CMOS Nanowire Biosensor Systems

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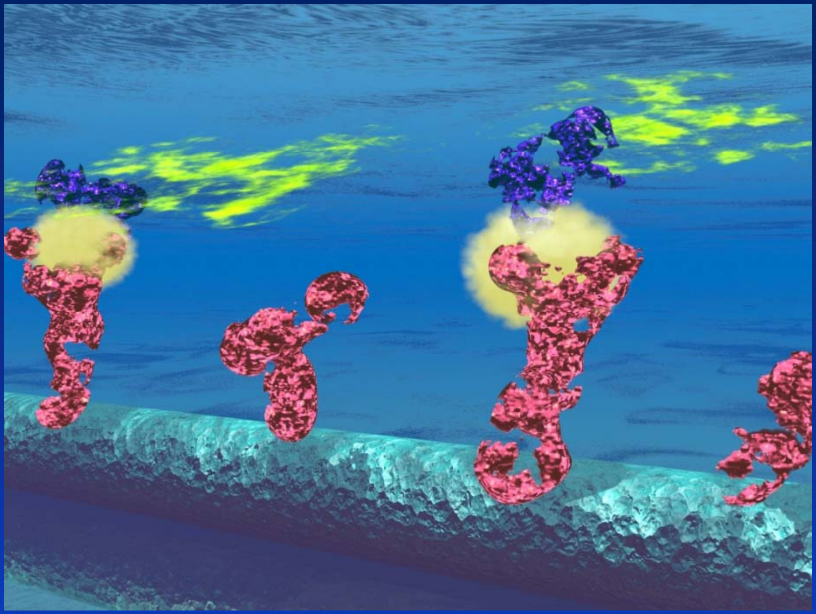
Yale University



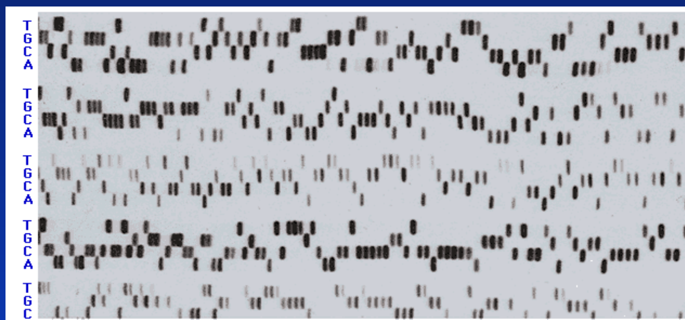
Departments of Applied Physics and Electrical Engineering
Yale Institute for Nanoscience and Quantum Engineering

with: Eric Stern, Alek Vacic, Nitin Rajan, David Routenberg, Erin Steenblock, Jason Criscione, Jason Park, Prof. Tarek Fahmy

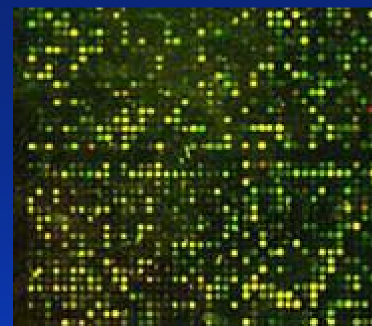
Thanks to: Jin Chen, James Klemic, Daniel Turner-Evans, Pauline Wyrembak , Cathy Jan
Labs of Profs. Ronald Breaker, Andrew Hamilton, Tarek Fahmy

Current Macromolecular Sensing

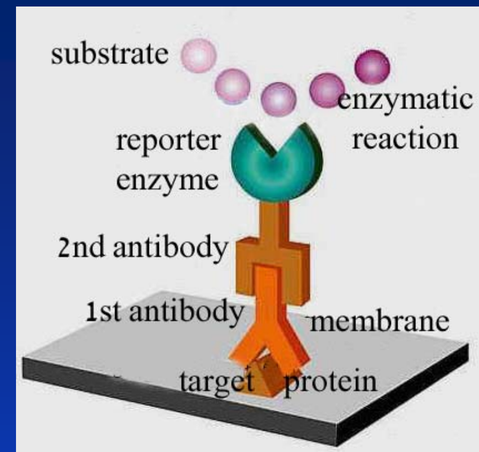
Labeled sensing



DNA sequencing, radiotag

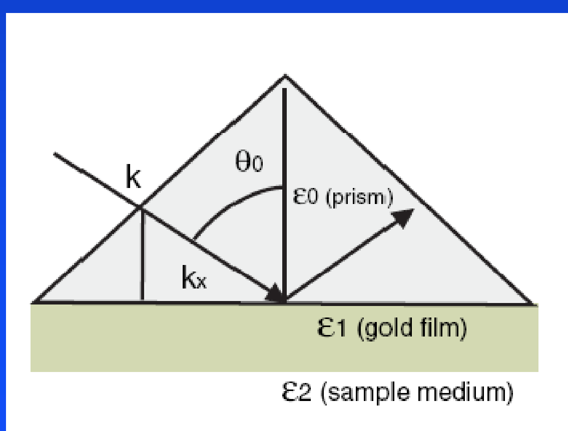


DNA array, fluor

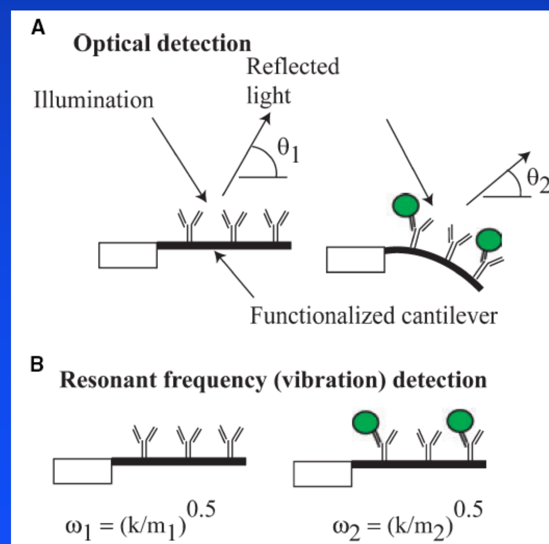


ELISA: Indirect fluor

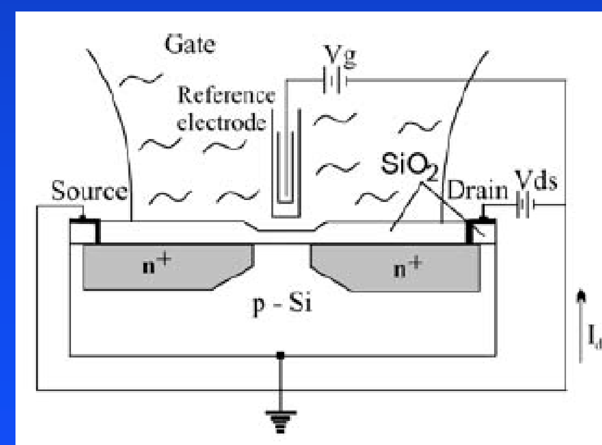
Unlabeled sensing



Surface plasmon resonance

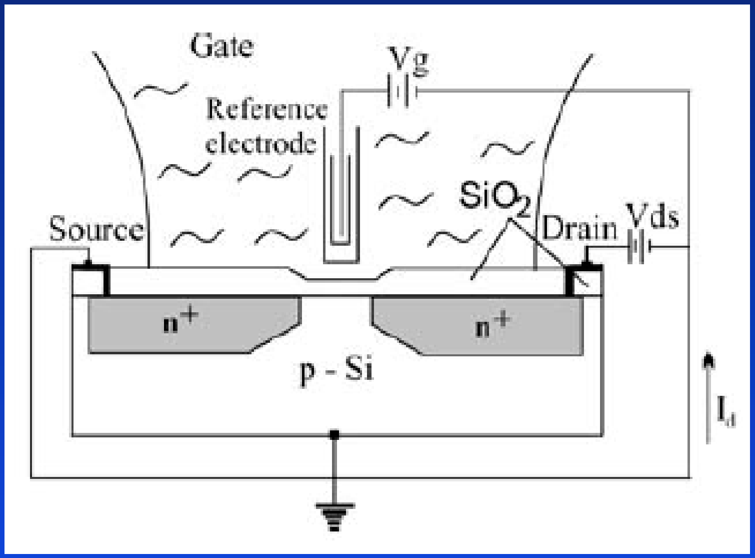


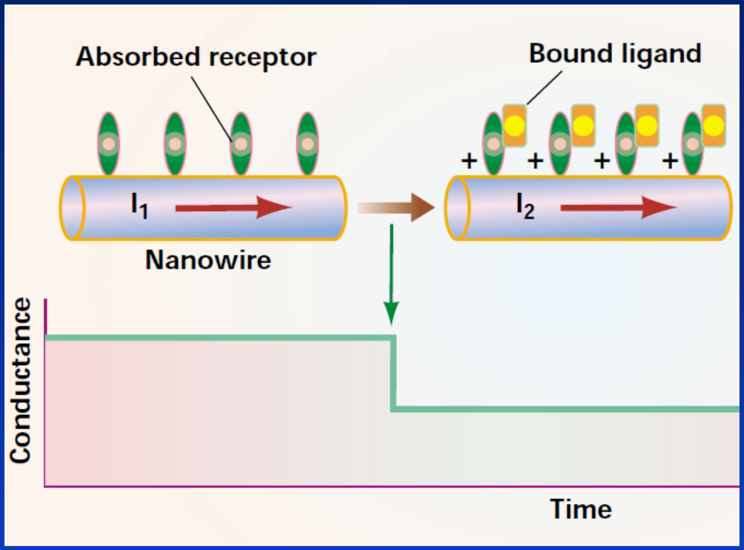
Suspended cantilever



Electrical : ISFET

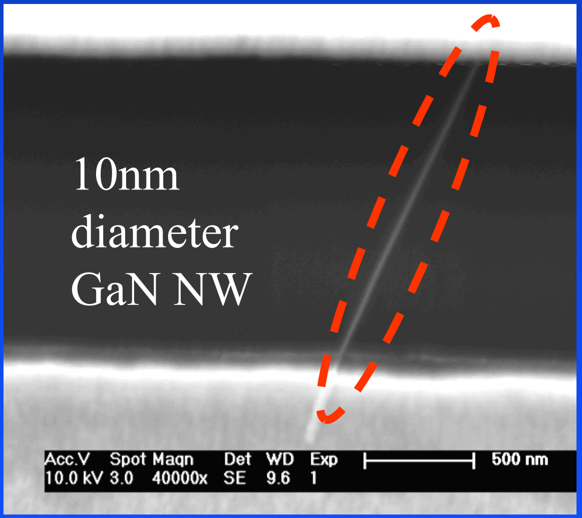
Nanowire biosensors (unlabeled detection)



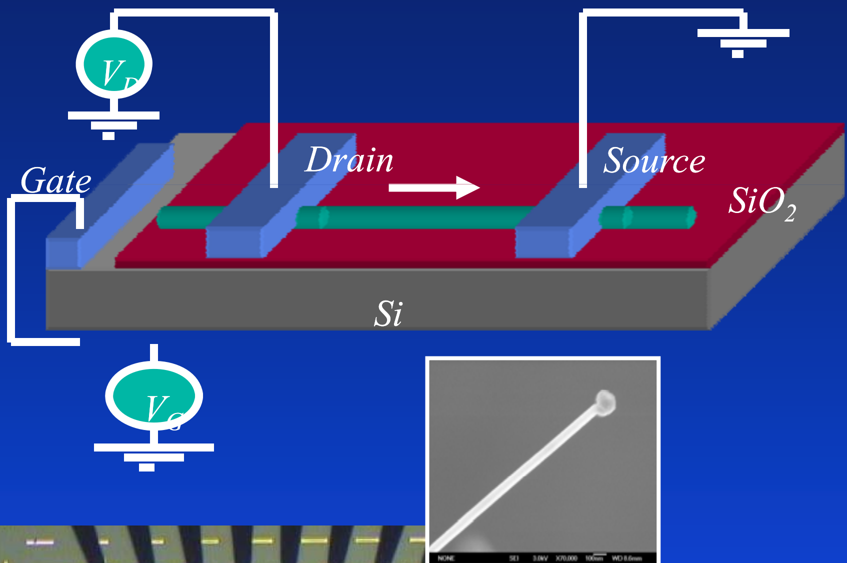


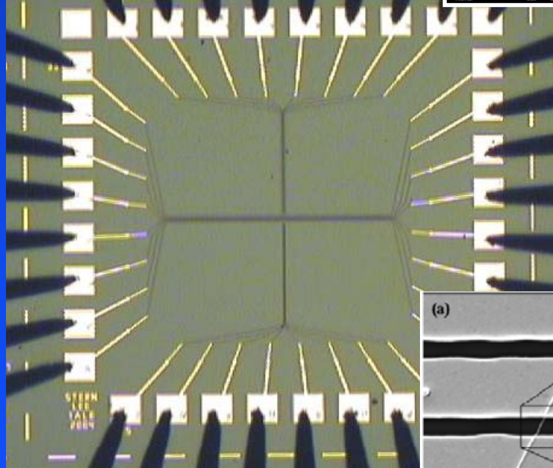
ISFETs detection limits typically ~ μM

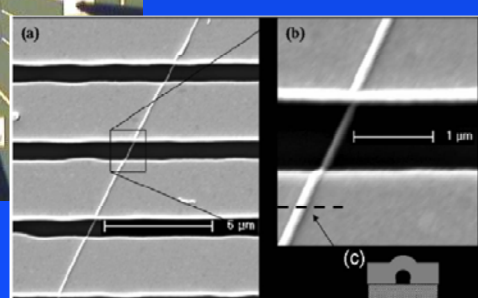
$$\frac{1}{I}\frac{dI}{dQ} \sim \frac{1}{r}$$



