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The technology and applications of bionanosensors.

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1. Introduction

Recently, nanotechnology has revolutionized research in important areas of molecular biology. Probes has been developed to study interactions at cellular and molecular level in real time, and to provide sensing probes that have far higher sensitivity than conventional methods. The use of this technology is not only limited to cutting edge research, but is presently making its way into clinical use where it may represent a fast and cost efficient method for diagnostics and screening.

With this report we wish to give a short overview of some of these bionanoprobes that are currently being used and developed and to give the reader an insight into the possibilities of these new type of devices and how they are manufactured and the underlying physical principles that govern their operation.

1.1 History

One of the earliest modern ways of studying biological systems is radio-isotope measurements that can be used to detect specificity and affinity of different molecular interactions. From the mid 1980:s fluorescence techniques started to evolve together with powerful techniques for image analysis which resolved the issues with safety and signal clarity often found with the previous method. However, both these techniques use tagged molecules to visualize the molecular processes. In all areas involving tagged reporter molecules problems like non-uniform labeling, noise and signal quenching are readily observed[1]. To overcome the problems many other non-labeling techniques for sensing molecules have been developed. These new types of sensors can be categorized into optical, mechanical and electrical sensors. In all of these areas nanotechnology can be utilized.

2. Nano Cantilevers

Currently MEMS (Micro Electro Mechanical Systems) sensor devices are being used in great variety of different sensor applications. The recent development in nanotechnology and fabrication has made it possible to create a new generation of sensory devices, NEMS (Nano Electro Mechanical Systems). An example of the NEMS technology being developed today is nano cantilevers that can be used as biological sensors.

The basic idea is that biological material can attach itself to a coated cantilever. The adsorption causes some fundamental change to the characteristics of the cantilever. This can be either a change in mass (due to the very small mass of the cantilever itself) or a change of the surface tension in the cantilever. This then represents the two major approaches for using cantilevers as detectors.

2.1 Resonance Cantilevers

Electromechanically driven resonating nano cantilevers have been constructed and theoretical models describing the interacting forces have been created[2, 3]. By applying an AC voltage between the cantilever and a nearby electrode called the driver the cantilever is excited and oscillates. The displacement of the cantilever can be measured as a DC voltage over the same (fig 1).

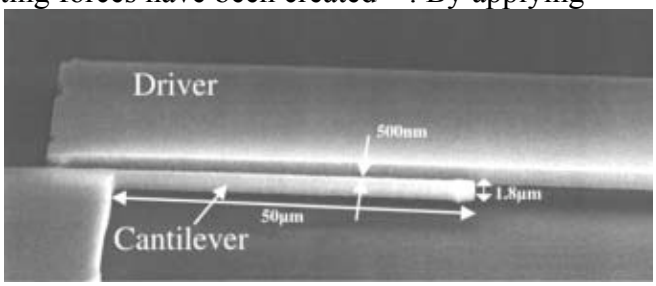

Fig. 1. SEM image of a working resonance cantilever detector (reproduced from reference [3]).

The displacement of the cantilever is a measurement of the amplitude of the oscillation. The resonance frequency of the cantilever is changed as additional mass attaches or detaches. The smaller the device, the more sensitive it becomes to mass changes since the resonance frequency is dependant on the total mass. Reaching into the nano region may make single molecule detection possible. To visualize this one can study the dependence of mass resolution per unit frequency on the dimensions of the cantilever.

$$\frac{\delta m}{\delta f} \approx const \cdot \frac{k}{f_{res}^3} \propto l^3 \cdot t \ (g \cdot Hz^{-1})$$

$$\begin{cases} k = C_{material} \dfrac{w^3}{l^3} \cdot t \ (N \cdot m^{-1}) \\ f_{res} = D_{material} \dfrac{w}{l^2} \ (Hz) \\ w - \text{Width of the cantilever} \\ l - \text{Length of the cantilever} \\ t - \text{Thickness of the cantilever} \end{cases}$$

Since an electrical signal is delivered directly on the device, it is possible to feed the signal to CMOS devices integrated on the same chip, thereby making this kind of detector highly suitable for small integrated detection systems, and keeping the signal path short in order to minimize noise.

