The Sensitivity Limits of Nanowire Biosensors

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Why Nano for Bio-detection?

'Shine' → high sensitivity!

*Sensitivity matters*: early diagnostics of disease (low concentration protein detection); genomics (e.g. DNA sequencing); biophysics research (e.g. single molecule techniques) …
1. Motivation and introduction

2. Nanowire FET biosensors: sensitivity limits?
   - A fundamental analysis: importance of length scales
   - Pushing sensitivity limits: pH, protein detections
   - Charge detection limits

3. Noise spectroscopy for bio-reaction

4. Perspective/Future directions
Nano for bio-detection: what have been demonstrated

- **Bio-bar-coded nanoparticle**
  - Mirkin group, Science 2003

- **Micromechanical device**
  - Fritz et al., Science 2000

- **Surf plasmon reson. of nanoparticle**
  - Chilkoti, Anal Chem 2004

- **Carbon Nanotube FET**
  - Dai group, PNAS 2003

- **Nanowire FET**

**Main idea:**
- Low concentration molecule binding on **surface**
- Large change in physical properties of **volume** (high surface-volume ratio)
Nanowire synthesis and FET fabrication

CVD synthesis of Si-nanowire

- **SiH₄** + **Au** → Si-nanowire
- CVD synthesis of Si-nanowire (e.g. L.J. Lauhon *et al.*, Nature 420, 57 (2002)).

Nanowire Field-Effect-Transistor

- **Si₃N₄** passivation layer (~60 nm)
- Doped *p*-type Si Nanowire
- 60 nm Ni for source and drain
- Channel length ~ 2 µm

- **S** (source) and **D** (drain)
- **Substrate or back gate**

- **I_{sd}** (nA) vs. **V_{sd}** (V)
- **G** (nS) vs. **V_{g}** (V)

NW-FET sensor array chip

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[Diagram of NW-FET sensor array chip with labels for S, D, G, and sample points, along with timing and buffer annotations.]
Nanowire FET as biosensor: basic principle

The field effect of molecule binding acts as a gate voltage.

$I_{sd}$ or $G$

+$\text{analyte}$

$\rightarrow$

The field effect of molecule binding acts as a gate voltage.

$I_{sd}$ or $G$

$time$

$time$
Nanowire FET sensor: ultra-sensitive, label-free, real-time, and multiplexible

What is the fundamental limit of sensitivity/response?

(That’s why nano matters!)
NW-FET sensitivity: the role of carrier screening

Typical doping level:

<table>
<thead>
<tr>
<th>(10^{16})</th>
<th>(10^{17})</th>
<th>(10^{18})</th>
<th>(10^{19})</th>
<th>(10^{20})</th>
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<tbody>
<tr>
<td>0.6</td>
<td>0.8</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>10</td>
<td>20</td>
<td>40</td>
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</tbody>
</table>

Debye screening length:

\[ \lambda = \sqrt{\frac{\varepsilon k_B T}{p e^2}} \]

Volume conductance:

\[ G \propto p \times \pi R^2 \]

\[ \Delta G \sim \Delta p \times 2\pi R \times \lambda \]

\[ \Delta G / G \propto \lambda / R \]

(surface-volume ratio effect!)

High carrier density, \( \lambda < R \)
NW carrier density & conductance changes in depth \( \sim \lambda \) near surface.

