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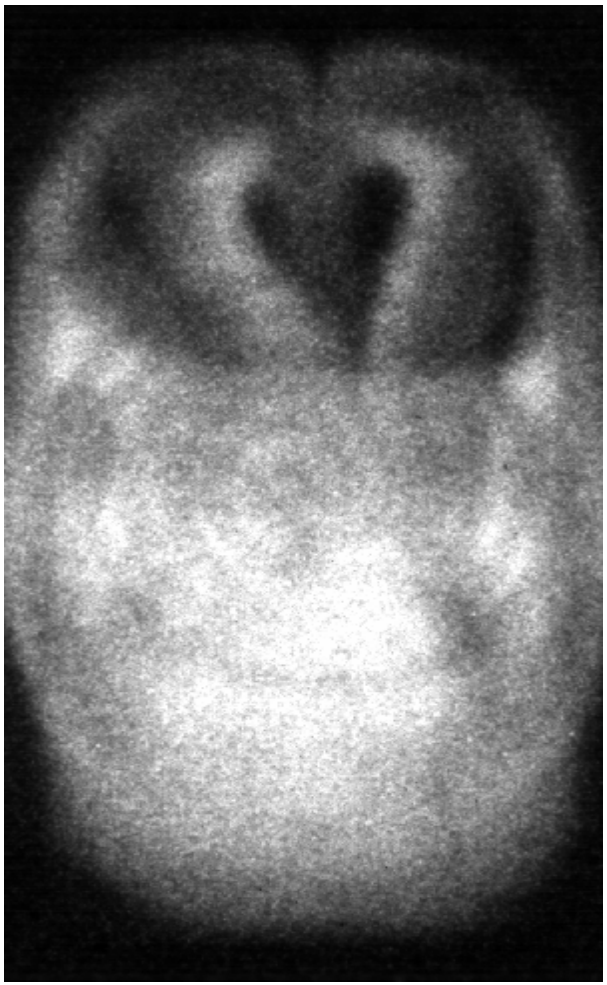
Chemistry with Droplets



Han Gardeniers
MESA+ Institute for Nanotechnology
University of Twente

Summer School in Nanofluidics
ICTP, Trieste, Italy

A challenge in synthetic chemistry research

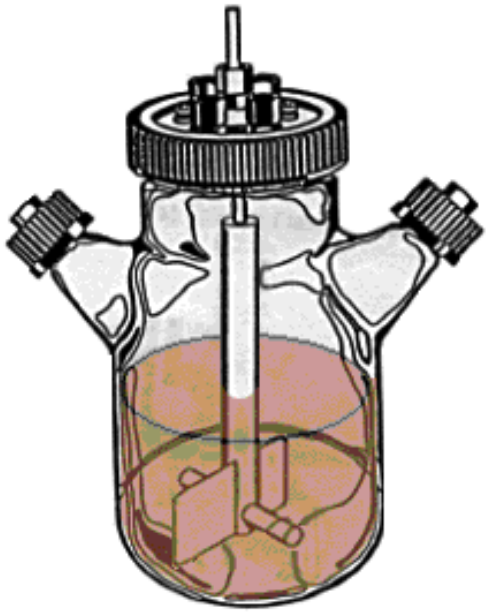
- In e.g. pharmaceutical research, there is a need to screen many many different chemical substances for their activity

- Down the line of medicine development, the production process for selected substances has to be optimized
- To save resources and the environment the volume of reactants, solvents and waste should be minimized

- So there is need for performing chemical reactions at as many different conditions as possible, in parallel, in small volumes.

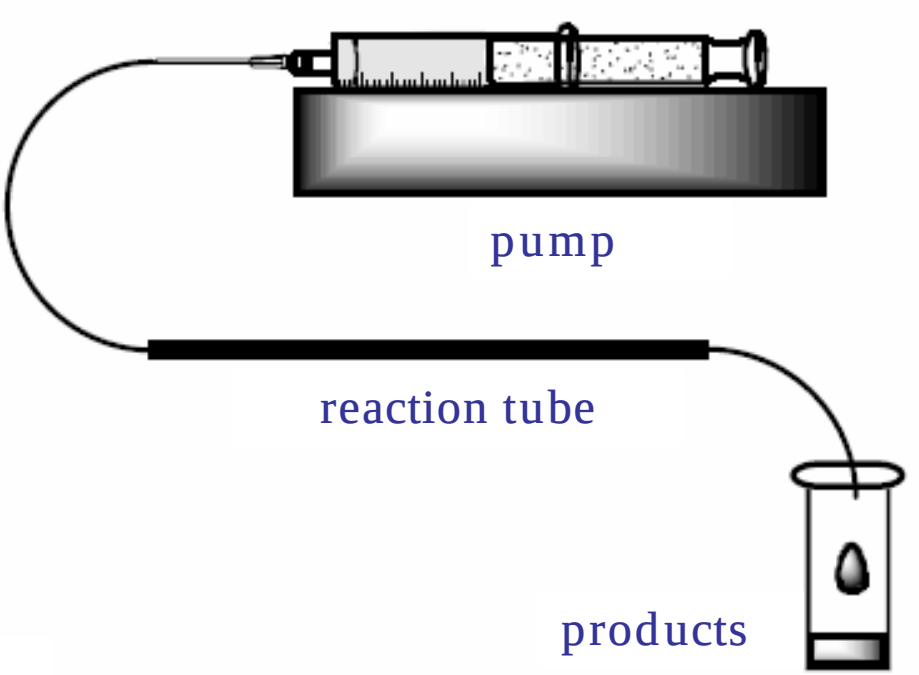
Basic reactor designs

batch

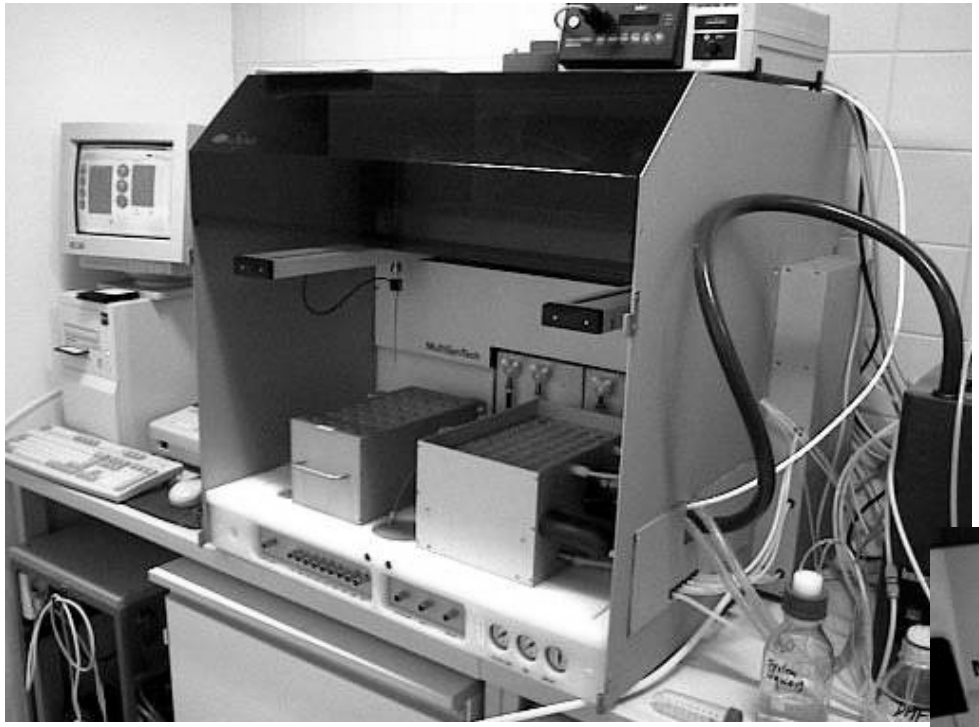


stirred continuously
products collected at end of proces

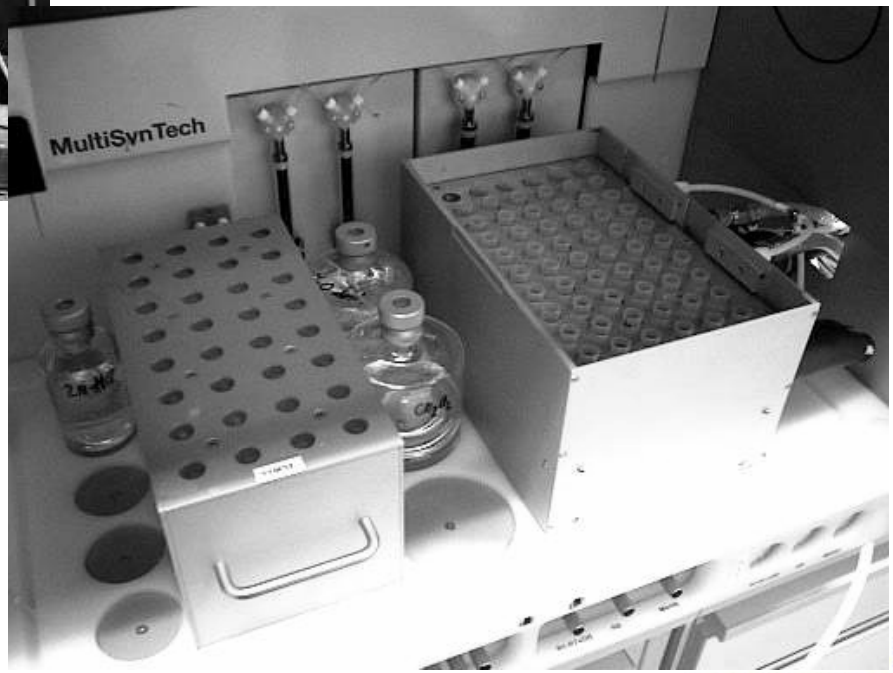
continuous flow



Small batch reactors in parallel



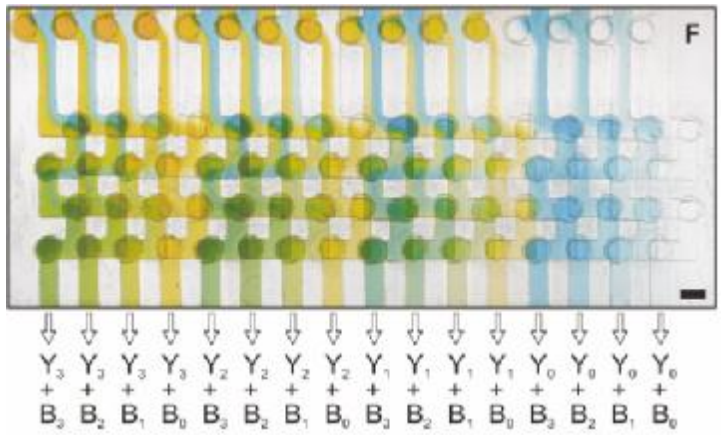
Synthesis Robot:
-Combination of Software and Hardware
-Reaction Block: -40 to 150°C, Filtration, Washing
-Programmed stirring
-Inert Gas / Vacuum / Pressure
-Fluid Handling

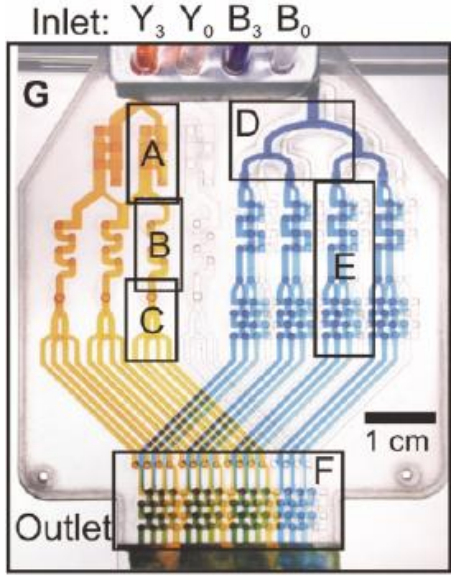


Chip-based microreactors

- complex microfluidic networks (e.g. for concentration series***)
- dangerous reaction conditions (high temperature, high pressure, toxic or explosive chemicals) can be tested safely because of small volumes and high heat transfer rates
- resources and waste are reduced
- a high surface-to-volume ratio helps when phase transfer or heterogeneous catalysis is involved

***





C. Neils e.a., Lab Chip 4, 2004, 342

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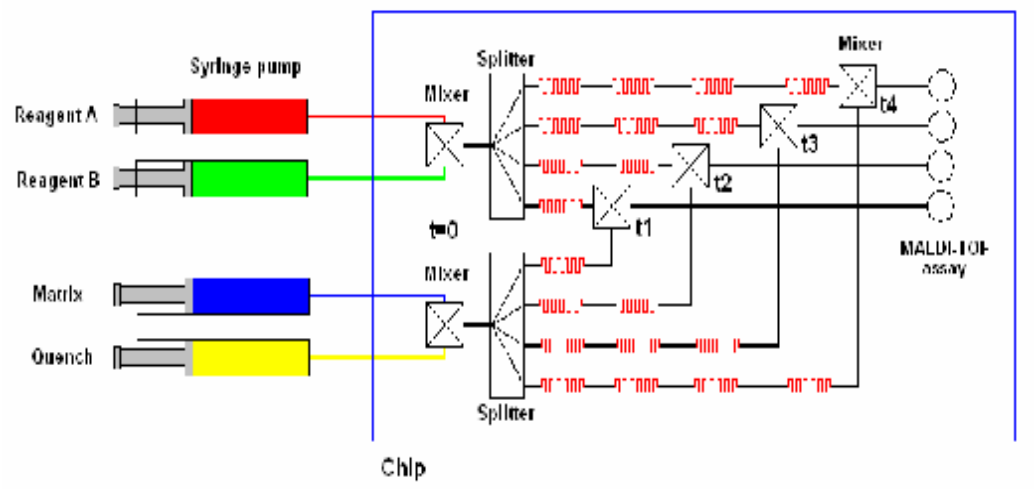
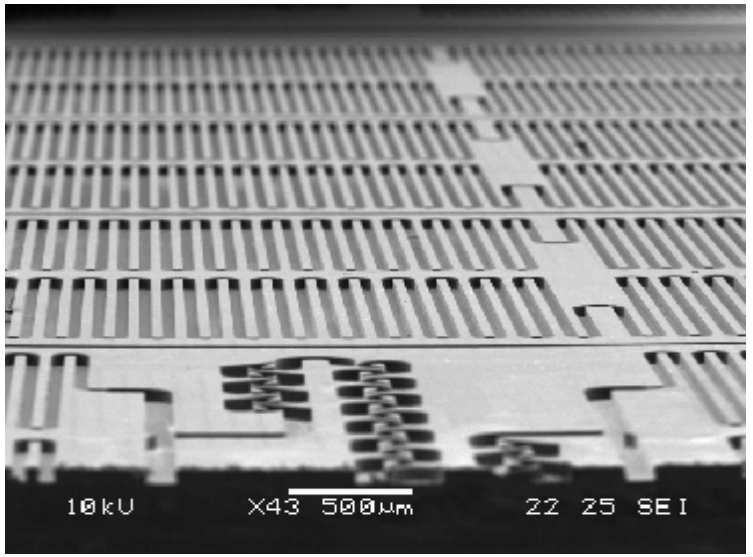
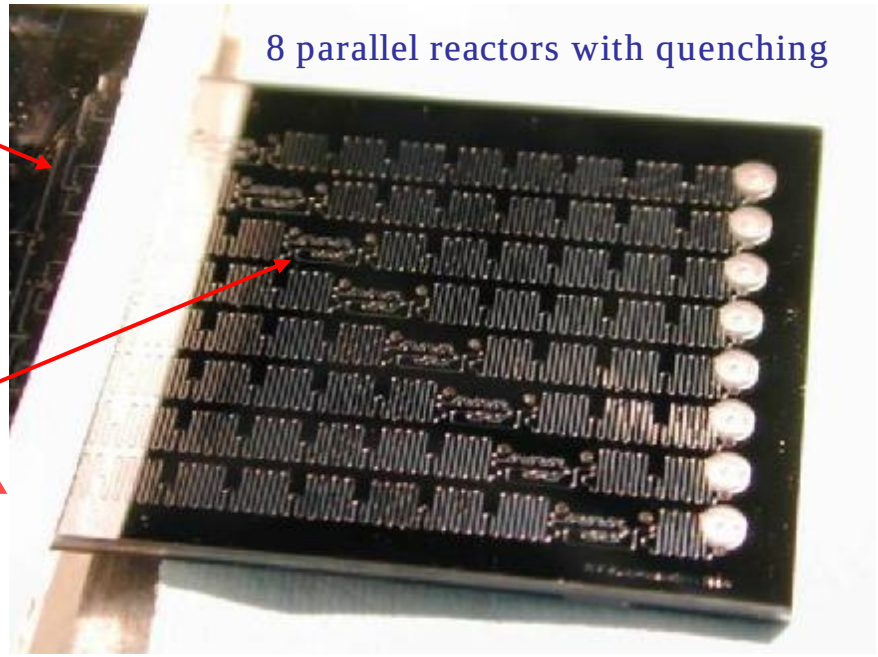
Reaction kinetic studies in parallel channels







