543 U6970/AM5019 實驗室晶片導論

微流體混合器/反應器暨生醫化材應用

Design of micro-mixers/micro-reactors & the applications

楊鏡堂 終身特聘教授

國立台灣大學 機械工程學系

國立台灣大學 生物技術研究中心 合聘研究員

國立台灣大學 工程科學與海洋工程學系 合聘教授

中華民國 一百零七 年 十月十九日

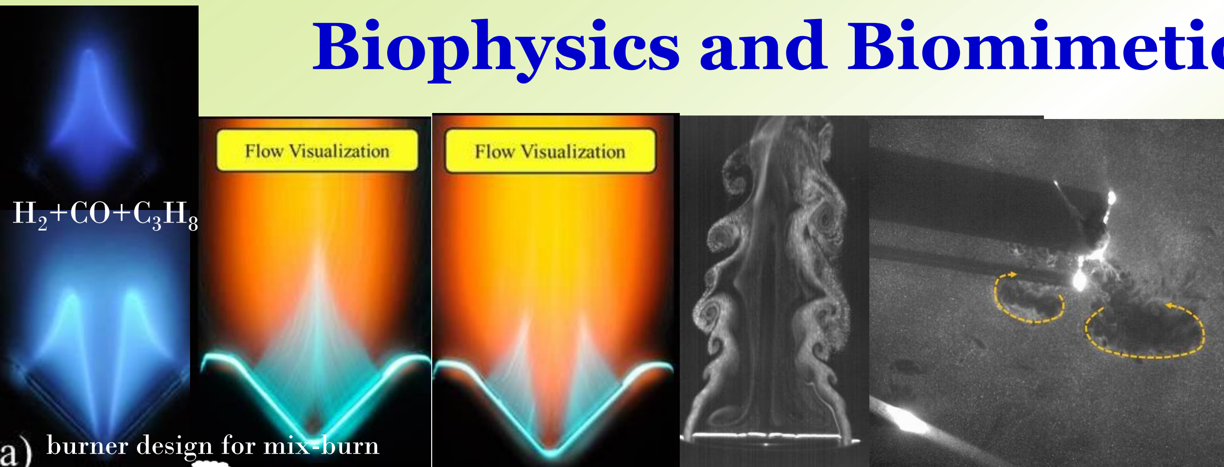
楊鏡堂教授 研發興趣

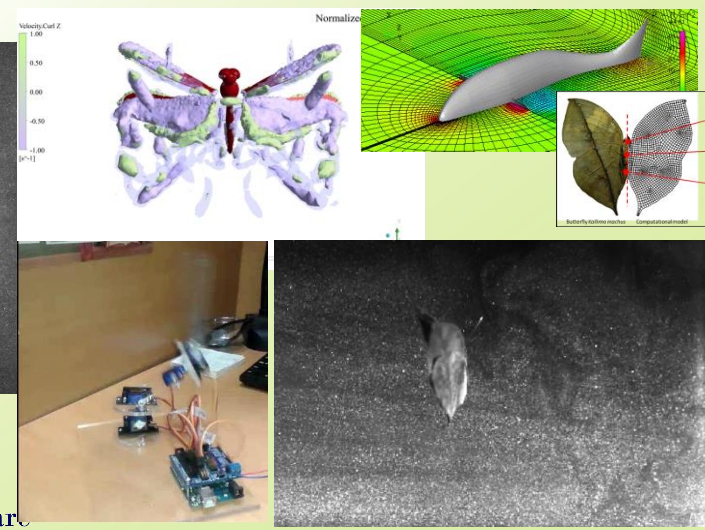
Fluid Mechanics + Thermodynamics (次領域)

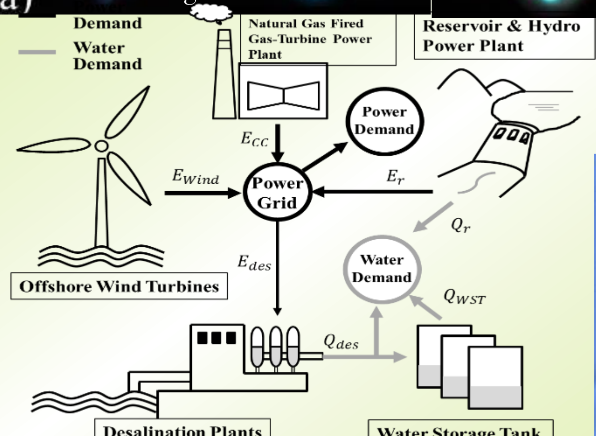
Energy and Combustion (1979~) + 強烈化學反應

Bio-microfluidics & Lab on a Chip (2002~) + 生醫化材

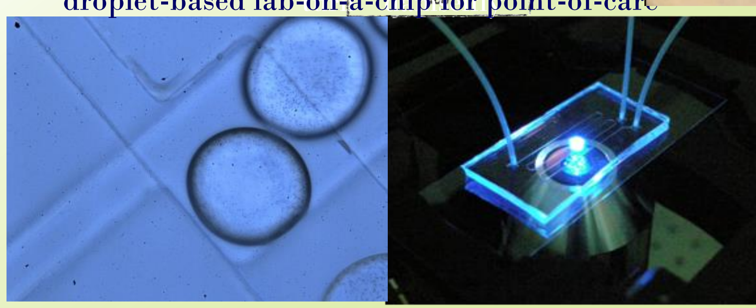
Biophysics and Biomimetics (2004~) + 生物

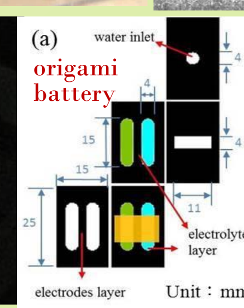






droplet-based lab-on-a-chip for point-of-care





楊鏡堂教授 個人資料

現職： **國立台灣大學 機械工程學系 終身特聘教授**

國立台灣大學 生物技術研究中心 合聘研究員

國立台灣大學 海洋工程與系統科學學系 合聘教授

台灣中油公司－ 獨立董事

行政院科技會報辦公室首席評議專家（綠能）

行政院能源及減碳辦公室－ 前執行長

教育： **美國威斯康辛大學 機械工程博士(能源組)**

國立成功大學 機械工程碩士

國立成功大學 造船工程學士

其他： 科技部傑出研究獎三次、孫方鐸教授力學獎章、*Science/Nature*專訪&報導(2014, 2011)

2016年東元獎(機械/能源/環境領域)、2018年宗倬章先生榮譽講座教授、

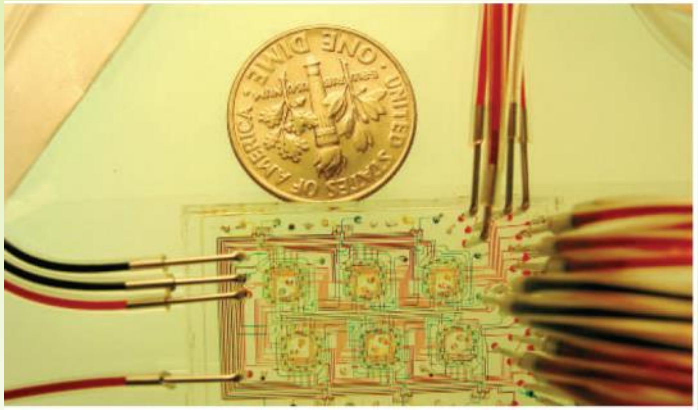
2007年中國工程師學會十大傑出工程教授獎、國家新創獎 (2018, 2015, 2014, 2008)

國家發明獎、Green Tech東元科技創新競賽亞軍 (2018, 2014, 2012)、150個學術獎項

校級公開賽冠軍: 游泳(自由式, 蝶式) 、 排球、壘球、網球

Micro-reactor/Lab on a chip

- High surface to volume ratio : improve heat and mass transfer
- Need only small quantities of reagents and sample
- Potentially portable
- High resolution and sensitivity
- Suitable for biological assay

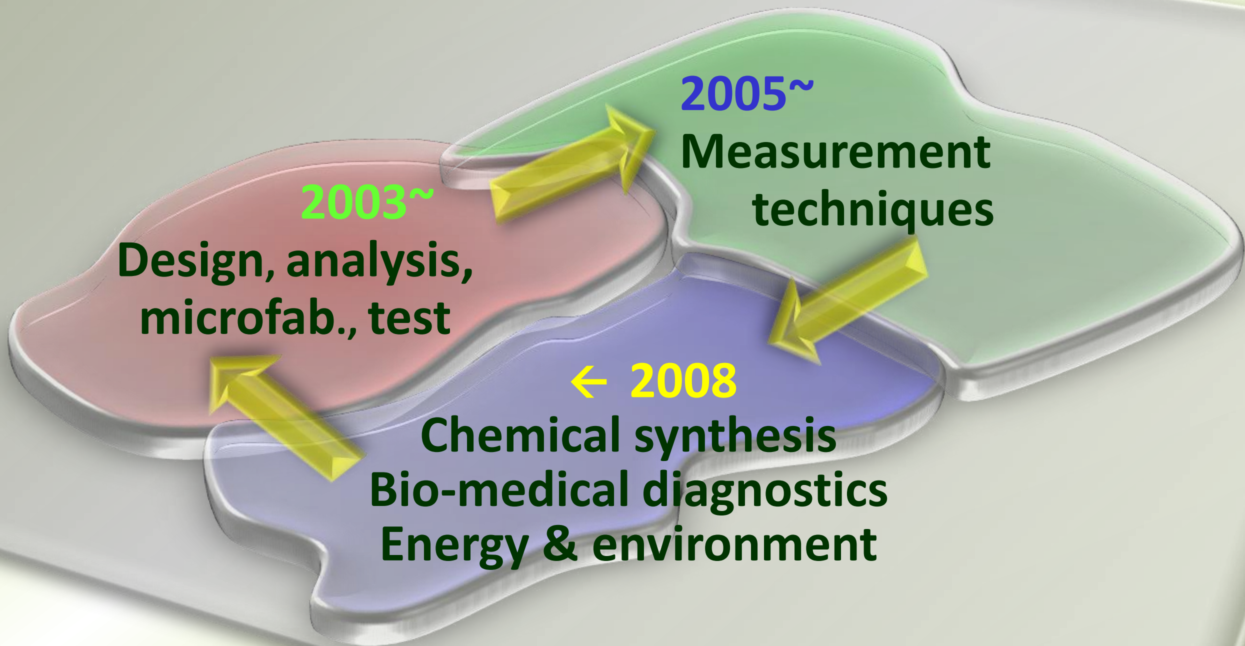


Balagadde *et al.*, *Science* (2005)

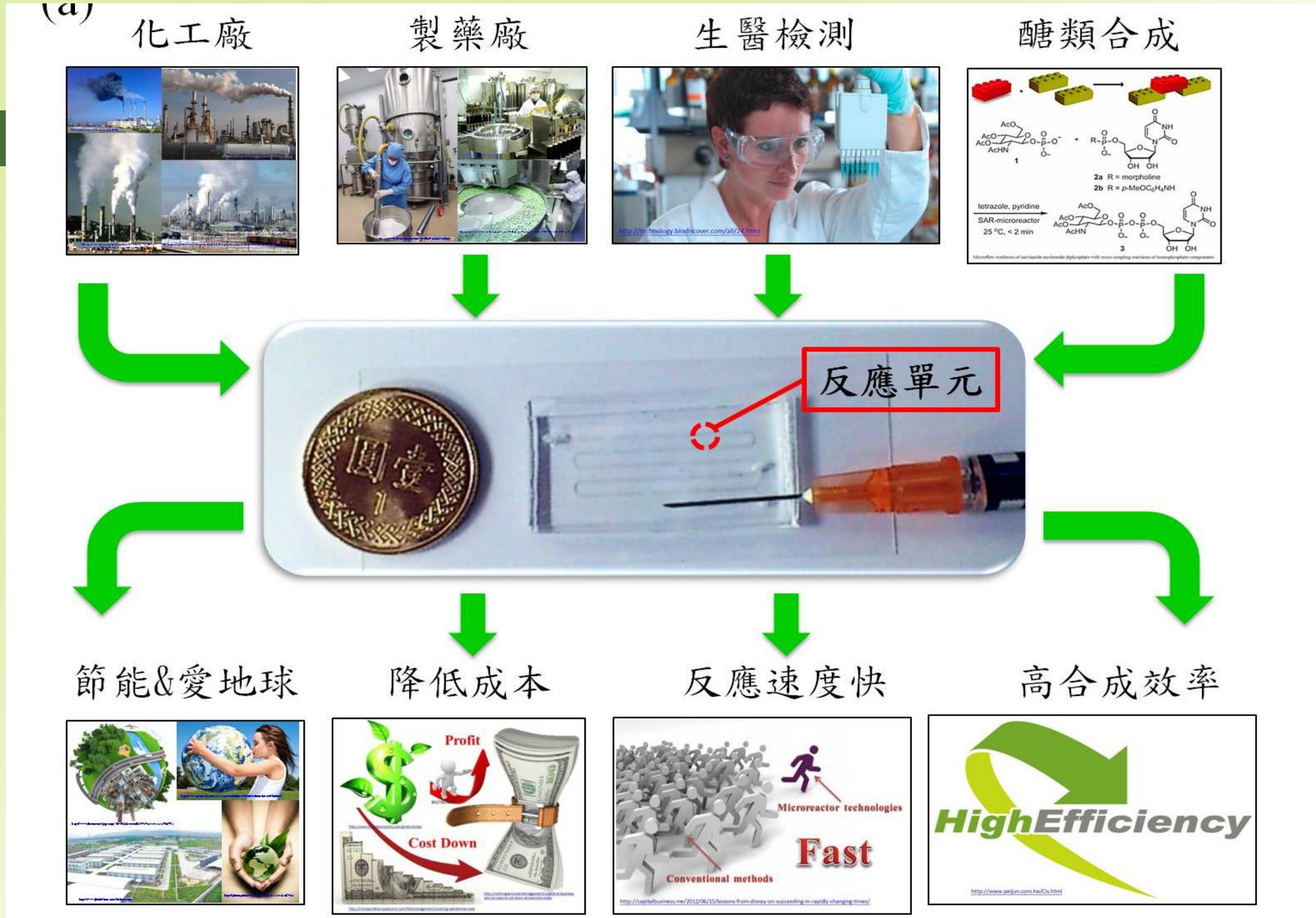
Extracted on 20121212 http://www.condenaststore.com/-sp/I-see-by-the-current-issue-of-Lab-News-Ridgeway-that-you-ve-been-work-New-Yorker-Cartoon-Prints_i8562947_.htm

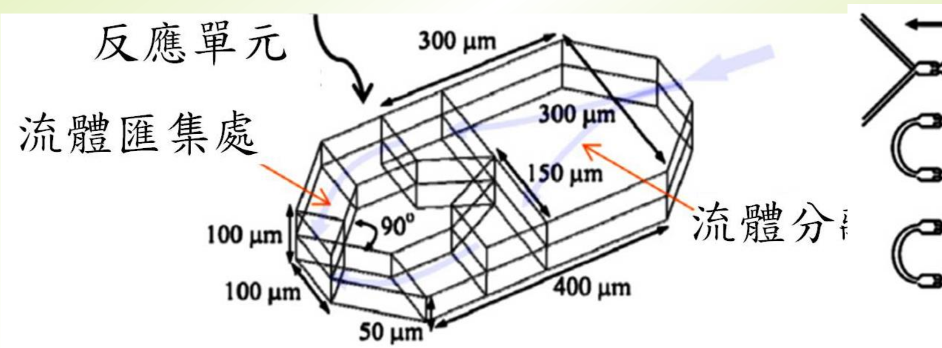
Contents of the Presentation

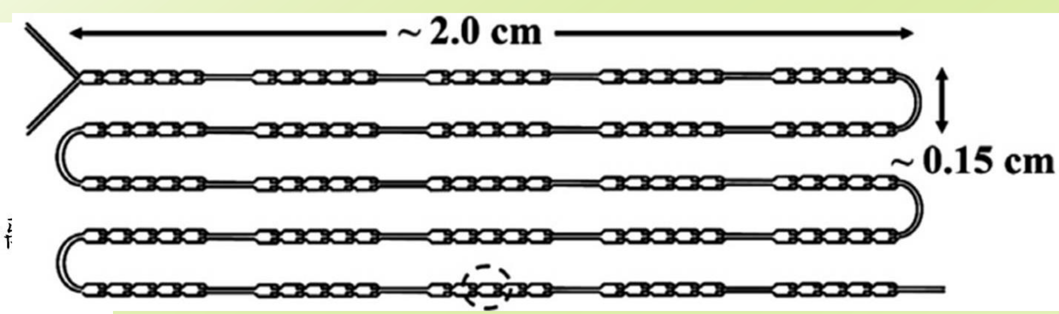
Micro-reactors for Bio-microfluidics
mixing/reaction/diagnostics



- **continuous flow reactors**
- **droplets-based elements for reactors**


(a)
化工廠
製藥廠
生醫檢測
醣類合成
反應單元
節能&愛地球
降低成本
反應速度快
高合成效率
Profit
Cost Down
Microreactor technologies
Fast
Conventional methods
HighEfficiency


反應單元
流體匯集處
300 μm
300 μm
150 μm
100 μm
90°
100 μm
50 μm
400 μm


~ 2.0 cm
~ 0.15 cm

NSC Projects

應用於生醫檢測之整合式微流體系統研發

NSC 100-2221-E-002-157, 2011/08-2012/07

-- 研發結合機械設計、流體力學、有機化學合成與生化分析整合之微全分析系統 (micro total analysis systems)

-- 突破傳統費時之檢測流程，主要研究包含微反應器設計分析、化學試劑與生醫流體混合、奈米粒子如奈米金球或磁珠與生醫流體待測物之鍵結、目標DNA之引入及分離篩選之訊號轉導量測技術研發，以達系統結合上的廣泛應用性及效率。

Scientific Aspects

- **Miniaturization Approach** (1980s ~ mid-1990s)

  silicon microfluidic devices:

  size effect

  power effect

- **Exploration of New Effects** (mid-1990s ~)

  actuators with no moving parts and nonmechanical pumping principles

  electrokinetic pumping, surface-tension-driven flows,

  electromagnetic forces, acoustic streaming

  new effects which mimic nature → nanotechnology

- **Application Developments**

  biomedical diagnostics, drug discovery, flow control, chemical analysis

  distributed energy supply and thermal management

  chemical production with microreactors

What is mixing？

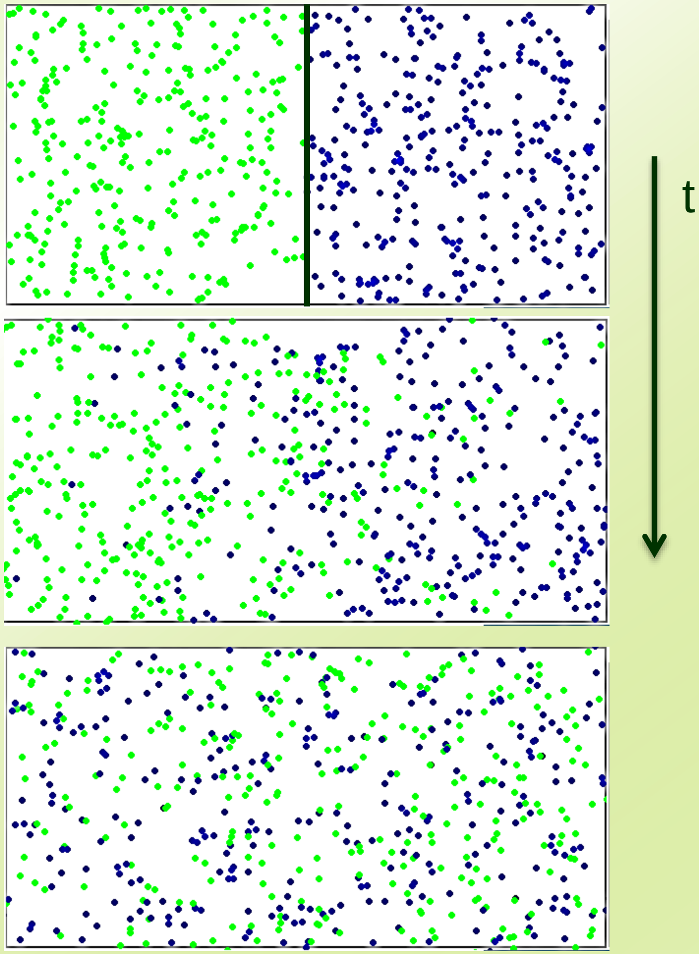
混合：

將兩種(or 兩種以上)不同的物、人或事摻雜在一起的行為。 *~from Wikipedia*

Ex.

物質的混合。
音樂的混合。
人類的混合。
社會的混合。
其他的混合。

藉由**某些手段**讓系統中的物質更均勻分布於系統中
Ex. Diffusion (Brownian Motion), convection, turbulence, stir, etc.



Mixing phenomena in our daily life

http://tw.aboluowang.com/life/2011/0316/%E5%92%96%E5%95%A1%E4%B8%8D%E7%82%BA%E4%BA%BA%E7%9F%A5%E7%9A%84%E5%A5%BD%E8%99%95-46561.html

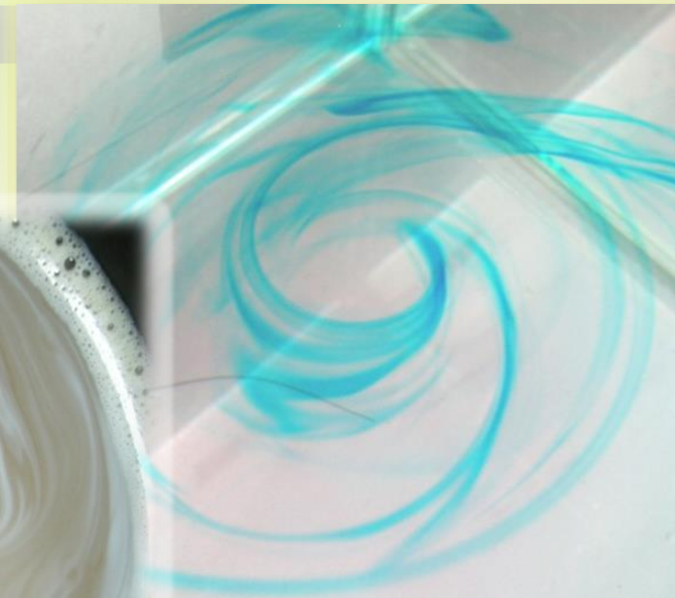
http://reisendame.files.wordpress.com/2007/11/smoke.jpg

http://www.blingcheese.com/image/code/5/smoke.htm

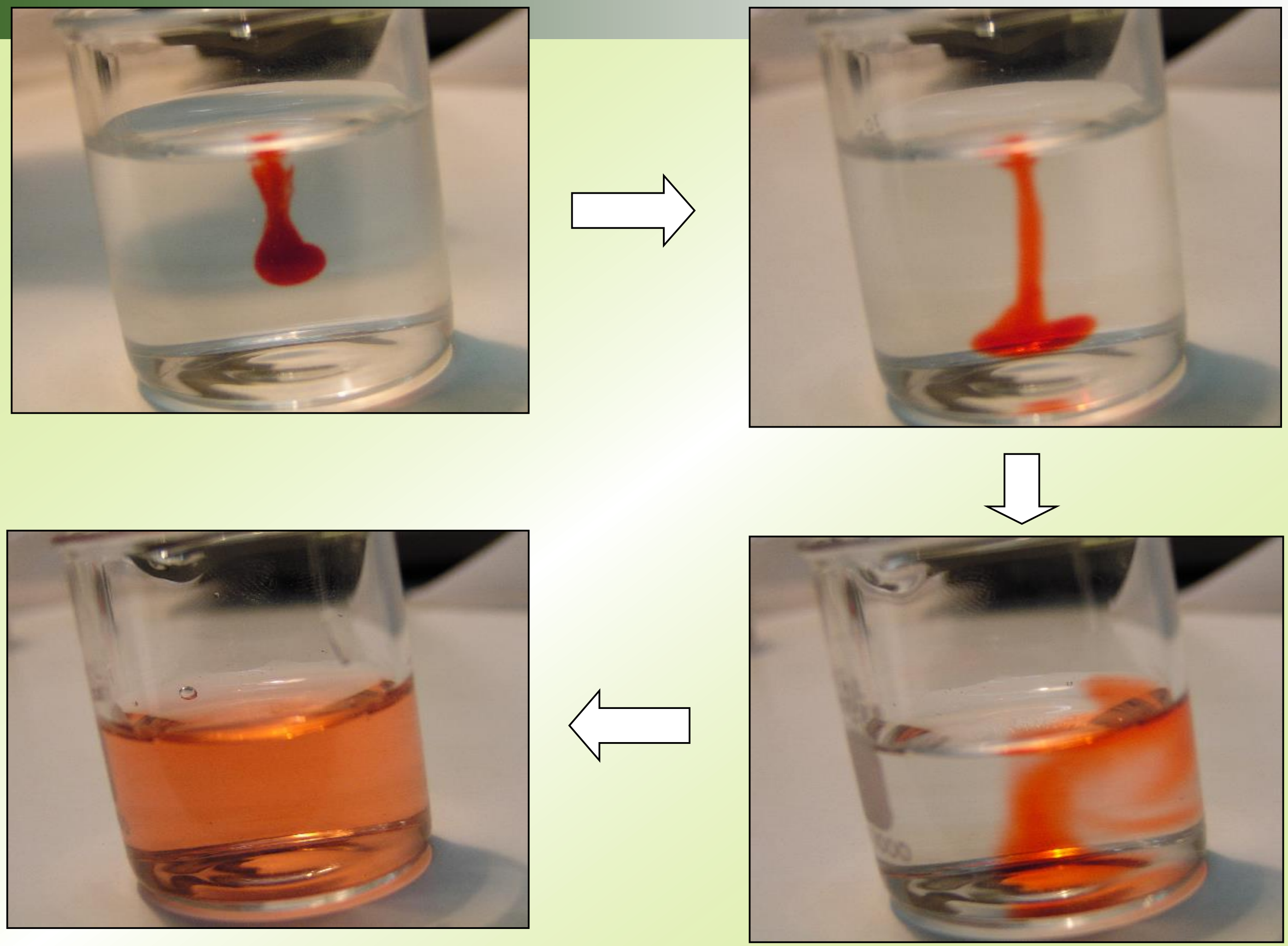
http://25011963.com/pro.cgi?mnm=data&no=1243871122&page=

Mixing is closely related to our daily life

混合現象無所不在



Mixing by Diffusion



Fluids may be mixed by purely non-zero concentration gradient and or enhanced by external agitation.

How does mixing happen?

Initial condition

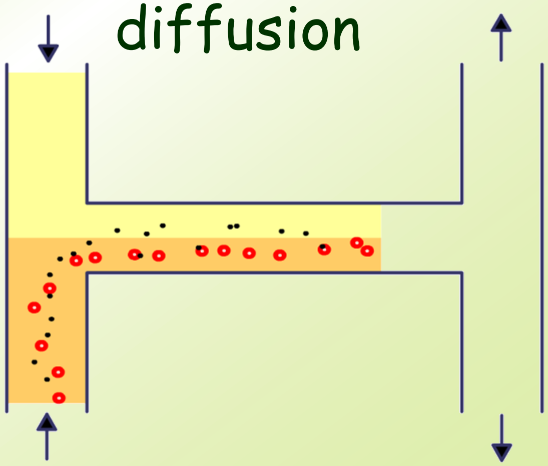
(Ottino *et al.*, 1989)

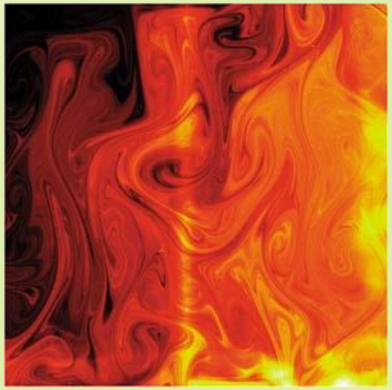
Flow

stretching

diffusion

breakup





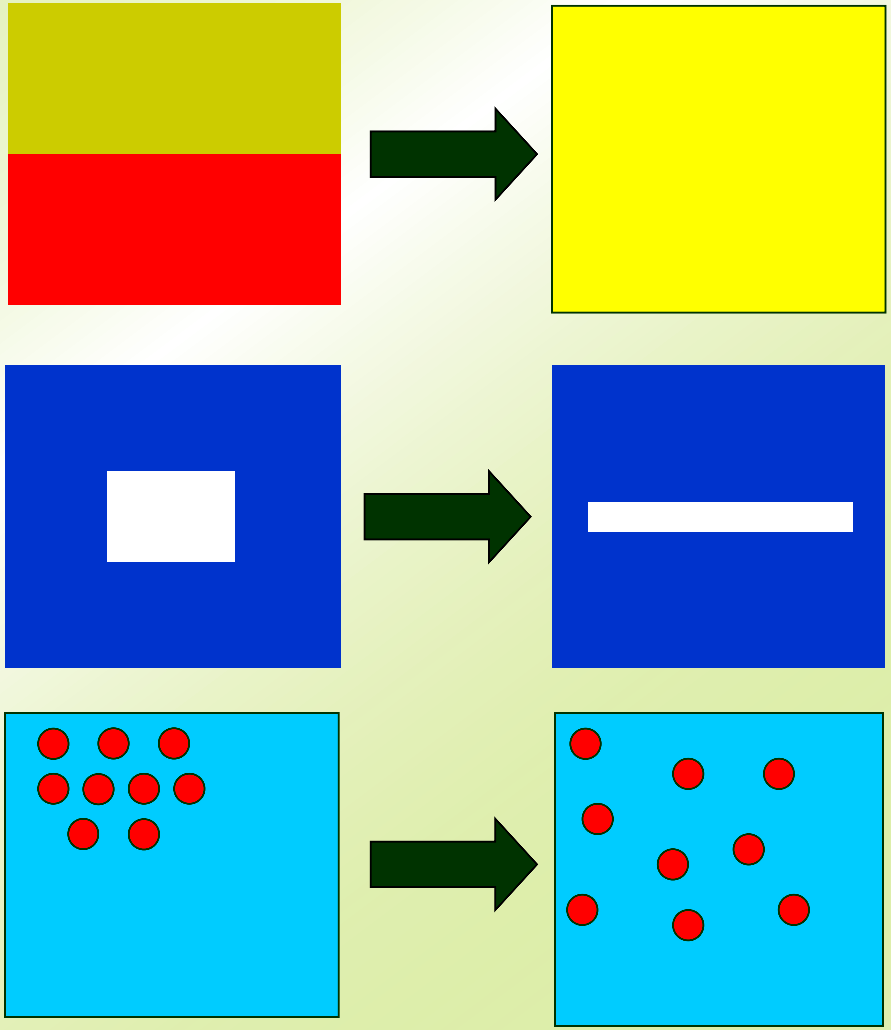
Ref. :http://www.tj.xinhuanet.com/ztbd/2005-06/09/content_4420148_10.htm ; www.micronics.net ; http://physicsweb.org

Three Types of Fluid Mixing

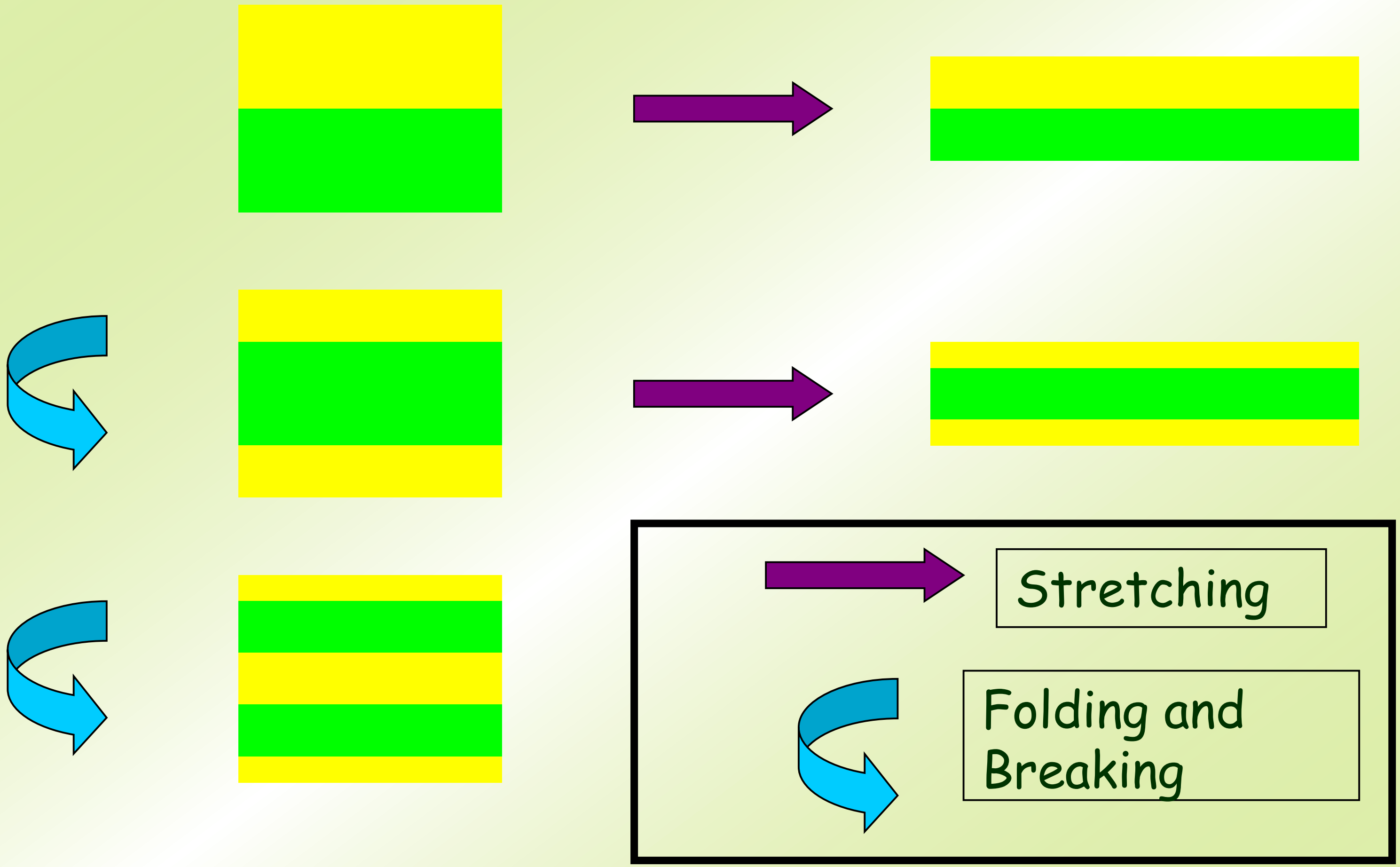
(a) Mixing of two miscible fluids

(b) Mixing of two immiscible fluids

(c) Mixing of two phases fluids



Fluid Mixing by Stretching and Folding



Mixing is promoted by periodic motion of the fluid. It is conducted by iterated stretching and folding of the interface here.

Research Trend

- 混合現象是自然界最常見的現象之一。
- 混合現象常發生於機械和化學領域 ，特別在分析化學和 燃燒工程領域中。
- 微流體領域的快速發展，微混合現象日益受到重視。特別是在 化學、化工和生化領域。

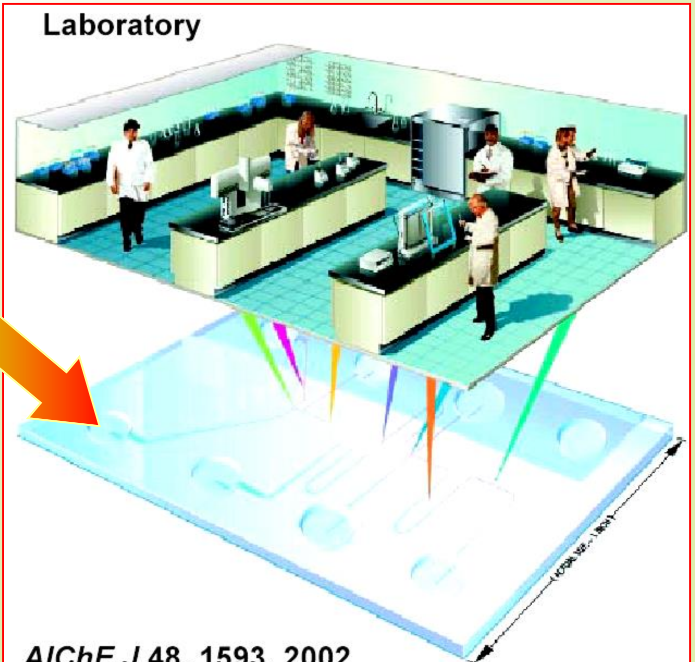
Manz *et al.*, *SNA-B.* 1990

過去

現在

未來

Miniaturization
Automation
Safety

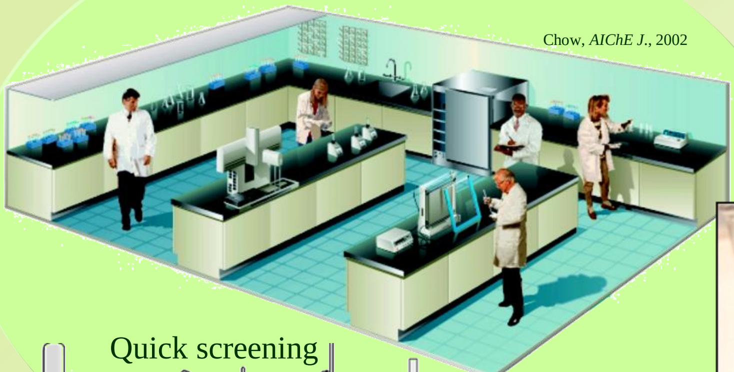


AIChE J 48, 1593, 2002

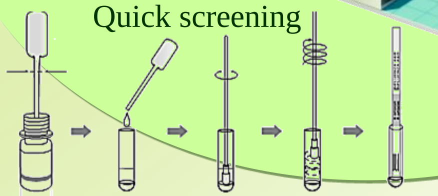
The importance of mixing

Biochemical / medical science

Chow, *AIChE J.*, 2002



Quick screening



Blood assay

http://jolex.web66.com.tw/web/NMD?postId=300539

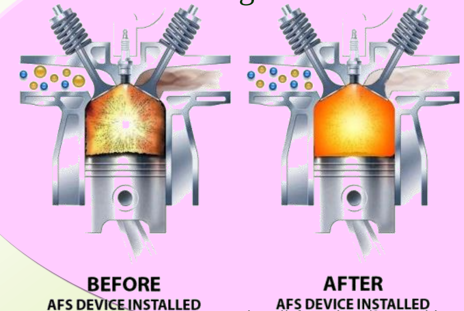
Chemical engineering

http://research.che.tamu.edu/groups/Froment/Website/Images/oil%20refinery%201.jpg

Jähnisch *et al.*, *Angew. Chem. Int. Ed.*, 2004

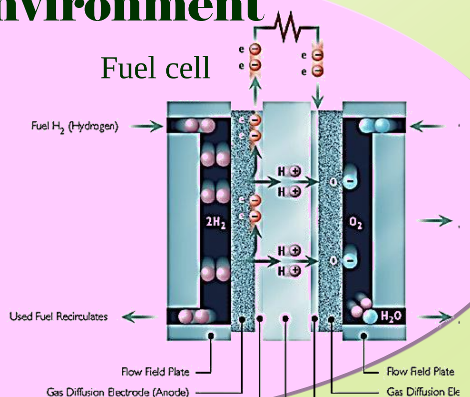
Energy /environment

Engine



http://afsnorth.ca/?page_id=51

Fuel cell



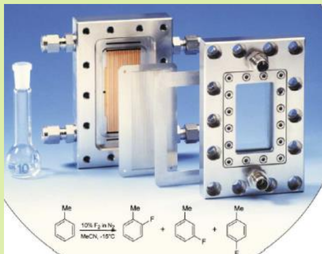
http://www.cntech.com.cn/news/media/h000/h15/img200705231159190.jpg

Reactions are crucially dominated by mixing

Research Motive– Application

Xi'an Huian Chemical

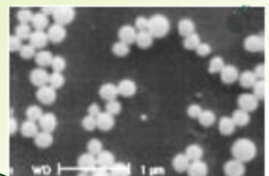
CHEMICAL & Engineering News



Jähnisch et al., 2004, Angew. Chem. Int. Ed.

Chemical Engineering

- Organic synthesis
- Hazardous chemical reactions
- Nanopowder production

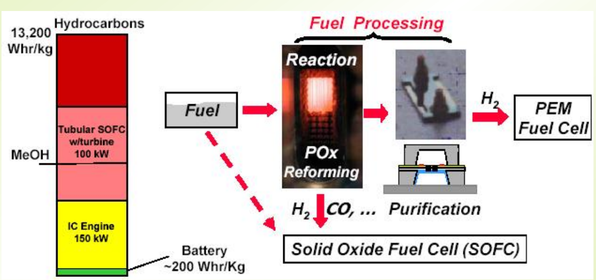


Johnson and Prud'homme, 2003, AIChE J.

μ–mixing, reaction

Mechanical Engineering

- Combutsion

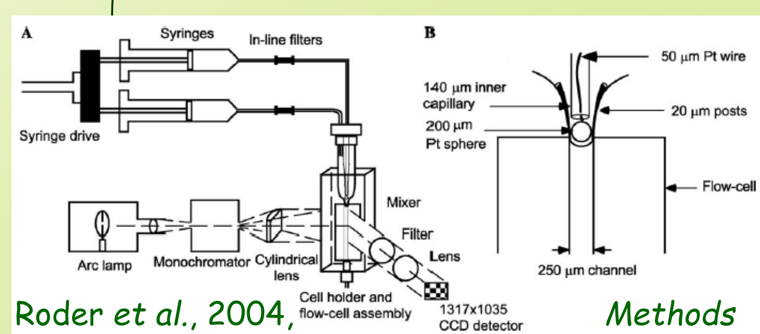


Jensen K. F., 2002

Bio-Chemistry

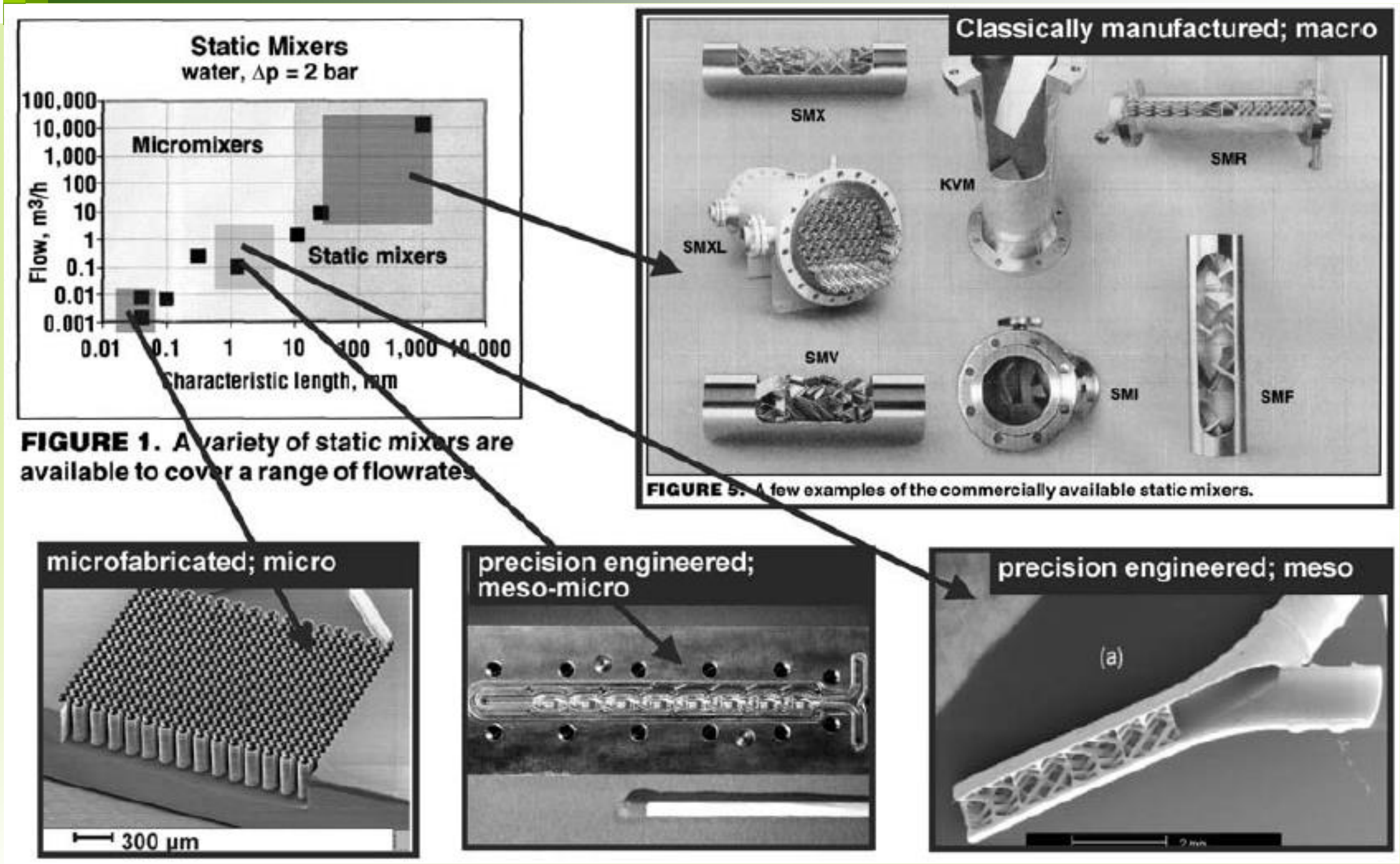
Manz, 1990, SNA-B

- Lab-on-a-chip
- Quench-flow analysis



Roder *et al.*, 2004, *Methods*

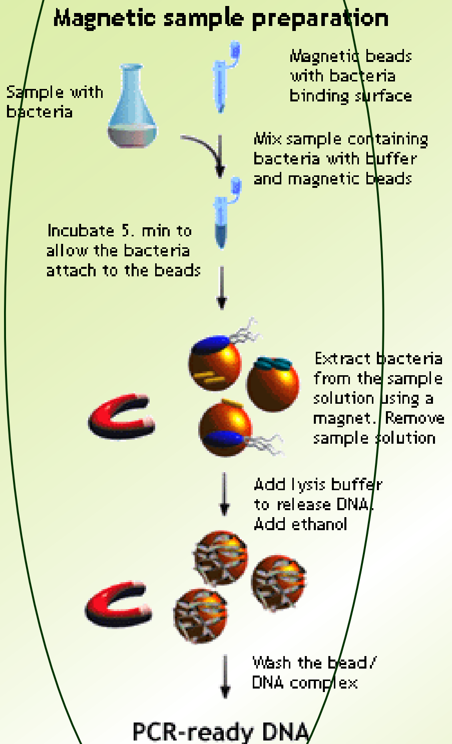
Size Evolution



Bayer et al., 2003., Chem. Eng.

