

A Tri-Channel Oxide Transistor Concept for the Rapid Detection of Biomolecules Including the SARS-CoV-2 Spike Protein

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Solid-state transistor sensors that can detect biomolecules in real time are highly attractive for emerging bioanalytical applications. However, combining upscalable manufacturing with the required performance remains challenging. Here, an alternative biosensor transistor concept is developed, which relies on a solution-processed $\text{In}_2\text{O}_3/\text{ZnO}$ semiconducting heterojunction featuring a geometrically engineered tri-channel architecture for the rapid, real-time detection of important biomolecules. The sensor combines a high electron mobility channel, attributed to the electronic properties of the $\text{In}_2\text{O}_3/\text{ZnO}$ heterointerface, in close proximity to a sensing surface featuring tethered analyte receptors. The unusual tri-channel design enables strong coupling between the buried electron channel and electrostatic perturbations occurring during receptor–analyte interactions allowing for robust, real-time detection of biomolecules down to attomolar (aM) concentrations. The experimental findings are corroborated by extensive device simulations, highlighting the unique advantages of the heterojunction tri-channel design. By functionalizing the surface of the geometrically engineered channel with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody receptors, real-time detection of the SARS-CoV-2 spike S1 protein down to aM concentrations is demonstrated in under 2 min in physiological relevant conditions.

1. Introduction

Miniaturized biochemical sensors fabricated via high-throughput manufacturing methods promise cost-effective, large-volume production for use in various technology sectors.^[1] The present needs for biochemical detection are diverse and include environmental monitoring,^[2] security systems,^[3] and preventative medical care.^[4] An ideal biochemical sensing platform should be able to accommodate a wide range of applications in biological and chemical detections with high-sensitivity^[5] and selectivity.^[6] Among the various types of sensing platforms, a solid-state transistor sensor is a highly anticipated tool that could address these requirements as it provides the functionality of a transducer for converting a biochemical interaction into an amplified electrical signal.^[7] This characteristic enables direct readout without the need of

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bulky peripheral driving (opto)electronics, such as amplifiers, excitation light sources, and photodetectors.^[8]

For the successful use of solid-state transistors as biosensors, the transistor channel should exhibit a large surface area^[9] and tunable surface chemistry.^[10] The large surface area allows tethering of sufficient quantity of molecular receptors while the surface helps to preserve charge transport across the channel without unintentionally reacting with the environment. One widely reported biosensor technology platform is based on silicon-nanowire (Si-NW) transistors, but their manufacturing remains challenging.^[11–13] Alternative technologies such as thin-film transistors (TFTs) made of metal oxide semiconductors offer scalable manufacturing and intriguing physical properties.^[14–17] However, due to parasitic gating effects and associated performance deterioration,^[18–21] the use of metal oxide transistors as biosensors has remained limited with most effort focused on liquid-gated transistors (LGTs).^[6,22–24] In spite of being one of the most studied device, LGT biosensors face the detrimental Debye screening effect^[6,25–26]—a direct result of the operating principles that rely on electrochemical reactions^[27] or on the movement of analytes^[28] upon liquid-gating. Thus, managing or overcoming the Debye screening effect is critical for developing ultrasensitive transistor sensor technologies for emerging applications.^[29] Such technologies will largely benefit point-of-care systems in healthcare with the potential to mitigate existing challenges that include false results, long-waiting time, and the need for highly specialized equipment and trained staff.^[30]

Here, we introduce a nanometer-thin $\text{In}_2\text{O}_3/\text{ZnO}$ heterojunction (HJ) channel and combine it with a geometrically engineered tri-channel architecture several millimeters in size as a universal platform for selective and sensitive biosensing. The all-solid-state device consists of a central sensing channel and two side channels featuring a buried electron transporting heterointerface a few nanometers below the channel's surface. The flexible surface chemistry of the metal oxide allows direct functionalization of different types of receptors, making the device a versatile sensing platform. Despite being a TFT, the tri-channel architecture facilitates access to mm^2 -size sensing surface without compromising the sensor's electrical performance due to its enhanced electron mobility and ultrahigh surface-area-to-volume ratio ($10^6 \text{ cm}^2 \text{ cm}^{-3}$). These features enable simultaneous signal transduction and amplification in an all-solid-state TFT platform, enabling real-time detection of specific biomolecules down to attomolar (aM) concentrations. As a proof-of-concept, we demonstrate selective sensing of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike S1 protein in real-time with a limit of detection (LoD) of $865 \times 10^{-18} \text{ M}$ in phosphate buffered saline (PBS) and $<1 \times 10^{-15} \text{ M}$ in human serum (HS) in less than 2 min.

2. Quasi-2D Oxide Heterojunction Channel

We hypothesized that our recently developed solution-processed, high electron mobility $\text{In}_2\text{O}_3/\text{ZnO}$ HJ transistors^[31] offers certain features that could prove attractive for biosensing. First, the buried electron channel located at the oxide HJ is physically separated from the receptor units tethered on

its surface a few nm above.^[32–33] This feature is expected to prevent degradation of electron transport upon sensing (e.g., due to Coulomb scattering) and preserve the transistor's performance. This is not the case for most biosensor transistors reported to date where the channel interacts directly with the receptor units and hence the analyte. To overcome this, liquid gating has been exploited for detecting various analytes in the liquid phase.^[6,22,34] Second, the high electron mobility of the HJ TFTs offers the possibility for large electrical signals that are easy to detect and amplify even in large-size devices.^[32]

We fabricated HJ transistors using the staggered bottom-gate, top-contact (BG-TC) architecture shown in **Figure 1A**. High-resolution transmission electron microscopy (HRTEM) analysis (**Figure 1B**) of the channel reveals the formation of a well-defined HJ channel with thickness in the range of 8–10 nm. Atomic force microscopy (AFM) measurements show the existence of smooth layers as being deposited sequentially (**Figure 1C,D**). In_2O_3 exhibits the lowest peak-to-peak height (ΔZ) of 1.87 nm with a root-mean-square roughness (σ_{RMS}) value of 0.20 nm, which are comparable to that of SiO_2 ($\Delta Z = 1.91 \text{ nm}$, $\sigma_{\text{RMS}} = 0.21 \text{ nm}$). Subsequent deposition of ZnO atop In_2O_3 leads to a slightly rougher topography ($\Delta Z = 4.00 \text{ nm}$, $\sigma_{\text{RMS}} = 0.58 \text{ nm}$) indicative of a more textured surface.^[32,35]

The $\text{In}_2\text{O}_3/\text{ZnO}$ forms a type-II HJ where electrons migrate from the conduction band (CB) of ZnO to that of In_2O_3 , leading to the accumulation of electrons in the latter and in close proximity to the heterointerface (illustrated in **Figure 1E**).^[33] We note that our actual device stack is low-dimensional (**Figure 1B**) and as such it is difficult to probe with high enough accuracy (resolution) the change in the gradient of electron density distribution across the hetero-oxide interface where the higher density of electrons reside. From our modeled $\text{In}_2\text{O}_3/\text{ZnO}$ channel (**Figure S1**, Supporting Information) using the COMSOL Multiphysics simulation software (see the Experimental Section), the heterointerface might appear having a uniform electron distribution (**Figure S1C**, Supporting Information). However, this observation is simply the result of the low dimensionality of the transistor channel and closer examination of the data reveals a clear gradient in electron density across the $\text{In}_2\text{O}_3/\text{ZnO}$ heterointerface (**Figure S1A,B**, Supporting Information) in agreement with earlier experimental observations.^[33] To make this feature more visible, we highlighted the relative position of the $\text{In}_2\text{O}_3/\text{ZnO}$ stack in **Figure 1E**. In **Figure 1F,G**, we show representative sets of transfer and output current–voltage (I – V) characteristics for an $\text{In}_2\text{O}_3/\text{ZnO}$ HJ transistor with electron mobility and current on–off ratio of $>22 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ and $>10^8$, respectively.

3. All Solid-State Tri-Channel Transistor Sensor

To investigate the suitability of the $\text{In}_2\text{O}_3/\text{ZnO}$ transistors for biosensing, we fabricated devices based on a tri-channel configuration on 4 inch Si wafers (**Figure 2A**). The source–drain (S–D) electrodes are deposited atop the $\text{In}_2\text{O}_3/\text{ZnO}$ channel followed by the deposition of another ultrathin (2–4 nm) protective ZnO layer. Next, the deoxyribonucleic acid (DNA) intercalator^[36–37] 1-pyrenebutyric acid (PBA) was functionalized directly onto ZnO^[38] acting as the DNA receptor. A second functionalization step using butyric acid (BA) was also applied to

