Microfluidic principles
Basic principles

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Content and scope of the course

Outline

- Basics of fluid dynamics
- Existence of different types of flow regimes
  - Laminar *vs*. turbulent flow
  - How to predict the flow regime? ⇨ Reynolds number (*Re*)
- Laminar flow: properties
- Mixing under laminar flow conditions
- Diffusion phenomena

- **Pumping in microfluidic systems**
  - Hydrodynamic pumping (pressure-driven pumping)
  - Electro-driven pumping
  - Other pumping strategies

- **Laminar flow** platforms (continuous flow)

- **Droplet** platforms (discrete/segmented flow)

Fluid dynamics - basics

- **Navier Stokes equation (conservation of impulse)**

$$\rho\left(\frac{\partial \vec{v}}{\partial t} + (\vec{v}.\nabla)\vec{v}\right) = -\nabla\vec{p} + \mu\nabla^2\vec{v} + \vec{F}$$

Acceleration | Convective acceleration | Pressure gradient | Viscous forces | External forces

v: flow component in x-direction
also equations or y- and z-direction

“Simplified” expression

$$\vec{0} = -\nabla\vec{p} + \mu\nabla^2\vec{v}$$

- Steady flow, no external forces applied on the liquid
- Viscous regime

Fluid dynamics - basics

- **Conservation of mass (continuity equation, liquid)**

$$\frac{\partial \rho}{\partial t} + div(\rho u) = 0$$

For incompressible fluids $\partial\rho/\partial t = 0$, and the equation becomes:

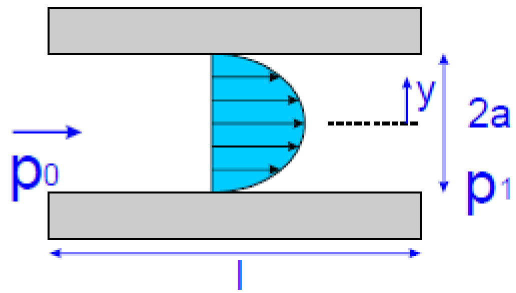
$div\ \mathbf{u} = 0.$

Alternative ways to write this: $\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = 0$ and $\frac{\partial u_i}{\partial x_i} = 0$

- **Convection-diffusion equation (species in liquid)**

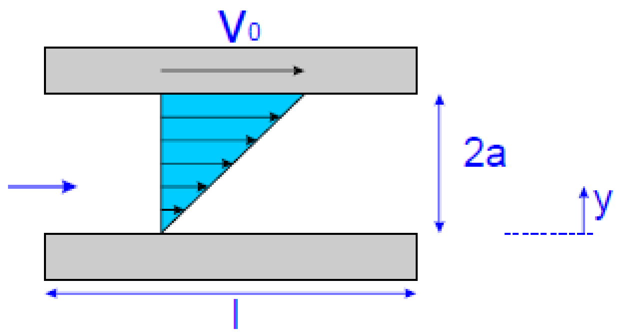
Steady state flow profiles

- **Pressure-driven flow (Poiseuille flow)**



$$v(y) = \frac{-1}{2\eta}\left(y^2 - a^2\right)\frac{dP}{dx}$$

- **Shear-driven flow (Couette flow)**



$$v(y) = \left(\frac{y+a}{2a}\right)v_0$$

Hydraulic resistance of common channel geometries

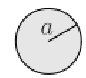
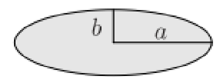
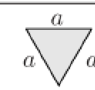
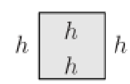
Constant ΔP → constant flow rate Q

$$\Delta P = R_{hyd} Q$$

Analogy with Ohm's law:

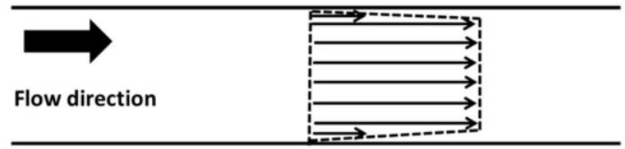
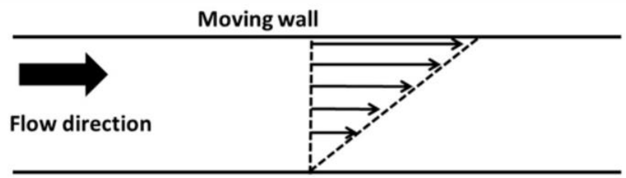
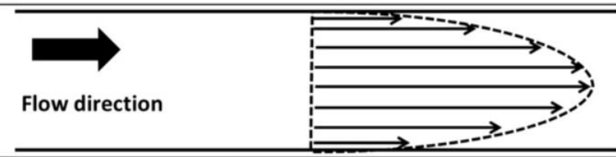
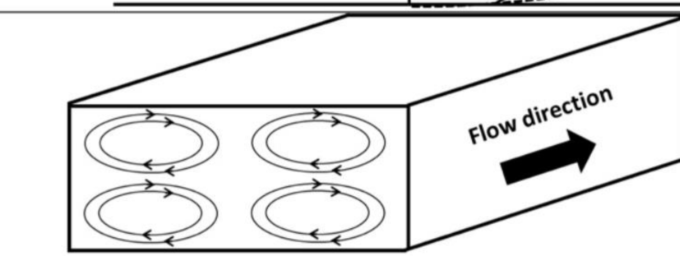
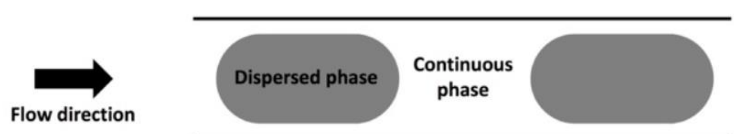
$$\Delta V = R\,I$$

Table 4.1 A list over the hydraulic resistance for straight channels with different cross-sectional shapes. The numerical values are calculated using the following parameters: $\eta = 1$ mPa s (water), $L = 1$ mm, $a = 100$ µm, $b = 33$ µm, $h = 100$ µm, and $w = 300$ µm.

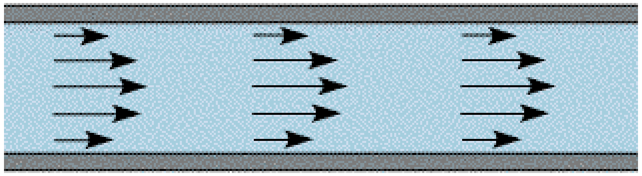
shape		R_{hyd} expression	R_{hyd} $[10^{11}\ \frac{\text{Pa s}}{\text{m}^3}]$	reference
circle		$\frac{8}{\pi}\,\eta L\,\frac{1}{a^4}$	0.25	Eq. (3.39b)
ellipse		$\frac{4}{\pi}\,\eta L\,\frac{1+(b/a)^2}{(b/a)^3}\,\frac{1}{a^4}$	3.93	Eq. (3.38)
triangle		$\frac{320}{\sqrt{3}}\,\eta L\,\frac{1}{a^4}$	18.5	Eq. (3.46)
two plates		$12\,\eta L\,\frac{1}{h^3 w}$	0.40	Eq. (3.30)
rectangle		$\frac{12\,\eta L}{1-0.63(h/w)}\,\frac{1}{h^3 w}$	0.51	Eq. (3.58)
square		$28.4\,\eta L\,\frac{1}{h^4}$	2.84	Exercise 4.4
parabola		$\frac{105}{4}\,\eta L\,\frac{1}{h^3 w}$	0.88	Eq. (3.80)
arbitrary		$\approx 2\,\eta L\,\frac{\mathcal{P}^2}{\mathcal{A}^3}$	–	Eq. (3.27a)

Bruus, Theoretical Microfluidics

Overview flow profile toolbox

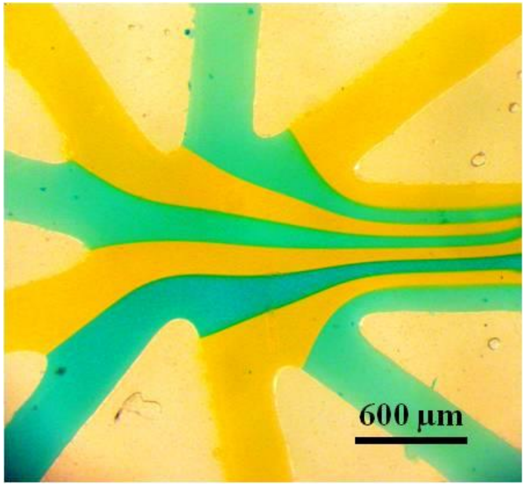
Plug flow	
Constant shear	
Linear shear	
Vortical flow	
Segmented flow	

Laminar *vs*. turbulent flow

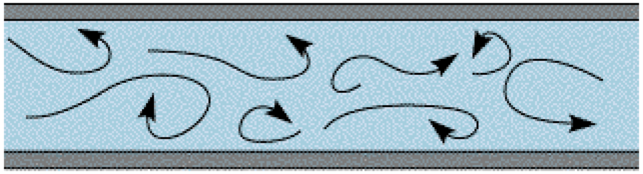


Laminar flow

Predictable, organized, deterministic

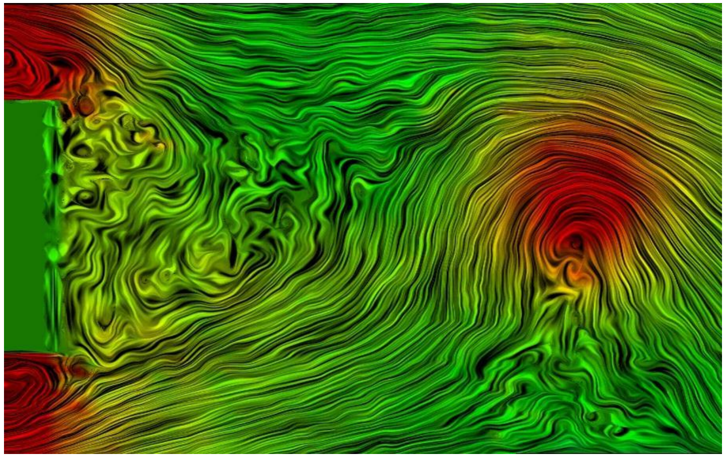


http://alcheme.tamu.edu



Turbulent flow

Chaotic, unpredictable, disorganized

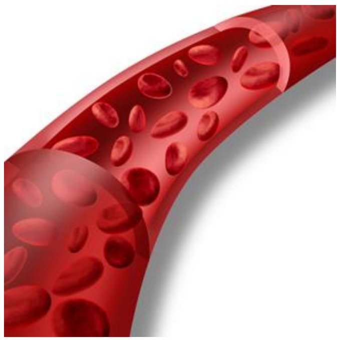


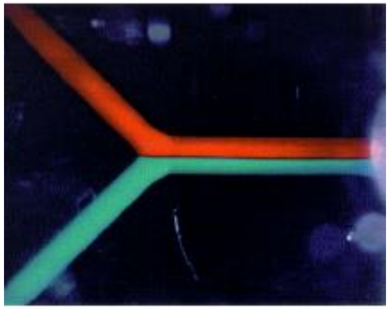
http://www.math.rug.nl/

⇨ **When do we have a laminar flow? When do we have a turbulent flow?**

Laminar *vs*. turbulent flow

⇨ **When do we have a laminar flow? When do we have a turbulent flow?**






Laminar flow

When?
- High viscosity
- Small dimensions
- Low flow-rate/velocity

Turbulent flow

When?
- Low viscosity
- Large dimensions
- High flow-rate/velocity

Important parameters
- Viscosity of the fluid
- Dimension of the flow
- Flow velocity / flow-rate

Laminar *vs.* turbulent flow

Reynolds number

$$Re = \frac{\rho v l}{\mu}$$

ρ density of the fluid (kg/m^3)
v average flow velocity (m/s)
l characteristic length of the flow (m)
μ viscosity of the fluid (cP or kg/m.s or Pa.s)

- Dimensionless number
- Ratio between the inertial forces and the viscous forces (bulk *vs.* surface)
- Measure for transition between a laminar (low Re) and a turbulent flow (high Re)

Examples

1. Microsystem

ρ water $= 1000$ kg/m^3
$v = 100$ μm/s
$l = 100$ μm
μ water $= 1$ cP $= 0.001$ kg/m.s

$$Re = \frac{10^3 \times 100 \times 10^{-6} \times 100 \times 10^{-6}}{0.001} = 10^{-2}$$

2. Large viscous flow

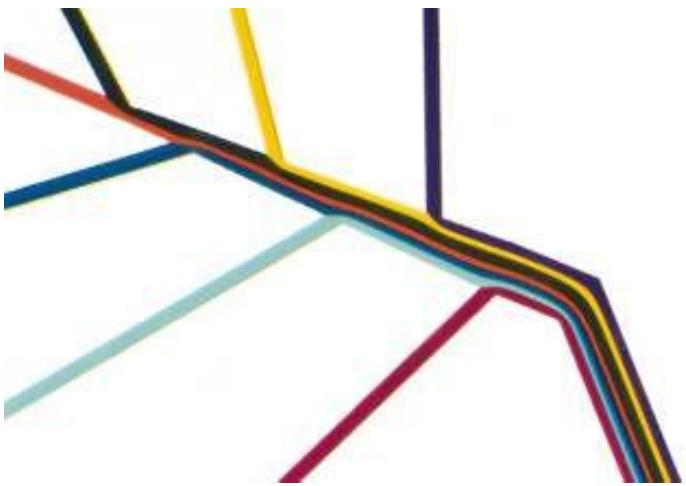
ρ honey $= 1420$ kg/m^3
$v = 1$ cm/s
$l = 5$ cm
μ honey $= 20$ kg/m.s

$$Re = \frac{1420 \times 10^{-2} \times 5 \times 10^{-2}}{20} = 0.035$$

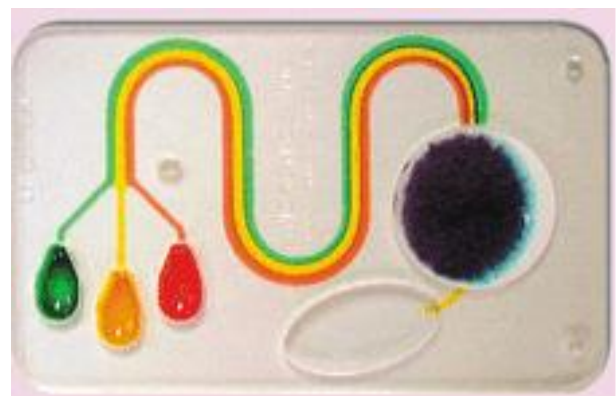
Microfluidics: laminar or tubulent flow?

