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Narrower Nanoribbon Biosensors Fabricated by Chemical Lift-off Lithography Show Higher Sensitivity

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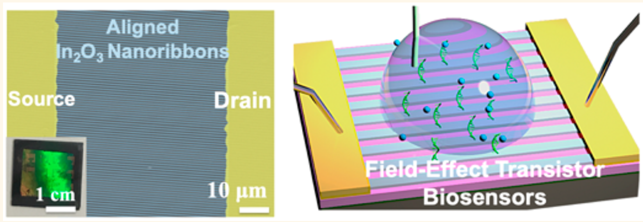
ABSTRACT: **Wafer-scale nanoribbon field-effect transistor (FET) biosensors fabricated by straightforward top-down processes are demonstrated as sensing platforms with high sensitivity to a broad range of biological targets. Nanoribbons with 350 nm widths (700 nm pitch) were patterned by chemical lift-off lithography using high-throughput, low-cost commercial digital versatile disks (DVDs) as masters. Lift-off lithography was also used to pattern ribbons with 2 μm or 20 μm widths (4 or 40 μm pitches, respectively) using masters fabricated by photolithography. For all widths, highly aligned, quasi-one-dimensional (1D) ribbon arrays were produced over centimeter length scales by sputtering to deposit 20 nm thin-film In_2O_3 as the semiconductor. Compared to 20 μm wide microribbons, FET sensors with 350 nm wide nanoribbons showed higher sensitivity to pH over a broad range (pH 5 to 10). Nanoribbon FETs functionalized with a serotonin-specific aptamer demonstrated larger responses to equimolar serotonin in high ionic strength buffer than those of microribbon FETs. Field-effect transistors with 350 nm wide nanoribbons functionalized with single-stranded DNA showed greater sensitivity to detecting complementary DNA hybridization *vs* 20 μm microribbon FETs. In all, we illustrate facile fabrication and use of large-area, uniform In_2O_3 nanoribbon FETs for ion, small-molecule, and oligonucleotide detection where higher surface-to-volume ratios translate to better detection sensitivities.**



KEYWORDS: *chemical lift-off lithography, soft lithography, nanofabrication, small-molecule sensing, DNA hybridization*

Label-free, ultrasensitive chemical and biological sensors that monitor biomarkers in body fluids and tissues have broad applications in healthcare and biomedical research, including cancer diagnostics,[1,2] DNA detection,[3−6] bacteria and virus detection,[7−9] and metabolite monitoring.[10−14] Developing sensors that provide accurate, real-time information regarding multiple analytes with high sensitivity and selectivity is at the heart of next-generation personalized medical devices, such as point-of-care measurements and implantable and wearable sensors.[15−25] Nanoelectronic field-effect transistor (FET) biosensors have been explored as platforms having unique properties and advantages toward the realization of these applications.

Indium oxide has been used to fabricate FET sensors with higher sensitivities, more straightforward surface functionalization, and greater stability in aqueous environments compared to other channel materials, including graphene and MoS_2.[26−28] Moreover, compared to other metal oxides, such as indium−gallium−zinc oxide, In_2O_3 is stable in buffers simulating physiological environments.[29,30] Bottom-up strategies were used to prepare In_2O_3 nanowires for use as gas sensors, chemical sensors, biosensors, and optical detectors.[31−34] However, similar to other bottom-up fabricated FETs, such as Si nanowires or carbon nanotubes, bottom-up fabricated In_2O_3 nanowire sensors suffer from poor device-to-device reproducibility due to random orientations and variable numbers of nanowires between electrodes.[35,36]

In contrast, top-down fabrication strategies, for example, soft lithography, soft lithographic molecular printing,[37−39] nanoimprint lithography,[40,41] and nanotransfer printing,[42−45] provide precise control over the morphologies and shapes of nanomaterials. Top-down In_2O_3 nanoribbons fabricated by straightforward photolithographic processes and low-temperature sputtering methods show high device uniformity and

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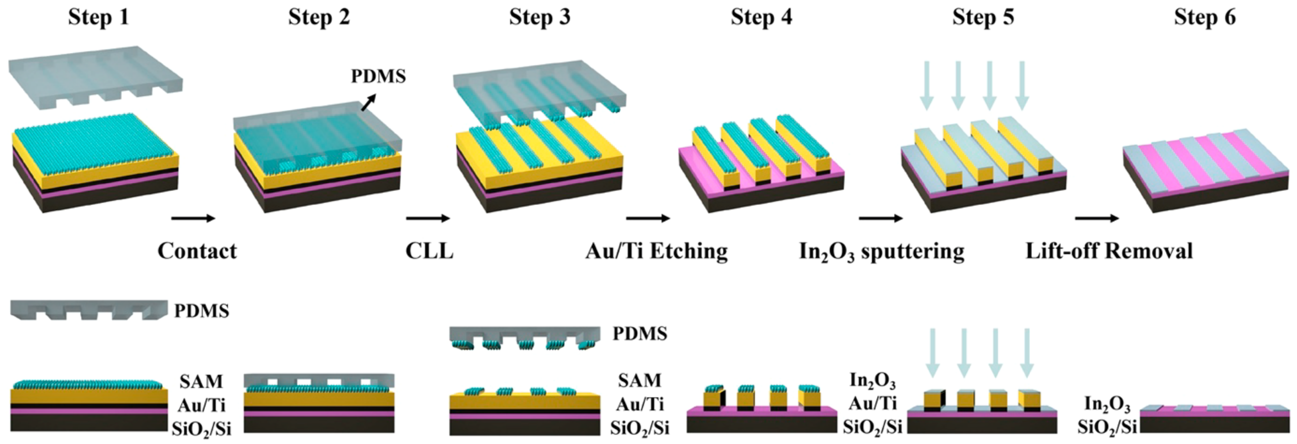

Figure 1. Schematic illustration of the fabrication process for In_2O_3 nanoribbons. Step 1: A Au layer (30 nm) was deposited over Ti (30 nm) on Si/SiO_2 (100 nm). A monolayer of 11-mercapto-1-undecanol was then self-assembled on the Au surface. Step 2: An oxygen plasma "activated" polydimethylsiloxane (PDMS) stamp with micro- or nanoribbon features was brought into conformal contact with the substrate. Step 3: Stamp removal from the surface (chemical lift-off lithography, CLL) lifted off self-assembled molecules in the contacted areas. Step 4: Selective etching processes removed Au and Ti in the unprotected (contacted) regions on the surface. Step 5: Sputtering was used to deposit In_2O_3 (20 nm) over the entire substrate. Step 6: The remaining Au/Ti structures were removed to obtain In_2O_3 nanoribbon arrays.

reproducibility.[30] We previously developed a lithography-free process involving sputtering In_2O_3 through shadow masks to fabricate ribbons of 25 μm width, ~16 nm thickness, and 500 μm length over centimeter scales.[30,46,47] These devices (previously referred to as nanoribbons due to the nanoscale height of the sputtered In_2O_3) had high field-effect mobilities (>13 $cm^2\ V^{-1}\ s^{-1}$), large current on/off ratios (>10^7),[30,46] and functioned as sensors in a variety of applications including pH sensing, cardiac biomarker detection, and wearable sensors for glucose monitoring.[30,46,47] Flexible multifunctional sensor arrays incorporating these 25-μm-wide ribbons have also been developed to measure temperature, pH, and the neurotransmitters serotonin and dopamine, simultaneously.[48] Nonetheless, ribbons fabricated *via* shadow masks are limited in lateral resolution to tens of microns.

