Integrated Low-cost, High-sensitivity Biosensors for Water Quality Monitoring

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Mini-colloquium Organized by Region 9 (Latin America) EDS/IEEE chapters (13 March 2012) – Playa del Carmen, Mexico

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Environment - Water

- **Most abundant molecule on earth**
- **Needed in every aspect of life**
  - Excellent polar solvent
  - Allows ions to move freely
  - Needed for every metabolic activity
  - Earliest life-forms evolved in water
- **70% of body weight**
  - 15% water loss can kill you!

http://en.wikipedia.org/wiki/Water
Use of Biosensors

- Biological sensors help identify pathogen
- Uniquely and rapidly identifying pathogens help prevent disease outbreaks
  - Pathogen detection requires laboratories and expensive equipment
  - Samples need to be brought from the environment to the laboratory, usually located far away
  - It takes a long time for the pathogen to be uniquely identified
  - Rapid treatment and containment of the pathogen may not be possible
- Goal: to develop affordable, highly sensitive and readily available biosensors based on mainstream technology
  - ADIAFOOD system – real time PCR technology - rapid detection by specifically identifying the DNA sequence of pathogens in a series of sequential steps
  - Enrichment: 8-18hrs
  - DNA Extraction: <30min
  - Amp./detection: 2hrs
Some Basics in Biosensors – Look at DNA
Pathogen Detection Method

- Specific detection of constituent molecules
- Detection by means of DNA structure
  - Very specific; DNA databases – pathogens
  - 1953, 1962 (Nobel)

DNA Molecule: Two Views

- Average helical twist of 35.6°; ~10.1 BPs/turn
Device to Detect or Store Charge and its Evolution
Simple Capacitors

Capacitance

- Amount of charge that can be stored for a given voltage difference (energy)

\[ Q = CV \]

- Depends on metal area and insulator

\[ C = \frac{\varepsilon_o \varepsilon_r A}{d} \]

- Larger areas = higher capacitance
- Thinner insulator = higher capacitance

1745 Ewald Georg von Kleist
Peter van Musschenbroek
Michael Faraday, 1800’s
C $\rightarrow$ S, Electrolyte, Biocapacitor
Conversion of Bio-Capacitor to a More Useful Device
Biological Transistor - BioFET

- **Need measure** $\Delta_{\text{semiconductor charge}}$
  - Add 2 terminals at surface: S & D
  - Semiconductor charge determines conductance of channel
  - For a fixed V, I depends on charge $\Rightarrow$ indirect dependence on DNA density

- **Charge-based detection**
  - Detect charge increase as DNA hybridization takes place
  - FET devices
    - Used as charge-sensing devices
    - High sensitivity
    - Integration biosensor + CMOS
    - Cheap electronic microarrays
    - Portability
  - Use a MOSFET, with G replaced by an electrolyte + reference electrode
  - Called a Biological FET or BioFET
Biological FET - BioFET

- Electrode-electrolyte-insulator-semiconductor-electrode system
- DNA probes fixed to insulator
- Hybridization of targets causes change in underlying silicon
- Major question: "How much does BioFET current change on hybridization?"

Uses mainstream CMOS technology
- Affordable
- Direct electrical conversion
- Integrated - signal proc. & telemetry circuits
- No fluorescent labeling
- No expensive μarray readers

Heat in vacuum at 150 °C, then treat with glycidoxypropyltrimethoxy silane (GPTMS) vapor at 85 °C
Currents & Model – pH ISFET

- Charge-sheet model - BioFET current - Diffusion + Drift
- Response of BioFET changes with pH value - Insulator surface charging

![Diagram of BioFET model]

- **IDS (mA)**
- **V_DS (V)**
- **V_ref**

- **pH7**
- **pH6**
- **pH5**

- $N_{SS} = -6.45 \times 10^{11} \text{ cm}^{-2}$
- $d_{ox} = 15.5 \text{ nm}$
- $\Phi_{ls} = -0.78 \text{ V (AgCl)}$

Model Calibration - BioFET

Comparison with published experimental results

- Good correlation between immobilization and hybridization shifts in threshold voltage
- Shows validity of the 1-D model


Properties of Bio-Sensors – Signal Characteristics
Electrolyte Nonlinearity

- **Screening charge**
  - Prevents charging the channel
  - Lowers sensitivity
  - Depends on electrolyte concentration

DNA Density, Length

- **DNA density**
  - Probe density ↑ - more sensitivity
  - Disadvantage - hybridize slower

