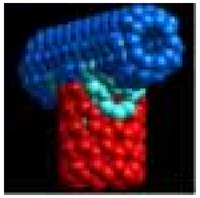
Bio-Nano-Info Fusion



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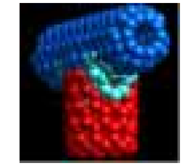
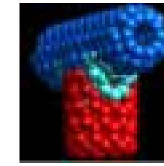
Acknowledgements: Jun Li, Alan Cassell, David Loftus, Lance Delzeit, Viktor Stolc, Jonathan Trent, Andrew McMillan. and Chad Paavola

Agenda

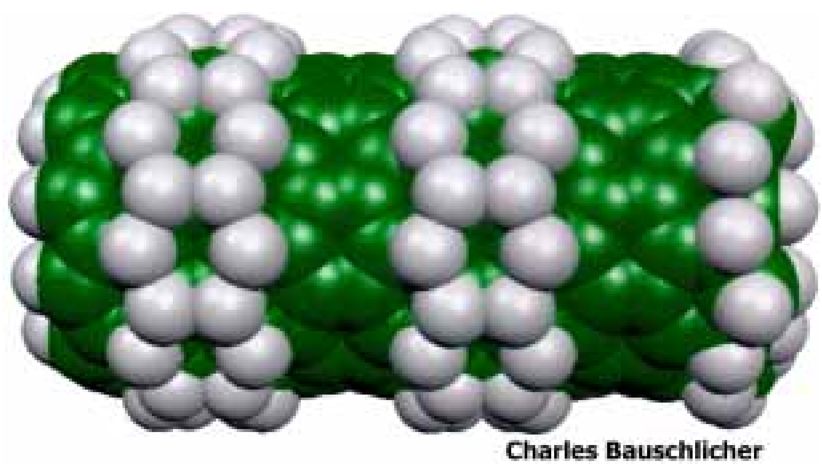


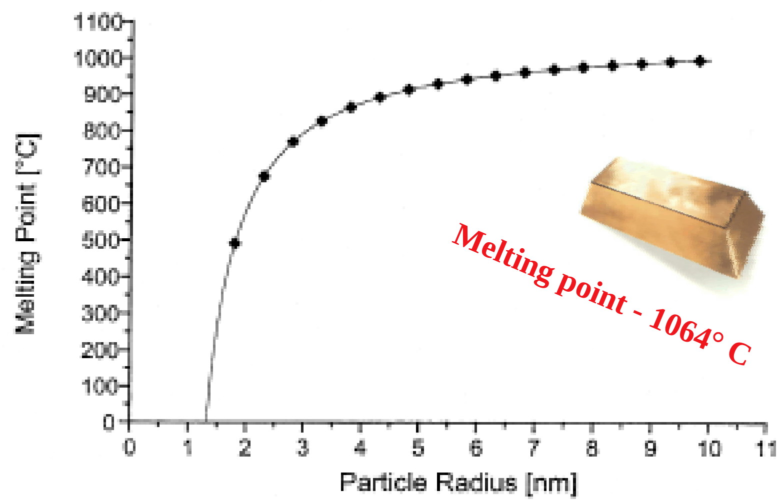
- Introduction
- CNT based biosensors
- CNT based chemical sensors
- Nanopore based gene sequencing
- CNT in biomedical applications
- Protein nanotubes
- Nanowire based devices



What is Nanotechnology?

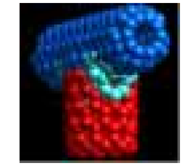
Nanotechnology is the creation of **USEFUL/FUNCTIONAL** materials, devices and systems through control of matter on the nanometer length scale and exploitation of novel phenomena and properties (physical, chemical, biological) at that length scale





Source: K.J. Klabunde, 2001

Manifestations of BIN Fusion



Bio

- Inspiration from biology or nature, to develop a new product; Examples: synthetic gecko, self-cleaning glass like lotus flower
- Biomaterial for known or new applications; Example: protein nanotubes
- Biotechnology application development; Example: biomedical and bio sensors

Nano

- Nano is an enabling technology, nanoscale materials, systems, architectures…

Info

- Integration of IT is needed for signal processing, i.e. converting signals or digits into useful knowledge
- IT applications development: electronics, computing, data storage, photonics…

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Nanotechnology for Defense Applications

NACNT

- Very high sensitivity, low power sensors for detecting chem/bio/nuclear threats

- Light weight military platforms, without sacrificing functionality, safety and soldier security
  - Reduce fuel needs and logistical requirements

- Reduce carry-on weight of soldier gear
  - Increased functionality per unit weight

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Challenges and Impact Areas

NACNT

Challenge	Technology
Finding & Tracking	**Nanosensors, enhanced IR recognition, high speed image processing**
Command & Control	**Nanoelectronics, quantum computing, processors with orders of magnitude more computing & storage capability**
Controlled Effects	**Nanoscale energetic materials, improved energy release rate, safer propellants**
Lightweight Platforms	**Nanocomposites, high performance and high temperature materials**

Source: Implications of Emerging Micro-and Nanotechnologies, National Academy Press, 2002, p. 195

Homeland Security Needs

- Detection: early warning sensors for chem, bio, nuclear threats
  - Extremely high sensitivity, extremely high selectivity
  - Reliable, robust
  - A platform that meets the needs (ex: hand-held, remote use….)
  - Low power consumption
- Protection: through filtration, adsorption, destructive adsorption or neutralization of agents

Nanotechnology can provide solutions

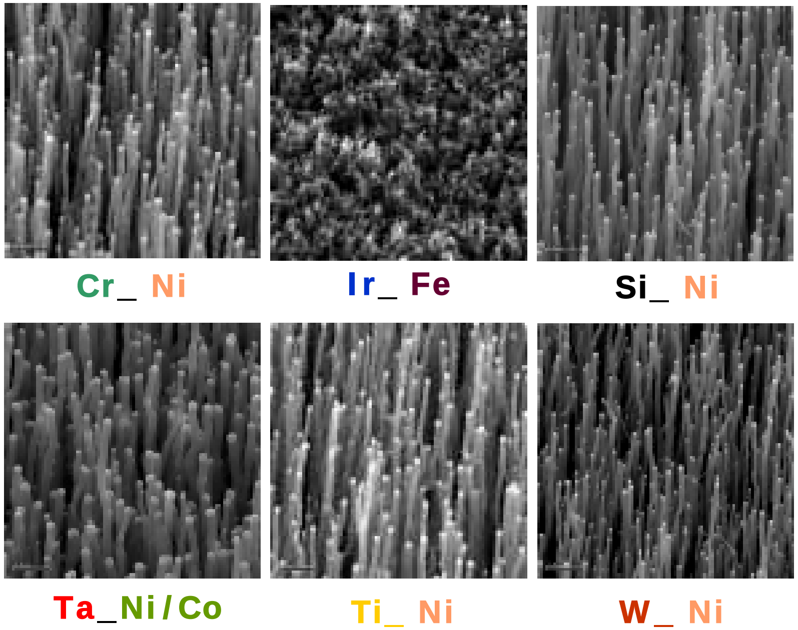
Plasma Reactor for CNT Growth

- Inductively coupled plasma reactor, with an rf-powered bottom electrode, separate heating stage to heat the wafer (in addition to plasma heating)

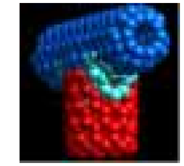
- DC plasma reactor with similar capabilities, but generally lower plasma efficiency and more power consumption

- ICP Operating conditions
  CH_4/H_2 : 5 - 20%
  Total flow : 100 sccm
  Pressure : 1 - 20 Torr
  Inductive power : 100-200 W
  Bottom electrode power : 0 - 100 W

Cassell et al., Nanotechnology, **15** (1), 2004

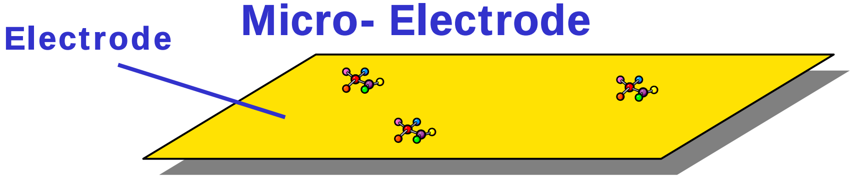


Nanoelectrode for Sensors

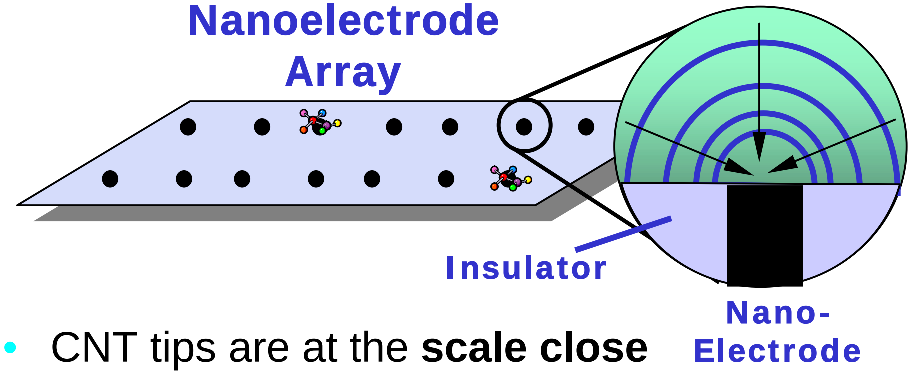


Nanoscale electrodes create a dramatic improvement in signal detection over traditional electrodes

Traditional Macro- or Micro- Electrode



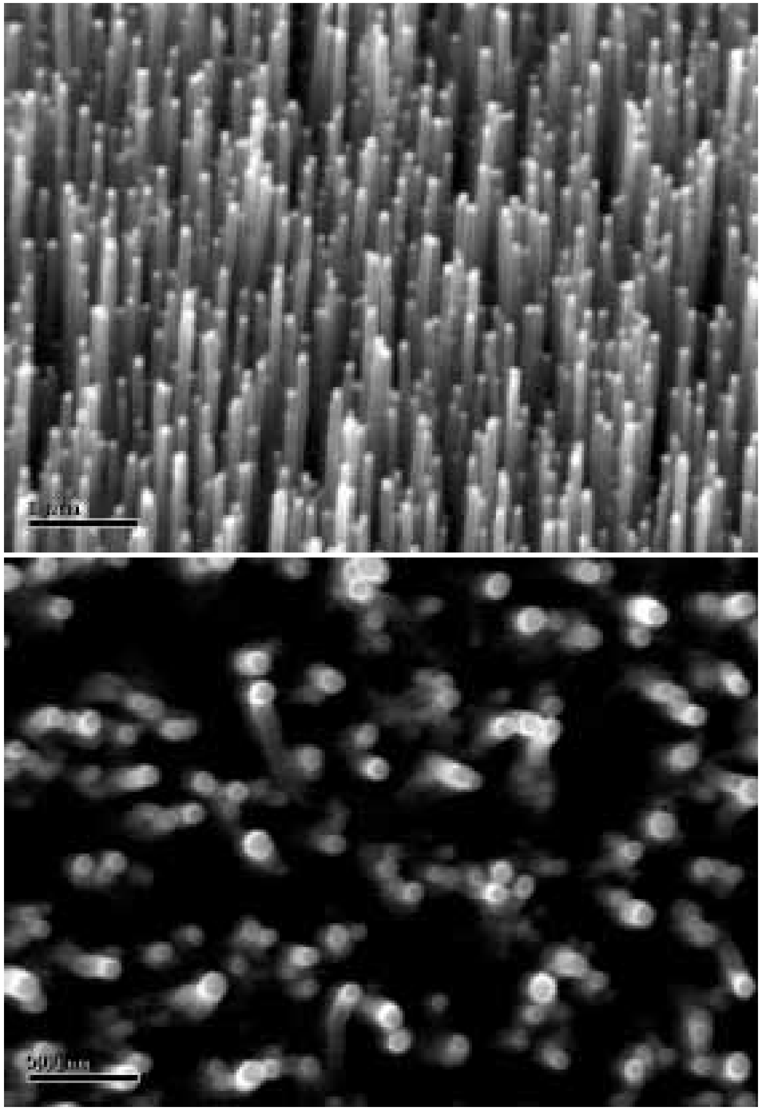
Nanoelectrode Array



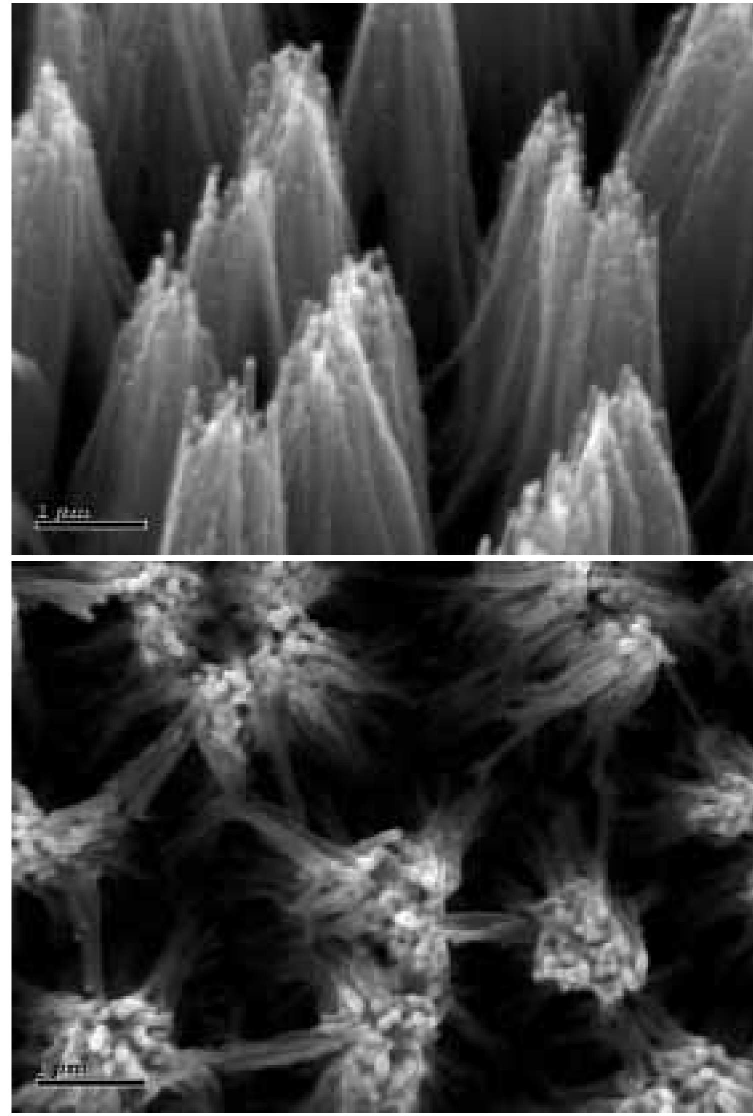
- **Scale difference** between macro-/micro- electrodes and molecules is tremendous
- **Background noise** on electrode surface is therefore significant
- **significant amount** of target molecules required

- CNT tips are at the **scale close to** molecules
- Dramatically **reduced background noise**
- Multiple electrodes results in **magnified signal** and **desired redundance** for statistical reliability.
- Can be combined with other electrocatalytic mechanism for magnified signals.

