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SMR 1564 - 25

SPRING COLLEGE ON SCIENCE AT THE NANOSCALE
(24 May - 11 June 2004)

BIOCHIPS - Part III

Rashid BASHIR
School of Electrical & Computer Engineering, Purdue University
West Lafayette, IN, USA

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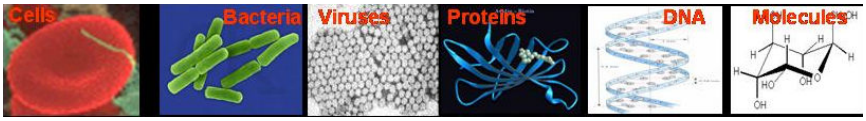
Key Topics

- Biochips/Biosensors and Device Fabrication
- Cells, DNA, Proteins
- Micro-fluidics
- Biochip Sensors & Detection Methods
- **Micro-arrays**
- **Lab-on-a-chip Devices**



1

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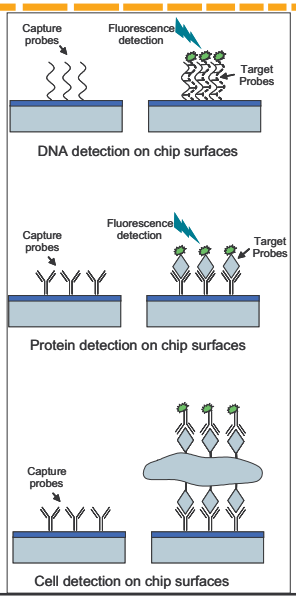
Optical Detection in Biochips

1. Fluorescence: Markers that emit light at specific wavelengths and enhancement, or reduction (as in Fluorescence Resonance Energy Transfer) in optical signal can indicate a binding reaction
2. Chemiluminescence: Generation of light by the release of energy as a result of a chemical reaction.

   - Light emission from a living organism is termed bioluminescence (sometimes called biological fluorescence),

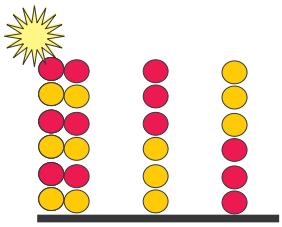
   - light emission which take place by passage of electrical current is designated electrochemiluminescence.



2

DNA Hybridization in Microarrays

- Basis for detection of unknown nucleotides
- Example: Bio-chips for identification of DNA
  - Hybridization of an unknown, flourescently tagged strand with a many known strands - reaction will determine the sequence of the unknown (or vice versa)
  - Strands can be lithographically (Affymetrix) or electronically (nanogen) defined at a specific location



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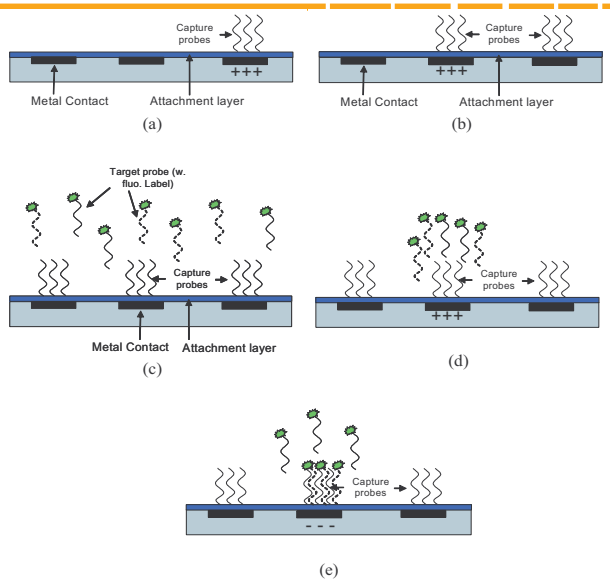
Electronic Placement of DNA Probes



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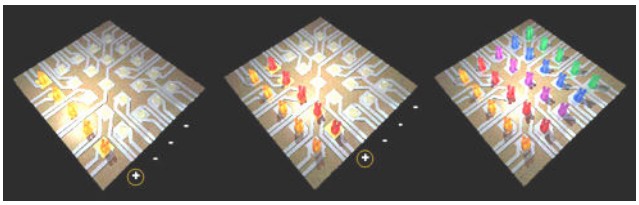
DNA Biochips (Nanogen)

