Introduction to BioMEMS & Medical Microdevices

Microfluidics Part 1 – Design & Fabrication

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Microfluidics

- Manipulation of small amounts of fluid, typically <1 nL.
  - Microducts
  - Micronozzles
  - Micropumps
  - Microturbines
  - Microvalves
  - Microsensors
  - Microfilters
  - Microneedles
  - Micromixers
  - Microreactors
  - Microdispensers
  - Microseparators

- Three basic designs:
  - Continuous flow.
  - Droplet based.
  - Digital

Image courtesy of Micronit
Basic Designs...

Continuous flow.

Drop-based.

Digital

Topics

- Rapid Prototyping Systems in PDMS (polydimethylsiloxane)
  - Example - Capillary Electrophoresis Device
    - Process Steps
      - Making the master
      - Casting PDMS
      - Plasma oxidation
      - Performing capillary electrophoresis
  - Results
  - Conclusions

- Large Scale Integration
  - Microvalves
  - Micromixers
  - Electric Field Driven Pumping
  - Micropumps

Image courtesy of Sylgard
PDMS

- Elastic modulus of ~1-3 Mpa – compliant and deformable.
- Optically transparent, biocompatible and oxygen permeable.
- Easily moldable – 2-part mix, vacuum de-bubble and pour.
- Sections can be oxygen plasma treated and “stacked” together allowing for complex microchannels.
- Suitable for biomimetic ECM scaffolds.
- Susceptible to medium evaporation, bubble formation and unwanted absorption of hydrophobic drugs/compounds.
Duffy et. al. compared PDMS vs silicate glass in a simple CE experiment separating six amino acids.

Channels are 50-µm-wide and deep.

1. Mold master was first designed with a CAD program, then a simple transparency was made as a mask.
2. Contact photolithography was used to expose a positive resist coated silicon wafer. Resist thickness was \( \sim 55 \, \mu m \).
3. Features greater than 20 \( \mu m \) could be realized.
4. Glass posts were placed upright for fluid reservoirs.
5. PDMS was then cast against the master to yield elastomeric replicas containing networks of channels.
6. Oxidation and sealing.
Oxidizing PDMS in a plasma discharge converts $-\text{OSi(CH}_3\text{)}_2\text{O}-$ groups at the surface to $-\text{O}_n\text{Si(OH)}_4 \cdot n$.

The formation of bridging, covalent siloxane (Si-O-Si) bonds by a condensation reaction between the two PDMS substrates is the most likely explanation for the irreversible seal.

PDMS seals irreversibly to itself, glass, silicon, silicon oxide, quartz, silicon nitride, polyethylene, polystyrene, and glassy carbon; in all cases, both surfaces here were cleaned and exposed to an oxygen plasma for 1 min.
This method of sealing PDMS devices retains the integrity of the channels, is carried out at room temperature and pressures, and is complete in seconds to minutes. (In contrast to anodic fusion bonding.)

A thin hydrophilic surface is formed on the channel walls.

Silanol groups are present on the walls of oxidized PDMS channels.

- When in contact with neutral or basic aqueous solutions, the silanol groups deprotonate (SiO\(^-\)).
  - Surface is negatively charged and has a high surface energy.
- Charged PDMS/silicate walls provide two main benefits for microfluidic systems over hydrophobic walls:
  - It is easy to fill oxidized PDMS channels with liquids.
  - Oxidized PDMS channels support EOF toward the cathode.
Performing CE...

- Comparisons of electrophoretic separations obtained in oxidized PDMS channels were compared to those obtained from fused silica capillaries and channels defined in glass.
- It was also possible to determine the velocity of EOF supported by oxidized PDMS and the importance of adsorption of analytes to the polymer on electrophoretic separations.
- Six amino acids labeled with fluorescein isothiocyanate (FITC) were used as an analyte.

Results…

Electropherograms of fluorescence intensity against time of a mixture of six amino acids labeled with FITC.

**Oxidized PDMS Capillary**

**Fused Silica Capillary**

The resolution of electrophoretic separations of negatively charged amino acids and protein charge ladders obtained in oxidized PDMS channels is comparable to (or slightly better than) those in the same length of fused silica capillaries used in conventional and other miniaturized CE systems.

Oxidized PDMS is charged under neutral and basic aqueous solutions, and, therefore, these channels support EOF.

