仿生與實驗室晶片導論- 2020

# 微流體混合器/反應器之設計、量測、生醫化材應用

## Design, measurement & application of micro-reactors


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中華民國 101 年 1 月 6 日@NTU

BEAM Lab

# Outlines

1. **Brief of microfluidics**

   微流體系統簡介

2. **Micro-mixing & design** (2004-2008, NTHU)

   微混合器設計

3. **Micro-reactors** (2008-2015, NTU)

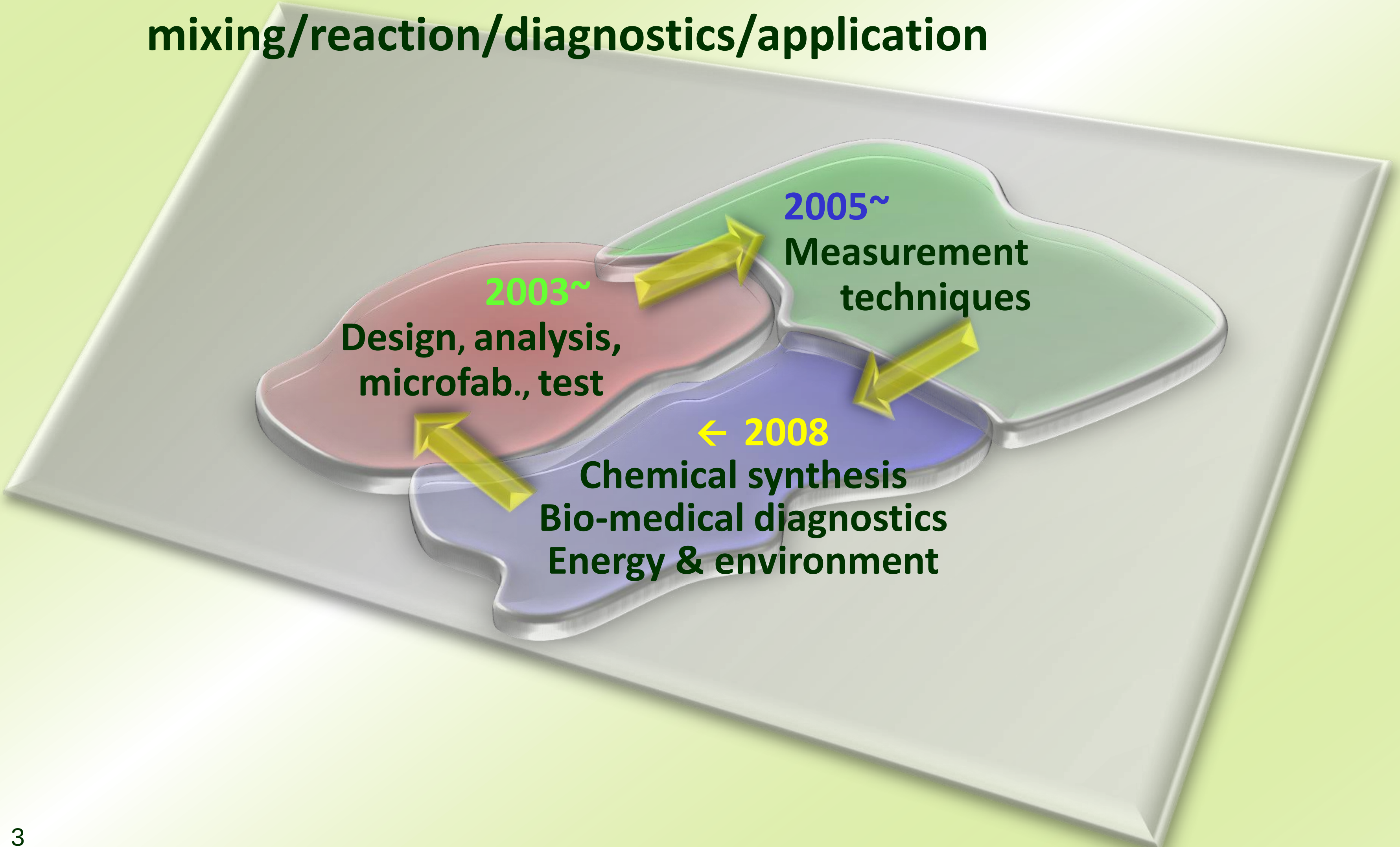
   微反應器設計

4. **Applications** (2010~)

   微反應器之生醫化材應用

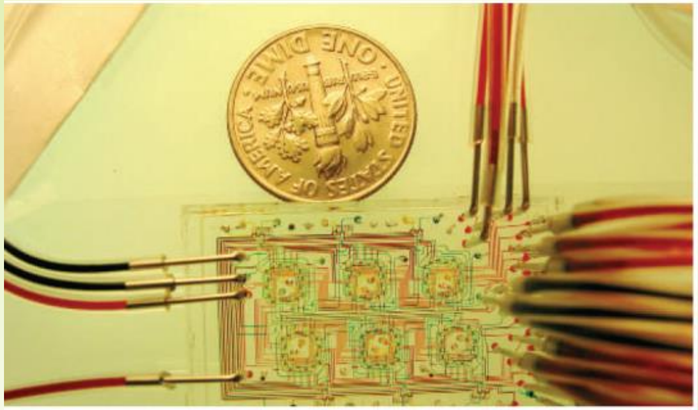
# Contents of the Presentation

mixing/reaction/diagnostics/application



# 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

# Scientific Aspects

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

  silicon microfluidic devices:
  size effect
  power effect

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

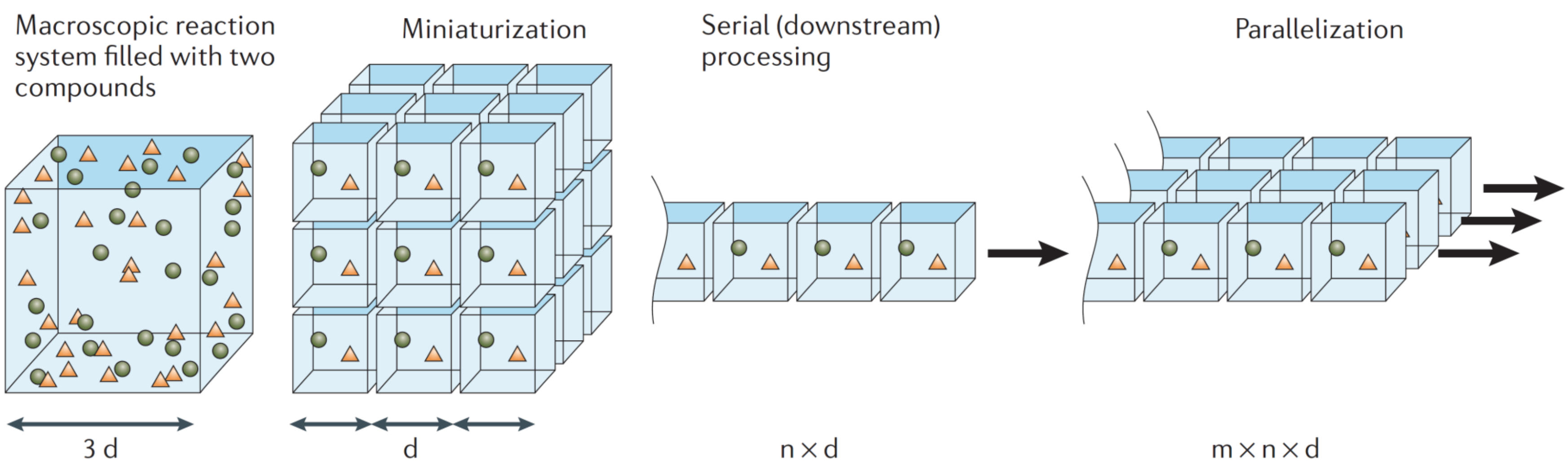
  actuators with no moving parts and nonmechanical pumping principles
  electrokinetic pumping, surface-tension-driven flows,
  electromagnetic forces, acoustic streaming
  new effects which mimic nature → nanotechnology

- **Application Developments**

  biomedical diagnostics, drug discovery, flow control, chemical analysis
  distributed energy supply and thermal management
  chemical production with microreactors

# What is gained by miniaturization?

d, length of edge; n and m, numbers of reaction systems serial and parallel, respectively.




| Parameter | Macroscopic example | Factor change | Microscopic example |
|---|---|---|---|
| Length of edge | 1 mm | d | 1 µm |
| Surface | 1 $mm^2$ | $d^2$ | 1 $\mu m^2$ |
| Volume | 1 µl | $d^3$ | 1 fl |
| Number of molecules | $10^9$ | $d^3$ | 1 |
| Diffusion time over d ($D = 10^{-6}\ cm^2 s^{-1}$) | 15 min | $d^2$ | 1 ms |
| *Example: in flowing systems* | | | |
| Linear flow rate | 1 µm/s | d | 1 mm/s |
| Separation time | $10^5$ s (>1 day)* | $d^2$ | 100 ms |
| *Example: in planar array* | | | |
| Number of volumes per microwell plate | 96 | $d^2$ | $10^8$ |

*Typically, for example, high-performance liquid chromatography in packed column.

Dittrich and Manz. (2006) Lab-on-a-chip: microfluidics in drug discovery. ***Nature Reviews Drug Discovery*** 5: 210-218.

# Various process steps of drug discovery using microfluidic methods

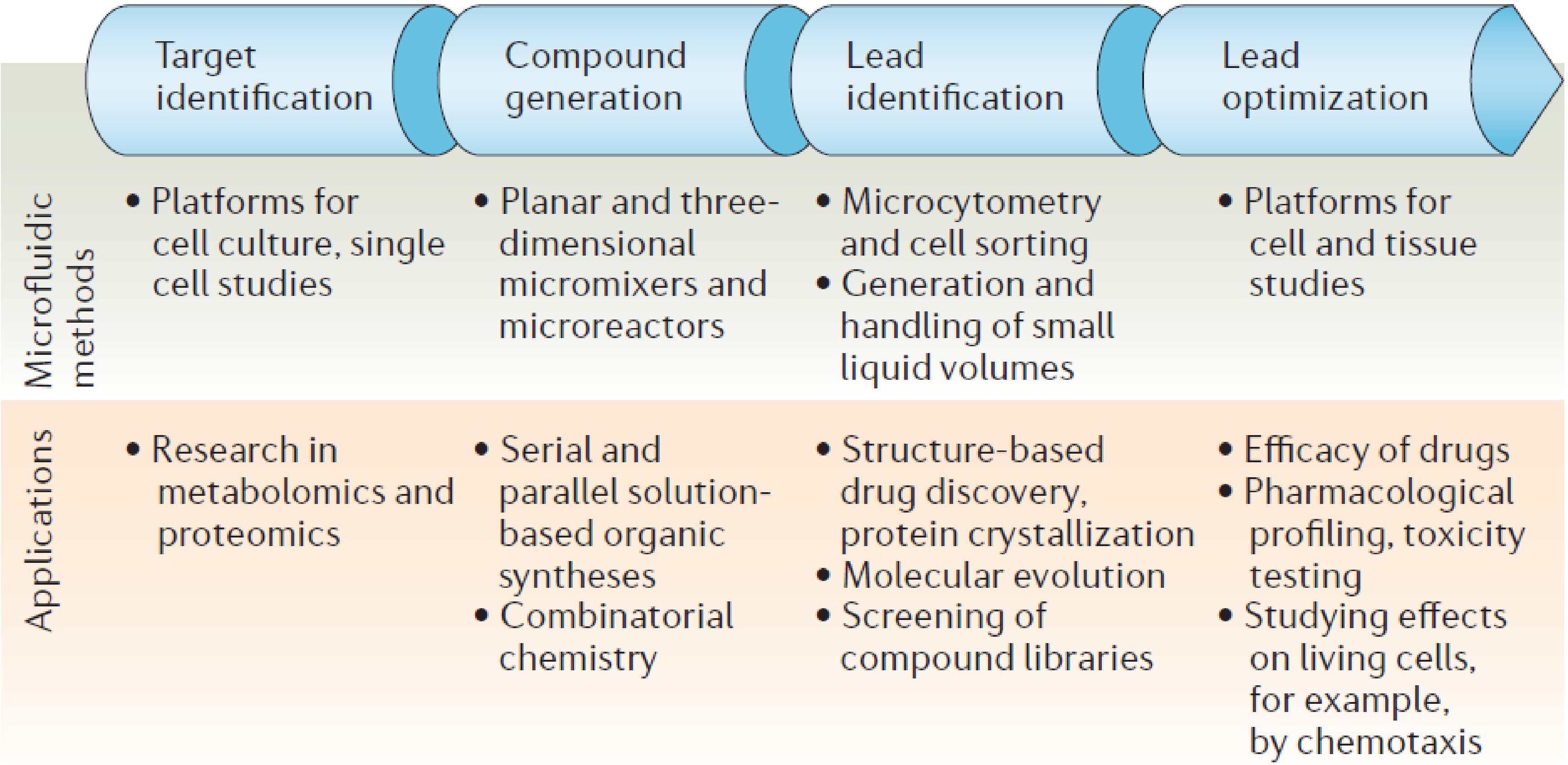
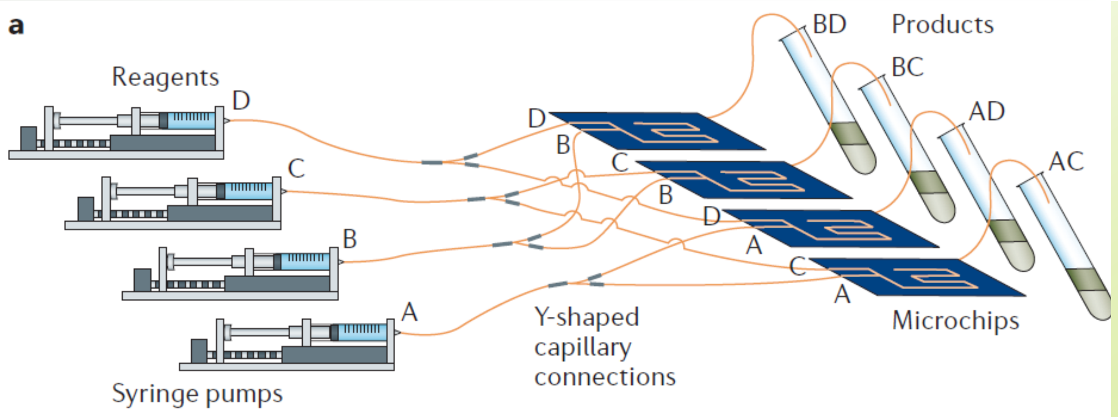



Figure 1 | **Microfluidics in drug discovery.** The figure depicts microfluidic methods, including respective applications, that are valuable for individual steps in the drug discovery process.

Dittrich and Manz. (2006) Lab-on-a-chip: microfluidics in drug discovery. ***Nature Reviews Drug Discovery*** 5: 210-218.

# Combinatorial syntheses in microfluidic chips



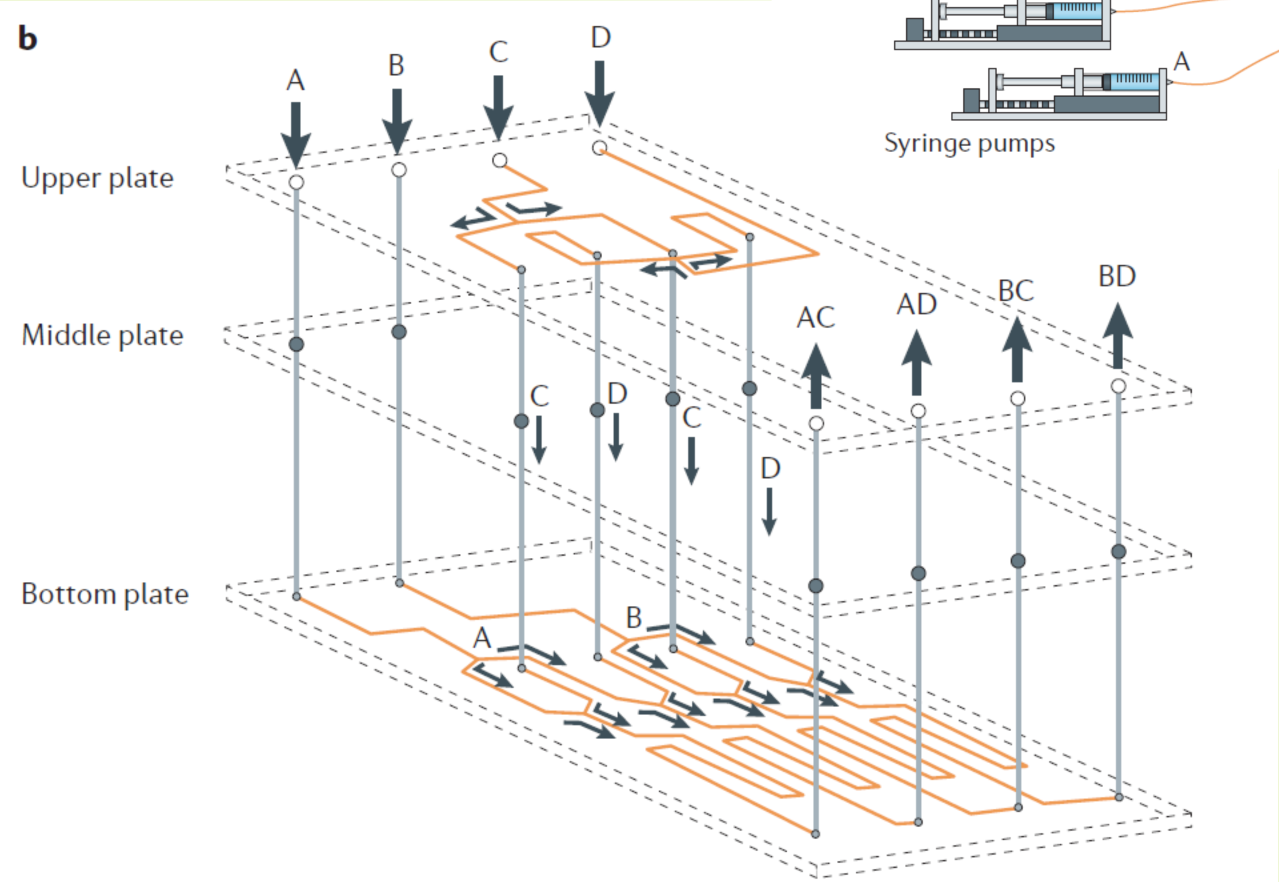




**Figure 2 | Combinatorial syntheses in microfluidic chips. a | Schematic views of a** microreactor system for 2 × 2 combinatorial syntheses composed of four microchips. **b** | Schematic views of a microreactor system for 2 × 2 combinatorial syntheses realized in one single three-dimensional microchip39.

Dittrich and Manz. (2006) Lab-on-a-chip: 5: 210-218.

# Gradient concentration generating device

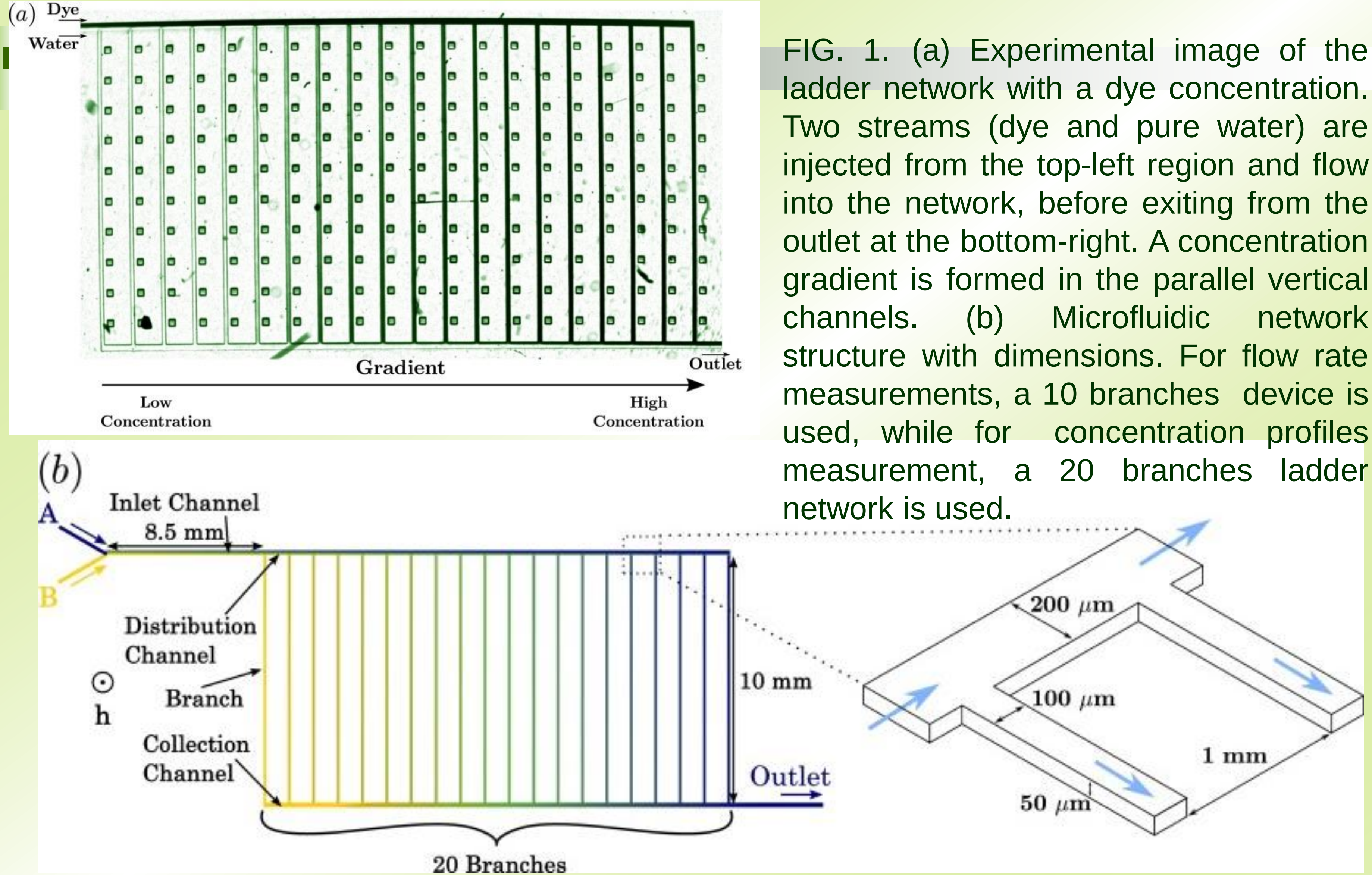
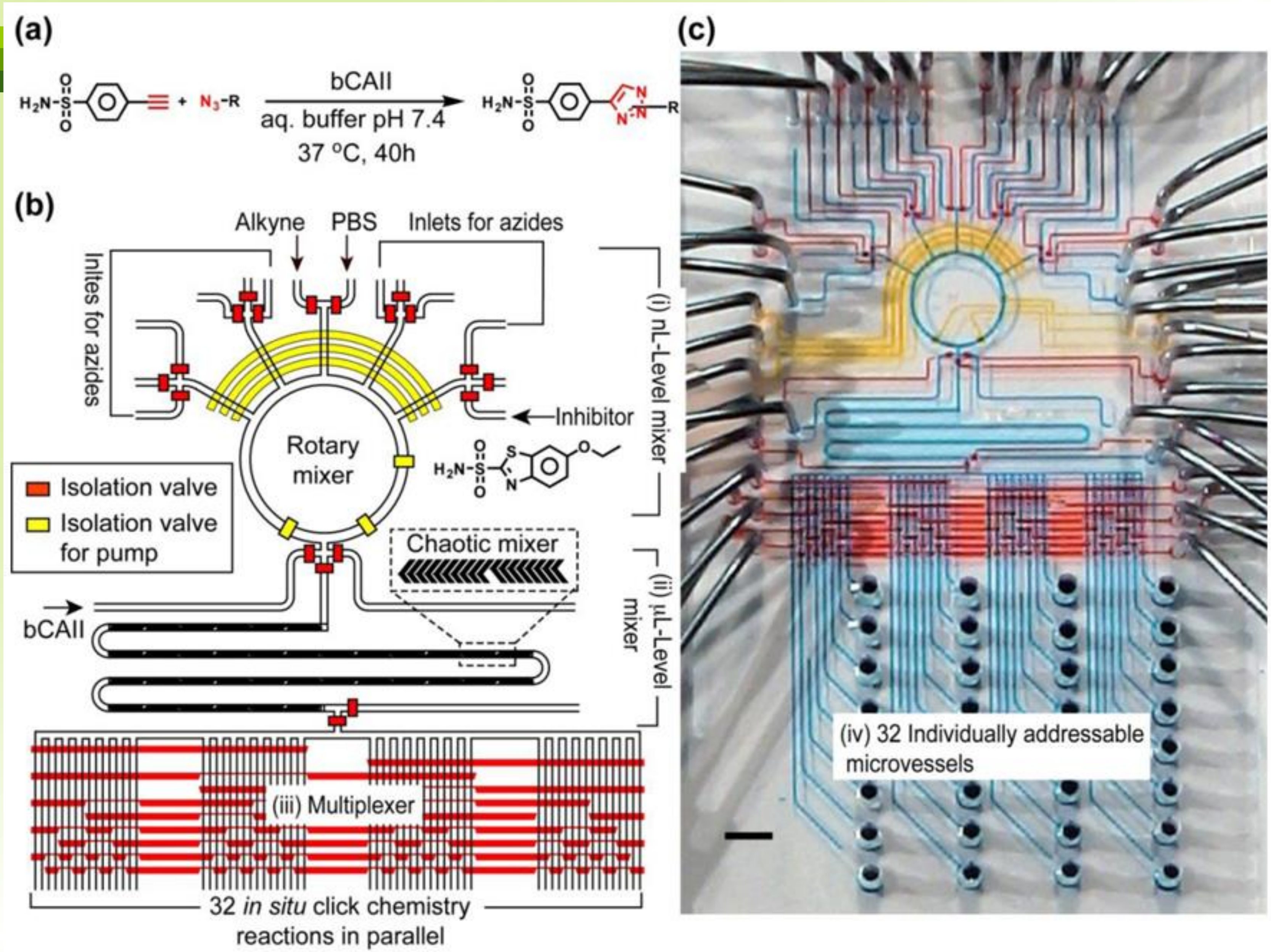



FIG. 1. (a) Experimental image of the ladder network with a dye concentration. Two streams (dye and pure water) are injected from the top-left region and flow into the network, before exiting from the outlet at the bottom-right. A concentration gradient is formed in the parallel vertical channels. (b) Microfluidic network structure with dimensions. For flow rate measurements, a 10 branches device is used, while for concentration profiles measurement, a 20 branches ladder network is used.

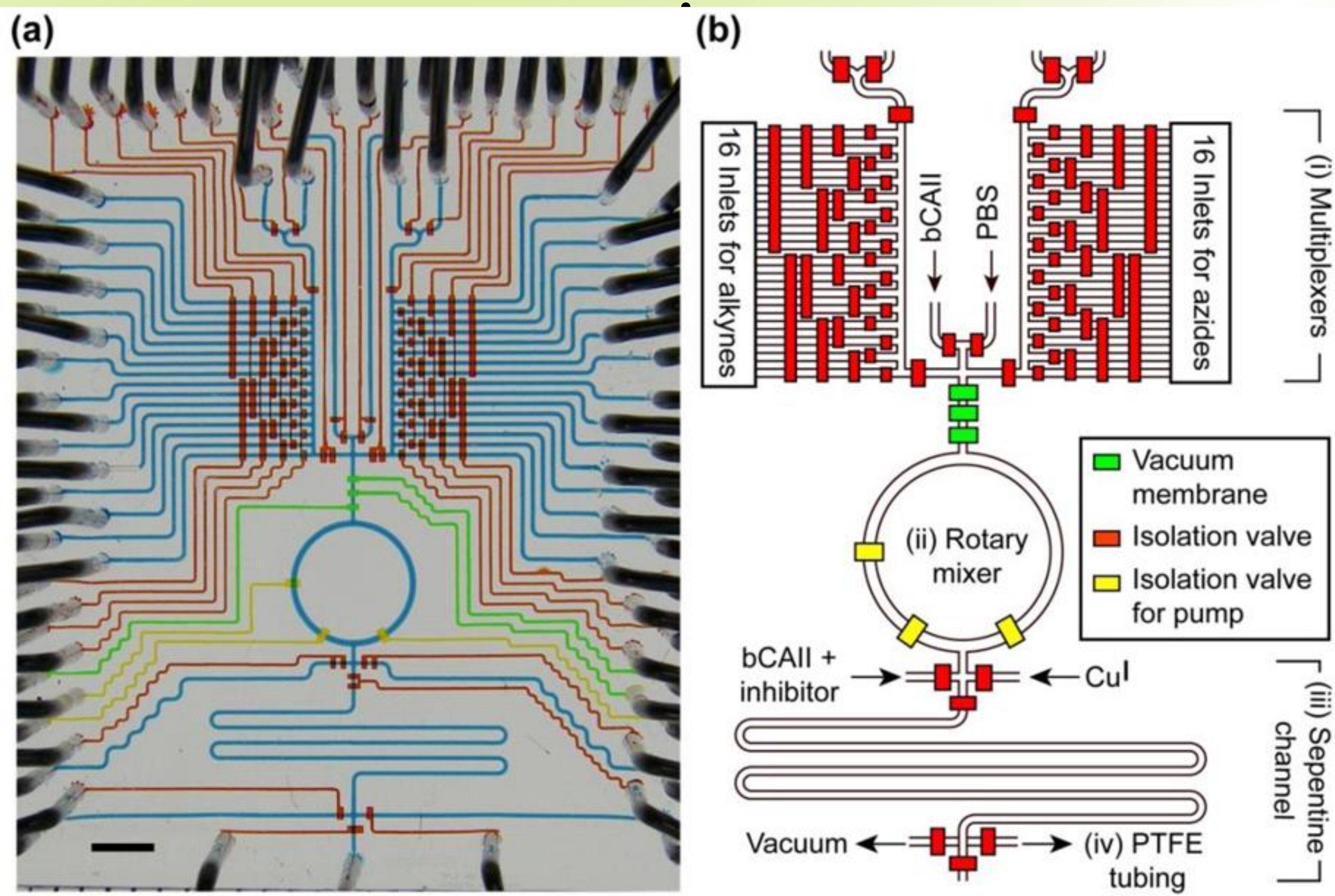
Guermonprez *et al*. (2015) Flow distribution in parallel microfluidic networks and its effect on concentration gradient. ***Biomicrofluidics*** 9(5):054119.

# First-generation microreactor for 32 chemistry reactions




Lin *et al.* (2009). Integrated Microfluidic Reactors. ***Nano Today*** 4(6): 470-481.

# Second-generation microreactor for 1024 chemistry




Lin *et al*. (2009). Integrated Microfluidic Reactors. ***Nano Today*** 4(6): 470-481.

# Comparison of conventional & high-throughput microreactors

Table 1

Summary of the comparison among the conventional 96-well approach and the two generations of screening microreactors.

| | Number of reactions | Enzyme (bCAII) (μg) | Alkyne (nmol) | Azide (nmol) | Total reaction volume (μL) | Sample preparation time | Hit identification time | Detction methods |
|---|---|---|---|---|---|---|---|---|
| 96 well | 96 | 94 | 6 | 40 | 100 | few mins | few mins | LC-MS |
| 1st-Generation | 32 | 19 | 2.4 | 3.6 | 4 | 58 sec | 58 sec | LC-MS |
| 2nd-Generation | 1024 | 0.36 | 0.12 | 0.12 | 0.4 | 15 sec | 15 sec | MRM |

- LC-MS (Liquid chromatography–mass spectrometry, 液相色譜法-質譜聯用)可測出各種化學組分並有可能確定其詳細結構。
- MRM (MR microscopy, 或μMRI, 磁共振顯微術)，它的最高空間解析度是4 μm，已經可以接近一般光學顯微鏡像的水平。MRM已經非常普遍地用作疾病和藥物的動物模型研究。

Lin *et al*. (2009). Integrated Microfluidic Reactors. ***Nano Today*** 4(6): 470-481.

# High-throughput multiplex devices for pathogen detection ( I )

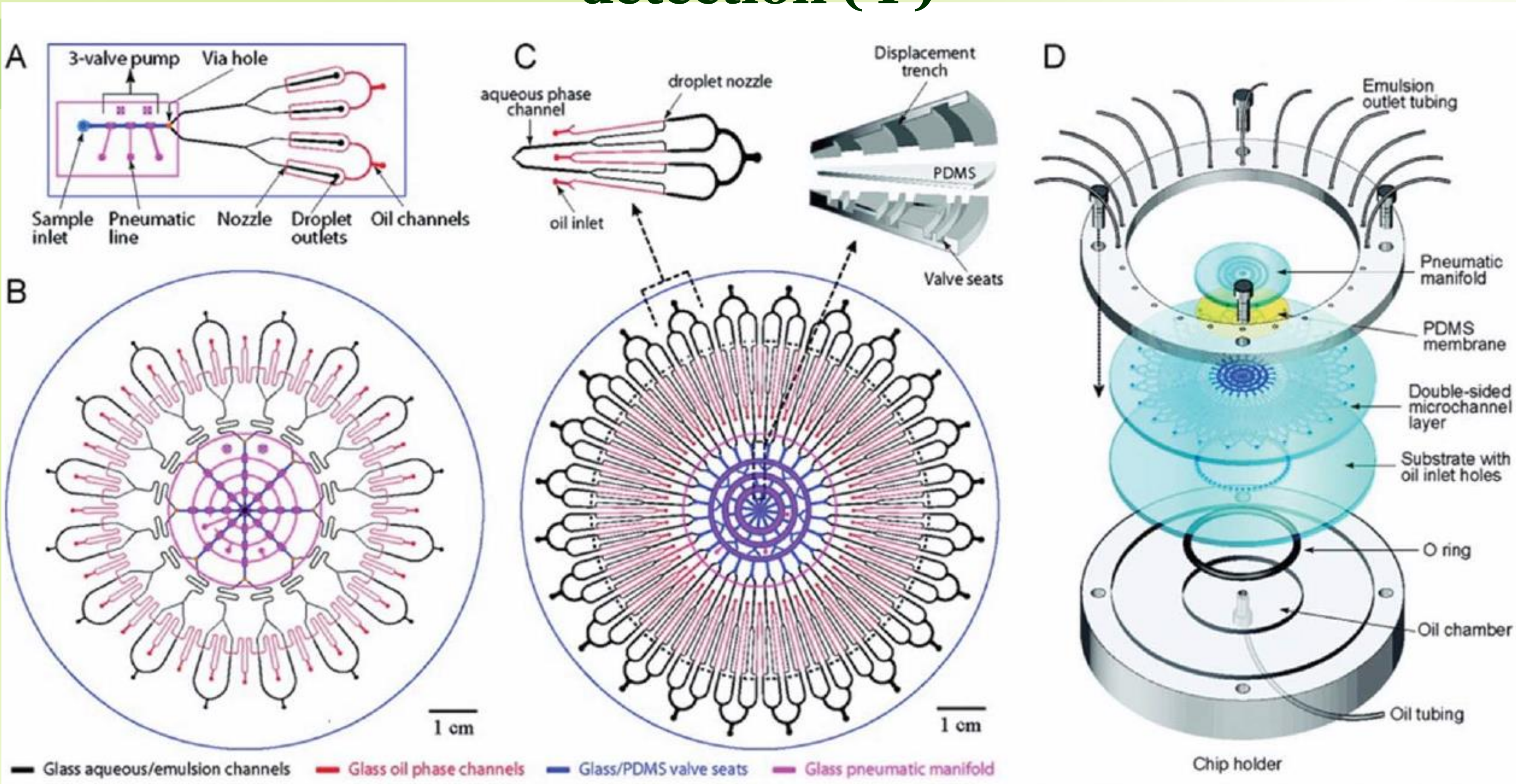



Fig. 4 (i) Schematic of microfluidic emulsion generator (MEGA) array device. (A) Design of a glass-PDMS-glass hybrid four-channel MEGA device and (B) layout of a 32-channel MEGA device. (C) Layout of a 96-channel MEGA device. (D) Illustration of complete four layer 96-channel MEGA device and the plexiglass assembly module. (Reproduced from Ref. 48 with permission from American Chemical Society.)

Foudeh *et al*. (2012) Microfluidic designs and techniques using lab-on-a-chip devices for pathogen detection for point-of-care diagnostics. ***Lab Chip*** 12(18): 3249-66.

# High-throughput multiplex devices for pathogen detection ( II )

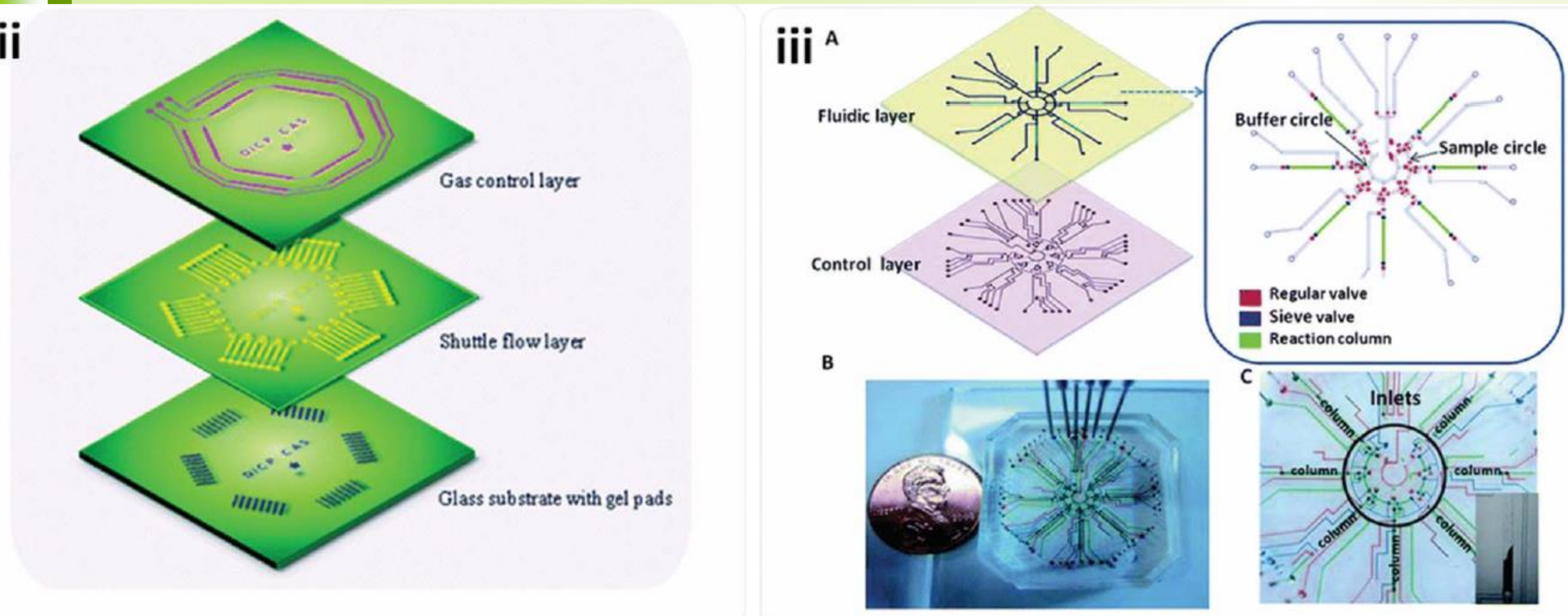


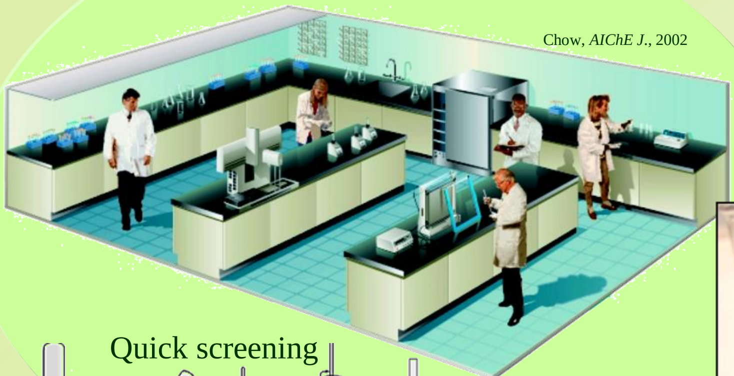

Fig. 4 (ii) Exploded view of the microfluidic chip containing shuttle flow channels, micropumps and microvalves. (Reproduced from Ref. 116 with permission from Royal Society of Chemistry.) (iii) (A) Schematic representation of an immunoreaction chip used for detection of algal toxins. Red and blue color represent the regular valves and sieve valves respectively. (B) and (C) Pictures of the microfluidic chip and central area of the chip. (Reproduced from Ref. 117 with permission from Royal Society of Chemistry.)

Foudeh *et al.* (2012) Microfluidic designs and techniques using lab-on-a-chip devices for pathogen detection for point-of-care diagnostics. ***Lab Chip*** 12(18): 3249-66.

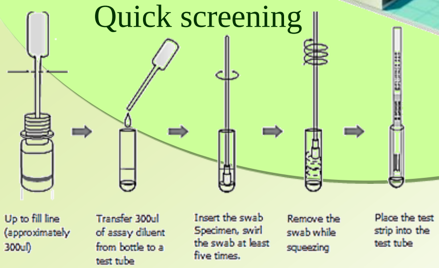
# The importance of mixing

## Biochemical / medical science

Chow, *AIChE J.*, 2002



Quick screening




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

Blood assay

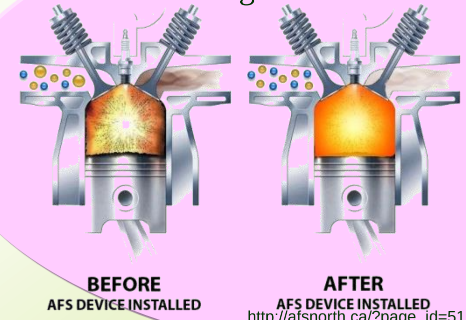

## Chemical engineering

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

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

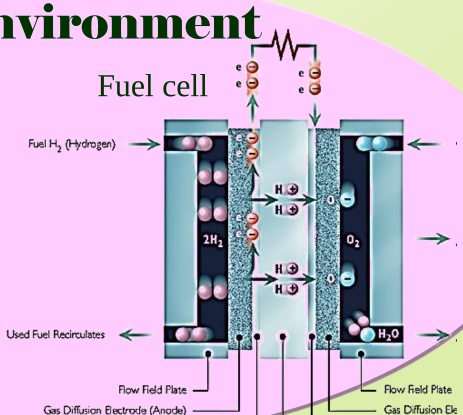
## Energy /environment

Engine




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

Fuel cell

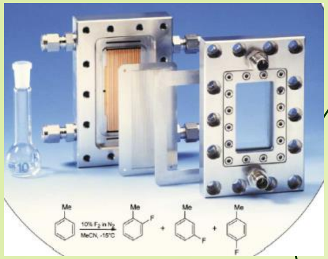



http://www.cntech.com.cn/news/media/h000/h15/img200705231159190.jpg

*Reactions are crucially dominated by mixing*

# Research Motive– Application

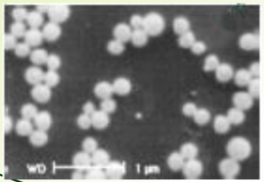
*Reactions are crucially dominated by mixing*



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

## Chemical Engineering

- Organic synthesis
- Hazardous chemical reactions
- Nanopowder production



Johnson and Prud'homme, 2003, AIChE J.

