]_{\text{in}}}{\displaystyle\sum_i^N P_{M_i^+}\left[M_i^+\right]_{\text{in}} + \sum_j^M P_{A_j^-}\left[A_j^-\right]_{\text{out}}},$$

where V_m is the Nernst potential, R and F are the ideal gas constant and the Faraday constant, respectively, T is the absolute temperature, and P_{M^+} and $[M^+]$ represent the permeability and concentration of an M^+ ion, respectively.[26] For the sake of simplicity, only monovalent ions are considered here. A nanowire FET device can measure changes in the ion concentration gradient, which yield variations of the intracellular potential exemplified by recording the dynamics of beating cardiomyocyte cells.[51,53]

5.2.   Nanowire diodes

The second class of nanowire devices is based on the diode junctions (Fig. 3C), where it is possible to synthesize junctions rationally in the nanowire axial or radial direction.[98–101] When a p-type and an n-type semiconductor are brought into contact, a built-in electrical field (Fig. 3C, lower) is established at the thermodynamic equilibrium to balance the diffusion of majority carriers: electrons for n-type and holes for p-type semiconductors, respectively. While this built-in electrical field is typically buried in planar semiconductor devices, it can be modulated by electrochemical potential in nanowire configurations[88] given their high surface-to-volume ratio. Moreover, nanowire diodes have been used for optoelectronics such as photovoltaic devices,[98–101] light emitting diodes (LEDs)[102] or even lasers.[102,103] In particular, near a photovoltaic junction (Fig. 3C, lower), light produces electron–hole pairs and yields quasi-Fermi levels,[26] E_F (e) for electrons and E_F (h) for holes, respectively, with an energy difference of eV_{ph}. The photo-generated carriers can yield a photocurrent I_{ph}, which is capable of modulating cellular activity through either capacitive or Faradaic processes (Fig. 3C, upper).[26]

6.   Multiscale bioelectric interfaces

Biological systems are hierarchical and spans many length scales, which sets a key design criteria for nanowired bioelectric interfaces. A unique aspect of nanowire devices is the

capacity to achieve highly localized sensing or modulation. This is mainly due to the precise synthetic control over the material structure and function using nanocluster catalyzed vapor-liquid-solid growth. For example, n-type/intrinsic/n-type[51] or p-type/n-type[88] kinked nanowires have been used to achieve highly localized electrical recording from cardiomyocytes, where the length and width of the FET intrinsic Si[51,104] or diode depletion region[88] of the sensors can be precisely controlled at the nanometer scale, matching the size of an organelle or even individual ion channels.

Given these controllable nanoscale interfaces in nanowire-based devices, which are a challenge for most planar semiconductor-based devices, the scaleup to mesoscopic and macroscopic multi-nanodevices levels can be realized through nanowire assembly,[30,105] device layout designs,[31] and mechanical manipulation.[31] Such multiscale biointerfaces allow for simultaneous probing of multiple cellular events in 3D with high spatiotemporal resolution, thereby suggesting future studies at the systems level.

6. 1.   Intracellular level

6. 1. 1.   Substrate-bound nanowires—One powerful aspect of nanowire-based bioelectronics is their capacity to facilitate intracellular recording.[51–53,88,106–109] Intracellular electrical signals are typically measured with microelectrodes, such as a patch clamp pipette. However, the size of these traditional electrodes cannot be scaled down to the nanometer level given fundamental limits of junction impedance scaling for electrochemical tools.[21] On the other hand, semiconductor devices can operate at the nanometer size regime without performance losses, and combined with synthetic control of nanowire geometry, cellular penetration is also possible.[51,52,88,106] For example, in conjunction with the surface modification of phospholipid bilayers, kinked nanowire FETs allowed cellular entrance through membrane fusion, with concomitant electrical recordings of internalized devices. [51,88] This synthetically-enabled point-like solid-state sensor records intracellular electrophysiology, with minimal chemical or mechanical invasiveness as expected for traditional microelectrodes. Besides membrane fusion or processes relevant to mechanical 'abrasion', electroporation[108] and optoporation[110] can assist with the cellular entrance of substrate-bound devices.

6. 1. 2.   Freestanding nanowires—In addition to substrate-bound devices, substrate-free semiconductor nanowires have been used for multiple intracellular studies, upon active cellular internalization. For example, Lee *et al.* showed that surface functionalization with trans-activating transcriptional activator (TAT) cell-penetrating peptides enabled Si nanowire internalization into both primary hippocampal and dorsal root ganglion (DRG) neurons (Fig. 4A), taking ~ 30–40 min upon nanowire-cell contact.[111] Without such TAT peptides, nanowire entrance into neurons was not observed.[28,43,111]

Specialized cells, such as macrophages and endothelial cells, have evolved to internalize foreign objects through phagocytic processes.[112,113] This mechanism has been leveraged for the cellular entry of non-functionalized silicon nanowires into endothelial cells, smooth muscle cells, multiple cancer cells, and glial cells.[24, 39] Zimmerman *et al.* have used a set of quantitative matrices and multiple drug assays to demonstrate Si nanowire internalization by

human umbilical vein endothelial cells (HUVECs).[28] In another recent study, Jiang *et al.* studied Si nanowire distribution in a co-culture of DRG and associated satellite glia.[43] Statistical analysis showed that ~ 87% of the nanowires in the regions of interest were colocalized with glia, ~ 3% with neurons, and ~ 10% were in the extracellular region (Fig. 4B). Perinucleus clustering of the overlapped nanowires, instead of random distributions, confirmed the active uptake of these nanowires into the glia.[43]

Upon internalization, guided active intracellular transport[28] enabled by motor proteins as well as uncontrolled cytoskeletal entanglement[29] of nanowires took place, allowing for the probing of many intracellular processes. For example, Zimmerman *et al.* used internalized kinked Si nanowires to probe intracellular force dynamics,[29] where the nanowire kink and tip served as anchoring points to enable effective bending of nanowires as opposed to in-plane or out-of-plane rotations. As semiconductor nanowires can yield photothermal and photoelectrochemical effects, active control of intracellular processes with nanowires has been vigorously pursued. Recently, Jiang *et al.* studied the optical activation of glia with internalized nanocrystalline and intrinsic nanowires[43] (Fig. 4C). Upon laser illumination, the targeted glial cell with intracellular nanowire displayed a fast concentration ramp for calcium ions followed by a gradual recovery. The calcium dynamics from a single glial cell could be controlled repetitively, suggesting a minimal invasiveness of this intracellular modulation approach.[43] Additionally, the triggered intracellular calcium signals from the glia can propagate to neighboring glia and DRG neurons, forming intercellular calcium waves (Fig. 4C). In this study, the targeted nanowires produced a photothermal effect upon laser excitation, which could either elicit reactive oxygen species (ROS)[114] or transiently depolarize/perforate intracellular membranes,[115] either of which can trigger the cytosolic calcium release from its organelle reservoirs, such as the endoplasmic reticulum and mitochondria. In addition to the intracellular calcium level control, the photothermal response of nanowires also produced a photoacoustic effect, which was used to bend and break cytoskeletal bundles inside single cells.[43]

