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Review

Challenges in the use of 1D nanostructures for on-chip biosensing and diagnostics: A review

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ABSTRACT

This review outlines the use of one-dimensional nanostructures (1D-NS) for the detection of biomolecules on a chip. The materials discussed here include carbon nanotubes, metallic and semiconducting nanowires and nanochannels. While nanotubes and naowires have predominantly been used as electrical detectors, nanochannels are promising frameworks for optical detection in applications such as separation, preconcentration and DNA mapping. The primary expectation for all the three types of 1D-NS lies in the promise for ultimate single molecule detection. Furthermore, the electrical double layer governs the physics behind biosensing in all the three systems. The review starts by shedding light on the advantages arising due to the use of 1D nanostructures, followed by a discussion of fundamental aspects such as double layer effects and sensing methodologies. After this, the three kinds of 1D-NS are introduced. The main focus of the review is an in-depth analysis of the current achievements in the field and the major challenges that are to be overcome for the widespread use of such nanostructures in applications such as lab-on-a-chip devices and point-of-care diagnostics.

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1. Introduction

Nanotechnology is emerging as a major discipline that is driving applications in a broad spectrum of fields through diverse strategies and architectures. Analytical (bio) chemistry, medical diagnostics (Merkoci, 2009), and environmental science (Krug, 2008) are undergoing revolutionary changes through the introduction of nanoscale materials and systems. Higher sensitivity and shorter response times are two main advantages of using nanosystems for analytical purposes. Furthermore, the current trend is towards the realization of miniaturized analytical systems such as lab-on-a-chip devices, where complete analytical stages will be integrated on just a single chip (Janasek et al., 2006). A major consequence will be the possibility to perform analysis and diagnostics on a desktop device or close to the patient in hospitals (Yager et al., 2006). Nanostructures are ideally suited for such devices, since they can be integrated easily as active elements on microscale chips along with other preprocessing stages (Lee et al., 2009). Unlike microelectronics applications – where billions of nanodevices must be prepared on a cm-sized chip to be competitive with conventional devices – the analytical applications require just a few active nanosensors to be integrated on a chip, which makes them highly viable for a variety of applications.

In this review, we will focus on one class of nanostructures namely one-dimensional nanostructures (1D-NS), wherein two dimensions are of the order of 100 nm or less. Typical examples of such structures include carbon nanotubes, nanowires and nanochannels. An incredible amount of research is being performed using such nanostructures just for analytical applications. The scope of this review will be restricted to the use of such materials as an active element in an analytical system. We will not discuss experiments where such nanomaterials are used to augment other microscale or bulk active materials. Reviews for the use of such configurations can be found elsewhere (Wang, 2006; Balasubramanian and Burghard, 2006; Chopra et al., 2007; Sadik et al., 2009).

The review starts with a discussion of fundamental aspects related to nanoscale devices namely the advantages of working at the nanoscale, the diverse sensing methodologies both currently prevalent and novel nanoscale-specific methods and finally the electrical double layer. Following this, the three kinds of 1D-NS that are a focus of this study will be introduced. The 1D-NS can be manufactured in a variety of different methods and the assembly into a device is specific to the application. Hence this discussion will include a short overview of those preparation methods that have been used to realize sensing devices. The fourth section is devoted to various challenges facing the use of 1D nanostructures and their deployment in real-life applications as well as their use in fundamental studies. The review concludes with a summary and perspectives for future directions.

2. Fundamentals

2.1. Why nanoscale?

In order to arrive at the challenges facing the use of 1D-NS for analytical applications it is important to have a closer look at the fundamental aspects related to the design of 1D-NS-sensors. The first question that arises is why a nanoscale active element is needed, or what can a nanoscale active element improve in a detection process. The major advantage of using a 1D-NS comes from the increase in sensitivity due to the high surface-to-volume ratio (Wanekaya et al., 2006). Every atom of a 1D-NS such as a SWCNT is a surface atom and hence it is an ideal system with maximized surface-to-volume ratio, using which it should be theoretically possible to attain absolute sensitivity. This aspect is reflected in a number of experiments, where generally a very low detection limit is observed using 1D-NS-based biosensors (Hahm and Lieber, 2004; Gao et al., 2007; Star et al., 2006). It is worth-mentioning here that selectivity of 1D-NS-biosensors is dependent mainly on the biochemistry, similar to the case of microscale or bulk systems and hence is not a major advantage at the nanoscale.

A further advantage of 1D-NS systems is the label-free nature of detection, especially when using nanowires and nanotubes as electrical detectors. In most of the cases, the analyte molecules do not require labeling as they can be detected directly on the surface through sensitive molecular interactions (Star et al., 2006; Wang, 2005a; Stern et al., 2007a). This is augmented by the fact that the biomolecules to be detected such as DNA and proteins have similar dimensions as that of 1D-NS. Furthermore, the small footprint of the 1D-NS-sensors reduces the demand on the amount of sample solution needed for performing the sensing trial. This is true also for optical detection using nanochannels (Levy and Craighead, 2010). The ability to detect with very low sample volumes may be crucial in some applications, where real-life samples are available in critically small amounts. Finally, the possibility to integrate a number of such devices on a small chip is another key advantage (Kim et al., 2009), as a consequence of which the size of the final analytical system is determined by the preprocessing and other control elements, and not anymore by the active element.

2.2. Sensing methodologies

There are mainly two sensing methodologies that are relevant to 1D-NS based detection systems, namely optical and electrical. Optical methodologies utilize the 1D-NS as a marker (such as carbon nanotubes) or as a system (such as nanochannels). Typically, zero-dimensional nanostructures such as quantum dots are used as labels in bioanalytical applications (Frasco and Chaniotakis, 2010). Recently, carbon nanotubes are also emerging as efficient labels for optical biosensors. In these experiments, either the fluorescence from semiconducting carbon nanotubes (Barone et al., 2005) or the Raman intensity (Chen et al., 2008) is used as the sensor signal. While in the former case the sensor works in solution, in the latter case, protein microarrays have been demonstrated in a sandwich configuration. Nanochannels, on the other hand are used as a framework, where the biomolecules can be detected with a higher sensitivity in comparison to their microscale counterparts (Tsukahara et al., 2010; Kovarik and Jacobson, 2009).

