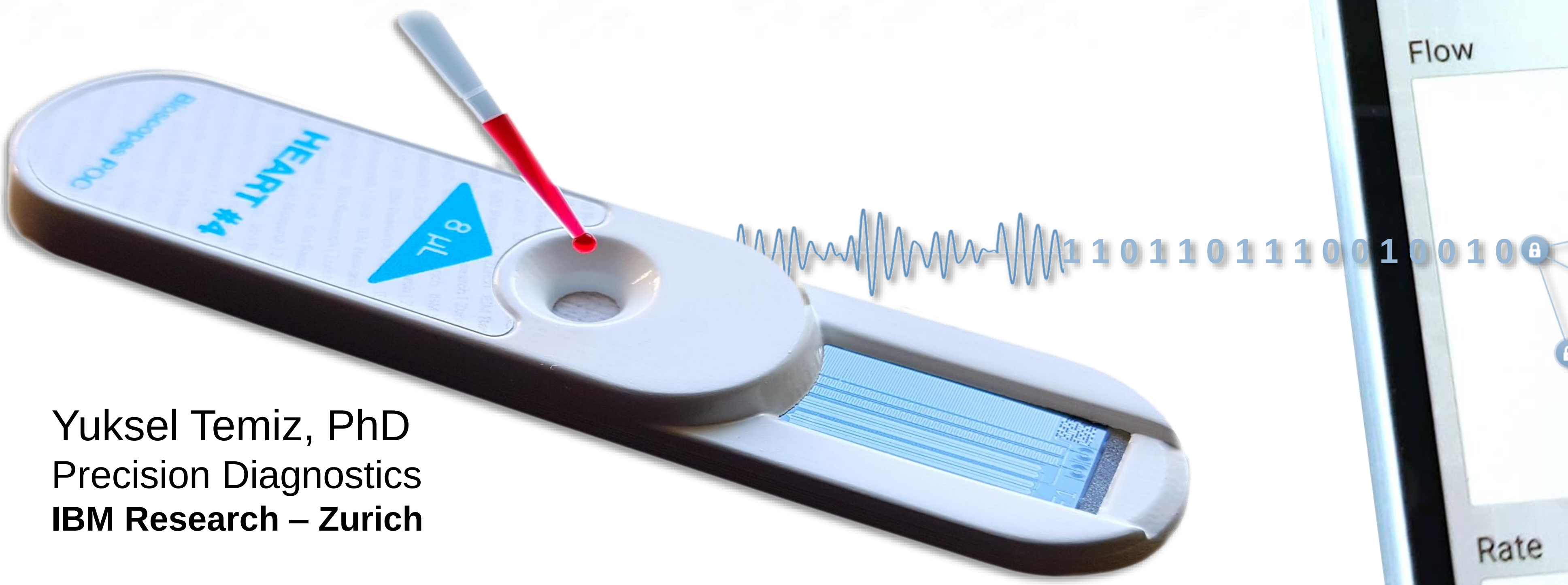
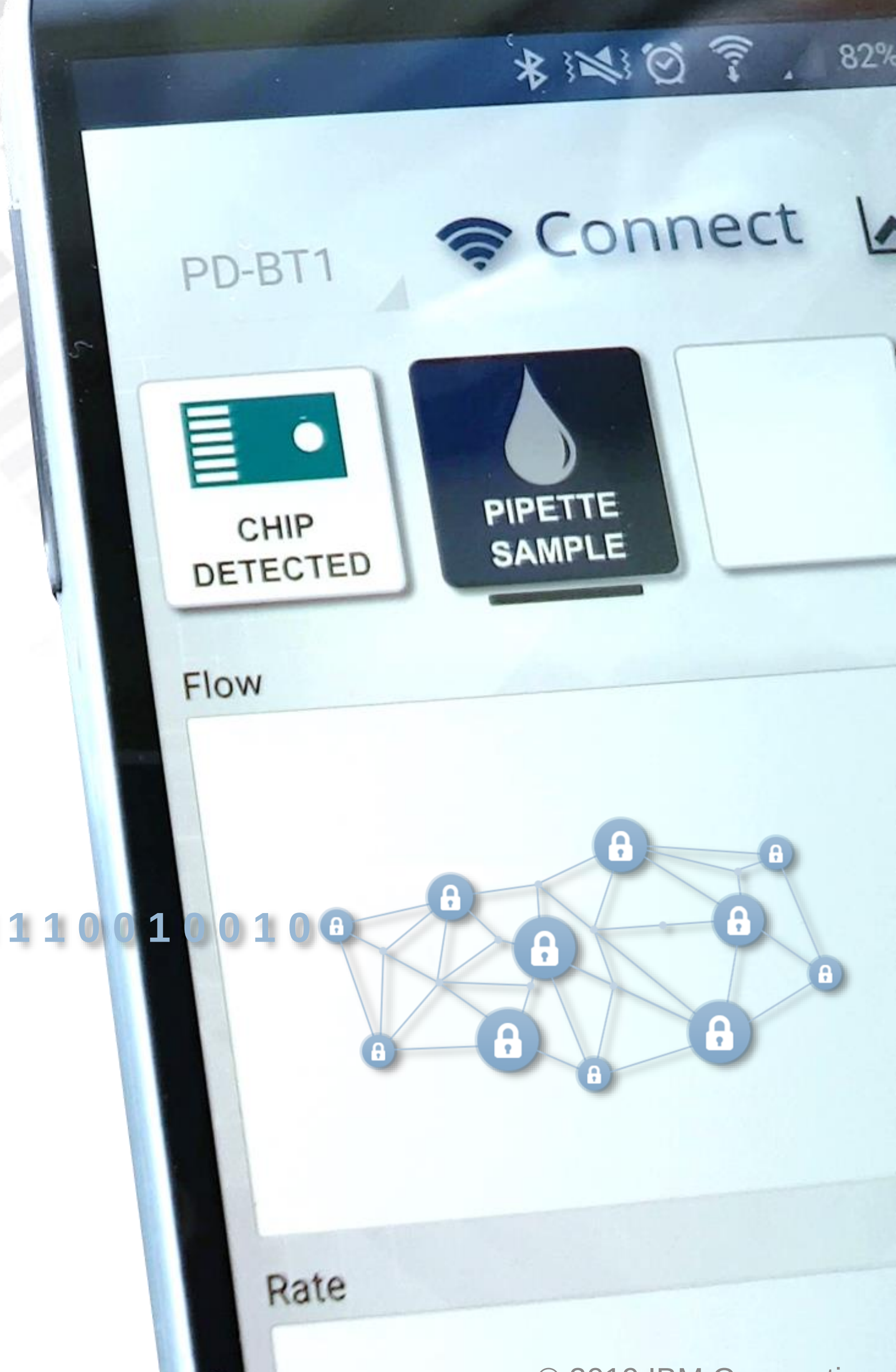
Digital Diagnostics: Connecting POC Devices to Smartphone





