

543 U6970/AM5019 實驗室晶片導論



液珠式微流體晶片之研發與應用

Droplet-Based Biochips

楊鏡堂 (Yang, Jing-Tang)

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

jtyang@ntu.edu.tw

中華民國一〇九年一月四日



蓮葉與玫瑰花的啟發暨生醫應用

Mimicrying lotus and rose and the inspired bio-application

楊鏡堂 (Yang, Jing-Tang)

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

jtyang@ntu.edu.tw

液珠式微流體晶片之研發與應用

大綱

液珠做為工作流體之流體晶片，除了可以改善連續流體因流道設計所造成的壓降能量損失，可降低元件複雜度與整合難度，亦可減少試劑的浪費殘留，達到更精準的反應控制。在微小尺度下，液珠具有高表面積與體積比的特性，能快速傳熱增加反應速率，在數位微流體系統中亦可容納少量樣本進行快速且多樣化的反應，實現高度平行化與獨立反應操控的目標，近年來已發展為微流體系統研究的重點。

本專題結合對生化分子自組裝技術、微液珠操控技術、接觸角與表面能階理論、微流體混合理論等領域，以及各種流體條件(表面張力、黏滯性)對液珠碰撞融合後流場及混合行為的關連等基礎學理與技術，討論流體混合行為與反應行為，進一步推展並完善開放式微液珠被動傳輸平台的設計，並將之應用於數位微流體生化反應調控的液珠式生醫檢測與液珠式生質柴油產製。

本次演講之主要內容是本研發團隊在液珠之相關研究成果，概分為三項：

- (1) 液珠移動、碰撞、混合、反應之流體動態分析
- (2) 液珠移動介面之分析及本實驗室所發展之幾種液珠操控技術
- (3) **應用實例**:生醫(可視化液珠式基因快篩技術)、個人化醫療檢測設計 (第11屆國家新創獎傑出學研新創技術)、能源(液珠式高速率低耗能生質柴油產製系統)(12屆國家新創獎傑出學研新創技術)、農業領域(12屆國家新創獎傑出學研新創技術)、藥物釋放設計

楊鏡堂教授

- 威斯康辛大學, 機械工程博士
- 國立成功大學, 機械工程碩士
- 國立成功大學, 造船工程學士

研究主題聚焦於以流體力學為主軸之跨領域整合型研究，涵蓋能環工程科技發展與策略規劃，綠色製造技術--有機合成技術 (flash synthesis)、生質燃料 (biofuel)與氫燃料等之奈微製程開發與燃燒、生化檢測 (DNA flash detection)，奈微米尺度熱流系統，仿生科技。

曾榮獲國科會傑出研究獎三次、2014年宗倬章先生講座教授、中國工程師學會傑出工程教授獎 (2007年)、中國機械工程師學會傑出工程教授獎 (2000年)；三次國家新創獎 (2015、2014、2008)、兩次Green Tech東元科技創新競賽亞軍暨人氣獎 (2014、2012)、2008年國家發明獎 (機械領域)，七項上銀科技機械碩士論文獎之榮譽 (銀質獎、銅質獎、優等獎、工具機特別獎、兩項佳作獎、一項晉級決審)，指導學生於2004-2015年期間共同榮獲全球或全國性學術獎項超過90項，包括九次全國力學會議學生論文競賽熱流能源組第一名，還有多項國際期刊與國際會議論文獎。



版权所有 杨长荣

09美国《国家地理》全球摄影大赛优秀参赛作品
<荷塘趣事> 摄影：杨长荣
www.huaxia-ng.com













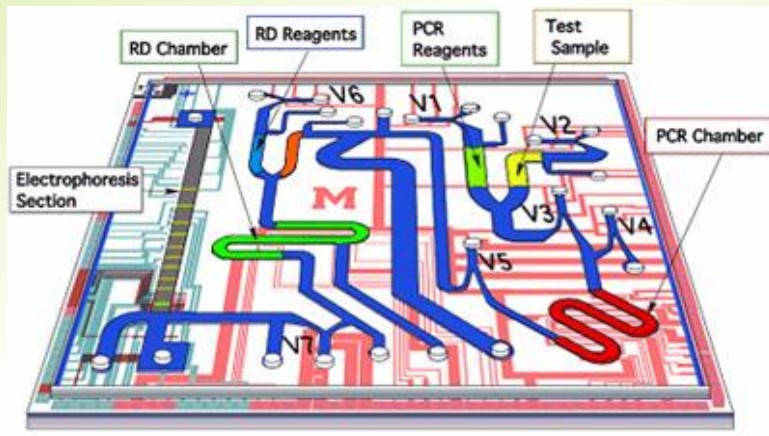


Film of Taro

Perspective

⊕ The Rise of μ -TAS

- 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



Pal *et al.*, *Lab Chip*. 2005



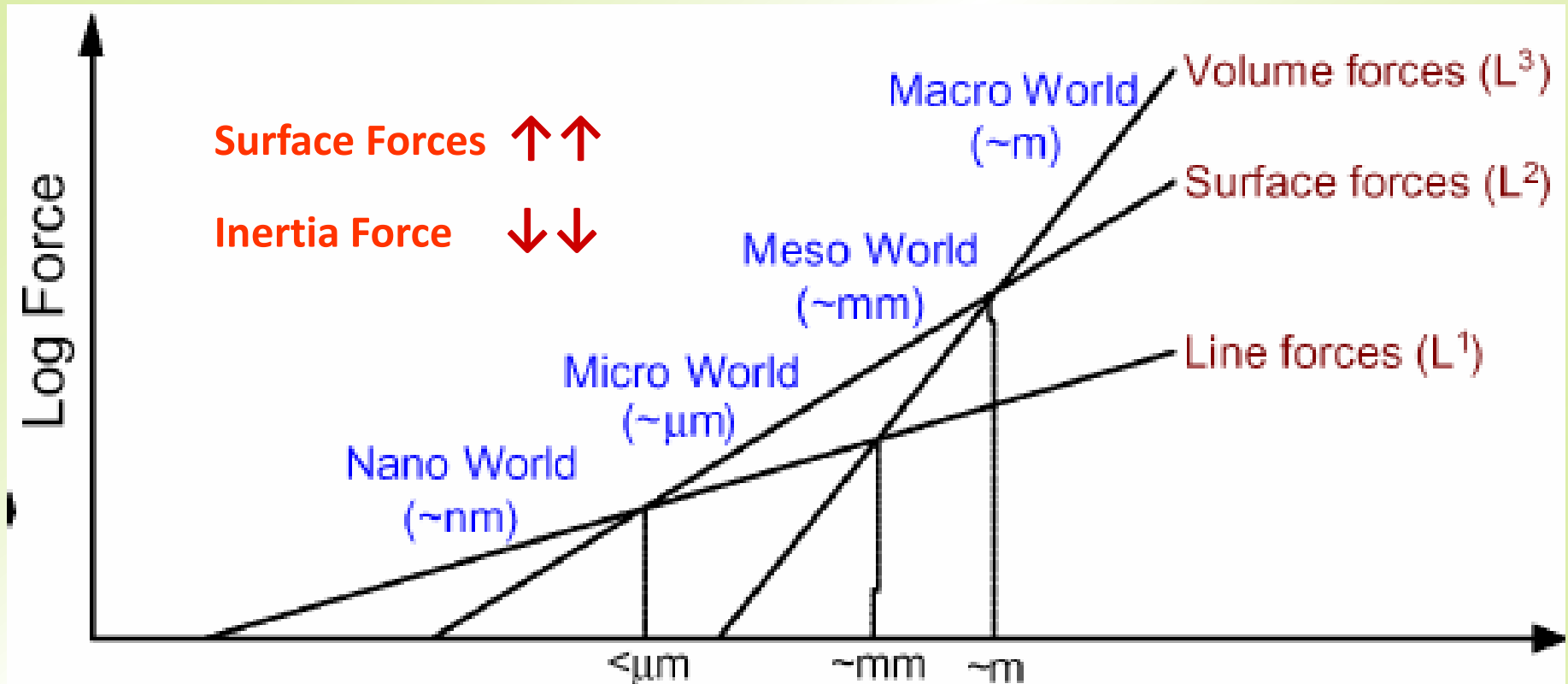
Extracted on 20121212 http://www.condenaststore.com/-sp/l-see-by-the-current-issue-of-Lab-News-Ridgeway-that-you-ve-been-work-New-Yorker-Cartoon-Prints_i8562947_.htm

微尺度效應

Volume force (mass) $\sim d^3$

Surface force (pressure, friction, electrostatic, diffusion) $\sim d^2$

Line force (surface tension) $\sim d^1$



What is the volume of a droplets ?

MICROFLUIDIC DEVICES

Micropumps/ valves/ flow sensors

Microfilters/ microreactors

Nanotechnology/ Nanodevices?

Microneedles

Microanalysis systems

1Å

1nm

1 μm

1mm

1m Length scale

1 aL 1 fL

1 pL 1 nL

1 μL 1 mL 1 L 1000 L Volume scale

Molecules

Smoke particles

Human hair

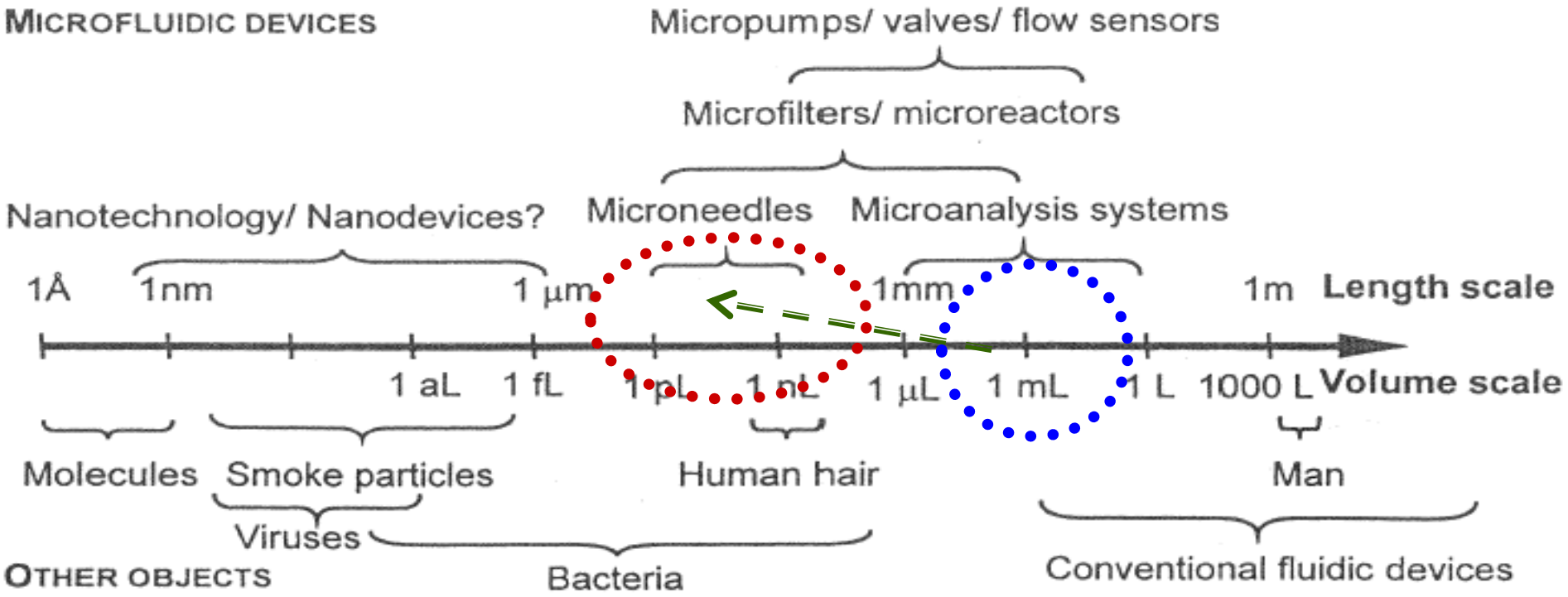
Man

Viruses

Bacteria

Conventional fluidic devices

OTHER OBJECTS



Characteristics of particles & particle dispersoids

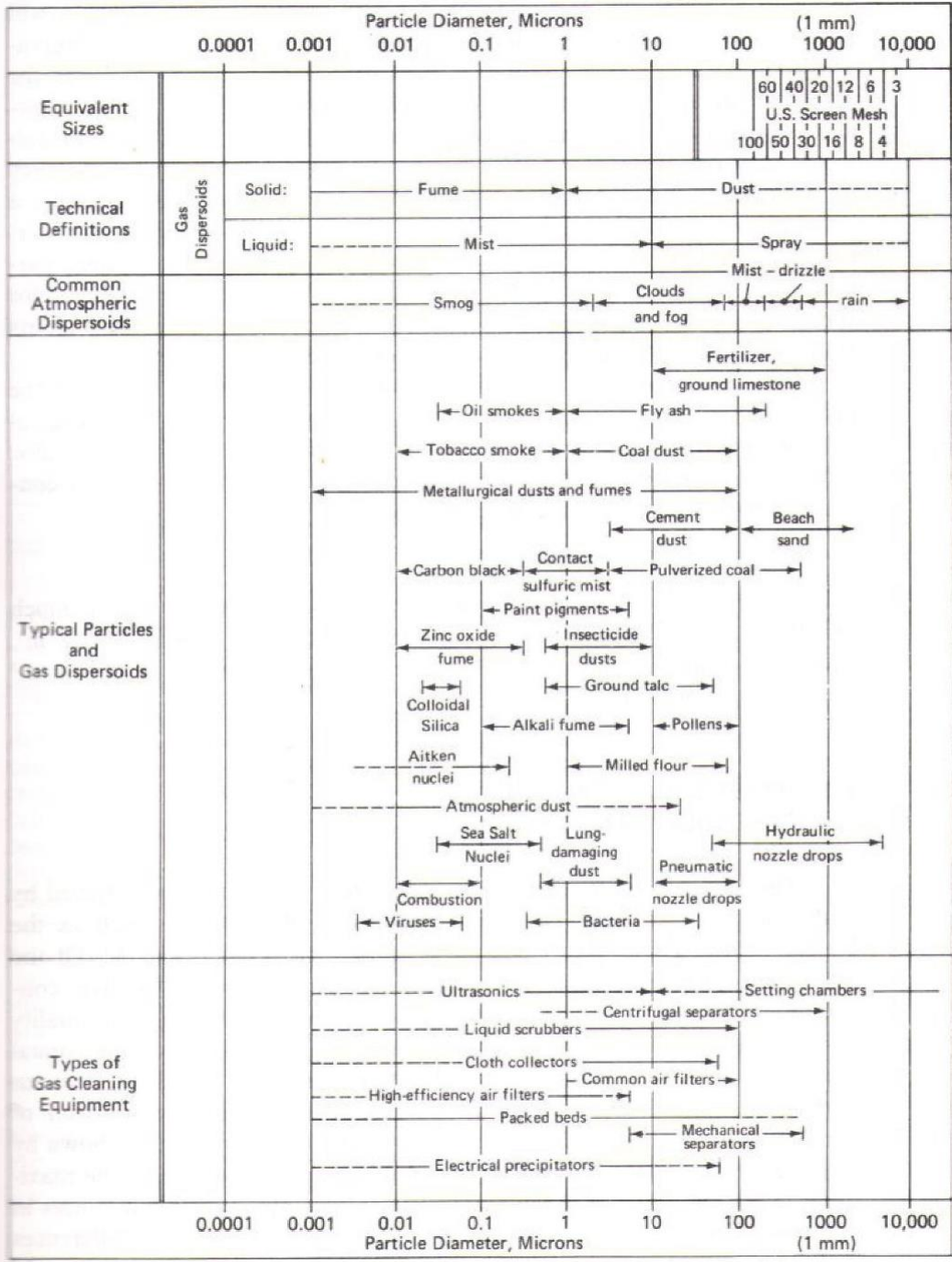


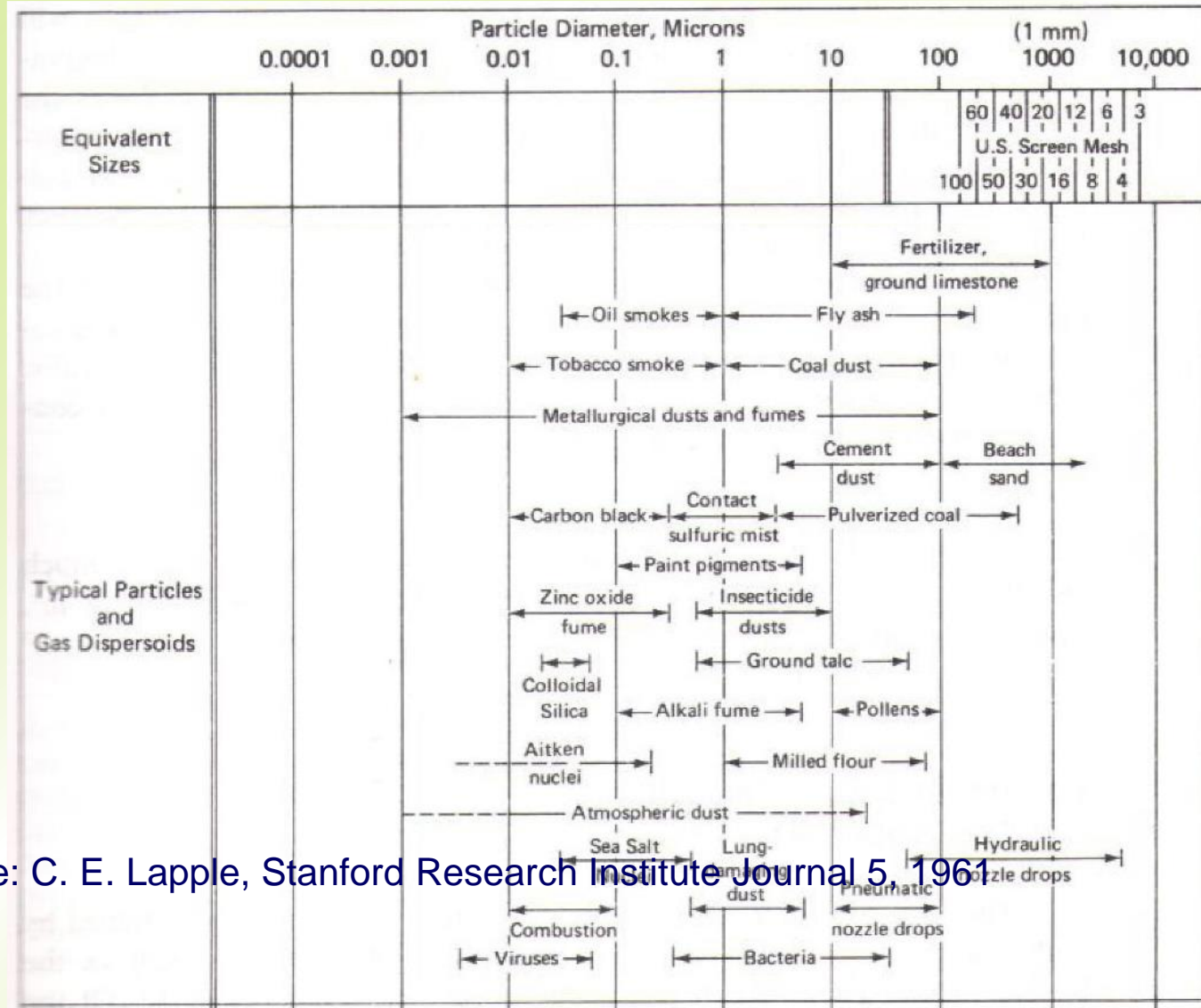
Figure 5-1 Characteristics of particles and particle dispersoids. (Source: C. E. Lapple, Stanford Research Institute Journal 5, 1961.)

Characteristics of particles & particle dispersoids

		Particle Diameter, Microns												
		0.0001	0.001	0.01	0.1	1	10	100	(1 mm)			10,000		
Equivalent Sizes									60	40	20	12	6	3
									U.S. Screen Mesh					
									100	50	30	16	8	4
Technical Definitions	Gas Dispersoids	Solid:	Fume				Dust							
		Liquid:	Mist				Spray							
Common Atmospheric Dispersoids		Smog				Clouds and fog			Mist - drizzle			rain		

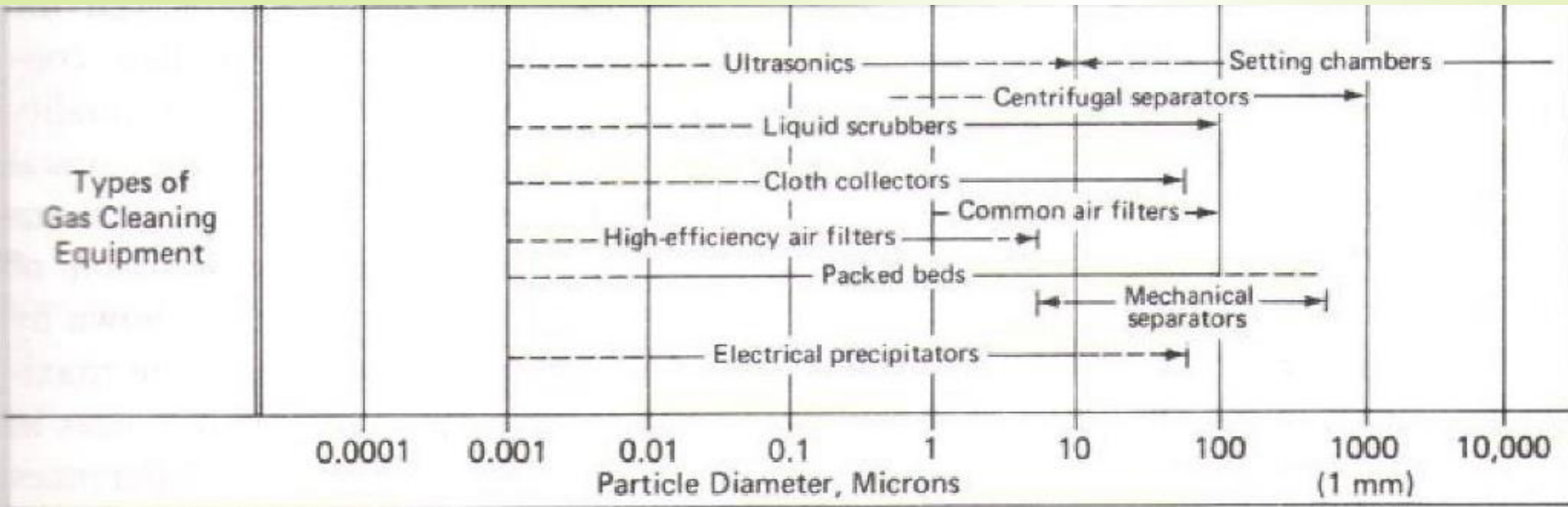
Source: C. E. Lapple, Stanford Research Institute Journal 5, 1961

Characteristics of particles & particle dispersoids



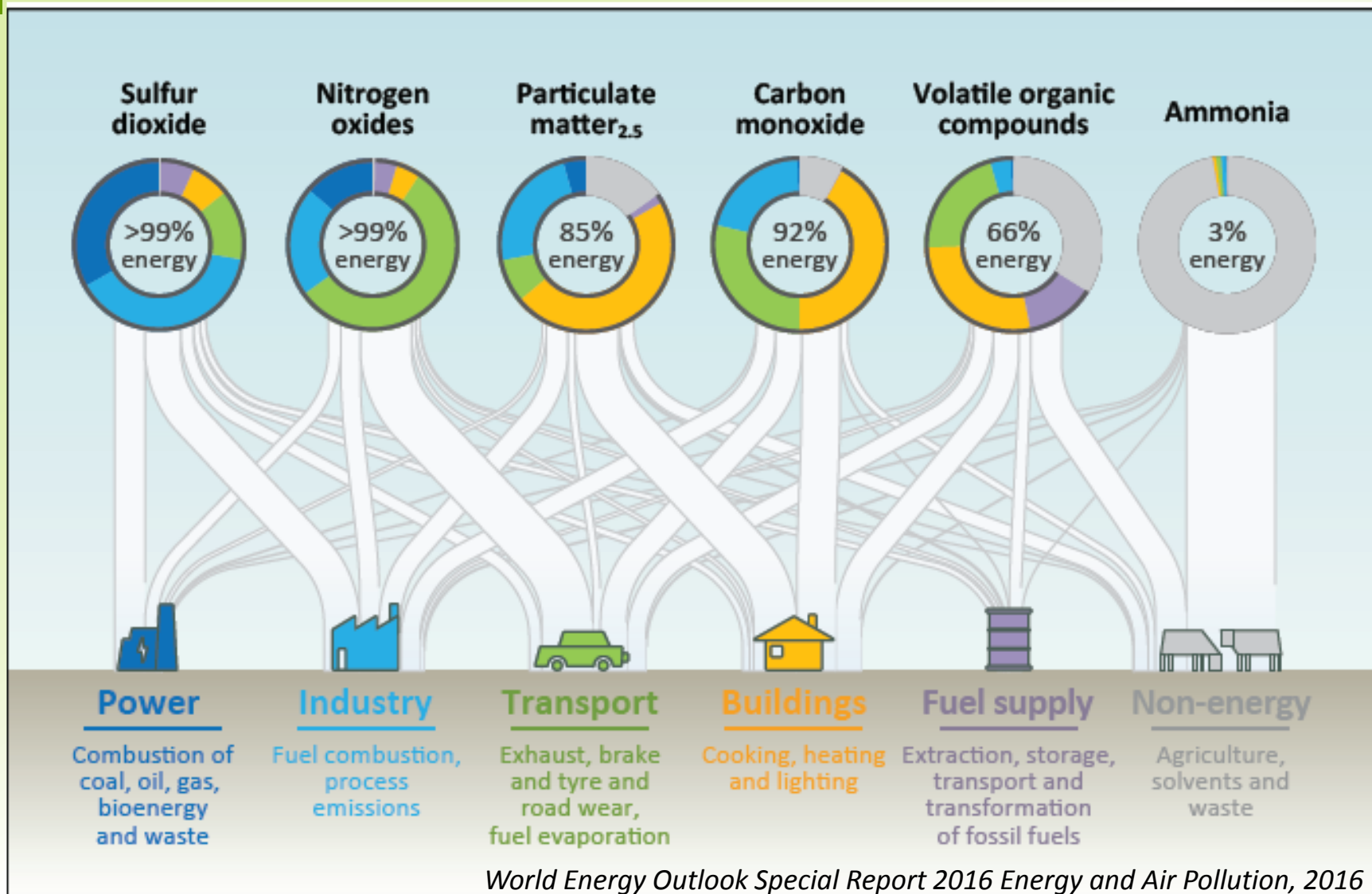
Source: C. E. Lapple, Stanford Research Institute Journal 5, 1961

Characteristics of particles & particle dispersoids



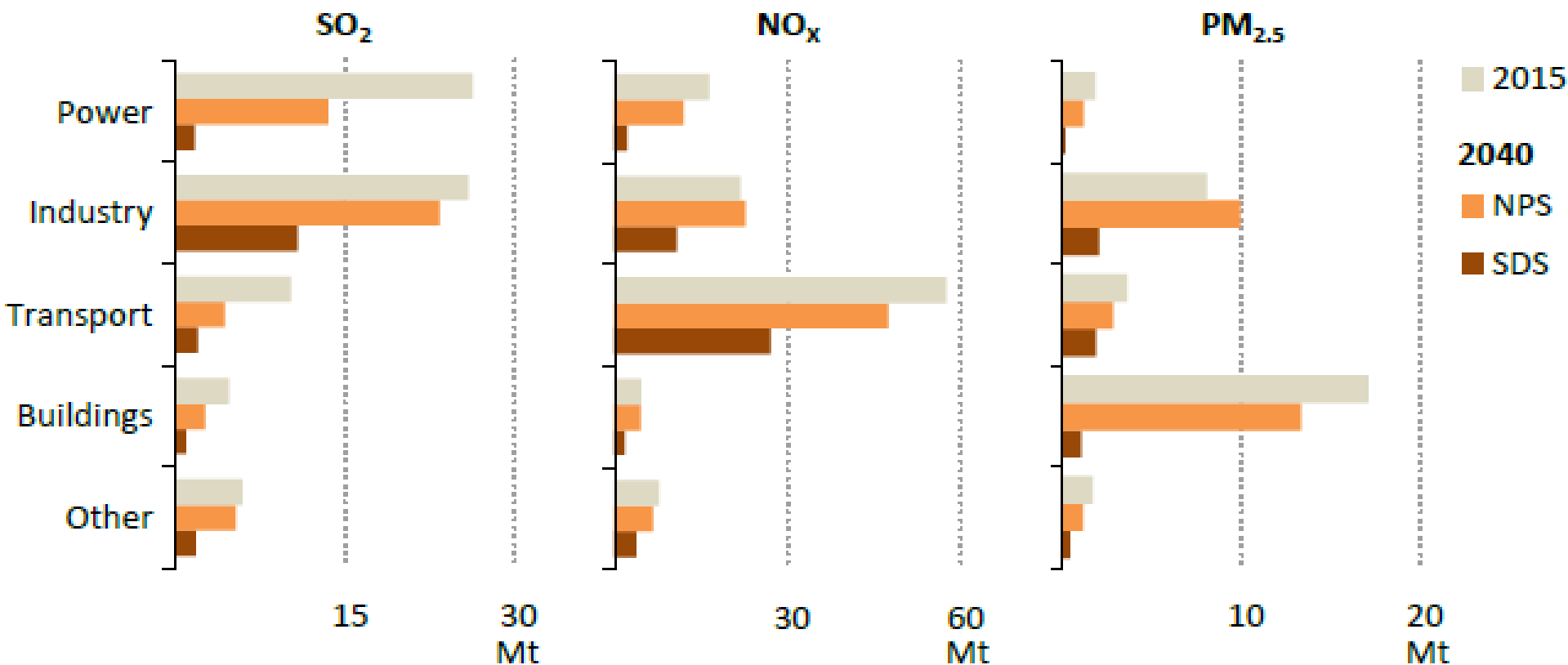
Source: C. E. Lapple, Stanford Research Institute Journal 5, 1961

人為排放空氣污染成分之來源分析-- 2015年 (Selected primary air pollutants and their sources, 2015)



Air pollution emissions by sector and scenario, 2015 & 2040

IEA, World Energy Outlook-2018



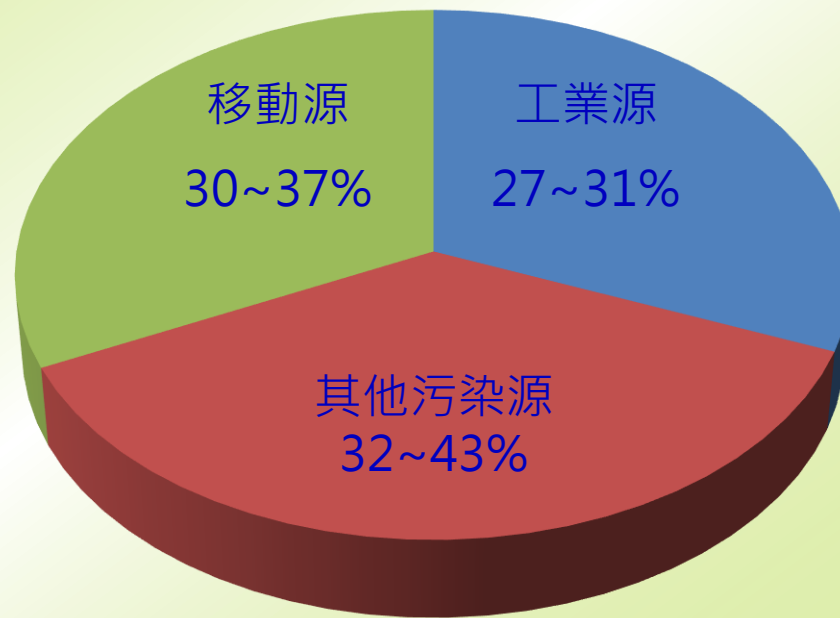
Pollutant emissions generally fall in the New Policies Scenario, but in most cases by much less than in the Sustainable Development Scenario

Notes: NPS = New Policies Scenario; SDS = Sustainable Development Scenario. Industry includes fuel combustion in the industry sector and transformation processes other than power generation.

Source: IEA analysis; International Institute for Applied Systems Analysis.

我國PM_{2.5}來源比率分析

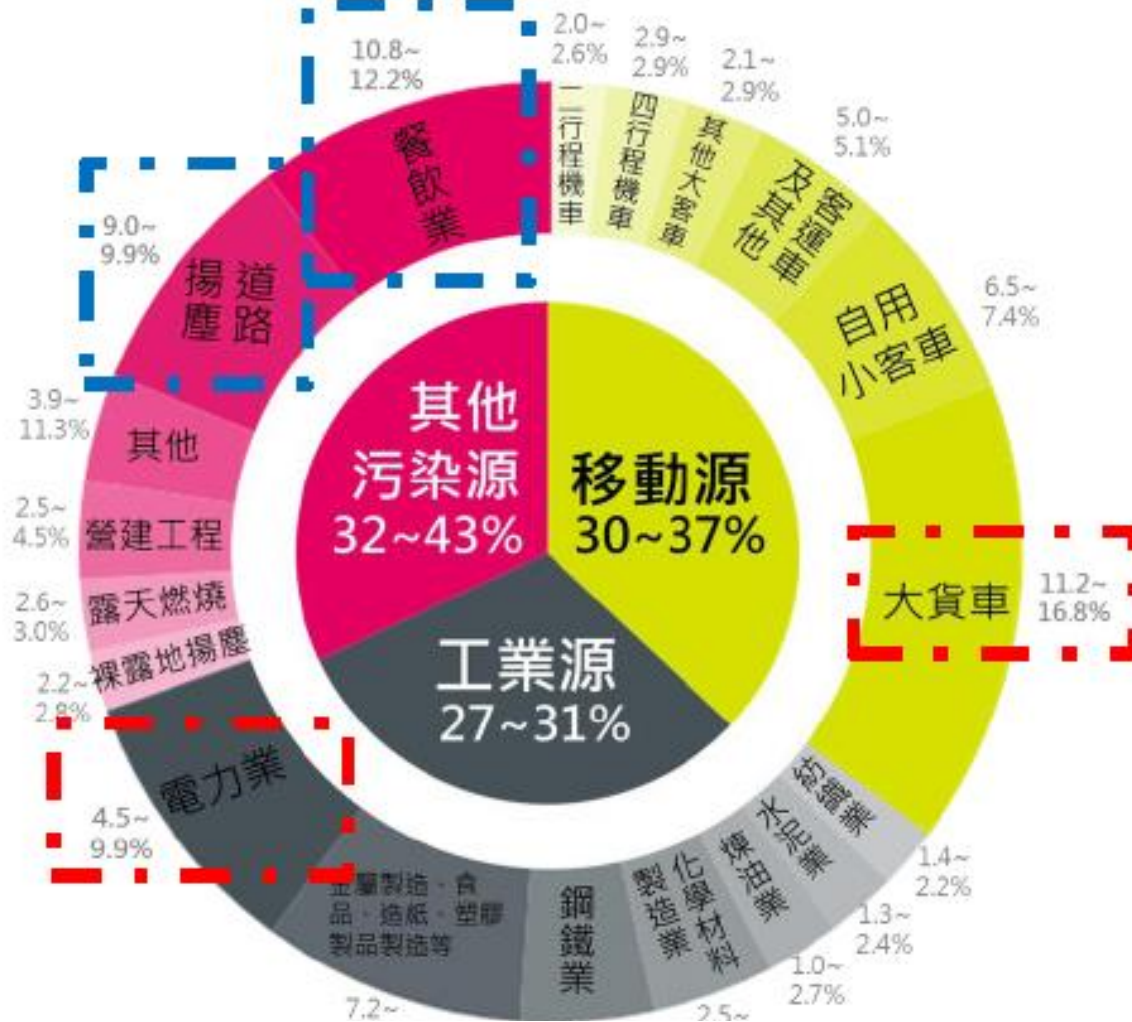
- 我國PM_{2.5}境外傳輸來源比率約為34~40%，境內污染源比率約為60~66%。
- 境內污染源中，移動源影響比率約為30~37%、工業源約為27~31%、其他污染源約為32~43%。



資料來源:環保署委託成功大學吳義林教授「台灣細懸浮微粒(PM_{2.5})成分與形成速率分析計畫」及雲林科技大學張良輝教授「強化空氣品質模式制度計畫(第二年)」研究成果
註：依據排放清冊 (TEDS 8.1版) 估算

我國境內PM_{2.5}來源比例分析

來源眾多，只管制單一污染源，無法產生全面性成效。



我國PM_{2.5}

境外傳輸來源比率

約為34~40%，

境內污染源比率

約為60~66%。

境內污染源中，

移動源影響比率約為30~37%，

工業源約為27~31%，

其他污染源約為

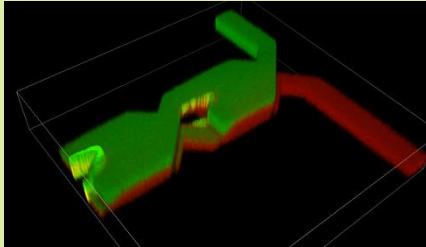
32~43%。

連續式流場 VS. 液珠式晶片



Digital Microfluidics

Fang & Yang, *Sens. Actuators, B*, 2009



Continuous flow

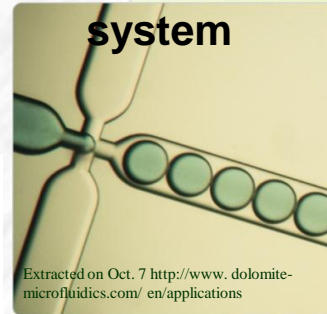


Extracted on Oct. 23
<http://blogs.rsc.org/chipsandtips/2010/06/18/connector-less-manipulation-of-small-liquid-volumes-in-microchannels/>

Droplet/plug flow
 (digital flow)

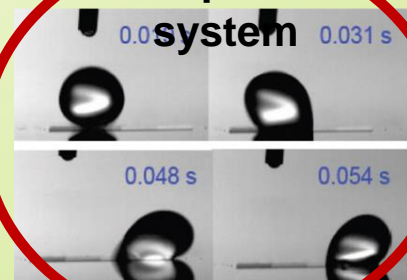
- ✓ Eliminate micropumps and valves
- ✓ Controllability
- ✓ Accurate dose control
- ✓ Surface area to volume ratio

closed system

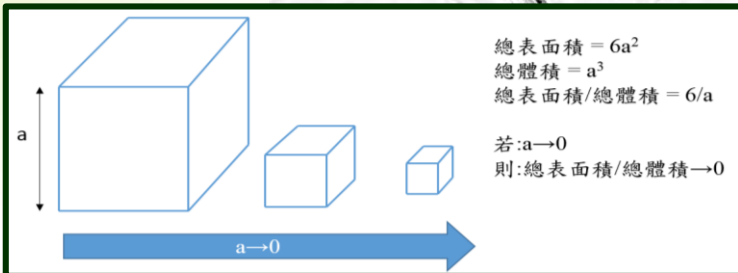


Extracted on Oct. 7 <http://www.dolomite-microfluidics.com/en/applications>

open system



Yang, *et al.*, *Langmuir*, 2008



- ✗ Unlimited to microchannels
- ✗ Maneuverability
- ✗ Vaporize

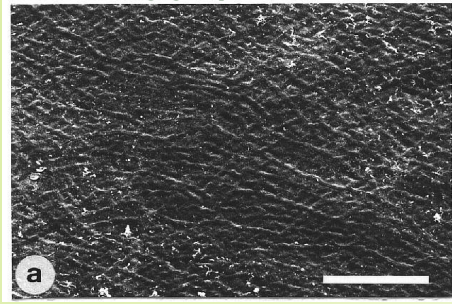


Science

Hydrophilic and Hydrophobic Features of Leaves

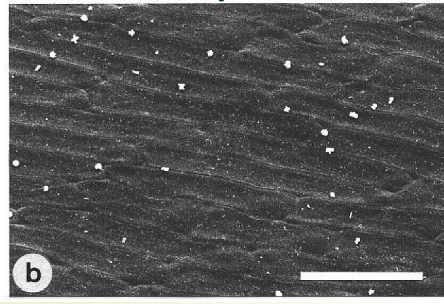
wetted plant leaf

55.4°



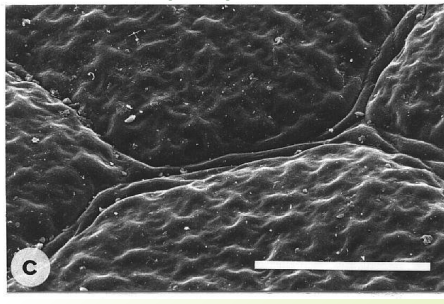
Gnetum gnemon

28.4°



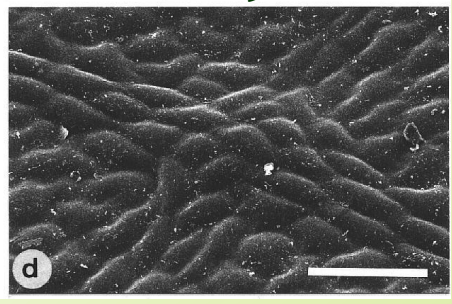
Heliconia densiflora

71.7°



Fagus sylvatica

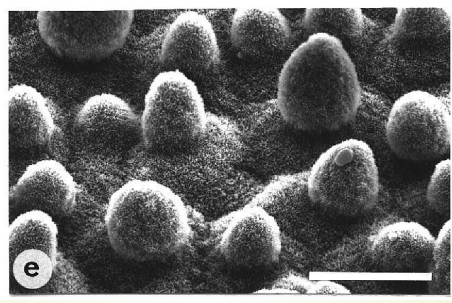
88.9°



Magnolia denudata

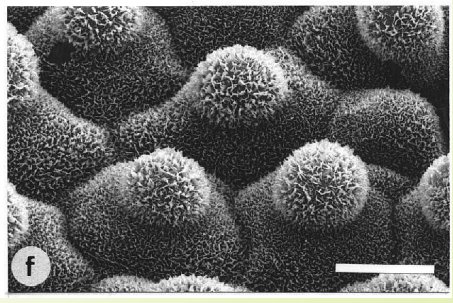
non-wetted plant leaf

160.4°



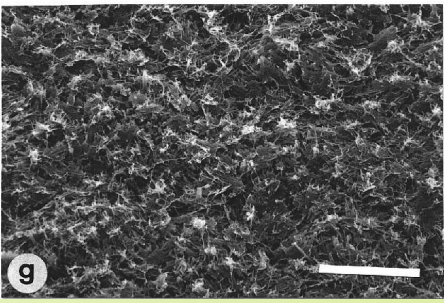
Nelumbo nucifera

159.7°



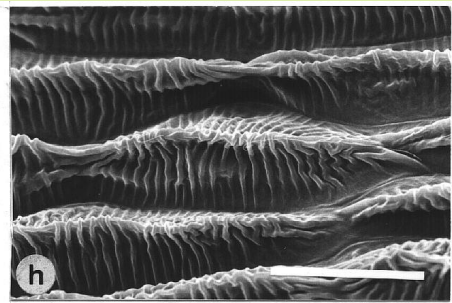
Colocasia esculenta

160.3°



Brassica oleracea

128.4°



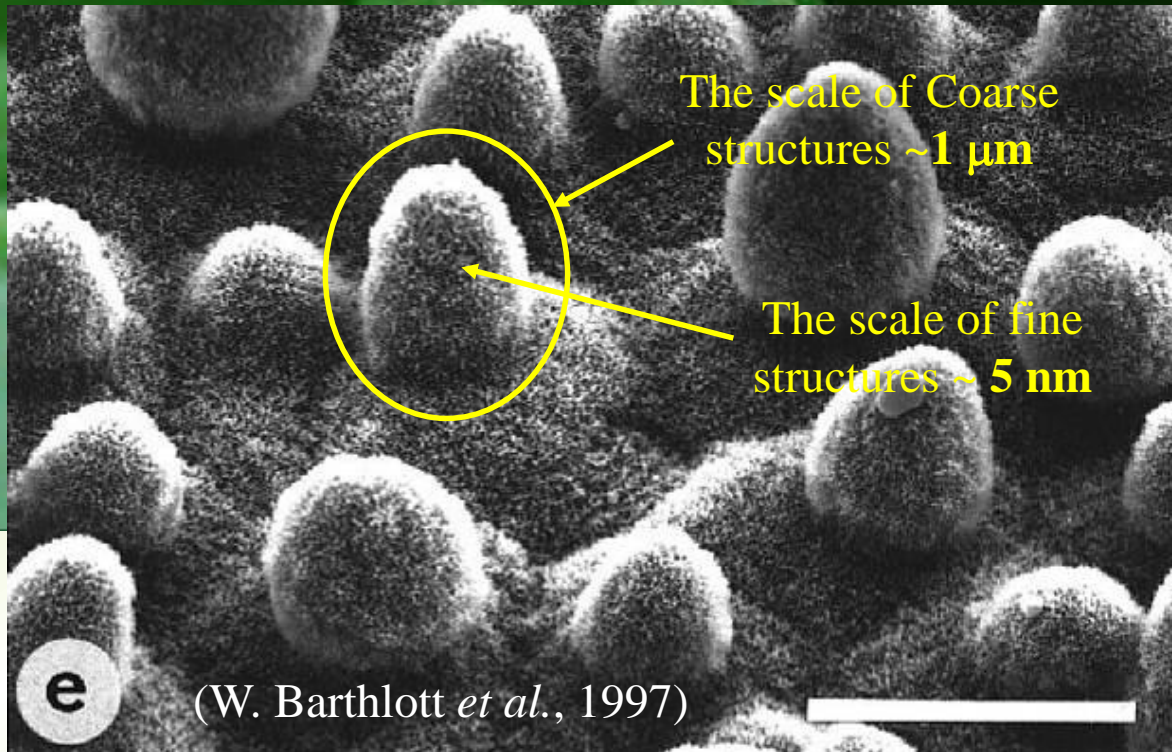
Mutisia decurrens

(Barthlott et al., 1997)

