Microfluidic Systems

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Lab-on-a-Chip
(Body Fluid In; Answer Out)

Fluid Handling, Amplification, Derivatization, Lysis of cells, Concentration, Extraction, Centrifugation

Sample Prep

Sample Separation

Electrophoresis, liquid chromatography Molecular exclusion, Field flow fractionation

Sample Detection

Fluorescence, UV/vis Absorption, Amperometric, Conductivity, Raman
Polymer Micropump

Self-Priming
Flexible
Biocompatible
Low Cost
Microfluidic System Concept

The Power of Integration: from Desktop to Handheld to Integrated Fluidic Chips
Concept

- One system to provide all of the possible required analyses for a given type problem
- All processing steps are performed on the chip
- No user interaction required except for initialization
- Portable bedside systems possible
Goals:

- Fast
- Portable
- Robust
- Easy to use
- Flexible
- Inexpensive
- Modular?
Considerations in Microscale Biomedical Analysis Systems

- Biocompatibility
  - Defined for each application and system
  - Cells, proteins, DNA, tissues all have different requirements
  - Typically low protein absorption, no leaching, “non-reactive”
- Harsh chemicals and environment
- Small sample handling
- Interfacing with macroscale world
- Pumps, valves, flow control
  - High pressures, flow rates, and volumes possible
- Sample injection
- Multimodal: Fluids, Electrical, Optical, etc.
- Interfaces with existing systems (standards)
Components

- Separation
- Mixing
- Reaction
- Sample injection
- Sample preparation
- Detection
- Pumping
- Transport (channels)
- Reservoirs
- Flow control
- Control
- Intelligence and Memory
- Power
- Display
- Other analysis
- Sample collection?

Don’t forget packaging!!
BIO MEMS for Analysis

Micro-titerplates for Biomedical Analysis (Steag Mikrotechnik, Dortmund)

Injection Molding

Multi-level Fluid handling system
Fluid Control Components

- Pumps, valves, channels
  - Pumps and valves of similar design
  - No perfect pumps or valves
- Generally require mechanical actuation
- Valve types
  - A: restriction perpendicular to flow
  - B: restriction parallel to flow
  - C: combination of A and B
  - D: phase change (freezing)
Microfluidic Scaling

- All flow is laminar (no turbulent mixing)
- Surface tension becomes significant
- No inertia effects
- Apparent viscosity increases
Pump Types

- Valved
  - Piezoelectric
  - Thermo
  - Pneumatic
  - Electrostatic

- Valveless
  - Electro hydrodynamic (EHD)
  - Diffusor
  - Electroosmotic (electrokinetic)
  - Bubble
Microfluidic Scaling: Pumping

- Mechanical (blister pouch)
  - I³
  - No fluid contact
  - Generic
  - Innovation in the blister pouch solves valving
  - Difficult to further miniaturize
  - Difficulty to multiplex

- Acoustic
  - I²
  - No fluidic contact
  - R & D
  - Generic
  - Doesn’t solve valving yet
  - ZnO technology still difficult to reproduce
  - Easy to further miniaturize
Microfluidic Scaling: Pumping

- Electroosmotic
  - $I^2$
  - Fluid contact
  - Development
  - Not generic
  - May solve valving
  - Mixing difficult to implement
  - Many parameters influence propulsion force
  - High voltage source is not convenient
  - Better for high-throughput screening and smaller samples

- Centrifugal
  - $I^3$
  - No fluid contact
  - Established
  - Generic
  - Solves valving elegantly
  - Widest dynamic range
  - Simple and inexpensive CD player for drive
  - Mixing easy to implement
  - Most functions demonstrated
  - Cell work possible
  - Sample preparation easier
  - Better for diagnostics
Electroosmotic Pumping

- Requires materials with surface charge
  - Preferably permanent
- Glasses and many polymers have permanent negative surface charge
- Positive charges assemble on surface
- Applied charges pull assembled charges
- Charges at surfaces drag bulk material
Micromixer

