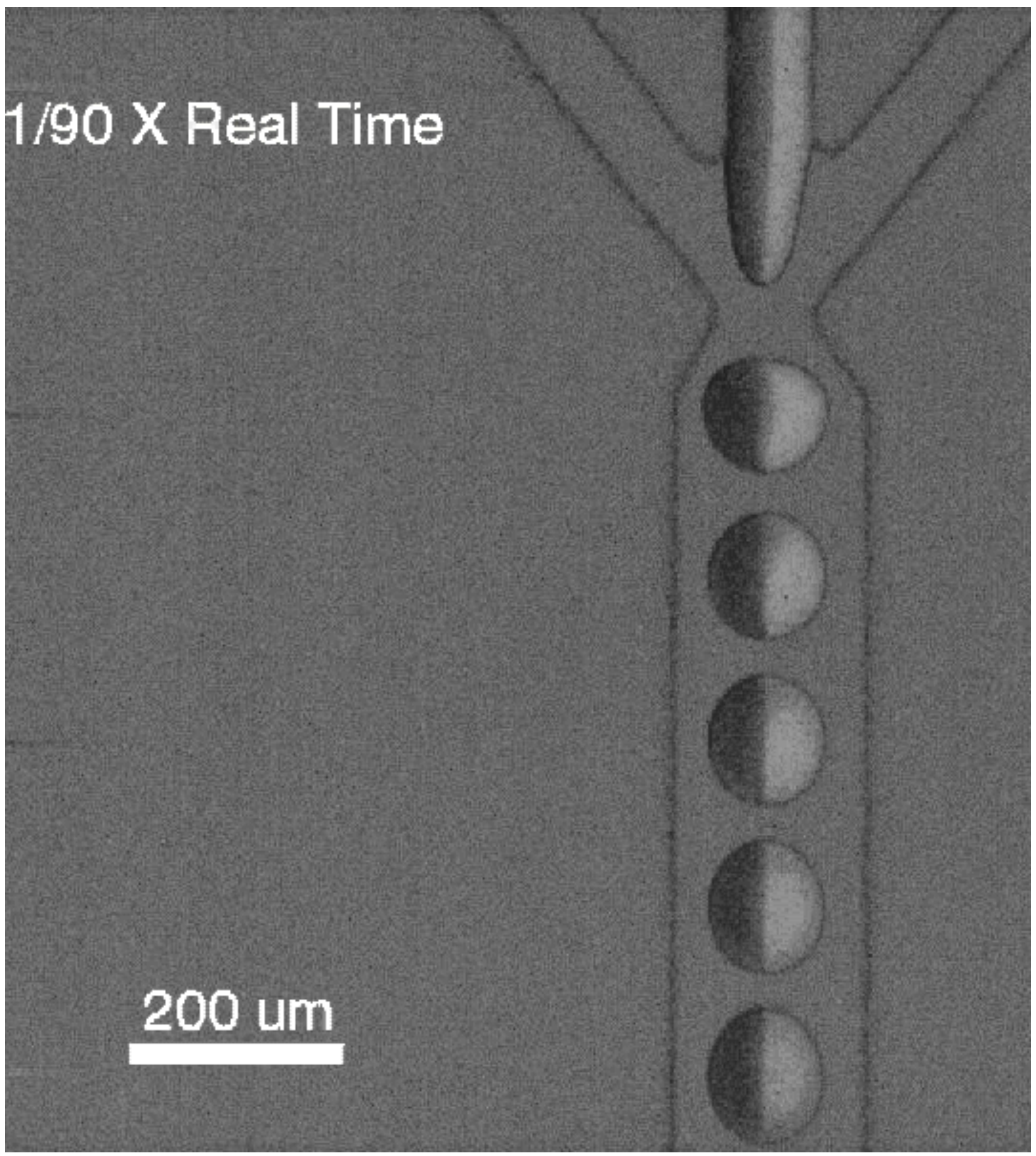
Microfluidics for chemical and biological engineering



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Chemical and Biomolecular Engineering
CHEE 1131
Fall 2012

Shepherd, Conrad, Lewis, *et al.*, *Langmuir* **22**, 8618–8622 (**2006**)

Fluid: physical definition

A fluid is a material that flows under an applied stress

Liquid: constant volume

Gas: volume of container

http://sciencekids.co.nz

Two physical properties of fluids:

- Viscosity: measure of fluid resistance to stress μ [mass/length-time]
- Density: ρ [mass/length^3]

Macroscale flows

Characteristics:

- Large length scales L
- Fast flow speeds V
- Turbulent flow

Many macroscale flows are characterized by large Reynolds number:

$$\text{Reynolds number Re} = \frac{\text{inertial force}}{\text{viscous force}} = \frac{\rho V L}{\mu} \gg 1\text{: turbulent}$$

Where do flows appear in a chemical plant?

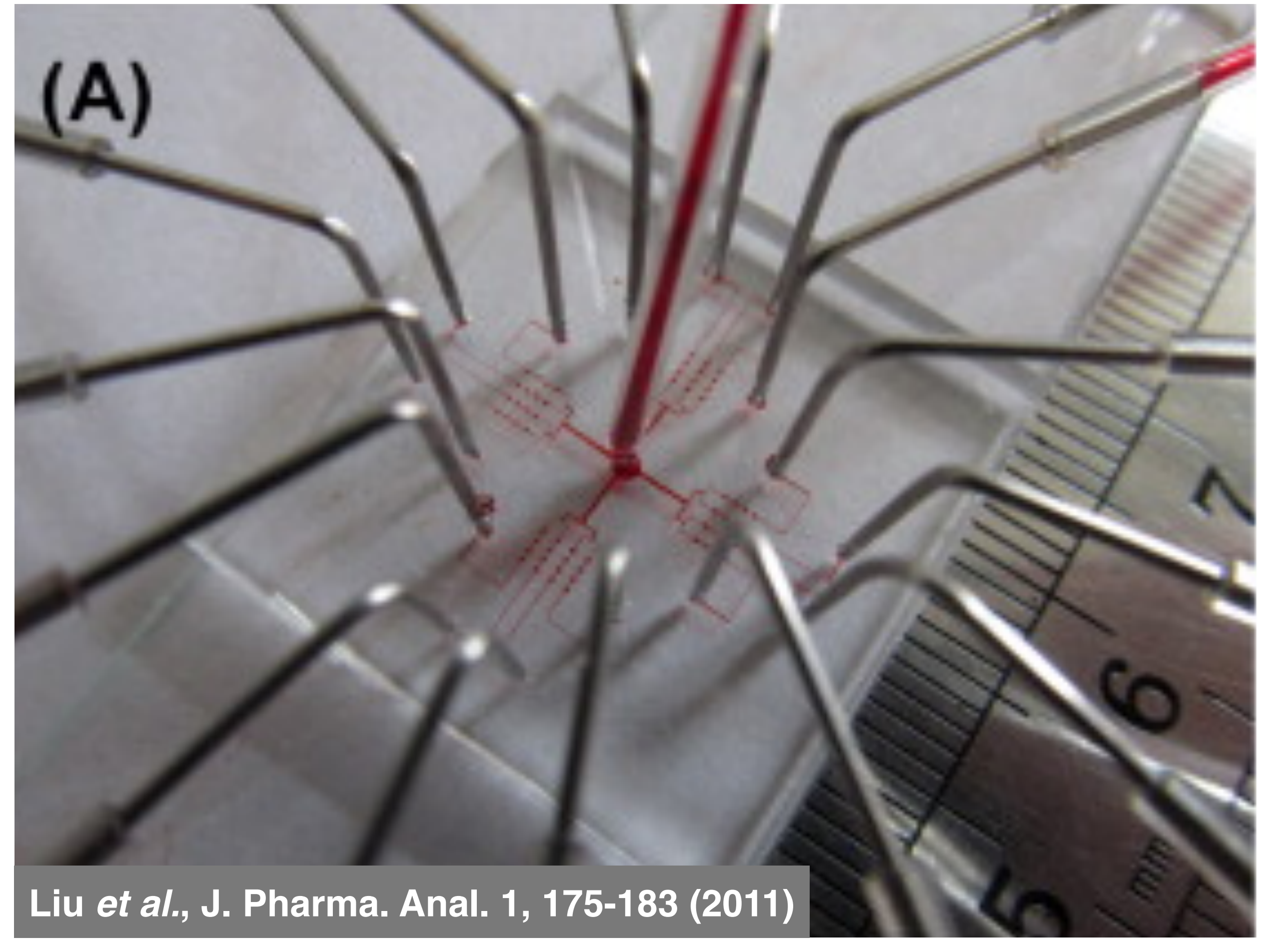
http://www.photo-dictionary.com/photofiles/list/687/1097petrochemical_plant.jpg

Flow examples in plants (unit operations)

- Combination: mixing operation to create a homogeneous system
    - Requires control over mixing streams
- Separation: separation of mixture components
    - Emulsification: creation of a liquid-in-liquid suspension
    - Distillation: separation of one liquid from another liquid
    - Evaporation: removal of a gas from a mixture
- Reaction: reaction among chemical species in a mixture
    - Synthesis: e.g. creation of particles or chemicals

Microfluidics: miniaturization of flows

The introduction of microfluidics or lab-on-a-chip devices allows unit operations to be carried out in a small format:

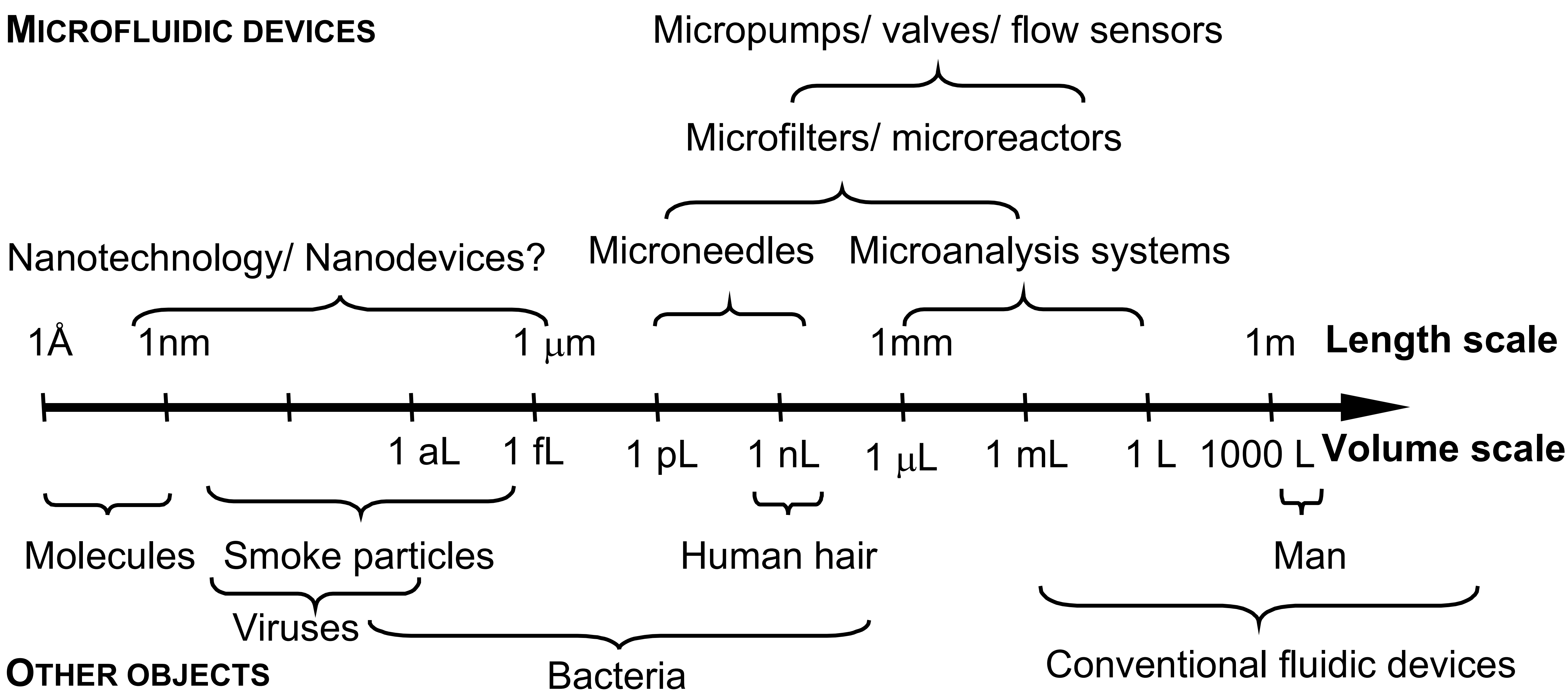


plant: meters to kilometers
piping: cm to m

device: mm to cm
channels: μm to mm

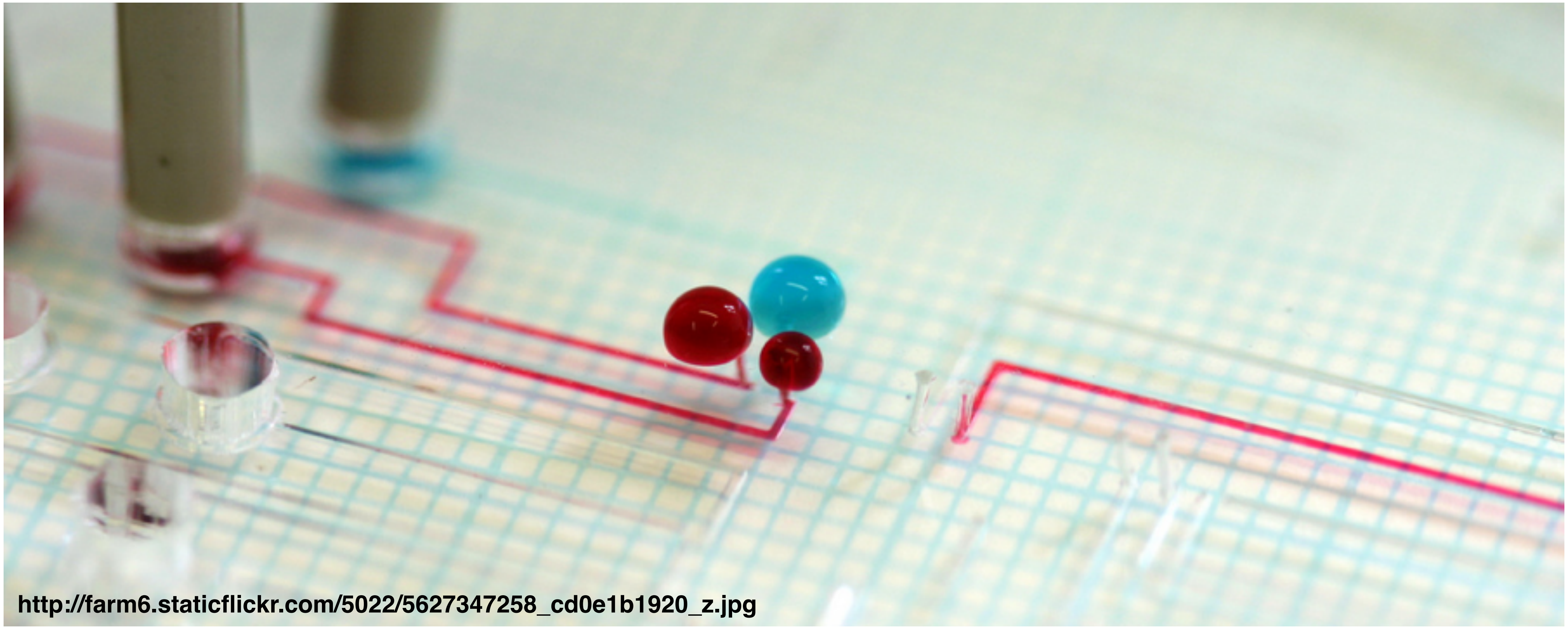
"Miniaturization puts chemical plants where you want them": R. F. Service, *Science* 202, 400 (1998)

Length scales for microfluidic flows



Nguyen and Wereley, *Fundamentals and Applications of Microfluidics*, 2nd ed. (2006)

Materials for microfluidics: elastomers



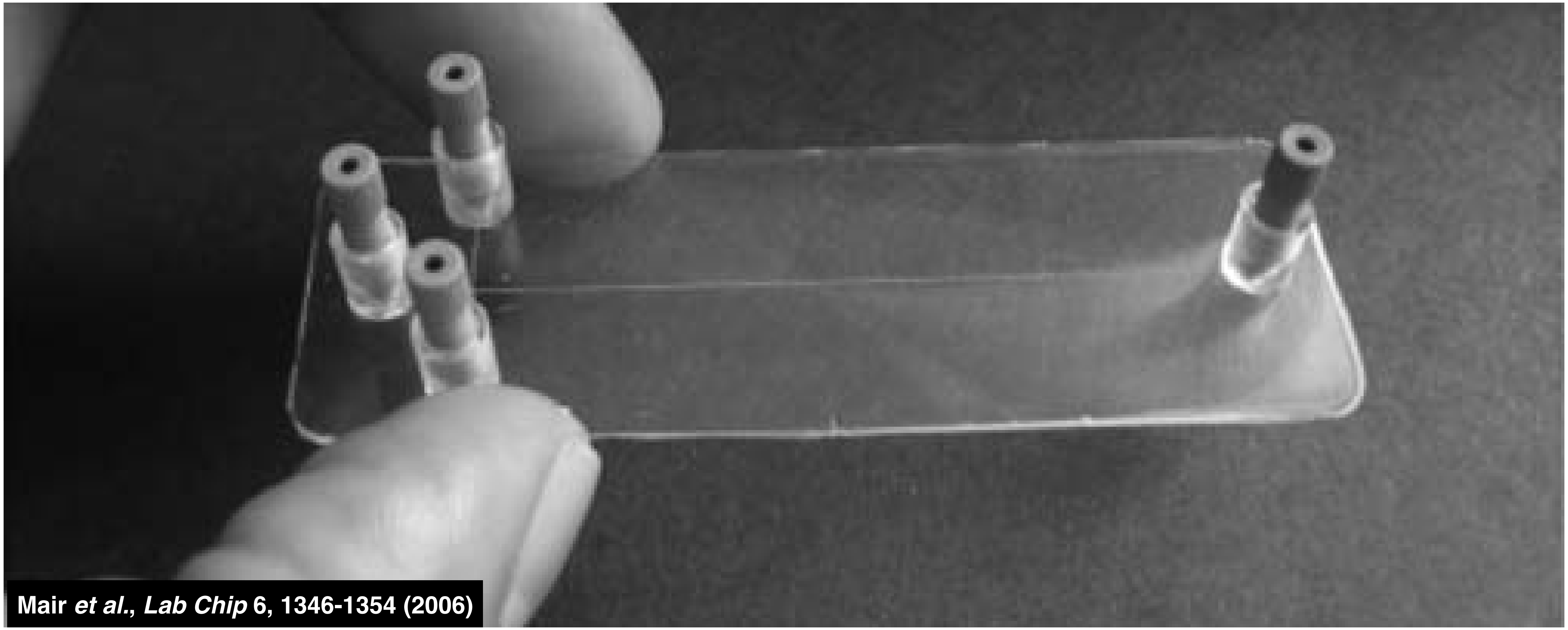
Advantages:

- Easy to prototype and replicate (via soft lithography)
- Cheap materials (polydimethylsiloxane, commercially available)

Disadvantages:

- Flexible and deformable (poor for high-pressure applications)
- Poor resistance to organic solvents

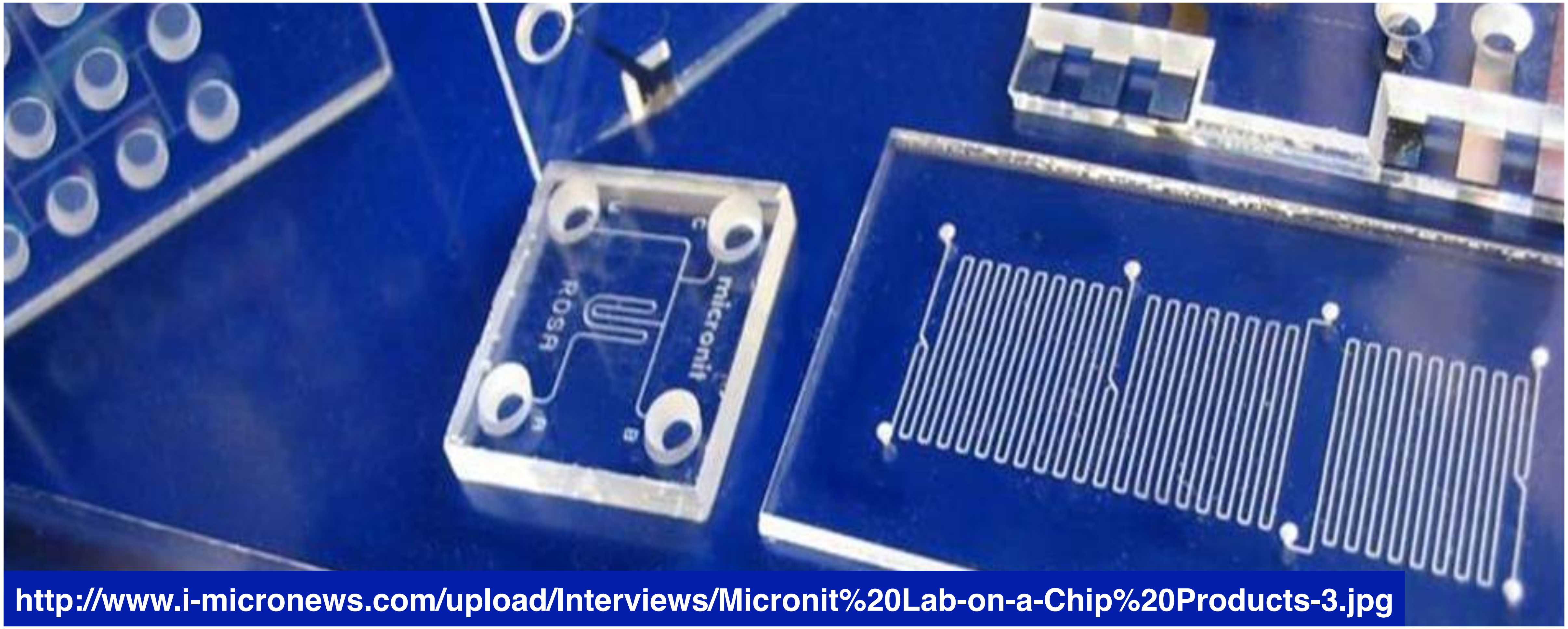
Materials for microfluidics: rigid plastics



Advantages:
- Easy to prototype and replicate (via injection molding)
- Cheap materials (polyolefins, commercially available)
- Operate at high pressure

Disadvantages:
- Poor resistance to organic solvents
- Fabrication is more difficult than lithographic-based techniques

Materials for microfluidics: glass



http://www.i-micronews.com/upload/Interviews/Micronit%20Lab-on-a-Chip%20Products-3.jpg

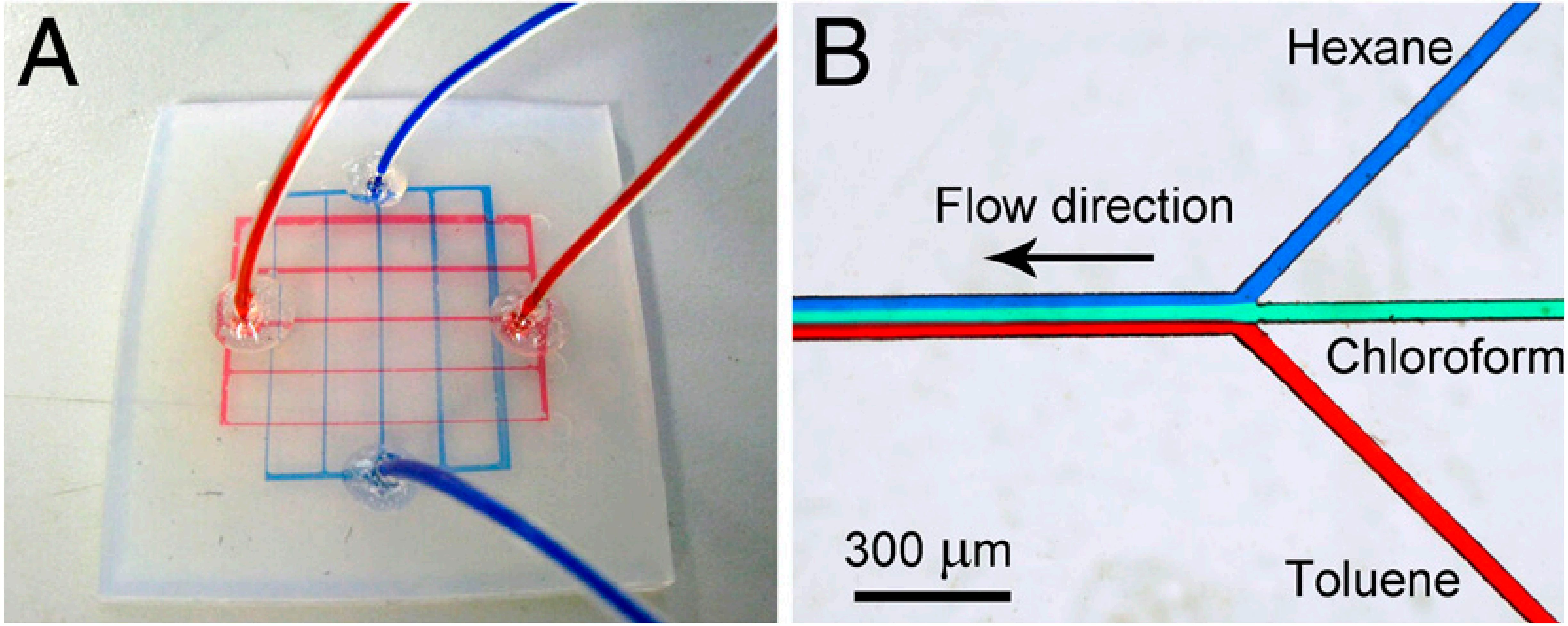
Advantages:

- Excellent resistance to solvents
- Rigid and non-deformable
- Compatible with high-pressure and biological applications

Disadvantages:

- Until recently, expensive to manufacture (new startups)
- High costs for design prototypes in money and time

Materials for microfluidics: Teflon



Ren *et al.*, *Proc. Natl. Acad. Sci. USA* **108**, 8162-8166 (2011)

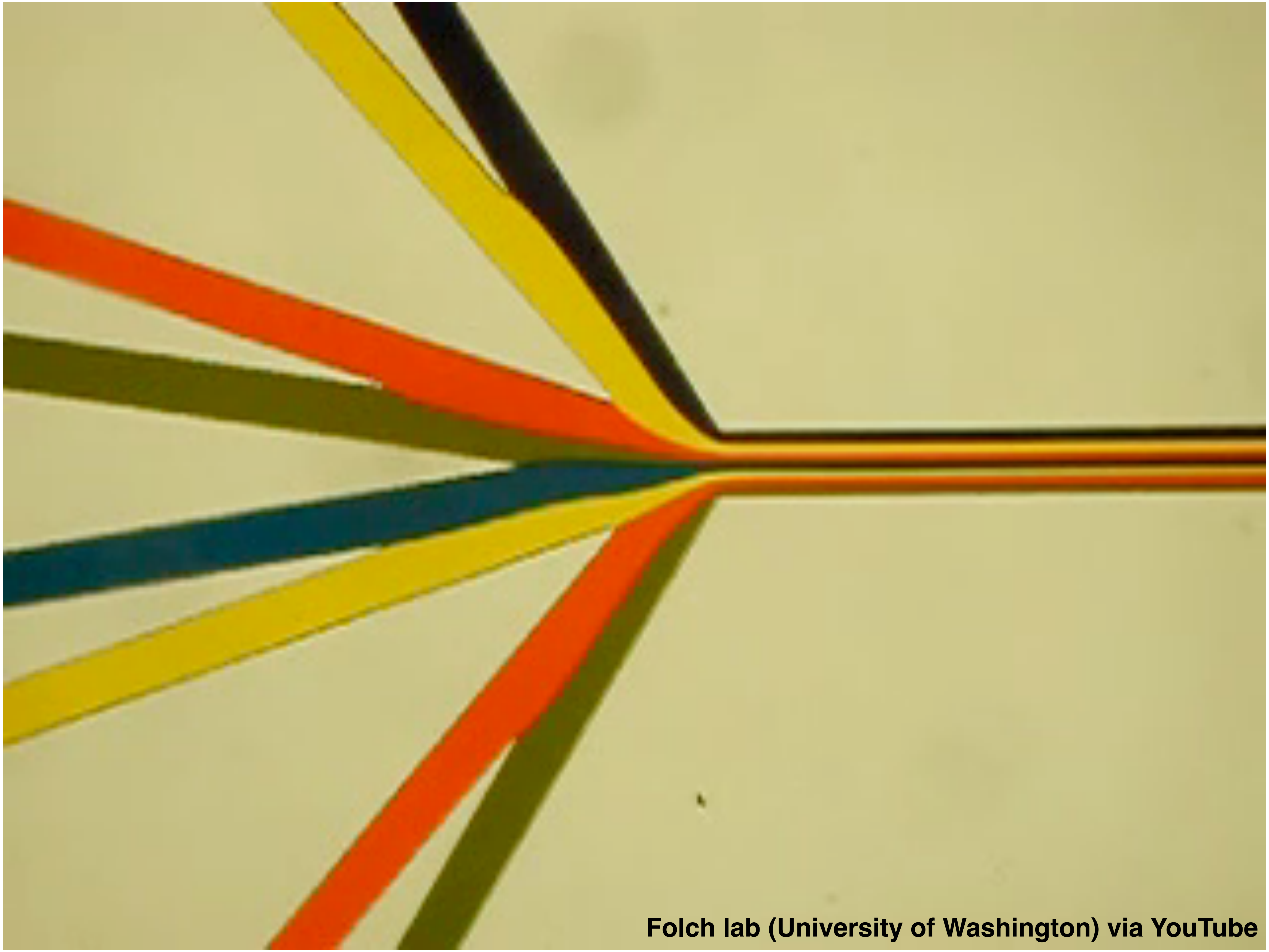
Advantages:

- Excellent resistance to organic solvents
- Rigid and non-deformable
- Minimal adsorption and fouling by biological molecules

Disadvantages:

- Not transparent, precluding direct imaging using microscopy

Microscale flow physics is different!



