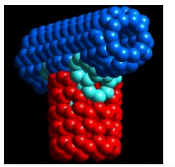
Development of NanoBiosensors for Diverse Applications



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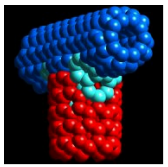
Biosensor Applications



- Lab-on-a-chip
- Cancer diagnostics
- Wide range of biomedical needs in diagnostics
- Pathogen detection
- Environmental monitoring (water quality for example)
- Food quality testing

What Do We Expect from a Well-Designed Sensor System?

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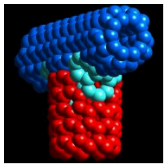

- First, a single device has no value. We need a **system** consisting of:
  - Sensor array
  - Preconcentrator (almost always needed)
  - Micropump? Microfan?
  - Sample handling, delivery, fluidics
  - Signal processing unit
  - Readout unit (data acquisition, processing, storage)
  - Interface control I/O
  - Integration of the above (nano-micro-macro)
- Criteria for Selection/Performance
  - Sensitivity
  - Absolute discrimination
  - Small package (size, mass)
  - Low power consumption
  - Rugged, reliable
  - Preferably, a technology that is adaptable to different platforms

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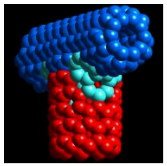
Why Nanomaterials/Nanosensors?



- Compared to existing systems, potential exists to improve sensitivity limits, and certainly size and power needs

- Why? Nanomaterials have a large surface area. Several other interesting properties at nanoscale as well.

- Measuring conductivity change upon adsorption of a gas/vapor on nanomaterial is effective for chemical sensing. Can be used with pattern recognition (E-nose)

- Conductivity change approach for biosensing is hard. Preferable

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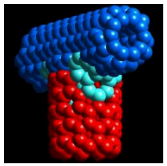
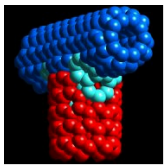
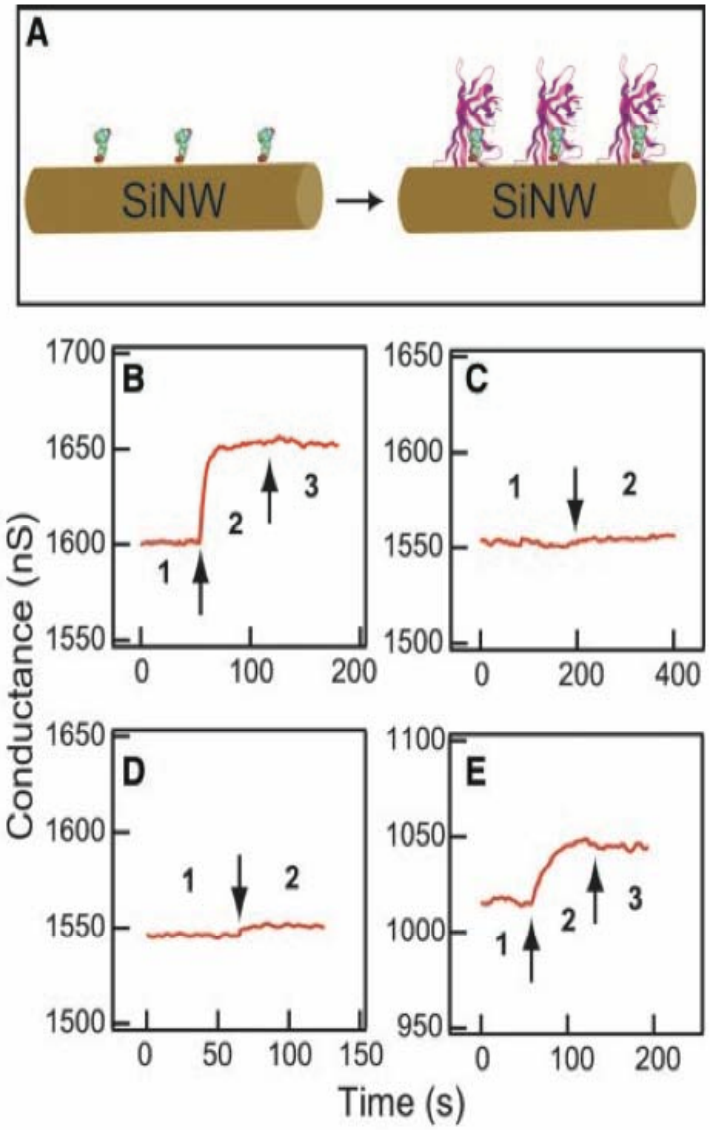
Some examples of Nano-biosensors