Lotus leaf

Lotus leaf, Super-hydrophobic surface

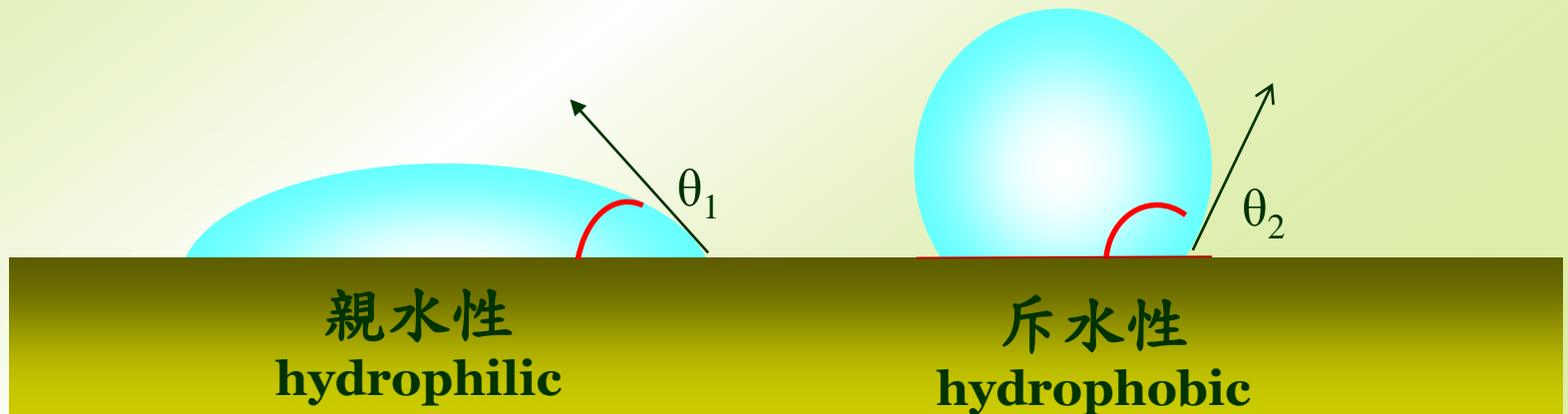
Apparent contact angle, $\theta_c \sim 160.4^\circ$



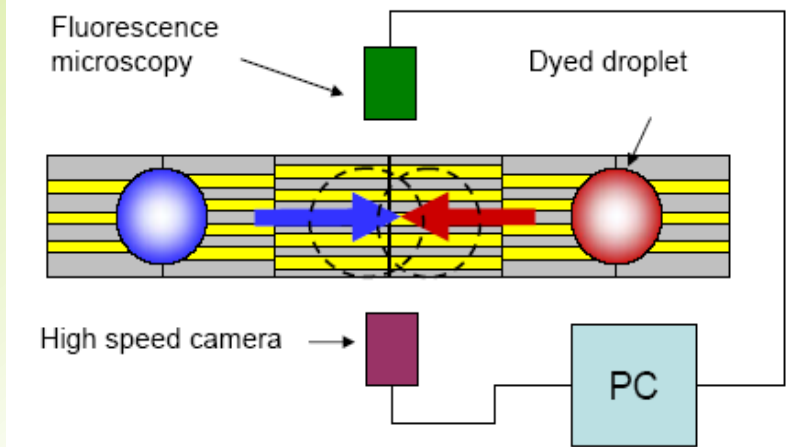
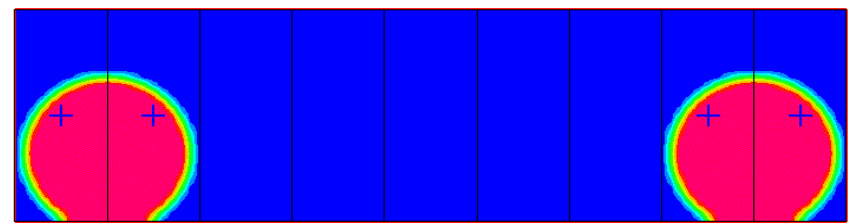
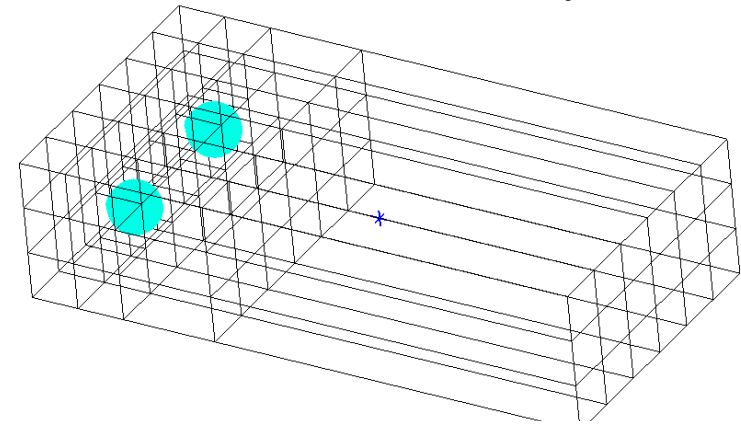
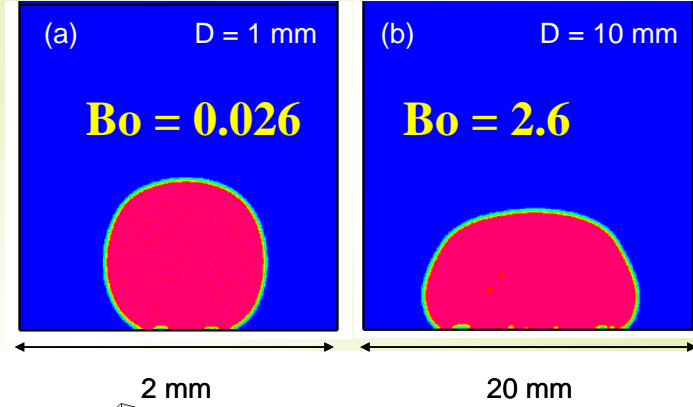
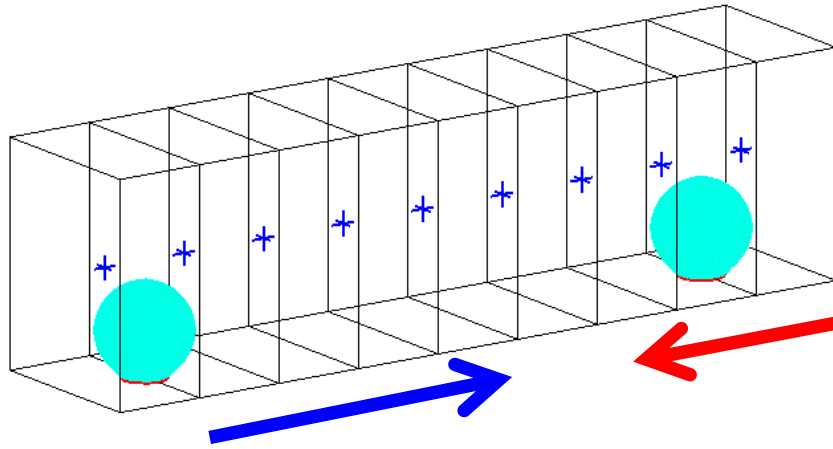
(W. Barthlott *et al.*, 1997)

親水性與疏水性

- 由水滴與表面之接觸角作為其親、疏水性之判斷：
 - 接觸角 $< 90^\circ$ \longrightarrow 親水性(hydrophilic)表面，如 θ_1
 - 接觸角 $> 90^\circ$ \longrightarrow 斥水性(hydrophobic)表面，如 θ_2



Challenges for Numerical Simulation



Collision and Mixing of two Droplets

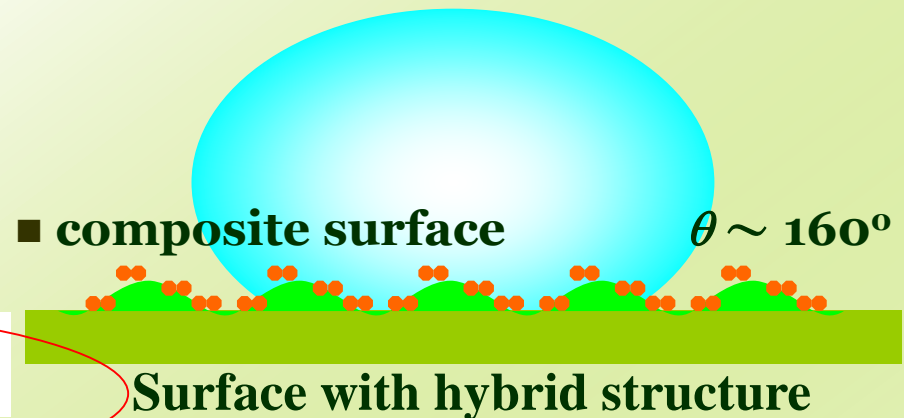
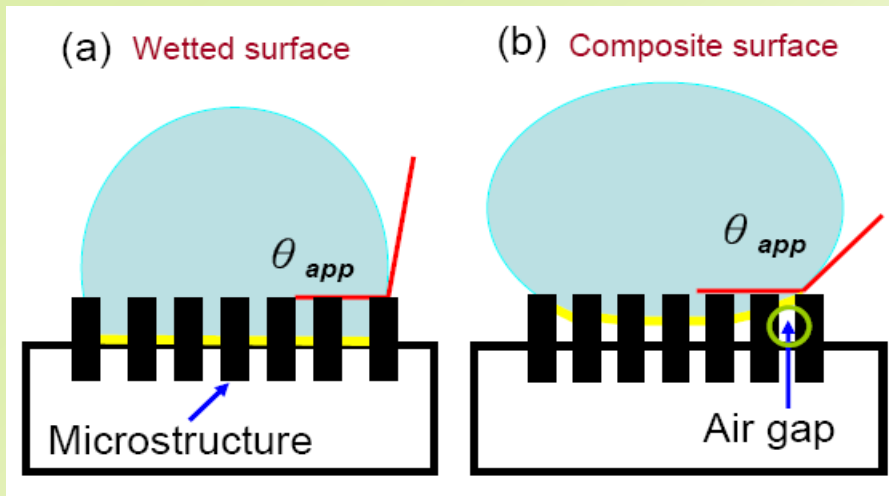
Michael Jackson ?

劉謙 ?



Technology

Schematics of Surface Effects



- Smooth surface

Young equation

$$\cos \theta_0 = (\gamma_{sv} - \gamma_{sl}) / \gamma_{lv}$$

- Wetted surface

Wenzel equation

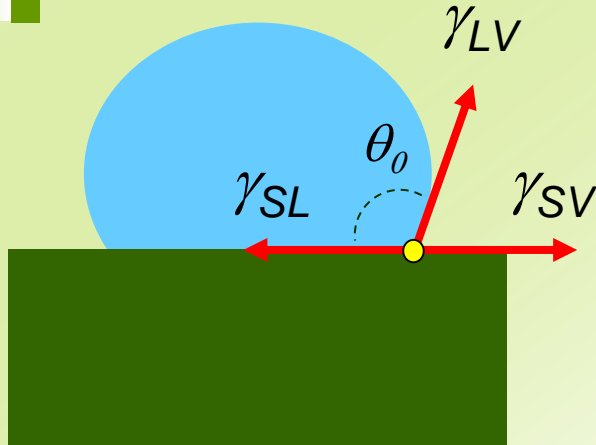
$$\cos \theta_{app} = r \cos \theta_0$$

- Composite surface

Cassie and Baxter Eq.

$$\cos \theta_{app} = f_1 \cos \theta_1 + f_2 \cos \theta_2$$

接觸角度與表面自由能



■ 平滑表面

Young equation

$$\cos \theta_0 = \frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}}$$

表面自由能

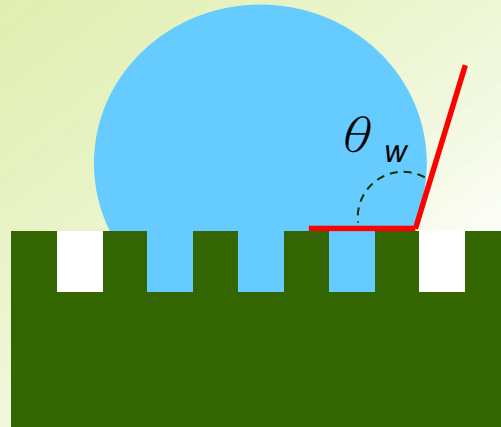
$$\frac{G_s}{\sqrt[3]{9\pi V^{2/3} \gamma_{LV}}} = (1 - \cos \theta_r)^{2/3} (2 + \cos \theta_r)^{1/3}$$

潤濕表面： $\theta_r \rightarrow \theta_w$

複合表面： $\theta_r \rightarrow \theta_c$

(Patankar,

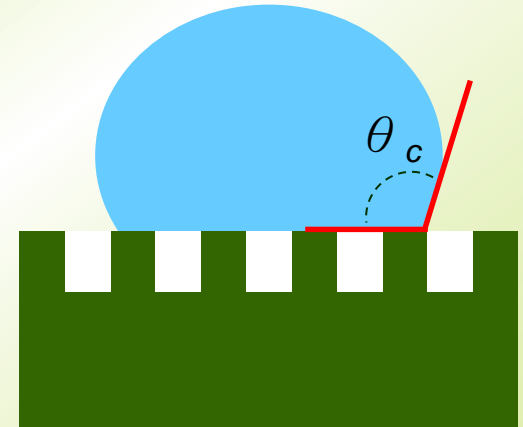
2000)



■ 潤濕表面

Wenzel equation

$$\cos \theta_w = \frac{r(\gamma_{SV} - \gamma_{SL})}{\gamma_{LV}} = r \cos \theta_0$$



■ 複合表面

Cassie and Baxter Equation

$$\cos \theta_c = f_1 \cdot \cos \theta_1 + f_2 \cdot \cos \theta_2$$

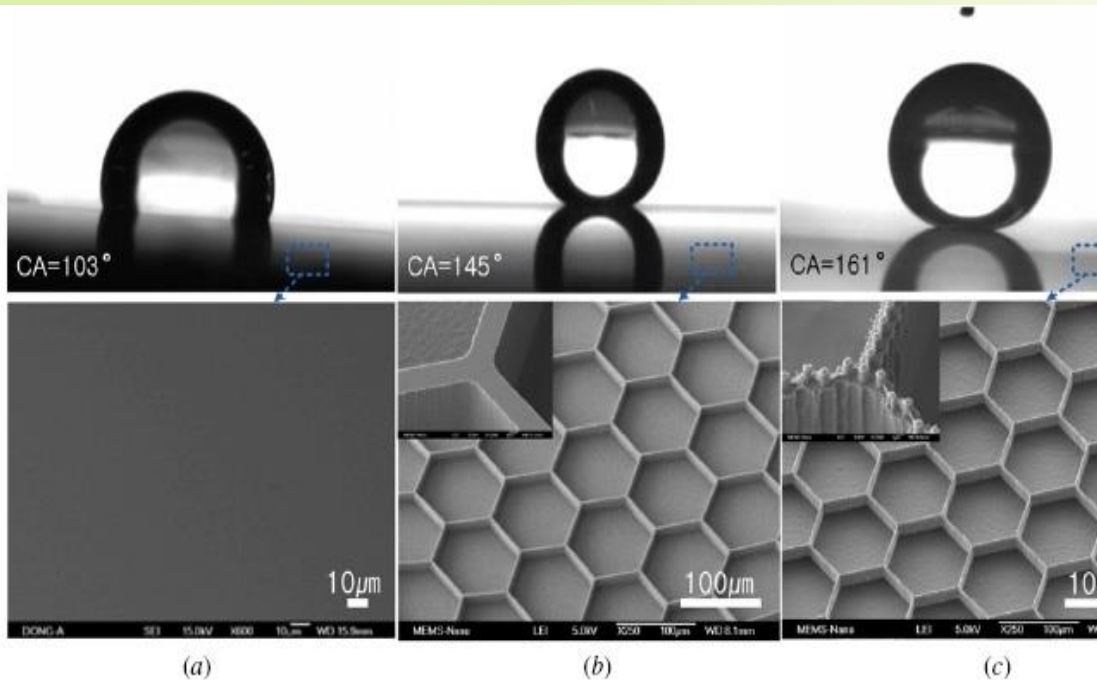
$$r = \frac{A_{actual}}{A_{projected}} \quad f_1 = \frac{A_{S-L}}{A_{total}} \quad f_2 = \frac{A_{V-L}}{A_{total}}$$

接觸角度, θ

表面自由能, G_s

Hybrid-structured surface

- Lee, S. M., Jung, I. D., and Ko, J. S. 2008. J Micromech Microeng, Vol. 18(12), pp. 125007.



W-W model

W-C model

C-C model

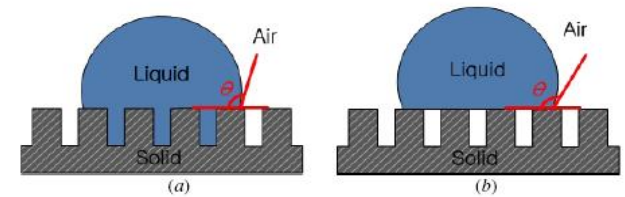
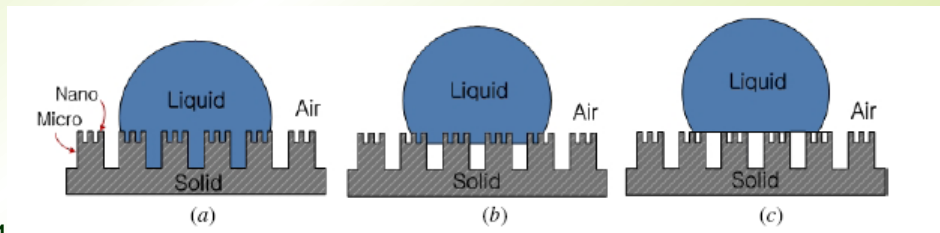
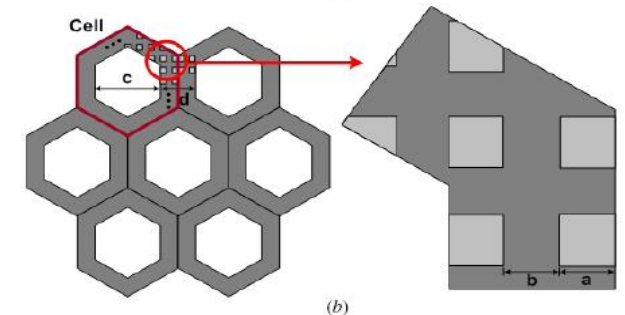
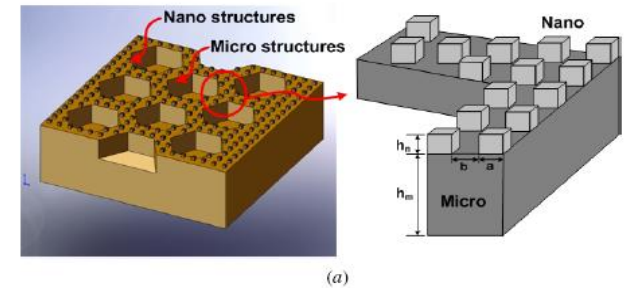
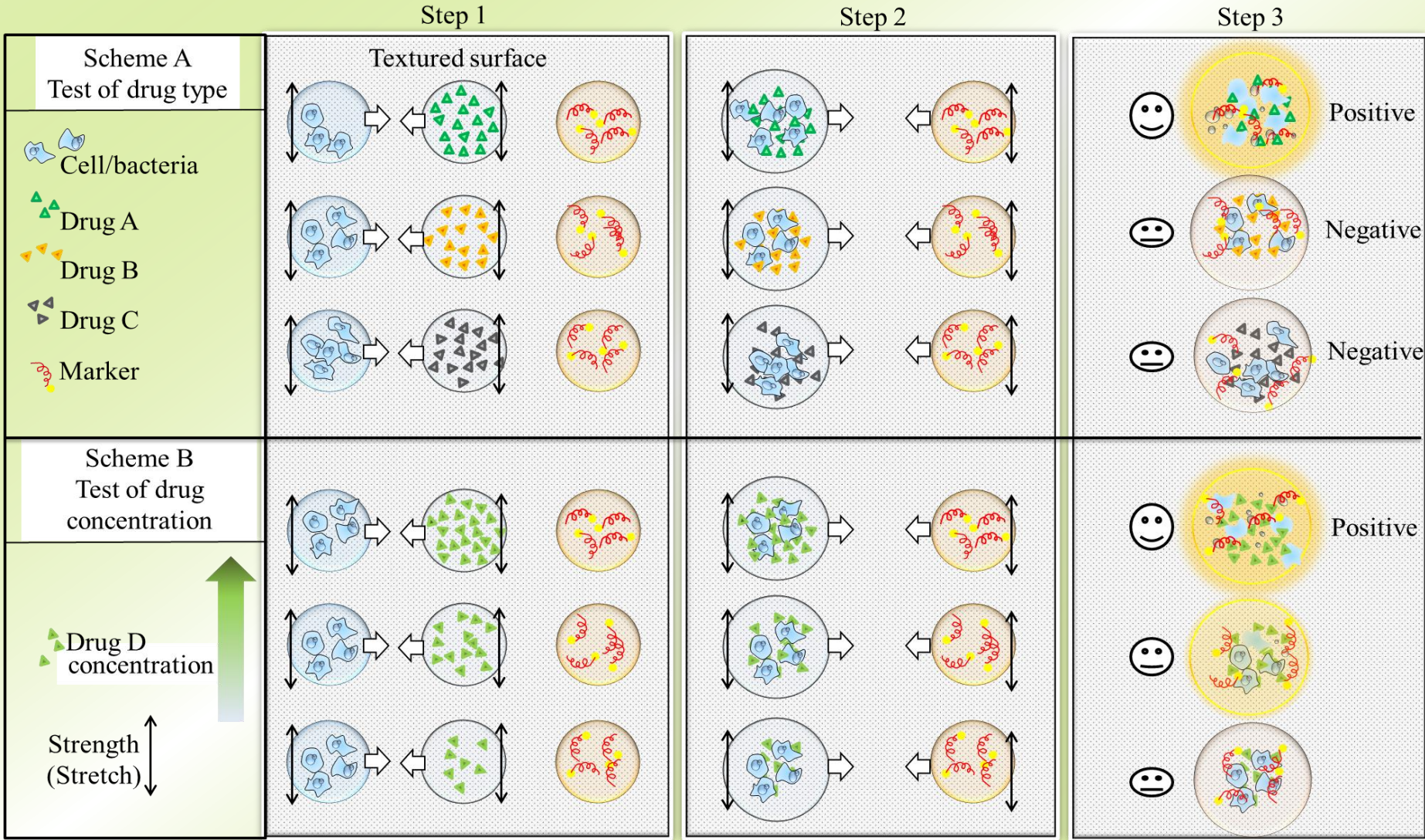
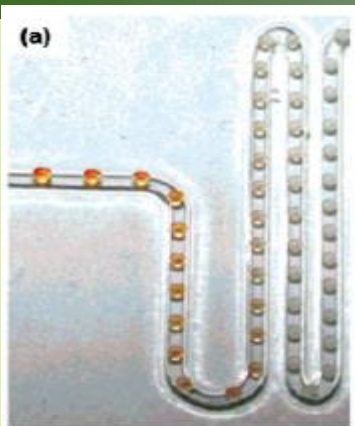


Figure 1. Wetting modes of liquid drops on a rough surface: (a) Wenzel mode; (b) Cassie-Baxter mode.

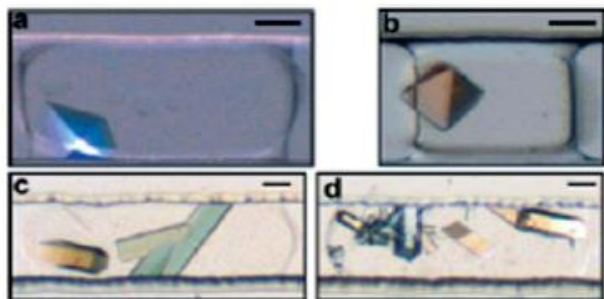




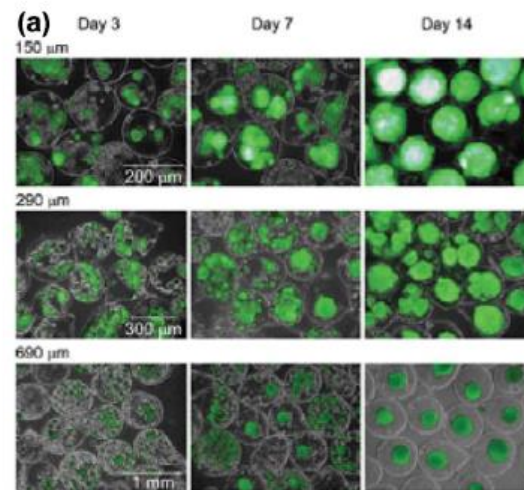
Droplet Applications



Cygan *et al.*, *Langmuir*, 2005



Hatakeyama *et al.*, *J. Am. Chem. Soc.*, 2006



Sugiura *et al.*, *Biomed. Microdev.*, 2007

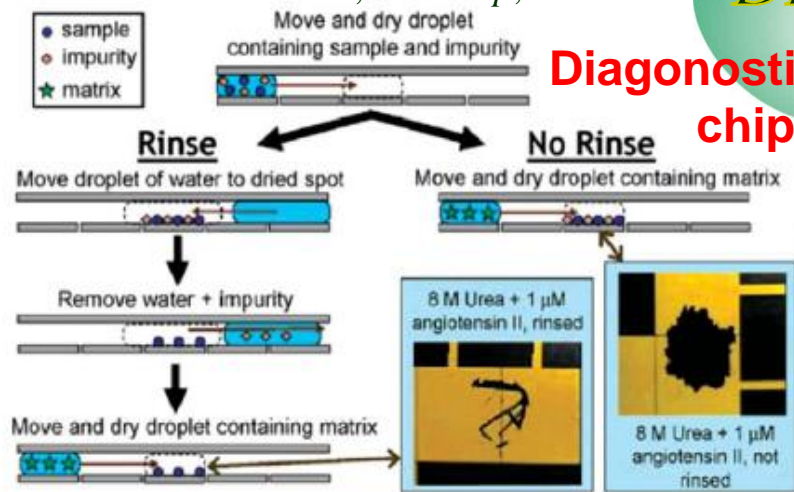
Drug discovery

Chemical reactions

Therapeutic agent delivery

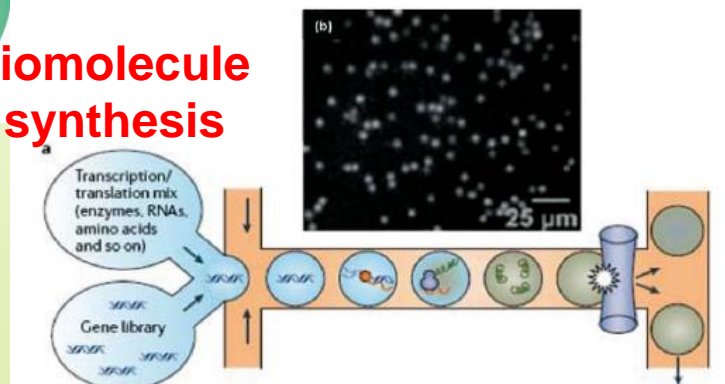
Droplet

Srinivasan *et al.*, *Lab Chip*, 2004



Diagnostic chips

Biomolecule synthesis

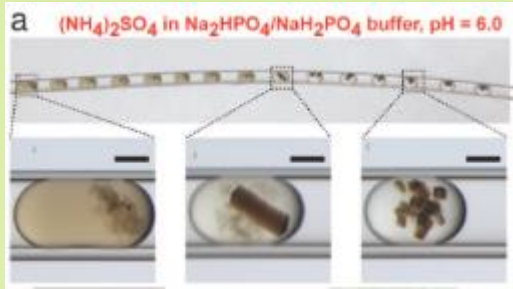


(a) Dittrich *et al.*, *Nat. Rev. Drug Discovery*, 2006

(b) Dittrich *et al.*, *ChemBioChem*, 2005

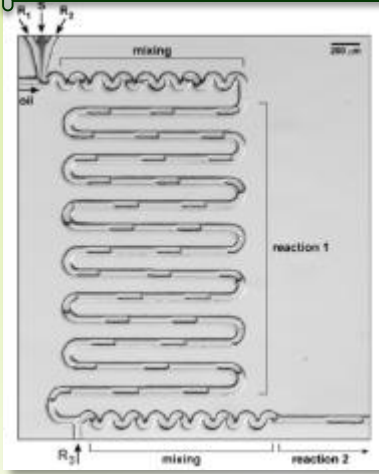
流道內液珠式微流體系統應用

蛋白質合成監控



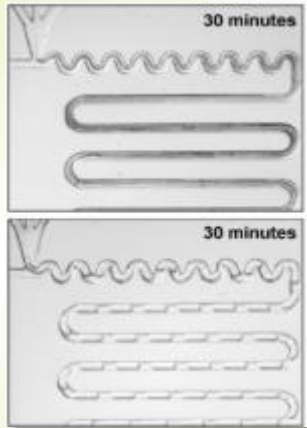
Li et al., P. Natl. Acad. Sci. USA, 2006/0

減少縱向擴散

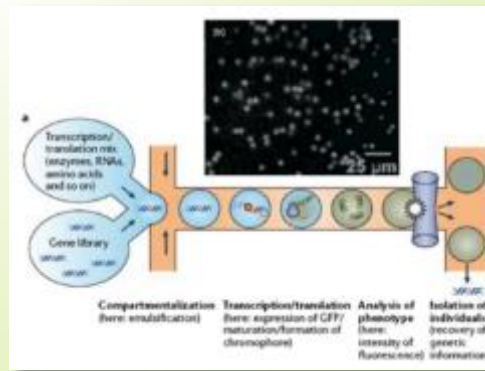


(Shestopalov et al., Lab Chip, 2004)

奈米粒子合成

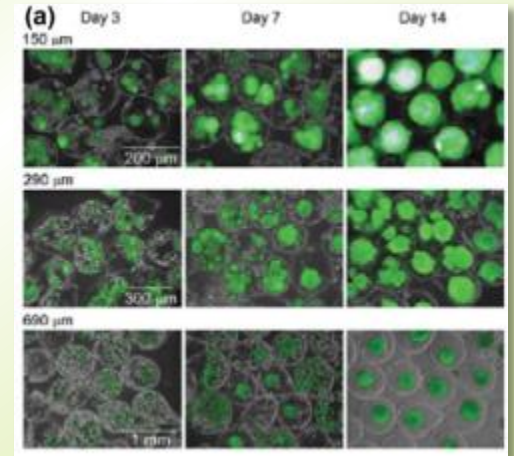


醫藥檢測篩選



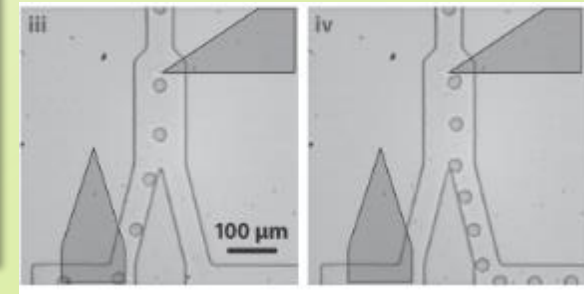
(Dittrich et al., Nat. Rev., 2006)

細胞包覆



(Sugiura. et al., Biomed Microdev., 2007)

高密閉性，可做細胞包覆，並平行監控。



(Ahn et al., Appl. Phys. Lett., 2006)

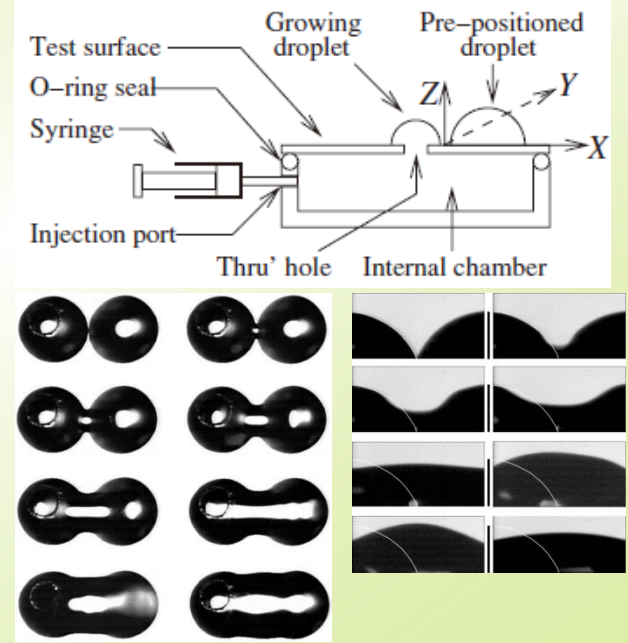
液珠外有薄膜保護隔絕產物沾附流道壁面

對個別液珠檢測篩選

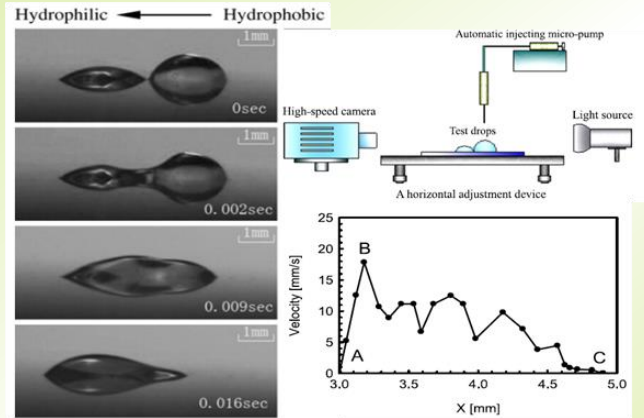
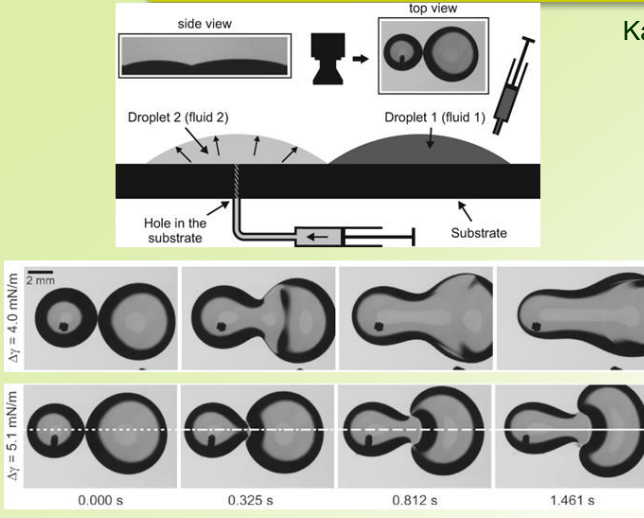
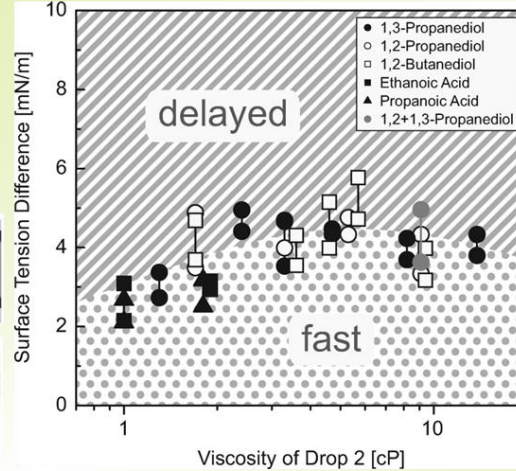
微液珠碰撞與融合

表面張力及黏滯性不同的液珠，接觸後的接合現象，可分為延遲接合與快速接合兩種。

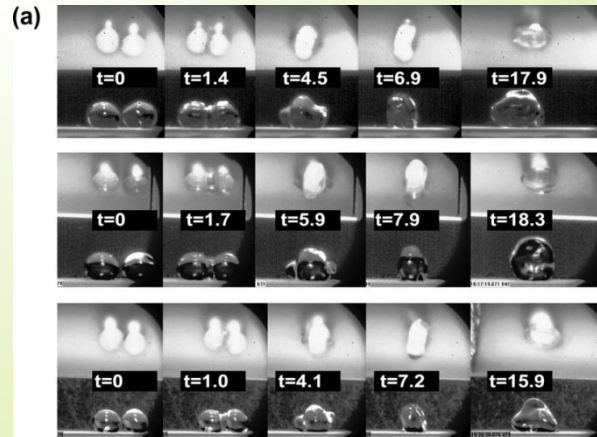
Kapur and Gaskell, *Phys. Rev. E*, 2007



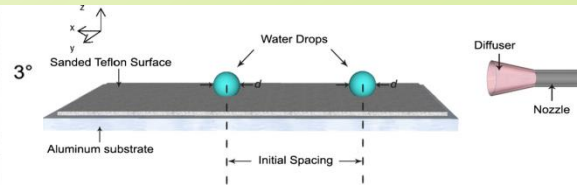
Karpitschka and Riegler, *Langmuir*, 2010



Wang et al., *J Supercond Nov Magn*, 2010



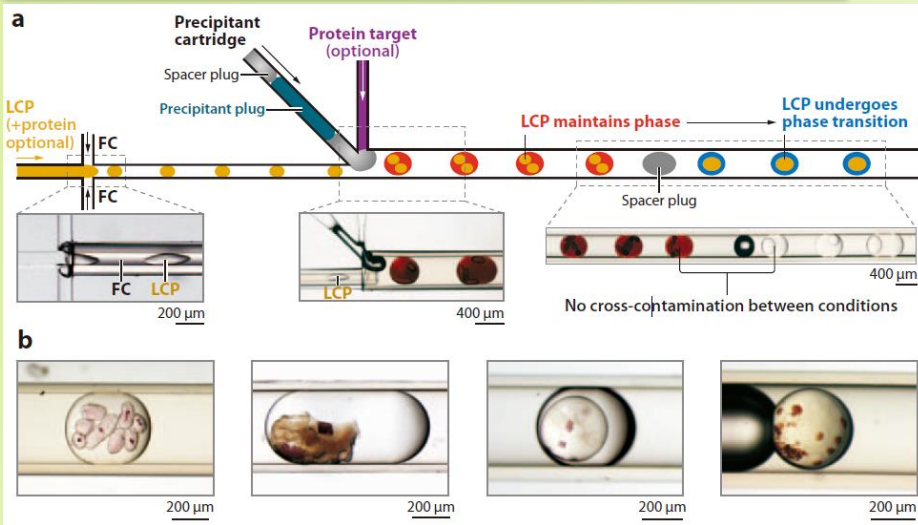
Nilsson and Nilsson, *J. Colloid interface Sci.*, 2011



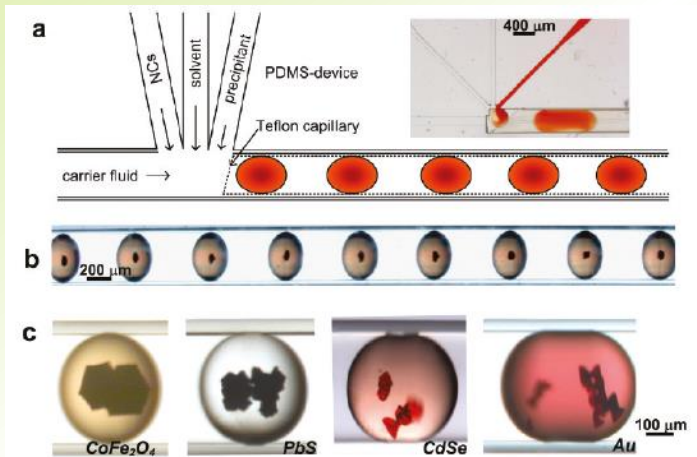
目前微液珠融合的相關研究，仍以輪廓變化以及流體混合為主

液珠式微反應器

Droplet-based microfluidic system for membrane crystallization within lipidic mesophases

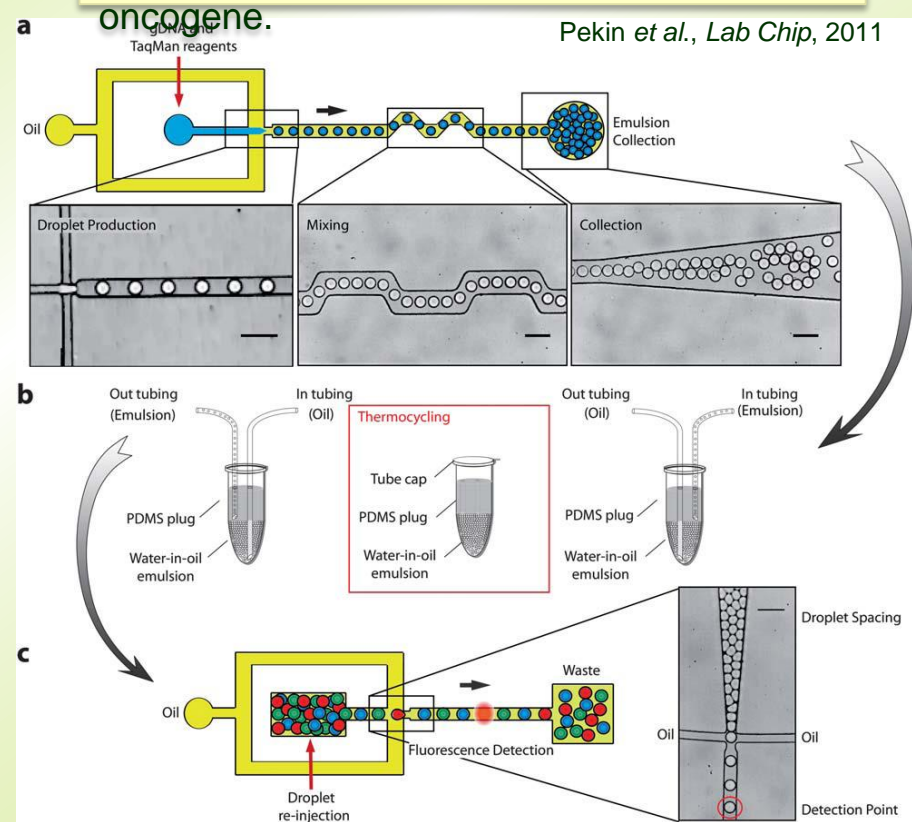


Li et al., *Microfluid. Nanofluid.*, 2010



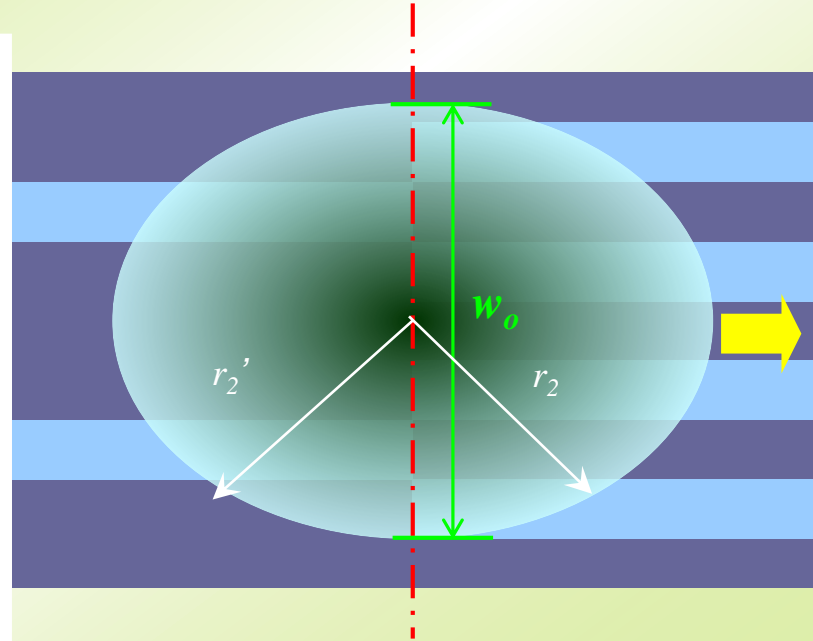
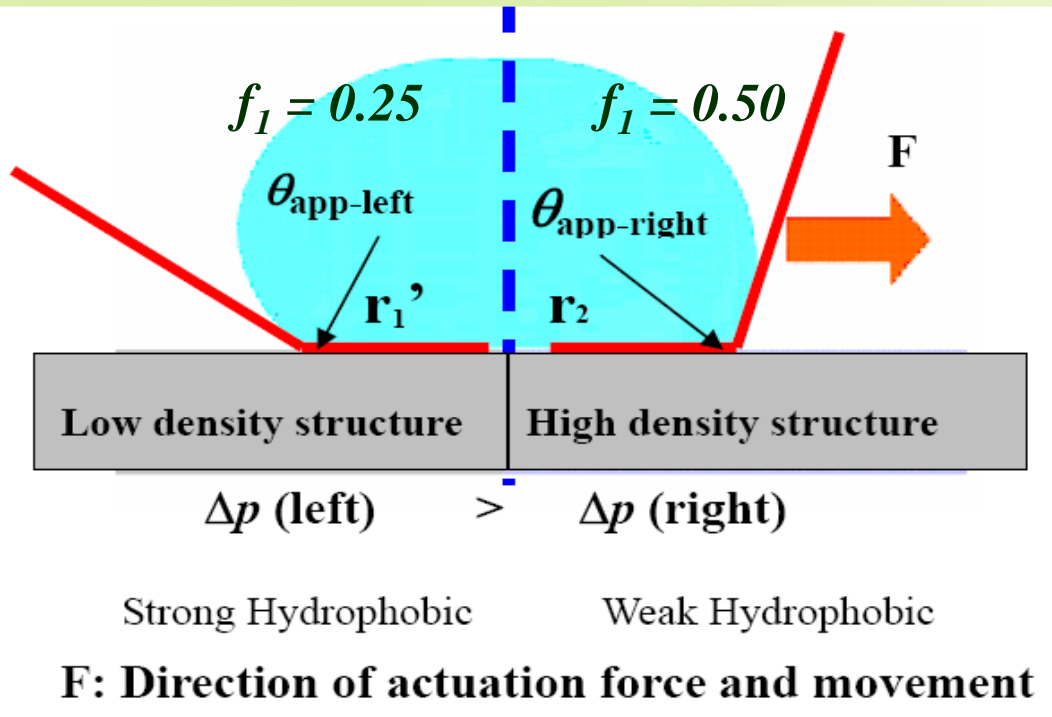
Bodnarchuk, *J. Am. Chem. Soc.*, 2011

Development and validation of a method to allowed the highly sensitive and quantitative detection of mutations in the KRAS oncogene.



