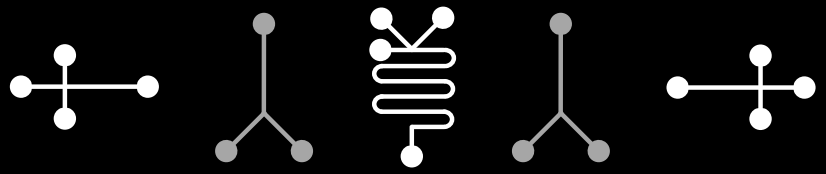
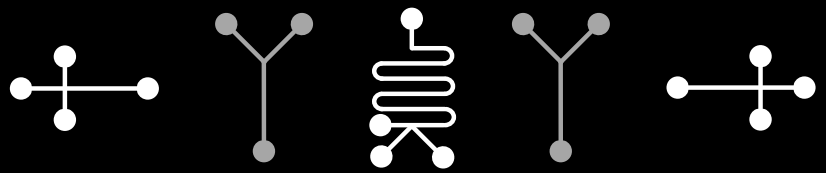
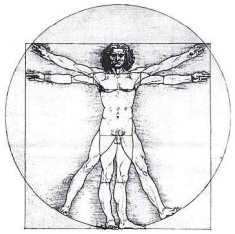


microfluidics for chemistry (... & a little biology)

Andrew deMello, ETH Zürich





sample
pre-treatment

sampling

chemistry & biology

reaction

separation & detection

isolation & collection

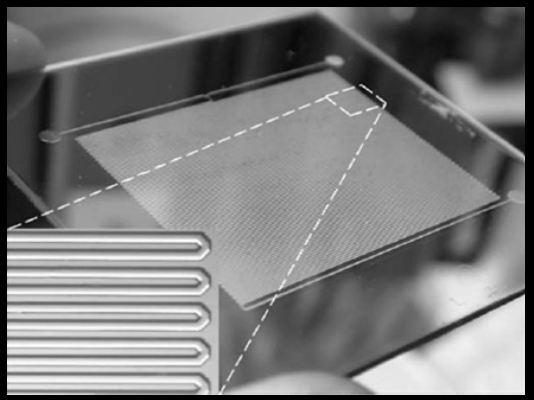
microfluidics?

"microfluidics describes the behaviour, control and manipulation of fluids that are geometrically constrained within sub-microliter environments…

…the use of microfluidic devices offers an opportunity to control physical and chemical processes with unrivalled precision, and in turn provides a route to performing chemistry and biology in an ultra-fast and high-efficiency manner"

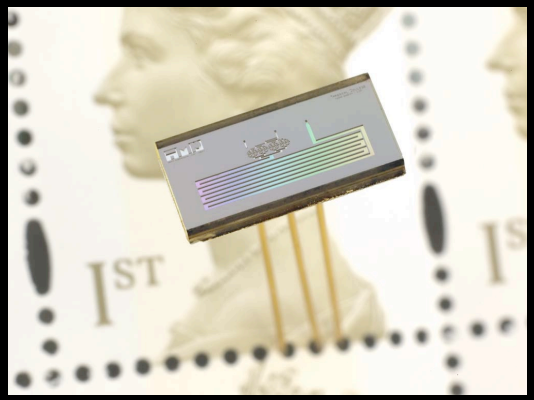
why miniaturize?

• cost economies through micromachining • reduced sample/reagent & power consumption • portability •



Angewandte Chemie 2007, 119, 2933

Anal. Comm. 2001, 36, 213



• superior performance (speed, efficiency & control) • facile process integration & automation • high analytical throughput • functionality •

"superior quality and rate of generation of chemical and biological information"

Whitesides Group, Harvard University

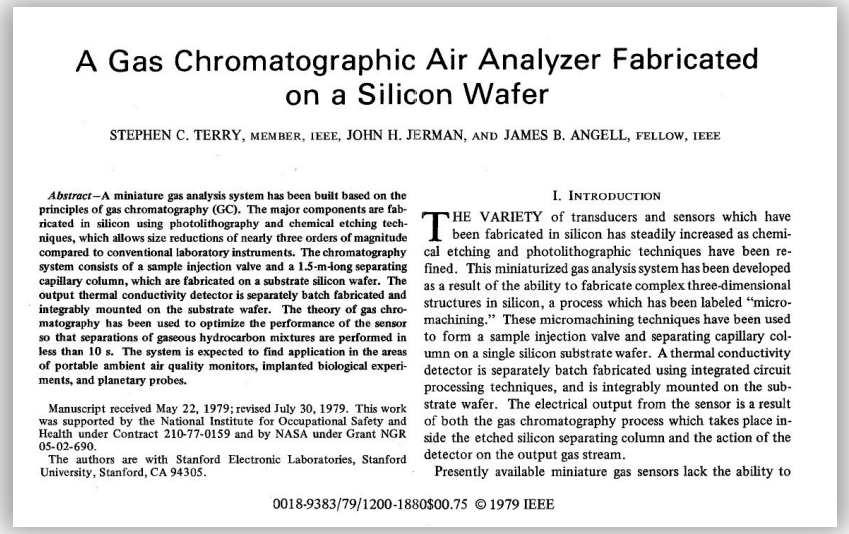
fluid flow on the small scale

- large surface area-to-volume ratios allow for highly efficient mass & heat transfer.
- mass and energy are transferred quickly when creating or homogenizing solute & temperature gradients.
- as scale decreases fluids are increasingly influenced by viscosity rather than inertia, which leads to laminar flow.
- high surface area-to-volume ratios ensure that surface tension influences and dominates fluid behaviour.

$$Re = \frac{\rho v \delta}{\mu} \qquad Pe = \frac{v\delta}{D} \qquad Ca = \frac{v\mu}{\gamma}$$

Chem, 2, 2017, 201; Nature Chemistry, 5, 2013, 905

the beginning: Stanford GC chip



A Gas Chromatographic Air Analyzer Fabricated on a Silicon Wafer

STEPHEN C. TERRY, MEMBER, IEEE, JOHN H. JERMAN, AND JAMES B. ANGELL, FELLOW, IEEE

Abstract—A miniature gas analysis system has been built based on the principles of gas chromatography (GC). The major components are fabricated in silicon using photolithography and chemical etching techniques, which allows size reductions of nearly three orders of magnitude compared to conventional laboratory instruments. The chromatography system consists of a sample injection valve and a 1.5-m-long separating capillary column, which are fabricated on a substrate silicon wafer. The output thermal conductivity detector is separately batch fabricated and integrably mounted on the substrate wafer. The theory of gas chromatography has been used to optimize the performance of the sensor so that separations of gaseous hydrocarbon mixtures are performed in less than 10 s. The system is expected to find application in the areas of portable ambient air quality monitors, implanted biological experiments, and planetary probes.

Manuscript received May 22, 1979; revised July 30, 1979. This work was supported by the National Institute for Occupational Safety and Health under Contract 210-77-0159 and by NASA under Grant NGR 05-02-690.

The authors are with Stanford Electronic Laboratories, Stanford University, Stanford, CA 94305.

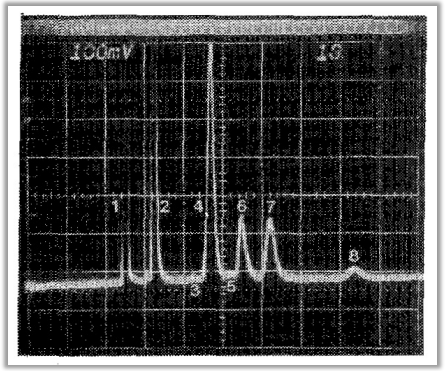
I. Introduction

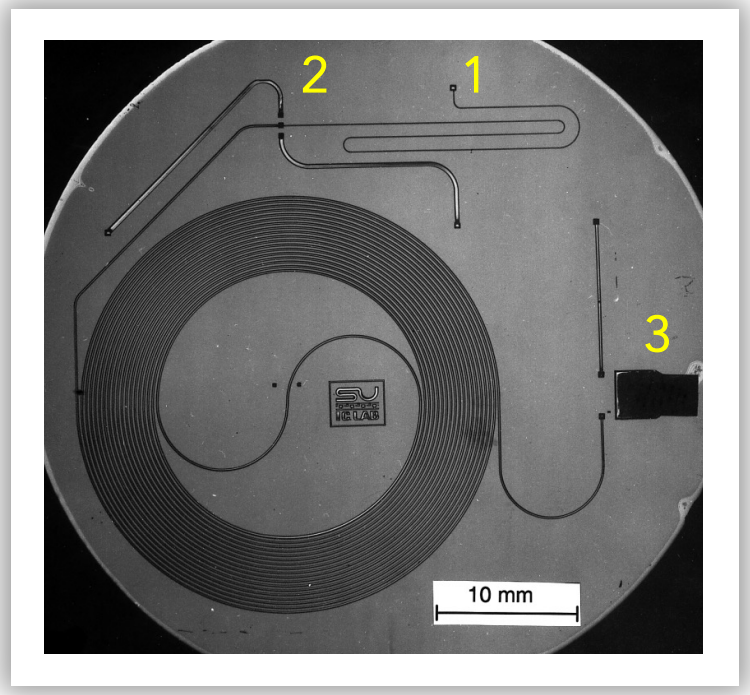
THE VARIETY of transducers and sensors which have been fabricated in silicon has steadily increased as chemical etching and photolithographic techniques have been refined. This miniaturized gas analysis system has been developed as a result of the ability to fabricate complex three-dimensional structures in silicon, a process which has been labeled "micromachining." These micromachining techniques have been used to form a sample injection valve and separating capillary column on a single silicon substrate wafer. A thermal conductivity detector is separately batch fabricated using integrated circuit processing techniques, and is integrably mounted on the substrate wafer. The electrical output from the sensor is a result of both the gas chromatography process which takes place inside the etched silicon separating column and the action of the detector on the output gas stream.

Presently available miniature gas sensors lack the ability to

0018-9383/79/1200-1880$00.75 © 1979 IEEE

chromatogram of 7 hydrocarbons using a silicone oil stationary phase and helium carrier





column width	200 um
column depth	30 um
column length	1.5 m

IEEE Trans. Electon Devices, 1979, 12, 1880

chromatography on a chip

Design of an Open-tubular Column Liquid Chromatograph Using Silicon Chip Technology

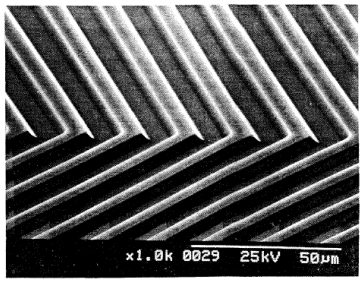
A. MANZ*, Y. MIYAHARA, J. MIURA, Y. WATANABE, H. MIYAGI and K. SATO
Central Research Laboratory, Hitachi Ltd., 1-280 Higashikoigakubo, Kokubunji, Tokyo 185 (Japan)

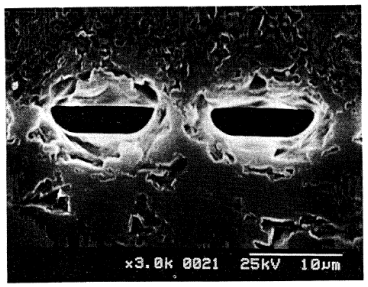
Abstract

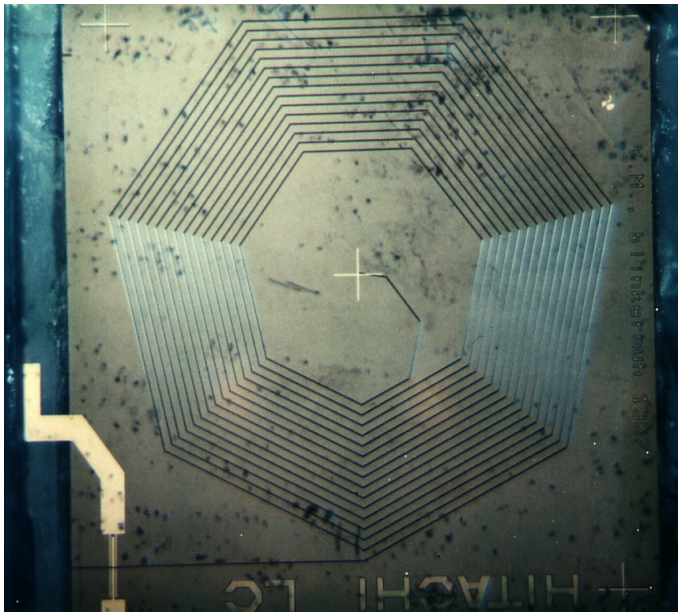
A novel concept of high pressure liquid chromatography is presented, involving a silicon chip with an open-tubular column and a conductometric detector, a chip holder and a pressure pulse driven injector using a conventional liquid chromatography pump and valves. The design and optimization of the chromatograph and the chip are discussed. A 5 × 5 mm chip containing an open-tubular column of 6 μm × 2 μm × 15 cm was fabricated, which has theoretical separation efficiencies of 8000 and 25 000 plates in 1 and 5 min, respectively. The total column volume is 1.5 nanoliter and the detection cell volume 1.2 picoliter.

non-retained component [2, 3]. Until now, only fused silica and glass capillaries have been used as columns. The use of a silicon wafer for producing an open-tubular LC column similar to the 'Stanford gas chromatograph' [4] seems attractive, especially for reducing the column inner diameter, the column length and for an easy positioning of the detection sensor. Such an LC chip is a combination of the high selectivity of an LC separation with the low production cost of a lesser selective chemical sensor and could be an excellent alternative for many types of conventional LC and sensing techniques.

Theory







column length	15 cm
cross-section	6 um x 2 um
column volume	1.5 nL
detection volume	1.2 pL

Sensors & Actuators B1, 1990, 249

making microfluidic devices is easy

Anal. Chem. **1998,** *70,* 4974−4984

Rapid Prototyping of Microfluidic Systems in Poly(dimethylsiloxane)

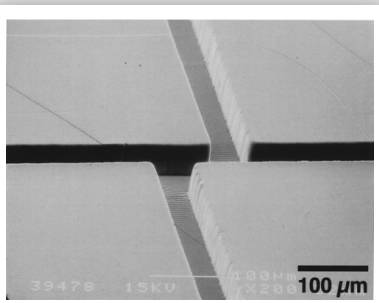
David C. Duffy, J. Cooper McDonald, Olivier J. A. Schueller, and George M. Whitesides*

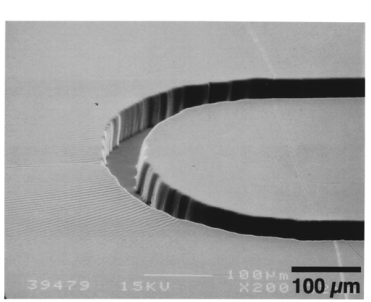
Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

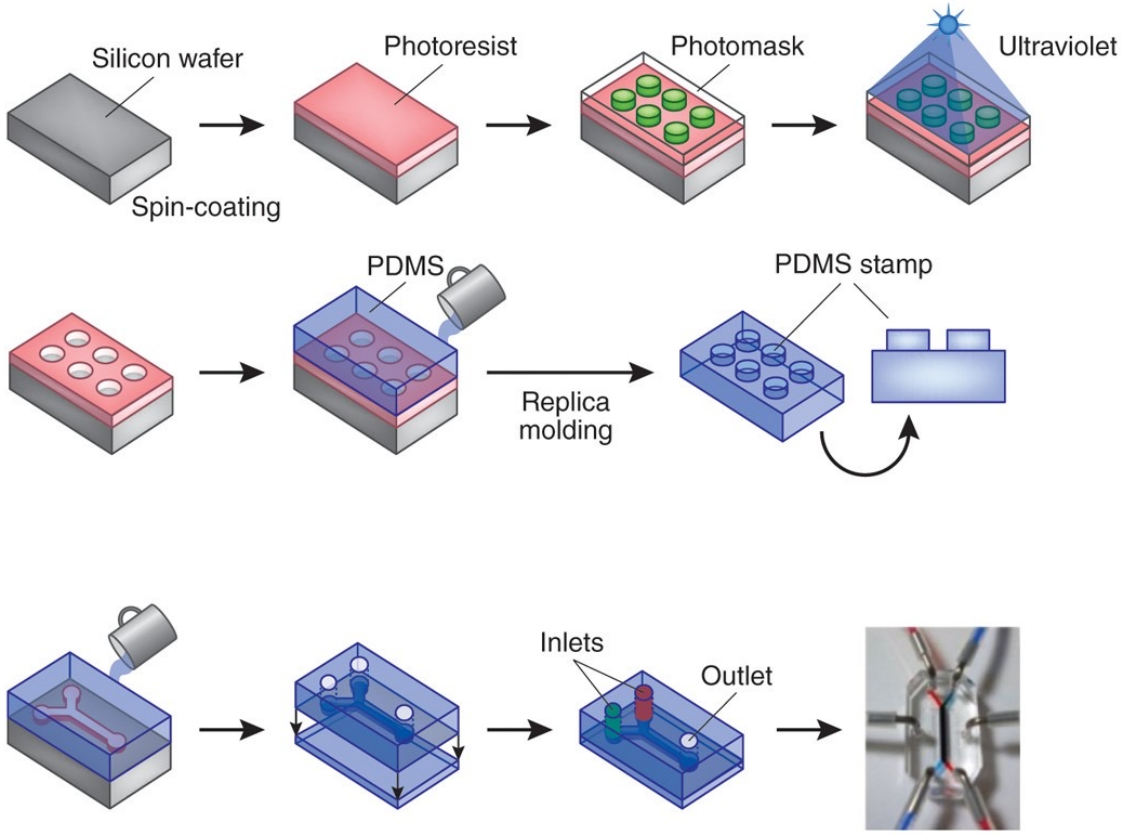
This paper describes a procedure that makes it possible to design and fabricate (including sealing) microfluidic systems in an elastomeric material—poly(dimethylsiloxane) (PDMS)—in less than 24 h. A network of microfluidic channels (with width >20 μm) is designed in a CAD program. This design is converted into a transparency by a high-resolution printer; this transparency is used as a mask in photolithography to create a master in positive relief photoresist. PDMS cast against the master yields a polymeric replica containing a network of channels. The

genetic analysis,[1] clinical diagnostics,[5−14] drug screening,[15] and environmental monitoring.[16]

