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Ultrasensitive in Situ Label-Free DNA Detection Using a GaN Nanowire-Based Extended-Gate Field-Effect-Transistor Sensor

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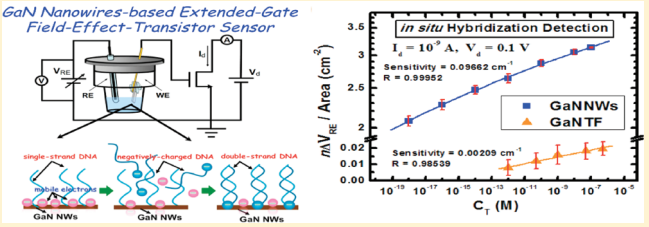
ABSTRACT: In this study, we have successfully demonstrated that a GaN nanowire (GaNNW) based extended-gate field-effect-transistor (EGFET) biosensor is capable of specific DNA sequence identification under label-free in situ conditions. Our approach shows excellent integration of the wide bandgap semiconducting nature of GaN, surface-sensitivity of the NW-structure, and high transducing performance of the EGFET-design. The simple sensor-architecture, by direct assembly of as-synthesized GaNNWs with a commercial FET device, can achieve an ultrahigh detection limit below attomolar level concentrations: about 3 orders of magnitude higher in resolution than that of other FET-based DNA-sensors. Comparative in situ studies on mismatches ("hotspot" mutations related to human p53 tumor-suppressor gene) and complementary targets reveal excellent selectivity and specificity of the sensor, even in the presence of noncomplementary DNA strands, suggesting the potential pragmatic application in complex clinical samples. In comparison with GaN thin film, NW-based EGFET exhibits excellent performance with about 2 orders higher sensitivity, over a wide detection range, 10^{-19}−10^{-6} M, reaching about a 6-orders lower detection limit. Investigations illustrate the unique and distinguished feature of nanomaterials. Detailed studies indicate a positive effect of energy band alignment at the biomaterials−semiconductor hybrid interface influencing the effective capacitance and carrier-mobility of the system.



Nanowires (NWs), having diameters comparable to the size of biological relevant molecules to be sensed, are one of the most discussed nanostructures for biosensing device applications.[1−3] On one hand their high surface-to-volume ratio offers the opportunity for efficient biobinding and high sensitivity in detecting biomolecules, on the other hand their structural advantage leads to the realization of nanoscale device fabrication.[1−5] The nanowire-based field-effect-transistor (NW-FET) is one of the most promising platforms for label-free sensing[6−8] because of its potential advantages in terms of miniaturization of the sensor-device, standardization of process/fabrication (including the synthesis of NWs), and excellent sensitivity for detection of charged biomolecules such as DNA. Without the requirement of expensive instruments and reagents, minute alteration in potential at the gate-surface due to charged biomolecules can be converted into detectable electric/voltage signals. Extended-gate FET (EGFET) is a further modification of the conventional FET-structure, where the sensing-part of the gate is extended from the FET-device to the detection-environment, providing a series of additional advantages such as the flexibility in gate-shape, separation of FET-device from the chemical or biological environment, and hence insensitivity of FET-characteristics to the ambient environment, ease in packaging, and passivation of sensing-surface (extended-gate).

GaN nanowires (GaNNWs), inheriting excellent optoelectronic properties from its wide direct bandgap semiconducting nature, along with the nanostructure-specific surface-dominated identities with direct transport path, exhibit significant advances in device applications.[9−11] Additionally, the inherent chemical robustness, nontoxicity, and biocompatibility of GaN have opened up the possibility for applications in biotechnology;[12−17] however, most of the reports on bioapplications are pertaining to the thin film configuration. Importance of the surface-dependent nature of GaNNWs is evident from our recent studies,[10,11,18] which unveil the strong surface-induced spatial-separation of charge-carriers between the core and surface of the nanowire. Such spatial-separation of carriers could readily be influenced by the ambient environment and hence alter the electronic behavior of NWs. Our very recent studies have demonstrated successful utilizations of GaN, in nanowire form, providing surface-enhanced binding sites and enhanced charge transfer, as a transducer in highly sensitive label-free DNA-sensing, using cyclic voltammetry, electrochemical impedance spectroscopy (EIS), and photoluminescence techniques.[4,5] Interestingly, the DNA-immobilized GaNNWs are found to possess remarkably distinct Faradaic characteristics compared to the unmodified NWs, exhibiting an evident DNA/GaNNWs hybrid interface, which play a crucial role in charge transfer phenomena.

