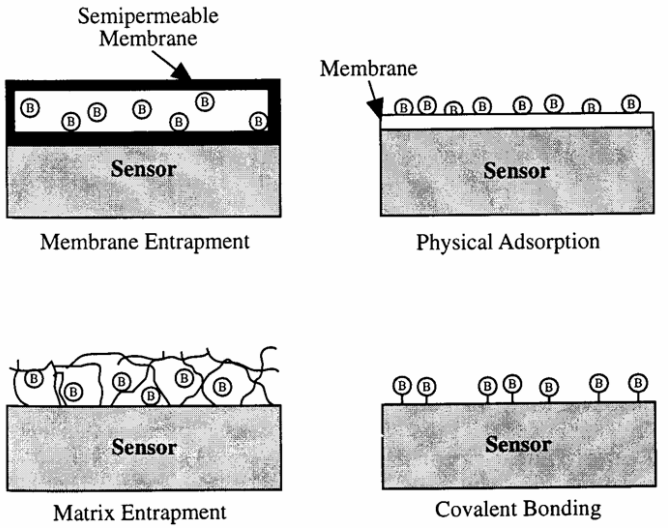
What is a Biosensor?

- Definitions
  - A device used to measure biologically relevant information
    - Oxygen electrodes, neural interfaces, etc.
  - A device using a biological component as part of the transduction mechanism
    - Antibodies
    - Enzymes
    - DNA, RNA
    - Whole cells
    - Whole organs/systems

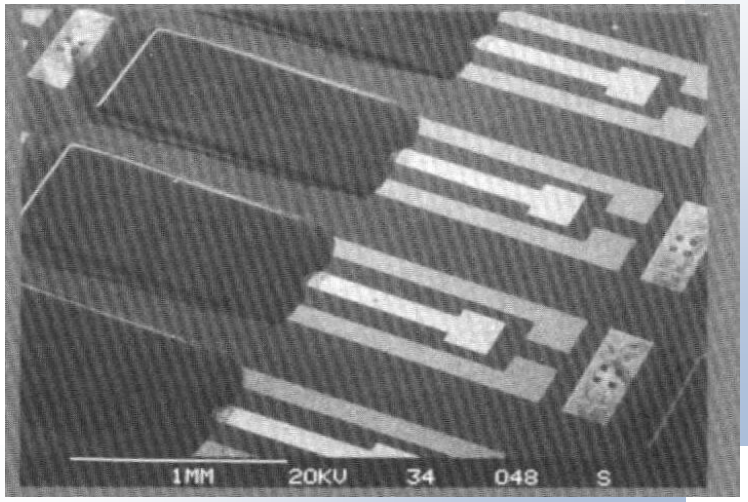
What is a Biosensor?

- Configuration
  - Can be developed from any basic sensor by adding a biological component
  - Usually incorporates a biomembrane
- Transduction
  - Electrical
  - Optical
  - Mechancial
    - Mass
    - Acoustic
  - Thermal
  - Chemical
  - Magnetic

Biomolecule Addition



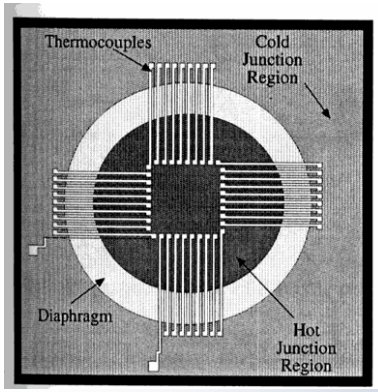
Enzymatic Addition

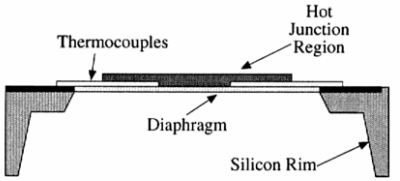


Calorimetric Biosensors

- Rely on biological molecules for transduction or detection
- Enzymes (or even cells) immobilized on a surface
- Enzymes catalyze a reaction which generates heat
- Heat is proportional to amount of substrate present