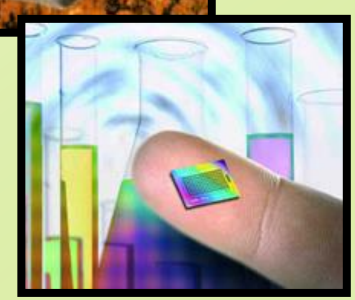
General flow chart of a chemical analysis

(Manz et al., Sens. Actuators, 1990)



sampling
↓
Transport
↓
Sample pretreatment
↓
Transport
↓
Detection
↓
Transport

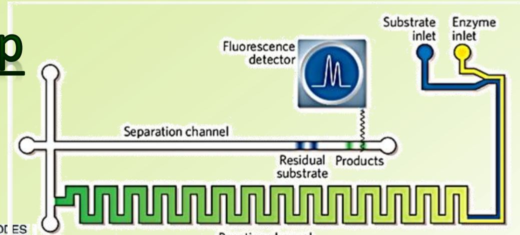
Ideal chemical sensor



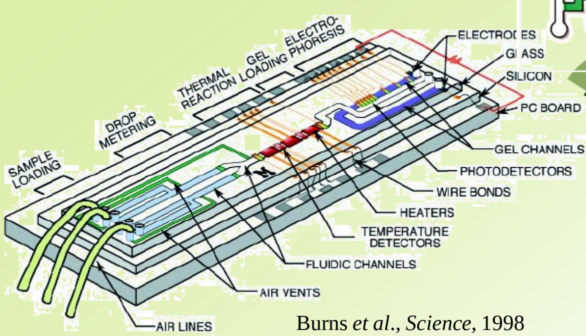
Ref. : http://www.ost.gov.uk/link/news/images/9903chip.jpg ; http://w4.siemens.de/en2/html/press/newsdesk_archive/index.html ; www.genpoint.com/ Files/illustration.html; http://www.ost.gov.uk/link/news/images/9903chip.jpg ; http://www.giannigiorgetti.com/pcr/

Merits of microfluidic mixing/reaction

m-TAS/Lab-on-a-chip



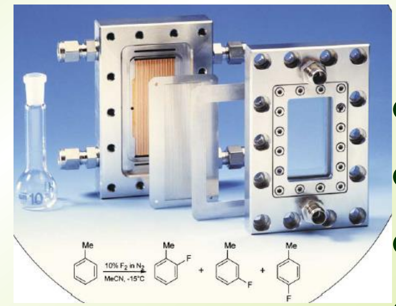
Haswell, *Nature*, 2006



Burns *et al.*, *Science*, 1998

- Low sample/reagent consumption
- Parallel process
- Rapid detection

Microreaction technology

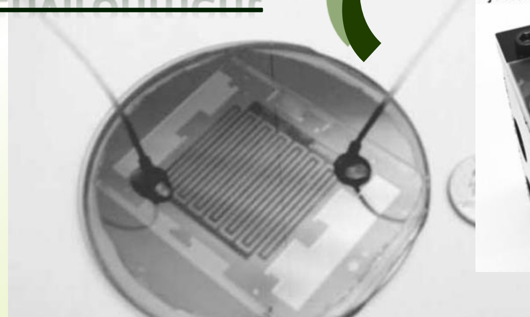

Jähnisch, *et al.*, *Angew. Chem. Int. Ed.*, *2004*

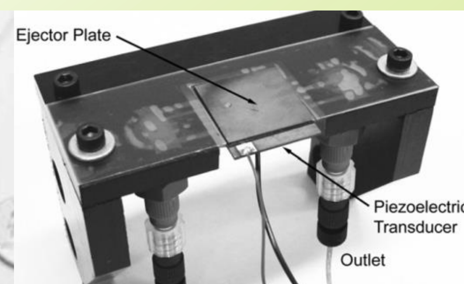
- High selectivity
- High safety
- Flash reaction
- Controllable


Hogan, *Nature*, 2006

Micromixers & Microreactors

Energy & Environment

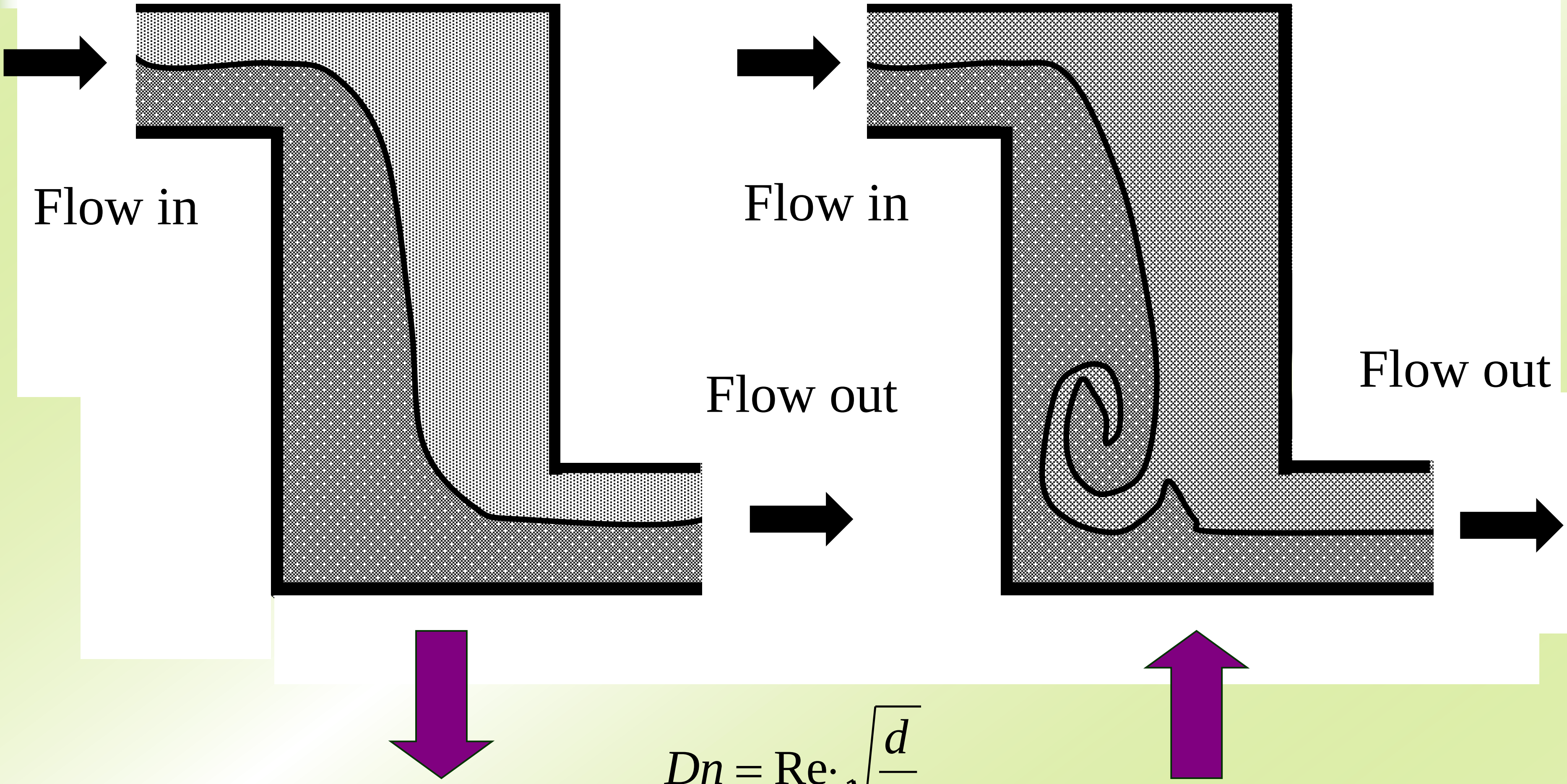

Pattekar and Kothare, *JMEMS*, 2004



Varady *et al.*, *JMM*, 2007

- **Green fabrication**
- **Eco-friendly usage**
- **Portable**

Mixing via Separated Flow and Vortex



$$Dn = \mathrm{Re} \cdot \sqrt{\frac{d}{R}}$$

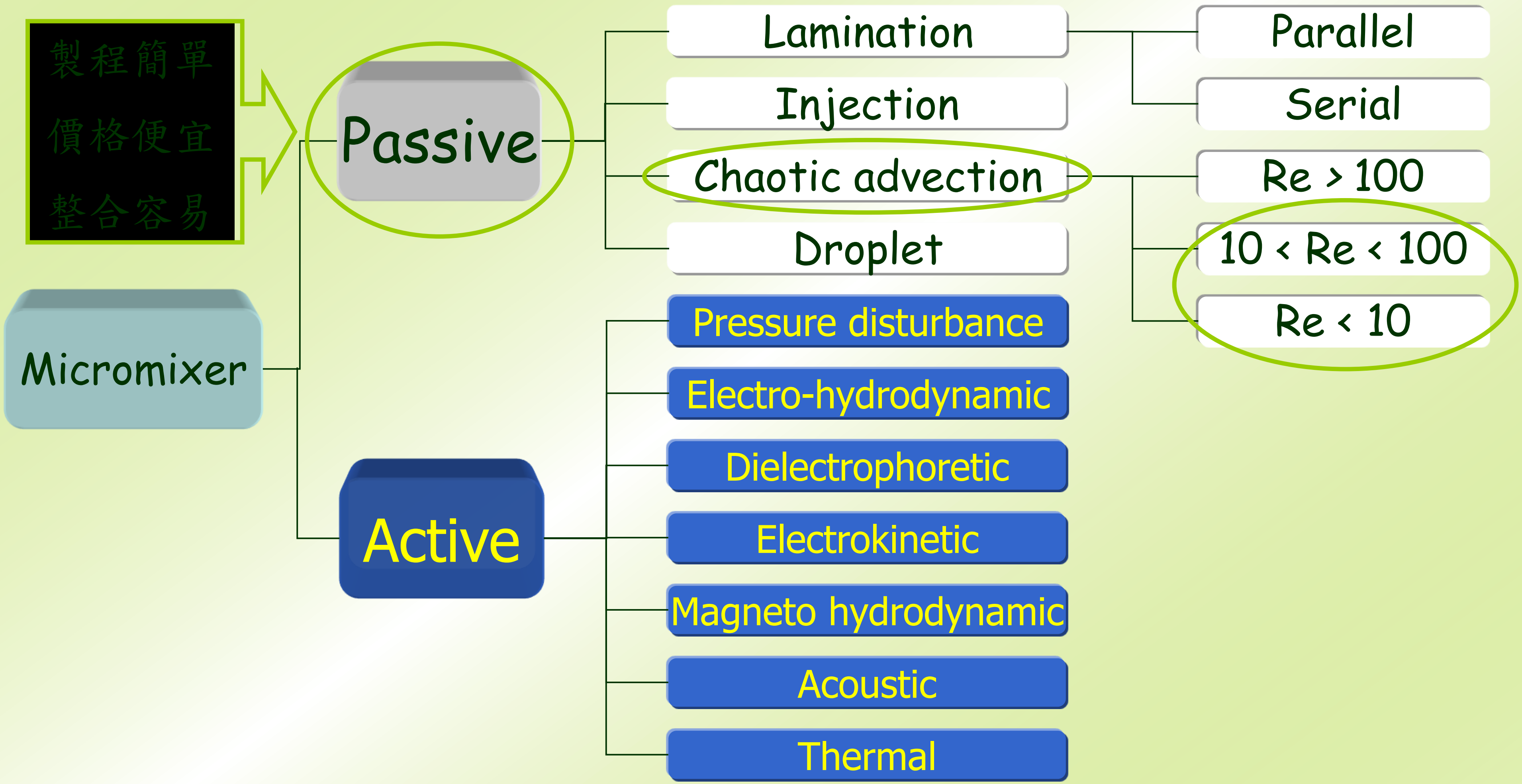
d represents the hydraulic diameter, and *R* is the radius of turning

Micromixer Types

- Micromixer
  - Passive
    - lamination
      - parallel
      - serial
    - Chaotic mixing
    - Nozzle injection in flow
    - Collision of jets
    - Coanda-effect
  - Active
    - Acoustic
    - Electrokinetic
    - Pressure disturbance
    - Electrowetting induced droplet shaking
    - Ultrasound/Piezoelectrically vibrating membrane
    - Magneto-hydrodynamic action
    - Thermal
    - Small impellers

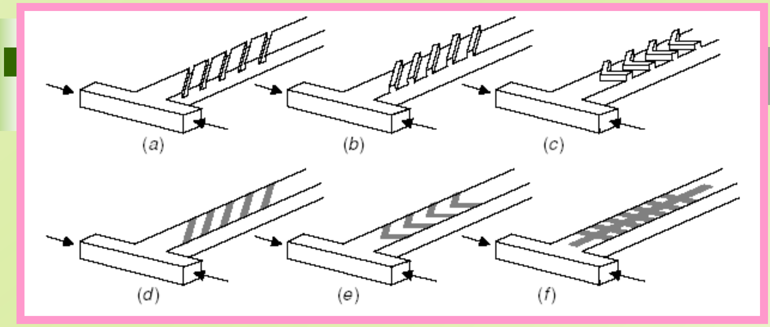
What else?

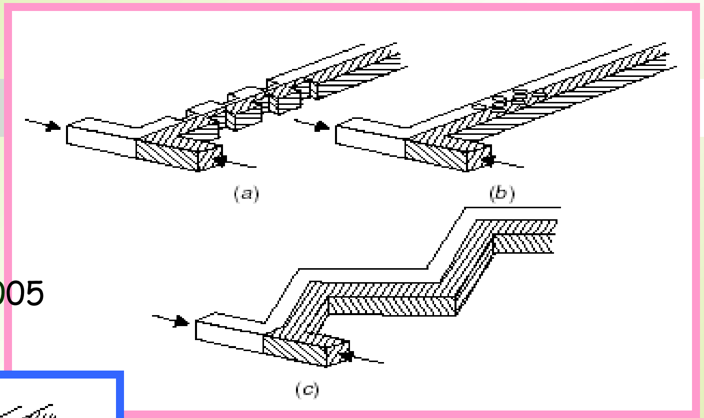
Micromixer Types



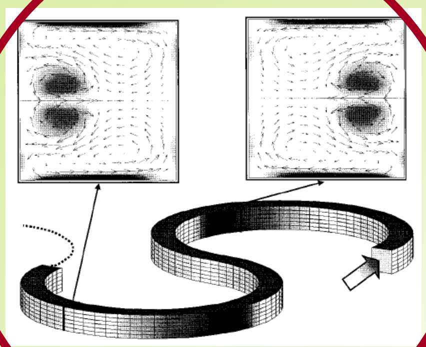
Ref. Nam-Trung Nguyen and Zhigang Wu, Micromixer – A Review, 2005, JMM

Various Micromixers

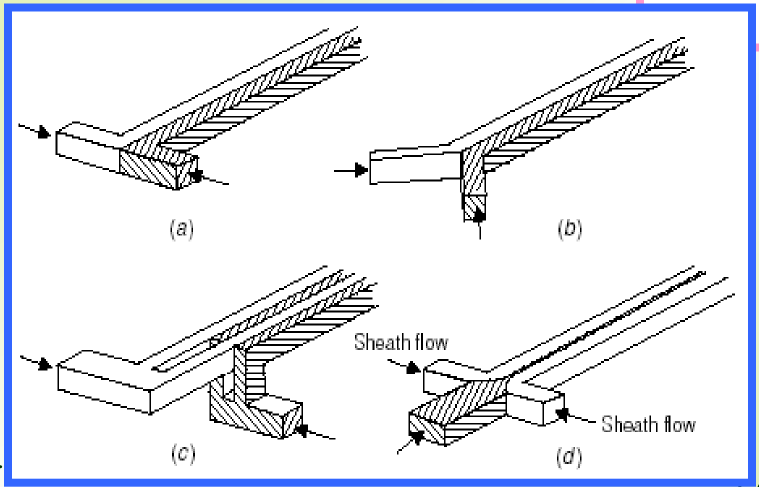


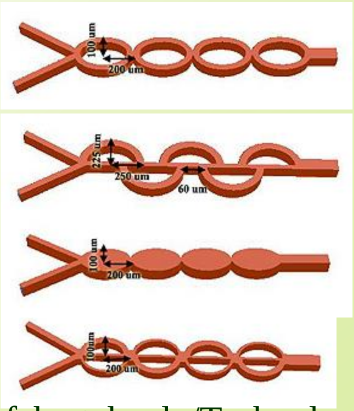


Nguyen and Wu, *JMM*, 2005

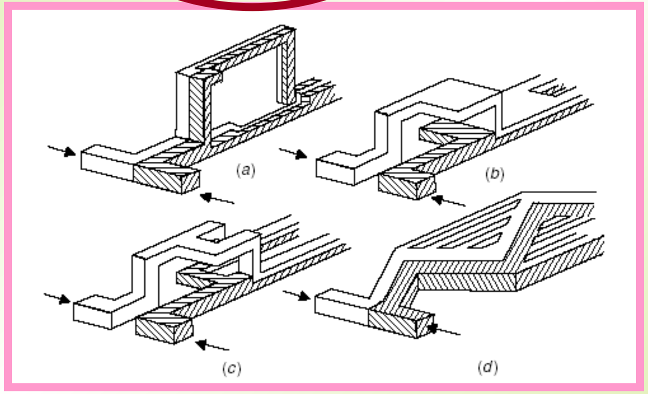


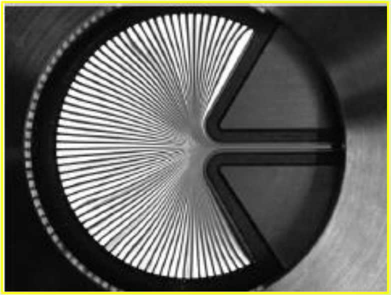
Schönfeld and Hardt, AIChE J.,2004



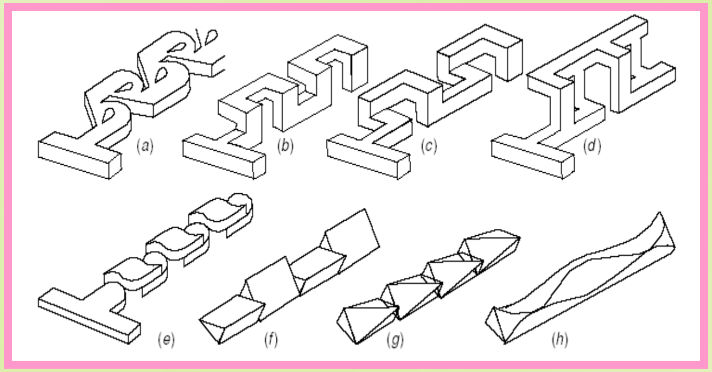


http://microfab.utah.edu/TechnologyLibrary/Micromixer/micromixerposter.htm

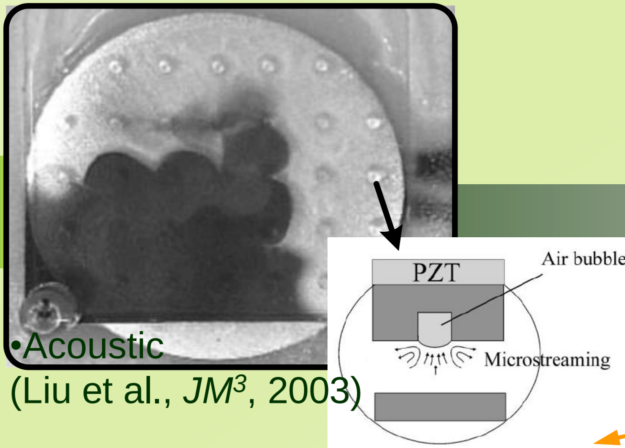




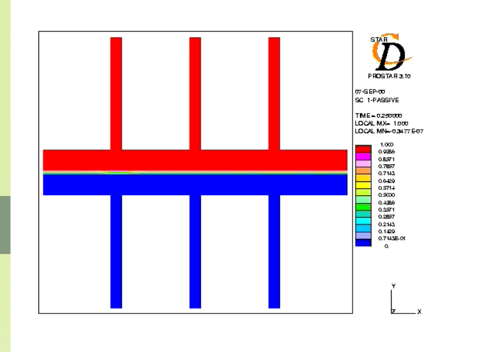
Lab et al., 2004.,
Chem. Eng. & Tech.



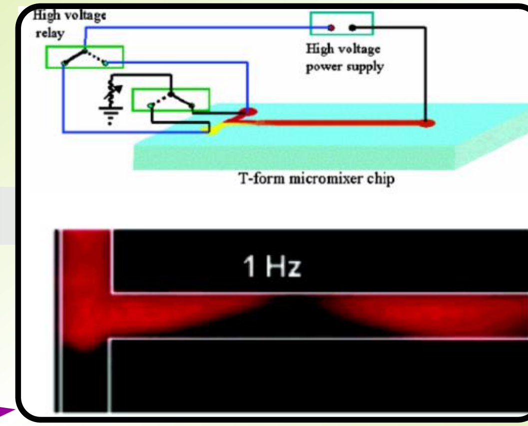
Fluid Propulsion



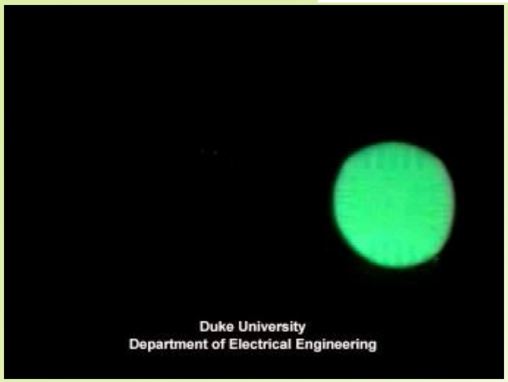
•Acoustic
(Liu et al., *JM*[3], 2003)



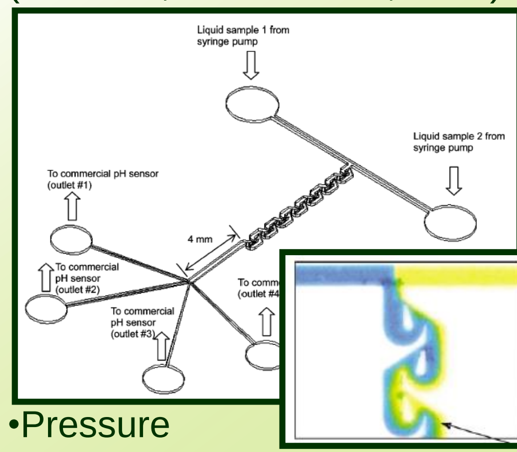
•Pressure Perturbations
(Niu and Lee, *JMM*, 2003)



•Electroosmosis
(Lin *et al.*, *Anal. Chem.*, 2004)



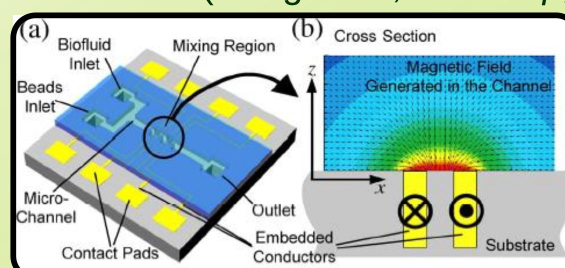
•Electrowetting
(Paik *et al.*, *Lab Chip*, 2003)



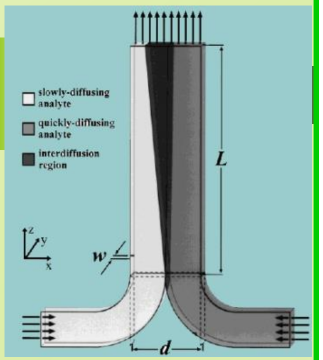
•Pressure
(Hong *et al.*, *Lab Chip*, 2003)

•Ultrasonic
(Yang & Maeda, *J. Chromatogr. A*, 2003)

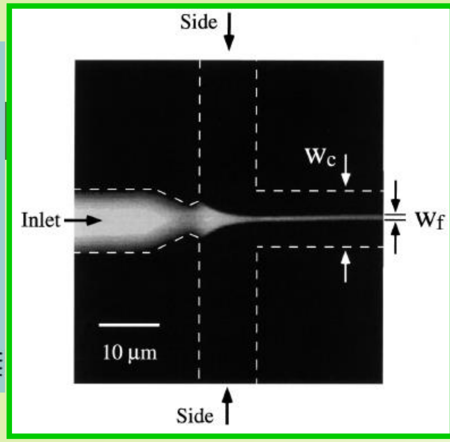
•Centrifuge
(Steigert et al., Sensor and Actuator, 2006)



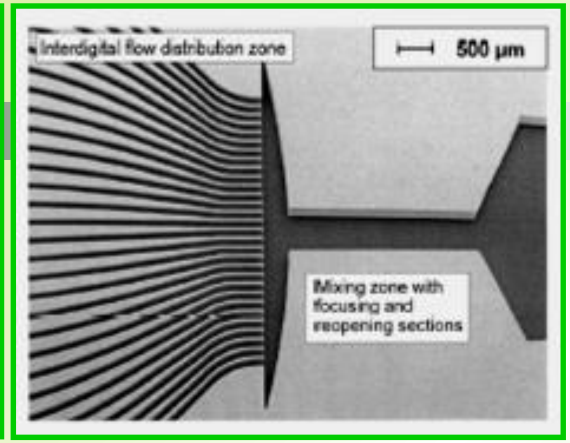
•Magnetic (Suzuki and Ho, *J. Microelectromech. Syst.*, 2004)



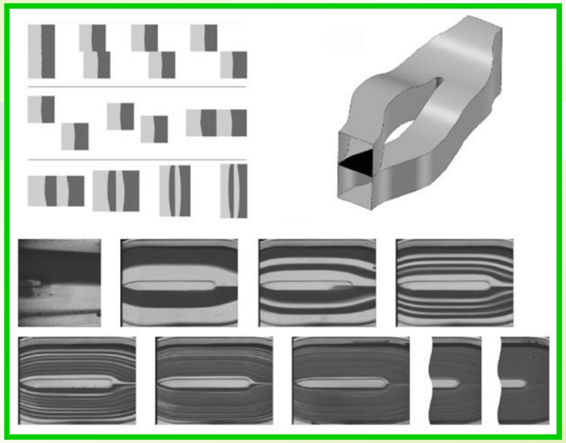
Kamholz *et al.*, *Anal. Chem.*, 1999



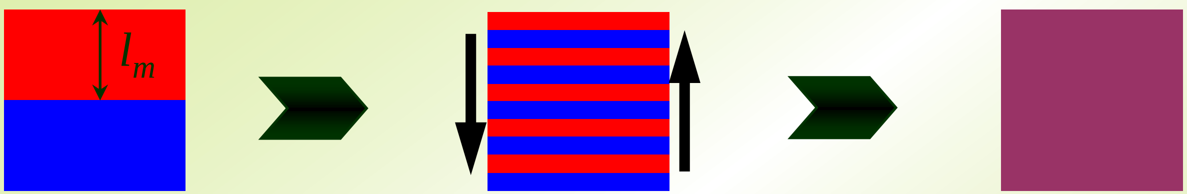
Knight *et al.*, *Phys. Rev. Lett.*, 1998



Hessel *et al.*, *AIChE J.*, 2003



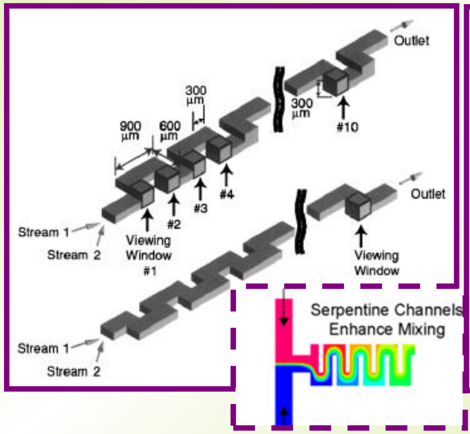
Schönfeld *et al.*, *Lab Chip*, 2004



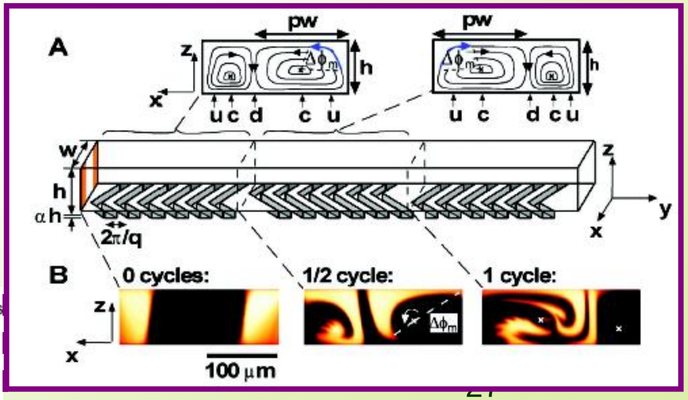
$$\Delta y_m \sim U \times \left(\frac{l_m^2}{D}\right) = \mathrm{Pe} \times l_m$$

$$\Delta y_m \sim \lambda \ln(\mathrm{Pe})$$

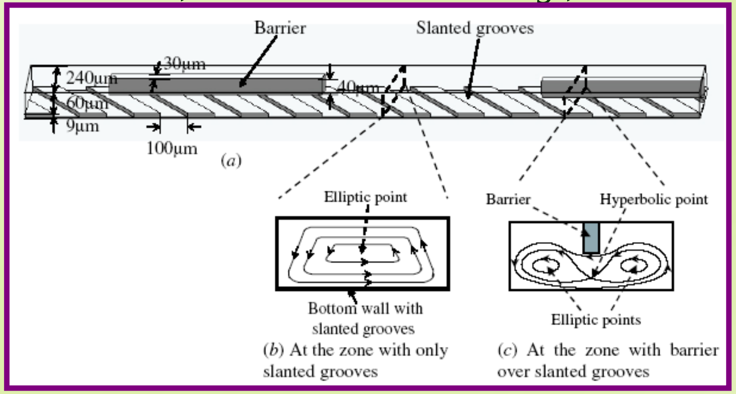
Liu *et al.*, *JMEMS*, 2000



Stroock *et al.*, *Science*, 2003



Kim *et al.*, *J. Micromech Microeng.*, 2004



Historical Development

巨觀流場
矽材料
基礎研究

→

微觀流場
高分子材料
應用研究

Aref, H., *JFM*, 1982 ；Ottino, J. M., 1989 → Chaotic advection

Veenstra *et al.*, *JMM.*, 1999；Kockmann *et al.*, 2003 → T type

Koch *et al.*, *JMM*, 1998 → lamellae

Branebjerg *et al.*, 1996 ；Jensen K., 1998 → hydrodynamic focusing

Branebjerg *et al.*, 1996；Hessel *et al.*, *AIChE J.*, 2003 → interdigital

Branebjerg *et al.*, 1996 ; Schönfeld *et al.*, *Lab Chip*, 2004 → split - recombine

Liu *et al.*, *JMEMS*, 2000; Stroock *et al.*, *Science*, 2002 → chaotic

Citated No. : 170 242 (2005/12/22)

1980 1990 2000 2010

Deficiencies of microfluidic mixing

Low Reynolds number (Re < 1)

- Viscosity-dominated system

$$\mathrm{Re} = \rho V D_h / \mu$$

- Diffusion-driven mixing

Fick's law

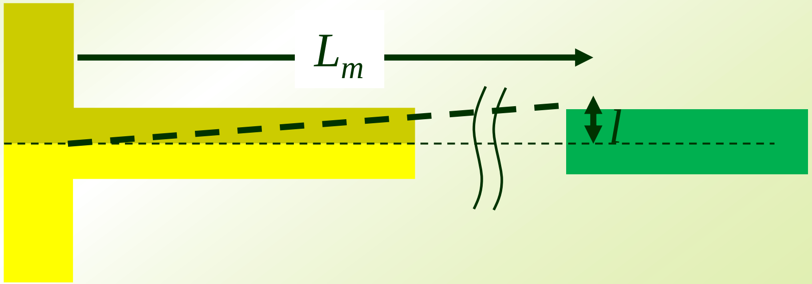
$$J = -D\nabla\phi \qquad J = -D\frac{\partial C}{\partial x}$$

$$\frac{\partial \phi}{\partial t} = D\nabla^2\phi \qquad \frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

$$n(x,t) = n(0)\,\mathrm{erfc}\left(\frac{x}{2\sqrt{Dt}}\right)$$

Diffusion length

Ex. Mixing of fluids in a straight microchannel



$l \sim (Dt)^{0.5}$ $\quad t = L_m / U \qquad \mathrm{Pe} = Ul/D$

$L_m \sim U \times (l^2/D)$

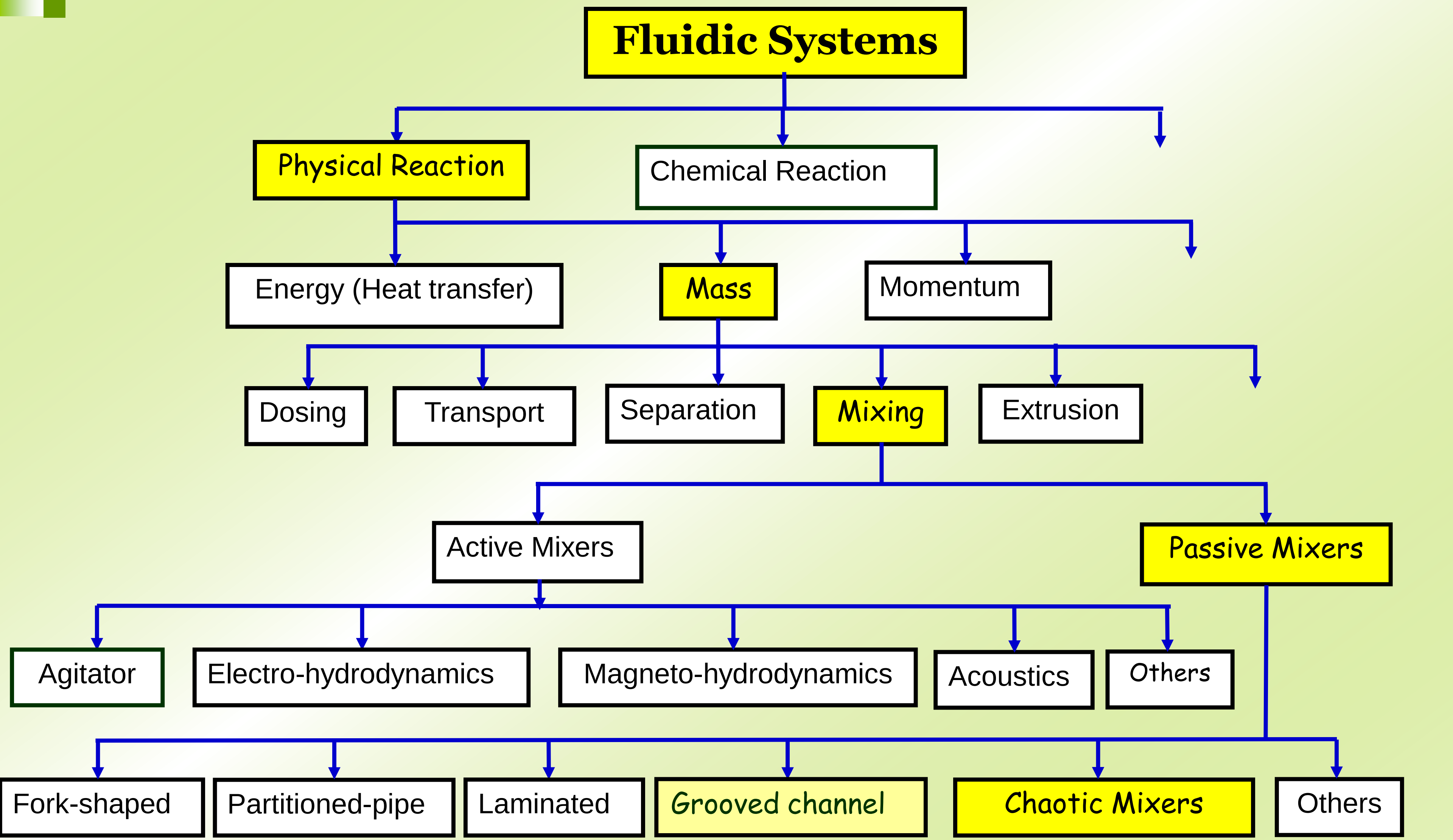
$L_m \sim \mathrm{Pe} \times l$

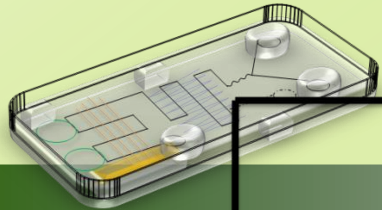
$U = 1$ mm/s, $D = 10^{-10}$ m^2/s, $l = 100$ μm

$L_m = 10$ cm !!

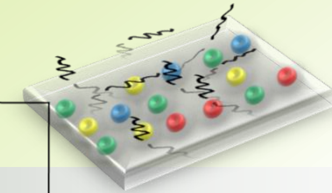
Structural design of microchannels (i.e. micromixers) is urgently required.

Detail Category of the Fluidic Elements





生物晶片技術



晶片實驗室/微流體晶片

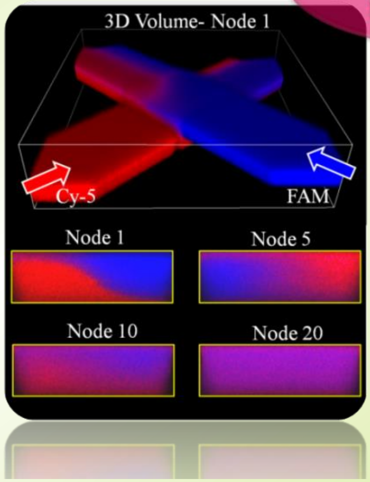
- 傳輸
- 分離
- 混合/反應
- 過濾/篩選
- 純化
- 檢測

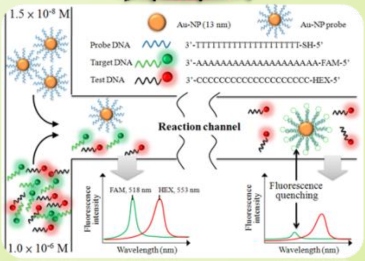
微陣列晶片

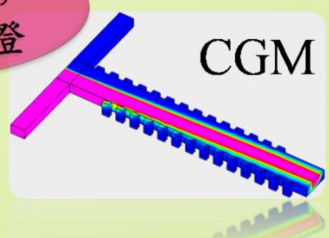
- 組織晶片
- 蛋白質晶片
- 醣晶片
- DNA晶片

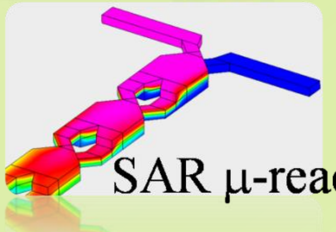
創新微生化反應器之設計分析與應用

- 量測技術的開發
- 元件設計，分析與驗證
- 先導應用與測試



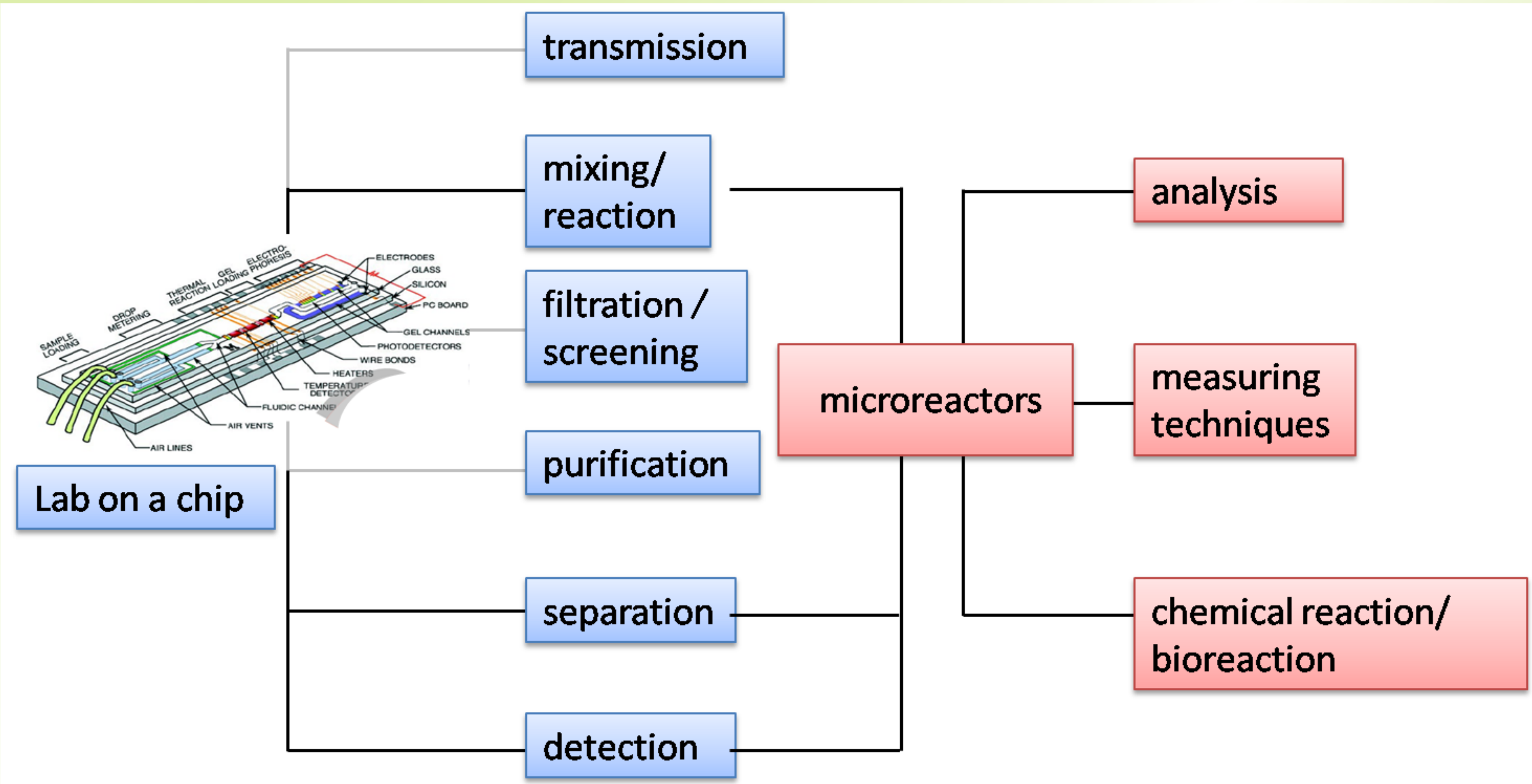




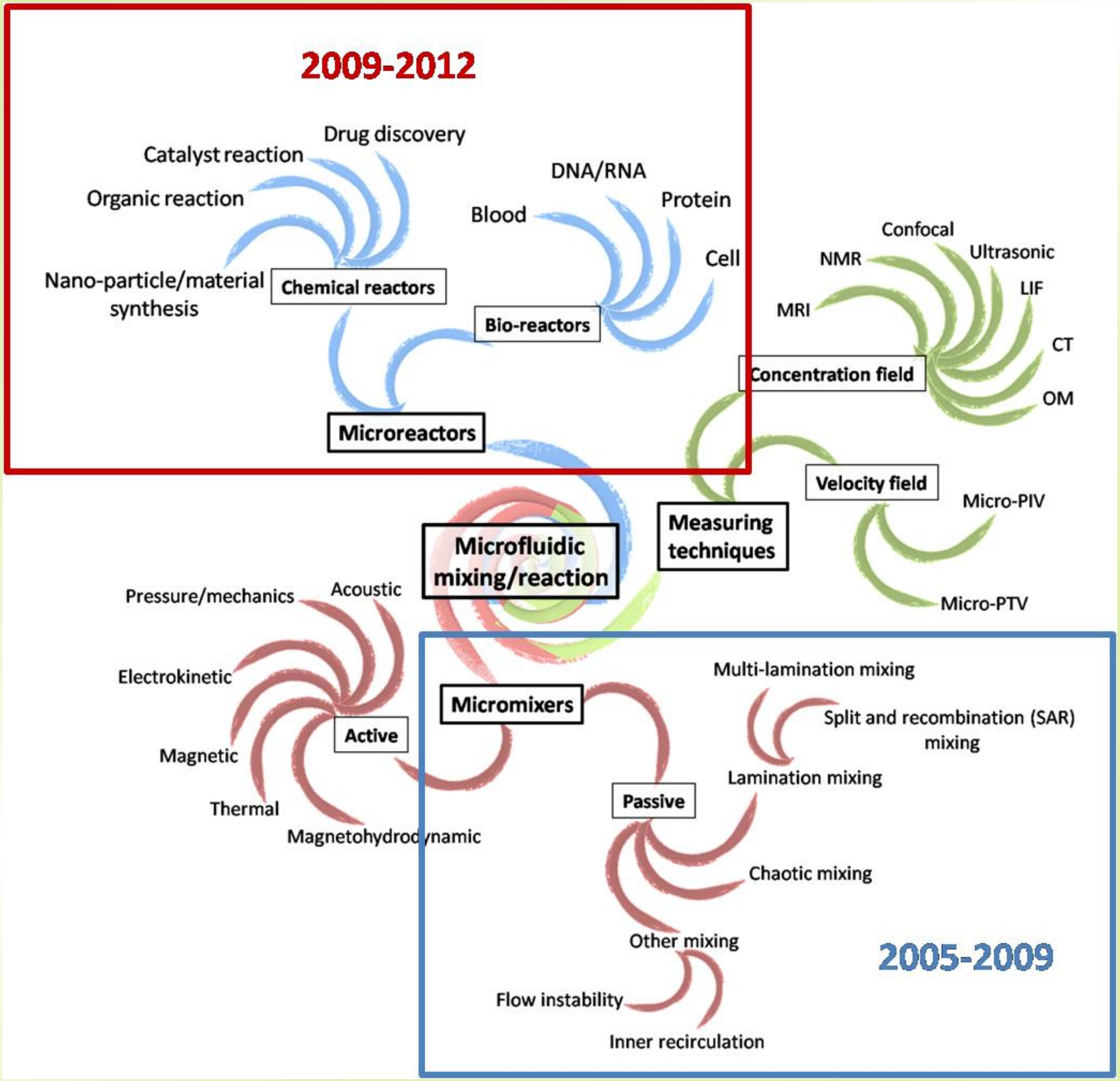


31

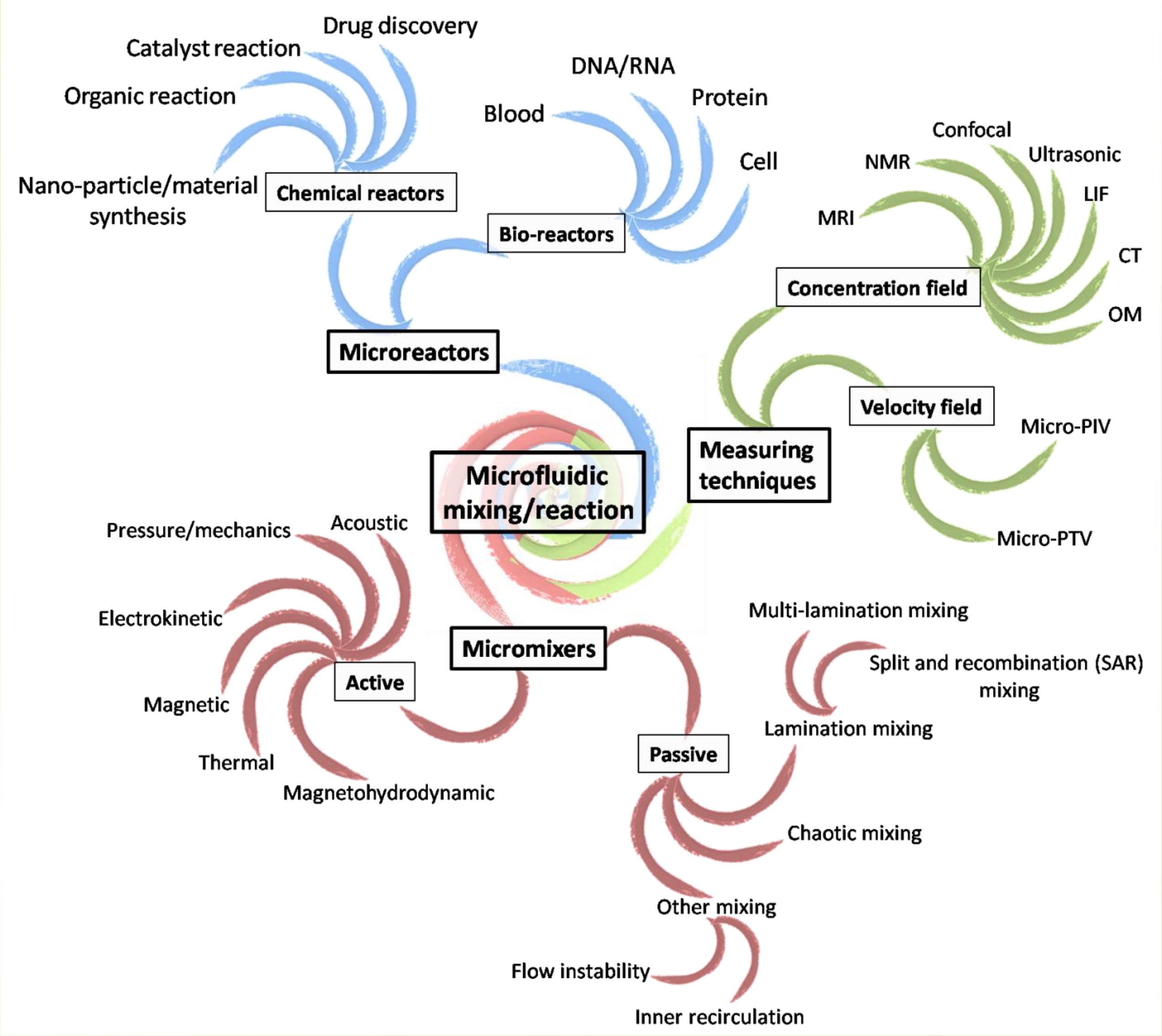
Research Targets in bio-medical diagnosis



Research Progress in Beam Lab.

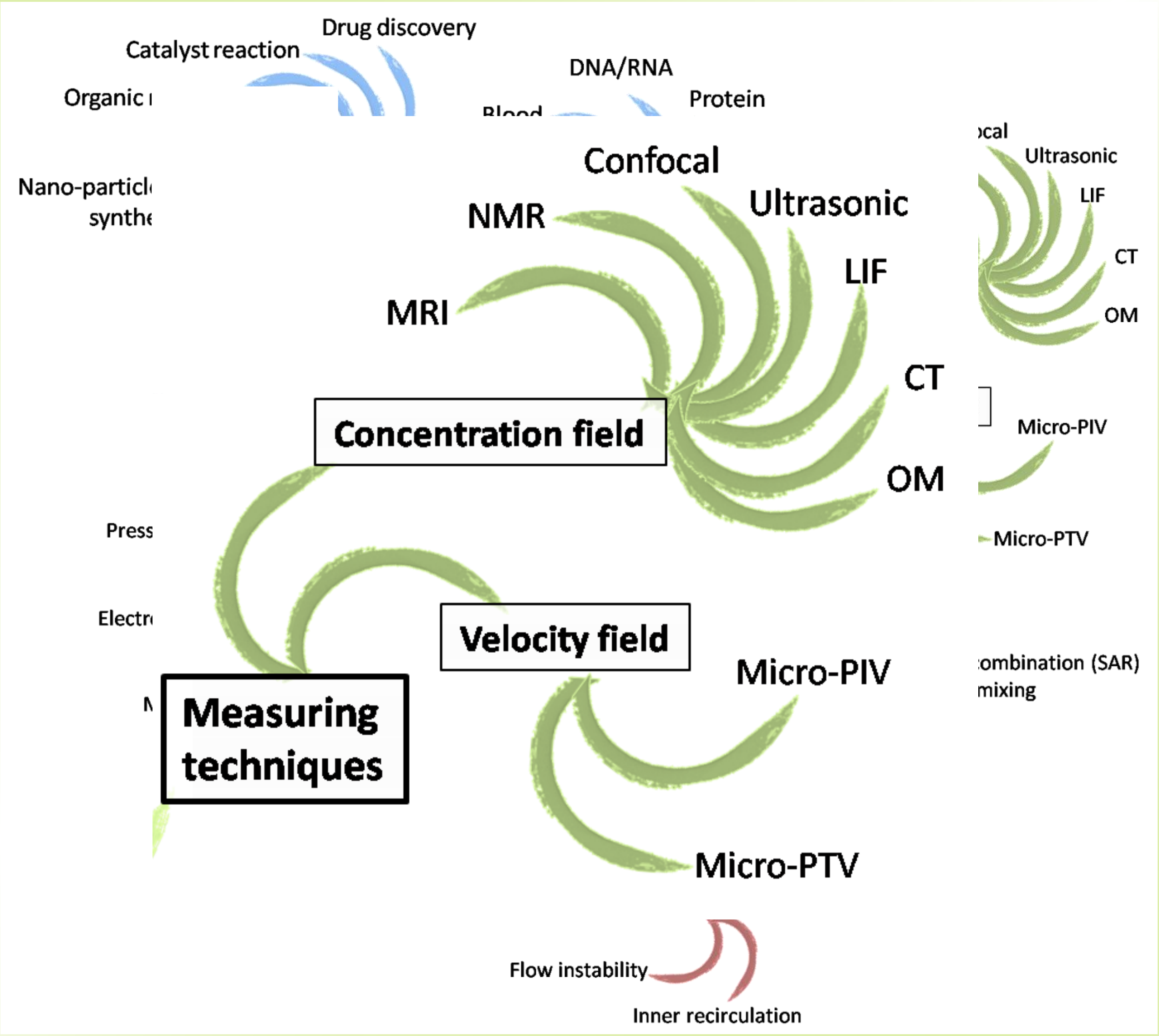


R&D Items

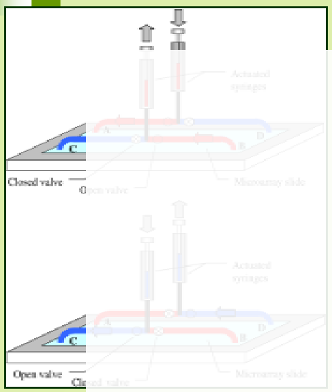


Drug discovery
Catalyst reaction
Organic reaction
Nano-particle/material synthesis
Chemical reactors
DNA/RNA
Protein
Blood
Cell
Bio-reactors
Microreactors
Confocal
Ultrasonic
NMR
LIF
MRI
CT
Concentration field
OM
Velocity field
Micro-PIV
Measuring techniques
Micro-PTV
Microfluidic mixing/reaction
Pressure/mechanics
Acoustic
Electrokinetic
Active
Magnetic
Thermal
Magnetohydrodynamic
Micromixers
Multi-lamination mixing
Split and recombination (SAR) mixing
Lamination mixing
Passive
Chaotic mixing
Other mixing
Flow instability
Inner recirculation

R&D Items


Drug discovery
Catalyst reaction
DNA/RNA
Organic
Protein
Confocal
Ultrasonic
NMR
LIF
MRI
CT
Concentration field
OM
Velocity field
Micro-PIV
Measuring techniques
Micro-PTV
Flow instability
Inner recirculation
Ultrasonic
LIF
CT
OM
Micro-PIV
Micro-PTV
mixing

Introduction



McQuain et al., Anal. Biochem., 2004

Kim *et al.*, *Analyst*, 2005

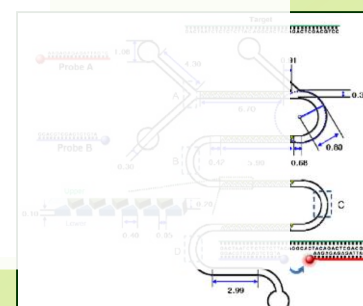
Micromixer / microreactor

- **Active**
  - Acoustic
  - Electric
  - Thermal
  - Magnetic
  - Mechanical
  - Other
- **Passive**
  - **Chaotic advection**
  - **Serial lamination (split-and-recombination, SAR)**
  - Parallel lamination
  - Other

Transverse component !!

Contact interface !!