8 parallel reactors with quenching

typical feature size: 50 µm

W. Bula et al. IMRET9,
Potsdam, sept. 2006

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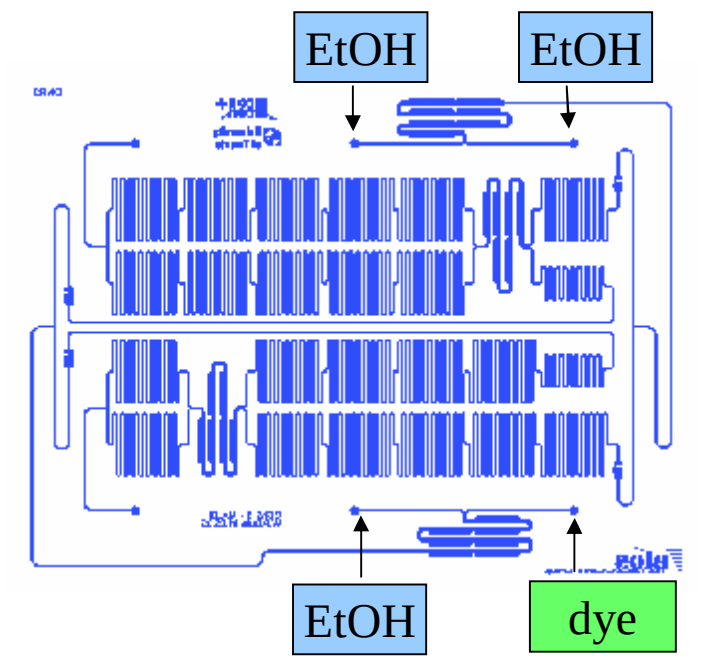
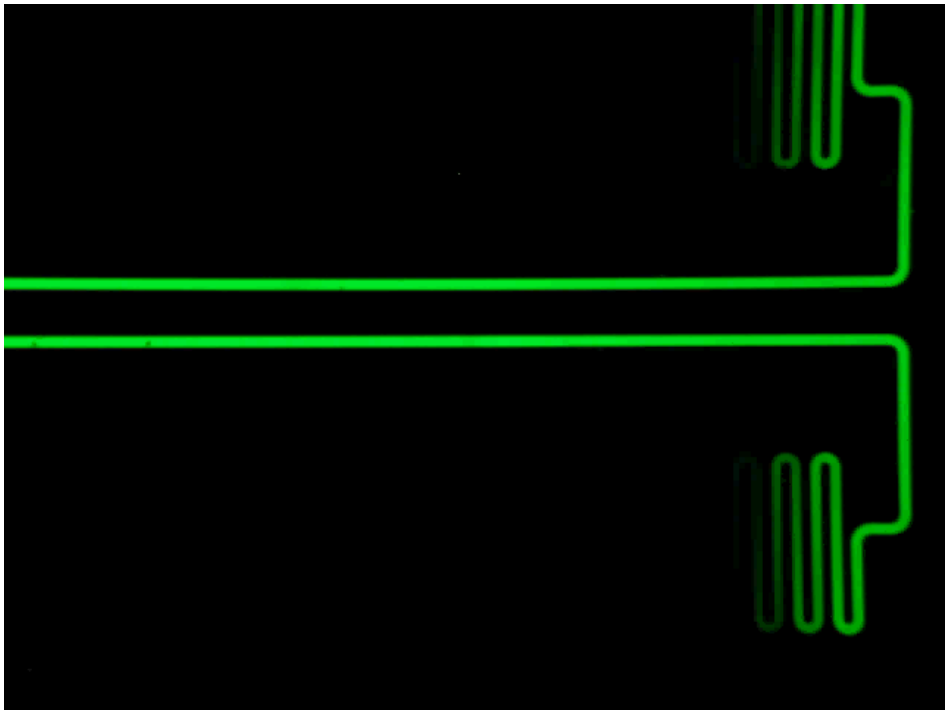
Test of parallel-processing concept



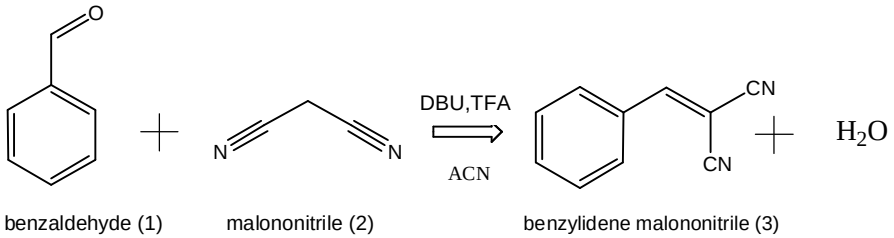


Transport of fluorescent dye plug through the chip. Total residence time ~ 1 min, flow rate 4 x 0.4 μL/min. Flow rate difference ~ 3 %.

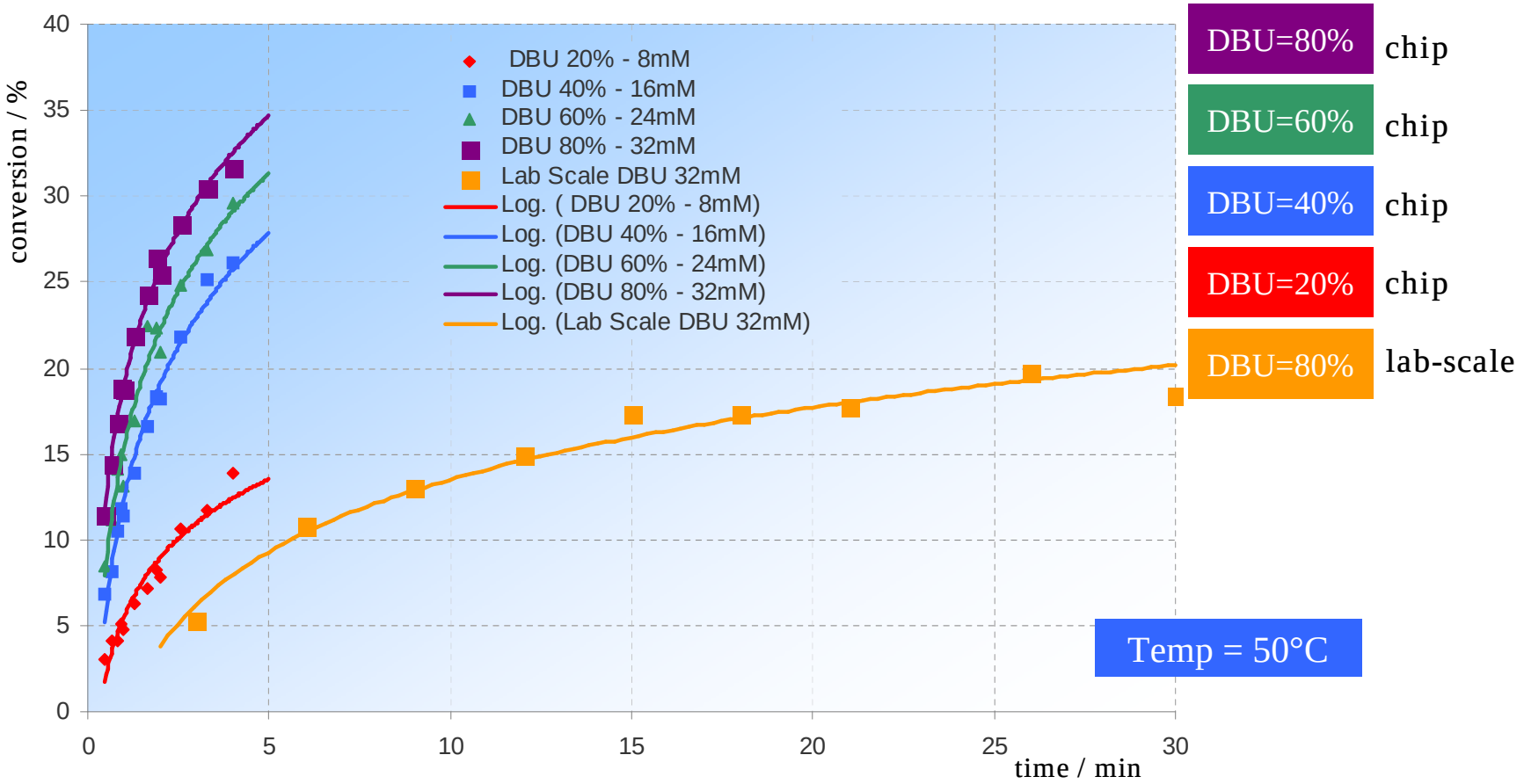
This difference is caused by non-uniformity of silicon etching. Note that hydraulic resistance is proportional to the square of both channel depth and width. For example, a 1 μm variation on a nominal channel depth of 50 μm will give rise to 4% flow variation. A variation of 2% in etching rate over a 4 inch wafer is not uncommon and depends on feature size and locally exposed etched surface area (loading)

Reaction kinetic curves

Knoevenagel condensation / UV-Vis absorption

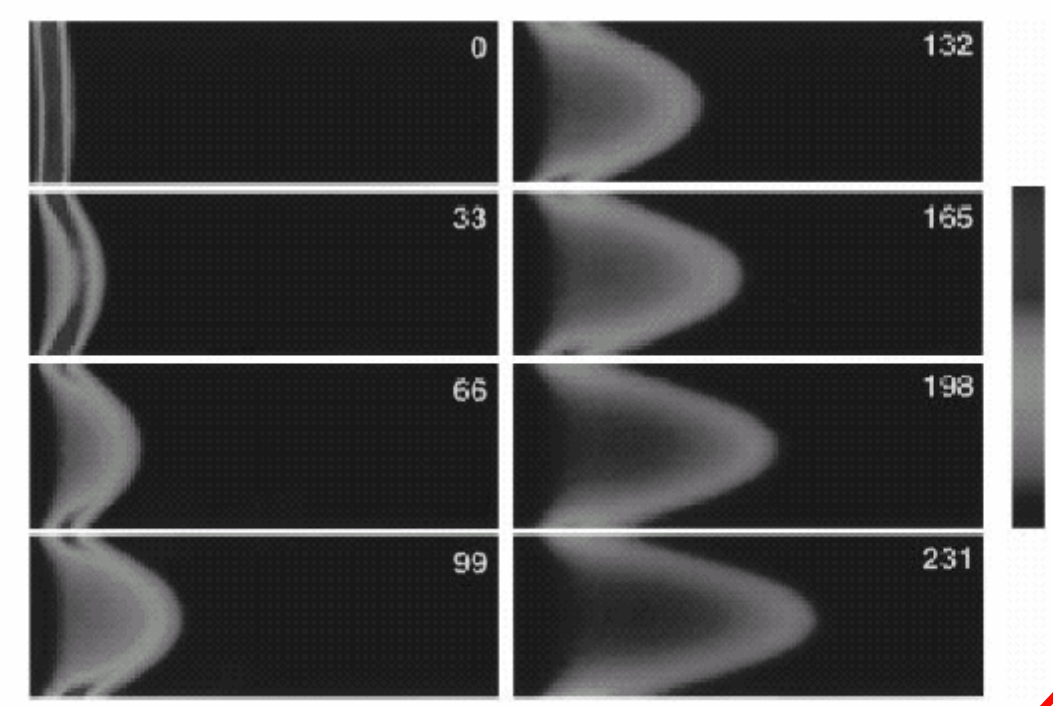


benzaldehyde (1) malononitrile (2) benzylidene malononitrile (3)



Note the much high conversion on the chip, compared to lab-scale:
Is this an ideal plug flow reactor, do we measure intrinsic kinetics?

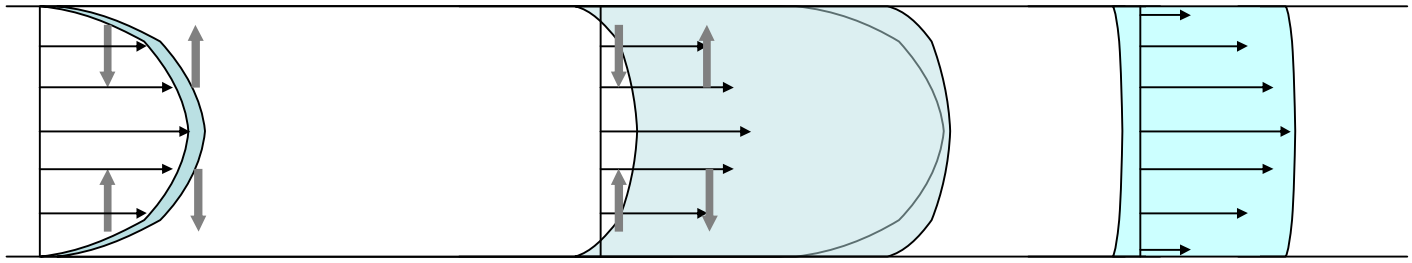
Axial (Taylor-Aris dispersion)



Parabolic flow profile in pressure-driven flow (short time-scale, numbers in ms)
From: Paul e.a. Anal.Chem. 70, 1998, p.2459.