Vapor-Liquid-Solid (VLS) nanowire FETs

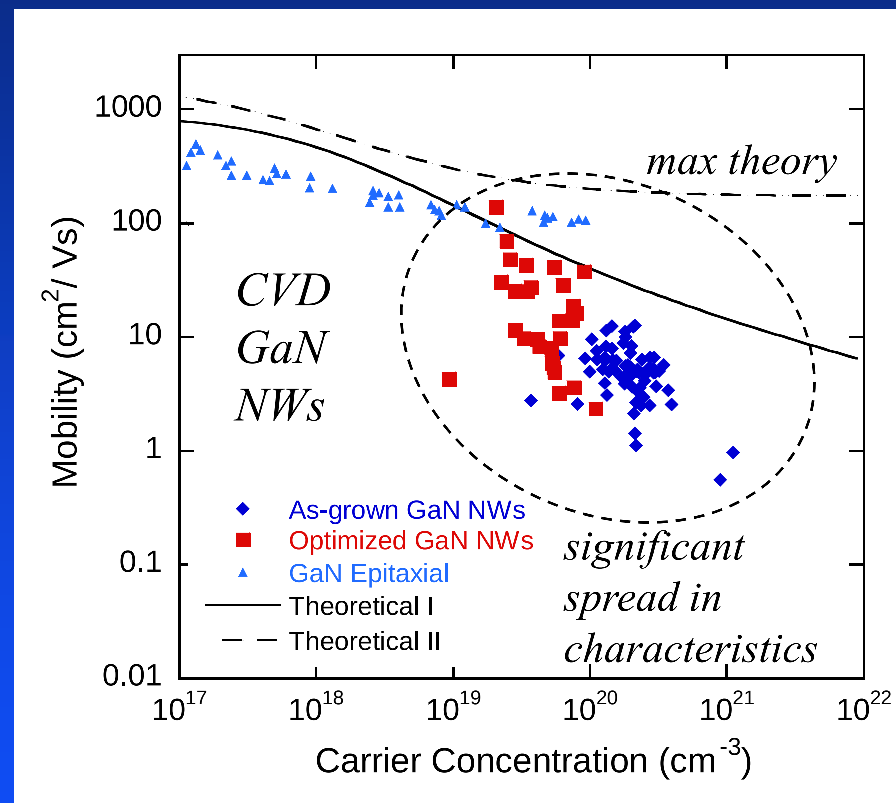






J. Vac. Sci. Technol. **B24**, 231 (2006).

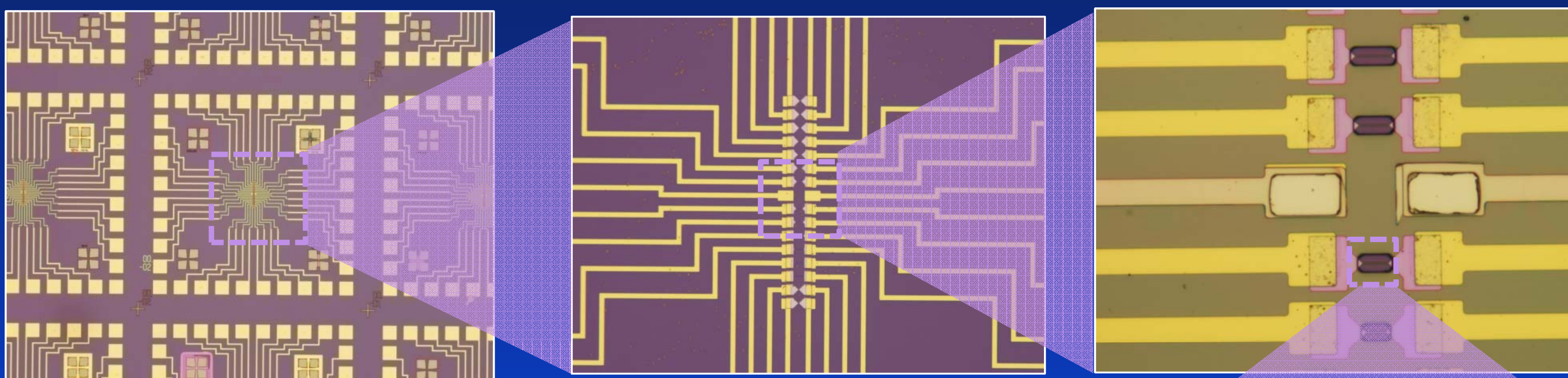
NW mobilities vs theoretical limits, epi

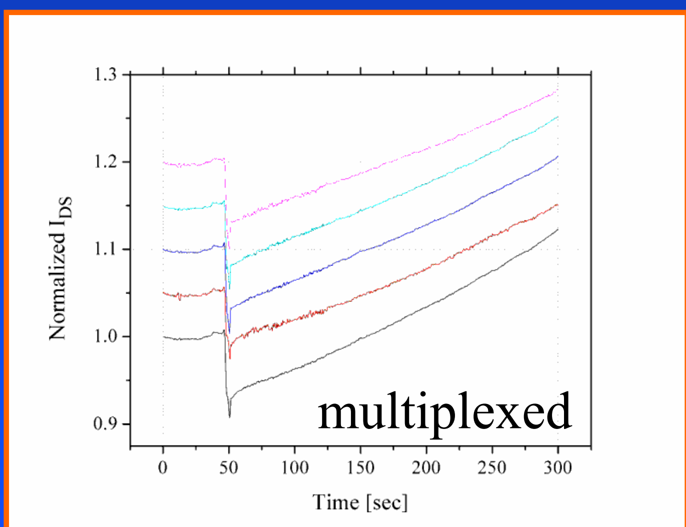


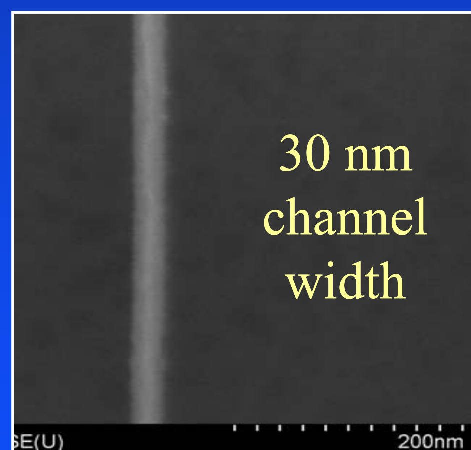
Braz. Jour. Phys. **36**, 824 (2006).

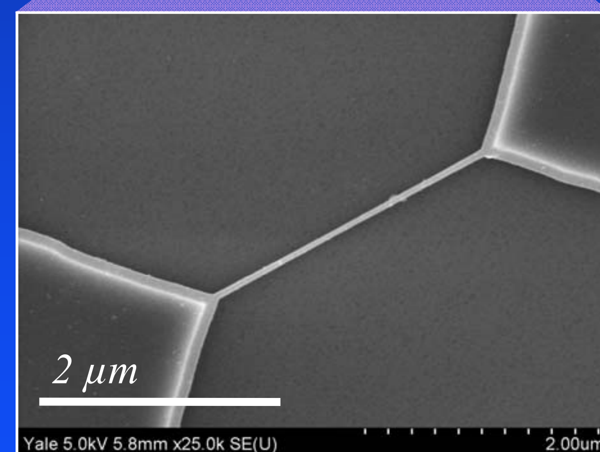
Appl. Phys. Lett. **88**, 053106 (2006) .

Silicon-on-insulator (SOI) CMOS Nanowires



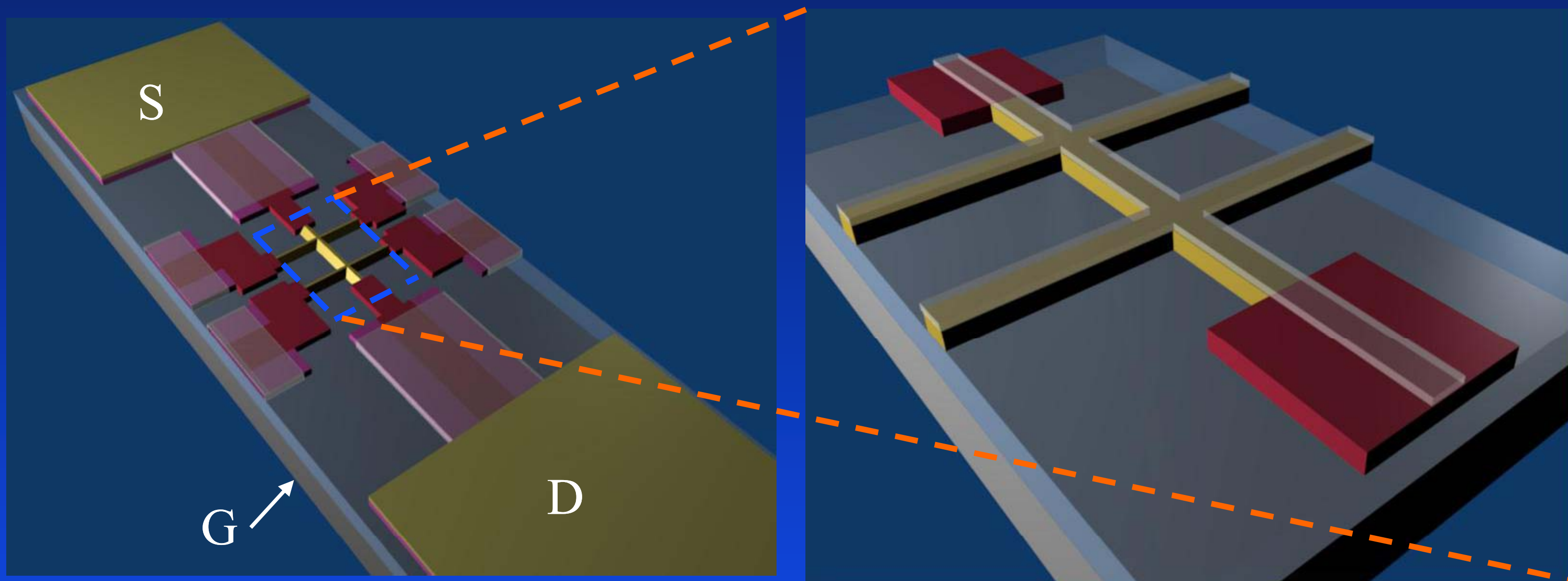


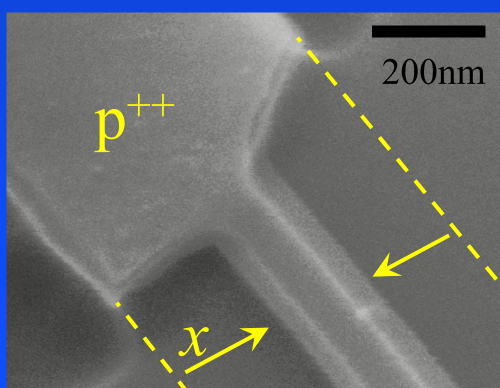


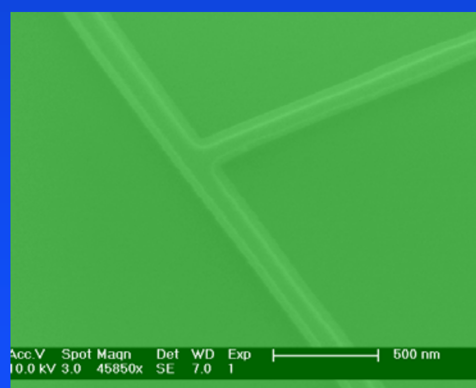


anisotropic etching

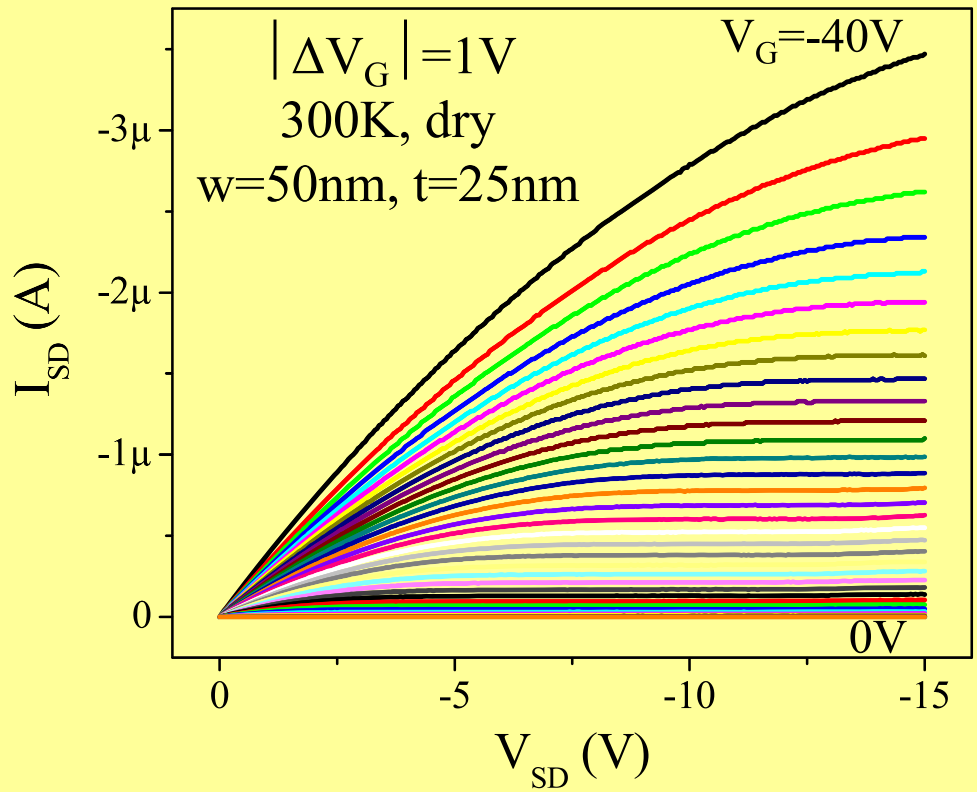
(100)/(111) etch rates ~ 1000:1, $dx_{(111)}/dt$ ~ 3Å/sec



