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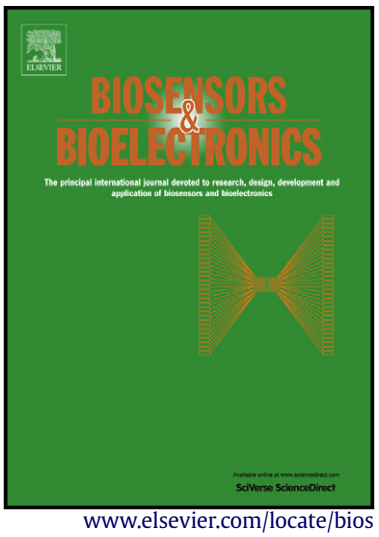

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Review

Synergizing Nucleic acid Aptamers with 1-dimensional Nanostructures as label-free Field-effect transistor biosensors

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Abstract

Since the introduction by Gold et al. in 1990, nucleic acid aptamers had evolved to become a true contender in biosensors for protein and cell detections. Aptamers are short strands of synthetically designed DNA or RNA oligonucleotides that can be self-assembled into unique 3-dimensional structures and can bind to different proteins, cells or even small molecules at a high level of specificity and affinity. In recent years, there had been many reports in literature in using aptamers in place of conventional antibodies as capture biomolecules on the surface. This is mainly due to the better thermal stability properties and ease in production. Consequently, also these characteristics allowed the aptamers to find use in field effect transistors (FETs) based upon 1D nanostructured (1D−NS) as label-free biosensing. In terms of designing label-free platforms for biosensors applications, 1D−NS FET had been an attractive option due to reported high sensitivities toward protein targets arising from the large surface area for detection as well as to their label-free nature. Since the first aptamer-based 1D−NS FET biosensor had surfaced in 2005, there had been many more improvements in the overall

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design and sensitivity in recent years. In this review, the latest developments in synergizing these two interesting areas of research (aptamers and 1D−NS FET) will be discussed for a range of different nanowire types as well as for the detection results.

Keyword: Nanowires, aptamers, biosensing, field effect transistors

1. Introduction

Biosensors are important analytical devices for sensing biological analytes utilising the principles of physical chemistry to detect the presence of proteins and other biological analogues and is useful for disease detection and prognosis(Bertok et al. 2012; Guilbault et al. 1995; Herrera-Lopez 2012; Hong et al. 2012; Kintzios 2007; Mascini 1992; Nakabayashi 1995; Seokheun and Junseok 2009; Vadgama 1993). Currently, there are numerous biodevices in market, worth a R&D investment of US$300 million(Luong et al. 2008) and with an estimated global market by 2015 of US$12 billion. This ensures that there will always be an impetus in the research for newer and more advanced detecting platforms(Luong et al. 2008; Mongra and Kaur 2012). Currently, there are many examples that harness the principles of optical sensing(Dhanekar and Jain 2013; Ren et al. 2013; Yoshikawa et al. 2012), potentiometric(Bratov et al. 2010; Israr et al. 2010; Lawal and Adeloju 2012, 2013), piezoelectric(Lu et al. 2012; Xiao et al. 2012; Xu 2012) and electrochemical(Afonso et al. 2013; Diallo et al. 2013; Silvestrini et al. 2013) devices aiming at delivering point-of-care analyses. Ranging from glucose sensors for diabetic patients (Heo and Takeuchi 2013; Xu et al. 2012) to life-threatening diseases like cancer (Chiriaco et al. 2013; Ji Yeong et al. 2013) and AIDS (Alyassin et al. 2009; Hassen et al. 2008), these devices proved to be highly specific and significantly faster compared to conventional prognostic methodologies. In most cases, attention given to time reduction for detection remains major motivation for the development of newer and more advanced sensing platforms.

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As a matter of fact, biosensor-based analytical systems are currently regarded as part of the inventory in several areas of research. In a broad sense, biosensors can be defined as devices that utilised the presence of biological or chemical receptors for the detection of analytes (molecules) typically associated with specific physiological diseases or disorders. The background information on the binding affinity as well as the kinetics of the interactions is widely reported in literature(Baleviciute et al. 2013; Cerminara et al. 2012; Duan et al. 2012; Ghosh et al. 2012; Knezevic et al. 2012). Biosensors can then be classified into two categories, namely label-based and label-free biosensors. In label-based biosensors, molecules tagged with fluorescence dyes (Kazakova et al. 2013; Wang et al. 2011; Zadran et al. 2012), quantum dots (Wang and Mountziaris 2013; Yu et al. 2012; Yuan et al. 2013; Zhou 2012), nanoparticles(Authier et al. 2001; Pingarron et al. 2008; Trewyn et al. 2007) are used for detection. These techniques of labeling reporter systems are very well-established and many of the reporter molecules are readily available. Furthermore, the instruments for detection and analysis can be inexpensive. However, the major drawback for these labeled systems is that the procedures for documenting the biosensing responses are often very time-consuming. Additionally, there is always the possibility that the labeled reporter interfere to the inherent property of the target molecule (Piston and Kremers 2007).

Instead, label-free biosensors, by definition, do not require the use of reporter elements (fluorescent, luminescent, radiometric, or colorimetric) to facilitate measurements. Actually, devices based upon isothermal titration calorimetry (ITC)(Cooper 2003; Day et al. 2002), nuclear magnetic resonance (NMR)(Spence et al. 2004), and surface plasmon resonance(El-Sayed et al. 2005; Homola 2008; Homola et al. 1999; Willets and Van Duyne 2007) require neither reporter labels nor surface-bound receptors. Unlike label- and reporter-based technologies that simply confirm the presence or the absence of a detector molecule, label-free techniques can provide direct information on analyte via changes in a physical bulk (e.g.: heat capacity) or surface (e.g.: plasmonic absorbance) property. Until recently, however, label-free

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technologies have failed to gain widespread application due to technical constraints, high user expertise requirements, and cost. While they have proved to be powerful tools in the hands of a skilled user, they cannot always be readily adapted to everyday lab use due to high technicality requirements. Nonetheless, the drive towards label-free approaches to complement or even displace other detection technologies remains highly attractive. Of them, one of the most popular label-free technology to have surfaced in recent years is the union of the concepts of field effect transistors (FET) and nanomaterials to form highly sensitive label-free nanowire FET biosensors(Bergveld 2003; Cui et al. 2001; Gao et al. 2007; Star et al. 2006).

The aim of this review is to critically present the ongoing effort to integrate aptamers within nanoFET devices used for biosensing. This review will be organized as follows: We will initiate by discussing the principles of FET devices based upon 1-dimensional nanostructures (1D−NS) and the issues pertaining to the nature of surface receptors for biosensors. The bulk of the review will be focused on the synergic approach towards aptamers and 1D-NSs in FET devices. Three classes of 1D nanosystems will be investigated, namely carbon nanotubes, conducting polymer nanowires, and silicon nanowires.

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2. Aptamers as sensing elements

In recent years, an exciting development in label-free biosensors has been the advocation of aptamer technology. Aptamers, in brief, are short strands of synthetically designed DNA oligonucleotide that will self-assemble into unique molecular recognition motifs in order to arrest different proteins at a high level of specificity and affinity(Jayasena 1999; Jing et al. 2011; Kim et al. 2009; Kwon et al. 2010; Lee et al. 2011; Liu et al. 2011; Pagba et al. 2010; So et al. 2005; Tombelli et al. 2005; Wilson and Szostak 1999; Yao et al. 2010). In an aqueous environment, an aptamer molecule undergoes considerable structural rearrangement, ultimately presenting itself into a most energetically

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favorable configuration that subsequently binds discriminatingly to a designated protein target. Using methods such as SELEX (systematic evolution of ligands by exponential enrichment), libraries consisting of thousands of potential oligonucleotides sequences can be raised readily and molecules can be easily found to bind to the target with high specificity (Jayasena 1999; Tombelli et al. 2005; Wilson and Szostak 1999). As these oligonucleotides are fully synthetic, it is also possible to use them to tag a diverse range of different detectors as well as nanoparticles, thus enabling aptamer use in many types of biosensors.

As mentioned, the major advantage for aptamers lays in their design capabilities by which they may replace antibodies as a viable source for highly specific molecular capture (Pratt et al. 2011; Xu et al. 2009). It had been shown that aptamers had the capacity to be tailored to bind even to the most demanding biomolecular targets, even where conventional antibody methodologies had failed Furthermore, aptamers can be attached easily to a range of different carrier molecules. Cell and protein biosensing are excellent examples of this (Pratt et al. 2011; Xu et al. 2009).

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3. Working principles of nanoFETs

In 2005 the first report of the use of a novel biosensor design in the form of nucleic acid based ligand on nanowire FET was released. This has subsequently propelled the development of an unique niche in the field of biosensor design. Hence, the purpose of this review is to discuss the virtue of this approach as well as to follow its gradual developments. Instead, it is not within the aims of this review to present or discuss neither the use of nanoFETs as such or the more general applications of aptamers in sensing. On both topics the interested reader may refer to recent relevant reviews(Allen et al. 2007; Du et al. 2013; Famulok and Mayer 2011; Grieshaber et al. 2008; Narducci 2011; Patolsky et al. 2006; Scarselli et al. 2012; Wanekaya et al. 2006; Wang et al. 2006b; Wei and Lieber 2006; Yang et al. 2007).

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For the sake of completeness, a bief description of nanoFET operating principles is in order. Comprising of a source, drain and gate electrodes, the sensing mechanism of FET devices relies upon the alteration of the charge density on the surface of the 1D−NS as a result of molecule adsorption (figure 1). For instance, if a biomolecule target has an overall negative charge and is adsorbed onto the surface of a n-type FET, this will result in an increase in the device resistance. Because of its nanosize dimension, 1D−NS FET devices had been shown to be ultrasensitive and highly selective sensors for label-free detection of metal ions, nucleic acids, proteins and virus. Compared to flat surfaces, due to teir much larger surface area for biomolecule contact, 1D−NS can enhance detection efficacy.

Figure 1. A schematic example of a nanowire FET biosensor device with the source, drain and gate electrode(Chen et al. 2011)

Quantitatively, charge transport in a 1D−NS FET can be decribed via ballistic conduction. Electrons (holes) injected by the drain (source) can travel through the channel and the 1D−NS, experiencing no scattering by either phonons or surface defects. This is actually the case for submicrometric integrated devices. Considering a 1D−NS, the total potential field experienced by charge carriers is the sum of a (crystalline) potential and of an eventual external perturbation.

