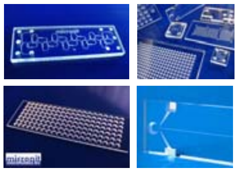
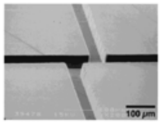
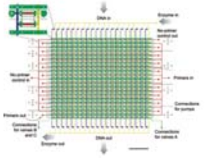
Introduction to BioMEMS & Medical Microdevices

Microfluidics Part 1 – Design & Fabrication

Prof. Steven S. Saliterman, http://saliterman.umn.edu/

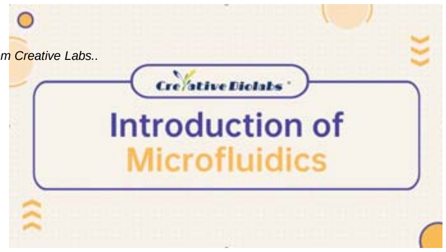






Introduction

Short Video from Creative Labs..



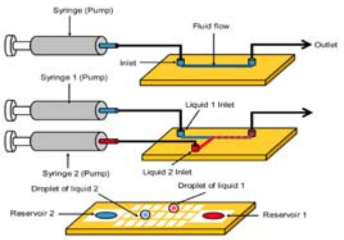
https://youtu.be/kDCkRawA8Zs

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

3 Basic Designs…



Continuous flow.

Drop-based.

Digital

Luka G, Ahmadi A, Najjaran H, et al. Microfluidics Integrated Biosensors: A Leading Technology towards Lab-on-a-Chip and Sensing Applications. *Sensors.* 2015;15(12):30011-30031.

Topics

- Rapid Prototyping Systems in PDMS (polydimethylsiloxane)
  - Process Steps
    - Making the master
    - Casting PDMS
    - Plasma oxidation
- Large Scale Integration
- Microvalves
- Micromixers
- Electric Field Driven Pumping
- Micropumps

Image courtesy of Sylgard

Making a PDMS Microfluidic Device Video…

Queen Mary University of London (15 minutes) https://youtu.be/lH-FCSxRvrU

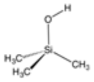
Steps…

1. Mold master is first designed with a CAD program, then a simple transparency was made as a mask.
2. Contact photolithography is used to expose a positive resist coated silicon wafer. Resist thickness was ~55 µm.
3. Features greater than 20 µm can be be realized.
4. Glass posts are placed upright for fluid reservoirs.
5. PDMS is then cast against the master to yield elastomeric replicas containing networks of channels.
6. Oxidation and sealing.

Duffy DC, McDonald JC, Schueller OJA, Whitesides GM. Rapid prototyping of microfluidic systems in poly(dimethylsiloxane). *Analytical Chemistry.* 1998;70(23):4974-4984.

Effect of Plasma Oxidation…

- Oxidizing PDMS in a plasma discharge converts silanol groups $\text{-OSi(CH}_3\text{)}_2\text{O-}$ at the surface to $\text{-O}_n\text{Si(OH)}_{4-n}$
- 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.



Duffy DC, McDonald JC, Schueller OJA, Whitesides GM. Rapid prototyping of microfluidic systems in poly(dimethylsiloxane). *Analytical Chemistry.* 1998;70(23):4974-4984.

- 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.

Duffy DC, McDonald JC, Schueller OJA, Whitesides GM. Rapid prototyping of microfluidic systems in poly(dimethylsiloxane). *Analytical Chemistry.* 1998;70(23):4974-4984.

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.

Melin J, Quake SR. Microfluidic large-scale integration: The evolution of design rules for biological automation. In: *Annual Review of Biophysics and Biomolecular Structure.* Vol 36.2007:213-231.

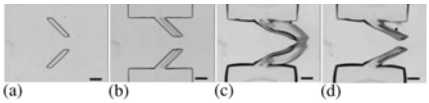
Microvalves

- 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.

Passive Valve…

- Hydrogel *check valve*:

  (a) Valve leaflets,
  (b) Anchors,
  (c) Expanding and closing the valve, and
  (d) Contacting and opening the valve.