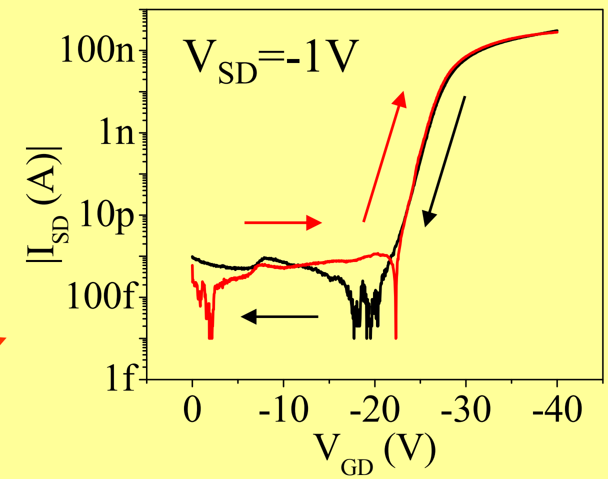


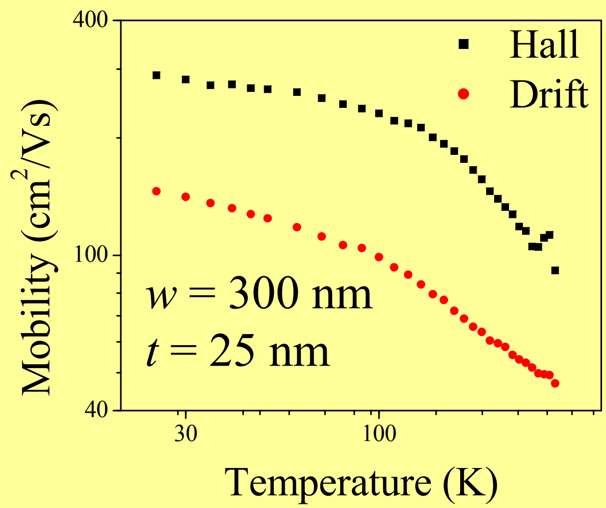


p-type accumulation mode (backgate) – 1st gen



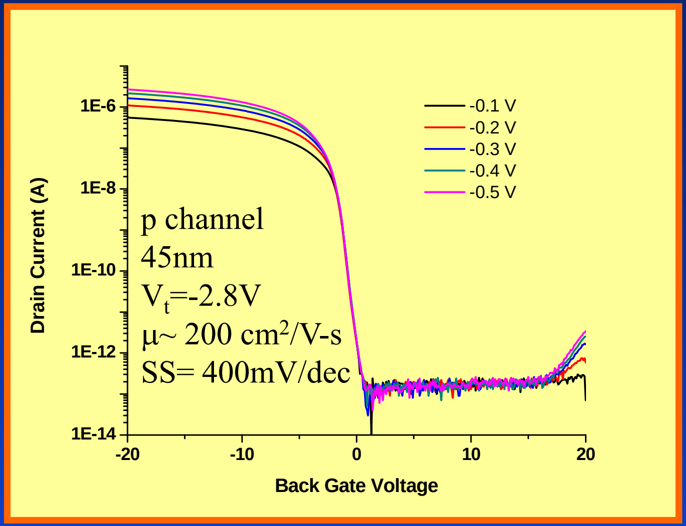
Fully depleted; $n_0 \sim 1\text{x}10^{15}$ cm^{-3}

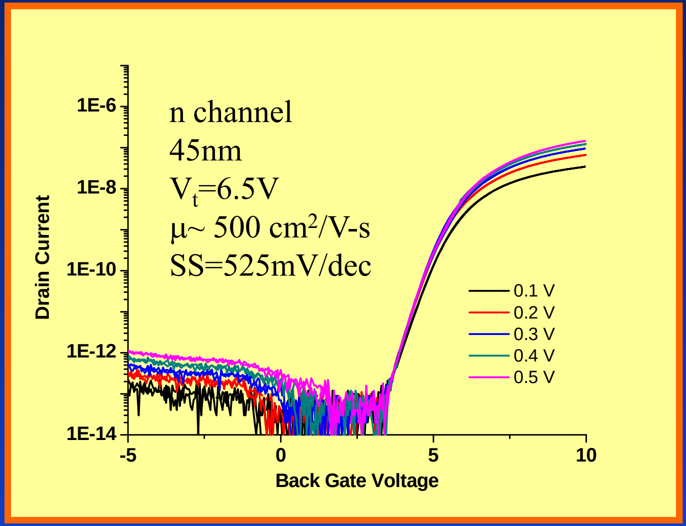


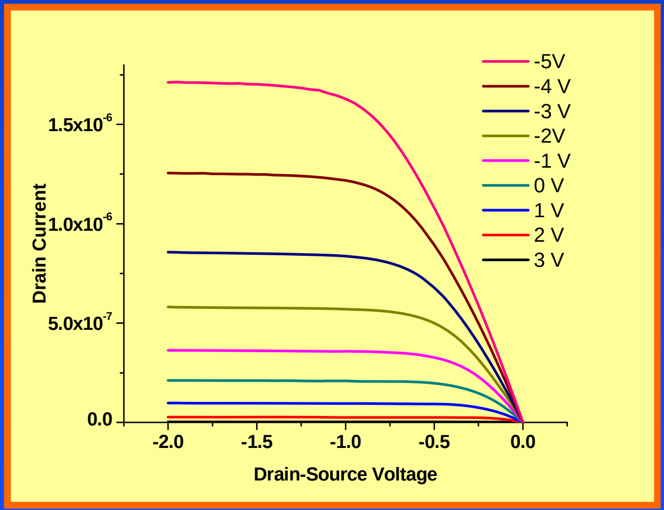


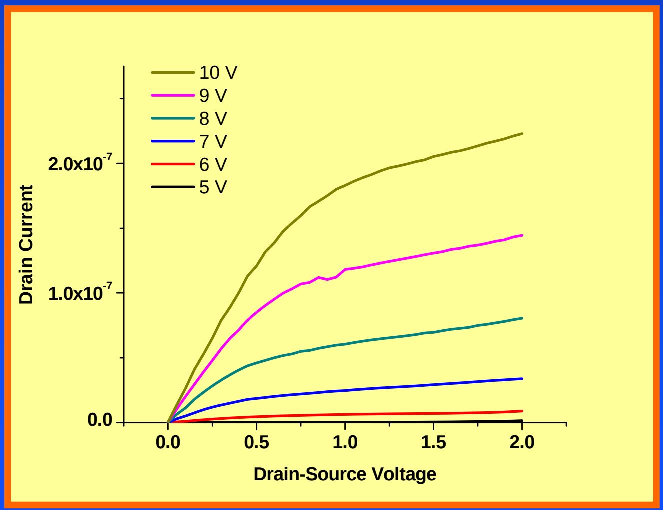
$\bar{\mu}$ = 54 cm²/V-s μ_{max} = 139 cm²/V-s

Complimentary devices – 2nd gen

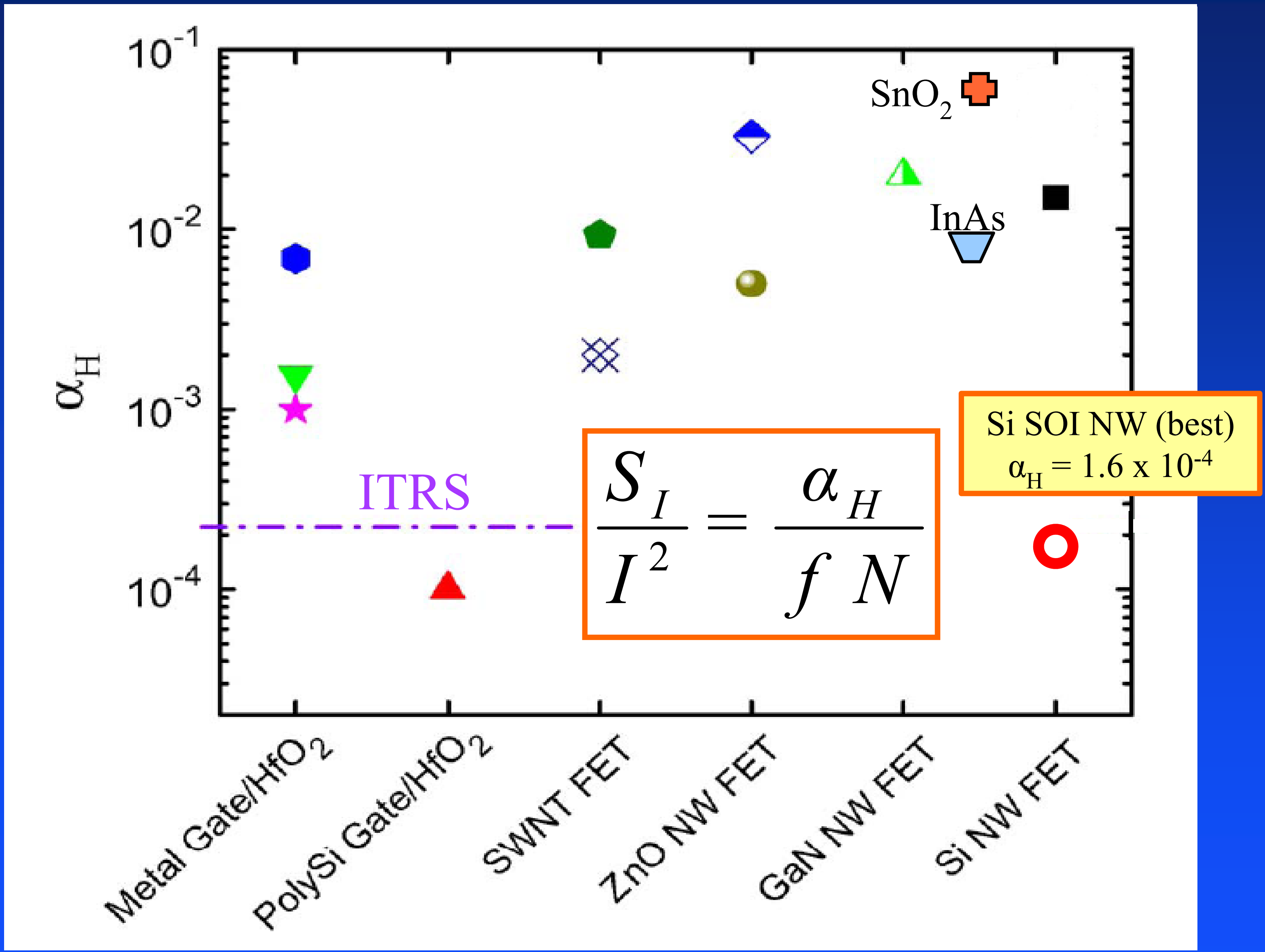




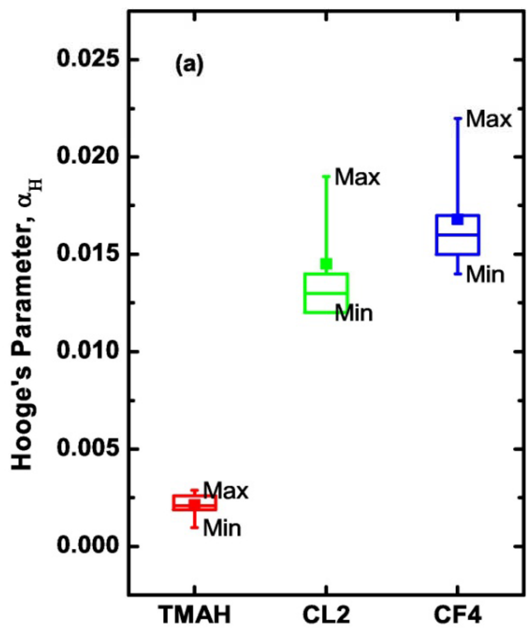


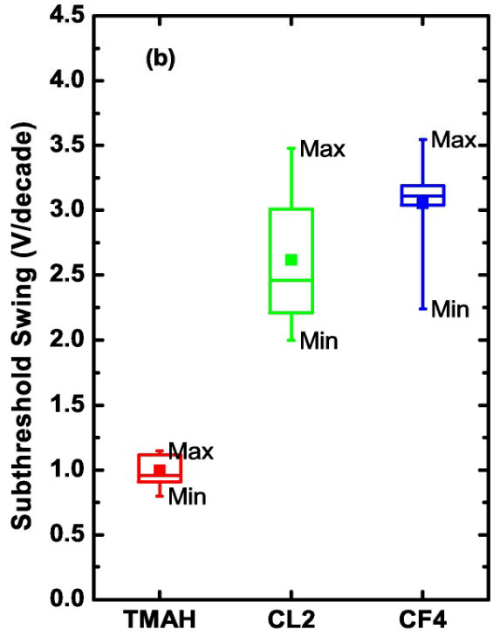


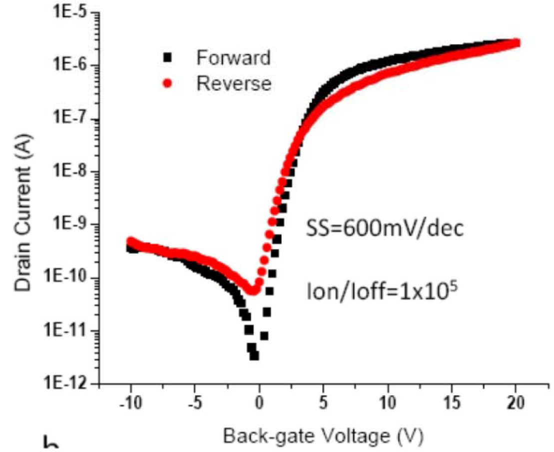
1/*f* noise of nanowires



Etch Process-Noise Correlation







$$S = 2.3\frac{kT}{q}\frac{(C_{ox} + C_{it} + C_d)}{C_{ox}}$$

Etch Type	TMAH	Cl_2	CF_4
μ_{FE} (cm^2/V•s)	170	180	100
Std. Dev. (cm^2/V•s)	10	50	20

N. K. Rajan *et al*, *Elect. Dev. Lett.* **31**, 615 (2010).

Operating Point

Linear Region:

$$\frac{dI_D/dV_0}{I_{D,initial}} = \frac{\beta V_{ds}}{\beta\left[V_0 V_{ds} - \frac{1}{2}V_{ds}^{\ 2}\right]} = \frac{1}{\left[V_0 - \frac{1}{2}V_{ds}\right]}$$

Subthreshold Region:

$$\frac{dI_D/dV_g}{I_{D,initial}} = \frac{\frac{q\eta}{kT} I_{D0}\exp\left[\frac{qV_{gs}\eta}{kT}\right]}{I_{D0}\exp\left[\frac{qV_{gs}\eta}{kT}\right]} = \frac{q\eta}{kT} = \frac{1}{S}$$

$$\beta = C_{ox}\mu W/L$$

$$V_0 = V_{gs} - V_t$$

$$\eta = \frac{d\phi_s}{dV_{gs}} = \frac{1}{1+(C_d/C_{ox})}$$

example

In Subthreshold Region

Subthreshold Swing = 190 mV/dec

S = 1/SS = 5.3

pH Response = 0.3 Dec/pH

In Linear Region

$G_m = 8.2 \times 10^{-6}$

$I_D = 8.0 \times 10^{-6}$ x Overdrive Voltage

$S = G_m / I_D = 1.03/ V_O$

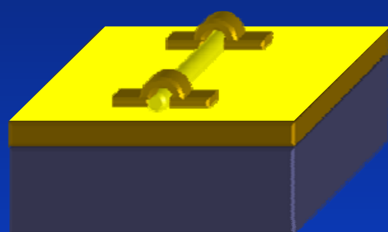
pH Response = $0.062/V_O$ Dec/pH

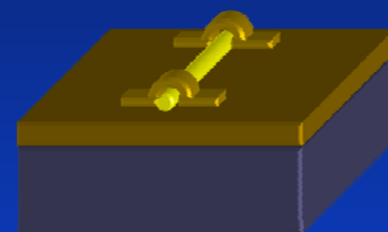
At 1 volt overdrive, sensitivity is decreased by 5X

Selective Functionalization

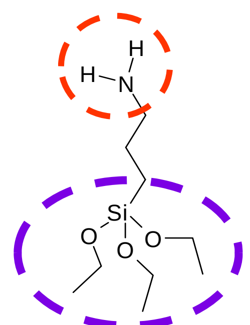
Dec-9-enyl-carbamic acid tert-butyl ester