Thermopile

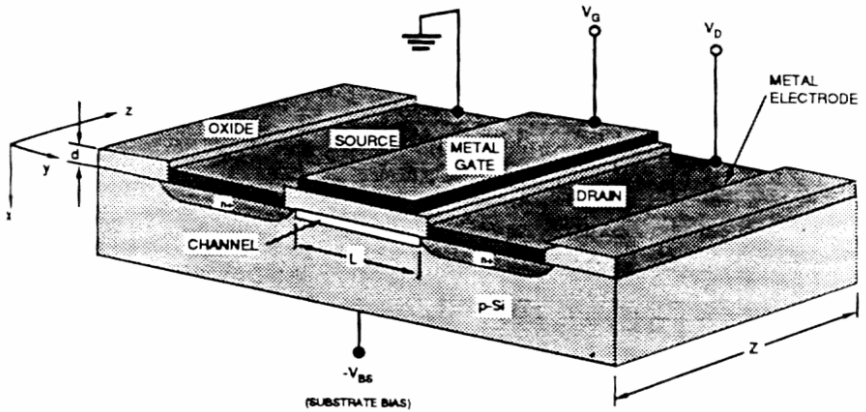




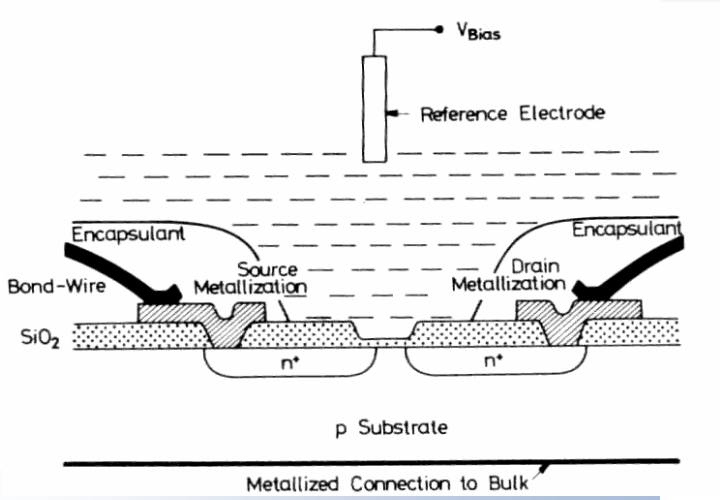
Field Effect Transistors

- Current from source to drain related to gate voltage
- Application of membranes to gate allows selective measurements
- Problems as biosensors
  - i) Membrane adhesion
  - ii) pH sensitivity
  - iii) Drift
  - iv) Coatings can help eliminate all
  - v) Nonlinear

Field Effect Transistor



ISFET



Arrays

- Advantages
  - Repetitive information
    - Increased confidence
    - Averaging
  - Variety of information
    - Multiple analytes
    - Multiple characterisitics
  - Amplification
  - Spatial resolution
- Disadvantages
  - Data processing
  - Cross talk
  - Fabrication and Packaging
  - General complexity

Natural Biosensor Arrays

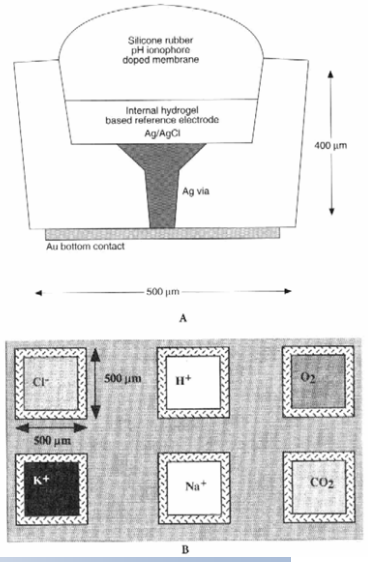
- Nose
- Tongue
- Eyes
- Touch
- Combined senses
- Data processing?

Electronic Nose

- Significant interest
- Usually an array of sensors
- Detect odors
- Detect volatile chemicals
  - Must adsorb to surface
- Pattern recognition
  - Mapping
  - Vector analysis
  - Fuzzy logic
  - Neural networks