Thus, the energy of the electronic states are modulated by the external perturbation. As a result, the drain current I_D (Landauer 1992)also depend on the external perturbation. In a standard MOSFET device, this states the fact that the gate controls the current flowing through the channel. In a 1D−NS FET, the current−voltage characteristics of the device is modulated instead by *any* external charged entity (Natori 2008). This is a key point in understanding the physical chemistry behind FET devices and of their application to sensing. On one hand, the mechanism of current modulation provides the extreme

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sensitivity of these sensors; on the other hand, 1D−NS FETs can also detect large biomolecules away from the sensing device, provided that the electric field that these biomolecules generate is large enough to perturb the nanowire/nanotube electronic structure.

It may be worth remarking that, in principle, the mechanism of biosensing of all types of 1D−NS is the same. Upon interaction of the target molecule with the aptamer, the local electric field sensed by the 1D−NS is modified by the presence of either the free charges or, more often, the dipoles or the multipoles associated with the target molecule. As a second possibility, the aptamer−target interaction modifies the dipolar and multipolar moments of the aptamer itself, leading to a modulation of the electric field sensed by the 1D−NS. This type of modulation may be set off in a likely manner with carbon nanotubes, silicon nanowires or silicon polymers. One noteworthy additional mechanism of sensing may be however exploited for carbon nanotubes, where the target molecule may modulate the Schottky barrier at the nanotube−metal contact junction. In this case the FET act as a current amplifier, the biosensing mechanism directly acting upon the charge flowing throud the metal−nanotube Schottky diode.

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4. Use of 1D nanostructures in biosensing

Nanostructures such as nanowires and nanoparticles had gained much attention for biosensing applications as their dimensions allow for high aspect ratios and volume detection(Bao et al. 2008; Chan et al. 2001; Himmelhaus and Takei 2000; Stewart et al. 2008; Wang et al. 2006a). Nanoparticles, for instance, have been extensively used for the detection of biomarkers with a high sensitivity(Afonso et al. 2013; Himmelhaus and Takei 2000). However, most reported approaches used chemical labeling that can be time-consuming and not economically viable. Furthermore, there is also a possibility of conformational deformation and steric hindrance from the chemical labels that may adversely affect the efficacy of biosensing

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system(Piston and Kremers 2007). So far, 1D−NSs such as the nanowires or nanotubes had already been considered as a practical commercial option(Duan et al. 2012; Gao et al. 2012; Gao et al. 2007; Kim et al. 2009; Lee et al. 2009; Xie et al. 2009). This is particularly so for platform-based detection devices where integration at high density within a small area can help signal amplification, thus improving sensitivity. Of the many nanostructure materials envisaged, several noteworthy materials such as **carbon nanotube-based**(Lee et al. 2011; Maehashi et al. 2009; Pacios et al. 2012; Star et al. 2006), **electrically conductive polymers**(Gerard et al. 2002; Guimard et al. 2007; Ramanavicius et al. 2006) and **silicon nanowires**(Cattani-Scholz et al. 2008; Gao et al. 2010; Gao et al. 2007) had gained much attention in literature due to their high surface area ratio and their well-established technological production methodologies. Much effort had been invested on carbon nanotube-based and conducting polymeric devices although certain weaknesses had been identified with these system. There are issues concerning the ability to align such 1D−NS along the correct axis on the surface, as well as of achieving high degree of reproducibility during its synthetic production(Lee et al. 2011; So et al. 2008). Still, the 1D quantum confinement properties of carbon nanotubes (CNTs) and the conductive nature of these polymers allows charge transport to be extremely sensitive towards the presence of adsorbates on the surface. Localising single nanowires onto gold contacts for conductive polymers had been demonstrated in the past via directed polymer growth on the surface but this process is too technical(Xie et al. 2009). Silicon is another attractive alternative that is readily available and is useful to obtain a highly precise mechanical alignment on the surface using standard microlithography. In addition, for application in biosensing, silicon is more commercially viable compared to other material currently contemplated.

5. Issues in the selection of surface receptors

Typically, using a 1D−NS surface without prior chemical functionalization of

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the right receptor may result in non-specific biofouling from all other proteins that are also present in the media (Wisniewski et al. 2000; Wisniewski and Reichert 2000) and this can easily give rise to false positives. Therefore, there is a need to passivate 1D−NS surfaces with a chemical molecule that can help to segregate the target biomolecule from the rest. Instead, from the viewpoint of the detection strategythe key challenge of 1D−NS FET devices is the selection for the right type of receptors on the surface. Ideally, the receptors should be coupled covalently onto the surface, as physisorption-type attachment is deemed unstable in aqueous solutions(Choi and Chae 2010). The portfolio of chemical methodology to anchor the receptor molecule on the surface is well studied(Blixt et al. 2004; Lemieux and Bertozzi 1998; Liu et al. 2010; Norberg et al. 2009). So, the main problem lies in the selection of the type of receptor. Ranging from single chemical compounds to bulky antibodies, the literature had offered much variety to date(Chan and Nie 1998; Cornell et al. 1997; Homola et al. 1999; Thevenot et al. 2001; Tombelli et al. 2005). The simplistic approach of using a small chemical molecule may be feasible at the laboratory level but can pose serious problems at the commercial stage due to non-specific biofouling. As a consequence, the most investigated receptors are by far antibodies, as they had been the mainstream in literature for decades(Skottrup et al. 2008; Vo-Dinh et al. 2000; Vodinh et al. 1987).

While antibodies had been proven to be highly specific to their target biomolecule, there are several drawbacks in their use for biosensing. Firstly, antibodies had to be traditionally raised from animal subjects and these can be costly and not suitable for commercialization. Secondly, due to the protein structure of a fully assembled antibody (Y-shaped), there can be plenty of steric hindrances arising from the protruding regions(Chen et al. 2003; Saerens et al. 2008). This may induce the antibody coverage to be far less than full. Since the platforms on which the antibodies reside on are typically nanostructures with dimensions spanning only in the hundreds of nanometers, the cluttering effect of stacking antibodies is a major issue. Further to decrease sensitivity the gaps in between antibodies may also allow for opportunistic proteins to adsorb on the uncovered surface, thus increasing

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false positives(Chen et al. 2003)(Chen et al. 2003).

Another important factor to consider when designing 1D−NS FET is the Debye screening effect(Elnathan et al. 2012; Stern et al. 2007). This is the damping of electrical fields caused by the interaction between the mobile charge carriers present within the ionic medium (e.g. an aqueous solution) and the target molecule. This interaction could severely hamper the detection level of the 1D−NS and should be a major consideration in selecting for the type of capture molecule. In general, under fixed solution strength, the further away is the molecule from the surface, the larger is the charge screeneing effect − and so the smaller is the detection signal(Stern et al. 2007). Therefore, when designing a device it is prudent to consider the overall size of the capture receptor in relation to the ionic strength of the detection environment and to the charge density.

Exclusive binding regions of the antibody, usually in the form of synthetic peptides or antibody fragment, can also be used(Saerens et al. 2008). However it is necessary to consider that the production of peptides leads often to poor yields for large sequences (>80 mers)(Camarero et al. 2004; Tam and Lu 1995) thus rendering this less commercially viable. There are also serious concerns towards post synthetic protein folding, as the peptide or antibody fragment had to be folded into the correct configuration prior to surface coupling to the 1D−NS. Thus, extreme care is due to the intricate folding/denaturation of the peptide sequence. These attributes had seemingly impeded peptide-based targeting agents as a long-term viable replacement for antibodies.

Not surprisingly, in recent years, some groups had decided to move away from antibody approach. In the course of doing so, there had been an emerging trend of using aptamers as capturing ligands on nanowires FET

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devices to produce the next generation of biosensors. The advantages are fairly straightforward:

1. Aptamers are fully synthetic and easily produced by the sequential phosphoramidite chemistry approach.
2. Secondly, aptamers can retain their bioactivity over a wide range of thermal conditions unlike antibodies.
3. As antibodies are typically 15-30 nm in size, accommodating them under the Debye screen length may pose a challenge. This would not be an issue with regard to aptamers as they are mostly below the Debye length even after attaining their structure in most cases.

Harnessing on the virtues of both nanowire sensitivity and aptamer flexibility, the first report on using both technologies began surfacing in 2005 and had subsequently underwent much development. Herein, Table 1 illustrates the list of notable papers published hence, using CNTs, conductive polymers and silicon nanowires to fabricate FET devices.

Table 1. A list of notable nanowire FET devices with aptamers as receptors

6. Carbon nanotubes (CNTs) FET

CNTs are extremely popular candidates for biosensing. CNTs are typically obtained via arc discharge(Demoncy et al. 1998; Gamaly and Ebbesen 1995), laser ablation(Arepalli 2004; Guo et al. 1995), chemical vapor deposition(See and Harris 2007; Sinnott and Andrews 2001), high pressure carbon monoxide decomposition(Bronikowski et al. 2001; Nikolaev 2004) or catalytic methods(Backes et al. 2010; Zhang et al. 2005). However, the surface of CNTs is relatively inert and nonreactive (like graphite) with the exceptions of the ends of nanotubes. Instead, the large π-systems at CNT sidewalls can form π-π transitional bonds with external aromatic systems in a way that is heavily influenced by CNT degree of curvature and chirality (Daniel et al. 2007). The surface, however, has to be chemically modified prior to covalent attachment of aptamers. This is often done by introducing functional groups such as carboxylic or hydroxyl groups, ketones, alcohols, esters, amines,

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thiols, and fluorine atoms via chemical methods such as acid reflux and plasma treatment(Daniel et al. 2007). Before CNTs can be used, purification is performed via high-temperature annealing, plasma treatment, or chemical methods to remove amorphous carbon and metal catalysts such as Fe and Co(Pumera 2007). Once nanotubes are oxidized and defects are created, moieties such as carboxylic groups or biomolecules can be bonded covalently with conventional carbodiimide chemistry(Ravindran et al. 2003; Singh et al. 2006). In the case of non-covalent bonding, a direct π- π transition stacking can be directly obtained. Polymers can also be used for protein conjugation to confer viable functional groups on the CNT surface(Hirsch 2002; O'Connell et al. 2001).

