Micro Electro Mechanical Systems for mechanical engineering applications

Lecture 13:
Device examples (1):
Lab-on-a-chip, DNA chip, Protein chip

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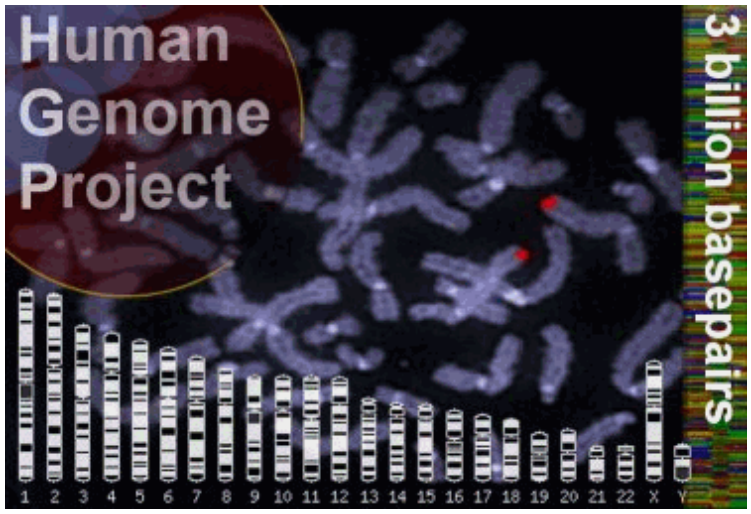
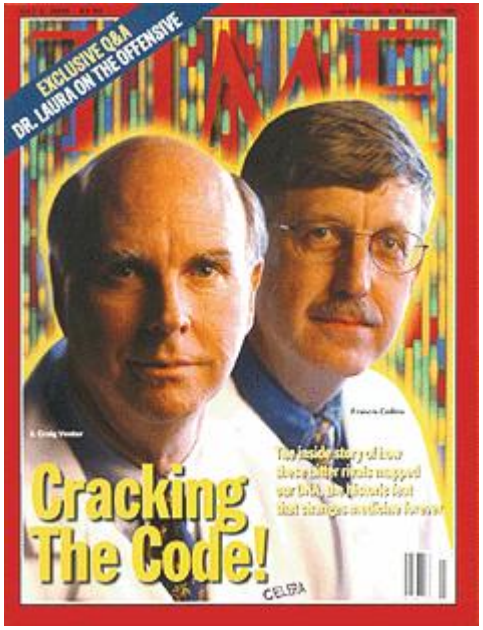
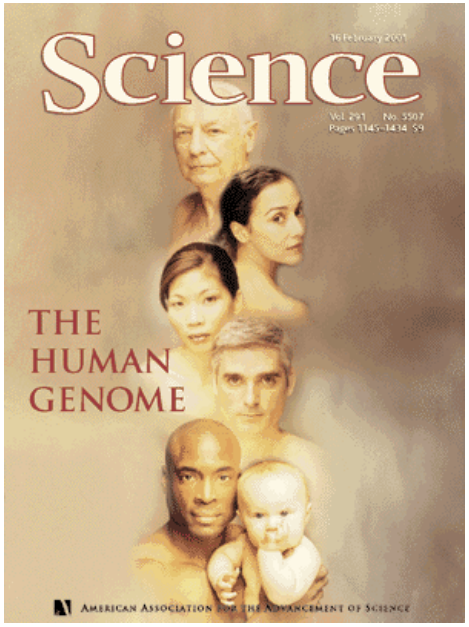
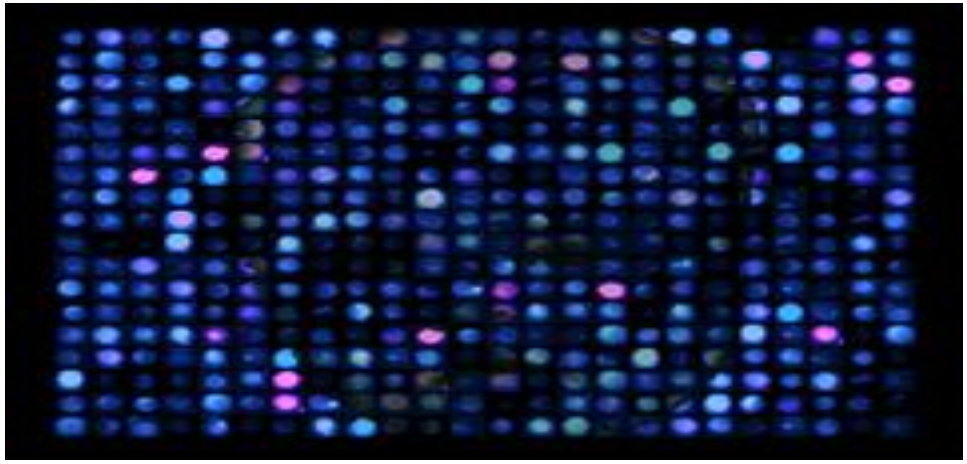
Why biochip? - Big bang of bio information

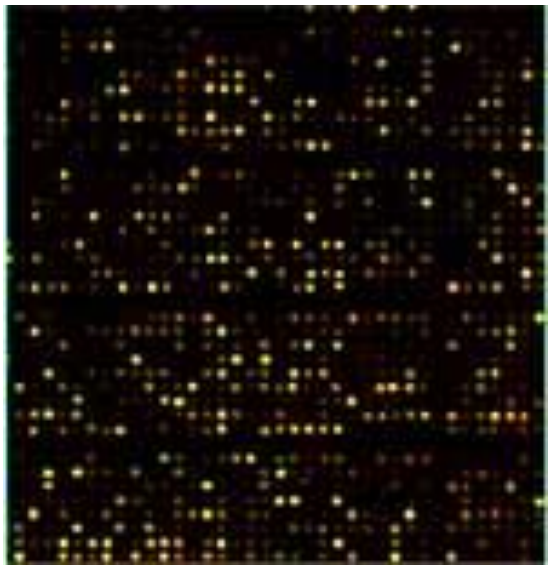


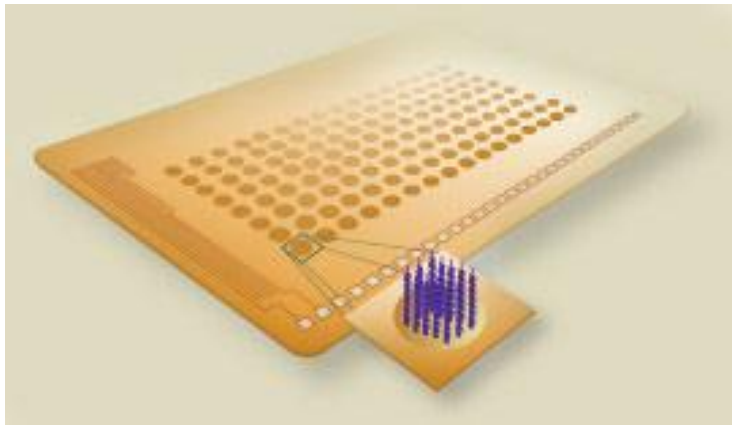


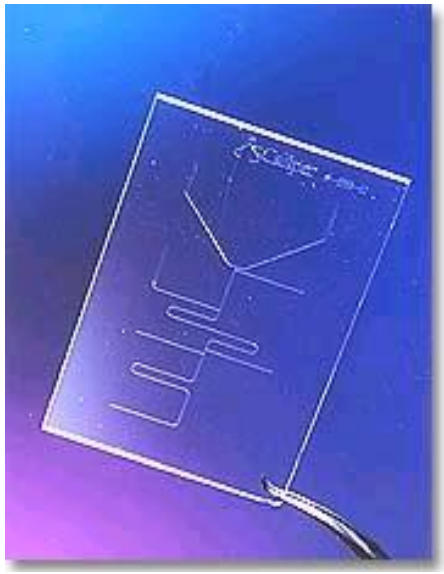




What is biochip?

