Nanowire nanosensors

by Fernando Patolsky and Charles M. Lieber*

The detection of biological and chemical species is central to many areas of healthcare and the life sciences, ranging from uncovering and diagnosing disease to the discovery and screening of new drug molecules. Hence, the development of new devices that enable direct, sensitive, and rapid analysis of these species could impact humankind in significant ways. Devices based on nanowires are emerging as a powerful and general class of ultrasensitive, electrical sensors for the direct detection of biological and chemical species.

Department of Chemistry and Chemical Biology,
Division of Engineering and Applied Sciences,
Harvard University,
12 Oxford Street,
Cambridge MA 02138, USA
*E-mail: cml@cmliris.harvard.edu

Here we discuss examples of detection using these new sensors, from proteins and DNA to drug molecules and viruses down to the ultimate level of a single molecule, and, moreover, show how advances in integration and multiplexing provide a clear pathway for diverse and exciting applications.

Central to detection is the signal transduction associated with selective recognition of a biological or chemical species of interest. Nanostructures, such as nanowires[1-7] and nanocrystals[8-12], offer new and sometimes unique opportunities in this rich and interdisciplinary area of science and technology. The diameters of these nanostructures are comparable to the sizes of biological and chemical species being sensed, and thus intuitively represent excellent primary transducers for producing signals that ultimately interface with macroscopic instruments. Inorganic nanowires and nanocrystals exhibit unique electrical[2-5,13-28] and optical[8-12] properties that can be exploited for sensing. The size-tunable colors of semiconductor nanocrystals, together with their highly robust emission properties, are opening up opportunities for labeling and optical-based detection of biological species that offer advantages compared with conventional organic molecular dyes widely used today[8-12]. The electronically switchable properties of semiconducting nanowires provide a sensing modality – direct and label-free electrical readout – that is exceptionally attractive for many applications[29-37]. The signals from electrically based devices can be directly routed to the outside world, electronic nanodevices are readily integrated into miniaturized systems, and, moreover, direct electrical detection dispenses with time-consuming labeling chemistry. These characteristics,

ISSN:1369 7021 © Elsevier Ltd 2005

together with ultrahigh sensitivity, suggest that nanowire devices could revolutionize many aspects of sensing and detection in biology and medicine. How can nanowires be configured into devices that provide these seemingly remarkable capabilities?

Nanowire field-effect sensors

The underlying mechanism for nanowire sensors is a field effect that is transduced using field-effect transistors (FETs)[29], the ubiquitous switches of the microelectronics industry. In a standard FET illustrated in Fig. 1A, a semiconductor such as *p*-type silicon (*p*-Si) is connected to metal source and drain electrodes through which a current is injected and collected, respectively. The conductance of the semiconductor between source and drain is switched on and off by a third gate electrode capacitively coupled through a thin dielectric layer[38]. In the case of *p*-Si or another *p*-type semiconductor, applying a positive gate voltage depletes carriers and reduces the conductance, while applying a negative gate voltage leads to an accumulation of carriers and an increase in conductance. The dependence of the conductance on gate voltage makes FETs natural candidates for electrically based sensing since the electric field resulting from binding of a charged species to the gate dielectric is analogous to applying a voltage using a gate electrode. This idea for sensing with FETs was introduced several decades ago[39-41], although the limited sensitivity of these planar devices has precluded them from having a large impact.

Semiconductor nanowires composed of Si and other materials can also function as FET devices[13-15,19-27]. One of the best-studied examples, Si nanowires (Fig. 1B), can be prepared as single-crystal structures with diameters as small as 2-3 nm[1-4,42,43] and have been shown, for both *p*-type and *n*-type materials, to exhibit performance characteristics comparable to or better than the best achieved in the microelectronics industry[20,21,24-27]. These attractive performance characteristics are also achieved with high reproducibility[24]; that is, the electronic characteristics of nanowires are well controlled during growth in contrast to carbon nanotubes. The high-performance switching characteristics of Si nanowires are important since it is one factor that affects sensitivity. More important to overcoming the sensitivity limitations of previous planar FET sensors is the one-dimensional morphology of these