Technology Features:

- Biochips for DNA detection, antigen-antibody, enzyme-substrate, cell-receptor and cell separation techniques.
- Takes advantage of charges on biological molecules.
- Small sequences of DNA capture probes to be electronically placed at, or "addressed" to, specific sites on the microchip.



www.nanogen.com

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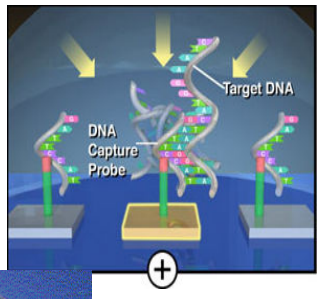
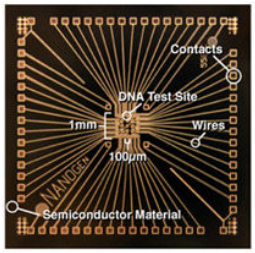
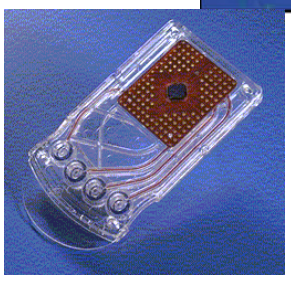
Technology Features

Hybridization.

- **A test sample can be analyzed for the presence of target DNA molecules by determining which of the DNA capture probes on the array bind, or hybridize, with complementary DNA in the test sample.**
- **Fluorescence output**







www.nanogen.com

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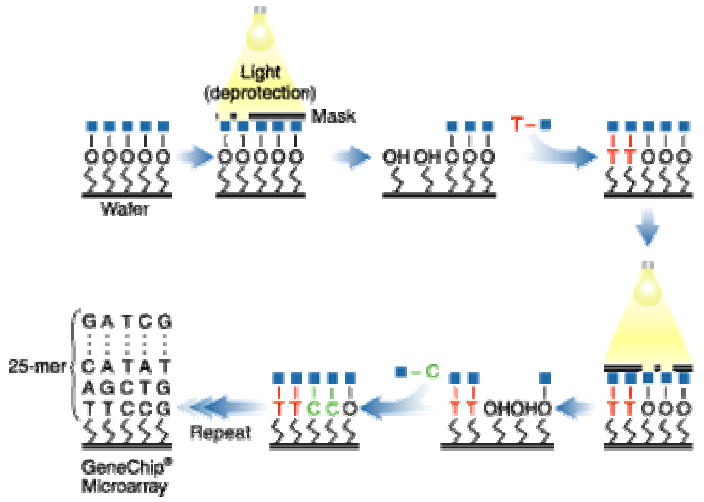
Light Directed DNA Synthesis on a chip (Affymetrix)



Fodor, et al. 1991, www.affymetrix.com

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Light Directed DNA Synthesis on a chip (Affymetrix)

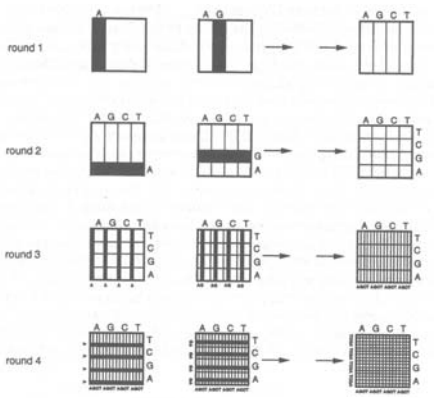
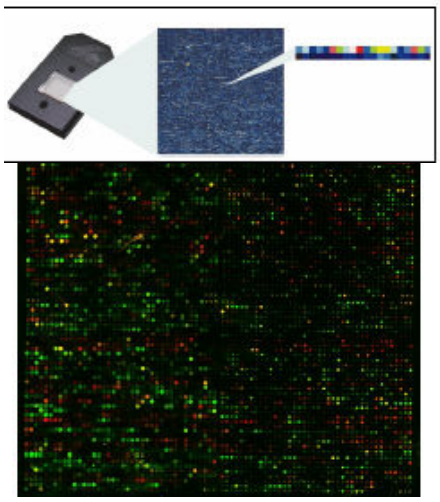