Surface-to-volume ratio is a critical parameter impacting nanobiosensor sensitivity, where higher ratios result in greater target sensitivities.[32,36,49−55] Here, we advance a generalizable, facile, top-down strategy for fabricating highly aligned In_2O_3 nanoribbons.[56,57] We employ chemical lift-off lithography (CLL), which is a soft lithography patterning approach that is cleanroom-free, high-throughput, and high-fidelity and enables micro- and nanopatterning to produce features as small as 15 nm.[58−65] In CLL, polydimethylsiloxane (PDMS) stamps with desired patterns are used to remove molecules self-assembled on Au surfaces selectively in the stamp contact areas. The remaining molecules in the noncontacted regions act as resists during wet etching to form three-dimensional features. We used CLL to pattern Au micro- and nanostructures, including Au nanoribbon, disk, square, and circle arrays, and to pattern other metal and semiconductor surfaces.[26,56,62,66]

Here, we combined sputtering with CLL to produce 20 nm thin-film In_2O_3 ribbons at 350 nm, 2 μm, or 20 μm widths and wafer scales. As-fabricated ribbons were aligned between source and drain electrodes with controllable orientations, numbers, and sizes. Micro- and nanoribbon FET biosensors with different aspect ratios were characterized and compared. The 350 nm wide nanoribbon FETs showed sensitivities for target detection greater than those of 20-μm-wide microribbon FETs, providing further evidence for the concept that higher surface-to-volume ratios confer greater sensitivities in nano-biosensing applications.

RESULTS AND DISCUSSION

The general In_2O_3 micro- and nanoribbon fabrication process is shown in Figure 1 and is described in detail in Materials and Methods. We fabricated ribbon features for subsequent In_2O_3 sputtering followed by a process to remove Au/Ti features, leaving behind In_2O_3 micro- or nanoribbons. We used commercial digital versatile disks-recordable (DVD-R) as templates to fabricate 350-nm-wide nanoribbons. These disks are economical, easily accessible masters (<\$0.5/disk). Blank DVD-R disks contain sub-micrometer grating features.[56,57] The DVD-R masters were prepared by a straightforward separation and rinsing process as previously described.[54,55] Hard PDMS (*h*-PDMS) was used to replicate the high-aspect-ratio DVD-R features.[56,57]

The DVD-R nanoribbon features, transfer of these features to *h*-PDMS, and further transfer to alkanethiol monolayers on Au have been characterized.[56,57] Previously, we deposited In_2O_3 *via* a sol−gel process with the Au/Ti layers deposited on top.[56] The self-assembled monolayers (SAMs) on Au were then patterned. The Au/Ti areas that were not contacted by activated *h*-PDMS served as wet etching masks. The stamp-contacted/exposed Au/Ti features were etched to expose the underlying In_2O_3.

Our previous patterning approach resulted in overetching, which limited precise patterning.[56] Even when overetching was avoided, etching undercut the protective Au/Ti features to produce In_2O_3 nanoribbons that were narrower and less reproducible compared to the features of the masters.[56,57] Further, nanoribbons patterned using the previous method had a high degree of line-edge roughness. Here, we addressed these previous shortcomings by sputtering thin-film In_2O_3 *after* Au/Ti etching, resulting in high-fidelity In_2O_3 nanoribbons fabricated over large areas.

Sputtering of In_2O_3 was carried out normal to the substrate surface such that undercut of the Au/Ti structures did not influence the widths of the resulting In_2O_3 nanoribbons. Nanoribbons (350 nm) were imaged before and after the lift-off process using atomic force microscopy (AFM), as shown in

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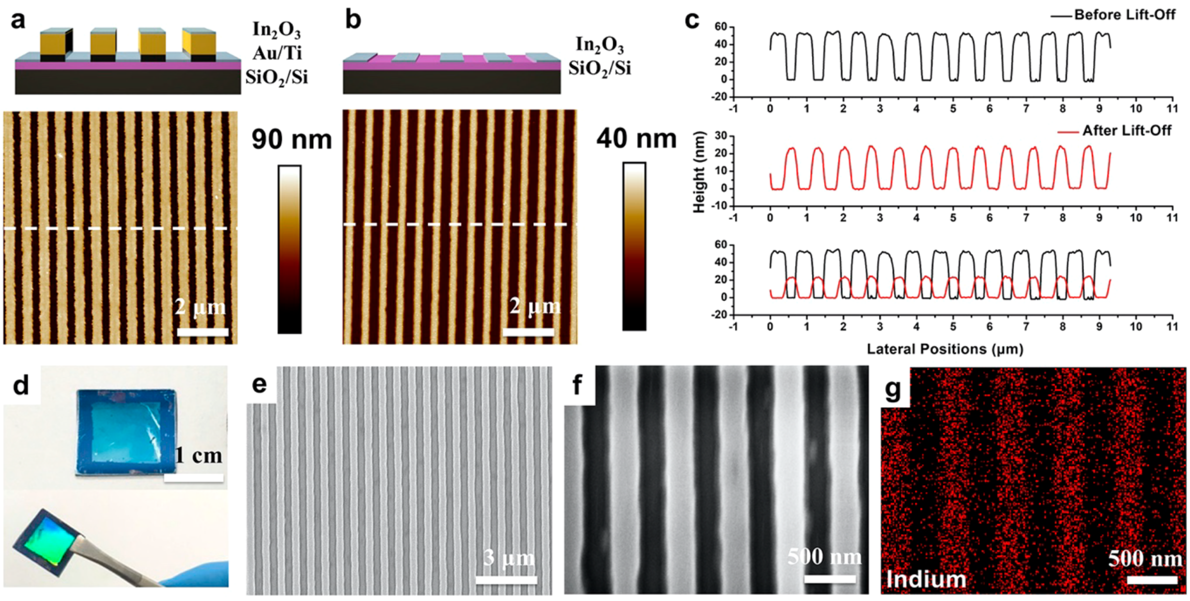

Figure 2. Atomic force microscope (AFM) images of 350 nm nanoribbon substrates (a) before (Step 5, Figure 1) and (b) after removing underlying Au structures (Step 6, Figure 1). (c) Height profiles from the AFM images in (a,b) across the nanoribbons. (d) Photographs of In_2O_3 nanoribbons at different viewing angles. (e,f) Scanning electron microscope (SEM) images of 350 nm wide In_2O_3 nanoribbons. (g) Energy-dispersive X-ray mapping of indium corresponding to the SEM image in (f).