- CNT based FET with probe attachment
- CNT Nanoelectrode array as biosensing platform
- Silicon nanowire with probe attachment
- Silicon CMOS transistor as platform

Example of SiNW in Biosensing





Detection of protein binding using a silicon nanowire device. (A) SiNW modified with biotin (left) and after streptavidin binding (right). (B) Conductance vs. time for biotin modified SiNW. 1, 2, and 3 correspond to regions of buffer solution, addition of 250 nM streptavidin and pure buffer solution respectively. (C) Conductance vs. time for unmodified nanowire. 1 and 2 have the same meaning as before. (D) Conductance vs. time for an biotin-modified NW. Region 1 is same as before and region 2 represents addition of 250 nM sreptavidin pre-incubated with biotin. (E) Conductance vs. time for a biotin modified NW. Region 1 as before, region 2 represents 25 pM streptavidin and region 3 pure buffer solution.

Lieber Group, Harvard

Nanoelectrode Array for Biosensors

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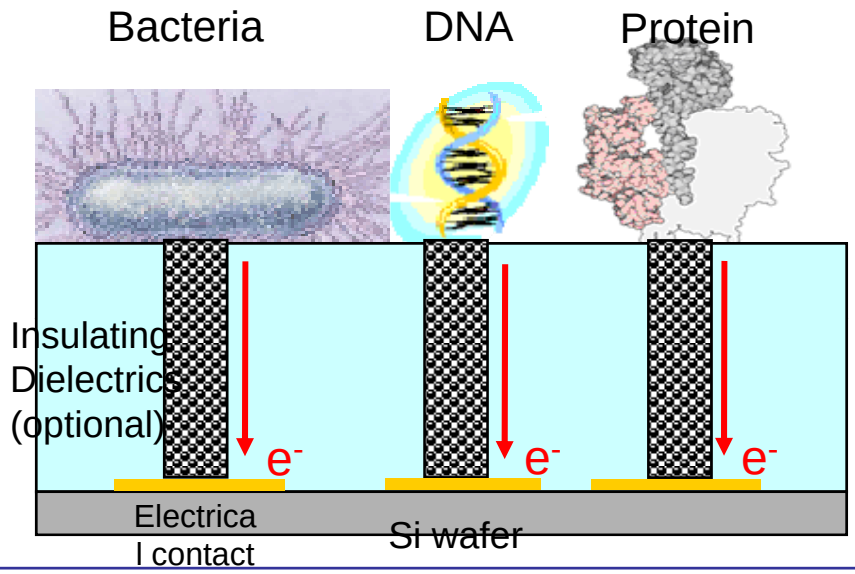
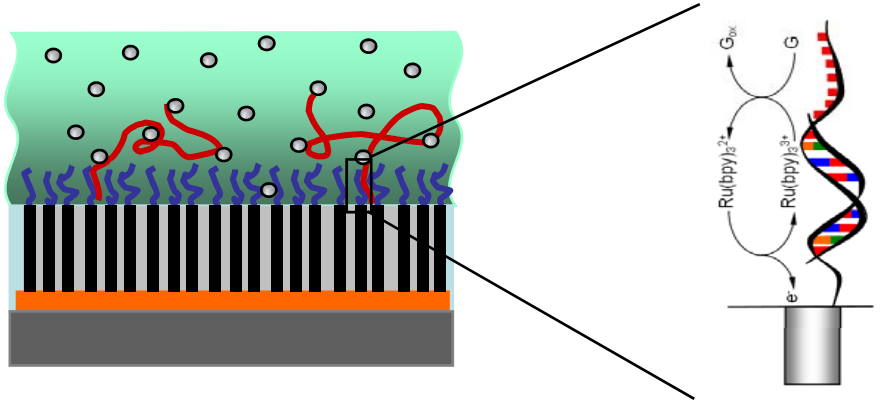
NACNT





Directly interface solid-state electronics with DNAs, RNAs, proteins, and microbes in a miniaturized multiplex chip for quick detection(Lock and Key approach)

- **MWNT array electrode functionalized with DNA/PNA probe as an ultrasensitive sensor for detecting the hybridization of target DNA/RNA from the sample.**
  - Signal from redox bases (Guanine) in the excess DNA single strands
- **The signal can be amplified with metal ion mediator oxidation catalyzed by Guanine.**

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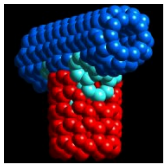
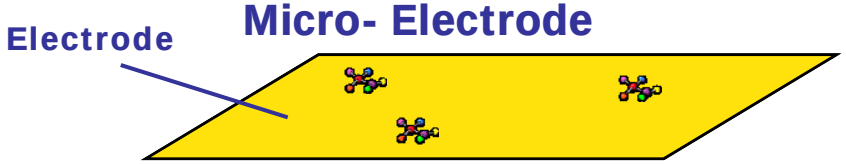
Nanoelectrode for Sensors



