M275: Micro- and Nanoscale Biosensing for Molecular Diagnostics

Magnetic Nanowires for Biosensing

Kamila Kunes & Ben Yang

Department of Electrical Engineering

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Executive Summary

Nanowire biosensors are systems designed at the nanometer scale in order to capture and relay quantitative information about the concentrations of biomarkers at an increasingly minute level. This opens up a cornucopia of information that can be collected. For example, the sensitivity of some nanowire biosensors enable diagnostic systems to use sweat rather than blood as, despite the extremely low concentrations of a target biomarker in sweat, the high sensitivity of nanowire biosensors are able to reliably enumerate our analyte of interest. With the current state of nanowire biosensors, there is a very established vein of research for electric field effect nanowire biosensors (nanofets). These nanofets mimic MOSFETs in operation principle as well as fabrication which enable electric nanofets to be easily integrated into existing technologies. In addition to conventional CMOS fabrication techniques, researchers have also adopted bottom up fabrication techniques that grow silicon nanowires from the ground up. Both of these approaches have their pros and cons and are covered in this report. Expanding past fabrication, electric nanofets have progressed from label based to label free and finally to aptamer based approaches–conquering problems with extra charges in samples, biofouling, and charge screening along the way. While these aptamer based approaches show great promise with high dynamic range and high levels of sensitivity, they are tough to develop. Furthermore, we question the initial assumption that electric field effects are the best ways to differentiate targets of interest. In this report we propose a novel magnetic based system that utilizes magnetic beads as labels. Similar to how gold nanobeads are used as labels for target antigens for paper-based Covid-19 tests, magnetic nanobeads are used as a biomarker label. While it may seem like a step back to return to a label based approach, magnetic beads have significantly less noise and provide a competitive level of sensitivity. Moreover, this labeling process is highly established and extremely common, in which the label is attached to the constant region of the antibody which is then bound to the target of interest at the binding site. When bound to the capturing antibody located on a magnetic nanowire, a change in magnetic field is induced which causes a change in the wire's resistance. This change in magnetic field is due to a domain wall shift. An external permanent magnet creates the initial magnetic field configuration, which first establishes the domain wall. A notch is created in the nanowire, which creates a bottleneck where all current must pass through. A change in magnetic field at this point affects the resistance immensely due to the aforementioned bottleneck. This resistance may be detected using a search current through the wire and measuring the change in current by probing the drain and source of the device. We propose this technology be integrated into a real sensor, as all research thus far consists solely of simulations. The device would

operate similarly to electric nanofet devices, in which it would measure the current differences through drain and source as well as have a substrate, oxide, and gate layer.

Part 1

At its core, nanowire biosensors are biosensors with a sensing region composed of nano-scale wires–hence the name. Based on the current state of the field, nanowire biosensors are primarily silicon-based and use the electric field to affect conductance much like MOSFETs. Thus to understand how most nanowire biosensors work, one must first learn how a MOSFET functions as the two are very striking images of each other.

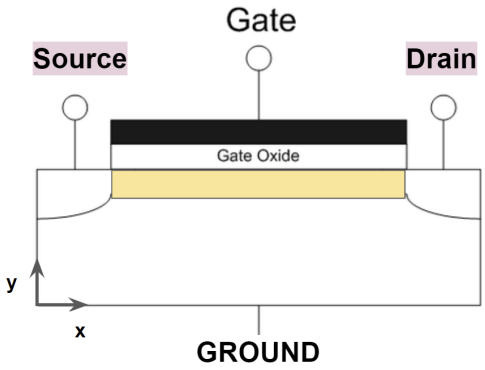

Figure 1. MOSFET Diagram [1]

The MOSFET is a four terminal device that, functionally speaking, can be simplified into three terminals. As illustrated in figure 1, one can consider the channel at the base to be a common ground. Highlighted in pink, the source and drain are where currents enter & leave the device. The voltage/current across these two terminals are what one measures. The gate acts much like a conventional gate in that it controls how much current can pass from source and drain. This is done through an electric field oriented between the gate and body (think ground). Modeling the gate to ground terminals as a capacitor, what we effectively have is the following: a device that can modify the conductivity (inverse resistance) of the yellow region by applying different amounts of voltage to the gate terminal. Since the conductivity/resistance of the region between source and drain has changed, the current across source & drain will inevitably change when applying a constant voltage across the two. One thing to note is that these sections (save the oxide & metal contact at gate) are almost always made of silicon doped to varying levels. This, as well, is true of nanowire biosensors that employ a FET based operating principle.

