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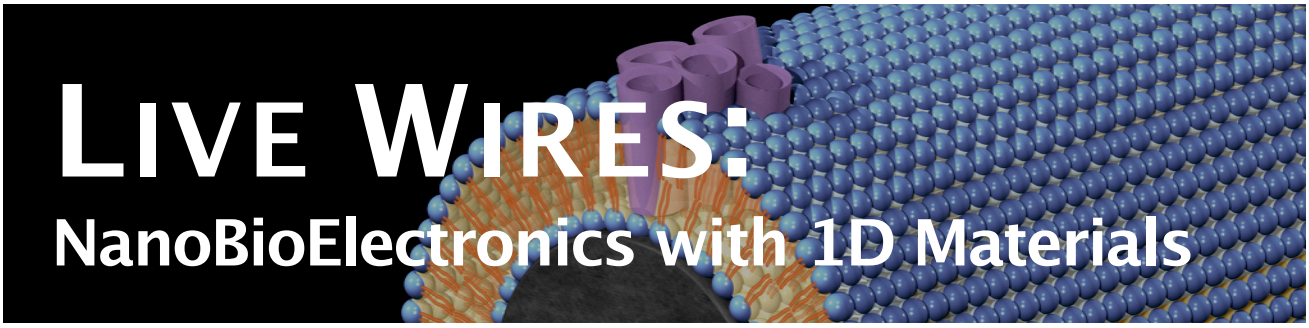

LIVE WIRES: NanoBioElectronics with 1D Materials

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Rapid progress in materials science and nanoscience and electrical engineering has led to the development of nanoelectronic platforms that have devices and components whose size and sensitivity comparable to the main elements of the biological systems. These developments open up an exciting possibility of building integrated systems in which electronic and biological components function side-by-side. However, to realize this vision of bionanoelectronics, researchers need to overcome a number of challenges ranging from materials incompatibility to drastic differences in operation principles. Fortunately, recent developments in biosensing, and device-level and tissue-level integrations have started to address these challenges.

Bionanoelectronics: Making a true biointerface

Even a quick glance at the modern world reveals a place where we coexist with an increasingly large number of machines and devices that assist us in most everyday tasks. The human body uses a large number of self-repairing and self-replicating machines driven by the ATP hydrolysis, currents of ions and small molecules, and cascades of protein interactions to generate motion, signaling, thought, and emotions [1]. Remarkably, the technology that we have built around us is based on

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similar design principles [2] yet uses completely different materials platform- man-made structures use inorganic materials, electron currents, and electric fields, and power themselves with fossil fuels or stored electrical energy. A reasonable explanation is that these differences represent the specialization necessary to achieve peak performance for a required task. After all, an F-22 fighter jet, that arguably represents one of the pinnacles of modern industrial engineering, can reach speeds of 1,600 mph, which easily bests the still impressive 125 mph top speed of the fastest bird (peregrine falcon). On the other hand, one of the world's biggest and fastest computers (IBM Blue GeneL) has computational and memory capacity comparable to that of the brain of a single rat, which is only 1/500 of the average human brain capacity [3].

Still, it is undeniable that utilizing some of the principles and components developed by the biological systems in *bioelectronic* devices could lead to a paradigm-shifting advances in biotechnology, medicine, and even artificial intelligence, computing and robotics. The contrasting ways of information handling in biological and man-made systems represent an obstacle for the practical realization of this vision of bionanoelectronics, and to overcome it we need to develop a versatile nanointerface that integrates enzymes, ion channels, and protein pumps with micro- and nanoelectronic circuitry. This interface should satisfy several main criteria: (1) it needs to let biomolecules operate as close to their natural state as possible, since this is what the evolution optimized them for; (2) it has to be efficient to minimize losses and enable efficient communication between the biological and inorganic components; (3) it has to be simple and versatile to achieve substantial technological impact without incurring prohibitive overall costs.

The early works on capacitive stimulation of live cells [4] and monitoring neuronal activity of cells using large-area silicon field-effect transistors [5] tested these ideas; however the materials platform was still inadequate for the task and the devices were too big and insufficiently sensitive. Discovery of one-dimensional inorganic materials, such as carbon nanotubes and silicon nanowires, had provided researchers with an opportunity to construct electronic interfaces (6-8) with components whose sizes are comparable to the size of biological molecules,

potentially leading to a much more efficient interface. One-dimensional nanomaterials also present two distinct length scales that are advantageous for assembling and building novel bio-nanoelectronic architectures. Nanometer cross-section of nanotubes and nanowires gives them enhanced surface sensitivity, and allows them to utilize the benefits of size effects, such as quantization and single-molecule sensitivity. At the same time, long axial dimensions of these materials, that can vary from a few tens of nanometers to several hundred micrometers and even millimeters [6], simplifies manipulation and assembly into functional devices, and enables macroscopic controls and readouts.

Integration of biological molecules into the 1D nanoscale platforms also raises an interesting set of basic scientific questions: we still know rather little about the basic principles that guide assembly and stability of bionanostructures at extreme curvatures [7], as well as the very ability of the biomolecules to interact with electronic elements. We will discuss some of the current efforts on building bionanoelectronic interfaces, their device use, as well as advances in our understanding of these interfaces.

The Building Blocks

Proteins: Motors, Relays, Channels, and Pumps. Despite having access only to a limited number of chemical building blocks such as 20 amino-acids and a few other chemical groups, biological systems have evolved a vast arsenal of protein machines that perform functions as diverse as protein synthesis and degradation, light capture and emission, locomotion, ion transport, and signal transduction. It is virtually impossible to provide a concise review of the smorgasbord of biological components available for the bionanoelectronics toolkit; therefore we refer the reader to the many excellent textbooks available on this subject [1].

1D Materials: Nanowires and Carbon Nanotubes. Development of 1D nanomaterials was initially motivated by the problems that continue to arise as downscaling of existing microelectronics driven by the Moore's Law has started to approach physical limits. These new types of materials have quickly found uses well

beyond conventional electronics. The two most important (and so far the most developed) classes of 1D materials are carbon nanotubes and inorganic semiconductor nanowires [8]. Carbon nanotubes, which are simple graphene sheets rolled up to form a tube [9], have excellent electrical properties [10, 11] that rival the best metals and semiconductors, which led to enormous progress in the fabrication of high-performance single nanotube transistors [12, 13] and nanotube thin-film devices [14] in the past decade. Semiconductor nanowires, which represent solid semiconductor rods, beams, or ribbons with two of the three dimensions in the ~100nm range or smaller, form a library of electronic and photonic building blocks that includes Group IV – Si and Ge nanowires, Group III-V InAs, GaAs, GaN nanowires, Group II-VI CdS, CdSe, ZnSe nanowires, and metal oxide nanowires such as ZnO and SnO_2. Controllable doping also allows nanowires to form nanoscale junctions critical for building high-performance electronics [15, 16]. Heterostructured nanowires utilizing the band offsets of different semiconductor materials have also emerged as an exciting extension of these materials [17], bringing to the nanoscale the superior electronic transport properties created by bandgap mismatch. Enhanced electronic transport properties have been confirmed in Si/Ge [18] and InAs/InP [17] core-shell nanowires.

Design, Assembly Strategies, and Configurations

Covalent Attachment. Regardless of the intended application, interfacing nanomaterials with biomolecules and cells is not straightforward, especially if the functionalities of both components have to be preserved. Cellular machinery functions best in salty water, which represents a less-than-ideal environment for electronic devices. Graphitic surfaces of carbon nanotubes and silicon oxide surfaces of Si nanowires readily bind biomolecules through strong π-π, hydrophobic, or ionic interactions; however these forces are often strong enough to alter conformations of biomolecules, and easily destroy delicate structures and obliterate their functions. Notably, substrate curvature also plays a role in stability and activity of proteins, though the outcome seems to be case-specific and less

predictable [19]. Clearly, some cushioning and protection approaches for both sides of the assembly are necessary.