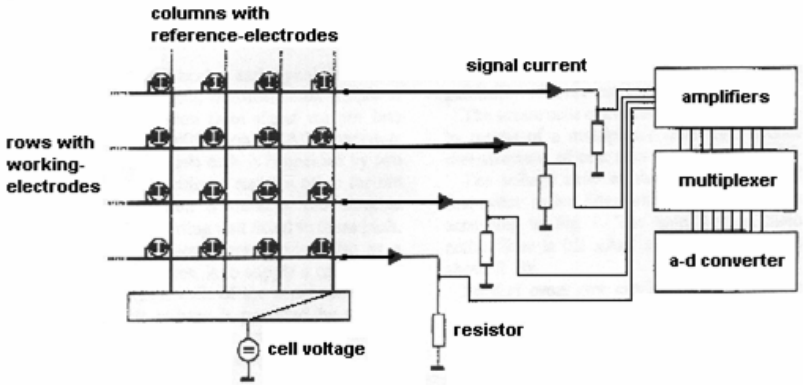
Typical Array

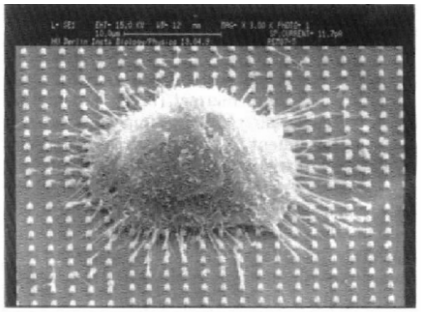
- Mulitple analytes on closely spaced array
- Vias for electrical connection
- Membrane for selectivity



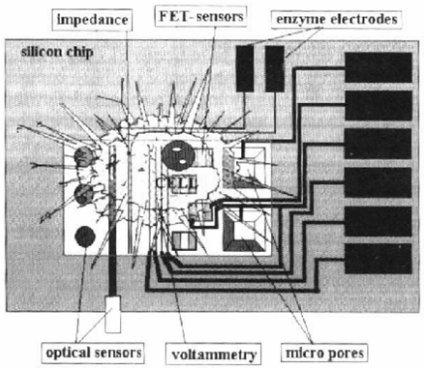
Spatial Sensor Array Layout

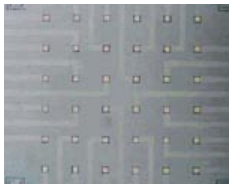
Sensor array on 30mm x 30mm Si substrate area