Microfluidics
- High surface-to-volume ratio ⇨ surface phenomena predominant
- Small dimensions (< 100 µm)
- Low velocities (< mL/s)

⇨ **Mostly laminar flow profiles**



Kenis et al., Science 285, 83 (1999)

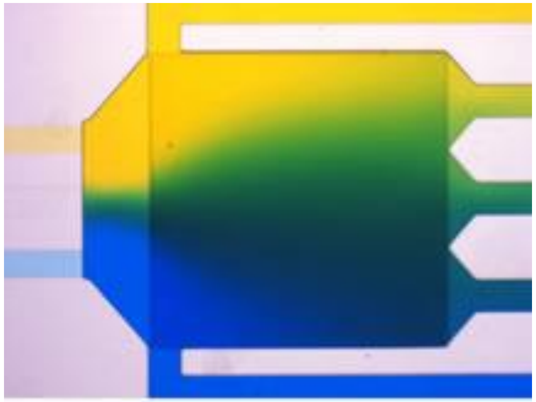


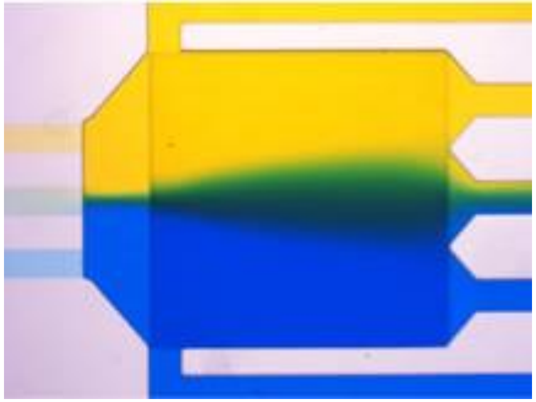
Micronics

Key-advantages
- Predictable flows, deterministic behavior
- Well-defined and controlled environment

Mixing in a laminar flow configuration?

- Mixing ⬄ turbulence (active transport)
- ????? No turbulence ⬄ no mixing ???





www.cellasic.com

How does mixing occur under laminar flow conditions?

⇨ Mixing occurs via **diffusion** of molecules between the flows (**passive transport** or “random walk”)

Diffusion

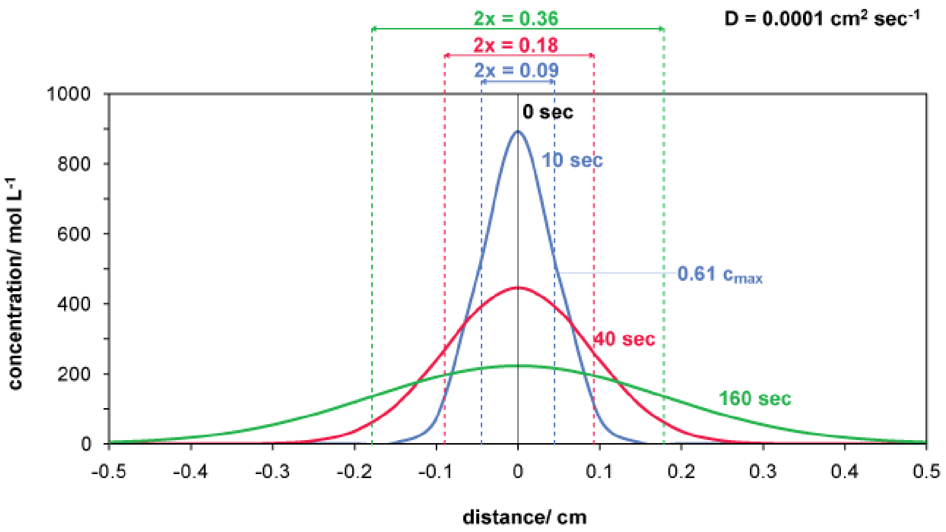
Diffusion: 1st Fick's law

$$J = -D\frac{dC}{dx}$$

J flux of molecules (mol/m^2.s)
D diffusion coefficient (m^2/s)
C concentration in species (mol/L or M)

⇨ The higher the concentration gradient, the more efficient the diffusive transport

Diffusion over time



Gaussian distribution
Average traveled distance

$$\bar{x} = \sqrt{2Dt}$$

Mixing by diffusion: is it efficient?

Mixing time

$$t = \frac{L^2}{2D}$$

t diffusion time (s)
L distance traveled by diffusion (m)
D diffusion coefficient (m^2/s)

Examples

1. **Sugar in hot coffee** (D ~ 8.10^{-10} m^2/s at 80°C; cup of ~10 cm)

$$t = \frac{(0.1)^2}{2\times8\times10^{-10}} = 6.25 \text{ x } 10^6 \text{ s} = 72 \text{ days!!!!}$$

⇨ **Better use a spoon for mixing!!!!**

2. **Small molecule in water** (D ~ 10^{-9} m^2/s in chemical glassware (~10 cm) and microchannel (~ 100 µm)

- L = 10 cm (chemical glassware) ⇨ $t = 10^7$ s!
- L = 100 µm (microchannel) ⇨ t = 10 s!

⇨ **The smaller the better!!!!**

Diffusion coefficient

Stokes-Einstein relation

$$D = \frac{k_B T}{6\pi\mu R}$$

k_B Boltzmann constant (J/K)
T temperature (K)
μ viscosity of the fluid (cP or kg/m.s)
R radius of the particle/molecule (m)

!!!!!! $\mu = \mathrm{f(T)}$!!!!!!

Examples

1. Diffusion coefficient of a virus in blood

$k_B = 1.38 \times 10^{-23}$ J/K
$T = 310$ K
μ blood $= 0.006$ kg/m.s
$R = 50$ nm

$$D = \frac{1.38 \times 10^{-23} \times 310}{6\pi \times 0.006 \times 50 \times 10^{-9}} = 7.6 \times 10^{-13}\ \mathrm{m^2/s}$$

2. Diffusion coefficient of a protein in aqueous solution

$k_B = 1.38 \times 10^{-23}$ J/K
$T = 298$ K
μ water $= 0.001$ kg/m.s
$R = 5$ nm

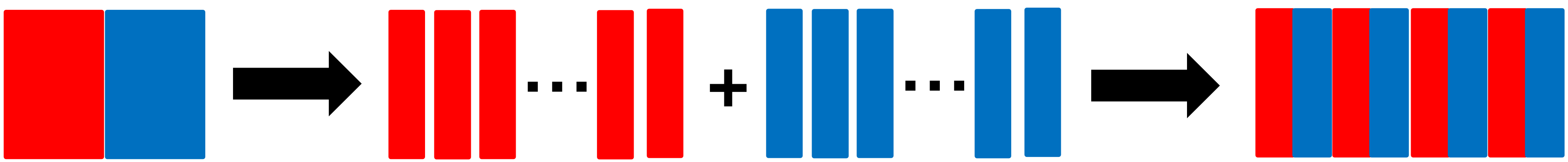
$$D = \frac{1.38 \times 10^{-23} \times 298}{6\pi \times 0.001 \times 5 \times 10^{-9}} = 4.36 \times 10^{-11}\ \mathrm{m^2/s}$$

Mixing in a laminar flow configuration?

- How to improve mixing in a laminar flow configuration?

  Diffusion more efficient for smaller distances

  ⇨ **Let's fragment the flow!**



Flow divided in n sub-flows

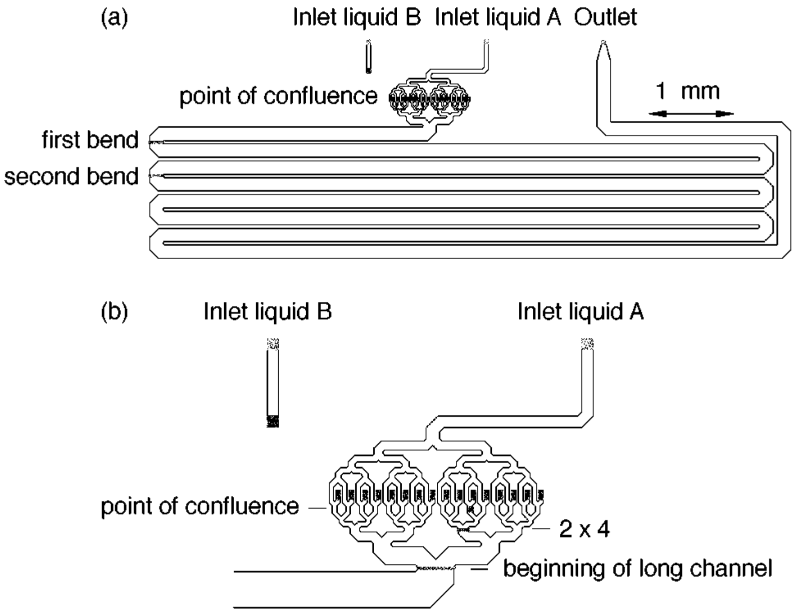
$$L' = \frac{L}{n} \quad \Rightarrow \quad t' = \frac{L^2}{2n^2 D}$$

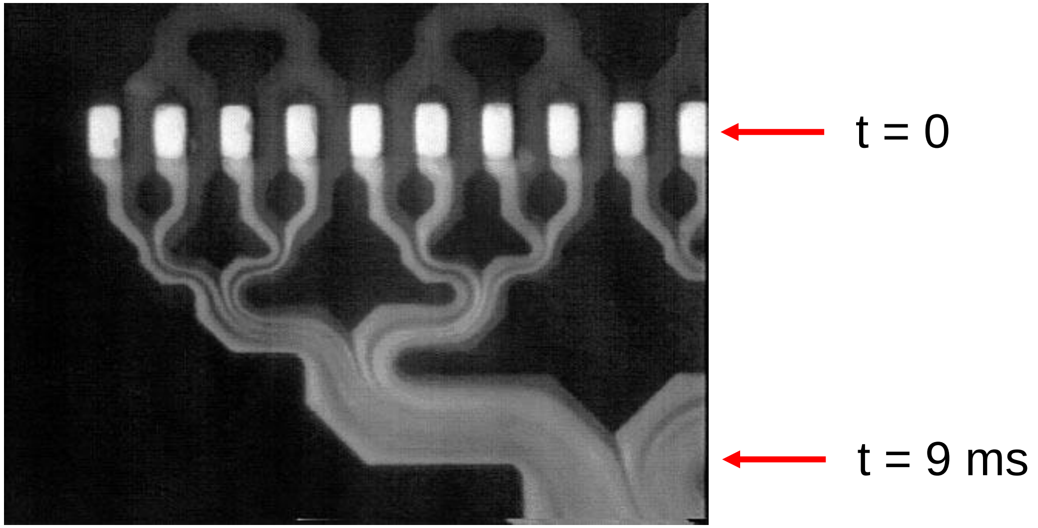
$n = 10 \rightarrow$ diffusion time 100 times lower!

- Small molecule in water (D ~ 10^{-9} m^2/s)
  - *L* = 100 µm (microchannel) ⇨ *t* = 10 s!
  - If 10x fragmentations *t* = 100 ms!

Mixing in a laminar flow configuration?

Mixing of two dyes in a fragmented flow (flow = 50 µL/min)





F. Bessoth et al., *Anal. Comm.* 1999, *36*, 213.

Commercially available (NanoMixer, Upchurch Scientific)

Taylor-Aris dispersion

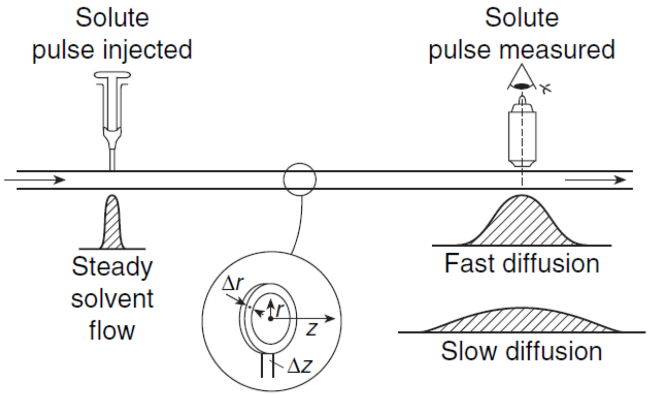
Bruus, Theoretical microfluidics, 2008

linear velocity (m/s)

channel dimension (m)

$$D_{ax} = D_m + \kappa \frac{v^2 d^2}{D_m}$$

Dispersion of Soluble Matter in Solvent Flowing Slowly through a Tube
Author(s): Geoffrey Taylor
Source: *Proceedings of the Royal Society of London. Series A, Mathematical and Physical Sciences*, Vol. 219, No. 1137 (Aug. 25, 1953), pp. 186-203
Published by: Royal Society

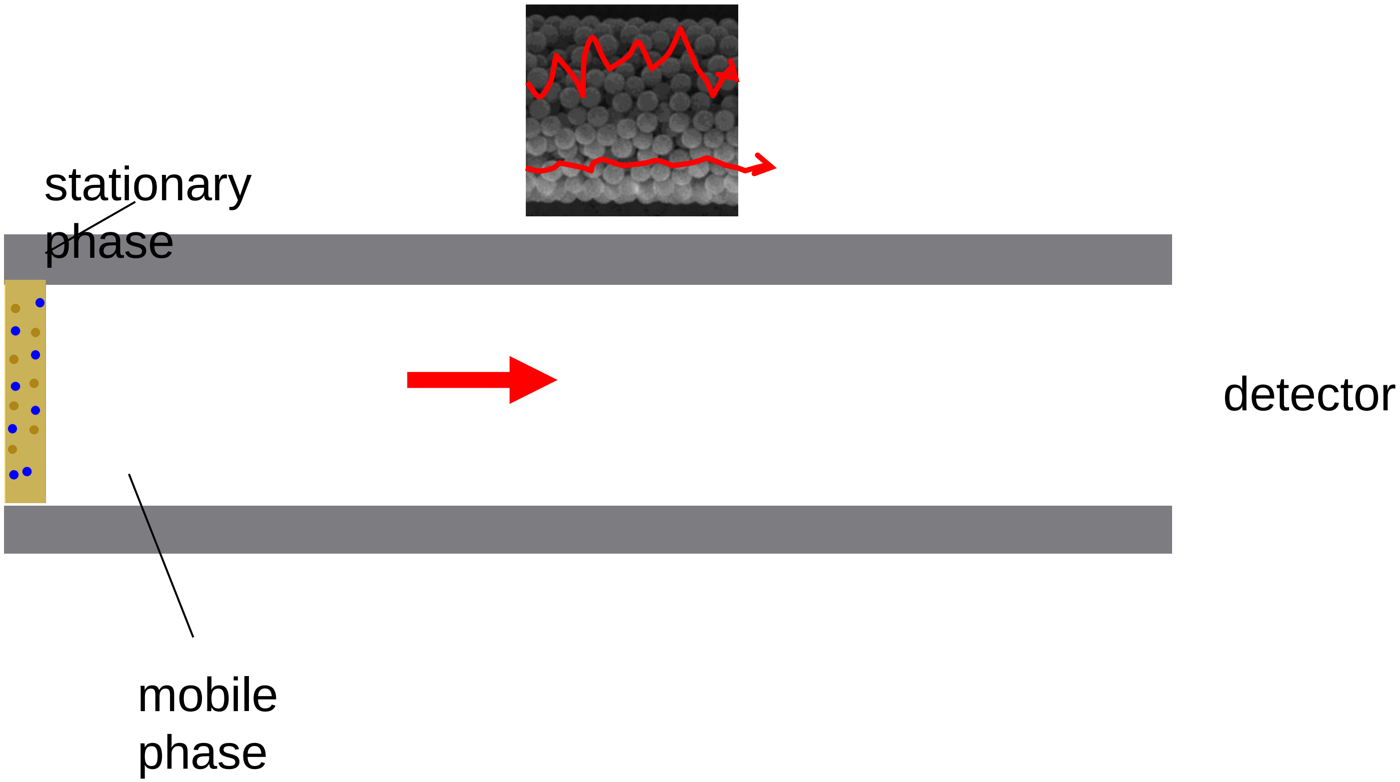


$\kappa = \frac{1}{192}$ (cylinder)

