Biochip and Microarrays for Rapid Assessment of New Chemicals

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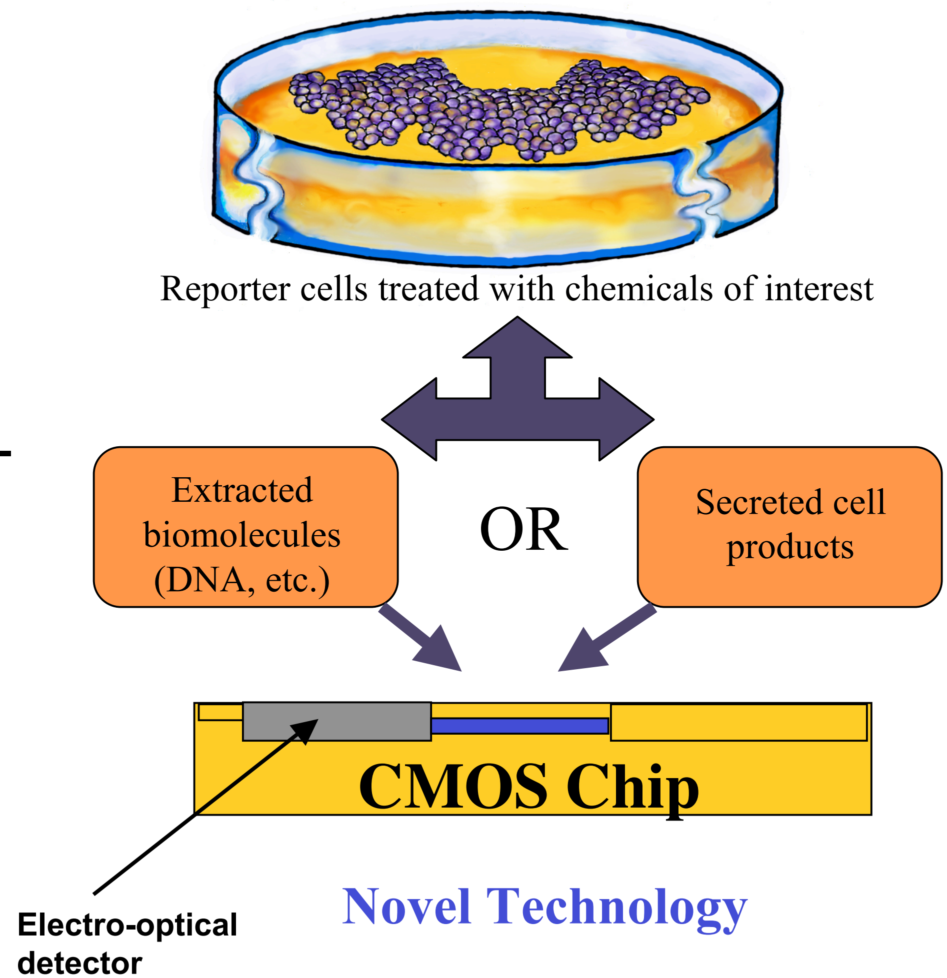
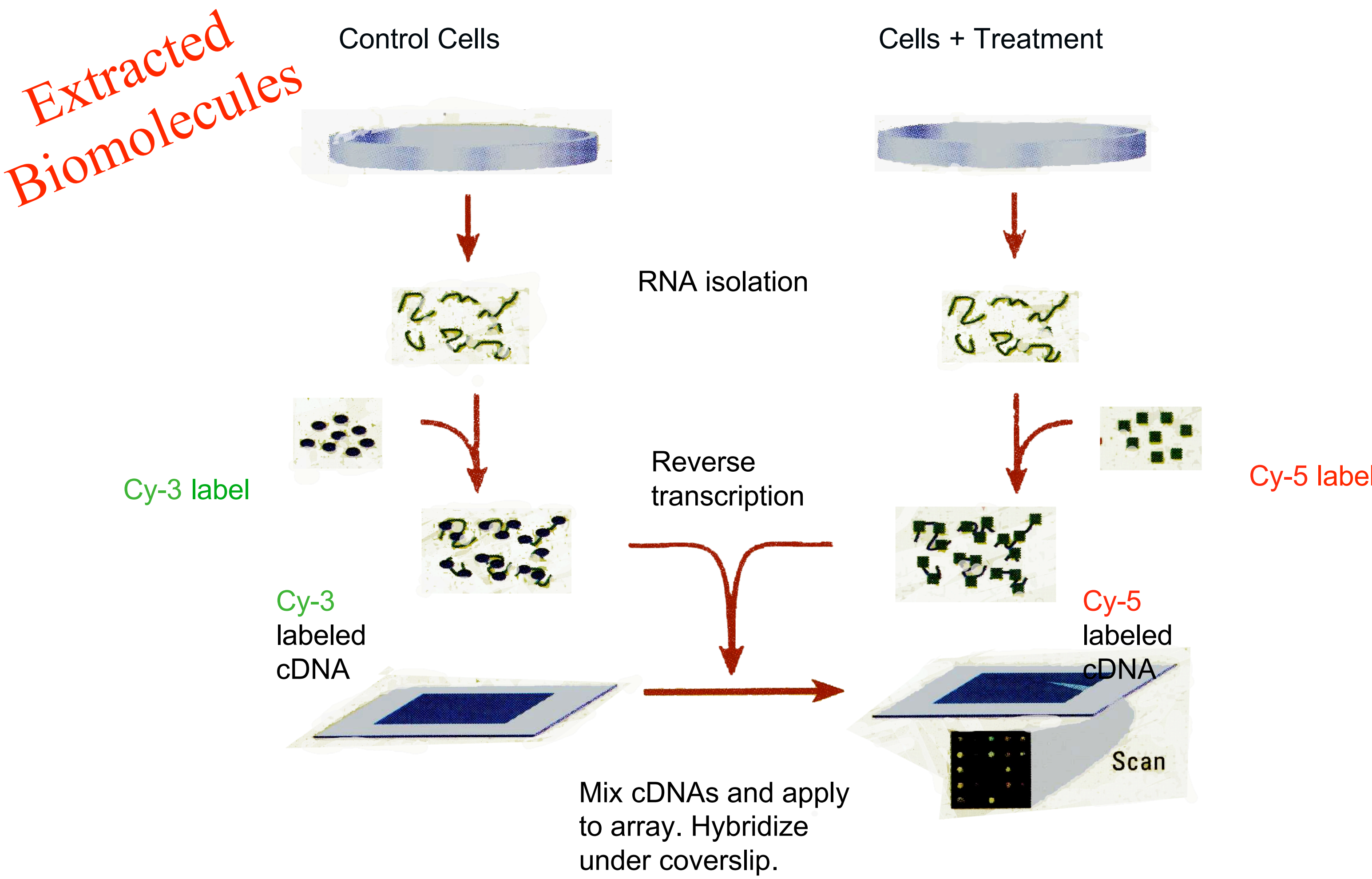
Project Objectives and Impact