Several approaches to surface functionalization of nanomaterials for biological applications exist. Covalent modification of native oxide using alkoxysilane derivatives and formation of self-assembled monolayers with linker moieties at the end is a common first step in fabrication of Si nanowire devices [20]. When the oxide layer is undesirable, it can be etched away with HF, leaving hydrogen-terminated Si surface, which can subsequently react with terminal olefin groups to form stable covalent Si-C bonds [21, 22]. Graphitic sidewalls of carbon nanotubes are highly resistant to covalent modifications and require high-energy treatments such as oxidation, fluorination, radical, carbene or diazonium chemistry to disrupt the graphite lattice [21].

Covalent functionalization does not significantly change electronic characteristics of Si nanowires due to their relatively large diameters (>10 nm). The situation is different for carbon nanotubes, where all atoms are on the surface. Nanotube electronic properties originate in the sp^2 structure of graphitic carbon, and inclusion of even small number of sp^3 sites along the nanotube can affect electronic properties and deteriorate device performance [22]. But sometimes formation of a single defect site through well-controlled removal of one or two atoms could create a precisely positioned bottleneck for electron transport, which could be used to study of dynamics of single biomolecules with high temporal resolution [23, 24].

Functional Integration with lipid membranes and membrane proteins: 1D lipid bilayers, assembly and physical properties. Although covalent modifications, described in the previous section, give researchers versatile tools for attaching biological functionality to the 1D materials, they at best provide only a chemical "anchor" without giving any additional capability to orient the molecule or to facilitate its function. Natural systems, in stark contrast, use structured environments, such as lipid membrane support and organize a large number of membrane proteins and receptors that can perform a host of functions ranging from

ion transport to signal transduction [1]. Functionalization of nanotubes and nanowires with lipid bilayers represents a robust and general strategy for using membrane proteins in nanobioelectronic devices. Lipid bilayers are virtually impermeable to ions and large molecules [25, 26], which makes them also suitable as a natural barrier that prevents non-specific adsorption, as well as a natural electrical insulator.

Lipid bilayers in two-dimensional (2D) planar geometries [27] as well as quasi-zero-dimensional (0D) geometries [28] are well-known; however common phospholipids do not spontaneously form 1D tubular structures in aqueous solutions unless they are forced into a metastable configuration by an external force [29-31]. Cylindrical lipid tubes ranging from 20 nm to 500 nm in diameter can also form spontaneously when the structure and shape of lipid molecules are carefully designed, such as in case of galactosylceramides, [32] and diacetylenic lipids [33]. The key to forming a lipid bilayer on a highly curved support surface of a 1-D nanomaterial is to make sure that the energy of the interactions of that surface with the lipid bilayer can counterbalance the elastic energy of the bilayer deformation [34]. Artyukhin et. al. demonstrated that lipid vesicle fusion on carbon nanotubes modified with several hydrophilic polymer layers produces a continuous lipid bilayer shell (1D bilayer) around the nanotube [35] (Figure 3C), and Huang et. al. showed that a similar lipid bilayer shell could assemble around a hydrophilic polysilicon nanowire without any polymer cushion layer [34] (Figure 3E). Lipid bilayer shells can also assemble on a larger nanowire structures, such as SnO2 nanowire waveguides [36] (Figure 3D). Another approach for building carbon nanotube-lipid hybrids involves placing the nanotube on a hydrophilic surface and then fusing lipid vesicles on that surface, as initially demonstrated by Zhou et. al. [37] (Figure 3F). Small dimensions of carbon nanotube ensure that the lipid bilayer can simply cover over the carbon nanotube without breaking the bilayer structure [38].

Bilayer fluidity, i.e. the ability of the lipid molecules to diffuse freely in the bilayer plane [27], is key to its stability, defect healing, and membrane protein incorporation. It is reasonable to expect that significant deformation of the bilayer

imposed by a nanotube and nanowire template would influence its fluidity and have a negative impact on the electrical properties of the assembly. Noy and co-workers used Fluorescence Recovery After Photobleaching (FRAP) experiments to investigate the bilayer fluidity in the 1D configuration on both nanotube and nanowire substrates (Figure 4). They measured in-plane diffusion coefficients of 2-4·10^{-11} cm^2/s for lipid bilayers adsorbed on polymer layer-modified carbon nanotubes [35]. This value is almost two orders of magnitude slower than the values observed for planar supported lipid bilayers on polymer substrates [39], which could reflect a large degree of bilayer imperfection on these substrates as well as strong charge-charge interactions of lipid headgroups with the polymer. Significantly variable recovery ratios (20-80%) observed in these experiments also point to bilayer imperfection. In contrast, lipid bilayers observed on smoother hydrophilic surface of silicon and polysilicon nanowires show near-complete recovery and fast diffusion coefficients (2-10·10^{-8} cm^2/s), indicating high quality of the lipid membranes formed on these substrates [34]. Besides the template surface properties, two other fundamental factors that influence bilayer mobility are the shape of the lipid molecules and the template surface curvature. Huang et. al. investigated these questions in the series of FRAP measurements on 1D bilayers on varying curvature Si nanowire substrates [34] (Figure 4). These bilayers used a variable ratio of cylindrical DOPC and conical DOPE lipid molecules to change the intrinsic curvature of the bilayer. Surprisingly, these experiments did not show a strong effect of the lipid composition on the bilayer mobility, which most likely reflects the ability of the bilayer to adapt to the changing substrate curvature. These measurements indicated that substrate curvature has only a weak effect on the bilayer fluidity with the smaller radii of curvature bilayers showing progressively faster diffusion (Figure 4). Interestingly, the measured diffusion coefficients follow the predictions of the free space model for nanowires larger than 50nm, but for smaller nanowires the measured values show significant deviation from the theory predictions (Figure 4). Most likely, these results point again at the

extraordinary ability of the lipid bilayers to adapt to the nanoscale curvature of the 1D substrates .

McEuen and co-workers studied diffusion of lipid molecules over a barrier presented by a carbon nanotube sandwiched between the planar lipid layer and a planar support surface (their experimental configuration limitations did not allow them to address the mobility of the lipid molecules in the bilayer directly over the nanotube); these experiments found that small single-wall nanotubes did not present a significant barrier for lipid molecule diffusion [37]. In contrast, the nanotube barrier had significantly impeded diffusion of a large protein (Tetanus Toxin Fragment C) inserted in the lipid bilayer [37].

Another bilayer property critically important for bioelectronic applications is its ability to block transport of ions and molecules. Martinez et. al. investigated blocking ability of lipid bilayers formed over highly-doped single silicon nanowire electrodes using cyclic voltammetry measurements [40] (Figure 5) and found that lipid barrier reduces the characteristic rate constant for the electrode reaction by at least an order of magnitude. Incorporating functional α-hemolysin protein pores in the lipid bilayer results in a partial recovery of the Faradic current due to the specific transport through the protein pore. These experiments showed that lipid-nanowire assemblies represent a robust and versatile platform for building new generation nanobioelectronic devices.

Biologically-templated assembly. A completely different set of assembly strategies relies on biological systems themselves the generate templates and sometimes even materials for creating new hybrid structures. Such bottom-up assembly techniques can potentially use the complexity of biosystems to fabricate dense functional nanostructures with spatial control extending to a few nanometers. Belcher and co-workers have developed an approach of selecting peptides from a combinatorial library of genetically engineered M13 bacteriophage that are tailored to template inorganic materials, and they have shown that such peptide sequences can control the crystal growth different inorganic materials [41] and grow inorganic nanowires of materials such as ZnS-CdS [42]. Another interesting example of the interaction of

microorganisms and 1-D nanostructures are bacterial nanowires [43]. *Shewanella oneidensis* bacteria can produce 50-150nm wide nanowires that are efficient electron conductors. Remarkably, bacteria produce networks of such nanowires to connect cells to cells and cells to mineral surfaces[44] providing us with a blue-print for devising energy producing devices based on such hybrid systems.

