Introduction to Lab-On-a-Chip
--- Introduction of basic concepts ---

實驗室晶片導論
--- 基礎概念簡介 ---

王安邦

Prof. Dr.-Ing. An-Bang Wang,

國立臺灣大學 應用力學研究所

Institute of Applied Mechanics, National Taiwan University

Syllabus

- ***What & Why Lab-on-a-chip (LOC)?***
- ***Application examples and LOC platforms***
- ***Components in LOC***
- ***Term-project assignment***

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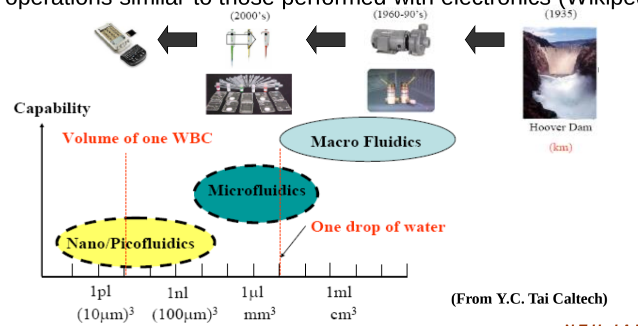
From Fluidics to Microfluidics

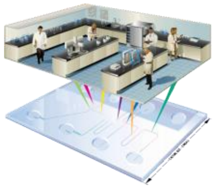
Fluidics (fluidic logic) is the use of a fluid to perform analog or digital operations similar to those performed with electronics (Wikipedia)



(From Y.C. Tai Caltech)

What are LOAC & μ-fluidics?

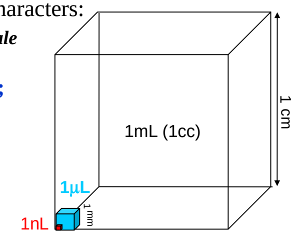
- ***There are different names used in the literature: μ-fluidic, MEMS-fluidics, μ-TAS, BioMEMS, biochip, LOAC, nanofluidics, nanoflows… etc.***
- ***μ-fluidic*** is the study of flows, which are circulating in artificial *μ*-systems. (Patrick Tabeling)
- ***μ-TAS***: **M**icro **T**otal **A**nalysis **S**ystems



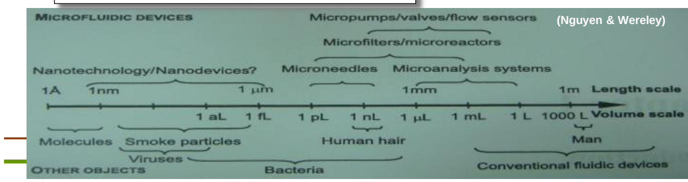
- ***LOAC (or LOC):*** combining different operations, which are originally performed in laboratories, in a single microdevice. (Berthier & Silberzan)

What is Microfluidics (LOAC)?

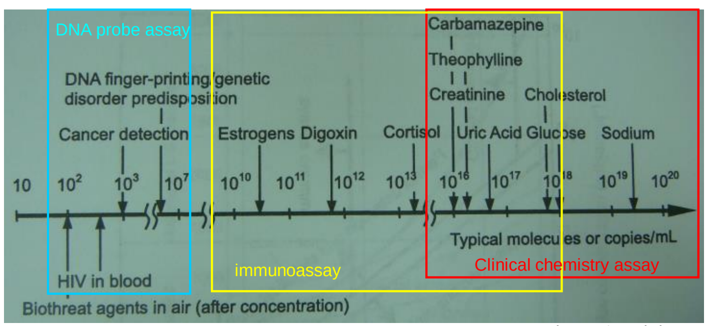
- ***Micro*** is the ***key*** and has at least one of the characters:
  - small size (not the ***overall size*** but the ***length scale*** that determine the flow behavior)
  - **small volumes (μL; nL; pL; fL (femto-); aL (atto-))**
  - low energy consumption
  - effects in the micro-domain...



- 1 L = (10 cm)^3
- **1 cc = (1 cm)^3** = 1 mL =10^{-3} L
- 1 fL or 1aL is still far away from molecular level



Concentration of diagnosis samples



(Nguyen & Wereley)

Why LOC (μ-fluidics)?

About 70% of the Earth is covered with water, and 97% of that is the salty oceans.

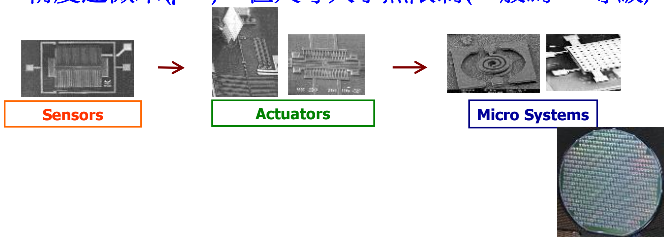
The human body is 72% saline (salt) water.

Wikipedia: A significant fraction of the human body is water. This **body water** is distributed in different compartments in the body. Lean muscle tissue contains about 75% water. Blood contains 83% water, body fat contains 25% water and bone has 22% water.

- **Why do we study LOAC (or μ-fluidic)?**
- **Do we have a clear purpose?**
- **What do we still need?**

MST & MEMS

- *MST*: **Micro-System-Technology**
- *MEMS: Micro-Electro-Mechanical System*
  精度達微米(μm)，但尺寸大小無限制(一般為cm等級)



Development of μ-systems

- Concept of microsystems (MEMS or MST): 1980s. (Applications in accelerometers, pedometer, printerhead, μ-mirrors …etc.)
- μ-TAS (bioMEMS, LOAC, μ-fluidics): 1990s (Applications in chemistry and biomedical field… etc.)

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Microfludic Platform @ AB WANG's Lab

Microfluidic components

- Microvalve — Patent
- Microflowmeter — Patent
- Micropump — Patent; HIWIN Golden AWARD + NTD $1,000,000
- Micromixer — Patent
- Microdistributor/ coater — Patents

(1 USD ~ 30 NTD)

Integrated microfluidic systems & Applications

- **Micro-squential control system** — FineTek 1st prize AWARD + NTD $200,000
- **Micro-liter POCT analysis system** — Patent
- Long-period Drug-delivery & Monitoring System — (On going project)
- Micro- reactor / emulsion system for novel materials — (On going project)
- Biomedical μm/nm 3D Printing system — (On going project)
- Compact Pattern Coating System — Patents; ChiMei 1st prize AWARD + NTD $1,000,000
- On-line Coating Film Measuring System — HIWIN Bronze AWARD + NTD $600,000
- **Compact Desktop Coating System** — HIWIN Golden AWARD + NTD $1,000,000; SpinTech Top AWARD + NTD $150,000

What is a microfluidic platform?

It's a toolbox …

- containing a reduced number of building blocks
- for a dedicated set of microfluidic operations
- that can easily be combined
- within a well defined (low cost) fabrication technology

The platform concept is not new …

- type setting in book printing ("Gutenberg bible")
- computer industry
- automotive industry

(Zengerle & Haeberle)

What is a microfluidic platform?

Microfluidic Operations in Lab-on-a-Chip field	Fabrication Technology
• fluid transport • fluid metering • fluid valving • fluid mixing • separation • concentration • detection • …	validated manufacturing technology for the whole set of fluidic operations seamless integration of different fluidic operations, ideally in a monolithic way

(Zengerle & Haeberle)

About Microfluidics

- „Micro" means at least one of the following features
  - **- small volumes (μl; nl; pl; fl)**
  - - small size
  - - low energy consumption
  - - effects of the micro-domain

…

(Zengerle & Haeberle)

Respimat
(Boehringer-Ingelheim microParts)

- ~10 Mio. units/year in 2005
- ~5 μm droplets for inhaling drugs

About Microfluidics

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…

(Zengerle & Haeberle)

Drug Delivery
Inside a Tooth

About Microfluidics

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  - small size
  - **low energy consumption**
  - effects of the micro-domain
  - ...

(Zengerle & Haeberle)

Electronic Fountain Pen

About Microfluidics

- „Micro“ means at least one of the following features
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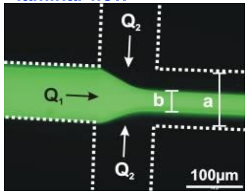
  - low energy consumption
  - **effects of the micro-domain**
    - **~ laminar flow**



hydrodynamic focusing

Science Magazine
2 July 1999

(Zengerle & Haeberle)

About Microfluidics

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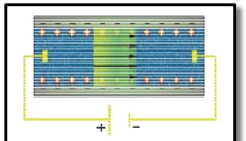
  - **effects of the micro-domain**
    - **~ laminar flow**
    - **~ surface tension**

(Zengerle & Haeberle)

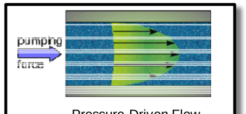
From the movie „ANTZ“ (Universal Pictures)

About Microfluidics

- „Micro“ means at least one of the following features
  - small volumes (µl; nl; pl; fl)
  - small size
  - low energy consumption
  - **effects of the micro-domain**
    - **~ laminar flow**
    - **~ surface tension**
    - ~ electrical surface charges