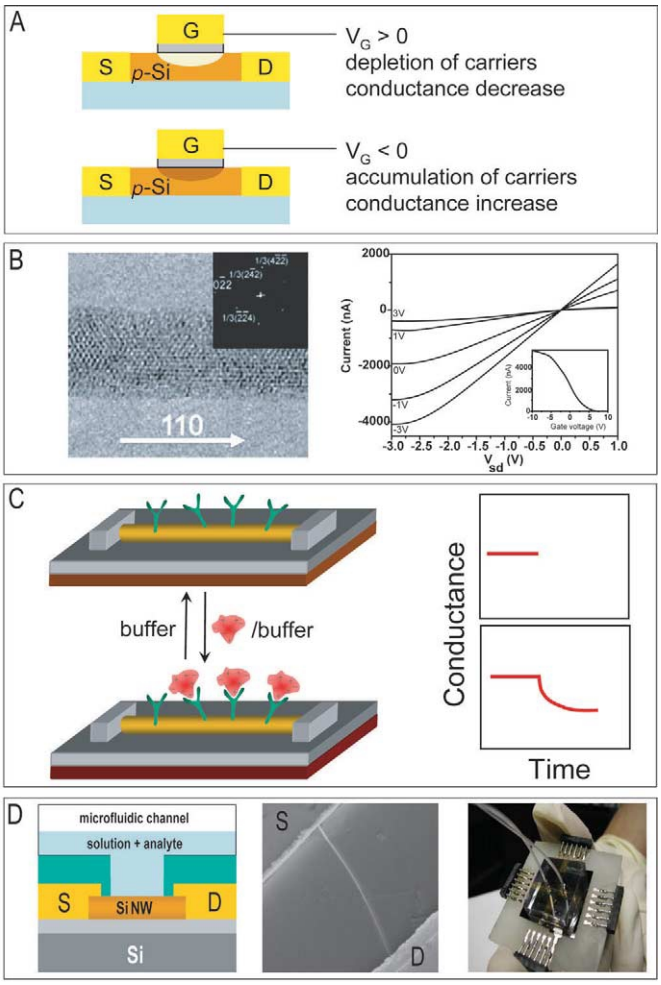

Fig. 1 Nanowire FET sensor. (A) Schematic of a regular planar FET device, where S, D, and G correspond to source, drain, and gate, respectively. (B) High-resolution transmission electron microscopy image and electron diffraction pattern for a 4.5 nm diameter single-crystal Si nanowire with <110> growth axis, and electrical transport data for a typical p-type nanowire that is characteristic of an FET. (C) Schematic of a Si nanowire-based FET device configured as a sensor with antibody receptors (green), where binding of a protein with net positive charge (red) yields a decrease in the conductance. (D) Cross-sectional diagram and scanning electron microscopy image of a single Si nanowire sensor device, and a photograph of a prototype nanowire sensor biochip with integrated microfluidic sample delivery.

nanoscale structures since binding to the surface of a nanowire leads to depletion or accumulation of carriers in the 'bulk' of the nanometer-diameter structure (versus only the surface region of a planar device)[29] and increases sensitivity to the point that single-molecule detection might be possible.

A general sensing device can be configured from the high-performance, field-effect nanowire transistors, as illustrated in Fig. 1C, where specific sensing is achieved by linking a recognition group to the surface of the nanowire. Si nanowires with their natural oxide coating make this receptor

linkage straightforward since extensive data exists for the chemical modification of silicon oxide or glass surfaces from planar chemical and biological sensors[44,45]. When the sensor device with surface receptor is exposed to a solution containing a macromolecule like a protein that has a net positive charge in aqueous solution, specific binding will lead to an increase in the surface positive charge and a decrease in conductance for a *p*-type nanowire device. Practically, we have developed a very reliable and flexible integrated nanowire sensor device, as shown in Fig. 1D, that incorporates a Si nanowire with well-defined *p*- or *n*-type doping, source drain electrodes that are insulated from the environment (so that only processes occurring at the Si nanowire surface contribute to electrical signals), and a microfluidic device for delivery of solutions being examined.

A model case: pH sensing

The first example demonstrating the ability of nanowire field-effect devices to detect species in liquid solutions was demonstrated in 2001 for the case of hydrogen ion concentration or pH sensing[29]. A basic *p*-type Si nanowire device was converted into such a sensor by modifying the silicon oxide surface with 3-aminopropyltriethoxysilane, which yields amino groups at the nanowire surface along with the naturally occuring silanol (Si-OH) groups of the oxide, as shown in Fig. 2A. The amino and silanol moieties function as receptors for hydrogen ions, which undergo protonation/deprotonation reactions, thereby changing the net nanowire surface charge. Significantly, as illustrated in Fig. 2B, *p*-type Si nanowire devices modified in this way exhibit stepwise increases in conductance as the pH of the solution, which is delivered through a microfluidic device, is increased stepwise from 2 to 9. The nearly linear increase in conductance with pH is attractive from the standpoint of a sensor, and results from the presence of two distinct receptor groups that undergo protonation/deprotonation over different pH ranges. From a mechanistic standpoint, the increase in conductance with increasing pH is consistent with a decrease (increase) of the surface positive (negative) charge, which 'turns on' the *p*-type FET via the accumulation of carriers.

The key role that the surface receptor plays in defining the response of the nanowire sensors was further tested by probing the pH response without modifying the silicon oxide surface layer. As illustrated in Fig. 2C, only the silanol group can function as a receptor for hydrogen ions in this case. Measurements of the conductance as a function of pH shown in Fig. 2D exhibit two different response regimes, unlike nanowire surfaces containing both amino and silanol receptors, where the conductance change is small at low pH (2 to 6) but larger and comparable to Fig. 2B for the high pH range (6 to 9). Moreover, the pH-dependent changes in conductance are in excellent agreement with previous measurements of the pH-dependent surface charge density derived from silica[46]. This comparison in these early experiments clearly demonstrated that the sensing mechanism was indeed the result of a field effect analogous to applying a voltage using a physical gate electrode.

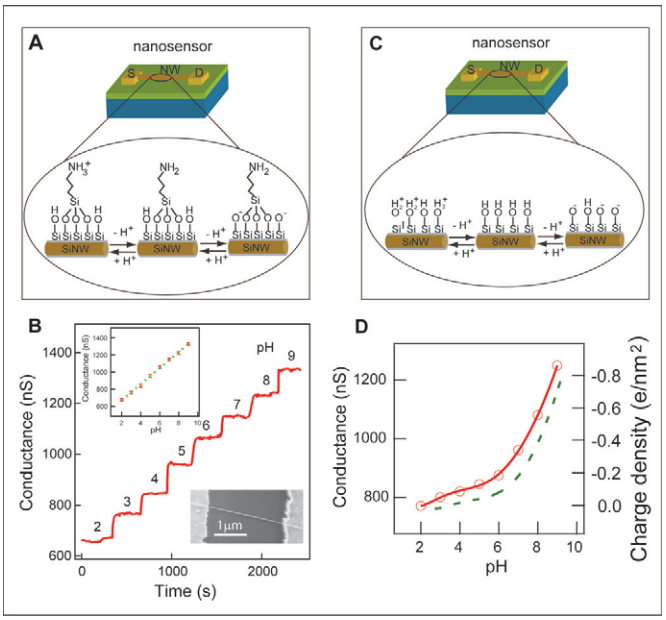

Fig. 2 Nanowire pH sensors. (A) Schematic of an amino-functionalized nanowire device and the protonation/deprotonation equilibria that change the surface charge state with pH. (B) Changes in nanowire conductance as the pH of solutions delivered to the sensor is varied from 2 to 9; inset is a plot of conductance data versus pH. (C) Schematic of an unmodified nanowire sensor containing silanol groups and the protonation/deprotonation equilibria that change the surface charge state with pH. (D) Conductance of an unmodified Si nanowire device (red) versus pH. The dashed green curve is a plot of the surface charge density for silanol groups on silica as a function of pH. (Adapted and reprinted with permission from[29]. © 2001 AAAS.)