Figure 2. Using the present fabrication process, In_2O_3 nanoribbons had heights of ~60 nm after In_2O_3 sputtering (Figure 2a), corresponding to the sum of the heights of the underlying Au and Ti layers. Sputtering does not add to the apparent height difference as In_2O_3 was sputtered atop both the patterned Au and the interleaved Si areas.

After the Au/Ti nanoribbon structures (and the overlying In_2O_3) were removed, uniform and continuous In_2O_3 nanoribbons with 350 nm widths and 20 nm heights remained, as shown *via* AFM (Figure 2b). To compare the widths and heights of the ribbons before and after removal of the Au templates, height profiles along the nanoribbons were analyzed (Figure 2c). The widths of In_2O_3 nanoribbons matched the spacing between the Au nanoribbons, demonstrating high-fidelity patterning and features characterized by sharp edges and high continuity.

Nanoribbons were fabricated on 1.5 cm × 1.5 cm Si wafers. The light blue In_2O_3 nanoribbon patterned region in the center of a representative wafer showed a strong iridescence when viewed at nonperpendicular angles under white light, indicative of periodic (diffraction) grating patterns on the surface (Figure 2d). Scanning electron microscopy (SEM) indicated that nanoribbons were continuous over tens of microns and highly defined at the single nanoribbon scale (Figure 2e,f). Energy-dispersive X-ray (EDX) mapping was performed (Figure 2g), where the indium $L_{\alpha 1}$ energy of 3.286 keV (Figure S1) was mapped and calculated (Table S1). The EDX images showed In_2O_3 nanoribbons with ~350 nm widths, consistent with the results from AFM and SEM imaging.

To construct micro- and nanoribbon FETs, the orientations of well-aligned In_2O_3 structures were identified by AFM or SEM. Source and drain electrodes were then fabricated perpendicular to the nanoribbons (Figure 3a) or microribbons. The Au/Ti source and drain electrodes were deposited on top of as-prepared In_2O_3 ribbons *via* electron-beam (e-beam) evaporation. Interdigitated electrodes with lengths of 1300 μm and widths of 45 μm were prepared (Figure S2). Electrodes aligned well with as-fabricated 350 nm wide In_2O_3 nanoribbons, as shown in the SEM images in Figure 3b,c. Substrates with 2- or 20-μm-wide In_2O_3 microribbons similarly demonstrated well-aligned configurations between the ribbons and electrodes (Figure 3d,e and Figure S3).

As discussed above and previously reported,[35,36] the orientations and numbers of nanowires or nanoribbons are challenging to control using bottom-up approaches. By contrast, using a top-down CLL patterning approach, orientations and numbers of ribbons were straightforwardly controllable based on the widths and pitches of the ribbons and the widths of the electrodes. For example, ~1850 350-nm-wide In_2O_3 nanoribbons were incorporated and aligned with each pair of electrodes. Transistor performances were tested using a bottom-gate top-contact configuration, where p^{++} Si served as the bottom gate and SiO_2 as the gate dielectric (Figure 3f). Transfer and output curves for 350-nm-wide In_2O_3 nanoribbon FETs are shown in Figure 3g,h, respectively, demonstrating current on/off ratios >10^6. The FETs with 2- or 20-μm-wide ribbons, or continuous thin-film In_2O_3 FETs showed similar characteristics in solid-state measurements (Figure S4).

The electrical performance of 350-nm-wide nanoribbon FET devices in a liquid environment was tested using solution gating, which corresponds to how devices were used for biosensing (*vide infra*). Each device was covered with a PDMS well filled with an electrolyte solution (Figure 4a). A Ag/AgCl reference electrode was used to apply a bias voltage through the electrolyte solution to gate each FET. Transfer and output curves for liquid-gated 350-nm-wide In_2O_3 nanoribbon FETs in phosphate-buffered saline (PBS) are shown in Figure 4b,c, respectively. The nanoribbon FETs fabricated here operated in a liquid environment with current on/off ratios of 10^3, transfer curve saturation behavior, low gate leakage currents (Figure 4d and Figure S5), and low driving voltages. Microribbon FETs with different widths or continuous thin-film FETs showed similar liquid-state performance characteristics (Figure S6).

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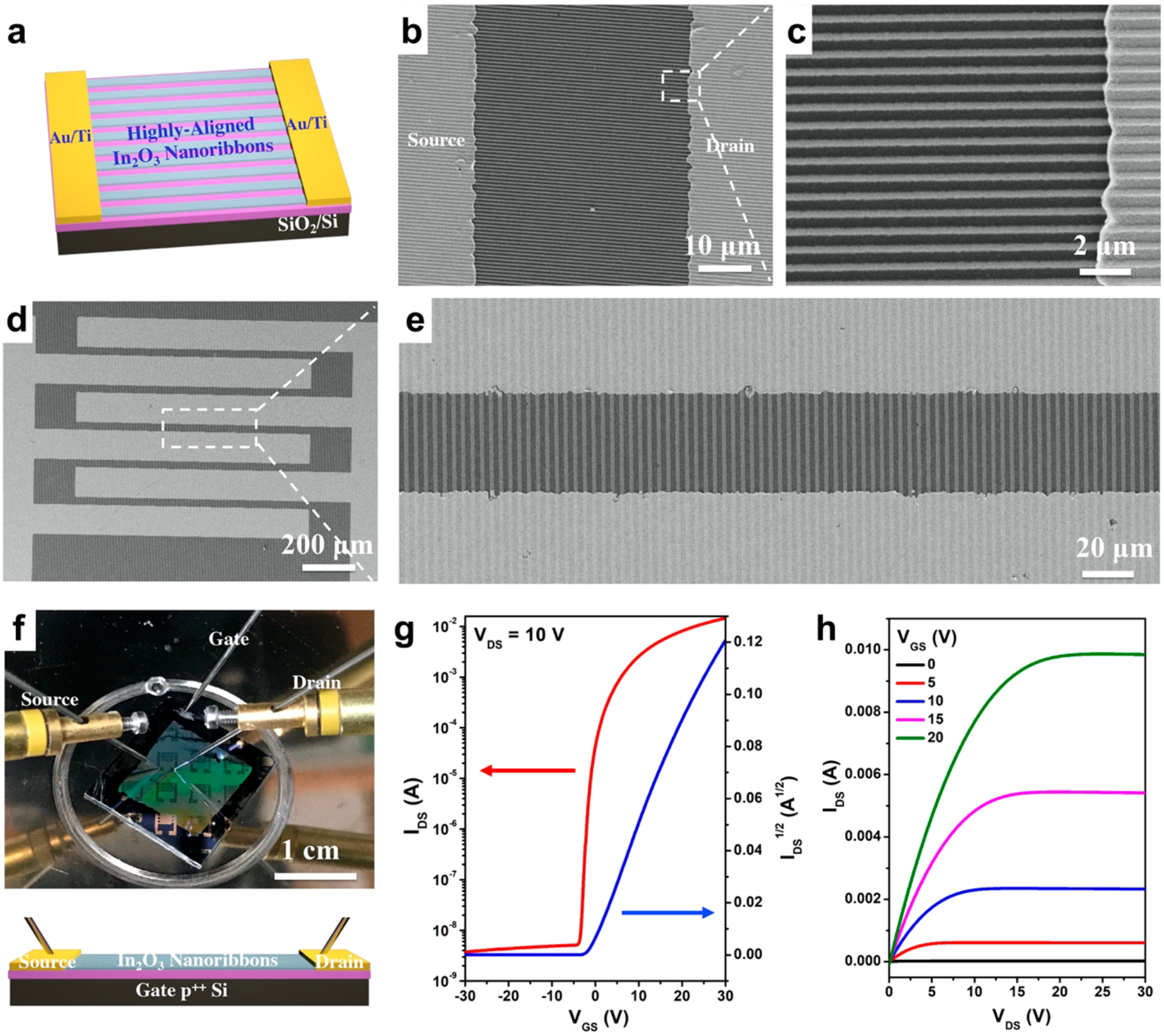

