CHEMICAL & BIOLOGICAL TRANSDUCERS

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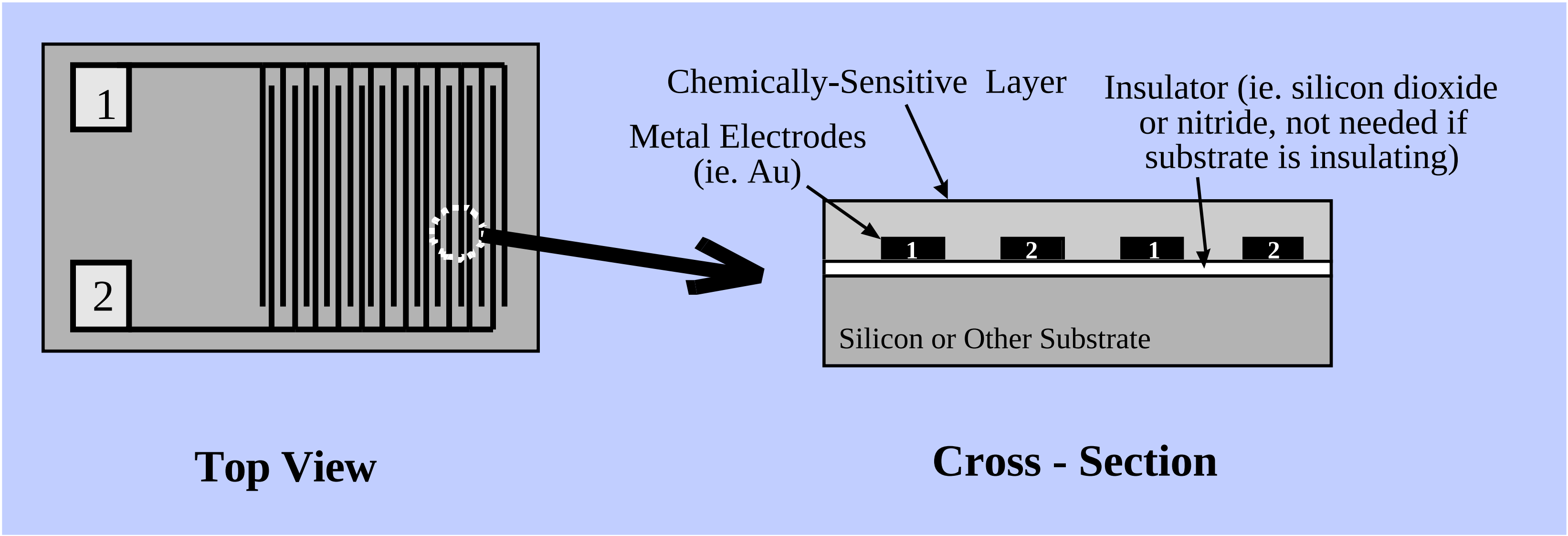
CHEMICAL TRANSDUCERS

- pH sensors
- ISFETs/ChemFETs for specific ions
- Conductivity-based gas sensors
- Microelectrodes
- Biosensors (molecular)
- Cell-based biosensors
- Separation systems (see Fluidics)

CHEMICAL TRANSDUCER CONCEPTS

- Electrochemical transduction (redox/voltammetry, conductivity, impedance spectroscopy, etc.) makes use of electrically-controlled reactions at electrode/electrolyte interfaces.
- ISFET/ChemFET transduction relies on direct modulation of active region of FET-like devices by charges at “gate” surface.
- Conductivity modulation in semiconductor films is a direct effect on resistance of two-terminal sensors.
- Biomolecular interactions (nucleic acids, immunoglobulins, etc.) are highly specific binding interactions that can be detected by changes in charge, mass, etc.
- Cell-based biosensors use whole, living cells as part of the transduction mechanism.

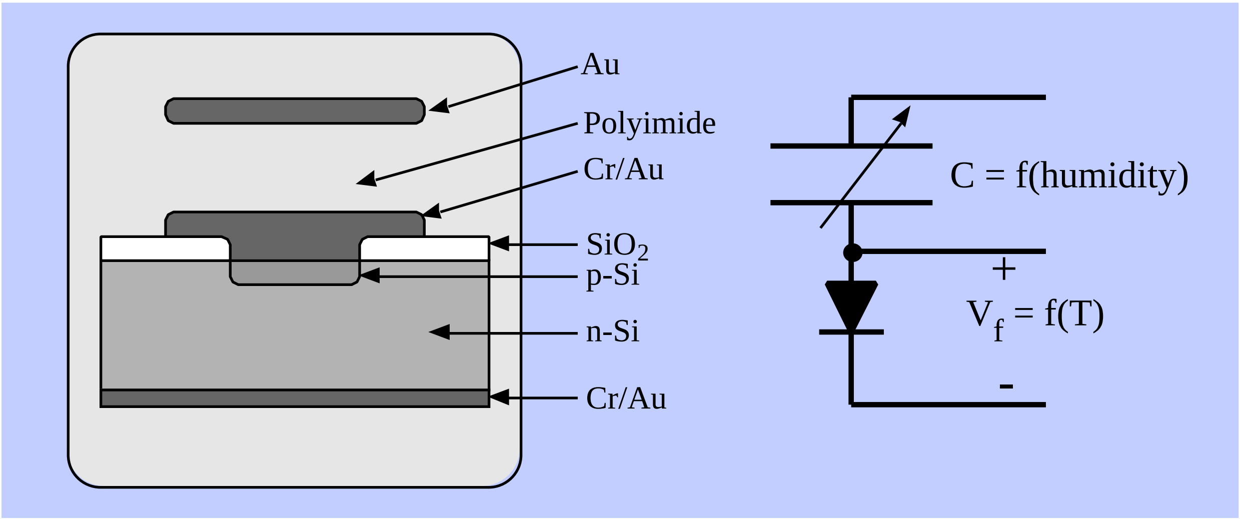
CHEMIRESISTORS

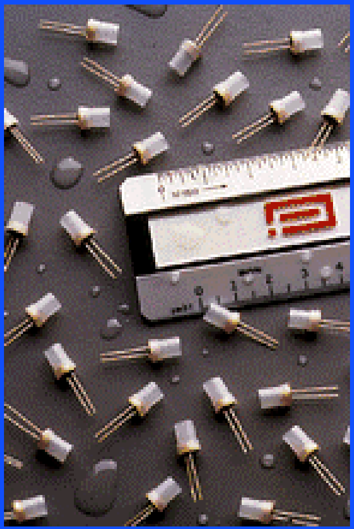


- **Some materials change their bulk resistance when exposed to certain chemicals (e.g. Cu in phthalocyanine as CCl_4 sensor).**
- **A major problem is cross-sensitivity (lack of selectivity), which some try to overcome by combining outputs of several overlapping sensors through neural nets, etc. ("electronic nose").**

CHEMICAPACITORS

- Chemicals entering a dielectric modulate the capacitance by varying ε_r, physically varying the gap, or other means.
- An example is polyphenylacetylene (PPA), a polymer that can be spun on from a benzene (dangerous) solution and is sensitive to CO, CO_2, N_2, and CH_4 (again, poor selectivity is a problem).
- Another example is polyetherurethane (PUT) with gas sensitivities in the -5 to +12 ppm/ppm.

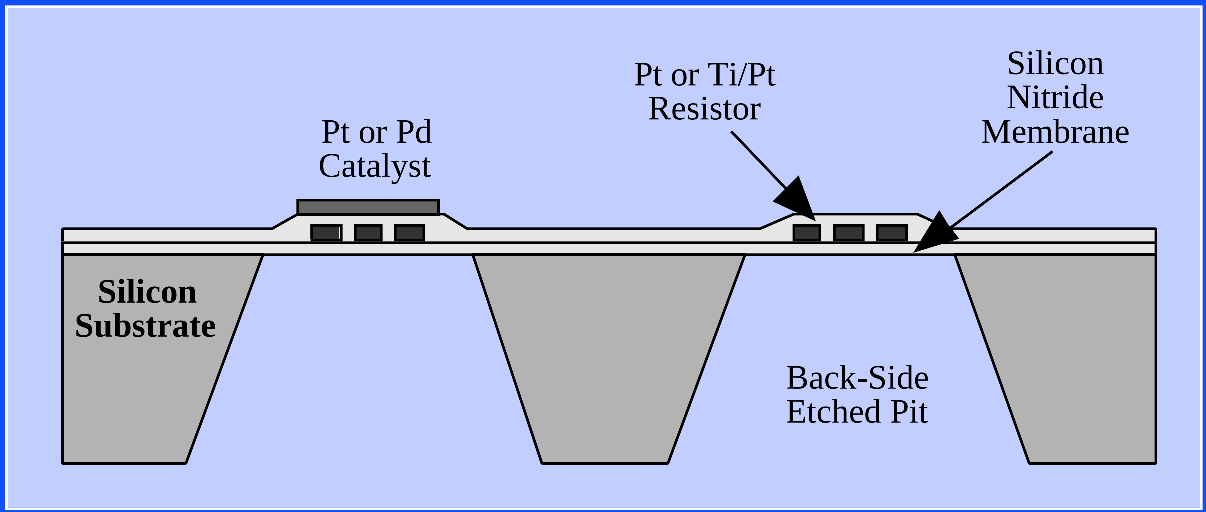




http://panametrics.com/div_pci/

Reference: Yamamoto, T., Murakami, K, Shimizu, H., and Takai, T., "An Integrated Temperature and Humidity Sensor," Transducers '87, Tokyo, Japan, 1987, pp. 658 - 660.

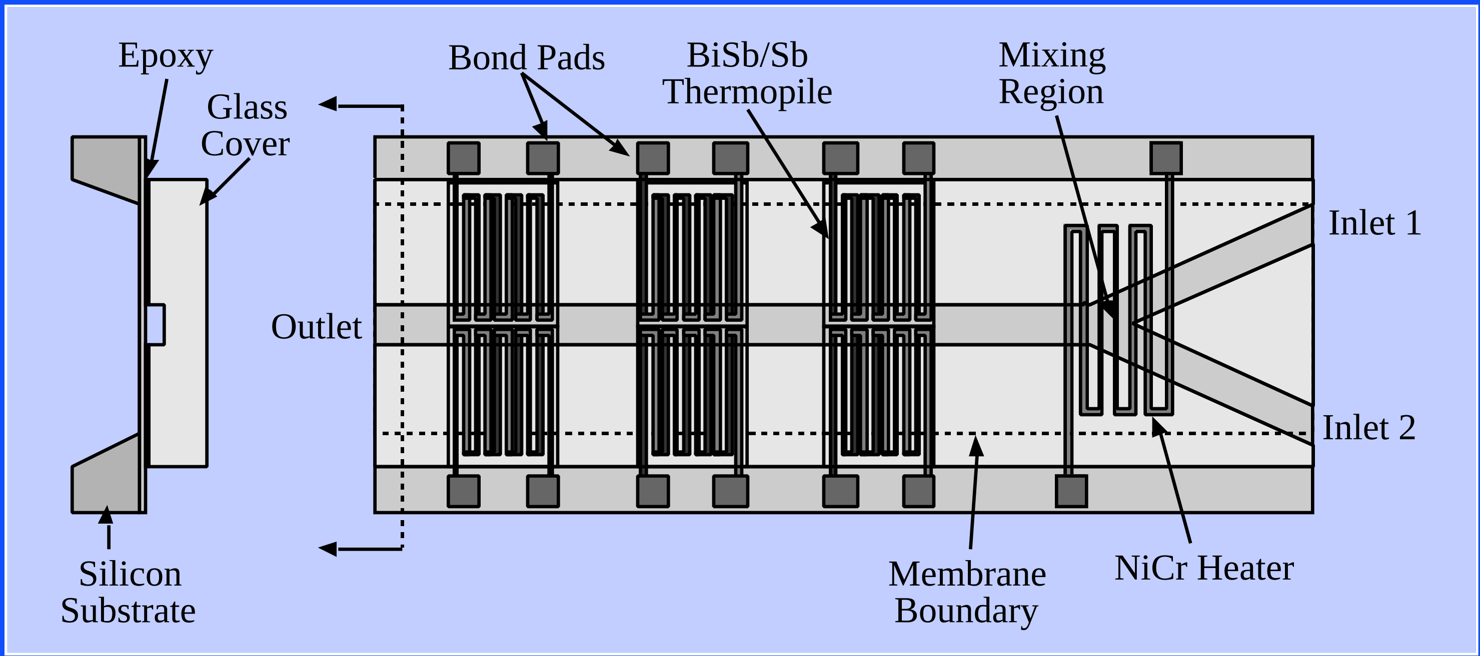
CALORIMETRIC CHEMICAL SENSORS



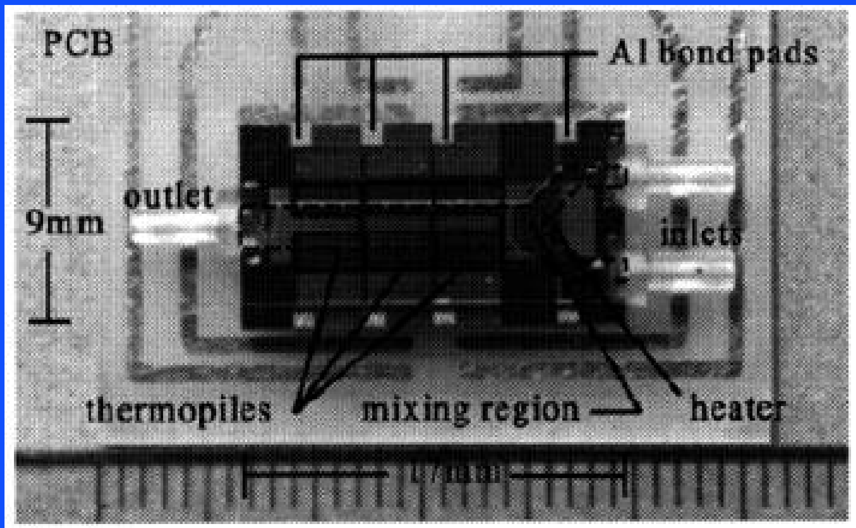
Reference: Zanini, M., Visser, J. H., Rimai, L., Soltis, R. E., Kovalchuck, A., Hoffman, D. W., Logothetis, E. M., Bonne, U., Brewer, L., Bynum, O. W., and Richard, M. A., "Fabrication and Properties of a Si-Based High Sensitivity Microcalorimetric Gas Sensor," Proceedings of the 1994 Solid-State Sensor and Actuator Workshop, Hilton Head Island, SC, June 13 - 16, 1994, pp. 176 - 178.

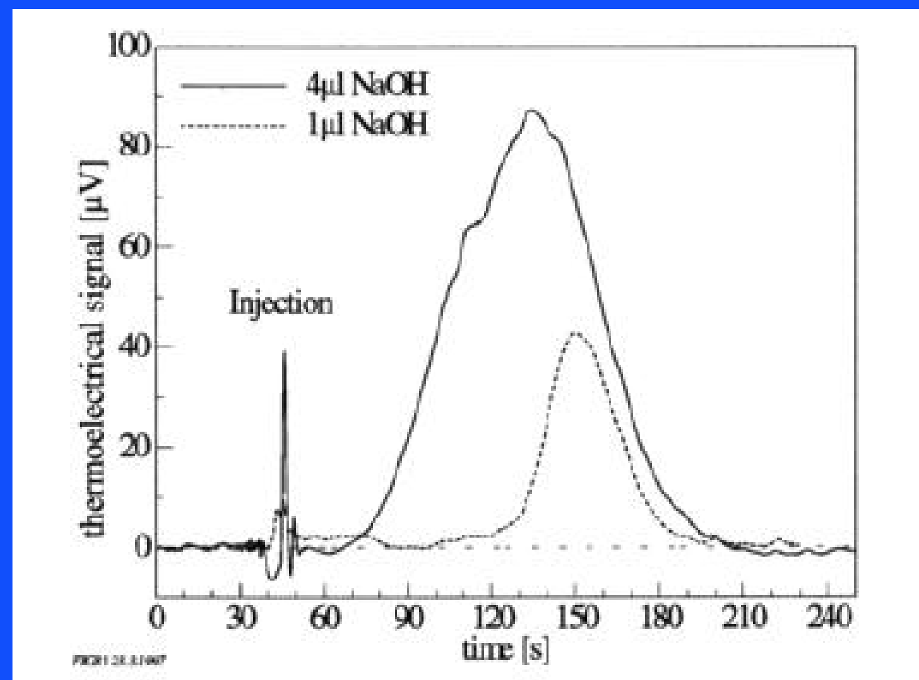
- **Heat of reaction is used to detect chemicals (catalyst leads to combustion and extra heat released).**
- **Works well for hydrocarbons, etc., (typical 0 - 4000 ppm).**
- **Poor selectivity, but can be used in arrays with neural networks or other combinatorial approaches.**

FLOW-THROUGH CALORIMETER



Reference: Zieren, M., and Köhler, J. M., "A Micro-Fluid Channel Calorimeter Using BiSb/Sb Thin Film Thermopiles," Proceedings of Transducers '97, the 1997 International Conference on Solid-State Sensors and Actuators, Chicago, IL, June 16 - 19, 1997, vol. 1, pp. 539 - 542.





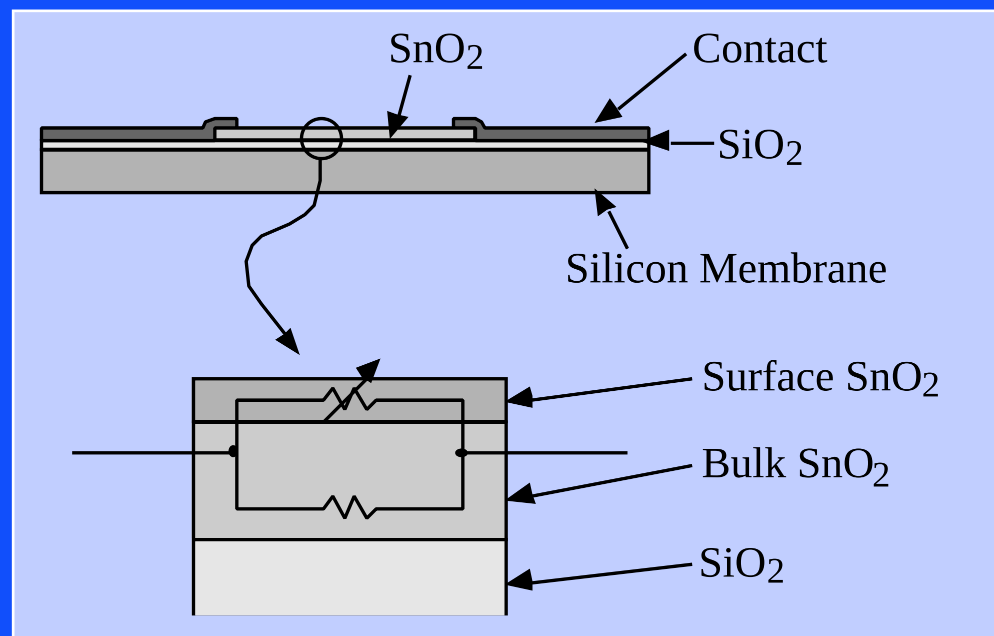
Source: Zieren, M., and Köhler, J. M., "A Micro-Fluid Channel Calorimeter Using BiSb/Sb Thin Film Thermopiles," Proceedings of Transducers '97, the 1997 International Conference on Solid-State Sensors and Actuators, Chicago, IL, June 16 - 19, 1997, vol. 1, pp. 539 - 542.

METAL OXIDE GAS SENSORS

- Direct modulation of resistance of (generally heated) metal oxides by gases adsorbing at the surface.
- Example: SnO_2, oxygen raises the resistance (removes electrons) and combustible gases lower the resistance (remove adsorbed oxygen, liberating electrons).
- Generally, a catalyst is used on the surface to promote the reactions.
- The overall thickness of the film should be as small as possible to maximize sensitivity (only the surface material is affected and is in parallel with the bulk resistance).

$$H_2 + O^- \longrightarrow H_2O + e^-$$

$$O_2 + 2e^- \longrightarrow 2\,O^-$$

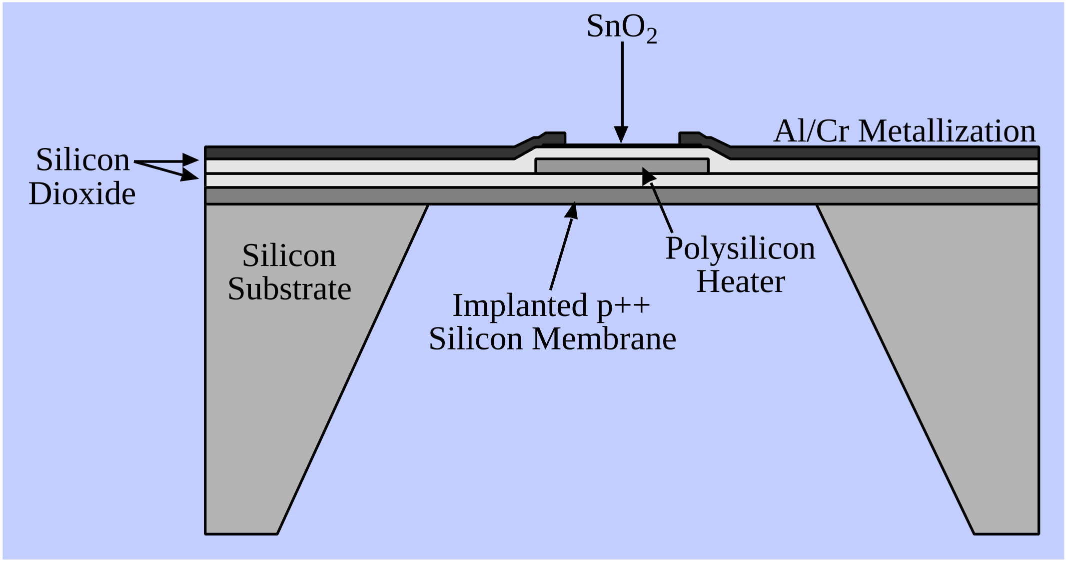


EXAMPLE METAL OXIDE SENSORS

Semiconductor	Suggested Additives	Gas to Be Detected	Reference
$BaTiO_3$/CuO	La_2O_3, $CaCO_3$	CO_2	Haeusler and Meyer (1995)
SnO_2	Pt + Sb	CO	Morrison (1994)
SnO_2	Pt	alcohols	Morrison (1994)
SnO_2	Sb_2O_3 + Au	H_2, O_2, H_2S	Morrison (1994)
SnO_2	CuO	H_2S	Tamaki, et al. (1997)
ZnO	V, Mo	halogenated hydrocarbons	Morrison (1994)
WO_3	Pt	NH_3	Morrison (1994)
Fe_2O_3	Ti-doped + Au	CO	Morrison (1994)
Ga_2O_3	Au	CO	Schwebel, et al. (1997)
MoO_3	none	NO_2, CO	Guidi, et al. (1997)
In_2O_3	none	O_3 (ozone)	Wlodarski, et al. (1997)

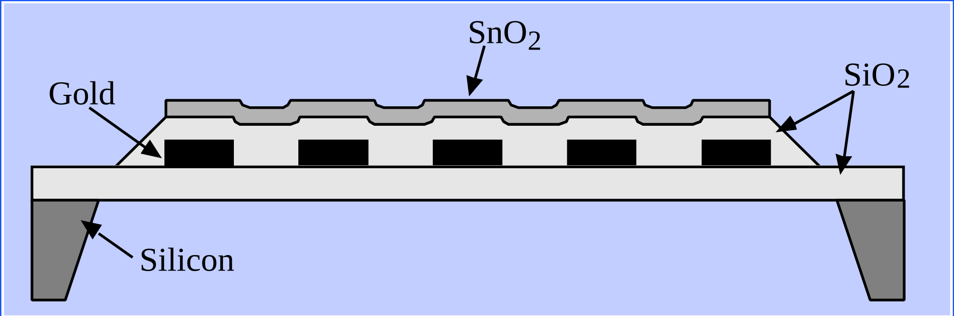
BASIC VERSUS CATALYZED REACTIONS: REDUCING THE ACTIVATION ENERGY FOR COMBUSTION

BASIC REACTIONS	CATALYZED REACTIONS
$H_2 \longrightarrow 2H$	$H_2 + 2\,Pt \longrightarrow 2(Pt - H)$
$O_2 \longrightarrow 2\,O$	$O_2 + 2Pt \longrightarrow 2(Pt - O)$
$2H + O \longrightarrow H_2O$	$2(Pt - H) + (Pt - O) \longrightarrow 3Pt + H_2O$



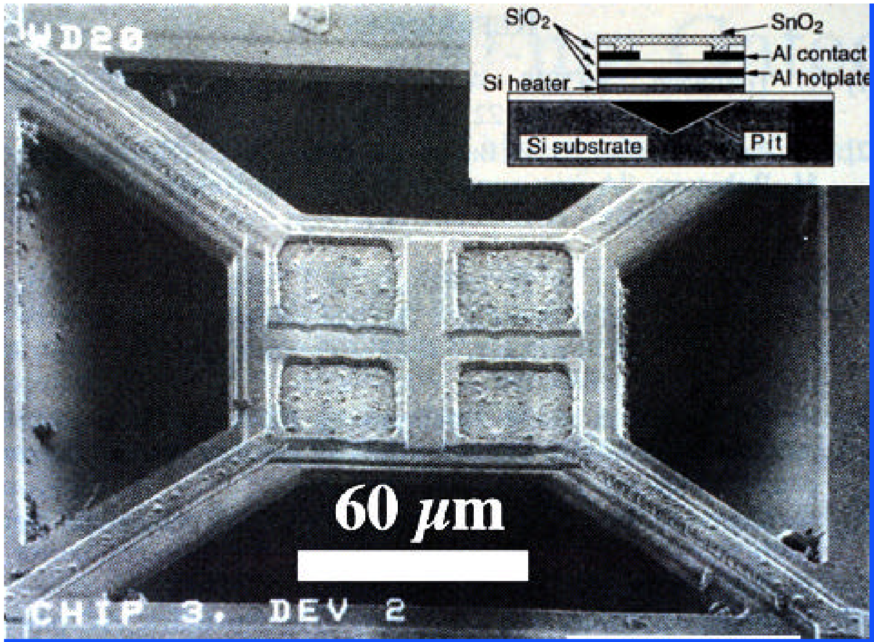
Reference: Chang, S.-C., and Hicks, D. B., "Tin Oxide Microsensors on Thin Silicon Membranes," Record of the IEEE Solid-State Sensors Workshop, 1986 (no page numbers used).

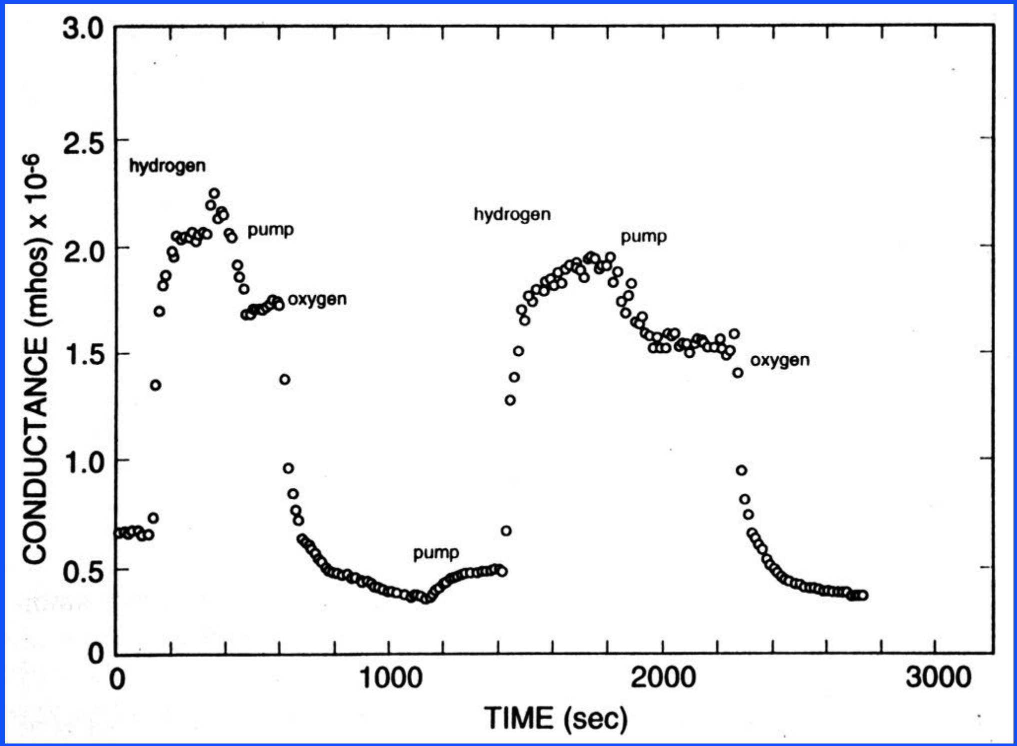
- **SnO_2, as shown in these CO sensor designs, can be sputter-deposited.**
- **Thermally-isolated membranes and other structures permit low-power operation at the elevated temperatures required (300°C for SnO_2).**



Reference: Demarne, V. and Grisel A., "An Integrated Low-Power Thin-Film CO Sensor on Silicon," Sensors and Actuators, vol. 13, 1988, pp. 301 -314.

POST-CMOS GAS SENSOR

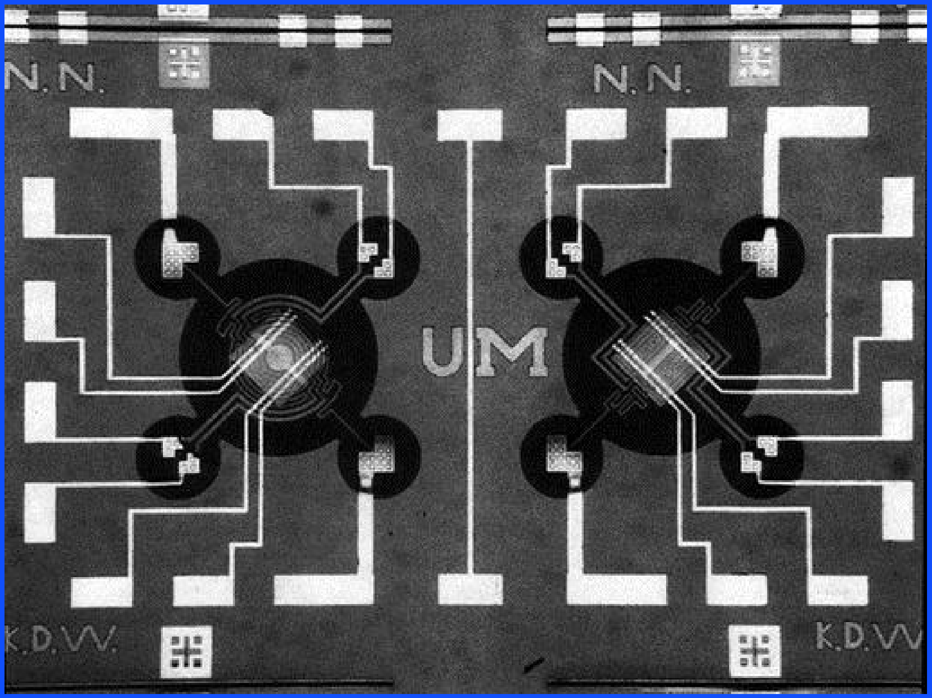


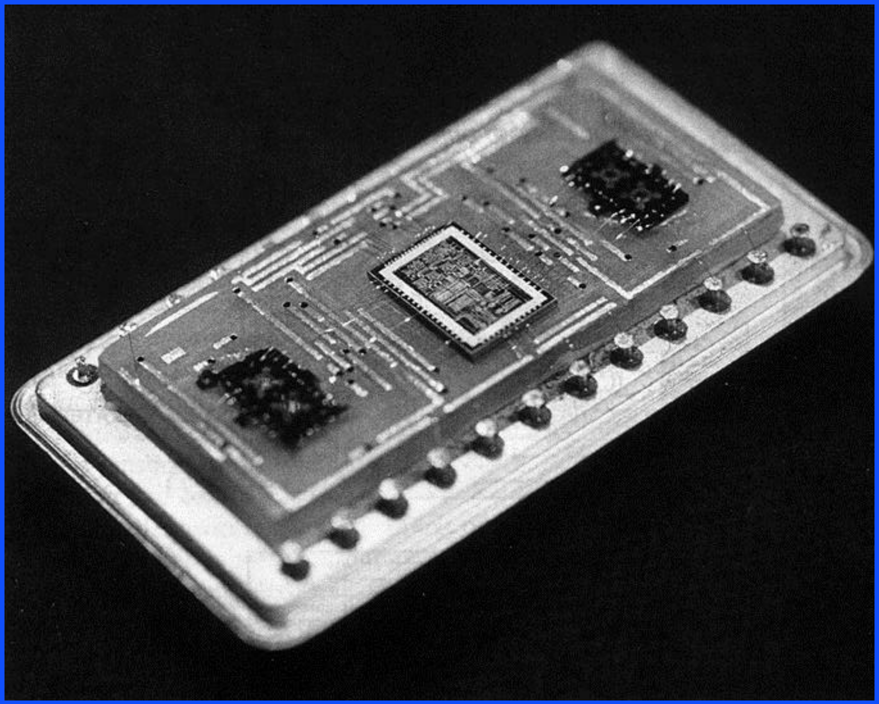


- Following a standard CMOS (MOSIS) process, EDP etching was used to undercut the sensor platforms.
- Reactive sputtering with heating of the platforms at the same time was used to deposit SnO_2.
- Responses down to 1 ms and thermal resistancs up to 8,000 K/W have been achieved.

Source: Suehle, J. S., Cavicchi, R. E., Gaitan, M., and Semancik, S., “Tin Oxide Gas Sensor Fabricated Using CMOS Micro-Hotplates and In-Situ Processing,” IEEE Electron Device Letters, vol. 14, no. 3, Mar. 1993, pp. 118 - 120.

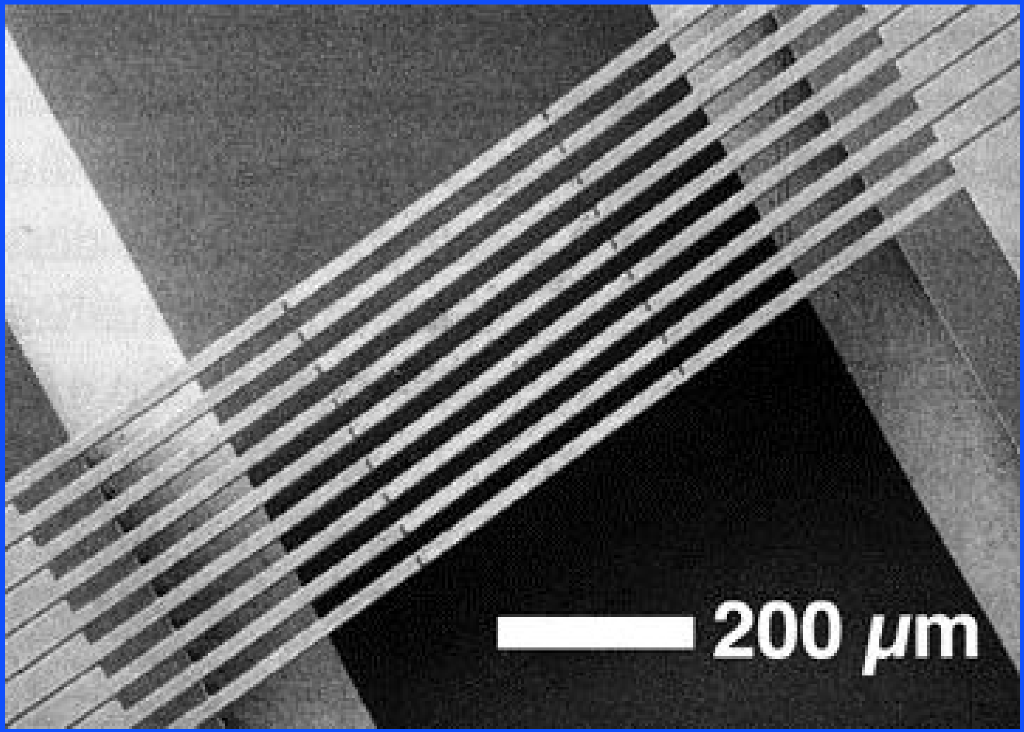
COMBINED GAS AND TEMPERATURE SENSOR: CHEMICAL AND THERMAL





Source: Johnson, C. L., Wise, K. D., and Schwank, J. W., "A Thin-Film Gas Detector for Semiconductor Process Gases," Digest of the International Electron Devices Meeting (IEDM), Washington, DC, Dec. 1988, p. 662.

FIGHTING THE SELECTIVITY PROBLEM: ARRAY GAS SENSORS



Array of three types of relatively non-selective catalytic metal gas sensors operated at three different temperatures each to improve selectivity.

Source: Fluitman, J. H., van den Berg, A., and Lemmerink, T. S., "Micromechanical Components for μTAS," Micro Total Analysis Systems, Proceedings of μTAS '94 Workshop, Twente, Netherlands, Nov. 21 - 22, 1994, pp. 73 - 83.

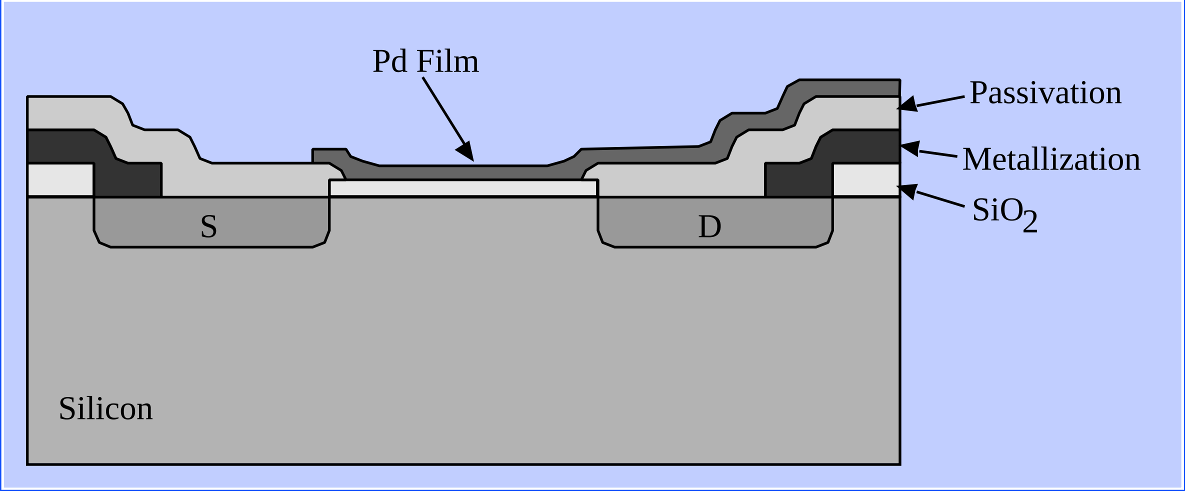
PLATINIDE HYDROGEN SENSORS

- Pd-gate FET operates due to adsorpition of H_2 (in some cases H_2S and NH_3) onto Pd, dissociation into H atoms and rapid diffusion of H atoms through Pd to adsorb at the metal/oxide interface, changing the work function, seen as a threshold voltage shift,

$$\Delta V_T = \frac{-\mu N \theta}{\varepsilon_o}$$

μ = dipole moment of interfacial hydrogen
N = density of adsorption sites
θ = fraction of surface sites covered, $0 < \theta < 1$
ε_o = dielectric permittivity of free space

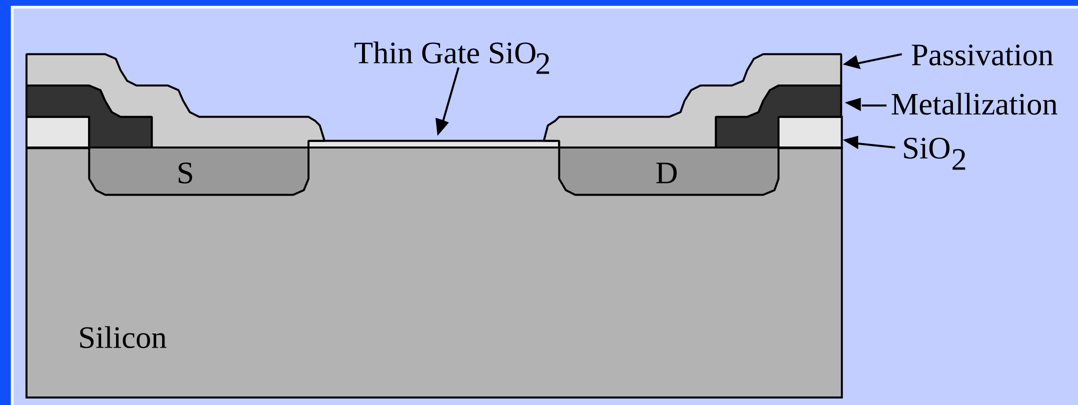
- Other gases that release hydrogen (H_2S, NH_3, etc.) can also be detected.

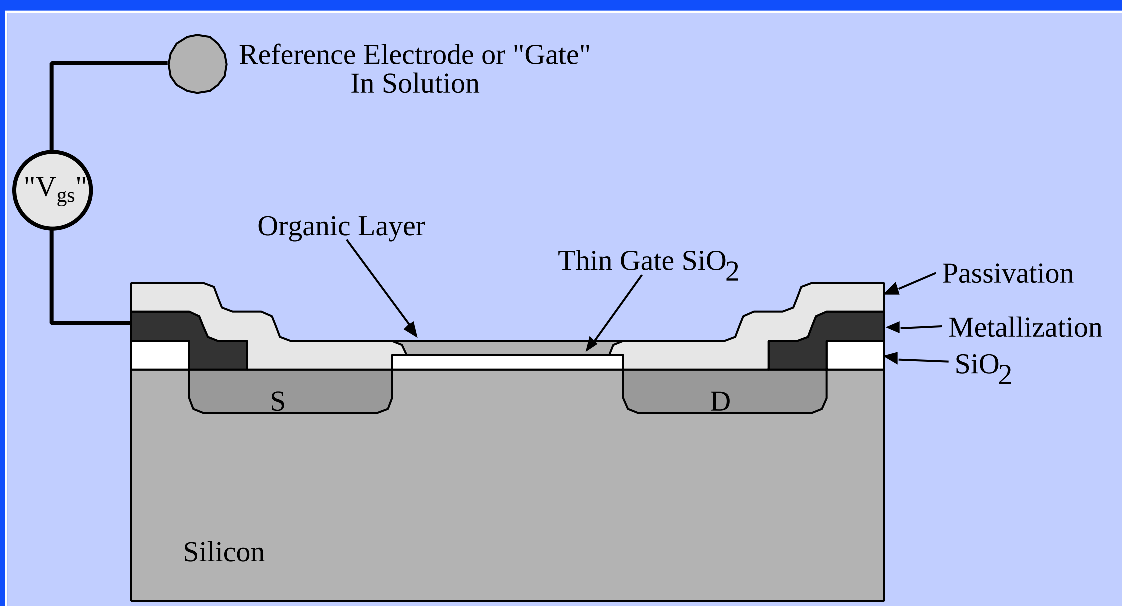


Reference: Lundstrom, I., Shivaraman, S., Svensson, C., and Lundkvist, L., "Hydrogen Sensitive MOS Field-Effect Transistor," Applied Physics Letters, vol. 26, 1975, pp. 55 - 57.

ISFET/CHEMFET STRUCTURES

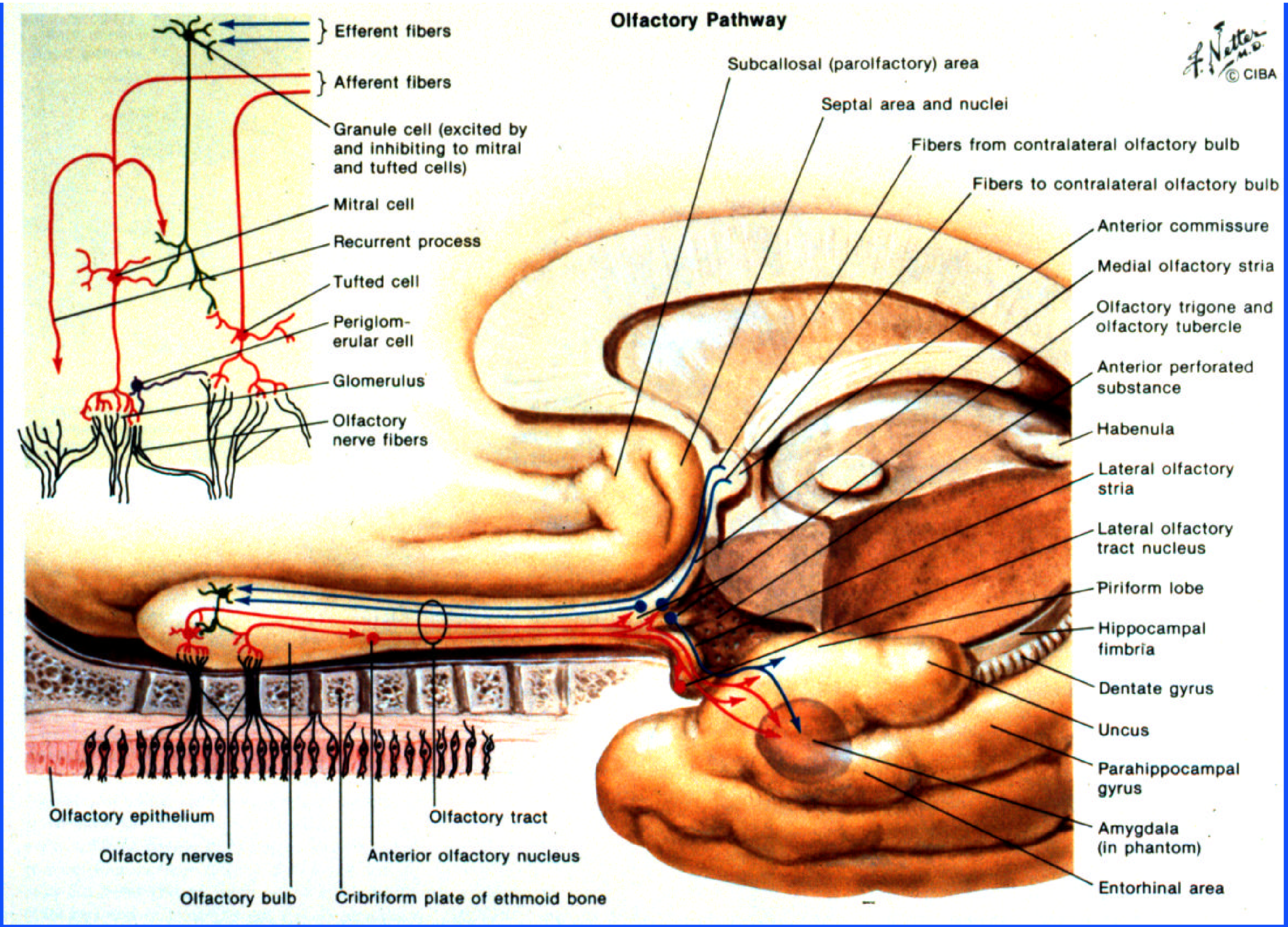
- **The ISFET is essentially an "open-gate" MOSFET.**
- **Hydrogen ions react with surface SiO_2 to form $SiOH_2^+$, functioning as a pH sensor.**
- **Non-specific adsorption can be a problem.**





- **The CHEMFET uses an additional organic layer (e.g. ion-selective) for more specific interactions.**
- **Screen printing or dip coating are often used to apply the layer(s).**

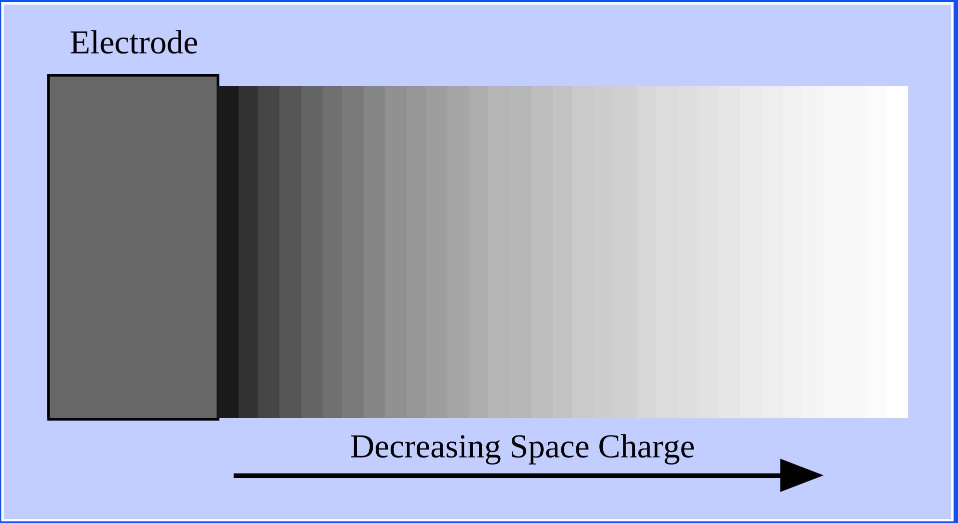
References: Bergveld, P., "Future Applications of ISFETs," Sensors and Actuators, vol. B4, nos. 1 - 2, May 1991, pp. 125 - 133, and Madou, M. J., and Morrison, S. R., "Chemical Sensing with Solid State Devices," Academic Press, Inc., Boston, MA, 1989.