Other instances of using biological templates for assembling inorganic one-dimensional structures include DNA, peptide nanotubes and biological microtubules [45]. Nanotubular structures ranging from sub-1 nm to ~1μm have been formed from dipeptides, linear peptides and cyclic peptides [46]. These peptide nanotubes have been used to form metallized nanowires [47] and 1-D radial heterostructures [48]. Similarly nanowires have been formed by metallization of collagen-related peptide fibers.[49] Double-stranded DNA nanotubes have also been used for the templated sythesis of metallic nanowires [50, 51]. The amalgamation of such biological 1-D nanostructures and synthetic nanotubes/nanowires in heterostructures remains largely unexplored and such hybrid bio-nano constructs offer new functionalities and new methods for assemblies.

Bionanoelectronics: Device Applications

Device platforms. Device-level integration of nanomaterials with proteins represents an important step towards building a bionanoelectronic interfaces. Among many electronic device architectures, nanotube and nanowire transistors, first developed in the end of the previous decade [52, 53], have found widespread use in bionanoelectronics. These devices, that typically consist of a nanowire connected to two lithographically-defined electrodes defined on a substrate surface. The device is usually gated either by a means of a back gate or through the solution in a "liquid gate" configuration [54]. As a platform, nanotube and nanowire transistors present several clear advantages: (1) they can operate in ionic solutions, which is a native environment for most biological systems; (2) they provide a natural and effective connection between the micron-size active area of the device and the macroscopic measurement equipment; (3) a single device chip can house

hundreds of individual devices, providing redundancy, ability to run parallel measurement and easy multiplexing possibilities; and (4) most important, transistor gain provides an effective means of amplifying very weak signals generated by the biological events.

Recognition sensing with biological targets. Electronic biosensing and detection represents the most developed area of bionanolectronics. Rapid progress in this area in the last decade reflects the clear advantages of electronic nanosensors: they are label-free and highly sensitive, have high throughput, and use smaller sample volumes due to their miniature size. Use of biological components in these devices builds upon these benefits by adding biocompatibility and specificity.

Contrasting semiconducting and metallic behavior of carbon nanotubes can make them perform two roles in biosensors. Semiconducting CNTs could form the core of an FET sensor [55, 56], and both semiconducting/metallic nanotubes could function as an electrode for electrochemical sensing [57]. The immobilization of proteins on CNTs [58, 59] provides a straightforward biological functionalization pathway. For example, glucose oxidase enzyme linkage to CNT surfaces endows CNT FETs with biomolecular diagnostic capabilities, such as pH sensing enzymatic activity monitoring [60]. Antobody modification of CNT devices allowed detection of pig serum albumin [61] and prostate-specific antigen (PSA) [62].

An extension of the antibody functionalization on CNTs using aptamers [63], which are shorter than antibodies and thus mitigate the issue of charge screening, has been used to detect Immunoglobin E down to a concentration of 250 pm [64]. RNA based Aptamers have been used to selectively sense *Escherichia coli* bacteria [65], as well as potentiometrically detect *Salmonella* Typhi [66]. A more sophisticated approach deals with the problem of non-specific adsorption by coating the CNT surface with a polymer layer, such as polyethylene oxide (PEO) containing Tween-20 and Pluronic P103, and subsequently functionalizing the CNT-polymer heterostructure [67]. Coating CNTs with poly(ethylene glycol) and poly(ethylene imine) eliminates non-specific binding of streptavidin on the sensing

surface of the FET; however functionalizing the polymer surface with biotin still enables streptavidin detection [68].

Thiolated single-stranded DNA (ssDNA) covering carbon nanotubes as well as gold electrical contacts to the devices, was used as a functionalization scheme for the detection of DNA hybridization [69, 70]. More recently, MartiÌnez et. al reported a polymer modification scheme to suppress non-specific binding in CNT FET based DNA sensing [71]. Other research on CNTs functionalized with nanoscale coatings of ssDNA on their surfaces, suggests that such hybrid structure is capable of detecting a wide variety of gases with detection limits as low as 1 ppm [72].

Use of CNTs as individual nanoelectrodes and CNT composite electrodes for biological applications has become popular over the past few years [57, 73, 74]. A notable development in interfacing CNT electrodes with biological components has been the functionalization of CNTs with redox active proteins and enzymes, such as Microperoxidase MP-11 [75], attached at the ends of SWCNTs on macro-electrode surfaces, to achieve direct electron transfer. Metallic CNTs based electrodes have also functioned as DNA sensors in various functional modification schemes [76].

Amongst inorganic nanowires, SiNWs have been the most popular candidate for the study of applications in biosensing [77, 78]. The pioneering work of Lieber and co-workers has demonstrated the use of SiNWs as detectors for proteins [79-81], DNA hybridization [82], and viruses [83]. Multiplexed detection of cancer markers with arrays of multiplexed nanowire FET sensors [84] (Figure 2A,B) provided one of the most impressive demonstrations of nanoelectronic biosensing to date and has clear implications for the future medical diagnostics devices. Apart from silicon, nanowires or nanobelts of materials such as In_2O_3 [85], ZnO [86], ZnS [87], SnO_2 [88], and GaN[89] have been used as FETs or nanoelectrode materials for biosensing. Given the distinct properties of silicon and these other wide-band semiconductor materials possess, it is easy to envision them as a basis for a future generation of non-intrusive highly-efficient and extremely sensitive multifunctional bioelectronic devices.

Nanobioelectronics with 1D lipid bilayers. As we mentioned in the previous sections, integration of lipid bilayers with nanotubes and nanowires provides an opportunity to use functional membrane proteins in nanostructures that replicate some of the biological signaling mechanisms. Alternatively, we can use the electronic device as an input method for control of the functionality of the biological molecule. Recently, Misra et. al. demonstrated some of these possibilities by incorporating ligand-gated and voltage gated peptide ion channels into lipid bilayer structure assembled on silicon nanowire transistors [90]. These experiments monitored proton transport through the peptide channels to exploit the sensitivity of the nanowire conductance to the solution pH. Researchers showed that when the lipid bilayer on the nanowire contained ion channel Gramicidin A, the device would respond to a change in solution pH, yet when the membrane channels were blocked by divalent cations, the device response was strongly diminished. Moreover, when researchers placed a voltage-gated channel, alamethicin in the lipid shell (Figure 6A), they were able to use the electric field of the device to open and close the protein pores in the bilayer: at positive gate voltages (+0.15V) ALM pores opened and the device was able to respond to the solution pH changes; however when the gate voltage was set back to 0V ALM pores closed and the pH sensitivity of the device was lost (Figure 6B,C). These proof-of-principle experiments demonstrate the possibility if using electronic devices to control membrane proteins; further experiments using more complex protein arrangements should realize the capabilities of this platform.

Cell and tissue interfaces

One exciting and challenging areas in biology where 1D nanomaterials may find future applications is electrical communication with cells and design of artificial nanobiocircuits. Typically, most cells do not use electrical signals to communicate. Instead, they use molecules and ions to talk to each other and to the world and cascades of protein-protein interactions to transmit and process information inside the cell. Nerve cells, on the other hand, use electricity to convey information, which makes them unique in their ability to speak the same language as man-made

electronic devices. Although micropipettes and microfabricated FET arrays have been used to record extracellular potentials and stimulate neurons, they either are difficult to multiplex or lack necessary spatial resolution. Charles Lieber and co-workers were first to realize that small diameters and higher sensitivity of nanowires provide a breakthrough capability to stimulate and record local signals at multiple positions along neuronal projections [91] (see also [92, 93]) (Figure 7 A,B). Recently, Lieber and colleagues demonstrated electrical recordings of live hearts using silicon nanowire transistor arrays (Figure 7C) [94]. Fabrication of nanowire devices on flexible polymer substrates [94, 95] brings us one step closer to seamless interfacing of live tissue with nanoscale electronics.