The self-assembly of inorganic nanocrystals (NCs) confined inside nanoliter droplets (plugs) into long-range ordered superlattices.

液珠移動機制

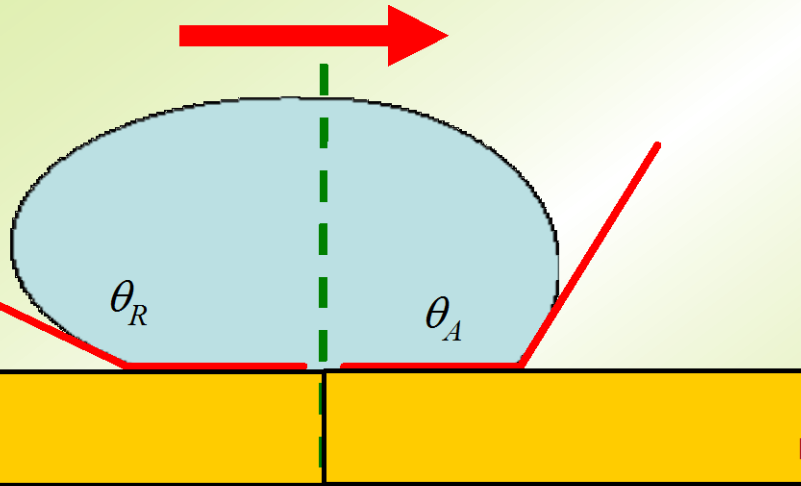


當液珠所受到驅動力大於阻滯力
液珠即可在表面移動。

液珠輸送及操控之方法彙整

Direction of actuation force and movement

微液珠傳輸的基本原則，液珠將從較斥水性(具有較大穩態接觸角)往較親水性表面(具有較小穩態接觸角)的方向傳輸。



主要的驅動機制與原理，來自於液珠與壁面接觸時，因外界能量的影響(溫度、電壓與光能場的強度分佈)或是底部接觸表面特性改變(例如微結構密度和化學薄膜親疏水性)。

而使液珠左半部與右半部界面上的氣液表面能自由能的不平衡，導致氣液界面的表面自由能階梯度變化(G_{LV})，而使微液珠沿梯度方向被驅動。

Basic Principle

More **Hydrophobic** surface
Larger contact angle

More **Hydrophilic** surface
smaller contact angle

Thermal method

Higher surface temperature

Lower surface temperature

Chemical method

lower free surface energy
between solid and vapor, G_{sv}

Higher free surface energy
between solid and vapor, G_{sv}

Electro-wetting method

Higher free surface energy
between solid and liquid, G_{sl}

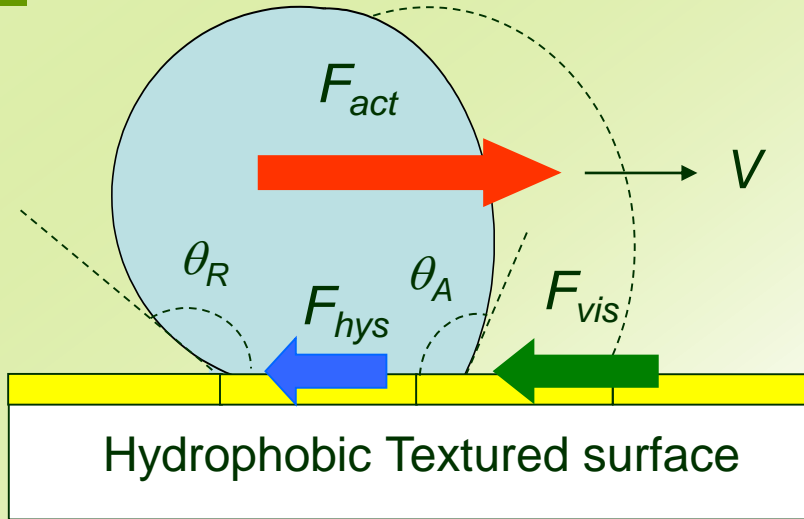
lower free surface energy
between solid and liquid, G_{sl}

Microstructure method

Lower density structure, f_1

Higher density structure, f_1

動力學分析 $\Sigma F = m a$



液珠於奈微米表面結構移動過程中，主要的力學作用機制包括**驅動力 (actuation force)**、**阻滯力 (hysteresis force)**和**黏滯力 (viscous force)**，這三者的合力作用造成液珠的表面輪廓形變，並主宰微液珠於壁面路徑表面上的運動狀態與動力大小。

$$F_{act} = -\frac{d\Delta G}{dx} \cong \pi R^2 \gamma_{LV} \left(\frac{d \cos \theta}{dx} \right)$$

在驅動力的部份，主要來自於表面微奈米結構密度梯度引發微液珠左右半部氣液介面上，表面自由能的梯度差所造成的驅動力。

$$-2\gamma_{LV} R (\cos \theta_{R_0} - \cos \theta_{A_0})$$

因遲滯現象所造成的阻滯力，相當於靜摩擦力。

$$F_{vis} \cong 3\pi\eta R V \ln \left(\frac{X_{max}}{X_{min}} \right)$$

微液珠動態運動中液珠本身與接觸面的黏滯力，相當於動摩擦力。

$$V \cong \frac{\gamma_{LV} R}{3\eta \ln(X_{max} / X_{min})} \left(\frac{d \cos \theta}{dx} \right)$$

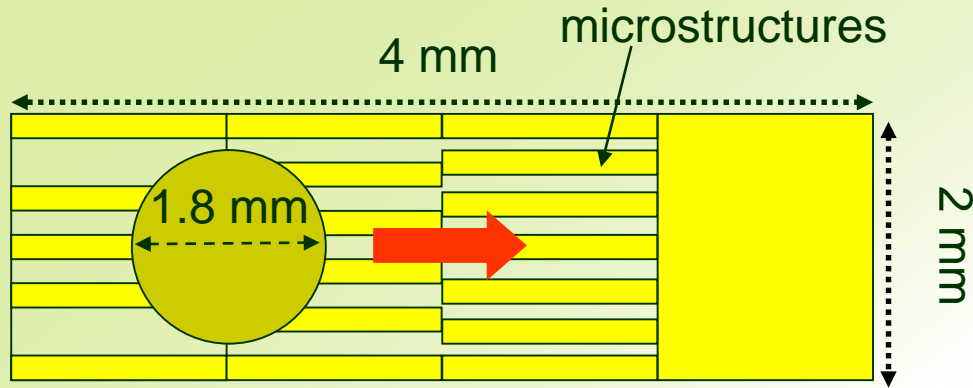
微液珠於表面傳輸時的平均穩態速度

能量轉換

$$E_K = \Delta G - W_{friction}$$

Note:

根據能量守恆和表面自由能的觀點，去探討液珠在移動過程中的能量轉換機制。



$$f_1=0.2 \quad f_1=0.35 \quad f_1=0.65 \quad f_1=1.0$$

f_1 : patterned density of microstructure

藉由液珠在移動前後穩態表面自由能的轉換，扣除因遲滯力和黏滯力所造成的摩擦能損和液珠表面震盪的內能損耗，應該等於液珠移動時的平均動能。

$$E_K = \Delta G - W_{friction}$$

$\Delta G_{s_{12}}$ 表示液珠在橫跨前後兩個具有不同微結構密度表面上，穩態表面自由的能階差。

G_{shape} 是指運動的液珠當開始停止移動到達穩定靜止於表面上這段期間，液珠表面震盪所造成的能量損耗。

$$W_{vis} = F_{vis} \times \Delta x$$

Unknown, but ...

$$\Delta G_{s_{12}} - G_b - W_{vis} - G_{shape} = \frac{1}{2} mv^2$$

Available (theory prediction and measurement)



Research Actions inspired by Lotus Leaf and Plants BEAM Lab at NTU

楊鏡堂 特聘教授

jtyang@ntu.edu.yw

國立台灣大學 機械工程學系

國科會能源計畫辦公室主任

May 17th, 2010 @ Chungli

研發策略與步驟

探索生存適應的物理

(Life among the Formulae of Physics)



模仿生物智慧



科技創新

Biophysics → Biomechanics → Biomimetics

Lotus and Microchips

Objectives of Our Research

Mimicking lotus leaf



N/MEMS, SAM

Ultra-hydrophobic surface



Gradient surface

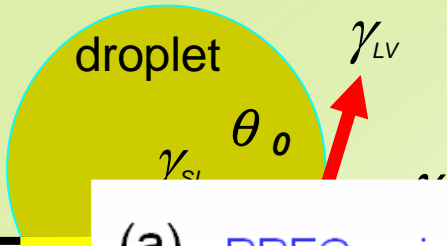
**Droplet spontaneous moving
and reacting on a microchip**

J. MEMS, 2006; Langmuir, 2008
JMM, 2009; Lab Chip, 2010a, 2010b, ...

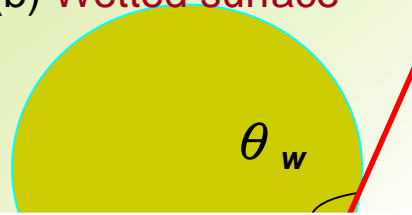
國家新創獎, 2007
生醫製藥領域之最高桂冠

Contact Angle & Surface Wettability

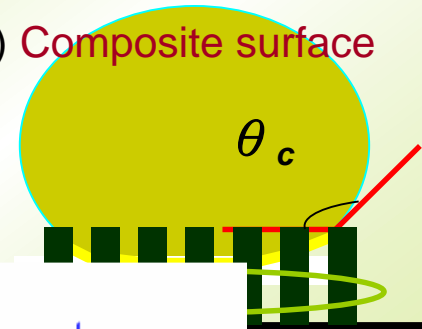
(a) Smooth surface



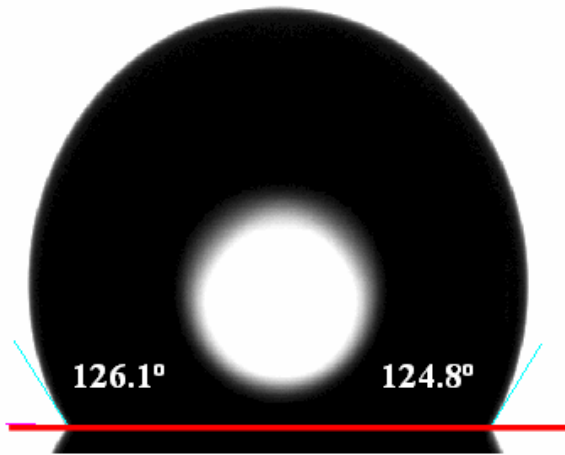
(b) Wetted surface



(c) Composite surface

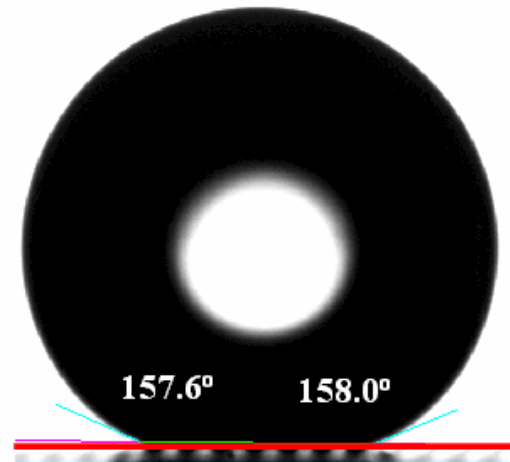


(a) PPFC, microstructure stature of 3.2 μm



Collapsed droplet

(b) PPFC, microstructure stature of 24.1 mm



Suspended droplet

os

surface

er Eq. (1944)

$$\theta_0 + f_1 - 1$$

parameter:

on of density of
ures, f_1

■ Smo

You

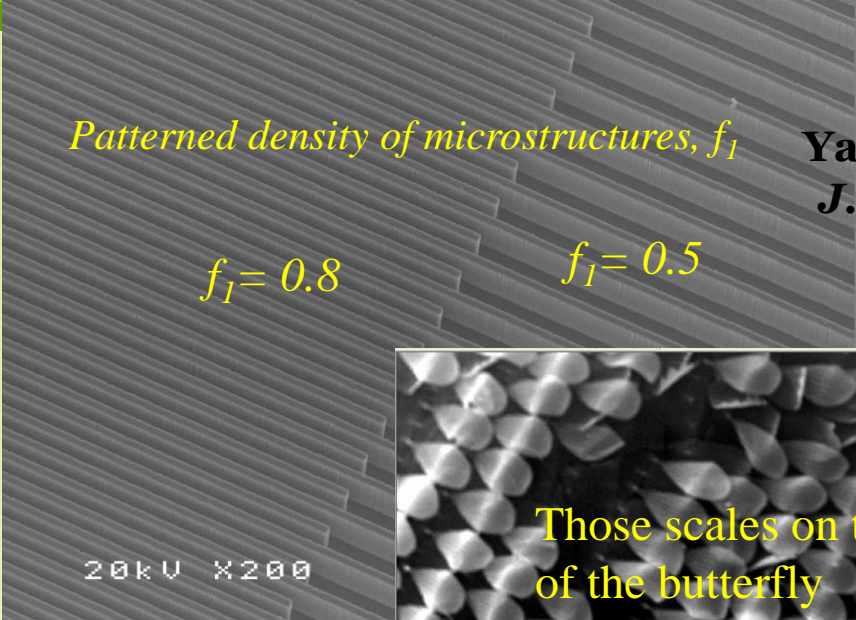
cos

■ Ju

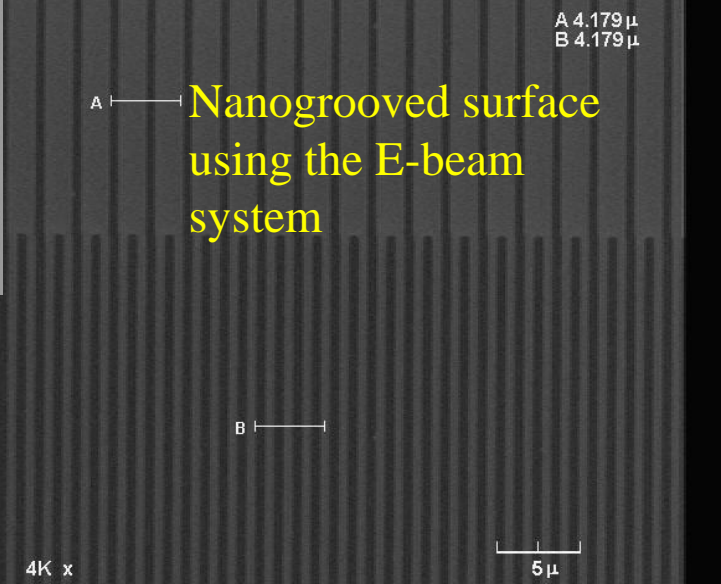
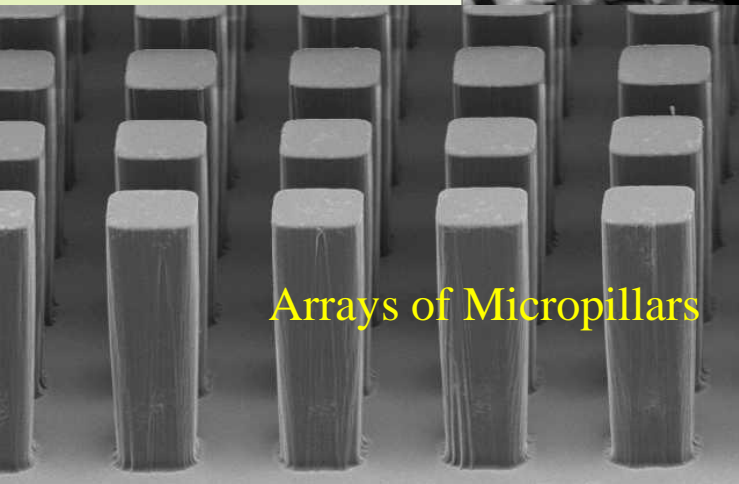
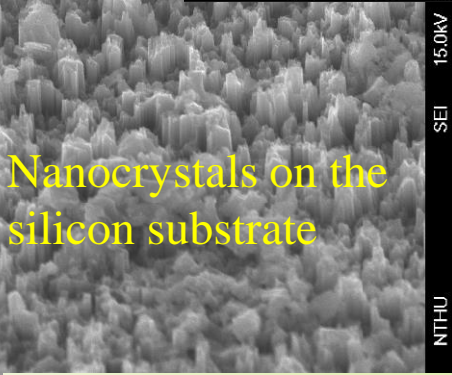
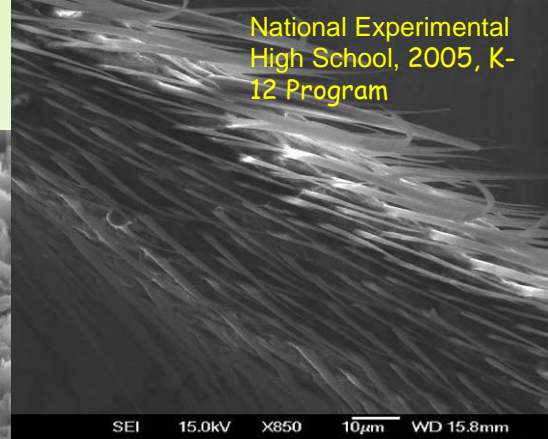
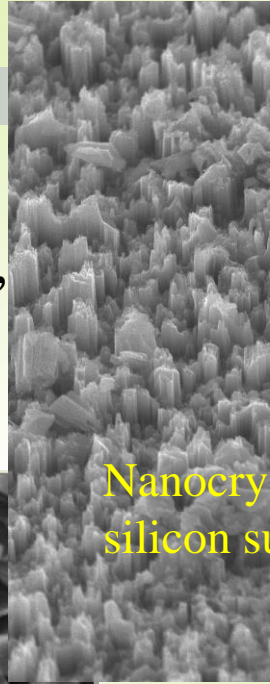
co

les

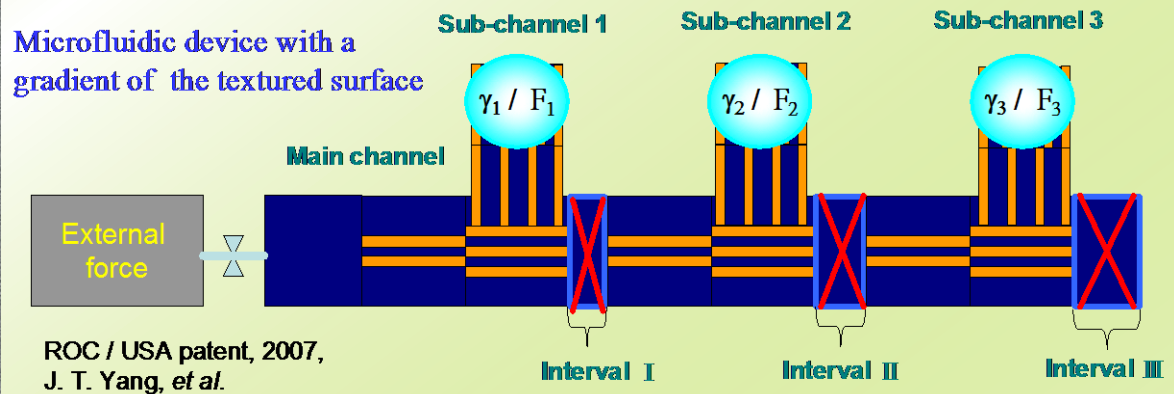
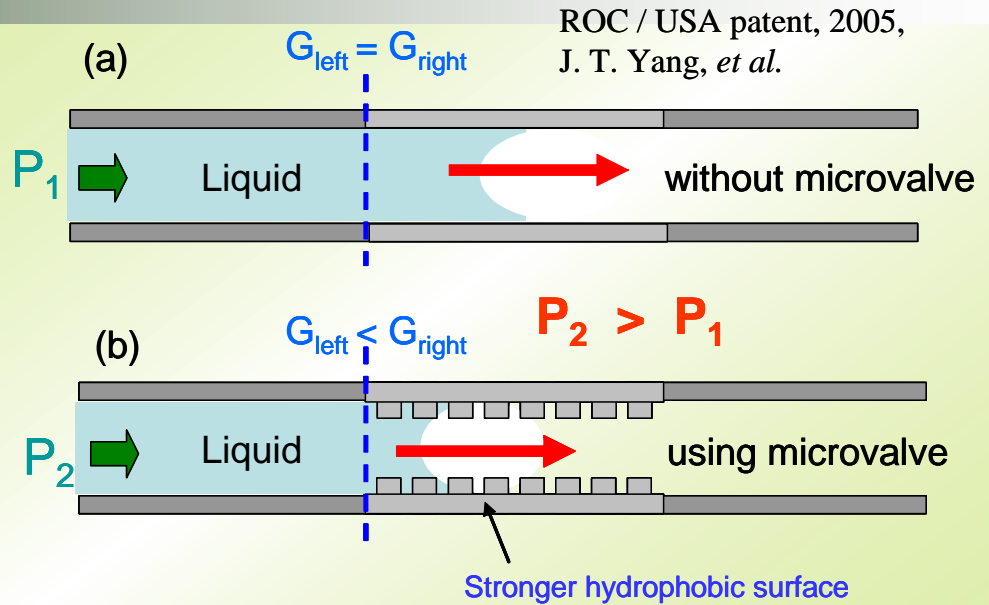
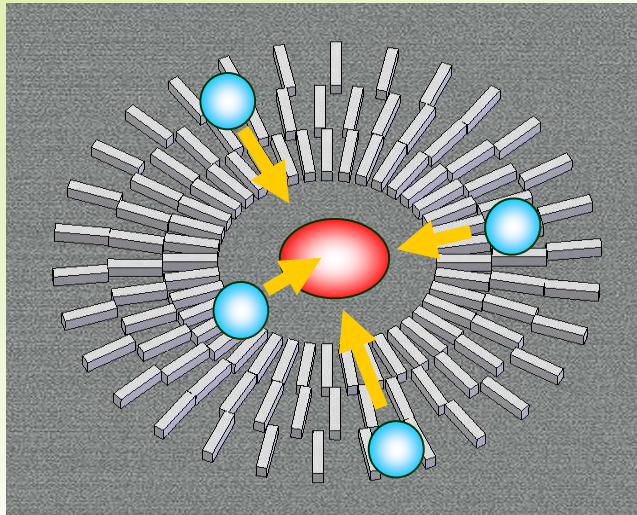
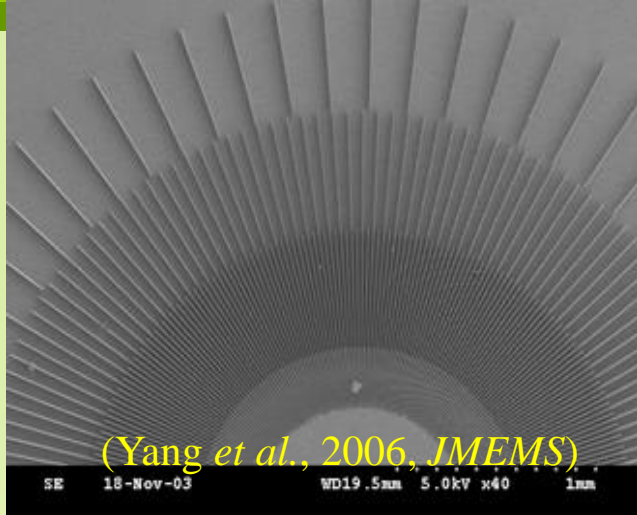
Surface Science & Art



Yang et al.,
J. MEMS,
2006



Engineering Application & Patents

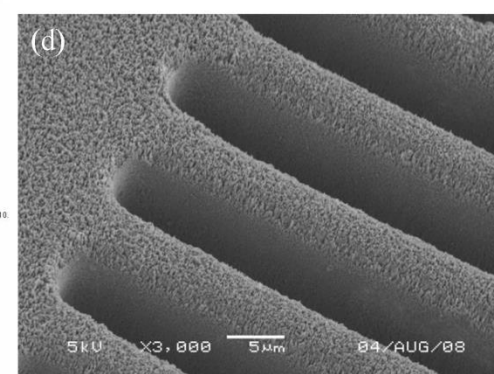
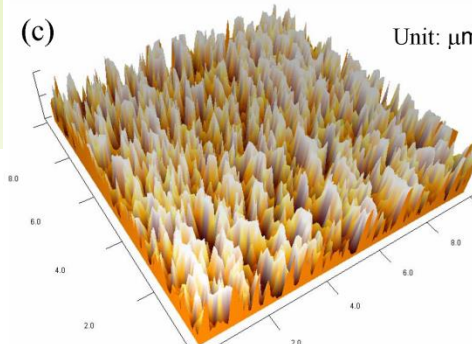
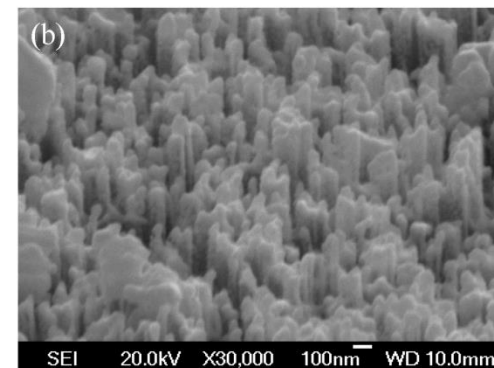
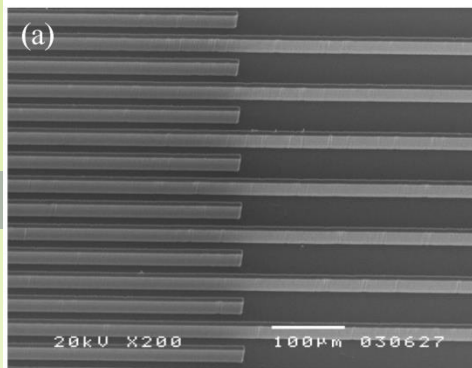
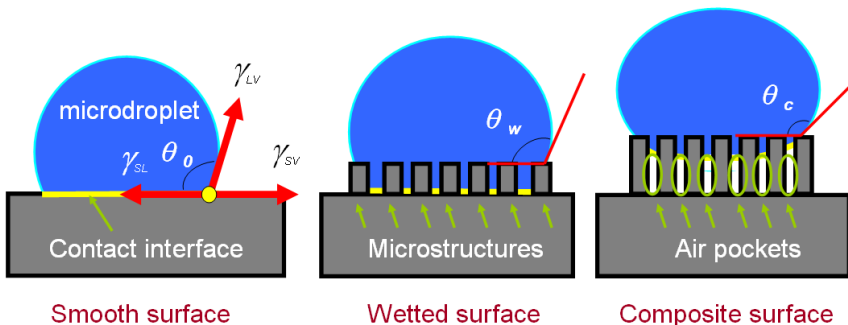


第一屆上銀碩士論文獎銅質獎, 2007
 第四屆國家新創獎, 2008

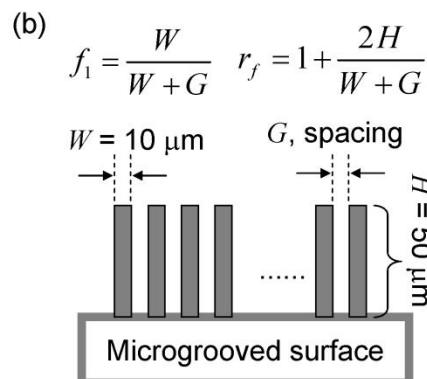
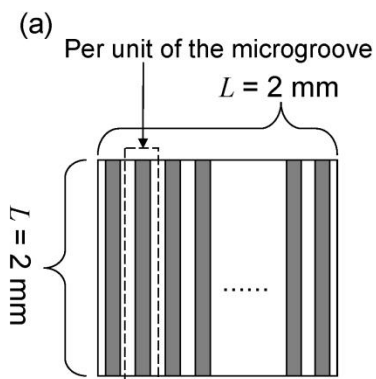
(J. MEMS, 2006, cited 83; Langmuir, 2008, cites 71)

Ultra-Hydrophobic Surfaces

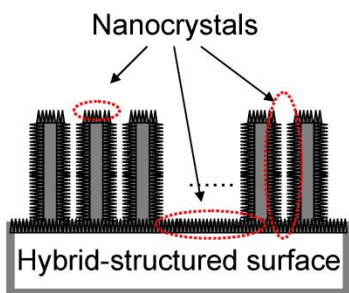
(a) Young's model (b) Wenzel's model (c) Cassie's model



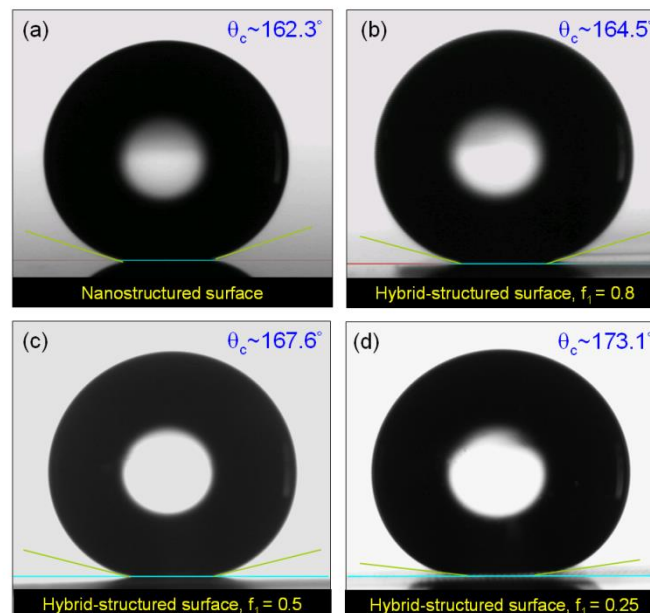
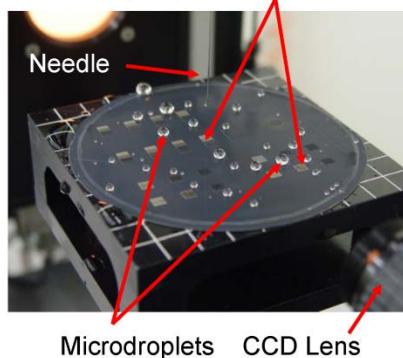
AFM scanning snapshot, resolution 256 by 256



(c) Those surfaces become more hydrophobic using a FDTS vapor.



(d) Hybrid-structured Pads

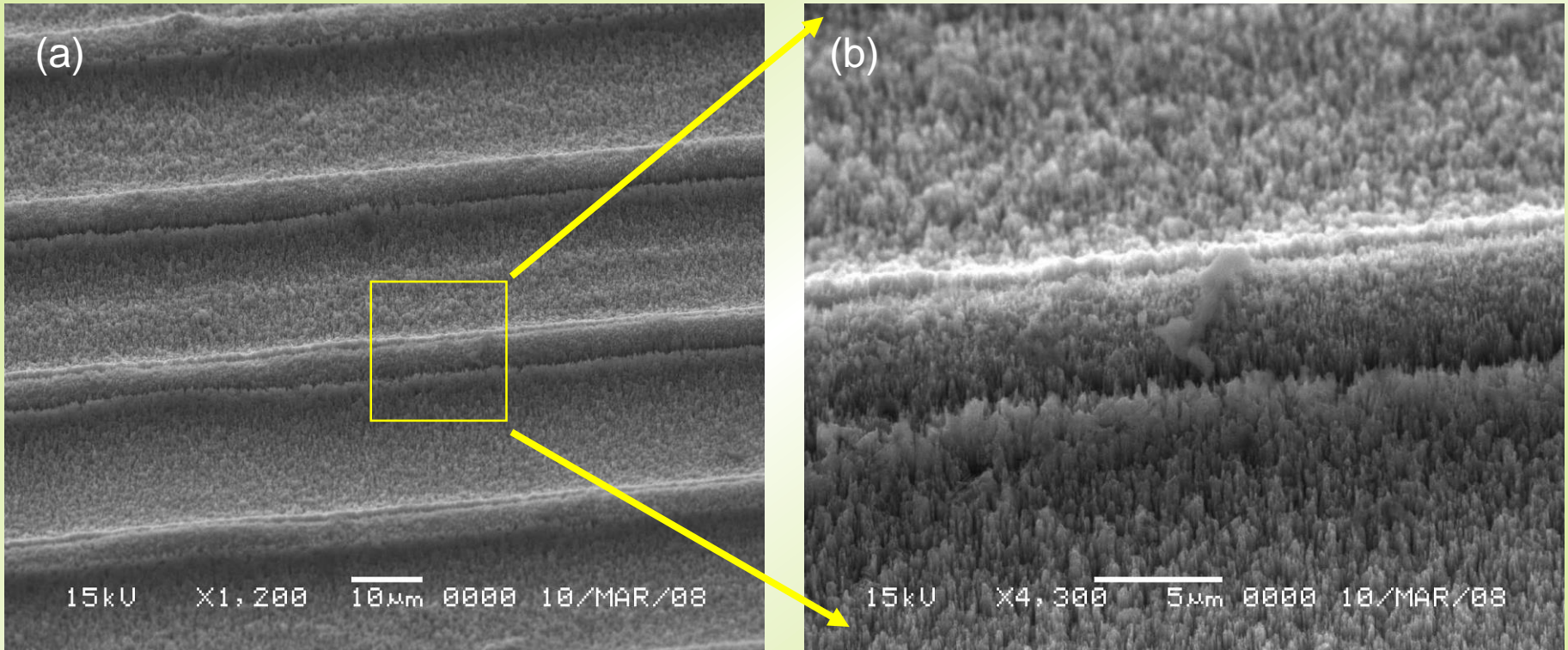


A droplet is falling on Si surface

J. T. Yang
Z. H. Yang,
C. Y. Yang
Dr. M. H. Hsu
Dr. Y. H. Lai
2009

Highlights of
JMM, 2009
(times cited: 35)

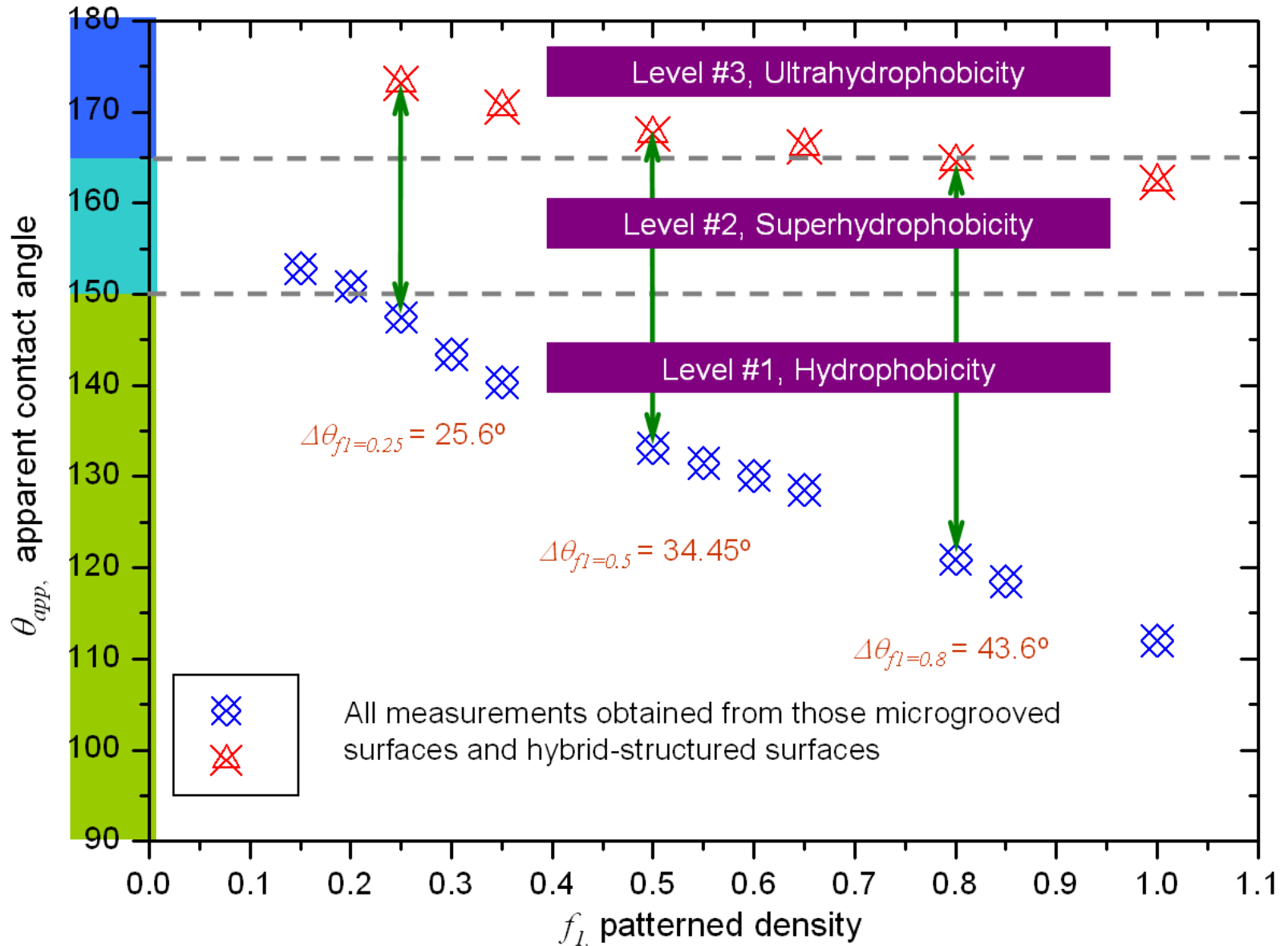
Hybrid structured surfaces



Photographic Scans of a Hybrid Structured Surface with a SEM: (a) The Sight Field at a Small Magnification; and (b) The Sight Field at an Increased Magnification

Surface Hydrophobicity of Three Levels

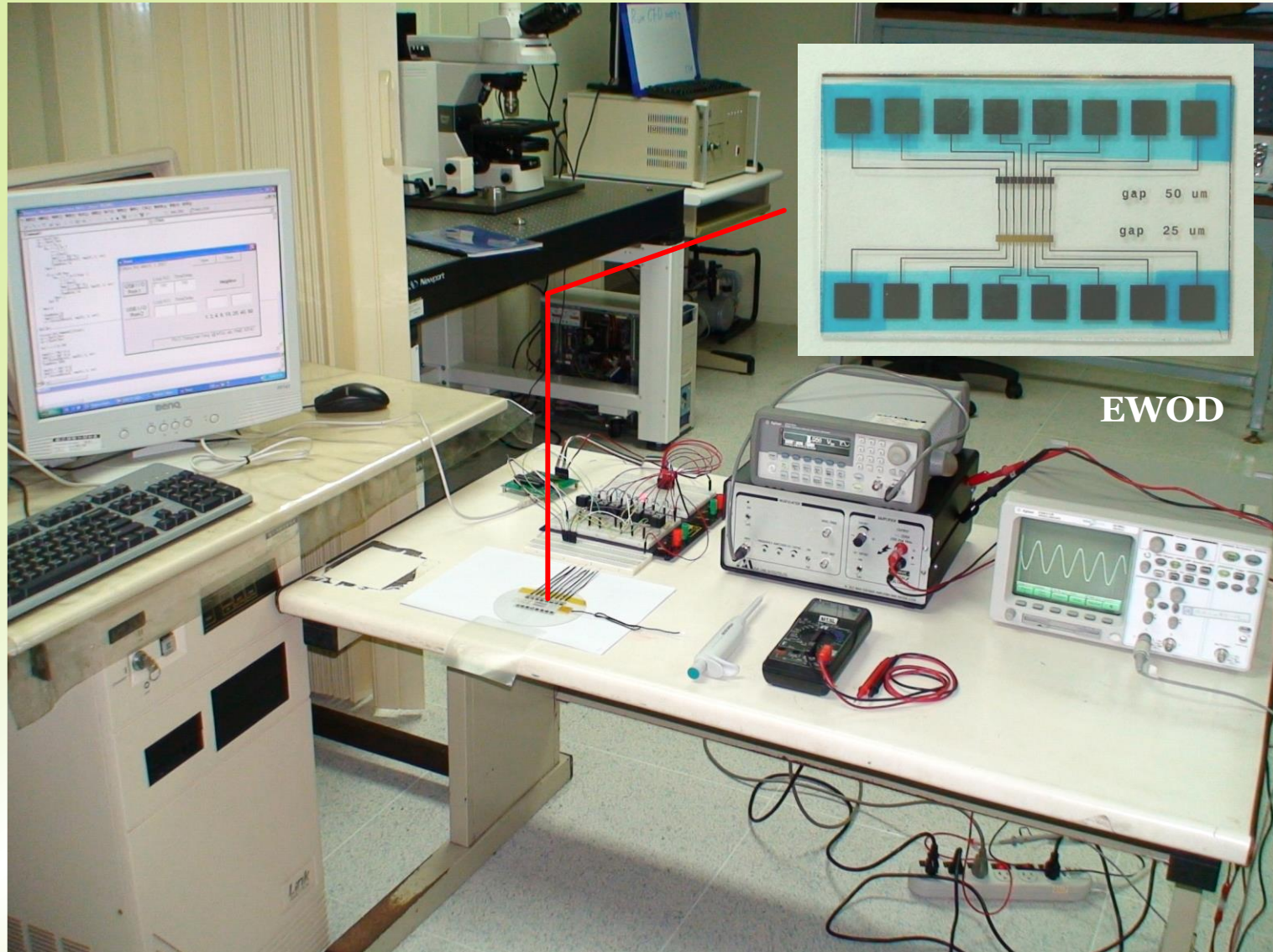
楊宗翰, 楊鏡堂

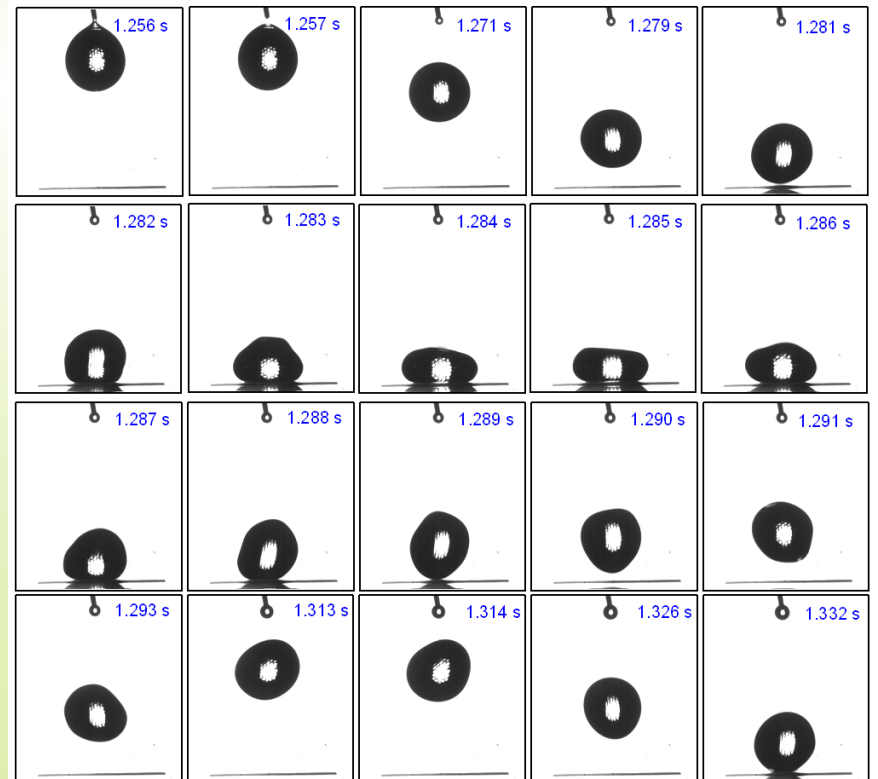
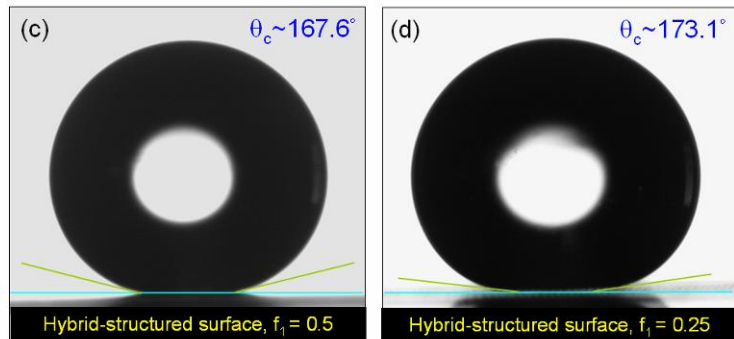
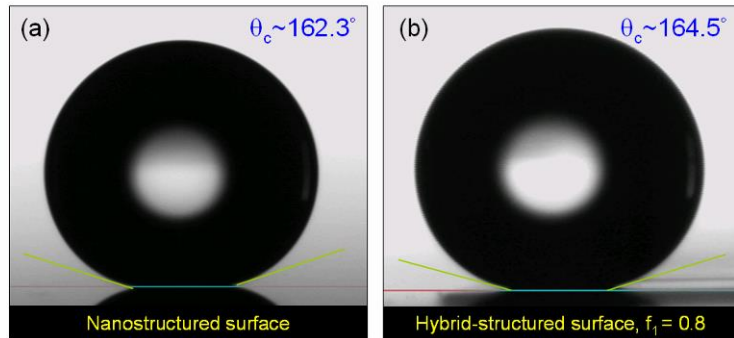
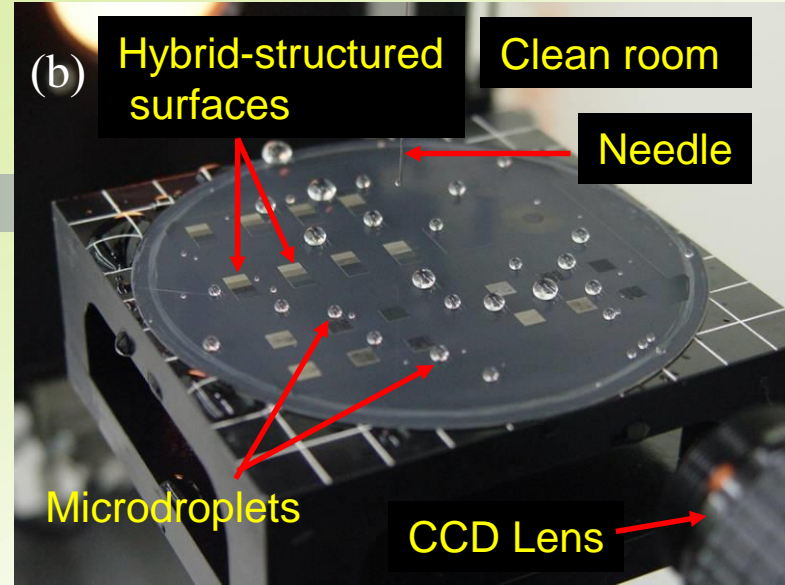
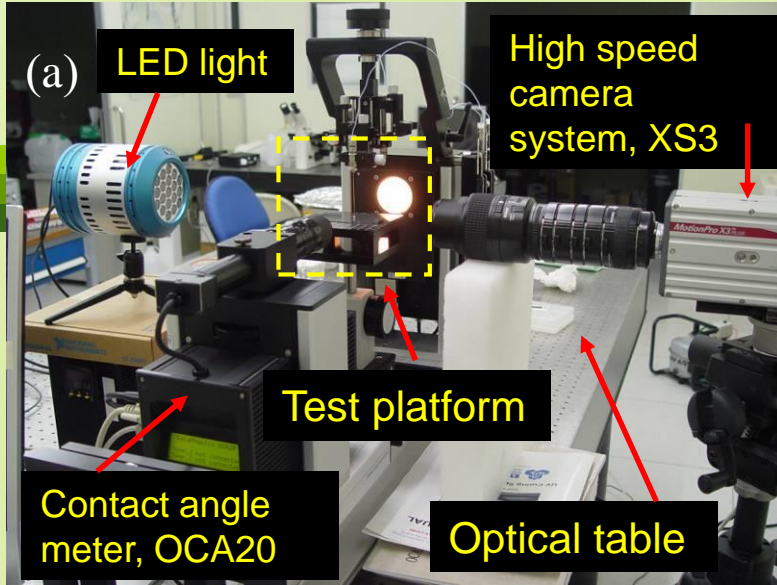