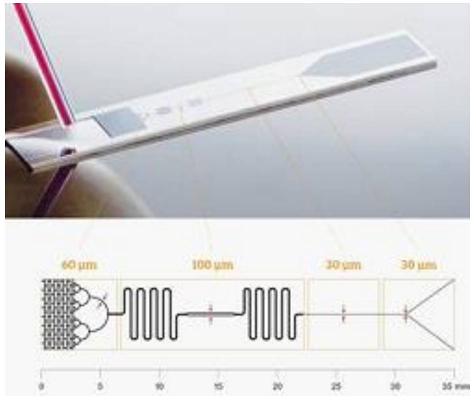
Yuksel Temiz, PhD
Precision Diagnostics
IBM Research – Zurich

Precision Diagnostics

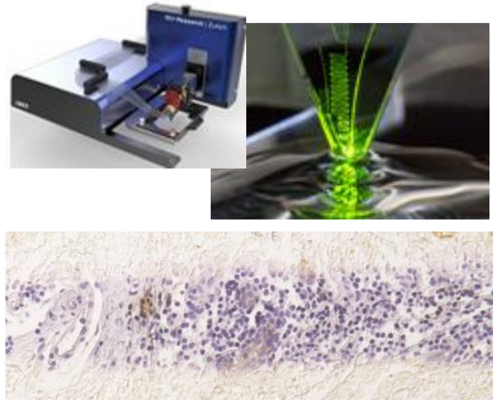
IBM Research - Zurich

Emmanuel Delamarche

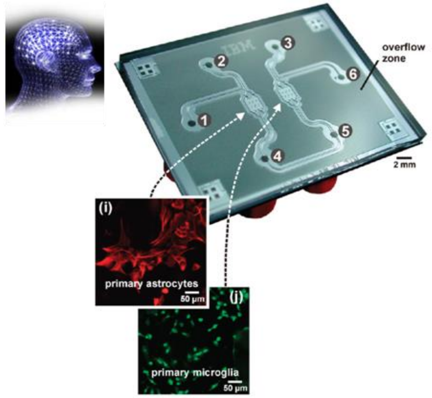
microfluidics for mobile health

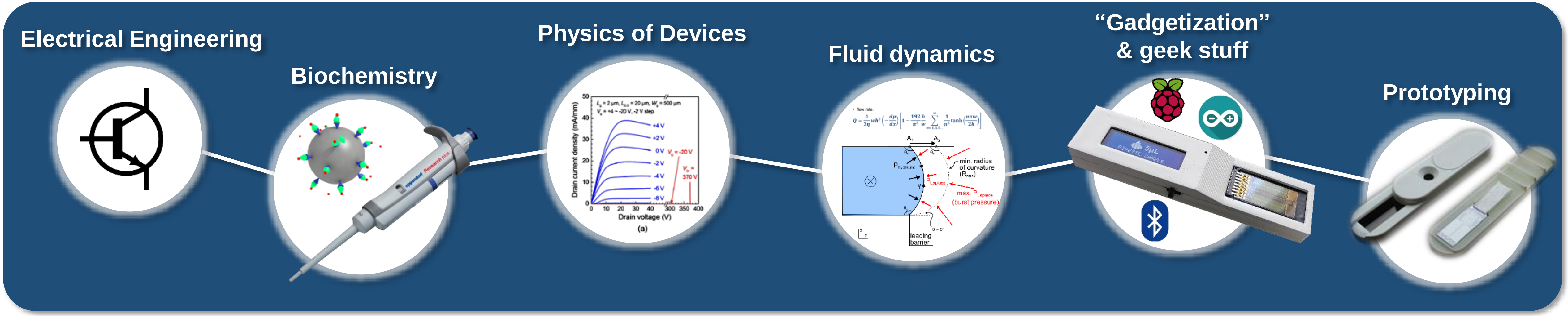


microfluidic probe



microfluidics for cell research





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From classical diagnostics to microfluidic-based point-of-care diagnostics