Because internalized Si nanowires show active transport along cytoskeletal filaments, the trajectory of the nanowires may yield interesting intracellular behavior. Jiang *et al.* simultaneously probed a single nanowire trajectory in a glial filopodium and the nearby calcium concentration, following a remote optical initiation of a calcium flux by a different nanowire within a glial network (Fig. 4D). This work suggested that calcium ions can trigger directional transport of intracellular cargo, based on the correlated local calcium and nanowire dynamics. Moreover, mean-squared displacement (MSD) analysis (Fig. 4D, right) revealed a calcium-dependent change of the nanowire transport modes from random or restricted diffusion at low or base intracellular calcium levels, and an active transport at an elevated calcium level.

6. 2. Single cell extracellular level

Since the time of the initial studies of electrical sensing of pH and proteins,[45] Si nanowire FETs have been actively pursued as extracellular recording tools (Fig. 5). The primary difficulty in recording cells as opposed to pH or molecules is that the nanowire/cell junction gap size (or the cleft size) can critically influence the recorded signal shape and amplitude.

[21,26] However, there are multiple methods to address this issue. First, decoupling the cell culture substrate from the device substrate independently controls the cell viability and device quality, and more importantly, establishes a precise biointerface in a subsequent mechanical manipulation step.[96] Cohen-Karni *et al.* demonstrated this idea by first culturing cardiomyocytes on a polydimethylsiloxane (PDMS) substrate, then aligning and pressing the cells over Si nanowire FET arrays with a micromanipulator (Fig. 5A).[96] The recorded signal amplitudes were highly dependent on the biointerface location and the pressure applied onto the PDMS backplane (Figs. 5B and 5C). Second, surface modification of the nanowire FET components, including the nanowire, source-drain electrode passivation layers and/or the substrate, has been used to attract cells as well as to reduce the cleft size.[46,116] For example, studies of functionalized gold mushroom microelectrodes suggest the feasibility of this surface approach.[116] Third, device geometry designs, including the use of sharp kinked nanowire and vertical structures as well as peripheral device components, such as a cellular cages[117] or guiding scaffolds,[118–120] can also help to achieve tight and more deterministic extracellular interfaces.

In addition to electrical sensing, nanowires have recently been used for the non-genetic optical modulation of single cell bioelectric activity through either photothermal or photoelectrochemical mechanisms.[23,26,41–43,121] The development of optogenetic approaches to cellular modulation is fueling substantial progress in neuroscience research, for example, allowing circuits to be spatiotemporally manipulated and functionally probed with unprecedented precision.[122–124] Despite ongoing efforts and significant progress in some areas[125–127] these tools are generally difficult to implement in larger-brained mammals, particularly non-human primates (NHPs). Therefore, several groups have pursued non-genetic alternatives with nanomaterials. Jiang *et al.* synthesized mesoporous Si nanowire bundles by the nanocasting method and measured a fast photothermal response to visible and near-infrared light.[41] Optical stimulation using 532 nm laser pulses demonstrated that these porous silicon particles can generate spike trains in dorsal root ganglia neurons up to 20 Hz.[41]

In addition, Parameswaran *et al.* used coaxial p-i-n Si nanowires consisting of a p-doped core, and intrinsic and n-doped shells,[42] to photoelectrochemically modulate primary rat DRG neuron excitability (Figs. 5D–5F). With a laser flash at a neuron-Si nanowire interface, photogenerated electrons move towards the n-type shell and holes move to the p-type core (Fig. 3C). The photocathodic process at the n-shell surface[42] can locally depolarize a target neuron, eliciting action potentials (Fig. 3C, Fig. 5D and Fig. 5E). The presence of atomic Au on the nanowire surface likely played the role of a catalyst in traditional photoelectrochemical devices, yielding a neural excitation behavior similar to that from electrochemical stimulation (Fig. 5F). These results suggest that Si nanowires can serve as an inorganic, biocompatible, biodegradable, non-genetic alternatives to optogenetics for wireless neuromodulation. Recently, Parameswaran *et al.* has extended this approach in arrays of coaxial p-i-n Si nanowires over a polymer mesh, and demonstrated photoelectrochemical stimulation and training of cardiocyocytes.[119]

Another process relevant to non-genetic biological modulation, and perhaps the closest functional analog to the microbial nanowires, is the solar-driven biofuel production through

semiconductor nanowire-enabled microbial interfaces.[35–37] For example, Liu *et al.* demonstrated that CO_2 reduction at neutral pH could be accomplished with an integrated semiconductor nanowire-bacteria system. Such solar-driven biosynthesis platforms can produce valuable products, such as polymers and complex pharmaceutical precursors.[35] Through a photoelectrochemical process, the Si nanowire array delivers reducing equivalents to the anaerobic bacterium *Sporomusa ovata*, which produces acetic acid with high efficiency. The resulting acetate can next be converted into value-added chemicals, such as n-butanol and polyhydroxybutyrate (PHB) by genetically-engineered *Escherichia coli*.[35] Interfacing biocompatible semiconductors with biological components therefore provides a new platform for programmable photosynthesis.[35,55,128,129]

6. 3. Synthetic tissue level

As a natural extension of the single-cell level interfaces, nanowire FETs or freestanding nanowires have been utilized for sensing[89,97] and stimulation[119] from tissue samples *ex vivo*, including high-density electrical recording from brain slices[89] and photoelectrochemical modulation of isolated hearts.[119] Here we focus solely on the discussion of synthetic tissues (Fig. 6), a fundamentally different approach that highlights the bottom-up construction of multiscale biointerfaces and holds the potential for seamless biointegration, thus achieving a new level of synthetic biology.