SEM, AFM, and Platform for EWOD Biochips– 2004-2008

楊鏡堂教授, 台大機械系

US Patent 7,189,359, 2007; cited 93





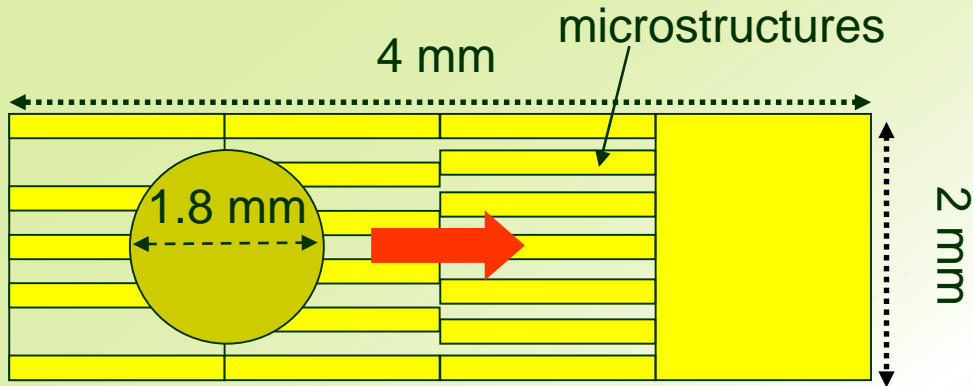
A droplet is falling on Si surface

能量轉換

$$E_K = \Delta G - W_{friction}$$

Note:

根據能量守恆和表面自由能的觀點，去探討液珠在移動過程中的能量轉換機制。



$$E_K = \Delta G - W_{friction}$$

$\Delta G_{s_{12}}$ 表示液珠在橫跨前後兩個具有不同微結構密度表面上，穩態表面自由的能階差。

G_{shape} 是指運動的液珠當開始停止移動到達穩定靜止於表面上這段期間，液珠表面震盪所造成的能量損耗。

$$f_1 = 0.2 \quad f_1 = 0.35 \quad f_1 = 0.65 \quad f_1 = 1.0$$

f_1 : patterned density of microstructure

藉由液珠在移動前後穩態表面自由能的轉換，扣除因遲滯力和黏滯力所造成的摩擦能損和液珠表面震盪的內能損耗，應該等於液珠移動時的平均動能。

Unknown, but ...

$$W_{vis} = F_{vis} \times \Delta x$$

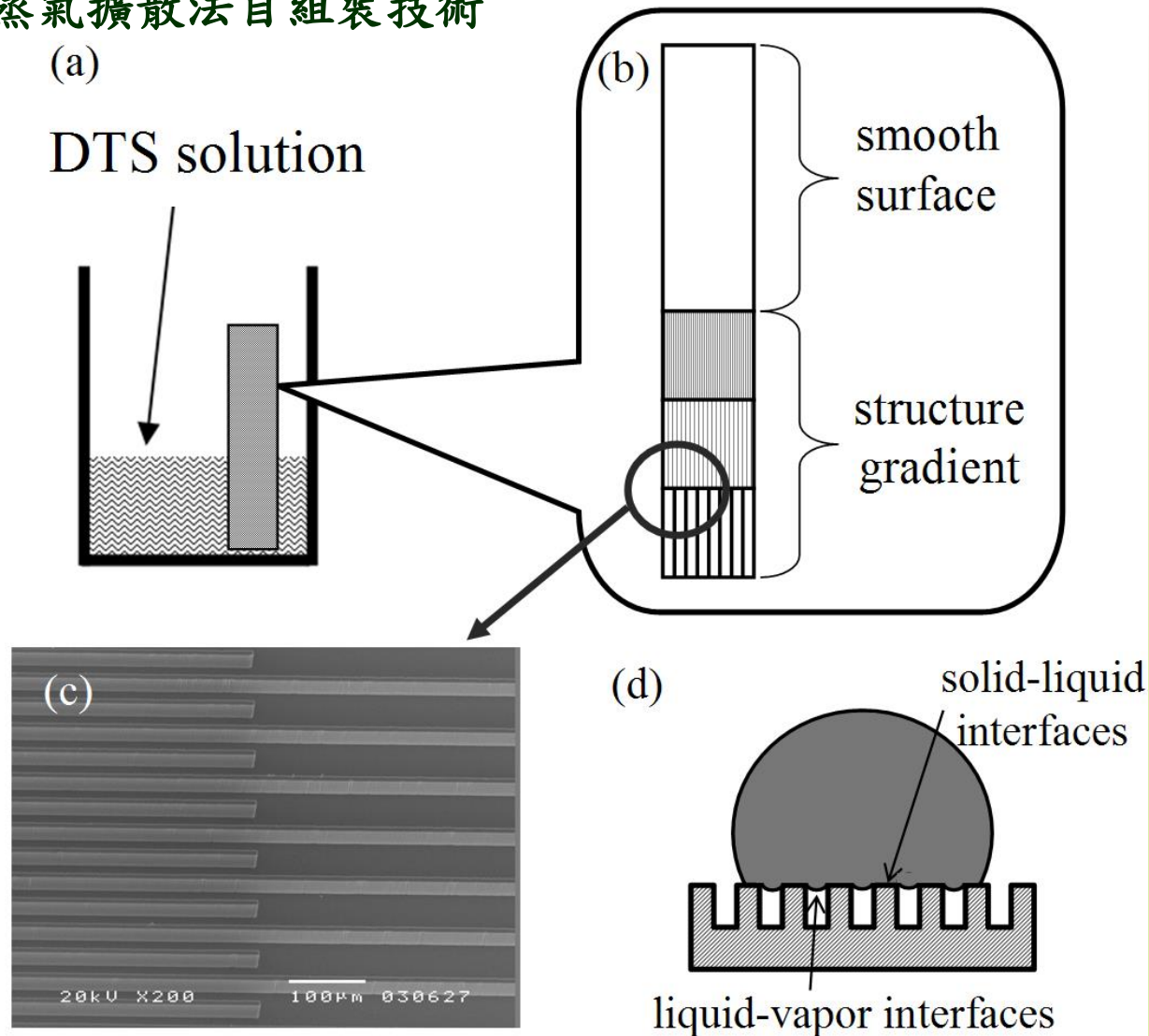
$$\Delta G_{s_{12}} - G_b - W_{vis} - G_{shape} = \frac{1}{2} mv^2$$

Available (theory prediction and measurement)

分子自組裝技術應用於表面改質

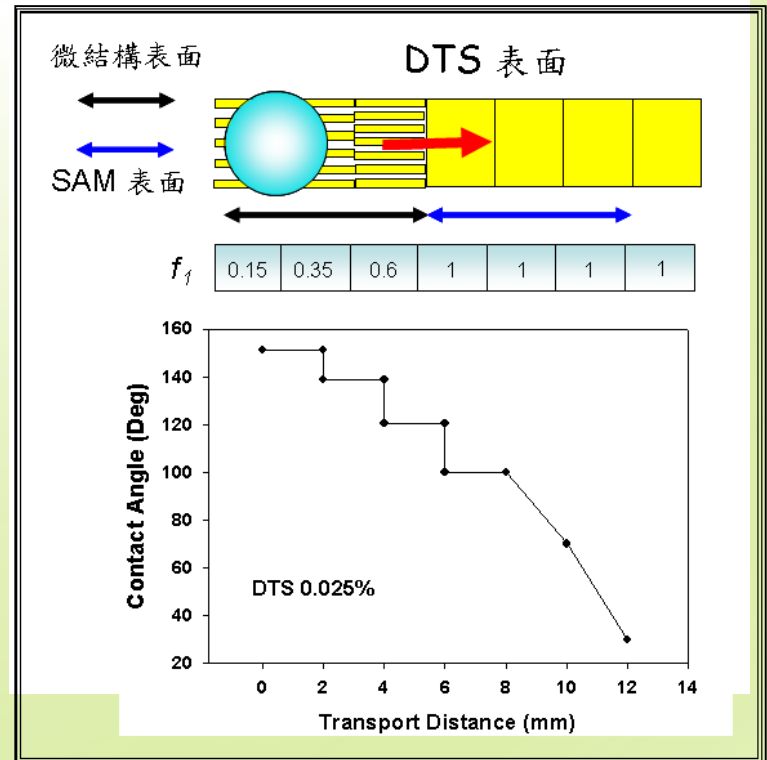
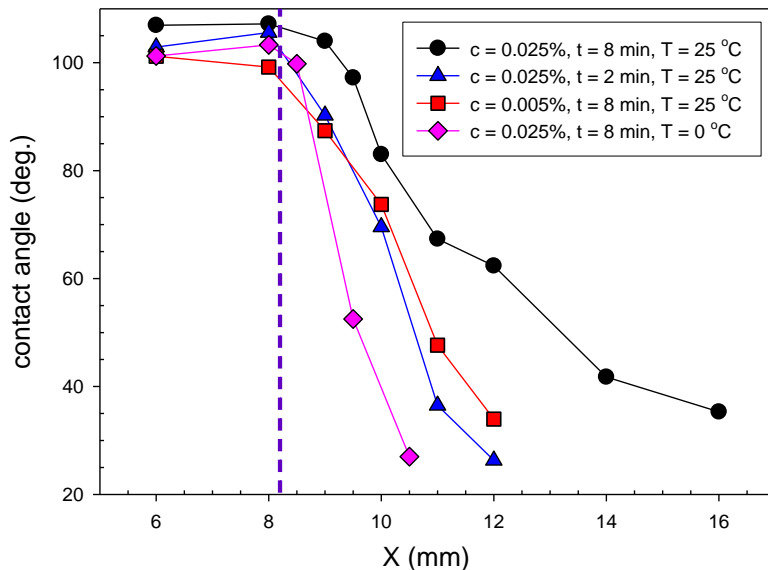
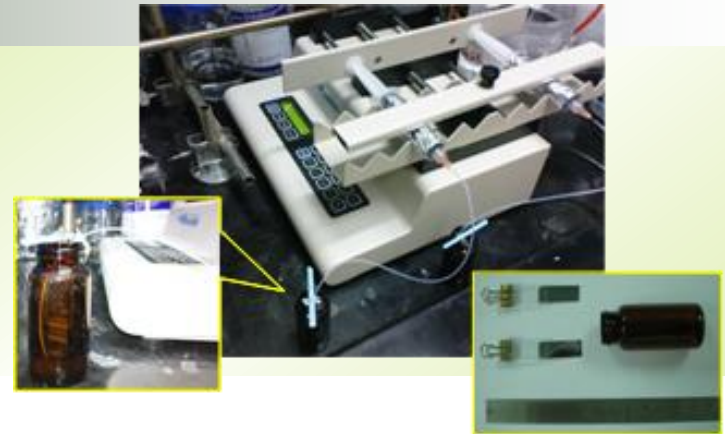
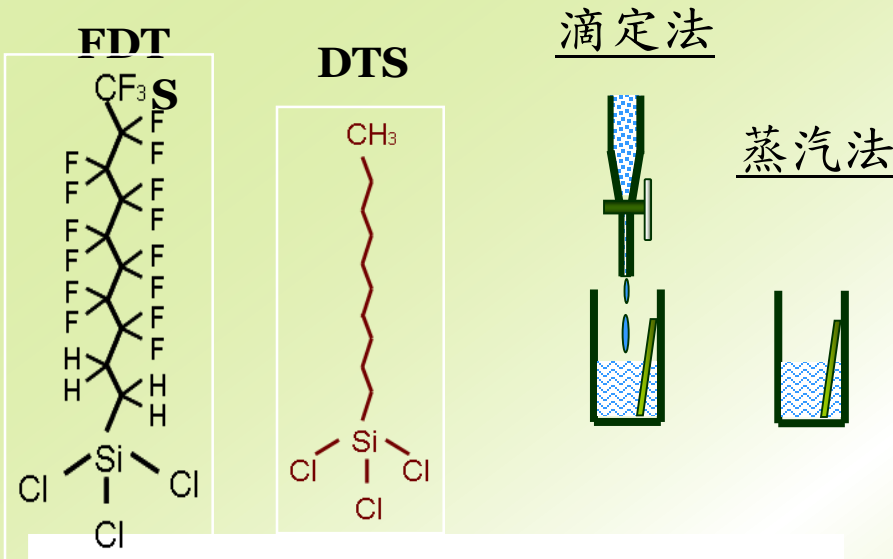
Lai *et al.*, *Lab Chip*, 2009; Yang *et al.*, ROC Patent, 2009.

浸泡/蒸氣擴散法自組裝技術



A Microchip using SAM & Gradient Surface

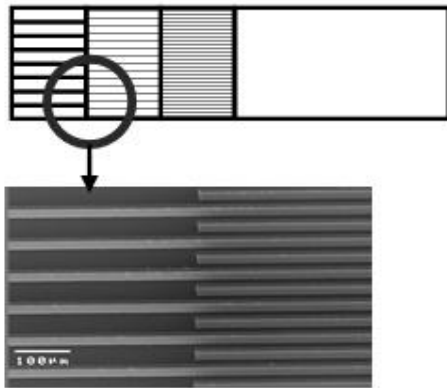
Lai, Yang, Shieh, *Lab Chip*, 2009



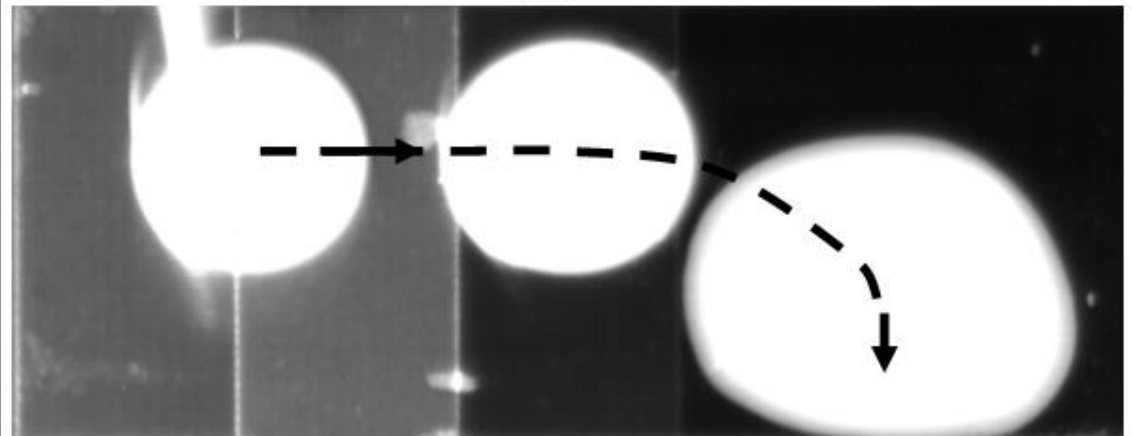
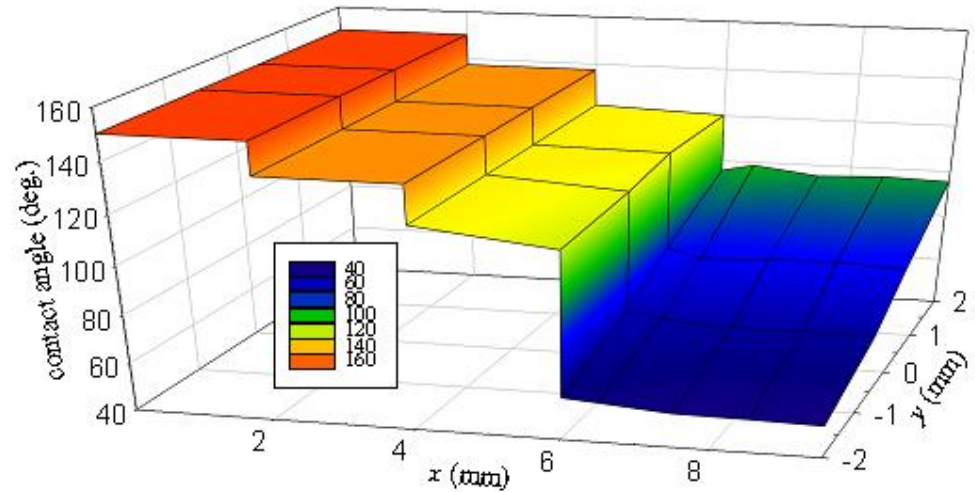
A biochemical droplet transporting across superhydrophobic to hydrophilic surfaces.

Lai, Yang,* Shieh, *Lab Chip* 2009 (times cited: 67)

a microstructure and SAM composition gradient surface



transport of droplets across superhydrophobic to hydrophilic surfaces



a double-direction gradient

玫瑰的“花瓣效應” -- Rose's 'Petal Effect'



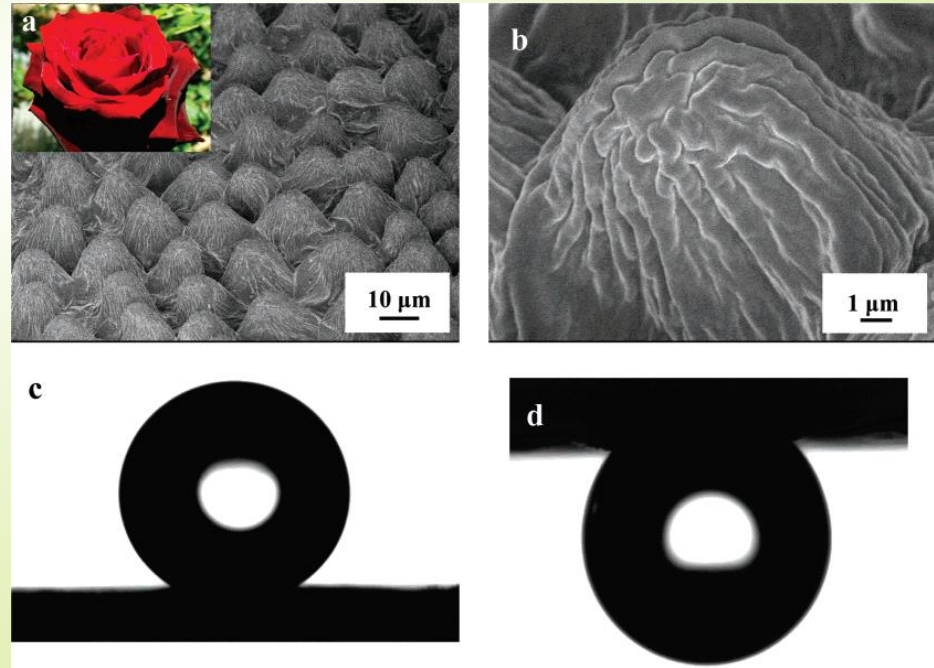
ScienceDaily (Apr. 25, 2008)

Petal Effect:

A Superhydrophobic State with High Adhesive Force

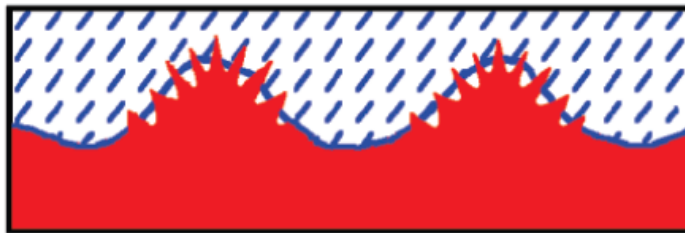
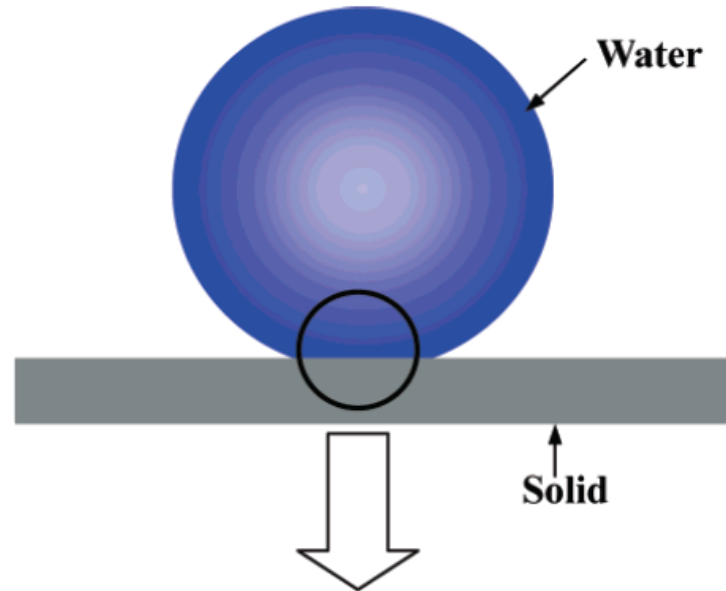
The rose's ability to grip water droplets in place, even when the flower is upside down.

This fascinating "petal effect" could lead to unique new adhesive materials, coatings and fabrics.



Feng et al., Langmuir, 2008.

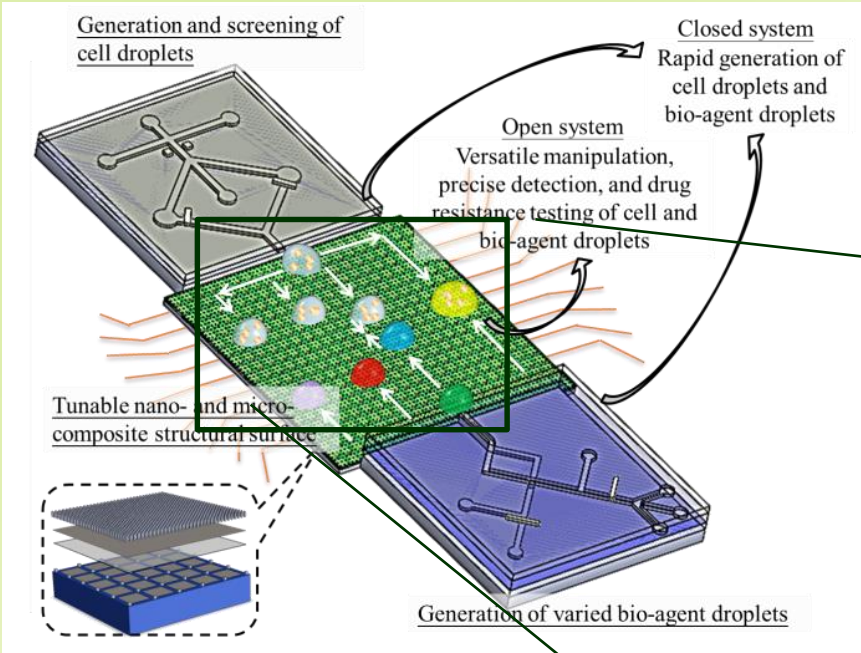
Petal Effect and Lotus Effect



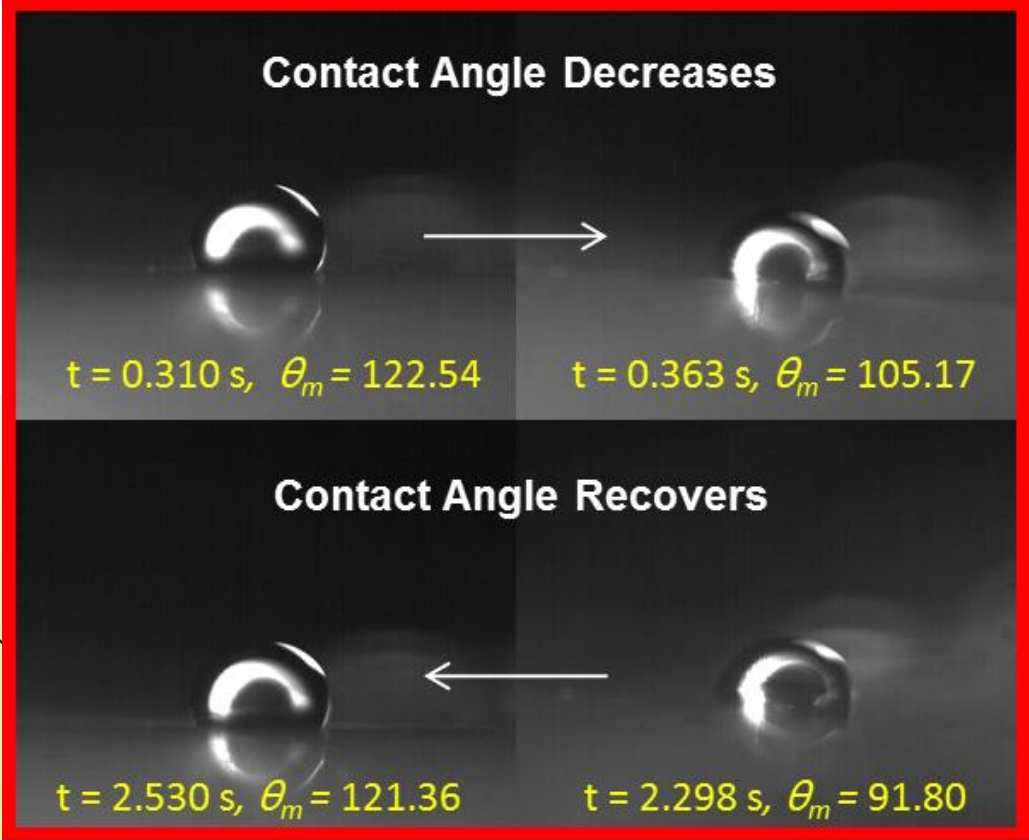
Petal (Cassie impregnating wetting state)



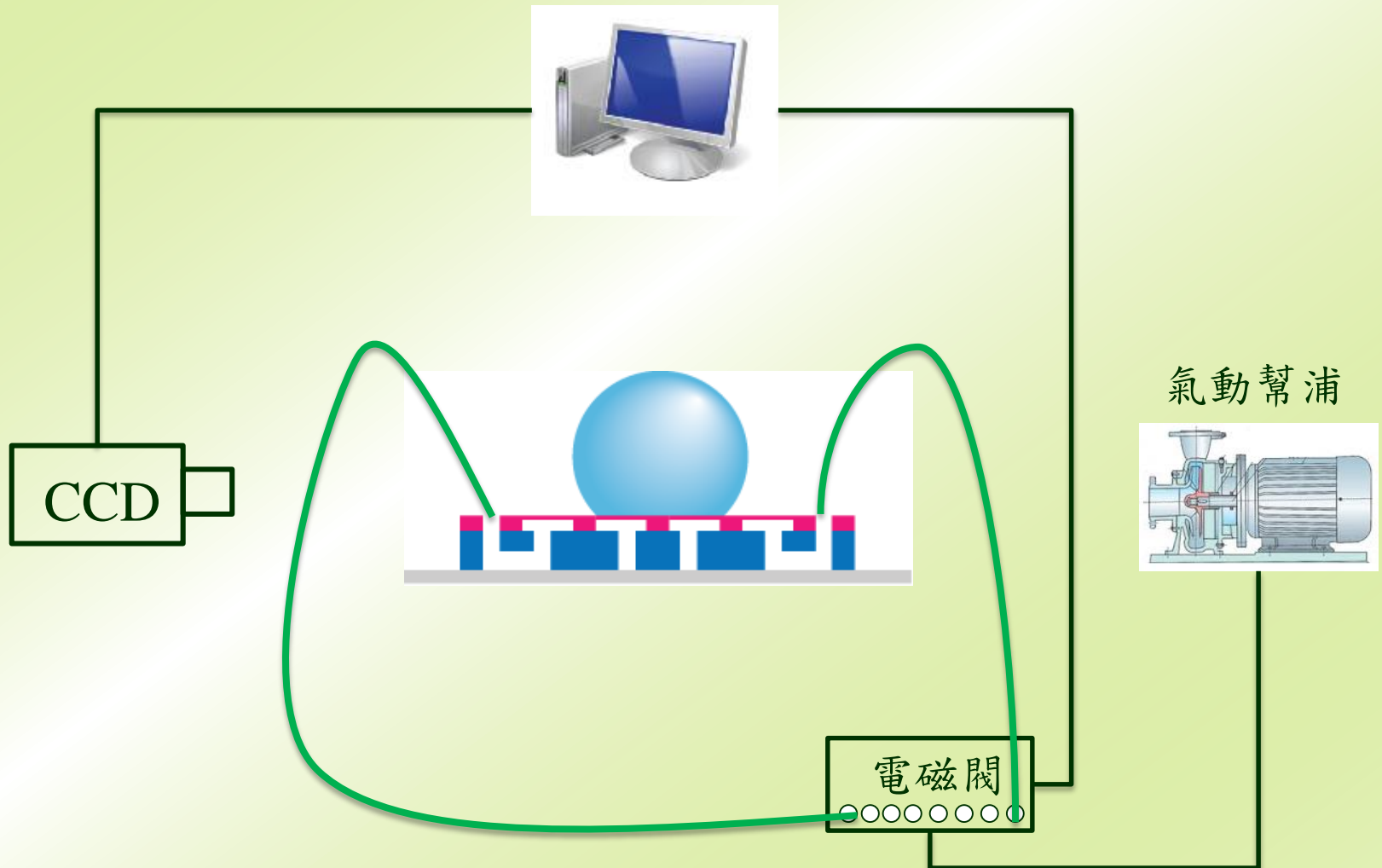
Lotus (Cassie's state)



Rose + Lotus 操控液珠平台



氣動操控系統架設



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

Lab on a Chip, 2014a

Transducers 2013

Target DNA loading and probe DNA-modified AuNP dripping



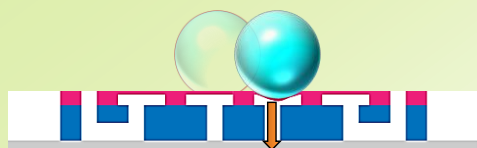
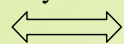
(a)

NH₂OH & HAuCl₄ dripping



(c)

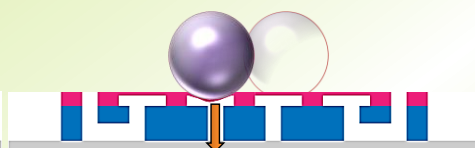
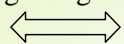
Mixing and hybridization



Air suction activated




(b)

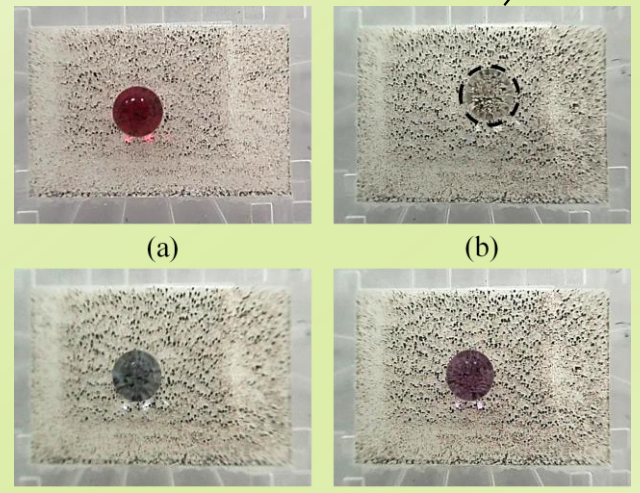
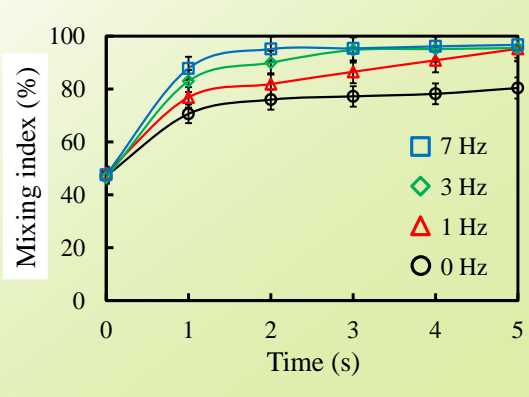
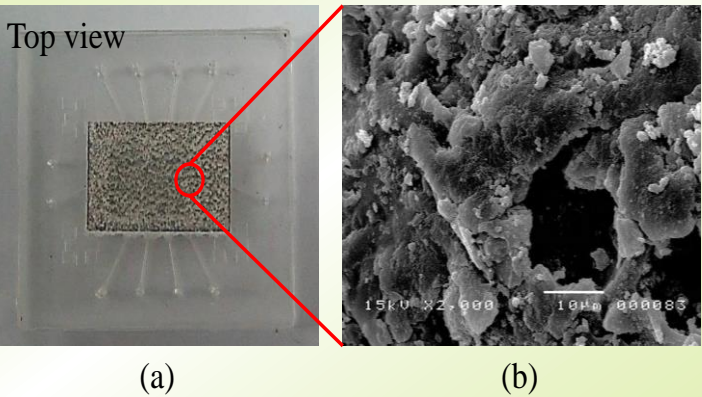
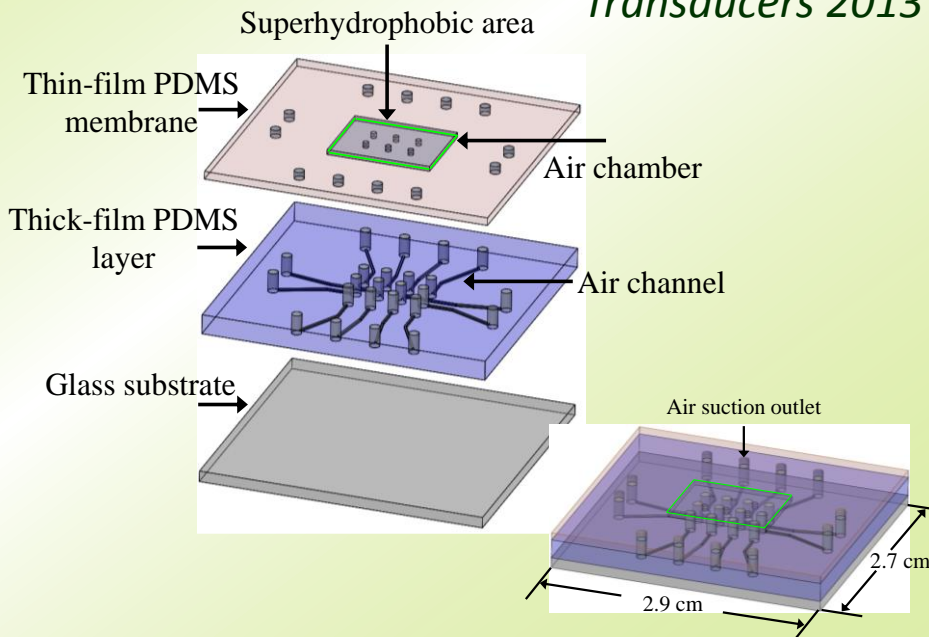
Mixing and growth



Air suction activated

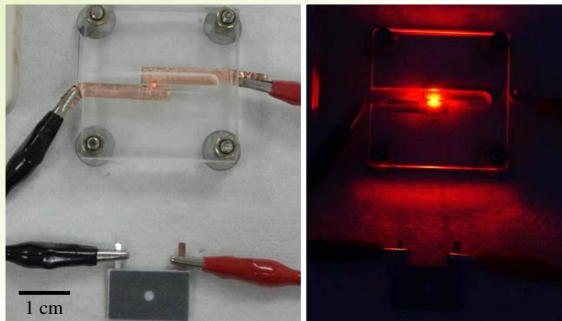
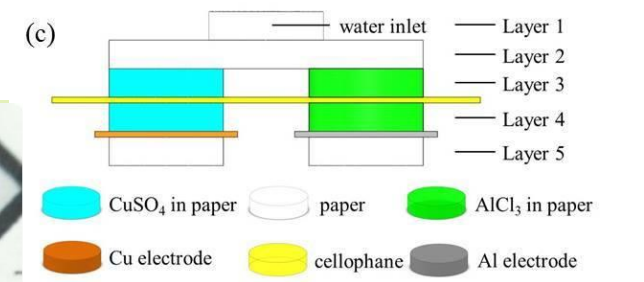
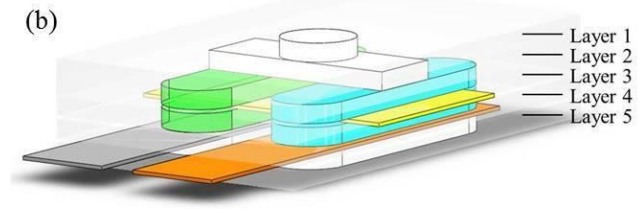
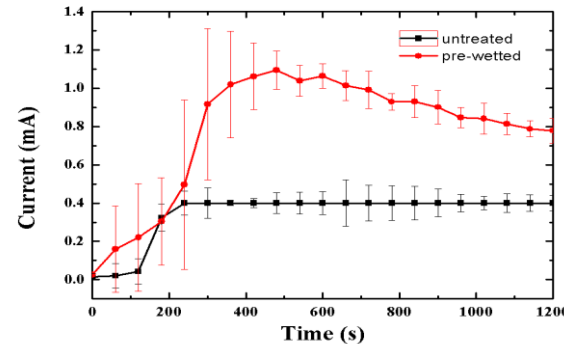
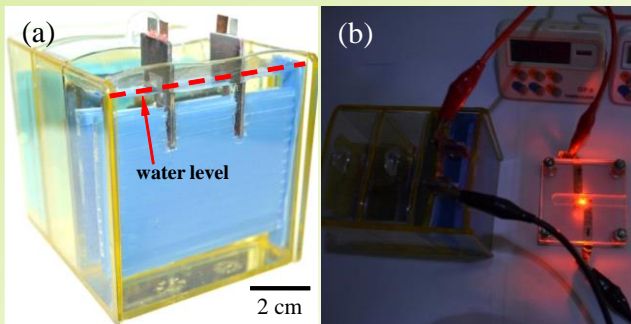
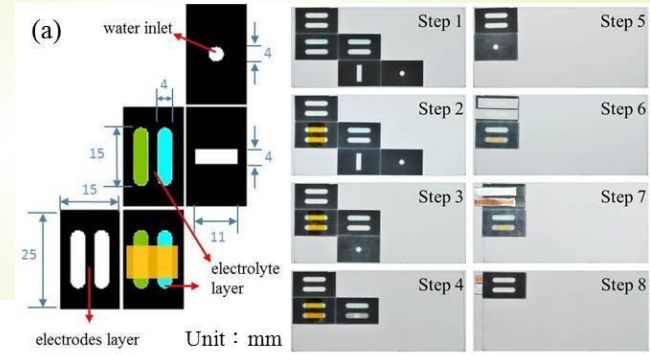
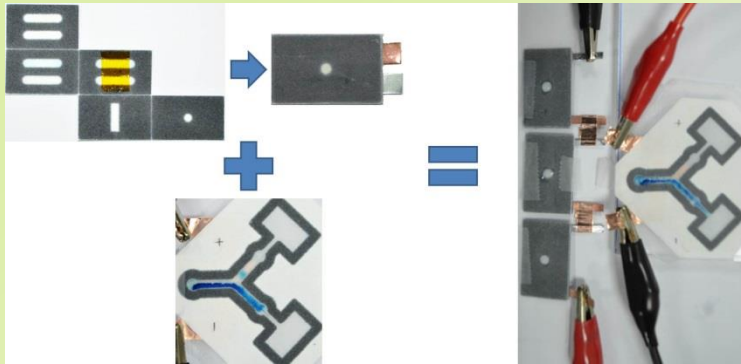
(d)