Critical flow properties in devices

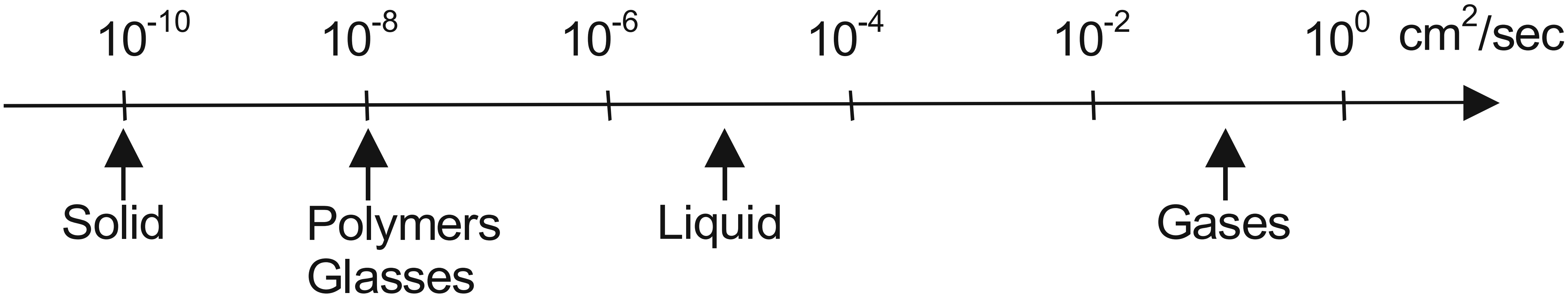
Reynolds number Re = $\dfrac{\text{inertial force}}{\text{viscous force}} = \dfrac{\rho V L}{\mu}$ « 1: laminar flow

Physical meaning: fluid elements follow straight streamlines, and fluid interfaces remain nearly parallel over long distances in microfluidic devices

Péclet number Pe = $\dfrac{\text{time to diffuse}}{\text{time to convect}} = \dfrac{V L}{D_0}$ » 1: fast convection

Physical meaning: diffusion is very slow compared to convection in microfluidic devices, and thus mixing requires special device designs

Combination: diffusion in microfluidics



Nguyen and Wereley, *Fundamentals and Applications of Microfluidics*, 2nd ed. (2006)

The mixing rate in microfluidic devices is determined by the flux of diffusion:

$$\underline{j} = -D_0 \frac{dc}{\underline{dx}}$$

flux of diffusion — species concentration [kg/m3]

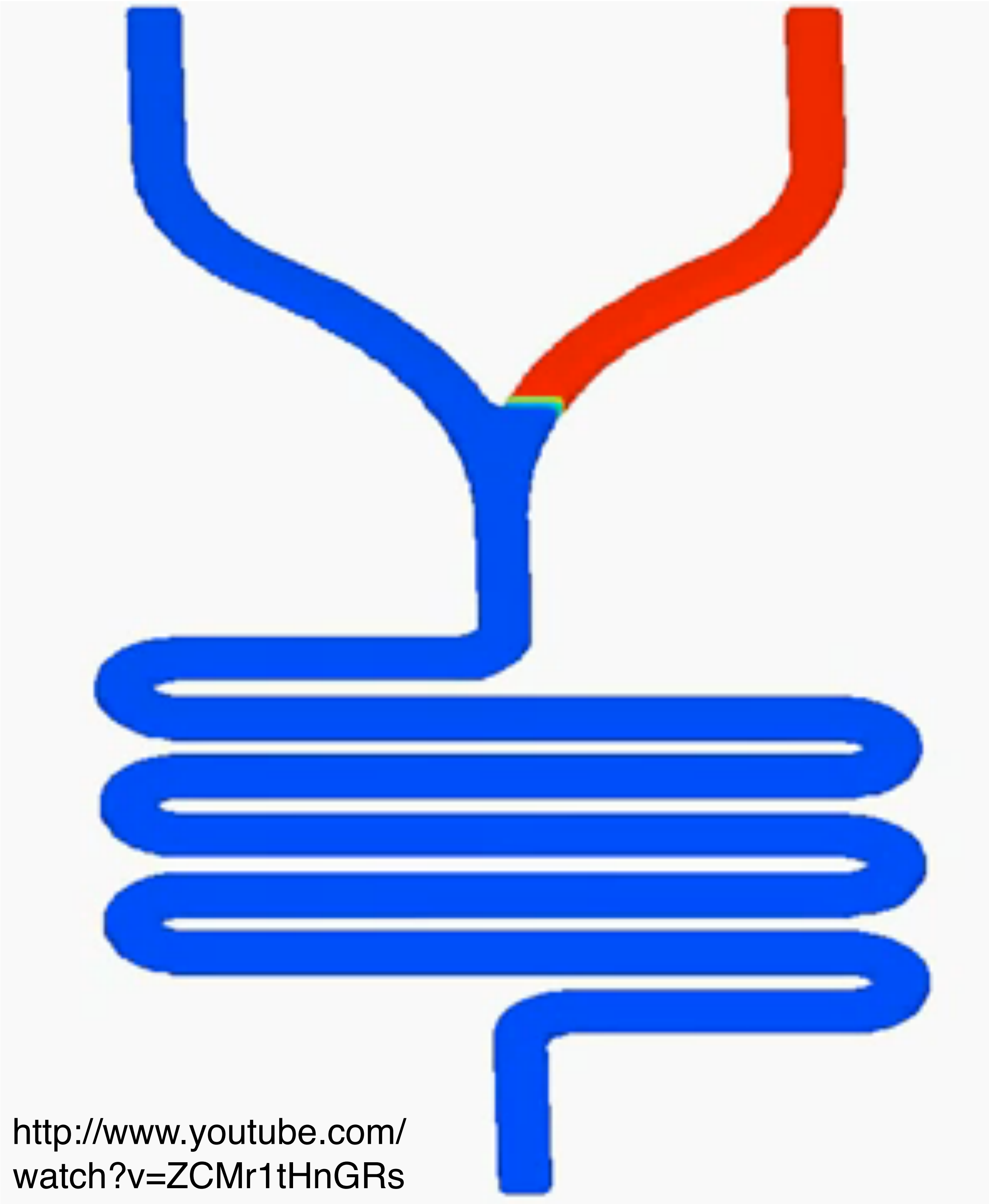
The diffusion coefficient D_0 is inversely proportional to viscosity:

e.g. for a spherical particle of radius *a*: $D_0 = \frac{k_B T}{6\pi\mu a}$

Finally, the mixing time is proportional to the square of the channel length.

Combination: passive micromixer

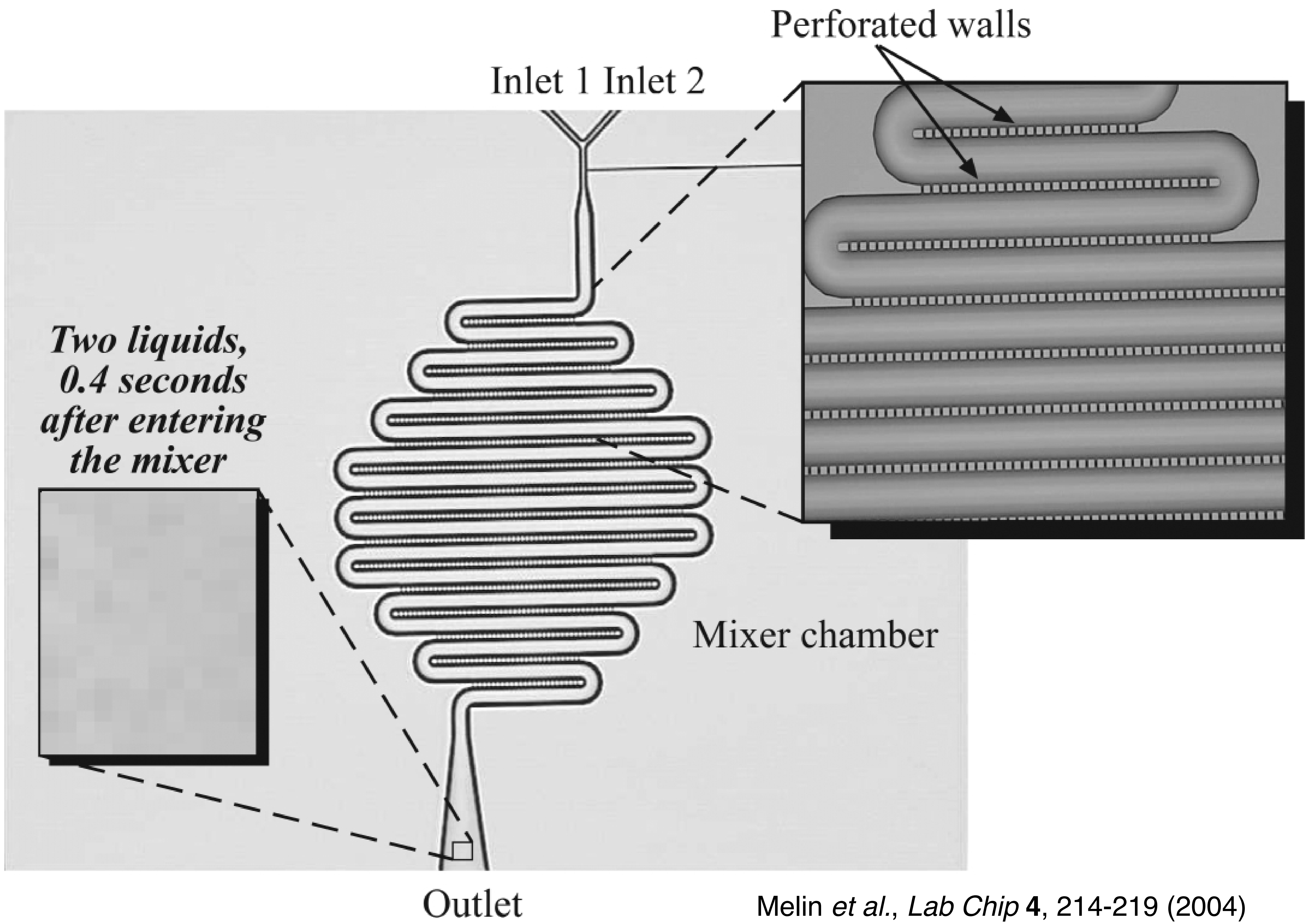
Key idea: Increase the length of the flow channel



http://www.youtube.com/
watch?v=ZCMr1tHnGRs

Combination: passive planar micromixer

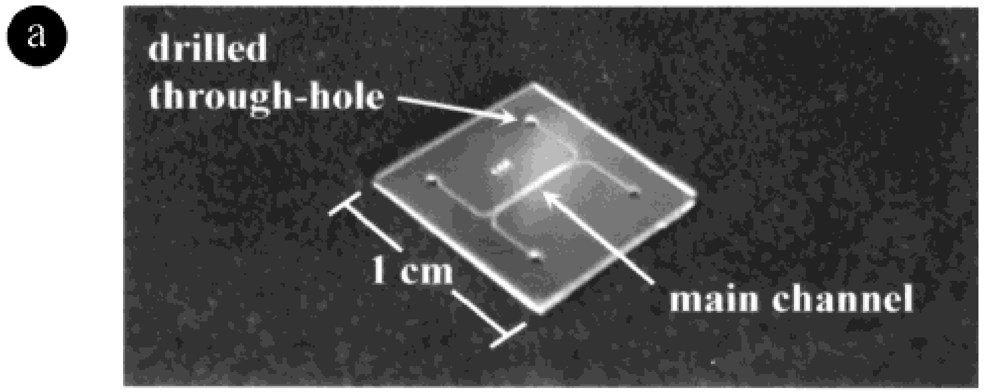
<u>Key idea</u>: Modify geometry to obtain mixing via changing flow pattern

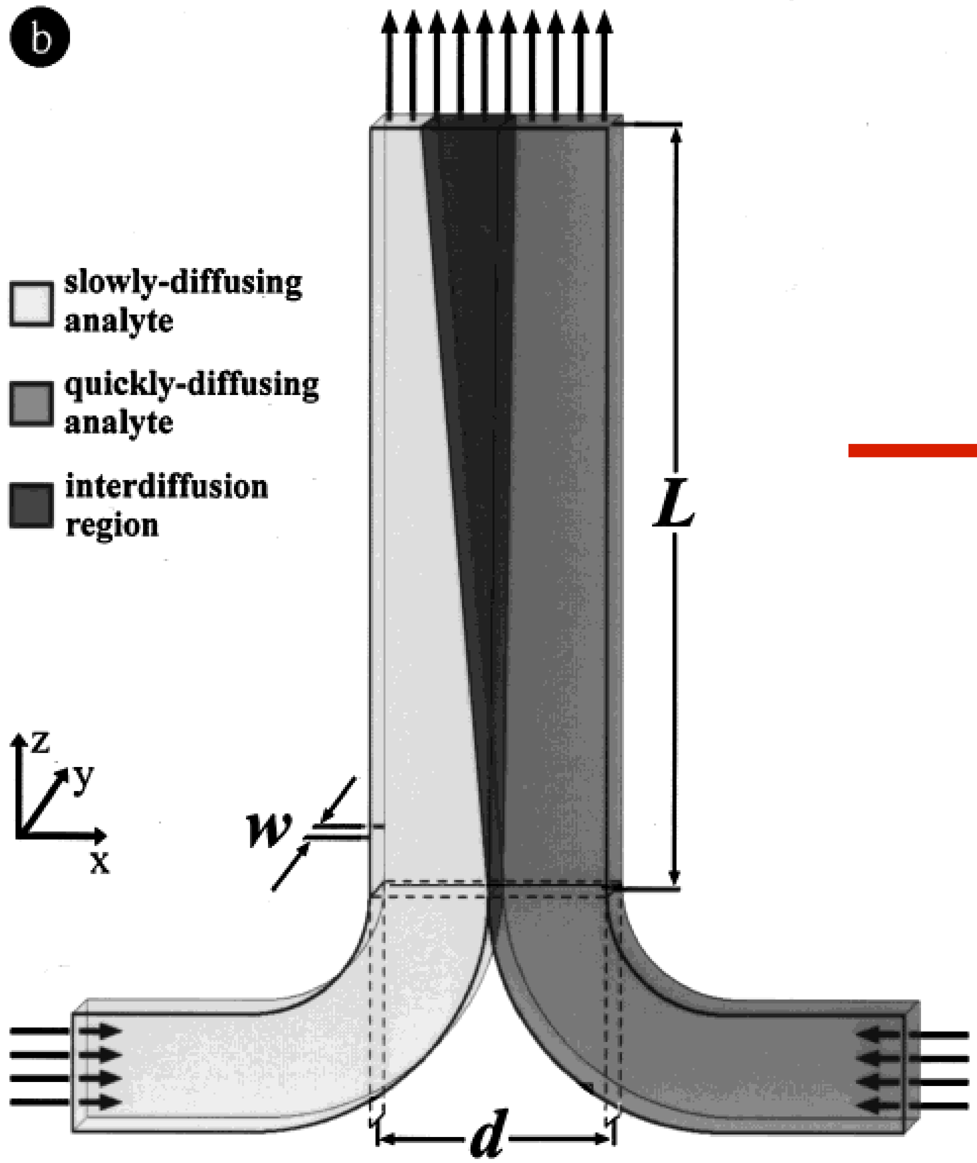


Melin *et al.*, *Lab Chip* **4**, 214-219 (2004)

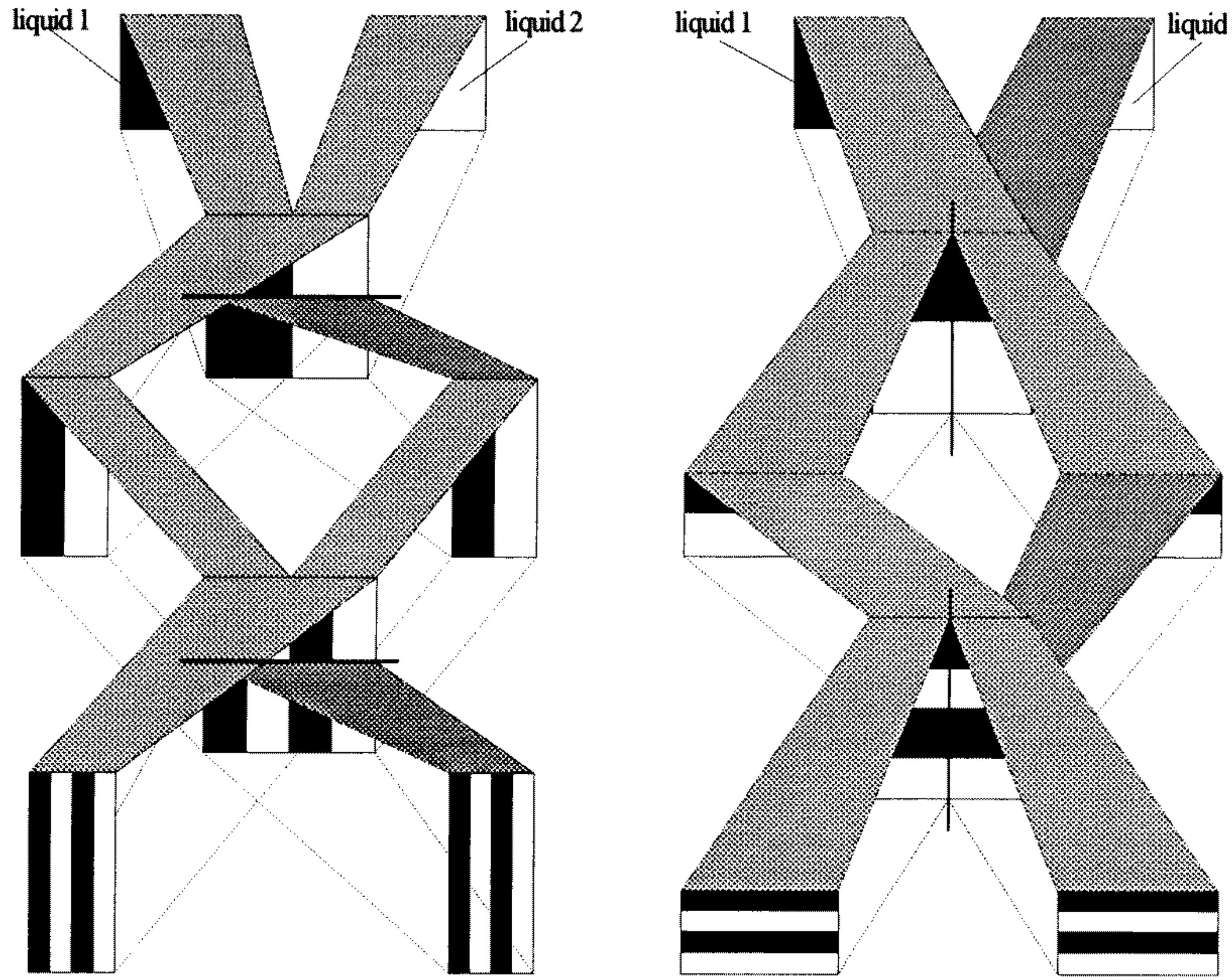
Combination: parallel lamination mixer

<u>Key idea</u>: Split streams to increase surface area and hence mixing





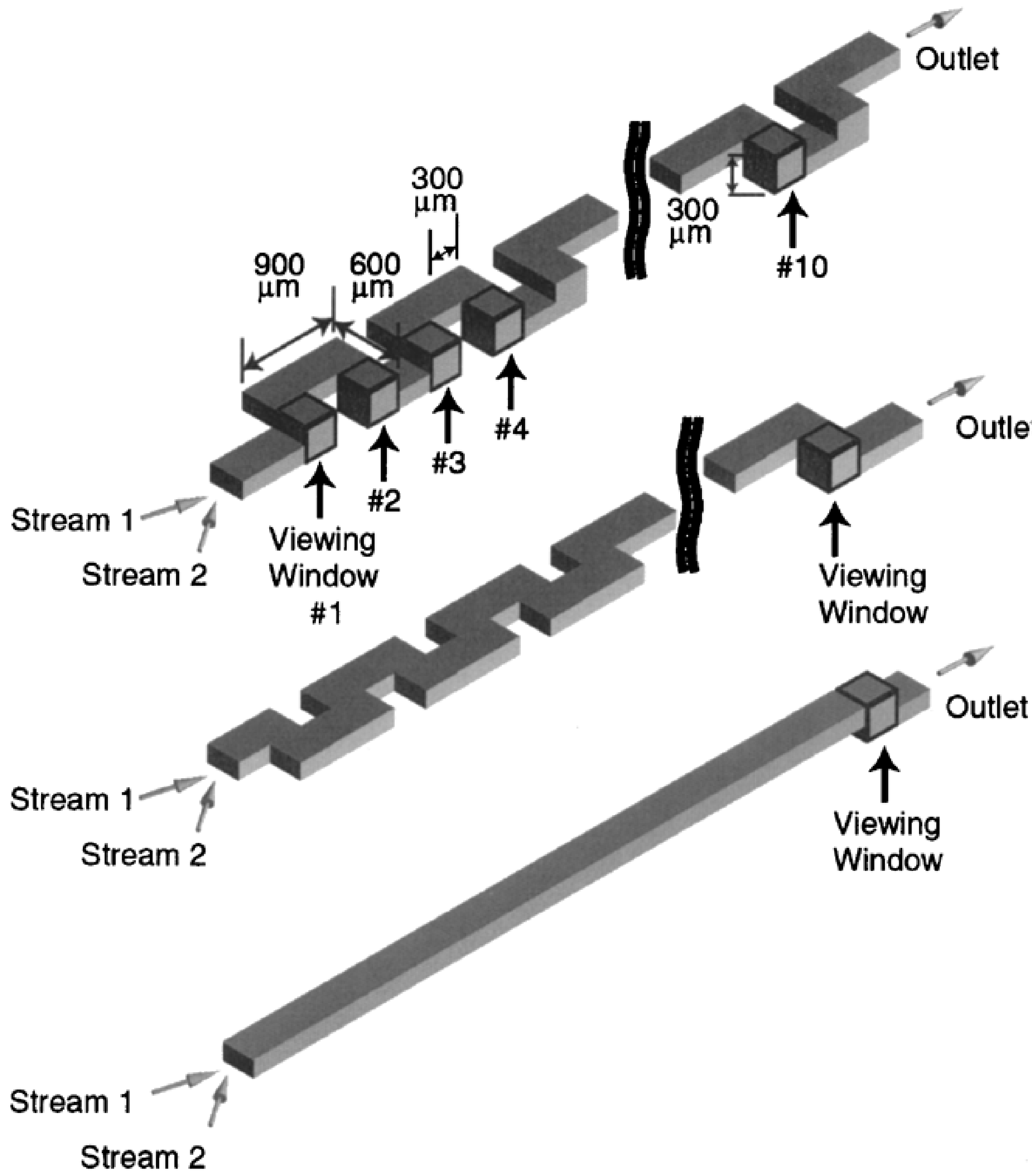
Kamholz *et al.*, *Anal. Chem.* **71**, 5340-5347 (1999)

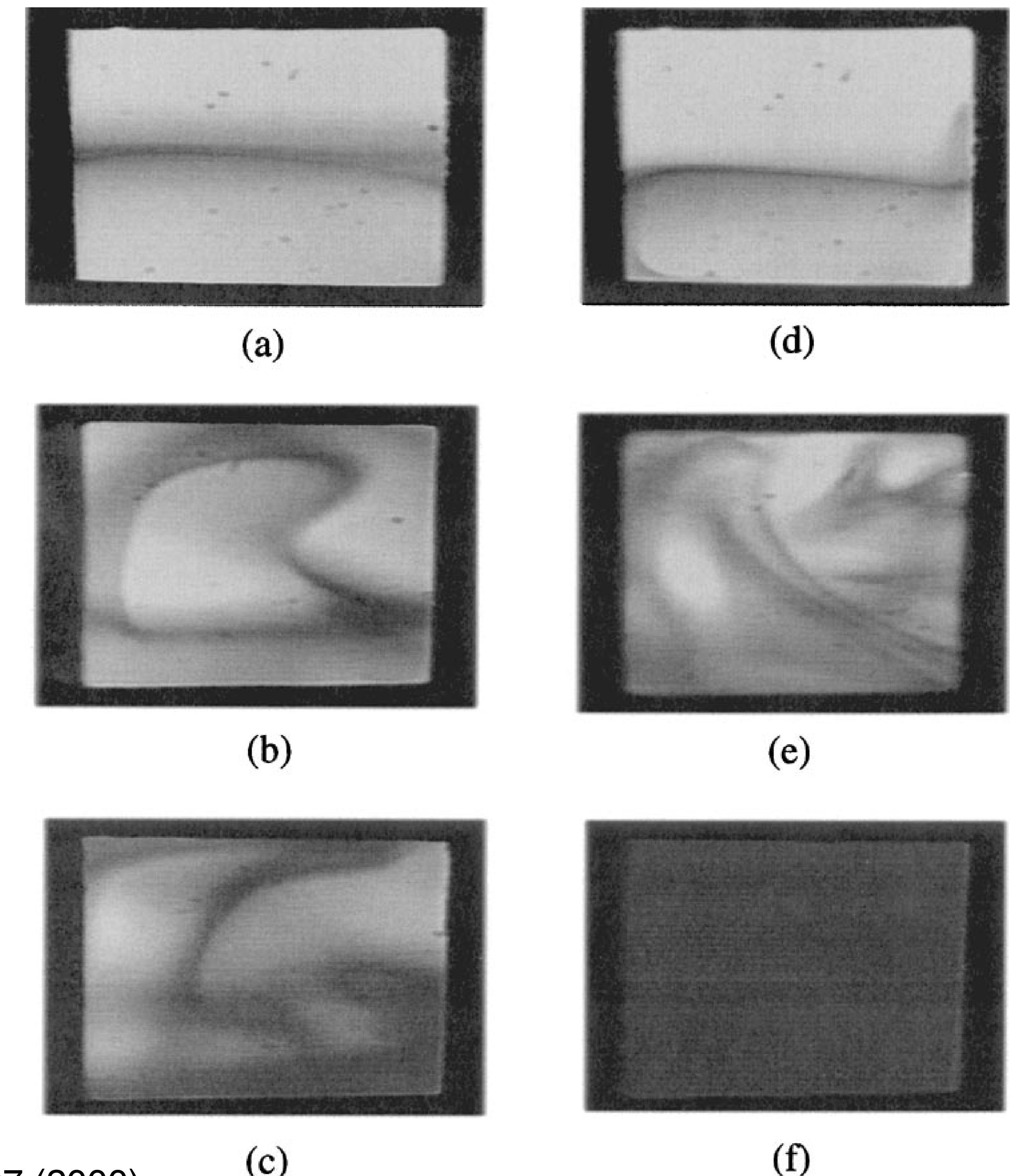


Schwesinger *et al.*, *J. Micromech. Microeng.* **6**, 99-102 (102)

Combination: 3-D serpentine mixers

<u>Key idea</u>: Add elements to “fold” fluid via three-dimensional structure

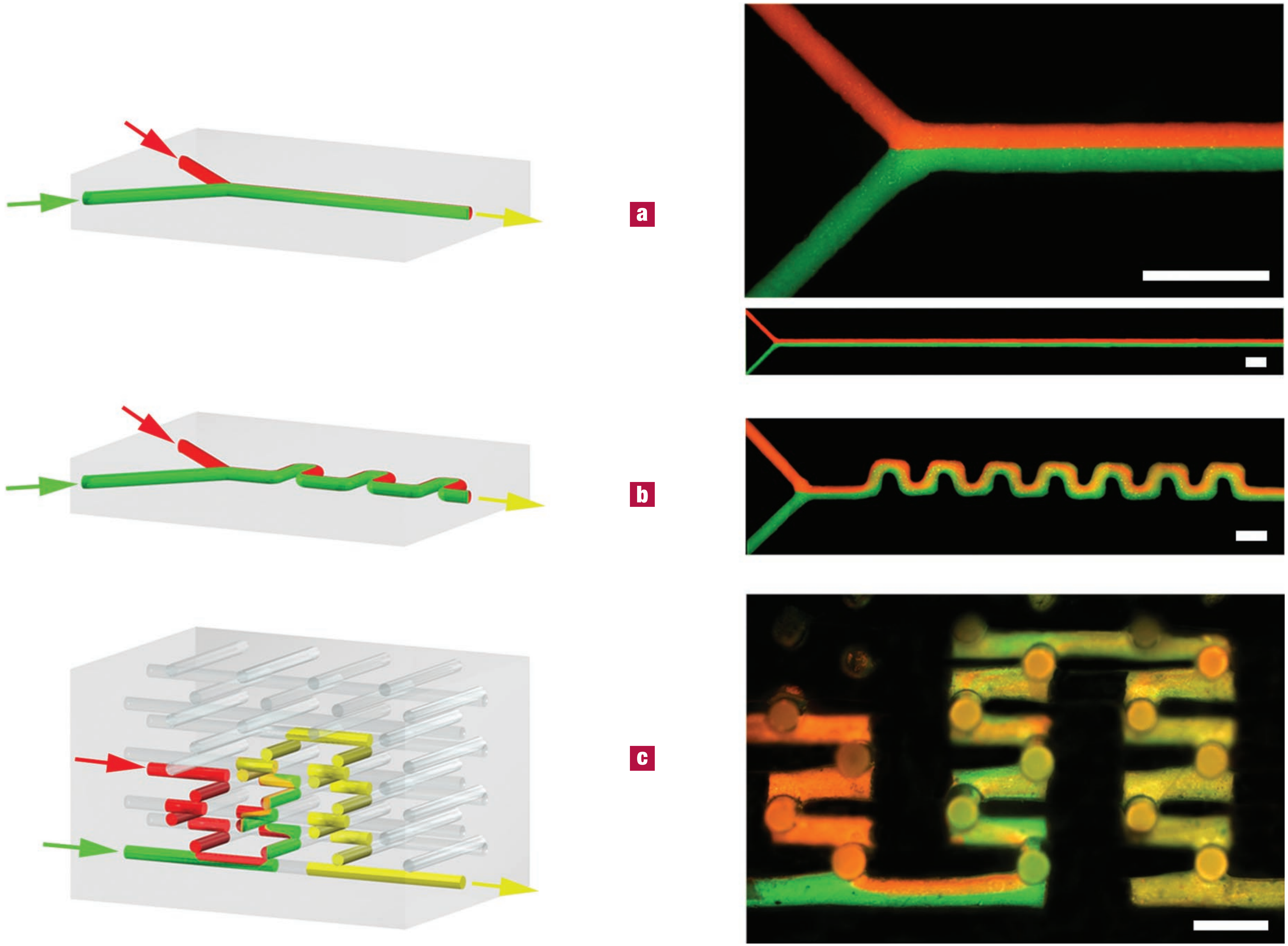




Liu *et al.*, *J. Microelectromech. Syst.* **9**, 190-197 (2000)