Refocusing back towards FET based nanowire biosensors, these devices deviate from MOSFETs in that the conducting region (previously highlighted in yellow) becomes a nanowire and doesn't extend into the z-plane. While the isolation layer (usually silicon dioxide) remains the same, nanowire FETs (nanofets) replace a metal gate with receptors that are tuned towards the biomolecules one is interested in measuring. Illustrated in figure 2, these nanofets usually have some receptors that act as the "gate" for this device. Upon the binding of our target of interest (dopamine in this case), the conductivity of the nanowire (where current between drain and source is flowing) will change–reflecting a rise or drop in current that we can measure.

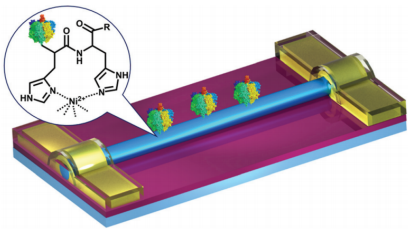

Figure 2. Nanofet Illustration [2]

Zooming out to a more birds eye view of nanowire biosensors, these devices more than prove their worth through their easy integration with conventional MOSFET techniques and significantly increased sensitivity & resolution. Since they very closely mirror MOSFETs in device structure as well as function, both the fabrication and measurement techniques can closely parallel that of MOSFETs–leading to significantly more streamlined integration with pre-existing fabrication infrastructure as well as combining with PCB technology for mobile biosensing applications. Due to the nano-scale nature of nanowires, these biosensors are able to provide an unparalleled level of sensitivity to diagnostics–even at the femtomolar scale. Moreover, newer nanofets have been able to sense with a very high dynamic range–from 10 fM all the way to 100 uM. These attributes combine to make nanowire biosensors a very exciting and rewarding technology to develop for everything from biomarker diagnostics and drug testing to real time monitoring with minimally invasive or implanted devices.

Shifting gears towards fabrication, there exists two main schools of thought when it comes to synthesizing nanofets. On one hand, the top down method takes a large piece of material and breaks it down to smaller and smaller fragments until nanoscale wires are formed. On the other hand, the bottom up method takes extremely small particles of a material, growing it into clusters and eventually, nanowires. Comparing these two approaches, the bottom up approach is able to produce nanowires that are extremely thin (even reaching 3 atoms in width) while the top down approach is only able to make

nanowires that are tens of nanometers wide. However, the bottom up approach results in nanowires being scattered randomly across the substrate causing problems with scaling fabrication as there is a much lower yield. Comparatively, the top down approach is compatible with CMOS techniques and can create orderly arrays of nanowires resulting in a much higher yield of functional devices than the bottom up approach [1]. As the fabrication of nanofets advances, even higher diagnostic capabilities combine with cheaper devices to further the field of biosensing.

Recent advancements have demonstrated this principle with the progression from label-based to label free and aptamer-based sensing elements. From its inception, nanowire biosensors have relied on there being a significant difference in charge to induce a measurable change in current when targeted biomarkers bind with receptors. However, this is a very ideal assumption that almost never works out in practice. With many particles of interest being electrically neutral such as glucose, researchers had to get creative with particle detection. From this initial round, there emerged many label based approaches that would introduce some electrical label that first binded to the target of interest. Thereafter, these labeled particles would bind on receptors (the "gate" of our nanofet system) and the labels' charges would induce a measurable difference in current across the nanofet. However, due to how a label-based approach is pre-amplifying the signal as well as being an indirect measurement, label-based development was dropped in favor of label free approaches. Yet, these label free approaches came with its own set of challenges. Due to the preexisting ions in sampled fluids (blood, sweat, cerebral spinal fluid, etc.), there is inherently a lot of noise in the sample that may overshadow any change in measured

