Microfluidics for lab-on-chips

**Microfluidic flows**
1. pressure-driven flows
2. capillary-induced flow
3. droplet microfluidics
4. evaporation-induced flows
5. electroosmotic flow

**Transport phenomena**
1. convection/diffusion
2. hydrodynamic dispersion
3. mixing strategies
4. droplet vs. coflow
5. concentration using µ-evaporators

**Applications**
1. crystallization
2. physical chemistry R&D (Flavie Sarrazin, Rhodia)

Jean-Baptiste Salmon
LOF, Pessac, France

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**Microfluidics**

Deals with the **behavior, precise control and manipulation** of fluids that are geometrically constrained to small, typically **submillimeter**, scales

Is it new?

Some elaborated microfluidic devices...:

- **leaves:**
  - pervaporation;
  - capillary effects;
  - protein, growth;

- **bombyx mori:**
  - micromixing;
  - shear aggregation of protein;
  - material processing (silk)
Is it new for scientists?
some pionnering experiments in fluid dynamics...

Poiseuille
1799-1869

"le mouvement des liquides dans les tubes de petits diamètres"

Jurin
1684-1750

"An account of some experiments shown before the Royal Society; with an enquiry into the cause of the ascent and suspension of water in capillary tubes"

The new things are...:
 micro-fabrication techniques for complex devices

building microstructures

building complex networks

Whitesides et al.
The new things are:
- micro-fabrication techniques for complex devices
- and massive integration

Protron MicroTeknik


A recent history...

ISI Web of Knowledge™

Search for:
- microtass
- first µTAS conference
- first µfluidic system, Manz et al.
- PDMS lithography

# hits vs. publication year
Is microfluidics a new scientific field?
no, it’s a new toolbox for research & developments

But scientific fields are useful to improve the microfluidic tools

chemistry

synthesis
nanoparticles
kinetics...

chemical engineering
data acquisition...

physics

hydrodynamics
soft matter...

material science
shaping,
assembly...

biology

structural biology
cellular biology
biological assays...

microfabrication

analytical tools...

chemical engineering
design µ-devices...

physics

hydrodynamics
analytical tools...

material science
material devices
coating...

biology

bio-compatibility
analytical tools...
Why miniaturizing?

1- microfluidics: size matters

At small length scales, transport phenomena can be precisely controlled:
- mixing
- thermal transfers
- concentration
- flows

At small length scales, surface effects are important and confinement plays a role

Typical numbers
\[ w = 1 - 100 \mu m \]
flow rates \[ Q = 1 - 1000 \mu L/hr \]
velocities \[ V = 1 \mu m/s - 1 \text{ m/s} \]
time scales \[ t = w/V = 1 \mu s - 100 \text{ s} \]

⇒ wide range of scales with « controlled » or even « new » experimental conditions

Why miniaturizing?

2- high-throughput screening

At small length scales, small volumes
⇒ perform high-throughput with small amounts of liquids

Typical numbers
\[ w = 1 - 1000 \mu m \]

volumes \[ w^3 = 1 \text{ fL} - 1 \mu L \]

from robotics mL...

... to microfluidics : nL
Why miniaturizing?

3- towards integrated lab-on-chip

i) creating mixtures with 64 ≠ reactants

iv) control the concentrations inside nL plugs

ii) mixing nanoliters volume

iii) store interesting mixtures in nL plugs

Complete Microfluidic Screening Platform for Rational Protein Crystallization
Lau et al. JACS 2007

Experimental microfluidics: microfabrication

⇒ micro-electronics & MEMS

⇒ high cost & long time of developments...
⇒ microfluidics needs flexibility and versatility

An excellent book... with many techniques

Microfluidics: Fundamentals of Microfabrication

⇒ micro-electronics & MEMS

⇒ high cost & long time of developments...
⇒ microfluidics needs flexibility and versatility

⇒ micro-electronics & MEMS
Experimental microfluidics: PDMS soft lithography

- mask
- soft lithography (≈ µm)
- resin mold
- PDMS molding and sealing

⇒ low cost, rapid developments, & versatile

Rapid Prototyping of Microfluidic Systems in Poly(dimethylsiloxane)

David C. Duffy, J. Cooper McDonald, Olivier J. A. Schneebeli, and George H. Whitesides

- « 3 dimensional » molds using alignment
- multilevels of PDMS channels
- actuation channel

⇒ valves, pump...

Unger et al. Science 2000
Experimental microfluidics: « a chip in a lab »

- waste
- heating elements
- microscope
- electronics
- syringe
- control
- measurements
- syringe pump
- microfluidic chip
- tubings
- channel dimensions ~ 100 µm

Recent developments of innovative microfabrication: « paper microfluidics »

⇒ photolithography or wax printing to define hydrophilic & hydrophobic zones in paper (= channels)

⇒ capillary wicking of fluids

⇒ low cost

⇒ analysis of glucose and proteins in urin

Towards «µPADS»
**Microfluidic paper-based analytical devices**

**3D devices with tape layers**


**Recent developments of innovative microfabrication:**
**«microfluidic stickers»**

Hard material (1 GPa)
Possibility of 3D networks
Tunable wetting properties

Bartolo et al. Lab Chip 2008
Some books, dvds ...

**Microfabrication**
- *Fundamentals of Microfabrication*

**Transport**
- *Transport Phenomena*

**Hydrodynamics**
- *Fluid Dynamics*

**Microfluidics**
- *Microfluidics*

**Soft Matter/Wetting/etc...**
- *Gouttes, bulles, perles et ondes*
- *Liquides: solutions, dispersions, émulsions, gels*

... and reviews

**Reviews of Modern Physics, Volume 77, July 2005**

*Microfluidics: Fluid physics at the nanoliter scale*  
Todd M. Squires*  
Department of Physics and Applied & Computational Mathematics, California Institute of Technology, Pasadena, California 91125, USA.  
Stephen R. Quake*  

**Engineering Flows in Small Devices:**

*Microfluidics Toward a Lab-on-a-Chip*  
H.A. Stone,  
A.D. Stroock,  
and A. Ajdari*  

*Avan. Chem. 2006, 78, 2375–2388*

**Reactions in Droplets in Microfluidic Channels**  
Helen Song, Delai L. Chen, and Rustem F. Ismagilov*  

Quizz

Microfluidics is ... :

A- a new scientific field ?
B- a toolbox to make R&D ?
C- flow in channels with dimensions above 1 mm ?
D- hum... what is microfluidics ??
Quizz

In microchannels:

A- flows are laminar because of the small length scales
B- turbulences often occur
C- it is very easy to mix
D- mixing is slow

Quizz

In microchannels:

A- flows are laminar because of the small length scales
B- turbulences often occur
C- it is very easy to mix
D- mixing is slow
Quizz

What is the volume of a box 10x10x10 μm ?