clinical analyzer

lab-on-a-chip / microfluidics research

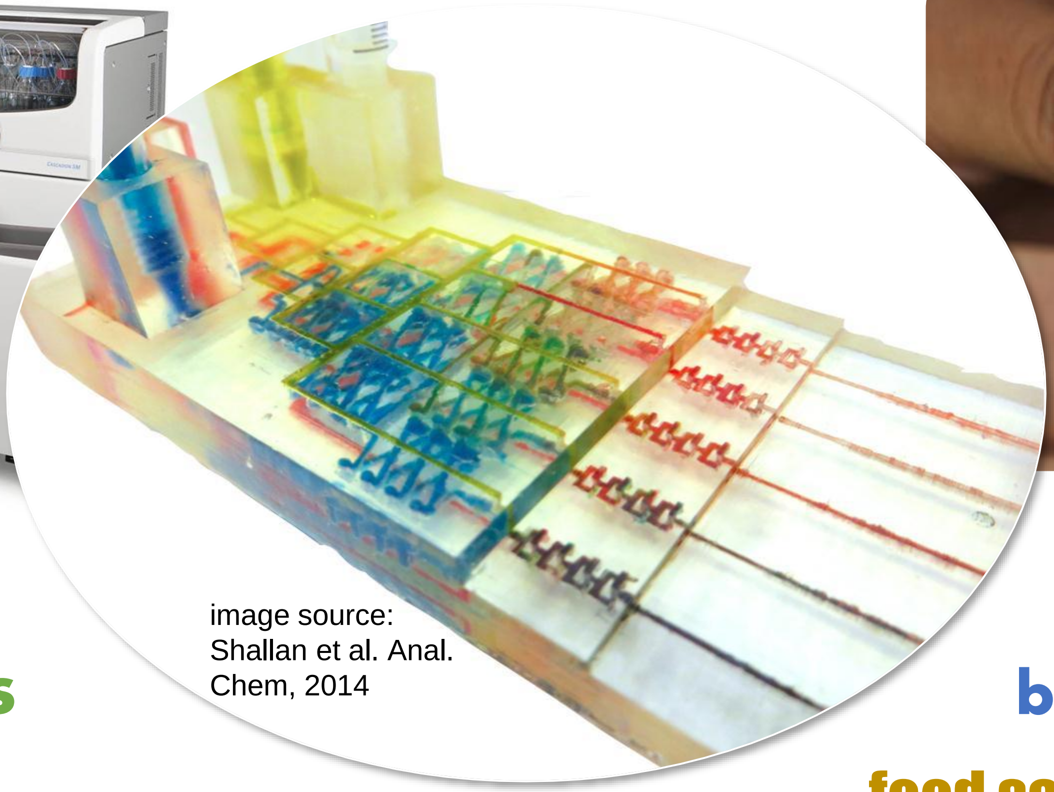

image source: Shallan et al. Anal. Chem, 2014

lateral flow assay

cardiovascular diseases

hormones

infectious diseases

cancer

environmental monitoring

chronic diseases

drugs

allergens

biohazards

food safety

agriculture

veterinary diseases

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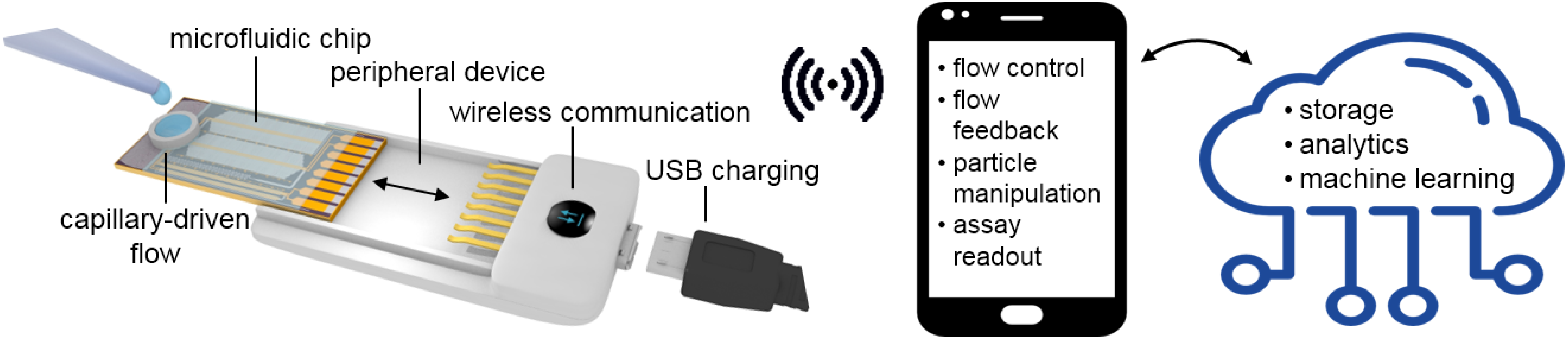
Our vision on using microfluidics and IoT for next-generation miniaturized assays



- **precision** - manipulation of small volumes of liquids with **precise release of integrated reagents**
- **portability** – microfluidic chip, chip peripheral, smartphone connection
- **intelligence** – real-time **flow monitoring**, failure detection and **flow path selection & flow control**
- **security – optical or electrical security codes** against counterfeiting

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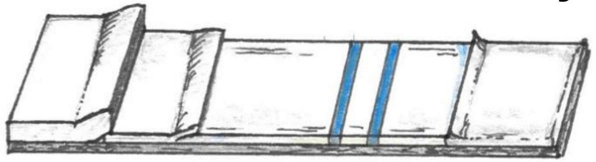
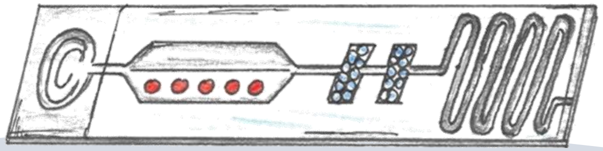
Transposing lateral flow immunoassays to capillary-driven microfluidics

classical lateral flow assays

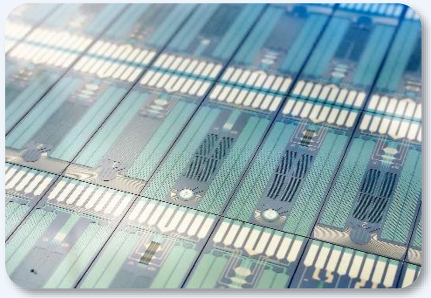


microfluidics with integrated reagents



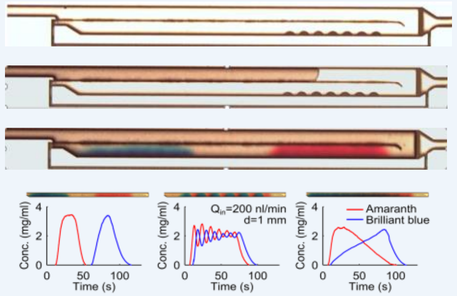
connected diagnostics

efficient fabrication of microfluidic chips



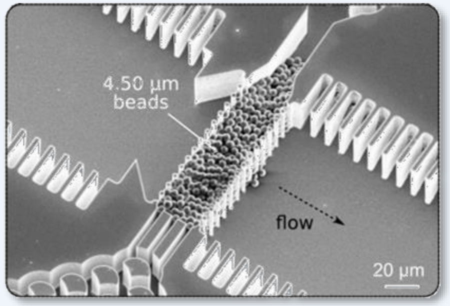
- ↑ 1-10 µL sample
- ↓ autonomous flow

integration and dissolution of reagents



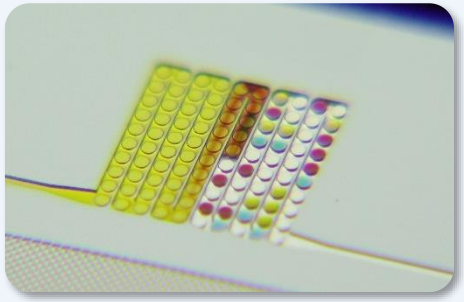
- ↑ inkjet spotting pg of reagents
- ↓ homogenous dissolution in nL volumes

integration of receptors



- ↑ assembly of microbeads
- ↓ optical readout

anti-counterfeiting features



- ↑ inkjet spotting codes
- ↓ optical/electrical readout using smartphone

flow control and monitoring

- ↑ flow protocol from smartphone
- ↓ modulating capillary flow

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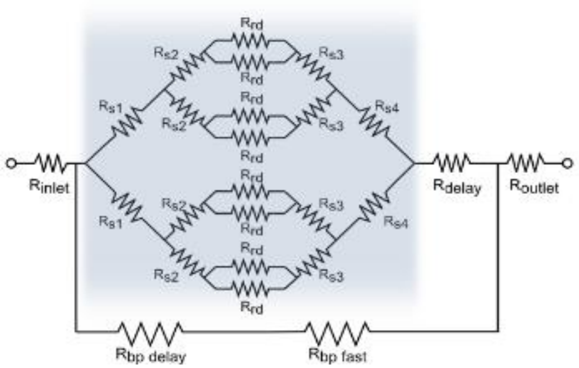
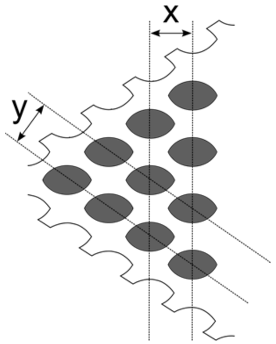
Precise encoding of the capillary-driven flow