2.2 Surface stress Cantilevers

Another way of using nano cantilevers is to measure the deflection of a cantilever that is induced by surface stress. One side of the cantilever is covered with a sensing film or receptor molecules. When a solution is passed over the cantilever, target molecules attach themselves to the sensitized surface. As they are attached they change the surface energy of the cantilever, which expands or contracts in order to balance the change. The deflection angle of the cantilever can be measured by nearby electrodes or by targeting a laser to the cantilever and measuring the angle of the reflected beam (similar to AFM). In the latter case, resolution down to sub Ångstrom is possible[4]. In this case the miniaturization has the same benefits as for the resonance cantilever when it comes to integration and signal pathways. In addition, a device with a thinner

sensing surface will show a higher deflection angle in response to identical binding events, thus giving better resolution.

Since so many different coatings can be applied, there is virtually no limit to the number of different biomolecules that can be detected. Since it is possible to integrate these devices into microfludic channels, the device can be rinsed with buffer solutions to purge the analytes from the cantilever after use. Arntzl and coworkers have shown successful detection of creatine and myoglobin in subsequent series with the same device[5].

3. Fiberoptical bioprobes

NSOM (Near-field Scanning Optical Microscopy) is a technique that has been around for some years now that gives a very good spatial resolution. The technique is based on optical fibers where one end is very thin (20-500 nm). When light is led in the fiber, it will create an evanescent field in the thin end since the diameter here is smaller than the wavelength of the light. The spatial resolution is very good because of the fact that the evanescent field only excites a very small volume since the intensity falls off exponentially from the tip of the fiber. Since the evanescent field mostly is used to excite fluorescent particles this method inherits the problems of fluorescent dyes. The fluorescent proteins or dyes can damage the functionality of the molecules they attach to and delivering the dyes inside a living cell involves penetrating the cell wall. On the other hand, probes based on this technology are not sensitive to static electricity, strong magnetic fields or surface potentials. The most common method of manufacturing NSOM probes is the so called “heat and pull” method. A strand of glass is heated locally, and then pulled apart. The shape of the tip depends strongly on the temperature used and the timing of the pulling[6].

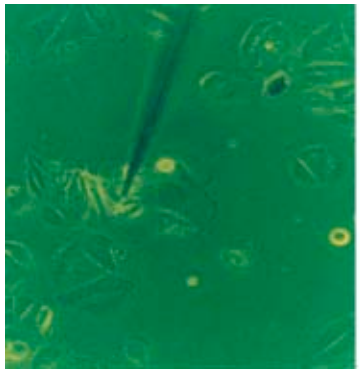

Fig. 2. Image of a fiberoptical bioprobe probing a single cell (reproduced from reference [7]).

A few years ago, a new method has been developed that uses the basics of NSOM but where the tip is covered with antibodies[6]. This makes it possible to sense molecules not labeled with GFP or similar fluorescent agents within a cell to determine the local distribution of the analyte within the cell (fig. 2). The method involves puncturing the cell membrane with a probe, but because of the small tip diameter of the probe (~40 nm) the damage caused to the cell is non fatal, and the cells are able to undergo further cell division[7]. The cells in this experiment were treated with BPT (benzo pyrene tetrol) and the tip of the probe covered with antibodies against BPT. The minimum amount of BPT that could be detected was 300 zeptomoles (10^{-21} moles). The fact that no fluorescent marker is left within the cell also improves cell vitality. This also helps to make a more realistic measurement of the analyte distribution since the fluorescent dye may be transported to locations within the cell where it is more likely to stay, and not necessarily to the sites that one may want to investigate.