Large-Scale Integration

- Integration of 100s of micromechanical valves.
- Assays with parallel operation (high throughput screening), multiple reagents, multiplexing, multistep biochemical processing and metering.
- A top-down approach simplifies the design of integrated microfluidic systems on a chip by providing a library of microfluidic components.
  - Software design of architecture.
  - Automated routing.
  - Explicit design rules for geometry and other dimensions.

Microvalves

- Rapid prototypes with PDMS generally entail simpler components than traditional MEMS devices.

- Passive Valves
  - Check Valves
    - Directional, like a diode.
    - “Smart” polymers, external stimuli.
  - Stop Valves
    - Surface modifications of hydrophobicity/hydrophilicity for immobilization of fluid and materials.
Hydrogel check valve:
(a) Valve leaflets,
(b) Anchors,
(c) Expanding and closing the valve, and
(d) Contacting and opening the valve.
Active Valve Types for MEMS & BioMEMS…

- Pneumatic
- Thermopneumatic
- Thermomechanical
- Piezoelectric
- Electrostatic
- Electromagnetic
- Electrochemical
- Capillary force
Push-up or Push-down PDMS Pneumatic Valve…

Push-down valve

Push-up valve

3-layer combination valve

Linear peristaltic pump with three membrane valves in a row.

Microfluidic Latch and Demultiplexer...

a) Latch
b) Normally closed seat valve
c) 3-valve network
d) Demultiplexer using vacuum-latched valves.

Microfluidic Multiplexer...

a) Microfluidic multiplexer, where $N$ vertical flow channels can be individually addressed by $2\log_2 N$ horizontal control lines. Valves are created only where a wide control channel (red) intersects a flow channel.

b) When each flow line contains different reagents, cross-contamination can occur because of dead volume at the output of the multiplexer.
Removal of Cross-Contamination…

Binary Tree Format Multiplexer

(a) Green sample is selected. (b) Green sample is flushed using adjacent buffer channel.

Economy of scale – performing combinatorial experiments with a minimum number of pipetting steps.

- “N × N = 400 reaction chamber matrix requires only 41 pipetting steps.
- Enlargement depicts one reaction chamber: White valves are used as peristaltic pumps and green valves are used for compartmentalizing reagents.
- Two differently sized green valves are used to compartmentalize reagents at two different pressures during the reagent-loading sequence.
- This reduces the number of individual control channels needed.”
Electrostatic valves are based on the attractive force between two oppositely charged plates:

\[ F = \frac{1}{2} \varepsilon_r \varepsilon_o A \left( \frac{V}{d} \right)^2 \left( \frac{\varepsilon_i d}{\varepsilon_r d_i + \varepsilon_i d} \right)^2, \]

where

- \( A \) is the overlapping plate area,
- \( d \) is the distance between plates,
- \( d_i \) is an insulator layer thickness,
- \( V \) is the applied voltage,
- \( \varepsilon_r \) (epsilon-relative) is the relative dielectric coefficient of the medium,
- \( \varepsilon_i \) (epsilon-insulator) is the relative dielectric coefficient of the insulator, and
- \( \varepsilon_o \) (epsilon-nought) is the permittivity of a vacuum.
MEMS Electromagnetic Valves…

- *Electromagnetic valves* offer the advantage of large deflection and disadvantage of size, low efficiency, and heat generation.

\[ F = M_m \int \frac{dB}{dz} dV, \]

where

- \( F \) is the vertical force of a magnetic field,
- \( M_m \) is the magnetization (A/m),
- \( V \) the volume of the magnet,
- \( B \) is the magnetic field (Tesla), and
- \( z \) is the direction in which the force is acting.

Micromixers

● **Passive mixers** have no moving parts, but instead rely on diffusion and geometry of the device.

● **Active mixing** increases the interfacial area between fluids and can be accomplished by piezoelectric devices, electrokinetic mixers, chaotic convection.

*Image courtesy of Micronit*
Passive Micromixer…

- **T-mixer** and **Y-mixer**.
Passive Micromixer…

- **Serpentine mixers:**

![Diagram of serpentine mixers](image)

Electrokinetics is a result of complex interaction among fluid species, electric field, induced thermal energy, dissolved ions, and object polarization.