Typical \( R \) of NW

Screening length \( \lambda \) for p-silicon

Typical doping level
NW-FET sensitivity: the role of carrier screening

Low carrier density, $\lambda > R$
Analyte molecules at surface gate the whole volume of nanowire

Debye screening length:
$$\lambda = \sqrt{\frac{\varepsilon k_B T}{pe^2}}$$
Nanowire-FET sensors: the limiting response

1. Non-degenerate semiconductors:
   \[ p = p_i \times \{\exp(E_i-E_F)/k_B T\} \]

2. NW conductance
   \[ G = p \times \pi R^2 \times e \mu /L \]

Low carrier density, \( \lambda > R \)

Analyte molecules at surface gate the whole volume of nanowire

NW sensor has the limiting (most sensitive) response in the long screening length regime:

\[ \Delta G/G = \exp(\Delta \phi/kT) - 1 \]
NW-FET sensitivity: the role of carrier screening

\[ \Delta G/G \rightarrow \exp(\Delta \phi/kT) - 1 \]
\( \lambda > R \) is reached in the subthreshold regime

NW sensor has the limiting (most sensitive) response in the long screening length (\( \lambda > R \)) regime:

\[
\frac{\Delta G}{G} = \exp\left(\frac{\Delta \phi}{kT}\right) - 1
\]
Nanowire sensor: pH Sensing

\[ \text{Si-OH} \leftrightarrow \text{Si-O}^- + \text{H}^+ \]

\[ \text{NH}_2 + \text{H}^+ \leftrightarrow \text{NH}_3^+ \]

\[ \text{pH} = -\log_{10}[\text{H}^+] \]
10nm diameter p-type silicon NW

\[
\Delta G/G (%) \quad 0 \quad 100 \quad 200 \quad 300 \quad 400 \quad 500 \quad 600 \quad 700
\]

\[
\text{time (s)} \quad 0 \quad 500 \quad 1000 \quad 1500
\]

\[
\text{pH} \quad 4 \quad 5 \quad 6 \quad 7 \quad 9
\]

40%
Pushing Sensitivity of Nanowire Sensors: pH sensing

10nm diameter p-type silicon NW

$\Delta G/G (%)$

4 5 6 7 pH 9

150%

40%

$G (\text{nS})$

$V_g (\text{V})$

0 0.1 0.2 0.3 0.4

-0.4 -0.2 0.0 0.2 0.4 0.6 0.8 1.0

0 1 10 100 1000

0 10 100 1000

1100
Pushing Sensitivity of Nanowire Sensors: pH sensing

10nm diameter p-type silicon NW

ΔG/G (%)

- subthreshold
- near threshold
- linear regime

pH

600%

150%

40%

G (nS)

Vg (V)

0 500 1000 1500

0

100

200

300

400

500

600

700

0.1 1 10 100 1000

-0.4 -0.2 0.0 0.2 0.4

0

200

400

600

800

1000
\[
\frac{\Delta G}{G} = \exp\left(\frac{\Delta \varphi}{kT}\right) - 1 \quad \text{for} \quad \Delta \varphi = 30 \text{mV/pH}
\]

\[
\Delta G = \Delta \varphi \times g_m \quad \text{for} \quad \Delta \varphi = 30 \text{mV/pH}
\]

Every pH change is equivalent to 30mV Vg shift in both regimes (also true for different NW diameter, doping level, etc.)
\[ \Delta G/G = \exp(\frac{\Delta \phi}{kT}) - 1 \] for \( \Delta \phi = 30 \text{mV/pH} \)

Electrochemical potential:
\[ \mu_{ec} = q \phi + k_B T \ln \left( \frac{[H^+]_s}{[H^+]_b} \right) \]

\[ \Delta \phi = k_B T/q \times \ln(10) \times \Delta \text{pH}_{\text{bulk}} \approx 59 \text{mV/pH} \]

If pH_{surface} can be kept constant

\[ \text{Si-OH} \leftrightarrow \text{Si-O}^- + \text{H}^+ \]

\[ \text{NH}_2 + \text{H}^+ \leftrightarrow \text{NH}_3^+ \]
For chemical reaction induced $\Delta \varphi$:

- The strongest response is indeed observed in subthreshold regime and $\Delta G/G = \exp\left(\frac{\Delta \varphi}{kT}\right)-1$
- chemistry doesn’t change ($\Delta \varphi$=const.)!
Cancer marker protein sensing - surface modification

