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Nanotransistors: Integrated Diagnostic and Therapeutic Tool of the

Future

The sensitive and selective detection of minute quantities of biological and chemical molecules in the human body has incredible significance in modern healthcare. While medical capabilities for treating diseases like diabetes, genetic defects, and cancer have advanced to the point where most individuals can be helped, it is too often the case that conditions like these are not detected early enough, or monitored with sufficient vigilance. New research in the field of nanowires has yielded evidence that nanowire based diagnostic and therapeutic methods may be the next great leap in monitoring and regulating chemical and biological events inside the human body. While astounding work has been done to synthesize these nanoscale wires, learn their properties, and assemble them into working nano-biodetectors, the surface of their potential as medical tools has only been scratched. This paper will begin by presenting an overview of the background necessary to understand nanowires, then discuss their synthesis and assembly into mechano-biological field effect transistors (FETs) and application to biodetection, and finally examine how this developing technology may be used in the future.

Nanowires: What are they and how are they made?

Silicon Nanowires (SiNWs) are just what they sound like, linear wires of silicon with a diameter from 20-100 nanometers (billionths of a meter). Because of their tiny

size, they exhibit special properties such as superconductivity, and extremely high sensitivity to outside electric fields.

On this small a scale, wires cannot be made by conventional methods, but must be synthesized in a manner similar to that of drugs and other small molecules. There have been hundreds of articles published documenting new ways to synthesize silicon nanowires, many of which are specialized to a specific function for the resulting wires, such as assembly into arrays, isolation of single wires, or long wire length. To give some idea of the general method of synthesizing SiNWs, I will summarize the most common method, Vapor Liquid Solid (VLS), and provide an overview of a less common method called thermal evaporation.

VLS is a process that is roughly analogous to standard recrystallizations done routinely in chemistry labs. Pure silicon is dissolved to supersaturation in a metal that has a very low melting point, in this case gallium. The solution is then heated to 400 degrees Celcius in a microwave plasma reactor. This creates silicon radicals in the vapor phase, which will cool and form nuclei of diameter equal to the diameter of the wire to be formed¹. These nuclei will then crystallize one dimensionally to form long wires that reach hundreds of micrometers, while maintain their minuscule width. These wires then precipitate out of the molten gallium for purification. This process is popular for the low temperature at which it is conducted.

Thermal evaporation based nanowire synthesis; silicon powder is crushed and prepared by hydraulic pressing, and then evaporated (above 1150 degrees Celsius). The vapor is passed over silicon wafer substrates where wires nucleate and expand one

¹ Sunkara et al. 2001; 1546-1548

dimensionally. Although this process is much more intensive than VLS, the resultant wires are much longer; the longest being between three and four millimeters in length².

It should be noted that the silicon wires considered in the devices discussed below were generally doped with boron so as to improve their conductivity by providing holes for efficient electron transport through the silicon crystal structure³.

Nanowire Field Effect Transistors

Though nanowires have incredible potential in fields like optoelectronics and microelectronics, their application in the biosensors that I will propose has everything to do with their use in nanoscale field effect transistors (FETs). FETs, the “ubiquitous switched of the microelectronics industry”⁴, are a two component system wherein the variable electric field at one electrode is used to control the current flowing between a source and drain electrode.

An FET is a U shaped conductor attached to a constant voltage source (battery) such that a current proportional to the resistance of the conductor is drawn. This attachment is made through the two ends of the U, while the bottom of the U is capacitively coupled to a third electrode through a thin dielectric. Charge flowing through this third (gate) electrode can have a “field effect” on the effective resistance of the U shaped conductor, such that a variation in the voltage presented to the circuit by the gate electrode will proportionally vary the current flowing through the U⁵.

For its application to biodetection, this standard model of an FET has been adapted. A nanowire biodetector has no gate electrode, but replaces it with a receptor

² Shi et al. 2005; 1733

³ <http://www.tpub.com/neets/book7/24e.html>

⁴ Palotsky and Lieber 2005; 21

⁵ <http://www.pbs.org/transistor/science/info/transmodern.html>

specific for some biological molecule. When this receptor binds its substrate, the charge on the substrate acts analogously to the voltage in the gate electrode, either increasing or reducing the resistance of the U shaped conductor, thereby changing the current drawn the by constant voltage⁶.