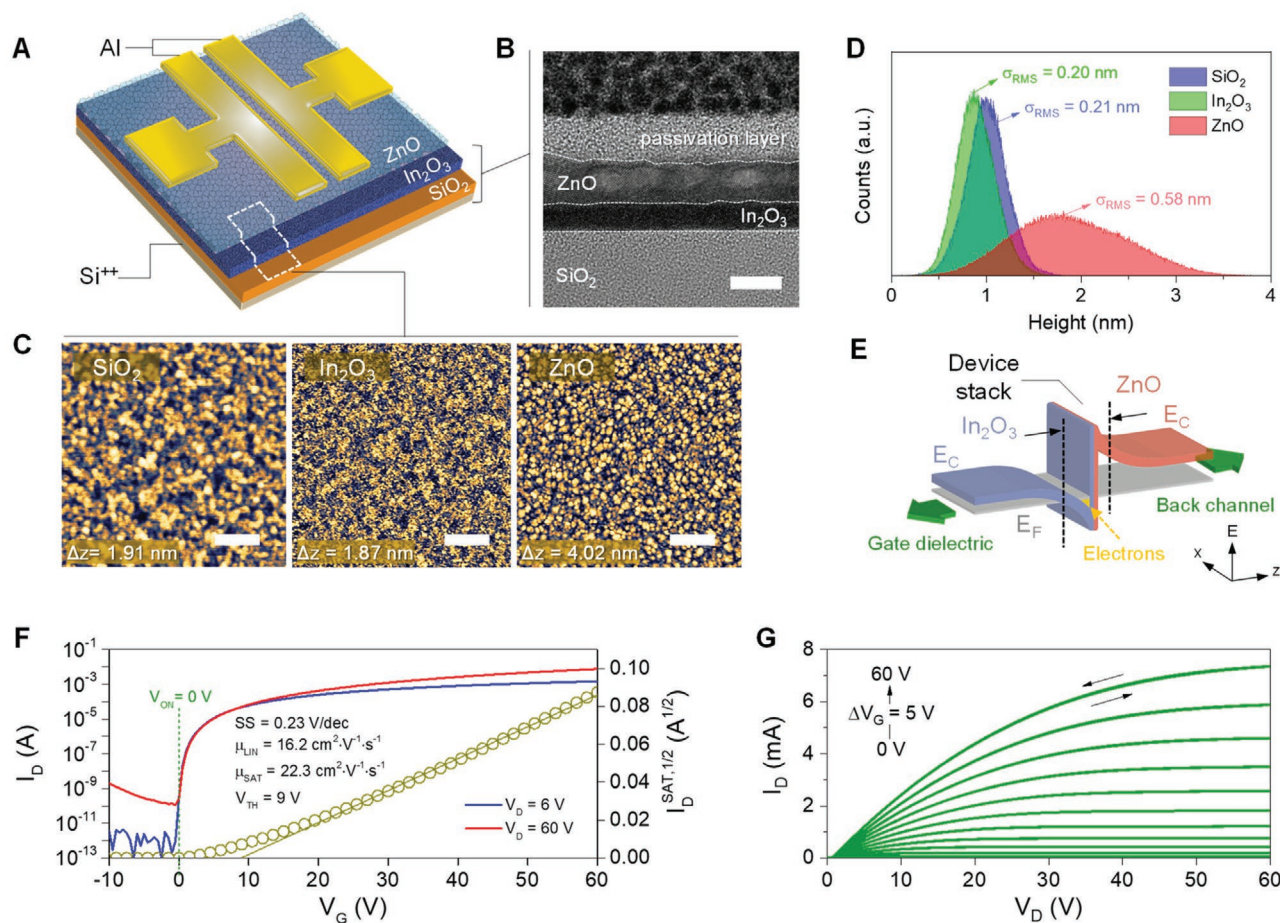


Figure 1. Fabrication and testing of metal oxide HJ transistors. A) Schematic of an In₂O₃/ZnO HJ transistor. B) HRTEM cross-sectional image of the channel region (scale bar = 5 nm). C) Intermittent AFM topography images of SiO₂, In₂O₃, and ZnO surfaces (scale bar = 200 nm). D) Height histogram extracted from the AFM data for each sequentially deposited layer. Corresponding peak-to-peak height difference (Δz) and root mean square surface roughness (σ_{RMS}) were derived from AFM image analysis. E) Schematic of energetic diagram for the In₂O₃/ZnO heterojunction. The discontinuity in the conduction band between ZnO and In₂O₃ results to the electron migration from ZnO to In₂O₃. Representative current–voltage (I – V) characteristics for an In₂O₃/ZnO transistor: F) transfer and G) output characteristics. Important device parameters are shown in panel (F). These include turn on voltage (V_{ON}), threshold voltage (V_{TH}), subthreshold swing (SS), linear mobility (μ_{LIN}), and saturation mobility (μ_{SAT}).

ensure complete passivation of the ZnO surface (see Figure S2 in the Supporting Information). The presence of BA helps to minimize the chemical interaction between the fluid (physiological or not) that is used to disperse the different analytes, and the surface of the SC (i.e., the upper ZnO layer). Importantly, the presence of BA does not affect the electronic characteristics of the device and hence its sensing capabilities, which will be discussed later. The presence of PBA on the heterojunction channel was verified using ultraviolet–visible (UV–vis) absorption measurements before and after functionalization as evidenced by the appearance of distinct absorption peaks associated with the pyrene unit (Figure S3, Supporting Information). The completed device consists of two identical “conventional” channels (hereafter termed CC) 100 μm in length (L), formed on the sides, and a third long ($L = 2000 \mu\text{m}$) “sensing” channel (hereafter termed SC) formed in the central region of the device between the S–D electrodes (see Figure S4 in the Supporting Information). This unique channel layout offers a large sensing area channel where the analyte-containing solution can be easily applied while avoiding direct contact with the S–D

electrodes (Figure 2B,C), which is known to induce parasitic gating effects.^[39]

In Figures S5 and S6 in the Supporting Information, we plot the transistor transfer and output characteristics, respectively, measured before and after PBA and BA functionalization. Unlike conventional transistor-based biosensors,^[22,40] our tri-channel device shows negligible changes in its operating characteristics following receptor functionalization. The narrow parameter distribution is better illustrated in Figure 2D, which shows the density plots^[41] of the dual-sweep transfer characteristics for 30 individual tri-channel transistors fabricated on a single wafer. Critically, the tri-channel transistors exhibit robust operation even when subjected to 90 repeated dual I – V sweeps with negligible leakage current (I_{C}), which is critical for optimal device operation and signal amplification (Figure S7, Supporting Information).^[42] We note that all devices were measured without any lightproof apparatus and under ambient atmosphere. These data demonstrate the high operational stability and reproducibility of the proposed tri-channel HJ transistor architecture.

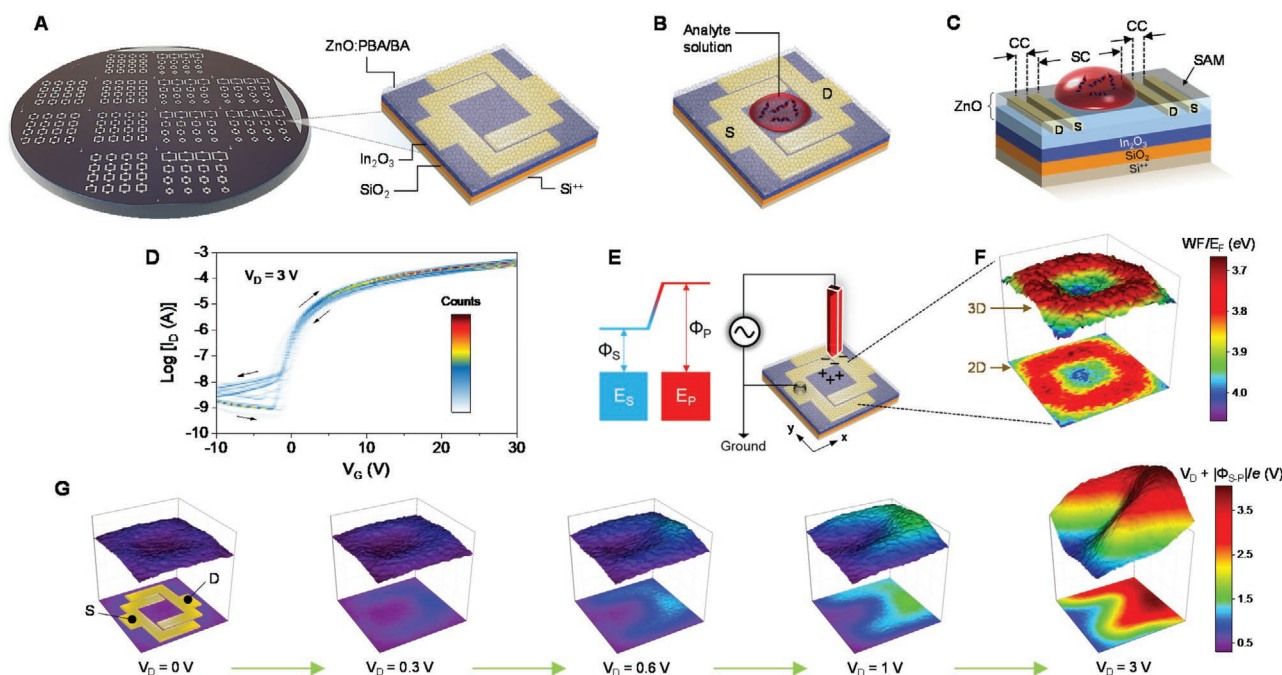


Figure 2. Design and structures of tri-channel transistor sensors. A) Tri-channel In₂O₃/ZnO HJ transistors fabricated on a 4 in. Si⁺⁺/SiO₂ wafer and schematic of the channel architecture. The source–drain (S–D) electrodes are covered by the top ZnO layer. The receptor molecule pyrenebutyric acid (PBA) and passivation molecule butyric acid (BA) are chemically tethered onto the ZnO surface. The role of BA, which is deposited after PBA, is to prevent direct interaction between the channel's surface and the liquids used to disperse the various analytes. B) Illustration of the direct application of analyte solution on the millimeter-scale sensing channel (SC) area of the sensor. C) Schematic of the tri-channel transistor depicting the location of the analyte solution within the SC and two conventional channels (CCs) on the sides. D) Density plots of forward–backward dual sweeps of current–voltage characteristics measured from 30 individual tri-channel transistor sensors fabricated on a wafer. E) Schematic of the scanning Kelvin probe (SKP) setup used. The SKP method relies on the application of a voltage to offset the surface potential between the sample (Φ_S) and the tip (Φ_P). The magnitude of this voltage is then used to calculate the energy difference between the sample (E_S) and the tip (E_P). F) 2D (top)/3D (bottom) maps of the electrostatic potential across a tri-channel transistor measured by SKP. The WF for the embedded Al-electrode areas is measured to be ≈3.8 eV while the E_F for the SC is ≈4.0 eV. G) Electrostatic potential maps measured at different source–drain potentials: V_D = 0, 0.3, 0.6, 1, and 3 V. The relative positions of the S–D electrodes are shown in the 2D map for V_D = 0 V.