Concluding Remarks

It is clear that integration of biological components with nanoelectronic platforms based on nanotubes and nanowires is both exciting and challenging. Rapid progress in development of electronic nanowire biosensors provides a testimony to the huge potential of the platform and a preview of what lies ahead. At the same time problems associated with the compatibility gap between biological world and nanomaterials and, more significantly, with the fundamental mismatch between the signal transduction mechanisms used in microelectronic and biological systems are real, and should not be underestimated. Fortunately, several approaches have emerged that promise to bridge these gaps and realize the vision of bionanelectronics. We hope to see continuing efforts to design and build more sophisticated circuits in which biological molecules work, interact, and communicate seamlessly with the nanotube and nanowire-based scaffolds, respond to optical signal, or even perform local switching or memory functions. On a higher complexity level, the emerging nanoelectronic tissue interfaces could revolutionize the way we do medical diagnostics, prosthetics, or even basic human-computer interactions. A vision of being able to write this article using a direct bioelectronic brain-computer interface instead of a conventional keyboard is still a dream, but current research already made the first steps towards making it a reality.

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References.

1. Alberts, B., et al., *Molecular Biology of the Cell*. 3 ed. 1994, New York: Garland.
2. Alon, U., *An introduction to systems biology. Design principles of biological circuits*. 2007, London: CRC Press. 301.
3. *The Blue Brain Project*. Available from: http://bluebrain.epfl.ch/.
4. Fromherz, P. and A. Stett, *Silicon-Neuron Junction: Capacitive Stimulation of an Individual Neuron on a Silicon Chip.* Physical Review Letters, 1995. **75**(8): p. 1670-1673.
5. Fromherz, P., et al., *A neuron-silicon junction: a Retzius cell of the leech on an insulated-gate field-effect transistor.* Science, 1991. **252**(5010): p. 1290-1293.
6. Park, W.I., et al., *Controlled Synthesis of Millimeter-Long Silicon Nanowires with Uniform Electronic Properties.* Nano Letters, 2008. **8**(9): p. 3004-3009.
7. Groves, J.T., *Bending Mechanics and Molecular Organization in Biological Membranes.* Annual Review of Physical Chemistry, 2007. **58**(1): p. 697-717.
8. Hu, J.T., T.W. Odom, and C.M. Lieber, *Chemistry and physics in one dimension: Synthesis and properties of nanowires and nanotubes.* Accounts of Chemical Research, 1999. **32**(5): p. 435-445.
9. Iijima, S., *Helical microtubules of graphitic carbon.* Nature, 1991. **354**(6348): p. 56-58.
10. Tans, S.J., et al., *Individual single-wall carbon nanotubes as quantum wires.* Nature, 1997. **386**(6624): p. 474-477.
11. Wilder, J.W.G., et al., *Electronic structure of atomically resolved carbon nanotubes.* Nature, 1998. **391**(6662): p. 59-62.
12. Avouris, P. and J. Chen, *Nanotube electronics and optoelectronics.* Materials Today, 2006. **9**(10): p. 46-54.
13. Javey, A., et al., *Ballistic carbon nanotube field-effect transistors.* Nature, 2003. **424**(6949): p. 654-657.
14. Cao, Q., et al., *Medium-scale carbon nanotube thin-film integrated circuits on flexible plastic substrates.* Nature, 2008. **454**(7203): p. 495-500.
15. Cui, Y., et al., *Doping and Electrical Transport in Silicon Nanowires.* The Journal of Physical Chemistry B, 2000. **104**(22): p. 5213-5216.
16. Misra, N., et al., *Laser activation of dopants for nanowire devices on glass and plastic.* Applied Physics Letters, 2008. **93**(12): p. 121116-3.
17. Jiang, X., et al., *InAs/InP Radial Nanowire Heterostructures as High Electron Mobility Devices.* Nano Letters, 2007. **7**(10): p. 3214-3218.
18. Lu, W., et al., *One-dimensional hole gas in germanium/silicon nanowire heterostructures.* Proceedings of the National Academy of Sciences of the United States of America, 2005. **102**(29): p. 10046-10051.

19. Kane, R.S. and A.D. Stroock, *Nanobiotechnology: protein-nanomaterial interactions.* Biotechnology Progress, 2007. **23**: p. 316-319.
20. Patolsky, F., G. Zheng, and C.M. Lieber, *Fabrication of silicon nanowire devices for ultrasensitive, label-free, real-time detection of biological and chemical species.* Nature Protocols, 2006. **1**(4): p. 1711-1724.
21. Bahr, J.L. and J.M. Tour, *Covalent chemistry of single-wall carbon nanotubes.* Journal of Materials Chemistry, 2002. **12**(7): p. 1952-1958.
22. Fan, Y.W., B.R. Goldsmith, and P.G. Collins, *Identifying and counting point defects in carbon nanotubes.* Nature Materials, 2005. **4**(12): p. 906-911.
23. Goldsmith, B.R., et al., *Monitoring single-molecule reactivity on a carbon nanotube.* Nano Letters, 2008. **8**(1): p. 189-194.
24. Goldsmith, B.R., et al., *Conductance-controlled point functionalization of single-walled carbon nanotubes.* Science, 2007. **315**(5808): p. 77-81.
25. Tien, H. and A. Ottova-Leitmannova, *Planar lipid bilayers (BLMs) and their applications*. 2003: Elsevier Amsterdam.
26. Walter, A. and J. Gutknecht, *Permeability of Small Nonelectrolytes Through Lipid Bilayer- Membranes.* Journal of Membrane Biology, 1986. **90**(3): p. 207-217.
27. Sackmann, E., *Supported membranes: Scientific and practical applications.* Science, 1996. **271**(5245): p. 43-48.
28. Lasic, D., *Liposomes: from physics to applications*. 1993: Elsevier Amsterdam etc.
29. Evans, E., et al., *Biomembrane templates for nanoscale conduits and networks.* Science, 1996. **273**(5277): p. 933.
30. Karlsson, A., et al., *Molecular engineering: networks of nanotubes and containers.* Nature, 2001. **409**(6817): p. 150-152.
31. Roux, A., et al., *A minimal system allowing tubulation with molecular motors pulling on giant liposomes.* Proceedings of the National Academy of Sciences, 2002. **99**(8): p. 5394.
32. Kulkarni, V.S., W.H. Anderson, and R.E. Brown, *Bilayer nanotubes and helical ribbons formed by hydrated galactosylceramides: acyl chail and headgroup effects.* Biophysical Journal, 1995. **69**: p. 1976-1986.
33. Schnur, J., *Lipid tubules: a paradigm for molecularly engineered structures.* Science, 1993. **262**(5140): p. 1669-1676.
34. Huang, S.-C.J., et al., *Formation, Stability, and Mobility of One-Dimensional Lipid Bilayers on Polysilicon Nanowires.* Nano Lett., 2007. **7**(11): p. 3355 - 3359.
35. Artyukhin, A.B., et al., *Functional one-dimensional lipid bilayers on carbon nanotube templates.* Journal of the American Chemical Society, 2005. **127**(20): p. 7538-7542.
36. Sirbuly, D.J., et al., *Biofunctional Subwavelength Optical Waveguides for Biodetection.* ACS Nano, 2008. **2**(2): p. 255-262.
37. Zhou, X., et al., *Supported lipid bilayer-carbon nanotube hybrids.* Nature Nanotechnnology, 2007. **2**(3): p. 185-190.
38. Roiter, Y., et al., *Interaction of nanoparticles with lipid membrane.* Nano Letters, 2008. **8**(3): p. 941-944.