After longer times*** diffusion "blurs" the parabolic shape

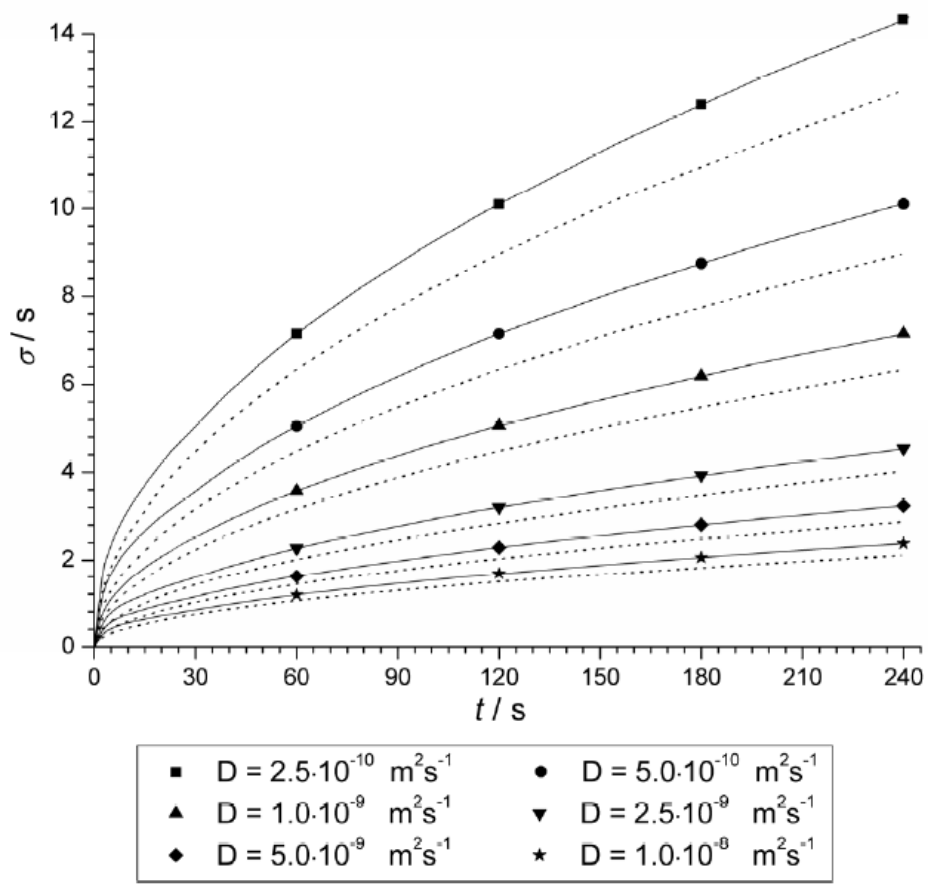
***For 50 μm wide/deep microchannel, radial mixing has occured within ~ 1 sec



Axial dispersion in a microreactor

Taylor-Aris: axial concentration distribution evolves diffusively:

$$D_{eff} = D\left(1+\frac{1}{210}\cdot Pe^2 \cdot f\left(\frac{d}{W}\right)\right) = D\left(1+\frac{1}{210}\left(\frac{U\cdot W}{D}\right)^2 f\left(\frac{d}{W}\right)\right)$$



Plot of standard deviation in straight channel (dashed line) and in meandering channel (solid line) as a function of residence time for different values of the mass diffusion coefficient.

Typical dispersion: 6s/240s = 2.5 %

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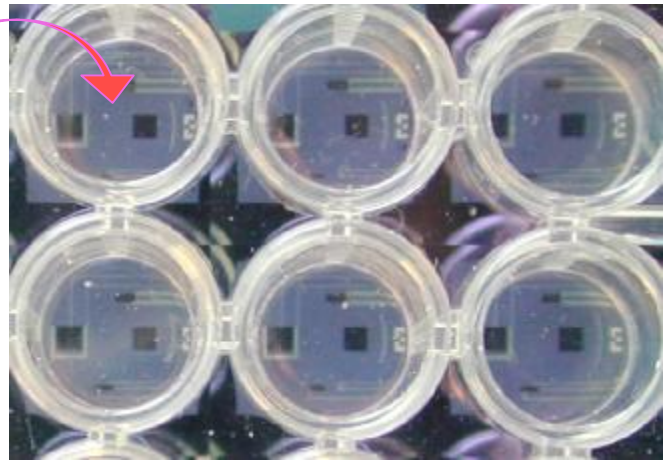
"Nanoreactors" in microreactors

cells (fermentation)

Saccharomyces cerevisiae



Micro titerplate with integrated sensors

two-phase systems

liquid-gas on a surface (batch)	liquid-gas in a microchannel (batch in flow)
liquid-liquid on a surface (batch)	liquid-liquid in a microchannel (batch in flow)

G-L flow patterns

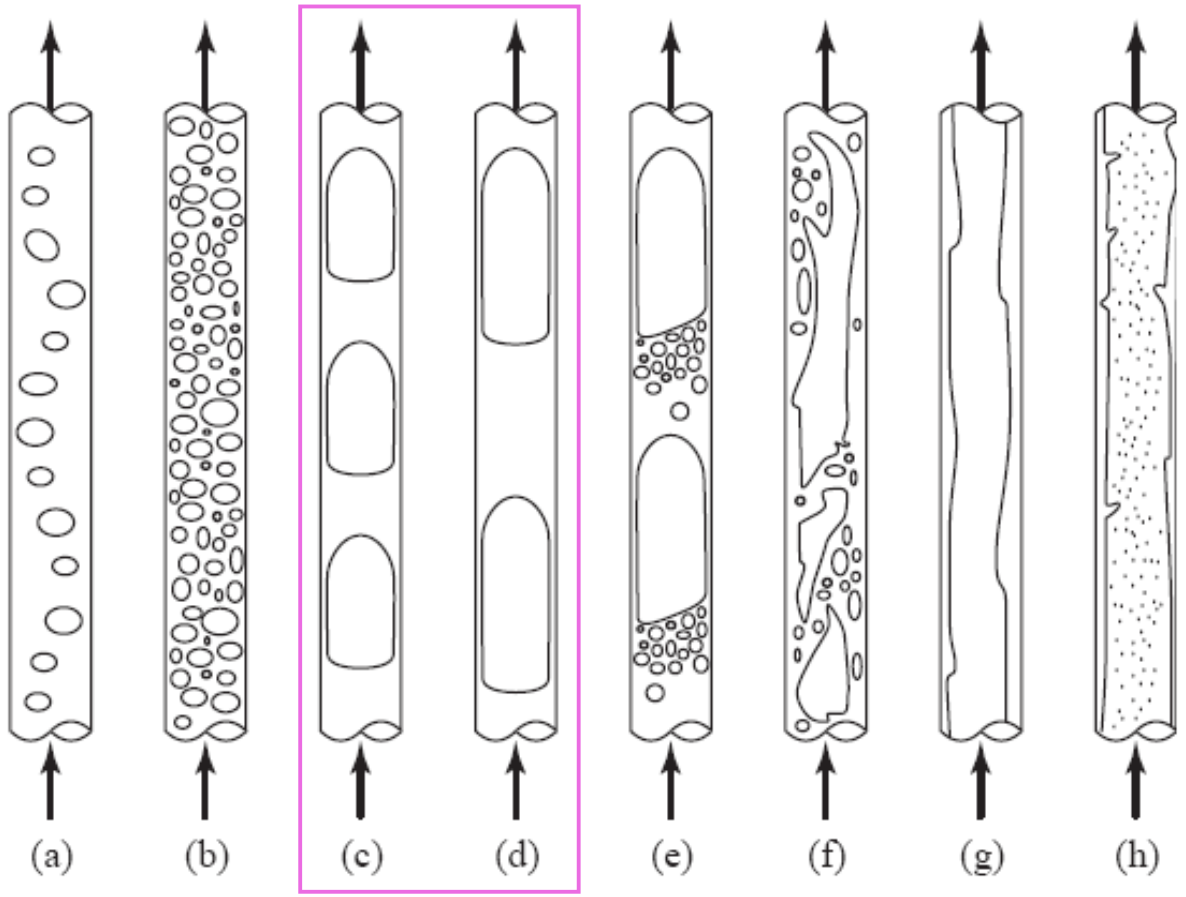
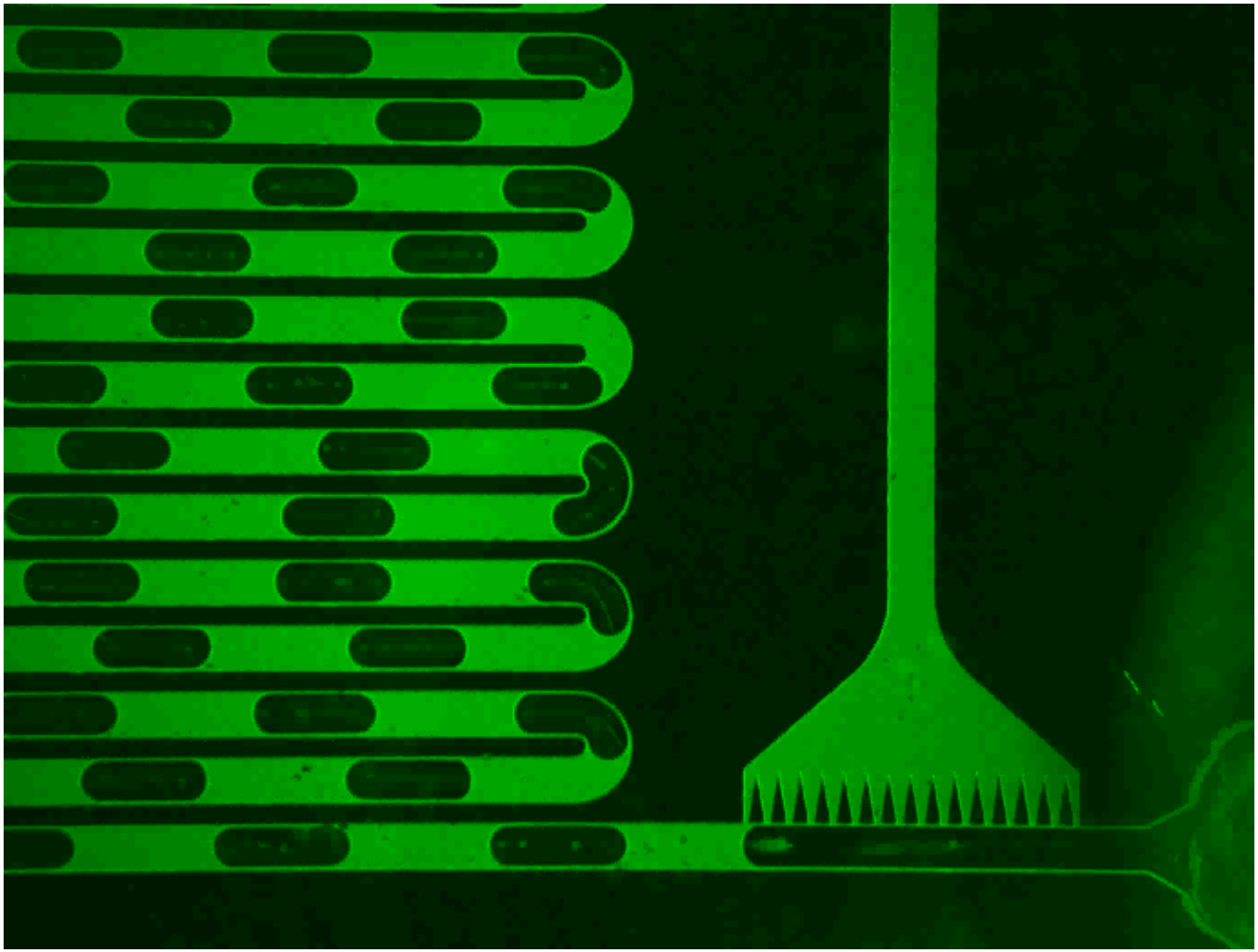


Fig. 1. Sketch of observed flow patterns in capillary channels. (a,b): bubbly flow, (c,d) segmented flow (a.k.a. bubble train flow, Taylor flow, capillary slug flow), (e) transitional slug/churn flow, (f) churn flow, (g) film flow (downflow only), (h) annular flow.

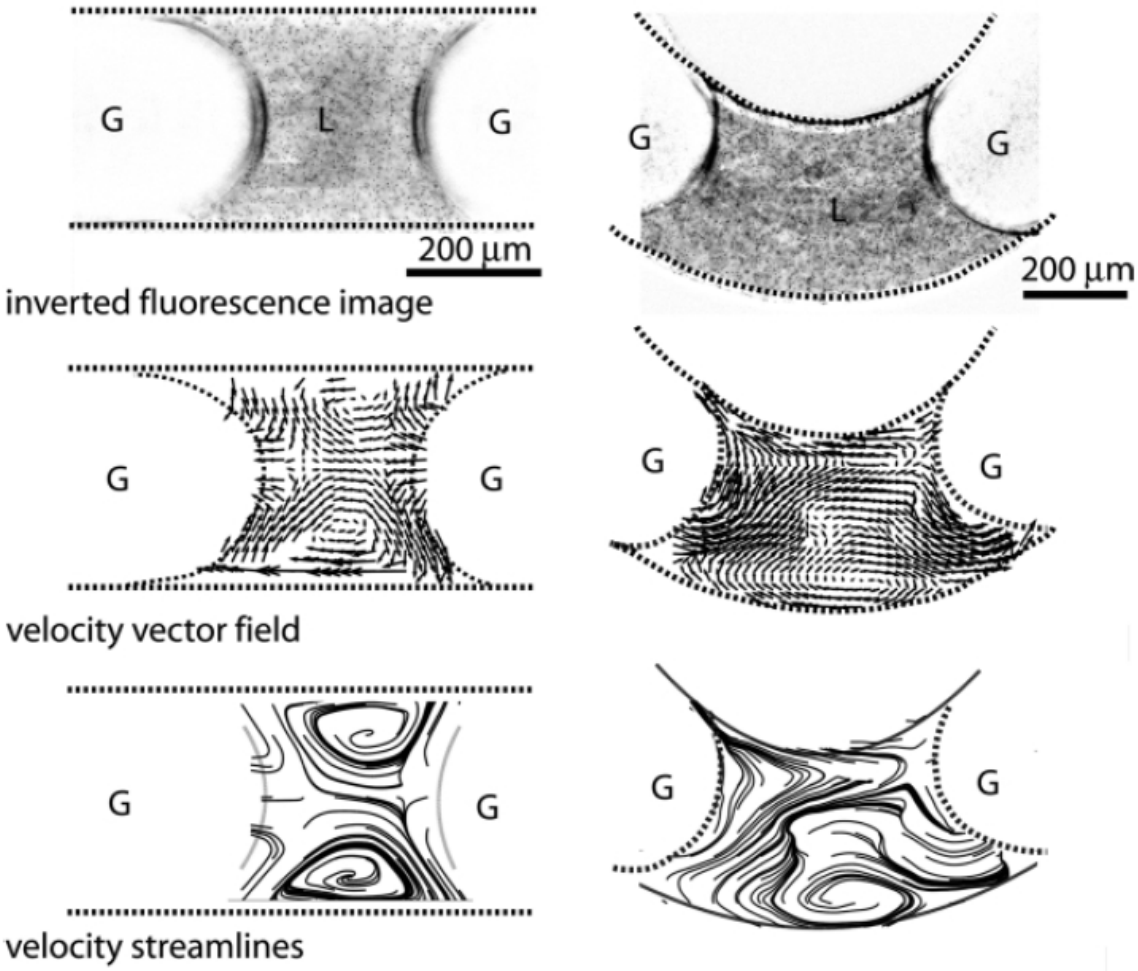
From: M.T. Kreutzer e.a. Chem. Eng. Sci. 60, 2005, 5895