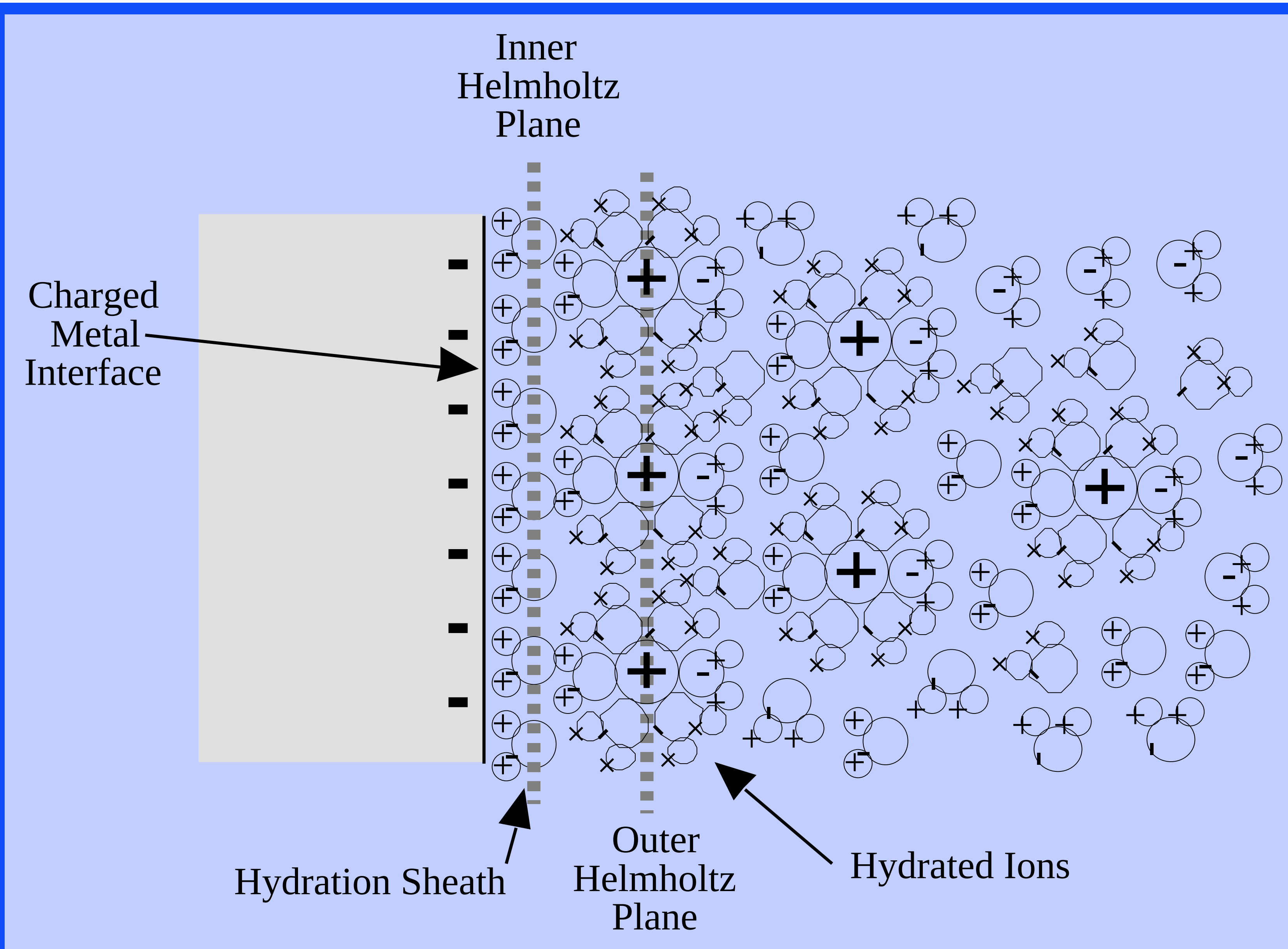
Source: Netter, F., "The CIBA Collection of Medical Illustrations: Volume 1, Nervous System, Part 1, Anatomy and Physiology," CIBA-GEIGY Corp., 1983.

ELECTROCHEMICAL TRANSDUCERS

- As opposed to electronic circuits, there are many more carriers (and they are roughly six order of magnitude lower mobility) in ionic solutions.
- A metal structure placed into an ionic solution, metal ions form due to oxidation, leaving behind electrons... eventually a space charge builds up and electrochemically opposes the oxidation reaction.



Carrier or Ion	Mobility, μ, in $cm^2/(s \cdot V)$
electron in Si	1.35×10^{3}
hole in Si	4.80×10^{2}
H^+ in H_2O	3.63×10^{-3}
OH^- in H_2O	2.05×10^{-3}
Cl^- in H_2O	7.91×10^{-4}
K+ in H_2O	7.62×10^{-4}
NH_4^+ in H_2O	7.61×10^{-4}
ClO_4^- in H_2O	7.05×10^{-4}
Na^+ in H_2O	5.19×10^{-4}
HCO_3^- in H_2O	4.61×10^{-4}
Li^+ in H_2O	4.01×10^{-4}



Inner Helmholtz Plane
Charged Metal Interface
Hydration Sheath
Outer Helmholtz Plane
Hydrated Ions

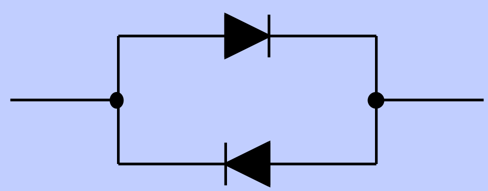
NONLINEARITY OF ELECTRODES

- **For large signals (large enough to carry out electrochemical reactions), electrodes are extremely nonlinear.**
- **The Butler-Volmer equation models its diode-like I-V characteristics.**

$$J = J_o\left(e^{\frac{(1-\beta)z\eta_t F}{RT}} - e^{\frac{-\beta z\eta_t F}{RT}}\right)$$

$$J = J_o\left(e^{\frac{qV}{\eta kT}} - e^{\frac{-qV}{\eta kT}}\right)$$

$$V_T = \frac{kT}{q} = \frac{RT}{F}$$



SENSING WITH ELECTRODES

- Sensing can be done potentiometrically or amperometrically.
- Potentiometry uses the characteristic potentials of reactions to identify them.
- The Nernst Equation gives the relationship between potential and concentrations of species. Example: pH with a metal oxide electrode:

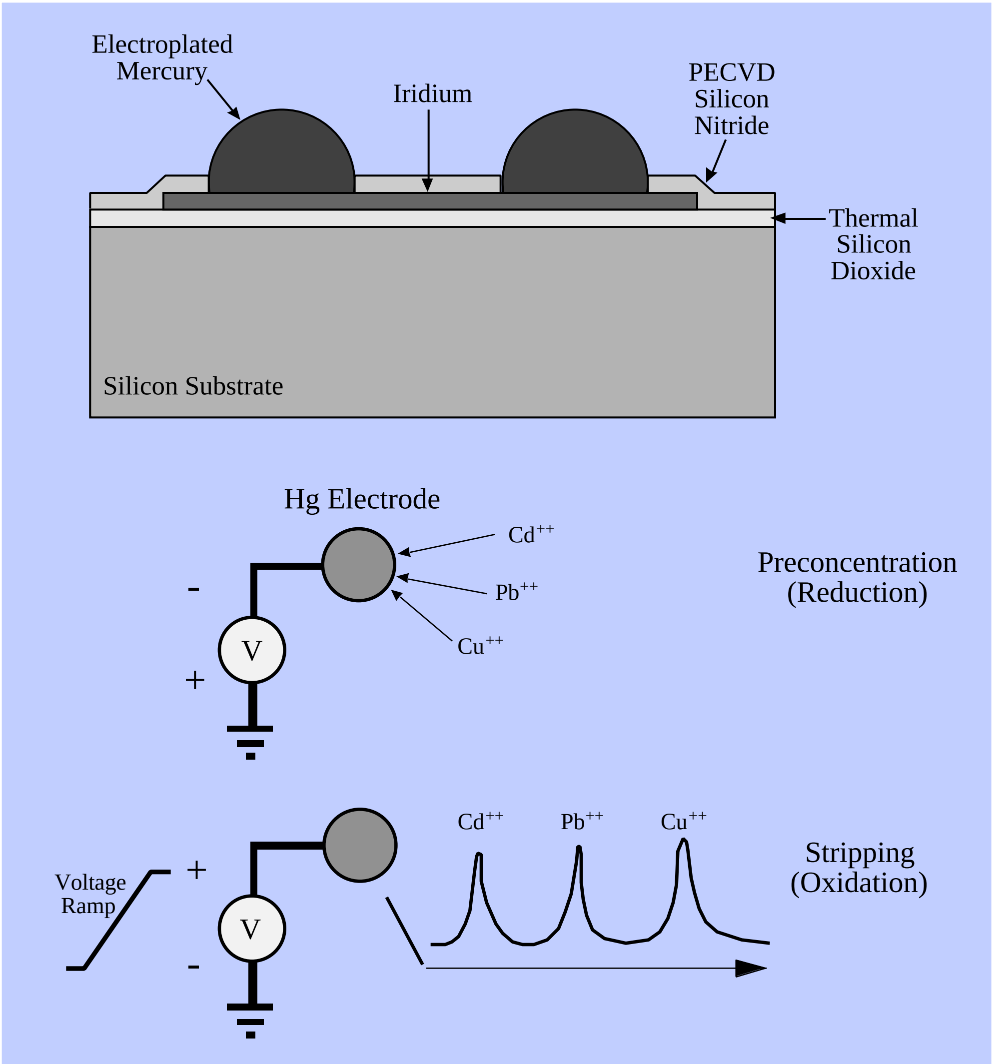
$$E = E^{o} + \frac{RT}{F}\ln\left(\frac{a_{MeO(OH)}\left[MeO(OH)\right]}{a_{MeO_2}\left[MeO_2\right]}\right) + \frac{RT}{F}\ln\left(a_{H^+}\right)$$

- Amperometry uses the limiting (maximum) current that can be carried by a reaction to measure the concentration of the rate limiting species using:

$$i_L(t) = nFAC\sqrt{\frac{D}{\pi t}} + \frac{nFACD}{r}$$

- The first term gives time domain info (Cottrell Equation) and the second gives the steady-state current.

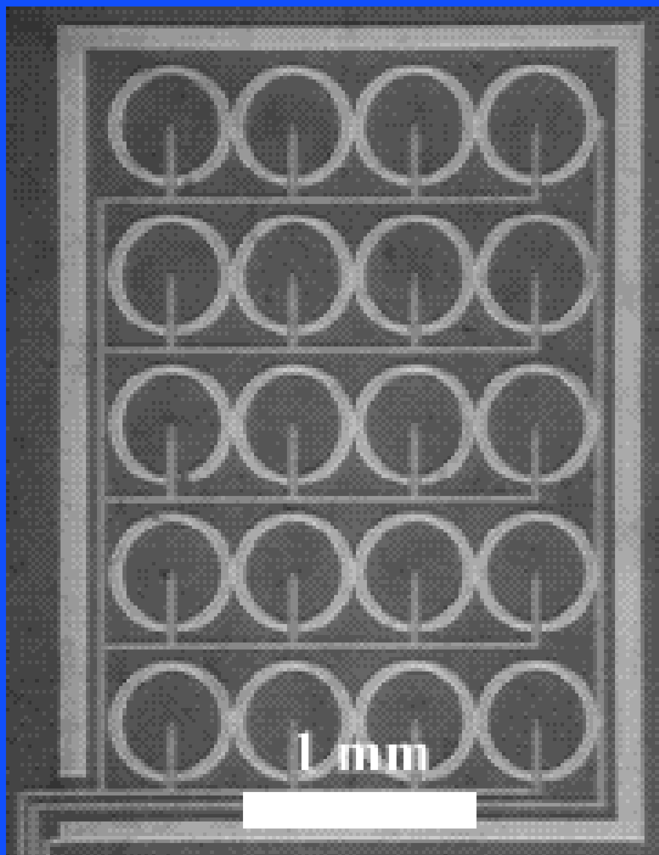
MICROELECTRODE VOLTAMMETRY

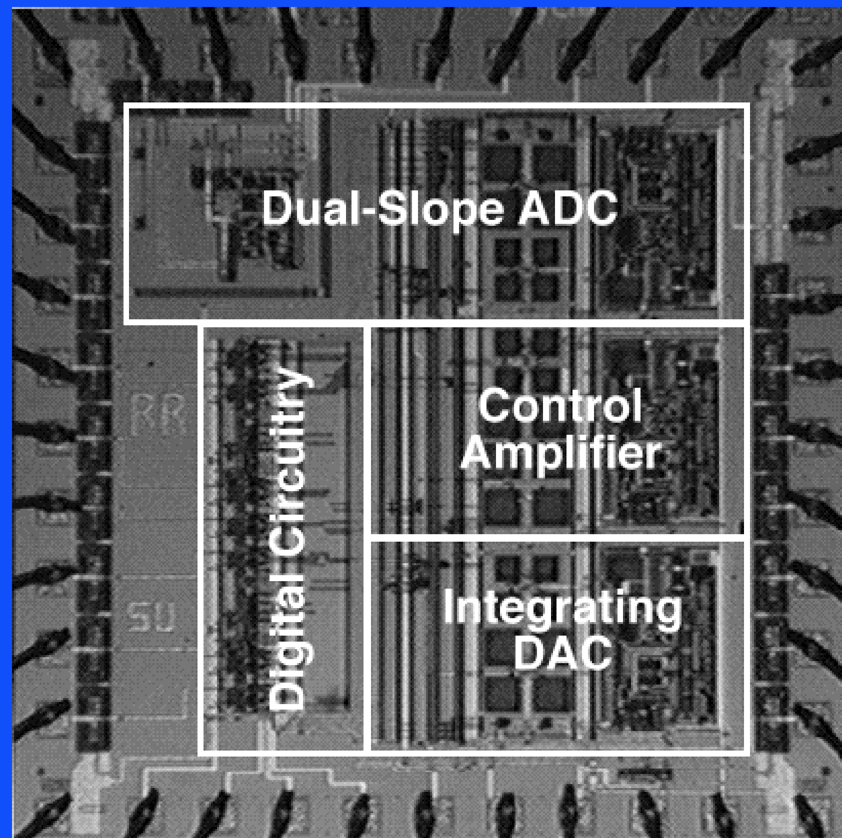


- **Thin-film iridium electrodes with mercury hemispheres allow preconcentration and stripping of heavy metal ions.**
- **Sensitivity down to below 1 PPB.**
- **An integrated potentiostat chip completed the two-chip sensor system and provided an 8-decade current input range.**

Reference: Kounaves, S. P., Deng, W., Hallock, P. R., Kovacs, G. T. A., and Storment, C. W., "Iridium-Based Ultramicroelectrode Array Fabricated by Microlithography," Analytical Chemistry, vol. 66, 1994, pp. 418 - 423.

STRIPPING VOLTAMMETRY SYSTEM

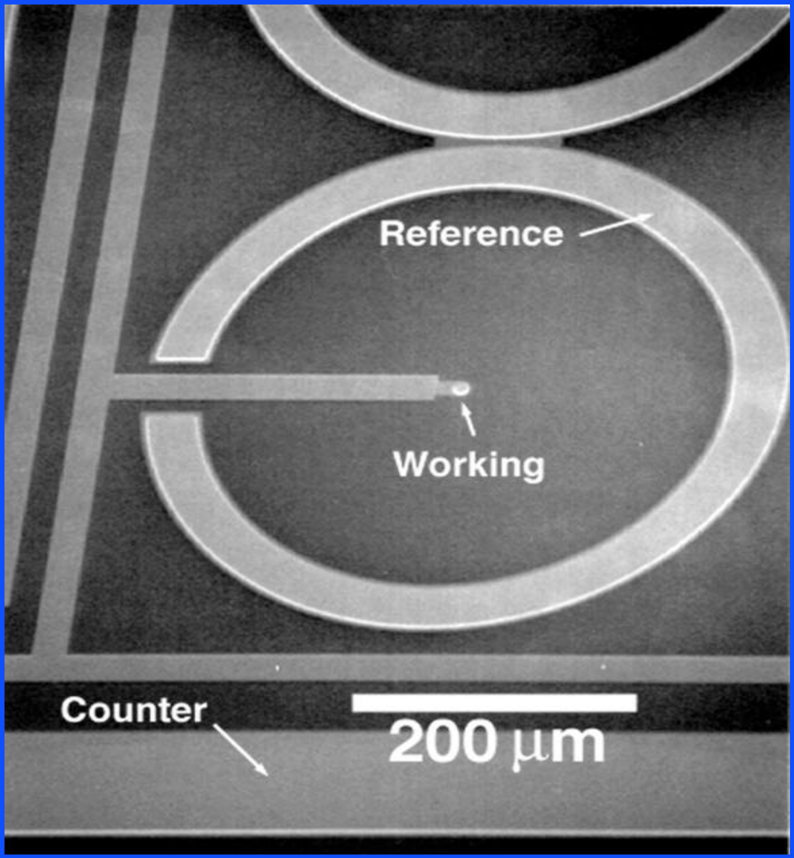


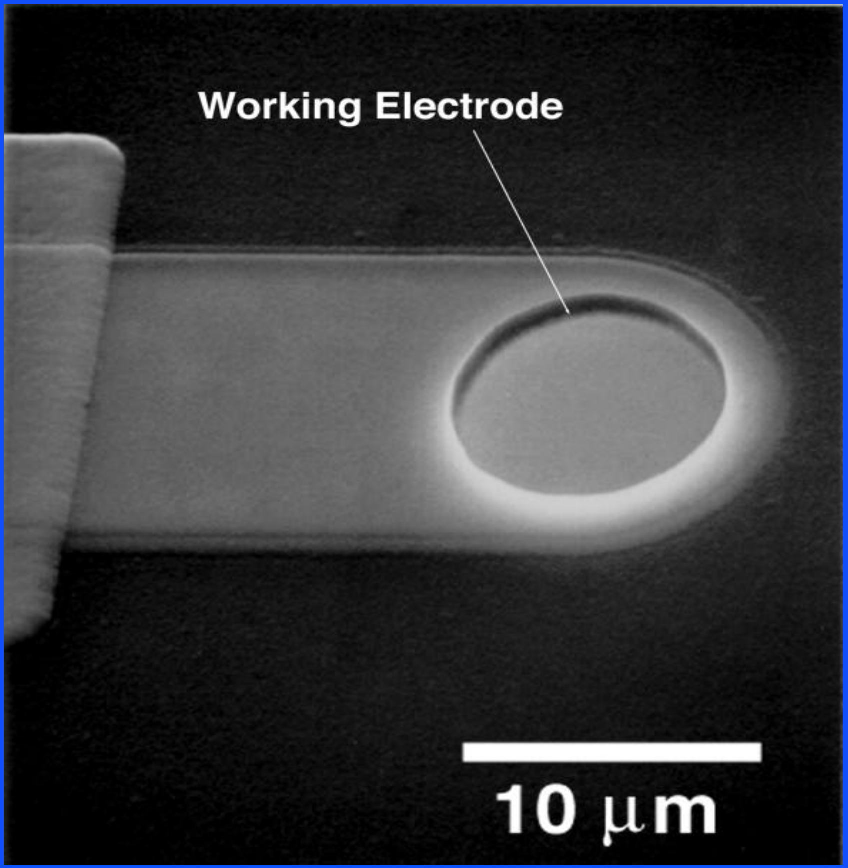


Reay, R. J., Kounaves, S. P., and Kovacs, G. T. A., "An Integrated CMOS Potentiostat for Miniaturized Electroanalytical Instrumentation,"Proceedings of the 1994 International Solid-State Circuits Conference, San Francisco, CA, Feb. 16 - 18, 1993, pp. 162 - 163.

Kovacs, G. T. A., Storment, C. W., and Kounaves, S. P., "Micromachined Heavy Metal Ion Sensor,"Sensors and Actuators B: Chemical, vol. 23, no. 1, pp. 41 - 47.

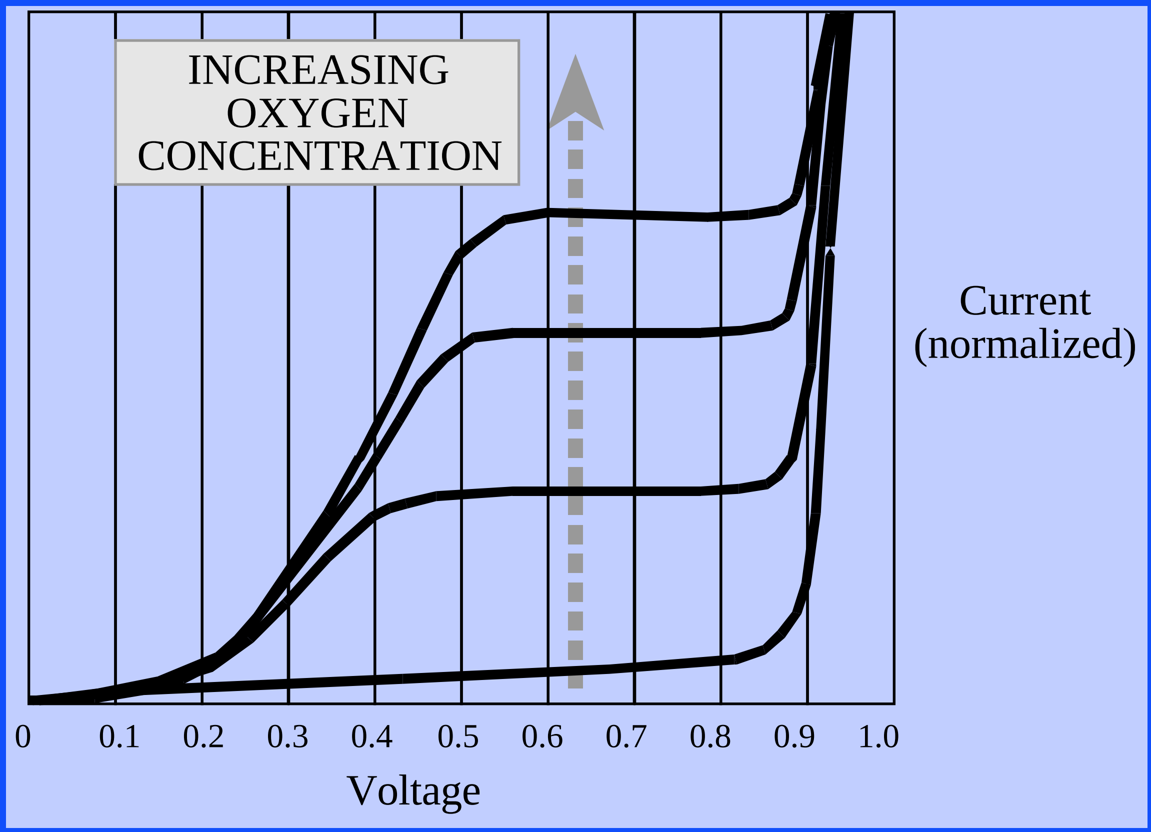
CARBIDE-COATED ION SENSOR FOR PROCESS FLUIDS





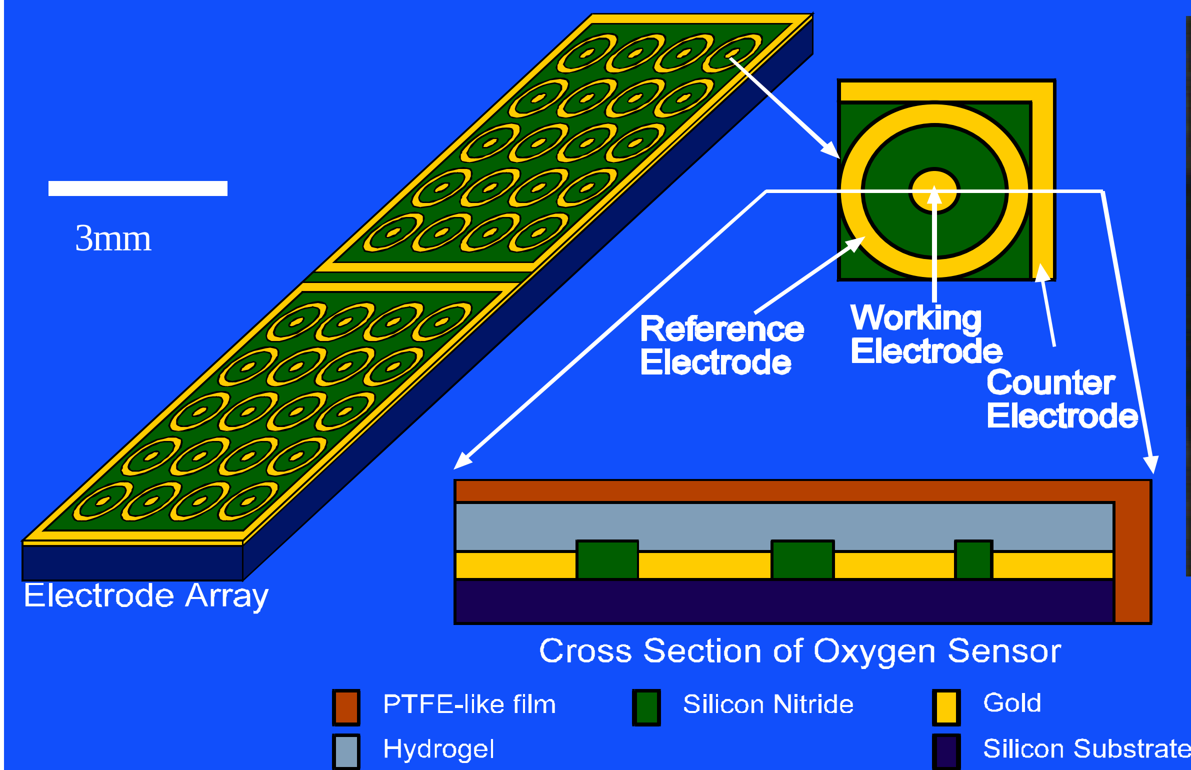
Reference: Flannery, A. F., Mourlas, N. J., Storment, C. W., Tsai, S., Tan, S. H., Heck, J., Monk, D., Gogoi, B., and Kovacs, G. T. A., "PECVD Silicon Carbide as a Chemically Resistant Material for Micromachined Transducers," Sensors and Actuators A, vol. 70, nos. 1 - 2, Oct. 1998, pp. 48 - 55.

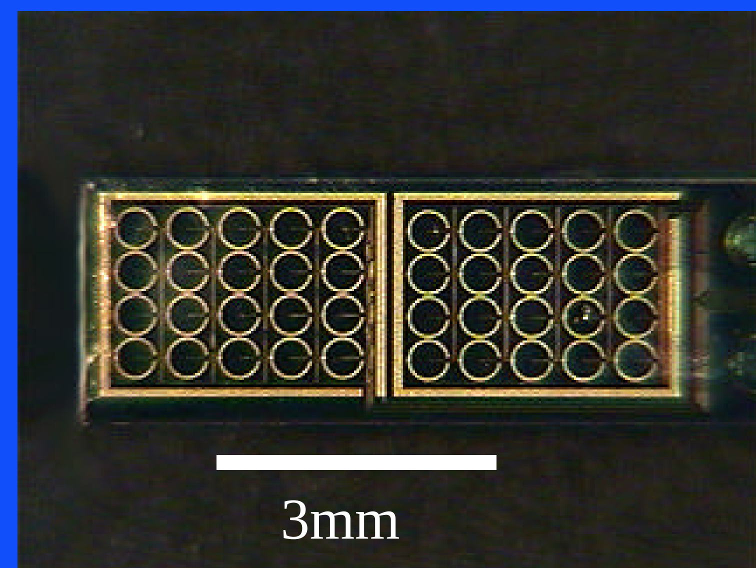
AMPEROMETRIC OXYGEN SENSOR (CLARK CELL)



Reference: Cobbold, R. S. C., "Transducers for Biomedical Measurements," John Wiley and Sons, New York, NY, 1974.

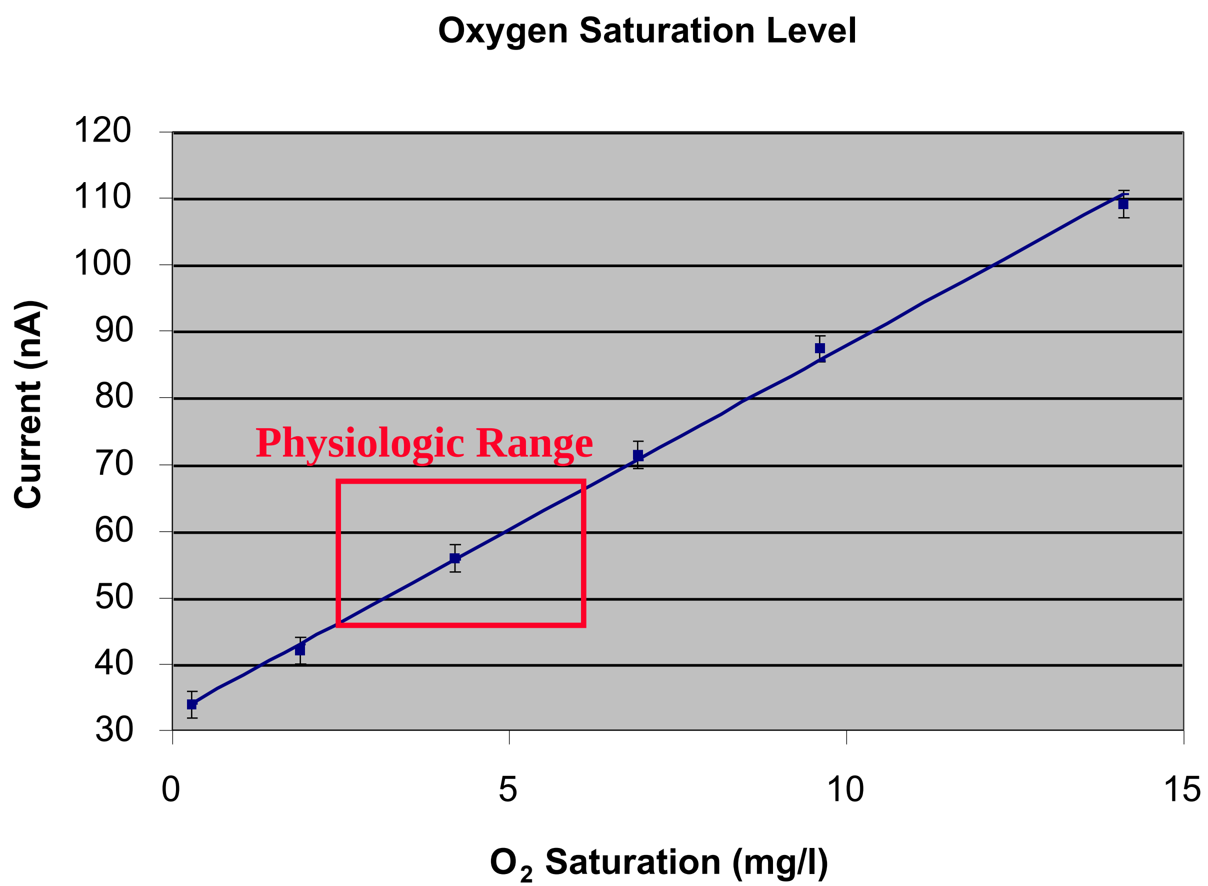
Miniaturized Clark Cell Oxygen Sensor





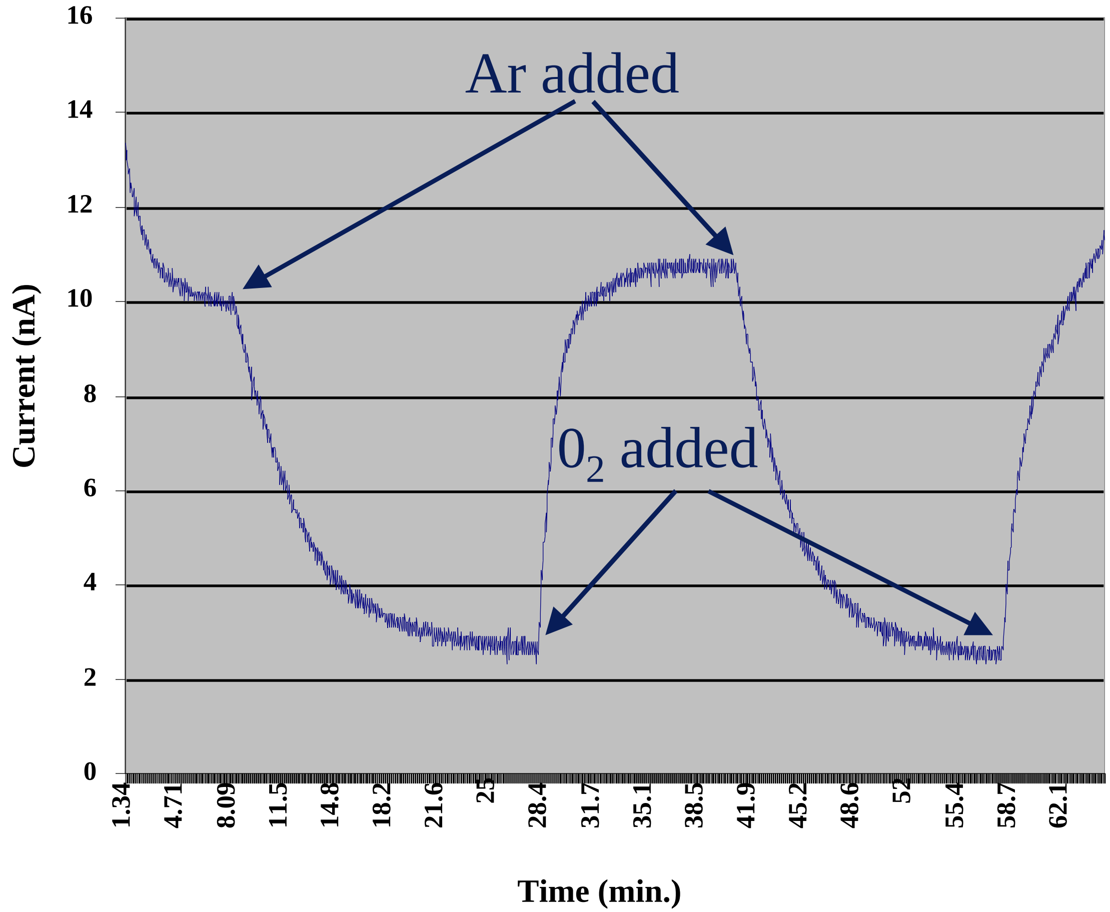
Courtesy G. McLaughlin, Stanford University.

CLARK CELL CALIBRATION RESULTS



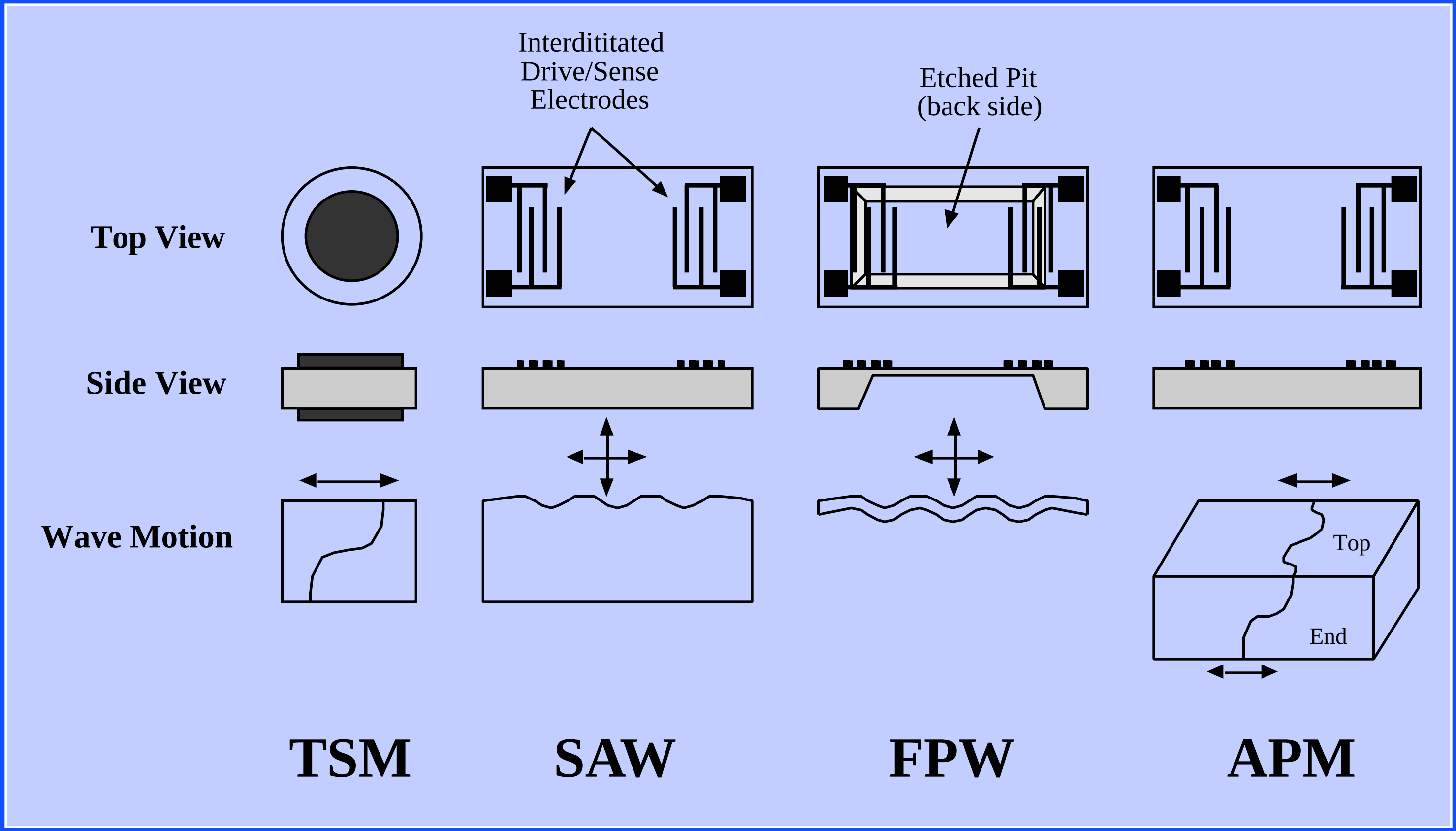
Courtesy G. McLaughlin, Stanford University.

CLARK CELL TIME RESPONSE



Courtesy G. McLaughlin, Stanford University.

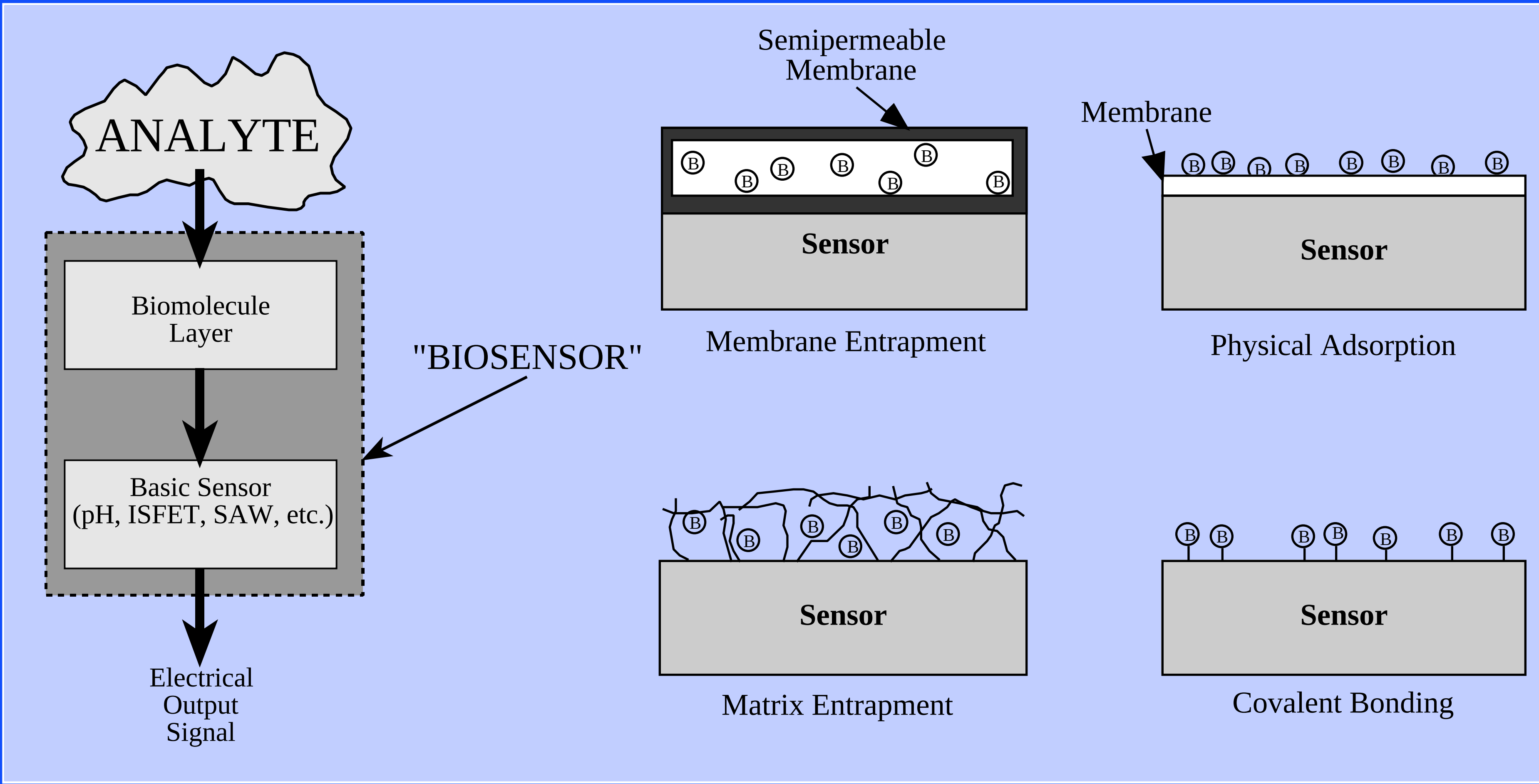
ACOUSTIC WAVE SENSORS



$$\Delta f = k f_o^2 \frac{\Delta m}{A}$$

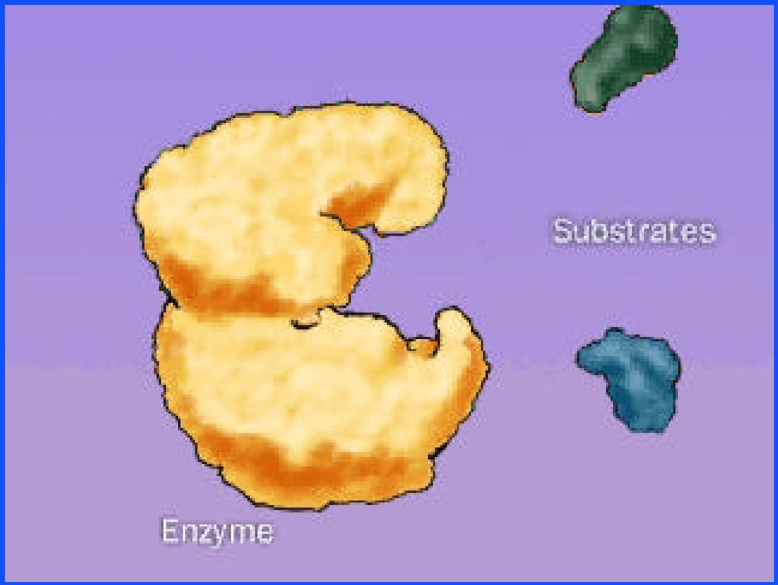
Reference: Grate, J. W., Martin, S. J., and White, R. M., “Acoustic Wave Microsensors,” Parts 1 and 2, Analytical Chemistry, vol. 65, 1993, pp. 940A - 948A and pp. 987A - 996A.

BIOMOLECULE-BASED SENSORS



Reference: Dewa, A. S., and Ko, W. H., "Biosensors," Chapter 9 in Semiconductor Sensors, S. M. Sze (ed.), John Wiley and Sons, Inc., New York, NY, 1994, pp. 415 - 472.