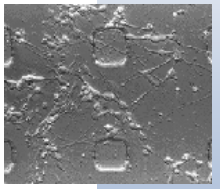


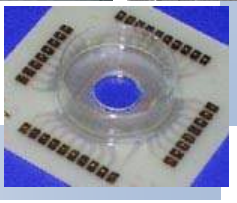


Microelectrode Arrays for Monitoring Cell Physiology



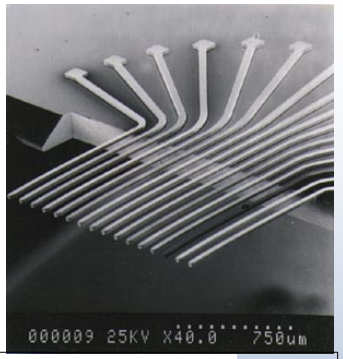




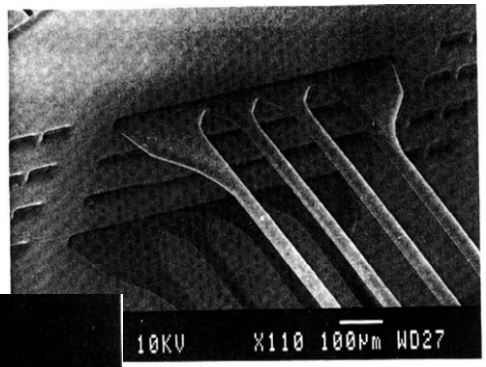


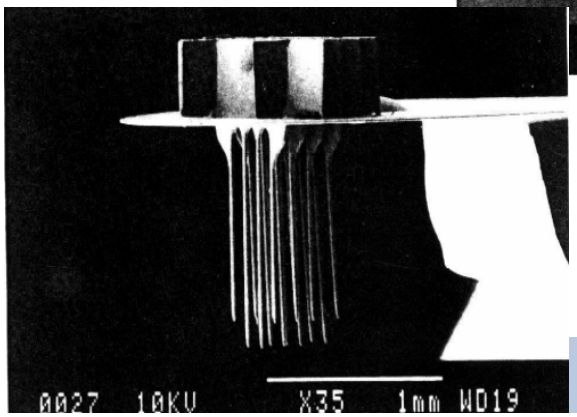
Neural Recording Arrays

- Types
- Design Issues
- Future Work

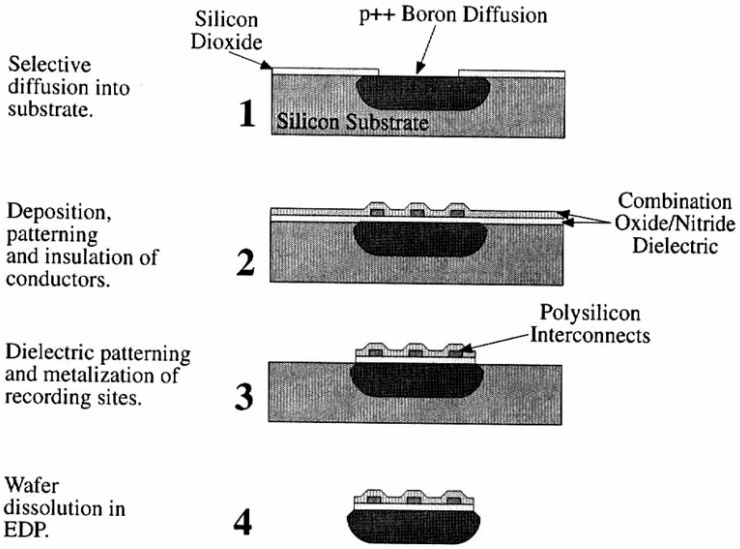


Michigan Arrays



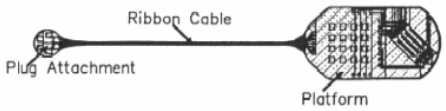


Michigan Array 2



Packaging

(a)



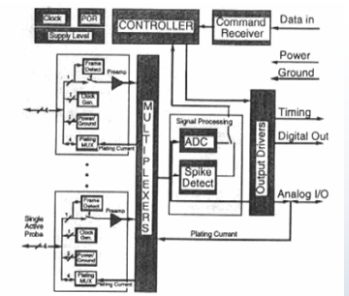


Fig. 11. Block diagram of a prototype recording system being explored as an entry point for platform-based signal processing.

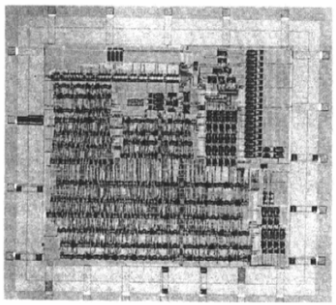
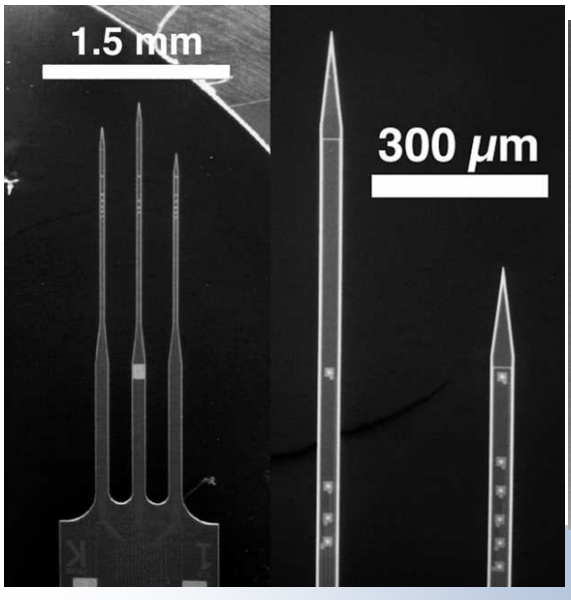
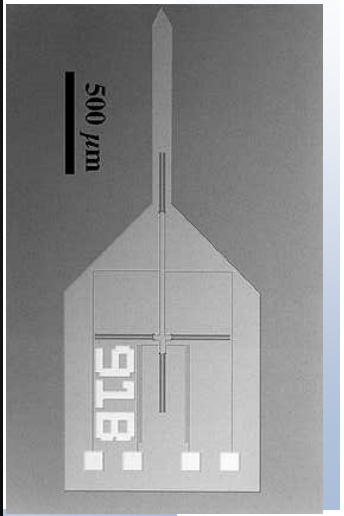


Fig. 12. Photograph of a platform signal processing circuit. The circuit was fabricated in a 2 μm, double-poly, double-metal CMOS process and measures 4.75 × 4.5 mm.