- Electroosmosis
- Electrophoresis
- Dielectrophoresis

Some of these can be applied to achieve pumping in microfluidic devices.
Electroosmosis

Electroosmosis is the motion of ionized liquid with respect to a stationary charged or polarized surfaces in presence of an applied electric field.

Popular pumping technique in microfluidic devices.

Classified as DC electroosmosis, time-periodic electroosmosis, AC electroosmosis and induced charge electroosmosis.

DC electroosmosis has a plug like velocity field in rectangular microchannels.

AC electroosmosis uses embedded electrodes, producing strong local fields for pumping. Cannot produce pressure buildup.

**DC Electroosmosis Flow**

*Electroosmotic flow* (EOF) occurs when the moving ions drag the surrounding fluid with them due to the viscous effect, creating “bulk flow.”

**Electrophoresis**

- Motion of the charged particles or macromolecules in an electrolyte solution under the action of an applied electric field.
- Used for separating one analyte from another or to concentrate a species from a dilute solution for detection or further processing.
- Subtypes - zone electrophoresis, moving boundary electrophoresis, isotachophoresis and isoelectric focusing.
For example, DNA separation
Dielectrophoresis is defined as the lateral motion imparted on uncharged particles as a result of polarization (relative to the surrounding medium) induced by non-uniform electric fields.
Dielectrophoresis

- Use of a non-uniform electric field to move uncharged particles.
- An electric field is applied to the particles through a liquid or electrolyte. It polarizes the particles and moves the particles towards the appropriate electric field zone.
- If the particle is more (less) polarizable than the media, it moves towards the higher (lower) electric field regions, which is known as positive (negative) dielectrophoresis.
- It is possible to move particles in a preferred direction, which can introduce a fluid motion due to the viscous interaction between the particles and fluid. This is known as traveling wave dielectrophoresis (twDEP).
A) EDL next to a negatively charged surface. The stern layer (compact layer) consists of an inner and outer Helmholtz layer.
B) The qualitative plot of co-ion (anions) and counterions (cations) distribution in an electric double layer.
EDL about a Spherical Particle...
1. Most materials obtain a surface charge when they are brought into contact with an aqueous solution.
2. Both glass and polymer microfluidic devices tend to have negatively charged surfaces.
3. Ionization of acidic vs basic surface groups.
4. Different affinities for ions of different signs to two phases:
   - The distribution of anions and cations between two immiscible phases such as oil and water,
   - Preferential adsorption of certain ions from an electrolyte solution onto a solid surface, or
   - Preferential dissolution of ions from a crystal lattice.
5. Charged crystal surfaces.

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Surface Tension and Capillary Effects

Hydrophilic ($0^\circ < \theta < 90^\circ$)

Hydrophobic ($90^\circ < \theta < 180^\circ$)

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The energy balance in the liquid column and driving pressure are calculated as follows:

\[
2\pi r_o h (\gamma_{SG} - \gamma_{SL}) = \Delta p \pi r_o^2 h \quad \text{and} \quad \Delta p = \frac{2\gamma_{LG} \cos \theta}{r_o},
\]

where

\(\gamma_{SG}, \gamma_{SL}, \text{and} \ \gamma_{LG}\) (gamma) are interfacial tensions (N/m),

\(r_o\) is the capillary radius (m),

\(h\) is the height of the column (m), and

\(\Delta p\) is the pressure difference across the gas-liquid interface.
Specified in more familiar terms of *surface tension* and *specific weight* the height is determined as follows:

\[ h = \frac{2\sigma \cos \theta}{\gamma r_0}, \]

where

\( \sigma \) (sigma) is the surface tension (N/m) (same as \( \gamma_{LG} \)), and

\( \gamma \) (gamma) is specific weight of the fluid (N/m\(^3\)).
Types of micropumps:
- Conductive polymer.
- Electric field.
- Magnetic.
- Peristaltic.
- Rotary.
- Ultrasonic.
Upon negative bias application, ions move from the electrolyte into the CP layer causing volume expansion, contraction occurs when positive bias is applied.

(Polypyrrole (PPy). (Trifluoromethyl–sulfonil)imide (TFSI). Dodecylbenzenesulfonic ions (DBS). 1-ethyl-3-methyl-imidazolium (EMI).)