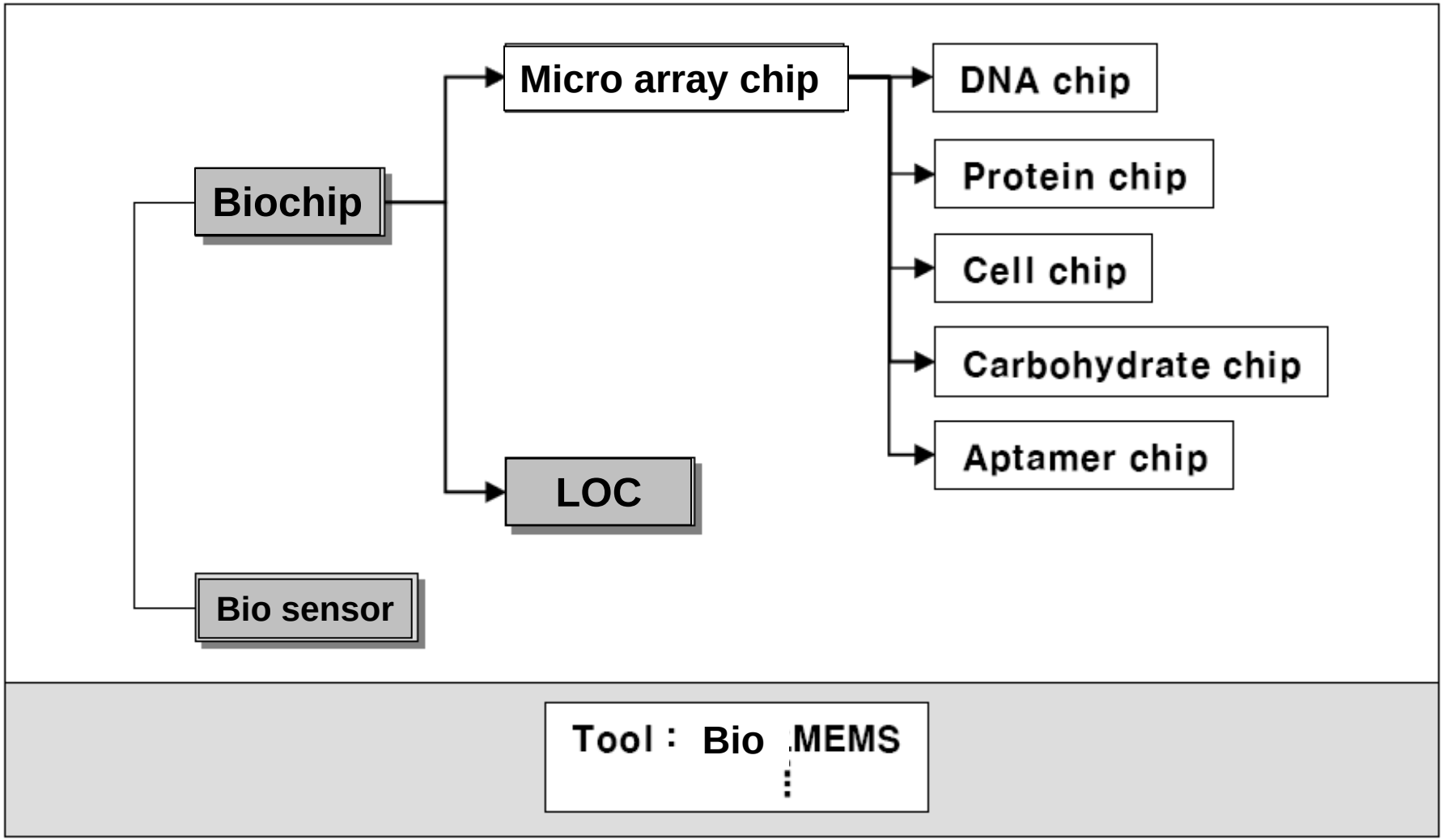






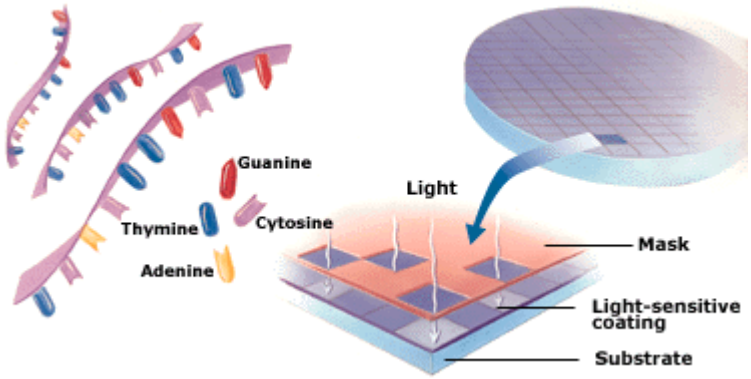
- Devices which allow super-high-speed, high-sensitive analysis of biologically active DNA, Protein, Cells that are highly integrated on glass, silicon or polymer substrates.

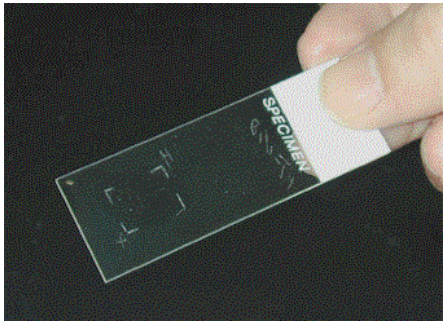
Types of biochip

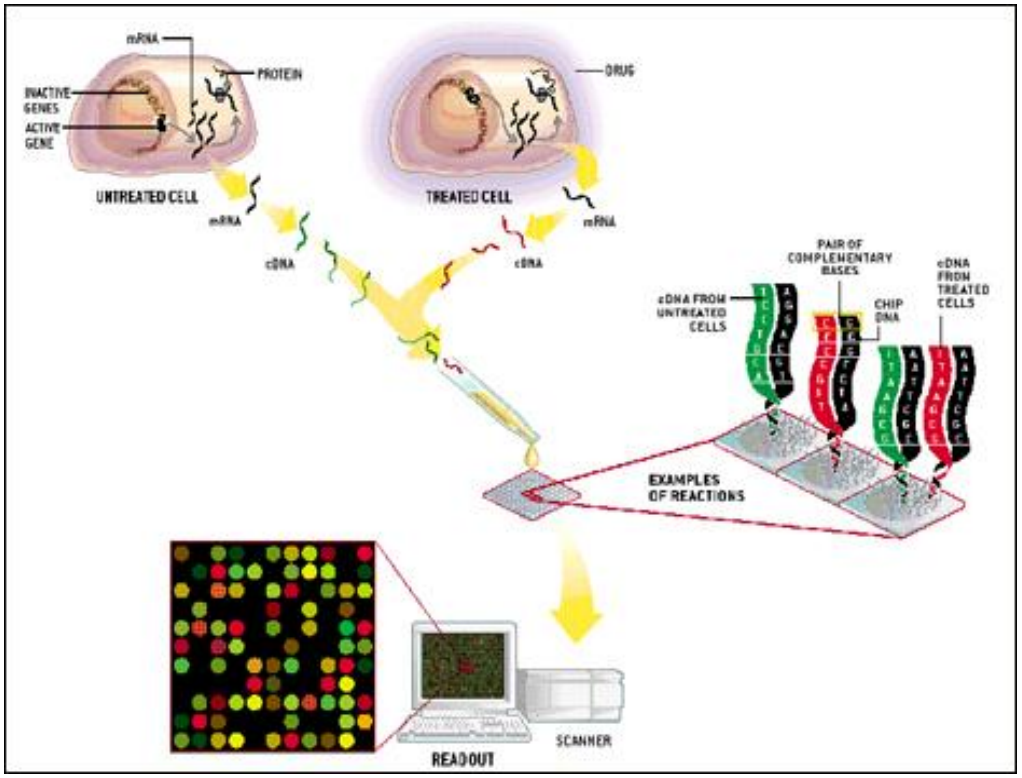


DNA chip - *functional genomics*

- Chip which allows to check gene expression or mutation by adhering highly integrated Oligonucleotide, cDNA, genomic DNA, etc. on its substrate

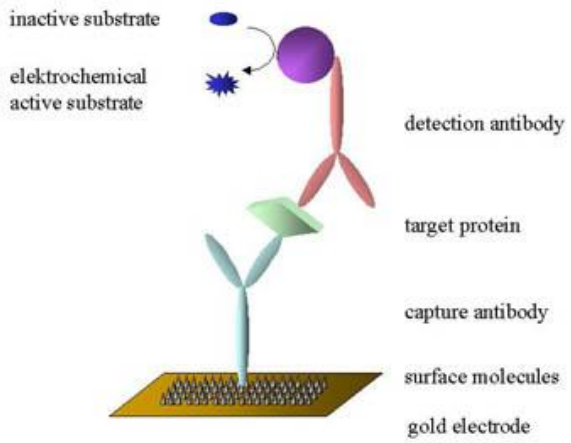


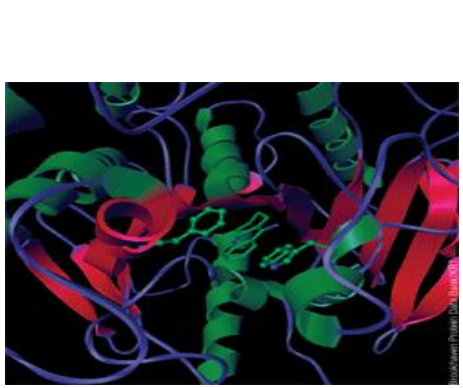


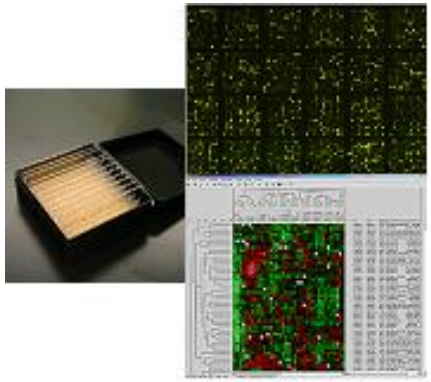


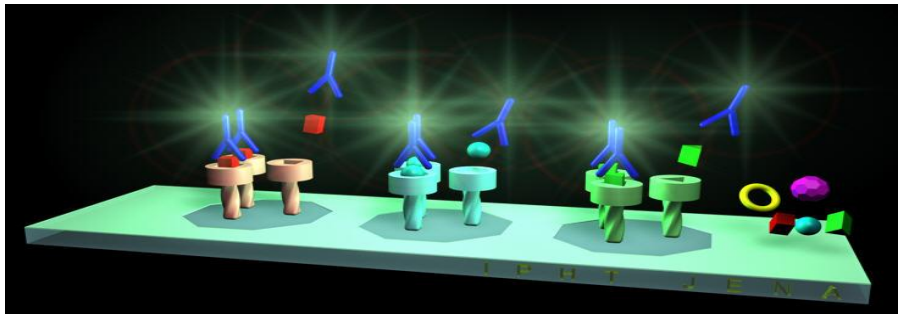
Protein chip - *proteomics*

- Chip that has ligands and proteins those can react with specific protein on its surface
- Proteins could be segregated, checked and quantitatively analyzed on the chip