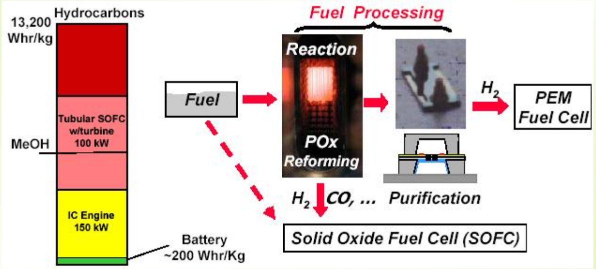
Xi'an Huian Chemical

CHEMICAL & Engineering News

μ–mixing, reaction

## Mechanical Engineering

- Combutsion

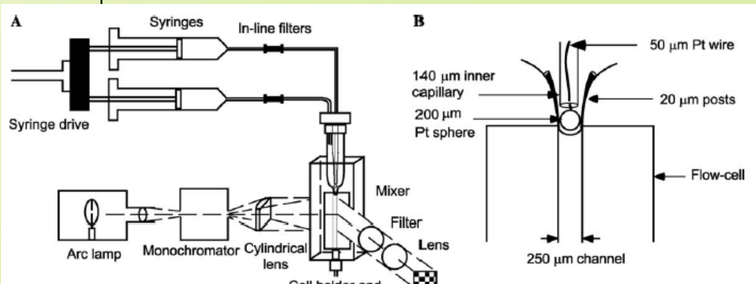



Jensen K. F., 2002

## Bio-Chemistry

Manz, 1990, SNA-B

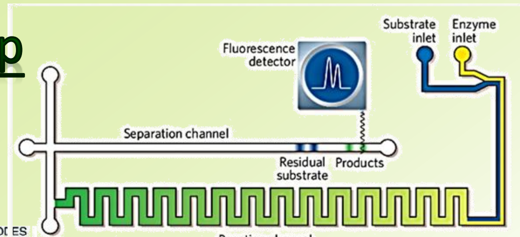
- Lab-on-a-chip
- Quench-flow analysis



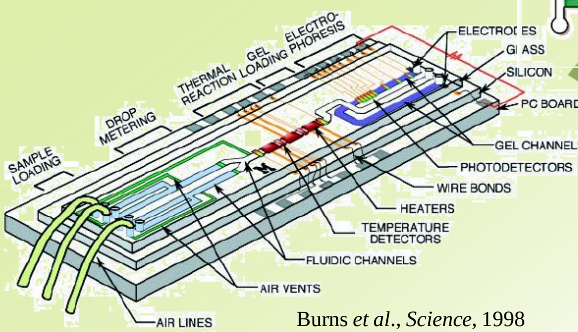

Roder *et al.*, 2004, *Methods*

# Merits of microfluidic mixing/reaction

## m-TAS/Lab-on-a-chip




Haswell, *Nature*, 2006

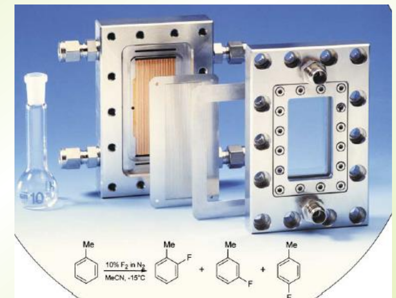



Burns *et al.*, *Science*, 1998

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

## Micromixers & Microreactors

## Microreaction technology

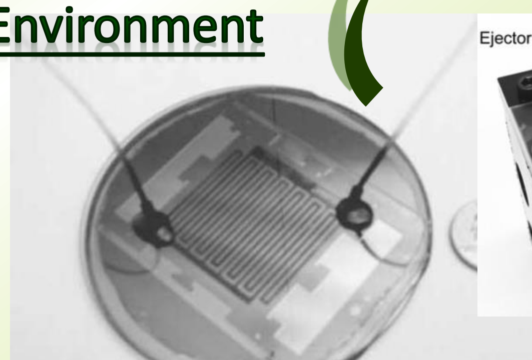


Jähnisch, *et al.*, *Angew. Chem. Int. Ed.*, *2004*

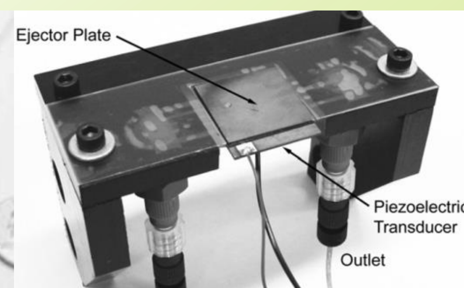
- High selectivity
- High safety
- Flash reaction
- Controllable

Hogan, *Nature*, 2006

## Energy & Environment



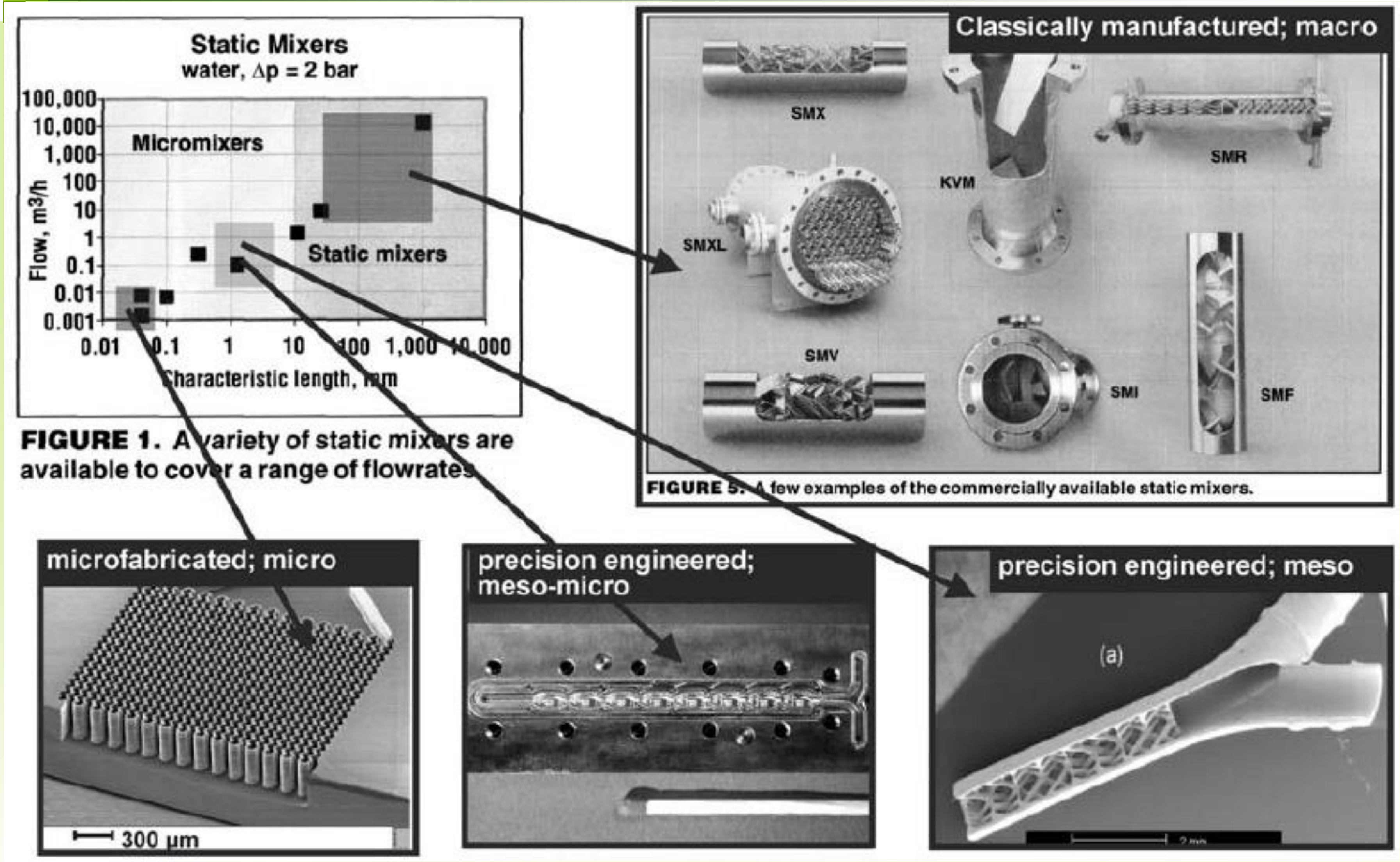
Pattekar and Kothare, *JMEMS*, 2004




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

- Green fabrication
- Eco-friendly usage
- Portable

# Size Evolution




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

# 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。

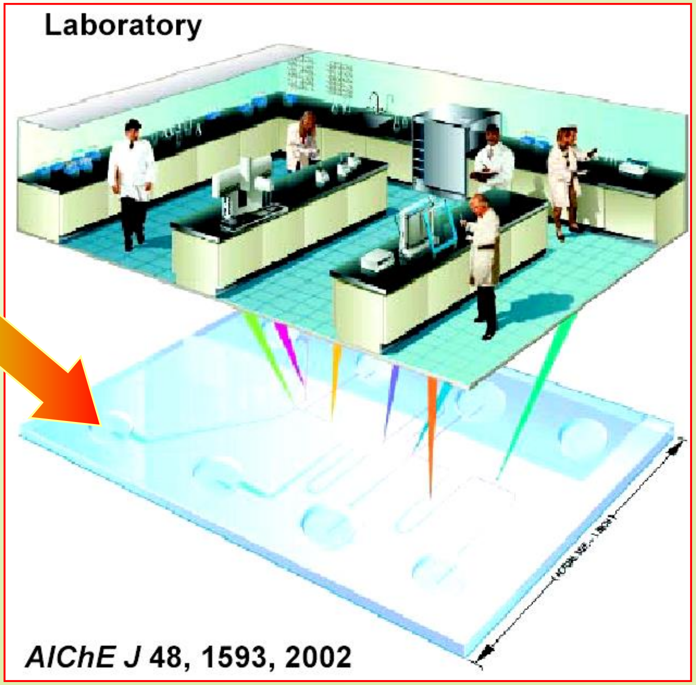

Manz *et al.*, *SNA-B.* 1990

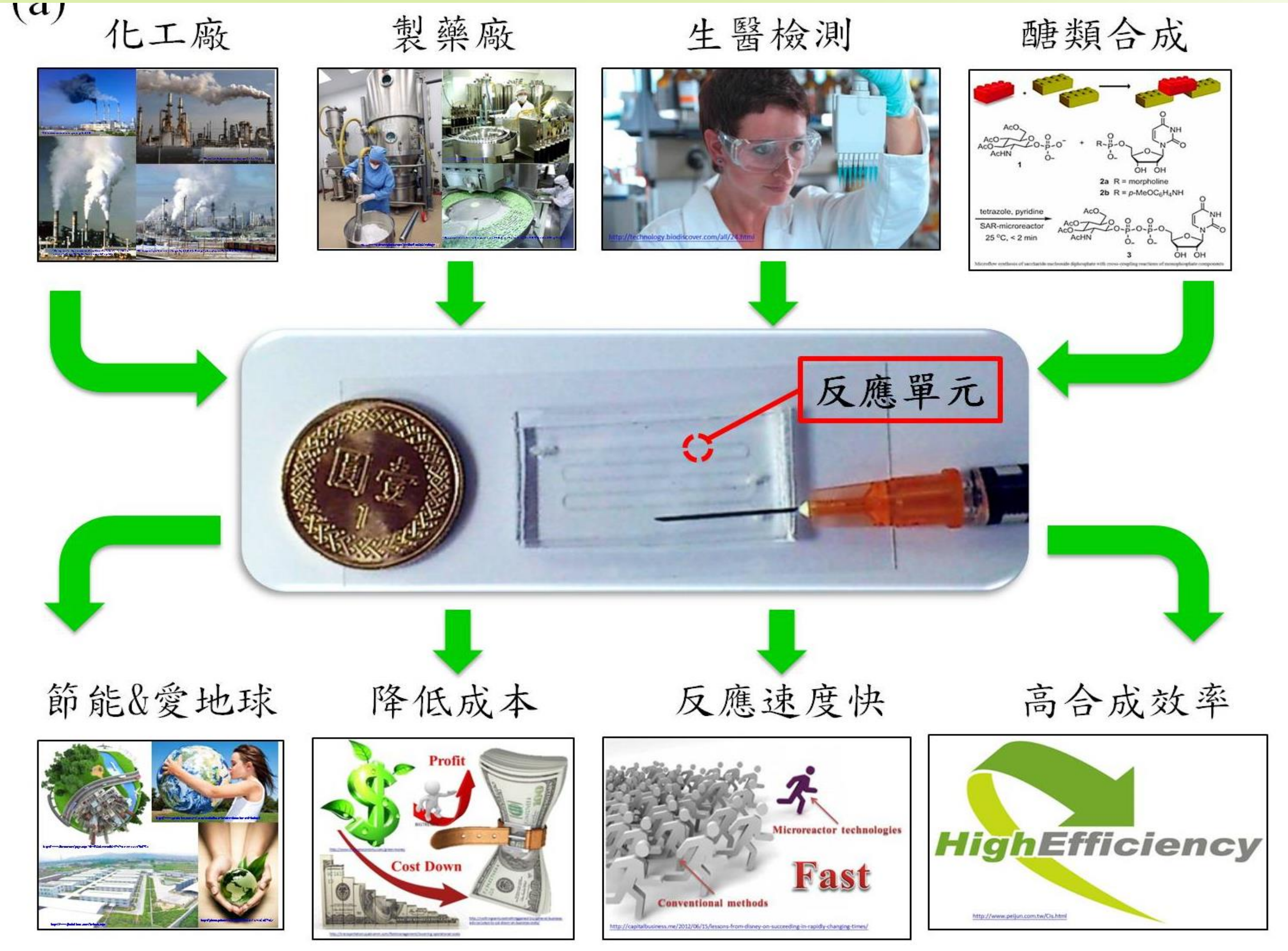
過去

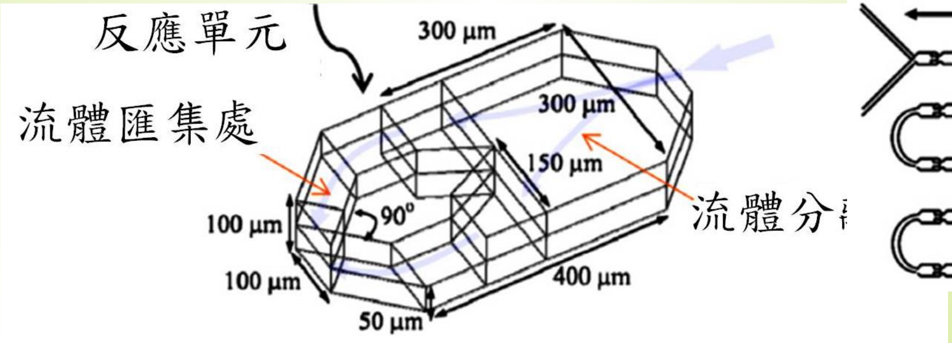
現在

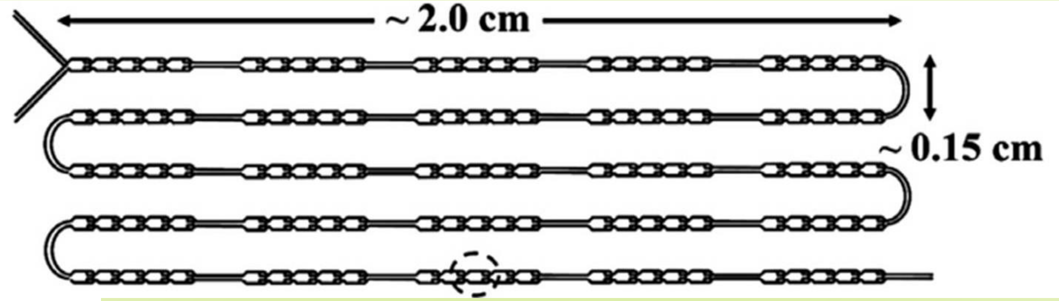
未來

Miniaturization
Automation
Safety




(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

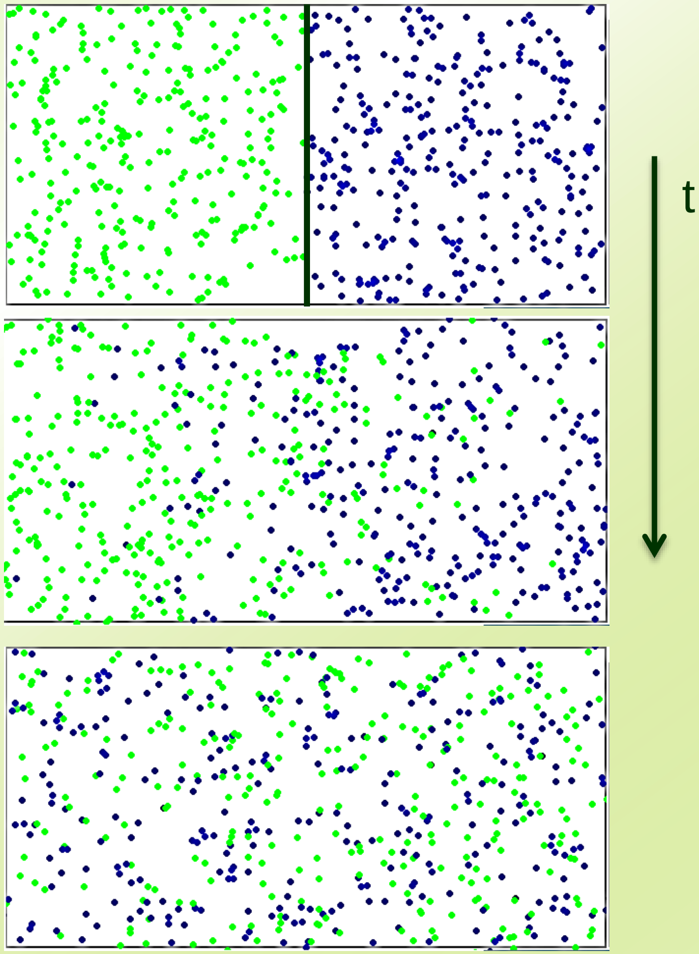

反應單元
流體匯集處
300 μm
300 μm
150 μm
100 μm
90°
100 μm
400 μm
50 μm
流體分


~ 2.0 cm
~ 0.15 cm

# 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

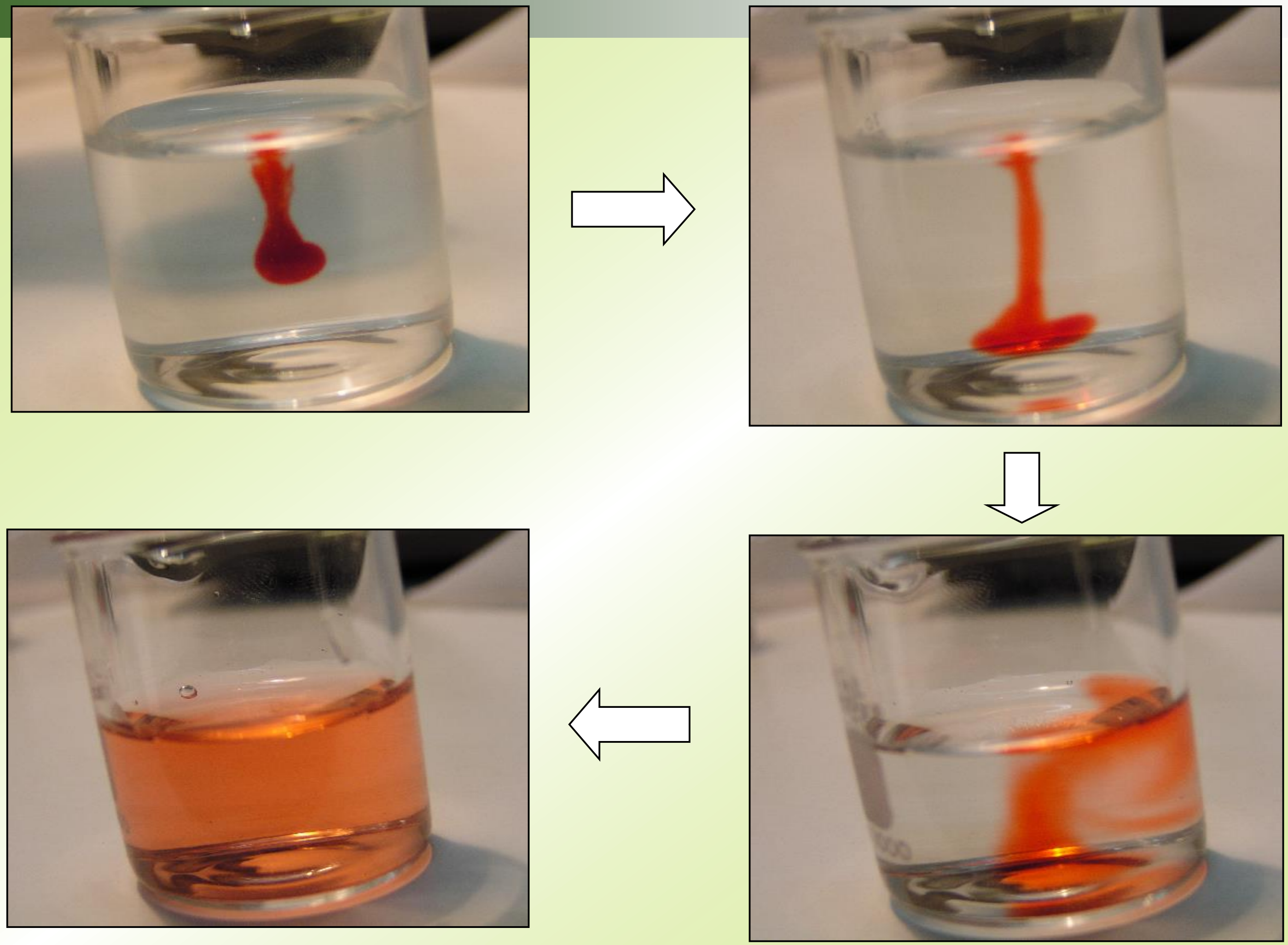
http://www.blingcheese.com/image/code/5/smoke.htm

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.

仿生與實驗室晶片導論- 2020

# Micro-mixers

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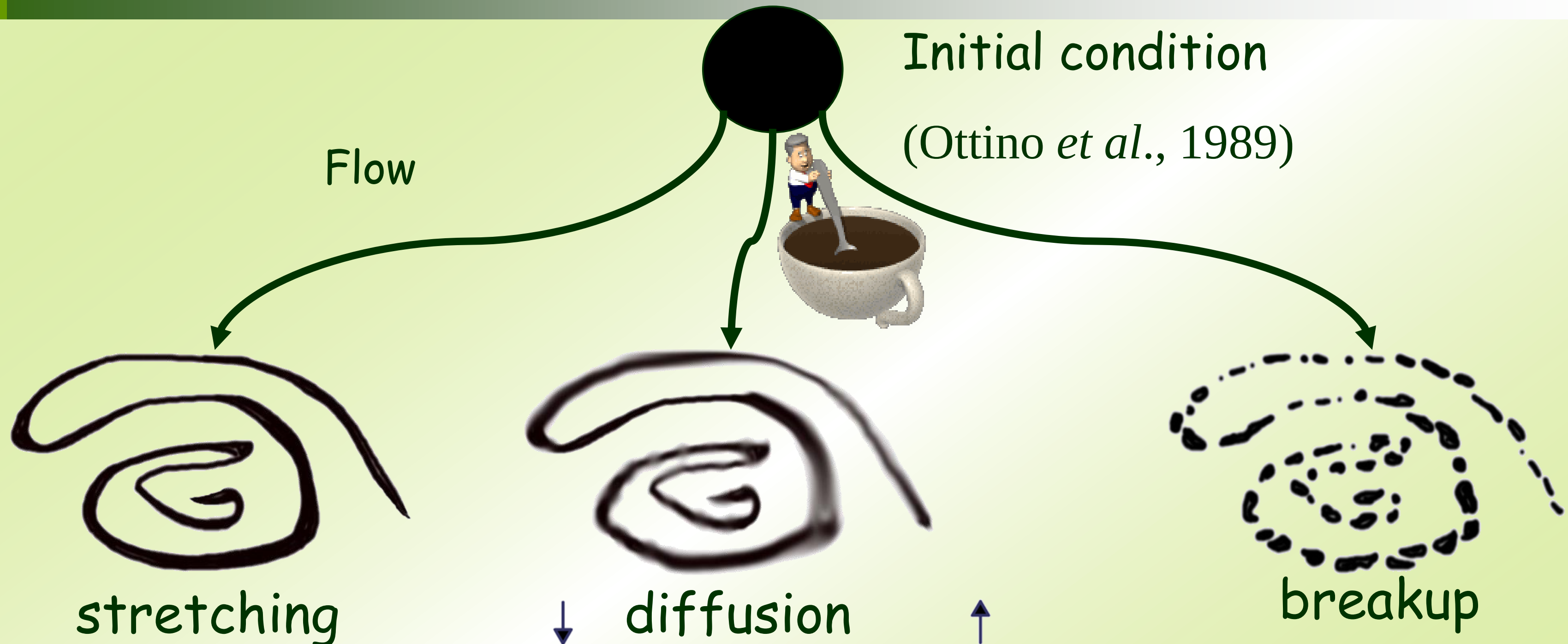
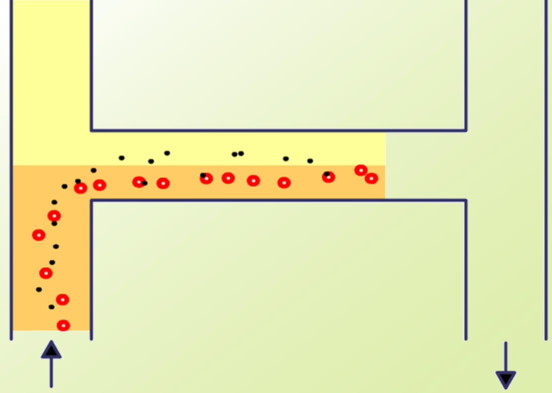
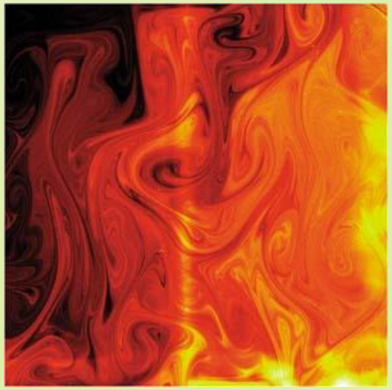
中華民國 110 年 1 月 6 日

BEAM Lab

# How does mixing happen?



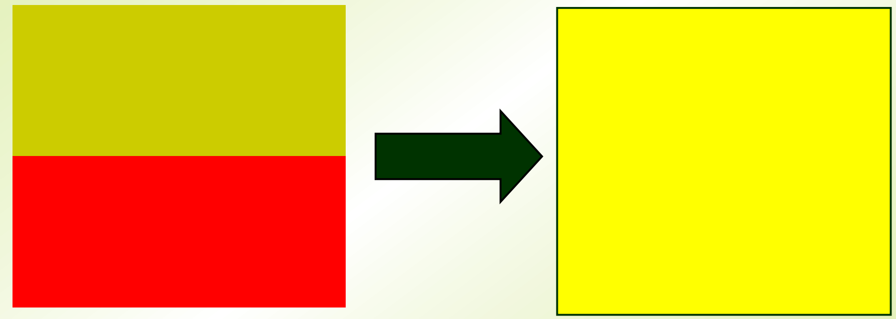





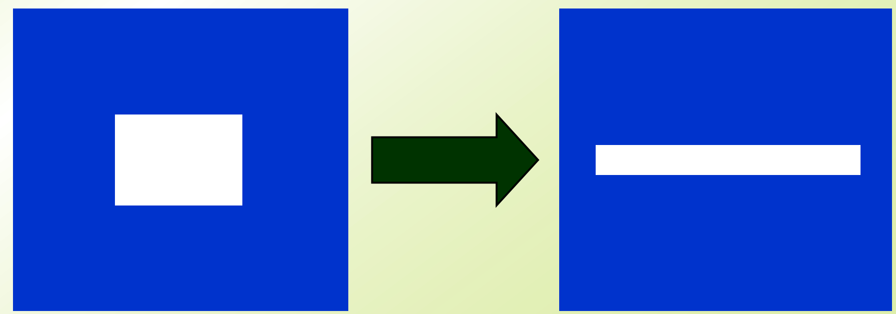
***Ref.*** :http://www.tj.xinhuanet.com/ztbd/2005-06/09/content_4420148_10.htm ; www.micronics.net ; http://physicsweb.org

# Three Types of Fluid Mixing

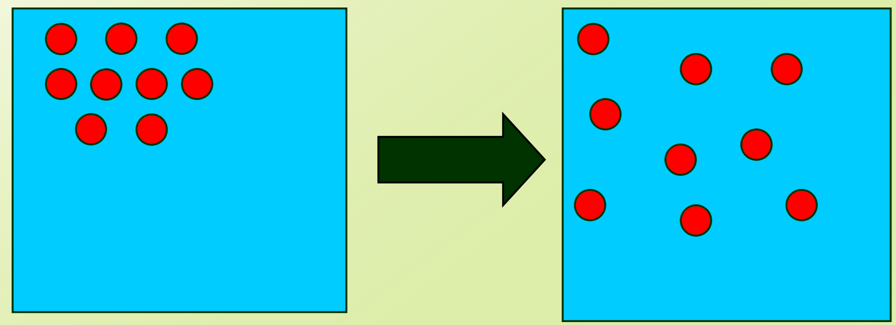
(a) Mixing of two miscible fluids



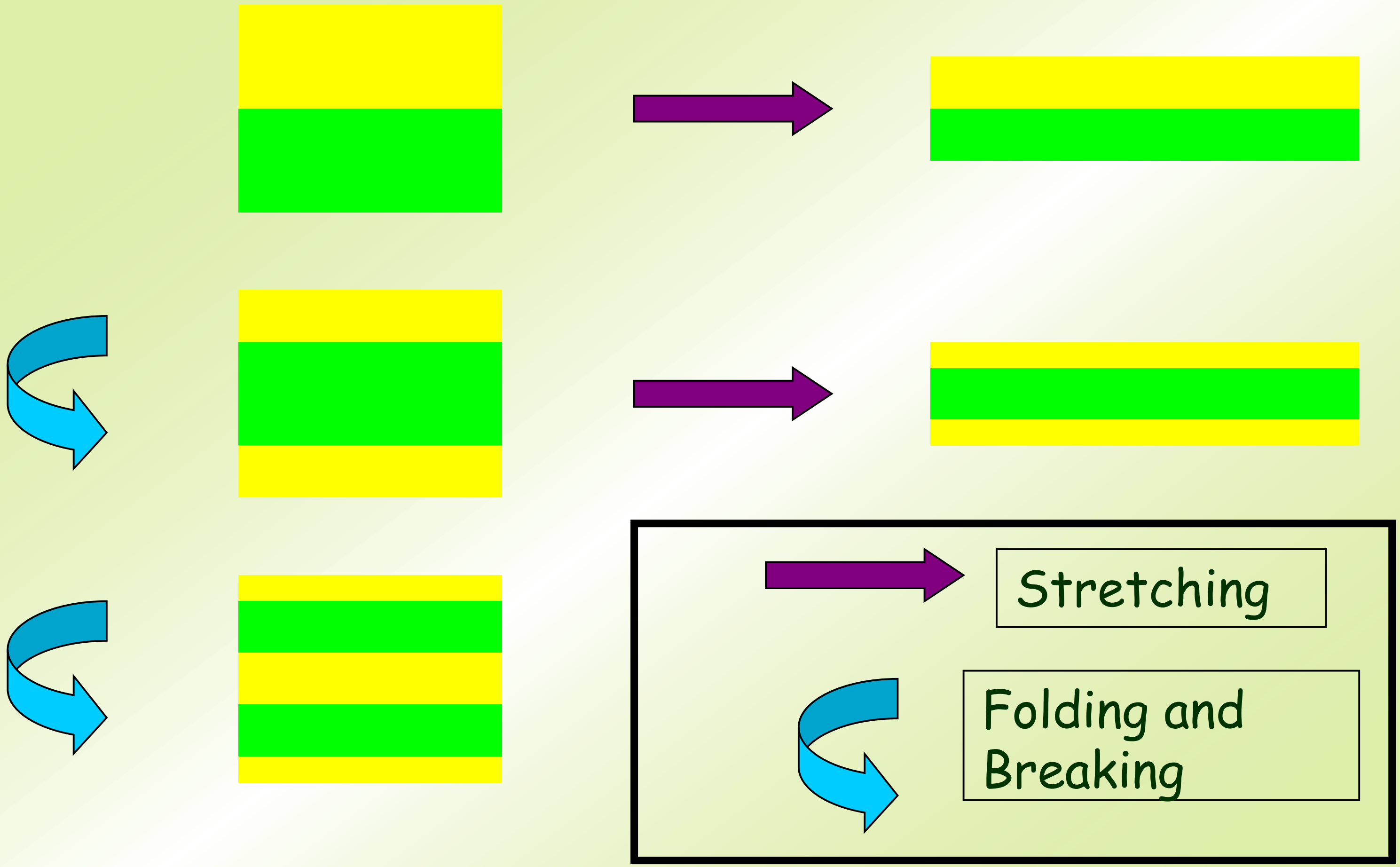
(b) Mixing of two immiscible fluids



(c) Mixing of two phases fluids

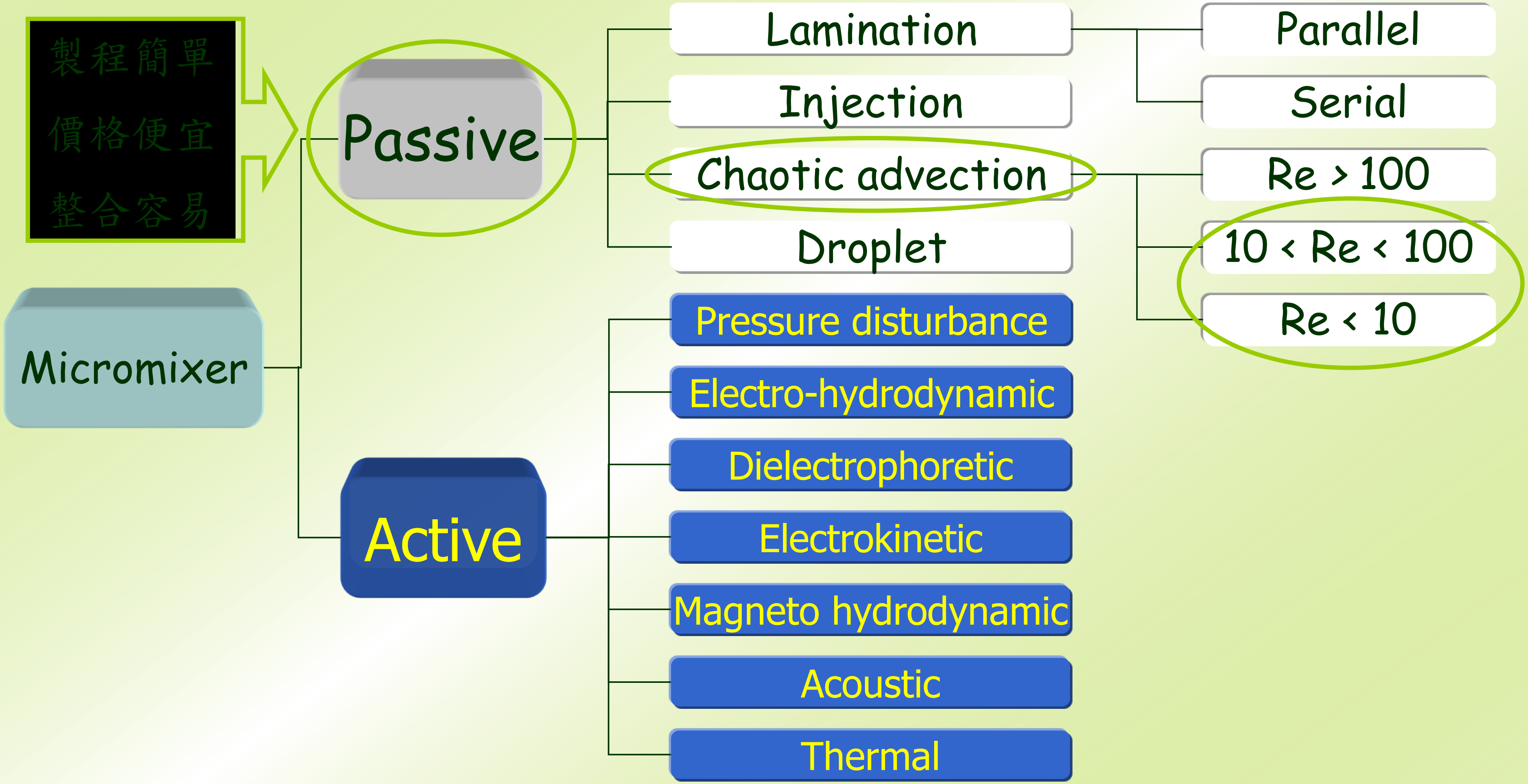


# Fluid Mixing by Stretching and Folding



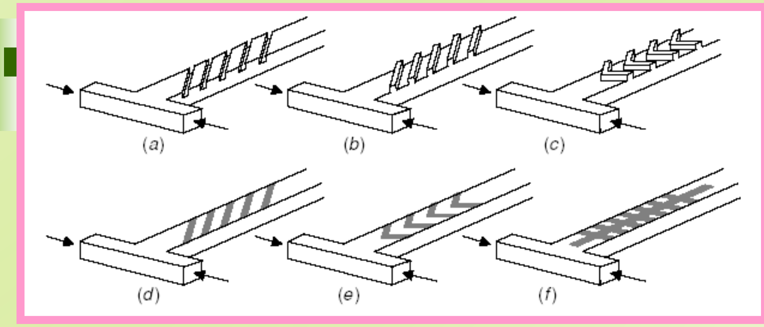

Mixing is promoted by periodic motion of the fluid. It is conducted by iterated stretching and folding of the interface here.

# Micromixer Types

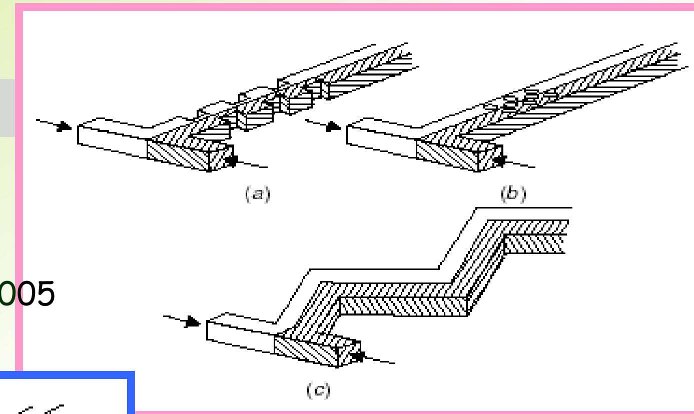


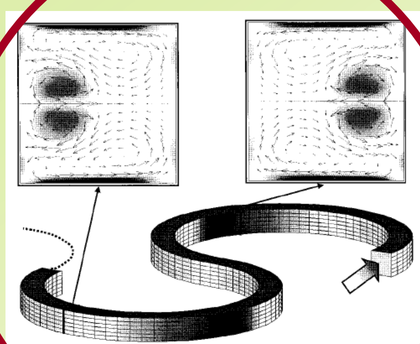

Ref. Nam-Trung Nguyen and Zhigang Wu, Micromixer – A Review, 2005, JMM

# Various Micromixers

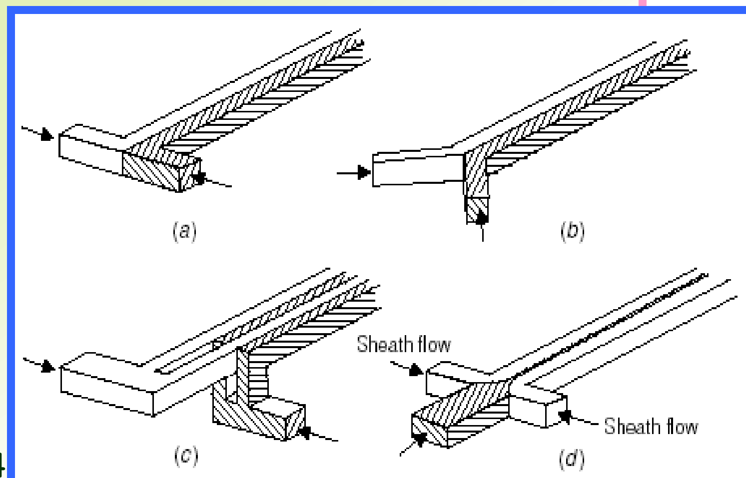


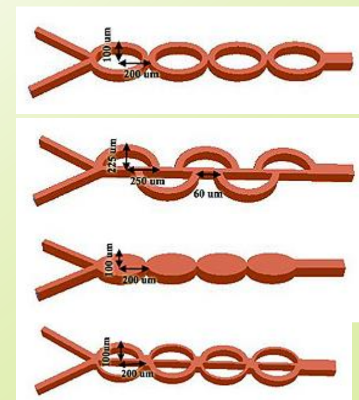

Nguyen and Wu, *JMM*, 2005



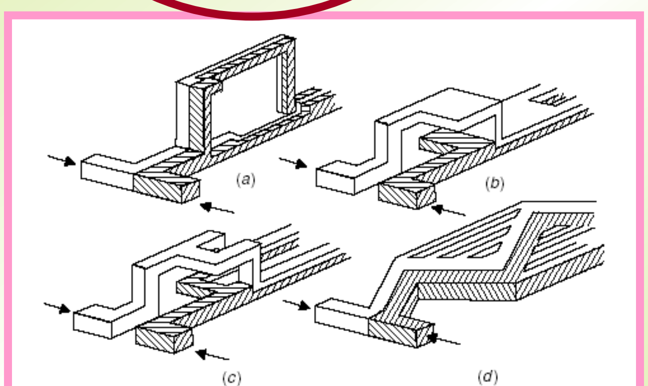



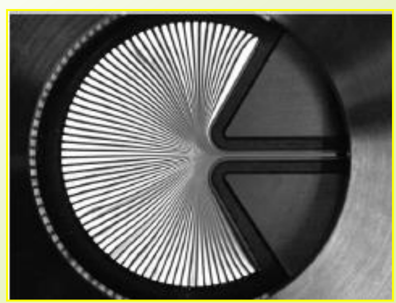
Schönfeld and Hardt, AIChE J.,2004



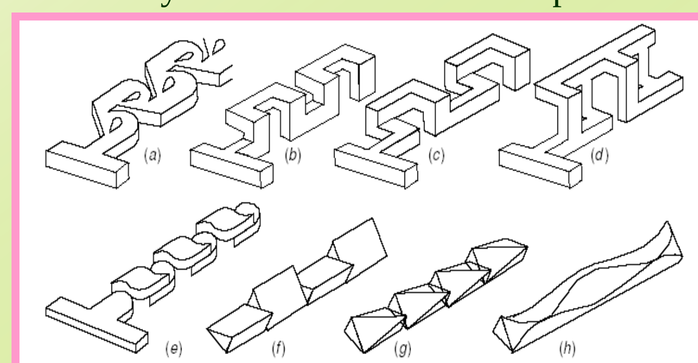




http://microfab.utah.edu/TechnologyLibrary/Micromixer/micromixerposter.htm

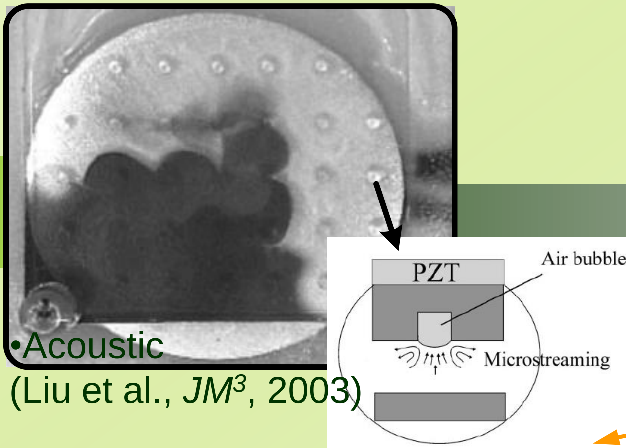


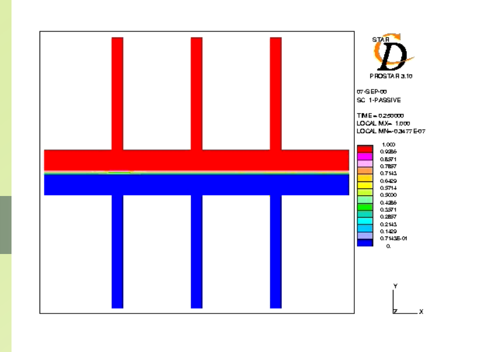
Lab et al., 2004.,
Chem. Eng. & Tech.