Figure 3. (a) Schematic illustration of the field-effect transistor (FET) configuration using In_2O_3 nanoribbons (or microribbons) as the channel material aligned perpendicular to source and drain electrodes. (b,c) Scanning electron microscope images of 350-nm-wide In_2O_3 nanoribbons with source and drain electrodes. (d,e) Scanning electron microscope images of 2-μm-wide In_2O_3 nanoribbons with source and drain electrodes. (f) Photograph (top) and schematic illustration (bottom) of the solid-state measurement setup for In_2O_3 nanoribbon (and microribbon) FETs, where p^{++} Si serves as the bottom gate. The lavender layer is SiO_2. Transfer (g) and output (h) characteristics of representative 350 nm In_2O_3 nanoribbon FETs.

Ion-sensitive FETs (ISFETs), where FETs respond to changes in environmental ion concentrations, are used for a majority of FET chemical and biological sensing applications.[67−71] To investigate the performance of In_2O_3 nanoribbon ISFETs, we conducted pH sensing by systematically increasing the hydrogen ion concentrations of the solutions contacting FETs. We previously compared the pH sensitivities of 25-μmwide In_2O_3 ribbon FET sensors having different ribbon heights.[30] Microribbons having thinner, 10- or 20-nm In_2O_3 films showed higher sensitivities to pH compared to thicker microribbons (*e.g.*, 50-nm In_2O_3 films). Here, micro- and nanoribbons with constant 20 nm heights were used to compare the effects of changing ribbon widths.

Threshold voltage changes of ISFETs were determined for 350-nm-wide nanoribbons from pH 5 to 10. Representative transfer curves (drain current to gate voltage) are shown in Figure 4d. Time-related increases in drain current were observed with decreasing pH values (Figure 4e), which is typical for *n*-type semiconductor gate-voltage modulation behavior.[27,46,47] At lower pH values, there are greater numbers of positively charged hydrogen ions in solution, leading to higher currents as more negative charge carriers are generated in *n*-type channels. Here, In_2O_3 was functionalized with (3-aminopropyl)triethoxysilane (APTES), where the terminal amine undergoes protonation and deprotonation with changes in pH. Notably, In_2O_3 FETs are less stable at low pH due to the chemical nature of metal oxides, which react with acids to form salts.[56]

Relative pH sensing responses for 350-nm *vs* 20-μm-wide In_2O_3 nanoribbon FETs were compared (Figure 4f). Device currents for both configurations increased as the [H^+] increased (*i.e.*, pH decreased). Surface-to-volume ratios for FETs with different ribbon widths were calculated (see Supporting Information, Figure S7). Ribbons with 350 nm widths had a 10% increase in surface-to-volume ratio compared to ribbons with 20 μm widths (Table S2). Yet, this modest increase in surface-to-volume ratio was sufficient to produce increased pH sensitivity, particularly at lower pH (P < 0.01) (see Table S3 for full statistics). These findings provide

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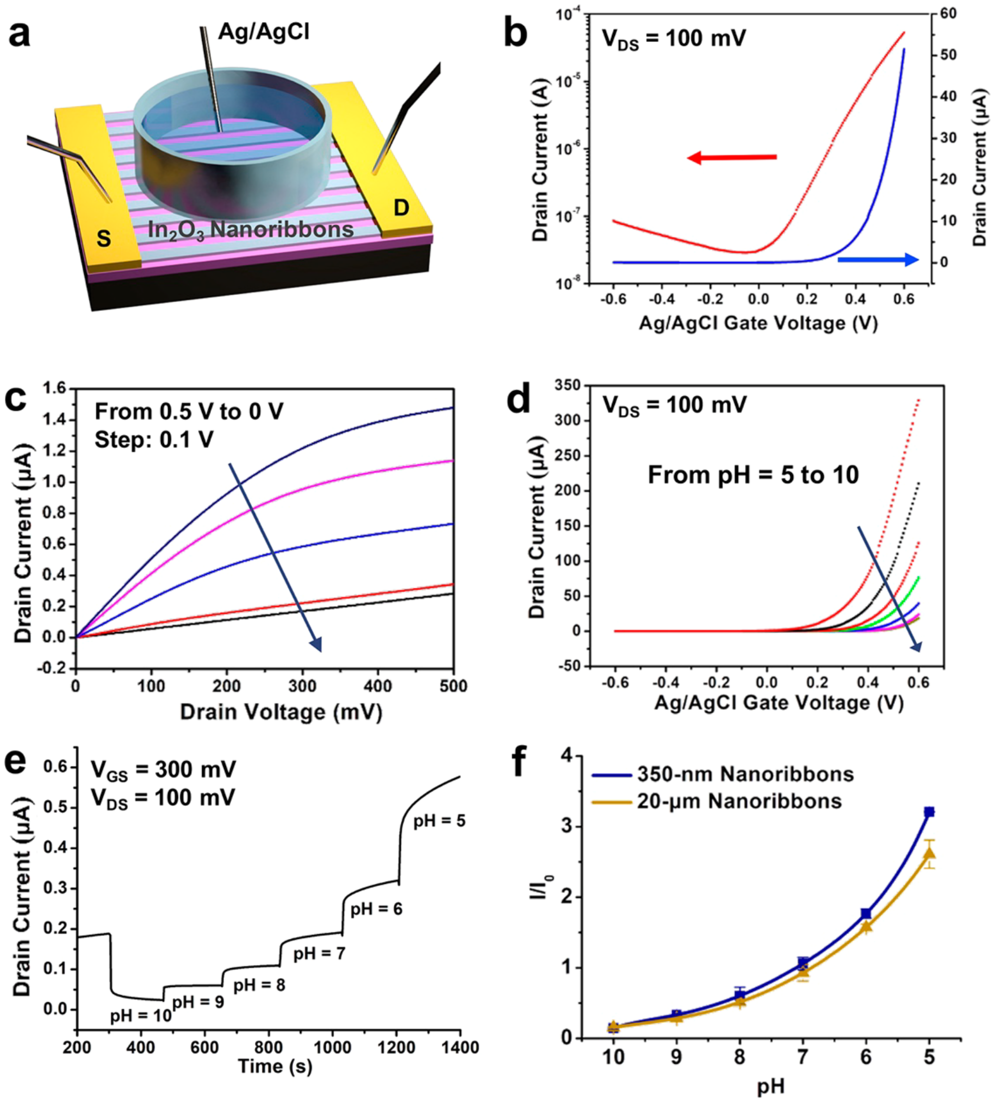