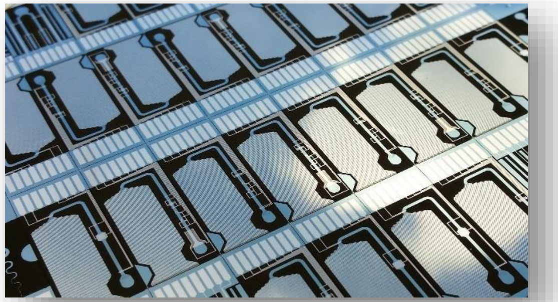
capillary pressure & flow resistance

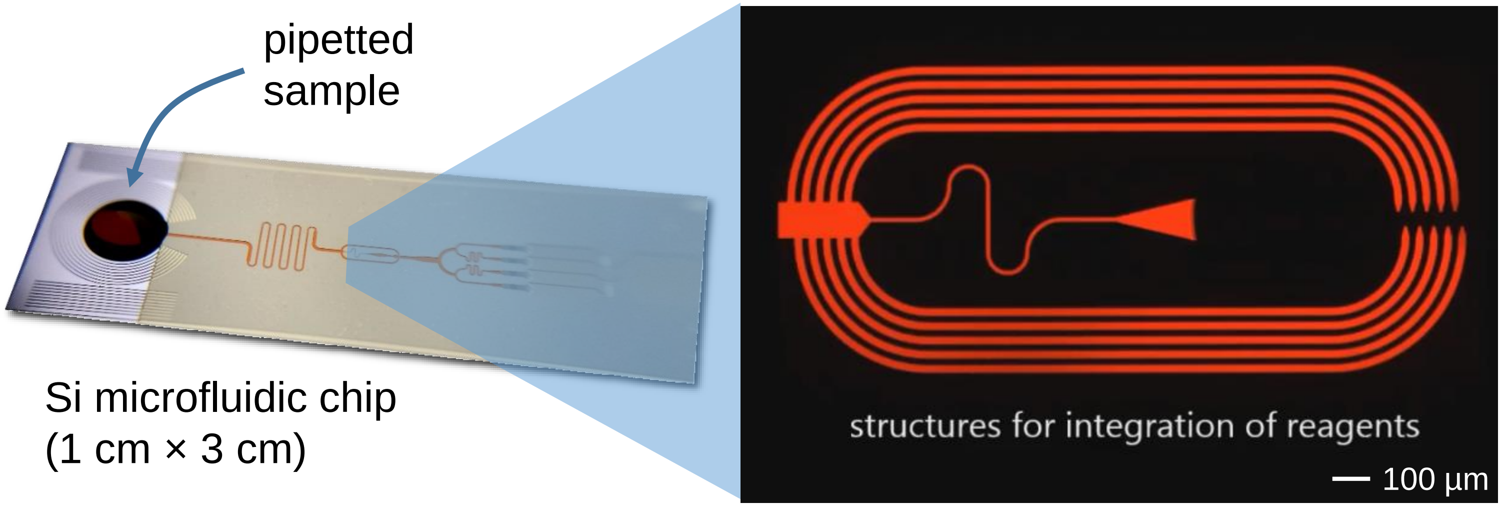


microfluidic chip design



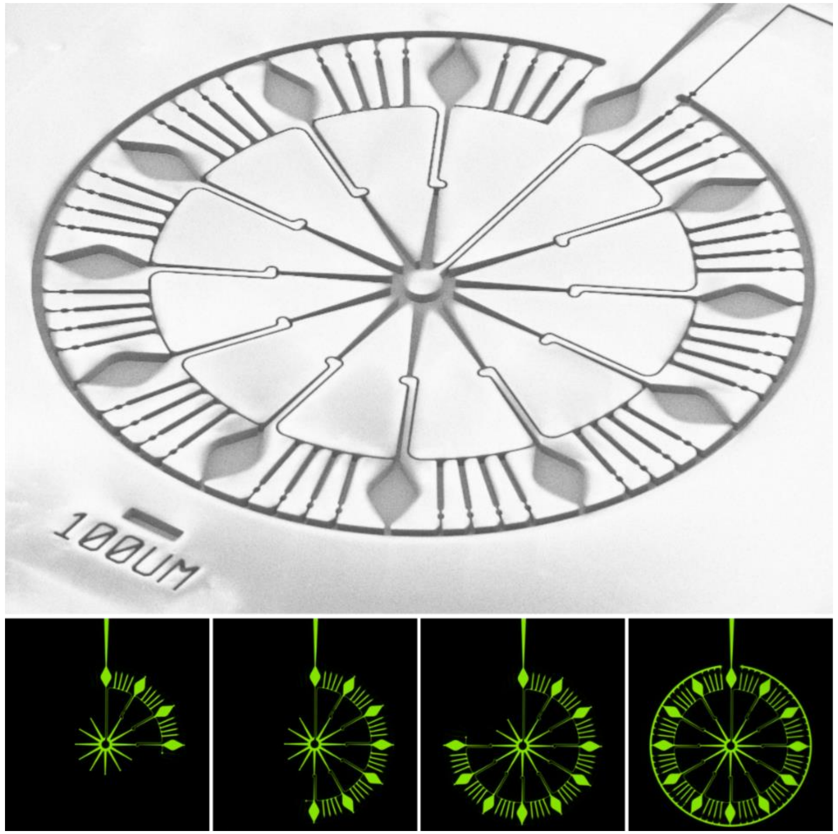
microfluidic chip fabrication





https://www.youtube.com/watch?v=KuDddH3nWO0

a microfluidic watch running autonomously using capillary-driven flow and passive valves