39. Zhang, L.Q., M.L. Longo, and P. Stroeve, *Mobile phospholipid bilayers supporetd on a polyion/alkylthiol layer pair.* Langmuir, 2000. **16**(11): p. 5093-5099.
40. Martinez, J.A., et al., *Highly-efficient biocompatible single silicon nanowire electrodes with functional biological pore channels.* Nano Letters, 2009. **9**(3): p. 1121–1126.
41. Whaley, S.R., et al., *Selection of peptides with semiconductor binding specificity for directed nanocrystal assembly.* Nature, 2000. **405**(6787): p. 665-668.
42. Mao, C., et al., *Viral assembly of oriented quantum dot nanowires.* Proceedings of the National Academy of Sciences of the United States of America, 2003. **100**(12): p. 6946-6951.
43. Gorby, Y.A., et al., *Electrically conductive bacterial nanowires produced by Shewanella oneidensis strain MR-1 and other microorganisms.* Proceedings of the National Academy of Sciences, 2006. **103**(30): p. 11358-11363.
44. Ntarlagiannis, D., et al., *Microbial nanowires: Is the subsurface â€œhardwiredâ€?* Geophys. Res. Lett., 2007. **34**.
45. Fritzsche, W., et al., *Wiring of metallized microtubules by electron beam-induced structuring.* Nanotechnology, 1999. **10**(3): p. 331-335.
46. Scanlon, S. and A. Aggeli, *Self-assembling peptide nanotubes.* Nano Today. **3**(3-4): p. 22-30.
47. Reches, M. and E. Gazit, *Casting Metal Nanowires Within Discrete Self-Assembled Peptide Nanotubes.* Science, 2003. **300**(5619): p. 625-627.
48. Carny, O., D.E. Shalev, and E. Gazit, *Fabrication of Coaxial Metal Nanocables Using a Self-Assembled Peptide Nanotube Scaffold.* Nano Letters, 2006. **6**(8): p. 1594-1597.
49. Gottlieb, D., et al., *Self-assembled collagen-like peptide fibers as templates for metallic nanowires.* Journal of Materials Chemistry, 2008. **18**: p. 3865.
50. Burley, G.A., et al., *Directed DNA Metallization.* Journal of the American Chemical Society, 2006. **128**(5): p. 1398-1399.
51. Jan, R., et al., *Construction of highly conductive nanowires on a DNA template.* Applied Physics Letters, 2001. **78**(4): p. 536-538.
52. Tans, S.J., A.R.M. Verschueren, and C. Dekker, *Room-temperature transistor based on a single carbon nanotube.* Nature, 1998. **393**(6680): p. 49-52.
53. Cui, Y. and C.M. Lieber, *Functional nanoscale electronic devices assembled using silicon nanowire building blocks.* Science, 2001. **291**(5505): p. 851-853.
54. Rosenblatt, S., et al., *High performance electrolyte gated carbon nanotube transistors.* Nano Letters, 2002. **2**(8): p. 869-872.
55. Artyukhin, A.B., et al., *Controlled Electrostatic Gating of Carbon Nanotube FET Devices.* Nano Letters, 2006. **6**(9): p. 2080-2085.
56. Larrimore, L., et al., *Probing Electrostatic Potentials in Solution with Carbon Nanotube Transistors.* Nano Letters, 2006. **6**(7): p. 1329-1333.
57. Heller, I., et al., *Individual Single-Walled Carbon Nanotubes as Nanoelectrodes for Electrochemistry.* Nano Letters, 2004. **5**(1): p. 137-142.
58. Fabrice, B., et al., *Helical Crystallization of Proteins on Carbon Nanotubes: A First Step towards the Development of New Biosensors.* Angewandte Chemie International Edition, 1999. **38**(13-14): p. 1912-1915.

59. Bradley, K., et al., *Charge Transfer from Adsorbed Proteins.* Nano Letters, 2004. **4**(2): p. 253-256.
60. Besteman, K., et al., *Enzyme-Coated Carbon Nanotubes as Single-Molecule Biosensors.* Nano Letters, 2003. **3**(6): p. 727-730.
61. Kojima, A., et al., *Protein Sensor Using Carbon Nanotube Field Effect Transistor.* Japanese Journal of Applied Physics, 2005. **44**(4A): p. 1596.
62. Li, C., et al., *Complementary Detection of Prostate-Specific Antigen Using In2O3 Nanowires and Carbon Nanotubes.* Journal of the American Chemical Society, 2005. **127**(36): p. 12484-12485.
63. So, H.-M., et al., *Single-Walled Carbon Nanotube Biosensors Using Aptamers as Molecular Recognition Elements.* Journal of the American Chemical Society, 2005. **127**(34): p. 11906-11907.
64. Maehashi, K., et al., *Label-Free Protein Biosensor Based on Aptamer-Modified Carbon Nanotube Field-Effect Transistors.* Analytical Chemistry, 2006. **79**(2): p. 782-787.
65. Hye-Mi, S., et al., *Detection and Titer Estimation of <I>Escherichia coli</I> Using Aptamer-Functionalized Single-Walled Carbon-Nanotube Field-Effect Transistors13.* Small, 2008. **4**(2): p. 197-201.
66. Gustavo, A.Z.-G., et al., *Immediate Detection of Living Bacteria at Ultralow Concentrations Using a Carbon Nanotube Based Potentiometric Aptasensor.* Angewandte Chemie International Edition, 2009. **9999**(9999): p. NA.
67. Chen, R.J., et al., *Noncovalent functionalization of carbon nanotubes for highly specific electronic biosensors.* Proceedings of the National Academy of Sciences of the United States of America, 2003. **100**(9): p. 4984-4989.
68. Star, A., et al., *Electronic Detection of Specific Protein Binding Using Nanotube FET Devices.* Nano Letters, 2003. **3**(4): p. 459-463.
69. Tang, X., et al., *Carbon Nanotube DNA Sensor and Sensing Mechanism.* Nano Letters, 2006. **6**(8): p. 1632-1636.
70. Star, A., et al., *Label-free detection of DNA hybridization using carbon nanotube network field-effect transistors.* Proceedings of the National Academy of Sciences of the United States of America, 2006. **103**(4): p. 921-926.
71. MartiÌnez, M.T., et al., *Label-Free DNA Biosensors Based on Functionalized Carbon Nanotube Field Effect Transistors.* Nano Letters, 2009. **9**(2): p. 530-536.
72. Staii, C., et al., *DNA-Decorated Carbon Nanotubes for Chemical Sensing.* Nano Letters, 2005. **5**(9): p. 1774-1778.
73. Punbusayakul, N., et al., *Double-Walled Carbon Nanotube Electrodes for Electrochemical Sensing.* Electrochemical and Solid-State Letters, 2007. **10**(5): p. F13-F17.
74. Yun, Y., et al., *Nanotube electrodes and biosensors.* Nano Today, 2007. **2**(6): p. 30-37.
75. Gooding, J.J., et al., *Protein Electrochemistry Using Aligned Carbon Nanotube Arrays.* Journal of the American Chemical Society, 2003. **125**(30): p. 9006-9007.

76. Wang, S.G., et al., *DNA biosensors based on self-assembled carbon nanotubes.* Biochemical and Biophysical Research Communications, 2004. **325**(4): p. 1433-1437.
77. McAlpine, M.C., et al., *Highly ordered nanowire arrays on plastic substrates for ultrasensitive flexible chemical sensors.* Nature Materials, 2007. **6**(5): p. 379-384.
78. Stern, E., et al., *Label-free immunodetection with CMOS-compatible semiconducting nanowires.* Nature, 2007. **445**(7127): p. 519-522.
79. Cui, Y., et al., *Nanowire Nanosensors for Highly Sensitive and Selective Detection of Biological and Chemical Species.* Science, 2001. **293**(5533): p. 1289-1292.
80. Wang, W.U., et al., *Label-free detection of small-moleculeâ€"protein interactions by using nanowire nanosensors.* Proceedings of the National Academy of Sciences of the United States of America, 2005. **102**(9): p. 3208-3212.
81. Zheng, G.F., et al., *Multiplexed electrical detection of cancer markers with nanowire sensor arrays.* Nature Biotechnology, 2005. **23**(10): p. 1294-1301.
82. Hahm, J.-i. and C.M. Lieber, *Direct Ultrasensitive Electrical Detection of DNA and DNA Sequence Variations Using Nanowire Nanosensors.* Nano Letters, 2003. **4**(1): p. 51-54.
83. Patolsky, F., et al., *Electrical detection of single viruses.* Proceedings of the National Academy of Sciences of the United States of America, 2004. **101**(39): p. 14017-14022.
84. Zheng, G., et al., *Multiplexed electrical detection of cancer markers with nanowire sensor arrays.* Nat Biotech, 2005. **23**(10): p. 1294-1301.
85. Ishikawa, F.N., et al., *Label-Free, Electrical Detection of the SARS Virus N-Protein with Nanowire Biosensors Utilizing Antibody Mimics as Capture Probes.* ACS Nano, 2009. **3**(5): p. 1219-1224.
86. Kang, B.S., et al., *Enzymatic glucose detection using ZnO nanorods on the gate region of AlGaN/GaN high electron mobility transistors.* Applied Physics Letters, 2007. **91**(25): p. 252103-3.
87. He, J.H., et al., *ZnS/Silica Nanocable Field Effect Transistors as Biological and Chemical Nanosensors.* The Journal of Physical Chemistry C, 2007. **111**(33): p. 12152-12156.
88. Cheng, Y., et al., *Mechanism and Optimization of pH Sensing Using SnO2 Nanobelt Field Effect Transistors.* Nano Letters, 2008. **8**(12): p. 4179-4184.
89. Chen, C.-P., et al., *Label-Free Dual Sensing of DNA Molecules Using GaN Nanowires.* Analytical Chemistry, 2008. **81**(1): p. 36-42.
90. Misra, N., et al., *Bioelectronic Silicon Nanowire Devices Utilizing Functional Membrane Proteins.* Proc. Natl. Acad. Sci. USA, 2009: p. in press.
91. Patolsky, F., et al., *Detection, stimulation, and inhibition of neuronal signals with high-density nanowire transistor arrays.* Science, 2006. **313**(5790): p. 1100-1104.
92. Fromherz, P. and M. Voelker, *Comment on "Detection, Stimulation, and Inhibition of Neuronal Signals with High-Density Nanowire Transistor Arrays".* Science, 2009. **323**(5920).