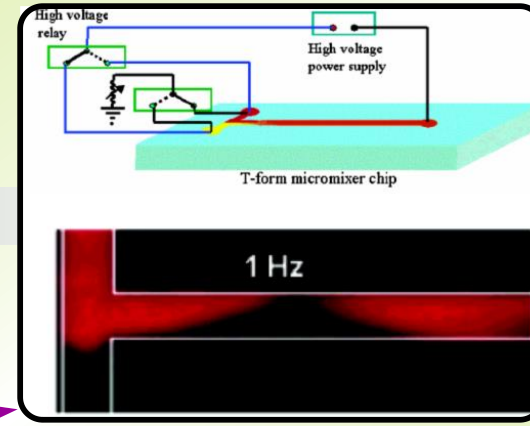
# Fluid Propulsion



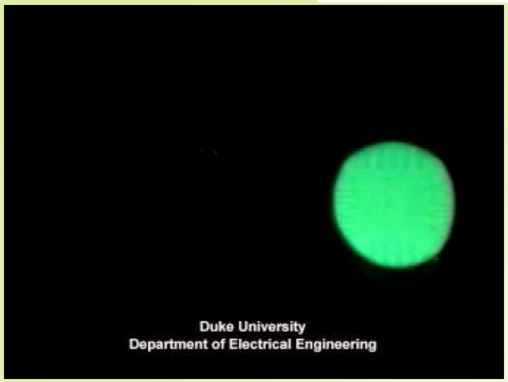

•Acoustic
(Liu et al., *JM³*, 2003)



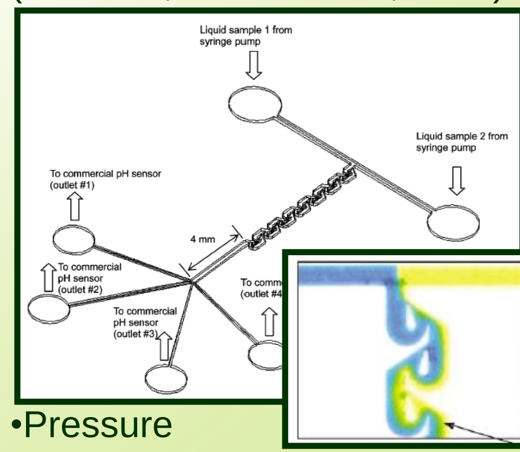
•Pressure Perturbations
(Niu and Lee, *JMM*, 2003)




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



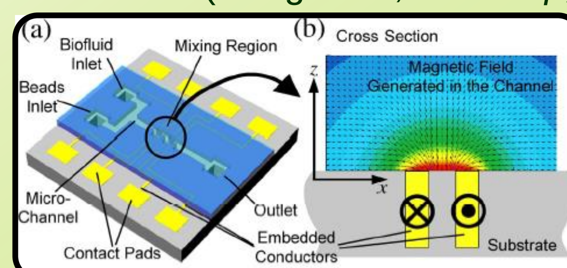

•Electrowetting
(Paik *et al.*, *Lab Chip*, 2003)



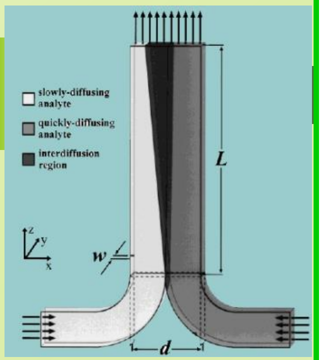

•Pressure
(Hong *et al.*, *Lab Chip*, 2003)

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

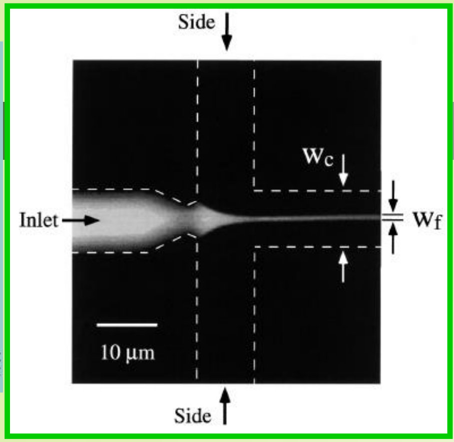
•Centrifuge
(Steigert et al., Sensor and Actuator, 2006 )



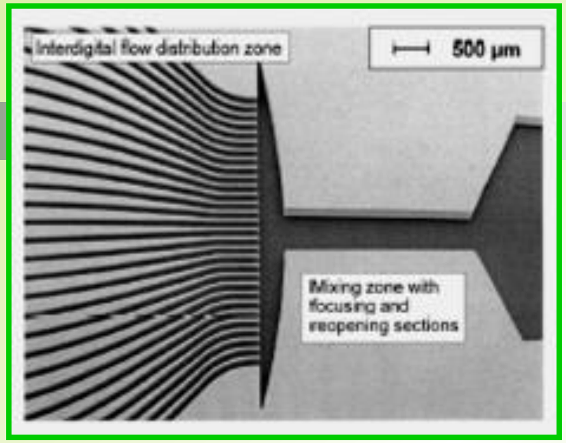

•Magnetic (Suzuki and Ho, *J. Microelectromech. Syst.*, 2004)



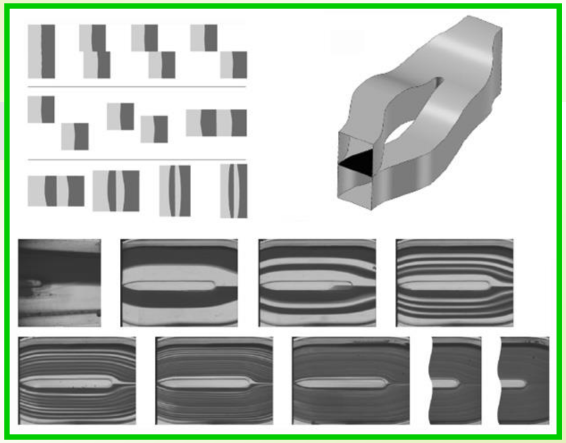

Kamholz *et al.*, *Anal. Chem.*, 1999



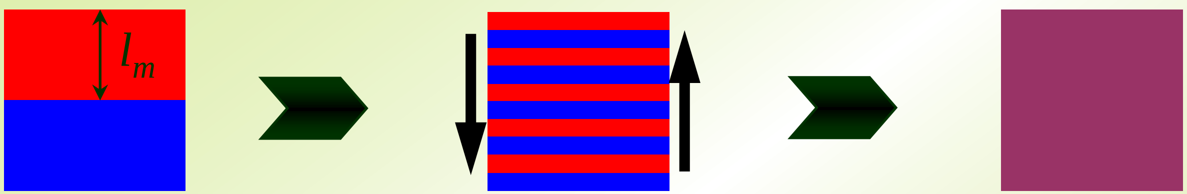

Knight *et al.*, *Phys. Rev. Lett.*, 1998




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



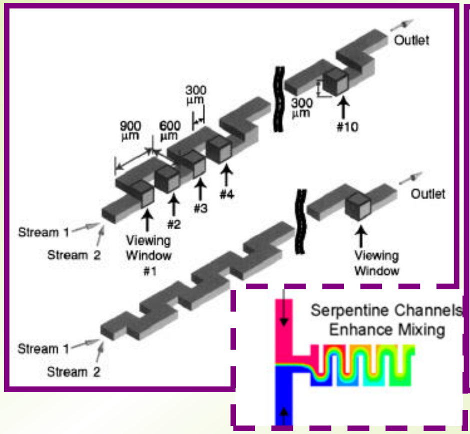
Schönfeld *et al.*, *Lab Chip*, 2004



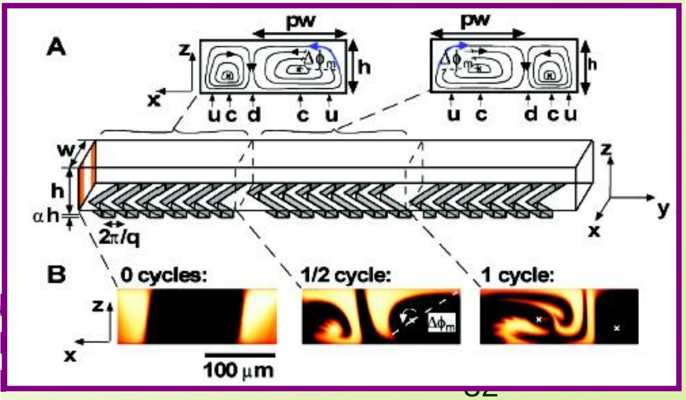

$$\Delta y_m \sim U \times \left( \frac{l_m^2}{D} \right) = \mathrm{Pe} \times l_m$$

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

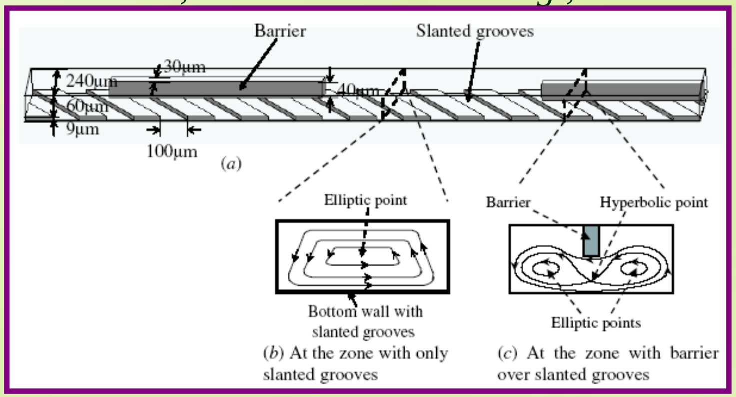
Liu *et al.*, *JMEMS*, 2000

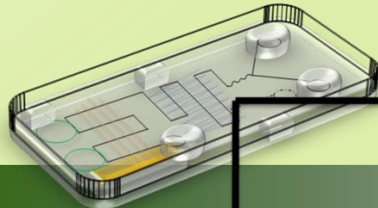



Stroock *et al.*, *Science*, 2003

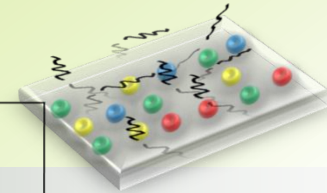



Kim *et al.*, *J. Micromech Microeng.*, 2004





# 生物晶片技術



## 晶片實驗室/微流體晶片

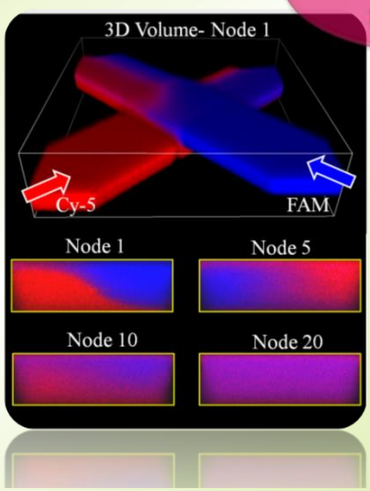
- 傳輸
- 分離
- 混合/反應
- 過濾/篩選
- 純化
- 檢測

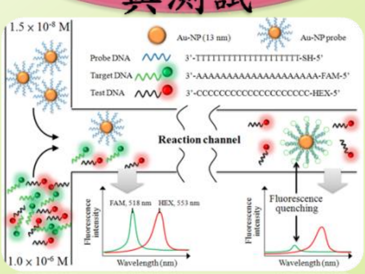
## 微陣列晶片

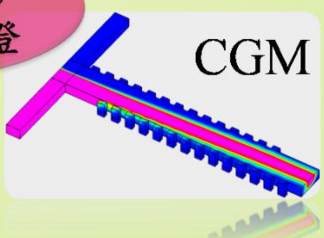
- 組織晶片
- 蛋白質晶片
- 醣晶片
- DNA晶片

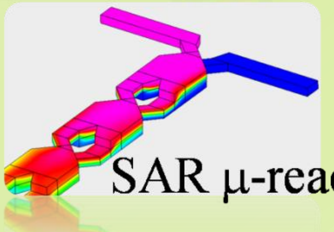
## 創新微生化反應器之設計分析與應用

- 量測技術的開發
- 元件設計，分析與驗證
- 先導應用與測試



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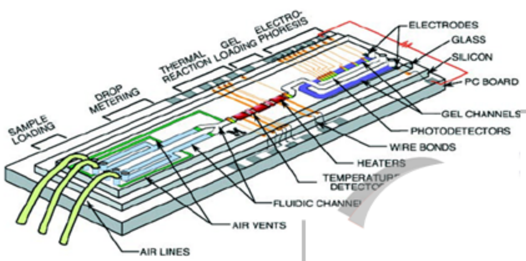
# Research Targets in bio-medical diagnosis



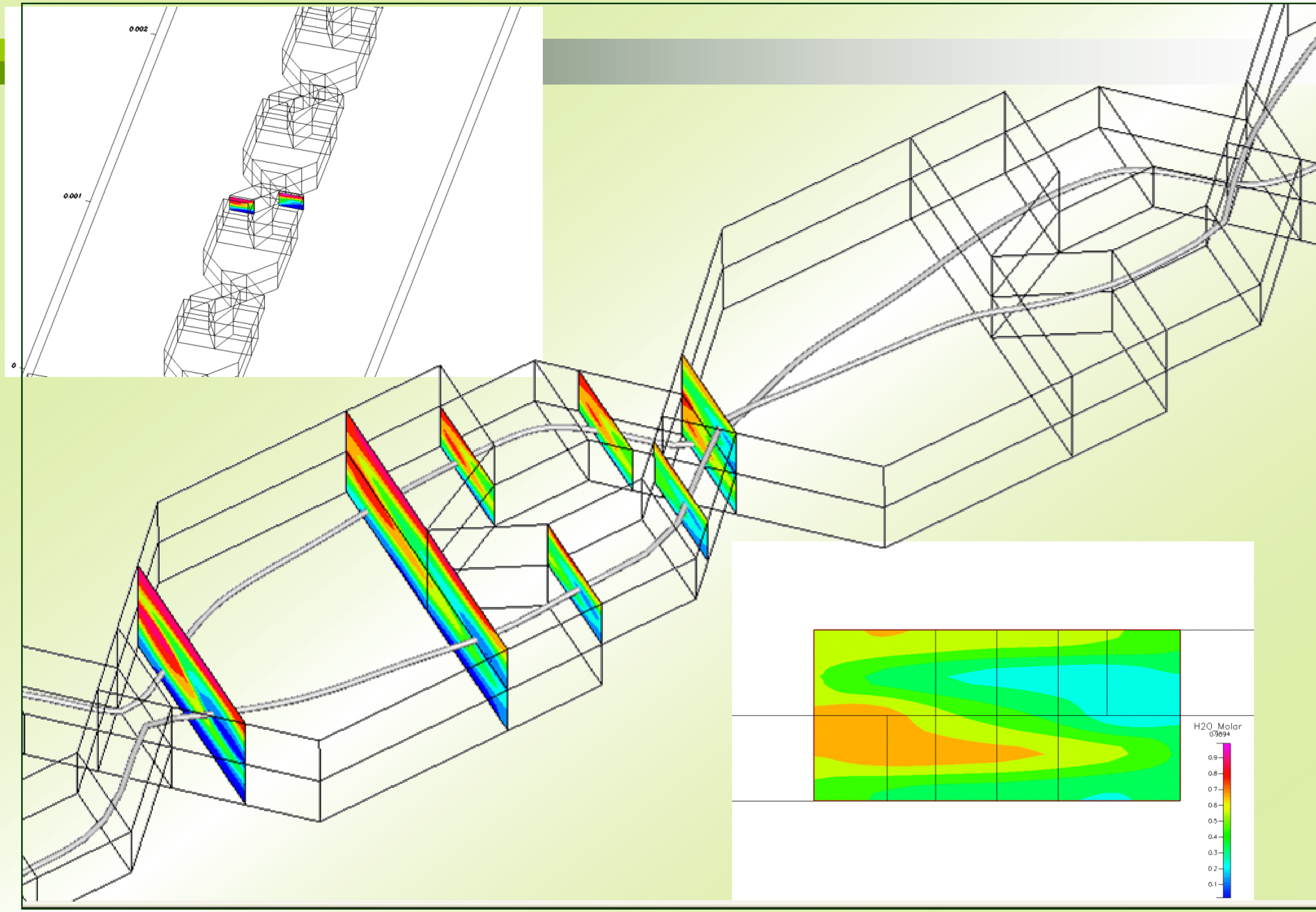

Lab on a chip

- transmission
- mixing/ reaction
- filtration / screening
- purification
- separation
- detection

microreactors

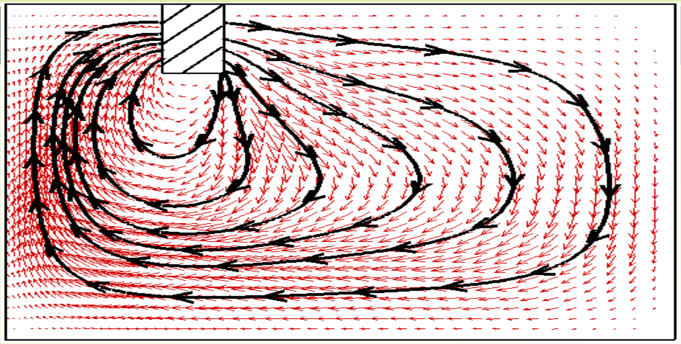
- analysis
- measuring techniques
- chemical reaction/ bioreaction

# Numerical Simulation

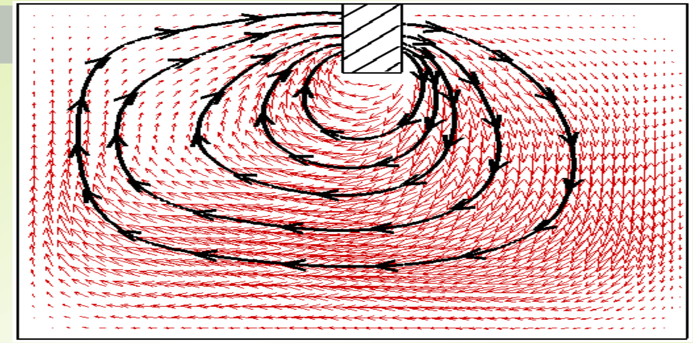



T-type BEM T-type

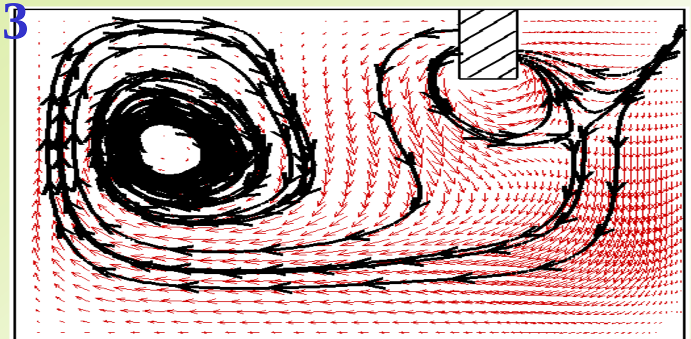
# Topological Characteristics of Flow Field



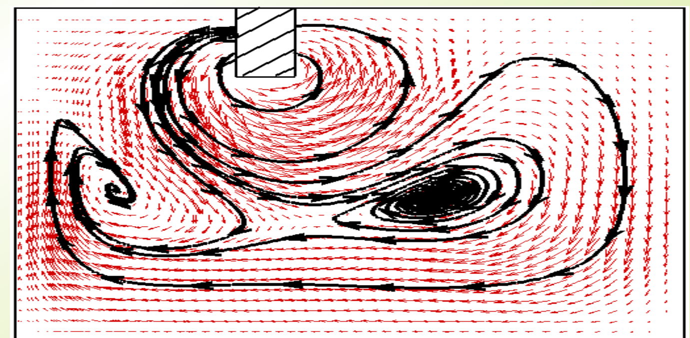
(a) inclined groove No. 1



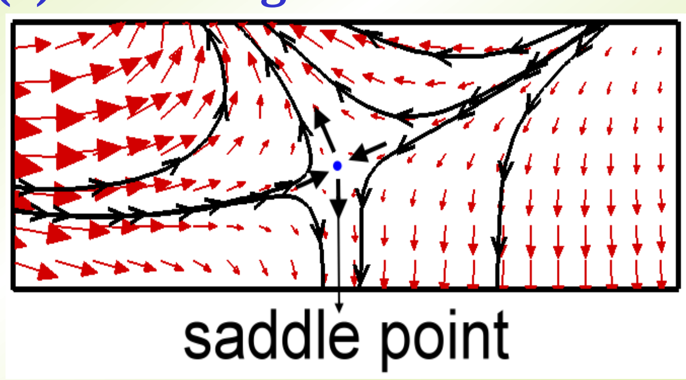
(b) inclined groove No. 3



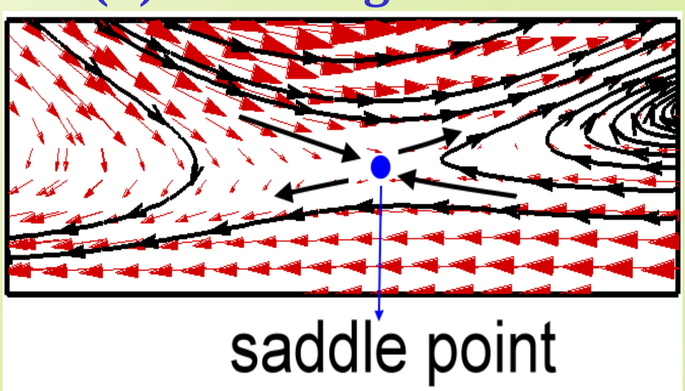
(c) inclined groove No. 5



(d) inclined groove No. 7




(e) enlarger graph of (c)




(f) enlarger graph of (d)

# Micromixers (optimization of chaotic micromixers)

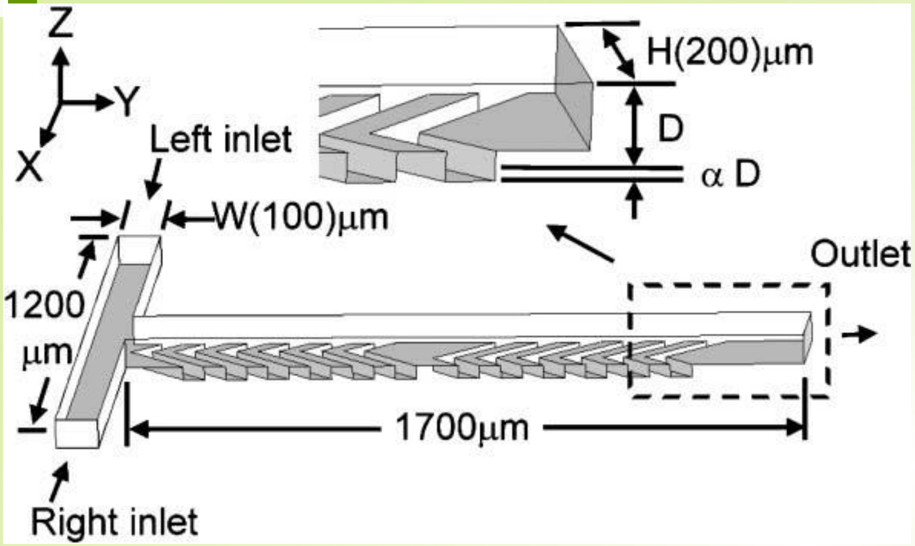
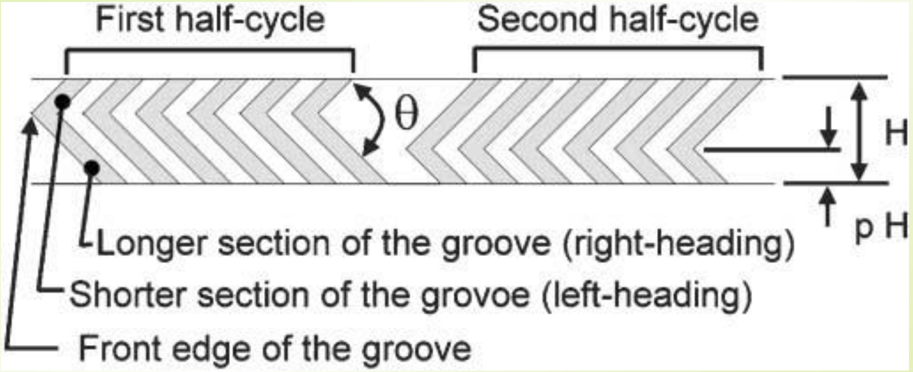



**Table 1** Numerical values of geometric parameters

| No. | Parameter | 1 | 2 | 3 |
|---|---|---|---|---|
| A | Asymmetry index ($p$) | 0.21 | 0.33 | 0.45 |
| B | Depth ratio of the groove ($\alpha$) | 0.07 | 0.13 | 0.18 |
| C | Upstream to downstream channel width ratio ($W/H$) | 0.5 | 1 | 1.5 |
| D | Groove intersection angle ($\theta$) | 60° | 90° | 120° |

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

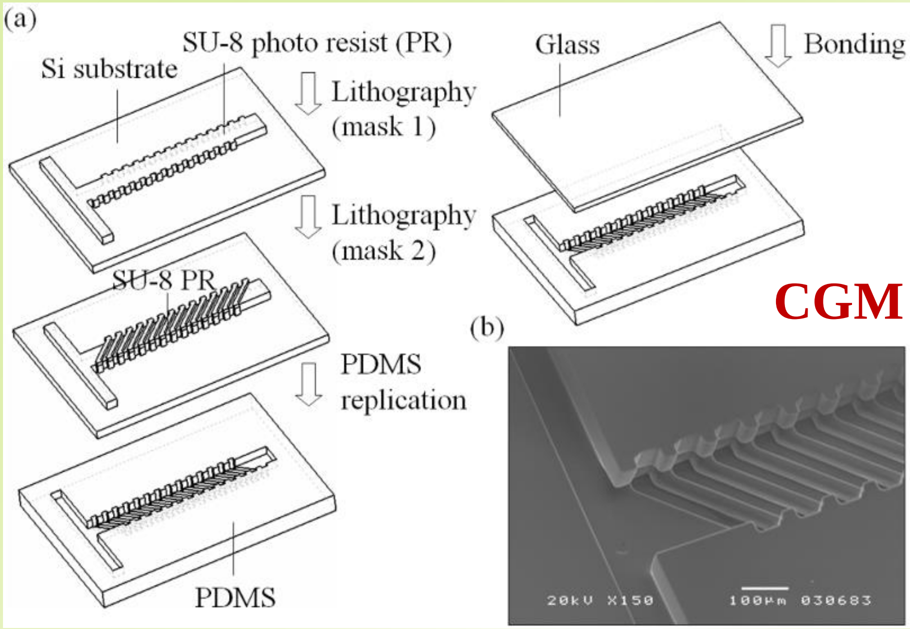
depth ratio of the groove ~ asymmetry index > groove intersection angle > Upstream to downstream channel width ratio.

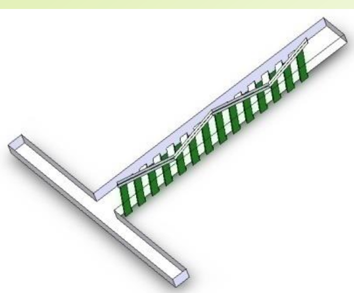


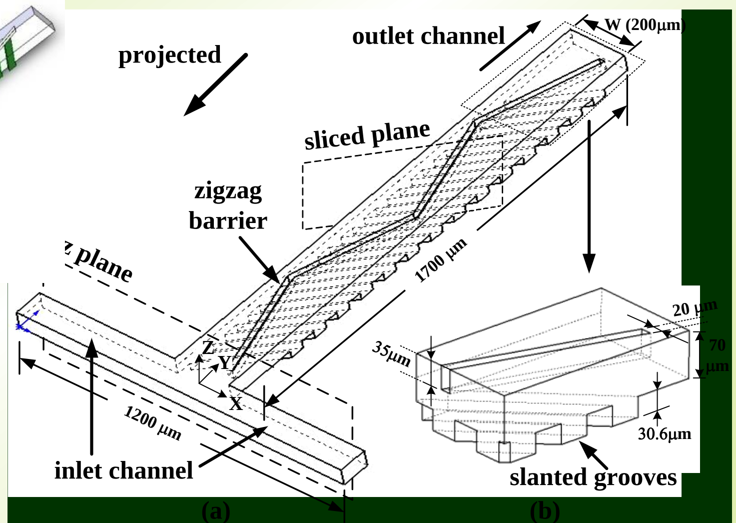

Yang *et al*., *Lab Chip*, 2005
*times cited > 169*

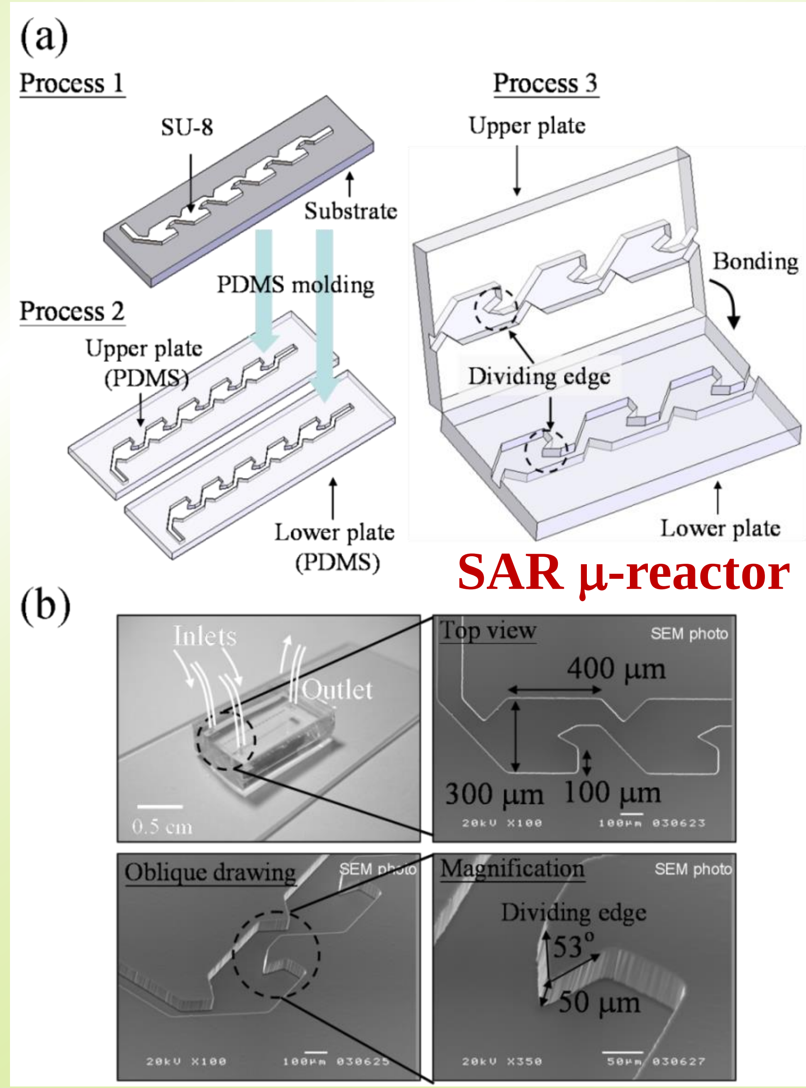
Stroock *et al*, *Science*, 2005, herringbone micromixer

# Design and Micro-fabrication



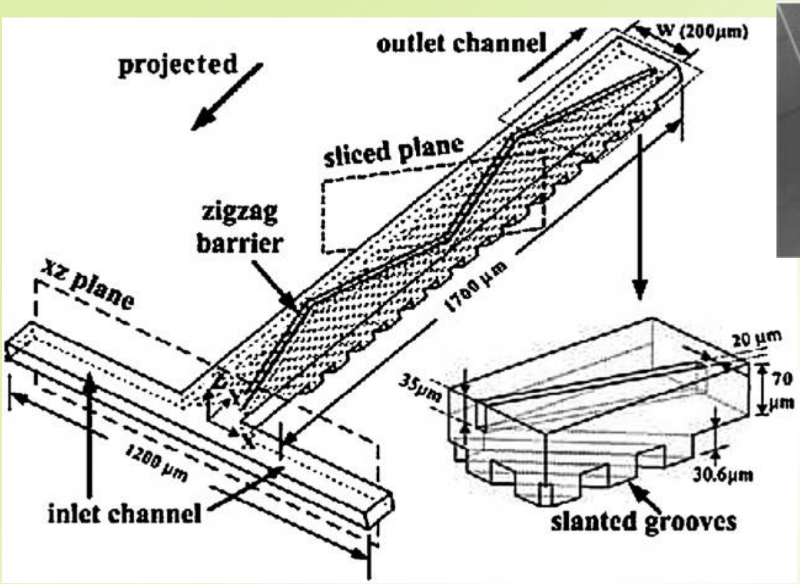



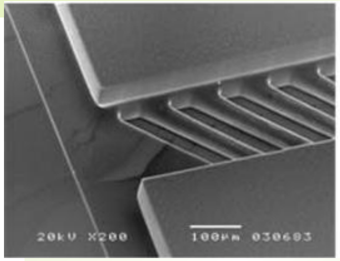


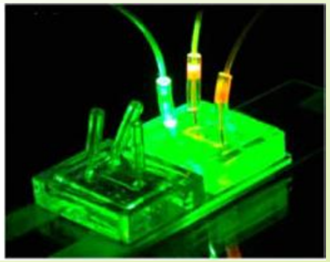
# Micromixers (chaotic micromixers)

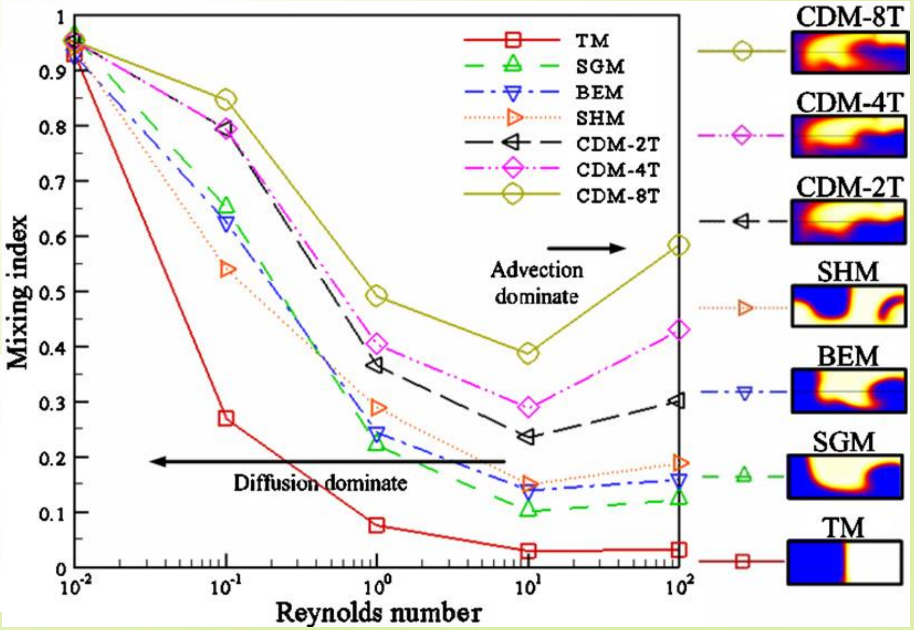
Circulation–disturbance micromixer (CDM)

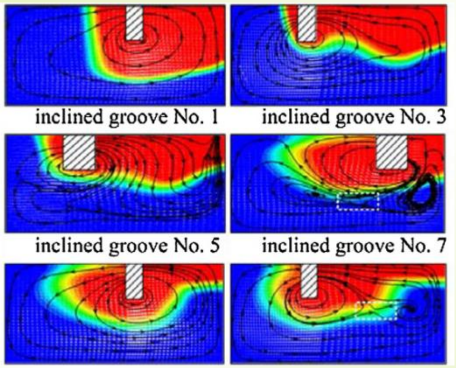


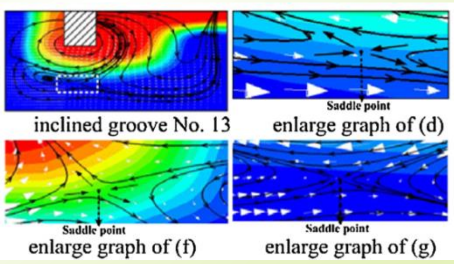









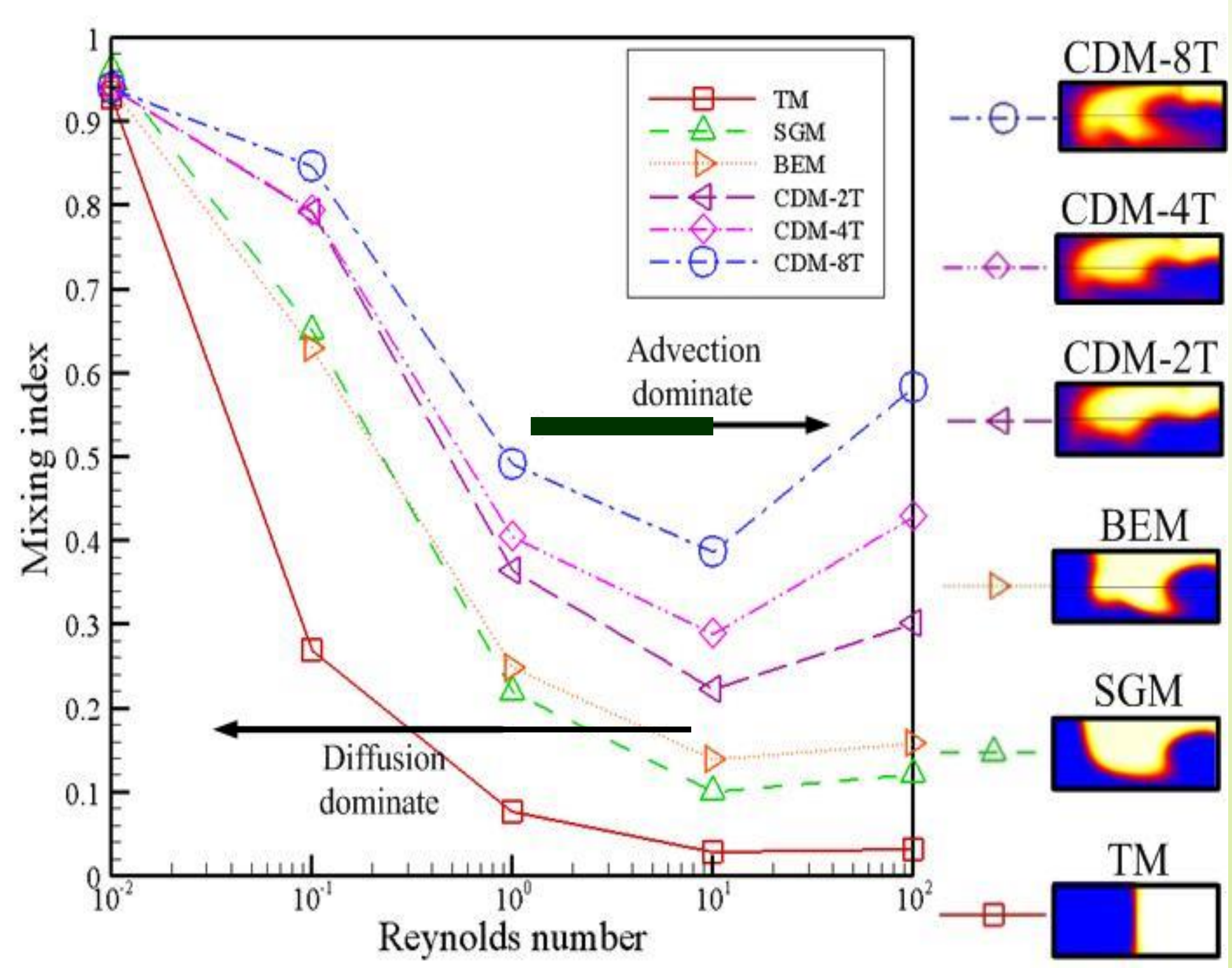



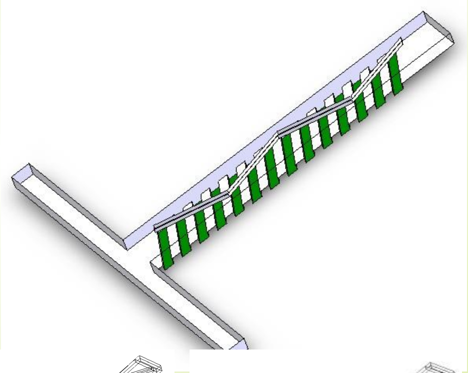



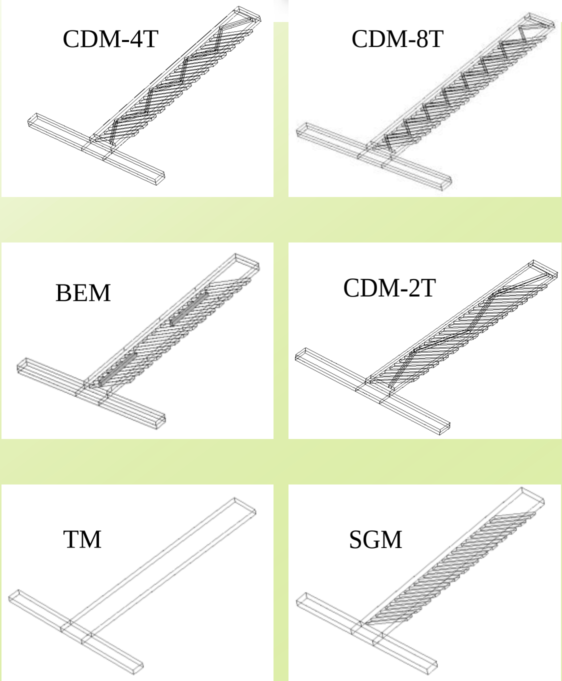

Yang *et al*., *JMM*, 2007, CDM

# Enhanced Mixing Performance by CDMs

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



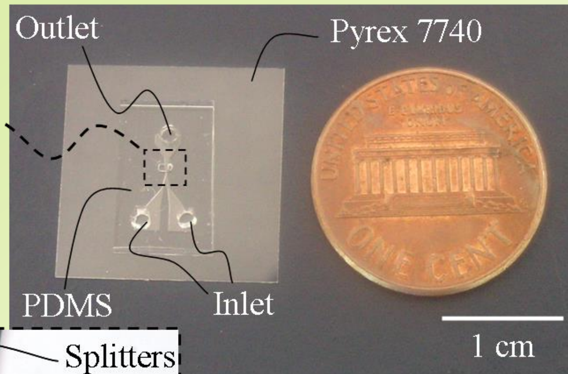





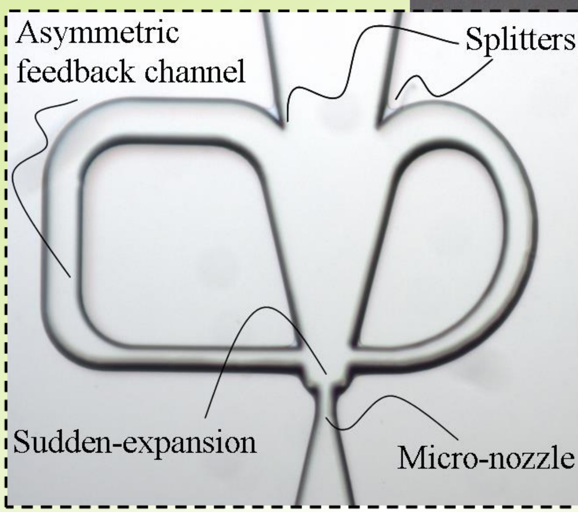

Compared with a slanted groove micromixer at Re = 10, CDM-2T increases 132%, CDM-4T increases 183% and CDM-8T **increases 280%.**

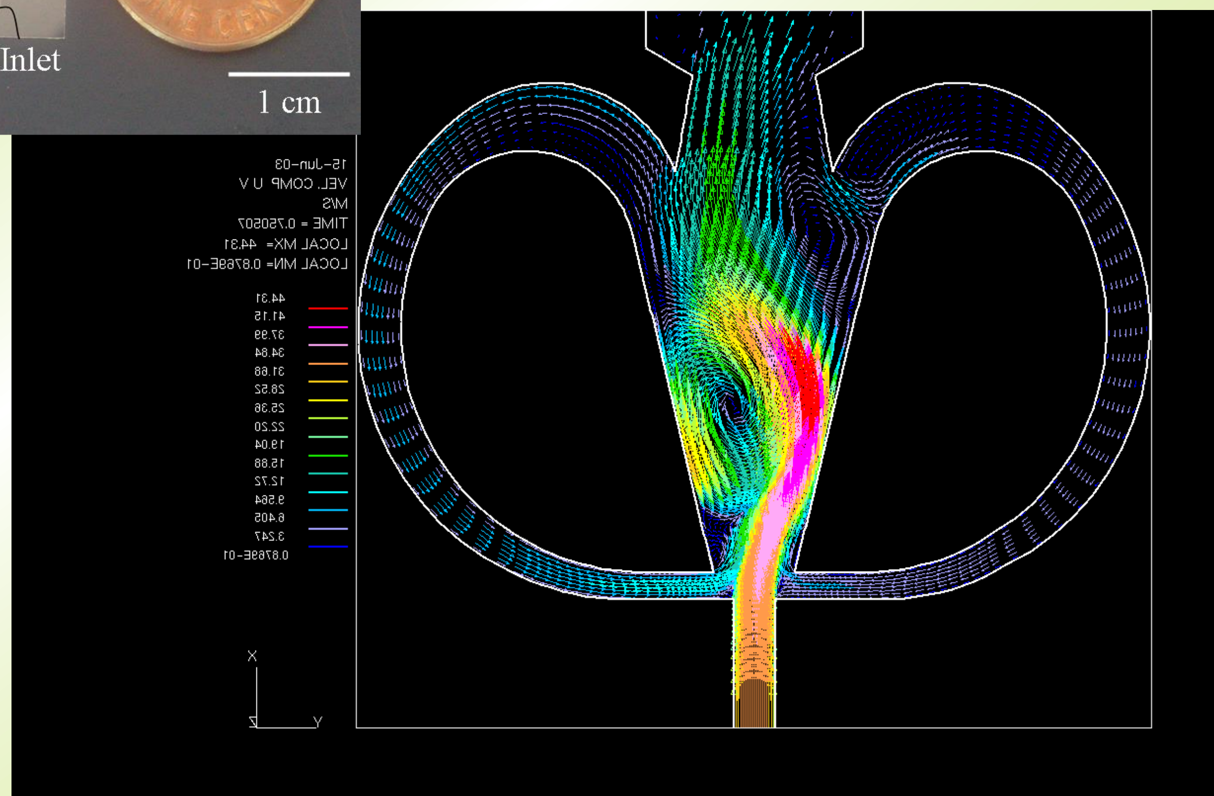
# Microfluidic Oscillator

## 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**

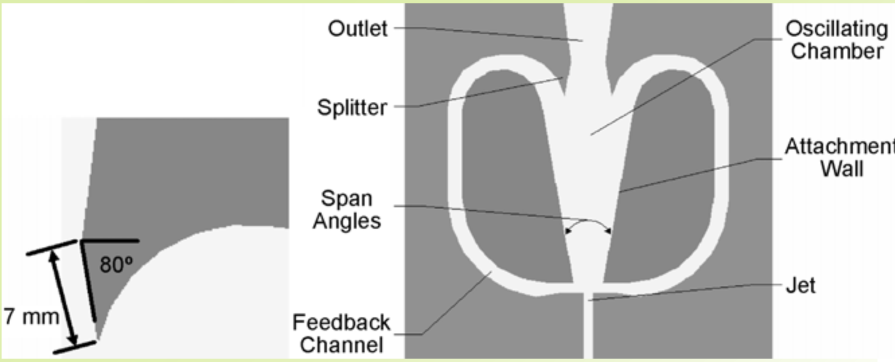
**ROC Patent, 2007**

**2008 National Invention Prize**

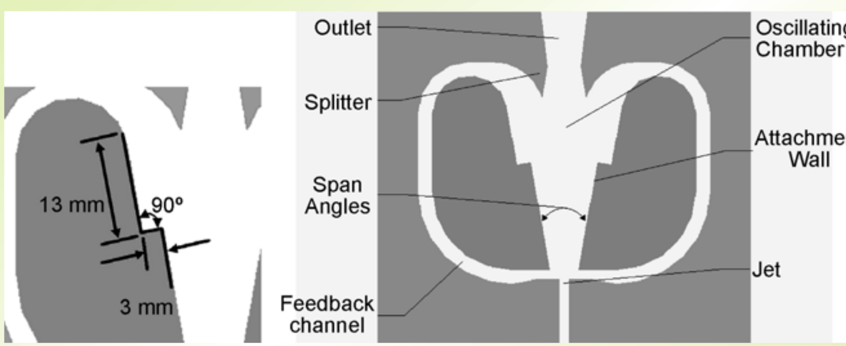
**US Patent, 2009**

# A novel fluidic oscillator incorporating step-shaped attachment walls

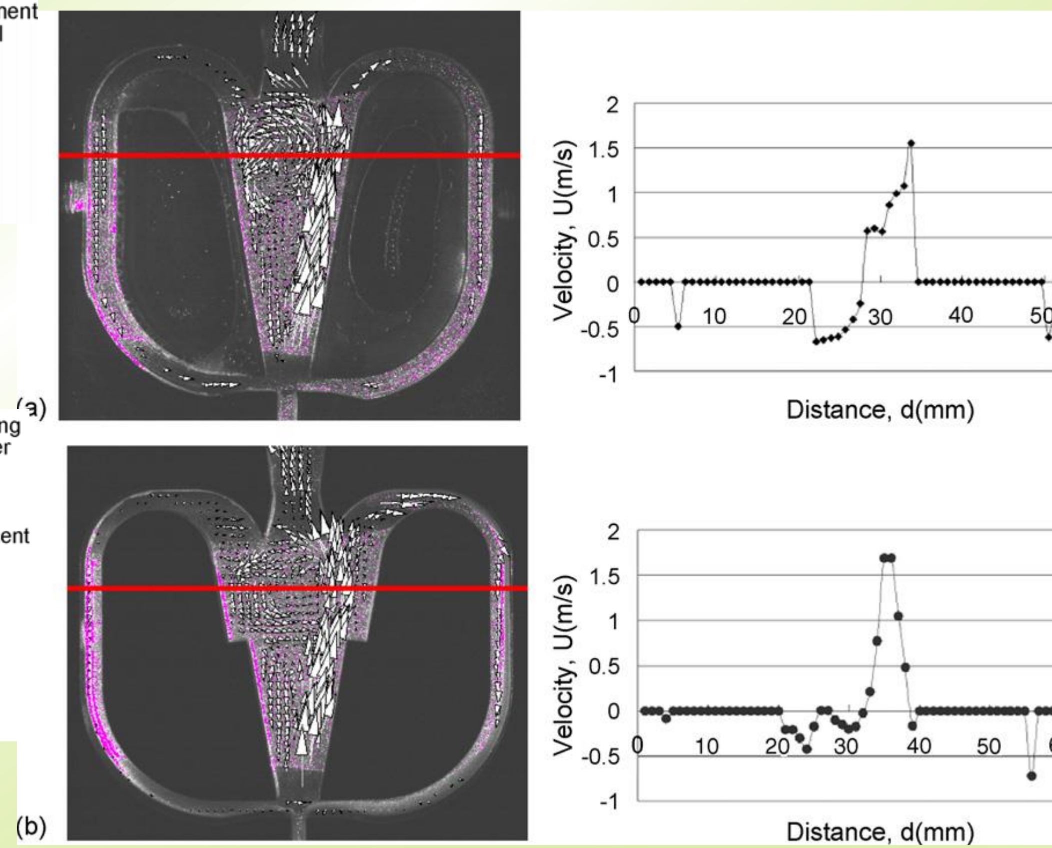
Yang *et al.*, *Sensor & Actuators A: Physical*, 2007.
times cited > 65
Chen *et al.*, *J. Mechanics*, 2006; times cited > 23




Configurations of the plane-wall oscillator and splitter.