In the future, nanosized optical probes may be useful in studying the cell structure/ function and intracellular transport. The mode of entry of viruses, molecules and signaling substances are areas of great interest for life sciences where these probes may play an important roll.

4. SERS (Surface Enhanced Raman Scattering) Biosensors

Raman spectroscopy is a method to probe vibrational and rotational energy levels within a molecule. In the Raman process, the molecule interacts with the incoming photon in an inelastic scattering event, whereby a photon is emitted that has the energy of the photon plus or minus an energy level within the molecule. It should be noted that unlike normal absorption/emission, the incoming photon does not have to correspond exactly to the energy difference between two electronic energy levels of the molecule. This makes it possible to get more information about the molecules vibrational and rotational energy levels with a monochromatic photon beam. However, the main problem is that the Raman scattered photons are very few compared to the incoming photons. Thus photons scattered in other processes can very easily drown the Raman signal. To overcome this problem, it is possible to use SERS, which enhances the scattered photon flux by many orders of magnitude (up to 10^{14} in some cases). This is done by introducing metal colloids, often made of gold. Metal colloids are very small particles of metals (10-100 nm radii) that are evenly dispersed in a liquid. These colloids do not settle for a long period of time, and can therefore be stored for a reasonable amount of time.

When the particles are hit by incoming photons, a surface plasmon, *i.e.* an electric resonant field on the surface, is created by the excited free electrons. When Raman-active molecules are adsorbed onto the surface of metal particles, they are submitted not only to the electromagnetic radiation of the incoming photons, but also by the resonant electric field of the metal particles. Since the induced field is now much stronger, the Raman signal will also be much greater since the outgoing signal is proportional to the square of the field it is subjected to[8].

5. SPR (Surface Plasmon Resonance) Biosensors

Plasmons are the quantized description associated with longitudinal waves of charge density propagating in the material. Surface plasmons are a subset of the eigenmodes of the electrons, which are bound to regions in the material where the optical properties reverse, *i.e.* the interface between a dielectric and conducting medium. Surface plasmons are characterized by the strong evanescent electromagnetic fields at the surface[9].

In a typical SPR biosensing experiment, one interactant in the interactant pair (*i.e.* a ligand or biomolecule) is immobilized on an SPR-active gold-coating on a glass slide, and the other interactant is present in a buffer solution that is induced to the surface (fig. 3). When light (visible or near infrared) is shone through the glass slide and onto the gold surface at angles and wavelengths near the so called "surface plasmon resonance" condition, the refractive index and thus the optical reflectivity of the gold changes very sensitively with the presence of biomolecules attached on the gold surface or in a thin coating (often some kind of polymer) on the gold. For a range of angles near the SPR condition, where the local metal surface's reflectivity changes linearly with the angle, the reflectivity at a fixed angle varies with time proportional to the change in effective refractive index (Δn_{eff}) near the gold surface. This change in Δn_{eff} can then be converted to adsorbate coverage versus time[10]. The high sensitivity (below 10 pg/mm^2 [11]) of the optical response is due to the fact that it is a very efficient, collective excitation of the conduction electrons near the gold surface. The extent of binding between the two interactants is easily observed and quantified by monitoring the change in reflectivity.

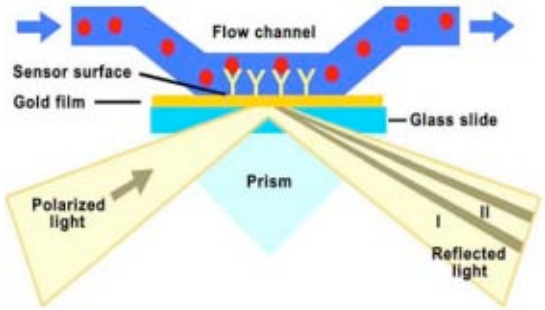

Fig. 3. Schematic setup of a SPR biosensor utilizing a flowcell structure (reproduced from reference [10]).