\( V = 1 \ \text{pL} \)

What is the volume of a box 1x1x1 mm ?

\( V = 1 \ \text{µL} \)

Quizz

Can a microfluidic chip produce tons of chemical products ?

Why not ?

1 channel with (width = 100 µm) and flow rate = 500 µL/hr produces 4 liters / year

One chip of 5x5 cm² containing 250 channels and may produce 1000 liters / year
Quizz

PDMS is...

A- an elastomer of silicon ?
B- an hydrophobic material ?
C- transparent to visible light ?
D- easy to mold on resins ?
Microfluidics for lab-on-chips

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**Microfluidic flows**

1. **pressure-driven flows**
   - flow at low Reynolds number
   - mass conservation
   - analogy with electricity

2. capillary-induced flow

3. droplet microfluidics

4. evaporation-induced flows

5. electroosmotic flow
Hydrodynamics of simple fluids

Navier-Stokes equation

Physics of (simple) fluids: fundamental principle
\[ m \ a = \sum F \]

Forces:
- pressure \( p \)
- viscous forces
- gravity
- electrostatics…

⇒ Navier-Stokes equation:
\[
\rho \left( \partial_t + v \cdot \nabla \right) v = -\nabla p + \eta \Delta v + F
\]

acceleration (inertia)
pressure forces
viscous forces
volumic forces

Microfluidics = small length scales \( L \) (1-100 µm)

\[
\rho \left( \partial_t + v \cdot \nabla \right) v = -\nabla p + \frac{\eta \Delta v}{\eta v/L^2} + F
\]

Reynolds number \( Re = \frac{\text{inertial forces}}{\text{viscous forces}} = \frac{\rho v^2/L}{\eta v/L^2} = \frac{\rho L v}{\eta} \)

Microfluidics ⇒ \( Re < 1 \) ⇒ inertial effects are negligible

example: water at 1 mm/s in a 50 µm microchannel \( Re = 0.05 \)
From Navier-Stokes to Stokes equation: low Reynolds number

small Reynolds number \( Re = \frac{\rho LV}{\eta} \)

Navier Stokes \( \Rightarrow \) Stokes equation:

\[
0 = -\nabla p + \eta \Delta v
\]

viscous forces = pressure forces

\( \Rightarrow \) there is no acceleration/inertia

+ boundary conditions

Boundary conditions

\( \eta_A \dot{\gamma}_A = \eta_B \dot{\gamma}_B \)

\( v_A = v_B \)

\( \Rightarrow \) continuity of tangential velocities and stress

\( v = 0 \)

\( \Rightarrow \) liquids « adhere » to solids

(not true if one looks at the nanoscale on hydrophobic surfaces)
\[ 0 = -\nabla p + \eta \Delta v \]

⇒ velocity along the pressure gradient

⇒ Coriolis forces acting at large scales, not in small geometries (no inertia)

---

**Quizz**

does it apply in at low Reynolds numbers? \[ p + \rho v^2 / 2 = \text{cste} \]

No, the Bernoulli equations concern inertia and flows without viscosity
mass of the liquid \[ M = \int \rho d^3r \]

mass lost by the flow during \( dt \) \[ \int \rho v dt dS \]

\( \Rightarrow \) conservation of mass:

\[ \partial_t \rho + \nabla \cdot (\rho v) = 0 \]

\( \Rightarrow \) with incompressibility (mass = volume)

\[ \nabla \cdot v = 0 \]

**Quizz**

find the error

flow rate = volume of liquid / (time surface) 
= volume of liquid / time 
= volume of liquid / surface 

\[ vdtS = \text{volume of liquid flowing through } S \text{ in } dt \]

\[ vdtS = Qdt \]

\( \Rightarrow \) flow rate = volume of liquid / time
from global to local relations

\[ Q_1 + Q_3 = Q_2 + Q_4 \]

write the conservation of the flow rate

\[ \nabla \cdot v = 0 \]
Low Reynolds number flow

Stokes equation:
\[ 0 = -\nabla p + \eta \Delta v \]
(viscous forces = pressure forces)
and continuity equation
\[ \nabla \cdot v = 0 \]
and boundary conditions

Quizz

Some important properties of low Reynolds number hydrodynamics

which flow is solution of Stokes equation?

if \( v \) is a solution \(-v\) is also a solution

inertial effects \( Re > 1 \)
**Quizz**  

Some important properties of low Reynolds number hydrodynamics

\[ \nabla \cdot \mathbf{v} = 0 \]

\[ 0 = -\nabla p + \eta \Delta \mathbf{v} \]

if higher flow rates are imposed  
(ex: \(2Q+2Q\))

what happens for the entrance length?

**Tubes, channels and hydrodynamic resistance**

for infinite long and large planes

\[ \nabla \cdot \mathbf{v} = 0 \]

\[ 0 = -\nabla p + \eta \Delta \mathbf{v} \]

\[ \Delta P = P_i - P_0 \]

\[ Q = \int dSV \]

\[ R = \frac{12\eta L}{w h^3} \]
Hydrodynamic resistance

Analogy with the Ohm law

\[ \Delta P = RQ \quad \iff \quad U = RI \]

\[ R = \frac{12\eta L}{wh^3} \quad \Rightarrow \quad \text{strong dependance with } h \]

ex: \( Q = 100 \mu\text{L/hr} \)
channel length 2 cm
width 100 \( \mu \)m
water 1 mPa.s

\[ \Delta P \sim 1 \text{ bar for } h = 10 \mu\text{m} \]
\[ \Delta P \sim 1 \text{ mbar for } h = 100 \mu\text{m} \]

\( \Rightarrow \) leakages & high pressure drops often occur

hydrodynamic resistance

\begin{align*}
\text{cylinders} & \quad \Delta P \\
\text{microchannels} & \quad \Delta P
\end{align*}

\[ R \approx \frac{\eta L}{wh^3} \]

\( \Rightarrow \) viscosity \( \eta \) and length \( L \) : linear dependances
\( \Rightarrow \) geometry of the channel: power 4
How to find the scaling?

force balance

\[ \Delta P = P_i - P_o \]

pressure forces \( (P_i - P_o) \pi R^2 \sim R^2 \Delta P \)

shear forces \( \sim 2 \pi RL \eta \frac{U}{R} \)

no inertia: \( \sum F = 0 \Rightarrow \frac{\Delta P}{L} \sim \eta \frac{U}{R^2} \)

Network properties

conservation of mass: \( Q_1 + Q_2 = Q_3 \)

\[ R = (\sum R_i^{-1})^{-1} \]

\[ R = \sum R_i \]
**First example:**

fast and long kinetics

Example: time scales from 1 s to 10 min

with \( V = 1 \text{ mm/s} \) \( \Rightarrow \) \( L = 60 \text{ cm} \) and \( X_{(1\text{s})} = 1 \text{ mm} \)

