## Flexure-FET biosensor to break the fundamental sensitivity limits of nanobiosensors using nonlinear electromechanical coupling

Ankit Jain<sup>1</sup>, Pradeep R. Nair, and Muhammad A. Alam<sup>1</sup>

School of Electrical and Computer Engineering, Purdue University, West Lafayette, IN 47907

Edited by L. B. Freund, University of Illinois, Urbana, IL, and approved March 30, 2012 (received for review March 5, 2012)

In this article, we propose a Flexure-FET (flexure sensitive field effect transistor) ultrasensitive biosensor that utilizes the nonlinear electromechanical coupling to overcome the fundamental sensitivity limits of classical electrical or mechanical nanoscale biosensors. The stiffness of the suspended gate of Flexure-FET changes with the capture of the target biomolecules, and the corresponding change in the gate shape or deflection is reflected in the drain current of FET. The Flexure-FET is configured to operate such that the gate is biased near pull-in instability, and the FET-channel is biased in the subthreshold regime. In this coupled nonlinear operating mode, the sensitivity (S) of Flexure-FET with respect to the captured molecule density  $(N_s)$  is shown to be exponentially higher than that of any other electrical or mechanical biosensor. In other words, while  $S_{\text{Flexure}} \sim e^{(\gamma_1 \sqrt{N_s} - \gamma_2 N_s)}$ , classical electrical or mechanical biosensors are limited to  $S_{classical} \sim \gamma_3 N_S$  or  $\gamma_4 \ln(N_S)$ , where  $\gamma_i$  are sensor-specific constants. In addition, the proposed sensor can detect both charged and charge-neutral biomolecules, without requiring a reference electrode or any sophisticated instrumentation, making it a potential candidate for various low-cost, point-of-care applications.

label-free detection | genome sequencing | cantilever | spring-softening | critical-point sensors

Nanoscale biosensors are widely regarded as a potential can-didate for ultrasensitive, label-free detection of biochemical molecules. Among the various technologies, significant research have focused on developing ultrasensitive nanoscale electrical (1) and mechanical (2) biosensors. Despite remarkable progress over the last decade, these technologies have fundamental challenges that limit opportunities for further improvement in their sensitivity (Fig. 1A) (3-6). For example, the sensitivity of electrical nanobiosensors such as Si-Nanowire (NW) FET (field effect transistor) (Fig. 1B) is severely suppressed by the electrostatic screening due to the presence of other ions/charged biomolecules in the solution (7), which limits its sensitivity to vary linearly (in subthreshold regime) (3, 7) or logarithmically (in accumulation regime) (4, 7, 8, 9) with respect to the captured molecule density  $N_s$ . Moreover, the miniaturization and stability of the reference electrode have been a persistent problem, especially for lab-onchip applications (1). Finally, it is difficult to detect charge-neutral biological entities such as viruses or proteins using chargebased electrical nanobiosensor schemes.

In contrast, nanomechanical biosensors like nanocantilevers (10, 11) (Fig. 1*C*) do not require biomolecules to be charged for detection. Here, the capture of target molecules on the cantilever surface modulates its mass, stiffness, and/or surface stress (5, 11, 12). This change in the mechanical properties of the cantilever can then be observed as a change in its resonance frequency (dynamic mode), mechanical deflection, or change in the resistance of a piezoresistive material (static mode) attached to the cantilever (6, 13). Unfortunately, typical optical detection schemes (10) require complex instrumentation which may preclude them from many low-cost point-of-care applications. Further, the re-

sponse of nanomechanical biosensors varies only linearly (5) or logarithmically (6, 14, 15) with the change in the mass or surface stress of the cantilever, and therefore these sensors may not be sufficiently sensitive to detect target molecules at very low analyte concentrations, unless sophisticated, low-noise setup is used.