APTES

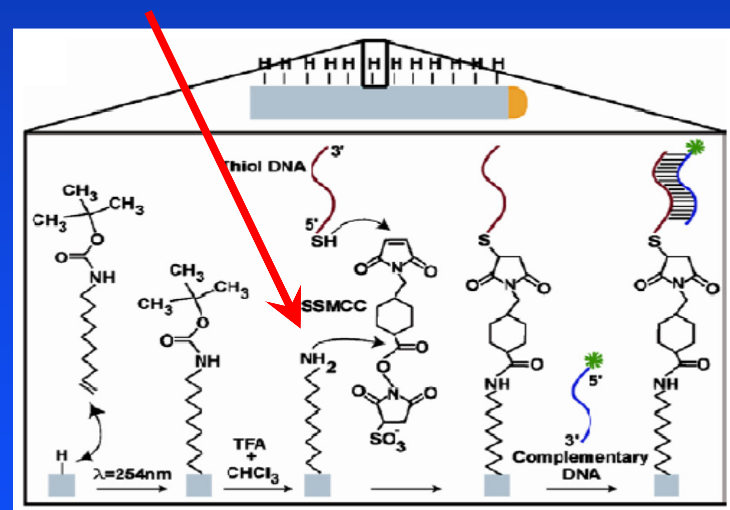




Ratio of Si sensor area to parasitic important

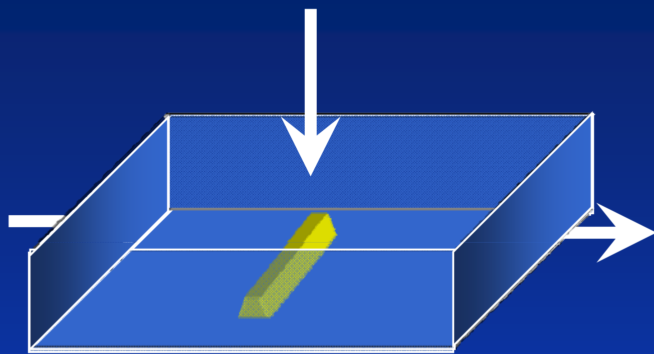


3-aminopropyl-triethoxysilane



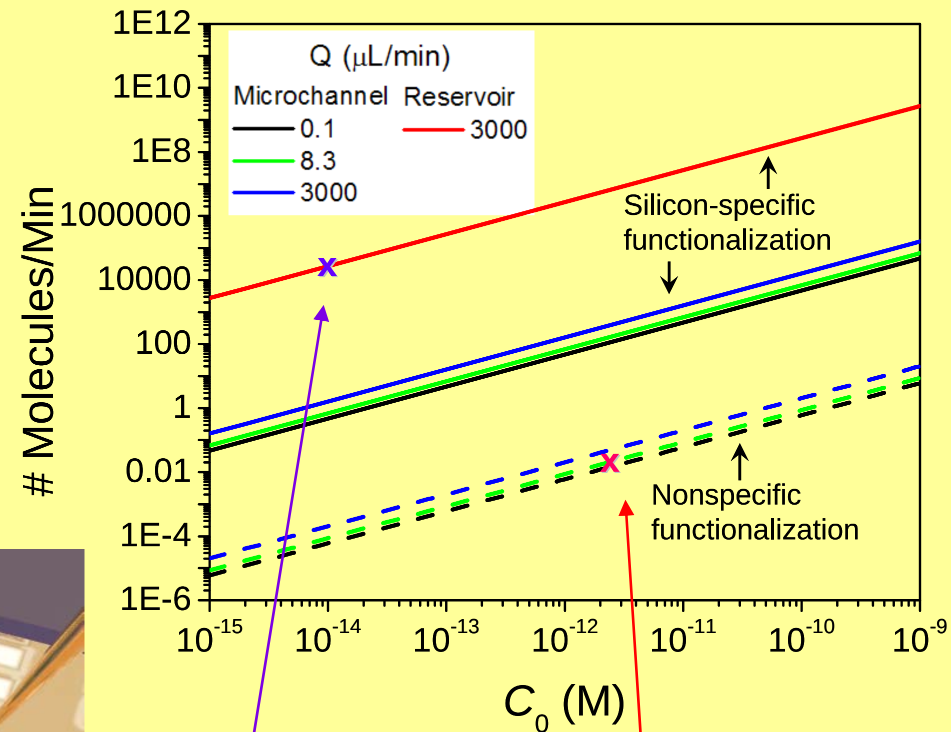
Fluid Considerations

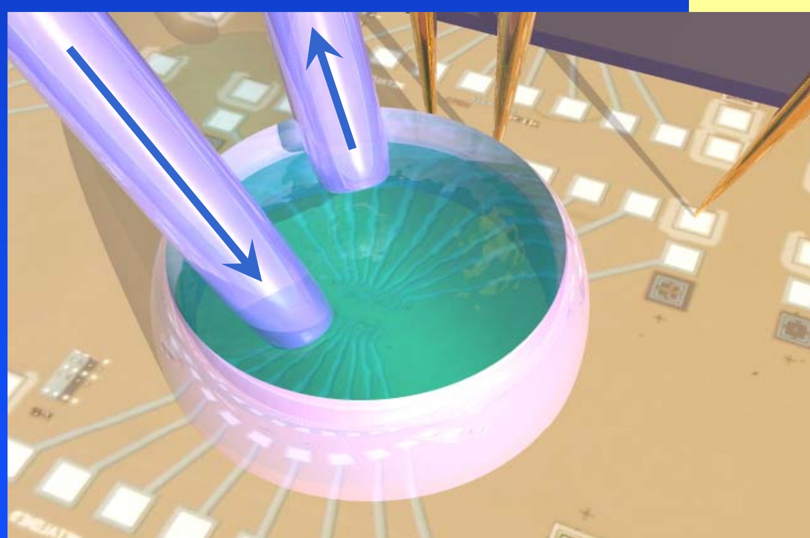
Nano Lett **5**, 803 (2005)



$$J_z = -D\frac{d^2C_0}{dz^2} + u_z C_0$$

0

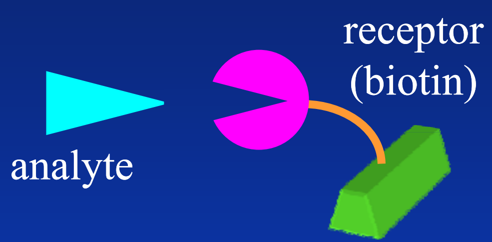




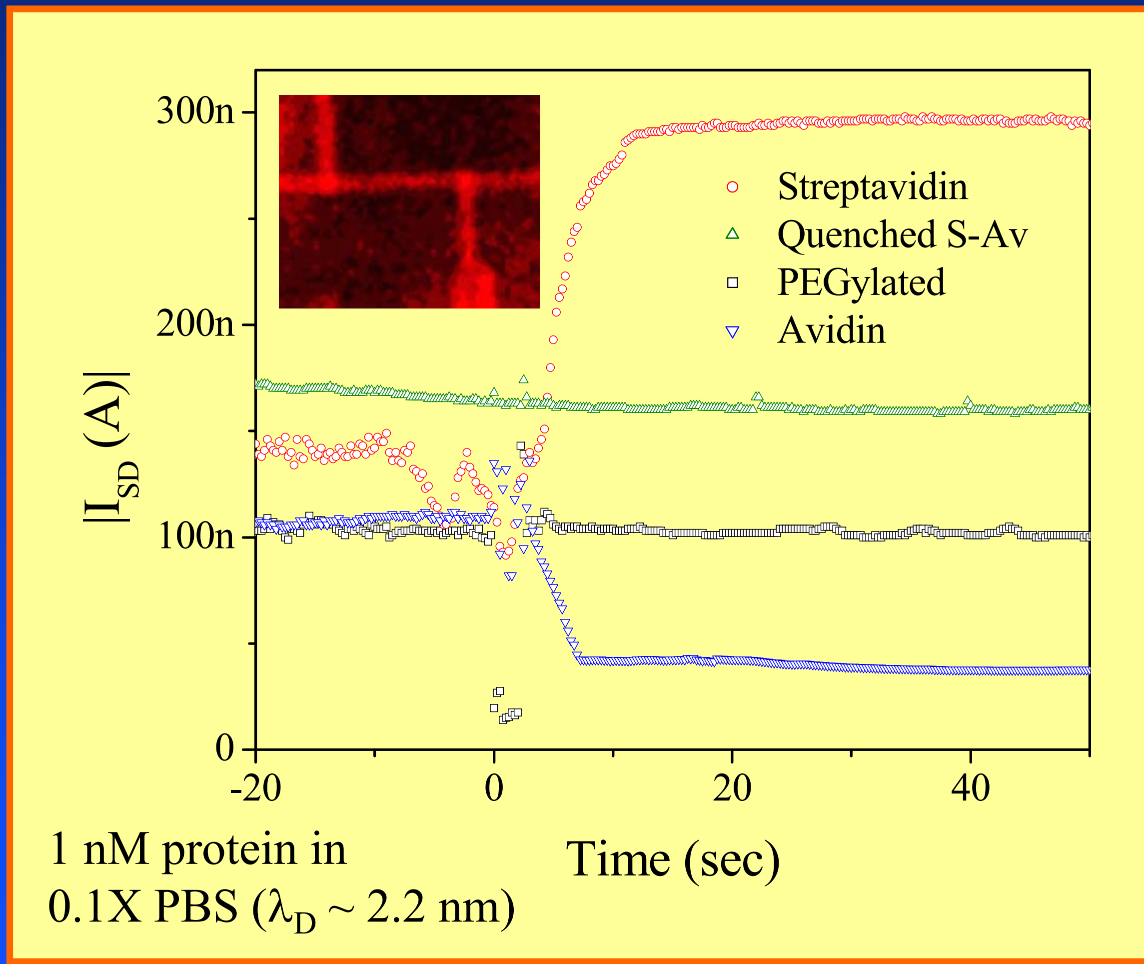
x = microfluidics
Science **293,** 1289 (2001)

x = mixer (resorvoir)
Nature **445,** 519 (2007)

Biotin-Avidin & Streptavidin Sensing

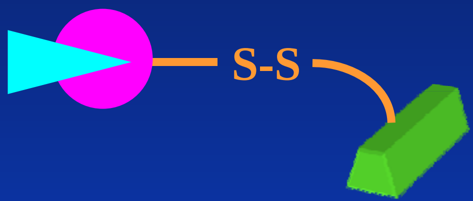


- p-type accumulation mode, biotinylated NW device
- avidin
  - positive charge
  - ⇒ current decrease
- streptavidin
  - negative charge
  - ⇒ current increase
- poly(ethylene glycol) (PEG)-ylated device, quenched avidin controls

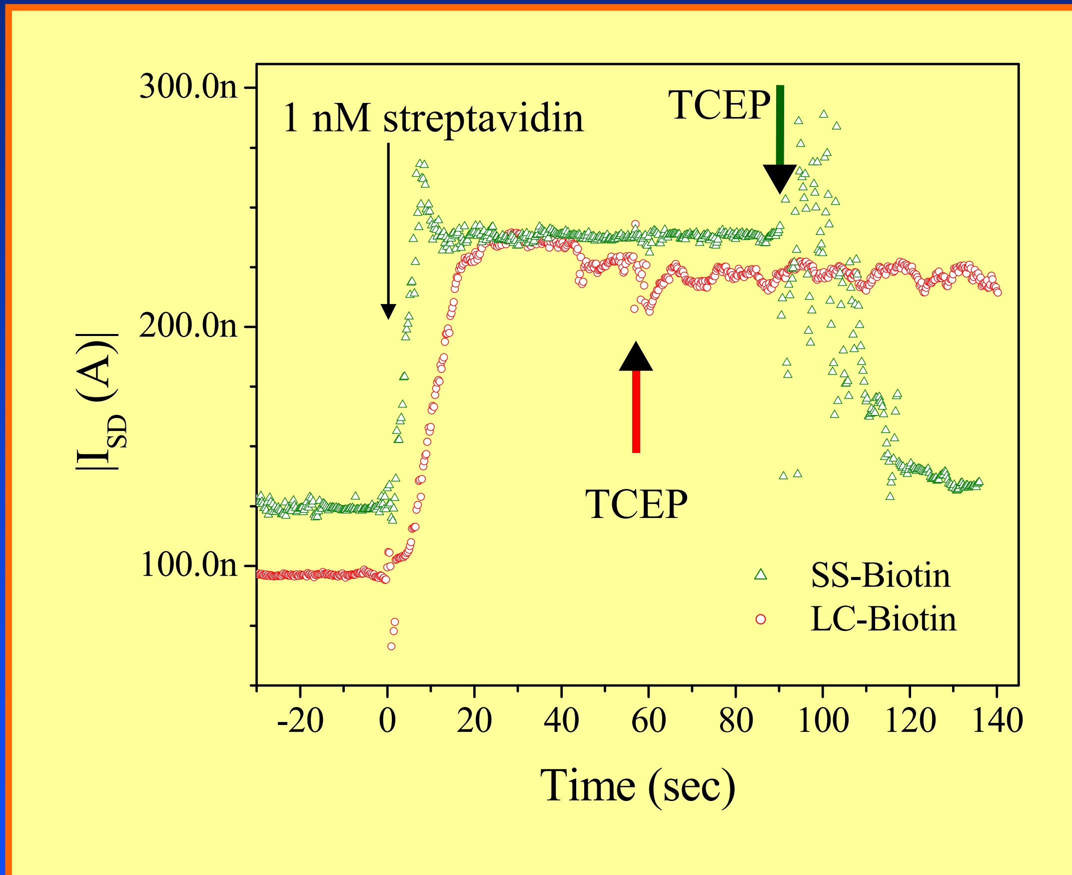


Nature, **445**, 519 (2007)