Conceptually, this electronically-active synthetic tissue construction involves four steps (Fig. 6A).[31] First, nanoscale building blocks, such as kinked or straight Si nanowires, are synthesized to incorporated desired electronic and/or photonic properties. Second, individual electronic components, such as FETs or electrical stimulators are aligned, for example into a parallel or U-shaped arrays,[30,105] and connected using either e-beam lithography or photolithography to provide access to individual device components. Third, the individual device components are organized into a flexible and macroporous scaffold containing the semiconductor devices and insulated metal interconnects. The macroporous bio-nanoelectronic scaffold can also be combined with conventional biomaterials used for tissue engineering, such as collagen or alginate hydrogel, or electrospun poly(lactic-co-glycolic acid) (PLGA) fibers (Fig. 6B). This nanoelectronics scaffold can mimic the dimensions and mechanical properties of the naturally occurring extracellular matrix.[4,31,130] Finally, cells are seeded into the scaffold for maturation, after which the engineered 3D tissues are integrated with the embedded nanoelectronics used for in-situ sensing and stimulation (Fig. 6C). This platform has been utilized to record and manipulate the electrophysiology of 3D tissues in real time. For example, the scaffold enabled the mapping of conduction pathways and the evolution of action potentials (Fig. 6D) in developing cardiac tissue with sub-millisecond resolution, in 3D.[31,32] As a proof-of-concept demonstration of hybrid cellular devices for potential implants, an engineered vascular tissue construct was fabricated (Fig. 6E) to sense the pH level of different saline solutions that were running through the vessel lumen (Fig. 6F).[31]

A key to achieving these nanoelectronics-innervated synthetic tissues is the design and fabrication of fibrous and macroporous nanoelectronics. While the initial studies only used a simple folding or bending approach to achieve the 3D architecture from planar freestanding

devices, other methods, such as controlled bucking,[131] 3D printing,[132–135] and origami/ Kirigami[131,136] also hold promise for more complex structures. Additionally, the starting molecular and subcellular length scales should be considered for targeted biointegration. For example, previous work[137] suggested that the different size dependence of chemical, electrostatic, mechanical and thermal energy terms lead to convergence at the molecular and subcellular length scales. At these scales, there would be fewer barriers for the energy exchange among different energy terms. Therefore, the boundary between biological and non-biological components, and the boundary between hard and soft materials, both become blurred.[26] Understanding this basic principle would allow us to select the best material dimensions, device geometry and physical properties for exploring future unknowns in the realm of synthetic tissues.

6. 4. Live animal level

Semiconductor nanowire-based nanoelectronics can enable synthetic interfaces with biological cells and tissues. However, in order for these devices to translate ultimately to a clinical setting, they must be delivered to tissues within the body[27,38–40,54,138] through minimally-invasive implantation procedures, and also exhibit durability without foreign-body immune response over their intended lifetime.

A new class of devices, injectable mesh electronics, has recently been developed[27,38–40,54,139] that offers promise in meeting these constraints. While the initial device elements of injectable electronics consist of semiconductor nanowires[27,31,140], a similar delivery system has been adopted for metal electrodes[27,31,140] and would be suitable for metal nanowires, 2D nanomaterials, and conducting polymers/hydrogels in the future. The freestanding mesh design[27,31] has enabled the following major advances. First, the open mesh structure, which was based upon the macroporous scaffold designs discussed above,[31] has significantly reduced the weight and the bending stiffness of the device, such that simple application of pressure could incorporate and then deliver an electronic recording system into the brain (Fig. 7A). In the study by Liu *et al.*, glass needles with outer diameters on the scale of hundreds of micrometers were used to inject the mesh device arrays (Fig. 7B) into the lateral ventricle and hippocampus of live mice[27]. The inputs/outputs of the probe were connected to a flexible flat cable using conductive ink, which was then folded and attached to the dorsal surface of the animal's cranium. This delivery method reduces the invasiveness of the surgery since the dimensions of the cranial window that are needed are much smaller than those used for delivering other recording platforms (Fig. 7A). Second, the mesh device has a tissue scaffold-like open framework, allowing for the neural regrowth and network formation across the device after implantation. Such a 3D and interpenetrated biointerface would also suggest a future hybrid biomedical device, where synthetic and naturally-occurring functions can be integrated in a closed loop. Third, the lacey mesh structure reduces the general feature size of the entire device down to a sub-micrometer level. This, together with the low device bending stiffness and the minimal physical barrier for neural regrowth, has yielded significantly fewer immune responses (Fig. 7C).[27,54] Finally, the lightweight and flexible device backbone suggests a faithful contact between the electronic sites and the cell bodies, producing an "always moving with the brain" biointerface during normal body motion in contrast to stiffer probes.

Chronic recordings from the somatosensory cortex of freely behaving mice have shown that mesh nanoelectronics yield reliable measurements of neural activity upon injection (Figs. 7D and 7E).[38] Principal component analysis of the recorded data suggests that with this mesh configuration it was possible to, unprecedentedly, track the activity of individual neurons up to 34 weeks.[38] Additionally, Fu *et al.* designed mesh electronics that can perform both chronic recording and stimulation via the incorporation of low impedance electrodes. Modified probe geometries, including cylindrical configurations with built-in strains,[140] have also been developed for injectable mesh electronics. Work by Xie *et al.* demonstrated that this configuration permitted easy integration of the freestanding Si nanowire FET probes to the printed circuit board, as the end of the flexible probe remained attached to the silicon substrate. Freezing of the cylindrical probe in liquid nitrogen produced a transient increase in device rigidity, such that the devices could penetrate the rodent brains by simple stereotaxic surgery.[140] The minimally invasive administration and seamless integration of mesh nanoelectronics into brains can provide revolutionary opportunities for fundamental and neuroscience and biomedical research and may one day lead to implants that monitor and modulate patient health.

7. Future outlook

While semiconductor nanowired biointerfaces have mimicked biological signaling in several remarkable ways, the unique semiconductor functions and numerous device configurations suggest many untapped future opportunities in both fundamental studies and translation applications. We expect that future research may yield important breakthroughs, especially in fundamental biophysical studies (Fig. 8A), precision medicine (Fig. 8B) and synthetic biology (Fig. 8C) through (1) the design and implementation of biomimetic semiconductor-based materials and devices that display cellular specificity, (2) the in-depth probing of developmental, physiological and bioelectric aspects of cellular interactions, and (3) the innovation of new hybrid or composite materials where multiple signaling pathways, both biological and non-biological, can be integrated in a seamless manner.

7.1. Organelle biophysics

Intracellular signal transduction is the basis of various biological activities and cellular processes.[52,61,62,141,142] Traditionally, our understanding of the intracellular dynamics has been limited to biological, chemical and genetic interactions. However, over the last several decades studies have demonstrated that cells also employ electrical[143–157] and mechanical[142,158–162] signals for subcellular level communication. These signals can be manifested as a transient voltage variation across an intracellular membrane[144,145] or as a force transduction across a cytoskeleton network.[142] Despite significant progress in optical imaging, most biophysical questions at the organelle level are still unresolved. This highlights the opportunities for semiconductor-based biointerfaces because these systems can be designed to display ample device configurations and biophysical signal transduction mechanisms. Only nanoscale-sized semiconductors are feasible because their spatial dimensions are similar to the macromolecular assemblies that are crucial for function and signal transduction[31,51,163] in organelles.