To overcome the respective limitations of classical electrical and mechanical nanoscale biosensors, we propose the concept of a Flexure-FET biosensor that integrates the key advantages of both technologies but does not suffer from the limitations of either approach. The Flexure-FET consists of a nanoplate channel biased through a thin-film suspended gate (Fig. 1D). Although the structure is similar to that of a suspended-gate FET (16), nano-electromechanical (NEM) FET (17), or resonant gate transistor (18), we call the device Flexure-FET to emphasize its distinctive nonlinear operation specifically optimized for ultrasensitive detection of biomolecules. As shown in Fig. 1E, the ultra high sensitivity arises from the coupling of two electromechanical nonlinear responses, namely (i) spring-softening (19) in which stiffness decreases nonlinearly with the applied gate bias  $V_G$  and vanishes at the pull-in point (for detailed discussions on pull-in instability, see refs. 20, 21), and (ii) subthreshold electrical conduction (22) in which current depends exponentially on the surface potential (Fig. S1). Such nonlinear electromechanical coupling enables exponentially high sensitivity for Flexure-FET sensors (Fig. 1A), which is fundamentally unachievable by exclusive use of existing nanoscale electrical or mechanical biosensors. Moreover, the reliance of change in stiffness (23, 24) ensures screening-free detection of charged/neutral molecules, with no need for a reference electrode, and the measurement of drain current for detection requires no complex instrumentation. It should be noted that from a mechanical perspective, the Flexure-FET operates close to pull-in instability, a critical point. Similar critical point sensing has also been reported for vapor sensors (25) that operate close to bucking-instability (25) and for mass sensors that operate close to saddle-node bifurcation (26), and their higher sensitivity has been confirmed experimentally. However, beyond the critical point sensing, the integrated transistoraction in the subthreshold regime provides the Flexure-FET an additional exponential sensitivity (and simpler direct current readout) that could not be achieved by the classical nonlinear sensor schemes.

## **Theory of Flexure-FET**

Sensor Configuration Before Target Capture. The operating principle of Flexure-FET can be understood using the well established

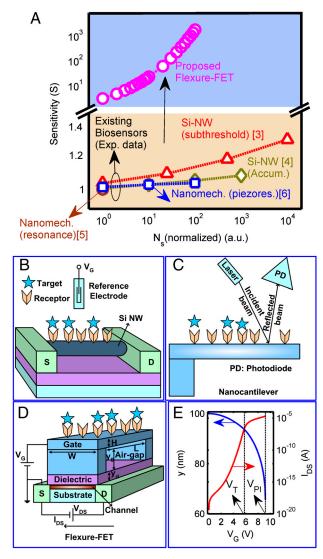
Author contributions: A.J., P.R.N., and M.A.A. designed research; A.J. performed research; A.J., P.R.N., and M.A.A. analyzed data; and A.J., P.R.N., and M.A.A. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

<sup>&</sup>lt;sup>1</sup>To whom correspondence may be addressed. E-mail: jankit@purdue.edu or alam@purdue.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1203749109/-/DCSupplemental.

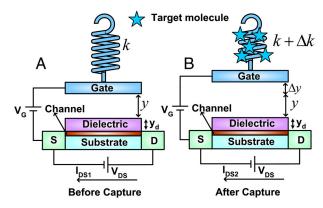


**Fig. 1.** (*A*) Sensitivity *S* of different types of biosensors; e.g., (*B*) electrical (Si-NW FET) in which transduction is achieved by modulation of channel conductivity (*G*) when charged biomolecules are captured by the gate. (*C*) Transduction in cantilever-based nanomechanical biosensors is achieved by change in its mass, stiffness, or surface stress. Nanocantilever can be operated in dynamic mode (mass change-based detection using shift in resonance frequency) or in static mode (surface stress change based detection using piezo-resistive material). (*D*) Proposed Flexure-FET biosensor in which transduction is achieved due to change in the stiffness of the suspended gate. (*E*) Operation of Flexure-FET below pull-in. Displacement of the suspended gate (*y*) and drain current ( $I_{DS}$ ) as a function of applied gate bias  $V_G$ . The *y* changes rapidly near pull-in ( $V_G \approx V_{Pl}$ ) and  $I_{DS}$  increases exponentially with  $V_G$  in the subthreshold regime ( $V_G < V_T$ ).

spring-mass model (Fig. 2) (17, 18). With the application of gate bias  $V_G$ , the gate moves downward toward the dielectric (y vs.  $V_G$  curve in Fig. 1E), and the corresponding increase in gate capacitance is reflected in the increased drain current  $I_{\text{DS}}$ , as shown in Fig. 1E. The static behavior of the device is dictated by the balance of spring and electrostatic forces; i.e.,

$$k(y_0 - y) = \frac{1}{2}\epsilon_0 E_{\text{air}}^2 A,$$
 [1]

where  $k = \frac{aEWH^3}{12L^3}$  is the stiffness,  $\alpha$  is a geometrical factor, *E* is the Young's modulus, *W* is the width, *H* is the thickness, *L* is the length of the gate electrode,  $y_0$  is the air-gap, *y* is the position of the gate electrode,  $\epsilon_0$  is the permittivity of free space,  $E_{air}$  is the electric field in the air, and A = WL is the area of the gate