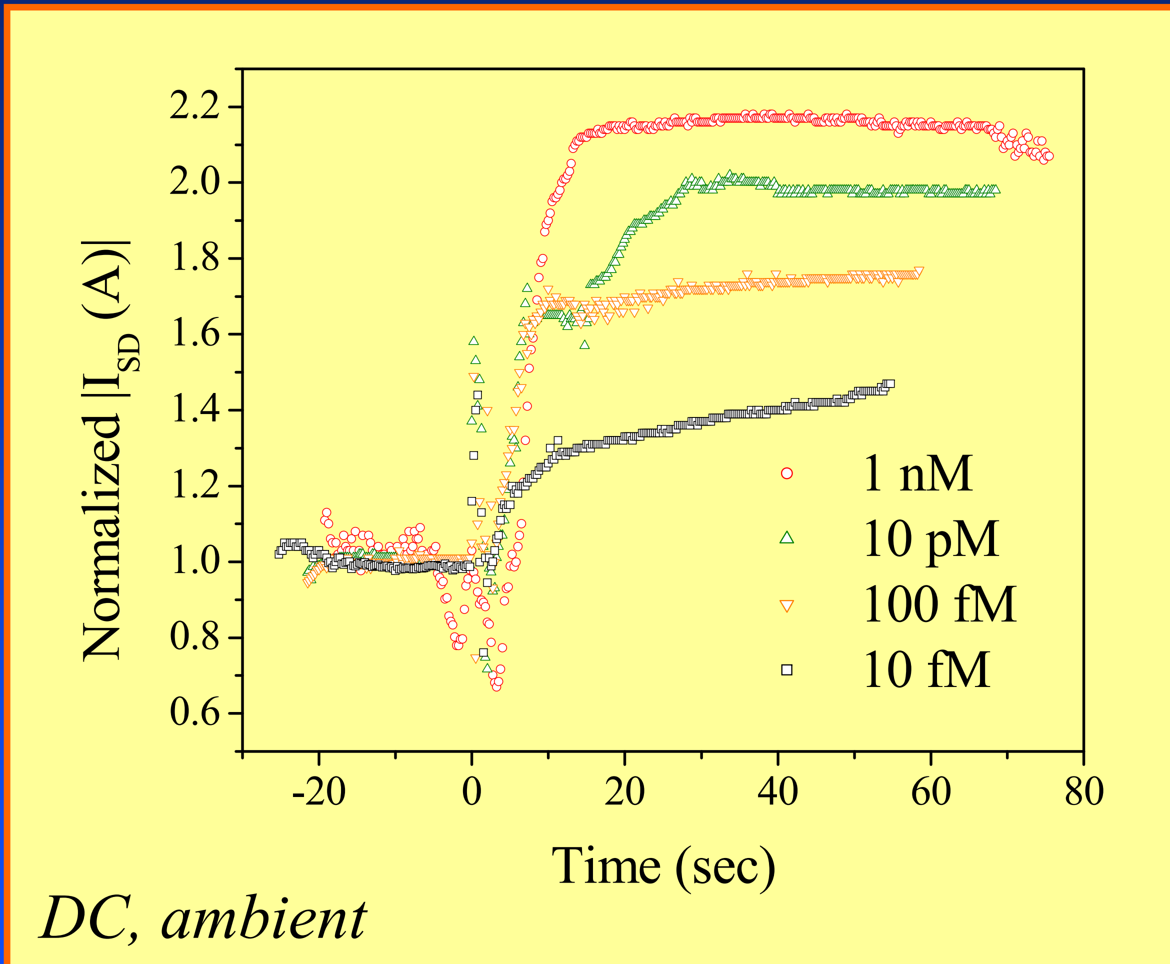
Proving Protein Presence: Cleavage Response



- p-type accumulation
- Red: functionalization with LC-biotin (inert PEG linker)
- Green: functionalization with SS-biotin (dithiol linker)
- Arrow: Addition of reducing agent TCEP (tris(2-carboxyethyl)phosphine)
- SS-biotin functionalized sensor exhibits cleavage



Sensitivity: Concentration Dependence



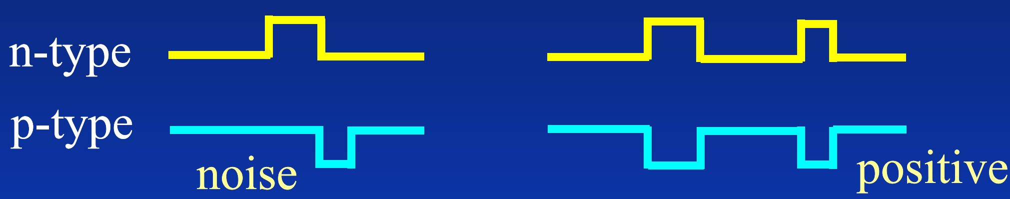
- initial S/N ~ 140 (@10fM)

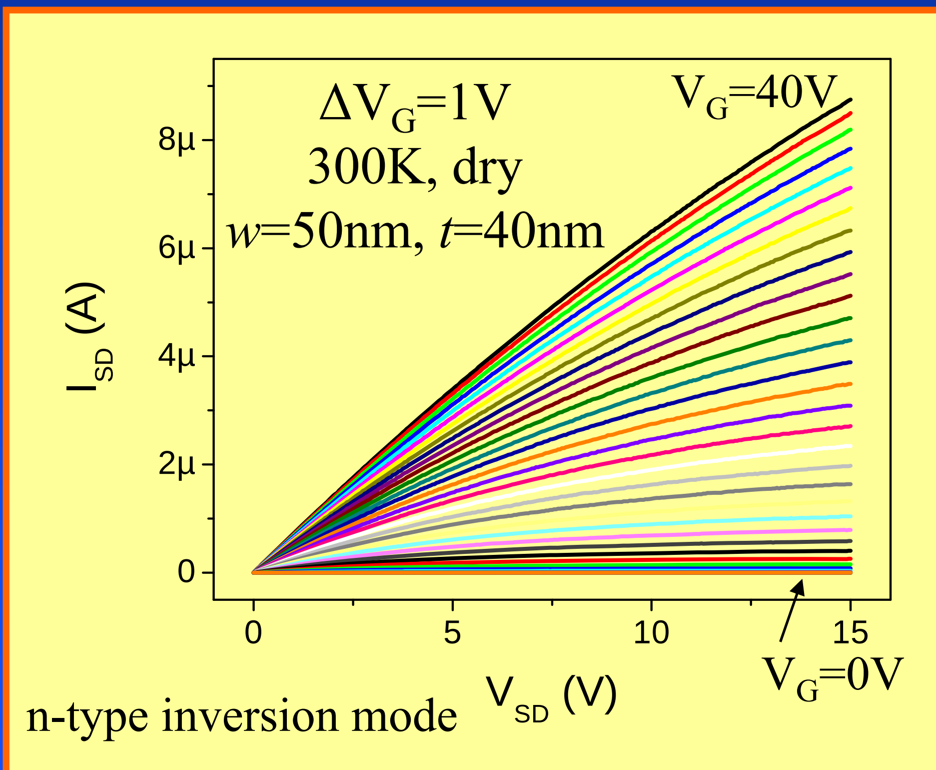
  ⇒ <100 aM limit (< 3 fg/ml)

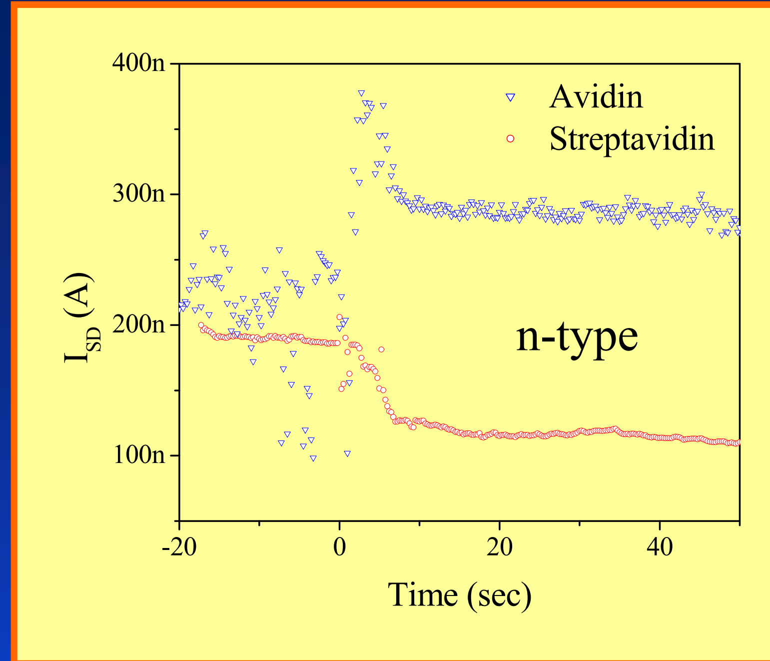
  (1 aM = 30 molecule per mm^3)

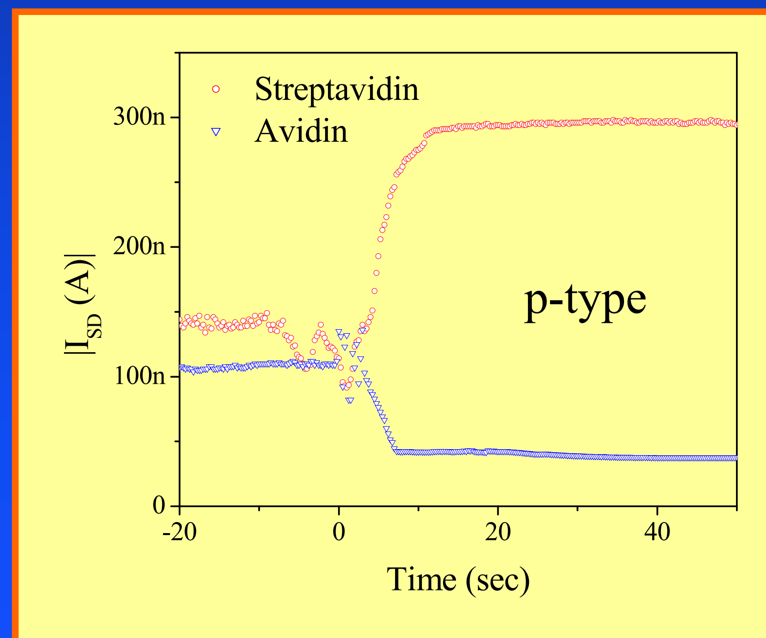
Complementary Sensing

- Critical for error detection
- n-type inversion (on same wafer)

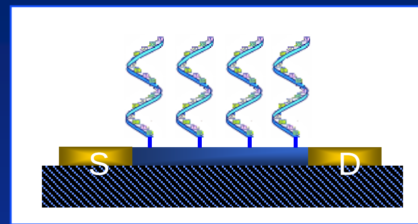




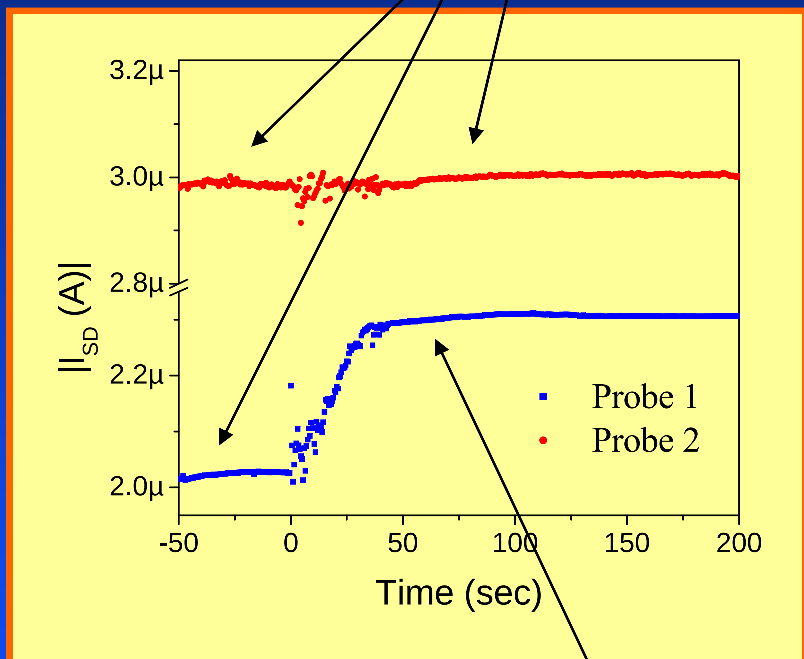


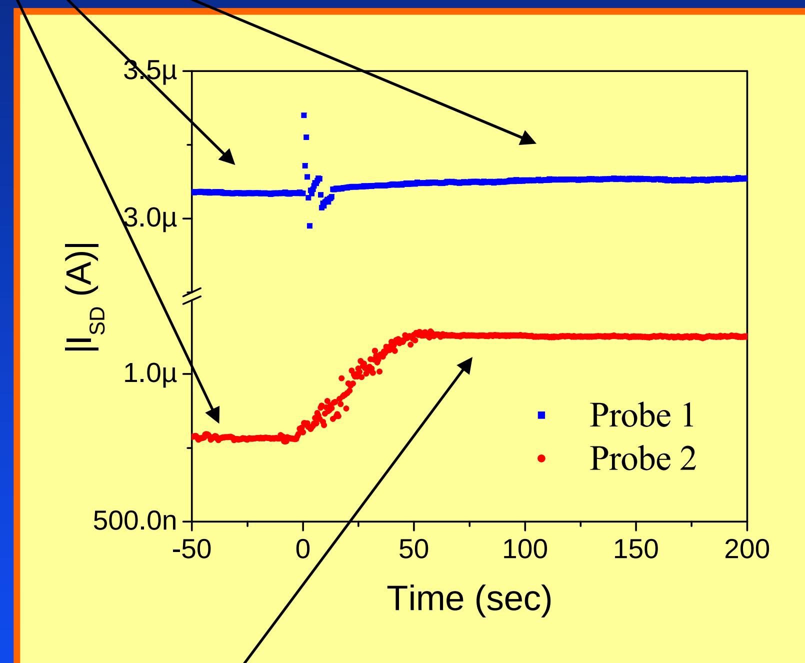


DNA sensing: criss-cross

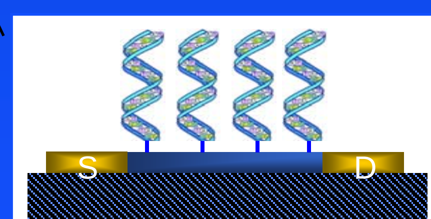


• Capture1 is the complementary strand of Probe1;
• Capture2 is the complementary strand of Probe2