In this review, all CNTs examined will be taken as single-walled CNTs unless otherwise stated. The first attempt using DNA aptamer functionalised carbon nanotube FET to capture thrombin was reported by So et al. in 2005(So et al. 2005). As shown in figure 2, So chemically passivated the sidewalls of the nanotubes to form carbamate linkage with NH_2-terminated Thrombin binding aptamer, with CNTs positioned between two gold pads. It is important to note that CNT FETs do typically exhibit p-type characteristics. Against the backdrop of another antagonist protein, Elastase, So had successfully produced the first CNT-based FET for the detection of thrombin. Thrombin is an attractive candidate due to its high proteolytic characteristics and had been widely used as a demonstrative biosensor target. A droplet of 1.5 μM Thrombin solution led to an abrupt drop of the drain current that reached a saturation level within 100 seconds. For comparison, CNTs without any thrombin aptamer attached onto the surface did not register reduction in electrical conductance while the antagonist, Elastase, also did not cause any reduction in conductance. The sensitivity was reported to be of 10 nM (figure 2d).

Figure 2. Binding of thrombin on the surface of CNTs via pyrene π- π transition stacking on surface (top) and the real-time detection profile of 1.5 μM (c). (d) shows the lowest detection limit of approximately 10 nM(So et al. 2005).

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Another important CNT-FET application by Maehashi et al. showed in 2007 the advantage of aptamers in relation to the Debye screening length (figure 3)(Maehashi et al. 2007). Since aptamers are smaller than antibodies, they fit well within the limits of the Debye screening length and are therefore expected to impart a greater sensitivity to the sensor. Actually, aptamers for immunoglobulinE (IgE) were functionalized onto the CNT surface by first incubating the CNTs with 1-pyrenebutanoic acid succinimidyl ester to form stable π- π transition stacking along the backbone of the CNTs while exposing the ester. The succinimidyl ester then reacted with the amino-terminated DNA aptamer (Figure 3).Sensitivity towards the target molecule was found to be very much dependent on where the target molecule binds along the length of the nanotube.A time dependent source-drain current (I_{SD}) was recorded upon introduction of IgE at various concentrations (from 250 pMto 160 nM). The graph in figure 3A (inset) shows that when different concentrations were added, step-wise reduction in current signals were observed. Interestingly, CNT FETs were found to be able to detect concentrations of IgE ten times lower than the levels required for detecting IgE in certain related physiological disorders (~10 nM). In the absence of any aptamer on the CNTs, an increase in conductance (figure 3B inset) was anyway observed that was attributed to the non-specific adhesion of the IgE, resulting in an overall negative charge on the CNTs. This observation further emphasizes on the need for passivation. While actually the binding with aptamers had resulted in 'protrusion' of the antibody further away from the CNTs and well above the Debye screening length, the charged regions of the IgE were within the Debye screening length. Therefore, a significant reduction in conductance in the aptamer-CNTs system could be observed. For comparison, using an anti-IgE antibody in place of the aptamer(figure 3C, inset)no change in conductance was observed, a situation arising from the fact that the overall length of the capture antibody had span across the Debye length already, thus masking the target signature.

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Figure 3. Label-free detection of IgE with aptamer based CNT FETs device. The discussion of debye layer was presented (top) as shown on the virtues of using aptamers instead of antibody. Lowest detection limit was found to be at 250 pM (right)(Maehashi et al. 2007).

Figure 4. Binding and sensing of entire *e.coli* bacterium on CNTs functionalized with aptamer. (Left) Dilution factors accounting for the number bacterium binded on the surface. (right top) light microscopy image of *e.coli* bacterium interfacing with CNTs. (right bottom) the electrical measurement of the detection in the presence of a control (*salmonella*)(So et al. 2008)

Apart from sensing for small biomolecule, aptamer-based CNT FETs can also be used for arresting and sensing the entire cell body. As reported by So et al. as well (coincidentally the first group to report aptamer based CNT FETs in 2005), SWNT-based RNA aptamer FET could be produced for the detection and capture of E.coli DH5α bacterium for the purpose of detecting food-borne pathogens (So et al. 2008).In order to facilitate for the detection of the whole E.coli bacterium, the source and drain were fabricated 5 μm apart. A triple source-drain array was obtained on silicon substrates via photolithography. As shown in figure 4 left inset, dilution series from 10^{-1} to 10^{-4} were studied in order to determine the detection limit for the E.coli bacterium. On CNTs without aptamers, even at concentrations of 10^{6} colony forming units (cfu) per ml there was not any notable response. On aptamer functionalized CNTs, a reduction of >50% in conductance was observed. The serial dilutions were then performed, showing response down to a 10^{-1} dilution. Furthermore, when another bacterium, *Salmonella typhimurium KCTC 1925*, was added, there was no registered reduction in conductance (figure 4). This suggests that the device was highly specific to E.coli bacterium. Results were overall compatible to those derived from conventional cell count.IgE detection with DNA aptamer based CNT FETs was further quantified by analysing the surface coverage of IgE using Langmuir absorption isotherms (Maehashi et al. 2009). The coverage of IgE on the CNT was found to properly correlate to IgE concentrtions. Furthermore, a threshold of sensitivity of 250 pM was measured, indeed very competitive when compared to aptamer-based flat-surfaced biosensors (Liss et al. 2002) (Gokulrangan et al. 2005), .

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As an alternative approach, An et al. reported in 2010 a dielectrophoretically aligned CNTs film suspended on silicon surface through Au contacts(An et al. 2010). The CNTs were collectively organized into a thin film (as shown in figure 5). For the attachment of DNA anti-thrombin aptamers, the surface of the CNTs was prepared to present COOH groups that were coupled using carbodiimides with an amino-terminated aptamer strand. The assay was performed in stepwise fashion and detection was noticed for concentrations as low as 70 pM, attaining saturation at 70 nM. The array also did not respond to VEGF protein which was the control. This demonstrated that conjoined arrays of multiple CNT bundles help increasing the sensitivity due to collective surface binding effects.

Figure 5. Detection of thrombin with suspending CNTs films bundles functionalized with aptamers. (a-d, top) SEM images of the supended film bundles. (a-d, bottom) Real time detection of thrombin as well as a control protein, VEGF(An et al. 2010)

Another unusual approach in using CNT FETs was reported by Lee et al. in 2011(Lee et al. 2011). An aptamer-based sandwich arrangement was positioned directly over the source and drain electrodes (figure 6, top set).

Figure 6. Using a dual aptamer sandwich CNT FETs system to detection for non polar molecule. (A-E top) graphic schematic of the sandwich system. (Bottom A and B) The mechanism of the bisphenol detection as well as the different analogues for the same molecule. (Bottom C and D) Real time detection of the Bisphenol A(Lee et al. 2011).

Bisphenol, an endocrine disruptor and a serious contaminant to the environment, was used, which also happened to be relatively non-polar. The gold source and drain were first functionalized with anti-Bisphenol aptamers, and Bisphenol already tagged with different negatively charged aptamers was then introduced to the surface. In a fashion similar to ELISA, the surface-bound aptamers arrested the Bisphenol from solution and further conferred negative charge onto the surface. This in turn changed the existing Schottky barrier height between the gold contact and the CNTs. Even at a

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concentration of 10 pM the device was sensitive enough to detect a drop in conductance, with saturations beyond 100 pM. This was quite significant considering the levels of detection reported by other similar FET devices in literature at that point of time. Control experiments were also carried out using three different analogues of Bisphenol. The current aptamer used to arrest the Bisphenol in solution was only sensitive towards the original Bisphenol while no significant response its analogues was observed. The change in Schottky barrier height seemed to be an excellent way to modulate the conductance in the FET device. This was clearly demonstrated when an even more negatively charged moiety, Biotin, was added to the tagged Bisphenol precursor in solution prior to surface attachment. The detection attained was at levels as low as 10 fM.

A different arrangement between CNTs and aptamers was proposed by Liu et al in 2011(Liu et al. 2011). In this setup (figure 7), CNTs were grown via chemical vapor deposition (CVD) between the electrodes, leaving a gap which was subsequently bridged by the anti-thrombin G4 aptamer via EDC/NHS assisted coupling to the acidified ends. The efficiency of charge transport (CT) may be ascribed to the intrinsic π-π transition stacking effect from the 4 guanosines upon binding to the thrombin, which rigidifies from the final conformation. This in turn would enhance charge transport in the system, and the high sensitivity thereof. As an alternative possibility, intrinsic π-π transition stacking could provide an alternative pathway for charge transport. Detection limit for thrombin as low as 2.6 fM was measured (figure 7 right). The conformational structure of the aptamer was speculated to reinforce detection.

Figure 7. A unusual CNT FETs system that uses the aptamers to bridge between the CNTs for the detection of thrombin (a-b, left). (b, right top) illustrates the mechanism by which the aptamers 4-guanosine π- π transition stacking can help to improve electrical conductivity and (c-h, right) are the detection profile of thrombin(Liu et al. 2011).

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In 2012 a new detection limit for Thrombin by CNT FETs of 20 pM was reported. Pacios et al.(Pacios et al. 2012) passivated the entire device with Poly(methyl methacrylate) (PMMA) leaving uncovered only the CNT channel, the region around the source and the drain electrode as well as the electrical contact points on the surface. Pyrenes was then adsorbed onto the CNT sidewall via π- π transitional stacking and its carboxylic group was used for the anchoring of amine-terminated aptamer via carbodiimide chemistry. The unreacted pyrene on the surface was then terminated with Polyethylene glycol (PEG) that also served as anti-biofouling agent on the nanotubes. A larger number of CNT FETs device on a single chip (up to 24) was used. This, in conjunction with the PEG coating on the CNTs, helped to reduce noise level. Using such an approach, a detection threshold for thrombins as low as 20 pM could be achieved. By adsorption measurements it was also possible to demonstrate that there was a negligible non-specific binding interaction on the CNTs.

In summary, CNTs have shown a large usability as functionalized channels in FETs. Yet, the unavailability of techniques to scale up CNT−based devices still motivates the search for alternative FET geometries more compatible with bulk production.

7. Conducting polymers nanowires (CPNWs)

Conductive polymers are a class of polymers that, as the name suggests, can conduct electricity. There is a wide range of different conductive polymers in literature but the two major classes that had been used in the context of aptamer based FET are polypyrrole (PPy) and Poly(3,4-ethylenedioxythiophene) (PEDOT). The key feature in conductive polymers is that they have backbones that comprises of sp^2 carbon centers and this permits for the mobility of electrons. PPy can be obtained using oxidative polymerization of the monomer, typically with Iron (III) chloride (Henry et al.