Electrical methods rely on the use of an electrical measurement as a sensor signal. A simple electrical element is a resistor and a sensor that uses resistance as the sensor signal is often termed a chemiresistor. Due to the improved surface-to-volume ratio of 1D-NS-elements, this configuration is highly suited for the realization of biosensors. Other similar methods include the measurement of capacitance or in general the impedance of the device. In case of the active element being a semiconductor, a back-gate can be used to modulate the conductance of the device. Some kinds of metallic nanostructures (such as carbon nanotubes) also show a slight modulation in conductance with the back-gate voltage. This field-effect transistor (FET) configuration has been extensively used in 1D-NS-sensors. In all these cases, affinity-based detection is employed, where the analyte interactions with a bound receptor directly change the resistance or capacitance characteristics of the 1D-NS and the sensor responses are measured in air (Star et al., 2003; Besteman et al., 2003).

In order to detect an analyte based on a reaction (for e.g. enzymatic reaction), electrochemical methods are used. Here, individual or few nanowires/nanotubes act as the working electrode in an electrochemical cell realized on a chip (Balasubramanian and Burghard, 2006; Wei et al., 2009; Wanekaya et al., 2006). Amperometric detection is widely used, where the current is measured at

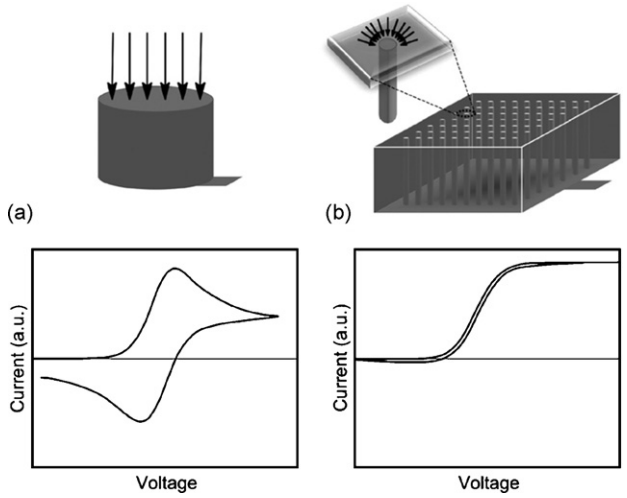

Fig. 1. (a) Macroscopic electrode with planar diffusion and its corresponding cyclic voltammogram. (b) Nonplanar radial diffusion at a nanoelectrode and the corresponding steady state voltammogram when cycling at a slow rate. Both cases were conducted in an aqueous solution containing ferrocene (reprinted with permission from Wei et al., 2009).

a constant applied voltage at which the reaction is known to occur. In principle, this is a direct nanoscale analogue of microscale or bulk electrochemical electrodes. The main advantage of a nanoscale electrode is its ability to mediate fast electron kinetics with a wide range of electroactive species (Wang, 2006). Furthermore, the capacitance of the electrode is considerably reduced due to the smaller surface area leading to a lower RC time constant enabling the possibility to observe fast electron transfer and the associated reaction dynamics (Andrieux et al., 1990; Wei et al., 2009). Further benefits include the possibility to work in poorly conducting media and improved mass transfer due to radial nonplanar diffusion (Wei et al., 2009; Zoski, 2002) as shown in Fig. 1. It is also possible to use other electrochemical methods such as voltammetry, potentiometry and impedance-based detection. However, the extensive amount of research available in these configurations utilizes 1D-NS mainly as an additional sensor component to improve the performance of a microscale electrochemical sensing system (Hu and Hu, 2009; Siqueira et al., 2010; Vaddiraju et al., 2010; Wei et al., 2009; Xu et al., 2009; Yogeswaran and Chen, 2008).

An important aspect to be considered while using electrochemical methods of detection is the use of a reference electrode. Many strategies have been developed to realize reliable reference electrodes on-chip (Guth et al., 2009; Suzuki et al., 1999). Ag/AgCl is the electrode of choice, which gives the most stable reference potential. Platinum has also been used as a pseudo reference electrode in many applications, although it has some limitations such as potential drifts over long intervals (Lisdath et al., 1990). The use of a reference electrode in general is important for measurements in liquid where reproducibility over long time intervals is necessary such as in reusable sensor systems (Guth et al., 2009) (Table 1).

There is a third configuration, namely the ion selective field-effect transistor (ISFET) configuration. In this configuration, an FET is coupled to a potentiometric sensing element (Bergveld, 2003). Potentiometric detection works by measuring the potential of an electrochemical cell when there is no current flowing through the system, under which conditions, the measured potential is related to the concentration of the electroactive species (Bard and Faulkner, 2000). An FET coupled to the electrochemical cell amplifies this potential, and thereby the reaction can be monitored sensitively. An ISFET comprises of a semiconductor contacted by source and drain electrodes with an appropriate reference electrode acting as the gate. The source and drain electrodes are passivated and only the active element is in contact with the solution containing the analyte to be detected. The reference electrode that is in contact with the solution is used to tune the conductance of the transistor channel. In such a scenario, the electrical double layer at the interface between the active material and the liquid serves as the gate capacitor modulating the conductance (Balasubramanian et al., 2008).

The ISFET configuration is ideally suited for affinity-based detection, whereby the receptor is immobilized on the semiconductor surface. When analytes dock on the surface of the transistor channel with the receptor, they produce variations in the surface potential and in turn changes in the gate capacitance, which can be detected as a shift in the threshold voltage or a change in the sub-threshold swing of the transistor characteristics (Heller et al., 2008). A number of sensors based on nanotubes and nanowires demonstrated until today fall under this category (Heller et al., 2008; Besteman et al., 2003; Bradley et al., 2003; Tang et al., 2006; Maroto et al., 2007; Pachauri et al., 2010; Vlandas et al., 2010). They are often referred to as liquid-gated or electrochemically-gated field-effect transistors.