Stability of CNT Array

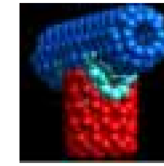


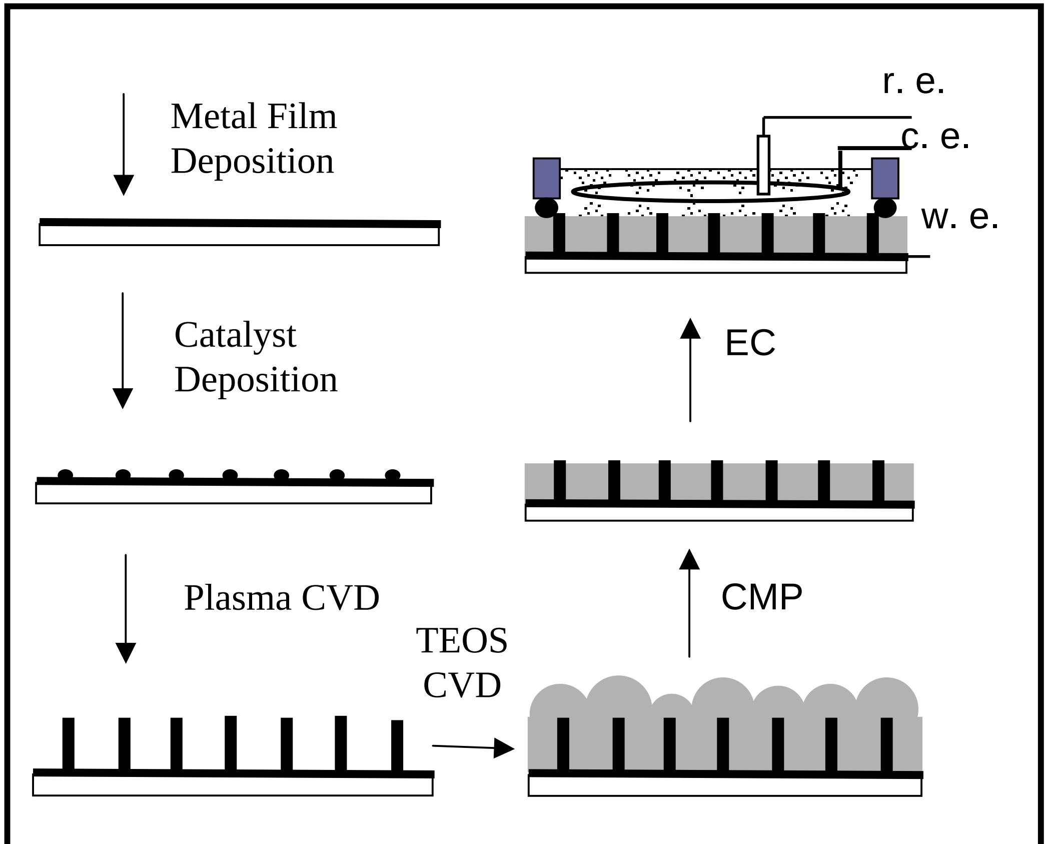
As-grown sample



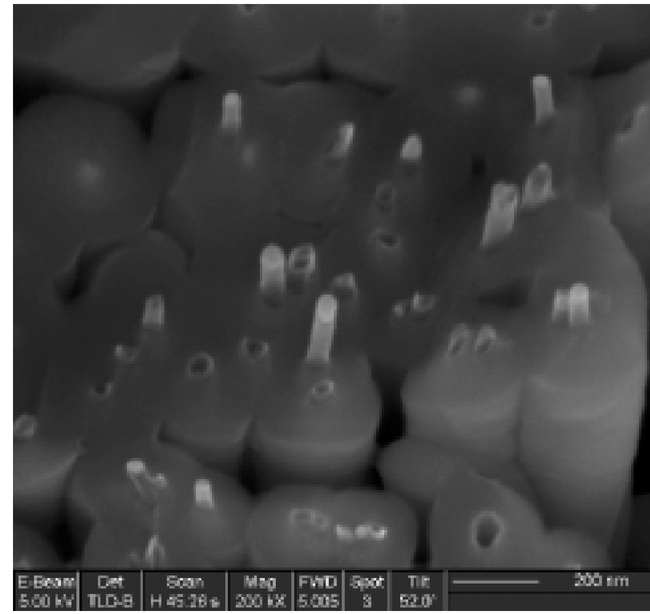
After taking out from solution

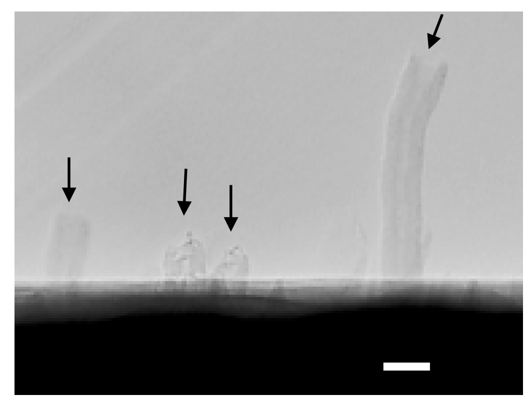
Fabrication of Carbon Nanotube Electrodes





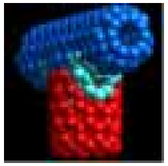
Embedded CNT Array
After planarization

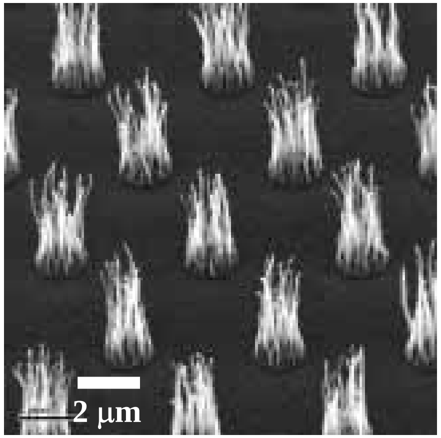


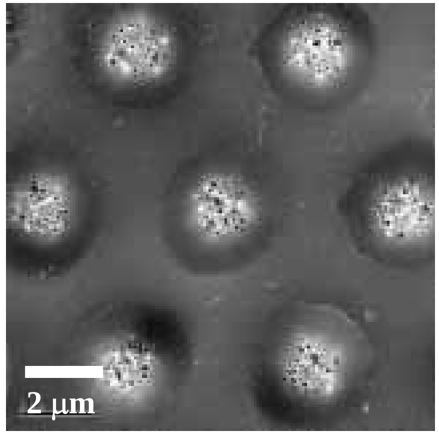


50 nm

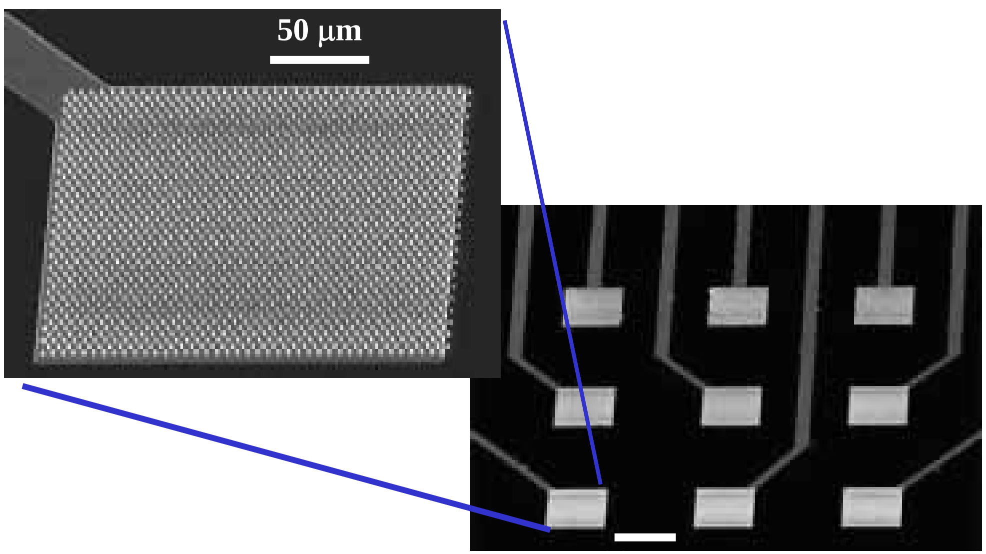
CNT Nanoelectrode Array

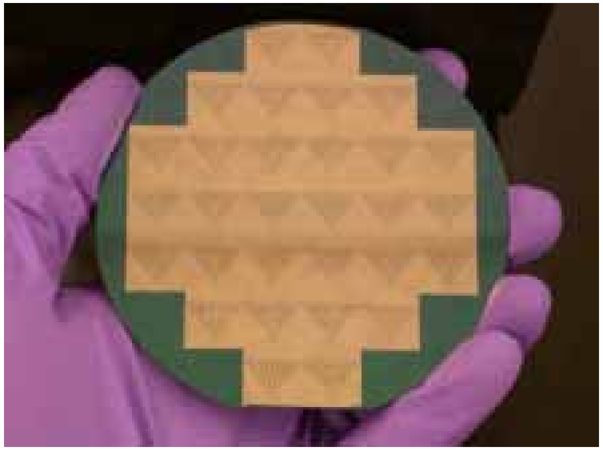






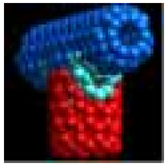
- Carbon nanotubes grown vertically on substrate
- CNTs encapsulated in SiO_2, exposing only tips to analyte
- Fabrication involves only reliable, low-cost microfabrication techniques
- Scale of nanotubes makes miniature, multiplex arrays feasible

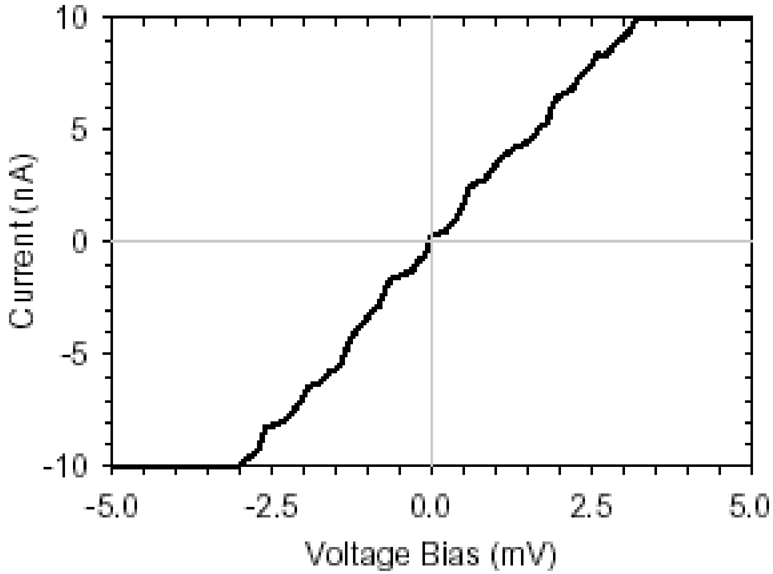


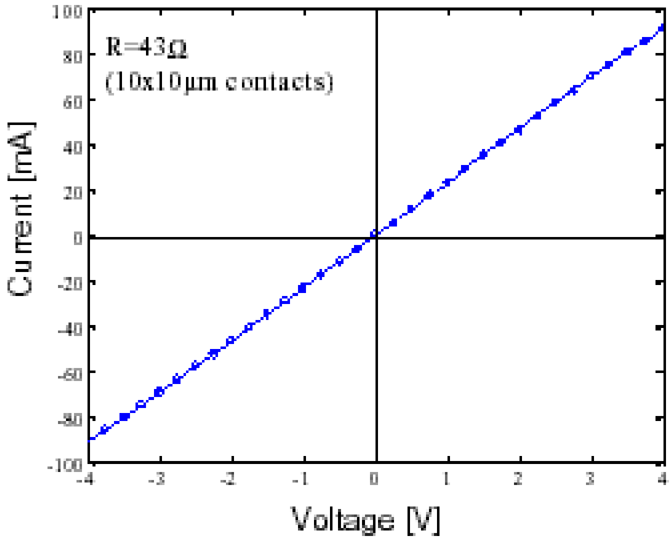


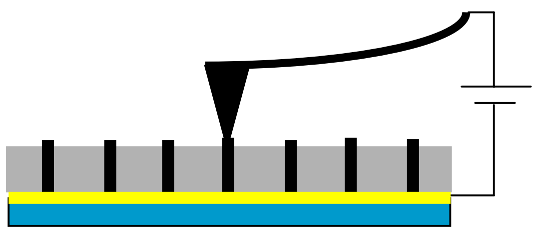
J. Li, H.T. Ng, A. Cassell, W. Fan, H. Chen, J. Koehne, J. Han, M. Meyyappan, *Nano Letters*, **3**(5), 597-602 (2003).

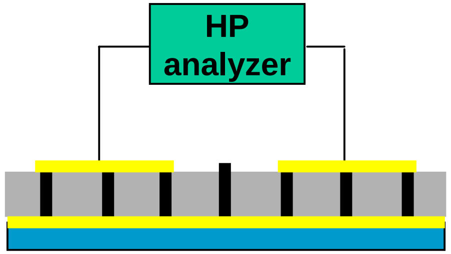
Electrical Properties of MWCNTs











Current Sensing AFM

Metallic CNTs

Resistance: ~ 50-300 kOhm

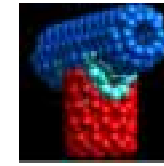
10 μm x 10 μm Cr contact pads

~ 500 to 600 CNTs

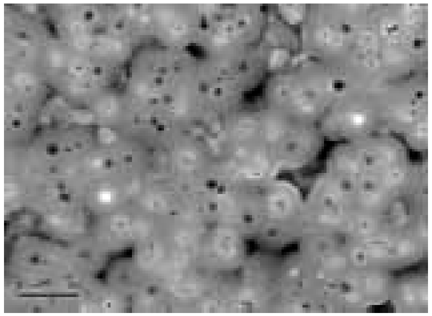
⇒11-13 kΩ / CNT

In the range of a quantumn conductance

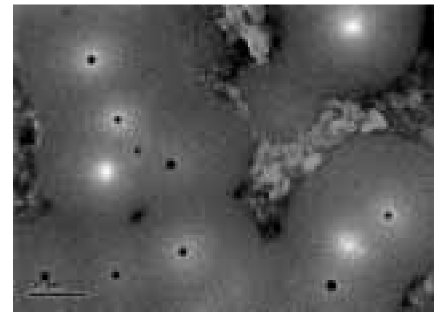
$G_0 = 2e^2/h$ (~12.9 kΩ).



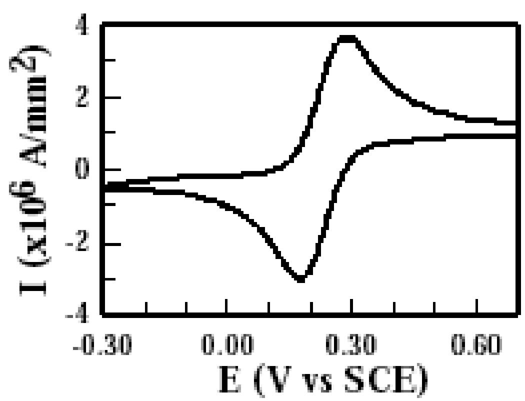
Carbon Nanotube Electrodes at Different Densities

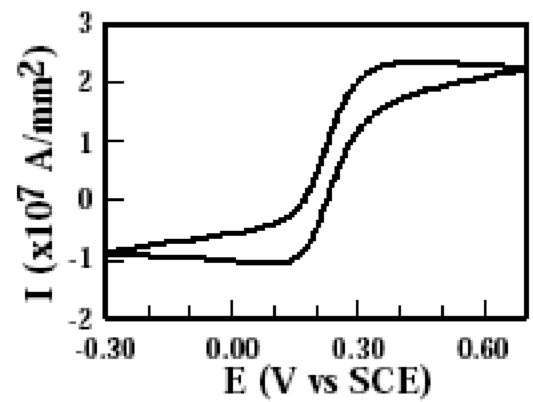


CNT coverage: ~ 20%
(~3.0x10^9 CNTs/cm^2)
Average nearest-neighbor distance:
~300 nm



CNT coverage: < 1%
(~1x10^8 CNTs/cm^2)
Average nearest-neighbor distance:
> 1500 nm

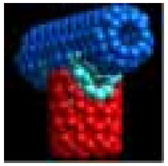




CV in 1mM $K_4Fe(CN)_6$ in 1M KCl at 20 mV/s

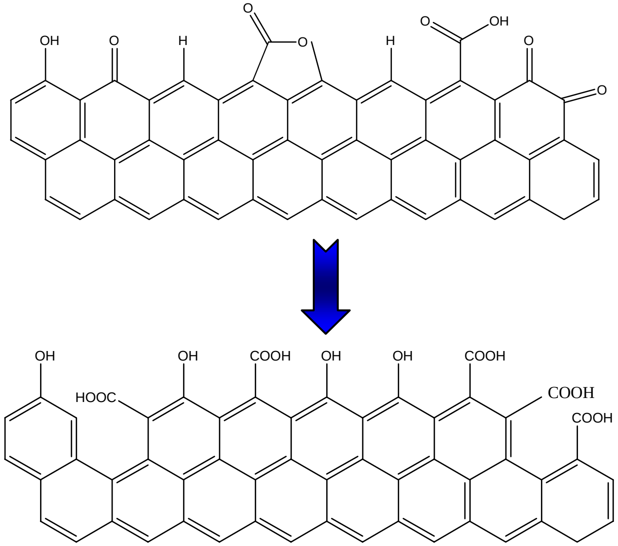
J. Li, H. T. Ng, A. Cassell, W. Fan, H. Chen, Q. Ye, J. Koehne, J. Han, M. Meyyappan, *Nano. Lett.*, 2003, **3** (5), 597.