**Fig. 2.** (*A*) and (*B*). Equivalent spring-mass model of Flexure-FET. Stiffness changes from *k* to  $k + \Delta k$  after the capture of biomolecules, and therefore position of the gate changes from *y* to  $y + \Delta y$ , which results in the modulation of drain current from  $I_{DS1}$  to  $I_{DS2}$ .

electrode. The electric field below the membrane  $E_{\text{air}}$  is equal to  $\epsilon_s E_s(\psi_s)$ , where  $\epsilon_s$  is the dielectric constant of the substrate, and

$$E_{s}(\psi_{s}) = \sqrt{\frac{2qN_{A}}{\epsilon_{0}\epsilon_{s}}} \left[ \psi_{s} + \left( e^{-\frac{q\psi_{s}}{k_{\mathrm{B}}T}} - 1 \right) \frac{k_{\mathrm{B}}T}{q} - \left( \frac{n_{i}}{N_{A}} \right)^{2} \left( \psi_{s} - \left( e^{\frac{q\psi_{s}}{k_{\mathrm{B}}T}} - 1 \right) \frac{k_{\mathrm{B}}T}{q} \right) \right]^{\frac{1}{2}}, \qquad [2a]$$

where  $E_s(\psi_s)$  is the electric field at the substrate-dielectric interface (22, page 64, for a detailed derivation of Eq. 2a),  $\psi_s$  is the surface potential, q is the charge of an electron,  $N_A$  is the substrate doping,  $k_B$  is the Boltzmann constant, T is the absolute temperature, and  $n_i$  is the intrinsic carrier concentration in the substrate. The voltage drop in air  $(y\epsilon_s E_s(\psi_s))$ , dielectric  $(\frac{\psi_d}{\epsilon_d}\epsilon_s E_s(\psi_s))$ , and substrate  $(\psi_s)$  can be related to the applied gate bias  $V_G$  as follows-

$$V_G = \left( y + \frac{y_d}{\epsilon_d} \right) \epsilon_s E_s(\psi_s) + \psi_s,$$
<sup>[2b]</sup>

where,  $y_d$  is the dielectric thickness and  $\epsilon_d$  is the dielectric constant. Eqs. 1 and 2 are solved self-consistently for y and  $\psi_s$  at each  $V_G$ . The corresponding inversion charge density  $(Q_i)$  in the channel and drain current  $(I_{DS})$  are given by

$$Q_{i} = \frac{qn_{i}^{2}}{N_{A}} \int_{0}^{\psi_{s}} \frac{e^{\frac{q\psi}{k_{B}T}} - 1}{E_{s}(\psi)} d\psi,$$
 [3]

$$I_{\rm DS} = \mu_n L Q_i \frac{V_{\rm DS}}{W},$$
 [4]

where  $\mu_n$  is the channel mobility for electrons,  $V_{\text{DS}}$  is the applied drain to source voltage. Fig. 1*E* shows the steady-state response of Flexure-FET as a function of biasing voltage  $V_G$ , obtained from the numerical simulations of Eqs. 1–4.

**Flexure-FET Response to Target Capture.** For transduction, the proposed Flexure-FET biosensor utilizes the change in suspended gate stiffness from k to  $k + \Delta k$ , (12, 24, 27–29) due to the capture of biomolecules. The change in stiffness due to the capture of biomolecules has been demonstrated by several recent experiments of mass sensing using nanocantilever-based resonators (12, 27, 28) (Fig. S2). This well known observation of stiffness change has been attributed to the change in the membrane thickness, Young's modulus, and/or surface stress of the beam (12, 23,

24, 30). Indeed, Craighead (27) suggests its use as a basis of a new class of mechanical biosensor.

In the following analysis, we model change in k by change in the effective thickness H of the gate ( $\Delta H$ ), although it should be stressed that the conclusions do not depend on the particular hypothesis regarding  $\Delta k$ . For now, we ignore the details of the spatial distribution of molecules associated with random sequential adsorption (31) and assume a uniform distribution of adsorbed molecules on the sensor surface. Therefore, the conservation of volume suggests  $\Delta H = N_s A_t H_t$ , where  $N_s$  is the area density,  $A_t$  is the effective cross-sectional area, and  $H_t$  is the effective thickness of the target molecule. Using the fact that  $k = \frac{\alpha E W H^3}{12L^3}$ , the change in stiffness  $\Delta k$  due to  $\Delta H (\ll H)$  can be related to adsorbed molecule density  $N_s$  as follows:

$$\frac{\Delta k}{k} \approx \frac{3N_s A_t H_t}{H}.$$
 [5]

For simplicity, we have taken the Young's modulus of captured molecules to be the same as that of the membrane, but this is obviously not necessary, and the theory can be generalized by the methods developed in Tamayo, Ramos, Mertens, and Calleja (23).