Cancer marker protein sensing

\[ \text{[Ab]} + \text{[PSA]} \xrightleftharpoons[k_d]{k_a} \text{[Ab/PSA]} \]

\[ [\text{Ab/PSA}]_{eq} = \frac{[\text{Ab}][\text{PSA}]}{K_d+[\text{PSA}]} \]

Disassociation constant

\[ K_d = \frac{k_d}{k_a} \]

\( K_d \approx \text{nMS} \) (e.g. Saerens et al, J. Bio. Chem. 2004)
Pushing Sensitivity of Nanowire Sensors
- cancer marker protein sensing

For a given protein concentration, detection is greatly improved in the subthreshold regime!

(Δφ~15mV for 15pM PSA in both regimes)
Pushing Sensitivity of Nanowire Sensors
-cancer marker protein sensing

For a given protein concentration, detection is greatly improved in the subthreshold regime!

(\Delta \phi \sim 15\text{mV} \text{ for } 15\text{pM PSA in both regimes})
Nanowire Sensor detection limits
-linear vs. subthreshold regime

Detection limit reduced from pMs to fMs by operating nanowire sensor in the subthreshold regime where screening length $\lambda > R$!
Surface charge detected:

\[ \Delta Q = \left[ C_{DL} + \frac{1}{(C_{SiO2}^{-1} + C_{NW}^{-1})} \right] \times \Delta \varphi \times L \]
Surface charge detected:
\[ \Delta Q = \left( C_{DL} + \frac{1}{C_{SiO2}^{-1} + C_{NW}^{-1}} \right) \times \Delta \phi \times L \]

Solving Poisson-Boltzmann equation
\[ \Delta \rho(r), \Delta \phi(r). \]
Surface charge detected:
\[ \Delta Q = \left[ C_{DL} + \frac{1}{C_{SiO_2}^{-1} + C_{NW}^{-1}} \right] \times \Delta \phi \times L \]

Solving Poisson-Boltzmann equation
\[ \Delta \rho(r), \Delta \phi(r). \]
\[ Q_{NW} = \int_{0}^{R} \Delta \rho \times e \times 2\pi r \, dr \]
\[ C_{NW} = \frac{dQ_{NW}}{d\Delta \phi} \]

For \( R \approx 10\) nm, \( L = 1\) μm
- \( C_{NW} \approx fF \rightarrow aFs \)
- \( C_{DL} \approx fFs \)
- \( C_{SiO_2} \approx \sim fFs \)

\[ C_{NW} \approx e^2 \times \left( \rho \pi R^2 / k_B T \times 2\lambda_{Si}/R \right), \quad \text{high } \rho \]
\[ C_{NW} \approx e^2 \times \left( \rho \pi R^2 / k_B T \right), \quad \text{low } \rho \]
Surface charge detected:
\[ \Delta Q = [C_{DL} +\frac{1}{C_{SiO2}^{-1} + C_{NW}^{-1}}] \times \Delta \phi \times L \]
\[ \to C_{DL} \times \Delta \phi \times L \quad \text{(in subthreshold)} \]
\[ \approx 2\pi \varepsilon / \ln(1 + \lambda_{DL}/R) \times \Delta \phi \times L \]
\[ \varepsilon = 80, \quad L: \text{device length}, \quad R: \text{nanowire radius} \]

<table>
<thead>
<tr>
<th></th>
<th>Linear</th>
<th>Subthreshold</th>
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<tbody>
<tr>
<td>( \Delta \phi_{min} )</td>
<td>5mV</td>
<td>0.66mV</td>
</tr>
<tr>
<td>( \Delta Q_{min} ) (I.S.=10mM)</td>
<td>~300e</td>
<td>~40e</td>
</tr>
<tr>
<td>( \Delta Q_{min} ) (I.S.=10\mu M)</td>
<td>~50e</td>
<td>~6e</td>
</tr>
</tbody>
</table>