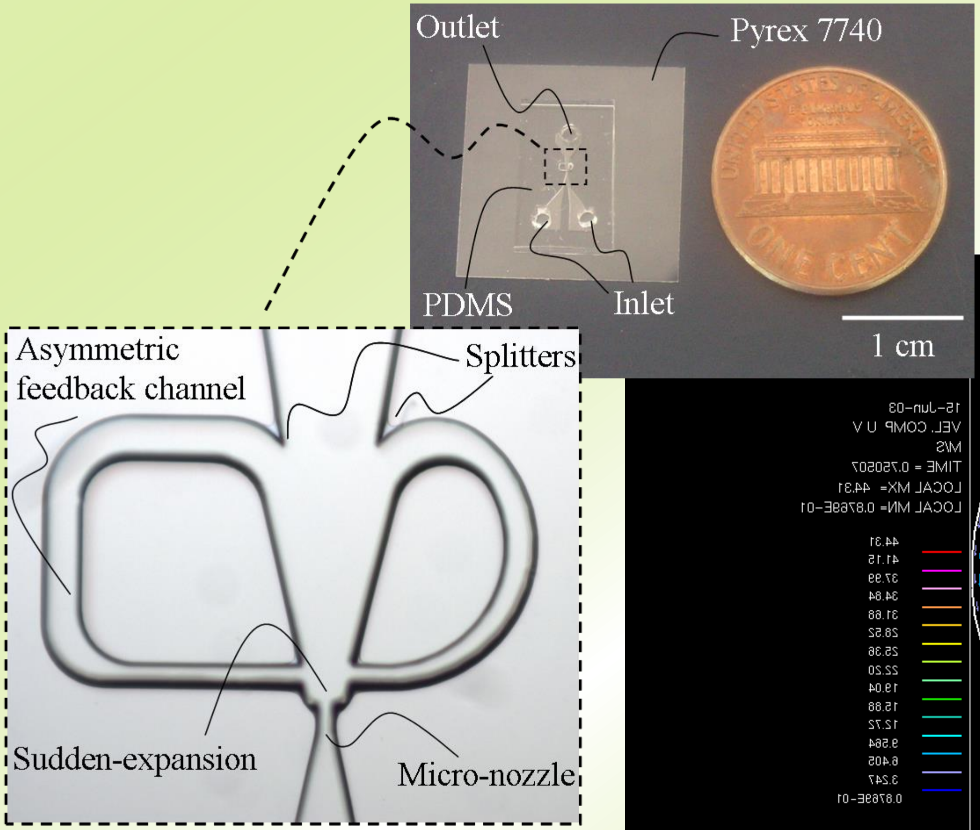



**Configuration of the step-wall oscillator**

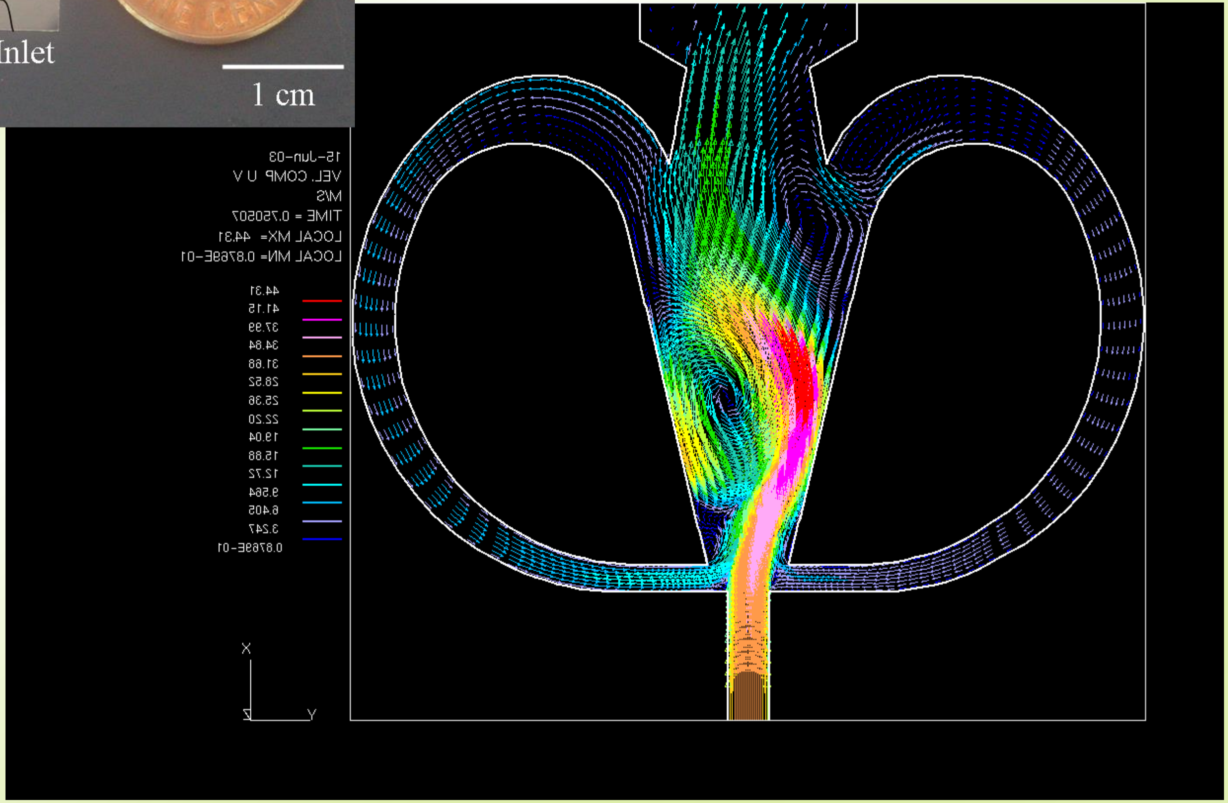


# Microfluidic Oscillator

## 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**

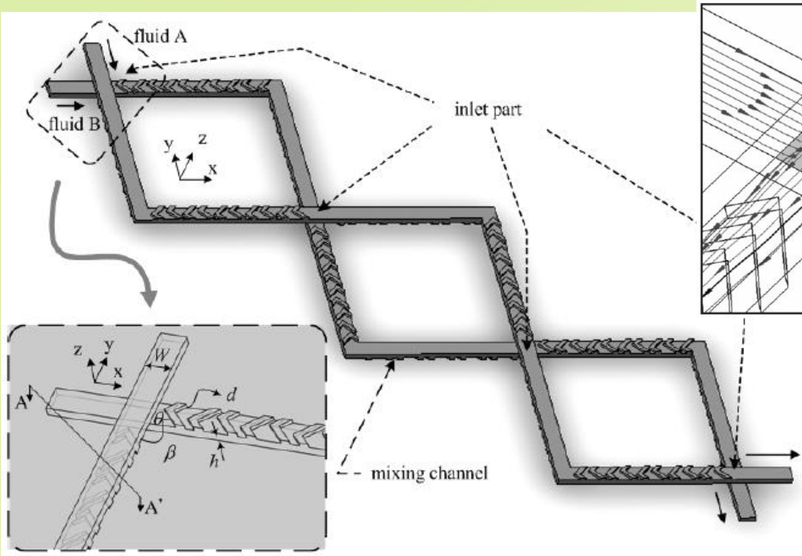
**ROC Patent, 2007**

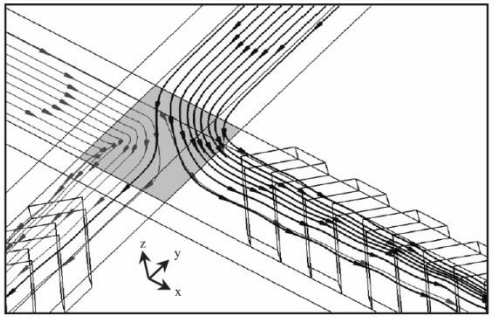
**2008 National Invention Prize**

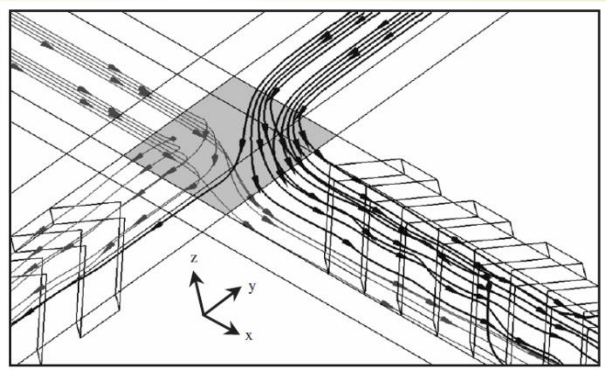
**US Patent, 2009**

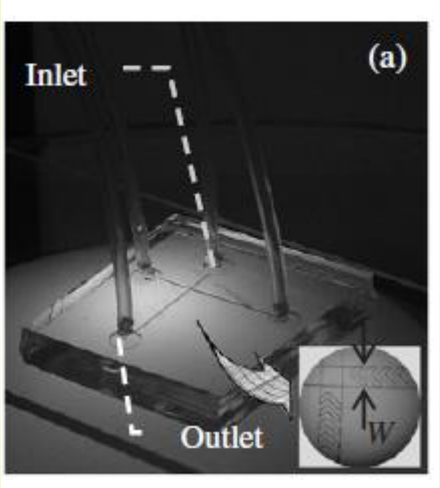
# Overlapping Crisscross Micromixers

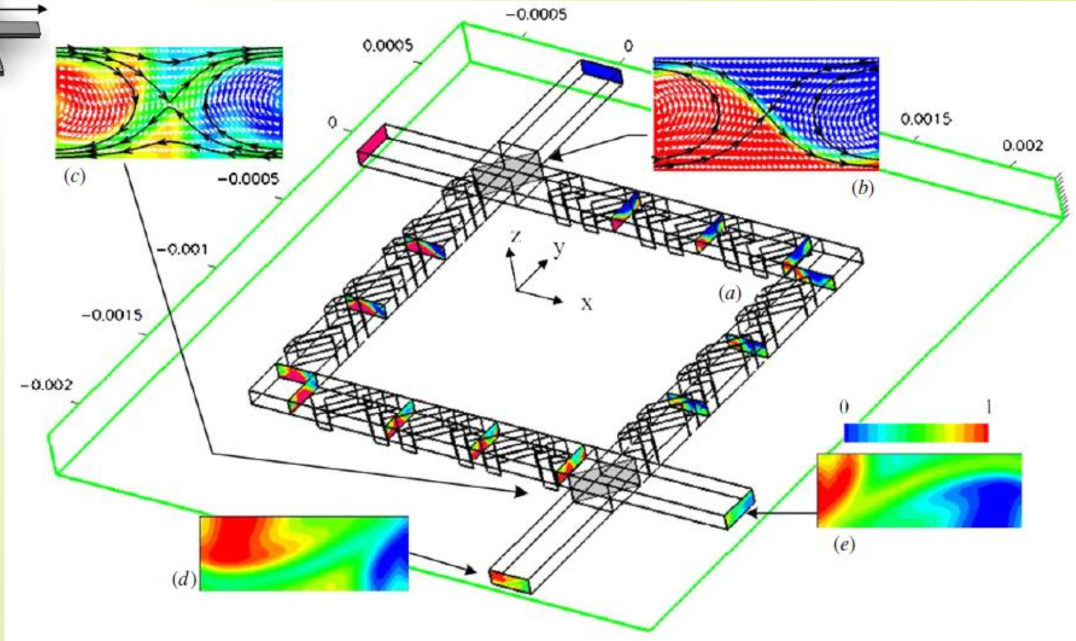
Wang & Yang, JMM Highlights of 2006, Chemical Engineering Science (CES), 2006





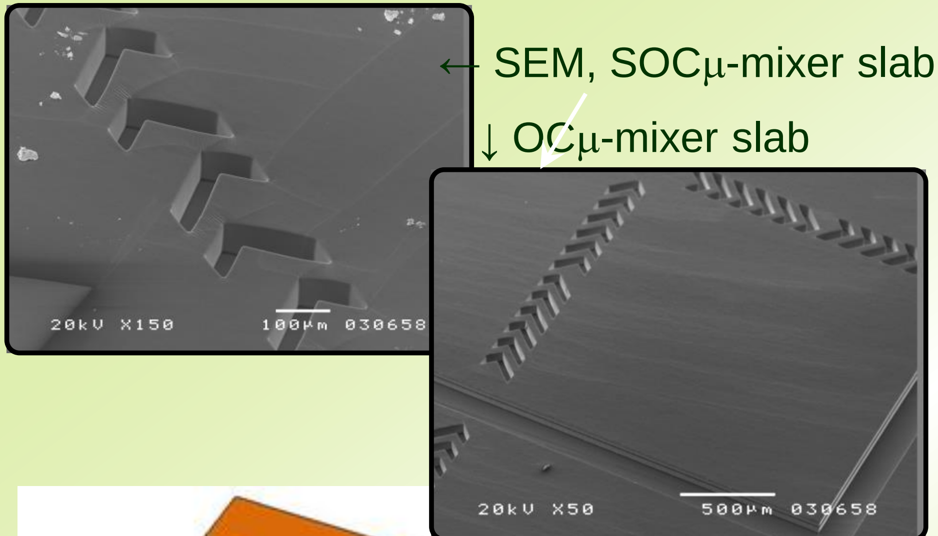


# Overlapping-Crisscross Micromixer

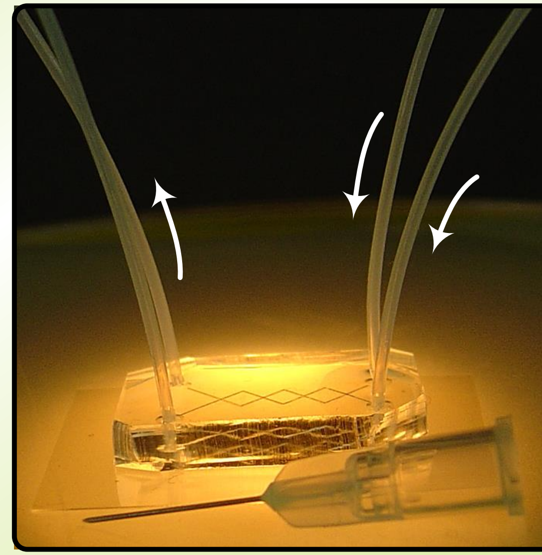
Wang and Yang, *JMM*, 2006.

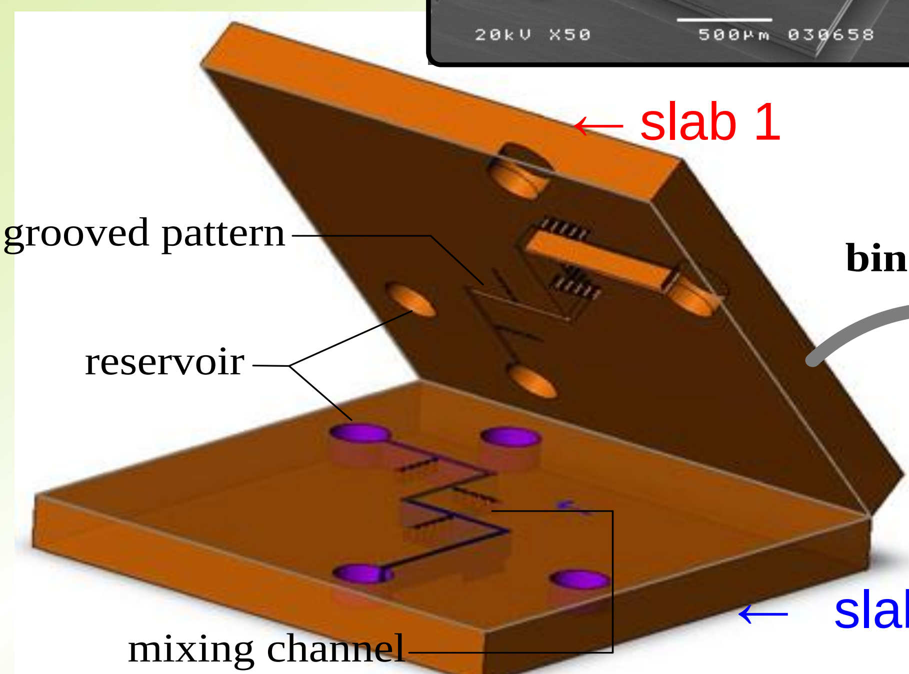
Finished **2006 *JMM Highlight***



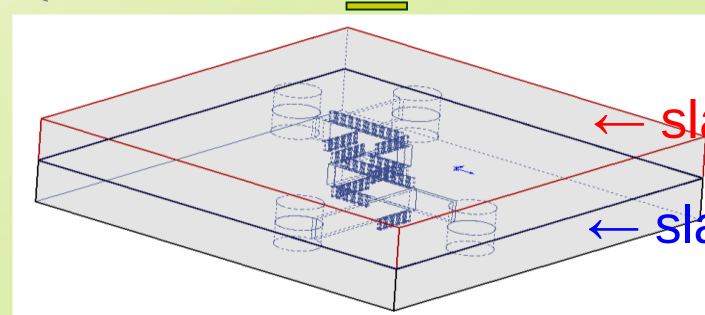

← SEM, SOCμ-mixer slab

↓ OCμ-mixer slab

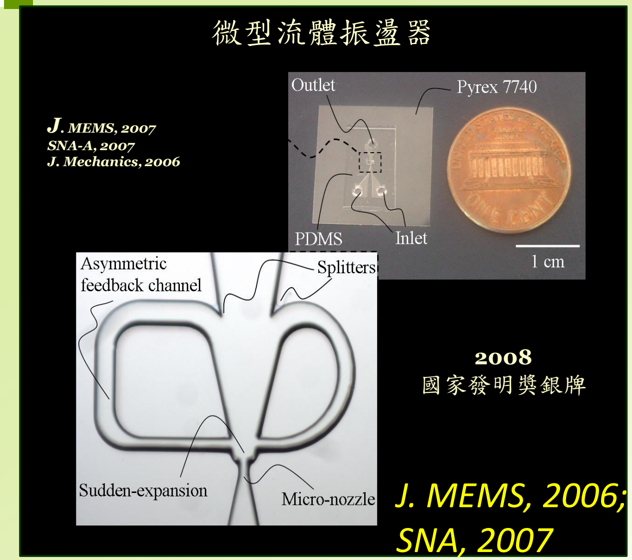


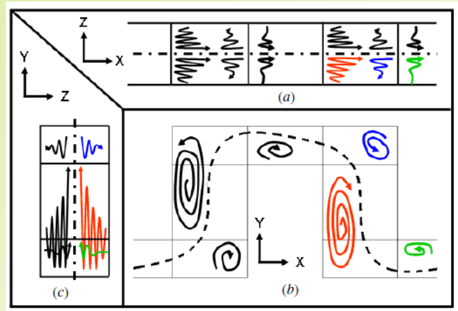



**binding**

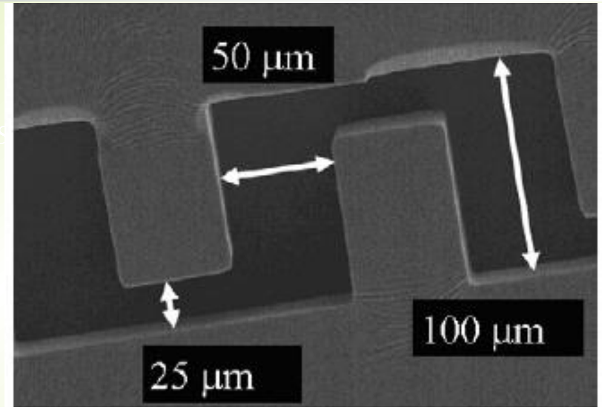


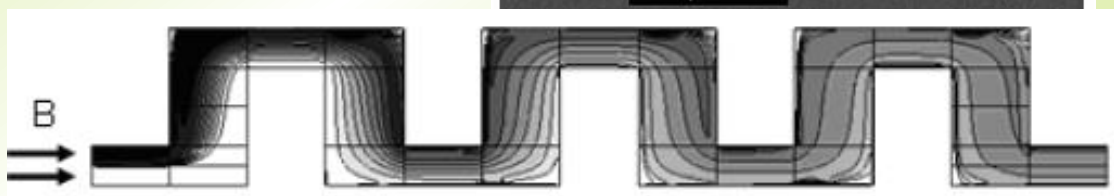
# **Various Micromixers** developed by Beam Lab.

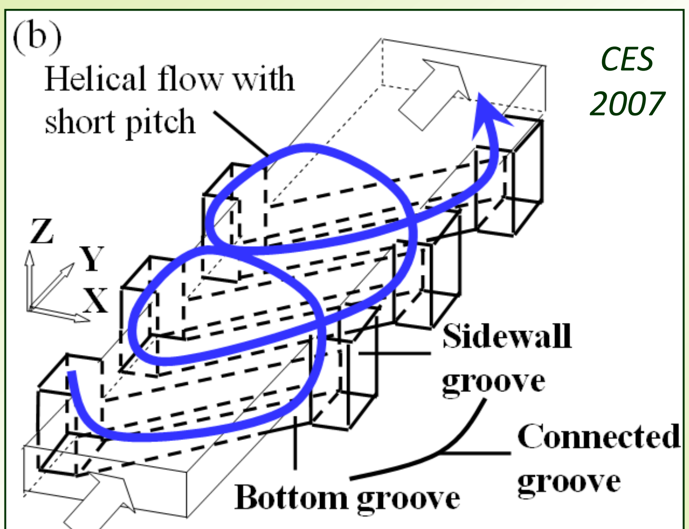


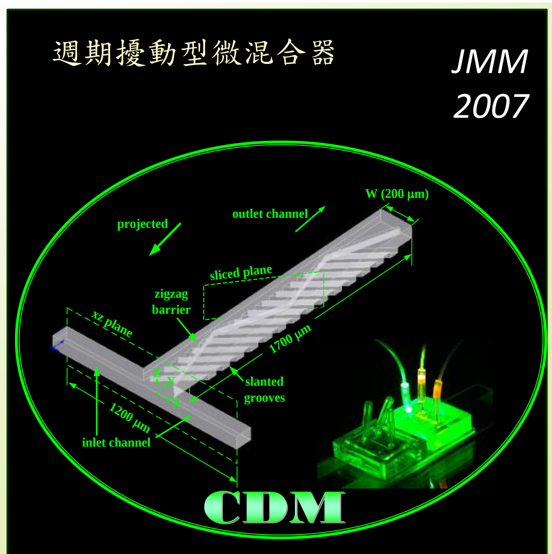

JMM, 2006; IJHMT, 2007

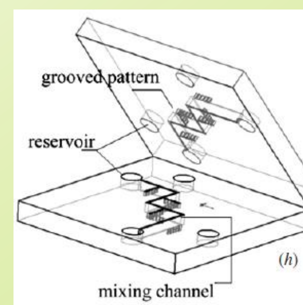


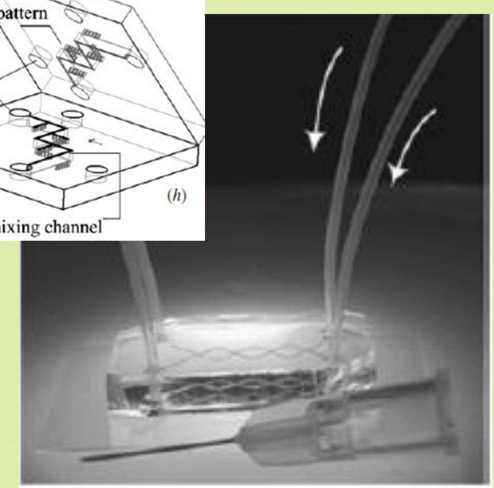




Connected-groove micromixer (CGM)

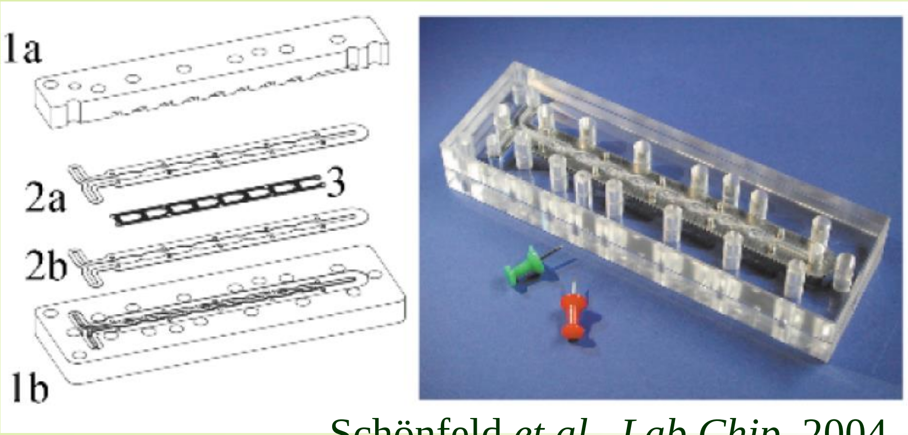


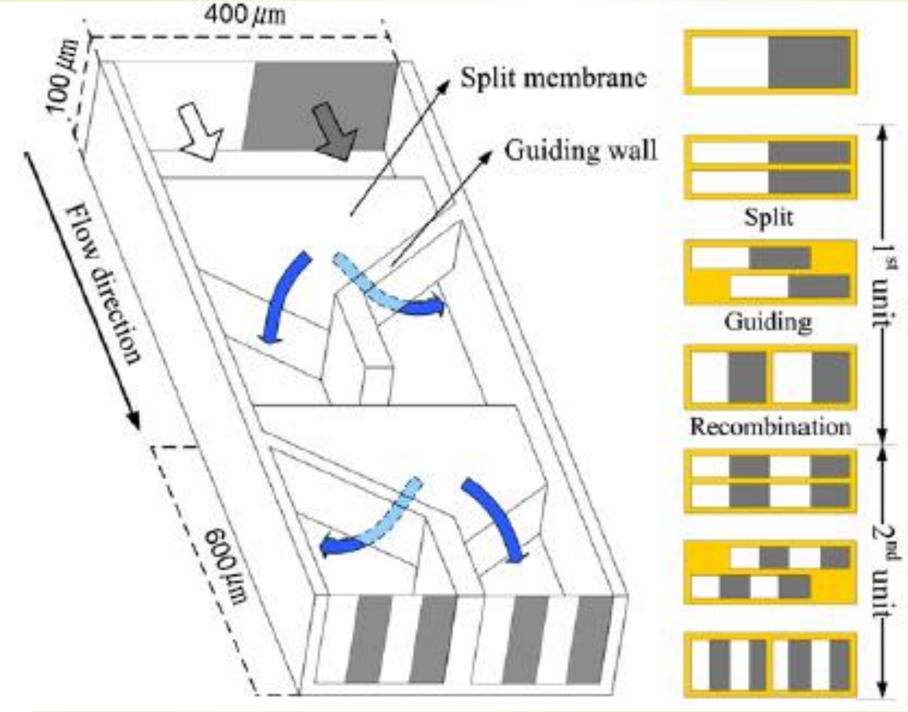



# **Micromixers** (Lamination micromixers)

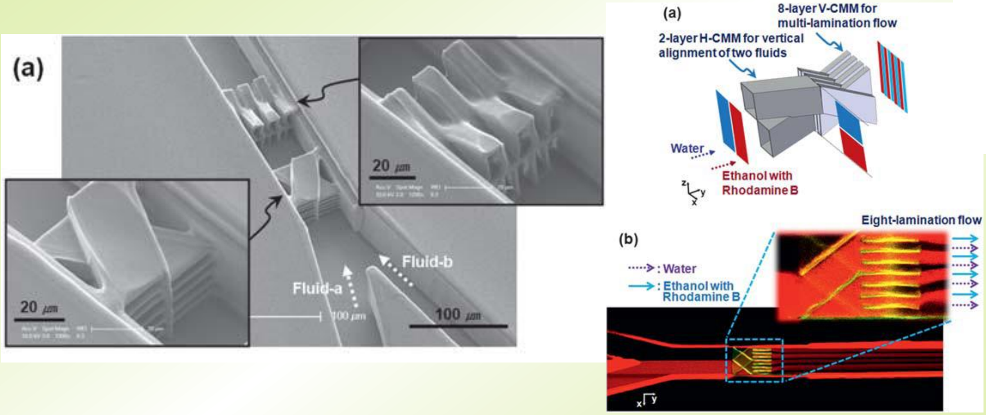
## Serial lamination- split & recombination (SAR)




Schönfeld *et al.*, *Lab Chip*, 2004




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




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

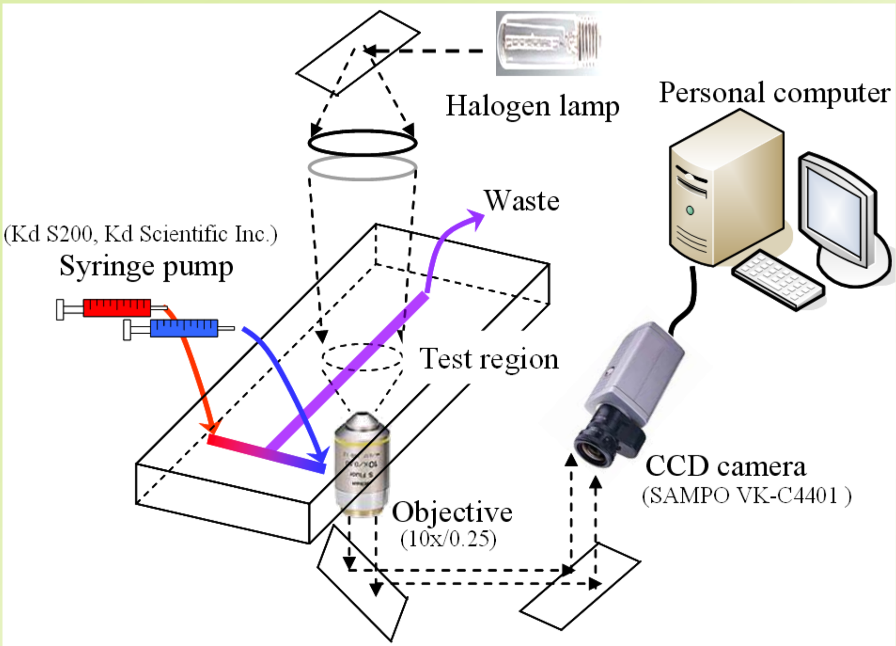
Intermediate layer

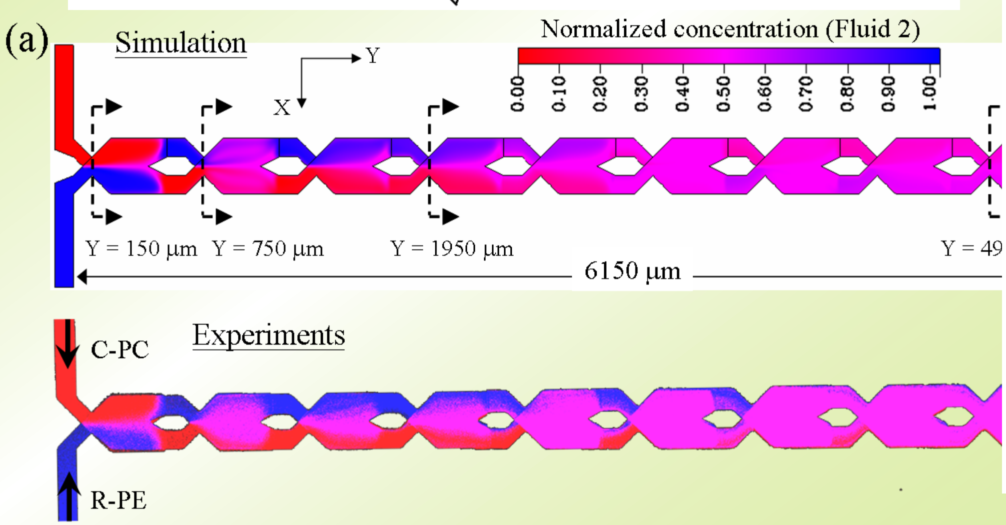
Separate channels

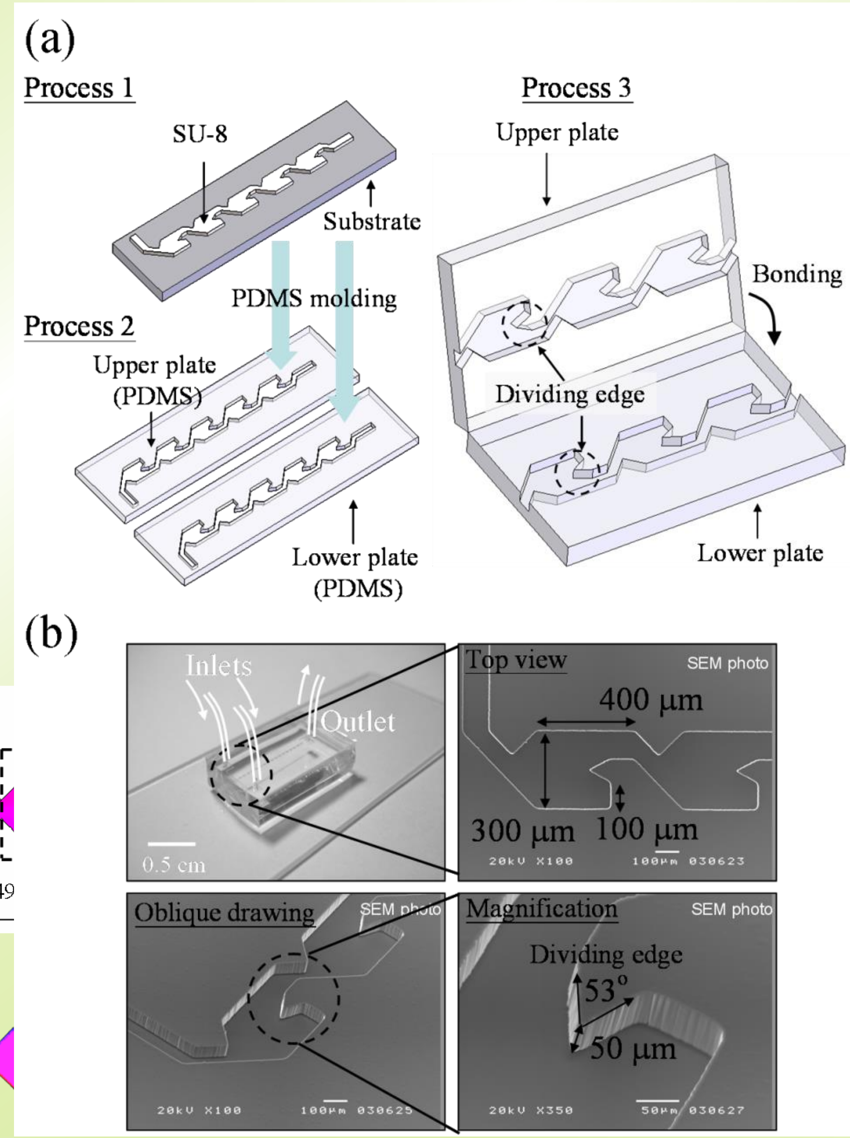
Confluent channels

# A Novel Microreactor with 3D Rotating Flow

方偉峰 楊鏡堂, 2009 — *Sensors and Actuators B- Chemical, 2009*

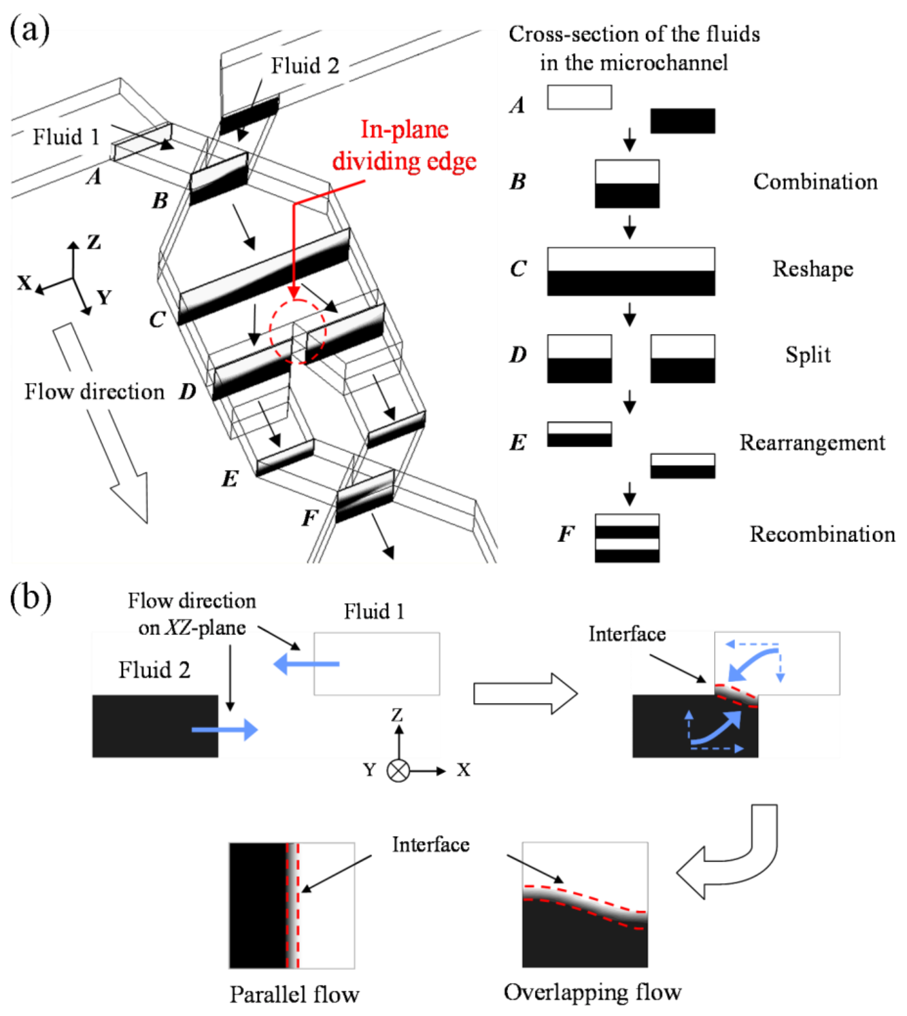


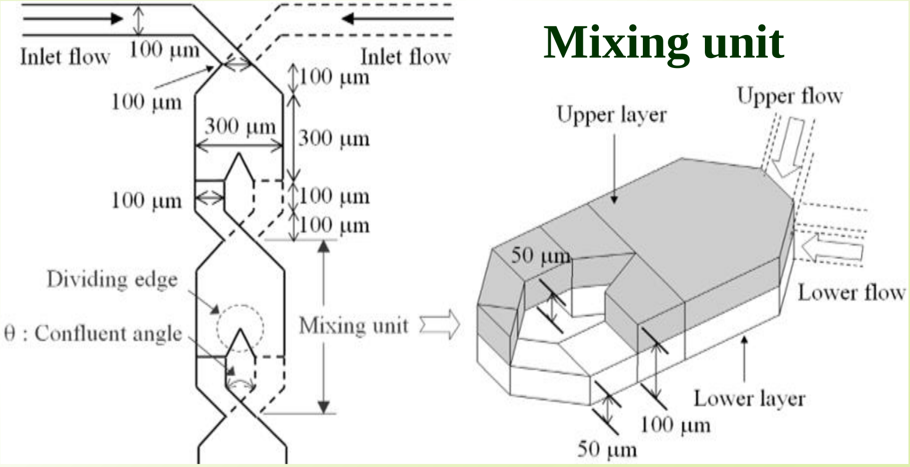



# **Micromixers-** SAR μ-reactor/μ-mixer

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




*SAR + Chaotic advection*

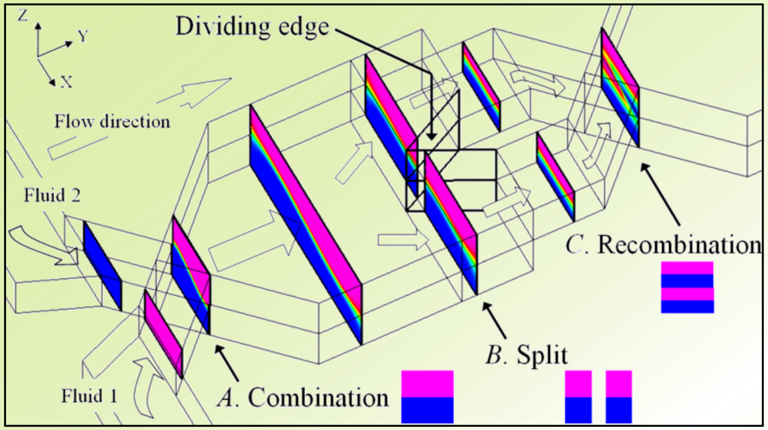
Strong transverse advection and stretching

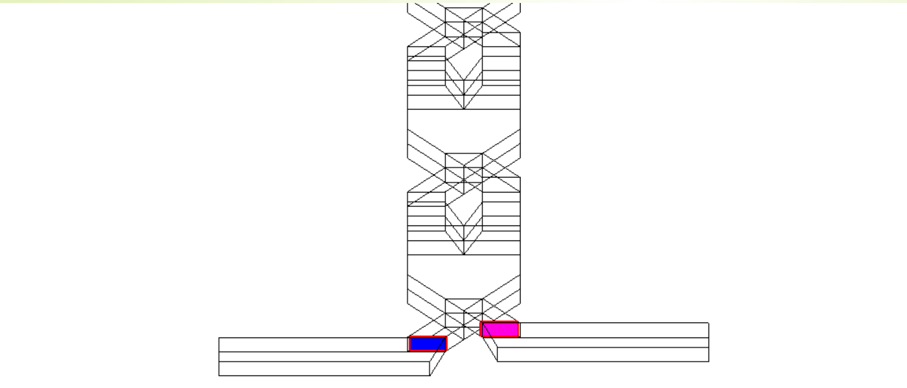
*Fang & Yang, Sensors & Actuators B: Chemical,* 2009