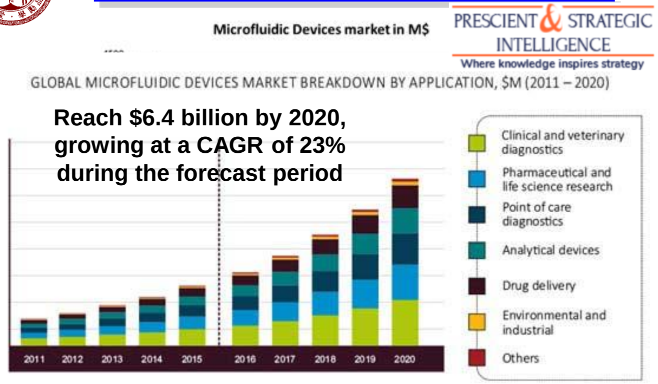
Electroosmotic (電滲) Flow



Pressure Driven Flow

(Zengerle & Haeberle)

Market of Microfluidics



Reach $6.4 billion by 2020, growing at a CAGR of 23% during the forecast period

Markets for Microfluidics

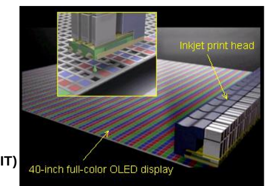
Printing

(Zengerle & Haeberle)

Markets for Microfluidics

Printing

Industrial Automation



www.epson.co.jp/e/newsroom/ news_2004_05_18.htm

Flowsensors for air conditioning (HSG-IMIT)
50.000 units in 2005

(Zengerle & Haeberle)

http://www.litrex.com/Products.htm

Markets for Microfluidics

(Zengerle & Haeberle)

Printing

Industrial Automation

Industrial Dispensers

Markets for Microfluidics

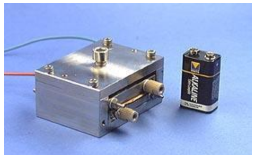
(Zengerle & Haeberle)

Printing

Industrial Automation

Industrial Dispensers

Chem. Process Engineering



Microreactor (IMM-Mainz)

Markets for Microfluidics

(Zengerle & Haeberle)

Printing

Industrial Automation

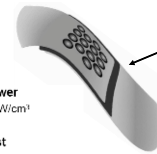
Industrial Dispensers

Chem. Process Engineering

Power Systems

Micro FuelCell, Fujitsu

myFC FuelCellSticker



Fuel Cells for Mobile Electronics

- High Power
  - 600mW/cm³
- Low Cost
  - *Less* than €1 per Watt

Markets for Microfluidics

(Zengerle & Haeberle)

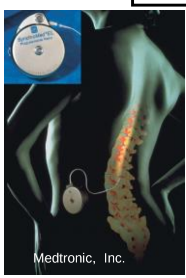
Printing

Industrial Automation

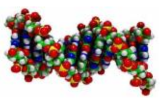
Industrial Dispensers

Chem. Process Engineering

Power Systems



Medtronic, Inc.



Life Science

Bio-Disk Vision

Identify the health status of a patient

- from one single droplet of blood
- within few minutes
- at the point of care

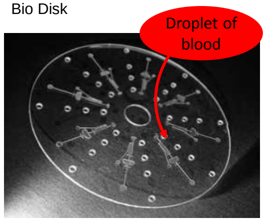
That's basically a challenge for

- Miniaturization
- Integration
- Automation

(Zengerle & Haeberle)

Bio-Disk Platform

Bio Disk



- application specific disk
- low-cost disposable

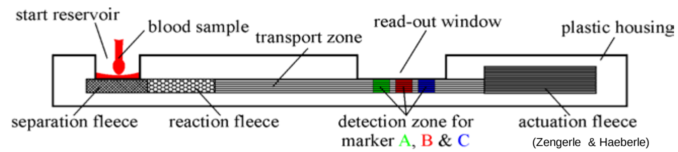
Mobile Player

- process control by frequency
- integrated detection unit

(Zengerle & Haeberle)

Examples for Microfluidic Platforms: Capillary Test Stripes

The **low-cost gold standard** the MEMS people and especially the Lab-on-a-Chip community have to compete with!



(Zengerle & Haeberle)

--- Some Issues in Microfluidic Systems

About Typical Biofluids

- Water based solutions
  - Small content of biological molecules (proteins, DNA, enzymes, ...)
  - Sometimes mixtures with glycerol (antifreeze)
  - Sometimes addition of surfactants (reduces surface tension or holds biological content in solution)
- DMSO (Dimethylsulfoxid)
  - Freezes at 18°C
  - Viscosity: 2.3 x water
  - Surface tension between water and alcohol (44 mN m^{-1})

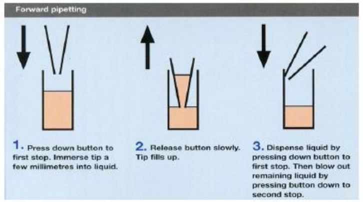
Ducrée and Zengerle

Aspiration, Dispensation & Pipetting

Dispensation =
delivery of defined volume of fluid

Aspiration =
sampling of liquid

Pipetting =
aspiration & dispensation



Ducrée and Zengerle

Manual Pipettes

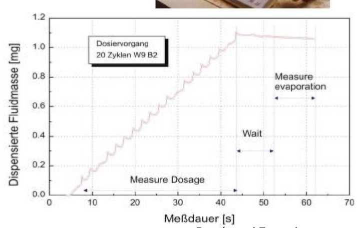
Limitations
- Capillary forces suck in more fluid than wanted
- Liquid kept back at wall of tip due to adhesive forces
- Gas volume inside tip compressible (influenced by hydrostatic pressure of liquid)

Possible improvements
- Tips containing piston reduce gas dead volume
- Physical limit:
  Volume: 200 nl
  Accuracy: 10 %

Ducrée and Zengerle

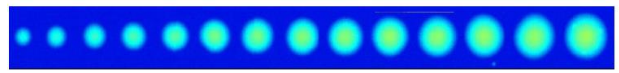
How to Measure Nanoliters?

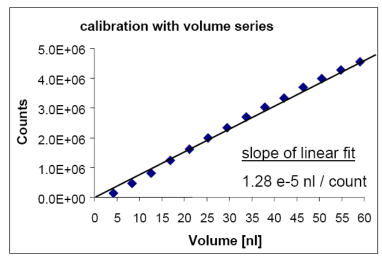
Gravimetric Measurement
- Mass corresponds to volume, for water:
  - 1 ml = 1 g
  - 1 µl = 1 mg
  - 1 nl = 1 µg
- Minimization of evaporation by high humidity atmosphere near balance
- Measurement & correction of evaporation



Ducrée and Zengerle

Calibration of Photometric Measurement





volumes dispensed with proprietary **NanoJet**-device

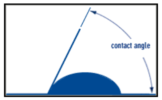
Ducrée and Zengerle

Static Contact Angle

- Three Phases: Contact angle at equilibrium

Young: $F_{SL} - F_{SV} + F_{LV}\cos\theta = 0$

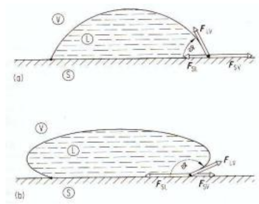
$$\Rightarrow \cos\theta = \frac{\sigma_{SV} - \sigma_{SL}}{\sigma_{LV}}$$



(Ducrée and Zengerle)

liquid	solid	θ
water	SiO_2	52.3°
water	glass	25.0°
water	Au	0.0°
water	Pt	40.0°
water	PMMA	73.7°
ethanol	glass	0.0°
mercury	glass	140.0°

(Bruus)

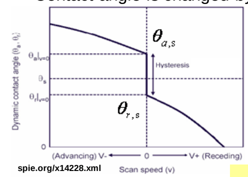


(Indizes: Vapor,Liquid,Solid)

Ducrée and Zengerle

Dynamic Contact Angle

Contact angle is changed by moving the contact line



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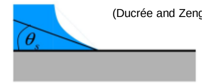
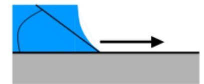
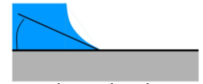
(Ducrée and Zengerle)



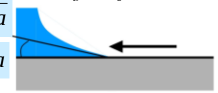
static



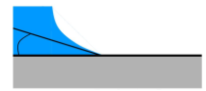
advancing $\theta_a > \theta_s$



advanced static $\theta_a > \theta_{a,s} > \theta_s$



receding $\theta_r < \theta_s$



receded static $\theta_r < \theta_{r,s} < \theta_s$

Bracke-Joos (1989): $Ca = \frac{\eta u}{\sigma}$

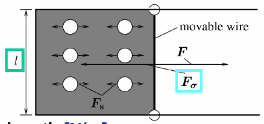
$$\cos\theta_d = \cos\theta_s - 2(1+\cos\theta_s)\sqrt{Ca}$$

Voinov & Tanner: $\theta_d^3 - \theta_s^3 = 94Ca$

$$\theta_d \approx \theta_s + \frac{94Ca}{3\theta_s^2}$$ **(for Ca <<1)**

Surface Tension & Surface Energy

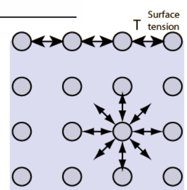
- Definition $\sigma = \frac{F_\sigma}{l}$



(Ducrée and Zengerle)

Surface tension s: Force per unit length [N/m]

- The term „tension" is bad choice (Commonly referred to as force per **area**)
- Microscopical Phenomenon relates to
  - Energy required to **transport molecule** from **bulk** to **surface** region



hyperphysics.phy-astr.gsu.edu/hbase/surten.html

- More physical definition of surface tension:

(Surface Energy): Energy needed to extend surface

$$W = F_\sigma dx = 2\sigma l\, dx$$

- **Systems always search to minimize Energy = minimize Surface/Interface (with highest Energy)**

(Ducrée and Zengerle)

Surface Tension of Liquids

substance	temperature in K	σ in 10^{-3} Nm^{-1}
helium	4	0.12
hydrogen	19	2.5
nitrogen	90	6.0
carbon dioxide	248	9.1
argon	85	13.1
ethylic ether	293	17
ethanol	293	22
petroleum	293	26
benzol	293	29
mineral oil	293	36
glycerin	293	63
mercury	298	484
tungsten	3683	2400
water	273	75.6
	293	72.5
	323	67.8
	373	58.8

(Ducrée and Zengerle)

@20°C

liquid	γ [mJ/m^2]
water	72.9
mercury	486.5
benzene	28.9
methanol	22.5
ethanol	23.0
glycerol	63.0
blood	~60.0

(Bruus)

(Ducrée and Zengerle)

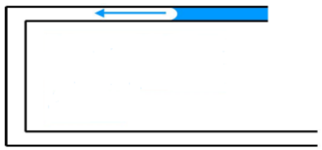
Capillaries without gravity – self filling

- Steady state:

Viscous Pressure loss =

Capillary Pressure

$$\frac{8\eta}{R^2}x(t)u(t)+\frac{2\sigma}{R}\cos\theta=0$$



Differential Equation:

$$\frac{dx}{dt}=-\frac{1}{x(t)}\frac{R\sigma\cos\theta}{4\eta}$$

Boundary Condition:

$$x(0)=x_0$$

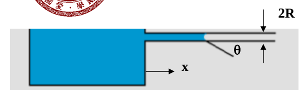
Solution:

$$x(t)=\sqrt{\frac{1}{2}\frac{\sigma\cos\theta R}{\eta}t+x_0}$$

$$u(t)=\frac{\sigma\cos\theta R}{2\eta\sqrt{2\frac{\sigma\cos R}{\eta}t+x_0}}$$

(Ducrée and Zengerle)

Liquid feeding into open channel



Force equilibrium: (inertia force) = (viscous force) + (interface force)

$$\frac{d}{dt}\left(m\frac{dx}{dt}\right)=2\pi R\tau\cdot x+2\pi R\sigma\cos\theta$$

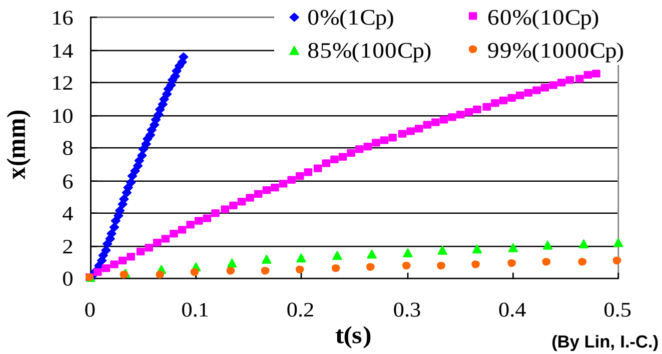
$$\frac{d}{dt}\left(x\frac{dx}{dt}\right)+\frac{8\mu\cdot x}{\rho R^2}\frac{dx}{dt}-\frac{2\sigma}{\rho R}\cos\theta=0$$

Because feeding velocity is quite small in microfluidic system, the inertia term can be neglected.

$$x=\sqrt{\frac{\sigma R\cos\theta}{2\mu}t}$$

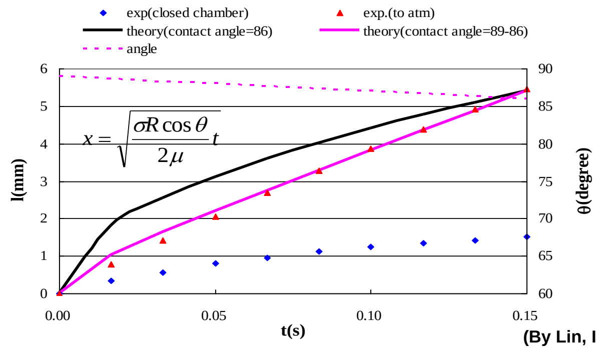
(By Lin, I.-C.)

Viscous Effect (Experiments)



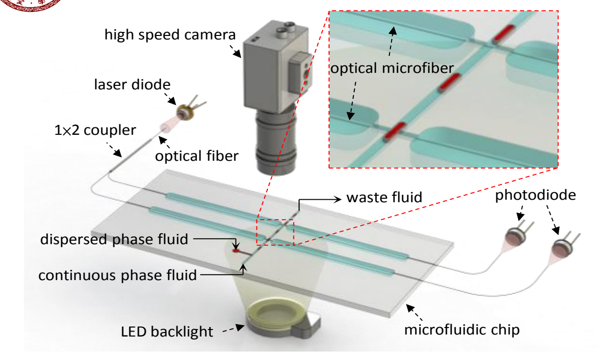
(By Lin, I.-C.)

Comparison Results



(By Lin, I.-C.)

Sample Properties Measurement (I)

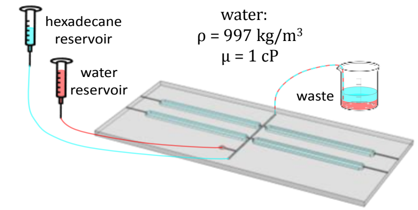


Sensors and Actuators –B: Chemical, 222 pp. 721–727, 2016

Sample Properties Measurement (II)

Hexadecane:
$\rho = 770$ kg/m^3
$\mu = 3$ cP

Gravity-Actuated Two-Phase-Flow Generation



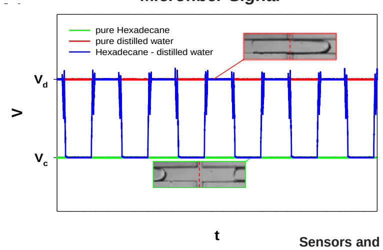
$$\Delta P = RQ \text{ (Hagen–Poiseuille equation)}$$

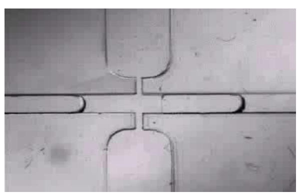
$$\rho g h = \frac{128\mu L}{\pi d^4} Q$$

$$h \propto \frac{\mu}{\rho} \Rightarrow h_{hexadecane} \sim 3.88 h_{water}$$

Sample Properties Measurement (III)

Microfiber Signal

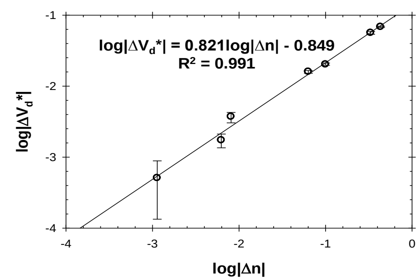




Sensors and Actuators –B: Chemical, 222 pp. 721–727, 2016

The amplitude of the square-wave-like signal reveals the refractive index difference between the droplet and the carrier fluid.

Test Results of Different Fluids

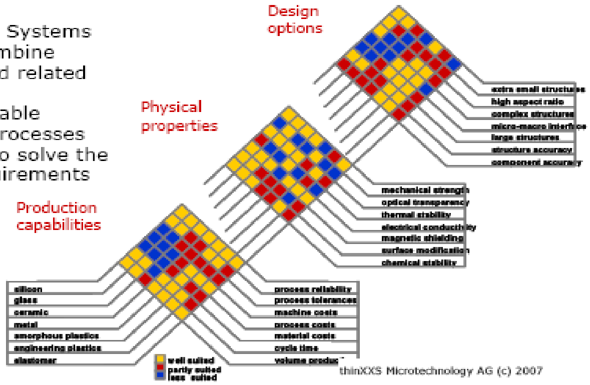


The resolution for refractive index measurement reached around 0.001.