It can be often found in the literature that back-gated FETs are also operated in liquids. Although many publications have demonstrated a sensing response using such devices, the concept of this device poses some problems. First, whenever a material is immersed in a liquid, the surface charge has to be controlled using a well-defined reference, in the absence of which unknown drifts become unavoidable (Larrimore et al., 2006; Minot et al., 2007). Secondly, using a back-gate not only changes the surface potential of the active system but also changes the surface charge of the insulating oxide, as has been observed clearly in many nanochannel studies (Sparreboom et al., 2009; Zhou et al., 2008). This in turn might introduce shifts, which cannot be neglected, as the nanosystem lies within the double layer of the device substrate. Thirdly,

Table 1
showing the total ionic strength (I) and the Debye screening length (κ^{-1}) of various electrolyte solutions (1 mM PBS, 0 or 1 mM $NiCl_2$, pH = 7.5, T = 25 °C) (reprinted with permission from Birner et al., 2008).

Ion	0 mM KCl	10 mM KCl	50 mM KCl	90 mM KCl	140 mM KCl
$[H_2PO_4^-]$	0.303	0.256	0.214	0.192	0.176
$[HPO_4^{2-}]$	0.697	0.740	0.786	0.808	0.824
$[PO_4^{3-}]$	0.135×10^{-4}	0.206×10^{-4}	0.335×10^{-4}	0.430×10^{-4}	0.524×10^{-4}
$[Na^+]$	1.697	1.740	1.786	1.808	1.824
$[K^+]$	0	10	50	90	140
$[Cl^-]$	0	10	50	90	140
$[Ni^{2+}]$	0	1	1	1	1
$[Cl^-]$	0	2	2	2	2
$[H^+]$	0.316×10^{-4}	0.316×10^{-4}	0.316×10^{-4}	0.316×10^{-4}	0.316×10^{-4}
$[OH^-]$	0.316×10^{-3}	0.316×10^{-3}	0.316×10^{-3}	0.316×10^{-3}	0.316×10^{-3}
I (mM)	2.393	15.481	55.573	95.616	145.648
κ (nm^{-1})	0.159	0.405	0.768	1.007	1.243
κ^{-1} (nm)	6.277	2.468	1.302	0.993	0.805

back-gated field-effect characteristics are often imposed with a prominent hysteresis (Star et al., 2006), which is another important disturbance in the use of the device as a stable sensing system. While repeated use of such sensors appears not feasible due to the drift from one measurement cycle to another, these sensors have played a vital role in understanding the interactions of analytes on the surface of 1D-NS-sensors.

2.3. The electrical double layer

As soon as any metal or semiconductor is brought in touch with a liquid a double layer is formed (Bard and Faulkner, 2000). The double layer formed at the interface between the nanoscale system and the liquid is where electron transfer or charge variation takes place. Furthermore the capacitance of the EDL constitutes the gate capacitance of the ISFET (Bergveld, 2003; Rosenblatt et al., 2002). In nanochannels, the double layer dictates a number of processes, as its size becomes comparable to the channel dimensions (Sparreboom et al., 2010). With very small nanochannels (cross-section less than twice the double layer thickness), the EDL of opposite surfaces might even overlap under certain conditions (Kovarik and Jacobson, 2009).

Two factors play an important role in the formation of the EDL namely solution pH and ionic strength. The surface of a material in contact with the liquid carries a certain charge, which is a function of the solution pH and the isoelectric point (Stryer, 1995; Holme and Peck, 1998; Skoog and West, 2003). This charge density in turn determines the surface potential as shown in Fig. 2(A). Ions of opposite charge in the solution assemble at the surface forming the electrical double layer. Hence the thickness of the EDL or the Debye screening length is a function of the ionic strength of the solution as shown in the calculated curve in Fig. 2(B). It is apparent that the Debye screening length increases exponentially with decreasing ionic strength. Depending on the kind of ions present in the solution, the dielectric constant of the EDL and hence the capacitance varies, which in turn influences the device characteristics.

For most of the applications, based on 1D-NS, the surface is usually negatively charged. This is due to the fact that surfaces such as glass or SiO_2 have a very low isoelectric point (pI) of around 3 and hence with aqueous solutions at neutral pH, the surface is negative. This phenomenon has been utilized to control flow in many nanochannel applications (Yuan et al., 2007; Daiguji, 2010). For carbon nanotubes and nanowires that are used as electrical sensors, it has to be kept in mind that the active material lies in a sea of negative charge. If the ionic strength of the solution is very low, the extension of a screening positively charged layer might be very large and the 1D-NS might be submerged inside this layer.

On the other hand, the 1D-NS itself also possesses an EDL, which is related in the same way to the ionic strength as the surface where the 1D-NS is placed. The thickness of this layer has important consequences for the detection capability. For affinity-based detection it might be important to have the binding event happen within the EDL (Roy and Gao, 2009; Zhang et al., 2008). This might mean that the EDL has to be large enough to accommodate big receptors such as antibodies. However, a large EDL would imply a low ionic strength, which would mean that the system would go further away from a realistic scenario, since most biological fluids work at high ionic strength (0.1 M or more) (Stryer, 1995). This tradeoff has to be carefully analyzed while realizing 1D-NS-based sensors.

3. Materials

As the main focus of this review is on the challenges of realizing 1D-NS-analytical systems, we will only give a brief overview of the various 1D-NS materials. Extended reviews can be found in the literature for nanotubes and nanowires (Chopra et al., 2007; Liu, 2008; Roy and Gao, 2009; Shen et al., 2009; Yogeswaran and Chen, 2008) and nanochannels (Bocquet and Charlaix, 2010; Persson and Tegenfeldt, 2010; Tsukahara et al., 2010).