L-G, Taylor flow (slug flow)



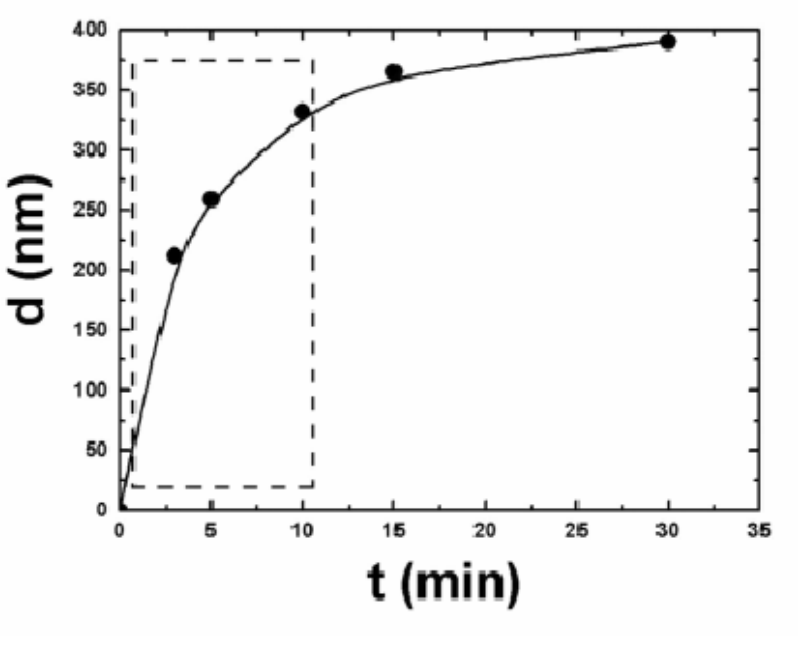
From: A. Günther e.a. Lab Chip4, 2004, p.278

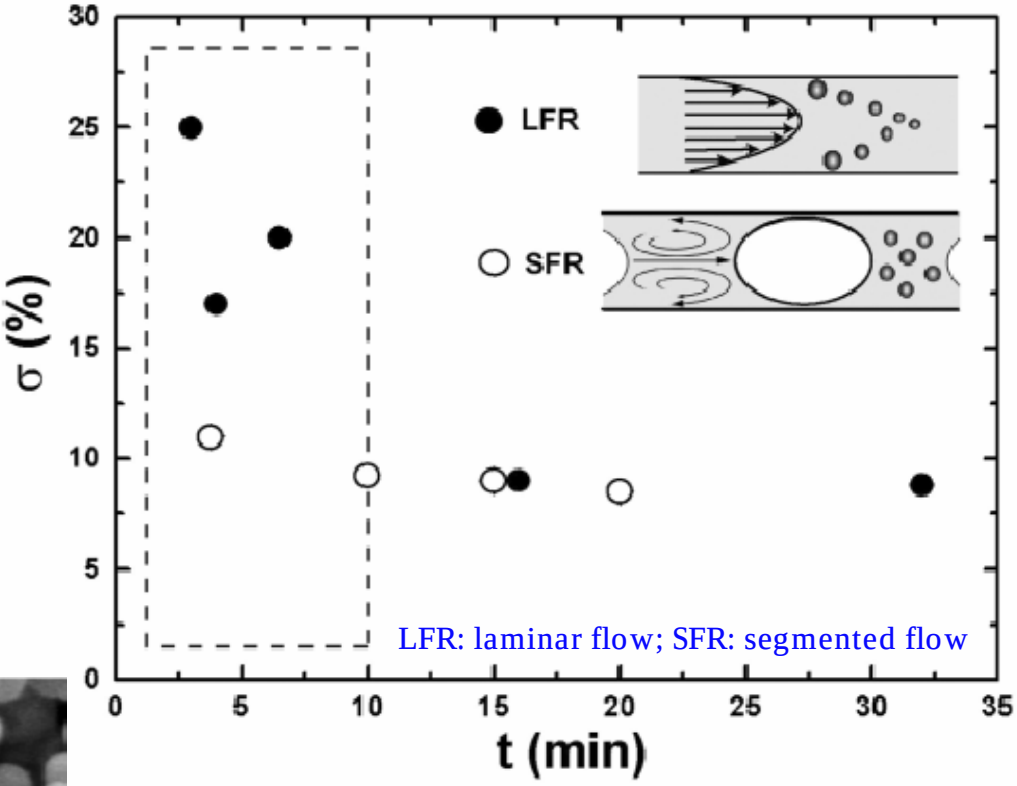
Mixing inside slugs

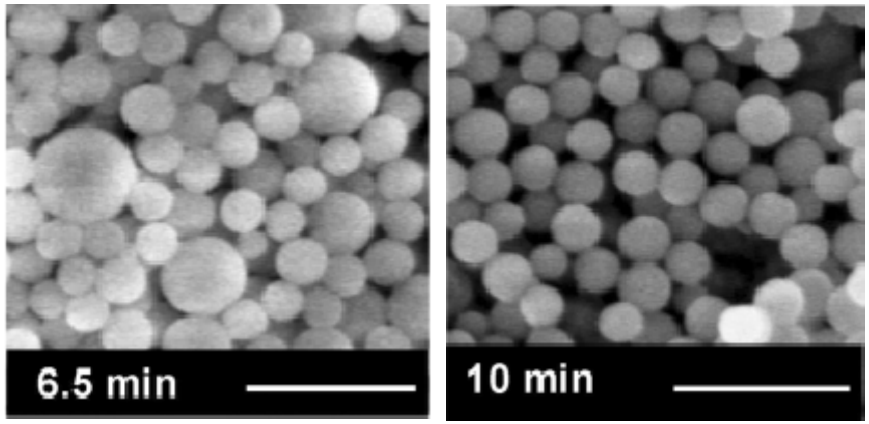


From: A. Günther e.a. Lab Chip4, 2004, p.278

Growth of nanoparticles in microchannels







Silica nanoparticles. Scalebar 1 μm

A. Günther e.a., Lab Chip 4, 2004, 278

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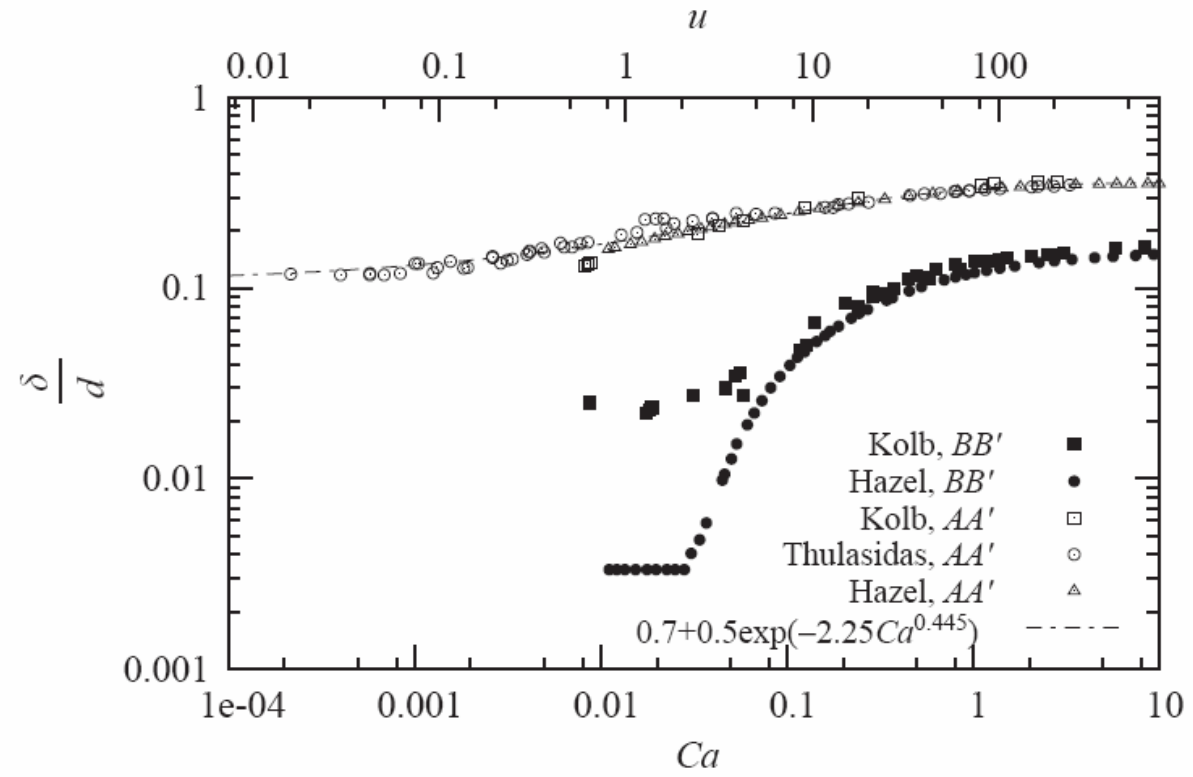
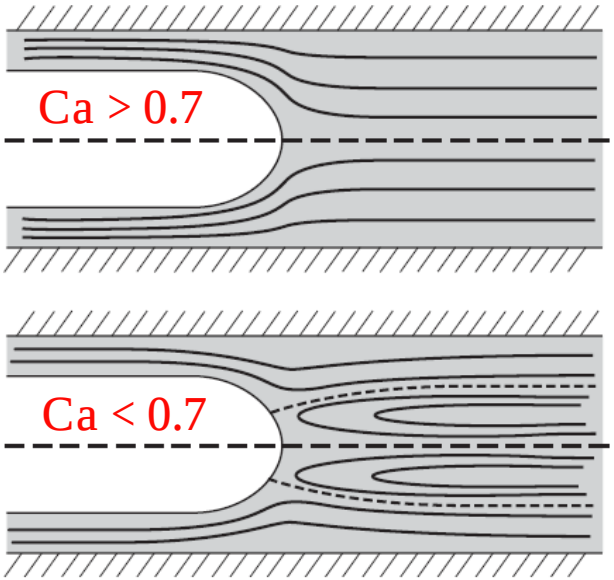
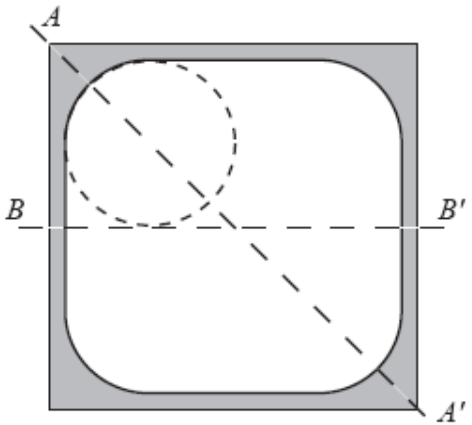
Thin film in Taylor flow





Relative film thickness δ (channel width d), for square channel, as f(Ca) (calcation of u assumes water)



Capillary number Ca = η u / σ
with η viscosity, u velocity, σ surface tension

From: M.T. Kreutzer e.a. Chem. Eng. Sci. 60, 2005, 5895

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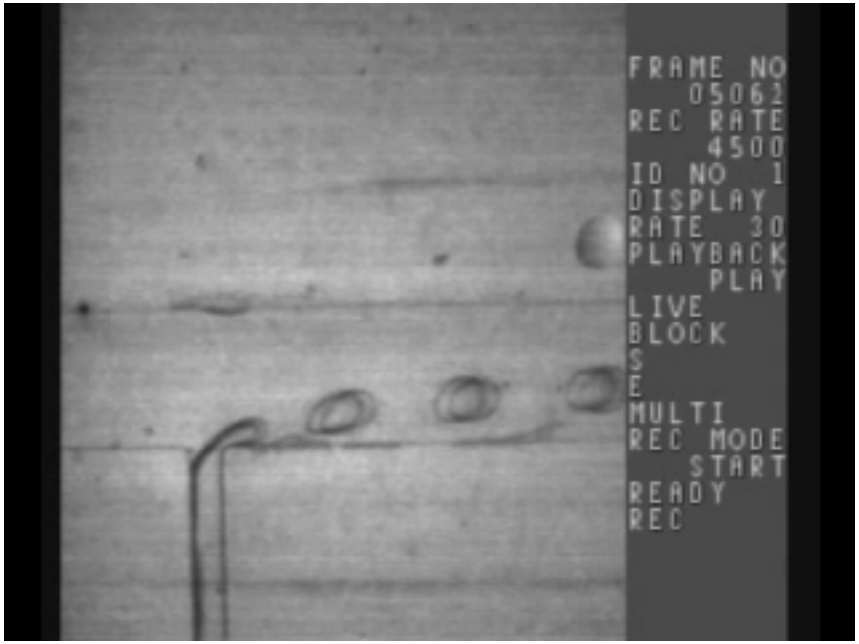
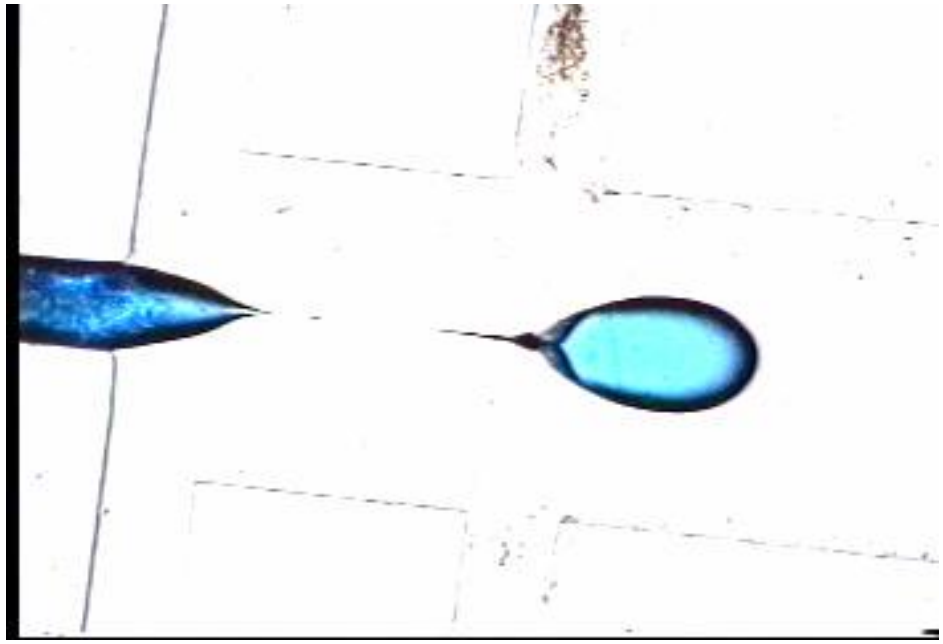
L-L, droplet formation in microchannels