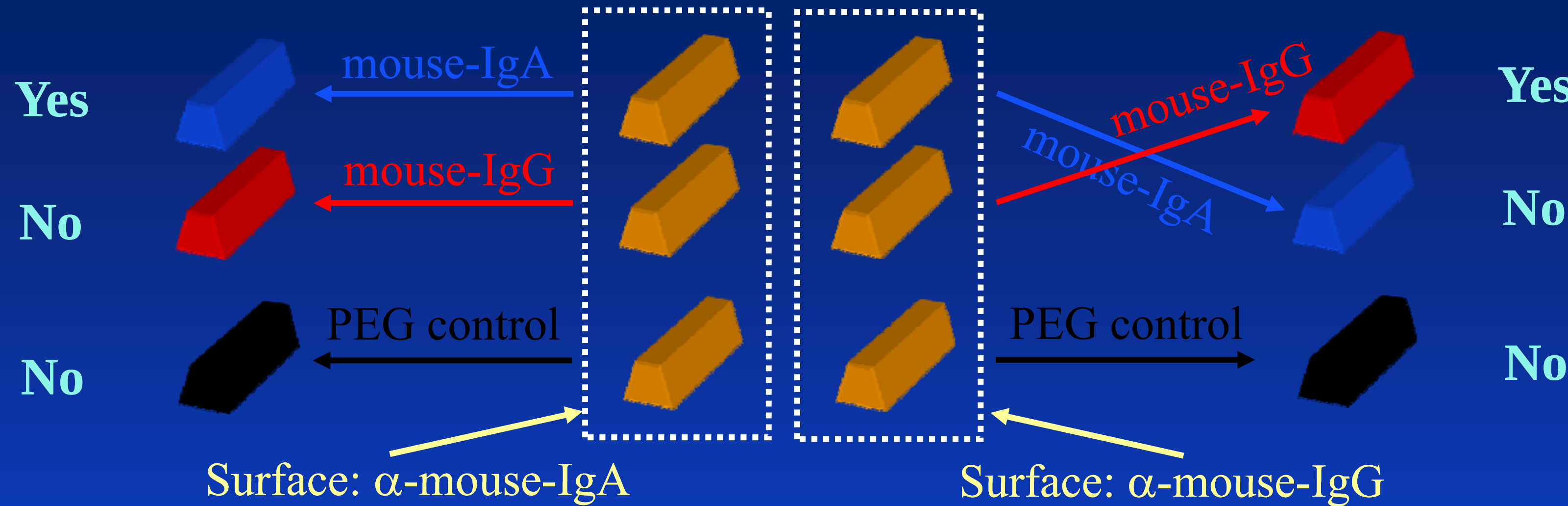


Surface: Capture1

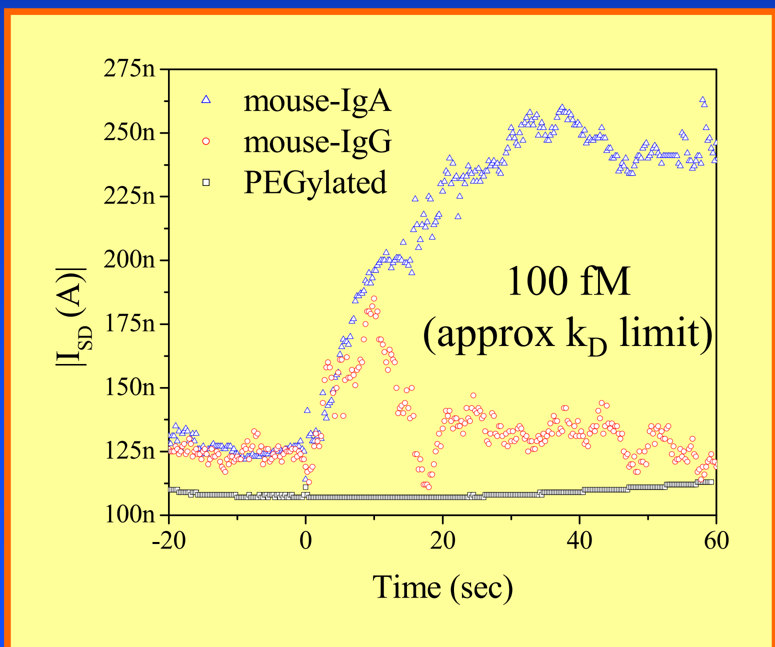


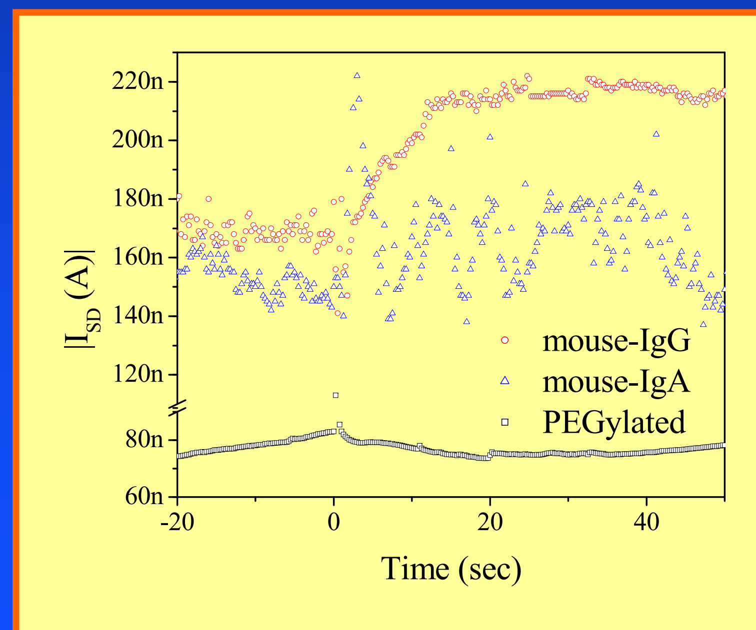
Surface: Capture2

Crisscross Protein Assay: Antibody-Antigen Specificity



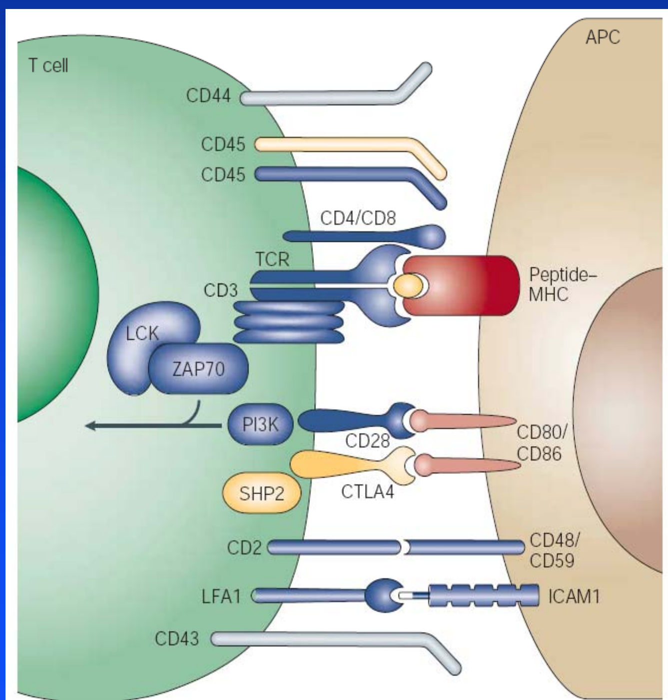
100 fM mouse-IgG/IgA in 1.5 mM bicarbonate (λ_D ~ 6.8 nm)



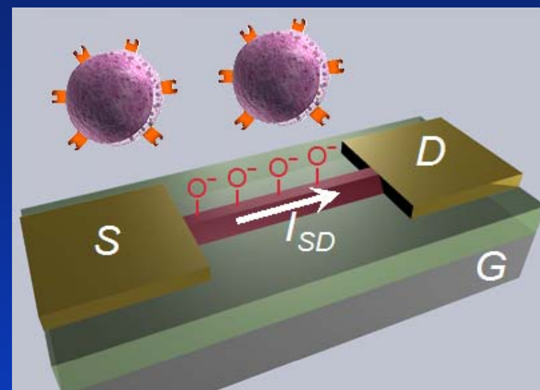


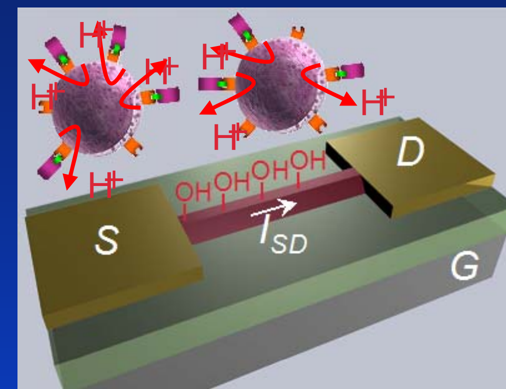
Unlabeled Cellular Detection

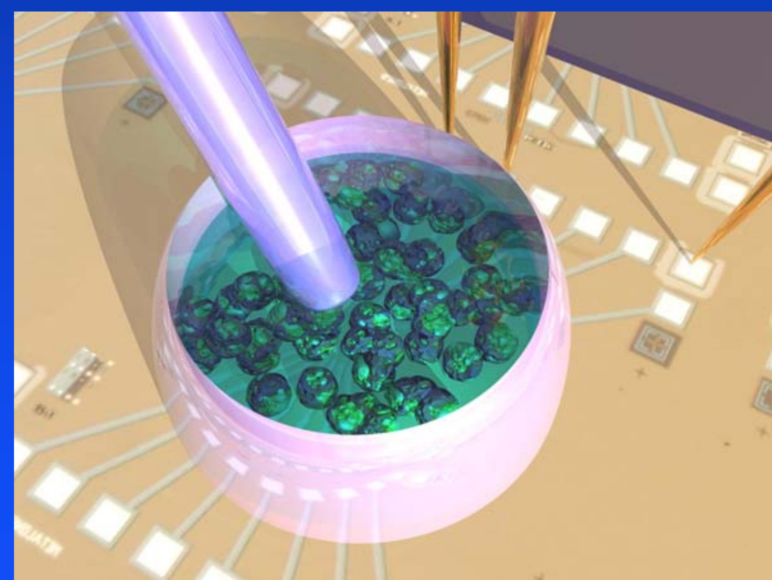
- Most cells (including pathogenic) release H^+ in response to specific stimulation