To better understand the electrostatic potential landscape across the unconventional tri-channel device, we performed scanning Kelvin probe (SKP) measurements (Figure 2E). Figure 2F shows the 2D (bottom) and 3D (top) work function (WF) or Fermi energy (E_F) maps for a tri-channel device measured. The influence of the buried Al electrodes beneath ZnO results in local potential changes (3.8–4 eV), with a higher potential observed in the middle of the SC region. SKP measurements were also performed while applying a drain bias (V_D) in the range of 0–3 V (Figure 2G; the respective location of the device illustrated for V_D = 0 V image). The application of low voltages (e.g., V_D = 0.6–1 V) causes a substantial change within the SC, while increasing the applied bias to 3 V affects the potential landscape across the entire SC region, suggesting strong coupling between the SC and the two side CCs. Thus, the tri-channel architecture appears to enable spatially decoupling of the signal transduction occurring within the SC region from the current-driving CCs.

To understand how the tri-channel geometry impacts the electrical characteristics of the sensor, we built a simplified numerical model (Figures S8 and S9, Supporting Information) to simulate the electric potential distributions across the entire tri-channel device under a static state condition of V_G = 8 V and V_D = 3 V (Figure S8A, Supporting Information). Figure S8B in

the Supporting Information shows the modeled result in the presence of a circular-shaped analyte pattern (i.e., a realistic approximation of our sensing experiments), while Figure S8C in the Supporting Information shows the data in the presence of a square shaped analyte pattern. In both cases, the density of the modeled analyte was considered to be $3.3 \times 10^9 \text{ cm}^{-2}$. The square shaped analyte exhibits a stronger perturbation on the electrostatics of the device, when compared to circular shaped analyte. This phenomenon can be clearly observed in the presence of higher surface charge densities and in particular when increasing from 3.3×10^9 to $6.7 \times 10^{10} \text{ cm}^{-2}$ (Figure S9, Supporting Information). In all sensing scenarios, the electric potential gradient can readily reach the source–drain 90° corners for a square-shaped analyte while for a circular-shaped analyte area, the changes are relatively less apparent when reaching the 90° corners and appear mostly at the center of the SC.

The calculated drain current obtained for Figure S8A (no analyte), Figure S8B (a circular-shaped analyte), and Figure S8C (a square-shaped analyte) in the Supporting Information are 371, 377, and 383 μA, respectively. The excess currents of 6.2 and 11.5 μA for a circular- and a square-shaped analyte device can then be obtained by subtracting the baseline current (i.e., no analyte) from the total current of the analyte-containing

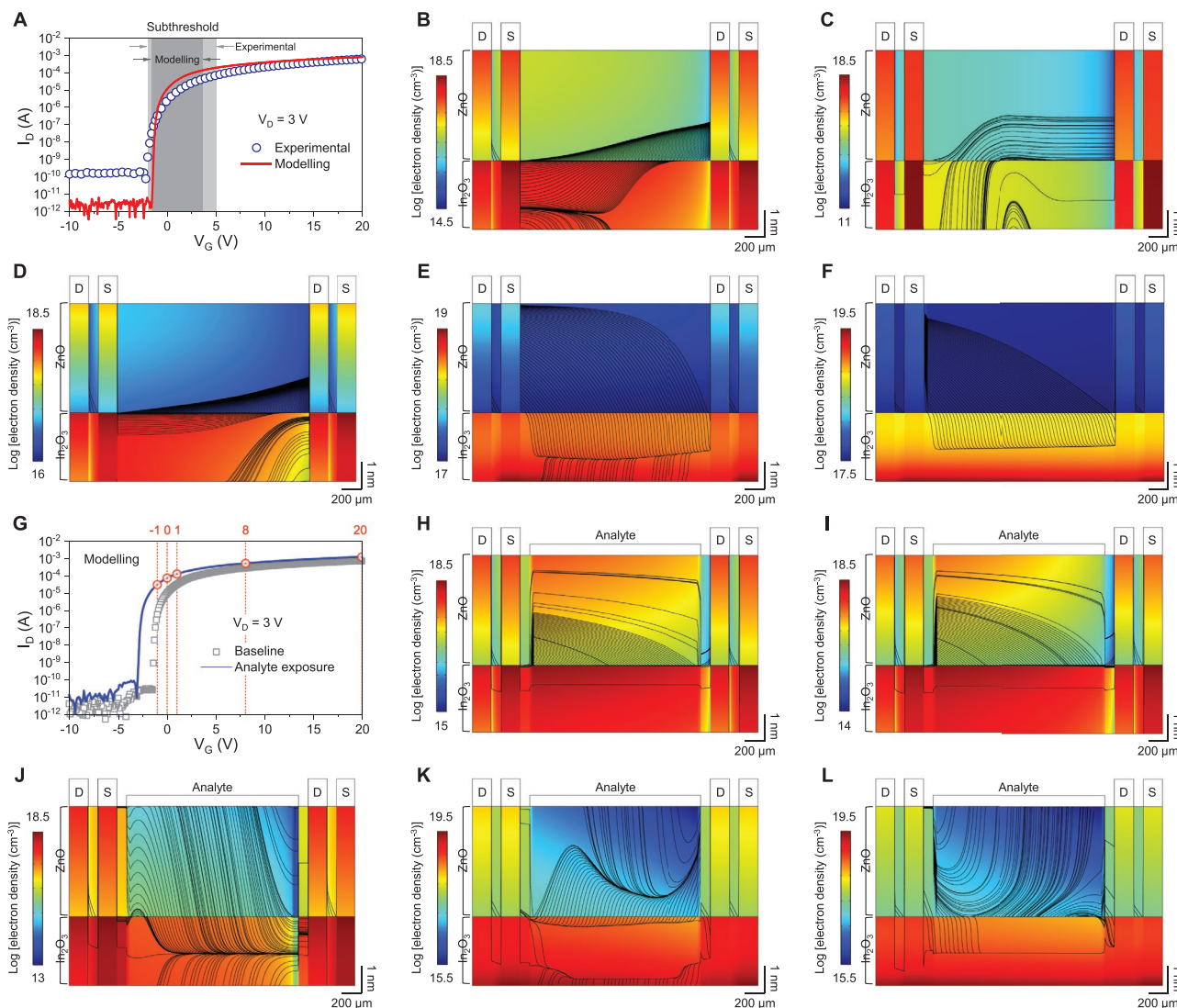


Figure 3. Physical principles of tri-channel transistor sensors. A) Transfer current–voltage characteristics of tri-channel transistor sensors obtained from experiment and modeling using COMSOL Multiphysics. The applied drain voltage (V_D) was +3 V, and the subthreshold regions are indicated in gray. B–F) Corresponding COMSOL simulations showing the electron density distributions along the cross-section of the $\text{In}_2\text{O}_3/\text{ZnO}$ heterostructure under the source and drain electrodes (labeled as S and D, respectively) and the electron flow streamlines within the channel regions, with different gate voltages (V_G) applied: B) –1 V; C) 0 V; D) 1 V; E) 8 V; F) 20 V, and a constant $V_D = 3$ V. G) Modeled transfer current–voltage characteristics ($V_D = 3$ V) for baseline and under the exposure of simulated surface-charged analytes. H–L) Corresponding COMSOL electron density distributions under the influence of simulated analytes when applying $V_D = 3$ V and H) $V_G = -1$ V; I) $V_G = 0$ V; J) $V_G = 1$ V; K) $V_G = 8$ V; L) $V_G = 20$ V to the transistor sensors. The electrodes and analytes are shown to indicate their positions with respect to the devices.

devices. The circular-shaped analyte device, which closely resembles the shape of a real-world analyte droplet, yields $\sim 50\%$ less current than the square-shaped analyte device. Therefore, in our effort to study how the channel geometry affects charge flows, we utilized one half of a square-shaped analyte to model the influence of the analyte on the current–voltage characteristics of a tri-channel device in order to approximate the presence of a circular-shaped analyte. Further details are provided in the Experimental Section. **Figure 3** shows the cross-sectional view along the center of the tri-channel device (relative position indicated by arrows a and b in Figure S8B in the Supporting Information). We can then simplify the geometric setting of the analyte by integrating each cross-section shown in Figure 3

along the out of plane direction (relative position indicated by arrows c and d in Figure S8B in the Supporting Information) for one half of the length of an actual tri-channel device to obtain a current level close to the condition with the presence of a circular-shaped analyte.

Figure 3A shows the simulated and measured transfer characteristics for a representative transistor. The small difference seen in the subthreshold region between the modeled and experimental I – V data is attributed to the presence of trap states in the channel that are difficult to be captured, with high enough accuracy, by the model.^[43–44] The slightly higher off current, on the other hand, measured for the real device is due to the combination of a large common Si^{++} gate electrode that

was used in this study and the unpatterned layout of the semiconductor. The latter features are known to give rise to parasitic fringe surface currents forming between the S/D and the gate electrode, although in the present case their contribution is very small (≈ 0.1 nA) and hence negligible. Apart from these minor discrepancies, the model provides a good description of the tri-channel transistor operation and validates its ability to describe the operating characteristics of the sensor.