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Left movie from: T. Nisisako e.a., Lab Chip 2, 2002, 24

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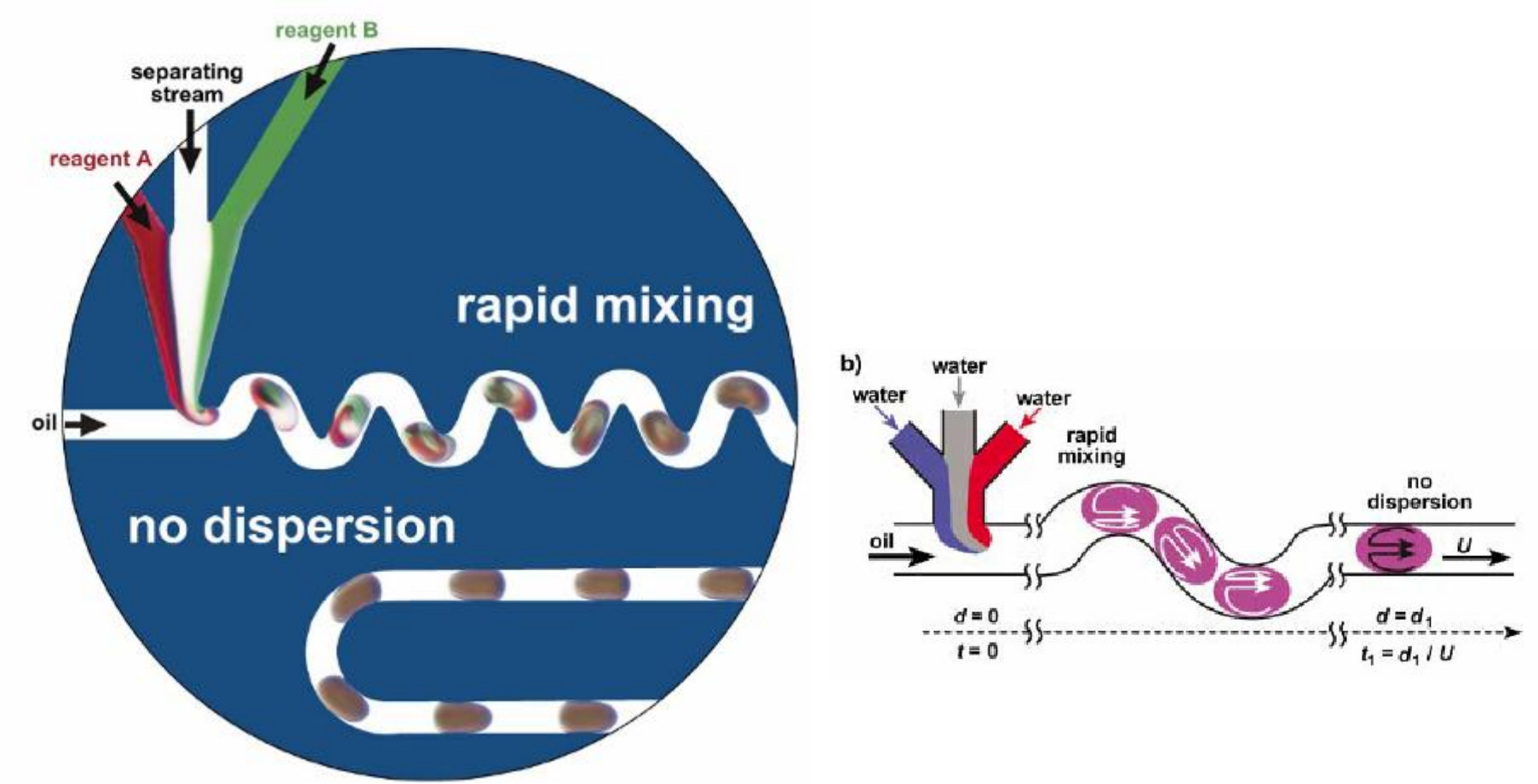
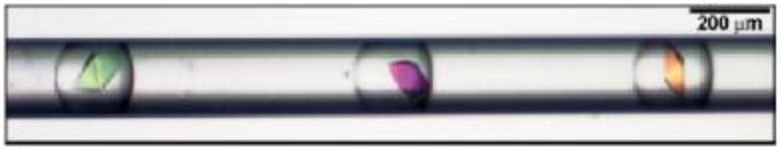
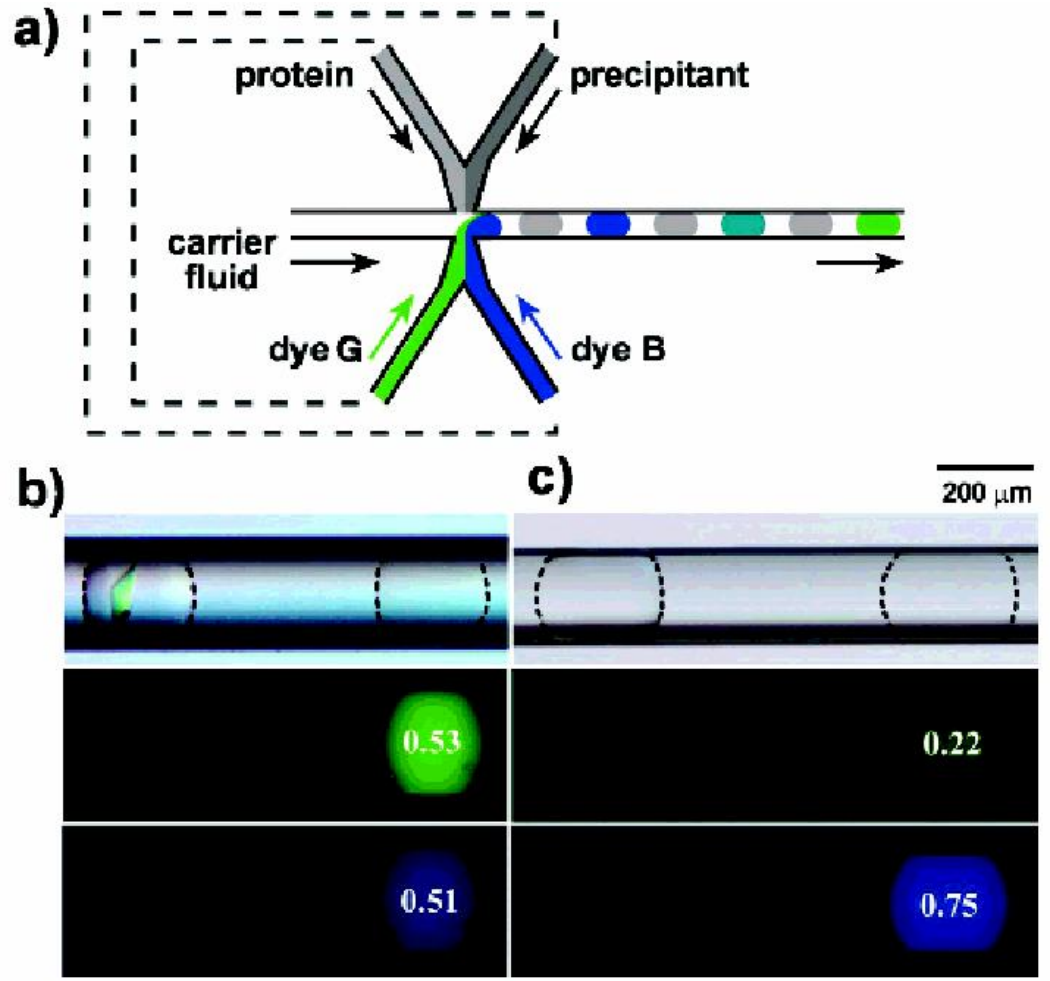
Time-periodic recirculating flow inside the droplets caused by the shearing interaction with the walls



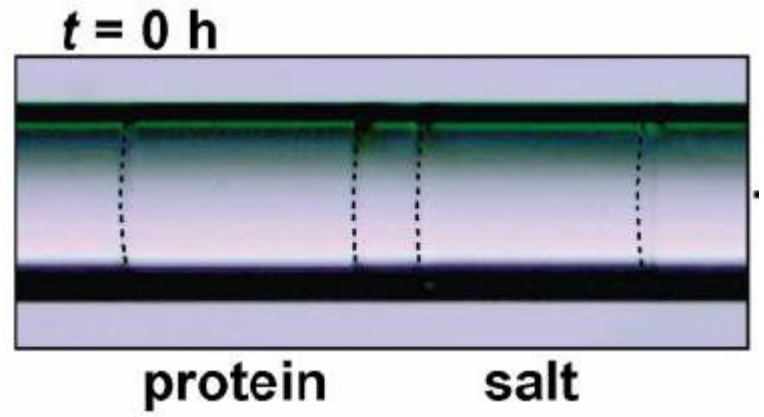
H. Song, J.D. Tice and R.F. Ismagilov, *A microfluidic network for controlling reaction networks in time,* Angew. Chem. Int. Ed. 42, 2003, 768-772

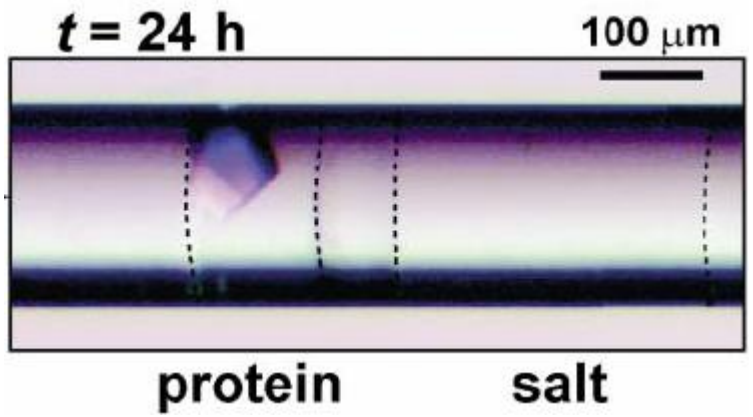
Protein crystallization

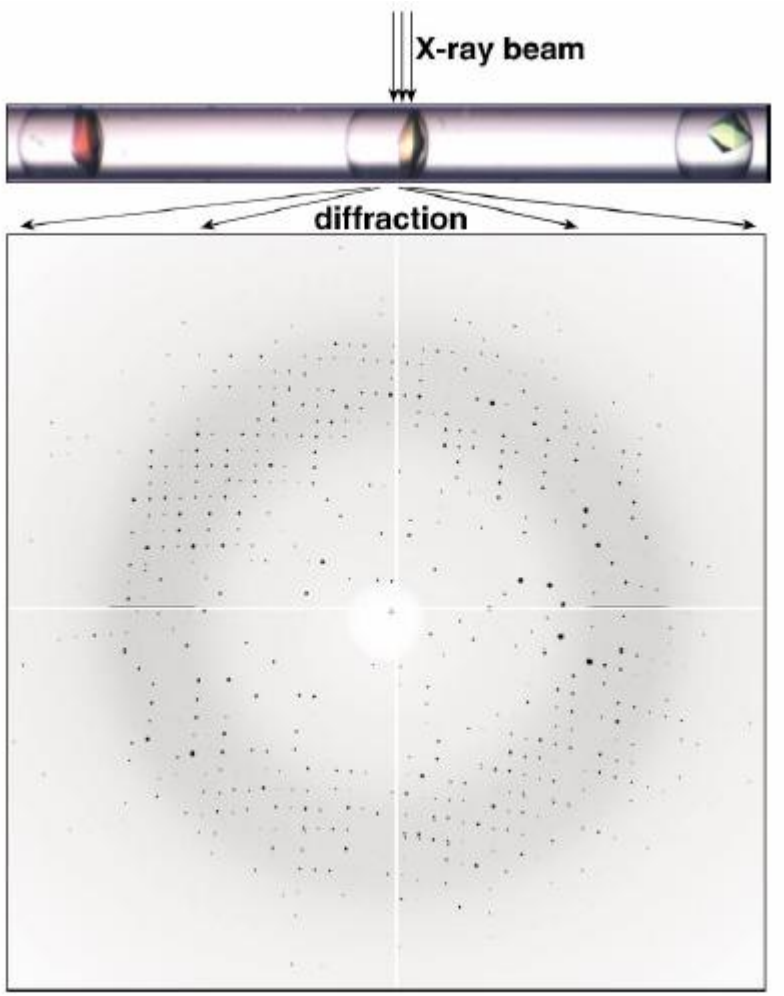




Direct X-ray analysis in capillary

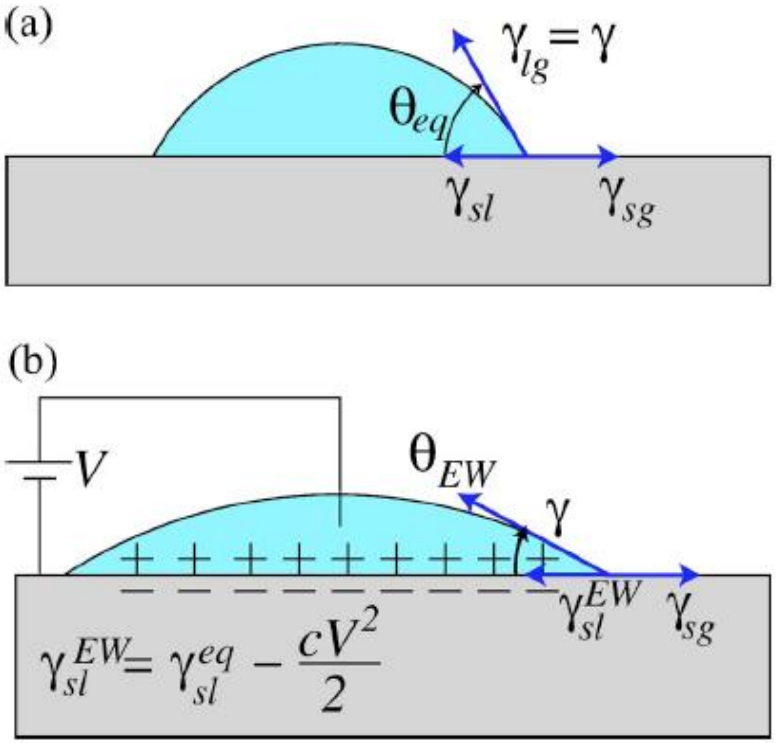






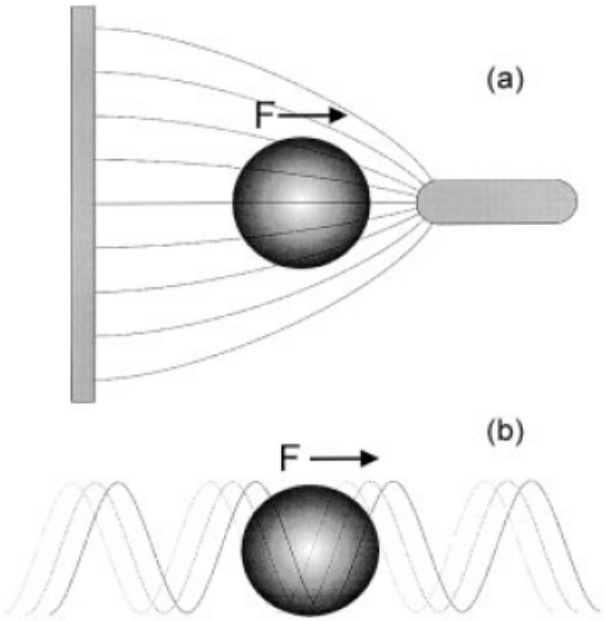
B. Zheng e.a. Angew. Chem. Int. Ed. 43, 2004, 2508