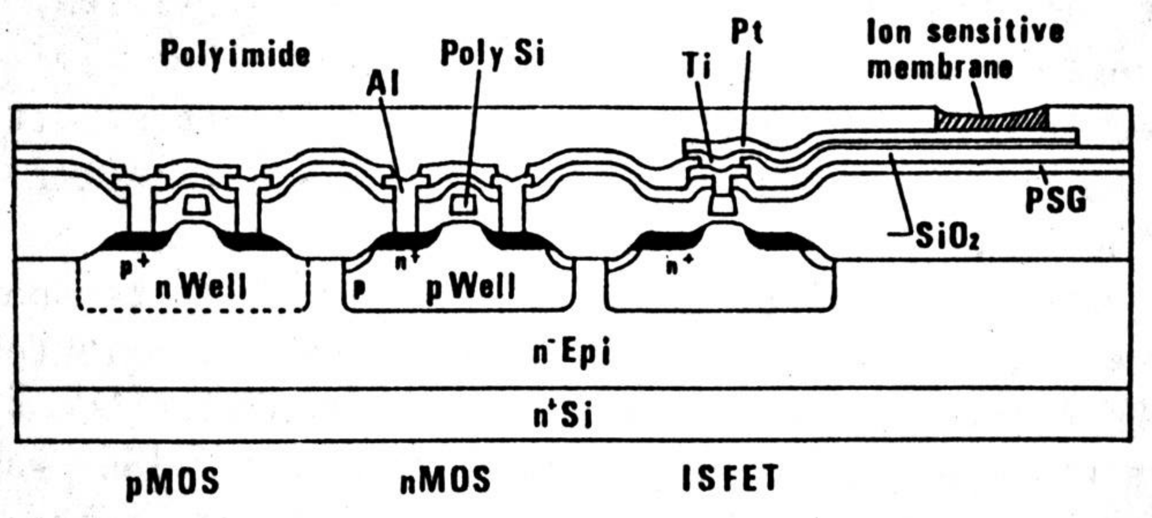
ENZYMES

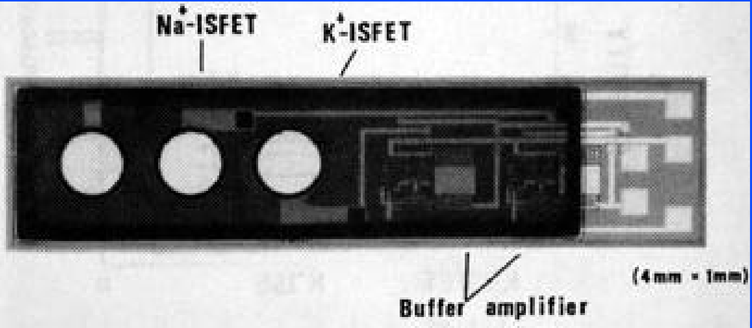


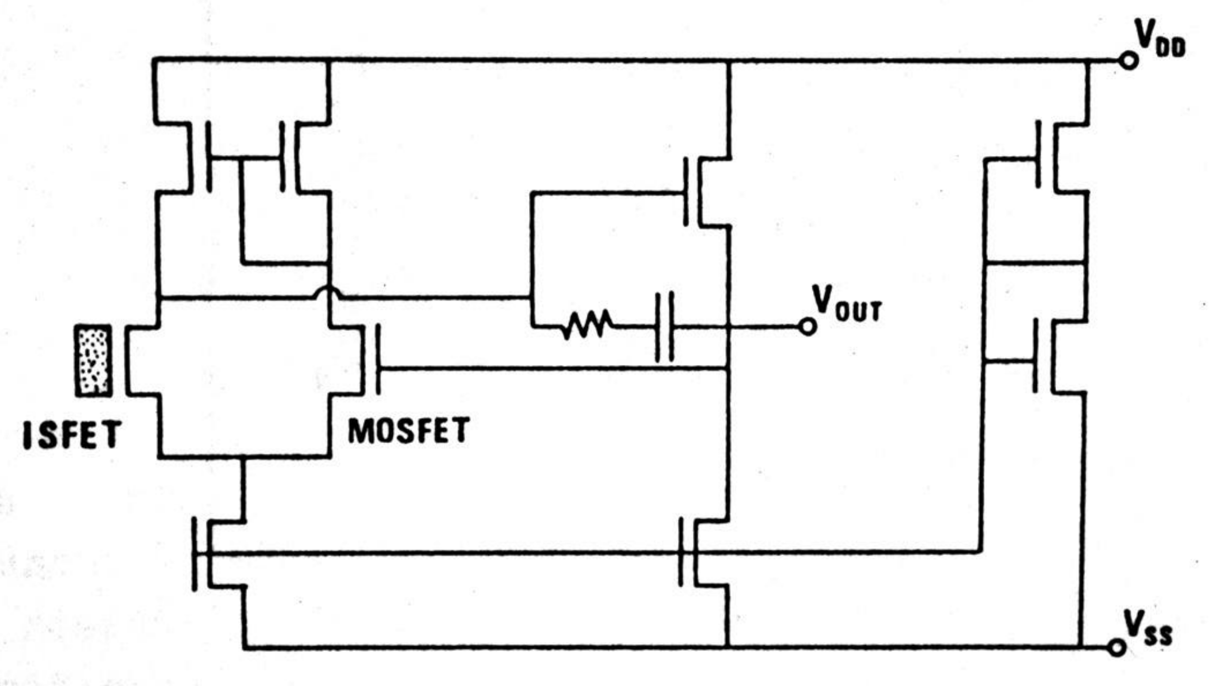
Movie courtesy Prof. H. C. Heller, Stanford University.

Source: Purves, Orians, Heller, and Sadava, "Life: The Science of Biology," Sinauer Associates/W.H. Freeman & Co., New York, 1999.

Analyte	Enzyme	Sensed Species
Glucose	Glucose Oxidase	H_2O_2 or O_2
L-Amino Acids	L-Amino Acid Oxidase	H_2O_2
Alcohols	Alcohol Oxidase	O_2
Uric Acid	Uricase	O_2
Phosphate	Phosphatase/Glucose Oxidase	O_2

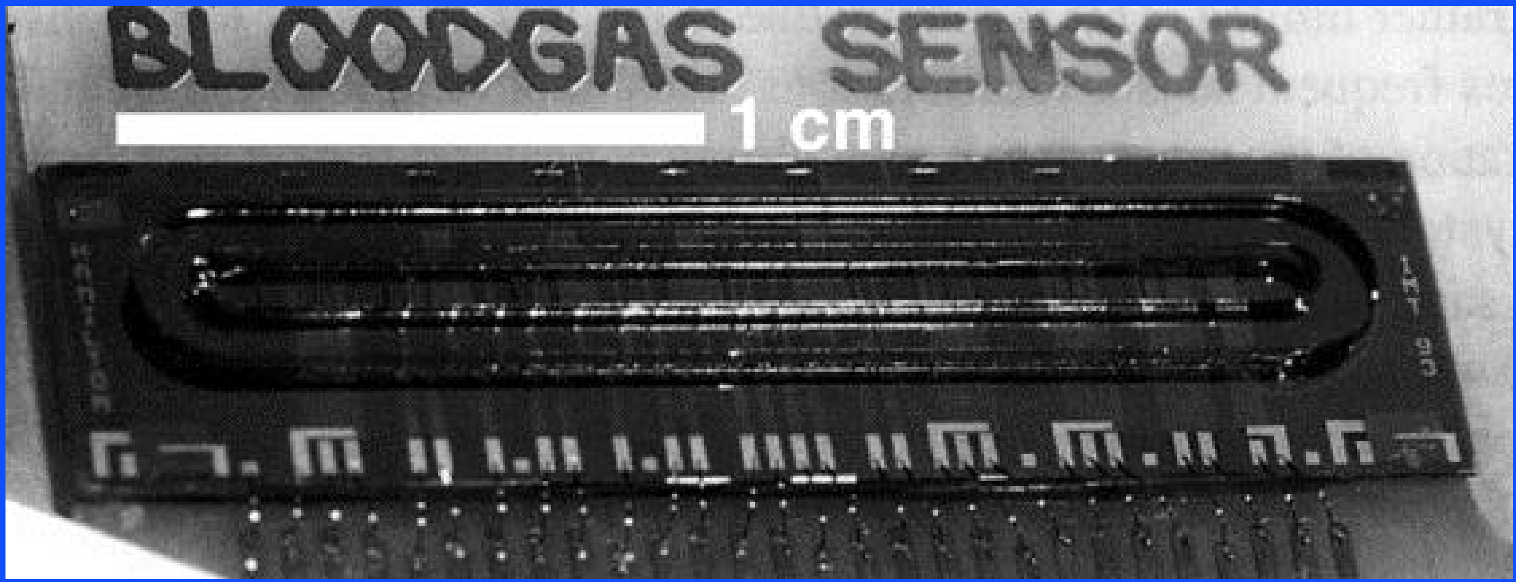






Source: Tsukuda, K., Miyahara, Y., Shibata, Y., and Miyagi, H., "An Integrated Micro Multi-Ion Sensor Using Platinum-Gate Field-Effect Transistors," Proceedings of Transducers '91, the 1991 International Conference on Solid-State Sensors and Actuators, San Francisco, CA, June 24 - 27, 1991, pp. 218 - 221.

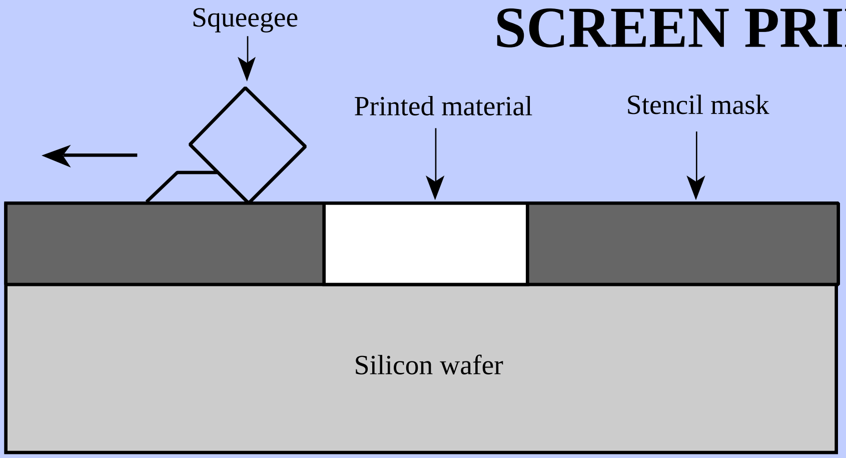
MULTISENSOR ARRAY FOR BLOOD GASES

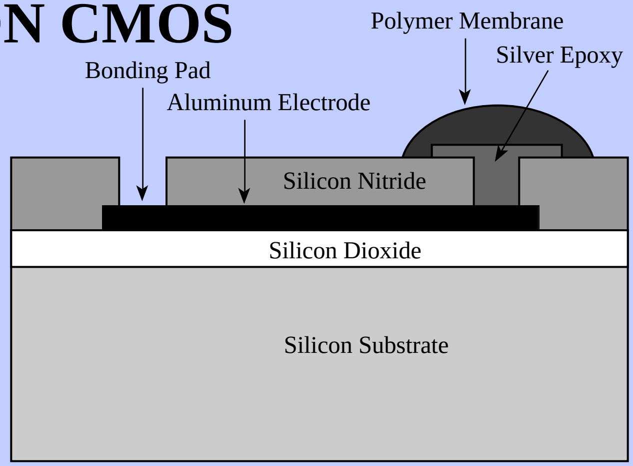


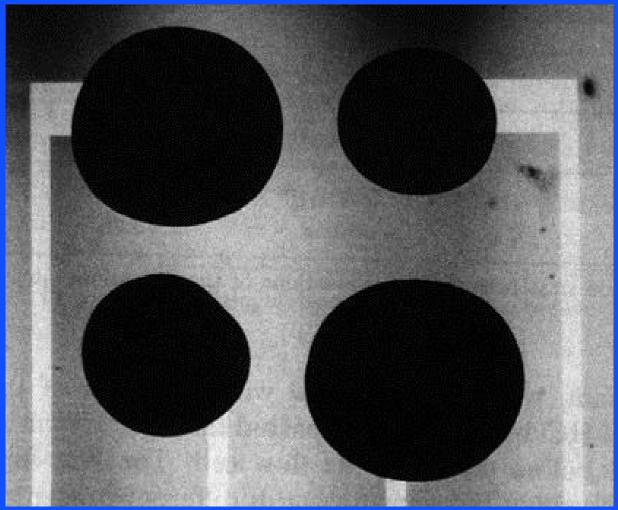
Includes pH, pCO_2 and PO_2 sensors.

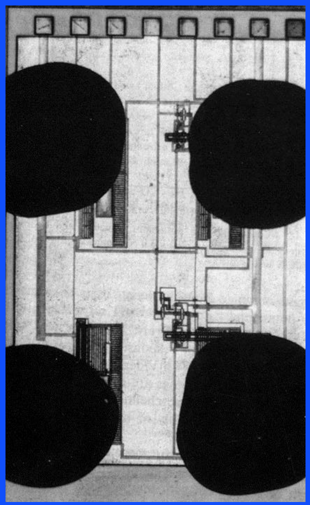
Source: Arquint, P., van der Schoot, B. H., and de Rooij, N. F., "Combined Blood Gas Sensor for pO_2, pCO_2 and pH," Micro Total Analysis Systems, Proceedings of µTAS '94 Workshop, Twente, Netherlands, Nov. 21 - 22, 1994, pp. 191 - 194.

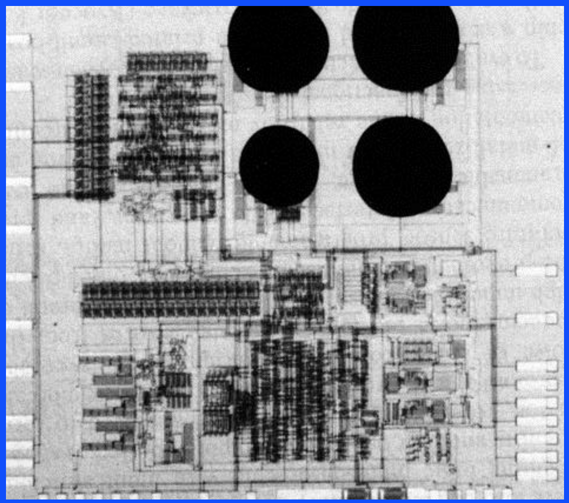
SCREEN PRINTING ON CMOS





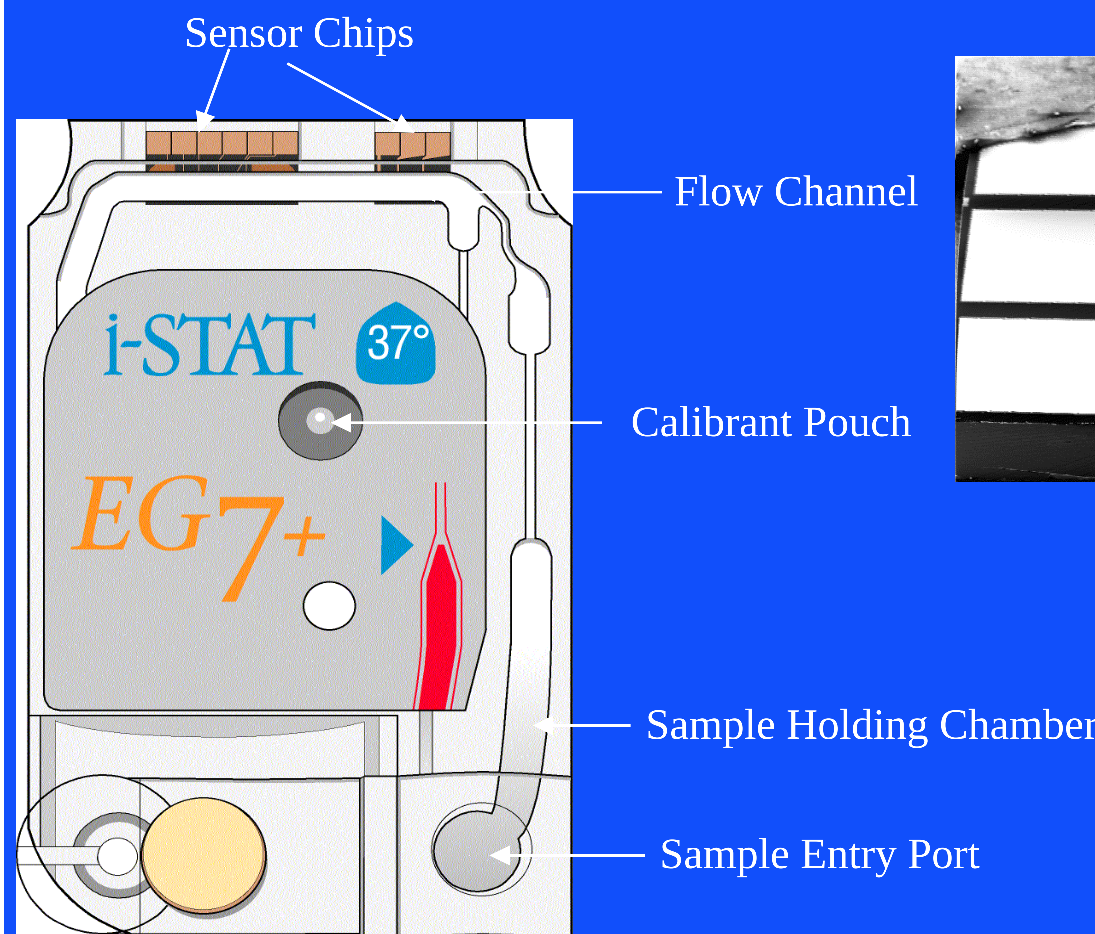


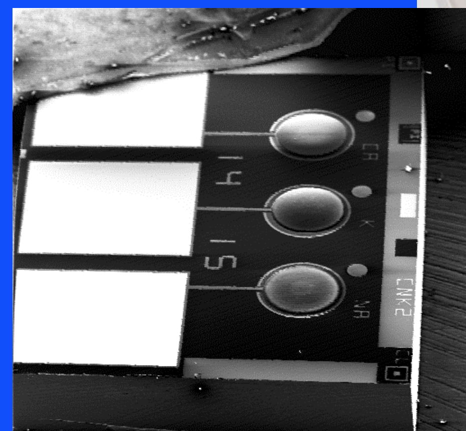


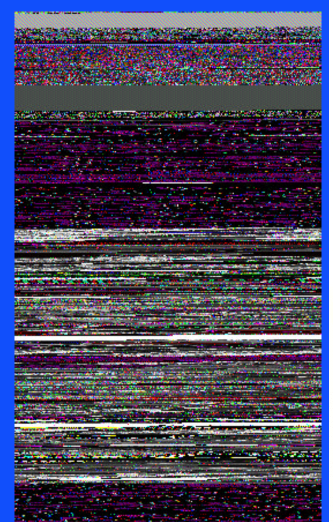


Goldberg, H. D., Brown, R. B., Liu, D. P., and Meyerhoff, M. E., "Screen Printing: A Technology for the Batch Fabrication of Integrated Chemical-Sensor Arrays," Sensors and Actuators B, vol. 21, 1994, pp. 171 -183.

COMMERCIAL DEVICE

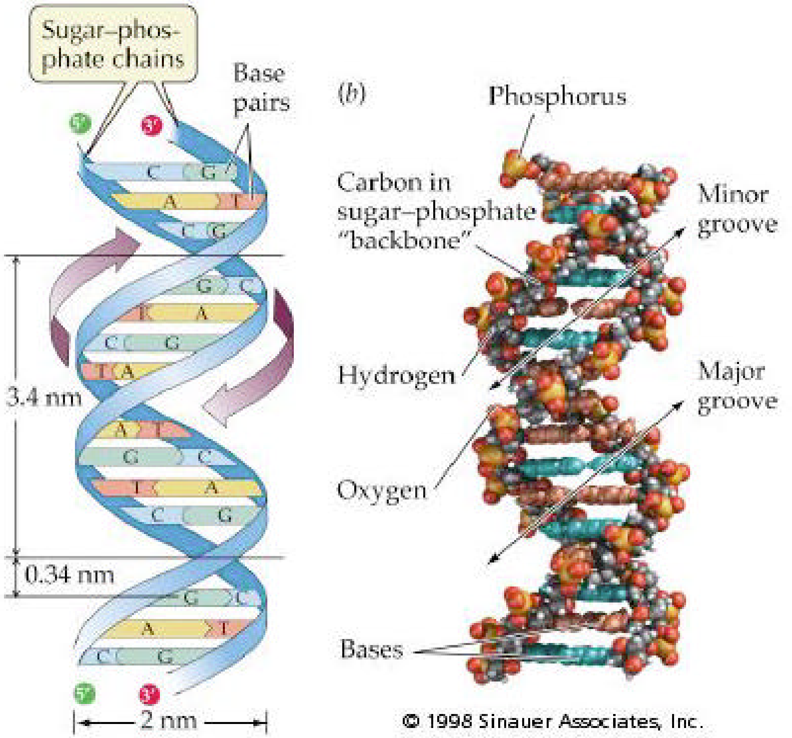






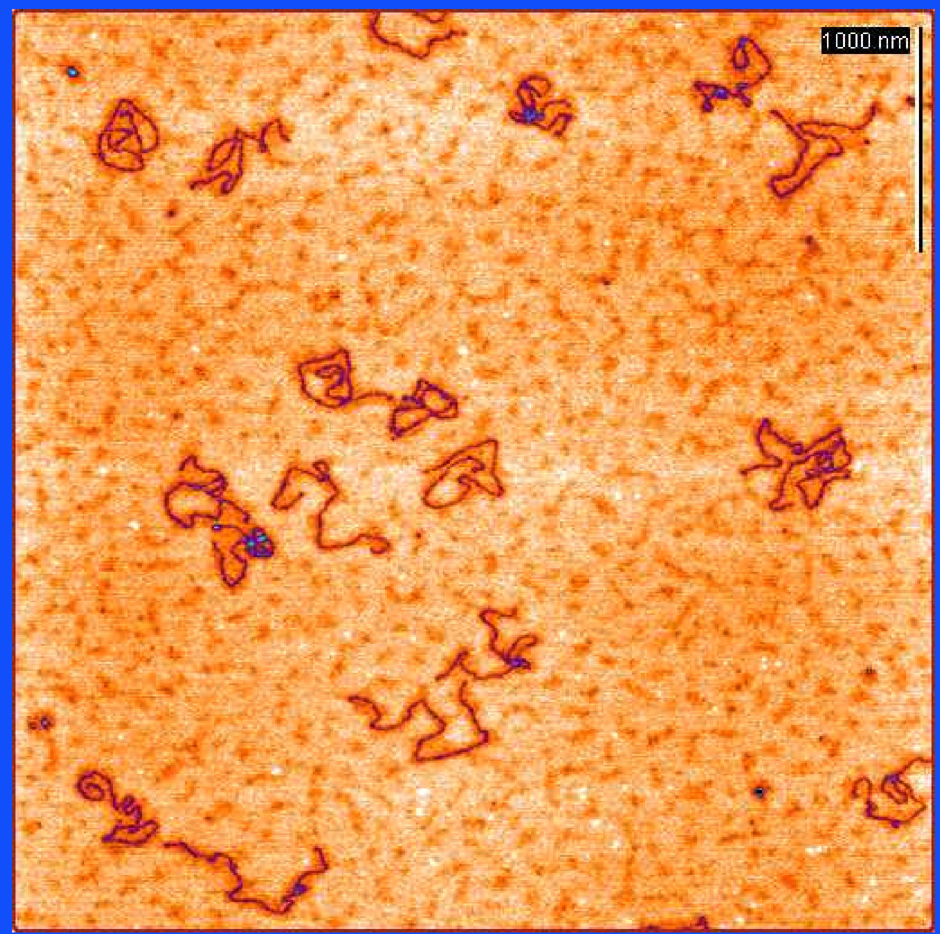
Courtesy Dr. Anca Varlan, I-Stat.

EXAMPLE RECOGNITION MOLECULE: DNA



Courtesy Prof. H. C. Heller, Stanford University.

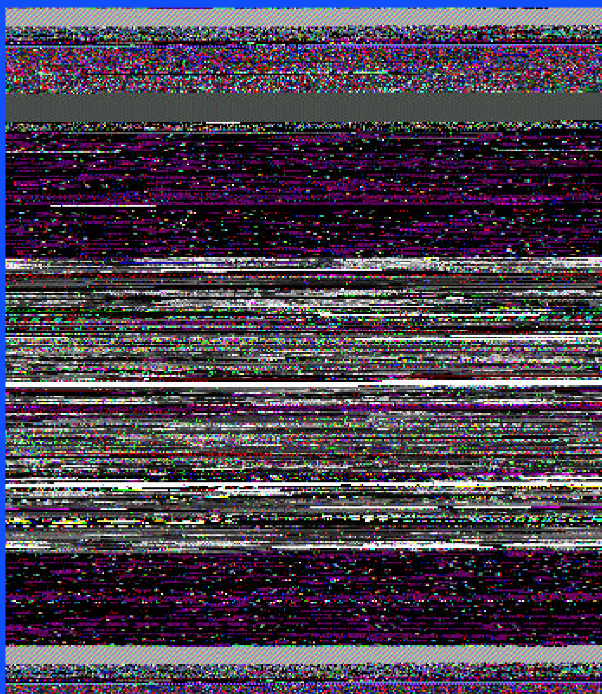
Source: Purves, Orians, Heller, and Sadava, "Life: The Science of Biology," Sinauer Associates/W.H. Freeman & Co., New York, 1999.



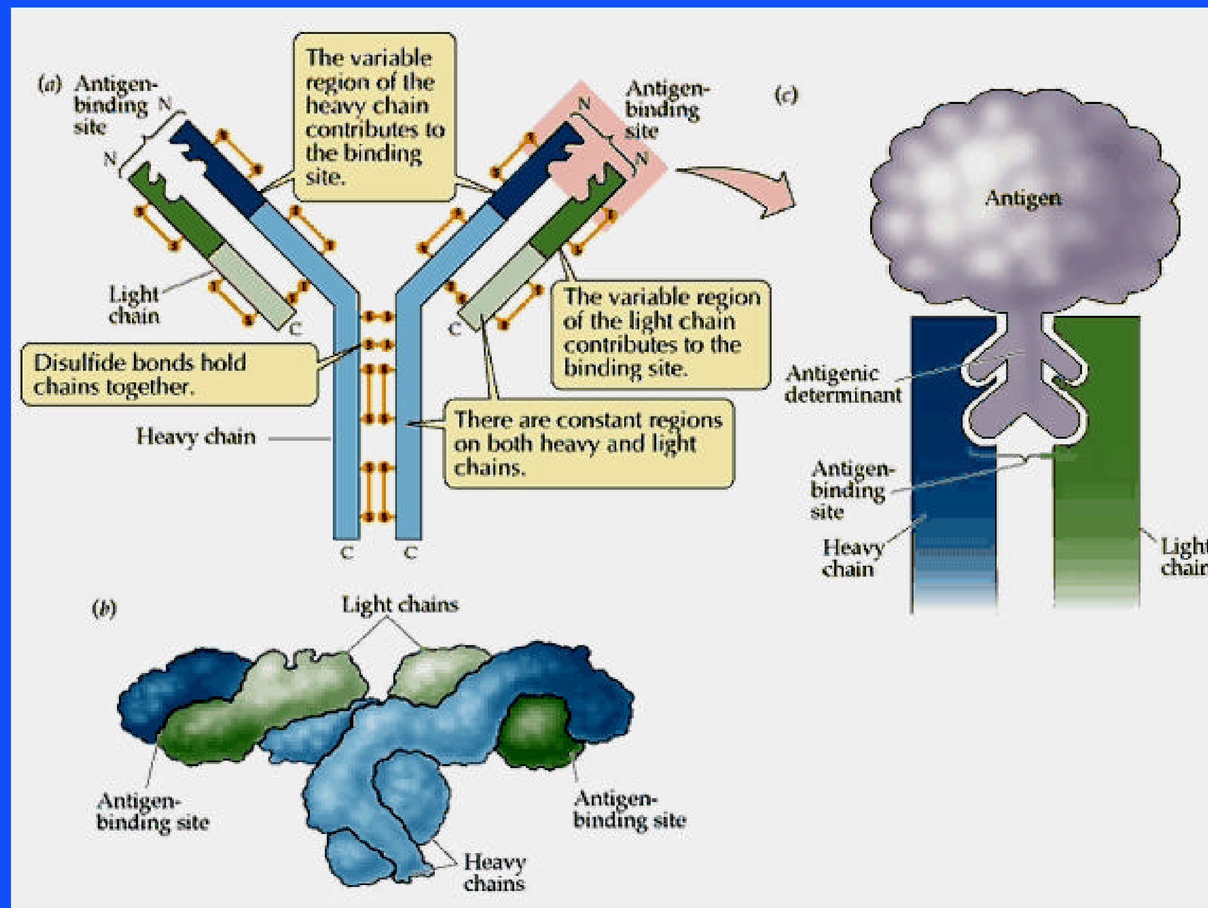
DNA molecules on a mica substrate, imaged using a scanning probe microscope.

Source: Moscow University, www.spm.genebee.msu.su/

EXAMPLE RECOGNITION MOLECULE: ANTIBODIES

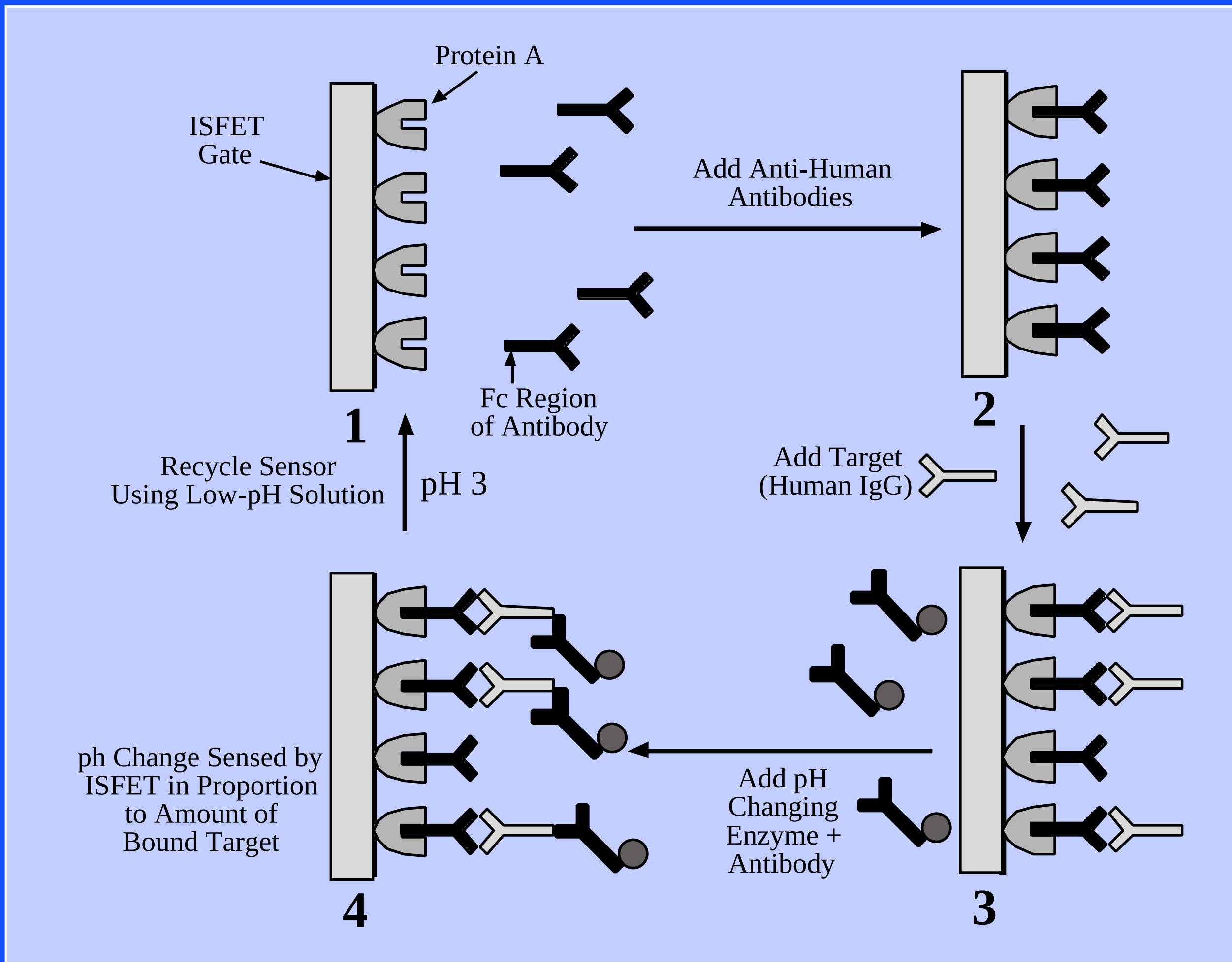


Courtesy Prof. H. C. Heller, Stanford University.



Source: Purves, Orians, Heller, and Sadava, “Life: The Science of Biology,” Sinauer Associates/W.H. Freeman & Co., New York, 1999.

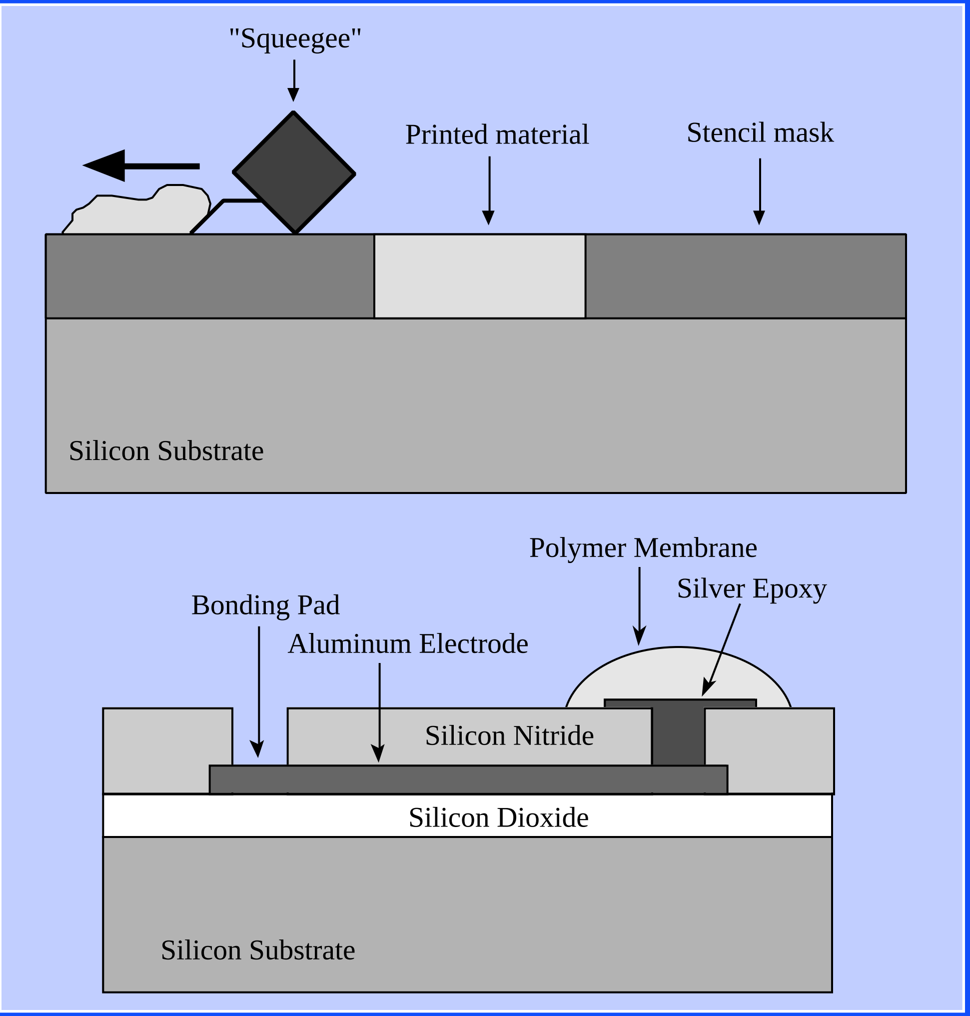
ANTIBODY-TO-pH TRANSDUCTION



Reference: Colapicchioni, C., Barbaro, A., Porcelli, F., and Giannini, I., "Immunoenzymatic Assay Using CHEMFET Devices," Sensors and Actuators, vol. B4, nos. 3 - 4, June 1991, pp. 245 - 250.

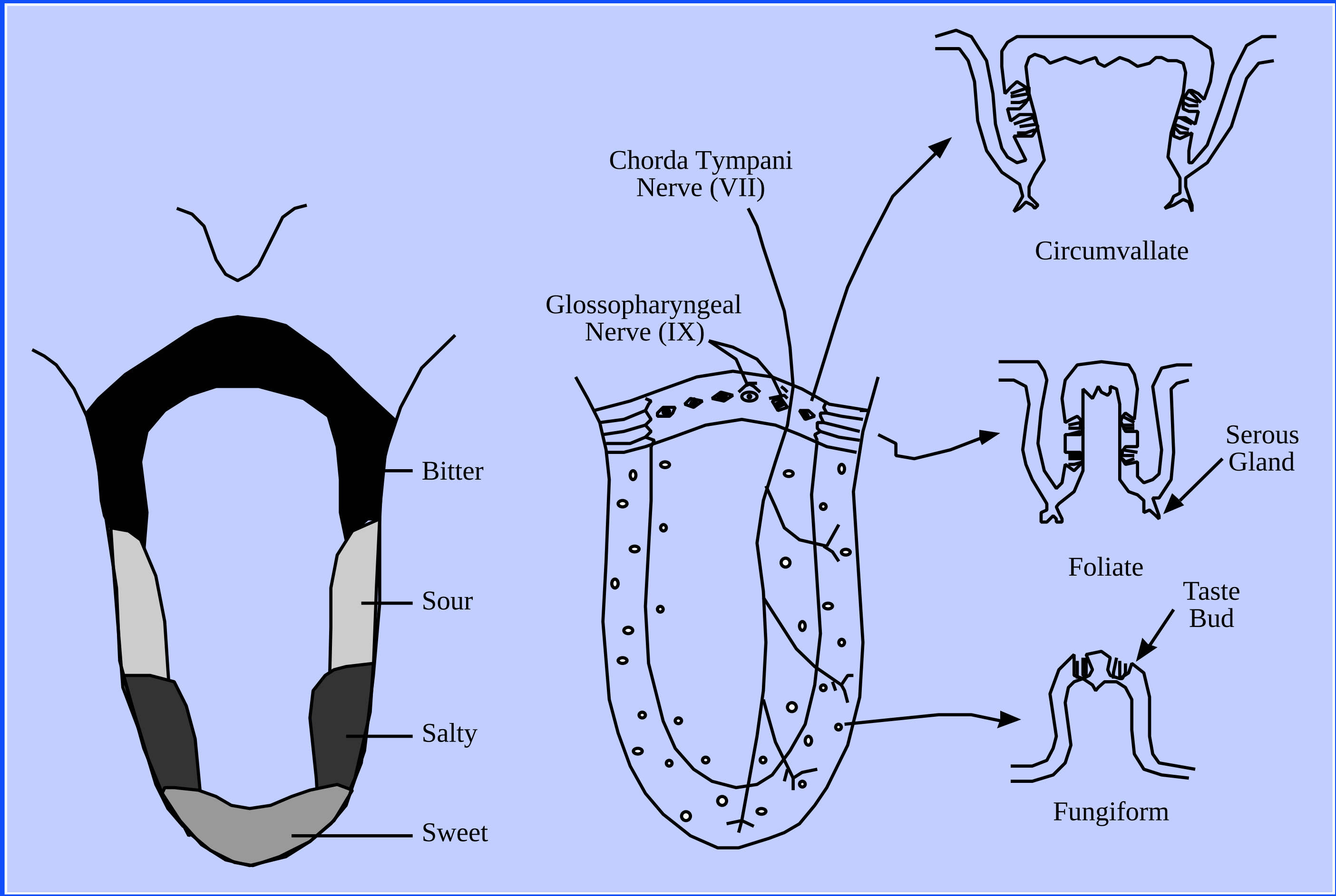
CMOS-COMPATIBLE BIOSENSOR PROCESS

- Goldberg, et al., (1994) demonstrated an approach to screen-printing biosensors on CMOS.
- Silver epoxy was used to couple between the CMOS metallization (Al) and ionophore-loaded polymer membranes.
- One design had serial interface, A/D, gain stage, band-gap reference, temperature sensor, K^+, Ca^{2+}, NH_4^+ and pH sensors.

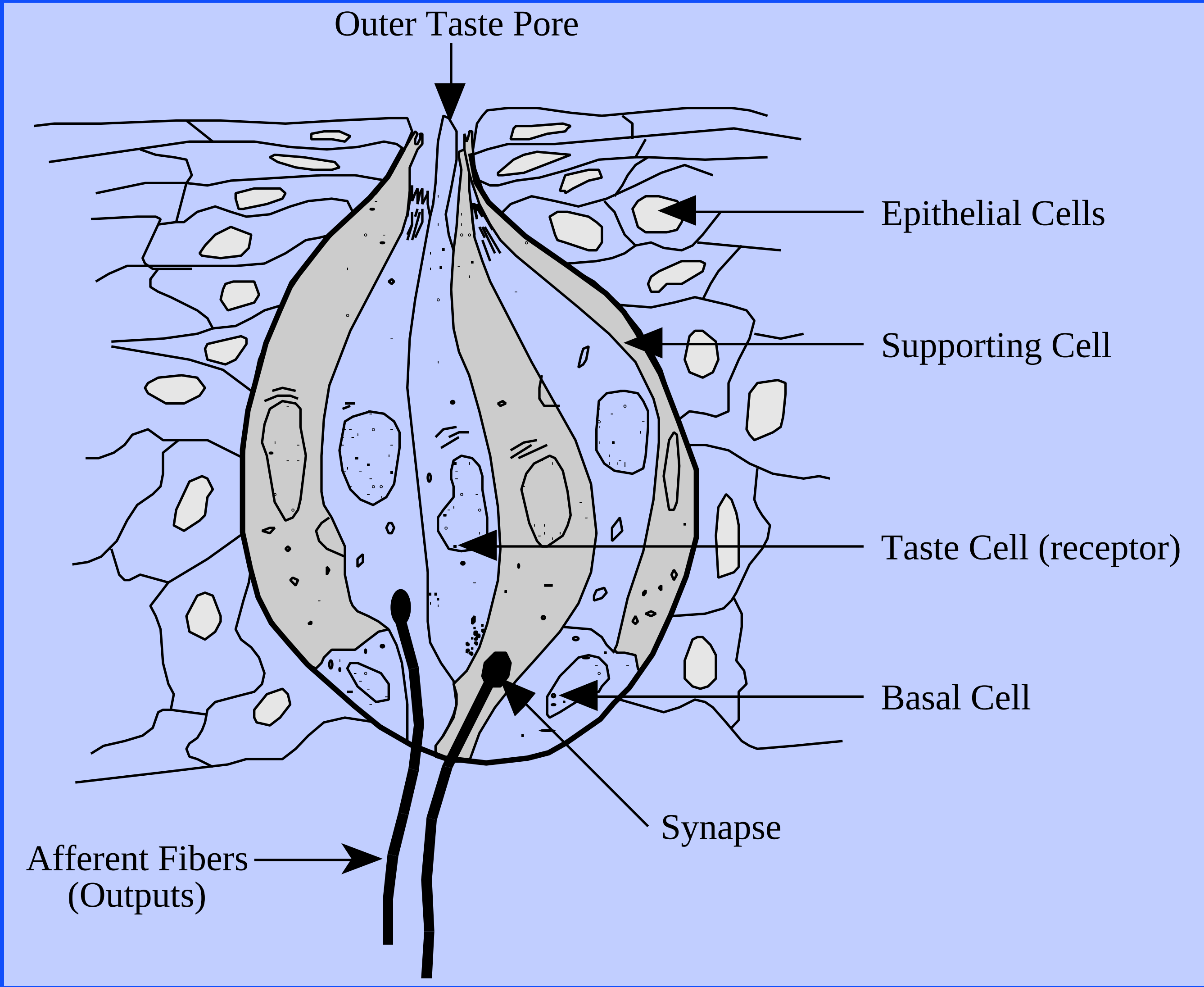


Reference: Goldberg, H. D., Brown, R. B., Liu, D. P., and Meyerhoff, M. E., "Screen Printing: A Technology for the Batch Fabrication of Integrated Chemical-Sensor Arrays," Sensors and Actuators B, vol. 21, 1994, pp. 171 -183.

BIOLOGICAL TASTE SENSORS

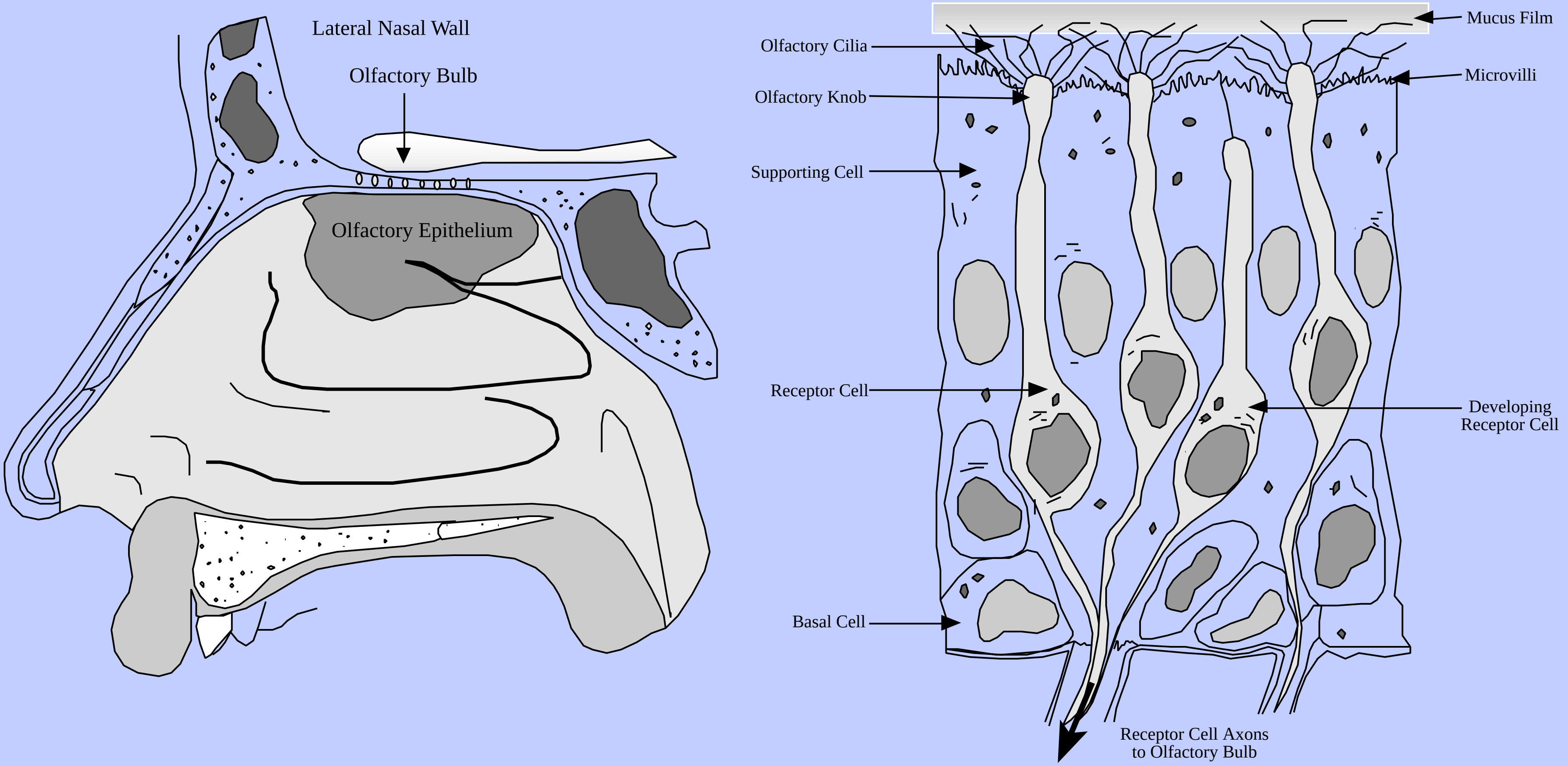


Reference: Dodd, J., and Castellucci, V. F., "Smell and Taste: The Chemical Senses," Chapter 34 in "Principles of Neural Science," Kandel, E. R., Schwartz, J. H., and Jessell, T. M., [eds.], Third Edition, Elsevier Science Publishing Co., Inc., New York, NY, 1991, pp. 512 - 529.