The main function of a transistor biosensor is to induce a perturbation in the channel current upon exposure to an external stimulus (analyte). To best illustrate this process in our sensor, we used the postprocessing streamline tool for visualizing the electron concentration and the streamlines of the channel current flow. Figure 3B–F shows the static distributions of the electron density and the streamlines of the current flow within the $\text{In}_2\text{O}_3/\text{ZnO}$ heterostructure biased at $V_D = 3$ V and $V_G = -1, 0, 1, 8$ and 20 V. The results are in good agreement with our experimental observations and reveal the staggering enhancement in the current density within the In_2O_3 of the heterointerface.^[32,43] Next, we modeled the electrical characteristics of the device in the presence of an analyte. We hypothesize that the analyte species interacts with the surface-tethered receptor units and induce free charges at the surface of the SC region. To establish the sensing condition close to the limit of detection for our sensor, we assumed the number of additional charges induced by the analyte to be equivalent or lower than the number of mobile charges in the channel. Based on the literature,^[45] as well as on our own work on similar heterojunction metal oxide channels,^[32] device operation will remain largely unaltered when the additional electron concentration does not exceeds 10^{17} cm^{-3} .^[35] To ensure that this condition is satisfied, we used a more conservative estimation for the analyte-induced electron density of 10^{16} cm^{-3} and a channel thickness of 10 nm (Figure 1B). The equivalent surface charge density due to analyte was then derived from the modeling yielding a value of $\approx 10^{10} \text{ cm}^{-2}$, which will be considered next for the different device operating scenarios.

Figure 3G shows the modeled transfer characteristics for a tri-channel (inset, Figure 3G) $\text{In}_2\text{O}_3/\text{ZnO}$ sensor while Figure S10 in the Supporting Information displays similar calculations for a single layer In_2O_3 and a $\text{In}_2\text{O}_3/\text{ZnO}$ HJ transistors based on the conventional channel geometry (insets in Figure S10A,C in the Supporting Information) before (baseline) and after exposure to analyte (analyte exposure). The tri-channel $\text{In}_2\text{O}_3/\text{ZnO}$ transistor shows a large response to the analyte (surface charge $\approx 10^{10} \text{ cm}^{-2}$) with the transfer curve shifted toward more negative V_G bias. This is not the case for In_2O_3 and $\text{In}_2\text{O}_3/\text{ZnO}$ transistors with conventional channel geometry (Figure S10B,D, Supporting Information), where the analyte induces only a small perturbation in the current around the subthreshold regime consistent with filling of subgap states.^[46] The modeled electron density and current flow for the tri-channel transistor biased at $V_D = 3$ V and $V_G = -1, 0, 1, 8$, and 20 V, are presented in Figure 3H–L, while the corresponding modeling results for the conventional channel In_2O_3 (at $V_D = 3$ V, $V_G = 1$ V) and $\text{In}_2\text{O}_3/\text{ZnO}$ (at $V_D = 3$ V, $V_G = -1$ and 1 V) transistors are shown in Figure S11A,B and Figure S11C–F, respectively, in the Supporting Information. Strikingly, we find that unlike geometrically engineered $\text{In}_2\text{O}_3/\text{ZnO}$ HJ transistors (Figure 3H–L),

electron flow in the In_2O_3 device is pinned at the interface with the gate dielectric while being fully decoupled from the surface/analyte (Figure S11B, Supporting Information). From these data we conclude that the tri-channel design is highly sensitive to the presence of surface charges as compared to conventional channel design, while single layer In_2O_3 transistors are not ideal for solid-state biosensing applications.

Next, we consider the scenario where the $\text{In}_2\text{O}_3/\text{ZnO}$ HJ transistors are operated in depletion ($V_G = -1$ V) and in the presence of analyte (i.e., additional $\approx 10^{10} \text{ cm}^{-2}$ on the SC surface). Clear perturbations in the current flow are observed for both tri-channel $\text{In}_2\text{O}_3/\text{ZnO}$ (Figure 3H–L) and conventional channel $\text{In}_2\text{O}_3/\text{ZnO}$ (Figure S11D,F, Supporting Information) transistors. The broader distribution of streamlines seen in the tri-channel is consistent with the large negative shift in the turn-on voltage (V_{ON}) of the device (Figure 3G). Regardless of the biasing scenarios (depletion or accumulation), the tri-channel architecture shows much stronger coupling to the analyte. Specifically, we find the electron flow streamlines to extend ≈ 1 nm beneath the SC surface (Figure 3H–L) due to the asymmetric design of the source–drain electrodes,^[47] which prevent the local electric field to fully pinch-off the channel at lower V_G biasing. As the V_G increases (e.g., +20 V), the benefits associated with the presence of a higher electron density in the $\text{In}_2\text{O}_3/\text{ZnO}$ become even more apparent as the area beneath the sensing surface remains free from electrostatic screening induced by the gate (Figure 3L). Nevertheless, it is known to be more advantageous for solid-state transistor sensors to be operated within the subthreshold region as it yields optimal sensitivity due to the higher signal gain.^[48]

To further highlight the key role of the side CCs, we carried out additional simulations on conventional single channel architectures and compared the results against those obtained for tri-channels, focusing on how the CCs perturbs the electric field and redistributes the charges within the semiconducting heterojunction under similar biasing condition ($V_G = V_D = 3$ V). To make our simulation more perceivable, the length of the SC in the lateral direction (i.e., parallel to the gate dielectric) was reduced by a factor of 2×10^3 while the CC and top electrodes were reduced by a factor of 10^3 (Figure S12, Supporting Information). We then assumed a low surface charge density of $5 \times 10^9 \text{ cm}^{-2}$ as the modeled analyte to examine how the CCs enhances the ability of the device to detect minute perturbations caused by the analyte–receptor interactions during sensing. As shown in Figure S12A in the Supporting Information, in regions 1 (i.e., areas highlighted by red dashed squares), the conventional single channel design (top) shows a significantly larger pinched-off region than the tri-channel device (bottom), while in regions 2 (i.e., areas highlighted by black dashed squares), the tri-channel design (bottom) is able to sustain a significantly higher electron concentration within the SC. These observations highlight the key role of CCs in helping induce a stronger electric field, unpinning the channel current under the drain electrode of the SC and enhancing the electron extraction under the source electrode in the SC region. Figure S12B in the Supporting Information shows the corresponding electric field distributions across the conventional channel (top) and the tri-channel (bottom) architecture, further corroborating the proposed mechanism and the key role of the

CCs. Importantly, the simulations protocol developed here can be seen as a powerful predictive tool that in the future could be exploited to further advance the tri-channel sensor design and lead to improved sensor capabilities.

4. Receptor Engineering for Ultrasensitive and Real-Time Biosensing

To demonstrate that the working principle of our all-solid-state tri-channel transistor is fundamentally different from that of conventional liquid-gate transistor biosensors, we studied the ability of our transistors to detect different types of DNAs (analytes) dispersed in deionized (DI) water rather than in a high ionic strength (and hence electrically conductive) solution often used in LGT sensors.^[6] In the latter case, the high strength ionic medium (electrolyte, buffer solution, etc.) represents an essential component as it facilitates the movement of charged species (or charges), which in turn “gate” the sensor's electrical signal (channel current).^[6,22–24] In contrast, the operation of the solid-state tri-channel sensor developed here does not rely on such electrochemical processes since sensing stems purely from the electronic interactions occurring between the surface tethered receptors (i.e., PBA) and the analyte species (i.e., DNA). To prove this, double-stranded DNA (dsDNA) and single-stranded DNA (ssDNA) of different sequences were dispersed in DI-water solutions and applied directly onto the SC area while recording the device's electrical response. **Figure 4A** depicts the envisioned interaction between dsDNA and PBA where the pyrene units on PBA intercalate into the dsDNA.^[49] **Figure 4B–D** shows the measured transfer characteristics ($V_D = 3$ V) in the presence of different concentrations of 20 base-pair segments of synthetic DNAs based on single-stranded adenine (A) [abbreviated as A20], and thymine (T) [abbreviated as T20], as well as their complementary dsDNA (AT)20. For (AT)20, a much larger change in the transistor's transfer characteristics is observed with the lowest dsDNA concentrations studied down to 100×10^{-18} M (**Figure 4B**). The strong response is attributed exclusively to the intercalation of the pyrene units into the minor grooves of the double-stranded (AT)20 since the presence of DI water has no measurable effect (**Figure S13**, Supporting Information). The progressive shift of V_{ON} toward more negative V_G seen in **Figure 4B** is consistent with the modeling results of **Figure 3G** where we considered the presence of additional free charges on the surface of the SC. This observation indicates that pyrene–DNA association generates free electrons that are then injected into the channel. Further evidence supporting our hypothesis comes from sensing experiments involving the single-stranded A20 (**Figure 4C**) and T20 (**Figure 4D**) where only minute changes are observed in the transistors' characteristics due to the absence of pyrene–DNA intercalation.

