Silicon Nanobelt Field Effect Transistors Toward Hepatocellular Carcinoma Detection

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ABSTRACT SUMMARY

We have used the local oxidation of silicon (LOCOS) process to fabricate a silicon nanobelt field effect transistor (NB FET). This approach is completely compatible with complementary metal oxide semiconductor (CMOS) technology, yet it avoids the need for expensive lithography tools to define the nanoscale pattern. We employed the fabricated NB FET as a biomolecular sensor for the early, real-time, label-free screening of hepatocellular carcinoma (HCC). To increase the accuracy of HCC screening and prevent false positive identification, we tested the ability of our NB FET to determine alpha-fetoprotein (AFP) as a cancer marker, a DNA fragment from hepatitis B virus (HBV), and the solution pH—all of which can be used as markers for the onset of HCC. By tuning the gate voltage, the linear electrical response of the system toward AFP extended over its concentration range from 45 pM (3 ng mL^{-1}) to 1.5 nM (100 ng mL^{-1}), allowing the screening of HCC. The system also exhibited linearity toward the DNA fragment from HBV over the range from 10 fM (49 fg mL^{-1}) to 1 pM (4.9 pg mL^{-1}); the detection limit was ca. 3.2 fM. The electrical response toward the solution pH underwent a stepwise decrease upon increasing the pH from 6.40 to 7.39. This multiplex sensing of AFP, HBV, and the solution pH suggests that our direct, label-free, ultrasensitive biosensor in a microfluidic chip might be applicable as an HCC detector in real samples.

INTRODUCTION

There is increasing need to develop ultrasensitive and selective biological sensors for disease detection, drug discovery, and biomedical diagnostics.[1] For example, ultrasensitive biological detection systems that allows the early detection of genetic disorders are expected to improve preventative health care. At present, the most widespread techniques for detecting biomolecules are based on enzyme-linked immunosorbent assays (ELISAs) and polymerase chain reactions (PCRs). The ELISA method determines the level of an antigen in a sample through the magnitude of a fluorescence signal; its drawbacks include the need for a fluorescent label and relatively insensitive detection. The PCR method utilizes enzymatic replication to amplify a deoxyribonucleic acid (DNA) fragment; it also has problems relating to fluorescent labeling and the long periods of time required to amplify traces of DNA. The development of real-time, label-free sensing devices that overcome the drawbacks of ELISA- and PCR-based methods remains a considerable challenge. Several solid state field effect transistors (FETs), including ion-sensitive FETs (IS FETs) and extended-gate FETs (EG FETs), have been adapted to function as effective chemical and biomolecular sensors. More recently, such sensors based on quasi one-dimensional (Q1D) semiconductor nanostructures, such as nanotubes,[8] nanowires, and nanobelts, have attracted considerable attention because of their distinct electrical, optical, and magnetic properties. The large surface-to-volume ratios and selective binding of charged biomolecules onto these nanostructures' surfaces can result in significant changes in electronic conductance in the channel of the nanostructure. Hence, the real-time, label-free detection of ultratrace levels of molecules in biological samples has become a real possibility. Cheng et al. were the first to utilize tin oxide nanobelt FETs for the sensing of solution pH, although the switching on/off current ratio, which was related to the method's sensitivity, was limited to only three orders of magnitude because of interference from defects and contamination. To the best of our knowledge, no silicon nanobelt FETs exhibiting excellent field effects have been developed previously for ultrasensitive biomolecule sensing.

EXPERIMENTAL METHODS

In the first step, stacked films of tetraethyl orthosilicate (TEOS)-oxide and silicon nitride were sequentially deposited as the masking layer on a silicon-on-insulator (SOI) wafer substrate. The active region was then patterned through low-resolution lithography and plasma etching, followed by thermal oxidation growth. The surface presenting a silicon nitride pattern avoids oxidation of the underlying silicon, while allowing only the unmasked silicon to be intentionally oxidized. An active region comprising the nanobelt, source, and drain was, therefore, self-defined as a result of the suitable capping effect of the silicon nitride regions. Moreover, the underlying silicon film in Figure 1a was shrunk to form a nanobelt having a thickness of ca. 5 nm as a result of lateral oxygen diffusion during the oxidation process. This phenomenon, the well-known "bird's beak" effect, can self-reduce the width of a nanobelt to less than the expected width of the exposure system.

RESULTS AND DISCUSSION

Figure 1a displays a cross-sectional transmission electron microscopy (TEM) image of the silicon nanobelt. The width of the nanobelt decreased from 500 nm (for the structure formed through relatively inexpensive optical I-line lithography) to 150 nm and the thickness decreased from 50 nm originally to ca. 5 nm after LOCOS processing (inset of Figure 1a). We attribute the improved sensitivity of the silicon NB FET biosensor (see below) to this significant shrinkage of dimensions while retaining a large detection region at the surface. Prior to characterizing the electrical response of this NB FET sensor in

a liquid phase, we used PDMS to fabricate a 50 um–wide microfluidic channel that we sealed onto the chip using oxygen plasma (Figure 1b); the fluid flowing through the active region was delivered by an automatic syringe pump (Model 780270, Kd Scientific, USA).