Combining Eqs. 1 and 2b, we get  $k(y_0 - y)y^2 \approx \epsilon_0 \hat{A}(\hat{V}_G - \psi_s)^2/2$ . Now, the change in gate position  $\Delta y$  for small change in stiffness  $\Delta k$  due to capture of biomolecules is given as

$$(3y - y_0)\Delta y^2 + y(3y - 2y_0)\Delta y \approx \frac{\epsilon_0 \mathcal{A}(V_G - \psi_s)^2}{2} \frac{\Delta k}{k^2}.$$
 [6]

If Flexure-FET is biased close to pull-in ( $V_G \approx V_{PI}, y \approx \frac{2}{3}y_0$ ), the nonlinear  $\Delta y^2$  term dominates the linear  $\Delta y$  term in Eq. 6. It is essential to bias the Flexure-FET in this nonlinear, close-to-pull-in regime for maximum sensitivity. Using Eqs. 5 and 6, we find

$$\Delta y \approx \sqrt{\frac{\epsilon_0 \mathcal{A} (V_G - \psi_s)^2}{2(3y - y_0)}} \frac{\Delta k}{k^2} \approx \beta \sqrt{N_s},$$
[7]

where  $\beta = \sqrt{\frac{3\epsilon_0 A(V_G - \psi_s)^2}{2(3y - y_0)} \frac{A_t H_t}{Hk}}$  is a bias and device dependent constant.

Since the electrostatic force in subthreshold regime is given by  $\frac{1}{2}\epsilon_0 E_{air}^2 A = q\epsilon_s \psi_s N_A A$  (Eq. 2a), the corresponding change in the surface potential  $\Delta \psi_s$  is obtained by perturbation of Eq. 1; i.e.,

$$\Delta \psi_s \approx \frac{-k\Delta y + \Delta k(y_0 - y)}{q\epsilon_s N_A A}.$$
[8]

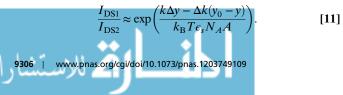
Using Eqs. 2a, 3, and 4, we can calculate the drain current  $I_{DS}$  in the subthreshold regime as follows,

$$I_{\rm DS} \approx \frac{\mu_n L\left(\frac{V_{\rm DS}}{W}\right) \left(\frac{q n_i^2}{N_A}\right) \left(\frac{k_{\rm B}T}{q}\right)}{\sqrt{\frac{2q N_A}{\epsilon_0 \epsilon_s}}} \frac{e^{\frac{q w_s}{k_{\rm B}T}}}{\sqrt{\psi_s}}.$$
[9]

Now, the ratio of the drain current before  $(I_{DS1})$  and after  $(I_{DS2})$  capture of biomolecules (in terms of the change in surface potential  $\Delta \psi_s$ ) is given by

$$\frac{I_{\rm DS1}}{I_{\rm DS2}} \approx \exp\left(-\frac{q\Delta\psi_s}{k_{\rm B}T}\right).$$
 [10]

Using Eqs. 8 and 10, the ratio  $I_{DS1}/I_{DS2}$  is given by



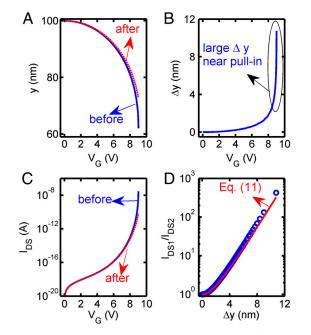
Therefore, if Flexure-FET is operated close to pull-in and in subthreshold regime, sensitivity S (using Eqs. 5, 7, and 11) is given by

$$S_{\text{Flexure}} \equiv \frac{I_{\text{DS1}}}{I_{\text{DS2}}} \approx \exp(\gamma_1 \sqrt{N_s} - \gamma_2 N_s), \quad [12]$$

where  $\gamma_1 = \frac{k\beta}{k_B T \epsilon_s N_A A}$  and  $\gamma_2 = \frac{3(y_0 - y)kA_i H_i}{k_B T \epsilon_s N_A A H}$ . The sensitivity *S* is defined as  $I_{\text{DS1}}/I_{\text{DS2}}$ , because  $I_{\text{DS}}$  decreases after capture (see next text section).