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Table 1. Sequences of Oligonucleotides DNA Used in This Experiment

	sequences of DNA oligonucleotides
probe (ssDNA)	5′-HS-$(CH_2)_6$-ATGGGCCTCCGGTTC-3′
wild type (WT)	5′-GAACCGGAGGCCCAT-3′
Arg249Ser	5′ -GAACCGGAGTCCCAT-3′
Arg248Gln	5′ -GAACCAGAGGCCCAT-3′
negative control (NC)	5′ -CCCCCCCCCGGGGGGGGG-3′

In this study, by integration of the advantages of the GaN, NW-structure, and EGFET, an innovative and efficient DNA sensor (GaNNWs-EGFET) has been achieved. Despite that most of the NW-based studies have focused on single-NW-based devices, the critical processes for the integration of individual NWs into thin-film-based sensor-chips are the limiting factors for pragmatic application or large scale manufacturers. While a bundle of as-synthesized NWs could be utilized, without requiring any manipulation, in order to achieve a more realistic, user-friendly, and efficient platform[10] for sensor[4,5]or photodetector[11] applications. Moreover, here, our approach has simplified the sensor-architecture, as described below, by integrating the as-synthesized GaNNWs on Si substrates with a commercial FET device with a metal wire. We report the ease-in-fabrication and advantages of GaNNWs as EGFET electrodes for the human p53 tumor-suppressor gene sensing via label-free real time measurement. A comparison with its thin film (GaNTF) configuration has also been discussed in this study.

EXPERIMENTAL SECTION

Chemicals and Reagents. The following chemicals and reagents were used in the experiments: saline sodium citrate buffer 20× (SSC), sulfuric acid (98%), nitric acid (63%), methanol, and (3-mercaptopropyl) trimethoxysilane (MPTS) from Sigma-Aldrich, Inc.; Cleland's REDUCTACRYL Reagent from Merck, Inc. (DE); duplex buffer (30 mM Hepes + 100 mM potassium acetate) from Integrated DNA Technologies, Inc. All of the reagent solutions were made with deionized water (resistivity ≈ 16.8 MΩ cm^{-1}) from Millipore, Inc.

Human p53 Tumor-Suppressor Gene Sequence and Mutant Genes. Probe oligonucleotide (ssDNA) sequence is adopted from the human p53 gene, along with its fully complementary (wild type, WT) target. For the selectivity detection, two single base pair mutated sequences, Arg248Gln and Arg249Ser, which are important "hotspot" residues observed in lung and liver cancers, respectively, along with a fully noncomplementary sequence (NC) have been employed as targets. All sequences (Table 1) were purchased from Integrated DNA Technologies, Inc.

Structure of EGFET Sensor. An extended-gate FET sensor with a GaNNWs or GaN thin film (GaNTF) electrode consists of two parts: the GaN electrode, where DNA probes are immobilized, and the FET structure, which transduces the hybridization events on the GaN electrode into electrical signals. The GaNNWs (25−100 nm) were grown on a silicon substrate coated with Au catalyst, using Ga as the source material and NH_3 (10 sccm) as the reactant gas, in a tubular furnace (substrate temperature 900 °C) by the air pressure chemical vapor deposition technique. GaNTF was purchased from Epitech Technology Corp. (Taiwan). The extended gate was fabricated by connecting the GaN sample, fixed by a metal holder, to the gate of a commercial n-MOSFET (metal-oxide-semiconductor field-effect-transistor, CD4007, Taiwan) via a metal wire (Figure 1).

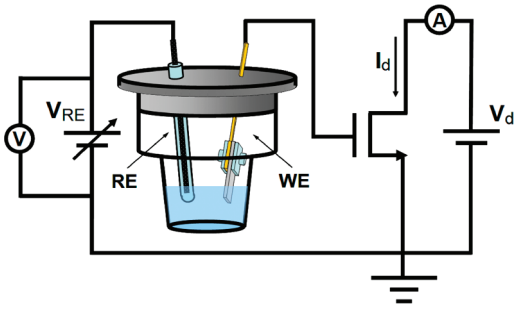

Figure 1. Solution-based *in situ* DNA-sensing setup based on EGFET design, using GaNNWs (or GaNTF) as an extended-gate (working electrode, WE). The bias, V_{RE}, reference electrode voltage, is applied to the sensor through the reference electrode (RE), Ag/AgCl (Sat. KCl). V_d, drain voltage; I_d, drain current. Here G, D, and S stand for gate, drain, and source components of the FET-structure, respectively.

