Microsystems engineering at the interface of physics biology and chemistry

Andreas G. Andreou

Electrical and Computer Engineering and Whitaker Biomedical Engineering Institute
Johns Hopkins University
outline

• Introduction
  – hybrid microsystems (I): why?
  – emerging technologies
  – hybrid microsystems (II): how?
• Integrating Nano, Micro and Macro
  – u-incubator
  – and beyond
• Concluding Remarks
outline

• Introduction
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Hybrid Microsystems
Complex structures at the interface of physics, chemistry and biology

How: Multidomain and multiscale integration from nano to micro and macro using both top down and bottom up fabrication methods.

Why: Increased structural complexity to attain improved performance / higher system functionality and or lower cost.

- solid, liquid and gas or vapor state
- electromagnetic and electromechanical
- organic and in-organic
- CMOS and other material systems
- electronic and ionic
- living and non-living
biotechnology applications

• Stem cell research
• Viral transfection
• Gene therapy
• Nanoparticle drug delivery
• Monitoring intra/intercellular signaling pathways
• Biosensors for hazardous substance monitoring
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Emerging Technologies

Microsystems

- Quantum Computing
  - DNA Computing
  - Quantum Cellular Automata
- Self Assembly
  - Soft Lithography
  - uFluidics
-罩o-CMOS
  - SOI-CMOS
  - 3D-CMOS
- Plastic Electronics
  - Photonic Crystals
- Carbon Nanotubes
  - Molecular Devices
- Giant Magnetoresistance
- Coulomb Blockade
- Interband Tunneling
- Resonance Tunneling
- Single Quantum Flux
  - Electron Interference
  - Spintronics
- Emerging

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ISR, University of Maryland College Park, 12/04/2007
silicon CMOS

Human Hair

100 $\mu$m

Human Cell

10 $\mu$m

MOS transistor

Gate

Source

Drain

Gate Oxide

P-substrate(Bulk)

10 nm

1 nm

100000000 X

500 nm

Blue
silicone: PDMS poly-(dimethylsiloxane)

- Optically transparent
- Electrically insulating
- Stable to chemicals
- Bio-compatible
- 50 times cheaper than silicon
PDMS Fabrication Replica Molding

soft-lithography and replica molding
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micro-electronics scaling: Moore’s law

Cramming more components onto integrated circuits

With unit cost falling as the number of components per circuit rises, by 1975 economics may dictate squeezing as many as 65,000 components on a single silicon chip

By Gordon E. Moore
Electronics, Volume 38, Number 8, April 19, 1965

1. More transistors per unit silicon area
2. Lower energy costs for computation

Intel Core 2 Duo “Extreme” CPU

200,000,000 components
micro-fluidics scaling: Moore’s law no more

Scaling in Microfluidics

- Caliper Technologies
- ACLARA BioSciences
- Fluidigm
- Chemical Sensors

Channel Width (microns)

Year

a new paradigm for integration

“Fabrication of a single 2 gram silicon DRAM microchip requires 32kg of water and 41MJ of energy and produces 1.7kg of waste”

E. Williams and R. Ayres and M. Heller, Environmental Science and Technology, 2002
system architecture

Simple, Low-Cost Disposable Components
Reconfigurable
Low Cost
Environmentally Friendly

Highly Functional Reusable Components
Actuation
Sensing
Feedback
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cell culture today

Incubator

Flask

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Photography by Andreas Andreou
history of cell-tissue culture and incubation

the growth of cells derived from living tissue in an artificial medium

1882 – beating heart in salt solution, Sydney Ringer

1885 - embryonic chick cells maintained \textit{in vitro}, Wilhelm Roux

1907 - \textit{in vitro} tissue culture (nerve growth), Ross G. Harrison, Johns Hopkins University
our goal

Incubator

Culture Flask

Waste

Computer

DAQ

Chip-Scale Incubators
the state of the art

Kovac and DeBusschere, Proceedings of the IEEE, June 2003

2 hours in ambient environment
TISSUE CULTURE: A CRITICAL SUMMARY.*

By H. M. CARLETON, Lecturer in Histology, University of Oxford.
(From the Department of Physiology.)

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The adjunct of the experimental method to histology, or to any other descriptive science, is always invaluable. In fact, the recent experimental trend of microscopical anatomy would seem to justify the assumption that the histological researches of the future will be based more on the physiology and dynamics of the cell than on descriptive morphology.

The in vitro cultivation of animal tissues is one of the latest experimental acquisitions of biology, and the aim of this article is to furnish a critical summary of the more important researches up to date, and the theoretical considerations to be derived therefrom with the minimum of personal bias.

1. The Conditions of Tissue Culture.

Certain conditions limiting the possibility of the in vitro cultivation of tissues have to be observed. They comprise:

(i) The Nature of the Culture Medium.—For tissues to survive outside the organism it is necessary that they be surrounded by an "indifferent" (i.e. a more or less isotonic and nontoxic) medium, or better still, by one which is also nutritive. Thus, mammalian tissues will grow in hanging drop preparations in standard or modified Ringer-Locke solution, to which a small amount of glucose or bouillon is often added (Lewis and Lewis 46; A. H. Drew 49).

* Received April 27th, 1933.

H. M. CARLETON

The growth of tissues in purely inorganic solutions appears to be due to the absorption of nutriment by the living from the dead and disintegrating cells in the centre of the "implant." (I employ this word throughout this article to designate the piece of tissue under cultivation.) Clotted lymph (Harrison 41) or clotted plasma (Carrel 1; Burrows 1; Champy 11) are other media most frequently employed. The growth of tissues in these is due partly to the absorption of nutritive substances from the lymph or plasma, partly to the reason mentioned above. It was also found by Carrel 4 that the addition of "embryonic extract" (i.e. the substances derived from fetal tissues by destruction of the cells by freezing) to the plasma markedly favoured growth.