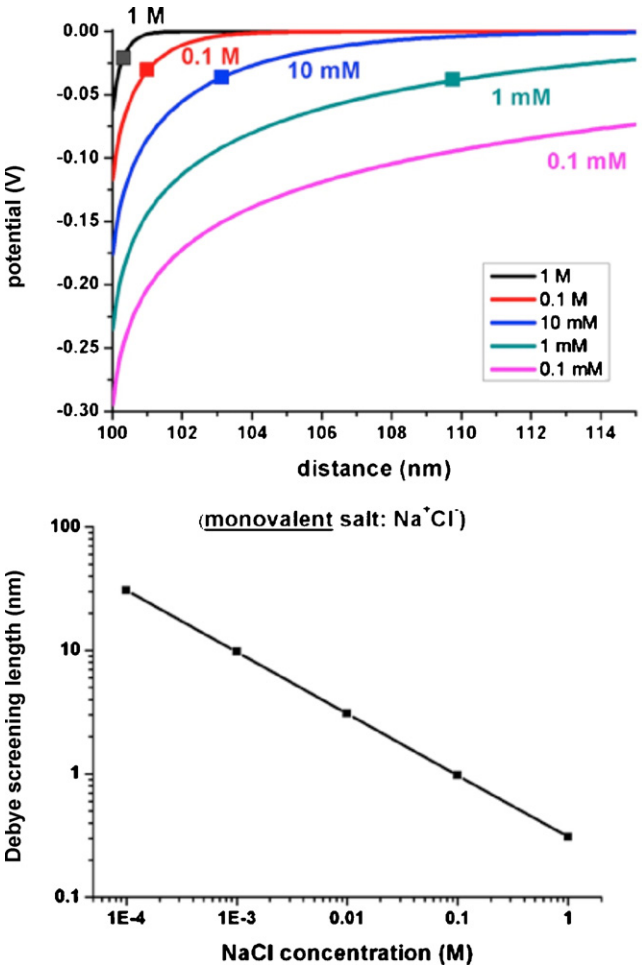

Fig. 2. Effect of ionic strength on the surface charge and electrical double layer (simulation): (A) the dependence of the surface potential on distance from the SiO_2 substrate. 100 nm corresponds to the surface and larger distances extend into the solution. The square dots denote the extent of the electrical double layer. (B) The dependence of the Debye screening length on the concentration of NaCl in the buffer. (reprinted with permission from http://www.nextnano.de/).

3.1. Carbon nanotubes

Single-walled carbon nanotubes (SWCNTs) can be imagined as cylinders obtained by a rolling a single sheet of graphitic carbon atoms. They are an ideal class of 1D-NS, since every atom is a surface atom and are hence expected to exhibit ideal sensitivity at the single molecule level. They can be synthesized in a number of ways: arc-discharge, laser ablation and chemical vapor deposition (CVD) (Jorio et al., 2008). Depending on their physical structure (also referred to as chirality), the nanotubes can be metallic or semiconducting (Jorio et al., 2008). In order to fabricate devices based on individual SWCNTs, it is important to separate metallic from semiconducting tubes (Hersam, 2008). For amperometric sensors, metallic nanotubes are ideally suited, while for FET-based detection semiconducting nanotubes are preferred. For the latter case, a key prerequisite is a certain amount of transconductance, i.e. the possibility to modulate the conductance in a small gate voltage range. Interestingly, unlike bulk or microscale metals, metallic nanotubes are unique in the sense that they also show a slight modulation in

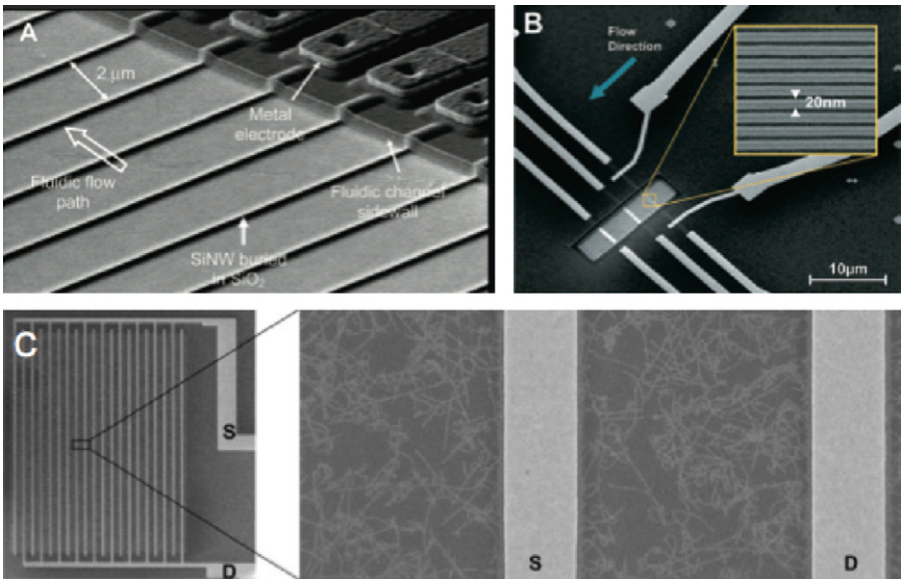

Fig. 3. Examples of 1D-NS-sensors-on-chip: (A) a silicon nanowire sensor array where the contacts are passivated with SiO_2. The diameter of the individual wires is around 5 nm. (B) Silicon nanowire sensor array with each device comprising of 10 nanowires each with a diameter of 20 nm. The sample is passivated with a silicon nitride membrane. (C) An interdigitated sensing device using single-walled carbon nanotube networks. The electrodes are not passivated here. Scale bar is 10 μm. (reprinted with permission from Gao et al., 2007; Bunimovich et al., 2006; Star et al., 2006, respectively).

conductance with gate voltage due to the finite density of states and the presence of defects (Bockrath et al., 2001). Utilizing this aspect, field-effect sensors based on metallic SWCNTs have been demonstrated (Maroto et al., 2007; Vlandas et al., 2010). Currently, it is possible to procure separated metallic and semiconducting tubes (CoMoCAT, 2001, http://www.nanointegris.com/).