Combination: 3-D microvascular networks

Key idea: Split streams in 3-d geometries to enhance mixing

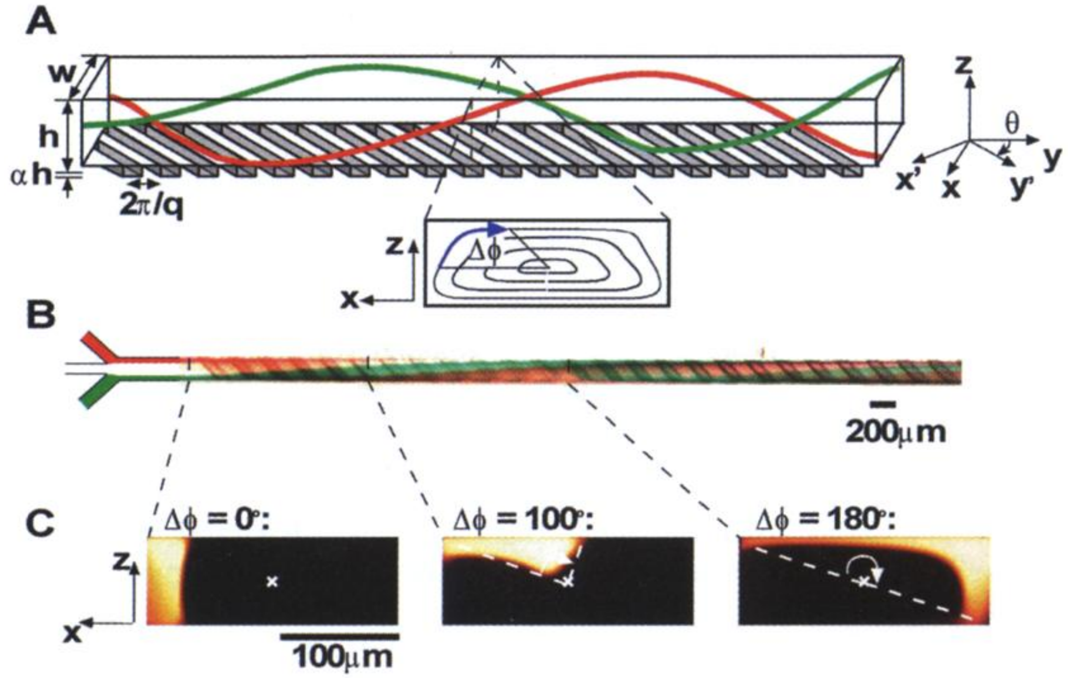


Therriault *et al.*, *Nat. Mater.* **2**, 265-271 (2003)

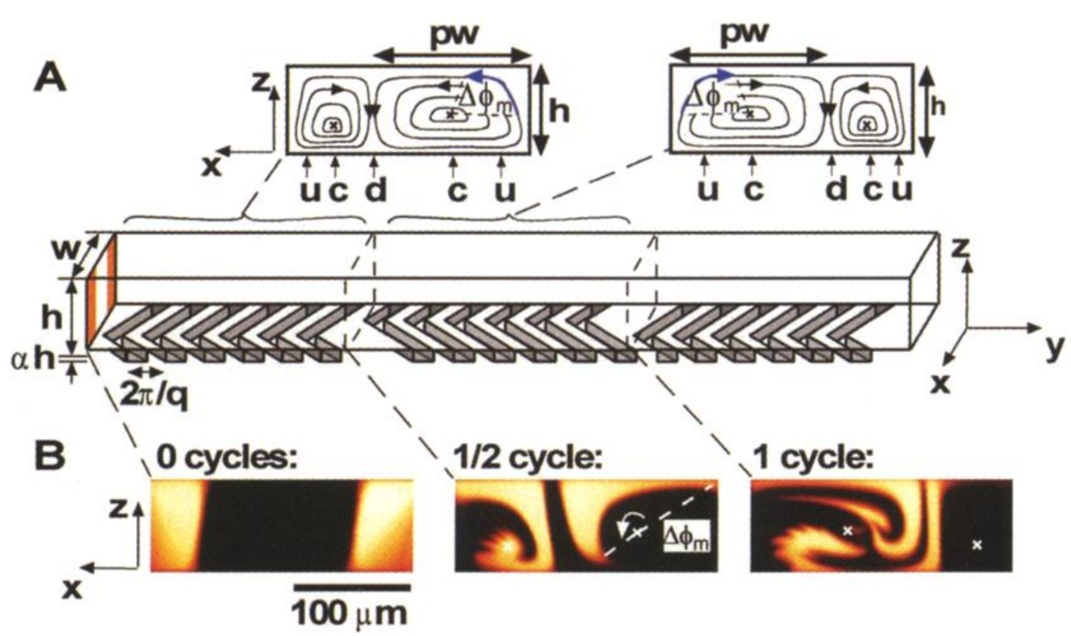
Combination: herringbone micromixers

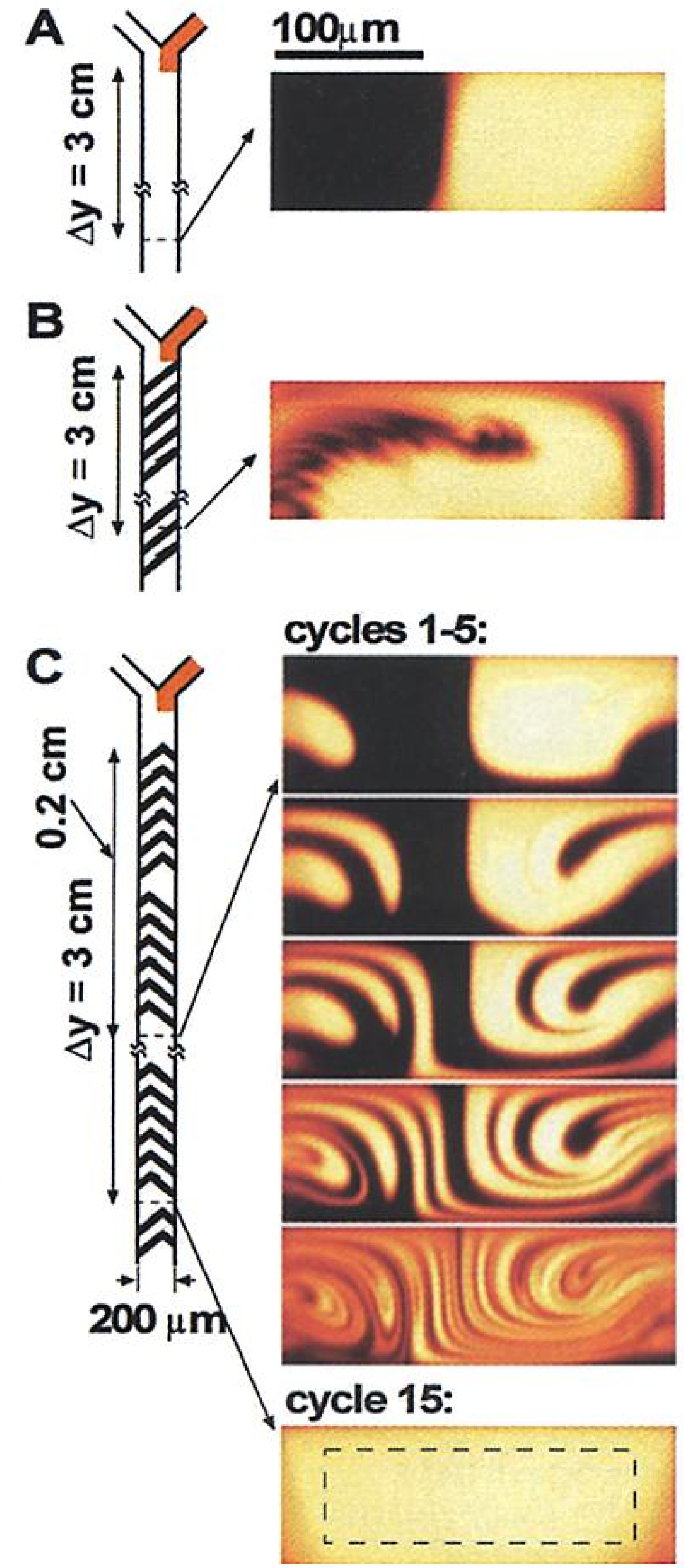
Key idea: Add elements to “fold” fluid via chaotic advection

Slanted ridges:



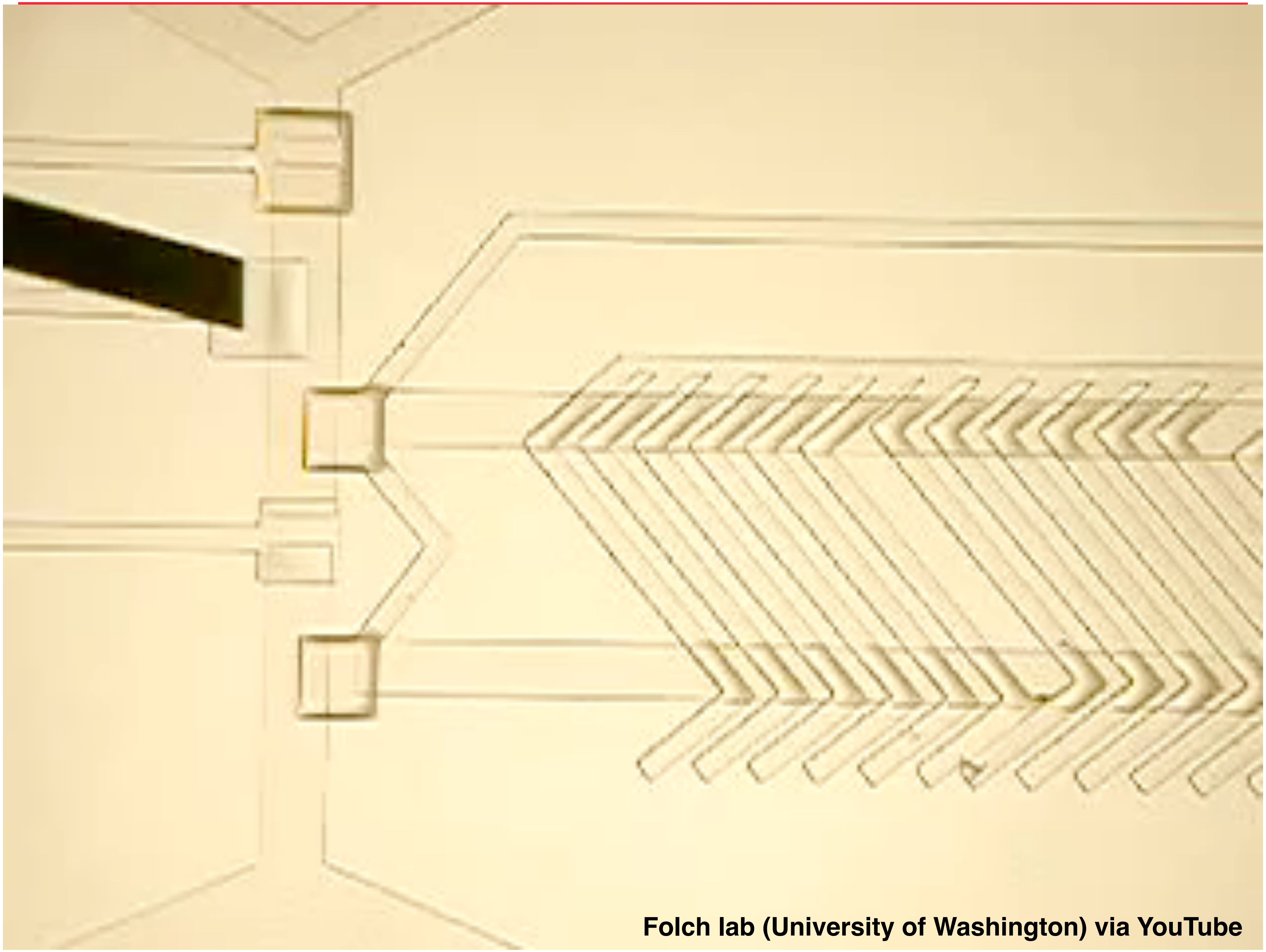
3-D herringbone:





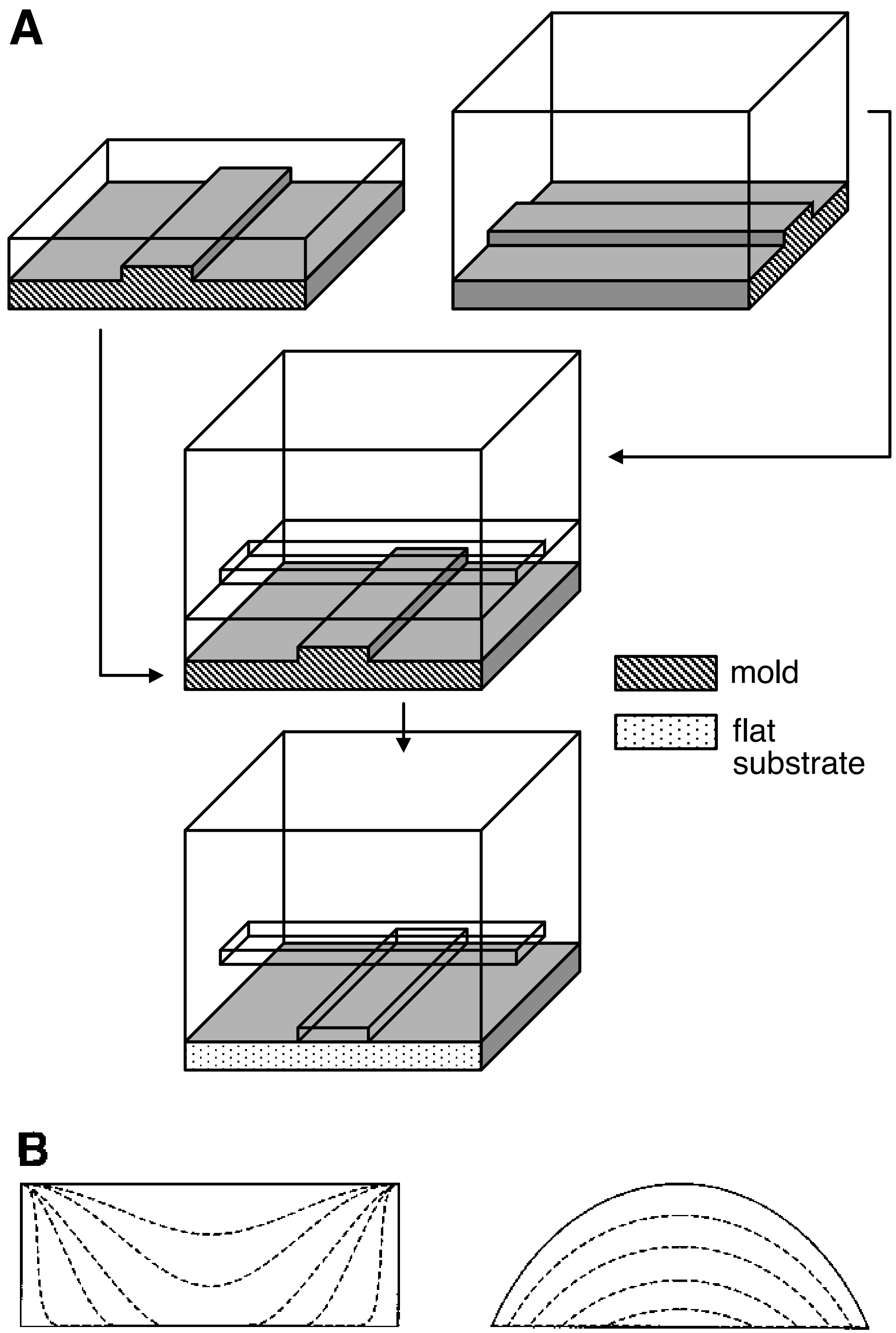
Stroock *et al.*, *Science* **295**, 647-651 (2002)

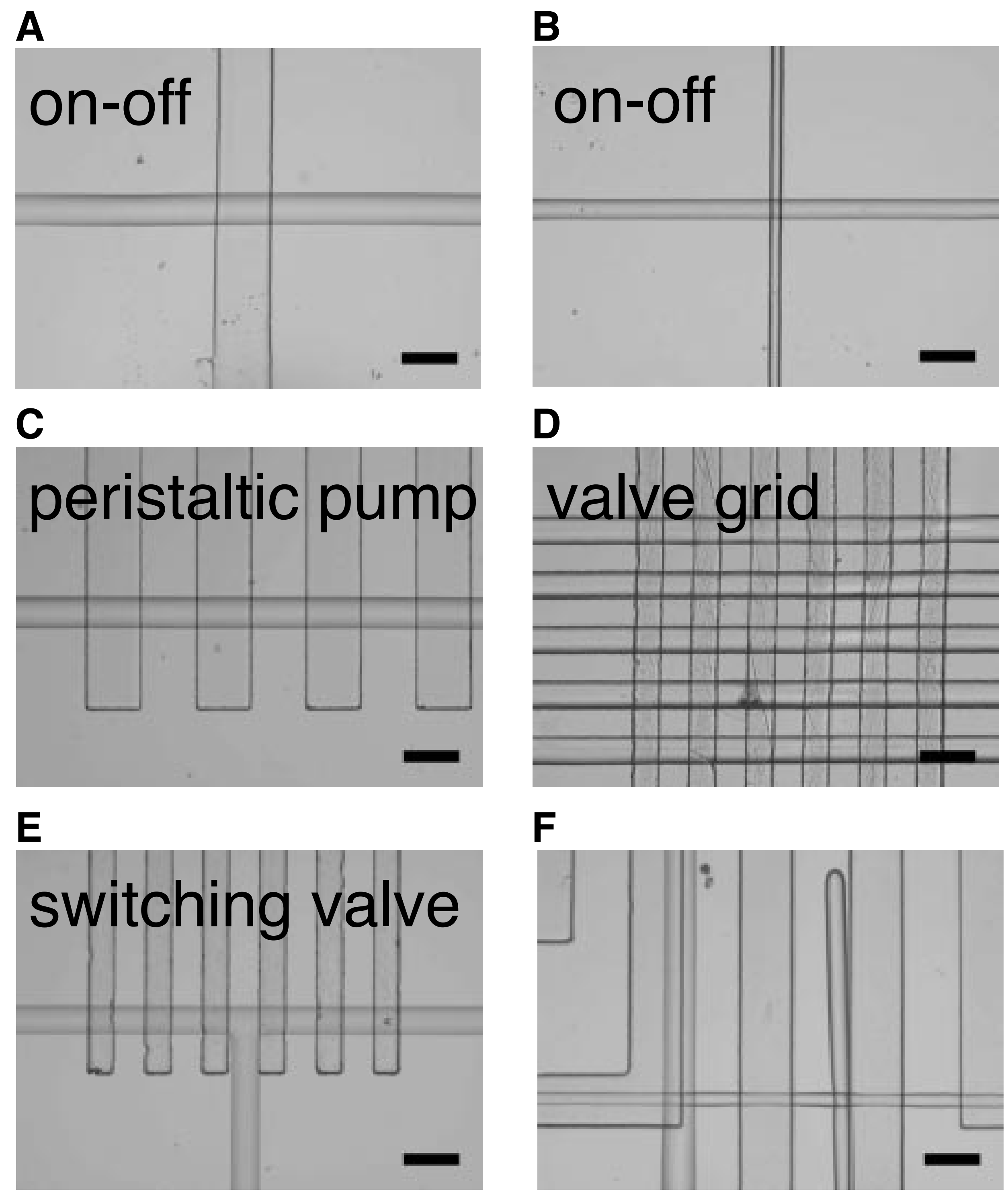
Combination: herringbone mixer movie



Combination: microfluidic valving

<u>Key idea</u>: Fabricate a plastic valve that is separately actuated with air



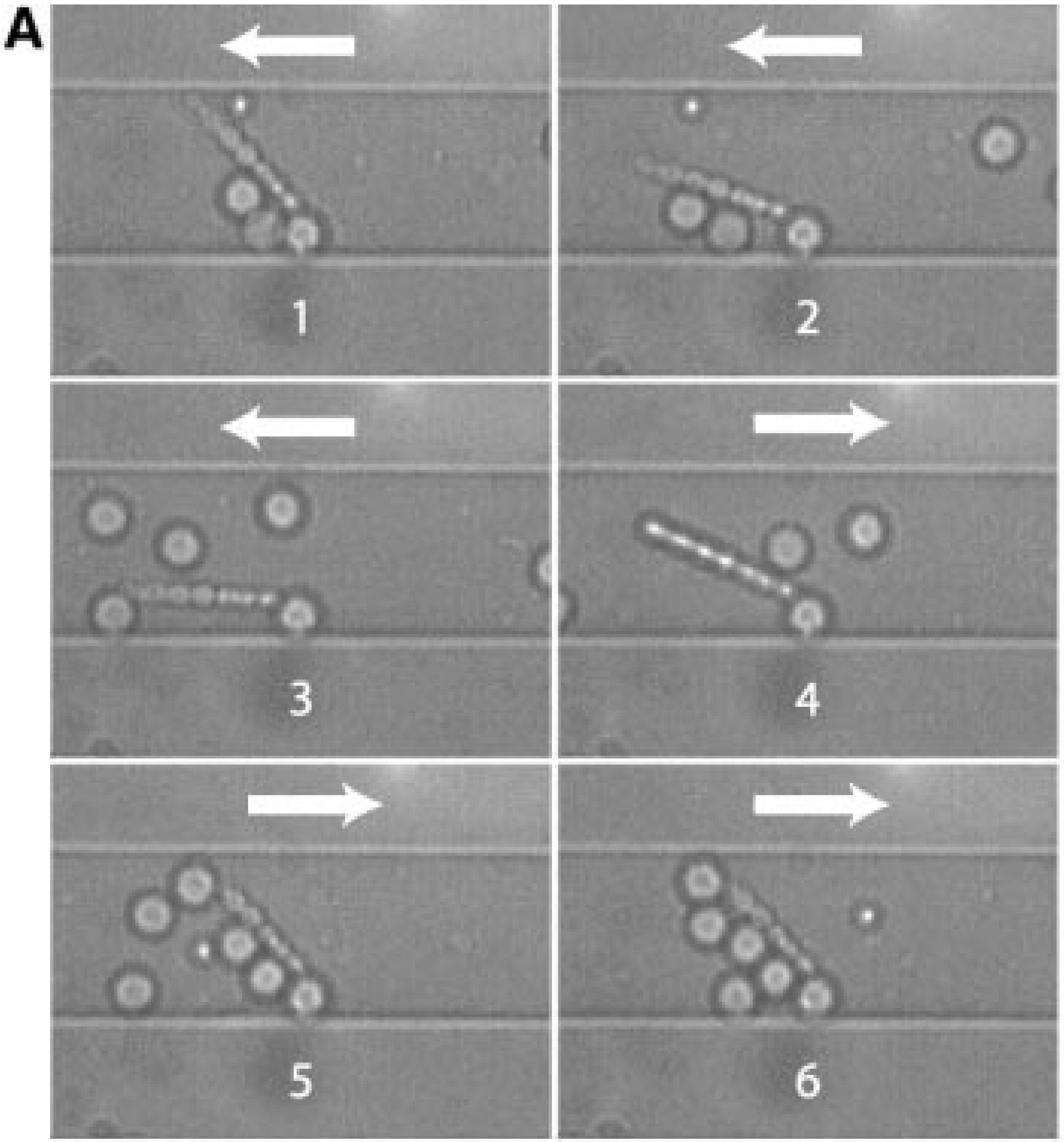


Unger *et al.*, *Science* **288** 113-116 (2000)

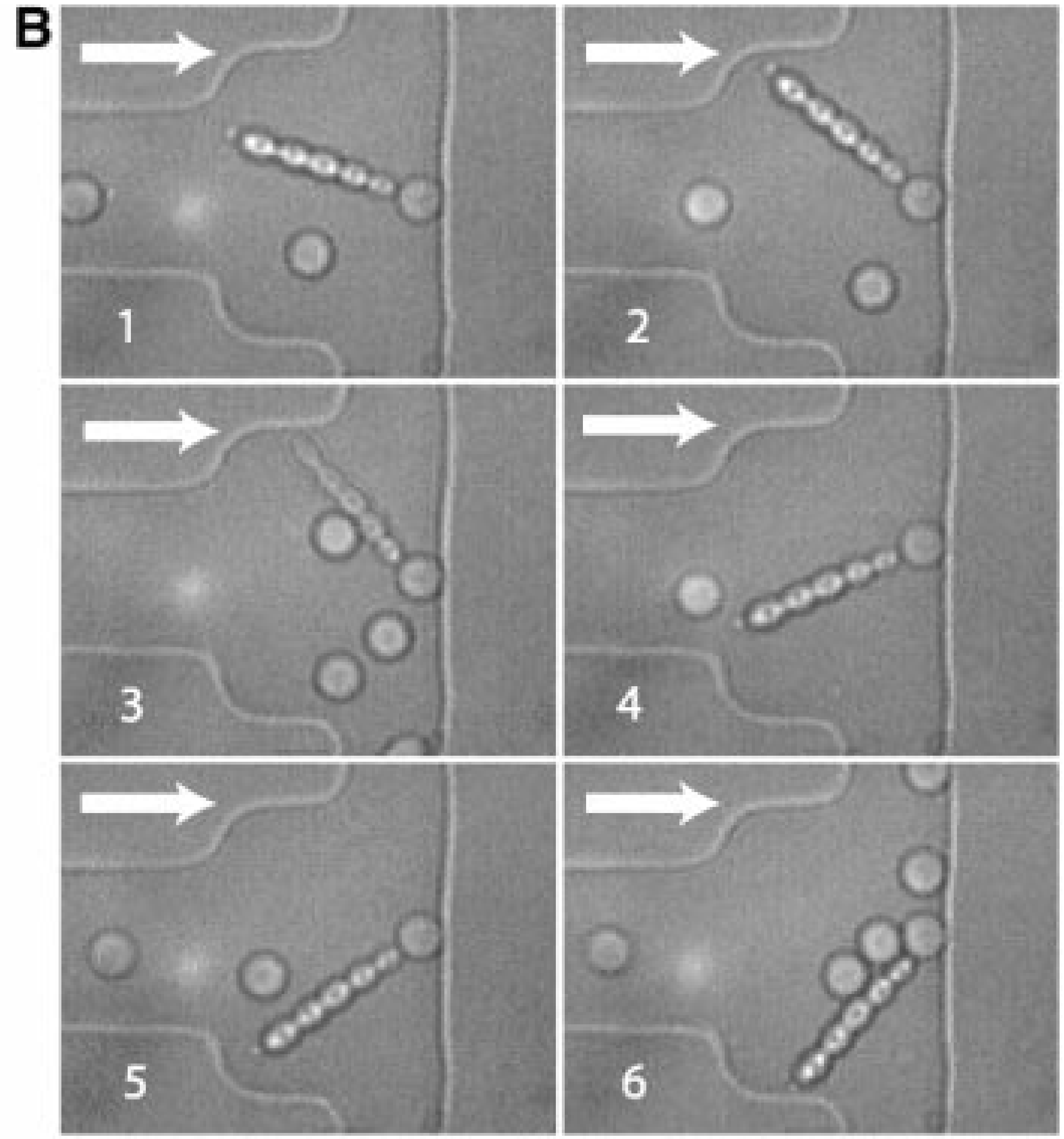
Combination: colloid valves

<u>Key idea</u>: Incorporate micron-sized colloidal particles into devices

passive valve



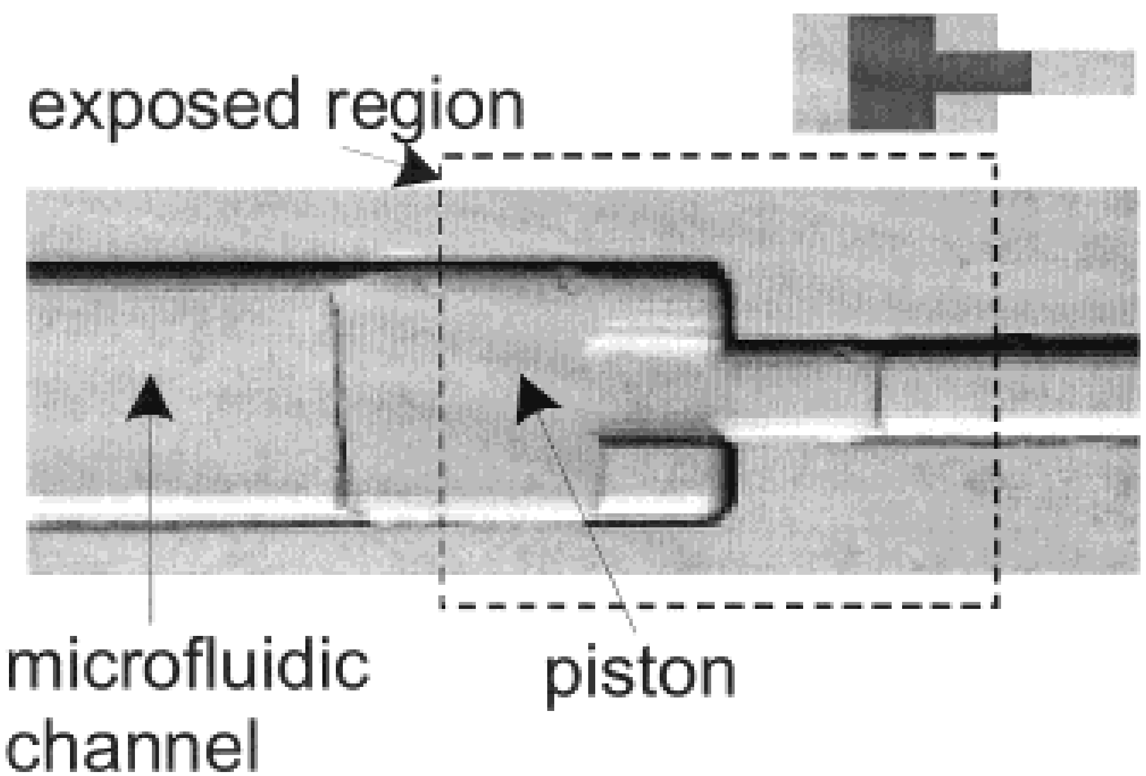
actuated valve

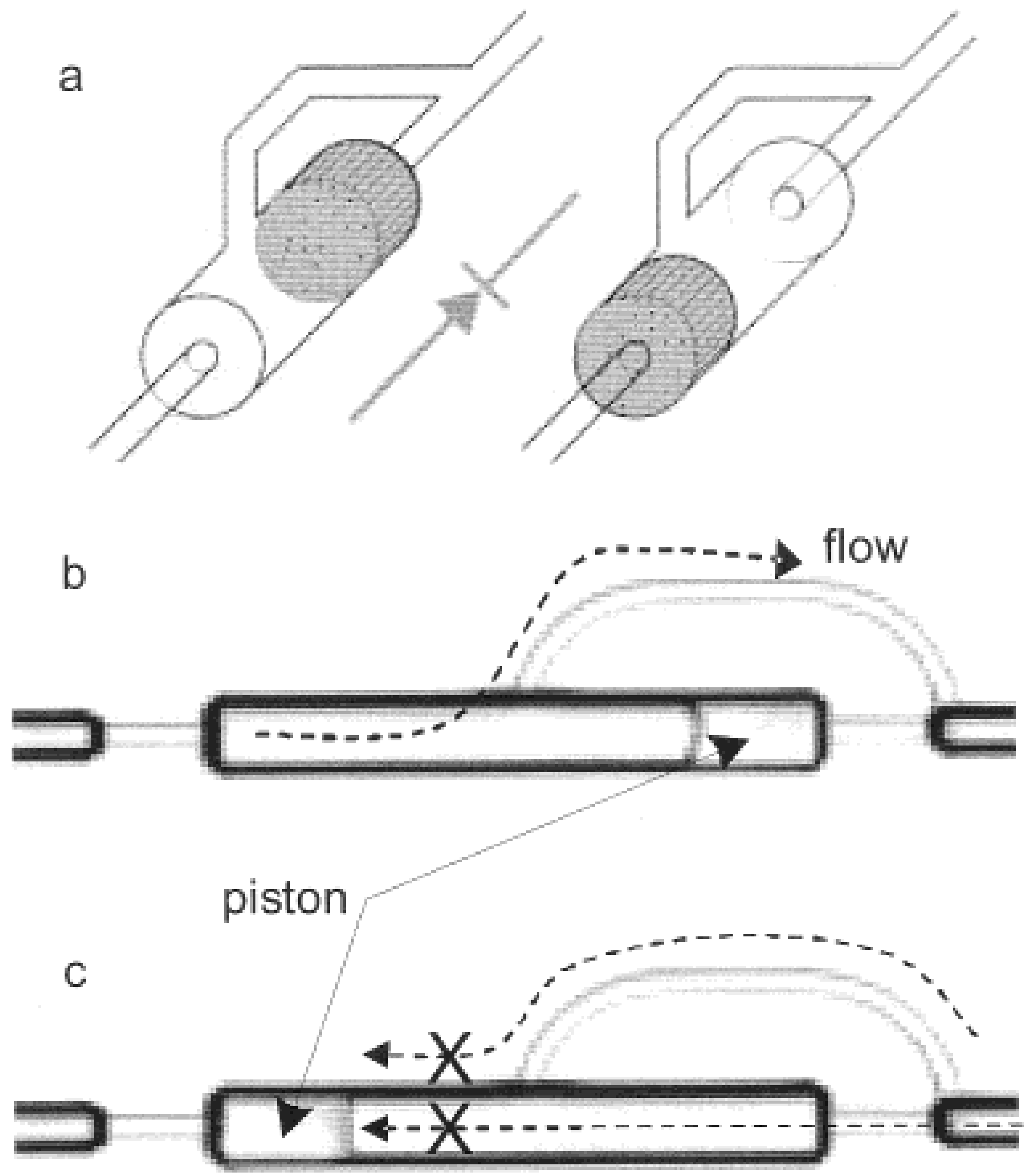


Terray *et al.*, *Science* **296**, 1841-1844 (2002)