\( \Rightarrow \) huge pressure drops and long microchannels

**Quizz**

Network for logarithmic increase of the residence times ?

\[
\begin{array}{cccccccccc}
Q/2 & Q/4 & Q/8 & Q/16 & Q/32 & Q/64 & Q/128 & R & R/2 & R/2 & R/2 & R/2 & R/2 & R/2 & R/2 & R/2 & Q/128 \\
\hline
Q/2 & t=1 s & Q/4 & t=3 s & Q/8 & t=7 s & Q/16 & t=15 s & Q/32 & t=31 s & Q/64 & t=63 s & Q/128 & t=127 s \\
\end{array}
\]

\( \Rightarrow \) low pressure drops, network of short microchannels

**Second example:**

« coflow »

High aspect ratio microchannel \( h \ll w \)

Situation of no-mixing (large flow rates, small diffusivities...):

\[
\begin{align*}
\frac{\Delta P}{L} &= R_1 \frac{Q_1}{w_1} = R_2 \frac{Q_2}{w_2} \\
\Rightarrow \quad \frac{\eta_1 Q_1}{w_1} &= \frac{\eta_2 Q_2}{w_2} \\
\Rightarrow \quad \text{measurements of widths } w_1 \text{ and } w_2 \text{ gives the viscosity ratio } \frac{\eta_1}{\eta_2}
\end{align*}
\]

Guillot et al., Langmuir 2006
Microfluidic flows

1- pressure-driven flows

2- capillary-induced flow
   surface tension
   Laplace law
   imbibition

3- droplet microfluidics

4- evaporation-induced flows

5- electroosmotic flow

Third example: hydrodynamic focusing

large $Q_s$ & small $Q_i$

$\Rightarrow$ high focusing

Brief introduction to surface tension

Surface tension?

\[ \gamma \]  molecules at interfaces

\[ \Rightarrow \text{surface tension wants to minimize interfaces} \]

\[ \Rightarrow \text{surface tension} = \text{energy/surface} = \text{force/length} \]

orders of magnitude for fluids:

molecular energy of cohesion / molecular area

\[ \gamma = \frac{E_c}{a^2} \sim \frac{kT}{a^2} = 20 \text{ mN/m} \]

ex: soap film

Claget, Fermigier, Quéré
Laplace law: capillary pressure

\[ \pi P_b R^2 = \pi P_o R^2 + 2\pi R \gamma \]
\[ \Delta P = 2\gamma / R \]

for two radii of curvature:

\[ \Delta P = \gamma C = \gamma \left( \frac{1}{R_1} + \frac{1}{R_2} \right) \]

Example of microfluidic capillary pump

\[ \Rightarrow \text{capillary pressures are important for confined geometries} \]

\[ R_1 > R_2 \]
\[ P_1 < P_2 \]
\[ P_2 \]

\[ \Delta P = 2\gamma / R_2 = 140 \text{ Pa} \]
\[ Q = 180 \text{ µL/hr} \]

Clanet, Fermigier, Quéré

Berthier and Beebe, 2007
Imbibition: capillary-induced flow

Whitesides et al.

Clanet, Fermigier, Quéré

dynamics of imbibition: diffusive spreading

\[ l(t) \sim \sqrt{t} \]

Imbibition: Washburn equation

\[ \sim P_0 - \frac{\gamma}{h} \quad P_0 \]

\[ U = \frac{dl}{dt} \]

\[ \Delta P = R(t)Q(t) \quad \Rightarrow \quad \frac{\gamma}{h} \sim \frac{\eta l(t)}{h^3}h^2 \frac{dl}{dt} \]

\[ \Rightarrow \quad l \frac{dl}{dt} = \frac{\gamma h}{\eta} \quad \Rightarrow \quad l \sim \sqrt{Dt} \]

\[ D = \frac{\gamma h}{\eta} \]
Back to paper microfluidics

Washburn law \( l(t)^2 \sim Dt \Rightarrow \) decreasing velocities

constant velocities through imbibition?

\[ \Delta P = [R_1 + R_2(t)]Q(t) \]

constant flow rate for \( R_1 \gg R_2(t) \)

Shaping paper microfluidics: constant velocities with imbibition

\[ \begin{align*}
    R_2(t) \\
    R_1 > R_2(t)
\end{align*} \]

Mendez & Stone, 2010
Mendez et al. Langmuir 2010
Microfluidic flows

1- pressure-driven flows
2- capillary-induced flow
3- droplet microfluidics
   - capillary effects
   - confinement & wetting
   - traffic
4- evaporation-induced flows
5- electroosmotic flow

monodisperse droplets can be generated when two immisble fluids flow in microchannels

Two-phase flow microfluidics: experimental facts

Some typical numbers
- droplet velocities: 10 µm/s – 1 cm/s
- droplet volume 1 pL – 1 µL (10 µm - 1 mm)
- frequency production 1 – 1000 Hz

Anna et al., Appl. Phys. Lett. 2003
Two-phase flow microfluidics

The Rayleigh Plateau instability (simple explanations)

\[ E_s = 2\pi RL\gamma = 2V\gamma/R \]

\[ E_s = 4\pi NR_c^2\gamma = 3V\gamma/R_c \]

if \( R_c > 3R/2 \) ⇒ droplets are energetically favorable

⇒ surface tension is responsible for the formation of droplets in microfluidics

Two-phase flow microfluidics: the complexity

⇒ surface tension is responsible for the formation of droplet in microfluidics BUT...

- confinement
- geometries of the channel
- walls and wetting properties
- hydrodynamics (viscosities, flow rates, ...)
- inertial effects for Re ~ 1
- surfactants

⇒ there is today no simple and accurate theory to predict all the observed complexity
Role of confinement and hydrodynamics


silicon oil
glycerol & water

role of confinement and hydrodynamics
to stabilize jets vs. droplets

Surfaces and relative wetting are important


hexadecane

different regimes for different flow rates:

hydrophobic channels (eg. PDMS):
water-in-oil-in dispersions.

hydrophilic channels (eg. glass)
oil-in-water dispersions.

wetting on the PDMS walls

can you picture the flow in 3D?
Double emulsions: a challenge
tuning the wetting properties

Okushima et al. Langmuir 2004

coating of PDMS with polymer:

Barbier et al. Langmuir 2006

⇒ traffic of droplets has also to be controlled...