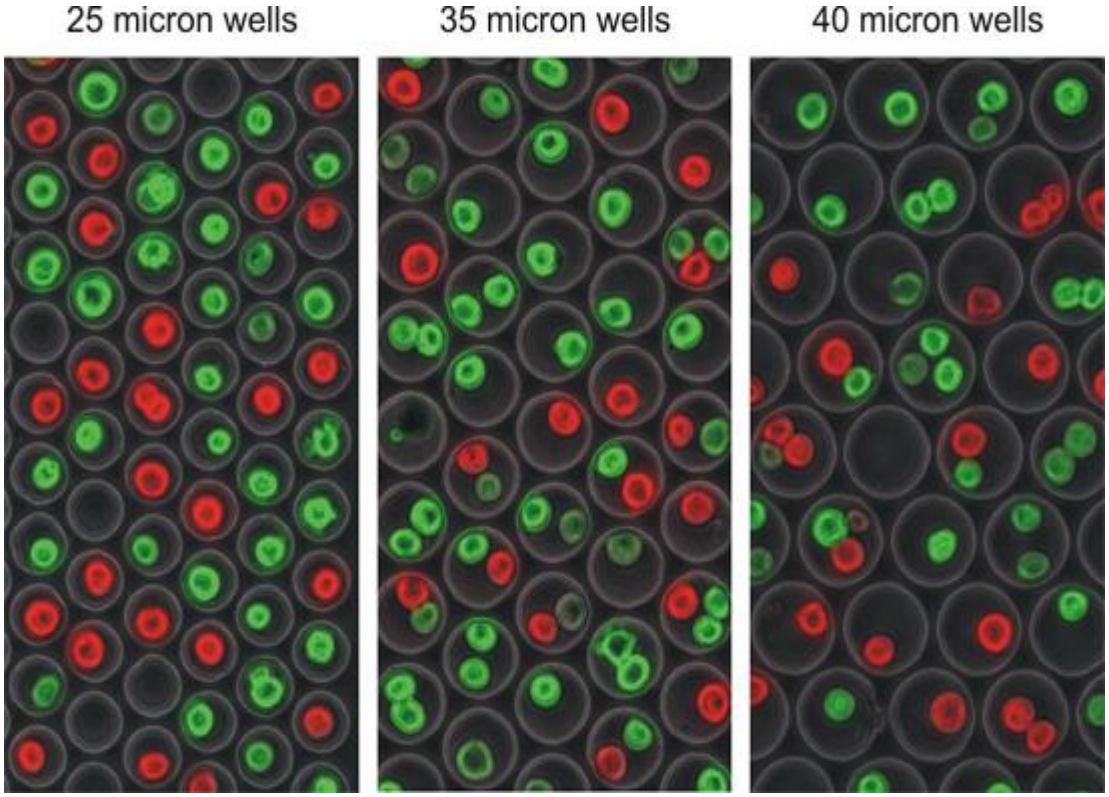


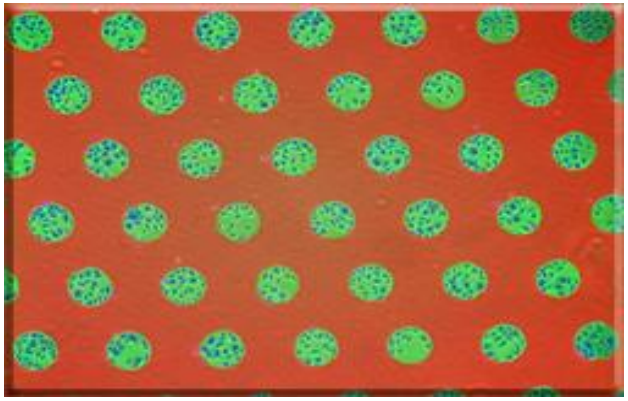


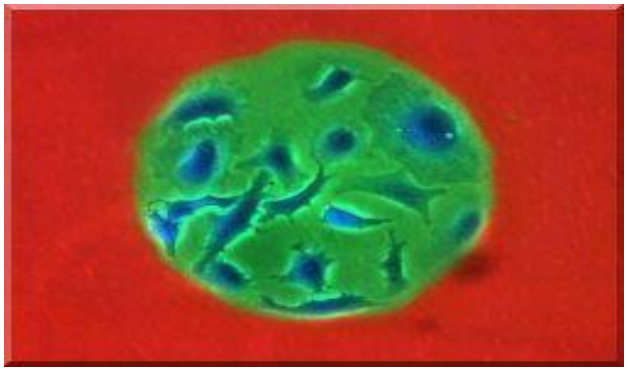


Cell Chip - *functional cellulomics*

- Detection of physiological signal by real-time reaction of live cells which was impossible by existing methods





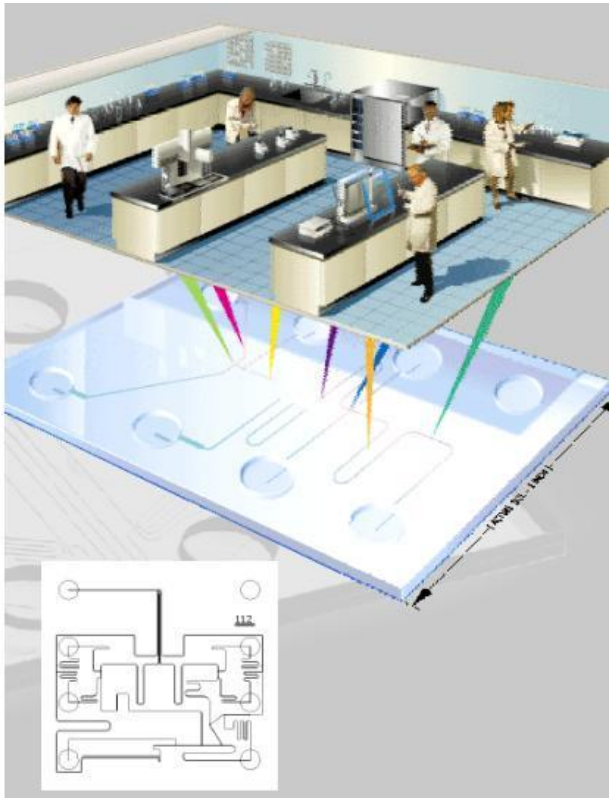


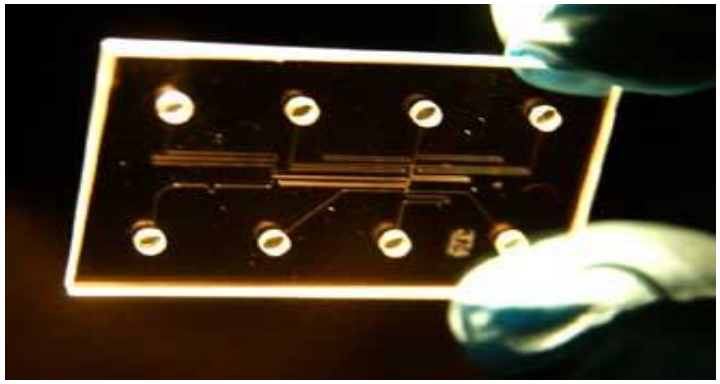
Lab on a Chip

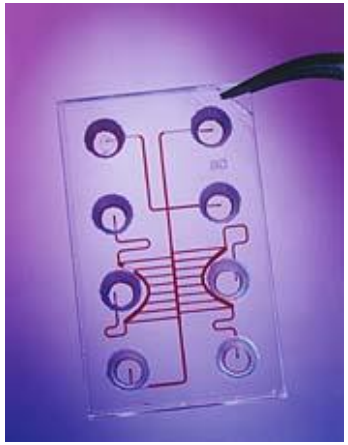
- Micro fab. techniques, Micro/nano fluidics techniques are applied
- Dilution, mixing, reaction, separation of sample could be accomplished on a chip

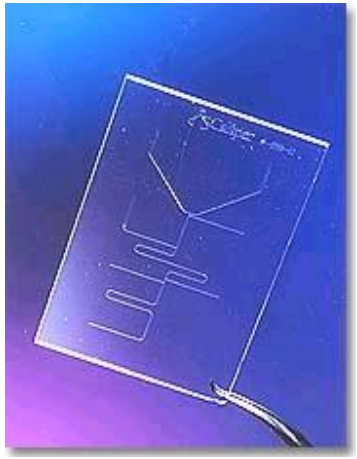
Lab-on-a-chip

- **Features**
  - Miniaturisation
  - Automation
  - Integration
- **Benefits**
  - Data Quality/Reproducibility
  - Reagent savings