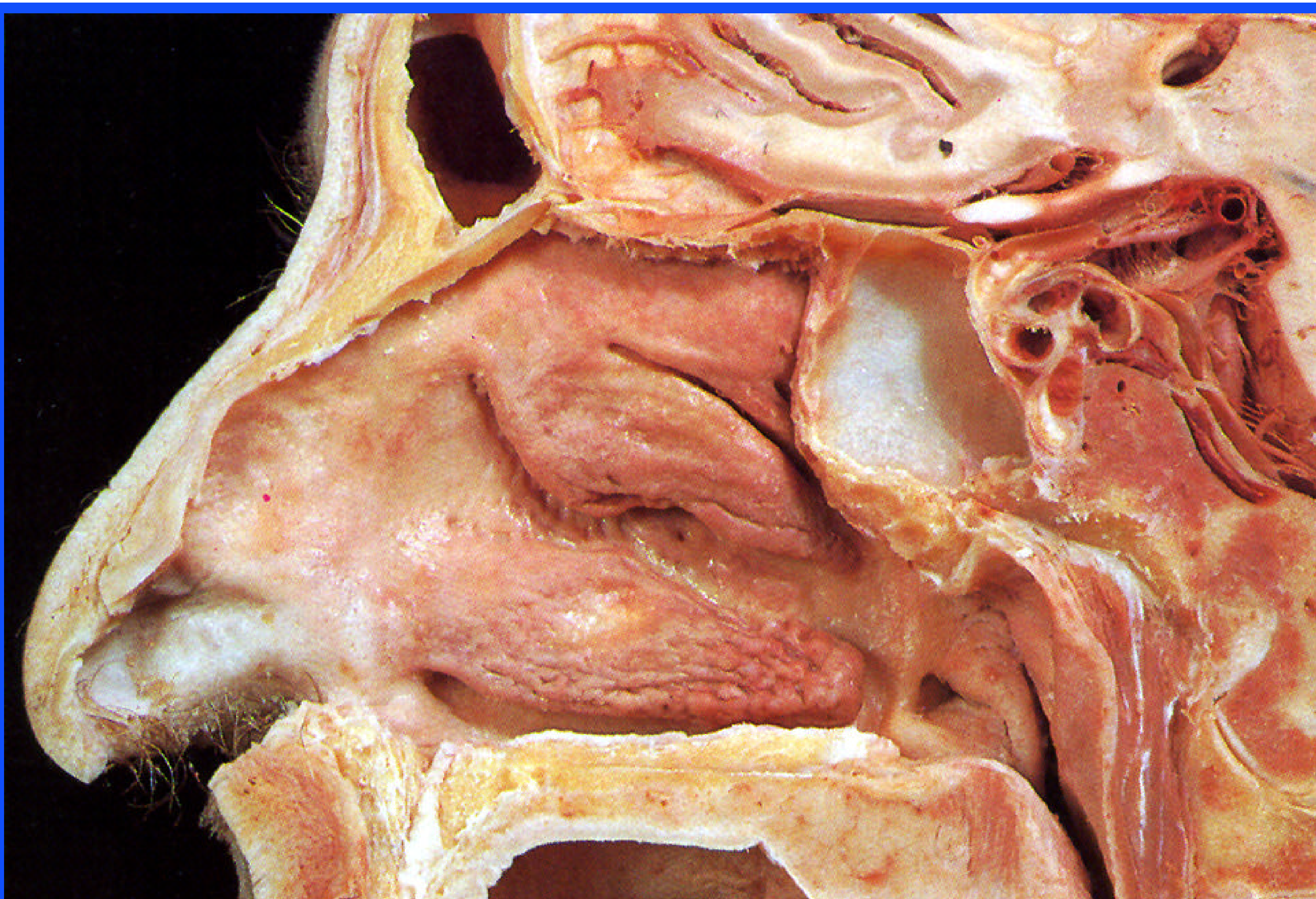


Reference: Dodd, J., and Castellucci, V. F., "Smell and Taste: The Chemical Senses," Chapter 34 in "Principles of Neural Science," Kandel, E. R., Schwartz, J. H., and Jessell, T. M., [eds.], Third Edition, Elsevier Science Publishing Co., Inc., New York, NY, 1991, pp. 512 - 529.

BIOLOGICAL ODOR SENSORS

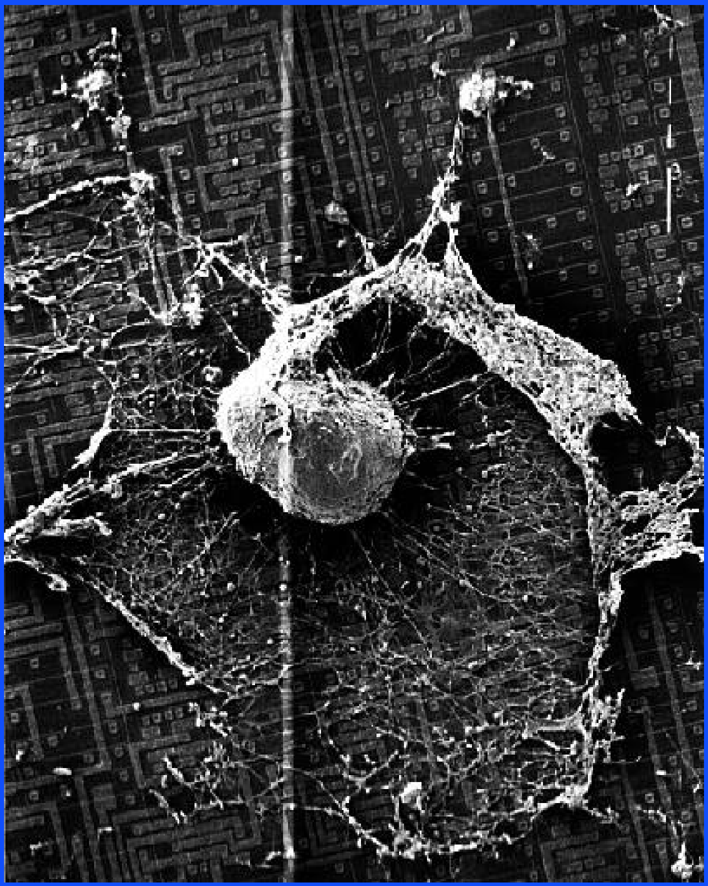


Reference: Dodd, J., and Castellucci, V. F., "Smell and Taste: The Chemical Senses," Chapter 34 in "Principles of Neural Science," Kandel, E. R., Schwartz, J. H., and Jessell, T. M., [eds.], Third Edition, Elsevier Science Publishing Co., Inc., New York, NY, 1991, pp. 512 - 529.



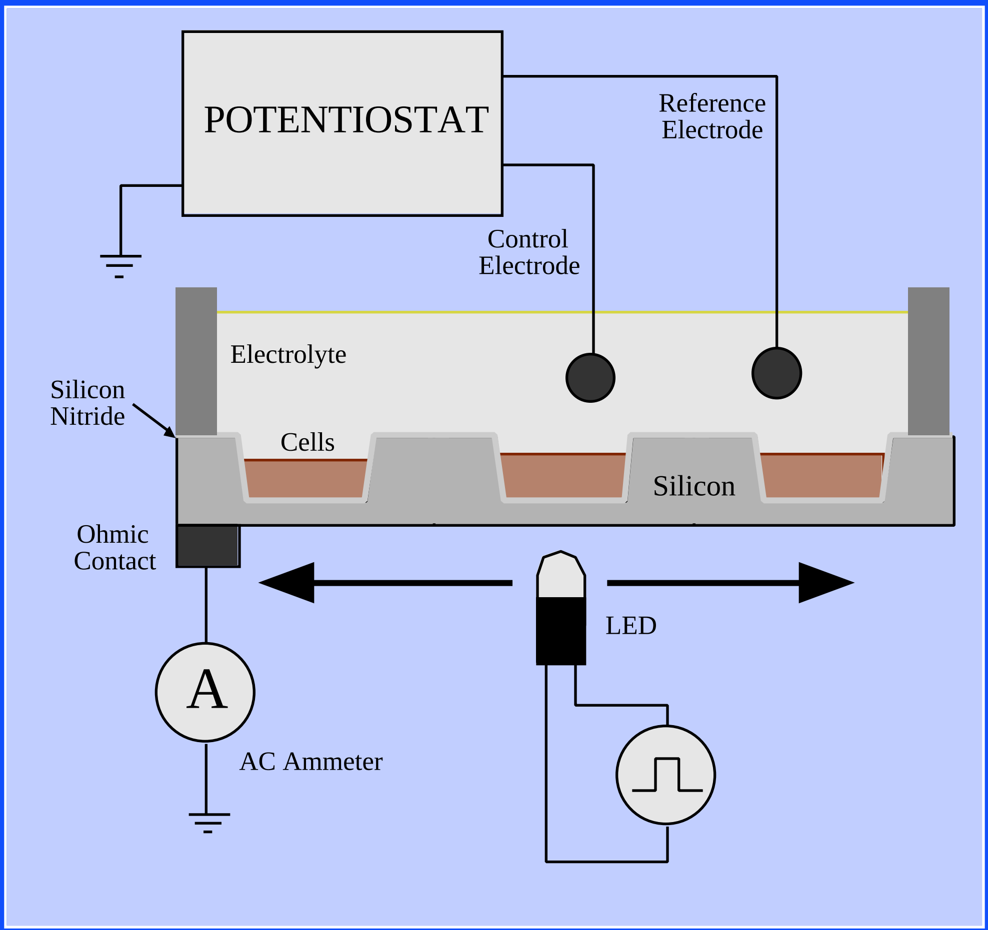
Source: Gosling, J. A., Harris, P. F., Humpherson, J. R., Whitmore, I., and Willan, P. L. T., "Atlas of Human Anatomy," J. B. Lippincott Co., Philadelphia, PA, 1985.

HYBRID BIOSENSORS



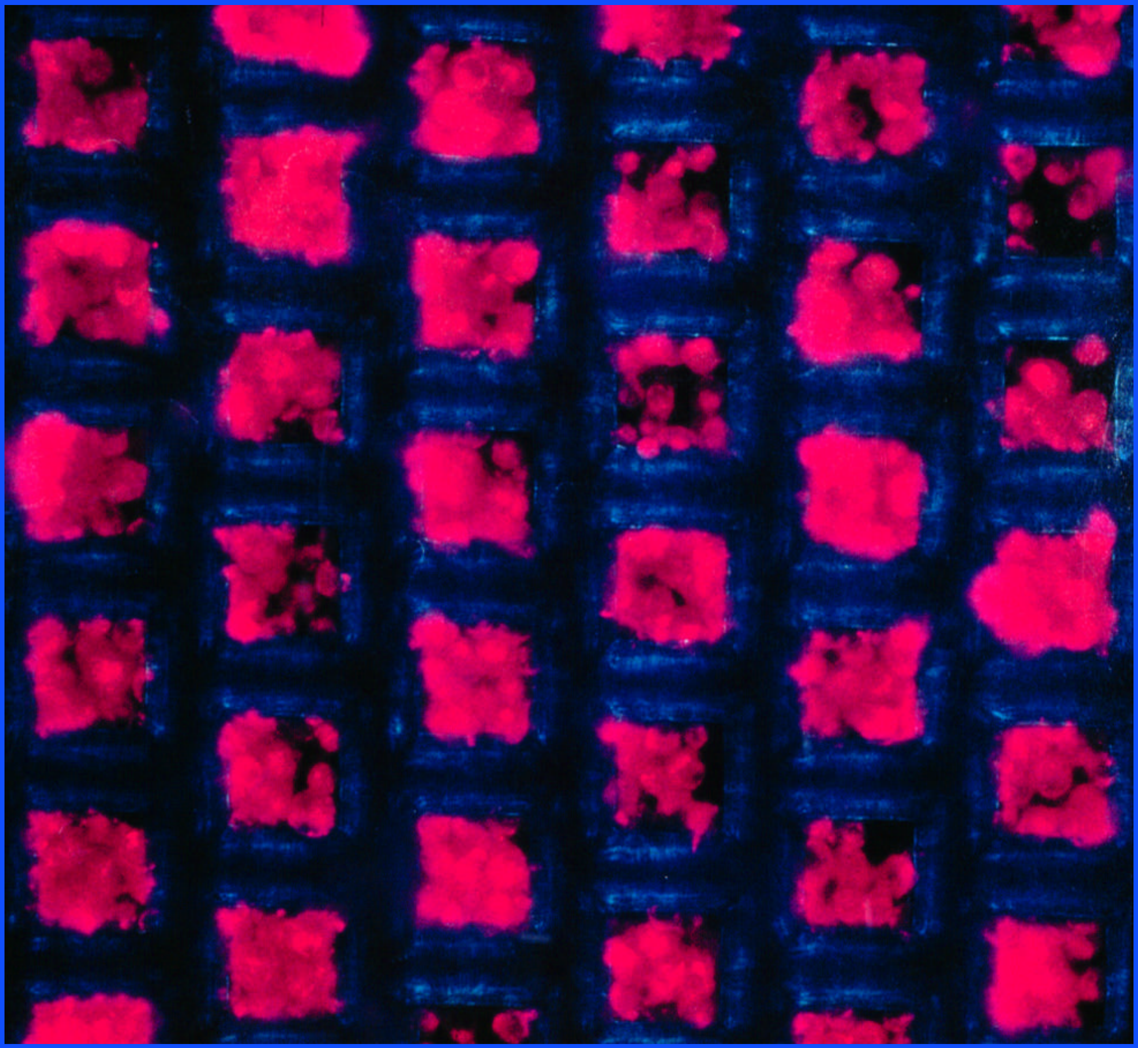
- This type of sensor makes use of whole, living cells as part of the transduction mechanism, taking advantage of very specific molecular sensors that have evolved in organisms.
- Can grow many types of cells directly on top of integrated circuits complete with arrays of thin-film electrodes.
- Requires suitable surfaces for cellular compatibility and resistance to corrosion/blockage of alkali ions.
- Can grow cells on such surfaces for many months.

HYBRID BIOSENSOR: MICROPHYSIOMETER



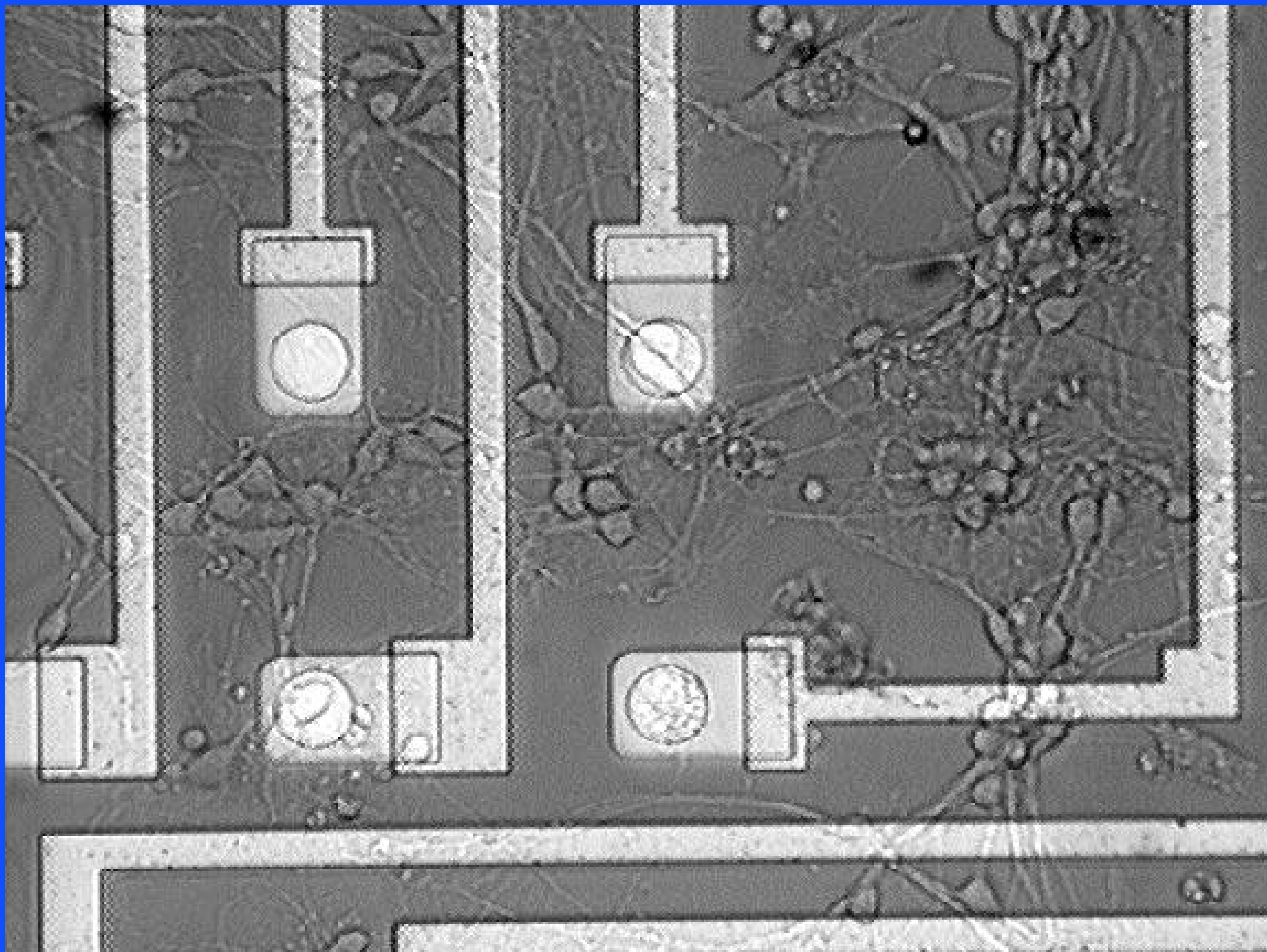
- Extracellular pH (indicator of metabolic state) is measured using light-addressing.
- A pulsed LED is used to generate electron-hole pairs in a silicon substrate containing cells in wells.
- The pH can be computed from the resulting AC signal, representing pH-induced changes in the SiO_2/electrolyte interface.
- This device is commercially available from Molecular Devices, Inc., Sunnyvale, CA.

Reference: Parce, J. W., Owicki, J. C., et al., “Detection of Cell-Affecting Agents with a Silicon Biosensor,” Science, 246 (4927), 1989, pp. 243- 247.

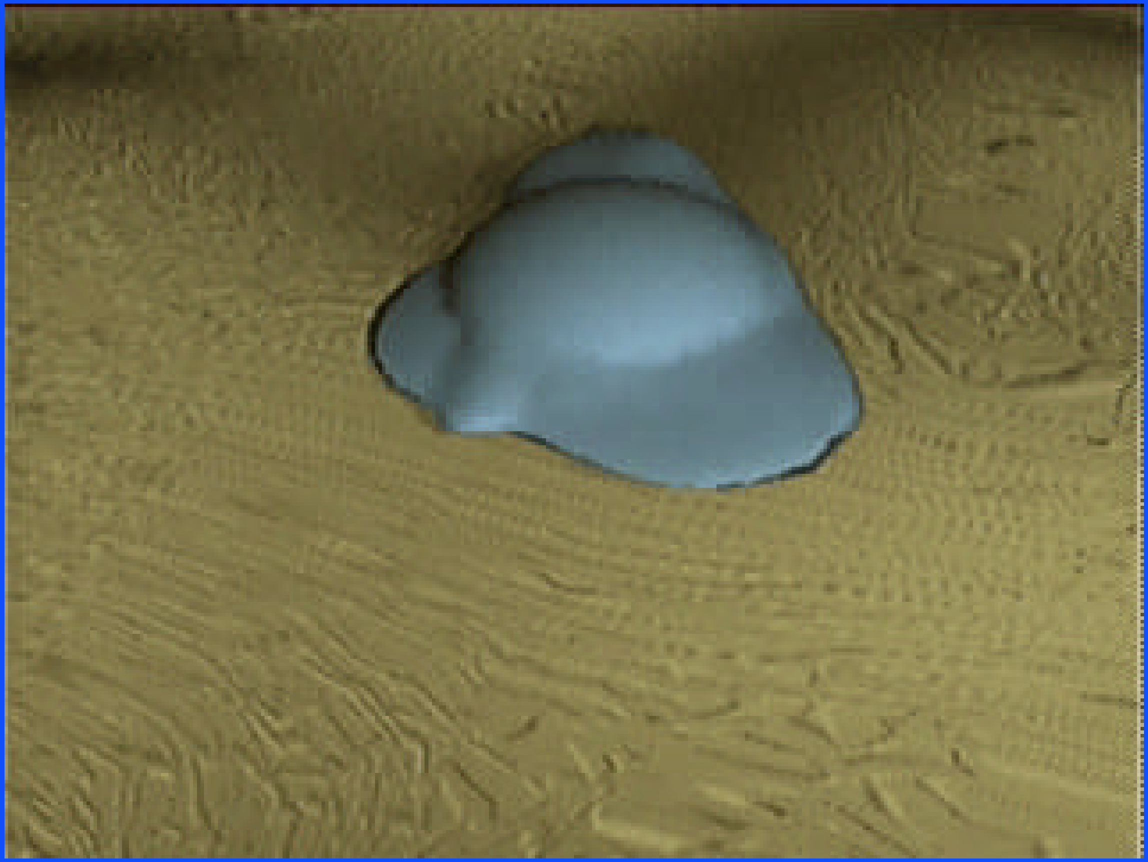


Source: Parce, J. W., Owicki, J. C., Kersco, K. M., Sigal, G. B., Wada, H. G., Muir, V. C., Bousse, L. J., Ross, K. L., Sikic, B. I., and McConnell, H. M., “Detection of Cell-Affecting Agents with a Silicon Biosensor,” Science, vol. 246, no. 4927, Oct. 13, 1989, pp. 243 - 247.

HYBRID BIOSENSOR EXAMPLE

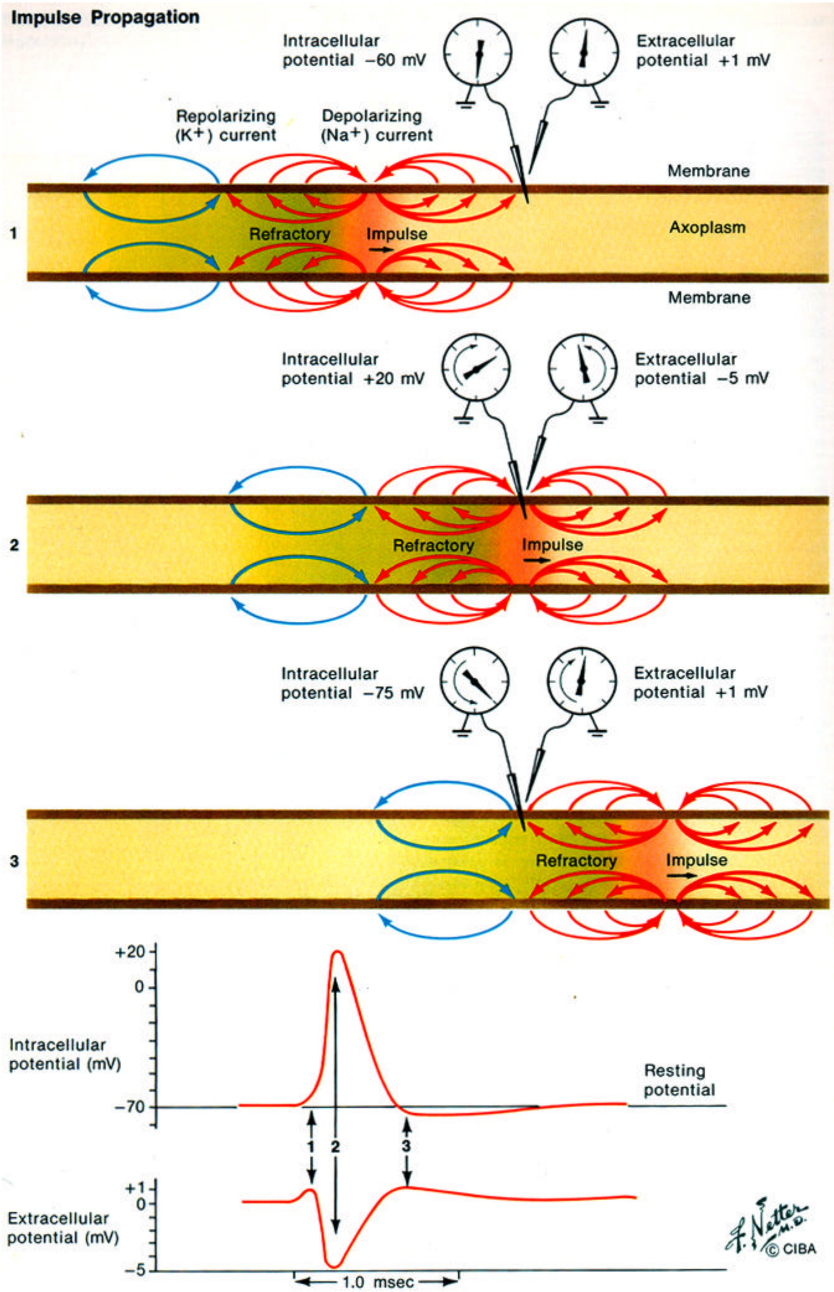


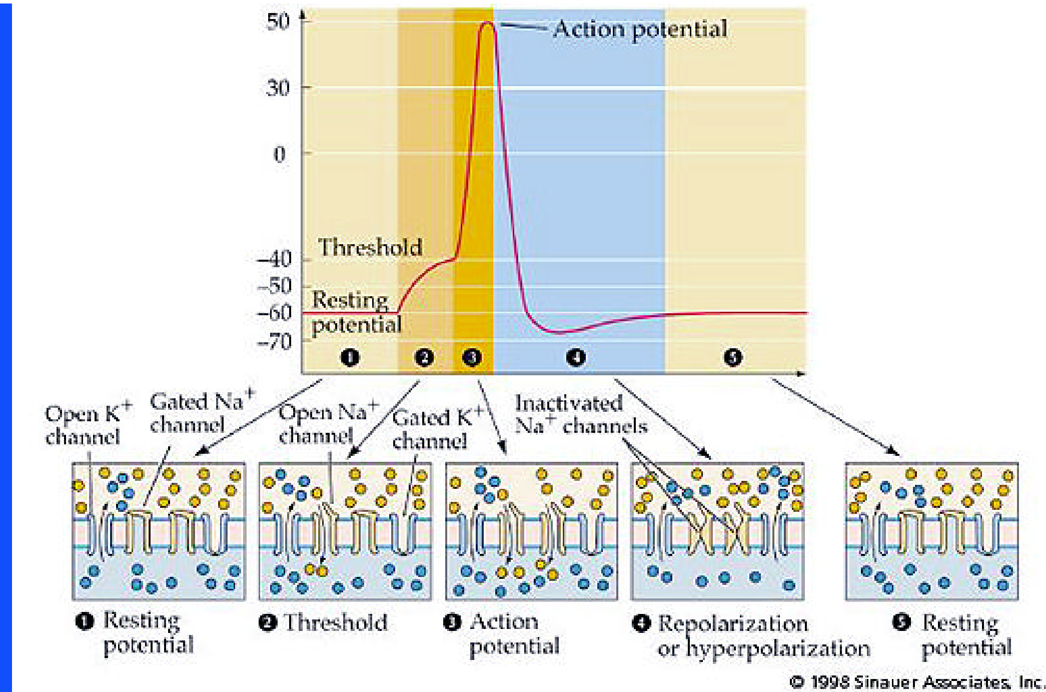
CELLS ON SURFACES



Movie courtesy Prof. H. C. Heller, Stanford University.

Source: Purves, Orians, Heller, and Sadava, “Life: The Science of Biology,” Sinauer Associates/W.H. Freeman & Co., New York, 1999.



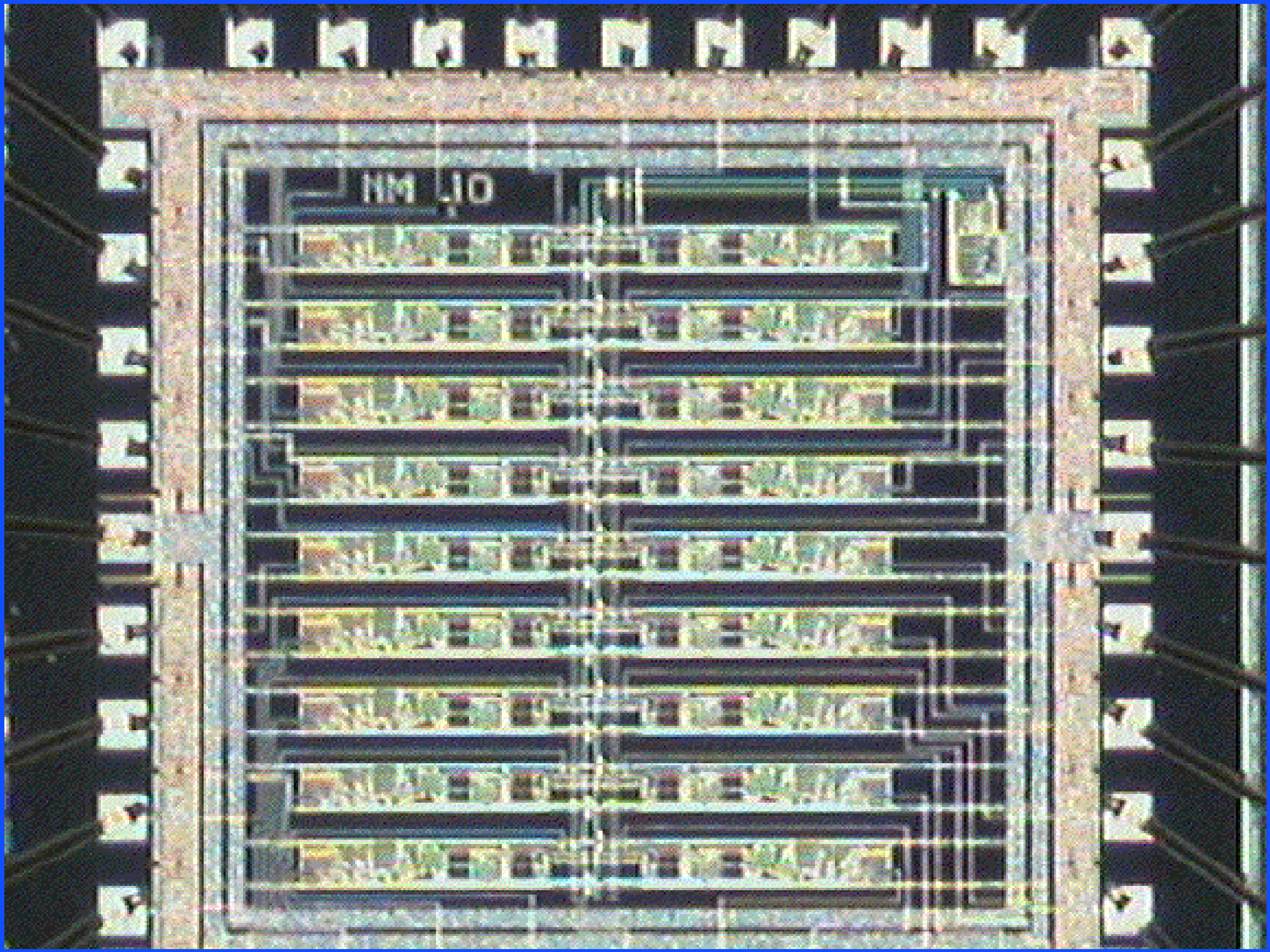


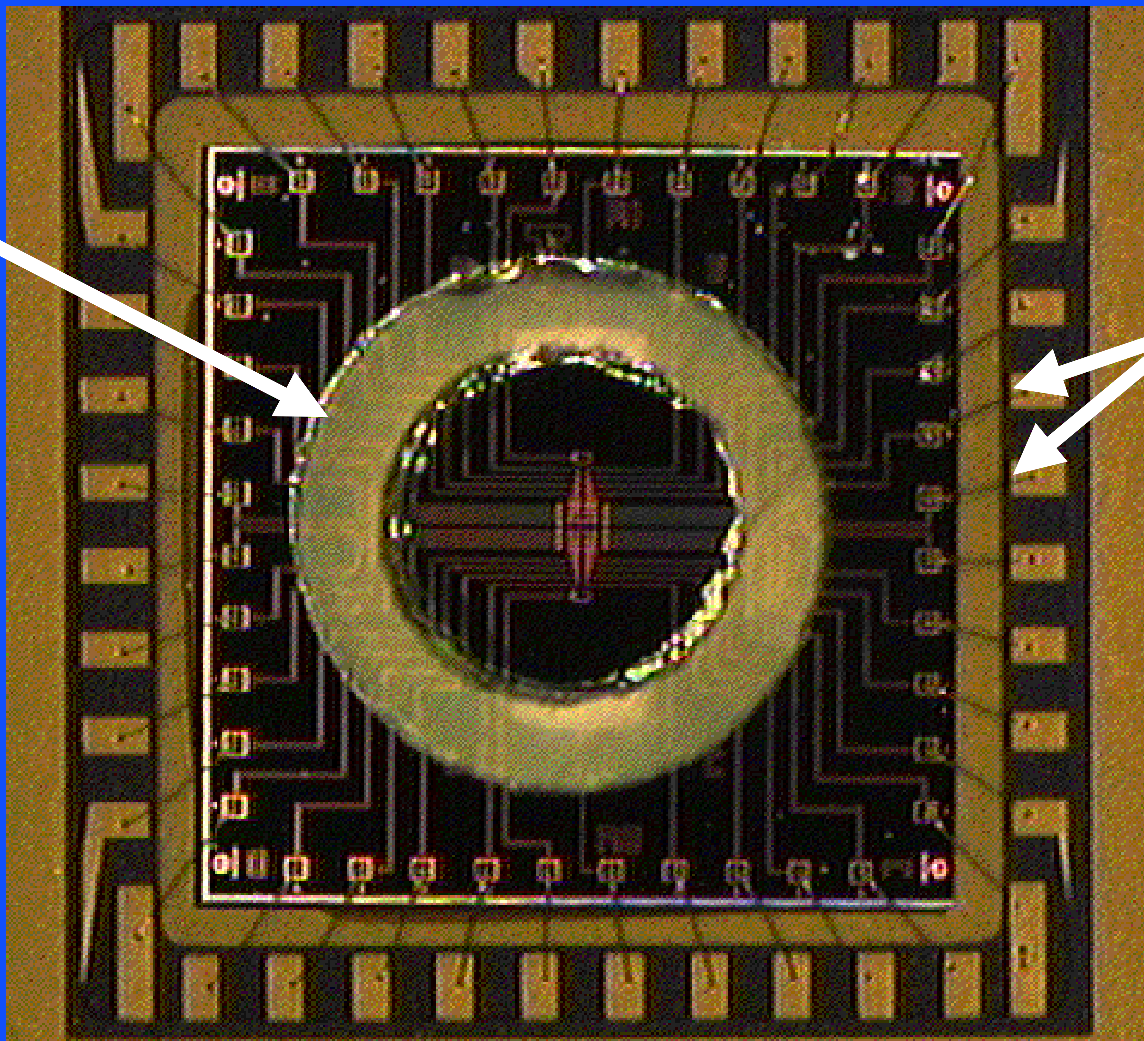
Courtesy Prof. H. C. Heller, Stanford University.

Source: Purves, Orians, Heller, and Sadava, "Life: The Science of Biology," Sinauer Associates/W.H. Freeman & Co., New York, 1999.

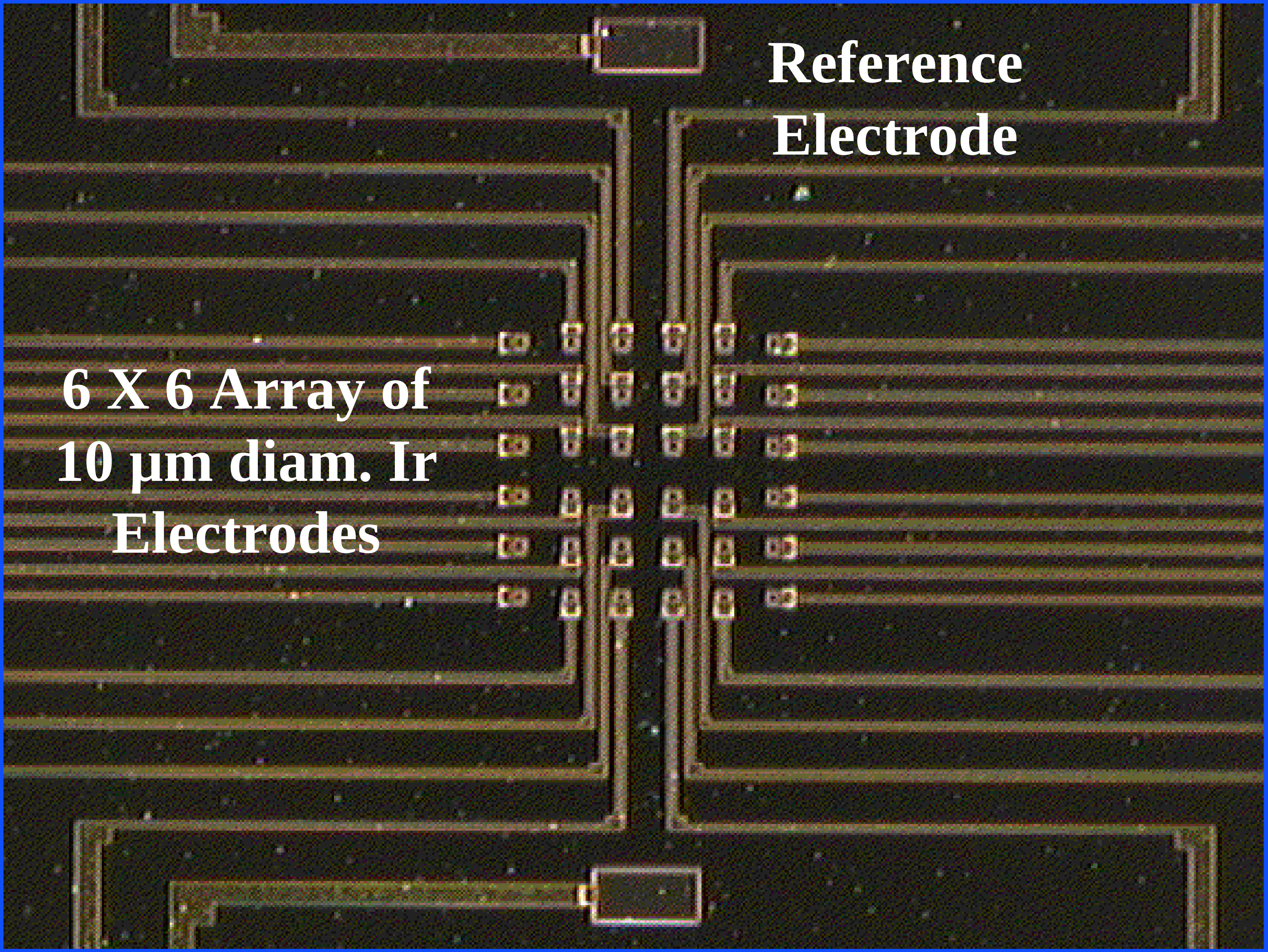
Source: Netter, F., "The CIBA Collection of Medical Illustrations: Volume 1, Nervous System, Part 1, Anatomy and Physiology," CIBA-GEIGY Corp., 1983.