Hiraoka, M et al. Miniaturized pumps and valves, based on conductive polymer actuators, for lab-on-a-chip application. MEMS 2013, Taipei, Taiwan, January 20 – 24, 2013
Stacked CP Actuator…

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Fabricated Pump…

a) Photographs of the fabricated pump. The actuator is sealed in a plastic cavity.
b) Picture of assembled units.
c) A close-up picture of the stacked layers with electrodes bonding.

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Assembled Genotyping Device…

a) LOC system for genotyping diagnostic with assembled pumps and valves. One way valves made by silicone fin are set for defining flow directions.
b) Details of the Si part of the LOC
c) LOC under operation with flow generated by the pumps in the microchannel.

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Hiraoka, M et al. Miniaturized pumps and valves, based on conductive polymer actuators, for lab-on-a-chip application. MEMS 2013, Taipei, Taiwan, January 20 – 24, 2013
Microfluidic device design, fabrication, and testing protocols

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Abstract: This protocols document describes the design considerations and software tools to design a microfluidic device, fabrication protocols for making master molds and the final polydimethylsiloxane (PDMS) device, and testing of the completed microfluidic device.

1. Using AutoCAD.
2. Dimensional Considerations.
4. Microfluidic device Fabrication.
Review

Review: Electric field driven pumping in microfluidic device

Pumping of fluids with precise control is one of the key components in a microfluidic device. The electric field has been used as one of the most popular and efficient nonelectrical pumping mechanisms to transport fluids in microchannels from the very early stage of microfluidic technology development. This review presents the fundamental physics and theories of the different microscale phenomena that arise due to the application of an electric field in fluids, which can be applied for pumping of fluids in microdevices. Specific mechanisms considered in this report are electroosmosis, AC electroosmosis, AC electrothermal, induced charge electroosmosis, traveling wave dielectrophoresis, and liquid dielectrophoresis. Each phenomenon is discussed systematically with theoretical rigor and role of relevant key parameters are identified for pumping in microdevices. We specifically discussed the electric field driven body force term for each phenomenon using generalized Maxwell stress tensor as well as simplified effective dipole moment based method. Both experimental and theoretical works by several researchers are highlighted in this article for each electric field driven pumping mechanism. The detailed understanding of these phenomena and relevant key parameters are critical for better utilization, modulation, and selection of appropriate phenomena for efficient pumping in a specific microfluidic application.

Keywords:
Dielectrophoresis / Electroosmosis / Electrothermal / Lab-on-a-chip / Micropump

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Summary

● Rapid Prototyping Systems in PDMS (polydimethylsiloxane)
  ● Example - Capillary Electrophoresis Device
    ● Process Steps
      ● Making the master
      ● Casting PDMS
      ● Plasma oxidation
      ● Performing capillary electrophoresis
    ● Results
    ● Conclusions

● Large Scale Integration
● Microvalves
● Micromixers
● Electric Field Driven Pumping
● Mechanical Pumps
● Addendum – Comparison of continuous flow, droplet-based and digital microfluidics.
## Comparison of Types of Microfluidics

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<th>Continuous-Flow Microfluidics</th>
<th>Droplet-Based Microfluidics</th>
<th>Digital Microfluidics</th>
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<td><strong>Operating Method</strong></td>
<td>Motion of continuous fluid in micro-channels</td>
<td>Motion of droplets in micro-channels using streams of immiscible fluids</td>
<td>Motion of discrete droplets on an array of planar electrodes</td>
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<td><strong>Flow Actuation</strong></td>
<td>Mechanical (syringe) pumps, Pneumatic pressure, Electrokinetic</td>
<td>Mechanical (syringe) pumps, Pneumatic pressure</td>
<td>Electrowetting On Dielectric, Dielectrophoresis</td>
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<tr>
<td><strong>Advantages</strong></td>
<td>Ease of fabrication and operation, suitable for applications that require a continuous flow with relatively high sampling volume, and being compatible with most of current screening and sensing mechanisms</td>
<td>Ease of fabrication and operation, suitable for a applications that require isolated reaction sites to avoid cross contamination</td>
<td>Lower sample consumption, scalability, better localization, reconfigurability, and portability</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>High sample volume consumption compared to other microfluidic systems, possible contamination, and not being scalable due to fabrication and physical limitations</td>
<td>No control over individual droplets, challenging to create droplets of different sizes using the same setup, and challenging to implement stable gas-liquid systems</td>
<td>Complicated fabrication procedure, and bio-adsorption and evaporation</td>
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