Biochips and Micro-Arrays for Rapid Assessment of Chemical Toxicity

Task 425.012

by

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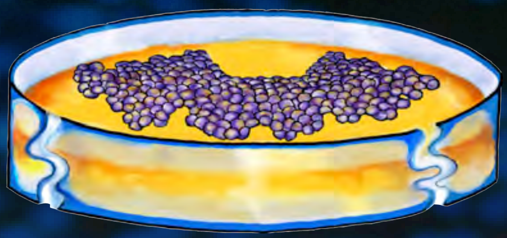
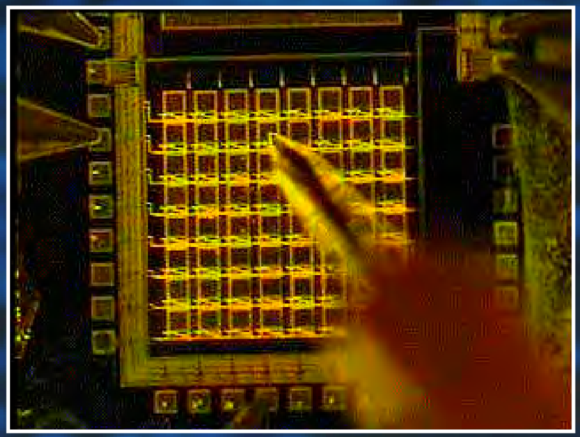
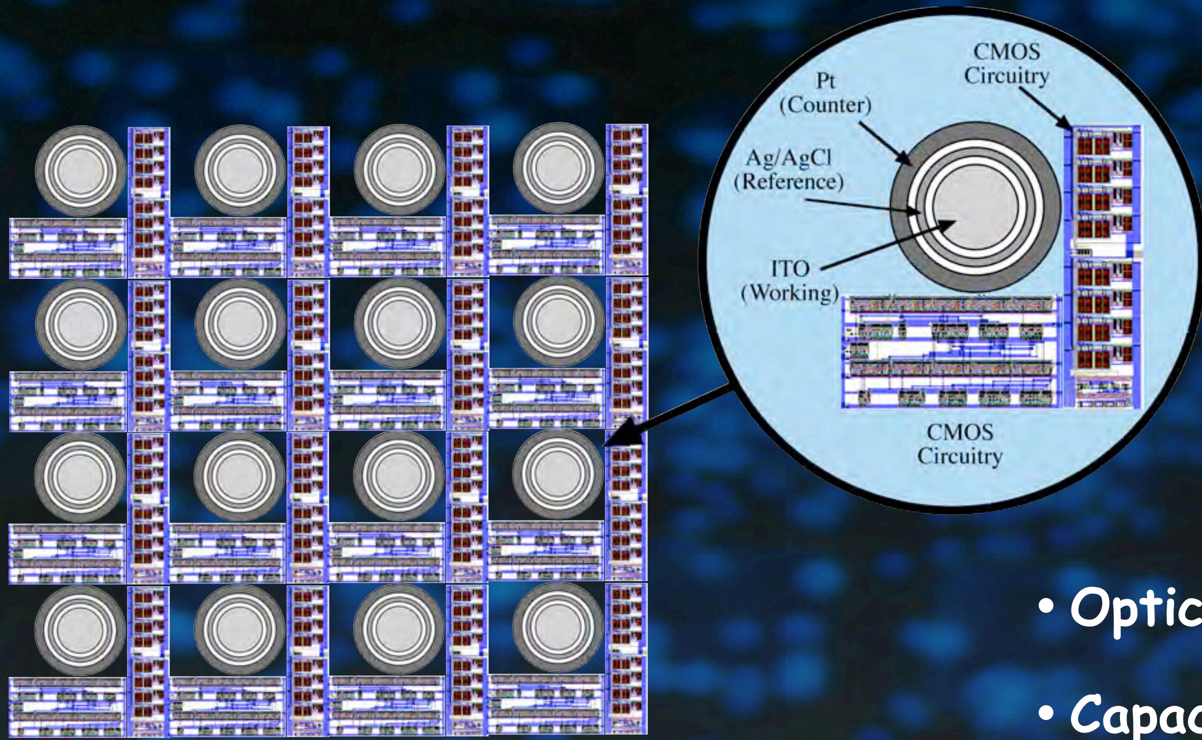
Rapid Assessment of Chemicals and Process Chemistries



- **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.**



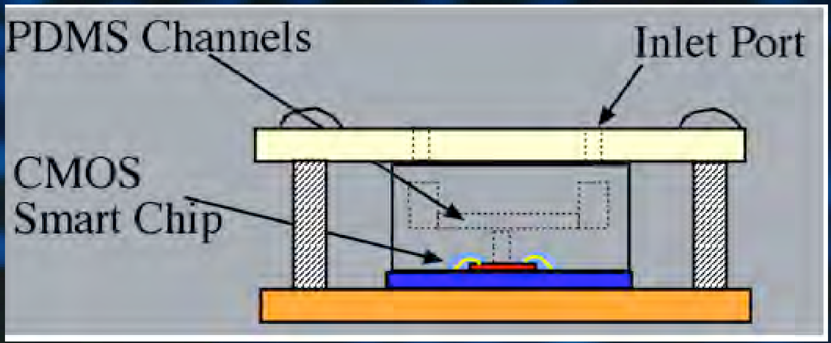
Biosensor Fusion



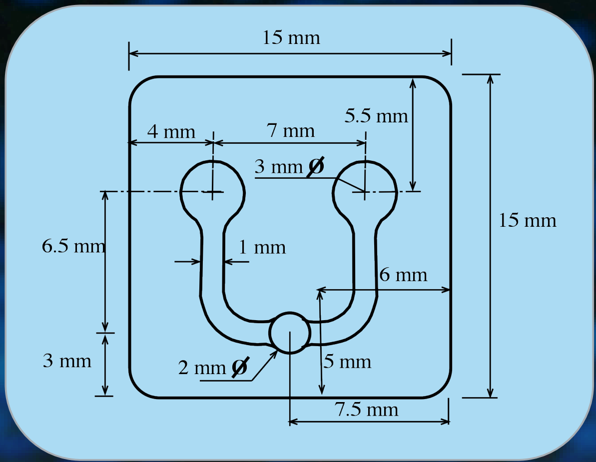
- Optical Sensors
- Capacitance Sensors
- Electrochemical Sensors
- Electrical Sensors