18-CHANNEL CMOS FILTER/AMPLIFIER ARRAY CHIP

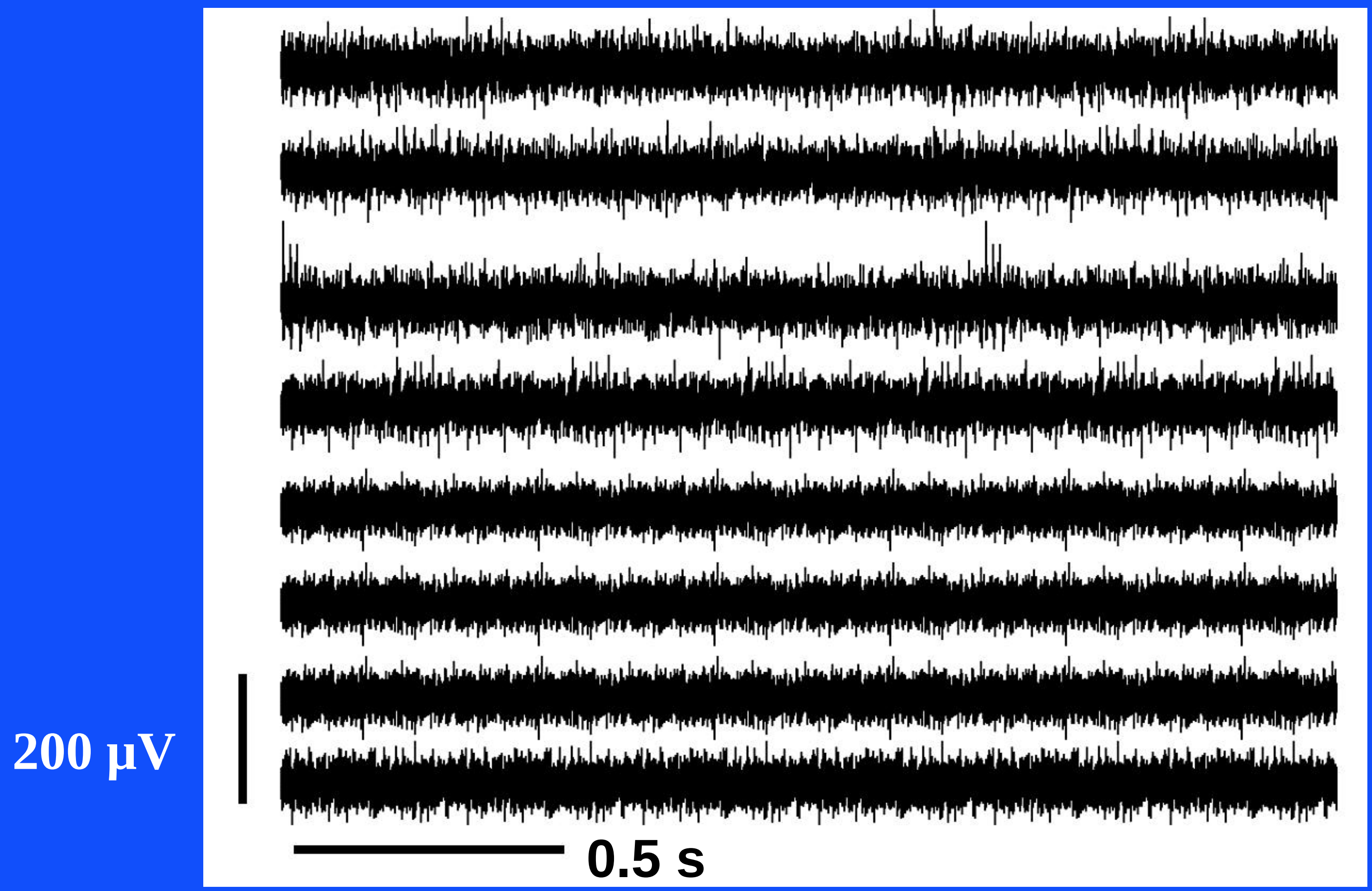




(Note: bond wire insulation not shown)

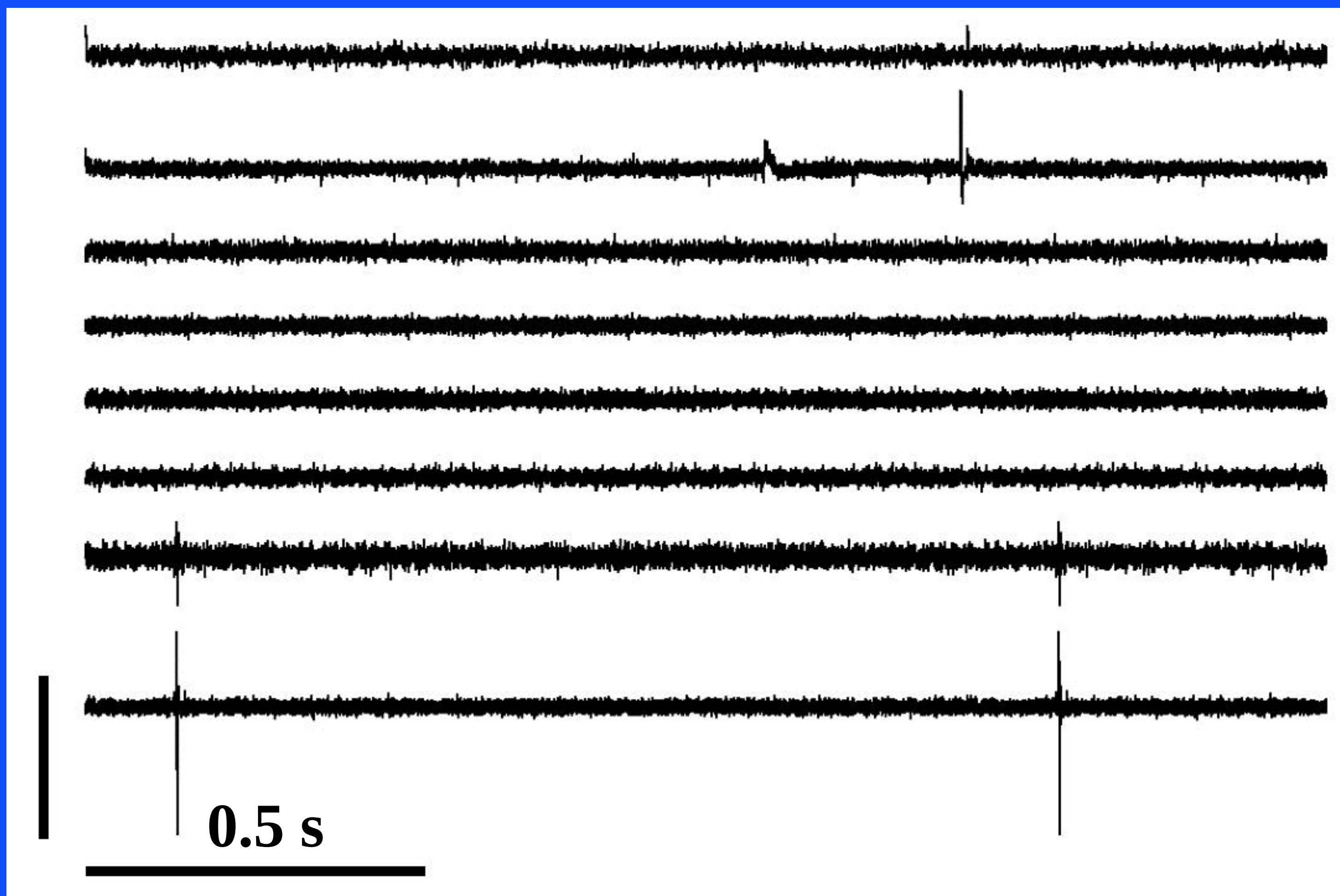

Reference Electrode
6 X 6 Array of 10 µm diam. Ir Electrodes

8-CHANNEL RECORDINGS FROM DORSAL ROOT GANGLION CELLS

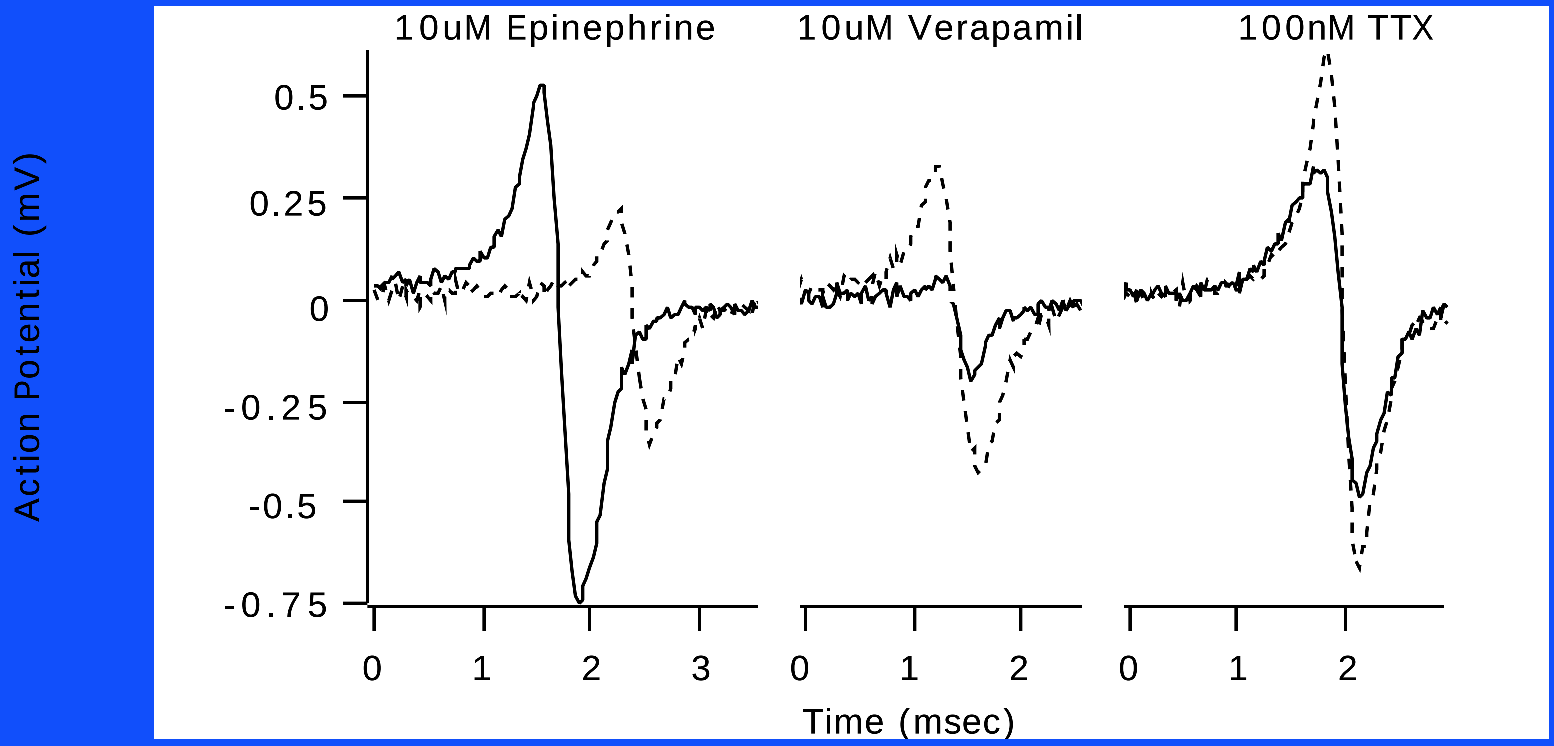


8-CHANNEL RECORDINGS FROM CHICK MYOCARDIAL CELLS

200 µV



AP MODULATION WITH PHARMACEUTICALS / TOXINS

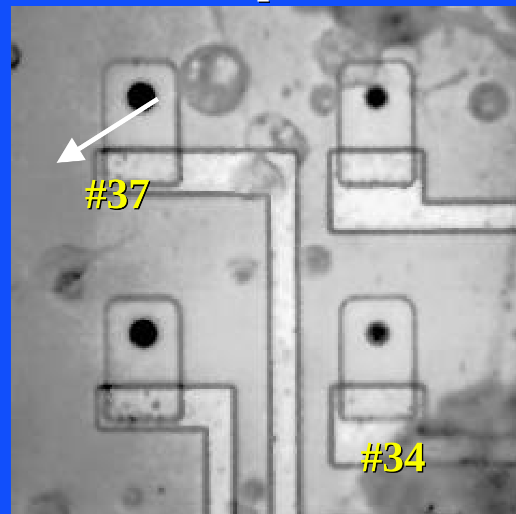


Reference: Borkholder, D. A., DeBusschere, B. D., and Kovacs, G. T. A., "An Approach to the Classification of Unknown Biological Agents with Cell Based Sensors," Proceedings of the Solid-State Sensor and Actuator Workshop, Hilton Head, South Carolina, June 8 - 11, 1998, pp. 178 - 182.

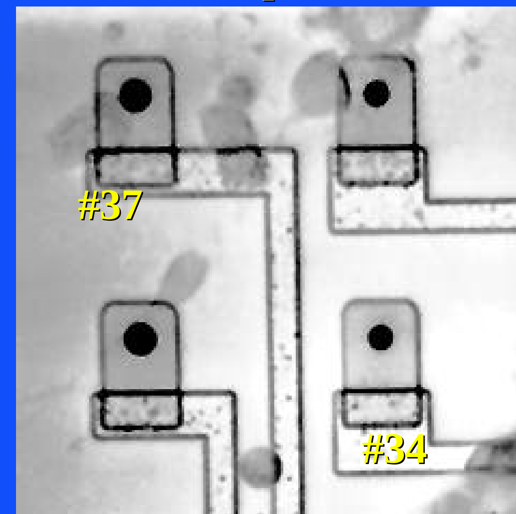
Courtesy Dr. D. Borkholder, Stanford University and Cepheid.

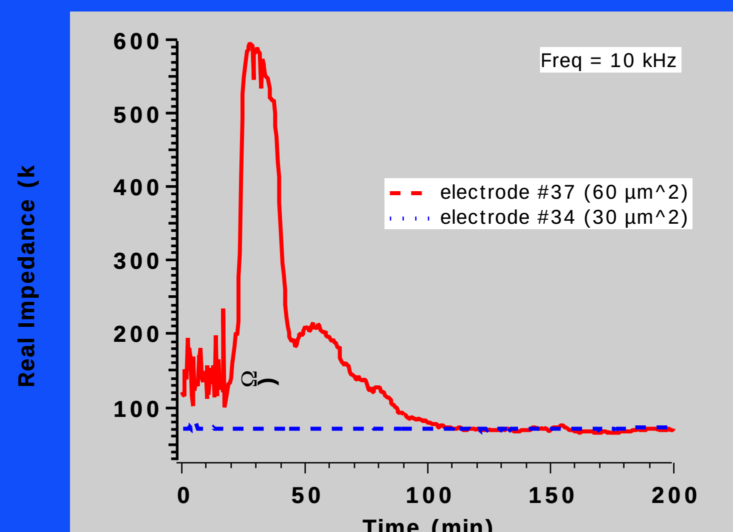
NG108 MOTILITY: SINGLE-CELL

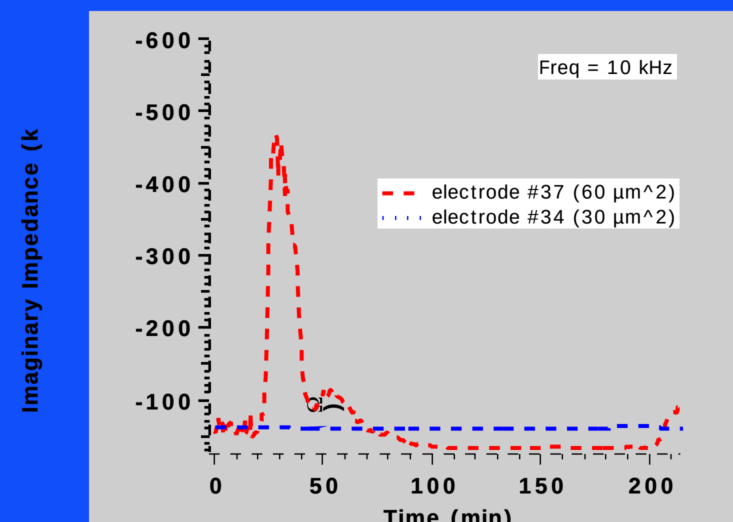
Before Experiment



After Experiment





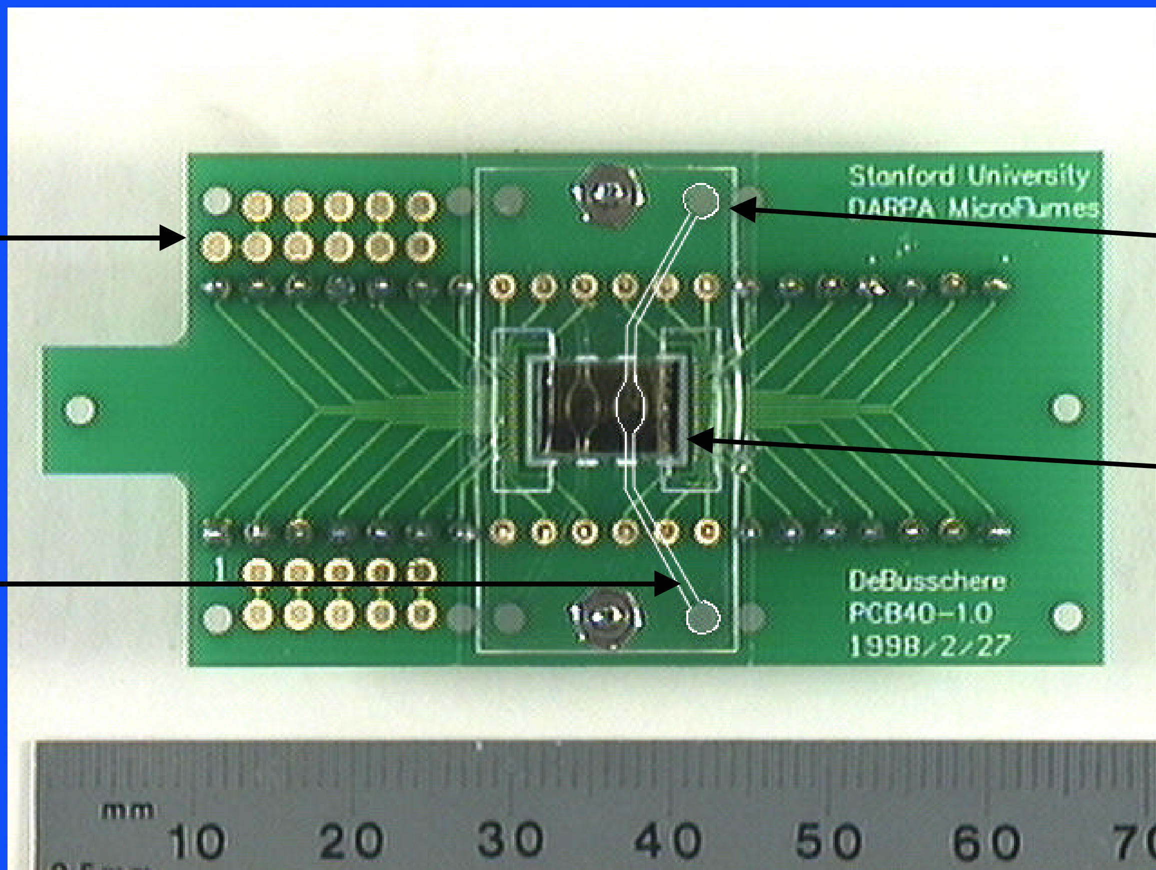


Courtesy Dr. D. Borkholder, Stanford University and Cepheid.

INTEGRATED CELL CARTRIDGE ENABLES HAND-HELD BIOSENSOR

Cartridge PC Board

Highlighted Fluidics Channel

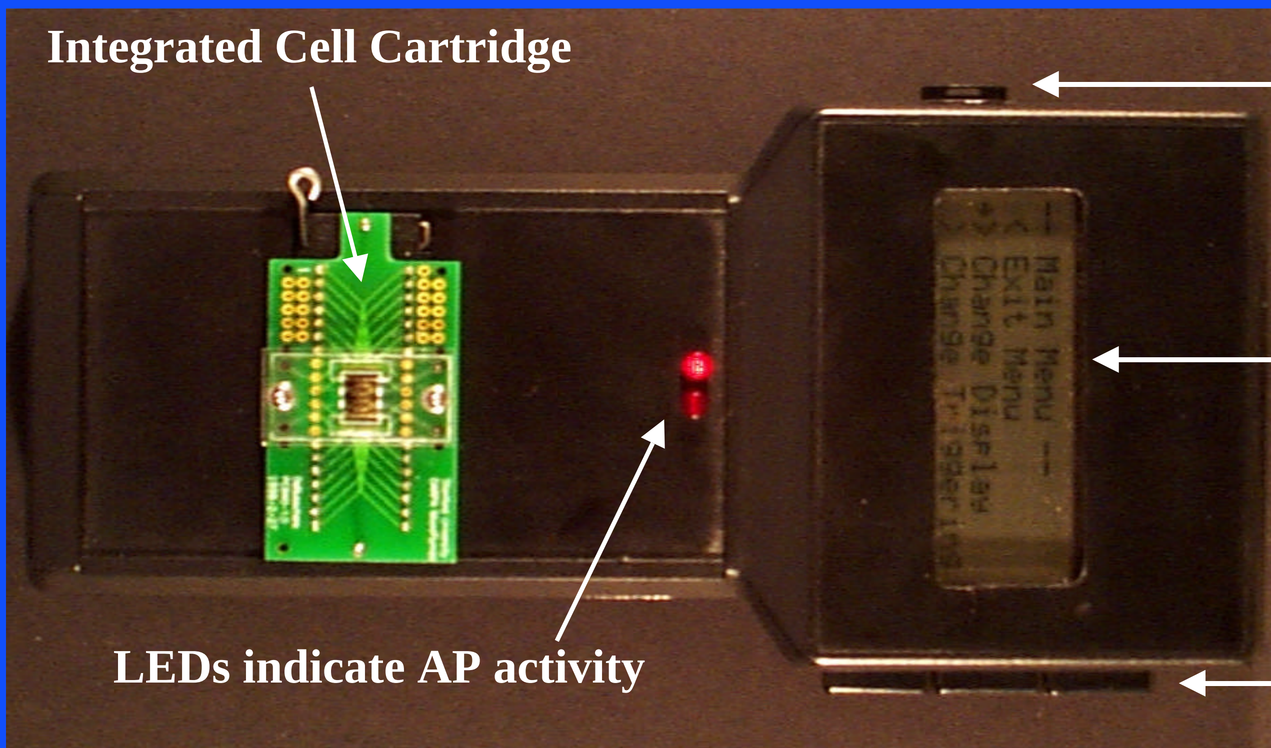


Septa (Fluidic Interconnect)

Silicon Die & Chambers

Courtesy D. DeBusschere, Stanford University.

PROTOTYPE HAND-HELD BIOSENSOR



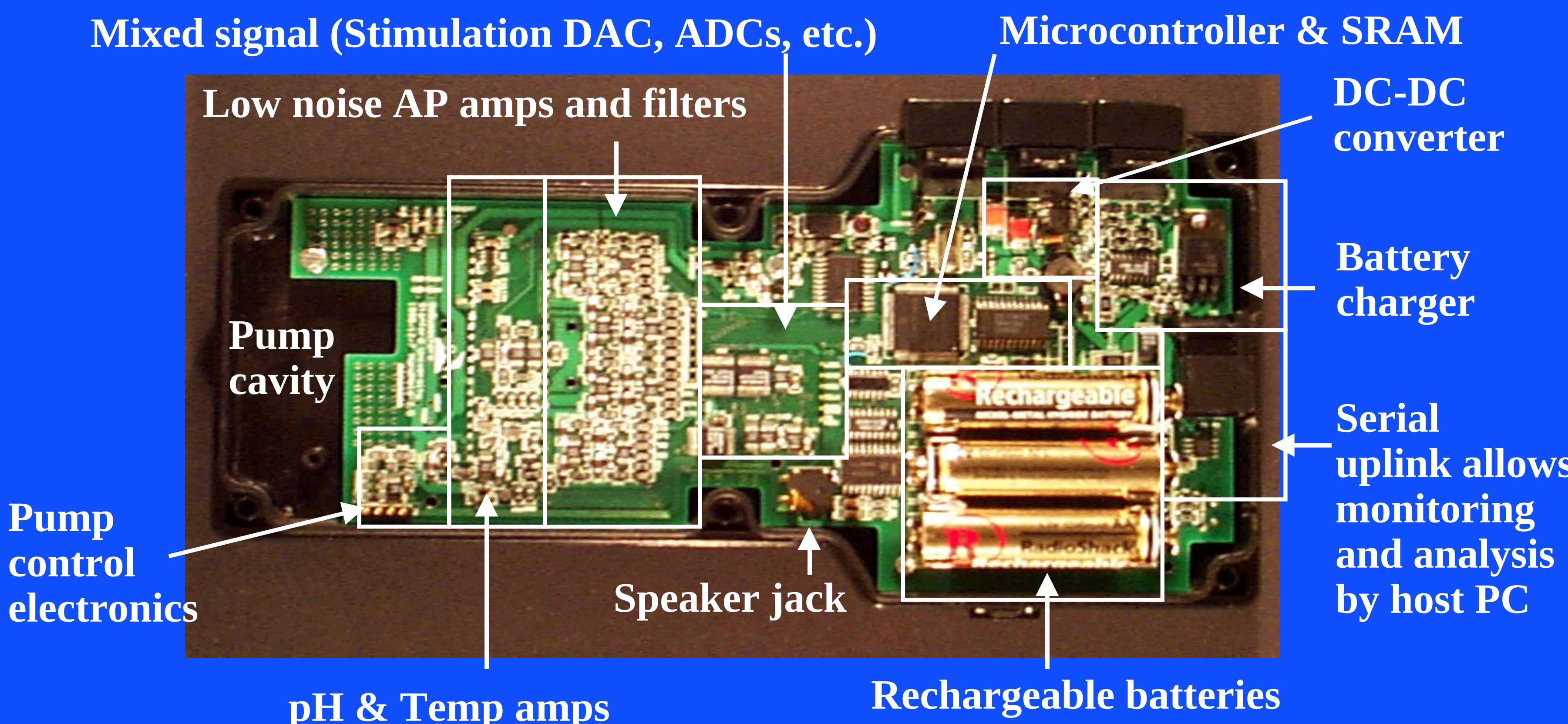
Removable flash memory cartridge (2MB) for data storage

LCD for system control and real time graphing of experimental data

Buttons for menu selections

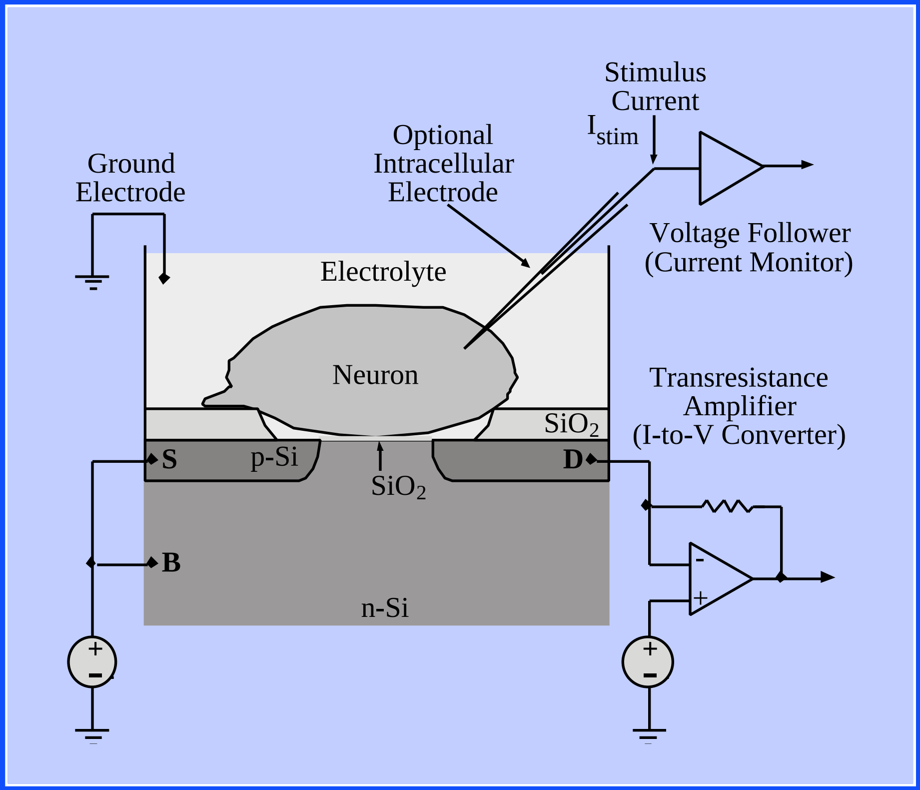
Courtesy D. DeBusschere, Stanford University.

“GUTS” OF THE INSTRUMENT



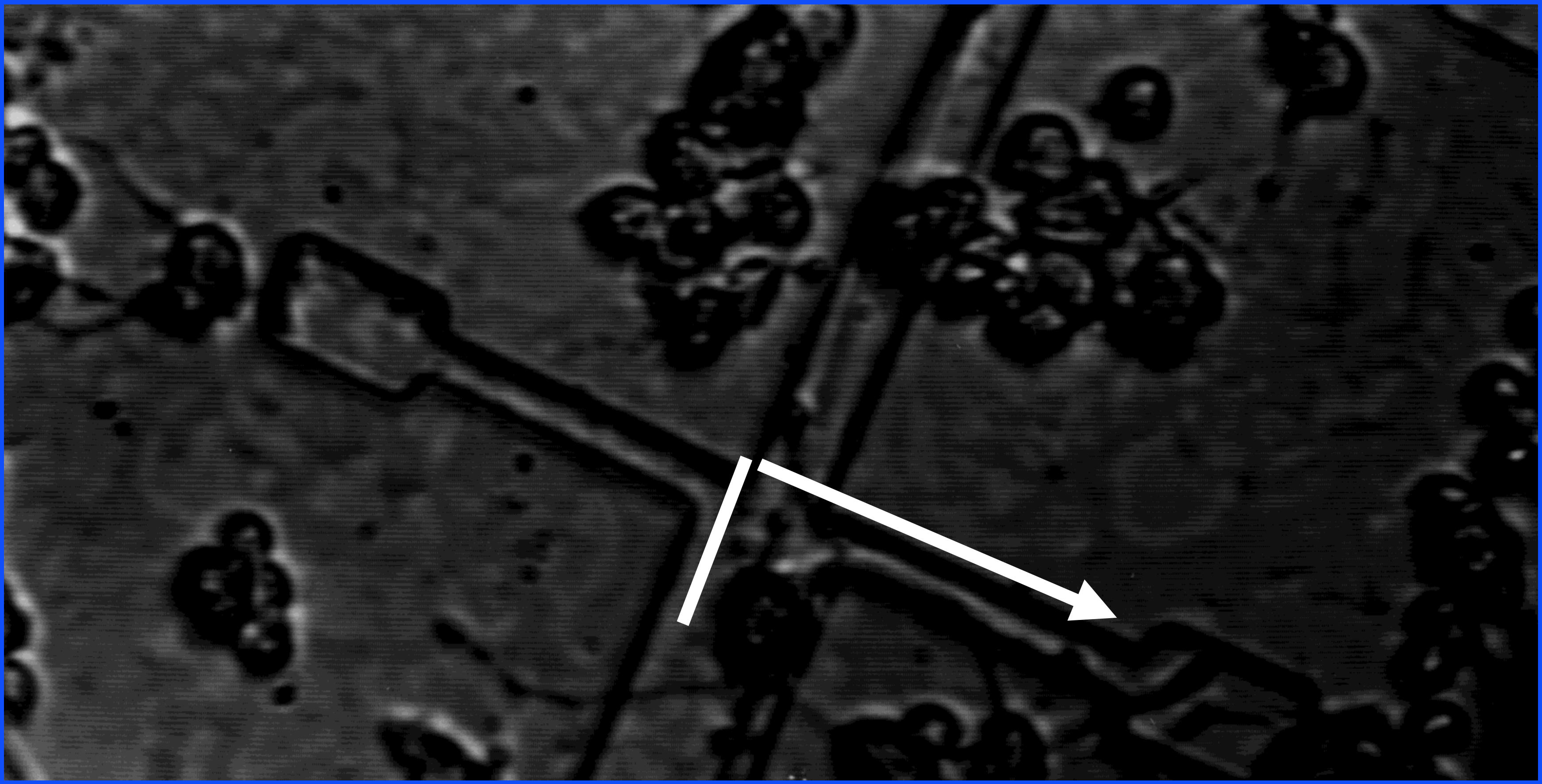
Courtesy D. DeBusschere, Stanford University.

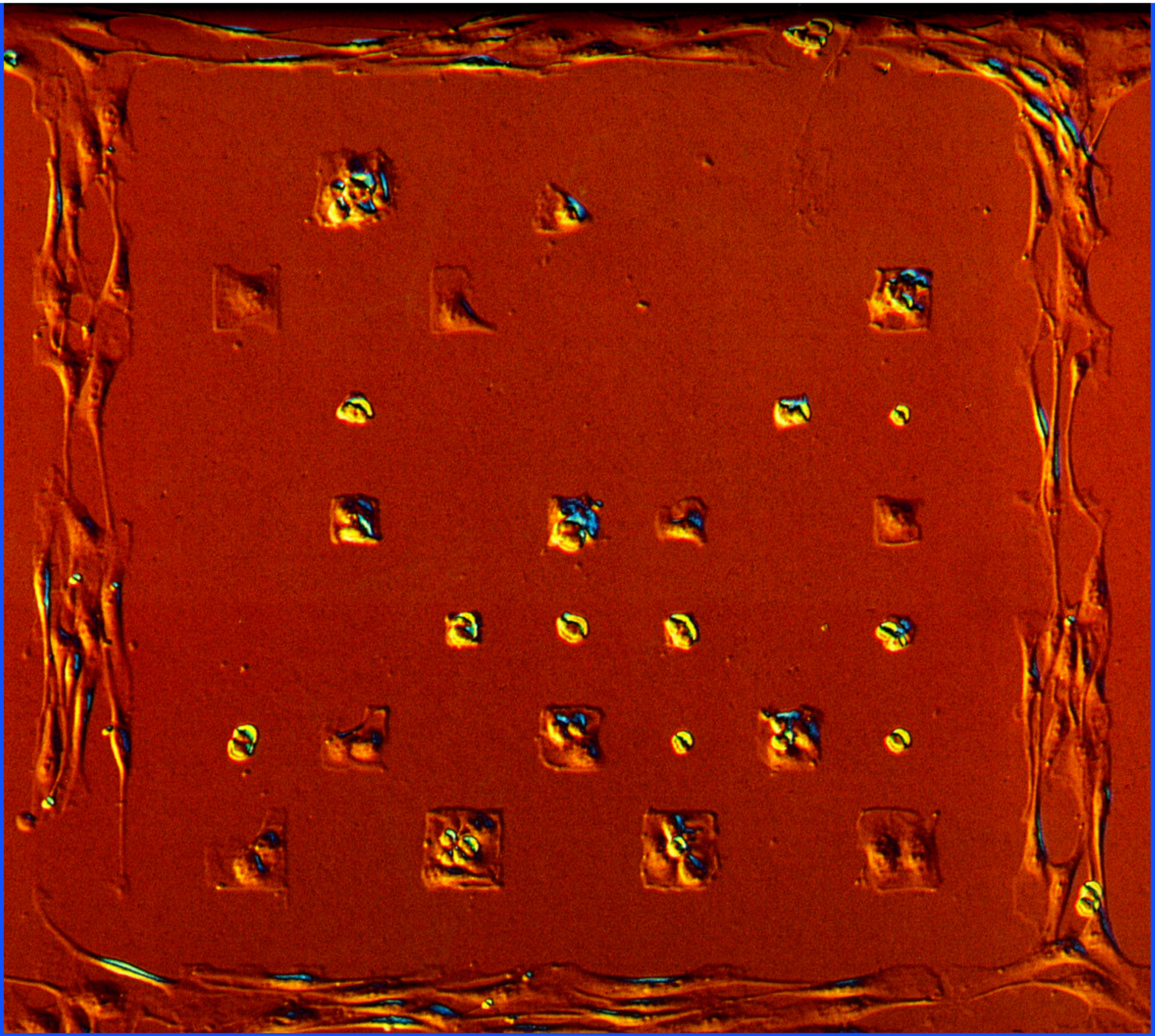
DIRECT NEURON-TO-FET COUPLING



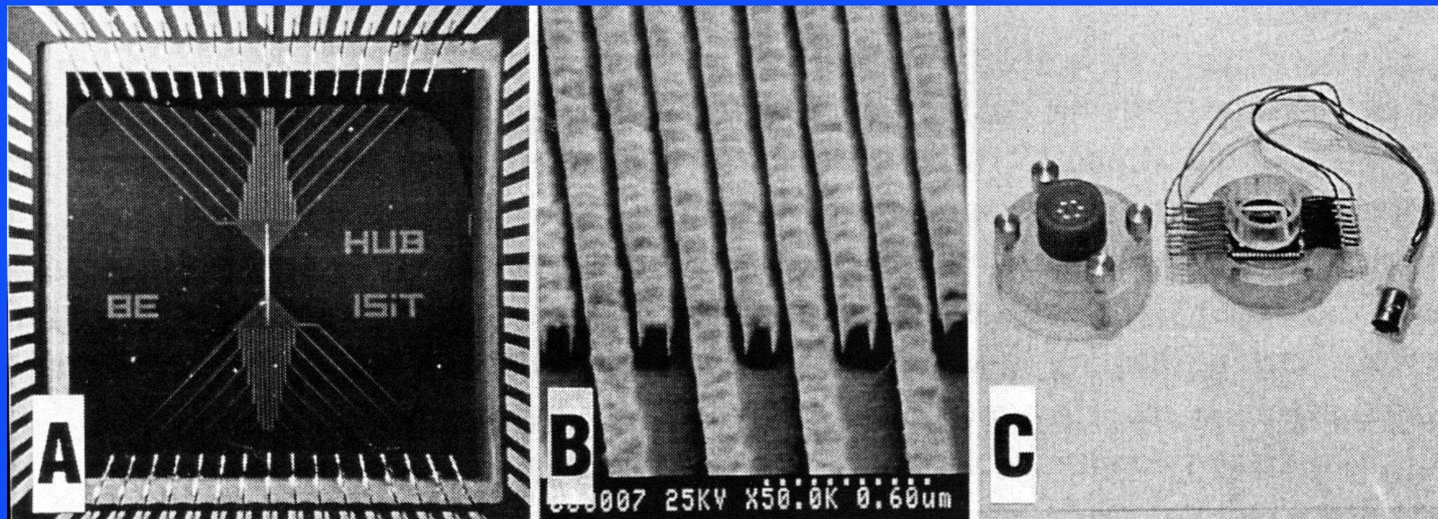
Reference: Fromherz, P., Offenhäusser, A., Vetter, T., and Weis, J., "A Neuron-Silicon Junction: A Retzius Cell of the Leech on an Insulated-Gate Field Effect Transistor," Science, vol. 252, no. 5010, May 31, 1991, pp. 1290 - 1293.

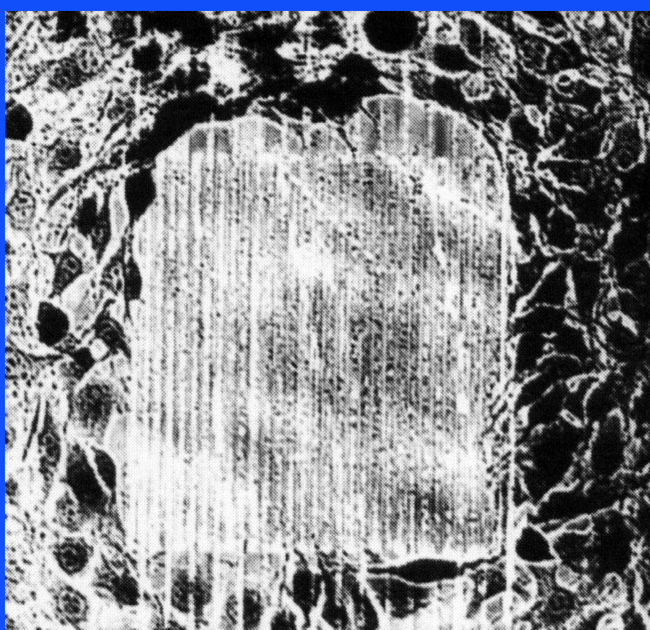
CONTROLLED OUTGROWTH OF NEURONS





Courtesy Prof. G. Whitesides, Harvard University. Reference: Mrksich, M., and Whitesides, G. M., "Patterning Self-Assembled Monolayers Using Microcontact Printing: A New Technology for Biosensors?" TIBTECH, vol. 13, 1995, pp. 228 - 235.





Interdigitated 170 nm width ultramicroelectrode results for 28 hours of culture of fibroblasts under 1.5V, 5 MHz fields, showing cell “repulsion.”

Source: Fuhr, G., and Wagner, B., "Electric Field Mediated Cell Manipulation, Characterization and Cultivation in Highly Conductive Media," Micro Total Analysis Systems, Proceedings of µTAS '94 Workshop, Twente, Netherlands, Nov. 21 - 22, 1994, pp. 209 - 214

PRACTICAL ISSUES FOR CHEMICAL SENSORS

- **Sensitivity**
- **Selectivity**
- **Repeatability**
- **Testing**
- **Calibration**

PRACTICAL ISSUES FOR CHEMICAL SENSORS

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- Selectivity
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CHEMICAL ACTUATOR: REVERSIBLE ELECTROLYSIS

- **Hamberg, et al. (1995) demonstrated a reversible electrolytic gas generation scheme using Cu and Pt electrodes and $CuSO_4$ solution.**
- **If the Pt is made anodic and the Cu cathodic, catalytic release of O_2 at the anode and Cu deposition at the cathode will occur.**

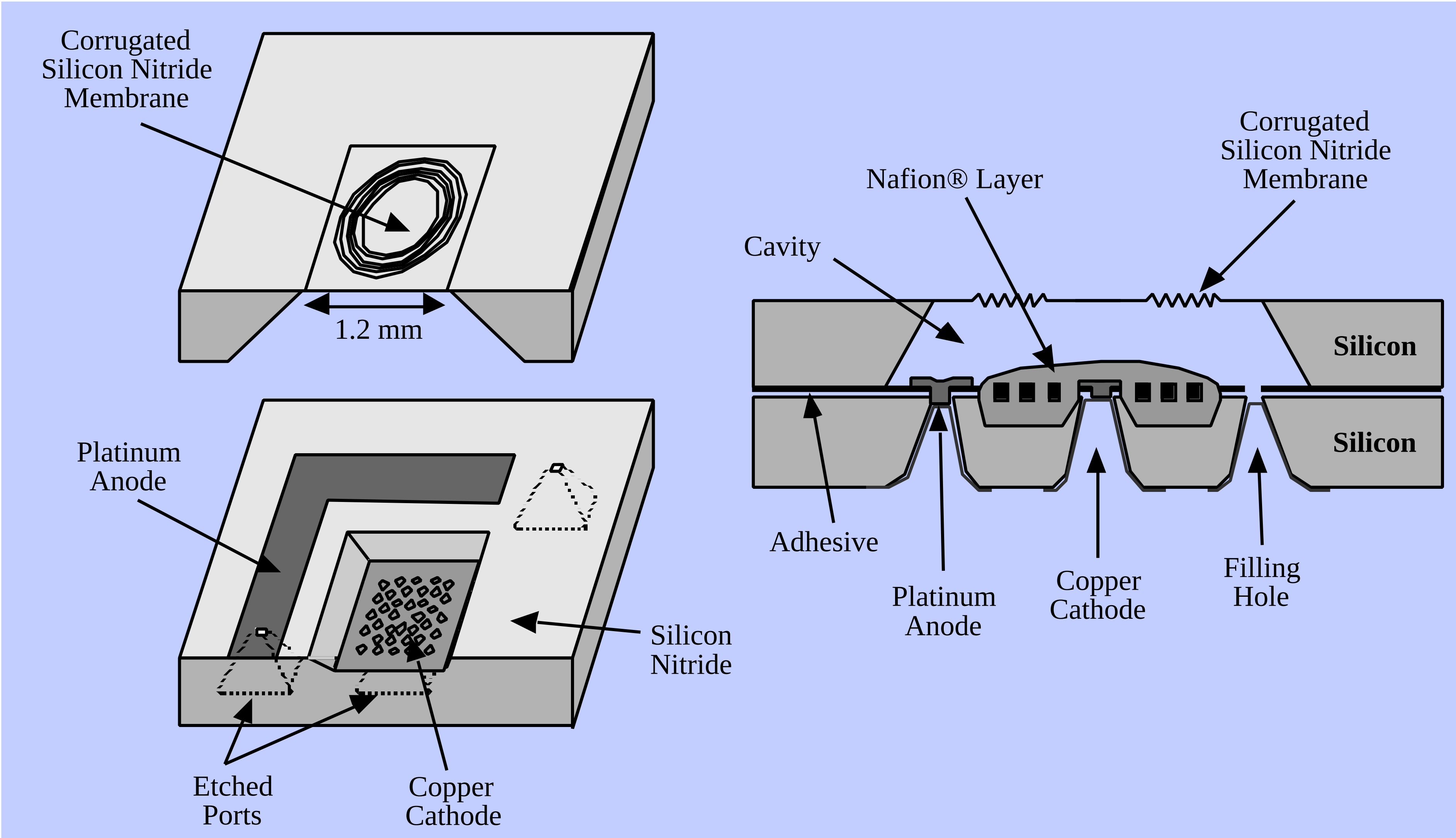
$$\text{(anode)}\quad 2H_2O \longrightarrow O_{2(g)} + 4H^+ + 4e^-$$

$$\text{(cathode)}\quad Cu^{2+} + 2e^- \longrightarrow Cu_{(s)}$$

$$\text{(overall reaction)}\quad 2H_2O + 2Cu^{2+} \longrightarrow O_{2(g)} + 4H^+ + 2Cu_{(s}$$

- **The reaction was carried out in a sealed, micromachined chamber with a corrugated silicon nitride membrane.**
- **Only 20mbar pressure for 1.5 µm deflections were possible over 1 minute, reversing in 5 minutes, with only 10µW power consumption.**

Reference: Hamberg, M., Neagu, C., Gardeniers, J. G. E., Ijntema, D. J., and Elwenspoek, M., "An Electrochemical Micro Actuator," Proceedings of the IEEE Micro Electro Mechanical Systems, Workshop, Amsterdam, the Netherlands, February 2, 1995, p. 106-110.



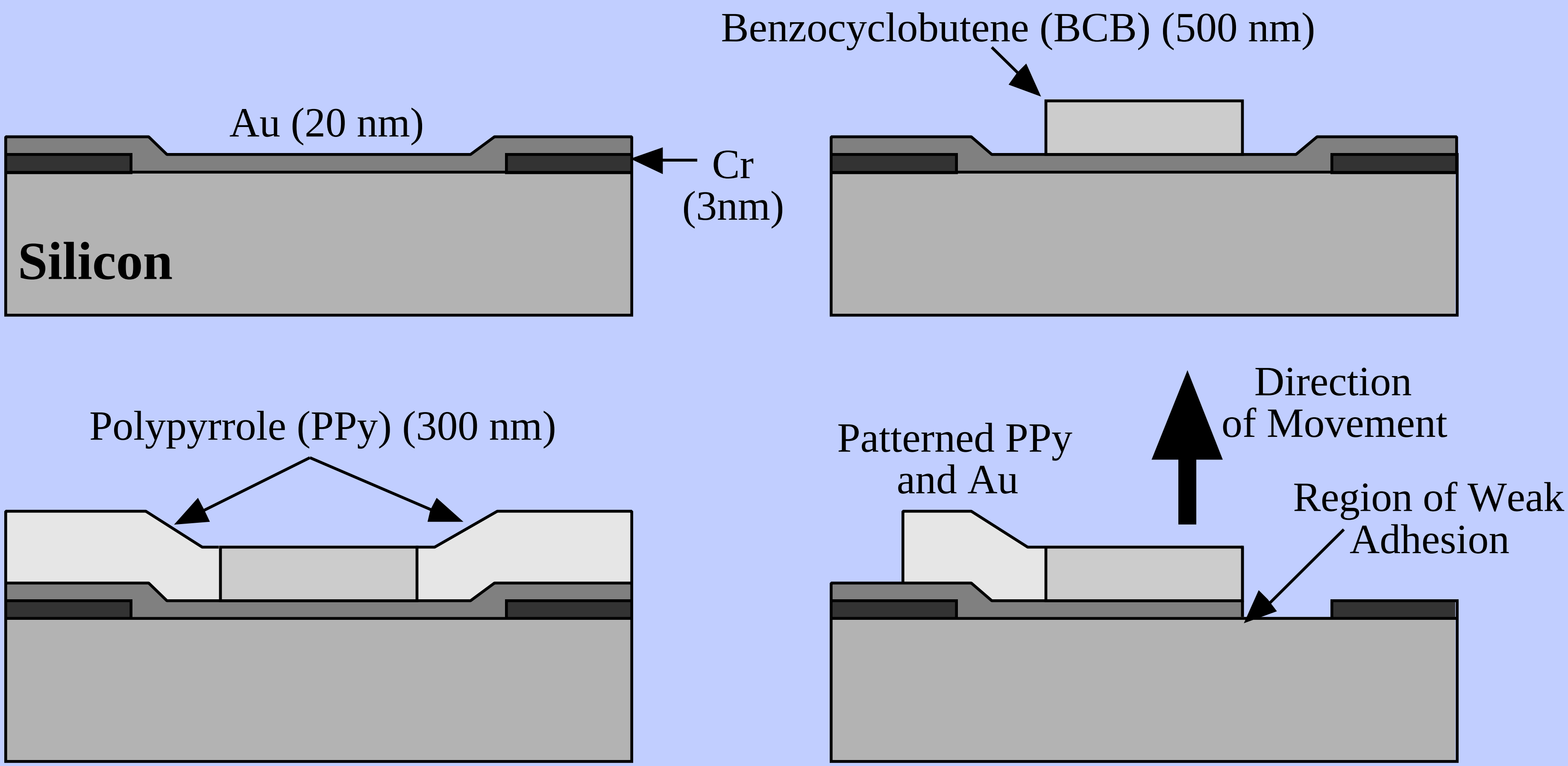
Reference: Hamberg, M., Neagu, C., Gardeniers, J. G. E., Ijntema, D. J., and Elwenspoek, M., "An Electrochemical Micro Actuator," Proceedings of the IEEE Micro Electro Mechanical Systems, Workshop, Amsterdam, the Netherlands, February 2, 1995, p. 106-110.

POLYPYRROLE EXPANSION CHEMICAL ACTUATORS

- It is well known that conducting polymers of the polypyrrole (PPy) family can be grown electrochemically and are capable of significant (several percent) physical expansion when doped with a suitable molecule (e.g. dodecylbenzene sulfonate) and when cations such as Na are present.
- Smela, et al. (1995) demonstrated the electrically controlled expansion of PPy thin films that were doped in such a manner and fabricated as micro-hinges that, when contracted, would raise flaps of an inert, rigid, polymer (benzocyclobutene).
- When operated in an aqueous salt solution, the flaps could bend through nearly 90° within 0.5 - 10 seconds (depending on PPy thickness) when the voltage was raised from -1.0 to +0.35 V.
- They used selective removal of a Cr sticking layer to form regions of Au that were so weakly adherent to the underlying Si that the hinges self-released.

References: Smela, E., Inganäs, O., and Lundrström, I., "Differential Adhesion Method for Microstructure Release: An Alternative to the Sacrificial Layer, Proceedings of Transducers '95, Stockholm, Sweden, June 25 - 29, 1995, vol. 2, pp. 350 - 351.