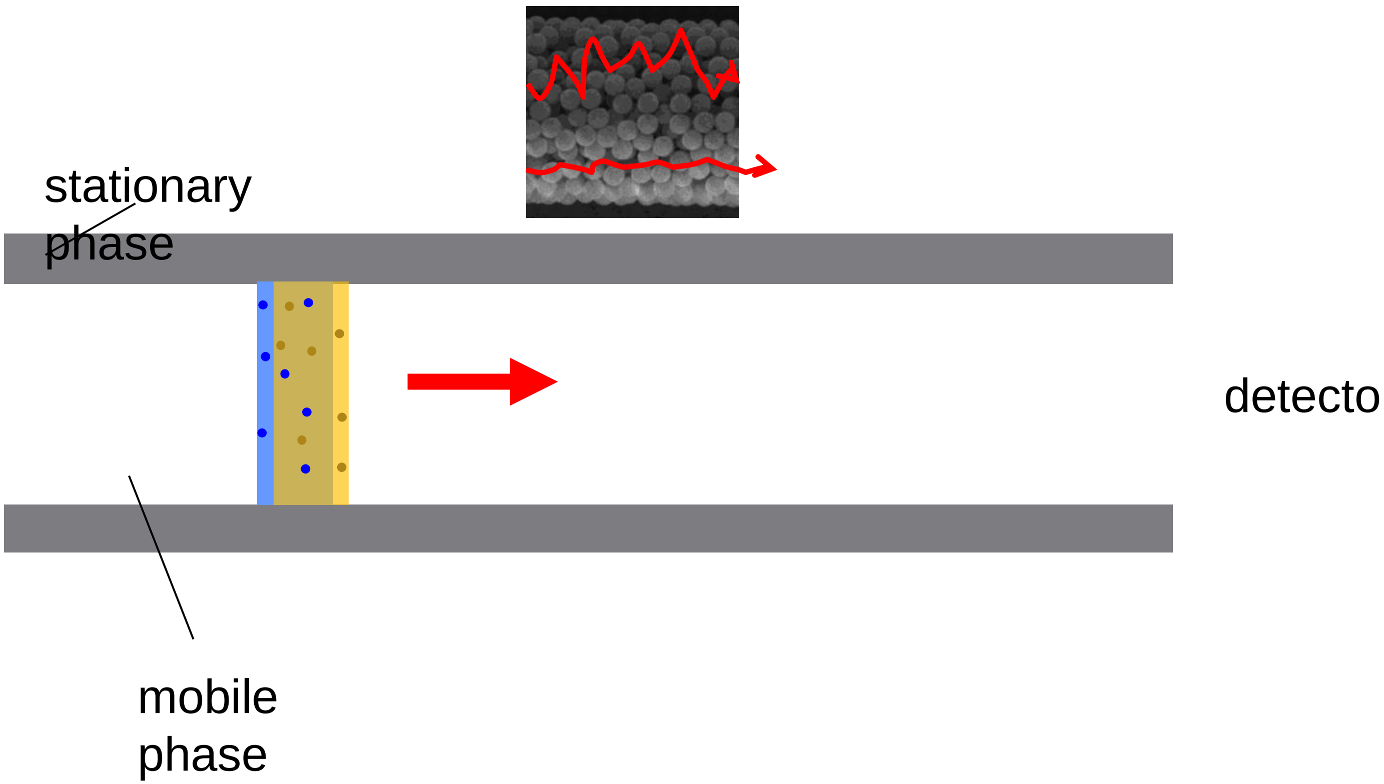
$\kappa = \frac{1}{210}$ (rectangular channel)