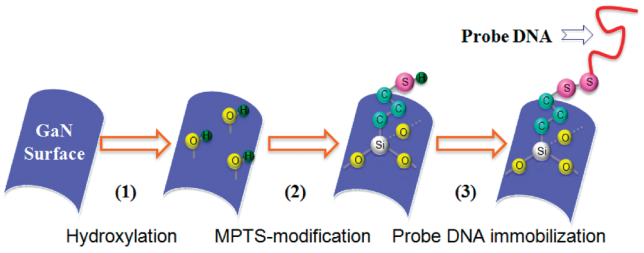

Figure 2. Steps in probe DNA immobilization and corresponding surface-modifications of GaNNWs (or GaNTFs): (1) hydroxylation, (2) MPTS-modification, and (3) probe DNA immobilization.

Immobilization of DNA Probes. Prior to the immobilization of probe DNA strands on the GaN surface (Figure 2), the pristine GaN was hydroxylated in acidic solution (0.12 M H_2SO_4 + 0.52 M HNO_3) at room temperature (RT) for 1 h. Then hydroxylated GaN were treated with MPTS in methanol solution (volume ratio 1:10), at room temperature (RT) for 1 h. Probe DNA strands were first reacted for 30 min with Cleland's REDUCTACRYL Reagent, which helped to break the disulfide bond between thiol-modified DNA strands. Then the probe DNA strands were collected from the microspin column via centrifugation. Immediately following, the MPTS-modified GaN were incubated in probe DNA solution at 4 °C for 24 h to immobilize the DNA probes on the GaN surface.

***In Situ* Detection of DNA-Hybridization.** The probe (ssDNA) immobilized GaN sample (working electrode, WE), as an extended-gate of the EGFET device, was subjected to the fully complementary WT targets in duplex buffer for *in situ* DNA-hybridization sensing. By application of a bias to the sensor through the reference electrode (RE), Ag/AgCl (Sat. KCl), the drain current (I_d) vs reference electrode bias voltage (V_{RE}) characteristics have been monitored at different concentrations of target-DNA by increasing the DNA-concentration at a time interval of 30 min. The volume of DNA (in buffer solution) added every time was maintained at 50 μL. All sensing measurements were performed under the drain voltage, V_d = 0.1 V, maintaining the "linear (ohmic) region" of I_d-V_d characteristics of FET. Keithley 4200-SCS was employed for FET-operation.

In Situ Selectivity Detection. Probe DNA-immobilized GaNNWs were subjected to various target DNA sequences in