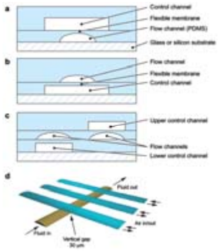


Beebe, DJ, et al, “Physics and applications of microfluidics in biology.” *Annual Review of Biomedical Engineering* 4, pp. 261-286 (2002).

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

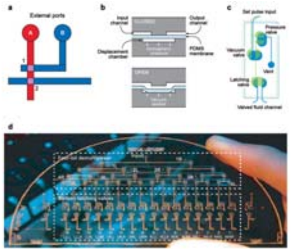
Linear peristaltic pump with three membrane valves in a row.

Unger MA, Chou HP, Thorsen T, Scherer A, Quake SR. 2000. Monolithic microfabricated valves and pumps by multilayer soft lithography. Science 288:113–16

Microfluidic Latch and Demultiplexer…

a) Latch
b) Normally closed seat valve
c) 3-valve network

d) Demultiplexer using vacuum-latched valves.



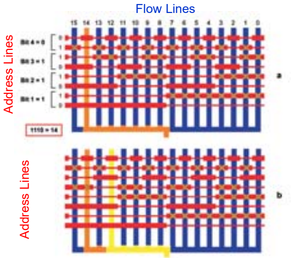
Grover WH, Ivester RHC, Jensen EC, Mathies RA. 2006. Development and multiplexed control of latching pneumatic valves using microfluidic logical structures. Lab Chip 6(5):623–31

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.

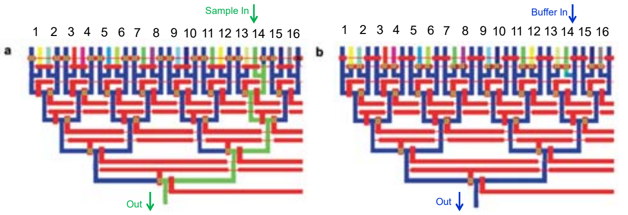
b) When each flow line contains different reagents, cross-contamination can occur because of dead volume at the output of the multiplexer.



Melin J, Quake SR. Microfluidic large-scale integration: The evolution of design rules for biological automation. In: *Annual Review of Biophysics and Biomolecular Structure*. Vol 36.2007:213-231.

Removal of Cross-Contamination…

Binary Tree Format Multiplexer



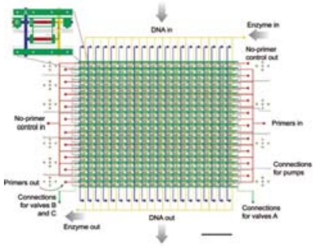
a) Green sample is selected.

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

Melin J, Quake SR. Microfluidic large-scale integration: The evolution of design rules for biological automation. In: *Annual Review of Biophysics and Biomolecular Structure*. Vol 36.2007:213-231.

Polymerase Chain Reaction Chip…

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.

Liu J, Hansen C, Quake SR. 2003. Solving the "world-to-chip" interface problem with a microfluidic matrix. Anal. Chem. 75(18):4718–23

MEMS Electrostatic Valves…

- *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,
ε_r (epsilon-relative) is the relative dielectric coefficient of the medium,
ε_i (epsilon-insulator) is the relative dielectric coefficient of the insulator, and
ε_o (epsilon-nought) is the permittivity of a vacuum.

Nguyen, NT and ST Wereley, *Fundamentals and Applications of Microfluidics*, Artech House, Boston, MA (2002).

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.

Nguyen, NT and ST Wereley, *Fundamentals and Applications of Microfluidics*, Artech House, Boston, MA (2002).

Micromixers

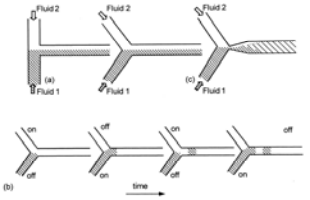
- Passive mixers have no moving parts, but instead rely on diffusion and geometry of the device.