SPR biosensors are used to study DNA-RNA, cell-protein, drug-protein interactions and absorption and desorption processes at bare or coated surfaces[11]. Advantages with this technique are that it is performed in real time and its high sensitivity without any added labeling substances. In addition to this it should be mentioned that SPR biosensors are well suited to be implemented in flowcells enabling quick changes of buffers[9, 10, 11].

6. Redox cycling

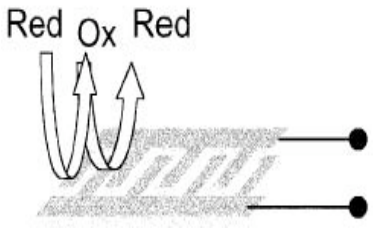

Fig. 4. Example of interdigitated electrodes for redox cycling (reproduced from reference [12]).

Redox cycling is a process of great interest in biological systems, since many processes are governed by the reduction and oxidation of biomolecules. The basic idea is to have two electrodes of opposite charge. Reduction and oxidation takes place at the different electrodes. A common way of constructing this on a micro/nano scale are the interdigitated electrodes which can be integrated directly on a chip (fig. 4). With modern technologies such as nano imprint lithography it is possible to construct electrodes on a chip which are only a few nanometers wide. The performance of such electrodes improve as the size of the electrodes decrease. This is mainly due to that the electrodes can be positioned closer together, leading to faster diffusion between the electrodes. Mass transport is also increased because of radial diffusion, smaller electrodes give a lower background current and a reduced ohmic drop since the current is smaller.

Not only is it possible to detect the diffusion speed/size and concentration of the redox molecules, but it is also possible to use this approach for indirect measurements as detectors. The indirect method involves using a redoxable molecule that may bind to specific sites on other molecules, when it binds it picks up or leaves an electron, and detaches itself after that process (fig. 5). This has been done for DNA and specific proteins[12].

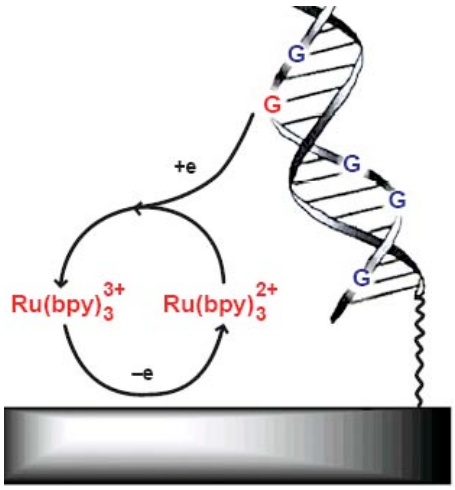

Fig. 5. Indirect detection of DNA through a redoxable molecule (Ru) (reproduced from reference [12]).

7. FET based sensors

7.1 MOSFET

The MOSFET (Metal Oxide Semiconductor Field Effect Transistor) is the most commonly known and used of the FETs[13]. In contrast to a BJT (Bipolar Junction Transistor) a FET does not have to transmit a gate current in order to obtain transistor functionality, instead the FET only utilizes the electric field (potential) over the gate to vary the source-drain current. A MOSFET is either p- or n-type, these terms refer to the doping of the source and drain contacts. In further discussions the n-type MOSFET (nmos) will be used. The source and drain regions are created in a p-type substrate, and between them a thin layer (at least 4-6 monolayers) of oxide is present at the surface, and on top of this there is the metal contact called gate (fig. 6).

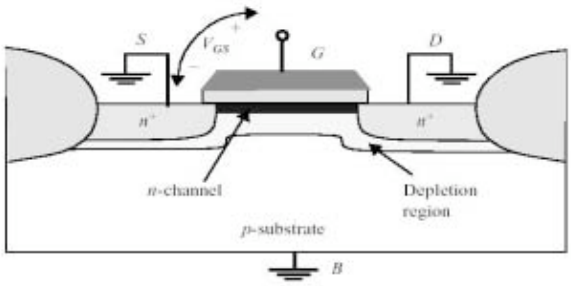

Fig. 6. Basic schematic structure of a n-type MOSFET (reproduced from reference [14]).