Biochamber Design

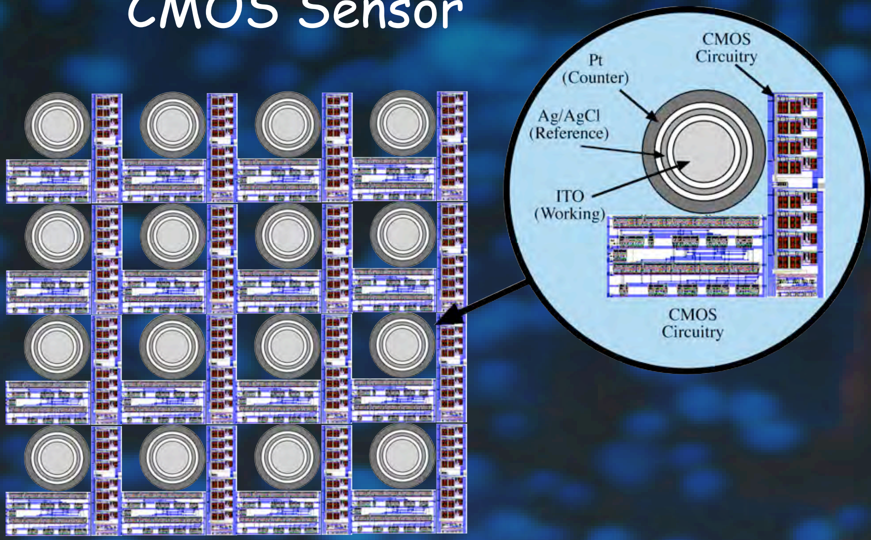
Environmental Chamber



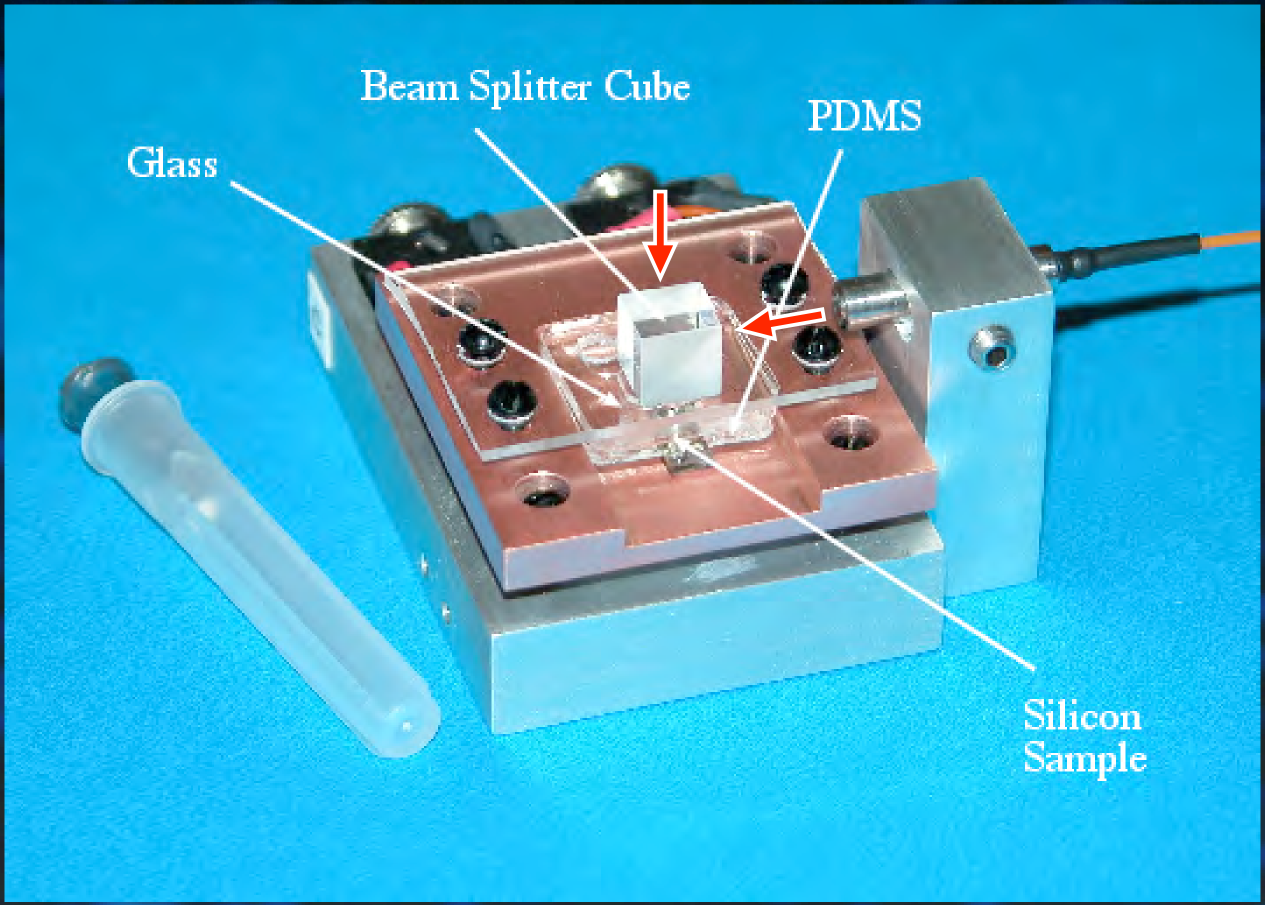
Biofluidics



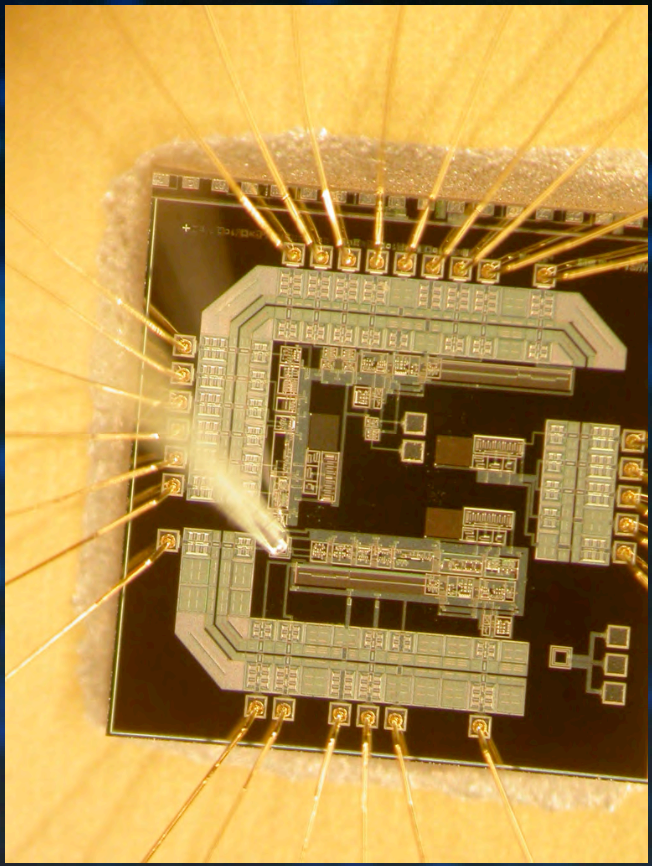
CMOS Sensor



Biochamber Design



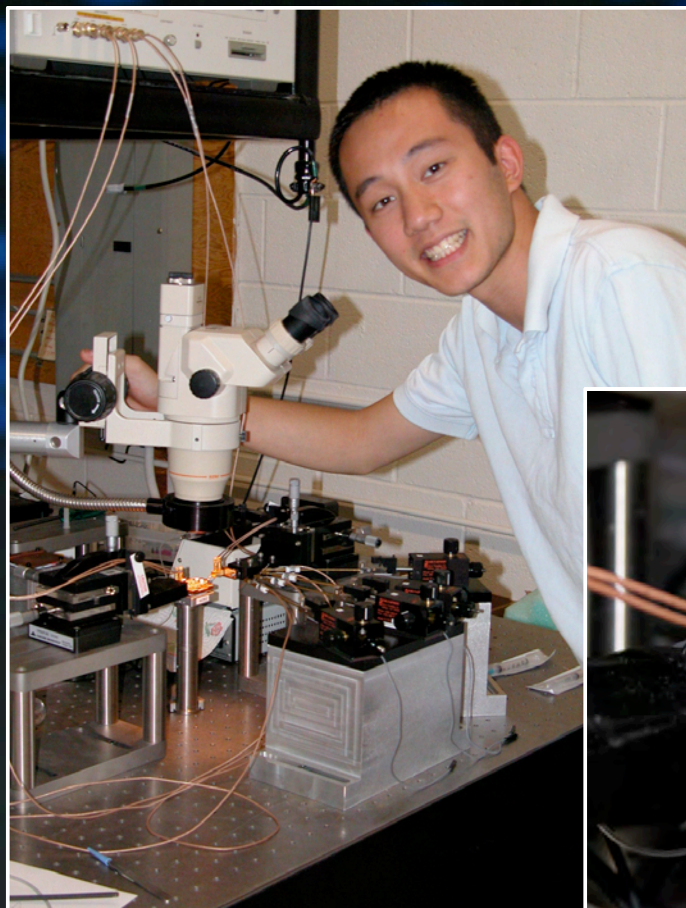
CMOS Prototyping

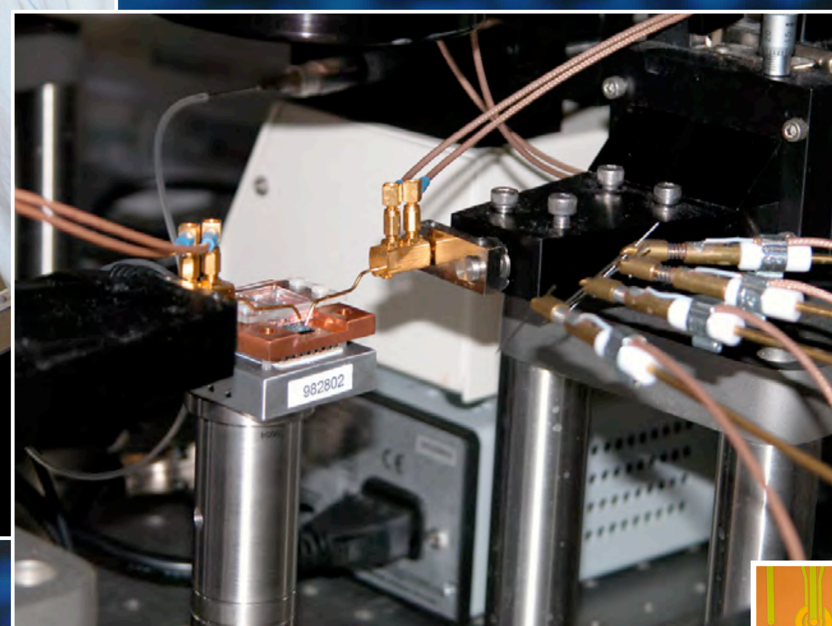


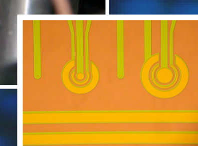
- Optical Sensors
- Capacitance Sensors
- Electrochemical Sensors
- Electrical Sensors