Stanford Arrays





Flexible Polymer Electrodes

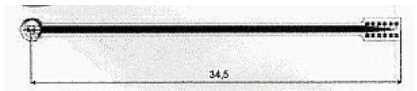
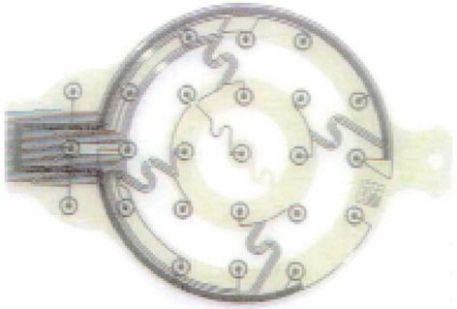


Figure 4. Design of a sieve electrode with 9 ring electrodes and an additional counter electrode w/o shielding. The length is in mm



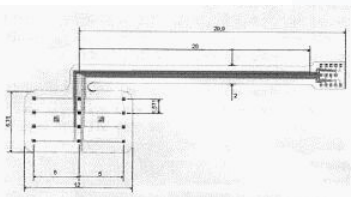


Figure 6. Design of a 12 channel cuff-electrode with integrated interconnects. Dimensions in mm

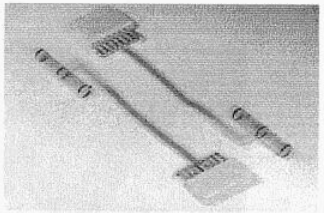
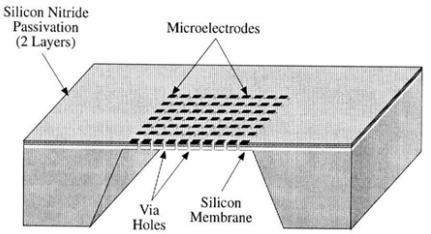
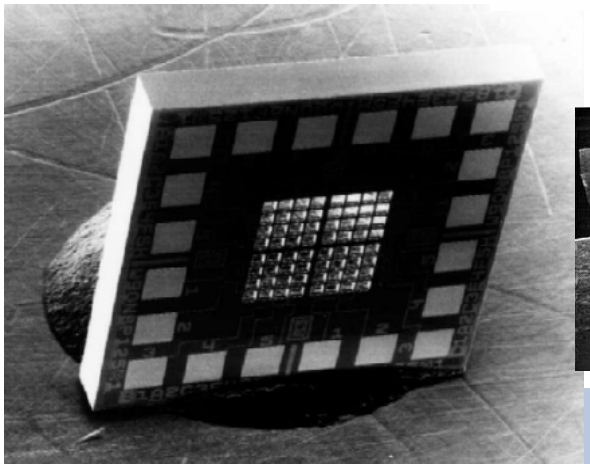
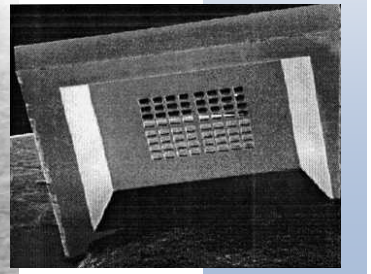


Figure 7. Cuff-type electrodes with 3 channels and standard connectors for acute applications