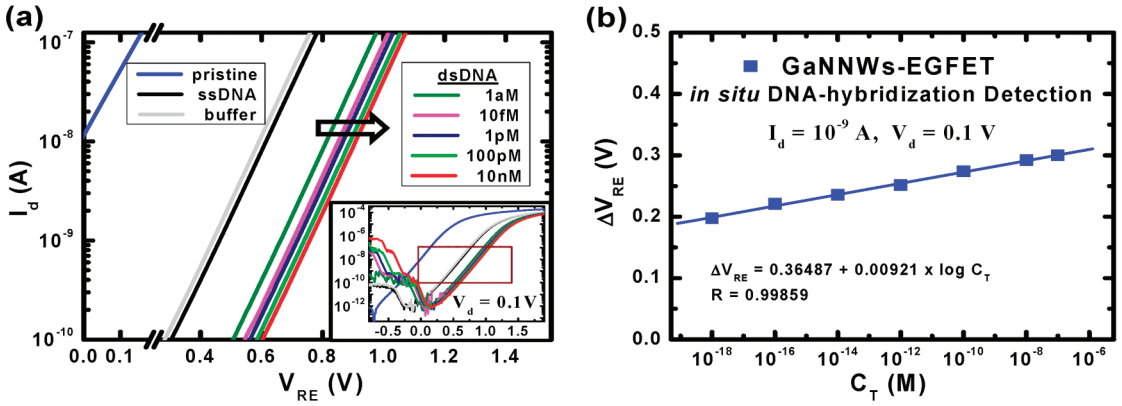

Figure 3. *In situ* DNA-hybridization sensing: (a) I_d-V_{RE} characteristics of GaNNWs-EGFET on the selected V_{RE}-span, as indicated by a black box in the inset. The arrow indicates the increase in the target DNA concentration (C_T). The inset shows the data for the whole range of V_{RE}. (b) Relationship between FET response (change in V_{RE}, ΔV_{RE}), and C_T: $\Delta V_{RE} = V_{RE}$(dsDNA) − V_{RE}(ssDNA). The line shown in the figure indicates the linear fitting.

the following order: negative control (noncomplementary, NC), single mismatches Arg248Gln and Arg249Ser, and fully complementary (WT) targets. The measurement procedure was the same as the *in situ* hybridization detection.

RESULTS AND DISCUSSION

Easy Assembly of GaN-Based EGFET. EGFET has been developed by modifying a conventional MOSFET employing GaNNWs or GaNTF as an extended gate. In traditional FET, the sensing material (e.g., GaNNWs) is directly synthesized on the "gate" of the FET device, which generally leads to complicacy in the fabrication process, device-design, and maintenance. Especially, the synthesis of GaN requires very high temperature treatment, which can have antagonistic effects on the FET-device structure and its inherent characteristics. Additionally, during the "in situ" operation in solution, the device needs to be well designed to be insulated (other than the sensing part) from the solution-medium (sensing environment) in order to avoid the solution-influence. As per our EGFET design (Figure 1), it can be easily assembled with a commercial FET device, bread-board, and GaN sample, where only the GaN sample is immersed in the solution, and it can be easily assembled by a simple metal wire with the FET device. Hence, the FET device is completely isolated from the sensing environment, contributing to low cost and ease in design and maintenance, as well as user-friendly real-time in situ sensing operation.

***In Situ* DNA Hybridization Sensing of GaNNWs-EGFET.** Prior to the DNA hybridization detection, GaNNWs (and GaNTF) were subjected to the specific surface-modification and the subsequent immobilization of probe DNA strands (ssDNA), as shown in Figure 2 and described in the Experimental Section. The performance of GaNNWs-EGFET for *in situ* detection of DNA hybridization is demonstrated in Figure 3. The typical I_d-V_{RE} characteristics of n-MOSFET (Figure 3a) exhibit a continuous shift of I_d-V_{RE} curve toward the positive V_{RE}-direction due to the ssDNA-immobilization and subsequent increase in target DNA concentration. Such positive shifts in the gate voltage, generally, indicate the development of negative charges on the gate-surface caused by DNA hybridization.

In solution, under an electric field, the accumulation of mobile-cations on the GaN-surface, with RE at positive V_{RE}, would result in the generation of a depleted region (space-charge region) in n-MOSFET. With an increase in V_{RE} ($>V_{th}$, threshold voltage), an inversion layer is induced in the channel between the source and drain, adjacent to the gate-surface inside the n-MOSFET. The magnitude of I_d is determined by the effective electrical impedance of the surface inversion layer at a fixed V_d. The DNA molecule has negatively charged phosphate groups on the sugar chains (phosphate backbone) with one negative charge per base in an aqueous solution. Hence, as a consequence of the DNA-immobilization on the GaN-surface, the mobile-cations are partly neutralized/entrapped (by DNA molecules) before reaching the GaN-surface, which in turn decreases the cation-accumulation and hence the distribution of bias-voltage at the gate. Such a change of the charge-density on the GaN-surface results in an increase of impedance and hence a decrease in I_d, due to which a positive shift in the V_{th} is supposed to be observed with a subsequent shift of the I_d-V_{RE} curve toward the positive V_{RE}-direction. Further hybridization with target DNA (dsDNA formation) provides more negatively charged molecules on the GaN-surface and hence extends the shift to more positive V_{RE}: the effect is more visualized from the continuous shift of the I_d-V_{RE} curve, with the increase in target DNA concentration.