Combination: in-situ piston

Key idea: Photopolymerize parts in place in microfluidic devices



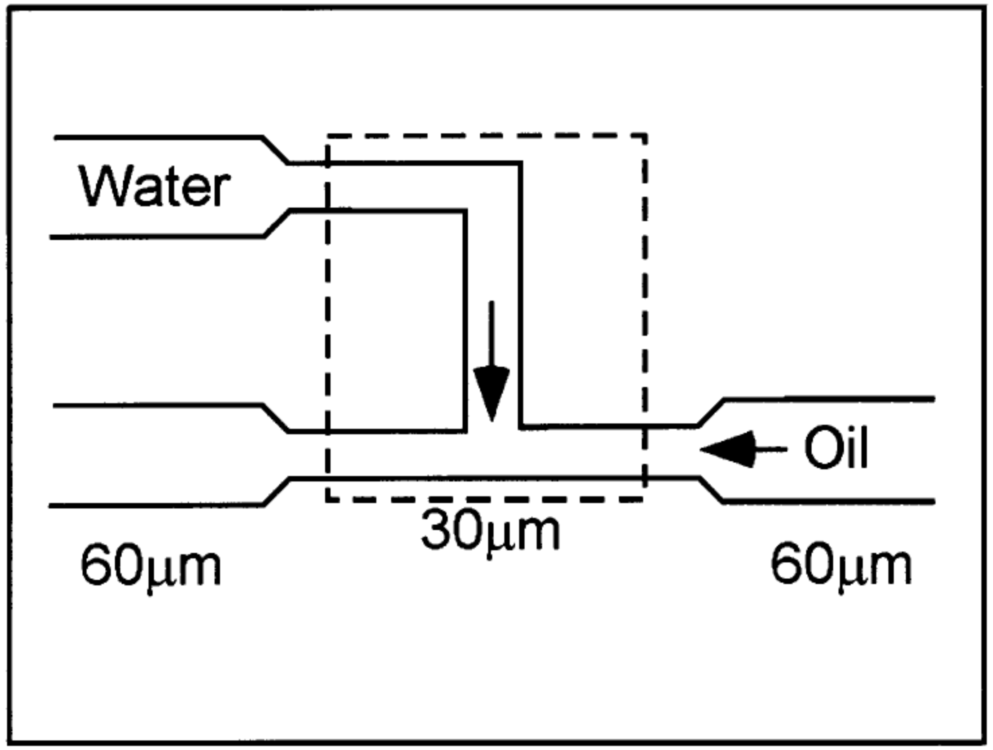


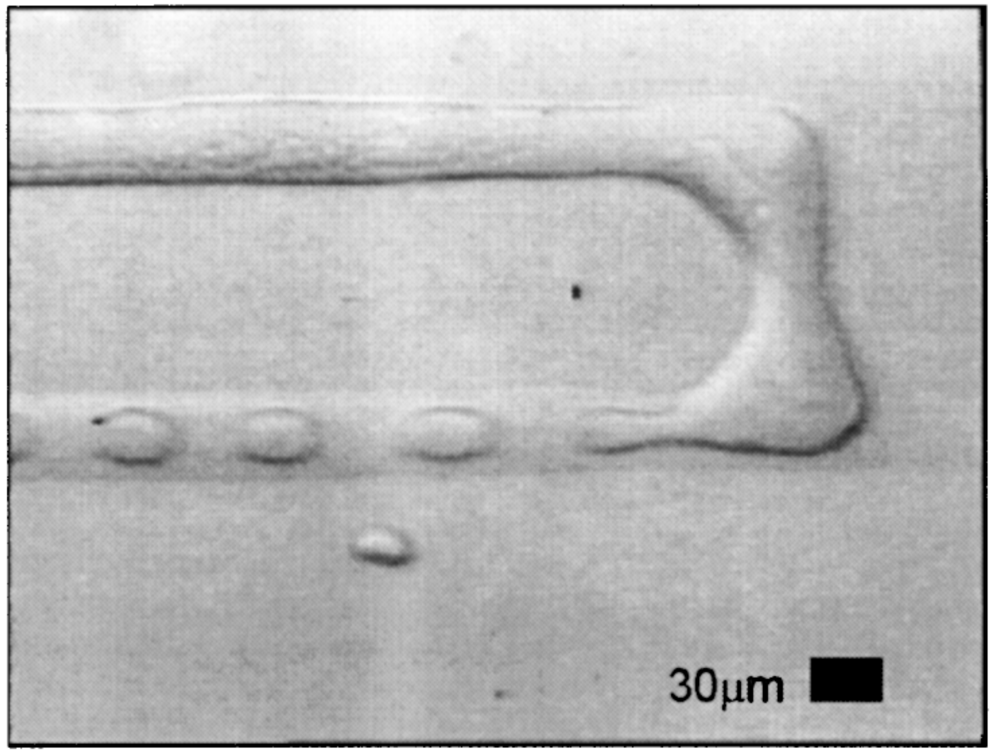
Hasselbrink *et al.*, *Anal. Chem.* **74** 4913-4918 (2002)

Separation: emulsification ("droplets")

Key idea: Exploit the Rayleigh-Plateau instability to create emulsion drops

Wikipedia



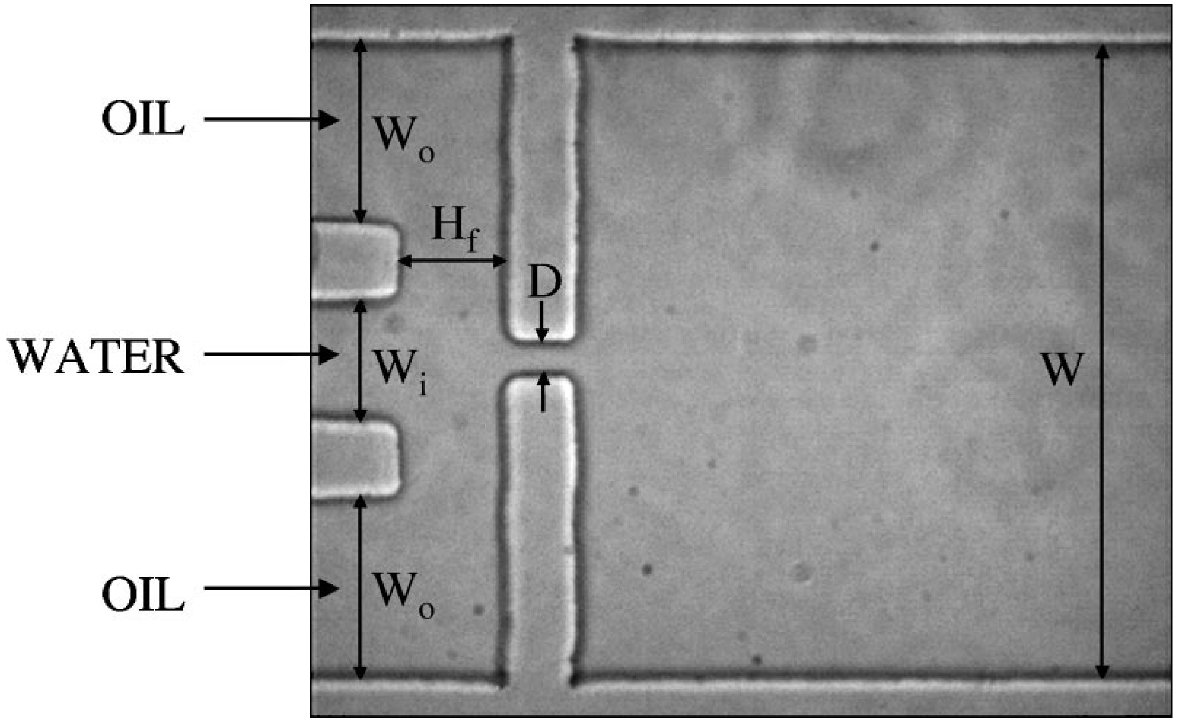


Stress: elongates jet of liquid
Surface tension: minimizes surface area
Result: jet breaks up into drops

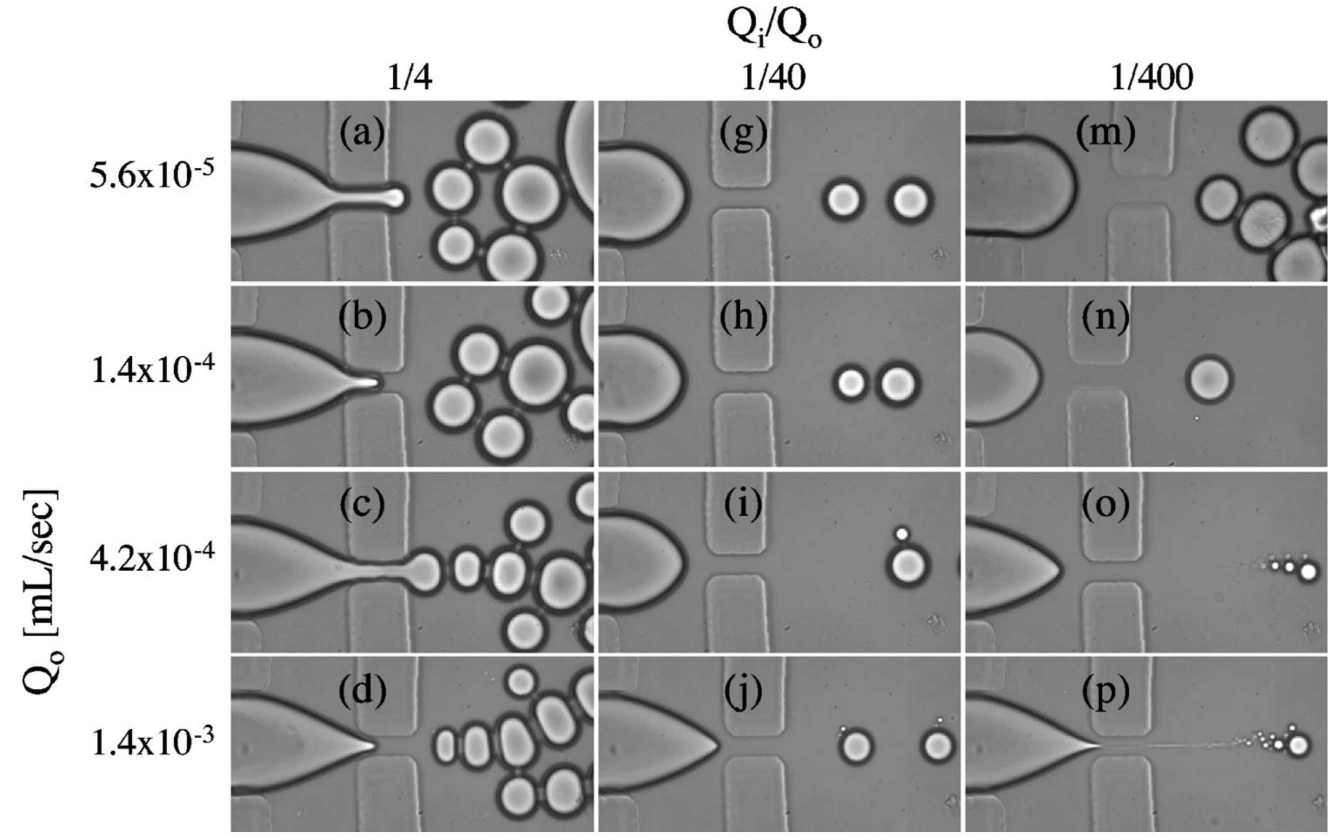
Thorsen *et al.*, *Phys. Rev. Lett.* **86** 4163-4166 (2001)

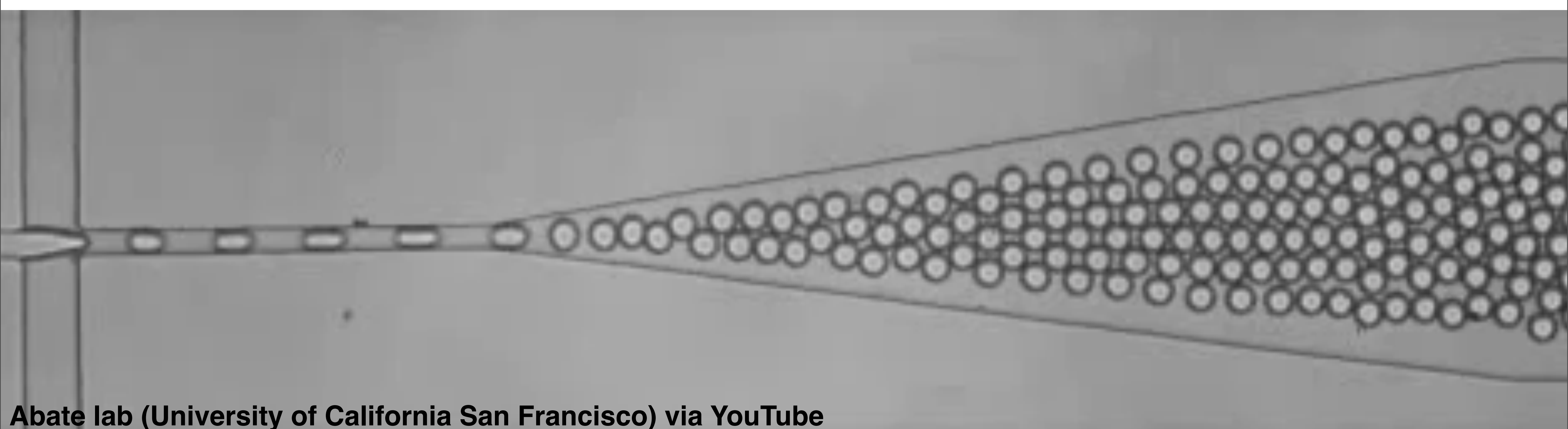
Emulsification: flow-focusing

Key idea: "Pinch off" droplets using a flow-focusing geometry

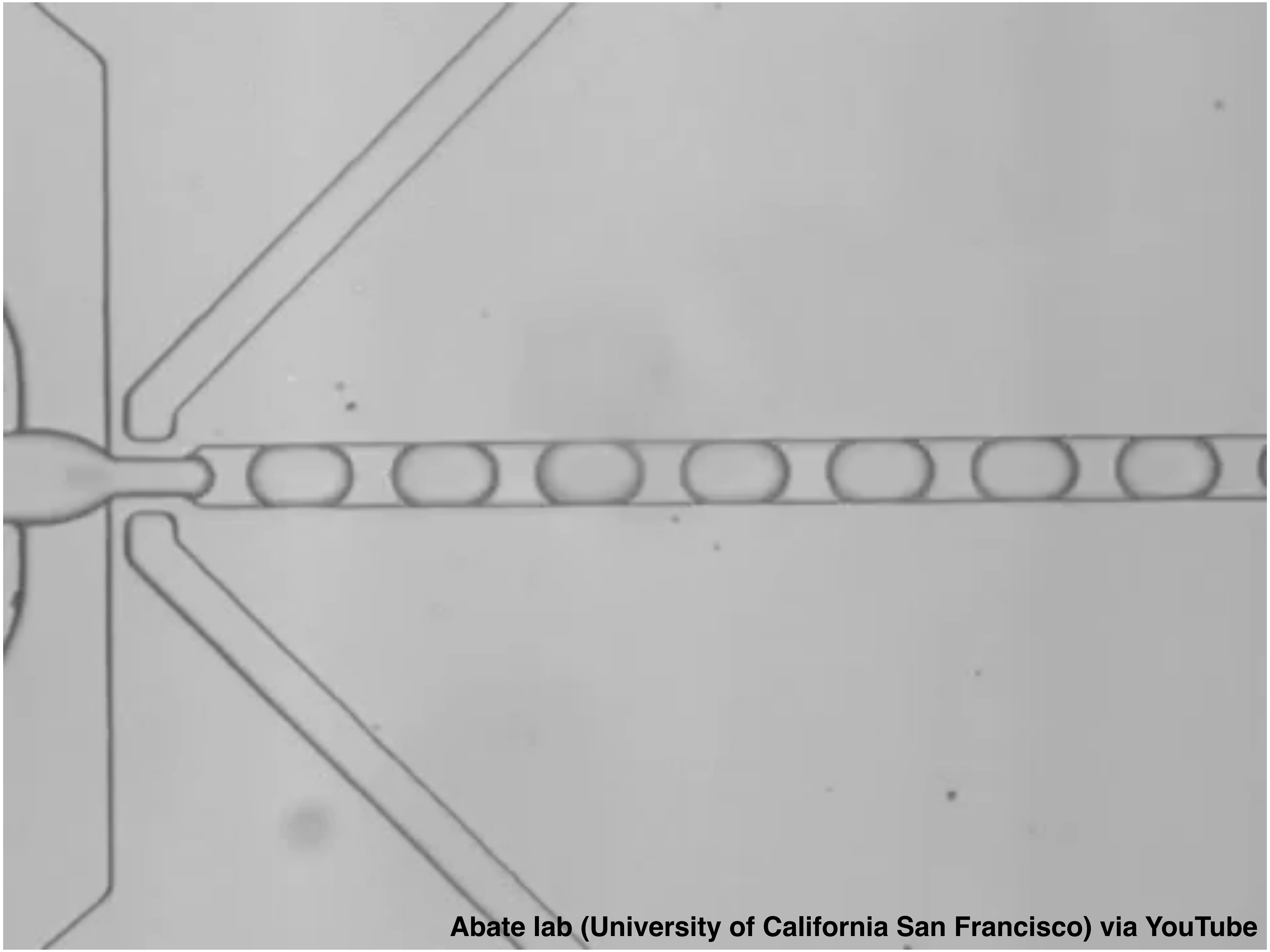


Anna *et al.*, *Anal. Chem.* **74** 4913-4918 (2002)



