Extensions upon the Versatile BioLab-On-A-Chip

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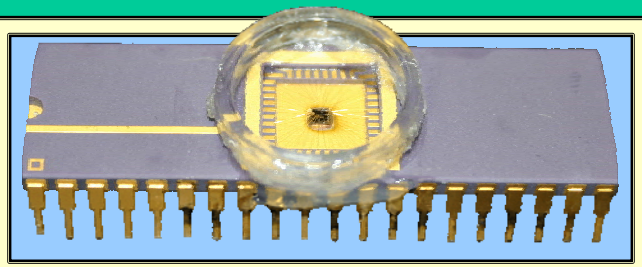
Overview

- The ongoing cell clinics project at the University of Maryland strives to replace the infrastructure of a cell-biology laboratory with highly functional lab-on-chip devices – the single chip pictured at center monitors extracellular signals from electrically active cells.
- Many applications including physiology, whole cell studies, environmental monitoring and remote biosensing will be enabled by CMOS bioamplifiers integrated with microelectromechanical systems forming lidded microvials to contain cells.



Future Work

- Analysis of data obtained through monitoring of BAOSMC and PC12 cells
- Validation of extracellular potentials acquired using bioamplifier versus standard electrophysiological means such as the whole-cell patch clamp
- Testing of chips designed for neurite outgrowth monitoring upon receipt in Fall 2006

Sensor Design and Applications

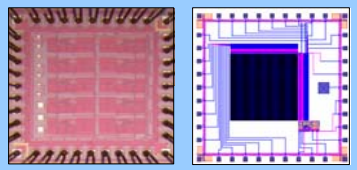
Legacy Amplifier Design

- Array of ten 1:1 electrode-to-bioamplifier units used to record extracellular potentials
- Low voltage and low noise differential bioamplification with 40dB gain with 3kHz cutoff frequency

Neurite Outgrowth Sensor Design

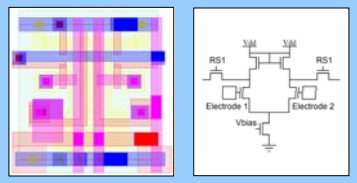
- Vastly increased spatial resolution allowing greater precision and new applications, e.g. monitoring developing cell processes
- 128 x 128 array of pixels – electrodes with pre-amplification units
- Nine different chips designed and submitted for fabrication for various circuit configurations and process constraint combinations
- In-pixel pre-amplification configurations
  - Single-transistor common-source amplifier
  - NMOS-only differential amplifier with local and global references
- Designs use 2 or 3 metal layers with electrodes defined using commercial or in-house window cuts
- Fabrication in commercially available 0.5 µm CMOS process

Chip Designs



Legacy | New

In-Pixel Pre-Amplifier



Layout | Schematic

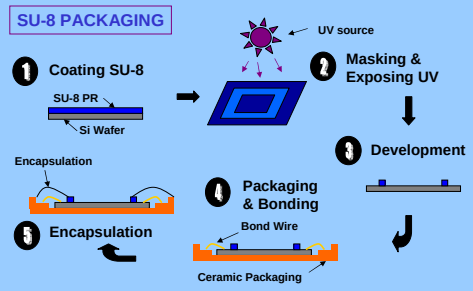
Packaging and Encapsulation

Historical Procedure

- Pre-packaged in 40-pin DIP chip package
- Electrolessly plate Al electrodes with Au to decrease noise, prevent corrosion from cell media, and enhance electrochemical compatibility
- Employ 2-step UV-curing process with Loctite™ 3340 to attain 2-level encapsulation of bond wires for electrical and chemical isolation
- Attach well to contain medium using biocompatible commercial RTV

Encapsulation Exploration

- Existing materials exhibit degradation over time that compromises cell viability in addition to undesired aqueous absorption that compromises packaging over extended periods under cell culture conditions
- Investigation of biocompatible SU-8 photoresist due to low aqueous absorption
- Replace Loctite™ encapsulation by placing SU-8 perimeter outside electrode area and backflow encapsulating material onto bond wires
- Masks of variable lateral thickness and shape have been designed



Cell Culture on Chip

Multiple Cell Lines

- Bovine Aortic Smooth Muscle Cells (BAOSMC)
- Rat Pheochromocytoma Cell Line (PC12)

Pre-chip Cultivation & Care

- Incubation at 37°C, 5% CO_2
- Routine subculture at 60-80% confluence

Mutation and Stimulus

- Nerve Growth Factor (NGF) added to PC12 cells to enable differentiation of neuronal processes using collagen as adhesion promoter
- Sodium Nitroprusside (SNP) introduced to modulate membrane potential of BAOSMC

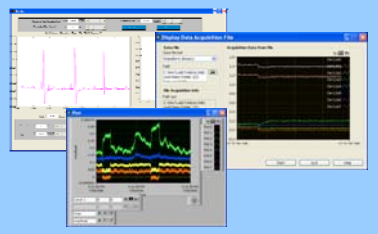
Current Issues

- Loctite™ 3340, presently used for biocompatible packaging has limited reliability, necessitating further exploration into encapsulation materials and biocompatibility testing

Data Acquisition

Software Methodology

- Legacy MATLAB program written using MathWorks Data Acquisition Toolbox used for long-term monitoring of PC12 cells
- Drawbacks of legacy software include lack of simultaneous file I/O (buffered write-back) to store continuous data without information loss and absence of real-time readout for monitoring ongoing experiments
- Recently explored National Instruments NI-DAQmx Tools package for online sampling of BAOSMC's activity in order to address these issues



Hardware Setup

- Place cells and media into chip well
- Mount chip onto test board within Faraday cage
- Place shielded setup inside incubator
- Acquire data using data acquisition card and record to storage disk