The effect of the DNA molecule has been confirmed by adding the blank (buffer) solution under controlled conditions. The ssDNA-modified GaNNWs-EGFET did not exhibit any considerable response. At most, with an increase in the volume of solution added, the I_d-V_{RE} curve shifted toward the negative V_{RE}-direction (as shown in Figure 3a), which is a quite obvious consequence due to the increase in mobile-cations with the electrolyte-volume. In addition, the surface-modification by MPTS, forming a self-assembled monolayer (SAM) on the GaN-surface, also exhibited the positive shift in the I_d-V_{RE} curve in the presence of negatively charged thiol groups (data not shown here): the phenomenon can also explain the anomalously large increase in V_{th} after ssDNA-immobilization, compared to the values derived from pristine GaNNWs-EGFET.

Feasibility of using V_{RE} as a parameter for DNA-sensing based on the GaNNWs-EGFET sensor is established as evident from Figure 3b that exhibits the change in V_{RE} (ΔV_{RE}), obtained at fixed I_d (10^{-9} A, the value in the "linear regime" of I_d-V_{RE} characteristics), as a function of target-DNA concentrations (C_T). ΔV_{RE} shows a linear correlation over a wide range of C_T (~12 orders). The lowest C_T detected by the GaNNWs-EGFET sensor is down below attomolar, which is of ~3 orders of magnitude higher in resolution compared to other FET-based DNA-sensors.[6,19−21]

Solution Debye Length Control. In order to achieve an optimal platform for label-free sensing using GaNNWs-EGFET, it is important to account the effect of the solution Debye length (λ_D), within which the number of net positive charges approaches the number of negative charges on the DNA-modified GaN-surface with distance, resulting in an exponential decay of the electrostatic potential arising from the GaN-surface. Beyond λ_D, DNA molecules are completely shielded by counterions in the electrolyte due to electrostatic interactions resulting in the net charge to be zero and hence cannot be detected.[8,22]

Since λ_D is determined by the ionic strength (or concentration) of the electrolyte (buffer) solution, it is possible to directly improve the magnitude of FET response (ΔV_{RE}) by decreasing the buffer concentration (n_i), i.e., increasing λ_D. Figure 4 demonstrates the FET response in different n_i under active measurement condition (I_d = 1 nA, V_d = 0.1 V), for a dsDNA-modified GaNNWs-EGFET (C_T = 1 nM). These data demonstrate the importance of maintaining a constant buffer concentration, at $n_i \sim 0.01\times$, at a constant pH, during all sensing measurements. A further decrease in n_i reveals a tendency of saturation in the ΔV_{RE} value, most probably due to the lowering of hybridization efficiency in low concentrated buffer solution.

***In situ* Detection of Single Base-Pair Mutation in the Human p53 Gene.** The ssDNA-immobilized GaNNWs-EGFET sensor is capable of distinguishing a single base-pair mutation, suggesting the excellent specificity of the sensor toward the fully complementary (WT) target only, exhibiting the positive value of ΔV_{RE}, even in presence of mutations (Arg248Gln and Arg249Ser) and noncomplementary (NC) strands. Figure 5a represents a typical FET response of the sensor for different target DNA sequences, suggesting its potential for pragmatic application with complex clinical samples.

In addition, the effect of detection time on the FET response (Figure 5b) reveals that for WT target, the response time was shorter than 30 min, while the other targets did not response even after 10 h (Figure 5b shows only 5 h range). Moreover, the positive ΔV_{RE} response after adding WT is definitively attributed to DNA hybridization on the GaNNWs. The GaNNWs-EGFET exhibits highly selective and rapid detection of DNA-hybridization phenomena.

Thin Film and Nanowires Comparison. Figure 6 demonstrates an elucidated comparison between the GaN thin film and NW based EGFET sensors: both the sensors exhibit a similar linear trend, increase in positive ΔV_{RE} ($n\Delta V_{RE}$, normalized to the corresponding V_{RE} value of the ssDNA-modified GaN-based sensor) with C_T, as shown in Figure 6a. Interestingly, the lowest detection limit of GaNNWs-EGFET can effortlessly achieve an ~6 orders lower level, in magnitude, than GaNTF-EGFET. In addition, the NWs-based sensor also exhibited an excellent performance with ~2 orders of higher sensitivity, as estimated from the slope of $n\Delta V_{RE}-C_T$ linear fitting over a wide detection range from 10^{-19} to 10^{-6} M, in comparison with the GaNTF one, suggesting the unique "surface-dominating" nature of nanostructures and hence their high sensitivity to the surface-immobilized biomolecules.