Eq. 12 is the key result of the paper and shows how nonlinear interaction between mechanical (spring-softening) and electrical (subthreshold) aspects of sensing leads to an exponential sensitivity to capture of biomolecules. Such gain in sensitivity is impossible to achieve exclusively by electrical or mechanical sensing mechanisms.

Numerical Confirmation of Flexure-FET Response. The compact analytical expression of sensitivity of the Flexure-FET sensor can be validated by the self-consistent numerical solution of Eqs. 1-4. The results for the change in sensor characteristics due to the capture of biomolecules are summarized in Fig. 3. For example, Fig. 3A shows y vs.  $V_G$  before and after capture of target molecules. After the capture, the gate moves up (for a fixed  $V_G$ ) due to increased restoring spring force (because of increase in the k; Fig. 3A). Interestingly, change in gate position  $\Delta y$  is maximum close to pull-in due to spring-softening effect, as shown in Fig. 3B (see Figs. S3, S4 and S5 in SI Text for experimental validation). The change in gate position  $\Delta y$  is directly reflected in change in  $I_{\rm DS}$ . Fig. 3C shows  $\hat{I}_{\rm DS}$  vs.  $V_G$  before and after capture of biomolecules. Interestingly,  $I_{DS}$  decreases after capture due to increased separation between the gate and the dielectric (hence decreased capacitance). The corresponding ratio of the currents



**Fig. 3.** Change in the sensor characteristics due to capture of target molecules on the surface of the gate, (*A*)*y* vs. *V*<sub>G</sub> before and after capture, and (*B*) corresponding change in the position of gate electrode  $\Delta y$  vs. *V*<sub>G</sub>. The  $\Delta y$  increases rapidly near pull-in due to spring-softening effect. The capture of target molecules is directly mirrored in the change in *I*<sub>DS</sub>. (*C*) *I*<sub>DS</sub> vs. *V*<sub>G</sub> before and after capture, and (*D*) corresponding ratio of the two currents *I*<sub>DS1</sub> (before capture) and *I*<sub>DS2</sub> (after capture) as a function of  $\Delta y$ . Symbols denote the numerical simulation and solid line analytical formula (Eq. 11). The device considered has the following typical parameters:  $L = 4 \ \mu m$ ,  $W = 1 \ \mu m$ ,  $H = 40 \ nm$ ,  $E = 200 \ GPa$ ,  $y_0 = 100 \ nm$ ,  $y_d = 5 \ nm$ ,  $e_s = 11.7$ ,  $e_d = 3.9$ ,  $N_A = 6e16 \ cm^{-3}$ .

Jain et al.

Down

 $I_{\text{DS1}}$  (before capture) and  $I_{\text{DS2}}$  (after capture) increases exponentially with  $\Delta y$  (Fig. 3D), and becomes maximum near pull-in. Note that the results from detailed numerical simulations are accurately anticipated by Eq. 11, thus validating the analytical model described in the previous section. Therefore, by operating the Flexure-FET close to mechanical pull-in and in electrical subthreshold regime, orders of magnitude change in  $I_{\text{DS}}$  can be easily achieved for typical surface density of  $N_s = 5 \times 10^{12} \text{ cm}^{-2}$ , projected area of the biomolecule,  $A_t = \pi R_t^2$  with  $R_t = 1$  nm, and  $H_t = 5.1$  nm. These parameters translate to just an equivalent  $\Delta k \sim 6\%$ . Note that to achieve the maximum sensitivity, it is important to bias the Flexure-FET in subthreshold regime below pull-in (i.e.,  $V_T \approx V_{\text{PI}}$ ).

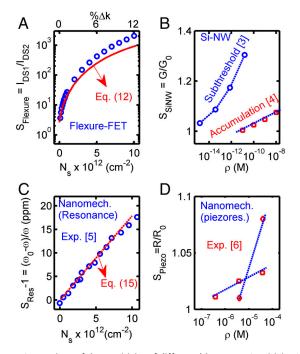
## **Comparison with Classical Sensors**

Next we compare the sensitivity of the proposed Flexure-FET sensor with the current nanoscale electrical/mechanical biosensors. Fig. 4*A* indicates that the Flexure-FET sensors are exponentially sensitive to change in stiffness or captured molecule density  $N_s$  (symbols: numerical simulation, solid line: analytical result; Eq. 12). In the following, we explain the origin of linear (or logarithmic) sensitivity for electrical and mechanical nanoscale biosensors.

