

CMOS Biosensors for Cell-Based Sensing

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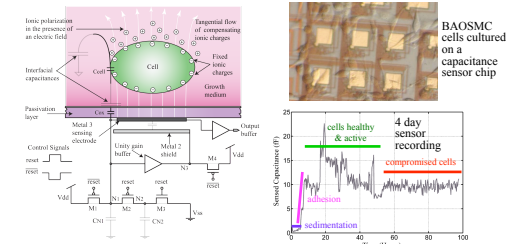
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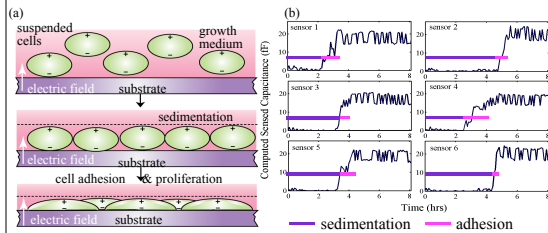
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Integrated
Biomorphic
Information
Systems

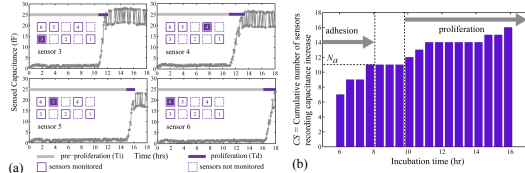
Cell Capacitance Sensing



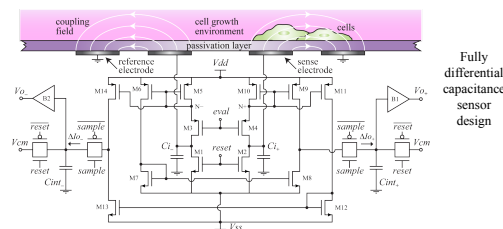
- Substrate attachment, and capacitive coupling with that substrate, is a sensitive indicator of cell morphology
 - Unhealthy cells adhere weakly, low C
 - Healthy cells adhere strongly, high C
 - Vials with individually addressable lids fabricated over the sensors
- Cells are plated and cultured in an enclosure on the chip (on the passivated surface of the chip) and the capacitance recorded.
- Capacitance measurements have been shown to correlate with cell viability, adhesion, and proliferation



Sedimentation and adhesion. (a) Illustration of sedimentation and adhesion of anchorage-dependent cells. (b) Capacitance traces indicating BAOSMC cells undergoing sedimentation and adhesion.



Proliferation. (a) Capacitance traces indicating MDA-MB-231 cells undergoing proliferation. The squares display the relative location of the sensor. (b) Cumulative number of sensors that recorded capacitance increase (CS) vs. time.

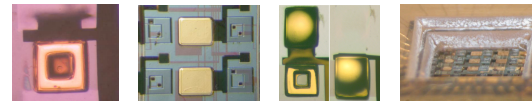


Cell Clinics: Lab on a Chip

- MEMS-VLSI Technology for cell-based sensing
- Microstructures for cell manipulation and confinement
 - CMOS sensor chip surmounted by a well containing cell medium
 - Vials with individually addressable lids fabricated over the sensors
- Cell populations in each vial monitored continuously & independently

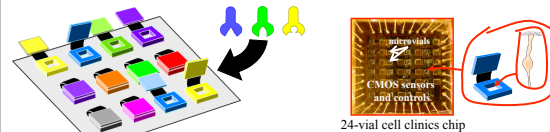
Technology Status

- Several different kinds of sensors / actuators designed, fabricated, tested
 - Electrical activity, Capacitance, Fluorescence, Contact imager, Potentiostat
- Cells loaded into electroded vials
- Lidded vials fabricated on CMOS die
- Lidded vials operated in cell medium
- Biocompatibility of all materials confirmed
- Bond wires encapsulated for operation in cell medium

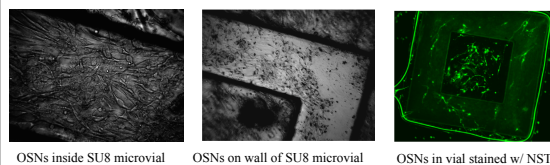


Olfactory Sensing: Nose on a Chip

- Monitor electrical activity of olfactory sensory neurons (OSNs)
- Correlate activity across multiple, distinct OSNs
- System needs to:
 - Provide stimulus through microfluidic system
 - Measure output of multiple OSN populations simultaneously
 - Keep cells happy by providing food and removing waste



Array of vials, each with OSNs sensitive to a particular smell



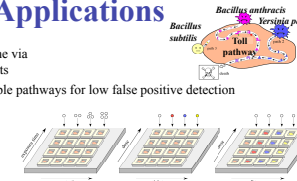
Other Applications

Pathogen Detection

- Monitor cell signaling pathways in real time via fluorescence of functionalized quantum dots
- Correlate signatures across time and multiple pathways for low false positive detection

Pharmacology / Toxicity Screening

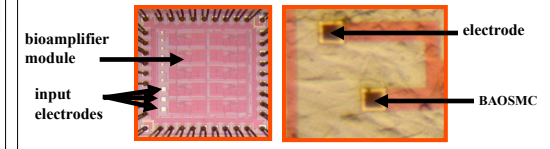
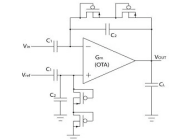
- Rapid combinatorial screening of cells
- Multiple tests in parallel on distinct populations of cells, each of which is separately and continuously monitored



Electrical Sensing

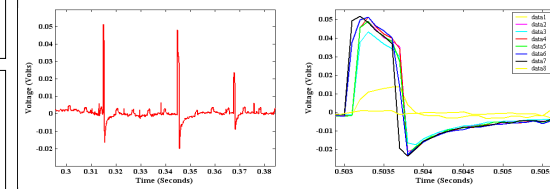
Bioamplifier 1.0: 10 x 1 Array in 0.5µm CMOS

- Amplifies weak extracellular potentials originating from electrically active cells
- Designed and fabricated in commercially available 0.5µm CMOS process. Power Supply = +/-1.5 V, Gain = 100, Bandwidth = 3 kHz, Input Referred Noise = 25µV



The bioamplifier test chip comprises an array of 10 bioamplifier modules connected to an array of on-chip gold-plated electrodes. Bovine aortic smooth muscle cells (BAOSMC) cultured on chip surface. These cells exhibit spontaneous electrical activity.

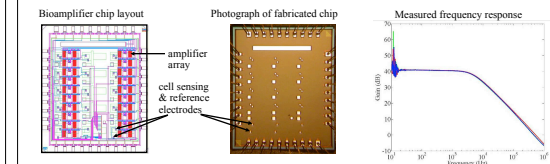
Measured Action Potentials



High quality action potentials obtained from BAOSMC cultured on 10x1 array. Spike amplitudes before amplification ~700mV. Action potential propagating across the on-chip cellular network from electrode 7 to electrode 2 in approximately 1ms.

Bioamplifier 3.0: 5 x 3 array in 130nm CMOS

- Amplifier designed and fabricated in 130 nm, 8-metal, 1-poly, CMOS process.
- Same design as 10x1 array. Power supply = ±1.25V, Gain = 40 dB, Bandwidth = 3 kHz, Input referred noise ~ 50 µV.



Bioamplifier 3.0: 128 x 128 array in 0.5µm CMOS

- To obtain data from fine neural processes, dense array needed.
- 128 by 128 array fabricated in 0.5µm 3-metal 2-poly CMOS process. Pitch of electrodes is ~10µm.
- Preamplifiers are single transistor amplifiers in each cell of array.
- Final amplification is 100, Bandwidth 10kHz.