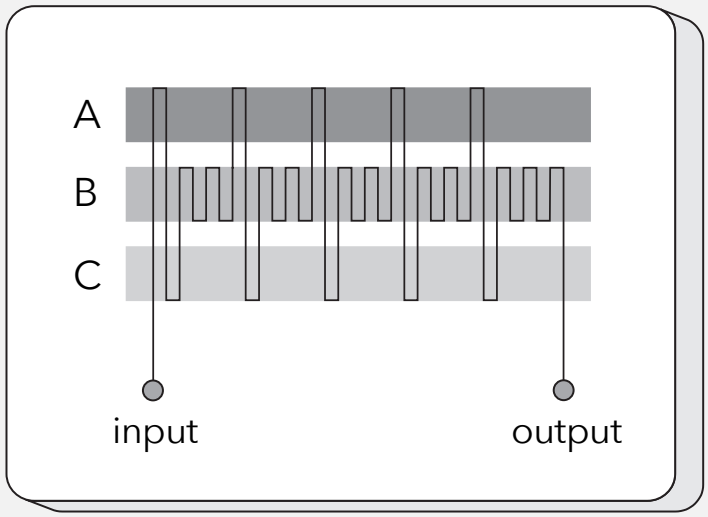
μTAS perform the functions of large analytical devices in small, often disposable, units.[1−4] The potential benefits of μTAS, relative to systems of conventional size, include (i) reduced consumption of samples and reagents, (ii) shorter analysis times, (iii) greater sensitivity, (iv) portability that allows in situ and real-time analysis, and (v) disposability. As a consequence of these potential benefits, there has been considerable interest in the development of μTAS.[8,9]

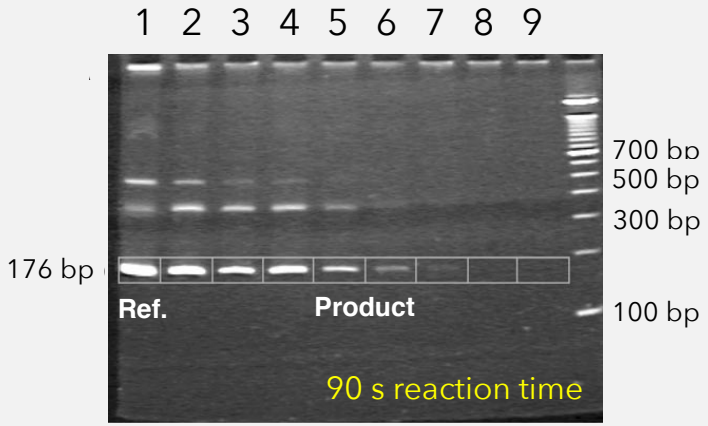


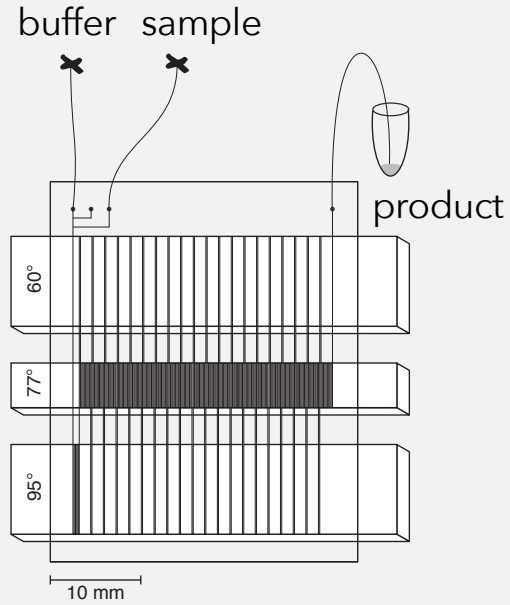




Analytical Chemistry, 1998, 70, 4974





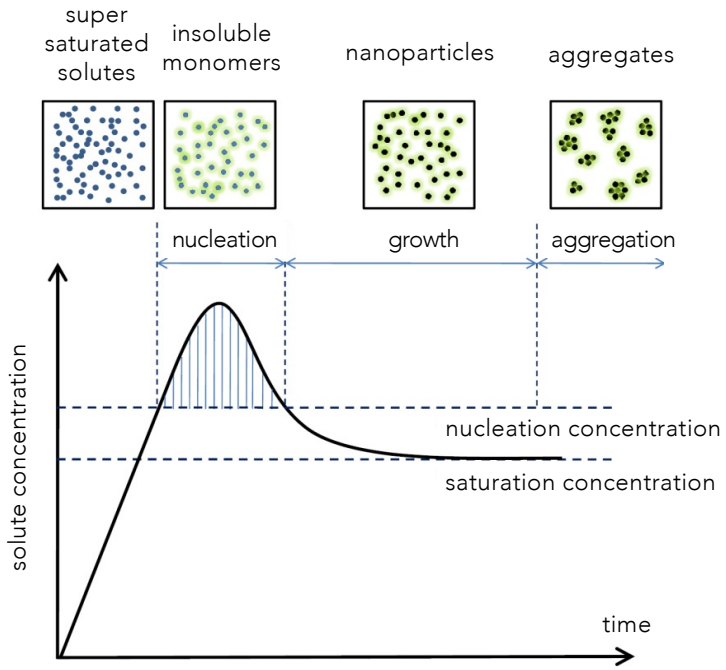


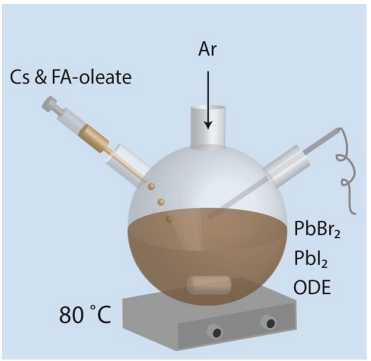
continuous flow PCR

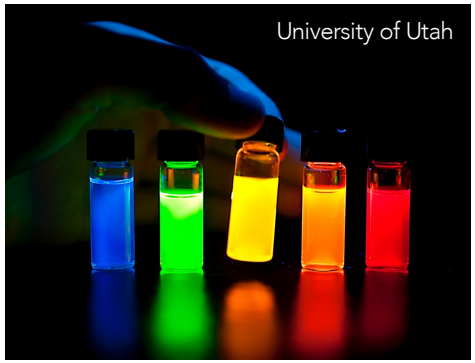
- 20-cycle PCR of DNA gyrase gene of Neisseria gonorrhoeae in times as low as 90 seconds.
- utility compromised by high surface area-to-volumes and residence time distributions.

Science, 1998, 280, 246

bottom-up nanocrystal synthesis







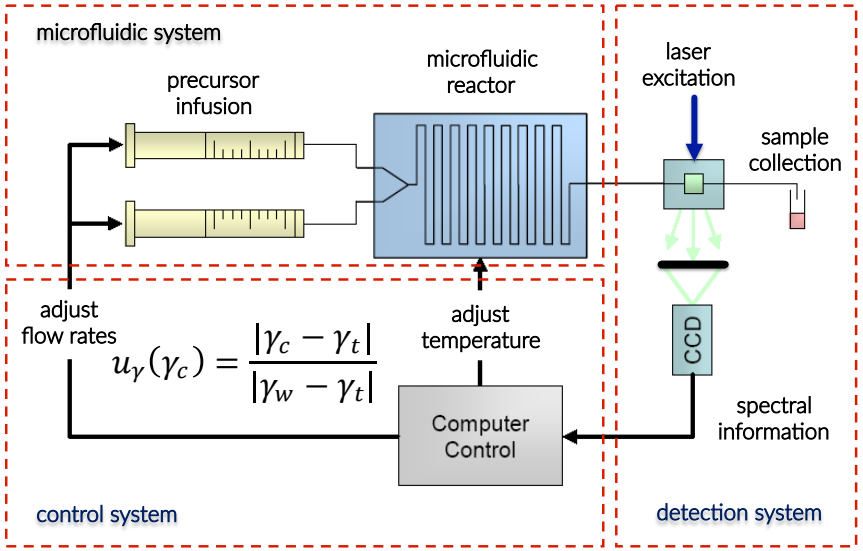
- nanoparticles are characterized by crystal radii which are small relative to Bohr radius → tunable optical and electronic properties.
- properties depend on the size & shape of nanoparticles.
- high monodispersity needed for many applications.
- current synthetic routes are complex & rely on constrained growth, kinetic control or post hoc product selection to yield high quality particles.
- rapid nucleation and controlled growth enabled by ensuring rapid reagent mixing and uniform reaction conditions.

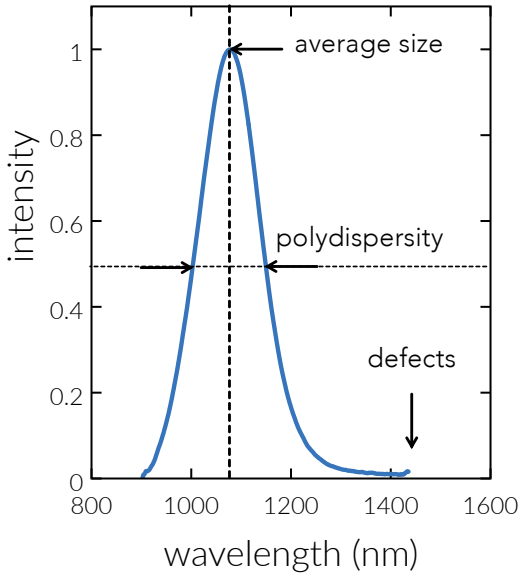
Chemical Communications, 2002, 1136, ACS Nano 2018, 12, 5504

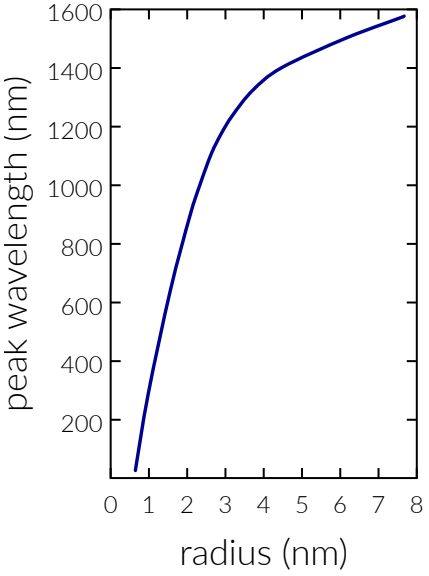
- aim is to create an autonomous 'black-box' system to controllably synthesize nanoparticles.
- the system incorporates a reactor, detector, control algorithm and a means of changing system variables (such as temperature, reaction time and reagent concentration).
- the system is updated in a way that aims to minimize a scalar dissatisfaction coefficient describing an observation.

$$U(\lambda_c, I_c) = \left(k\alpha \frac{|\lambda_c - \lambda_t|}{|\lambda_w - \lambda_t|} + 1\right)\left(k\beta \frac{|I_c - I_t|}{|I_w - I_t|} + 1\right) - \frac{1}{k}$$

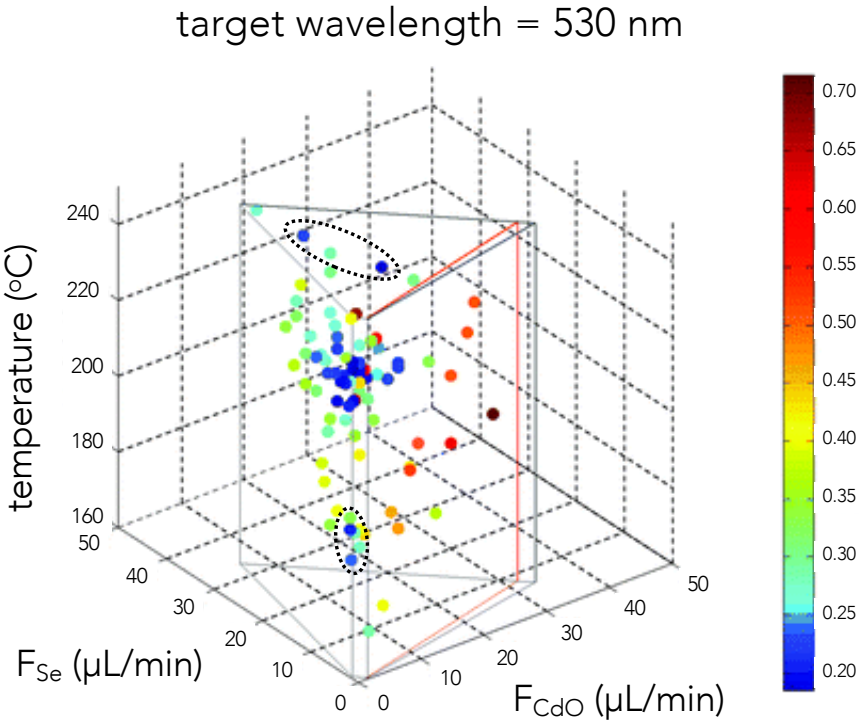
intelligent synthesis



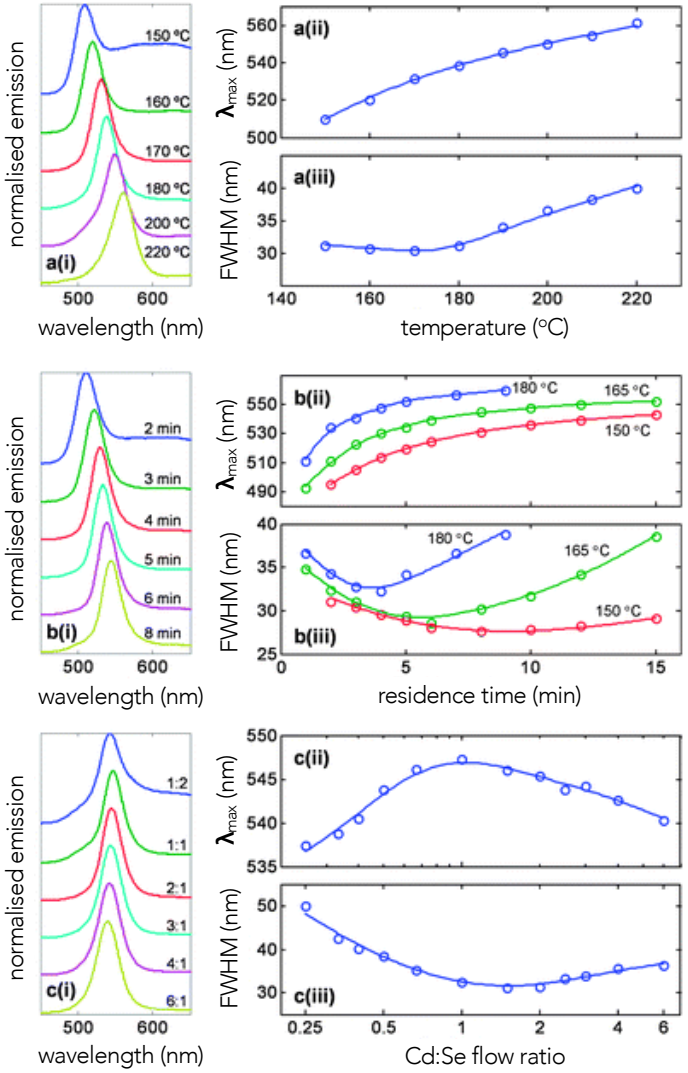




Lab Chip, 2008, 7, 1434

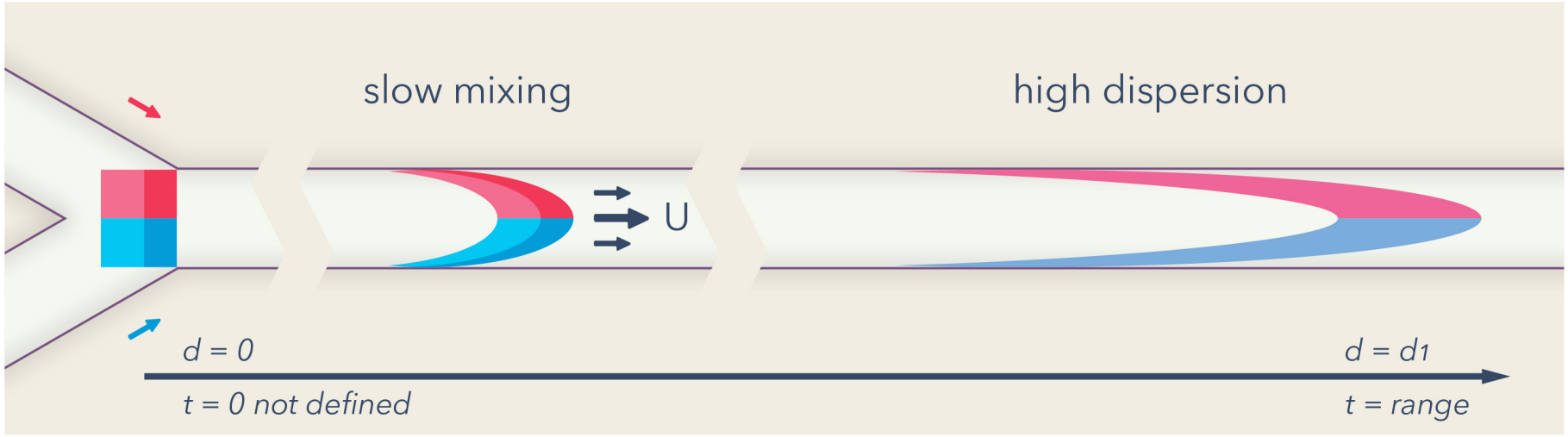


optimization of particle properties



Lab Chip, 2008, 7, 1434; Lab Chip 2011, 11, 1221

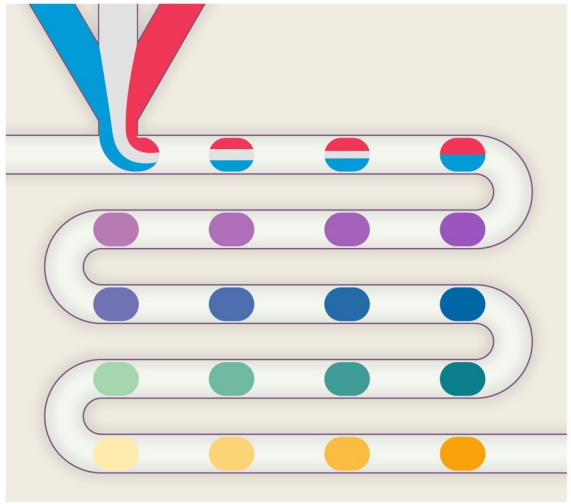
...but continuous flows are problematic

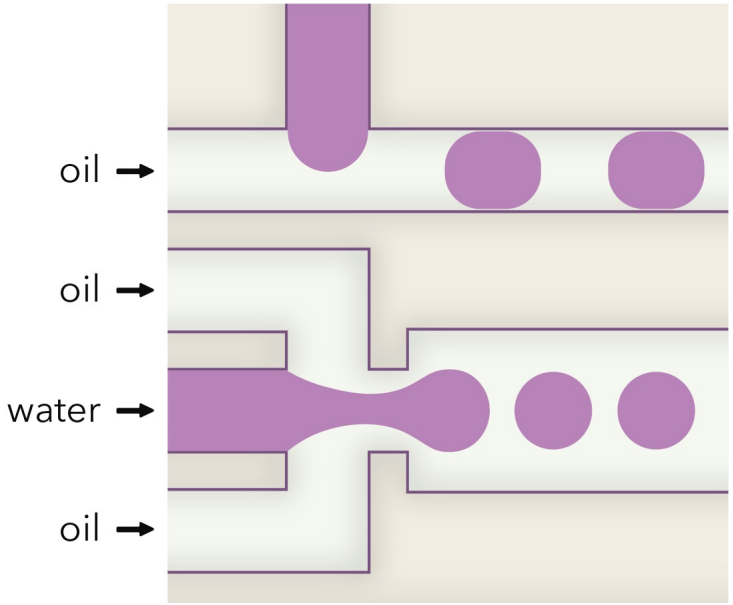


$$\Delta\tau(\alpha) = \tau(\alpha) - \frac{\bar{\tau}}{2} = \frac{\bar{\tau}}{2}\left(\frac{1}{\sqrt{1-\alpha}} - 1\right)$$