Two-phase flow microfluidics =
« digital microfluidics »

⇒ forming droplets of any fluid, using any other fluid phase, in any microdevice may be difficult

*It often requires:*

- surface modifications (silane, plasma, polymers...)
- playing with surface tension (role of the dispersing fluid)
- find the hydrodynamic conditions of droplet formation
- play with the geometries (hydrodynamic focusing, T-junction...)
- add surfactants

⇒ forming droplets of any fluid, using any other fluid phase, in any microdevice may be difficult

*It often requires:*

- surface modifications (silane, plasma, polymers...)
- playing with surface tension (role of the dispersing fluid)
- find the hydrodynamic conditions of droplet formation
- play with the geometries (hydrodynamic focusing, T-junction...)
- add surfactants
Droplet traffic

importance of the capillary number

\[ Ca = \eta V / \gamma \]

low capillary number:
⇒ no breaking

high density:
partition

low density:
hydrodynamic filter

⇒ droplets act as « local » hydrodynamic resistances
low capillary numbers: no breakage
droplets = small resistances

Droplet traffic control
by-pass regulation

... but it depends on the number of droplets in the arms


Droplet traffic control
break-up

charged drops at junction

Quizz

Why don’t we observe the microchannel?

Because silicon oil and reticulated PDMS have the same optical index.

Quizz

droplets break at high or low capillary numbers?

\[ \text{Ca} = \frac{\eta V}{\gamma} \]

capillary number = viscous forces / capillary forces

Stone et al.
Microfluidic flows

1- pressure-driven flows
2- capillary-induced flow
3- droplet microfluidics
4- evaporation-induced flows
   pervaporation through PDMS
   microfluidic pump
5- electroosmotic flow

Verneuil E et al., EuroPhys. Lett. 2004
Randall et al. PNAS 2005

passive concentration
Control of the permeation

Typical velocities:
PDMS membranes ≈ 10 µm ⇒ \( v_e \approx 20 \text{ nm/s} \)
\( h = 10 \mu m \) & \( L_0 = 10 \text{ mm} \) ⇒ \( v_0 = 20 \mu m/s \)
An efficient microfluidic pump?

\[ Q = S \frac{v_e}{t_e} \]

\( Q \) = induced flow rate
\( S \) = membrane surface
\( v_e \) = evaporation velocity
\( t_e \) = evaporation time
\( V = \) volume of the \( \mu \)-evaporator

Typical numbers for 1 \( \mu \)-evaporator:
PDMS membranes \( \approx 10 \) \( \mu \)m \( \Rightarrow v_e \approx 20 \) nm/s
\( w = 50 \) \( \mu \)m, \( L = 10 \) mm \( \Rightarrow Q \approx 40 \) nL/hr

for 100 \( \mu \)-evaporators:
\( Q \approx 4 \) \( \mu \)L/hr

Quizz

can you cite a « common » example of microevaporator-based pump?

\[ \frac{\text{Air}}{\text{Leaf Membrane}} = \frac{\text{Soil}}{\text{Root Membrane}} \]

Wheeler and Stroock, Nature 2008
Microfluidic flows

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Some simple ideas: surfaces under water

Common materials aquire charges in aqueous solutions
- crystal defects
- adsorption of ions into the material
- ionization of surface groups

For glass and PDMS

\[
\text{eg. } M\text{-OH} + \text{OH}^- \leftrightarrow M\text{-O}^- + H_2O \quad \text{for basic pH}
\]

charged layer

electroneutrality

surface charges
\[ \Delta \phi = \frac{\rho}{\epsilon} \quad \text{Poisson equation with charge density} \quad \rho = \sum z_i c_i \]
\[ c_i = c_0^i \exp(-z_i \phi / kT) \quad \text{Boltzmann equation for concentrations of ions} \]

solve the equation in the case \( z_i \phi \ll kT \)

Debye-Huckel approximation (small potential): \( z_i \phi < kT \)
\[ \Delta \phi = \sum \frac{z_i^2 c_0^i}{\epsilon kT} \phi = \kappa^2 \phi \quad \text{with} \ 1/\kappa \text{ dimension of length} \]

\[ \Rightarrow \text{solution} \quad \phi = \xi \exp(-\kappa y) \quad \frac{\xi}{1/\kappa} \text{Debye length} \]
(1-100 nm, 1 µm for pure water at pH 7)

\[ \eta \frac{\partial^2 V}{\partial y^2} + \rho(y) E = 0 \]

charge distribution (with Debye-Huckel approximation)
\[ \rho(y) = -\epsilon \kappa^2 \phi(y) \quad \& \quad \Delta \phi = \kappa^2 \phi \Rightarrow \phi(y) = \xi \frac{\cosh(\kappa y)}{\cosh(\kappa h)} \]

\[ \Rightarrow \quad V(y) = -\frac{\varepsilon E}{\eta} \left( 1 - \phi(y)/\xi \right) \]
apparent « slip » over the surfaces ⇒ « plug » flow (uniform profile)

and electroosmotic velocity:

$$V_s \approx \frac{\epsilon \xi E}{\eta}$$

**Some simple ideas:**

**electroosmosis**

**electro-osmosis vs. pressure-driven flows**

$$Q \sim \frac{R^4 \Delta P}{\eta L} \quad Q \sim \epsilon \xi \frac{R^2 \Delta \phi}{\eta L}$$

$R^2$ vs. $R^4$

⇒ electroosmotic flow are adapted to microfluidics (small $R$)
**electroosmosis vs. electrophoresis?**

**electroosmosis**: fluid motion relative to stationary charged walls under applied $E$

**electrophoresis**: motion of a particle under applied $E$

\[ V = \epsilon E \xi / \eta \]

⇒ electrophoresis only cannot sort particles with different mass but different $\xi$

⇒ electrophoresis and electroosmosis often occur simultaneously

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**Microfluidics for lab-on-chips**

**generalities**
1- microfluidics ?
2- why ?
3- how ?

**transport phenomena**
1- convection/diffusion
2- hydrodynamic dispersion
3- mixing strategies
4- droplet vs. coflow
5- concentration using $\mu$-evaporators

**applications**
1- crystallization
2- physical chemistry R&D
(Flavie Sarrazin, Rhodia)

Jean-Baptiste Salmon
LOF, Pessac, France
Transport phenomena in microfluidics

1- convection/diffusion in microfluidics
2- hydrodynamic dispersion
3- mixing strategies
4- droplet vs. coflow for chemistry
5- active concentration in μ-evaporators

Mixing through diffusion: transport equation

conservation of mass:

\[
\frac{dN}{dt} = - [J_d(x + dx) - J_d(x)] \\ dy \\ dz + \ldots
\]

\[
\Rightarrow \quad \partial_t C + \nabla . J_d = 0
\]
Mixing through diffusion: Fick law and diffusion equation

\[ \partial_t C + \nabla J_d = 0 \]

\[ \Rightarrow \partial_t C = D \Delta C \]