Taking bioelectric studies as an example, semiconductor nanowires could be used to target and subsequently probe cytoskeletal filaments, mitochondria, and endoplasmic reticulum (ER), and study their unknown bioelectric behaviors (Fig. 8A). Cytoskeletal filaments are promising because recent theoretical studies suggest that these polar filaments can be a key source of intracellular bioelectric heterogeneity.[147,148,164] Mitochondria also represent a good target as they contain an enzymatic series of electron donors and acceptors.[165–168] The ER is where protein folding occurs; bioelectric modulation of ER redox states may yield changes in the concentration of unfolded proteins and the level of cellular stresses that are related to hypoxia/ischemia and insulin resistance, etc. Semiconductor nanowire devices can provide new tools to test these hypotheses, to revise and/or formulate new hypotheses based on previously inaccessible data, and even to study the bioelectric interaction networks (*i.e.*, interactome) among different organelles and their impact on gene expression and intracellular cargo transport.

7.2. Precision electronic medicine

Electronic sensing and stimulation methods are crucial tools for investigating biological and medical questions, such as the functional organization of the neocortex, which in humans constitutes ~80% of the brain by mass. In mice, optogenetic photostimulation approaches are fueling great progress in fundamental neural circuitry and disease mechanism studies, but these tools have proven difficult to implement in larger-brained mammals. In addition, conventional electrode-based electrical methods still have many drawbacks such as mechanical invasiveness and a lack of cellular selectivity. These limitations in the conditional methods have significantly impeded the development of personalized medical interventions for patients who suffer from neuropsychiatric and neurodegenerative disorders, or impaired functioning due to trauma or amputation.

Recent development of "tissue-like" mesh electronics[27,31] and other relevant platforms can produce a cellular level, minimally invasive, and chronic biointerface to the brain.[27,38–40,54] With nanowire surface modification and topography optimization, or control of the electrochemical processes from associated electronic components, these tissue-like implants could produce a bidirectional electrical interface that targets specific cell types and is uniquely tailored for individual human subjects (Fig. 8B). With feedback control, these biointegrated electronics systems may allow for the precise diagnosis and coordinated delivery of medical intervention to patients with a wide range of phenotypes.

7.3. Synthetic biology

Synthetic biology traditionally refers to the reprogramming of cells with unusual biological functions, relying heavily on genetic engineering.[169–172] Synthetic biology focuses on constructive approaches to probing and controlling biological components. To use synthetic biology for potential biomedical applications, one would need to improve the reliability of the individual parts and cellular circuits, avoid adverse effects, and enhance the performance of engineered cells *in vivo*. Monitoring the output of cellular circuits in traditional synthetic biology relies largely on fluorescent proteins, which can be slow and is prone to errors. To advance the field of synthetic biology, new concepts and tools are needed for fast, minimally invasive, reliable and real-time monitoring and delivery of the outputs/inputs for more

diverse cellular circuits. Additionally, it is especially important to establish multiplexed inputs and outputs for tuning and characterizing the dynamic and stochastic behavior of different synthetic circuits. In this regard, the field could benefit from non-biological components from which many orthogonal signals can be delivered into a single biological system.

Similar to the biological counterparts, the use of semiconductor nanowires to regulate and monitor cellular activities, and to establish an internal feedback loop, such as a negative auto-regulatory network, is feasible and could lead to transformative discoveries (Fig. 8C). The ability to create bioelectric and/or biophotonic interfaces within cells may also suggest new ways of constructing responsive and adaptive cellular machines for translational biomedical research.[31,173–176] We believe that the merger of nanowires and their associated devices in nanoelectronics and nanophotonics,[177,178] with the current practices of synthetic biology, promises to yield major leaps in materials research, biophysics, bioengineering and hybrid information processing.[170–172,179,180] Last, these ideas for synthetic biology also couple directly at the ultimate subcellular scale to the suggestions above for precision electronic medicine. Synthetic nanowired biointerfaces, which are enabled by rich emerging and seamlessly-integrated hybrid building blocks, provide a pathway towards numerous fundamental research and translational medicine area that can be fruitful for many decades, and to a level well beyond what natural biological nanowires reach!

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Biography

Bozhi Tian received his Ph.D. degree in physical chemistry from Harvard University in 2010. He is an associate professor at the University of Chicago, working on semiconductor-enabled fundamental studies of subcellular biophysics and soft matter dynamics. Dr. Tian's accolades from his independent career include the Inaugural ETH Materials Research Prize for Young Investigators (2017), Presidential Early Career Awards for Scientists and Engineers (2016), and TR35 honoree (2012).

