Microfluidics for chemical and biological engineering

Jacinta C. Conrad

University of Houston
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Fluid: physical definition

A fluid is a material that flows under an applied stress

Liquid: constant volume
Gas: volume of container

Two physical properties of fluids:
- **Viscosity**: measure of fluid resistance to stress $\mu$ [mass/length-time]
- **Density**: $\rho$ [mass/length$^3$]
Macroscale flows

Characteristics:
- Large length scales \( L \)
- Fast flow speeds \( V \)
- Turbulent flow

Many macroscale flows are characterized by large Reynolds number:

\[
\text{Reynolds number } \text{Re} = \frac{\text{inertial force}}{\text{viscous force}} = \frac{\rho VL}{\mu} \gg 1: \text{turbulent}
\]
Where do flows appear in a chemical plant?

http://www.photo-dictionary.com/photofiles/list/687/1097petrochemical_plant.jpg
Flow examples in plants (unit operations)

- **Combination**: mixing operation to create a homogeneous system
  - Requires control over mixing streams
- **Separation**: separation of mixture components
  - Emulsification: creation of a liquid-in-liquid suspension
  - Distillation: separation of one liquid from another liquid
  - Evaporation: removal of a gas from a mixture
- **Reaction**: reaction among chemical species in a mixture
  - Synthesis: e.g. creation of particles or chemicals
Microfluidics: miniaturization of flows

The introduction of microfluidics or lab-on-a-chip devices allows unit operations to be carried out in a small format:

Length scales for microfluidic flows

**MICROFLUIDIC DEVICES**
- Micropumps/ valves/ flow sensors
- Microfilters/ microreactors
- Microneedles
- Microanalysis systems

**Nanotechnology/ Nanodevices?**
- 1Å
- 1nm
- 1μm
- 1mm
- 1m

**Length scale**

**Volume scale**
- 1 aL
- 1 fL
- 1 pL
- 1 nL
- 1 μL
- 1 mL
- 1 L
- 1000 L

**Other objects**
- Molecules
- Smoke particles
- Viruses
- Human hair
- Bacteria
- Bacteria
- Conventional fluidic devices
- Man

Advantages:
• Easy to prototype and replicate (via soft lithography)
• Cheap materials (polydimethylsiloxane, commercially available)

Disadvantages:
• Flexible and deformable (poor for high-pressure applications)
• Poor resistance to organic solvents
Microfluidic physics is different! 1

University of New Mexico (DeMoss and Cahill) (http://panda.unm.edu/flash/viscosity.phtml)
Critical flow properties in devices

Reynolds number \( \text{Re} = \frac{\text{inertial force}}{\text{viscous force}} = \frac{\rho V L}{\mu} \ll 1 \): laminar flow

Physical meaning: fluid elements follow straight streamlines, and fluid interfaces remain nearly parallel over long distances in microfluidic devices
Microscale flow physics is different! 2
Critical flow properties in devices

Reynolds number \( \text{Re} = \frac{\text{inertial force}}{\text{viscous force}} = \frac{\rho V L}{\mu} \) \( \ll 1 \): laminar flow

**Physical meaning**: fluid elements follow straight streamlines, and fluid interfaces remain nearly parallel over long distances in microfluidic devices

Péclet number \( \text{Pe} = \frac{\text{time to diffuse}}{\text{time to convect}} = \frac{V L}{D_0} \) \( \gg 1 \): fast convection

**Physical meaning**: diffusion is very slow compared to convection in microfluidic devices, and thus mixing requires special device designs
Combination: passive planar micromixer

Key idea: Modify geometry to obtain mixing via changing flow pattern

Combination: parallel lamination mixer

**Key idea:** Split streams to increase surface area and hence mixing

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Combination: 3-D microvascular networks

**Key idea:** Split streams in 3-d geometries to enhance mixing

Combination: herringbone micromixers

Key idea: Add elements to “fold” fluid via chaotic advection

Slanted ridges:

3-D herringbone:

Combination: herringbone mixer movie
Combination: microfluidic valving

Key idea: Fabricate a plastic valve that is separately actuated with air

A

on-off

on-off

peristaltic pump

valve grid

switching valve

mold
flat substrate

Combination: colloid valves

**Key idea:** Incorporate micron-sized colloidal particles into devices

**passive valve**

**actuated valve**

Combination: in-situ piston

**Key idea:** Photopolymerize parts in place in microfluidic devices

Separation: emulsification ("droplets")

Key idea: Exploit the Rayleigh-Plateau instability to create emulsion drops

Stress: elongates jet of liquid
Surface tension: minimizes surface area
Result: jet breaks up into drops

Emulsification: flow-focusing

**Key idea:** “Pinch off” droplets using a flow-focusing geometry

Anna et al., Anal. Chem. 74 4913-4918 (2002)

Abate lab (University of California San Francisco) via YouTube
Droplets + valving = adjustable sizes