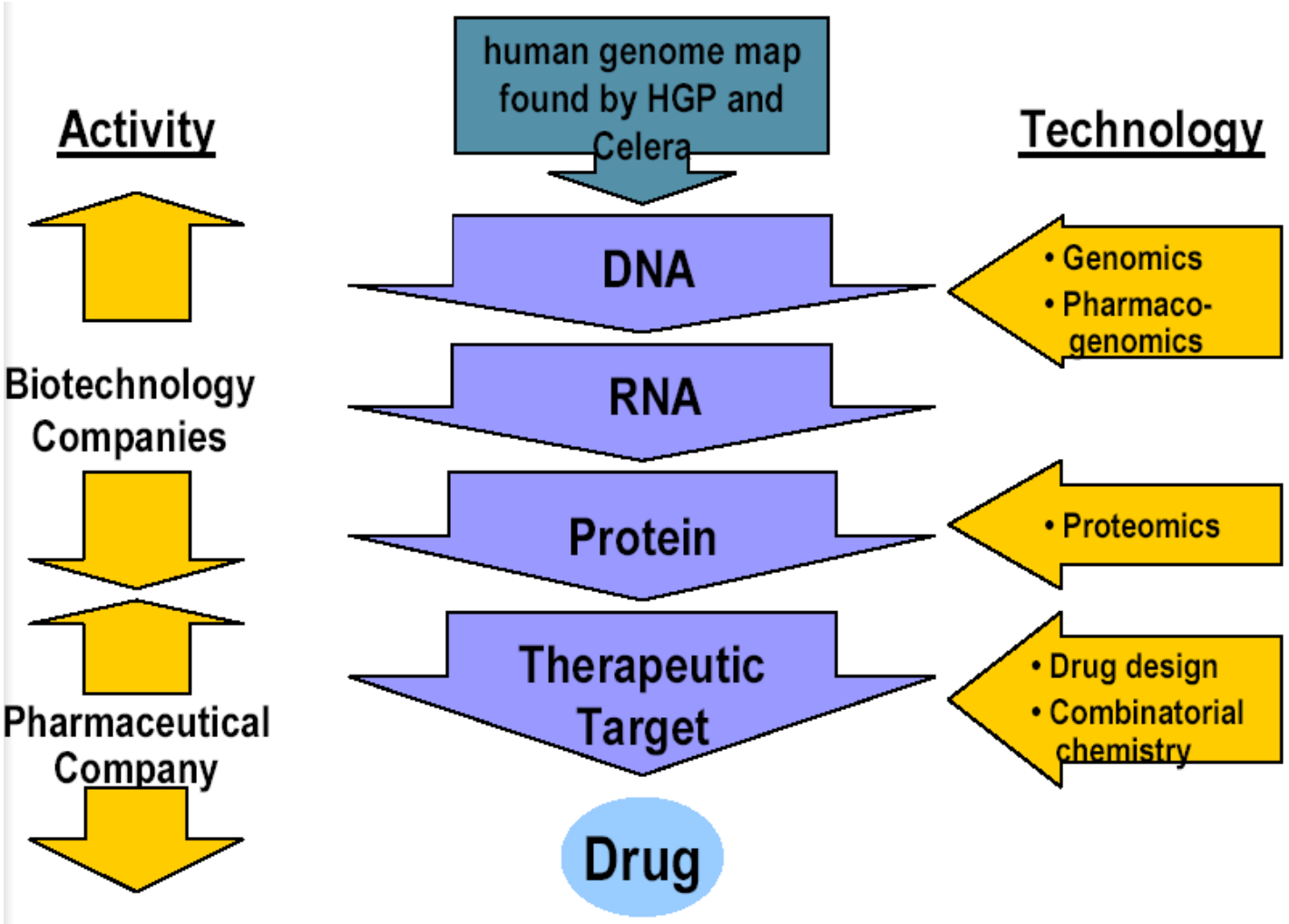




Advantages and Applications of LOC

- Advantages
  - Shorter processing time
  - Less sample/reagent required
  - Disposable
  - Automation possible
  - Parallel operation : high throughput
  - Integration possible
- Applications
  - Detection and diagnosis
  - Synthesis and analysis
  - Interaction and interrogation
  - Treatment (drug delivery)

Lab-On-A-Chip Applications to Genomics & Proteomics

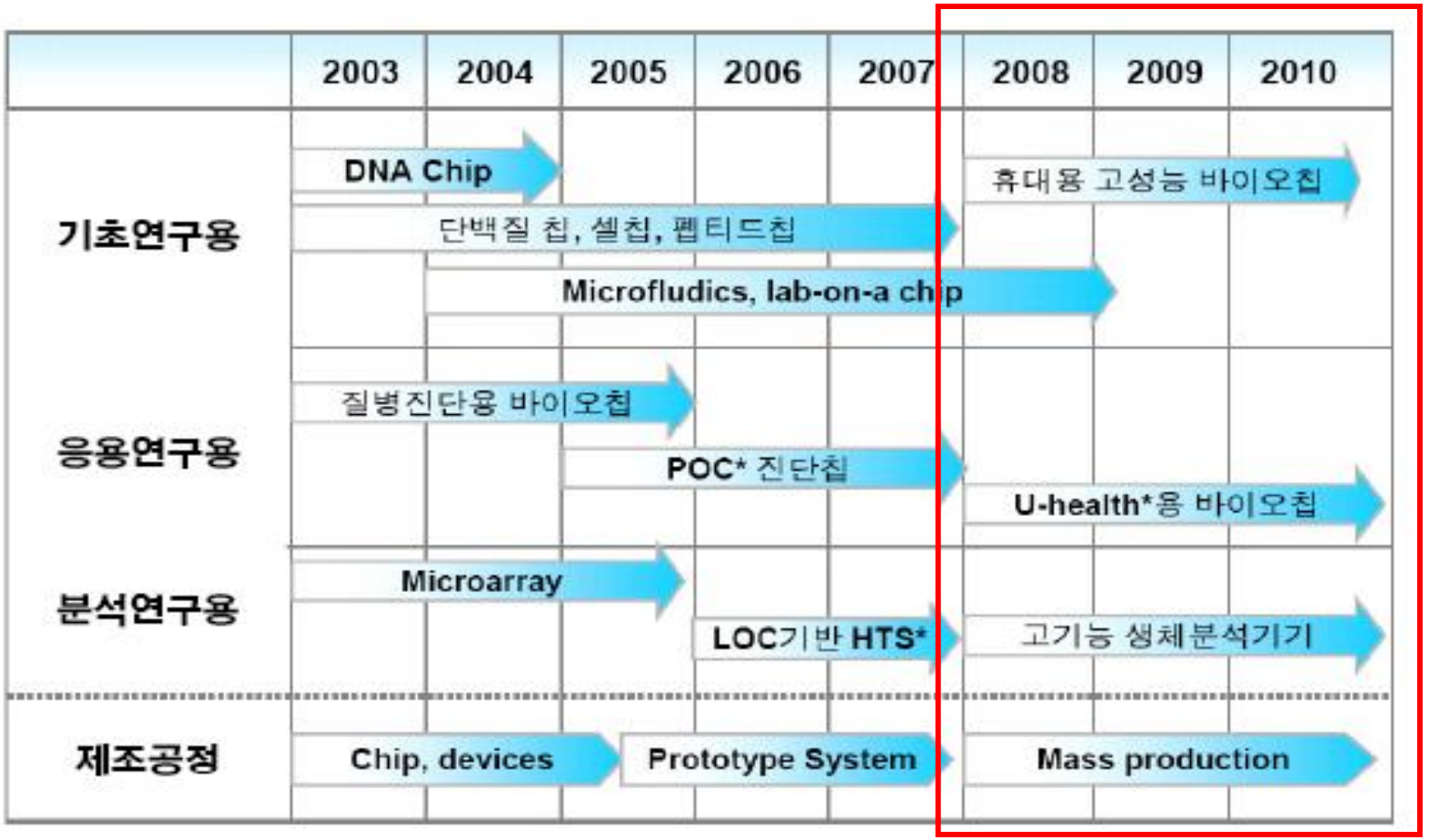


Applications & Vision

Chips for research	various platform → various data
	gathering data
	researcher's choice by market
Chips for diagnosis	various products → same result
	reliability, sensitivity, accuracy are needed
	restricted by law and regulations

Most chips were for research so far

Roadmap of Bio-chip Technique



참고자료: 2002 LG경제연구원, "국내 Bio-IT 산업의 현황과 과제" (2005.9). 원출처: 전자부품연구원(KETI)
* POC: Point of Care(자가진단), U-health: Ubiquitous health, HTS: High Throughput Screening, 이해를 돕고자 원본자료를 일부 수정함.

1. DNA chip - A chip for genomics

- Device that measures mRNA concentrations is called a DNA chip or DNA microarray.

- Working assumption: the concentrations of the mRNA molecules in a cell define its “biological state”

- There are two ways performing this job

(a) cDNA microarrays (spotted microarrays)

- see the animation:

http://www.bio.davidson.edu/courses/genomics/chip/chip.html

(b) Oligonucleotide microarrays (Affymetrix chips)

Applications of DNA Microarrays

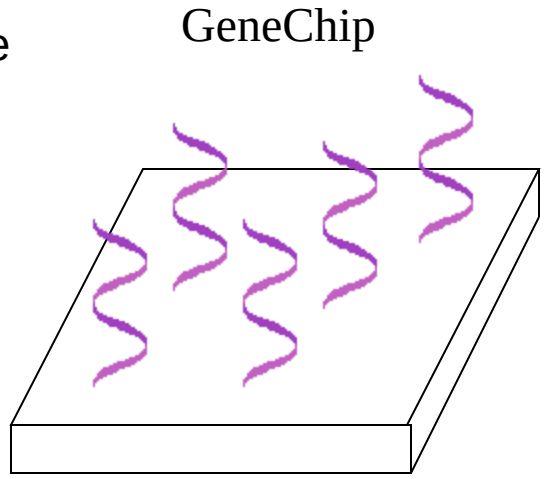
- DNA Microarrays are used to study gene activity (expression)
  - What proteins are being actively produced by a group of cells?
    "Which genes are being expressed?"