- 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…

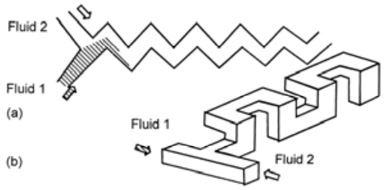
- *T-mixer* and *Y-mixer*:



Nguyen, NT and ST Wereley, *Fundamentals and Applications of Microfluidics*, Artech House, Boston, MA (2002).

Passive Micromixer…

- *Serpentine mixers:*



Liu, RH, et al., "A passive micromixer: three-dimensional serpentine microchannel." *Proceedings of Transducer '99*, pp. 730-733 (1999).

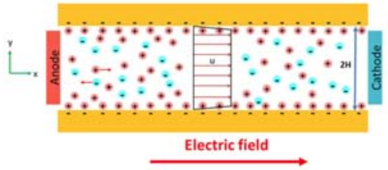
Electric Field Driven Pumping

- 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.

Hossan MR, Dutta D, Islam N, Dutta P. Review: Electric field driven pumping in microfluidic device. *Electrophoresis*. 2018;39(5-6):702-731.

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."

Hossan MR, Dutta D, Islam N, Dutta P. Review: Electric field driven pumping in microfluidic device. *Electrophoresis*. 2018;39(5-6):702-731.

- 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.

Hossan MR, Dutta D, Islam N, Dutta P. Review: Electric field driven pumping in microfluidic device. *Electrophoresis*. 2018;39(5-6):702-731.

Gel Electrophoresis…

For example, DNA separation in gel:

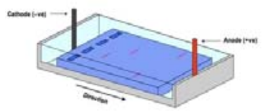


Image courtesy of Bioninja

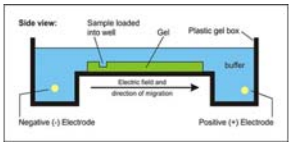


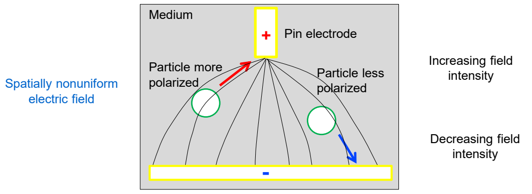
Image courtesy of Orbit Biotech

Migration through the medium (typically agarose gel) is dependent on the charge and size of the molecule, and characteristics of the medium.

- 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).

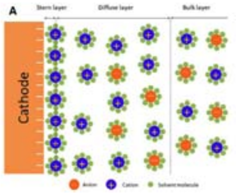
Hossan MR, Dutta D, Islam N, Dutta P. Review: Electric field driven pumping in microfluidic device. *Electrophoresis*. 2018;39(5-6):702-731.

Dielectrophoresis…

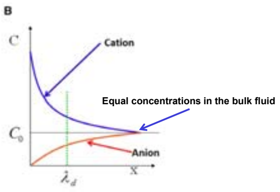


Dielectrophoresis is defined as the lateral motion imparted on uncharged particles as a result of polarization (relative to the surrounding medium) induced by non-uniform electric fields.

Electric Double Layer



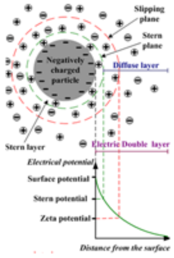
A) EDL next to a negatively charged surface. The stern layer (compact layer) consists of an inner and outer Helmoltz layer.



B) The qualitative plot of co-ion (anions) and counterions (cations) distribution in an electric double layer.

Hossan MR, Dutta D, Islam N, Dutta P. Review: Electric field driven pumping in microfluidic device. *Electrophoresis.* 2018;39(5-6):702-731.

EDL about a Spherical Particle…



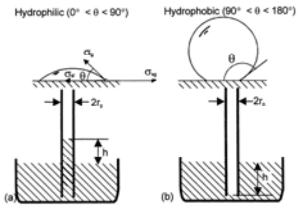
Kopeliovich, D. Stabilization of colloids, SubsTech.com, 2013

Origin of Surface Charge…

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.

Li, D. *Electrokinetics in Microfluidics*, 1st ed., Vol. 2., Elsevier, Amsterdam (2004).

Surface Tension and Capillary Effects



Nguyen, NT and ST Wereley, *Fundamentals and Applications of Microfluidics*, Artech House, Boston, MA (2002).