This charge based change in resistance is caused by the electrostatics of charge flowing through a U shaped wire. Unaffected, charge will not evenly distribute on the cross-sectional area of the U, but flow in a small sub-area through the center of the U. When a positive charge is brought near to this U by a gate electrode of bound biomolecule, it attracts the flowing electrons, widening the channel through which they flow; decreasing resistance and increasing current. When a negative charge is brought near to the U, the flowing electrons will be repulsed to constrict the area in which they travel; increasing resistance and decreasing current.

While standard FETs will work on any scale, ultrasensitive biosensor- FETs must be done on the nanoscale. This is necessary because of the relatively weak donating and withdrawing effects of small charged biomolecules. If a macro scale wire was the U shaped conductor in a biosensor FET, the resistance change due to the field of a single biomolecule would be insignificant. The minuscule diameter of nanowires however, allows this small localization of charge to become a significant gate to the flow of current in the FET.

Nano-FET Biodetectors

While the model of FET as a biodetector has been solidified and characterized, much of the research currently being done in this field is focused upon getting specific biomolecules to bind to the FET dielectric when present.

⁶ Palotsky and Lieber 2005; 21

The early work on this challenge was done using well characterized ligand receptor interactions, such as the high affinity of biotin and streptavidin⁷. By adhering biotin molecules to the dielectric at the gate of the FET, Cui et al. were able to detect small concentrations of streptavidin by monitoring the current through the transistor with what is effectively a small ammeter. This same group was able to sense Ca²⁺ ion presence by functionalizing SiNWs with calcium binding protein calmodulin⁸.

While these specific ligand/receptor interactions are valuable for demonstrating the possibilities that nanowire nanosensors hold, if they are ever to become a standard method of biodetection, there will need to be a much more general approach to specific ligand binding. Two innovative approaches have been proposed and demonstrated to accomplish two different things; selectively binding biological antigens, and specific DNA sequences.

Monoclonal Antibody Linked Nanotransistors

The immunologic, antibody based technique takes advantage of the incredible specificity of antibodies, and their high affinity for binding antigens. In a biodetector, antibodies can be linked to the gate point dielectric in an FET such that they will bind their antigen bringing its charge close to the FET. The goal is that when this binding occurs, the current in the wire jumps from a baseline value (FET bound only to the antibody) to a higher or lower current (when the FET is bound to the antibody/antigen complex). This technology has been demonstrated by covalently attaching anti-influenza A monoclonal antibody to a nano-FET at the gate. This device was readily able to detect virus at concentrations as low as the pico-molar range. Furthermore, it was selective to

⁷ Yi et al. 2001; 1290

⁸ Yi et al 2001; 1292

its influenza A target, and showed no current change when exposed to the very similar paramyxovirus⁹.

Using the already mature technology of producing monoclonal antibodies against any antigen, we should theoretically be able to make a sensor specific to virtually any biological molecule. While this is appealing, there are already many existing forms of immunological assays for biological molecules, including enzyme linked immunosorbent assay, radio immunological assays, and the like. What makes this nanowire linked approach any better? The advantage here lies not only in the clarity of results, but also in the incredible sensitivity of these sensors. Because the amount of change in the net resistance of a nanowire (due to antigen binding) is decoupled from the current running through the nanowire, we can use relatively large currents (though still small on any other scale) in the nanowire in order to see very small changes in resistance. Thus there is no need for a large amount of substrate binding to allow detection. To prove this unparalleled sensitivity of these nanosensors, Palotsky and Lieber have been able to show that their nanodevice can detect a single viral particle using the exact methods described above¹⁰.

One challenge that is going to have to be addressed is the difficulty of individually attaching a certain kind of antibody to each FET. This is a work intensive process that is hard to standardize. I believe that a better approach would be to attach a generic receptor for the antibody Fc constant region to all of the FETs, and only make them specific after this by simply adding mAb to be bound by the receptor. In this protocol, the specificity of a nanotransistor does not have to be built in the chemistry of

⁹ Palotsky et al. 2004; 14024

¹⁰ Palotsky et al. 2005; 26-7

its construction, but can be added after the fact. The resulting ability to easily make ultrasensitive, ultraspecific biochemical detectors should allow medicine to make a quantum leap below the concentration threshold of current detection techniques.