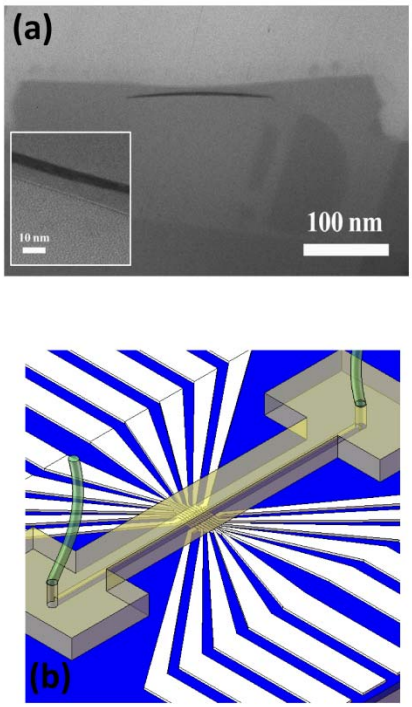

Figure 1. Fabrication of the silicon NB FET. (a) Cross-sectional TEM image of the nanobelt. Inset: enlarged TEM image of the nanobelt. (b) Schematic representation of the sealed microchannel onto the NB FET biosensor.

Although this biosensor was very sensitive when biased at gm,max, it was not suitable for AFP detection because the threshold limit value of the AFP concentration in relation to liver injury is ca. 5–20 ng mL^{-1}. A patient whose AFP concentration is above the threshold limit value is likely to suffer from HCC. To detect AFP concentrations in this critical range and, thereby, allow specific HCC diagnosis, we tuned the applied gate voltage (Vg = 0.5 V) to a higher value so that the sensor would operated with relatively worse sensitivity; in this case, the detection range extended from 3 ng mL^{-1} (45 pM) to 600 ng mL^{-1} (9 nM). Figure 2a displays the detection response with respect to various AFP concentrations; note that each concentration was measured using a different device. Therefore, to provide a more definitive comparison, we normalized the currents by dividing by the value of ID of the AFP pre-injected (i.e., blank) sample to observe the minute variations in each run. Because the isoelectric point (pI) of AFP antigen is ca. 4.57, AFP in PBS buffer solution (pH 7.4) exhibits net negative charge. The observed concentration-dependent decreases in ID are consistent with the amounts of negatively charged AFP antigen bound to the antibody receptor in the n-channel FET devices. The normalized current shift exhibited good linearity with respect to the logarithm of AFP concentrations ranging from 3 to 100 ng mL^{-1} (Figure 2b). Beyond a concentration of 100 ng mL^{-1}, the currents remained almost fixed, possibly because of saturation of the binding sites in the detection region.

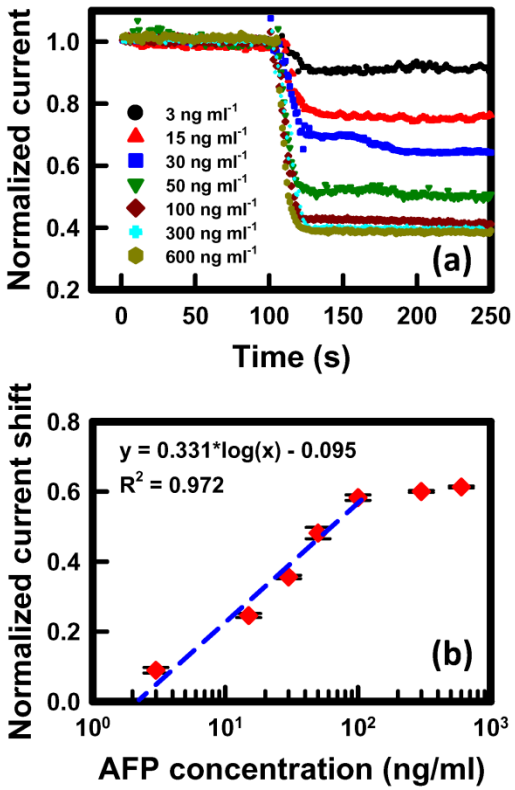

Figure 2. Electrical response of the NB FET sensor toward AFP. (a) Detection response toward AFP concentrations ranging from 3 to 600 ng mL–1. (b) Normalized current shift plotted as a function of AFP concentration.

CONCLUSION

We have used the LOCOS isolation process and CMOS-compatible technology to fabricate novel silicon NB FETs. The shrunken nanobelts, which had high surface-to-volume ratios, were used to detect HCC. We found that our NB FET biosensor could detect AFP, a biomarker for HCC, at concentrations ranging from 3 to 100 ng mL^{-1}, the most critical range for screening HCC. We anticipate that our NB FET sensor might operate as a real-time, label-free, ultrasensitive detection system for screening diseases in the future.

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