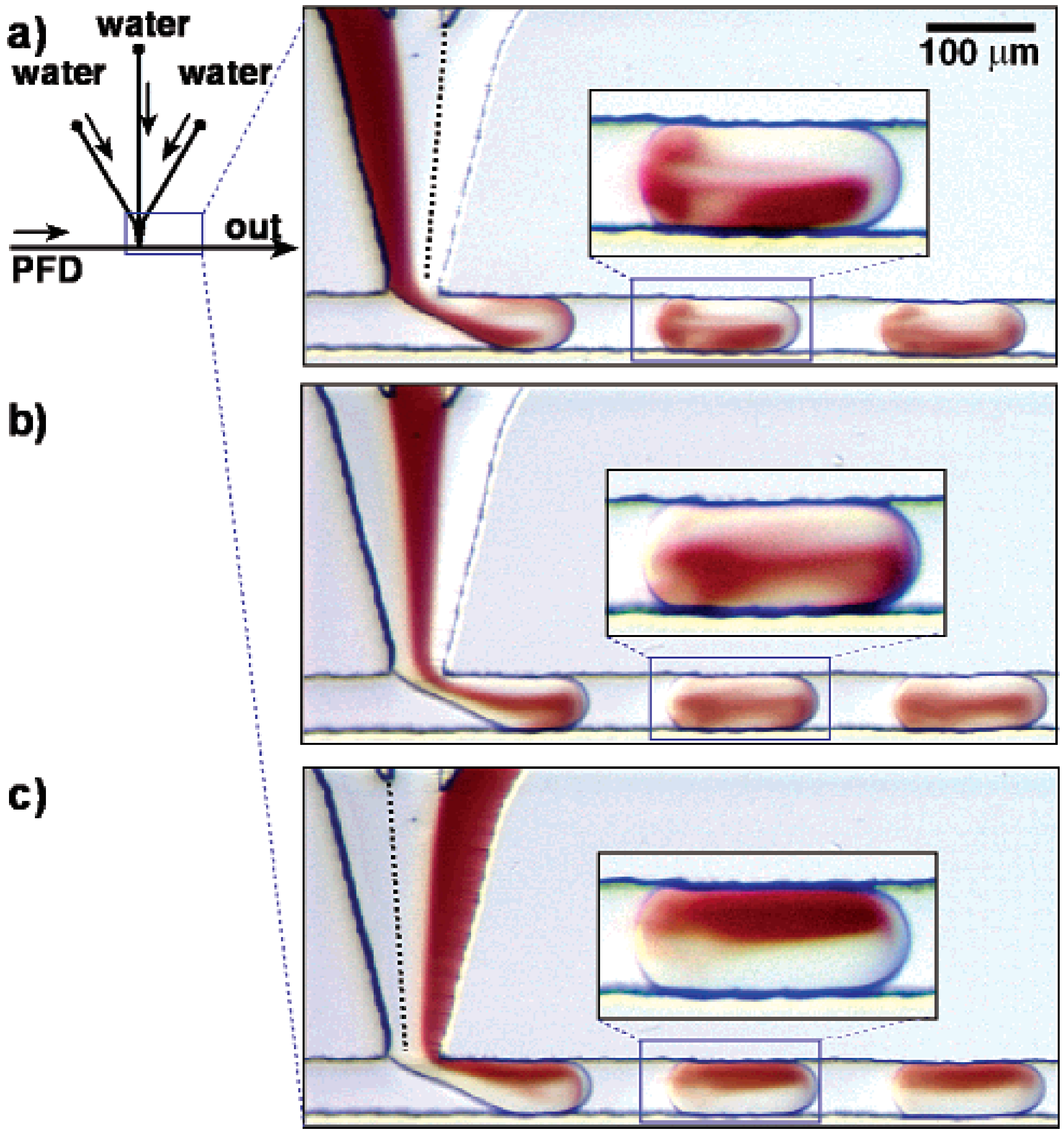


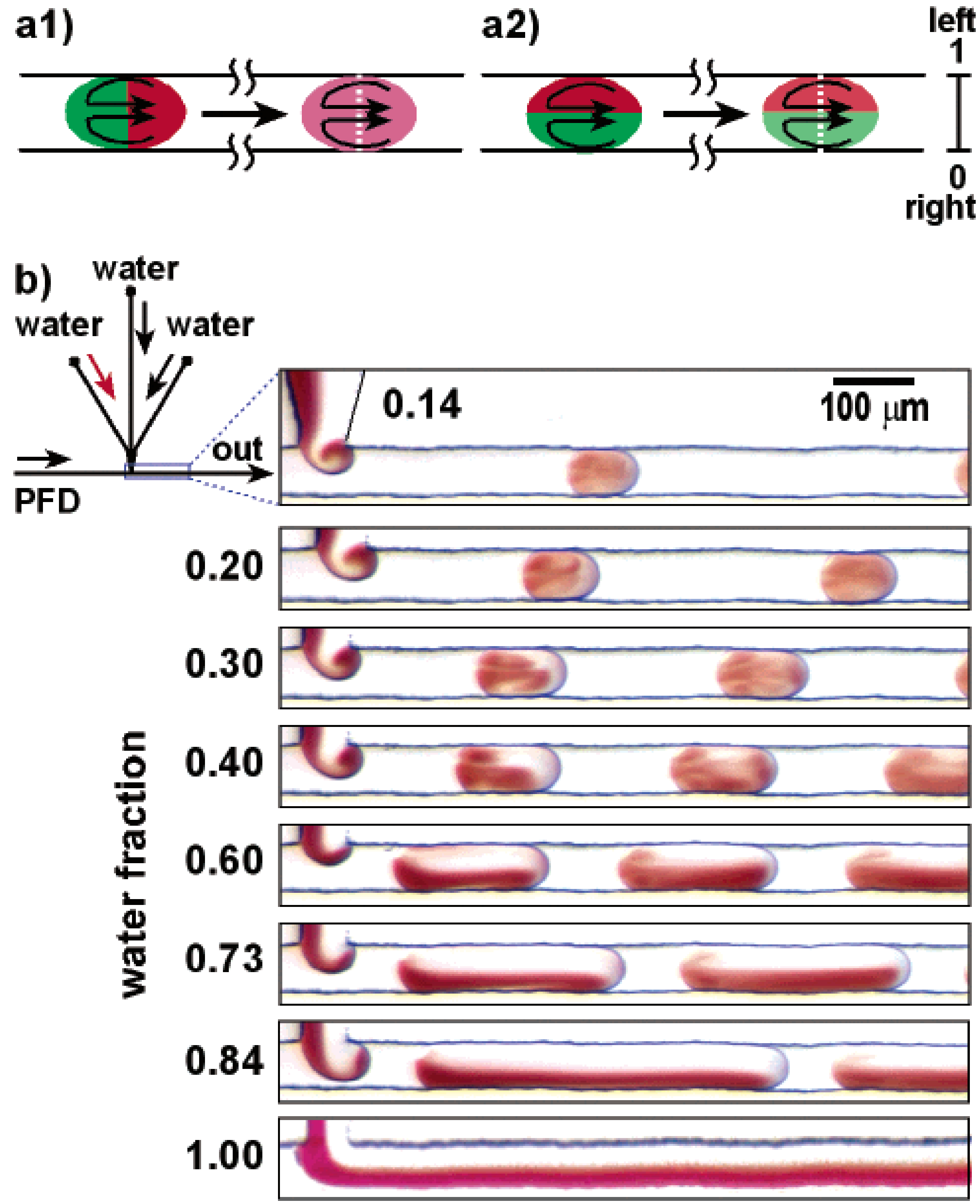
Droplets + valving = adjustable sizes



Emulsification: enhanced mixing in drops

Key idea: Recirculation within drops enhances mixing rates

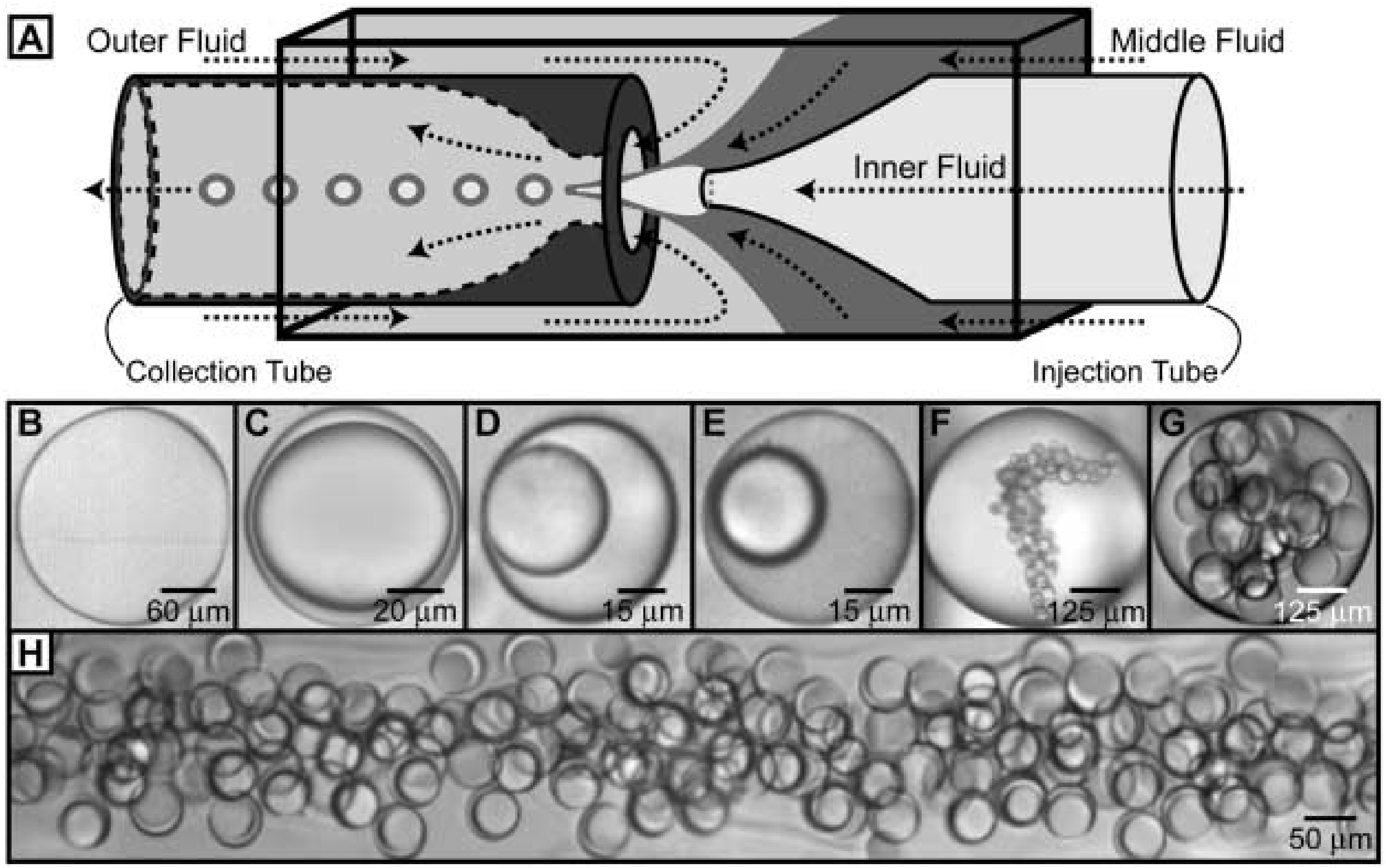




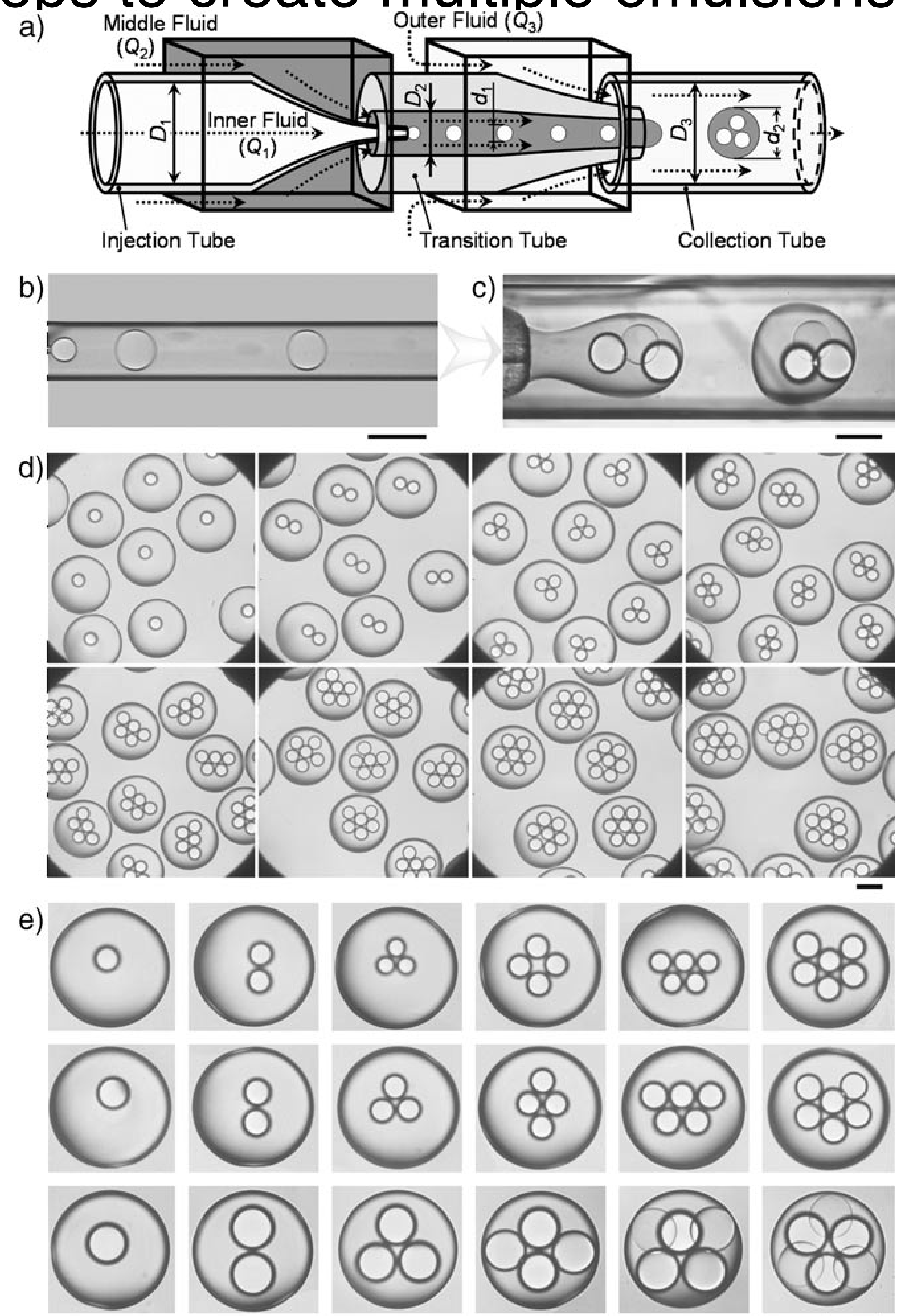
Tice *et al.*, *Langmuir* **19** 9127-9133 (2003)

Emulsification: drops in drops (in drops...)

Key idea: Encapsulate drops in other drops to create multiple emulsions



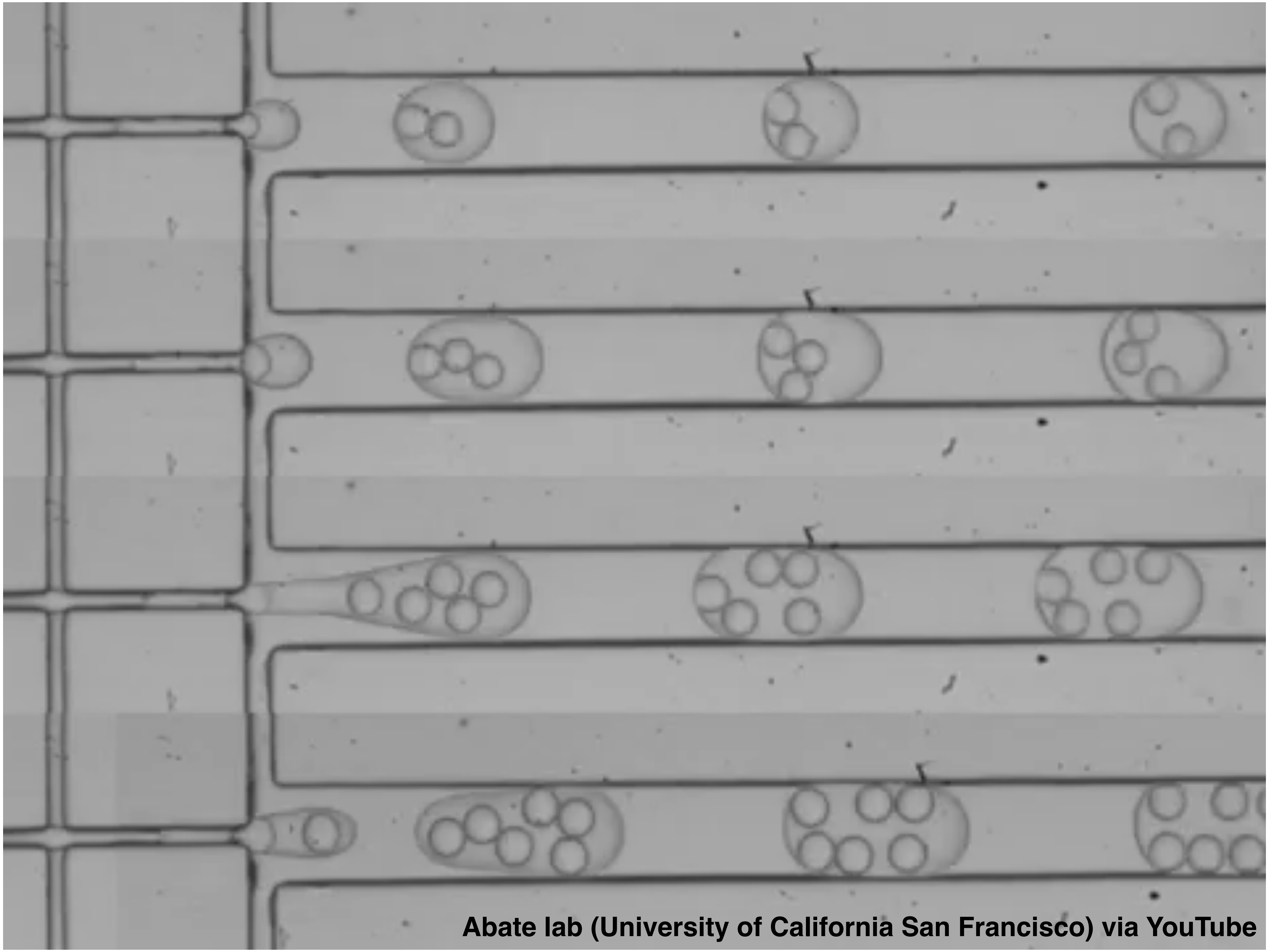
Utada *et al.*, *Science* **308** 537-541 (2005)



Chu *et al.*, *Angew. Chem. Int. Ed.* **46** 8970-8974 (2007)

Drops in drops: tune flow rates

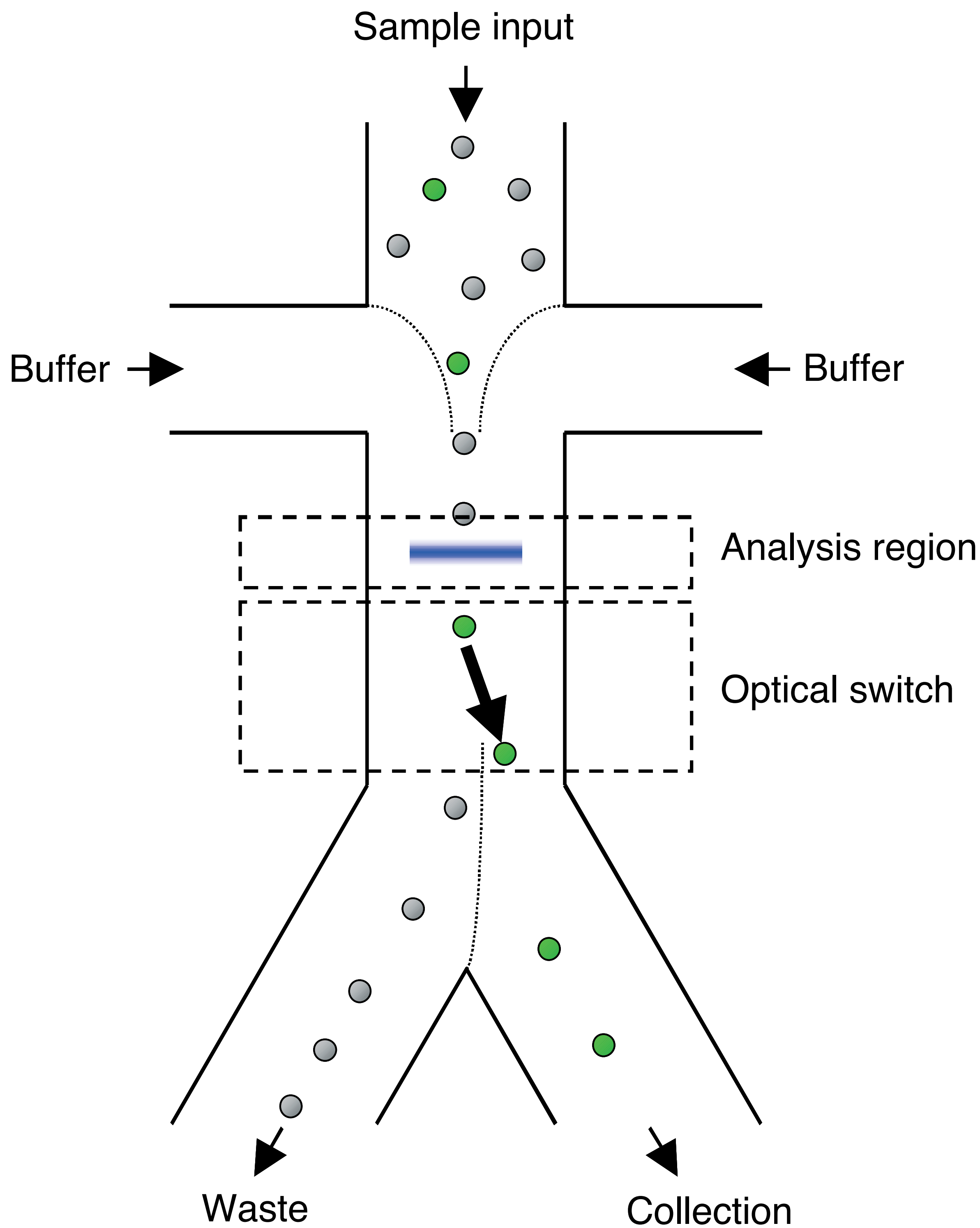
increasing inner fluid flow rate

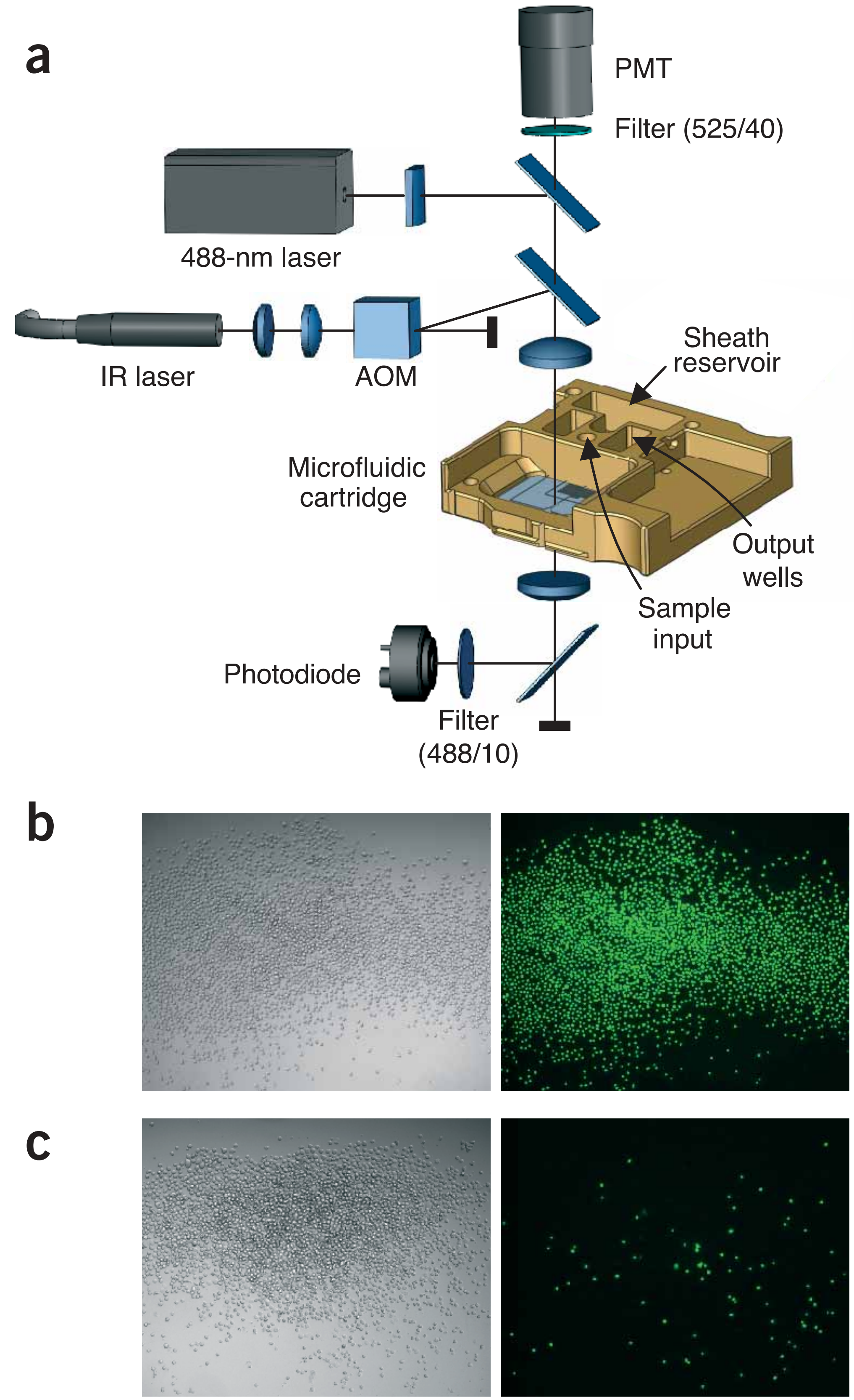


Abate lab (University of California San Francisco) via YouTube

Separation: cell sorting via optical forces

Key idea: Use radiation pressure to sort cells in a microfluidic device

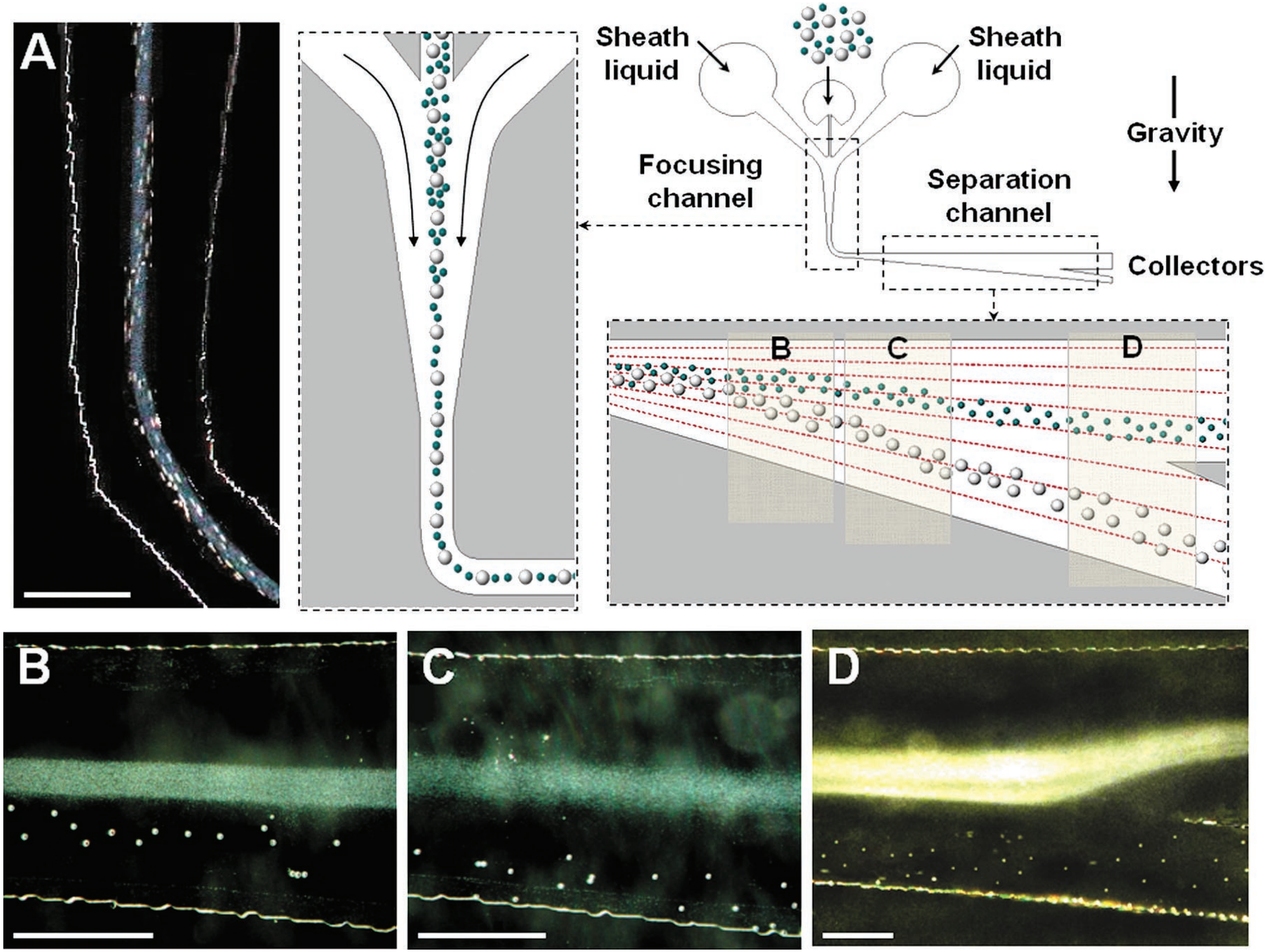




Wang *et al.*, *Nat. Biotechnol.* **23** 83-87 (2005)

Separation: particle sorting via gravity

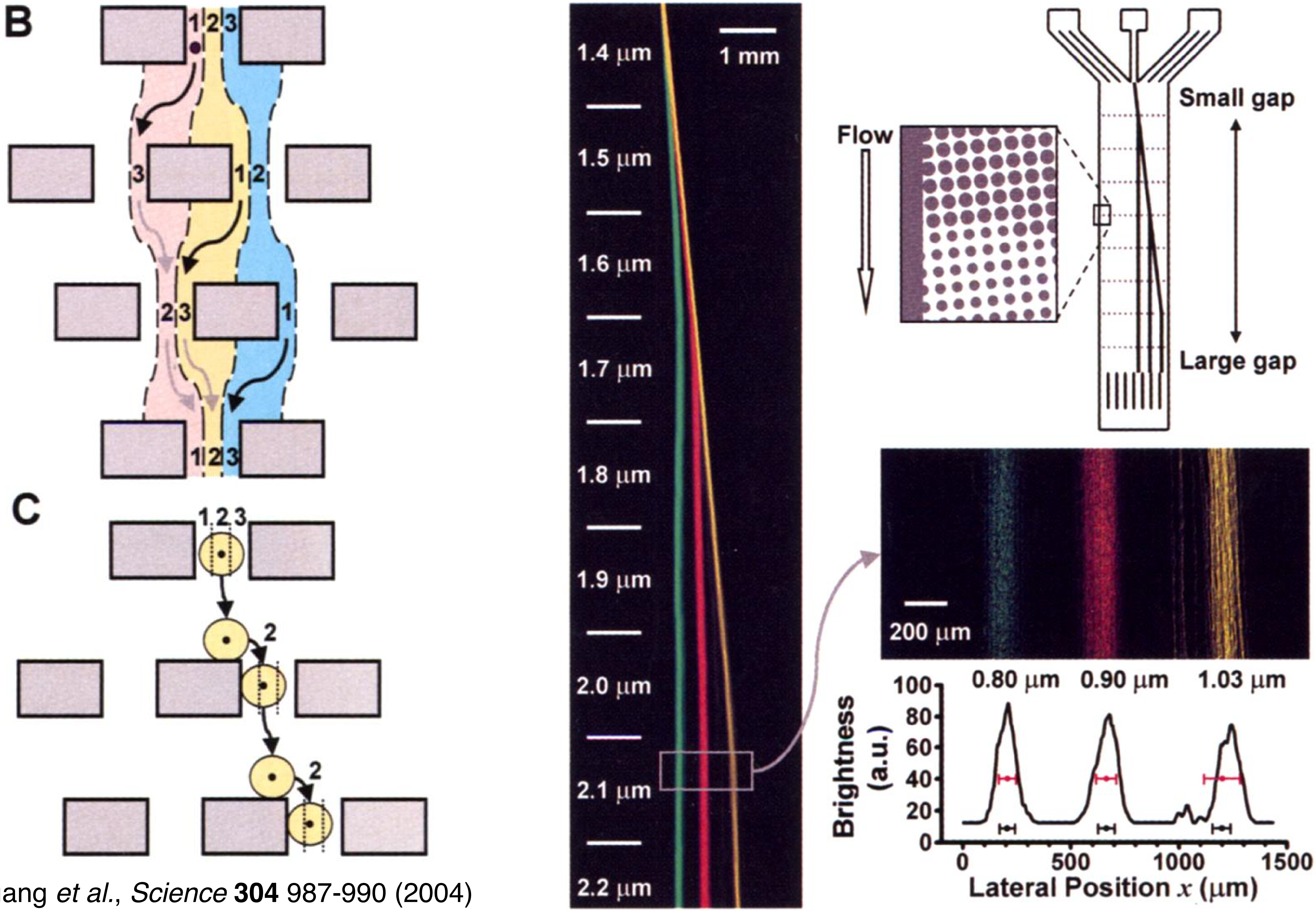
<u>Key idea</u>: Use gravity to sort particles of different mass



Huh *et al.*, *Anal. Chem.* **79** 1369-1376 (2009)

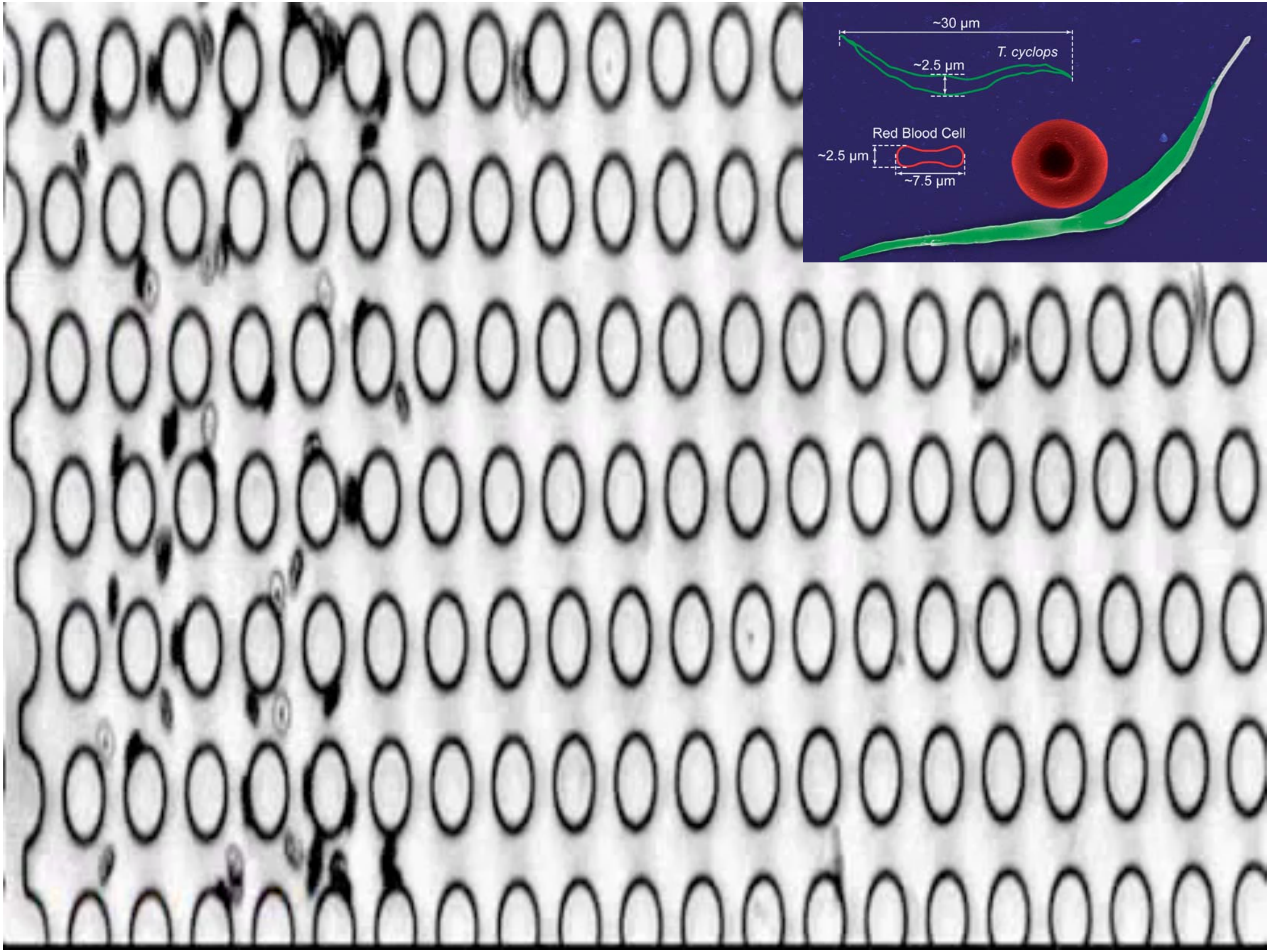
Separation: deterministic lateral displacement

Key idea: Particles of different diameter follow different streamlines



Huang *et al.*, *Science* **304** 987-990 (2004)