Electrical manupilation of droplets



Wetting and electrowetting

Review: F. Mugele e.a., J. Phys. Condens. Matter 17, 2005, p.S559



Dielectrophoresis: particle suspended in alternating E-field with magnitude or phase gradient experiences pos. or neg. forcedepending on whether particle is more or less polarizable than medium

Review: M.P. Hughes, Electrophoresis 23, 2002, 2569

Droplet manipulation by electric fields

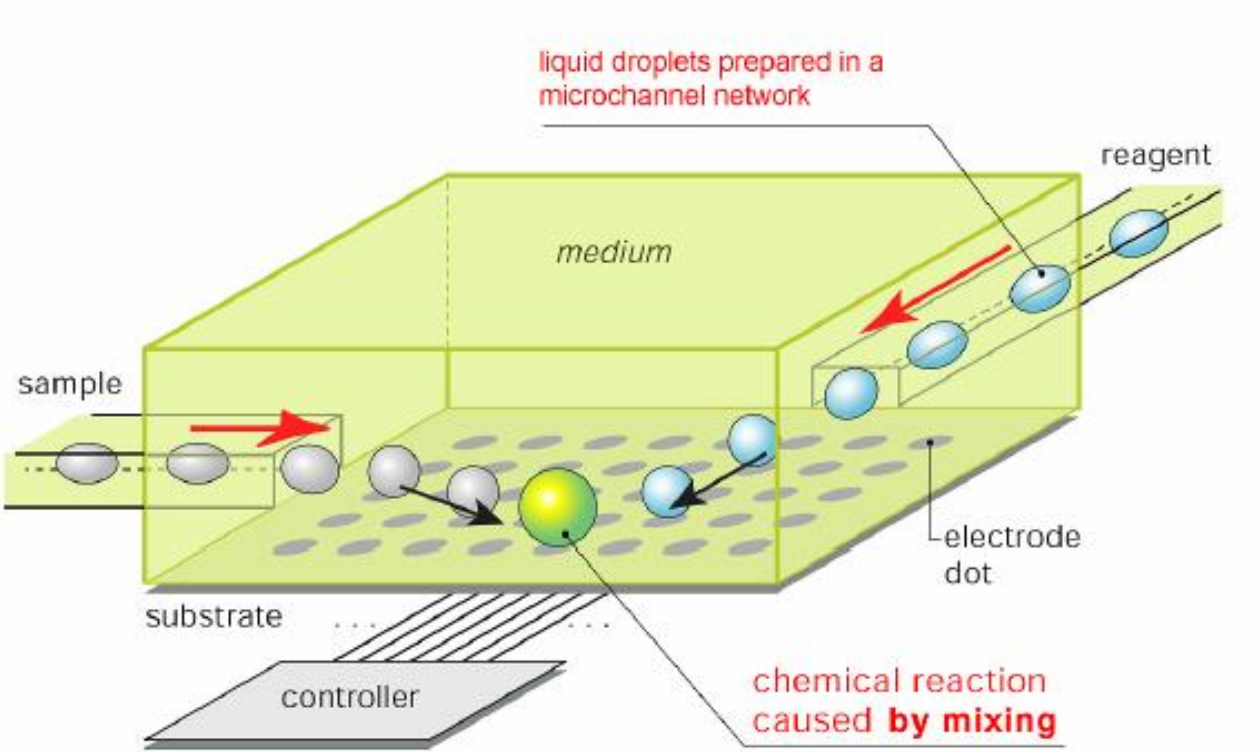
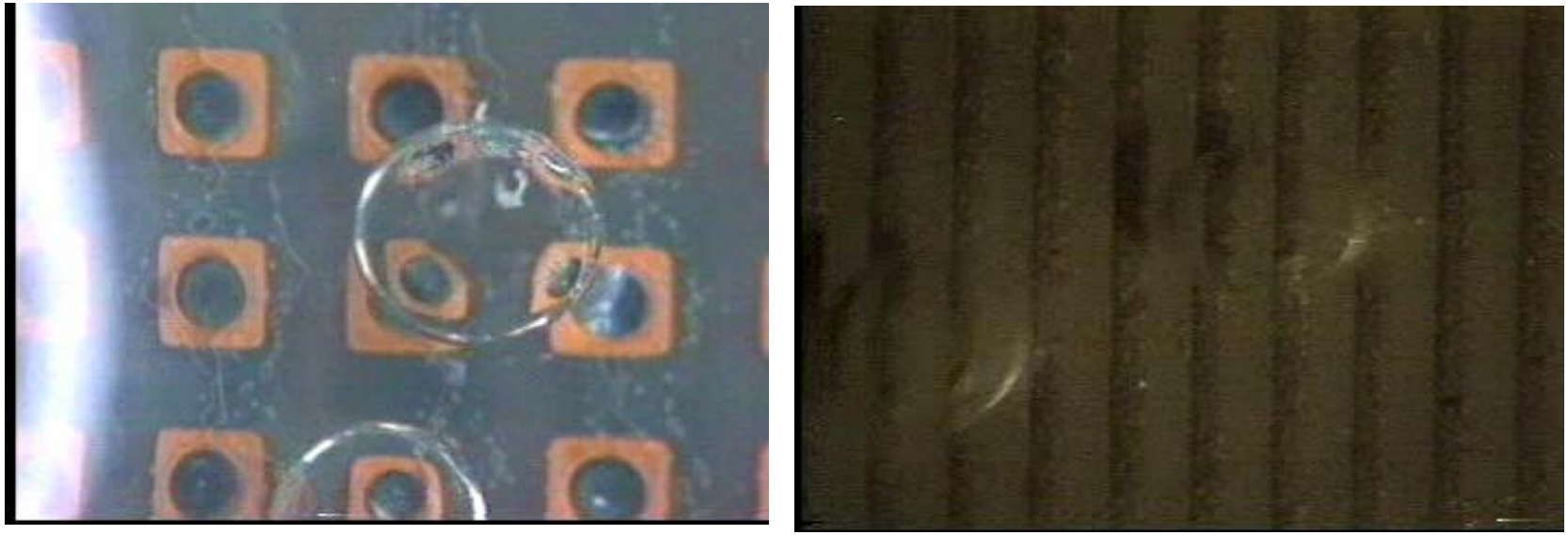


Figure 8. A schematic of the electrical actuation of micro droplets prepared in a microchannel network

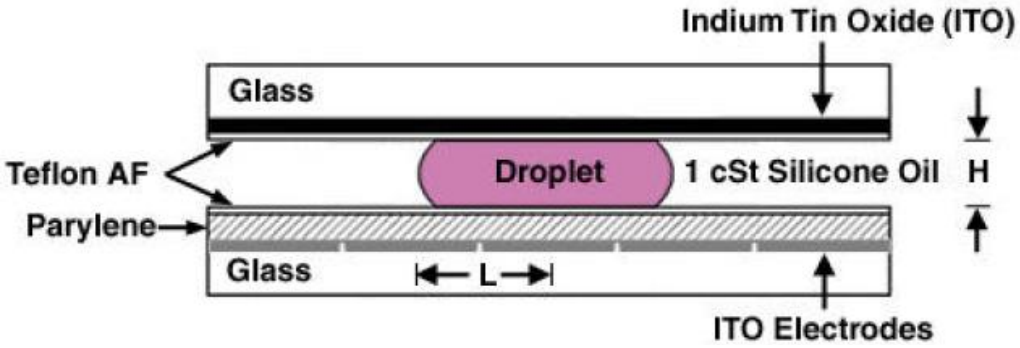
Higuchi, Torii and Yamamoto, University of Tokyo

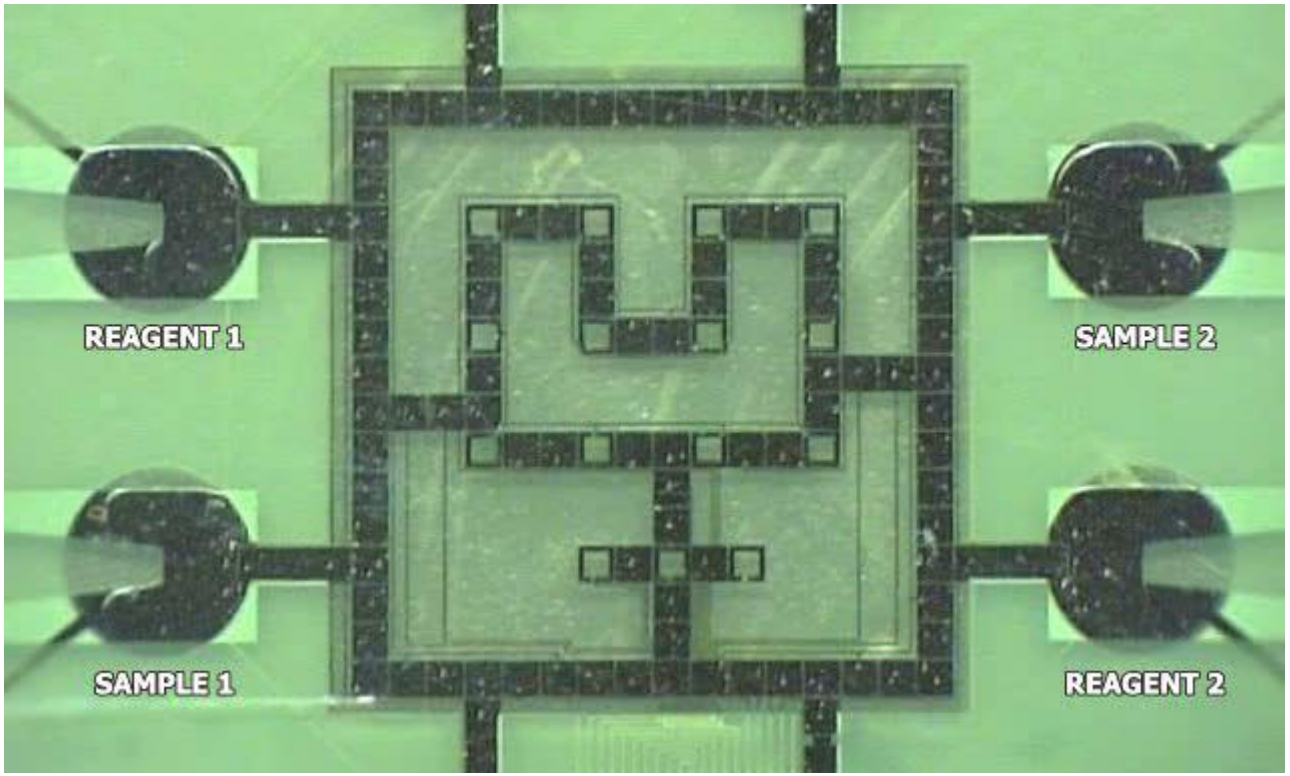
Droplet manipulation by electric fields



T. Taniguchi e.a. Lab Chip 2, 2002, 19

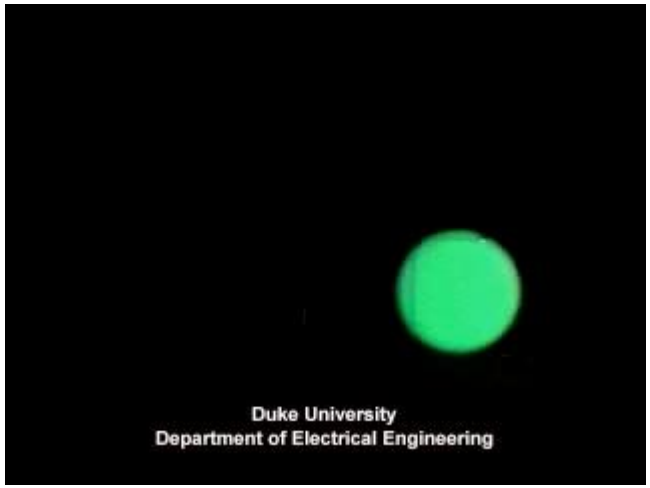
Electro wetting on dielectric (EWOD)

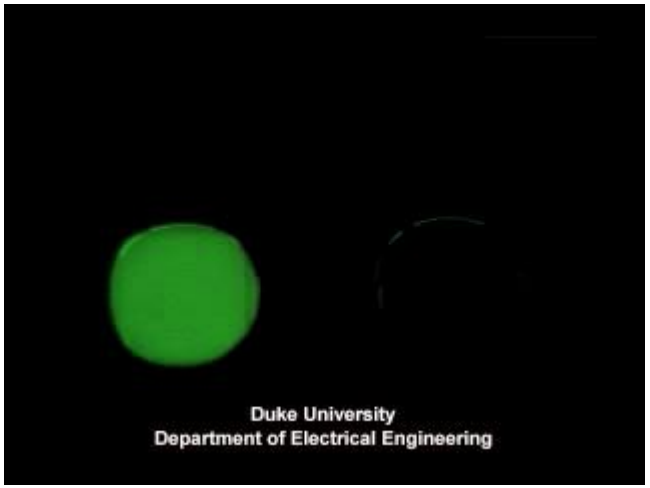


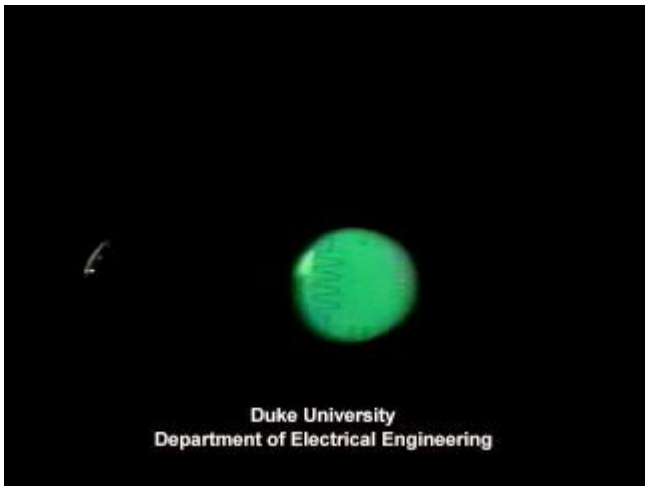


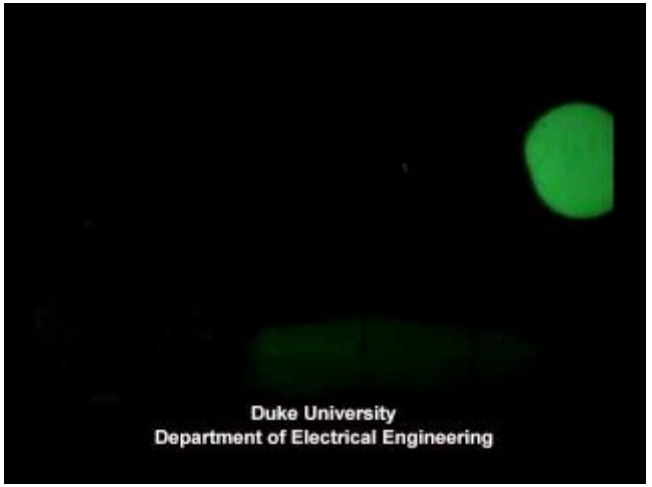
V. Srinivasan e.a., Lab Chip 4, 2004, p.310