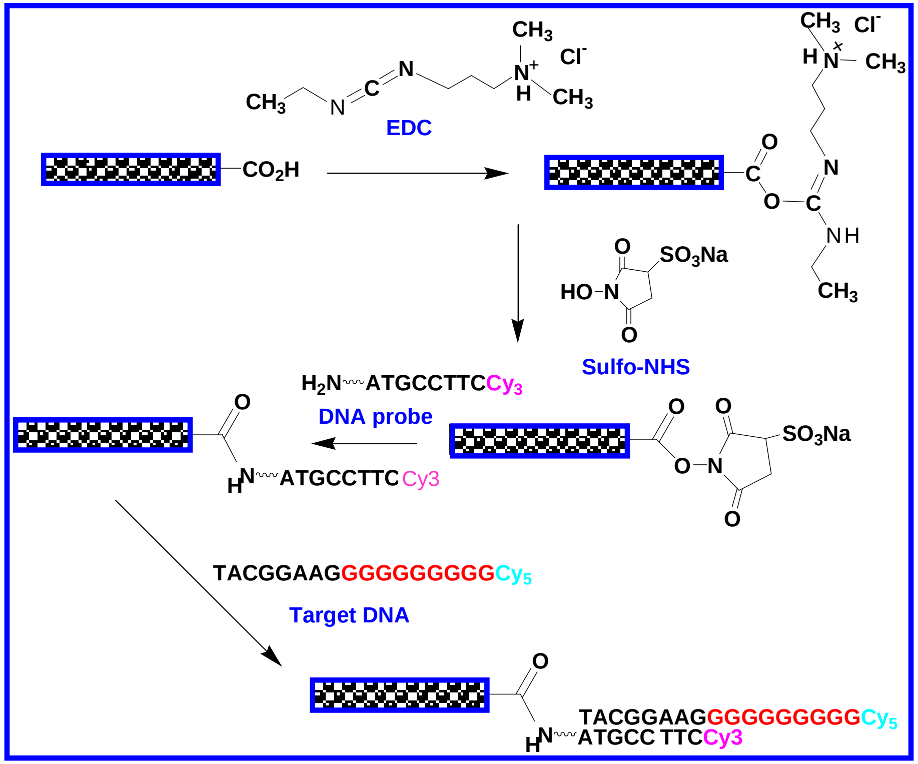
CNT Functionalization and Hybridization

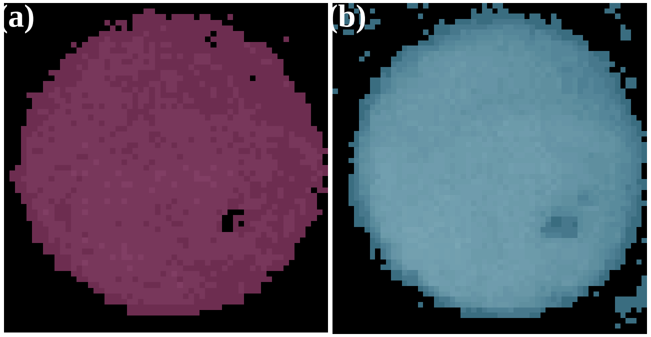


Electrochemically produce carboxylic acid groups on the surface in 1M NaOH

Highly selective reaction of primary amine with surface carboxylic acid group





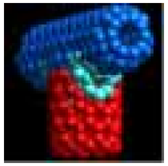


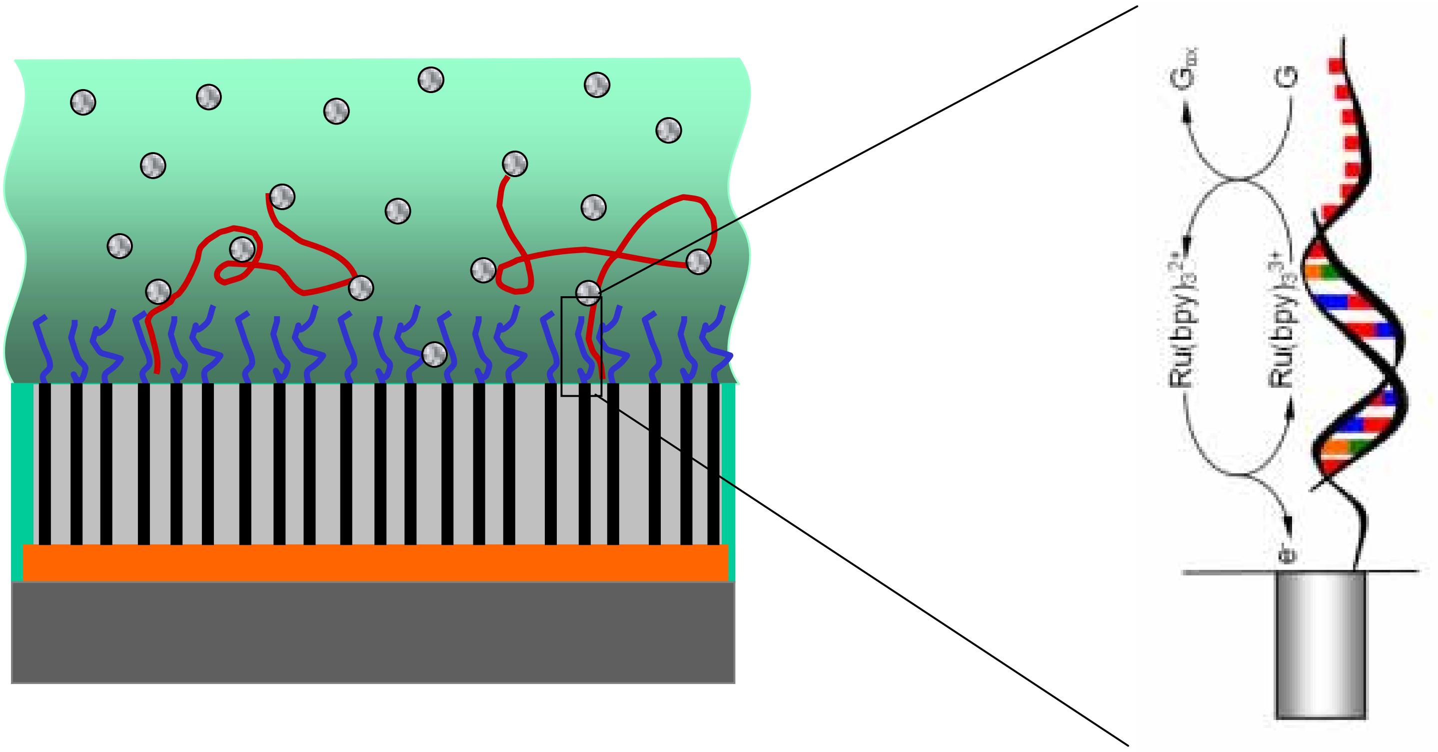
Cy3 Scan: Probe DNA

Cy5 Scan: Target DNA

J. Li, et al., *Nano. Lett.*, 2003, 3 (5), 597.

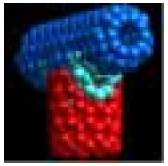
CNT DNA Sensor
Using Electrochemical Detection

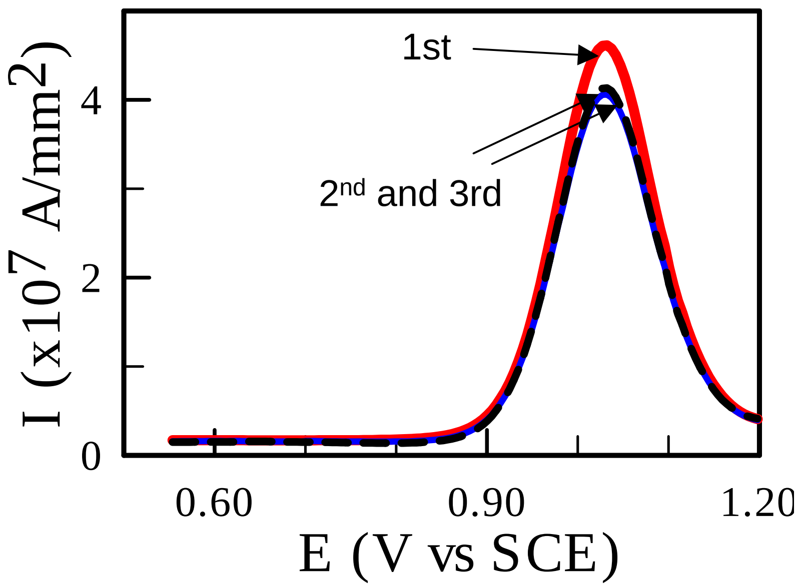


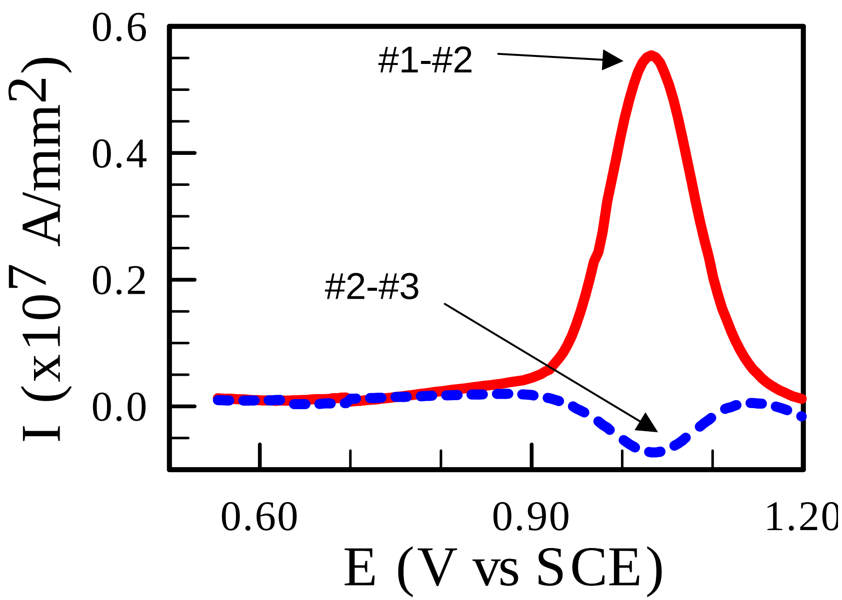


- **MWNT array electrode functionalized with DNA/PNA probe as an ultrasensitive sensor for detecting the hybridization of target DNA/RNA from the sample.**
  - Signal from redox bases (Guanine) in the excess DNA single strands
- **The signal can be amplified with metal ion mediator oxidation catalyzed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

Electrochemical Detection by AC Voltametry







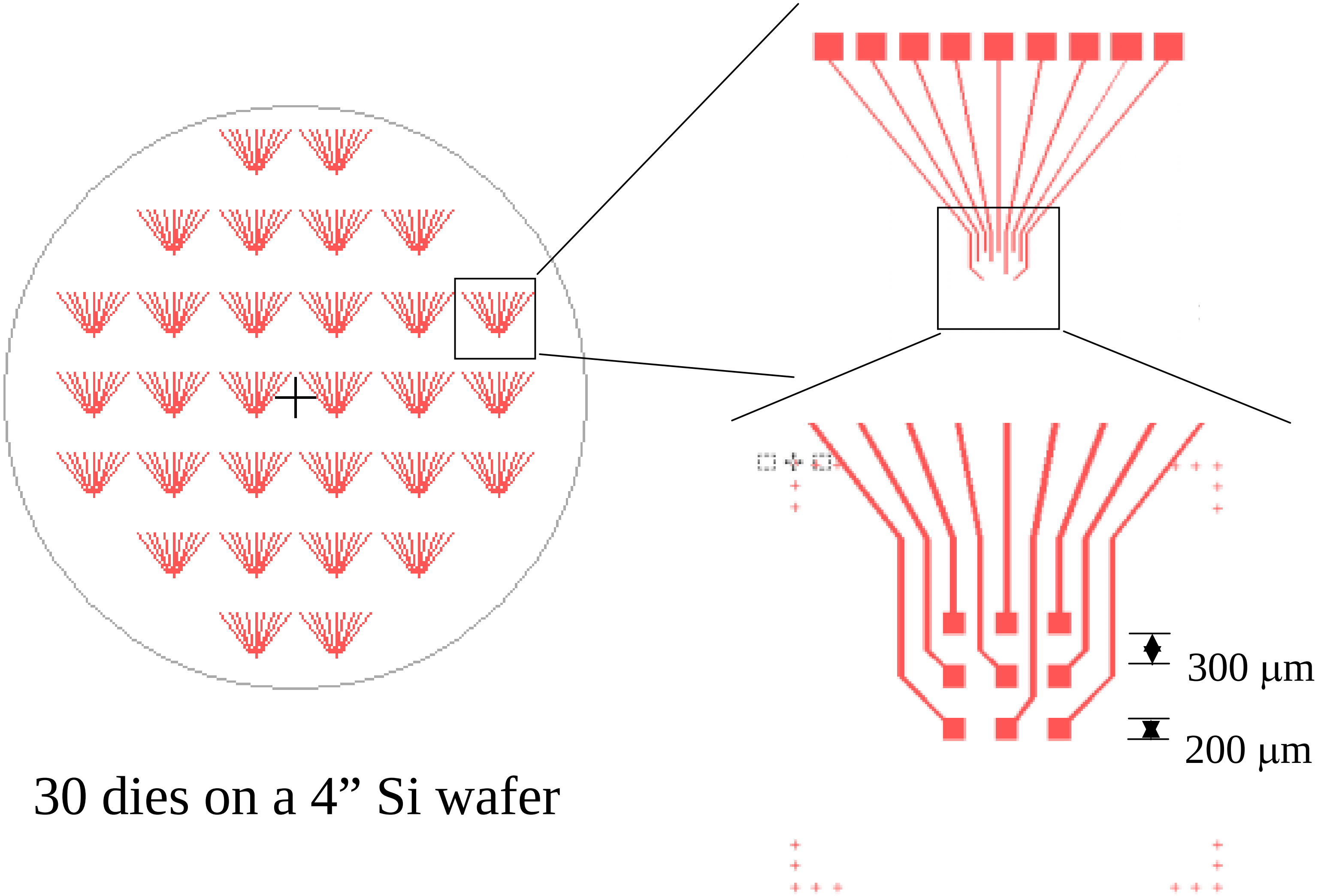
1st, 2nd, and 3rd scan in AC voltammetry

1st – 2nd scan: mainly DNA signal

2nd – 3rd scan: Background

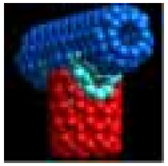
J. Li, H. T. Ng, A. Cassell, W. Fan, H. Chen, J. Koehne, J. Han, M. Meyyappan, *Nano. Lett.*, 2003, 3, 597.