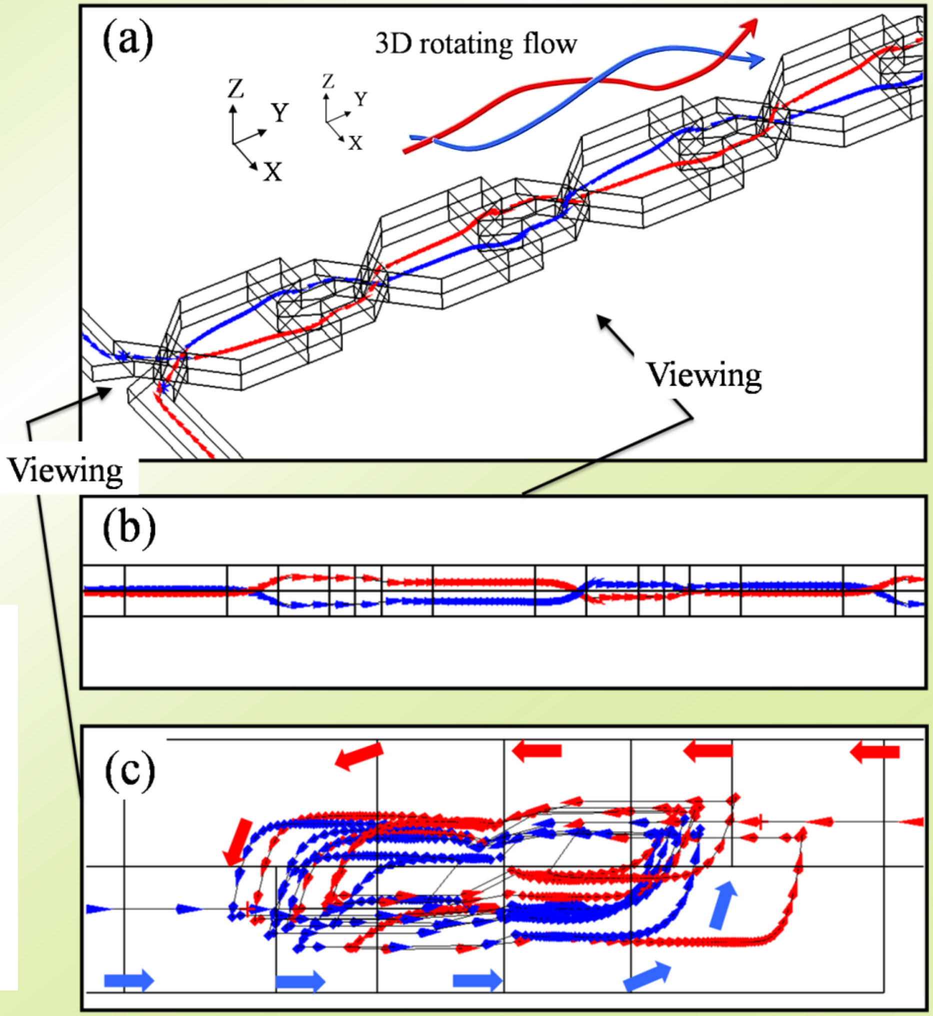
# Micromixers- SAR μ-reactor/μ-mixer

*Sensors & Actuators B: chemical*, 2009

## Flow field



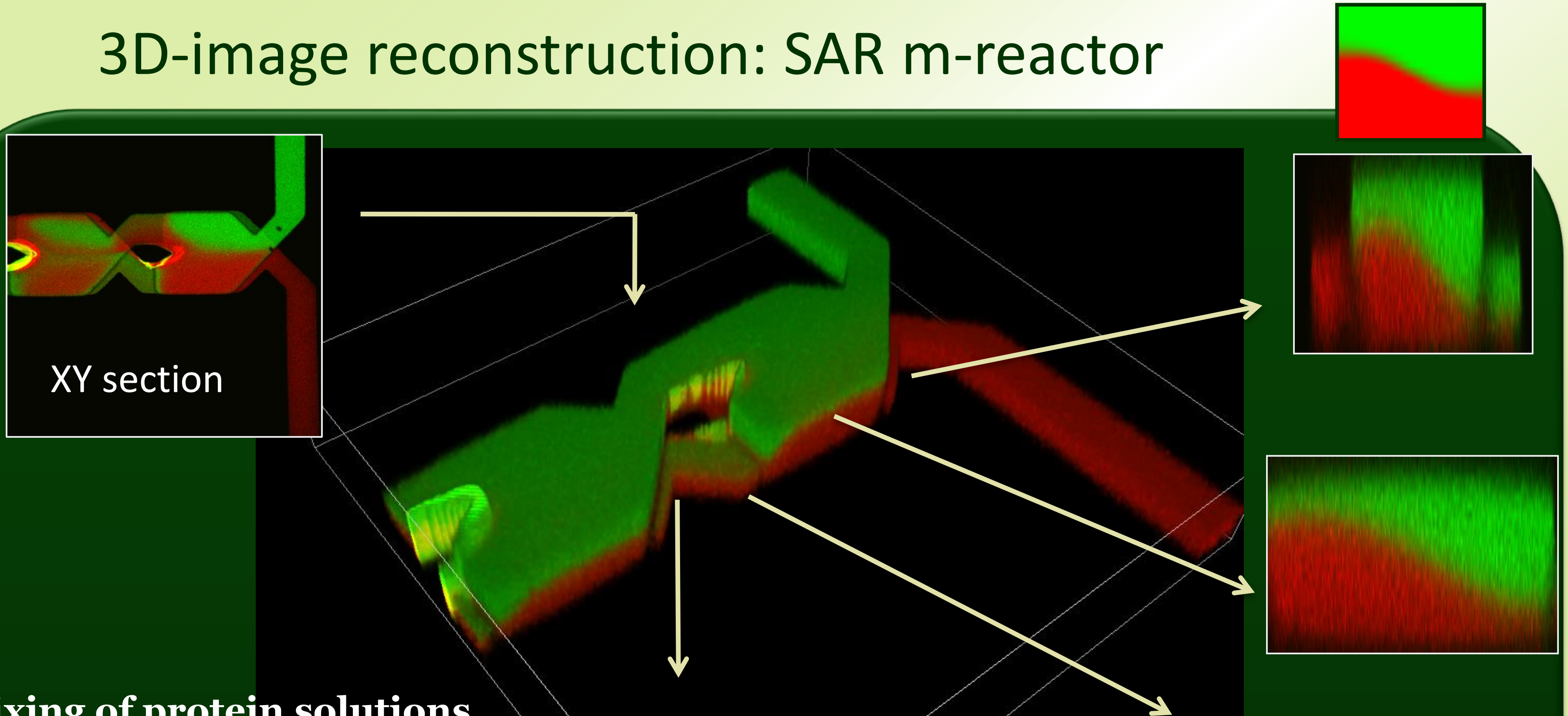





# Performance Test of a SAR μ-Reactor

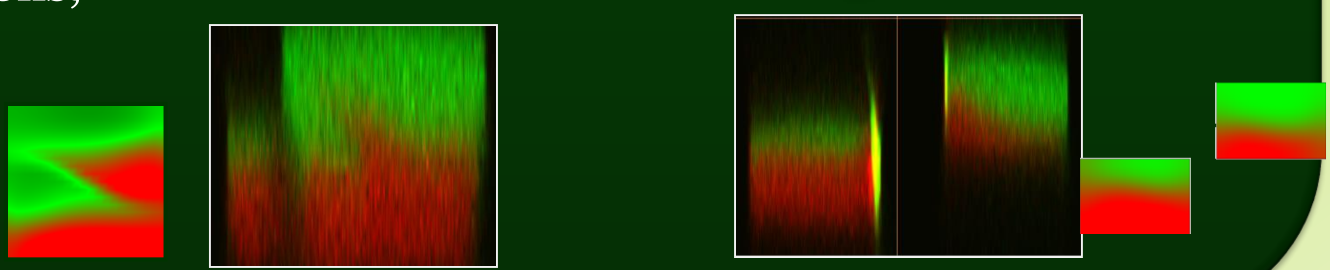
*Fang & Yang, Sensors and Actuactors B, 2009*

## 3D-image reconstruction: SAR m-reactor

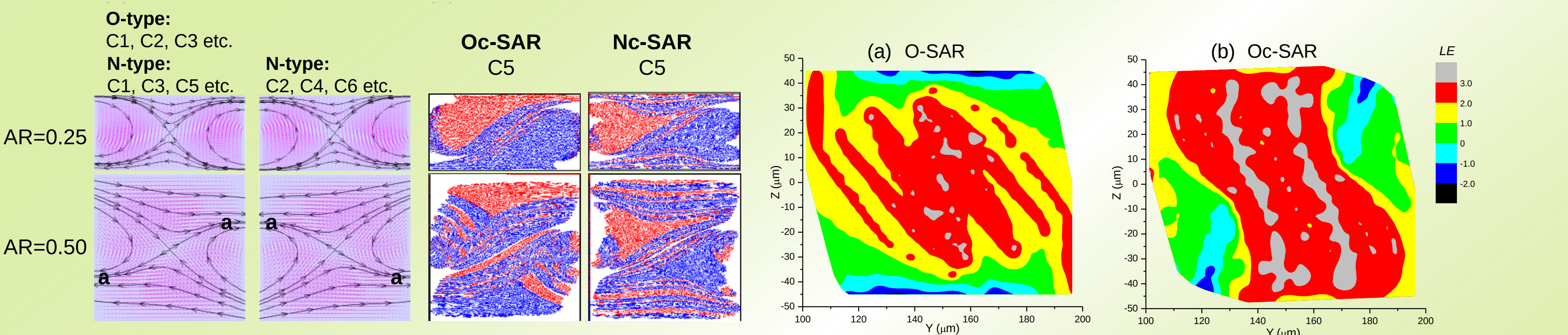


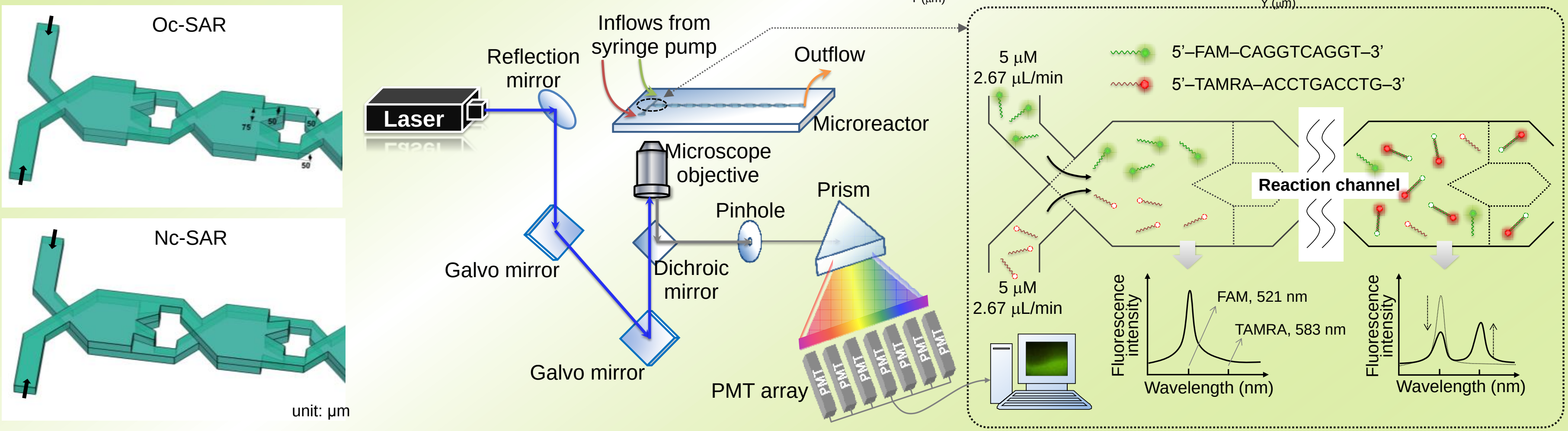

**Mixing of protein solutions, C-PC and R-PE, in a novel SAR μ-reactor**

***Con-focal microscopy***



# 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.

仿生與實驗室晶片導論- 2020

# Micro-reactors

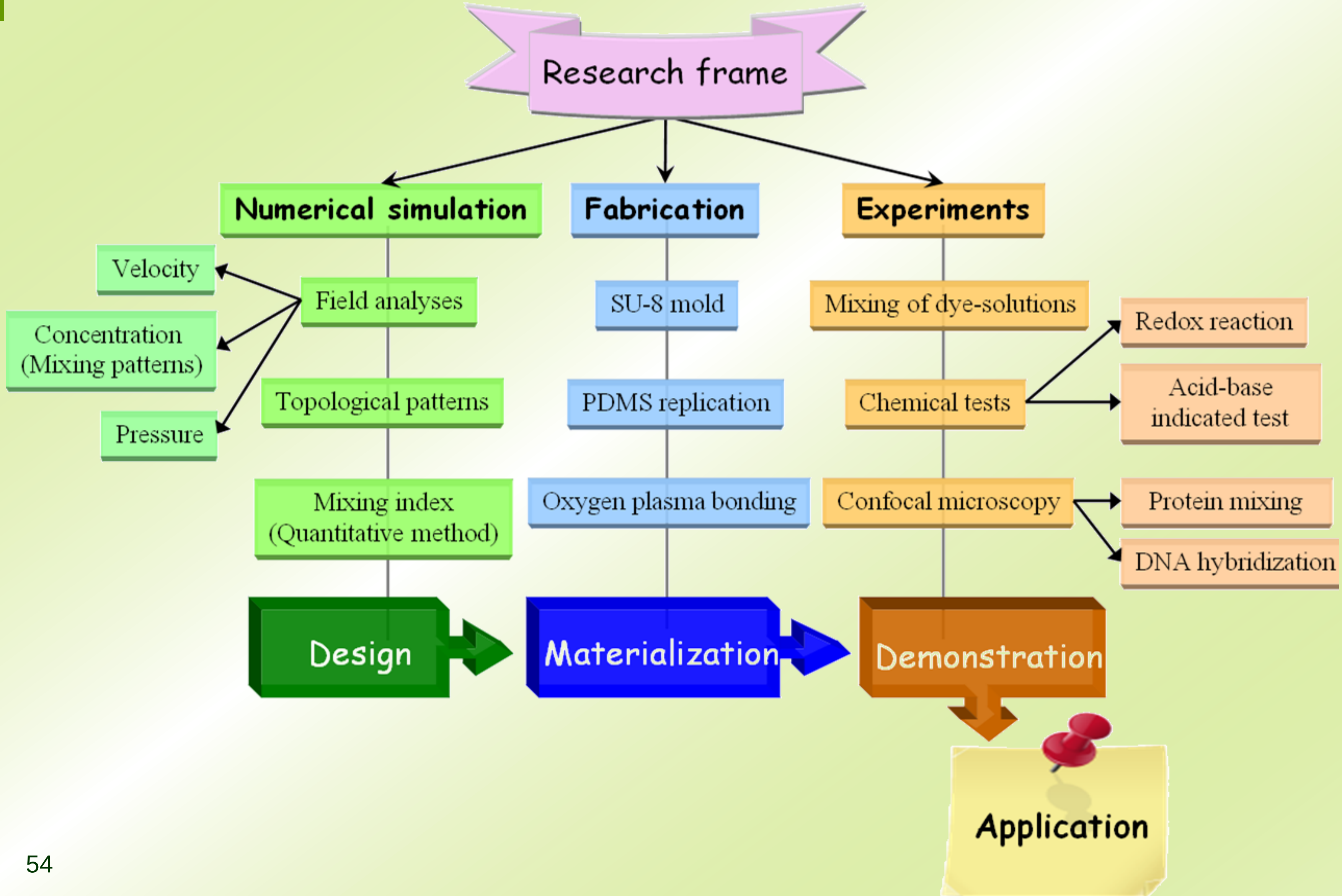
楊鏡堂 終身特聘教授

國立台灣大學 機械工程學系

中華民國 110 年 1 月 6 日

BEAM Lab

# Methodology

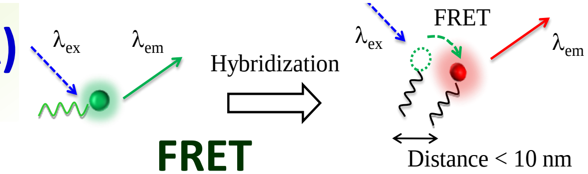


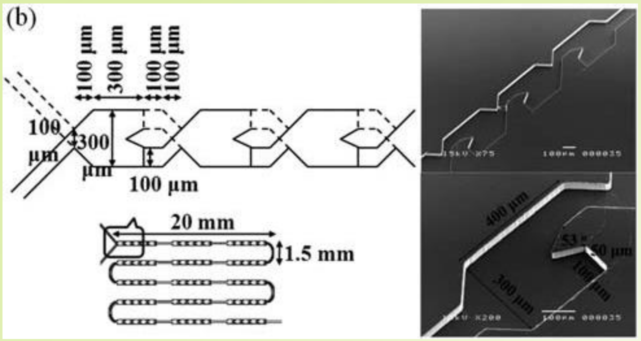
# Enhanced mobile hybridization of gold nanoparticles decorated with oligonucleotide in microchannel devices

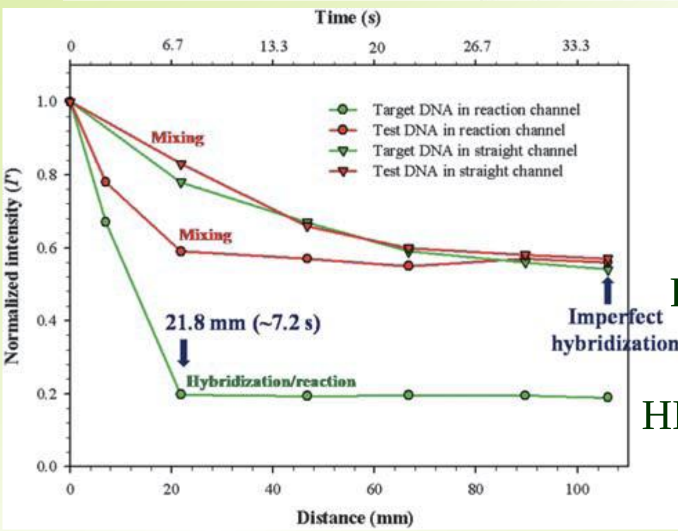
M. H. Hsu, W. F. Fang, Y. H. Lai, **J. T. Yang,*** T. L. Tsai, and D. B. Shieh

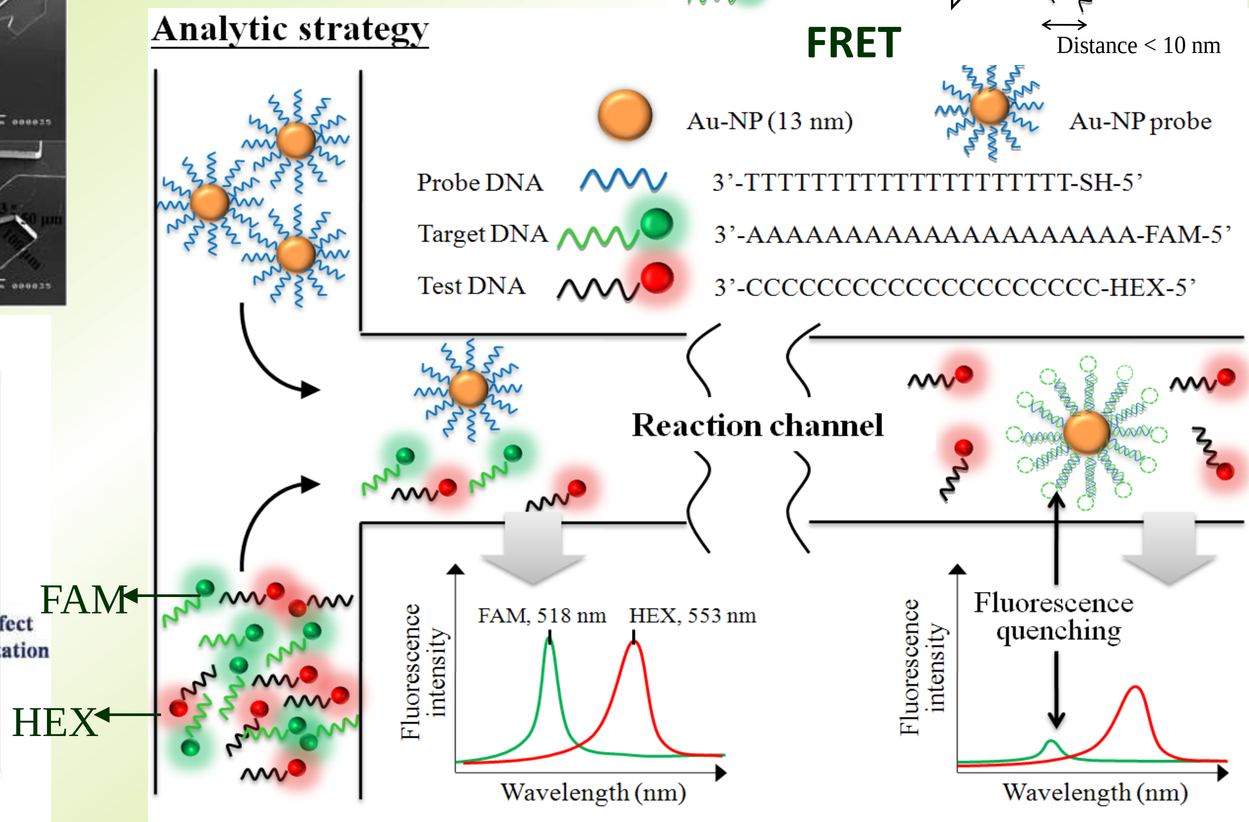
*Lab on a Chip*, Vol. 10, pp. 2583-2587, 2010

## FRET of two complementary oligonucleotides (short DNA)



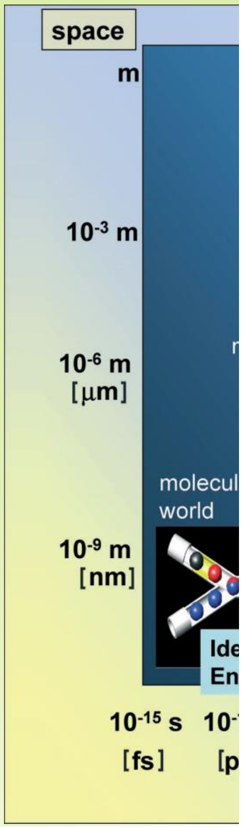



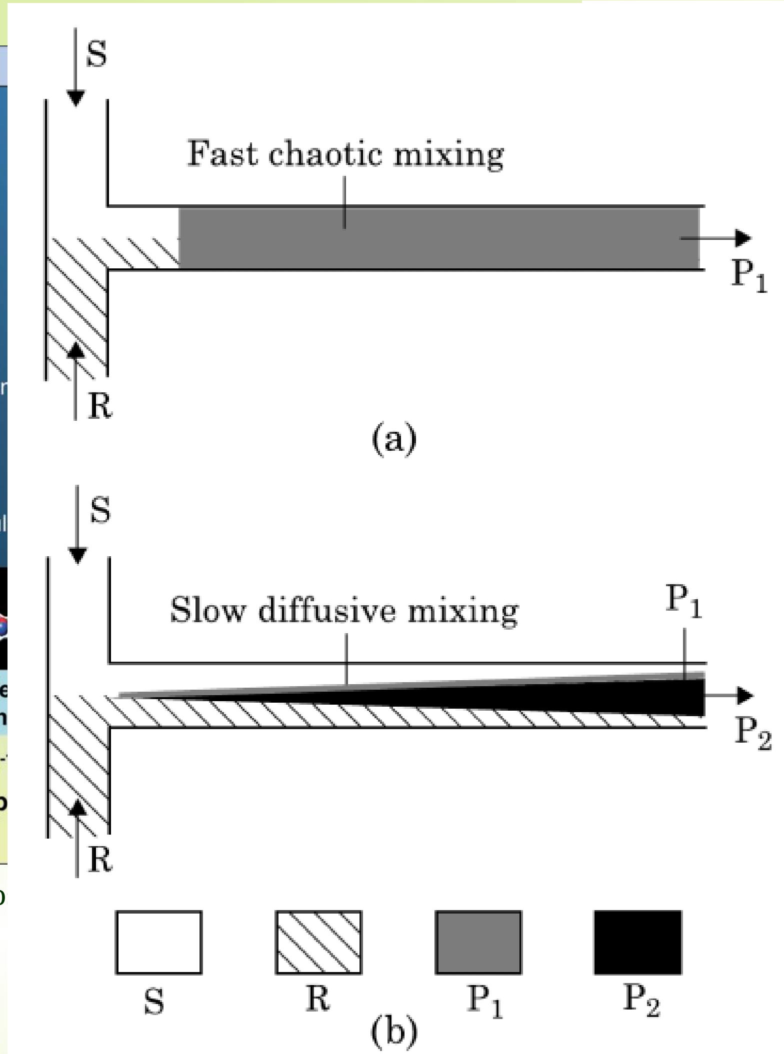



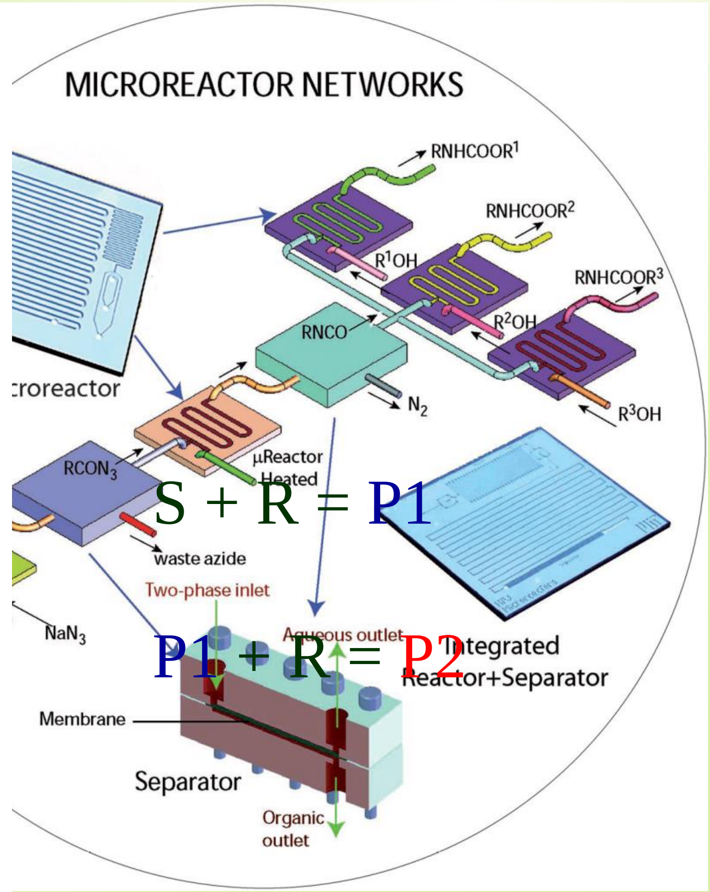

The effect of the structure in the microreactor enables the reaction to attain saturation in only 7.2 s, a duration much less than for traditional static hybridization (12-20 hours). In medical tests, one can diagnose the result in a flow channel in real time.

# Microreactors




Yo




S + R = P1

P1 + R = P2

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

# Microreactors (Oxidation reaction)

## Swern-Moffatt oxidation of cyclohexanol in microreactors

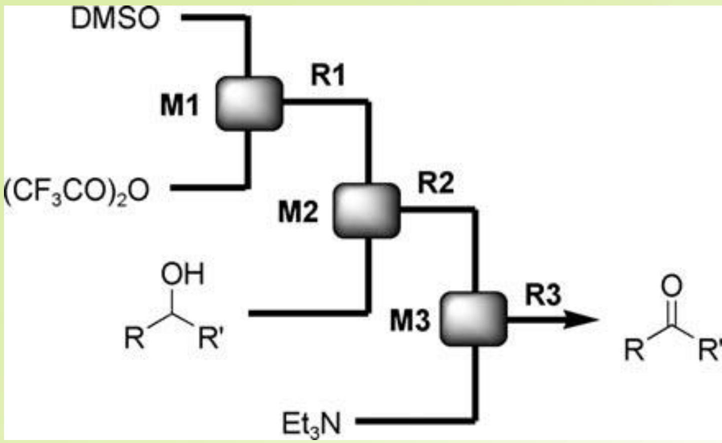
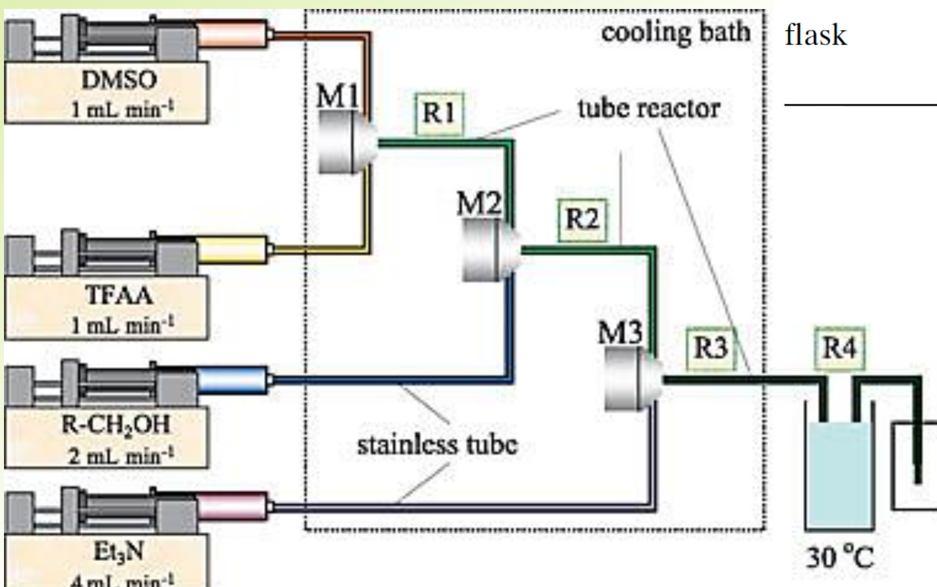



Table 1. Swern-Moffatt oxidation of cyclohexanol using a microreactor and a flask.

| 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 |

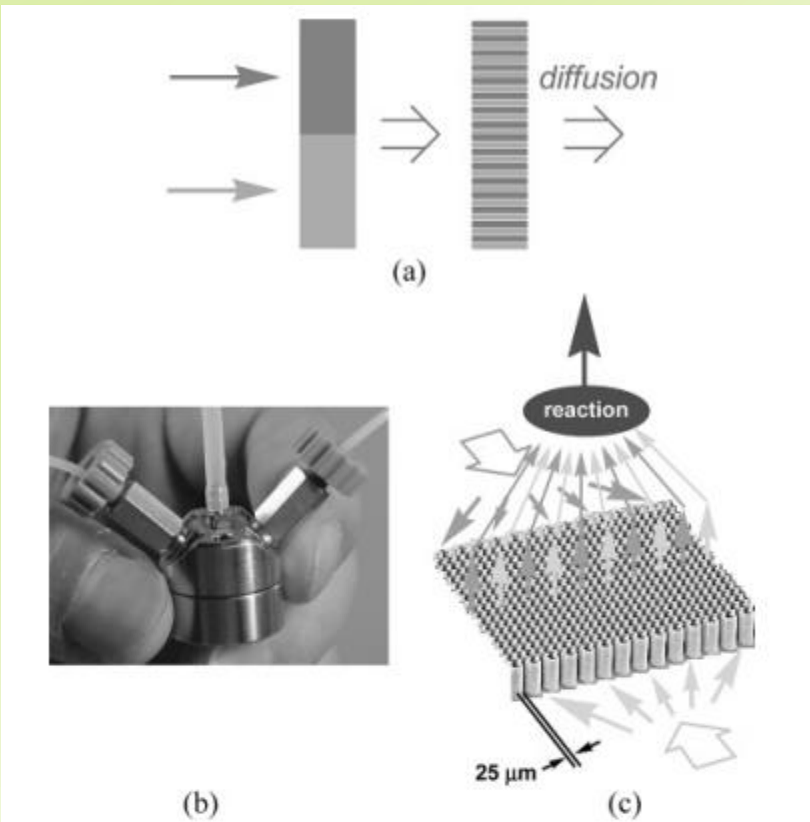


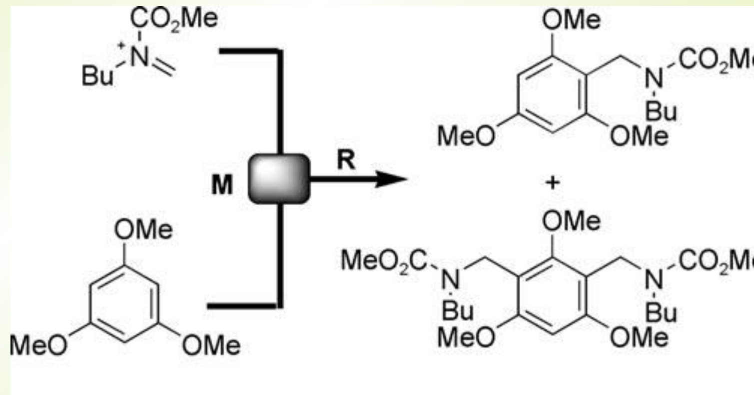

Hazard, explosible !!

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

# Microreactors (Competitive Consecutive Reactions)

Friedel–Crafts reaction of cyclohexanol in microreactors

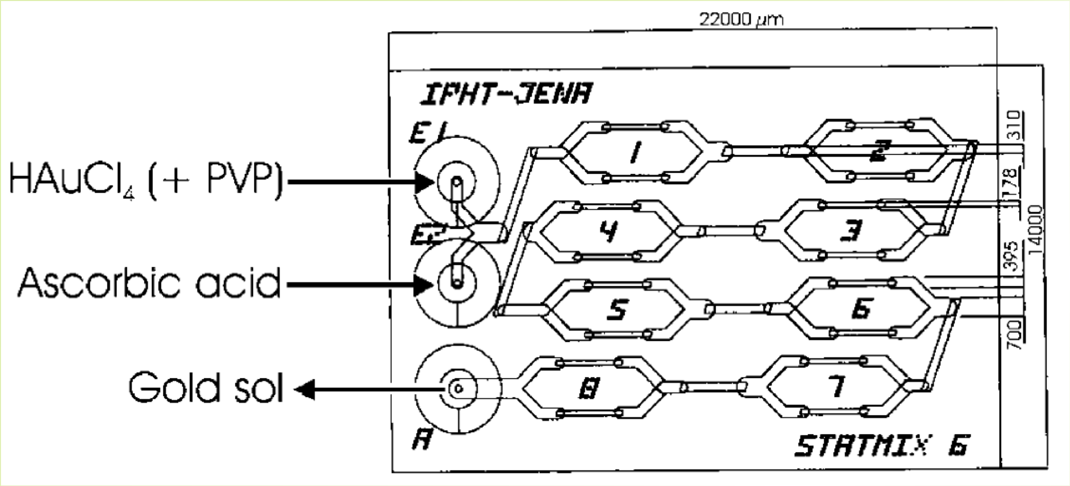


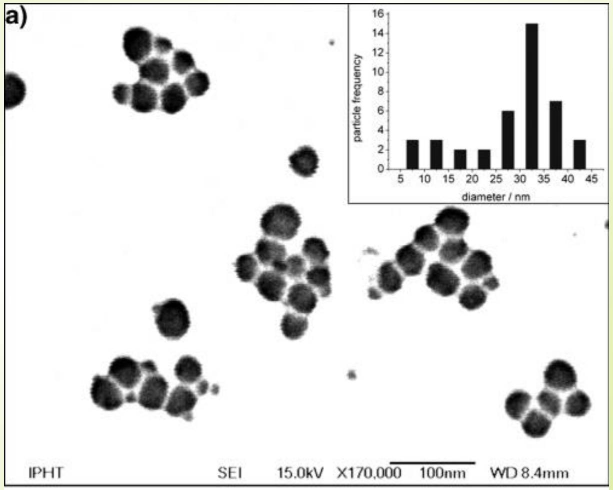




| | monoalkylation product | dialkylation product |
|---|---|---|
| microreactor | 92% | 4% |
| flask | 37% | 32% |

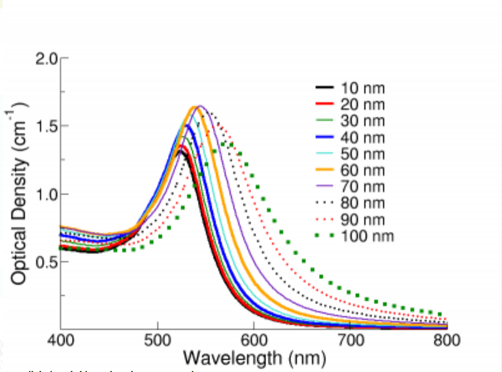
Nagak *et al.*, *JACS*, 2005

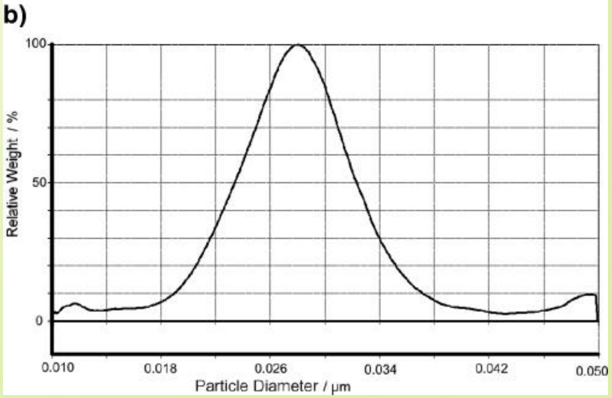
# Microreactors (Synthesis of gold nanoparticles)







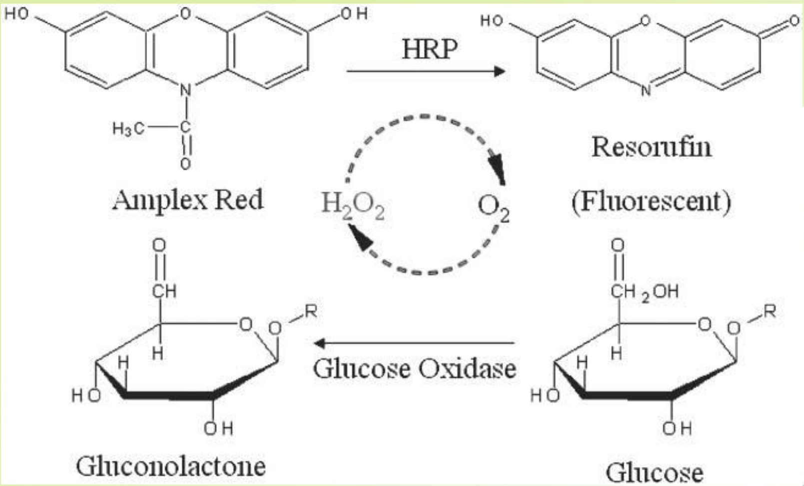



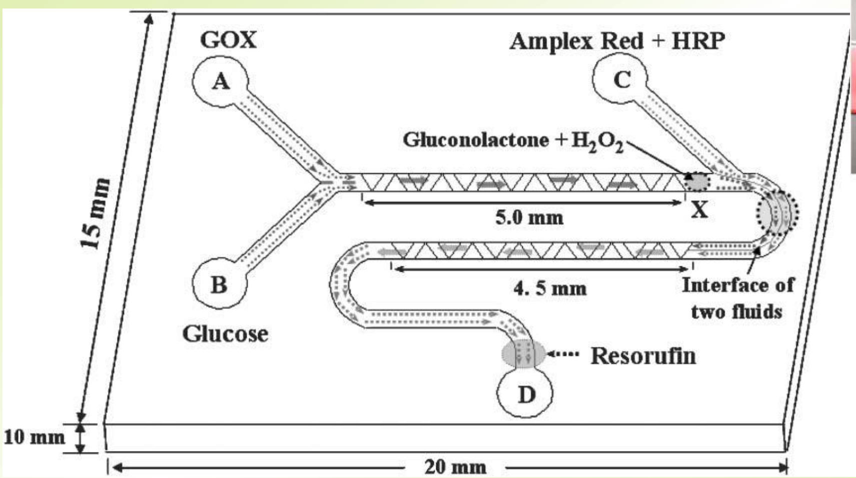

http://www.nanocomposix.com/kb/gold/optical-properties

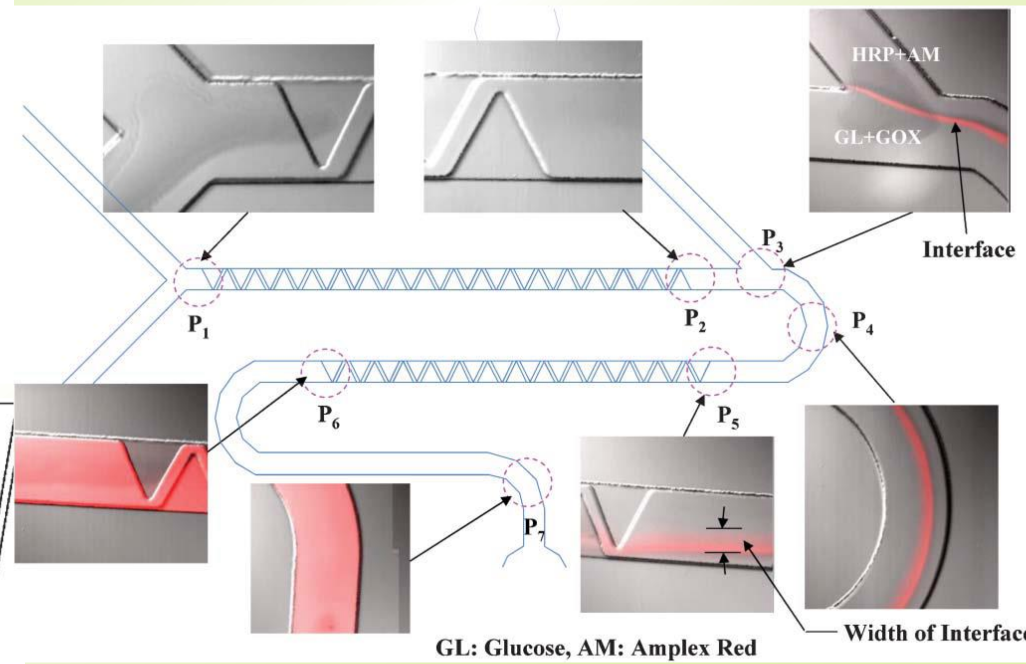
http://www.malvern.com/LabEng/industry/nanotechnology/gold_silver_nanoparticles.htm

Wagner and Köhler, *Nano Lett*, 2005

# **Microreactors** (Glucose-catalyst reactions)



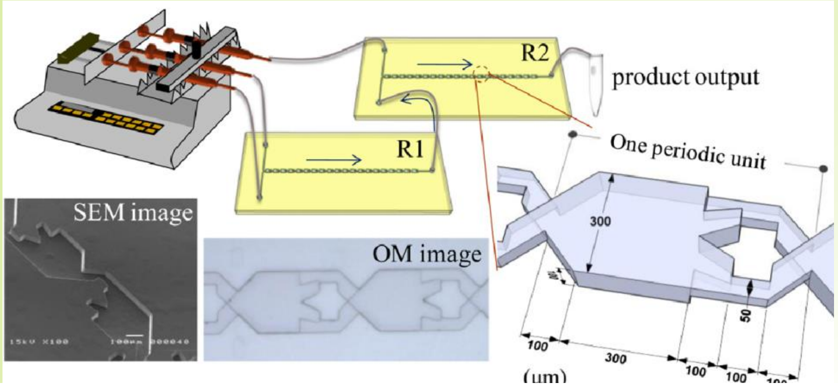



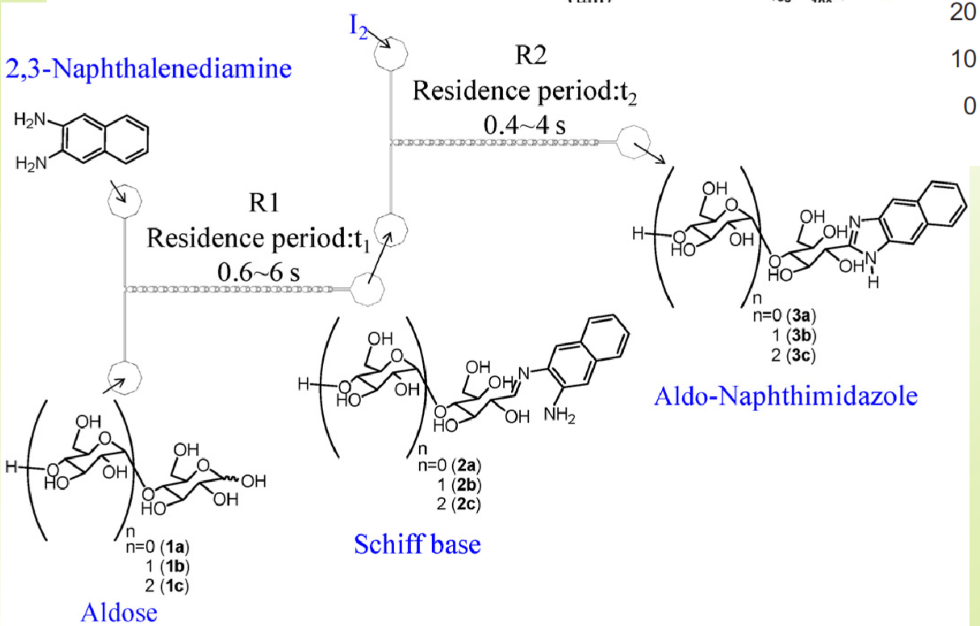

Kim *et al.*, *Analyst*, 2005

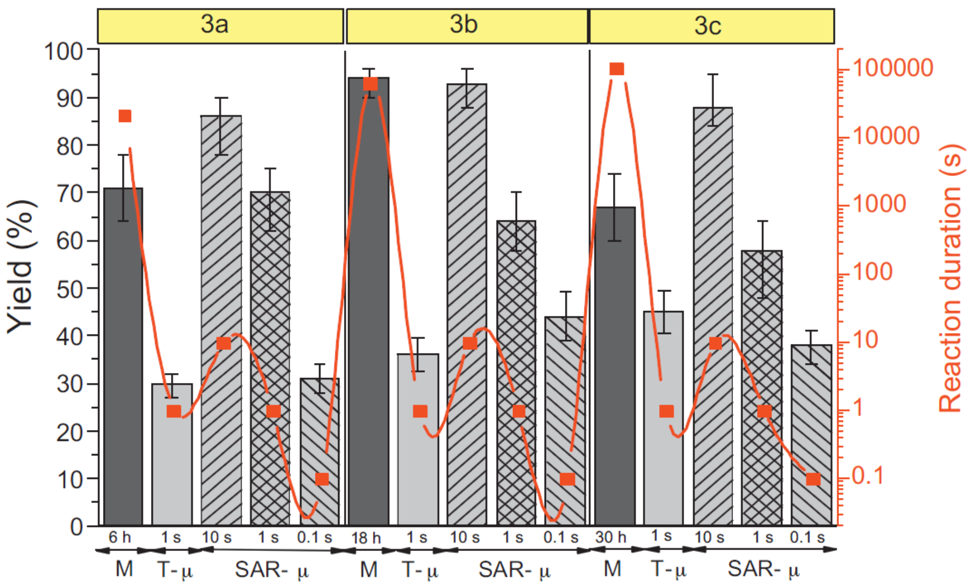
# **Microreactors** (Flash synthesis of carbohydrate derivatives)

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 :

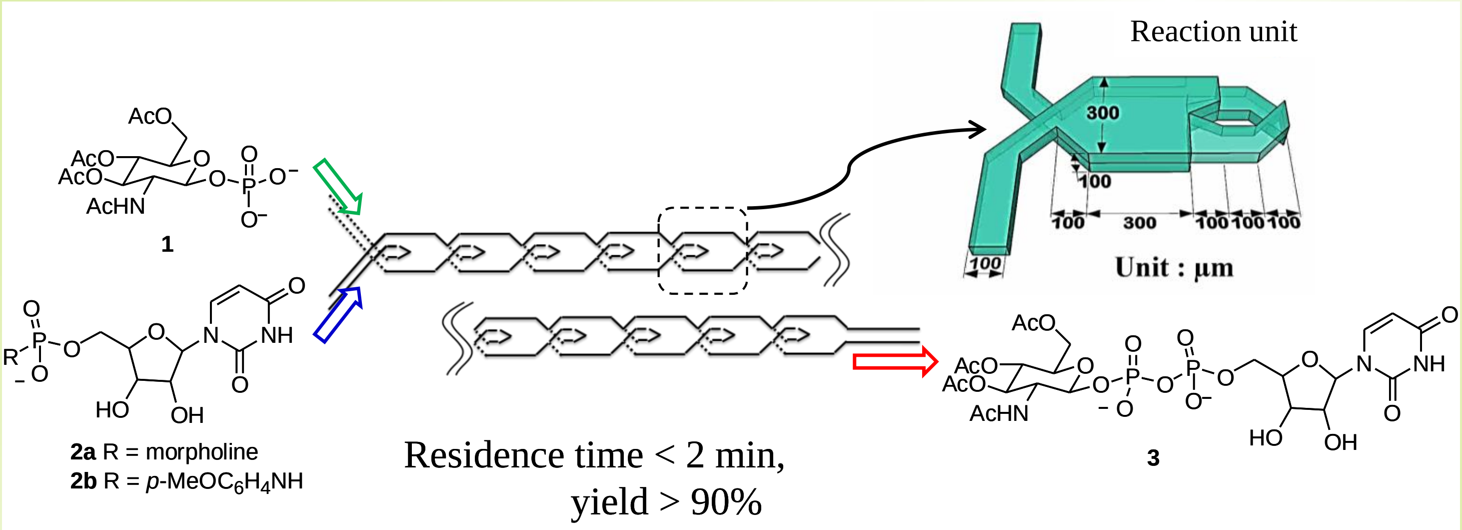
0.1 ~ 10 s

Temp. RT

# Microreactors (Microflow Synthesis of Saccharide Nucleoside Diphosphate)

*Chemical Engineering Journal (CEJ), 2012*

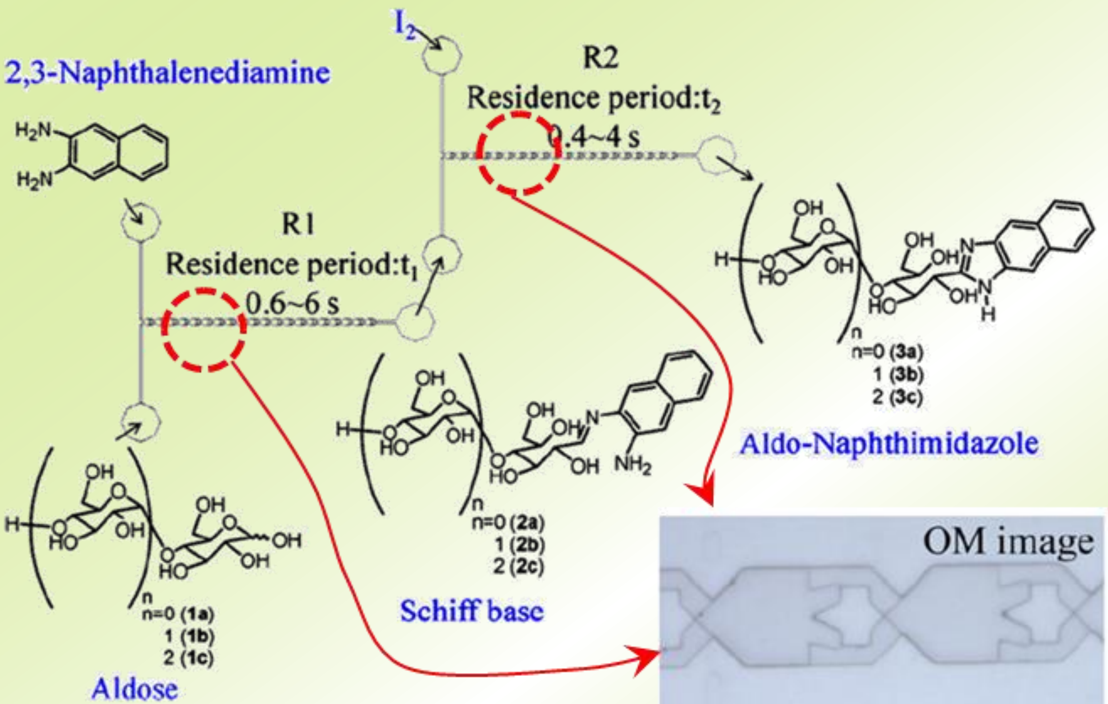
## Applications of SAR μ-reactor



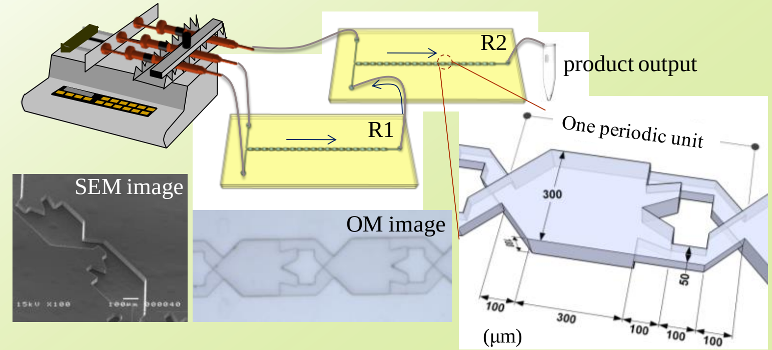

- With our microreactor technology, the enhanced reactivity of reagents is phenomenal.
- 85% conversion and 94% yield of cross-coupling reactions were achieved in tens of seconds.
- The duration of the reactions was diminished $>10^5$ fold.