Cell Preparation

Electrical Measurements



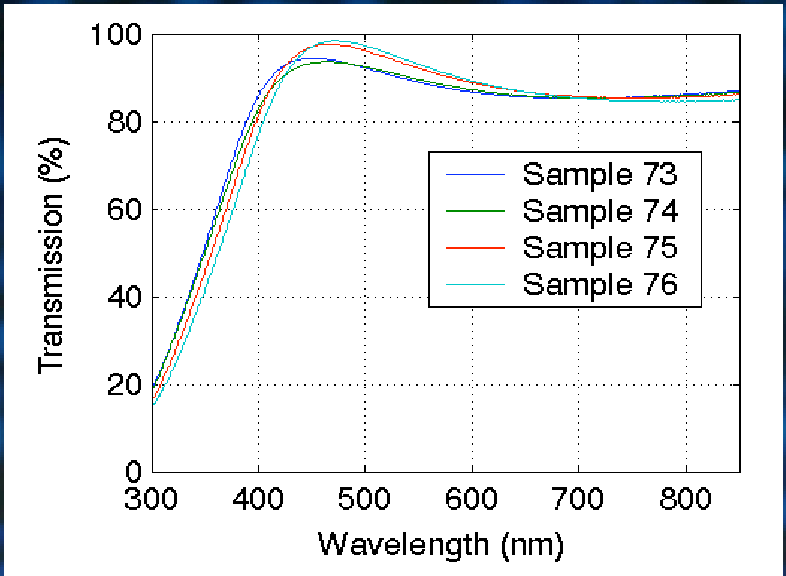


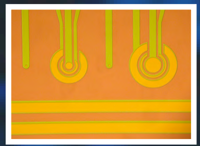


Indium Tin Oxide Fabrication

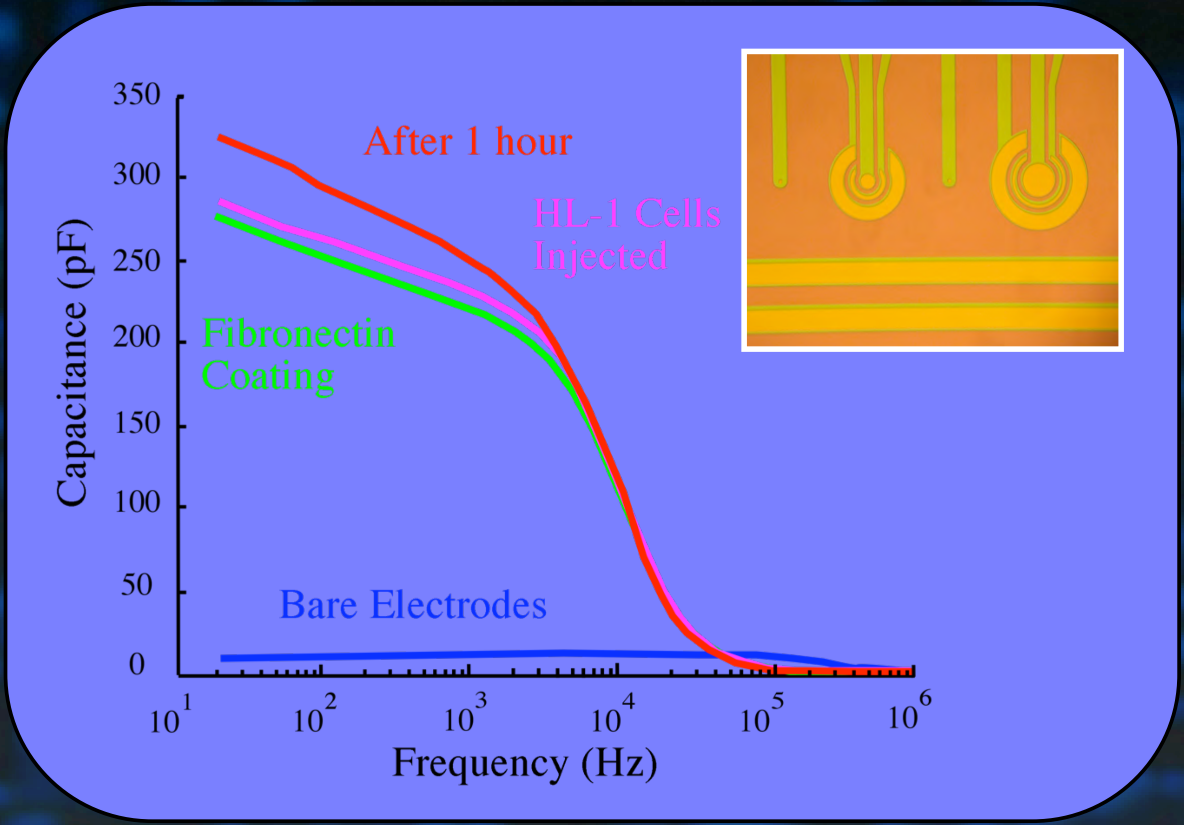
Indium Tin Oxide (ITO) Fabrication

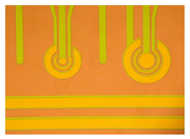
Optical Transmission





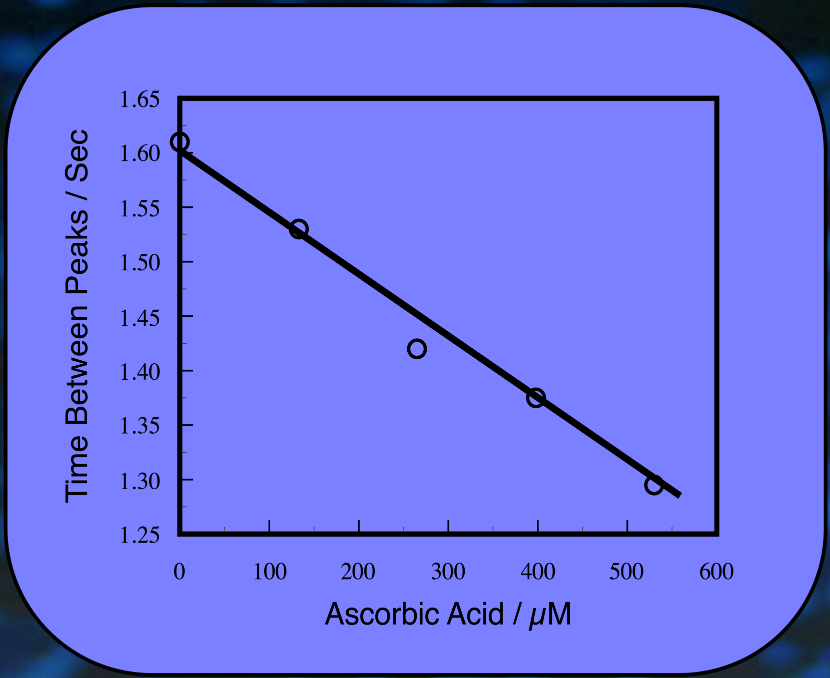
Electrical Measurements





Chemical Measurements

- Measured Acetic Acid in PBS
- Electrochemical Sensor
- First Step Toward Cell Culture Media

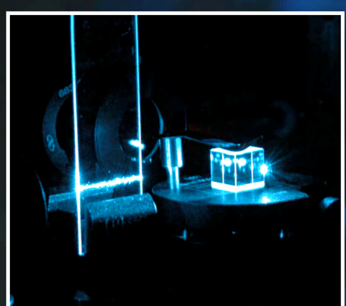


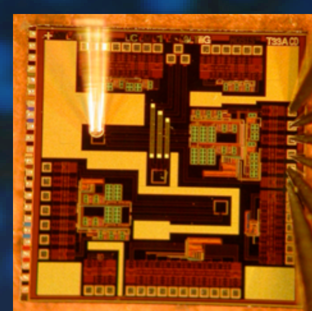
Optical Measurements

Flourescent
- -YFP
- -GFP
- -Fret

Autoflourescent
- -Luciferase
- -Acquarin

Absorbance

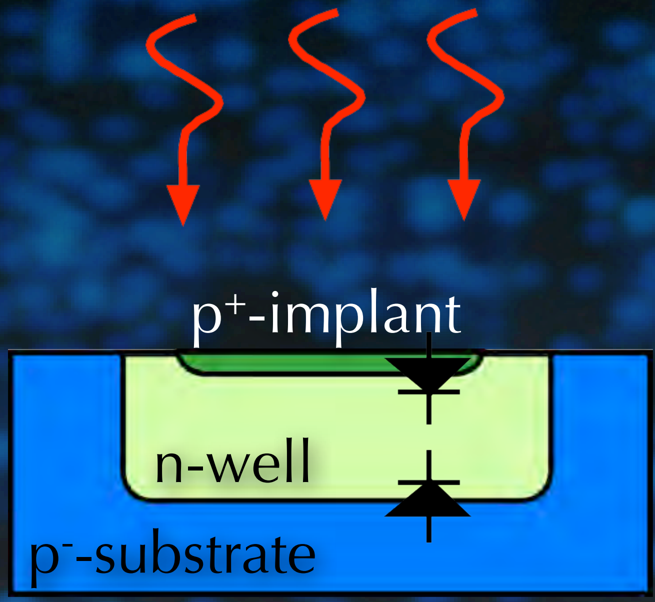


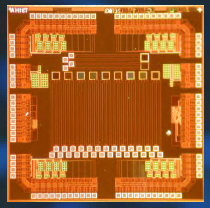


CMOS Photodetectors

Photo-generation of Electron-Hole Pairs

$$G_p(\lambda, x) = \alpha(\lambda)(1 - R(\lambda))\Phi(\lambda)e^{-\alpha(\lambda)x}$$





CMOS Photodetectors

Minority Carrier Diffusion Equation

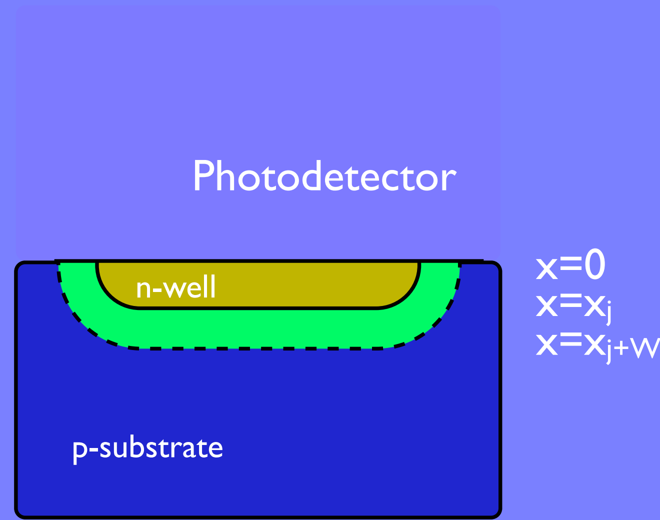
$$\frac{\partial \Delta p_n}{\partial t} = D_p \frac{\partial^2 \Delta p_n}{\partial x^2} - \frac{\Delta p_n}{\tau_p} + G_L$$