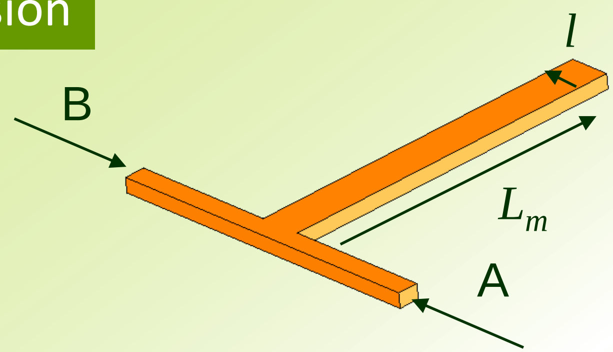
Pappaert *et al.*, *J. Chromatogr. A*, 2003



Chen *et al.*, *Biosens. Bioelectron.*, 2008

Micromixers (chaotic advection)

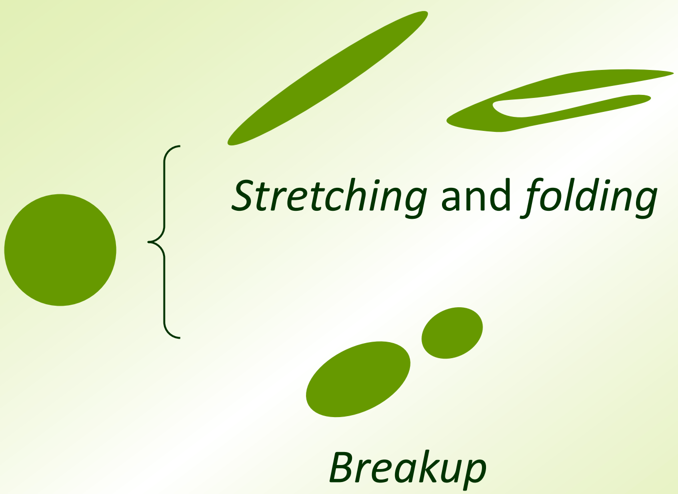
Molecular diffusion

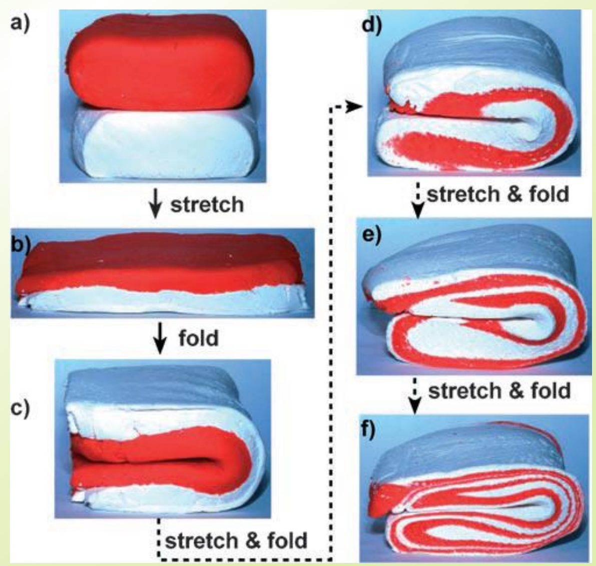


$$L_m \sim U \times (l^2/D) = \mathrm{Pe} \times l$$

$$\mathrm{Pe} = \mathrm{U}l/D$$

Chaotic advection





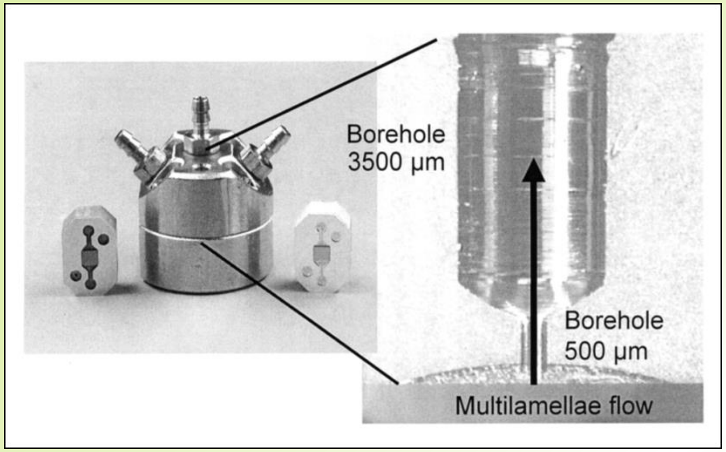
$$L_m \sim \lambda \ln (\mathrm{Pe})$$

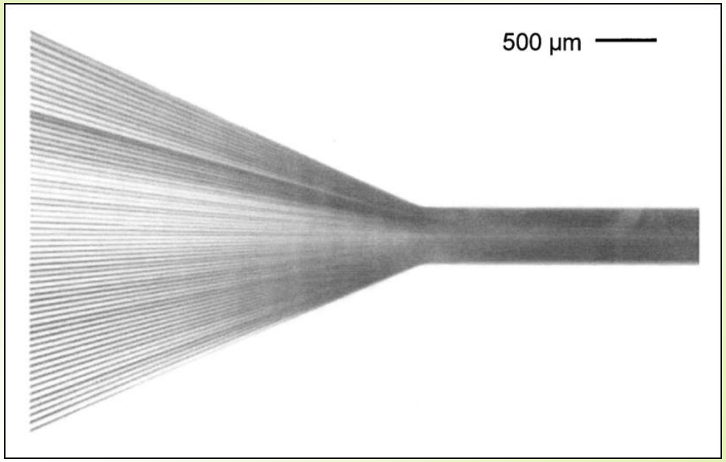
Ottino, J. M., 1989

Elongating the material interface

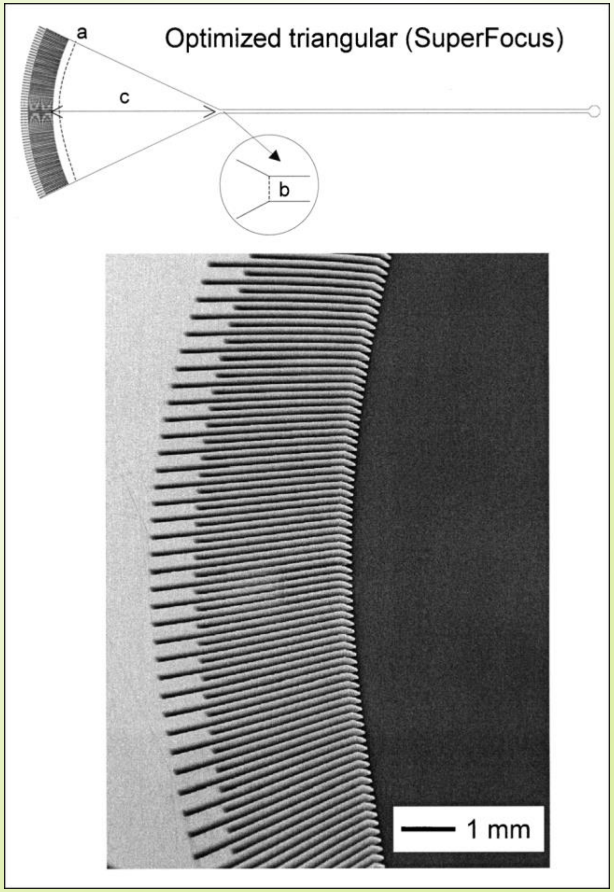
Micromixers (Lamination micromixers)

SuperFocus interdigital micromixer





Parallel lamination

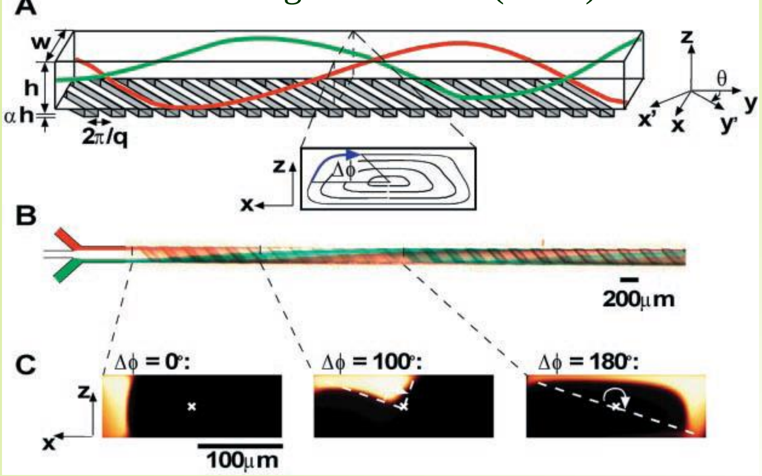


Hessel *et al.*, *AIChE J.*, 2003a,b

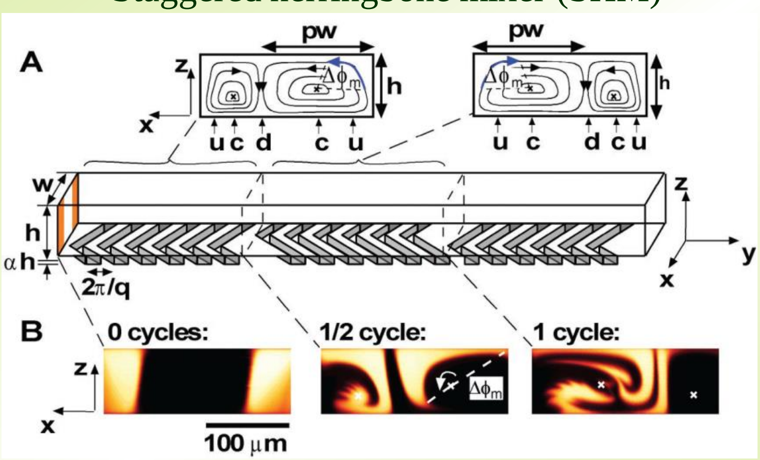
Times cited > 200

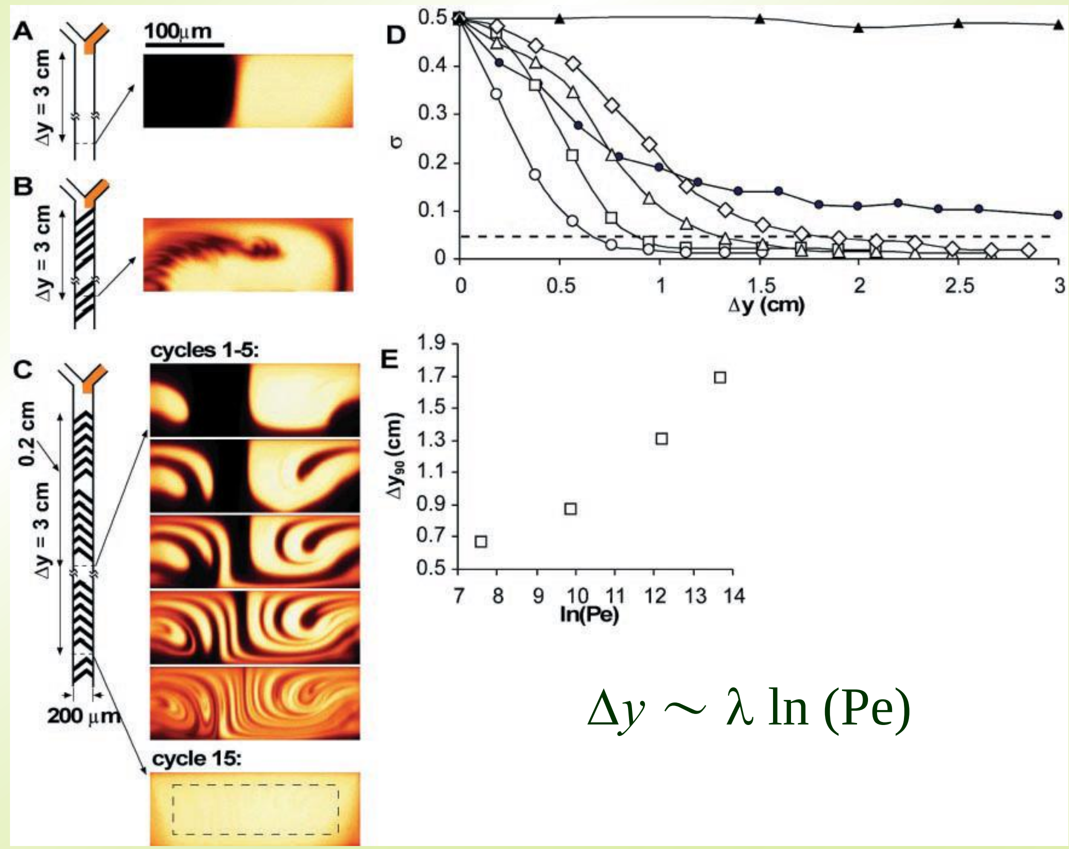
Micromixers (chaotic micromixers)

Slanted-groove mixer (SGM)



Staggered herringbone mixer (SHM)





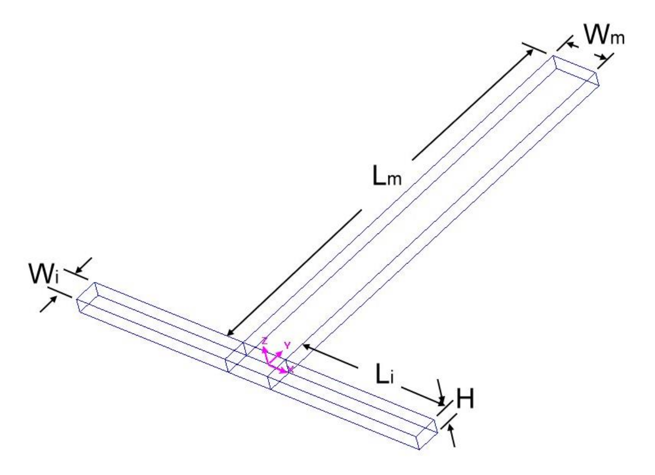
$$\Delta y \sim \lambda \ln(\mathrm{Pe})$$

Stroock *et al.*, *Science*, 2002

times cited > 1620

Numerical Model and Simulation

三維不可壓縮的穩定流場的統御方程式為：



連續方程式

$$\frac{\partial u_k}{\partial x_k} = 0$$

動量方程式

$$u_k \frac{\partial u_i}{\partial x_k} = -\frac{1}{\rho}\frac{\partial p}{\partial x_i} + \frac{\mu}{\rho}\frac{\partial}{\partial x_k}\left(\frac{\partial}{\partial x_k} u_i\right)$$

濃度方程式

$$u_k \frac{\partial c}{\partial x_k} = D\frac{\partial}{\partial x_k}\left(\frac{\partial c}{\partial x_k}\right)$$

Software：ESI　CFD-GEOM, CFD-ACE+, CFD-VIEW, CRADLE。

Boundary Conditions

邊界條件：

入口處: u_x = constant , $u_y = 0$, $u_z = 0$, c = constant, p = constant

出口處：$\frac{\partial u_i}{\partial x_y} = 0$ $\frac{\partial c}{\partial x_y} = 0$ $p = 0$

邊界處: $u_i = 0$ (no slip condition)

U_i : 在i方向上的速度
p : 壓力
ρ: 流體的密度
μ: 流體的黏滯係數
D: 分子擴散係數
c: 成份濃度

微流體元件之設計與模擬分析

-網格獨立

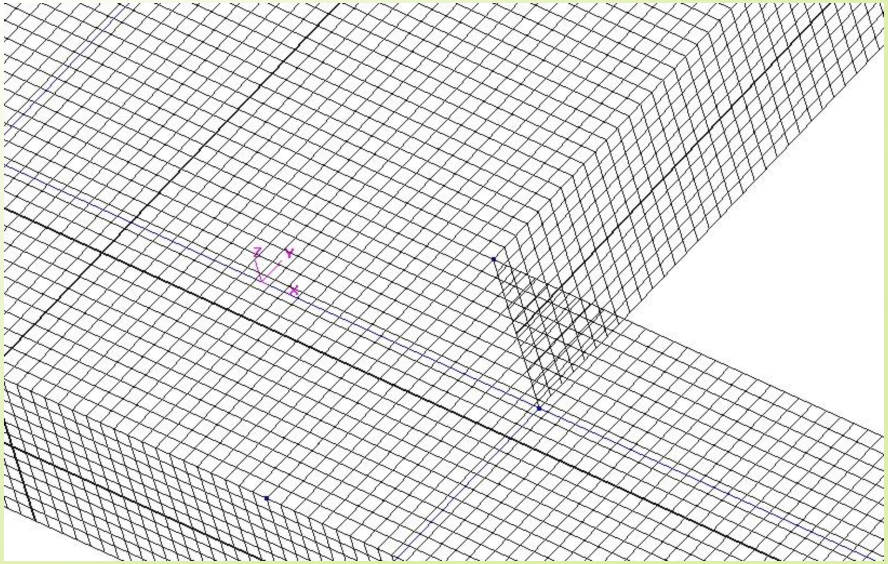
　　解壓力速度的偶合問題上是採用 SIMPLEC的方法。解速度場時是使用中心差分法(central differencing scheme with blending set to 0.1)。 解濃度場時是使用二階的迎風差分法(second-order upwind scheme) (CFD-ACE 2002 user manual)。黏滯係數和擴散係數設為常數，無化學反應發生，濃度已經過正常化(normalized)，右入口處的濃度為1，左入口處的濃度為0 。收斂的條件為獨立參數在兩次相隔的計算(sweeps)中必須符合：

$$\max\left|\frac{\phi^{n+1}-\phi^{n}}{\phi_r}\right|\leq 10^{-4}$$

其中 ϕ_r：參數的參考值

ϕ^n：參數的第n次計算值

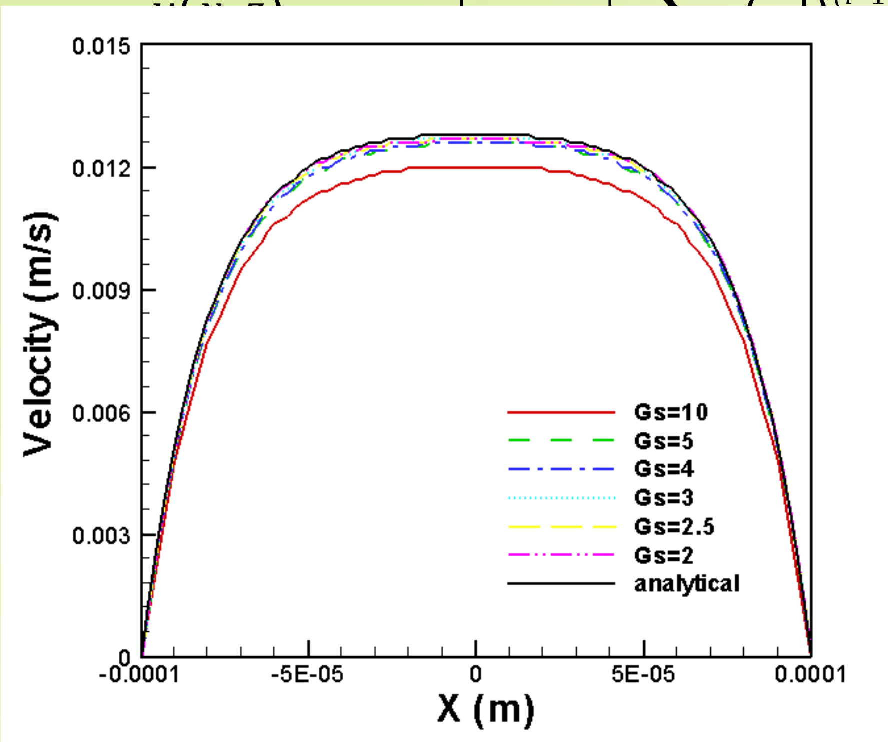
ϕ^{n+1}：參數的第n+1次計算值

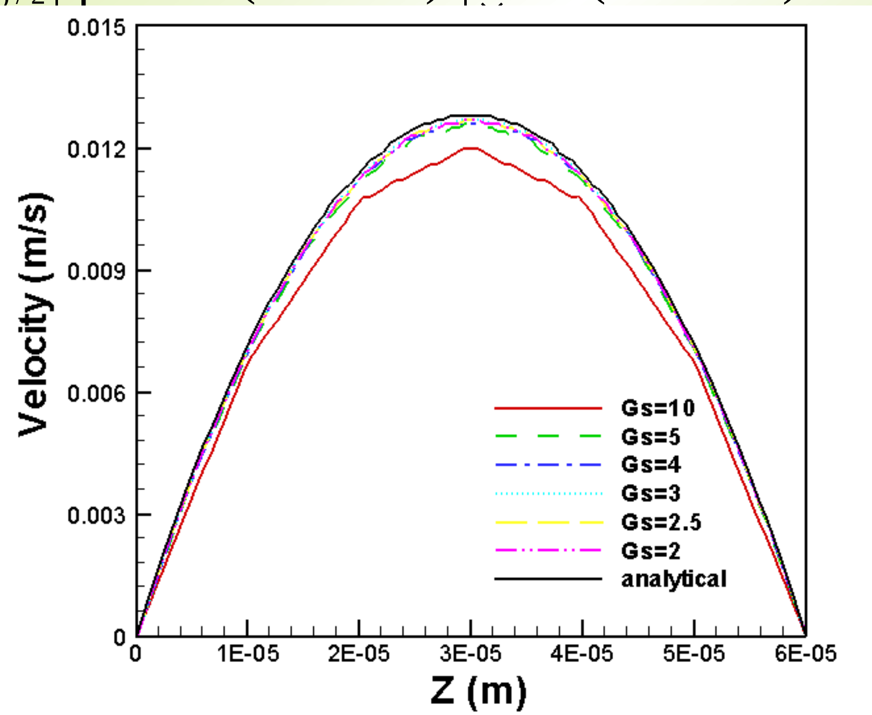


模擬分析結果之驗證

-網格獨立

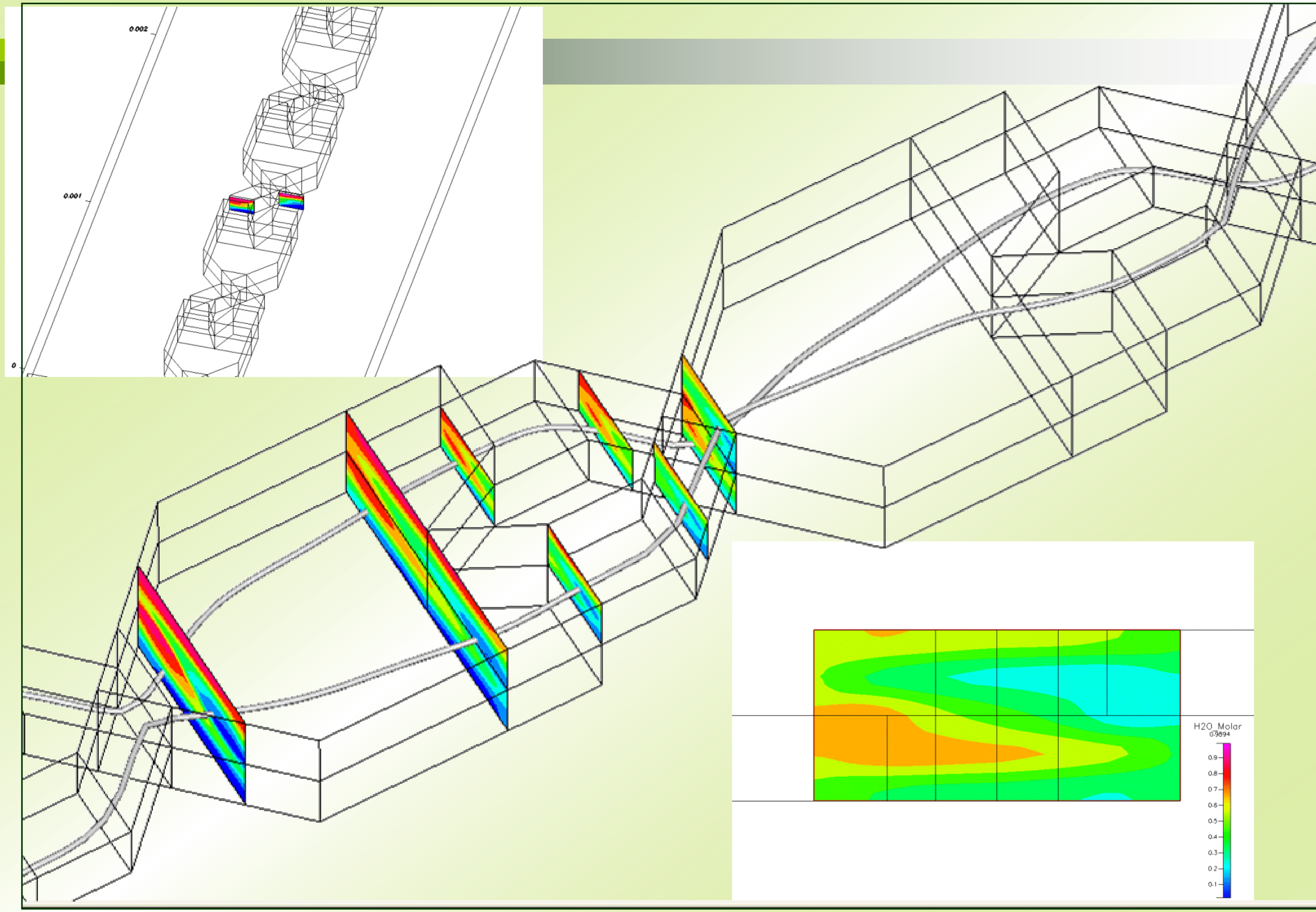
$16a^2 \left(dP \right) \sum^{\infty} \ldots (-1)^{(i-1)/2} \left[1 \ldots \cosh(i\pi z/2a) \right] \ldots \cos(i\pi x/2a)$





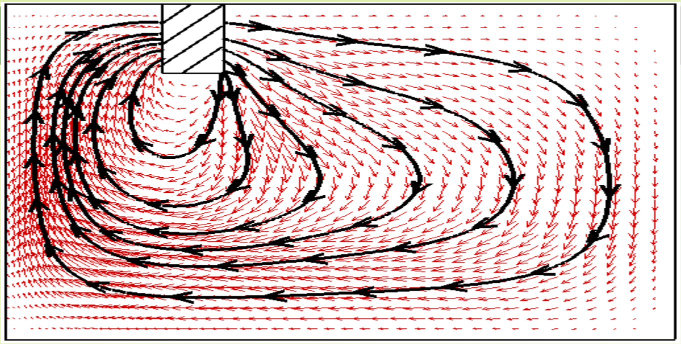
在y = 200 μm，z = 30 μm處各種格點尺寸計算模擬和解析解的 x方向速度分佈比較圖

在x = 0，y = 200 μm處各種格點尺寸計算模擬和解析解的z方向速度分佈比較圖

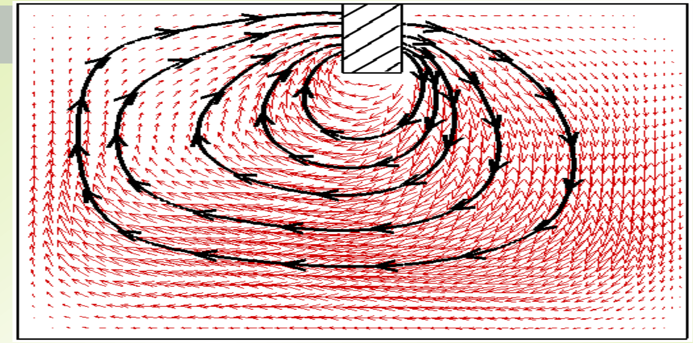


T-type CDM T-type

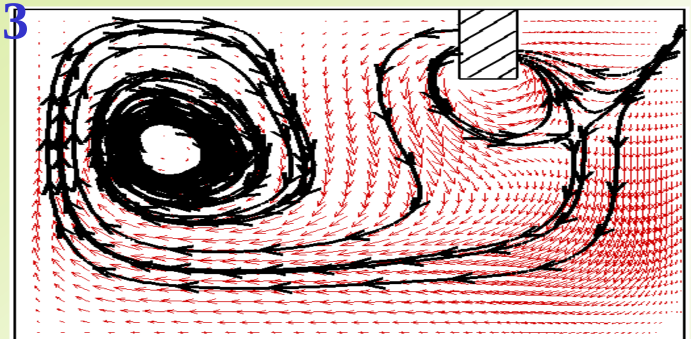
Topological Characteristics of Flow Field



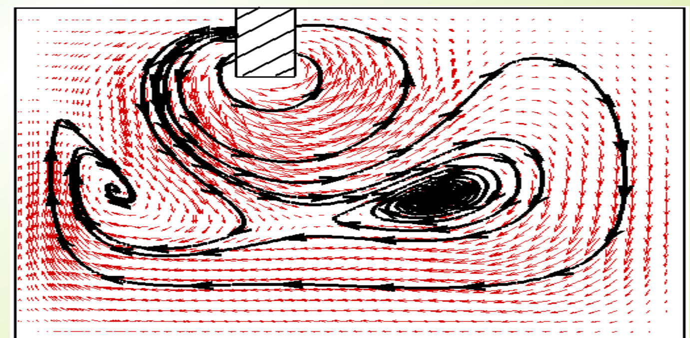
(a) inclined groove No. 1



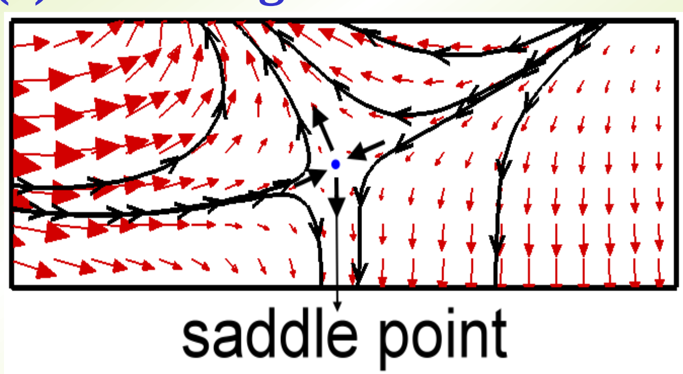
(b) inclined groove No. 3



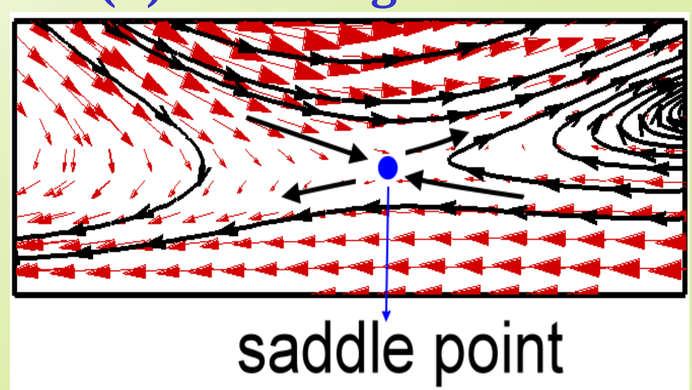
(c) inclined groove No. 5



(d) inclined groove No. 7



(e) enlarger graph of (c)



(f) enlarger graph of (d)

Micromixers (optimization of chaotic micromixers)

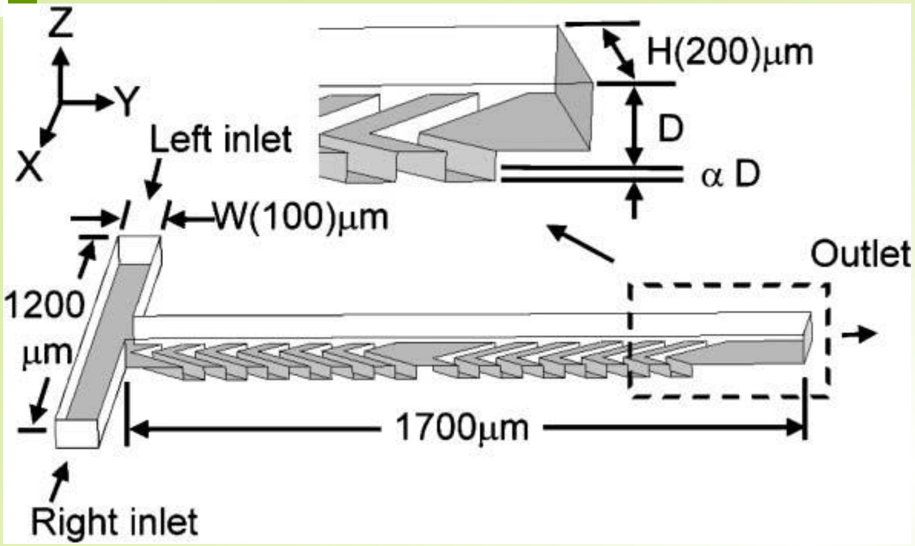
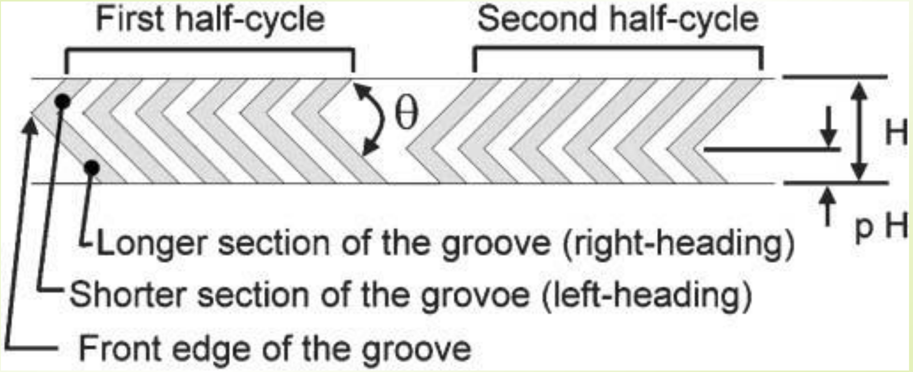


Table 1 Numerical values of geometric parameters				
No.	Parameter	1	2	3
A	Asymmetry index (p)	0.21	0.33	0.45
B	Depth ratio of the groove (α)	0.07	0.13	0.18
C	Upstream to downstream channel width ratio (W/H)	0.5	1	1.5
D	Groove intersection angle (θ)	60°	90°	120°

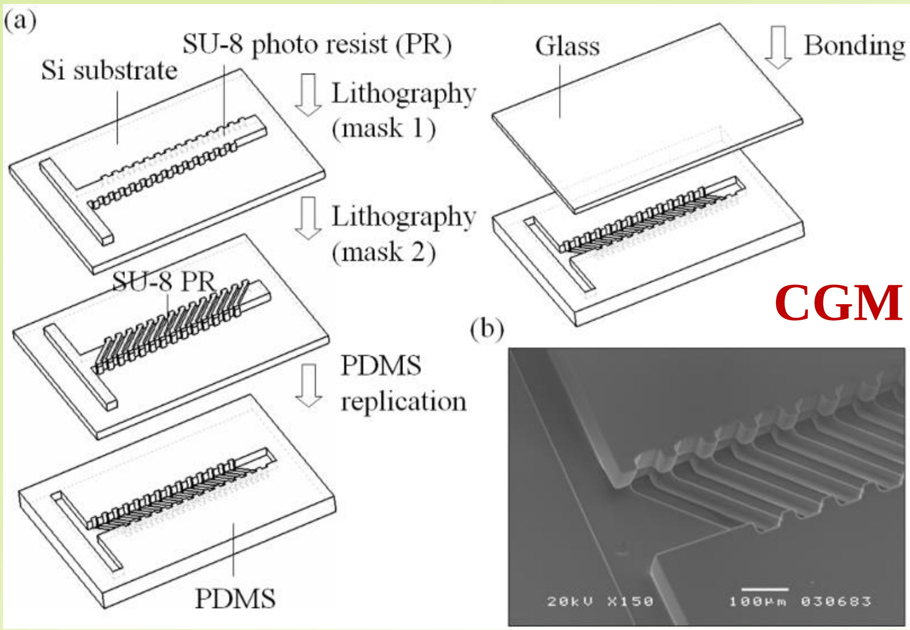


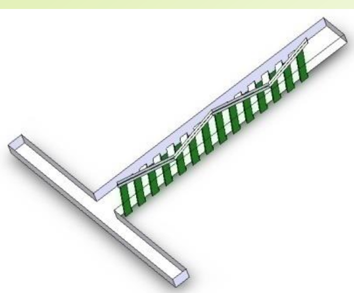
Geometric parameter analysis, based on both the simulation results and the *Taguchi method*, reveal the relative effectiveness as:

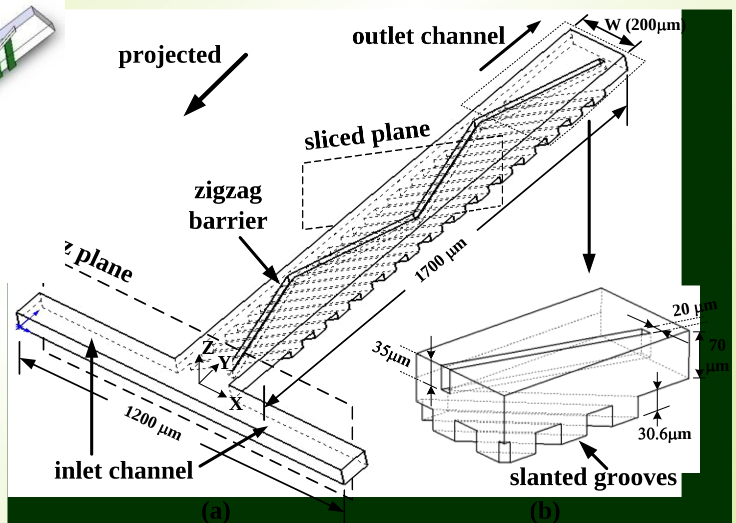
depth ratio of the groove ~ asymmetry index > groove intersection angle > Upstream to downstream channel width ratio.

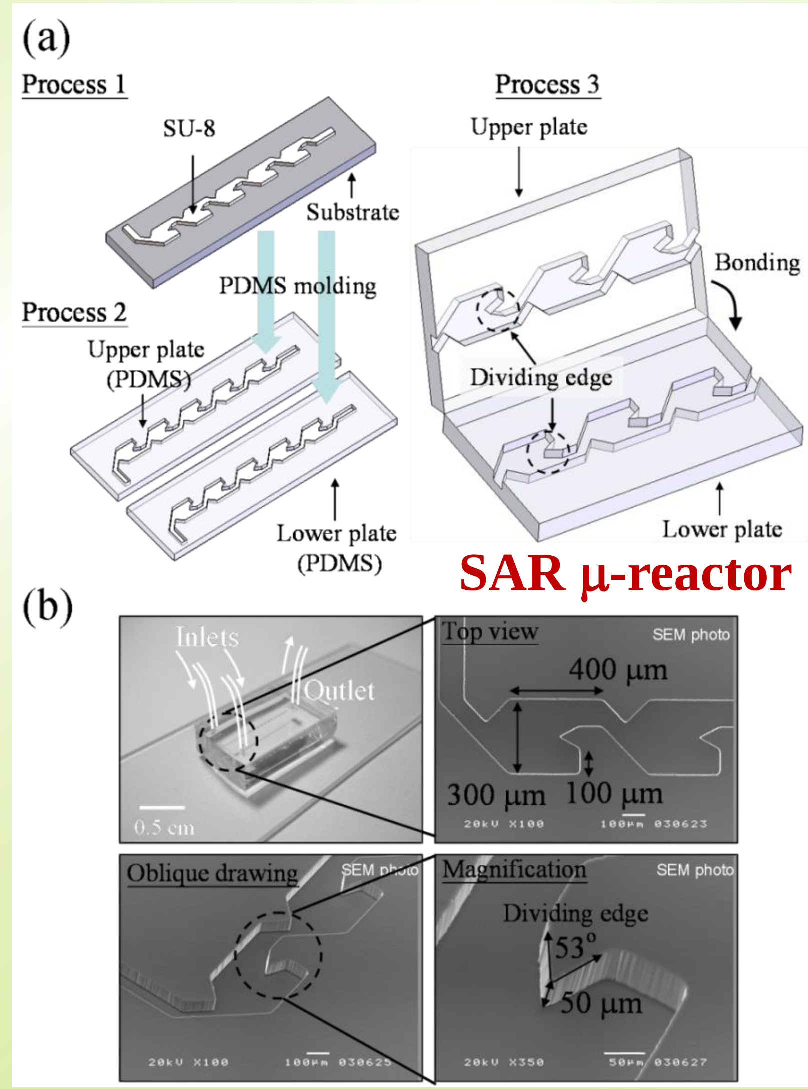
Yang *et al.*, *Lab Chip*, 2005
times cited > 152

Design and Microfabrication



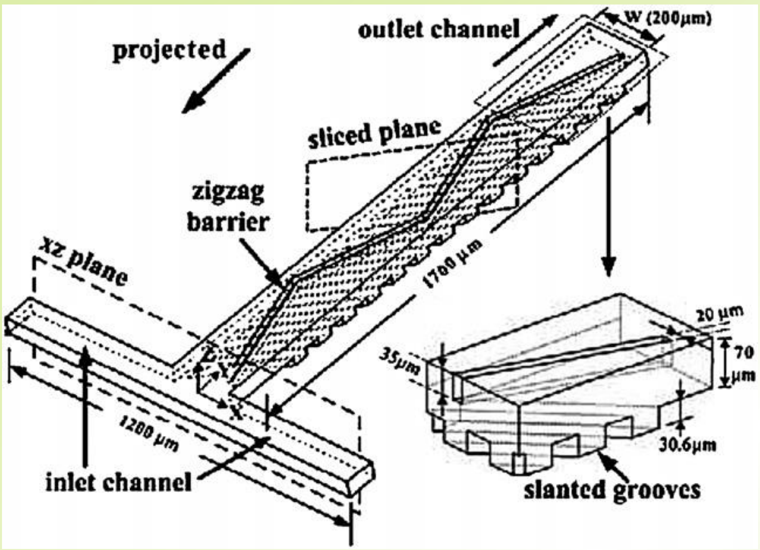


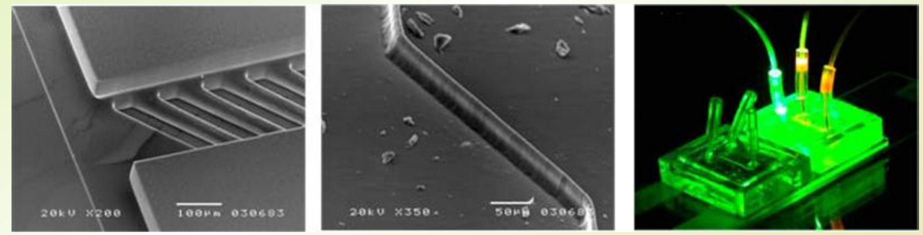


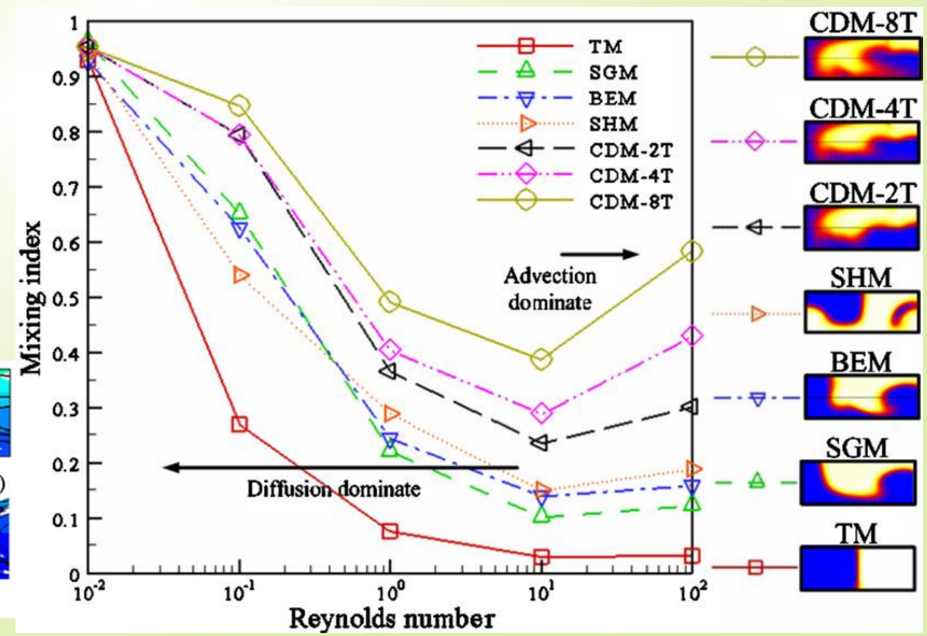


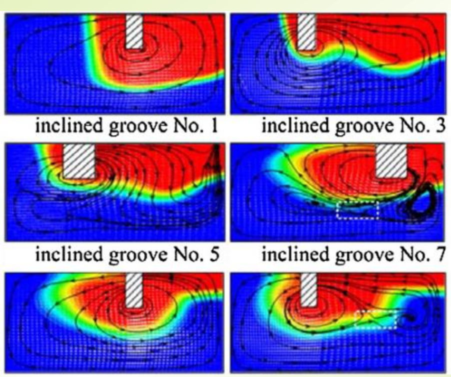
Micromixers (chaotic micromixers)

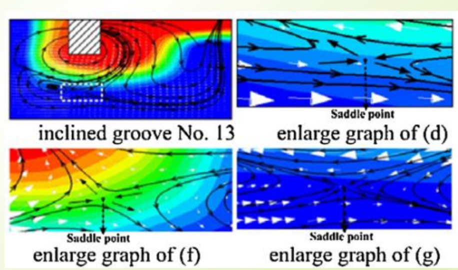
Circulation–disturbance micromixer (CDM)







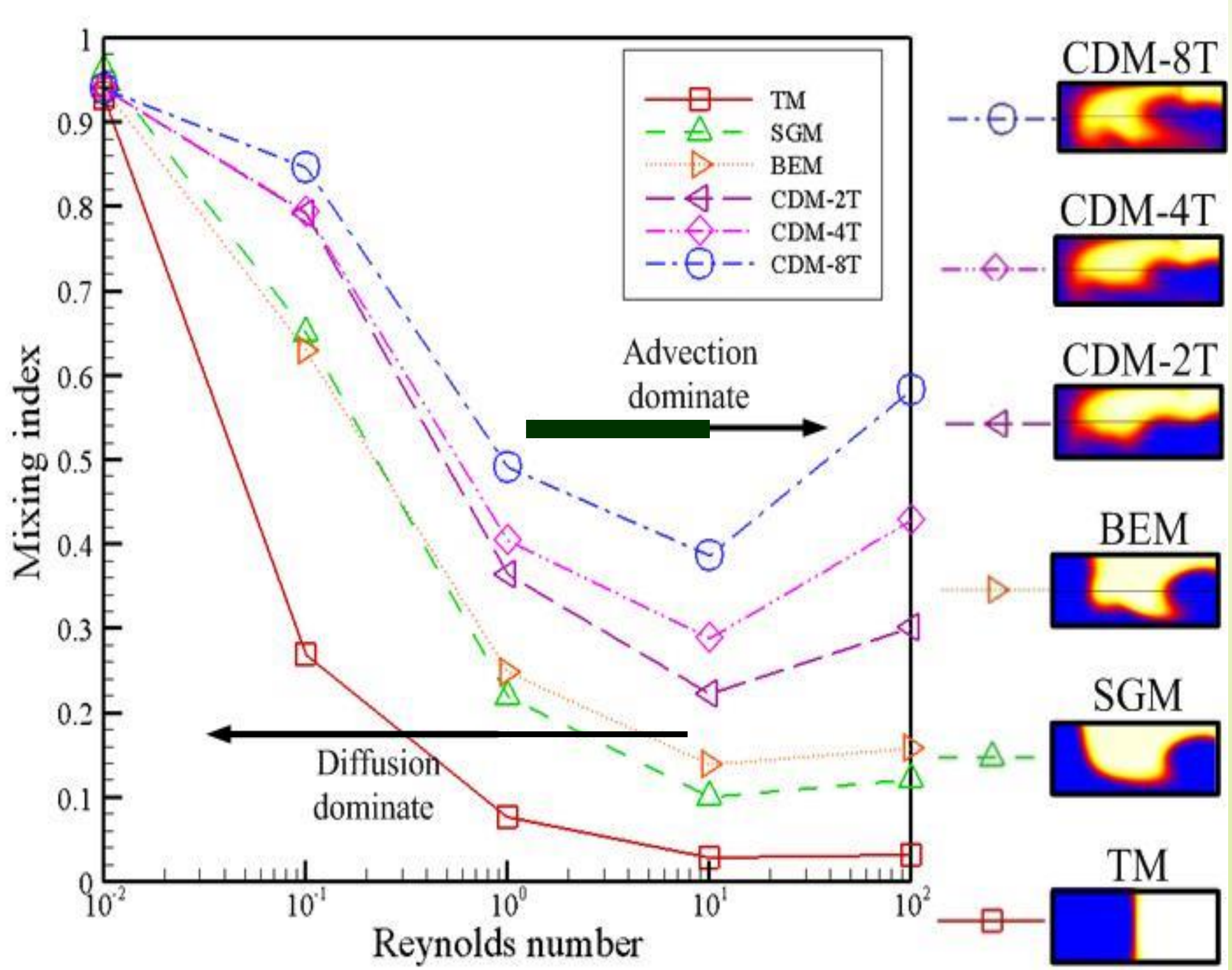


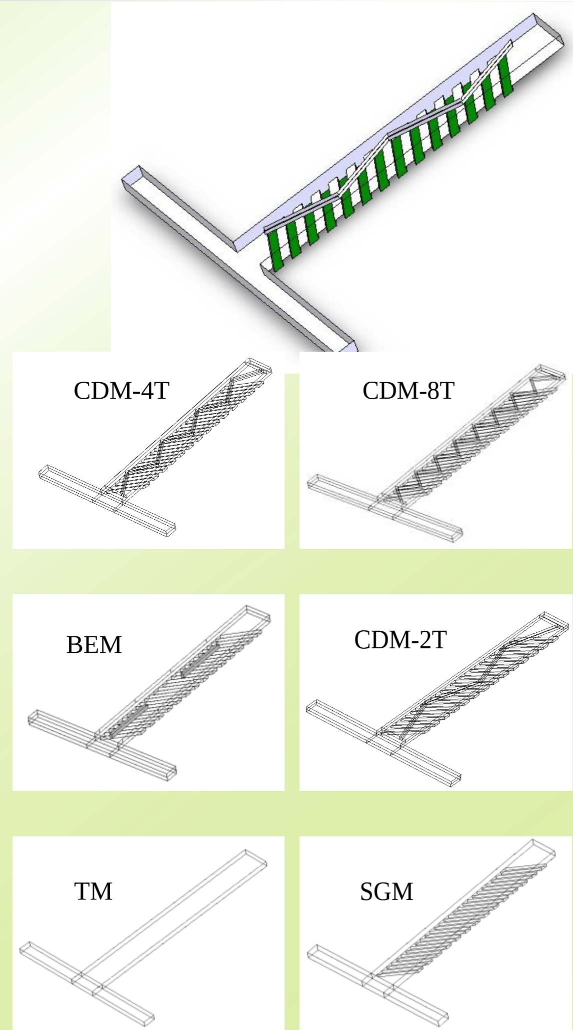


Yang *et al.*, *JMM*, 2007

Enhanced Mixing Performance by CDMs

Yang *et al.* *JMM*, Vol. 17, 2007

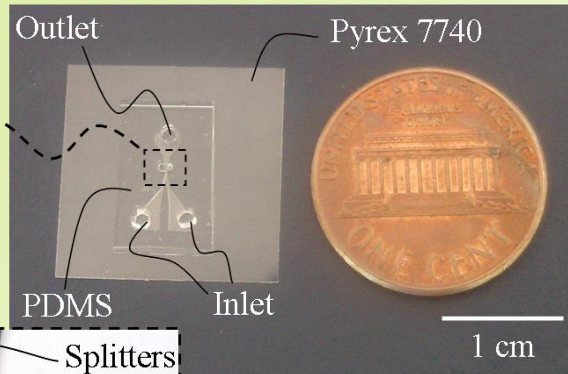




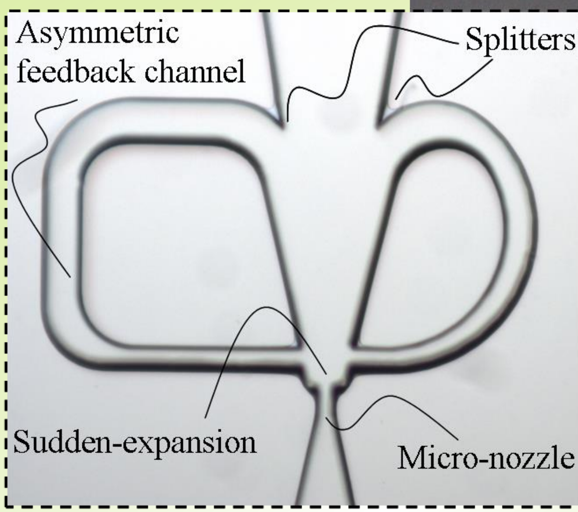
Compared with a slanted groove micromixer at Re = 10, CDM-2T increases 132%, CDM-4T increases 183% and CDM-8T **increases 280%.**

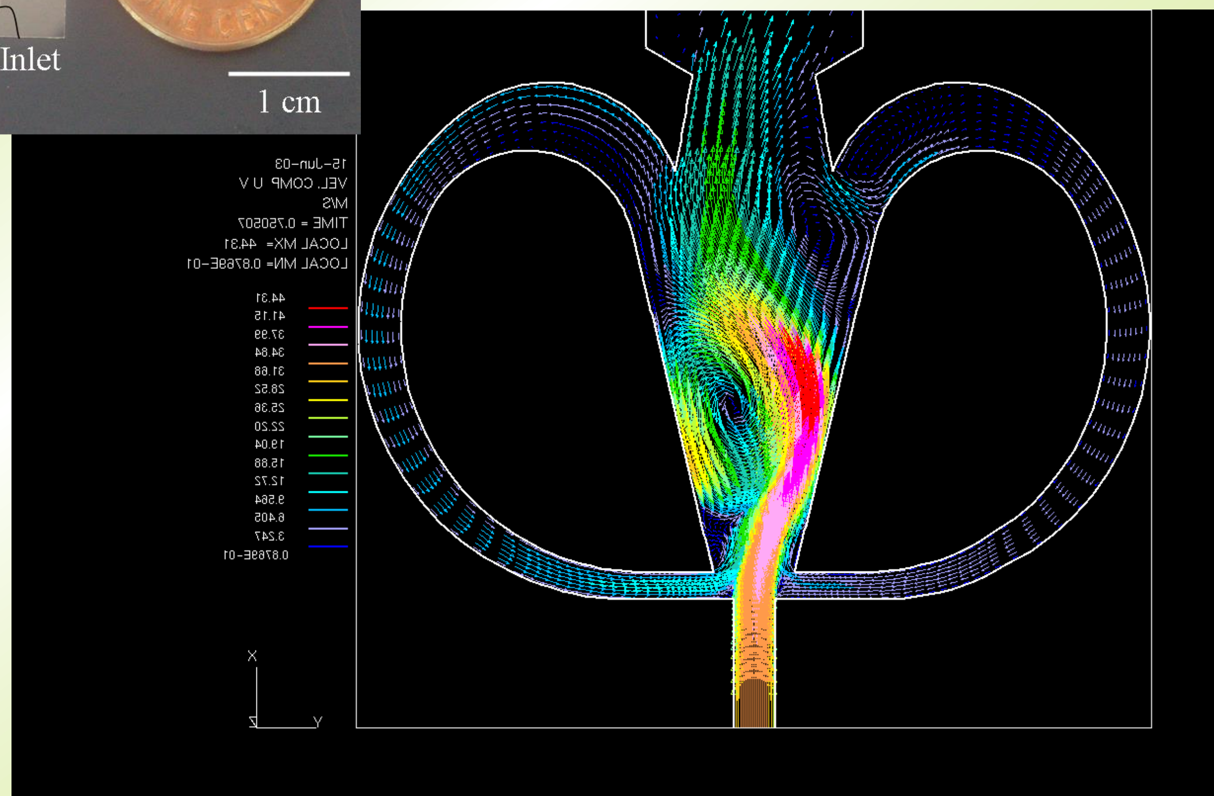
Microfluidic Oscillator

μ-mixer, μ-reactor, μ-nozzle, μ-distributor



← 微流體振盪晶片實品照片與比例





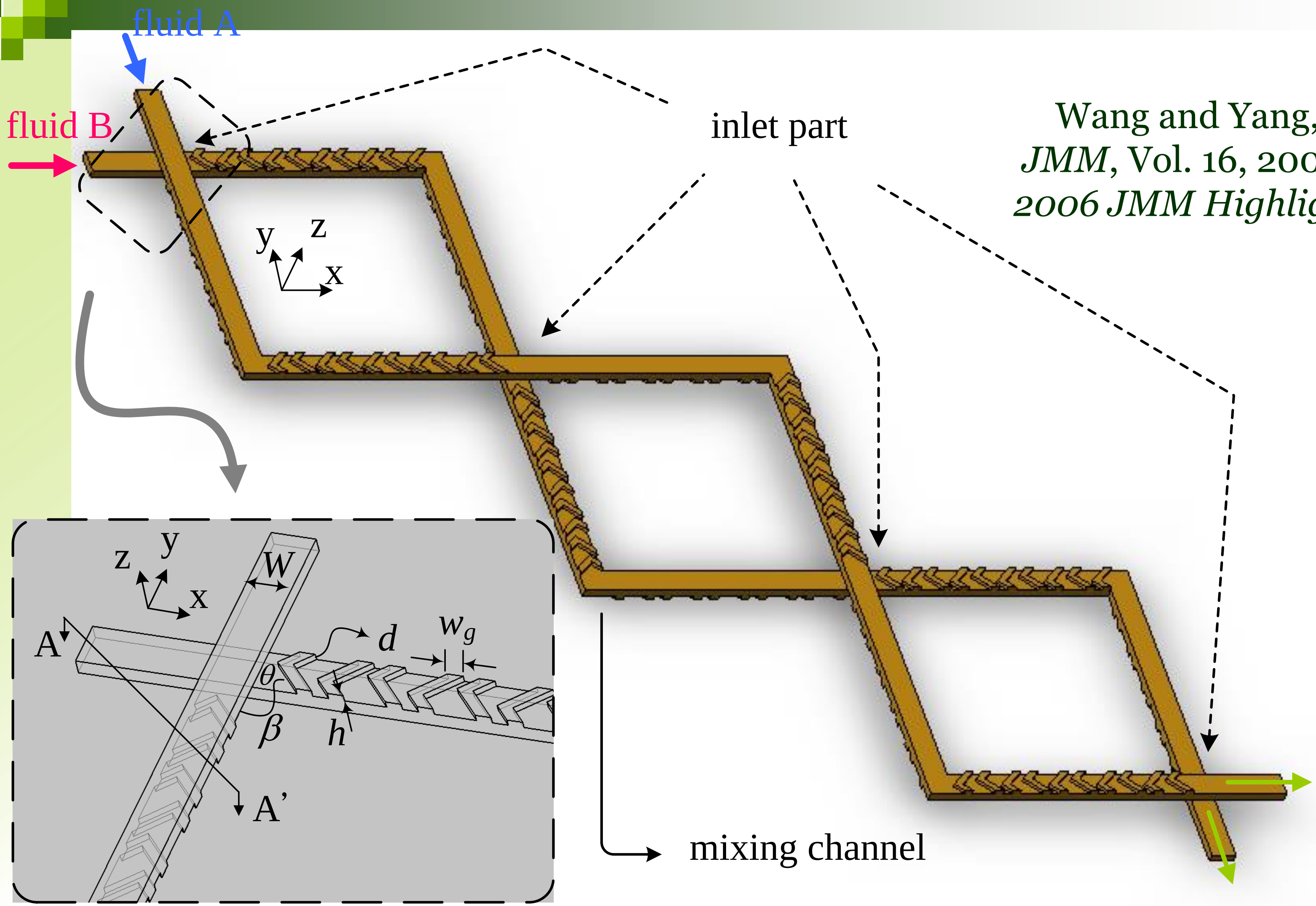
Yang et al., *J. MEMS*, 2006

ROC Patent, 2007

2008 National Invention Prize

US Patent, 2009

Device description of OCμ-mixer



Wang and Yang,
JMM, Vol. 16, 2006.
2006 JMM Highlight

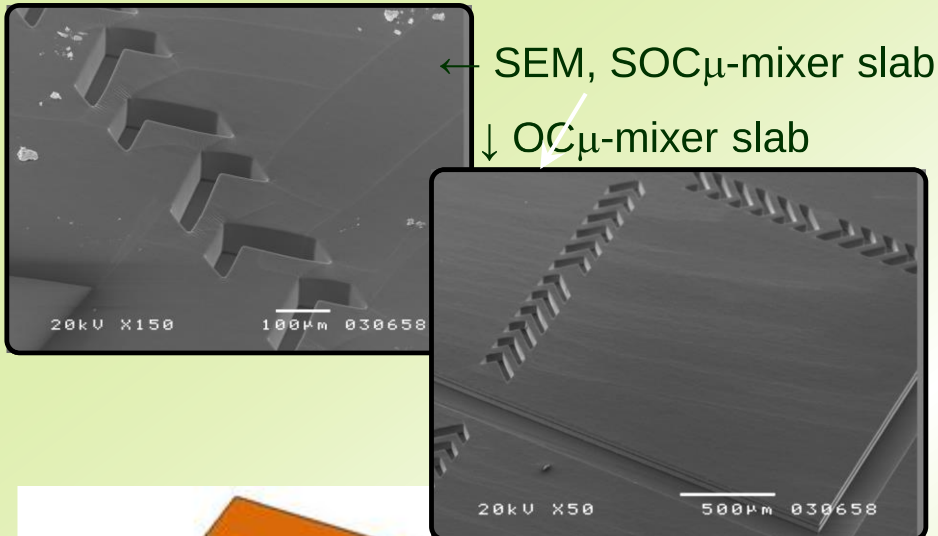
Overlapping-Crisscross Micromixer

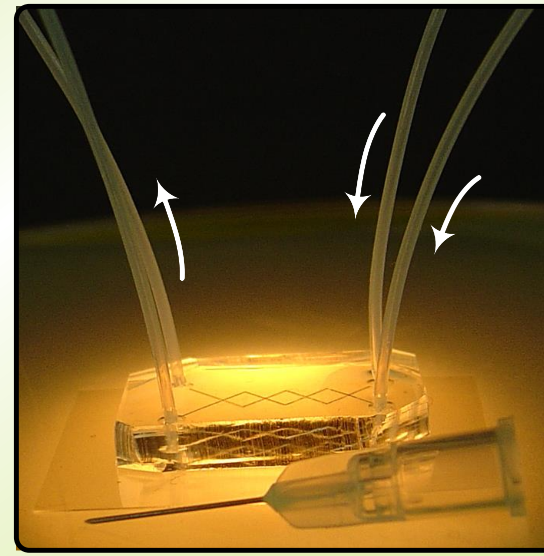
Wang and Yang, *JMM*, 2006.