Sensors and Actuators –B: Chemical, 222 pp. 721–727, 2016

Choice of Materials

Hybrid Micro Systems (HMS) to combine materials and related components made by reliable production processes best suited to solve the product requirements

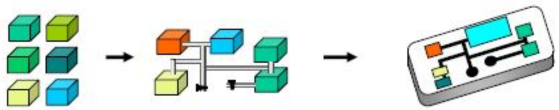


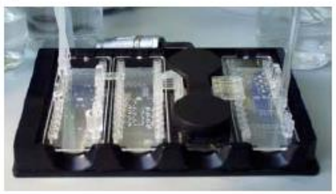
thinXXS Microtechnology AG (c) 2007

Syllabus

- What & Why Lab-on-a-chip (LOC)?
- Application examples and LOC platforms
- ***Components in LOC***
- Term-project assignment

Concept of Microfluidic Module (I)



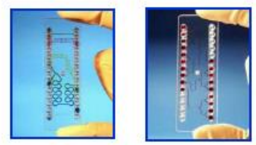


thinXXS Microtechnology AG (c) 2007

Concept of Microfluidic Module (II)

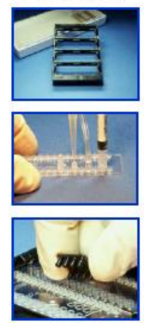
Library of standard slides:

pumping



mixing / splitting

accessories:



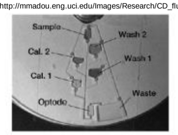
microplate-frame

thinXXS Microtechnology AG (c) 2007

Types of valve (I)

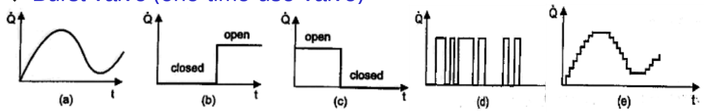
- Passive (or check) & Active valve
- Analog or Digital
  - Analog (or proportional) valve: change valve opening →change fluidic resistance →change flowrate
  - Digital (fully open or close) valve: by PWM (pulse-width modulation) or No. of valves to form the proportional flow control.
- Burst valve (one-time-use valve)

http://mmadou.eng.uci.edu/images/Research/CD_flu1.gif



Flow order: Cal. 1→Wash 1→Cal. 2→Wash 2→Sample

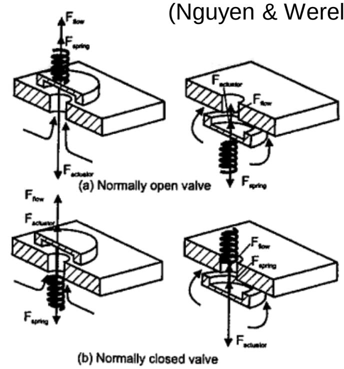
(Nguyen & Wereley)



Types of valve (II) Normally Open & Closed (NO & NC)

- Normally closed
- Normally open
- Bistable (can actively open or close; an off-state is not defined)

(Nguyen & Wereley)



Actuation principles of active valves

a) Pneumatic
b) Thermo-pneumatic
c) Thermo-mechanical
d) Piezoelectric
e) Piezoelectric
f) Electrostatic
g) Electromagnetic
h) Electrochemical
i) Chemical

Actuator
- Moving function
- Holding function
- Dynamic function

(Nguyen & Wereley)

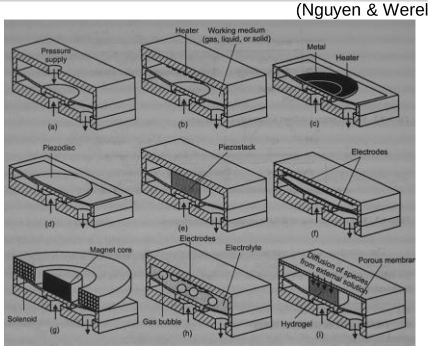
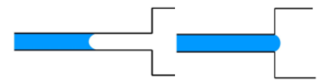
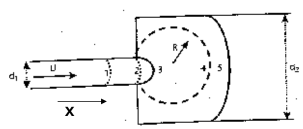


Figure 6.4 Basic actuation concepts for an active microvalve: (a) pneumatic; (b) thermopneumatic; (c) thermomechanic; (d) piezoelectric; (e) piezoelectric; (f) electrostatic; (g) electromagnetic; (h) electrochemical; and (i) chemical.

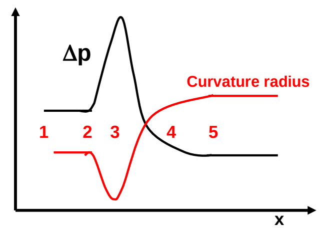
Capillary Priming: Capillary Stop

- ***Sudden channel opening*** **stops capillary flow due to suddenly decreasing capillary force by the geometry singularity**
- Usage: Control of capillary priming
- Problem: Stop is unstable!



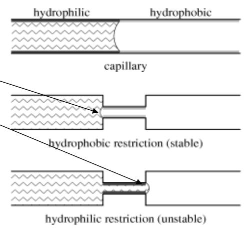


$$\Delta p = \frac{2\sigma}{r}\cos\theta$$



Hydrophobic Barrier in Microchannel

- Effect of Constriction Material
  - ➢Hydrophobic: stable
  - ➢ Hydrophilic: unstable



Round channel

$$\Delta p = 2\,\sigma\cos\theta\left[\frac{1}{r_1}-\frac{1}{r_2}\right]$$

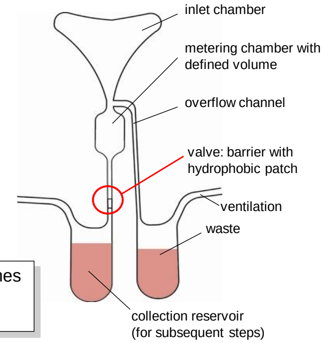
Rectangular channel

$$\Delta p = 2\,\sigma\cos\theta\left[\left(\frac{1}{w_1}+\frac{1}{h_1}\right)-\left(\frac{1}{w_2}+\frac{1}{h_2}\right)\right]$$

(Ducrée and Zengerle)

Fluidic Operations on Disk by Capillary Stop

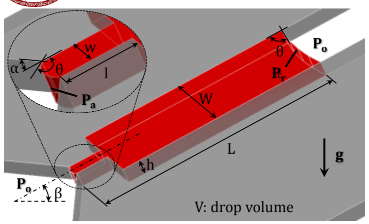
1. liquid transport
2. liquid valve
3. **liquid metering**
4. liquid switch
5. separation by density
6. mixing
7. detection
   - ◆ ELISA
   - ◆ FIA



metering of volumes down to 5 nL demonstrated

(Zengerle & Haeberle)

Capillary-Gravitational Valve



(Wang et al., *Sensor Actuat. B-Chem.*, 2016)

$$\Delta P_a = P_o - P_a = 2\sigma\left[\frac{\cos(\theta_c+\alpha)}{w}+\frac{\cos\theta_c}{h}\right]$$

$$\Delta P_r = P_r - P_o = -2\sigma\cos\theta_c\left(\frac{1}{w}+\frac{1}{h}\right)$$

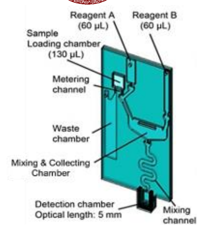
$$\Delta P_g = -\rho g L\sin\beta = \Delta P_a + \Delta P_r$$

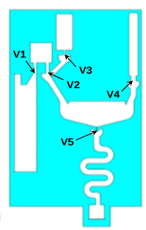
$$\text{where}\quad L = \frac{\frac{V}{h}+(W-w)l}{W}$$

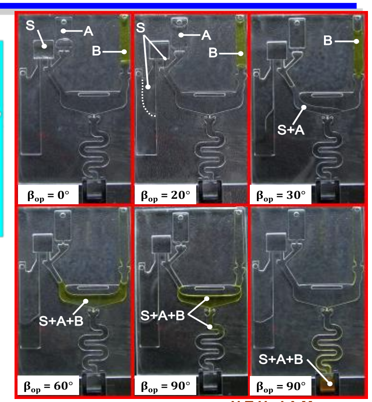
$$\beta_{op} = \sin^{-1}\left\{\frac{2\sigma W}{\rho g\left[\frac{V}{h}+(W-w)l\right]}\left[\frac{\cos\theta_c}{W}-\frac{\cos(\theta_c+\alpha)}{w}\right]\right\}$$

With an appropriate set of geometric design (α, w, W, h, and l), sequential control can be realized by simply changing β_{op}.

Sequential Control by Capillary-Gravitational Valve



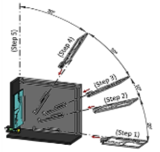




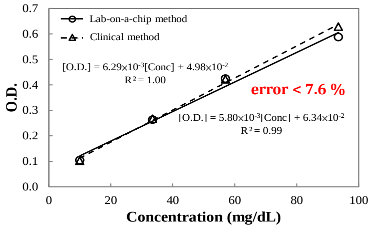
0° : load samples
20° : open V1 (S metering)
30° : open V2 & V3 (S + A)
60° : open V4 (S + A + B)
90° : open V5 (detecting)

Lab-on-a-Chip vs. Clinical Method

Lab-on-a-chip method:



Clinical method:



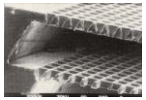
The lab-on-a-chip is suitable for point-of-care-test (error < 10%) in remote areas.

Micropumps

1. Microdisplacement Pumps
2. Electric-Field Mediated Pumping
3. Magneto-Hydrodynamic Pumping
4. Acoustic Streaming
5. Pumping by Interfacial Tension
6. Miscellaneous

Micromembrane pump (Debiotech Lausanne, CH)

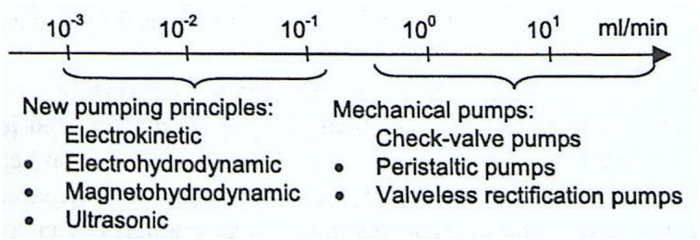
Electroosmotic Pump) (M. Ramsey, ORNL, USA)



Electrohydrodynamic Micropump (FhG-IFT, Munich)

Ducrée and Zengerle

Flow rate range of μ-pump



***Microdisplacement* Pumps (MDP)**

- Constituents
  - Pump chamber
  - Actuation
  - Flow rectifiers
    - Check valves
    - Fixed-geometry valves
    - Active valves
      - Peristaltic
      - Thermoviscous

Actuation principles
- Mechanical
- Pneumatic
- Thermomechanical
- Thermopneumatic
- Piezoelectric
- Electrostatic
- Electromagnetic
- ...