For R~10nm, L=1\mu m
\( C_{NW}: fF \rightarrow aFs \)
\( C_{DL}: fFs \)
\( C_{SiO2}: \sim fFs \)

* Calculated for per \( \mu m \) NW with R=10nm
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4. Perspective/Future directions
Nanowire FET noise as a probe for biochemical reactions--motivation

Fluctuation–dissipation theorem: the response of a system to an external perturbation is related to the fluctuations of the system in thermal equilibrium.

\[ \bar{v}_n^2 = 4k_B TR \]

Johnson noise $\rightarrow R$ or $T$

AFM tip noise $\rightarrow \omega_{\text{reson}}$ & $Q$

Hutter, Bechhoefer *RSI* (1993).

‘spin noise’ $\rightarrow$ hyperfine splittings


*Noise can give useful information without disturbing the system!*
Nanowire FET noise as a probe for biochemical reactions--motivation

Fluctuation–dissipation theorem: the response of a system to an external perturbation is related to the fluctuations of the system in thermal equilibrium.

Can we obtain reaction kinetics from the noise of bio-sensors at equilibrium?

Reaction Kinetics

\[
[\text{Ab}] + [\text{Ag}] \quad \xrightarrow{k_a} \quad [\text{Ab}/\text{Ag}] \quad \xleftarrow{k_d}
\]
Protein binding induced Lorentzian noise

- PSA binding/unbinding at equilibrium adds a Lorentzian noise to the 1/f noise of NW.
- Lorentzian noise still presents in low concentrations which are not detectable in time domain.
Summary

1. Sensitivity limits of nanowire biosensors
   • Where to achieve the best sensitivity? *subthreshold.*
     reduced carrier screening → efficient molecule gating;
     $\Delta G/G \rightarrow \exp(\Delta \phi /kT) - 1$.
   • Pushing sensitivity limits: pH, protein detections
     pM PSA (linear) → fM PSA detection (subthreshold)
   • Charge detection limits (a few e’s)

2. Probing bio-reaction by device noise
   • protein binding induced Lorentzian noise
(1) Towards single molecule detection and reaction dynamics study

Bio-Apps

- single molecule study
- reaction dynamics
- capacitance sensing
- biomolecule manipulation and electrokinetics
- protein/DNA/cell

Initial approaches: higher mobility / shorter channel devices; suthreshold regime sensing…

Label free & direct electrical study of single biomolecules and their reaction dynamics
Nanowire Research: Future Directions

(2) capacitance sensing ($\varepsilon$ effect);

**Bio-Apps**
- single molecule study
- reaction dynamics
- **capacitance sensing**
- biomolecule manipulation and electrokinetics
- protein/DNA/cell

Conductance $\rightarrow$ **charge** of biomolecules
Capacitance $\rightarrow$ **dielectric properties** of biomolecules
Nanowire Research: Future Directions

Physics

• diffusive vs. ballistic transport in 1D
• single particle vs. many-body
• thermal/thermoelectric properties
• charge vs. spin transport

Quantized at low $T$!

1D hole gas, Lu et al, PNAS 2005,
Xiang et al, Nature 2006

Hetero-structures will enable novel physics study
in clean (‘ballistic’) 1D nanostructures

How to directly probe ballistic holes in NW?
How about heat transport?...
Nanowire Research: Future Directions

**Development**
- new materials, structures
- addressable arrays
- micro-fluidics, lab on a chip
- novel devices, energy solutions
- proteomics, genomics
  - drug discovery, cell biology

**Physics**
- diffusive vs. ballistic
- single particle vs. many-body
- charge vs. spin transport
- electric/thermal properties

**Bio-Apps**
- single molecule study
- reaction dynamics
- capacitance sensing
- biomolecule manipulation and electrokinetics
- protein/DNA/cell

*\( \tau_{on} \) \( \tau_{off} \)*

\( C \) \( S \) \( Y \) \( d \)
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Thank You!