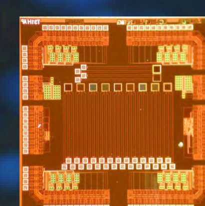
Photo-generation of Electron-Hole Pairs

$$G_p(\lambda, x) = \alpha(\lambda)(1 - R(\lambda))\Phi(\lambda)e^{-\alpha(\lambda)x}$$

Boundary Condition

$$D_p \left. \frac{\partial \Delta p_n}{\partial x} \right|_{x=0} = S_p \Delta p_n(0)$$





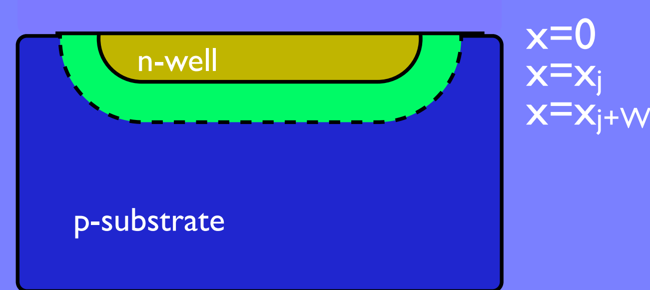
CMOS Photodetectors

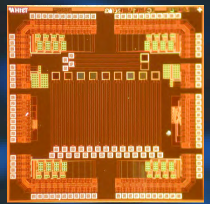
Change in Minority Carrier Concentration

$$\Delta p_n = \frac{\alpha \Phi (1-R)\tau_p}{\alpha^2 L_p^2 - 1}\left[\frac{\left(\frac{S_p L_p}{D_p} + \alpha L_p\right)\sinh\left(\frac{x_j - x}{L_p}\right) + e^{-\alpha x_j}\left(\frac{S_p L_p}{D_p}\sinh\left(\frac{x}{L_p}\right) + \cosh\left(\frac{x}{L_p}\right)\right)}{\frac{S_p L_p}{D_p}\sinh\left(\frac{x_j}{L_p}\right) + \cosh\left(\frac{x_j}{L_p}\right)} - e^{-\alpha x}\right]$$

Hole Current Density

$$J_p = -qD_p \left(\frac{\partial p_n}{\partial x}\right)\bigg|_{x_j}$$





CMOS Photodetectors

Photocurrent Generation in the Depletion Region

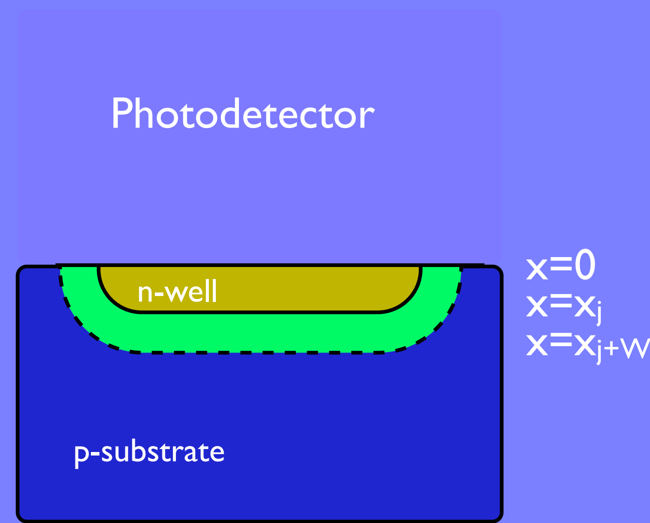
$$J_{dr} = q\Phi(1-R)e^{\alpha x_j}(1-e^{-\alpha W})$$

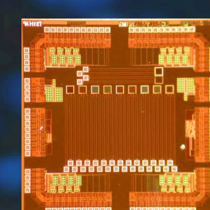
Total Photocurrent Density

$$J(\lambda) = J_p(\lambda) + J_n(\lambda) + J_{dr}(\lambda)$$

Internal Spectral Response

$$SR(\lambda) = \frac{J_p(\lambda) + J_n(\lambda) + J_{dr}(\lambda)}{q\Phi(\lambda)(1-R(\lambda))}$$

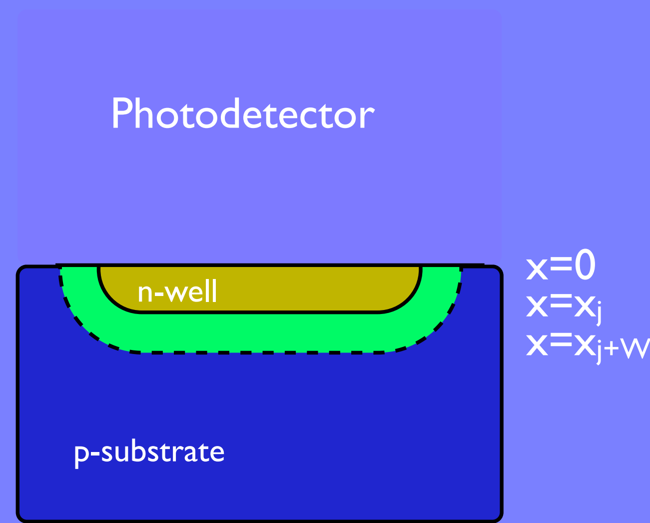


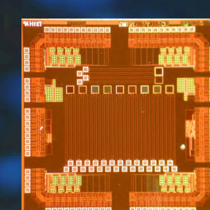


CMOS Photodetectors

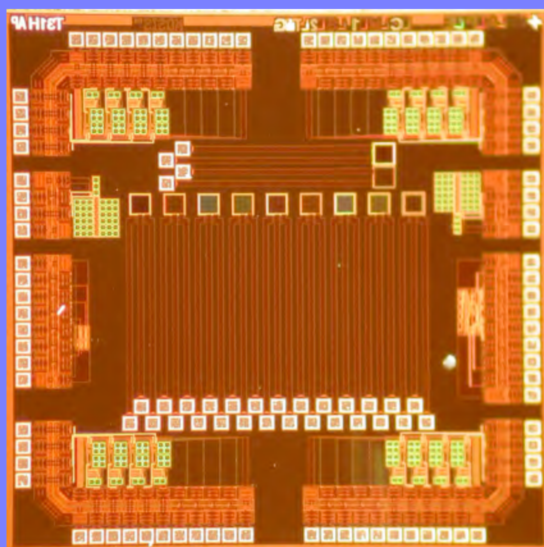
Spectral Response

$$SR(\lambda) \approx \frac{1 + {S_p}/{\alpha D_p}}{\frac{S_p L_p}{D_p}\sinh\left(\frac{x_j}{L_p}\right) + \cosh\left(\frac{x_j}{L_p}\right)}$$

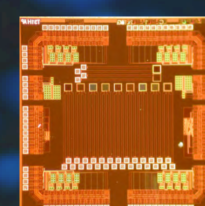




CMOS Photodetectors

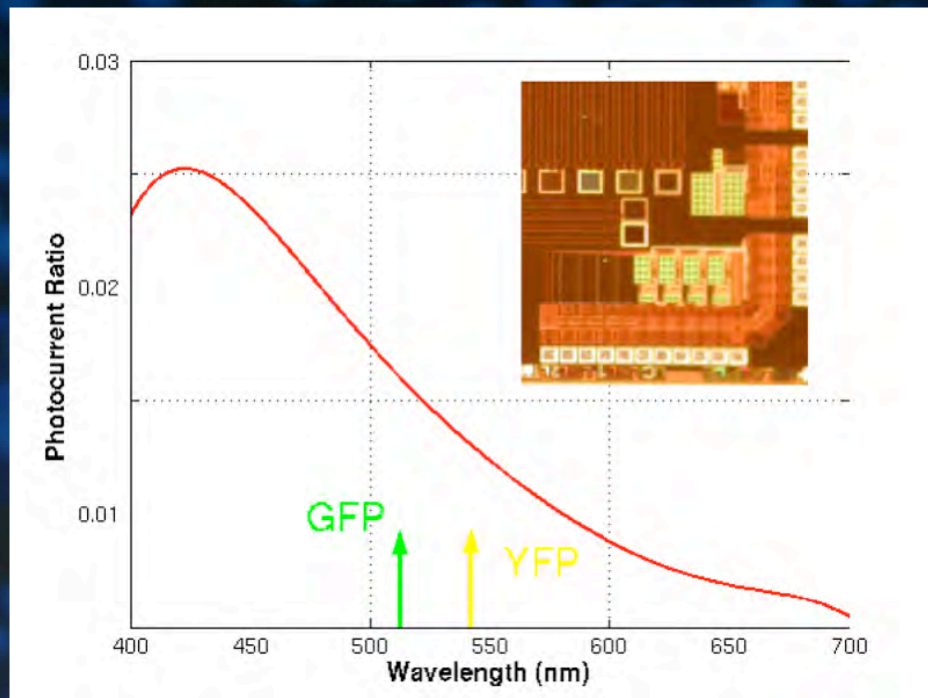


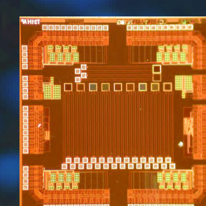
	Photodiode								
	#1	#2	#3	#4	#5	#6	#7	#8	#9
Glass	■		■		■		■		■
Metal #3									■
Poly 2					■	■	■	■	
Poly 1			■	■			■	■	