3 µm feature size, 70 capillary valves, total volume: 5 nL

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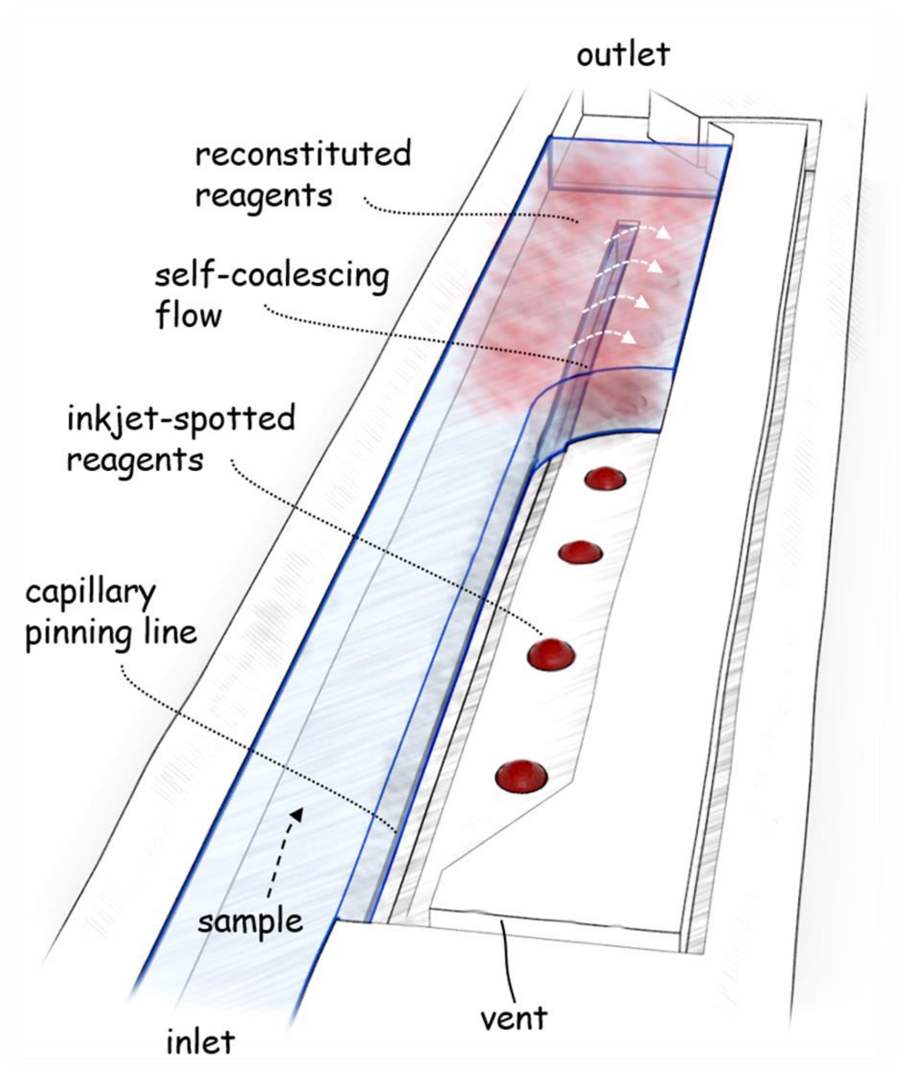
A common problem: Strong accumulation of reagents at the liquid front

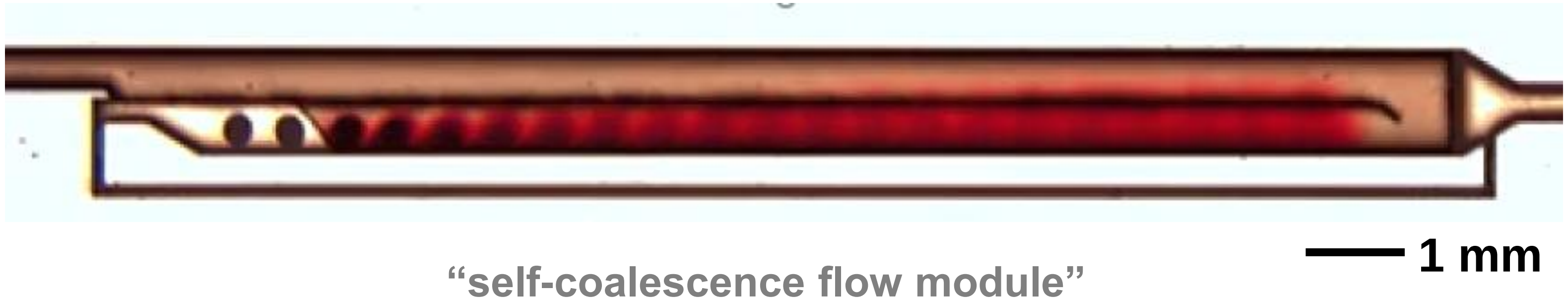
- inkjet-based deposition of reagents in microstructures
- reagents dissolve and accumulate along flow direction

~1 nL amaranth dye solution (30 mg/ml) deposited at each spot (250 µm pitch)

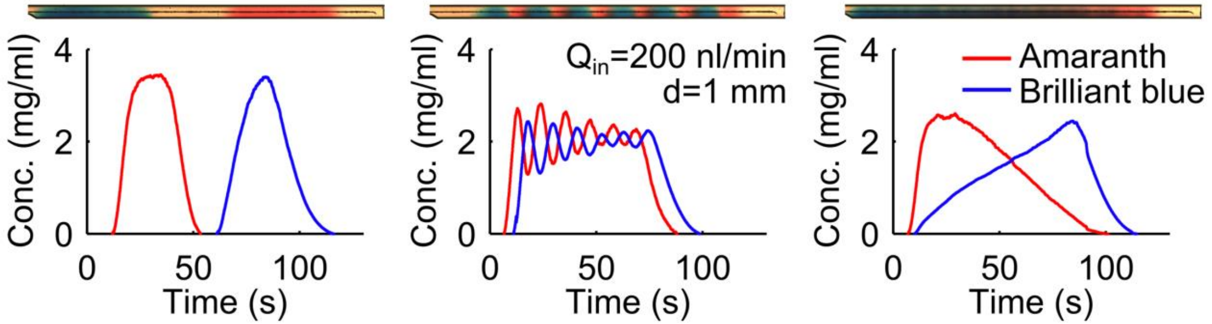
Self-coalescence flow module for integrating and dissolving reagents in microfluidics



- a scalable approach for uniform dissolution of dried reagents
- compatible with active pumping and capillary-driven flow