- How?
  - When a cell is making a protein, it translates the genes (made of DNA) which code for the protein into RNA used in its production
  - The RNA present in a cell can be extracted
  - If a gene has been expressed in a cell
    - RNA will bind to "a copy of itself" on the array
    - RNA with no complementary site will wash off the array
  - The RNA can be "tagged" with a fluorescent dye to determine its presence

- DNA microarrays provide a high throughput technique for quantifying the presence of specific RNA sequences

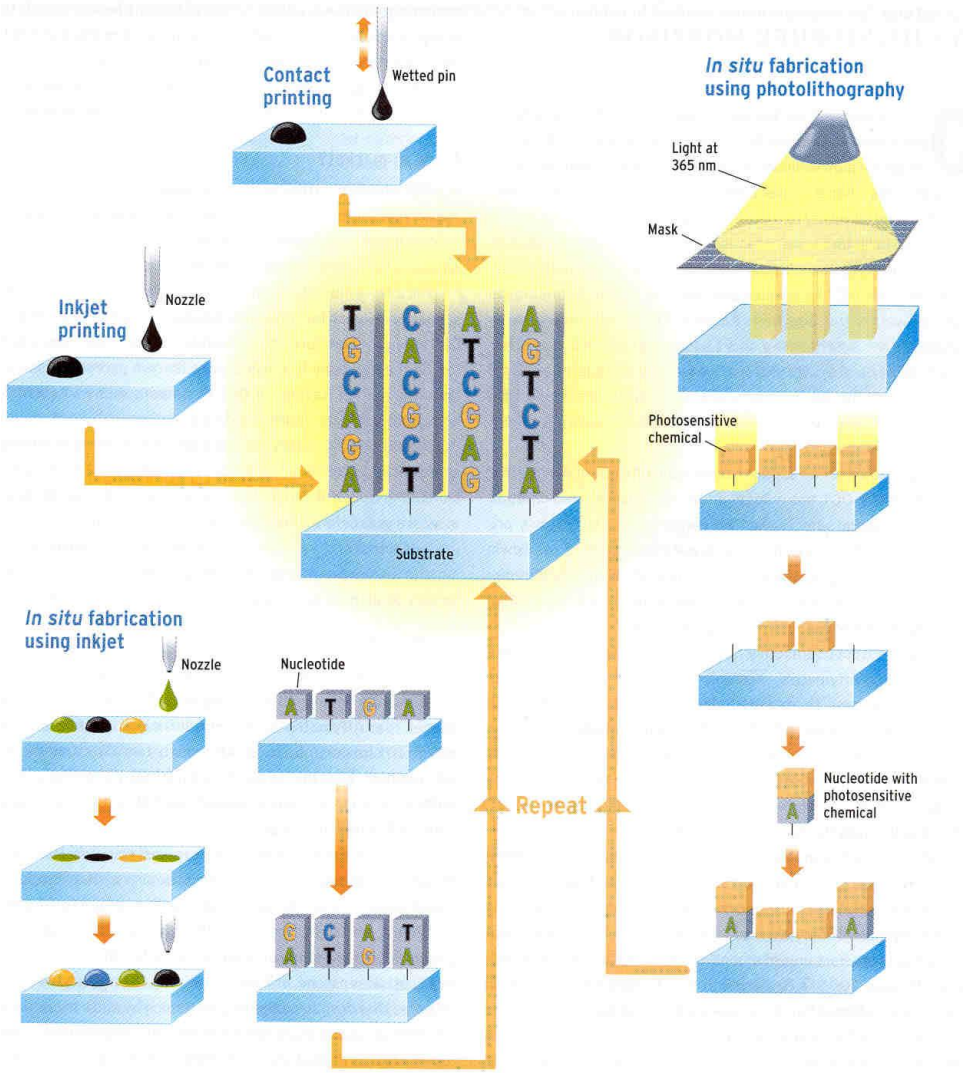
DNA Microarrays

- Each probe consists of thousands of strands of identical oglionucleotides
  - The DNA sequences at each probe represent important genes (or parts of genes)
- Printing Systems
  - Ex: HP, Corning Inc.
  - Printing systems can build lengths of DNA up to 60 nucleotides long
  - 1.28 x 1.28 + cm glass wafer
    - Each “print head” has a ~100 μm diameter and are separated by ~100 μm. (≈ 5,000 – 20,000 probes)
- Photolithographic Chips
  - Ex: Affymetix
  - 1.28 x 1.28 cm glass/silicon wafer
    - 24 x 24 μm probe site (≈ 500,000 probes)
  - Lengths of DNA up to 25 nucleotides long
  - Requires a new set of masks for each new array type



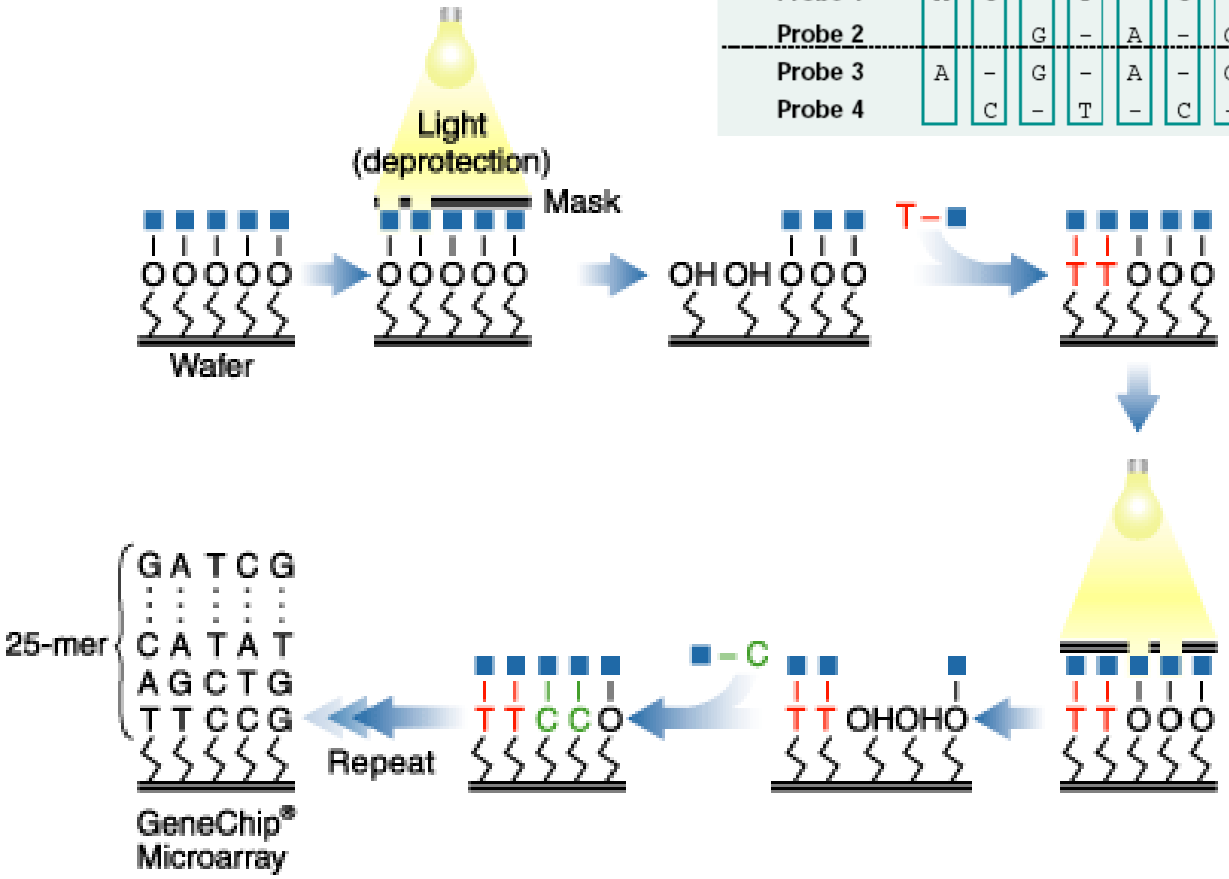
Fabrication of DNA Microarrays

- Fabrication via Printing
  - DNA sequence stuck to glass substrate
  - DNA solution pre-synthesized in the lab
- Fabrication *In Situ*
  - Sequence "built"
  - Photolithographic techniques use light to release capping chemicals
  - 365 nm light allows 20-μm resolution



