Nanotechnology Enabled
Biological and Chemical Sensors

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• Carbon Nanofiber (CNF) Nanoelectrode Array for Biosensors

• CNF Nanoelectrode Array for Deep Brain Stimulation

• Gas/Vapor Sensors for Medical Diagnosis

• CNT in Ophthalmological Applications
Nanoelectrode Array for Biosensors

Directly interface solid-state electronics with DNAs, RNAs, proteins, and microbes in a miniaturized multiplex chip for quick detection (Lock and Key approach)
Nanoscale electrodes create a dramatic improvement in signal detection over traditional electrodes.

- **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 result in **magnified signal and desired redundancy** for statistical reliability.

Candidates: SWNTs, MWNTs, Vertical CNFs or Vertical SiNWs

Source: Jun Li
Nanoelectrode Array Fabrication

- Metal Film Deposition
- Catalyst Deposition
- Plasma CVD
- TEOS CVD
- CMP

As Grown

SiO₂ Encapsulated

(a) (b)
Potential for Cancer Diagnostics

- Probe molecule that would serve as signature for specific cancer cells to be attached to CNF ends.
- Current flow upon hybridization through CNF electrode to signal processing IC chip.
CNF array electrode functionalized with DNA probe as an ultrasensitive sensor for detecting the hybridization of target DNA from the sample.

- Signal from redox bases (Guanine) in the excess DNA single strands

- The signal can be amplified with metal ion mediator.
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 CNF Density ⇒ Lower Detection Limit

Current Techniques for Deep Brain Stimulation

**WHY: Effective Clinical Technique**
- DBS has been clinically effective in the treatment of movement disorder

**HOW: Four Interrelated Hypothesis**
- Paradox of similar effects to lesioning of target structure is explained by the following:
  - Depolarization Blockage
  - Synaptic Inhibition
  - Synaptic Depression
  - Stimulation Induced Modulation of Pathways

**PROBLEMS: Indiscriminate Activation**
- Stimulation indiscriminately affects all tissue around the electrode (size: 1.27mm diameter with four 1.5mm contacts)
- Crude method without feedback

**IMPROVEMENTS:**
Targeted Activation to specific location down to sub mm scale
- Obtain feedback information – such as neurotransmitter levels
Current Techniques for Electrochemical Monitoring of Neurotransmitters with Carbon Fiber Electrodes


**HOW: Cyclic Voltammetry (CV)**
Carbon fiber micro-electrodes (10um dia.)
Best detection is 500nM with temporal resolution of tens of milliseconds
Most neurotransmitters are electrochemically active (i.e. dopamine & glutamate)

**IMPROVEMENTS: Requirements for Electrodes**
1. Ultrahigh sensitivity: ~ 1 nM
2. Fast speed: ~ 10 ms resolution
3. Good for long-term implantation
Vertical Aligned CNF Array: A Novel Electrical Neural Interface

Three-dimensional neural network

Micro-electrode Array (MEA)

~10 micron

Nanoelectrode Array (NEA)

500 nm

2 μm
Goal: To Develop an Integrated Multiplex Chip as an Implantable Device for DBS and Electrochemical Recording

Possible Applications
- Parkinson’s Disease
- Epilepsy
- Other Neurological Disorders

Stimulating Electrode: uncoated CNFs with large surface area

Recording Electrode: embedded in SiO$_2$ with ultrahigh sensitivity
Polypyrrole Coated Vertically Aligned CNF Array for Neurostimulation

Polypyrrole coating applied to increase the capacitance and decrease the impedance

As-grown CNF Array

Polypyrrole Coated CNF Array

High Capacitance ($C_0 = \Delta i/2v$)
Noble metal $\sim 20 \mu F/cm^2$
As-grown CNF array: $0.4 \mu F/cm^2$
Ppy-coated CNF array: 40 to 100 $\mu F/cm^2$

Low Impedance
At 1 kHz, the impedance is negligible compared to the solution resistance

Biocompatibility of Polypyrrole Coated Vertically Aligned CNF Array

PC12 Cell on Polypyrrole Coated CNFs

- Brush-like polypyrrole coated CNFs make intimate physical contact with PC12 cells
- PC12 cells observed to spread and differentiate on CNF array

- Polypyrrole coated CNFs support cell growth and proliferation

Stimulation of Rat Hippocampal Slice by Polypyrrole Coated Vertically Aligned CNF Array

**Experiment:** Measure voltage for a given stimulation current

Stimulation by:
- W wire
- Pt Microelectrode
- CNFs
- PPy coated CNFs

1) Only PPy coated CNFs were able to stimulate tissue under 1 mA stimulation current.
2) Only PPy coated CNFs did not induce the electrolysis of water (less than 1 mA and 1V)

[Graph showing voltage response vs. stimulation current]

Mayo Clinic’s Sterilizable WINCS Unit

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

Examples: Acetone in diabetes patients NO in asthma patients

• In these cases, simple chemical sensors with pattern recognition can be valuable.
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. Example: SWCNTs have a surface area $\sim 1600 \text{ m}^2/\text{gm}$ which translates to the size of a football field for only 4 gm.

- Large surface area $\rightarrow$ large adsorption rates for gases and vapors $\rightarrow$ changes some measurable properties of the nanomaterial $\rightarrow$ basis for sensing
  - Dielectric
  - Capacitance
  - Conductance
  - Deflection of a cantilever

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

SWCNT Sensor Testing

- Test condition:
  Flow rate: 400 ml/min
  Temperature: 23 °C
  Purge gas: N₂ & Carrier gas: Air

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

Preliminary tests show a sensitivity of 10 ppm for acetone. Further studies are needed for interfering chemicals and pattern recognition.

Detection limit for NO₂ is 4 ppb.
Nanosensing Approach: Selectivity

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

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
Retinal Cell Transplantation

- 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”).

Courtesy: David Loftus
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:
The Obvious Strategy: Natural Substrates for Retinal Transplantation
  - Anterior Lens Capsule (*basal lamina*)
  - Descemet’s Membrane (posterior cornea)

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.

**Solution:**

**Carbon Nanotube Bucky Paper**

*A meshwork of carbon nanotubes formed into a paper-like structure*
RPE cells grown on Carbon Nanotube Bucky Paper

As-prepared bucky paper

SEM Image after growth of RPE results

Light micrograph/histological staining of RPE grown on bucky paper

- Confluent monolayer, with uniform orientation of cells
- 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
- Artificial Blood Vessels
- Tissue Engineering
- Hemostatic Bucky Paper / Wound Healing
- Long Duration Space Flight – How to deliver medical therapy?
  - Acute injury
    - Hemostatic Bucky 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

Implantable Physiological Sensors
- Remote sensing
- Early medical intervention
- Novel medical countermeasures
  - Cardiovascular physiology
• Nanotechnology is an enabling technology that will impact almost all economic sectors: one of the most important and with great potential is the health/medical sector.
  - Nanomaterials for drug delivery
  - Early warning sensors
  - Implantable devices
  - Artificial parts with improved characteristics
• Carbon nanotubes and nanofibers show promise for use in sensor development, electrodes and other biomedical applications.