**Electrical Nanobiosensors.** For Si-NW FET biosensors, which also have the optimal sensitivity in subthreshold regime (3), sensitivity S is defined to be the ratio of conductance G (after) and  $G_0$  (before) capture of target molecules (assuming conductance increases after the capture). Therefore, using Eq. 9, S can be approximated as

$$S_{\text{SiNW}} \equiv \frac{G}{G_0} \approx \exp\left(\frac{q\Delta\psi_s}{k_{\text{B}}T}\right).$$
 [13]

Unfortunately, the detection of biomolecules in a fluidic environment involves electrostatic screening by other ions in the solution.



**Fig. 4.** Comparison of the sensitivity of different biosensors. Sensitivity *S*(*A*) Flexure-FET (symbols denote the numerical simulation). (*B*) Si-NW biosensors in subthreshold and accumulation regime. (*C*) Resonance mode nanomechanical biosensors. (*D*) Surface stress change-based piezoresistive nanomechanical biosensors, as a function of  $N_s$  or  $\rho$ . In (*B*–*D*), symbols are the experimental data and the line is the guide to the eye.

Consequently, the surface potential scales logarithmically with biomolecule density; i.e.,  $(q/k_BT)\Delta\psi_s \propto \ln(\delta N_s)$  (7), where  $\delta$  is a constant that depends on ionic strength and properties of dielectric/fluid interface. Therefore, optimal sensitivity of Si-NW biosensors is given by

$$S_{\rm SiNW} \propto \delta N_s.$$
 [14]

In Fig. 4B, S is plotted against volume concentration  $\rho$ , as the captured molecule density  $N_s \propto \rho$  [linear regime of Langmuir isotherm (7)]. Therefore, all the conclusions regarding the dependence of sensitivity on  $N_s$  also hold for  $\rho$ . It should be noted that the reported sensitivity in the subthreshold regime (3) is actually sublinear (Fig. 4B), below the maximum sensitivity limit defined by Eq. 14 that can be achieved in this sensing regime. In the accumulation or the inversion regimes,  $S_{\text{SiNW}} \propto \Delta \psi_s$  (7), and therefore,  $S_{\text{SiNW}} \propto \ln(N_s)$ , as shown in Fig. 4B (4, 7). Similar logarithmic dependence of sensitivity was reported in other references (8, 9) as well.

**Mechanical Nanobiosensors.** For nanomechanical biosensors such as resonance mode nanocantilever, the sensitivity *S* is defined as  $\omega_0/\omega$ , where  $\omega$  is the resonance frequency after the capture of target biomolecules, and  $\omega_0$  is the resonance frequency before capture. Using the well known fact that  $\omega = \sqrt{\frac{k}{m}}$ , where *k* is the stiffness and *m* is the initial mass of the cantilever, *S* is given by

$$S_{\text{Res}} \equiv \frac{\omega_0}{\omega} \approx 1 + \frac{1}{2} \frac{\Delta m}{m} = 1 + \frac{1}{2} \frac{N_s W L m^*}{m}, \qquad [15]$$

where  $m^*$  is the mass of individual biomolecule and  $\Delta m = N_s WLm^*$  is the added mass of the biomolecules. Therefore, the sensitivity of mechanical biosensor can only vary linearly with  $N_s$ . This theoretical prediction is confirmed by experimental data (5) in Fig. 4C. We emphasize that the nanomechanical biosensors—with careful design and appropriate instrumentation can be extraordinarily sensitive; indeed, zeptogram mass detection (32) has been reported. Eq. **15** simply suggests that the sensitivity of such sensor still varies linearly with respect to  $N_s$ .

It is also important to realize that the linear sensitivity with  $N_s$  is achieved only if the change in stiffness due to capture of molecules is negligible. In general, however, capture of target molecules increases stiffness of the membrane. If this increase in stiffness compensates the corresponding increase in the mass, there might be no change in resonance frequency at all (12, 28), and the sensitivity could be vanishingly small. One must independently measure the change in the stiffness (29, 30) to decouple the mass effect from stiffness effect so that the mass of the adsorbed molecule can be correctly estimated. In contrast, the Flexure-FET relies only on the change in the stiffness and works in the static mode, and therefore requires no more than a simple measurement of the drain current.