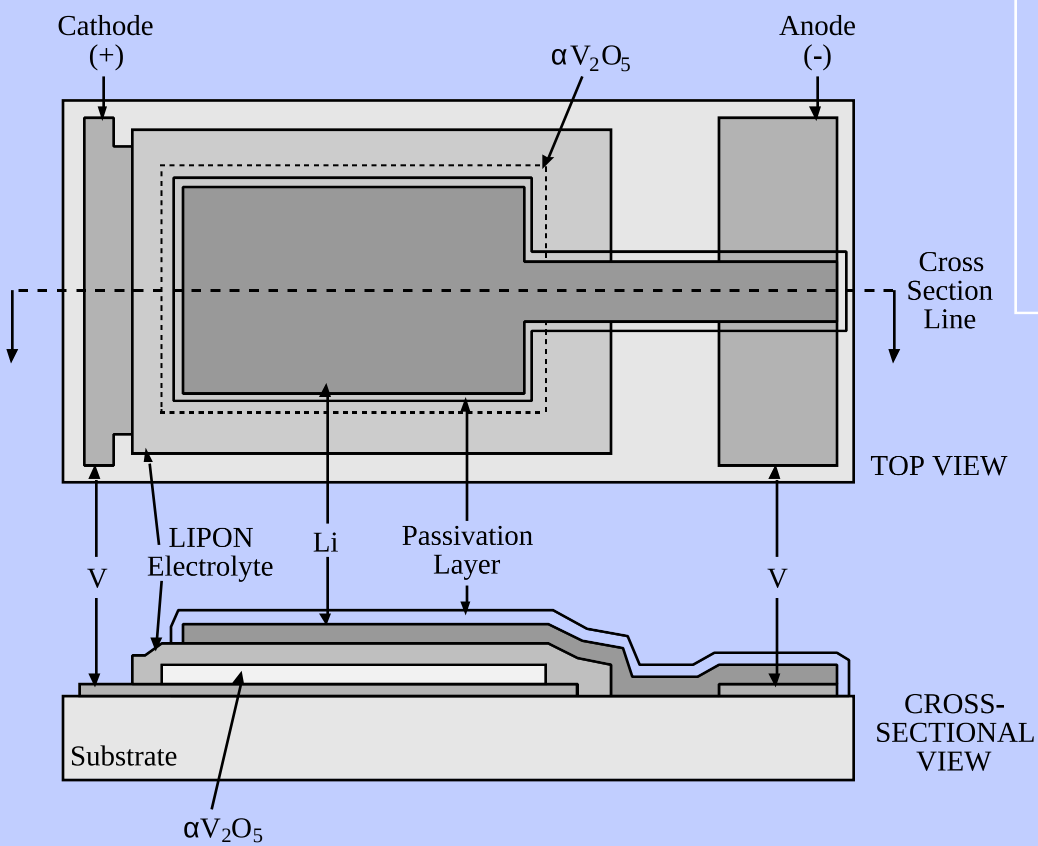
Smela, E., Inganäs, O., and Lundrström, I., "Self-Opening and Closing Boxes and Other Micromachined Folding Structures," Proceedings of Transducers '95, Stockholm, Sweden, June 25 - 29, 1995, vol. 2, pp. 350 - 351.

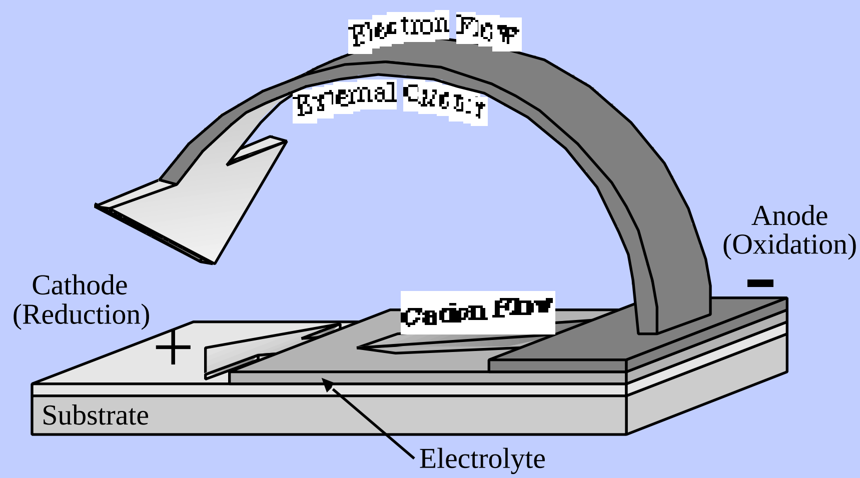


References: Smela, E., Inganäs, O., and Lundrström, I., "Differential Adhesion Method for Microstructure Release: An Alternative to the Sacrificial Layer, Proceedings of Transducers '95, Stockholm, Sweden, June 25 - 29, 1995, vol. 2, pp. 350 - 351.

Smela, E., Inganäs, O., and Lundrström, I., "Self-Opening and Closing Boxes and Other Micromachined Folding Structures," Proceedings of Transducers '95, Stockholm, Sweden, June 25 - 29, 1995, vol. 2, pp. 350 - 351.

THIN-FILM BATTERIES





Reference: Bates, J. B., Gruzalski, G. R., Dudney, N. J., Luck, C. F., Yu, X.-H., Jones, S. D., "Rechargeable Thin-Film Lithium Microbatteries," Solid State Technology, vol. 36, no. 7, July 1993, pp. 59 - 64.

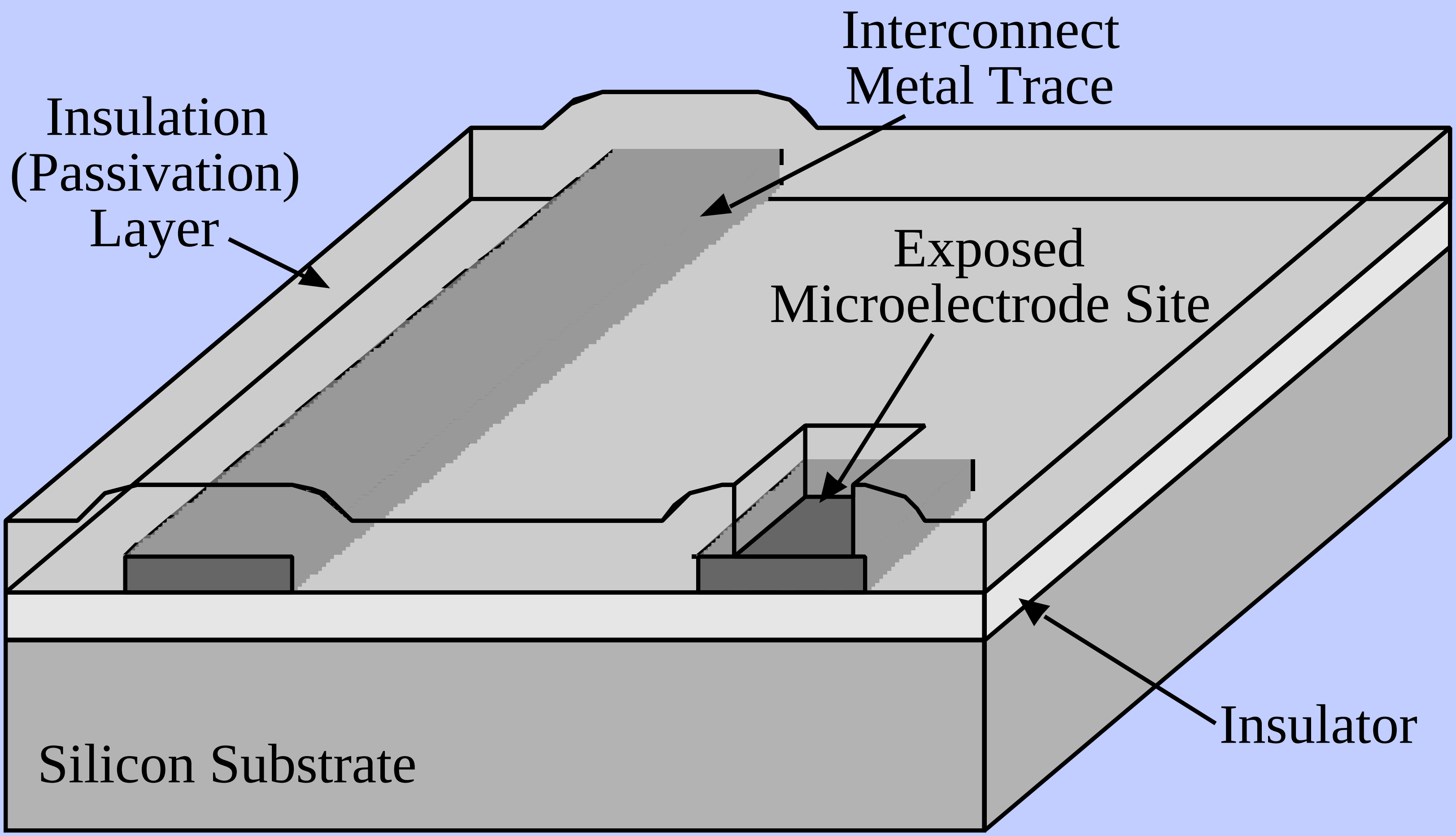
BIOLOGICAL TRANSDUCERS

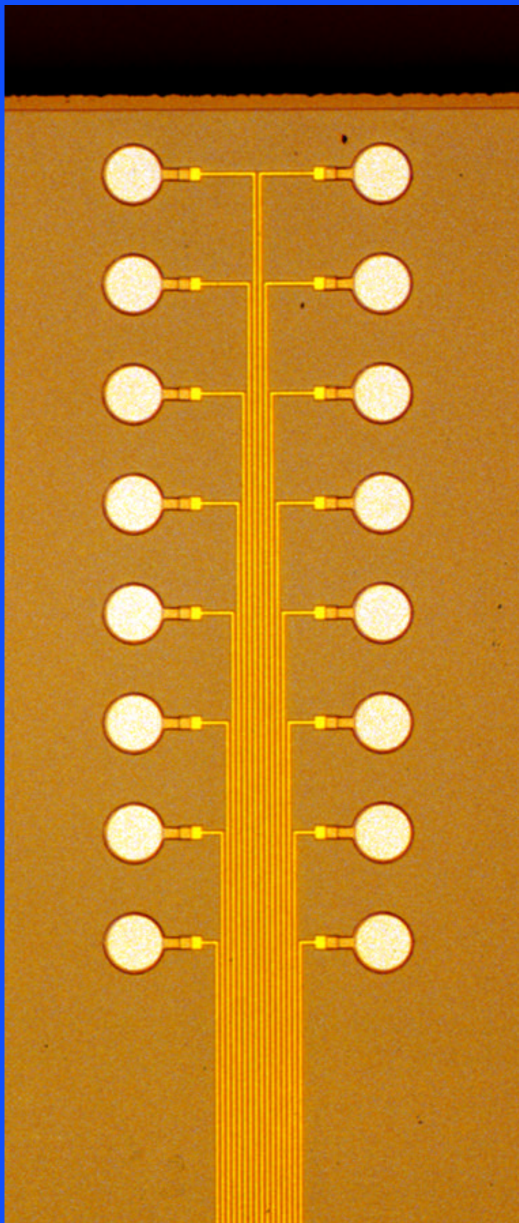
- Neural interfaces
- Cultured tissue systems
- Others

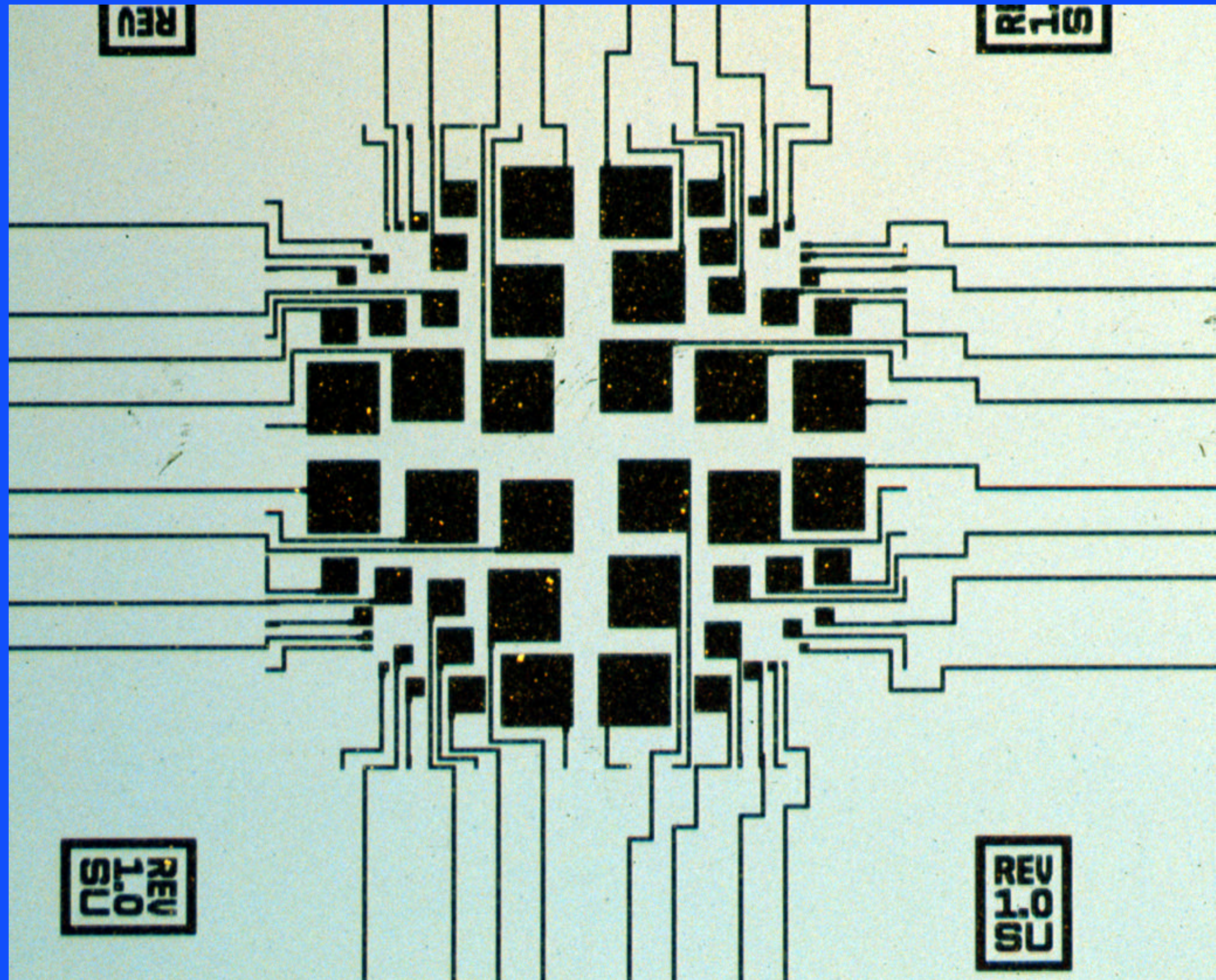
BIOLOELECTRIC TRANSDUCER CONCEPTS RECAP

- Electrically active cells (neural, muscular, etc.) generate small currents in short "spikes" (action potentials) - discussed already.
- These currents are due to ions (e.g. Na^+, K^+) moving across the cell membrane through protein channels.
- Extracellular recording from close proximity to cells can pick up these signals (≈ 100 - 1000 µV).
- Many thin-film electrode designs can be used, and they are generally simple to fabricate.

GENERIC MICROELECTRODE



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1.0
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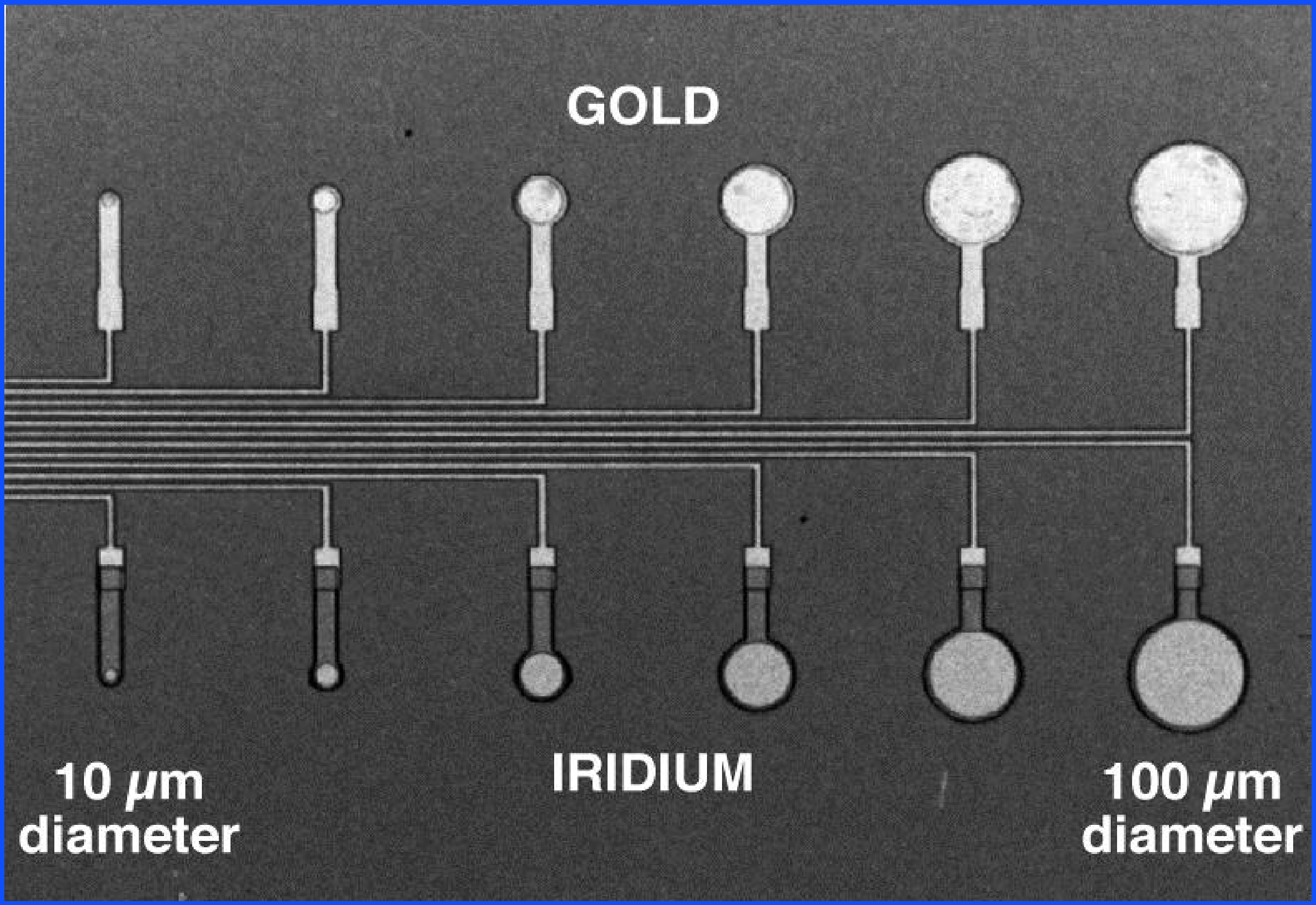


- **Electrode sizes can be comparable to neural cells or larger.**
- **Nearly arbitrary geometries are possible.**
- **Multiple electrode materials can be combined on a single array.**

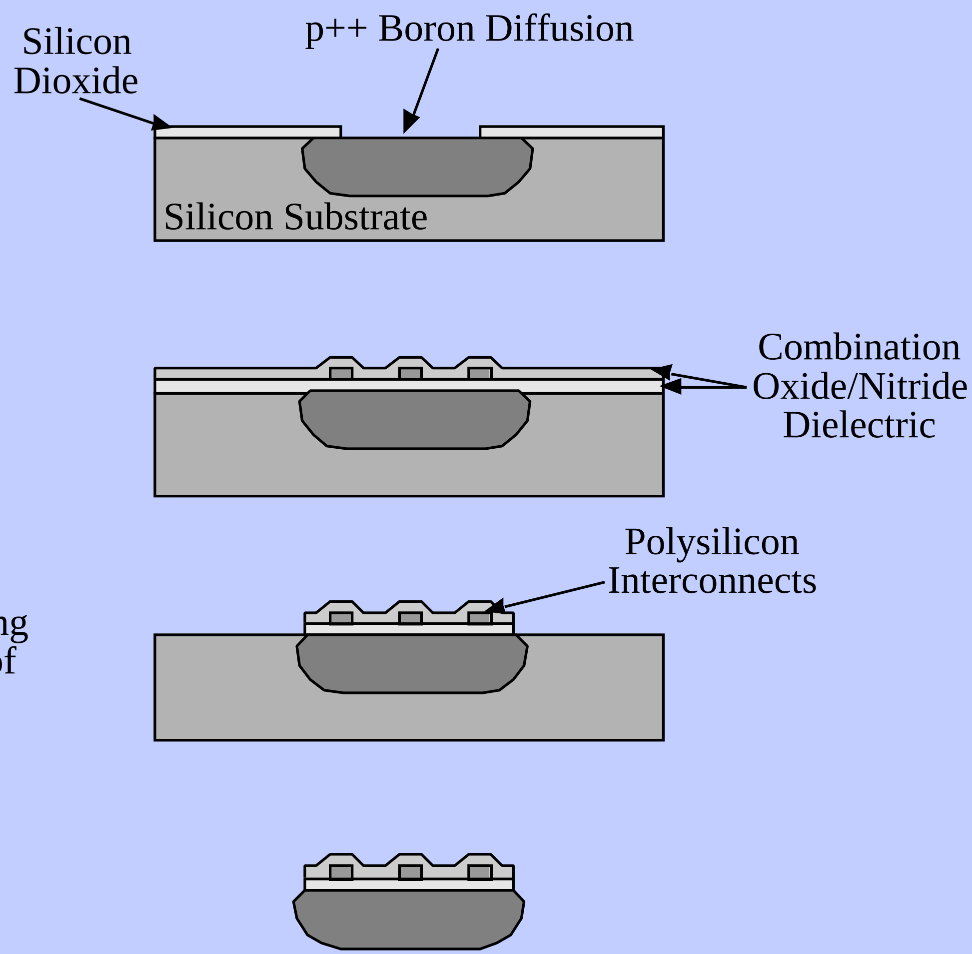
PENETRATING CORTICAL PROBES

Selective diffusion of substrate.

Deposition, patterning and insulation of conductors.

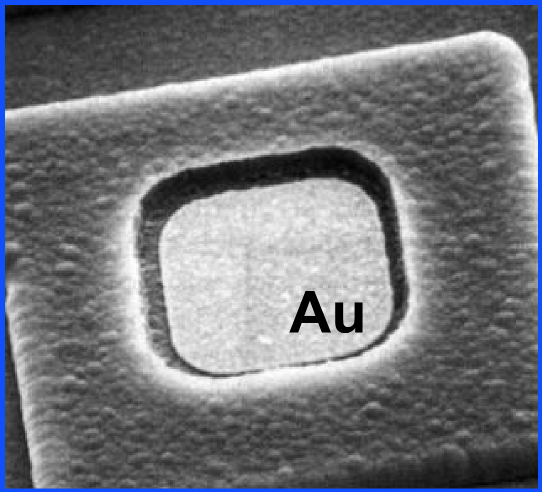
Dielectric patterning and metalization of recording sites.

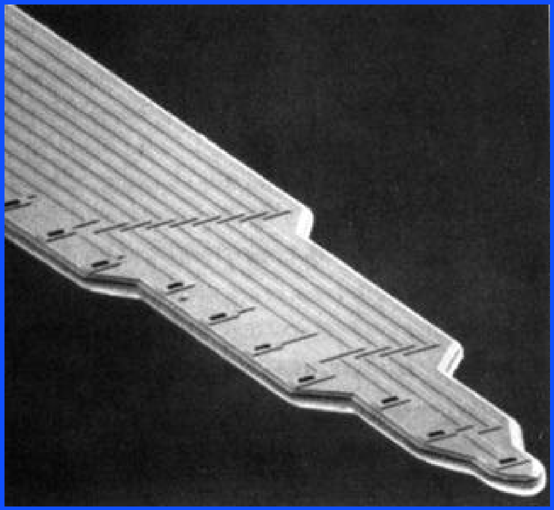
Wafer dissolution in EDP.

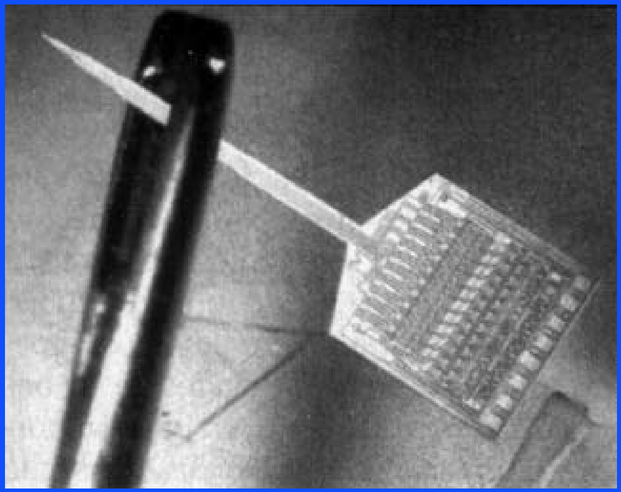


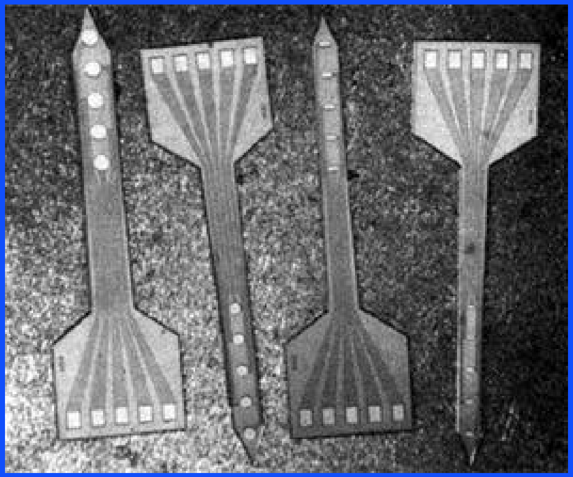
Reference: Najafi, K., Wise, K. D., and Mochizuki, T., “A High-Yield IC-Compatible Multichannel Recording Array,” IEEE Transactions on Electron Devices, vol. ED-32, no. 7, July 1985, pp. 1206 - 1211.

Courtesy Prof. K. Wise, University of Michigan.



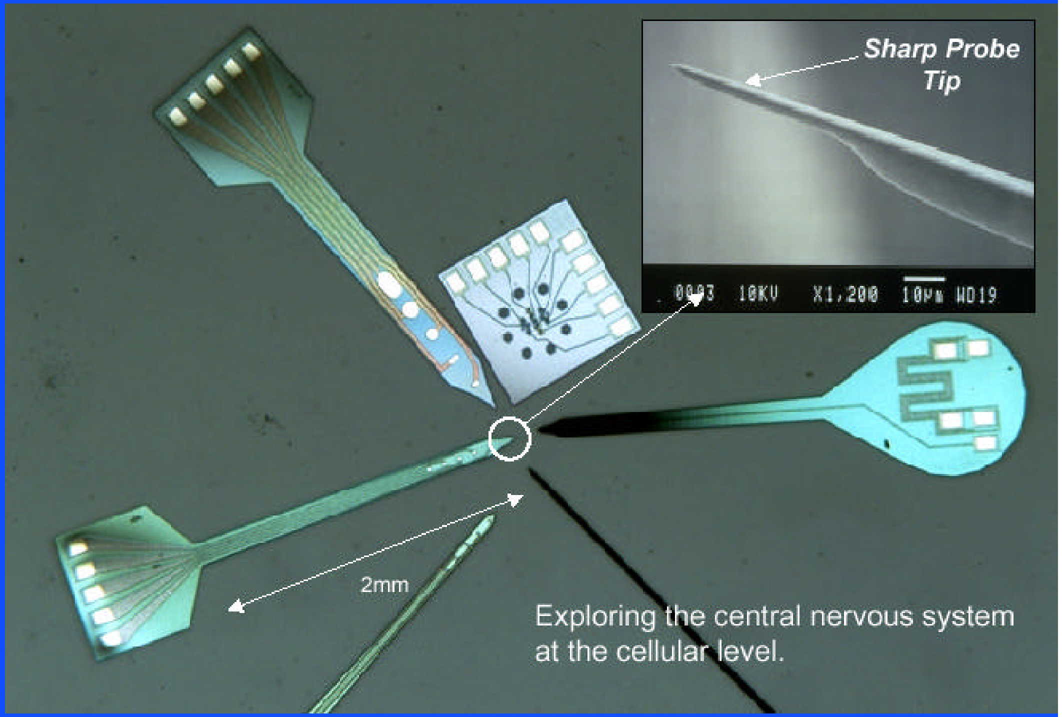


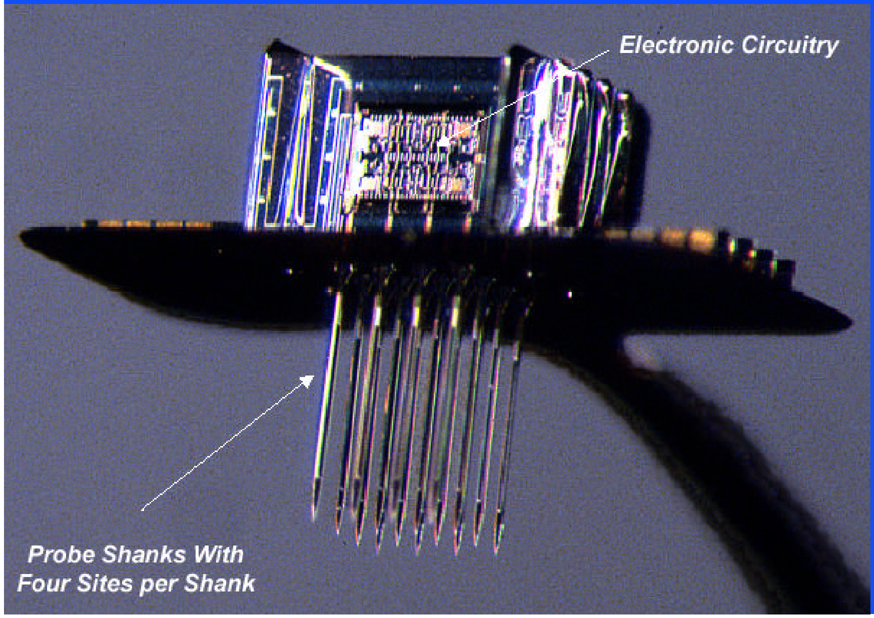




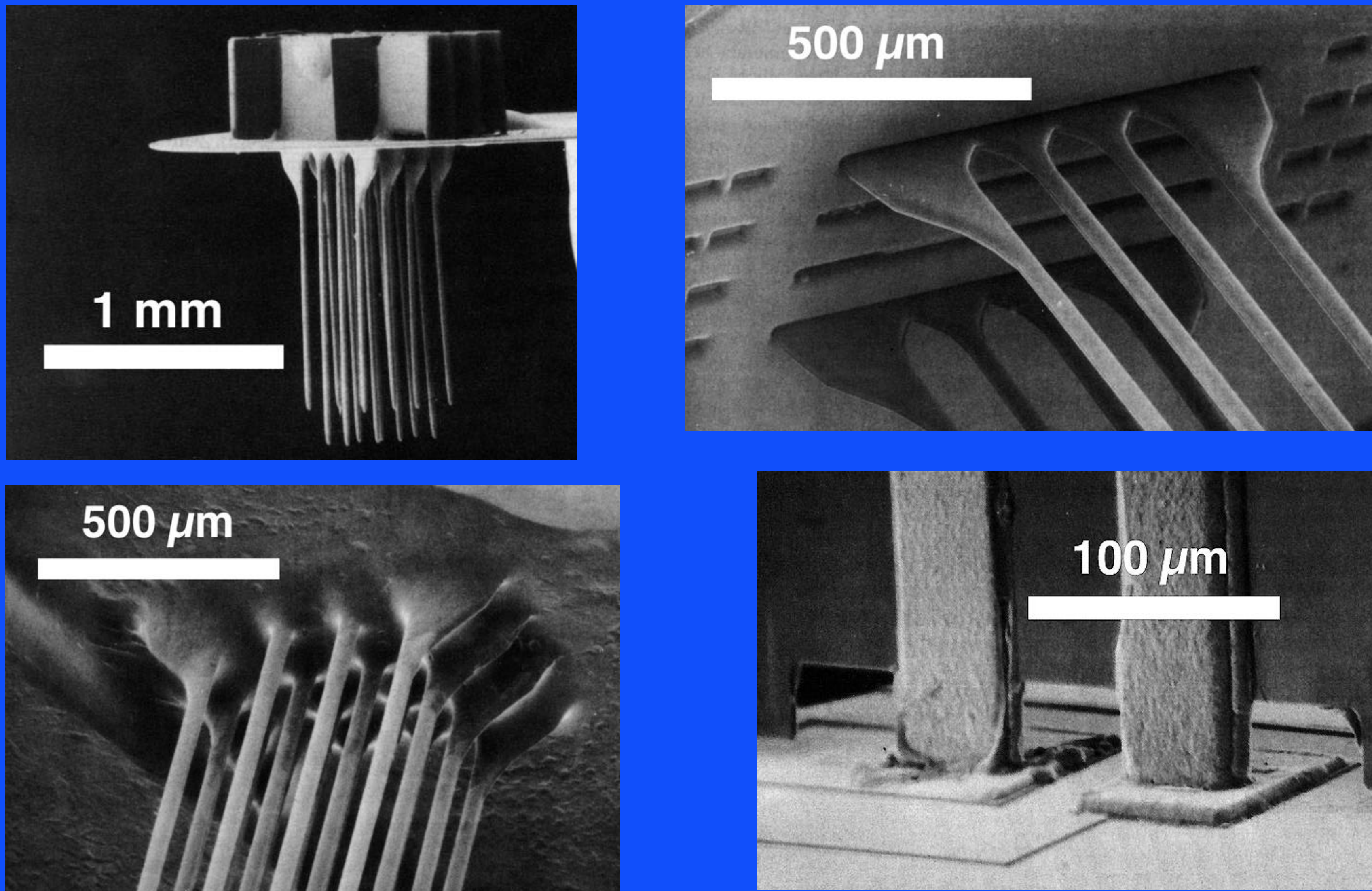
Source: Najafi, K., "Solid-State Microsensors for Cortical Nerve Recordings," IEEE Engineering in Medicine and Biology Magazine, vol. 13, no. 3, June/July 1994, pp. 375 - 387.

MICHIGAN CORTICAL PROBES

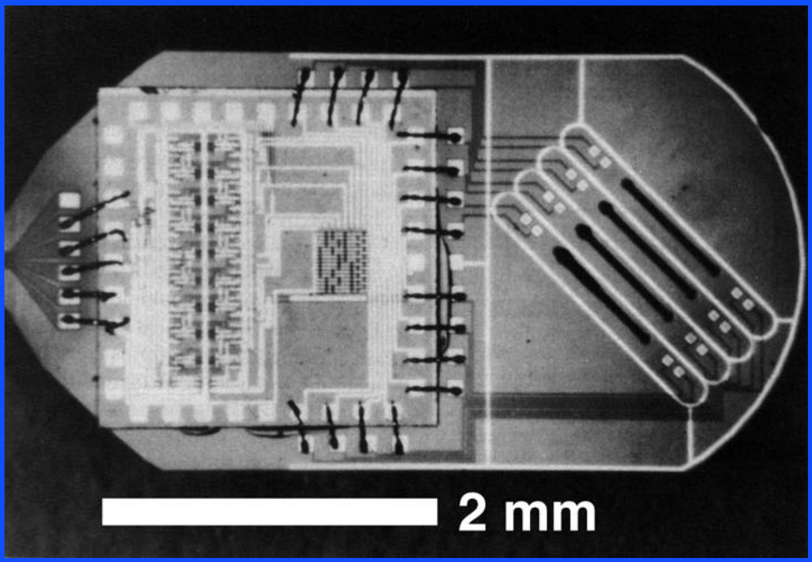


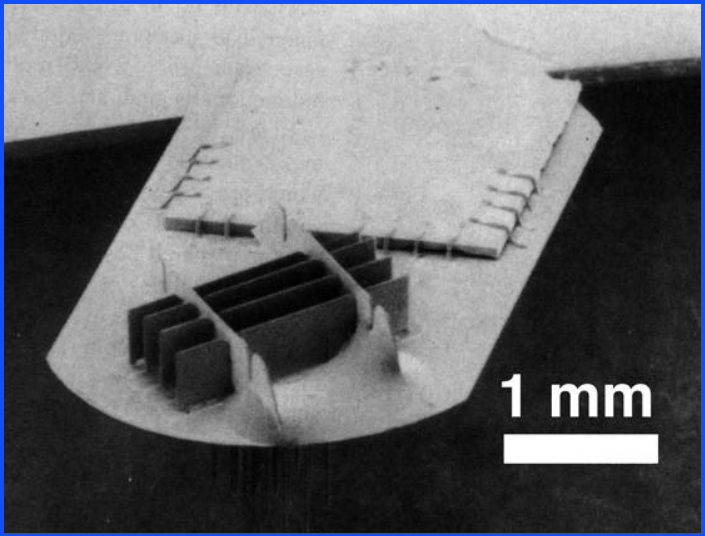


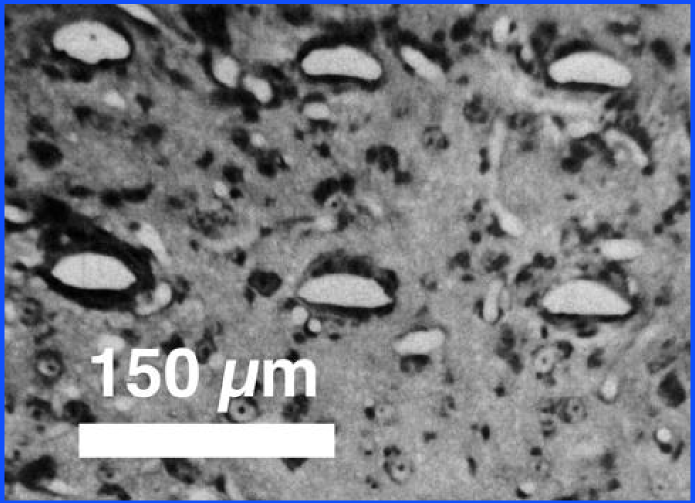
Courtesy Prof. K. Wise, University of Michigan.



Source: Hoogerwerf, A. C. and Wise, K. D., "A Three-Dimensional Microelectrode Array for Chronic Neural Recording," IEEE Transactions on Biomedical Engineering, vol. 41, no. 12, Dec. 1994, pp. 1136 - 1146.

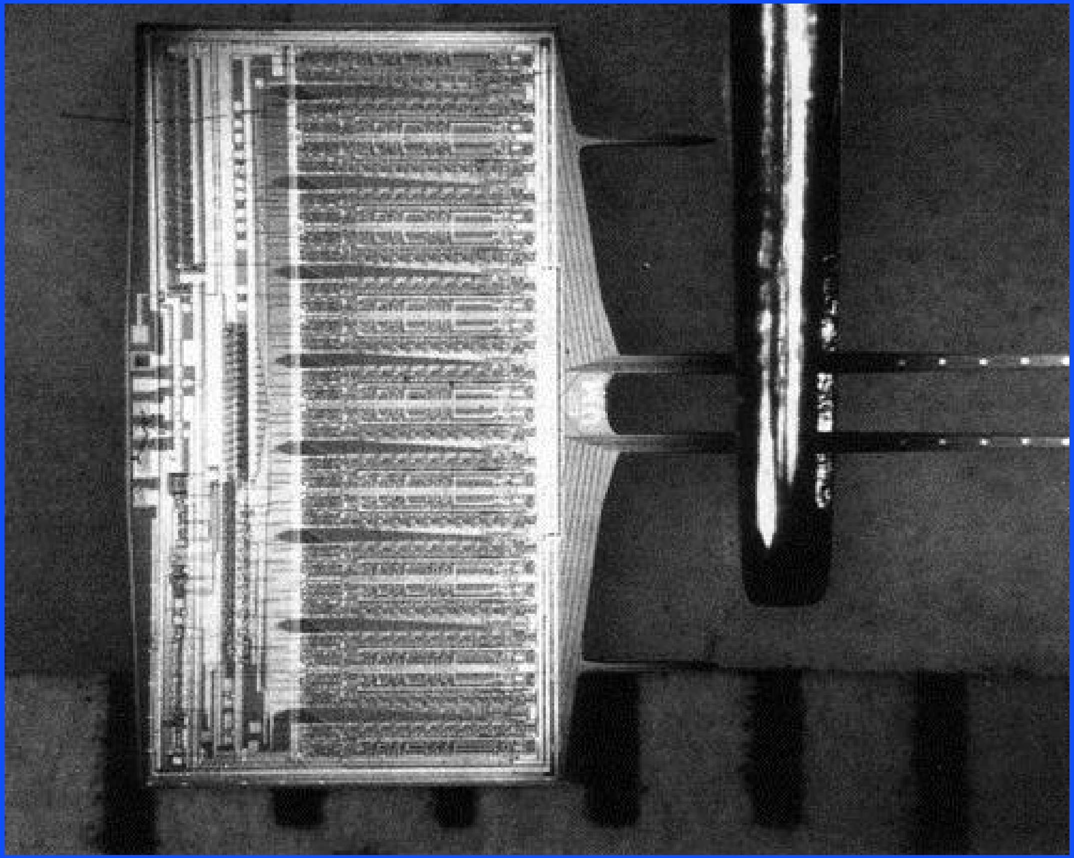






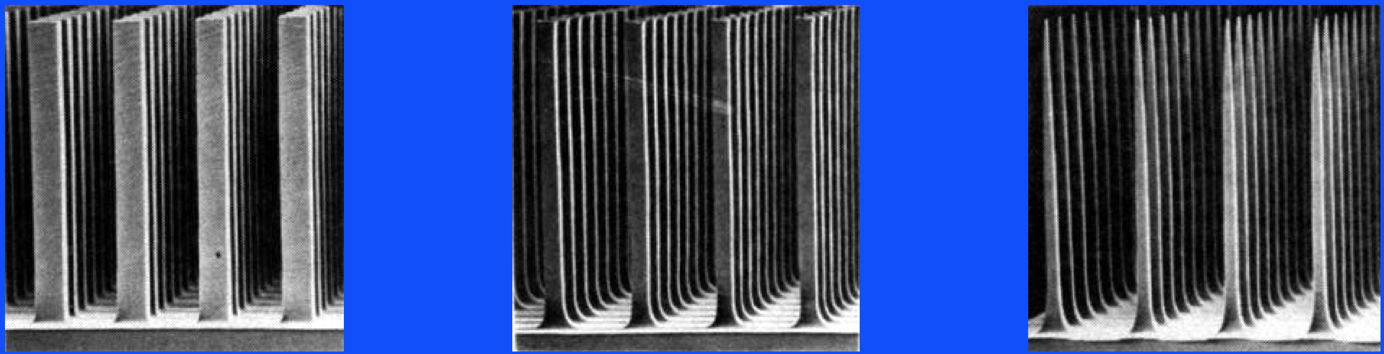
Source: Hoogerwerf, A. C. and Wise, K. D., "A Three-Dimensional Microelectrode Array for Chronic Neural Recording," IEEE Transactions on Biomedical Engineering, vol. 41, no. 12, Dec. 1994, pp. 1136 - 1146.

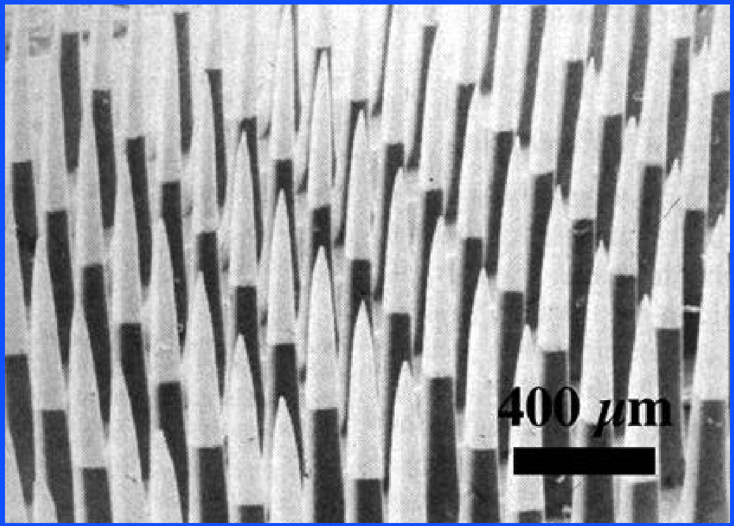
MIGHIGAN MULTISITE NEUROSTIMULATOR PROBE

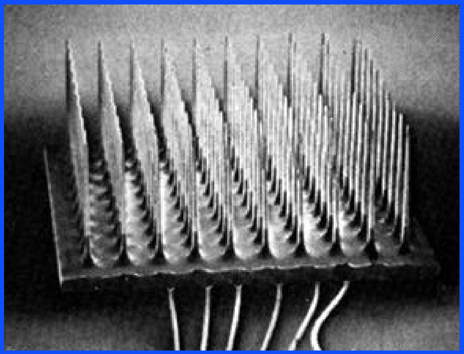


Najafi, K., “Solid-State Microsensors for Cortical Nerve Recordings,” IEEE Engineering and Biology Magazine, June/July 1994, pp. 375 - 387.

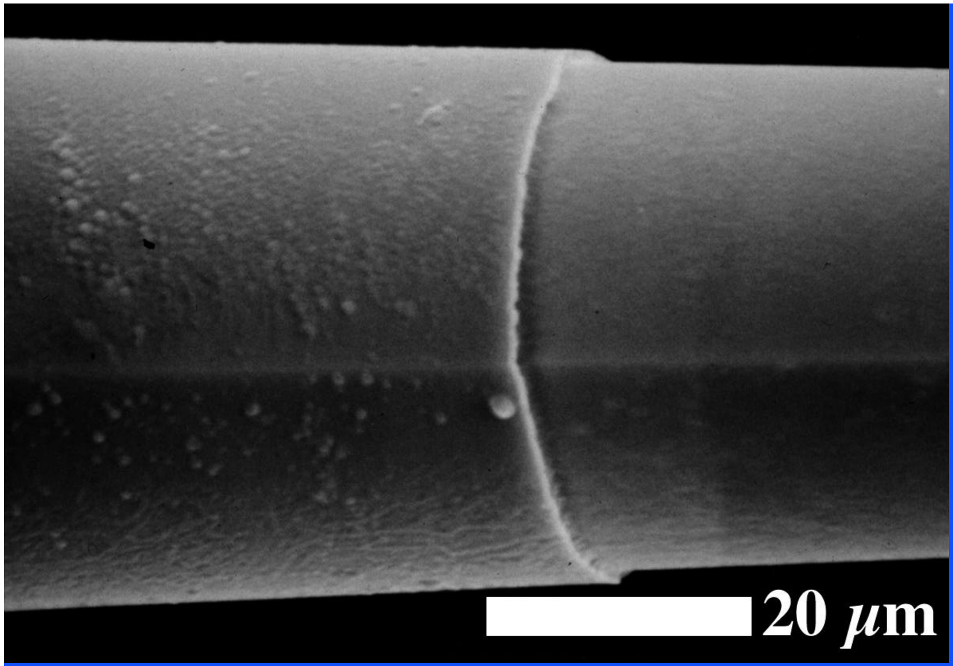
UTAH PENETRATING ARRAYS

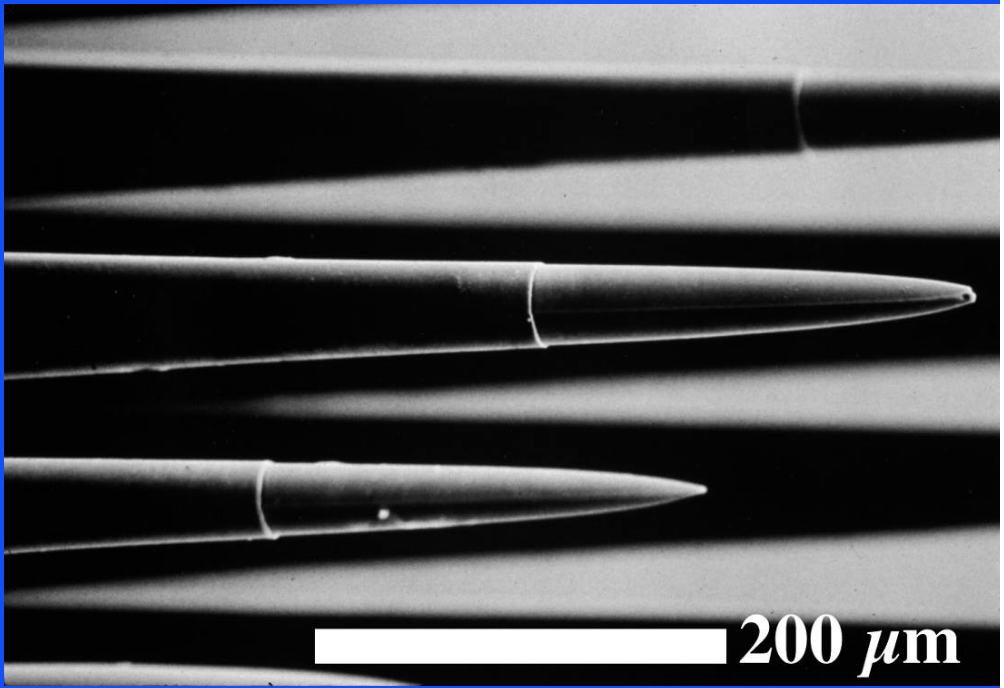






Courtesy Prof. R. Normann, University of Utah.