Fick’s law: \( J_d = -D \nabla C \)

Einstein law: \( D \approx \frac{k_B T}{6 \pi \eta R} \)

Some values:
- A small molecule in water: \( D = 10^{-9} \text{ m}^2/\text{s} \)
- A molecule in a gas: \( D = 10^{-5} \text{ m}^2/\text{s} \)

Try to find a “natural” variable for \( \partial_t C = D \partial_x^2 C \)

\[ u = \frac{x}{(2Dt)^{1/2}} \]

\[ \rightarrow \partial_u^2 C + u \partial_u C = 0 \]

Quizz transport

Brownian motion = microscopic view of diffusion

Random walk with steps \( r_i \)

\[ R(t) = \sum r_i \]

Find the relation between \( t \) and \( < R^2 > \)

\[ < R^2 > \sim Dt \]

Remember some values:

\( D = 10^{-9} \text{ m}^2/\text{s} \) for a small molecule in water
\( D = 10^{-5} \text{ m}^2/\text{s} \) for a molecule in a gas
Mixing through diffusion
spreading through diffusion

Conservation: \( \partial_t C = D \Delta C \)

Example: small "pulse of concentration" at \( x=0 \)

\[
C(x, t = 0) = C_0 \delta(x, t) \quad \Rightarrow \quad C(x, t) = \frac{C_0}{\sqrt{4\pi Dt}} \exp \left( -\frac{x^2}{4Dt} \right)
\]

Some values:
- A small molecule in water
- A colloid of 200 nm in water
- A molecule of gas

- \( \rightarrow 50 \mu m \) in 1 second?
- \( \rightarrow 1 \mu m \) 1 mm?
- \( \rightarrow 5 \) mm 10 min?
- \( \rightarrow 50 \) mm 5 days?
- \( \rightarrow 50 \) ms 50 ms?

Convection and diffusion

\( J_d \) diffusive flux & \( J_c \) convective flux

\[
J_c = Cv
\]

Conservation: \( \partial_t C + \nabla \cdot (J_c + J_d) = 0 \)

\[
\Rightarrow \quad \partial_t C + v \cdot \nabla C = D \Delta C
\]

Convection Diffusion
\[
vC/L \quad DC/L^2
\]

Péclet = convective transport/diffusive transport
\[
P_e = vL/D
\]

Péclet = diffusion time/convective time
\[
L^2/D \quad L/v
\]
example: diffusion in a coflow

\[ \partial_t C = v(x, y, z) \partial_x C(x, y, z) + D \Delta C(x, y, z) \]

\[ v(z) \partial_x C = D \Delta C \]

* for which conditions can we assume that \( \partial_z C = 0 \)?

\[ \frac{\partial v}{\partial y} > h \frac{\partial^2}{\partial x^2} \text{ i.e. } x > v \frac{\partial^2}{\partial x^2} \]

\[ \rightarrow v \partial_x C = D (\partial^2_x + \partial^2_y) C \]

* what happens if Pe >> 1? \( v \partial_x C / D \partial^2_x C \sim \text{Pe} \gg 1 \)

\[ \rightarrow v \partial_x C = D \partial^2_y C \]

example: diffusion in a coflow

\[ C(x, y) \sim 1 + \text{erf} \left( \frac{y}{2 \sqrt{D x/v}} \right) \]

\[ \Rightarrow \text{mixing width } w(x)^2 = D x / v \]

\[ w(x)^2 = D t \text{ and } t = x / v \]

Mixing is complete for \( X = L_m \) when \( w(L_m) = w \)

\[ DL_m / v = w^2 \Rightarrow L_m = \text{Pe} \ w \]

and \( \text{Pe} = v w / D \)
Diffusion is not efficient to rapidly mix in microfluidics

Example: small molecule (D=10^{-9} m^2/s), w = 500 µm, v = 1 mm/s
Pe = 500

diffusion time \( t_D = \frac{w^2}{D} = 250 \) s

length for a sufficient residence time \( L_m = P e w = v t_D = 25 \) cm

mixing length:

\( L_m = P e w \) and \( P e \gg 1 \)
⇒ mixing strategies?

Some applications of the slow diffusion:
reaction-diffusion dynamics

\( \delta x = 10 \) µm ⇔ \( t \approx 1 \) ms – 1 s
with \( v \approx 10 \) µm/s – 1 cm/s

⇒ stationary measurements

diffusion coefficients of small molecules

kinetics of chemical reactions

≈ 10 – 1000 ms

Yager et al., Biophys.J. 2001
Baroud et al. Phys Rev E, 2005
Salmon et al., Anal. Chem 2005
Some applications of the slow diffusion:

H-filter

example:

small molecules ($D_1 = 10^{-9} \text{ m}^2/\text{s}$)
dust (colloids > 100 nm, $D_2 < 10^{-12} \text{ m}^2/\text{s}$)

$v = 1 \text{ mm/s}$  residence time = 10 s
$L = 1 \text{ cm}$

$w_1 = (D_1 t) = 100 \mu\text{m}$
$w_2 = (D_2 t) < 3 \mu\text{m}$

Yager et al., Dertinger et al., Anal. Chem 2001

Some applications of the slow diffusion: concentration gradients

mixing over width $w$ in the long serpentine ($L > v w^2/D$)

negligible « transverse » resistances

Dertinger et al., Anal. Chem 2001
Some applications of the slow diffusion: playing with geometries

Campbell et al., Lab Chip 2007

Dertinger et al., Anal. Chem 2001

One still recovers homogeneous concentration for $L > \nu w^2 / D = \text{Pe} w$

Quizz

Complete with arrows

- $\eta V/\gamma$
- $\rho L V/\eta$
- $L V/D$

convection vs. diffusion ?
Re: impulsion
Pe: mass

viscous stress vs. capillarity ?

diffusion vs. capillarity ?
Quizz back to hydrodynamics find some similarities…

\[
\rho (\partial_t + v \cdot \nabla)v = -\nabla p + \eta \Delta v \\
(\partial_t + v \cdot \nabla)\phi = D \Delta \phi
\]

Navier-Stokes

Convection-diffusion equation

without gradients of pressure \( \eta/\rho \) is the « diffusion » coefficient of the velocity

what is the time scale for the velocity to diffuse over \( L \)?
what is the time scale for the velocity to be convected at velocity \( v \) on \( L \)?

\[
\tau_d = \frac{L^2}{(\eta/\rho)} \\
\tau_c = \frac{L}{v}
\]

\[
\tau_d/\tau_c = \frac{\rho Lv}{\eta} = \text{Re}
\]

equivalence \( \text{Re} / \text{Pe} \)

transport of velocity / mass

Back to hydrodynamics: start-up of a flow

Navier-Stokes

\[
\rho \partial_t v = \eta \partial_y^2 v \\
\Rightarrow \text{diffusion equation with } D = \eta/\rho
\]