Details of Affymetrix chip

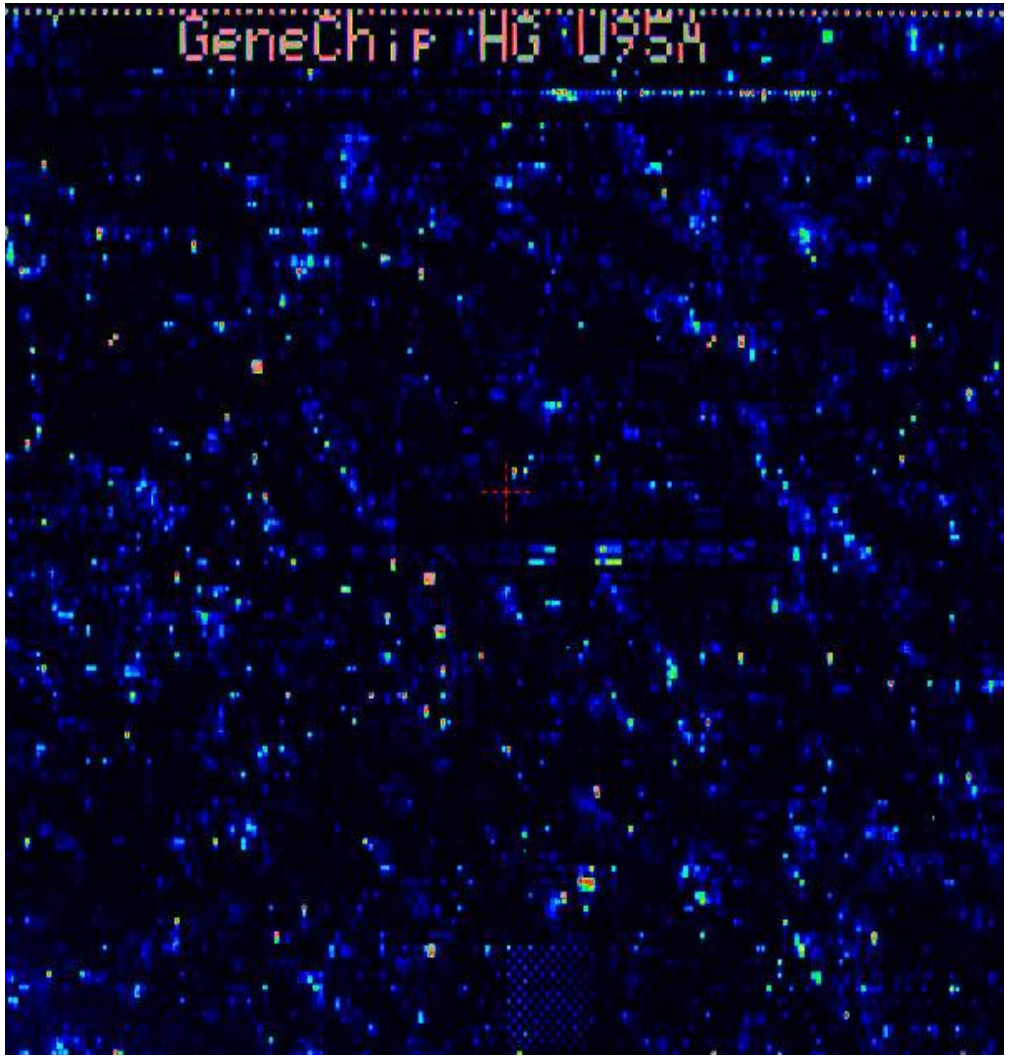
Mask Cycles	1	2	3	4	5	6	7	8	Probes Synthesized
	A	C	G	T	A	C	G	T	
Probe 1	A	C	-	T	-	C			A C T C
Probe 2			G	-	A	-	G	T	G A G T
Probe 3	A	-	G	-	A	-	G		A G A G
Probe 4		C	-	T	-	C	-	T	C T C T



Typical Result

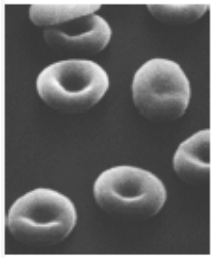
- A light source scans the array, causing the dyes to fluoresce
- The glow is picked up by a sensor and is used to determine the relative abundance of the RNA
- This information must be processed to determine the level of activity for each expressed gene

GENEARRAY™ SCANNER

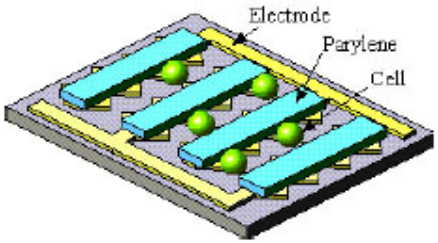


Lab on a chip + DNA chip? = DNA Analysis (1)