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

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

where

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

r_o is the capillary radius (m),

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

Δp is the pressure difference across the gas-liquid interface.

Nguyen, NT and ST Wereley, *Fundamentals and Applications of Microfluidics*, Artech House, Boston, MA (2002).

- Specified in more familiar terms of *surface tension* and *specific weight* the height is determined as follows:

$$h = \frac{2\sigma\cos\theta}{\gamma r_o},$$

where

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

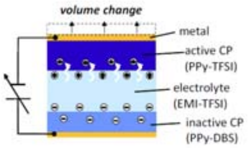
γ (gamma) is specific weight of the fluid (N/m^3).

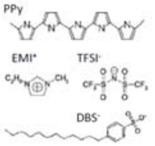
Nguyen, NT and ST Wereley, *Fundamentals and Applications of Microfluidics*, Artech House, Boston, MA (2002).

Micropumps

- Types of micropumps:
  - Conductive polymer.
  - Electric field.
  - Magnetic.
  - Peristaltic.
  - Rotary.
  - Ultrasonic.

Conductive Polymer Pump…



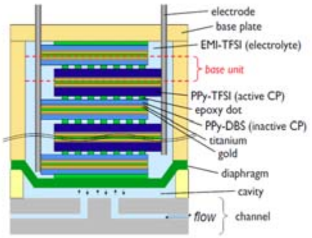


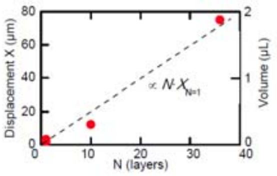
Upon negative bias application, ions move from the electrolyte into the CP layer causing volume expansion, contraction occurs when positive bias is applied.

(Polypyrrole (PPy). (Trifluorometyl–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

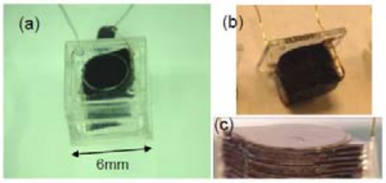
Stacked CP Actuator…





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

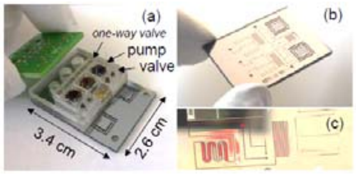
Fabricated Pump…



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.

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

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.

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

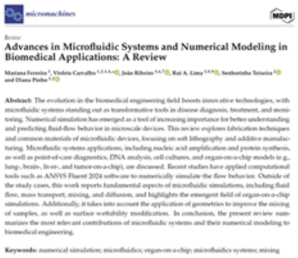
Addendum

- Supplemental reading:
  - Scott S, Ali Z. Fabrication Methods for Microfluidic Devices: An Overview. *Micromachines*. Mar 2021;12(3)319. doi:10.3390/mi12030319.
  - Su RT, Wang FJ, McAlpine MC. 3D printed microfluidics: advances in strategies, integration, and applications. *LChip*. Mar 2023;23(5):1279-1299. doi:10.1039/d2lc01177h.
  - Ferreira M, Carvalho V, Ribeiro J, Lima RA, Teixeira S, Pinho D. Advances in Microfluidic Systems and Numerical Modeling in Biomedical Applications: A Review. Review. *Micromachines*. Jul 2024;15(7):30. 873. doi:10.3390/mi15070873.
  - Musharaf HM, Roshan U, Mudugamuwa A, Trinh QT, Zhang J, Nguyen NT. Computational Fluid-Structure Interaction in Microfluidics. Review. *Micromachines*. Jul 2024;15(7):42. 897. doi:10.3390/mi15070897
- Comparison of types of microfluidics.
- PDMS physical characteristics.

Key Points

- Microfluidics allows us to reduce laboratory analysis to the chip level.
- Rapid prototyping system in PDMS (polydimethylsiloxane) is a simple method for testing new microfluidic systems.
    - Some process steps include making the master, casting the PDMS and plasma oxidation bonding.
- Advanced analysis systems can be created with large scale integration.
- Conduits, valves, mixers, reaction chambers, etc. are easily made.
- Fluid pumping can be accomplished by conductive polymers; electric and magnetic fields; peristaltic and rotatory pumps; and ultrasonic techniques.