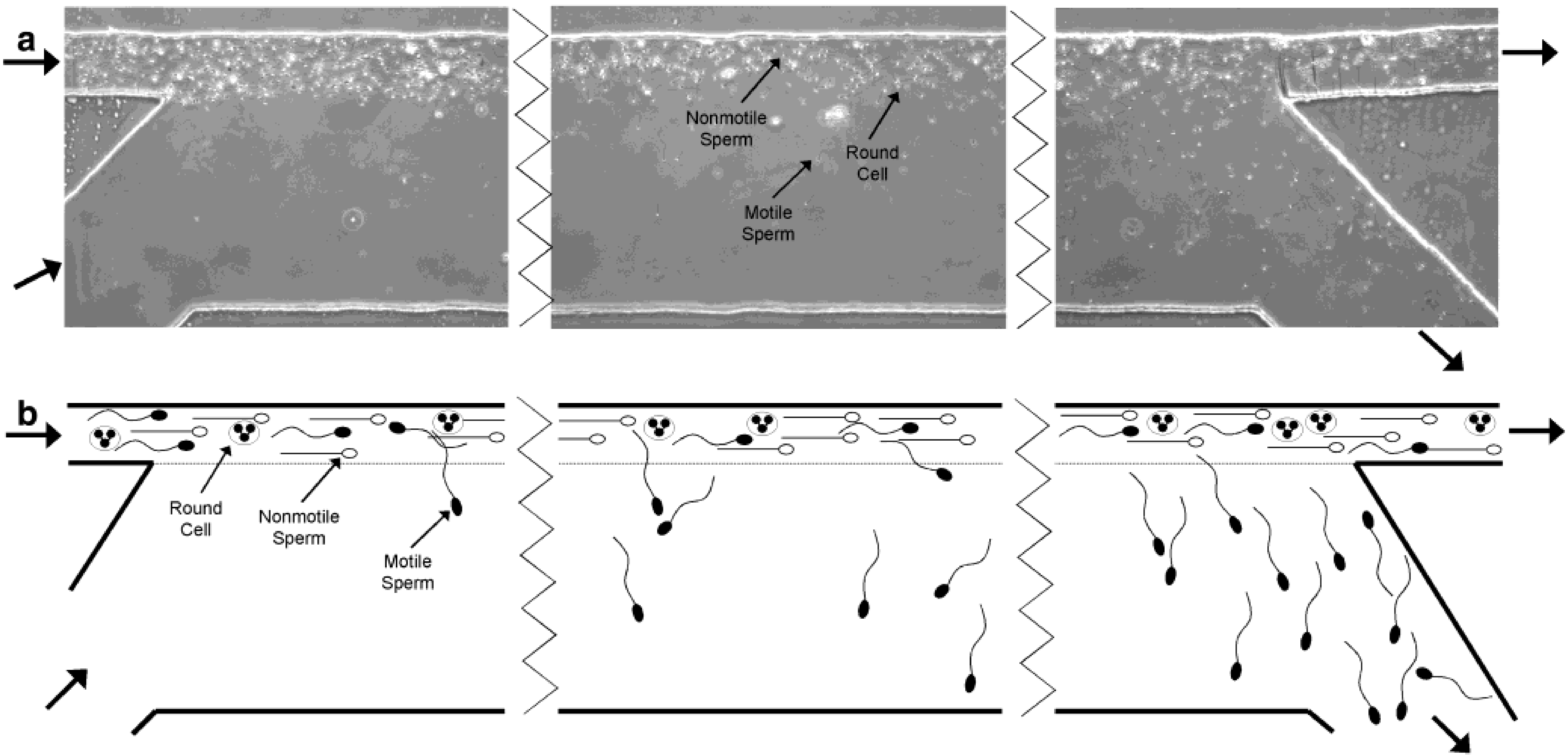
Separation of parasites from blood



Holm *et al.*, *Lab Chip* **304**, 1326-1332 (2011)

Separation: motile sperm sorter

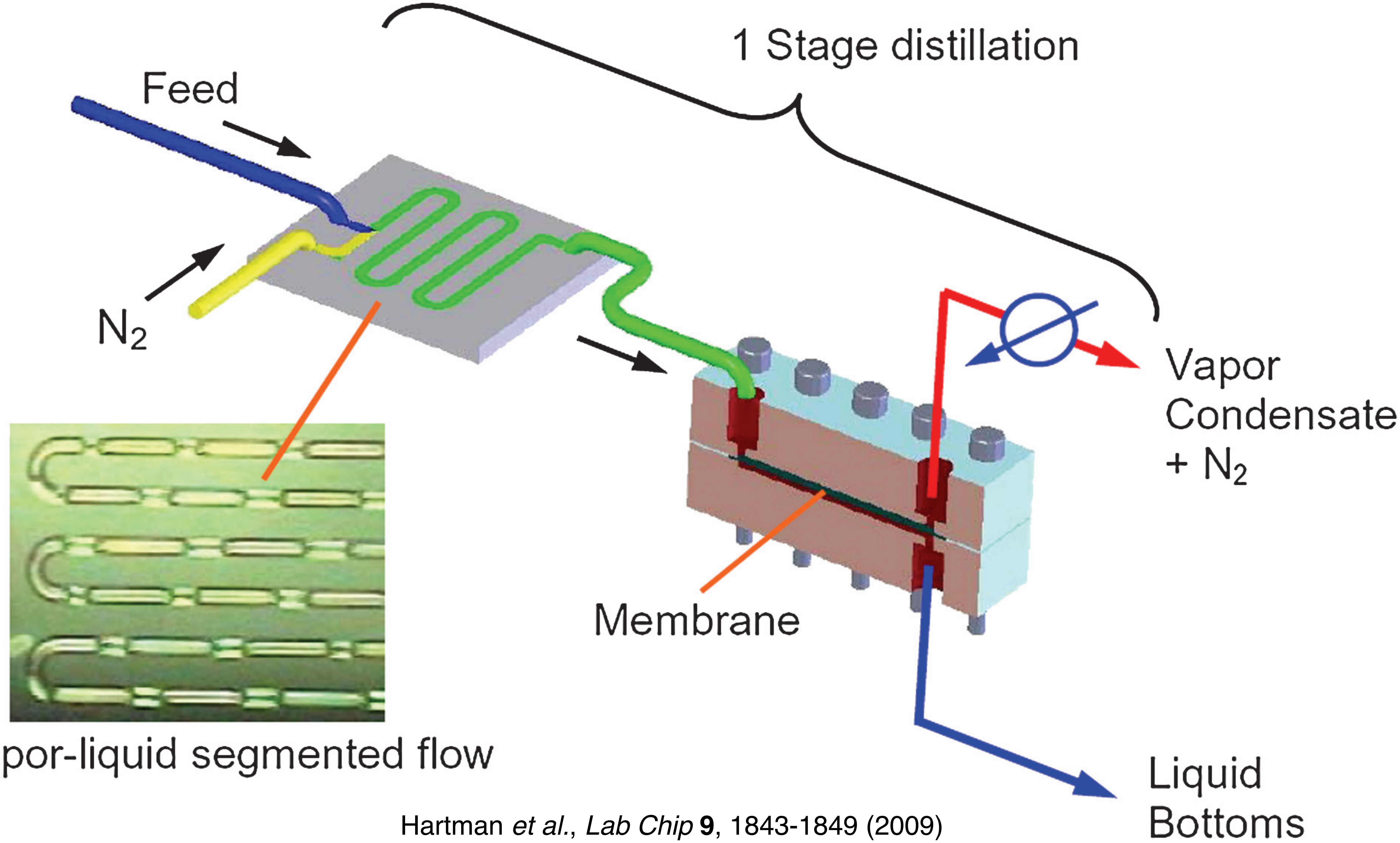
Key idea: Live cells swim across laminar streamlines



Cho *et al.*, *Anal. Chem.* **75** 1671-1675 (2003)

Separation: distillation

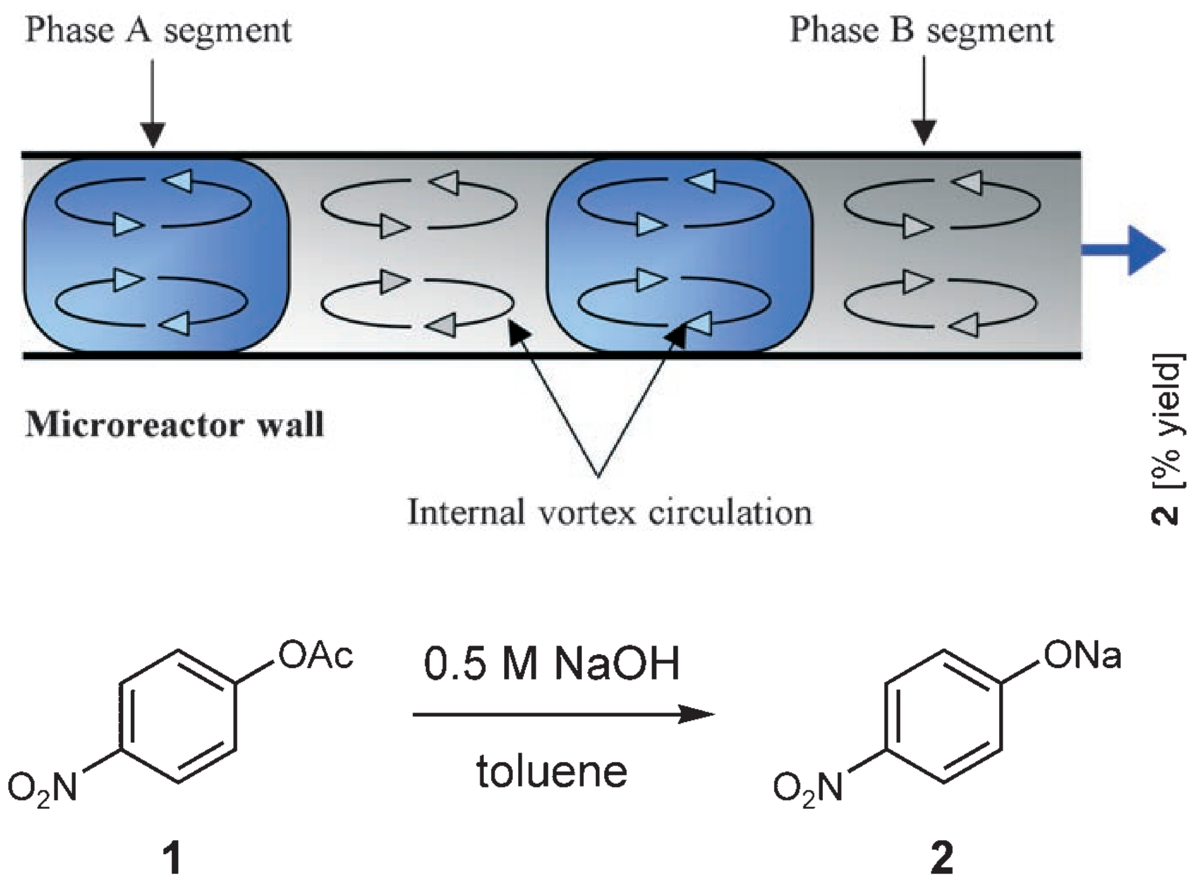
Key idea: Establish vapor-liquid equilibrium in segmented flow and separate vapor using capillary forces

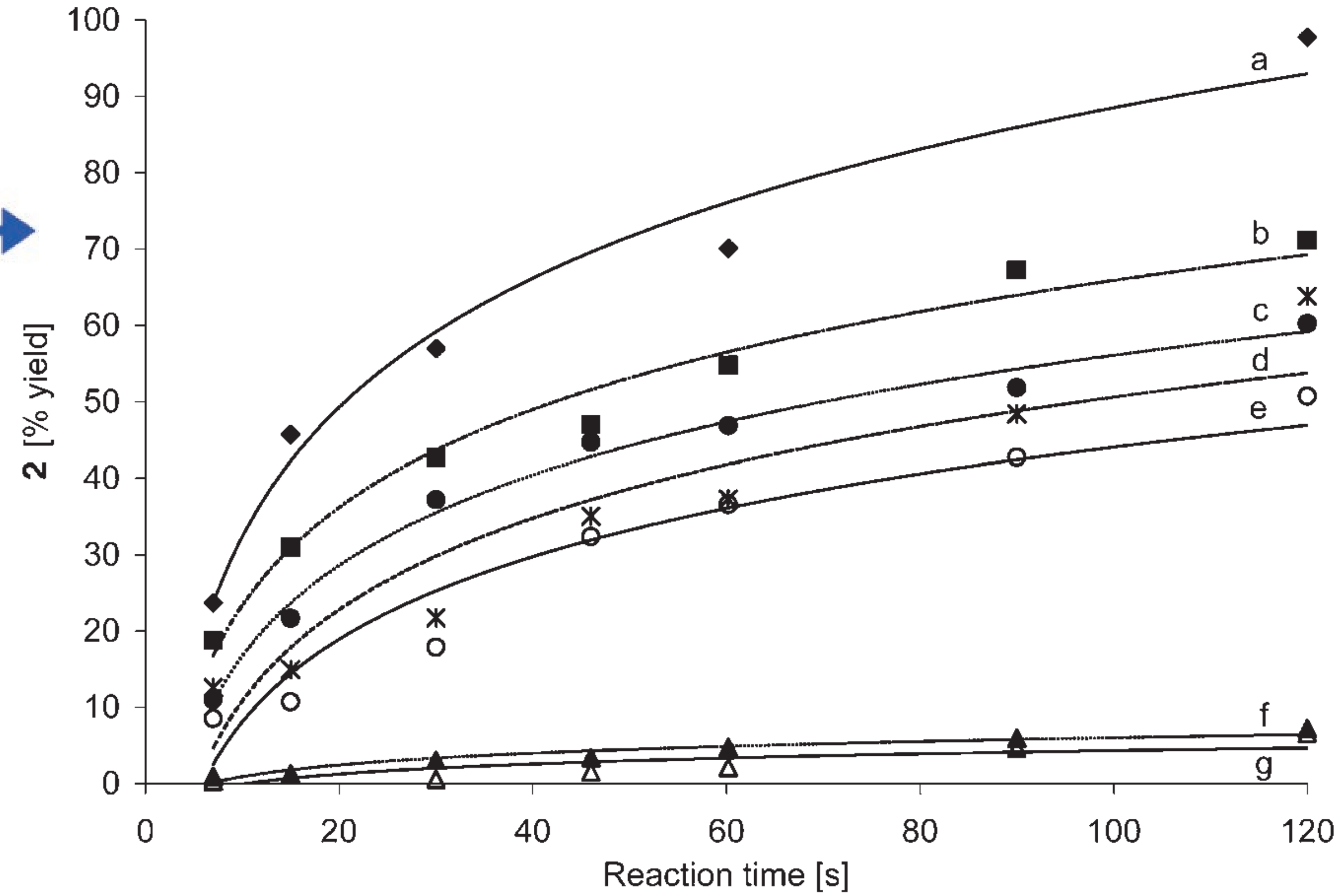


Hartman *et al.*, *Lab Chip* **9**, 1843-1849 (2009)

Reaction: drops as microreactors

<u>Key idea</u>: Drops increase reaction rates by increasing surface-to-volume ratio, reducing diffusion distances, and enhance heat and mass transfer

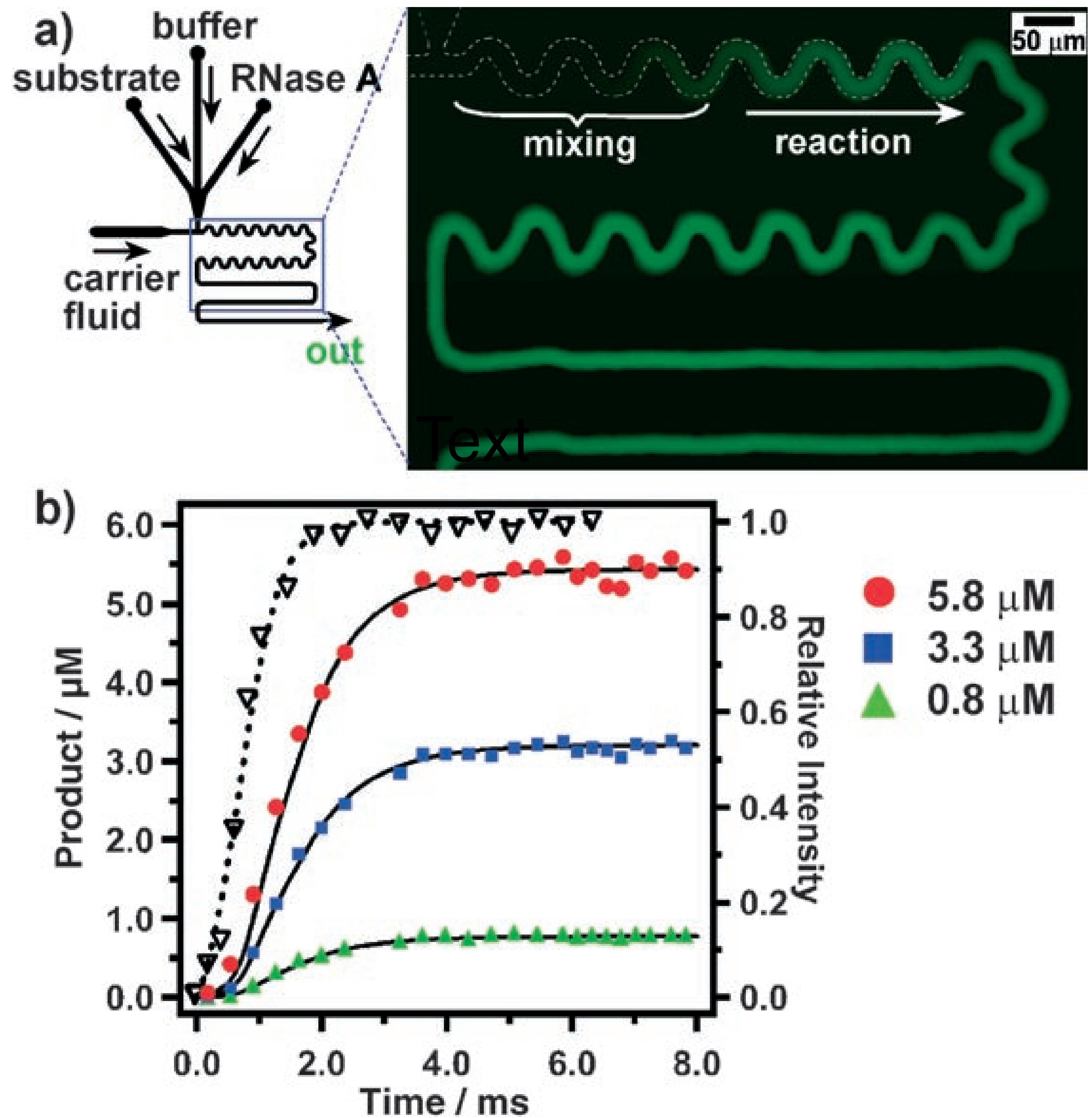




Ahmed *et al.*, *Adv. Synth. Catal.* **348** 1043-1048 (2006)

Reaction: enzyme kinetics

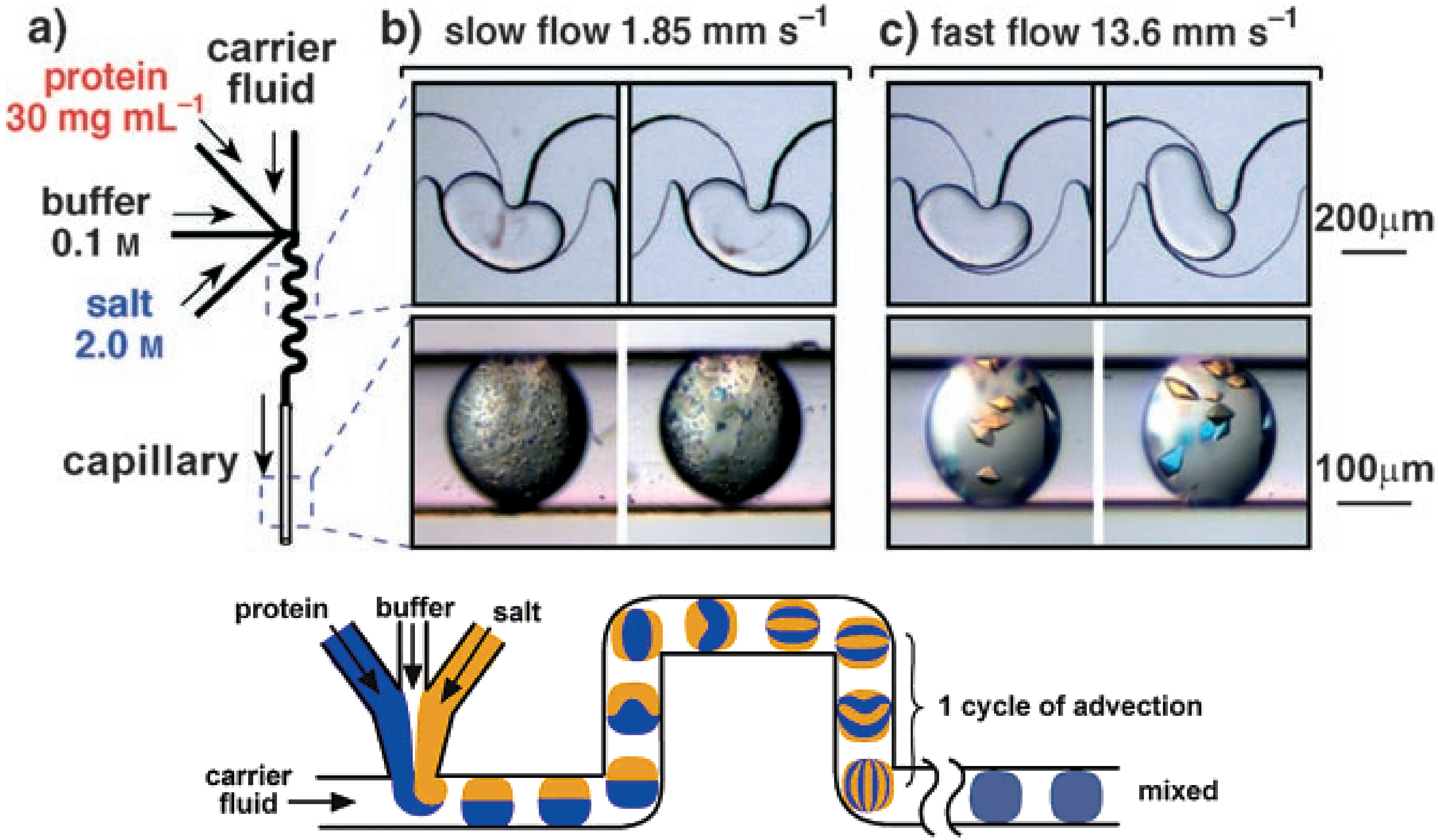
Key idea: Design a droplet-based microfluidic system to extract kinetic parameters of an enzymatic reaction



Song and Ismagilov, *J. Am. Chem. Soc.* **125** 14613-14619 (2003)

Reaction: nucleation

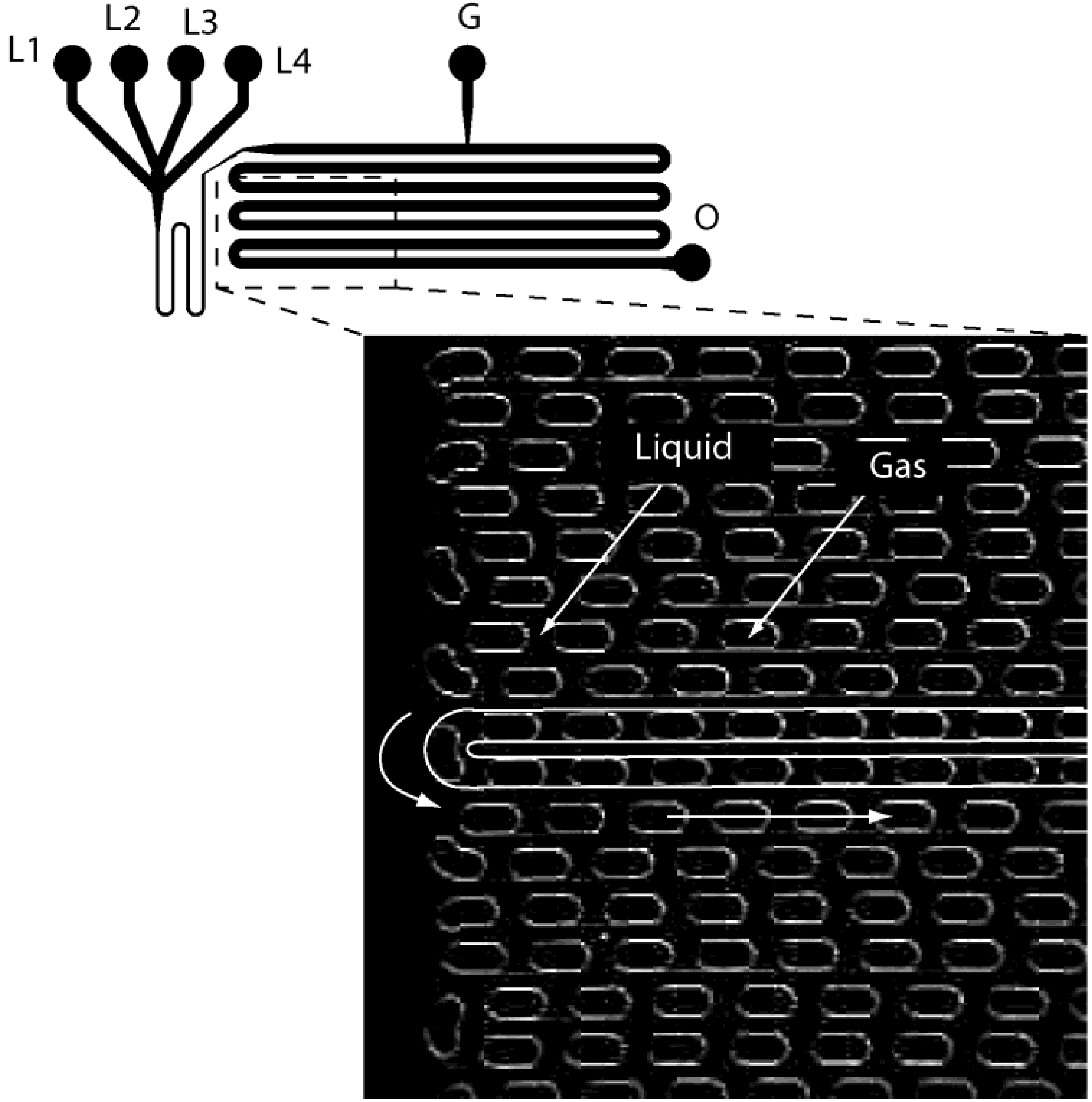
Key idea: Design a droplet-based microfluidic system to study effect of mixing on nucleation of protein crystals

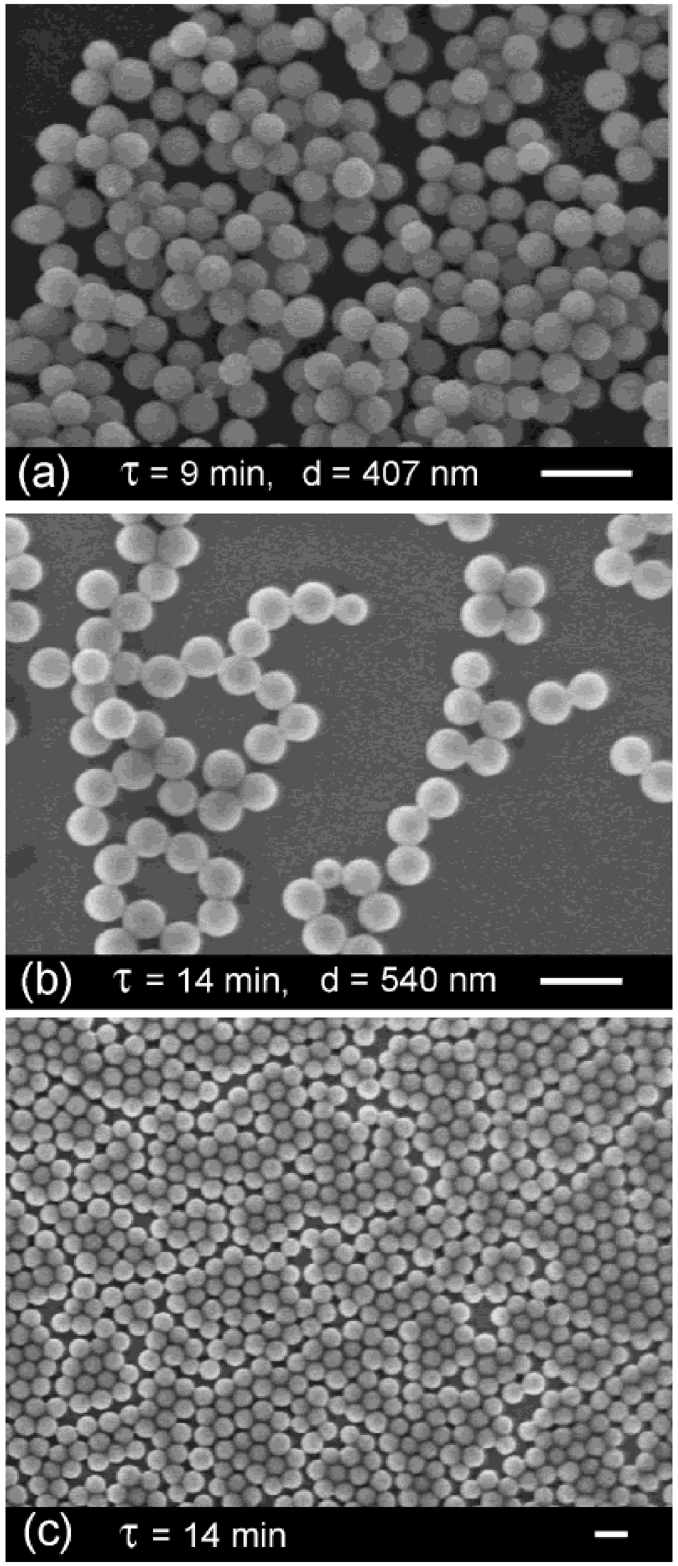


Chen *et al.*, *J. Am. Chem. Soc.* **127** 9672-9673 (2005)

Reaction: nanoparticle synthesis

<u>Key idea</u>: Use of gas slugs to separate small liquid reaction volumes increases the monodispersity of microfluidically-produced particles