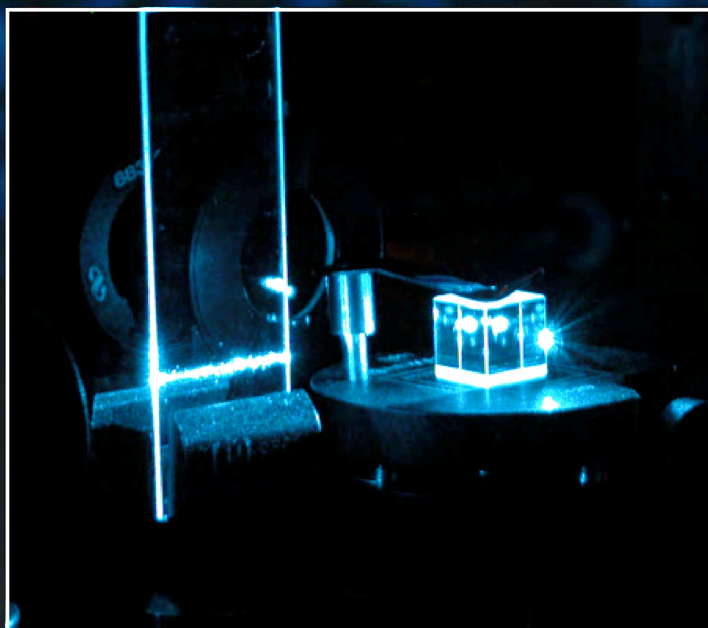
Optical Measurements

Experimental Charicterization of Spectroscopic Detectors

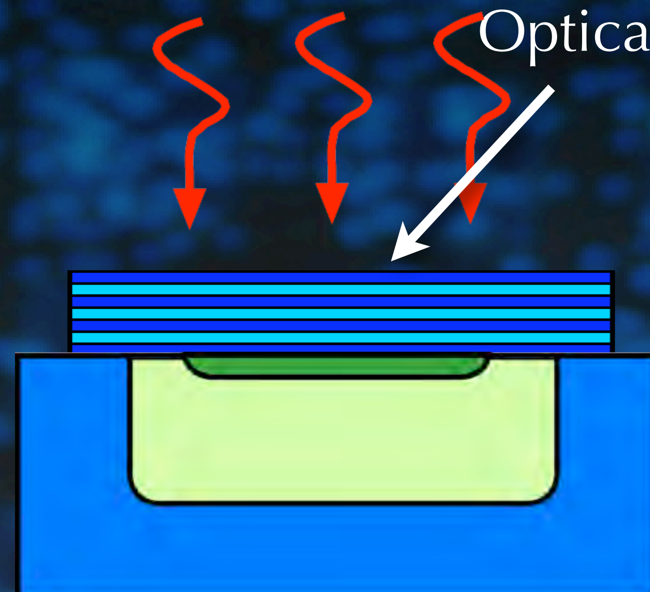


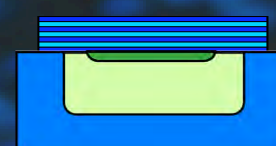


Optical Filter

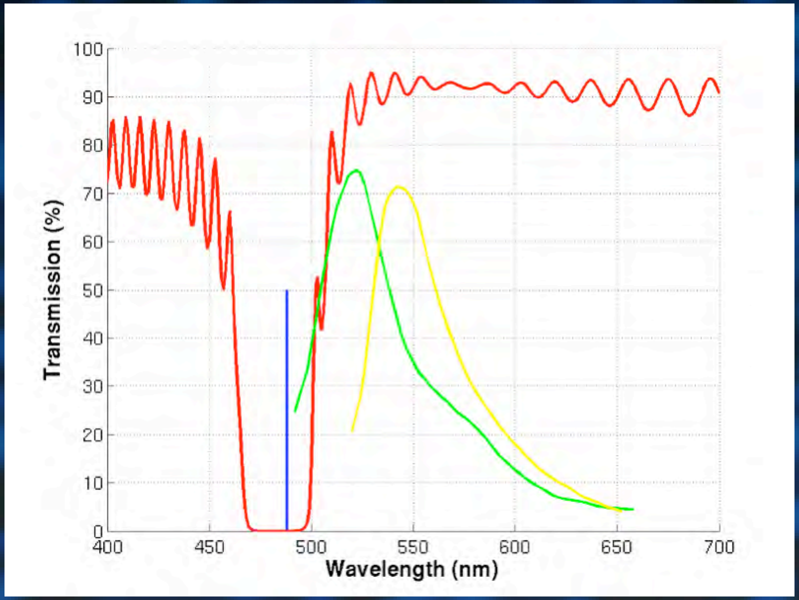


Less Than 0.1% of light
at 488nm transmits





Optical Filter Measurement

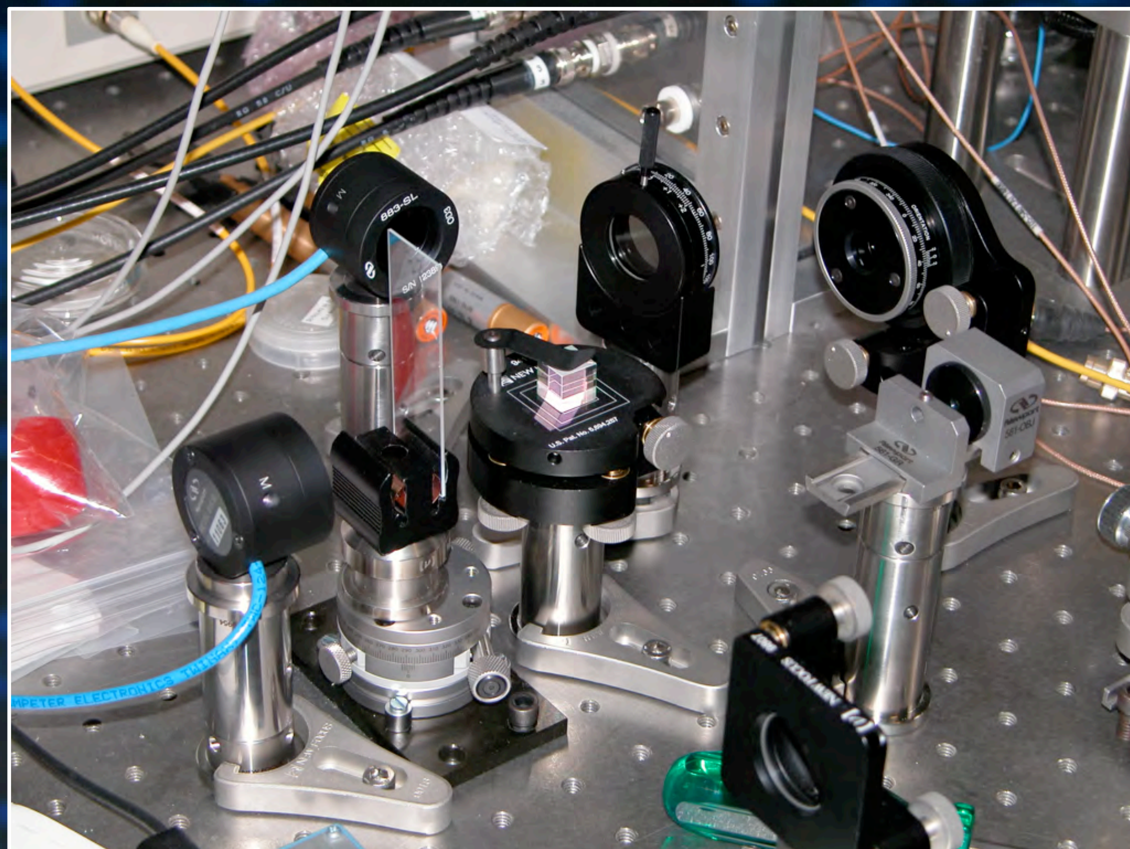


Absorption Measurements

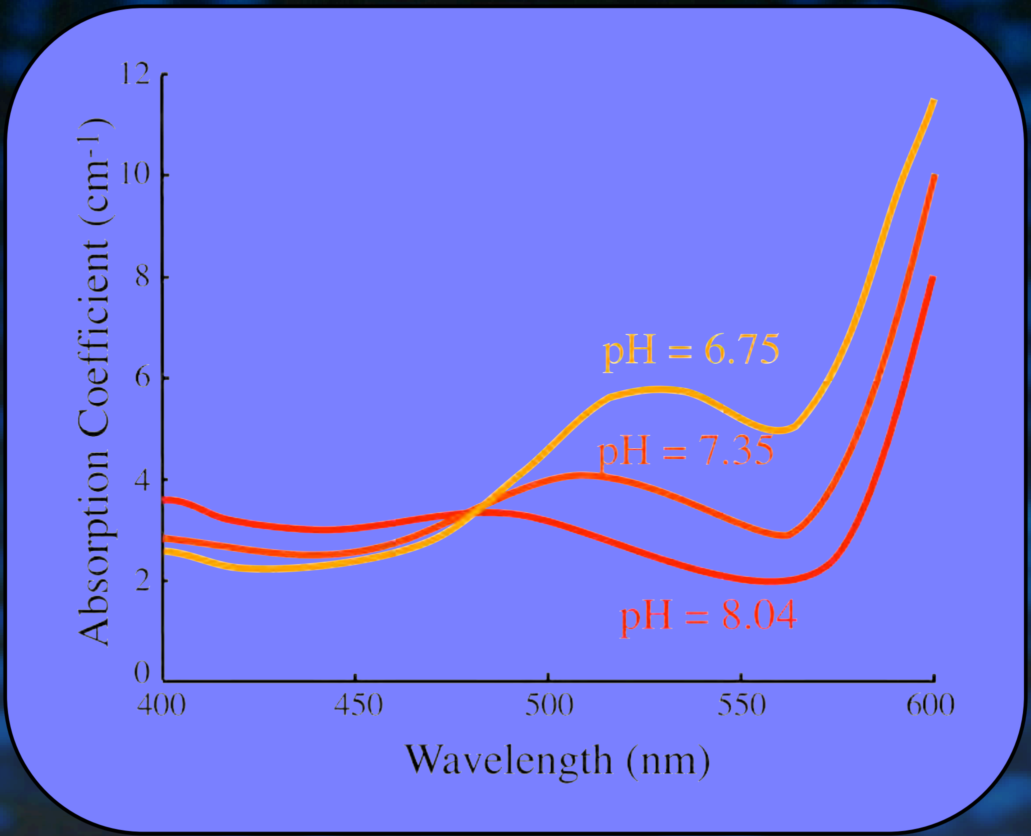
Phenol red is a common additive to cell culture media and is used to qualitatively determine pH changes based on color change on the cell culture media.