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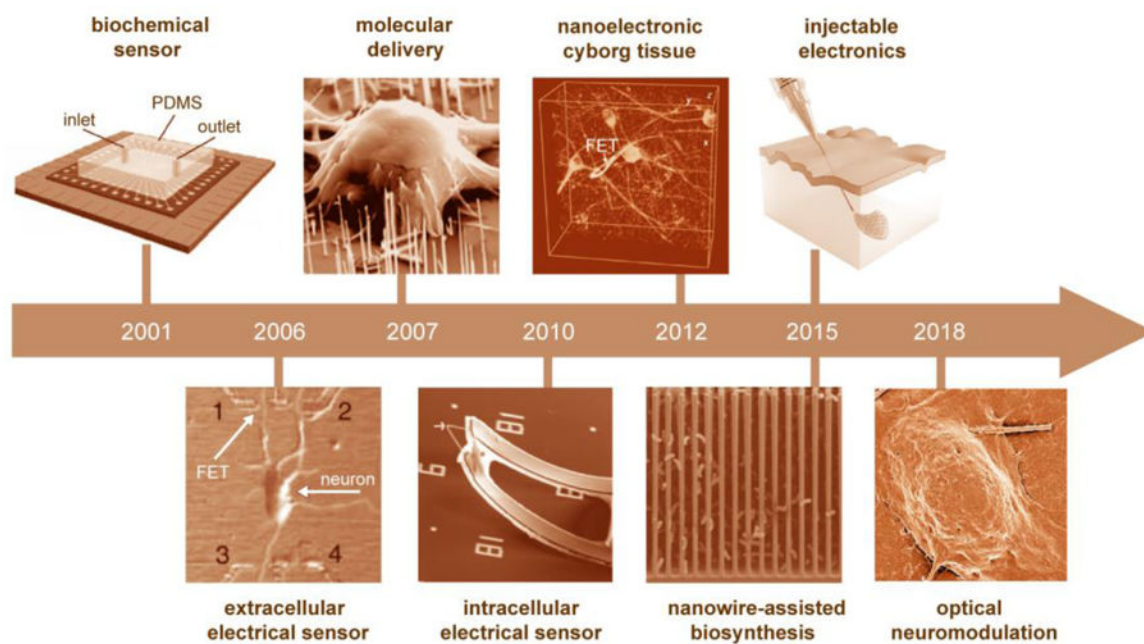
Figure 1. Timeline of semiconductor nanowire-enabled biointerfaces.
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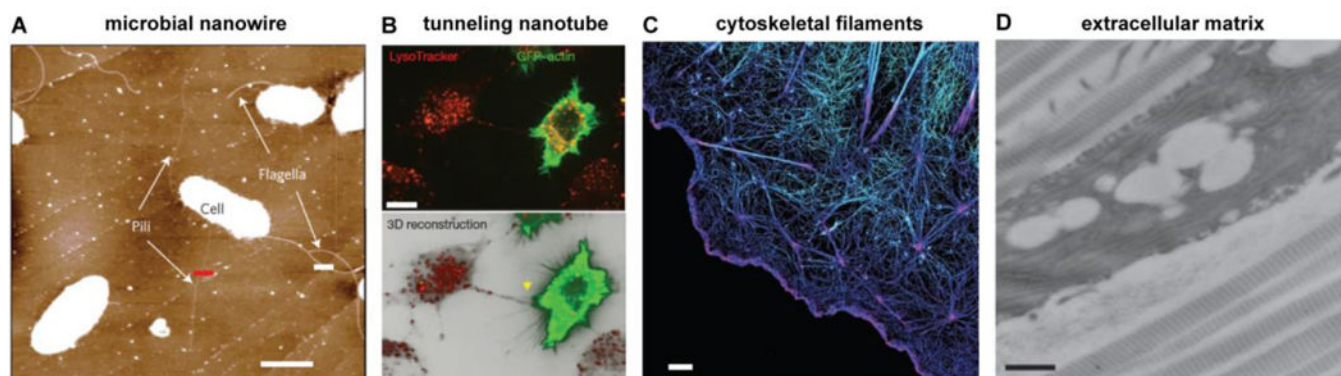
Figure 2. Naturally occurring nanowires.
(**A**) AFM image of *G. sulfurreducens* cells with pili and flagella filaments, used for charge propagation studies. Scale bar, 1 μm. Reprinted with permission from ref 9, Copyright 2014 Nature Publishing Group. (B) Intercellular tunneling nanowires (yellow arrow), showing transfer of LysoTracker labeled vesicles between untransfected cells and CAD cells transfected with GFP-actin. This study suggests that tunneling nanotubes may be important in the spreading of prions within neurons in the CNS and PNS. Scale bar, 10 μm. Reprinted with permission from ref 57, Copyright 2009 Nature Publishing Group. (C) Dual-objective stochastic optical reconstruction microscopy (STORM) image of actin in a BSC-1 cell, showing 3D networks with distinct organizations in sheet-like cellular protrusions. Other cytoskeletal structures, such as microtubules and intermediate filaments have also been studied with super-resolution imaging extensively. Scale bar, 2 μm. Reprinted with permission from ref 59, Copyright 2012 Nature Publishing Group. (D) A TEM image of a tendon fibroblast flanked by D-periodic collagen fibrils. These fibrils are the major tensile elements in vertebrate tissues. Scale bar, 500 nm. Reprinted with permission from ref 5, Copyright 2013 Nature Publishing Group.