Supplemental Reading



micromachines

Review

Advances in Microfluidic Systems and Numerical Modeling in Biomedical Applications: A Review

Mariana Ferreira, Violeta Carvalho, João Ribeiro, Rui A. Lima, Senhorinha Teixeira and Diana Pinho

Abstract: The evolution in the biomedical engineering field boosts innovative technologies, with microfluidic systems standing out as transformative tools in disease diagnosis, treatment, and monitoring. Numerical simulation has emerged as a tool of increasing importance for better understanding and predicting fluid-flow behavior in microscale devices. This review explores fabrication techniques and common materials of microfluidic devices, focusing on soft lithography and additive manufacturing. Microfluidic systems applications, including nucleic acid amplification and protein synthesis, as well as point-of-care diagnostics, DNA analysis, cell cultures, and organ-on-a-chip models (e.g., lung-, brain-, liver-, and tumor-on-a-chip), are discussed. Recent studies have applied computational tools such as ANSYS Fluent 2024 software to numerically simulate the flow behavior. Outside of the study cases, this work reports fundamental aspects of microfluidic simulations, including fluid flow, mass transport, mixing, and diffusion, and highlights the emergent field of organ-on-a-chip simulations. Additionally, it takes into account the application of geometries to improve the mixing of samples, as well as surface wettability modification. In conclusion, the present review summarizes the most relevant contributions of microfluidic systems and their numerical modeling to biomedical engineering.

Keywords: numerical simulation; microfluidics; organ-on-a-chip; microfluidics systems; mixing

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Review

Computational Fluid–Structure Interaction in Microfluidics

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Fabrication Methods for Microfluidic Devices: An Overview

Simon M. Scott and Zulfiqur Ali

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Ruitao Su, Fujun Wang and Michael C. McAlpine

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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.
3. Master Fabrication Protocols.
4. Microfluidic device Fabrication.
5. Device Testing Protocols.

Reading…

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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 nonmechanical pumping mechanisms to transport fluids in microchannels from the very early stage of microfluidic technology development. This review presents 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 phenomenon for efficient pumping in a specific microfluidic application.

Keywords:
Dielectrophoresis / Electroosmosis / Electrothermal / Lab-on-a-chip / Micropump
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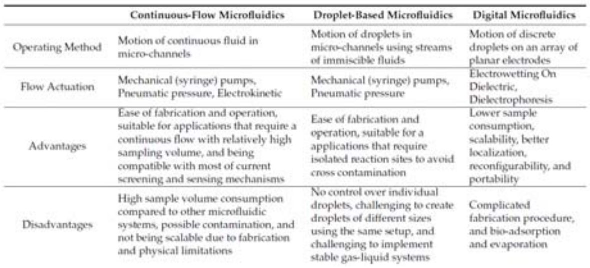
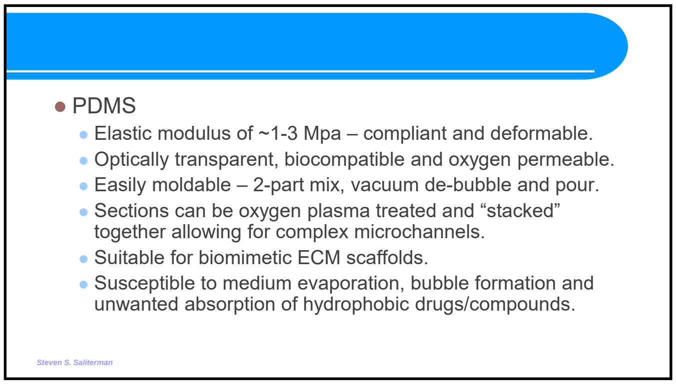
Comparison of Types of Microfluidics



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

Luka G, Ahmadi A, Najjaran H, et al. Microfluidics Integrated Biosensors: A Leading Technology towards Lab-on-a-Chip and Sensing Applications. *Sensors.* 2015;15(12):30011-30031.



- 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.

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