In an effort to quantify the sensor's response, we analyzed the change in V_{ON} as a function of increasing analyte concentration. This shift reflects the increase in the electron concentration (Δe_{areal}) within the channel and is given as^[50]

$$\Delta e_{areal} = \frac{C_{areal} [V_{ON}(conc.) - V_{ON}(init.)]}{q} \quad (1)$$

where C_{areal} is the areal capacitance of the gate dielectric (34.4 nF cm⁻²), q is the elementary charge, $V_{ON}(init.)$ is the initial V_{ON} measured in the presence of blank solution (no analyte), and $V_{ON}(conc.)$ is the transistor's V_{ON} measured upon application of the analyte at each concentration. For simplicity, we assume all electrons are confined in a 2D plane at the vicinity of the oxide HJ.^[33] **Figure 4E** shows the evolution of Δe_{areal} as a function of analyte concentration measured using a tri-channel sensor. (AT)20 induces the highest Δe_{areal} , a direct consequence of the large V_{ON} shift observed in **Figure 4B**. These results demonstrate unambiguously that pyrene–(AT)20 intercalation produces signals several orders of magnitude larger than the nonintercalating ssDNAs of A20 and T20. Moreover, the data showcase the ability of the tri-channel sensor to differentiate between double- and single-stranded DNAs without the need for complex fluorescence labeling.^[51] To this end, the DNA conformation with respect to the substrate (i.e., lying-down or standing up) should not be critical as sensing relies exclusively on the charge transfer upon pyrene–DNA association. This hypothesis is corroborated by the sensor's ability to selectively detect different analytes, such as avidin and SARS-CoV-2 spike S1 protein, which will be discussed latter. The ability of our sensor to facilitate such a strong coupling between the minute receptor–analyte interactions and charge transport, without compromising the channel transconductance (g_m) (see text and **Figure S14** in the Supporting Information), is a result of three unique device attributes:

- The geometrical engineered tri-channel design that enables strong coupling between current transport across the device and receptor–analyte interactions in the surface.
- The use of a high electron mobility heterojunction metal oxide semiconductor featuring a buried channel.
- The versatile surface chemistry and the electronic properties of the metal oxides employed.

Due to the diverse range of biosensor transistor technologies to date,^[5–6] there is currently no clear consensus on the important figures of merit that can be used to define the performance of such devices. Here, we attempt to draw an analogy from the field of phototransistors, since both types of sensors act as transducers with a highly V_G -dependent response, and define two practical figures of merit, namely, the responsivity ($R_{analyte}$) and sensitivity ($S_{analyte}$) (**Figure S15**, Supporting Information). We first investigated the suitability of our tri-channel biosensor TFTs for real-time sensing of (AT)20 at an extremely broad range of analyte concentrations (10^{-18} to 10^{-6} M), while simultaneously assessing the sensors' ability to operate in aqueous conditions.^[9,52] Specifically, we monitored the evolution of ΔI_D at $V_G = -1$ V and $V_D = 3$ V, as a function of time for different (AT)20 concentrations. The biasing condition was chosen to maximize the sensor's response by operating it in the subthreshold region^[48] (**Figure S16**, Supporting Information). **Figure 4F** shows a representative real-time recording of $\Delta I_D/I_0$ (where $I_0 = 3.16 \times 10^{-8}$ A) for analyte concentrations in the range 10^{-18} to 10^{-6} M, where a clear response across the entire range is observed. Even at 100×10^{-18} M of (AT)20, the tri-channel TFT shows a significant increase in ΔI_D by ≈ 30 times (**Figure 4G**) in less than 2 min. This represents the highest response signal

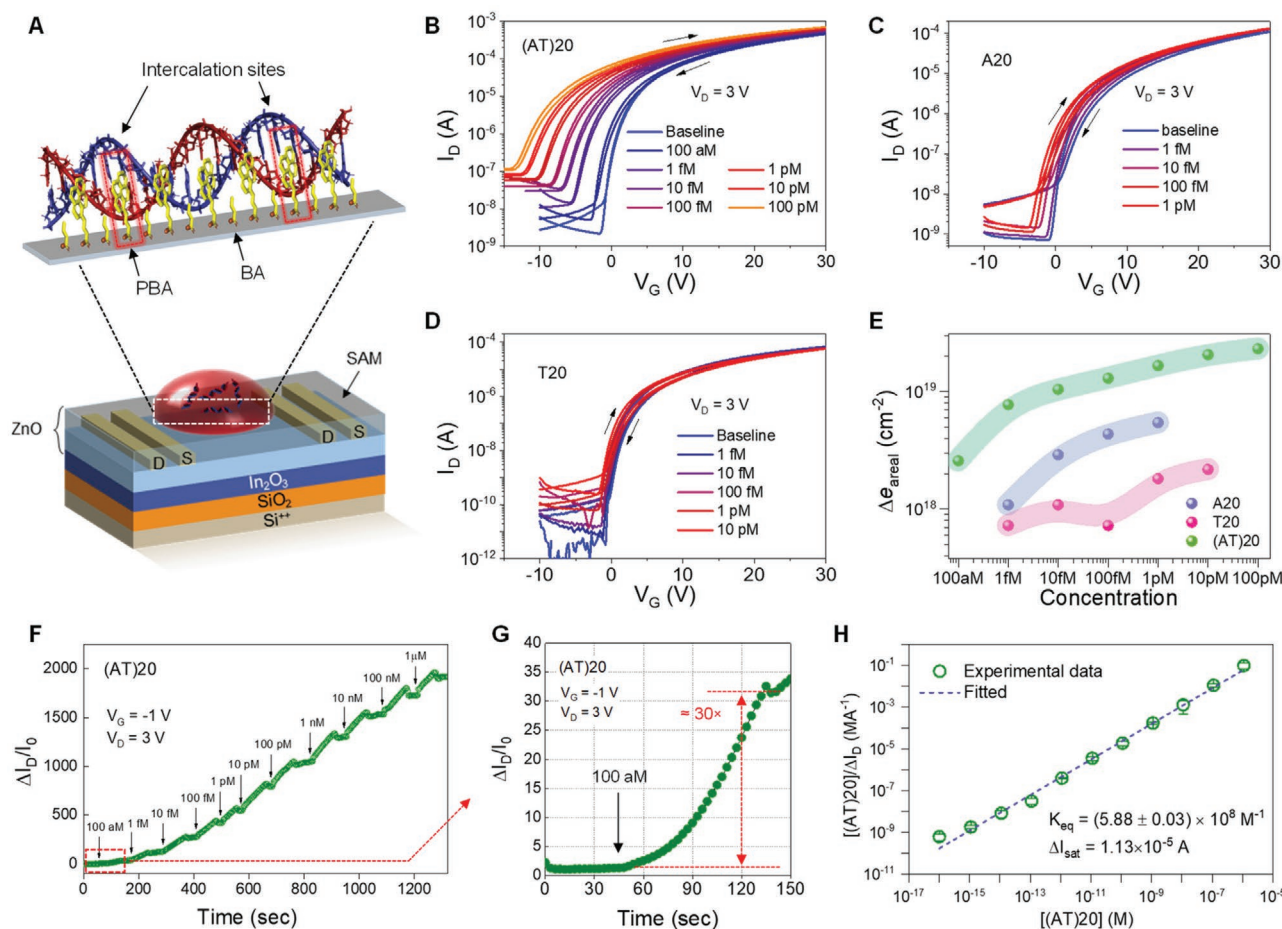


Figure 4. Tri-channel transistor sensor for synthetic DNA sensing. A) Illustration of the envisioned intercalation between the pyrene units and dsDNA. B–D) Transfer I – V characteristics ($V_D = 3$ V) measured from PBA/BA functionalized tri-channel transistor sensors with the presence of three types of DNA analytes: B) (AT)20; C) A20; D) T20 at different analyte concentrations. E) Plot of the increase in areal charge carriers Δe_{areal} that results from the sensing activity of the tri-channel transistor sensor to the analytes as a function of analyte concentration. Δe_{areal} is calculated from the shift in the turn-on voltage of the device upon the application of analyte solution. AT(20) shows the highest response due to its interaction via intercalation with pyrene units of the PBA-functionalized tri-channel transistor sensor. F) Real-time response measured from a PBA/BA-functionalized solid-state tri-channel transistor sensor operated at $V_G = -1$ V and $V_D = 3$ V upon exposure to synthetic (AT)20 with concentrations from 100×10^{-18} to 1×10^{-6} M. Panel (G) recorded response to 100×10^{-18} M showing ≈ 30 times enhancement in I_D . The arrows indicate the time when the different analyte concentrations were applied to the SC area of the tri-channel transistor. H) Fitting of experimental results of synthetic AT(20) sensing at different analyte concentrations according to the Langmuir adsorption isotherm. The error bars denote standard deviations from three real-time measurement sets.

reported to date for biosensing transistors, including liquid-gated devices.^[5–6,24] Importantly, the sensor's sensitivity can be tuned by the V_G as shown in Figure S17 in the Supporting Information where the S_{analyte} is plotted versus (AT)20 concentration for different V_G (-1 , 0 , $+1$ V). Even at suboptimal biasing conditions (i.e., $V_G = 1$ V), the measured I_D for 100×10^{-18} M (AT)20 increases to 4.2 μA ($\Delta I_D \approx 2.8$ μA), which is $\approx 300\%$ higher than the baseline signal ($I_0 \approx 1.4$ μA) (Figure 4B). The large ΔI_D indicates that the actual sensitivity of the tri-channel sensors is well below 100×10^{-18} M. To this end, we note that in the literature the most frequently reported parameter is the LoD, which is determined by the minimum detectable signals that are often far from suitable for real-time monitoring.^[5–6,40,53]

To further demonstrate the capabilities of our ultrahigh S_{analyte} tri-channel sensor, we analyzed the sensing kinetics using the linear form of the Langmuir adsorption isotherm.^[54,55] Figure S18A in the Supporting Information displays a series

of such measurements taken from Figure 4F but replotted by setting the time (t) at which the different concentrations of analyte were applied, to 0 s. Figure S18B in the Supporting Information shows a representative trace for 1×10^{-12} M of (AT)20 where three different sensing stages can be distinguished:

- Concentration-limited diffusion stage where an accelerated diffusion process takes place as the analyte concentration increases.
- Association of analyte with the tethered receptor moieties, i.e., “primary” sensing process.
- Dissociation of analyte–receptor complexes before reaching a thermodynamic equilibrium.