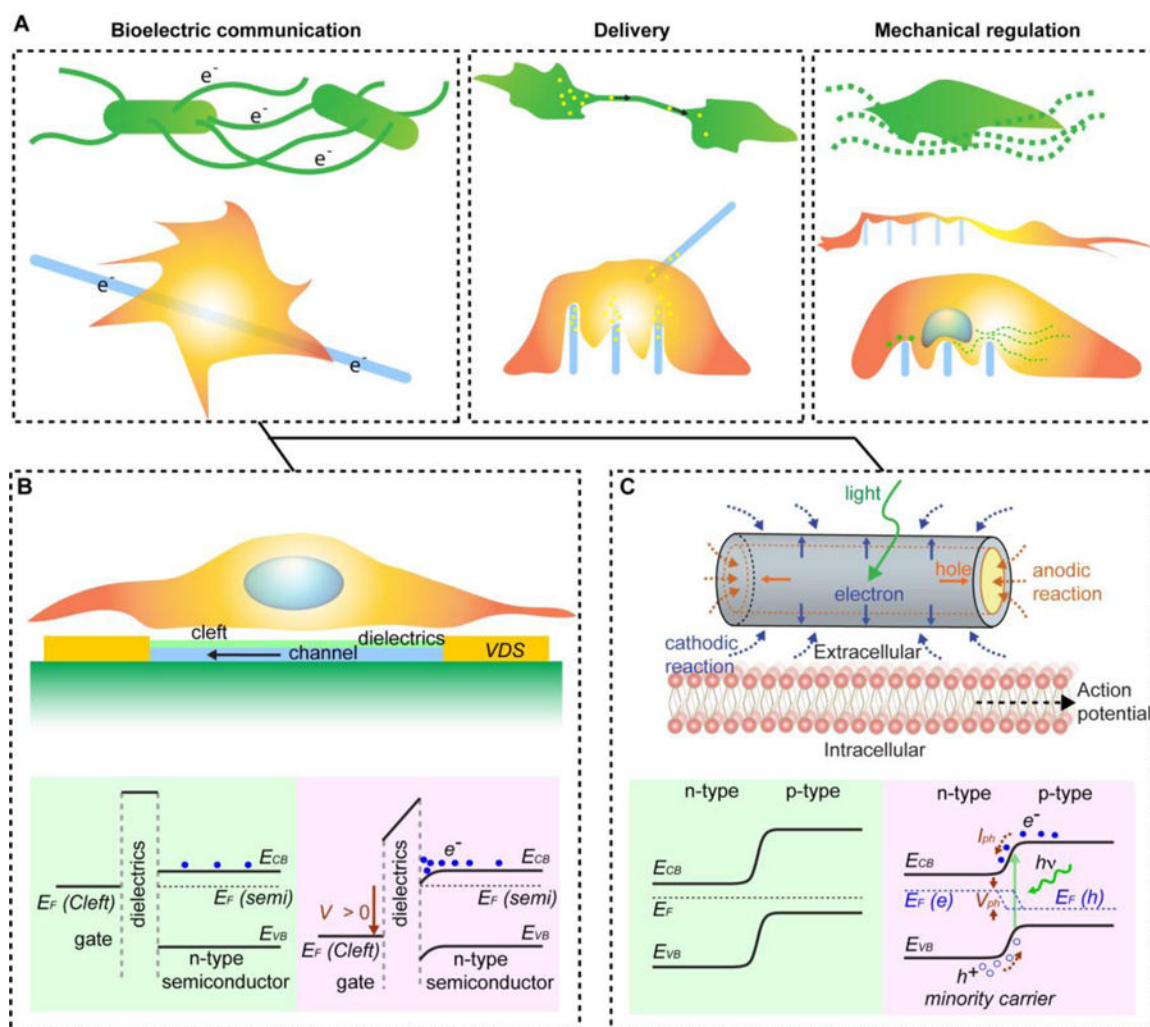
Figure 3. Semiconductor analogs of biological nanowires.
(**A**) Semiconductor nanowires for bioelectric sensing and stimulation (left), molecular delivery (middle) and mechanical regulation (right). The upper schematics show the structures and roles of naturally occurring nanowires, while the lower ones highlight either the current or the future biointerface studies enabled by semiconductor nanowires. Schematic diagrams and operation principles for (**B**) nanowire FET sensor, and (**C**) nanowire photoelectrochemical stimulator.
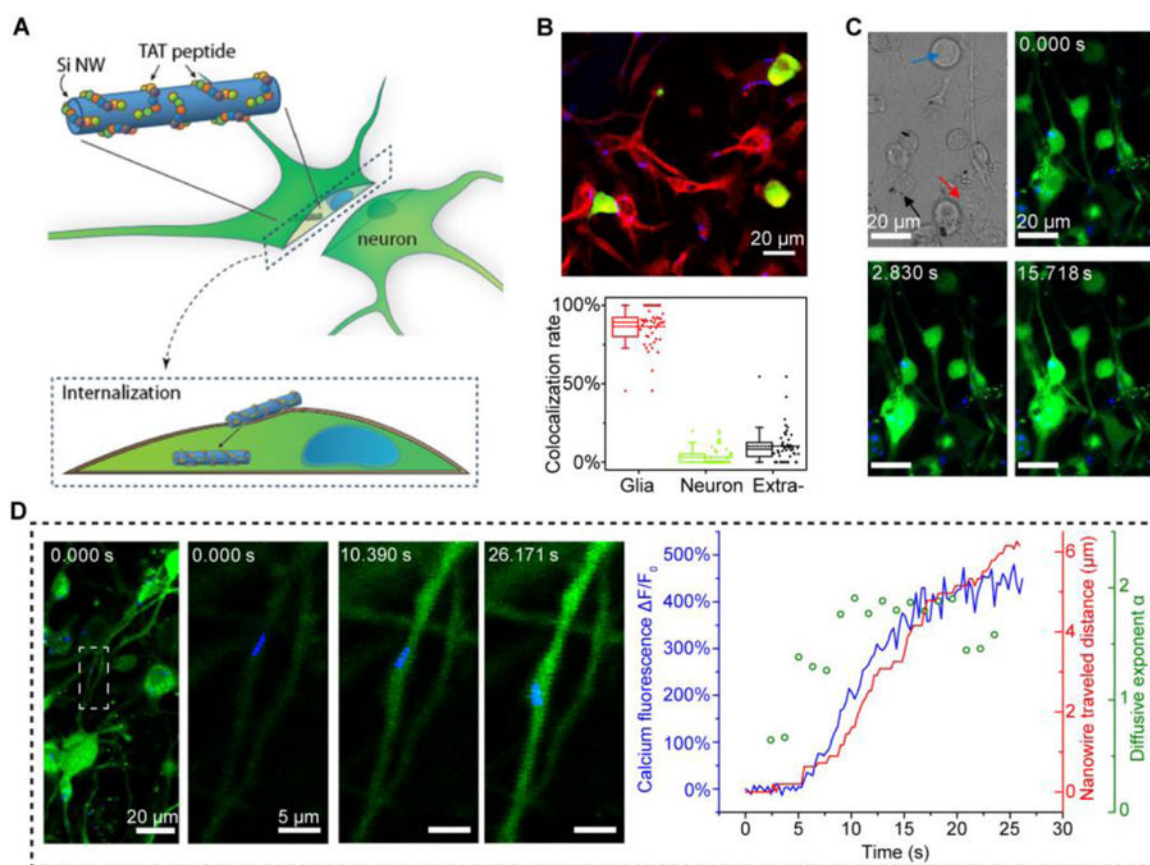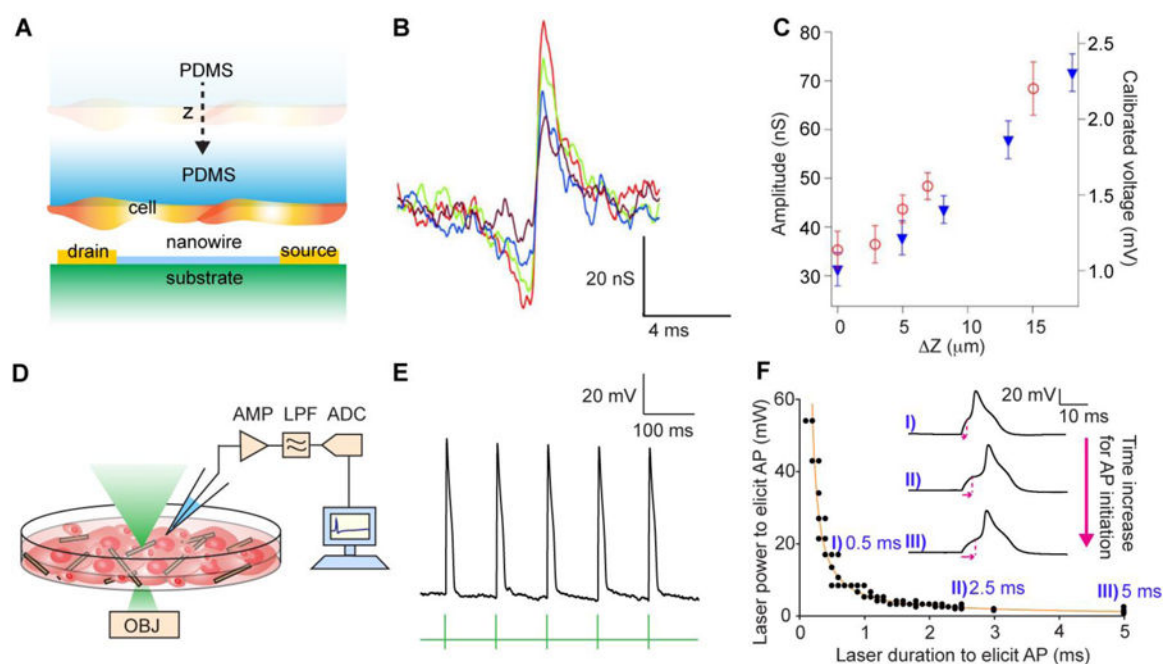
Figure 4. Intracellular biointerfaces.
(**A**) TAT peptide enables neuronal internalization of Si nanowires. Without surface modification, neurons won't internalize the nanowires. Reprinted with permission from ref 111, Copyright 2016 American Chemical Society. (**B**) A confocal microscope image (top), showing that glial cells use phagocytosis for Si nanowire internalization. DRG neurons and glial cells are labeled in green and red, respectively. Statistical analysis (bottom) reveals that ~ 87% of total nanowires overlap with glial cells, ~ 3% with DRG neurons, and ~ 10% left extracellularly. (**C**) Internalized Si nanowires in glia can excite adjacent neurons upon light stimulation. (**D**) Internalized Si nanowires allowed cytoskeletal transport studies. The nanowire location in a glial protrusion is tracked while the nearby calcium dynamics