- Pumping cycle
  - Supply phase
    - Underpressure
  - Pump phase
    - Overpressure

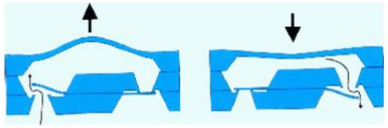
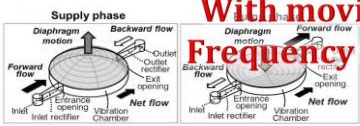


Fig. 6.1. Working principle of displacement pumps, in this case with two ch valve rectifiers (JD: ask Roland for source)

Ducrée and Zengerle

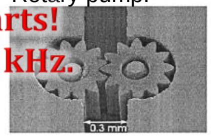
Common Microfluidic Actuators

Vibrating diaphragm:



(Wang and Hsieh., *Lab Chip.*, 2012)

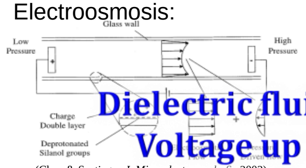
Rotary pump:



(Döpper et al., *J. Micromech. Microeng.*, 1997)

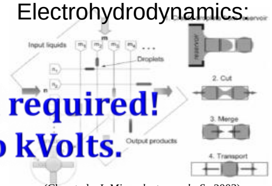
With moving parts!
Frequency up to kHz.

Electroosmosis:



(Chen & Santiago, *J. Microelectromech. S.*, 2002)

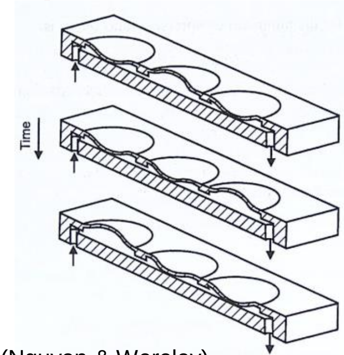
Electrohydrodynamics:



(Cho et al., *J. Microelectromech. S.*, 2003)

Dielectric fluid required!
Voltage up to kVolts.

Peristaltic Micromembrane Pump



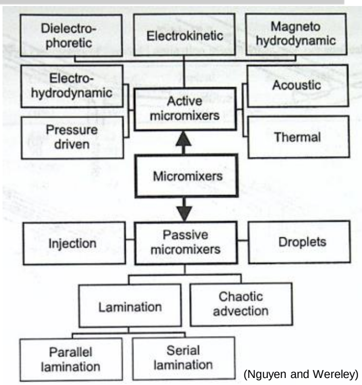
(Nguyen & Wereley)

Peristaltic(蠕動) pump:
- No rectification valves required
- Need three or more pump chambers with actuating membranes

Types of Micromixers

Passive mixing concepts:
- parallel/serial lamination
- injection
- chaotic advection
- droplet mixing

Active mixing concepts (based on disturbance types):
- pressure-driven
- temperature-induced
- electrohydrodynamic
- dieelectrophoretic
- electrokinetic
- magnetohydrodynamic
- acoustic



(Nguyen and Wereley)

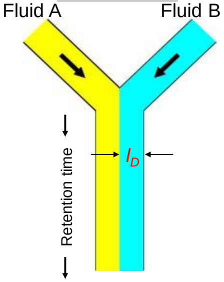
Mixing in Laminar Flow

- Mixing process is defined by flow device geometry
  - passive structures
  - control of diffusion-length (l_D)
  - fast mixing as well as defined slow mixing possible
- Well defined **retention time** in laminar flow:

$$t_r = \frac{l_{\text{channel}}}{v_{\text{mean}}}$$

  - v_{mean}: mean flow velocity
  - l_{channel}: length of channel
  - Channel length defines the time available for mixing

$$t_D = \frac{l_D^2}{D}$$



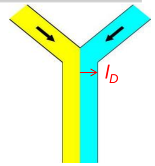
„Y-mixer“

Zengerle and Kloke

Mixing by Diffusion in Microchannels

- Diffusion length l_D: half channel width

$$t_D = \frac{l_D^2}{D}$$

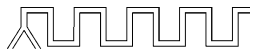


- Required channel length $l_{required}$ for diffusional mixing:

$$l_{required} \ge v_{mean} t_D = \frac{v_{mean} l_D^2}{D}$$

- Microchannel example
  - Cross-section: 200 x 200 µm
  - v_{mean}= 2.5 cm s^{-1} (flow rate = 1 µL s^{-1})
  - **$l_{required}$ = 83 cm** (D = 0.3 × 10^{-9} m^2 s^{-1})
  - → unrealistic channel length
  - ➔ reduction of diffusion length required!

Meander-channel



elongated channel with low area consumption

Zengerle and Kloke

Parallel lamination micromixer

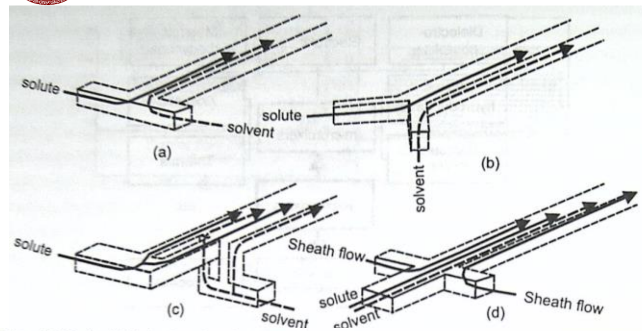


Figure 10.17 Parallel lamination micromixer: (a) T-mixer; (b) Y-mixer; (c) parallel lamination with multiple streams; and (d) hydraulic focusing.

Serial Lamination Mixer

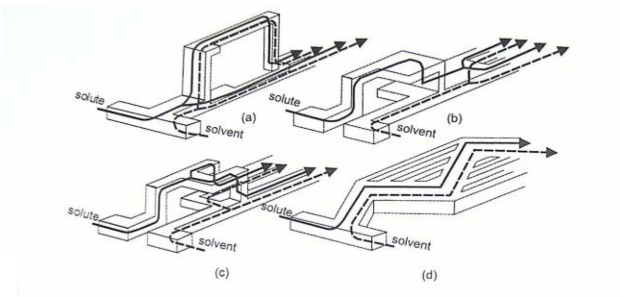
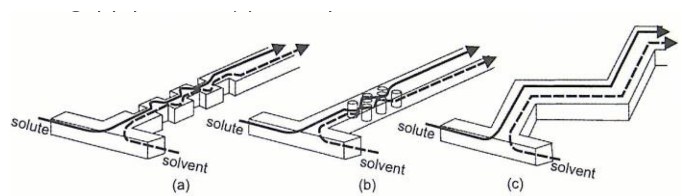


Figure 10.18 Serial lamination mixer: (a) join-split-join; (b) split-join [8]; (c) split-split-join [40]; and (d) multiple intersecting microchannels [41].

(Nguyen and Wereley)

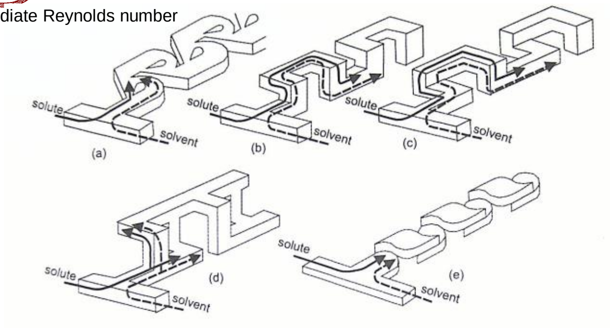
Passive Micromixers



(Nguyen and Wereley)

Passive Micromixers

@ intermediate Reynolds number



(Nguyen and Wereley)

Figure 10.20 Micromixer designs for mixing with chaotic advection at intermediate Reynolds numbers: (a) modified Tesla-structure; (b) C-shape [53]; (c) L-shape [54]; (d) connected out-of-plane L-shapes [55]; and (e) twisted microchannel [56].

Passive Micromixers

@ low Reynolds number

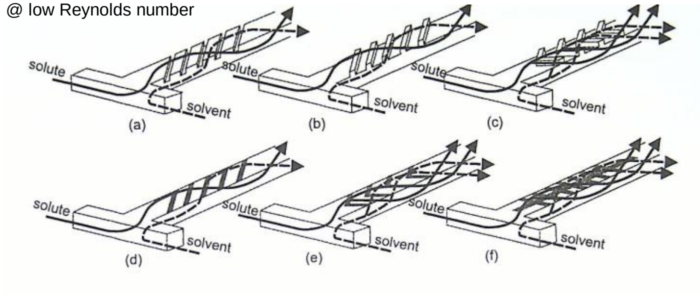
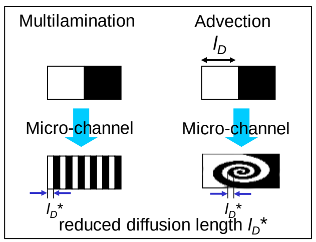


Figure 10.21 Modification of mixing channel for chaotic advection at low Reynolds numbers: (a) slanted ribs; (b) slanted grooves [61, 62]; (c) staggered-herringbone grooves [61, 62]; and (d–f) Patterns for surface modification in a micromixer with electrokinetic flows [64].