 Target DNA
  Probe DNA-modified AuNP
  NH₂OH & HAuCl₄



Origami Paper-Based Fluidic Batteries for Portable Electrophoretic Devices

Lab on a Chip, 2014b



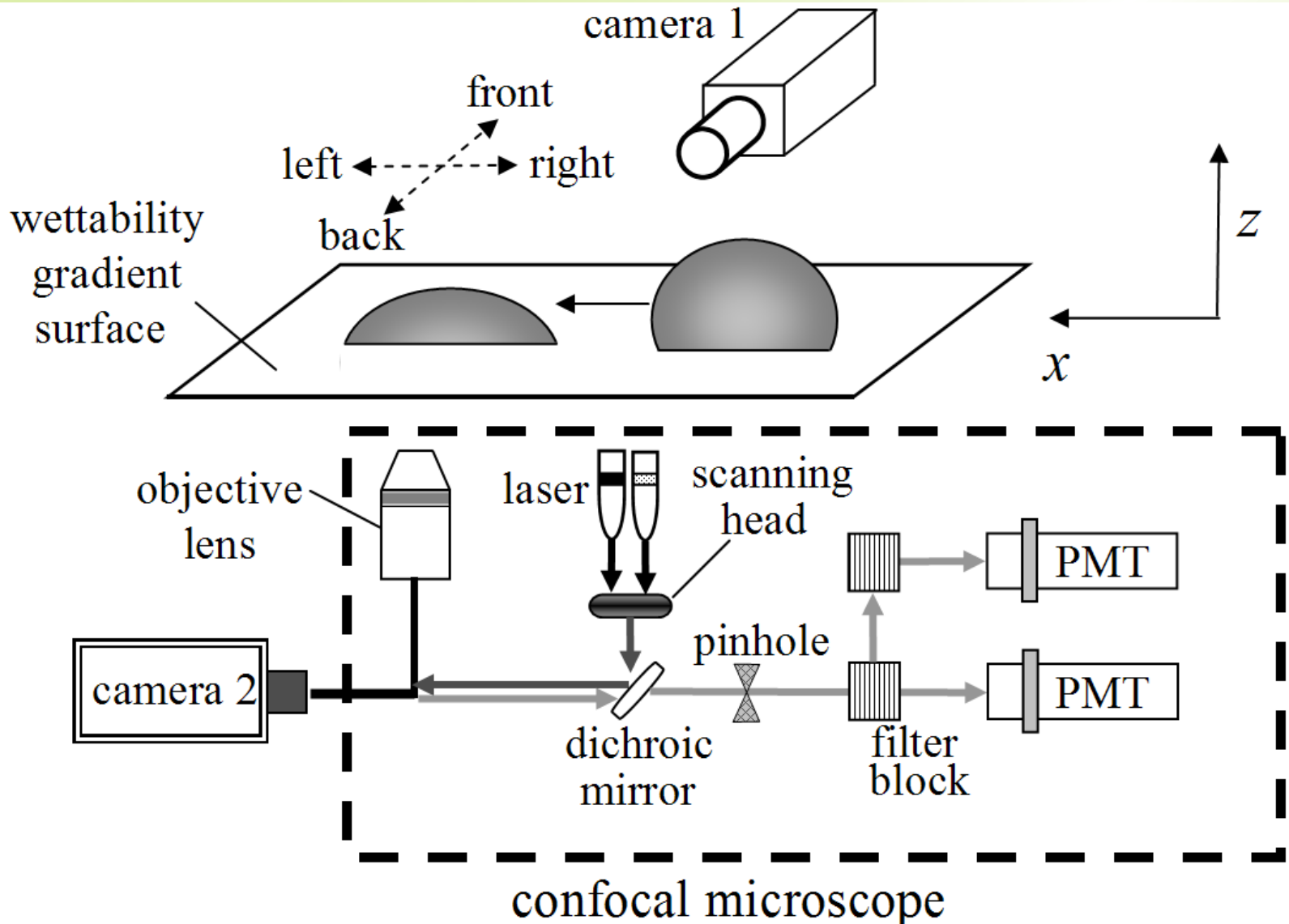
μ-TAS 2013



Application

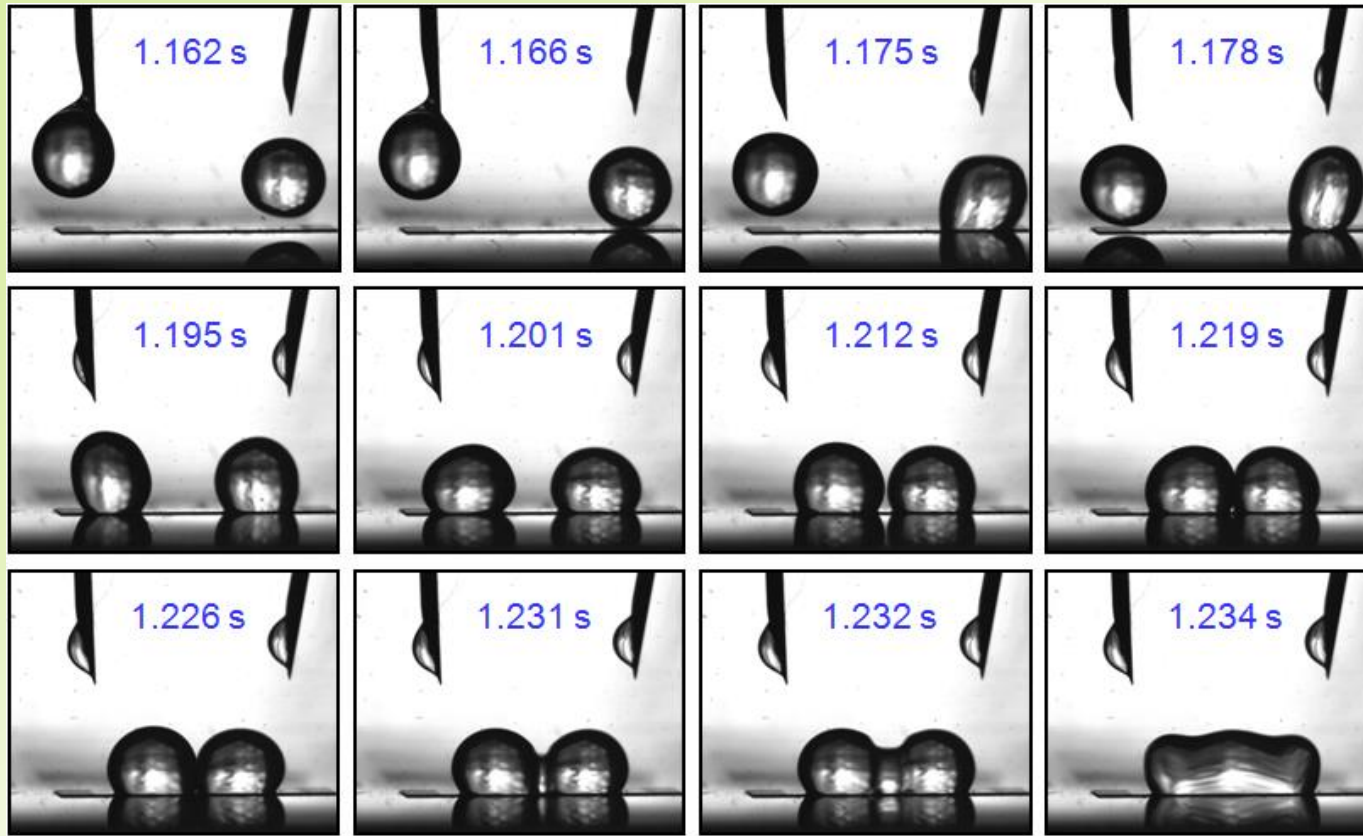
Multi-color Micro-PIV & Species Concentrations

Lai and Yang, *Lab Chip*, 2010



Sequence of images during two droplets collision

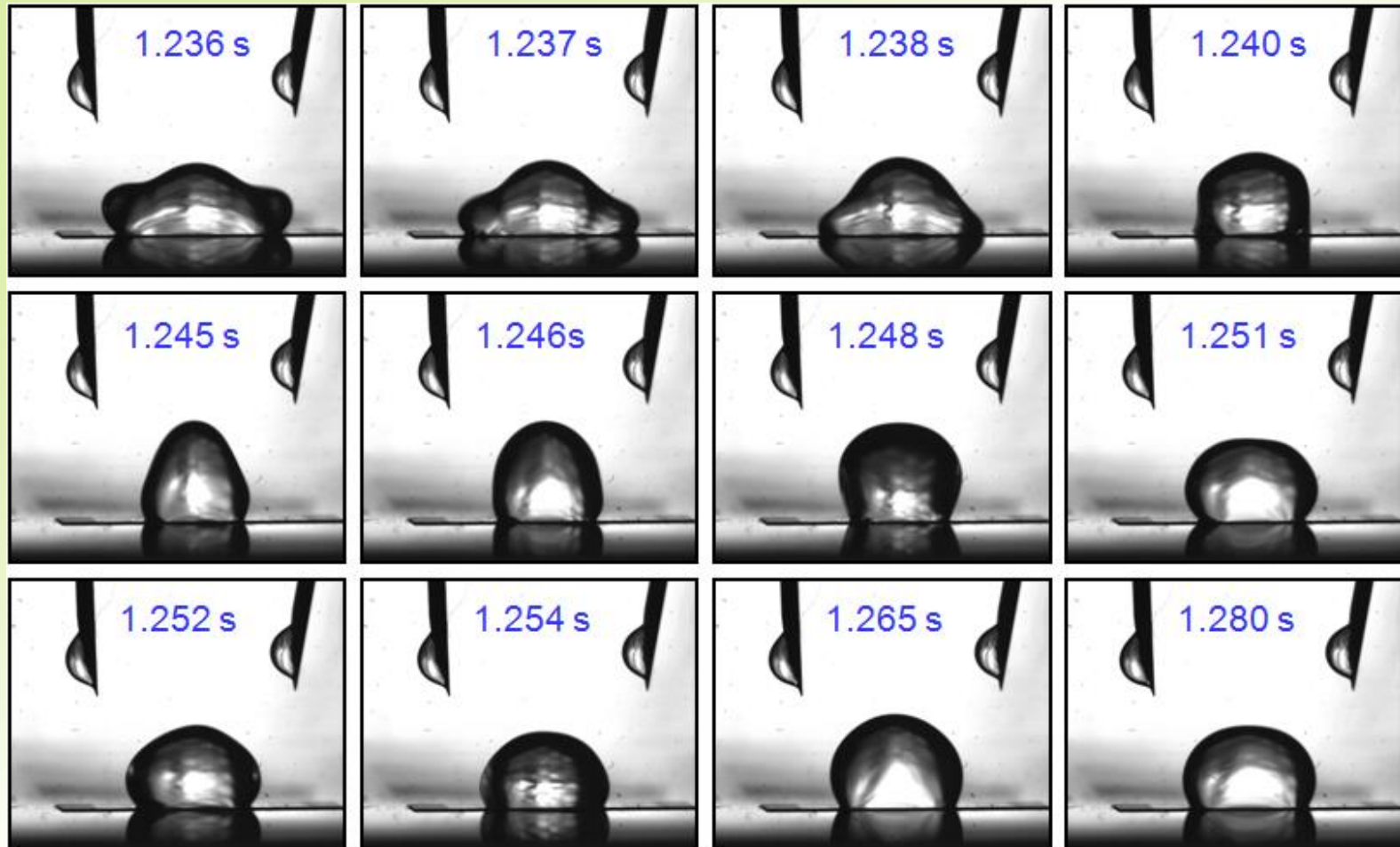
(1)



- Each droplet of volume $5 \mu\text{L}$ (DI water).
- Transport path: 8 mm by 2 mm.
- Two average velocities of 58.14 mm/s and 54.35 mm/s .

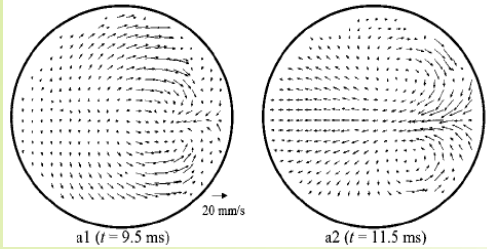
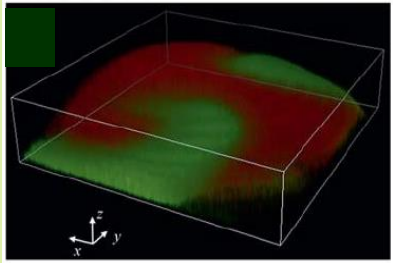
Sequence of images during two droplets collision

(2)

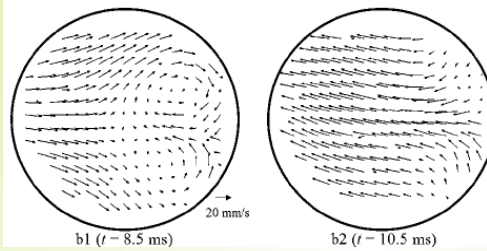
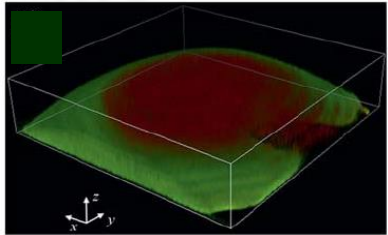


微液珠碰撞融合行為

Mode A

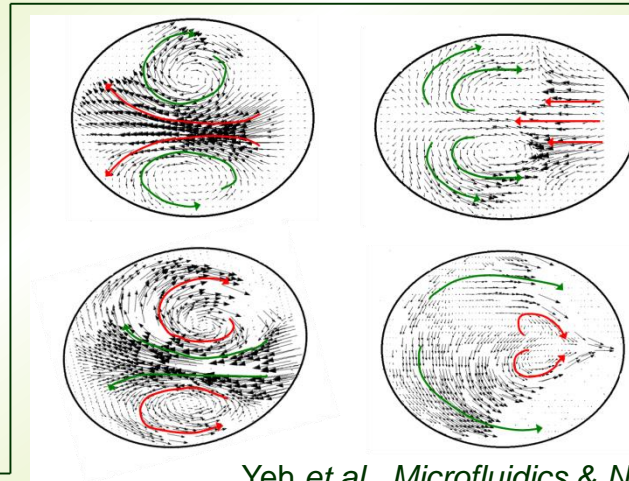


Mode B

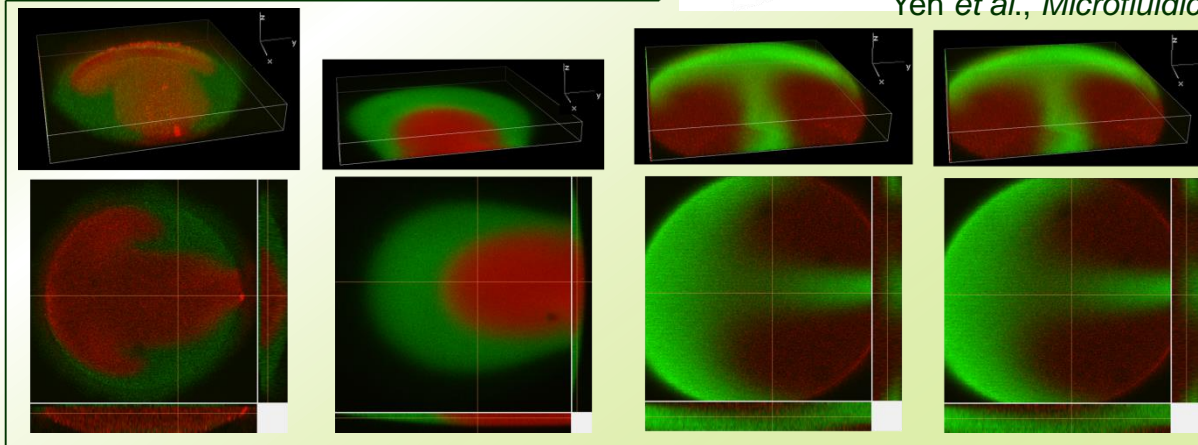


Lai et al., *Lab Chip*,
2010

使用micro-PIV以及共軛焦顯微鏡進行微液珠融合過程的行為分析，結合流場與三維混合圖形探討不同流體之融合行為差異。

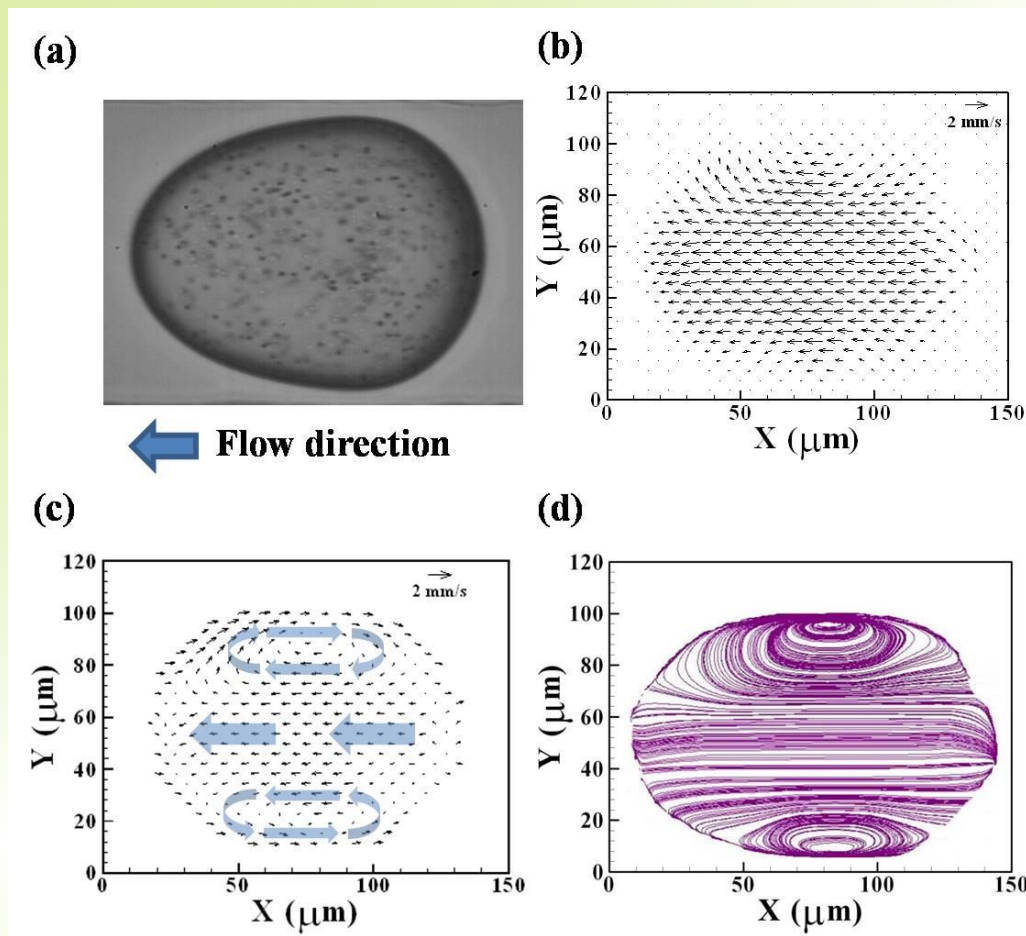


Yeh et al., *Microfluidics & Nanofluidics*, 2012



Droplets in a Straight Channel

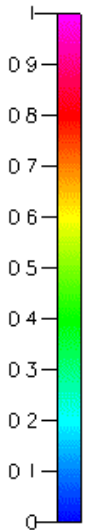
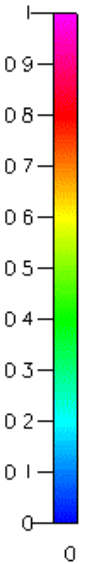
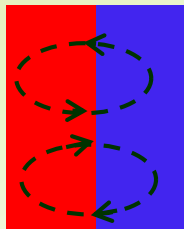
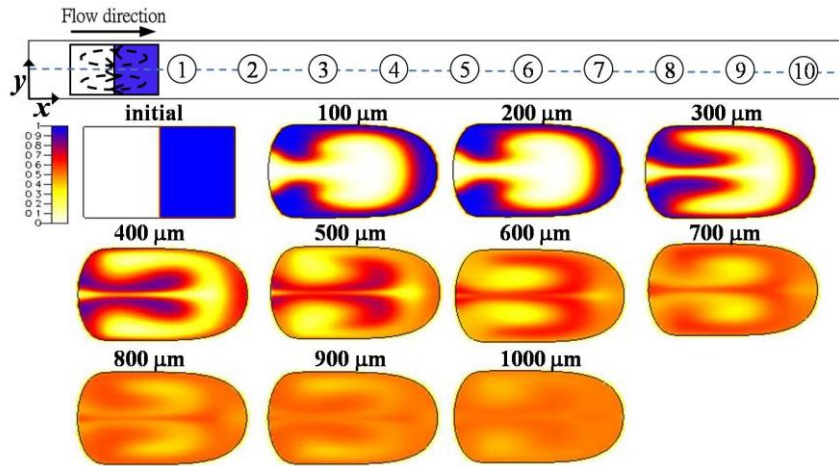
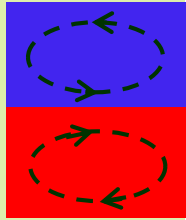
Tung, Li., and Yang, *Microfluidics & Nanofluidics*, 2009
cited 46



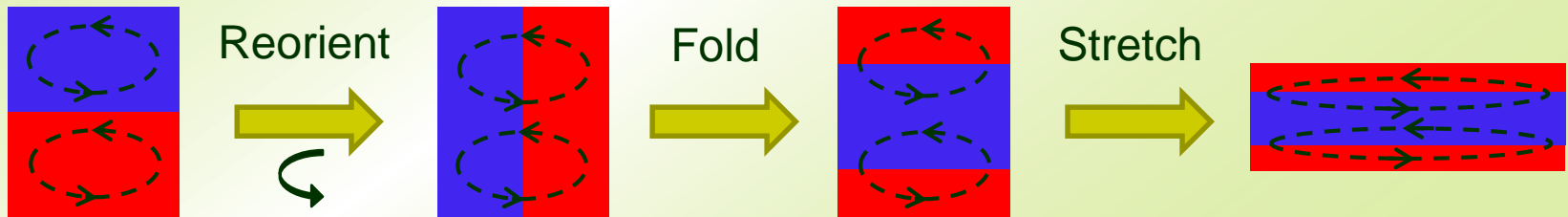
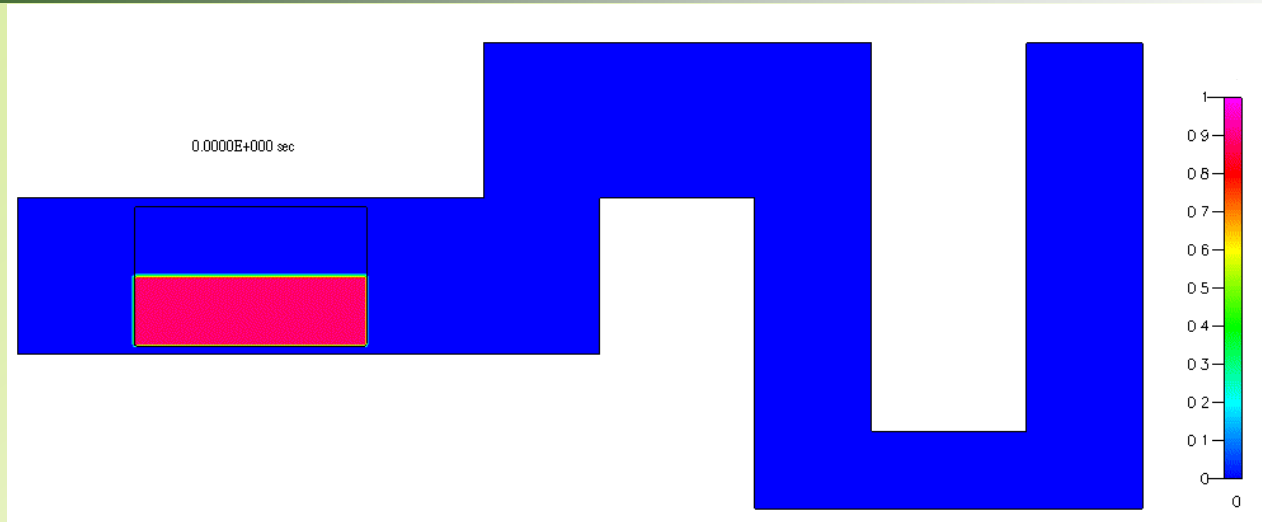
Micro-PIV measurement of the velocity field inside an aqueous moving droplet. (a) Original image, (b) velocity field, (c) velocity field after subtracting velocity of the droplet and (d) the streamlines at the center of the droplet.

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

Microfluidics and Nanofluidics, 2009 (times cited 46)



Mixing Mechanism

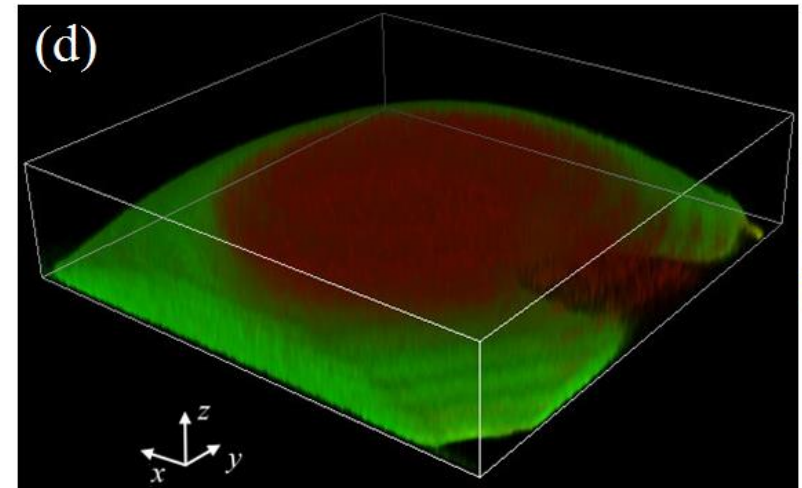
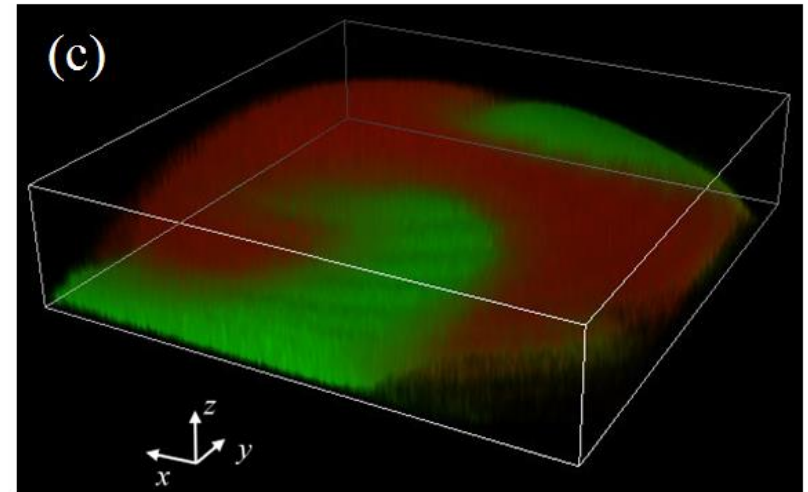
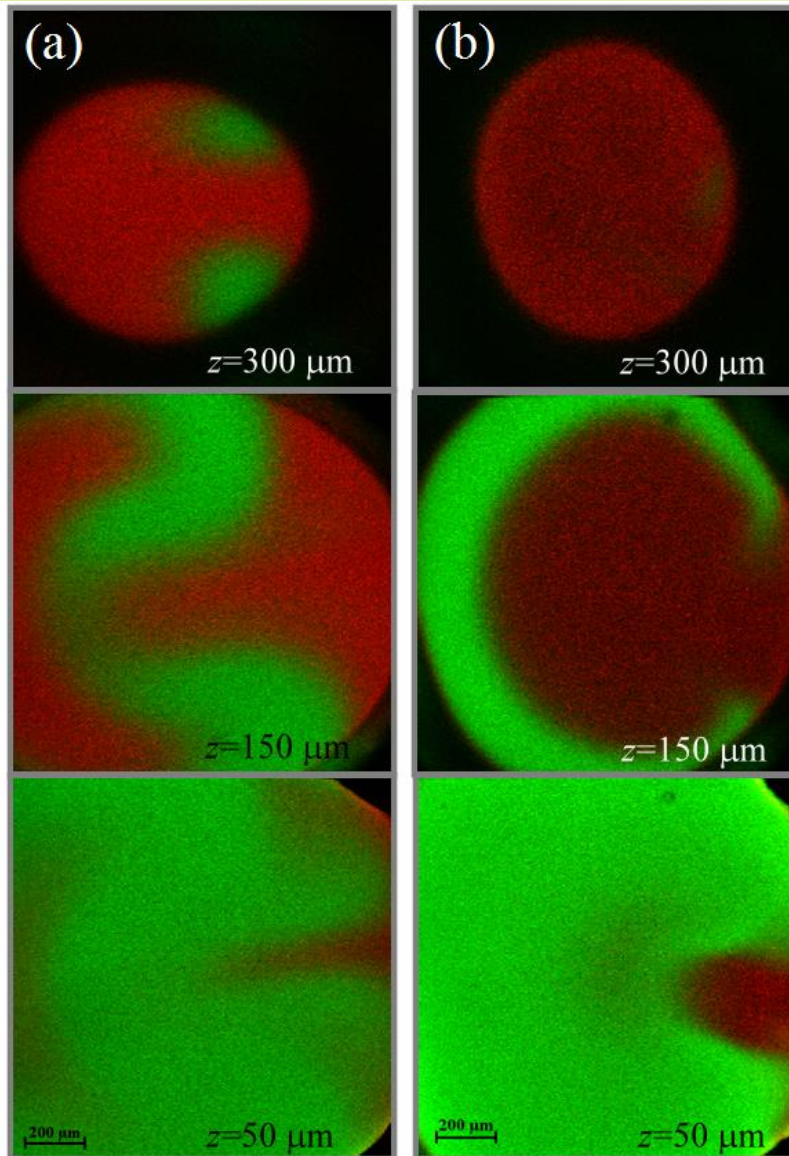


Mixing is promoted by periodic motion of the fluid. It is conducted by iterated **reorientation**, **stretching** and **folding** of the interface here.

DNA hybridization in Reaction Channels

Lab Chip, 2010; Beam Lab., NTU

Application and pilot-test

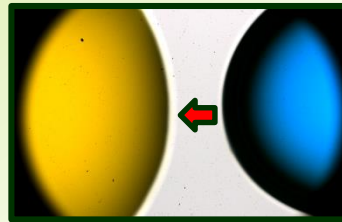


Mixing Test— food coloring & chemical reaction

Sometimes a color change is the result of a chemical reaction. Sometimes it is just the result of mixing colors.

MNF, 2013

Tartrazine (stationary droplet)



Indigo Carmine (moving droplet)

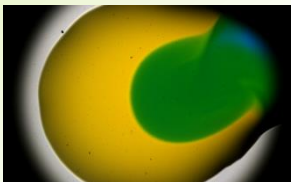
Round-head shaped



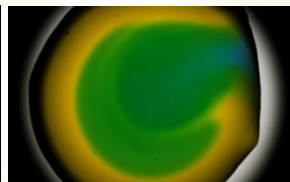
Mushroom-shaped



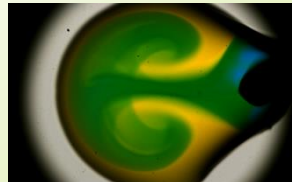
Heart-shaped



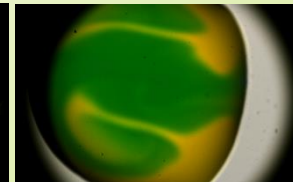
T = 0.100
74 s



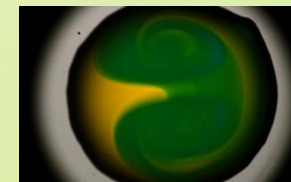
T = 1.000
s



T = 0.100
s



T = 1.000
s



T = 0.100
s



T = 1.000
s

1280 × 800 pixels, 3200 fps, 512X Slow motion

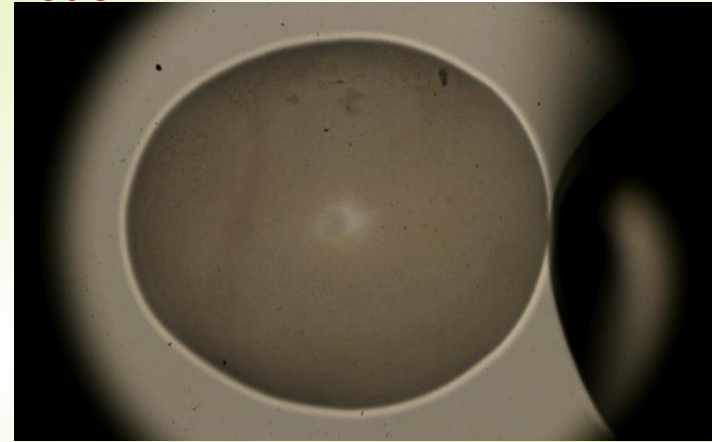
Chemical Reaction in Droplets

Mode C

1280 × 800 pixels, 3200 fps
512X Slow motion

Mode D

MNF, 2015



T = 5 ms



T = 25 ms



T = 50 ms



T = 1.000
s



T = 25 ms



T = 250
ms



T = 1.500
s

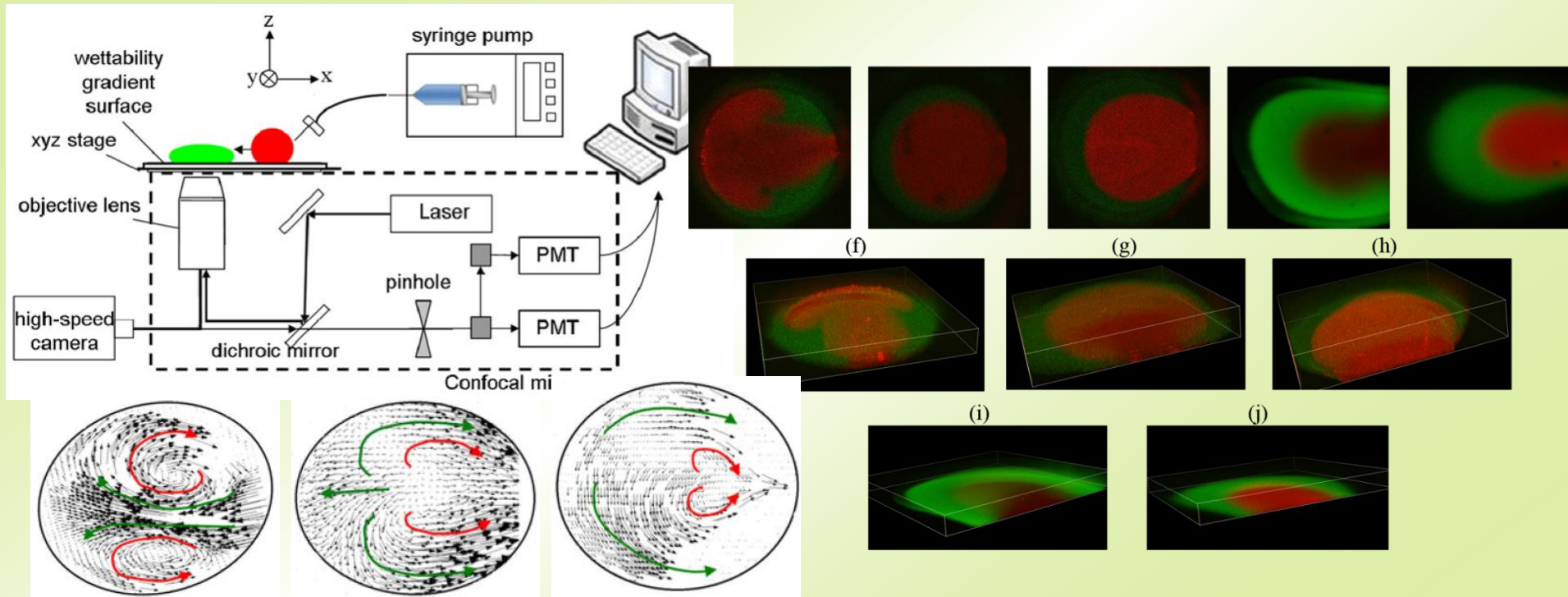


T = 2.500
s

Droplets Coalescence and Mixing with Identical and Distinct Surface Tension on a Wettability-Gradient Surface

S. I. Yeh, W. F. Fang, H. J. Sheen, J. T. Yang*

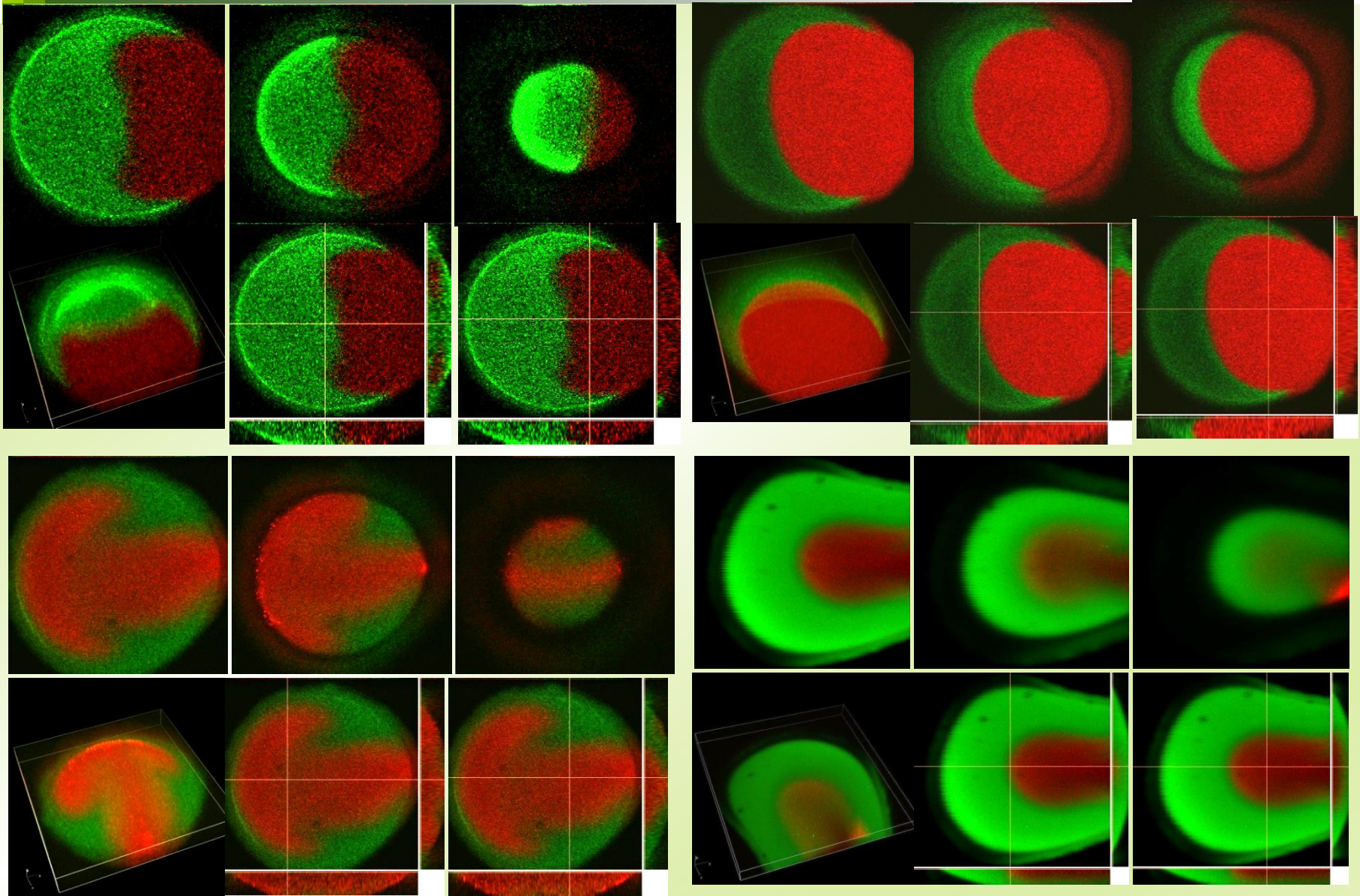
Microfluidics and Nanofluidics, doi: 10.1007/s10404-012-1096-2, 2013



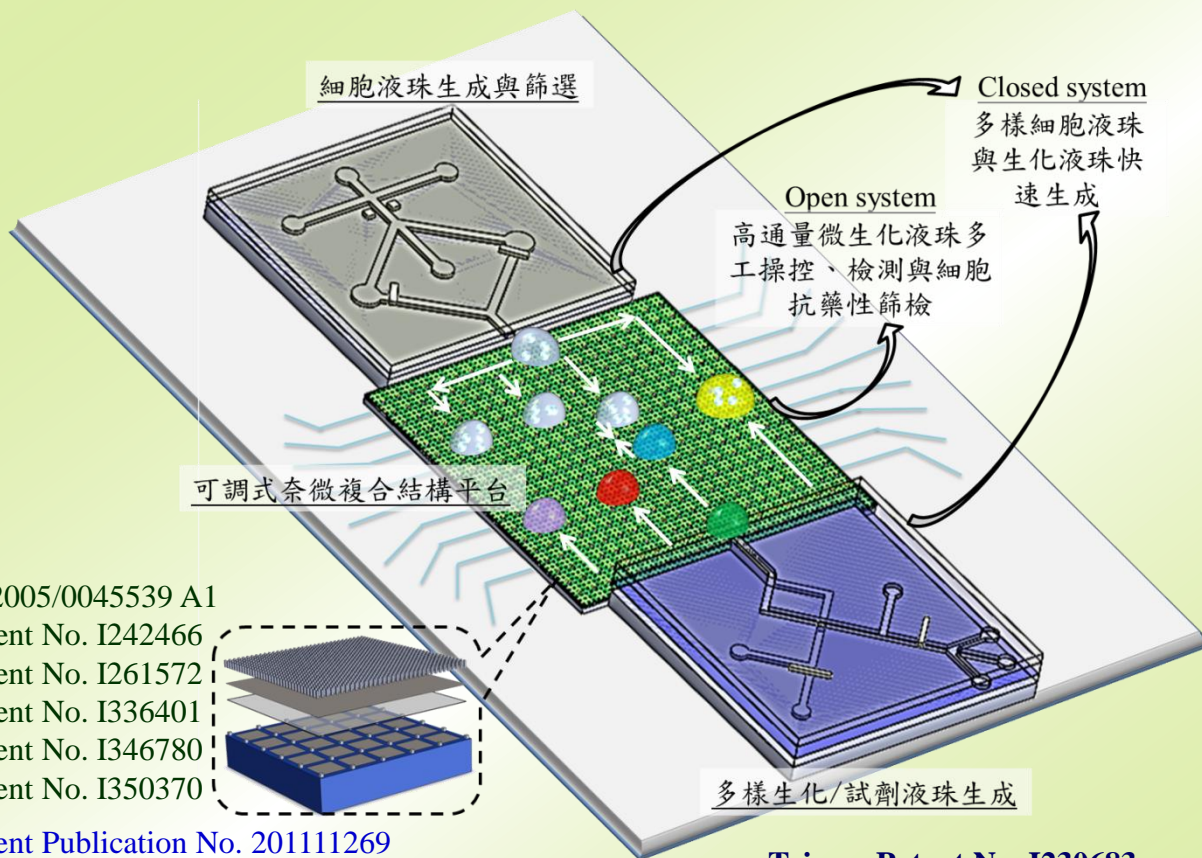
This study investigates the influence of different viscosities and surface tensions on droplet coalescence and mixing processes after a head-on collision between a moving droplet and a stationary droplet by micro-PIV and micro-LIF technique.

Reconstruction of Species Concentrations Interior the Colliding Droplets

楊鏡堂, 台大機械, 2011



計畫構想 (平台系統)



系統特點

- ✓ 具**高通量**之微液珠生成，可**自動化且同步**多功**操控**微液珠進行**平行化處理**，縮短**試驗時程**
- ✓ 包**覆細胞或試劑**(候選藥物)的微液珠可被**有效地篩選、分類與運用**，**避免細胞與試劑浪費**
- ✓ 可**操控**之微液珠**體積範圍廣**(pL~ μ L)，且**體積小於傳統檢測所需體積的數十倍以上**
- ✓ 此系統對**周邊的相容性高**，取樣方便，利於後端的處理與檢驗分析。可**推廣至其他細胞相關之基礎研究與分析**

US Patent 2005/0045539 A1
Taiwan Patent No. I242466
Taiwan Patent No. I261572
Taiwan Patent No. I336401
Taiwan Patent No. I346780
Taiwan Patent No. I350370

Taiwan Patent Publication No. 201111269
Taiwan Patent Publication No. 201113524
Taiwan Patent Publication No. 201038465
Taiwan Patent Publication No. 201038635
Taiwan Patent Publication No. 201111272

JMM Highlights, 2009

Institute of Physics IOP Select, 2009

Taiwan Patent No. I230683

JMM Highlights, 2006

film

An overlapping crisscross micromixer using chaotic mixing principles

Lilin Wang and Jing-Tang Yang

Highlights of *J. Micromech. Microeng.* 16 (2006) 2684–2691

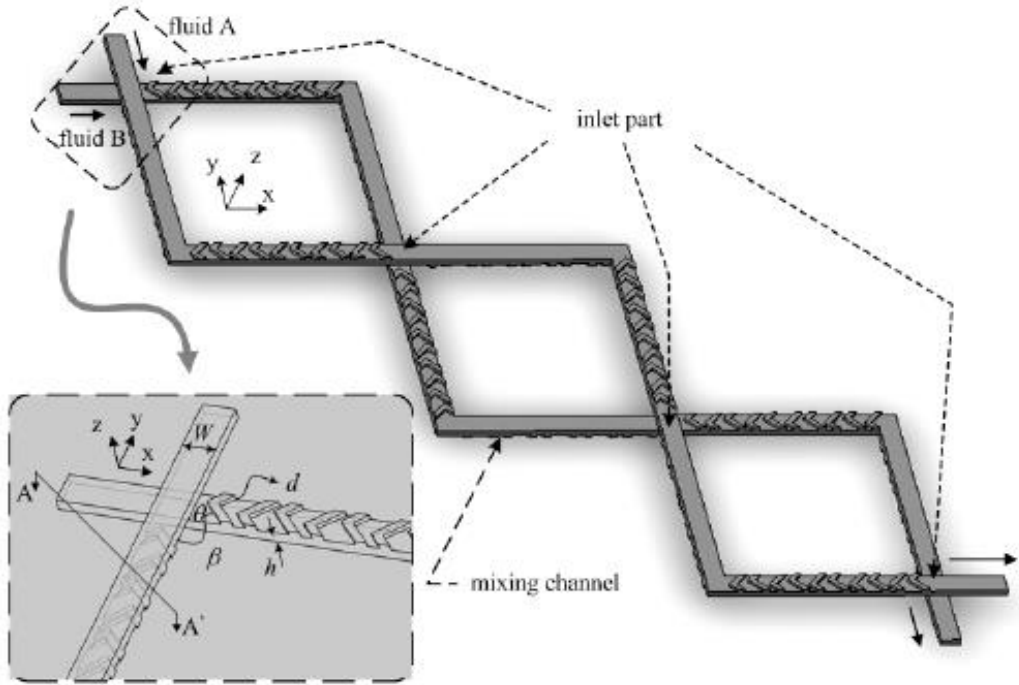


Figure 1. Schematic diagram of a staggered overlapping crisscross micromixer.

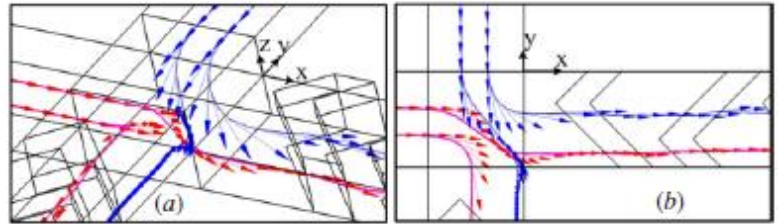
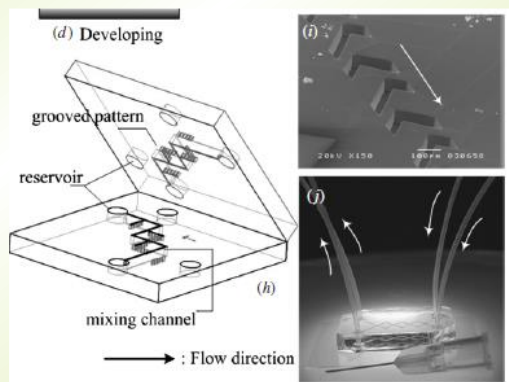


Figure 3. Lagrangian trajectories of the SOC μ -mixer from (a) a vertical view and (b) a front view near the crisscross junction.