Fabrication of Genechip

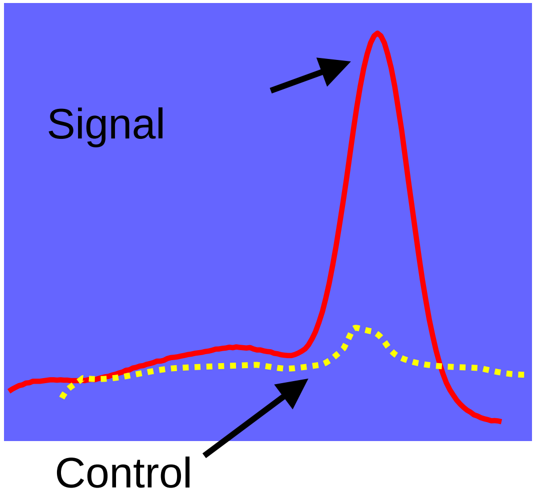


30 dies on a 4” Si wafer

Simple Devices for Quick Molecular Analysis



Handheld
Diagnostic Device



Workstation

Potential applications:

(1) Health monitoring and astrobiology study in outer space
(2) Early cancer detection
(3) Infectious disease detection
(4) Environmental monitoring
(5) Pathogen detection

Nanotechnology Advantages for Chemical Sensors

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NACNT

- High surface area to volume ratio of SWCNTs (~ 1600 m^2/g)
- Low energy barrier (Room temperature sensing)
- Small size
- Low power consumption (1mW/sensor)
- Easy integration

Nanomaterial + Chip (micro) ⟶ Macro sensing system

Nano-Micro-Macro Hierarchy

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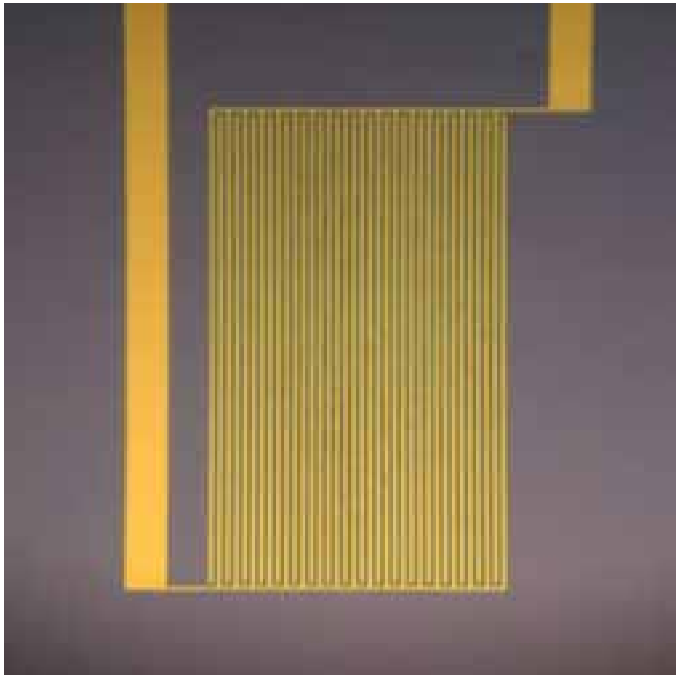
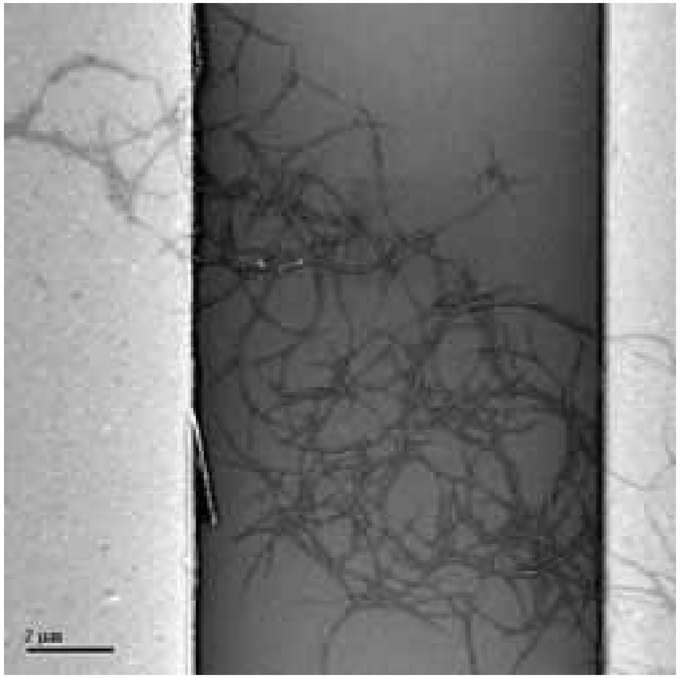
NASA Ames SWCNT Chemiresistor

NACNT

- **Senses small molecules as well as large molecules**
- **Under development for NASA cosmochemistry applications as well as for HS needs**





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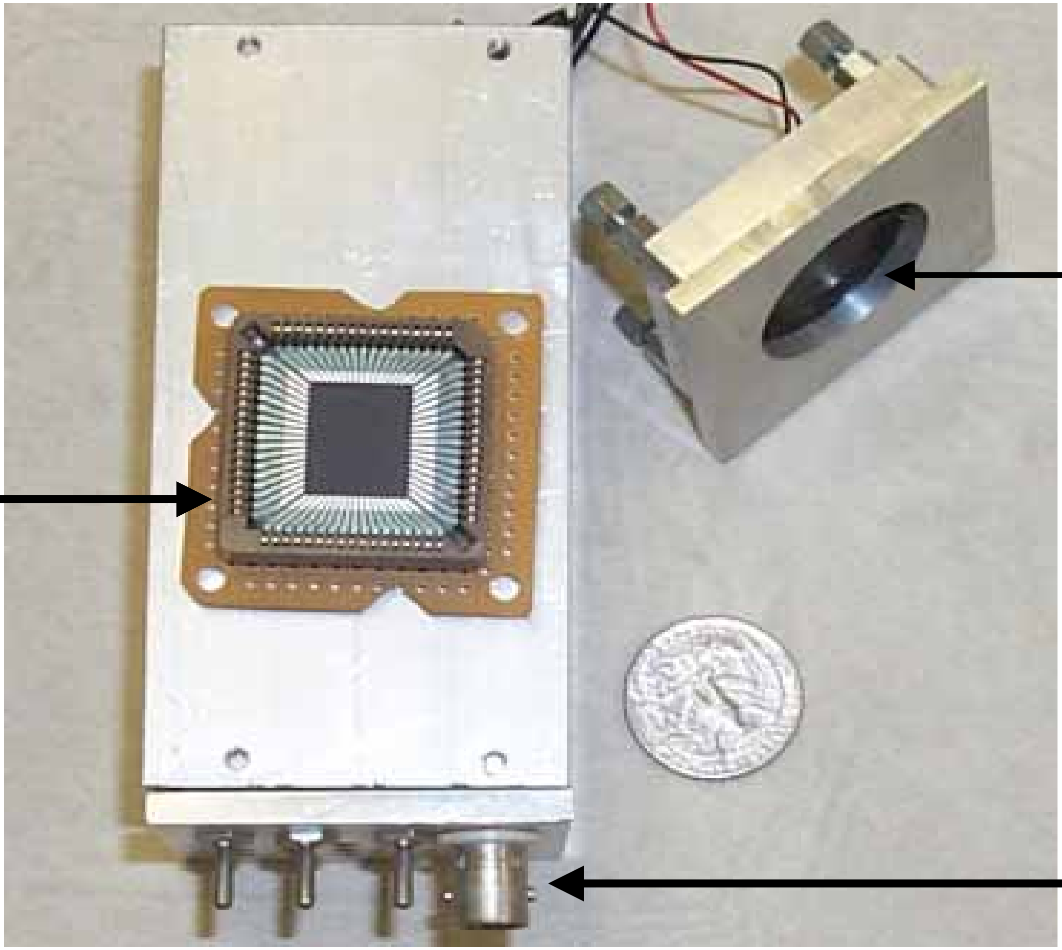
Handheld Device for in-situ Gas and Vapor Detection

NACNT

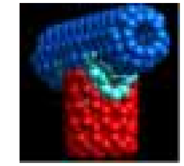


Sensor module Will be placed inside the fan

Fan blow vapor sample in

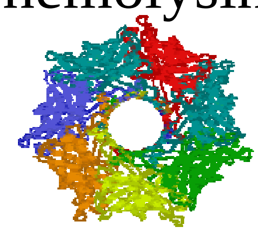
Front panel control

DNA Sequencing with nanopores
The Concept

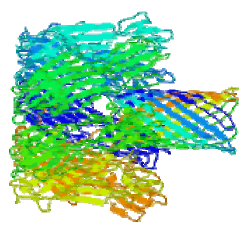


- Nanopore in membrane
- DNA in buffer
- Voltage clamp
- Measure current

α-hemolysin pore

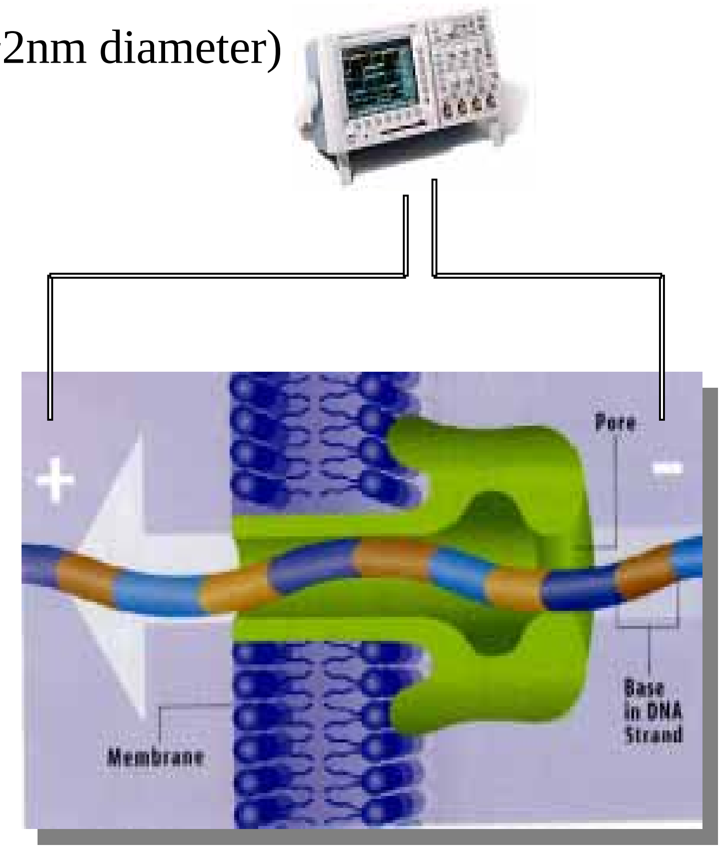


Axial View

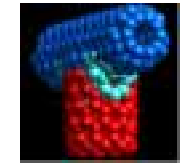


Side View

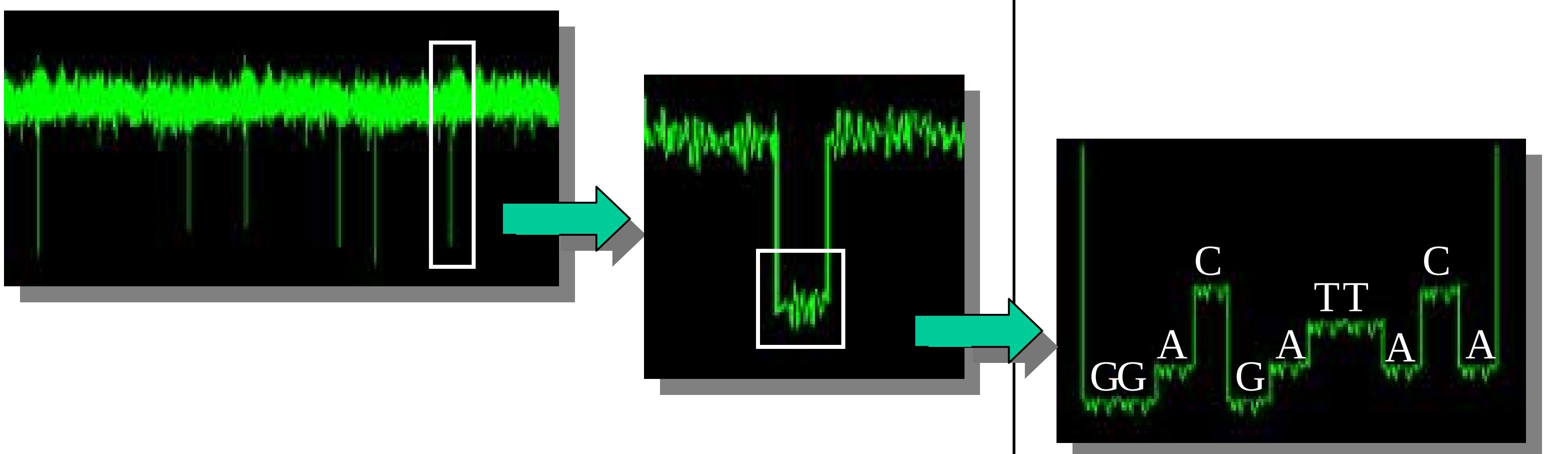
(~2nm diameter)



G. Church, D. Branton, J. Golovchenko, Harvard
D. Deamer, UC Santa Cruz



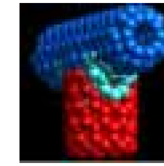
The Sequencing Concept



Present

Future

Potential Advantages of Solid-State vs Protein nanopores



- Interaction with single nuclotides
  - ~20 nucleotides in αHL simultaneously
- Slower translocation
  - 1-5 μs /nucleotide in αHL
- Resistance to extreme conditions
  - Temperature
  - pH
  - Voltage

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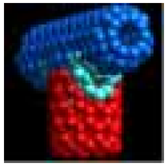
Challenges & Tasks



- Fabrication of the solid-state nanopore
  - Size (diameter, length)
  - Geometry
  - Composition
  - Reproducibility
- Experimental
  - Signal to noise
- First task is to characterize the pore and then characterize the DNA

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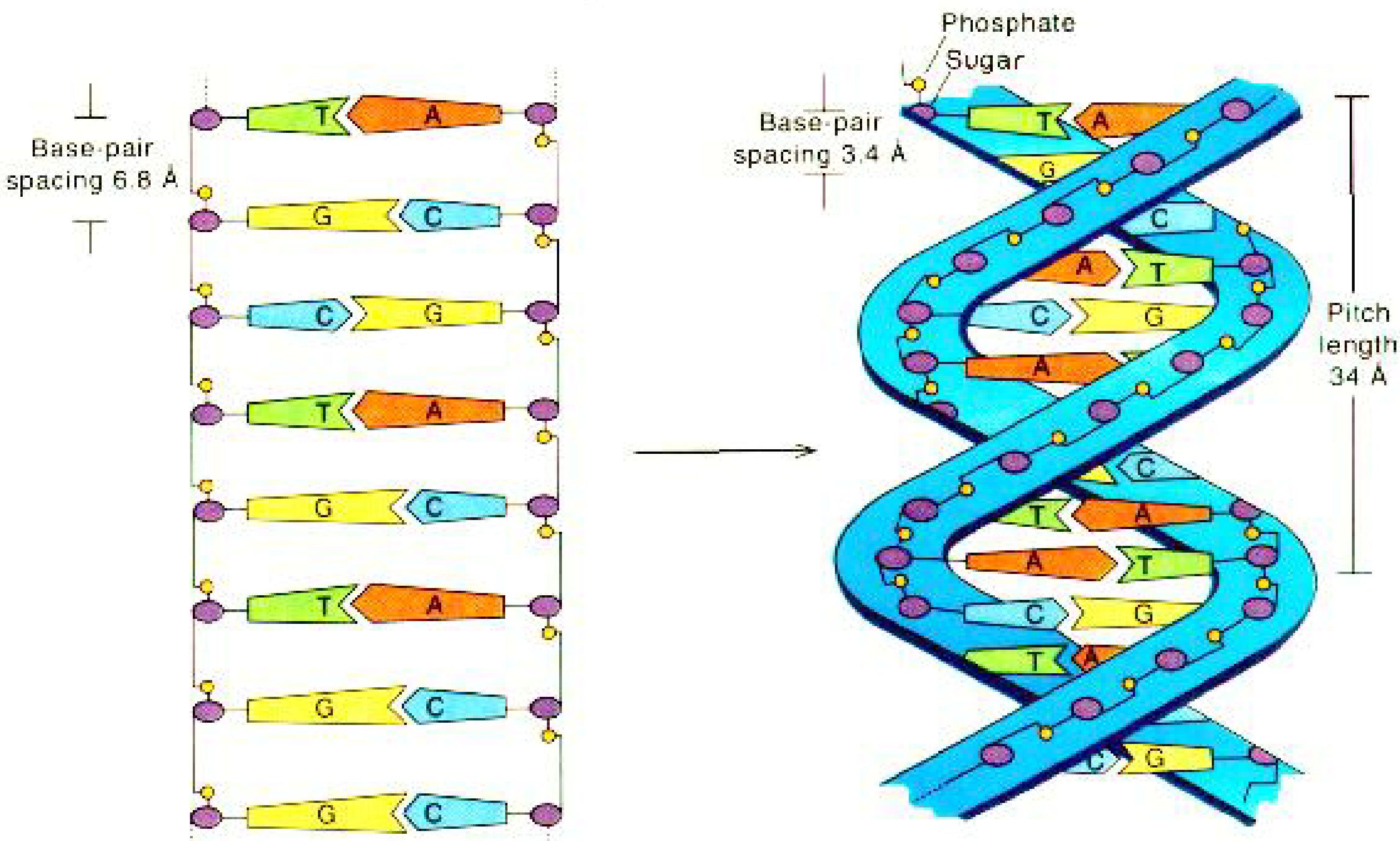
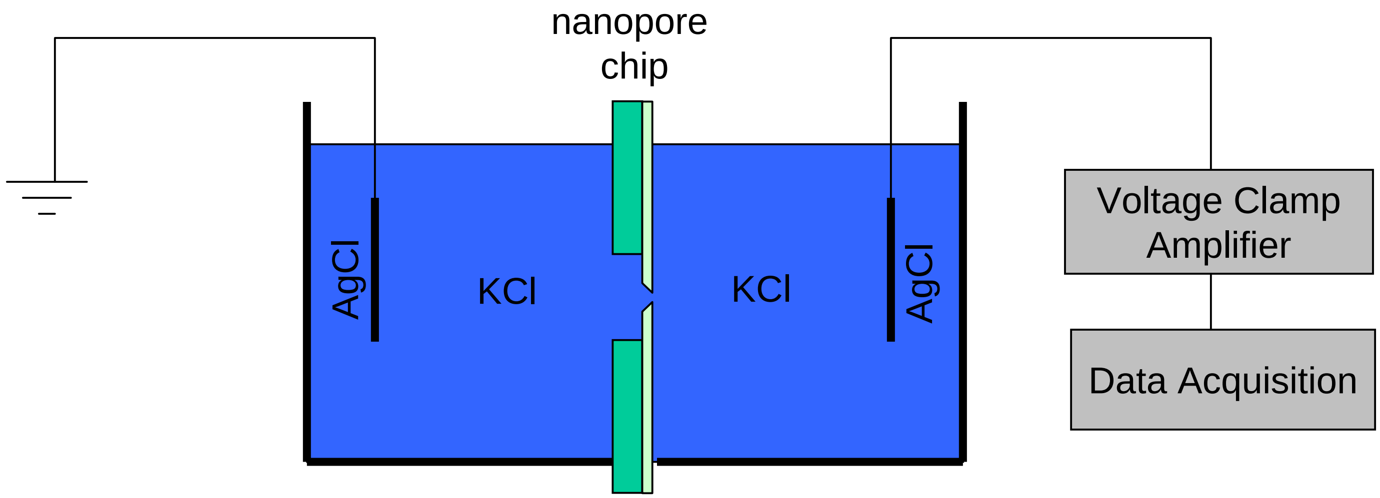
Nanopore Dimensions Determined by DNA Structure