(Nguyen and Wereley)

Multilamination & Advection

- Category
  - Continuous flow & passive mixing
- **Multilamination**
  - Geometrically actuated
  - Controlled flow-fragmentation
- **Advection**
  - Hydrodynamically actuated
  - Perpendicular flow in channel
  - Laminar "stirring effect"
- Reduction of diffusion length
  - Initially: half channel width
  - Reduced thickness $l_D^* = l_D / n$
  - **→ Mixing time reduces to t_D / n^2 !!**

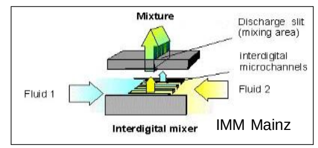


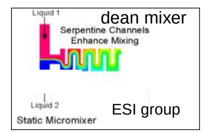
$$t_D = \frac{l_D^{2}}{D}$$

Zengerle and Kloke

Passive Continuous Mixing

- principle of down-scaling of diffusion length in microfluidics
- mixing by pure diffusion
  - $t = \frac{l^2}{D}$
- improved mixing by multilamination
  - split and recombine mixer
  - interdigital mixer
- advection
  - dean mixer
  - staggered hering bone mixer (advection at small Re)!!

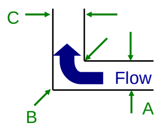




Dean Mixer

- **Advection by centrifugal forces (Dean effect)**
  - Centrifugal force in channel bend
  - Maximum force in channel center (parabolic velocity-profile)
    - inner stream is deflected to the outside
  - Deformation of interface = **Advection**
  - Effect scales with Dean number

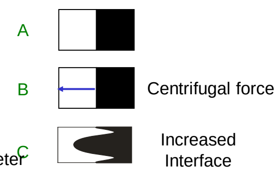
Dean- Effect



Dean number

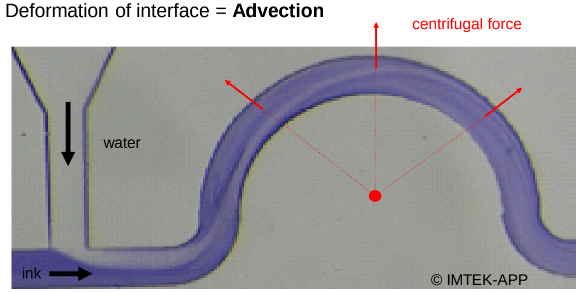
$$De = Re\sqrt{\frac{d_{hd}}{r}}$$

Re = Reynolds number
d_{hd} = hydraulic diameter
= 4 * channel cross-section / wetted perimeter
r = radius of curvature of bend

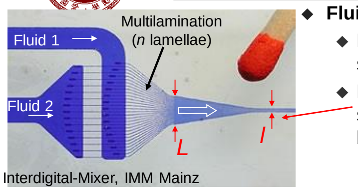


Dean Mixer

- Centrifugal force in channel bend
- Maximum force in channel center (parabolic velocity-profile)
- Deformation of interface = **Advection**



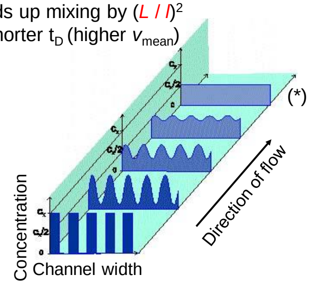
Interdigital Mixer (IMM-Mainz)



Interdigital-Mixer, IMM Mainz

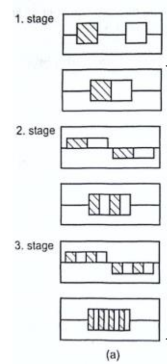
- **Fluidic phenomena used**
  - Multilamination: speeds up mixing by n^2
  - Hydodynamic focussing: speeds up mixing by $(L / l)^2$ but shorter t_D (higher v_{mean})

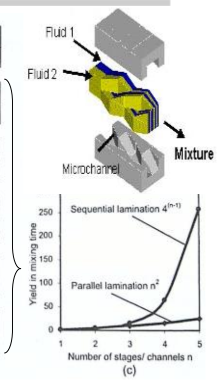
After Multilamination
- Thin lamellae in mixing-channel
- Diffusion perpendicular to direction of flow
- Homogenized concentration after certain channel length (*)



Split and Recombine

- Caterpillar Mixer (Sequential lamination mixer)
  - Fluids to be mixed introduced into the device as two parallel streams
  - By special surface shaping of channel walls, referred to as caterpillar structure, each fluid stream split into two substreams
  - Four such substreams recombined to a multi-laminated fluid system
  - Process repeated several times





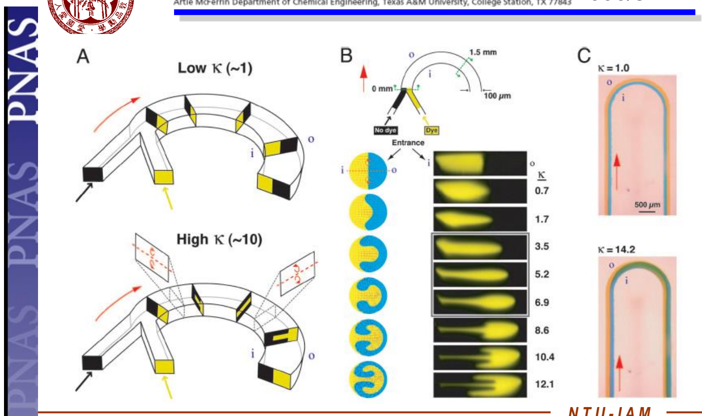
Ducrée and Zengerle (Nguyen and Wereley)

Multivortex micromixing

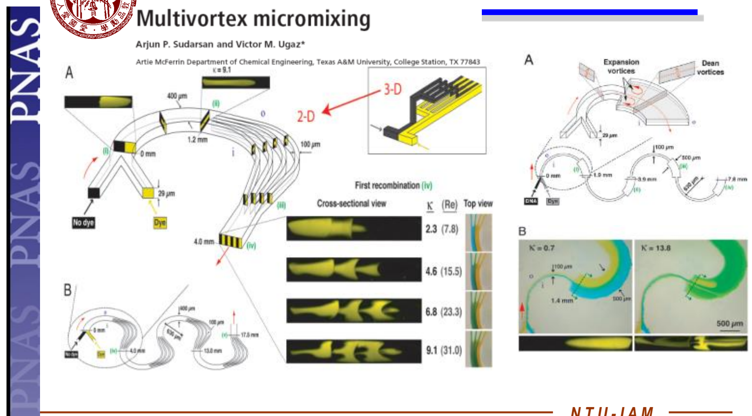
Arjun P. Sudarsan and Victor M. Ugaz*

Artie McFerrin Department of Chemical Engineering, Texas A&M University, College Station, TX 77843

2006/5



Dean +Interdigital/Expansion Mixer



Strengths and Challenges

	Strengths	*Challenges*
Interdigital Mixer	Small lamellae of uniform thickness	Two fluidic layers, high aspect ratio channels → expensive
Split and Recombine Mixer	Cascadable concept	Complex 3-dimensional structure → expensive
Dean-Mixer	Simple microchannel → cheap	High flow rates required

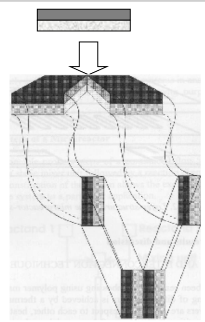
→ Every mixer has certain characteristics

→ Many different mixing principles have been presented

➔ Choose appropriate mixer for your application!

Moebius Mixer

- Two vertically stacked flows
- Flow split in horizontal plane
- Each subflow rotated by 90°
- Rejoining of flows
  - Four lamellae



Ducrée and Zengerle

Danfoss Lamination Mixer

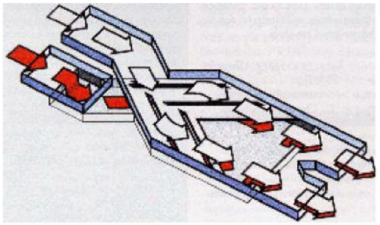


Fig. 11.10. Danfoss lamination mixer. Two broad liquid streams of small height are laminated with a large contact surface to effectuate fast diffusion. In a single-stage alignment, mixing times of 100 – 300 ms are observed, for multiple lamination in repetitive steps mixing times of a few ms are predicted (JD: ask Roland for source, Danfoss, MCM collaboration?)