Another class of nanocantilever sensor involves operation in the static mode, where the capture of the target molecules introduces a surface stress, which in turn bends the cantilever. The displacement  $\Delta y$  of the tip can in principle be measured using sophisticated optical readout methods, but a simpler approach can be used instead: One can measure the change in surface stress by measuring the change in the resistance of a piezoresistor attached to the cantilever. For these piezoresistive-based cantilever biosensors, the sensitivity is defined as the ratio of resistance before ( $R_0$ ) and after (R) the capture of biomolecules. Fig. 4D shows a logarithmic dependence of S on  $\rho$ . Similar logarithmic dependence for surface stress change has also been reported (14, 15). We therefore conclude that these static mode sensors do not exceed linear sensitivity limit of classical sensors. We summarize the results discussed in this section in Fig. 1*A*, where the sensitivity of various types of nanobiosensors has been plotted against normalized  $N_s$ , *defined* as the ratio of the measured quantity (either  $\rho$  or  $N_s$ ) to the minimum measured  $\rho$  or  $N_s$  of the available data. Fig. 1*A* allows us to conclude that the Flexure-FET biosensor will be exponentially more sensitive compared to existing nanoscale electrical or mechanical biosensors.

Finally, we emphasize that each of the three sequential physical phenomena associated with the operation of Flexure-FET (stiffness change due to capture of biomolecules, pull-in instability, subthreshold conduction) (Fig. S1) has been individually confirmed by numerous experiments based on electromechanical resonators (18, 33) and suspended-gate FET (34). We provide a summary of these experiments in the *SI Text* (Figs. S2, S4, S5, and S6). In the *SI Text*, we also suggest that a simple reconfiguration of existing electromechanical resonators or suspended-gate FET in Flexure-FET mode can give rise to exponential sensitivity (Fig. S7).

## Conclusion

In this paper, we have demonstrated how the Flexure-FET nanobiosensor achieves exponentially high sensitivity by combining two nonlinear characteristics of spring-softening and subthreshold conduction. This extreme high sensitivity of Flexure-FET, therefore, breaks the fundamental limits of linear or logarithmic sensitivity of classical nanoscale electrical or mechanical biosen-

- 1. Bergveld P (2003) Thirty years of ISFETOLOGY—What happened in the past 30 years and what may happen in the next 30 years. *Sensor Actuat B-Chem* 88(1):1–20.
- Arlett J, Myers E, Roukes M (2011) Comparative advantages of mechanical biosensors. Nat Nanotechnol 6:203–215.
- Gao X, Zheng G, Lieber C (2010) Subthreshold regime has the optimal sensitivity for nanowire FET biosensors. Nano Lett 10:547–552.
- Bunimovich Y, et al. (2006) Quantitative real-time measurements of DNA hybridization with alkylated nonoxidized silicon nanowires in electrolyte solution. J Am Chem Soc 128:16323–16331.
- Ekinci K, Roukes M (2005) Nanoelectromechanical systems. Rev Sci Instrum 76 (061101):1–12.
- Wee K, et al. (2005) Novel electrical detection of label-free disease marker proteins using piezoresistive self-sensing micro-cantilevers. *Biosens Bioelectron* 20:1932–1938.
   Nair P, Alam M (2008) Screening-limited response of nanobiosensors. *Nano Lett* 8:1281–1285.
- Cheng M, et al. (2006) Nanotechnologies for biomolecular detection and medical diagnostics. Curr Opin Chem Biol 10:11–19.
- Zheng G, Patolsky F, Cui Y, Wang W, Lieber C (2005) Multiplexed electrical detection of cancer markers with nanowire sensor arrays. Nat Biotechnol 23:1294–1301.
- Lavrik N, Sepaniak M, Datskos P (2004) Cantilever transducers as a platform for chemical and biological sensors. *Rev Sci Instrum* 75:2229–2253.
- Hwang K, Lee S, Kim S, Lee J, Kim T (2009) Micro- and nanocantilever devices and systems for biomolecule detection. Annu Rev Anal Chem 2:77–98.
- Gupta A, et al. (2006) Anomalous resonance in a nanomechanical biosensor. Proc Natl Acad Sci USA 103:13362–13367
- Boisen A, Thundat T (2009) Design & fabrication of cantilever array biosensors. Mater Today 12:32–38.
- Wu G, et al. (2001) Bioassay of prostate-specific antigen (PSA) using microcantilevers. Nat Biotechnol 19:856–860.
- Zhang J, et al. (2006) Rapid and label-free nanomechanical detection of biomarker transcripts in human RNA. Nat Nanotechnol 1:214–220.
- Abele N, et al. (2005) Suspended-Gate MOSFET: bringing new MEMS functionality into solid-state MOS transistor. Proceedings of IEEE International Electron Device Meeting (IEDM) pp 479–481.
- Kam H, Lee DT, Howe RT, King T-J (2005) A new nano-electro-mechanical field effect transistor (NEMFET) design for low-power electronics. *Proceedings of IEEE International Electron Device Meeting (IEDM)* pp 463–466.
- Nathanson HC, Newell WE, Wickstrom RA, Davis JR, Jr (1967) Resonant gate transistor. IEEE Trans Electron Dev 14:117–133.