EWOD mixing



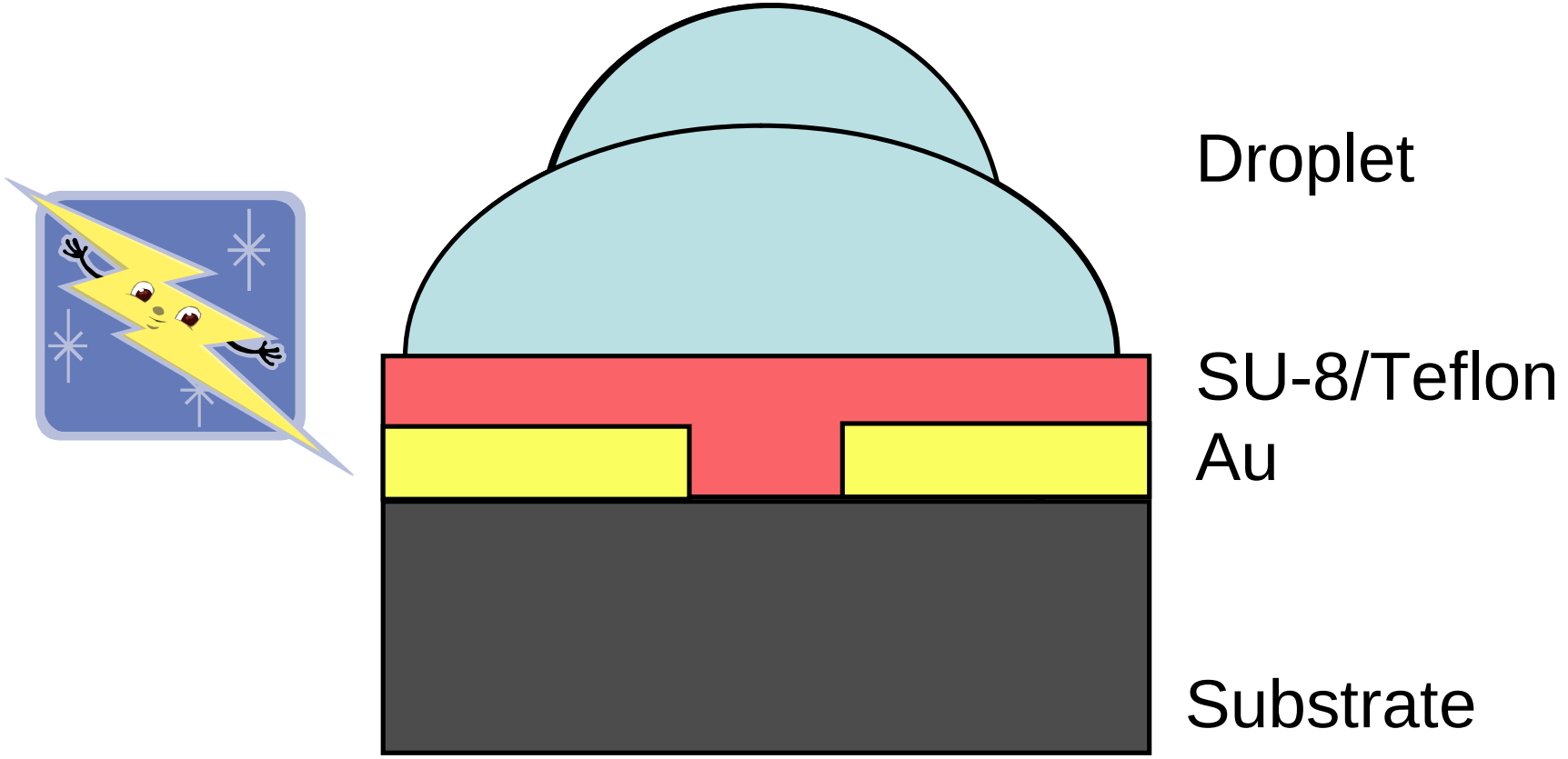




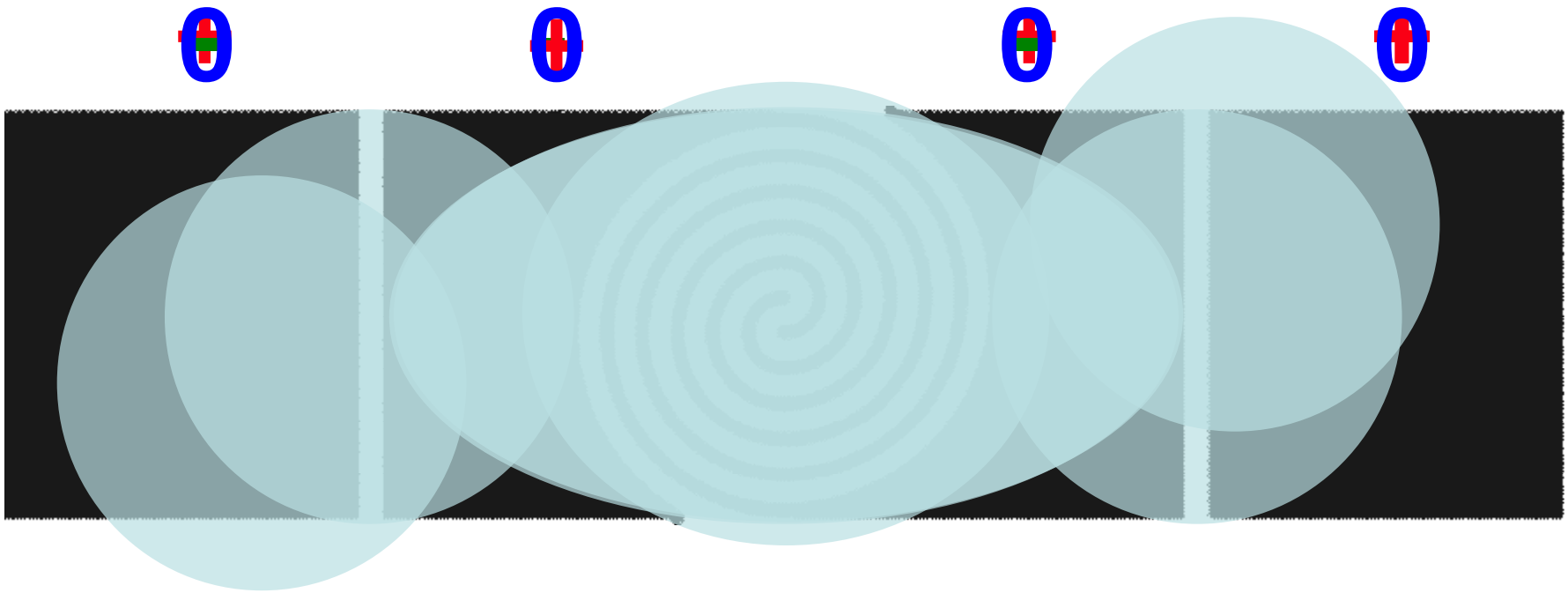


P. Paik e.a., Lab Chip 3, 2003, p.253

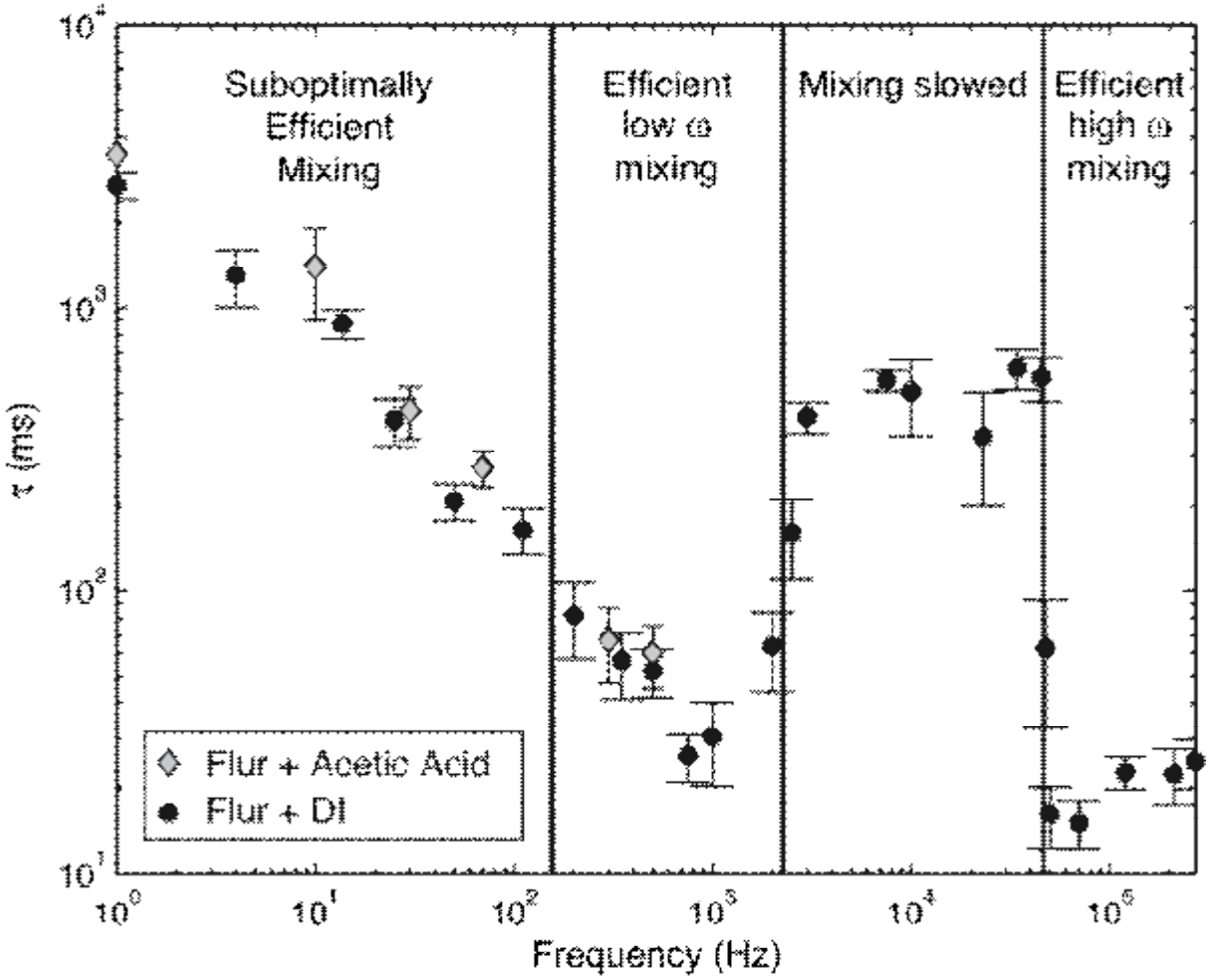
Mixer based on electro-wetting



Mixer Operation



Four Mixing Regimes



Left = DI / Right = Fluorescein

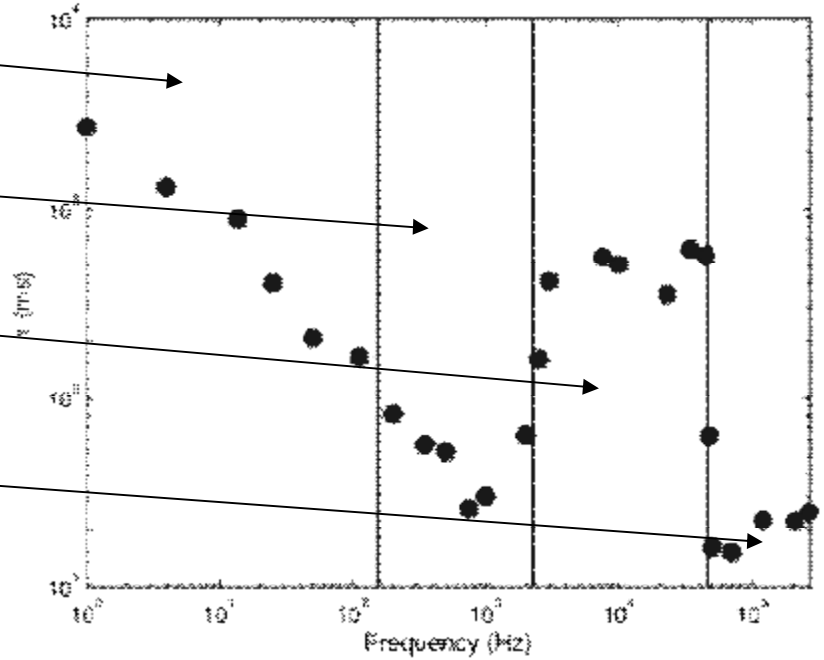
Four Mixing Regimes:

movie 4 Hz

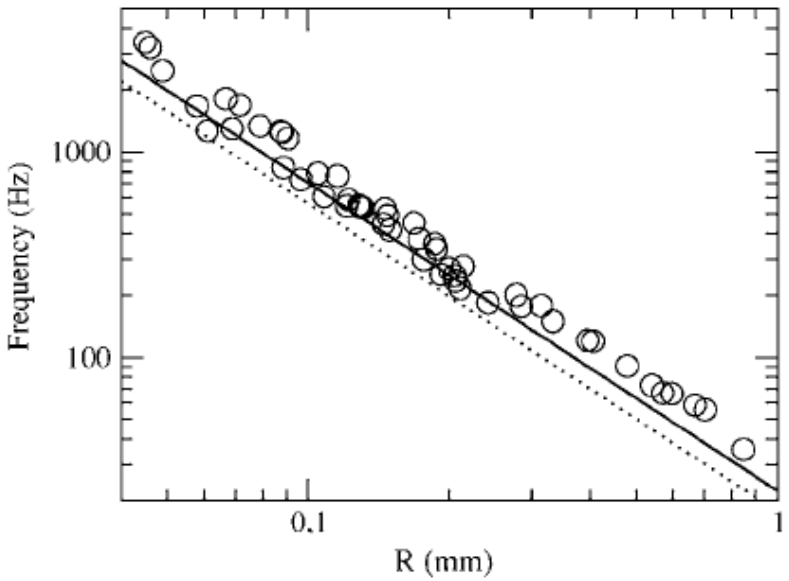
movie 500 Hz

movie 7.5 kHz

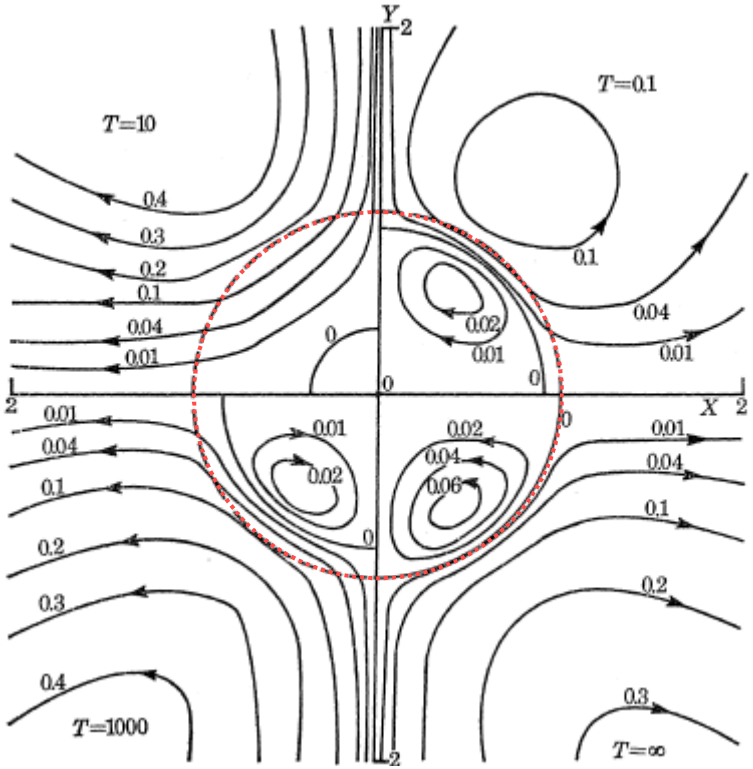
movie 210 kHz



at 250 V, 500 Hz: good mixing < 20 ms
for 1 μl droplets without Joule heating



Eigenfrequency of supported drops
F. Celestini e.a. Phys. Rev. E 73, 2006, p. 041602