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2001; Zhang et al. 2006). The polymerization process can also be guided into completion by additional monomers with different functionalities; for example, Pyrrole-3-carboxylic acid (P3CA) is used in conjunction to decorate the sidewalls with COOH moieties(De Giglio et al. 2004), (Shi et al. 2010). These enable for additional covalent coupling of aptamers or biomolecules along the sidewalls of the nanowires. PEDOT is an environmentally friendly polymer and is also widely used due to its optical transparency as well as its high electrical conductivity. It is often used in conjunction with poly(styrenesulfonate) (PSS) that improves its solubility and stability(Groenendaal et al. 2000; Kirchmeyer and Reuter 2005).

Figure 8. The assembly of PPy:P3CA nanowire with aptamers for the detection of thrombin. Note that the nanowires had also been covalently anchored on the surface. (right) SEM and graphical illustration of the system as well as the real time detection profile (right bottom)(Yoon et al. 2008)

The first report on using conductive polymers in aptamer-FET platforms made use of PPy to detect thrombin(Yoon et al. 2008). P3CA was incorporated into the PPy monomers to produce COOH moieties on the surface. As shown in figure 8, nanowires approximately 200-250 nm long were fabricated and chemically functionalized using silanes. The nanowires were then anchored between interdigitated gold source and drain electrodes spaced by 10 μm (figure 8). A reference electrode (Ag/AgCl 3m NaCl) and a Pt counter electrode were also provided for gate control. Amine-terminated aptamers were then introduced onto the surface of the PPy nanowires and coupled to the COOH to form stable amine linkage. The P3CA functionalized along the backbone of the polymer had a large dipole moment (2.06 D) and thrombin aptamer was negatively charged. Thus, the negative aptamer charge is screened when the aptamer-thrombin complex is formed. This reduces the hopping rate of charge carriers along the backbone of the polymer by increasing the Coulomb interaction between the positively charged polymer chains. The detection for the presence of thrombin in solution was achieved by monitoring the change in the source-drain current (I_{SD}). The sensitivity was

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found to increase with the density of COOH groups. This result is significant towards understanding effects of surface coverage of receptors. A detection limit of thrombin at approximately 50 nM could be achieved. Control tests with BSA protein showed no detectable change in conductance. Results were compatible to those from CNTs published by Lee et al. in 2005 (detection limit at 10 nM) and this was also due in part to the deployed array system deployed which amplified the signals obtained.

Use of PEDOT was also reported for the detection of VEGF(Xie et al. 2009). Nanowires were electrochemically grown between the electrodes rather than being deposited directly onto the surface. This significantly reduced the manufacturing complexity (figure 9, inset). Detection of thrombin was performed at pH 5 (below the isoelectric point of thrombin (7.05)), resulting in a positively charged thrombin. After binding of thrombin to the aptamer-tagged PEDOT, a decrease of 50% in conductance was measured with a variation of <10% across the devices after 1 h of incubation. Furthermore, two random DNA strands (28 mer and 49 mer long) with no specificity were used as control. A significantly lower current change ($\Delta I/I_o$) on the surface (-0.07±0.02 and -0.25±0.04, respectively) was determined, compared to that observed with the thrombin aptamer (-0.68±0.11). The device was sensitive over a range of concentration from 1 nM to 1 μM, i.e. over the appropriate range of standard physiology.

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Figure 9. Self assembly of PEDOT nanowires using ac electric field to form across the source and drain electrode. (a-b, right) single wires across the space of the 2 electrodes. The nanowires were then tagged with aptamers for the detection of thrombin (a-b, right)(Xie et al. 2009)

The possibility of reusing biosensing device was exploited by Kwon et al. in 2010(Kwon et al. 2010), PPy-COOH nanowires were first anchored across source and drain electrodes patterned on glass surface that had originally been functionalized with amino terminated silanes. The anchorage reaction

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was allowed to proceed via a condensation mechanism mediated by 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (DMT-MM) to form stable carboxamide bond (figure 10). The same DMT-MM mediated condensation was also performed to attach an RNA based anti-VEGF aptamers on the nanowire. Reaction conditions were milder compared to carbodiimide coupling and the process could be carried out in a single step (figure 10, right). VEGF detection limit scaled with the reciprocal of the CNT diameter. A control without any aptamer attachment did not register any response towards the VEGF protein. It is also noteworthy that the system could be reused up to three times with excellent reproducibility.

Figure 10. PPy nanowires across the electrodes anchored via DMT-MM condensation chemistry (left). (a-b, right) The detection of VEGF at real time was as shown(Kwon et al. 2010).

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8. Silicon Nanowires

Compared to CNTs and conducting polymer nanowires, silicon nanowires (SiNW) FET had remained highly unexplored in literature. Unlike CNTs, the fabrication of SiNW is usually more technically demanding, and can be pursued either with a top-down or a bottom-up approach. In the bottom-up approach such as vapor-liquid-solid (VLS) method (Westwater et al. 1997; Wu and Yang 2001) using $SiCl_4$ and H_2 as nutrients. Au nanoclusters were utilised as catalysts while dibrorane or phosphine were used as dopant precursors in the silicon nanowire fabrication. In the top-down approach, photolithography produces a suitable pattern on the silicon surface that is then selectively etched away by reactive ions (Hsu et al. 2008; Zschech et al. 2007). Another top-down approach that had gained popularity in recent years is the metal assisted chemical etching method by which gold patterned on the surface act as cathode while the silicon at the interface act as the anode (Chartier et al. 2008; Huang et al. 2011; Huang et al. 2008). In the presence

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of HF and H_2O_2, silicon subsequently gets oxidised and dissolved into solution. This results in a fast etching at the patterned areas.

Functionalizing silicon chemistry has also been very well studied in the past and is much more simple compared to the CNTs modification. The underlying chemistry often utilizes the native oxide present on the surface. Silanisation is a widely preferred surface modification strategy by which organofunctional alkylsilane molecules react with surface hydroxyl group to form stable covalent Si-O-Si linkage (Fadeev and McCarthy 1999, 2000; Oner and McCarthy 2000). The advantage of this approach is that it is very fast and easy to perform under standard conditions while its slight drawback is that it is a rather time dependent process, and achieving complete monolayer surface coverage is not easy. Hydrosilylation is another method of surface chemical passivation where hydrogen-terminated silicon surfaces react towards unsaturated organic compounds (Buriak and Allen 1998; Corey and Braddock-Wilking 1999; Romano and Narducci 2007). The interfacing would subsequently form a stable Si-C bond with the organic compounds. There are many reports suggesting high surface coverage of the linkage that is resistant towards further oxidation on the surface. In both of the mentioned chemical functionalization, simple organic moieties act as spacers to which biomolecules and aptamers are chemically bonded, typically via conventional carbodiimide or isocyanate chemistry.

To the best of the authors' knowledge, there are only two notable research articles that focus on synergizing SiNW and aptamer to form FET biosensors by a group at Pohang University of Science and Technology in South Korea. In their first paper Kim et al. mounted an anti-thrombin aptamers on the surface of the SiNW (Kim et al. 2009). Nanowires were grown via the VLS method and the surface was functionalized with 3-aminopropyl diethoxysilane, that was then converted into a carboxylic acid. Anti-thrombin aptamers with an amine terminal group were then anchored tsurface the moiety. The surface was then developed into its final FET form (source-drain layout) via electron-beam lithography.

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Figure 11. Silicon nanowire with anti-thrombin aptamer functionalized via conventional carbodiimide chemistry. (Right) detection of the thrombin and subsequently in blood serum at real-time(Kim et al. 2009).

Real time detection was performed with the addition of thrombin solutions at a concentration of 330 pM. The pH of the solution was fixed at 5.4 and this resulted in a positively charge thrombin molecule that could effectively screen the negative charge of the DNA aptamer. Thus, the SiNW charge depletion resulted in a decrease of the conductance (figure 11, right). Blood was also tested. Since thrombin exists in high concentration in blood serum, a massive drop in conductance was observed as a result of the system saturation. The inset graph in figure 11 also illustrates the SiNW FET system without any aptamers as the control. No notable change in the conductance was observed, confirming the high specificity of the aptamer.

In a second paper Lee et al. reported about VEGF detection (Lee et al. 2009). The SiNW was produced in a similar fashion but different doping types were used so as to correlate the FET response to the type of majority carriers. In p-type silicon, the presence of the aptamers and the protein (negatively charged) can actually deplete the charge carriers and thus decrease the current. In the n-type silicon, the reverse occurs, the charge carrier density increasing due to the electron enhancement. The current is therefore also expected to increase. As shown in Figure 12, the trends for the different silicon dopants were as expected for (A) n-type and (B) p-type. The reported detection limit were 1.04 nM and 104 pM for the n-type and the p-type SiNW, respectively. The detection limit for thrombin was excellent compared to other existing device at the point of publication (2009).

Figure 12. Schematic of SiNW tagged with anti-VEGF aptamers and organized in an array on silicon surface. The profile of n-type and p-type SiNW gate voltage before surface functionalization was also examined (D-E, right) (A-B, right) Detection of VEGF with (A, right) n-type and (B, right) p-type silicon. The inset graph for (A, right) represents the detection without aptamers functionalized while the instet graph for (B,

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right) represents the sensitivity of the p-type silicon(Lee et al. 2009).

9. Conclusions

This review had discussed many aspects of the fabrication of nanowire and aptamer-based FET biosensors since their introduction in 2005. The basic layout of the FET (source, drain and gate electrodes) remained the same but there have been several enhancements with regards to its implementation (e.g. aptamers bridging electrodes or sandwich devices). So far, CNTs systems are the mainstay for interfacing aptamers and nanowires FET but there is also much promise offered by both conductive polymers and SiNW systems. The sensitivity offered by these hybrid systems as reported in literature had been excellent and improving over the years. Furthermore, there is a lot of potential in using them for biological screening considering the low biofouling level reported so far. Another interesting feature is the possibility of reusing such platforms, a factor that might represent a major cost-saving advantage as compared to other commercially available biosensors. Despite the fact that only a few biological species had been examined using these synergized systems, it can be safely anticipated that there will be a steady increase in biosensor types considering the ever-increasing demands for label-free biosensors.