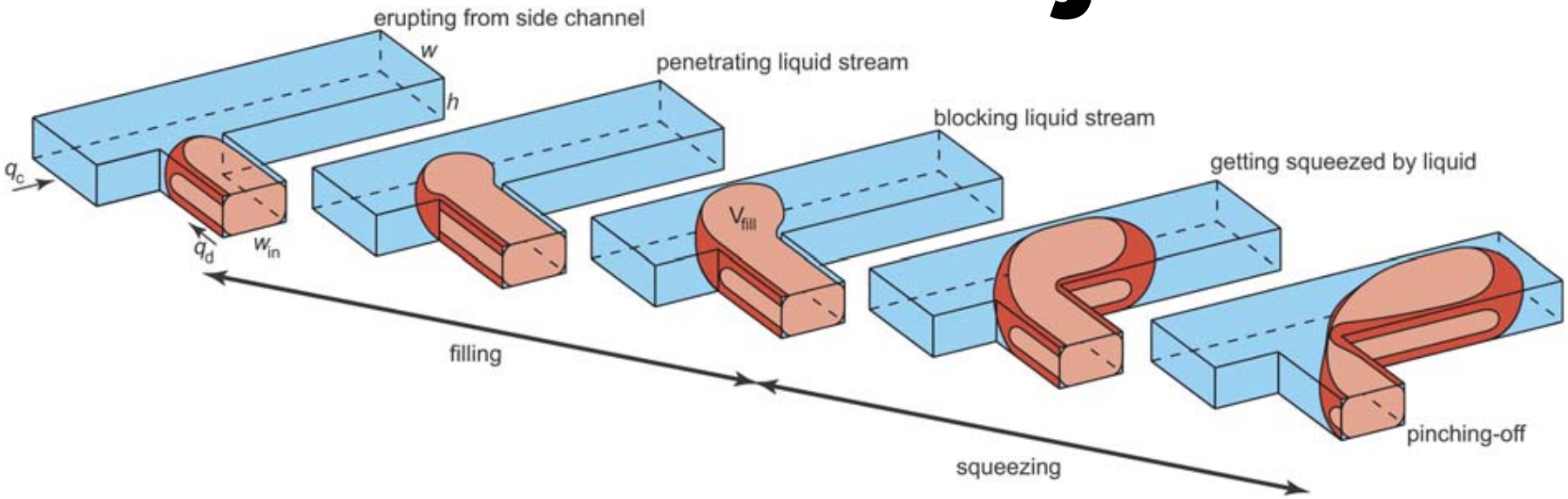
- droplets are completely isolated and define individual chemical/biological reactors.
- droplets can be generated using passive tools such as flow-focusing geometries and tee-junctions.
- droplet volumes can be defined with precision (i.e. monodisperse).
- mass transport occurs without dispersion (no residence time distributions).
- droplet size and payload can be varied rapidly and precisely.
- droplets can be generated at frequencies > 1 kHz.

droplet-based microfluidics



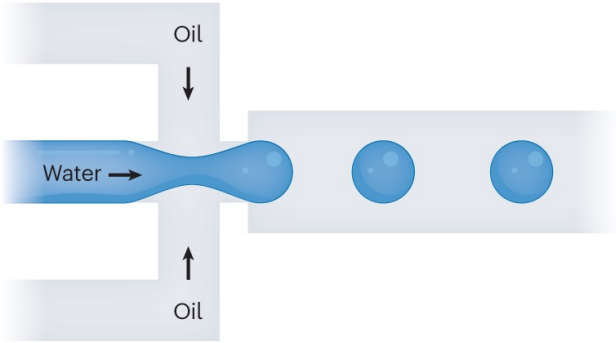


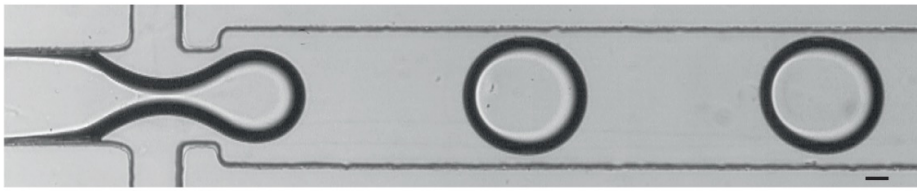
T junctions

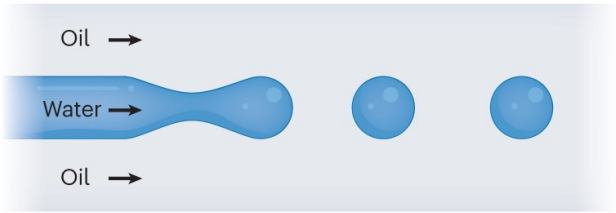


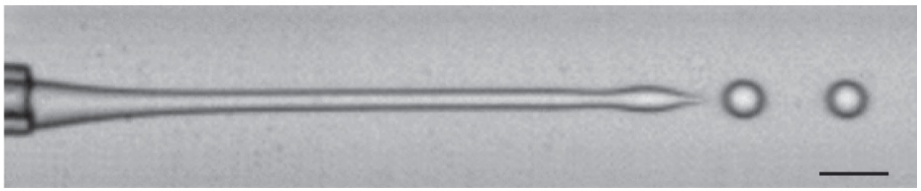
- continuous and dispersed phase are injected from two branches of a T-junction.
- droplets arise as a result of the shear force and interfacial tension at the fluid-fluid interface.
- $\sigma_{w/o}$ must be sufficiently high in order to avoid destruction of plugs by shear.
- droplets are large enough to touch the channel walls but do not wet the walls since $\sigma_{w/s} > \sigma_{w/o}$ (w = water, o = oil, s = substrate).
- at low *Ca*, pressure build up is responsible for droplet formation, at high *Ca*, viscous shear is important.

flow focusing and co-flows



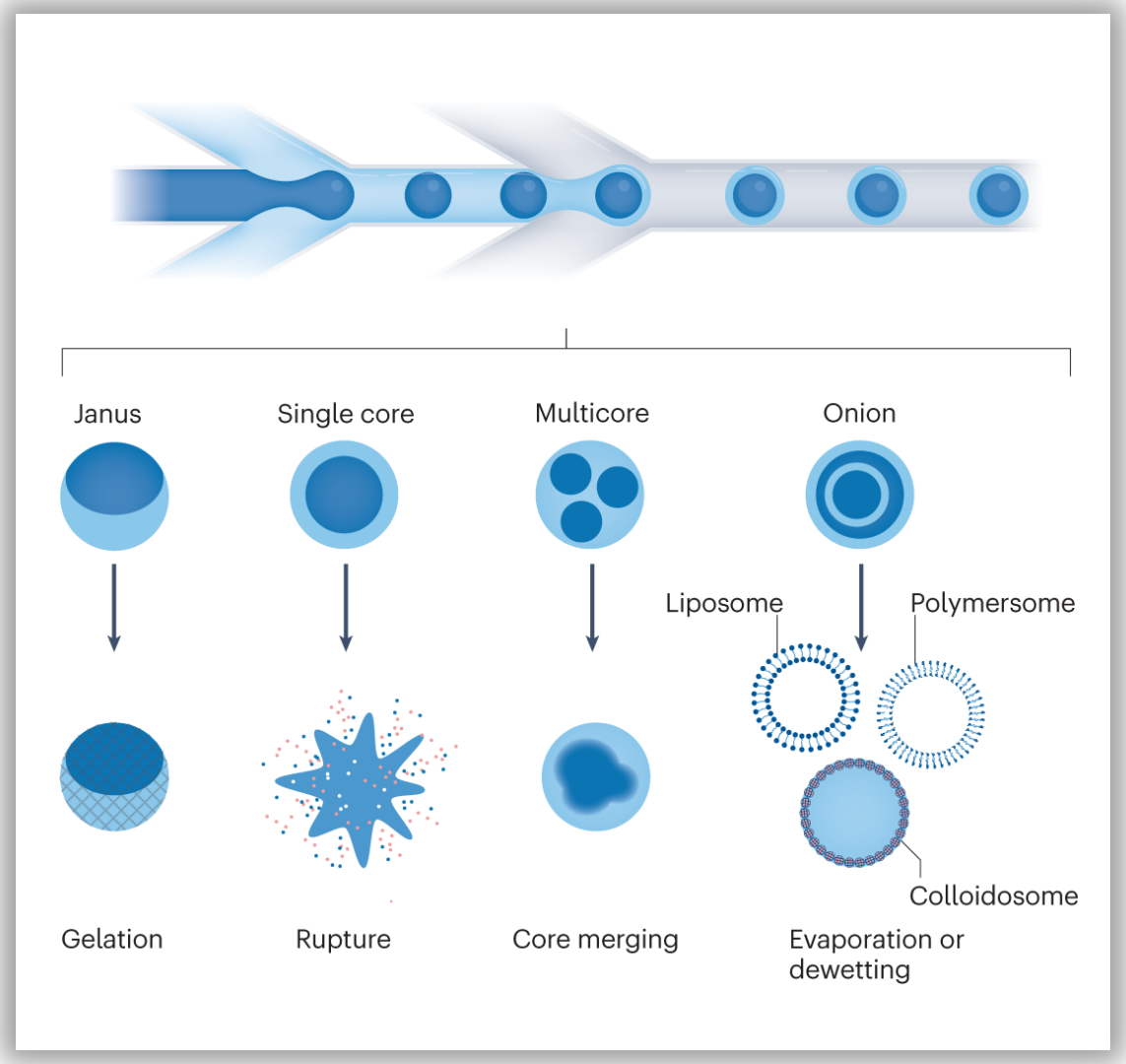






- flow-focusing geometry - 3D or 2D immiscible flows are accelerated before entering a nozzle or constriction, where pressure & viscous stress elongate the inner fluid, which eventually breaks.

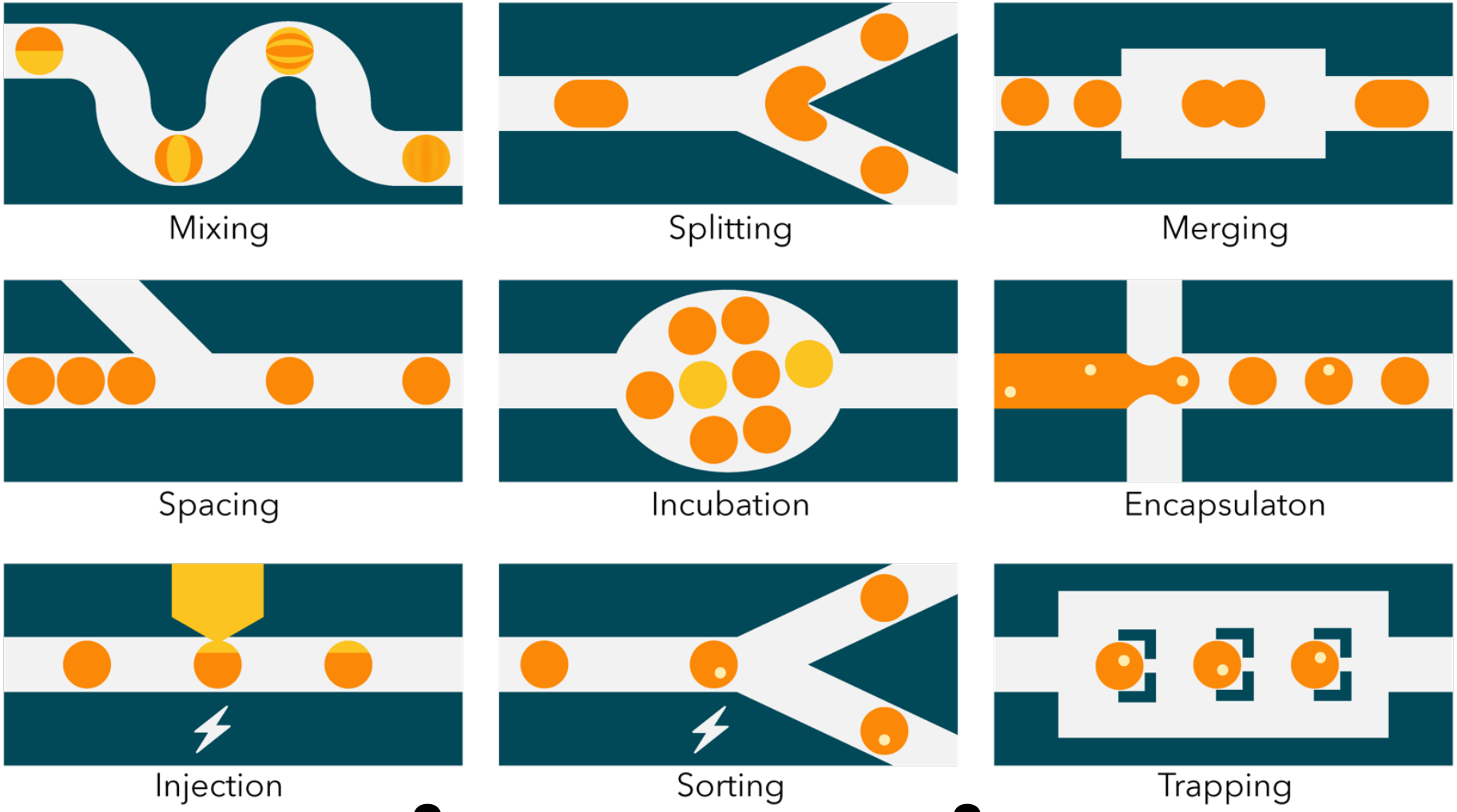
- co-flow geometry - dispersed and continuous phase fluid streams are united by co-flowing immiscible fluids through a tapered capillary in which streamwise forces exceed interfacial tension.



Nature Reviews Methods Primes 2023 3, 32

emulsion templating

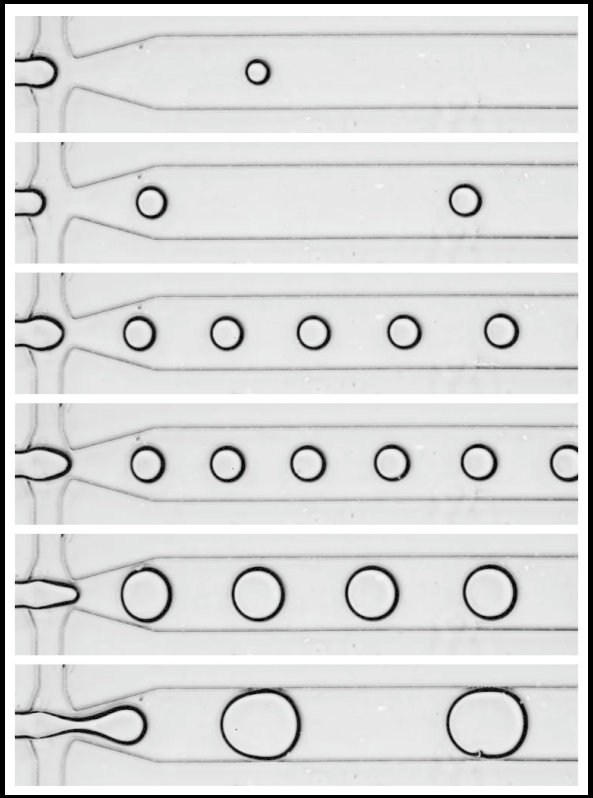
- multiple emulsion templating involves encapsulating a droplet in another droplet of an immiscible phase.
- double emulsion, biphasic Janus particles, multicore double emulsions and onion-shaped multiple emulsions can be controllably formed.
- thermal, pH or chemical cues can be used to gel, rupture or merge internal structures.
- dewetting can transform multiple emulsions into unilamellar liposomes, polymersomes and colloidosomes.