Nonetheless, one point should be noted that even the performance of the GaNTF-based sensor is highly satisfactory, with the detection limit around the picomolar level over a wide detection range $10^{-12}-10^{-6}$ M, compared with other DNA-sensors.[7,23−27] The observation proves the importance of large band gap semiconductors like GaN for biomolecule−semiconductor hybrid system based applications: alignment of relevant electronic levels on both sides at the hybrid biomolecule−semiconductor interface is the essential requirement for the efficient and direct electronic charge exchange. A study by M. Stutzmann et al. revealed the competency of the wide band gap semiconductors, which can cover almost the entire range of energy band positions of the bioorganic systems like DNA molecules, in comparison to other semiconductors like Si and GaAs or metals for bioelectronics applications.[10,28]

Regarding the uniqueness of the NW-structure, the presence of trap states and the resulting strong band bending at the NW-surface[17] has been reported to account for the excellent sensitivity of NWs. Here, the immobilization/hybridization

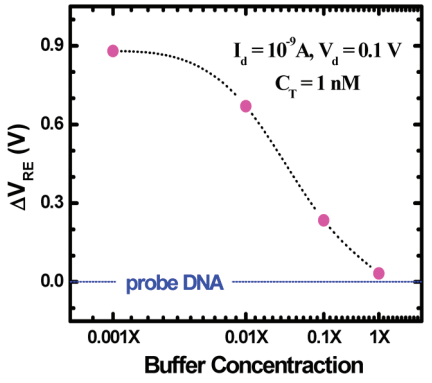

Figure 4. Effect of electrolyte-concentration: FET response (ΔV_{RE}) vs ionic concentration of the buffer solution. The line shown is a guide for the eye only.

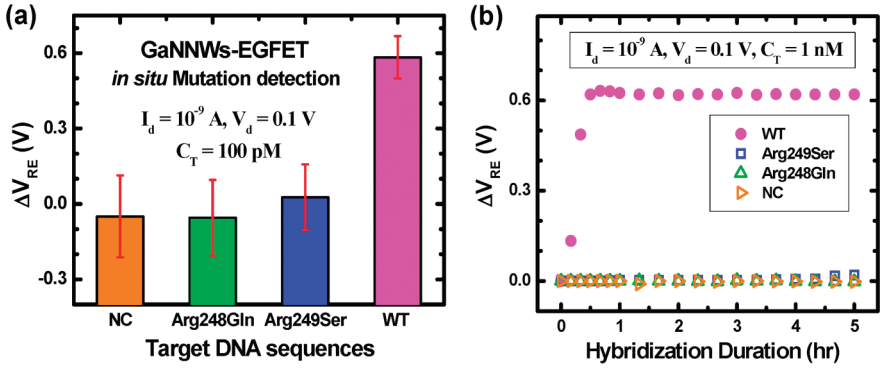

Figure 5. (a) *In situ* DNA-selectivity; detection, FET response (ΔV_{RE}) for different target DNA sequences; (b) corresponding ΔV_{RE} responses as a function of time, illustrating the hybridization duration for different target sequences.

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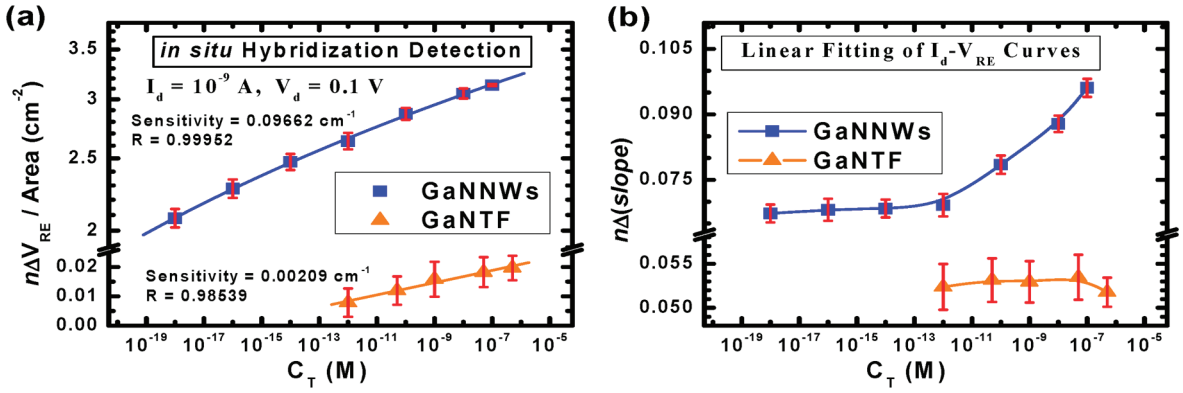