93. Timko, B.P., F. Patolsky, and C.M. Lieber, *Response to Comment on "Detection, Stimulation, and Inhibition of Neuronal Signals with High-Density Nanowire Transistor Arrays".* Science, 2009. **323**(5920).
94. Timko, B.P., et al., *Electrical Recording from Hearts with Flexible Nanowire Device Arrays.* Nano Letters, 2009. **9**(2): p. 914-918.
95. Cohen-Karni, T., et al., *Flexible electrical recording from cells using nanowire transistor arrays.* Proceedings of the National Academy of Sciences of the United States of America, 2009. **106**(18): p. 7309-7313.
96. Bethune, D.S., et al., *Cobalt-catalysed growth of carbon nanotubes with single-atomic-layer walls.* Nature, 1993. **363**(6430): p. 605-607.
97. Streifer, J.A., et al., *Covalent functionalization and biomolecular recognition properties of DNA-modified silicon nanowires.* Nanotechnology, 2005. **16**(9): p. 1868-1873.
98. Zhang, Y.B., et al., *Functionalized carbon nanotubes for detecting viral proteins.* Nano Letters, 2007. **7**(10): p. 3086-3091.

Figures.

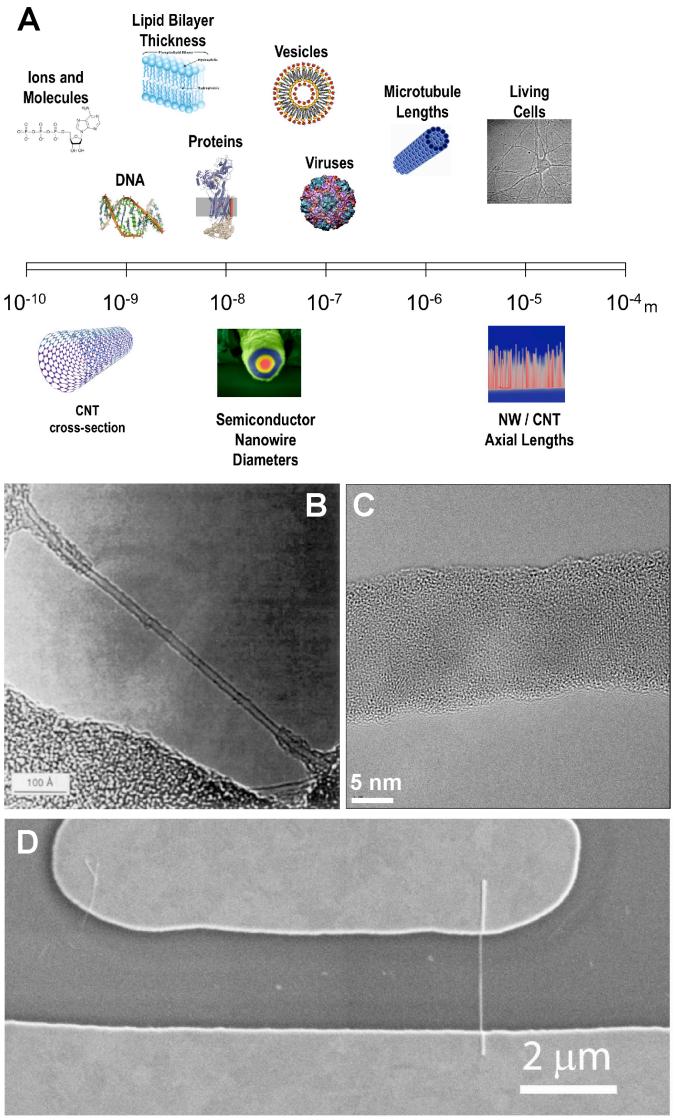

Figure 1. **1D nanomaterials and devices**. (**A**). Comparative size of some key biological structures and nanomaterials. (**B**) TEM image of a single-wall carbon nanotube, from [96]. (**C**) TEM image of a VLS-grown Si nanowire. (**D**) SEM image of a nanowire transistor gate region showing a single nanowire bridging two microfabricated electrodes, from [90].

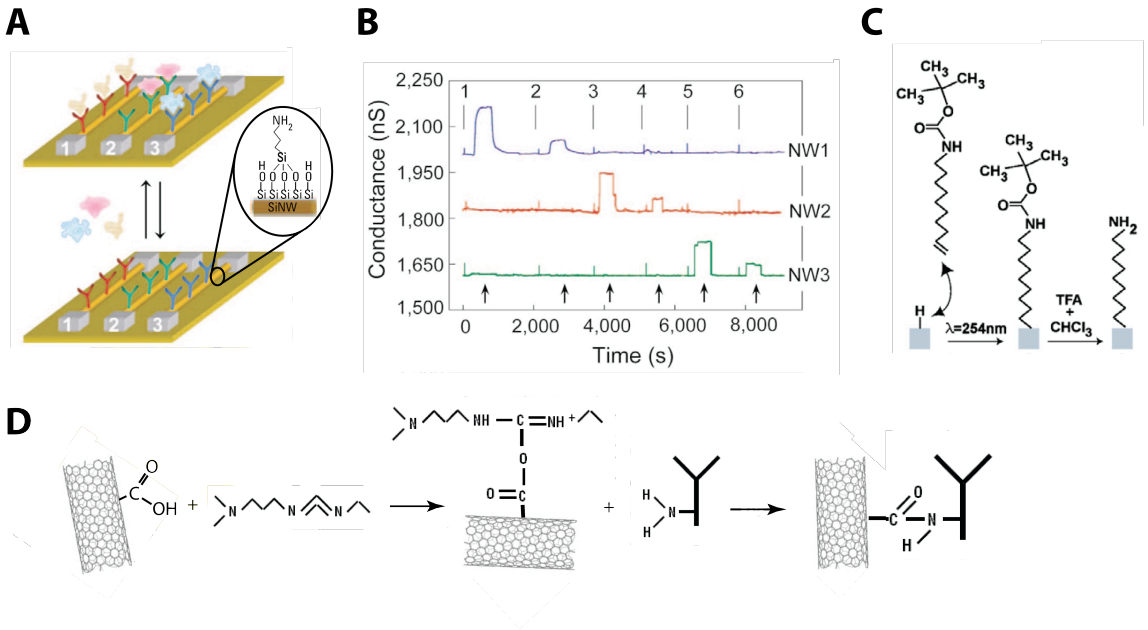

Figure 2. Direct covalent modification of nanotubes and nanowires with biological molecules. (**A**) Silicon oxide surface is modified to expose primary amine functional groups to which antibodies against specific protein markers can be coupled. (**B**) Conductance vs. time data recorded for simultaneous detection of three proteins (PSA, CEA, and mucin-1) using a nanowire array in which NW1, NW2 and NW3 were functionalized with antibodies for PSA, CEA and mucin-1, respectively. (**C**) Covalent functionalization of hydrogen-terminated silicon nanowire surface as demonstrated in [97] for nanowire-DNA coupling. (**D**) Proteins can be covalently attached to oxidized surfaces of carbon nanotubes using EDAC coupling. This method was used in [98] to functionalize carbon nanotube sensors with viral proteins. (A) and (B) taken from [81].