“self-coalescence flow module”



ultra precise release of reagents in a flow of solution

O. Gökçe, S. Castonguay, Y. Temiz, T. Gervais, E. Delamarche, ***Nature*** 574, 228–232, **2019**

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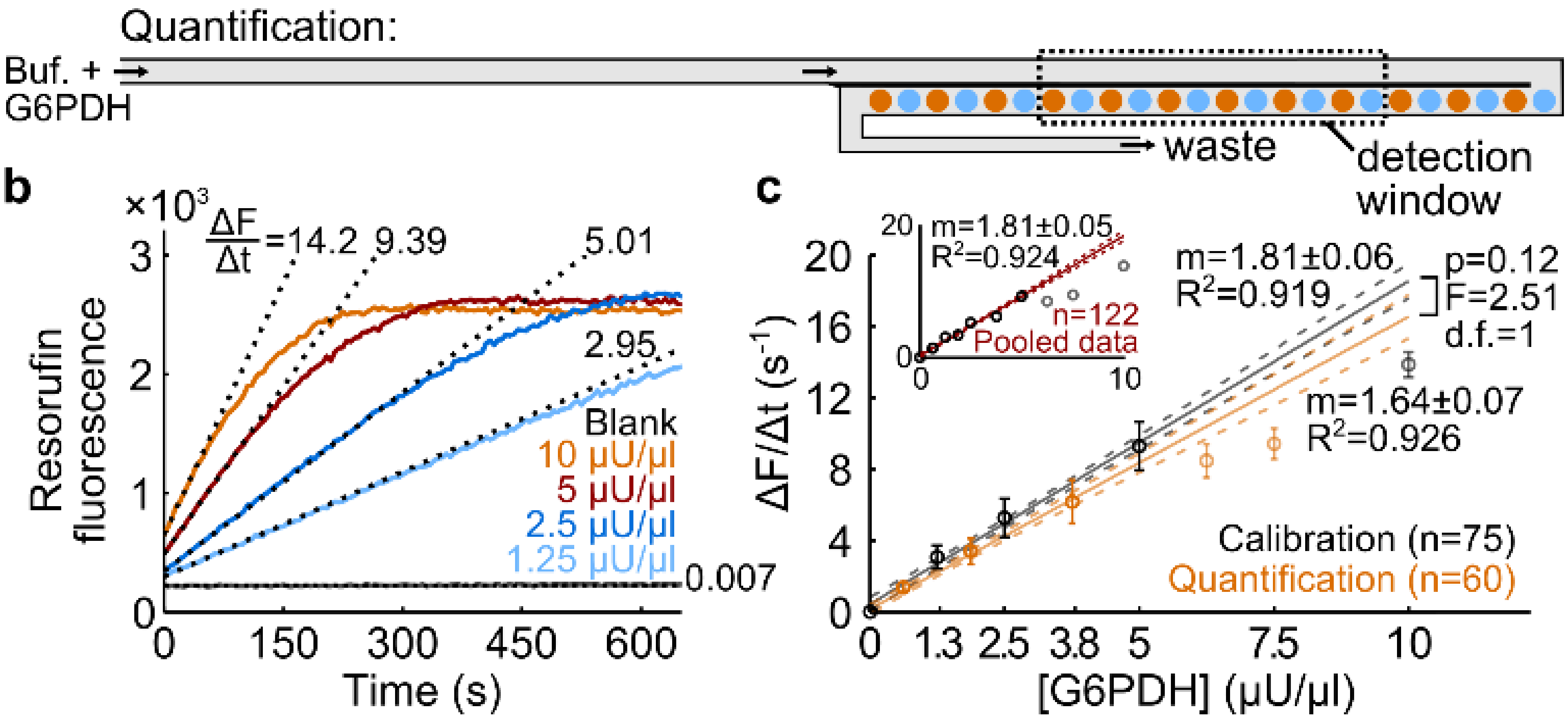
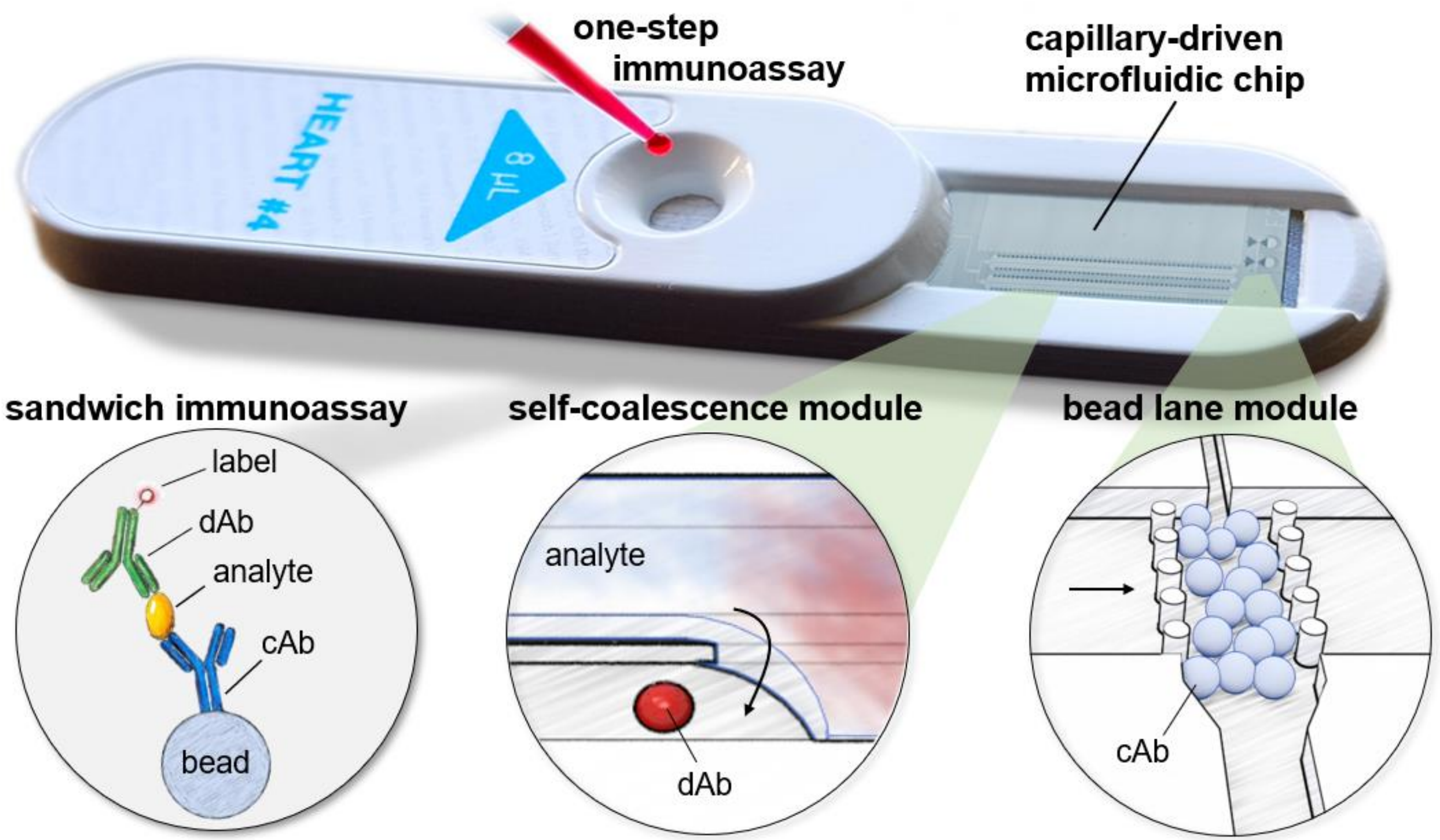
Assay for measuring G6PDH activity using a self-coalescence flow module