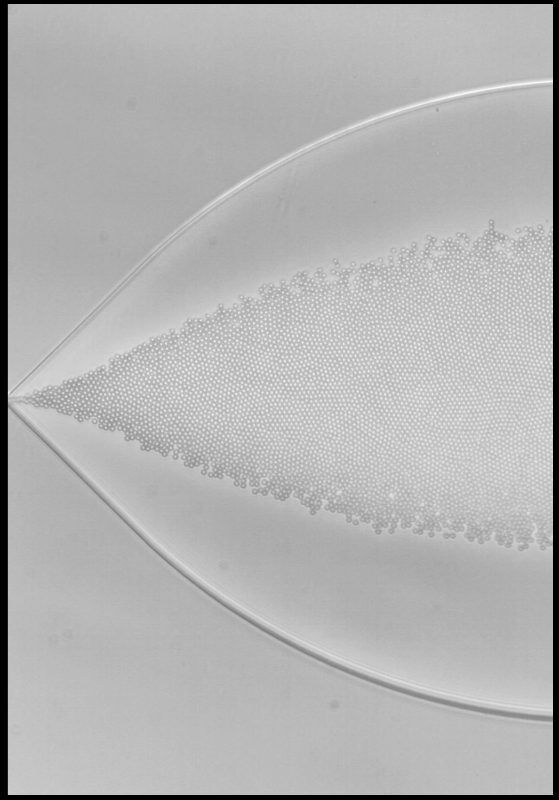
unit operations

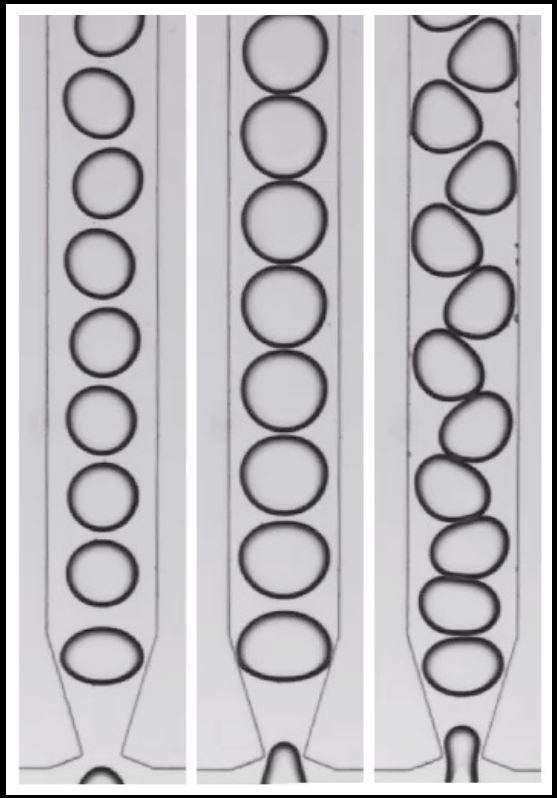
droplet generation

37-790 pL, 50-1000 Hz

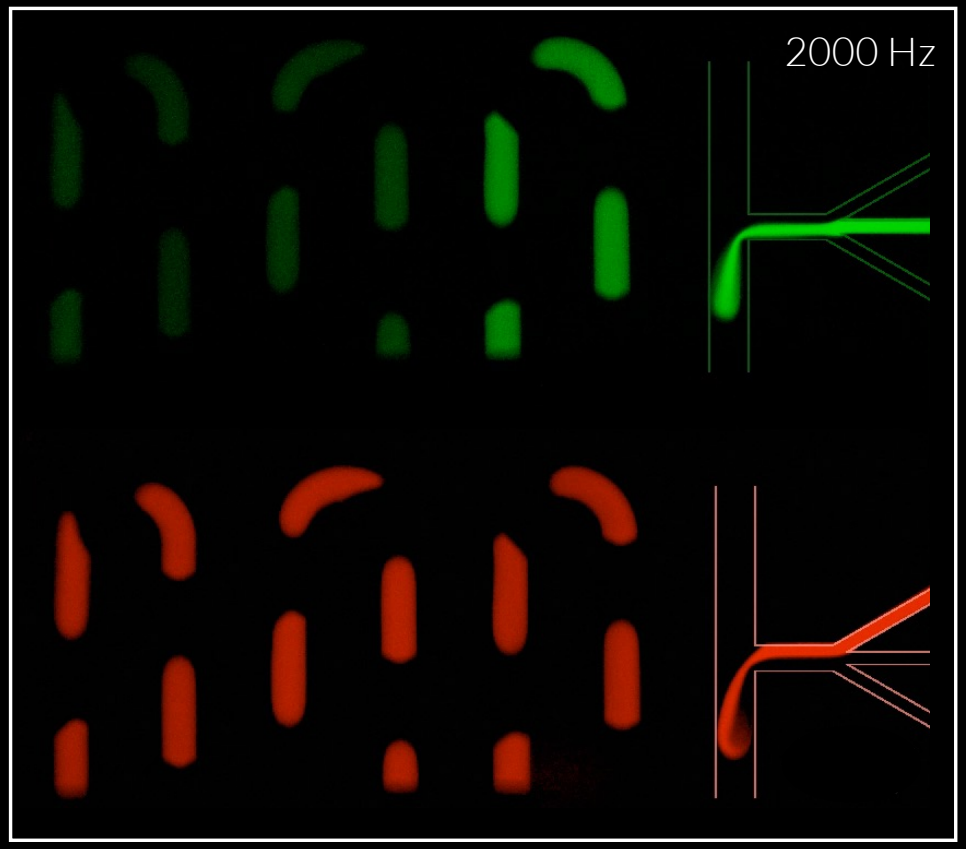


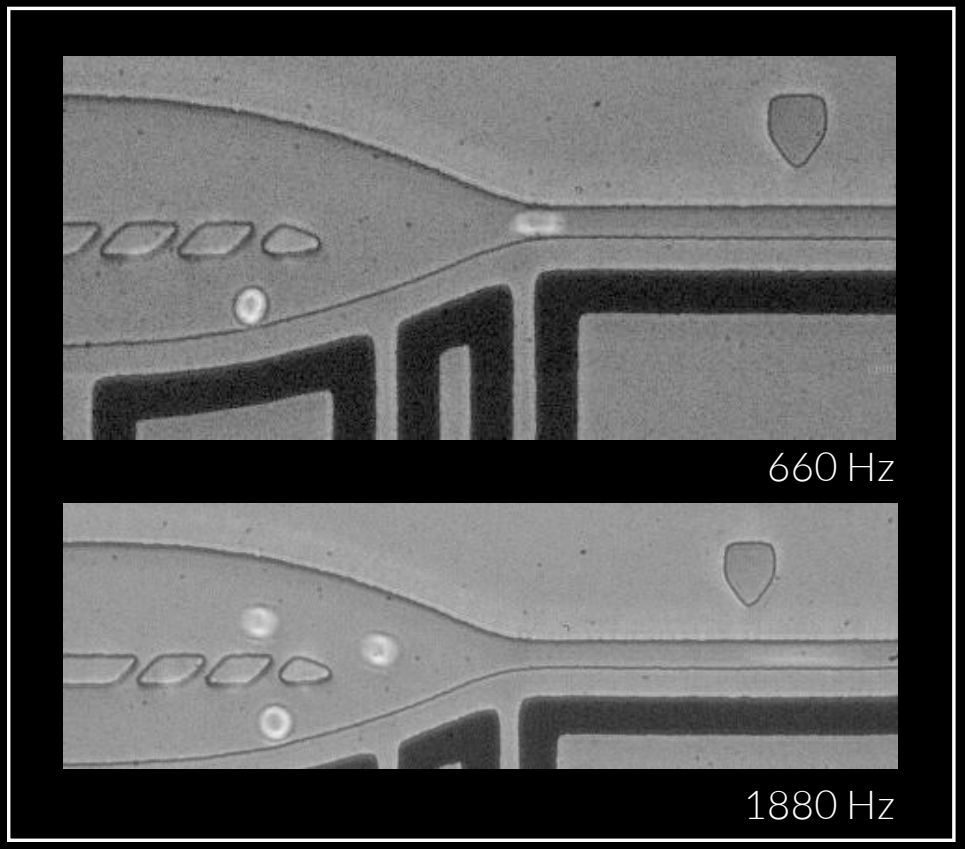
75 fL, 22,000 s^{-1}



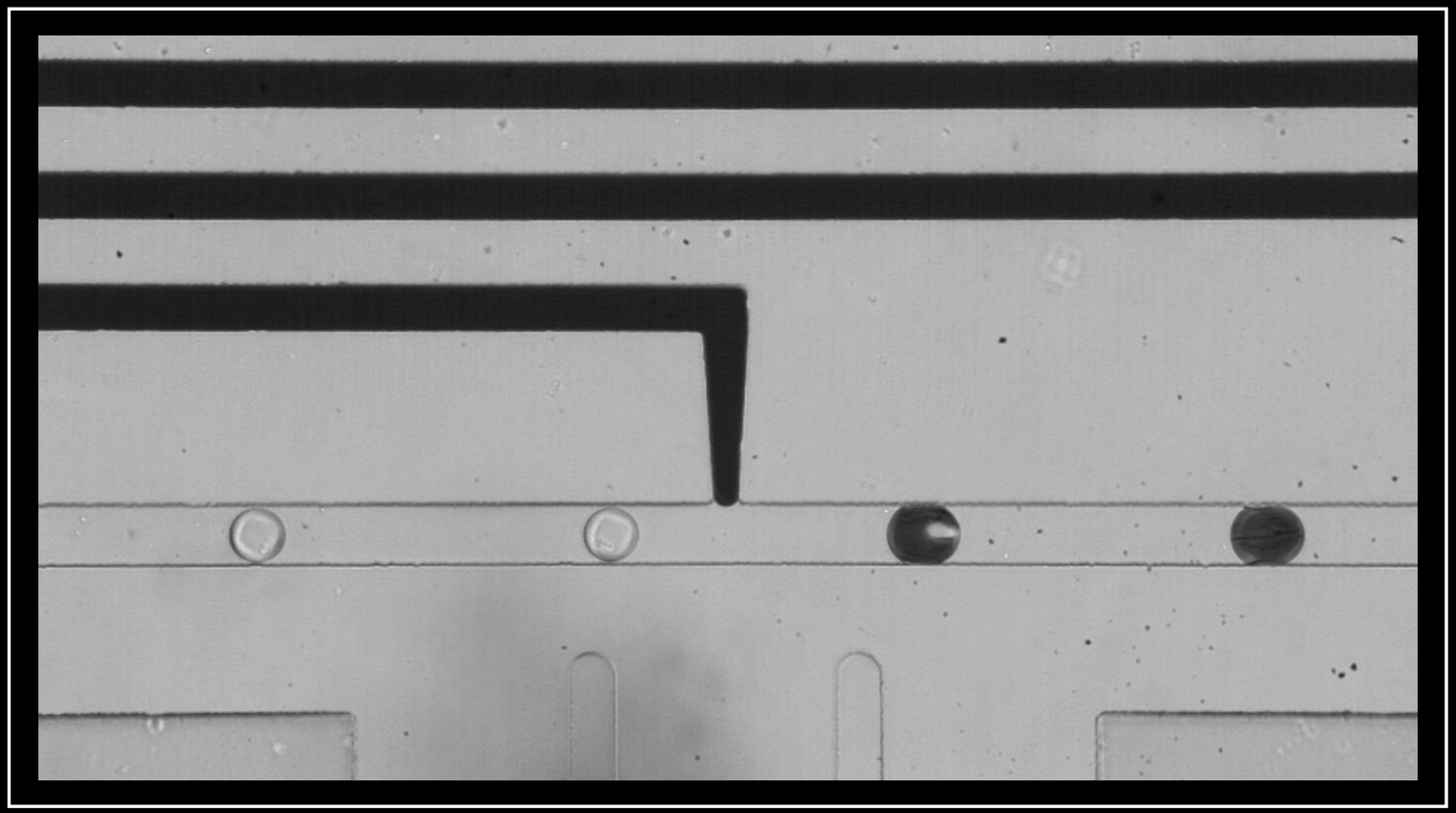


280-370 pL, 1000 Hz



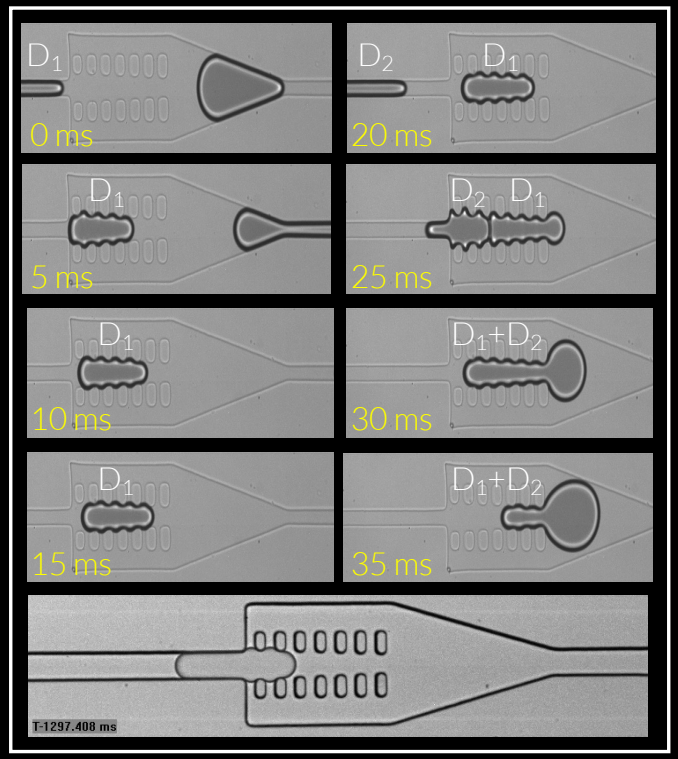


payload control

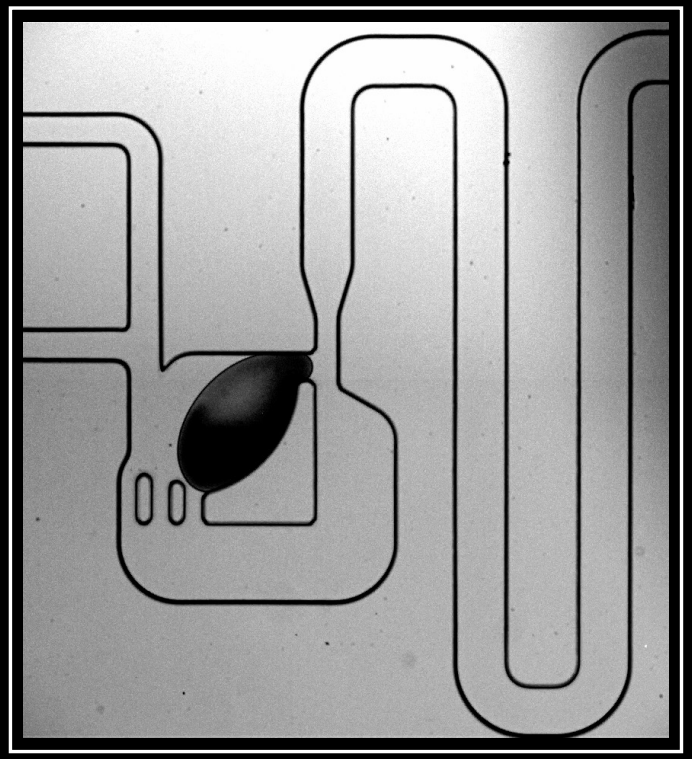


payload control

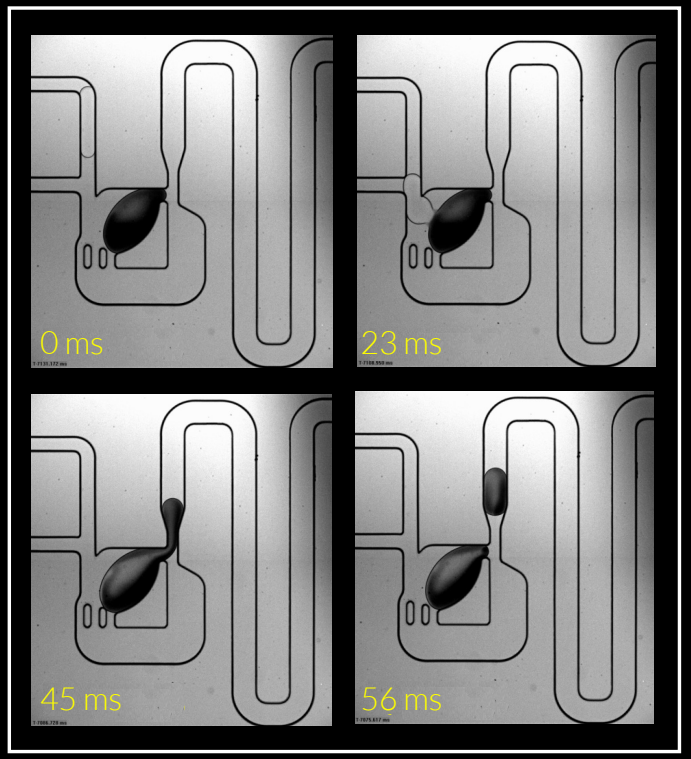
fusion and dilution



Lab Chip 2008, 8, 1837

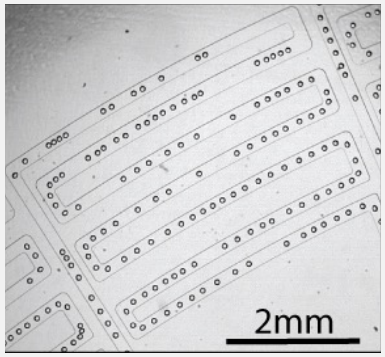


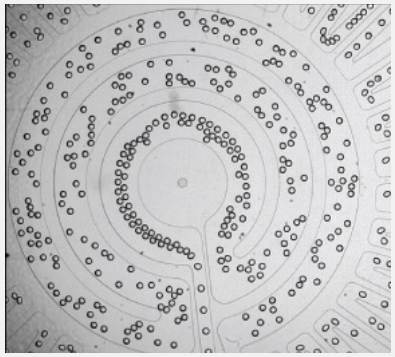
Nature Chemistry 2011, 3, 428

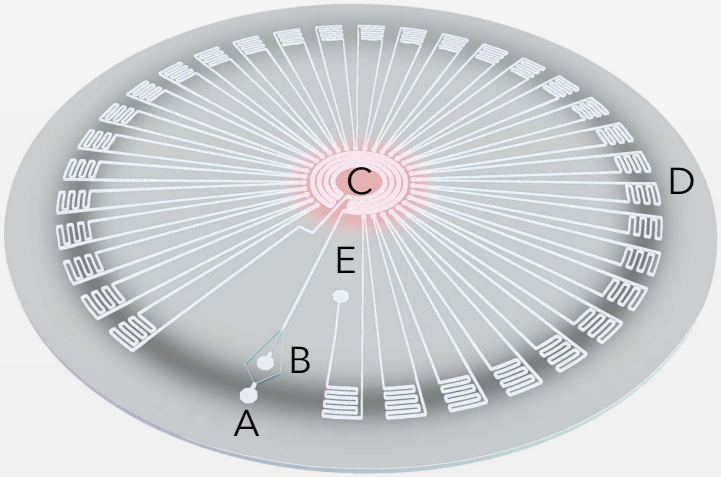


Nature Chemistry 2011, 3, 437

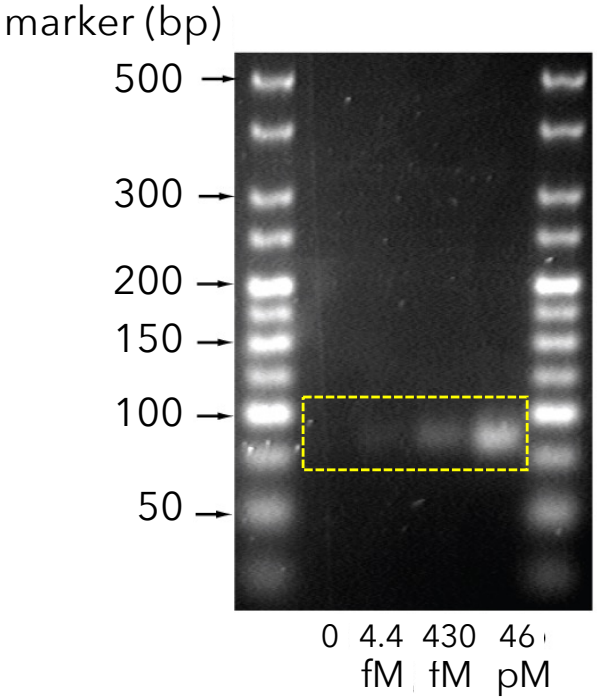
exploitation of differences in the hydrodynamic resistance of the continuous phase and surface tension of the discrete phase through the use of passive structures







(A) oil inlet, (B) aqueous inlets, (C) hot zone, (D) annealing and template extension zone, (E) emulsion outlet.