Figure 4. (a) Schematic illustration of a liquid state measurement where a Ag/AgCl electrode serves as the top gate. Transfer (b) and output (c) characteristics of 350-nm-wide In_2O_3 nanoribbon field-effect transistors (FETs) in the liquid-gate setup shown in (a). (d) Transfer curves of 350-nm-wide In_2O_3 nanoribbon FETs in solutions of pH 10 to 5. (e) Real-time current responses from a representative 350-nm-wide In_2O_3 nanoribbon FET exposed to commercial buffer solutions of pH 10 to 5. (f) Current responses relative to baseline for solutions of pH 10 to 5 using 350-nm- or 20-μm-wide ribbon In_2O_3 FETs. I/I_0 is current normalized to the baseline pH before the experiments (I_0, pH 7.4). Error bars are standard errors of the means with $N = 3$ FETs for each configuration.

evidence that FETs with nanoscale features having higher surface-to-volumes are associated with higher ion sensitivities.

Debye screening in high ionic strength solutions presents challenges for FET biosensing in physiological environments.[49,72,73] Overcoming Debye-length limitations enables the detection of biological targets *ex vivo* and *in vivo* to extend potential uses of FET biosensors for medical and biological applications, such as sensing in body fluids for point-of-care or at-home monitoring. We developed aptamer-based FET biosensors for small-molecule detection under high ionic strength conditions.[14,20,26] Aptamers, which are single-stranded oligonucleotides isolated specifically for adaptive target recognition, are functionalized on semiconductor surfaces. Upon target binding, aptamers undergo conformational rearrangements involving their negatively charged backbones (and associated solution ions), resulting in charge redistribution near semiconductor surfaces. Signal transduction arising from aptamer charge redistribution has enabled direct detection of charged as well as neutral small-molecule targets under physiological conditions.[14]

Aptamers that selectively recognize serotonin were covalently immobilized on In_2O_3 (and SiO_2) ribbons (Figure 5a). Aptamers on the SiO_2 dielectric contribute minimally to target-induced currents. We conducted neurotransmitter sensing by adding increasing concentrations of serotonin into the PBS solutions above FETs. Representative transfer curves for 350-nm-wide In_2O_3 nanoribbon FETs at different serotonin concentrations are shown in Figure 5b. Calibrated response curves comparing the performance of 350-nm- *vs* 20-μm-wide ribbons both having 20-nm thin-film In_2O_3 are shown in Figure 5c.

Nanoribbons with 350 nm widths showed a trend toward larger calibrated responses to serotonin compared to those of 20-μm-wide nanoribbons ($0.1 < P < 0.05$). Differences in performance for the two FET configurations were apparent at serotonin concentrations between 100 fM and 1 nM, where

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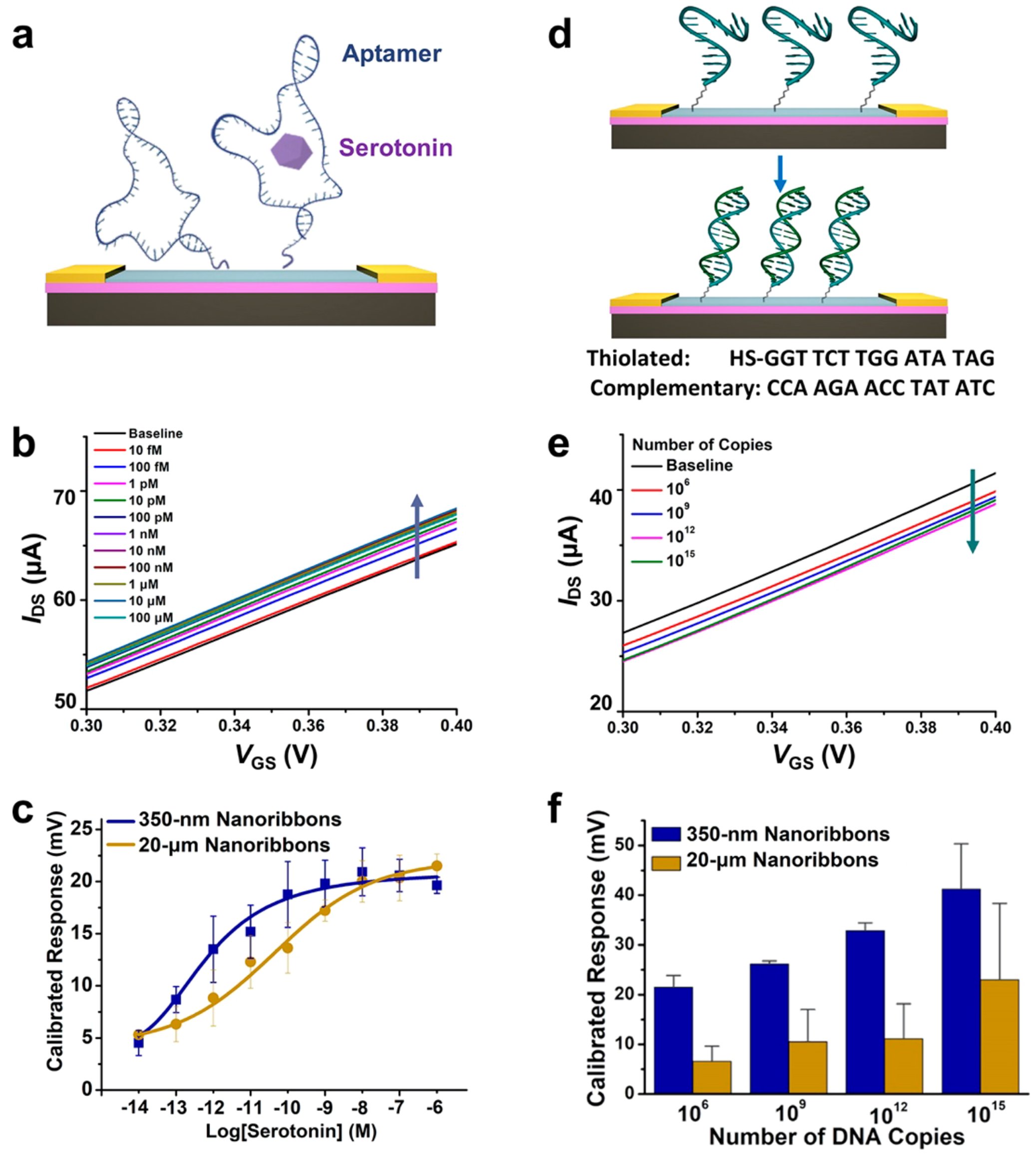