Ducrée and Zengerle

Mixing by Lamination Flow & Micro-plumes

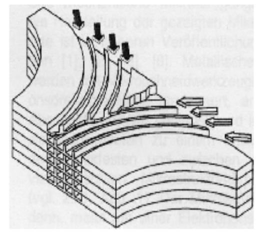


Fig. . Parallel mixer designed at FZ Karlsruhe (JD: ask Roland for details) 1

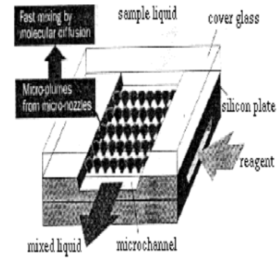


Fig. 11.12. Diffusional mixer. In a crossflow arrangement, reagent plumes enter the sample stream through micronozzles. The high surface-to-volume ratio assures rapid mixing (JD: ask Roland for source, microplumes concept demonstrated in)

Ducrée and Zengerle

Mixing by Coanda-Effect

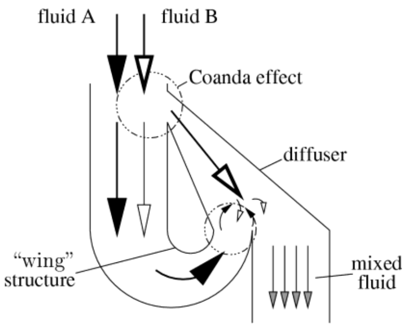
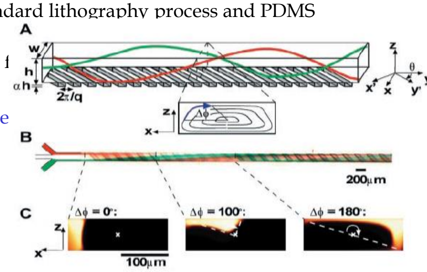


Fig. 11.16. In-plane Coanda mixer

Ducrée and Zengerle

"Staggered Hering Bone Mixer" (1)

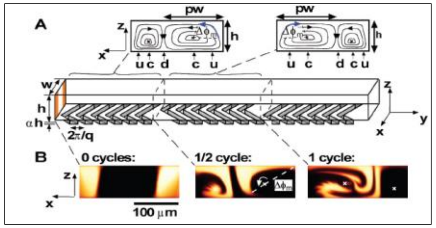
- staggered hering bone structures
  - fabricated with standard lithography process and PDMS molding
- steady pressure-driven f
- generation of vortex
- → advection at small Re
  0 < Re < 100

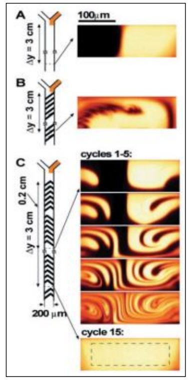


A. D. Stroock, S. K. W. Dertinger, A. Ajdari, I. Mezic, H. A. Stone, G. M. Whitesides, Science, 295, 647-651, 2005.

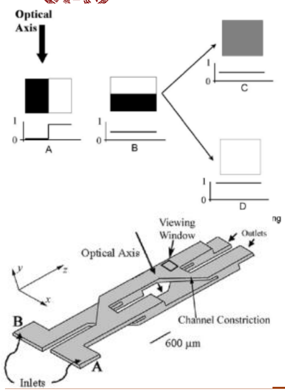
"Staggered Hering Bone Mixer" (2)

- improved mixing
  - asymmetric V-structures
  - periodically alignment of periodical structures

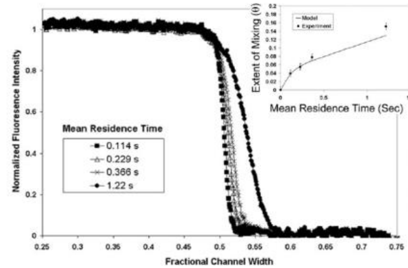




Quantification of mixing



- Munson & Yager(2004)
- pH-dependent fluorescein concept



Active Micromixers

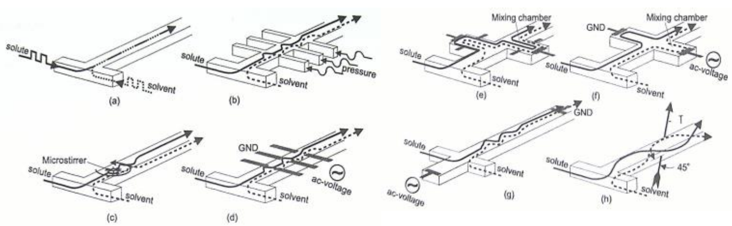


Figure 10.22 Active micromixers: (a) serial segmentation; (b) pressure disturbance along mixing channel; (c) integrated microstirrer in the mixing channel; (d) electrohydrodynamic disturbance; (e) dielectrophoretic disturbance; (f) electrokinetic disturbance in a mixing chamber; (g) electrokinetic disturbance in a mixing channel; and (h) disturbance caused by thermocapillary convection induced by a tranverse temperature gradient.

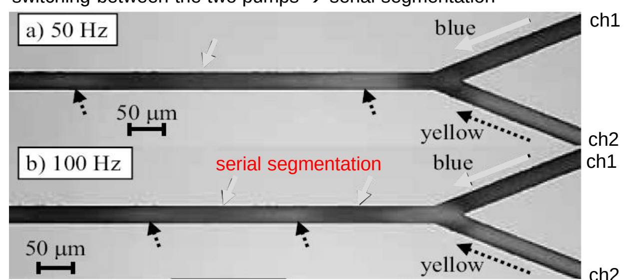
(Nguyen and Wereley)

Active Continuous Micromixer

K. Sugano et al.
Proc. of IEEE MEMS 2006, pp. 546-549, 2006.

pulsed mixing:

- two piezoelectric micropumps (ch1 & ch2)
- Y-shaped connection of channels
- switching between the two pumps → serial segmentation

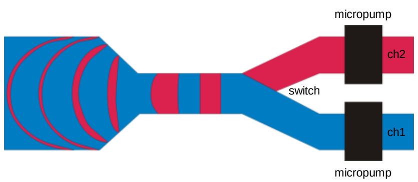


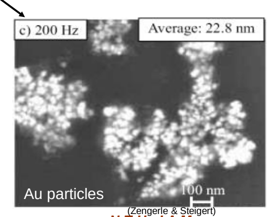
Active Continuous Micromixer

K. Sugano et al.
Proc. of IEEE MEMS 2006,
pp. 546-549, 2006.

pulsed mixing:

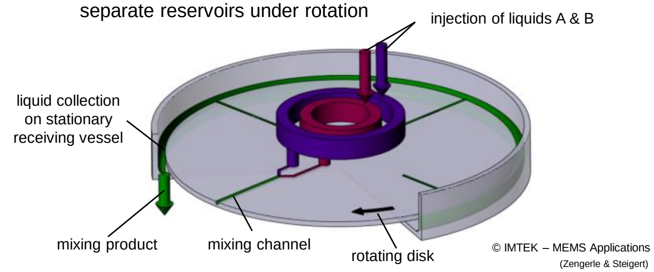
- two piezoelectric micropumps (ch1 & ch2)
- Y-shaped connection of channels
- switching between the two pumps → serial segmentation
- expansion after junction → thin vertical lamellae (taylor dispersion)
- application: production of gold nanoparticles





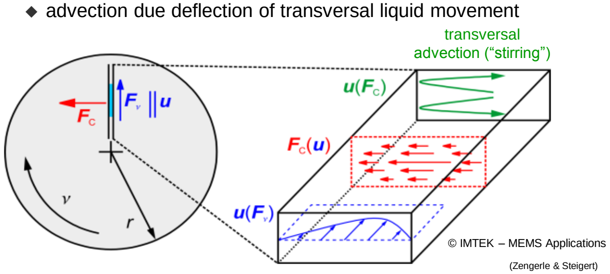
The Centrifugal Micromixer

- mixing in rotating microchannels
  - pumping *via* rotation:
    centrifugal force F_n moves liquid through radial channels
  - two liquids A & B are injected into
    separate reservoirs under rotation



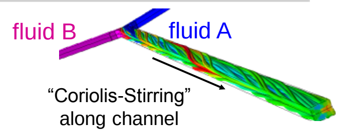
The Centrifugal Micromixer

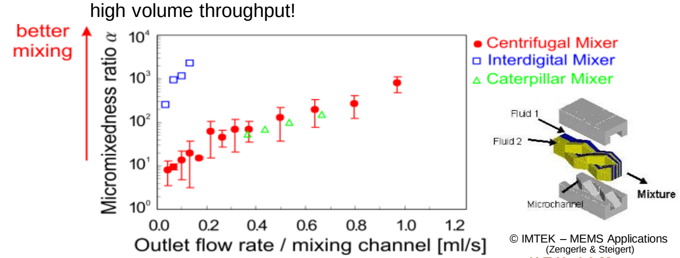
- mixing is induced by the "Coriolis-Stirring" effect
  - transversal Coriolis force F_C on flowing liquid (velocity *u*)
  - most pronounced in centre of the channel
  - advection due deflection of transversal liquid movement



The Centrifugal Micromixer

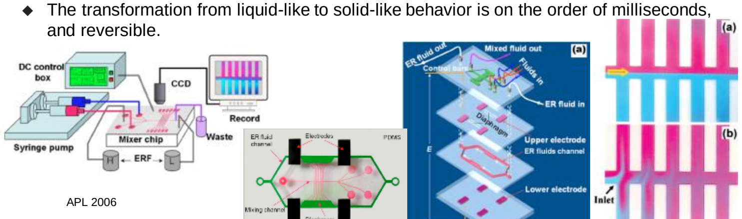
- mixing Performance
  - micromixedness ratio α
    = measure for mixing
  - high mixing quality at very
    high volume throughput!





ER/GER fluid-controlled Mixing

- Electrorheological (ER) or Giant Electrorheological (GER) fluid-controlled valves.
- ER fluids are suspensions of extremely fine non-conducting particles (up to 50 μm diameter) in an electrically insulating fluid. The apparent fluid viscosity changes by an order of up to 100,000 in response to an electric field, and back reversibly (Winslow effect), with response times on the order of ms.
- The transformation from liquid-like to solid-like behavior is on the order of milliseconds, and reversible.