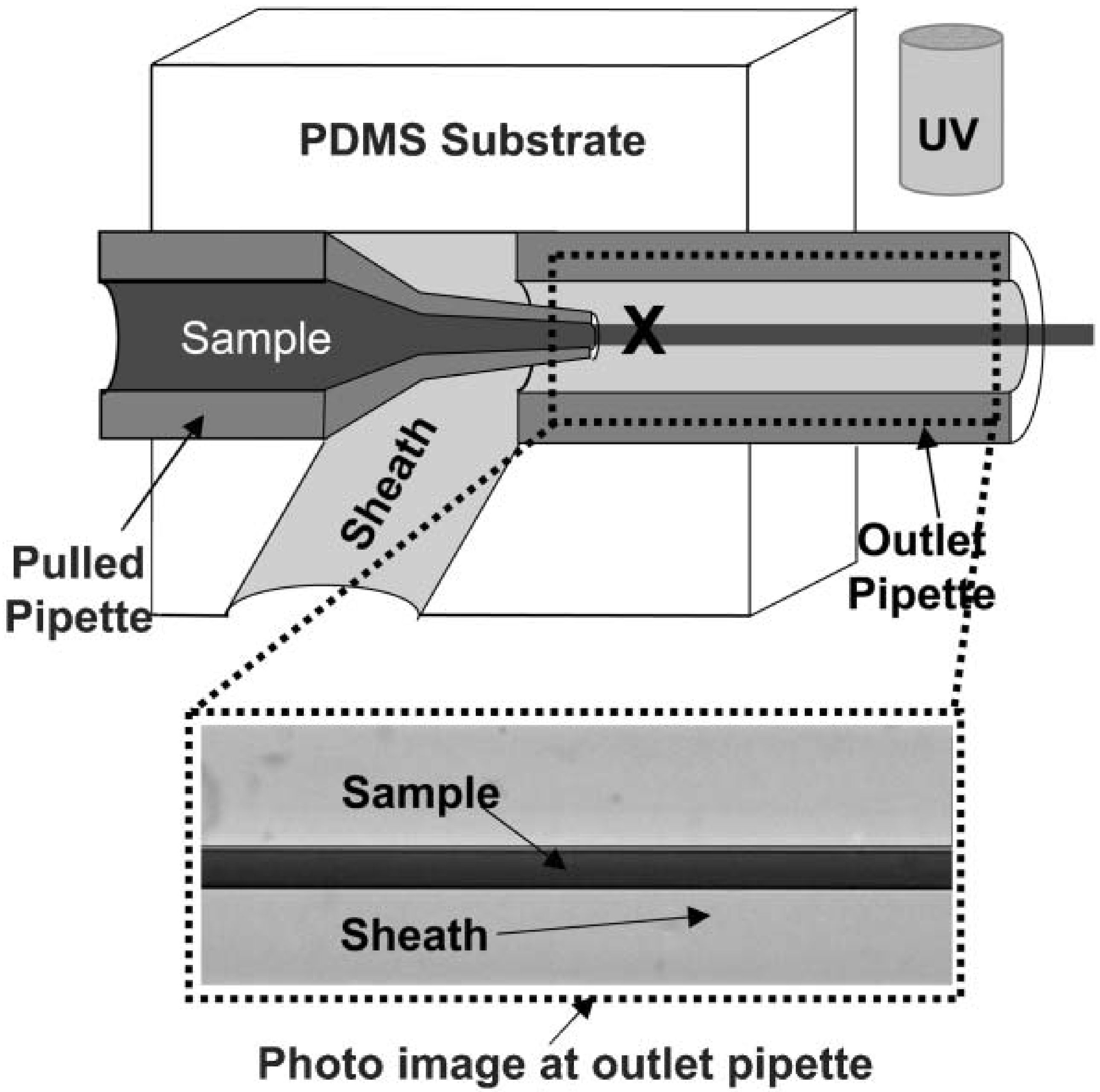


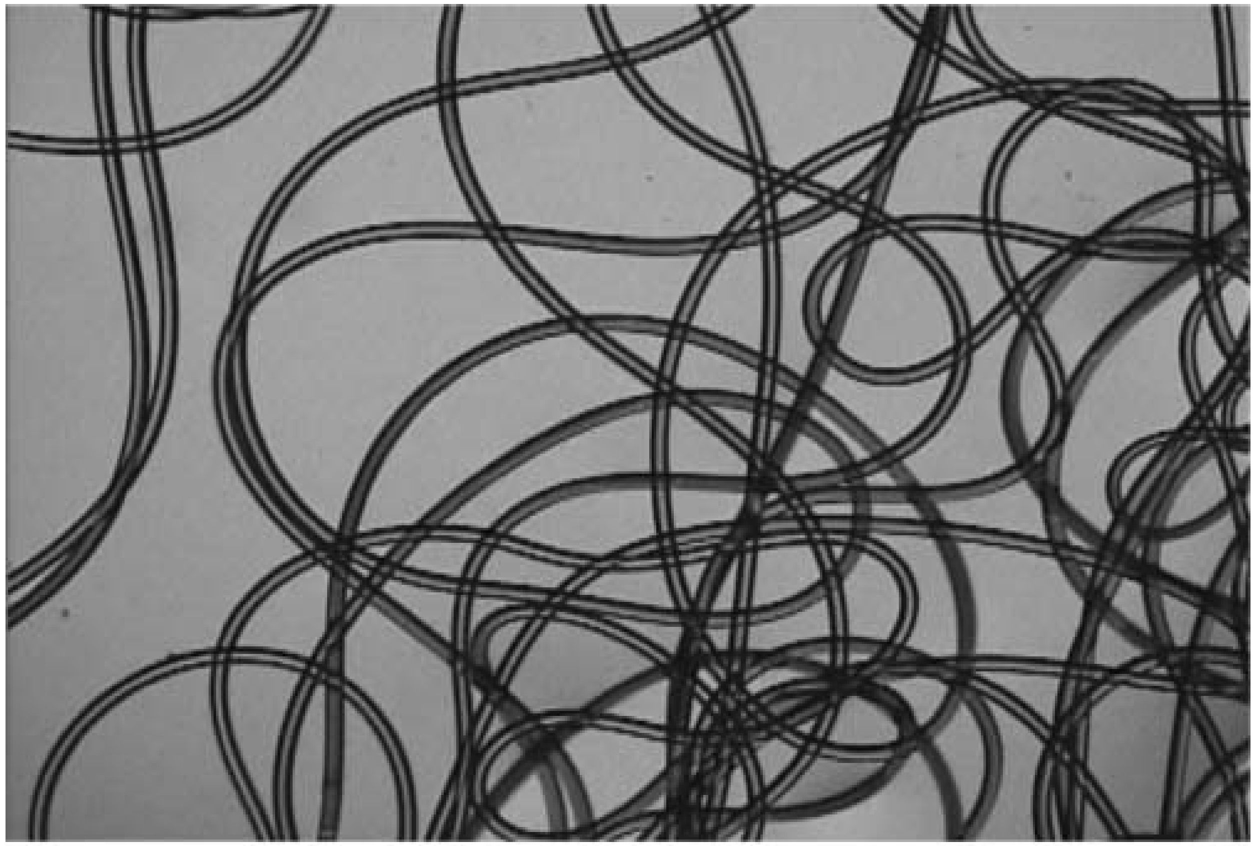


Khan *et al.*, *Langmuir* **20** 8604-8611 (2004)

Reaction: microfiber synthesis

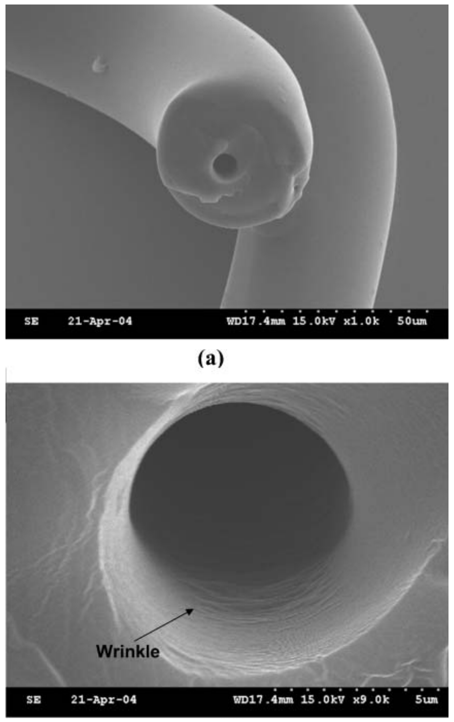
Key idea: Photopolymerize a flow-focused stream “on the fly”





microfibers

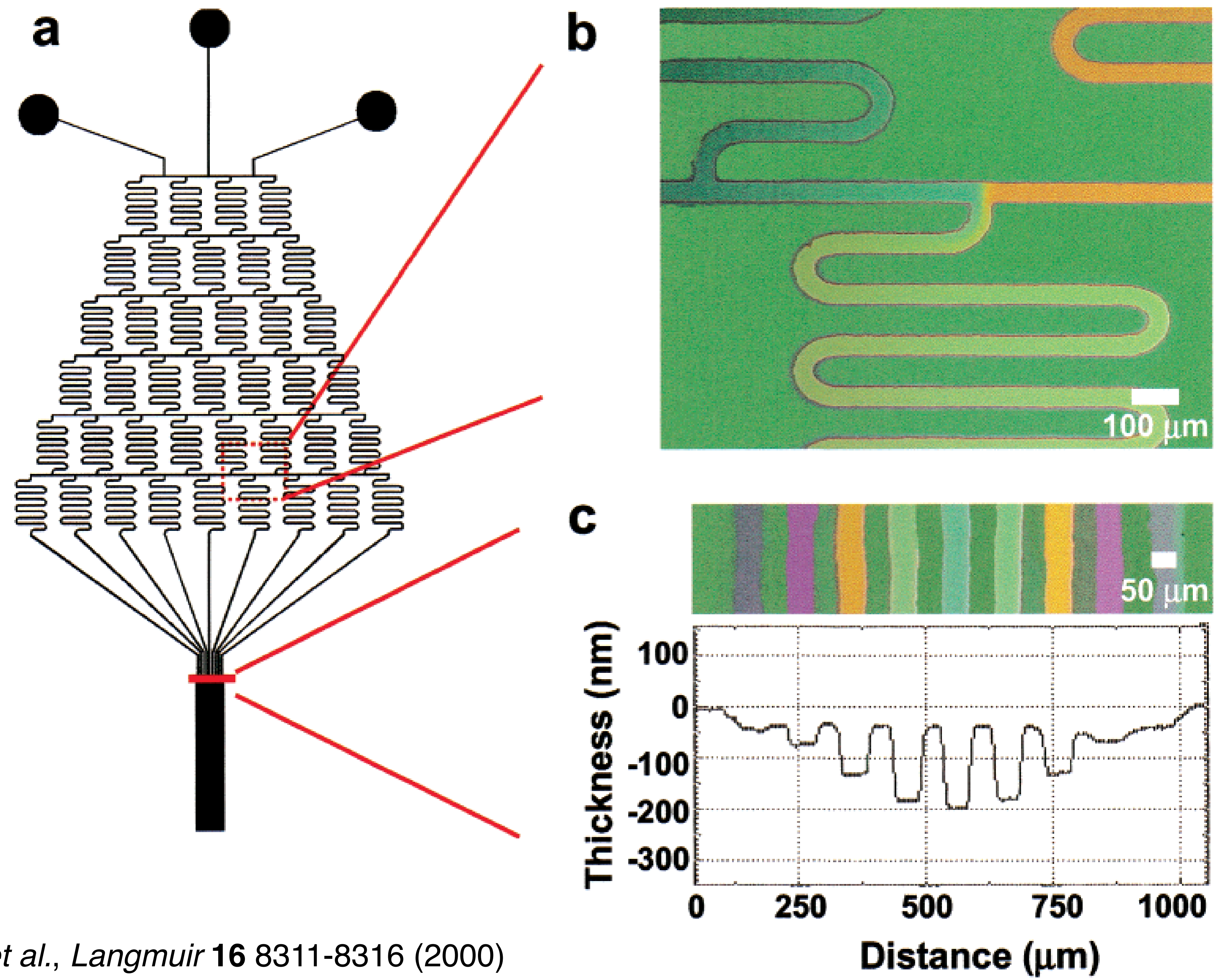
microtubules



Khan *et al.*, *Lab Chip* **4** 576-580 (2004)

Reaction: gradient etching

Key idea: Gradients in reactant composition generate differences in etching rates through a surface

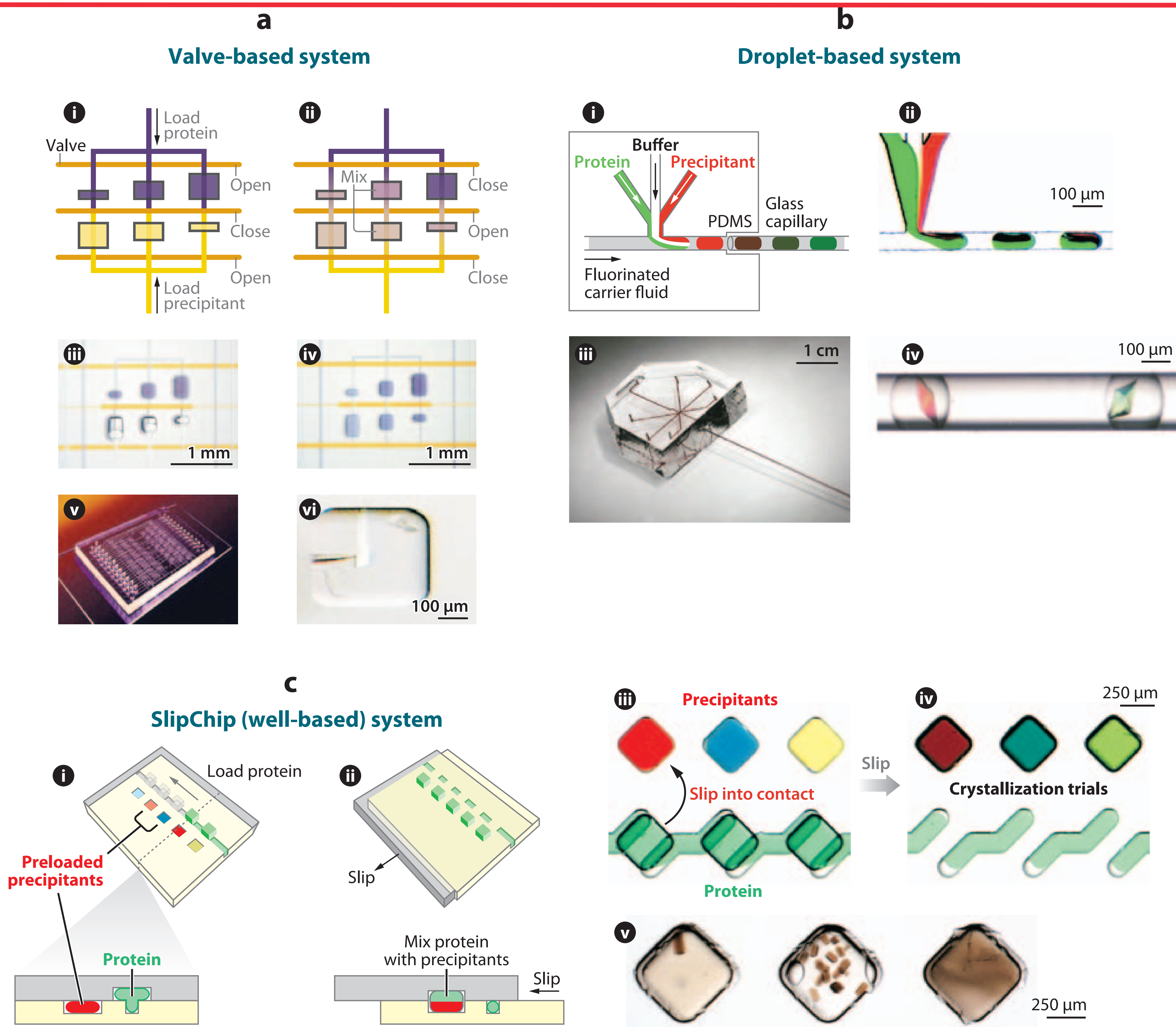


Jeon *et al.*, *Langmuir* **16** 8311-8316 (2000)

Applications of microfluidics

- Chemical synthesis
  - Especially for high-value components
- Controlled release
  - Pharmaceuticals
  - Cosmetics
- Biotechnology
  - Genomics and sequencing
  - Biodetection
  - Directed evolution
- Models of biological processes
  - Microvasculature and veination
  - Chemotaxis and chemical response

Application: crystallization

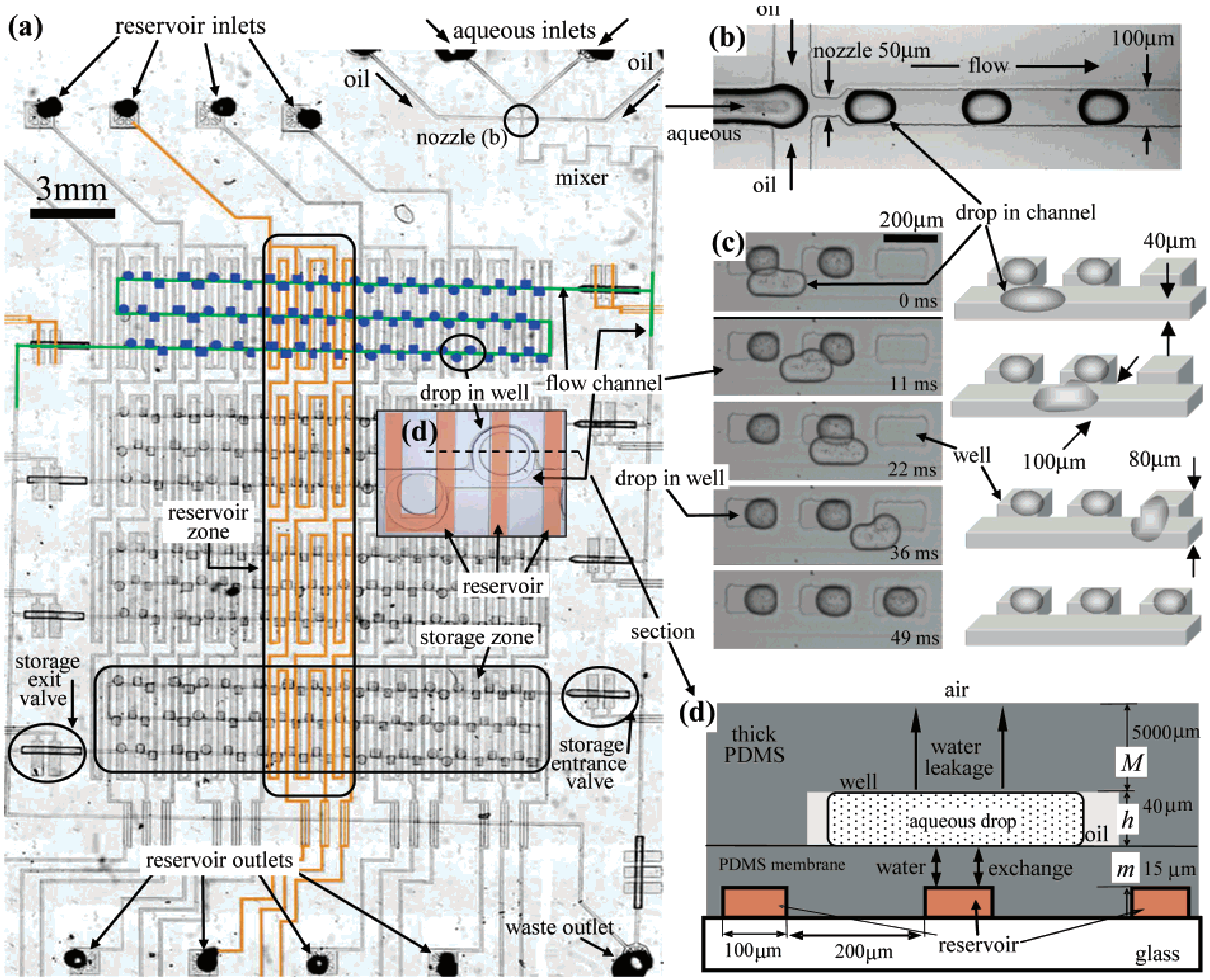


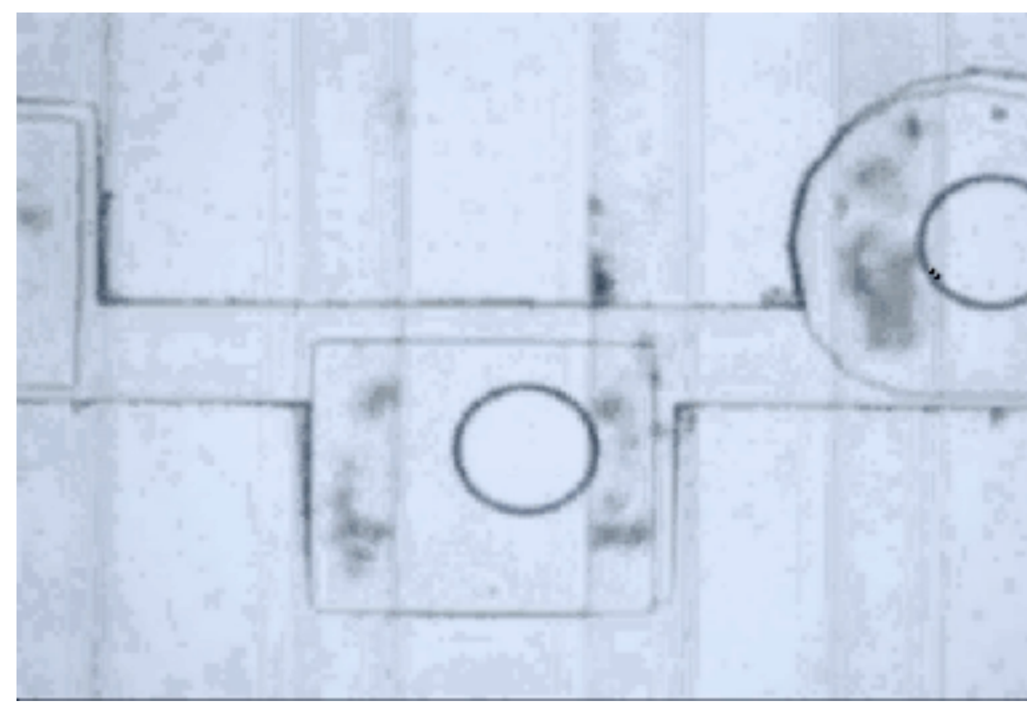
Review article: Li and Ismagilov, *Annu. Rev. Biophys.* **39**, 139-158 (2010)

Protein crystallization in "Phase Chip"

Goal of research: determine conditions and kinetic pathways for crystallization of biological proteins (e.g. xylanase)

<u>Key idea</u>: Change salt concentration "on chip" in an integrated microfluidic device to trigger crystallization



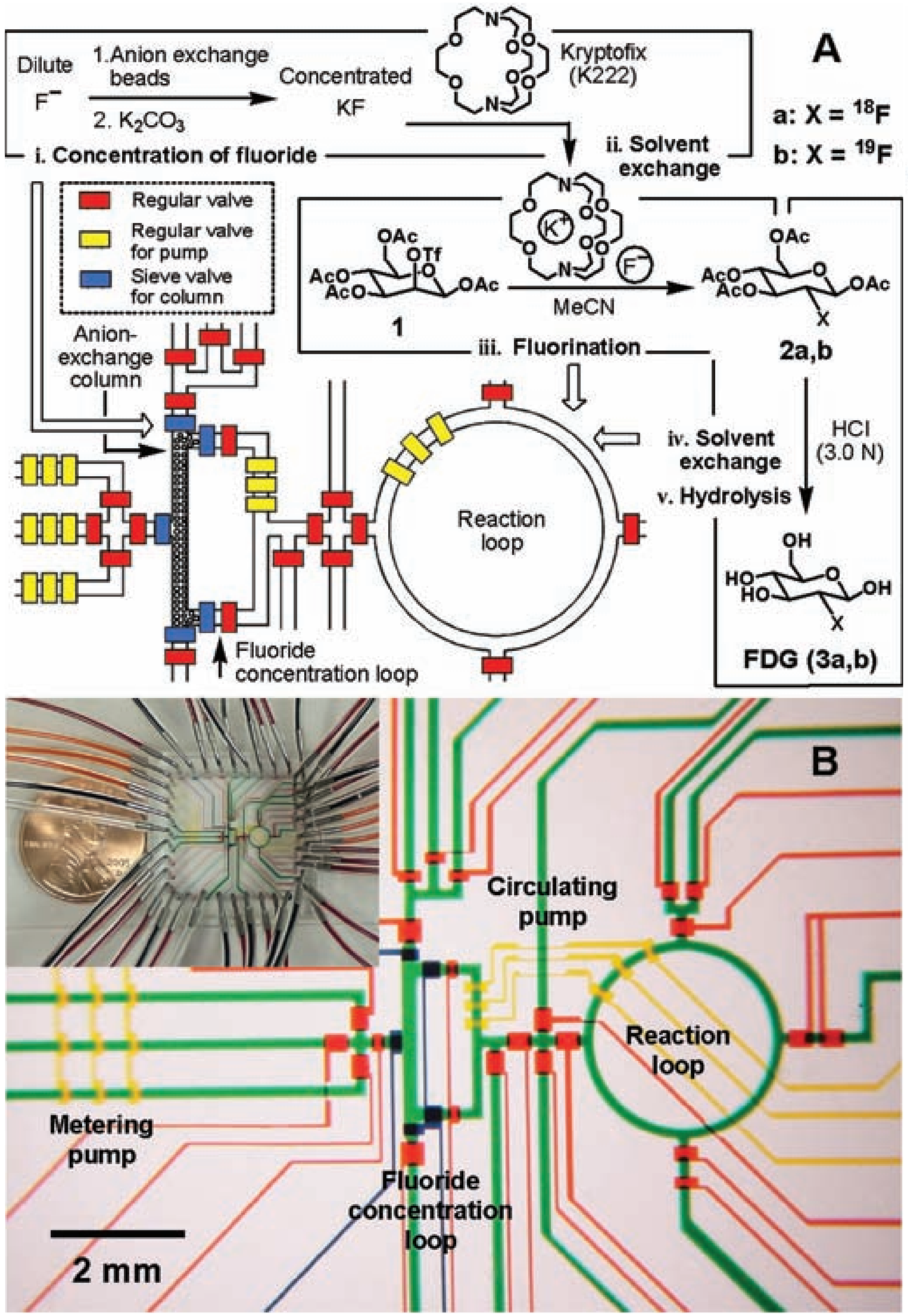


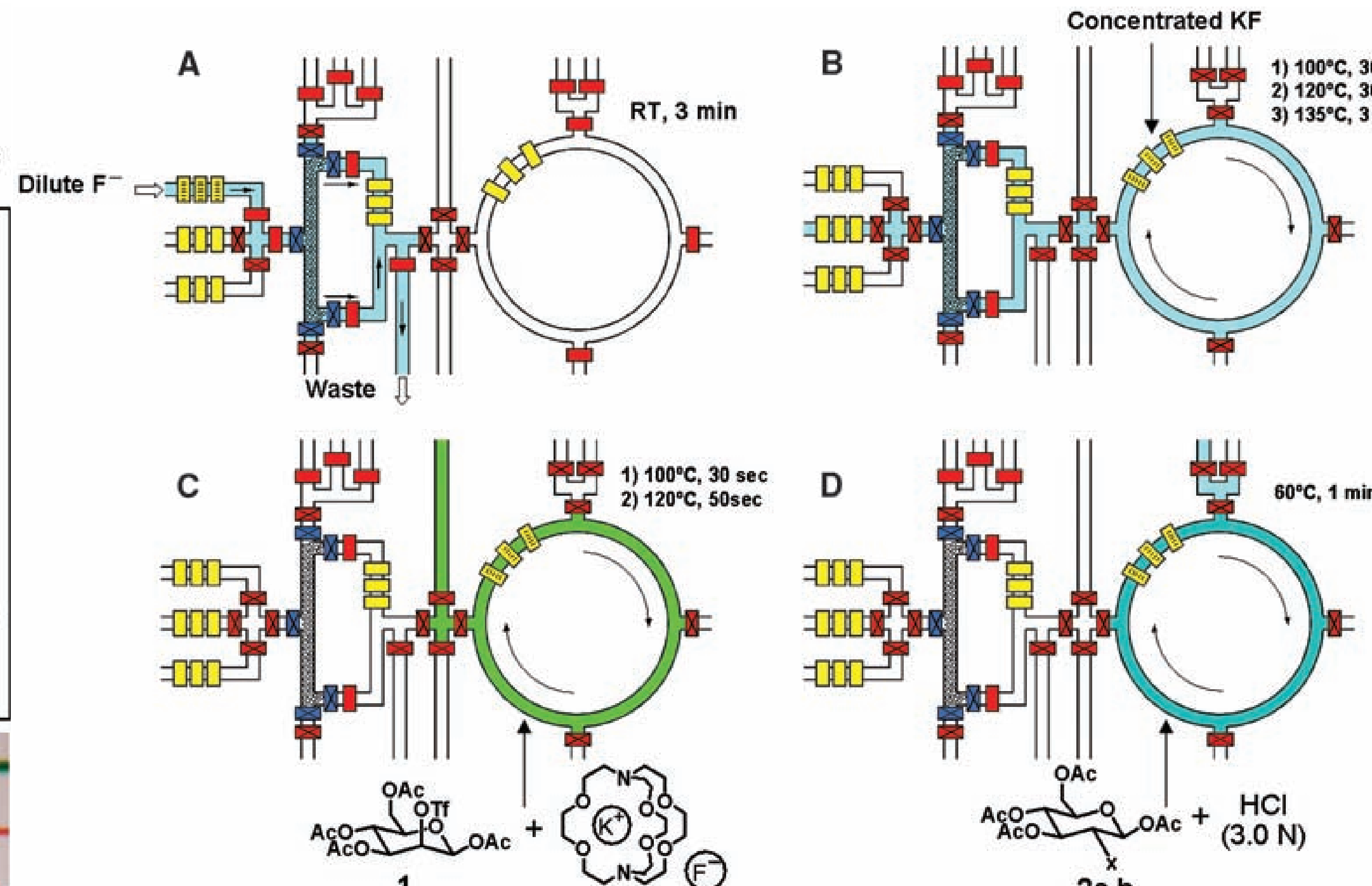
Kim *et al., J. Am. Chem. Soc.* **129**, 8825-8835 (2007)