Figure 5. (a) Schematic illustration of serotonin detection using aptamer-functionalized In_2O_3 field-effect transistor (FET) biosensors. (b) Representative transfer curves for serotonin responses from 10 fM to 100 μM for 350-nm In_2O_3 nanoribbon FET biosensors. (c) Calibrated response curves for serotonin from 350-nm- *vs* 20-μm-wide In_2O_3 nanoribbon FET biosensors. Error bars are standard errors of the means for $N = 3$ 350-nm-wide nanoribbon and $N = 2$ 20-μm-wide nanoribbon devices. (d) Schematic illustration of DNA hybridization detection. (e) Representative transfer curves for responses for complementary DNA hybridization (10^6 to 10^{15} copies) for 350-nm In_2O_3 nanoribbon FET biosensors. (f) Calibrated responses for complementary DNA hybridization for 350-nm- *vs* 20-μm-wide In_2O_3 nanoribbon FET biosensors. Error bars are standard errors of the means for $N = 2$ 350-nm-wide nanoribbon and $N = 3$ 20-μm-wide microribbon devices.

sensor responses were linear for both configurations but left-shifted for 350-nm-wide nanoribbons. Tuning nanoribbon widths provides another strategy for shifting overall device sensitivities, in addition to truncating or destabilizing aptamer stems and/or changing aptamer surface densities.[14,20] These strategies will be important for translation to *in vivo* sensing applications where target concentrations vary widely, such as serotonin concentrations in the gut (micromolar range)[74] *vs* the brain extracellular space (nanomolar range).[75]

Previously, we found that even small changes in pH affect aptamer–FET sensor responses.[48] This effect was attributed to H^+-associated changes in charge redistribution around aptamers and near FET surfaces. For *in vivo* applications where the environmental pH varies, for example, in conjunction with neuronal burst firing, we showed that incorporation of a separate pH sensor as part of a multiplexed device differentiated changes in pH from changes in neurotransmitter concentrations.[48] In previous work, we also carried out control experiments to determine target-specific detection using unfunctionalized FETs and FETs functionalized with a scrambled serotonin aptamer sequence, as well sensing in the presence of structurally similar interferants, which indicated that serotonin–aptamer FETs are highly selective.[14,48] Moreover, we have investigated real-time serotonin sensing (femtomolar–micromolar) with a temporal resolution of ≤5 s, which was limited by the measurement system response time.[48]

In addition to ions and small molecules, oligonucleotide sensing is important for clinical diagnostics, such as genotyping for cancer immunotherapy and for diagnosing infectious

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diseases.[5,6,76−79] Here, label-free DNA detection was performed on micro- and nanoribbon FET biosensors. Thiolated single-stranded DNA (ssDNA) was covalently immobilized onto In_2O_3 (and SiO_2). Solutions containing 10^6 to 10^{15} copies of complementary oligonucleotide (~1 fM to ~1 μM) were added to the sensing environment in artificial cerebrospinal fluid (aCSF) (Figure 5d). The aCSF was diluted 10-fold to increase the Debye length and thereby to maximize low copy-number detection.

Representative transfer curves for 350-nm-wide In_2O_3 nanoribbon FETs at different target DNA copy numbers are shown in Figure 5e. Calibrated responses are compared in Figure 5f for the performance of 350-nm nanoribbon *vs* 20-μm microribbon In_2O_3 FETs. Nanoribbons with 350 nm widths showed higher sensitivity to DNA hybridization than that of the 20-μm-wide microribbons ($P < 0.05$).

The direction of change for *n*-type In_2O_3 FET transfer characteristics is due to gating effects associated with negatively charged oligonucleotides.[14,20] For aptamer-based sensing, the serotonin aptamers used here reorient away from FET surfaces upon target binding, resulting in increases in concentration-related currents in $i-V$ sweeps due to increased transconductance.[14] For DNA hybridization, decreases in currents in the $i-V$ sweeps with increasing DNA concentrations are due to the accumulation of net negative surface charge, which occurs upon DNA hybridization.[76] In a previous study, we observed negligible sensor responses to non-complementary target sequences.[76] We differentiated sequences with single-base mismatches. The highly sensitive platform developed here and in our recent work[76] portends a reagentless strategy for oligonucleotide (DNA, RNA) sensing, which can be developed for the detection of a wide variety of infectious agents, including the severe acute respiratory-related coronavirus 2 (SARS-CoV-2).[79,80]

Relationships between FET sensitivity and surface-to-volume ratio have been investigated using different types of channel materials.[32,36,49−55] Silicon nanowires with dimensions ≥50 nm have been most often investigated.[36,50,54] Silicon nanowires with higher surface-to-volume ratios have higher sensitivities toward pH, protein, and DNA detection.[36,50,54] For example, Linnros and colleagues studied silicon-on-insulator (SOI) nanowires with widths of 50−170 nm fabricated by electron-beam lithography having a 100-nm semiconductor layer.[54] For their smallest, 50-nm nanowires, the surface-to-volume ratio was only 2/100 nm^{-1} (*i.e.*, 0.4/20 nm^{-1}), which is 60% less than the surface-to-volume ratio of our 20-nm thin-film In_2O_3 FETs (*i.e.*, 1/20 nm^{-1}; see Supporting Information for calculations and Table S2).

For bottom-up fabricated cylindrical nanowires, the surface-to-volume ratio is related to $2/r$, where r is the nanowire radius. In principle, Si nanowires with diameters larger than 80 nm (*i.e.*, surface-to-volume ratio 1/20 nm^{-1}) have surface-to-volume ratios lower than those in the microribbon, nanoribbon, and thin-film FETs investigated here. For instance, Sun and co-workers produced Si nanowire devices for sensing protein adsorption.[36] Fabrication involved nanowire contract printing and SEM to select and to remove nanowires, individually producing devices with specific numbers and diameters of nanowires. Single nanowire devices were grouped by diameter ranges (*i.e.*, 60−80, 81−100, and 101−120 nm). The smallest, 60-nm nanowires had surface-to-volume ratios of 2/30 nm^{-1} (*i.e.*, 1.3/20 nm^{-1})—a 17% increase over the surface-to-volume ratio of the 350-nm nanoribbons investigated here (Table S2).

Williams and co-authors explored the effects of surface-to-volume ratio in the context of ssDNA hybridization with complementary single-stranded peptide nucleic acids functionalized on Si nanowire FETs having widths of 50, 100, 200, 400, and 800 nm.[50] The Si semiconductor layer was 50 nm. For these sensors, the signal-to-volume ratios were 3/50, 2/50, 1.5/50, 1.25/50, and 1.125/50 nm^{-1}, respectively (*i.e.*, 1.2/20, 0.8/20. 0.6/20, 0.5/20, and 0.45/20 nm^{-1}, respectively). Hybridization sensitivity was linear for nanowires with widths between 800 and 100 nm. A sharp increase in sensitivity to DNA hybridization for the 50-nm-wide Si nanowires was attributed to nonlinear increases in conductance at small nanowire diameters, which was determined experimentally and *via* simulation.