The rate of the “primary” sensing process shown in Figure S18B in the Supporting Information is representative of a zero-order reaction and is independent of the analyte

concentration or the method with which it is being applied. For each concentration, a distinct peak between association and dissociation stages is observed and attributed to the immobilization of analyte species by the tethered receptors.^[56–58] Therefore, and regardless of the sensing method, the existence of two-phase kinetics relates solely to the association and dissociation stages. Using the high-fidelity sensing data from Figure S18 in the Supporting Information, the equilibrium constant (K_{eq}) was calculated yielding values of $(5.88 \pm 0.03) \times 10^8 \text{ M}^{-1}$ (Figure 4H).

In addition to short synthetic DNA, we also tested natural dsDNA extracted from calf thymus tissue, which has much longer DNA sequences. Figure 5A,B, respectively, show the transfer characteristics ($V_D = 3 \text{ V}$) and real-time response recorded at fixed $V_D = 3 \text{ V}$ and $V_G = -1 \text{ V}$ (Figure S19, Supporting Information; $I_0 = 2.63 \times 10^{-8} \text{ A}$). The response is similar to that recorded for (AT)20 indicating that the sensing mechanism remains identical for the natural dsDNA. Even

when aM concentrations of the dsDNA is applied, the recorded signal ($\Delta I_D/I_0$) increases by more than 100 $\times$ (inset of Figure 5B), further corroborating the unprecedented sensitivity of the tri-channel sensor. When compared to (AT)20, the sensor exhibits stronger response to natural dsDNA with a higher binding constant K_{eq} of $(8.71 \pm 0.01) \times 10^9 \text{ M}^{-1}$ (Figure 5C). This difference is attributed to the stronger interaction between the longer sequence of calf thymus DNA and the surface-tethered pyrene receptor.

We further investigated the possibility of sensing the formation of the positively charged biotin–avidin pair—an important complex for biochemical analysis.^[59] For this sensing purpose, we functionalized the surface of ZnO with biotin, acting as the receptor, and then applied a DI-water-based solution containing avidin (analyte) at different concentrations. Figure 5D reveals a systematic shift in V_{ON} of the transistors toward more positive V_G with increasing avidin concentration. This trend indicates

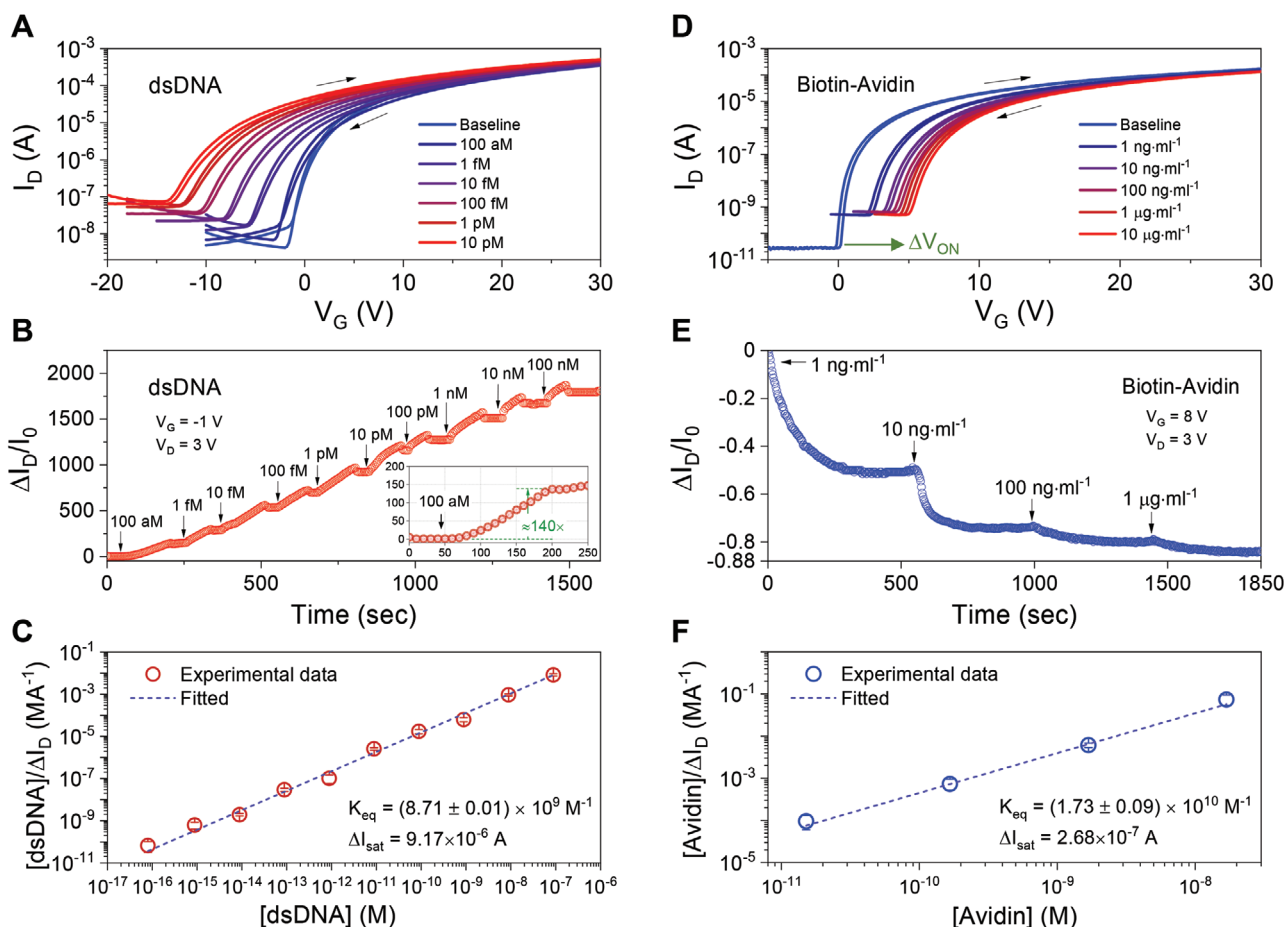


Figure 5. Attomolar detection of natural biomolecules. A) Transfer characteristics ($V_D = 3 \text{ V}$) of a PBA/BA-functionalized tri-channel transistor sensor measured in the presence of natural dsDNA extracted from calf thymus. B) Real-time response of a tri-channel transistor sensor to different concentrations (100×10^{-18} to $100 \times 10^{-9} \text{ M}$) of natural dsDNA. Inset: The sensor's response to $100 \times 10^{-18} \text{ M}$ of the analyte is ≈ 140 times higher than the baseline signal. For this experiment, the device was operated at $V_G = -1 \text{ V}$ and $V_D = 3 \text{ V}$. C) Fitting of the experimental results for natural dsDNA at different analyte concentrations according to the Langmuir adsorption isotherm. The error bars denote standard deviations from three real-time measurement sets. D) Transfer characteristics ($V_D = 3 \text{ V}$) measured from a biotin-functionalized tri-channel transistor sensor subject to different concentrations of avidin. E) Real-time response obtained from the biotin-based tri-channel transistor sensor biased at $V_G = 8 \text{ V}$ and $V_D = 3 \text{ V}$. The avidin concentration was varied from 10 ng mL^{-1} to $1 \mu\text{g mL}^{-1}$. The arrows indicate the time when the avidin was applied to the SC area of the sensor. F) Fitting of experimental results of avidin sensing at different analyte concentrations according to the Langmuir adsorption isotherm. The error bars denote standard deviations from three real-time measurement sets.

a continuously reducing electron concentration in the channel due to the positively charged nature of avidin and its electron accepting character. Figure 5E shows real-time sensing of different concentrations of avidin. A higher voltage bias setting that used $V_D = 3$ V and $V_G = 8$ V (Figure S20, Supporting Information; $I_0 = 1.89 \times 10^{-5}$ A) was employed to compensate for the depleted electron concentration in the channel (manifested as a positive shift in V_{ON}) due to the biotin–avidin association. Analysis of the binding constant between avidin and surface-immobilized biotin (Figure 5F), yields a K_{eq} of $(1.73 \pm 0.09) \times 10^{10} \text{ M}^{-1}$. The latter is lower than that reported for free avidin–biotin pairs (10^{13} – 10^{15} M^{-1})^[60–61]—a result attributed to the likelihood of the smaller quantity of tethered biotin receptors. It is noticeable that although biotin–avidin is known to be one of the strongest biological pairs, the sensitivity of the avidin sensor is lower than that of the dsDNA one due to the low charge density associated with avidin. Therefore, the binding strength between the receptor and analyte species does not appear to determine the sensitivity of the tri-channel sensor.

To summarize, the sensing mechanism in our all-solid-state tri-channel transistor sensors is different to that of liquid-gated sensor platforms.^[5–6,22–28] The sensing process was successfully modeled by considering the generation of free charges on the SC's surface upon receptor–analyte association (Figure 3G–L) and highlighted the strong coupling to the channel current. The higher gradients in the SC observed toward the HJ/analyte interface with a higher electron density highlights how majority carriers are introduced and transported across the device upon receptor–analyte interaction. Importantly, the sensor can be easily repurposed via receptor engineering to detect both negatively (DNAs) as well as positively charged analytes (biotin–avidin). In the case of biotin–avidin interaction, the channel current was shown to reduce due to the electron accepting nature of the formed complex. Another key feature of our tri-channel sensor is the large size SC and its ability to accommodate a high density of receptors, which enable dynamic sensing over an extraordinary wide range of analyte concentrations.