When a positive bias is applied over the gate, this will create a surplus of positive charges in the metal plate. These will repel the positively charged holes in the substrate, exposing the negatively charged acceptor atoms close to the oxide, resulting in the downward bending of the band levels in the substrate. While this holds, one says that the transistor is being depleted. At a certain gate bias the intrinsic Fermi level will go under the Fermi level for the system close to the oxide, and thus there will be a greater probability of finding electrons then holes in this region. This condition is called inversion since the electrons are the majority carrier in a p-doped substrate in the region near the oxide, the inversion layer. If the bias is increased even further one will reach the point where the electron density in the inversion layer is the same as the hole density in the neutral substrate, this is called strong inversion. With strong inversion the capacitance of the device will in principle not change since all the changes in charge occurs in the thin layers close to the oxide. With strong inversion the electron density is high enough to support the current between the source and drain, i e it acts like a conducting channel. The bias needed to obtain strong inversion is called the threshold voltage and is a very important factor in the description of functionality of the MOSFET[14].

7.2 ISFET

In the field of biosensors the so called ISFETs (Ion Selective Field Effect Transistors) has gained quite a lot of attention. They first appeared in the 1970:s for measurements of pH and ion concentrations like Na^+, K^+ and Ca^{2+} instead of the sensitive glass electrodes[15]. Some of the benefits of using ISFETs are that they are very durable and robust and only needs a minimal degree of maintenance, which implies that they are well suited for long term real-time measurements and feedback setups in a wide range of environments. The construction of the ISFETs also makes them very insensitive to extreme environments so they can work in very large ranges of temperature and pH for example. One must also take into account the high sensitivity and fast response from FET-devices used here, and in addition to this, the extensive knowledge in processing and manufacturing of FET-devices will make development and on-chip implementation of this technique easier.

The main part of an ISFET is an ordinary MOSFET with the gate electrode replaced by a chemically sensitive surface, a solution and a reference electrode (RE) (fig. 7). On a purely electronic level the MOSFET and ISFET are essentially the same component. One of the most important changes is that in addition to the intrinsic physical part one also has to take the potential of the RE (constant) and the interfacial potential at the solution/oxide interface into account when calculating the threshold potential[16].

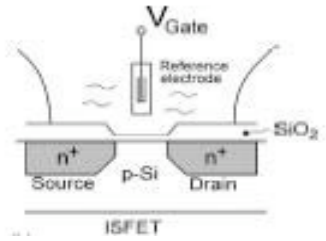

Fig. 7. Basic schematic structure of a n-type ISFET (reproduced from reference [16]).

For ordinary pH measurements basically any kind of metal or semiconductor oxide will work since they will contain hydroxyl groups. For silicondioxide (SiO_2) one will have SiOH groups in equilibrium with the ions (H^+ and OH^-) in the solution. This hydroxyl group in the oxide can be protonated and deprotonated, thus a change of pH in the solution will give rise to a change in the SiO_2 surface potential[15].

$$SiOH \Leftrightarrow SiO^- + H^+ \qquad 15$$
$$SiOH + H^+ \Leftrightarrow SiOH_2^+$$

The reactive SiOH groups are also very good for establishing covalent bonding to organic molecules and polymers for measurements on more advanced systems.

In later years, many different variations on the ISFET biosensor like ENFET:s (ENzyme-linked Field Effect Transistors) and IMFET:s (IMmuno Field Effect Transistors) has appeared, most of them work by having modified the gate surface by different biological or chemical species. One of the latest trends in this subject is to produce and characterizes nanoscale ISFET:s, often using single-walled carbon nanotubes (SWCNTs) or semiconducting nanowires (SNWs). These structures are interesting because of their large surface-to-volume ratio which enables detection, by a change in conductance, of very small charge fluctuations, their small size which bodes well for lab on a chip implementation and their ability to perform highly sensitive real-time measurements.