Cussler, Diffusion, 2009

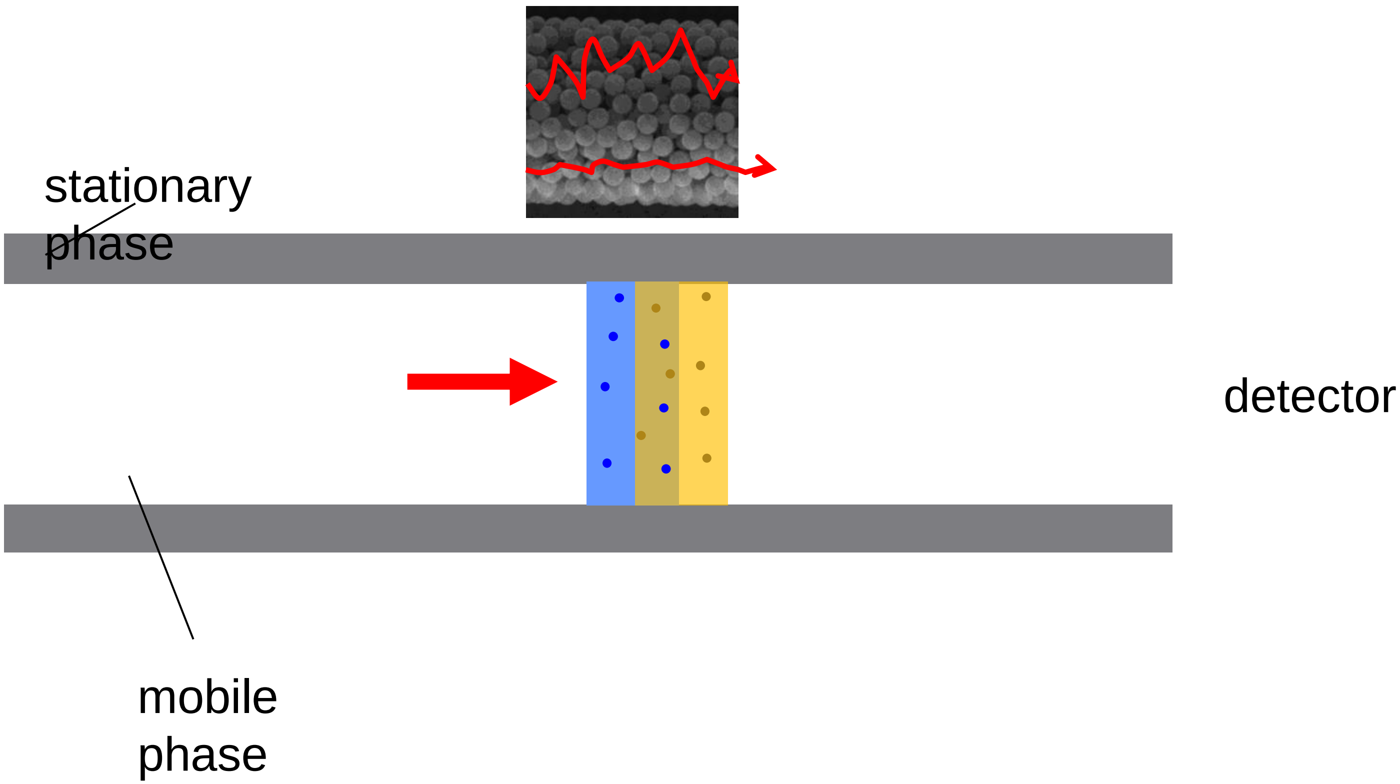
Reducing dispersion with structuring



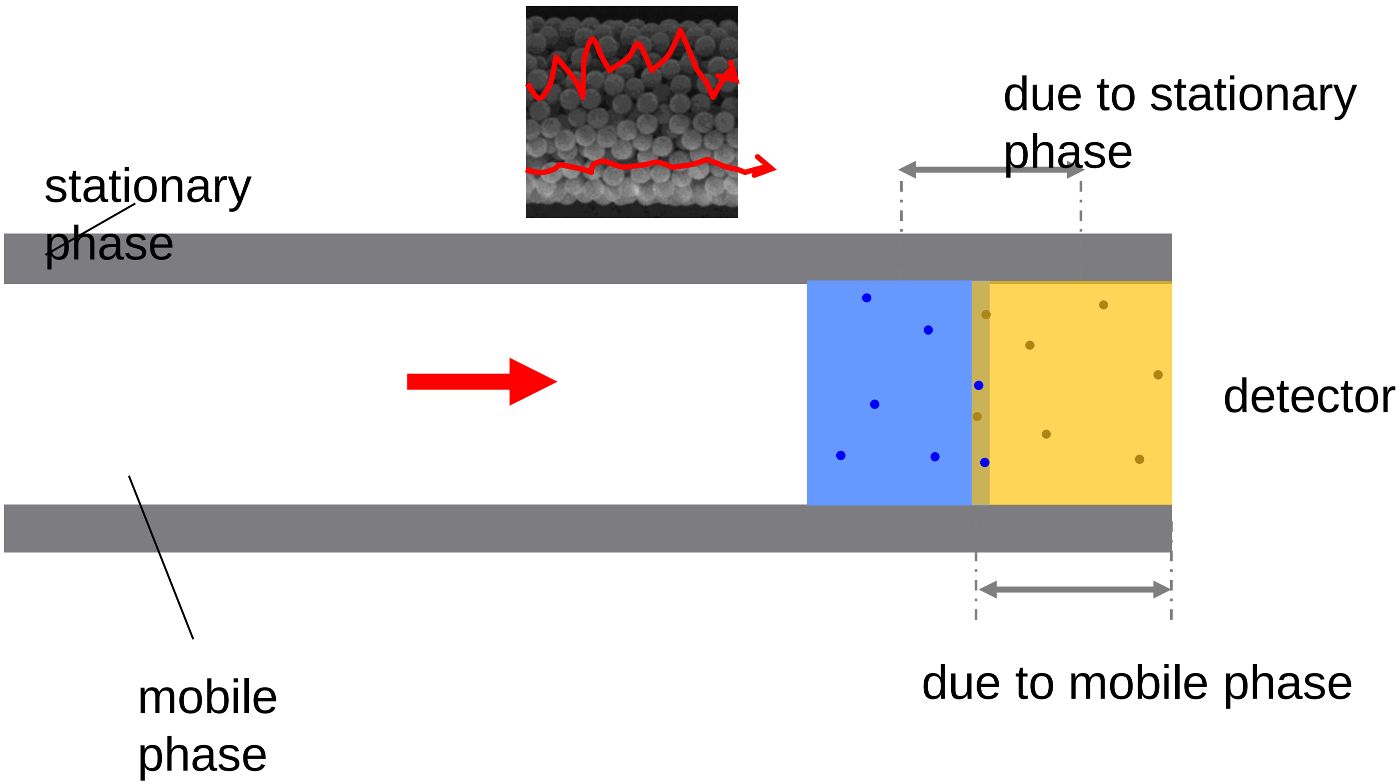
Reducing dispersion with structuring



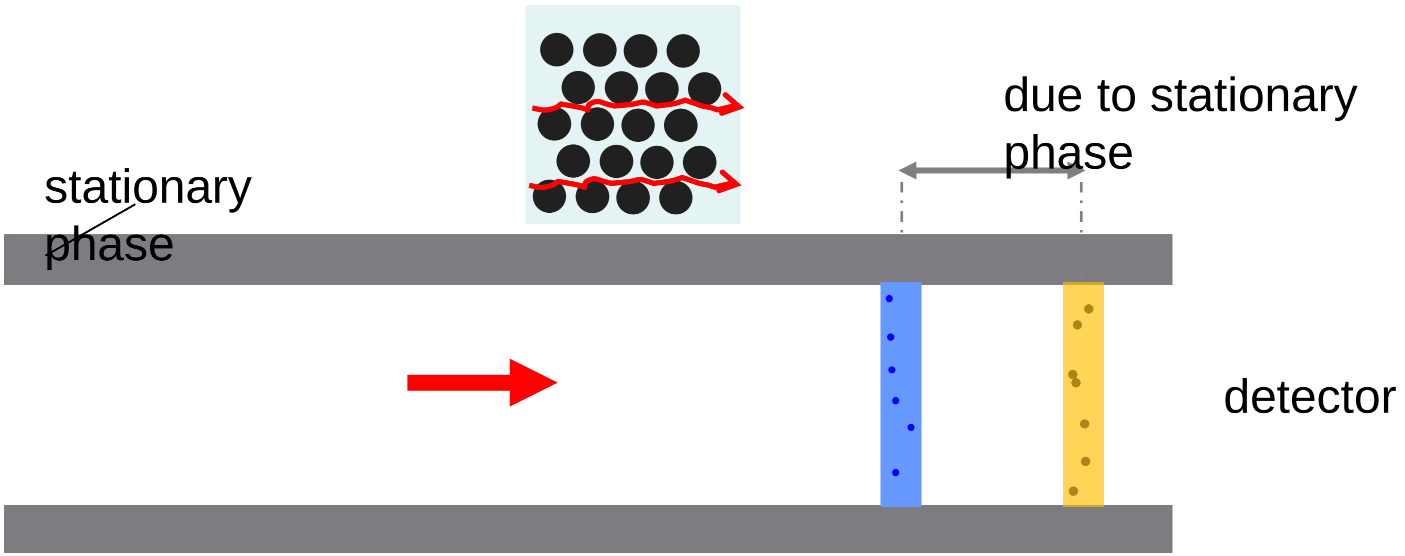
Reducing dispersion with structuring



Reducing dispersion with structuring

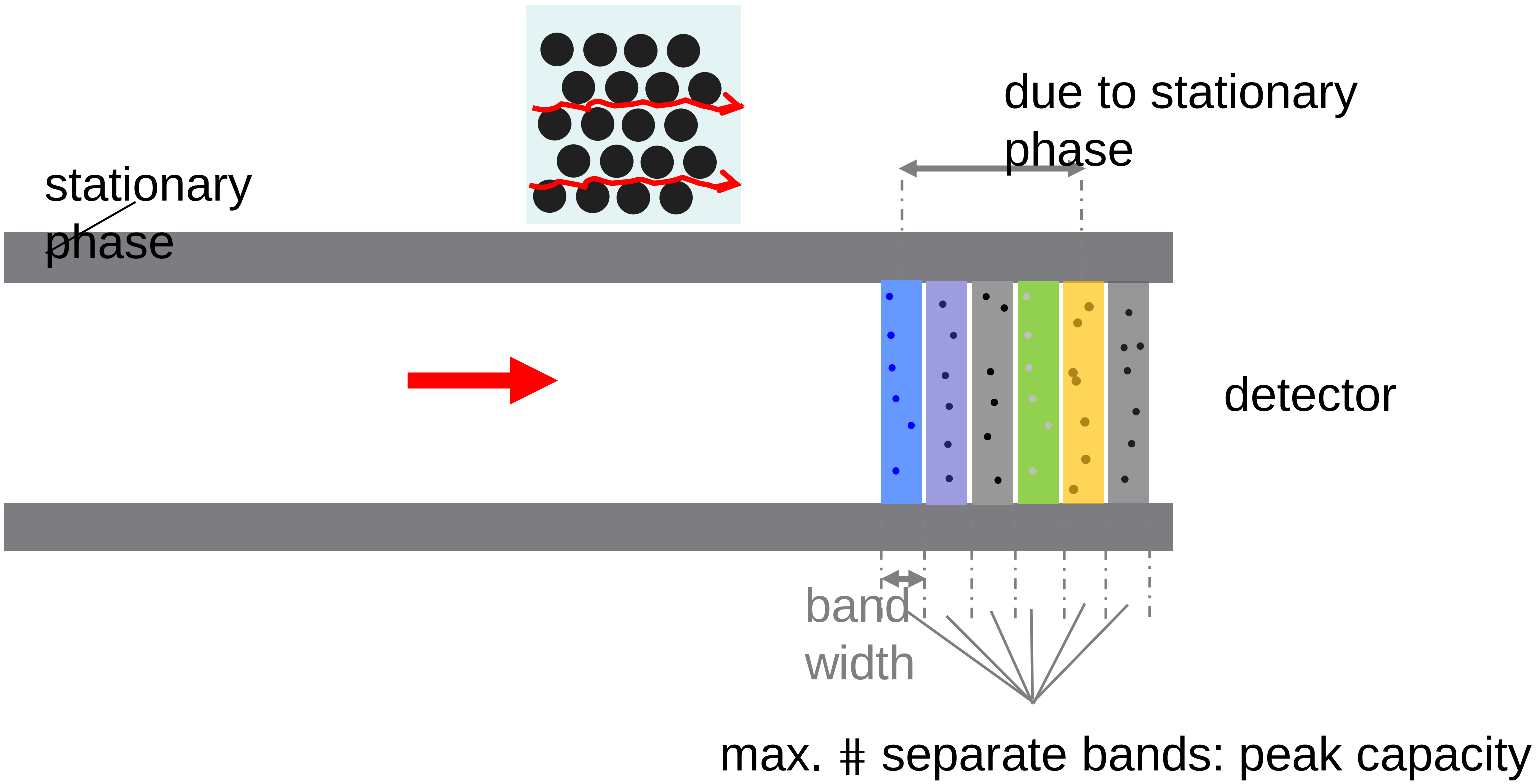


Reducing dispersion with structuring



In absence of mobile phase dispersion

Reducing dispersion with structuring

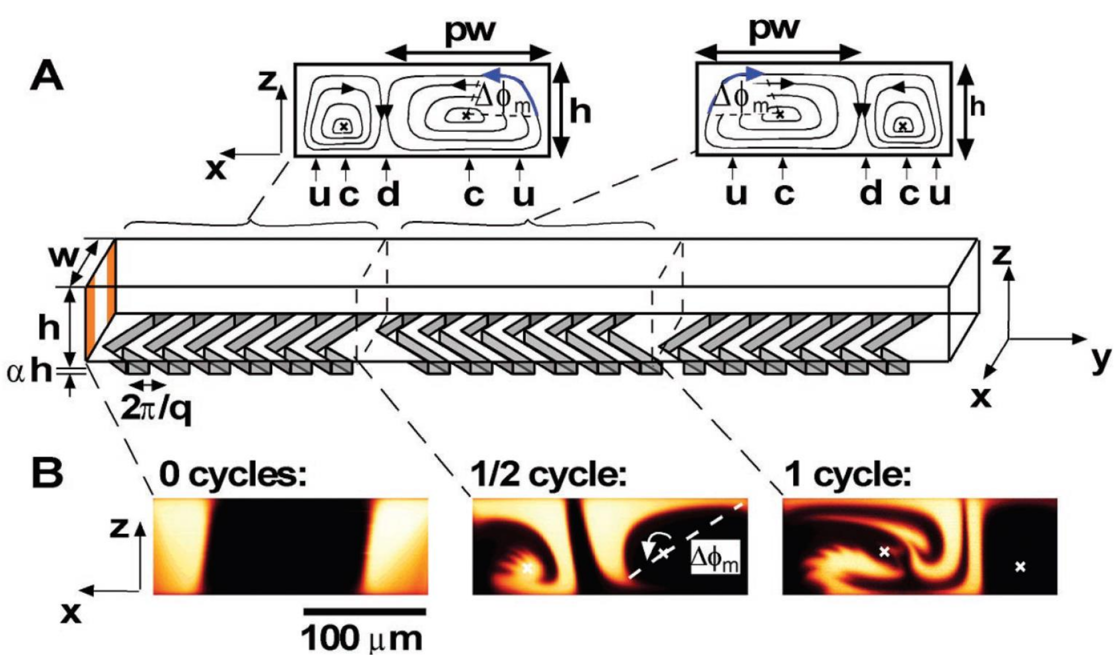


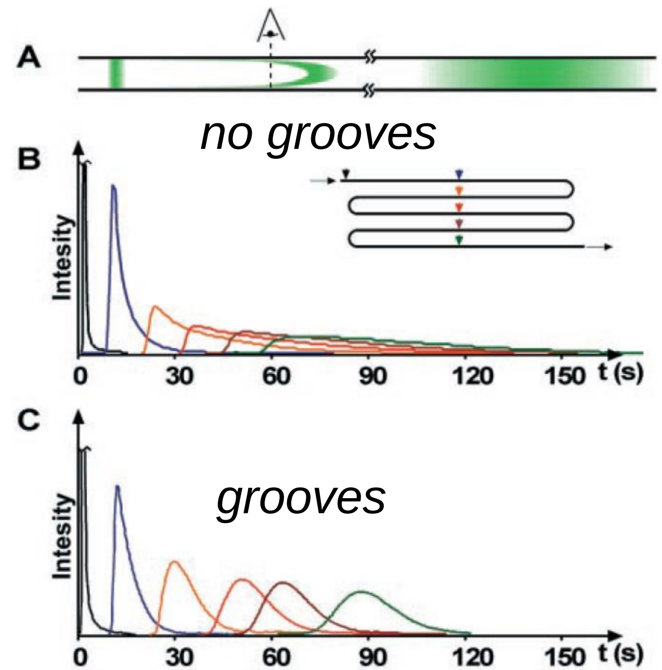
Taylor-Aris dispersion

Chaotic Mixer for Microchannels

Abraham D. Stroock,[1*] Stephan K. W. Dertinger,[1]
Armand Ajdari,[2] Igor Mezić,[3] Howard A. Stone,[4]
George M. Whitesides[1*]

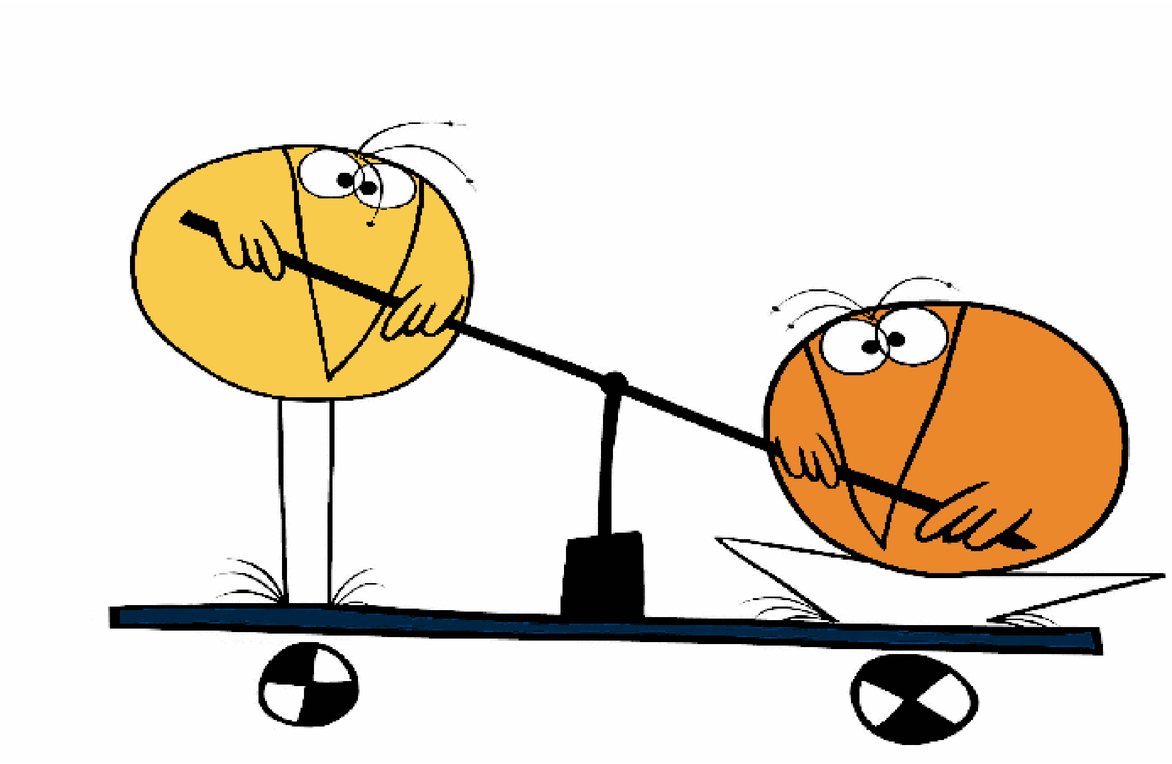
www.sciencemag.org SCIENCE VOL 295 25 JANUARY 2002





70 µm x 200 µm channel

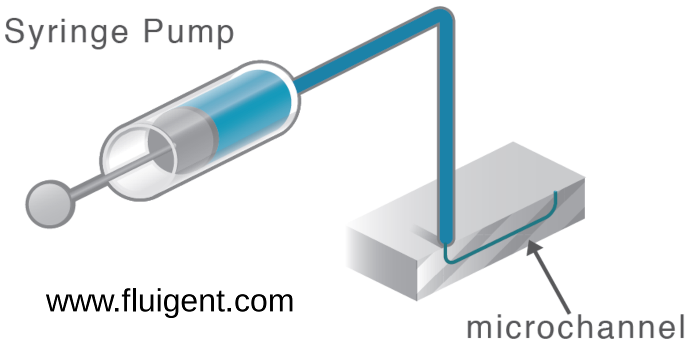
How to pump in a microfluidic device?



- How would you pump fluids in a microfluidic device?

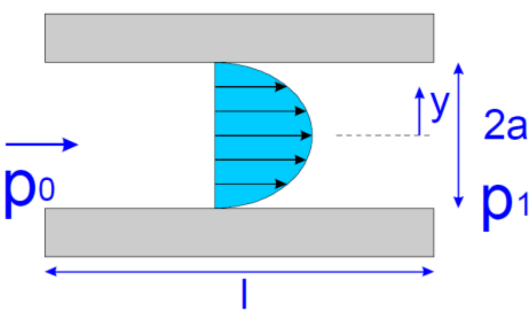
How to pump in a microfluidic device?

- **Pressure-driven flow**



- Broad range of velocities
- Suitable for any fluid

- **Parabolic flow** profile
  Poiseuille flow



$$v(y) = \frac{1}{2\mu}(y^2 - a^2)\frac{dP}{dx}$$

Rect. channel (w>>h): $Q = \int_0^w \mathrm{d}y \int_0^h \mathrm{d}z \, \frac{\Delta p}{2\eta L}(h-z)z = \frac{h^3 w}{12\eta L}\Delta p.$

- **Flow resistance**
  Hagen-Poiseuille equation

$$R_{flow} = \frac{\Delta P}{Q} = \frac{8\mu L}{\pi r^4}$$

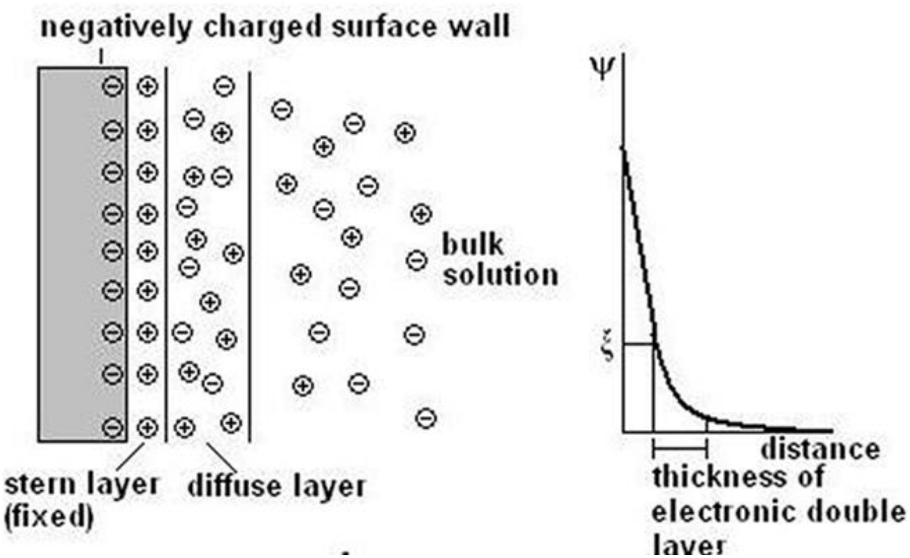
ΔP pressure drop
Q volumetric flowrate
μ viscosity of the fluid
L length of the channel
r radius of the channel

- **Parabolic flow** profile: molecular dispersion
- The smaller the channel, the higher the resistance, the higher the risk for leakages!!

How to pump in a microfluidic device?