Spectroscopic photodetectors fabricated in a standard CMOS technology can be used to monitor this color change. The spectroscopic photodetectors also have applications in distinguishing fluorescent markers.

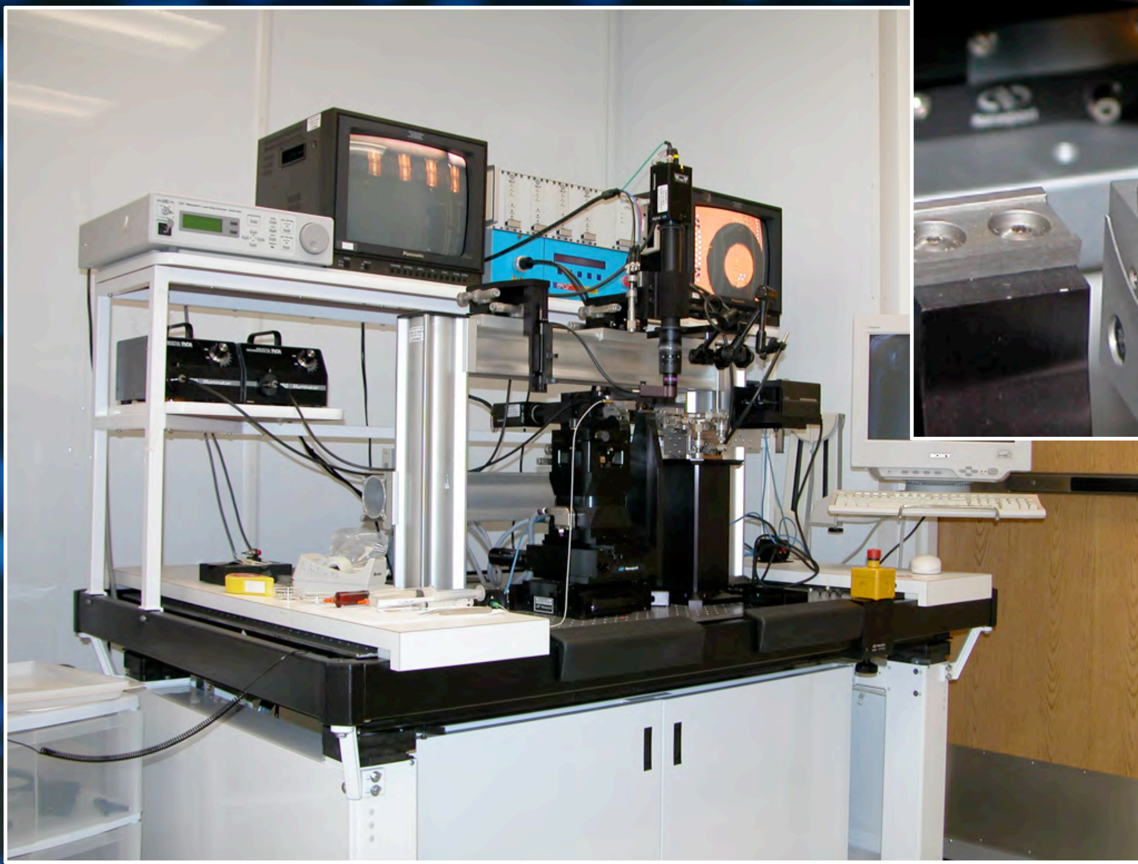
Optical Measurements

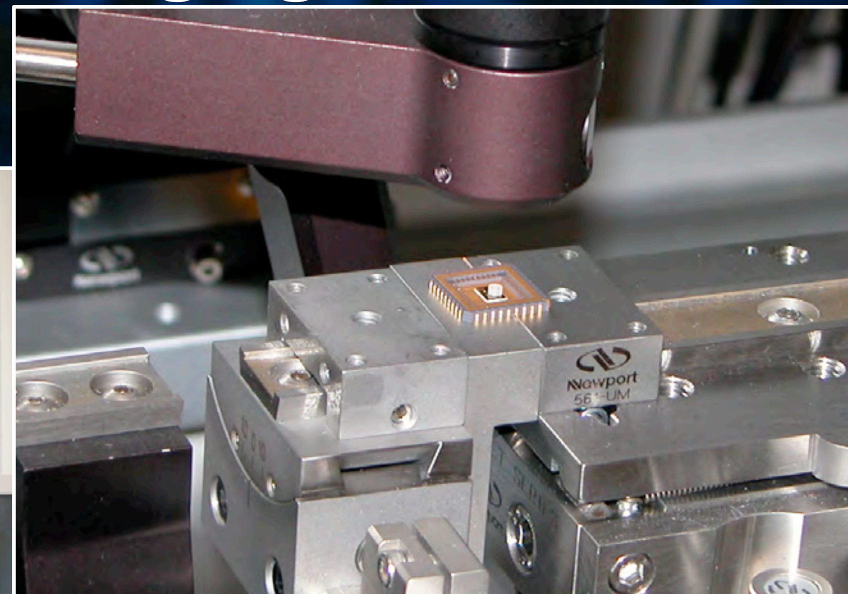


Optical Measurements



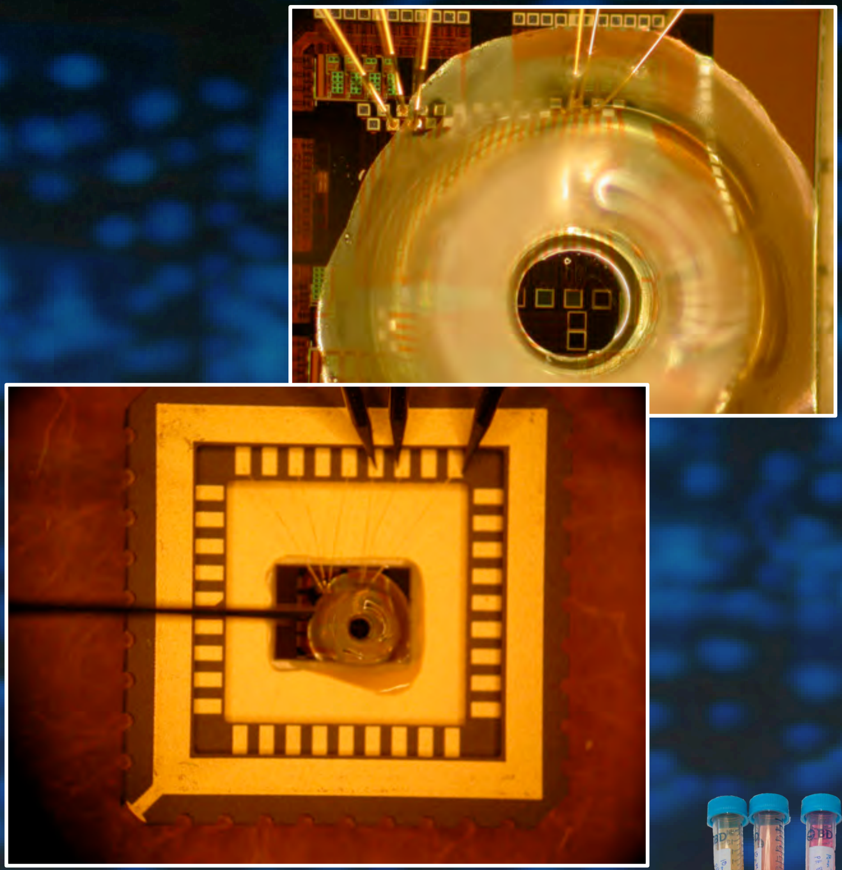
CMOS Packaging



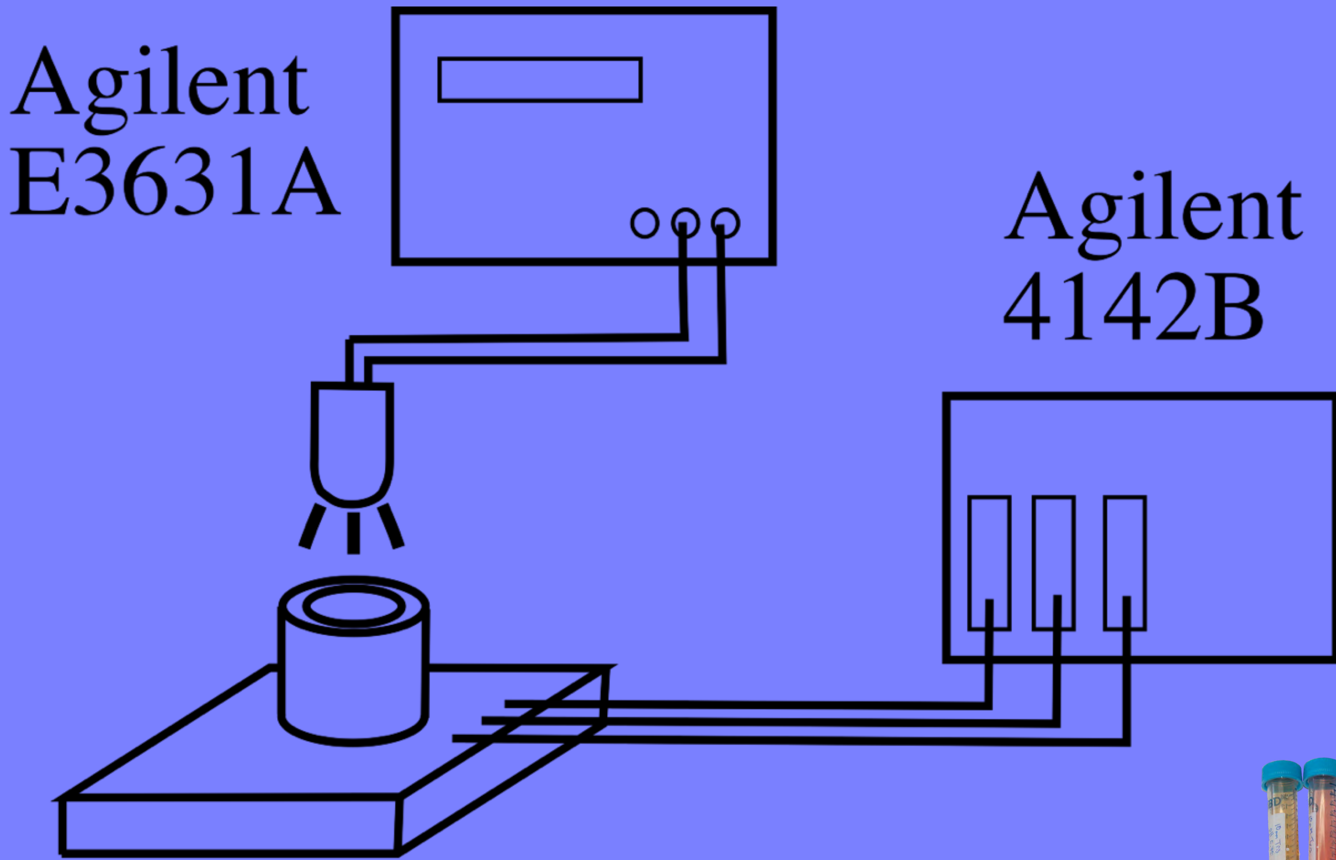


CMOS Packaging