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

*Chemical Engineering Journal*, 2011



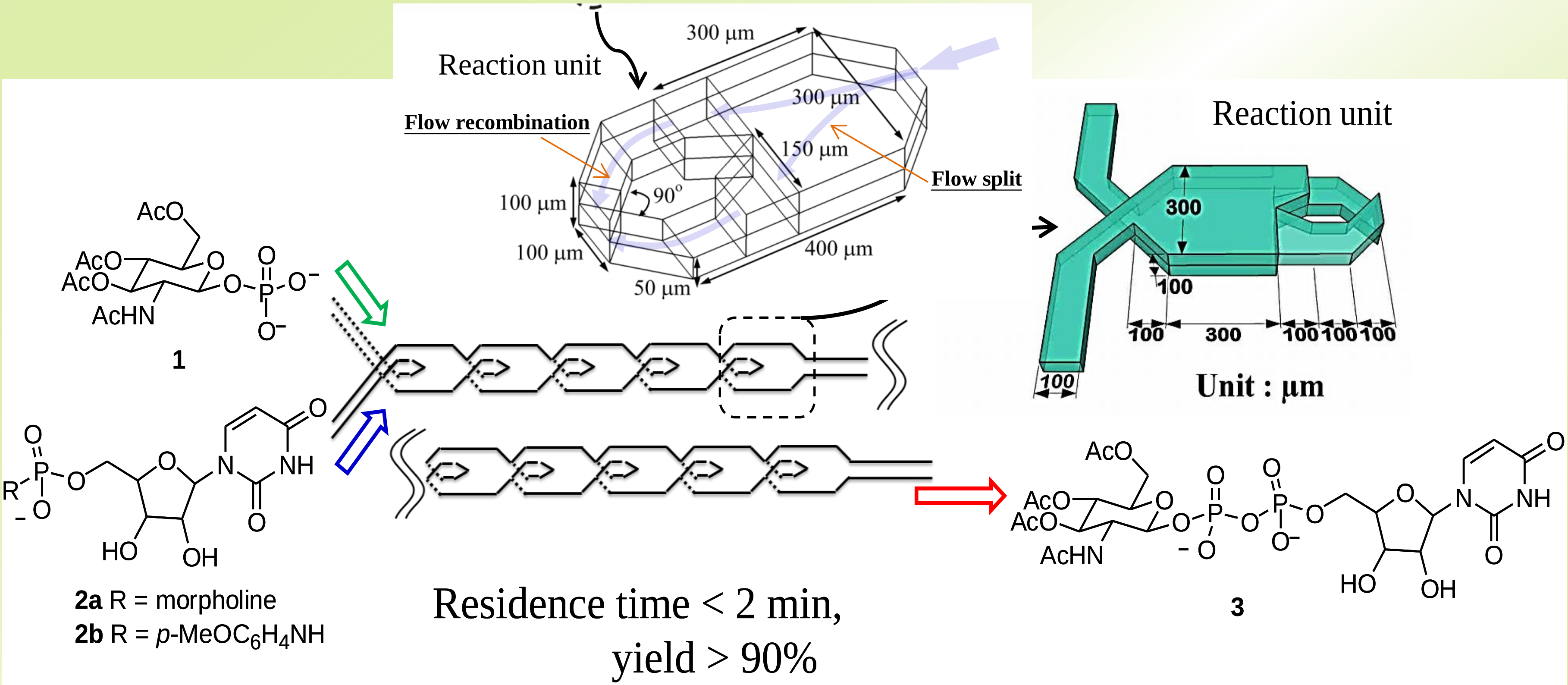

**The SAR-microreactor required just seconds (0.1 to 10 s), which was about $10^{-3}$~$10^{-6}$ the duration for the macro flask.**




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

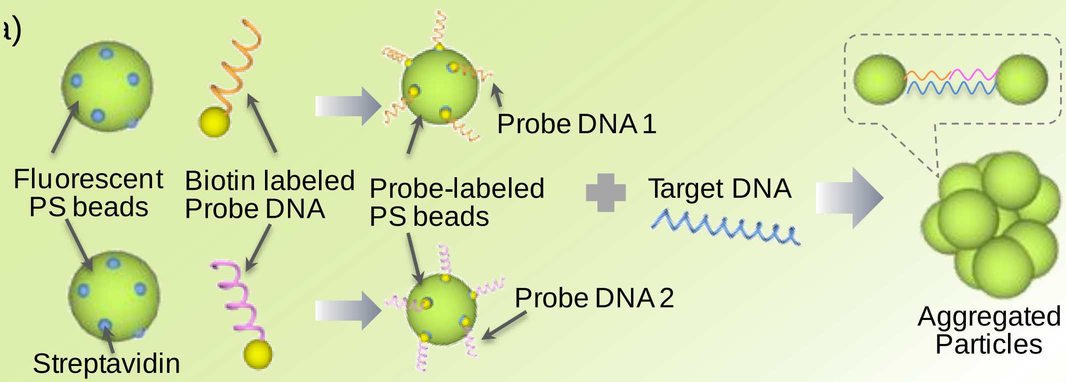



With this microreactor possessing the SAR mechanism that dramatically enlarges the material interface to promote the fluidic mixing, 85 % conversion of a cross-coupling reaction (GlcNAc monophosphate reacting with UMP-morpholidate) to the diphosphate (acetylated UDP-GlcNAc) was achieved in 10 s, which 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.**

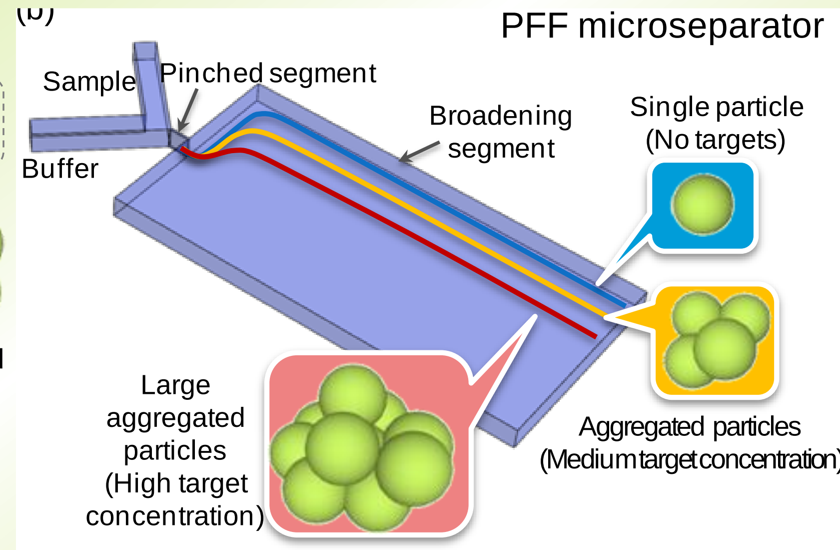
# DNA diagnosis in a micro-separator based on particle aggregation

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***

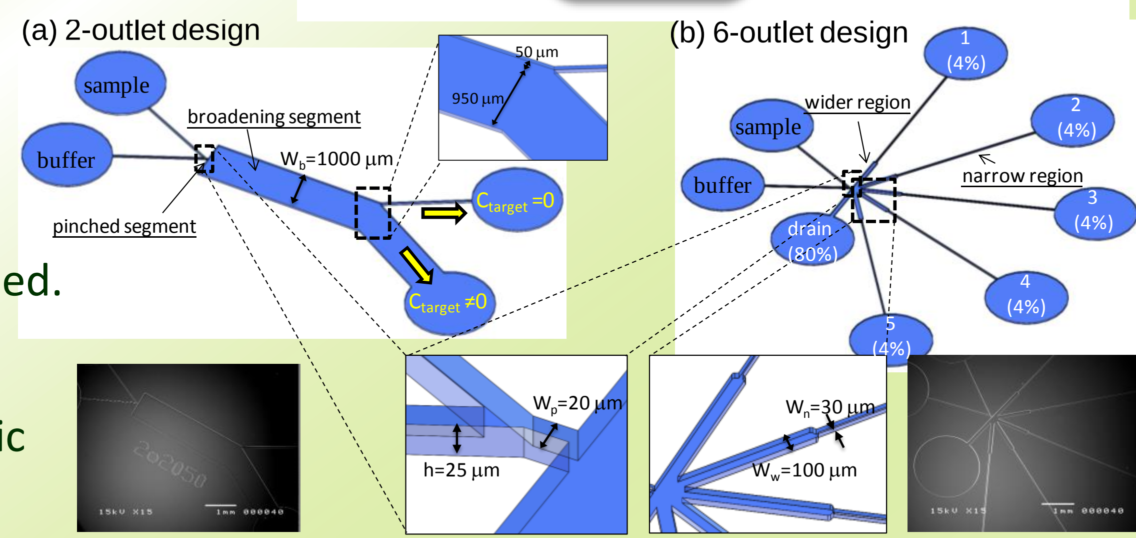
*Biosensors and Bioelectronics*, Vol. 50, pp. 8-13, 2013




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'



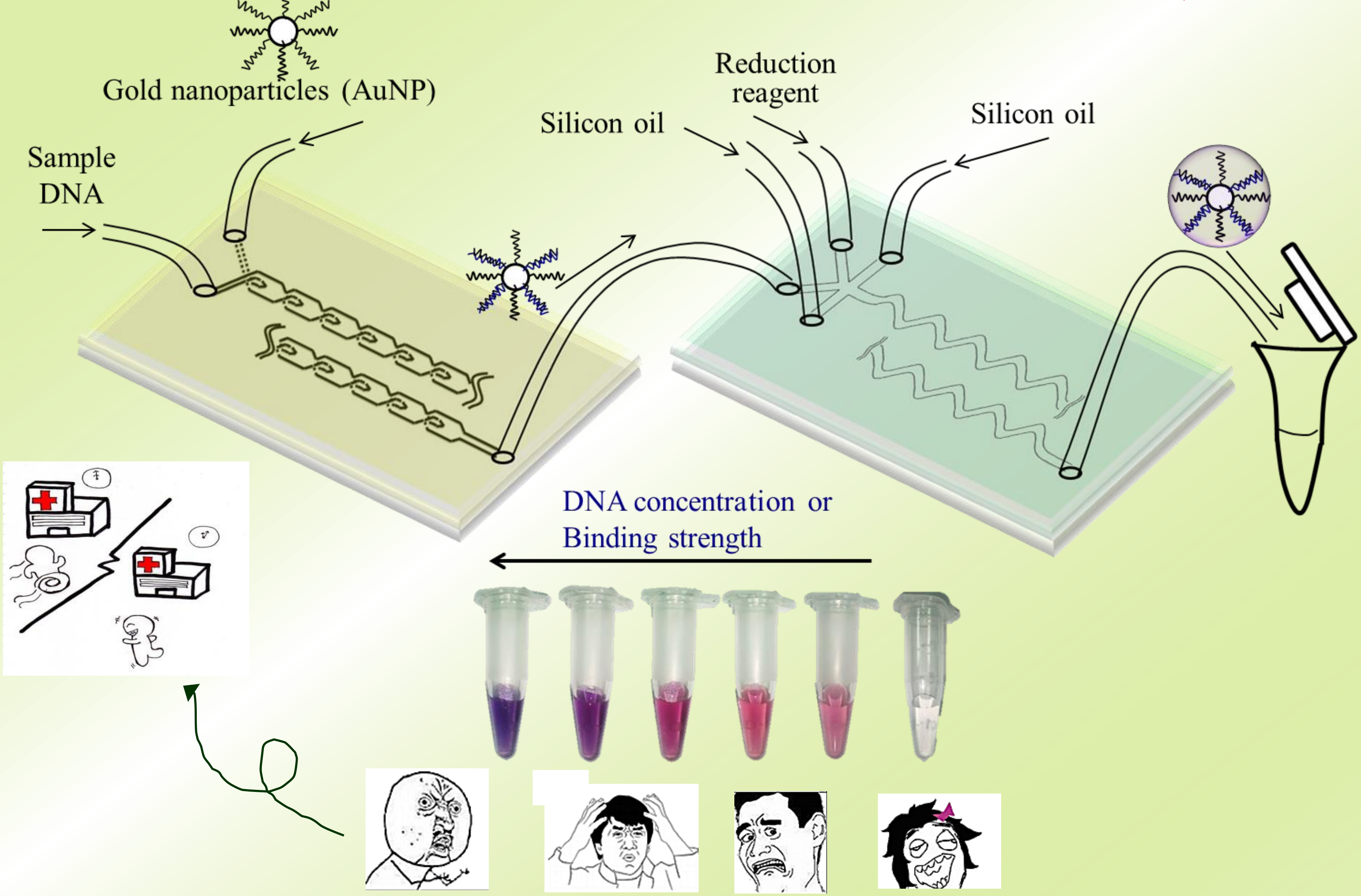

A novel aggregation-based method to execute oligonucleotide detection in a PFF (pinched flow fractionation) microseparator is proposed & developed. The label-free target DNA hybridizes with the probe DNA on the surface of microspheres and causes the polymeric aggregate, thus enlarging the average size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




*One of the most downloaded articles (Oct. 2013)*

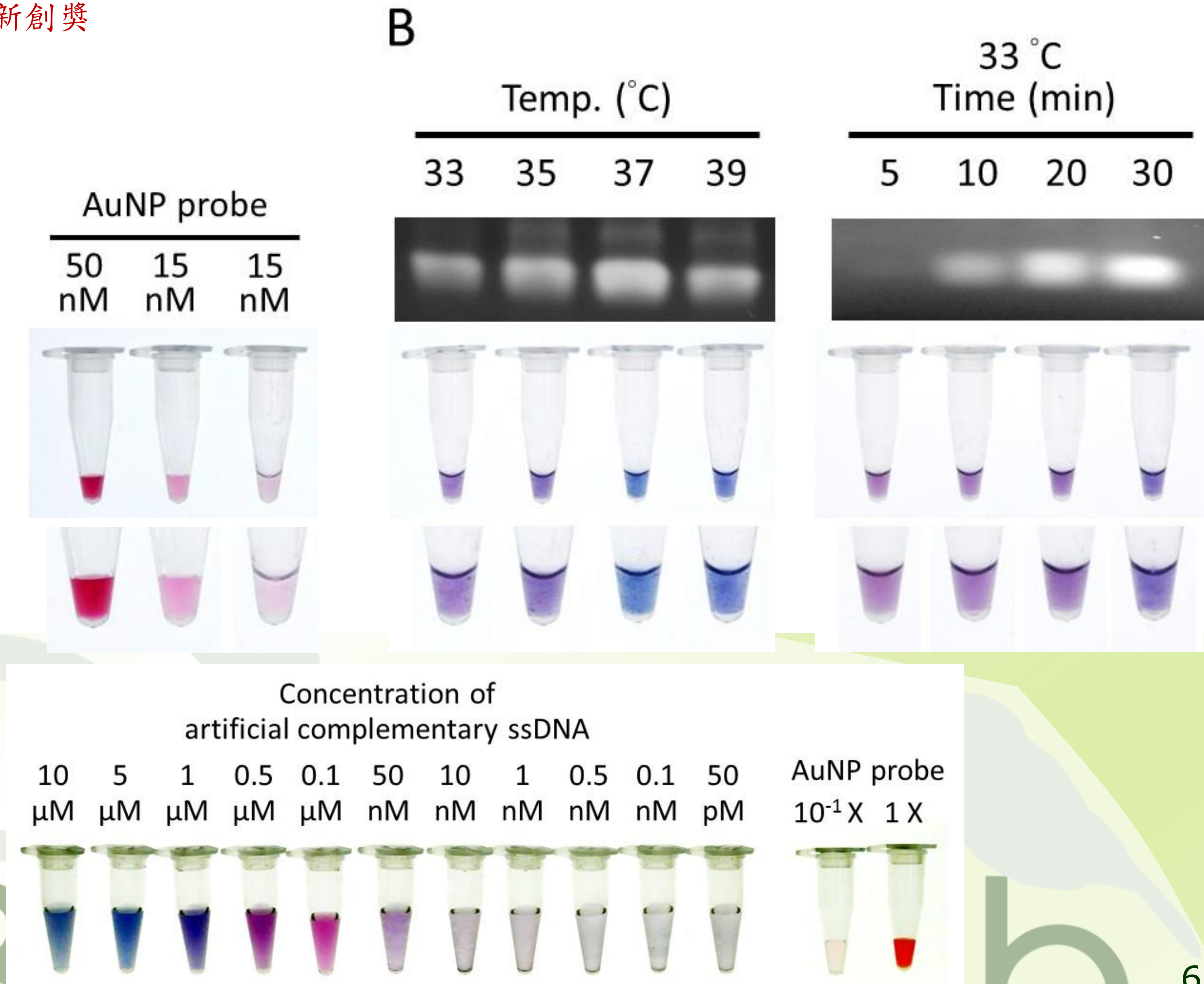
# Next-generation microfluidic system for rapid DNA screening

第11屆國家新創獎



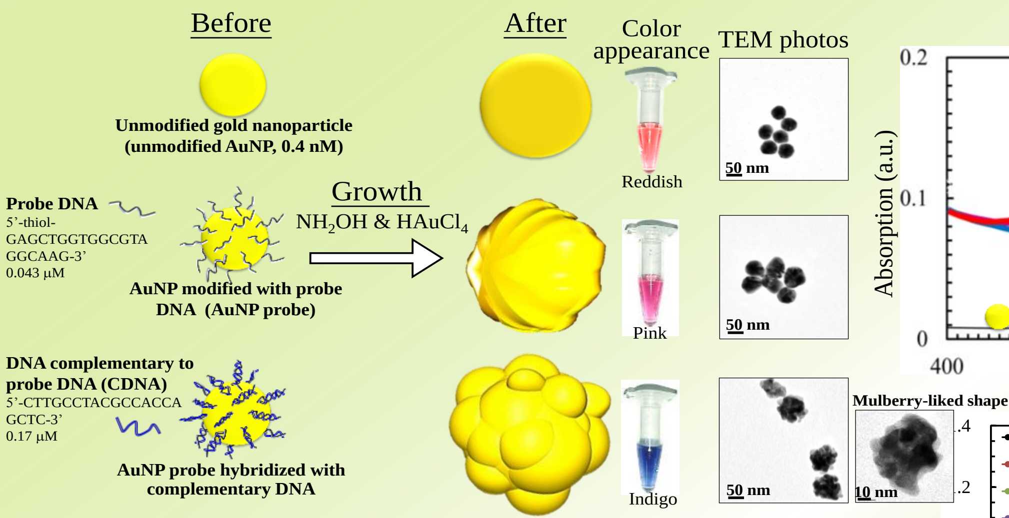
# 植物病害之可視化分子診斷- 以番茄黃化捲葉病毒病為例

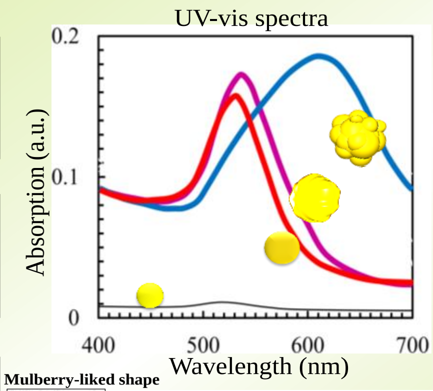
第15屆國家新創獎

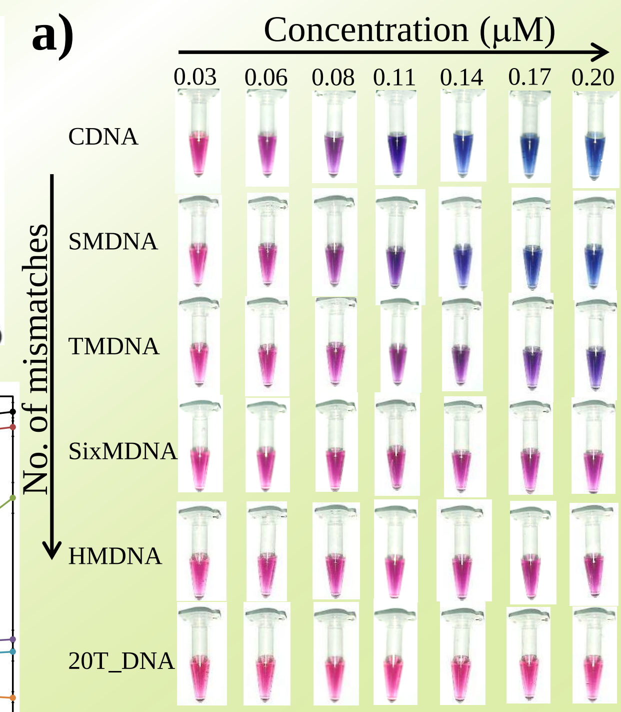


# Hybridization-mediated growth of gold nanoparticle probes for visual and spectrophotometric screening of DNA mismatch

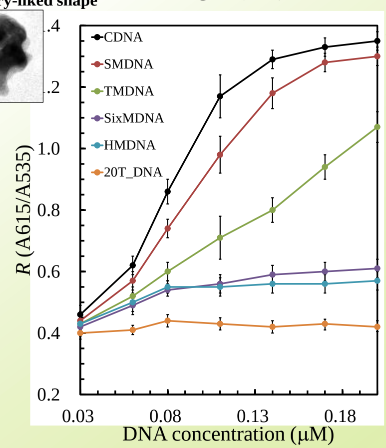
W. F. Fang, W. J. Chen, and **J. T. Yang**,* *Sensors and Actuators B- Chemical, 2013*



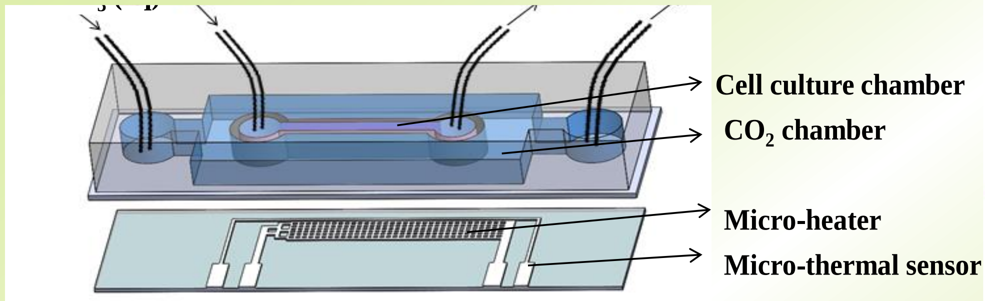

| | Sequence (20 mer) |
|---|---|
| Probe DNA | 5'-thiol-GAGCTGGTGGCGTAGGCAAG-3' |
| CDNA | 5'-CTTGCCTACGCCACCAGCTC-3' |
| SMDNA | 5'-CTTGCCTACTCCACCAGCTC-3' |
| TMDNA | 5'-CTTGCCTACTTTACCAGCTC-3' |
| SixMDNA | 5'-CTTGCCTTTTTTTCCAGCTC-3' |
| HMDNA | 5'-CTTGCGGTTT TTTGGAGCTC-3' |
| 20T_DNA | 5'-TTTTTTTTTTTTTTTTTTTT-3'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



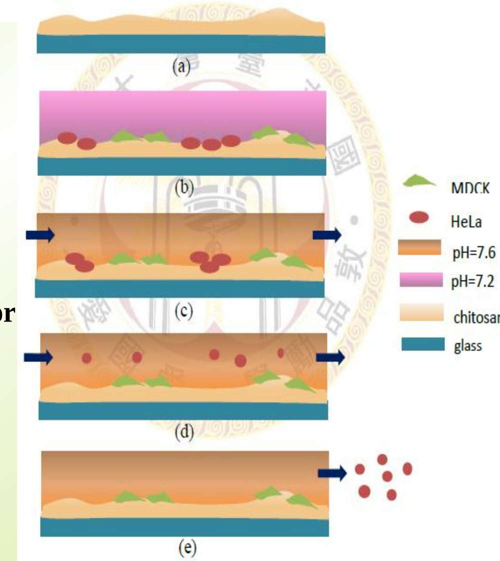

A novel color approach to detect rapidly and conveniently DNA samples is proposed based on a concept of DNA hybridization-mediated growth of AuNP probes. With this method, one can not only evaluate semi-quantitatively the target DNA but also screen mismatches of DNA samples with a naked eye or simple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

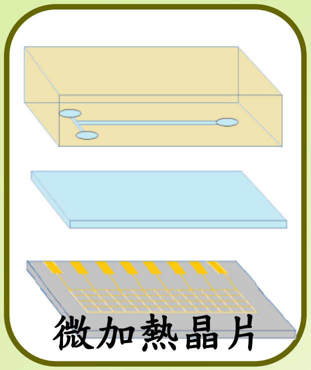
# Cell Culture & Fractionation on a Microfluidic Chip with Programmable Modules of Temperature & CO2

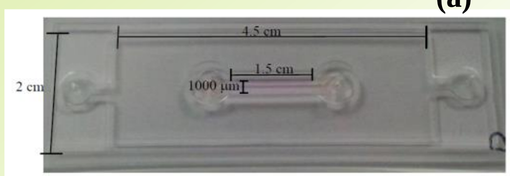
μTAS-2013
submitted to *Lab Chip*




(a)

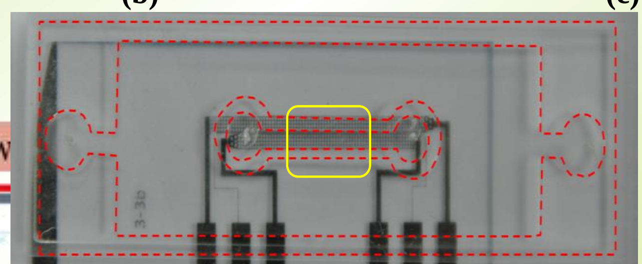


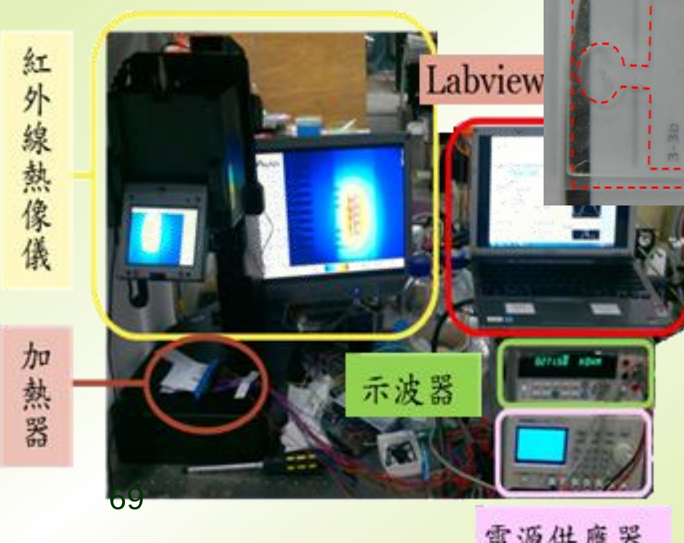




(b)

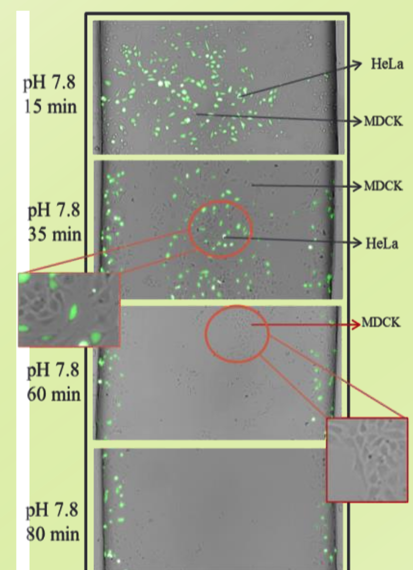
(c)



(d)

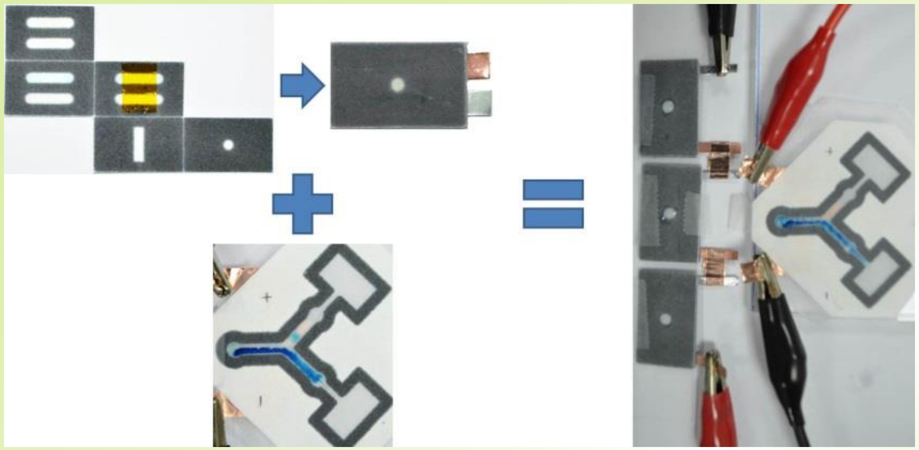


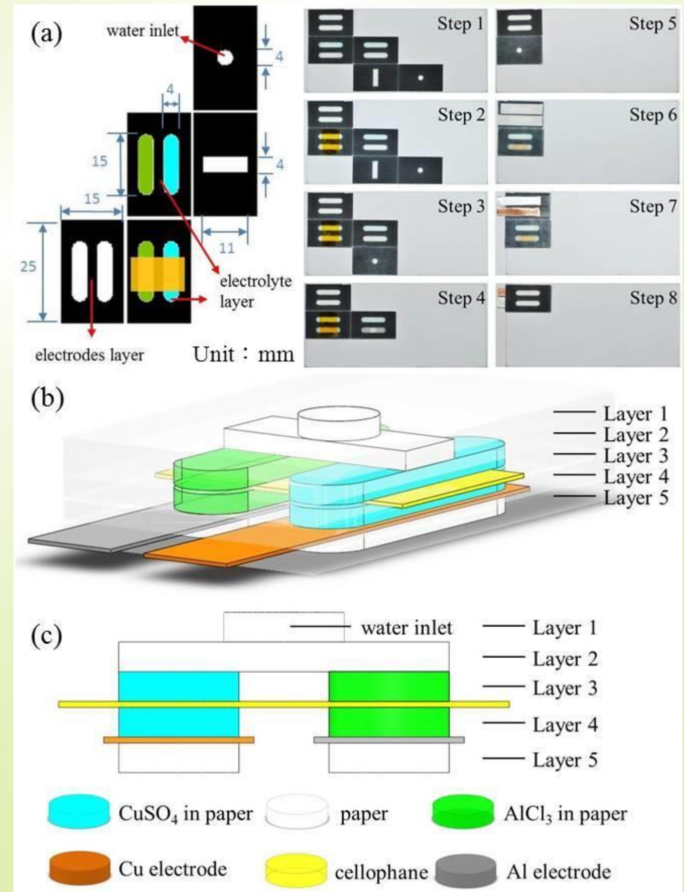


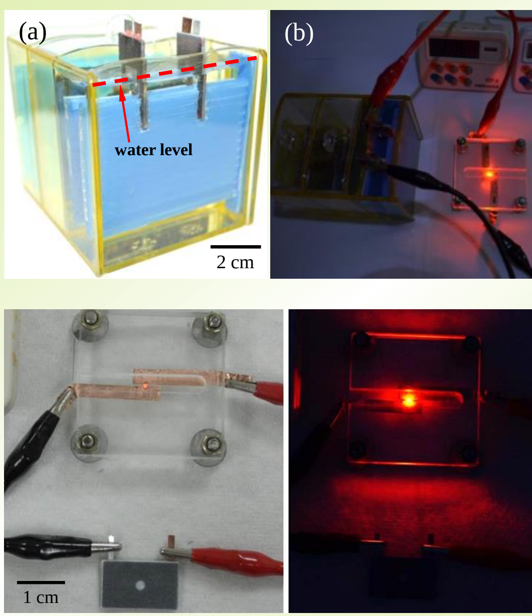


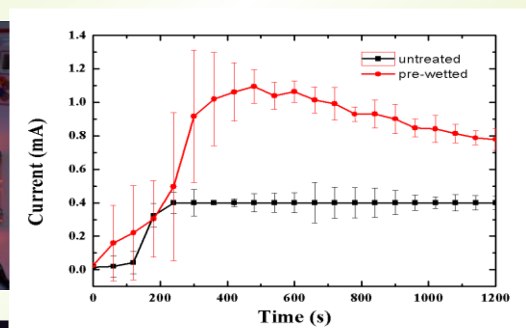
# Origami Paper-Based Fluidic Batteries for Portable Electrophoretic Devices

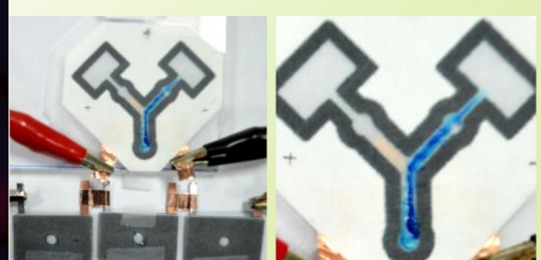
S. S. Chen, C. W. Hu, Y. C. Liao,*J. T. Yang,* μTAS-2013; *submitted to Lab on a Chip*





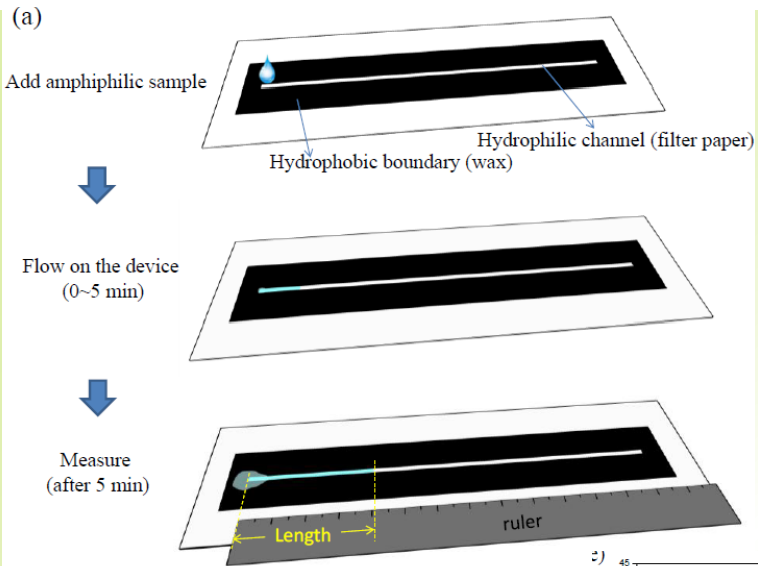



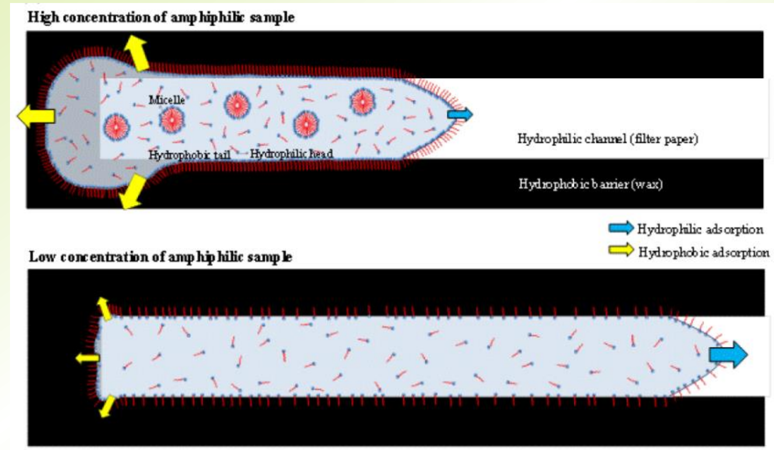



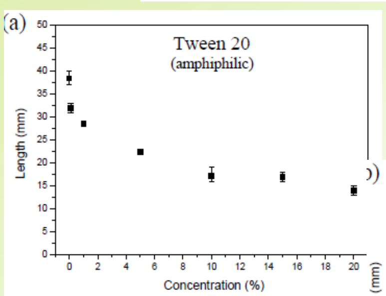



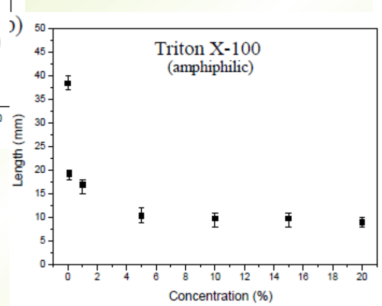
# Detection of an Amphiphilic Biosample in a Paper Microchannel Based on Length

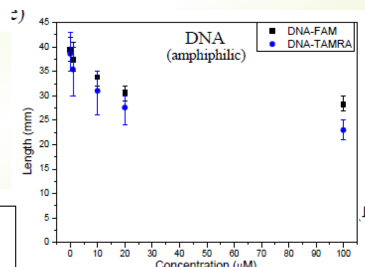
Yu-Tzu Chen and **Jing-Tang Yang,*** *Biomedical Microdevices*, 2015

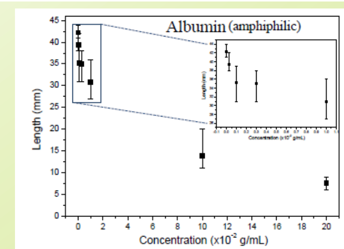


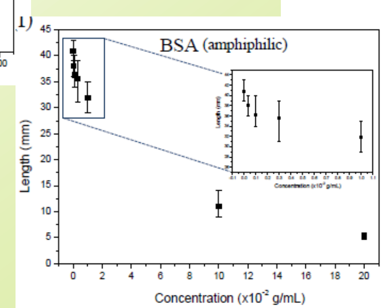



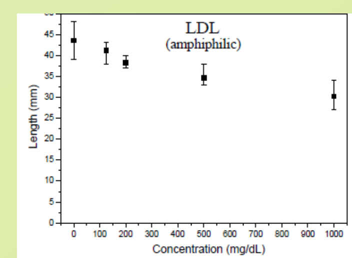




We developed a simple method to achieve semiquantitative detection of an amphiphilic biosample through measuring the length of flow on a microfluidic analytical device (μPAD) based on paper.

仿生與實驗室晶片導論- 2020

# Measurement Techniques

楊鏡堂 終身特聘教授

國立台灣大學 機械工程學系

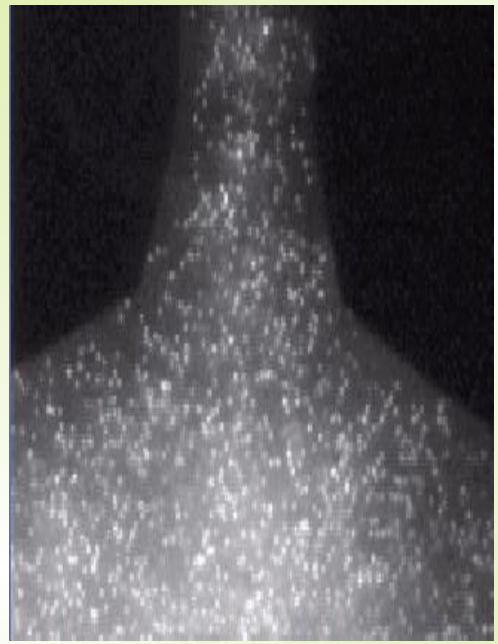
中華民國 110 年 1 月 6 日

BEAM Lab

# Measurement of Fluid Mixing

Colors Recognition

Tracing Particles



Chemical Indicator

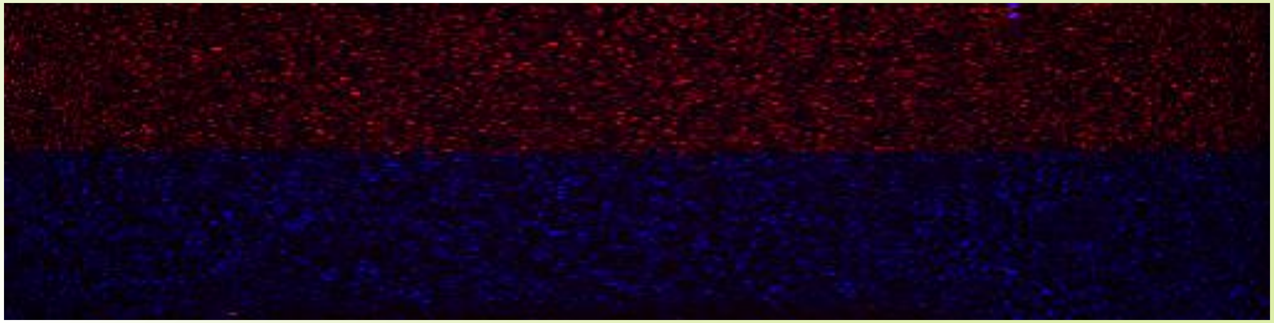
The characteristics of fluid mixing is measured via colors recognition, tracing particles, and chemical indicator. In this research, the mixing degree is quantized by the computation of  the standard deviation of grayscale values which are analogous to the constitution of fluid. Velocity field is measured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

# Measurement Techniques

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

Mass transfer & momentum transfer ? All in one ?