Star and coworkers have reported detection of specific protein binding (biotin-streptavidin) by using a nanotube based FET (fig. 8). In order to eliminate the effects of non specific protein binding a the nanotube was coated with a thin layer (<10 nm) of polymer. Vital differences between uncoated nanotube-streptavidin and biotin-streptavidin binding were noticed which made the authors suggest that the biotin-streptavidin binding has more complex propertied than ordinary charge transfer. It is suggested that this binding may lead to structural deformations is introduced in the nanotube which in turn induces new scattering sites for electrons in the nanotube[17].

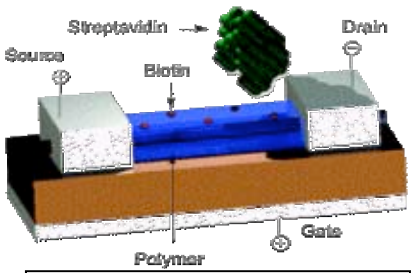

Fig. 8. Illustration of the device used by Star and coworkers (reproduced from reference [17]).

Hamh and coworkers have managed to use boron doped silicon nanowires with attached PNA (Peptide Nucleic Acid) for real-time detection of DNA and DNA variations in fluid flow systems[18] (fig. 9).

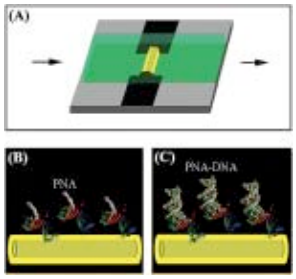

Fig. 9. Illustration of the device used by Hamh and coworkers (reproduced from reference [18])

According to a report from 2003[15] Lauwers and coworkers have presented a fully integrated multi parameter chip for continuous monitoring of blood gases, ions, pH and biomolecules by conductometric measurements. This represents a major improvement because of the heavily reduced consumption of blood, time and resources. It is possible that the concept presented here could be used for in vivo applications in clinical use for screening and diagnosis. Arrays of SWCNTs and SNWs could also be used to monitor individual cells, thus studying response of collective living systems.

8. Experimental Part

8.1 Introduction

The background for doing this experiment is to show how InAs nanowire FET based transistors can be constructed and used as a sensitive biosensor. The reason for using nanowires (NWs) in the biosensor FET is that the small size gives it some unique properties. Unlike ordinary FETs that are built into a substrate, the charge carriers in a NW may not only be depleted or accumulated on the surface, but also in the bulk, due to the relative low diameter of the NW. This makes the NW more sensitive to charges in its environment (in this case a change of pH). The change in charge carriers has a profound effect on the conductance of such devices and this is represented in the electrical signal measured from the device. For more information about FET transistors it is referred to the review section covering this subject above.

The NW can be coated with biological sensing material that makes it react specifically to certain biomolecules, but in this experiment measurements will be performed with a bare NW, i.e. it reacts to any background charge in its environment. The basic sensitivity of the uncoated NW will give some idea on how sensitive this type of devices can be made.
Experiments have previously been done in Charles Lieber's lab with both coated and uncoated silicon NWs where a pH sensitivity of 100±20 nS/pH was obtained for a coated surface[19].

8.2 Construction

The original purpose of the device was to be used in electrical measurement and characterization of NWs without any analyte present. The NWs were made of InAs, 300 nm thick, supplied by the Solid state department of Lund University. Using the edge of a paper, the NWs were scraped off the growth substrate and deposited on an oxidized Si surface. On the surface, a predefined marker grid, in order to determine the position of NWs, and gold contacts was present. Both the gold contacts and the marker grids were predefined with EBL. The locations of the NWs were investigated using SEM, and the coordinates of the ends of the NWs were noted. Special caution was taken to avoid exposing the NWs for a longer period of time, since the high energy electrons from the SEM may damage the structure and most likely, deposit carbon residues from inside the SEM onto the NWs.