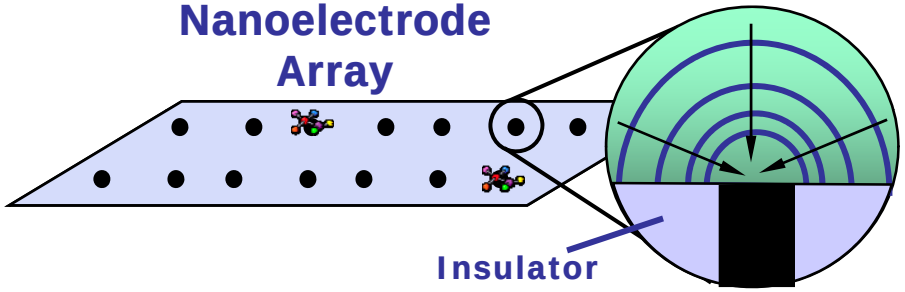
Nanoscale electrodes create a dramatic improvement in signal detection over traditional electrodes

Traditional Macro- or Micro- Electrode



- **Scale difference** between macro-/micro- electrodes and molecules is tremendous
- **Background noise** on electrode surface is therefore significant
- **Significant amount** of target molecules required

Nanoelectrode Array

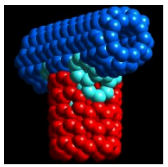


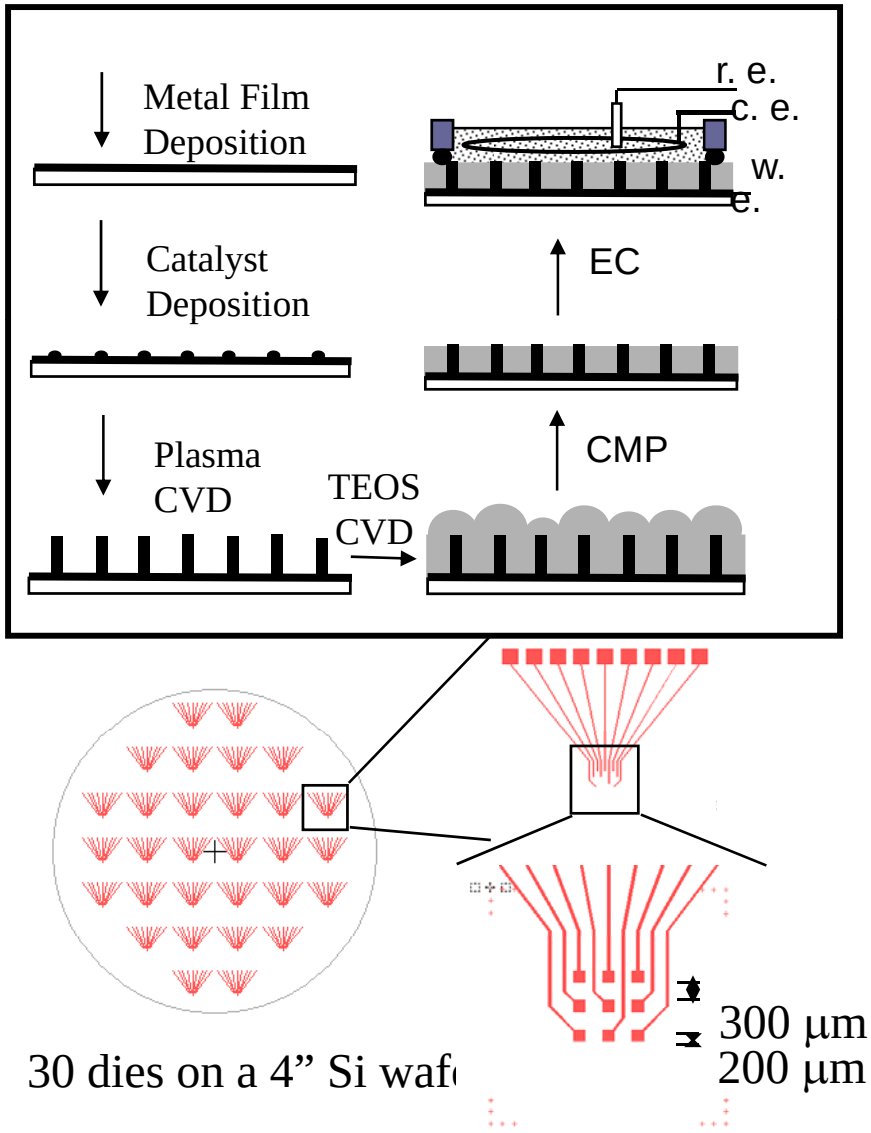
- CNT tips are at the **scale close to** molecules
- Dramatically **reduced background noise**
- Multiple electrodes result in **magnified signal** and **desired redundance** for statistical reliability.