The assembly of SWCNTs into electrical devices has long been done at an individual device basis. Nanotubes dispersed in an aqueous or organic solution are deposited on a substrate and are randomly contacted by electrodes using electron-beam lithography resulting in a very low throughput. Many strategies have been developed to overcome this hurdle. One promising alternative is based on AC dielectrophoresis to position the nanotubes at desired locations on a chip (Duchamp et al., 2010; Marquardt et al., 2006). Other methods based on the use of catalyst seeds at predefined locations have also been reported (Kong et al., 1998). However they have not established as a major route for obtaining sensors based on individual or few CNTs. Another common alternative to overcome this hurdle is use of carbon nanotube networks (see Fig. 3C). This is a viable route based on CVD for large-scale fabrication, which does not require any kind of prepatterning using catalyst seeds (Star et al., 2006). Although the devices might probably show slightly lower sensitivity due to the increased number of CNTs, the possibility to make devices on a large scale is an important aspect that might push the use of CNT-based devices for realistic applications.

3.2. Nanowires

Nanowires come in many variants, which can be classified as metallic or semiconducting. Metallic nanowires are grown directly in solution or by using templates such as porous alumina (Wang, 2005b). The nanowires are subsequently suspended in solution and used for fabricating sensing devices (Lin et al., 2008; Aravamudhan et al., 2007). An alternative form of a metallic nanowire is a conducting polymer nanowire (Wanekaya et al., 2006; Ramanathan et al., 2005). Analogous to SWCNTs, nanowires have also been assembled by dielectrophoresis directly from solution (Van der Zande et al., 1999; Smith et al., 2000; Englader et al., 2005).

Semiconducting nanowires can be grown by a number of different methods, which can be classified under top-down or bottom-up approaches (Heath, 2008; Duan and Lieber, 2000; Roy and Gao, 2009; Shen et al., 2009). Among the major semiconducting nanowires, silicon nanowires play a leading role due to the existing technology of conventional microelectronic devices based on silicon. High quality nanowires can be synthesized separately and transferred to device substrates and are subsequently randomly contacted. Alternatively, towards silicon nanowires, large-scale fabrication of device arrays by direct lithographic methods (Li et al., 2004) or pattern transfer techniques (Melosh et al., 2003) with wide applications in a number of biosensors has been successfully demonstrated (Patolsky et al., 2006) (see Fig. 3(A) and (B)). In addition to silicon, a number of other metal-oxide nanowires (Shen et al., 2009) appear very promising and competitive. Among them, zinc oxide (Wang, 2009) and indium oxide (Li et al., 2005) wires are the major candidates. Some of the metal-oxide wires such as ZnO nanowires can be fabricated using simple routes in aqueous solutions at low temperatures. Gold nanoparticles immobilized at predefined electrode locations serve as growth promoters and direct the growth of the ZnO nanowires at desired locations. Based on this strategy, ZnO nanowire pH sensors in an ISFET configuration have been demonstrated (Pachauri et al., 2010).

3.3. Nanochannels

Unlike carbon nanotubes and nanowires, nanochannels are a class of 1D-NS, which find applications in preprocessing stages of an analytical system. Some examples of such applications include separation, preconcentration and DNA linearization and mapping (Kovarik and Jacobson, 2009; Levy and Craighead, 2010). Here we will focus only on nanostructures wherein two dimensions are on the order of 100s of nm. Such structures have to be differentiated from nanoslits, where only the height is of the order of 100s of nm and the width is in the micron range. The most common method involves the use of sacrificial layers to prepare the nanochannels directly on chip (Douville et al., 2008). Using this strategy even vertical arrays of nanochannels have been reported (Sordan et al., 2009). Nanoimprint lithography has also been widely used to fabricate arrays of nanochannels (Guo et al., 2004). Another common fabrication method is based on elastomeric substrates. Here controllable cracks introduced in an elastomer serve as a master for

the fabrication of the nanochannels (Huh et al., 2007; Park et al., 2009). The conditions however, have to be carefully optimized to obtain closed channels, as one of the major problems here is ceiling collapse, which blocks the nanochannels even during fabrication. Although a number of nanoslits have been demonstrated using glass-based chips (Douville et al., 2008), there are very few examples of nanochannels on glass chips. This is due to the fact that the etching of glass is mostly isotropic, as a result of which it is difficult to control the lateral dimensions of the channel in the nm range.

4. Challenges

4.1. Device aspects—fabrication and contacts

The first step in the realization of a biosensor involves the fabrication of the device. It is still a major challenge to routinely fabricate cost-effective scalable biosensors based on individual or few 1D-NS, especially with CNTs. While with silicon nanowires the possibility to grow large-scale arrays is now well established (Zheng et al., 2005), CNTs still suffer from a number of hurdles as mentioned before. For ZnO nanowires, the bottom-up approach involving direct growth of the nanostructure at a site-specific location seems to be a promising route for obtaining sensors routinely (Wang, 2009). Electron-beam lithography (EBL) is widely used to fabricate prototype devices, which might be important to clarify the sensing mechanism. However for the 1D-NS-sensors to be competitive with conventional biosensors, it will be important to deploy alternate techniques such as photolithography or nanoimprint techniques. In the case of carbon nanotubes, the length is a limiting factor when using such alternate techniques. Most CNT products available in the market (CoMoCAT, 2001, http://www.nanointegris.com/) have very short lengths in the order of 1 micron. However, the feature size obtainable with photolithography is just at the limit here. A related aspect is the change in the diameter or electronic structure of the nanotube over micron distances (Roy and Gao, 2009).

1D-NS-electrical devices that sense the analyte directly in liquid will require passivation of the contacts. It will also be required for devices where the receptors are immobilized via non-specific interactions globally on the substrate. Silicon nanowire devices have mostly been experimented with passivated contacts (Bunimovich et al., 2006; Gao et al., 2007), albeit with the help of EBL. On the contrary, most of the carbon nanotube sensors have been demonstrated without passivation of the contacts (Star et al., 2006; Heller et al., 2008; Tang et al., 2006; Maroto et al., 2007; Besteman et al., 2003). The crucial role of bare contacts exposed to the liquid has been highlighted in a number of works (Tang et al., 2006; Gui et al., 2007). While the sensor might still show a response to analyte, it has to be kept in mind that the receptors on the contacts will dominate the sensing response. There are also examples where the non-passivated contact acts as the active component of the device (Byon and Choi, 2006; Yeh et al., 2009). In such a scenario the surface-to-volume ratio is determined by the contact (due to the larger surface area) and not anymore by the 1D-NS itself. In such a situation the fundamental advantage of using the 1D-NS is lost leading to a tremendous loss in sensitivity. This can be clearly seen in the sensors that have been demonstrated for DNA. With passivated silicon nanowires the detection limit for small nucleotide sequences is in the femtomolar range (Gao et al., 2007; Hahm and Lieber, 2004; Bunimovich et al., 2006). By comparison as shown in Fig. 4, the best achieved detection limit until now for non-passivated carbon nanotube sensors is in the picomolar range—three orders of magnitude higher (Star et al., 2006). The challenge here is to passivate contacts without the use of EBL. More work has to be done in this direction to elucidate the advantage of one technique or the other.