Single Stranded Peptide Nucleic Acid (PNA) linked Nanotransistors

While the mAb approach to detecting most biomolecules is promising for protein and small molecule detection, a similar, but novel approach has been tested for detection specific DNA sequences. Here, the specificity of the mAb is replaced by using a single stranded PNA linked to the transistor. PNA is a DNA analog which binds single stranded DNA with a much higher affinity than is seen in DNA-DNA binding. The goal here would be to attach a known PNA sequence to the nanowire transistor, and then expose it to a person's DNA library. If binding is indicated, then the person contains the complementary genetic sequence to the PNA. If zero or reduced binding is seen, a DNA mutation in the person's genome is indicated. This protocol has been proven experimentally in the detection of the F508 mutation in the cystic fibrosis (CF) gene. In this experiment, it was shown that PNA functionalized nanotransistors were able to easily distinguish between full matched and mismatched complementary DNA at a concentration of only 10 femtomolar¹¹. While this data is impressive, the mutation in the F508 gene is a fairly significant codon deletion. There is currently no data on the selectivity of PNA when there is only a single point mutation.

Clinical Applications of Nanowire Diagnostics- The Near Future

The clinical applications of nanowire biodetectors at their current state is not a stretch of the imagination. Charles Lieber, the Harvard University researcher responsible for the CF mutation detector described above, already has plans to commercially sell his

¹¹ Hahm et al. 2003; 52

genetic detector. It is feasible that these detectors could be used in hospitals for sensitive and instant genetic and serological assays within a matter of years.

Since the data yielded by these sensors is already electrical in nature, it should be very easy to interface these sensors with computers or even handheld devices which could display and save data. If this data/display interface was made sufficiently user-friendly, it could even be up-linked to in-home biosensors like glucose monitors which might require much less blood than existing technology.

While this improvement in diagnostic technology is appealing, it is hardly a gigantic advance in medical care. These nanosensors would see use only in the traditional diagnostic timeframe; a patient feels sick, goes to the doctor, and gets a test which the doctor interprets before giving treatment. In this situation, much of the sensitivity of these sensors is wasted, because by the time you feel sick whatever chemical abnormality is bothering you is probably concentrated enough to be detectable by traditional methods. Using this nanotransistor based diagnostic technology to its fullest will require a whole new approach towards health monitoring.

Integrated and Comprehensive Nanotransistor Arrays: a Scenario for 2025

It is reasonable to hope that by 2025 science will have advanced to the point where we can not only build nanowire nanotransistors cheaply, but also functionalize their surfaces with any biological receptor we please. Under conventional methods, this would give doctors the appealing, but less than revolutionary ability to detect almost any chemical abnormality at its smallest concentration. Still though, the sensitivity of these transistors seems largely wasted, as by the time that a chemical abnormality or

malignancy gives us a reason so seek treatment, it has usually been brewing for months or years. In 2025, when we reach this point when our time taken to seek care and not our diagnostic technology is the limiting factor on treatment, it is time for a paradigm shift in diagnostic methods.

I envision a system where the blood of every person is continually monitored for all relevant chemical and biological molecules. Glucose, PSA, thyroid hormone, IL-2, TNF, LDL, oncofetal antigen, all of these things could be monitored continuously by an implanted nanotransistor array exposed to the bloodstream. This array would be a simple chip with several hundred or thousand antibody-linked nanotransistors, each of which would be specific for a biologically relevant molecule. Each transistor would be linked to a small ammeter attached to a central processing unit. This unit could be programmed to monitor the currents through each of the FETS, looking for changes from baseline indicating binding of a specific substrate to its FET-linked antibody receptor.

To take this one step further, the transistor could even be functionalized with large numbers of antibody molecules. Knowing that binding of a substrate to one antibody should produce a quantized change in resistance of the nanowire, the total change in resistance (calculated by voltage/current) would be indicative of the number of ligand bound receptors and therefore the concentration of substrate in the body as related by the dissociation constant of the antibody/antigen interaction.

Using this protocol which relies upon the specificity of the immune system and the sensitivity of boron doped SiNWs, this array could conceivably collect data on the presence and concentration of an almost infinite number of biological molecules. If a patient needed to monitor his own internal status, it could be linked to a hand-held PDA

type device or small computer. If a medical professional was monitoring the patient, the data could be sent on the internet directly to the doctor, whose computer would use simple upper and lower boundaries of normal to decide which data to highlight for review, and which to archive. If an abnormality was detected, such as an elevated PSA level, the doctor would know to contact the patient, and the patient could receive an alert to contact the doctor. This not only allows a person to get help as soon as a problem is indicated, but it will make a doctor much more efficient by eliminating time spent finding out that healthy people have nothing wrong!

