Packaging Bio-amplifiers to Monitor Extra-cellular Activity

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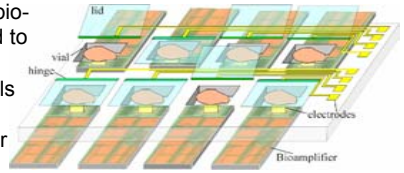
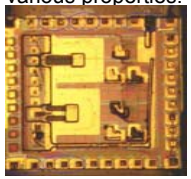
Cell Clinics Project Overview

➢Integrated on-chip bio-lab systems designed to capture, contain, and analyze individual cells and their electrical, biochemical and other various properties.



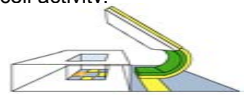


➢Custom VLSI bio-amplifier designed for low voltage operation amplifies weak extra-cellular electrical signals from on-chip electrodes. Other custom sensors and systems such as imagers, capacitance sensors, dielectrophoresis arrays, and potentiostats are in development.

➢Devices fabricated through the MOSIS integrated circuit fabrication service using a commercial CMOS process.

➢On-chip MEMS lidded microvials with actuated hinges close upon capture of cell by responding to electrochemical potential. Microvials contain sensors to monitor cell activity.

➢Potential applications in medicine, physiology, individual cells studies, environmental monitoring, biomedical implants, and remote bio-sensing.



Biocompatibility Study

➢Biocompatibility of different silicones used for injection molding must be determined as they will be in direct contact with cells. Non-biocompatible materials will harm the cells and adversely affect measurements.

Experimental Procedure

➢2 Polytek™ silicones tested

➢4 silicone rings of each type formed by filling liquid silicone into a 9-hole mold block (see insert).

➢2x4 silicone rings inserted into 8 wells in multi-well plate. 8 control left empty. All wells seeded with 3500 cells/cm^2 of BASMC and allowed to grow for 10 days with every other day monitoring and changing of cell growth medium.

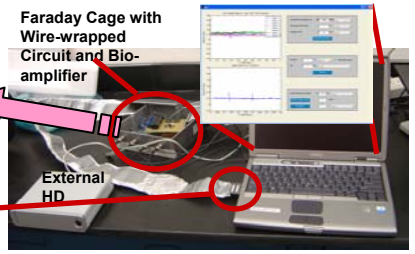
➢Cell confluence levels in each well estimated by averaging measurements of cell densities microscope.

Results

➢S1: not biocompatible
S2: biocompatible; 95%, 98% statistical significance levels.

➢Very little intra-experiment variation: cells in different wells of the same type exhibited the same behavior.

Long Term Monitoring Setup



➢Fixture w/bio-amplifier circuit and live cells (in incubator) connected to PCMCIA data acquisition card in laptop PC with external hard disk for data streaming.

➢Designed for long term (>24 hours), continuous monitoring.

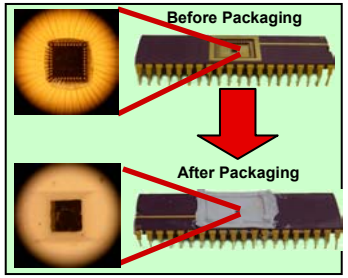
➢Matlab™ program designed to acquire, record, and display extra-cellular voltages from cells through the bio-amplifier, and to detect, and display voltage potential spike events in recorded data or real time through graphical user interface.

Summary

➢Proved watertight seal of silicon mold/chip passivation layer interface.

➢Successful encapsulation and insulation of bondwires.

➢Minimal variation between two different trials using the packaging assembly.

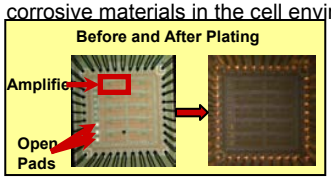


Custom Chip Packaging

Why package bio-labs-on-a-chip?

➢Protect cells in growth medium from toxic packaging materials in the 40-pin DIP chip package, since cell environment is on the surface of the chip.

➢Isolate and insulate exposed bondwires in 40-pin DIP chip package from corrosive materials in the cell environment.



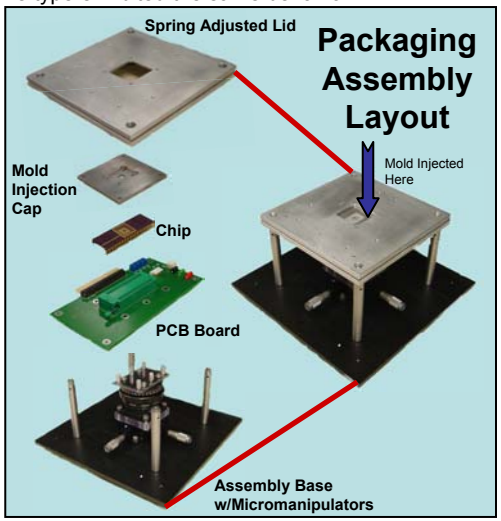
Injection molding packaging method

➢Bio-amplifier electrodes are electrolessly plated with gold because aluminum bioelectronic interfaces suffer corrosion in the cell environment and is not biocompatible, and to decrease noise during measurements.

➢Custom packaging assembly built to allow injected silicone material to form around the chip, creating a well to contain the cell solution, and insulating and encapsulating the bondwires.

➢Assembly has 3-axis micromanipulators and rotational manipulator for alignment and injection. Curing can be done directly on PCB circuit board.

➢Packaging issues include protecting delicate bondwires in the chip package that are easily detached or shorted, and providing a watertight seal.



Future Work

➢Reduce variation in the packaging process, and determine biocompatibility of more silicones.

➢Package Bio-amplifiers w/MEMS structures chip for testing and long term recordings for extra-cellular activity.

➢Package other Cell Clinics sensors that require a stable bioelectronic interface such as imagers, capacitance sensors, and dielectrophoresis arrays.

Acknowledgements

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