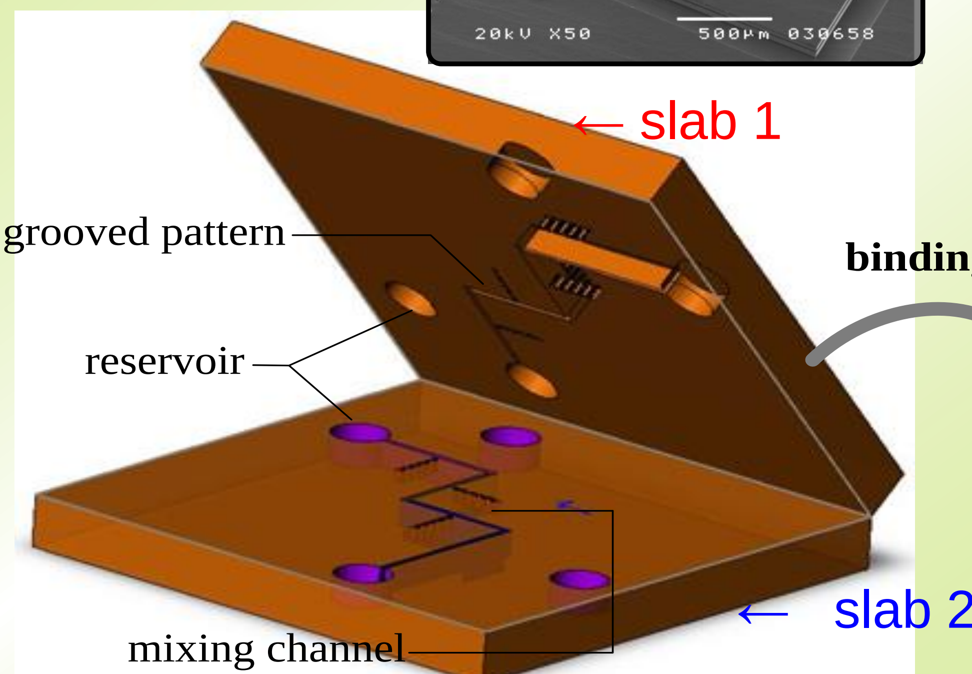
Finished **2006 *JMM Highlight***

← SEM, SOCμ-mixer slab

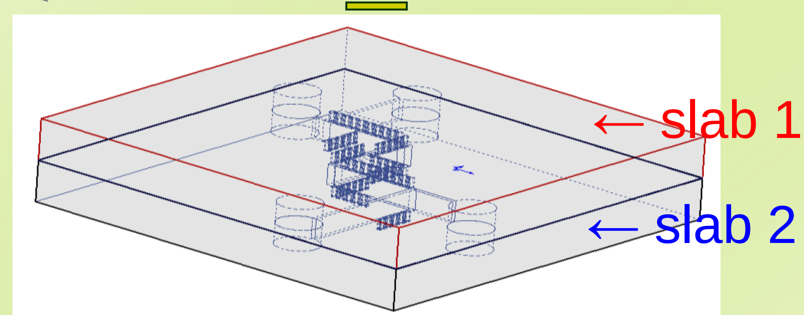
↓ OCμ-mixer slab



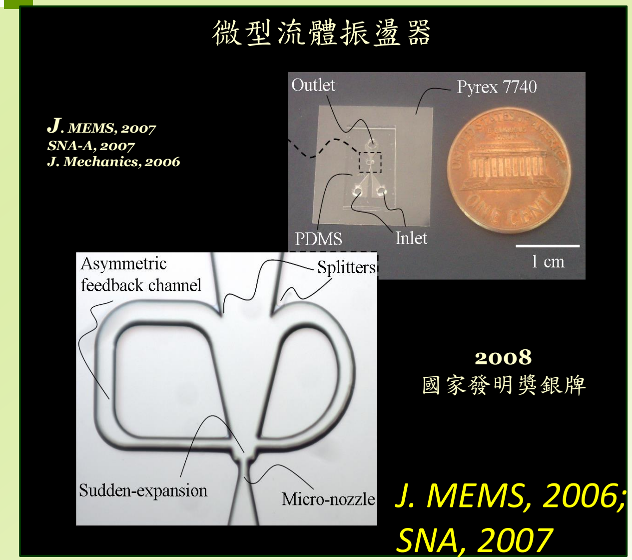


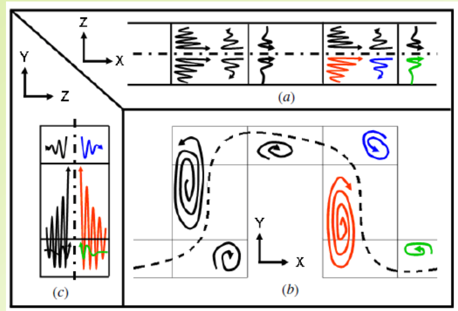


binding

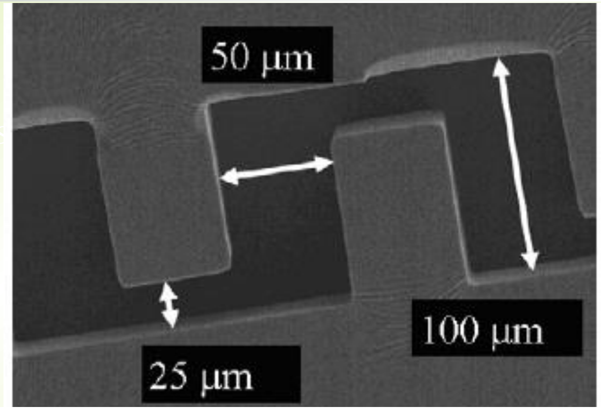


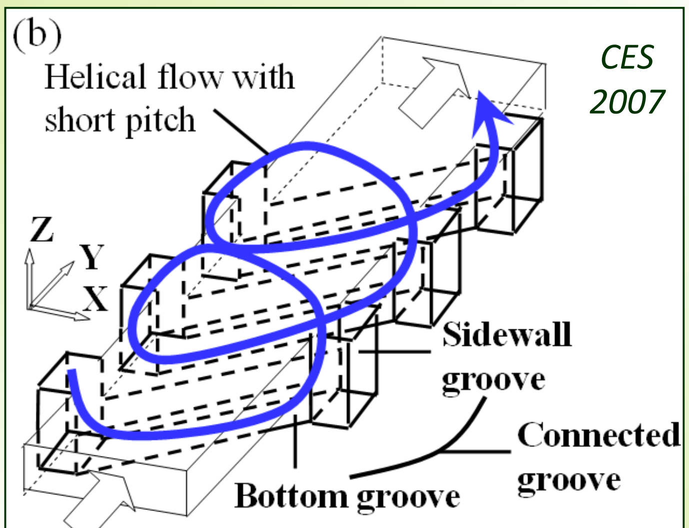
Various Micromixers developed by Beam Lab.



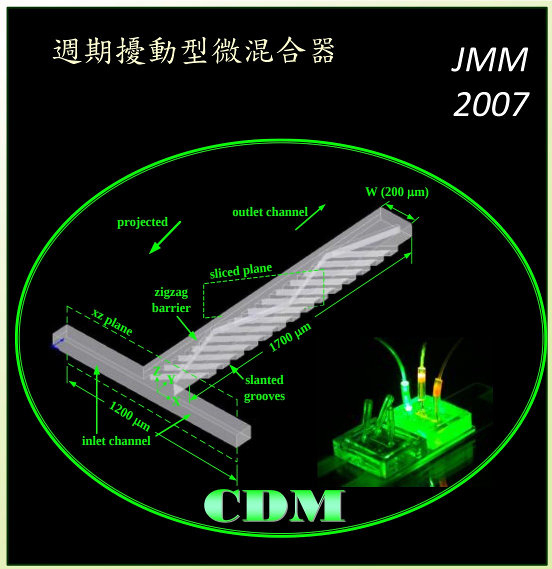


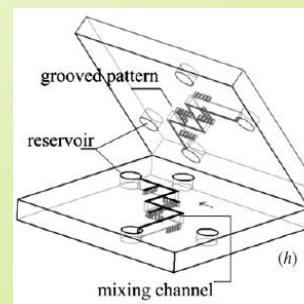
JMM, 2006; IJHMT, 2007

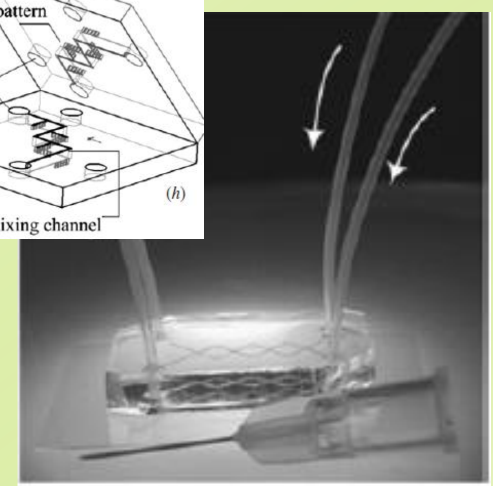




Connected-groove micromixer (CGM)

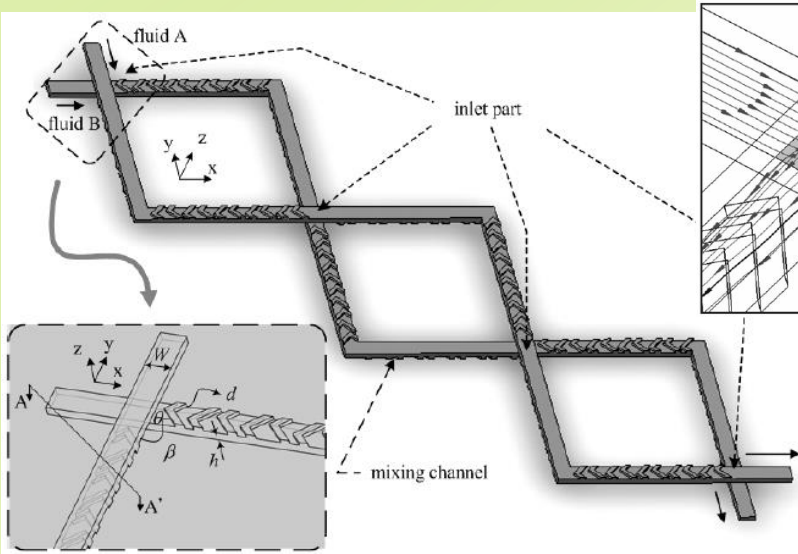


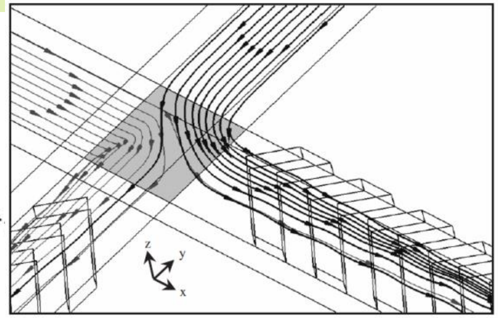


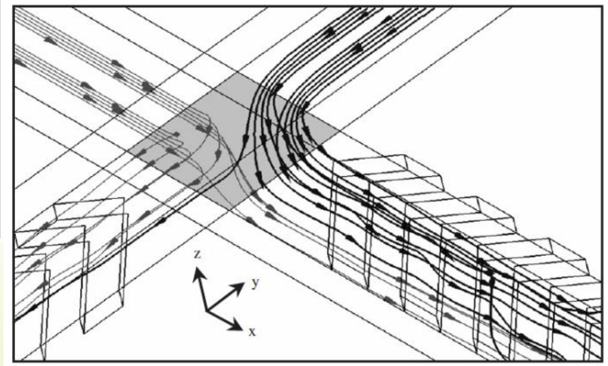


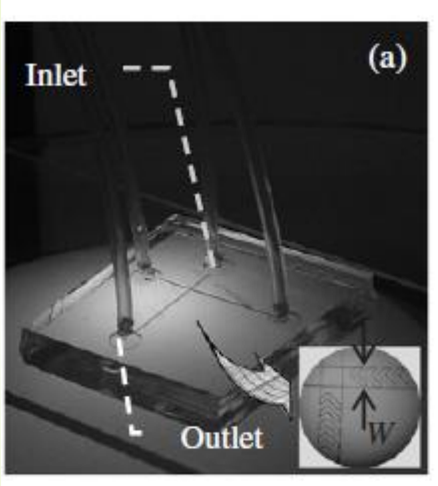
Overlapping Crisscross Micromixers

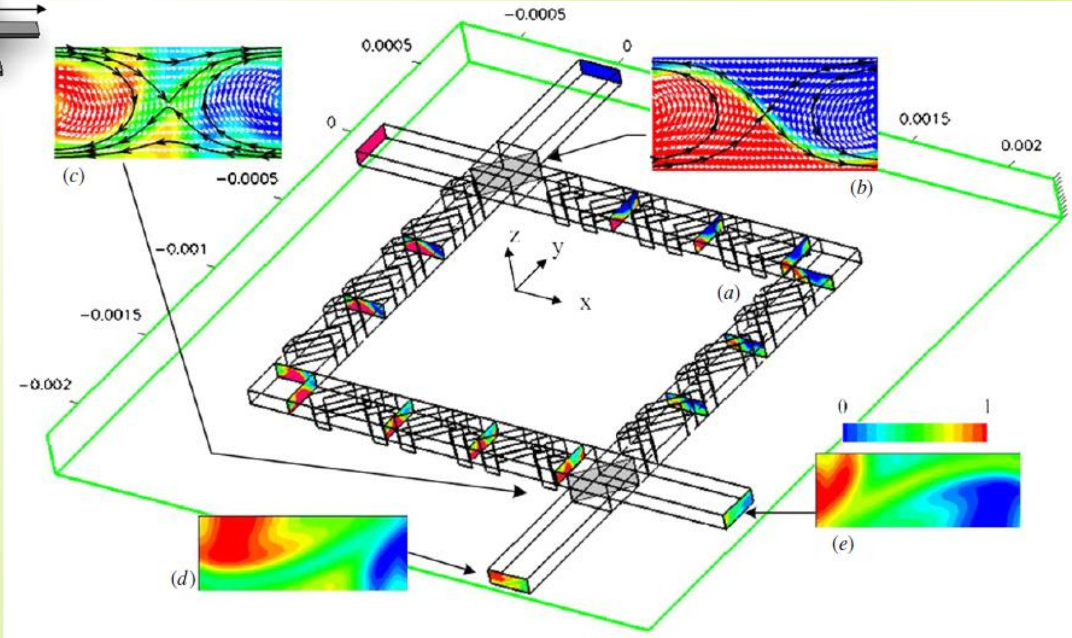
Wang & Yang, JMM Highlights of 2006, Chemical Engineering Science (CES), 2006





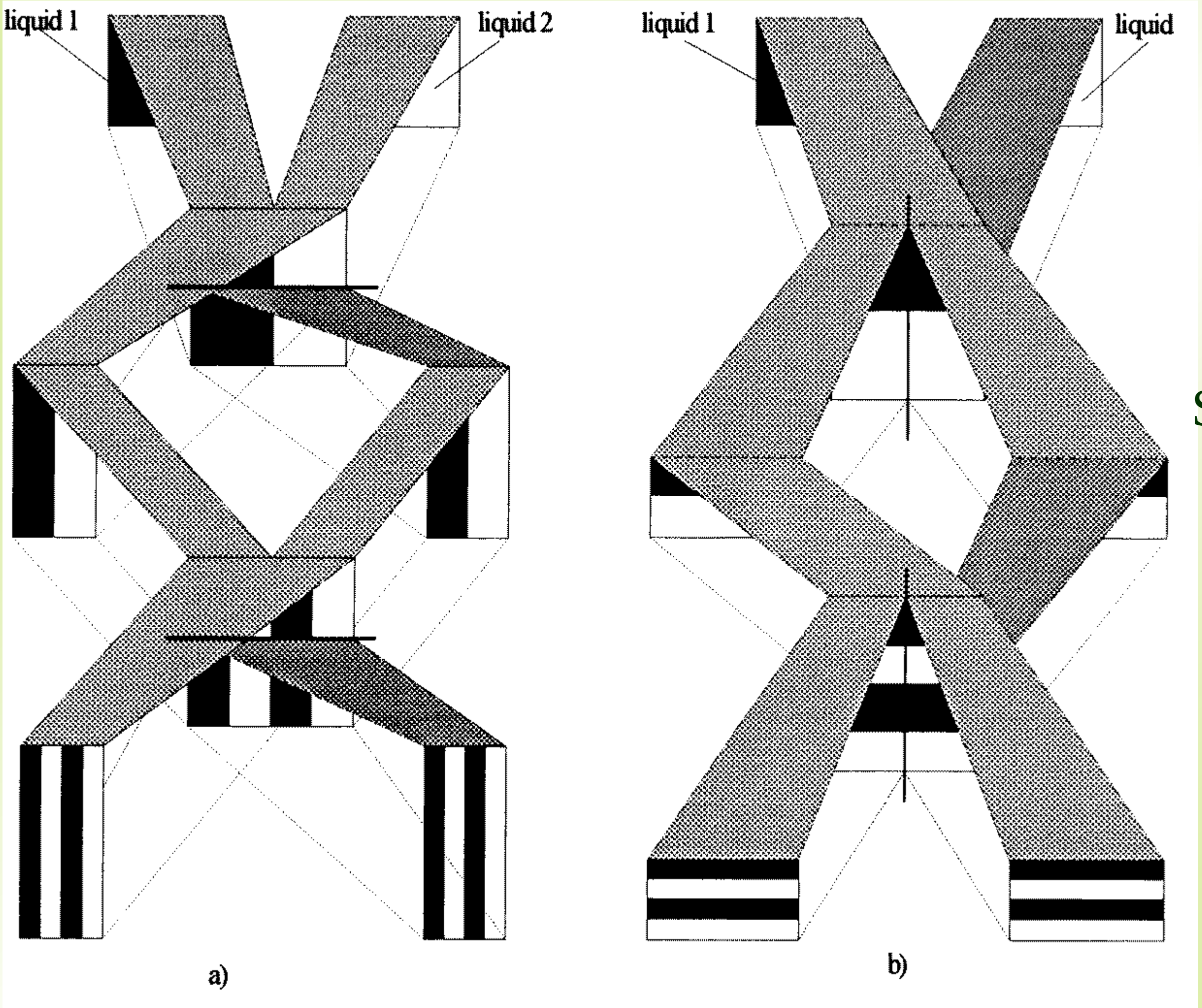






Micromixers (Lamination micromixers)

Serial lamination- split & recombination (SAR)



Exponential increase in contact interface

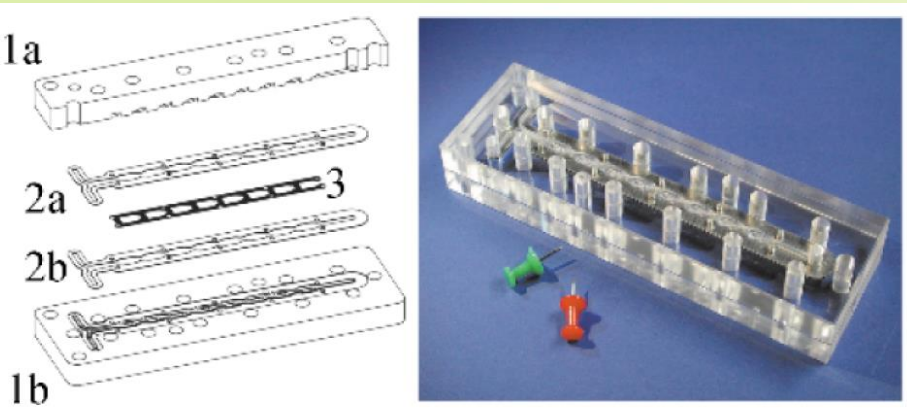
Suitable for melt polymer

Multiform properties of biochemical solutions

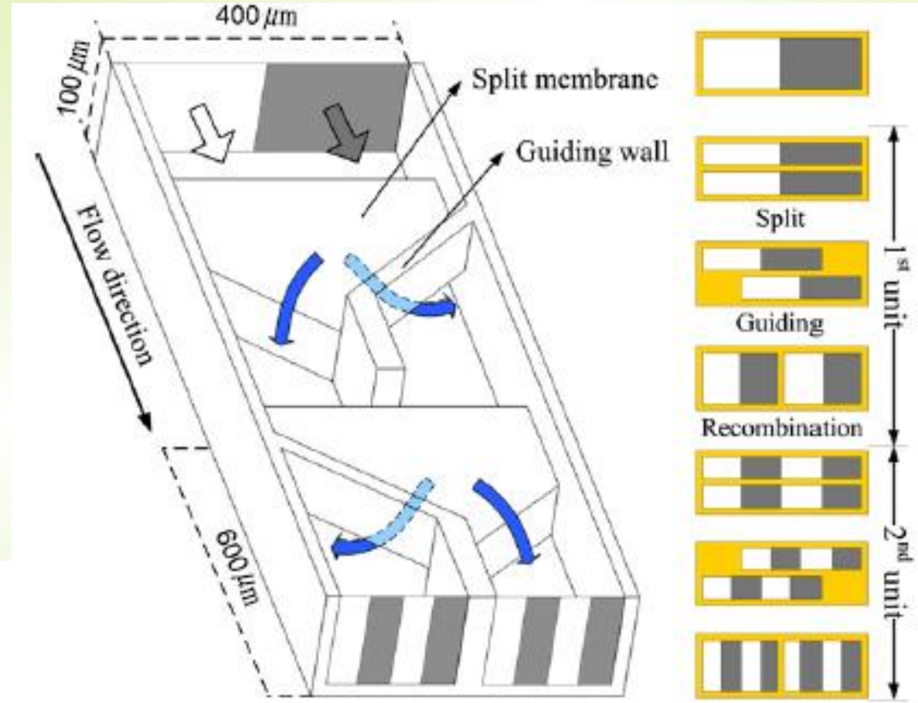
Schwesinger *et al.*, *JMM*, 1996

Micromixers (Lamination micromixers)

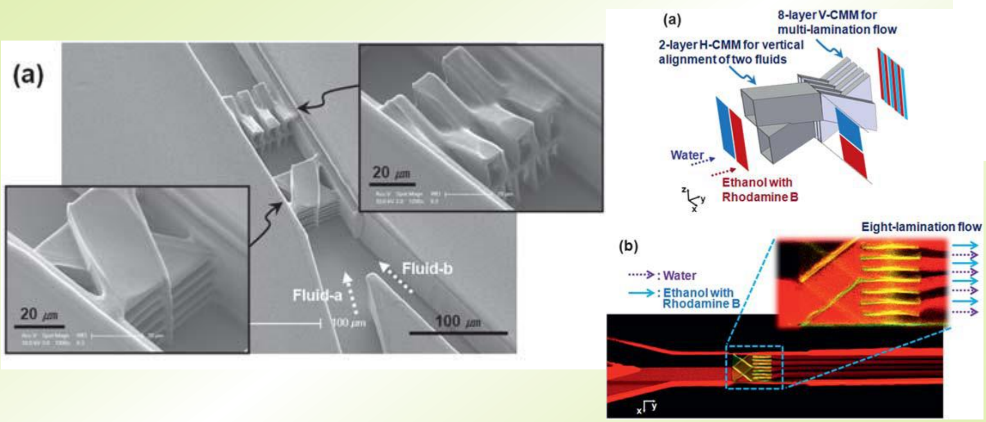
Serial lamination- split & recombination (SAR)



Schönfeld *et al., Lab Chip*, 2004



Lee *et al*., *JMM*, 2006



Lim *et al*., *Lab Chip, 2010*

Intermediate layer

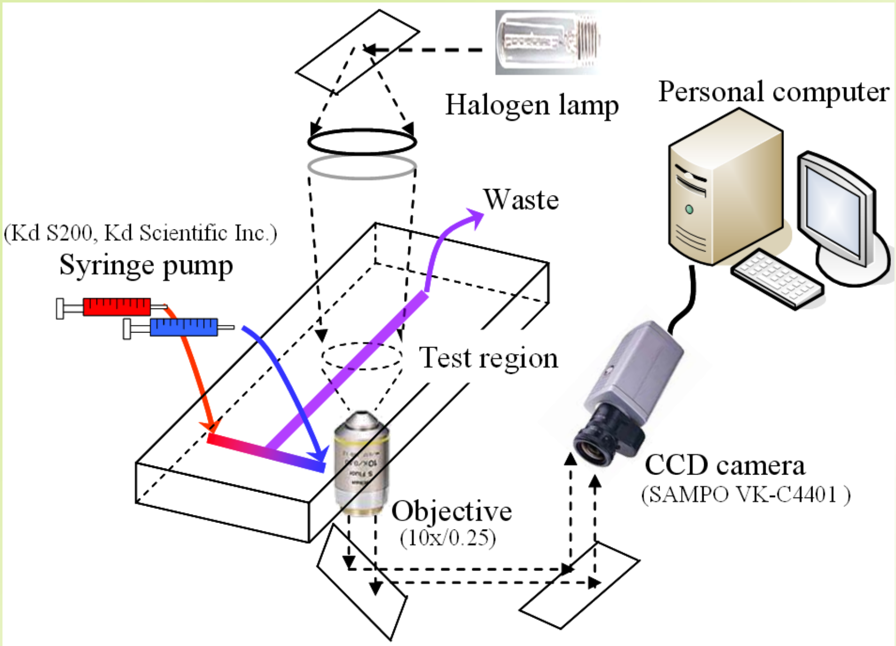
Separate channels

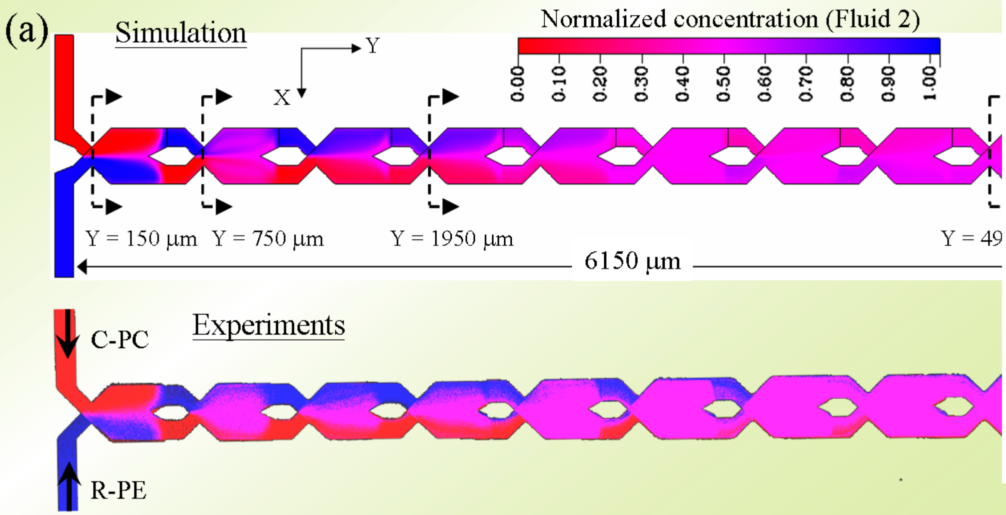
Confluent channels

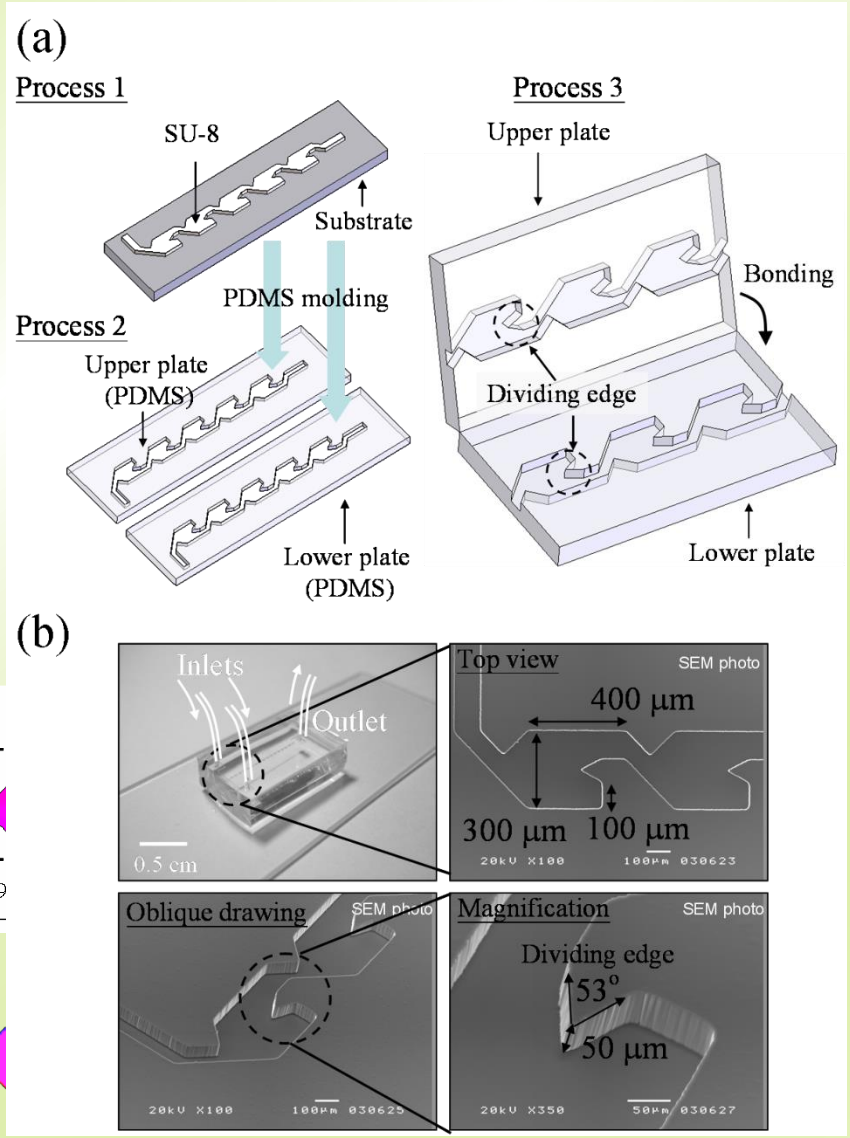
A Novel Microreactor with 3D Rotating Flow

方偉峰 楊鏡堂, 2009

Sensors and Actuators B- Chemical, 2009

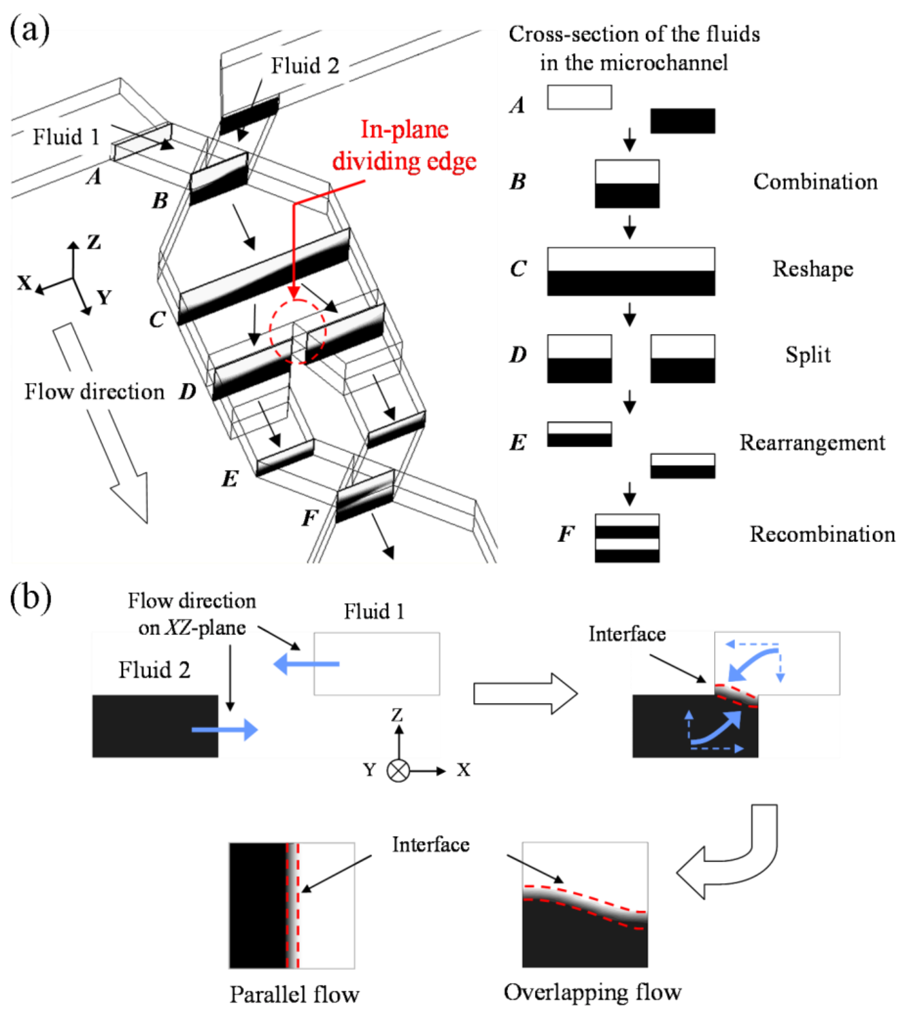


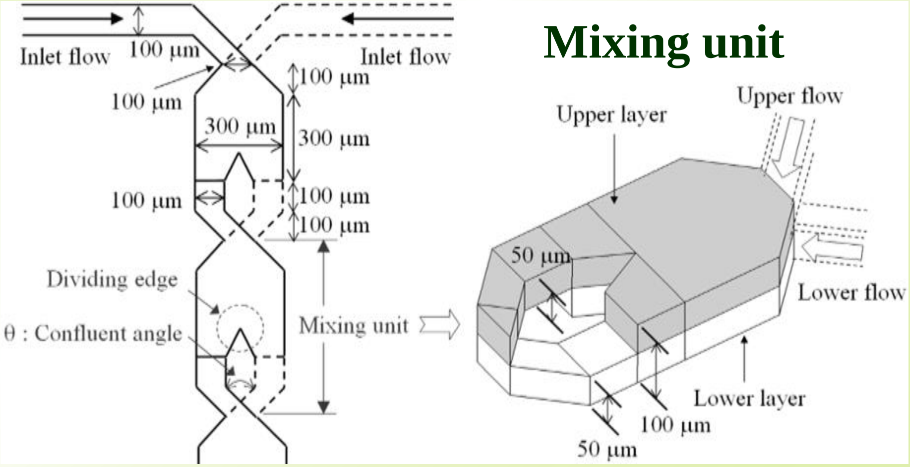




Micromixers- SAR μ-reactor/μ-mixer

Design concept (SAR μ-reactor/μ-mixer)





SAR + Chaotic advection

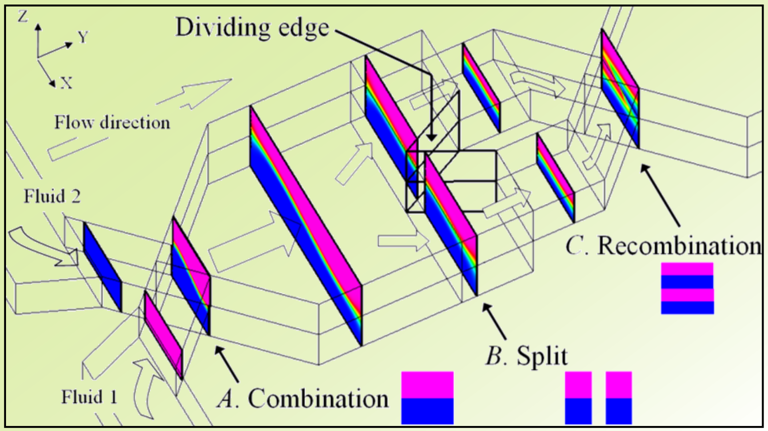
Strong transverse
advection and stretching

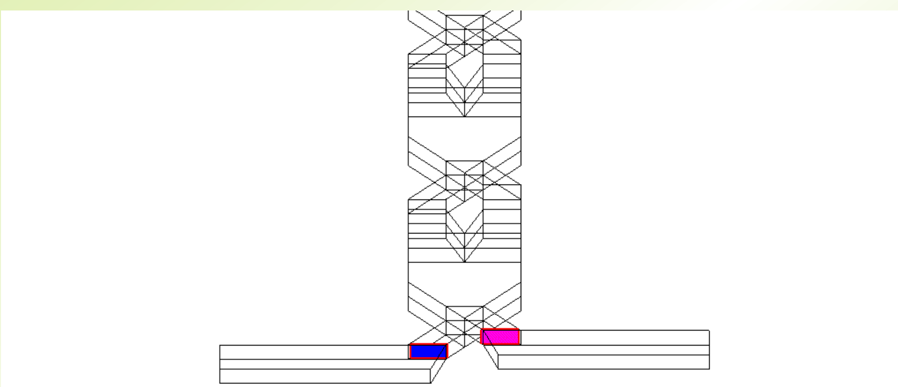
Fang & Yang, Sensors & Actuators B: Chemical, 2009

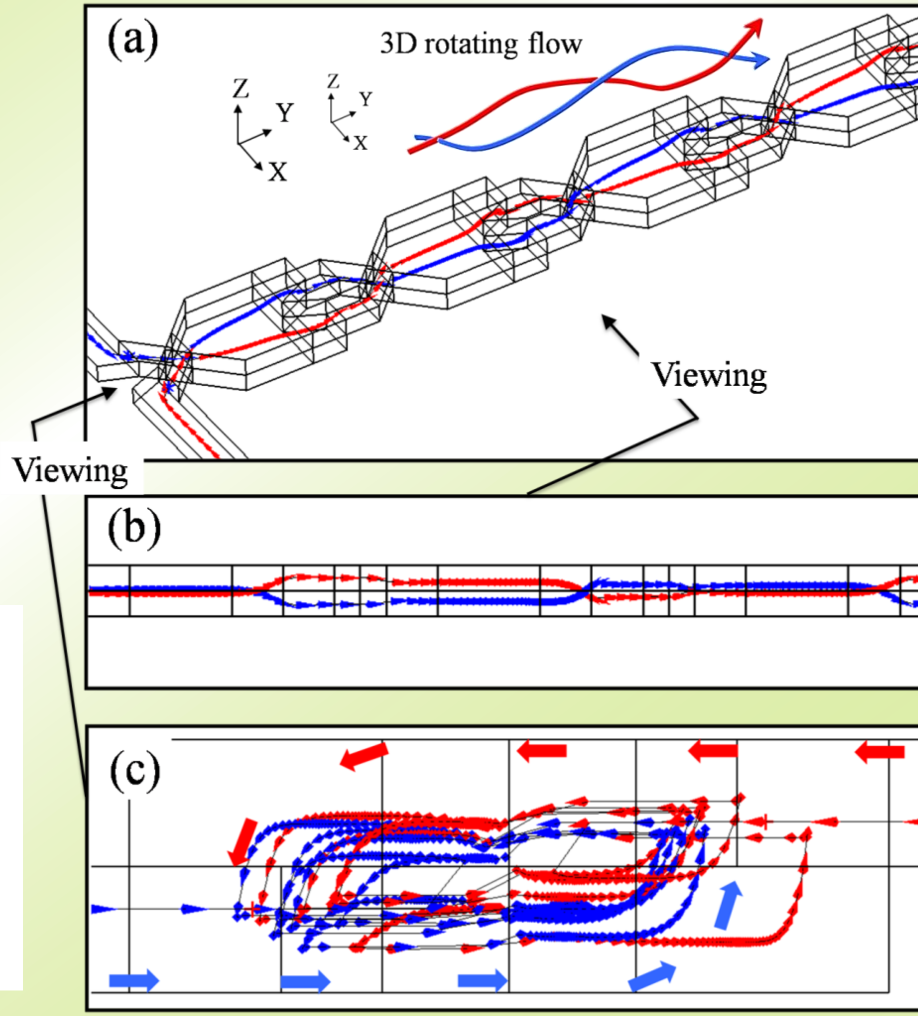
Micromixers- SAR μ-reactor/μ-mixer

Sensors & Actuators B: chemical, 2009

Flow field



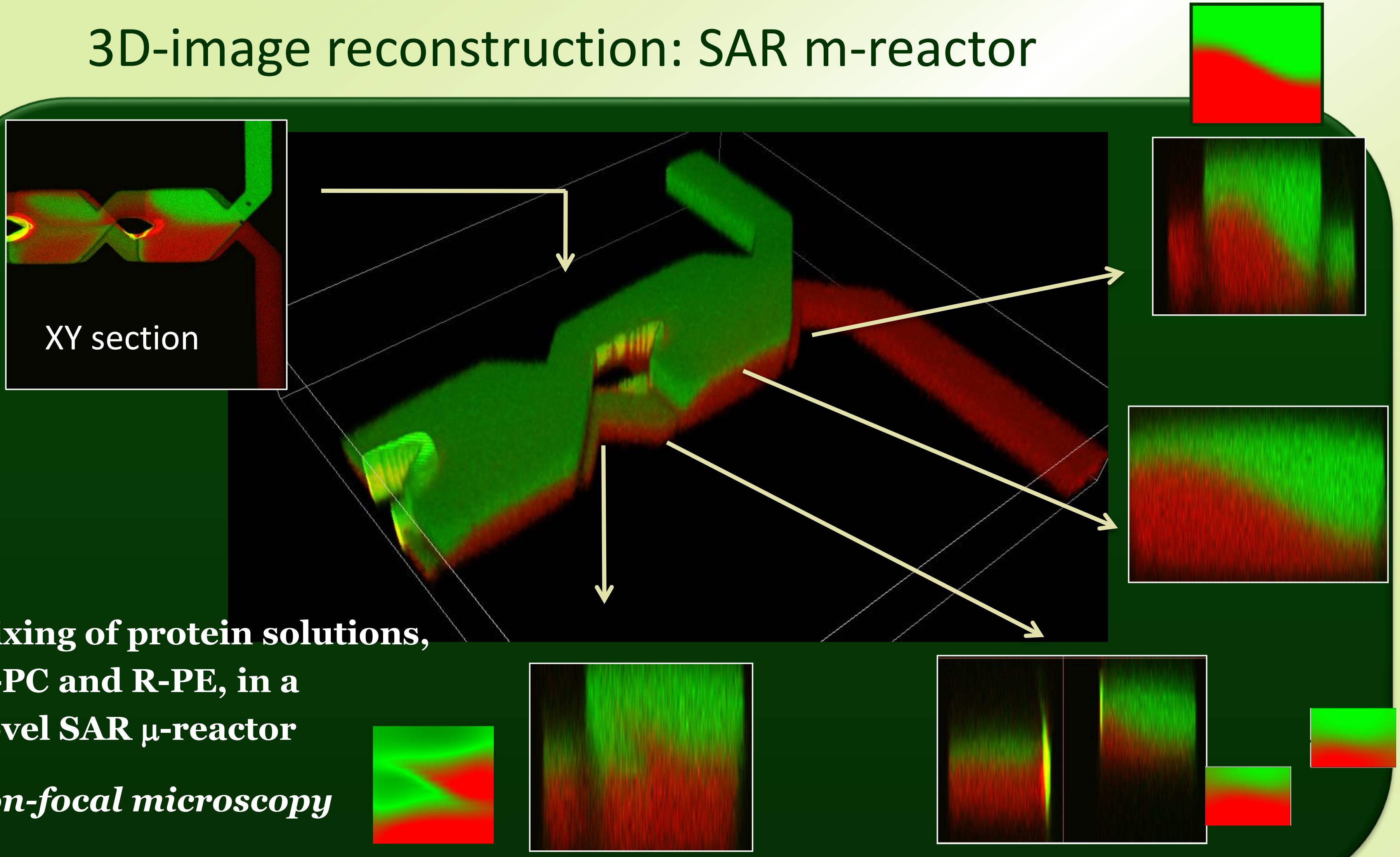




Performance Test of a SAR μ-Reactor

Fang & Yang, Sensors and Actuators B, 2009

3D-image reconstruction: SAR m-reactor



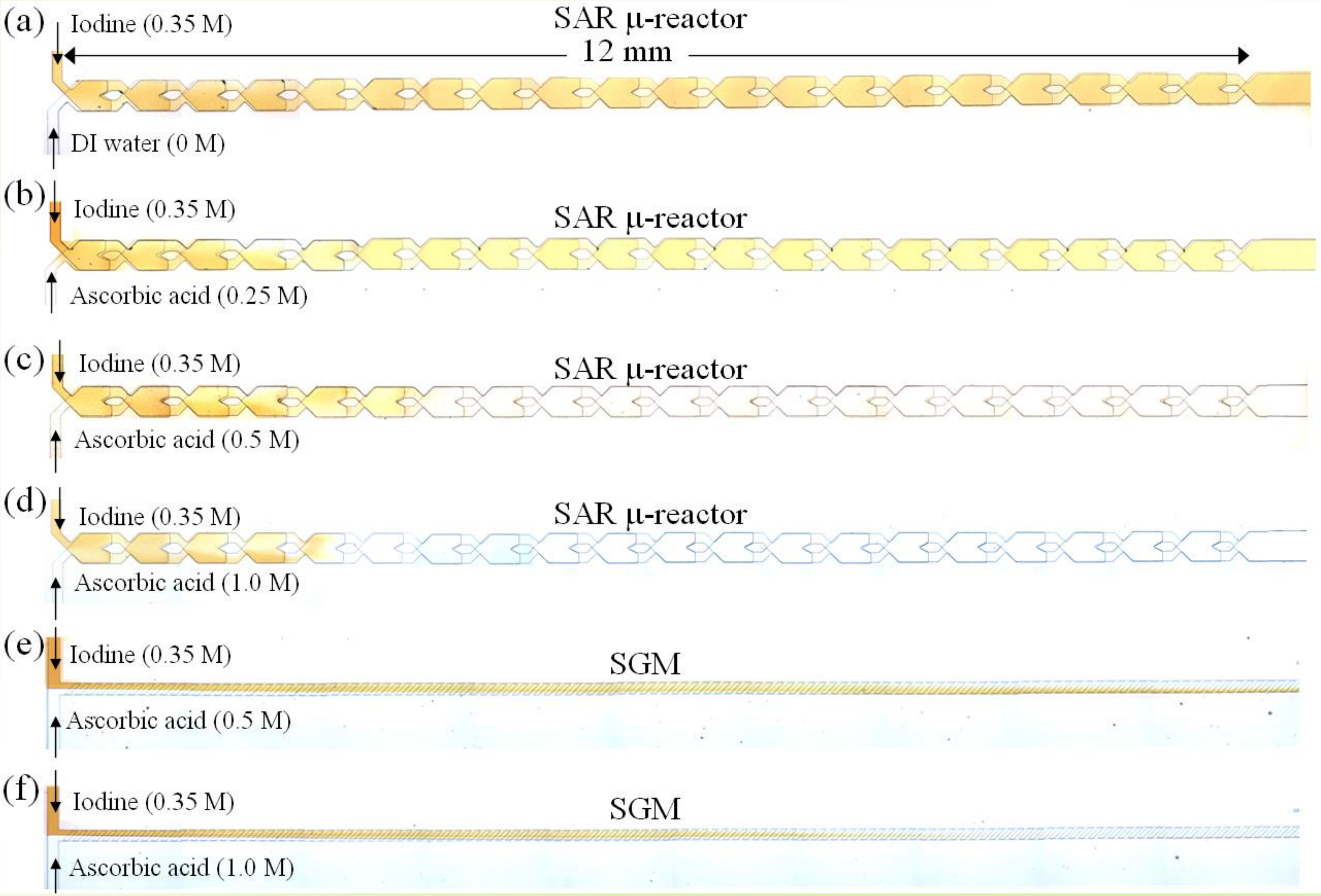
Mixing of protein solutions, C-PC and R-PE, in a novel SAR μ-reactor