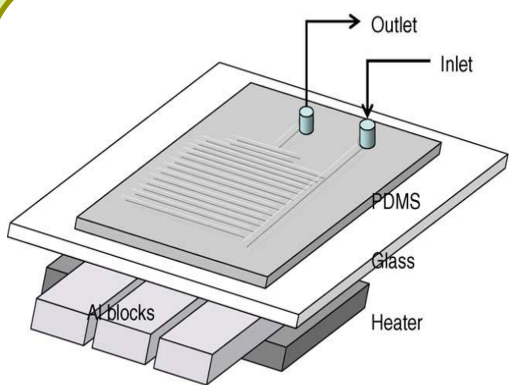
*~ absolutely yes !*



# 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)

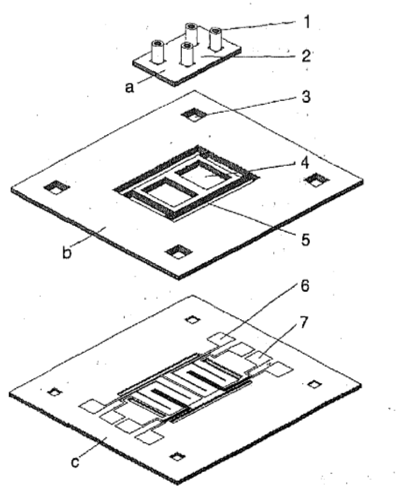
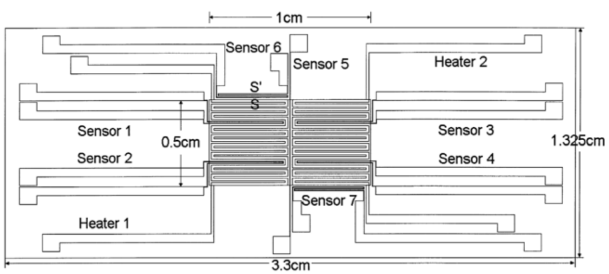


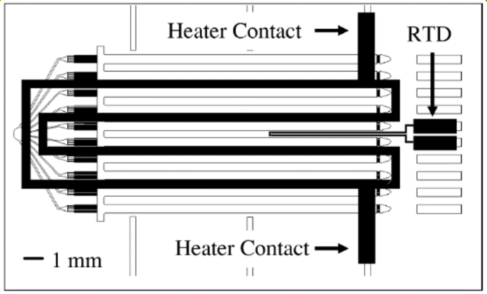

Fig. 4. Sketch of two-chamber chip. 1, Inlet; 2, cover; 3, adjustment; 4, reaction chamber; 5, air chamber; 6, thin-film heater; 7, temperature sensor; a, cover; b, topside; c, backside.

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

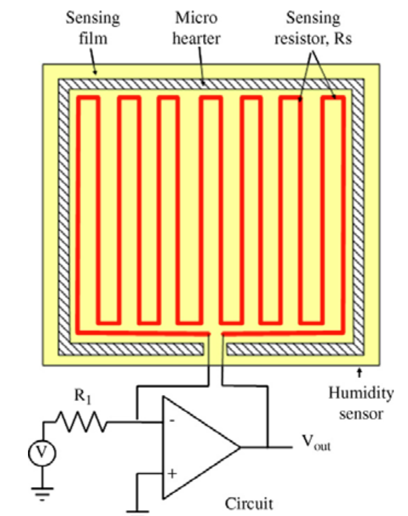



Lao *et al.*, *Sensors and Actuators A: Physical,* 2000

## 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

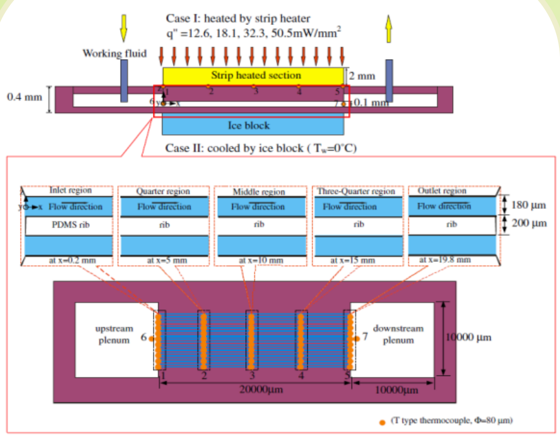



Fig. 1. Schematic of the test microchannel.

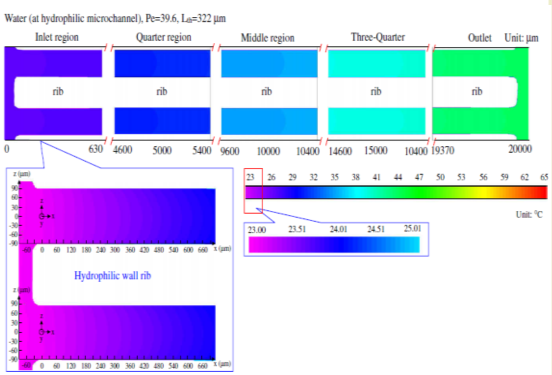



Fig. 4. Temperature distribution at x = 0, 0.5, 1, 1.5, 2 mm of water in hydrophilic microchannel at Q = 17.5 mm³/s.

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

溫度感測器搭配溫控程式

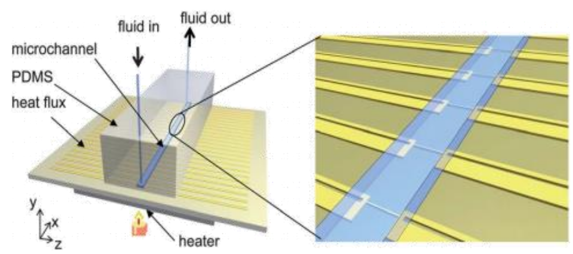



**Fig. 3** Experimental setup, microchannel and instrumented borosilicate substrate.

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

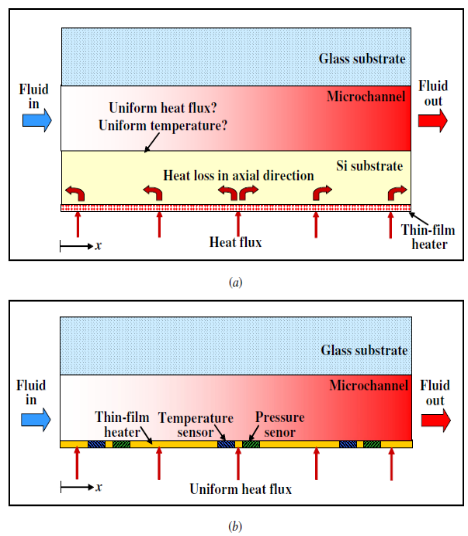
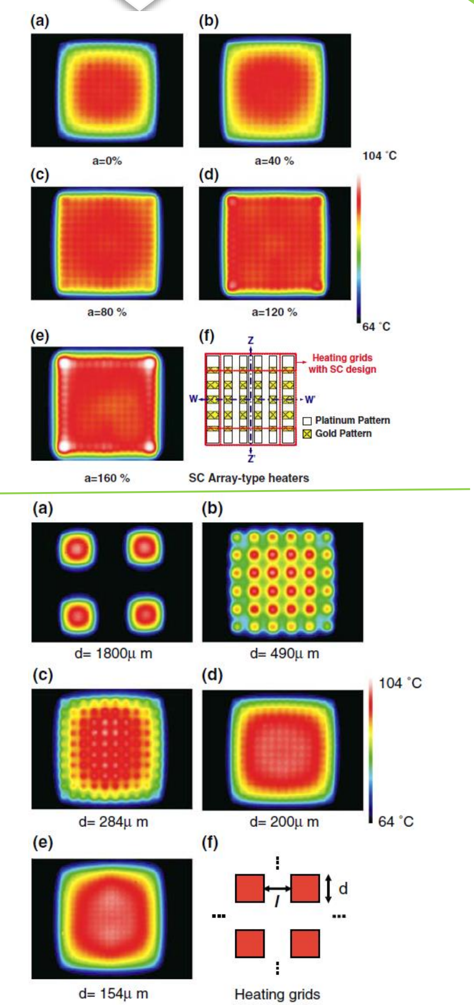



**Figure 1.** Schematic cross section of heat convection flow with (*a*) silicon substrate, and (*b*) thin-film cap.

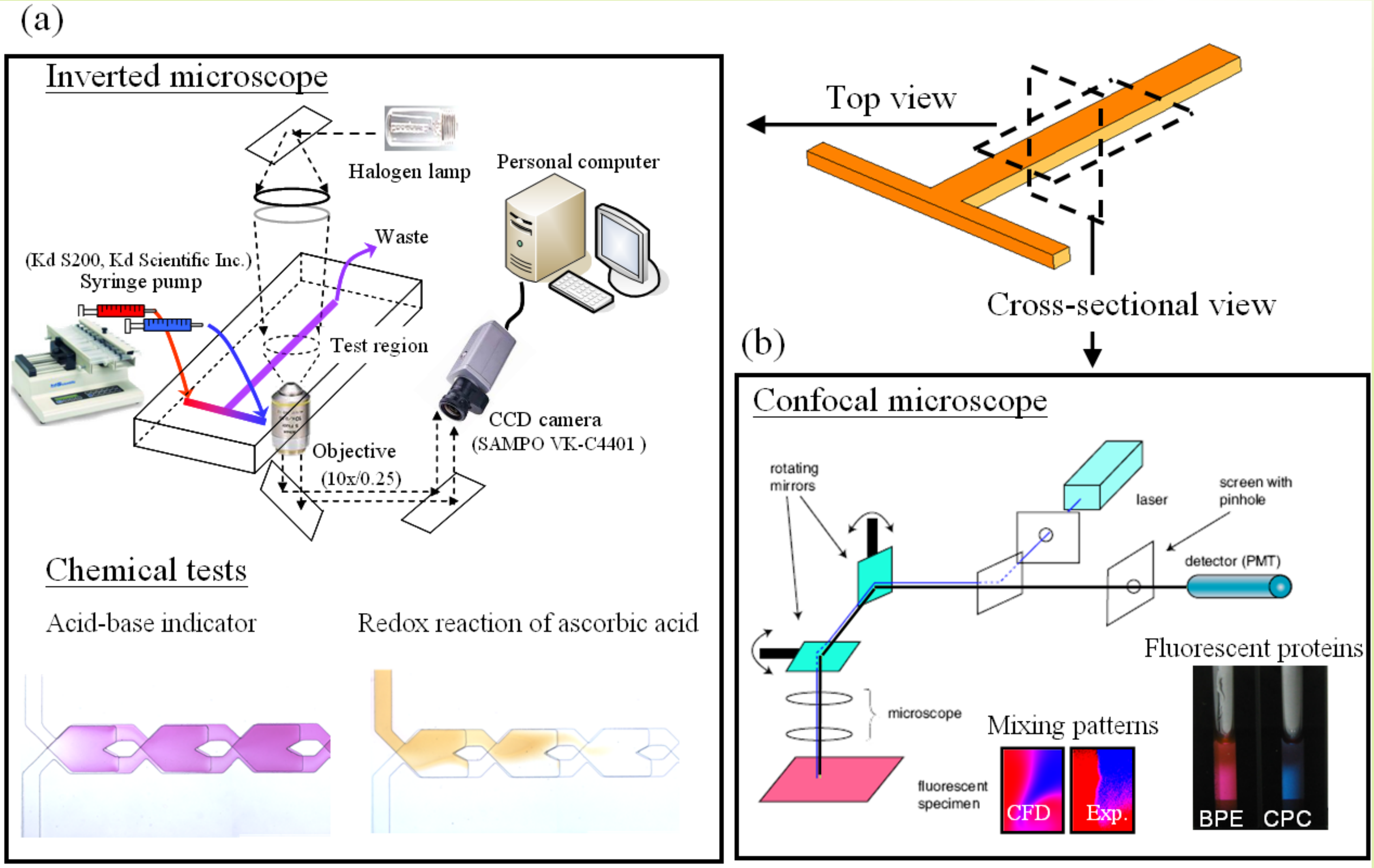
Lee *et al.*, *J.Micromech. Microeng.*, 2011

紅外線熱像儀

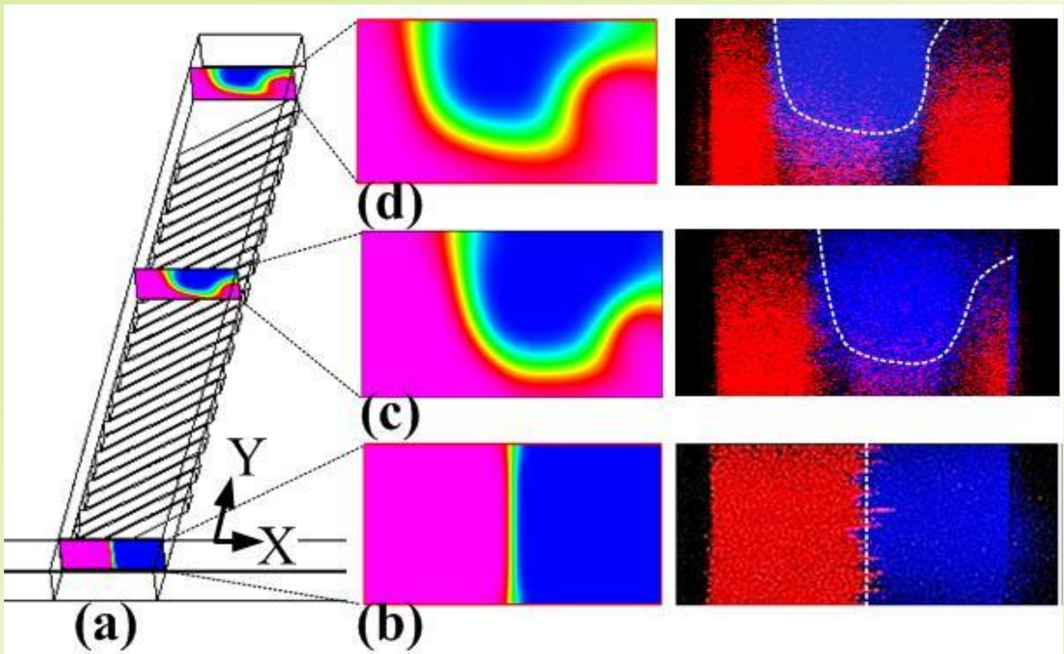


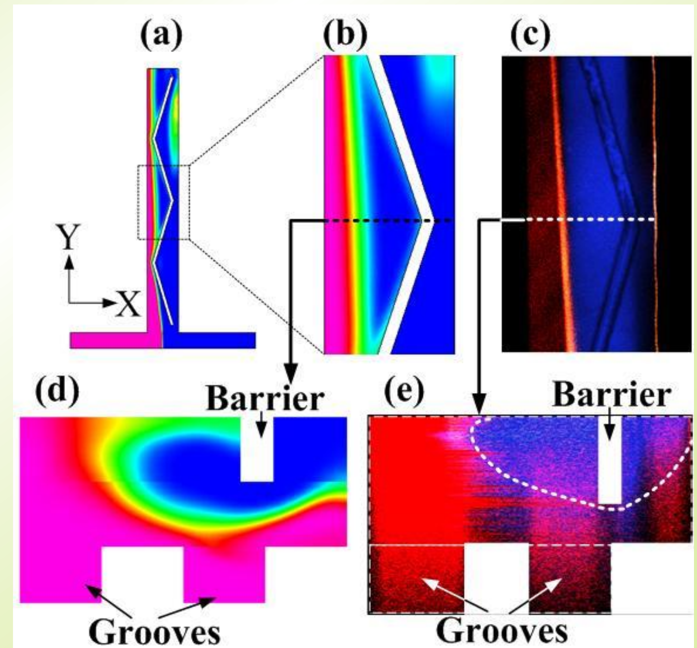

Hsieh *et al.*, *Microfluid Nanofluid*, 2009

# Flow Visualization without Dyes



# Micro laser-induced fluorescence (μ-LIF)



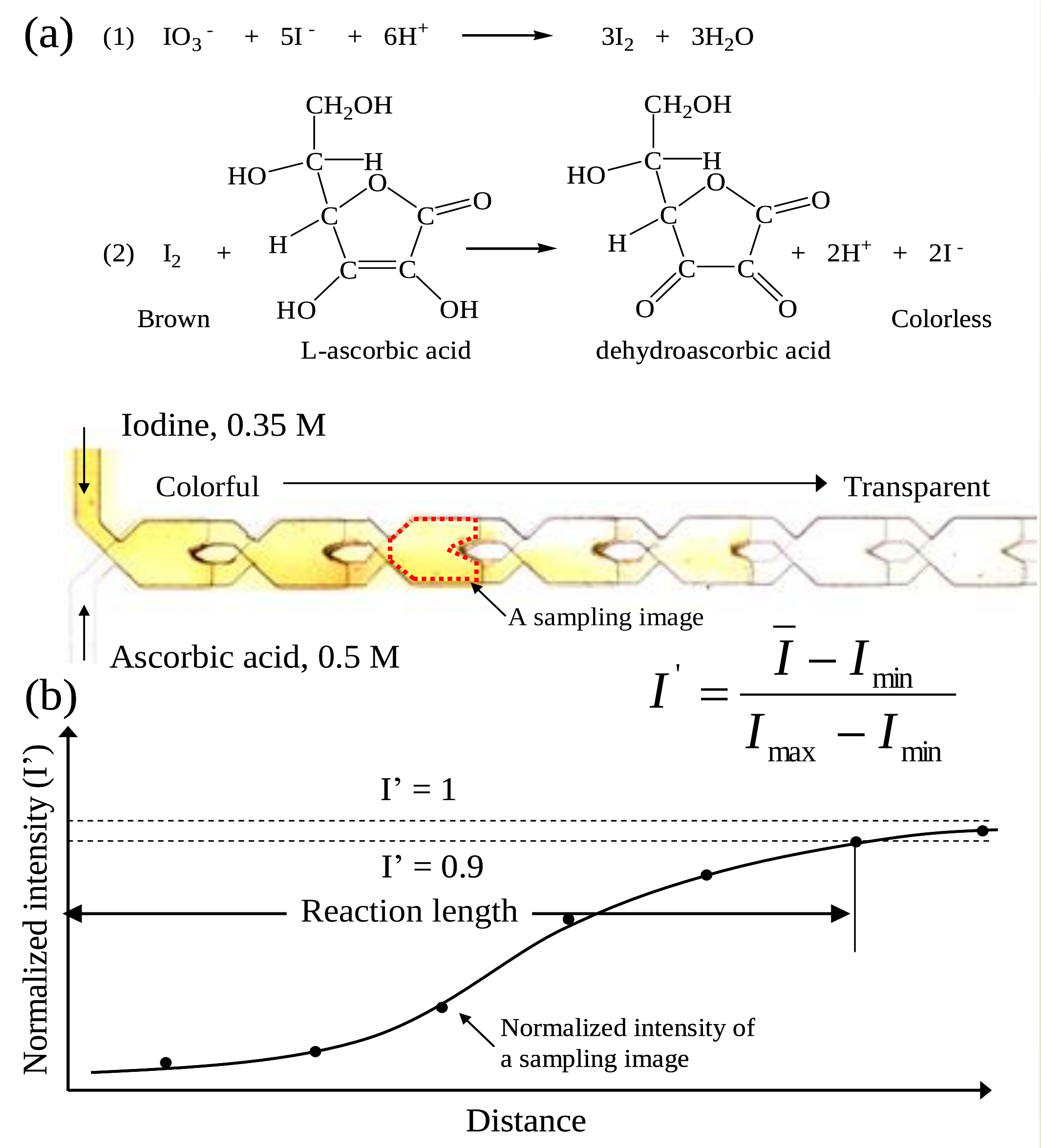




Two fluorescent proteins – B-phycoerythrin (BPE, 0.5 μM, Far East Bio-Tec Co., Ltd.) and Allophycocyanin alpha subunit (ApcA, 2 μM, Far East Bio-Tec Co., Ltd.) – served to monitor the mixing performance.

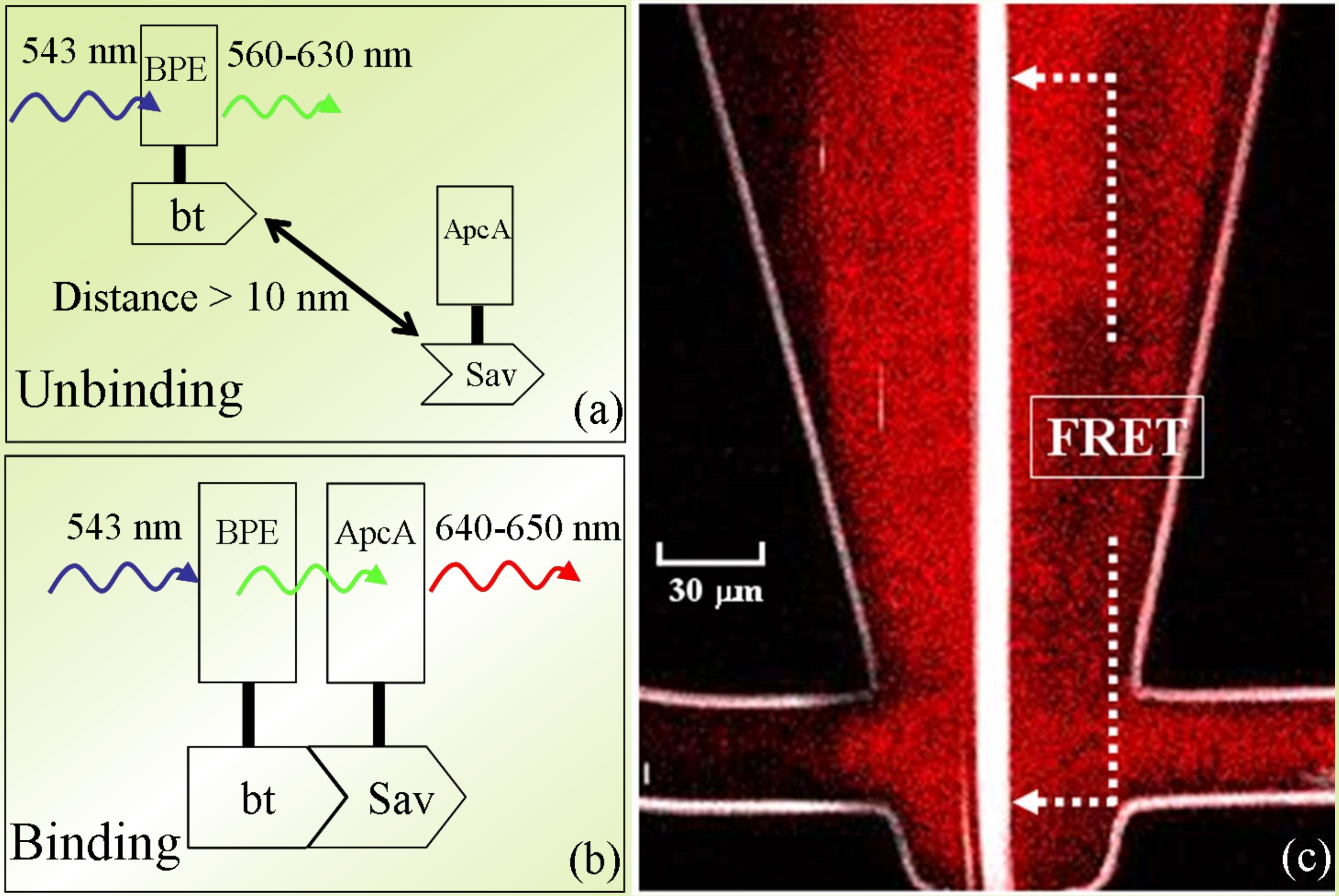
# Experiments – redox reaction

**Redox reaction of ascorbic acid with diiodine**

Fading process of diiodine



# 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)

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

Tung and Yang, *Microfluidics & Nanofluidics*, 2008

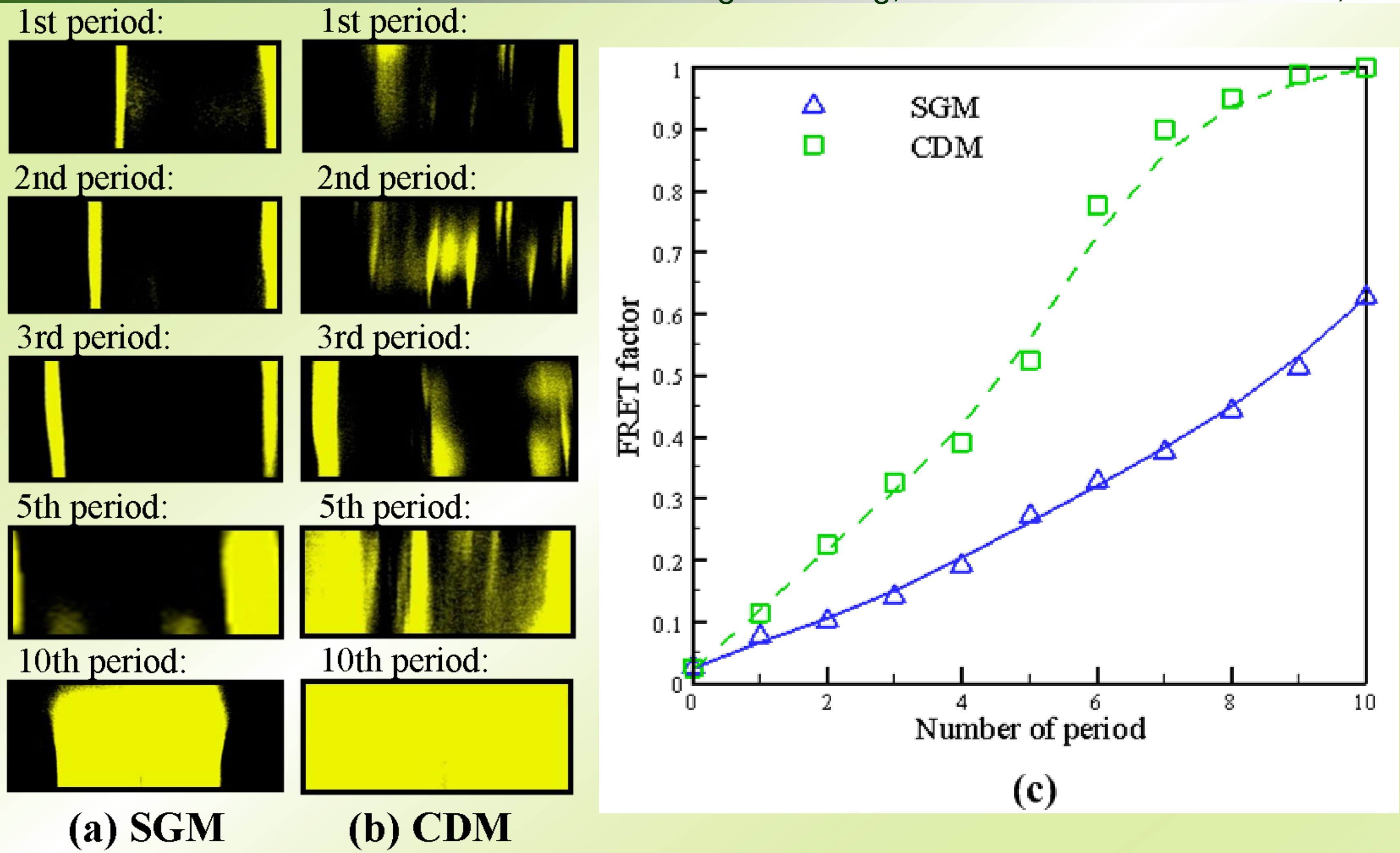
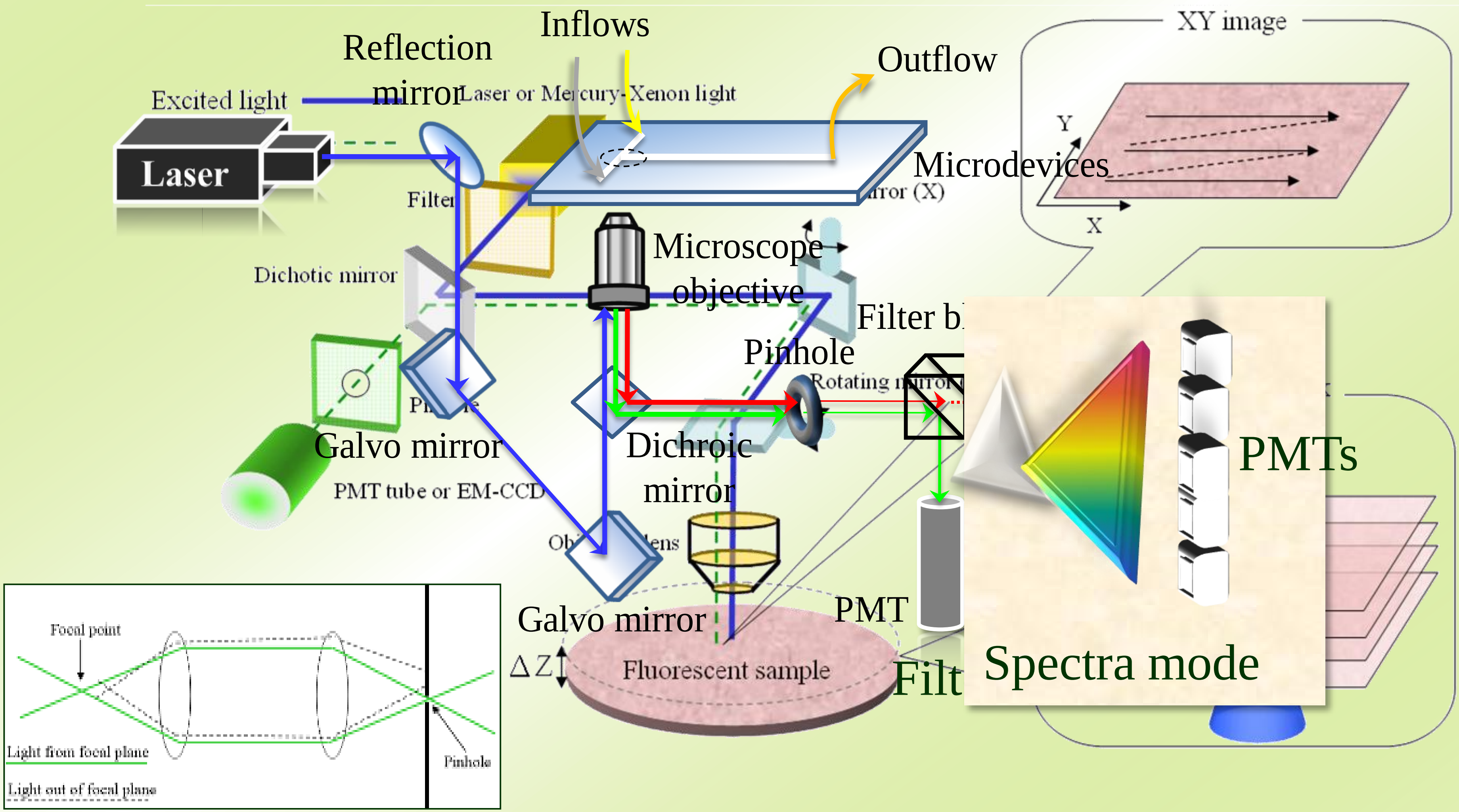
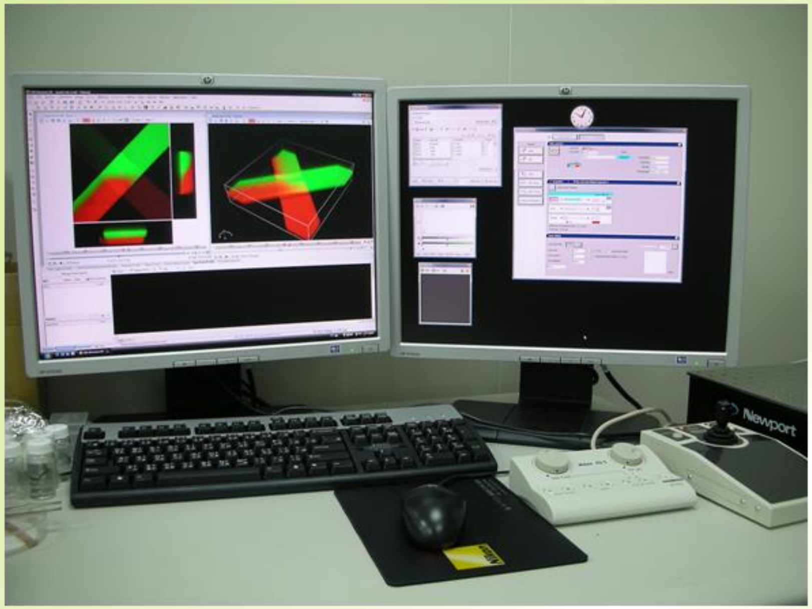



Fig. 9 Results of FRET in (a) SGM, (b) CDM. (c) The distribution of the FRET factor plotted to the 10th period for SGM and CDM.

# Confocal Fluorescence Microscopy



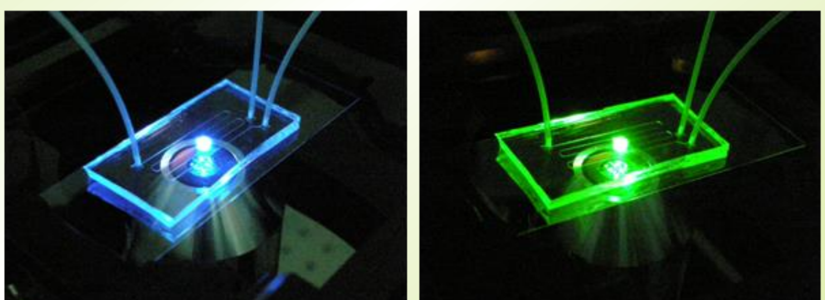
# Confocal Microscope (Nikon A1R)




Monitor and operation interface


Nikon A1R

4



Test section (light excitation on chip)

5

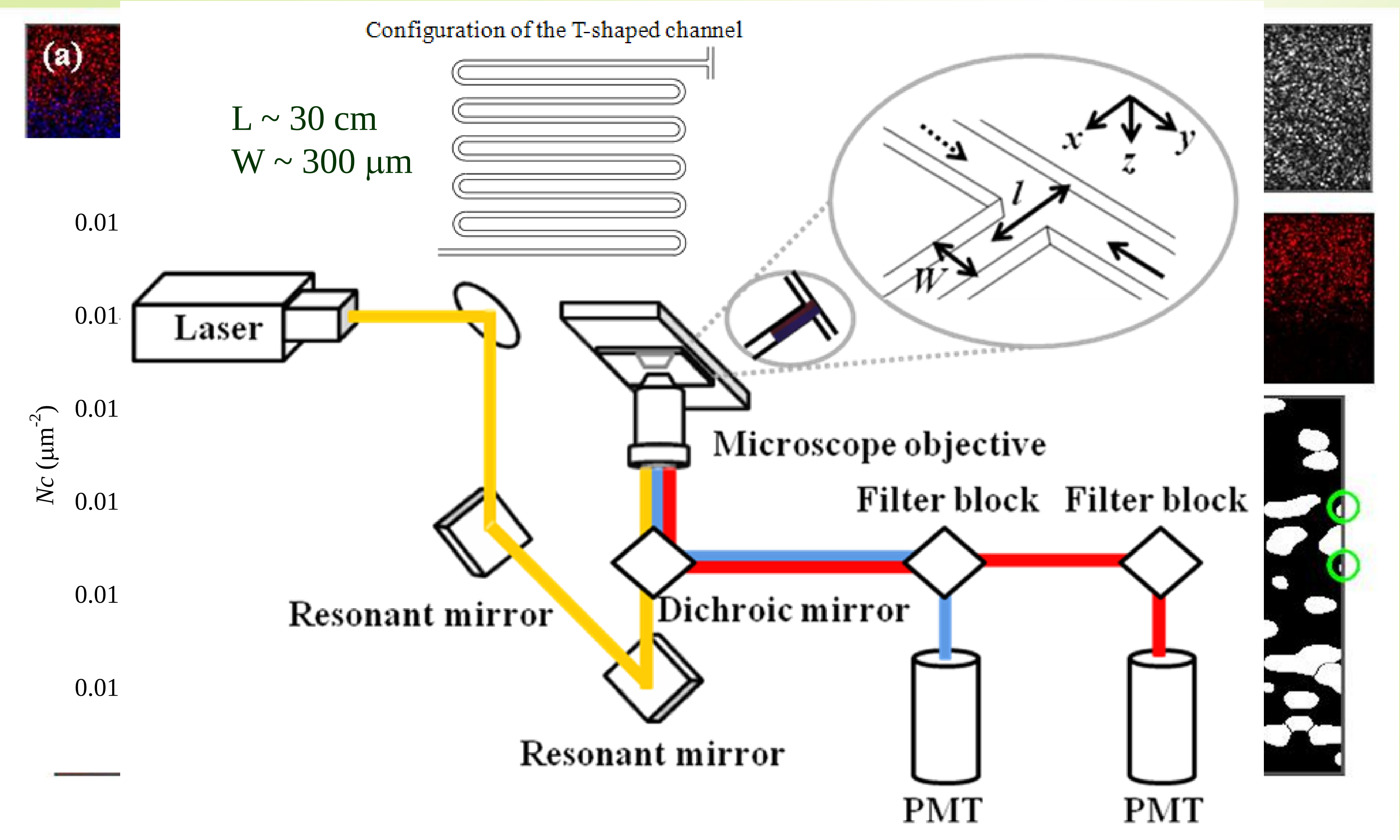
Syringe pump


83

# Measuring Techniques (simultaneous measurement)

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

## Simultaneous measurement (micro-PIV & particle counting method)

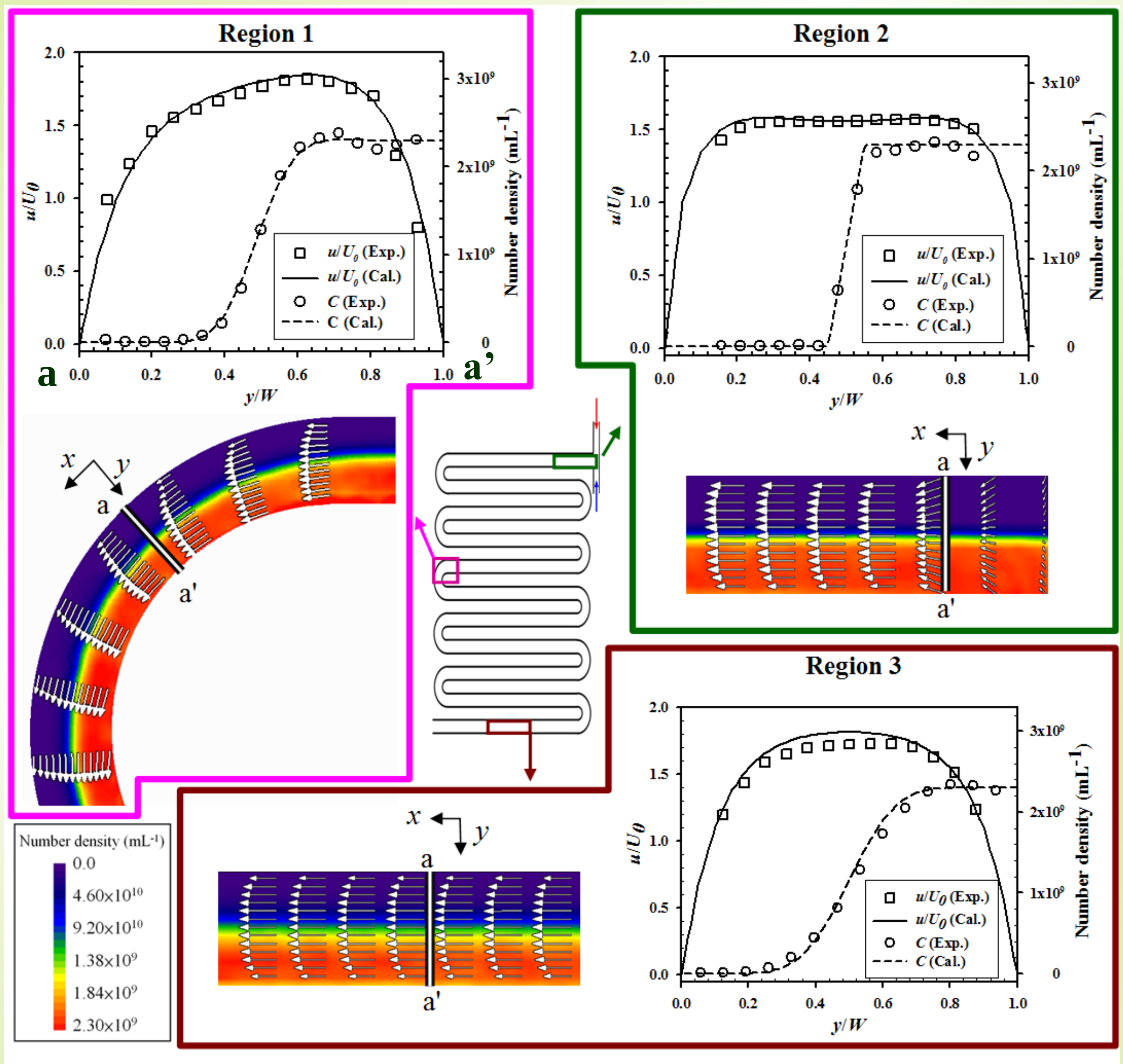


# **Measuring Techniques** (simultaneous measurement )

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

Simultaneous diagnosis of velocity and concentration fields

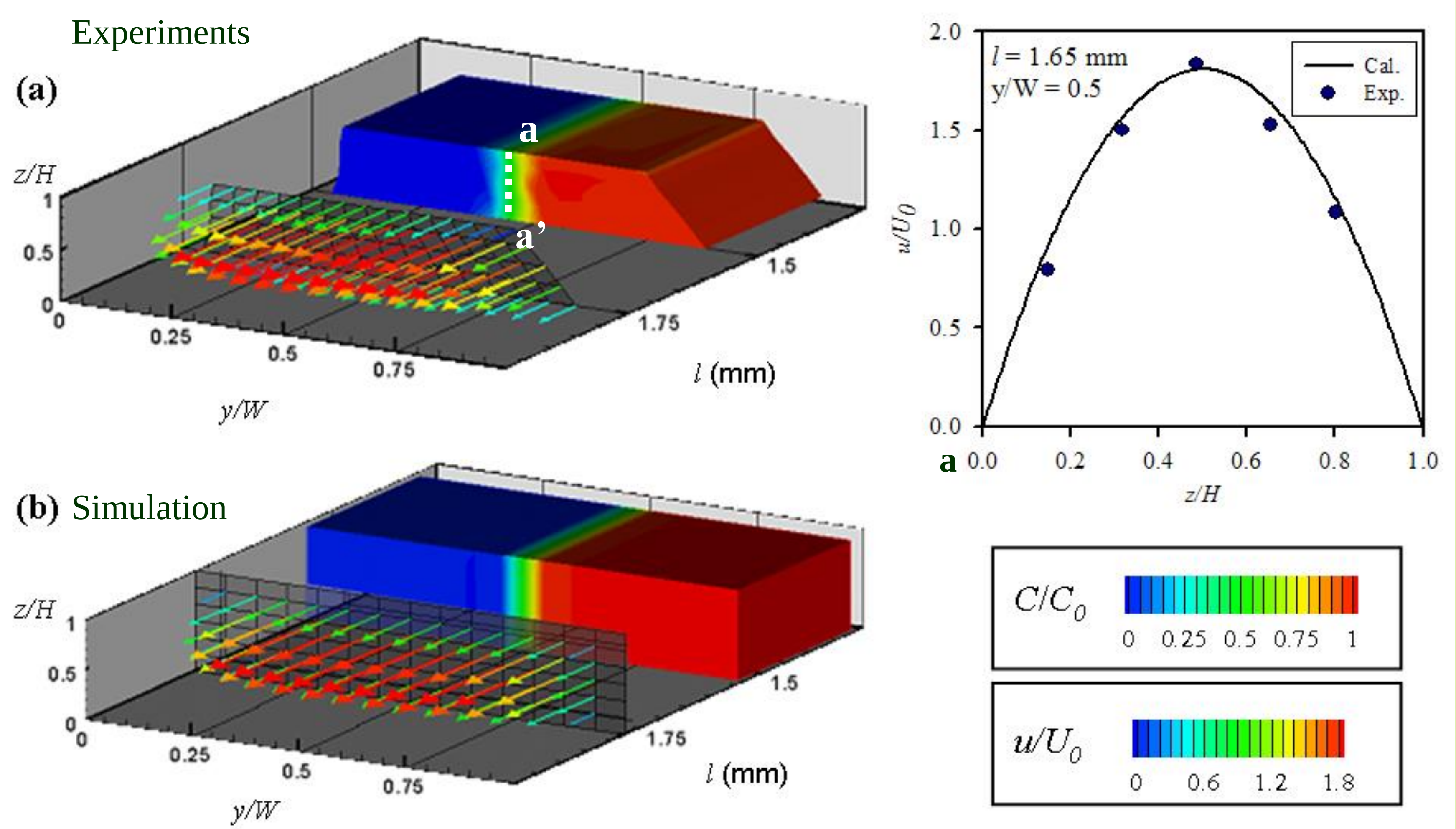
The maximum relative errors for both velocity and concentration fields between experimental and numerical results are about 5 %