Candidates: ~~SWNTs~~, ~~MWNTs~~, Vertical CNFs or Vertical SiNWs

Source: Jun Li

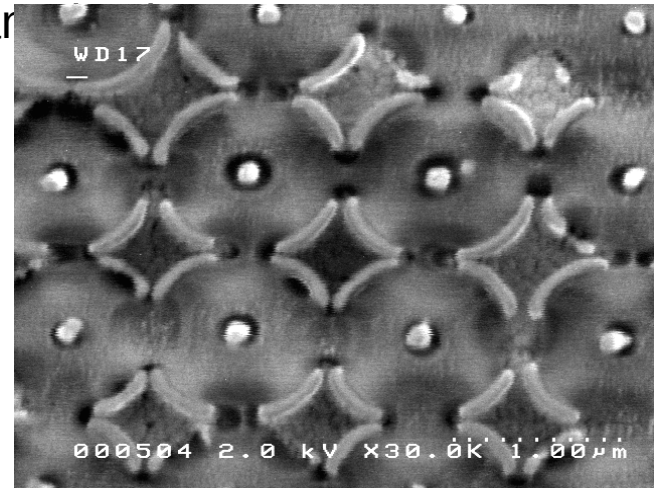
Nanoelectrode Array Fabrication

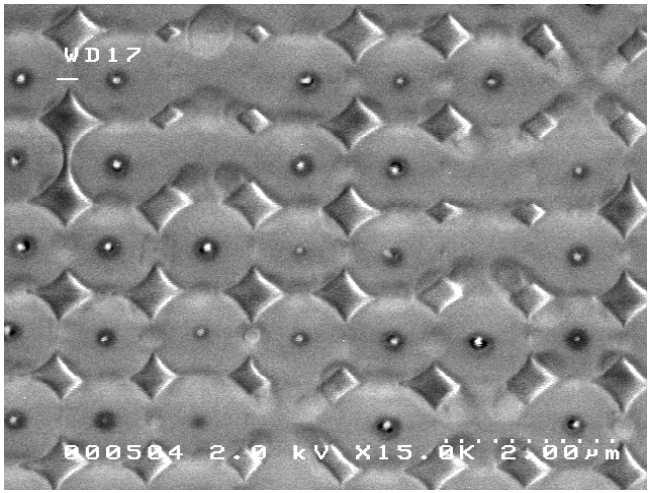




30 dies on a 4” Si waf

Embedded CNT Arrays after plar





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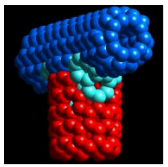
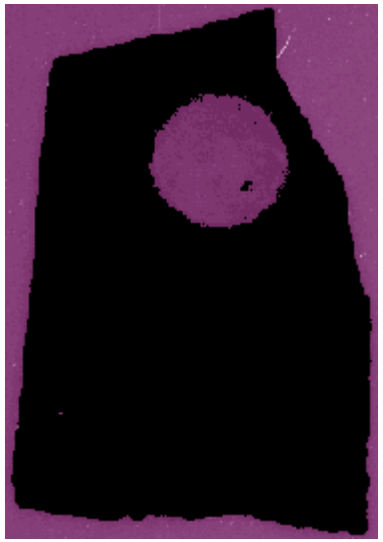
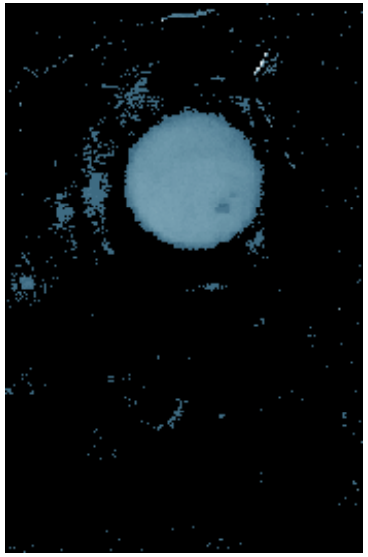
Functionalization of DNA