Detection of proteins and DNA

Biological macromolecules, such as proteins and nucleic acids, are typically charged in aqueous solution and, as such, can be detected readily by nanowire sensors when appropriate receptors are linked to the nanowire active surface. The first example of detecting proteins in solution was carried out by our group using *p*-type Si nanowire devices in which the

molecule biotin, which binds with high selectivity to the protein streptavidin, was linked to the oxide surface of the nanowires, as illustrated schematically in Fig. 3A[29]. When solutions of streptavidin protein are delivered to nanowire sensor devices modified with biotin receptors, we find that the conductance increases rapidly to a constant value, and that this conductance value is maintained after the addition of pure buffer solution, as shown in Fig. 3B. These results are consistent with the net negative charge on streptavidin at the pH of these experiments (i.e. causing accumulation of carriers in *p*-type material) and the very small dissociation rate of the streptavidin-biotin system, respectively[47].

The key role of the biotin surface receptor for specific detection of streptavidin has also been demonstrated in several other experiments. For example, addition of a streptavidin solution to an unmodified Si nanowire does not produce a change in conductance, as shown in Fig. 3C. Blocking the streptavidin binding sites also leads to an absence of response from biotin-modified Si nanowire devices. In addition, this initial work showed that real-time electrical detection could be carried out down to concentrations of at least 10 pM, below the detection level required for a number of disease marker proteins. These experiments show that there is little nonspecific binding of the protein, that the binding interaction is highly specific, and that nanowire devices are ultrasensitive detectors, and thus provided clear indication that this approach could lead to the development of sensor devices of real value.

More recently, Si nanowire field-effect devices have been investigated as sensors for the detection of single-stranded DNA[33], where the binding of this negatively charged polyanionic macromolecule to *p*-type nanowire surfaces leads to an increase in conductance. Recognition of the DNA target molecules is carried out with a complementary sequence of single-stranded material, which in our studies was complementary peptide nucleic acids (PNAs)[48,49], as illustrated in Fig. 3D. PNA was used as a receptor for DNA detection since the uncharged PNA molecule has a greater affinity and stability than corresponding DNA recognition sequences[48,49]. Studies of *p*-type Si nanowire devices modified with a PNA receptor designed to recognize wild type versus the DF508 mutation site in the cystic fibrosis transmembrane receptor gene show that the conductance increases following addition of a 60 fM wild-type DNA sample solution, as shown in Fig. 3E. The increase in

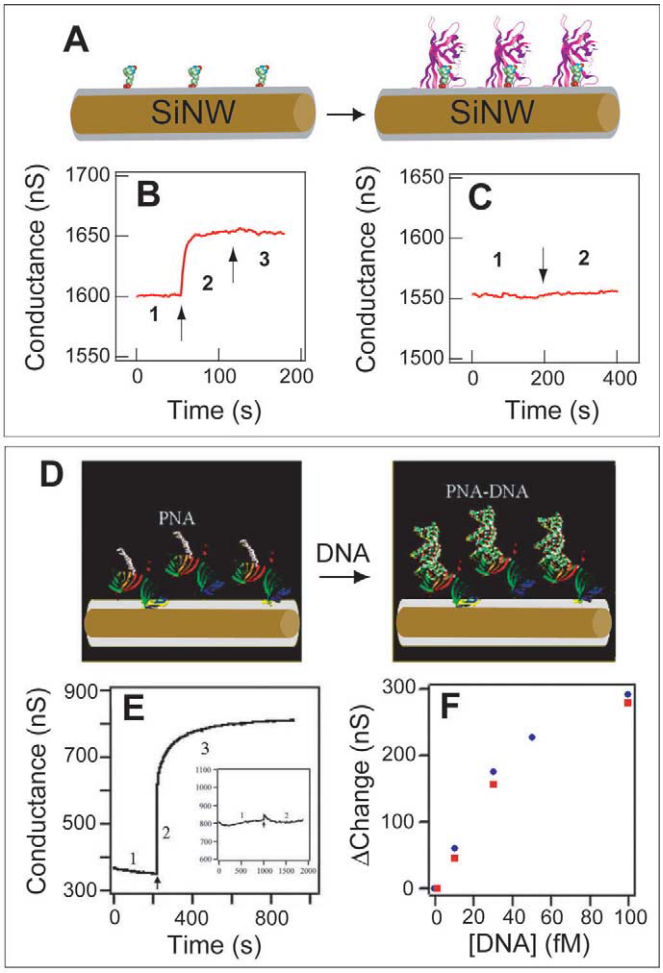

Fig. 3 Real-time detection of proteins and DNA. (A) Schematic of a biotin-modified Si nanowire and subsequent binding of streptavidin to the modified surface. (B) Plot of conductance versus time for a biotin-modified Si nanowire, where region 1 corresponds to the buffer solution, region 2 corresponds to the addition of 250 nM streptavidin, and region 3 corresponds to pure buffer solution. (C) Conductance versus time for an unmodified Si nanowire, where regions 1 and 2 are the same as in (B). (D) Schematic of a Si nanowire sensor surface modified with PNA receptor before and after duplex formation with target DNA. (E) Si nanowire DNA sensing where the arrow corresponds to the addition of a 60 fM complementary DNA sample and the inset shows the device conductance following addition of 100 fM mutant DNA. (F) Conductance versus DNA concentration, where data points shown in red and blue are obtained from two independent devices. (Reprinted with permission from[29,33]. © 2001 AAAS and 2004 ACS, respectively.)

conductance for the *p*-type Si nanowire device is consistent with an increase in the negative surface charge density associated with the binding of negatively charged DNA at the surface and, moreover, careful control experiments show that the binding response is specific to the wild-type sequence and that the sequence with the DF508 mutation site does not show this stable change in conductance (Fig. 3E, inset)[33]. The sequence specificity in these experiments is a critical first step toward the development of the nanowire devices for genetic-based disease detection.