- **Rapid assessment of chemicals and process chemistries**
- **Important for both chemical suppliers (starting materials) and equipment suppliers/end users (for process-generated by-products, interactions of multiple chemicals, proprietary chemistries in R/D stage, etc.)**
- **A first step towards an on-line ESH monitor.**



Introduction: Microarray Measurement



Spots with more Cy3 are genes down-regulated by treatment
Spots with more Cy5 are genes up-regulated by treatment
Mixed spots are genes unaffected by treatment

Introduction: Power of the Approach

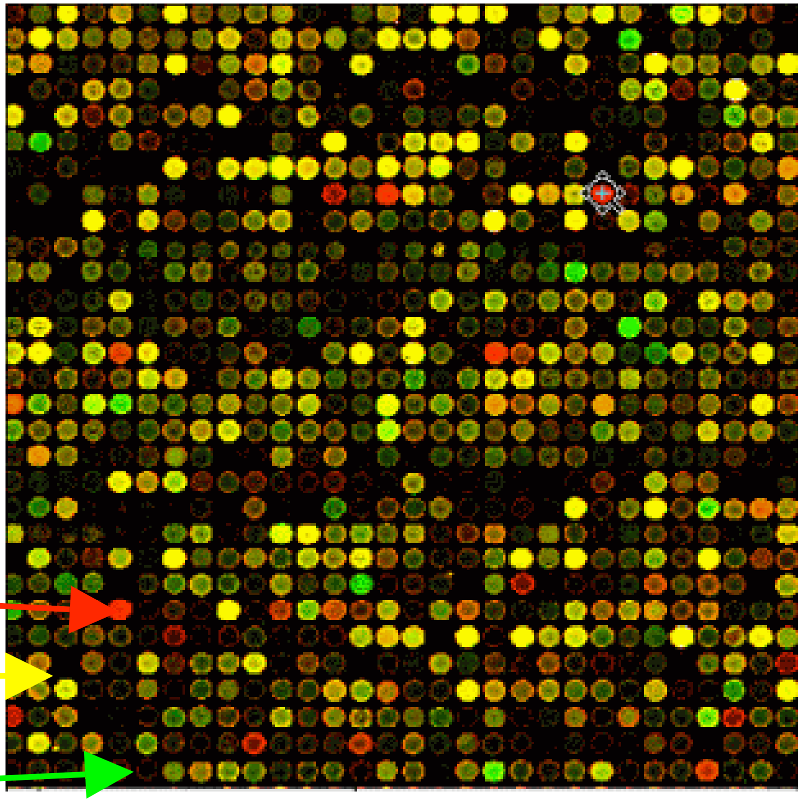
Extracted Biomolecules

Obtain information about differential gene expression across diverse set of arrayed molecules in a single experiment

Red = more cy5 than cy3

Yellow = "equal" cy5 and cy3

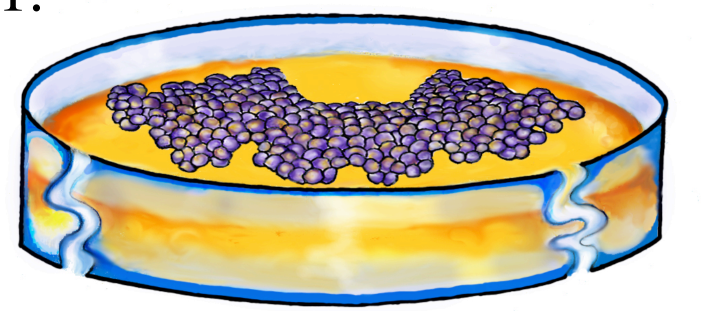
Green = more cy3 than cy5



Secreted Cell Products

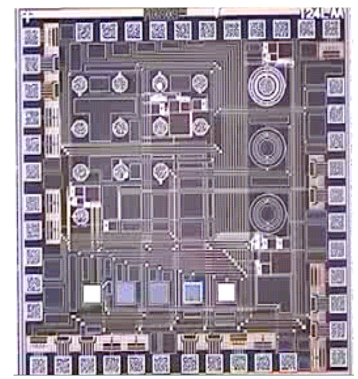
Toxicity Testing Using Alkaline Phosphatase Reporter

1.