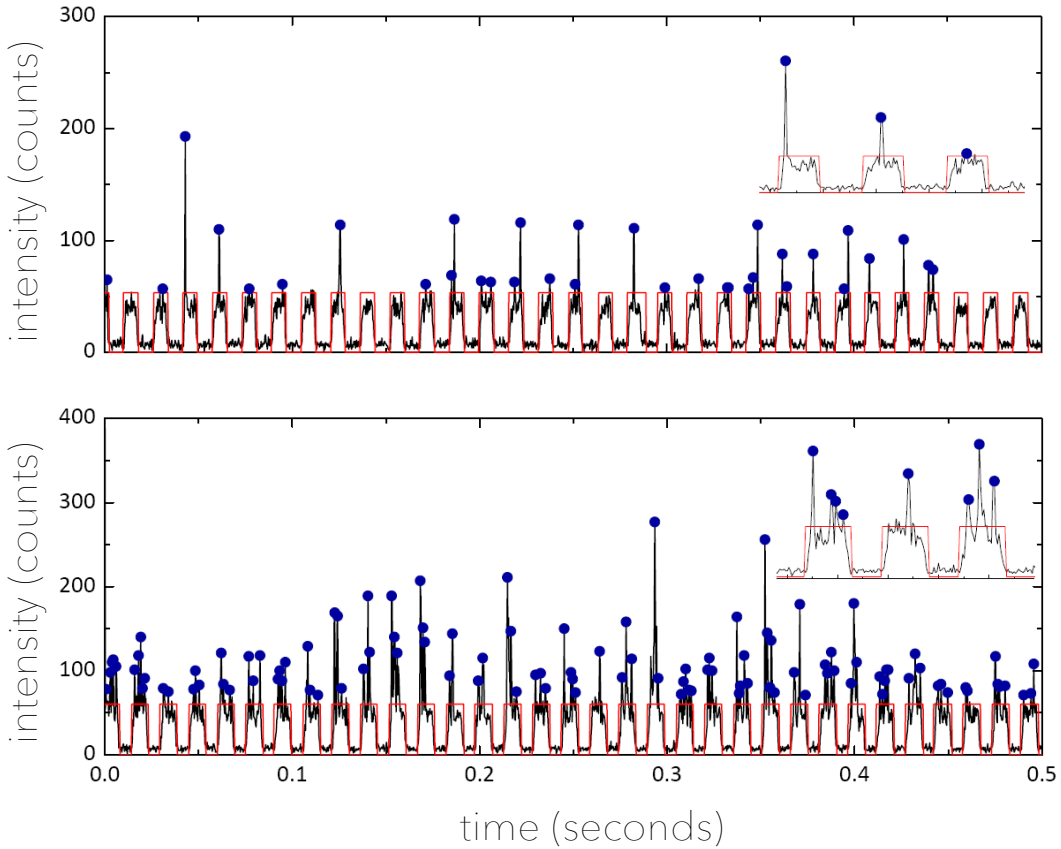


- 0.3 template/droplet and high amplification factors (<10^6).
- online assay of droplets enables efficient digital PCR.

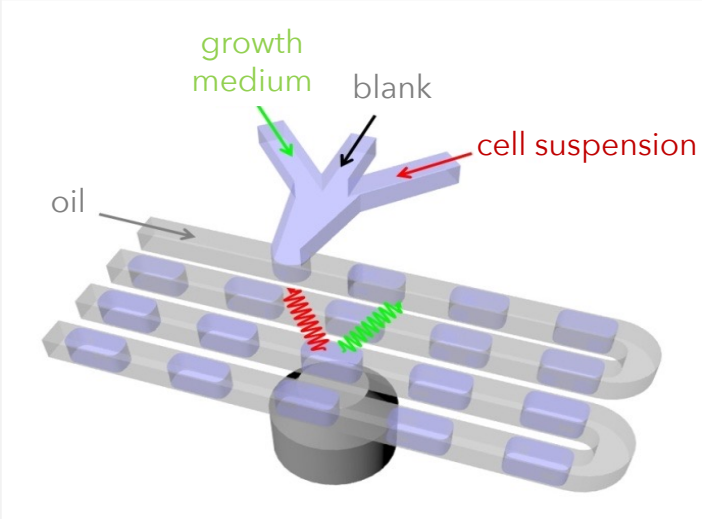
droplet PCR

Analytical Chemistry 2009, 81, 306

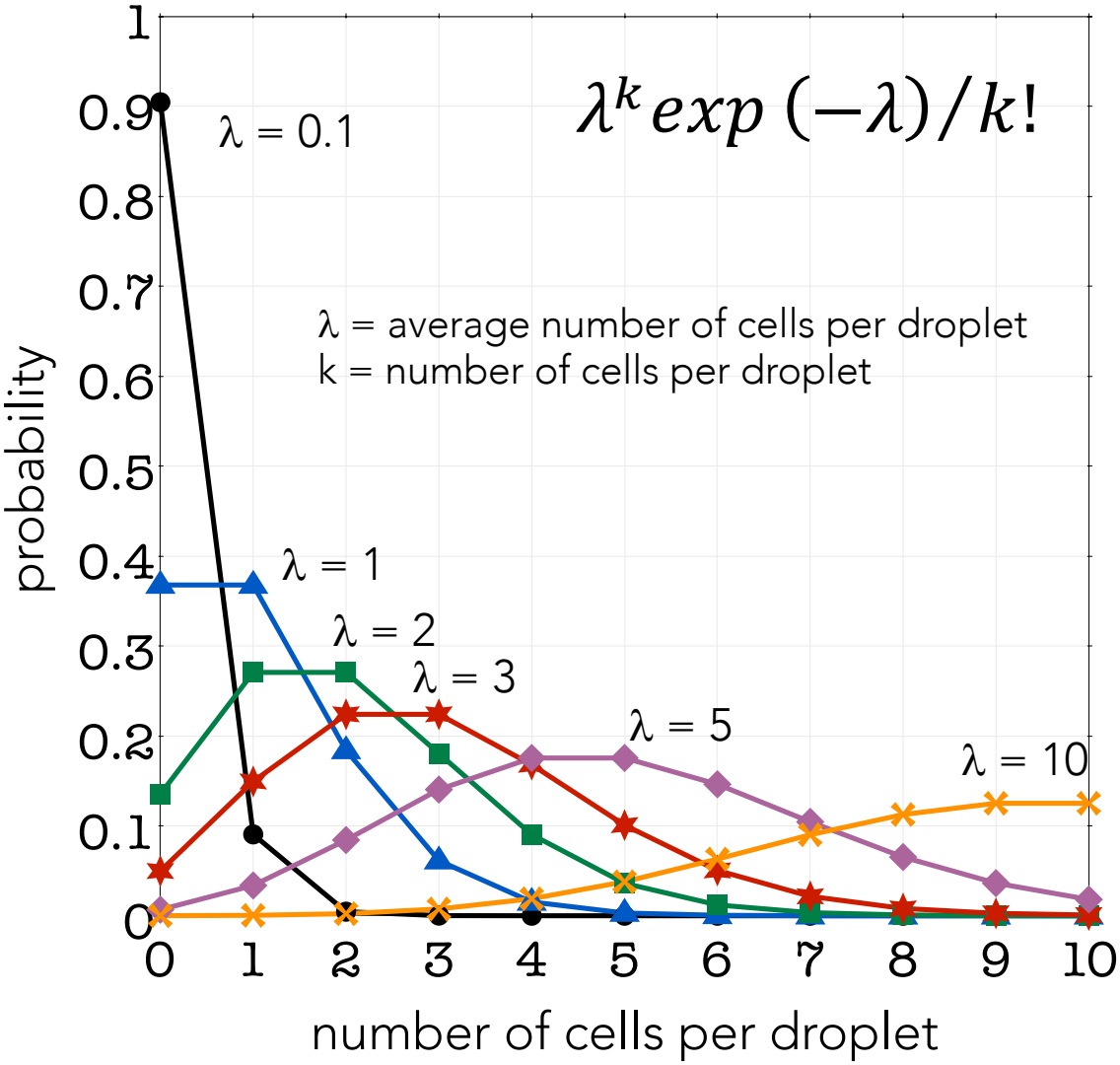
single cell analysis

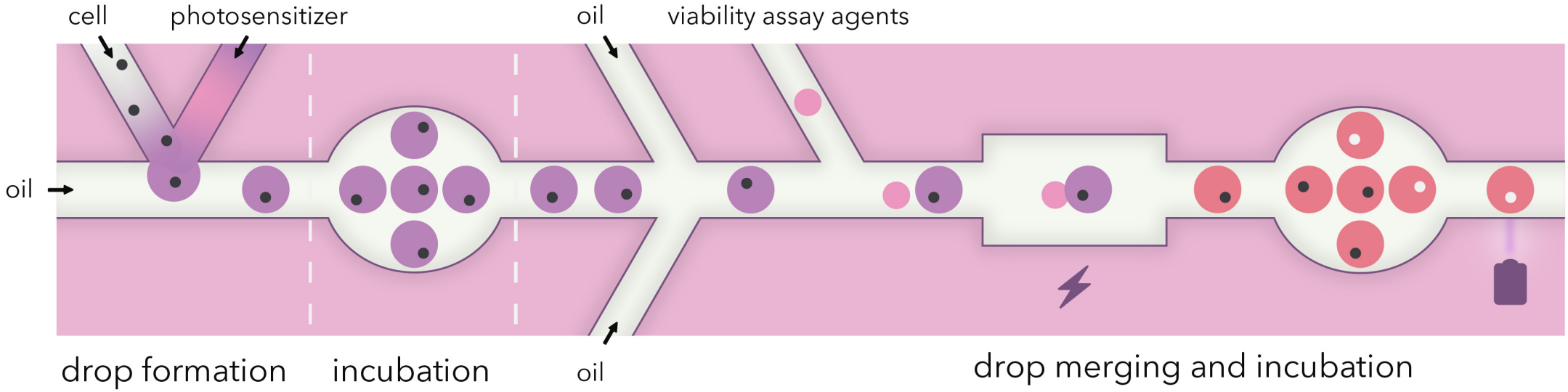


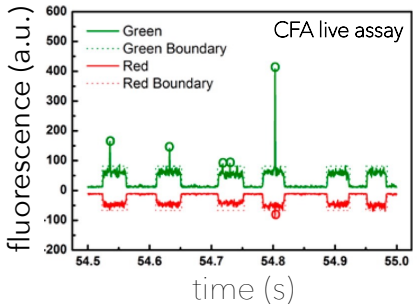
Chemical Communications 2007 1218

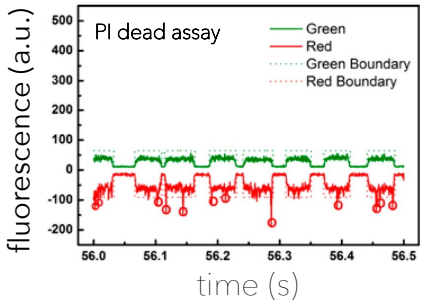


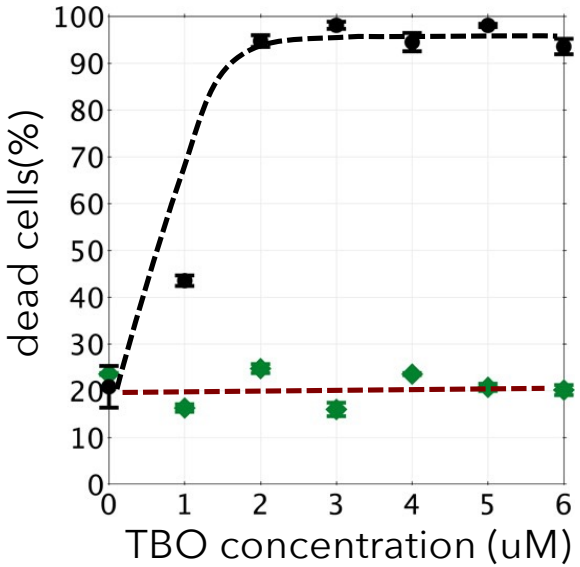
- control of input streams can be used to dose individual droplets with single or small numbers of cells.
- reduced droplet volumes remove problems associated with dilution and allow for single cell analysis.
- passive loading of cells into droplets is random and described by Poisson statistics.
- burst width/height used to statistically assess cell phenotype.


$\lambda^k exp\,(-\lambda)/k!$
λ = 0.1
λ = average number of cells per droplet
k = number of cells per droplet
λ = 1
λ = 2
λ = 3
λ = 5
λ = 10
probability
number of cells per droplet
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0 1 2 3 4 5 6 7 8 9 10





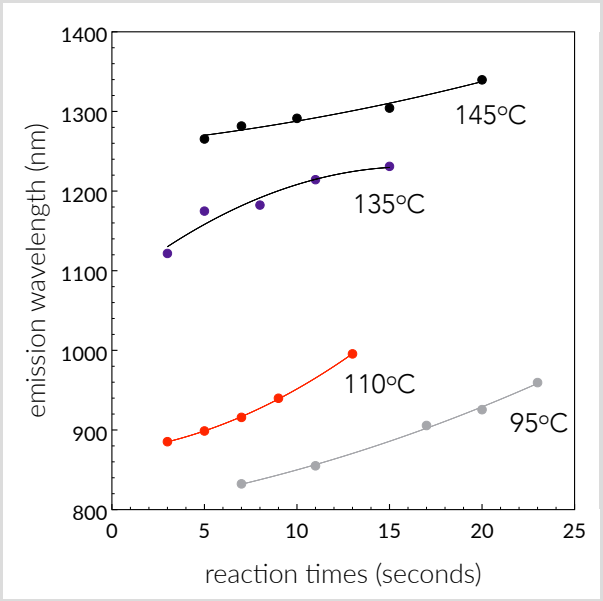


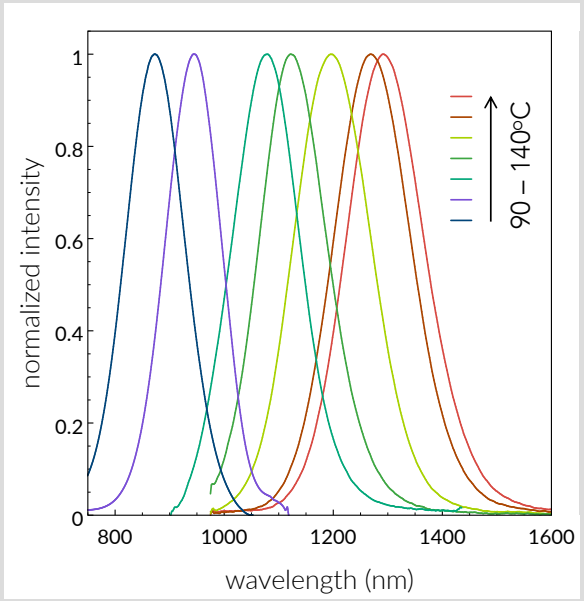


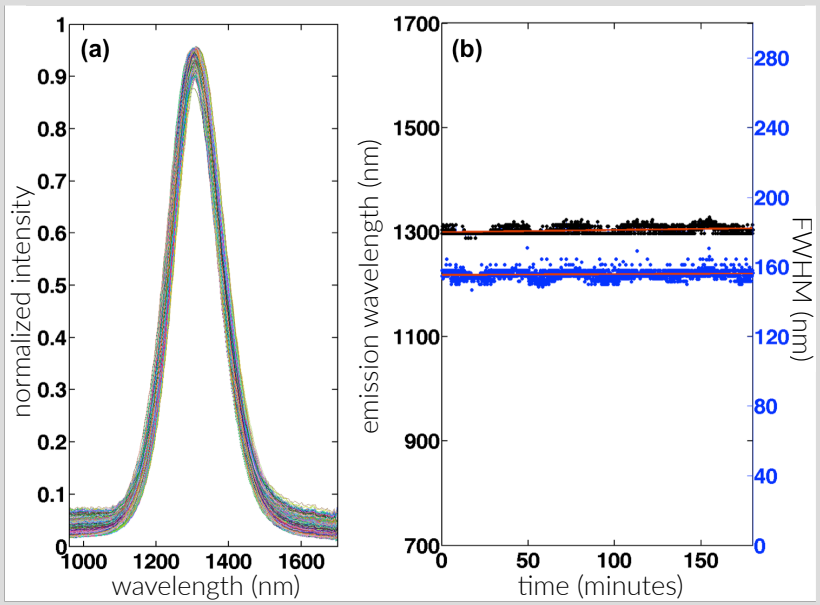
high-throughput droplet screening

- integrated droplet-based platform for high-throughput assessment of PDT photosensitizer efficacy.
- system encapsulates cells & sensitizer in droplets, exposes droplets to light, performs viability assays, incubates droplets & scores cell viability.

Analytical Chemistry 2014, 85, 8866







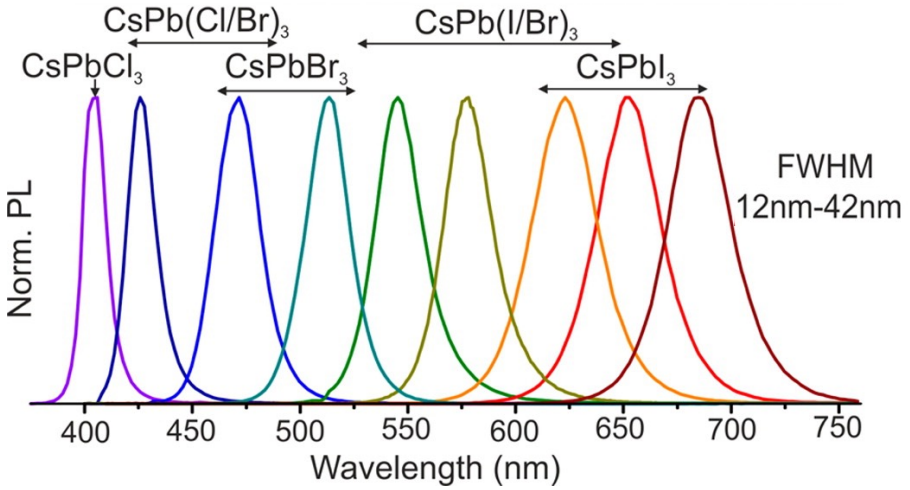
IV-VI quantum dot synthesis

- real-time monitoring allows for rapid optimization of reaction conditions and the synthesis of high quality PbS nanocrystals (emitting between 765–1600 nm) without any post-synthetic processing.
- NIR-emitting nanoparticles (with quantum yields above 30%) successfully used in Schottky solar cells with power conversion efficiencies of 4%.