Figure 6. Comparative study between GaN nanowires and thin film based sensors: (a) Dependence of FET-response ($n\Delta V_{RE}$) on target DNA concentration (C_T) for *in situ* DNA-hybridization detection: $n\Delta V_{RE} = [V_{RE}(\text{dsDNA}) - V_{RE}(\text{ssDNA})]/V_{RE}(\text{ssDNA})$. The lines shown in the figure indicate the linear fitting. (b) Normalized values of Δ(slope) (change in slope values) (estimated from the linear fitting of corresponding I_d-V_{RE} curves) as a function of C_T: $n\Delta(\text{slope}) = [\text{slope(dsDNA)} - \text{slope(ssDNA)}]/\text{slope(ssDNA)}$. The lines shown are a guide for the eye only.

of DNA-molecules on the NW-surfaces led to the alteration of the energy level alignment by band flattening via trap state passivation and/or charge redistribution.[4] Such surface-specific nature of GaNNWs has played definitely a minor role in the GaNTF case, which is also supported by the significant difference in their conductivity (the magnitude of I_d) and hence in ΔV_{RE} responses.

Interestingly, the detailed analysis by linear fitting of the I_d-V_{RE} curves reveals a prominent feature distinguishing the NWs-based sensor from the GaNTF one: the dependency of the Δ(slope) values (change in slope of I_d-V_{RE} curves) on C_T. The slope value equals $(\mu W C_0 V_d)/L$ (in the linear regime of I_d-V_d characteristics), where μ is the field-effect mobility, C_0 represents the effective capacitance per unit area of the gate insulator including the extended DNA-modified GaN electrode and gate oxide of the FET device. The ratio of W and L (the effective width and length, respectively) includes the structure factor of the extended part of the gate. Figure 6b shows that the normalized values of Δ(slope), for GaNNWs-EGFET, exhibit exponential like growth with C_T while for GaNTF-EGFET vary within the measurement-error regime. On the other hand, the estimated threshold voltage V_{th} exhibits the similar behavior like V_{RE} observed in Figure 6a. Since V_{th} is inversely proportional to C_0, the latter can be considered to decrease with the increase in C_T. However, for NWs, the product μC_0 ($\propto$ slope) is found to be increased with C_T (Figure 6b), which is only possible if and only if μ increases with C_T during *in situ* DNA-hybridization. The phenomenon supports our previous observations on the EIS responses of the same DNA-modified GaNNWs,[4] where the electron-transfer resistance R_{et} at the GaN/DNA interface decreases with C_T. Both the R_{et} and μ are related to the existence of band-bending at the GaNNWs surface, as per conventional understanding; hence, the increase in μ (and decrease in R_{et})[4] with C_T would definitely be attributed, not unreasonably, to the surface band flattening phenomena, as a result of surface states passivation and/or charge redistribution at the GaN/DNA interface. The role of C_0 cannot be avoided, especially for GaN like wide band gap materials, as evident from the GaNTF case. The surface band-bending is not that prominent for GaNTF as for GaNNWs, and hence the product μC_0 is mostly dominated by large C_0 values. The contending behavior between μ and C_0 is vividly exposed for GaNNWs: where at lower C_T, the μC_0 varies very slowly; while at high C_T, μ dominates over C_0. The surface-sensitivity and band-alignment phenomena can justify the importance of GaN, especially in NWs-form, in DNA-sensing applications.

CONCLUSIONS

In this study, an EGFET-based sensing technique has been demonstrated, utilizing GaNNWs as the extended-gate material. Our simple EGFET-design facilitates easy assembly and real-time operation for DNA detection. Our sensor displayed an ultrahigh sensitivity in the level of 10^{-18} M with excellent specificity toward the fully complementary target only, during real time detection in a complex system of foreign sequences including the single base-pair mutation. Moreover, GaNNWs-EGFET has clearly outperformed its thin film counterpart, revealing the enormous potential of NW-structures for biosensor and bioelectronic applications, which may be much wider in detecting different classes of biomolecules.

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