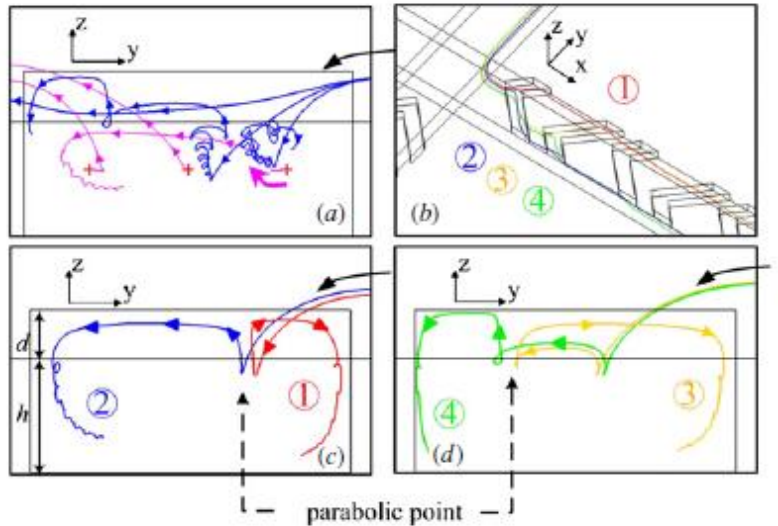
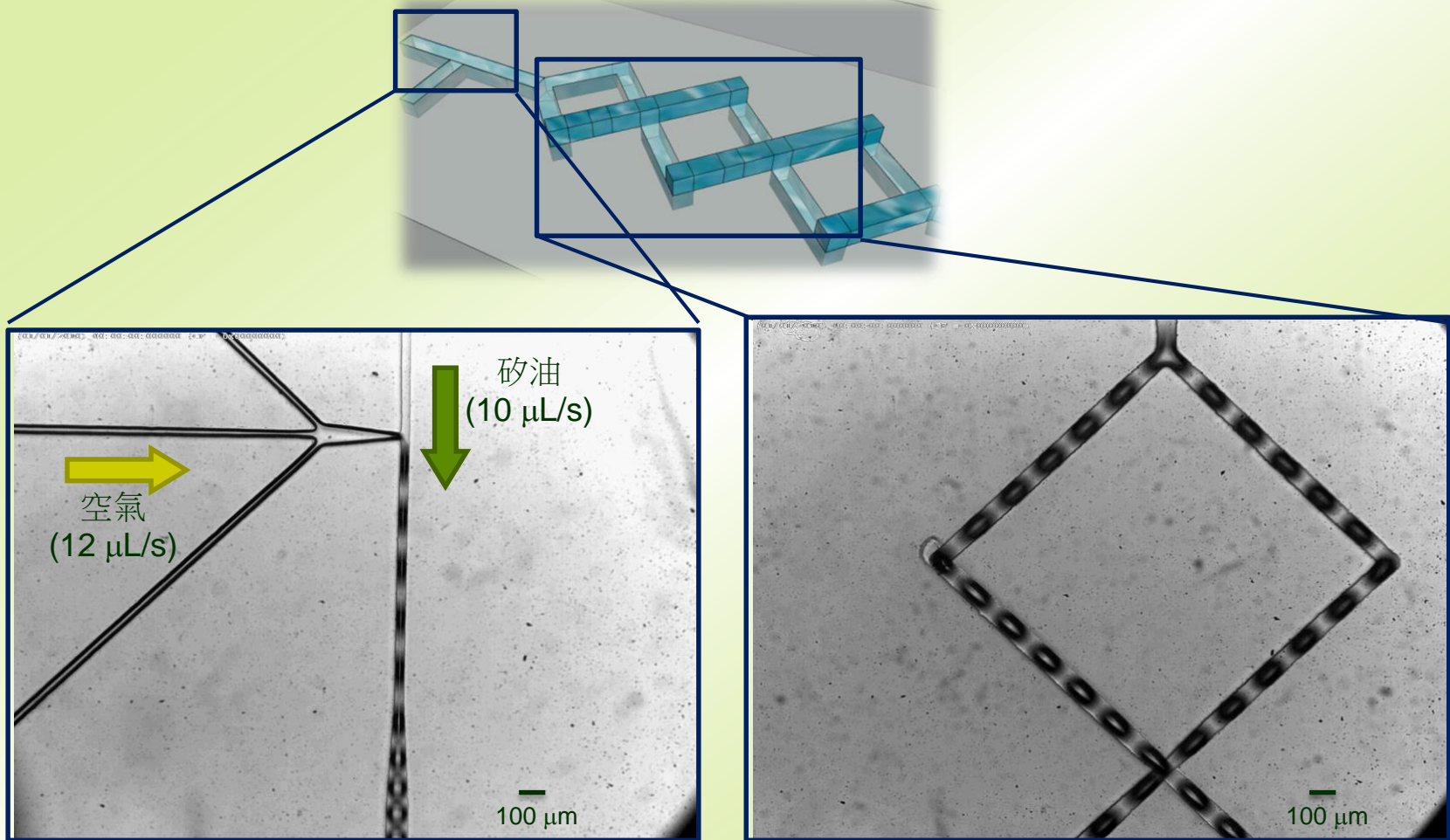


Figure 4. Lagrangian trajectories of the SOC μ -mixer displayed from (a), (c)–(d) end views through the x -direction mixing channel, and (b) a vertical view.

Preliminary Tests

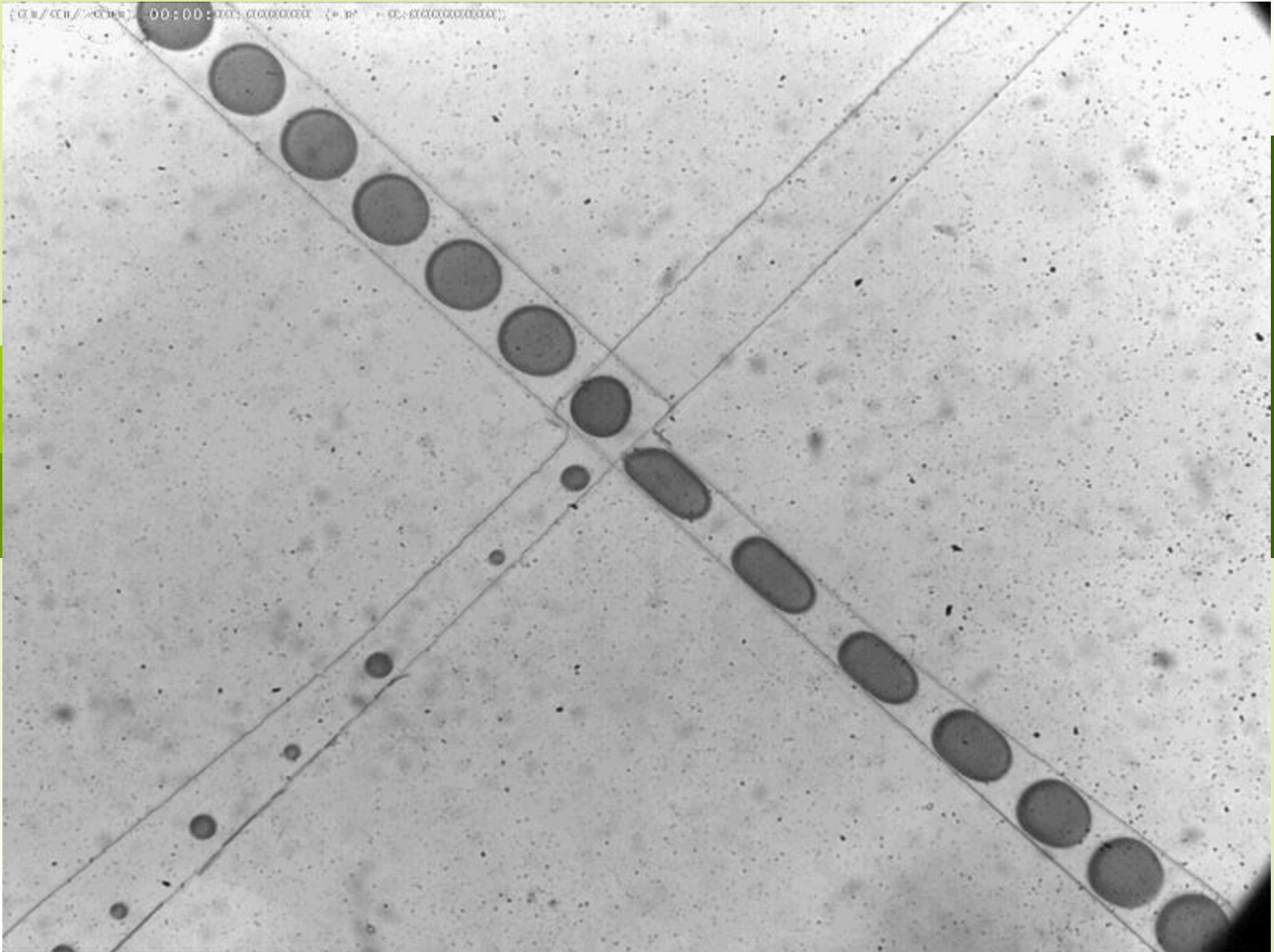


Yang et al., *Microfluidics & Nanofluidics*, 2011

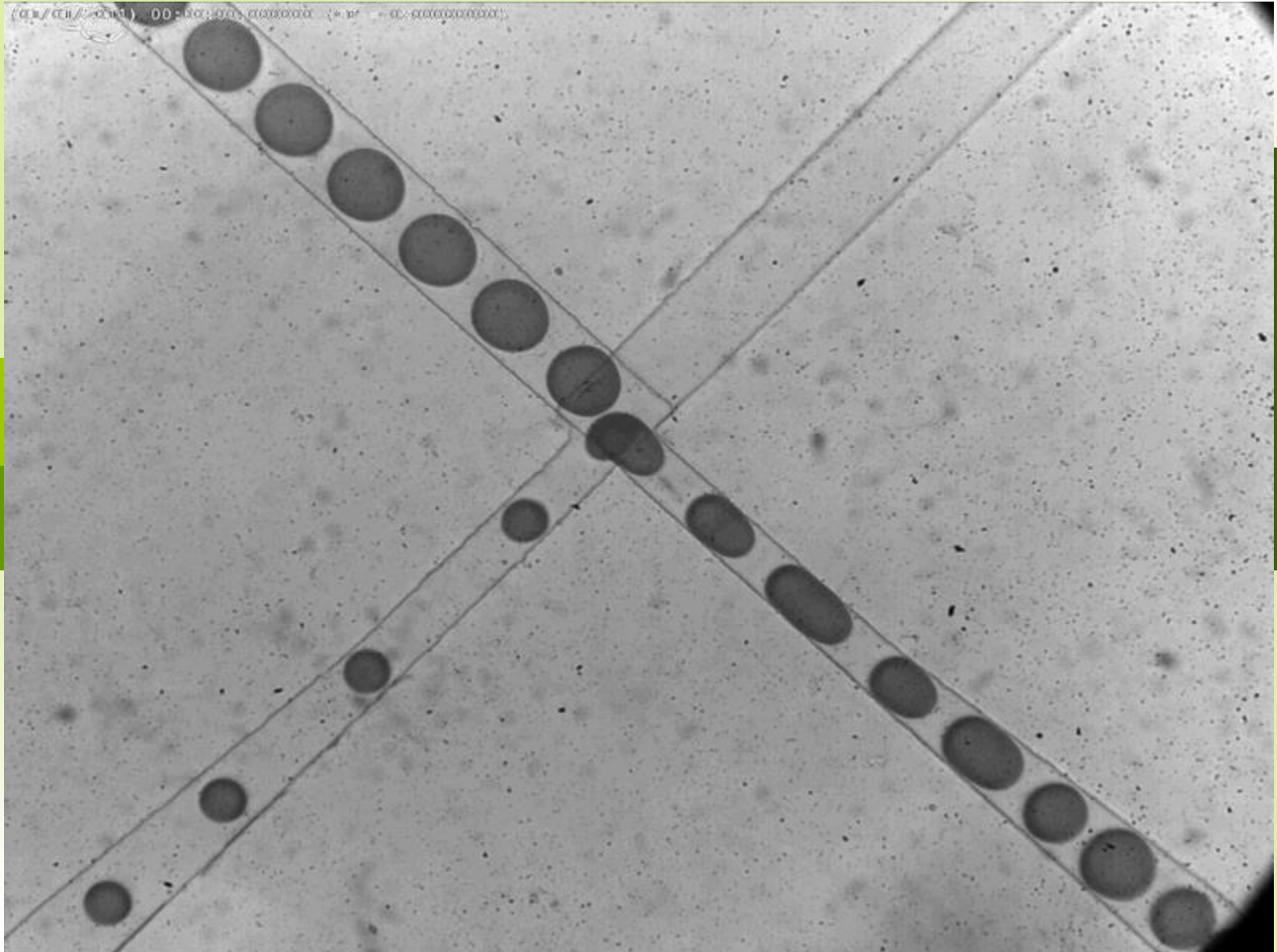


張偉軍碩士論文, 2011

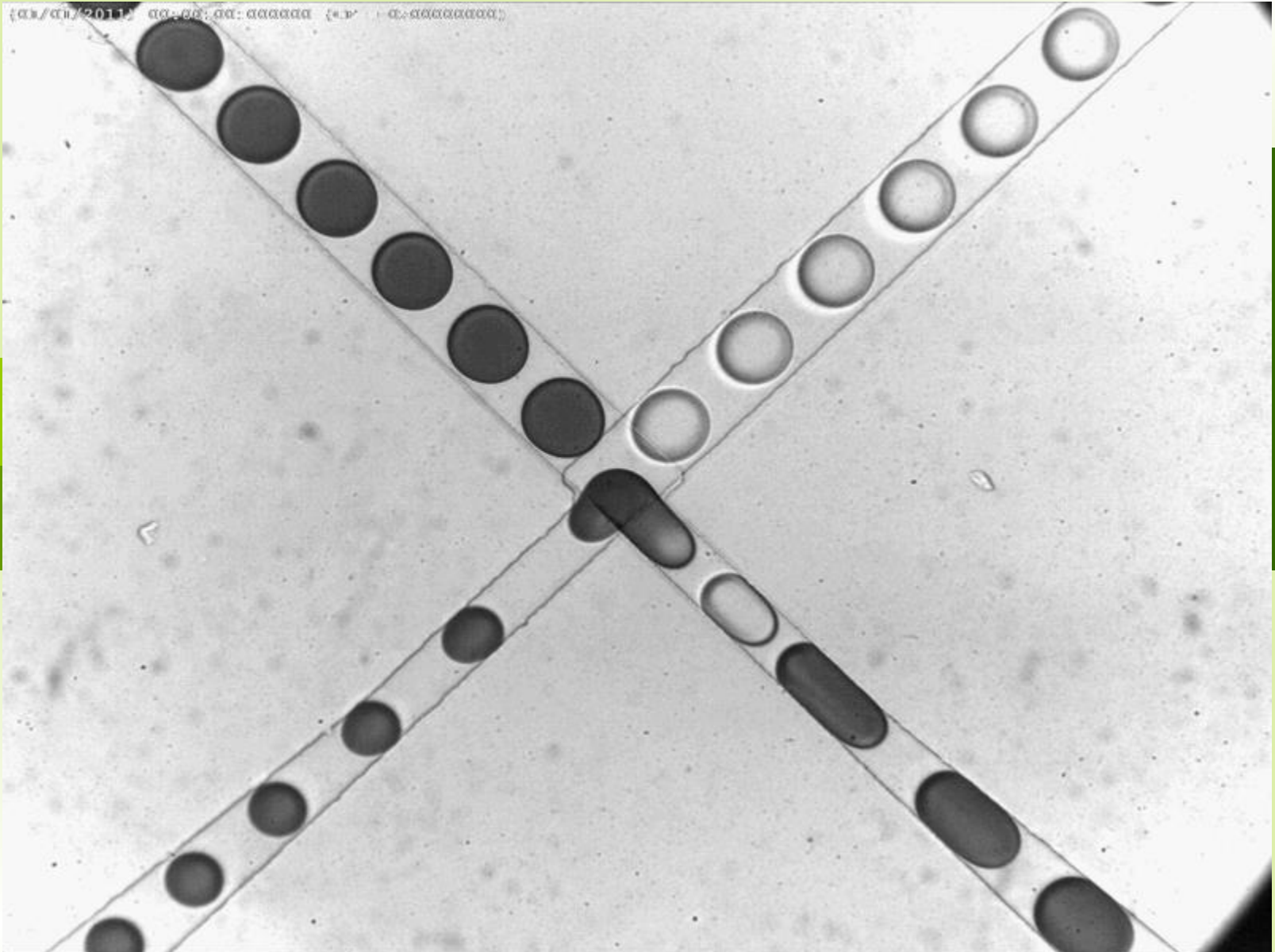
Droplet Fission (1)



Droplet Fission (2)

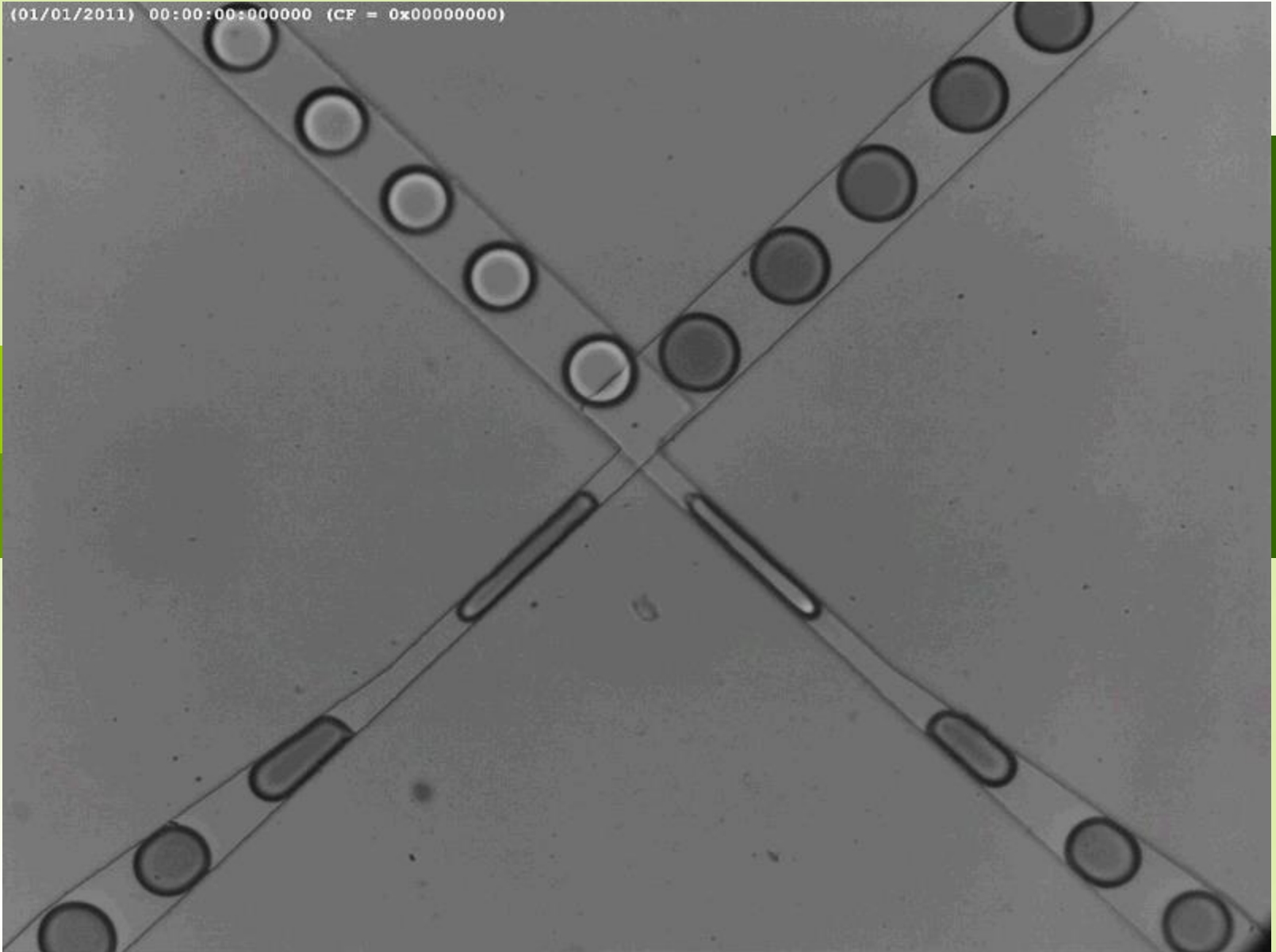


Droplet Fusion (1)

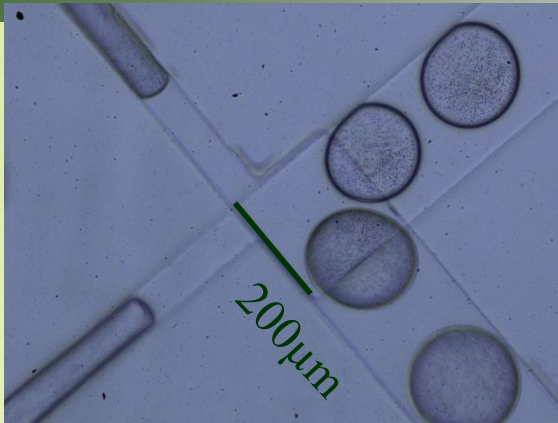


Droplet Fusion (2)

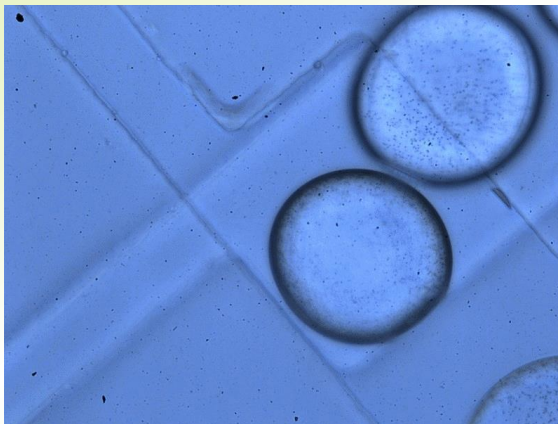
(01/01/2011) 00:00:00:000000 (CF = 0x00000000)



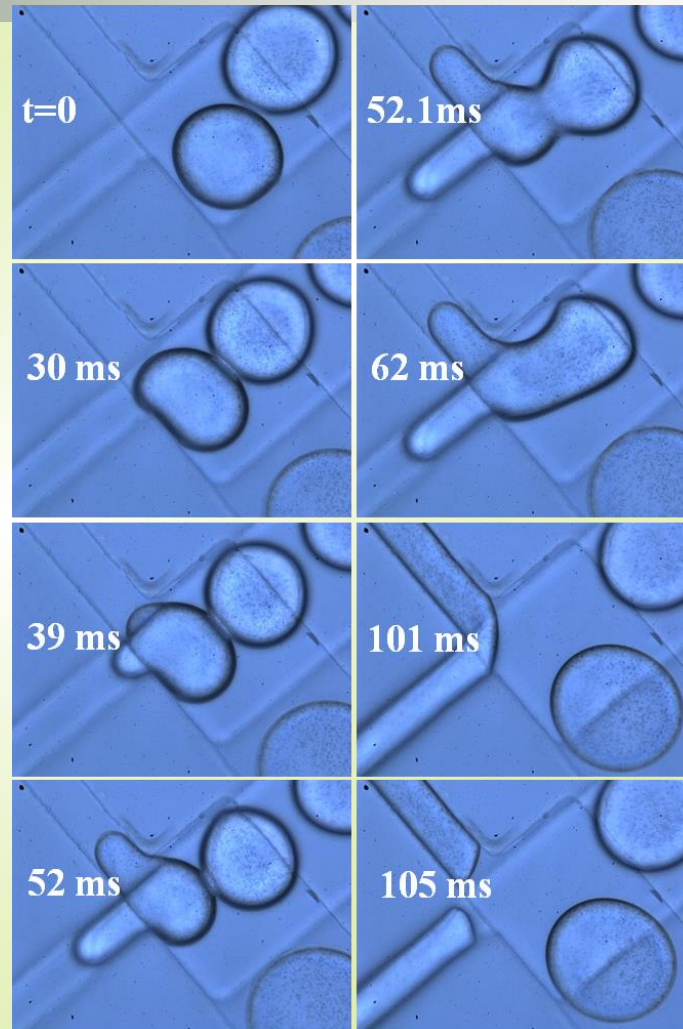
Visualization of Droplets Fusion and Fission



Frame rate : 1000 fps
Spatial resolution : 63.9 μm/pixel



Frame rate : 6000 fps
Spatial resolution : 2.13 μm/pixels

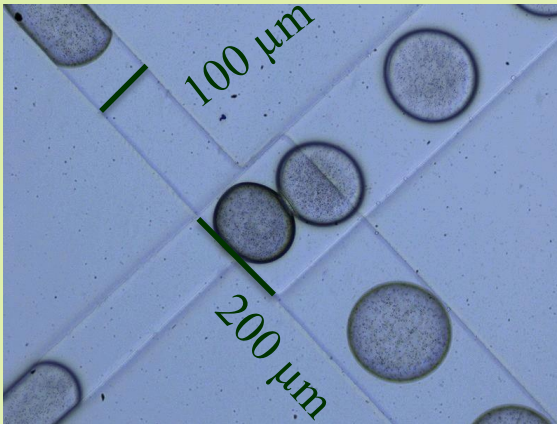


Phantom V310
high-speed CMOS camera
Observation zone : 800 × 600 pixels

Mechanism

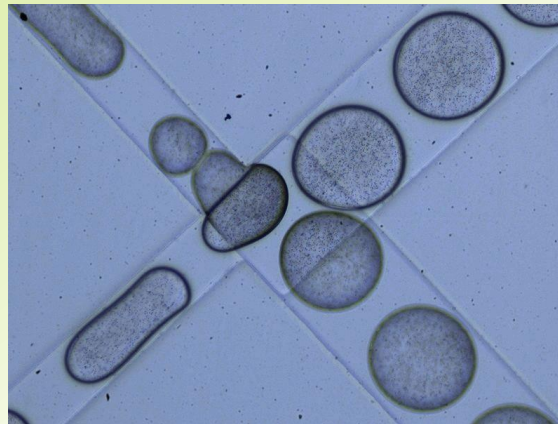
Droplets Fusion, Fission, and Distribution

(a.) fusion and fission



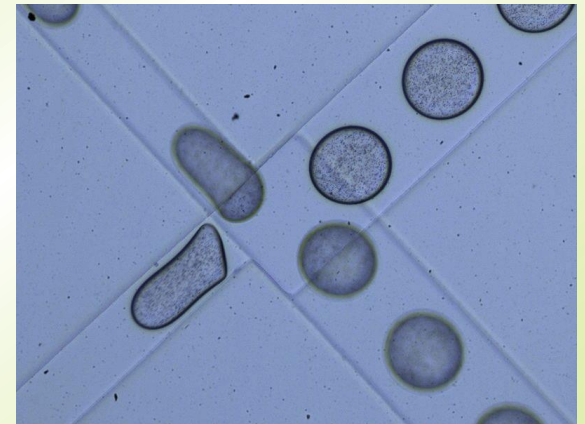
Deep of single layer: 51 μm
 DI water: 0.5 $\mu\text{l}/\text{min}$
 Silicone oil: 1 $\mu\text{l}/\text{min}$
 Re: 0.031 ; Ca: 0.0006

(b.) fission and distribution

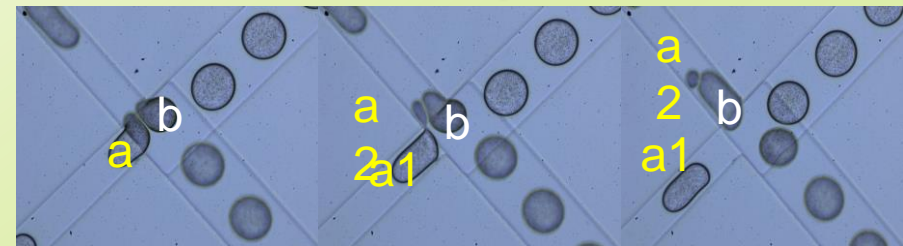
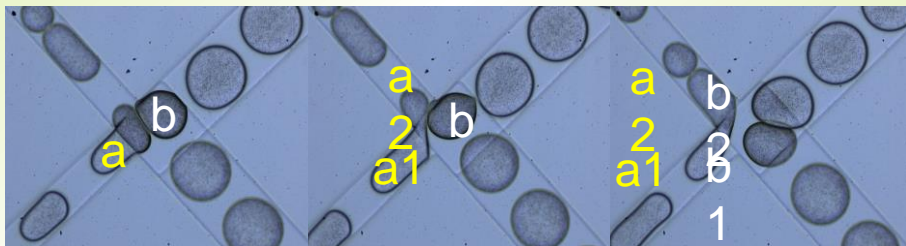


Deep of single layer: 51 μm
 DI water: 2 $\mu\text{l}/\text{min}$
 Silicone oil: 2 $\mu\text{l}/\text{min}$
 Re: 0.083 ; Ca: 0.0016

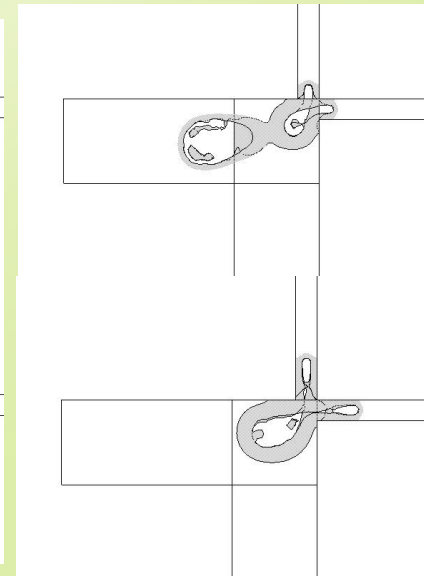
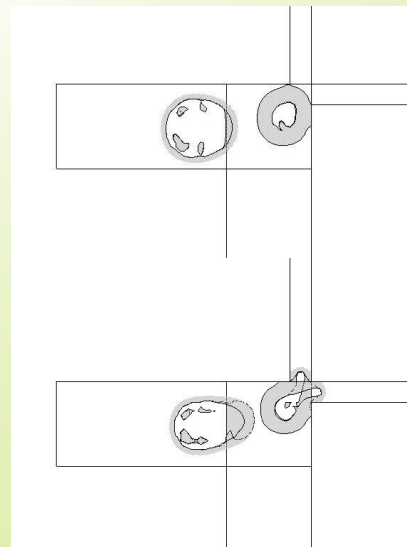
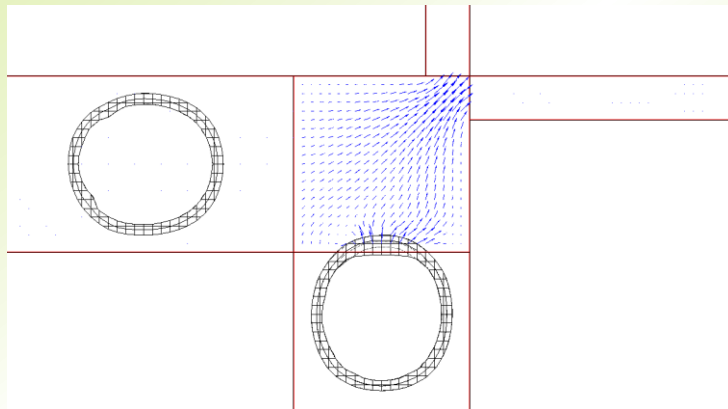
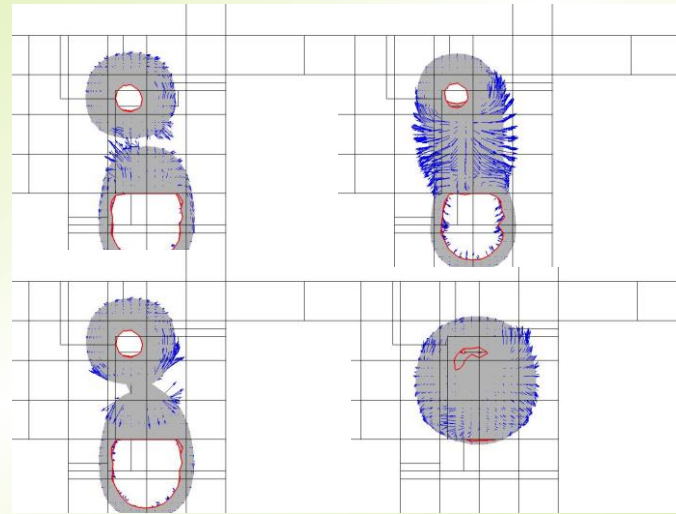
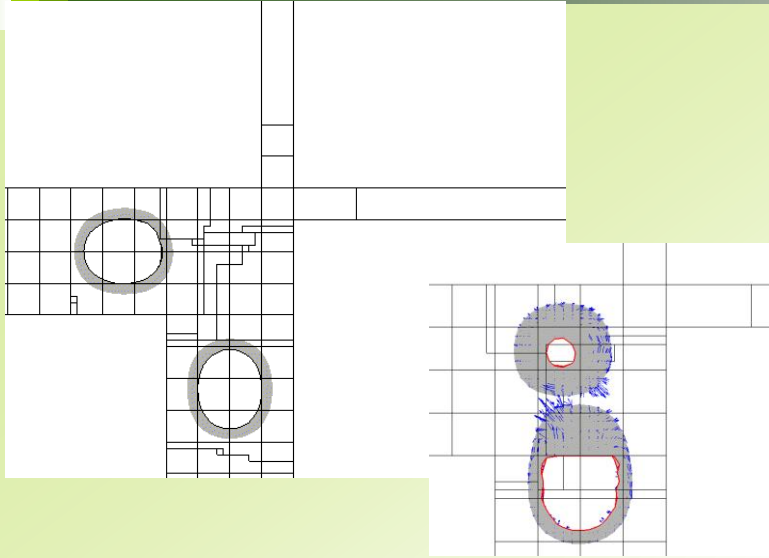
(c.) fission and distribution



Deep of single layer: 51 μm
 DI water: 2 $\mu\text{l}/\text{min}$
 Silicone oil: 5 $\mu\text{l}/\text{min}$
 Re: 0.145 ; Ca: 0.0028



Droplets Simulation





台大的實驗室的幾項技術發展

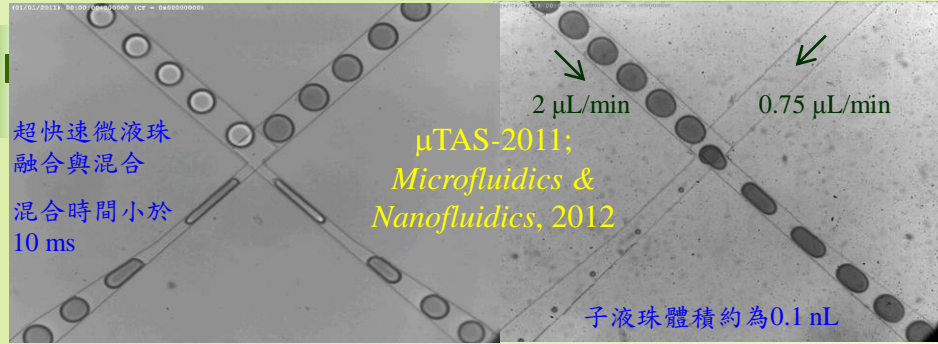
(2008-2016)

- A. 液珠碰撞反應之平台與分析技術
- B. 基因變異之液珠型目視檢測平台
- C. 生質柴油製程之毫米級系統
- D. 胰島素目視檢測平台
- E. 番茄與蘭花之病毒檢測技術 (王子明博士)
- F. PLGA製藥技術 (葉思沂教授)

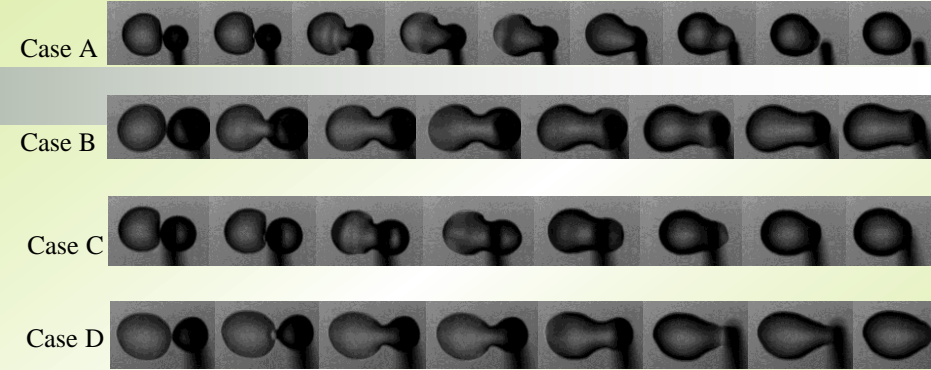
簡報大綱

1. 奈微流體技術與系統之優劣
2. 簡介連續式微流體系統與液珠型微流體技術

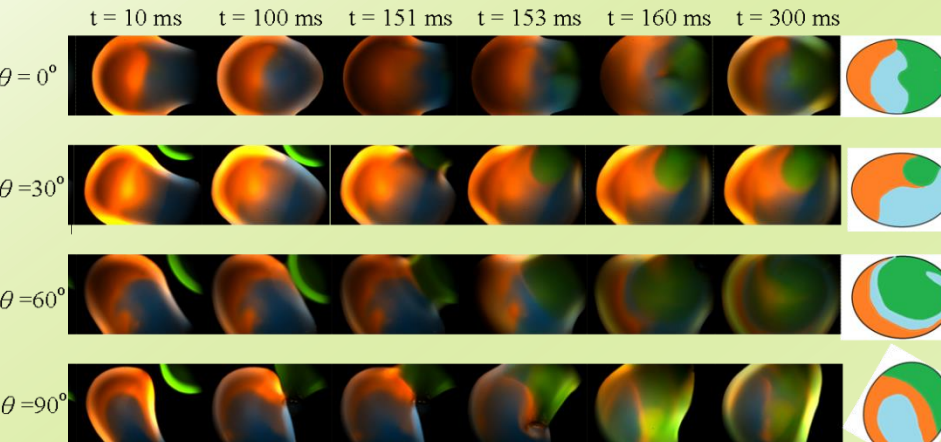
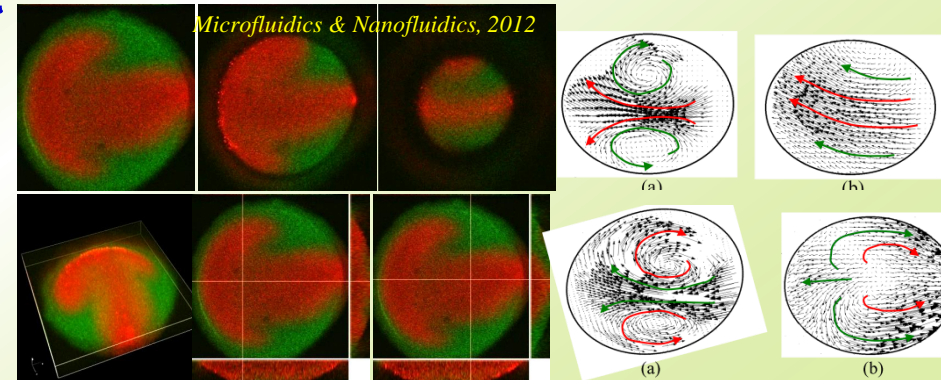
Progress of droplet-based microfluidics



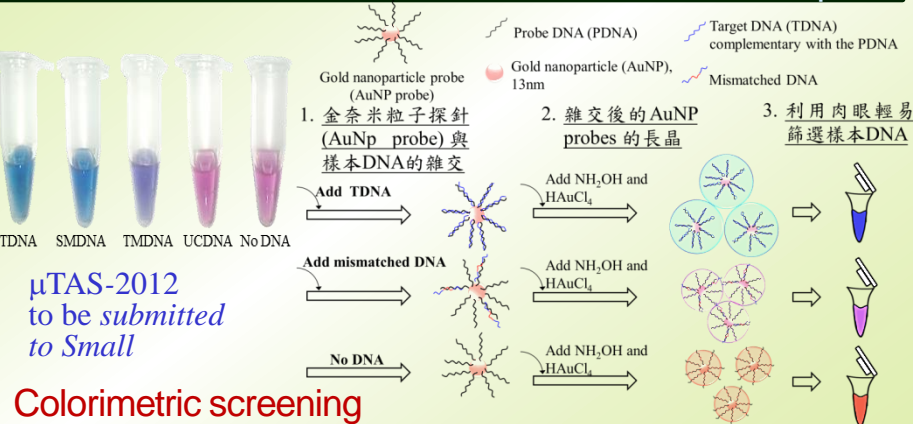
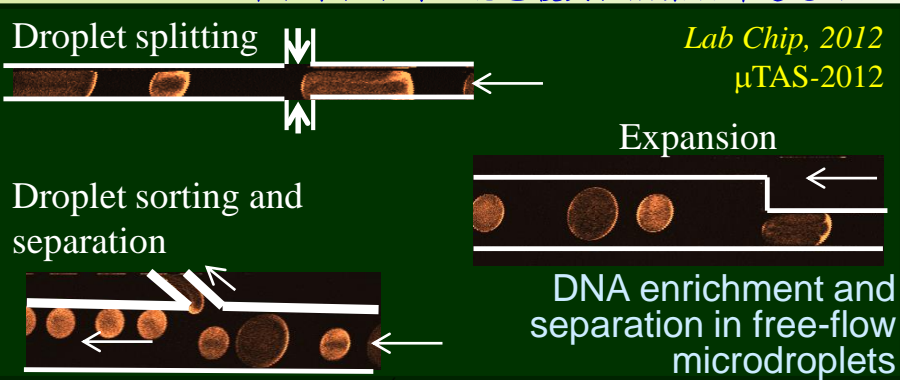
Fusion and fission of droplets → 研發糖尿病新藥篩檢的平台奈微液珠細胞包覆與抗癌藥物篩選應用之研究



Coalescence and Mixing of Colliding Droplets



To be submitted to Biomicrofluidics



Colorimetric screening of DNA using hybridization-mediated AuNP probes



■ **New Progress...**

Bio-Microfluidics & Lab-on-a-Chip

Continuous flow

Microreactor

DNA detection

Carbohydrate synthesis

Protein analysis

Cell manipulation

(trapping, separation, tec.)