Abate lab (University of California San Francisco) via YouTube
Emulsification: enhanced mixing in drops

**Key idea**: Recirculation within drops enhances mixing rates

Emulsification: drops in drops (in drops…)

Key idea: Encapsulate drops in other drops to create multiple emulsions

Utada et al., Science 308 537-541 (2005)

Drops in drops: tune flow rates

Abate lab (University of California San Francisco) via YouTube
Separation: cell sorting via optical forces

Key idea: Use radiation pressure to sort cells in a microfluidic device

Separation: deterministic lateral displacement

Key idea: Particles of different diameter follow different streamlines

Huang et al., Science **304** 987-990 (2004)
Separation of parasites from blood

Holm et al., Lab Chip 304, 1326-1332 (2011)
Separation: motile sperm sorter

Key idea: Live cells swim across laminar streamlines

Key idea: Establish vapor-liquid equilibrium in segmented flow and separate vapor using capillary forces

Hartman et al., Lab Chip 9, 1843-1849 (2009)
Reaction: drops as microreactors

**Key idea:** Drops increase reaction rates by increasing surface-to-volume ratio, reducing diffusion distances, and enhance heat and mass transfer.

Key idea: Design a droplet-based microfluidic system to extract kinetic parameters of an enzymatic reaction.

Reaction: nucleation

**Key idea:** Design a droplet-based microfluidic system to study effect of mixing on nucleation of protein crystals

Reaction: nanoparticle synthesis

**Key idea:** Use of gas slugs to separate small liquid reaction volumes increases the monodispersity of microfluidically-produced particles.
Reaction: microfiber synthesis

Key idea: Photopolymerize a flow-focused stream “on the fly”

Khan et al., Lab Chip 4 576-580 (2004)
Key idea: Gradients in reactant composition generate differences in etching rates through a surface

Applications of microfluidics

- Chemical synthesis
  - Especially for high-value components
- Controlled release
  - Pharmaceuticals
  - Cosmetics
- Biotechnology
  - Genomics and sequencing
  - Biodetection
  - Directed evolution
- Models of biological processes
  - Microvasculature and veination
  - Chemotaxis and chemical response
Application: crystallization

Goal of research: determine conditions and kinetic pathways for crystallization of biological proteins (e.g. xylanase)

Key idea: Change salt concentration “on chip” in an integrated microfluidic device to trigger crystallization

Application: on-chip multistep synthesis

Goal of research: demonstrate optimized synthesis for sensitive compound

**Key idea:** Move all operations “on chip” in an integrated microfluidic device

- Microfluidic synthesis increased yield (38%) and purity (97.6%)
- Dramatic increase in time (14 min vs 50 min)

Application: programmable release

Goal of research: controllably release multiple components in a pharmaceutical or cosmetic formulation

Key idea: Sequentially dissociate bilayer membranes in a double emulsion

Commercialized technology: Capsum

Capsum (France) markets encapsulation technologies to luxury cosmetics manufacturers such as Amore Pacific (Korea)
Application: directed evolution

Goal of research: identify mutants of horseradish peroxidase enzyme with higher catalytic activity

Key idea: Use ultrahigh throughput screening to remove inactive mutants


- 108 enzyme reactions screened in 10 h (1,000× faster)
- Sample volume: < 150 μL of reagent (1,000,000× cheaper)
Application: cancer detection

Goal of research: capture rare circulating tumor cells (CTCs) in patients’ bloodstreams for cancer detection and monitoring

Key idea: Increase surface encounter rate using chaotic advection

- Cancer cells detected at ~400 CTCs/mL
- Imaging-based platform identified new CTC clusters

Application: tissue engineering

Goal of research: model complex vascular phenomena, including angiogenesis and thrombosis

Key idea: Use microfluidic channels as a model for microvasculature

Application: whole genome sequencing

Goal of research: analyze genome of single cells and microbial consortia without sample contamination

Key idea: Create multiplexed chip to sort, cultivate cells and identify, amplify, and sequence whole genomes

Challenges

- Scale-up
  - Transition from “lab scale” devices to plant-scale operations
  - 2-d to 3-d layouts
- Interplay between parallelized chips
  - Need to generate uniform flow across multiple devices
  - Synchronization and chaotic effects
- Clogging and unsteady flow
Summary of lecture

• Microfluidics enables mini “chemical plants”
  - Exceptional control over reactions and mixing
  - Naturally achieves continuous production
• Optimal usages of microfluidic devices:
  - Specialty chemicals and high-value chemicals
  - Hard-to-produce molecules (especially biomolecules)
• Industries impacted by microfluidics
  - Biotechnology: genome sequencing, protein crystallization
  - Chemical synthesis: radiolabeled molecules
  - Manufacturing: designer specialty cosmetics
• Opportunities abound for chemical and biomolecular engineers to design new microfluidic processes