For In_2O_3 nanoribbon FETs, sensor sensitivity can be increased by reducing nanoribbon dimensions using In_2O_3 sol−gel processing to produce thinner semiconductor layers[26,27,56] and/or *via* CLL with masters fabricated by e-beam lithography to pattern features as small as 15 nm.[58−65] To extend our findings beyond the feature sizes investigated experimentally, we performed finite element analysis simulations to predict FET sensitivities with respect to a number of different nanoribbon widths. As shown in Figure S8, increased sensitivity was predicted for FETs with smaller widths given the same In_2O_3 thickness (20 nm), which is attributed to higher surface-to-volume ratios. Similar to the findings of Williams and colleagues, we observed the greatest increases in FET responses for features with widths <100 nm.[50]

Here, we focused on top-down approaches using soft lithography. Traditional top-down approaches, such as e-beam lithography (EBL), also offer precise control over the orientations, sizes, and numbers of quasi-1D nanostructures, thereby enabling fabrication of biosensors with high reproducibility.[81] Nonetheless, top-down fabrication of sub-micrometer features needed to achieve high surface-to-volume ratios requires techniques that are challenging to translate for broad applications. For example, commonly used EBL methods are low-throughput and suffer from high equipment and usage costs.

Bottom-up approaches involving 1D nanomaterials (*e.g.*, Si nanowires, SiNWs) have also been used to fabricate FETs with high surface-to-volume ratios, which increased device sensitivities.[82−84] However, fabrication of Si-based nanomaterials, including SiNWs, often relies on silicon-on-insulator wafers, which are considerably more expensive (>$500 per 4 in. wafer) than standard Si wafers (<$50 per 4 in. wafer).[85] Together, these drawbacks present significant barriers to the use of many types of nanomaterials in actual biomedical applications and necessitate the development of high-throughput, cost-effective, and precise fabrication strategies for biosensors, such as the method described herein.

CONCLUSIONS AND PROSPECTS

Highly aligned In_2O_3 nanoribbon FETs were fabricated by chemical lift-off lithography using commercially available DVD-R disks as nanostructured templates and low-temperature sputtering to produce 20-nm In_2O_3 thin films. Nanoribbon FET sensors have high surface-to-volume ratios that imparted greater sensitivity for ion, small-molecule, and oligonucleotide detection, all other factors being equal. The fabrication and sensing approaches reported herein represent

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generalizable strategies for improving electronic biosensing by fabricating high surface-to-volume ratio nanoscale features for applications where high and/or tunable sensitivities are critical.

This top-down, large-scale nanolithography strategy to fabricate metal-oxide nanoribbons can be implemented as a high-throughput, cost-effective, cleanroom-free means of production. Even so, nanostructure surface-to-volume ratio is only one of many parameters that impacts nanobiosensor sensitivity. Other factors include semiconductor material, doping, and nanowire/nanostructure densities. If surface receptors are employed for selective biosensing, receptor type (*e.g.*, protein, nucleic acid), density, and target affinity, as well as the ionic strength of the sensing environment and biofouling will influence performance. Nonetheless, we demonstrate unequivocally through experimentation and simulation that surface-to-volume ratio impacts biosensor responses under physiologically relevant conditions.

MATERIALS AND METHODS

Materials. Prime quality 4 in. Si wafers (P/B, 0.001−0.005 Ω-cm, thickness 500 μm) were purchased from Silicon Valley Microelectronics, Inc. (Santa Clara, CA). Sylgard 184 silicone elastomer kits (lot #0008823745) were purchased from Ellsworth Adhesives (Germantown, WI). Indium(III) nitrate hydrate (99.999%), iron nitrate, thiourea, ammonium hydroxide (30% w/v in H_2O), hydrogen peroxide (30% v/v in H_2O), ethylenediaminetetraacetic acid disodium salt dihydrate (EDTA), 3-phosphonopropioninc acid, (3-aminopropyl)triethoxysilane (APTES), trimethoxy(propyl)silane, and 3-maleimidobenzoic acid *N*-hydroxysuccinimide (MBS) were purchased from Sigma-Aldrich (St. Louis, MO) and used as received. UltraPure nuclease-free distilled water was purchased from Thermo Fisher Scientific (Waltham, MA) and used as received. The masters templated for lift-off lithography were commercially available DVD-R recordable 16× speed 4.7 GB blank disks (Memorex).

Water was deionized before use (18.2 MΩ-cm) using a Milli-Q system (Millipore, Billerica, MA). The serotonin aptamer (/5ThioMC6-D/CG ACT GGT AGG CAG ATA GGG GAA GCT GAT TCG ATG CGT GGG TCG), thiolated ssDNA (/5ThioMC6-D/GG TTC TTG GAT ATA G), and complementary ssDNA (CTA TAT CCA AGA ACC) were synthesized by Integrated DNA Technologies, Inc. (Coralville, IA). The Ag/AgCl reference electrodes were purchased from World Precision Instruments, Inc. (Sarasota, FL).

Buffer Solutions. Phosphate-buffered saline solution was purchased from Thermo Fisher Scientific (Waltham, MA, #10010023) and used as received. Artificial cerebrospinal fluid solution was NaCl (14.7 mM), KCl (0.35 mM), $CaCl_2$ (0.1 mM), NaH_2PO_4 (0.1 mM), $NaHCO_3$ (0.25 mM), and $MgCl_2$ (0.12 mM). A detailed procedure for preparation appears in the Supporting Information.

Fabrication of Masters. Photomasks for 2 μm wide and 4 μm pitch lines or 20 μm wide and 40 μm pitch lines were designed using the AutoCAD software suite (Autodesk, Inc.). Positive photoresist SPR700-1.2 (Rohm & Haas Co., Philadelphia, PA) was used for patterning Si by photolithography. The exposed Si was selectively etched using deep reactive ion etching (Plasma-Therm, LLC, Petersburg, FL). The resulting masters were then coated with trichloro(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)silane as a release layer. The DVD-R masters for 350 nm wide nanoribbons were prepared by a separation and rinsing process as previously described.[56,57]

Fabrication of In_2O_3 Micro- and Nanoribbon FETs. The general fabrication process is illustrated in Figure 1. The Si substrates with 100 nm SiO_2 were coated with 30 nm Ti followed by 30 nm Au using a CHA solution electron-beam evaporator (CHA Industries, Inc., Fremont, CA) under high vacuum (10^{-8} Torr) at an evaporation rate of 0.1 nm/s. Preparation of *h*-PDMS stamps, CLL patterning, and wet etching processes for nanoribbon fabrication were carried out as previously reported.[56,57] Briefly, an ethanolic 1 mM solution of 11-mercapto-1-undecanol was used to form SAMs on Au surfaces by incubation with substrates for 12 h. Oxygen-plasma-activated DVD-templated *h*-PDMS stamps were brought into contact with SAMs. The soft PDMS stamps for CLL patterning of 2- and 20-μm ribbons were made from Si masters fabricated by conventional photolithography, as described above. The CLL was carried out similar to patterning for 350-nm nanoribbons.