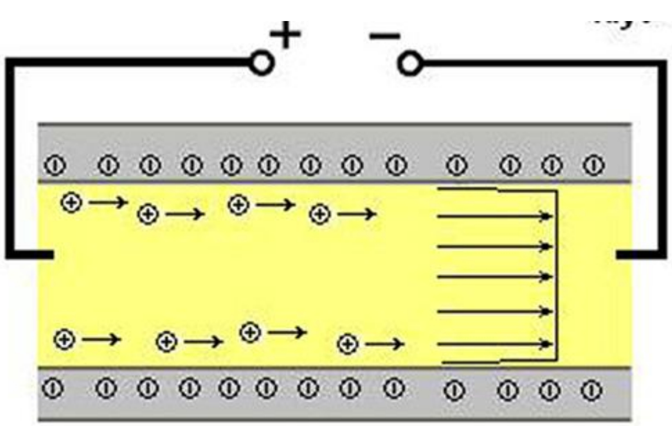
- **Electro-driven flow** (or electro-osmotic pumping)

Pumping based on surface effects only for **charged liquids**



- Capillary walls: charged (negatively)
- ⇨ Accumulation of counter-ions at the surface
- ⇨ Stern layer: counter-ions
- ⇨ Diffuse layer: ions of both charges

- Application of an electric field
- ⇨ Migration of cations towards the cathode
- ⇨ Creation of a bulk flow towards the cathode
- ⇨ **Electro-osmotic flow**



- EOF velocity: $v_{EOF} = \mu_{EOF} E$

With $\mu_{EOF} = \frac{\varepsilon \xi}{\mu}$, EOF mobility; E electric field; ε dielectric constant; ξ zeta potential; μ viscosity of the fluid

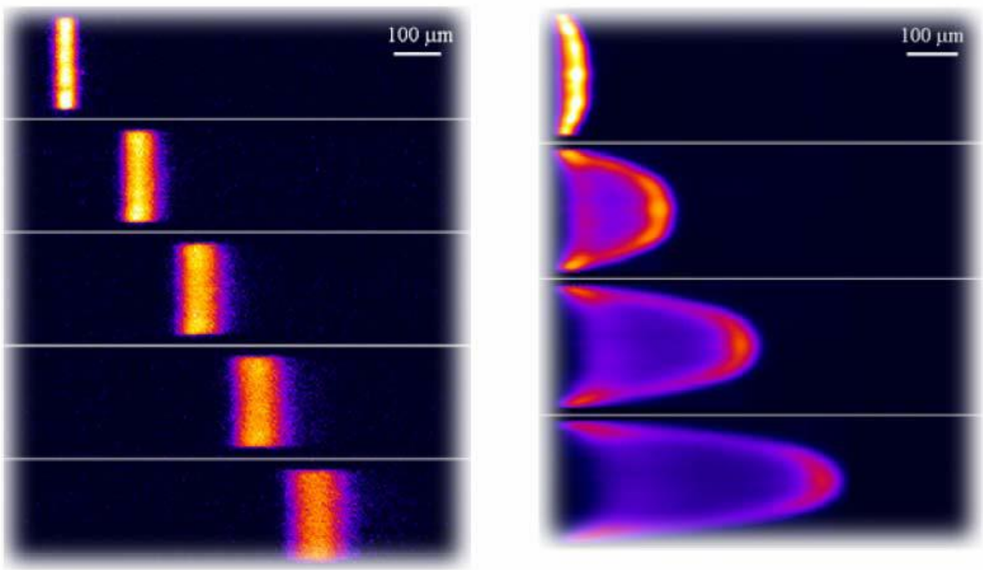
http://www.bioscience.org

How to pump in a microfluidic device?

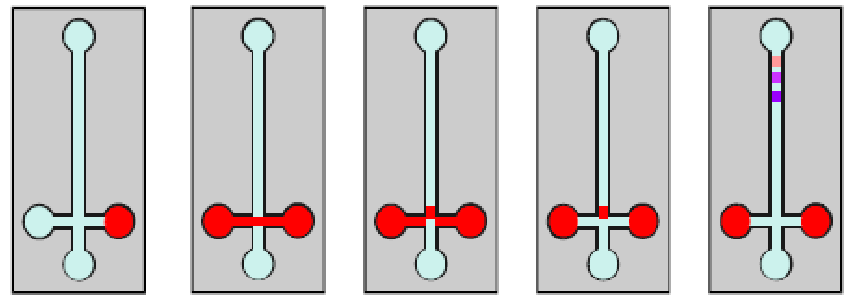
Electro-driven pumping or **EOF-pumping** (electro-osmotic flow)

- flat flow profile: plug-flow

liquid control ⇔ switching voltages



Electro- *vs*. pressure-driven flow profile



CE-based separation in a microchip
1-2. Sample introduction;
3-4. Sample injection;
5. Sample separation

⇨ **Simple integration in microfluidics**

CE = capillary electrophoresis

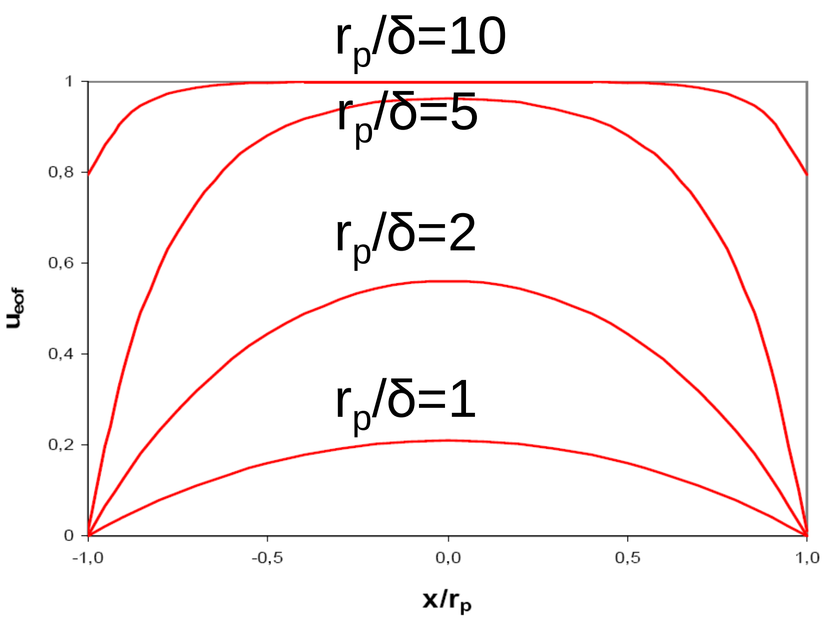
EOF: double layer overlap

For small channels:

- Parabolic-like flow profile
- Significant reduction of achievable flow velocity in sub-micron channels

$$u_{eof} = \frac{\varepsilon_0 \varepsilon_e \zeta E}{\eta}\left[1 - \frac{2 I_1(r_p/\delta)}{(r_p/\delta) I_0(r_p/\delta)}\right]$$

$$\delta = \sqrt{\frac{\varepsilon_0 \varepsilon_e k T}{2 N_a e_0{}^2 C_s}}$$

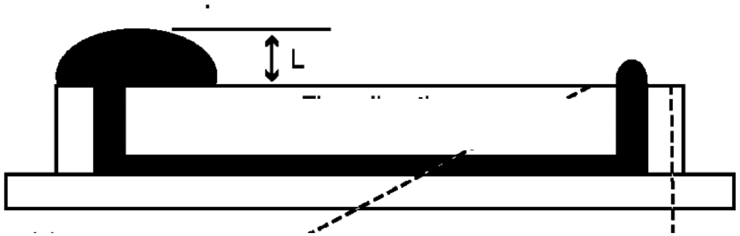


k: Boltzmann constant
N_a Avogadro's number
T: temperature,
C_s the ionic strength,
r_p the radius of the channel
e_0 the elementary charge unit.

C_s: the ionic strength,
r_p: the radius of the channel
e_0: the elementary charge unit
δ: double layer thickness

How to pump in a microfluidic device?

- **Passive pumping**: creation of a flow using surface tension



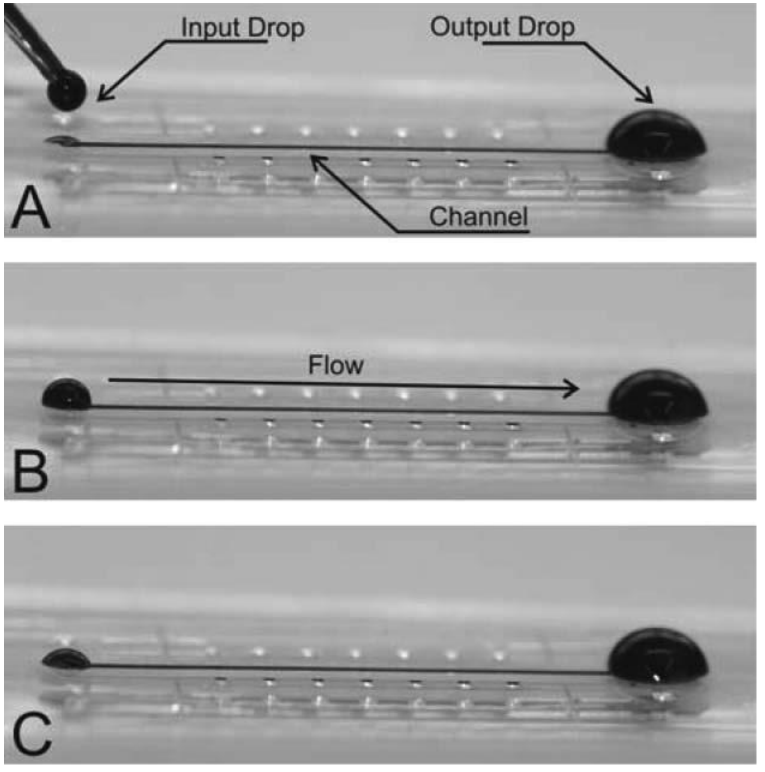
Interfacial pressure in droplets

$$\Delta P = \frac{2\gamma}{R}$$

γ interfacial tension (N/m)
R radius of the droplet (m)

⇨ **The smaller the droplet, the higher pressure**

- In which direction does the flow go?

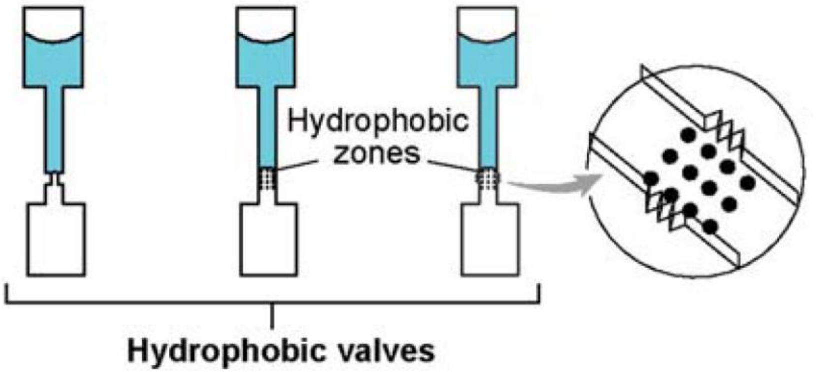


Walker et al., 2002

Berthier et al., 2007

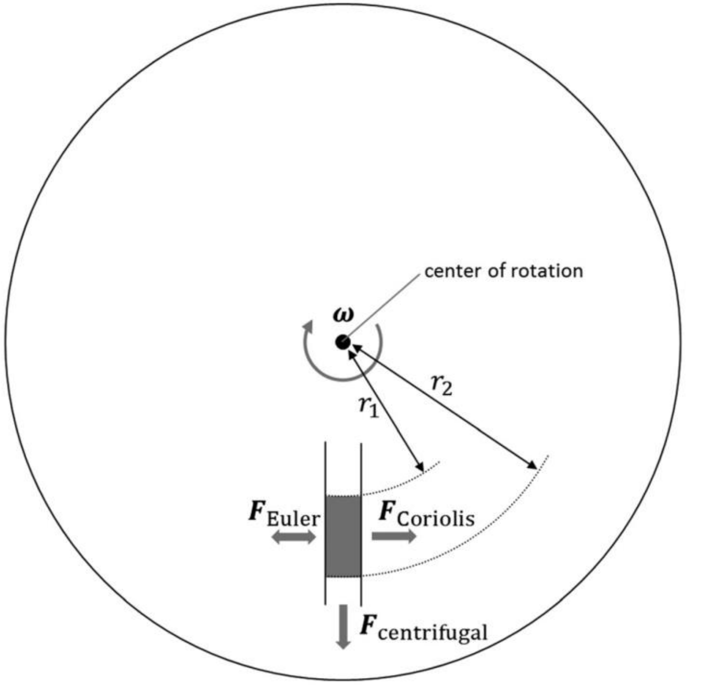
How to pump in a microfluidic device?

- **Centrifugal pumping**



Valve creation
hydrophobic treatment of the surface

- Lower spinning speed: no flow
- Higher spinning speed: flow

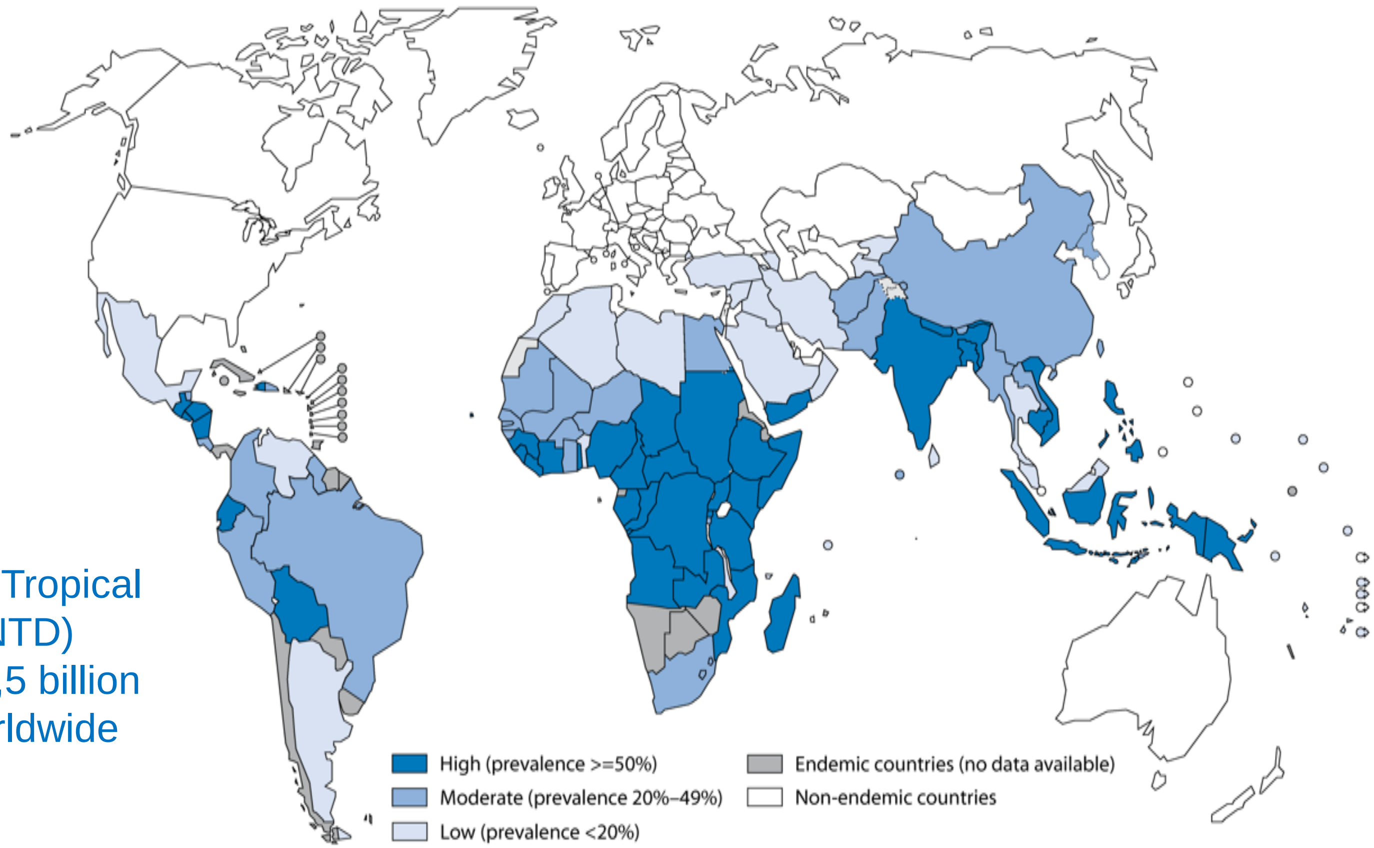


CD rotation ⇨ fluid motion.