5. Detection of SARS-CoV-2 Spike S1 Protein

To demonstrate the potential of the tri-channel transistors in a real-world sensing scenario, we engineered our devices by immobilizing SARS-CoV-2 antibody acceptors designed for specific binding to the SARS-CoV-2 spike S1 protein (Figure 6A).^[53] The receptor-binding domain of the spike protein is known to bind the human cell receptor angiotensin-converting enzyme 2 (ACE2), followed by subsequent viral entry. During binding the positively charged polybasic cleavage site on the spike protein binds strongly with the negatively charged human cell receptor ACE2.^[62] We hypothesized that such an interaction induces electrostatic perturbations that could become detectable by the tri-channel transistor.

To test our hypothesis, we first examined the ability of the sensor to operate under physiological-relevant conditions. The electrical characteristics of the antibody-tethered sensor show negligible change upon application of different concentrations of the high ionic strength PBS solution directly onto the SC (Figures S21 and S22, Supporting Information). Next, a series of

PBS solutions containing different concentrations of the SARS-CoV-2 spike S1 protein were prepared and applied onto the SC while the transfer characteristics of the sensor were recorded for each analyte concentration (Figure 6B; Figure S23A, Supporting Information). A clear and systematic shift in V_{ON} toward more negative gate voltages with increasing analyte concentration is observed. Strikingly, even at $10 \times 10^{-18} \text{ M}$ the sensor's response remains large and clearly visible in the quasi-static transfer characteristics of Figure 6B, indicating a high sensitivity.

To demonstrate the versatility of our tri-channel sensor platform, we performed real-time sensing measurements of the SARS-CoV-2 spike S1 protein. Prior to this, the tri-channel sensor was biased at $V_G = -1$ V and $V_D = 3$ V to acquire a baseline channel current of $\approx 1 \mu\text{A}$ ($\Delta I_D/I_0 = 0$). Following, PBS solutions containing varying concentrations of the SARS-CoV-2 spike S1 protein were applied sequentially to the SC while the sensor current being recorded in real-time (Figure S23B, Supporting Information). Evidently, the sensor can detect the analyte across an ultrawide range of concentrations (10×10^{-18} to $100 \times 10^{-12} \text{ M}$) demonstrating the tremendous potential of the technology. Similar to dsDNA real-time sensing measurements, the recorded signal ($\Delta I_D/I_0$) for each concentration increases and reaches an equilibrium followed by a small dip due to the diffusion limited, association and dissociation stages discussed previously.

We also examined the specificity of our sensor toward the SARS-CoV-2 spike S1 protein by comparing its real-time response against that of Middle East respiratory syndrome coronavirus (MERS-CoV) spike protein due to their genome similarities.^[63] As can be seen in Figure 6C, the tri-channel sensor can differentiate between the two proteins under physiological relevant conditions. For the MERS-CoV protein, the sensor shows no response with the signal remaining largely unaltered with increasing analyte concentration from 1×10^{-15} to $100 \times 10^{-12} \text{ M}$. On the contrary, exposure to SARS CoV-2 spike S1 protein leads to a strong and systematic signal increase with increasing analyte concentration. The lowest concentration at which these differences are detectable can be deducted from Figure 6C yielding $\approx 1 \times 10^{-15} \text{ M}$.^[53] Finally, the $\text{LoD}^{[64]}$ was estimated by applying the International Union of Pure and Applied Chemistry (IUPAC) protocol^[65] to the calibration plot for SARS-CoV-2 spike S1 protein in Figure S23C in the Supporting Information yielding a value of $865 \times 10^{-18} \text{ M}$.

Finally, we examined the ability of our tri-channel sensor to detect the presence of the SARS-CoV-2 spike S1 protein directly in HS. Figure S24A in the Supporting Information displays the real-time response of the tri-channel sensor to tenfold HS (control sample) and the same HS containing different concentrations of the SARS-CoV-2 spike S1 protein. Unlike the negligible response observed toward the blank tenfold HS solution for up to 800 s (blue symbols), the sensor exhibits a clear response to HS containing SARS-CoV-2 spike S1 protein down to $1 \times 10^{-15} \text{ M}$ concentration in well under 2 min. Moreover, the sensor's response is linear across all studied concentrations with a coefficient of determination $R^2 = 0.98$ (Figure S24B, Supporting Information). These results further showcase the tremendous potential of our tri-channel oxide sensors for use in rapid point-of-care diagnosis of COVID-19 and beyond.

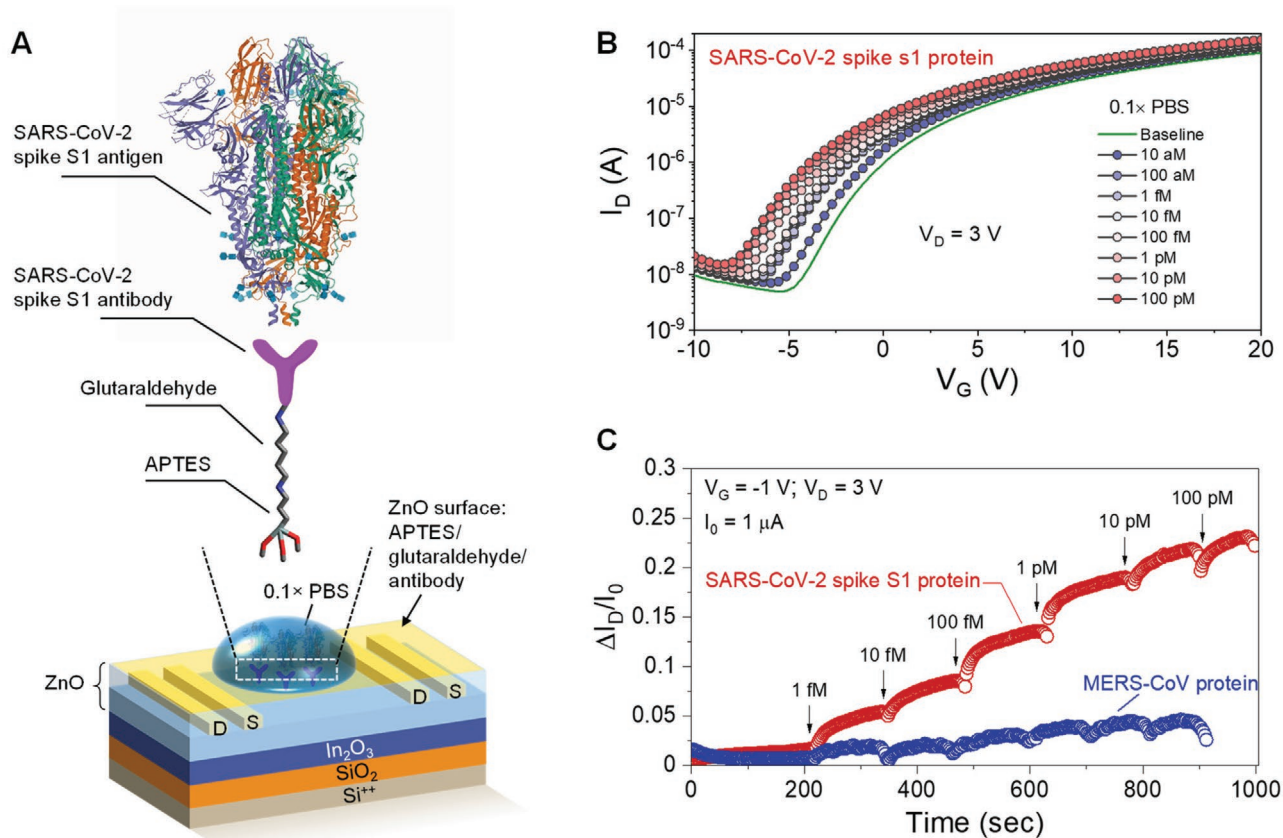


Figure 6. Detection of SARS-CoV-2 spike protein. A) Schematic of the SARS-CoV-2 spike S1 protein detection. The SARS-CoV-2 spike S1 antibody is anchored onto the sensor platform after the sequential modification of oxide surface with 3-aminopropyltriethoxysilane (APTES) and glutaraldehyde. B) Transfer characteristics ($V_D = 3$ V) of a fully functionalized tri-channel transistor sensor measured in the presence of the SARS-CoV-2 spike protein in 0.1× phosphate-buffered saline (PBS, baseline). C) Real-time response of the tri-channel transistor sensors to different concentrations (1×10^{-15} to 100×10^{-12} M) of the SARS-CoV-2 spike protein and the MERS-CoV protein in 0.1× PBS.

6. Conclusion

We developed simple-to-manufacture, millimeter-scale, all-solid-state metal oxide transistor sensors that can detect the presence of various biomolecules down to attomolar concentrations in real time while being operated under physiologically relevant environments. Our study highlights a new tri-channel concept that combines high sensitivity and a large dynamic range in an all-solid-state platform fully compatible of sensing liquid-phase analytes. The versatile surface chemistry of the metal oxide semiconductors employed allows for the incorporation of different receptor units (e.g., antibodies, enzymatic recognition elements, aptamers), which is anticipated to enable the detection of a broader range of biomolecules with high reliability, sensitivity, and specificity. Furthermore, the ability to distinguish between negatively and positively charged biomolecules as well as between the SARS-CoV-2 and MERS-CoV spike proteins, under physiological relevant environments, showcases the universality of the sensing platform, which can be readily exploited for addressing most urgent and practical sensing applications.