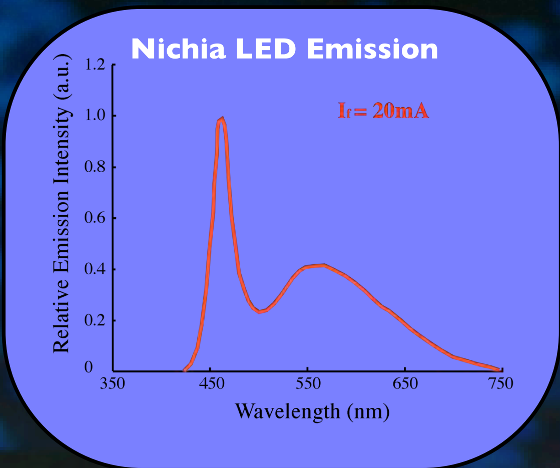
- Optical Measurements
- Easy fluid injection
- Reservoir for quick evaluation

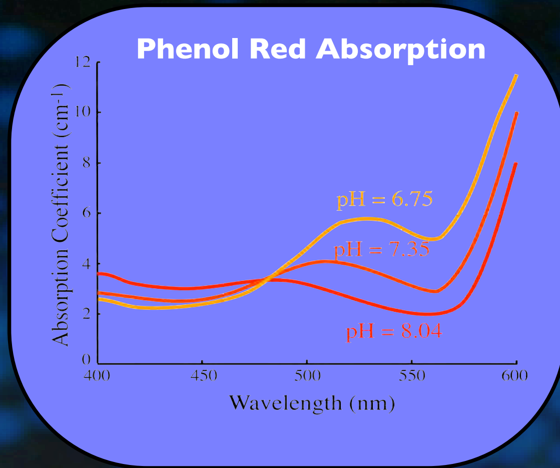


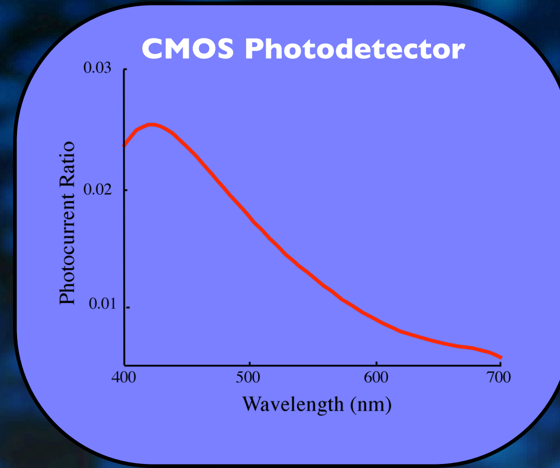
CMOS Photodetectors



CMOS Photodetectors

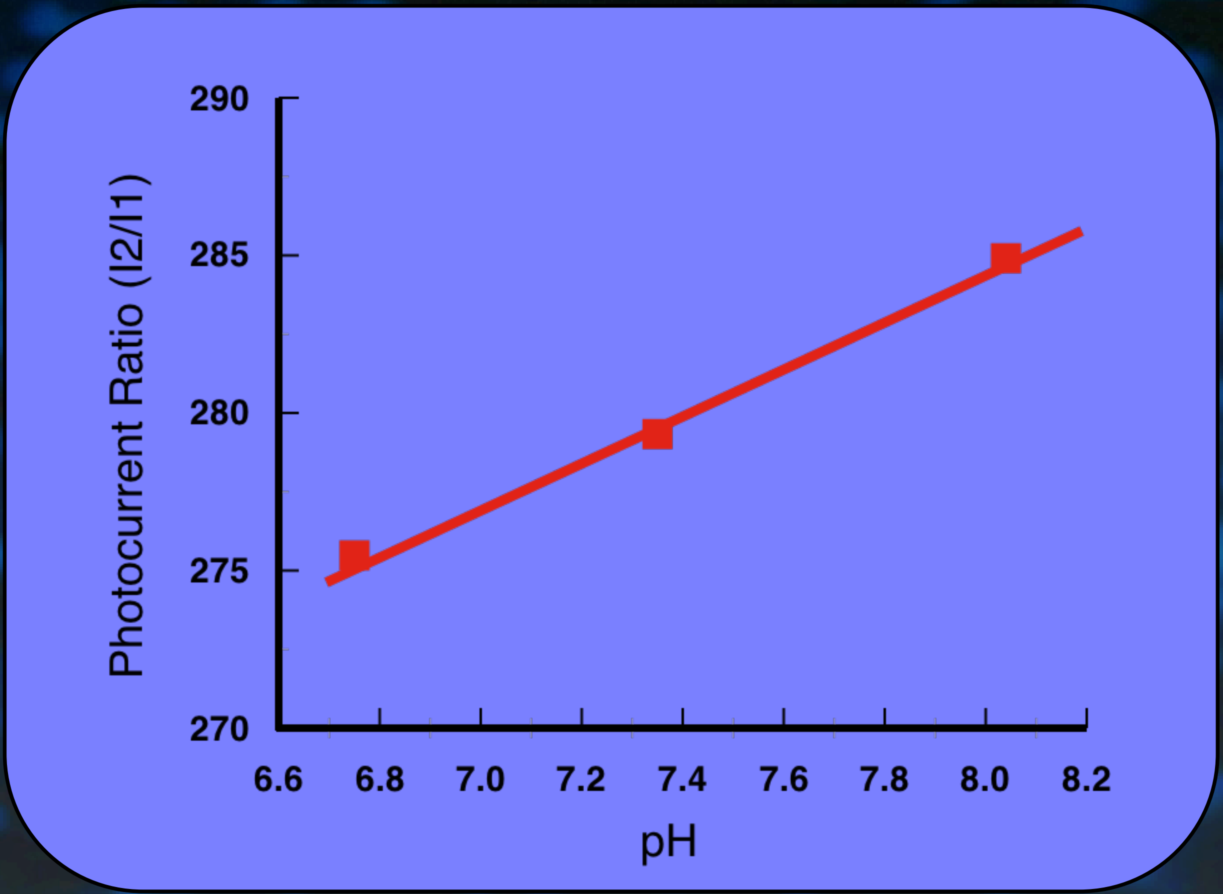






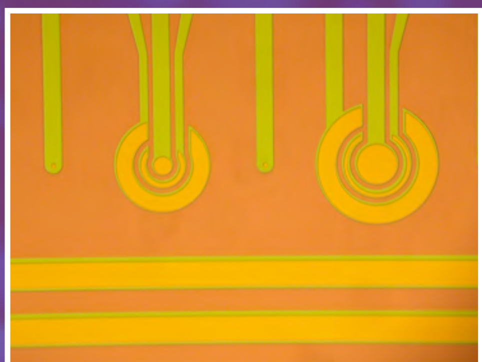
$$S = \frac{\int E(\lambda) e^{-\alpha(\lambda)t} \frac{I_2(\lambda)}{I_1(\lambda)} d\lambda}{\int E(\lambda) e^{-\alpha(\lambda)t} d\lambda}$$