Con-focal microscopy

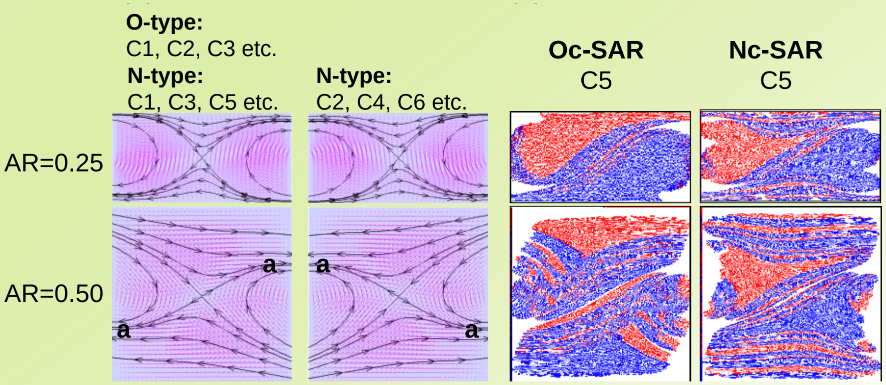
Micromixers- SAR μ-reactor/μ-mixer

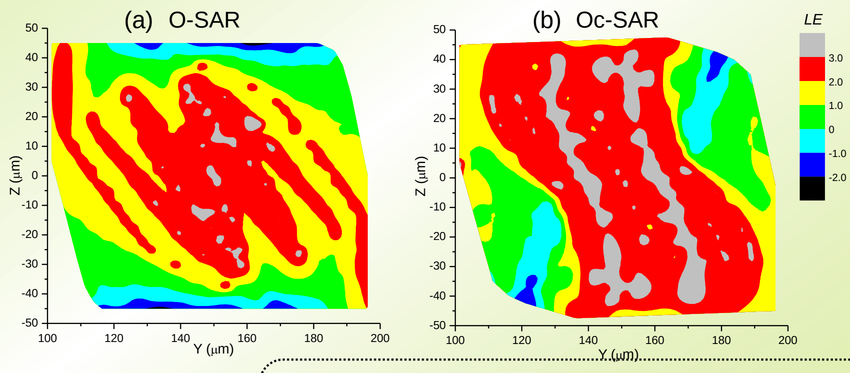
Sensors & Actuators B: chemical, 2009

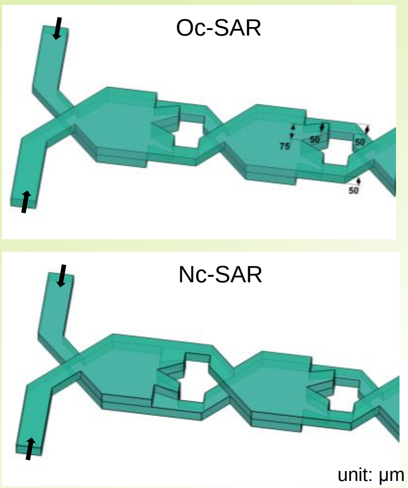
Reaction experiments (ascorbic acid and diiodine)

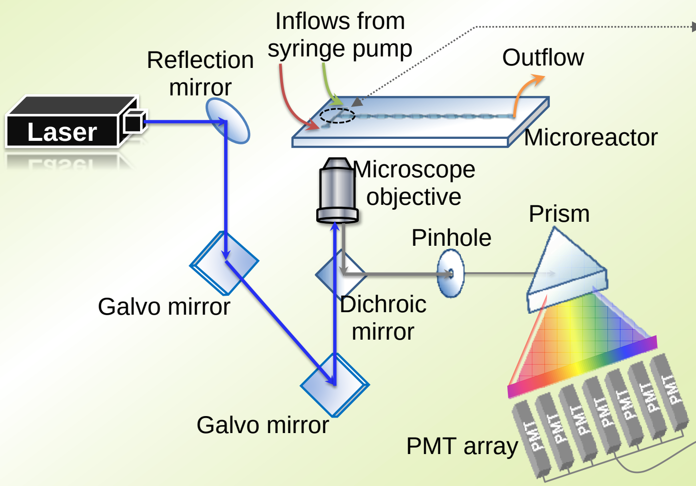


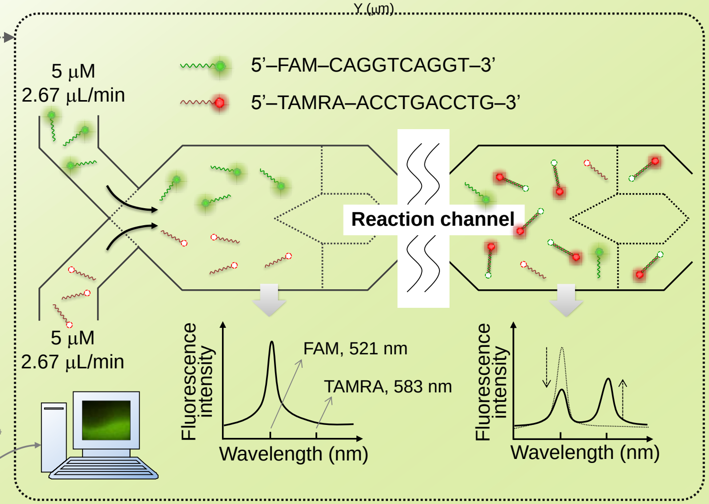
Analysis of chaos & FRET reaction in split-and-recombine microreactors, *Chen et al., Microfluidics and Nanofluidics, 2011*







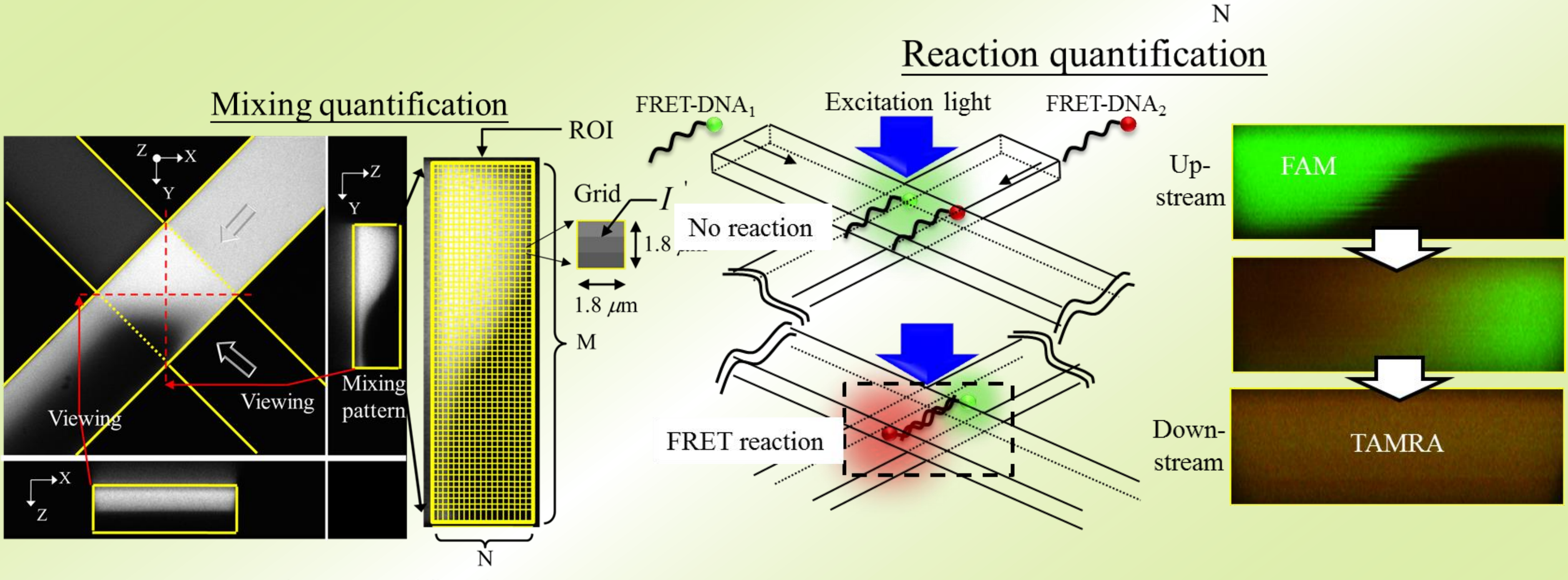




Through analysis of the chaos, we revealed numerically the dynamic mixing governed by multi-lamination and chaotic mechanisms in the devices. How the devices affected the rate of hybridization was thereby assessed, verifying that FRET is a technique capable of estimating the practical applicability of these devices.

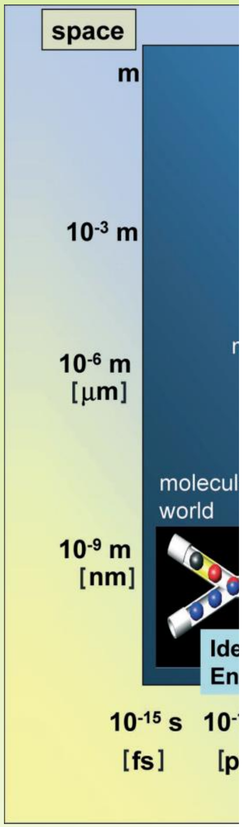
Characterization of microfluidic mixing and reaction in microchannels *via* analysis of cross-sectional patterns

Fang *et al.*, *Biomicrofluidics*, 2011

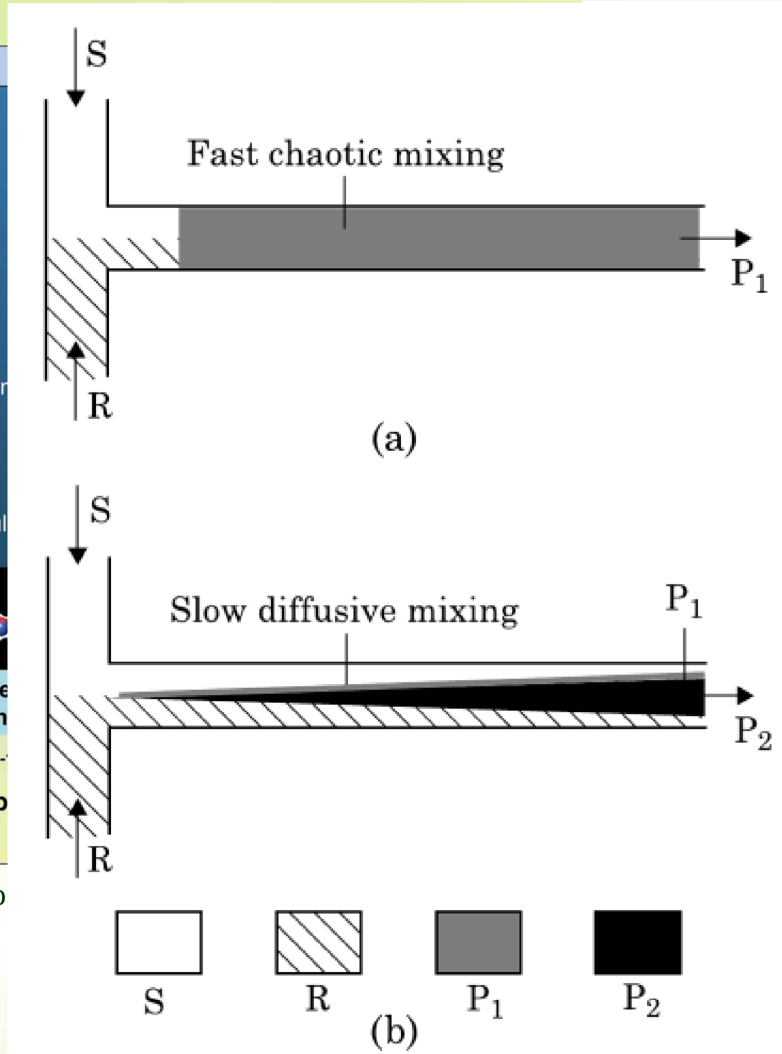


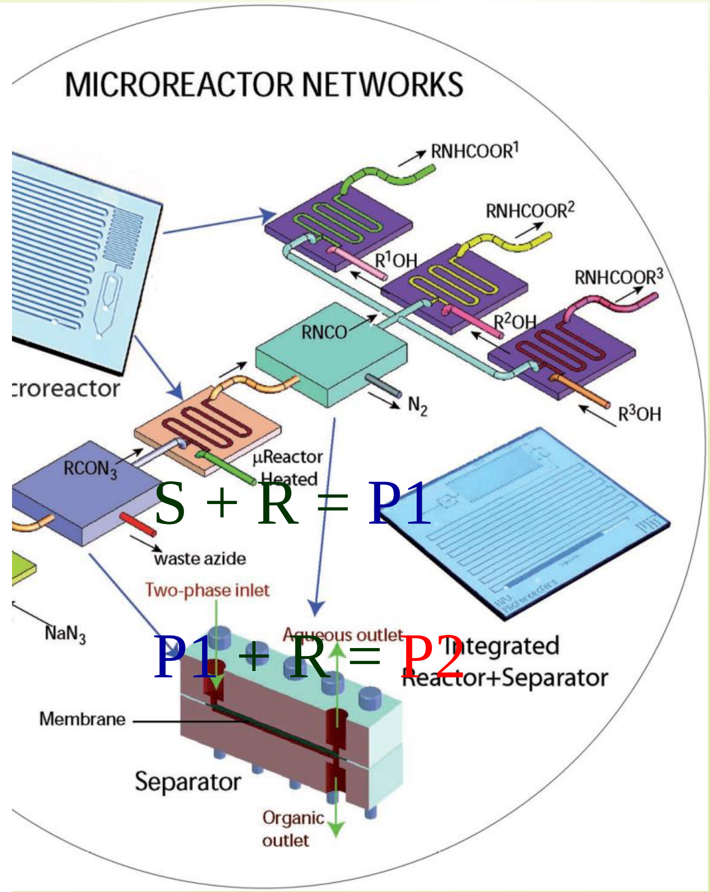
A quantification approach based on a confocal-fluorescence microscope is proposed to characterize fluid mixing precisely in microchannel devices. The approach is qualified for use to inspect microfluidic mixing, to disclose flow behavior, and to diagnose biochemical and chemical reactions in microfluidic devices.

Microreactors



Yo





Sahoo *et al.*, *Angew. Chem. Int. Ed.*, 2007

Microreactors (Oxidation reaction)

Swern-Moffatt oxidation of cyclohexanol in microreactors

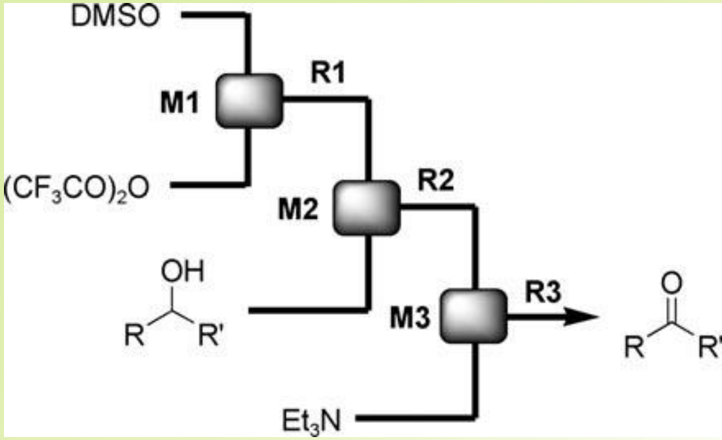
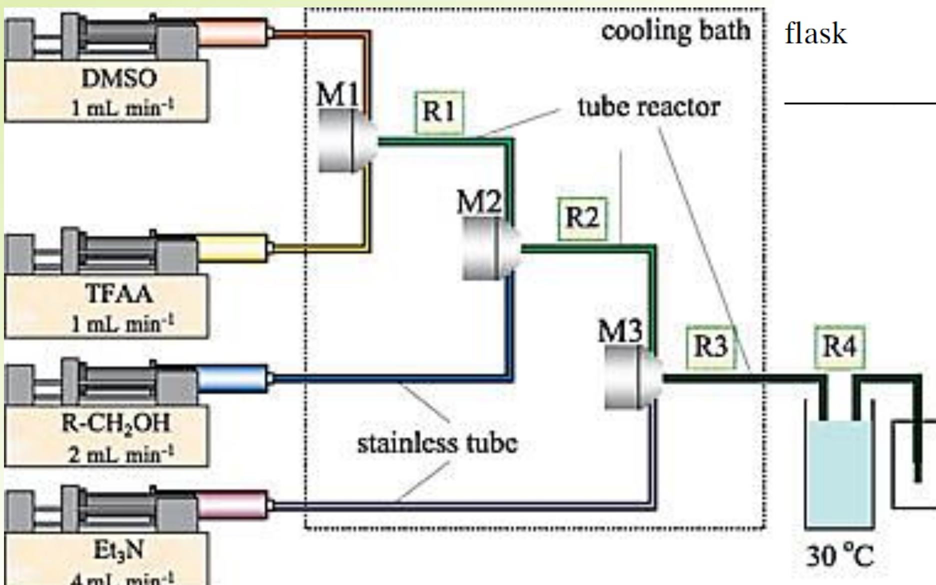


Table 1. Swern-Moffatt oxidation of cyclohexanol using a microreactor and a flask.

Method	Residence time t_{R1} [s]	T [°C]	Selectivity of cyclohexanone [%]
micro-reactor	2.4	−20	88
	0.01	0	89
	0.01	20	88
flask		−20	19
		−70	83

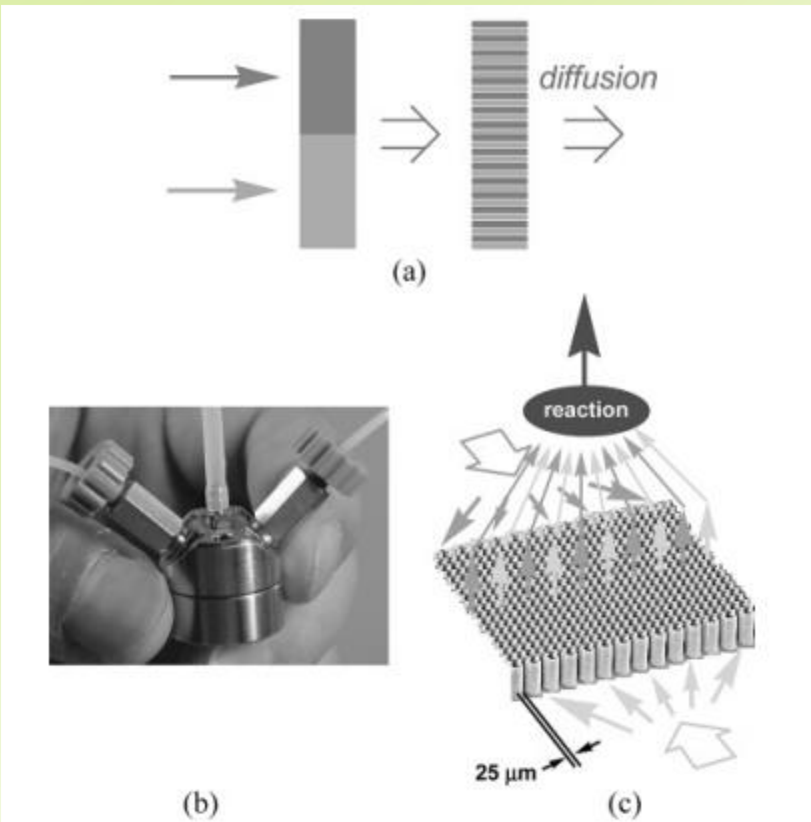


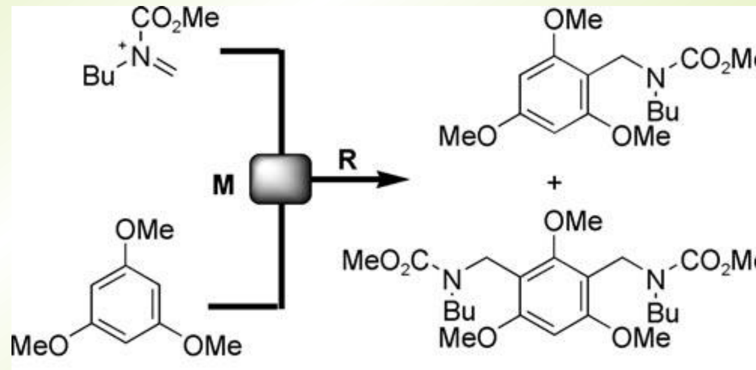
Hazard, explosible !!

Kawaguchi *et al.*, *Angew. Chem.*, 2005

Microreactors (Competitive Consecutive Reactions)

Friedel–Crafts reaction of cyclohexanol in microreactors

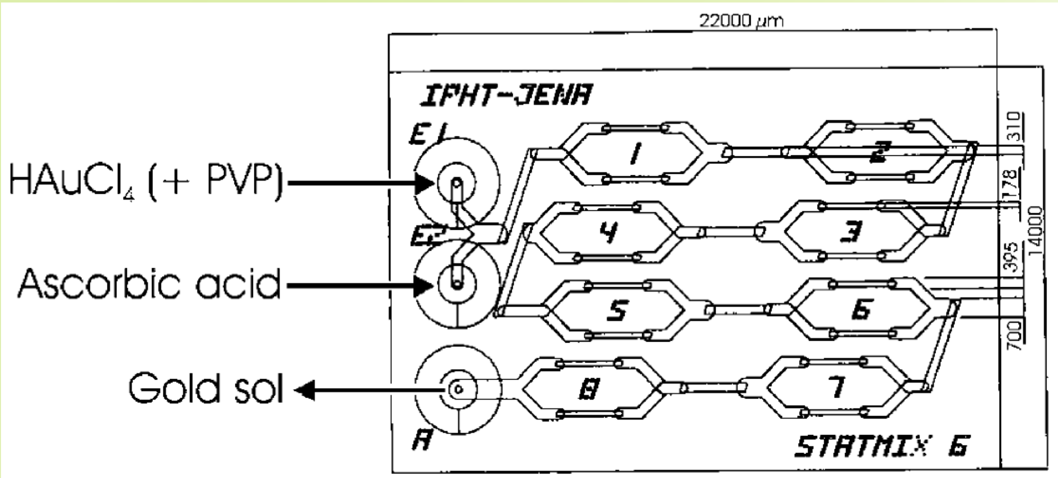


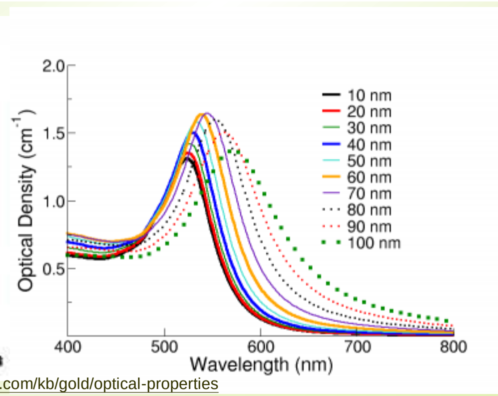


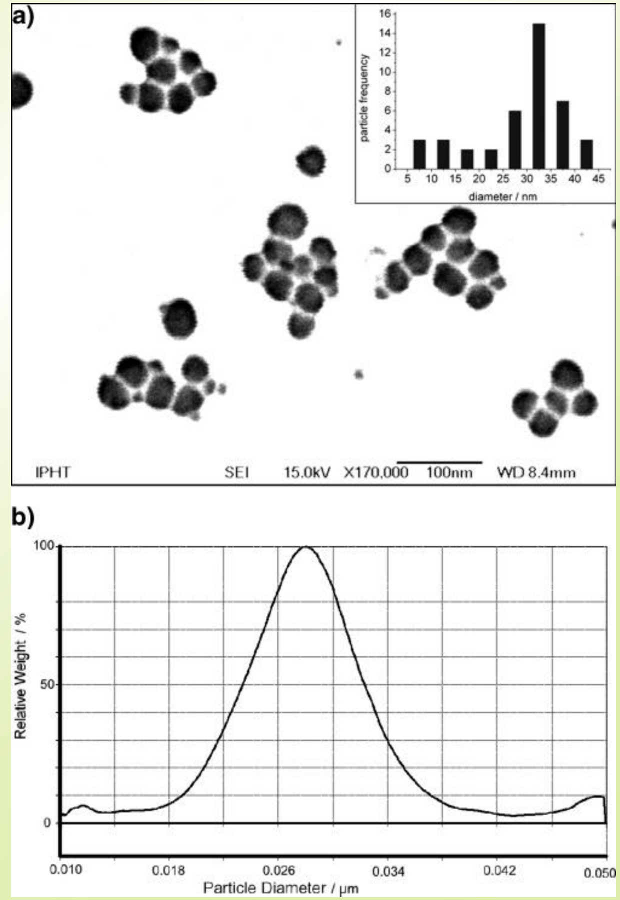
	monoalkylation product	dialkylation product
microreactor	92%	4%
flask	37%	32%

Nagak *et al.*, *JACS*, 2005

Microreactors (Synthesis of gold nanoparticles)





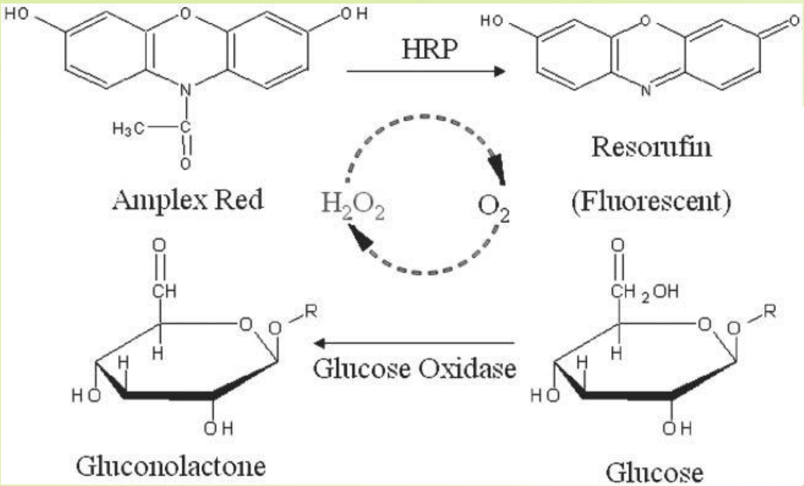


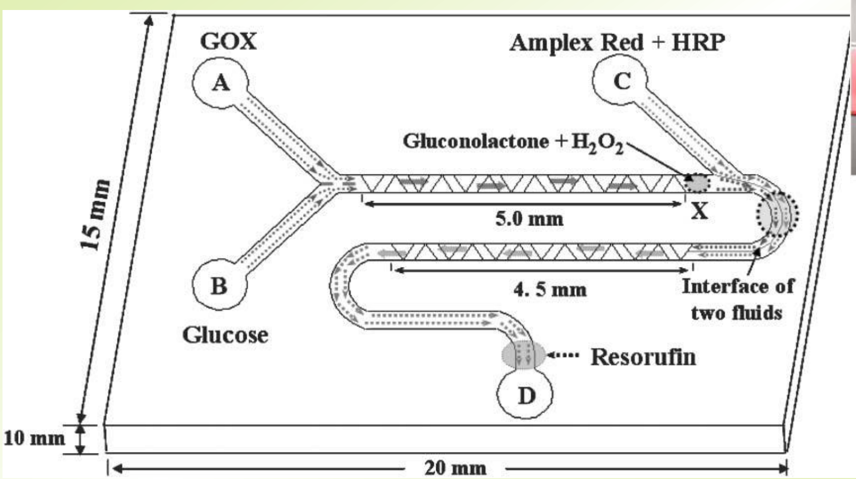
http://www.nanocomposix.com/kb/gold/optical-properties

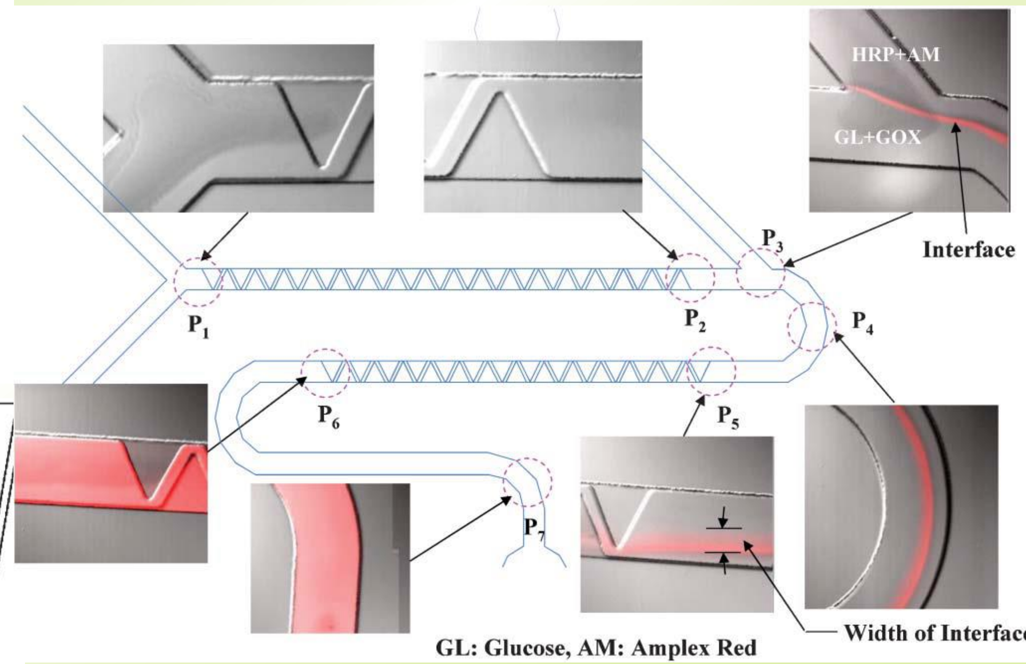
http://www.malvern.com/LabEng/industry/nanotechnology/gold_silver_nanoparticles.htm

Wagner and Köhler, *Nano Lett*, 2005

Microreactors (Glucose-catalyst reactions)







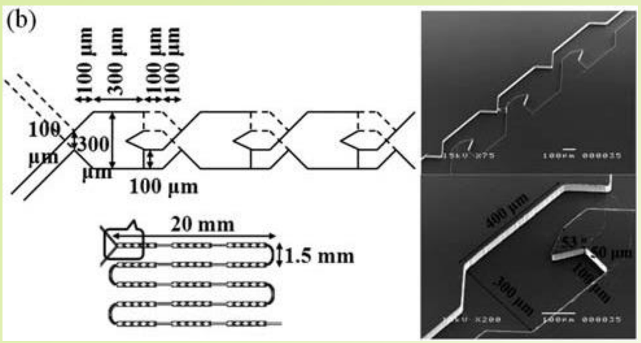
Kim *et al*., *Analyst*, 2005

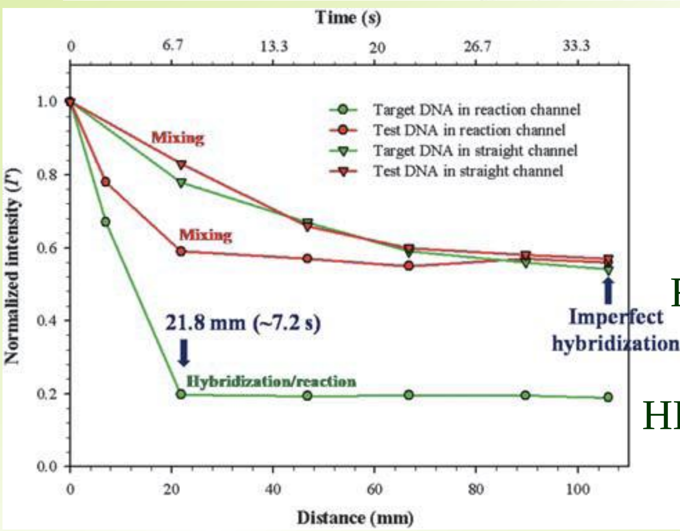
Enhanced mobile hybridization of gold nanoparticles decorated with oligonucleotide in microchannel devices

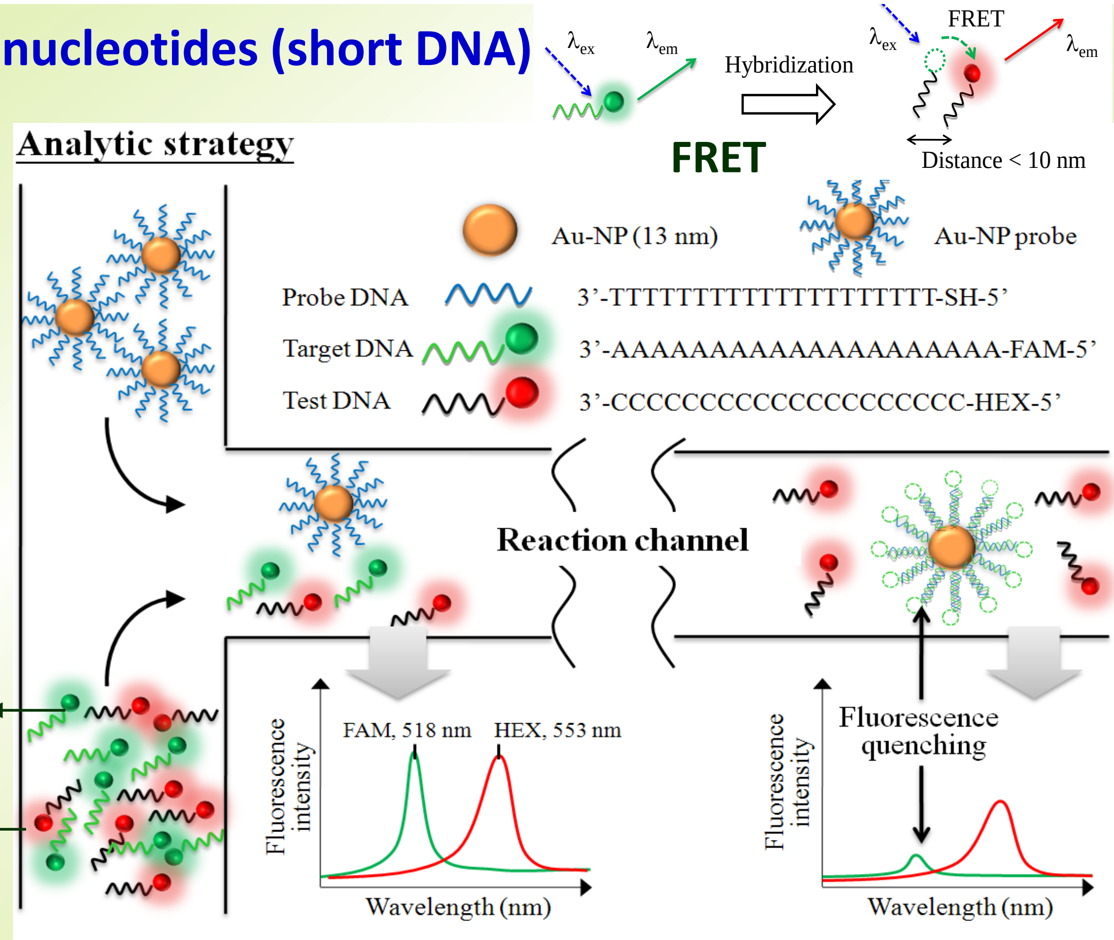
M. H. Hsu, W. F. Fang, Y. H. Lai, **J. T. Yang,*** T. L. Tsai, and D. B. Shieh

Lab on a Chip, Vol. 10, pp. 2583-2587, 2010

FRET of two complementary oligonucleotides (short DNA)



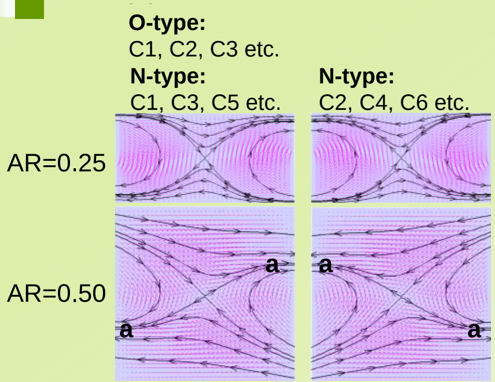


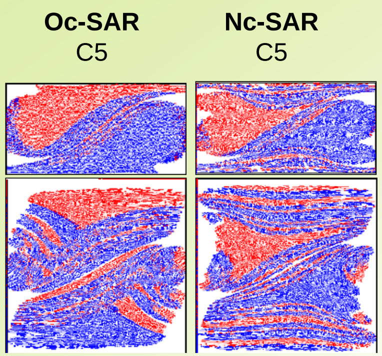


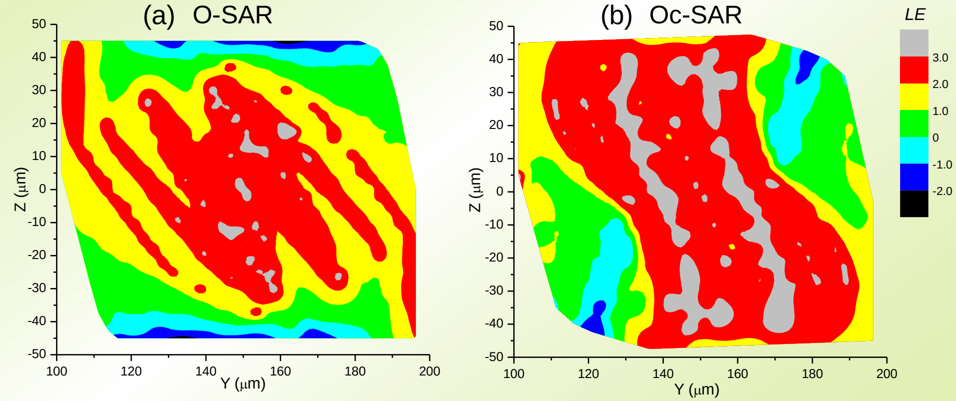
The effect of the structure in the microreactor enables the reaction to attain saturation in only 7.2 s, a duration much less than for traditional static hybridization (12-20 hours). In medical tests, one can diagnose the result in a flow channel in real time.

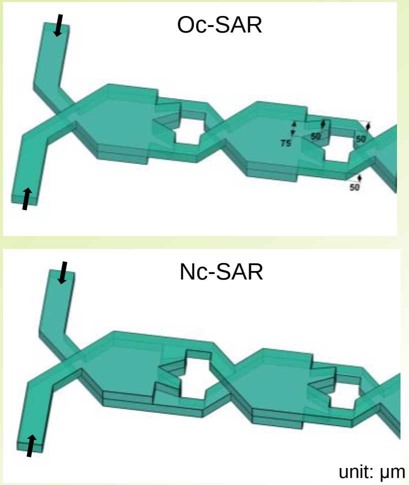
Analysis of chaos & FRET reaction in split-&-recombine microreactors

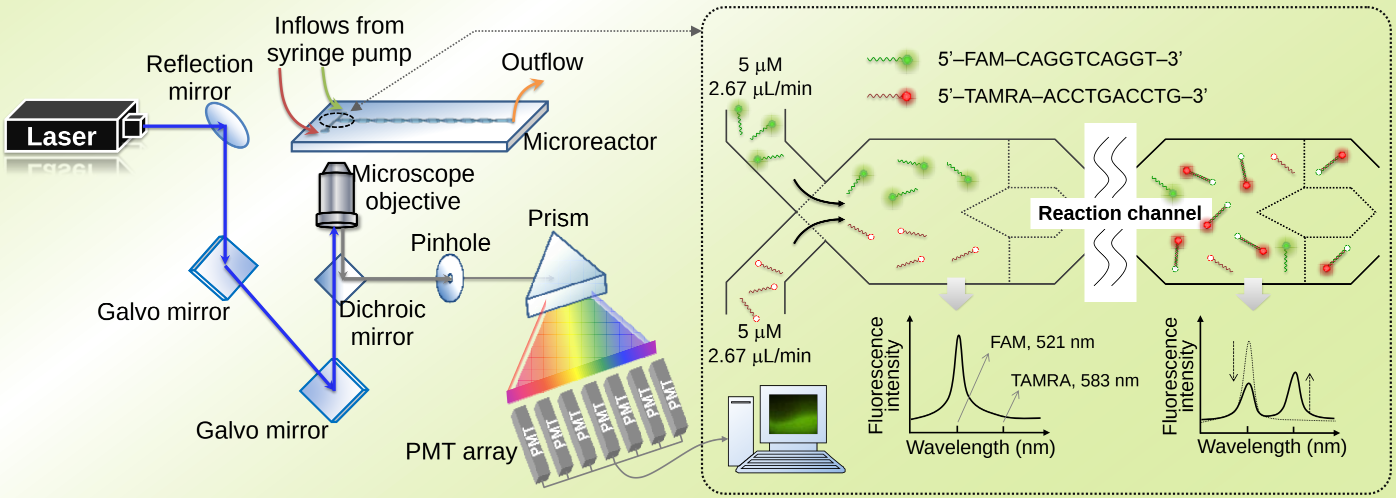
Microfluidics and Nanofluidics, 2011









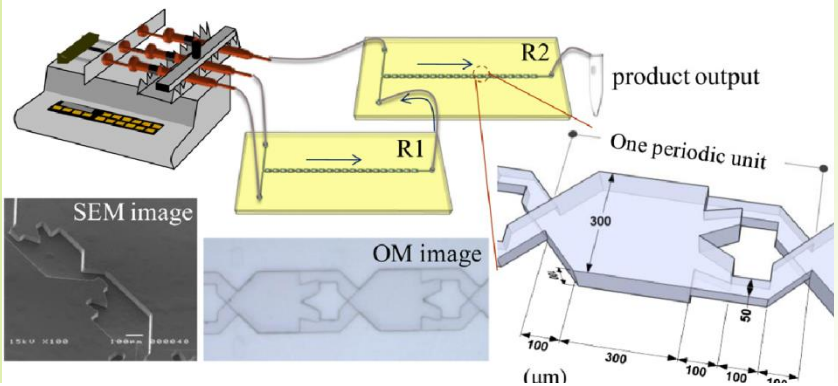


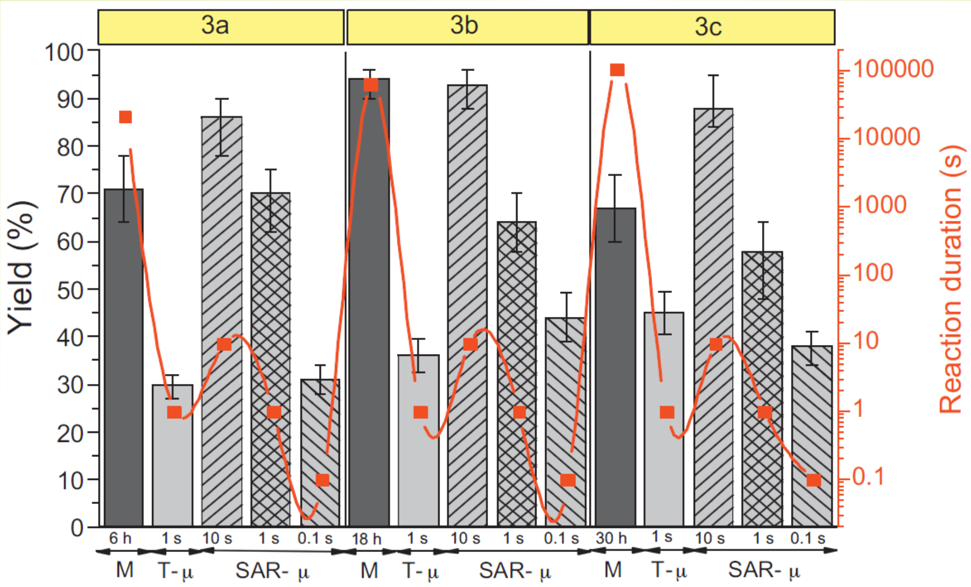
Through analysis of the chaos, we revealed numerically the dynamic mixing governed by multi-lamination and chaotic mechanisms in the devices. How the devices affected the rate of hybridization was thereby assessed, verifying that FRET is a technique capable of estimating the practical applicability of these devices.

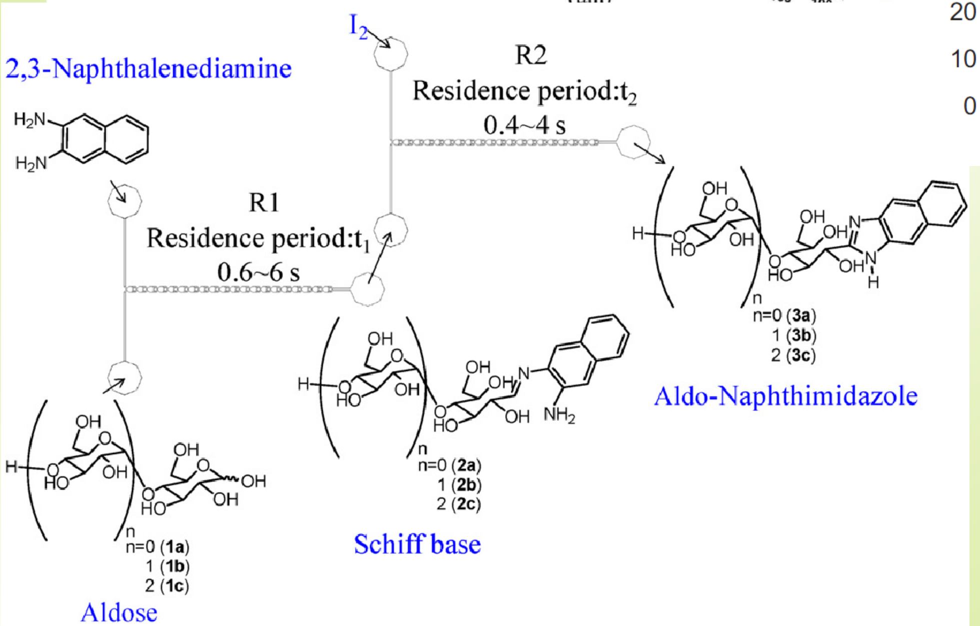
Microreactors (Flash synthesis of carbohydrate derivatives)

Yang *et al.*, *Chemical Engineering Journal (CEJ)*, 2011

Applications of SAR μ-reactor







Macro flask:

6 h to 30 h

Temp. above 100 ^{o}C

SAR μ-reactor :

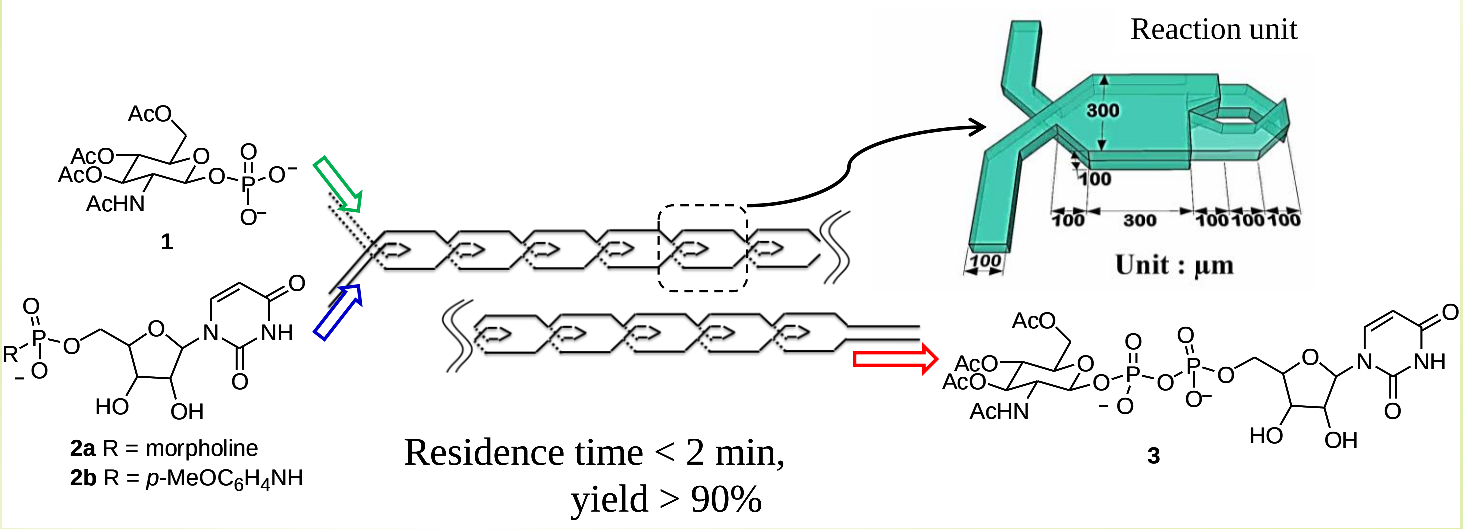
0.1 ~ 10 s

Temp. RT

Microreactors (Microflow Synthesis of Saccharide Nucleoside Diphosphate)

Chemical Engineering Journal (CEJ), 2012

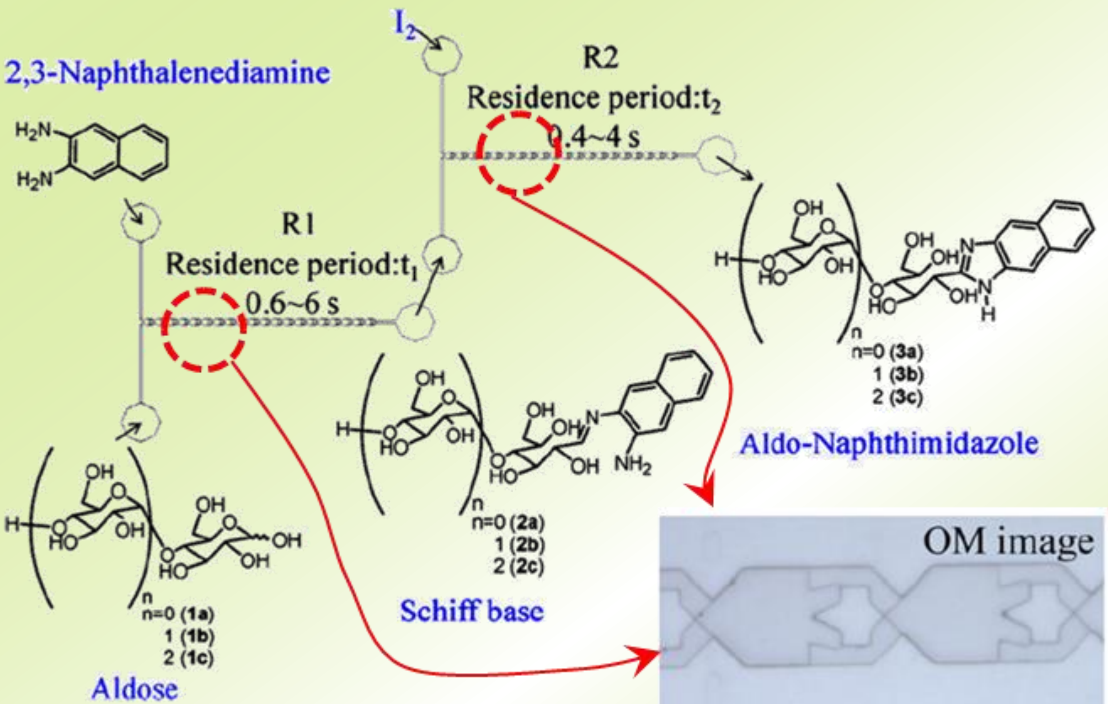
Applications of SAR μ-reactor



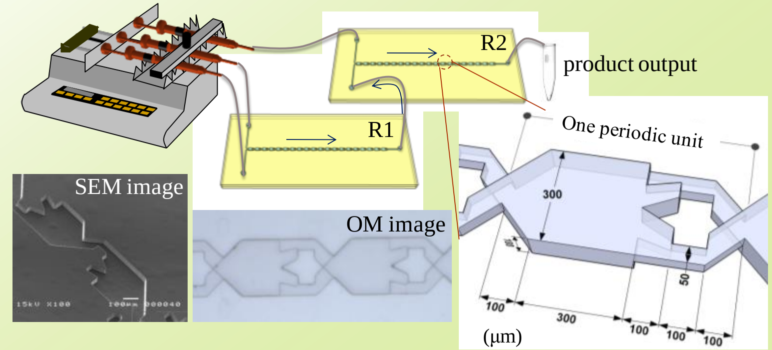
- With our microreactor technology, the enhanced reactivity of reagents is phenomenal.
- 85% conversion and 94% yield of cross-coupling reactions were achieved in tens of seconds.
- The duration of the reactions was diminished $>10^5$ fold.