Application: on-chip multistep synthesis

Goal of research: demonstrate optimized synthesis for sensitive compound

Key idea: Move all operations "on chip" in an integrated microfluidic device





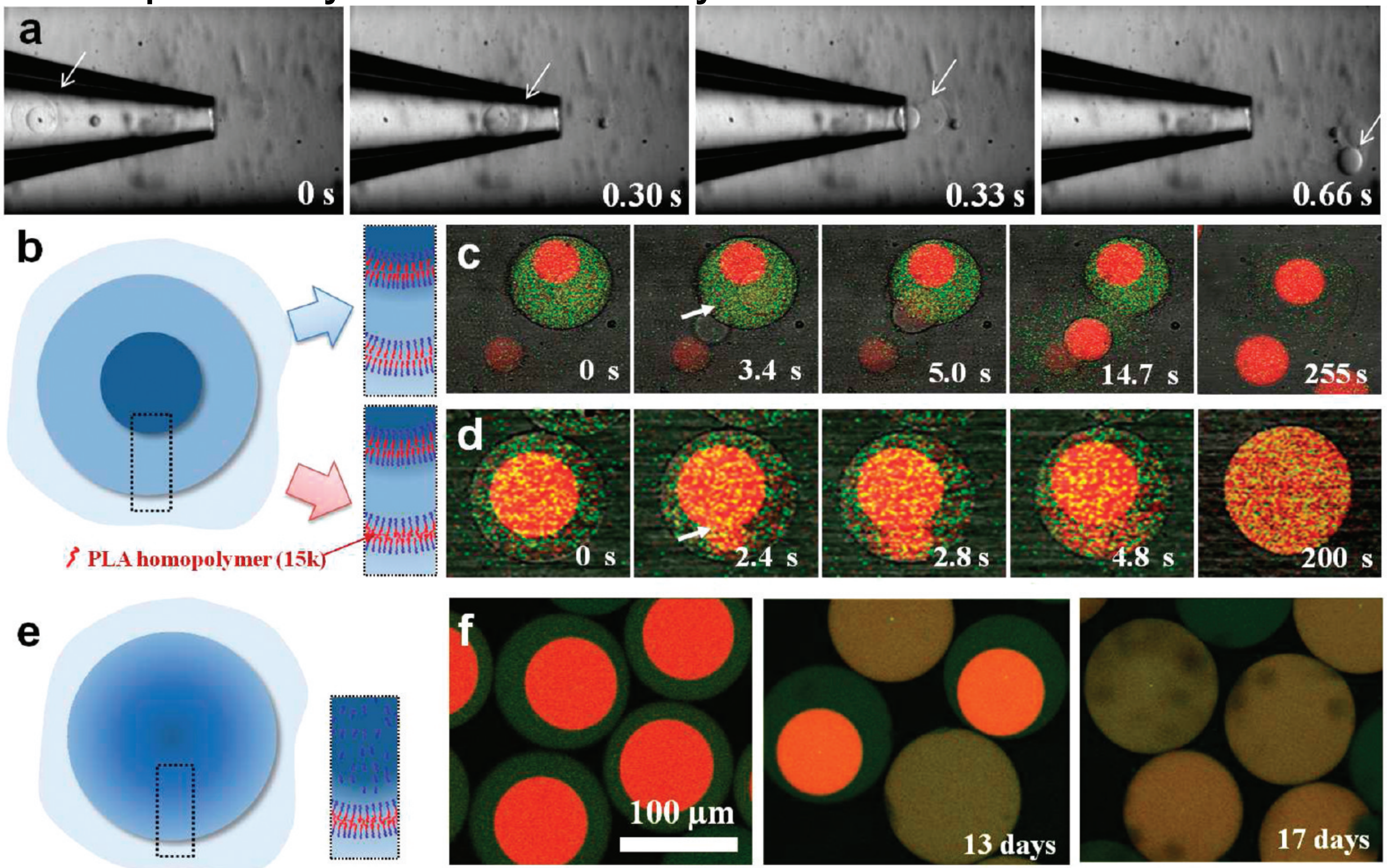
- Microfluidic synthesis increased yield (38%) and purity (97.6%)
- Dramatic increase in time (14 min vs 50 min)

Lee *et al.*, *Science* **310**, 1793-1797 (2005)

Application: programmable release

Goal of research: controllably release multiple components in a pharmaceutical or cosmetic formulation

<u>Key idea</u>: Sequentially dissociate bilayer membranes in a double emulsion



Kim *et al.*, *J. Am. Chem. Soc.* **133** 15165-15171 (2011)

Commercialized technology: Capsum

Capsum (France) markets encapsulation technologies to luxury cosmetics manufacturers such as Amore Pacific (Korea)

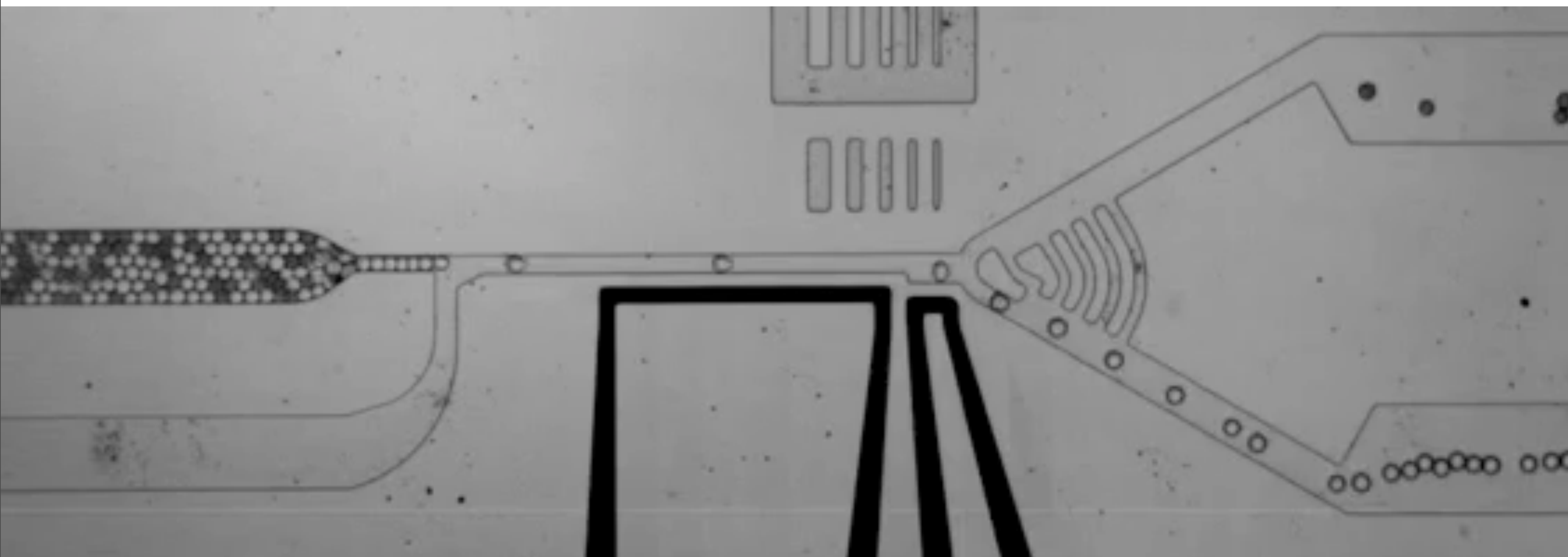

capsum.eu

amorepacific.com

Application: directed evolution

Goal of research: identify mutants of horseradish peroxidase enzyme with higher catalytic activity

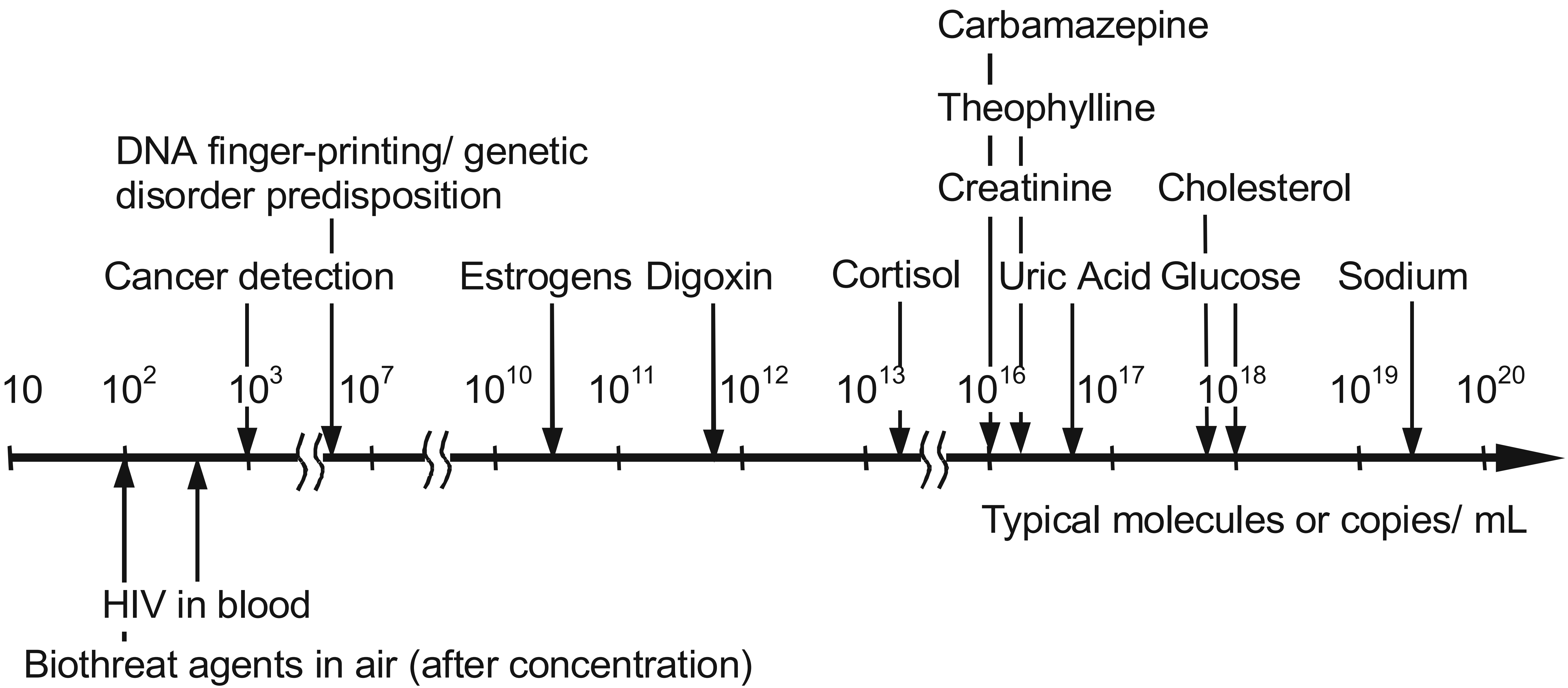
<u>Key idea</u>: Use ultrahigh throughput screening to remove inactive mutants



Agresti *et al.*, *Proc. Natl. Acad. Sci. USA* **107** 4004-4009 (2010)

- 108 enzyme reactions screened in 10 h (1,000× faster)
- Sample volume: < 150 μL of reagent (1,000,000× cheaper)

Diagnostics: typical analyte concentrations

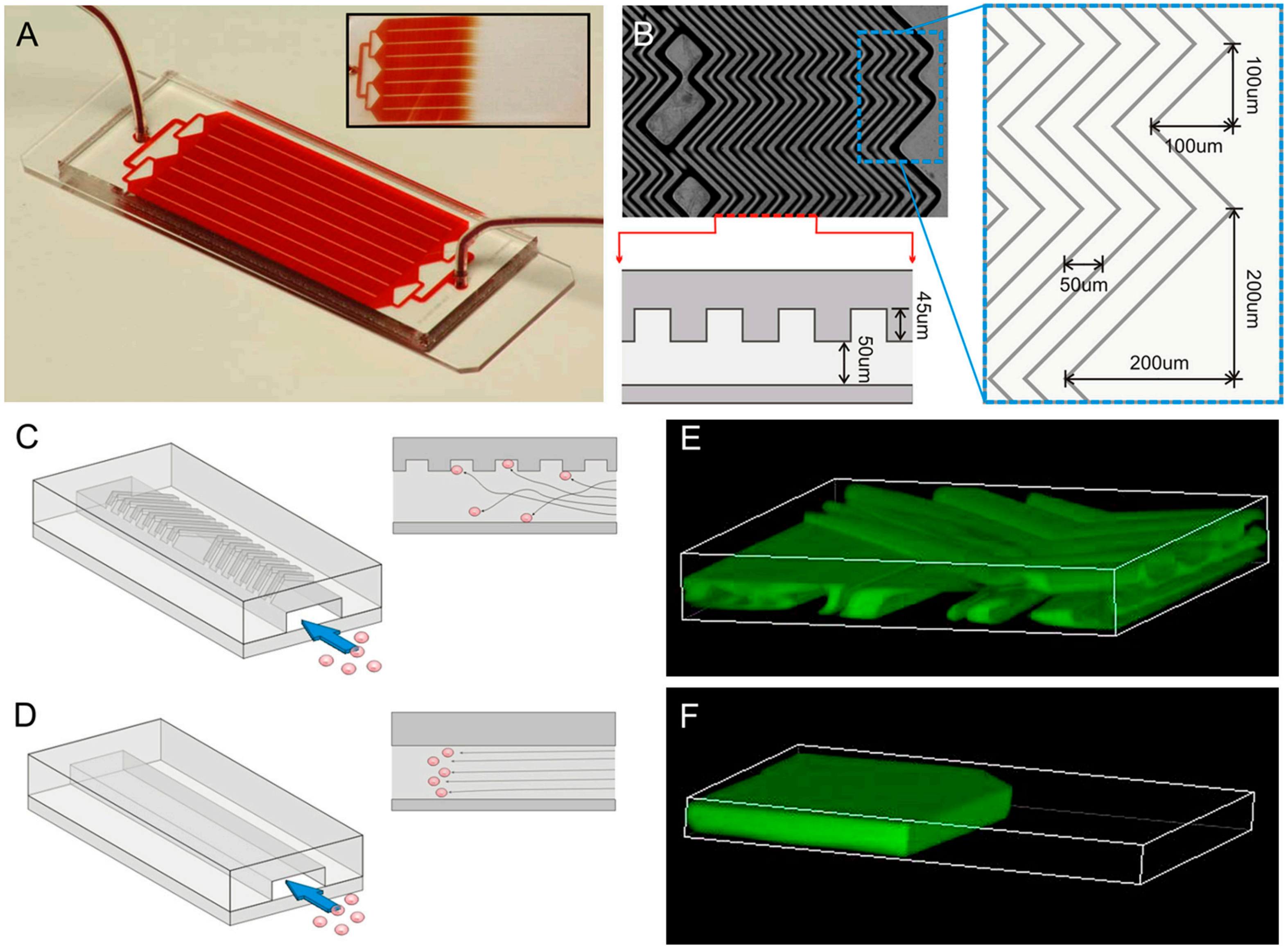


Nguyen and Wereley, *Fundamentals and Applications of Microfluidics*, 2nd ed. (2006)

Application: cancer detection

Goal of research: capture rare circulating tumor cells (CTCs) in patients' bloodstreams for cancer detection and monitoring

<u>Key idea</u>: Increase surface encounter rate using chaotic advection



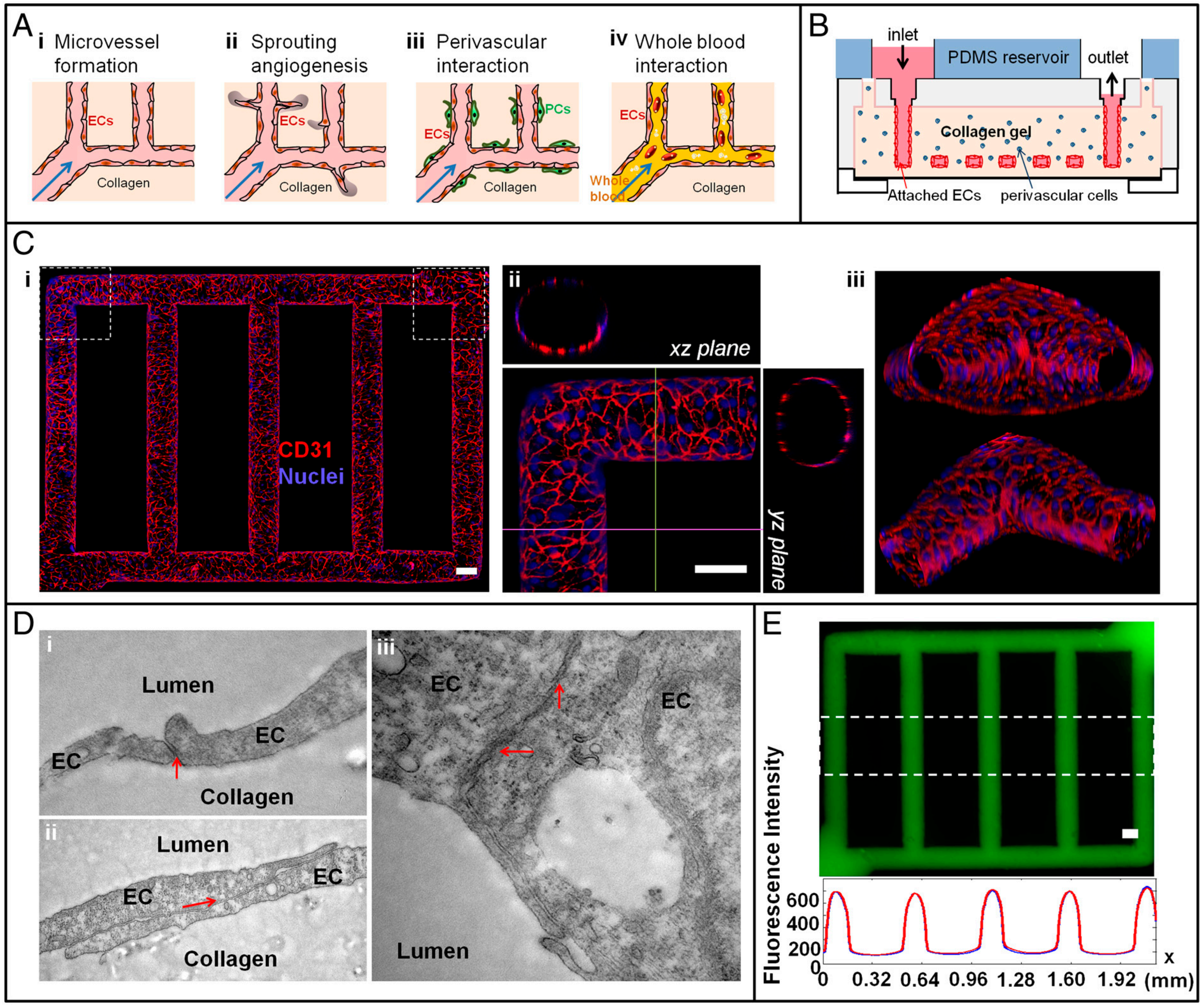
- Cancer cells detected at ~400 CTCs/mL
- Imaging-based platform identified new CTC clusters

Stott *et al.*, *Proc. Natl. Acad. Sci. USA* **107** 18392-18397 (2010)

Application: tissue engineering

Goal of research: model complex vascular phenomena, including angiogenesis and thrombosis

Key idea: Use microfluidic channels as a model for microvasculature

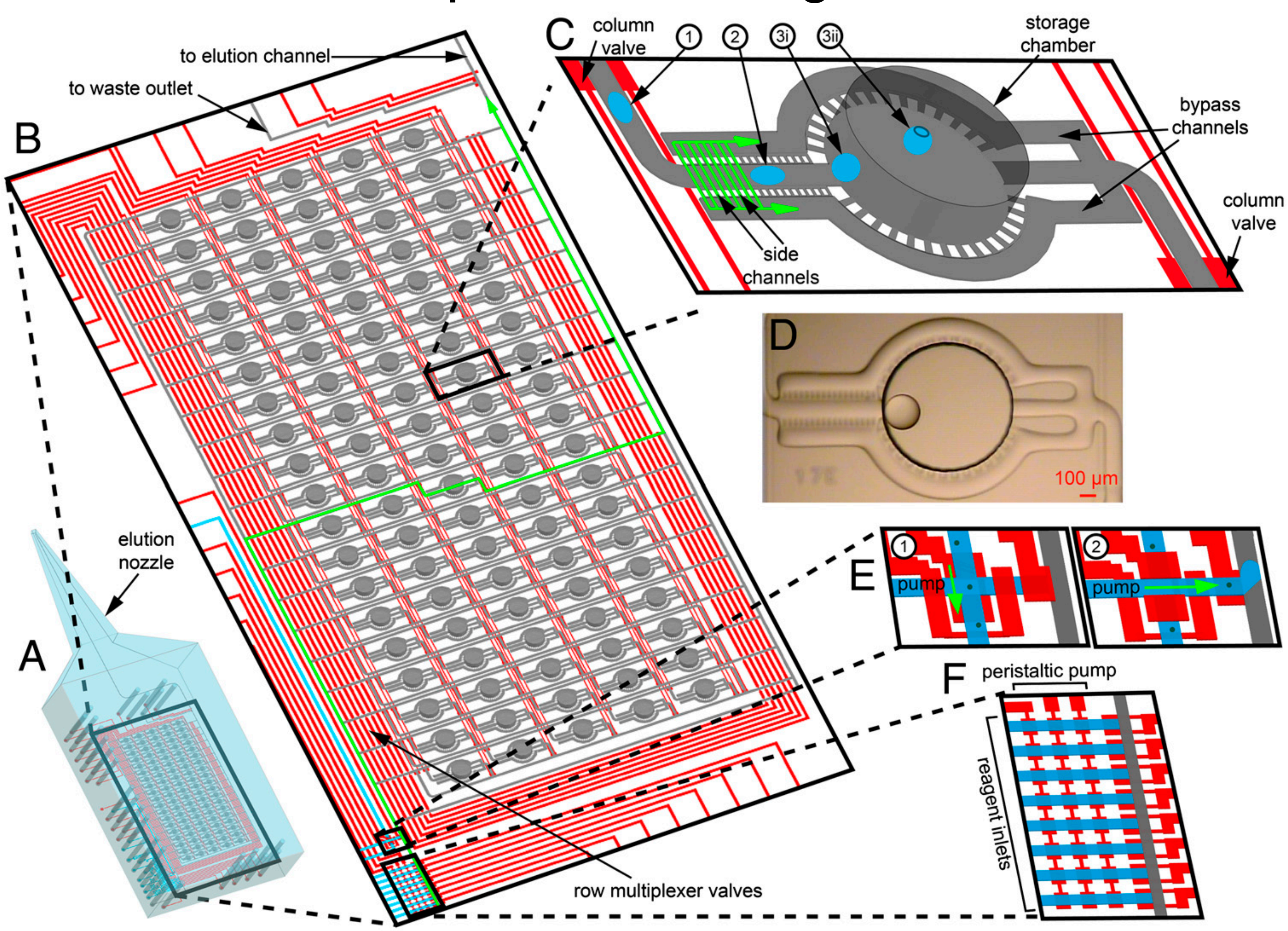


Zheng *et al.*, *Proc. Natl. Acad. Sci. USA* **109** 9342-9347 (2012)

Application: whole genome sequencing

Goal of research: analyze genome of single cells and microbial consortia without sample contamination

Key idea: Create multiplexed chip to sort, cultivate cells and identify, amplify, and sequence whole genomes

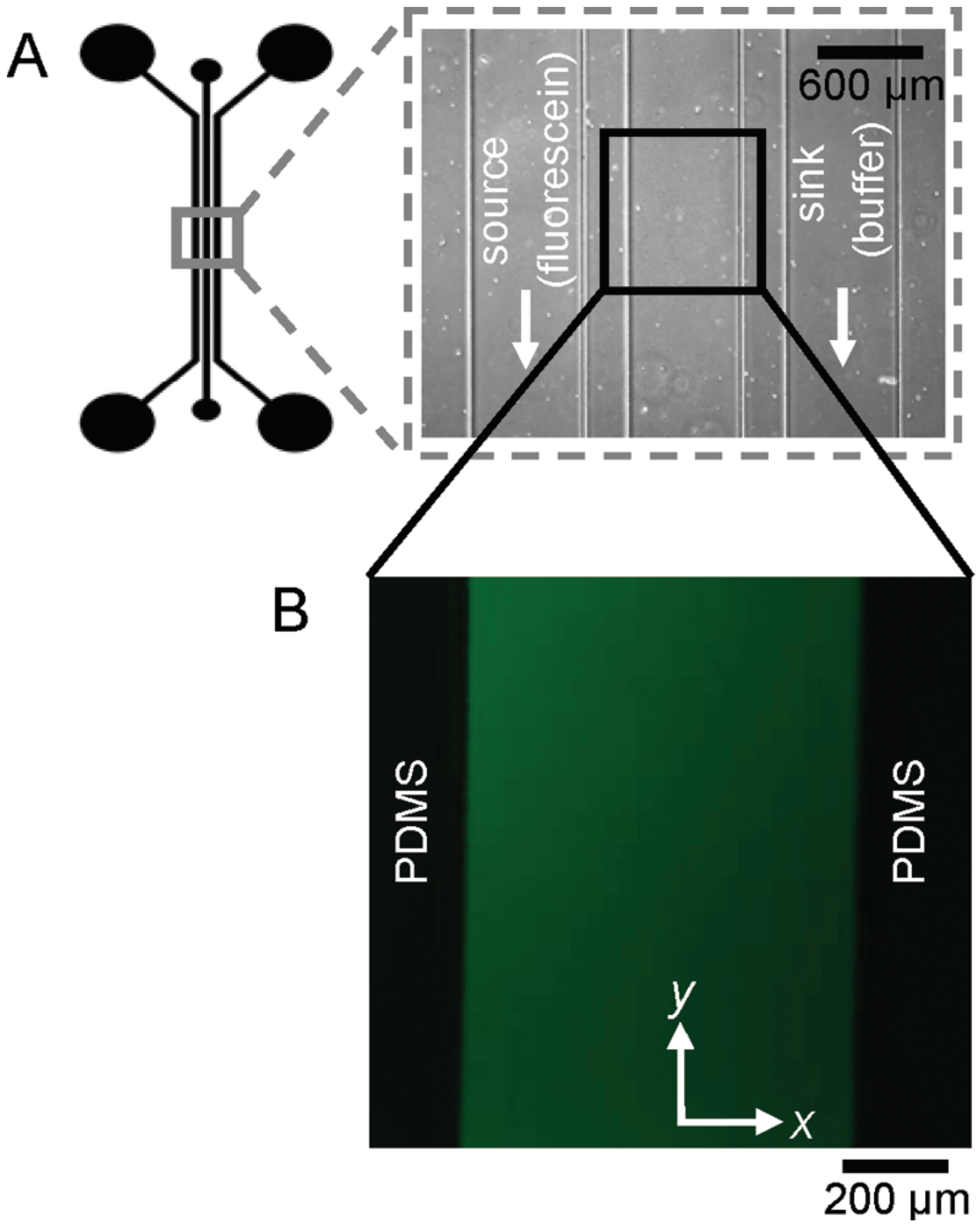


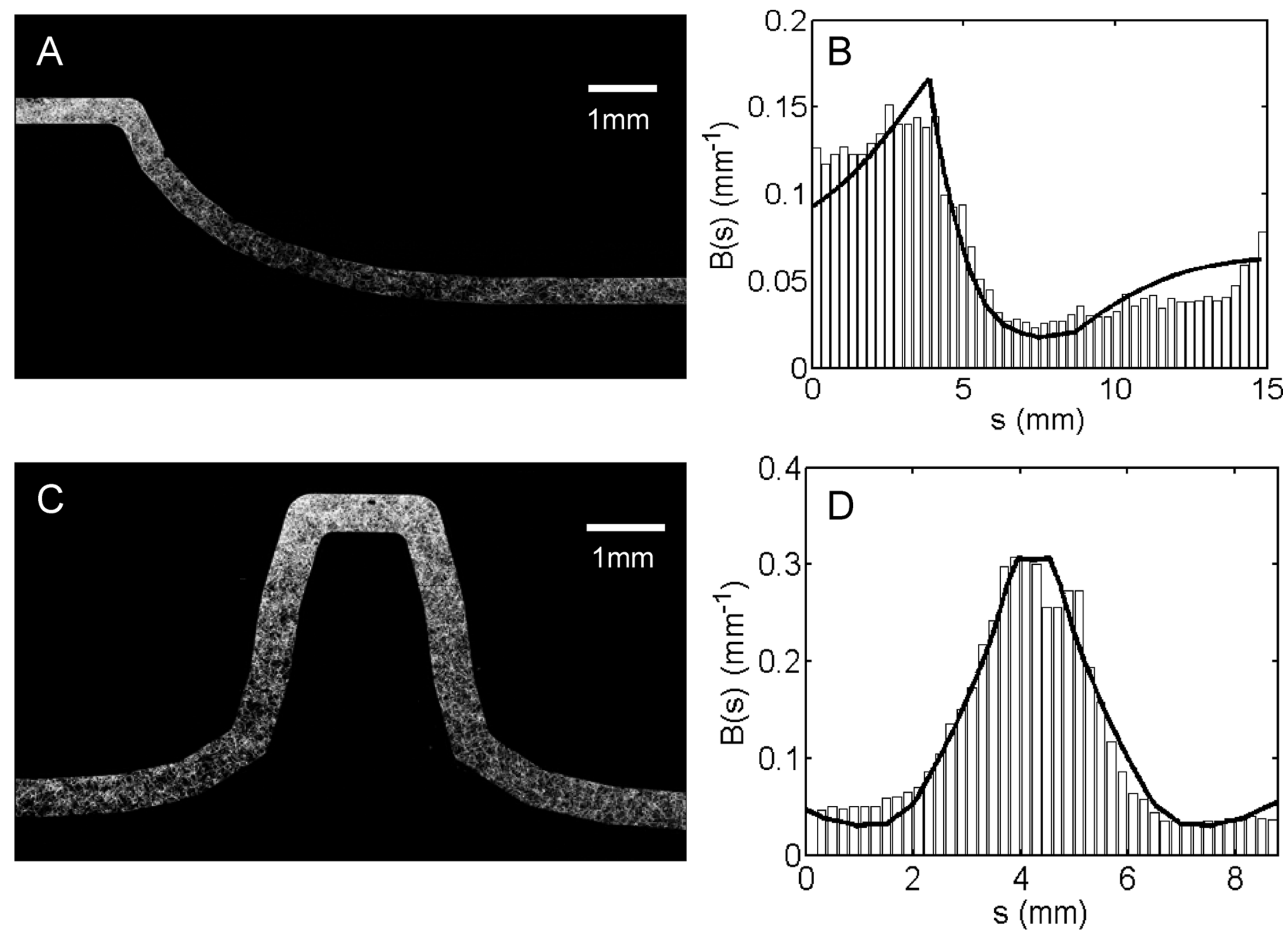
[53] Leung *et al.*, *Proc. Natl. Acad. Sci. USA* **109** 7665-7670 (2012)

Application: chemotaxis

Goal of research: study the motion of bacteria and/or mammalian cells in response to chemical signals

Key idea: Use gradient generators to control the (nonlinear) spatial concentration of chemoattractant





Ahmed *et al.*, *Nano Lett.* **10** 3379-3385 (2010)

Challenges

- Scale-up
  - Transition from “lab scale” devices to plant-scale operations
  - 2-d to 3-d layouts
- Interplay between parallelized chips
  - Need to generate uniform flow across multiple devices
  - Synchronization and chaotic effects
- Clogging and unsteady flow

Summary of lecture

- Microfluidics enables mini “chemical plants”
  - Exceptional control over reactions and mixing
  - Naturally achieves continuous production
- Optimal usages of microfluidic devices:
  - Specialty chemicals and high-value chemicals
  - Hard-to-produce molecules (especially biomolecules)
- Industries impacted by microfluidics
  - Biotechnology: genome sequencing, protein crystallization
  - Chemical synthesis: radiolabeled molecules
  - Manufacturing: designer specialty cosmetics
- Opportunities abound for chemical and biomolecular engineers to design new microfluidic processes