⇒ « diffusion of the velocity » \( \delta^2 \sim \frac{\eta}{\rho} t \)

developed profile for \( \tau \sim \rho L^2/\eta = \text{Re} \frac{L}{U} \)

for water, \( L = 100 \ \mu m, \ t = 10 \ ms \)
Mixing is slow in microfluidics

Quizz

mixing in a coflow

\[ \tau_d = \frac{w^2}{D} \]

\[ L_m = \frac{\tau_d}{v} \]

Mixing is complete for \( L_m = Pe \ w \)

\[ Pe = \frac{vw}{D} \]

Transport phenomena in microfluidics

1- convection/diffusion in microfluidics

2- hydrodynamic dispersion

3- mixing strategies

4- droplet vs. coflow for chemistry

5- active concentration in µ-evaporators
Hydrodynamic dispersion:  
*Taylor – Aris dispersion*

Each time scale \( t_d \): step \( t_d \)  
random walk of step \( W_d \)

\[
W = v t_d = v h^2/D
\]

\[
t = N t_d
\]

\[
W = N^{1/2} W_d = (v^2 h^2/D t)^{1/2}
\]

Squires et al. Rev. Mod. Phys. 2005

---

for \( t >> t_d \sim h^2/D \) i.e. \( L >> Pe h \)

Hydrodynamic dispersion:  
*Taylor – Aris dispersion*

\[
W \sim (v^2 h^2/D) t^{1/2}
\]

« effective » diffusion coefficient \( D_{\text{eff}} = v^2 h^2 / D = Pe^2 D \)

\( \Rightarrow D_{\text{eff}} \sim 1/D \): large solutes are efficiently more dispersed than small ones

\( \Rightarrow \) but do not forget molecular diffusivity \( D \): total dispersion \( (D + D_{\text{eff}}) \)

\( \Rightarrow \) some prefactors:

- circular channels: \( D_{\text{eff}} = v^2 h^2 / (48 D) \)
- shallow channels: \( D_{\text{eff}} = v^2 h^2 / (210 D) \)
Dispersion of the residence times

Initial pulse diffuses according to
\[ C(x, t) = \frac{C_0}{\sqrt{4\pi D_e t}} \exp\left(-\frac{x^2}{4D_e t}\right) \]

Dispersion of the residence times for a tube of length L:
\[ \delta_t(t) = \frac{1}{\sqrt{4\pi D_e t}} \exp\left(-\frac{(L-vt)^2}{4D_e t}\right) \]

Mean residence time \( \tau = \frac{L}{v} \) but dispersion:
\[ w/\tau = 2\left(\frac{D_e}{vL}\right) + 8\left(\frac{D_e}{vL}\right)^2 \]

Hydrodynamic dispersion: Lévêque dispersion

Non-dimensionalized transport equation:
\[ (1-(2z)^2) \frac{\partial}{\partial x} C = \left(\frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}\right) C \]

\[ x = X/(hP_e); \quad y = Y/h; \quad z = Z/h; \quad Pe = Uh/D \]

\[ t > \frac{h^2}{D} \text{ i.e. } x > 1 \Rightarrow \text{no dispersion} \]

Example: \( h = 100 \mu m, D = 10^{-9} m^2/s, V = 1 \text{ mm/s} \)
\[ Pe = 100, X > 1 \text{ cm} \]
Hydrodynamic dispersion: origin of the 1/3 exposant:

\[ v(z) = \gamma z \quad \Rightarrow \quad \gamma z \partial_x C = D(\partial_y^2 + \partial_z^2)C \]

find a new length scale ?

\[ l = \sqrt{D/\gamma} \]

non dimensionalized equation:

\[ (\partial_u^2 + \partial_v^2)C = \frac{1}{3} u(u \partial_u F + v \partial_v F) \]

with:

\[ u = z/(x^{1/3}l^{2/3}) \]
\[ v = y/(x^{1/3}l^{2/3}) \]

⇒ close to the wall: dispersion \( w \sim x^{1/3} \)

Stone, Phys.Fluids 1989

Hydrodynamic dispersion: 2D vs. 3D models ?

3D \( (1-(2z)^2) \partial_z C = (\partial_y^2 + \partial_z^2)C \)

2D \( \partial_z C = \partial_y^2 C \)

⇒ small differences…

Salmon et al., J. Appl. Phys. 2007
Hydrodynamic dispersion: Lévéque dispersion within chemical reactions


Salmon et al., J. Appl. Phys. 2007

Transport phenomena in microfluidics

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Passive mixing strategies:  
**ex: hydrodynamic focusing**

\[ w_f = 100 \text{ nm} - 1 \mu\text{m} \]

\[ t_d = \frac{w_f^2}{D} = 10 \mu\text{s} - 1 \text{ ms} \Rightarrow \text{fast mixing} \]

⇒ but hydrodynamic dispersion  
due to the top and bottom walls  
⇒ small heights are needed

\[ 3D \text{ hydrodynamic focusing} \]

\[ \frac{\partial C(r, t)}{\partial t} = \frac{D}{r} \left( \frac{\partial C}{\partial r} + r \frac{\partial^2 C}{\partial r^2} \right) \]

⇒ access to fast kinetics < 1 ms  
⇒ no dispersion (axisymmetric flow)

**Problem of initial conditions?**

near a wall, edge... : velocities vanishe  
⇒ « stagnant » region  
⇒ long residence time  
⇒ need for Computational Fluid Dynamics (CFD)  
to solve the profiles and the exact concentration field
Passive mixing strategies: ex: the groove mixer

\[ J = \text{fluid flux that tends to align the flow along the "easy axis"} \]

in a confined channel:

helical stream lines


Passive mixing strategies: chaotic mixing

it works at \( \text{Re} = 0 \)

hydrodynamic dispersion is also reduced

Stroock et al. Science, 2002
Passive mixing strategies: mixing length

\[ \Delta r \sim w/2^N \Rightarrow \Delta r \sim w \exp(-y/\lambda) \]

mixing is complete for \( L_m = v\Delta r^2/D \Rightarrow L_m \approx \lambda \log(\text{Pe}) \)

for a simple co-flow: \( L_m = v\Delta r^2/D \Rightarrow L_m \approx w\text{Pe} \)

\[ Stroock \text{ et al. Science, 2002 } \]

\[ \Rightarrow \text{need for 3D structures} \]
Active mixing: rotary mixer

\[ \text{Pe} = \frac{U_0 h}{D} \]
\[ \tau_D = \frac{h^2}{D} \]