Flash synthesis of carbohydrate derivatives in split-and-recombine microreactors

Chemical Engineering Journal, 2011



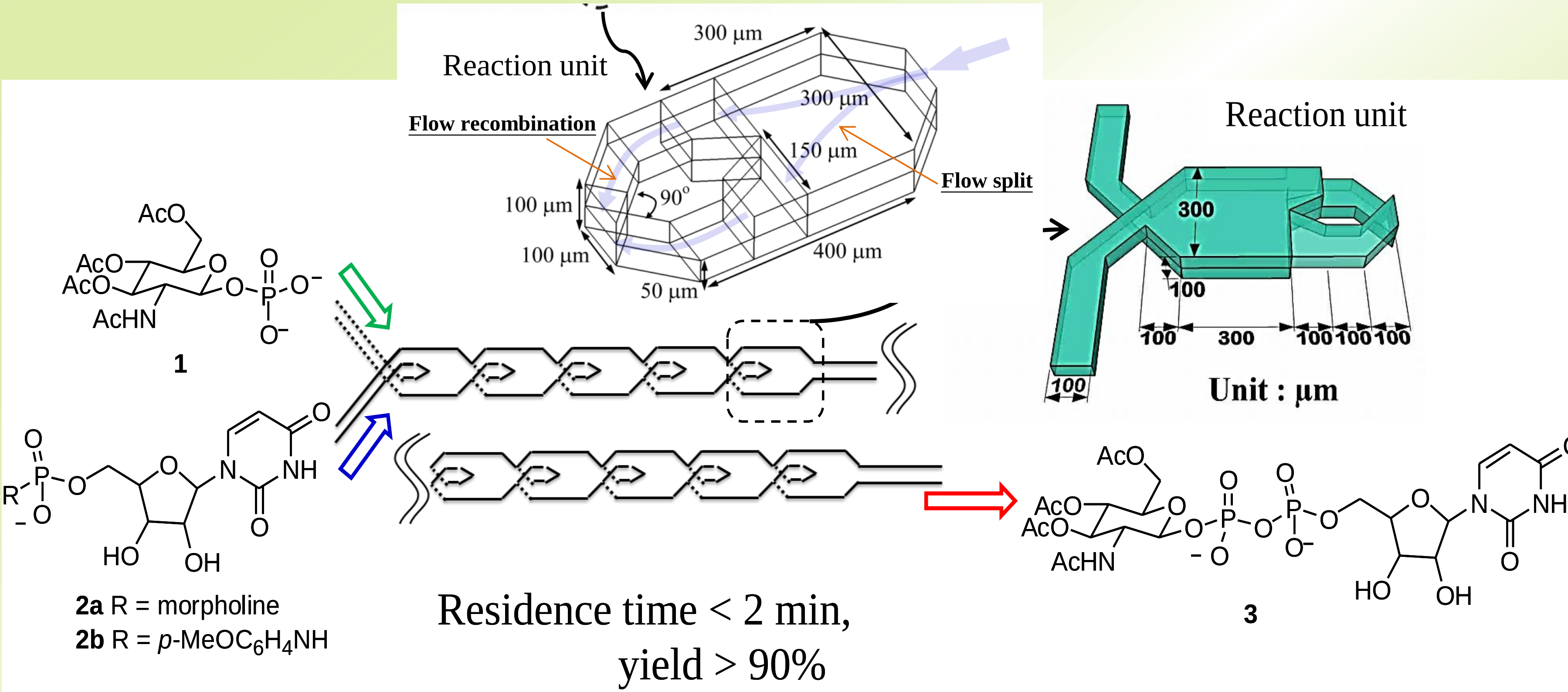
The SAR-microreactor required just seconds (0.1 to 10 s), which was about 10^{-3}~10^{-6} the duration for the macro flask.



An efficient and rapid synthesis of carbohydrate derivatives was accomplished using a split-and-recombine (SAR) microreactor. Using two steps reaction process in SAR-microreactors, the carbohydrate derivatives, aldo-naphthimidazoles were generated by linkage of naphthalenediamine with mono-, di- or trialdoses in less than 10 s with satisfactory yield.

Microflow Synthesis of Saccharide Nucleoside Diphosphate with Cross-coupling Reactions of Monophosphate Components

Chemical Engineering Journal, 2012

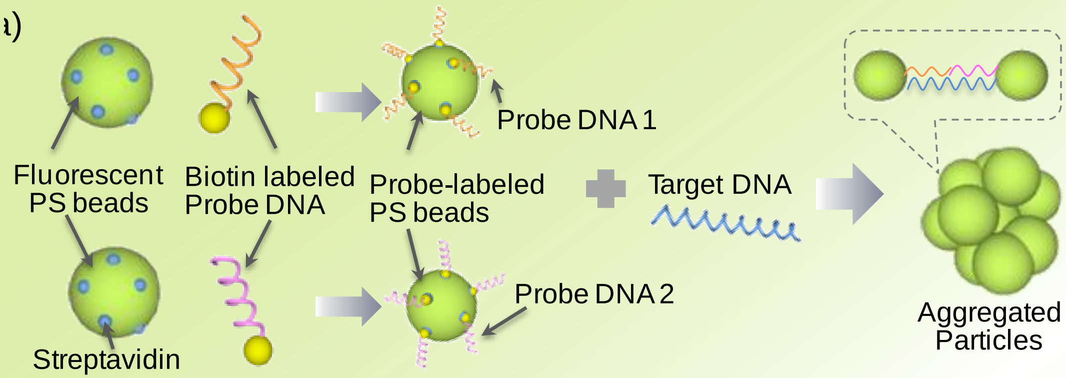


With this microreactor possessing the SAR mechanism that dramatically enlarges the material interface to promote the fluidic mixing, 85 % conversion of a cross-coupling reaction (GlcNAc monophosphate reacting with UMP-morpholidate) to the diphosphate (acetylated UDP-GlcNAc) was achieved in 10 s, which is a small fraction of the two days for 80 % conversion with a conventional batch reactor; **the duration of reaction is hence decreased 10^5 fold.**

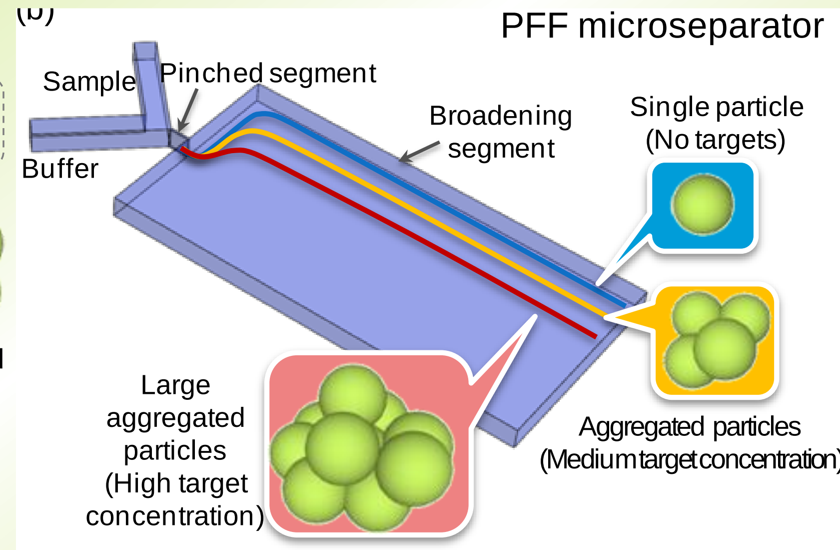
DNA diagnosis in a micro-separator based on particle aggregation

Y. T. Chen, Y. C. Liu, W. F. Fang, C. J. Huang, S. K. Fan, W. J. Chen, W. T. Chang, C. H. Huang, & **J. T. Yang***

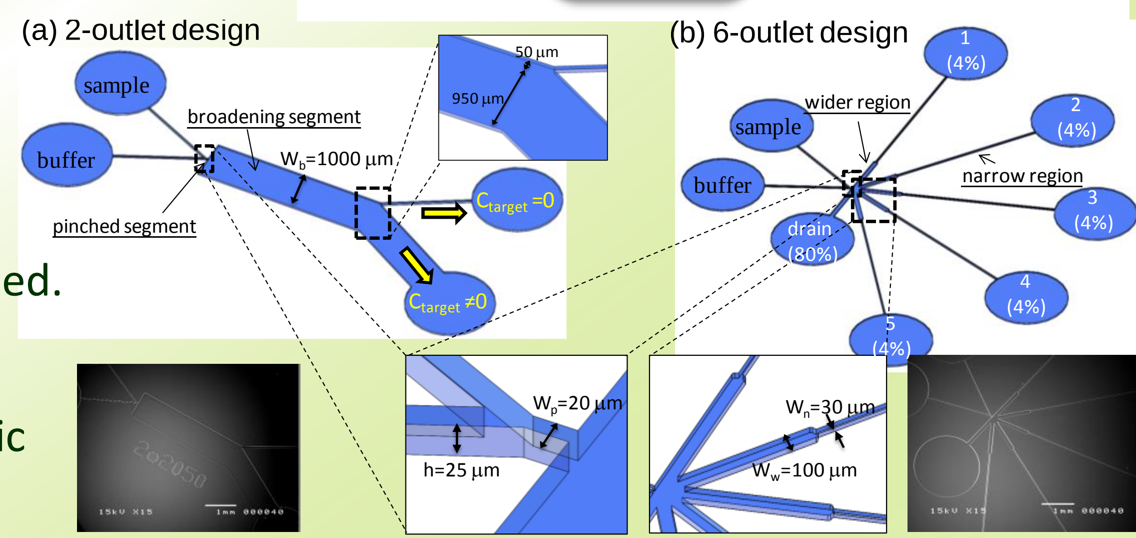
Biosensors and Bioelectronics, Vol. 50, pp. 8-13, 2013



Probe DNA-1:	Biotin-5'-GCGCT AGAGT CGTTT-3'
Probe DNA-2:	5'-CCTAT CGACC ATGCT-3'-Biotin
Target DNA:	5'-AGCAT GGTCG ATAGG AAACG ACTCT AGCGC-3'
Test DNA:	5'-GAGGG ATTAT TGTTA AATAT TGATA AGGAT-3'
1-mismatch DNA:	5'-AGCAT GGTTG ATAGG AAACG ACTCT AGCGC-3'

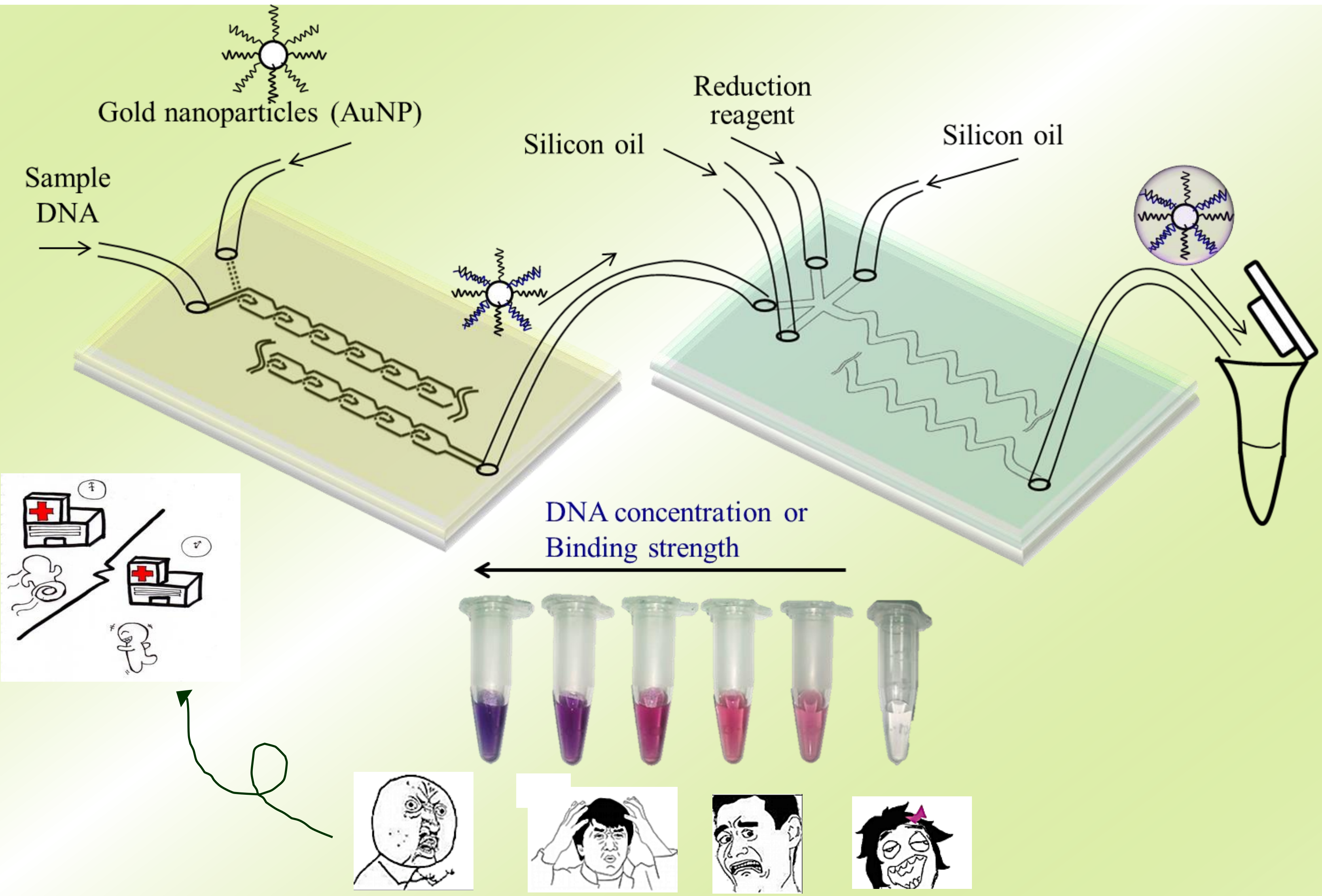


A novel aggregation-based method to execute oligonucleotide detection in a PFF (pinched flow fractionation) microseparator is proposed & developed. The label-free target DNA hybridizes with the probe DNA on the surface of microspheres and causes the polymeric aggregate, thus enlarging the average size of the aggregated particles.



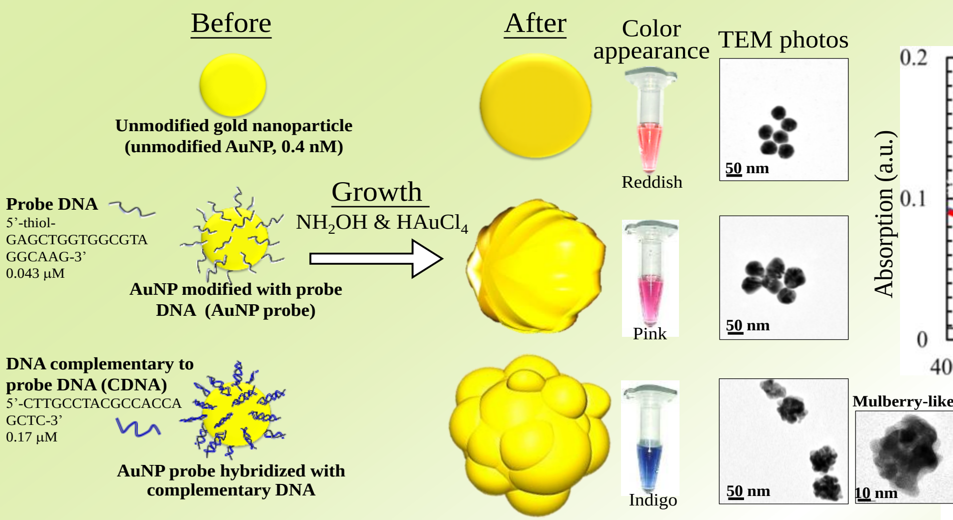
One of the most downloaded articles (Oct. 2013)

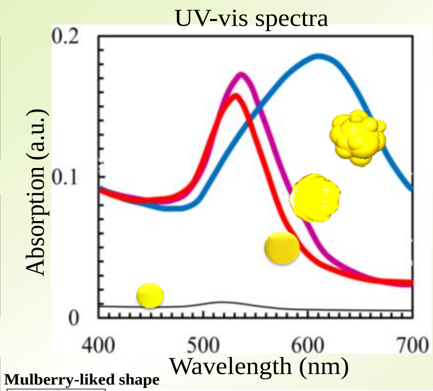
Next-generation microfluidic system for rapid DNA screening

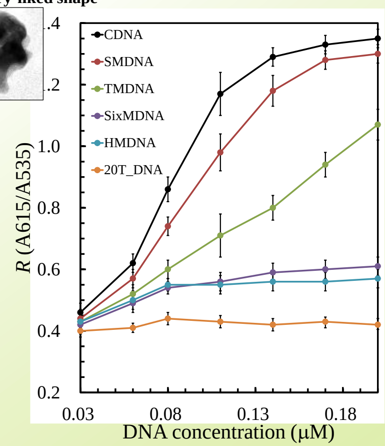


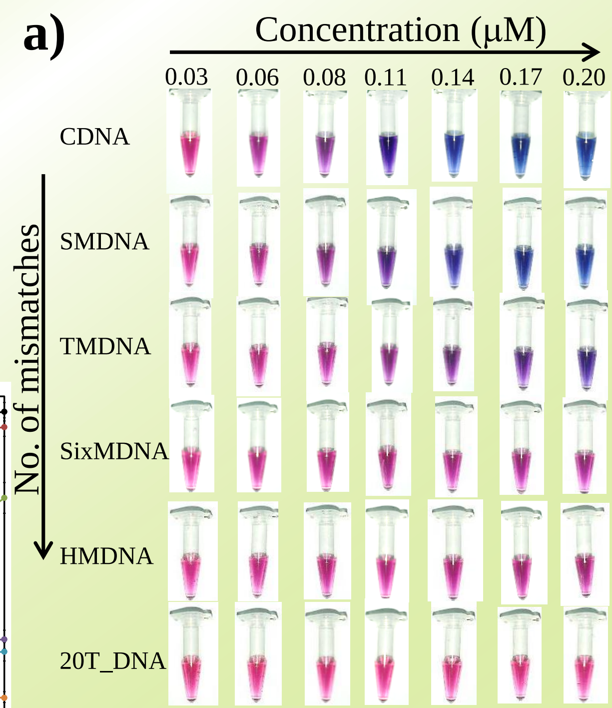
Hybridization-mediated growth of gold nanoparticle probes for visual and spectrophotometric screening of DNA mismatch

W. F. Fang, W. J. Chen, and **J. T. Yang**,* *Sensors and Actuators B- Chemical, 2013*









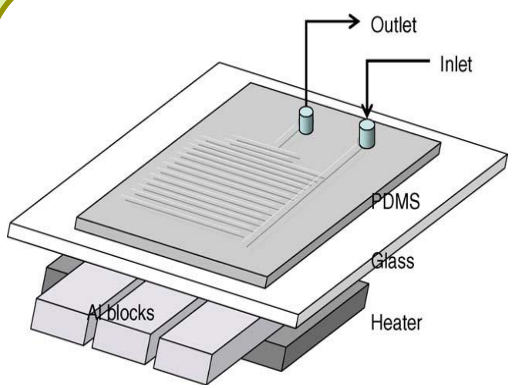
	Sequence (20 mer)
Probe DNA	5'-thiol-GAGCTGGTGGCGTAGGCAAG-3'
CDNA	5'-CTTGCCTACGCCACCAGCTC-3'
SMDNA	5'-CTTGCCTACTCCACCAGCTC-3'
TMDNA	5'-CTTGCCTACTTTACCAGCTC-3'
SixMDNA	5'-CTTGCCTTTTTTTCCAGCTC-3'
HMDNA	5'-CTTGCGGTTT TTTGGAGCTC-3'
20T_DNA	5'-TTTTTTTTTTTTTTTTTTTT-3'

A novel color approach to detect rapidly and conveniently DNA samples is proposed based on a concept of DNA hybridization-mediated growth of AuNP probes. With this method, one can not only evaluate semi-quantitatively the target DNA but also screen mismatches of DNA samples with a naked eye or simple spectrophotometer.

加熱器構型

● 外加金屬塊熱源 ● 蜿蜒狀 ● 環狀 ⊗ 條狀 ⊗ 圍欄狀 ⊗ 陣列狀

1.外加金屬塊熱源



Kim *et al.*, *Biochemical Engineering Journal,* 2006

2. 蜿蜒狀(serpentine-type)

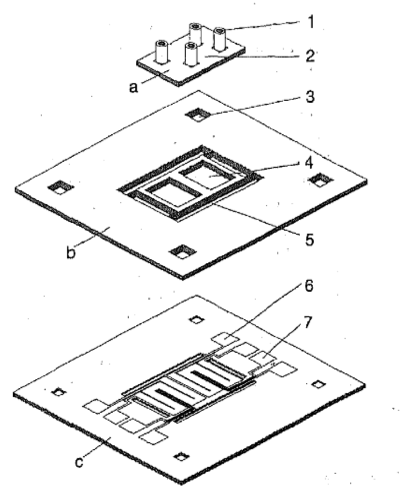
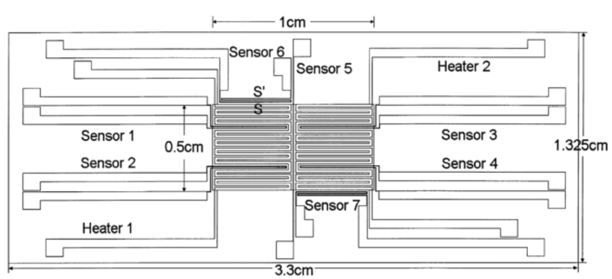


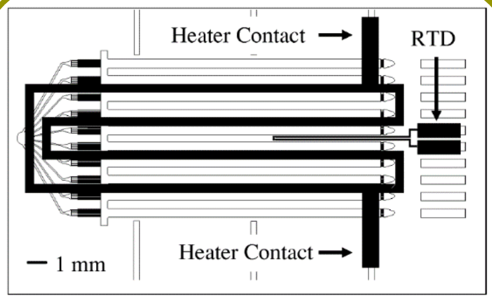
Fig. 4. Sketch of two-chamber chip. 1, Inlet; 2, cover; 3, adjustment; 4, reaction chamber; 5, air chamber; 6, thin-film heater; 7, temperature sensor; a, cover; b, topside; c, backside.

Poser *et al.*, *Sensors and Actuators A: Physical*, 1997

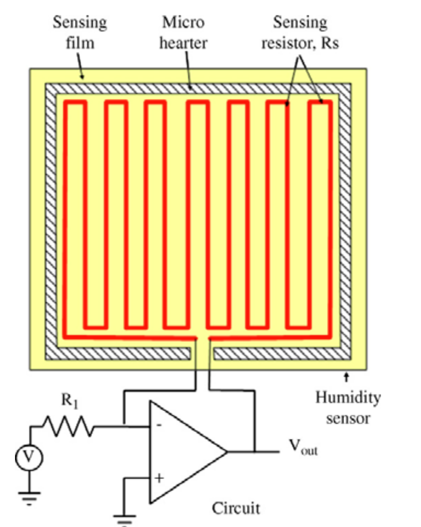


Lao *et al.*, *Sensors and Actuators A: Physical,* 2000

3.環狀



Losey *et al.*, *Journal of Microelectromechanical Systems*, 2002



Dai *et al.*, *Sensors and Actuators: B Chemical*, 2007

溫度量測

μLIF→螢光粒子
thermocouple

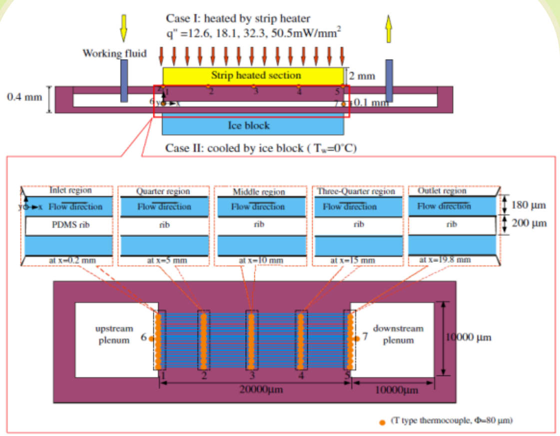
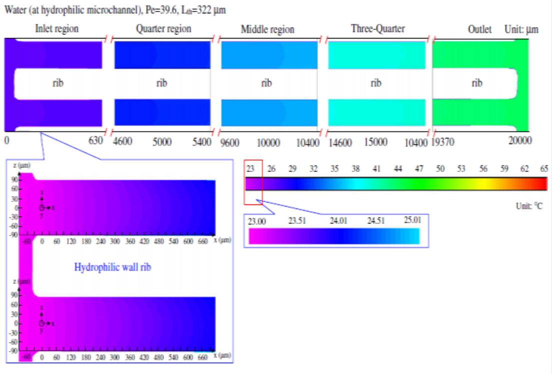


Fig. 1. Schematic of the test microchannel.



Hsieh *et al.*, *International Journal of Heat and Mass Transfer*, 2009

溫度感測器搭配溫控程式

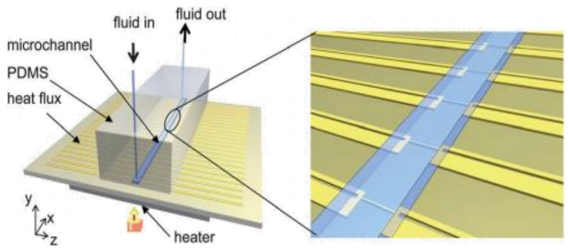


Fig. 3 Experimental setup, microchannel and instrumented borosilicate substrate.

Hamadi *et al.*, *Lab Chip*, 2012

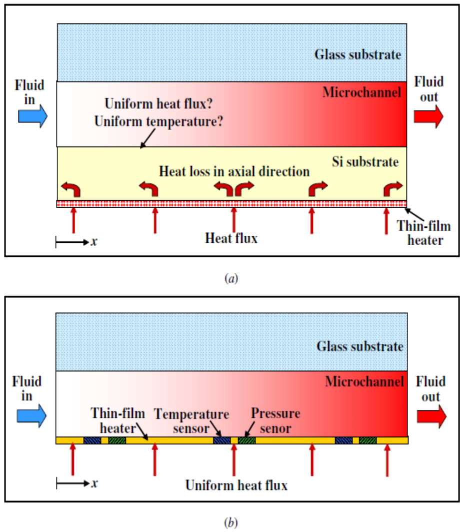
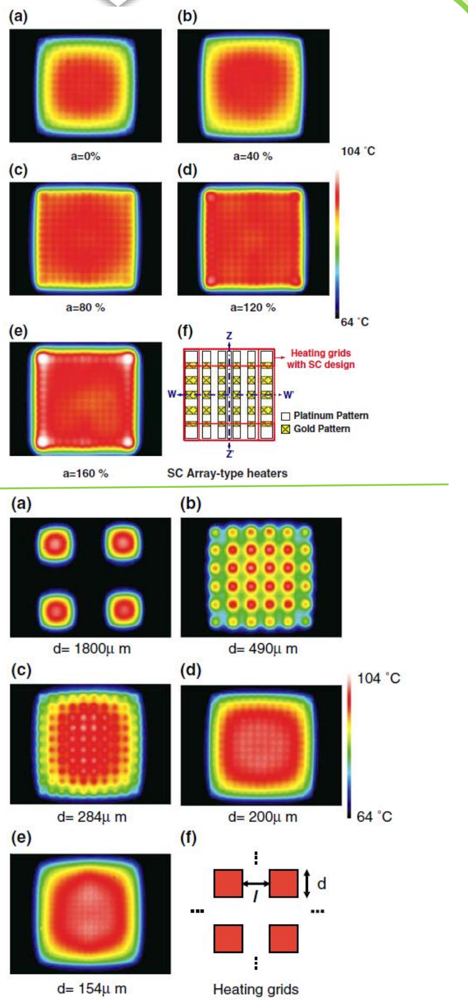


Figure 1. Schematic cross section of heat convection flow with (*a*) silicon substrate, and (*b*) thin-film cap.

Lee *et al.*, *J.Micromech. Microeng.*, 2011

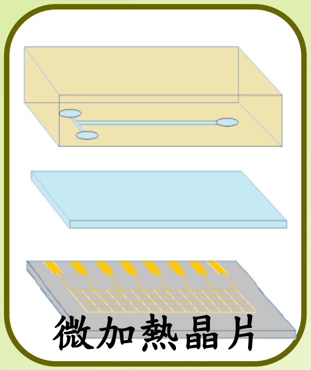
紅外線熱像儀

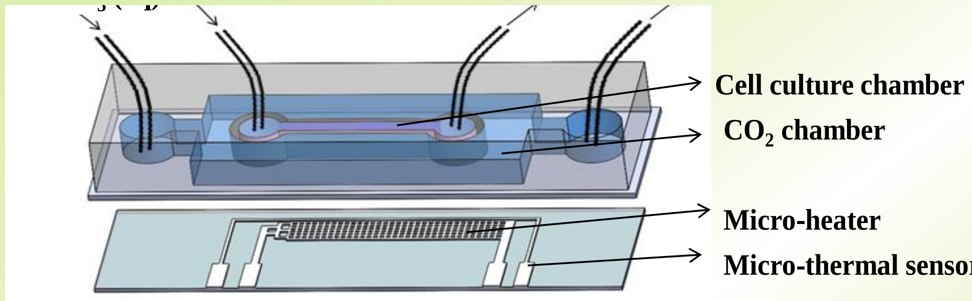


Hsieh *et al.*, *Microfluid Nanofluid*, 2009

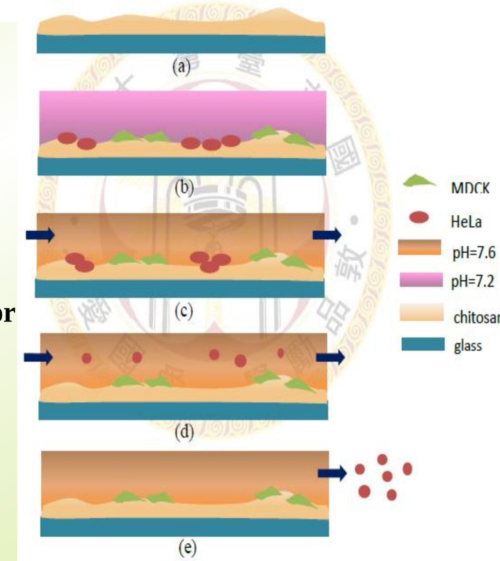
Cell Culture & Fractionation on a Microfluidic Chip with Programmable Modules of Temperature & CO2

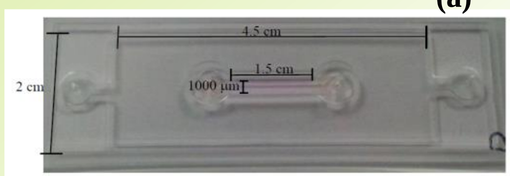
µTAS-2013
submitted to *Lab Chip*





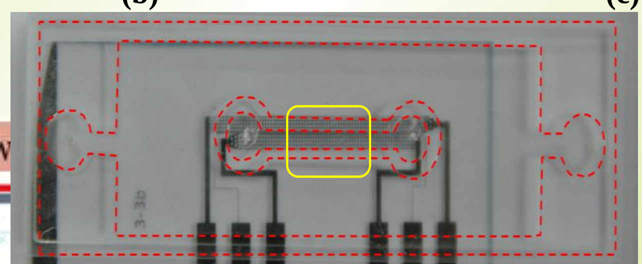
(a)



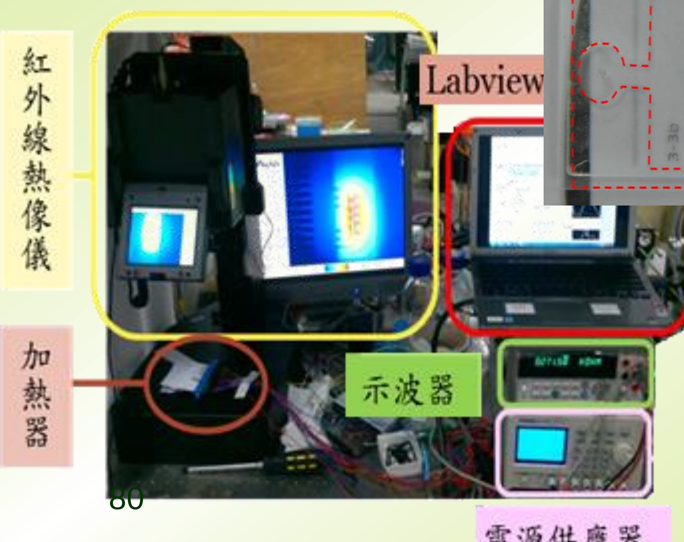


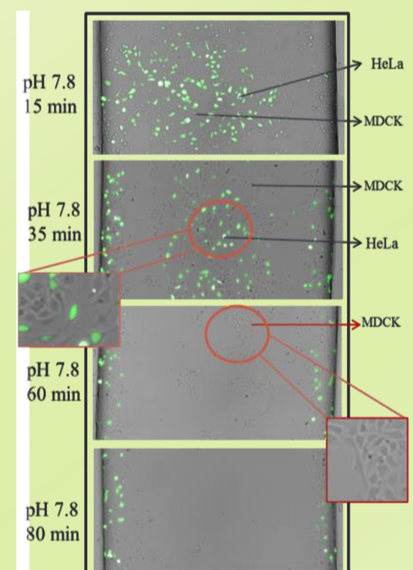
(b)

(c)



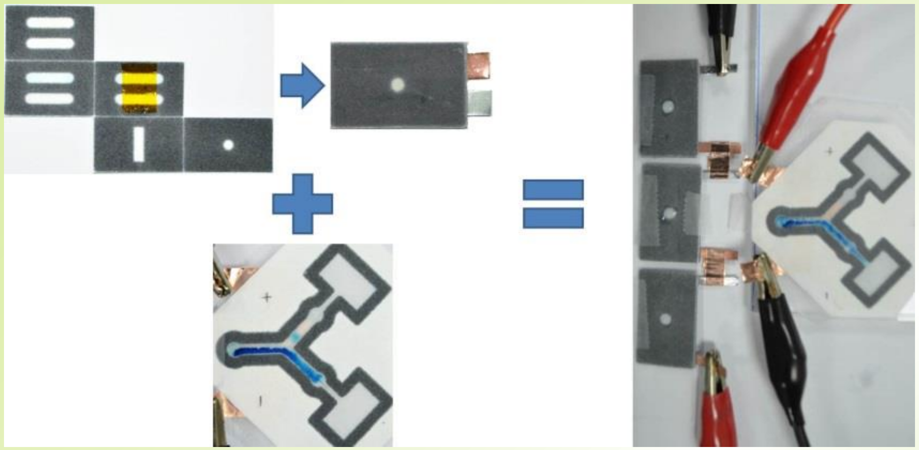
(d)

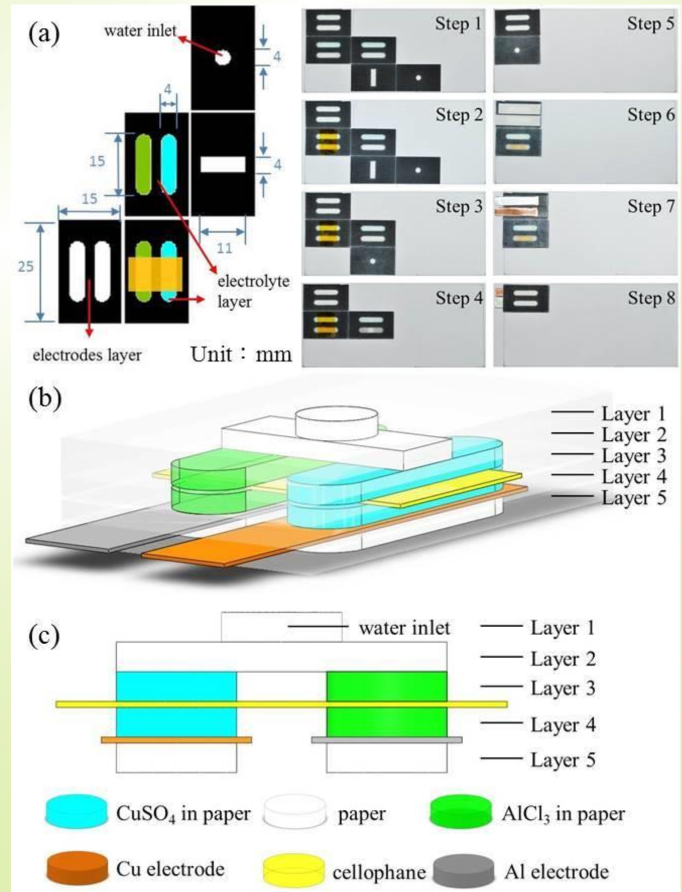


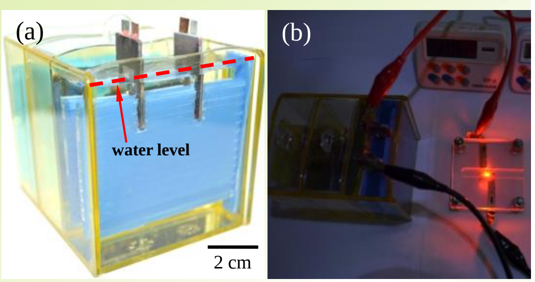


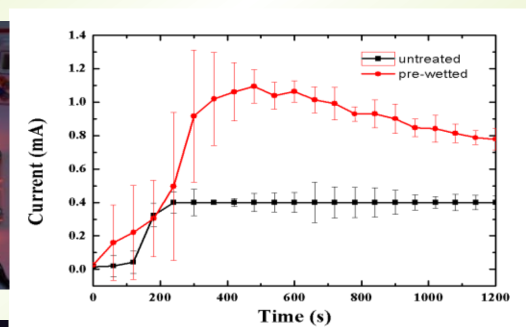
Origami Paper-Based Fluidic Batteries for Portable Electrophoretic Devices

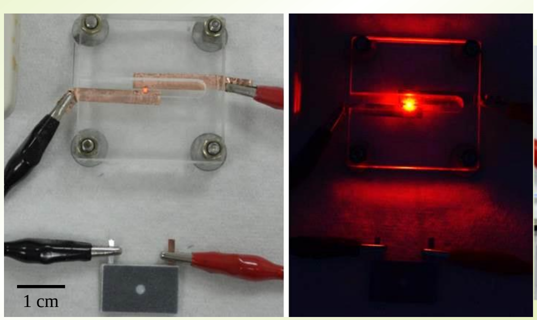
S. S. Chen, C. W. Hu, Y. C. Liao,*J. T. Yang,* μTAS-2013; *submitted to Lab on a Chip*

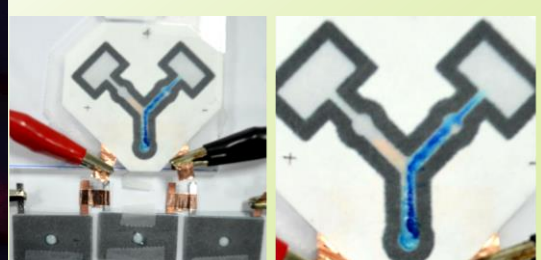






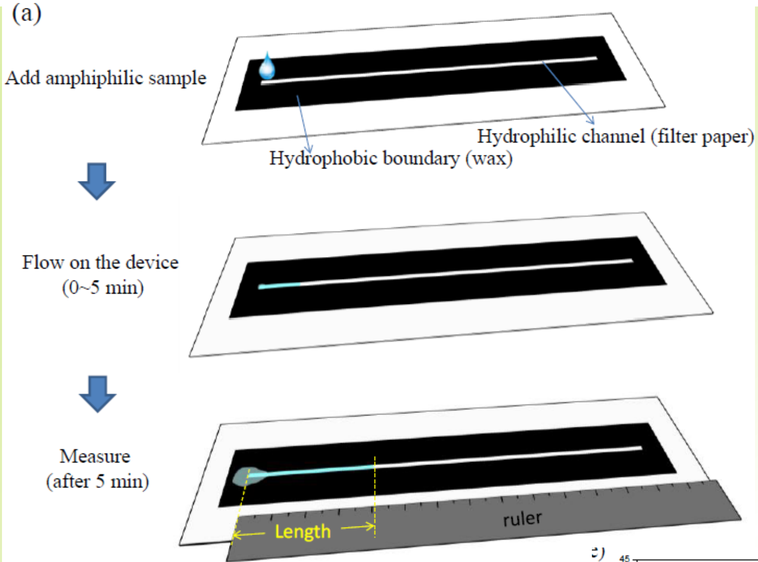


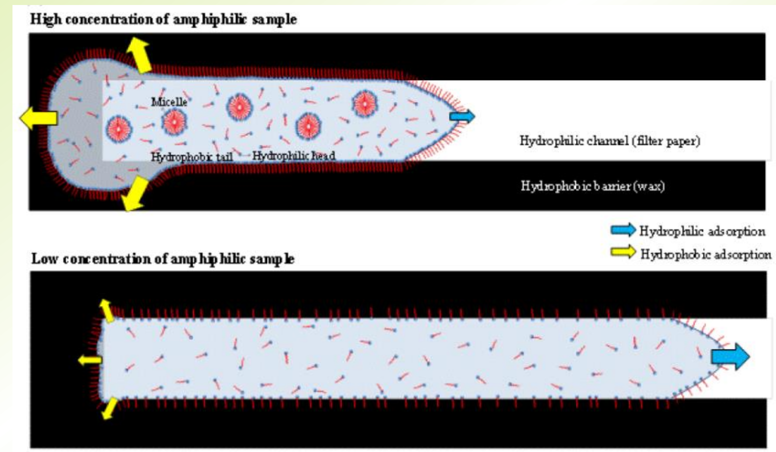


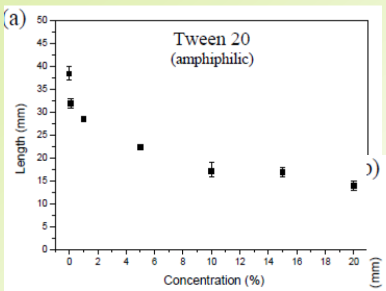


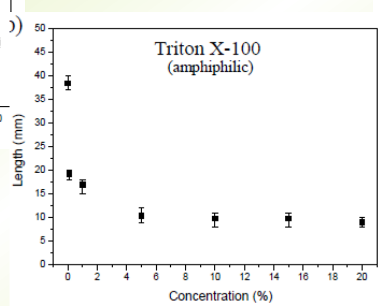
Detection of an Amphiphilic Biosample in a Paper Microchannel Based on Length

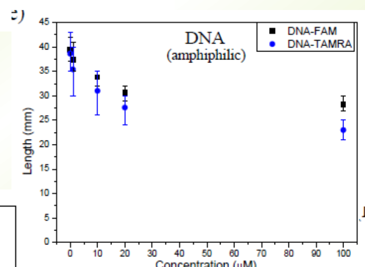
Yu-Tzu Chen and **Jing-Tang Yang,*** *Biomedical Microdevices*, 2015

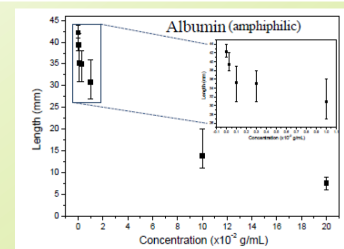


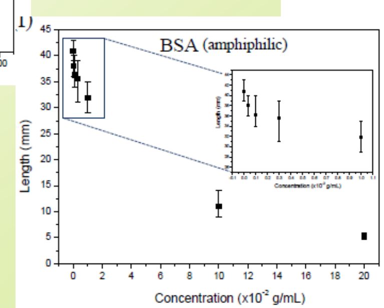


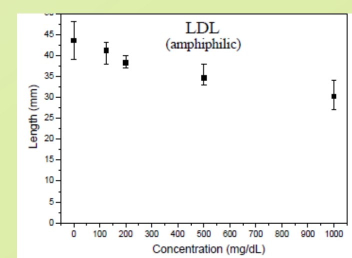








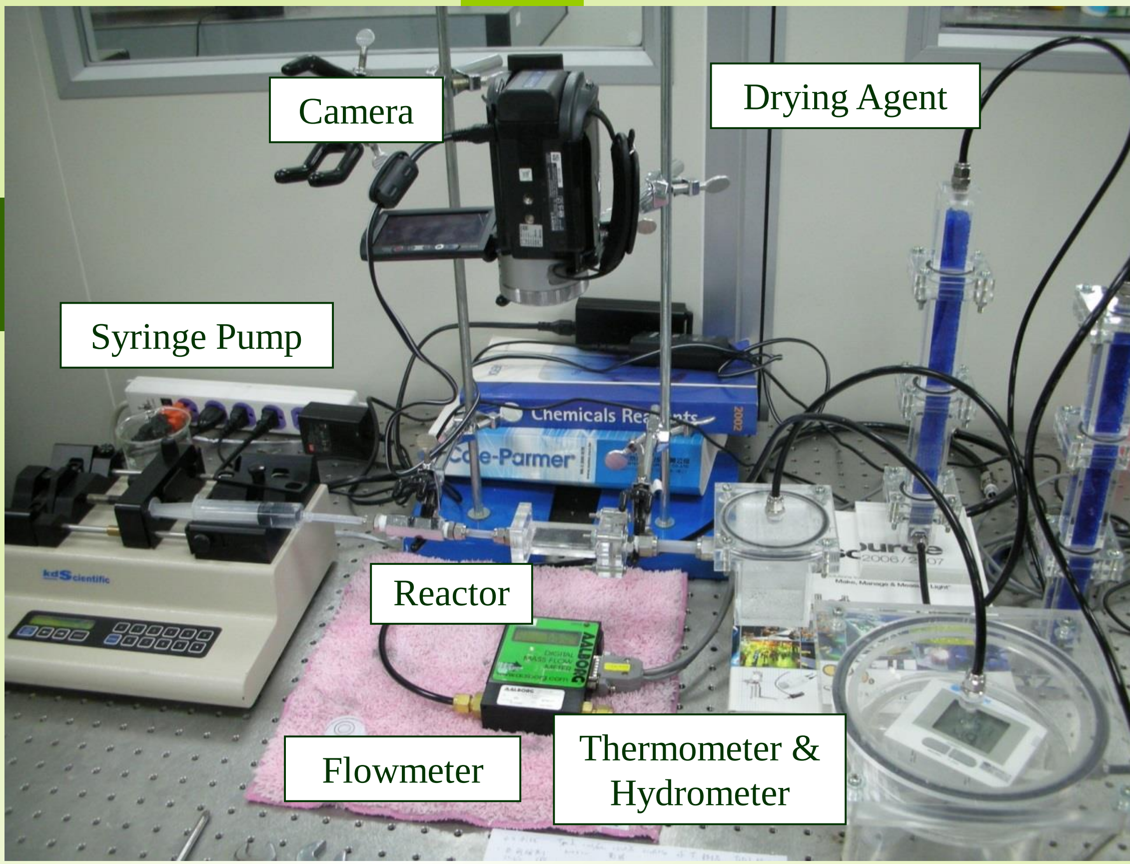


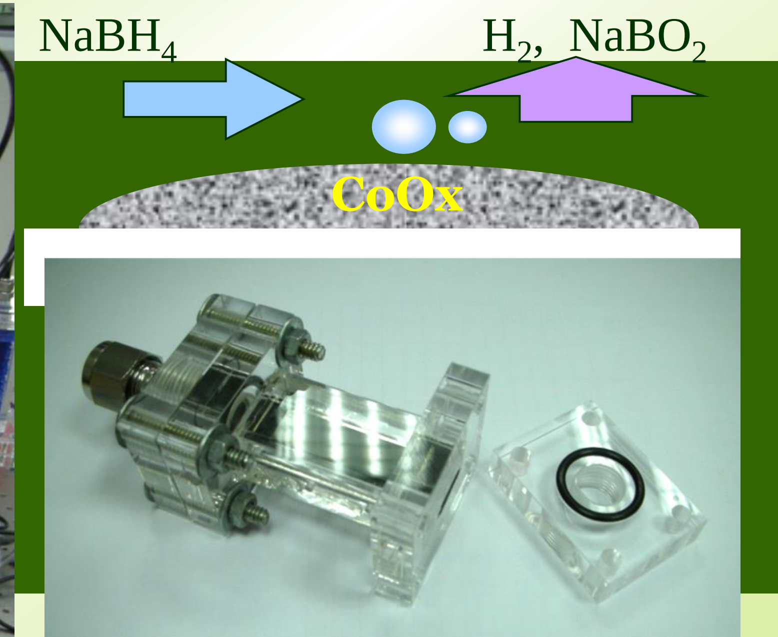


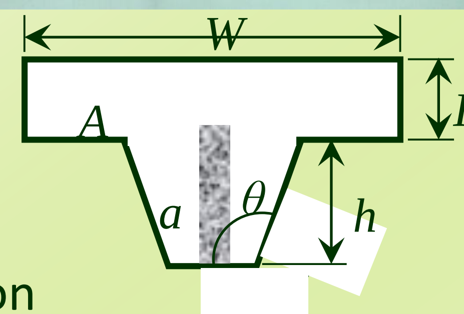
We developed a simple method to achieve semiquantitative detection of an amphiphilic biosample through measuring the length of flow on a microfluidic analytical device (μPAD) based on paper.

Design & testing of a novel catalytic reactor to generate hydrogen

Int. J. Hydrogen Energy, 2014

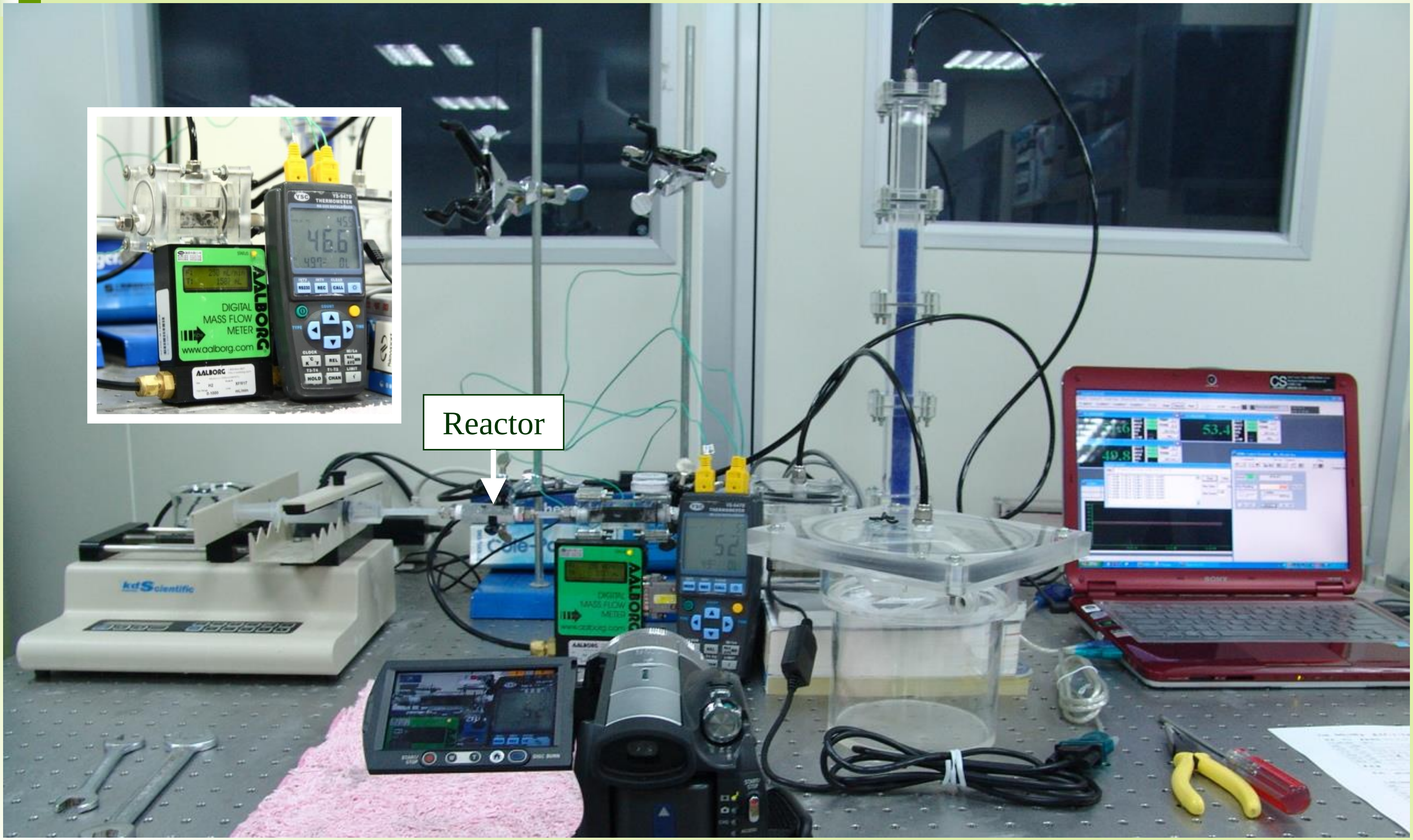






A catalytic reactor to generate hydrogen with a large conversion efficiency and a stable rate of generation is based on a p-shaped design that decreases the effect of hydrogen on the catalyst surface so as to increase the opportunities for contact between sodium borohydride ($NaBH_4$) and the catalyst.