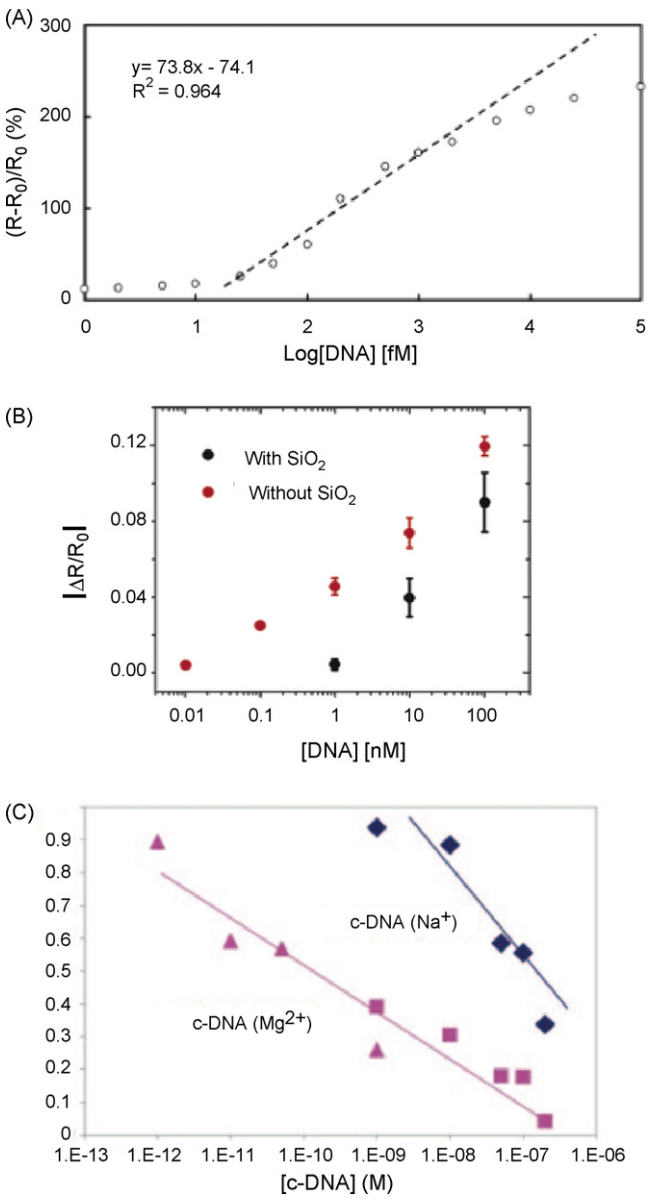

Fig. 4. Comparison of the reported sensitivities to small sequences of single-stranded DNA on 1D-NS-sensors shown in figure: (A) 5 nm-silicon nanowire FET sensor showing a limit of detection of around 10 fM using 21-bp PNA immobilized on the nanowires (corresponding to the device in A). (B) Sensor with 10 silicon nanowires each of diameter 20 nm showing a limit of detection of 10 pM for 16-bp DNA (corresponding to device in B). (C) Carbon Nanotube Network back-gated FET sensor showing a detection limit for 12-bp DNA in the pM range (corresponding to device in C) (reprinted with permission from Gao et al., 2007; Bunimovich et al., 2006; Star et al., 2006, respectively).

4.2. Sensitivity issues

Another reason for the lower sensitivity values for CNT-based sensors with respect to silicon nanowire sensors could be intrinsic to CNTs. The SiNW devices comprise usually of individual nanowires where their entire surface is available for the detection process. However, nanotubes very often tend to bundle (Jorio et al., 2008) resulting in a reduction in the effective surface area available for sensing processes. Although many prototype devices have been demonstrated with individual tubes, in order to assess the sensitivity limits of the sensors routine fabrication of individual tubes is necessary. In the absence of such a procedure, the current CNT-sensor technology is proceeding with the use of bundles or networks, with some compromise of loss in sensitivity. The

ultimate challenge here would be to demonstrate single-molecule sensitivity using routinely fabricated individual CNT devices or using the successful silicon nanowire arrays. One femotmole of DNA corresponds to 600 molecules in a microliter droplet placed over the sensor for detection. An improvement in the sensitivity by an order of magnitude or the use of appropriate nanoliter dosing systems might enable the detection of individual DNA sequences in real-time, which might revolutionize the field of nucleic acid-based on-chip diagnostics.

Secondly, the electrical double layer is an important aspect, which limits sensitivity to a large extent. It has been proposed that the binding event must occur within the EDL of the nanowire or the nanotube in order to maximize sensitivity (Stern et al., 2007b). However, it is difficult to realize immunosensors with immobilized antibodies that can lie within the EDL in physiological buffers. This is an important challenge, which still requires a number of systematic studies to understand the relationship between the binding process and the nature of EDL. Many research works have overcome this problem by using a buffer of low ionic strength or just working with water, where the ionic strength is rather undefined (Besteman et al., 2003; Roy and Gao, 2009). However, in order to maintain the nanoscale sensors competitive with conventional biosensors, it will be important to demonstrate sensing events in realistic buffer solutions with high ionic strength. A prudent strategy to overcome this hurdle involves the use of synthetic receptors of small size such as aptamers that are specifically designed for selected proteins (Maehashi et al., 2007; Nguyen et al., 2009; So et al., 2005).