# Measuring Techniques (simultaneous measurement)

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

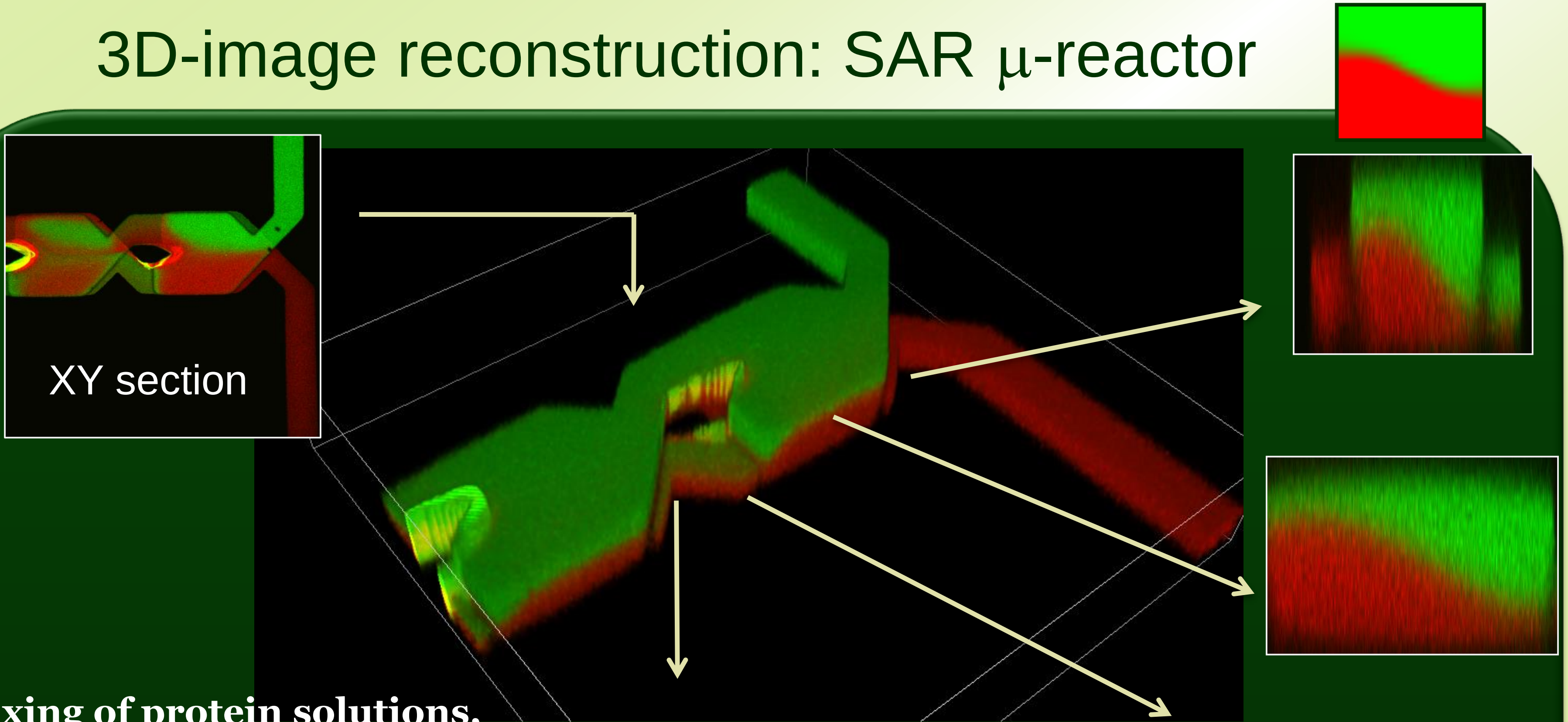
3D velocity and concentration fields



# Performance Test of a SAR μ-Reactor

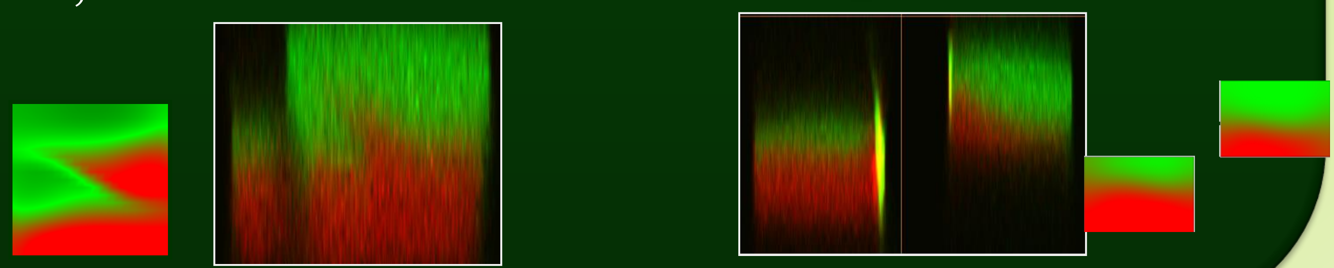
方偉峰 楊鏡堂, 2009

## 3D-image reconstruction: SAR μ-reactor




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

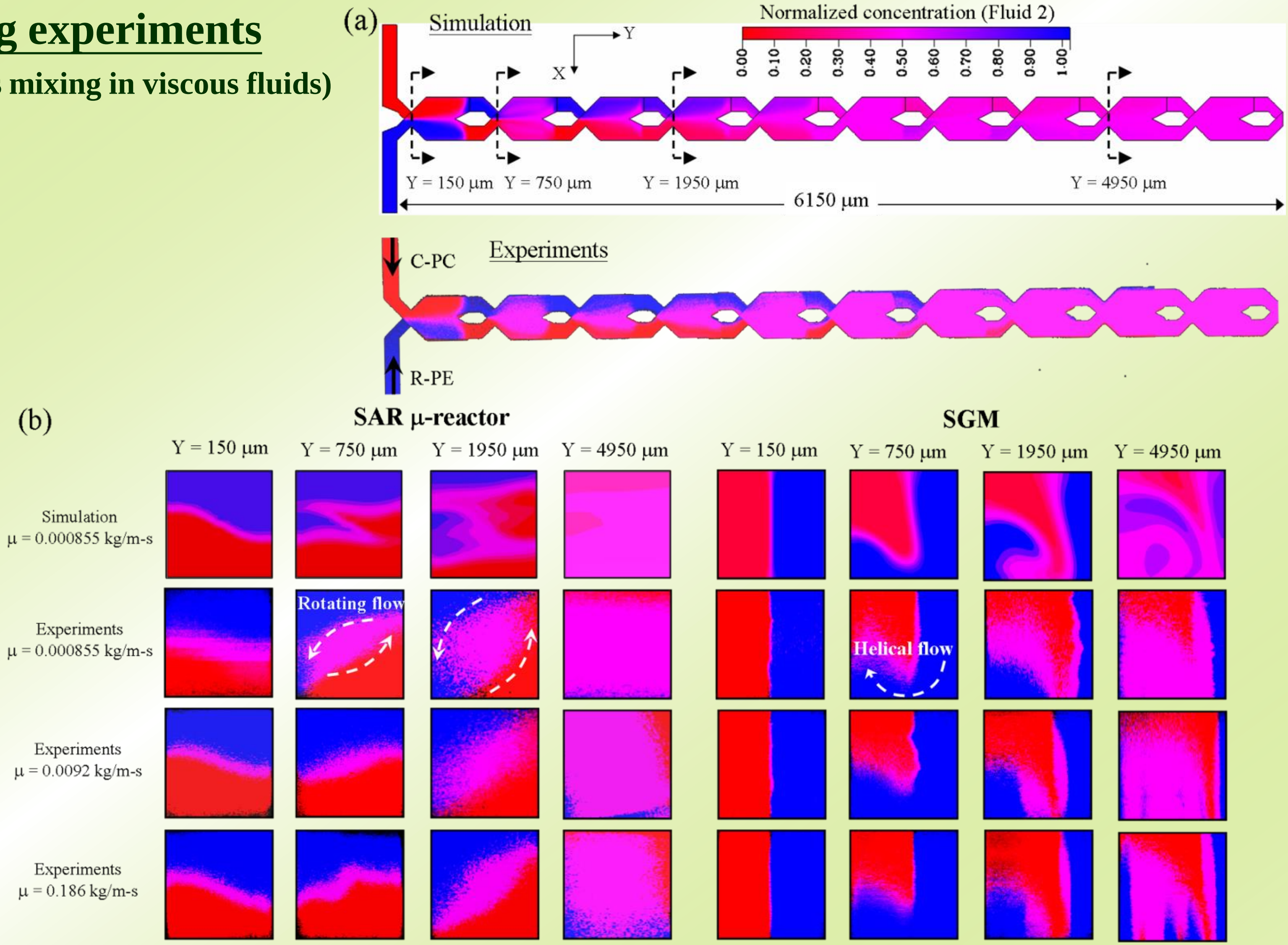
***Con-focal microscopy***



# Results and discussion- SAR μ-reactor

## Mixing experiments

**(Proteins mixing in viscous fluids)**



仿生與實驗室晶片導論- 2020

# Micro-reaction in droplets

楊鏡堂 終身特聘教授
國立台灣大學 機械工程學系

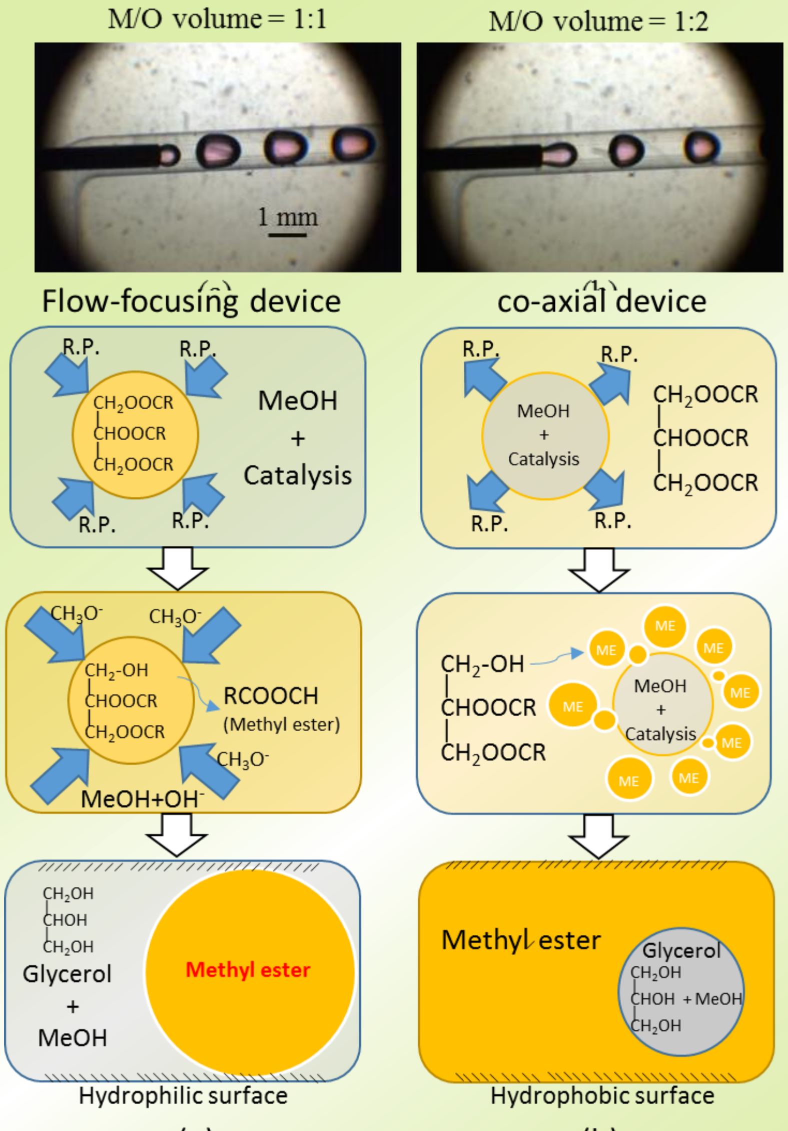
中華民國 110 年 1 月 6 日

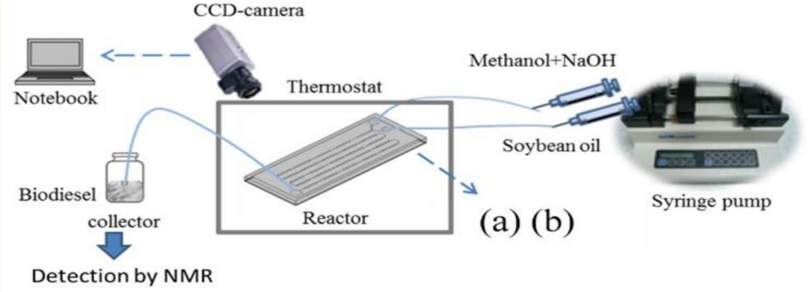
# Development of a millimetrically scaled biodiesel transesterification device that relies on droplet-based co-axial fluidics

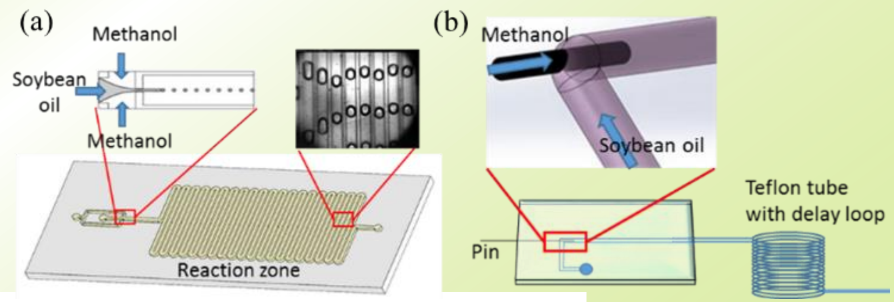
S. I. Yeh, Y. C. Huang, C. H. Cheng, C. M. Cheng, ** J. T. Yang*

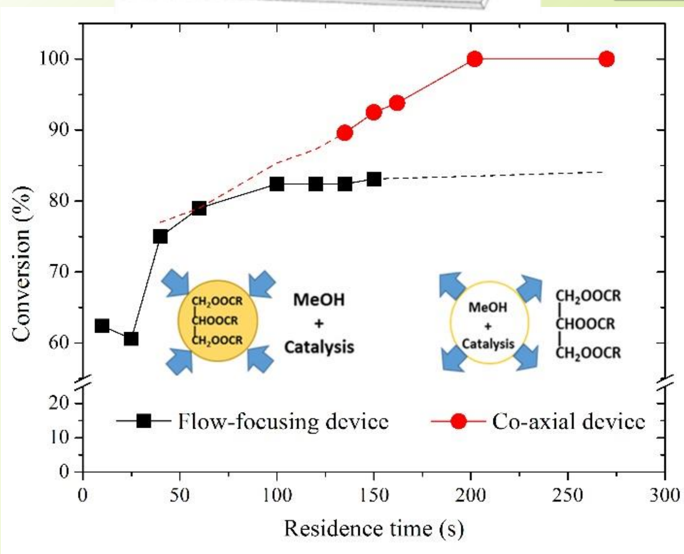
*Scientific Reports, 2017*

第12屆國家新創獎



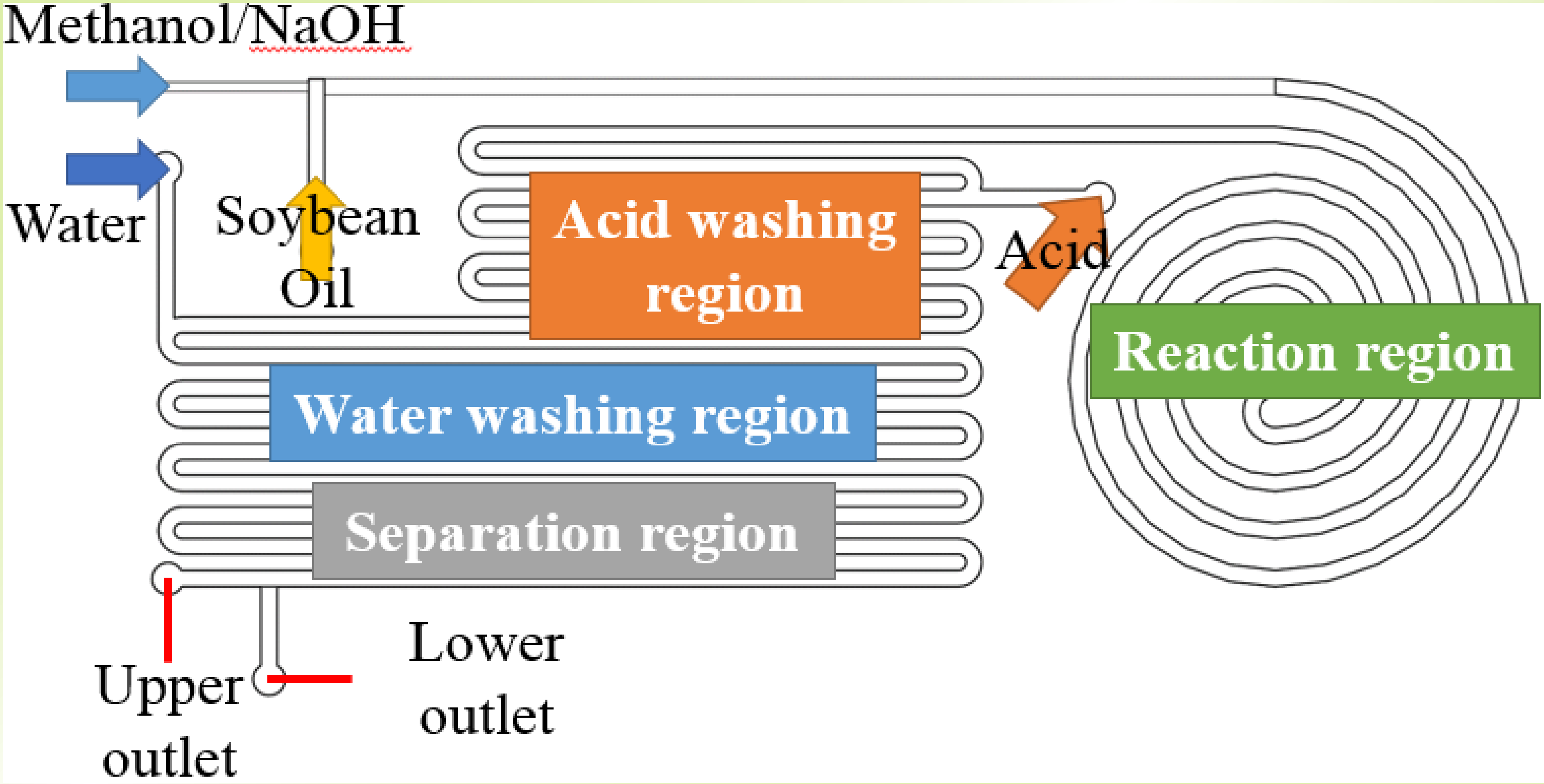



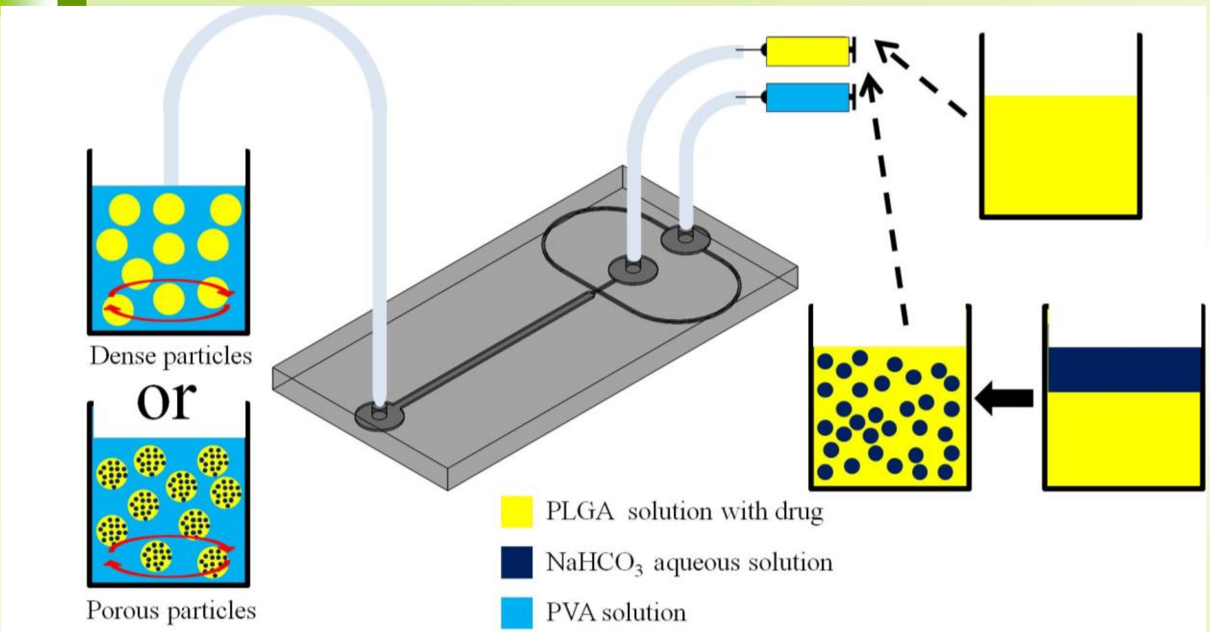
# Continuous Production of Biodiesel by a Passive Millimeter-Micrometer Fluidic System

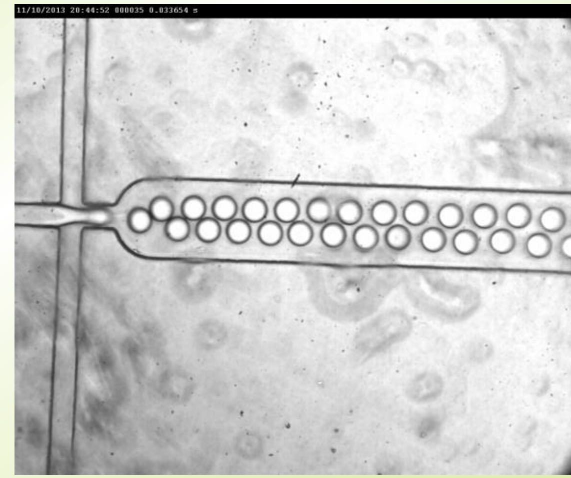
I-Lun Chen, Szu-I Yeh, and Jing-Tang Yang,* *MicroTAS-2017*



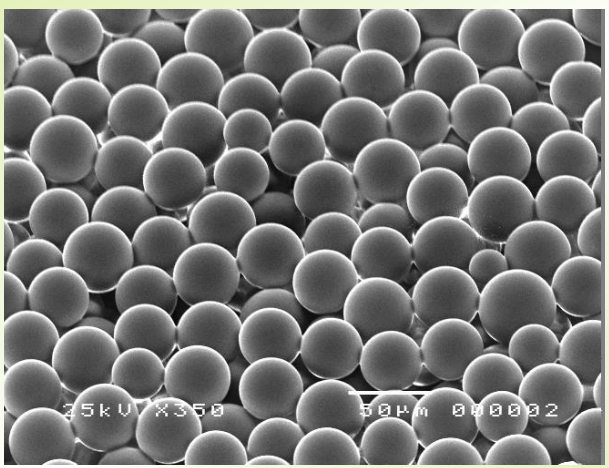
# Microencapsulation of Curcumin-Loaded PLGA Particles and Controlled Release in a Myoblast Culture

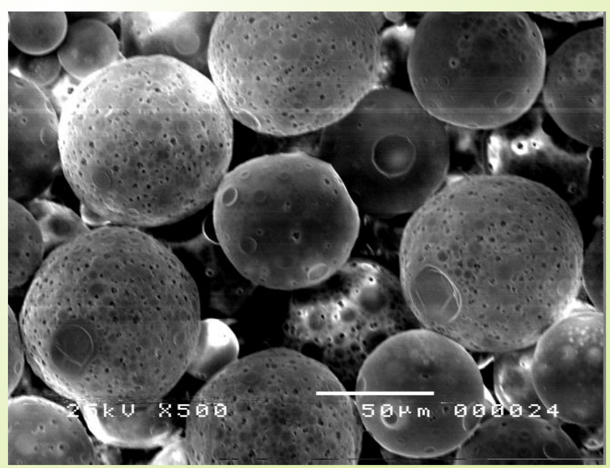
to be submitted



*μTAS-2014*

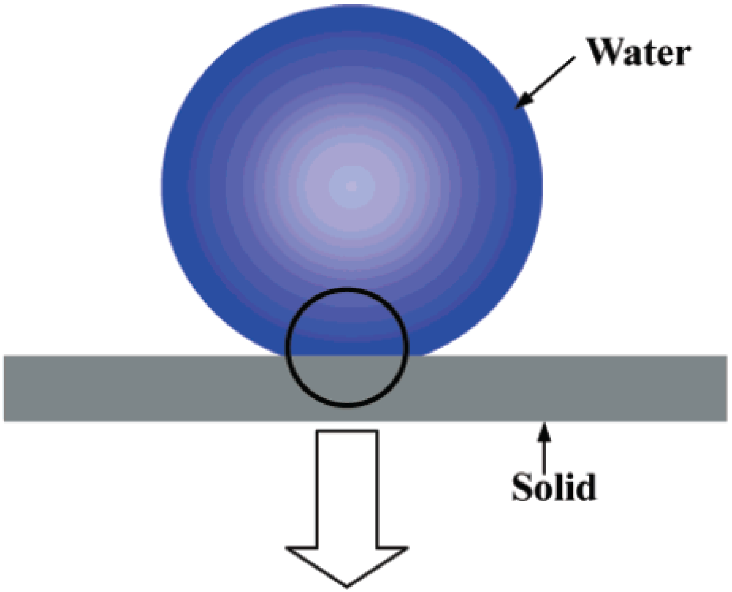


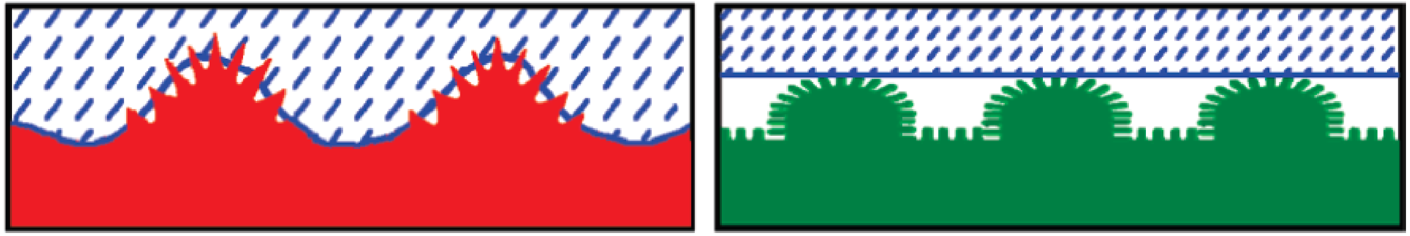




High-throughput Transesterification with Soybean Oil and Methanol by Micro-Scale and Mini-Scale Droplet-based Microsystems

*μTAS-2014*

# Petal Effect and Lotus Effect



Petal (Cassie impregnating wetting state)

Lotus (Cassie's state)

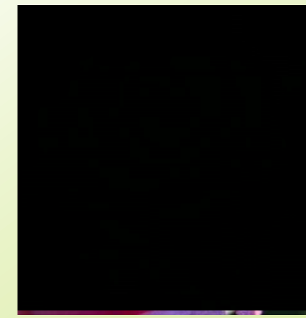
# Plant-Biomimetic（蓮葉與玫瑰花瓣的組合與創新生醫晶片）

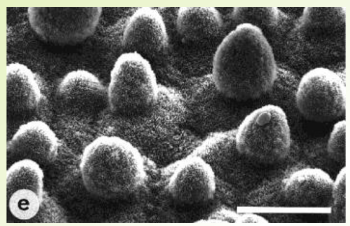
- **Lotus effect—superhydrophobic**

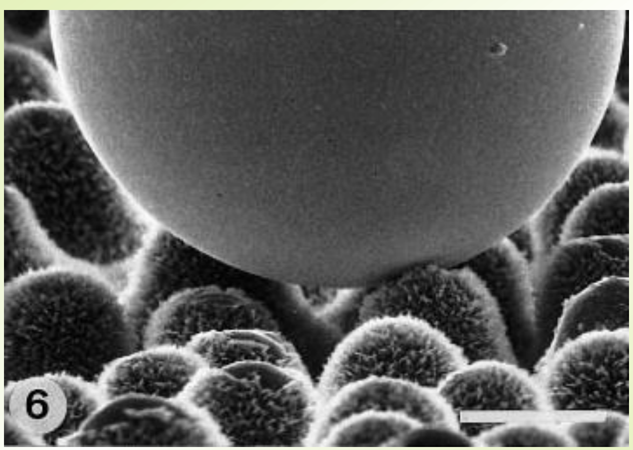
  **microstructure (5~10 μm) + nanostructure(5~200 nm)**

- **Petal effect— superhydrophobic & high hysteresis**

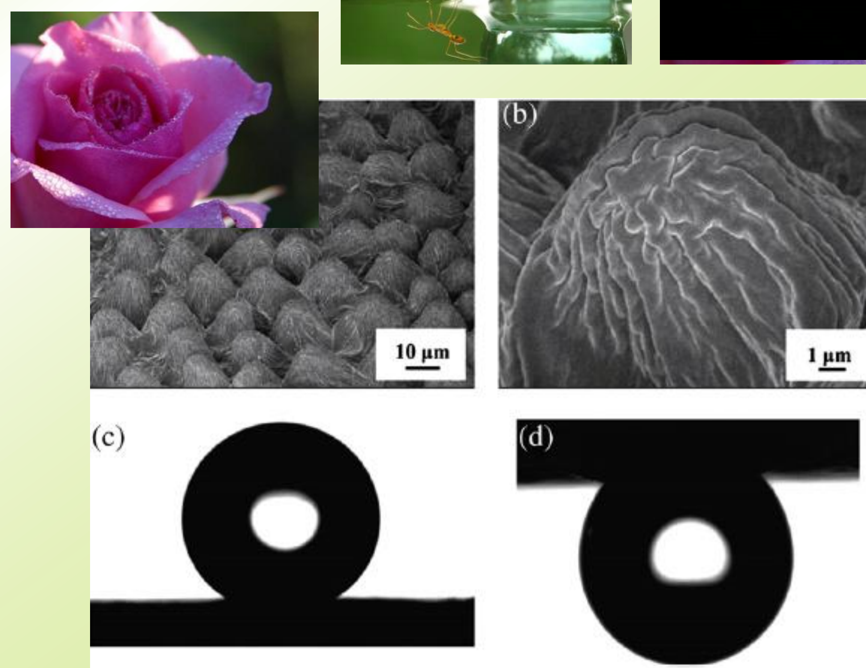
  **micropapillaes + nanofolds**






Barthlott *et al., Planta*, 1997



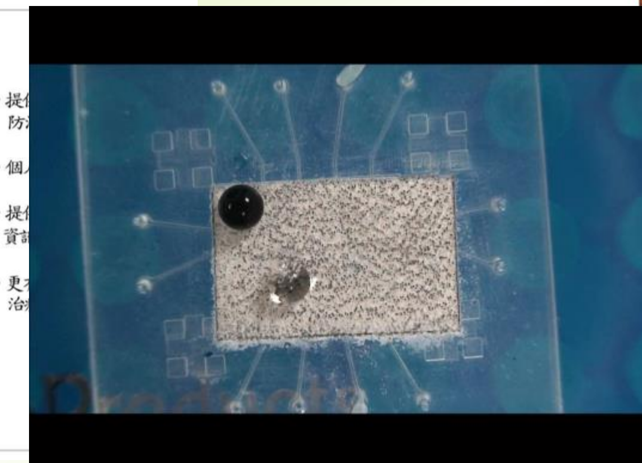

Feng *et al., Advances in Colloid and Interface Science*, 2011

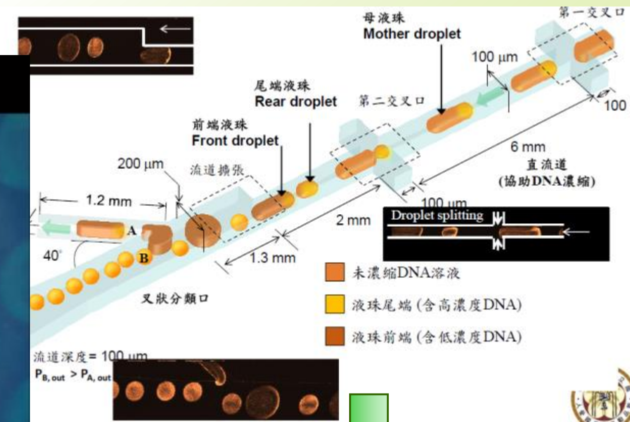
# 個人醫檢新紀元：可視化液珠式基因快篩技術

## Personalized Diagnostics at Sight: Droplet-based Gene Screening

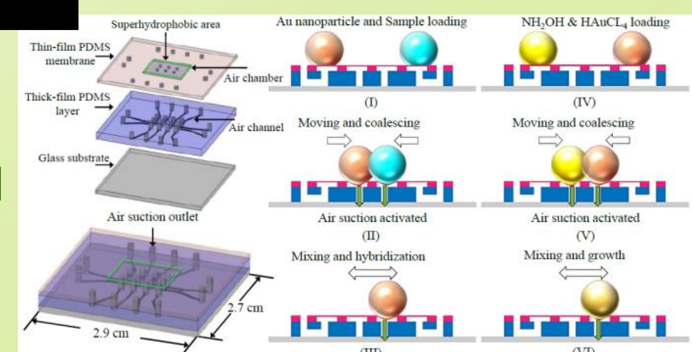
**Point-of-care model** 第11屆國家新創獎

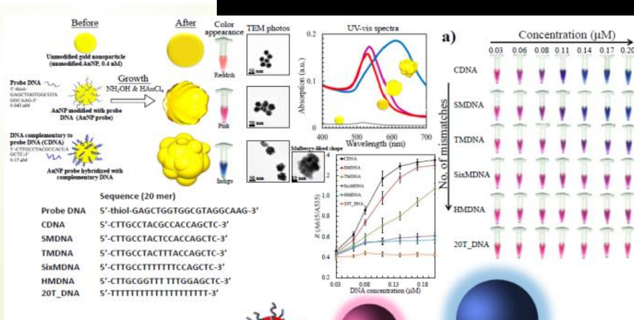
一種新的檢測技術和晶片系統，不需要昂貴的設備及複雜的步驟，即可自動化進行基因型診斷，檢測結果能用肉眼直接觀察得知，並具有可攜帶、微量藥品試劑消耗及快速篩選等優點，減少醫療資源浪費、發揮藥物的最佳藥效、針對每個人不同的體質，打造專屬個人的治療方式。本技術核心包含三大項目: (1) 發展一種利用金奈米粒子探針結合長晶方法，(2) 可攜式的液珠操控平台，(3) 被動式DNA濃縮技術。




*Lab Chip, 2012a*



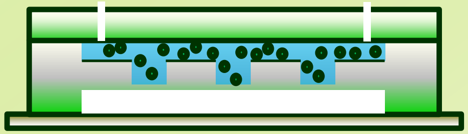

*SNB, 2014*

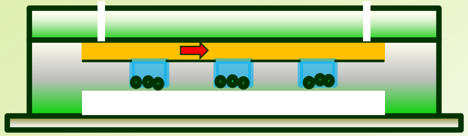
*Lab Chip, 2014b*

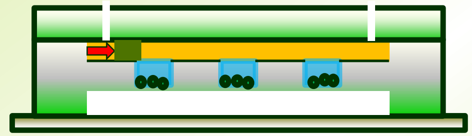
# Integrated Microfluidic Reactor Array for Large-Scale Drug Screening

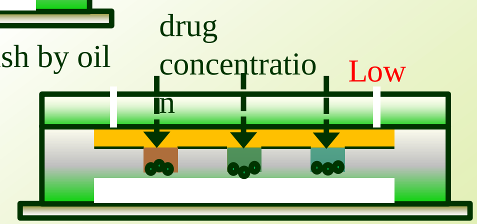
MOST 103-2221-E-002 -097-MY3

## Design & operating processes

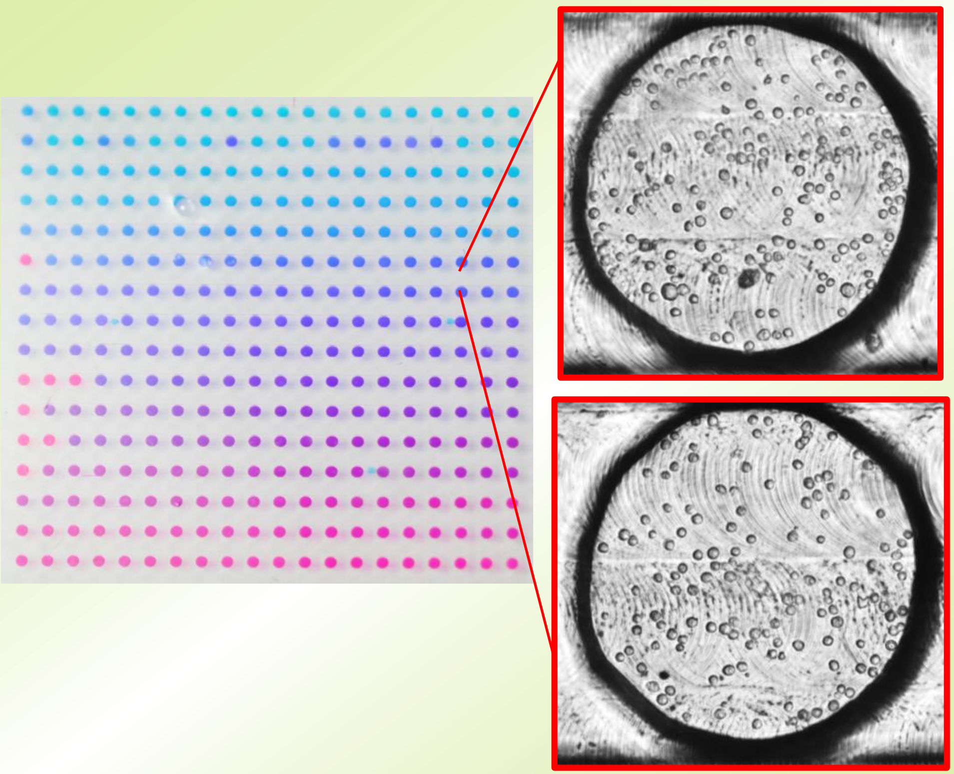

(a) Place cells into the liquid channel

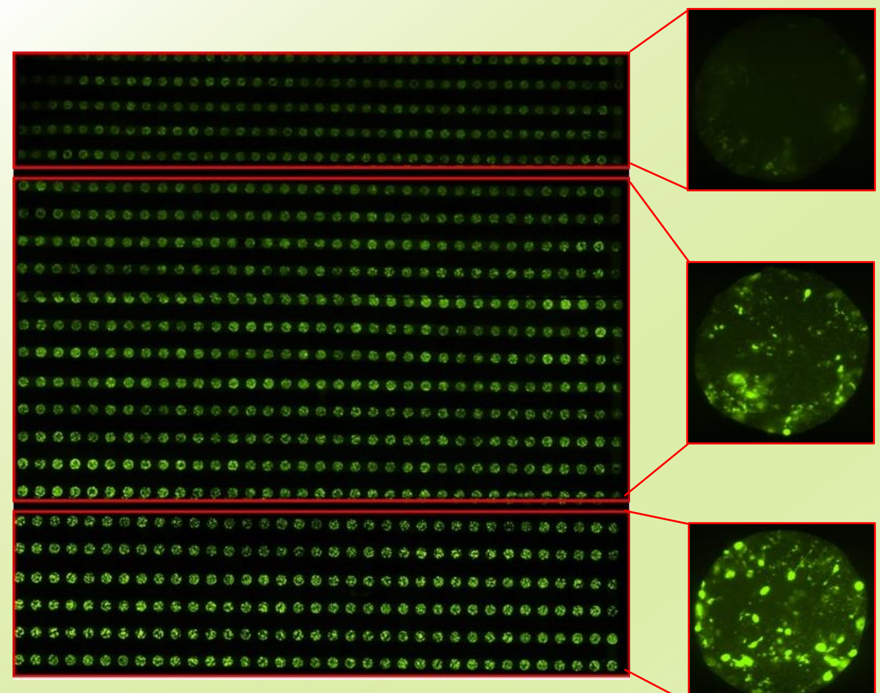

(b) Oil injection to form static droplets


(c) Inject drug plug and push by oil



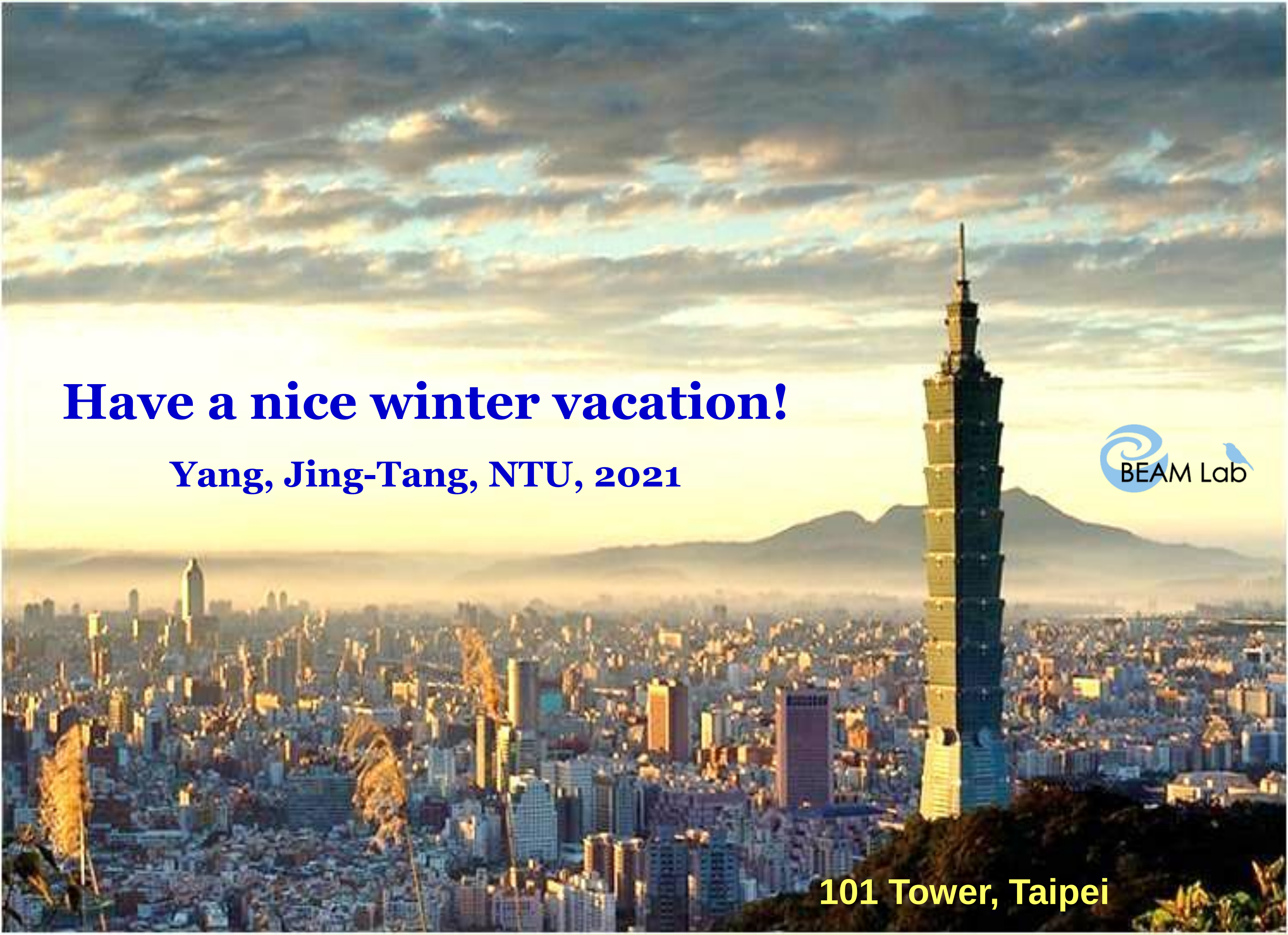
(d) Drug concentration gradient generated





# Have a nice winter vacation!

Yang, Jing-Tang, NTU, 2021



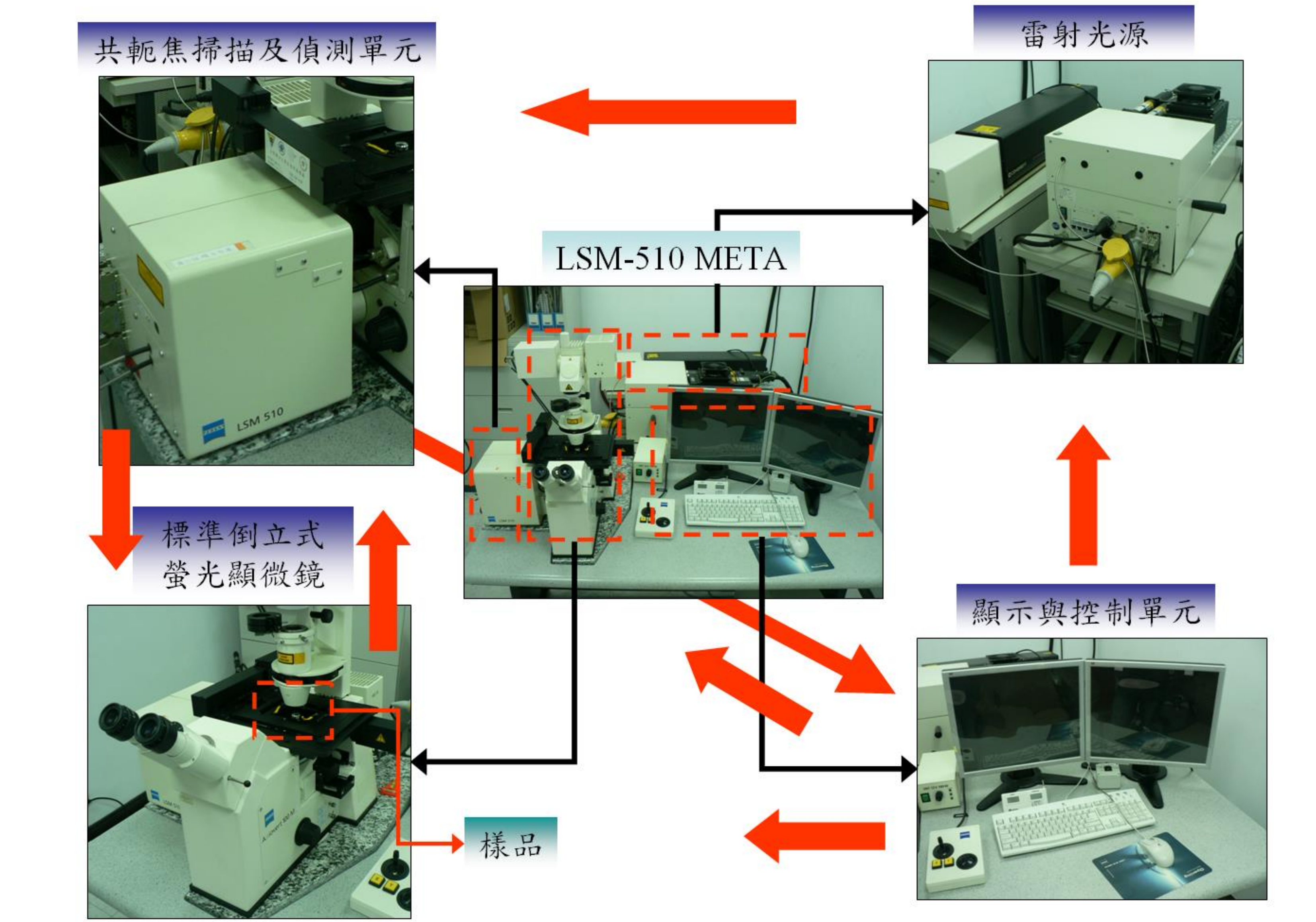
101 Tower, Taipei

# Q & A

楊鏡堂 終身特聘教授
國立台灣大學 機械工程學系

中華民國 110 年 1 月 6 日

# 雷射掃描共軛焦顯微鏡(LSM-510)之架構



# Results and discussion- SAR μ-reactor

## Concentration field