Madou et al, 2006

Zengerle et al, 2015

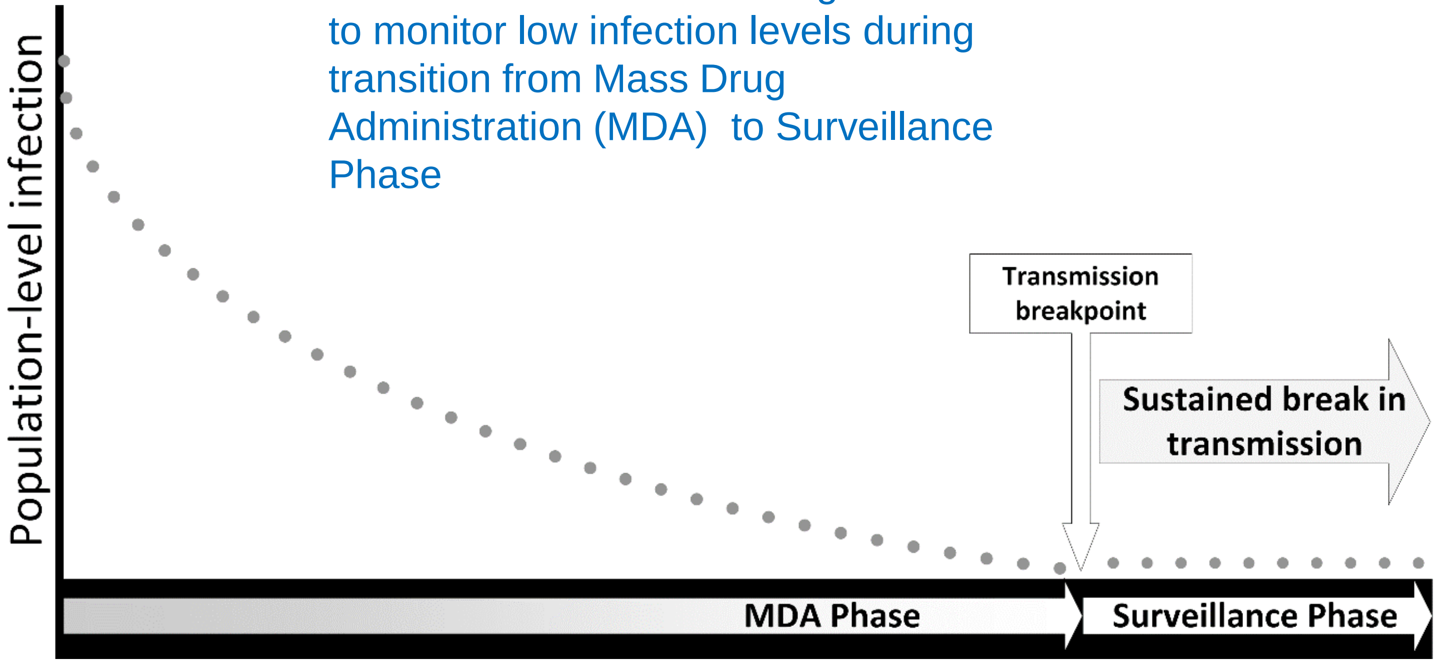
Soil Transmitted Helminth (STH) infections



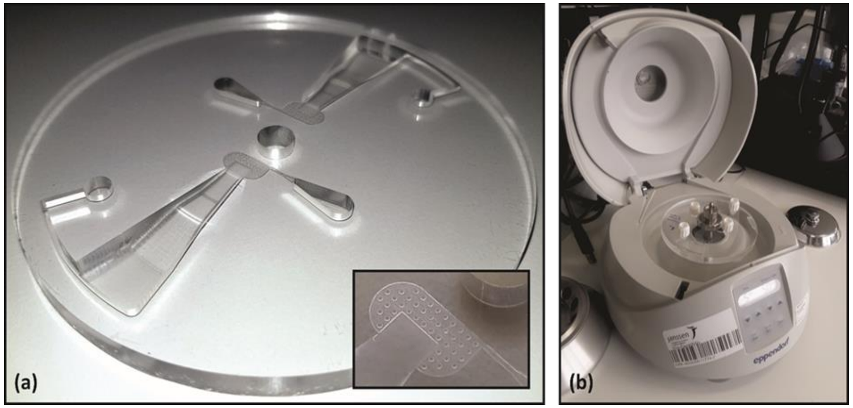
Neglected Tropical Disease (NTD) affecting 1,5 billion people worldwide

Control of STH infections

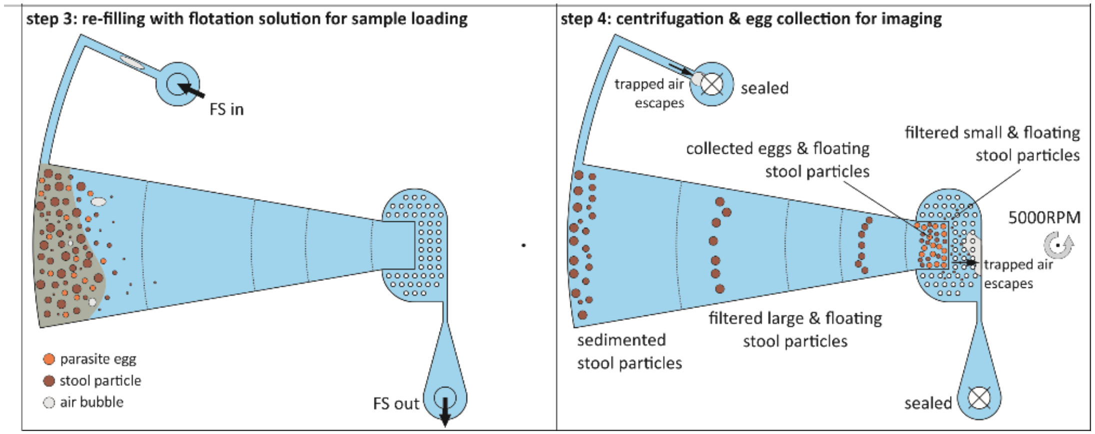
Need for more sensitive diagnostics to monitor low infection levels during transition from Mass Drug Administration (MDA) to Surveillance Phase



Single Image Parasite Quantification (SIMPAQ)

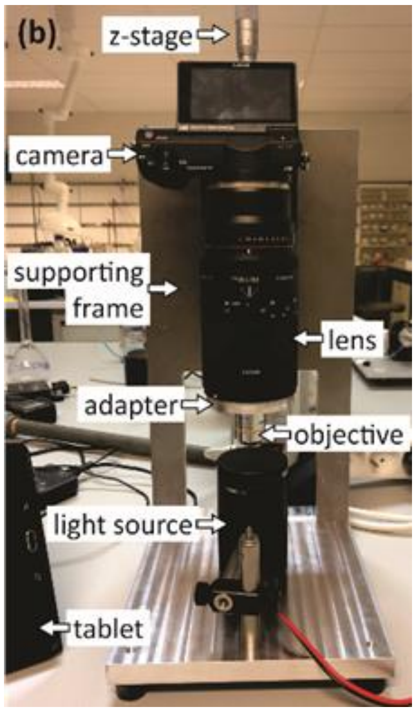


Lab-on-a-disc device using centrifugal forces to drive parasite eggs in flotation solution of stool to Field of View (FOV)

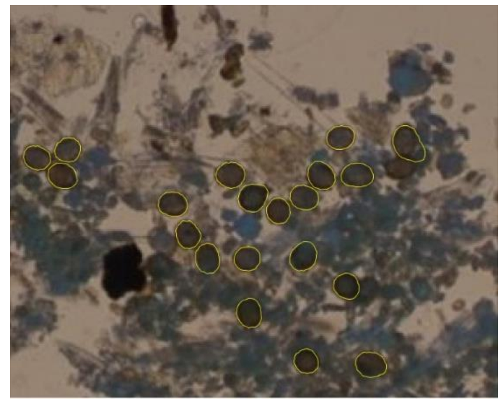


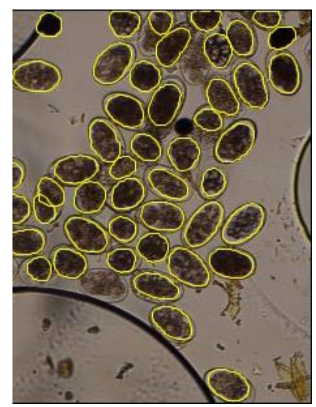
Sukas, S., Van Dorst, B., Kryj, A., Lagatie, O., De Malsche, W., Stuyver, L.J. (2019) Development of a Lab-on-a-Disk Platform with Digital Imaging for Identification and Counting of Parasite Eggs in Human and Animal Stool. *Micromachines*, *10*, 852.,

Single Image Parasite Quantification (SIMPAQ)

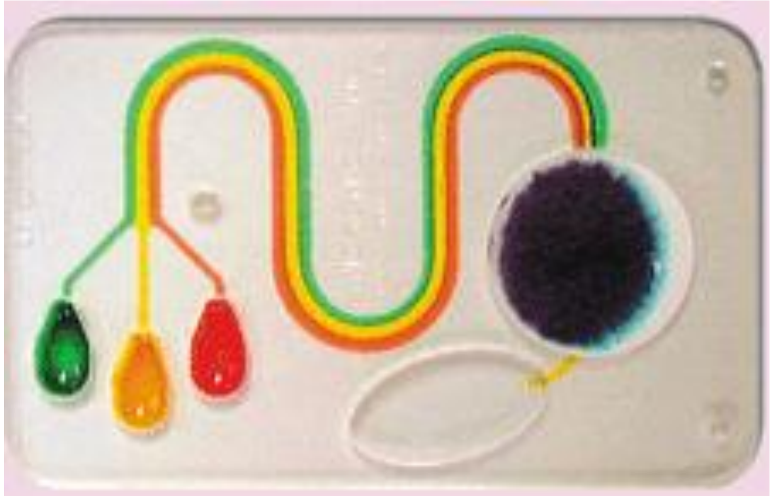


Test result captured in one picture for visual and/or automated analysis



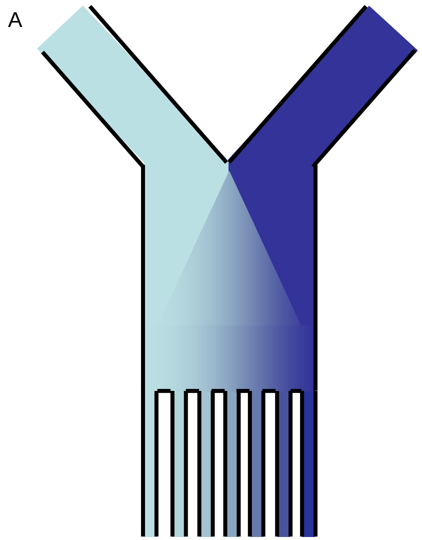


Laminar flow platforms

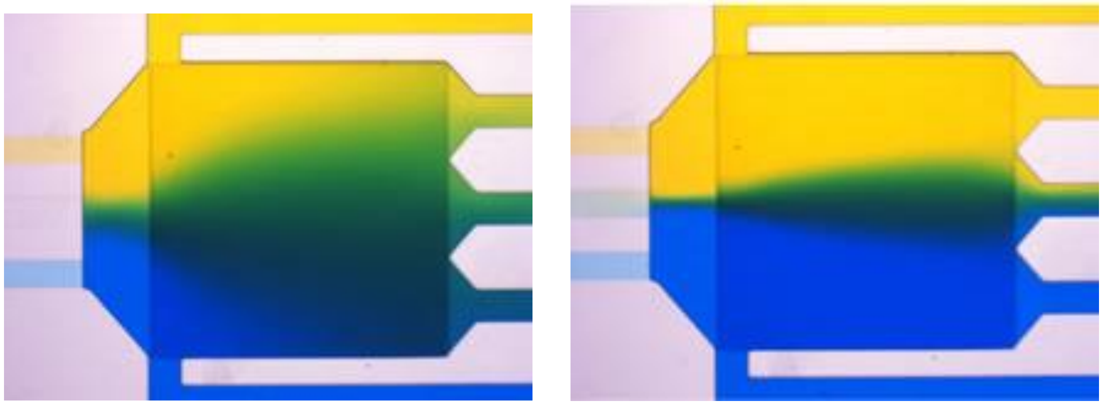


- Continuous flow microfluidic platforms
- Well-defined, deterministic flow
- Highly predictable and controlled flow
- Poor mixing efficiency
- Molecular transport solely based on diffusion

Laminar flow platforms – gradient generation



Courtesy Dr. van Uitert



www.cellasic.com

Applications

- **Cell biology**: Cells are not only responsive to the presence of certain substances but also to gradients thereof (chemotaxis).
- **Drug screening assays**: The effect of drugs is concentration-dependent and the effect of a drug must be studied for a range of concentrations.