Chemistry of Materials 2014, 26, 2975

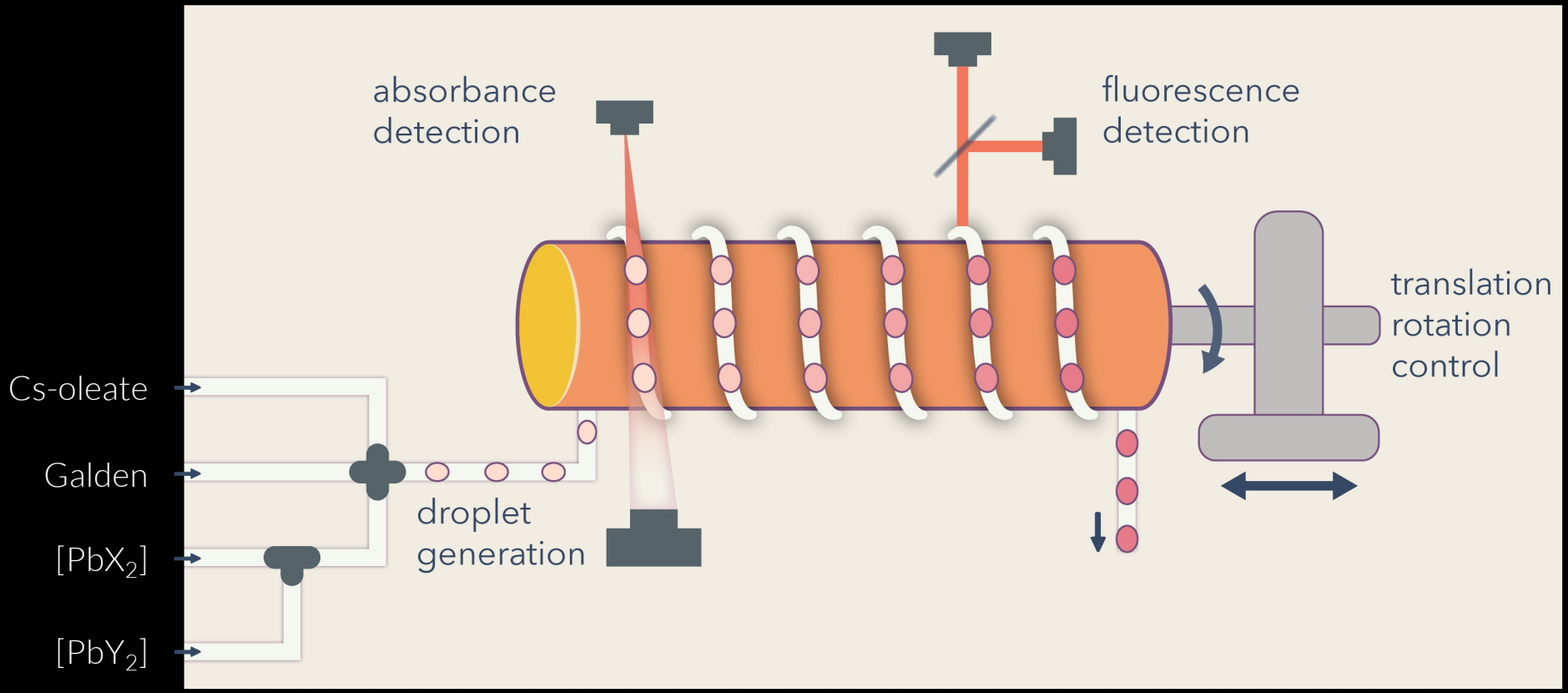
Nano Letters, 2015, 15, 3692

perovskite nanomaterials

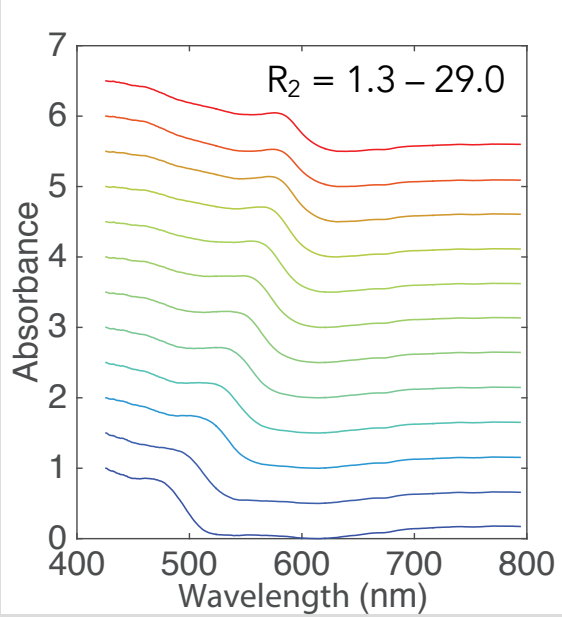


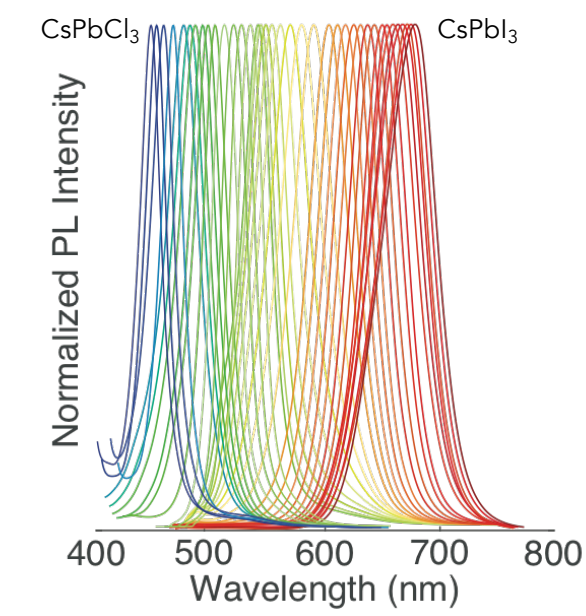
- organic-inorganic lead halide perovskites possess outstanding optoelectronic properties.
- compositional tuning of luminescence from blue to red is a key advantage over Cd-chalcogenides.
- realization of high quantum yields does not require electronic passivation, significantly reduces the complexity of the synthetic procedure.

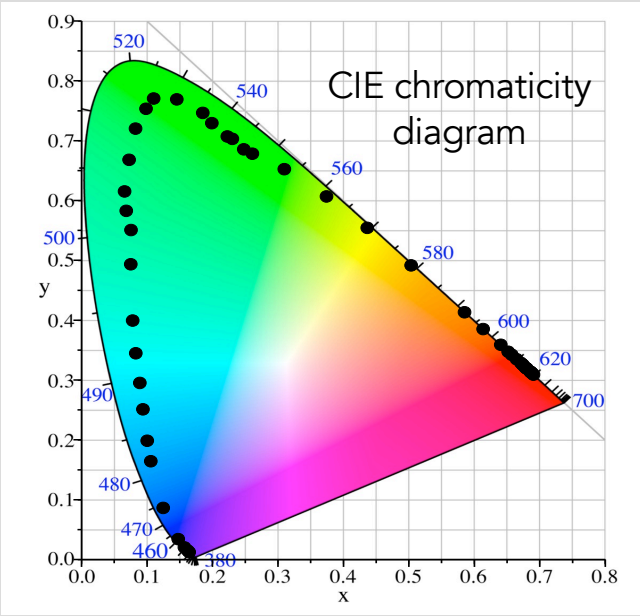
Nano Letters, 2016, 16, 1869



simple microfluidic reactors



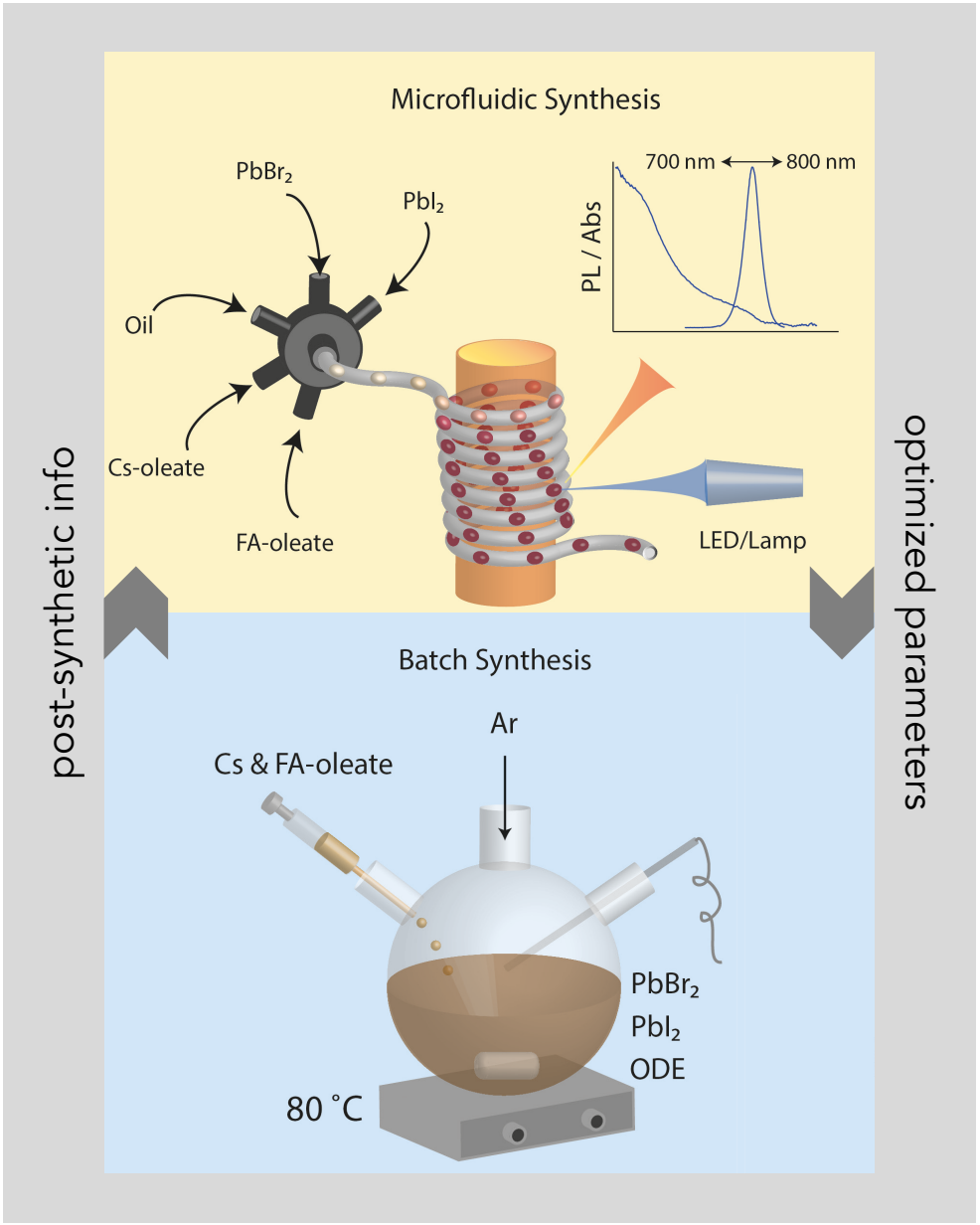




perovskite nanoparticle synthesis

- combination of online analysis and rapid mixing allows the rapid mapping of the reaction parameters.
- early-stage insight into the mechanism of nucleation suggests similarities with multinary metal chalcogenide systems, albeit with much faster reaction kinetics.

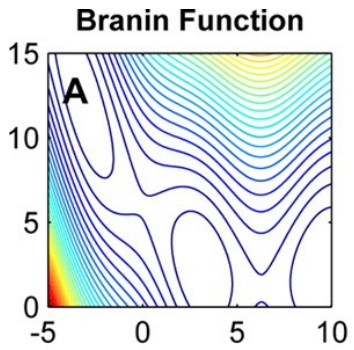
Nano Letters, 2016, 16, 1869

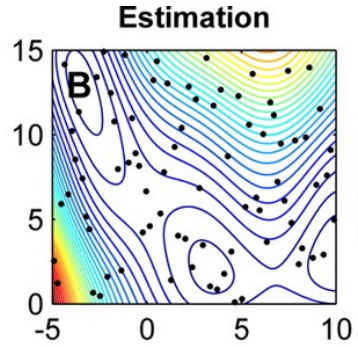


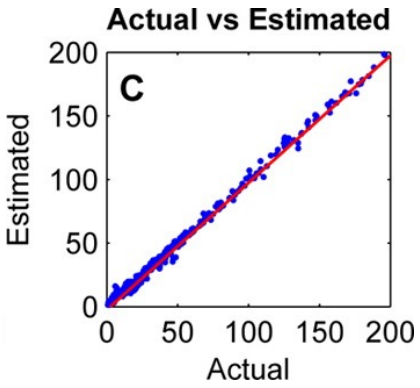
perovskite nanoparticle synthesis

- fine-tuning of PL of $Cs_xFA_{1-x}Pb(Br_{1-y}I_y)3$ NCs between 700 and 800 nm, with minimization of emission line widths (<40 nm), and maximization of PL quantum efficiencies (up to 89%) and phase/chemical stabilities.
- rapid screening of $FAPb(Cl_{1-x}Br_x)_3$ NCs with stable emission between 440-520 nm.
- microfluidically optimized conditions transferred to batch-scale synthesis platforms.

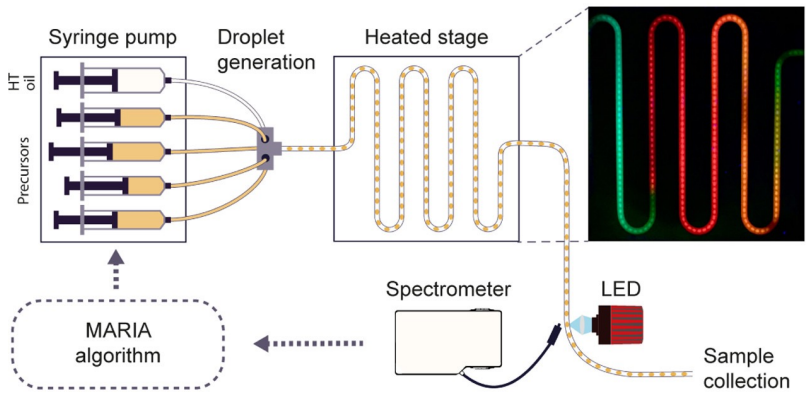
Nano Letters 2018, 18, 1246; ACS Nano 2018, 12, 5504



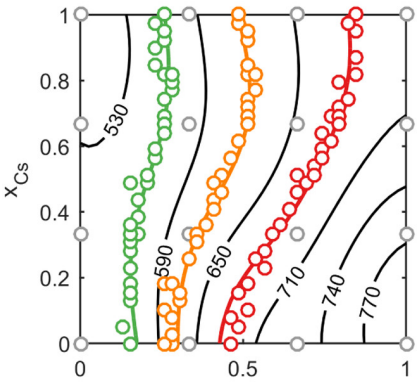


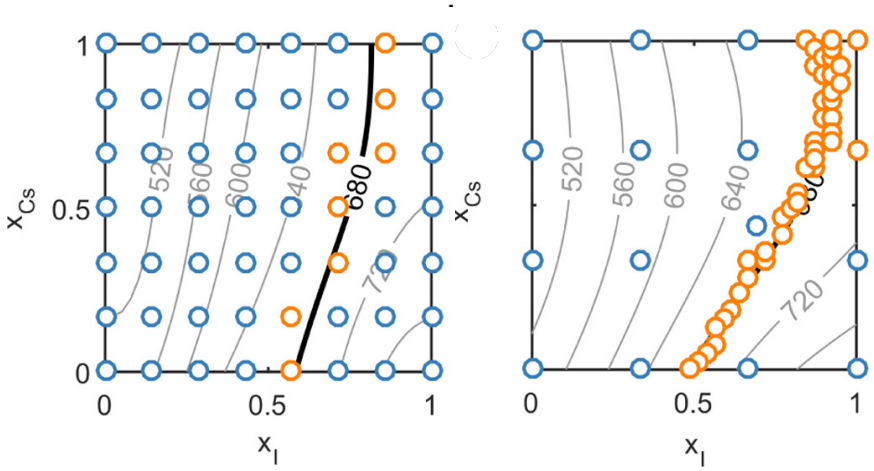


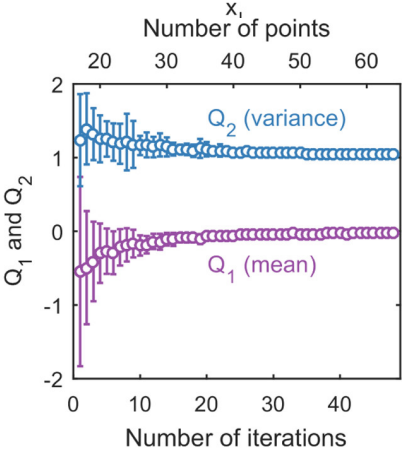
J. Phys. Chem. C, 2014, 118, 20026



ACS Appl. Mater. Interfaces 2018, 10, 18869

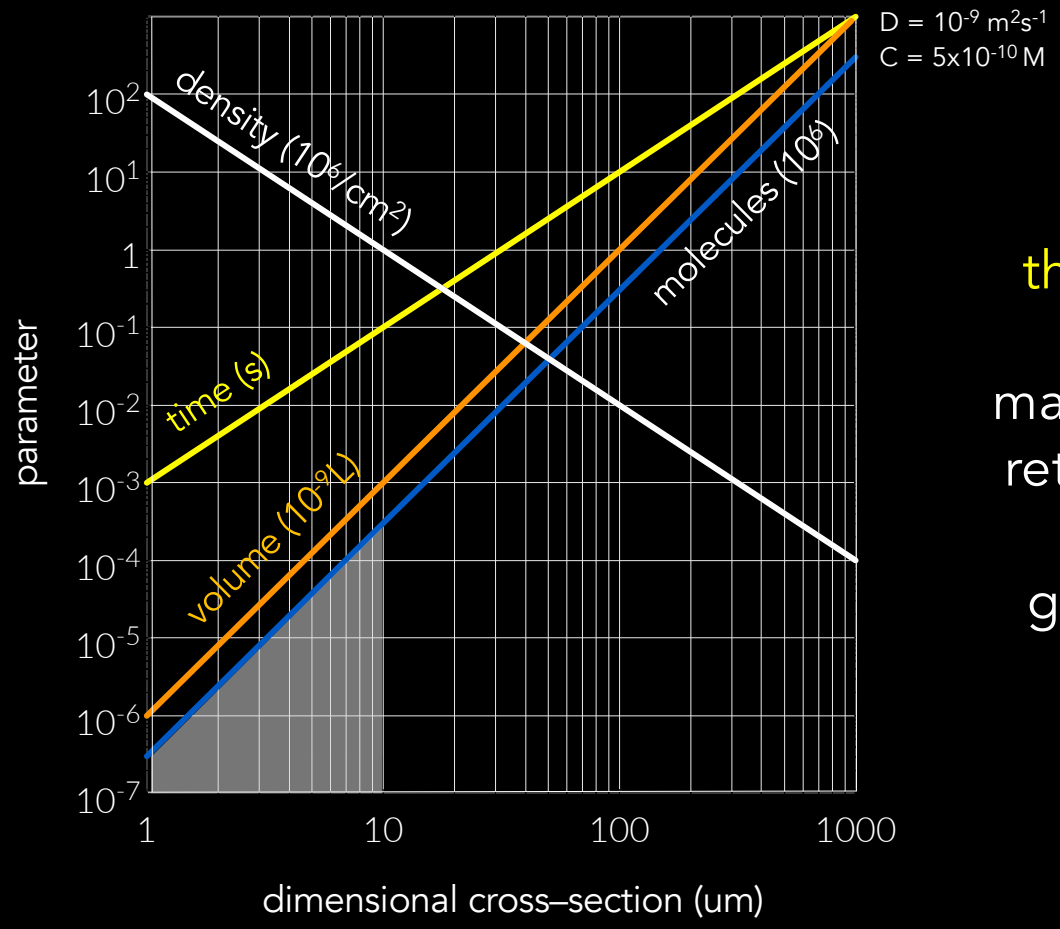






multiparametric automated regression Kriging interpolation & adaptive sampling (MARIA)