Flow pattern in droplet in DC electric field along X-axis, due to electrically induced surface stresses

Sozou, Proc. Royal Soc. London A 334 (1973) 343

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Enzymatic reaction kinetics by MALDI-MS

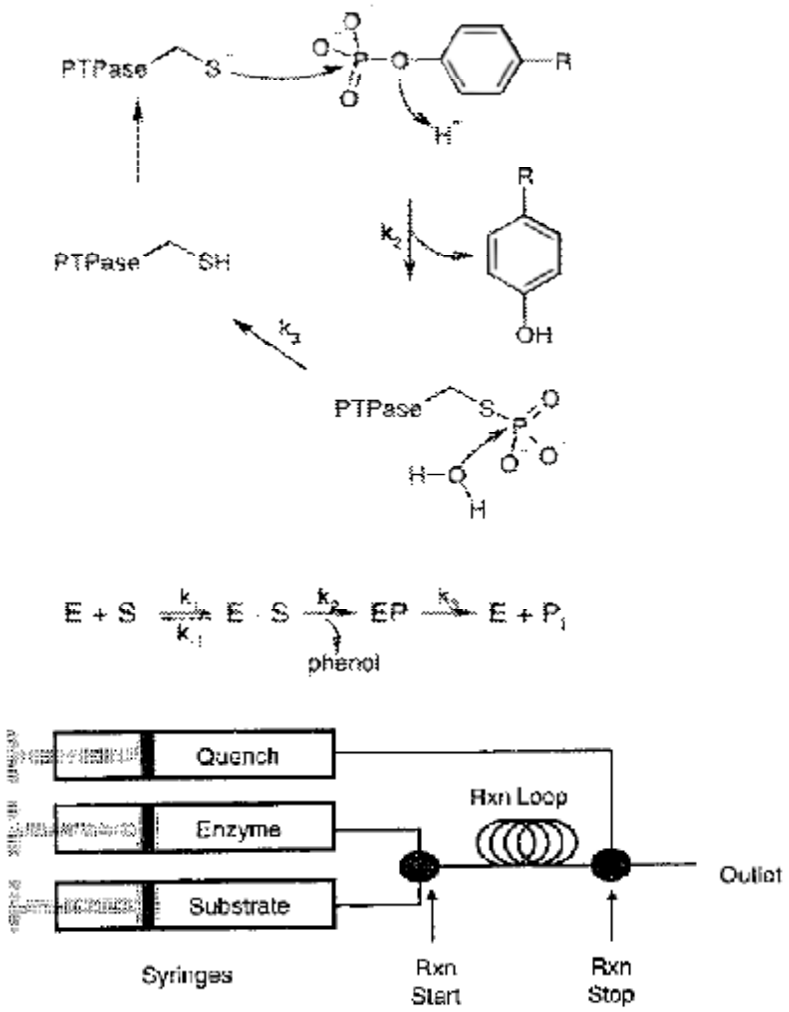
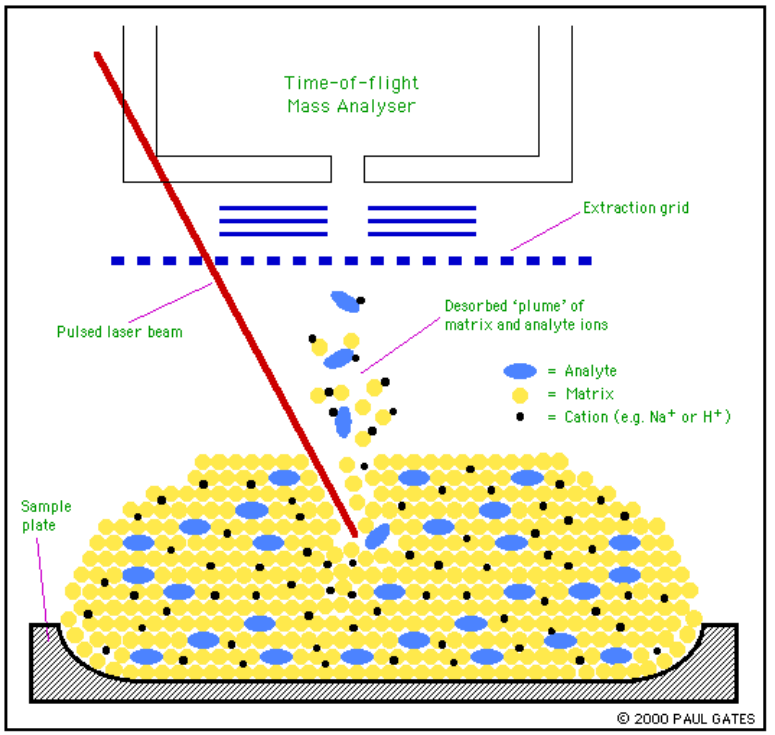


Figure 2. Block diagram of quench flow apparatus.

Houston et al., Anal Chem 72 (14), 2000, 3311

Protein Tyrosine Phosphatase

For $k_2 >> k_3$, detect EP Buildup



MALDI MS principle

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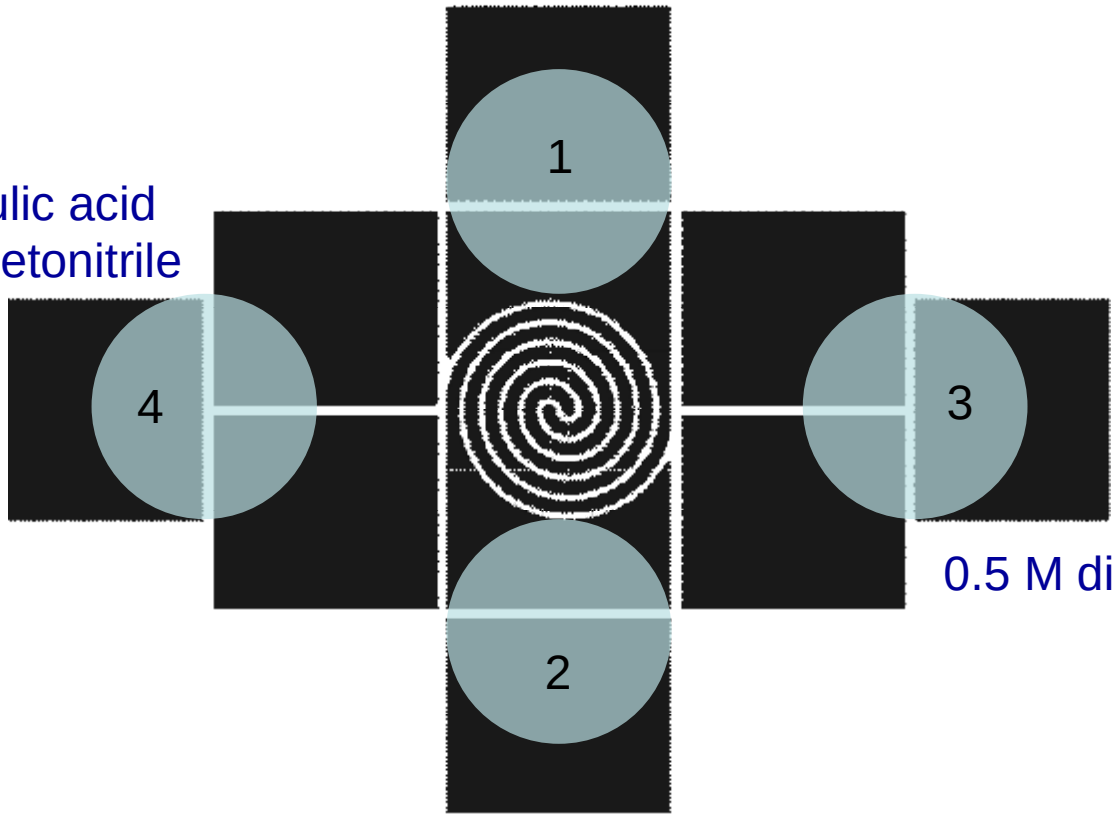
Mixer + 2 more droplet pads

0.7 µL 50 µM YOP51 PTPase



25 mg/ml ferulic acid
in 2:1 H_2O/acetonitrile

0.5 M dichloroacetic acid

20 mM p-nitrophenyl phosphate

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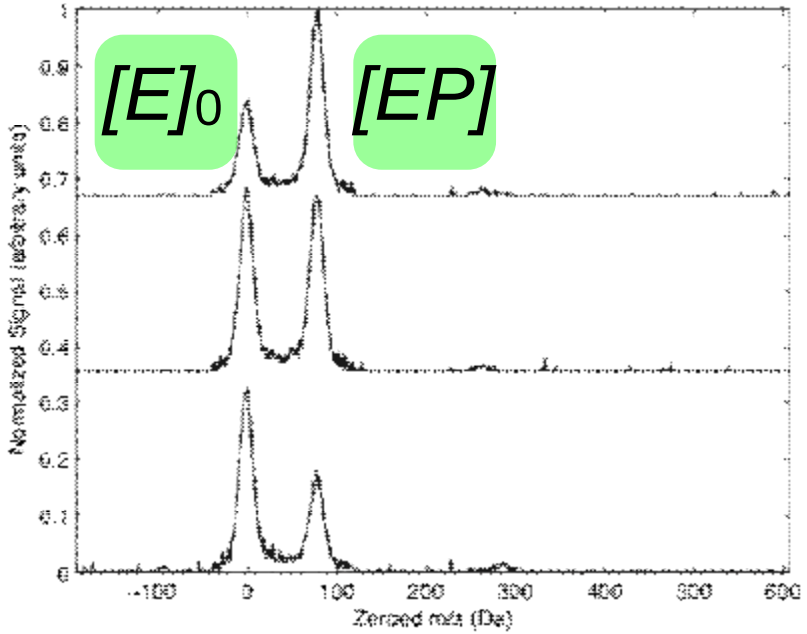
MALDI Results

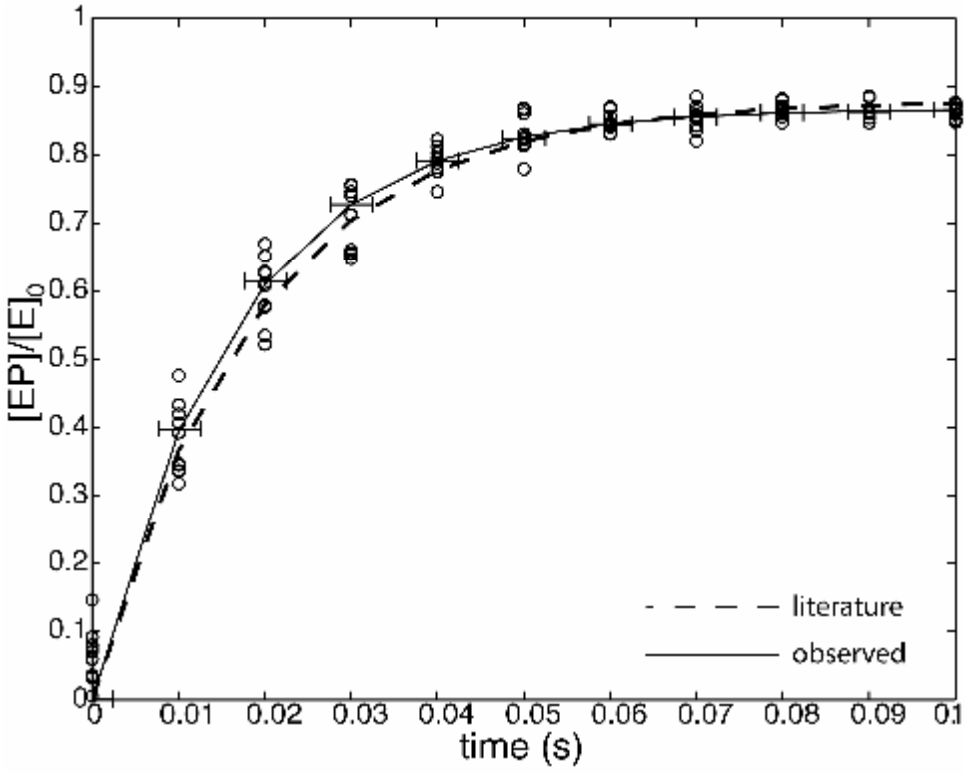


$$C = \frac{k_2 \cdot [E]_0}{(k_2 + k_3)^3 \cdot \left(1 + \frac{K_m}{[S]_0}\right)}$$

$$b = k_3 + \frac{k_2}{1 + \frac{(k_2 + k_3) K_m}{k_3 \cdot [S]_0}}$$

$$\frac{[EP]}{[E]_0} = C \cdot \left(1 - e^{-bt}\right)$$

Reaction kinetics results



$$C = \frac{k_2 \cdot [E]_0}{(k_2 + k_3)^3 \cdot \left(1 + \frac{K_m}{[S]_0}\right)}$$

$$b = k_3 + \frac{k_2}{1 + \frac{(k_2 + k_3) K_m}{k_3 \cdot [S]_0}}$$

$$\frac{[EP]}{[E]_0} = C \cdot \left(1 - e^{-bt}\right)$$