assay done with a single Self-Coalescence Module in 2 minutes, using few 100s nL

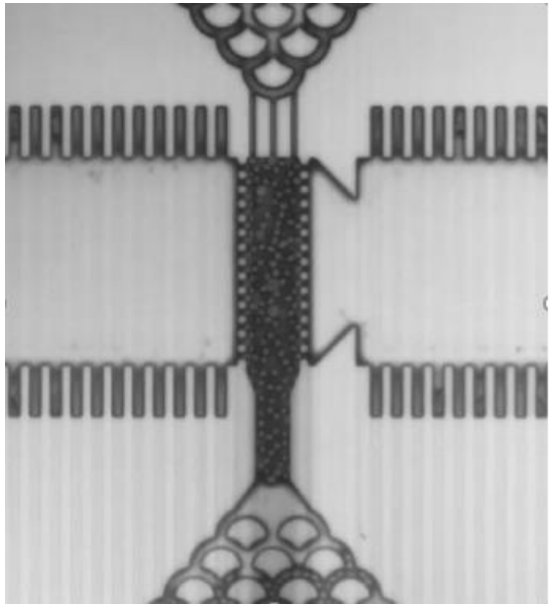


O. Gökçe, S. Castonguay, Y. Temiz, T. Gervais, E. Delamarche, ***Nature*** 574, 228–232, **2019**

Integration of receptor-coated microbeads to capillary-driven microfluidic chips



- only one pipetting step of the bead solution
- self-assembly and drying do the job of packing the beads
- 5µm beads packed in a 20µm×100µm area



E. Hemmig, Y. Temiz, et al., ***Anal. Chem.*** 92(1), 940-946, **2020**

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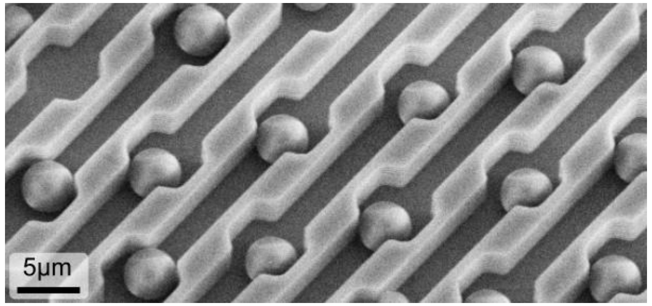
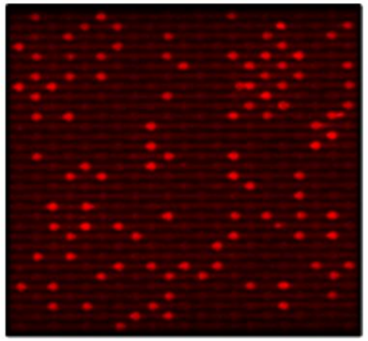
Proof-of-concept assays implemented on capillary-driven microfluidic chips with integrated reagents

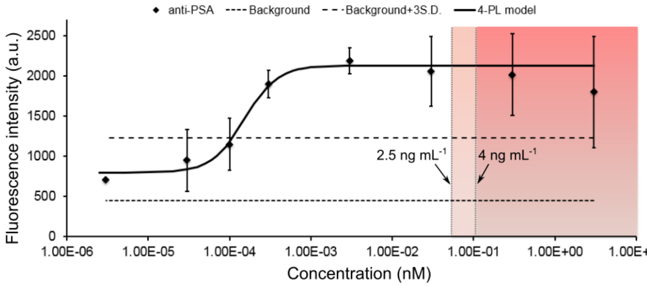
Single bead arrays for the detection of PSA





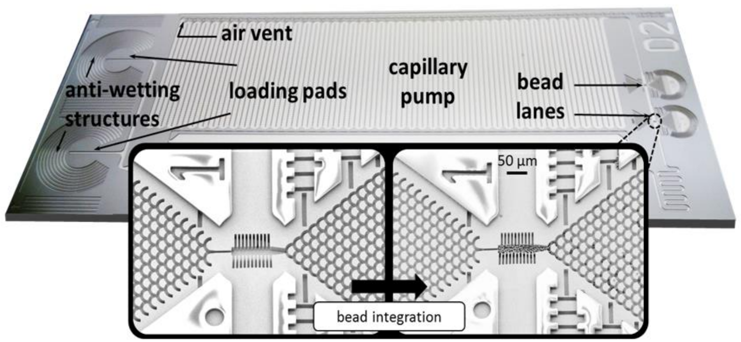
3.3 pg mL^{-1} PSA in PBS → washing buffer → 5.5 µg mL^{-1} Atto594-labeled dAbs → washing buffer.

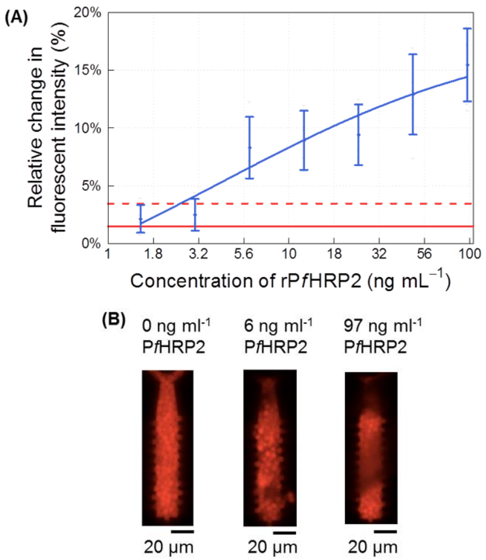
Assay time: ~20 min
LOD: 108 fM or 3.6 pg/ml



Y. Temiz et al., *SPIE Photonics West*, 2016

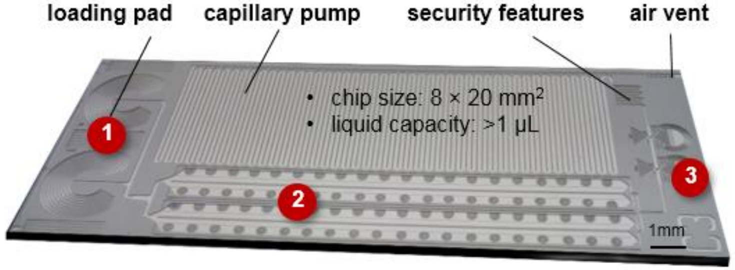
Immuno-gold silver staining assays for the detection of malaria