Cells are engineered to secrete the enzyme alkaline phosphatase in response to toxic insult

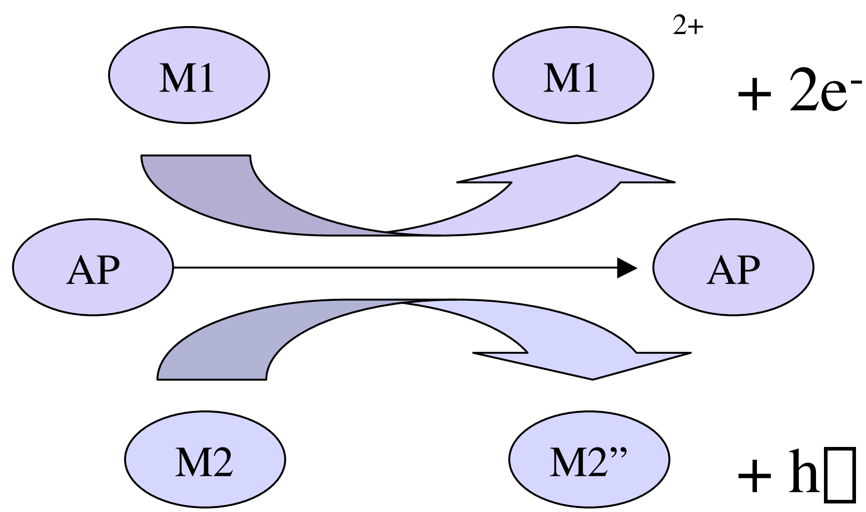
2.



Cells are arrayed onto biochip electrodes, which double as photodetectors

3.

Biochip is exposed to test chemical of interest in a matrix with two indicator chemicals. Alkaline phosphatase (AP) converts one chemical into an electron donor (measured electrochemically) and the other into a fluorophore (measured photometrically).

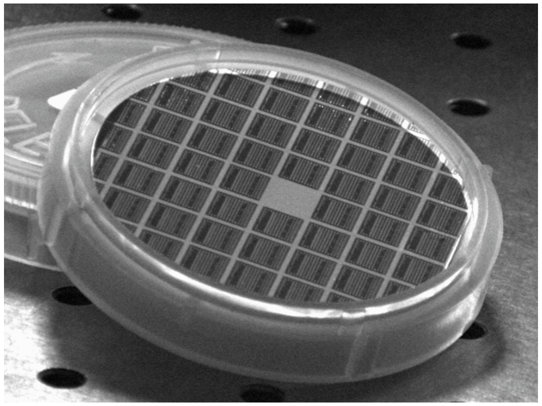


NSF/SRC Engineering Research Center for Environmentally Benign Semiconductor Manufacturing

Introduction: CMOS Substrates

Why CMOS ?

- Complementary Metal Oxide Semiconductor (CMOS)
- Replace "dumb" glass substrate with "smart" substrate capable of self-interrogation
- Introduce electronic control to printing, hybridization, and detection
- Couple advances in microelectronics to advances in microarrays

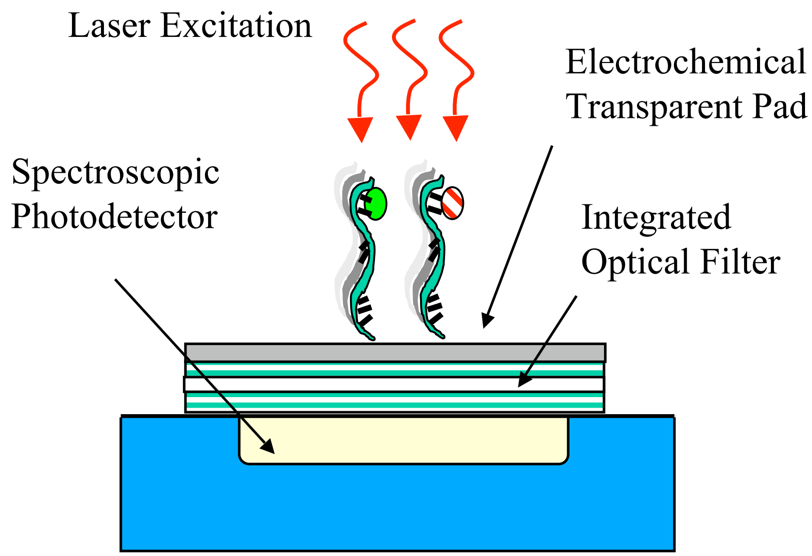


Why Miniaturize ?

1. Reduced Cost
2. Reduced Cost
3. Reduced Cost
4. Increased Reliability
5. Increased Functionality
6. Reduced Size

MultiSensor Fusion

A Single Hybridization Site



CMOS BioChip

- Electric field directed binding
- Hybridization site monitored with capacitance
- Electrochemical analysis at each pad
- On chip photodetectors

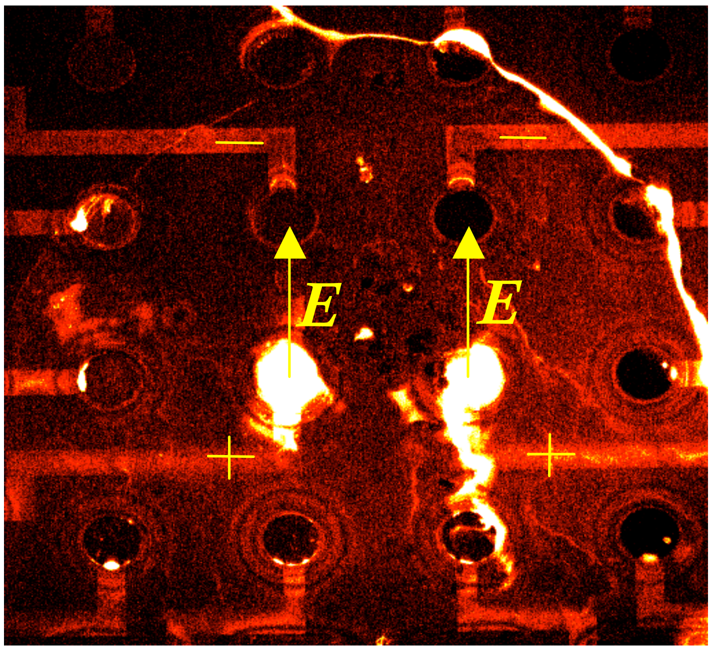
- Data transfer from chip in digital form for bioinformatics

Indium Tin Oxide (ITO)
(Transparent and Conductive)