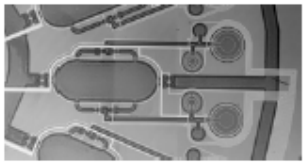
Blood, tissue, etc



Sample prep
- cell lysis
- purification
- concentration

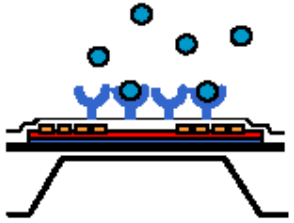


Reagent handling
- pumping/valving
- micromixing



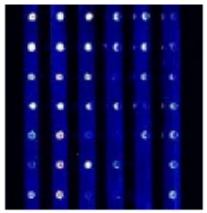
Amplification
- micro PCR

Labeling
- fluorescent dyes
- radiolabels
- binding events

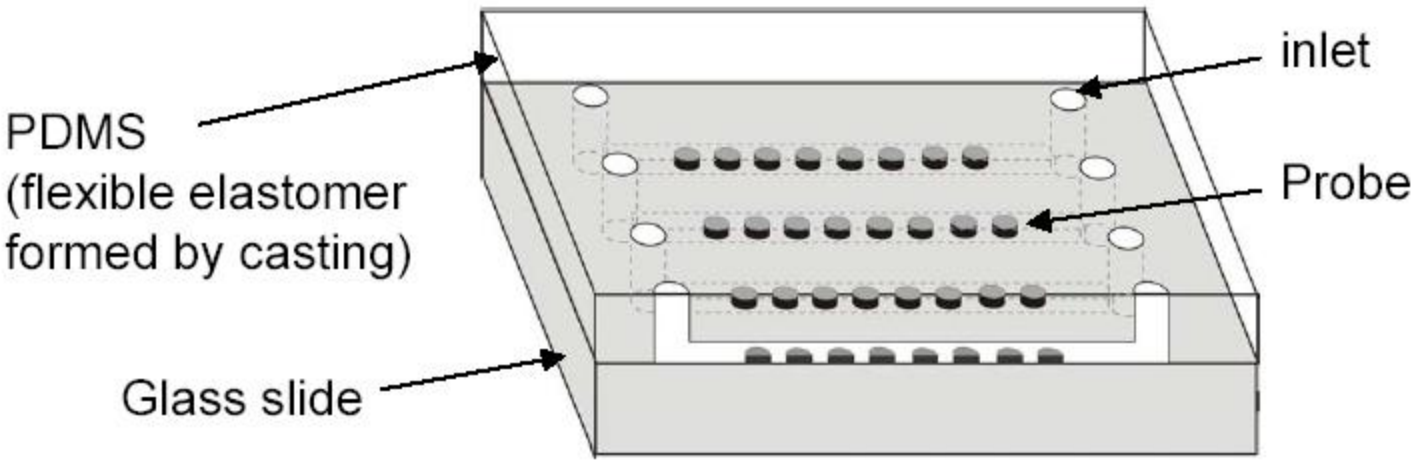


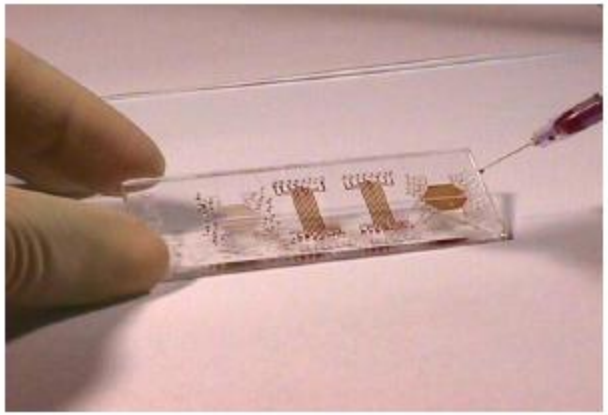
Separation
- CE
- LC
- IEF

Detection
- optical
- mass spec
- conductometric

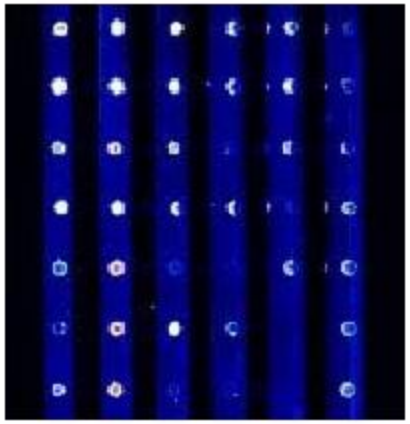


DNA Analysis (2) - Parallel DNA Channel Array





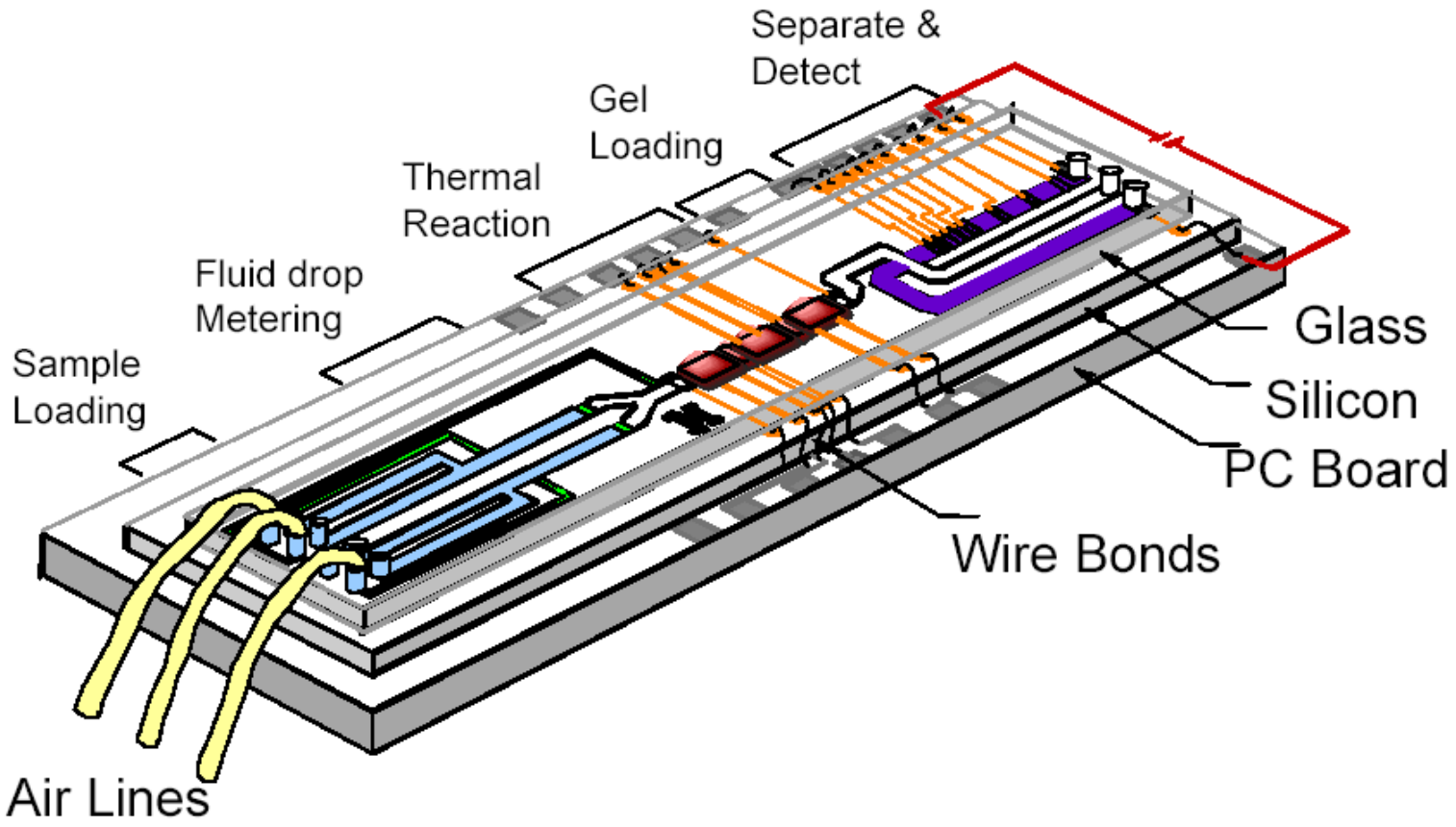
Manual loading of DNA sample



Resulting fluorescence data

Microfluidics Laboratory at Motorola Inc.

DNA Analysis (3) - Integrated DNA Analysis



C. Mastrangelo, U. Michigan

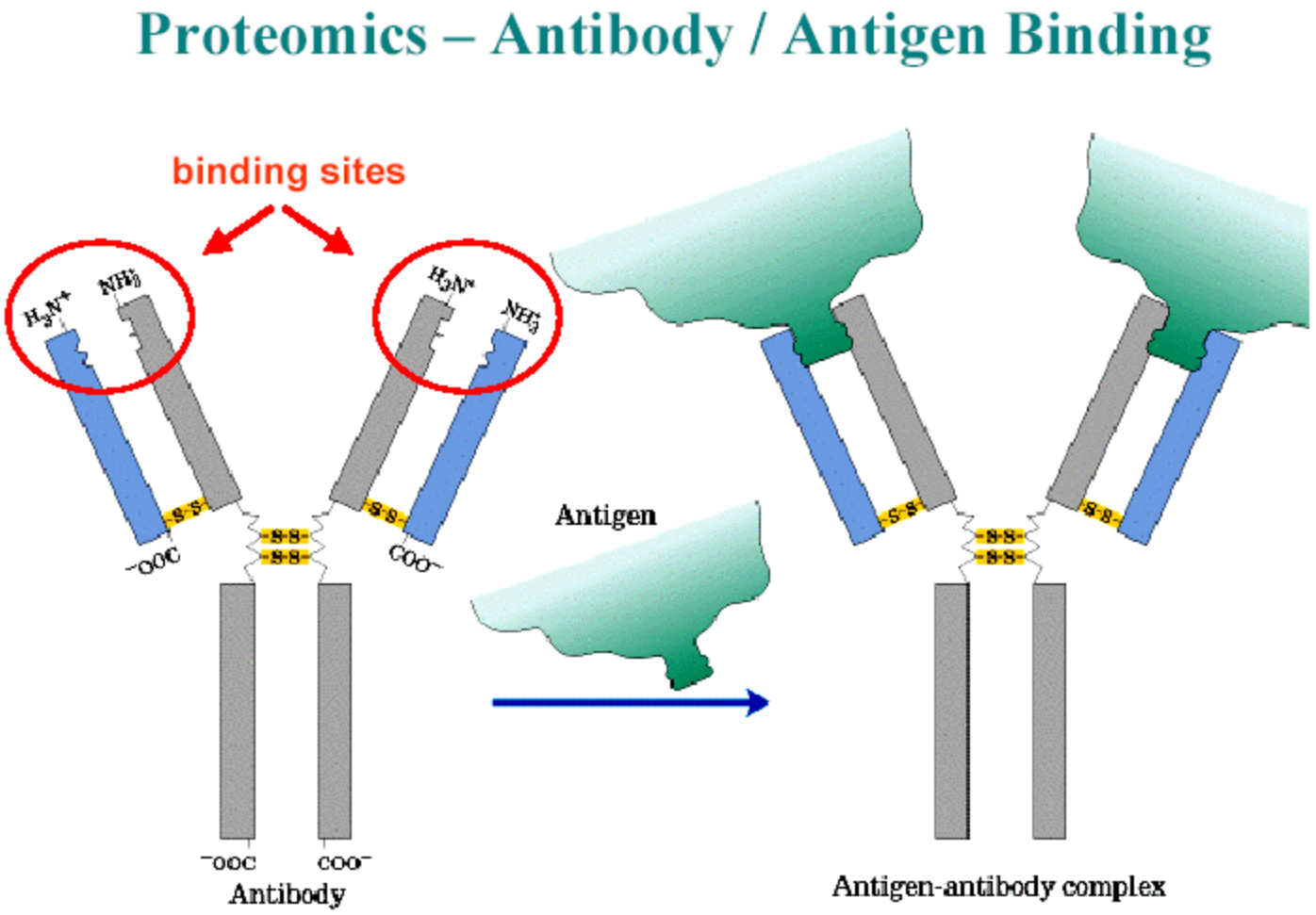
2. Protein chip - A chip for proteomics

Proteomics – Protein Arrays / Microarrays

- **Goal**
  - High-throughput analysis of protein expression / interaction
  - Adapt approach similar to DNA microarrays
  - Improves on speed vs. 2D electrophoresis

- **Approach**
  - No equivalent of hybridization for proteins
  - Exploit other biochemical binding reactions
    - Antibody–antigen
    - Receptor–ligand
    - DNA–protein…

Sensing mechanism for protein chip

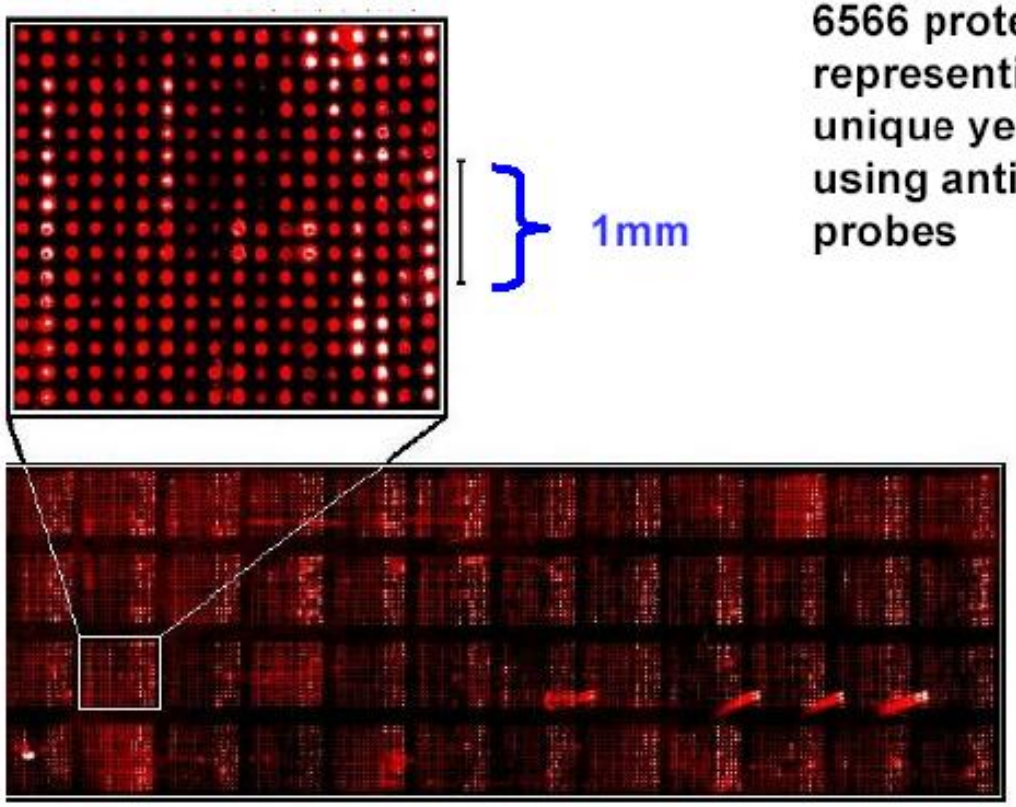


Methods for protein chip

- **Method**
  1. Place on glass slide many probes at known locations
     - Chemical probes
       - Ionic, hydrophobic, hydrophilic…
     - Biochemical probes
       - Antibody, receptor, DNA…
  2. Mix protein samples with probes, bind
  3. Wash off remaining proteins
  4. Collect & identify bound proteins with mass spectrometer
     - Surface Enhanced Laser Desorption / Ionization (SELDI)
- **Produces**
  - Protein expression profile
  - Protein interaction with probes