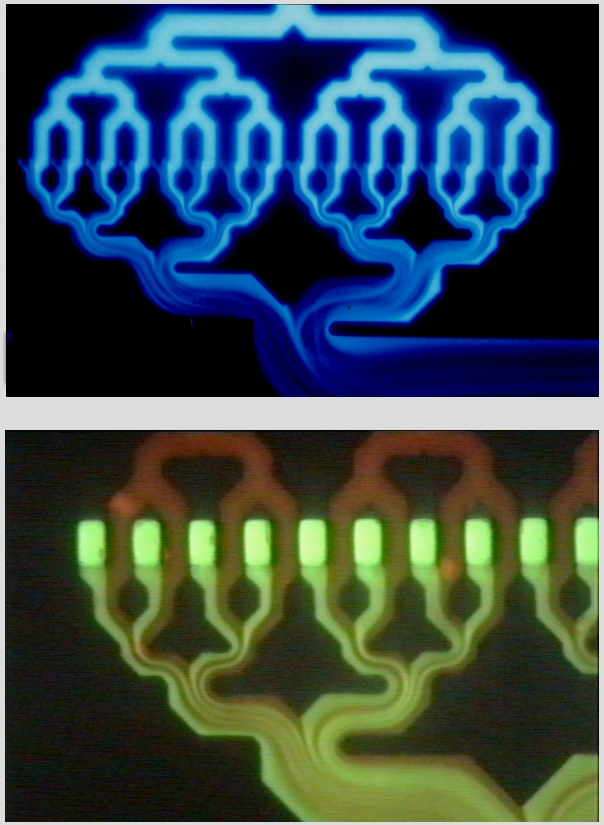
small molecule in water at room temperature



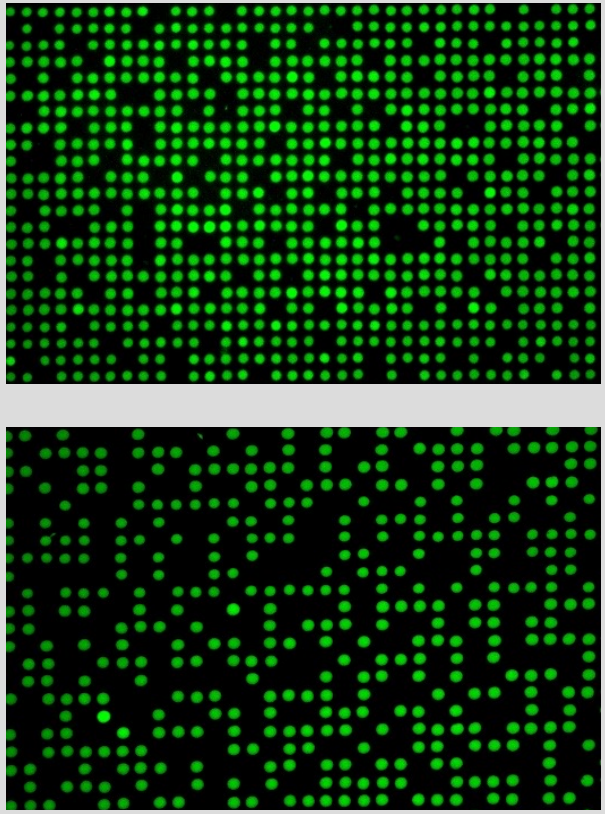
the challenge…

match information retrieval rate with information generation rate

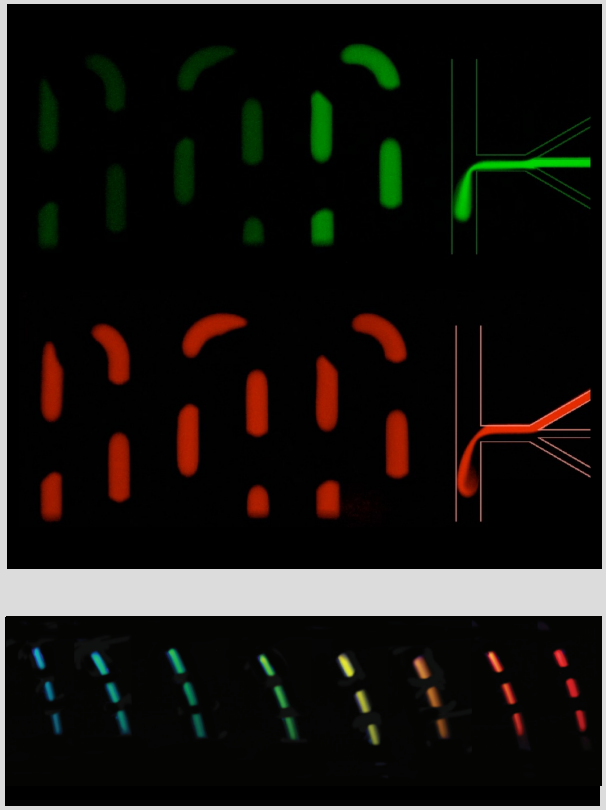
small volume detection



Anal. Comm. 2001, 36, 213

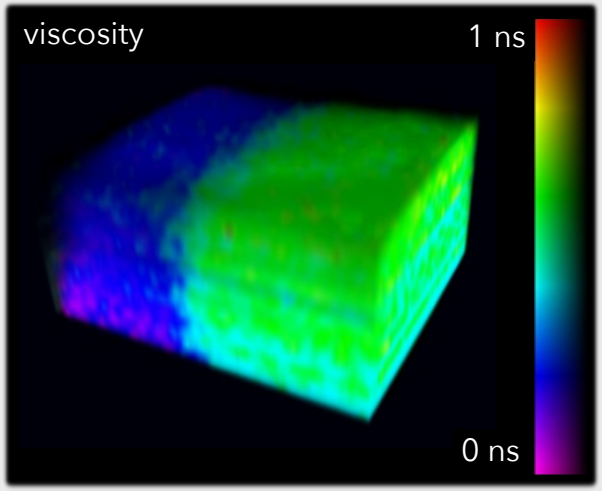


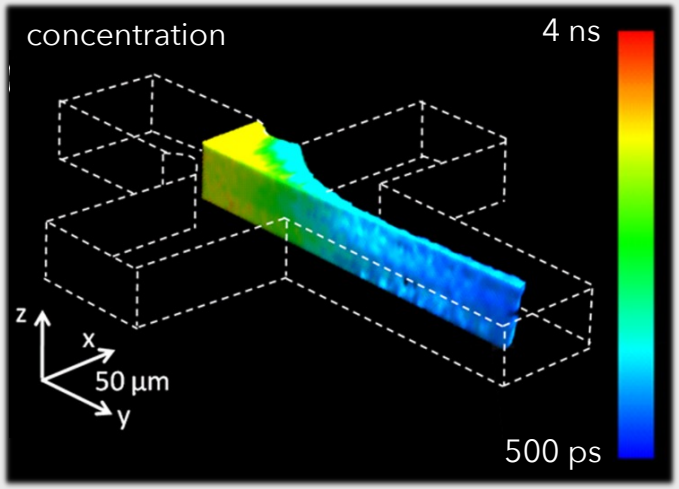
Anal. Chem. 2018, 410, 7019

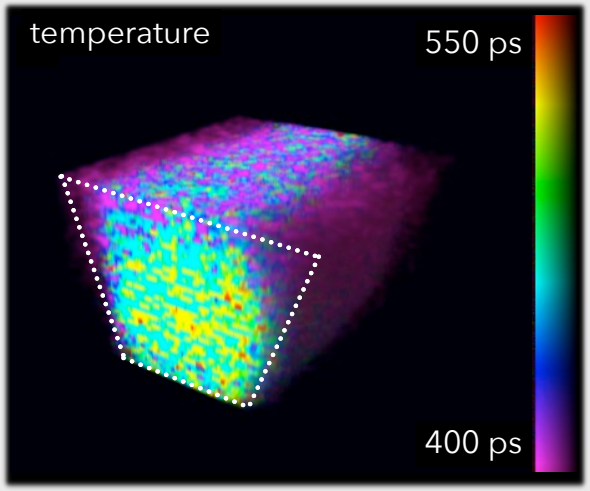


Nano Letters, 2016, 16, 1869

photoluminescence is great!







Optics Letters 2011, 33, 1187

Analytical Chemistry, 2015, 86, 10732

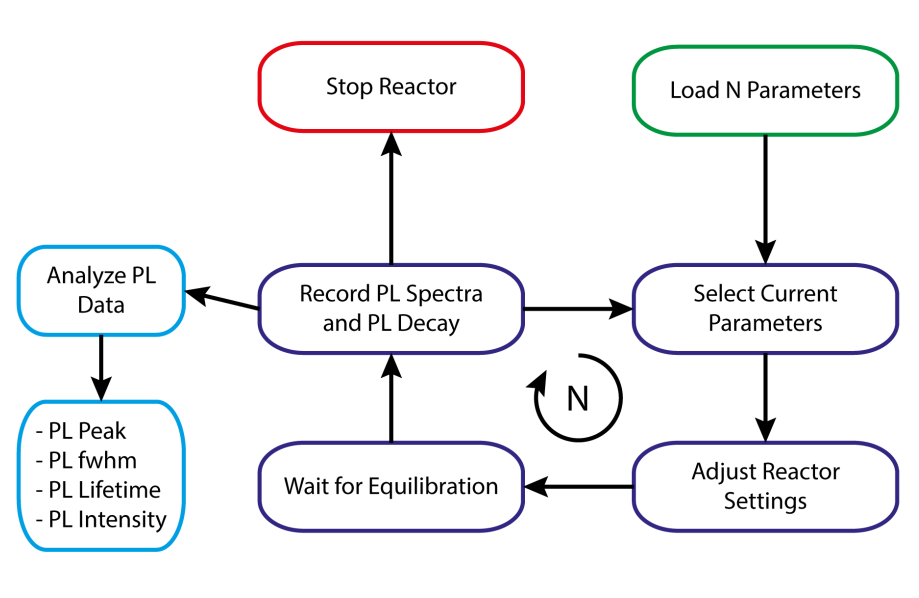
Angewandte Chemie 2007, 119, 2278

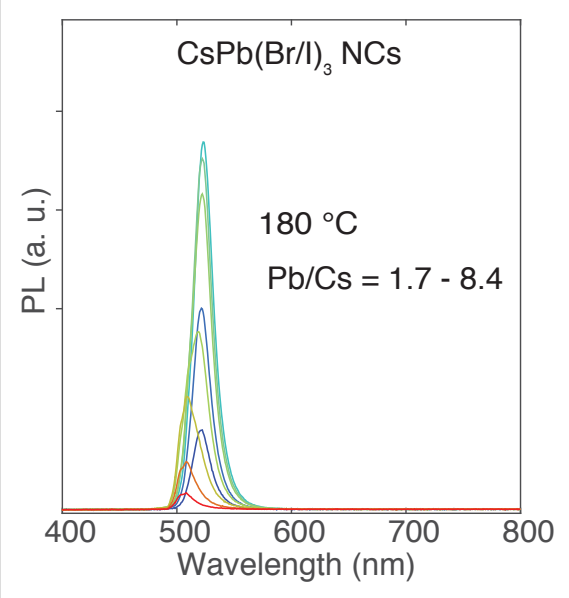
FLIM: maximizing info contrast

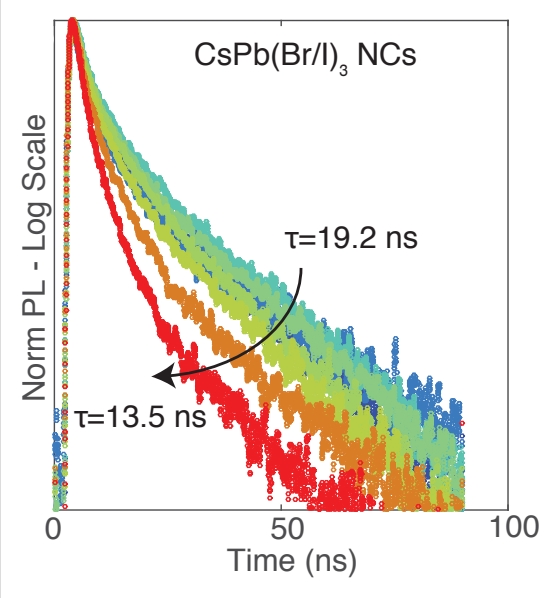
- high-speed fluorescence lifetime imaging of dynamic flows using **viscosity**-dependent lifetime of DASPI.
- quantitative **concentration** mapping using line-scanning confocal microscopy with sub-micron resolution.
- spatially resolved 3D **temperature** distributions extracted via two-photon excitation.

automated fluorescence lifetime tracking

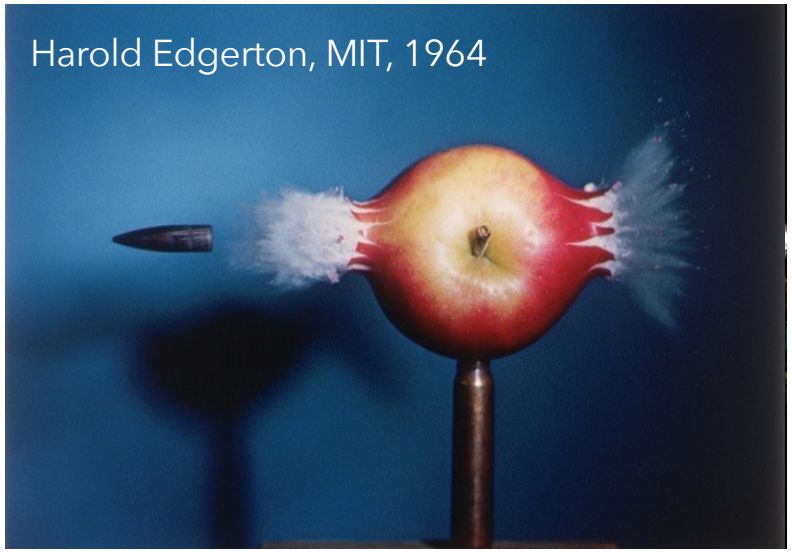
- caesium-based perovskite nanocrystals exhibit tunable emission in the visible region and also display a fluorescence lifetime that varies with anionic composition.
- time-correlated single photon counting measurements in flow allow rigorous extraction of fluorescence lifetimes.
- on-line extraction of PL lifetimes achieved using a fitting algorithm with sensitivity down to the single droplet level.