7. Experimental Section

Preparation of Metal-Oxide Precursors: ZnO and In₂O₃ precursor solutions were prepared by dissolving zinc oxide (99.99%; Sigma-Aldrich) in ammonium hydroxide (50% v/v; Alfa Aesar) at a concentration of 10 mg mL⁻¹ and anhydrous indium nitrate (99.99%; Indium Corporation) in 2-methoxyethanol (99.8%; Sigma-Aldrich) at a concentration of 20 mg mL⁻¹, respectively. As-prepared solutions were then stirred rigorously at room temperature for 24 h before use. This process yielded clear transparent oxide precursor solutions.

Fabrication of Low-Dimensional Oxide Transistors: Heavily doped silicon (Si⁺⁺) wafers with a thermally grown SiO₂ top-layer (100 nm) were used as the common gate electrode and the gate dielectric, respectively. Prior to the semiconductor deposition, the substrates were sonicated in a solvent bath each lasting for ≈ 10 min in the following sequence: 1) DI water with a Decon 90 detergent (5 vol%); 2) DI water; 3) acetone; 4) isopropanol. The solvent residue was dried with dry nitrogen over the substrate surface. As the last cleaning step, the substrates were exposed to ultraviolet (UV) ozone treatment for 10 min. The In₂O₃ ultrathin film was deposited by carrying out spin-casting of the as-prepared precursor solution onto the Si substrates at 6000 rpm for 30 s in ambient air, followed by a postdeposition thermal-annealing process for 60 min at 200 °C in ambient air. The top ZnO layer was deposited with the same procedure as that for the In₂O₃ layer. Fabrication of the transistors (channel width/length = 1000/100 μ m/ μ m) was completed with thermal evaporation of 40 nm thick Al top source and drain (S–D) electrodes through a shadow mask in high vacuum ($\approx 10^{-6}$ mbar).

Transistor Characterization: Electrical characterization of transistors was carried out using three micropositioners (EB-700, EVERBEING), a homemade probe station, and an Agilent B2902A source/measure unit. It was noted that all the voltages and currents of transistors described in this work were referenced to the source contact electrode.

Self-Assembled Layer Preparation and Surface Modification: To prepare the modified device for DNA sensing, first, PBA (97%; Sigma-Aldrich) solution (1 mg mL⁻¹ in anhydrous tetrahydrofuran (THF)) was applied on the surface of the transistor for 30 min and thoroughly rinsed with THF and dried under nitrogen atmosphere. BA (≥99%; Sigma-Aldrich) solution (1 mg mL⁻¹ in anhydrous THF) was then applied to the PBA modified surface for 30 min and thoroughly rinsed with THF and dried under nitrogen atmosphere. To prepare the modified device for avidin sensing, biotin (99%; Sigma-Aldrich) solution (0.8 mg mL⁻¹ in anhydrous ethanol) was first applied on the surface of the transistor for 30 min and thoroughly rinsed with ethanol and dried under nitrogen atmosphere. BA was then applied to fully passivate the uncovered surface following the same procedures above as for DNA sensor devices.

Analyte Preparation and Sensing: Deoxyribonucleic acid from calf thymus (Type XV, Activated, lyophilized powder), avidin (lyophilized powder, ≥10 units mg⁻¹ protein), A20, T20, and (AT)20 were purchased from Sigma and used as received. All analytes were well dissolved in MilliQ water (18.2 MΩ cm/25 °C) to reach the desired concentration according to the solution preparation instruction provided by the supplier. For the sensing process, the analyte solution was constantly applied onto the sensing area, and the electrical properties of the sensor devices were then recorded. For the real time sensing, the channel current was monitored during the continuous and consecutive application of analyte solution of different concentrations onto the same sensor device.

Ultraviolet–Visible Spectroscopy Measurements: The UV–vis transmission measurements were performed using a Shimadzu UV-2600 UV-Vis spectrophotometer. The samples were prepared on quartz substrates using the same deposition parameters described in the Experimental Section for oxide thin-film deposition and self-assembled monolayer formation.

High-Resolution Transmission Electron Microscopy Measurement: The samples for HRTEM analysis were prepared using the focused ion beam processing technique. A gold-plated layer with thickness of 5 nm was coated on sample via sputtering before the sample preparation to make its surface more conductive. The HRTEM images were acquired at 300 kV by a FEI Titan G2 80-300 microscope equipped with a high-brightness Schottky-field emission electron source and a high-resolution Gatan imaging filter Tridiem energy-filter.

Atomic Force Microscopy Measurement: Atomic force microscopy study was carried out in tapping mode using an Agilent 5500 atomic force microscope in ambient atmosphere. The approximate resonance frequency of the cantilever was 280 kHz and the force constant was 60 N m⁻¹.

Scanning Kelvin Probe Measurement: Scanning Kelvin probe investigations were carried out using a KP Technology system (model SKP5050/APS02) with a 1 mm tip. Scanning was achieved by taking an individual KP measurement in one location and then moving the motorized stage to bring the sample in position for the next KP measurement. This was repeated until data were gathered in a grid pattern of 60 × 60 points, spanning an area of ≈4 mm × 4 mm. For each point location, the tracking feature built into the software made sure to keep the average tip-to-sample-distance constant. Additional drain bias in the range of 0 to 3 V was applied using a Keithley B2400 Source-Meter unit. The WF and E_F values were calculated using Silver as the reference material. All measurements were carried out in ambient air at room temperature and relative humidity of ≈25%.

Real-Time Sensing Data Analysis of (AT)20, Natural dsDNA from Calf Thymus, and Avidin: To analyze the real-time response of the synthetic dsDNA (AT)20 (Figure 4H), natural dsDNA (Figure 5C), and avidin (Figure 5F), the sensing results at different analyte concentrations were fitted according to the linear Langmuir adsorption isotherm equation^[52]: $C_{\text{analyte}}/\Delta I_D = C_{\text{analyte}}/\Delta I_{\text{sat}} + 1/\Delta I_{\text{sat}}K_{\text{eq}}$, where ΔI_{sat} is the

estimated change of the saturated channel current upon increasing the concentration of analyte, and K_{eq} is the binding constant of analyte with its corresponding receptor.

Solution Preparation and Device Fabrication for Spike Protein Sensing Experiments: 3-Aminopropyltriethoxysilane (APTES) solution (99%), glutaraldehyde (GA) solution (70% in H₂O), bovine serum albumin (BSA, A2153), PBS (pH 7.4, 10×), and human serum (H4522) were purchased from Merck. SARS-CoV-2 spike S1 antibody (40150-R007), SARS-CoV-2 (2019-nCoV) Spike S1-His Recombinant Protein (40591-V08B1), and MERS-CoV Spike/S1 Protein (S1 Subunit, aa 1-725, His Tag) (40069-V08H) were purchased from Sino Biological (China). All chemicals were used as received without further purification. Stock solutions of spike proteins were prepared using nuclease-free water and further diluted to different concentrations in 0.1× PBS where necessary. For the SARS-CoV-2 spike protein sensing, the tri-channel transistors were first treated with UV-irradiation for 10 min, APTES solution (2 wt%) in toluene was pipetted onto the oxide surface and left for 15 min, followed by rinsing with toluene and annealing at 120 °C for 1 h. A GA linker was added to the terminal amino (–NH₂) groups of APTES using a solution of 0.8% GA in DI water for 10 min at room temperature, followed by rinsing with DI water and drying with compressed N₂ gas. The BSA (100 μg mL⁻¹) in PBS was added to the SC for 30 min to prevent the nonspecific bindings of the channel surface, followed by rinsing with PBS. In the following, a concentration of 200 μg mL⁻¹ of spike antibody solution was dropped onto the functionalized device and kept at room temperature for 5 h in order to immobilize the spike S1 antibodies via covalent bonding. To complete the immobilization process, the devices were rinsed with 0.1× PBS to remove unbound antibodies. The human serum was filtered using 0.2 × 10⁻⁶ m pore size Whatman syringe filter (6870-1302) and tenfold diluted in 0.1× PBS for real sample analysis. The SARS-CoV-2 spike structure in Figure 6A was adopted from the PDB ID:6VYB.^[66]

Device Modeling and Simulations: Oxide transistor sensors were modeled and simulated using the semiconductor module in COMSOL Multiphysics. The material and device parameters used in the modeling in this work were adopted from the previous studies on the same materials.^[32,67–68] The cross-sectional model was constructed based on the actual device dimensions shown in Figure S4 in the Supporting Information. The oxide semiconductors were modeled based on their material parameters taken from the previous reports.^[32–33,69] The In₂O₃/ZnO interface was modeled as a continuous quasi-Fermi-level heterojunction. The S–D electrodes were modeled as Ohmic contacts while the gate was modeled using the Thin Insulator Gate node, employing the same SiO₂ dielectric condition as the actual device stack. The analyte was modeled as equivalent surface charges. All the other boundaries were modeled as insulations, indicating no normal flux such as current and electric displacement filed. Due to the large aspect ratio of the ultrathin oxide structures, the mapped mesh was generated for the entire transistor channel area with fine rectangular meshes. The modeling data displayed in Figure 3 and Figures S10–S12 in the Supporting Information were based on the condition along the *a*–*b* plane shown in Figure S8B in the Supporting Information, followed by integration along the *c*–*d* direction (Figure S8B, Supporting Information) for half of the length of the SC region. This approach helps to overcome limitations associated with the desktop version of the COMSOL in solving high mesh densities based on the finite element analysis.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords

large-area electronics, metal oxide semiconductors, SARS-CoV-2, solid-state devices, solution process, transistors sensors

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