There are several other features of the nanowire DNA sensors that deserve mention. First, the studies of the conductance change versus target sequence concentration demonstrate that direct electrical detection is possible down to at least the 10 fM level, as shown in Fig. 3F. Significantly, this current detection limit demonstrated in our studies is substantially better than that demonstrated by existing real-time measurements, including SPR[49], nanoparticle-enhanced SPR[50], and quartz-crystal microbalance[51] for DNA detection. Second, Fig. 3F also illustrates that the DNA detection data obtained from independent Si nanowire devices exhibit very similar changes in conductance with increasing DNA concentration. Device-to-device reproducibility is an important validation of the potential of Si nanowires for development as integrated sensors, which could enable high-throughput, highly sensitive DNA detection for biology research and genetic screening.

A tool for drug discovery

Organic molecules that bind specifically to proteins are central to the discovery and development of pharmaceuticals[52-54], and thus represent an important target for sensors. A representative example of this area is the identification of molecular inhibitors to tyrosine kinases, which are proteins that mediate signal transduction in mammalian cells through phosphorylation of a tyrosine residue of a substrate protein using adenonsine triphosphate (ATP), as shown in Fig. 4A[52,55]. Deregulation of the phosphorylation process has been linked to a number of diseases including cancer[52,55,56]. To configure nanowire sensor devices for screening small-molecule inhibitors to tyrosine kinases, we linked the kinase Abl to the surface of Si nanowire FETs and investigated the binding of ATP and competitive inhibition of ATP binding with organic molecules, such as the drug Gleevec®, as shown schematically in Fig. 4B[34]. In this configuration, binding or inhibition of binding of the negatively charged ATP to Abl linked at the Si nanowire surface is detected simply as an increase or decrease in the conductance of the *p*-type nanowire device, analogous to studies discussed above for protein and nucleic acid binding.

Time-dependent data recorded from Abl-modified *p*-type Si nanowire devices exhibit reversible, concentration-dependent increases in conductance upon introducing solutions containing ATP. The increases in conductance are consistent with the binding of negatively charged ATP to Abl. Of perhaps greater importance is the ability to quantify inhibition of ATP binding by Gleevec and other small molecules shown in Fig. 4C. Plots of the normalized conductance recorded from Abl-modified *p*-type Si nanowire devices exhibit reversible decreases in conductance because of competitive inhibition of ATP binding by the different small molecules, as shown in Fig. 4D. Notably, the conductance decreases at constant small molecule concentration, which demonstrates that the degree of inhibition depends strongly on molecular structure with Gleevec > A1 > A2 > A3; the control biotin shows essentially no change above background as expected. These studies demonstrate the advantages of the nanowire devices over

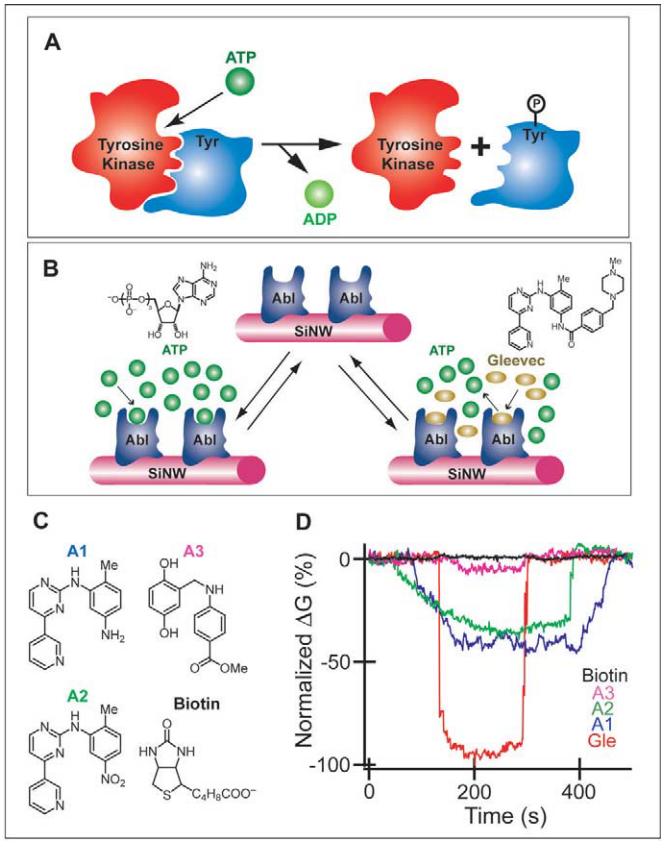

Fig. 4 Nanowire sensors for drug discovery. (A) Illustration of tyrosine kinase function, where ATP binds to the kinase active site and then phosphate is transferred to a tyrosine (Tyr) residue of the substrate protein. (B) Detection of ATP binding and small-molecule inhibition using a Si nanowire sensor device functionalized with the tyrosine kinase Abl. The kinase is covalently linked to the surface of a Si nanowire and then the conductance of the nanowire device is monitored to detect ATP binding and the competitive inhibition of ATP binding by Gleevec. (C) Structures of small molecules investigated for the inhibition of ATP binding to Abl. (D) Normalized conductance versus time data recorded from Abl-modified Si nanowire devices using solutions containing 100 nM ATP and 50 nM small molecule Gleevec (red), A1 (blue), A2 (green), A3 (pink), and biotin (black). (Reprinted with permission from[34]. © 2005 National Academy of Sciences, USA.)

existing methods in terms of rapid, direct, and high-sensitivity readout using minimal protein receptor, and thus suggest great potential of nanowire sensors as a new (nano) technology platform for drug discovery.