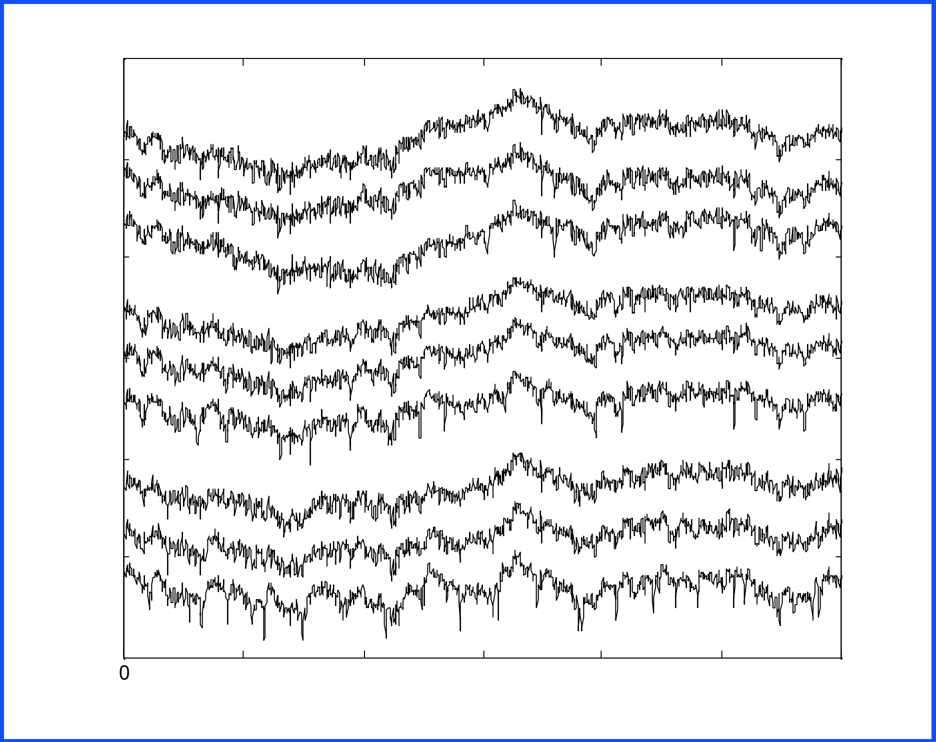


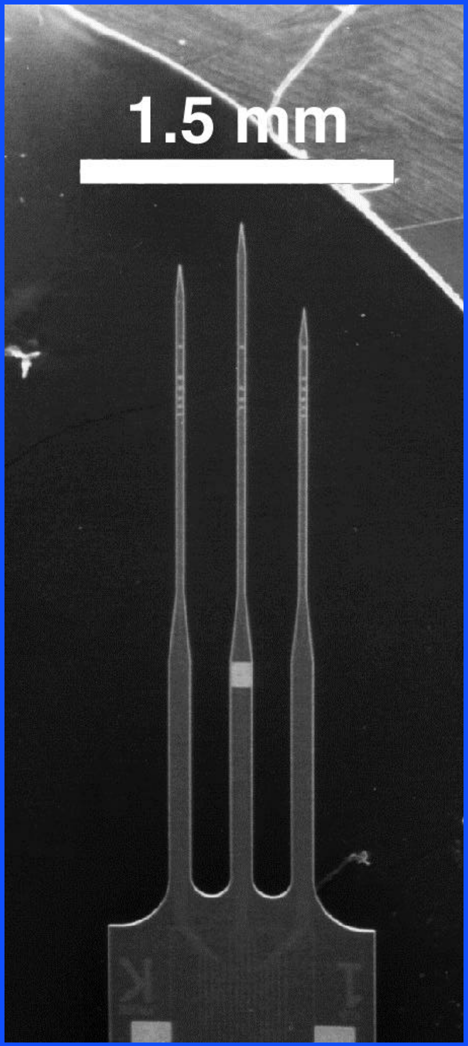


Courtesy Prof. R. Normann, University of Utah.

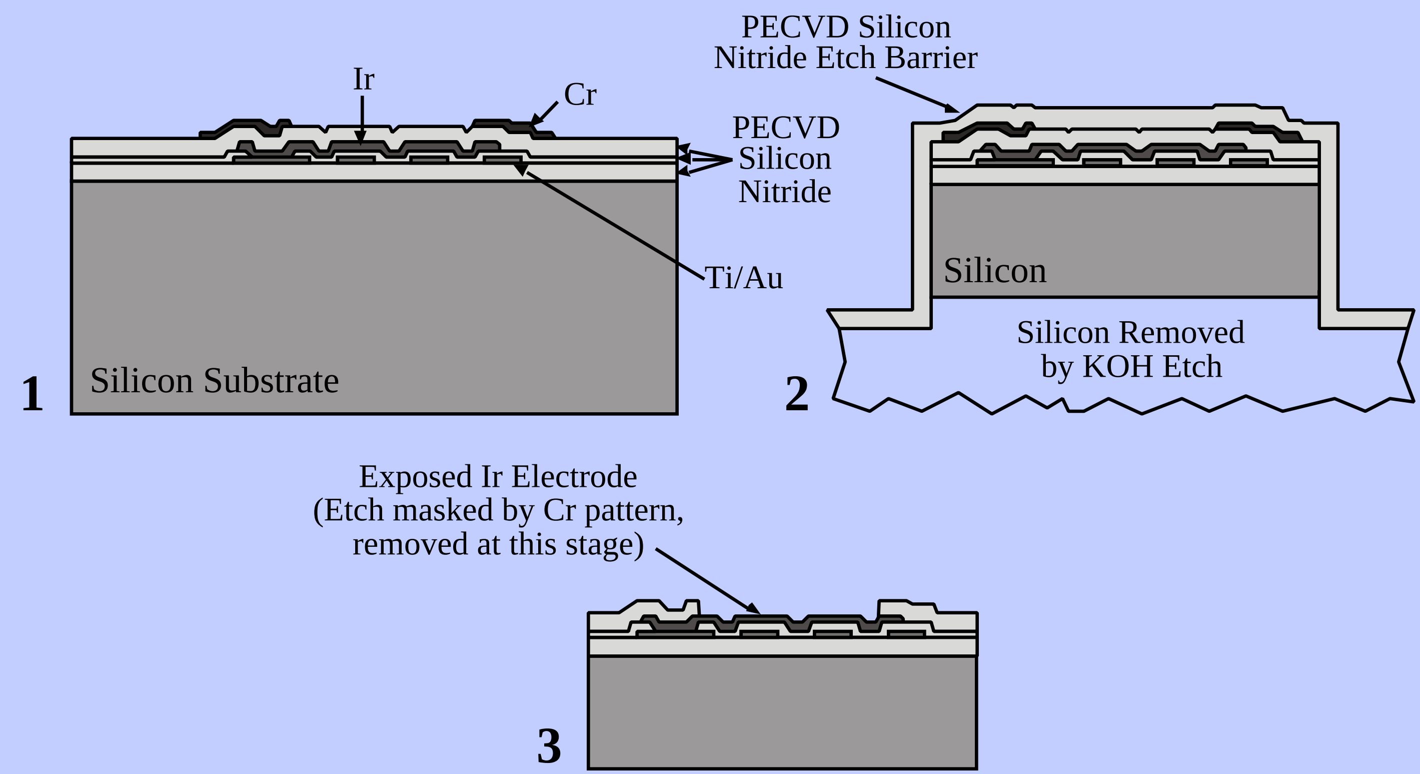
DRY-ETCHED CORTICAL PROBES

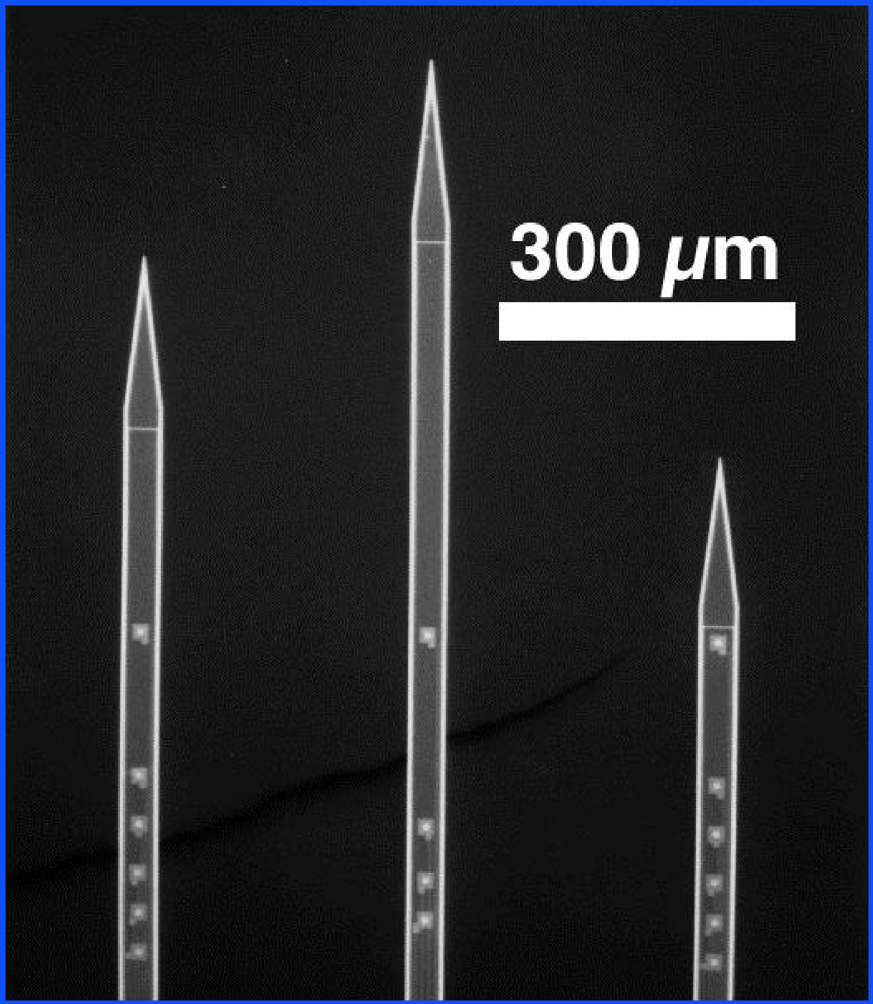
- **Plasma etch defined probe shape**
- **Multiple thin-film iridium electrodes**
- **Separate 18-channel amplifier chip.**

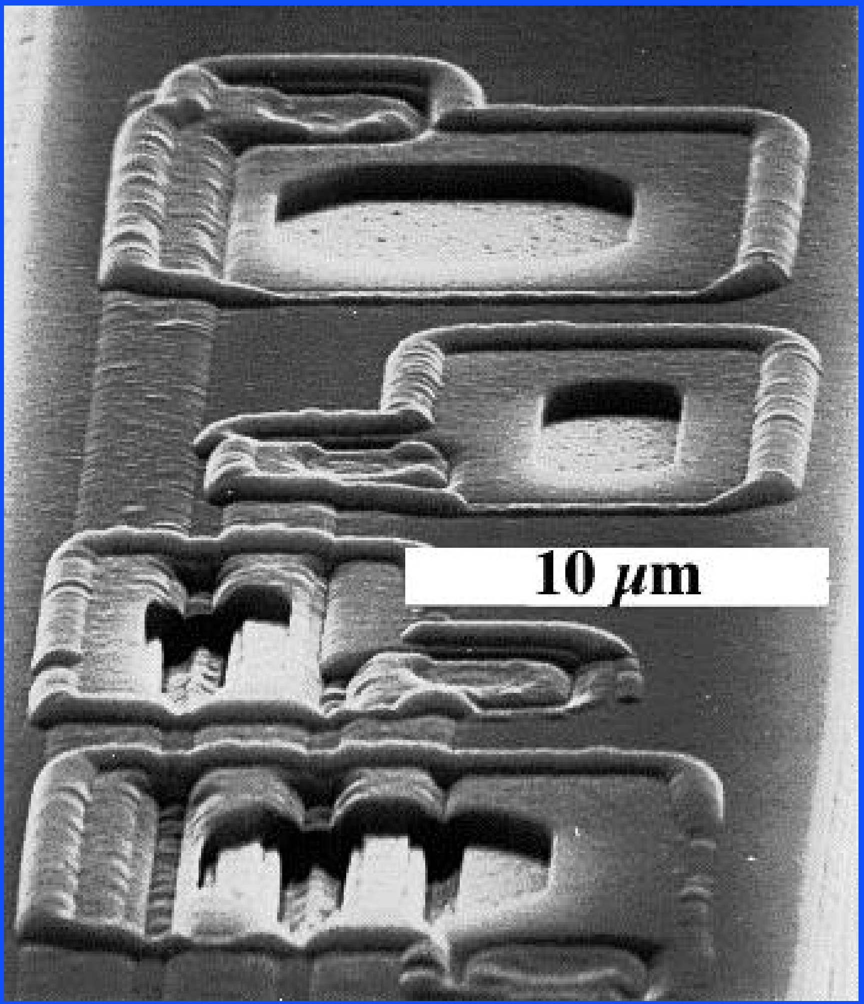




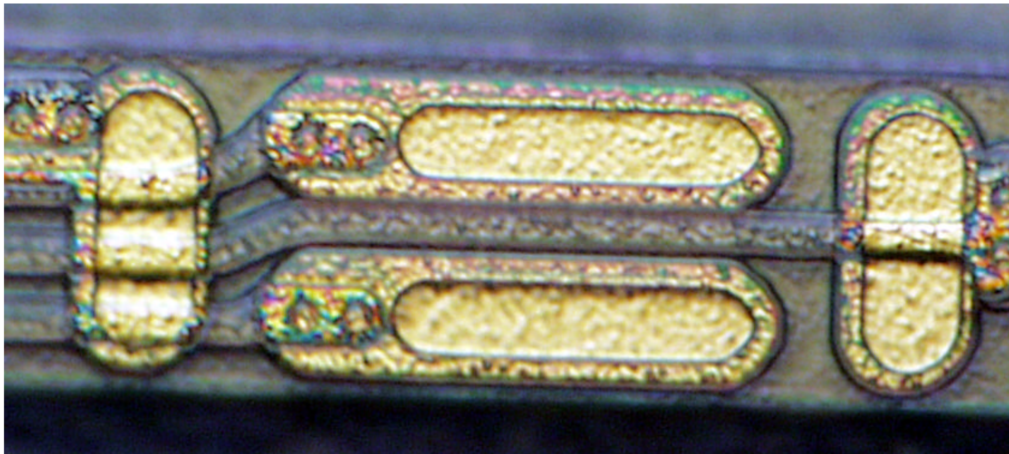
Reference: Kewley, D. T., Hills, M. D., Borkholder, D. A., Opris, I. E., Maluf, N. I., Storment, C. W., Bower, J. M., and Kovacs, G. T. A., "Plasma-Etched Neural Probes," Sensors and Actuators, vol. A58, no. 1, Jan. 1997, pp. 27 - 35.

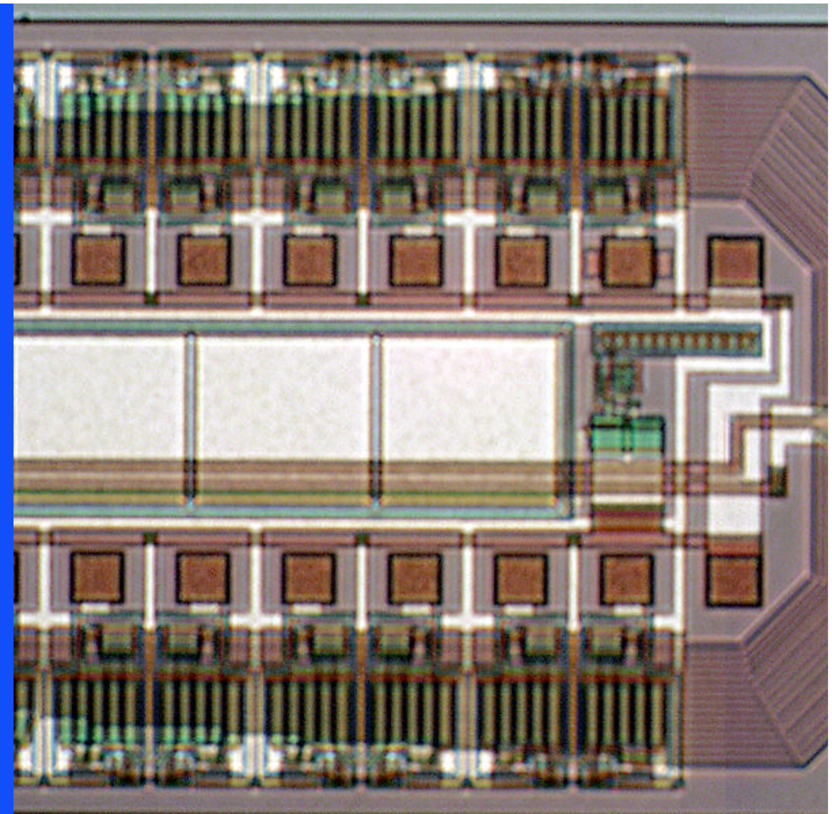

PECVD Silicon
Nitride Etch Barrier
Ir
Cr
PECVD
Silicon
Nitride
Ti/Au
Silicon
Silicon Removed
by KOH Etch
1
Silicon Substrate
2
Exposed Ir Electrode
(Etch masked by Cr pattern,
removed at this stage)
3



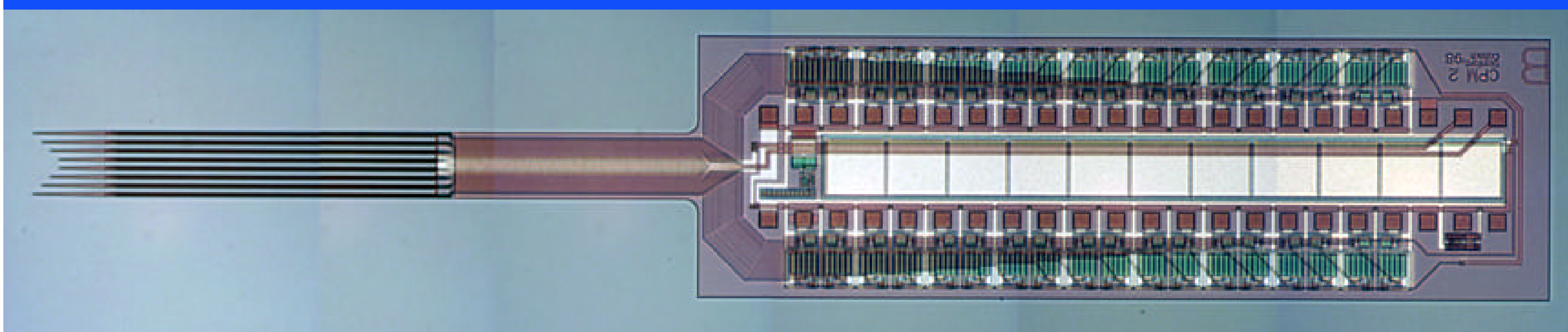


Reference: Kewley, D. T., Hills, M. D., Borkholder, D. A., Opris, I. E., Maluf, N. I., Storment, C. W., Bower, J. M., and Kovacs, G. T. A., "Plasma-Etched Neural Probes," Proceedings of the Solid-State Sensor and Actuator Workshop, Hilton Head, South Carolina, June 3 - 6, 1996, pp. 266 - 271.



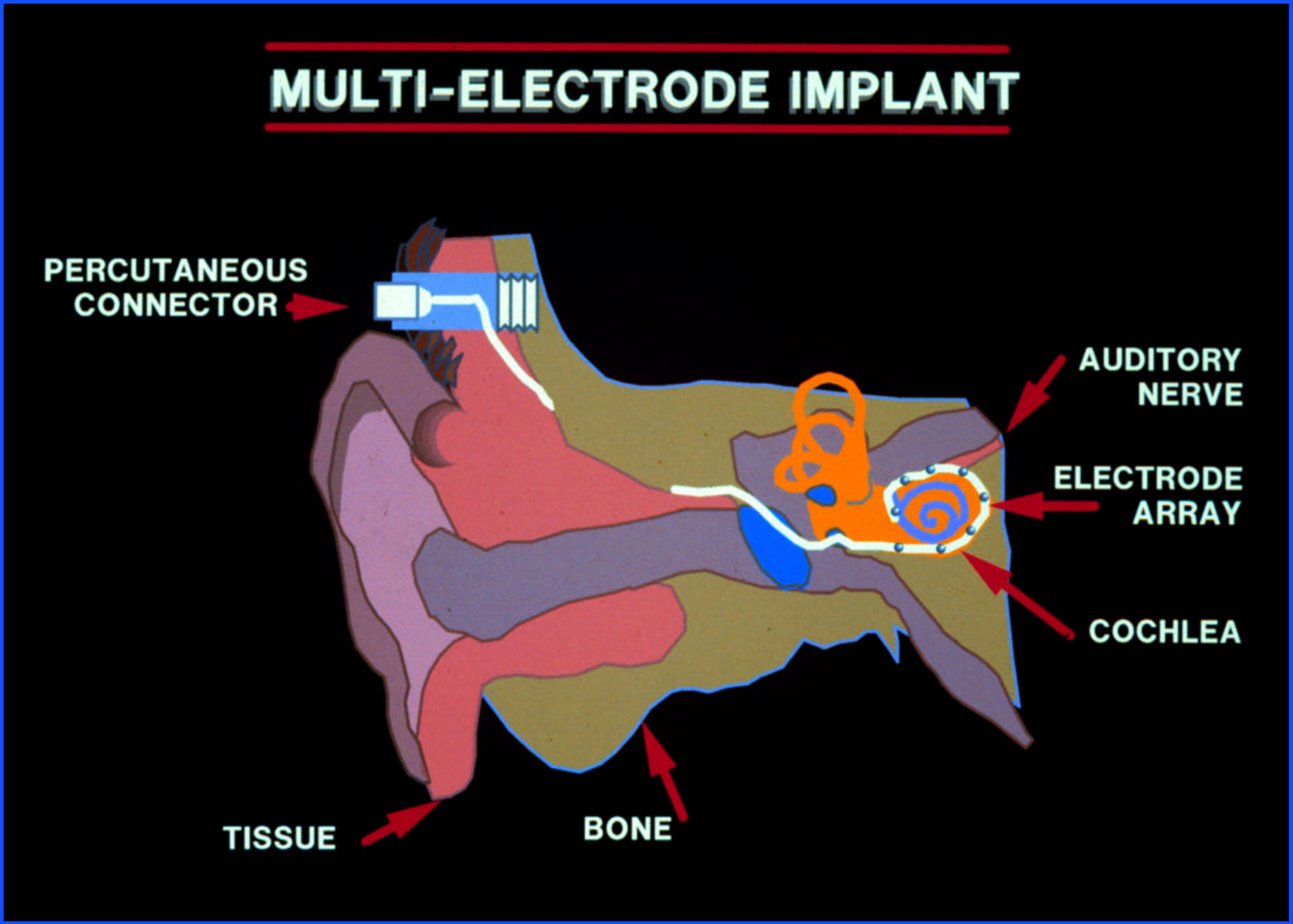


STANFORD/CALTECH NEURAL PROBES

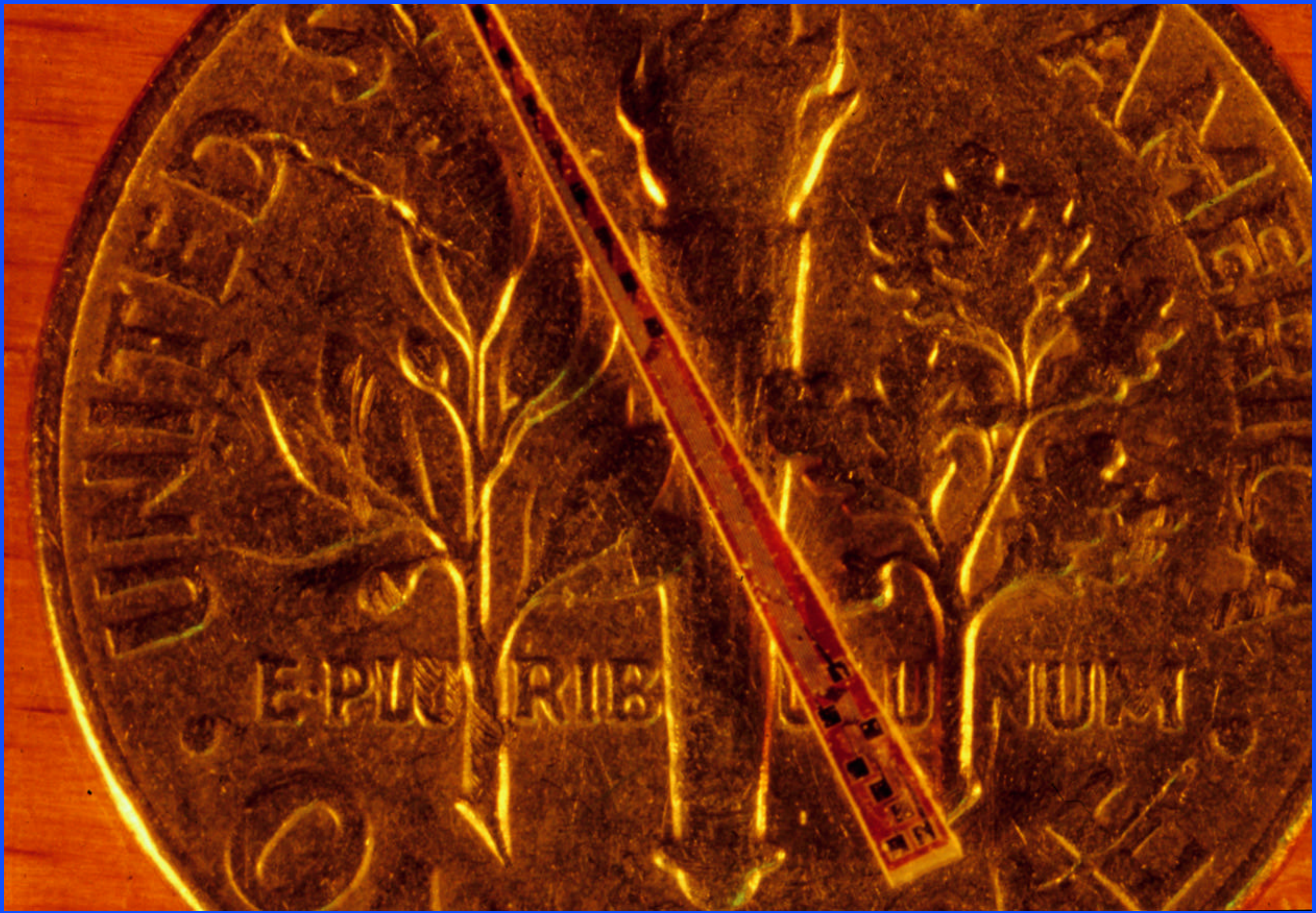


Courtesy M. Hills, Stanford University.

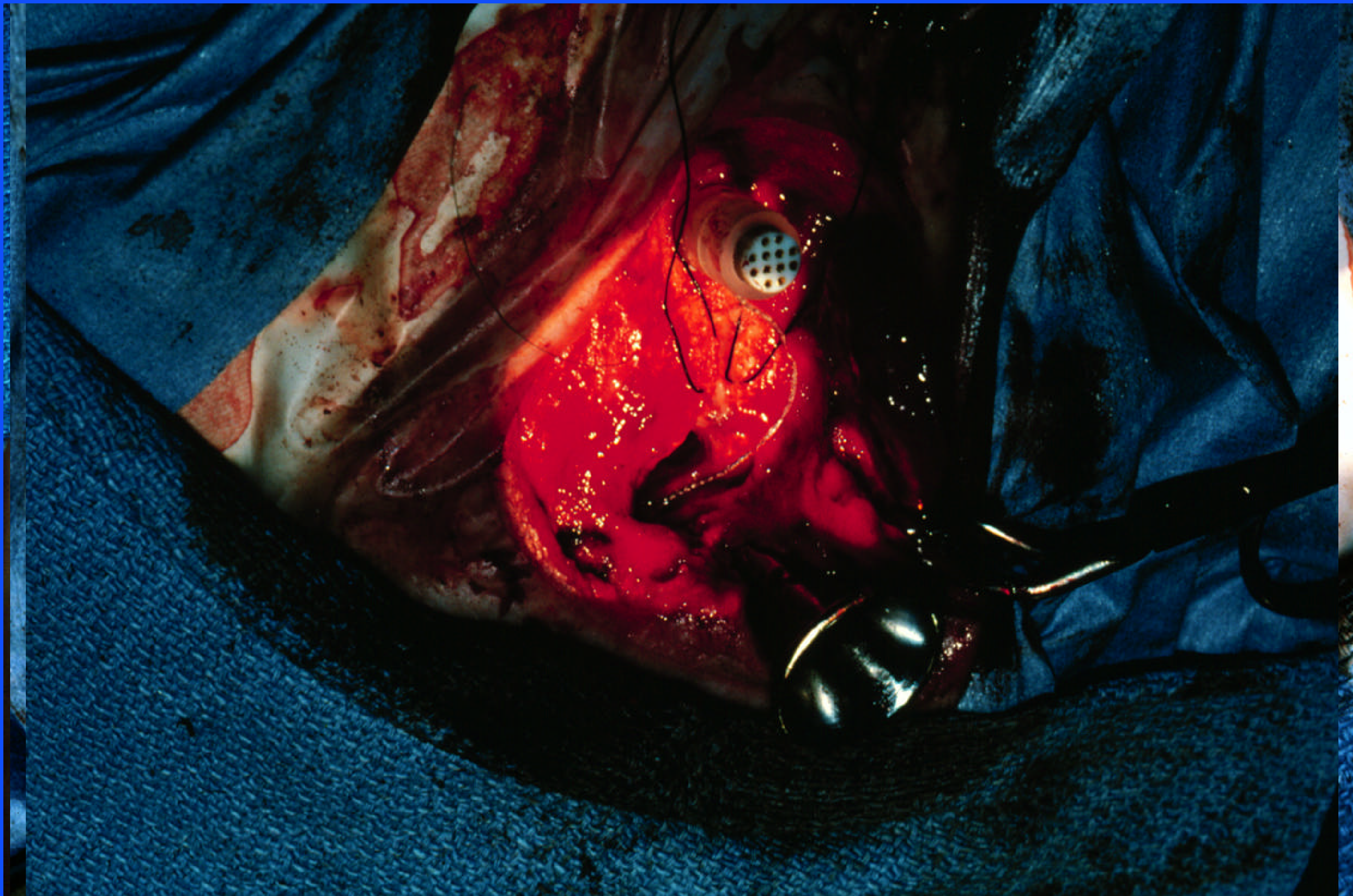
COCHLEAR PROSTHESES



Courtesy Prof. R. White, Stanford University.

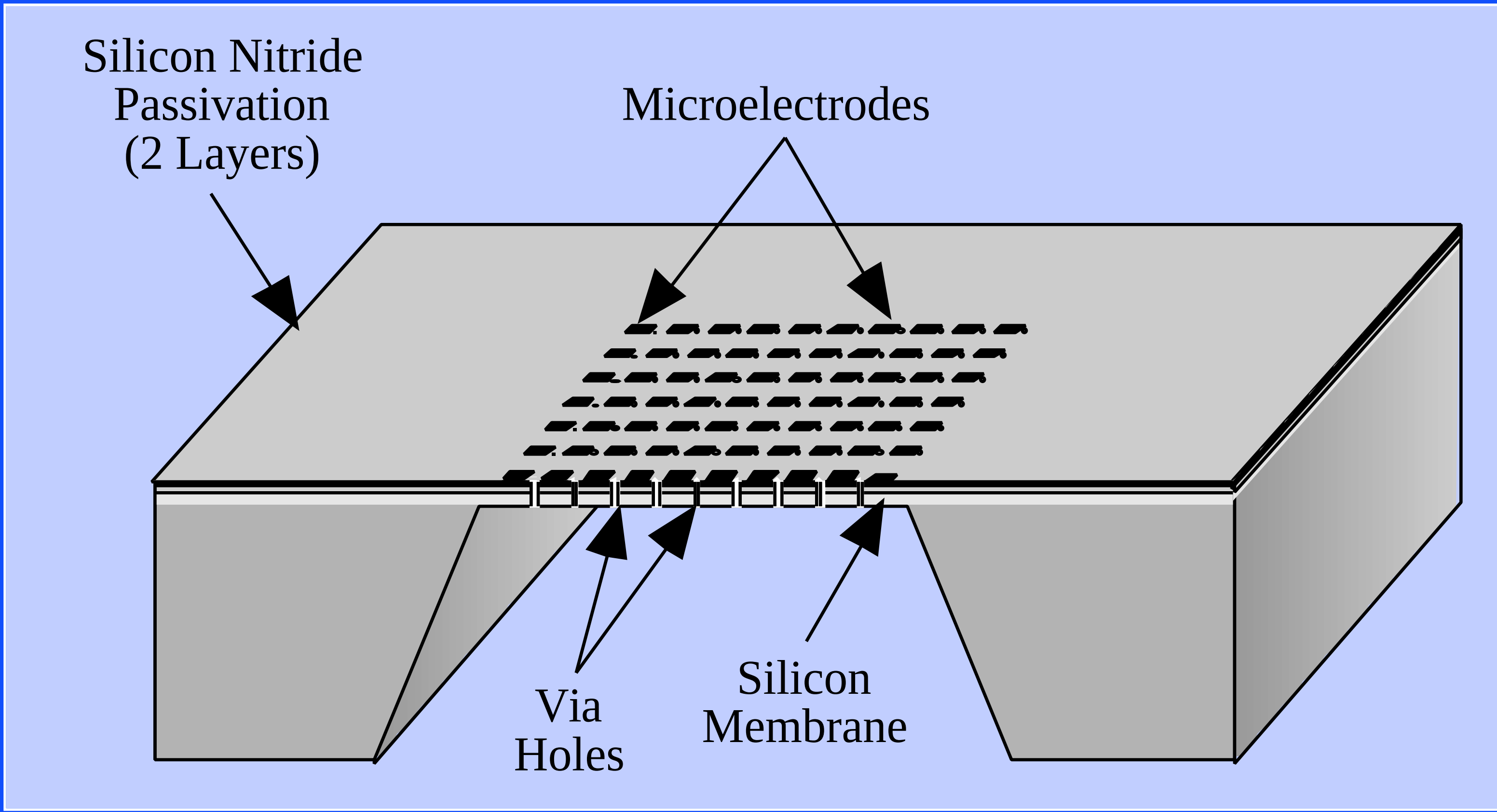


Courtesy Prof. R. White, Stanford University.



Courtesy Prof. R. White, Stanford University.

REGENERATION-TYPE ELECTRODE ARRAYS

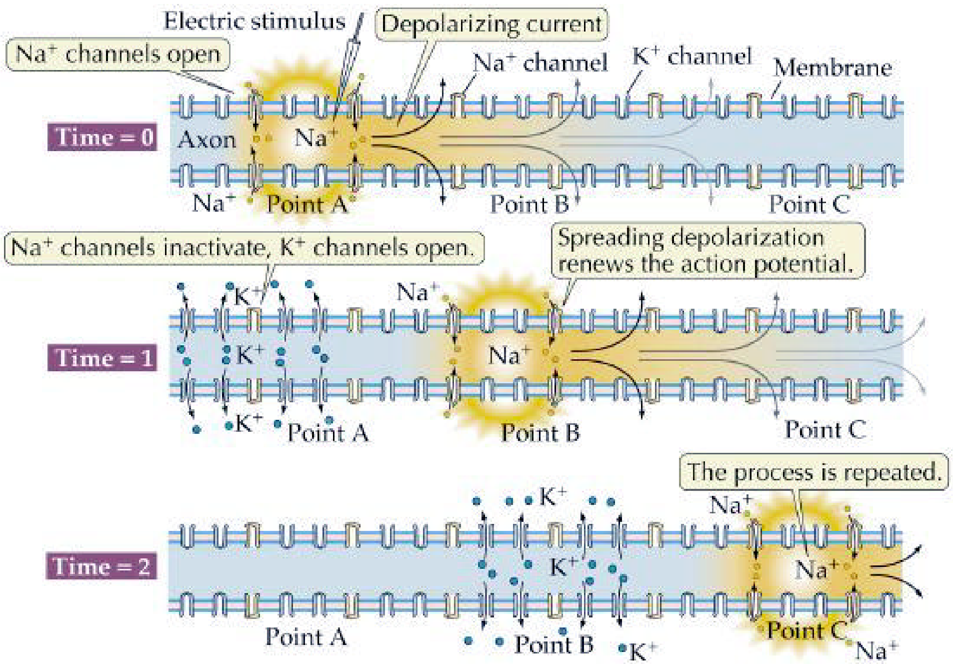


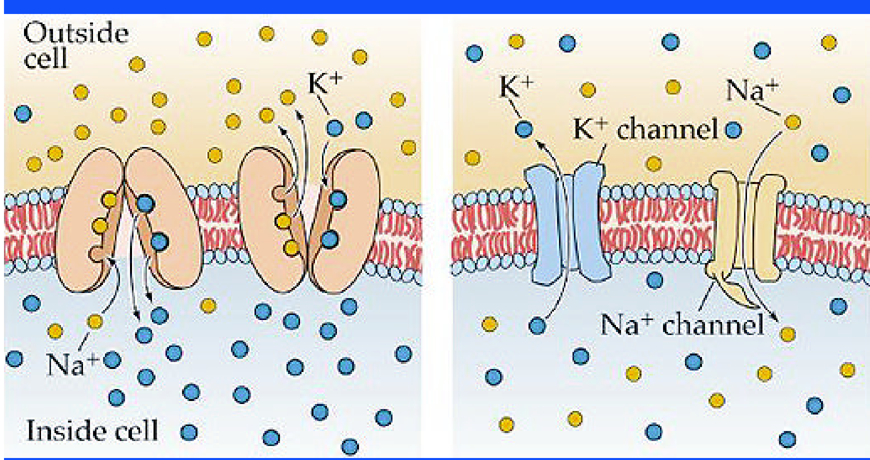
Reference: Kovacs, G. T. A., Storment, C. W., Halks-Miller, M., Belczynski, C. R., Della Santina, C. C., Lewis, E. R., and Maluf, N. I., "Silicon-Substrate Microelectrode Arrays for Parallel Recording of Neural Activity in Peripheral and Cranial Nerves," IEEE Transactions on Biomedical Engineering, June 1994, vol. 41, no. 6, pp. 567 - 577.

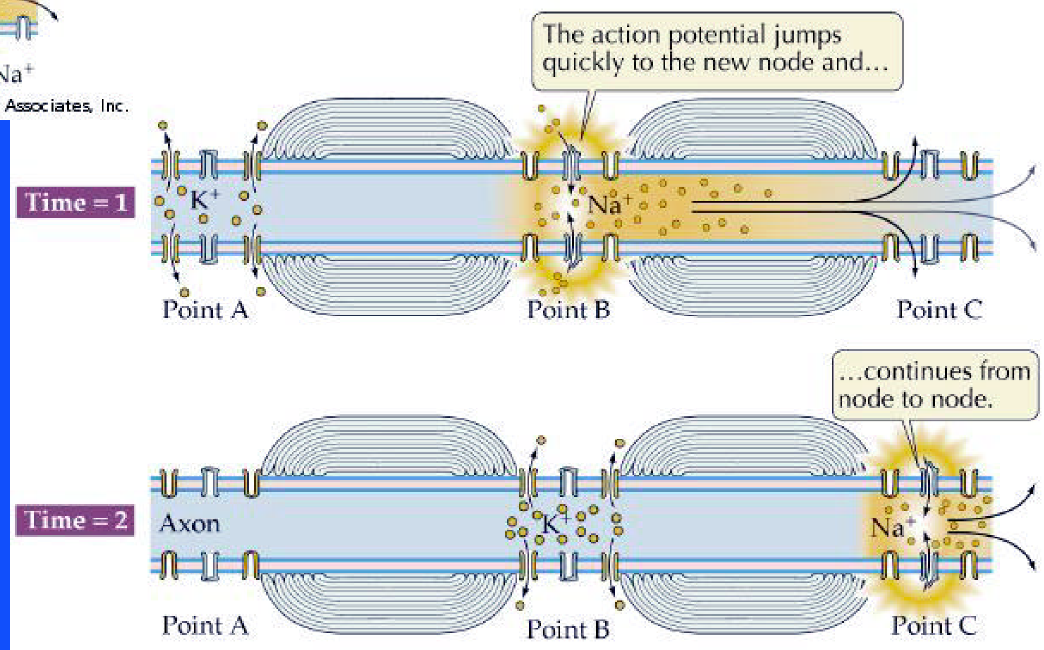
UNMYELINATED & MYELINATED AXONS

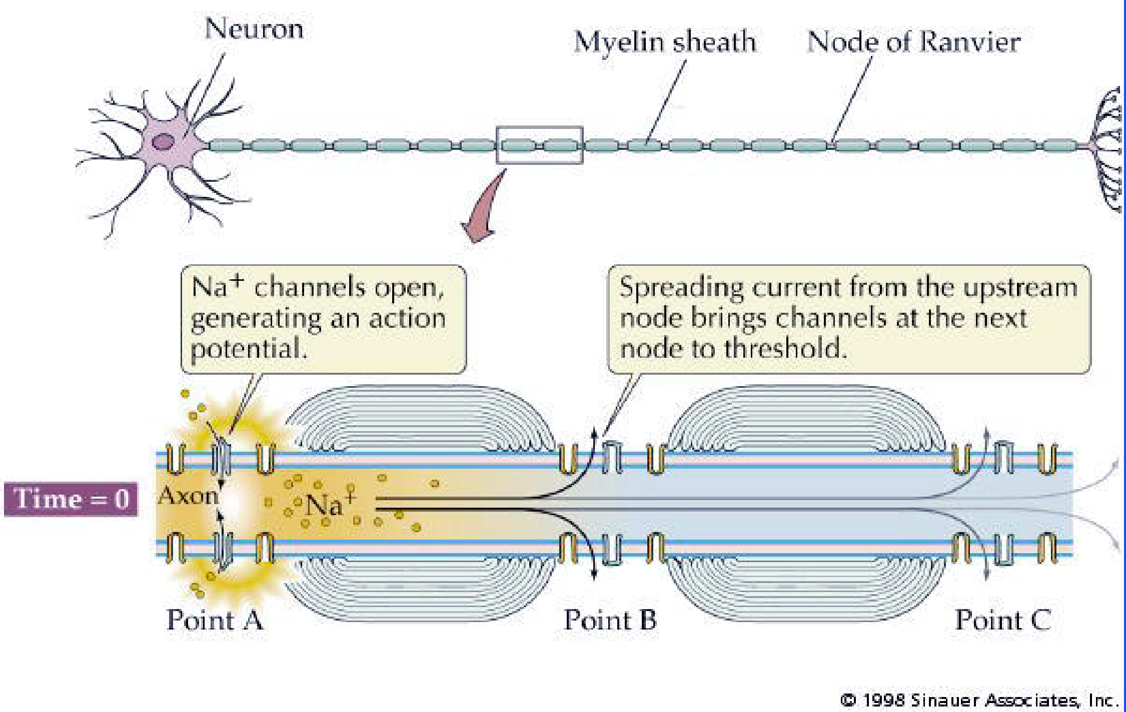
Courtesy Prof. H. C. Heller, Stanford University.

Source: Purves, Orians, Heller, and Sadava, “Life: The Science of Biology,” Sinauer Associates/W.H. Freeman & Co., New York, 1999.