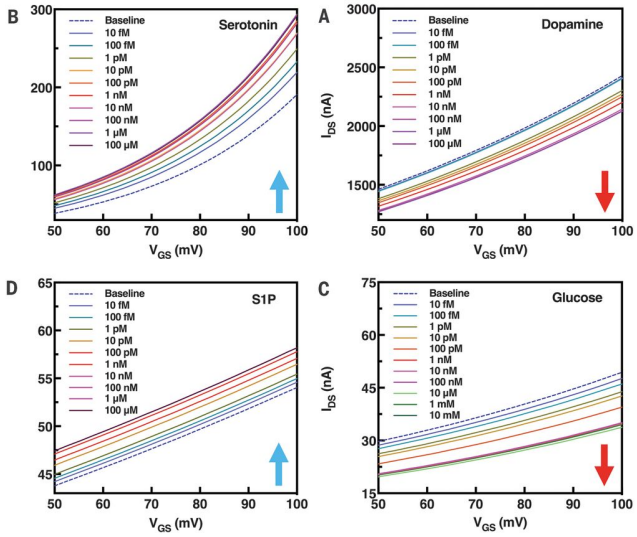

Figure 3. Experimental results for aptamer based nanowire biosensors [3]

current from the targeted molecules. Furthermore, there is a debye length problem where ions in the solution line up along the receptor's surface–forming a layer of charge that also overshadows any desired signal. To combat these two issues, the field has shifted towards aptamer based approaches. This approach uses the physical "curling" of aptamers (specially designed DNA or RNA molecules to "curl" upon interfacing with a biomarker of interest) and the negative backbone of DNA/RNA to induce a measurable signal. Through an aptamer based approach both the natural noise within samples and the debye layer screening effect can be bypassed. However, the fabrication of an aptamer requires a special touch and is largely a guess and check process that is required for every single new biomarker that needs to be tested. As shown in figure 3, aptamer based approaches have shown extremely high promise with both high dynamic range and extremely good sensitivity (10 fM). Moreover, these traits have been proven across a variety of important biomarkers from dopamine to serotonin. As a whole, aptamer based approaches show high levels of potential to expand the scale and scope of nanowire biosensors [3][4].

While aptamer based approaches do hold promise for the future of nanowire biosensors, we believe there exists another novel branch of nanowire biosensors which question the fundamental principle of nanofets. Rather than using an electric field effect to vary conductance, we propose using magnetic nanowires in conjunction with magnetic labels to build a magnetic nanofet. While this may seem like a step back with a return to a label based approach, magnetic nanofets have been demonstrated to have significantly lower levels of noise (due to the lack of magnetically significant particles in biological samples) as well as comparable levels of sensitivity. Furthermore, magnetic systems even hold potential for disease treatment as magnetic particles implanted within cells can be controlled to oscillate and "cook" the cells–effectively destroying, for example, cancer cells. However, returning to magnetic systems as whole, the magnetic labels can be detected with a variety of methods including giant magnetoresistance (GMR), magnetophoresis, and domain wall shifts using a notched nanowire. In this report, we focus on an approach that utilizes domain wall shifts. However, before diving into how our magnetic nanowire sensing system functions, it's important to understand the history of labeling technology.