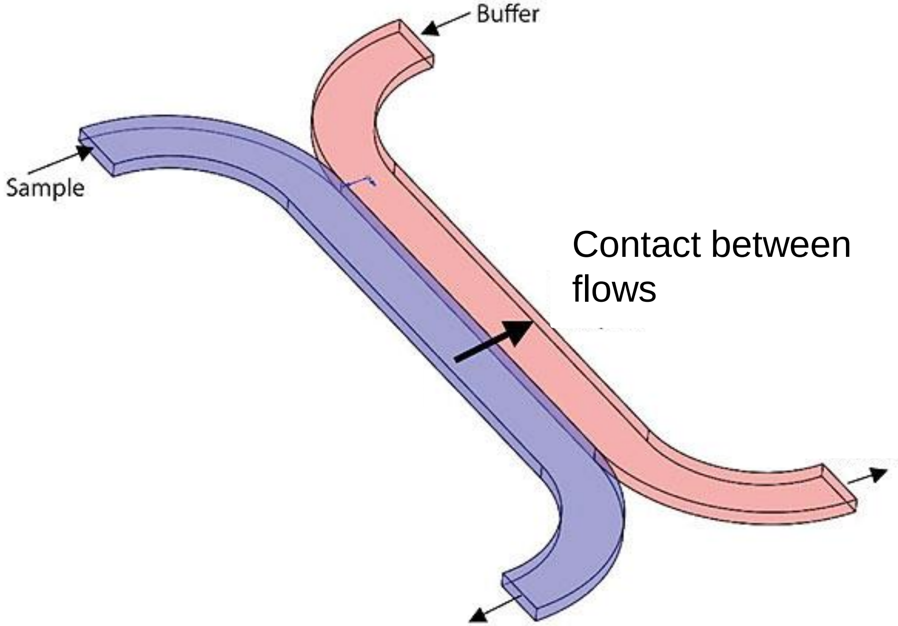
Laminar flow platforms

- **H-filter (sample purification)**

- What happens if my sample input contains both large and small molecules?

Small molecules; D = 10^{-9} m^2/s
t = 1 s ⇨ d_{diff} = 45 µm
2 s ⇨ 63 µm
5 s ⇨ 100 µm

Large molecules (proteins); D = 10^{-11} m^2/s
t = 1 s ⇨ d_{diff} = 4.5 µm
2 s ⇨ 6.3 µm
5 s ⇨ 10.0 µm



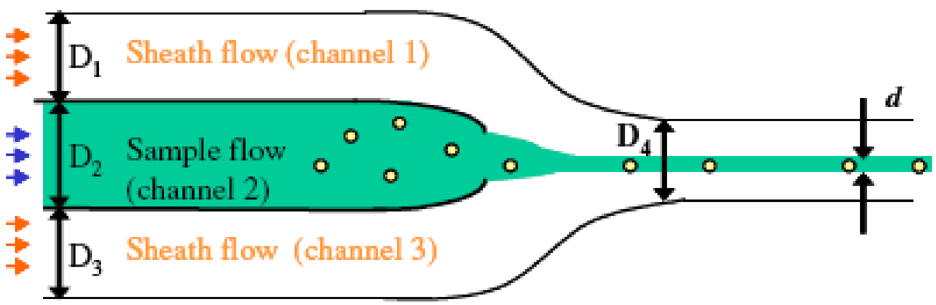
⇨ Removal of small particles and concentration of large particles

Yager et al., Nature, 2006

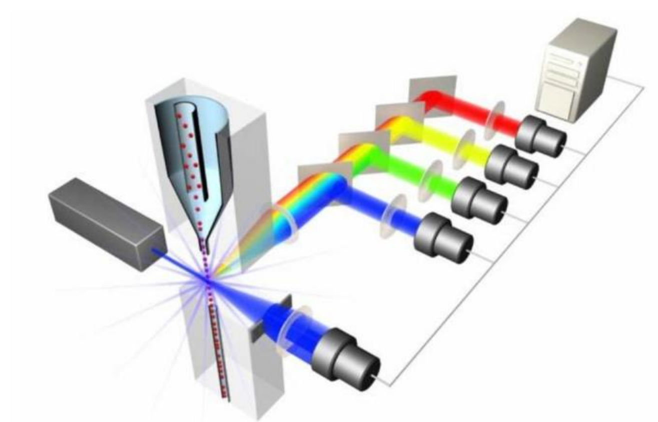
Laminar flow platforms

- **Flow focusing – gel polymerisation**

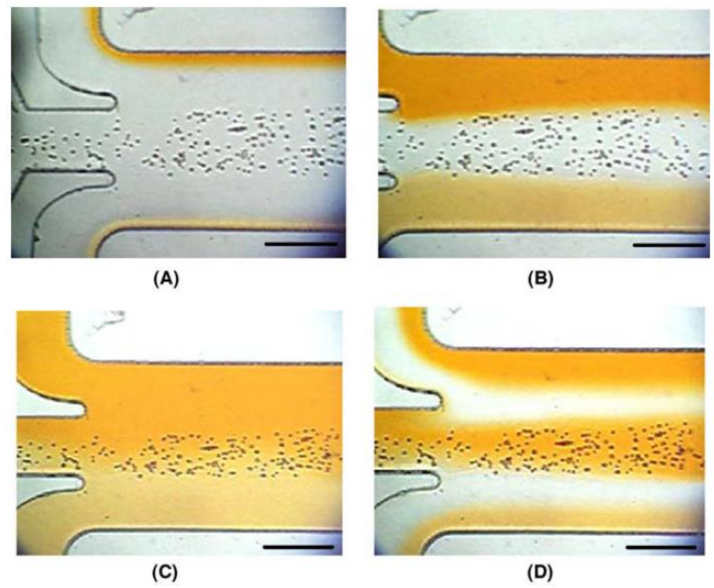
1. Hydrodynamic focusing

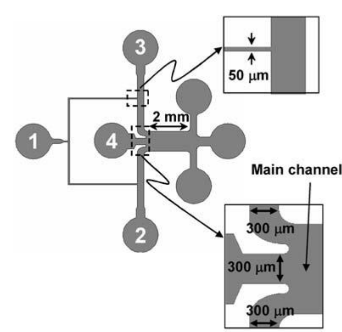


- Essential for cell analysis using flow cytometry
- 1 cell at a time in the flow
- Cell detection and analysis with a laser



2. Gel polymerisation in a channel



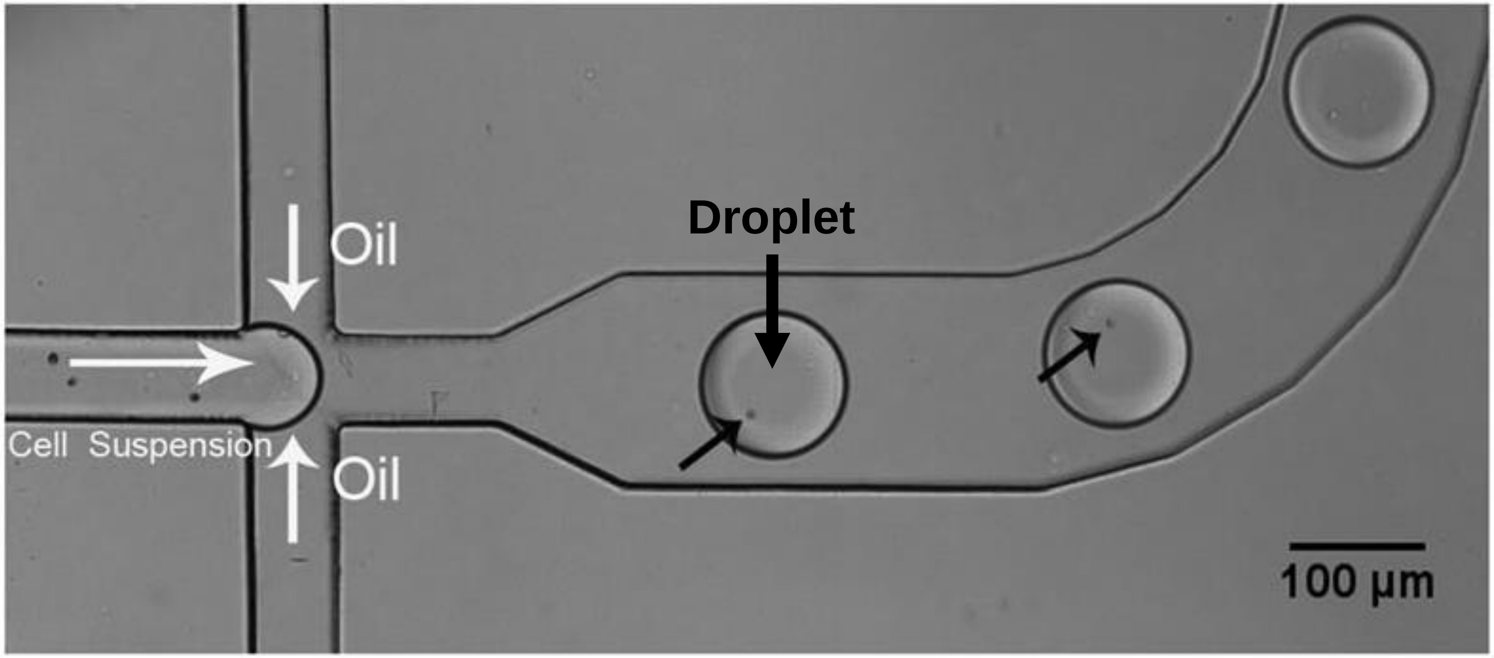


In situ polymerisation of a hydrogel for cell culture in a microdevice

Kim et al., 2007

Droplet microfluidics

Principle: Creation of aqueous droplets (fL-nL) in a continuous oil phase (or vice/versa*)



Motivations:

- **Material sciences**: creation of a well defined emulsion ⇨ particle synthesis with a narrow size distribution
- **Chemical & life sciences**: creation of smaller microreactors; higher reaction confinement; eventually single molecule reaction

Baroud et al., Lab Chip, 2010; Shui et al., Lab Chip, 2008.

Droplet microfluidic: generation

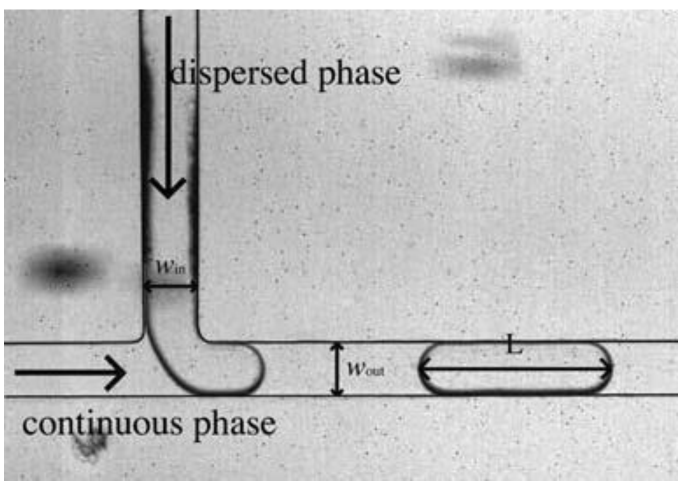
Capillary number

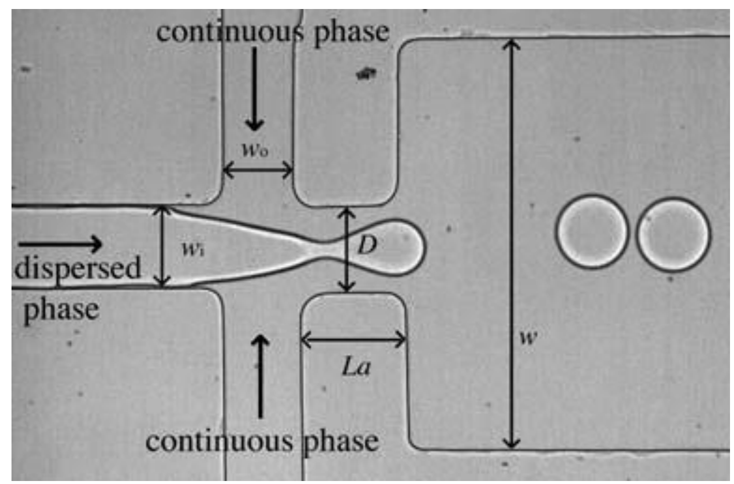
$$Ca = \frac{\mu v}{\gamma}$$

μ viscosity of the fluid (cP or kg/m.s or Pa.s)
v average flow velocity (m/s)
γ surface tension (N/m)

- Dimensionless number
- Ratio between the viscous forces and the interfacial forces

Droplet formation ⬄ interfacial forces dominant, so low Ca

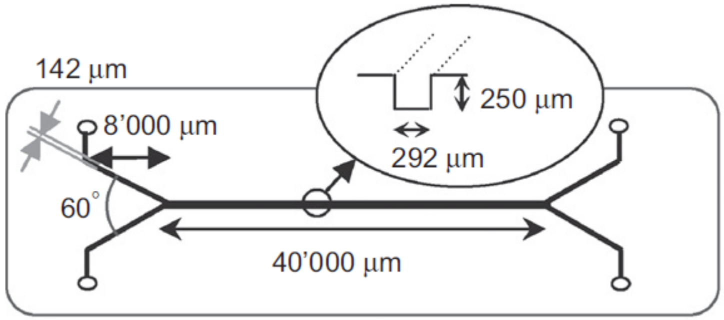


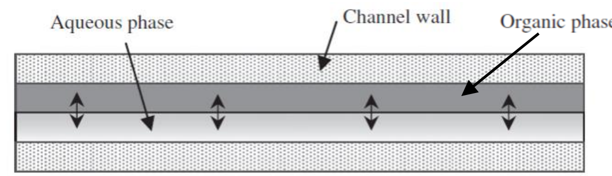


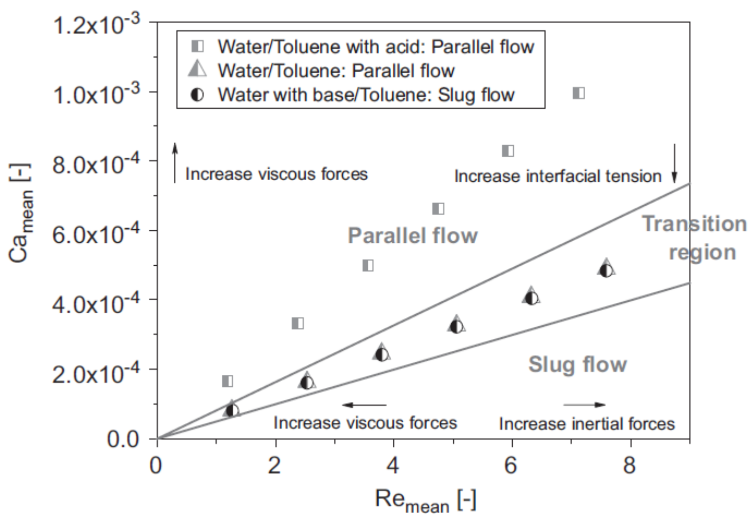
- Deviation in size distribution < 1-3% !!!!
- Addition of surfactants in the aqueous phase for droplet stabilization