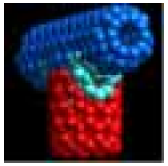


Methods



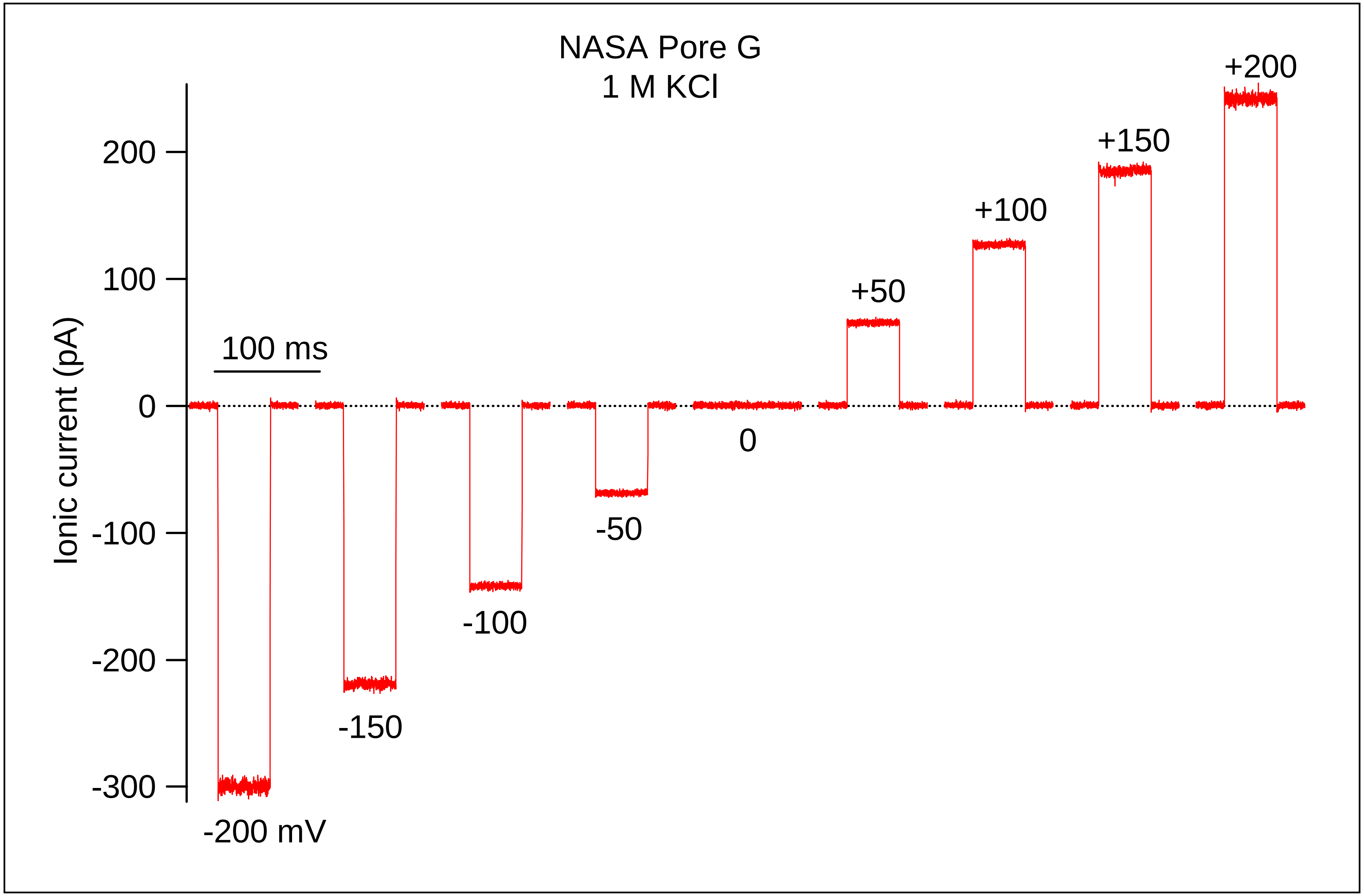
- Voltage-clamp amplifier designed to measure pA level currents
- Fast (up to 1GHz) data acquisition
- Software for automatic blocking event detection and recording

Conductance Measurements

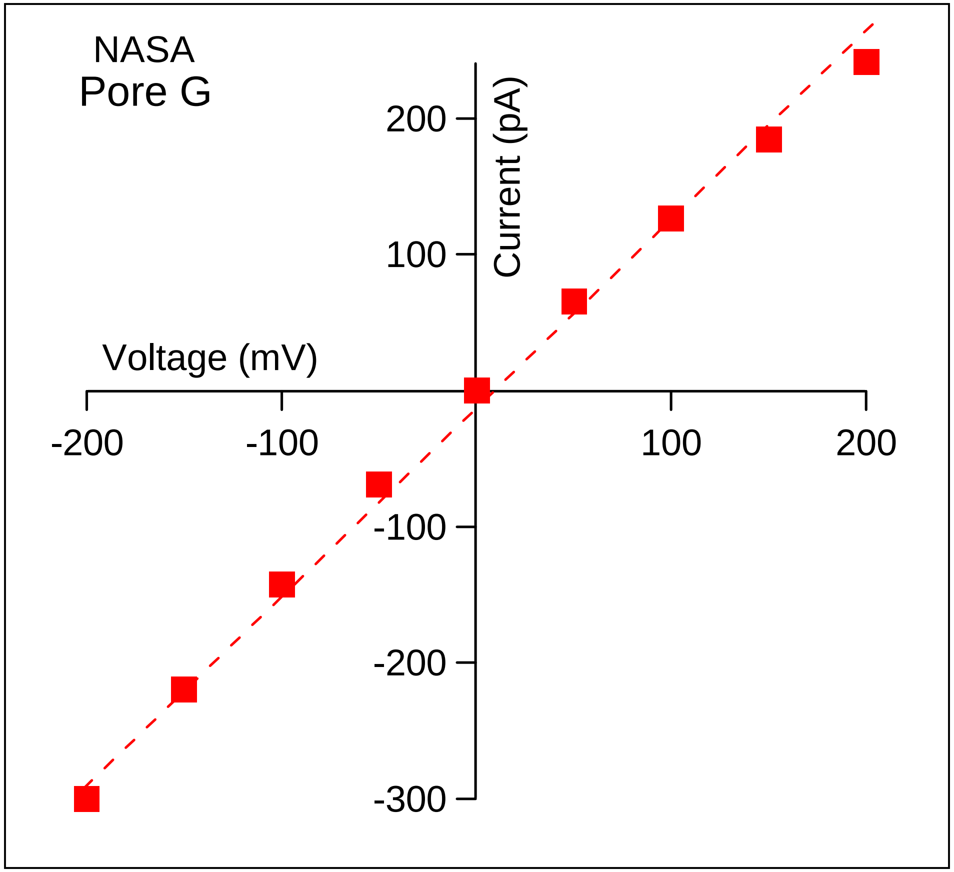


- Confirmation of pore size
- Understand basic functionality of artificial channels
- Feedback into modeling

Pore Ionic Current at Varying Voltage



Current-Voltage Relationship



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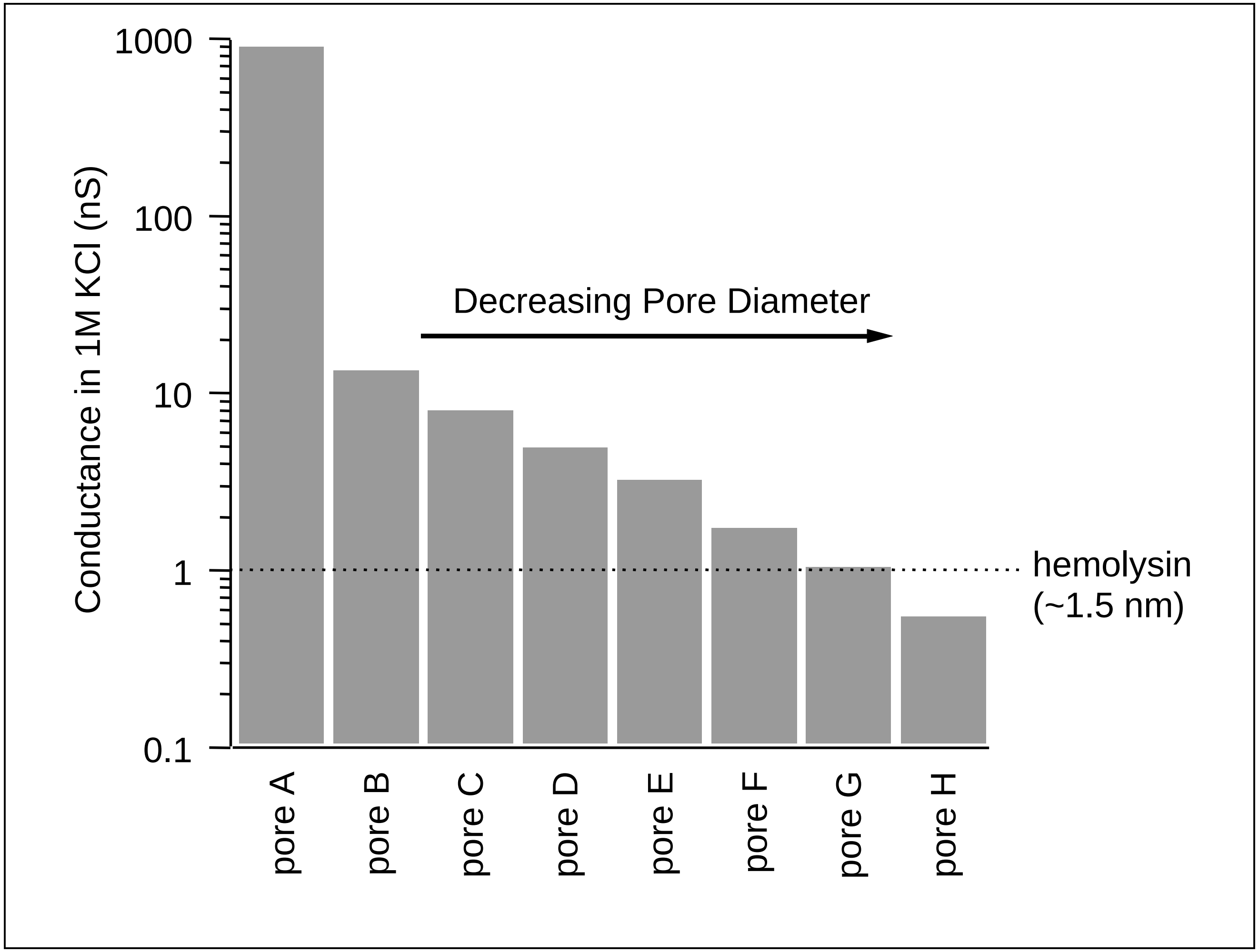
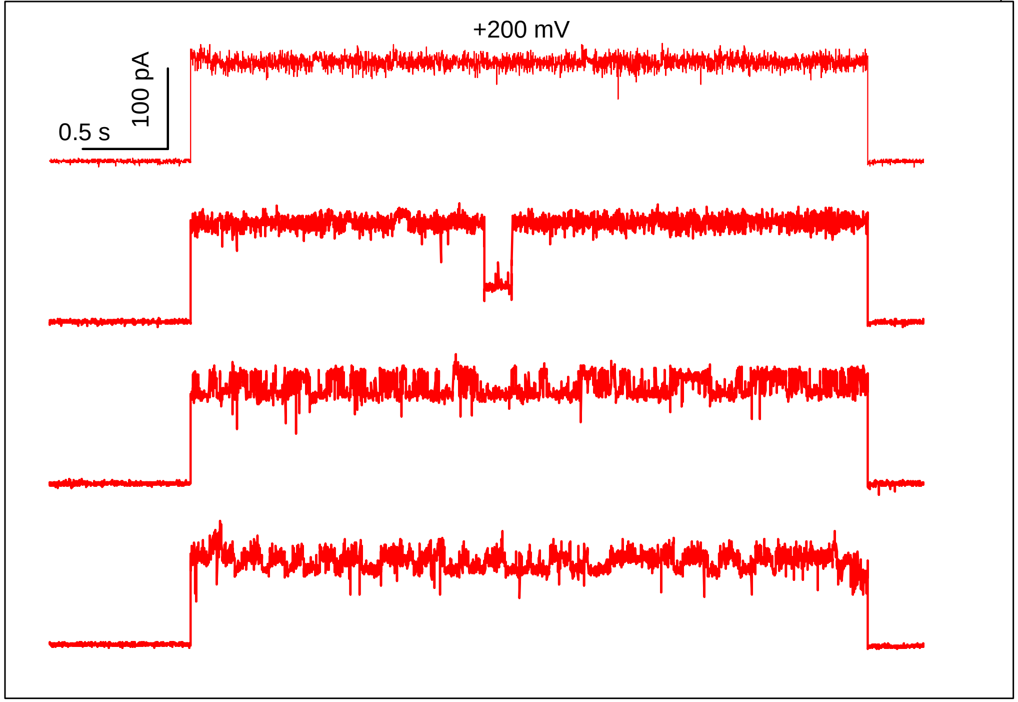
Conductance of NASA Pores