(2) Oxygen Supply.—For the implant to obtain sufficient oxygen it is necessary that it be very small and that it should lie at, or immediately beneath, the free surface of the culture medium. The respiratory requirements of the tissue impose a limitation on the size of the fragments under cultivation, and, even when these do not exceed the size of a small pin's head, aseptic degeneration of the central portion of the tissues occurs sooner or later owing to oxygen want. The degree of aseptic necrosis varies considerably in different animal groups; thus, in Birds it is very great, in Mammals intermediate, and in Amphibia and Reptiles far less marked.

(3) Temperature.—The optimum temperature for the in vitro growth of tissues approximates, naturally enough, to body heat. Mammalian cells are therefore incubated at 37° or 38° C., while those of English frogs (Rana temporaria) were found by H. W. Drew 89 to cultivate best at room temperature, growth in fact being inhibited at 37° C. Lambers 10 in the course of researches on the relation between the temperature and the growth-rate of the heart of chick embryos, has demonstrated that such tissues can be preserved, in a state of "suspended animation," in chick plasma or serum, or in isotonic saline media, at 6° C. for two weeks or more (but always under twenty days).

(4) Asepsis.—An adequate aseptic technique is a sine qua non. For, obviously, conditions such as the maintenance of body temperature, and the use of plasma or glucos-containing
Conditions for Cell Growth

Asepsis  •  Microfluidic Geometry
Oxygen Supply  •  Diffusion
Culture Medium  •  Fluid Flow and Volume
Temperature  •  Thermal Characterization
  •  On-Chip Electronics Design
  •  Electrical Interface
Hybrid Microsystem: Micro-Incubator (I)
Cellular Oxygen Supply: A Balancing Act

Atmospheric Oxygen

Rate of Oxygen Diffusion through PDMS

\[
\text{Flux} = \frac{D_{\text{PDMS}} \times \Delta C}{\text{thickness}}
\]

Maximum Oxygen Consumption

\[
1.00 \times 10^{-16} \frac{mol}{\text{cell} \times \text{sec}}
\]
heating and temperature measurement (I)
heating and temperature measurement (II)
Empirical Thermal Testing Setup

1. USB-TEMP with cold junction compensation
2. Small (40) gauge thermocouple
3. Micro-Incubator
4. XYZ stage micromanipulator
packaging: what works! (I)

$2.9 \times 10^{-9} \text{ W/m}^2$
why the obvious does not work!

1.8x10^-5 W/m^2
hybrid microsystem: micro-incubator (III)

hybrid microsystem: micro-incubator (II)
micro-incubator architecture
BHK: fibroblast morphology
what healthy cells look like!
cell growth in micro-incubator chip version 1

42 hours

60 hours
cell growth in micro-incubator chip version 2

72 hours (3 days)
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beyond the u-incubator (I)

- Devices
- Networks
- Architecture

Self-assembly

Energy

Information (human insight)

- molecules
- macromolecules
- cells

- nano-CMOS
- nanowires
- ribbons

Adaptation and Learning
beyond the u-incubator (II)

• Temperature Dependent Assay
  – Heater array chip\(^1\) for addressable temperature control

• Optical Assay
  – Imager array
  – Optical filtering needed for many applications

\(^1\) “CMOS Heater Array for Incubation Environment Cellular Study”, J. Blain Christen and A. Andreou, Proceedings of the 48th Midwest Symposium on Circuits and Systems. 2005
wireless communication (I)

RFID Tagged Array

Signaling Platform – Control and Gather Data
wireless communication (II)

Microfluidic Device Array

Signaling Platform – Control and Gather Data
3D CMOS

MIT Lincoln 3D 180 nm SOI CMOS technology

Wide dynamic range imager with NUC
Silicon cortex
SIMD microprocessor
Silicon retina
MEMS accelerometers
4 ch bio-electric amplifier
uRFID
Fabry-Perot interferometer
JHU multiproject site

50nm

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complex 3D matter: bottom up and top down

3D CMOS active structures design (top down)

Self Assembly (bottom up)
3D hybrid integration

- Electrical Stimulation & Recording
- Optical Detection
- Cell Culture
- Optical Input
- Thermal Control
- Mechanical Stimulation
self-assembly (II)
hybrid matter

- MOSFET to MOSFET (nano)
- Chip to chip (micro and nano)
- Macromolecule to macromolecule (nano)
- Energy supply: optical and radio frequency photons (macro and meso)
- Cell to virus to cell to chip (micro and nano)
year 2027

Johns Hopkins Medicine, Hospital and associated Medical Institutions have been turned into a historical museum for visitors in Baltimore.

Visitors can get a glimpse of how top tier medical care and research was carried out in the premier research hospital of the Nation back in the 20th century.

• Health care is done at home using patient monitor services and chip level implantable instrumentation, uTAS, and uMRI. Electronically programmed chips control delivery of drugs in a timely and precise fashion.
Acknowledgements

Jennifer Blain Christen,
Assistant Professor, ASU

MIT/LL and DARPA, 3D CMOS technology
Prof. Sachs and Prof. Elisseeff, cell-culture share facility
NSF grant ECS-0225489, “Cell Clinics On a Chip”
NSF graduate student fellowship to JBC
IEEE EDS and CAS DLP program
questions?