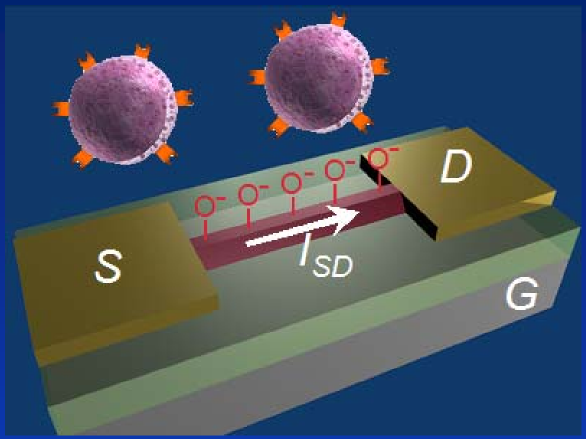
Nat Rev Immunol **3** (2003) 973

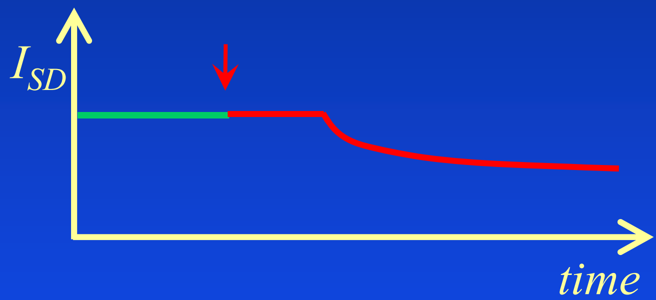


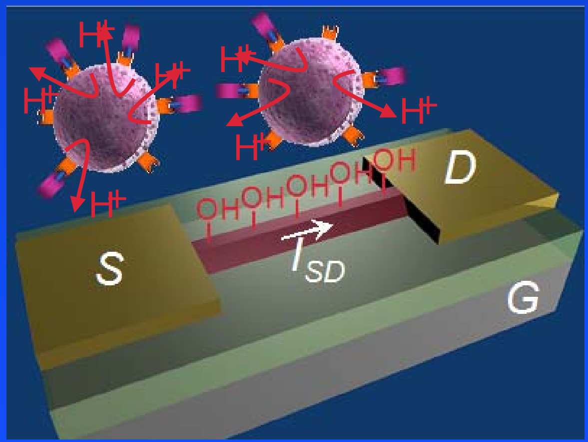


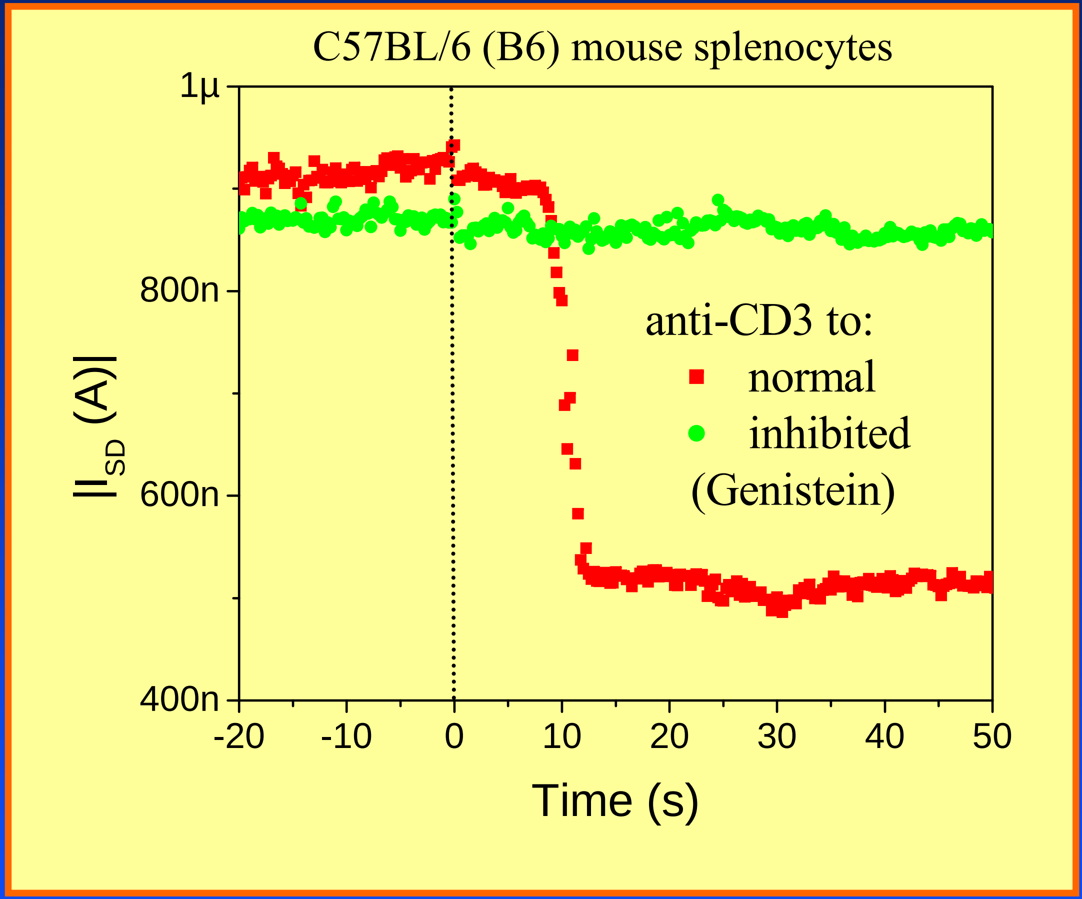


T-lymphocyte activation







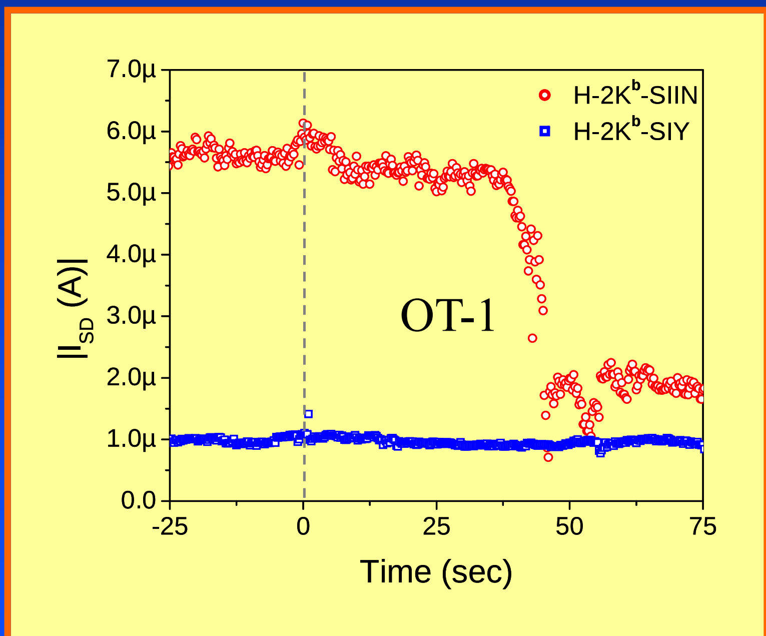


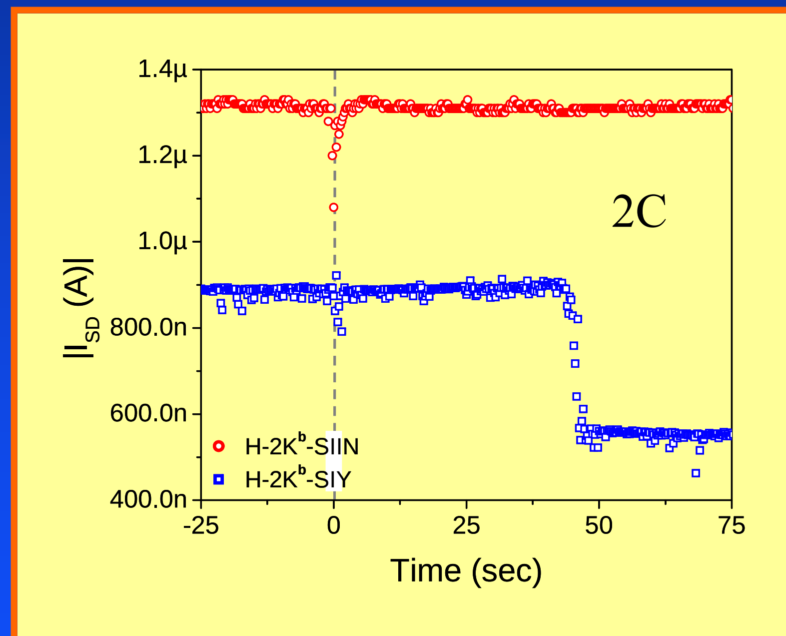
Real-time measurement of cell immune response dynamics

Transgenic peptide-specific MHC T-cell response

OT-1/2C transgenic murine $CD8^+$ T-cells

- OT-1 reacts to H-2K^b-SIIN, not H-2K^b-SIY
- 2C reacts to H-2K^b-SIY, not H-2K^b-SIIN



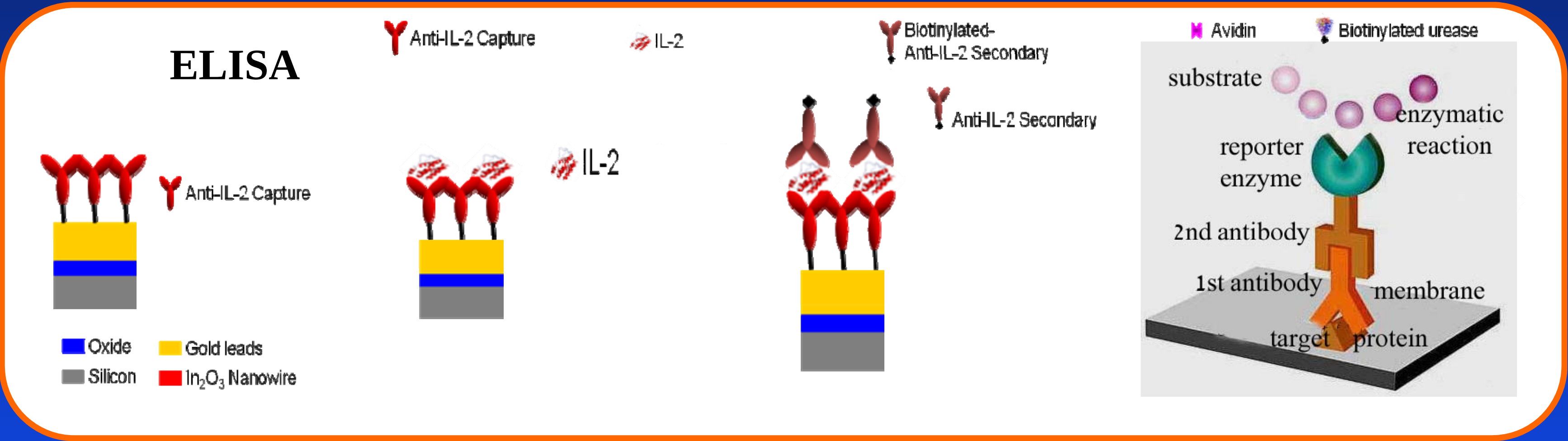


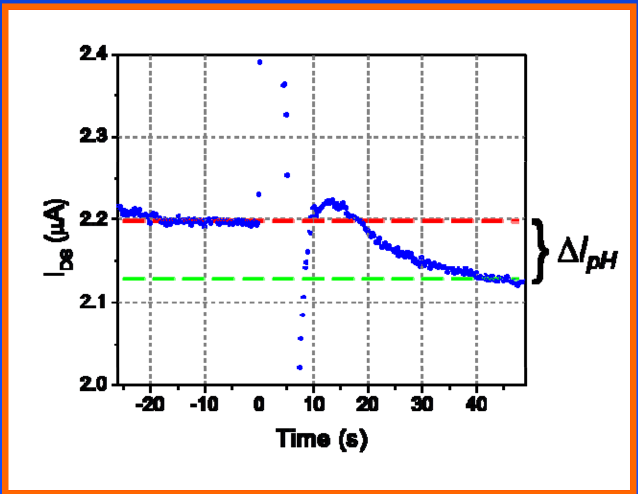
Model system for detecting autoimmune diseases and cancer

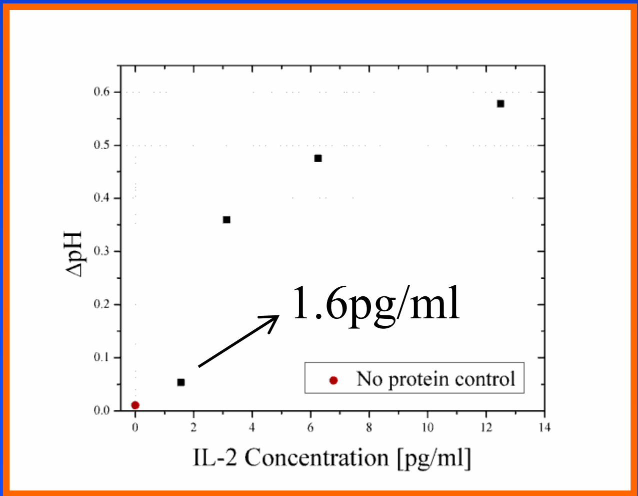
Nano Lett. **8**, 3310 (2008)

Nanowire electronic ELISA : ne-ELISA

ELISA: proven method for quantitative & sensitive protein assays
ne-ELISA: for short λ_{DEBYE} conditions, smaller samples





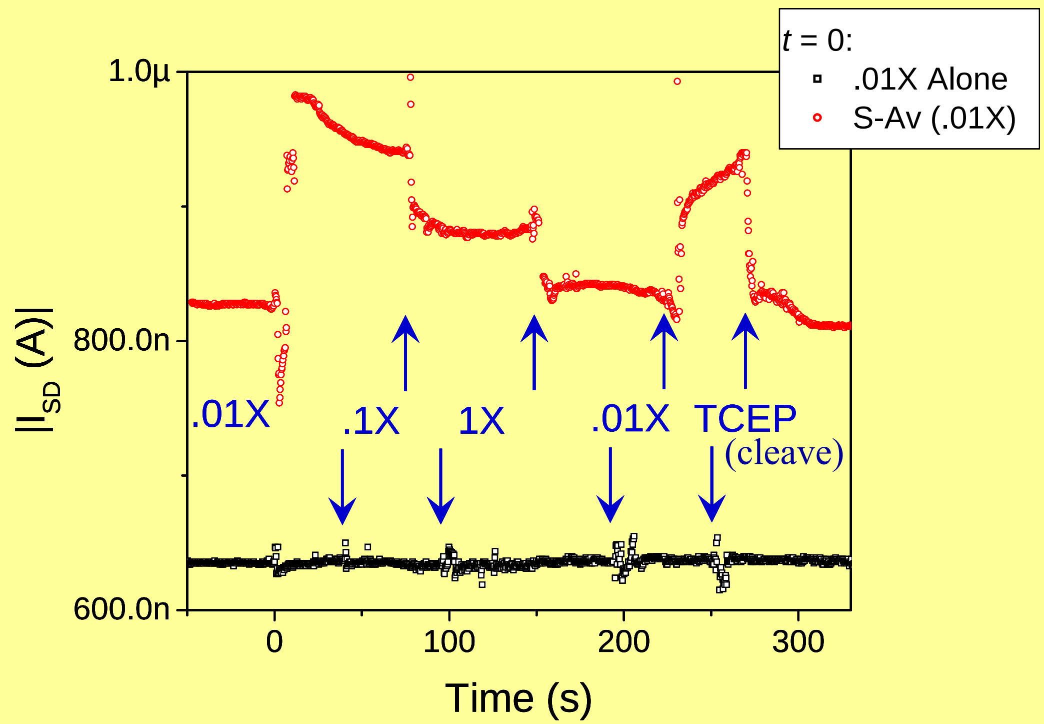


IL-2 detection limit
~ 2 pg/ml –

~10^4 less molecules of protein

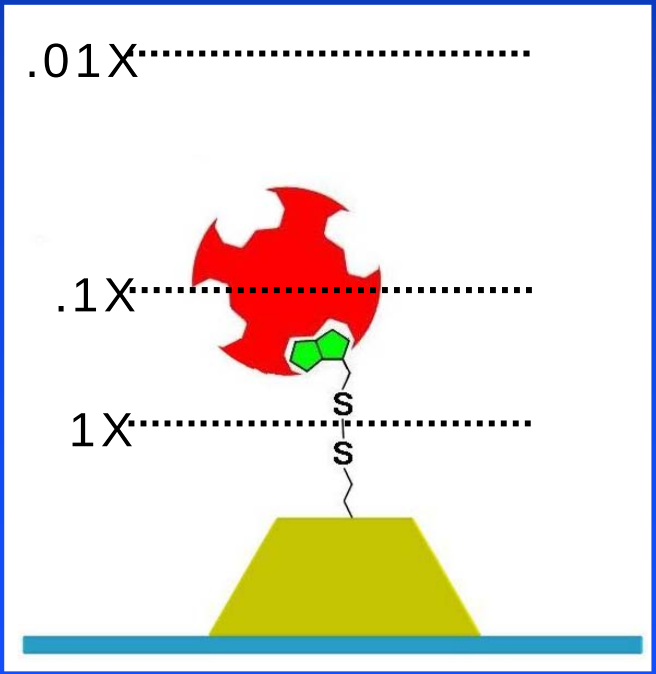
Small
DOI: 0.1002/smll.200901551

Debye Screening
The limitation of NW sensing



$$\lambda_D = \frac{1}{\left(4\pi l_B \sum_i z_i^2 \rho_i\right)^{1/2}}$$

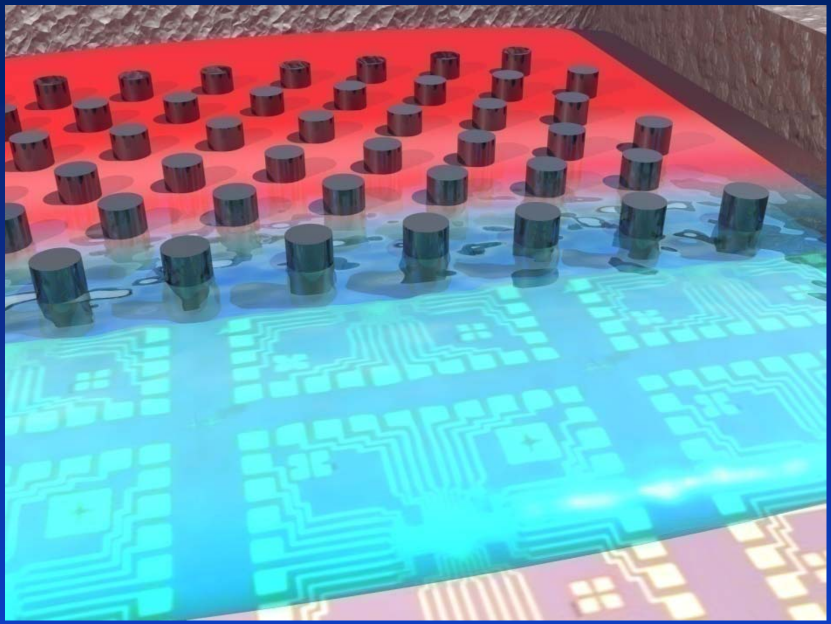
for 0.1 mM PBS,
$\lambda_D \sim 2.2$nm



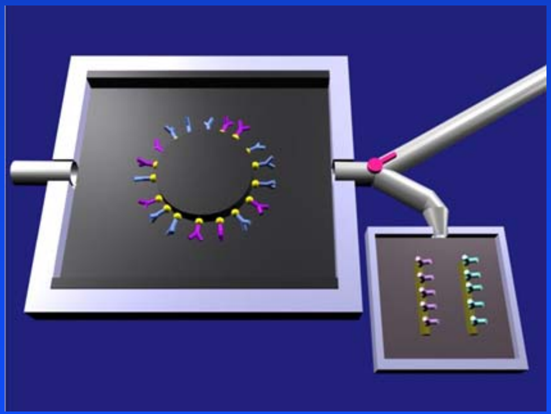
Stern *et al, Nano Lett.* **7**, 3405 (2007)