- Mixing is a surprising problem on the microscale
- Good mixing critical for many bioassays
- Recirculation mixes quickly
- This method thoroughly mixes the most viscous fluids in less than five seconds.
Electrohydrodynamic Mixing

Liquid sample with conductivity of $\sigma_1$

Liquid sample with conductivity of $\sigma_2$

Upper electrode

Glass

Lower electrode

Mixed liquid samples out

Microfluidic channel (etched silicon)
Electrohydrodynamic Convection

- Surface charges are induced at the interface.
- External electric fields make the induced charges move.
- Moving charges produce the shear force.
- Liquids are moving along with the induced charges and being mixed.
Mechanical Actuators

- Actuation mechanisms:
  - electrostatic = electrostatic attraction of charged plates
  - thermal = expansion of solids or fluids; phase change
  - shape memory alloy = considerable change in length (TiNi)
  - pneumatic/hydraulic = fluid pressure
  - piezoelectric = electrically induced strain
  - magnetic
  - chemical (including hydrogels)
  - biological
Kodak System

- Blister pouch used for pumping
- Commercially available
- Disposable pouch used with complex base system
Gate Valve

Steps:
- Current travels down platinum wires, heating the coil.
- The coils boil water to produce bubbles.
- Bubbles push on the cross’s arms and force it away from the main channel. (The valve open.)
- Bubbles generated on the other side of the arms closes the gate valve.
Magnetic Valve

- Example of a typical mechanical valve
- Can be attached to glass motherboard
- Modular
Channel Shapes and Types

- Hemispherical
- Rectangular
- Triangular
- Trapezoidal
- Round
Flow Measurement

- Turbine?
- Hot wire anemometer
- Ultrasonic
- Optically
- Others?
Advantages of Microfluidics
Structurally Programmable Arrays

- Valving accomplished by channel size reduction
- Program: hard wired into system
- Can also be done using hydrophobic sections

Chong Ahn, Univ. Cincinnati
Separations

- Chromatography
- Wide variety of methods
- Issues
  - Resolution
  - Field strength
  - Analysis time
  - Contaminants

- Electrophoresis
- Field-flow fractionation
- Gas and liquid chromatography
- Blotting (Directions)
- Size exclusion
- Affinity
Motivation for Lab on Chip

- Combination of chemical reactions, sample injection, and separation of reaction products in one system
- Speed up analysis times
- Reduce fluid handling
- Improve resolutions
- Reduce sample sizes
- Allow parallel processing
- Reduce costs
- Integrated signal detection and processing
- Smaller systems (portable)
Micro Gas Chromatograph

Principle Layout

3 Functional Layers
Stacked to Build a 3D MEMS Device

Courtesy Ed Overton, LSU
Electrophoresis

- Used to separate charged particles on basis of size and charge
- Electric fields are applied across gels which slow “large” particles moving through gel
- High resolution separations possible
Fabrication

- Fabricated on 4 inch square glass plates
- Cr/Au/Cr mask was used to etch glass plates
- HF/HNO$_3$ etchant used to etch channels
- 2 mm access holes drilled in second plate
- Air squeezed out and then bonded at 440 C for 2 h
Channel Layout

- Thick lines are 240 μm across
- Double T injector used
- Injection volume ~ 100 pL
- Injection to Detection distance is ~ 5 cm
Sample Handling in T Injector

Stack injection

Plug injection
Typical Operation and Detection

- **Operation**
  - 10 µL to sample reservoir
  - Sample moved using 1 kV into injection area
  - Separation performed by applying 6 kV across electrophoresis channel

- **Detection**
  - Laser-induced fluorescence
  - 488 nm argon ion laser
  - Emission collected by PMT (Passivated mesa transistor)
  - Observes a 11 pL volume
  - Bandpass filtered signal
  - Problems w/ scattering off curved glass surfaces and bonding process
  - Detection limit 30 pM
Nanofluidics in PMMA Microdevices