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Table 1. A list of notable nanowire FET devices with aptamers as receptors

Title of publication	Year	Type	Detection target	Aptamer type	Sequence	Lowest detection limit
Single-Walled Carbon Nanotube Biosensors Using Aptamers as Molecular Recognition Elements(So, H. M., Won, Kim, Kim, Ryu, Na, Kim and Lee 2005)	2005	Carbon	Thrombin	DNA	5'-GGTTGGTGTGGTTGG-3'	~10 nM
Label-Free Protein Biosensor Based on Aptamer-Modified Carbon Nanotube Field-Effect Transistors(Maehashi, et al. 2007)	2007	Carbon	Immunoglobulin E	DNA	5'-GCGCGGGGCACGTTTATCCGTCCCTCCTAGTGGCGTGCCCCGCGC-3'	250 pM
Detection and Titer Estimation of Escherichia coli Using Aptamer-Functionalized Single-Walled Carbon-Nanotube Field-Effect Transistors(So, Hye-Mi, Park, Jeon, Kim, Kim, Lee, Choi, Kim, Chang and Lee 2008)	2008	Carbon	Escherichia coli (whole cell)	RNA	5'-GGGAGAGCGGAAGCGUGCUGGGGUCGCAGUUUGCGCGCUUCCCUUCUCUCAUCACCGAAACAUAACCCAGAGGUCGAU-3'	3.1 x 10^3 CFU/ml
A Novel Sensor Platform Based on Aptamer-Conjugated Polypyrrole Nanotubes for Label-Free Electrochemical Protein Detection(Yoon, et al. 2008)	2008	polypyrrole	Thrombin	DNA	5'-GGTTGGTGTGGTTGG-3'	50 nM
Electric-Field-Assisted Growth of Functionalized Poly(3,4-ethylenedioxythiophene) Nanowires for Label-Free Protein Detection(Xie, Luo and Yu 2009)	2009	poly(3,4-ethylenedioxythiophene)	Thrombin	DNA	5'-T6GGT TGG TGT GGT TGG-3'	1 nM
Aptamer-Based Label-Free Immunosensors Using Carbon Nanotube Field-Effect Transistors(Maehashi, Matsumoto, Takamura and Tamiya 2009)	2009	Carbon	Immunoglobulin E	DNA	5'-GCG CGG GGC ACG TTT ATC CGT CCC TCC TAG TGG CGT GCC CCG CGC-3'	250 pM – 160 nM
The fabrication, characterization and application of aptamer-functionalized Si-nanowire FET biosensors(Kim, Lee, Yang, Jo and Hahn 2009)	2009	Silicon	Thrombin	DNA	5' -GGTTGGTGTGGTTGG-3'	~330 pM
Electrical detection of VEGFs for cancer diagnoses using anti-vascular endotherial growth factor aptamer-modified Si nanowire FETs(Lee, Hyun-Seung, Kim, Kim, Hahn and Jo 2009)	2009	Silicon	VEGF	RNA	5'-AUGCAGUUUGAGAAGUCGCGCAU-3'	1.04nM for N-type SiNW-FETs 104 pM for p-type SiNW-FETs
A high-performance VEGF aptamer functionalized polypyrrole nanotube biosensor(Kwon, Park and Jang 2010)	2010	polypyrrole	Vascular endotherial growth factor	RNA	5'- AUGCAGUUUGAGAAGUCGCGCAU-30	400 fM
Real-time, step-wise, electrical detection of protein molecules using	2010	Carbon	Thrombin	DNA	5' -GGTTGGTGTGGTTGG-3'	70 pM

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dielectrophoretically aligned SWNT-film FET aptasensors(An, et al. 2010)						
Aptamer sandwich-based carbon nanotube sensors for single carbon-atomic-resolution detection of non-polar small molecular species(Lee, Joohyung, Jo, Kim, Ahn, Lee, Kim and Hong 2011)	2011	Carbon	Bisphenol A	DNA	5'- GGGCCGTTCGAA CACGAGCATG-N60-GGACAGTACTCAG GTCATCCTAGG-3'	~ 10 fM of BPA
Single-Molecule Detection of Proteins Using Aptamer-Functionalized Molecular Electronic Devices(Liu, Song, Zhang, Luo, Wang, Guo, Steigerwald and Fang 2011)	2011	Carbon	Thrombin	DNA	5'-TTT TTT TGG TTG GTG TGG TTG GTT TTT TT-3'	2.6 fM
Real time protein recognition in a liquid-gated carbon nanotube field-effect transistor modified with aptamers(Pacios, Martin-Fernandez, Borrise, del Valle, Bartroli, Lora-Tamayo, Godignon, Perez-Murano and Jose Esplandiu 2012)	2012	Carbon	Thrombin	DNA	5'-TTTGGTTGGTGTG GTTGG-3'	20 pM

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Highlights

- We described all the developments on aptamer based field effect transistors from nanowire devices since its introduction in 2005
- Three materials of interest, namely silicon, carbon nanotubes and conductive polymers were investigated.
- The detection limit and sensitivity of each of the device were reported for the similar detection target over the years
- We had also highlighted upon the unique design of each of the device as well as the reusability of the device.

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Figures for the review

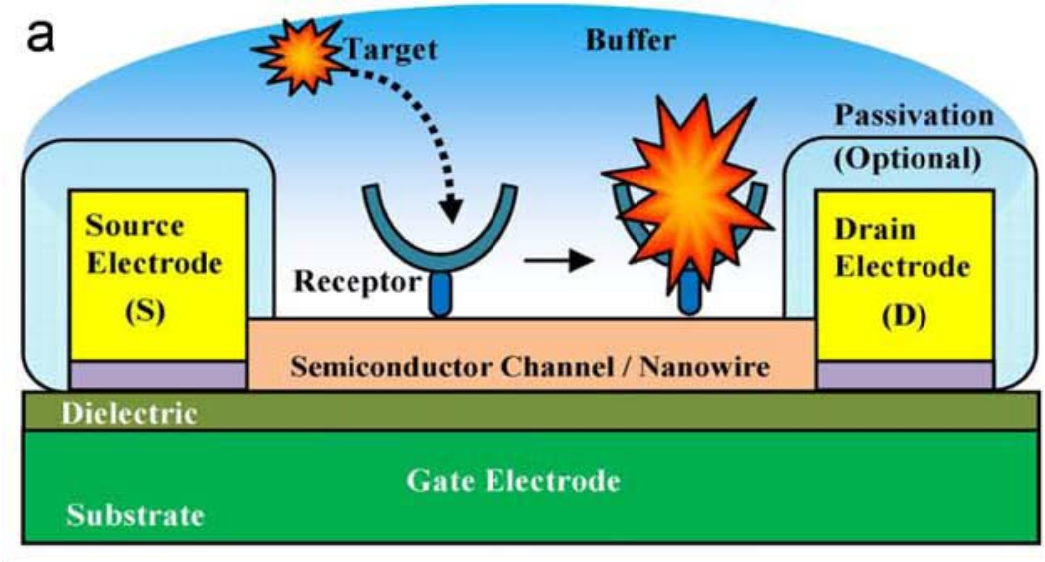

Figure 1. A schematic example of a nanowire FET biosensor device with the source, drain and gate electrode(Chen, Kuan- I., et al. 2011)

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Scheme 1. Binding of Thrombin on a SWNT-FET-Based Aptamer Sensor

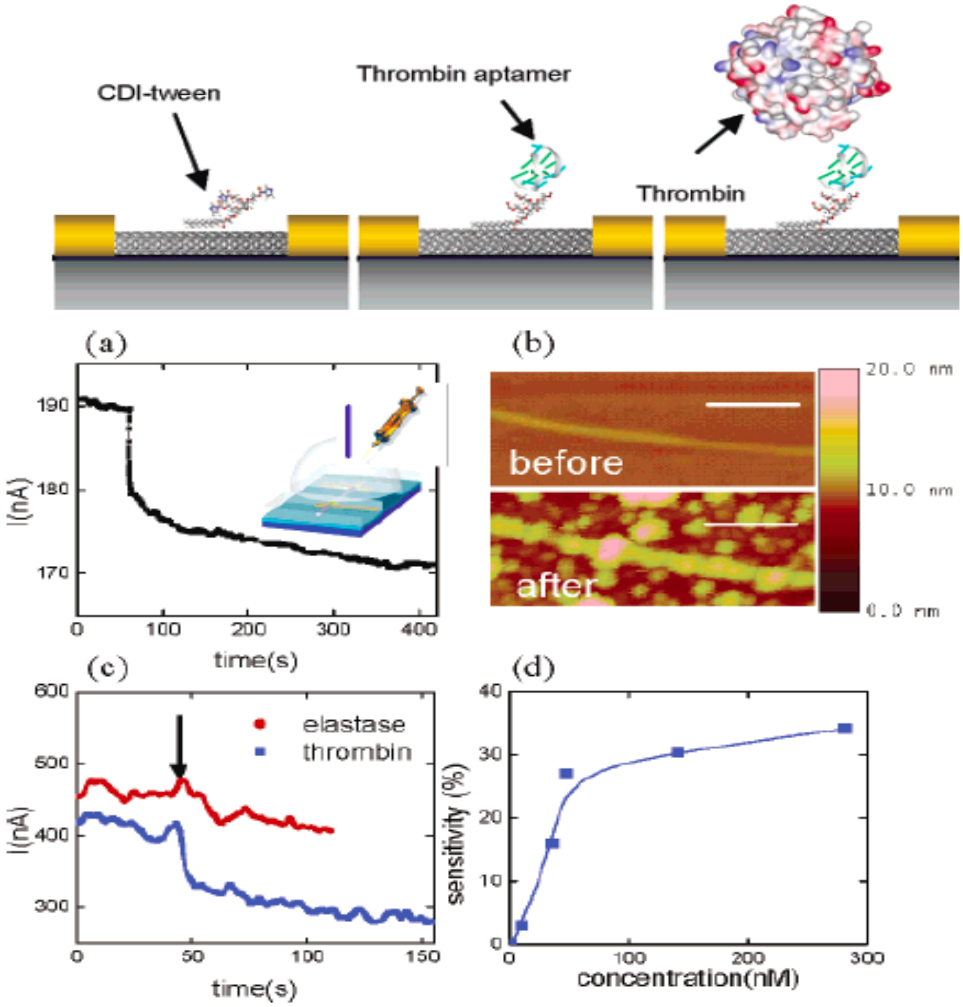

Figure 2. Binding of thrombin on the surface of CNTs via pyrene π- π transition stacking on surface (top) and the real-time detection profile of 1.5 μM (c). (d) shows the lowest detection limit of approximately 10 nM(So, H. M., Won, Kim, Kim, Ryu, Na, Kim and Lee 2005).