Regeneration Array

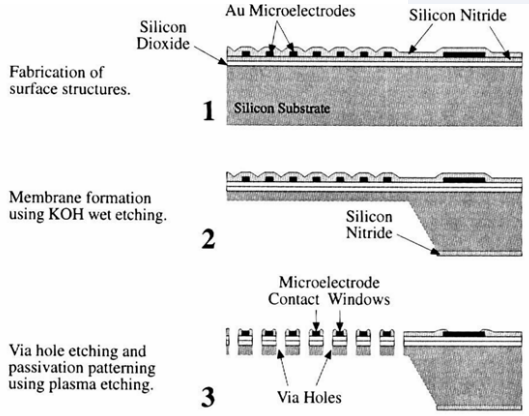






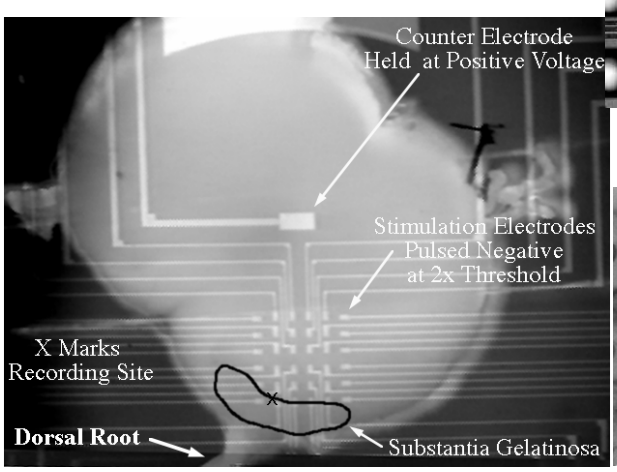
Regeneration Array Fabrication

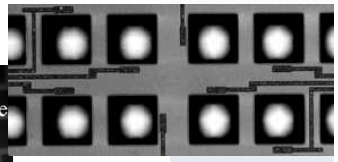
- Arrays of electrodes surrounding holes
- Nerves grow through holes and connect on opposite side
- Requires injury to animal