Part 2

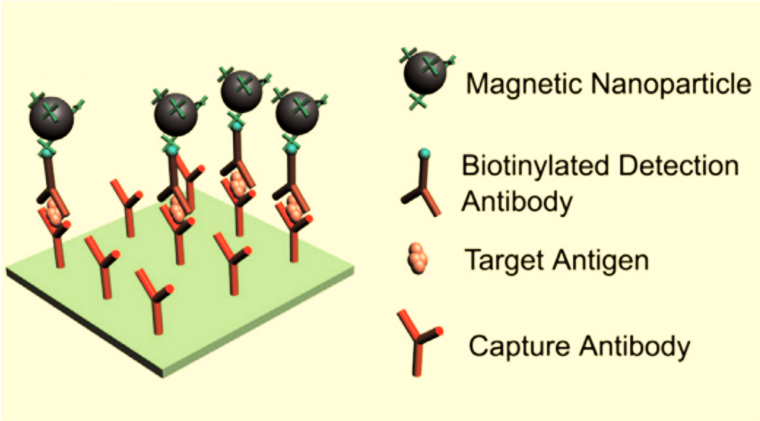

Figure 4. Antigen labeling visualization [5]

Labeling technology is a highly established practice in diagnostics. Its visualization can be seen in figure 4. Similar to the gold nanobead labeling found in many paper based diagnostics tests such as Covid or pregnancy tests, magnetic beads can be attached to the antibody's constant region. The target then binds to the binding site of the antibody when the sample is introduced.

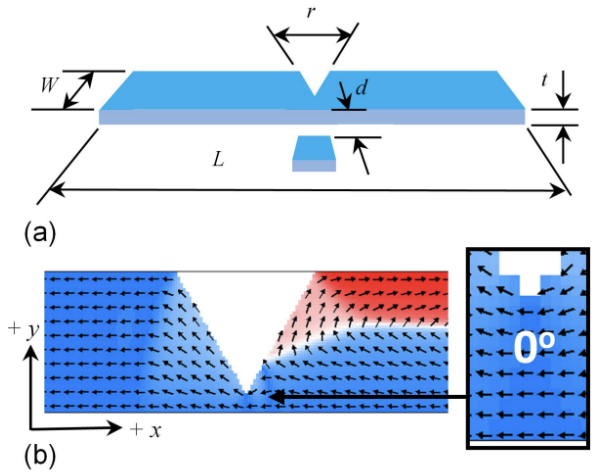

Figure 5. a) Notched nanowire with dimensions; r = 500nm, L = 5µn, W = 500nm, and t = 20nm
b) Graphical representation of nanowire with arrows indicating direction of magnetic field [6]

Figure 5 is a visualization of the permalloy nanowire (Ni80Fe20) that detects the presence of the magnetic labels. Search currents can be introduced through the nanowire and are affected by resistance changes. These changes are induced by a change of the magnetic field angle due to the proximity of

magnetic nanobeads. A 0.3 tesla magnetic field is induced by an external permanent magnet on the measuring device in positive y direction. This ensures that all “biosensor configurations are fully saturated” [6]. This saturation allows for a resistance measurement induced by a change in magnetic field rather than a creation of a magnetic field, which allows for higher sensitivity. The notch in the nanowire, which may be created by an ion beam, creates a bottleneck for the search current. Because all current must run through this thin portion of the wire, changes in magnetic field here have a great impact on the resistance of the wire. Larger sections of the wire also have a change of magnetic field, but this has a negligible effect on the overall resistance. This configuration allows for single label detections as demonstrated in figure 6.