For all formats, upon stamp removal, SAM molecules in the stamp-contacted areas were selectively removed, along with monolayers of Au atoms.[58,64] After the CLL process, Au etchant composed of 20 mM iron nitrate and 30 mM thiourea was used to etch the Au films (~30 min). A Ti etchant (113 mM EDTA, 3% hydrogen peroxide (v/v in H_2O) and 1.26% ammonia hydroxide solution (w/v in H_2O)) was used to etch to Ti for ~9 min. Wet etching transferred the patterns through the metal layers. After wet etching, substrates were oxygen-plasma-treated to remove remaining SAM molecules in the noncontact areas prior to In_2O_3 sputtering.

The In_2O_3 (~20 nm) was deposited onto the patterned substrates using a radio frequency sputtering process (Denton Discovery 550 Sputtering System, Nanoelectronics Research Facility (NRF), University of California, Los Angeles (UCLA)). Sputtering is a room temperature process, which is compatible with a variety of substrates including Si, glass, polyesters, and polyimide.[30,46,47] Metal removal was then performed by immersing substrates into Ti etchant for ~9 min under ultrasonication (Branson Ultrasonics, Danbury, CT), leaving In_2O_3 micro- or nanoribbons on Si/SiO_2 substrates. Devices were cleaned with water and dried under N_2 before measurements or further functionalization. Source/drain electrodes of 10-nm-thick Ti and 50-nm-thick Au were defined by conventional photolithography and deposited using a solution electron-beam evaporator (CHA Industries, Inc., Fremont, CA) under high vacuum (10^{-8} Torr) with an evaporation rate of 0.1 nm/s. An optical microscope image of the electrode configuration with respect to In_2O_3 nanoribbons is shown in Figure S2.

Characterization. Scanning electron microscope images were obtained using a Supra 40VP scanning electron microscope with an Inlens SE Detector (Carl Zeiss Microscopy, LLC, White Plains, NY). Atomic force microscope imaging was performed using a FastScan AFM with ScanAsyst-Air tips (Bruker, Billerica, MA). Electronic FET measurements were carried out on a manual analytical probe station (Signatone, Gilroy, CA) equipped with a Keithley 4200A SCS (Tektronix, Beaverton, OR) or an Agilent 4156B semiconductor parameter analyzer (Santa Clara, CA). Optical images were taken with a digital camera attached to a Zeiss Axiotech optical microscope.

Biosensing. For pH sensing, In_2O_3 surfaces were functionalized with APTES. Real-time source−drain current measurements were performed (i−t), where the gate voltage (V_{GS}) was held at 300 mV and the drain voltage (V_D) was held at 100 mV throughout. Buffer solutions of pH 7.4 were used to obtain stable baselines. Buffer solutions from pH 10 to 5 were sequentially added and removed using pipettes.

Thiolated serotonin aptamer or thiolated ssDNA (1 μM in nuclease-free water) were immobilized onto the oxide surfaces of FETs using APTES/PTMS (1:9, v/v) and MBS ester a as linker. Serotonin (final concentration 10 fM to 100 μM) or complementary ssDNA (final concentration 1 fM to 1 μM) in 1 μL aliquots were added into the buffer solutions (39 μL) over FETs and mixed with a pipet.

Source−drain current (I_{DS}) transfer curves were obtained, wherein gate voltages (V_{GS}) were applied from −200 to 400 mV with a step voltage of 5 mV, while the drain voltage (V_D) was held at 10 mV throughout. Five gate-voltage sweeps were repeated (five sweeps at 0, 5, and 10 min). The sweeps at each time point were averaged to determine each transfer curve. Calibrated responses were calculated by dividing the absolute sensor response (ΔI), which takes into account baseline subtraction, by the change in source−drain current with voltage sweep ($\Delta I_{DS}/\Delta V_G$).[14]

Statistics. Data for pH, serotonin, and ssDNA sensing were analyzed by two-way analysis of variance with ribbon width and target concentration as the independent variables (GraphPad Prism 7.04, San Diego, CA). Data for 10 nM, 100 nM, and 1 μM serotonin were

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excluded from the statistical analysis because sensor responses were saturated (Figure 5c). Two data points from the 20-μm-wide nanoribbon DNA sensing data were excluded from plotting and analysis due to external disturbance of the Ag/AgCl reference electrode noted during the measurements (Figure 5f).

Simulations. The COMSOL Multiphysics 5.2 program was used to simulate the relative responses of nanoribbons having different widths. Details for the model are from Shoorideh and Chui.[86] Here, In_2O_3 nanoribbons were designated to be 2 μm long and 20 nm thick, with widths varying from 5 nm to 20 μm. The In_2O_3 is intrinsically doped by oxygen vacancies at an estimated concentration of 2.5×10^{16} cm^{-3} *n*-type doping.[30] The substrate was 200-nm silicon dioxide. A surface charge density of 1.6×10^{-3} C/m^{-2} was added to model aptamer-induced charge change on the channels and the SiO_2 surface. Semiconductor physics was applied to compute the source−drain electric current when sweeping the gate voltage. The sensitivity was then calculated based on previous work.[14]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsnano.0c07503.

Supplemental methods, Tables S1−S3, Figures S1−S8; elementally quantified EDX analysis; surface-to-volume ratios; statistics summary; EDX spectrum; optical microscope image of interdigitated electrodes; optical microscope images of 20-μm-wide In_2O_3 nanoribbons with source and drain electrodes; solid-state transfer characteristics of In_2O_3 FETs with different ribbon widths; gate leakage current in the liquid state; simulation results; liquid-state transfer characteristics of In_2O_3 FETs with different ribbon widths; schematic of FET for surface-to-volume ratio calculations (PDF)

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Author Contributions

The experiments were designed by C. Zhao, Q.L., K.M.C., P.S.W., C. Zhou, and A.M.A. Data were collected by C. Zhao, Q.L., K.M.C., W.L., Q.Y., and X.X. and analyzed by C. Zhao, Q.L., and A.M.A. The simulations were designed and performed by T.M. and C.Z. Figures were prepared by C. Zhao and Q.L. The manuscript was written by C. Zhao, Q.L., K.M.C., P.S.W., C. Zhou, and A.M.A. with assistance from all authors.

Notes

The authors declare the following competing financial interest(s): Stem-loop receptor-based field effector sensor devices for sensing at physiological salt concentration. Co-inventors: A. M. Andrews, P. S. Weiss, N. Nakatsuka, M. N. Stojanovi, and K. A. Yang, nonprovisional U.S. and foreign patents filed 2019. PCT/US2019/046891.

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