Specific Scenario for Treating Diabetes in 2025

Diabetes is one of the most common diseases across the demographic board in the United States. This malfunction of the pancreas; which leads to reduced insulin and unregulated blood sugar, debilitates children, cripples adults, and blinds the elderly if it is not meticulously controlled with a strict regimen of diet, exercise, constant blood glucose tests, and insulin injections. One of the most taxing parts of this disease is in fact the constant attention that must be paid to monitoring it with constant finger pricks and insulin injections. Automated blood glucose monitors have in fact been proposed and brought to market, including the GlucoWatch by Cygnus and the CGMS by MiniMed¹², though they have not had great success as both need to be verified often with finger sticks, the former can cause persistent blisters after just a few days, and the latter costs \$1000 and is often used only on loan from a doctor.

The constant need for blood glucose monitoring makes diabetes a good target for continuous nanotransistor based monitoring. By invoking the multiple receptor method described in the last section, a nanotransistor exposed to the circulation should be able to

¹² http://www.joslin.org/education/library/test_wo_stick.shtml

easily monitor blood glucose concentration continuously. Just to reiterate, many glucose receptors could be covalently linked to the gate point on a nanotransistor such that receptor/binding events would modulate the current in the nanowire which would flow across an ammeter with the readings being sent to a central processing unit. Using a handheld interface with this processor, a person could know his or her blood sugar in real time, and never be surprised by an excessively high or dangerously low level.

This continuous monitoring system should effectively eliminate the necessity for finger sticking, and unpleasant blood sugar surprises, something that could greatly improve the quality of a diabetic life. But why stop there? When a person receives their blood sugar level, they usually need to modify it by injecting the appropriate amount of insulin as determined by their deviation from appropriate blood glucose level. As this information is already digitally stored in the central processor, it could be directed to an implantable drug pump such that a fluctuation in blood glucose could be immediately counteracted by insulin release. This circuit mimics the micro-regulation over time that is the major advantage of having a functional pancreas. The net result of this system would be full replacement of an organ function without attempt to replace the organ; a novel idea in the context of the present biomimetic focus of lost organ compensation. Though pumps like this exist today, they operate on an open loop system where the pump is patient controlled, and has no glucose sensor for automated action¹³.

Though I have used diabetes as an example of one way that nanowire based biodetection could improve the quality of medical care in the future, this is not the limit of the possibilities. This protocol of closed loop sensor/drug pump could be applied to any disorder which requires constant monitoring and medication. Countless numbers of

¹³ <http://personal.uncc.edu/macurran/macurran3/diabetes/inspump.htm>

these situations exist. Another example is prothrombin time tests and coumadin regulation, which primary care physicians and cardiologists spend countless hours looking after in their patients with coronary heart disease, atrial fibrillation, heart attack, or valve replacement. Though the point was touched on before, it is worth expanding upon the idea that these nanosensor arrays could theoretically detect most cancers very near to their point of mutation, when they start producing oncoproteins. We know of many proteinaceous cancer markers such as PSA, oncofetal antigen, and even more mutant gene markers like p21Ras and p50 which could be detected by the PNA probe discussed above. If cancer could be detected at these early stages, both chemotherapy and ablative procedures would need to be much less rigorous to eliminate the malignant tissue¹⁴.

Summary

After briefly describing the chemical and electrical composition of nanotransistors, I have offered my vision for the next step in exploiting the full potential of nanodiagnostics. By bringing the ultra-sensitive diagnostic test to the patient before there is reason to believe that it is needed, you bring the point of diagnosis out of the frame of the yearly doctor visits, and into the every day, where illness really occurs. Also by using the constant real-time sensing capability of nanotransistors, we can offer new closed loop monitoring and medication options to patients with chronic illness that require constant attention. Through both of these mechanisms, integrated nanotransistor biodetectors offer much promise to diagnose human illness faster, and control it more readily, yielding an overall improved quality of medical care and everyday life.

¹⁴ Wang et al. 2005

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