4.3. Selectivity issues

The selectivity of 1D-NS-sensors is determined by the receptors immobilized on the surface. In order to obtain high selectivity, the receptor must be chosen in such a way that it interacts only with the analyte of interest. While this is more a problem in biotechnology to obtain the appropriate receptor, we will not bring this up as a challenge for 1D-NS-sensors. Realistically speaking, the receptors also show a varying amount of cross-selectivity towards interferents. This can be mitigated to a certain extent by the use of an array of 1D-NS-sensors, each of which is functionalized with different receptors. In this way, the sensor signal would contain a vector of sensor responses, which can be treated as a pattern and related to the analyte of interest in the presence of interferents. An example is the determination of cancer biomarkers from breath samples (Peng et al., 2008).

The challenge in the case of sensor arrays is the capability to functionalize each device with a different receptor. With carbon nanotubes most of the functionalization routes have been concentrated on the use of standard coupling techniques based on carbodiimide coupling (Balasubramanian and Burghard, 2005). However, this requires the presence of COOH groups on the surface of the SWCNT. With silicon nanowires, and other oxide-based nanowires, silane coupling chemistry is widely employed. In many other cases, the receptors were left to immobilize non-specifically everywhere on the chip. Versatile methods for the site-specific immobilization of selected receptors at various locations on the same chip are yet to demonstrated. Photolithography or robotic spotting techniques that are utilized in the fabrication of DNA microarrays appear promising here (Khademhossaini et al., 2010).

With carbon nanotubes, however one unique method based on electrochemical modification (Balasubramanian and Burghard, 2008) appears to be promising for obtaining devices with different receptors on the same chip. This versatile technique allows the covalent or non-covalent coupling of organic end-groups or nanoparticles (Schlecht et al., 2007) in a very controlled manner. In addition, the most important aspect of this method is that only the devices that are addressed by the electrode undergo a coupling with the desired receptor. It has to be kept in mind that pristine nanotubes contain some surface functionality, which generates an eigenresponse even before functionalization with any kind of receptor (Back and Shim, 2006).

Finally, non-specific binding (NSB) is an important challenge in maximizing selectivity in 1D-NS-sensors. Since the active element has a very small footprint, even a small degree of NSB may affect the selectivity of the device to a large extent. In many cases this has been overcome with techniques known from microscale or microchip systems, where albumin or polyethyleneglycol-based coatings are deployed to avoid NSB (Roy and Gao, 2009; Grieshaber et al., 2008). It has to be kept in mind that these techniques modify the properties of the sensor surface (nanotube/nanowire) and in addition affects the pI of the surface on which the 1D-NS is positioned (such as microchannel). In this situation the effect of ionic strength and pH on the surface charge has to be reconsidered in order to determine the net effect on the sensor response. Again here systematic studies exemplifying this relationship are still lacking.

4.4. Reproducibility, stability and calibration

In order for a sensor to be reusable it is important to obtain data about the reproducibility and stability of the sensor characteristics. One of the major problems involving reproducibility and stability relates to surface effects. For example, the repeated use of a sensors leads to accumulation of analyte species or ions or salts on the surface of the nanostructure and around it (Squires et al., 2008). This could be due to electrostatic effects or just NSB. In any case, analytical systems based on 1D-NS would require some kind of an active method to clean the surface in order to avoid surface effects and drifts (Karajanagi et al., 2004; Squires et al., 2008). This is an important challenge, which has to be addressed especially when such systems are deployed in situations, where minimal human intervention is required. On the other hand, drift brought in by surface effects, that affect the reproducibility can be included in a model of the sensor response as discussed below. Other issues such as the stability of antibodies and maintenance of the activity of immobilized enzymes are similar to that of microscale or bulk systems and many approaches are available for such situations, which could also be applied for 1D-NS-based biosensors (Karajanagi et al., 2004).

1D-NS-devices may also be used as disposable biosensors. However it is more challenging to design a disposable system, as this would require complete corroboration of the sensing mechanism and the availability of a mechanistic model or a calibration curve that relates the sensor response for every device to the concentration of the analyte (Chen et al., 2004; Heller et al., 2008; Wunderlich et al., 2007). It is not enough if the device detects some analyte or not. Any new sensor should give an idea of the sensing mechanism or a good explanation of the concentration dependence. Due to the variations in device characteristics from one sensor to another, it appears as if every device needs to be calibrated separately before their deployment in a real-life scenario. This can be mitigated to a great extent once the mechanisms are well established in which case, the difference in the transport characteristics should also be included as part of the model. Other improvements include the use of unsupervised learning algorithms such as neural networks or principal component analysis in order to make the model adaptive to the device that is currently under consideration. Even for a reusable system, it is important to have such models in order to pass through quality control and other fundamental requirements before the systems can be deployed for widespread use.

4.5. System aspects

It is important to keep in mind, that any kind of biosensor will form part of a bigger analytical system at an application stage.