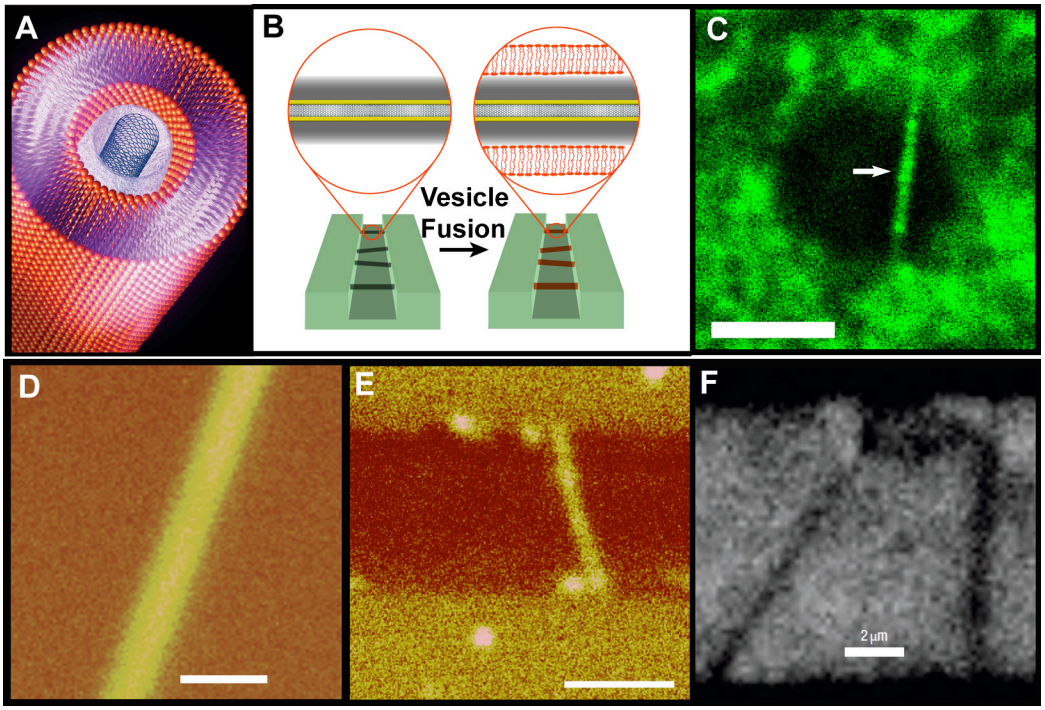

Figure 3. Lipid bilayer coatings on nanowire and nanotube templates. Artist's representation of a 1D bilayer structure on a polymer-coated carbon nanotube template. (Image by S. Dougherty, LLNL) **B**. Schematics of the lipid coating formation by vesicle fusion. **(C-E)**. Optical confocal microscopy images of a lipid bilayer formed on 1D substrates: **C**. Polyelectrolyte-coated single-wall carbon nanotube, from [35]. Scale bar: 5 µm. **D**. SnO_2 nanowire waveguide, from [36]. Scale bar: 1µm. **C**. Si nanowire stretched across a microfabricated channel, from [34]. Scale bar: 5 µm. In all examples lipid mixture was doped with a small fraction of a fluorescent dye to aid imaging. **(F).** Fluorescence image of a lipid bilayer formed on the surface that has several carbon nanotubes (dark lines), from [37].

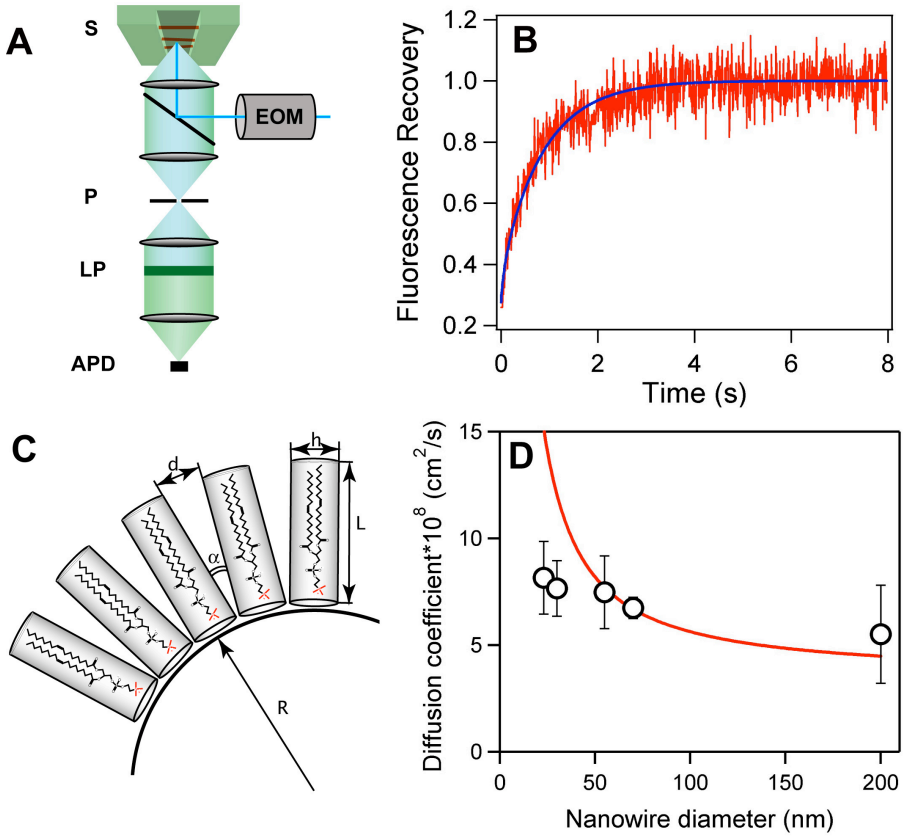

Figure 4. Mobility of 1D lipid bilayers supported on silicon nanowires. Top: (**A**) Schematic of the experimental setup used for the FRAP measurements: S – sample, P – pinhole, LP – long pass filter, APD – avalanche photodiode detector, EOM – electro-optical modulator. (**B**) Representative fluorescence recovery curve (red) and the corresponding diffusion model fit (blue) for a DOPC bilayer supported on a 55 nm diameter nanowire. **Bottom:** Comparison of the measured lipid mobility with the free space diffusion model. (**A**) Model schematics. Only the inner monolayer is shown for clarity. (**B**) Average experimental diffusion coefficients (circles) of DOPC-DOPE lipid bilayers on silicon nanowire templates and the diffusion coefficient values predicted by the free space diffusion model (red curve). From [34].