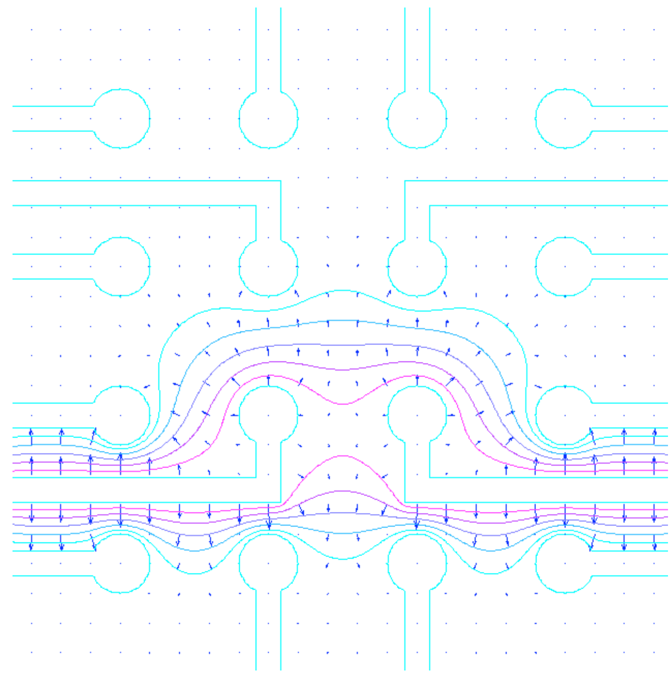
- Oxygen flow rate between 0 - 20 sccm
  - Best results around 20 sccm
- Deposition rate 28.6-33.3 Å / min
- Higher resistance values
  - Between 184 - 2×10^7 □
- Vacuum anneal temperature 225^{o} C for 2 hr

Introduction: E-Field Directed DNA

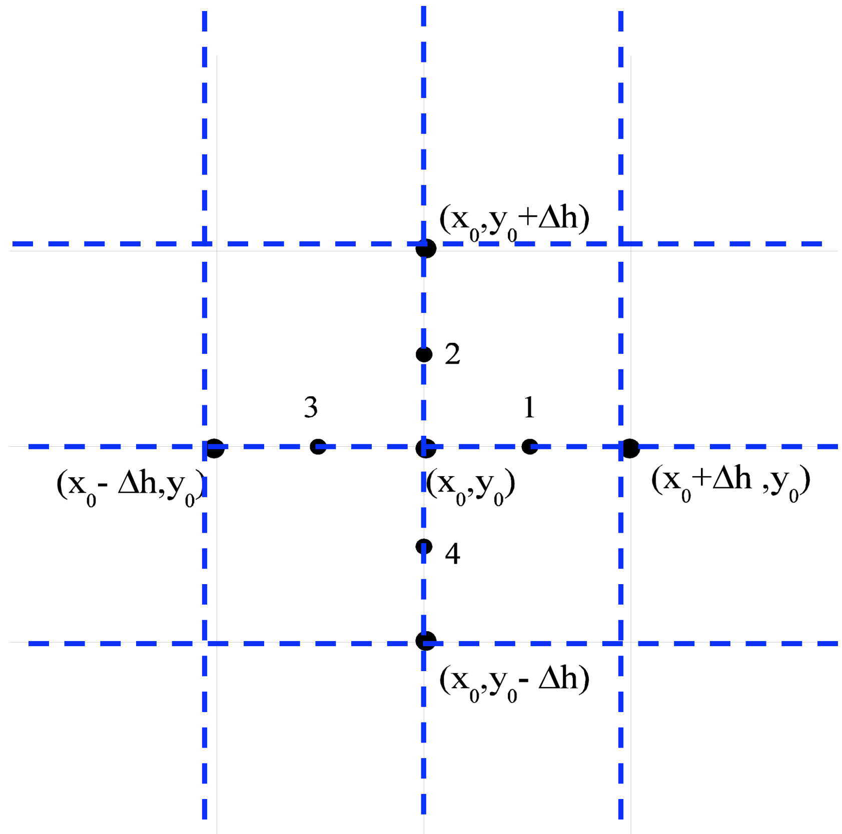
Confocal Image
of bound DNA



Simulated E-field



Grid for Finite Difference Method



$$V(x_0,y_0) = \{V(x_0+\Delta h, y_0) + V(x_0, y_0+\Delta h) + V(x_0-\Delta h ,y_0) + V(x_0, y_0-\Delta h) \} / 4$$

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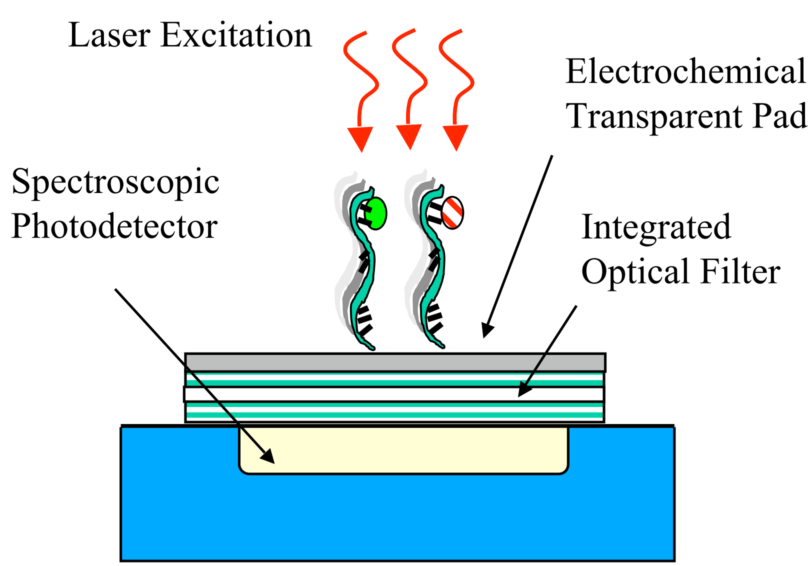