is monitored simultaneously, following a remote optical initiation of a calcium flux (green, calcium; blue, Si nanowires). The white dashed box shows the region for the intracellular transport study. Time series images show a calcium-correlated motion of the Si nanowire. Mean-squared displacement (MSD) analysis suggests a transition from restricted diffusion to active transport where motor proteins are involved. **B-D** are Reprinted with permission from ref 43, Copyright 2018 Nature Publishing Group.
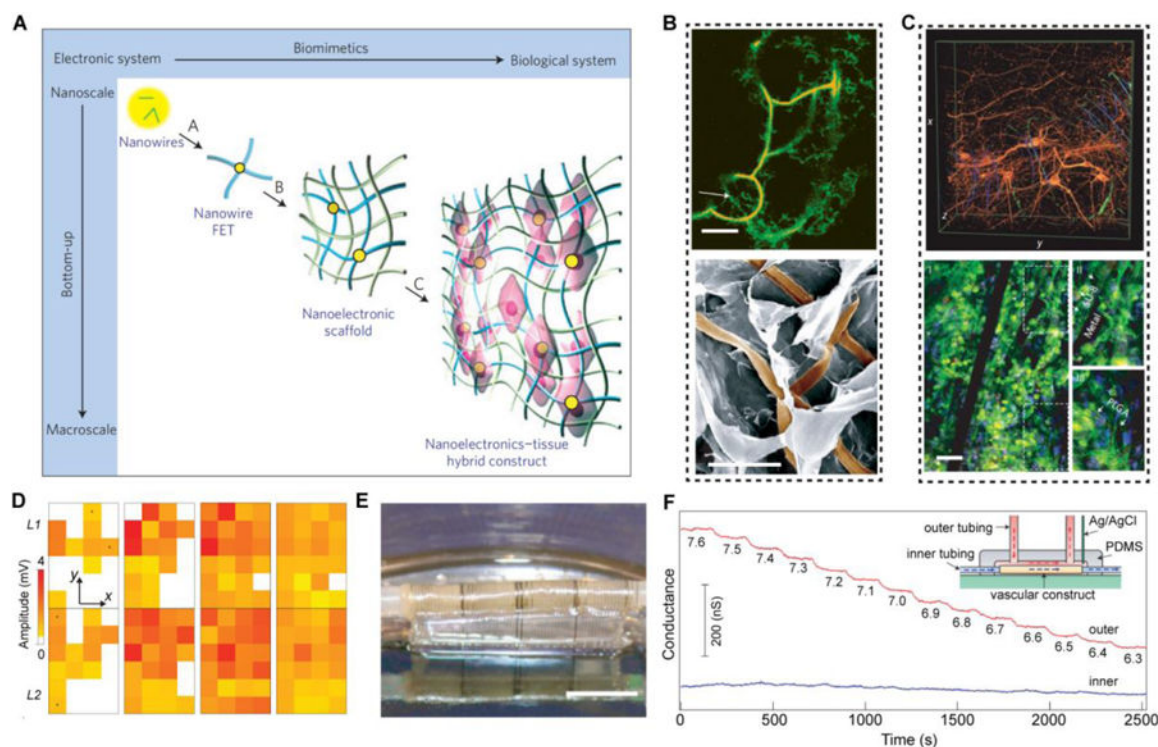
Figure 5. Single cell extracellular interfaces.
(**A-C**) Electrical recording from cultured cardiomyocytes. The cells were manipulated through PDMS substrate to establish a physical contact with the FET device (**A**). The amplitude of the recorded signals is dependent on the position change along Z (**B** and **C**). Traces are shown for Z at 0 μm (purple), 8.2 μm (blue), 13.1 μm (green), and 18.0 μm (red), with a corresponding signal increase from 31 to 72 nS. **B** and **C** are (**D-F**) Photoelectrochemical stimulation of DRG neurons with p-i-n coaxial Si nanowires. The nanowires are deposited onto DRG neuron surface in a drug-like manner (**D**). Optical excitation of the neuron/Si nanowire interface yielded deterministic control of neural firing patterns (**E**). Optical excitation curve confirmed the neural modulation mechanism is photoelectrochemical, instead of photothermal (**F**). **D-F** are Reprinted with permission from ref 42, Copyright 2018 Nature Publishing Group.