The outstanding challenge: whole blood sensing

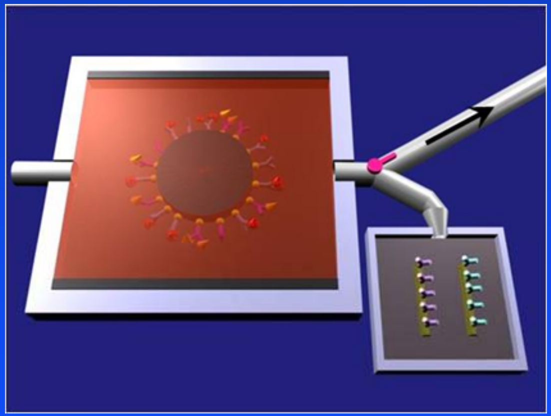
- High salt, very short λ_{Debye} (~0.8nm)
- Non-specific binding
- NW detection in blood until now has not been done



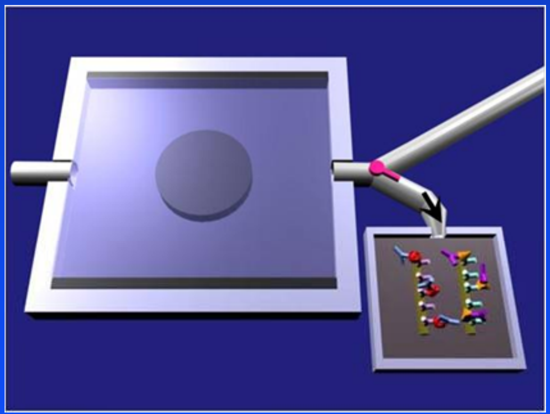
New approach: <u>capture-release</u>



Functionalize C-R region with 1st antibodies

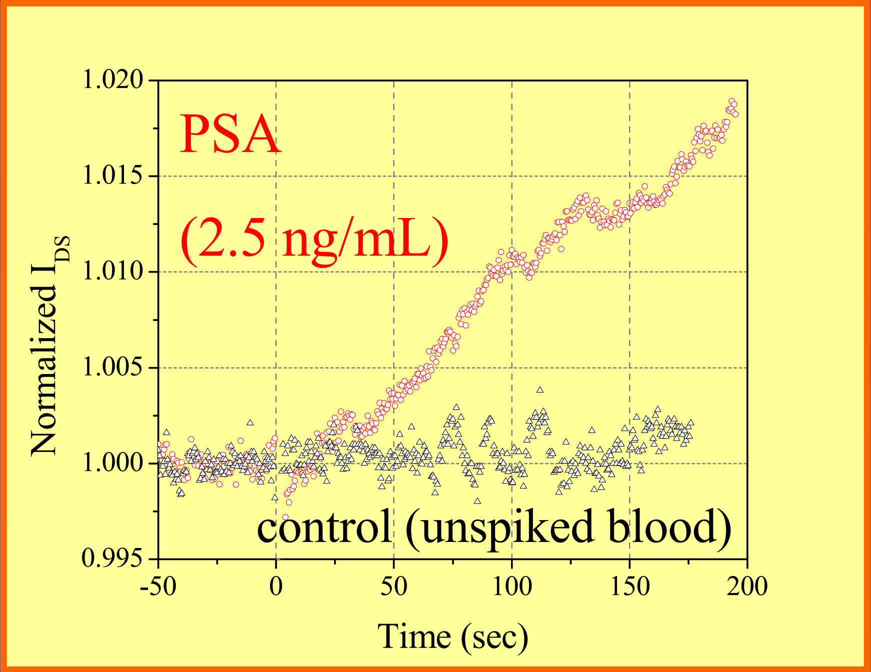


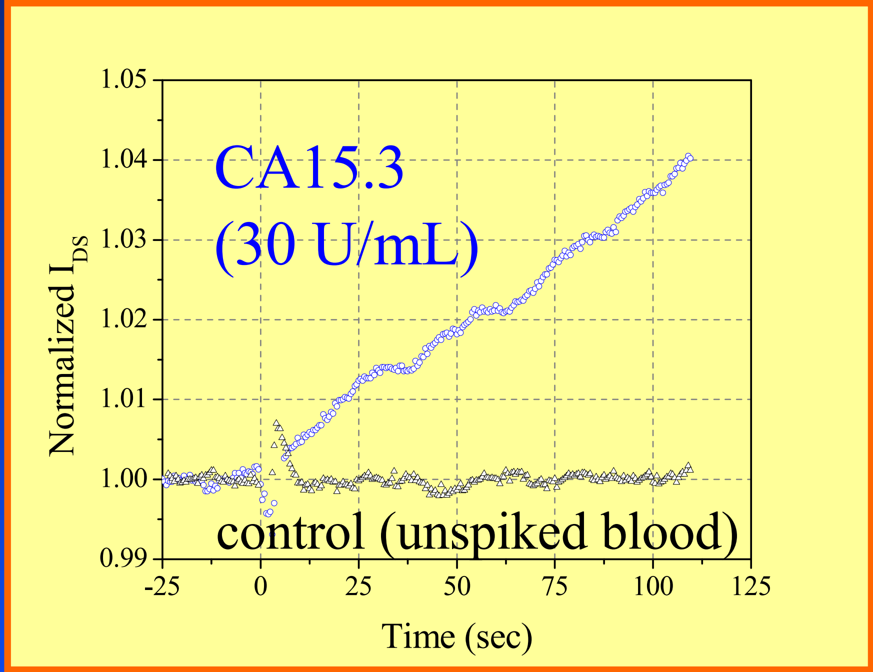
Blood introduction, protein absorption



Wash, release, capture on NWs with 2nd antibodies

Simultaneous quantitative measurement of cancer biomarkers using whole blood



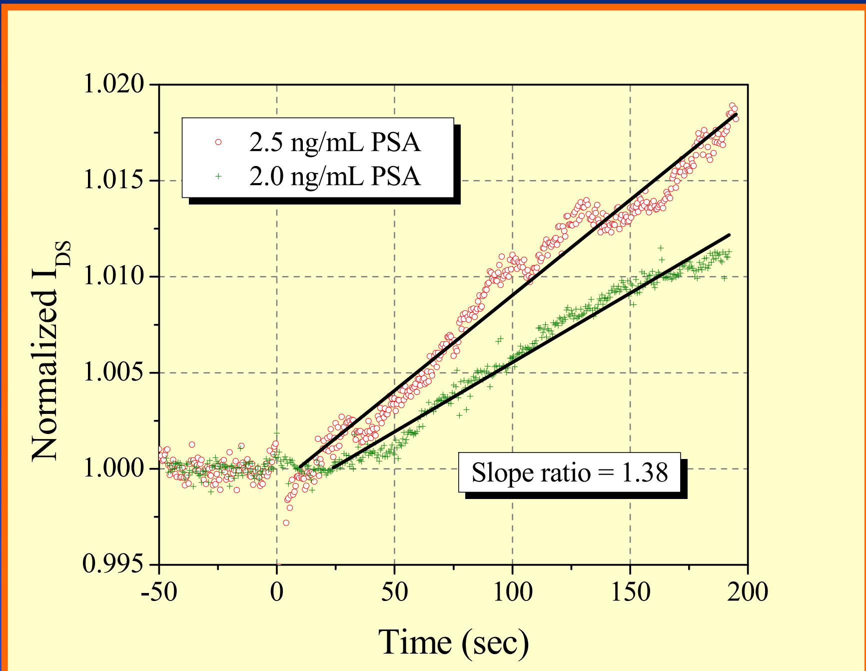


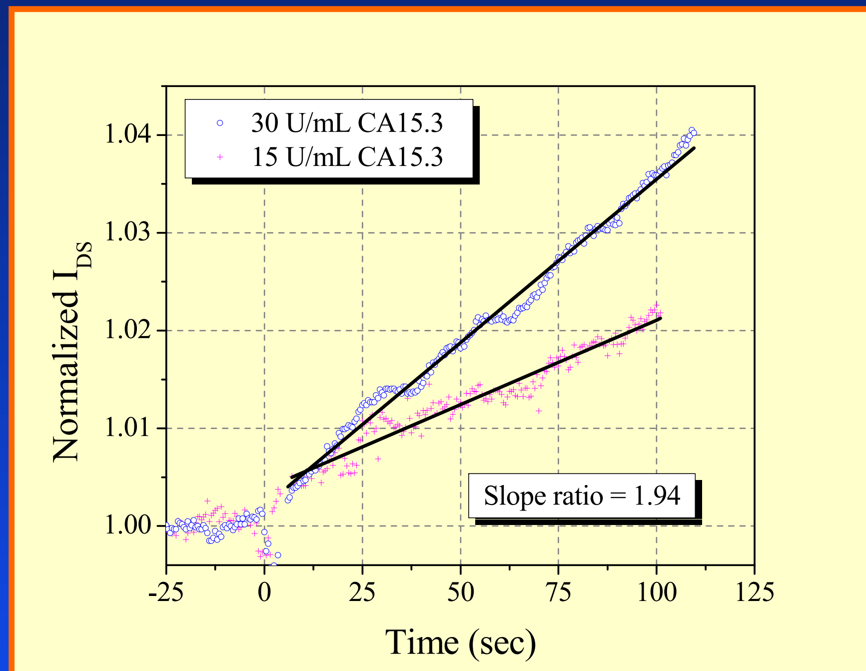
Clinically relevant range , accuracy & reproducibility < 10%
Minimum demonstrated: PSA, .2 ng/mL; CA 15.3, 3 U/mL

Stern et al., *Nature Nanotech.* **5**, 138 (2010).

Quantification

Initial rates proportional to analyte concentration





End point detection

vs

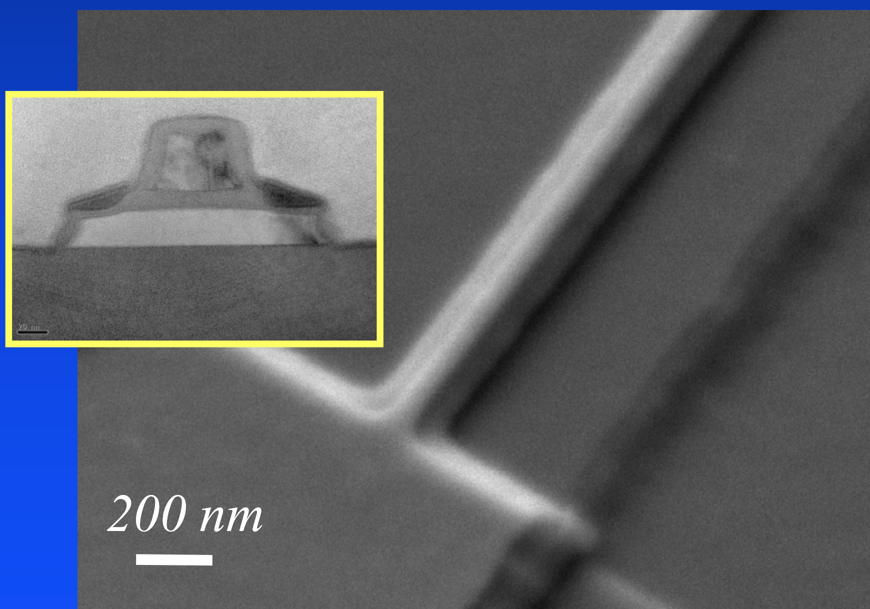
Initial kinetic rates

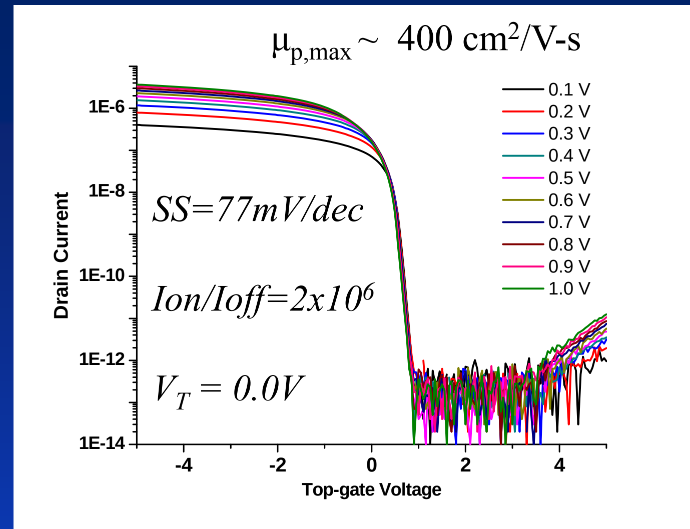
$$R(t) = \left[\frac{k_a c}{k_a c + k_d} - R_0\right]\left(1 - e^{-(k_a c + k_d)t}\right) + R_0$$

$$\frac{dR}{dt} = k_a c\,(1 - R) - k_d R$$

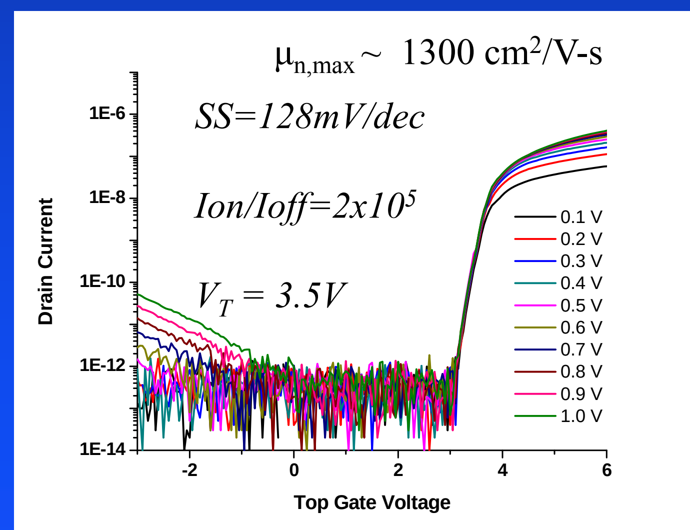
Homola J., *Anal Bioanal Chem* (2003) 377:528

Top gated Si NW





p-channel (accumulation)



n-channel (inversion)

Summary

- CMOS-integrable "NWs"
  - Label-free sensing to aM resolution
    - Enables system-level integration
    - Multiplexed
  - Macromolecular assays
  - Interesting device variants
- Real-time cellular immune response
  - Applicable to simple diagnostics
  - Immune response dynamics
- Point-of-care diagnostics
  - multiple biomarker assays, disease discovery
  - whole blood sensing