Once an adequate number of wire coordinates had been noted, the next step was to spin on resist in preparation of the EBL exposure. The resist (PMMA) layer had to be at least as thick as the thickness of the wires (300 nm) in order to completely cover the wire. Compared to conventional EBL lithography, 300 nm resist is rather thick and this led to a large proximity effect in the EBL test exposure. The test exposures was conducted on pure Si chips with no predefined pattern and covered with 300 nm resist. A pattern were designed in CAD for the EBL exposure, the pattern was constructed in such a way that each end of the NWs were to be coved by a contacting layer of gold, the contact was drawn to the existing predefined larger contact structures.

At this phase the deadline for the hand-in of the project paper was reached, and the following part only contains what was planned for the experiment. Once the EBL exposure was done the sample was to be inserted in a metallization machine that evaporated the gold that was to form the contacts on the sample. After this process, the contacts were to be bonded onto the legs of a larger chip.

8.3 Measurements

The measurement process was planned to be made with the help of a PC setup running Labview^{TM}. The sample is placed into a shielded box and a four-point measurement where all measuring devices and the sample box are connected to the same ground to minimize noise. I/V characteristics from different NWs were to be obtained.

The analyte we had prepared was based on an acetic acid solution that was mixed with distilled water in order to create 5 different solutions in the pH range of 3-7. Acetic acid was chosen in hope that the not so reactive acid would not damage the NWs. Small droplets of the solutions were to be applied onto the chip and measurements done for the whole range of pH concentrations available. To remove the analyte, the edge of a paper tissue edge was to be used, where droplets of pure distilled water were to be used in order to rinse the sample surface from the analyte. It was planned to use a bonded contact without a NW or a broken NW as a reference so the effect of the uncontacted electrodes could be measured.

8.4 Experimental conclusions

Not having done the actual electrical measurements, limits what conclusion can be drawn, but if we were to plan the whole experiment from start we would have planned the construction of the device differently. The current device was constructed for electrical characterization of the NWs without an analyte liquid present. The NWs used were 300 nm thick, which may be too thick, as mentioned in the introduction it is favorable to keep the surface-to-volume ratio high. In a second experiment we would have opted for a thinner NW (~40 nm). The application of the analyte and subsequent rinsing would probably also have posed a problem for the measurement, both when dispensing the liquid and absorbing it with tissue paper the NWs could have been damaged by mechanical pressure. The optimal construction is probably to integrate the NW device in a microfluidic channel, this would have lessen the risk of damage to the structure and would have made much more efficient rinsing.

9. Outlook

We have shown some different applications of nanotechnology biosensors that today represent both practical applications that are currently being used in research, for example opening up possibilities to explore processes at a cellular level that has previously been hindered by the lack of analytical tools. Other benefits are the generally higher sensitivity that can be reached with nanobioprobes. The fact that different functionalized nanosensors can be integrated onto a single chip, opens up huge possibilities in clinical use. They represent a cost efficient method for instant analysis with high resolution.

The bioprobes of today are much limited by manufacturing processes, cost effectiveness and a limit to what feature sizes are reproducible. The nano/micro bioprobes all benefit from development in general nanotechnology. Especially sensors based on devices that are used in general electronics, such as FETs, will probably experience large synergy effects since so much money and research is invested in these areas. Other types of novel electronic devices such as nanowires and quantum dots, may very well prove to have use for new types of biosensors not mentioned in this article as well. Since nanosensor development benefits from advances in a number of different fields such as molecular biology, nanotechnology, microelectronics and microfluidics, a rapid progress in the development and applications can be expected. Our belief is that within the next 10 years, the use of

devices using nanobiosensors will have grown many times over as compared today. They represent not only an additional method of analysis, but may entirely replace some of the current methods of analysis. In a longer perspective, they may very well become the standard method of analysis in life sciences.

10. Acknowledgements

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