Antibody probes: example 1

Monoclonal Antibody Capture Microarray

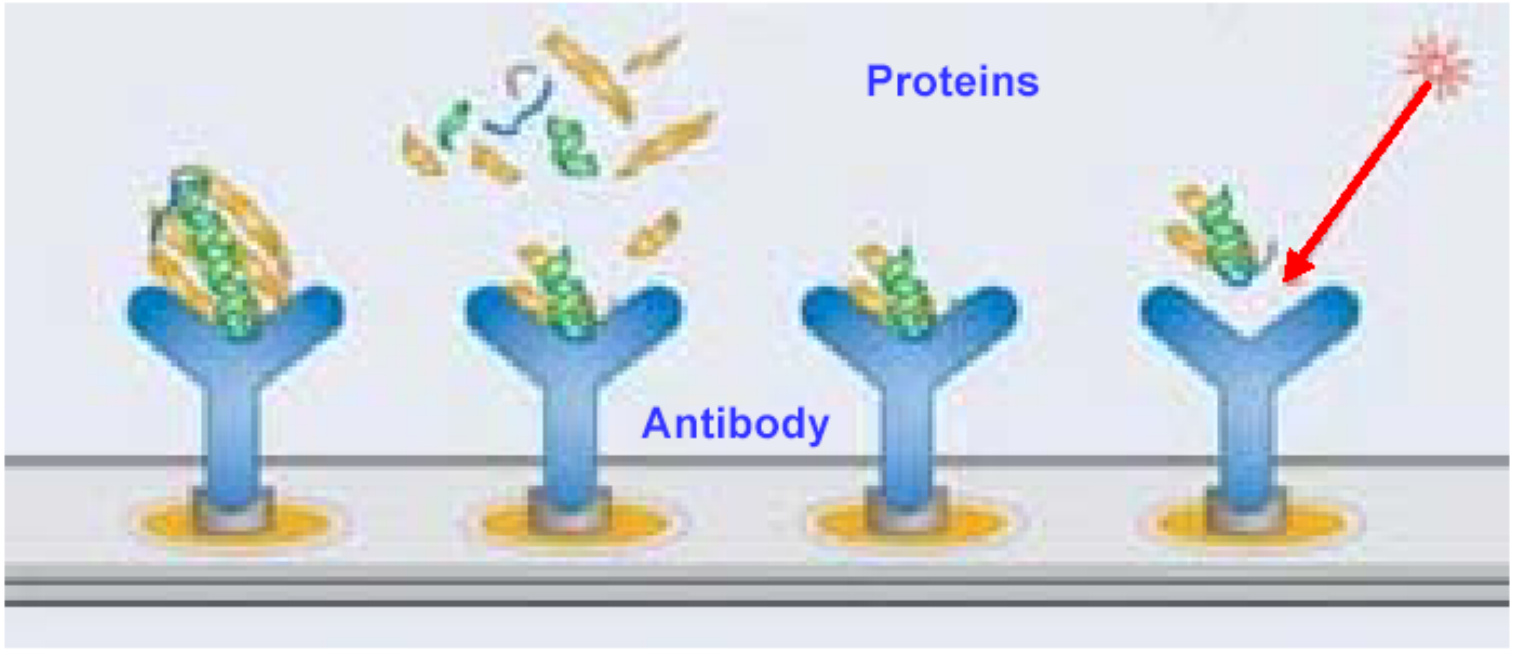


6566 protein samples representing 5800 unique yeast proteins, using anti-GST antibody probes

[Zhu+ 2001]

Antibody probes: example 2

Ciphergen Antibody Capture Protein Chip



1) Protein with antigen bound to antibody probe

2) Remainder of protein digested enzyme, leaving peptide antigen

3) Wash away protein fragments

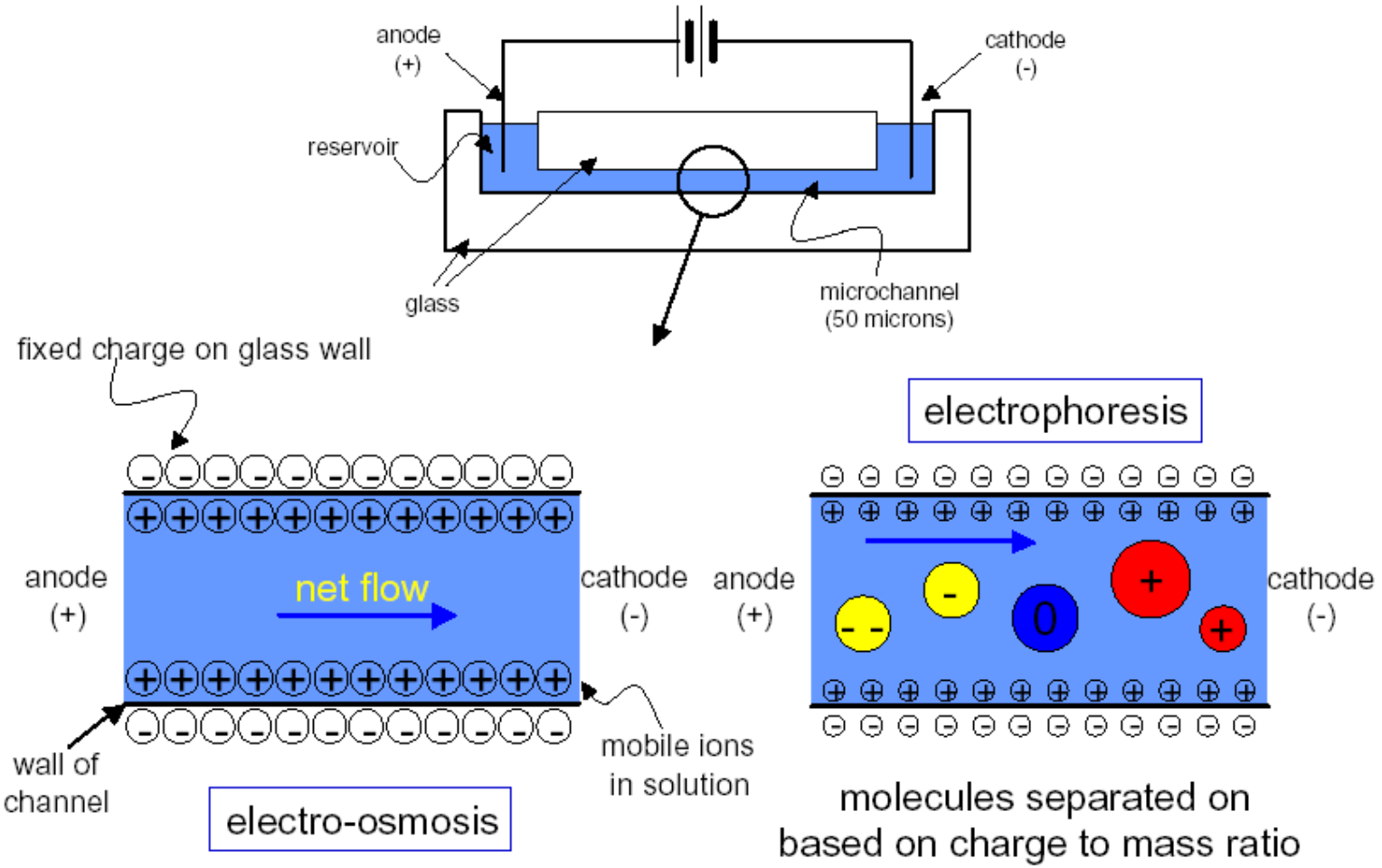
4) SELDI laser ionizes & desorbs epitope binding peptide, sends to mass spectrometer

Some issues of protein chip

- **Issues**
  - Protein–probe interaction may not be one-to-one mapping
    - Multiple proteins may bind to same site
  - Binding kinetics (strength of bond) differ for proteins
    - Intensity may be due to kinetics, not protein concentration
  - Protein structure / function affected by contact with surface
    - May not achieve bond as expected
- **Scale**
  - Currently less miniaturization than for DNA microarrays
  - Protein array
    - 8-16 spots of 96-well spot chips = ~1500 probes
  - Protein microarray
    - 10,000+ probes

Lab on a chip + Protein chip? = Capillary electrophoresis (1)

Lab-on-a-Chip Based on Capillary Electrophoresis



Lab on a chip + Protein chip? = Portable diagnostic device (2)