Spontaneous Blocking Events with Smaller NASA Pores

Spontaneous Blocking Events with Smaller NASA Pores



CNTs in Bio-Medical Applications

Project #1: NASA Stanford Vision Chip

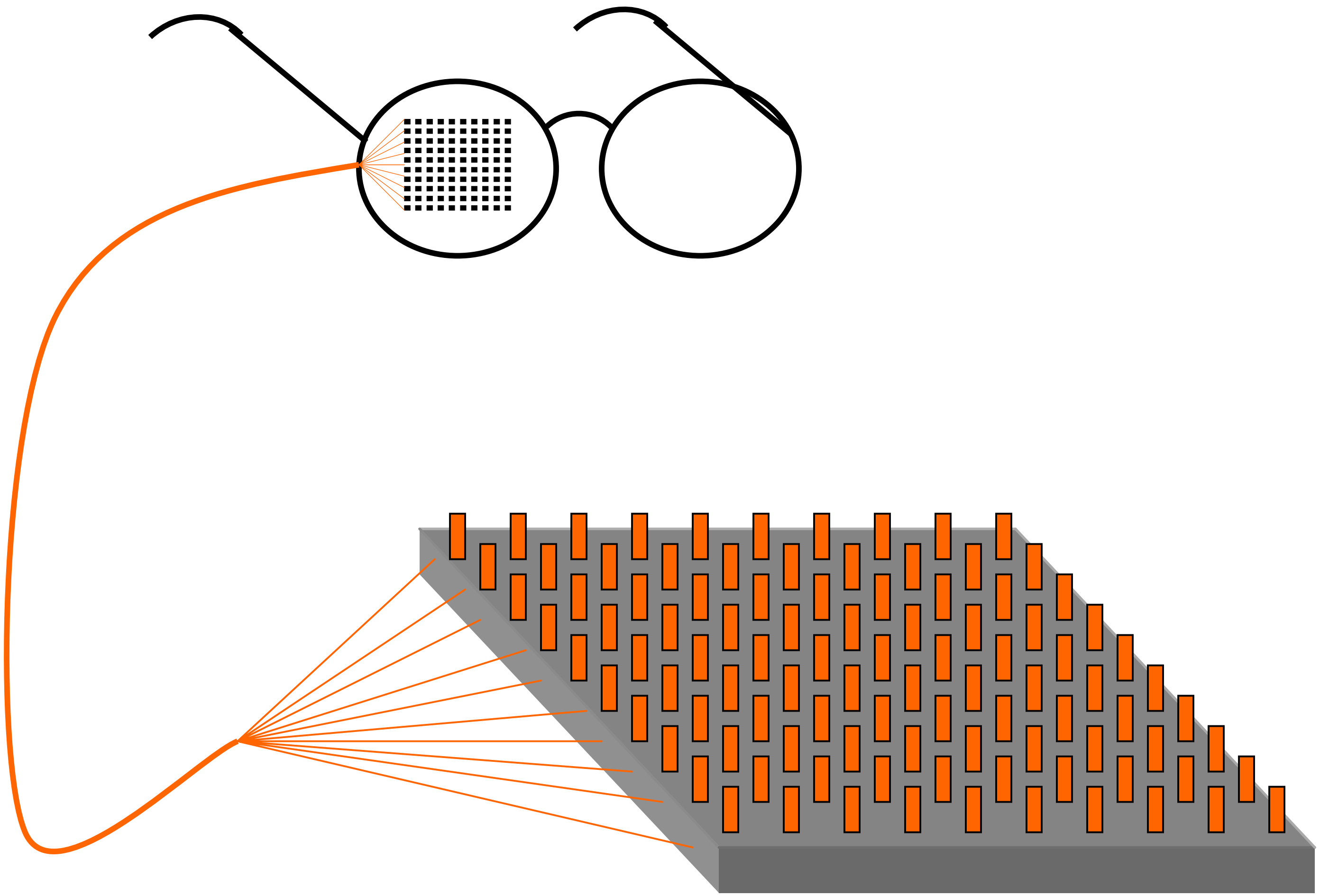
"Development of an implantable device consisting of an array of carbon nanotubes on a silicon chip for restoration of vision in patients with macular degeneration and other retinal disorders"

Project #2: Carbon Nanotube Bucky Paper for Retinal Cell Transplantation

"A meshwork of carbon nantotubes as a substrate for retinal cell growth and as a 'carrier' to facilitate surgical transplantation of retinal cells into the retina of patients with macular degeneration"

What is macular degeneration?

Vision Chip



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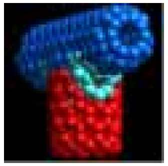
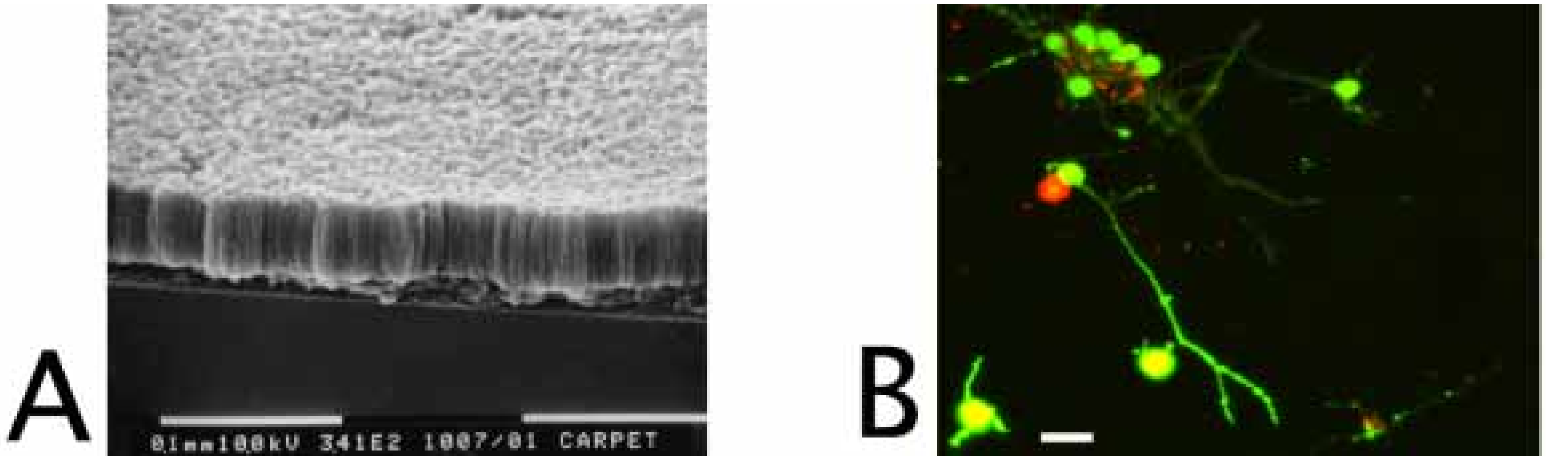
Carbon Nanotubes



- Mechanical Properties
- Electrical Properties
- Chemical Properties

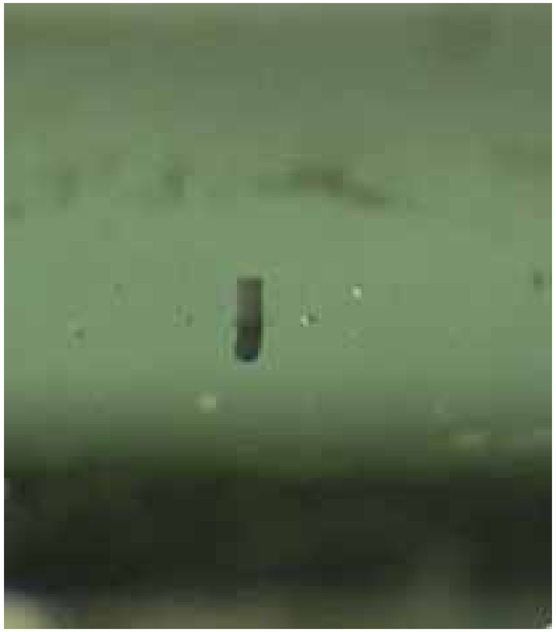
- “Engineer-ability”
- Biocompatibility

Preliminary Biocompatibility Data



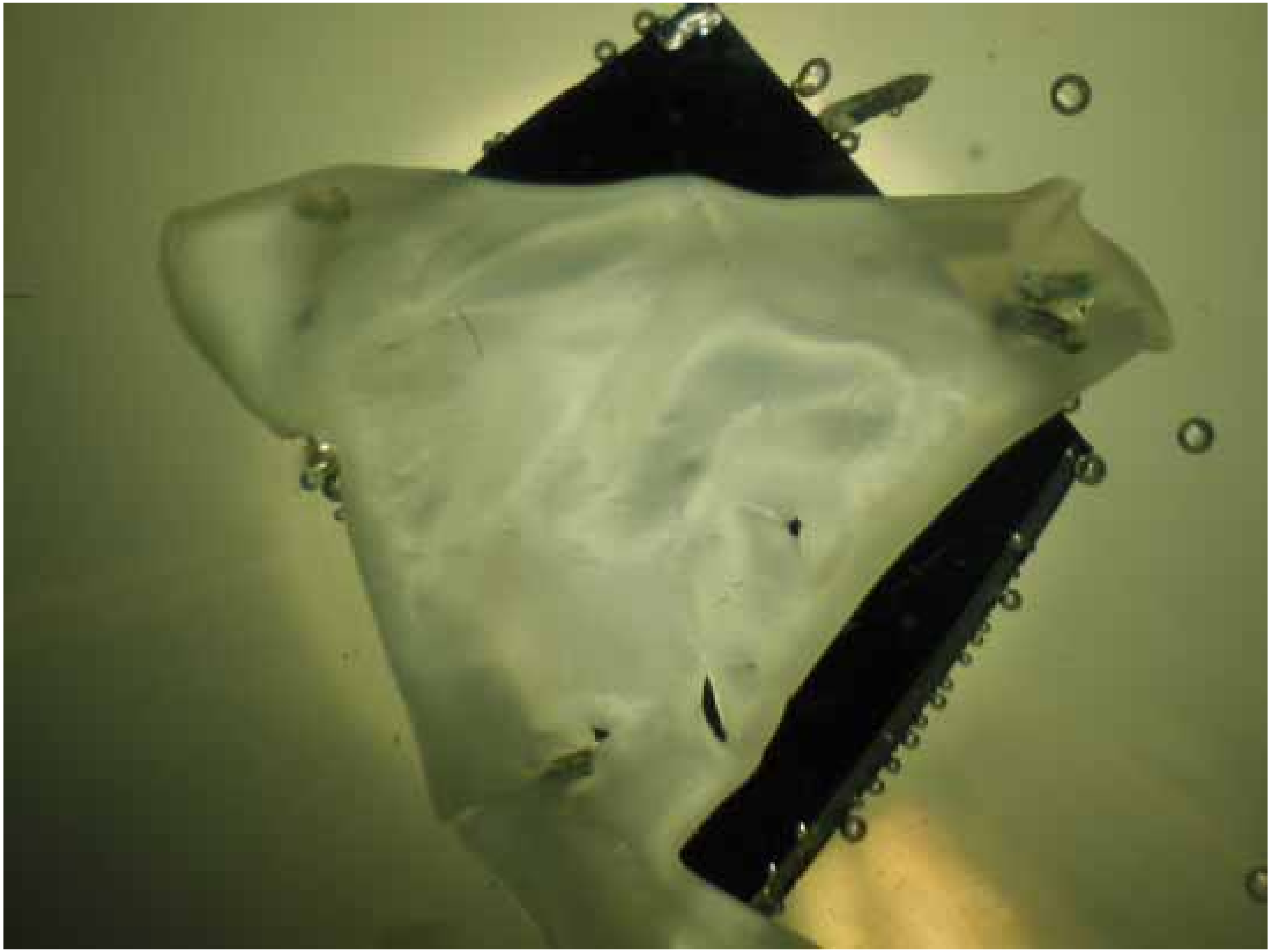
Carbon Nanotube Tower on a Silicon Chip

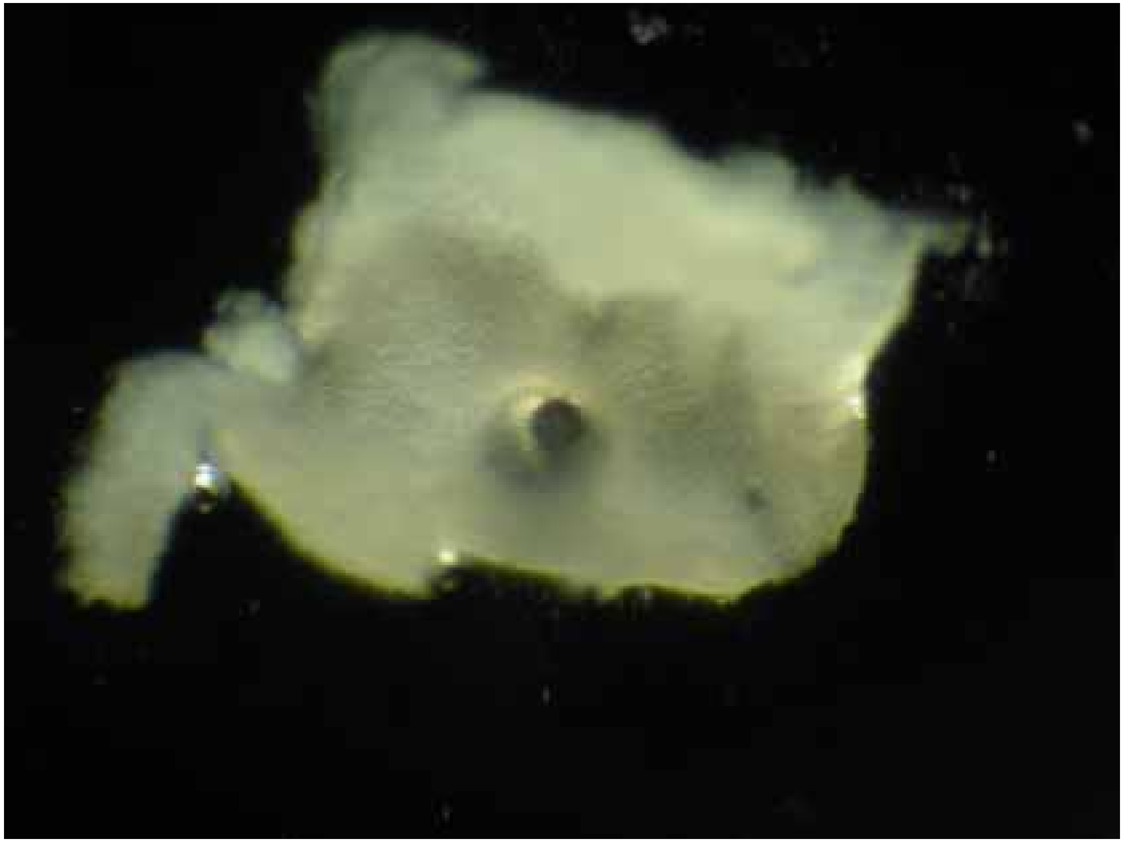
Tower consists of a bundle of multi-walled carbon nanotubes



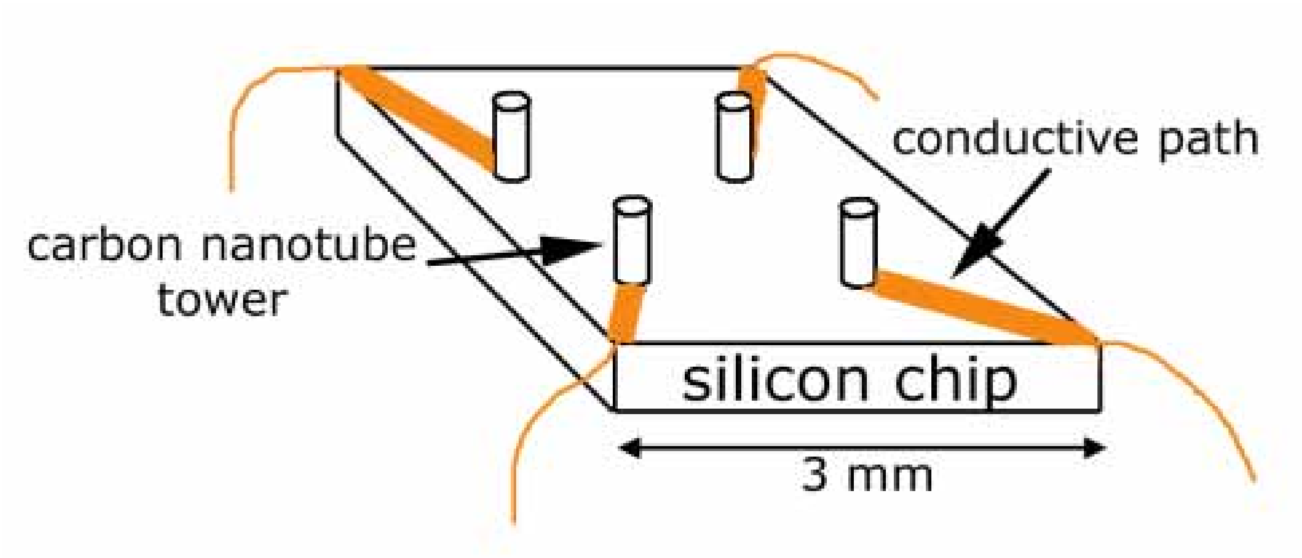
Hurdle #1: Tissue Biocompatibility

Hurdle #2: Mechanical Strength



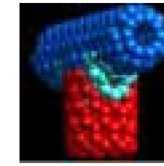


Hurdle #3: Electrophysiology Testing



Electrophysiology testing will consist of retinal tissue stimulation by the "Quad Chip," with recording of electrical activity in the ganglion cell layer adjacent to the CNT towers.