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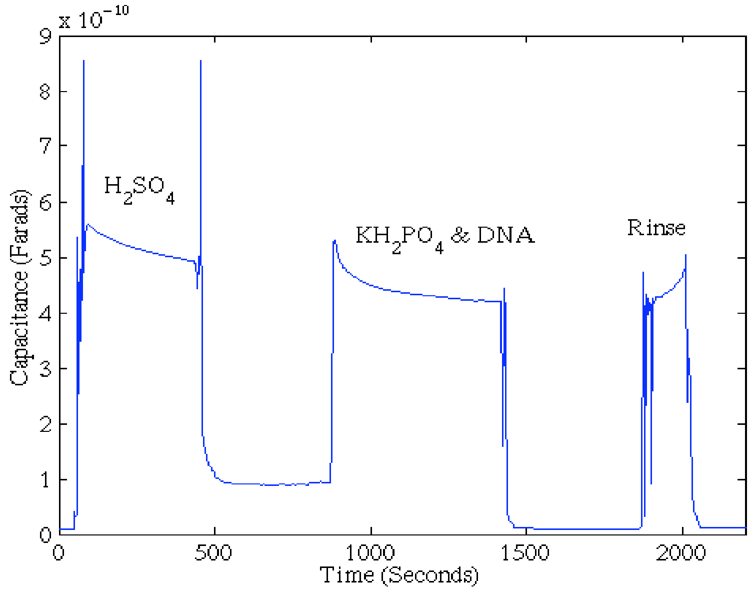
Hybridization Site Preparation

Capacitance Measurements

- Measured capacitance is used to monitor oxide formation and surface conditions at hybridization site.
- Capacitance measurements have been used to determine surface coverage of single stranded DNA to levels of (1-10) x 10^{12} molecules/cm^2
  A. Steel, et. al. Anal. Chem. 1998 p.4670
- Human chronic gonadotropin hormone have detection limits of 15 x 10^{-15} M
  C. Berggren, and G. Johansson, Anal. Chem. 1997 p. 3651



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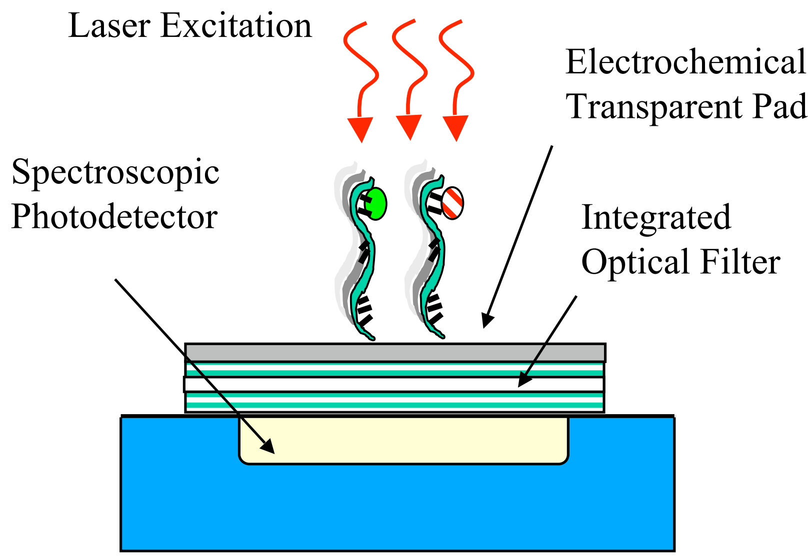

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Diffusion

- **1-D Finite Difference Equation:**

$$C(x_0, t + \Delta t) = C(x_0, t) + \frac{D \Delta t}{\Delta h2}(C(x_0 + \Delta h, t) - 2C(x_0, t) + C(x_0 - \Delta h, t))$$

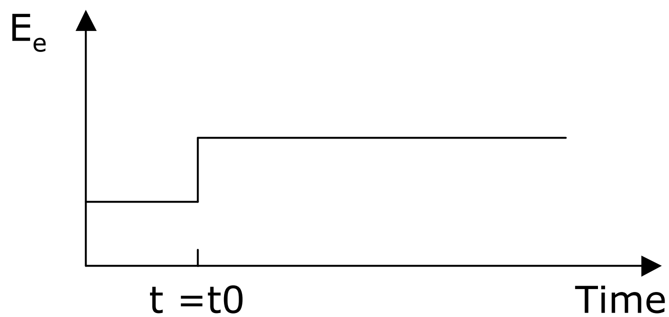
- **1-D Actual Value Equation:**

$$C(x_0, t) = C_{initial}\left(1 - erfc\left(\frac{x_0}{2\sqrt{Dt}}\right)\right)$$