Droplets flow

Open system

Multi-nucleotide
polymorphisms detection

Islet screening

Microchannel

PLGA synthesis (drug release)

DNA concentration

Biodiesel synthesis

Precision medicine

(concentration gradient of drug)

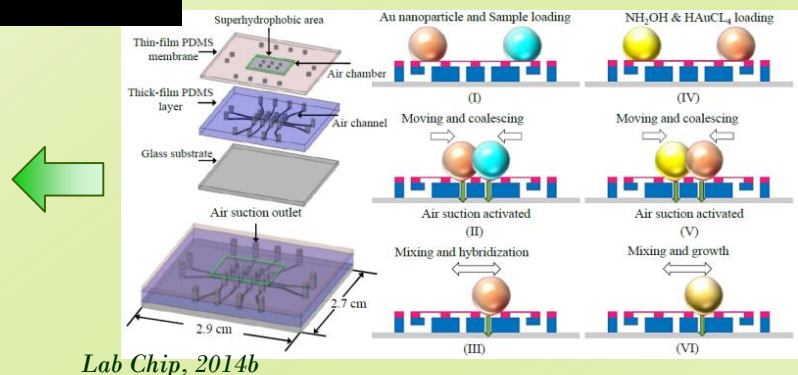
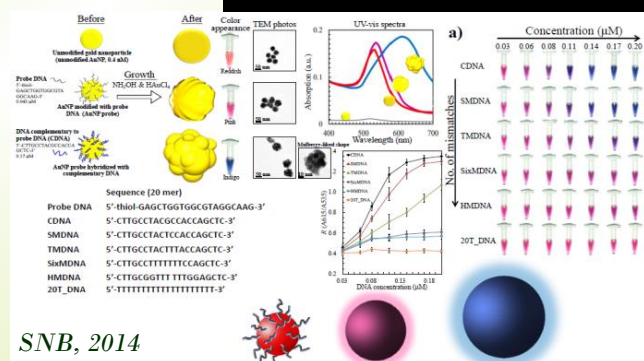
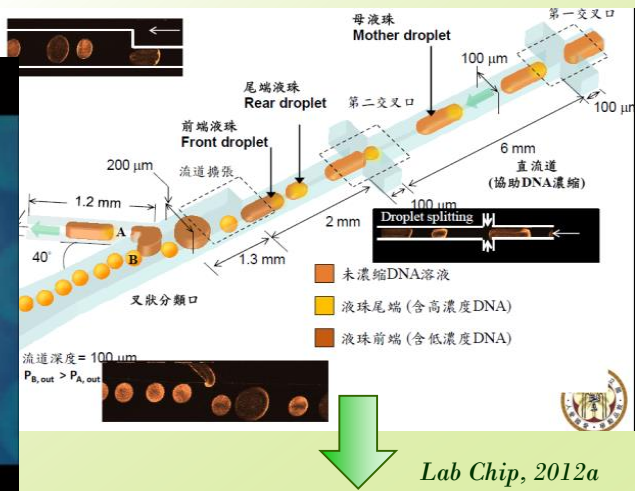
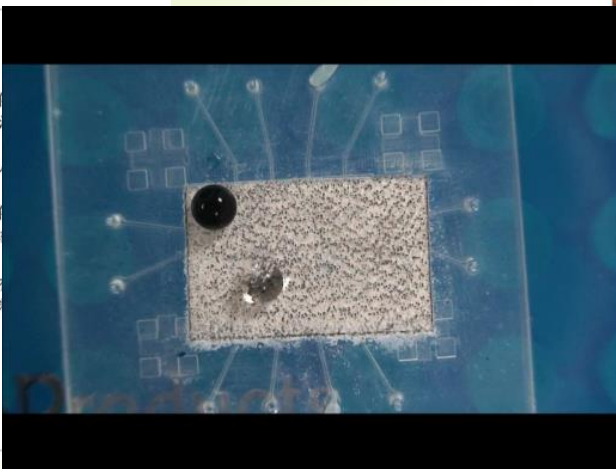
個人醫檢新紀元：可視化液珠式基因快篩技術

Personalized Diagnostics at Sight: Droplet-based Gene Screening

Point-of-care model

第11屆國家新創獎-2014

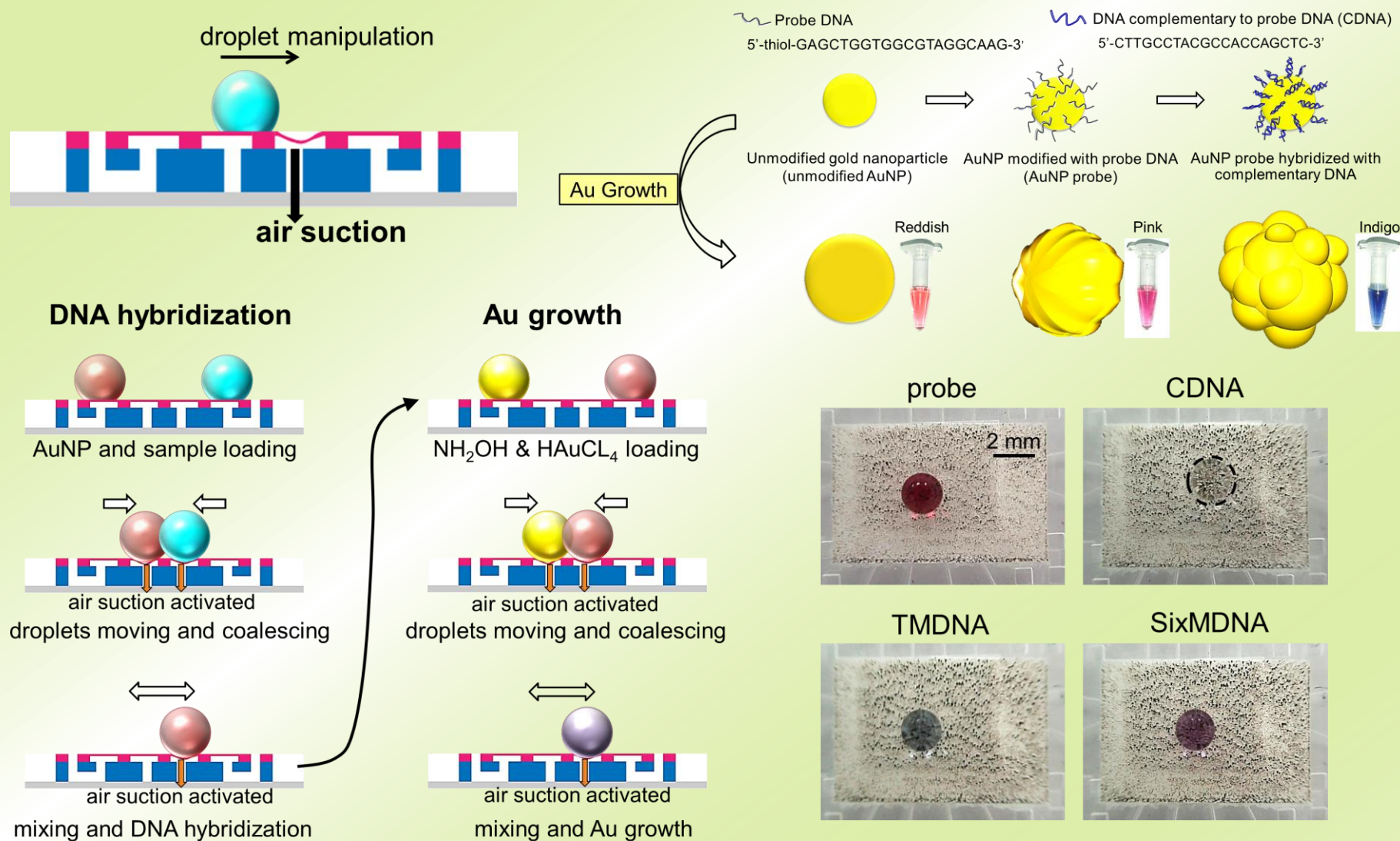
一種新的檢測技術和晶片系統，不需要昂貴的設備及複雜的步驟，即可自動化進行基因型診斷，檢測結果能用肉眼直接觀察得知，並具有可攜帶、微量藥品試劑消耗及快速篩選等優點，減少醫療資源浪費、發揮藥物的最佳藥效、針對每個人不同的體質，打造專屬個人的治療方式。本技術核心包含三大項目：(1) 發展一種利用金奈米粒子探針結合長晶方法，(2) 可攜式的液珠操控平台，(3) 被動式DNA濃縮技術。



A Biocompatible Open-surface Droplet Manipulation Platform for Multi-nucleotide Polymorphisms Detection

C. J. Huang, W. F. Fang, M. S. Ko, H. Y. E. Chou, and J. T. Yang*

Lab on a Chip, Vol. 14, pp. 2057-2062, 2014

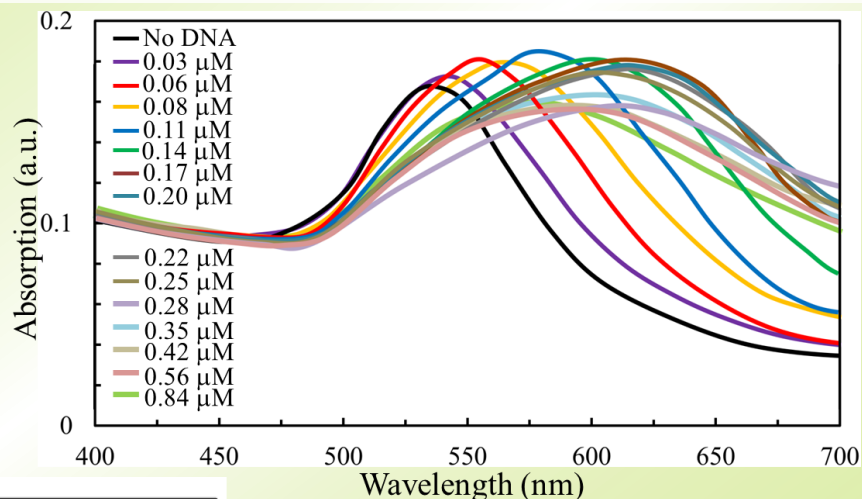
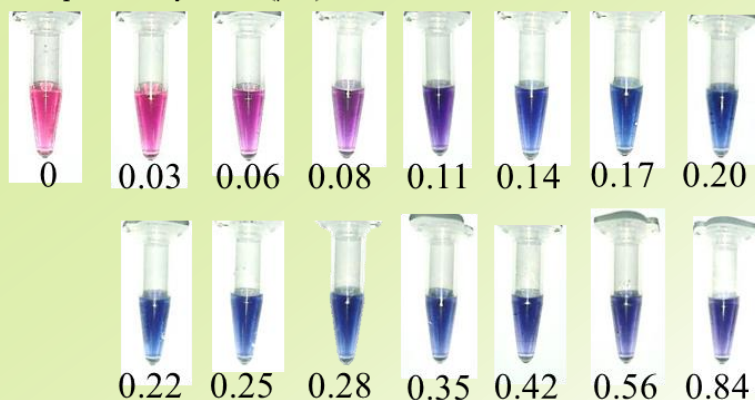


Colorimetric Determination of DNA Concentration and Mismatches using Hybridization-mediated Growth of Gold Nanoparticle Probes

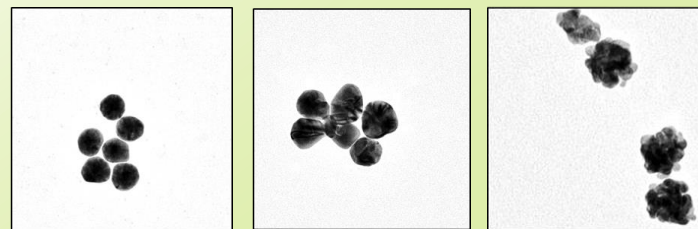
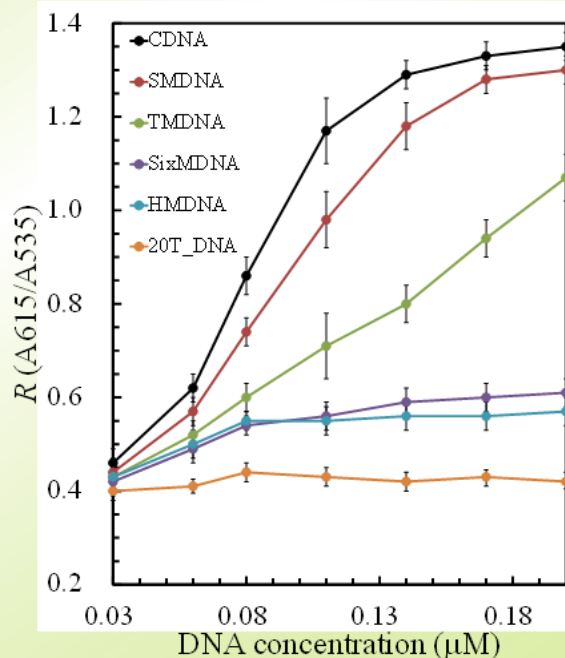
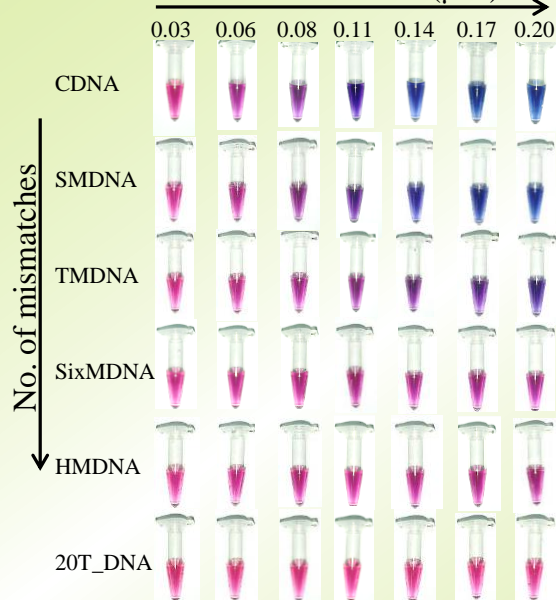
W. F. Fang, W. J. Chen, and J. T. Yang*

Sensors and Actuators B, Vol. 192, pp. 77-82, 2014

Complementary DNA (μM)



Concentration (μM)



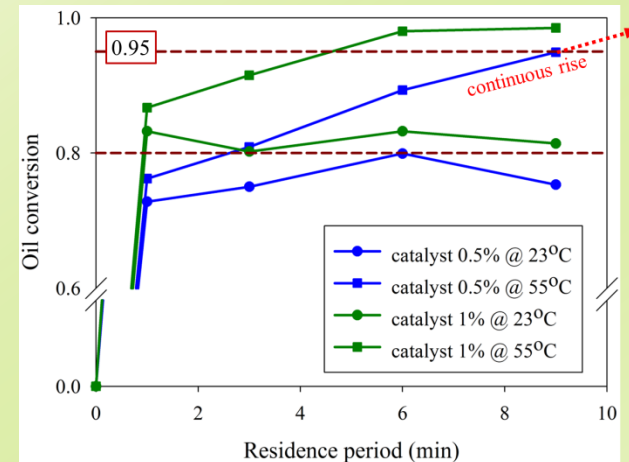
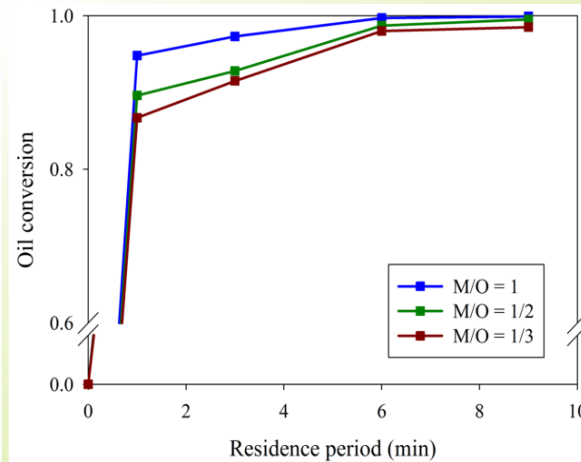
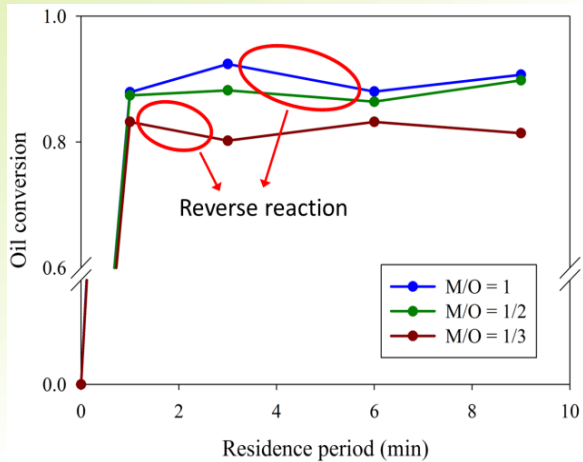
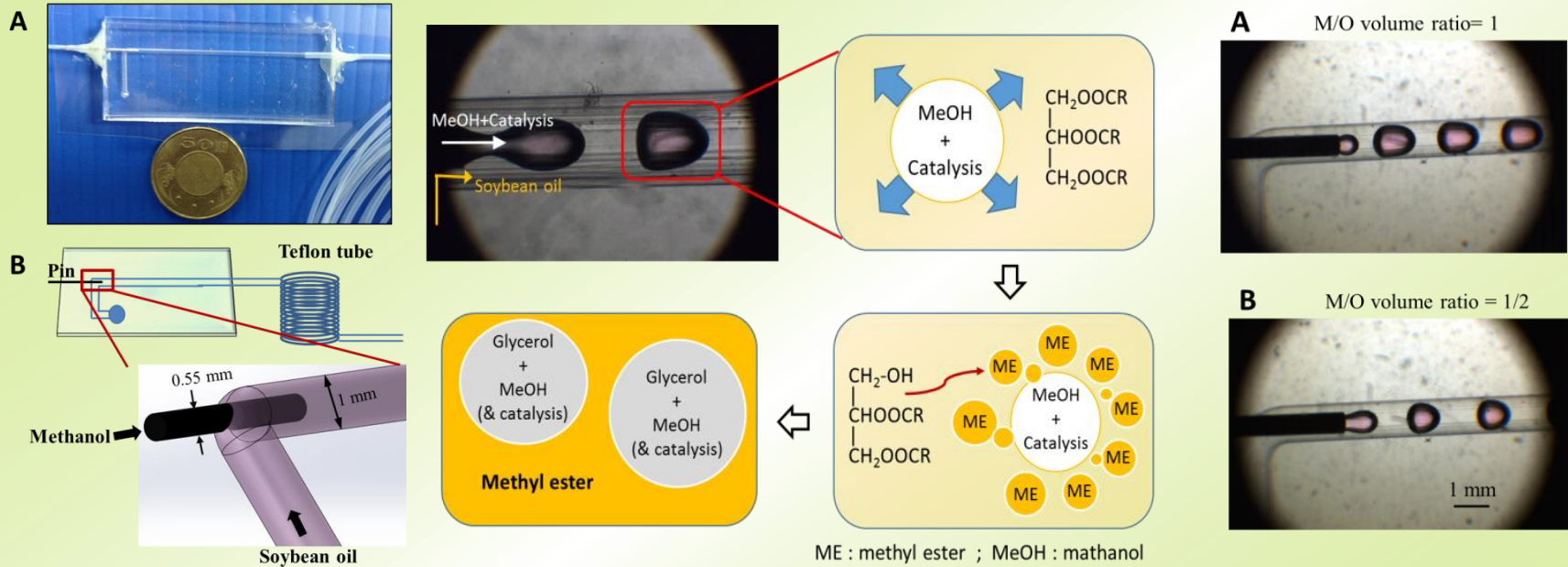
This method can be employed not only in semi-quantitative analysis of the given DNA but also in the identification of base-pair mismatches (SNP & MNP) of DNA samples

High-throughput Biodiesel Transesterification Device using the Droplet-based Co-axial Fluidic System

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

μTAS-2014, San Antonio, USA, October, 2014 (submitted);

第12屆國家新創獎-2015

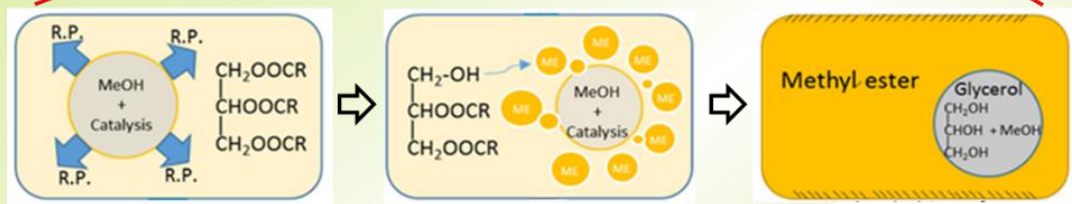
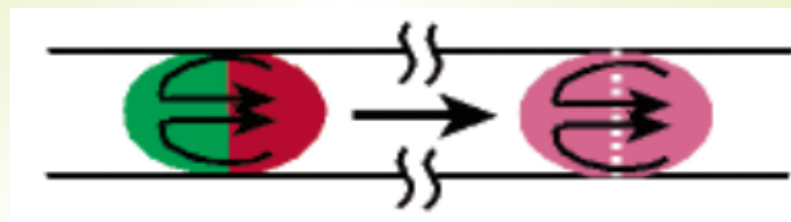
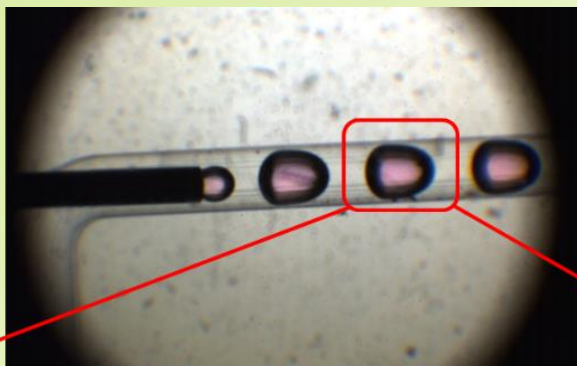


Separation and Purification of Biodiesel by a Millifluidic System

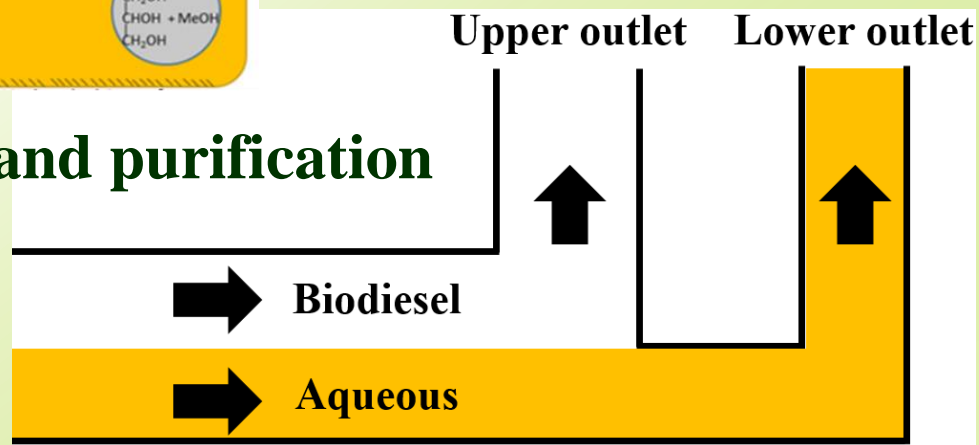
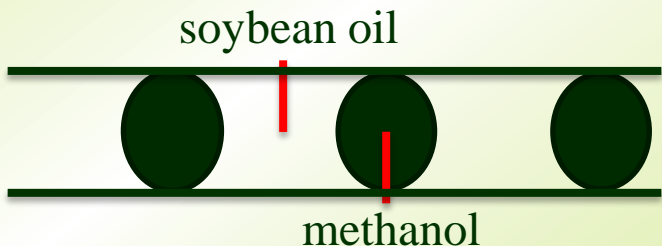
(in progress)

1. Droplet-based rapid reaction device

Key Techniques

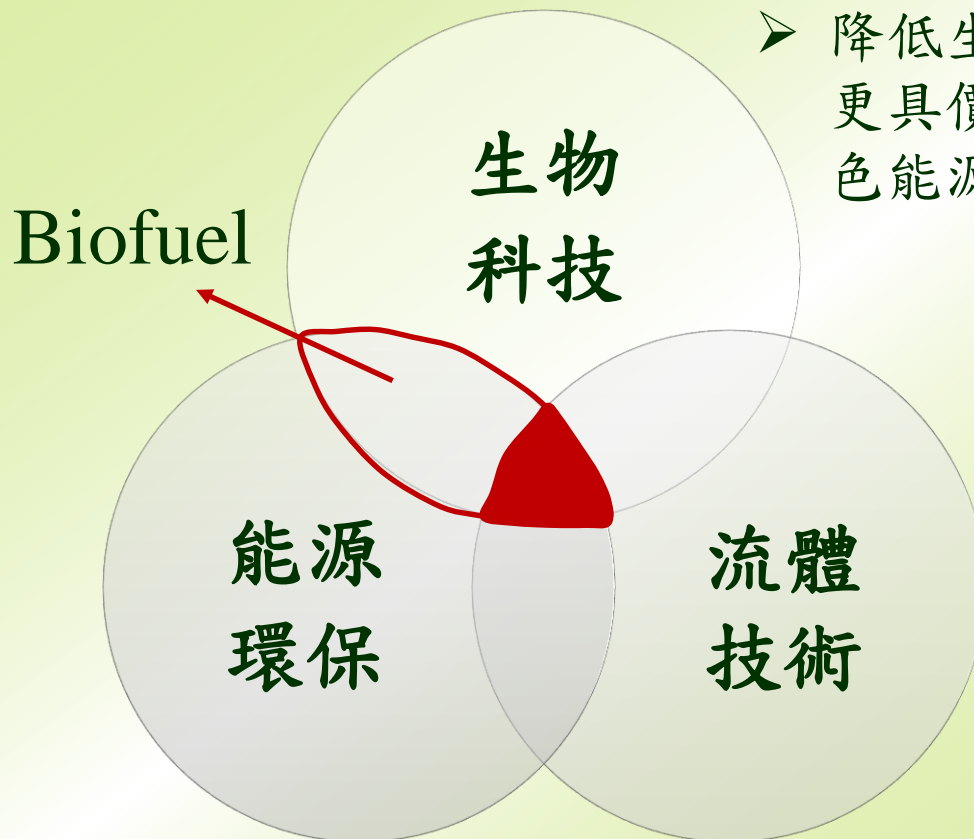


2. Passive device for separation and purification



重要創新與突破

創新的液珠式生質柴油產製系統



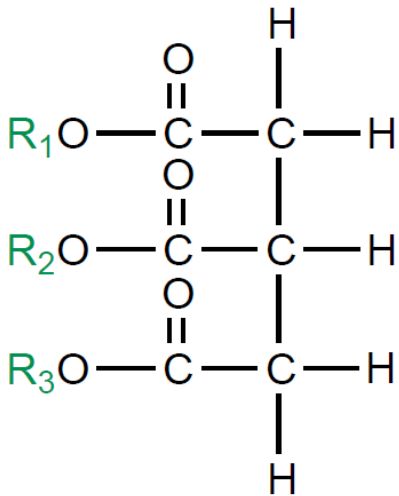
➤ 降低生質燃料產製成本，使其更具價格競爭力，突破目前綠色能源發展的主要瓶頸

- ☑ 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

Biodiesel

◆ Biodegradable

Transesterification

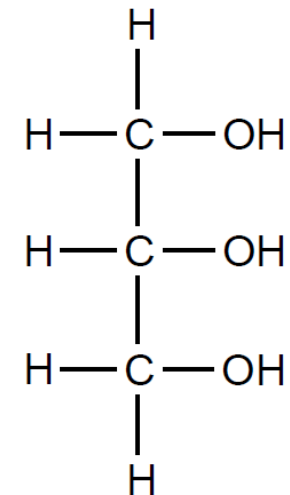


Triglyceride
(Soybean oil)

- Traditional industrial methods for biodiesel production**
- Need continuous stirring
 - High temperature and pressure
 - High energy consumption
 - Take several days

Methanol

+



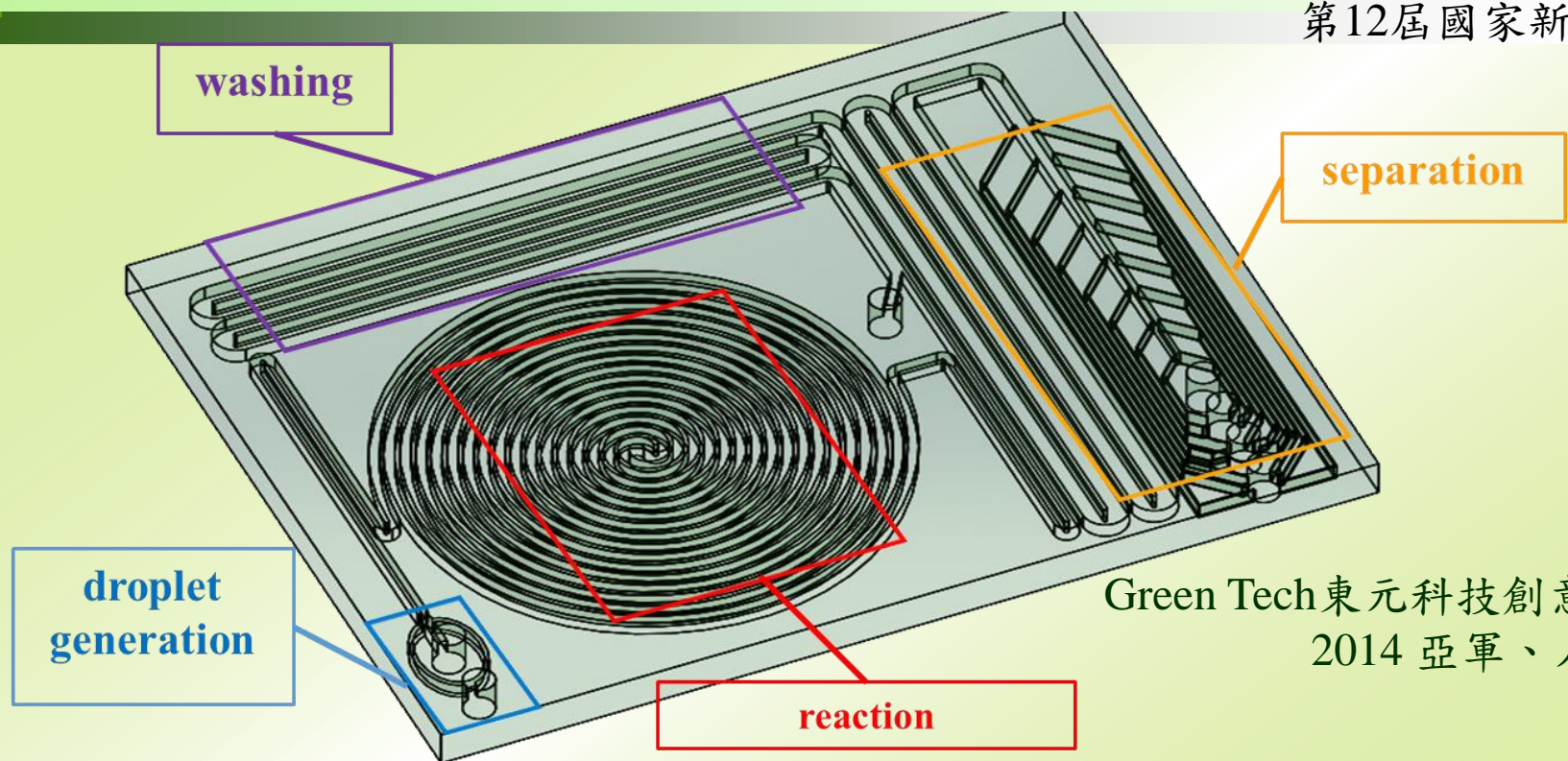
Glycerol
(1260 kg/m³)

Biodiesel
(880 kg/m³)



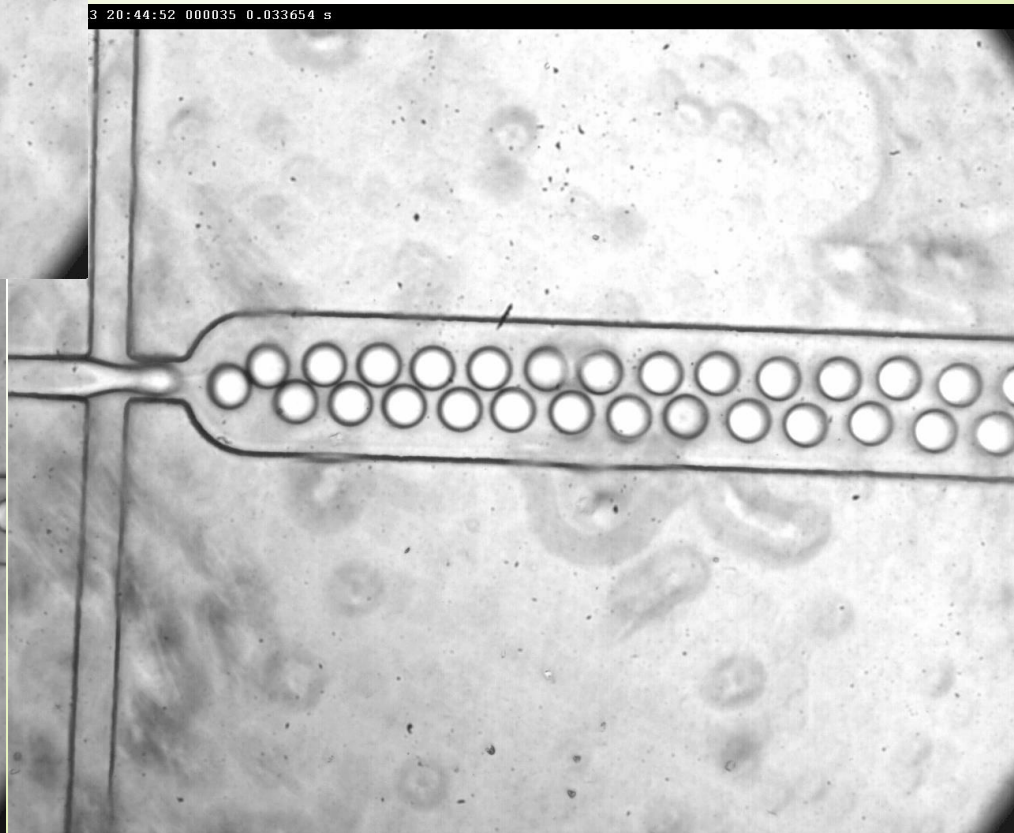
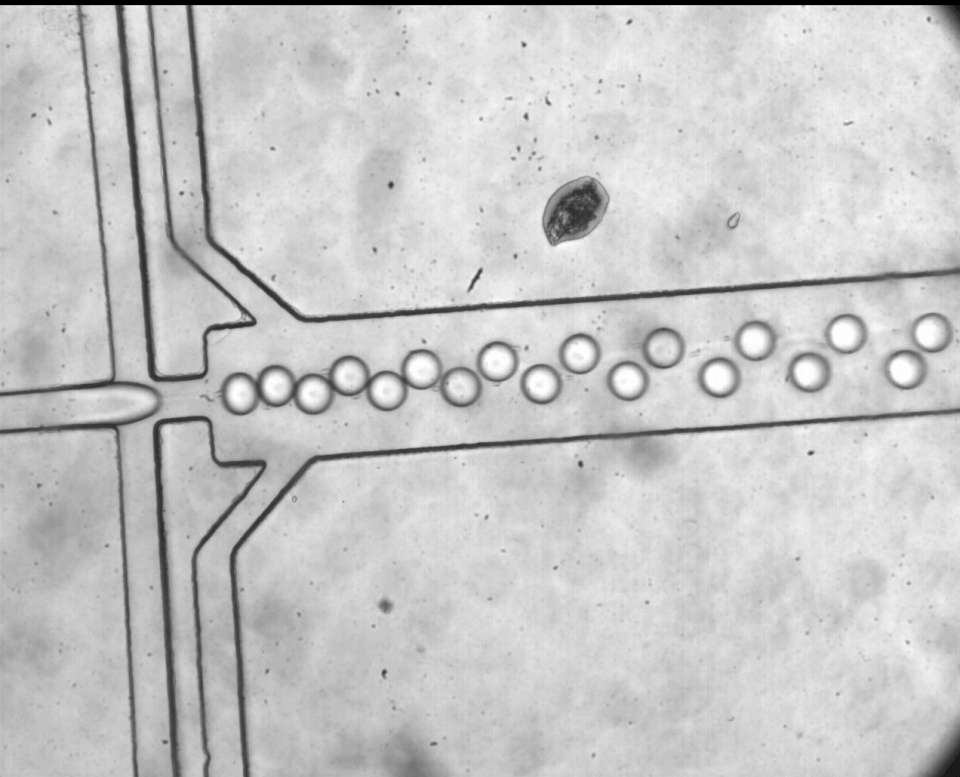
Biodiesel Production Chip

第12屆國家新創獎



Green Tech 東元科技創意競賽
2014 亞軍、人氣獎

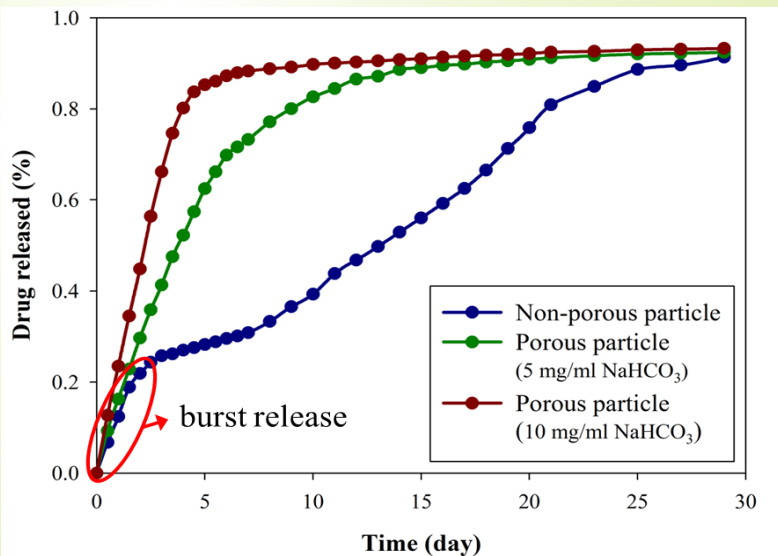
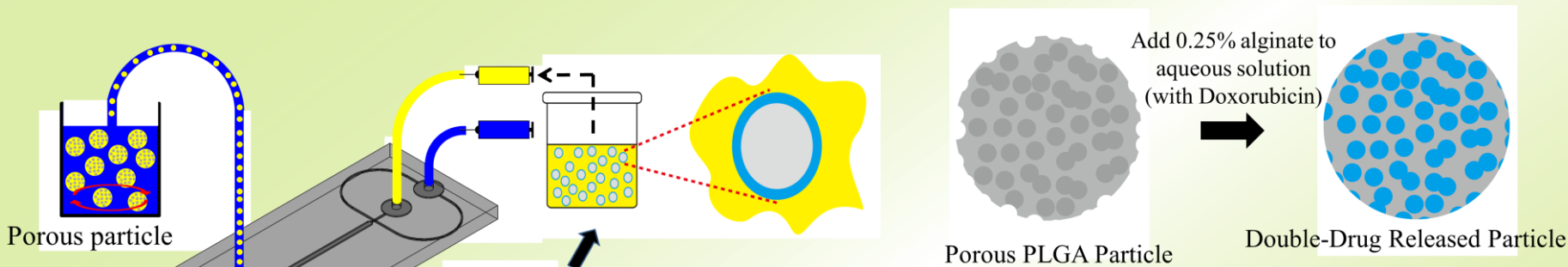
- **Faster reaction characteristic**
- **Inputs of raw materials, outputs of available products**
- **Low energy consumption and easy operation**



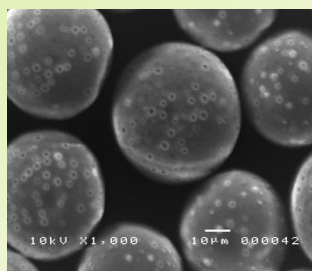
Microencapsulation of Dual-release PLGA Microparticle for Curcumin and Doxorubicin Released in Stages

S. I. Yeh, K. H. Yang, and J. T. Yang*
μTAS-2015, Gyeongju, Korea, October, 2015

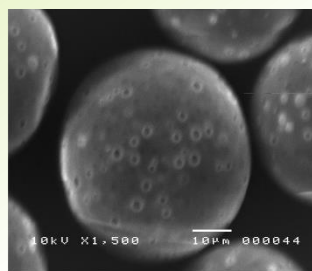
✧ Cooperating with NHRI



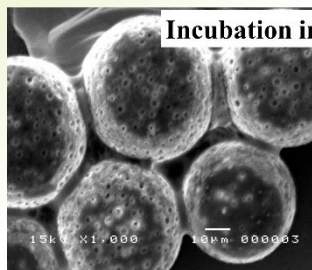
The dual-release of curcumin and doxorubicin would decrease the cardiotoxicity of chemotherapy drugs which is highly serviceable in cancer therapeutics and the clinical management of intractable diseases.



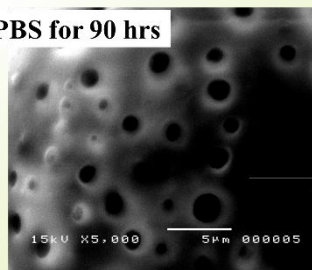
(a)



(b)



(c)



(d)

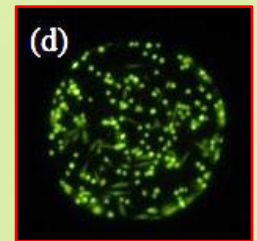
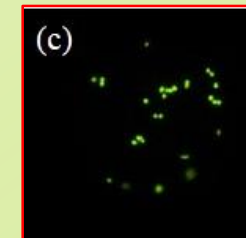
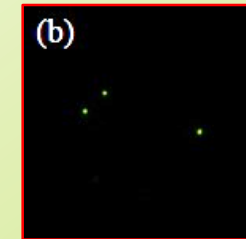
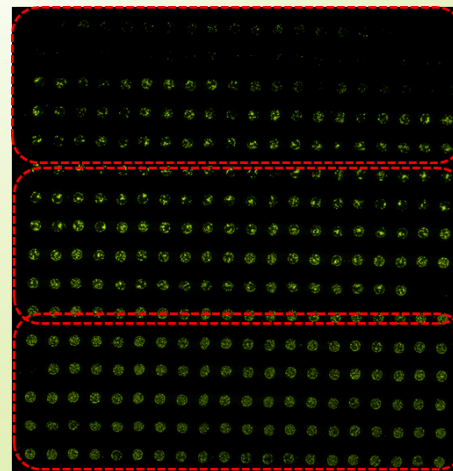
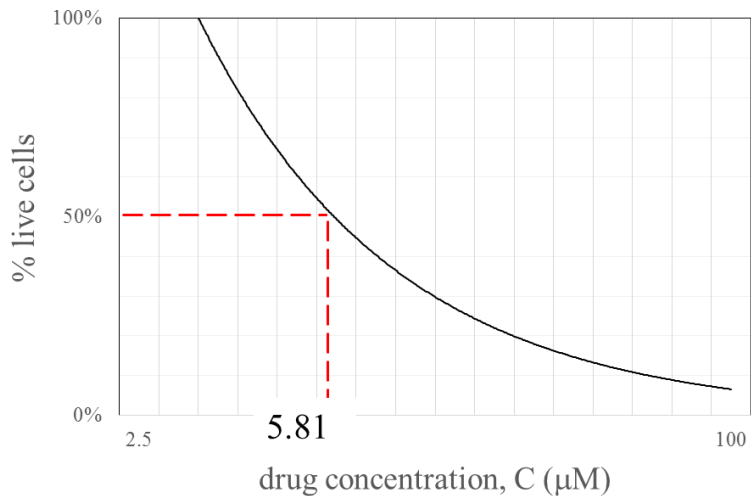
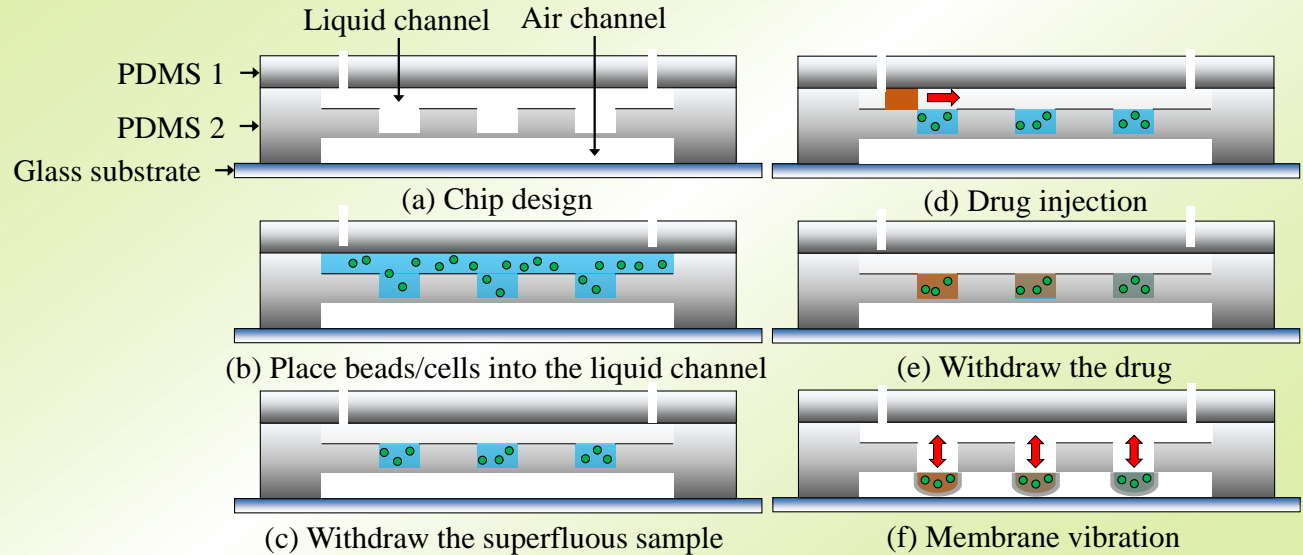
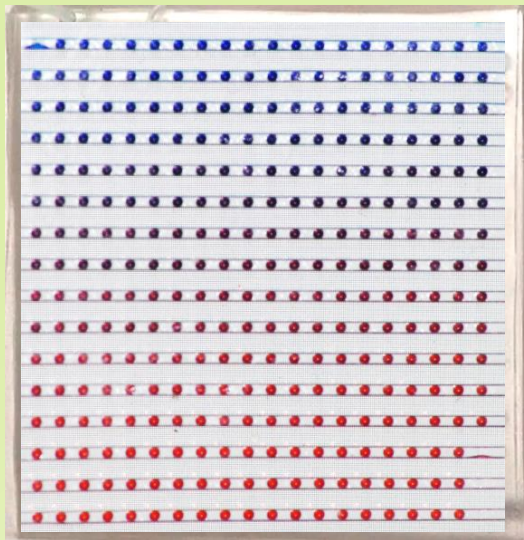
Incubation in PBS for 90 hrs

Microencapsulation of Dual-release PLGA Microparticle for Curcumin and Doxorubicin Released in Stages