Experimental Framework



第十五屆國家新創獎 學研新創獎

植物病害之可視化分子診斷
- 以番茄黃化捲葉病毒病為例

Visual molecular diagnostics for plant disease

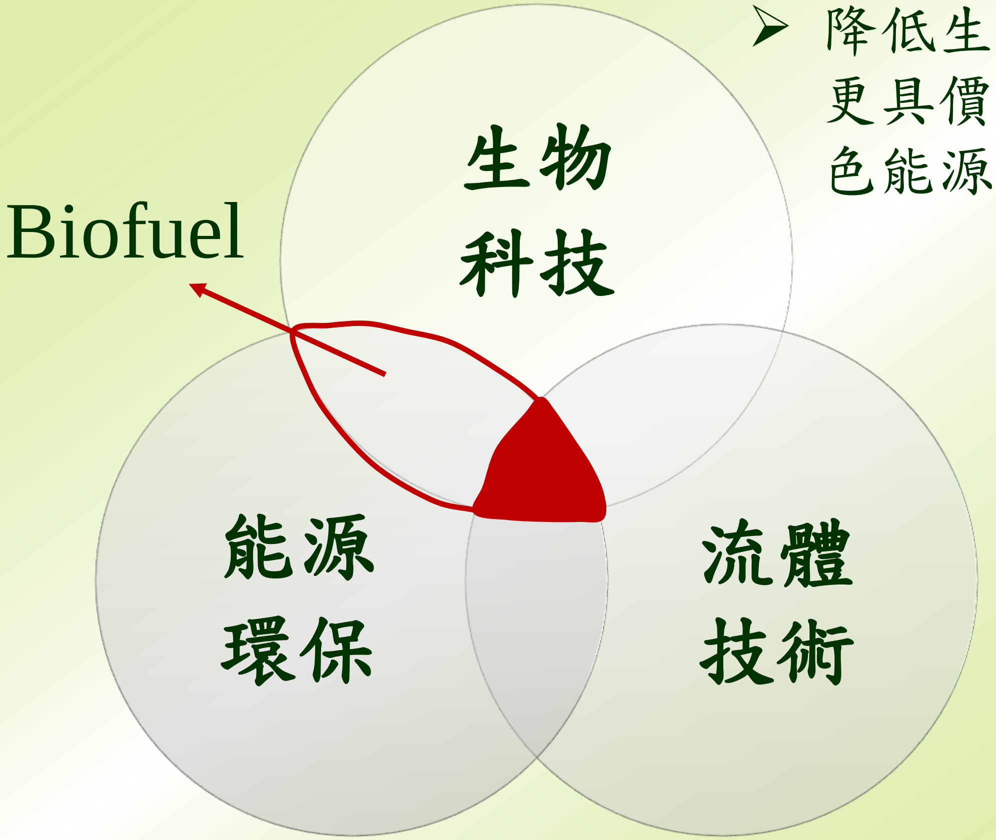
– a case study of Tomato yellow leaf curl virus disease

- 王子明、楊鏡堂

- 2018年09月27日 社團法人國家生技醫療產業策進會

國立臺灣大學 National Taiwan University
Department of Mechanical Engineering National Taiwan University 機械系
BEAM Lab

創新的液珠式生質柴油產製系統



- 降低生質燃料產製成本，使其更具價格競爭力，突破目前綠色能源發展的主要瓶頸

☑ 液珠式流體反應元件，具有高面積與體積比之反應優勢

☑ 液珠具有易操控之特性可進行後續分離與純化

☑ 本系統可在常溫/中溫下高速率進行生質柴油產製

財團法人
東元科技文教基金會
TECO Technology Foundation

綠色進化的煉油廠—

液珠式高速率低耗能生質燃料的創新生產方法與裝置

- **報告人：葉思沂**

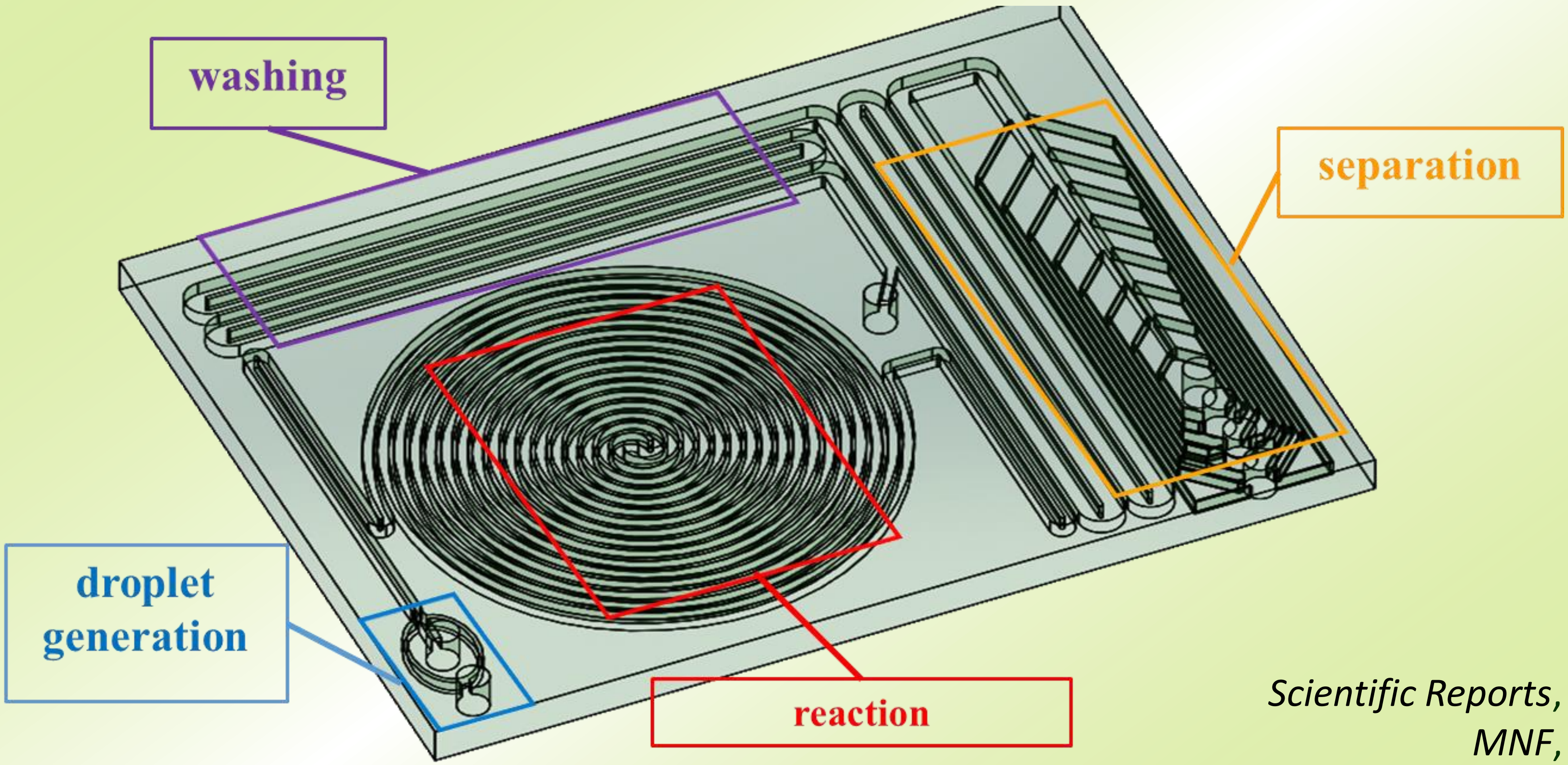
隊　　員：黃彥誠、朱旭剛

指導教授：楊鏡堂博士

國立台灣大學機械工程研究所

2014.08.26

Biodiesel Production Chip

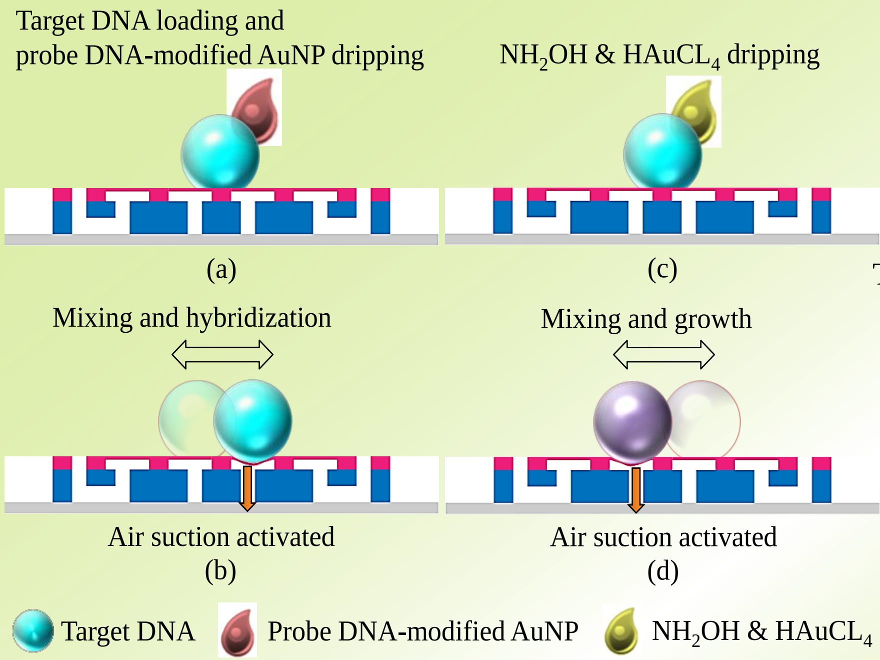


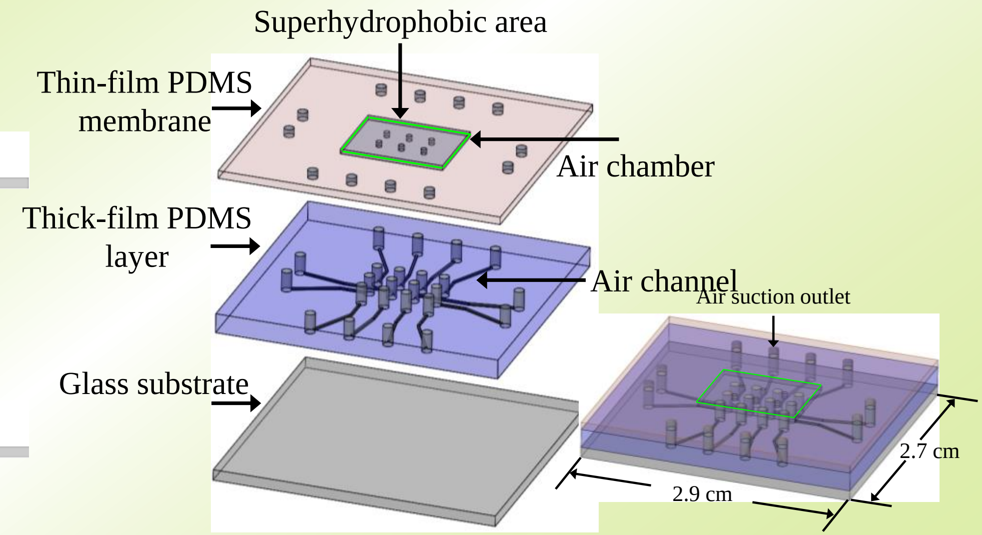
Scientific Reports, 2016
MNF, 2017

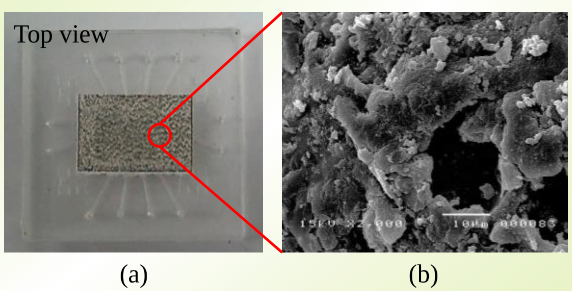
- **Faster reaction characteristic**
- **Inputs of raw materials, outputs of available products**
- **Low energy consumption and easy operation**

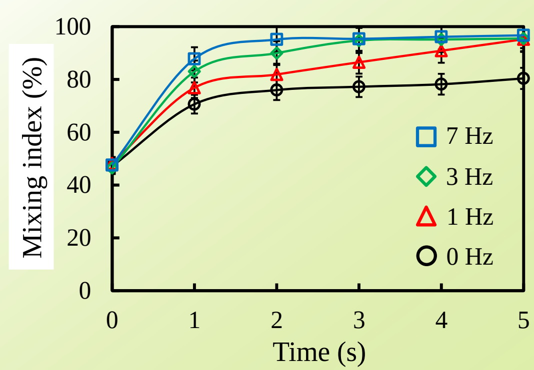
A biocompatible open-surface droplet manipulation platform for multi-nucleotide polymorphisms detection

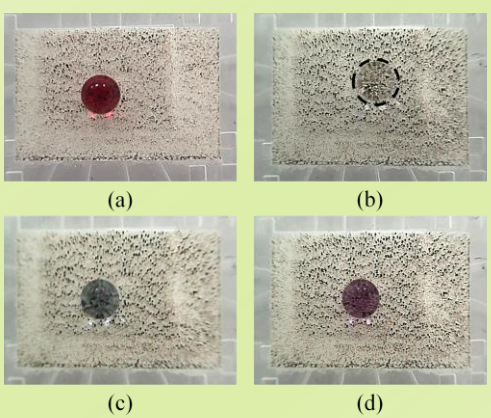
C. J. Huang, W. F. Fang, M. S. Ko, **J. T. Yang**,* *Transducer-2013*; *submitted to Lab on a Chip*





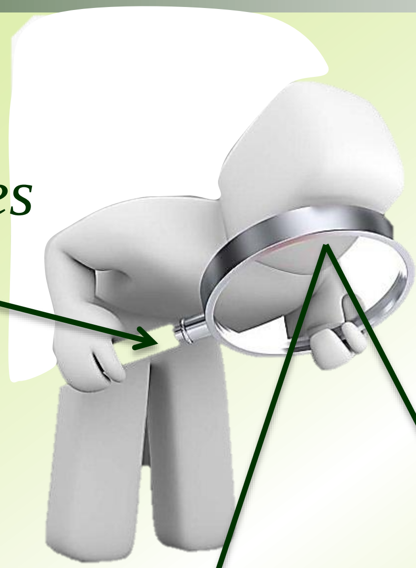






Measurement Techniques

Measuring techniques



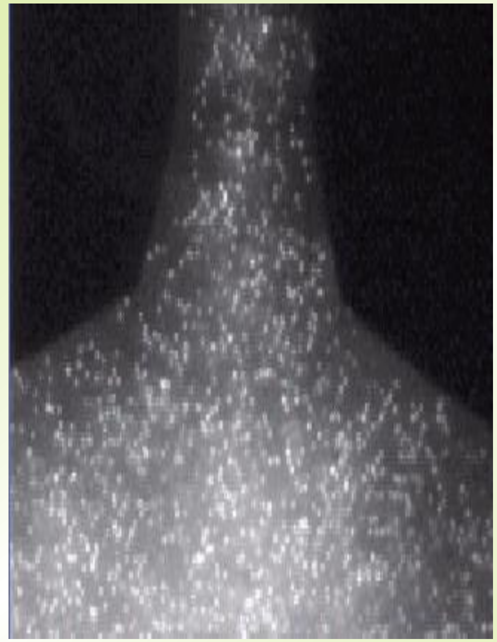
Magic !?

- ✓ to comprehend
- ✓ to verify
- ✓ to evolve

Measurement of Fluid Mixing

Colors recognition

Tracing Particles



Chemical Indicator

The characteristics of fluid mixing is measured via colors recognition, tracing particles, and chemical indicator. In this research, the mixing degree is quantized by the computation of the standard deviation of grayscale values which are analogous to the constitution of fluid. Velocity field is measured via tracing particles called particles image velocimetry.

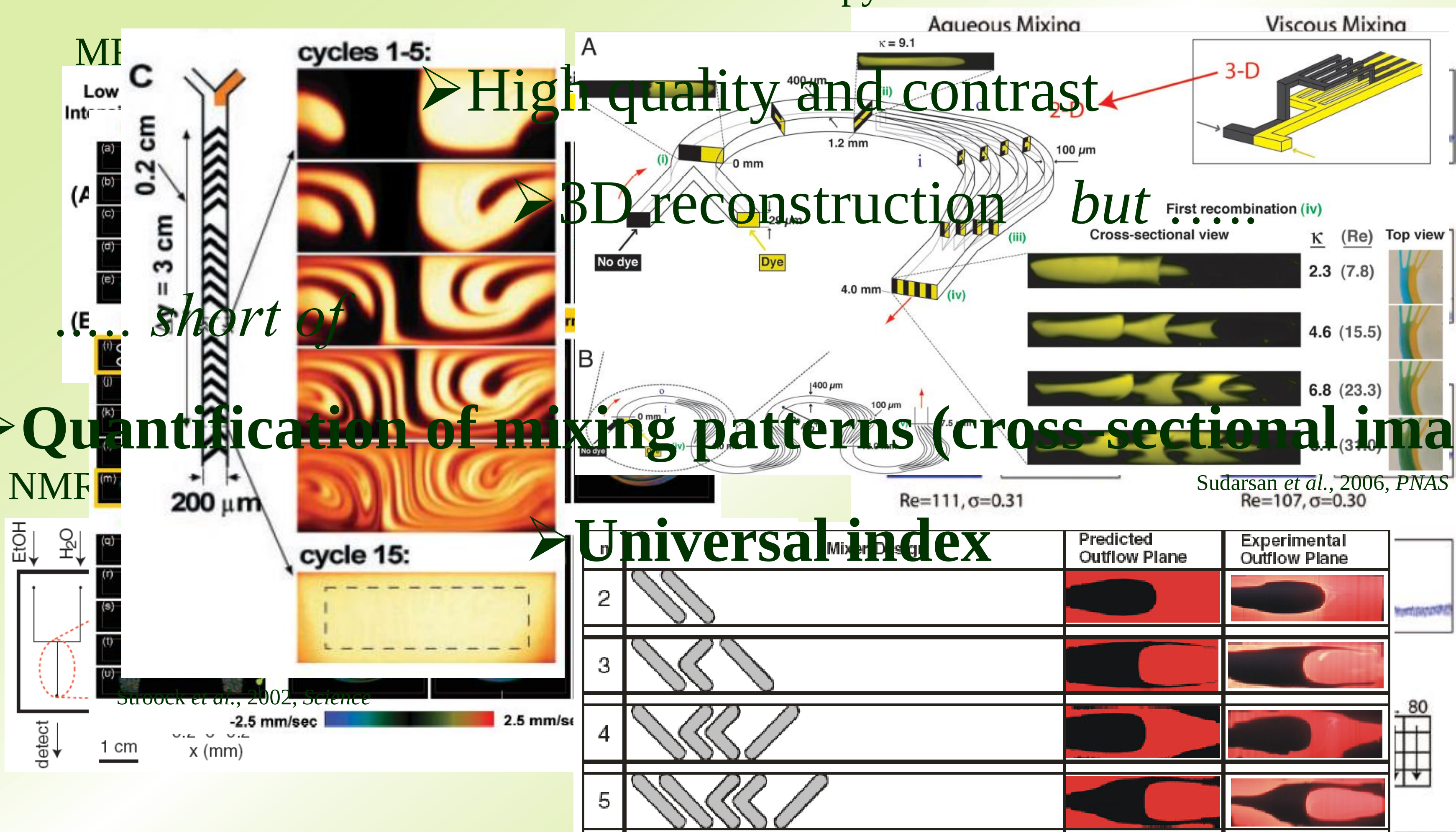
Measuring Techniques

Confocal microscopy

Synchrotron radiation circular dichroism, SRCD

MR

NMR



- High quality and contrast
- 3D reconstruction *but …..*

….. short of

- **Quantification of mixing patterns (cross-sectional images)**
- **Universal index**

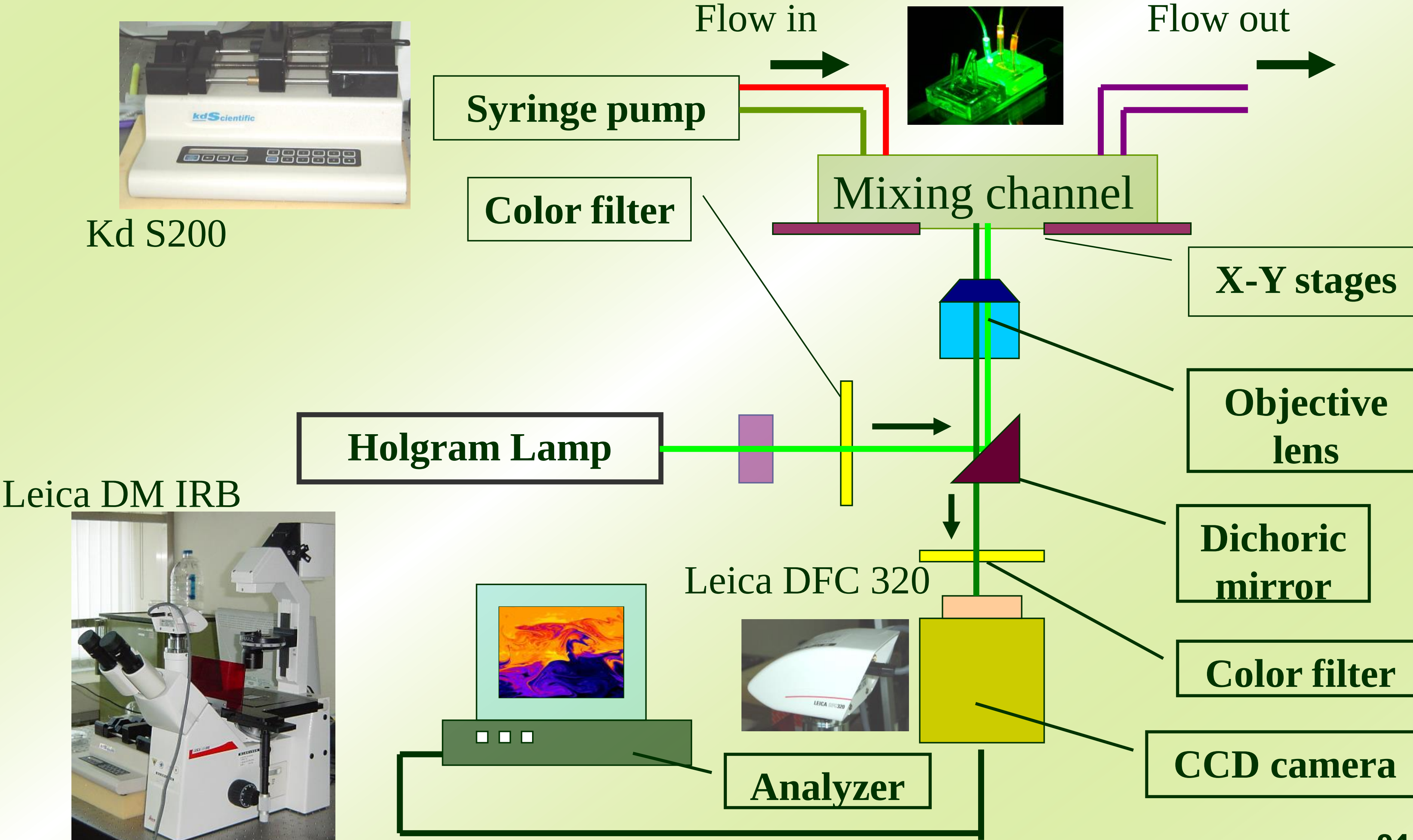
Stroock *et al.*, 2002, *Science*

Sudarsan *et al.*, 2006, *PNAS*

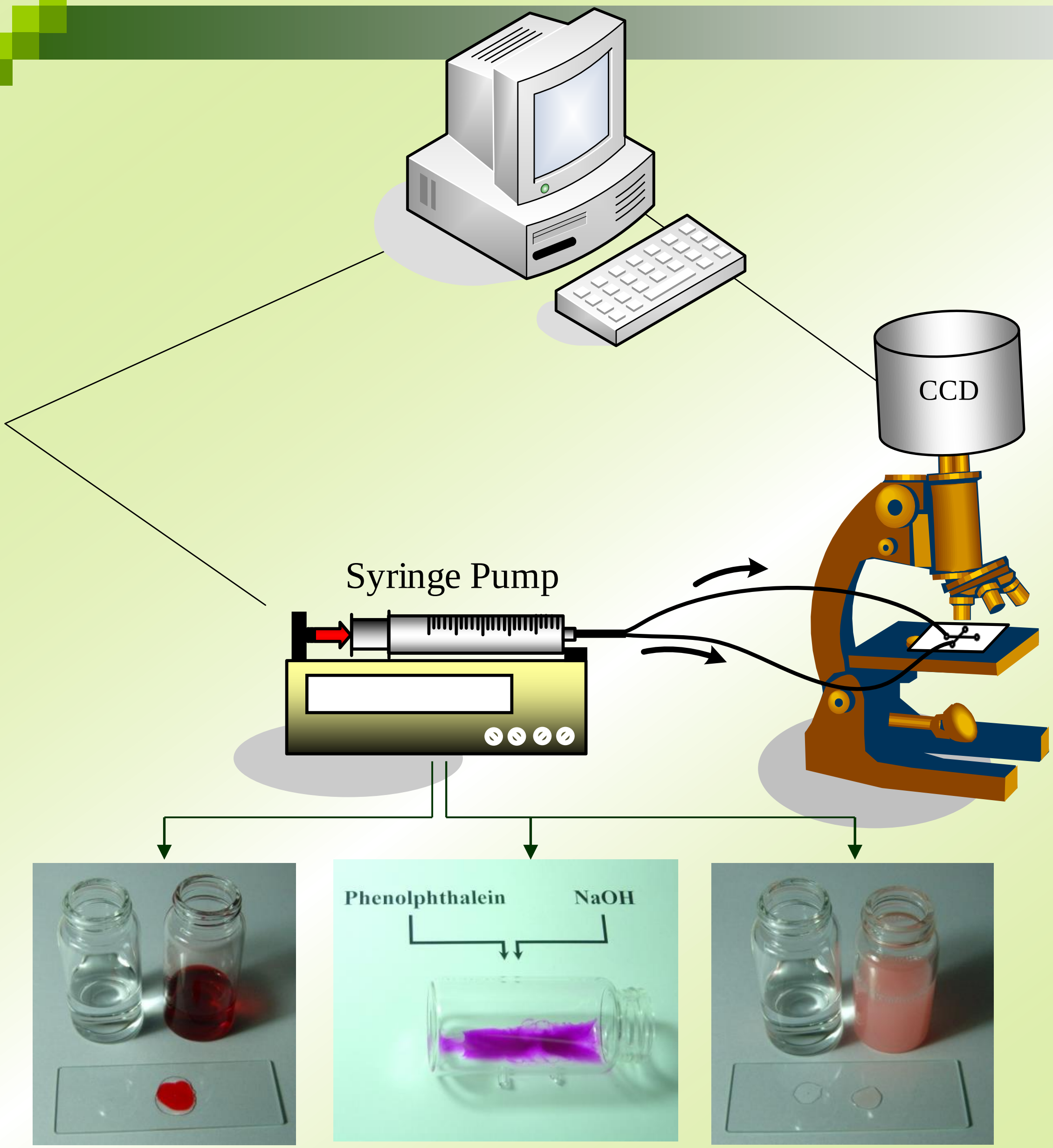
Kane *et al.*, 2008, *Anal. Chem.*

Howell *et al.*, 2008, *JMM*

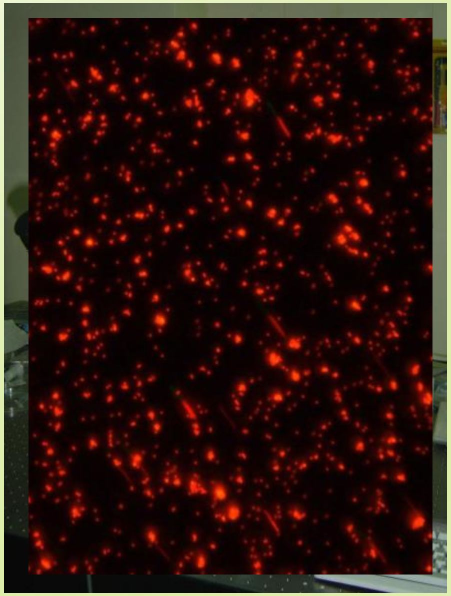
Schematic Diagram of Experimental Setup



Experimental Set-up



LSM 510

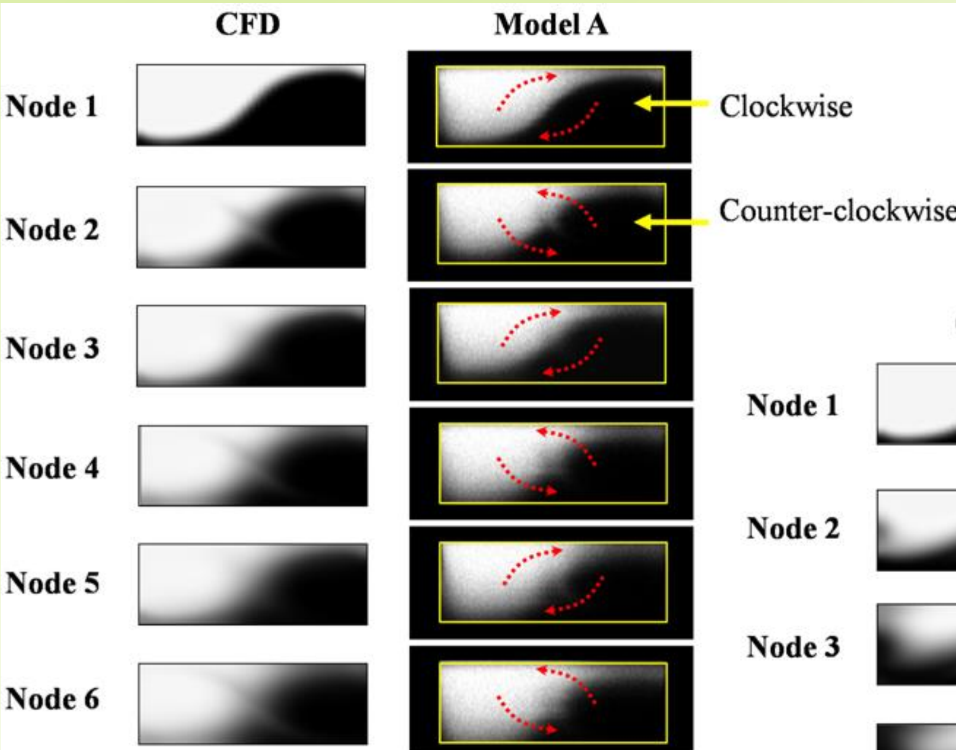


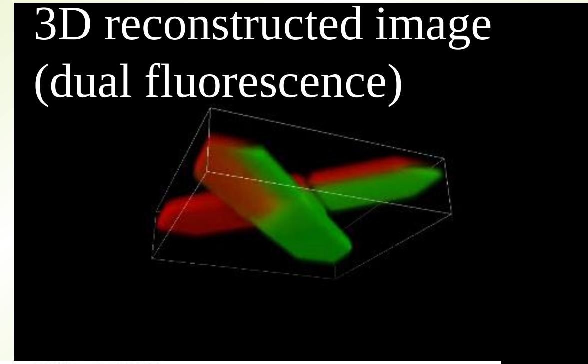
Leica DM IRM

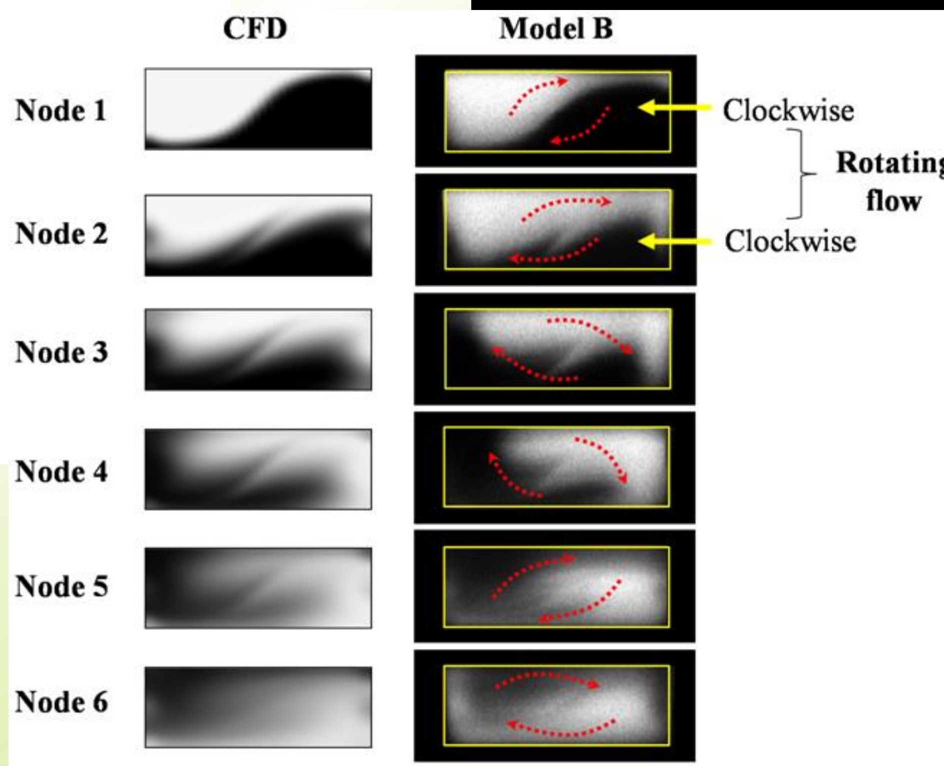
Measuring Techniques (Universal index)

Biomicrofluidics, 2011
(top 20 most downloaded articles, 2011/04, /05, and /06)

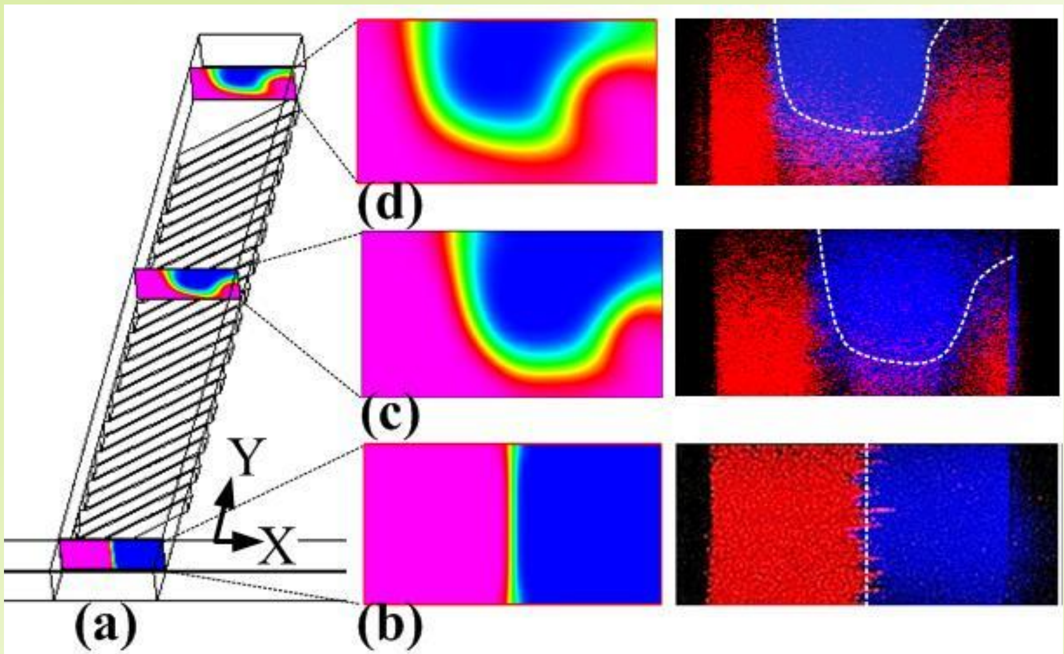
Mixing patterns

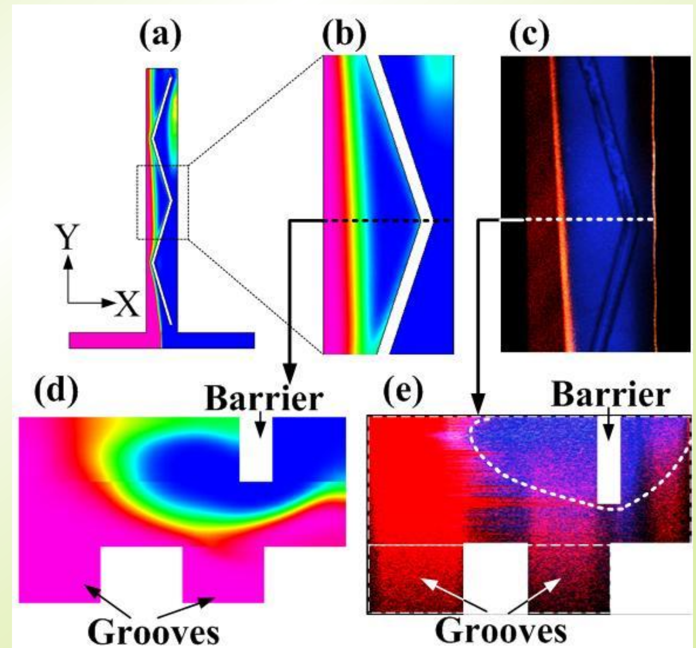






Micro laser-induced fluorescence (μ-LIF)



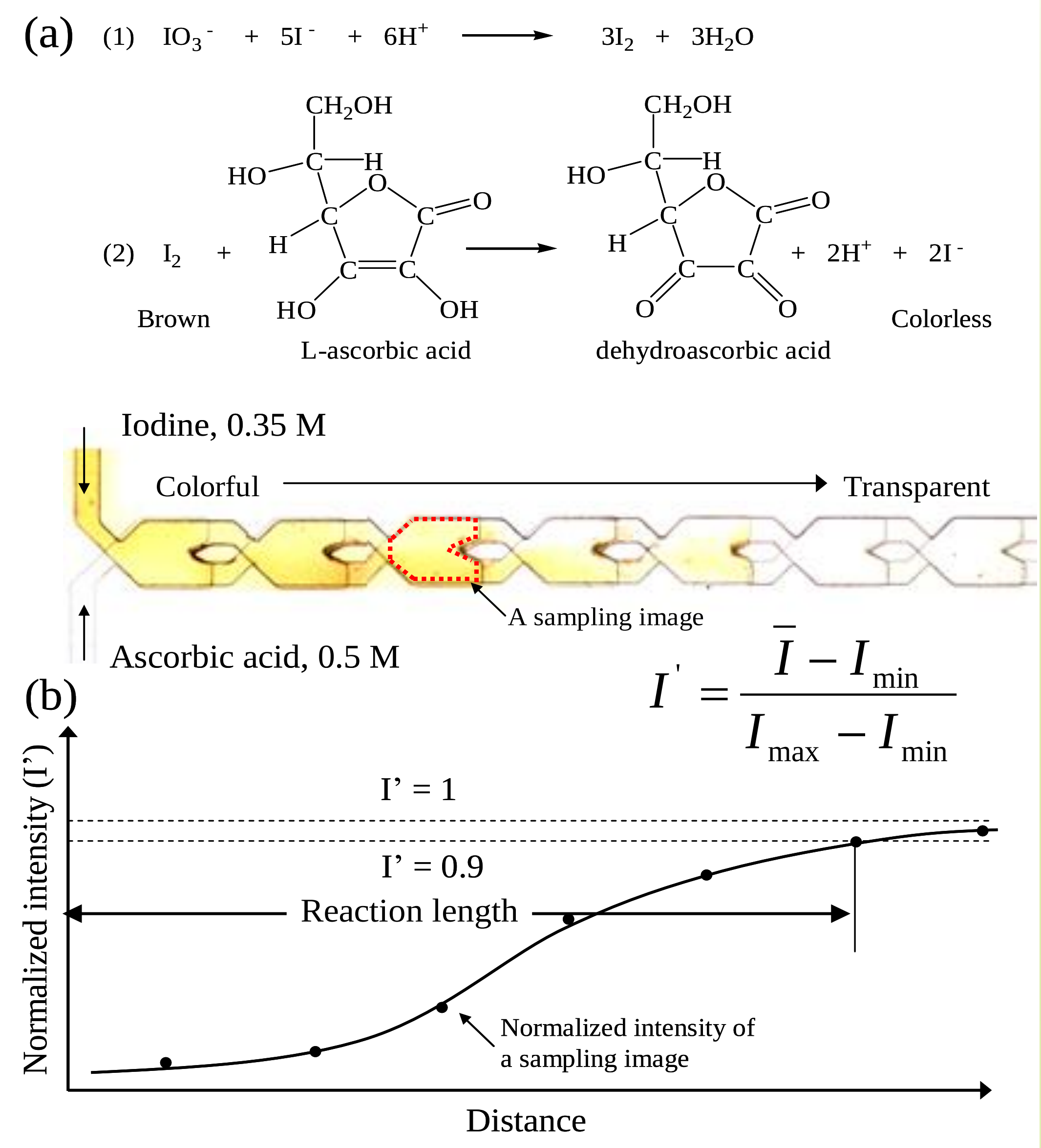


Two fluorescent proteins – B-phycoerythrin (BPE, 0.5 μM, Far East Bio-Tec Co., Ltd.) and Allophycocyanin alpha subunit (ApcA, 2 μM, Far East Bio-Tec Co., Ltd.) – served to monitor the mixing performance.

Experiments – redox reaction

Redox reaction of ascorbic acid with diiodine

Fading process of diiodine



$$I' = \frac{\bar{I} - I_{min}}{I_{max} - I_{min}}$$

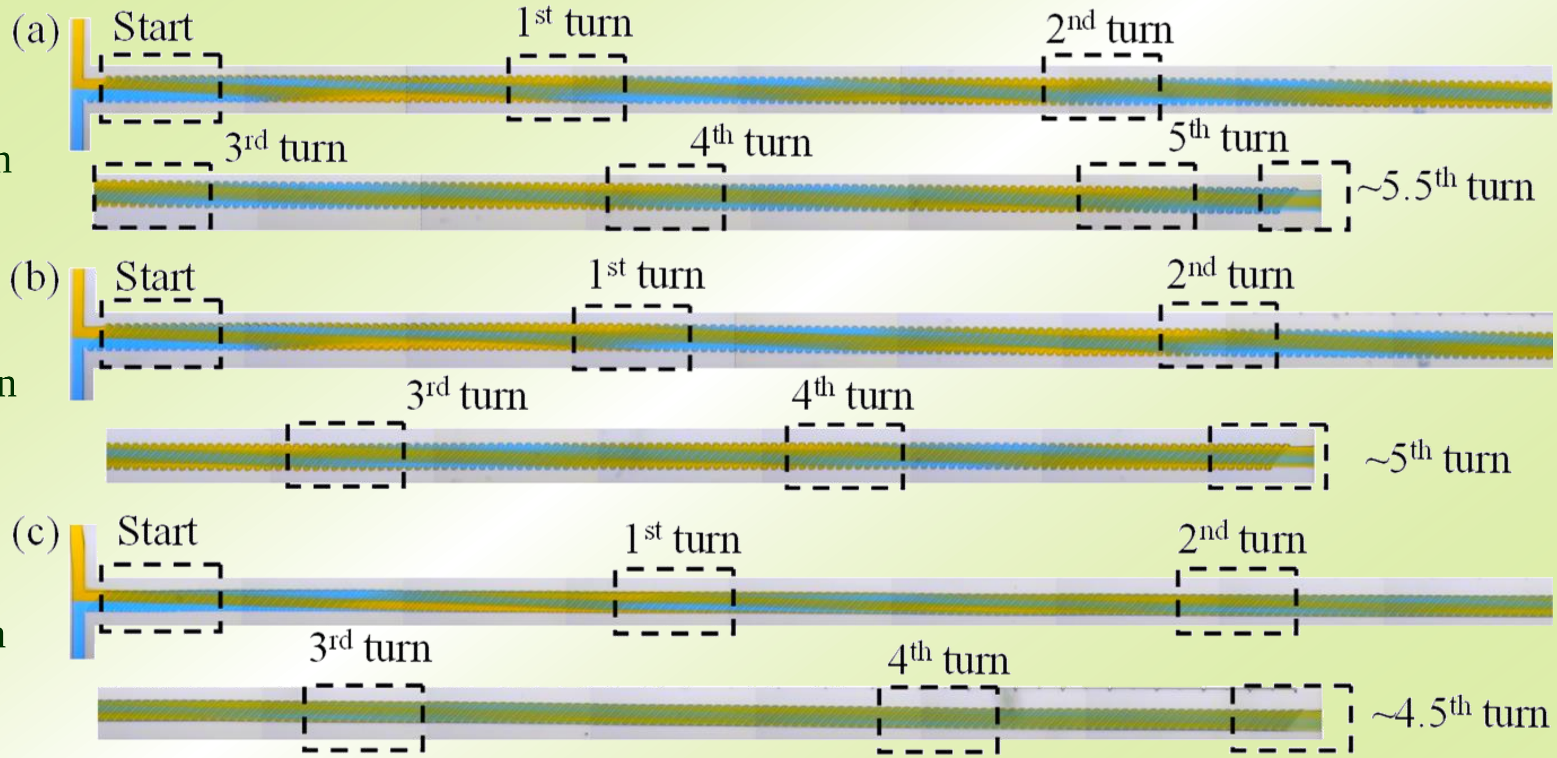
Flow Visualization with Dyes - CGM

Mixing between ighly viscous fluids with assistance of sidewall grooves

CGM-1
1 μL/min

CGM-1
10 μL/min

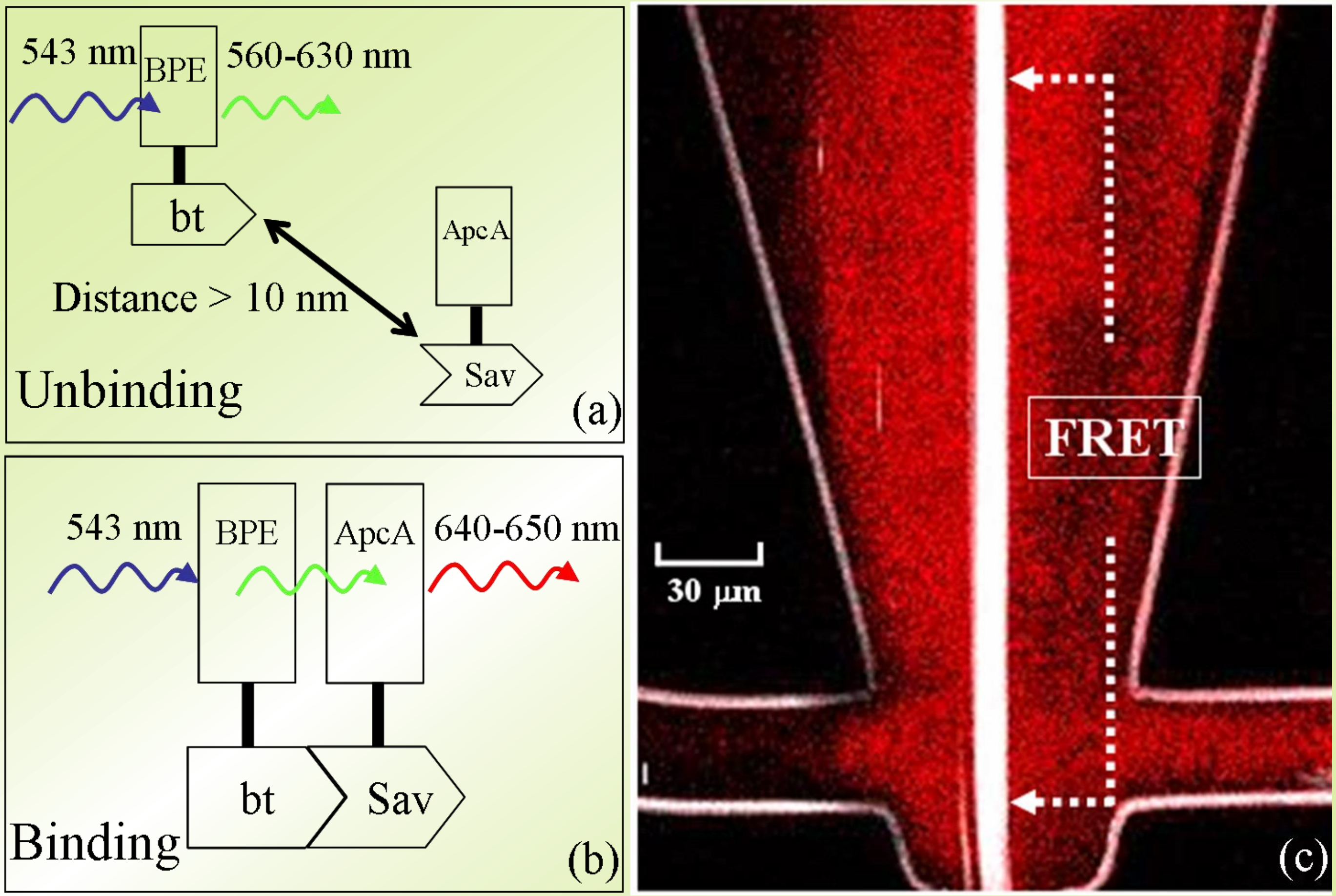
SGM
1 μL/min



We discovered that the number of turns of helical motion generated in CGM-1 are 0.5~1 more than that in SGM for Q = 1~100 μL/min.

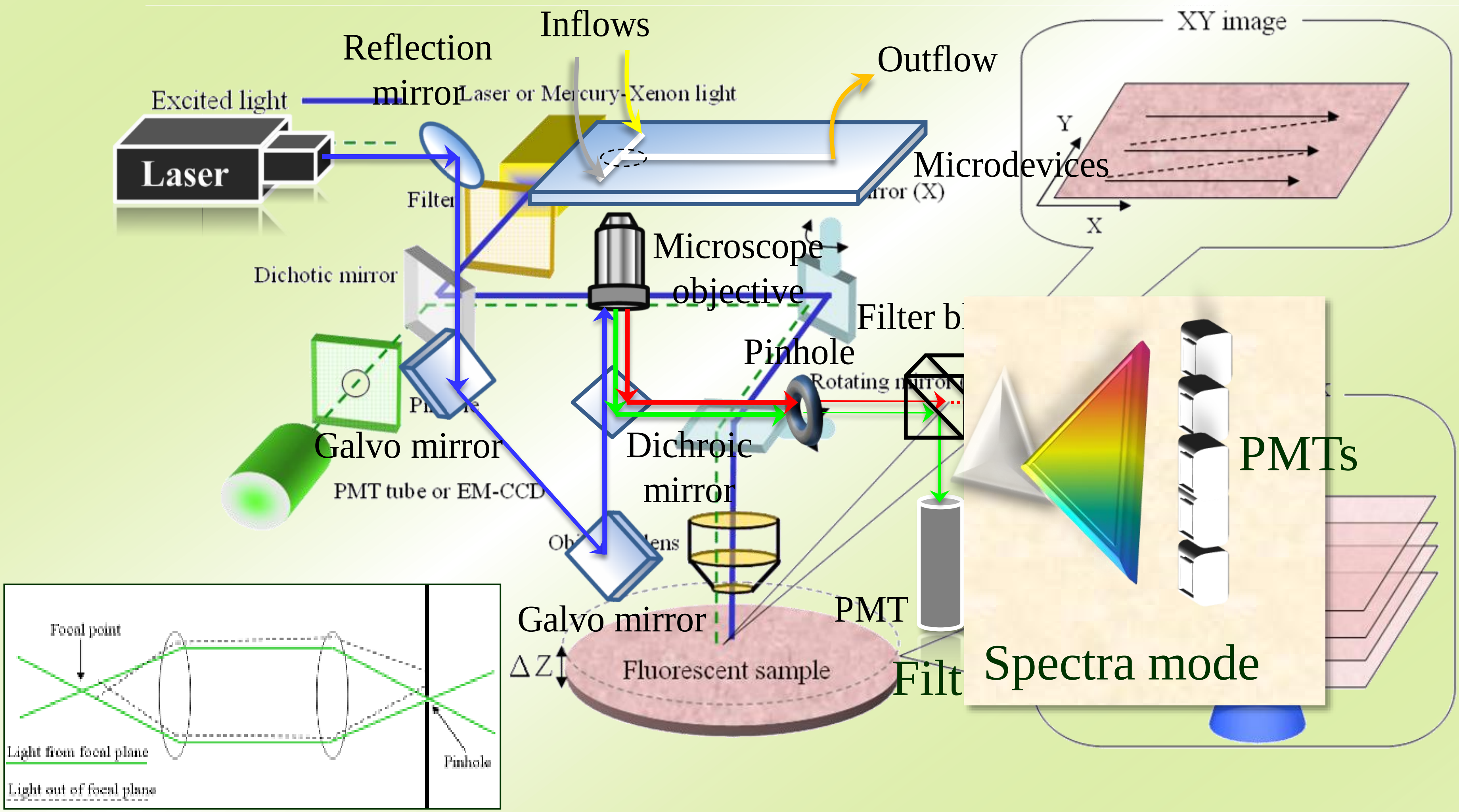
CGM-1 possessed a highly helical intensity (transverse component) relative to SGM.