Pushing sensitivity limits: detection of single viruses

The studies reviewed above demonstrate some of the exciting capabilities of nanowire sensors for the detection of both biological and chemical species in solution. While these studies implicitly show exquisite sensitivity unmatched by existing label-free sensor devices, they do not define the ultimate sensitivity of nanowire FET devices. To address this critical issue, our group recently carried out studies of the detection of viruses[35], which are among the most important causes of human disease[57] and an increasing concern as agents for biological warfare and terrorism[58,59], with the goal of determining whether the ultimate limit of one single entity could be detected reliably.

The underlying concept of our experiments is illustrated schematically in Fig. 5A. When a virus particle binds to an antibody receptor on a nanowire device, the conductance of that device will change from the baseline value, and when the virus unbinds again, the conductance will return to the baseline value. Significantly, delivery of highly dilute influenza A virus solutions, on the order of 80 aM (10^{-18} M) or 50 viruses/μl, to *p*-type Si nanowire devices modified with monoclonal antibody for influenza A produces well-defined, discrete conductance changes (Fig. 5B) that are characteristic of binding and unbinding of single negatively charged influenza viruses[35]. Definitive proof that the discrete conductance changes observed in these studies are the result of the detection of single virus binding/unbinding was obtained from simultaneous optical and electrical measurements using fluorescently labeled influenza viruses. The optical and electrical data in Fig. 5B show that, as a virus diffuses near a nanowire device, the conductance remains at the baseline value, and only after binding at the nanowire surface does the conductance drop in a quantized manner similar to that observed with unlabeled viruses; as the virus unbinds and diffuses from the nanowire surface the conductance returns rapidly to the baseline value. These parallel measurements also show that a virus must be in contact with the nanowire device to yield an electrical response, suggesting that it will be possible to develop ultradense nanowire device arrays without crosstalk in

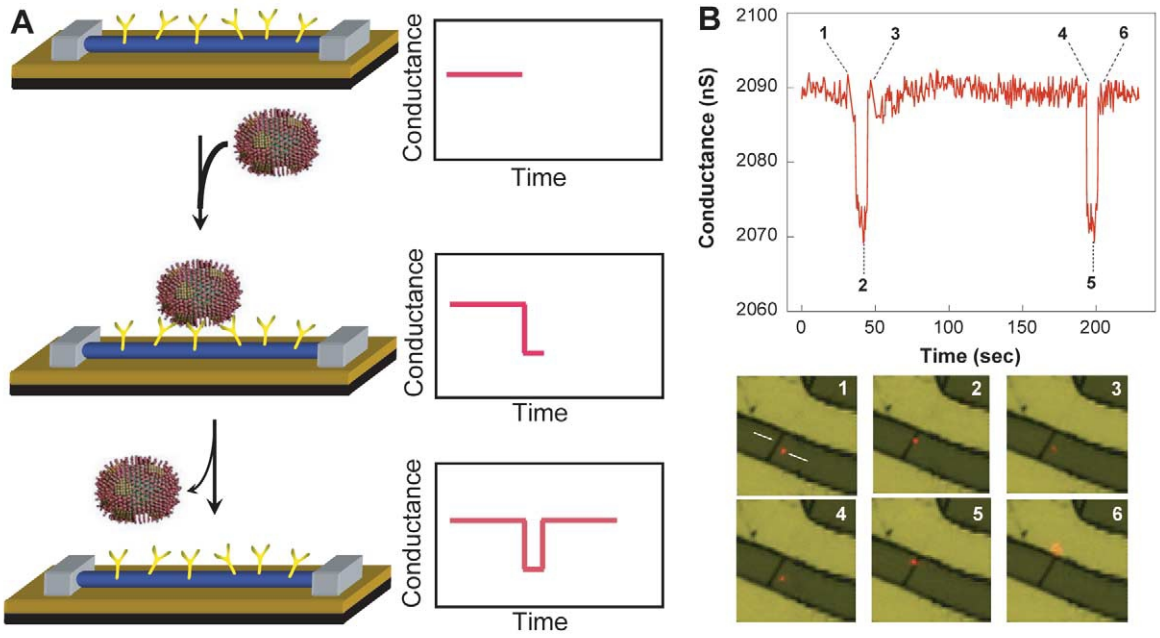

Fig. 5 (A) Schematic of a single virus binding and unbinding to the surface of a Si nanowire device modified with antibody receptors and the corresponding time-dependent change in conductance. (B) Simultaneous conductance and optical data recorded for a Si nanowire device after the introduction of influenza A solution. The images correspond to the two binding/unbinding events highlighted by time points 1-3 and 4-6 in the conductance data, with the virus appearing as a red dot in the images. (Reprinted with permission from[35]. © 2004 National Academy of Sciences, USA.)

future, where the minimum size scale is set by that of the virus.

In addition to meeting the ultimate sensitivity challenge of single-particle electrical detection with nanowire FET devices, this achievement of single-particle or stochastic sensing offers scientific advantages and opens up opportunities[60,61]: the sensor detection limit is not set by the receptor affinity for the target of interest as in equilibrium measurements; the analysis of single particle on/off times provides direct information about binding kinetics crucial to understanding virus-receptor interactions; and single-particle sensitivity enables simple charge-based detection of macromolecules.