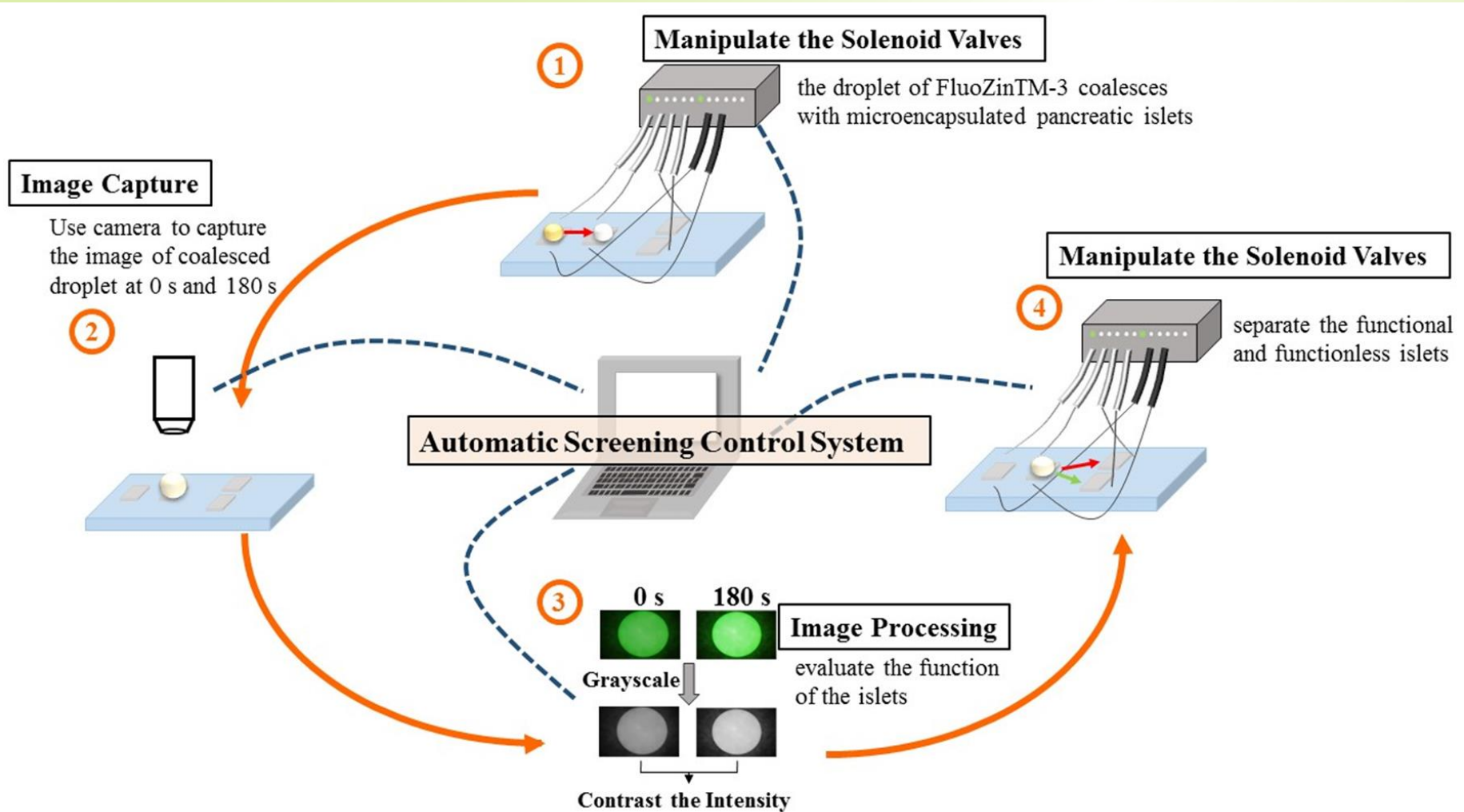
S. I. Yeh, C. C. Hau, C. J. Huang and J. T. Yang*

μ TAS-2014, San Antonio, USA, October, 2014

✧ Cooperating with NTUH



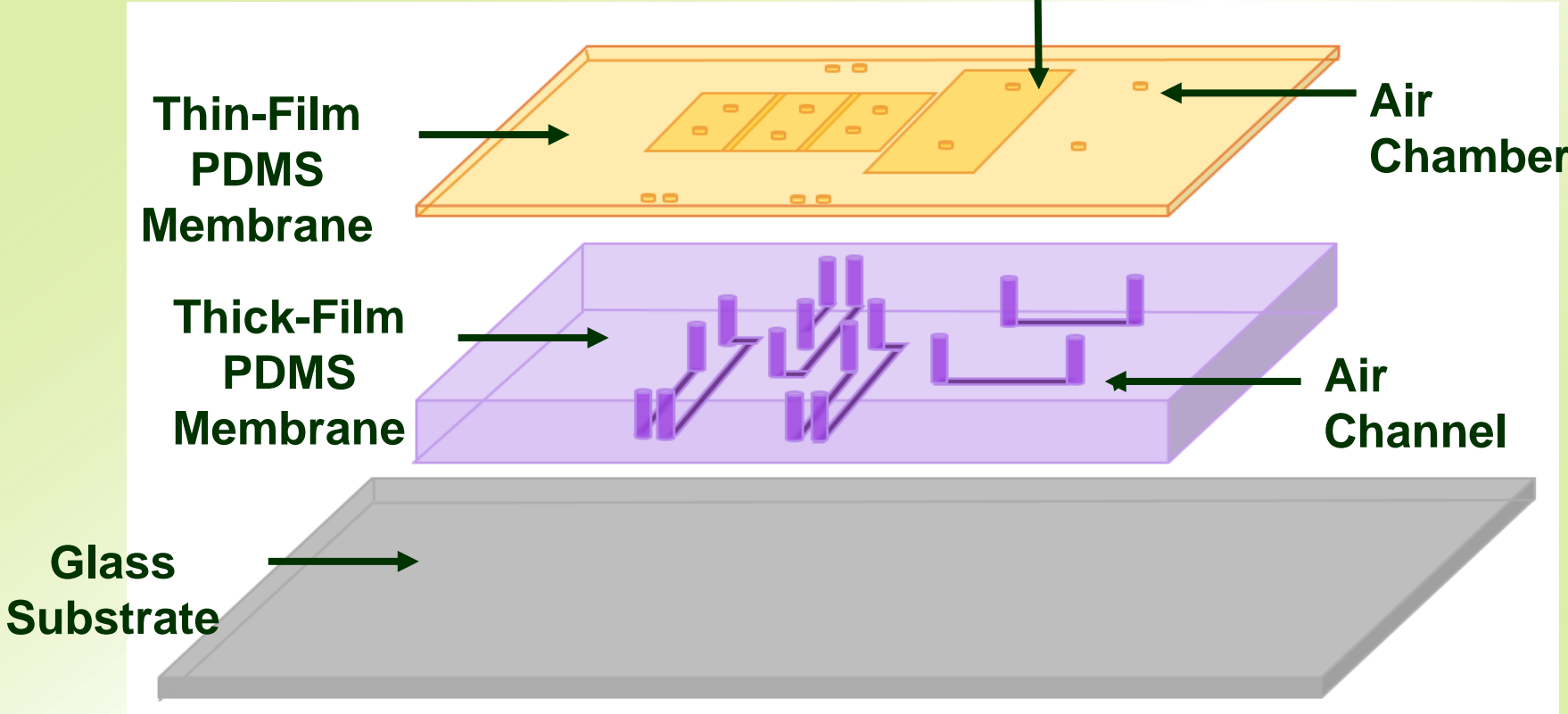
Assessment of Insulin Release Rate and Screening of Islet Cells on a Droplet-Manipulation Platform



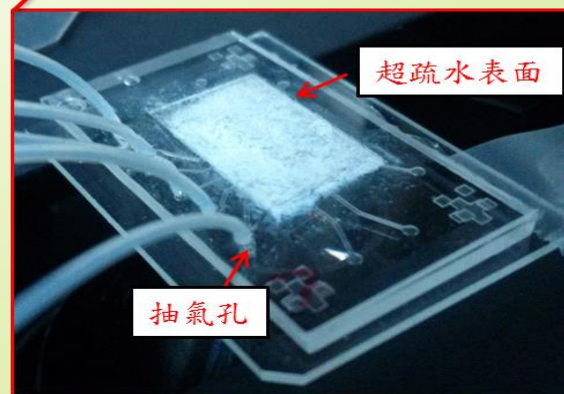
Development of an Automatic Screening System for Islet Function

Chip Design

Superhydrophobic Surface



Experimental setup





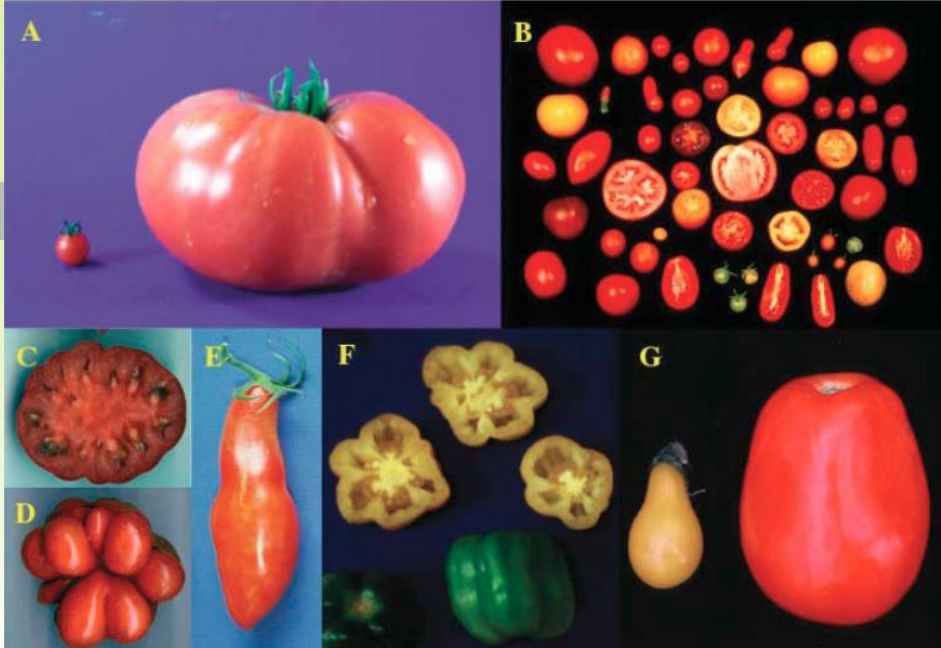
Tomato & Orchid



©Garden Delights

Text

<http://iuliesgardendelights.com/how-to-grow-184-varieties-of-heirloom-tomatoes-from-seed/>

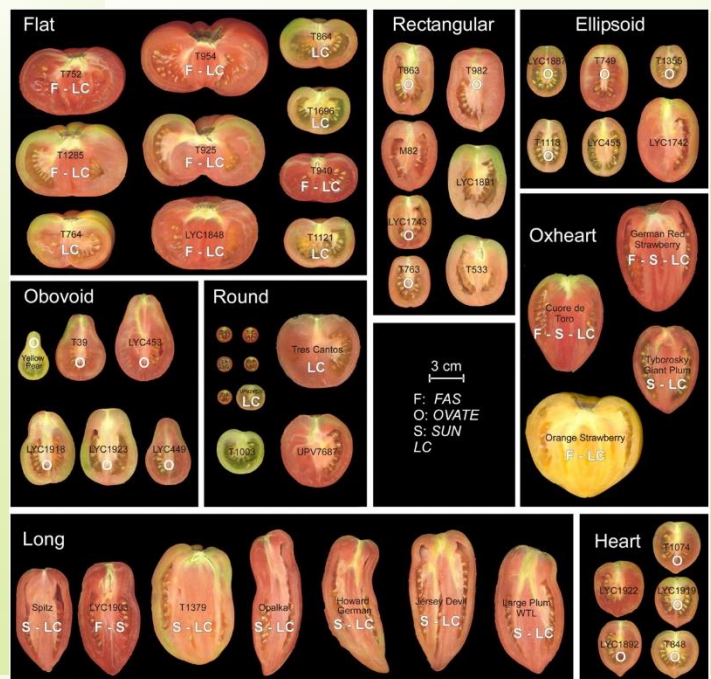


Tanksley *Plant Cell* 16 (2004):S181-S189.

<http://gizmodo.com/5917046/what-color-were-tomatoes-before-the-dinosaurs-all-died>



109 Zhang et al. *Nat. Commun.* 6 (2015):8635.

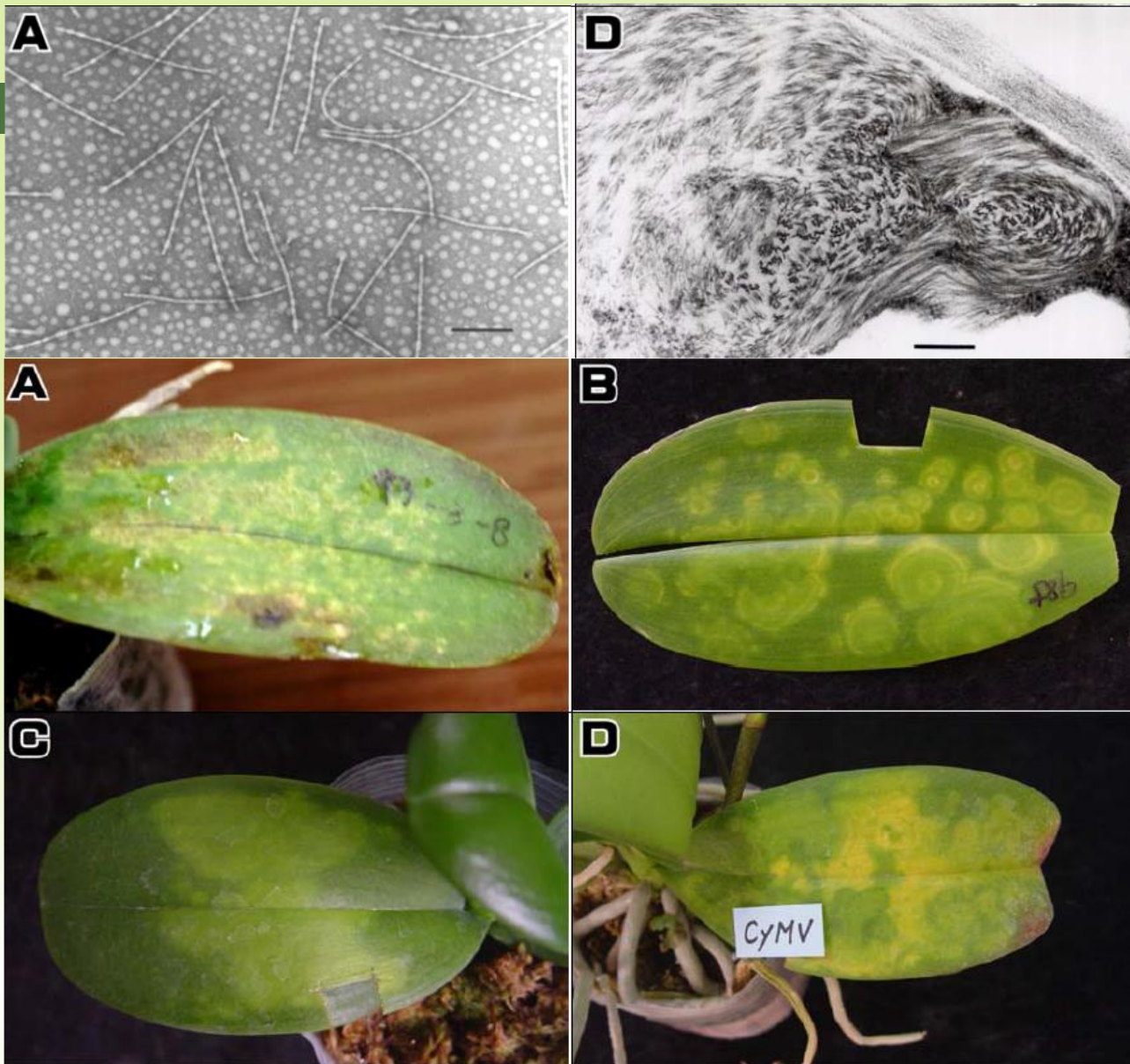


Rodríguez et al. *Plant Physiol.* 156 (2011):275-285.



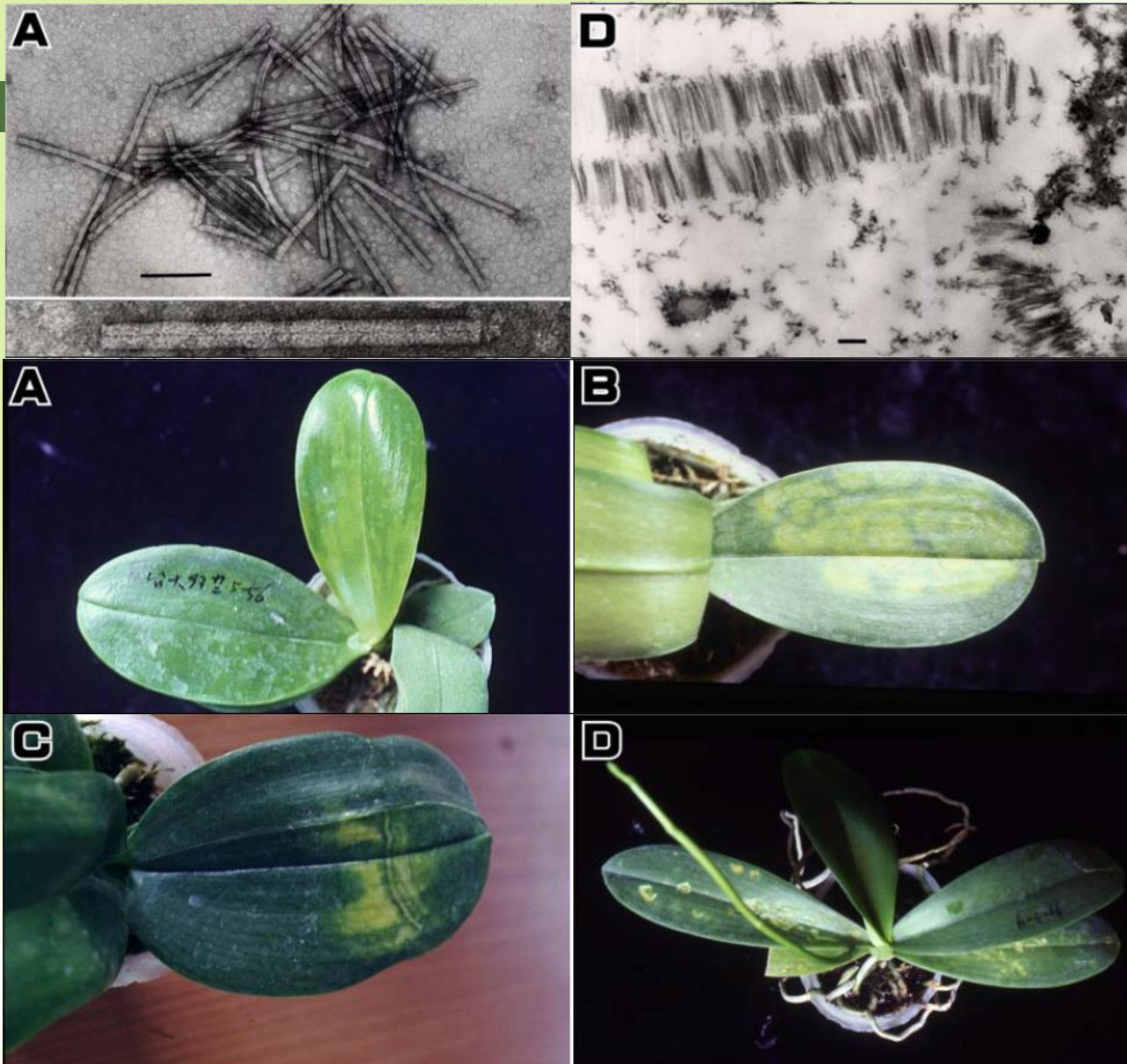
CymMV (*Cymbidium mosaic virus*) 蕙蘭嵌紋

病毒



陳慶忠等 (2006) 齒舌蘭輪斑病毒及蕙蘭嵌紋病毒感染蝴蝶蘭之病徵學及細胞病理學探討。臺中區農業改良場研究彙報93:15-27。

ORSV (*Odontoglossum ringspot virus*) 齒舌蘭輪斑病毒



陳慶忠等 (2006) 齒舌蘭輪斑病毒及蕙蘭嵌紋病毒感染蝴蝶蘭之病徵學及細胞病理學探討。臺中區農業改良場研究彙報93:15-

番茄的病毒病主要有番茄嵌紋病毒病、胡

瓜嵌紋病毒病、馬鈴薯Y病毒病、番茄斑點萎

凋病毒病及**番茄捲葉病毒病**。番茄捲葉病毒病

由**Tomato leaf curl virus (TLCV)**或**Tomato**

yellow leaf curl virus (TYLCV)所引起，是番茄

主要病害之一，病毒感染後造成葉片黃化及捲

曲等病徵，所造成番茄經濟損失可高達百分之

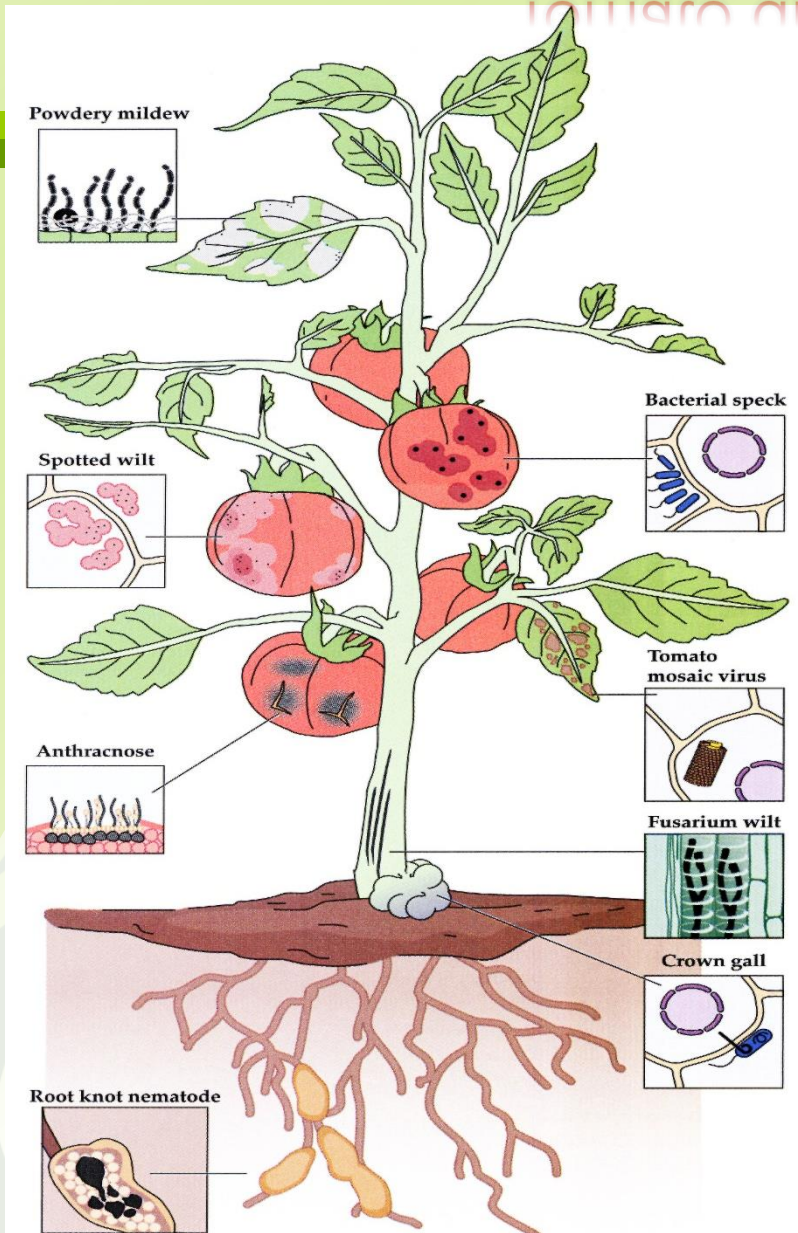
百。番茄捲葉病毒病只經由一種媒介昆蟲即**銀**

葉粉蝨(*Bemisia argentifolii*)傳播，銀葉粉蝨密

度越高，番茄捲葉病毒病發生越嚴重。



Tomato disease diagnosis

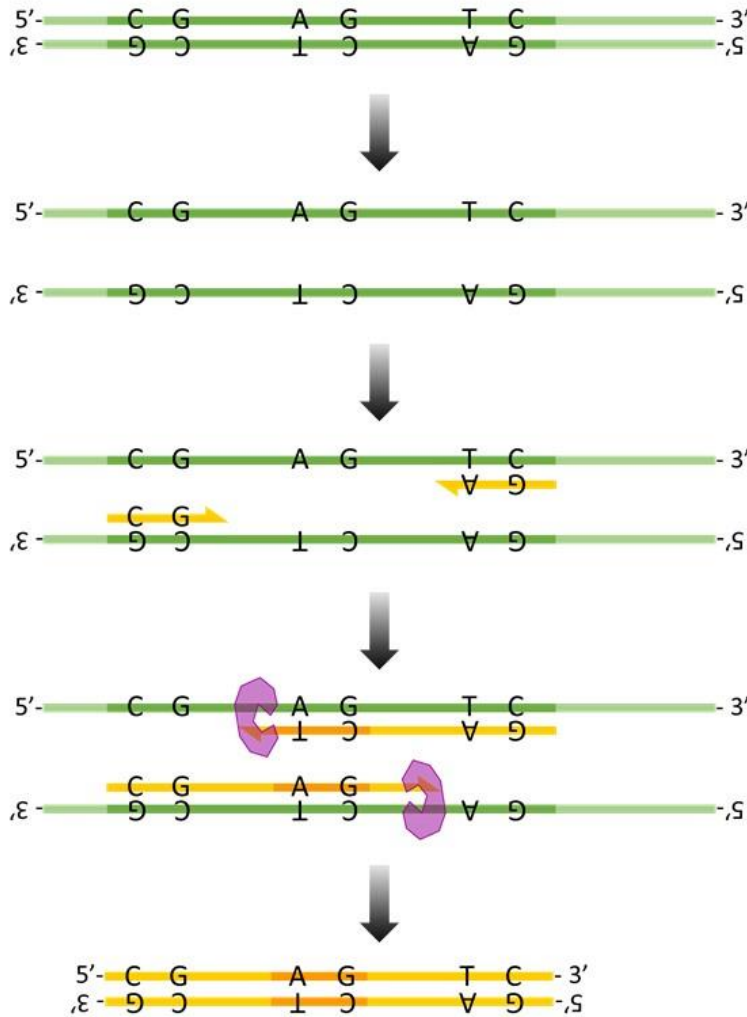


The symptoms applied to monitor tomato diseases are following as below:

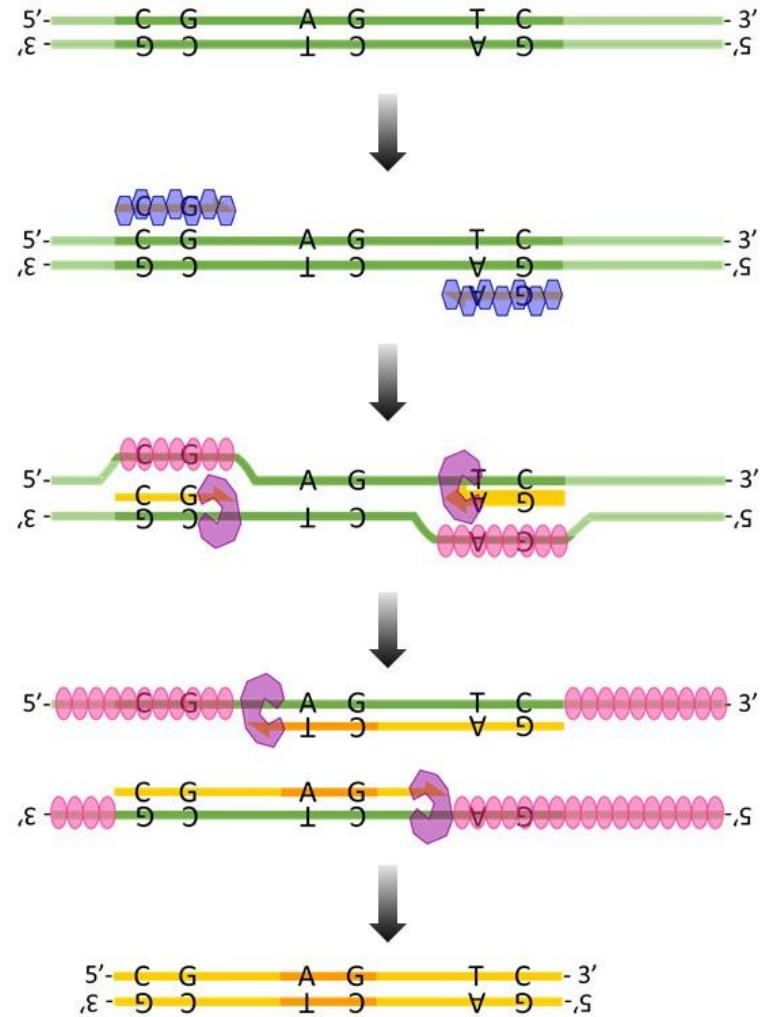
- 1) Problems on leaves
dark, gray, or white spots; yellowed or mottled foliage; curled leaves
- 2) Problems on stems
mushiness, dark, gray, or discolored streaks, mold, stunted growth
- 3) Problems at the crown
formations at the plant crown, rotting roots
- 4) Problems on fruit
sunken or discolored spots, mottled skin, mold, misshapen or undeveloped fruit

Introduction of recombinase polymerase amplification (RPA)

PCR



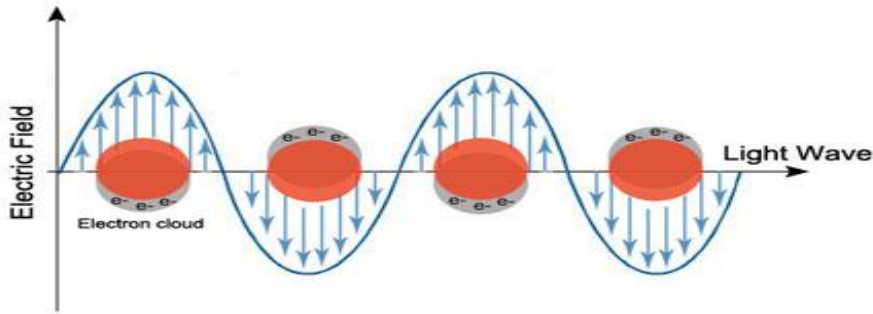
RPA



Basic concept of gold nanoparticles (AuNPs)

Surface plasmon resonance (SPR)

表面電漿共振



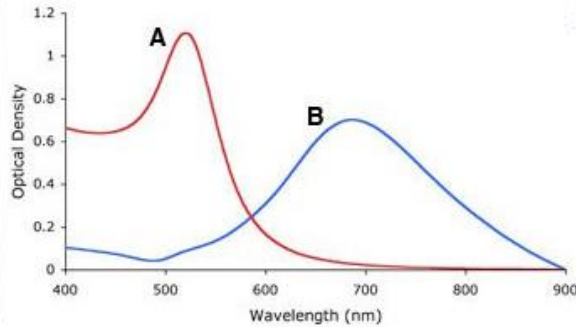
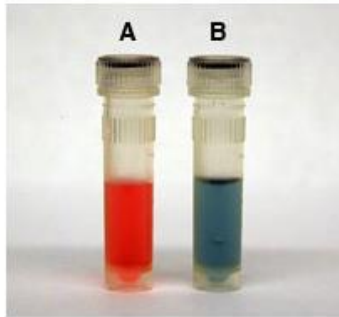
Different sizes of colloidal AuNPs



2 5 6 12 16 18 24 60 90 150 nm

<https://www.meritnation.com/ask-answer/question/how-does-size-of-particles-effect-the-colour-of-gold-sol/surface-chemistry/5788885>

Different sizes and sharps of AuNPs



Aggregation state of AuNPs

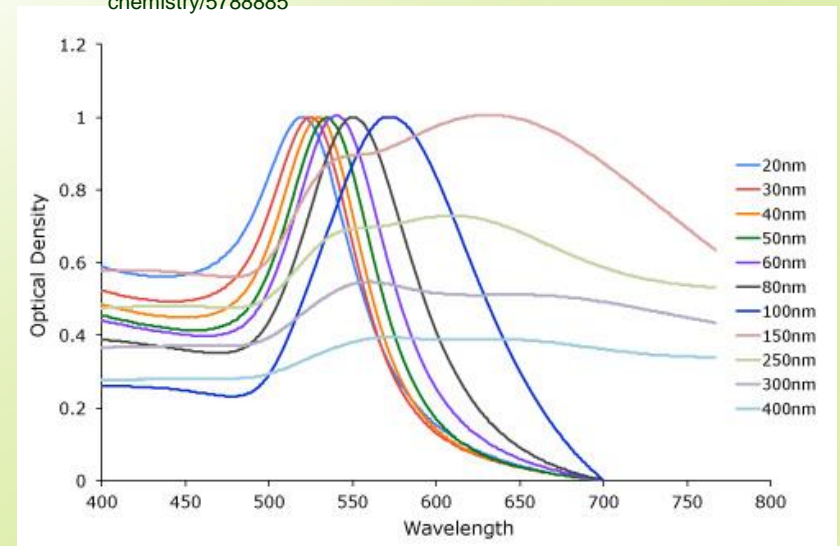
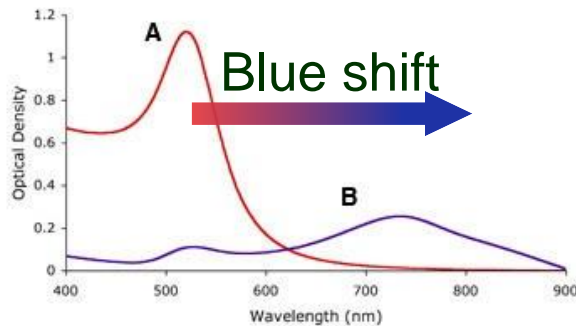
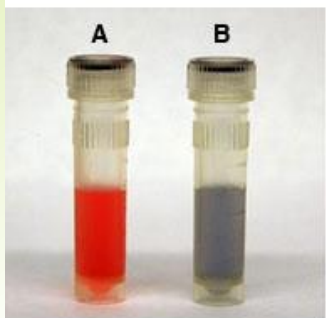
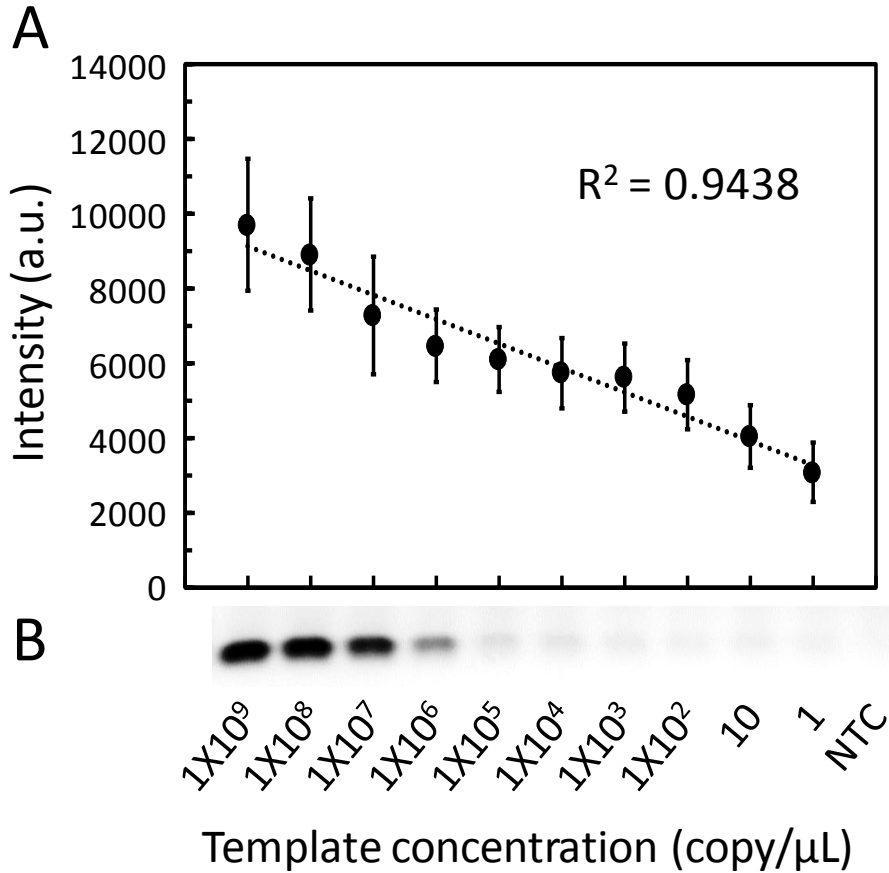


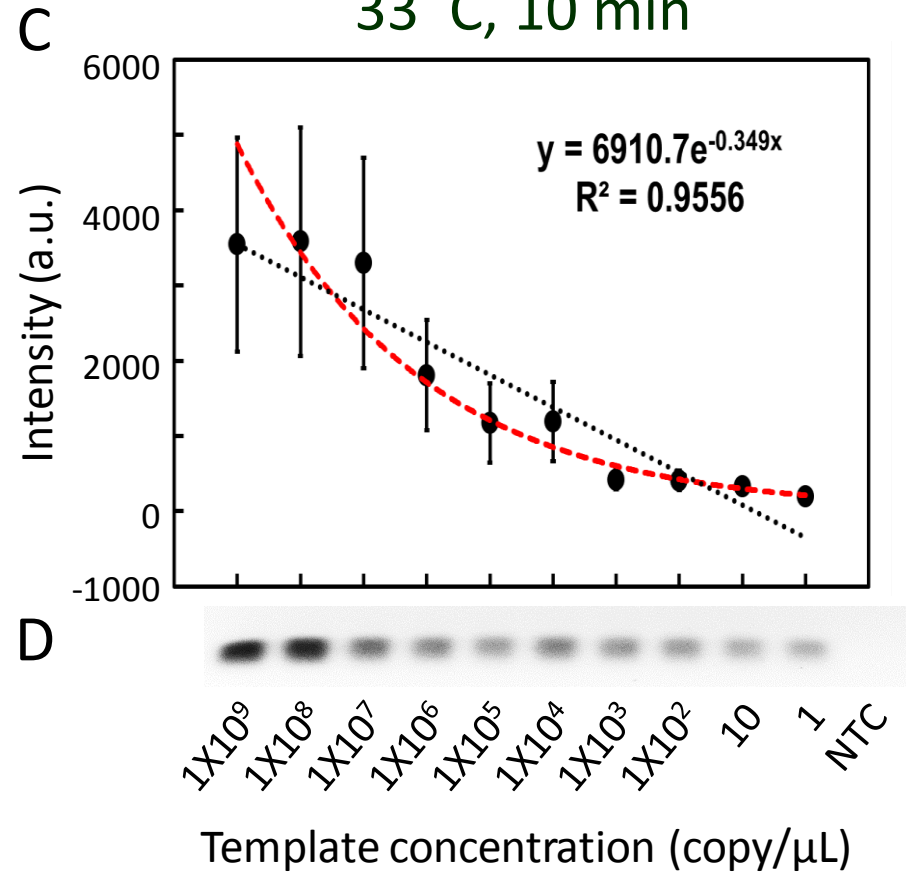
Figure 2. Gold nanoparticle size dependant surface plasmon resonance. Note the red-shift of the absorption maximum as the gold nanoparticle size increases.

Sensitivity of amplification effect

Conventional PCR (10 μ L)

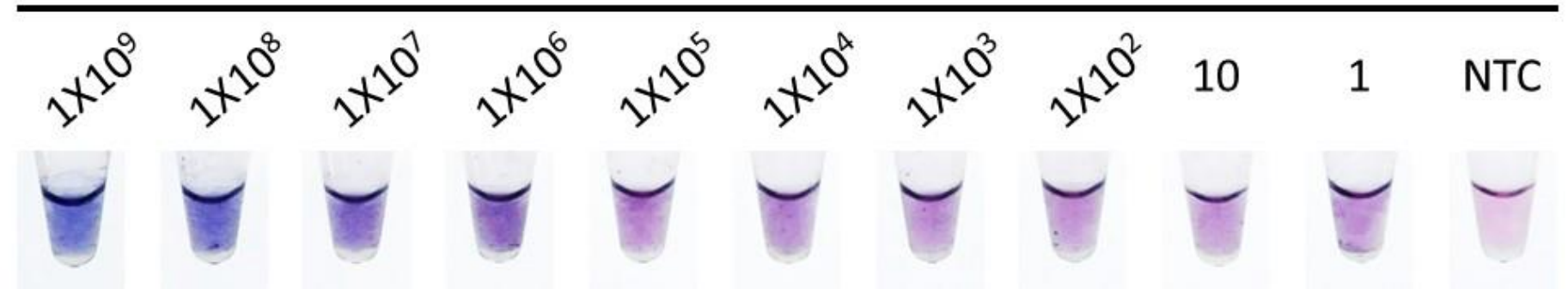


RPA (4 μ L) 33 $^{\circ}$ C, 10 min

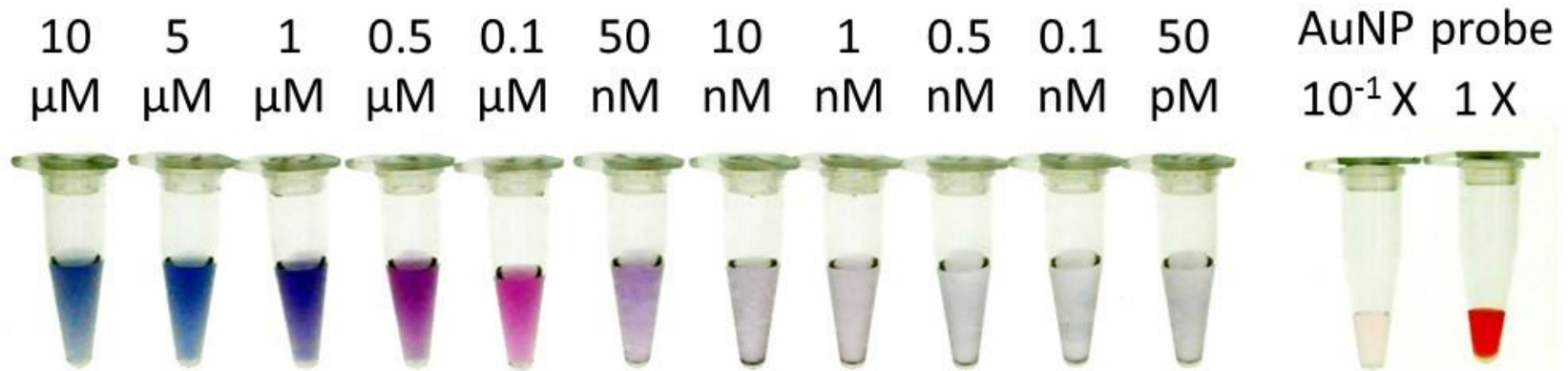


Sensitivity of colorimetric assay

Template concentration (copy/ μ L)



Concentration of artificial complementary ssDNA



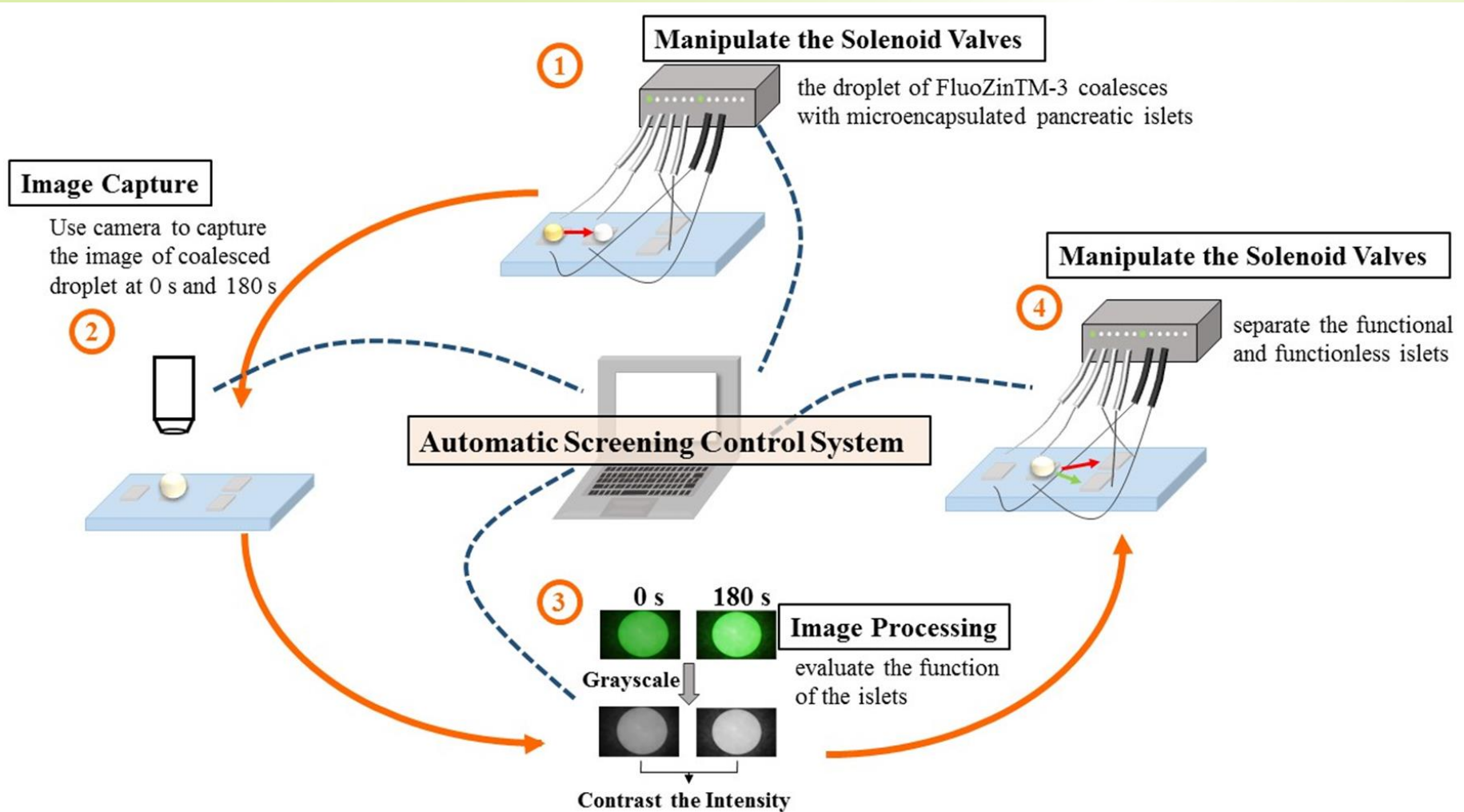


Thanks for your attention....

2018....

Financially supported by NSC & MOST since 2006....

Assessment of Insulin Release Rate and Screening of Islet Cells on a Droplet-Manipulation Platform





Thanks for your attention....

Financially supported by NSC projects since 2006....