Fluorescent Resonant Energy Transfer (FRET) in a Microreactor

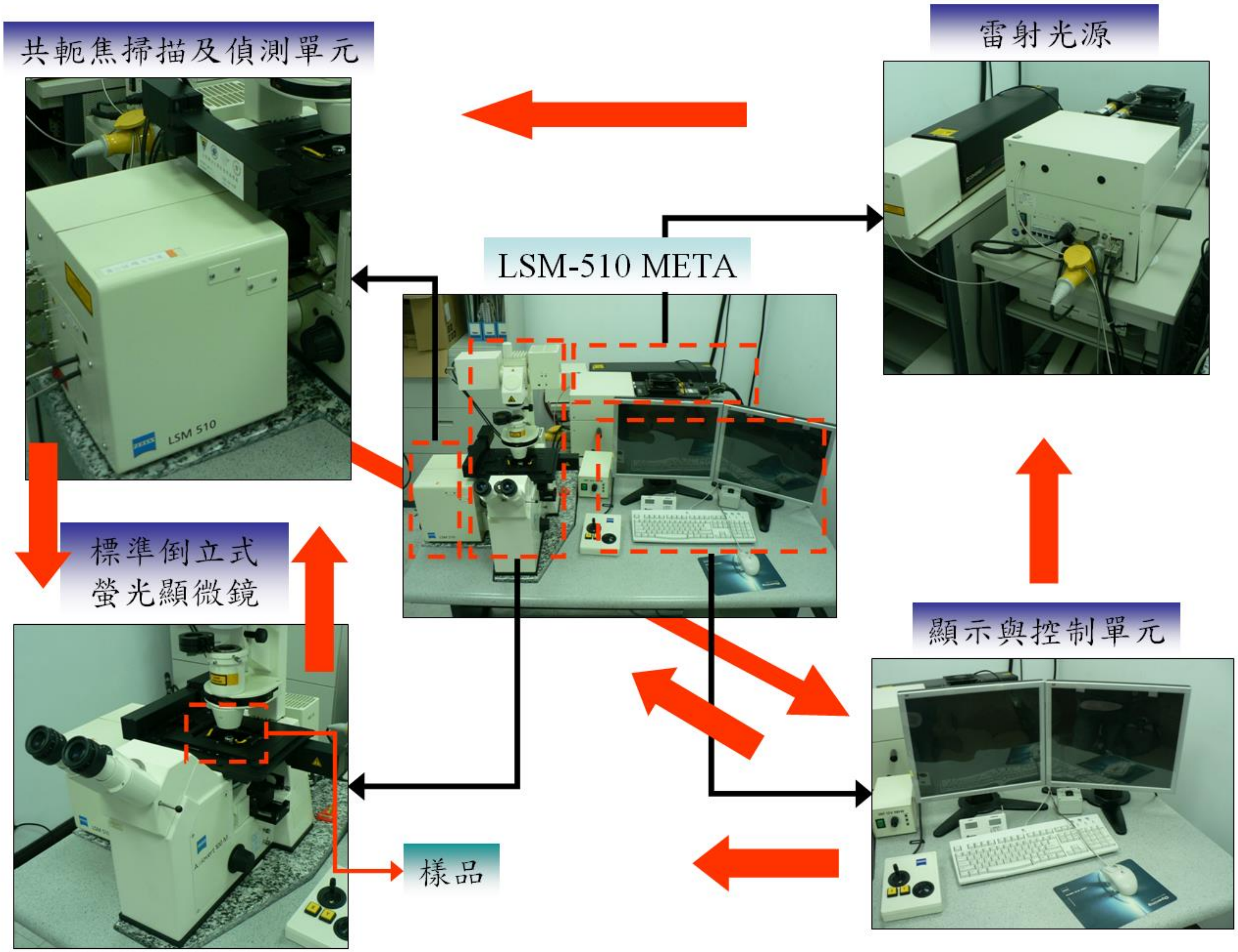


螢光共振分析概念 (a)當樣本間距大於10 nm時螢光共振將不會發生, (b)當樣本間距小於10 nm時螢光共振將受激發後發生, (c)螢光共振現象發生於二股流體界面處 (右圖中FRET的區塊僅因擴散機制出現在二流體之間)

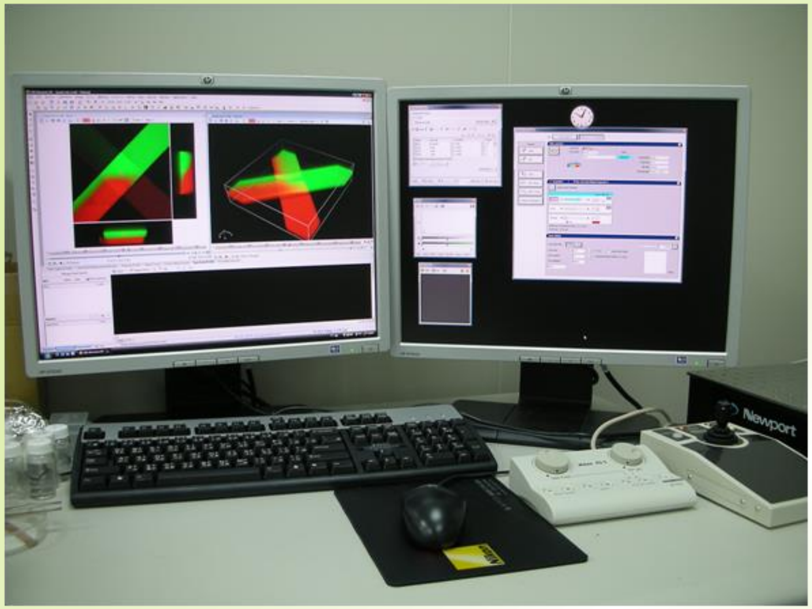
Confocal Fluorescence Microscopy



雷射掃描共軛焦顯微鏡(LSM-510)之架構



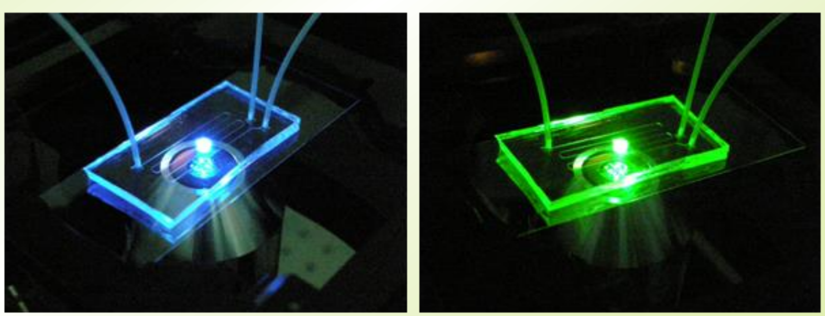
Confocal Microscope (Nikon A1R)



Monitor and operation interface

Nikon A1R

4



Test section (light excitation on chip)

5

Syringe pump

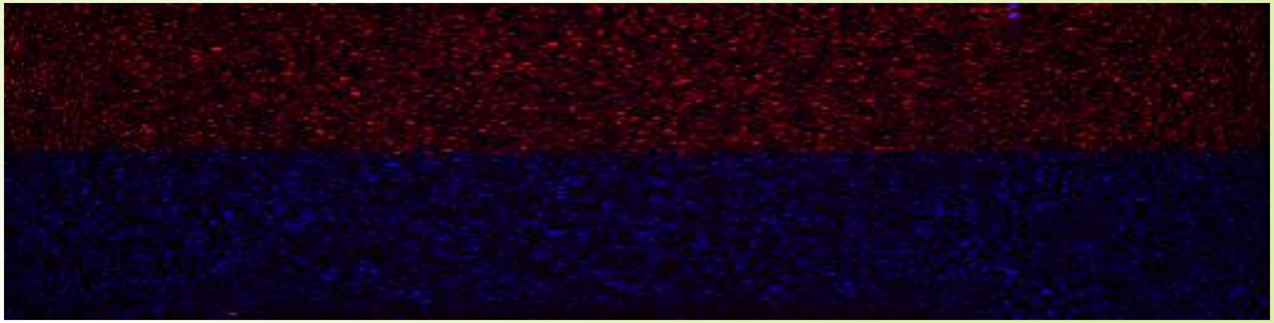
103

Measuring Techniques (simultaneous measurement)

Is it possible to achieve the simultaneous measurement of species velocities & concentrations in microdevices ?

Mass transfer & momentum transfer ? All in one ?

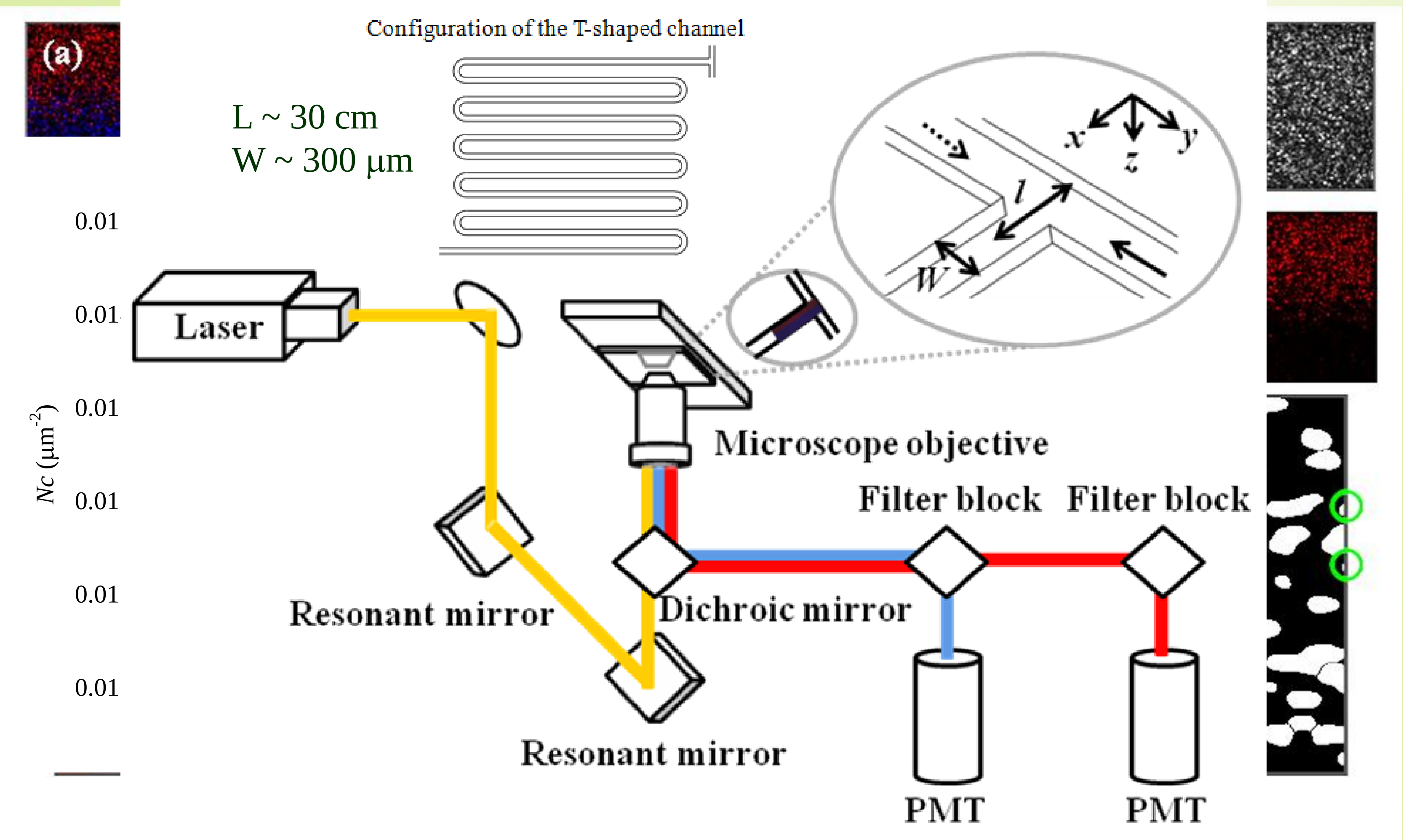
~ absolutely yes !



Measuring Techniques (simultaneous measurement)

Biomicrofluidics, 2010
(Top 20 most downloaded articles, 2010/04, and /06)

Simultaneous measurement (micro-PIV & particle counting method)

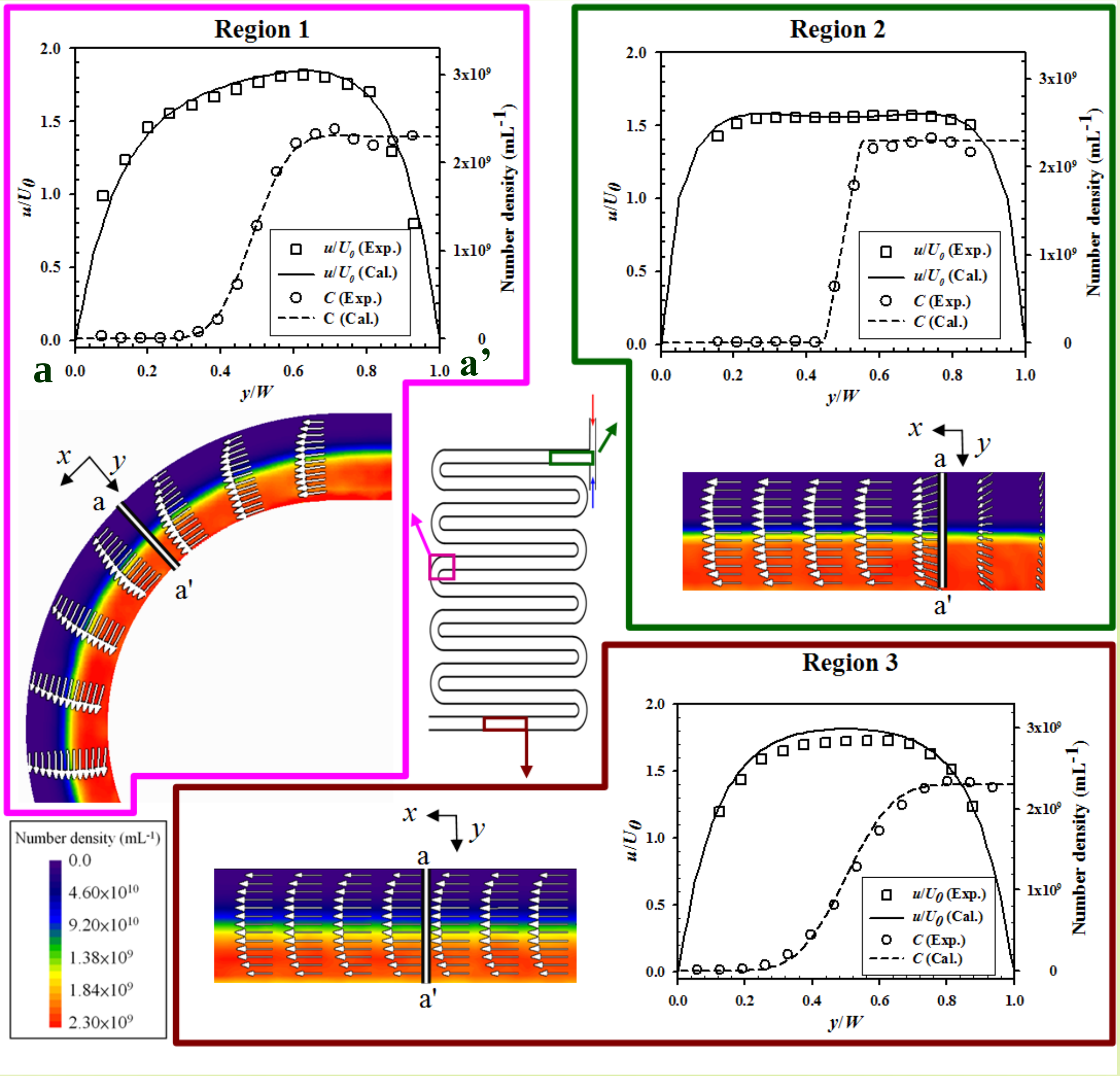


Measuring Techniques (simultaneous measurement)

Biomicrofluidics, 2010

(Top 20 most downloaded articles, 2010/04, and /06)

Simultaneous diagnosis of velocity and concentration fields

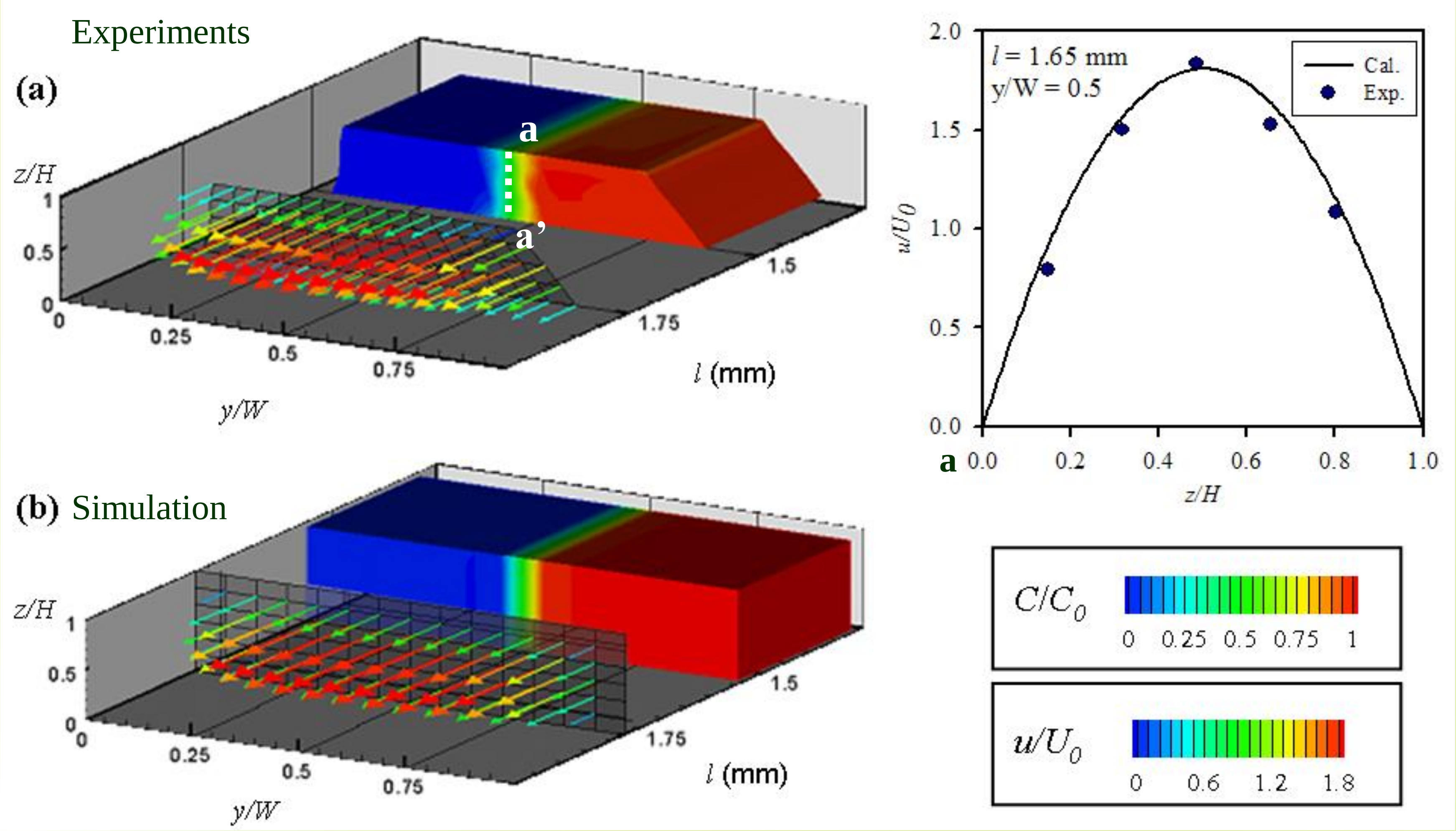


The maximum relative errors for both velocity and concentration fields between experimental and numerical results are about 5 %

Measuring Techniques (simultaneous measurement)

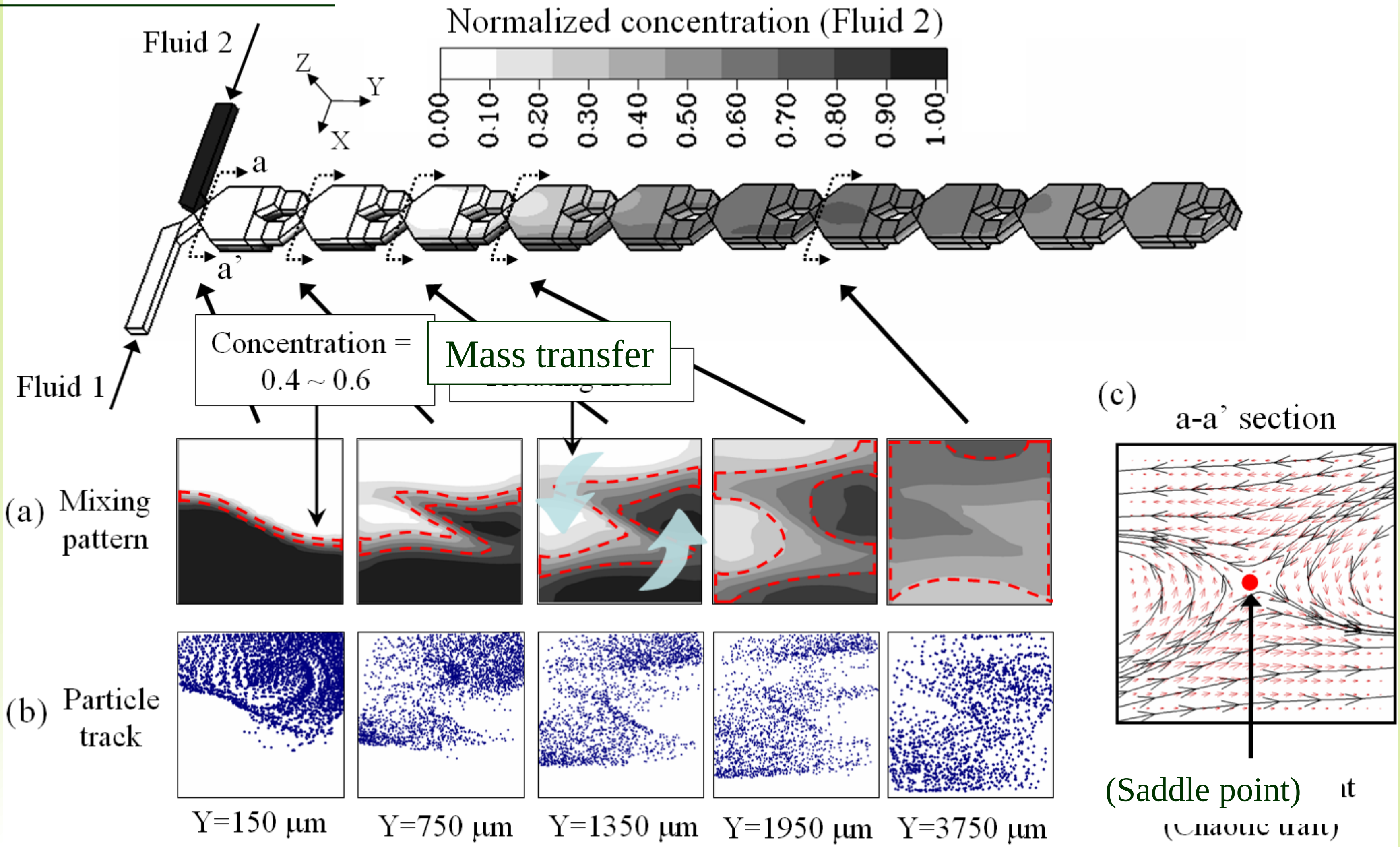
3D velocity and concentration fields

Biomicrofluidics, 2010
(Top 20 most downloaded articles, 2010/04, and /06)



Results and discussion- SAR µ-reactor

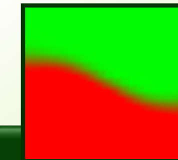
Concentration field

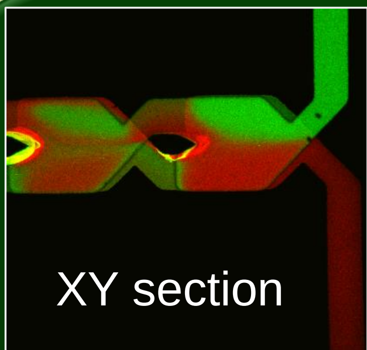


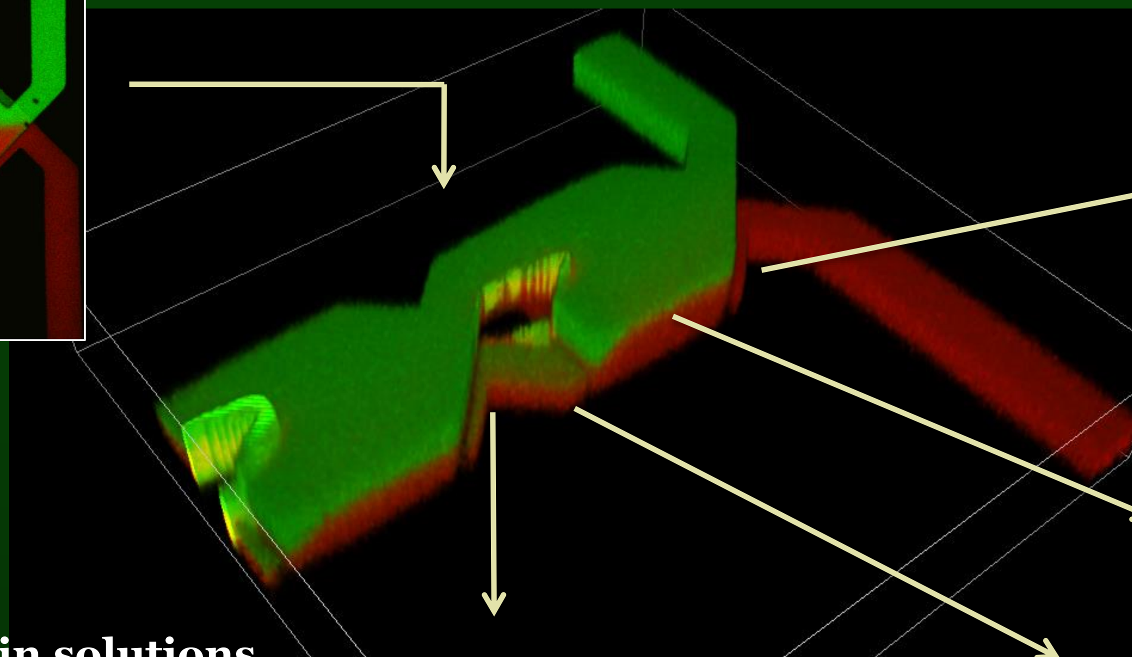
Performance Test of a SAR μ-Reactor

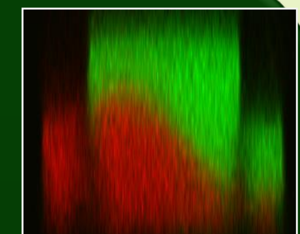
方偉峰 楊鏡堂, 2009

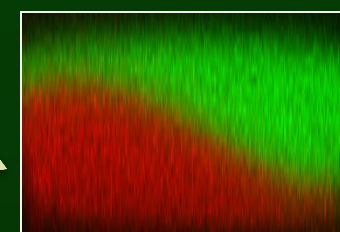
3D-image reconstruction: SAR μ-reactor





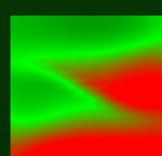


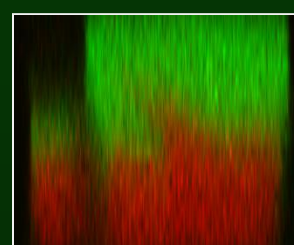


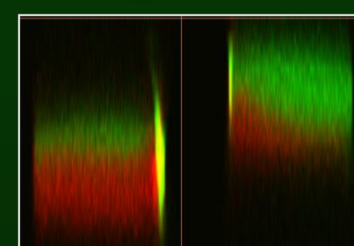


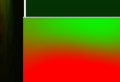
Mixing of protein solutions, C-PC and R-PE, in a novel SAR μ-reactor

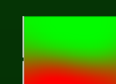
Con-focal microscopy











The analysis of protein binding in a CDM using fluorescence resonance energy transfer

Tung and Yang, *Microfluidics & Nanofluidics*, 2008

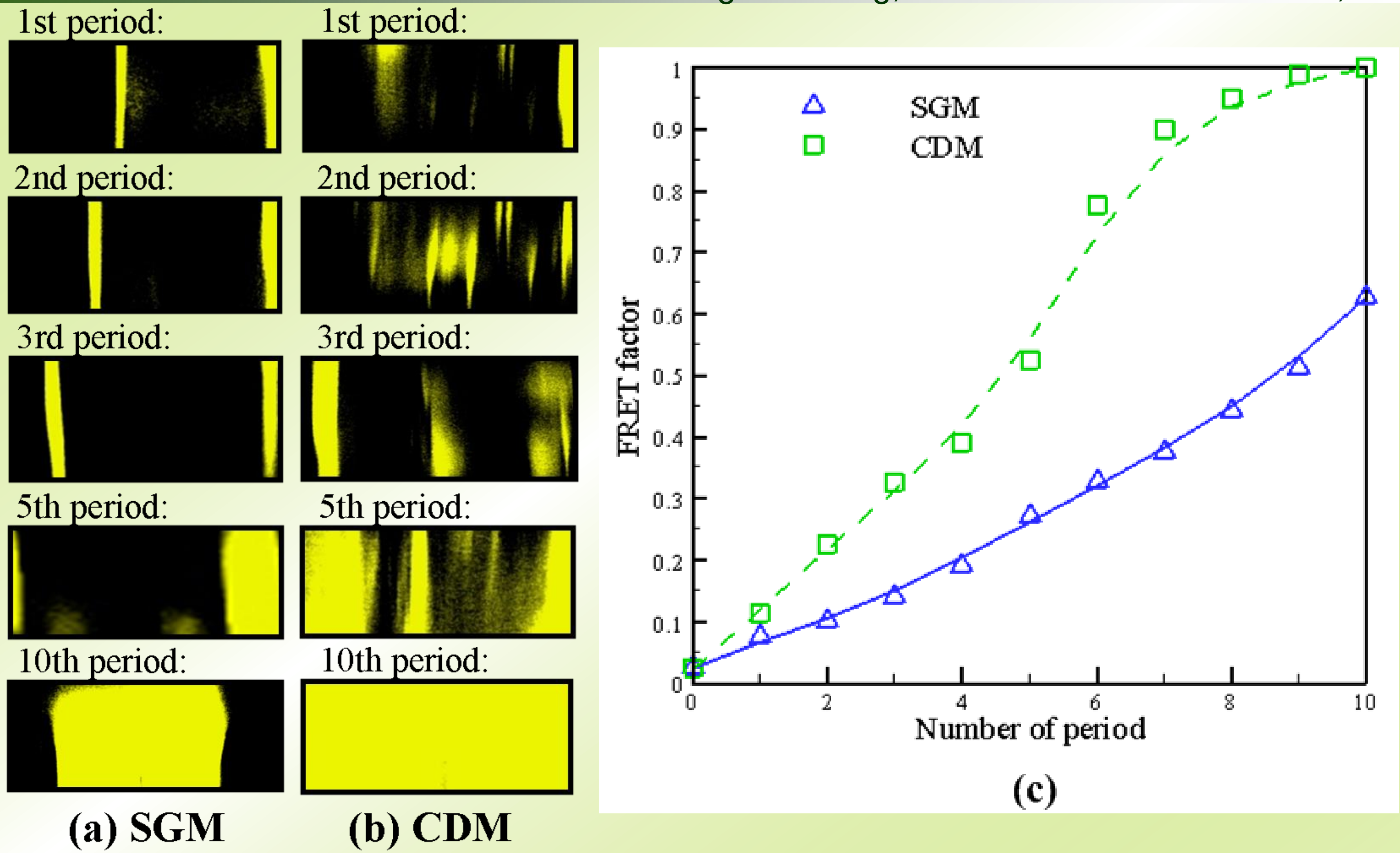
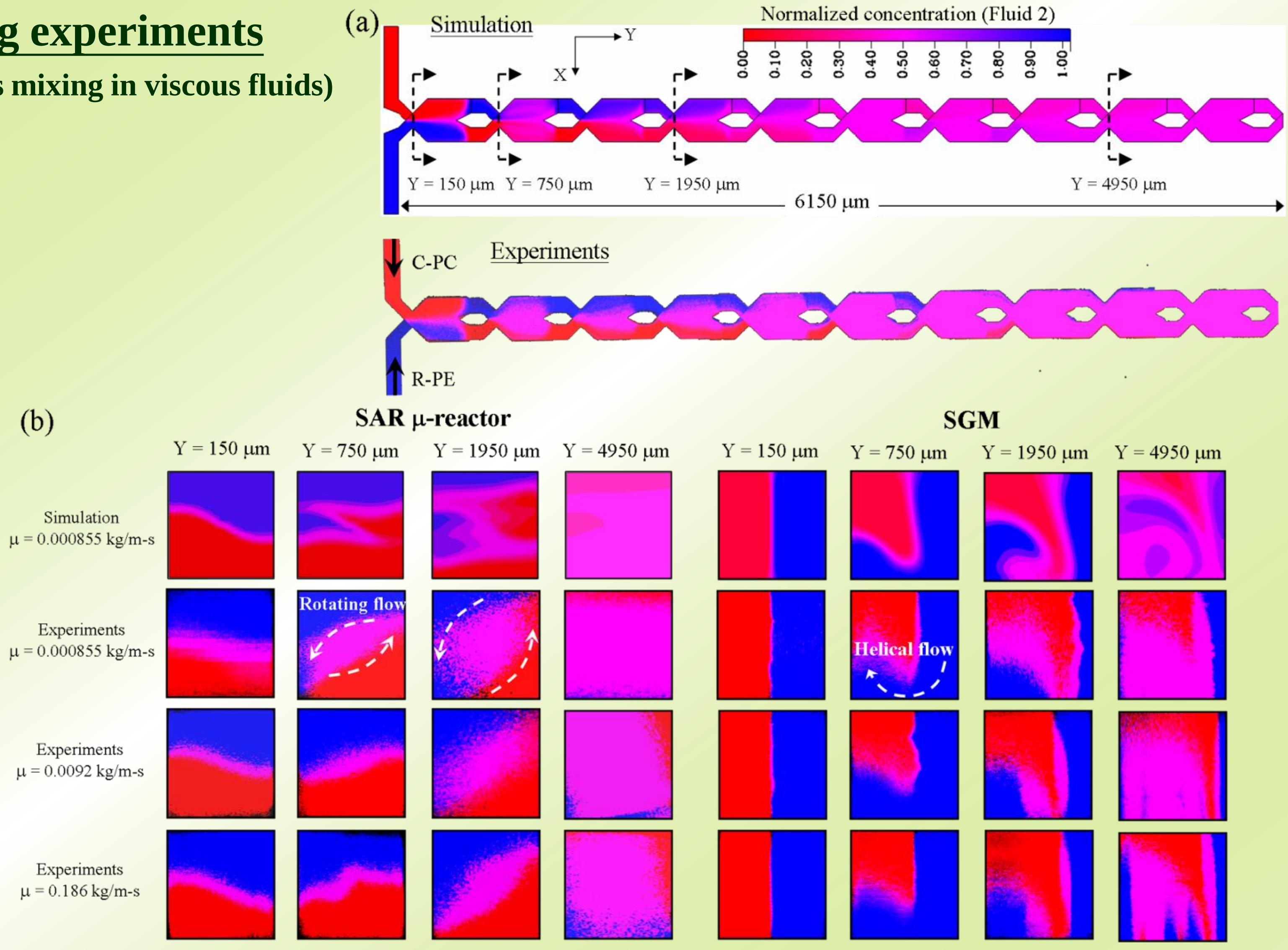


Fig. 9 Results of FRET in (a) SGM, (b) CDM. (c) The distribution of the FRET factor plotted to the 10th period for SGM and CDM.

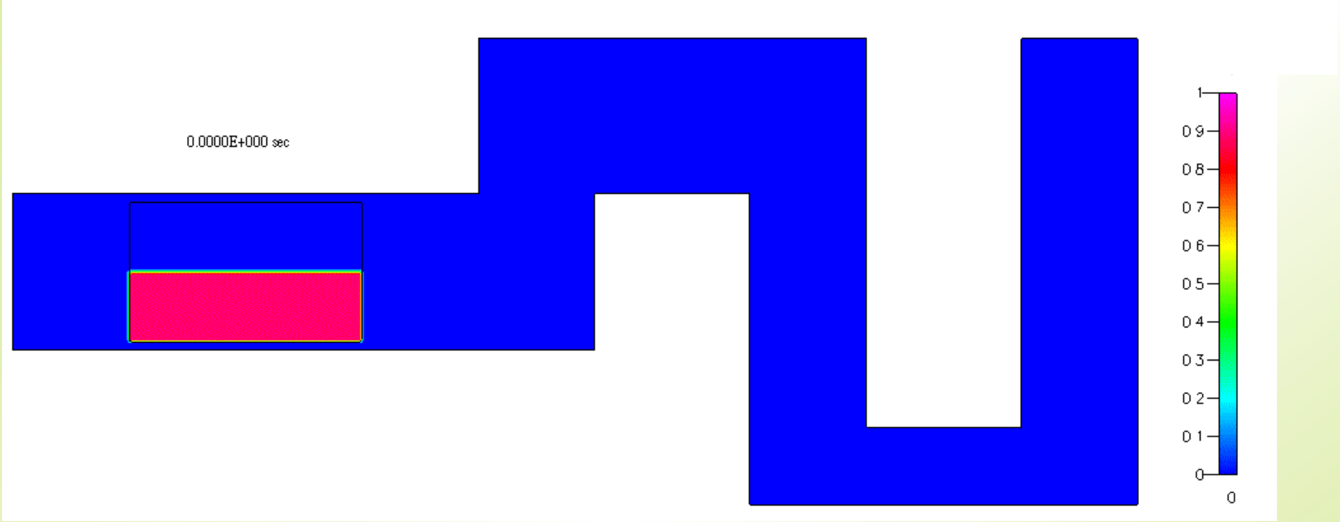
Results and discussion- SAR μ-reactor

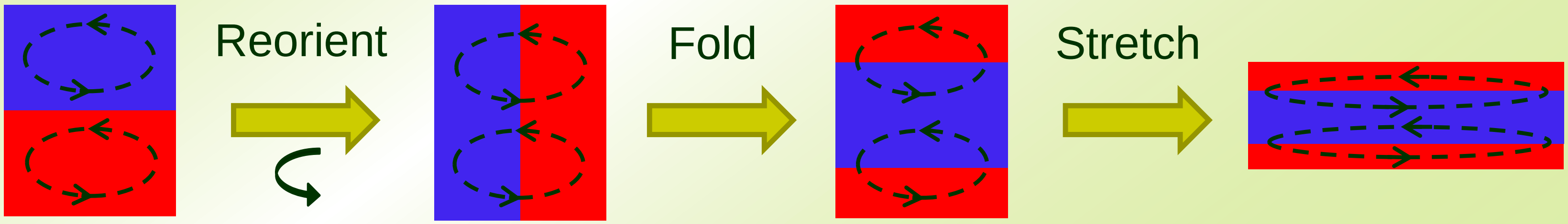
Mixing experiments

(Proteins mixing in viscous fluids)



Mixing mechanism

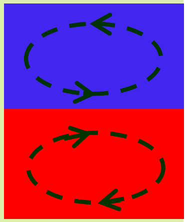


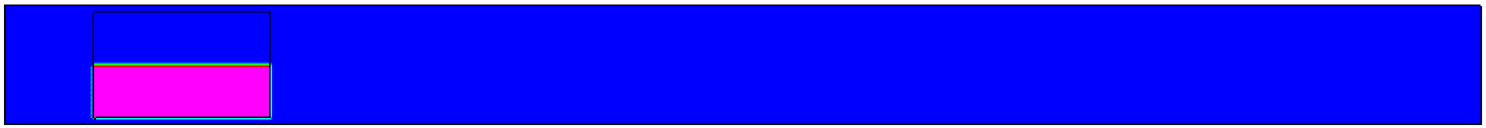


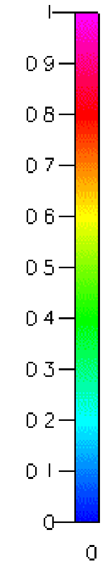
Mixing is promoted by periodic motion of the fluid. It is conducted by iterated reorientation, stretching and folding of the interface here.

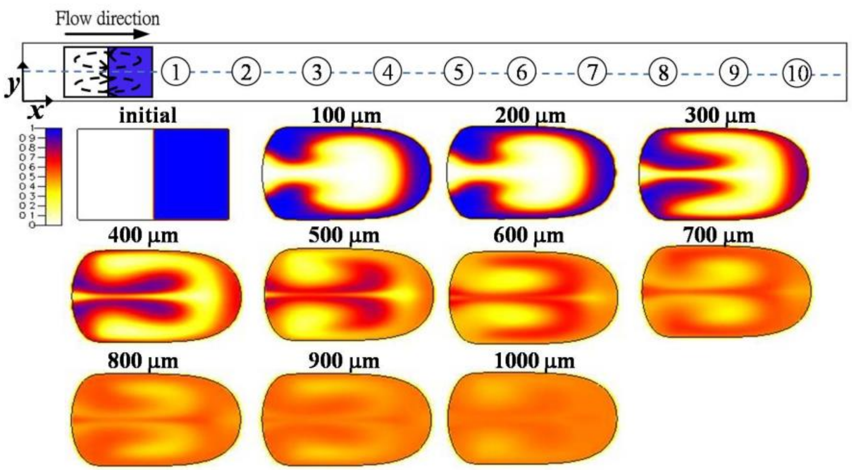
Mixing and Hydrodynamic Analysis of a Droplet in a Planar Serpentine Micromixer

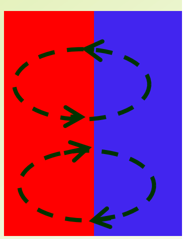
***Microfluidics and Nanofluidics*, 2009** *(times cited 17)*

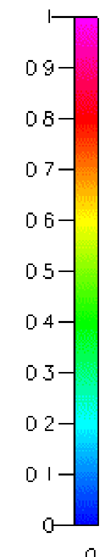






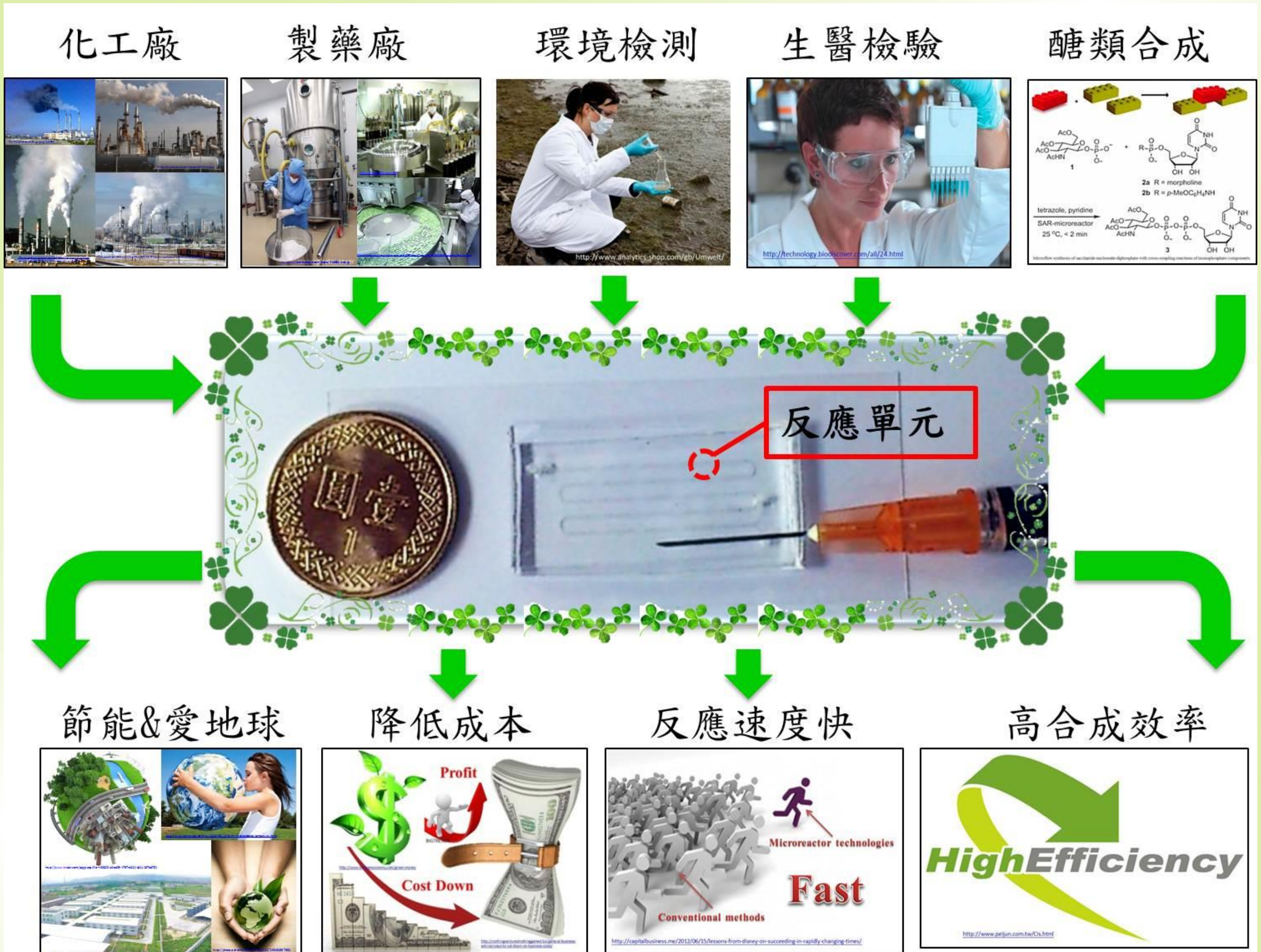






微反應器之特質

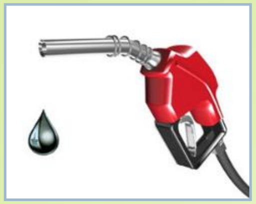
應用我們所研發的微反應器，提供各領域一個低成本、低耗能、高效率、高反應速度的綠色科技，使整個製造過程對地球更有善



Department of Mechanical Engineering
National Taiwan University

反應速率緩慢、效率不佳且成本較高。

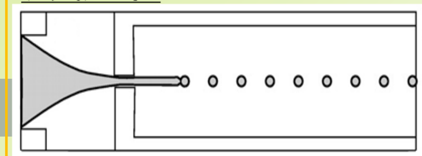
發展替代性能源



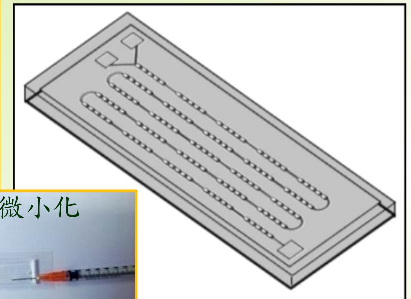
能源危機

微流體元件

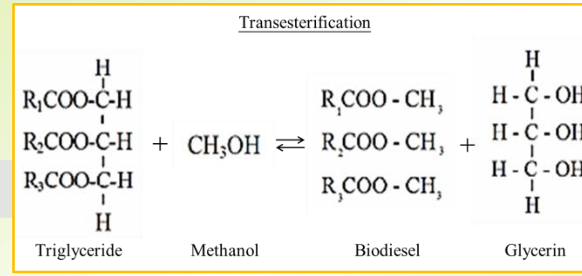
液珠式微反應器



連續流式微反應器



反應裝置微小化



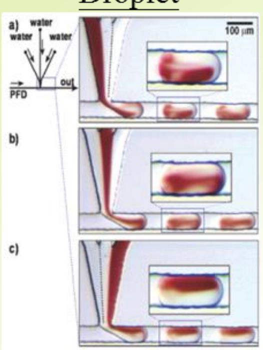
本研究即整合微流體元件與替代能源產製方法，開發一新式微流體反應器，提升能源產製速率、降低產製成本。

概念整合應用

微流體系統

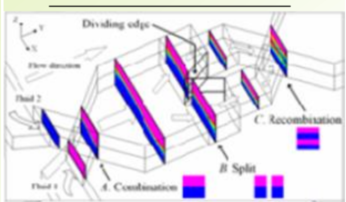
藉由尺度微小化以增加有效反應介面，使得反應效率大幅提升。

Droplet



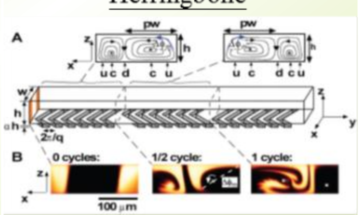
Tice *et al.*, *Langmuir*, 2003

SAR micro-reactor



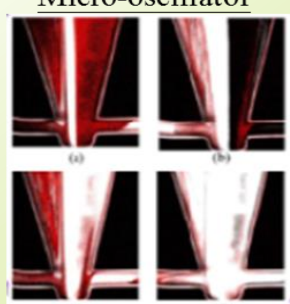
Fang *et al.*, *AIChEJ.*, 2008

Herringbone



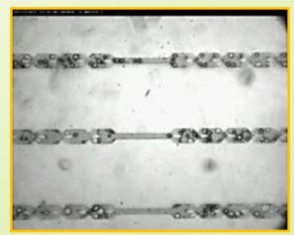
Stroock *et al.*, *Science*, 2003

Micro-oscillator

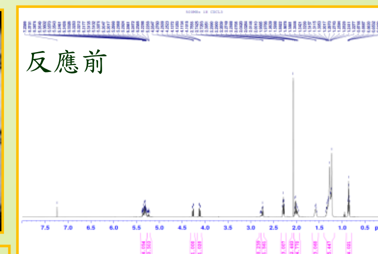


Yang *et al.*, *JMEMS*, 2007

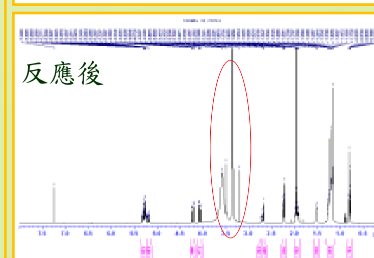
產率分析方法



反應前



反應後



分析儀器

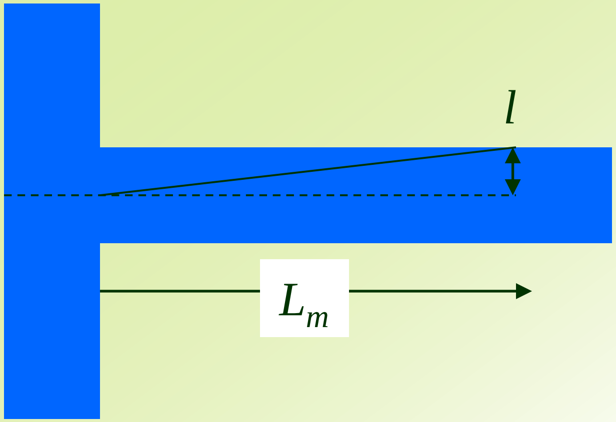
Bruker AVIII 500MHz FT-NMR

BEAM Lab

Chen, K. H., and Yang, J. T.

Q & A

Derivation



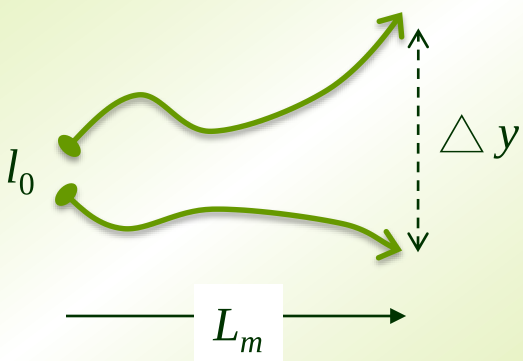
Einstein equation for diffusion

$l \sim (Dt)^{0.5} \longrightarrow t \sim l^2/D$

$t = L_m / U$

$L_m \sim U \times (l^2/D) = \mathrm{Pe} \times l$

$\mathrm{Pe} = Ul/D$



Chaotic advection

$t \sim \triangle y^2/D \qquad \triangle y = l_0 \exp(-L_m/\lambda)$ Ottino, 1989

$t = l_0^2 / D \bullet \exp(-2L_m/\lambda)$

$t = L_m / U$

$L_m \sim \lambda \ln(\mathrm{Pe})$

λ is a characteristic length determined by the geometry of trajectories in the chaotic flow.

Stroock *et al.*, 2002, *Science*