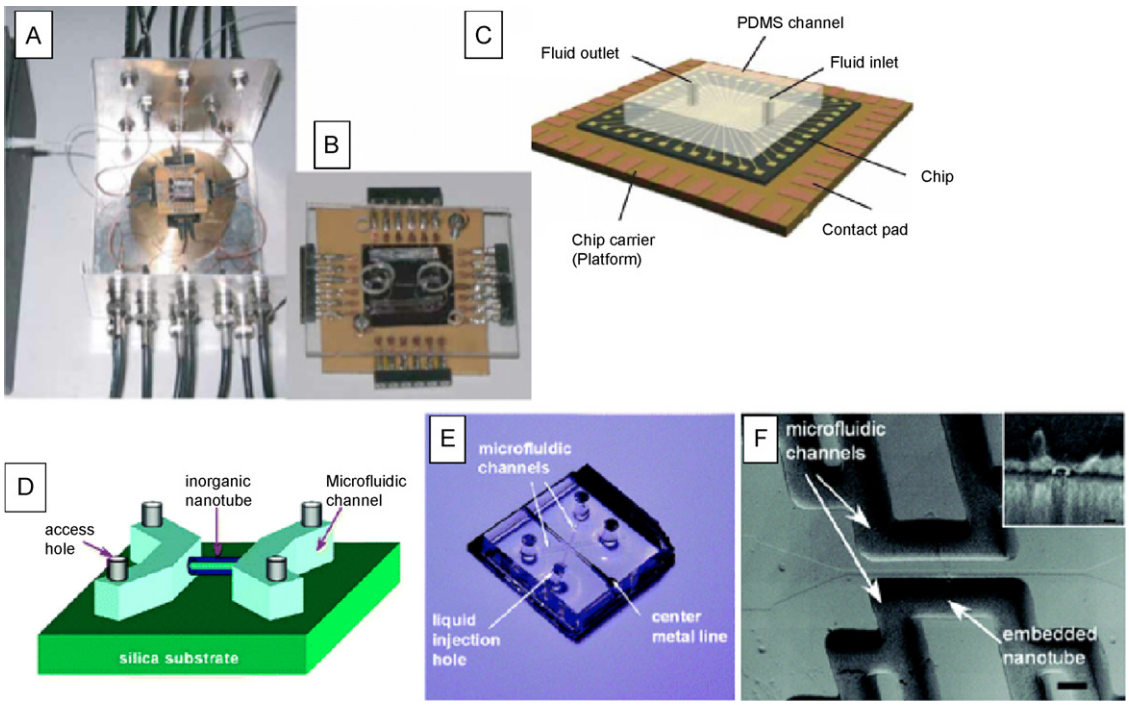

Fig. 5. (A–C) Setup for performing sensing with silicon nanowire FETs, showing optical images and a schematic of the nanowire sensor chip with integrated microfluidic sample delivery [reprinted with permission from Patolsky et al., 2006). (D–F) Integrated nanofluidic devices using inorganic nanotubes as nanochannels: (D) Schematic showing the nanotube bridging two microchannels, (E) a fully packaged nanofluidic device, (F) scanning electron micrograph of the active part of the nanofluidic device, scale bar 100 nm (reprinted with permission from Fan et al., 2005).

For this purpose, the interfaces, the chemistry, the dosing and the required physiological samples must be compatible and relevant for the application in question. In many cases, the samples require a considerable amount of preprocessing which have to be performed outside the chip (Kim et al., 2009). For lab-on-a-chip applications, the challenge is to introduce as many of these preprocessing stages on the chip as possible. Needles to say, there are very few works demonstrating this system aspect (see Fig. 5) (Fan et al., 2005; Patolsky et al., 2006; Stern et al., 2007a), as the principle of 1D-NS-sensors needs still to be established before such an integration can be attempted. This integration requires a lot of overhead and it is important to have a well-established strategy to obtain site-specific sensors with a 100% throughput and a clear calibration curve. Such a demonstration is important to justify the claims of high sensitivity and shorter response times, as this includes also the time for performing the preprocessing in a realistic analytical situation.

4.6. Detection of nucleic acids and proteins

The diagnostic field of nucleic acids is exploding with the use of microarrays coupled to fluorescence-based detection (Khademhossaini et al., 2010). The challenge for 1D-NS-based systems is the need for a competitive edge against such detection systems. One of the major claims of nanostructure-based detection is the achievement of higher sensitivity in comparison to current microarray techniques. However, it has to be kept in mind, that polymerase chain reaction is now routinely employed to amplify DNA sequences and hence the detection limit must not be ultralow for the detection of low number copies of DNA. On the other hand, every PCR cycle requires a certain amount of time and the ability to detect DNA sequences without the use of PCR might be a key pre-requisite for 1D-NS-based systems to be competitive with microarray based analytical techniques. In addition to this, the absence of a labeling step is expected to bring some reduction in the total response time. Such benchmarks are only beginning to appear (Star et al., 2006), and studies related to these aspects might give an impetus towards the use of 1D-NS-based sensors for nucleic acid diagnostics. The other challenge for the use of 1D-NS in genomics is to obtain high throughput data analogous to microarray data (Khademhossaini et al., 2010), which would either require multiple reuse of the same 1D-NS-chip or the availability of thousands of 1D-NS-devices on a single chip.

Unlike the case of nucleic acids, the use of microarrays for the detection of peptides is still in its infancy (Schena, 2004). This could be a suited opportunity for 1D-NS-biosensors, where they can make a timely contribution to their establishment as analytical systems. In comparison to the biosensing of metabolites and DNA, many proteins require the largest amount of preprocessing steps before they can be detected at the sensor surface. This might be the major challenge for the acceptance of 1D-NS-based protein chips. A wide variety of 1D-NS-sensors for the detection of various peptides have been demonstrated (Chen et al., 2004; Patolsky et al., 2004; Byon and Choi, 2006; Maehashi et al., 2007; Li et al., 2005; So et al., 2005; Star et al., 2003).

5. Summary and perspectives

In the midst of all these promising applications and herculean challenges, one should not forget that 1D-NS-based biosensors are expected to deliver a huge amount of fundamental knowledge related to biomolecular interactions occurring at the nanoscale. The explosive amount of research happening the field of nanochannel research is just one example for this situation. It is expected that fundamental biomolecular interactions can be understood at a single molecule level, which is not possible with current systems as they deliver average information about interacting molecules.

In this review, we have attempted to put together important results published until now using 1D nanostructures as biosensors or biosensing platforms, with promising applications in the area of bioanalytical chemistry and medical diagnostics. The review has

attempted to collect a wish list for the realization of biosensors based on 1D-NS that would enable the easy entry of such devices into real applications. These include absolute sensitivity, measurement of more than one analyte at once, shorter response times and finally the ability to perform easy field analysis of real-life samples using such devices. Based on the current state-of-the-art, we have attempted to crystallize the important challenges that are facing this field in order to demonstrate or achieve these goals. Once these challenges are addressed and efficient methods established to overcome the various hurdles outlined in this review, it can be expected that the nanoscale systems will bring in revolutionary changes in analytical science bringing considerable improvements in the field of lab-on-a-chip and point-of-care applications. Needless to say, the challenges listed here constitute only a preliminary list, which needs to be addressed in future experiments. Other aspects such as public acceptance, controlling modalities etc. might also play an important role in the widespread use of 1D-NS for applications.

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