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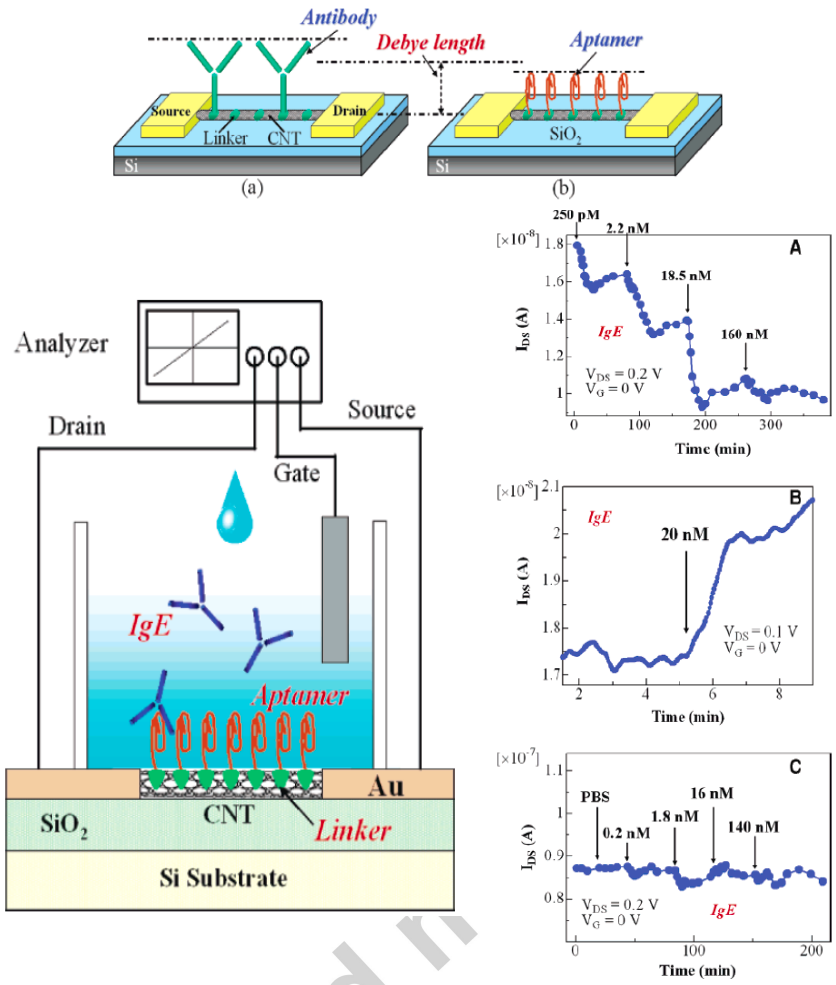

Figure 3. Label-free detection of IgE with aptamer based CNTs FET device. The discussion of debye layer was presented (top) as shown on the virtues of using aptamers instead of antibody. Lowest detection limit was found to be at 250 pM (right)(Maehashi, Katsura, Kerman, Takamura, Matsumoto and Tamiya 2007).

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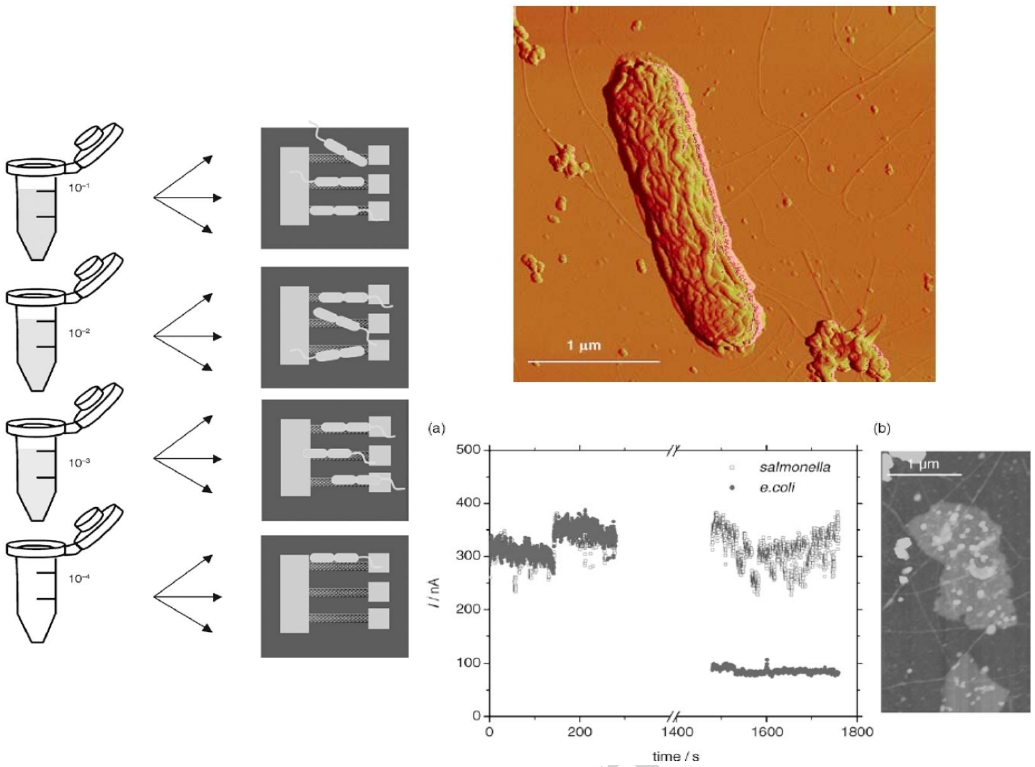

Figure 4. Binding and sensing of entire *e.coli* bacterium on CNTs functionalized with aptamer. (Left) Dilution factors accounting for the number bacterium binded on the surface. (right top) light microscopy image of *e.coli* bacterium interfacing with CNTs. (right bottom) the electrical measurement of the detection in the presence of a control (*salmonella*)(So, Hye-Mi, Park, Jeon, Kim, Kim, Lee, Choi, Kim, Chang and Lee 2008)

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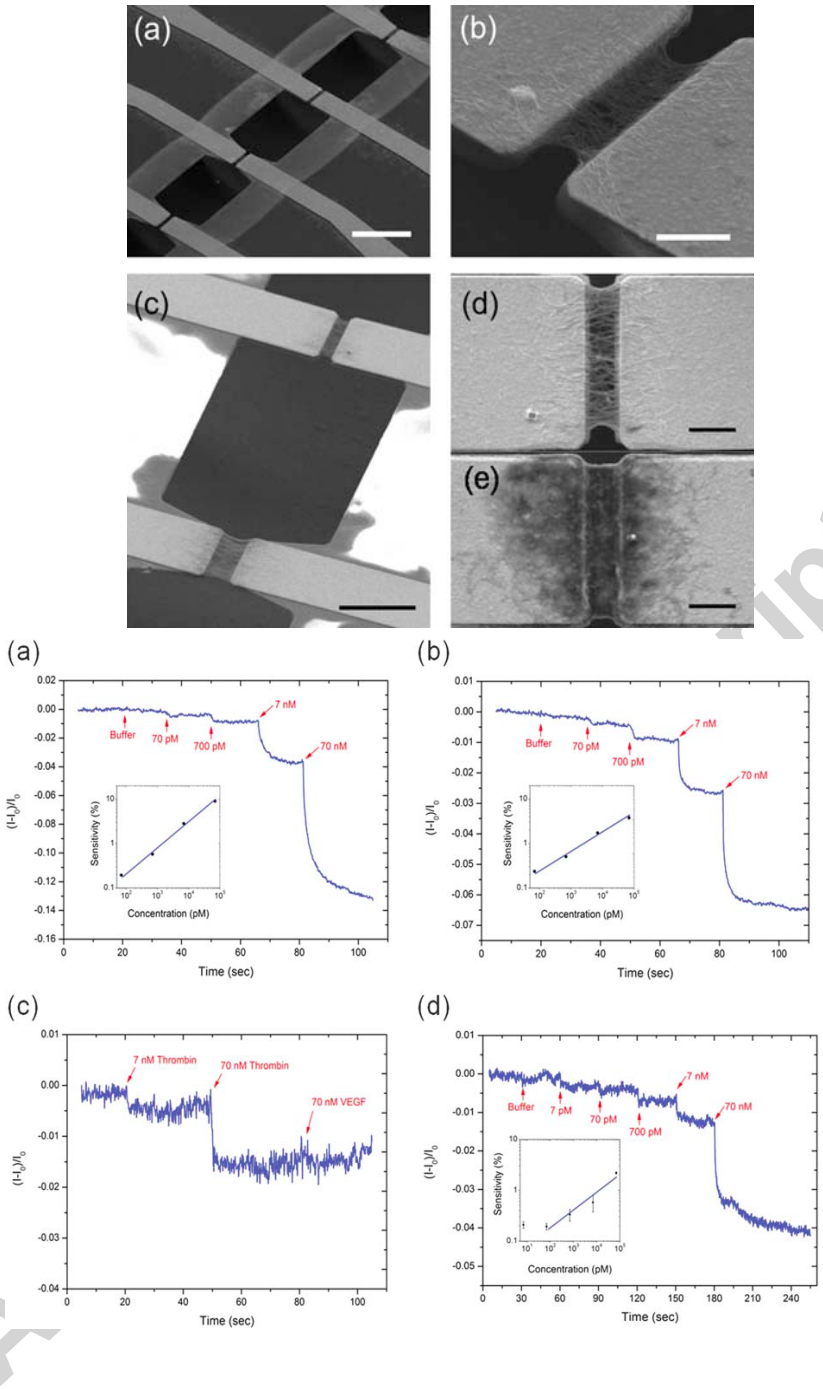

Figure 5. Detection of thrombin with suspending CNTs films bundles functionalized with aptamers. (a-d, top) SEM images of the supended film bundles. (a-d, bottom) Real time detection of thrombin as well as a control protein, VEGF(An, Kim, Hahn and Lim 2010)