Project #2 Retinal Cell Transplantion



- In the early stage of macular degeneration, retinal pigment epithelial (RPE) cells die, which leads to loss of photoreceptors. Solution?—replace the cells that are lost.

- RPE cells and iris pigment epithelial (IPE) cells can be harvested from the eye, grown in culture, then put back into the eye (“autologous transplantation”).

Problems with Retinal Cell Transplantation:

- Transplantation of suspensions of epithelial cells into the sub-retinal space fails to re-establish the proper architecture of the RPE layer. Instead of a sheet of uniformly oriented cells, you get a "jumble" of cells.

Solution:

- Establish the proper orientation of the epithelial cells prior to transplantation, by growing them in culture on a physical support:

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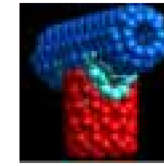


The Obvious Strategy:

Natural Substrates for Retinal Transplantation

- Anterior Lens Capsule (*basal lamina)*
- Descemet's Membrane (posterior cornea)

Experimental Results:

Excellent growth of retinal epithelial cells, assembly of true "epithelial architecture."

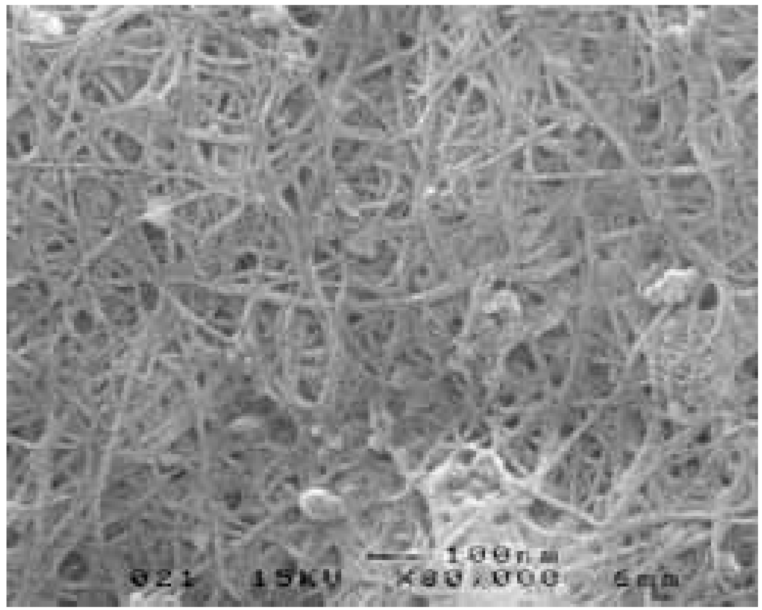
Problem!: Membranes with attached epithelial cells cannot be easily implanted into the eye, because the membranes are flimsy and tend to "curl up." They lack the mechanical properties necessary for surgical handling.

The Answer:

Carbon Nanotube Bucky Paper

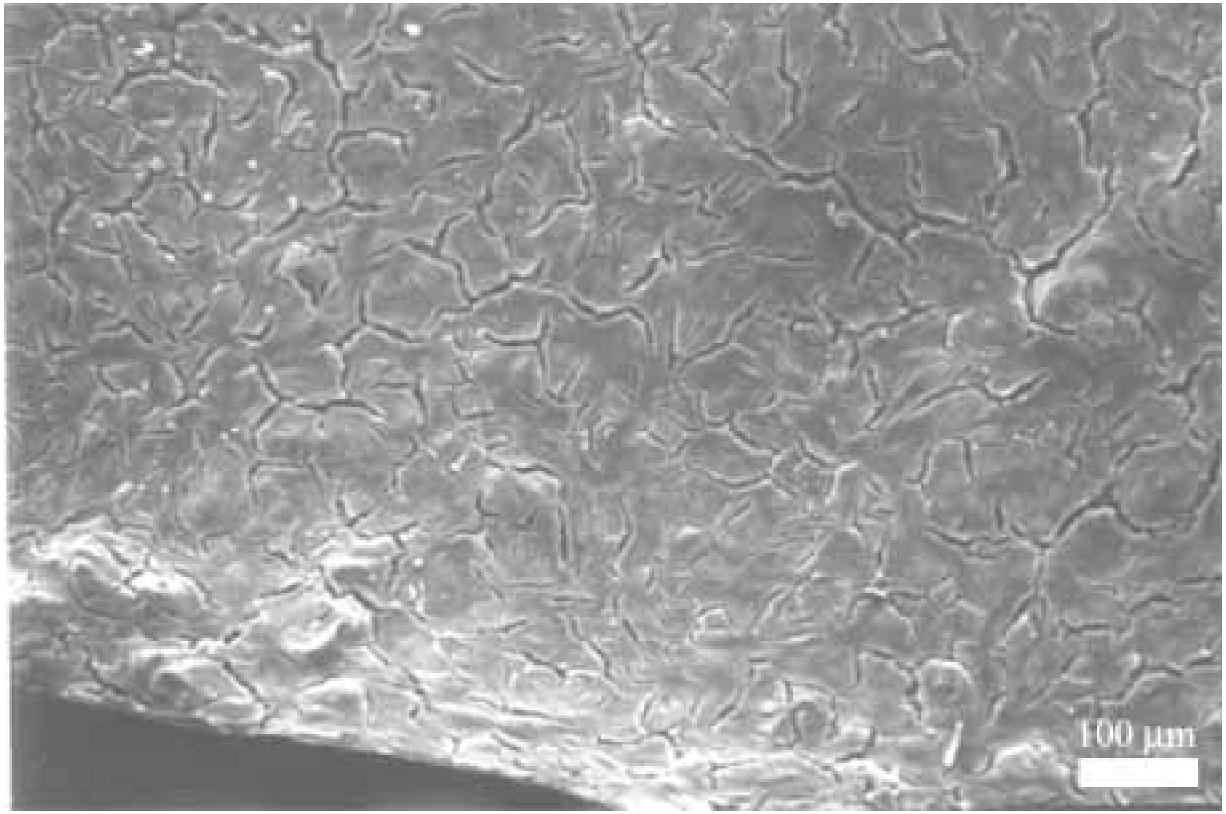
A meshwork of carbon nanotubes formed into a paper-like structure

Carbon Nanotube Bucky Paper



A meshwork of bundles of CNT’s

Scanning Electron Micrograph of RPE cells grown on Carbon Nanotube Bucky Paper

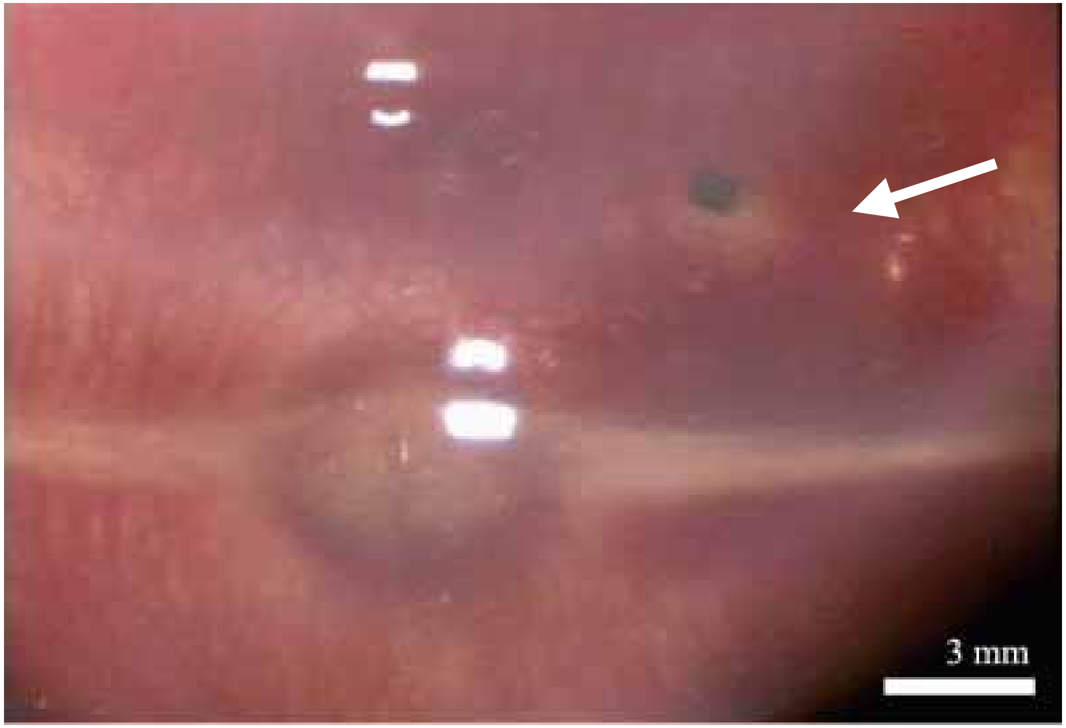


Result: Confluent monolayer, with uniform orientation of cells

Light Micrograph/Histological Staining of RPE Cells Grown on Carbon Nanotube Bucky Paper

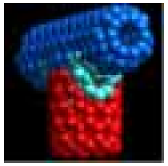
Result: Excellent attachment of RPE cells to the Bucky Paper surface; confirmation of correct apical/basolateral orientation

Implantation of Carbon Nanotube Bucky Paper into the Sub-Retinal Space of an Albino Rabbit



Result: Bucky paper is easily manipulated during surgery (does not tear and stays flat), and is immunologically well-tolerated by the eye.

Carbon Nanotube Biocompatibility



- **Vision Chip**
- **Retinal Cell Transplantation**
- **Islet Cell Transplantation**
- **Hemostatic Bucky Paper/ Wound Healing**
- **Artificial Blood Vessels**
- **Tissue Engineering**
- ?

NASA NEEDS:

Implantable Physiological Sensors
- •Remote sensing
- •Early medical intervention
- •Novel medical countermeasures
  - *Cardiovascular physiology*

Long Duration Space Flight –How to deliver medical therapy?
- •Acute injury
  - Hemostatic Bucly Paper
  - Bucky Paper for Wound Healing
- •Cancer Therapy
  - *Adoptive Immunotherapy Delivered by Encapsulated Cells*
  - *Immune Shielded Delivery of Chemotherapy*
- •Therapy for diabetes
  - *Transplantation of Islet Cells*

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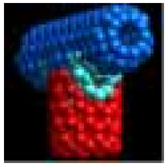
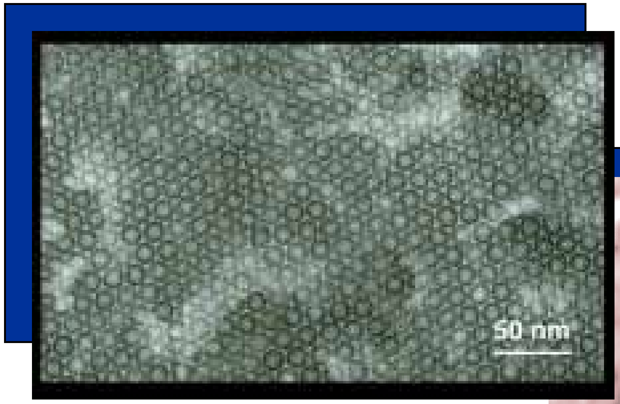
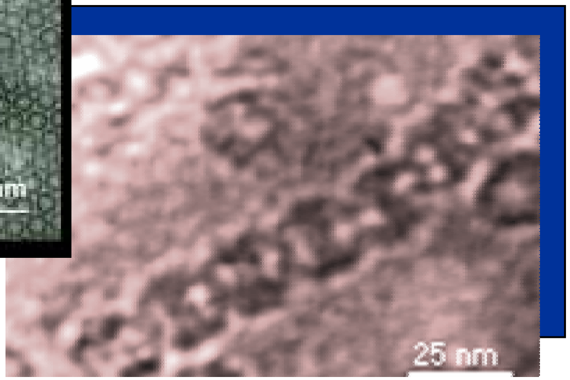
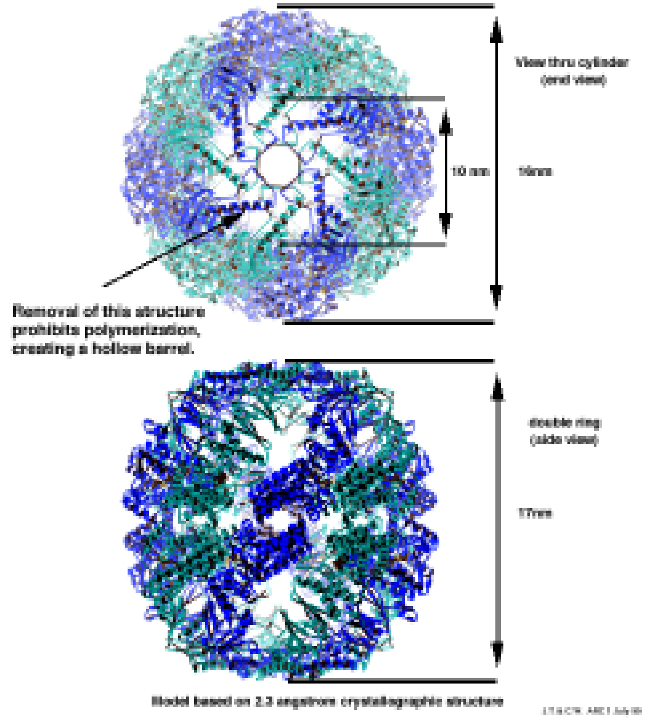
Protein Nanotubes



- Heat shock protein (HSP 60) in organisms living at high temperatures ("extremophiles") is of interest in astrobiology
- HSP 60 can be purified from cells as a double-ring structure consisting of 16-18 subunits. The double rings can be induced to self-assemble into nanotubes.