Assembling arrays and multiplexed detection

One extremely attractive feature of the nanowire FET sensors reviewed above is their potential for integration into electrically addressable sensor arrays. Our group has recently reported strategies that enable parallel and scalable integration of nanowire FET devices over large areas without the need to register individual nanowire-electrode interconnects[24,62-64], thus moving well beyond methods in which a serial lithography is used to connect nanostructures one-by-one. Electrically addressable arrays are fabricated by a process that uses fluid-based assembly, such as microfluidic[62] or Langmuir-Blodgett[24,63,64] methods, to align and set the average spacing of nanowires over large areas, and then photolithography to define interconnects, as shown in Fig. 6A. A key feature of this approach is that the metal electrodes defined by conventional lithography do not need to be registered to individual nanowires in an array to achieve a high yield of devices; only the position of the electrodes relative to a group of aligned nanowires needs to be fixed.

An example of a state-of-the-art sensor array fabricated in this way and containing greater than 100 addressable elements is shown in Fig. 6B, where all of the active nanowire sensor devices are confined to a central rectangular area on the device chip that overlaps with the microfluidic sample delivery channel illustrated in blue. Critical to the success of any integrated nanoelectronic array is the reproducibility of the device elements within the array. Significantly, measurements made on nanowire FET arrays have exhibited very reproducible and high-performance properties[24,64]. For example, plots of current versus gate voltage for nine devices all exhibit on/off current ratios greater than a million, as shown in Fig. 6C. Moreover, the histograms obtained from the analysis of transconductance and turn-on threshold voltage data are well defined, as illustrated in Figs. 6C and 6D, and highlight the reproducibility of nanowire FET devices. The relatively narrow distributions are quite promising for sensor and other applications, where uniformity of device characteristics is important.

The device arrays prepared in this way offer unique opportunities for label-free multiplexed detection of biological and chemical species, and our group has recently reported initial studies in this direction with the multiplexed detection of distinct viruses at the single-virus level[35]. Experiments were carried out as illustrated in Fig. 7A, where two different nanowire sensor devices are modified with antibody receptors specific for the different viruses. In dilute solutions, where single-molecule encounters dominate,

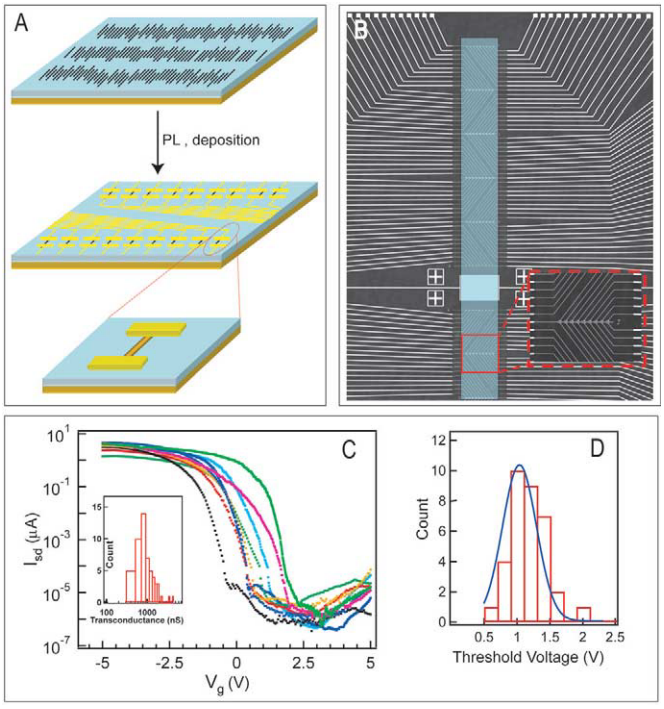

Fig. 6 Si nanowire device arrays. (A) Illustration of the nanowire assembly and metal contact deposition steps used to fabricate large nanowire arrays. (B) Optical image of the upper portion of a sensor device array, where the inset shows one row of individually addressable nanowire elements. The blue rectangle highlights the position of the microfluidic channel used to deliver samples and overlap the active elements. (C) Current (I_{sd}) versus gate voltage (V_g) for a sampling of Si nanowire FETs prepared in this way, where the histogram summarizes the transconductance values obtained from the same array of devices. (D) Histogram of the threshold voltage for devices with a five times higher nanowire density than shown in Fig. 6C. (Reprinted with permission from[24,35]. © 2004 ACS and National Academy of Sciences, USA, respectively.)