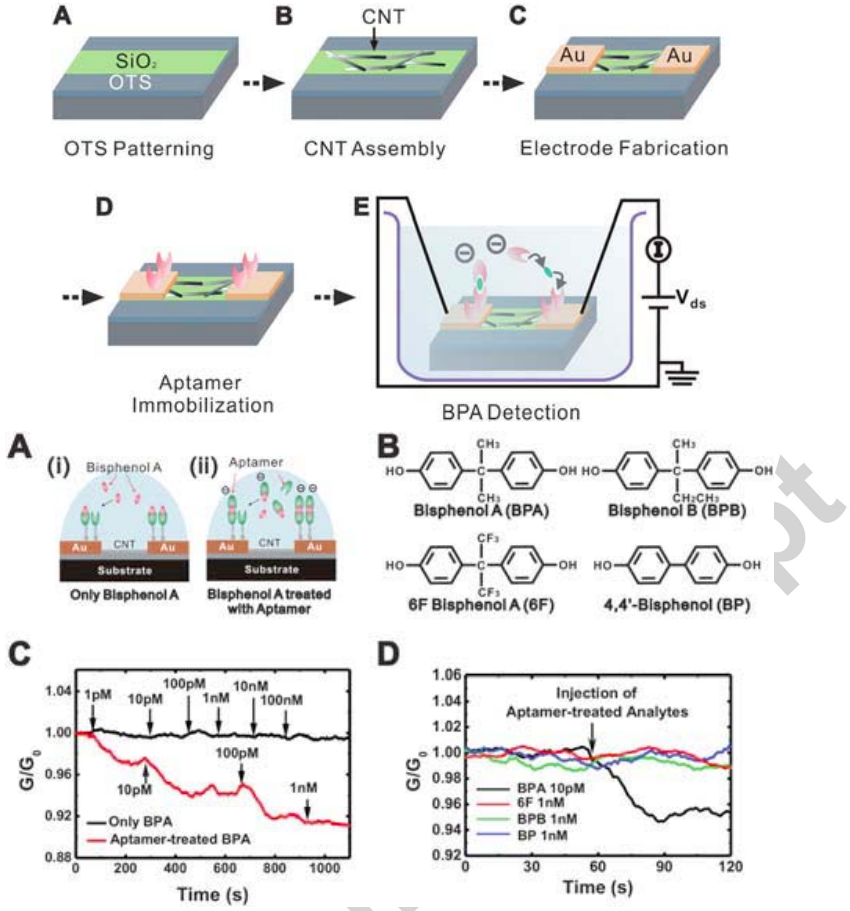

Figure 6. Using a dual aptamer sandwich CNTs FET system to detection for non polar molecule. (A-E top) graphic schematic of the sandwich system. (Bottom A and B) The mechanism of the bisphenol detection as well as the different analogues for the same molecule. (Bottom C and D) Real time detection of the Bisphenol A(Lee, Joohyung, Jo, Kim, Ahn, Lee, Kim and Hong 2011).

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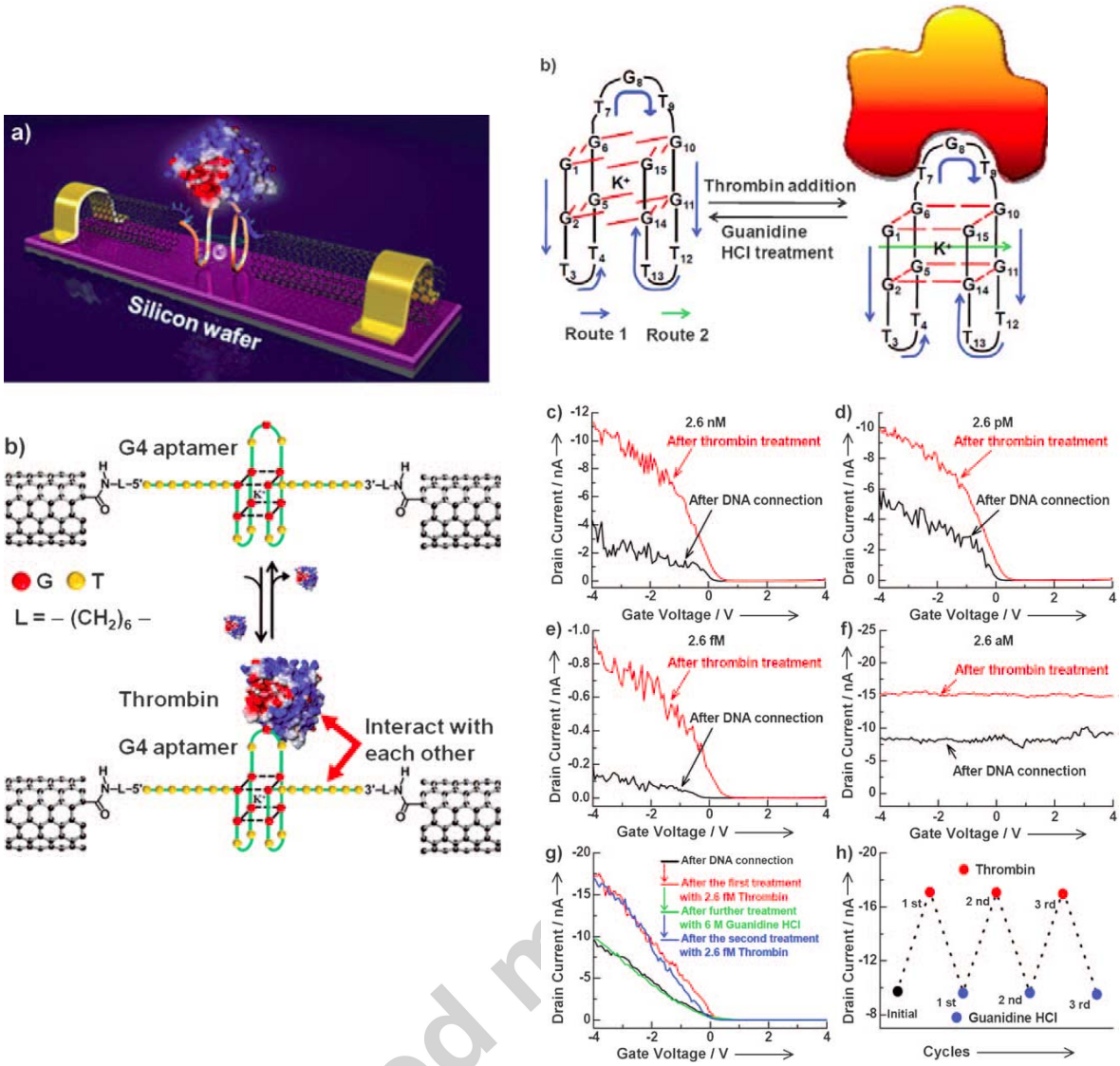

Figure 7. A unusual CNTs FET system that uses the aptamers to bridge between the CNTs for the detection of thrombin (a-b, left). (b, right top) illustrates the mechanism by which the aptamers 4-guanosine π- π transition stacking can help to improve electrical conductivity and (c-h, right) are the detection profile of thrombin(Liu, Song, Zhang, Luo, Wang, Guo, Steigerwald and Fang 2011).

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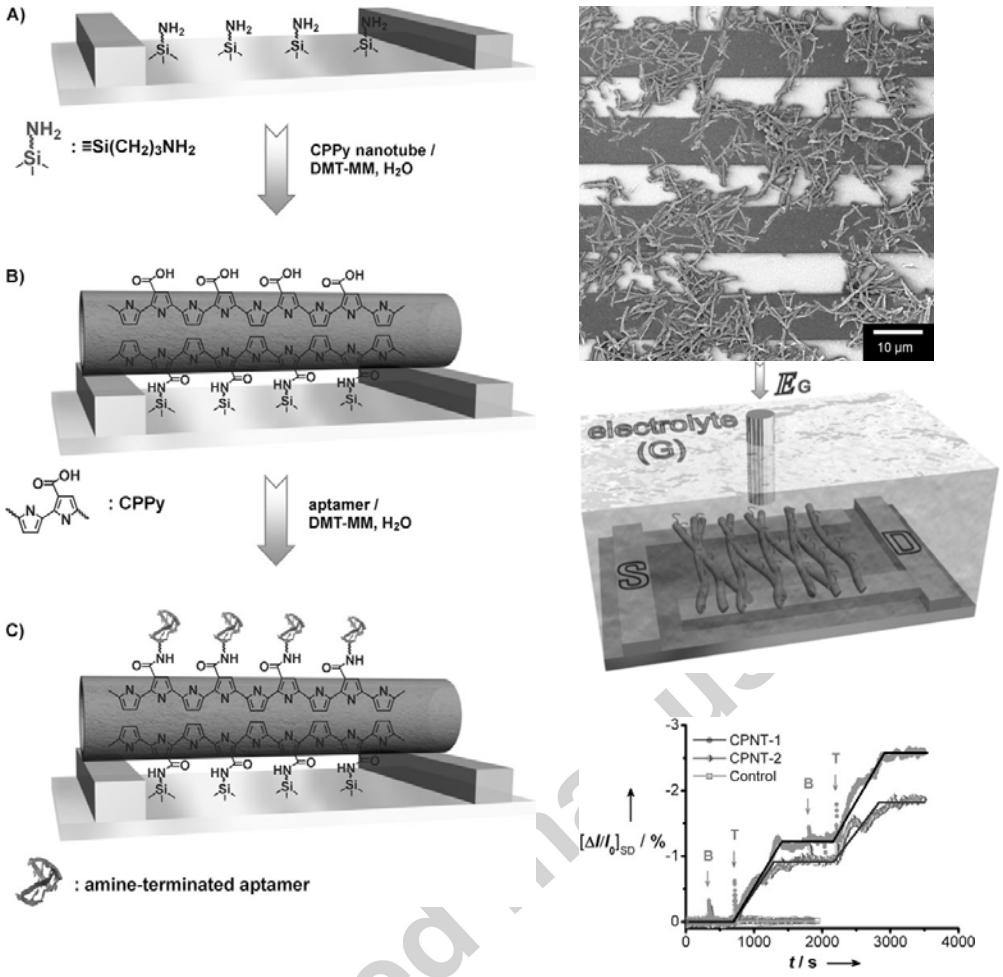

Figure 8. The assembly of PPy:P3CA nanowire with aptamers for the detection of thrombin. Note that the nanowires had also been covalently anchored on the surface. (right) SEM and graphical illustration of the system as well as the real time detection profile (right bottom)(Yoon, Kim, Lee, Kim and Jang 2008)