**Different regimes of mixing:**

**Diffusion limited** \( \text{Pe} \ll 1 \)
\[ \tau_1 = \frac{(2\pi R)^2}{D} = \frac{(2\pi R)^2}{h^2} \tau_D \]

**Taylor-Aris regime**, valid for:
\( \tau_D < \frac{2\pi R}{U_0}, \) i.e. \( \text{Pe} \ll \frac{2\pi R}{h} \)
\[ \tau_2 = \frac{(2\pi R)^2}{D_{\text{eff}}} \sim \frac{\tau_1}{\text{Pe}^2} \]

**Convective stirring regime** \( \text{Pe} \gg \frac{2\pi R}{h} \)

stirring reduce the mixing length \( h_{\text{eff}} \):
\[ \tau_3 \sim \text{Pe}^{-2/3}\left(\frac{h}{R}\right)^{4/3} \tau_1 \]

Squires et al. Rev. Mod. Phys. 2005

---

Active mixing: rotary mixer

valves using soft multilayer lithography

rotary mixer \( v = 5 \text{ nL} \)

Unger et al. Science 2000

Transport phenomena in microfluidics

1- convection/diffusion in microfluidics
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3- mixing strategies
4- droplet vs. coflow for chemistry
5- active concentration in µ-evaporators

Chemical reaction in microfluidics: coflow vs. droplets

- Coflow mixing is difficult
  \[ L_m \sim \text{Pe}_w \text{ and } \text{Pe} >> 1 \]
  hydrodynamic dispersion
  dispersion of the residence times

- Droplets:
  fast mixing
  no hydrodynamic dispersion

Evidence for hydrodynamic circulations within droplets

- Recirculations ⇔ boundary conditions (continuity of stress and velocity)

Streamlines in windings

Burns et al. Lab Chip 2001
Cristobal et al.
width of the striae:
\[ s(n) \sim w2^{-n} \]

time of mixing over the striae:
\[ t_d \sim s(n)^2/D \sim w2^{-2n}/D \]

corresponding convection time
\[ t_c = \frac{na}{w} \]

dimensionless parameter
\[ aw = \text{distance for stretch and fold} \]

Mixing complete for
\[ t_c = t_d \]
i.e.
\[ na/[w^2 - 2^{-2n}/D] \]
\[ \Rightarrow n \sim \log(Pe) \quad \text{for} \quad Pe \gg 1 \]
\[ \Rightarrow t_c \sim \frac{aw\log(Pe)}{U} \]

remember coflow mixing:
\[ t_m \sim \frac{wPe}{U} \]

Chaotic advection & mixing times

Small mixing times in small geometries by chaotic advection

for a 10X10 µm² channel


Sarrazin et al. 2006
Mixing times in different geometries and at different scales?

Example: large tubes and centered drops with viscous fluids at low flow rates

$t \approx 1 \text{ min}$

But always:

- mixing in droplet is more efficient than using simple co-flow
- there is no dispersion of residence times
- thermal transfers are more efficient
- solids can be transported in droplets

Using gas bubbles?

but liquids may flow between gas plugs ⇒ residence times distributions:

$\delta t(t) = \frac{1}{\sqrt{4\pi D_e t}} \exp\left(-\frac{(L-vt)^2}{4D_e t}\right)$

Günther et al., Lab. Chip 2004
Transport phenomena in microfluidics

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Microfluidics permeation-induced flows

Verneuil E et al., EuroPhys. Lett. 2004
Randall et al. PNAS 2005

passive concentration
Microfluidics permeation-induced flows

Control of the permeation

\[
h \frac{\partial v(x)}{\partial x} = v_e
\]

\[
v_0 = v_e \frac{L_0}{h}
\]

\[
v(x) = v_e \frac{x}{h}
\]

\[
\tau_e = \frac{h}{v_e}
\]

Typical velocities:

PDMS membranes ≈ 10 µm ⇒ \(v_e = 20\) nm/s

h = 10 µm & \(L_0 = 10\) mm ⇒ \(v_0 = 20\) µm/s

**Micro-evaporation for active concentration**

\[
v(x) = v_c x / h \]

\[
J_a = v(x) c(x) \]

\[
J_d = -D \partial_x c(x) \]

**conservation of the solute:**

\[
J_d(x) + J_a(x) = J_d(x + dx) + J_a(x + dx) \]

⇒ **conservation equation:**

\[
\partial_t C = D \partial_x^2 C + \partial_x (v(x) C(x)) \]

**Micro-evaporation for active concentration**

\[
J_a = v(x) c(x) \]

\[
J_d = -D \partial_x c(x) \]

accumulation « box » \( J_a \approx J_d \) ⇒ \( v_c p / h = -D / p \) ⇒ \( p = (D \tau_c)^{1/2} \)

**typical values:**

- small molecules \( D = 10^{-9} \text{ m}^2/\text{s} \) ⇒ \( p = 1 \text{ mm} \)
- colloids of 1 µm \( D = 10^{-13} \text{ m}^2/\text{s} \) ⇒ \( p = 10 \mu\text{m} \)

<table>
<thead>
<tr>
<th>Fluorescein</th>
<th>Colloids 0.1 µm diam.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloids 0.5 µm diam.</td>
<td>300 µm</td>
</tr>
<tr>
<td>Colloids 1.1 µm diam.</td>
<td></td>
</tr>
</tbody>
</table>
Micro-evaporation for active concentration

mass conservation:

$$hc_0 v_0 \Delta t = ph \Delta C$$

$$\Rightarrow$$ accumulation rate in the box

$$\frac{\Delta C}{\Delta t} = \frac{c_0 L_0}{\rho \tau_e}$$

50 micro-evaporators concentrating surfactant molecules and forming dense phases [Leng et al., Langmuir 2007]

Quizz
What is this movie?
Microfluidics for lab-on-chips

**Microfluidic flows**
1. Pressure-driven flows
2. Capillary-induced flow
3. Droplet microfluidics
4. Evaporation-induced flows
5. Electroosmotic flow

**Transport phenomena**
1. Convection/diffusion
2. Hydrodynamic dispersion
3. Mixing strategies
4. Droplet vs. coflow
5. Concentration using µ-evaporators

**Generalities**
1. Microfluidics?
2. Why?
3. How?

**Applications**
1. Microfluidic crystallization
2. Physical chemistry R&D (Flavie Sarrazin, Rhodia)

Some applications

1. Microfluidic crystallization
2. Physical chemistry R&D

Jean-Baptiste Salmon
LOF, Pessac, France
Microfluidic crystallization

thermodynamic phase diagrams

kinetics of nucleation/growth

nucleation and growth kinetics are important to control the final properties of the crystals

kinetics of nucleation

Nucleation: activated process

classical nucleation theory

nucleation rate $J$ (nuclei m$^{-3}$ s$^{-1}$)

$$J = A \exp \left( -\frac{B}{\log^2 S} \right)$$
structural biology
⇒ structures of proteins
⇒ high quality crystals for X-ray crystallography

Protein crystallization

gel/precipitate formation
favorable for nucleation
labile zone:
metastable zone:
optimal growth

McPherson, Luft, DeTitta...