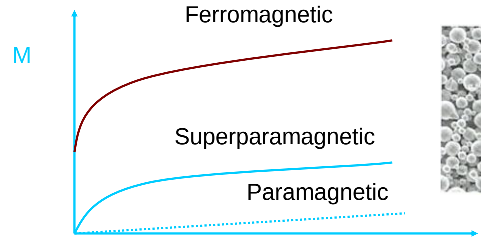


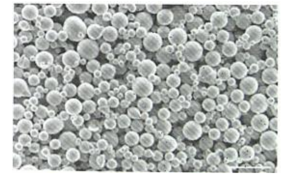
APL 2006

Xize Niu, Liyu Liu, Weijia Wen,[a] and Ping Sheng
Institute of Nano Science and Technology, Department of Physics, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China

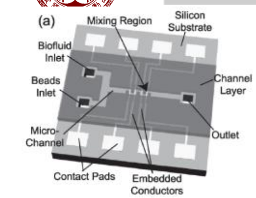
Magnetic particles

- Magnetic particles (beeds) of 50 nm to 2 mm are available
- Beads with both magnetic and fluorescent are advantageous.





Micro-mixer with magnetic beads

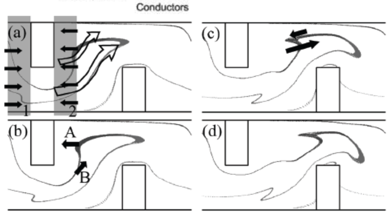


A MAGNETIC FORCE DRIVEN CHAOTIC MICRO-MIXER

Hiroaki Suzuki
Department of Mechanical Engineering, The University of Tokyo
7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

Chih-Ming Ho
Mechanical & Aerospace Engineering Department, University of California,
Los Angeles, USA 90095-1597

2002 MEMS



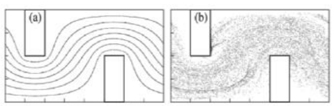


Fig. 11 Poincaré maps (a) without, (b) with perturbation.

Micro-mixer with magnetic particles

(Wang et al. 2008, Microfluid Nanofluid)

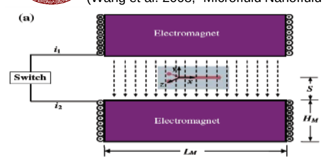
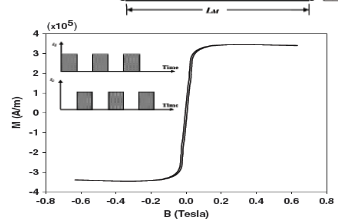
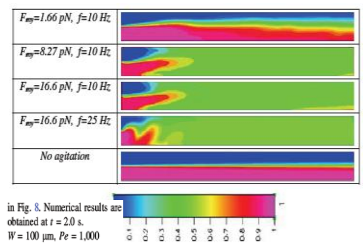


Table 1 Property of the magnetic particles CM-10-10

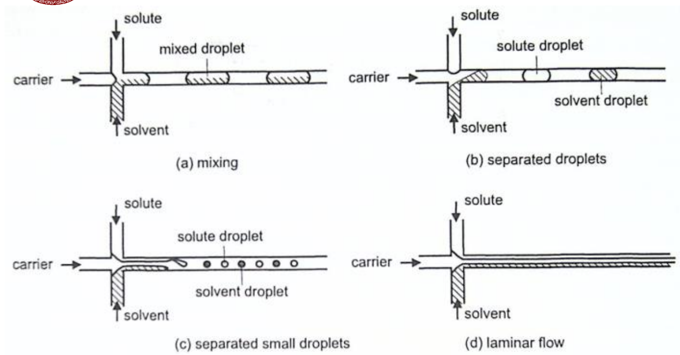
Susceptibility of the particle	χ_p	11.3
Particle radius	r_p	0.5×10^{-6} m
Particle volume	V_p	5.236×10^{-19} m^3
Particle density	ρ_p	1,580 kg/m^3
Particle mass	m_p	8.27×10^{-16} kg





in Fig. 8. Numerical results are obtained at $t = 2.0$ s. $W = 100$ μm, $Pe = 1{,}000$

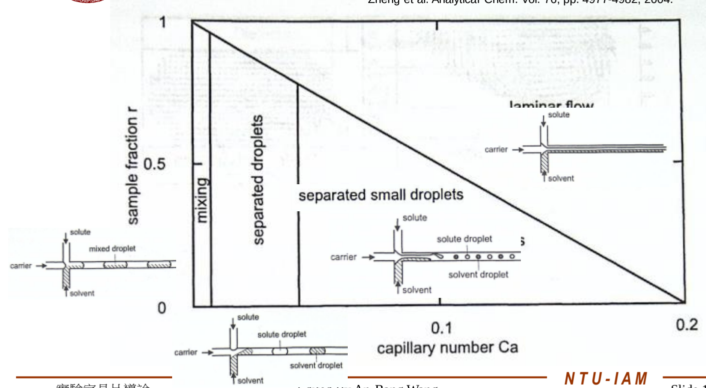
Mixing with droplets



Zheng et al. Analytical Chem. Vol. 76, pp. 4977-4982, 2004.

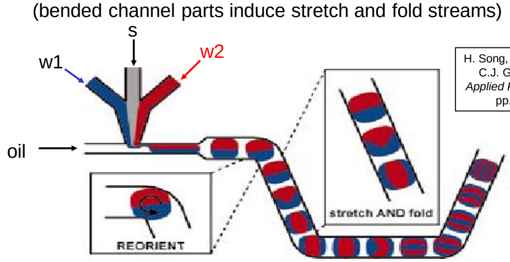
Droplet generation in Multiphase system

Zheng et al. Analytical Chem. Vol. 76, pp. 4977-4982, 2004.



Continuous & Batch: Mixing in Droplet

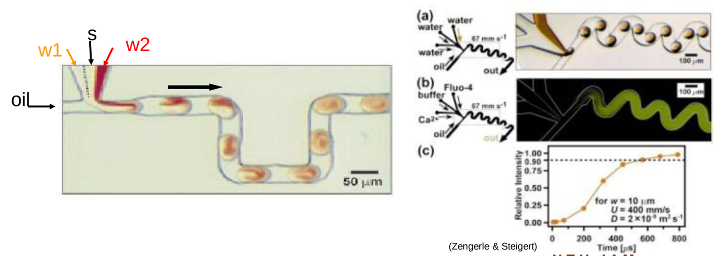
- continuous generation of droplets
  - injection of two miscible phases (w1 & w2) into single droplet immersed in immiscible phase (oil)
  - mixing within droplet (batch) along channel (bended channel parts induce stretch and fold streams)



H. Song, M.R. Bringer, J.D. Tice, C.J. Gerdts, R.F. Ismagilov *Applied Physics Letters*, 83(22), pp. 4664-466, 2003.

Continuous & Batch: Mixing in Droplet

- defined start of mixing within the droplet
  - separating stream (s) separates the two phases prior contact
  - position along channel corresponds to mixing time
  - → investigation of reaction kinetics in ms time-scale



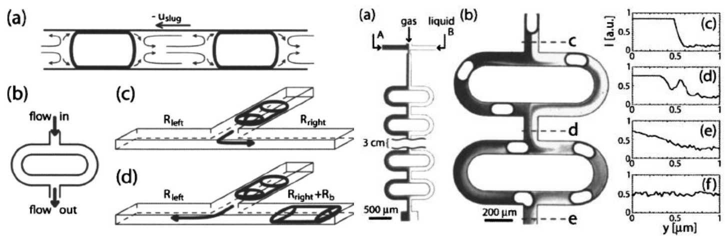
(Zengerle & Steigert)

Mixing with bubbles

Design for mixing using bubbles in branched microfluidic channels

Piotr Garstecki,[a] Michael A. Fischbach, and George M. Whitesides[b] — APL 2005

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts, 02138-2902



Syllabus

- *What & Why Lab-on-a-chip (LOC)?*
- *Application examples and LOC platforms*
- *Components in LOC*
- ***Term-project assignment***

Term projects in 2018/9:

1. Development of Quantum Dot microreactor & detection platform
   工業用量子點材料微反應器與檢測平台開發(史唯里、戴 勤、陳品帆)、(江淑菁)
2. Smart Contact lens for monitoring Chronic diseases
   智慧型醫用隱形眼鏡系統開發(吳伊敏、鄭珮妤、廖證傑)
3. High performance Western Blotting Integration System
   高效西方墨點法檢測平台開發(黃偉祐、林祐賢、康惟誠)
4. New enzyme-linked immunosorbent assay (ELISA) system
   全新高效酵素免疫分析系統(江佳玶、黃昱豪、吳宗翰)、(江淑菁)
5. qPCR or dPCR (何明樺?、高函潔?、張瑞?、林偉聖?)
   (https://zhuanlan.zhihu.com/p/27928162)

Concluding remarks

- A lab-on-chip is not simply a network of µ-channels.
- Monolithic silicon integration processes for lab-on-chip is not expected due to the high cost of large surface areas and opacity in visible wavelengths.
- Philosophy of functionality above miniaturization, simplicity above complexity: introduction of plastic micromachining.
- Polymer moulding (molding) technology has been quickly developed due to low cost (disposable), and high throughput issues.
- There's still plenty of rooms in the *Lab-On-A-Chip / µ-fluidics.*

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