Potential at the electrode

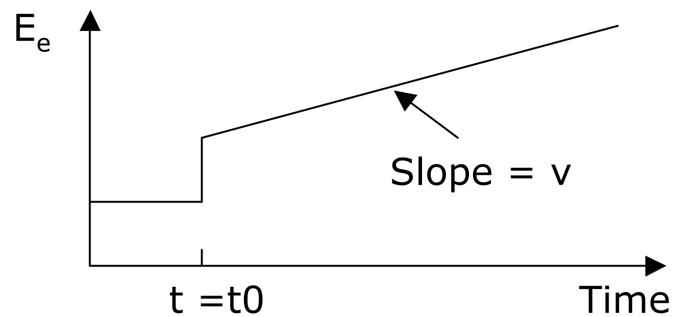
Potential Step

$$E_e = E_0 + \frac{RT}{nF}\ln\frac{C_A(x,y,t)}{C_B(x,y,t)}$$

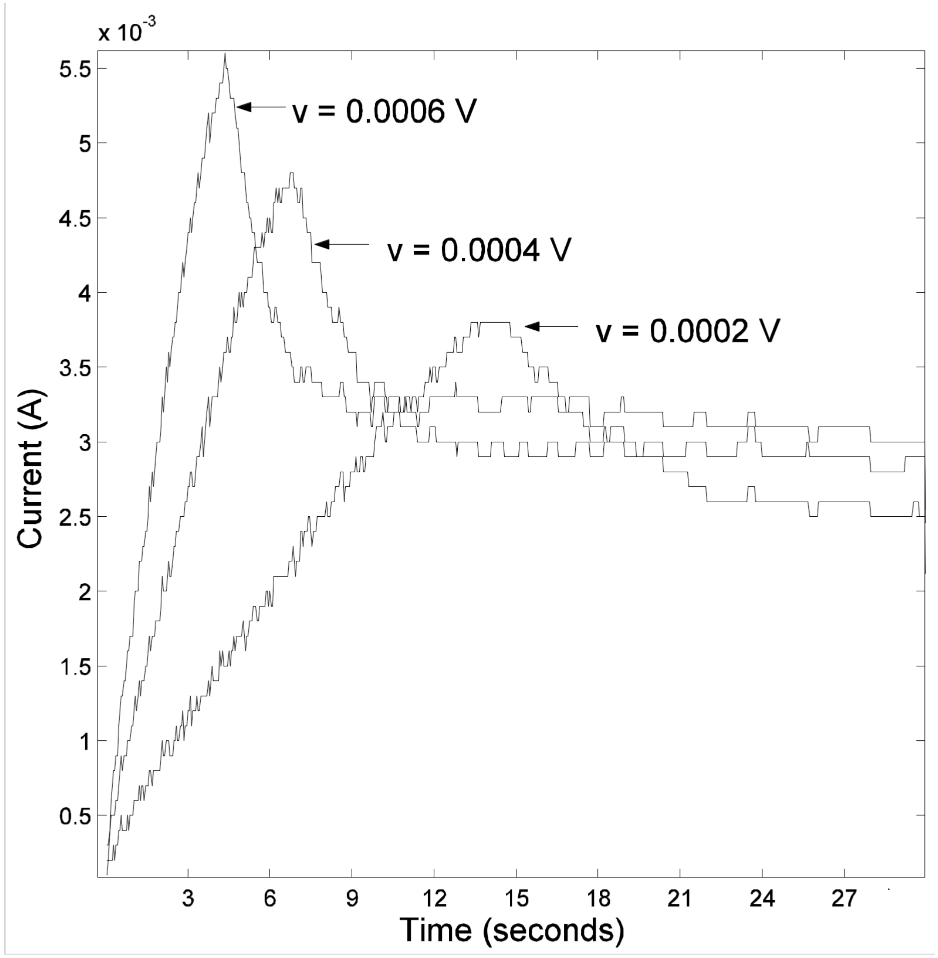


Potential Sweep

$$E_e = E_0 + \frac{RT}{nF}\ln\frac{C_A(x,y,t)}{C_B(x,y,t)} + vt$$



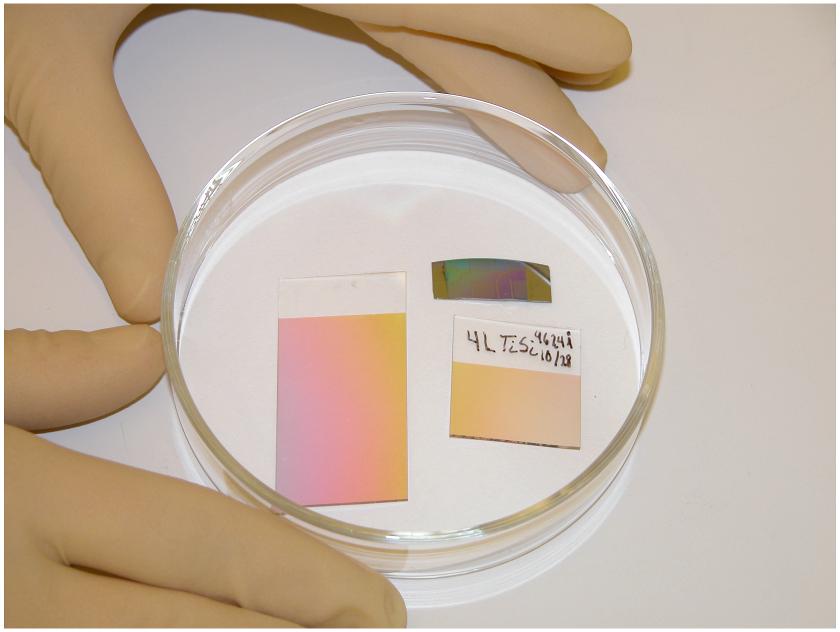
Cyclic Voltammetry Currents



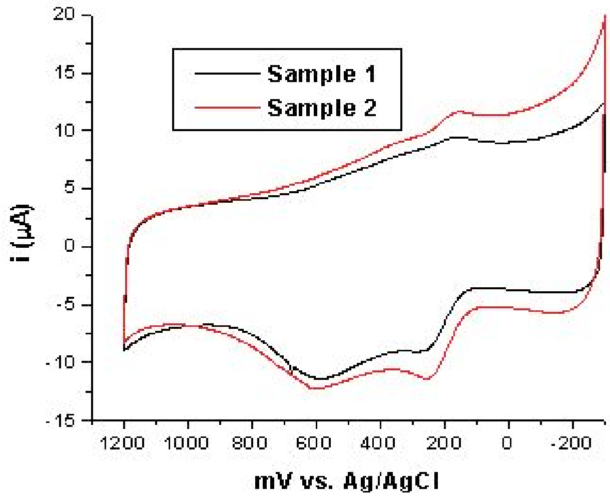
Current Plots for different sweep rates for t = 30 sec