⇒ need for an optimal kinetic path

Microfluidics and screening of crystallization conditions of proteins

1- random screening
- concentrations
- agent
- buffer
- pH,
- temperature
⇒ hits of crystallization

2- optimize crystallization
⇒ suitable crystals for X-ray diffraction

1- random screening ⇒ thousands of tests with small amount of samples
2- optimize crystallization ⇒ design of kinetic paths
control of mass transfers

⇒ microfluidic tools
Microfluidic free interface diffusion (FID)

Protein precipitation in 20 nL chambers

- Mixing by diffusion
- No convection
- Geometry \( \Rightarrow \) kinetic path

Hansen et al., PNAS 2002

144 independent 20 nL chambers
3 \( \mu \)L of proteins
Simply filled since PDMS is gas permeable

\( \Rightarrow \) Efficient crystallization of many proteins

Hansen et al., PNAS 2002
A recent similar system: microfluidic counter diffusion

- Microfluidics: no turbulence & mixing is governed by diffusion
- Diffusion of proteins in a channel filled with precipitant $\Rightarrow$ gradient of supersaturation

Chip in polycarbonate for in situ x-ray diffraction

Droplet-based microfluidics for protein crystallization

- Continuous screening (change of the flow rates)

Fluorinated oils prevent evaporation from the droplets for long time
**Droplet-based microfluidics for random screening**

Random screening with preformed array of precipitant

![Diagram of droplet-based microfluidics](image)

Array of precipitant droplets

Protein stream

Incubation of droplets

Precipitant + protein

Merging of the stream


**Droplet-based microfluidics and kinetic path**

Decoupling of nucleation/growth

![Diagram of kinetic path](image)

S=1

Time

Random screening without droplets and fluid pumps

priming 20 nL wells with degassed PDMS

incubation and crystallization of proteins

mixing between wells (similar to FID)

Towards rational screening: high throughput screening of phase diagram

⇒ the knowledge of phase diagrams enables rational screens for protein crystallization

⇒ perform screening of multiple phase diagrams with small amounts of proteins

solution: microfluidic formulator

16 buffers + 16 reagents + protein
mixing in 5 nL rotary mixer
Towards rational screening:
high throughput screening of phase diagram

mixing in 5 nL rotary mixer
concentration precision 1 pL
4000 titration / day = 8 µL protein sample

measuring the limit of precipitation region

1- explore complete phase diagrams with 100 nL of protein sample
2- identify conditions for protein crystallization
3- use FID

Hansen et al. PNAS 2004
Anderson et al. PNAS 2006
The Phase Chip: measuring phase diagram with osmotic control

Shim et al. JACS 2007

The Phase Chip: decoupling nucleation and growth

Microevaporation for crystallization

\[ \frac{\Delta C}{\Delta t} = \frac{c_0 L_0}{p \tau} \]

⇒ accumulation rate in the box

ex: reservoir of KCl solution

different length = different accumulation rates


Measuring density & nucleation kinetics

nucleation times

metastability

solubility

measure of the growth rate of the phase \( x(t) \) gives measurements of the density \( \rho \)

conservation of mass \( \rho \frac{dx}{dt} = J_0 \), with \( J_0 \) the inner flux in the microevaporator
Solubility measurements with droplet-based microfluidics

Temperature gradient on-chip

\[ \frac{\partial^2 T}{\partial x^2} = \frac{h(T - T_0)}{\lambda} \]

\[ w \lambda \frac{\partial^2 T}{\partial x^2} = h(T - T_0) \]

\[ l_c^2 = w \lambda / h \]

\( \lambda = 1 \text{ W/(m K)} \) \( \Rightarrow l_c \approx \text{ mm} \)

\( \lambda = 90 \text{ W/(m K)} \) \( \Rightarrow l_c \approx \text{ cm} \)

\( \Rightarrow \) linear temperature profiles of several cm are possible using silicon wafer

Laval et al., Lab. Chip. 2007

wafer & PDMS chip

Peltier modules

silicon oil solution solvent

concentration

outlets

20 mm

temperature

\( T_1 \)

\( T_2 \)

\( T \)

\( h(T - T_0) \)

\( \lambda \nabla T \)

silicon vs. glass wafer (w = 0.5 mm, h=30 W/m²K)
1- filling step

- silicon wafer & PDMS chip
- Peltier modules

2- crystallization step

- 20 mm

3- dissolution step

- solubility
- crystals
- no crystals

On-chip solubility measurements

adipic acid solution

Microfluidic device

- for screening polymorphic forms

- up to 300 droplets of 100 nL

- Peltier module
- Pt100

- silicone oil
- aqueous solution
- fluorinated oil

- outlet 1
- outlet 2

- ≈ 1 hour
- ≈ 250 µL of solution

Laval et al., Lab. Chip. 2007
Microfluidic screening of polymorphic forms

KNO₃/water
100 µL / concentration

crystallization/dissolution

25 mm

metastable form

stable form

[Kracek 1830, Balkanski 68]

large volume V ⇒ small nucleation time \( \tau_n = 1 / JV \)

\( (J \text{ nucleation rate}, \text{ growth time } \tau_g \sim V^{1/3}) \)

⇒ low supersaturations
⇒ polynuclear mechanisms
⇒ ease of polymorphic transformations

[Kashchiev 94, Sato 93]
Benefits of the « microfluidic » method

- small volume: high supersaturations
- small volume: mononuclear mechanism
- small volume: rare polymorphic transformations

V ≈ 100 nL

KNO₃/water

Microfluidic droplet method for nucleation kinetics

1- filling step

2- temperature quench

$V = 40 \, \text{g} \, /\, 100 \, \text{g}$

$T_p = 5.8 \, ^\circ \text{C}$

$T_p = 4.8 \, ^\circ \text{C}$

$T_p = 3.8 \, ^\circ \text{C}$

$T_p = 2.8 \, ^\circ \text{C}$

$T_p = 1.8 \, ^\circ \text{C}$

$T_p = 25 \, \text{mm}$
Evidence for impurities-mediated nucleation

KNO$_3$/water

$P(t) = \exp(-J/Vt)$

$\ln (P)$ vs. $t$ (s)

Comparison with heterogeneous nucleation model of Pound & La Mer:

$\Rightarrow$ distribution of impurities with different activities

[Pound 52, White 53, Turnbull 49]

More informations:
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