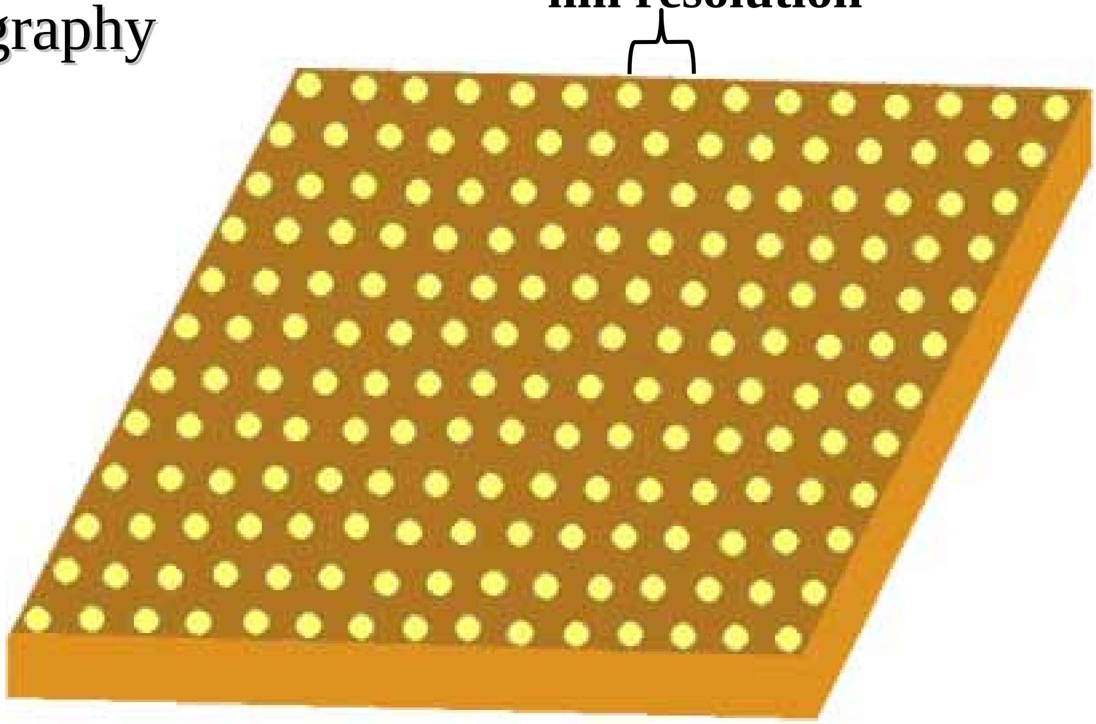




Extremophile Proteins for Nano-scale Substrate Patterning

Nano-scale engineering for high resolution lithography

Future: Bio-based lithography
- •Batch self-assembly
- •Evolving
- •Inexpensive



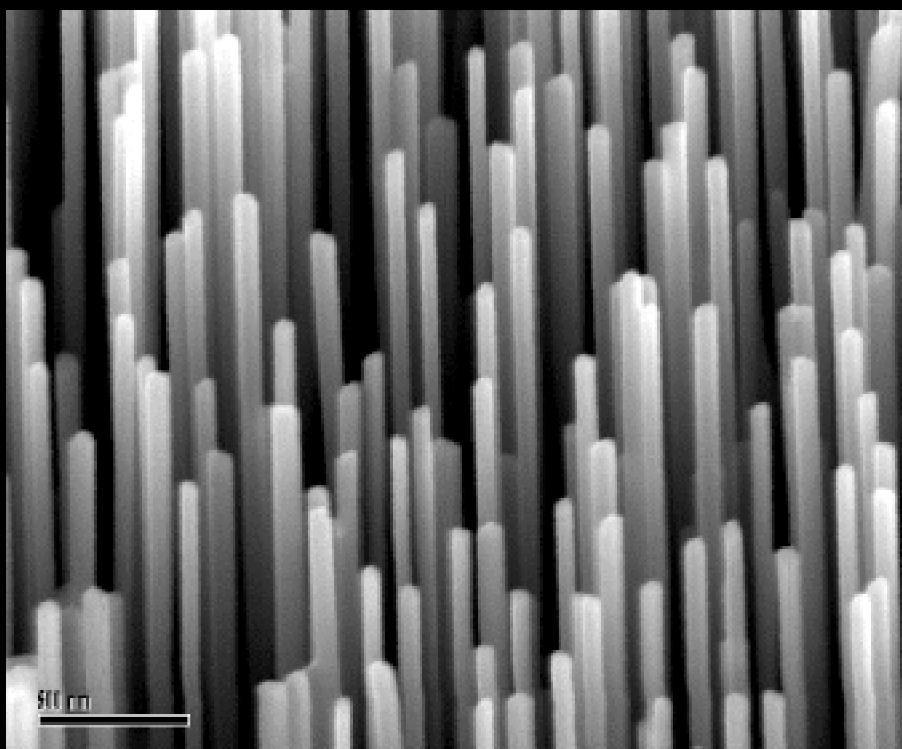
Motivations for selecting Single Crystalline Nanowires

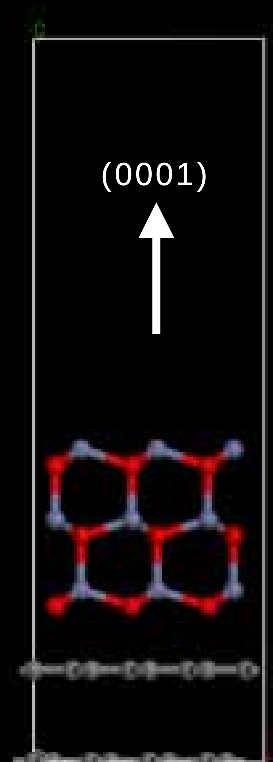
(in Nano-scale Electronics)

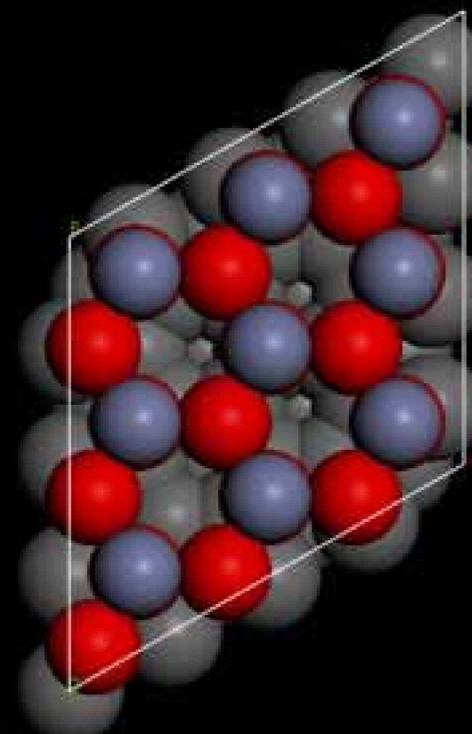
- ❖ High single crystallinity ⇒ Low defect density, grain boundary free
- ❖ Well-defined surface structural properties ⇒ Enhanced interfacial engineering
- ❖ Predictable electron transport properties ⇒ Predictable device performance
- ❖ Unique physical properties due to quantum confinement effects ⇒ Enhancement in device characteristics
- ❖ Tunable electronic properties by doping ⇒ Enhancement in device characteristics
- ❖ Truly bottom-up integration approach ⇒ Innovative fabrication schemes
- ❖ Potential to revolutionize nano-scale science and technology

Zinc Oxide Nanowires

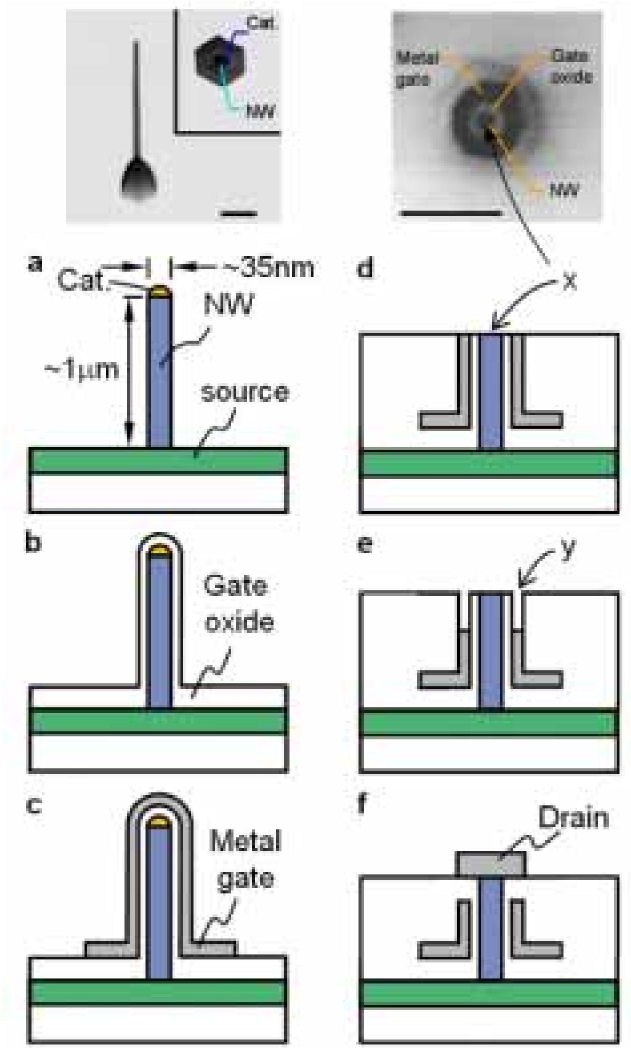
Understanding of the interfacial epitaxial relationship between potential substrates and nanowire structures ⇔ modeling and simulations ⇔ experiments ⇔ combinatorial approach



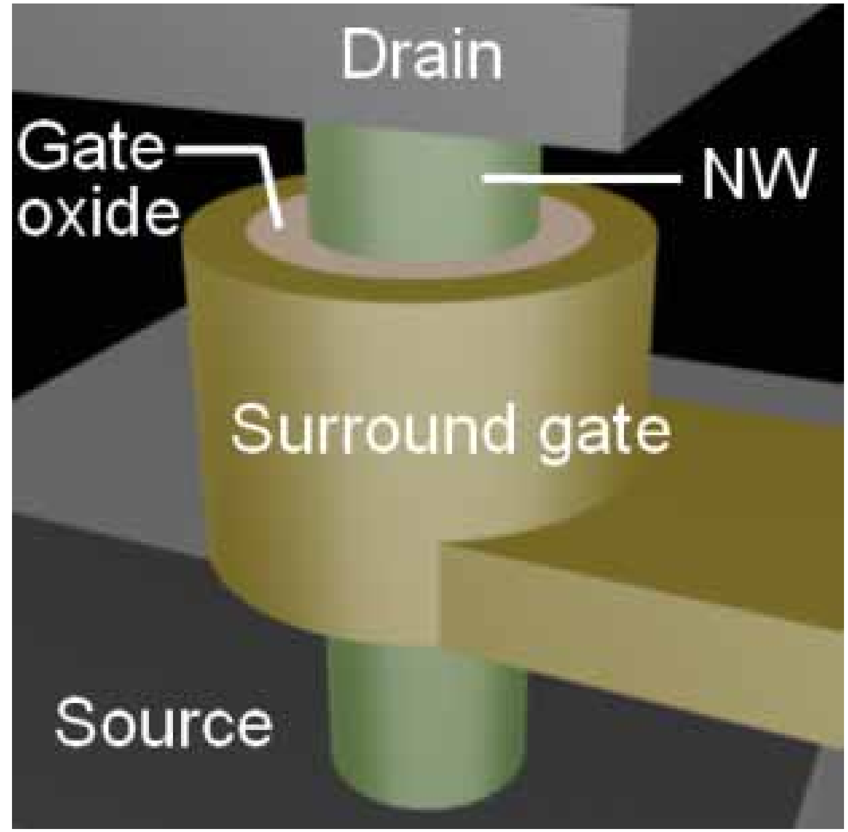




Vertical Surround-Gate Field Effect Transistor



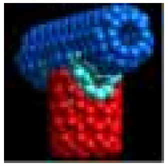
A process flow outlining the major fabrication steps of a VSG-FET.

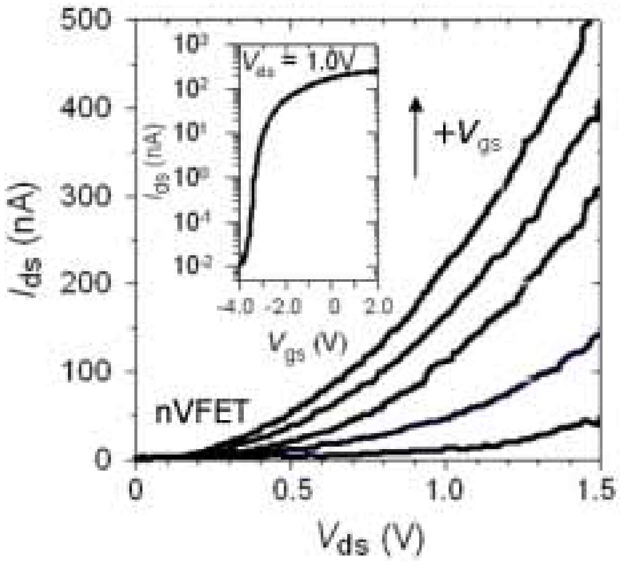


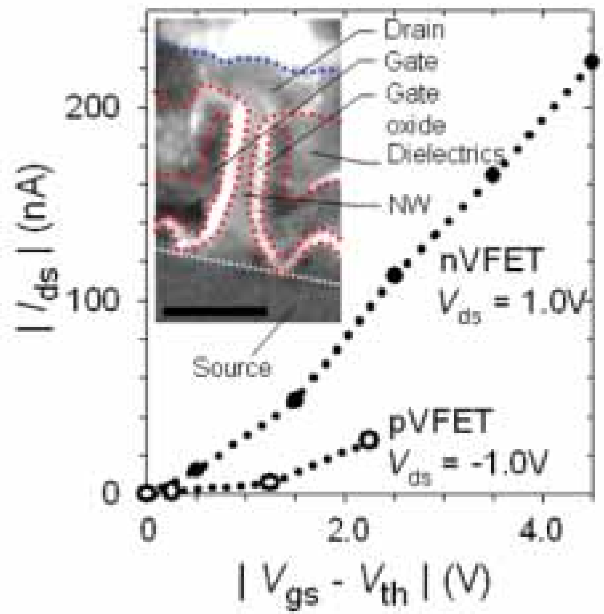
A schematic illustrating the device architecture of a VSG-FET.

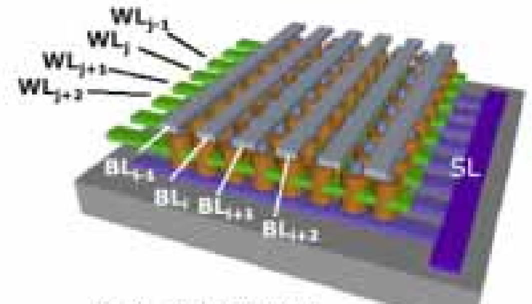
Ng *et al* (NASA Ames)

Vertical Surround-Gate Field Effect Transistor

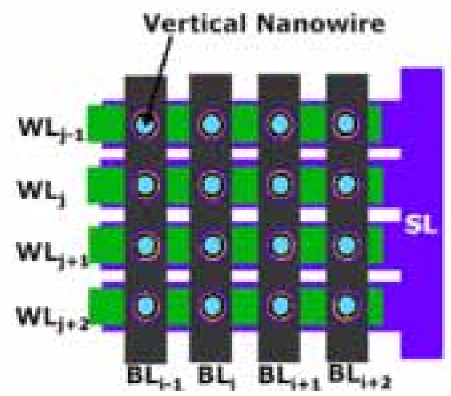


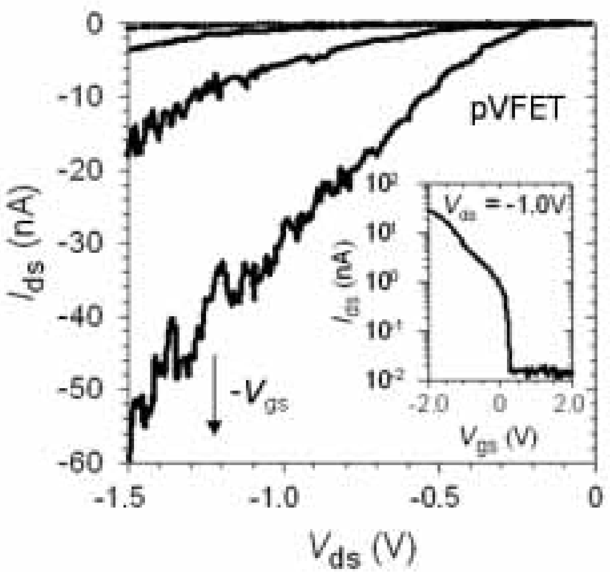






(B. Yu, et al, Invention disclosure @ NASA)





Unique features:

- **Bottom up 3D vertical nanowire array (>10Gb/cm²) ....High Density/Mobility**
- **Surround gate configuration .... Low Power and Extended Scalability**
- **Lithography-free gate/channel fabrication....................................Low Cost**
- **100% compatible with standard technology...... High Industry Acceptance**
- **Selection of channel material (Si, Ge, etc)..................Alternatives for high performance/cost**

Ng *et al* (NASA Ames)

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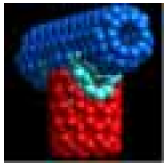
Summary



- 1-D Nanostructures such as carbon nanotubes and inorganic nanowires, show much potential for device and sensor development.

- BIN Fusion is an active area of research showing tremendous promise in the development of:
  - Biosensors
  - Gene sequencing
  - Novel nanostructured, multifunctional materials
  -
  -