Figure 6. Synthetic tissue interfaces.
(**A**) Bottom-up approach for nanoelectronics-innervated synthetic tissues. This approach yields an integrated hybrid cellular system from discrete electronic and biological building blocks, such as kinked Si nanowires. The electronic components can be either sensors or stimulators for potential closed-loop feedback control. (**B**) Synthetic scaffolds with Si nanowire FETs. A confocal fluorescence micrograph (upper) of a reticular nanoelectronics scaffold (orange) with collagen hydrogels (green), suggests a similar dimension of a Si nanowire FET (white arrow) and the collagen filaments. A SEM image (lower) of a mesh nanoelectronics hybridized with macroporous alginate structures, shows the epoxy ribbons from mesh (brown) used to support the electrical interconnects to nanowire FETs. Scale bars, 10 μm (upper) and 100 μm (lower). (**C**) Confocal fluorescence micrographs of synthetic neural and cardiac tissues with Si FETs. (**D**) 3D Si nanowire FET scaffold can be used for studying action potential (AP) evolution during the cellular development and maturation. The maps show the amplitudes of the spontaneous extracellular APs, recorded from 4 X 6 FET arrays in two layers (*L1* and *L2*) at 2, 4, 6 and 8 days in vitro (DIV). White squares denote locations where extracellular APs are below the detection limit. (**E-F**) Synthetic vascular tissues (**E**) with Si nanowire pH sensors (**F**) near the lumen. The pH sensing was done in a microfluidic system with both inner and outer tubing systems. **A-C**, **E** and **F** are Reprinted with permission from ref 31, Copyright 2012 Nature Publishing Group. **D** is Reprinted with permission from ref 32, Copyright 2016 Nature Publishing Group.
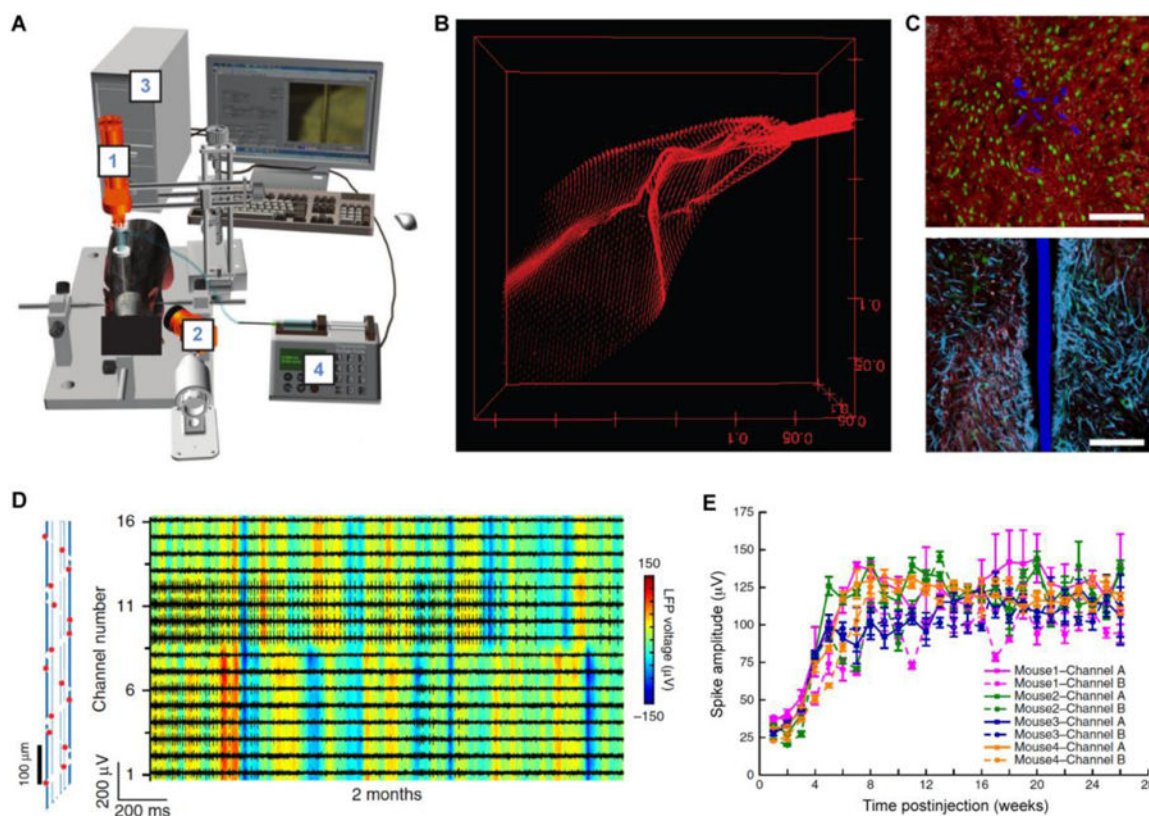
Figure 7. Injectable nano-bioelectronics for brain interfaces.
(**A**) **Schematic of the stereotaxic surgery station.** To position the needle into the targeted brain region, a motorized stereotaxic frame (**1**) with attached pipette holder is employed. An objective lens and a camera (**2**) are used for imaging the needle position, with images displayed on a computer monitor (**3**). For precise injection of the device and the saline, a syringe pump (**4**) is used. (**B**) A confocal fluorescence micrograph of a mesh nanoelectronics emerging from the tip (upper right) of a ca. 100 μm diameter needle. Reprinted with permission from ref 27, Copyright 2015 Nature Publishing Group. (**C**) The open framework of the mesh nanoelectronic device array yields minimal inflammatory immune response (upper), as compared with the response from a flexible thin-film probe. Color labels: neuron soma (NeuN, green), axon neurofilaments (NF, red), and reactive astrocytes (GFAP, cyan). Scale bars, 100 μm. (**D**) Representative 16-channel local field potential (LFP; heat map) with amplitudes color-coded according to the color bar on the far right from a mouse at 2 month post-injection. The high-pass filtered single-unit traces (sharp black spikes) are overlayed. The *y*-axis denotes the recording electrode index, with relative position marked by red dots on the schematic (leftmost). (**E**) Time evolution of average spike amplitudes of representative channels from four different mice, showing reproducible stable recordings up to 26 weeks. **D** and **E** are reprinted with permission from ref 38, Copyright 2016 Nature Publishing Group.
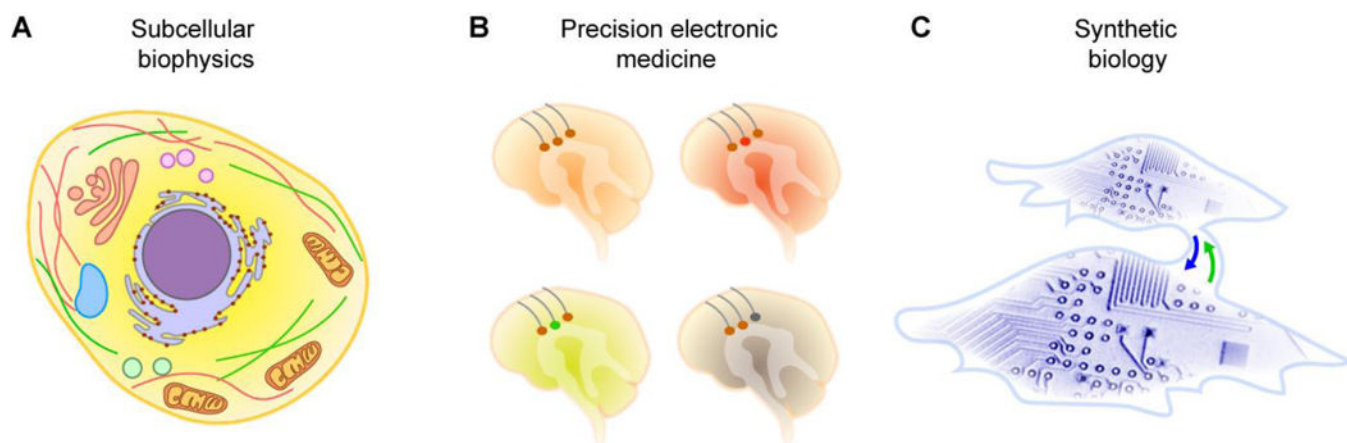
Figure 8. Future outlook.
Untapped future opportunities for fundamental studies and biomedical translation in the areas of (**A**) fundamental biophysical studies, (**B**) precision medicine and (**C**) and synthetic biology.