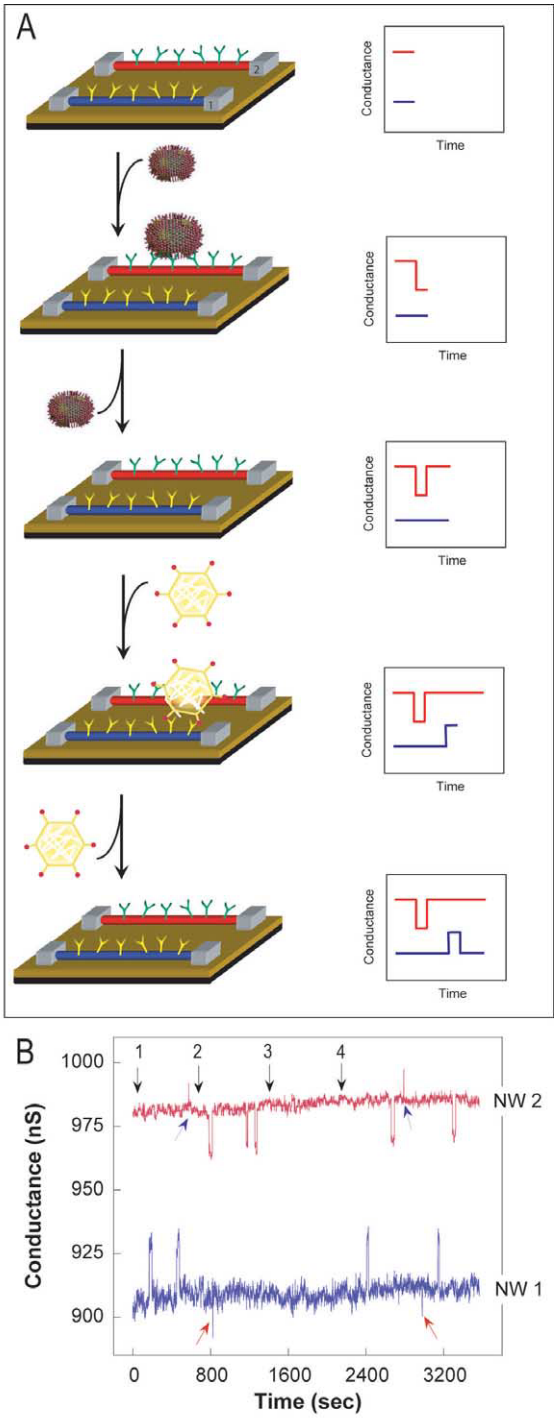

Fig. 7 (A) Schematic of multiplexed single-virus detection using Si nanowire devices modified with antibody receptors for specific viruses. The specific binding/unbinding and corresponding conductance changes are illustrated for two events involving viruses with opposite charges. (B) Simultaneous conductance versus time data from two Si nanowires elements, where NW 2 was modified with antibodies for influenza A (red data) and NW 1 was modified with antibodies for adenovirus (blue data). Black arrows 1-4 correspond to the introduction of adenovirus, influenza A, pure buffer, and a 1:1 mixture of adenovirus and influenza A. Small red and blue arrows highlight conductance changes corresponding to the diffusion of viral particles past the nanowire and not specific binding. (Reprinted with permission from[35]. © 2004 National Academy of Sciences, USA.)

selective multiplexed detection will manifest itself as discrete events characteristic of the binding/unbinding of the different target viruses at the different sensor elements. The surface charges on the two different viruses shown in Fig. 7A have opposite signs and thus lead to conductance decreases and increases when binding to the specific receptors on the respective nanowire devices.

This concept was implemented by modifying the surfaces of *p*-type Si nanowire devices in an array with antibody receptors specific either for influenza A (nanowire NW 2) or for adenovirus (NW 1). Simultaneous conductance measurements obtained when adenovirus, influenza A, and a mixture of both viruses are delivered to the devices, shown in Fig. 7B, demonstrate several significant points. First, delivery of adenovirus, which is negatively charged at the pH of the experiment[35], to the device array yields positive conductance changes for NW 1 with an on/off time similar to the selective binding/unbinding in single-device experiments. Well-defined binding/unbinding events are not observed from the nanowire device modified with the influenza virus receptor. Second, delivery of influenza A solutions yields negative conductance changes for NW 2 similar to the single device measurements of Fig. 5B, while well-defined bind/unbinding is not observed on NW 1. Last, delivery of a mixture of both viruses demonstrates unambiguously that selective binding/unbinding responses for adenovirus and influenza A can be detected in parallel by NW 1 and NW 2, respectively, at the single-virus level, as shown in region 4 of Fig. 7B. Significantly, the simplicity, single viral particle sensitivity, and capability of selective multiplexed detection directly suggest that nanowire sensors could serve as the key element in powerful viral-sensing devices for medical and bioterrorism applications.

Concluding remarks

We have shown that nanowire field-effect sensor devices modified with specific surface receptors represent a powerful detection platform for a broad range of biological and chemical species in solution. These nanowire sensor devices have a number of key features, including direct, label-free, and real-time electrical signal transduction, ultrahigh sensitivity, exquisite selectivity, and potential for integration of addressable arrays on a massive scale, which sets them apart from other sensor technologies available today. The examples described in this review illustrate unique

capabilities in the detection of proteins, viruses, and DNA to the analysis of small organic molecule binding to proteins, which has the potential to impact significantly on disease diagnosis, genetic screening, and drug discovery, as well as serve as powerful new tools for research in many areas of biology. In the near future, we argue that these advances could and should be developed at the commercial level in simple nanowire sensor devices that would represent a clear application of nanotechnology and, more importantly, a substantial benefit to humankind. Looking to the longer term, we believe the future is exciting from both science and technology perspectives. For example, we believe that advances in capabilities of assembling larger and more complex nanowire sensor arrays and integrating them with first conventional and later nanoscale electronics for processing will lead to exquisitely powerful sensor systems that help to enable the dream of personalized medicine in the future. Moreover, recognizing the fact that these nanowire sensors transduce chemical/biological binding events into electronic/digital signals suggests the potential for a highly sophisticated interface between nanoelectronic and biological information processing systems in the future. MT

Acknowledgments

We thank Gengfeng Zheng, Wayne Wang, Song Jin, Dongmok Whang, and Michael McAlpine for contributions to the work presented in this article. Charles Lieber acknowledges generous support of this work by the Defense Advanced Research Project Agency, National Cancer Institute, and Ellison Medical Foundation.