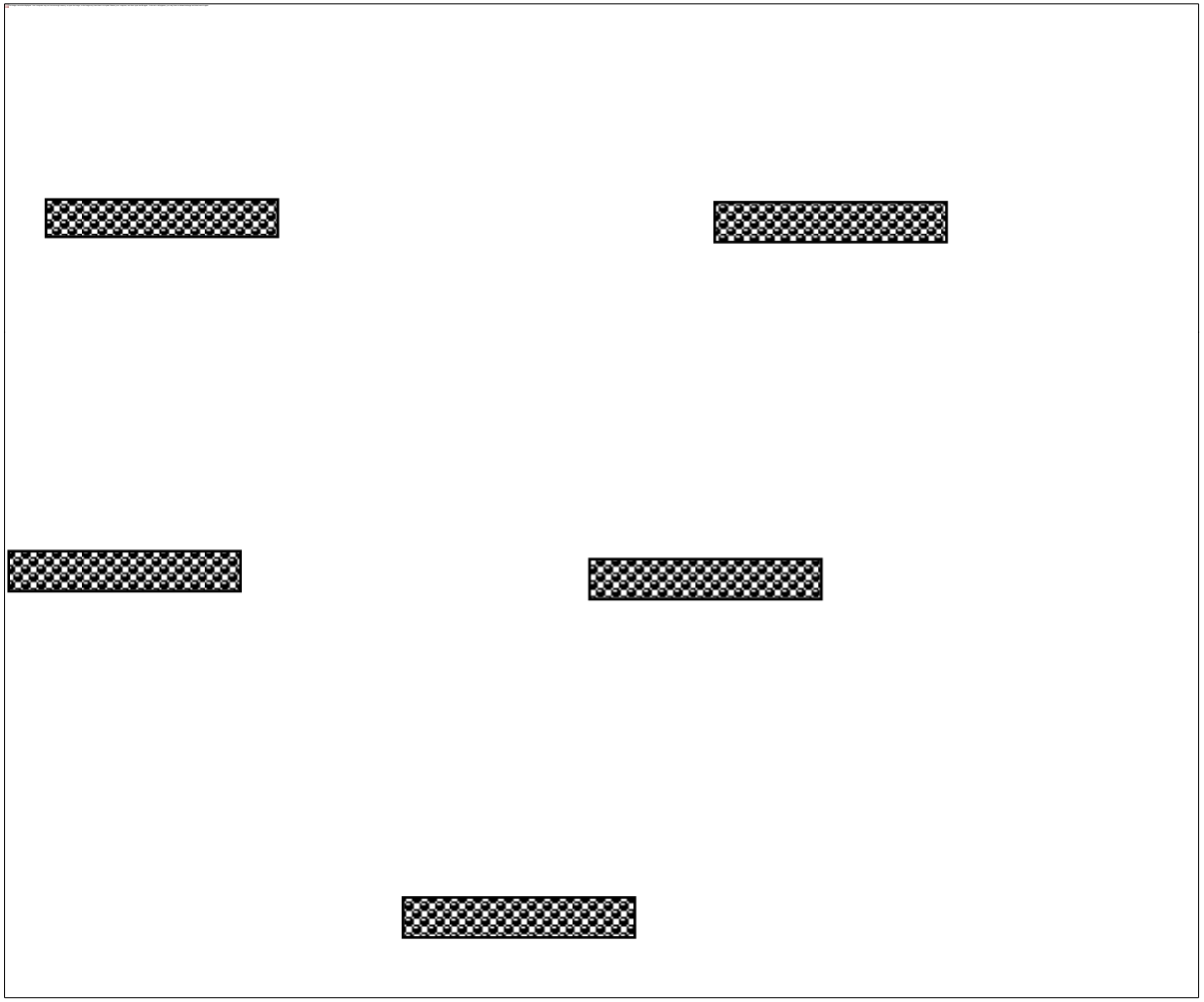




Cy3 image



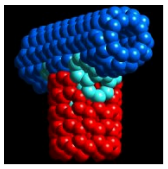
Cy5 image

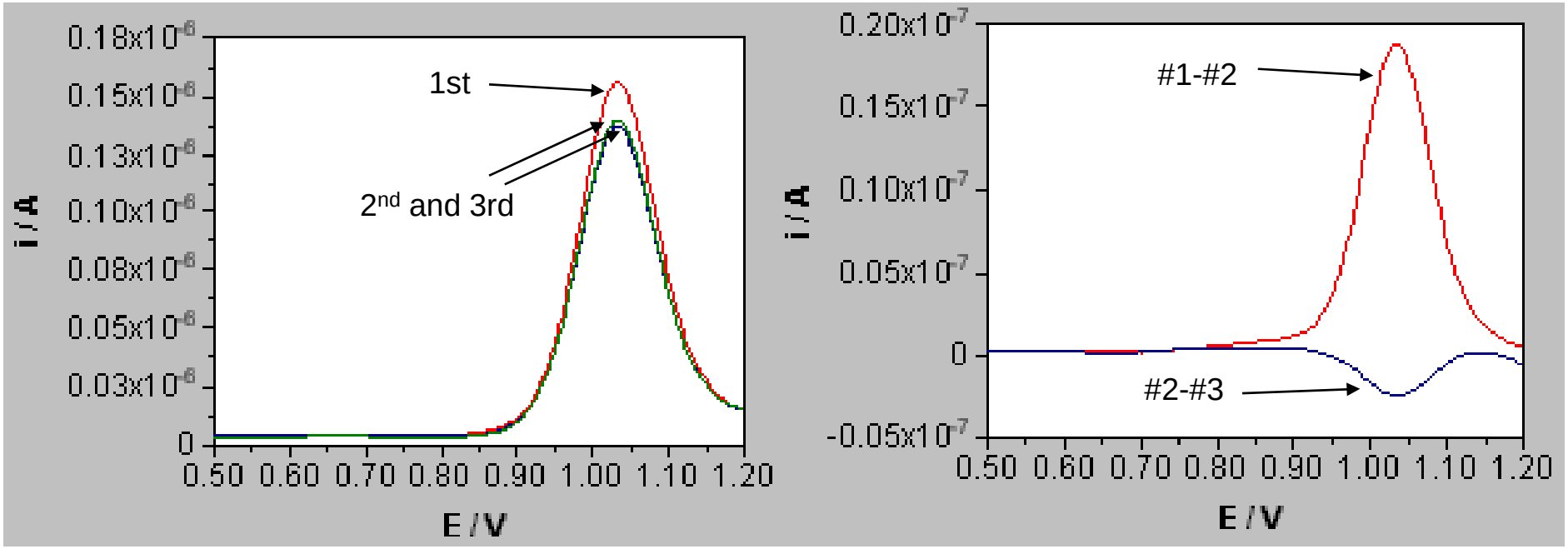


C. Nguyen et al, NanoLett., 2002, Vol. 2, p. 1079.

Electrochemical Detection of DNA Hybridization

- by AC Voltammetry





1st, 2nd, and 3rd scan in AC voltammetry

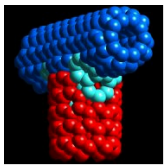
1st – 2nd scan: mainly DNA signal

2nd – 3rd scan: Background

Lower CNT Density ⇒ Lower Detection Limit

J. Li, H.T. Ng, A. Cassell, W. Fan, H. Chen, J. Koehne, J. Han, M. Meyyappan, NanoLetters, 2003, Vol. 3, p. 597.

Simple model for Biosensing



- Balance equation for probe or receptor molecule density N

$$\frac{dN}{dt} = k_f (N_o - N) \rho_s - k_r^N$$

- N_o: initial density of probes on the nanowire surface
- k_f, and k_r: rate constants for attachment and detachment
- ρ_s: density of the targets

- The first term on the right hand side represents the target-probe conjugation and the second term stands for detachment events.

$$+ V.\nabla\rho = D\nabla^2\rho$$

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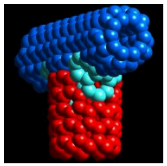
Insight from Modeling



- A one dimensional NW/NT based sensor can give one to four orders of magnitude higher detection limit than a planar thin film sensor

- Going further down to 0-d (spherical) geometry offers no further advantage

- Trade-off between the response time and detection limit

  - If you want femtomolar detection, incubation would take

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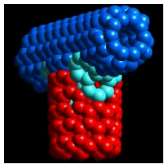
Gas/Vapor Sensors in Biomedical Applications



- Some diseases have specific markers which show up in excess concentration in the breath of sick people relative to normal people.