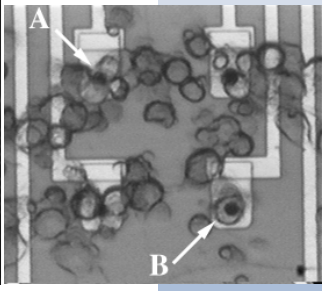


Source: Kovacs at Stanford

Stanford Cell Arrays

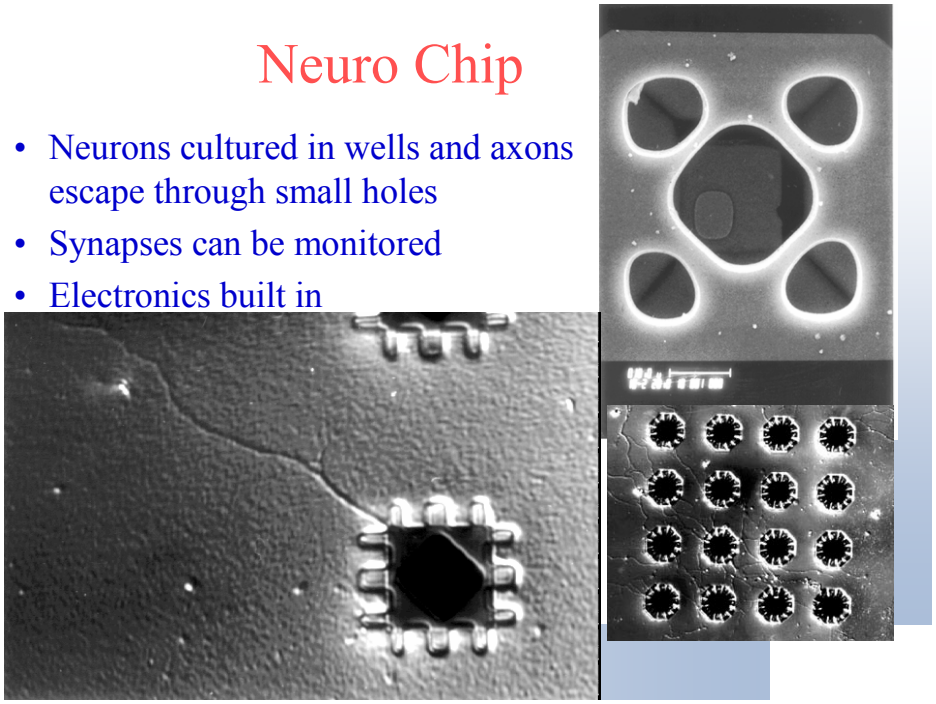






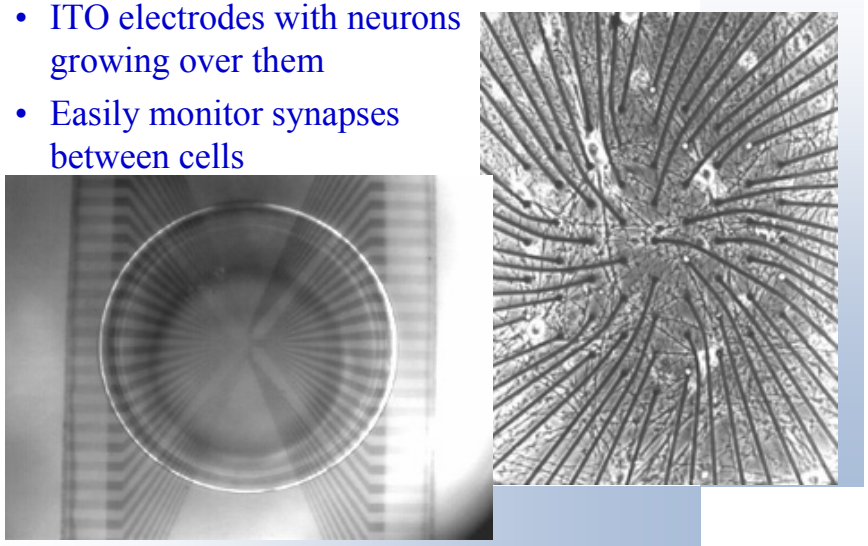
Neuro Chip

- Neurons cultured in wells and axons escape through small holes
- Synapses can be monitored
- Electronics built in



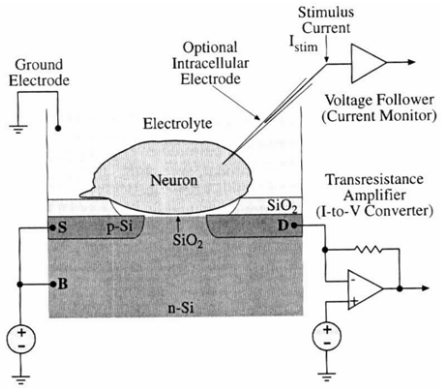
Cultured Neural Networks

- ITO electrodes with neurons growing over them
- Easily monitor synapses between cells



Neural Cell Measurement

- Neuron acts as gate on FET
- Cell must migrate to sensor



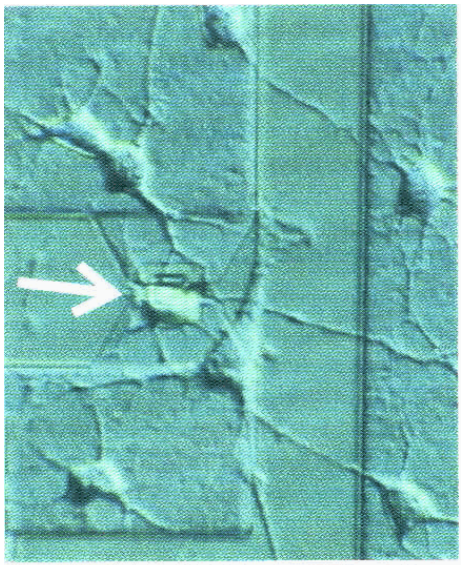
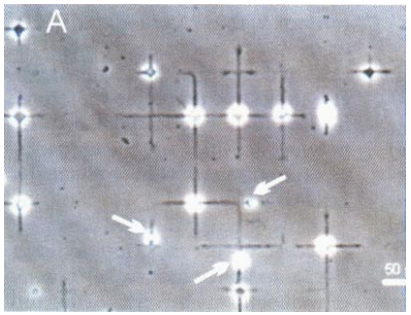


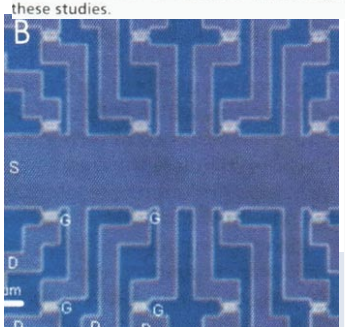
Fig. 3: Micrograph of a random network of hippocampal neurons cultured on the surface of a FET chip. One neuronal cell resides almost completely on the gate electrode of the transistor (cf. arrow).

Drug Screening



Neurons grow in small gaps
Cells constrained to grow over sensing electrodes
Drug can be introduced through perpendicular microchannels

Fig. 4: (A) Controlled adhesion of neuronal cells and guided outgrowth of their dendrites and axons on a patterned substrate. (B) Micrograph of the array of 4x4 field-effect transistors used in these studies.