Table 1. Combinatorial synthesis of polynucleotide probe arrays

Probe Length	Chemical Steps	Number of Possible Probes
4	16	256
8	32	65 536
12	48	16 777 216
16	64	$\sim 4.3 \times 10^9$
20	80	$\sim 1.1 \times 10^{12}$

Fodor, et al. 1991, www.affymetrix.com

Light Directed DNA Synthesis on a chip (Affymetrix)



- Fluorescence detection
- Ultimately will limit size of pixel in array

Applications:
Polynucleotide array
HIV resequencing
mRNA expression monitoring

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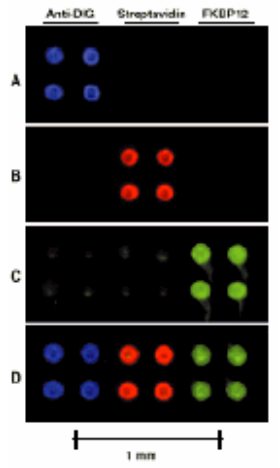
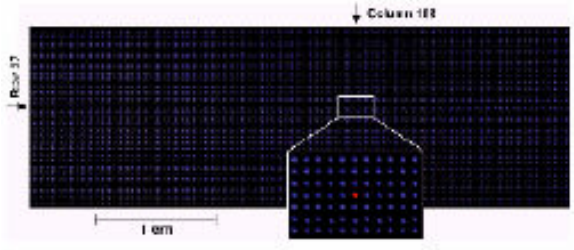
Protein Arrays





- Protein-Protein Interactions
- Protein small molecule interactions
- Derivatized substrates – glass, plastics
- High Throughput screening of chemical compounds

G. MacBeath, and S.L. Schreiber, Printing proteins as microarrays for high-throughput function determination, Science, 289, 1760, 2000.

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Note: Sensor Arrays

- Any of the individual sensors described earlier can be used in an array format to make micro/nano sensor arrays.
- The sensors in the array need addressing
- Each sensor can be functionalized with different bio-receptor molecule to detect different entities
- Examples, cantilever array, electrochemical detection in electrode arrays, cellular arrays for chemical detection, etc.

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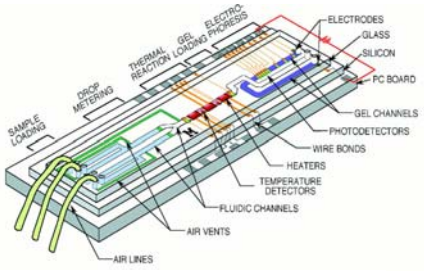
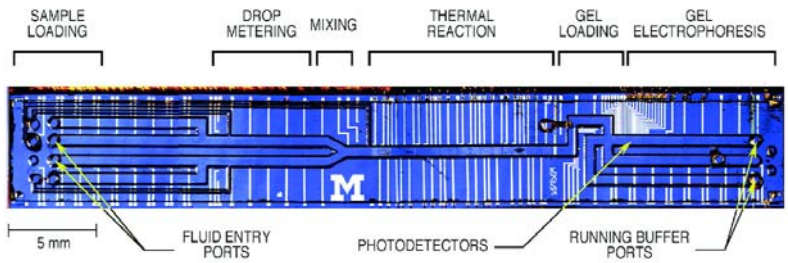
Lab-on-a-Chip/Integrated Devices

- Single chip device for DNA electrophoresis
- Sample loading and metering
- PCR on a chip (faster temperature cycling due to reduced thermal mass)
- Gel electrophoresis on chip