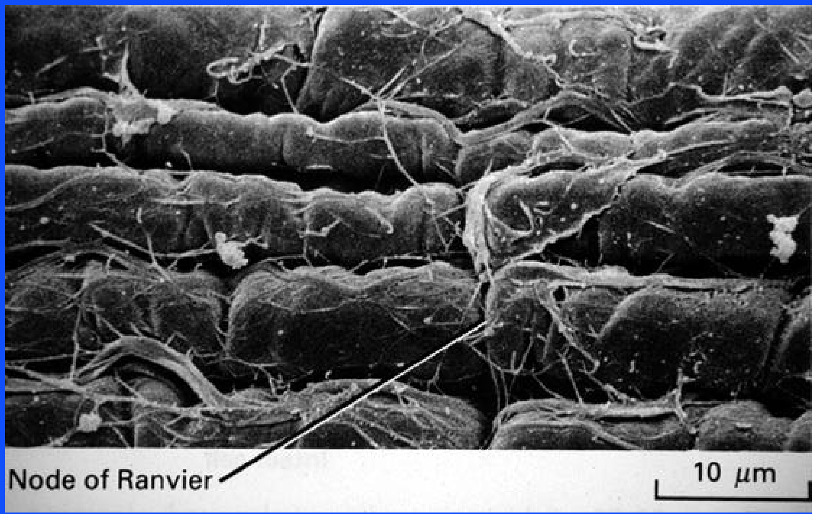




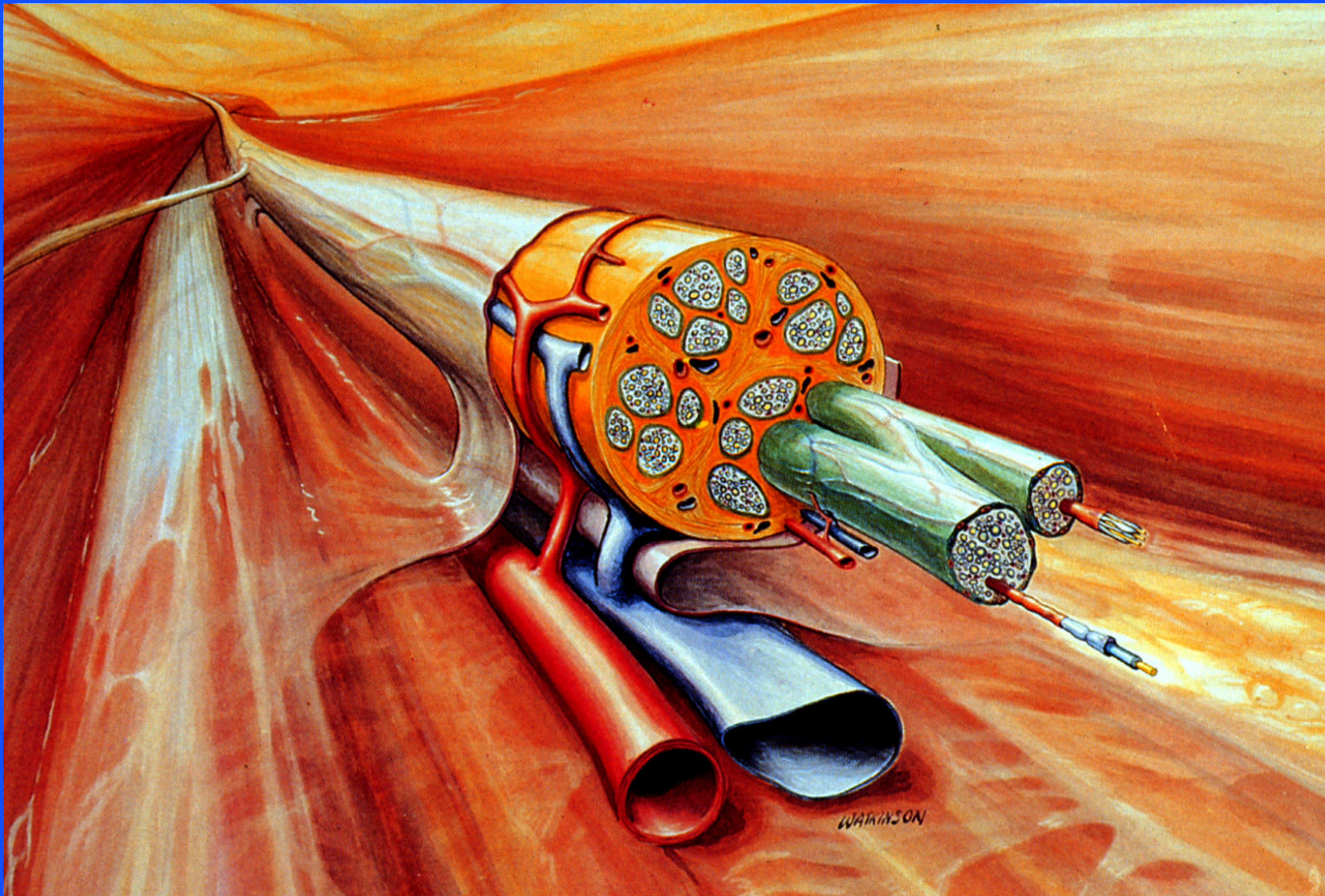


Courtesy Prof. H. C. Heller, Stanford University.

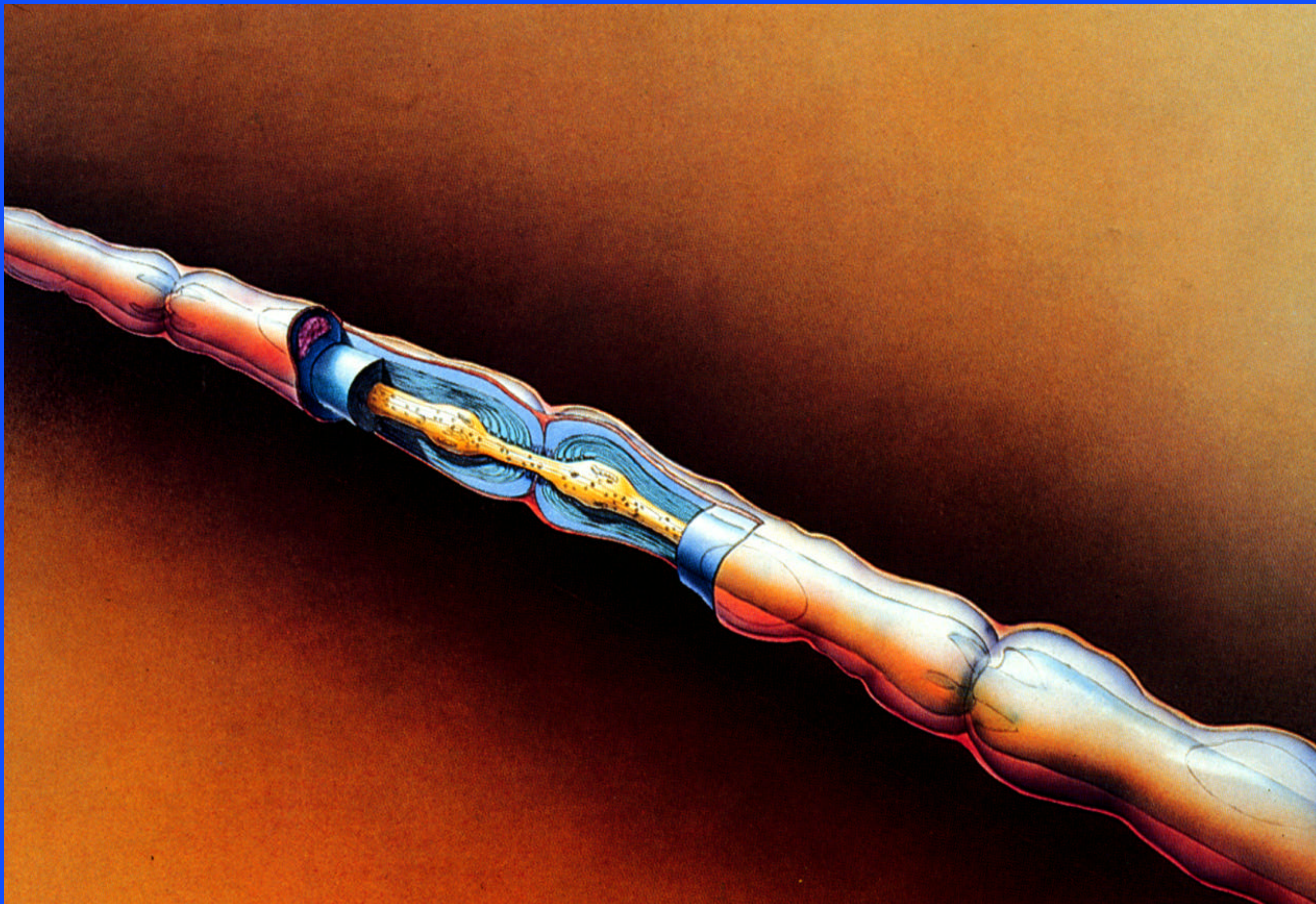
Source: Purves, Orians, Heller, and Sadava, "Life: The Science of Biology," Sinauer Associates/W.H. Freeman & Co., New York, 1999.



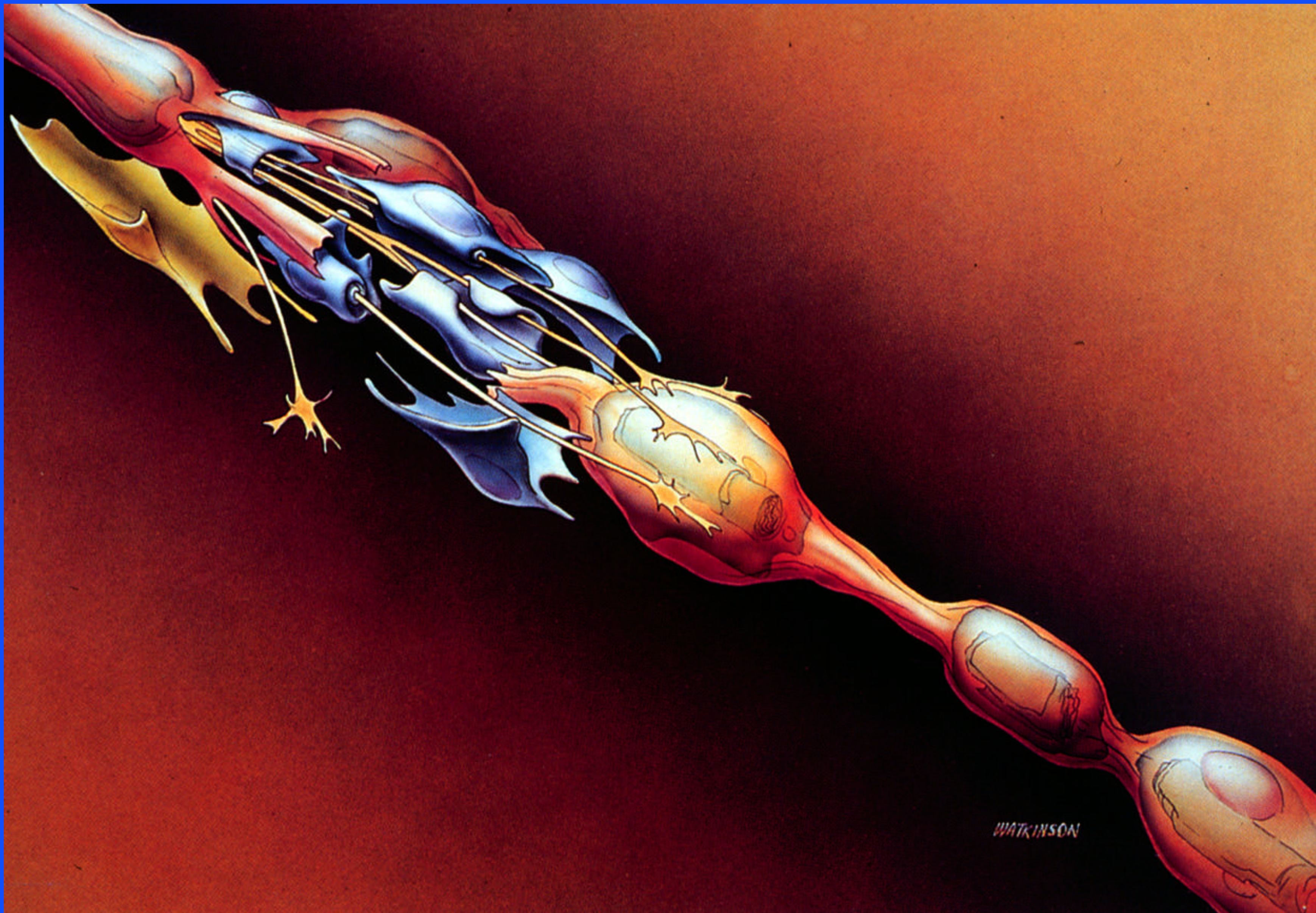
Source: Darnell, J., Lodish, H., and Baltimore, D., "Molecular Cell Biology," Second Edition, Scientific American Books, W. H. Freeman and Co., New York, NY, 1991.



Courtesy Prof. J. Rosen, Dartmouth University.

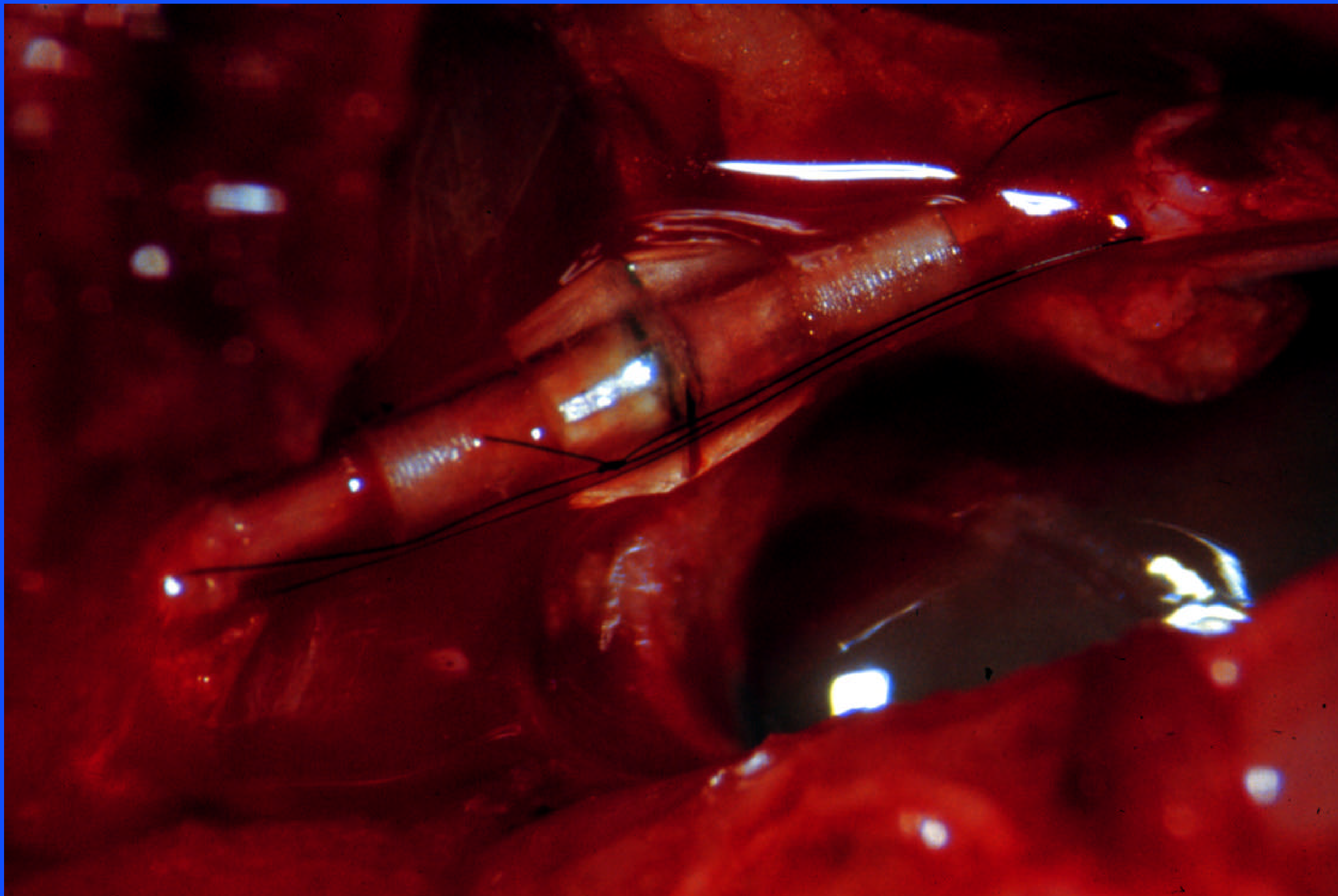


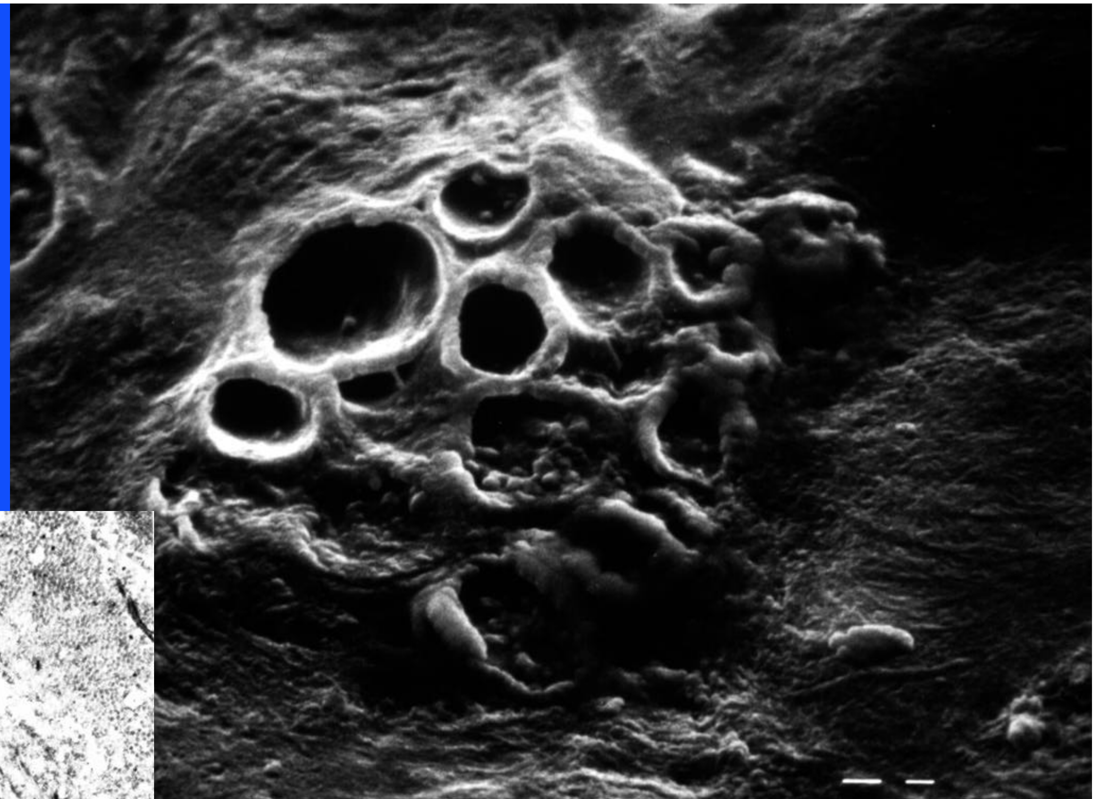
Courtesy Prof. J. Rosen, Dartmouth University.

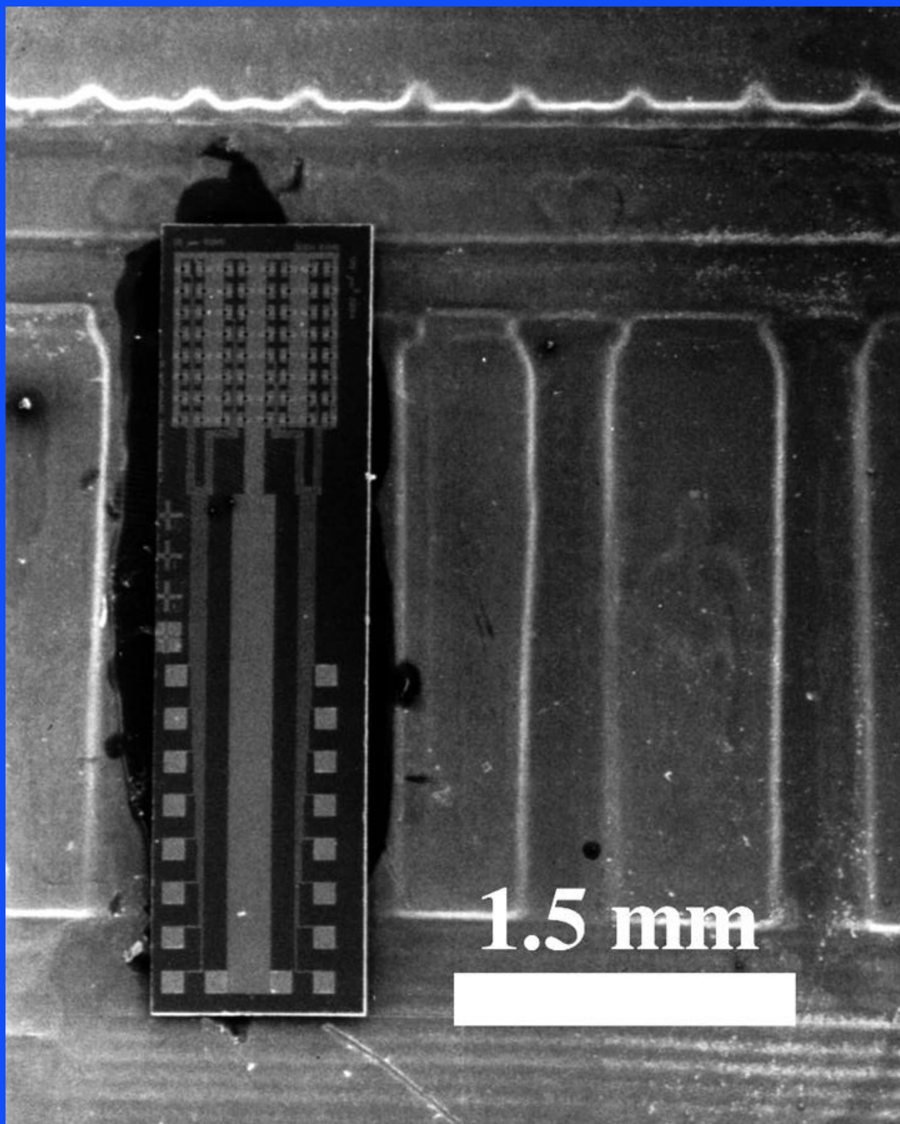


Courtesy Prof. J. Rosen, Dartmouth University.

Courtesy Prof. J. Rosen, Dartmouth University.



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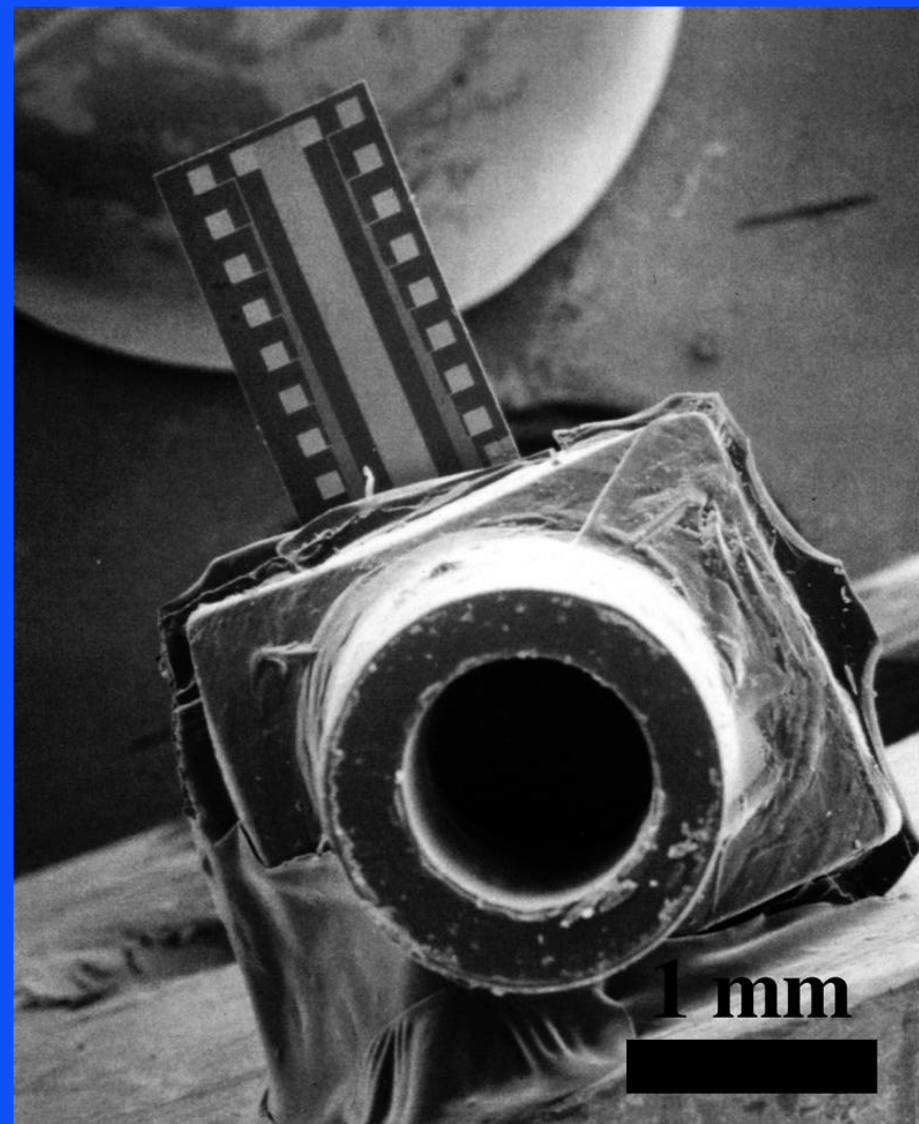
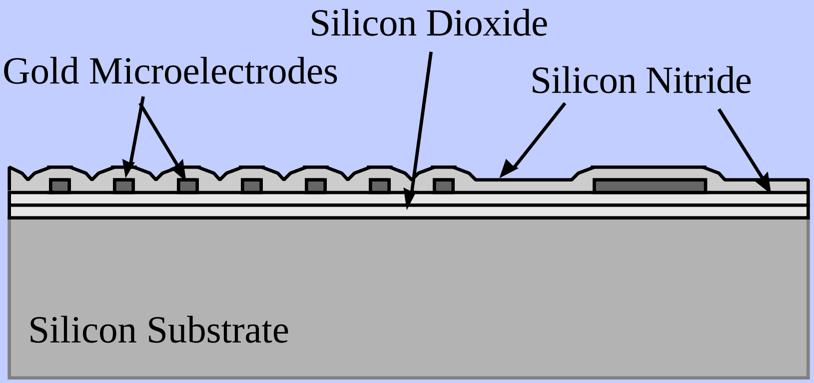
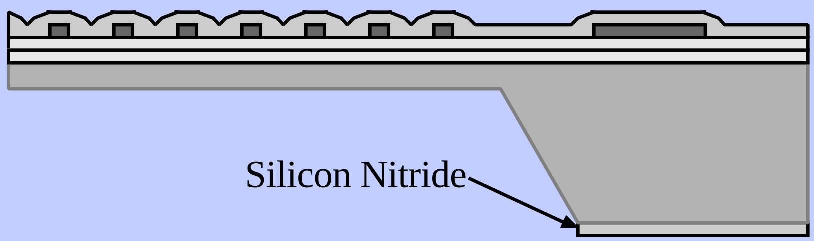

1 mm

1



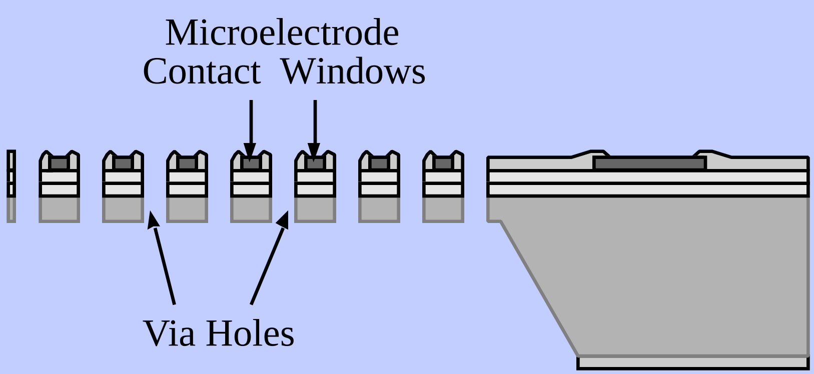
Fabrication of surface structures.

2



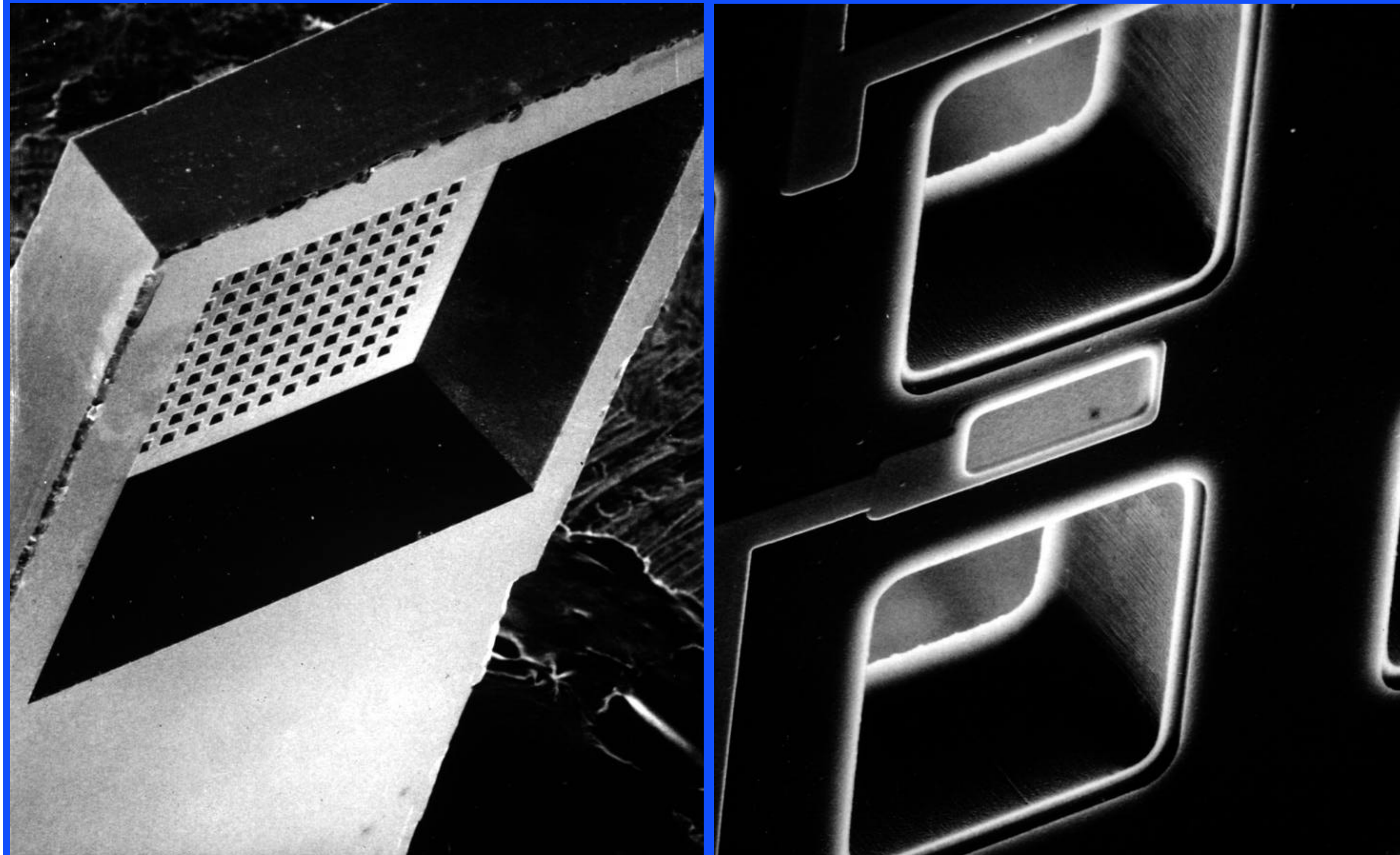
Membrane formation.

3

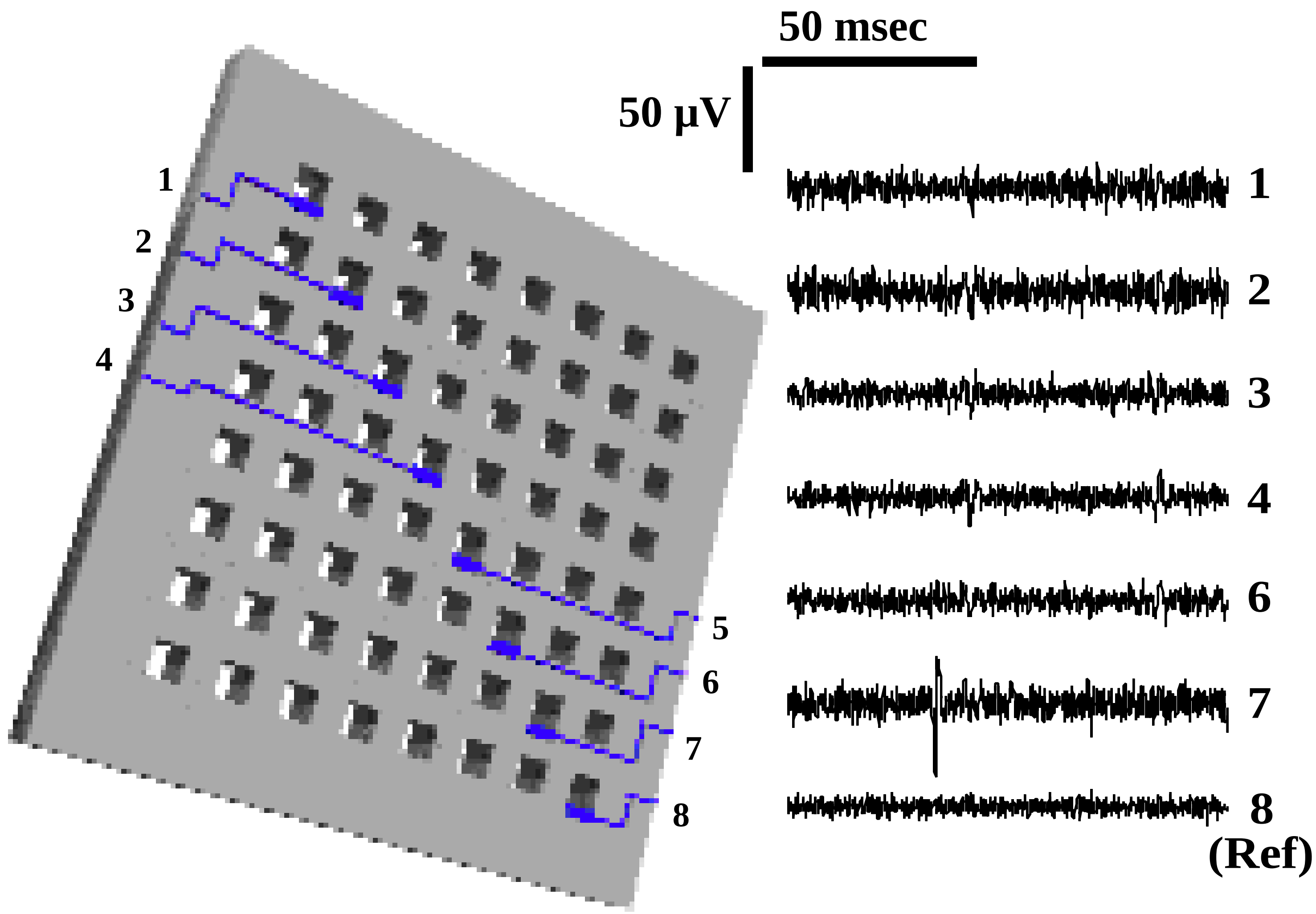


Via hole etching and passivation patterning.

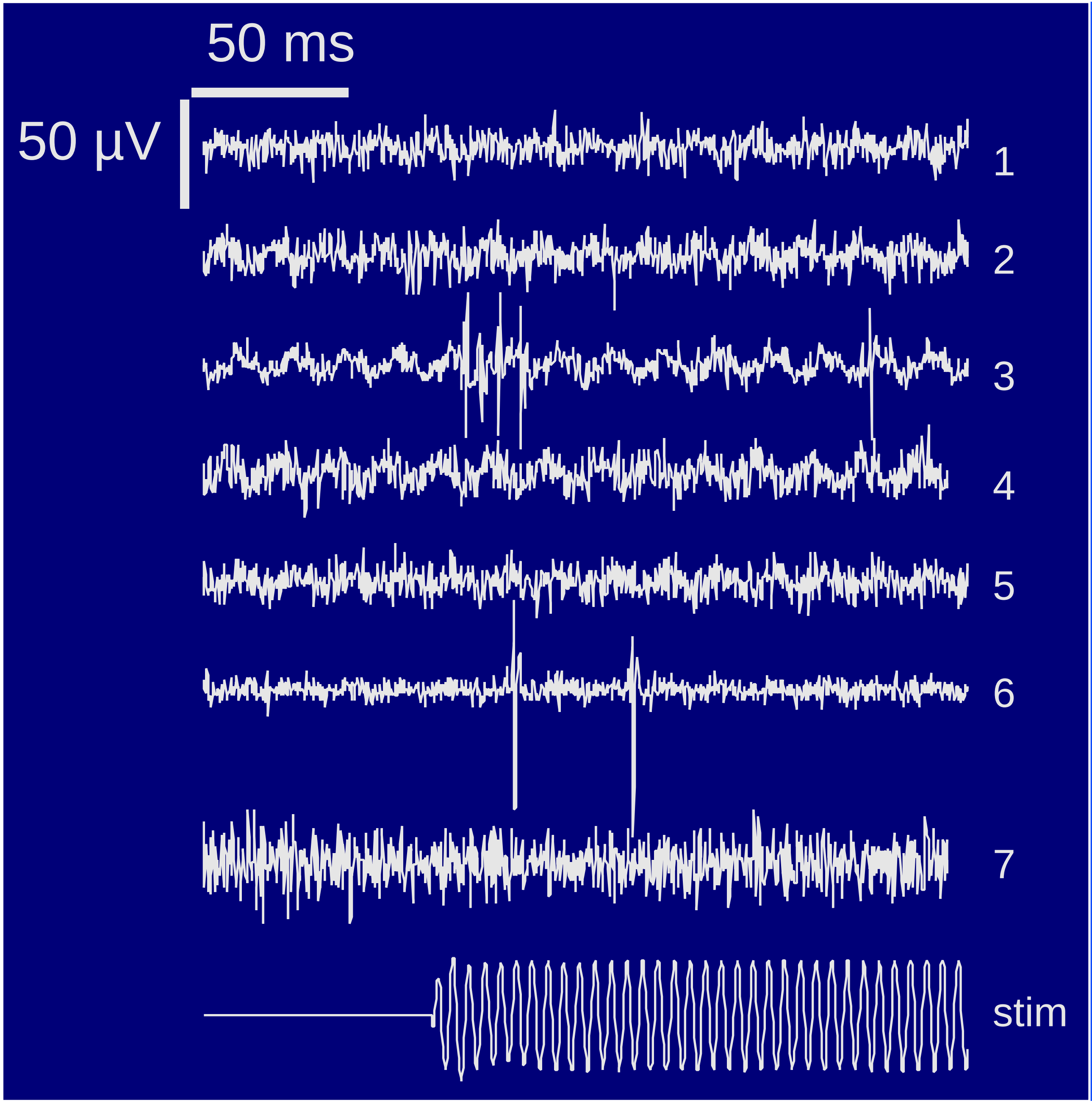
Reference: Kovacs, G. T. A., Storment, C. W., Halks-Miller, M., Belczynski, C. R., Della Santina, C. C., Lewis, E. R., and Maluf, N. I., "Silicon-Substrate Microelectrode Arrays for Parallel Recording of Neural Activity in Peripheral and Cranial Nerves," IEEE Transactions on Biomedical Engineering, June 1994, vol. 41, no. 6, pp. 567 - 577.



Courtesy C. Della Santina, U.C. Berkeley.



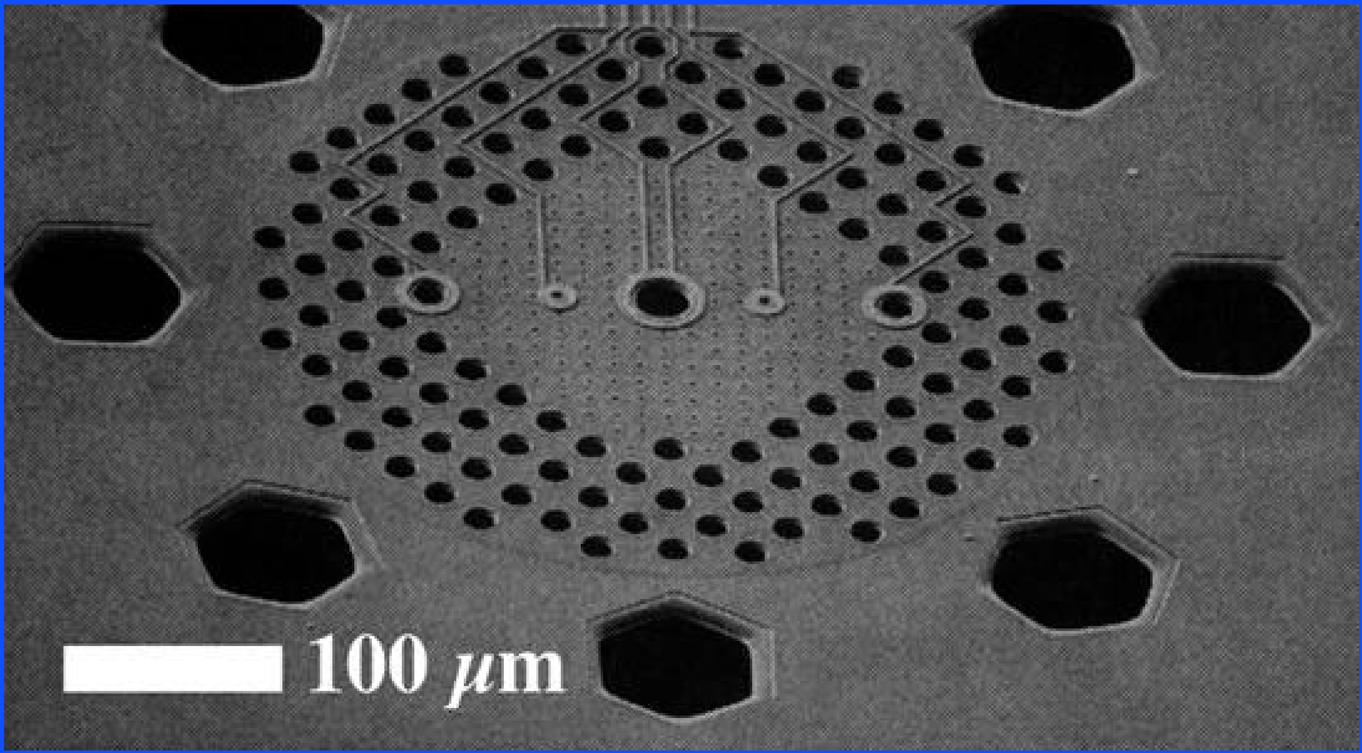
Reference: Kovacs, G. T. A., Storment, C. W., Halks-Miller, M., Belczynski, C. R., Della Santina, C. C., Lewis, E. R., and Maluf, N. I., “Silicon-Substrate Microelectrode Arrays for Parallel Recording of Neural Activity in Peripheral and Cranial Nerves,” IEEE Transactions on Biomedical Engineering, June 1994, vol. 41, no. 6, pp. 567 - 577.



NEURAL RECORDINGS FROM FROG AUDITORY NERVE USING REGENERATION ARRAY AND ACOUSTIC STIMULUS

Courtesy C. Della Santina, U.C. Berkeley.

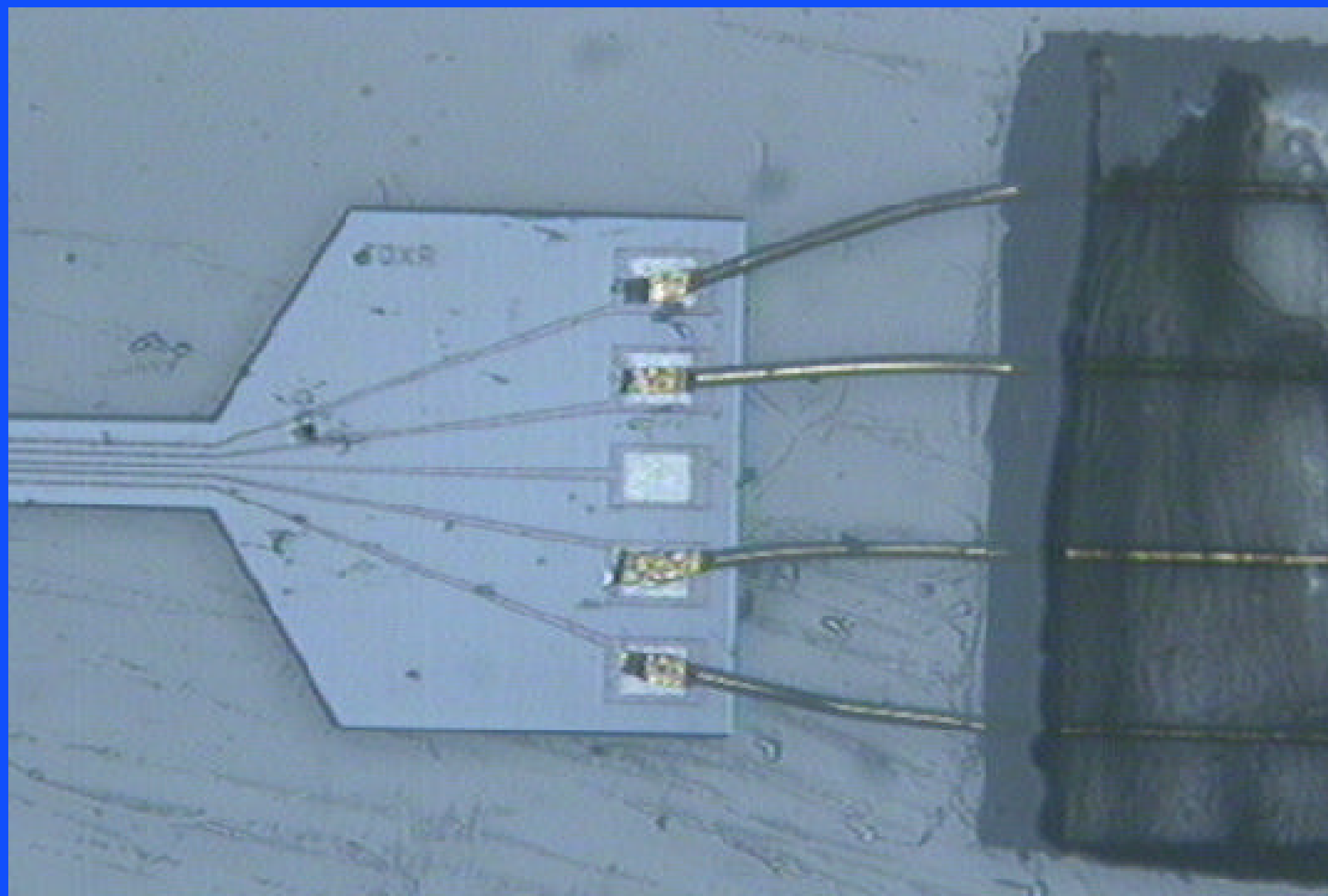
BORON-DOPED REGENERATION ARRAYS



Courtesy Prof. K. Najafi, University of Michigan.

Source: Najafi, K., "Solid-State Microsensors for Cortical Nerve Recordings," IEEE Engineering and Biology Magazine, June/July 1994, pp. 375 - 387.

PACKAGING AND INTERCONNECT FOR NEURAL PROBES



Courtesy PI Medical, Inc.

ISSUES FOR BIOLOGICAL TRANSDUCERS

- Practicality
- Biocompatibility
- Bioresistance
- Packaging for implant
- Interconnects
- Telemetry