sors. There are broad ranges of applications that can benefit from this sensitivity gain. For example, the current genome sequencing schemes require PCR (polymerase chain reaction) amplification of DNA strands because of the lower sensitivity of existing biosensors. The high sensitivity of Flexure-FET can eliminate the requirement of multiplication step and hence reduce the cost of sequencing. In addition, we recall that the proposed sensing scheme (i) can detect both charged and charge-neutral molecules, (ii) does not rely on reference electrode (the fundamental roadblock of Si-NW type biosensors), and (iii) obviates the need for any sophisticated and difficult-to-integrate instrumentation. The sensitivity of Flexure-FET can be further enhanced by choosing a softer membrane (having low stiffness) such as some polymer with low Young's modulus or an ultrathin membrane like graphene. Finally, let us emphasize that the sensing scheme is very general, which converts any change in the mechanical property of the gate electrode or change in the air-gap to the change in the drain current of the FET channel. Therefore, the proposed idea is not necessarily restricted to biomolecules detection but should find broader applications in gas/chemical/pressure sensing as well.

ACKNOWLEDGMENTS. We acknowledge discussions with Prof. R. Bashir (University of Illinois at Urbana-Champaign) and Jonghyun Go, financial support from National Institutes of Health (NIH, R01-CA20003), Materials, Structures and Devices (MSD) Focus Center, PRISM center, and computational resources from Network for Computational Nanotechnology (NCN).

- Torun H, Sarangapani K, Degertekin F (2007) Spring constant tuning of active atomic force microscope probes using electrostatic spring softening effect. *Appl Phys Lett* 91(253113):1–3.
- Krylov S, Maimon R (2004) Pull-in dynamics of an elastic beam actuated by continuously distributed electrostatic force. J Vib Acoust 126:332–342.
- Krylov S (2007) Lyapunov exponents as a criterion for the dynamic pull-in instability of electrostatically actuated microstructures. Int J NonLinear Mech 42:626–642.
- Yuan T, H NT (1998) Fundamentals of Modern VLSI Devices (Cambridge Univ Press, Cambridge, United Kingdom).
- Tamayo J, Ramos D, Mertens J, Calleja M (2006) Effect of the adsorbate stiffness on the resonance response of microcantilever sensors. *Appl Phys Lett* 89(224104):1–3.
- Waggoner P, Craighead H (2009) The relationship between material properties, device design, and the sensitivity of resonant mechanical sensors. J Appl Phys 105 (054306):1–14.
- Southworth D, Bellan L, Linzon Y, Craighead H, Parpia J (2010) Stress-based vapor sensing using resonant microbridges. Appl Phys Lett 96(163503):1–3.
- Kumar V, et al. (2011) Bifurcation-based mass sensing using piezoelectrically-actuated microcantilevers. Appl Phys Lett 98(153510):1–3.
- Craighead H (2007) Nanomechanical systems—measuring more than mass. Nat Nanotechnol 2:18–19.
- Ramos D, Tamayo J, Mertens J, Calleja M, Zaballos A (2006) Origin of the response of nanomechanical resonators to bacteria adsorption. J Appl Phys 100(106105):1–3.
- Gil-Santos E, et al. (2010) Nanomechanical mass sensing and stiffness spectrometry based on two-dimensional vibrations of resonant nanowires. *Nat Nanotechnol* 5:641–645.
- Sadeghian F, Goosen H, Bossche A, van Keulen F (2010) Application of electrostatic pull-in instability on sensing adsorbate stiffness in nanomechanical resonators. *Thin Solid Films* 518:5018–5021.
- Nair PR, Alam MA (2010) Theory of "selectivity" of label-free nanobiosensors: A geometro-physical perspective. J Appl Phys 107(064701):1–6.
- Yang Y, Callegari C, Feng X, Ekinci K, Roukes M (2006) Zeptogram-scale nanomechanical mass sensing. Nano Lett 6:583–586.
- Tilmans HAC, Legtenberg R (1994) Electrostatically driven vacuum-encapsulated polysilicon resonators part II. theory and performance. Sensors Actuat A-Phys 45:67–84.
- Abelé N (2007) Design and fabrication of suspended-gate MOSFETs for MEMS resonator, switch and memory applications. PhD thesis (Ecole Polytechnique Federale De Lausanne, Lausanne, Switzerland).