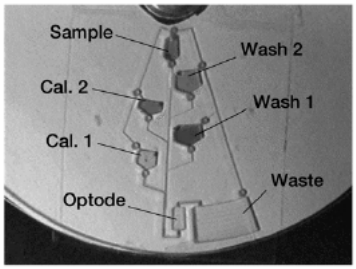




Burns, et al. 1998, Science, v 282, n 5388, Oct 16, 1998, p 484-487

CD Format Biochips

- Micro-fluidic devices on a CD type platform using centrifugal and capillary forces for liquid transport
- Cheap plastic CDs
- Optical detection systems

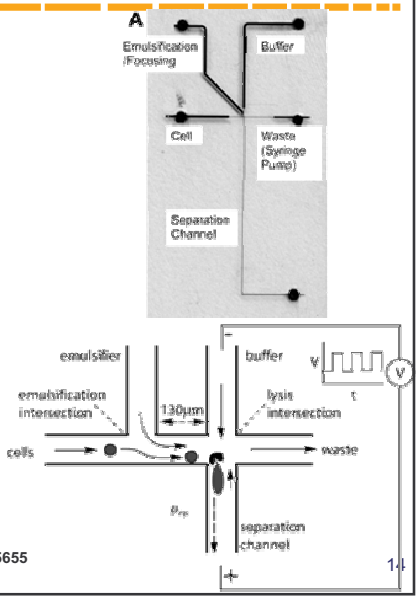


Flow order: Cal. 1➔Wash 1➔Cal. 2➔Wash 2➔Sample

Madou et al., 2001, Biomedical MicroDevices, v 3, n 3, 2001, p 245-54

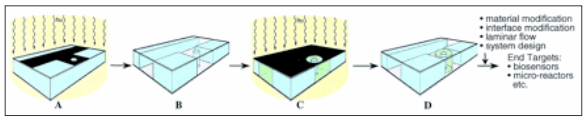
Cellular Analysis on Chip

- Plastic biochips using hydrodynamic transport of cells
- Electric field mediated lysing
- Fluorescence detection (off-chip detectors)
- Analysis time of about 10 cells/minute

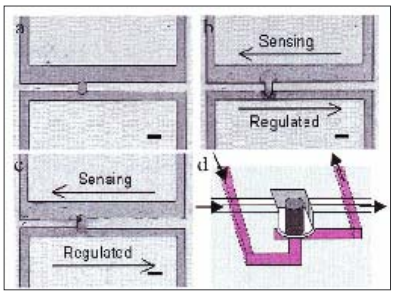


McClain, et al. Analytical Chemistry, v 75, n 21, Nov 1, 2003, p 5646-5655

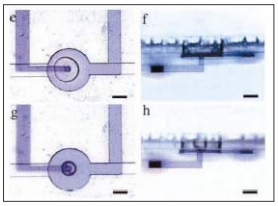
Polymer μSensor and Actuator

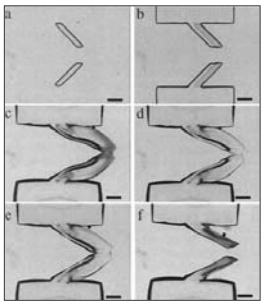


Process flow for the preparation of a hydrogel valve.



Hydrogel valve designs (2D and 3D)





A biomimetic valve based on bistrip hydrogel.

D.J. Beebe et al., Proc. Natl. Acad. Sci. U.S.A. **97**, 13488 (2000).

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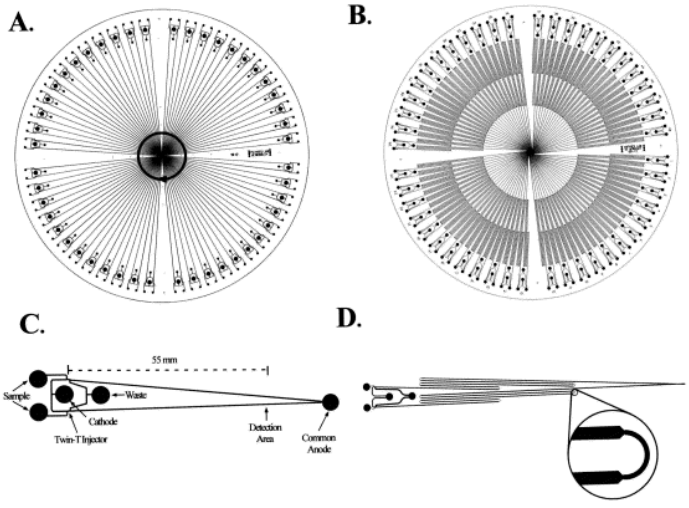
DNA Capillary Electrophoresis



Design of the 96-channel CAE microplate and radial scanner. Mask pattern used to form the 96 straight channel radial microplate on a 150-mm diameter wafer.