- **DNA length**
  - Longer DNA → more charge → higher sensitivity
  - Disadvantage → DNA tail charges are too far → not sensed

Operating Point

- **Reference electrode bias**
  - Gain (transconductance) limited by mobility degradation
  - Field-dependence of mobility

- **Drain bias**
  - Saturation - best sensitivity to DNA charges
  - Facilitates use of BioFET as an amplifier
Properties of Bio-Sensors – Noise Characteristics
Relevant Noise Models

- Mobility Fluctuation Theory ($\Delta \mu$)
- Number Fluctuation Theory ($\Delta n$)
- Correlated ($\Delta \mu - \Delta n$) Fluctuation
BiOFET with High-K Gate Material

- Using CVD, HfO_2 and Hf Silicate films were deposited on custom chips.
- BioFETs with HfO_2 and Hf Silicate gate insulators have been fabricated.

\[ C = \frac{\varepsilon_0 \varepsilon_r A}{d} \]

\[ Q = CV \]
Different dielectric constants

- Higher $K$ $\implies$ higher sensitivity
- Trap density increases with higher $K$ dielectrics
- Maximum SNR value decreases

<table>
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<tr>
<th>Insulator</th>
<th>$\varepsilon_r$</th>
<th>$N_t \times 10^{17}$ cm$^{-3}$ eV$^{-1}$</th>
<th>$\lambda$ (nm)</th>
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<td>Ta$_2$O$_5$</td>
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<td>610</td>
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Converting from Biotransistors to Biosensor System
BioFET Microarray Chip

14 × 7
50 × 50 μm
PMOS

7 × 7
50 × 50 μm
PMOS

7 × 7
50 × 1 × 21 μm
PMOS

7 × 7
50 × 50 μm
PMOS

7 × 7
50 × 50 μm
NMOS
Fabricated Biochip Prototype

- BioFET Arrays (5x5)
- Test MOSFETs
- Test OpAmps
- BioFET OpAmps
- Push-Pull Compensation Network
- Differential Pair
- Level Shifter
- VDD
- VSS
- In
- Out
- 13 March 2012

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Microfluidic Channels

- Post-processed chip in solution
- Hybridization tests

- Voltages constant - monitoring BioFET $I_{DS}$
- Electrolyte voltage fixed using Ag/AgCl reference electrode
- Mounting of capillary tubes, microfluidic channels & reference electrodes on array
Gen 2b chips consist of 7x7 FET arrays.
Gen 3 chips have two 7x7 arrays where each element is a pair of FETs for differential measurements
Also on-chip CMOS circuitry for **signal amplification/ sequencing**, and heating/temperature sensing
Post-processed Gen3 Chip
Detection of oligo hybridization on BioFET array

- All transistors show increase in threshold voltage shift upon hybridization - probe oligos for C. Jejuni
Ongoing Research
Nanowire Fabrication

- Optical microscope and SEM images of Si-NW BioFET
- The device has a gold-coated SiO₂ gate dielectric and an integrated Ag/AgCl reference electrode
- The width and length of Si-nanowire is ~50 nm and 5 µm, respectively
Ag/AgCl Electrode Formation

- Formation of the Ag/AgCl reference electrode: Electrochemical method
  - 0.1 M KCl with applying a constant voltage of 1V
  - The current decreases and then saturates
- Buffer solution: 0.1 x PBS (phosphate buffer solution, pH 7.2, Aldrich)
- Electrical Characterization: semiconductor parameter analyzer (K4200, Keithley)
Si-NW BioFETs were immersed in PBS buffer solution (pH 7.4, Aldrich)
Characteristic curves were measured by Keithley 4200 semiconductor analyzer system at room temperature
**pH Sensing Result**

- **pH Response**

![Graph showing pH response](image)

- The sensitivity: 40 mV/pH at $I_D=1$ nA

- During the 3 cycles of pH changes, the device shows distinguishable state under each pH conditions. (maximum $\sigma = 0.013$ V)
Application – Environment/Health

Portable Pathogen Detection

BioFET Sensor System

Detection of Pathogens in fluids

Rapid and accurate detection of oligonucleotides

Screening of patients and institutions

Drinking water

Waste water

Filtration and Concentration

Cell processing

DNA extraction and amplification

Microfluidic channel

Control, signal conditioning and processing electronics

Wireless transceiver

Control lines

Substrate (Si)

BioFET

Flow control system

Real world sample

DNA extraction and amplification

Microfluidic channel

Control, signal conditioning and processing electronics

Wireless transceiver

Control lines

Substrate (Si)
Acknowledgements

Many other collaborators