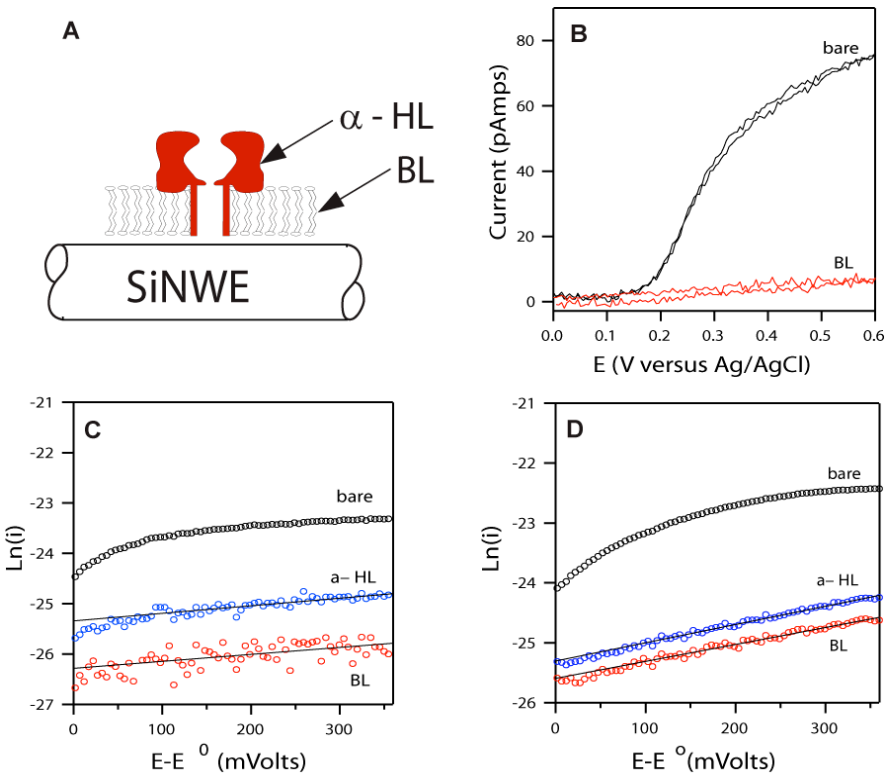

Figure 5. Barrier properties of lipid bilayers on nanowire templates. (**A**) Schematic of a Si nanowire coated by the lipid bilayer that incorporates a-hemolysin biological pore channel. (**B**) Faradic current response recoded before and after lipid bilayer formation onto SiNWE. (**C**) Tafel plot of the electrochemical response of a single SiNWE before, and after bilayer formation, and after subsequent a-hemolysin incubation. (**D**) Electrochemical response of a multiple SiNWE (same conditions and measurement sequence as used to record the data shown in (C). Solid lines in (C) and (D) represent best fits of the experimental data to the Tafel equation. From [40].

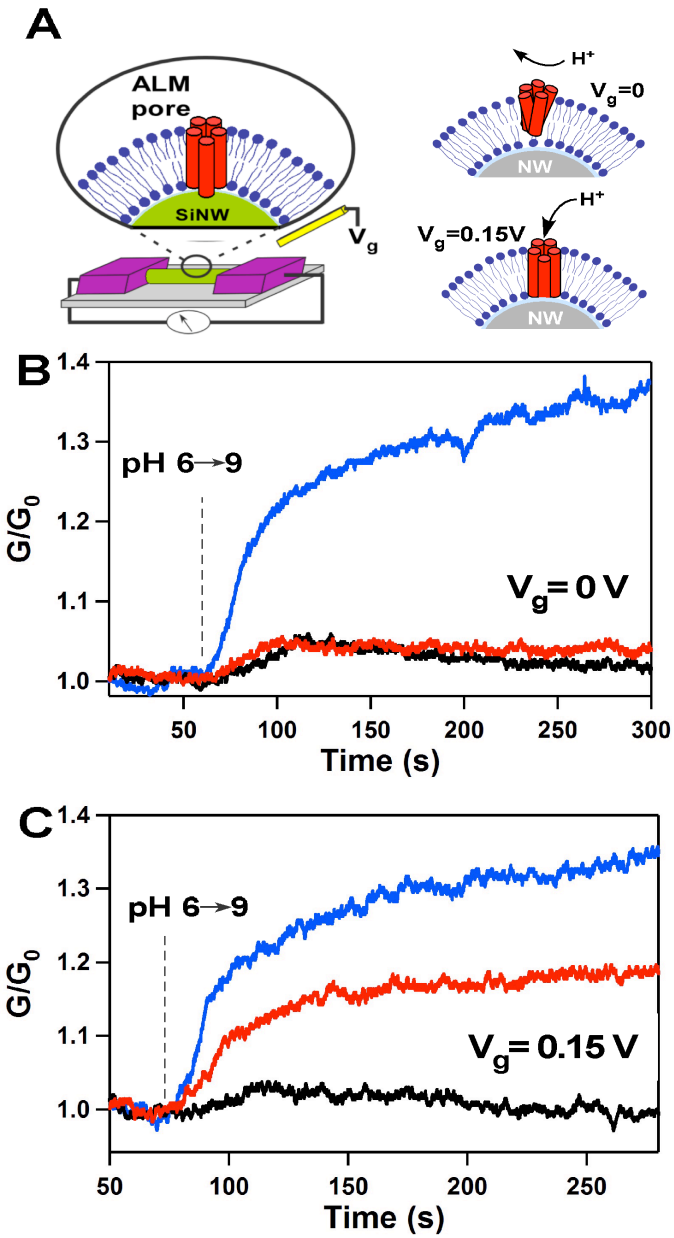

Figure 6. Bionanoelectronic devices utilizing functional membrane proteins. (**A**) (**Left**) Schematic of a NW transistor in which a SiNW (green) is connected to the source and rain electrodes (purple). The NW is covered with a lipid bilayer that incorporates ALM protein pores.(red). (**Right**). ALM conformation in the membrane at V_g=0 (closed state) and V_g=1 (open state). (**B**) Time traces of normalized conductance of the Si nanowire device held at gate bias of 0V recorded as the solution was changed from pH=6 to pH=9 for the uncoated nanowire (blue trace), coated nanowire (black trace), and the coated NW device incorporating ALM pores. (**C**) Time traces of a similar experiment recorded at gate bias of 0.15 V. Vertical dashed lines indicate the time when the pH of the fluid cell input stream was switched from the lower to the higher value.

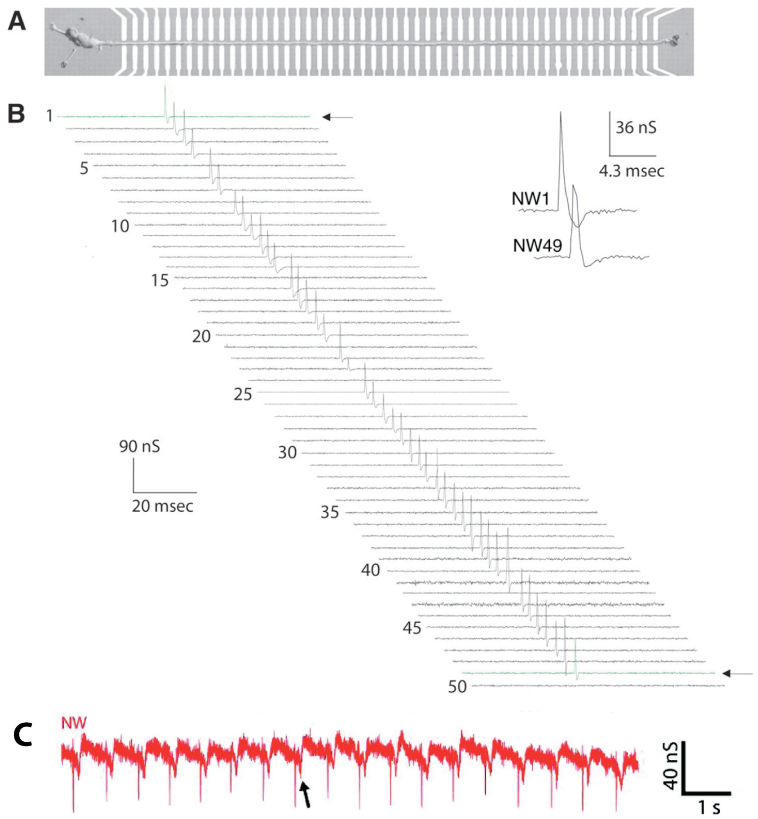

Figure 7. Nanowire-based cell and tissue interfaces. (**A**) Axon guided to grow along a predefined substrate surface path patterned with poly-lysine. Optical image shows the aligned axon crossing an array of 50 nanowire devices with a 10-μm inter-device spacing. (**B**) Electrical data from the same 50-device array. The yield of functional devices is 86%. The peak latency from NW1 (top arrow) to NW49 (bottom arrow) was 1060 μs. (**C**) Electrical recordings from an embryonic chicken heart with Si NW FET array. (A) and (B) are from [91]; (C) is from [94] .