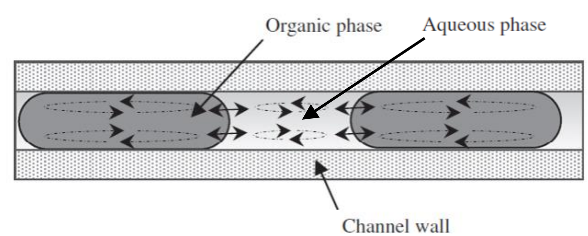
Parallel versus segmented flow

$$Ca = \frac{\mu v}{\gamma}$$







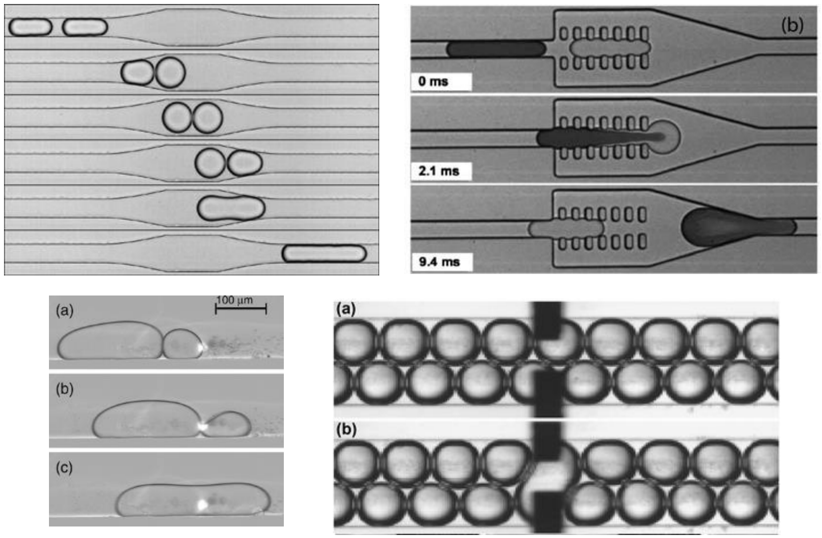


$$Re = \frac{\rho v l}{\mu}$$

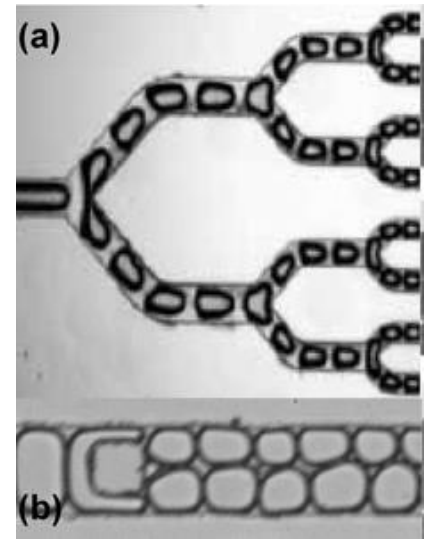
Anne-Laure Dessimoz, Laurent Cavin, Albert Renken, Lioubov Kiwi-Minsker, Chemical Engineering Science 63 (2008), 4035-4044.

Droplet microfluidic: the toolbox

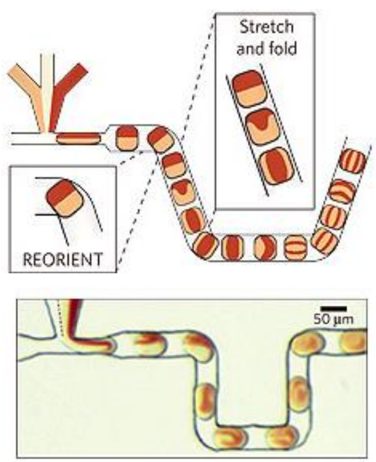
Droplet fusion



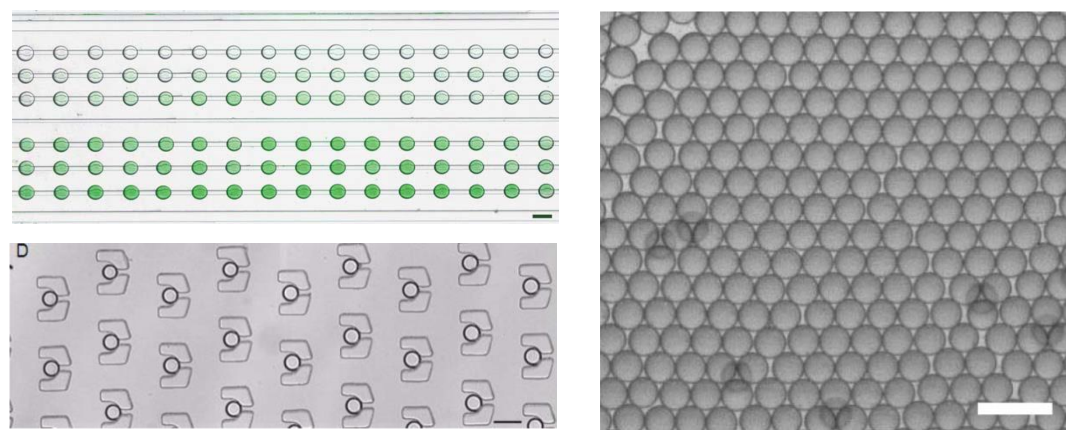
Droplet fission



Droplet mixing

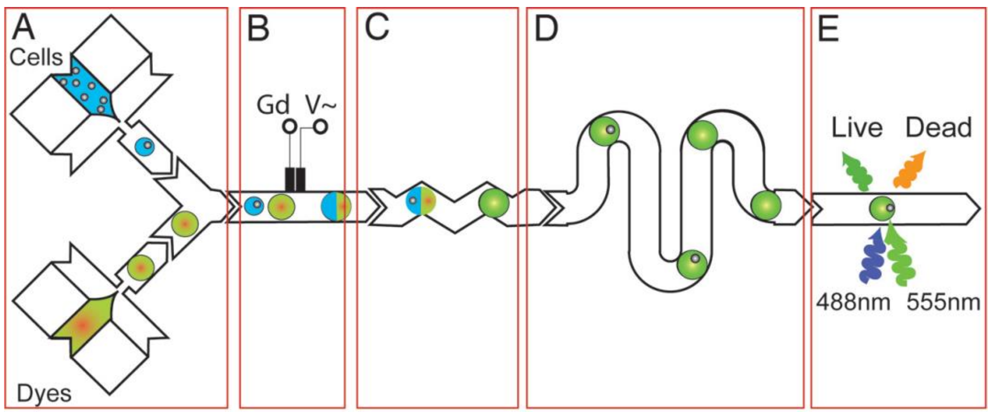


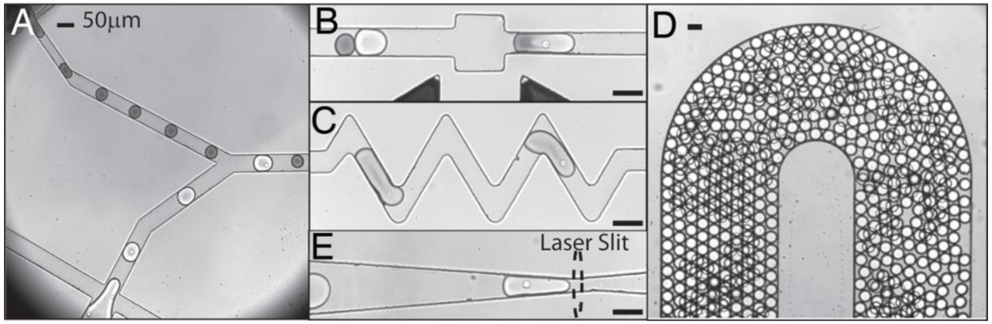
Droplet incubation - parking

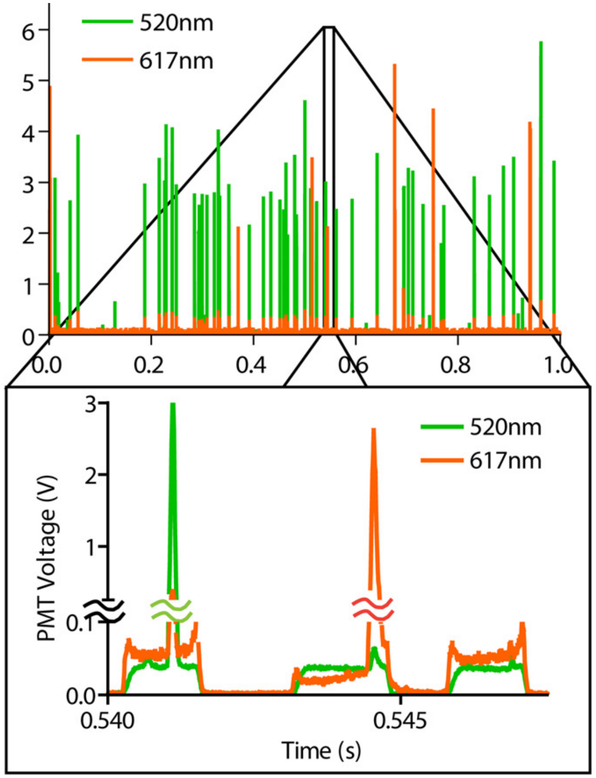


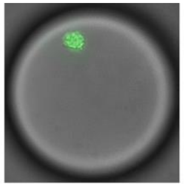
Droplet microfluidic – single cell analysis

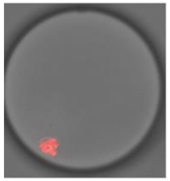
- Encapsulation of single cells in droplets: generation of 100-1000 droplets/s
- Incubation with specific drugs and on-chip read-out (live/dead assay)
- Drug-loaded droplets encoded with a dye for drug identification
- Cell viability determined with a live/dead assay (green cells viable; red cells dead)





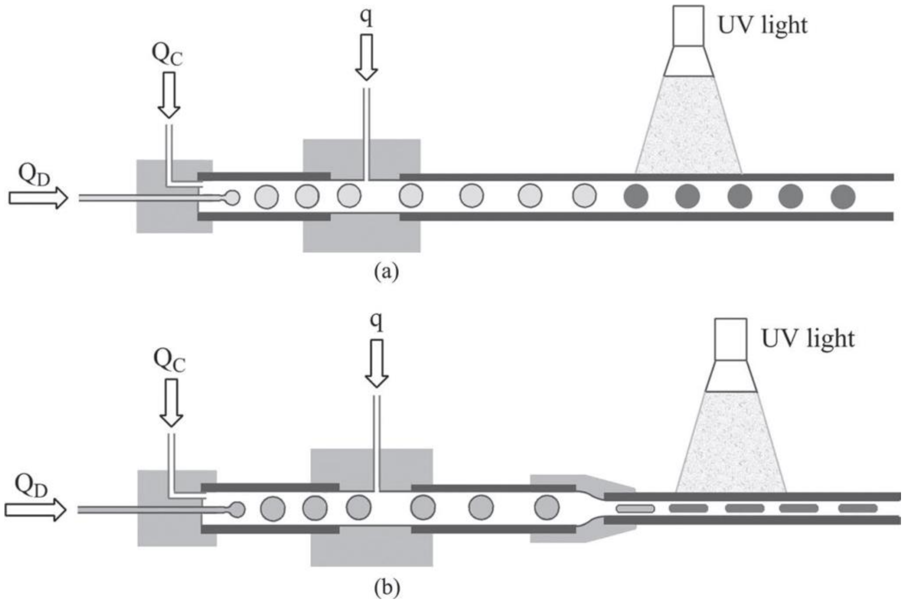






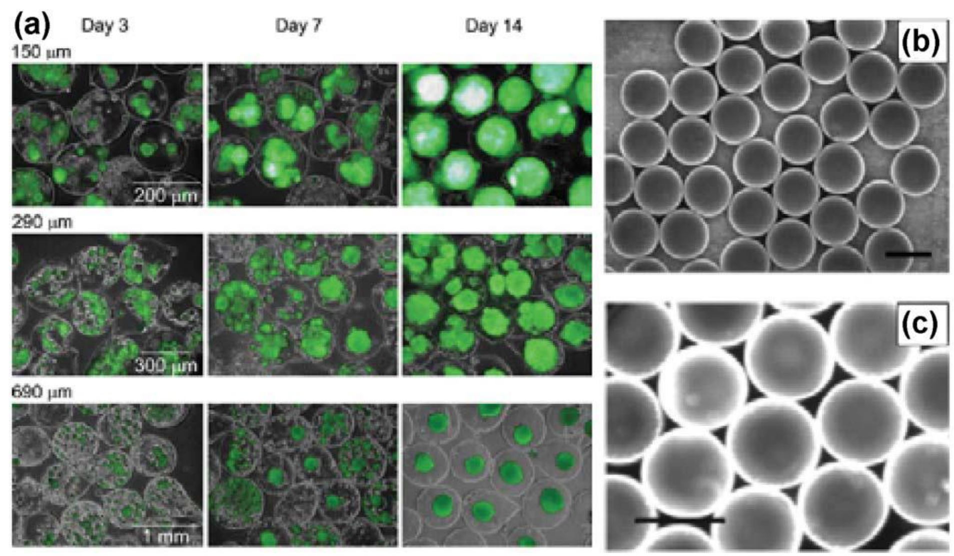
Bouzes et al., PNAS, 2009

Droplet microfluidic – particle polymerization



- Addition of polymerizing agents in the aqueous (disperse) phase
- Polymerization initiated using, e.g., UV light
- Shape of the particle dictated by fluidic structure

- Examples of hydrogel particles loaded with cells (green objects)
- Polymer nanoparticles
- Encapsulation of smaller beads in "larger" particles

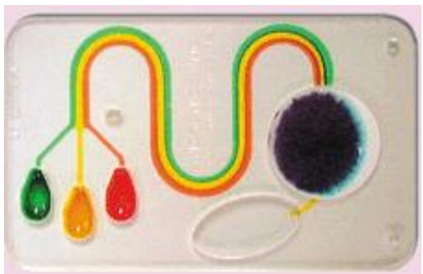


Wang et al., Small, 2011.

Teh et al., Lab Chip, 2008.

Conclusion

- **Microfluidic devices**
  - **Laminar flow** profile: deterministic behavior, highly controlled environment
  - **Reynolds number**: transition between turbulent and laminar flow



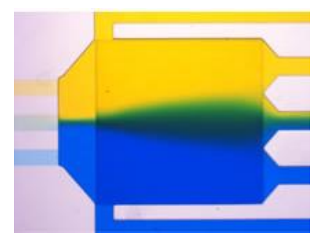
$$Re = \frac{\rho v l}{\mu}$$

ρ density of the fluid (kg/m^3)
v average flow velocity (m/s)
l characteristic length of the flow (m)
μ viscosity of the fluid (cP or kg/m.s or Pa.s)

  - **Diffusion**: important phenomenon at the microscale
  - **Mixing** depending upon diffusion under a laminar flow configuration

$$t = \frac{L^2}{2D}$$

t diffusion time (s)
L distance traveled by diffusion (m)
D diffusion coefficient (m^2/s)



- **Pumping** liquids at the microscale: hydrodynamic, electro-osmotic, passive, centrifugal, peristaltic pumping etc..
- **Important platforms**: laminar flow (Y-shape configuration); droplet microfluidics