REFERENCES

1. Morales, A. M., and Lieber, C. M., *Science* (1998) **279**, 208
2. Hu, J., *et al.*, *Acc. Chem. Res.* (1999) **32** (5), 435
3. Lieber, C. M., *MRS Bull.* (2003) **28** (7), 486
4. Cui, Y., *et al.*, In: *Nanowires and Nanobelts – Materials, Properties and Devices*, Wang, Z. L., (ed.), Kluwer Academic Publishers (2003), 3
5. Samuelson, L., *Materials Today* (2003) **6** (10), 22
6. Xia, Y., *et al.*, *Adv. Mater.* (2003) **15** (5), 353
7. Wang, Z. L., *Materials Today* (2004) **7** (6), 26
8. Niemeyer, C. M., *Angew. Chem. Intl. Ed.* (2001) **40** (22), 4128
9. Chan, W. C. W., *et al.*, *Curr. Opin. Biotechnol.* (2002) **13** (1), 40
10. West, J. L., and Halas, N. J., *Annu. Rev. Biomed. Eng.* (2003) **5**, 285
11. Alivisatos, P., *Nat. Biotechnol.* (2004) **22**, 47
12. Gould, P., *Materials Today* (2004) **7** (2), 36
13. Cui, Y., *et al.*, *J. Phys. Chem. B* (2000) **104** (22), 5213
14. Duan, Y., *et al.*, *Nature* (2001) **409**, 66
15. Cui, Y., and Lieber, C. M., *Science* (2001) **291**, 851
16. Huang, Y., *et al.*, *Science* (2001) **294**, 1313
17. Gudiksen, M. S., *et al.*, *Nature* (2002) **415**, 617
18. Huang, Y., *et al.*, *Nano Lett.* (2002) **2** (2), 101
19. Lauhon, L. J., *et al.*, *Nature* (2002) **420**, 57
20. Cui, Y., *et al.*, *Nano Lett.* (2003) **3** (2), 149
21. McAlpine, M. C., *et al.*, *Nano Lett.* (2003) **3** (11), 1531
22. Zhong, Z., *et al.*, *Science* (2003) **302**, 1377
23. Panev, N., *et al.*, *Appl. Phys. Lett.* (2003) **83** (11), 2238
24. Jin, S., *et al.*, *Nano Lett.* (2004) **4** (5), 915
25. Greytak, A. B., *et al.*, *Appl. Phys. Lett.* (2004) **84** (21), 4176
26. Wu, Y., *et al.*, *Nature* (2004) **430**, 61
27. Zheng, G., *et al.*, *Adv. Mater.* (2004) **16** (21), 1890
28. Bjork, M. T., *et al.*, *Nano Lett.* (2004) **4** (9), 1621
29. Cui, Y., *et al.*, *Science* (2001) **293**, 1289
30. Comini, E., *et al.*, *Appl. Phys. Lett.* (2002) **81** (10), 1869
31. Zhou, H. T., *et al.*, *Chem. Phys. Lett.* (2003) **369** (1-2), 220
32. Li, C., *et al.*, *Appl. Phys. Lett.* (2003) **82** (10), 1613
33. Hahm, J., and Lieber, C. M., *Nano Lett.* (2004) **4** (1), 51
34. Wang, W., *et al.*, *Proc. Natl. Acad. Sci. USA* (2005) **102**, 3208
35. Patolsky, F., *et al.*, *Proc. Natl. Acad. Sci. USA* (2004) **101**, 14017
36. Kolmakov, A. and Moskovits, M., *Annu. Rev. Mater. Res.* (2004) **34**, 151
37. Wan, Q., *et al.*, *Appl. Phys. Lett.* (2004) **84** (18), 3654
38. Sze, S. M., *Physics of Semicondutor Devices*, Wiley, New York (1981), 431
39. Bergveld, P., *IEEE Trans. Biomed. Eng.* (1972) **BME-19**, 342
40. Blackburn, G. F., In: *Biosensors: Fundamentals and Applications*, Turner, A. P. F., *et al.* (eds.), Oxford University Press, Oxford (1987), 481
41. Hafeman, D. G., *et al.*, *Science* (1988) **240**, 1182
42. Cui, Y., *et al.*, *Appl. Phys. Lett.* (2001) **78** (15), 2214
43. Wu, Y., *et al.*, *Nano Lett.* (2004) **4** (3), 433
44. Iler, R. K., *The chemistry of silica*, John Wiley & Sons, New York (1979)
45. Bartlett, P. N., In: *Handbook of Chemical and Biological Sensors*, Taylor, R. F., and Schultz, J. S. (eds.), IOP Publishing, Philadelphia (1996), 139
46. Bolt, G. H., *J. Phys.Chem.* (1957) **61** (9), 1166
47. Bayer, E. A., and Wilchek, M., *Methods Enzymol.* (1990) **184**, 49
48. Nielsen, P. E., *et al.*, *Science* (1991) **254**, 1497
49. Jensen, K. K., *et al.*, *Biochem.* (1997) **36** (16), 5072
50. He, L., *et al.*, *J. Am. Chem. Soc.* (2000) **122** (38), 9071
51. Hook, F., *et al.*, *Langmuir* (2001) **17** (26), 8305
52. Grosios, K., and Traxler, P., *Drugs Future* (2003) **28**, 679
53. Strausberg, R. L., and Schreiber, S. L., *Science* (2003) **300**, 294
54. Stockwell, B. R., *Trends Biotechnol.* (2000) **18** (11), 449
55. Becker, J., *Nat. Biotechnol.* (2004) **22**, 15
56. Blume-Jensen, P., and Hunter, T., *Nature* (2001) **411**, 355
57. Stadler, K., *et al.*, *Nat. Rev. Microbiol.* (2003) **1**, 209
58. Atlas, R. M., *Nat. Rev. Microbiol.* (2003) **1**, 70
59. Niiler, E., *Nat. Biotechnol.* (2002) **20**, 21
60. Weiss, S., *Nat. Struct. Biol.* (2000) **7**, 724
61. Zhuang, X., and Rief, M., *Curr. Opin. Struct. Biol.* (2003) **13** (1), 88
62. Huang, Y., *et al.*, *Science* (2001) **291**, 630
63. Whang, D., *et al.*, *Nano Lett.* (2003) **3** (9), 1255
64. Whang, D., *et al.*, *Jpn. J. Appl. Phys.* (2004) **43** (7B), 4465