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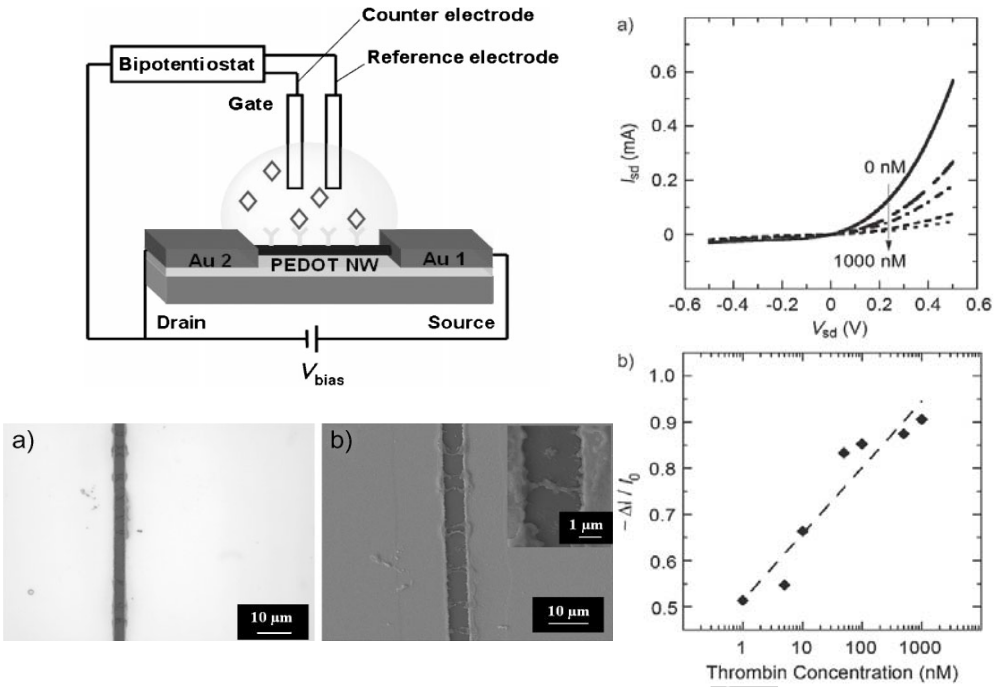

Figure 9. Self assembly of PEDOW nanowires using ac electric field to form across the source and drain electrode. (a-b, right) single wires across the space of the 2 electrodes. The nanowires were then tagged with aptamers for the detection of thrombin (a-b, right)(Xie, Luo and Yu 2009)

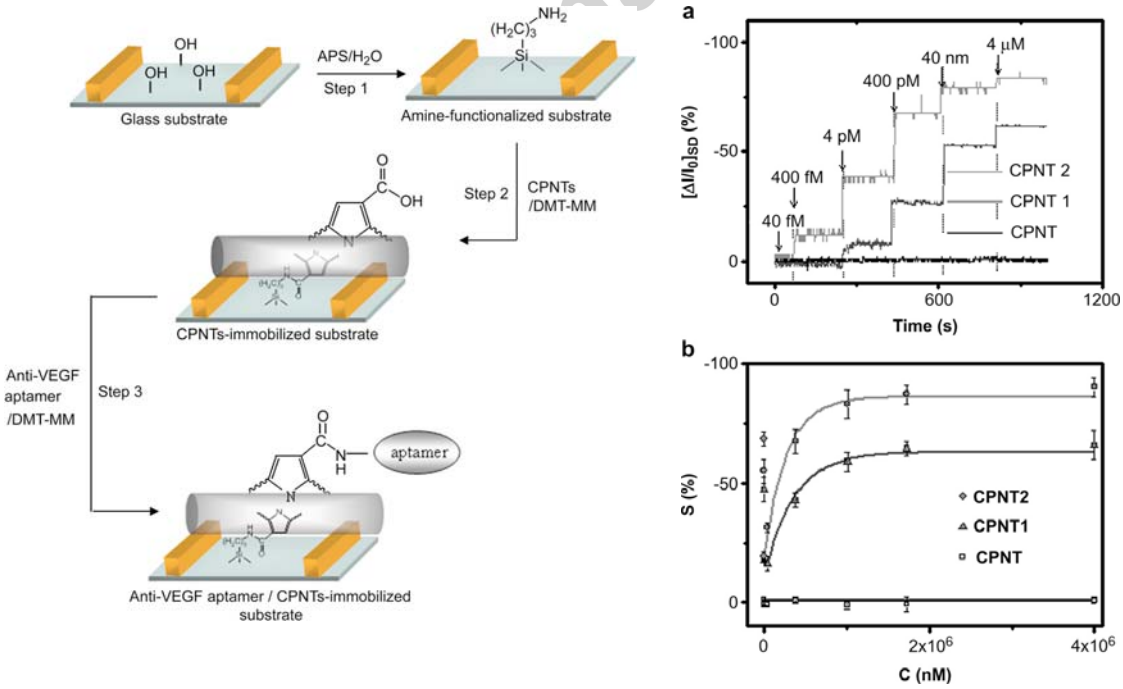

Figure 10. PPy nanowires across the electrodes anchored via DMT-MM condensation chemistry (left). (a-b, right) The detection of VEGF at real time was as shown(Kwon, Park and Jang 2010).

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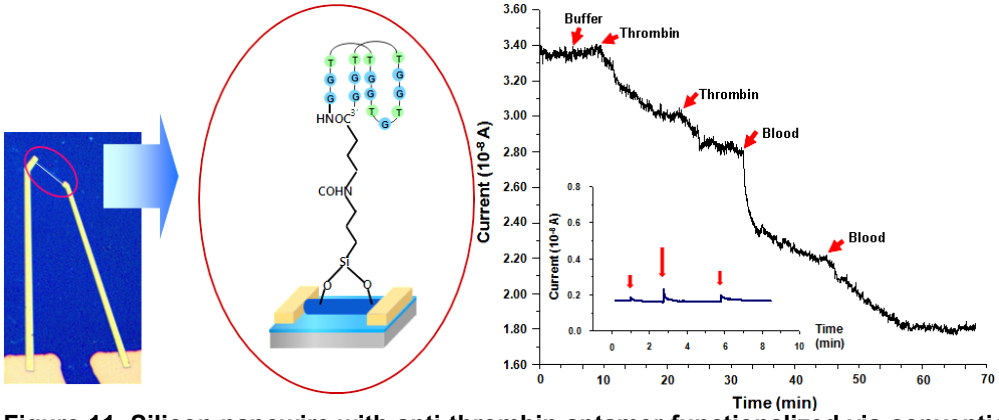

Figure 11. Silicon nanowire with anti-thrombin aptamer functionalized via conventional carbodiimide chemistry. (Right) detection of the thrombin and subsequently in blood serum at real-time(Kim, Lee, Yang, Jo and Hahn 2009).

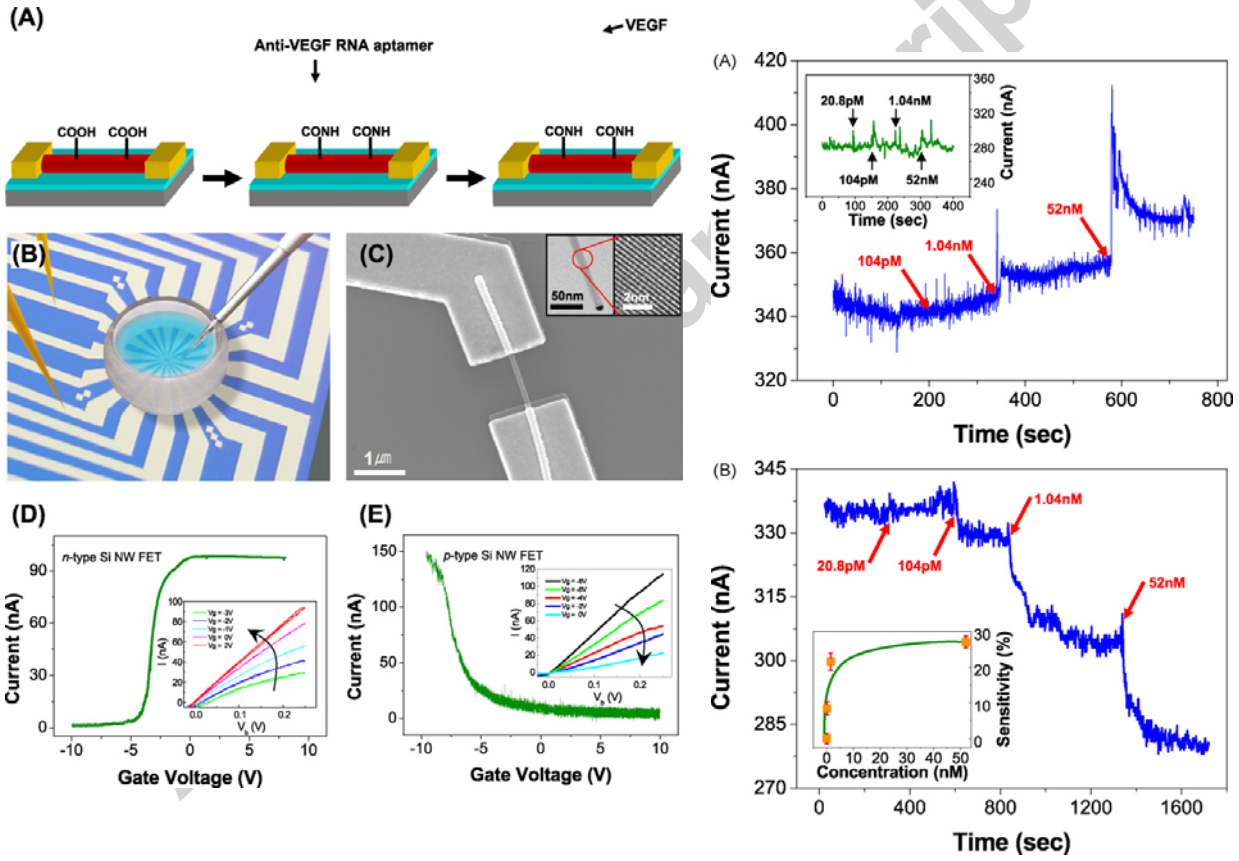

Figure 12. Schematic of SiNW tagged with anti-VEGF aptamers and organized in an array on silicon surface. The profile of n-type and p-type SiNW gate voltage before surface functionalization was also examined (D-E, right) (A-B, right) Detection of VEGF with (A, right) n-type and (B, right) p-type silicon. The inset graph for (A, right) represents the detection without aptamers functionalized while the instet graph for (B, right) represents the sensitivity of the p-type silicon(Lee, Hyun-Seung, Kim, Kim, Hahn and Jo 2009).