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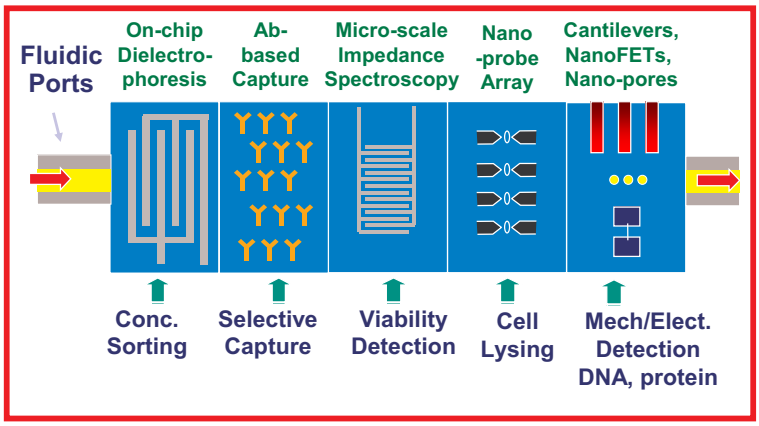
Integrated Systems for Study of Microorganisms and Cells



"Lab on a Chip" for Enabled by BioMEMS and Bionanotechnology

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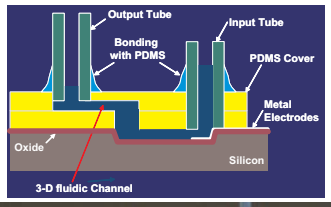
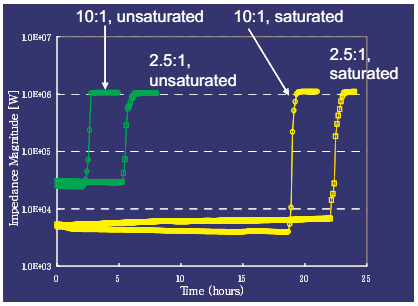
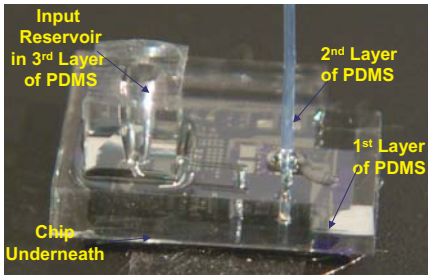
Micro-fluidic Polymer Devices for Culture Bacteria and Spores

- Growth of bacteria inside a micro-fluidic polymer chip
- Rapid detection and reduced time to result







Silicon Base, 3 PDMS layers, Top I/O port

Woo-Jin Chang, Demir Akin, Miroslav Sedlek, Michael Ladisch, Rashid Bashir, , "Hybrid Poly(dimethylsiloxane) (PDMS)/Silicon Biochips For Bacterial Culture Applications", Biomedical Microdevices 5:4, 281-290, 2003,

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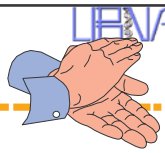
Future Directions

- Integrated device for analysis of single cells – applications and fundamental science
- Building cell by cell/tissue engineering using micro and nano fabrication techniques
- Integrated diagnostics and therapeutics (drug delivery)
- Tools for genetic manipulation of microorganisms and viruses – synthetic biology

Acknowledgements



Research Scientists/Post-docs:
- Dr. Demir Akin
- Dr. Dallas Morisette
- Dr. Rafael Gomez

Graduate Students:
- Sangwoo Lee
- Haibo Li
- Amit Gupta
- Hung Chang
- Yi-Shao Liu
- Samir Iqbal
- Oguz Elibol
- Angelica Davilia
- Kidong Park

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