  Example: acetone in diabetes patients
  NO in asthma patients

- In these cases, simple chemical sensors with pattern

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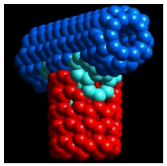
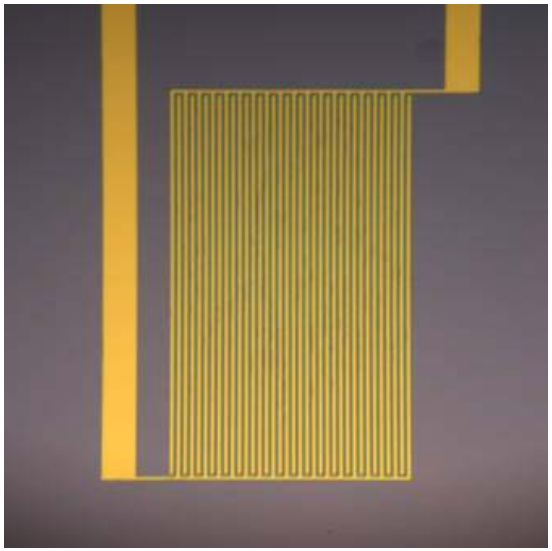
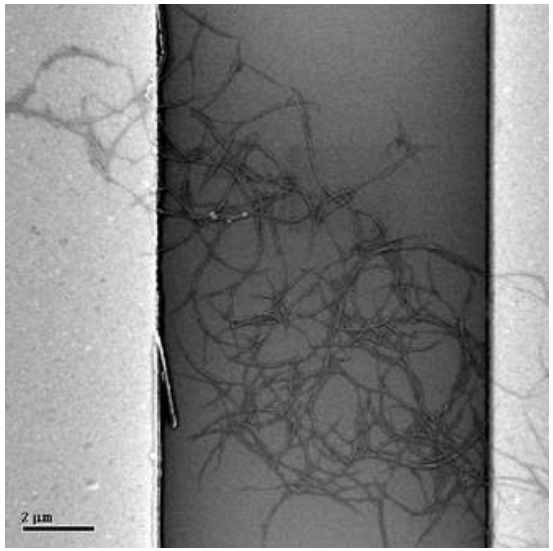
SWCNT Chemiresistor



- Easy production using simple microfabrication
- 2 Terminal I-V measurement
- Low energy barrier - Room temperature sensing
- Low power consumption: 50-100 µW/sensor





Processing Steps

1. Interdigited microscale electrode device fabrication
2. Disperse purified nanotubes in DMF (dimethyl formamide)
3. Solution casting of CNTs across the electrodes

Jing Li et al., Nano Lett., **3**, 929 (2003)

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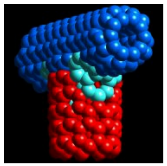
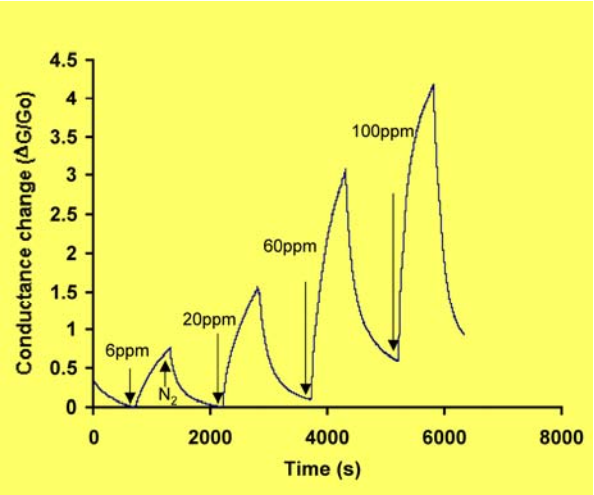
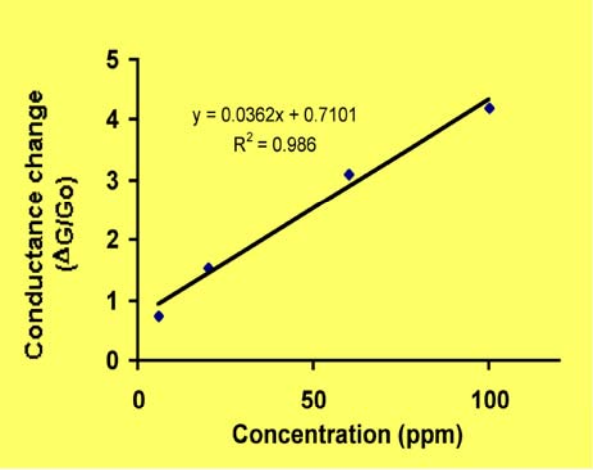
SWCNT Sensor Testing







Detection limit for NO_2 is 4 ppb.

- Test condition:
  Flow rate: 400 ml/min
  Temperature: 23 ^oC
  Purge gas: N_2 & Carrier gas: Air

- Measure response to various concentrations, plot conductance change vs. concentration

- Sensor recovery can be speeded up by exposing to UV light, heating or AC bias

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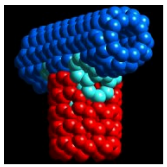
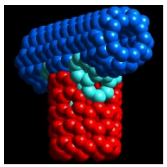
Gases/Vapors Tested