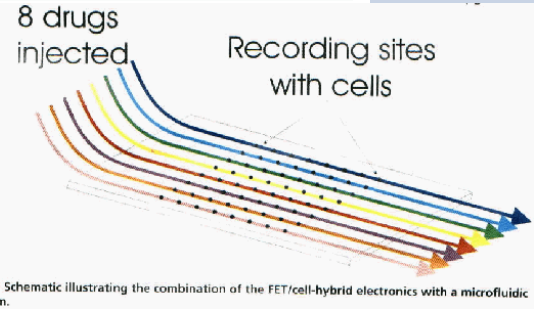
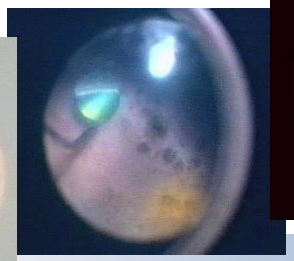
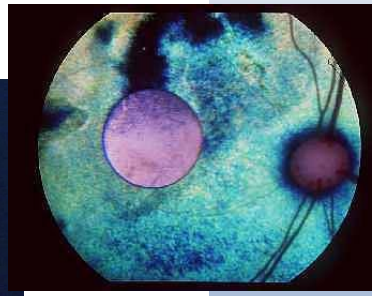


Fig. 5: Schematic illustrating the combination of the FET/cell-hybrid electronics with a microfluidic system.

Artificial Silicon Retina Arrays

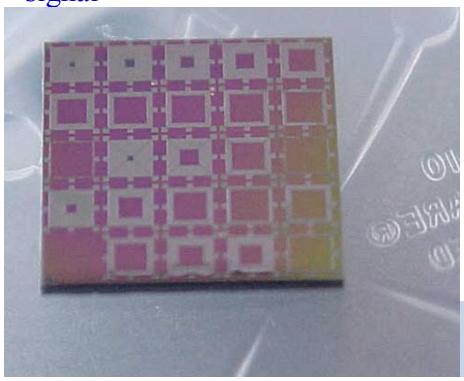
- 3500 silicon photodiodes
- Each connected to stimulating electrode
- Shown to generate neural response

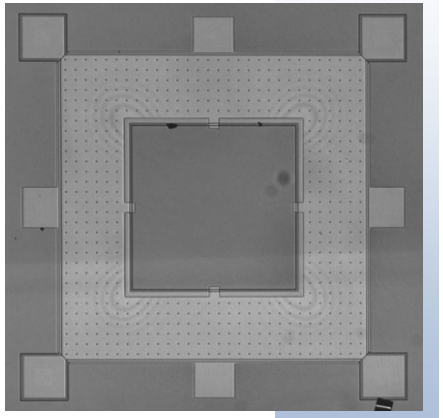




Tactile Displays

- Two layer polysilicon process with metallization
- Voltage applied and outer ring contracts
- Polyimide in center bubbles up to signal





Enzyme Bioreactor

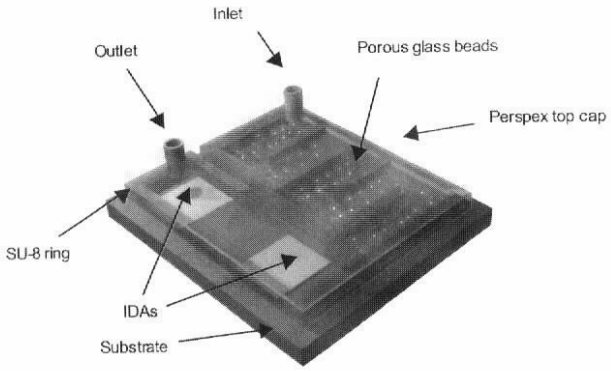


Fig. 1. Diagrammatic representation of an enzymatic microreactor.

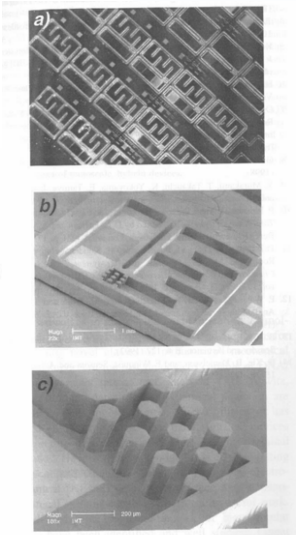


Fig. 2. Three views of a microreactor before completion with the top-cap, a) a optical image before wafer dicing showing several devices; b) SEM image of a single microreactor after dicing; c) SEM image showing a close up of the EPON SU-8 columns separating the two chambers.