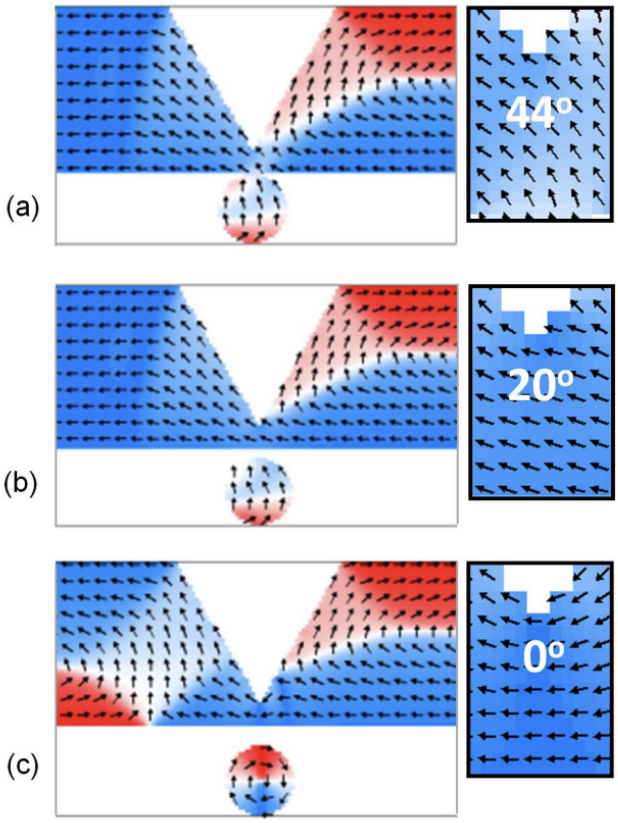

Figure 6. Simulation of magnetic nanobead approaching nanowire at a) 0nm, b) 30nm, and c) 60nm. Nanobead diameter = 200nm. Enlarged images of the trough of the notch shown on the right along with the change in magnetic field angle at that location [6]

The interactions of said magnetic nanobead labels and nanowire based sensors have been simulated [6]. As the bead approaches the notch, the magnetic field configuration changes within the

nanowire. This affects the overall resistance of the wire, which may be detected by a measurement of the search current. The resistance drops about 0.48% when a single marker is in proximity to the wire. A higher quantity of bindings will compound to a much greater percentage.

$$R(\theta) = R_{\text{perp}} + \delta R \cos^2(\theta)$$

Equation 1. Overall resistance in the nanowire. R_{perp} = resistance of the notch when the magnetic field direction is perpendicular to the current ($\theta = 90°$). δR = change in the resistance between 0° and 90° [6]

It should also be noted that the shape of the label also produces the advantage of having a closed domain structure as seen in figure 6. The magnetic field lines are tangential to the bead's surface, meaning label-label interactions are minimal and even negligible. This is not true for other label shapes.

This technology has only been simulated but we propose to attach these beads to antigens as a label and to use the same magnetic properties to detect biomarkers. Such detection would take place in vitro, only requiring a small biosample to acquire meaningful results due to the single label detection, nanoscale technology, and overall sensitivity due to the notched, magnetized nanowire. We propose the nanowire have periodic notches with capture antibodies attached to the unaltered side. The location of the label in relation to the notch must be taken into account as well. Labels nearest to the notch will induce a greater resistance than those farther away. We wish to minimize this effect by populating the nanowire with notches to ensure all bindings are near a notch. Moving past the sensing element, the rest of the device would closely resemble the FET devices described earlier, with a drain and source which allow the measurement of current changes. An external magnet would also be integrated in the device along the length of the sensor to induce the magnetic field as described.

The capabilities of magnetic-based nanowires and their potential in health care are immense. The proposed technology described thus far has diagnostic abilities that have the potential to demonstrate competitive sensitivity. Magnetic nanowires also have numerous further applications in the field of cancer. These nanowires can be inserted into cancer cells and 'excited' using a magnetic field. These nanoparticles vibrate and induce hyperthermia, which virtually 'cook' the cancer cells, resulting in their death. This has been proven by culturing cancer cells in a broth containing nanowires, which were absorbed by the cells. Nanowires are hypothesized to have greater impacts than nanobeads in this case due to the nanowires having a greater magnetic moment from its bar-like shape. This application still has

a selectivity issue where the nanowire is absorbed by all cells in proximity, and not simply cancer cells, which is the main cause of its absence in treatment options thus far. However, the magnetic nanowire itself has been proven to have low biotoxicity leading to potential applications in cell manipulation & positioning [7].

Due to the possible applications of magnetic nanowires extending from diagnostics, treatment, and checkups, this technology should be further researched. Magnetic labels specifically show high promise for effective performance while exhibiting low noise. While established technologies like aptamer based nanofets continue to be researched and optimized, magnetic nanofets emerge as a valuable addition to the field of nanowire biosensing–providing device designers a multitude of sensing options for the next-generation of health care services.

References

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