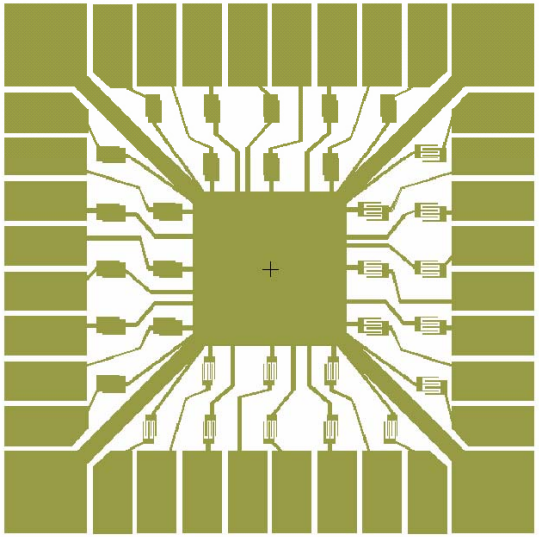


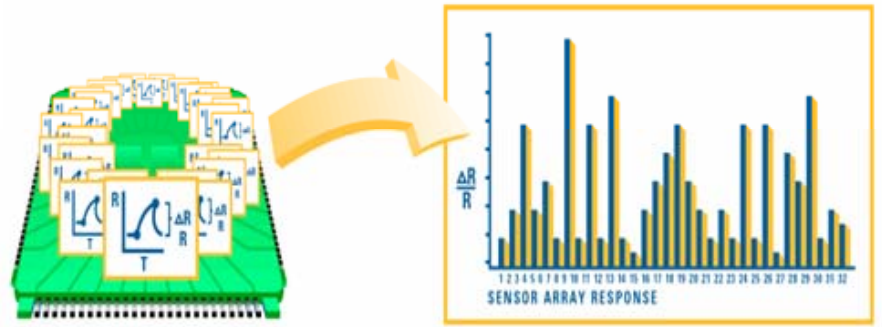
Analyte	Sensitivity/Detection limit
CH4	1ppm in air
Hydrazine	N/A
NO2	4.6ppb in air
NH3	0.5ppm in air
SO2	25ppm in air
HCl	5ppm in air
Formaldehyde	10ppb in N2/air
Acetone	10ppm in air
Benzene	20ppm in air
Cl2	10ppm in N2
HCN	10ppm in N2
Malathion	open bottle in air
Diazinon	open bottle in air
Toluene	1ppm in air
Nitrotoluene	256ppb in N2
H2O2	3.7ppm in air

Nanosensing Approach: Selectivity



- Use a sensor array
- Variations among sensors
  - physical differences
  - coating
  - doping





Using pattern matching algorithms, the data is converted into a unique response pattern

Operation:

1. The relative change of current or resistance is correlated to the concentration of analyte.
2. Array device “learns” the response pattern in the *training* mode.
3. Unknowns are then classified in the *identification* mode.
4. Sensor can be “refreshed” using UV LED, heating or purging

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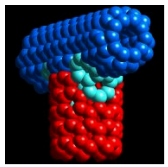
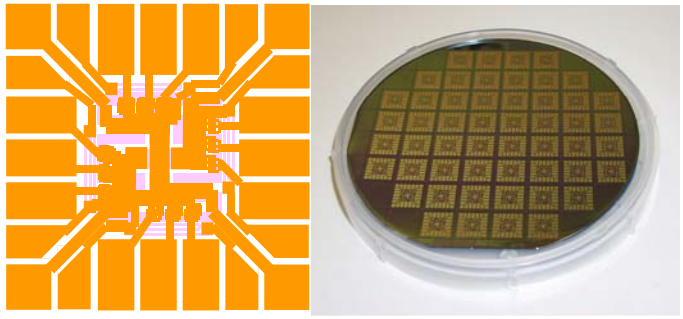
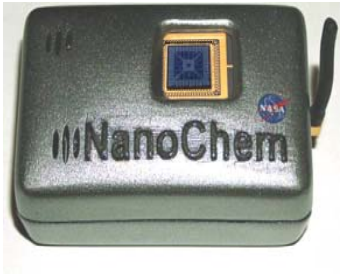
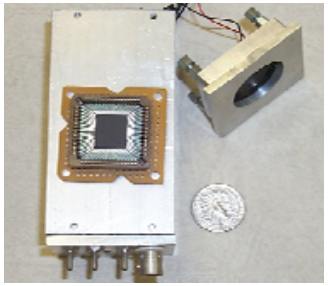
Scalable Array Approach (Multi-channel Sensing Chip)





- **12 to 96 sensing elements on a chip (1cm x 1cm) with heaters and thermistors.**
- **Number of sensing elements can be increased on a chip.**
- **Number of chips can be increased on a 4” wafer.**
- **Wafer size can be increased to 6”, 8”, or 12”.**
- **SWCNT solution-casting by ink jetting or using microarrays**





Features:

- Response time in seconds
- ppm/ppb detection levels
- Multichannel chip provides high sensitivity/multifunctions
- Integrated Temperature, Pressure, and Humidity sensing
- Integrated signal processing
- Low power demand (50 mW including all operations)
- Low cost microfabrication