Optical Measurements

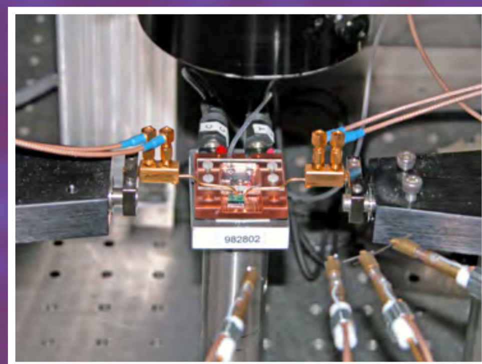


Cell Attachment

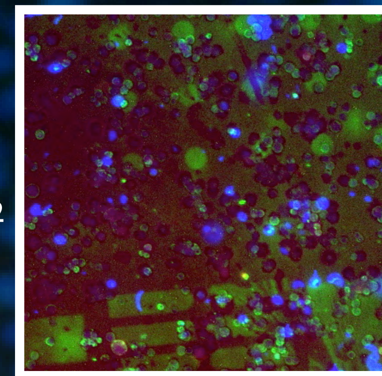
ITO Electrodes



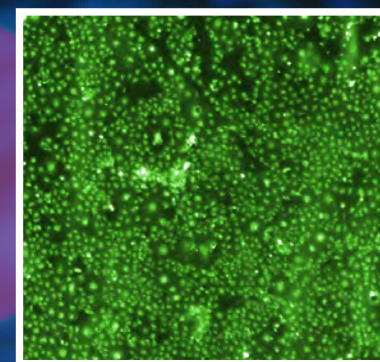
Biochamber



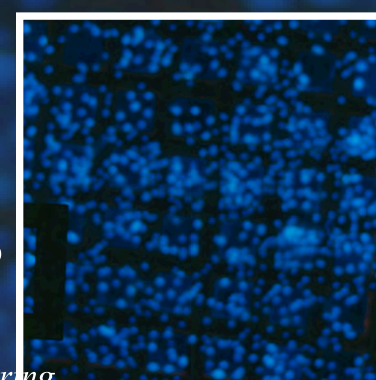
DU145 on Poly-L-lysine Patterned SiO_2



COS-7 on ITO Coated Silicon

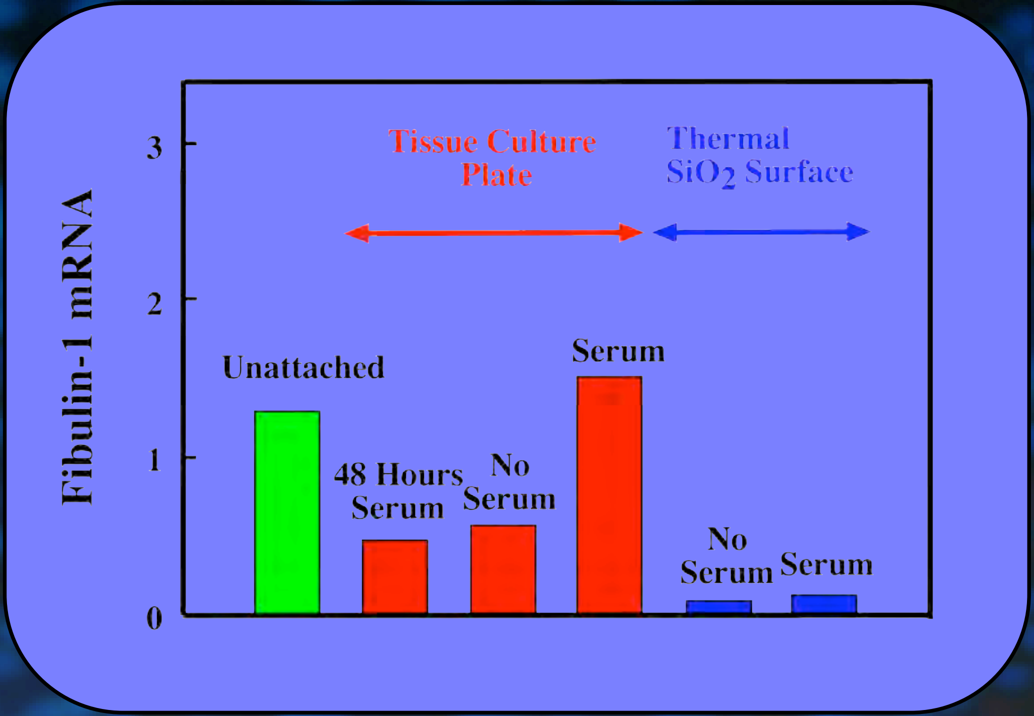


COS-7 on CMOS Chip



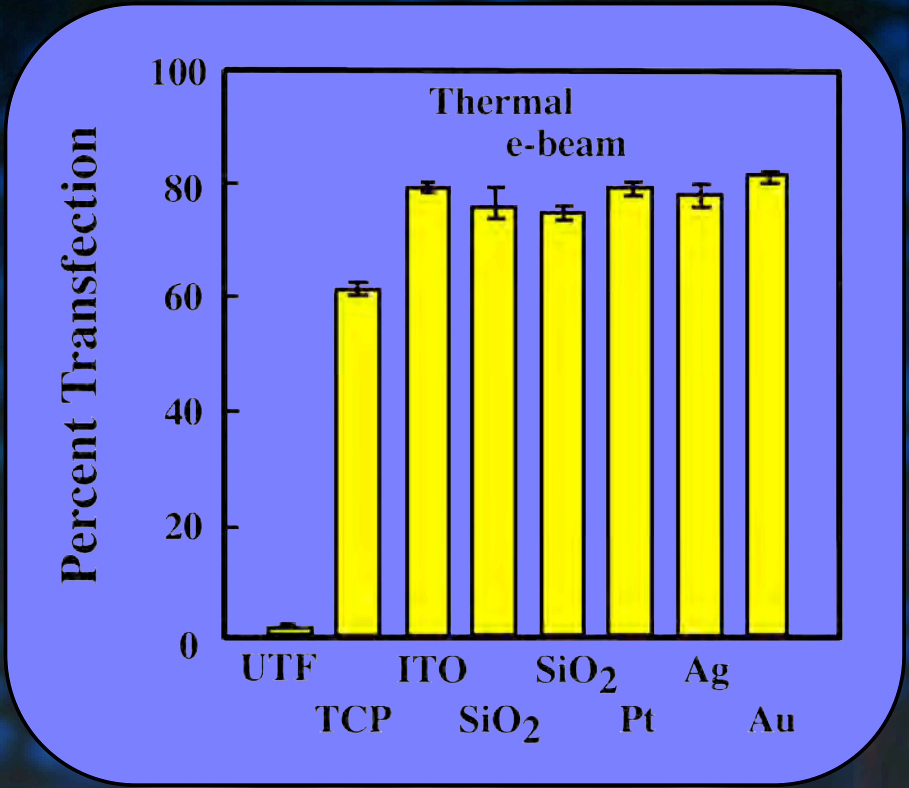
Fibulin-1 Expression

- Fibulin-1 is an extracellular matrix produced by COS-7 cells.
- Provides a measure of the cellular response to the substrate.
- SiO_2 provides a smaller stimulus than tissue culture plate!

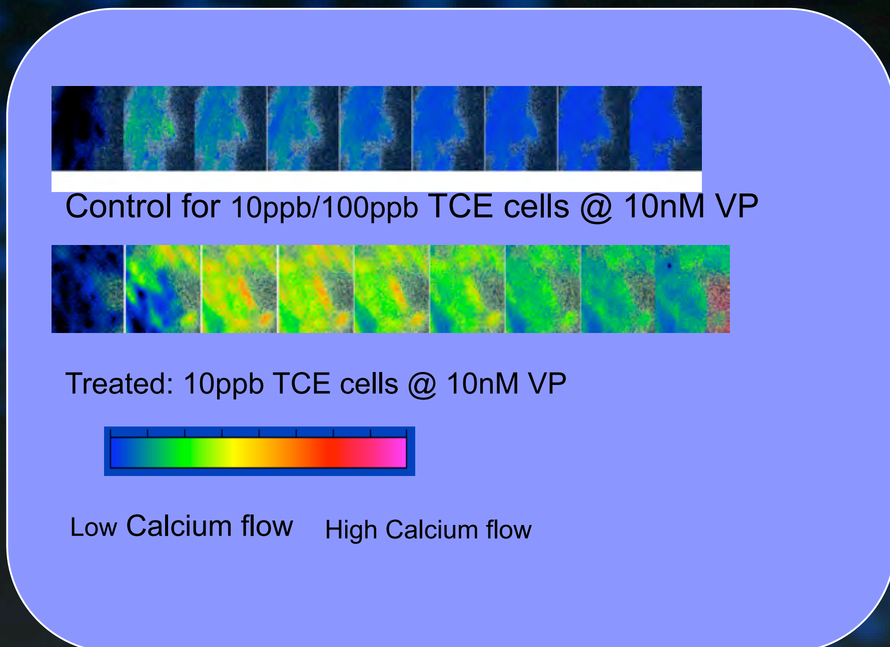


Percent Transfection

- Transfection is the introduction of DNA into animal cells.
- Changes in gene expression can be readily evaluated.
- Designed for real time monitoring with the biochip.



Chemical Toxicity Measurement



- Developed novel technique based on calcium handling in cells.
- P19 cells were exposed to low levels of TCE for 24 hours and then treated with vassopression to measure intracellular flux of calcium.
- Measured calcium flux by changes in fluorescence.

Summary

- Photodetector and optical characterization
- Developed techniques for cell attachment to semiconductor and insulator surfaces
- Demonstrated calcium measurement for toxicity.