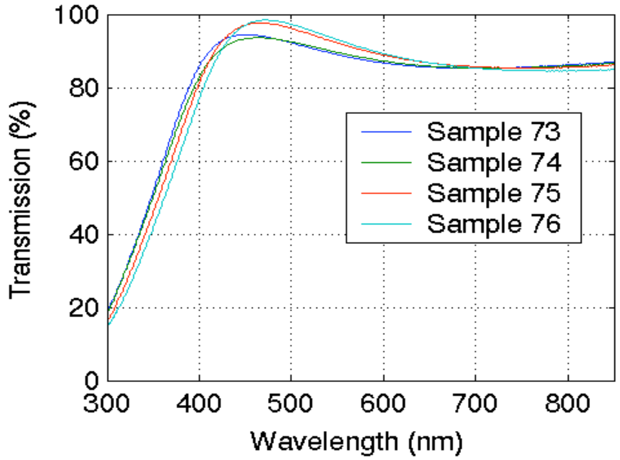
Indium Tin Oxide (ITO)

Fabrication



Characterization





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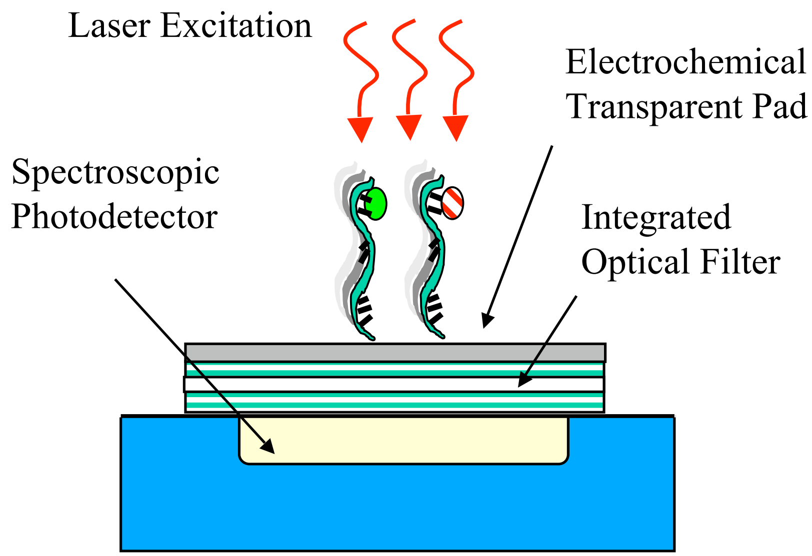

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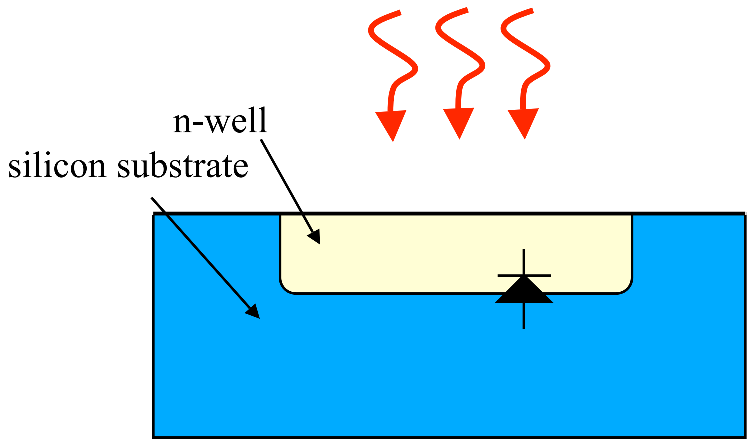
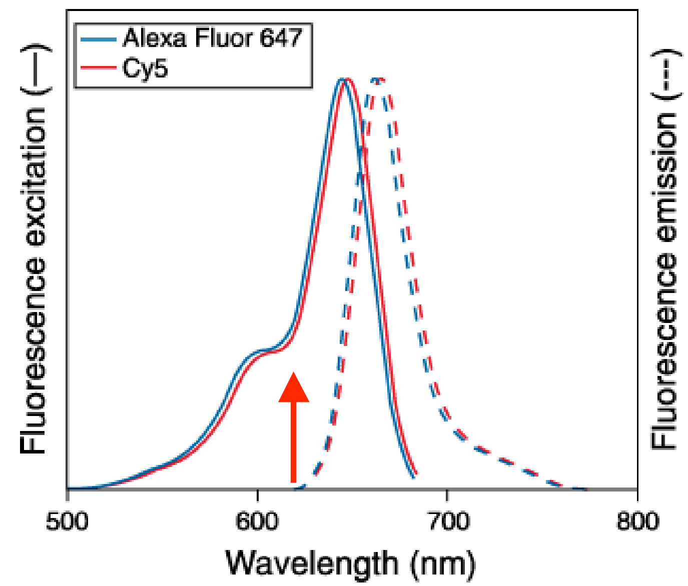
CMOS Photodetector