- Epi-illumination
- fluorescein seed
- Electrokinetically driven flow (reverse-polarity)
- Substrate Material: PMMA
- Channel dimensions: 20 nm (width) x 50 μm
Microfluidic Chips

Electroosmotic flow for pumping

Sometimes called electrokinetic pumping
Microfluidic Chip Fabrication

- Glass plate
  - Photoresist coat
  - Mask, expose, develop photoresist
  - Etch glass
  - Remove photoresist
- Etched glass plate
- Electroplate
- Separate
- Metal electroform
- Mold or emboss
- Molded plastic card
- Cover and seal

Completed fluidic card

Repeat 1000’s of times

Plastic cover layer
Microfluidic Chip Fabrication
System for Reading Chips

The NanoChip™ electronic chip contains platinum wires which are connected to a computer controller once the NanoChip™ is inserted into the NanoChip™ Molecular Biology Workstation.

The microchip is similar to that used in many computers and enables extremely precise control of each individual test site.

99-site test array. Each test site is electronically connected to the NanoChip™ system by a platinum wire.
Cartridge Concept

- In vitro sensors for multiple analytes
  - Modularity vs. integration
  - From Si to plastic and hybrid
Types of Detectors

- Optical
  - Fluorescence
  - Absorption (UV, etc)
  - Light scattering
  - Refractive index
  - Radiation

- Electrochemical
  - Amperometric
  - Potentiometric
  - Conductimetric

- Mechanical

- Thermal
  - Conductivity and Flame Ionization

- Chemical

- Magnetic
Detector Issues

- Volume
- Complexity
- Sensitivity
- Selectivity
- Bulk
- Cost
- Applicability
Fabrication Results

- Micrograph of detector wire across channel defined by polyimide
- Wire is 19 μm wide
- Location of wire eliminates all end effects
LabCD: A Bioanalytic / μ-TAS Platform

What are the necessary platform attributes to encompass:

– Drug discovery and development
– Life science research
– Clinical and molecular diagnostics

- **Flexible fluid processing**  wide range of volumes, flow rates, pressures
- **Flexibility in fluids**  wide range of viscosity, pH, ionic strength, aqueous, organic solvents, biological fluids
- **Flexibility in assay**  homogenous, heterogeneous, cell based
- **Detection options**  Colorimetry, fluorescence, luminescence
- **Integration**  World-interface + macrofluidics + microfluidics + temperature control + detection ...
- **Automation and simplicity**  replace labor intensive processes

From Gamera Biosciences
CD Fabrication

- machined (acrylic)
- microfab (PDMS)
Integrated Microfluidic System

- Integrated microfluidic subsystem for bio/chemical detection
- Surface mounted microfluidic components
- Electrochemical immunoassay
- Integrated micro controller and driving/detecting circuits
Microfluidic Motherboard
Challenges for Total Integration of Microfluidic Chips

- Reagent storage and reconstitution
- Integrated microvalves and micropumps
- Packaging
  - Interconnects (optimize → reduce → eliminate)
  - Filling / bubbles / dead volume
  - Leakage
- Surface functionalization
- Microflow measurement and characterization
- Control algorithms, data processing, and communications
- Integrated, ultrasensitive detection
- Heterogenous material integration
- Sensitivity limited by sample volume (front end amplifiers?)
- Low power
  - Harness energy from host or ambient
  - Low power pressure sources
Dispensing Well Plate (DWP) =

highly parallel nanolitre dispensing
device / technology

- non-contact dispensing of fixed volumes
- size of a standard micro well plate (96, 384, 1536 ... format)
- 96, 384 or 1536 different liquids are dispensed simultaneously
- simple & robust operation
- high precision (CV < 5 %)
Hot Embossed DWP 700 mm PP Chip

One DWP PP unit with reservoir, microchannel and nozzle
DWP Movies