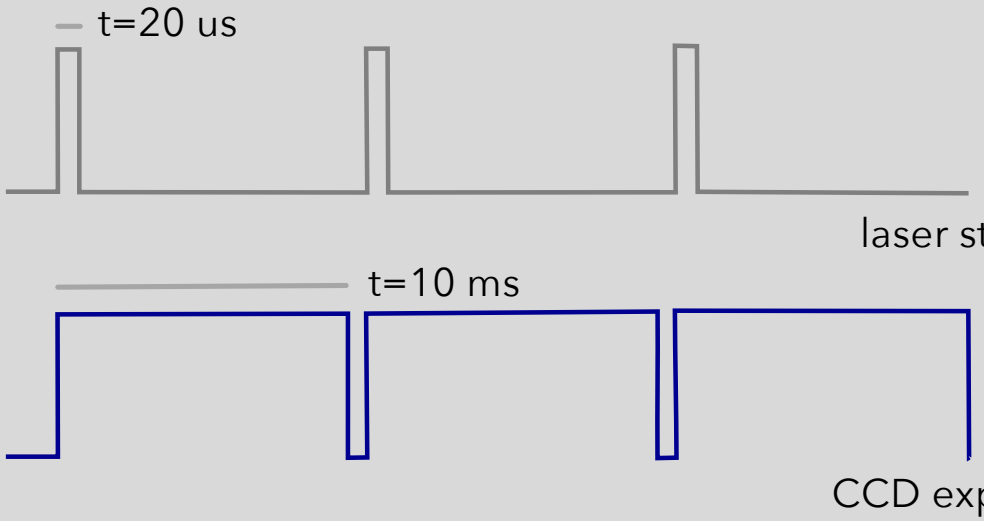


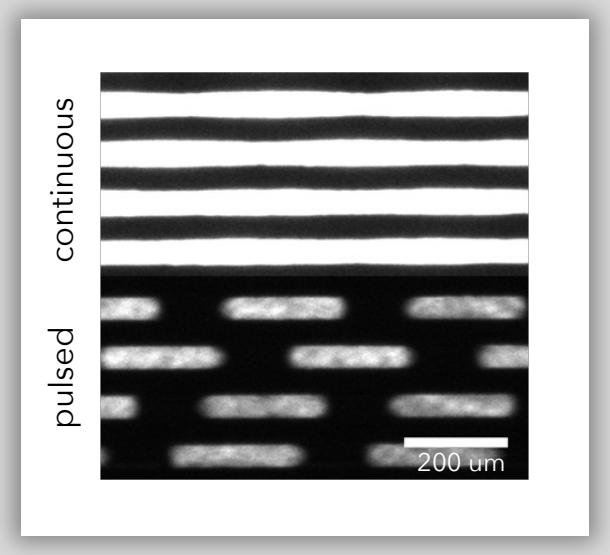




Chemistry of Materials 2020, 32, 27



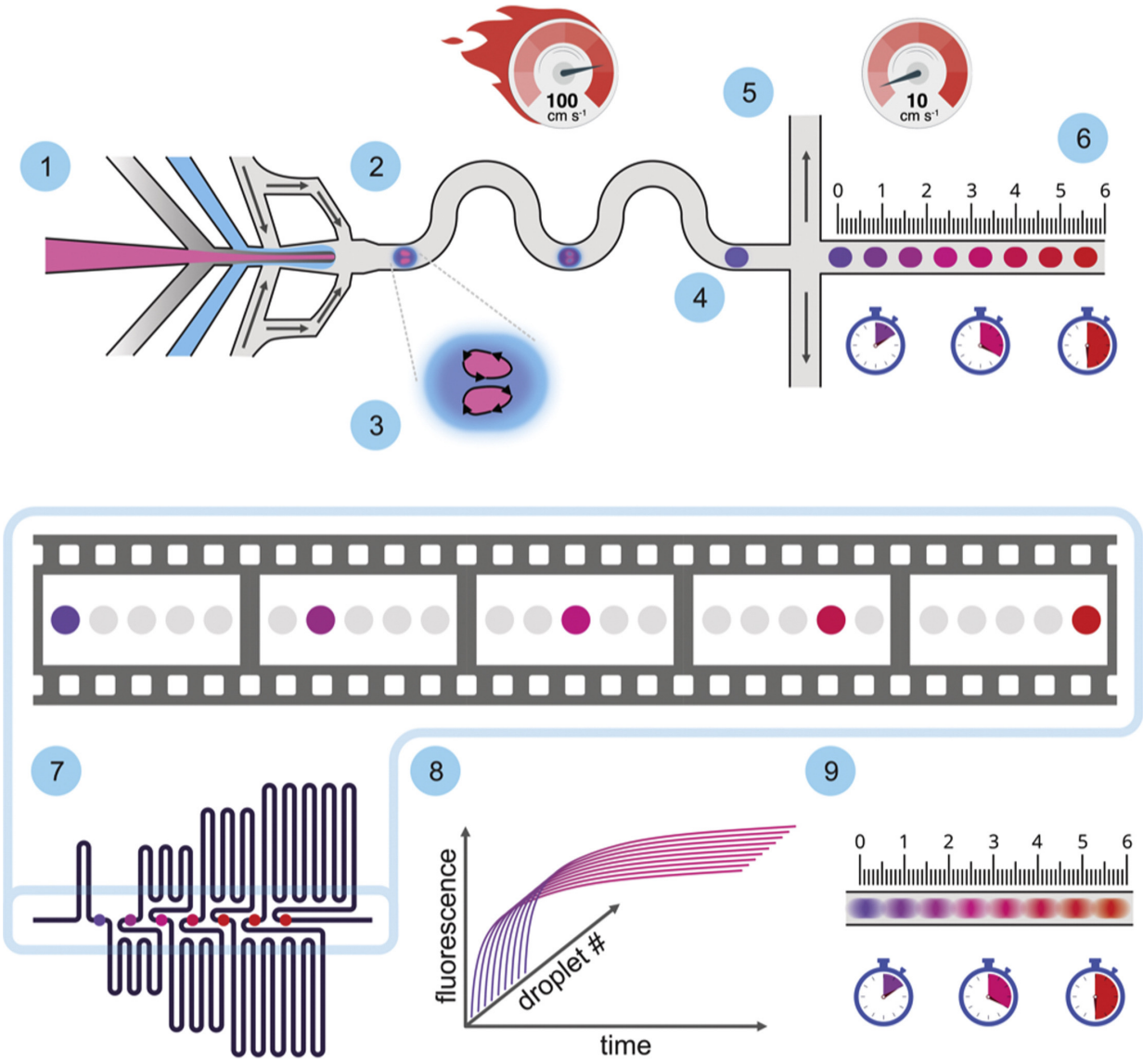




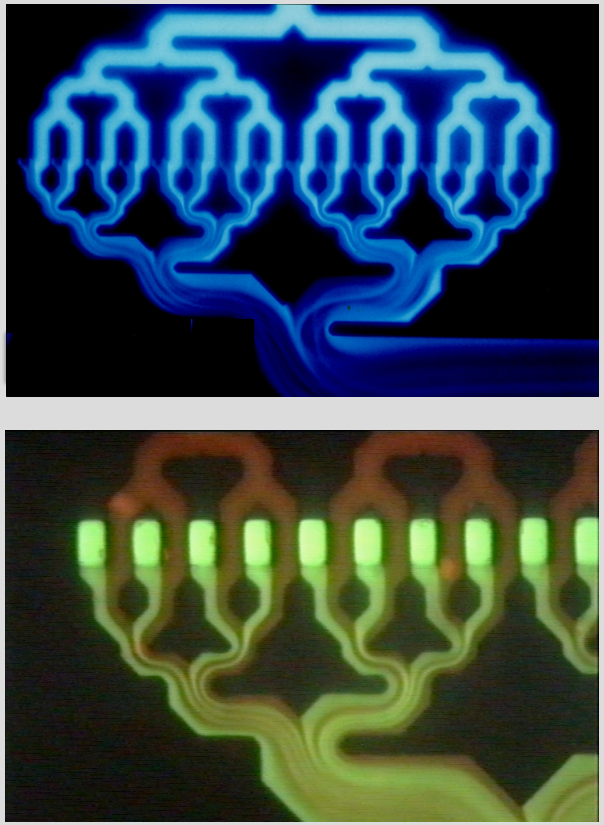
stroboscopic illumination can significantly reduce motion blur

exploring enzyme catalysis

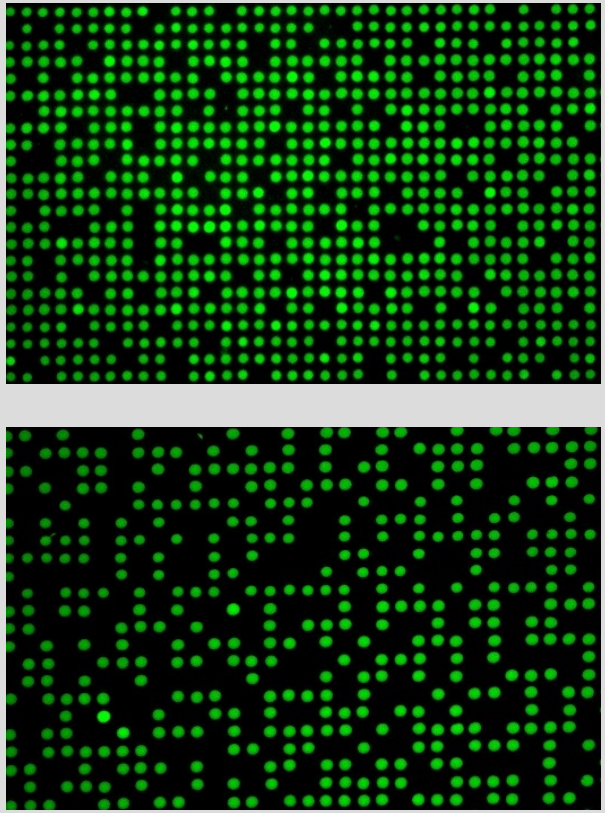
(1) inject substrate and enzyme solutions.
(2) accelerate droplets to 1 m/s.
(3) rapid mixing by chaotic advection.
(4) complete droplet mixing within 800 us.
(5) droplet deceleration to 10 cm/s.
(6) stroboscopic imaging of droplets
(7) droplet imaging over long times.
(8) fluorescence intensity plotted as a function of time for each droplet.
(9) droplets prevent dispersion and prevent concentration gradients.



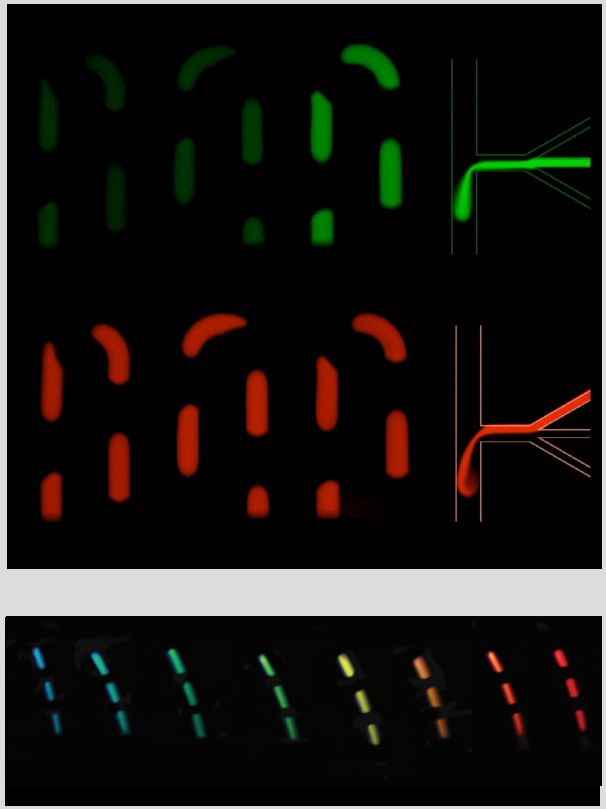
Chem 2021 7, 1066; Chem Catalysis 2022, 2, 2704, Nature Methods 2023, 20, 1479



Anal. Comm. 2001, 36, 213



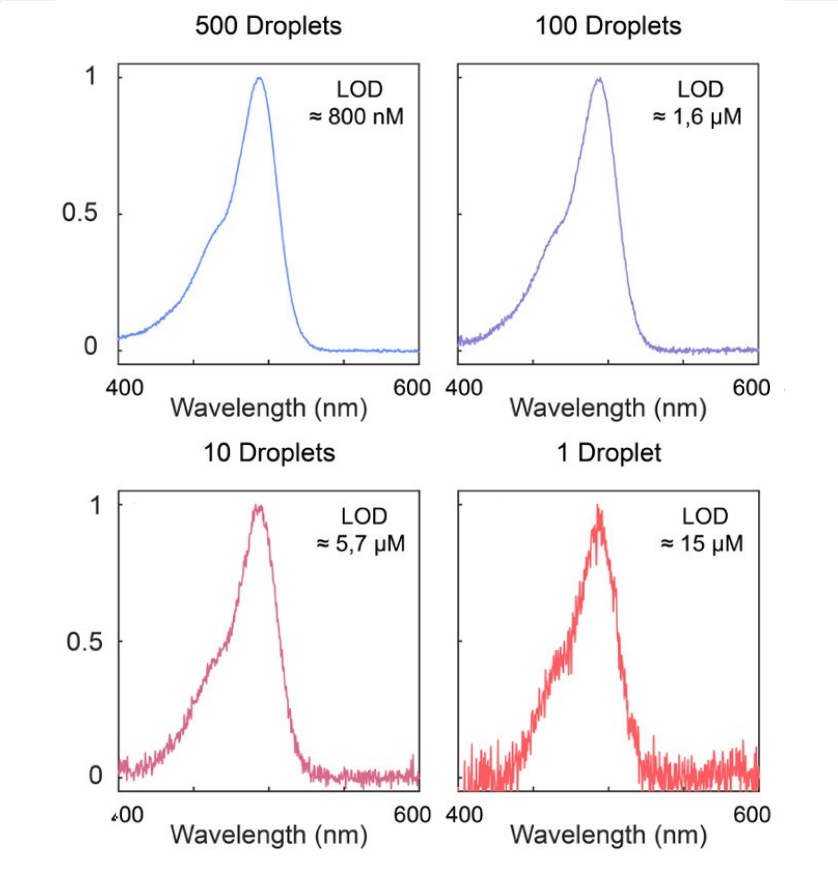
Anal. Chem. 2018, 410, 7019

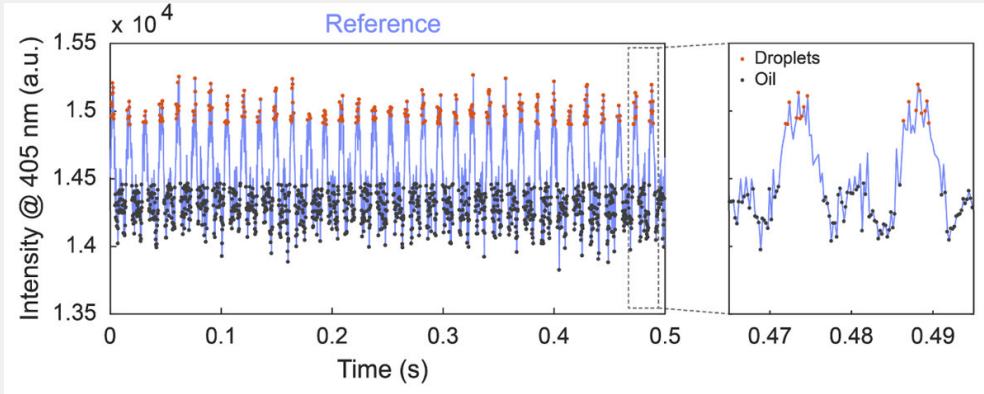


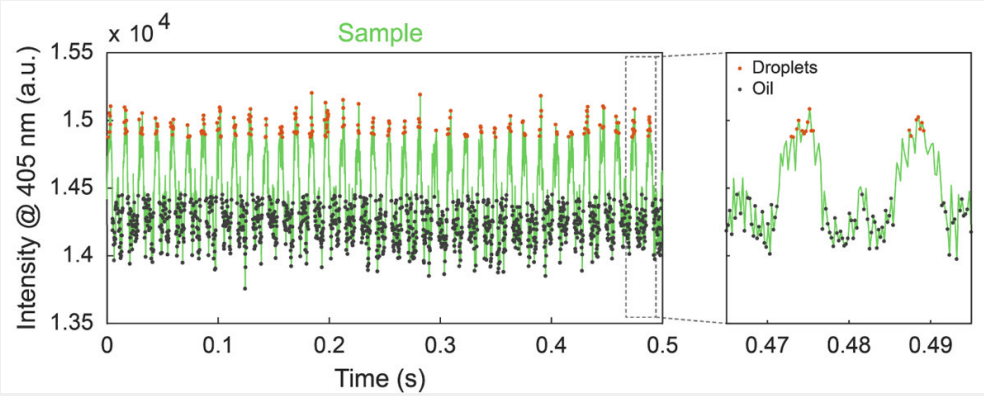
Nano Letters, 2016, 16, 1869

photoluminescence is limited

droplet absorbance spectroscopy







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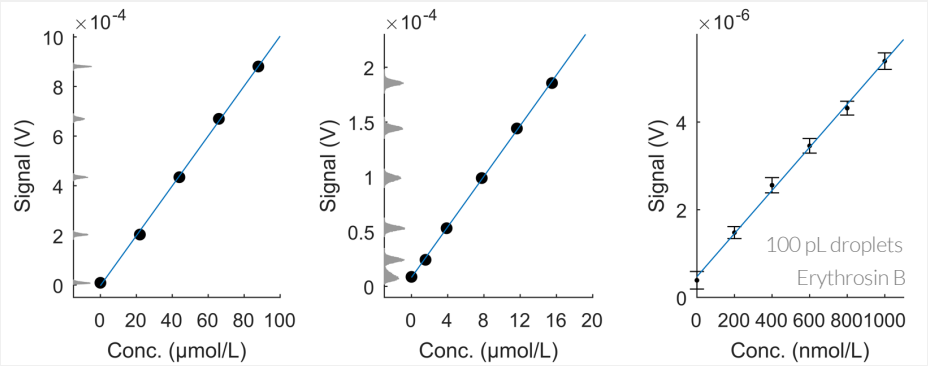
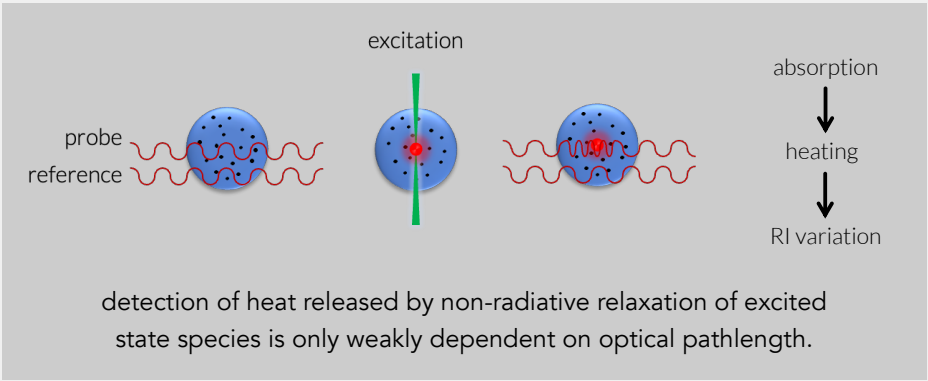
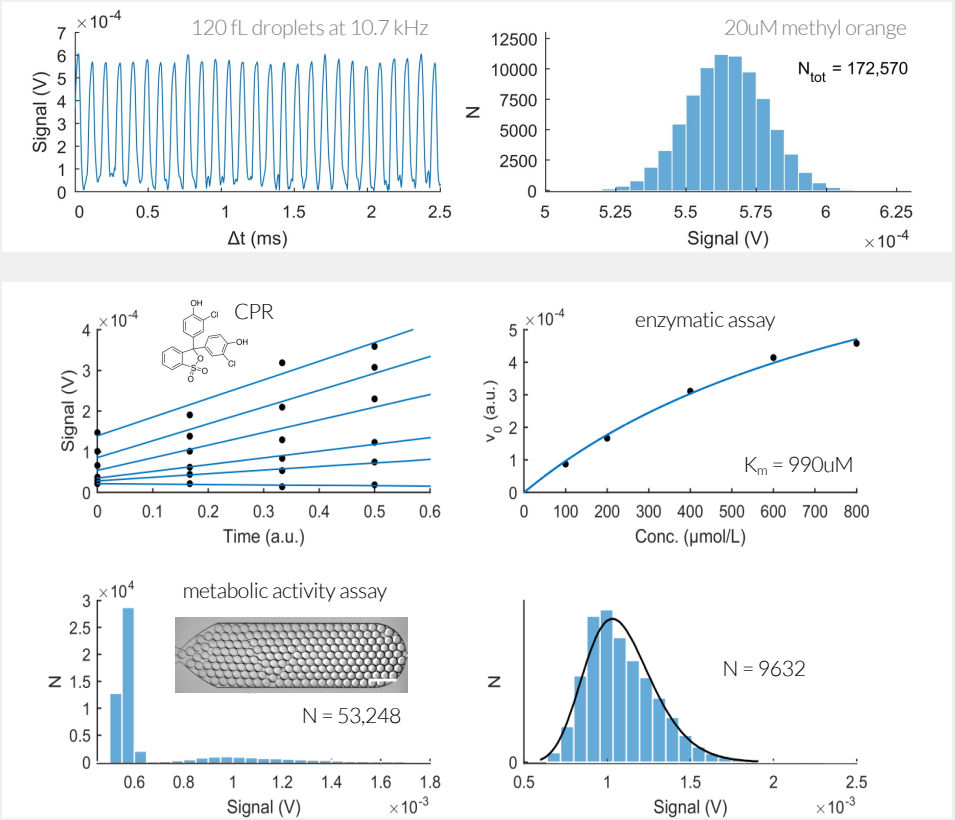
photothermal spectroscopy

single point absorbance measurements in fL-pL volume droplets at frequencies in excess of 10 kHz







Analytical Chemistry 2017, 89, 1994; Lab Chip, 2018, 17, 3654

the use of microfluidic tools in materials synthesis almost always engenders significant enhancements in efficiency, control, functionality & throughput …

… the marriage of microfluidic systems, optical detection methods and machine learning algorithms offers a route towards the rapid and robust generation of bespoke materials.