Lambert's Law

$$I = I_o e^{-\alpha(\lambda)\, x}$$

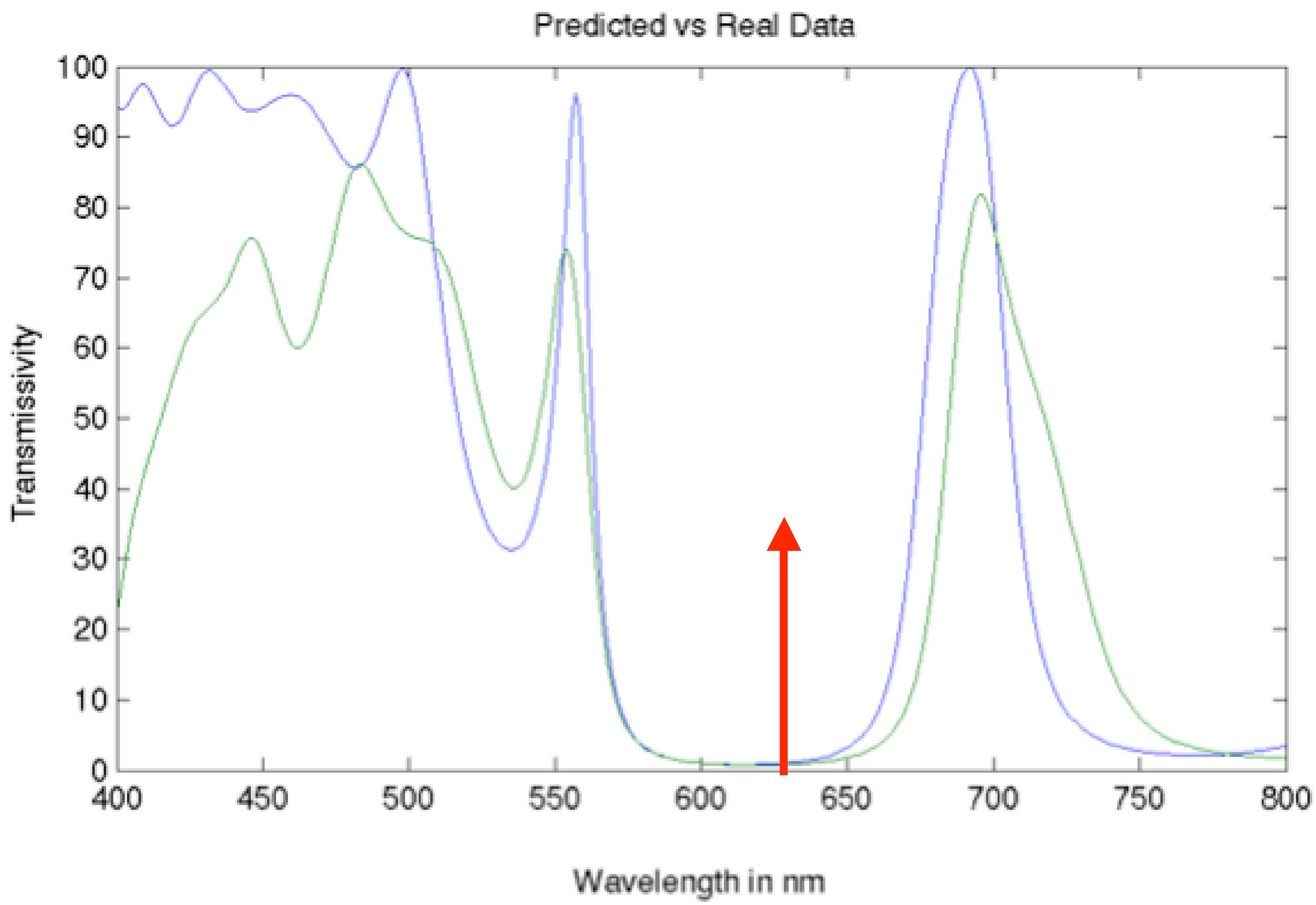


Dye #1
Alexis Flour 647



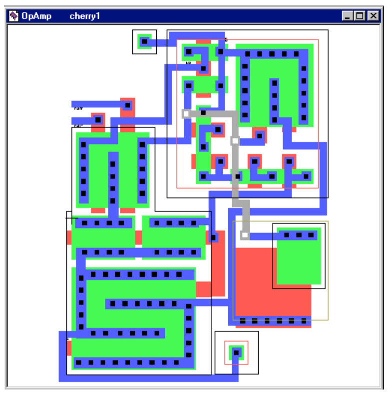
See Class Notes
OPTI 580 Microphotonics
Instructor: Prof. D. L. Mathine

Double Fabry-Perot Cavity Filter

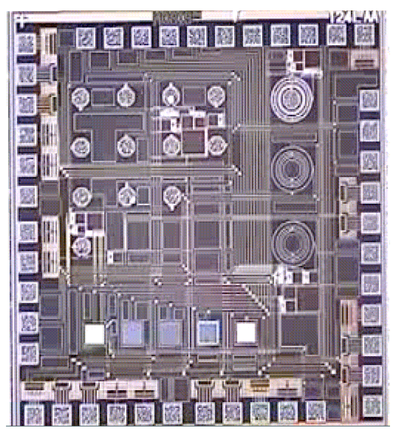


Characterization of CMOS chip for Chemical Analysis

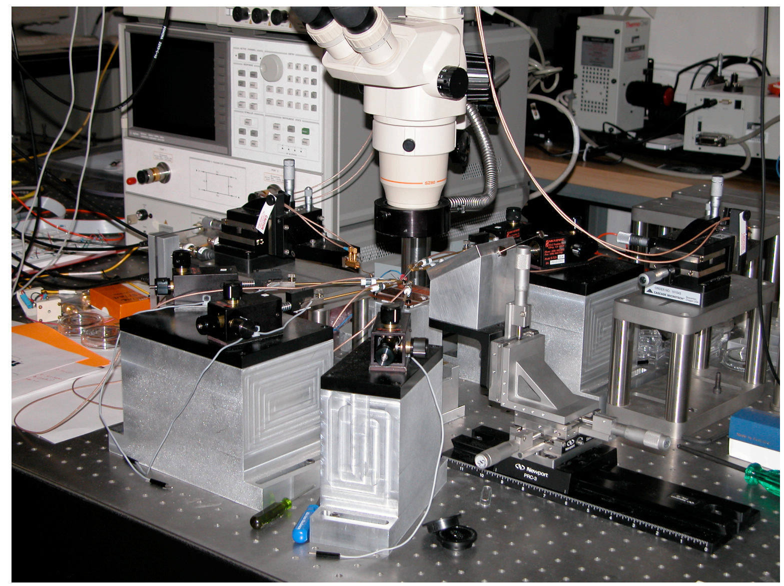
Design



Prototype Custom CMOS Chip



Experimental Test Bed



Future Plans

Next year plan:

•Engineer alkaline-phosphatase toxicity reporting cells
•Design next generation of CMOS biochip for biologically based electro-optical assays
•Assess electrochemical and photometric detection limits of system
•Optimize biochip surface chemistry

Long-Term Plans:

•Low-cost sensors for use by chemical suppliers (responsible for starting feed materials) and process engineers and ESH professionals (responsible for evaluation of new chemistries during and after the processing cycle)

•New generation of highly selective and inexpensive sensors for real-time and online monitoring in the manufacturing site.