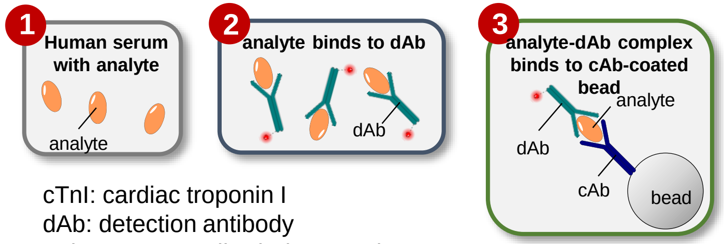




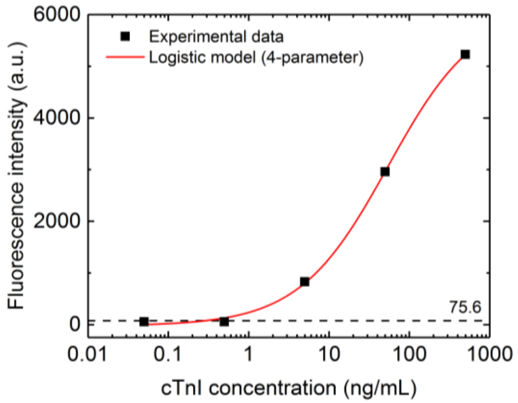
N. M. Pham et al., *Biomedical Microdevices*, 21, 2019

One-step sandwich immunoassay for the detection of Troponin-I



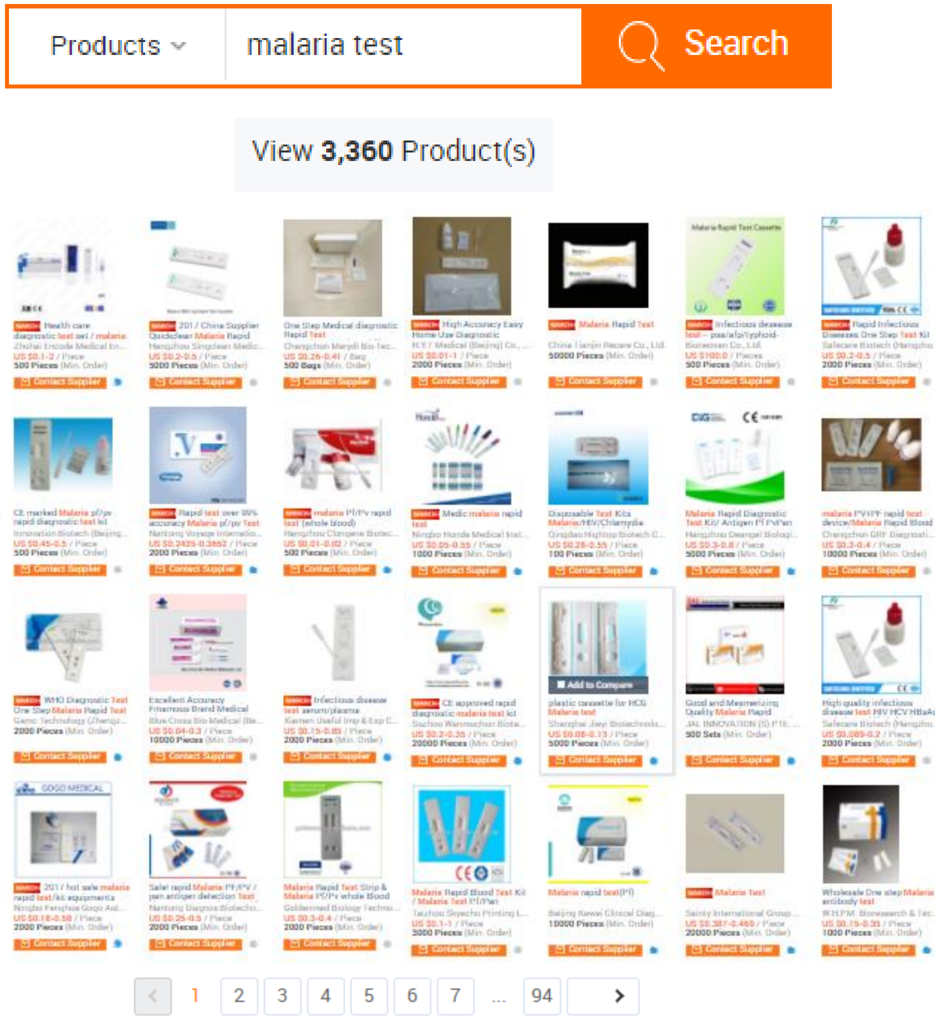


cTnI: cardiac troponin I
dAb: detection antibody
cAb: capture antibody (receptor)

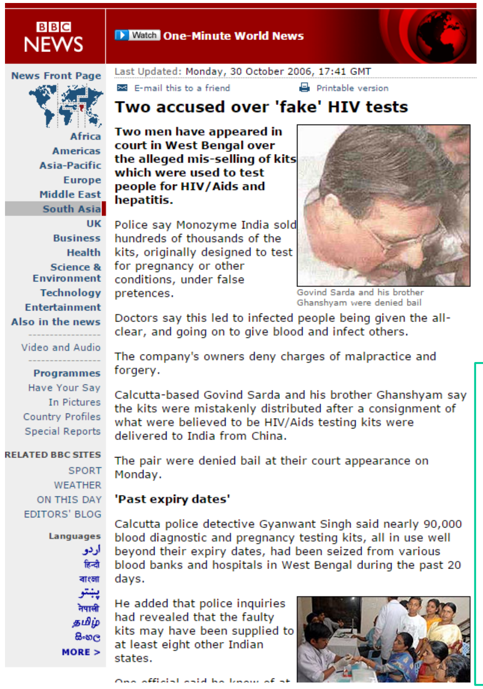


Hemmig et al., ***Anal. Chem.* 92, 2020**

Diagnostic tests and counterfeiting



- WHO estimates **8% of medical devices are counterfeit**
- just for **malaria** alone, **314 millions diagnostic tests were used in 2014**
- **were all these diagnostics genuine? NO**



Last Updated: Monday, 30 October 2006, 17:41 GMT

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Two accused over 'fake' HIV tests

Two men have appeared in court in West Bengal over the alleged mis-selling of kits which were used to test people for HIV/Aids and hepatitis.

Govind Sarda and his brother Ghanshyam were denied bail

Police say Monozyme India sold hundreds of thousands of the kits, originally designed to test for pregnancy or other conditions, under false pretences.

Doctors say this led to infected people being given the all-clear, and going on to give blood and infect others.

The company's owners deny charges of malpractice and forgery.

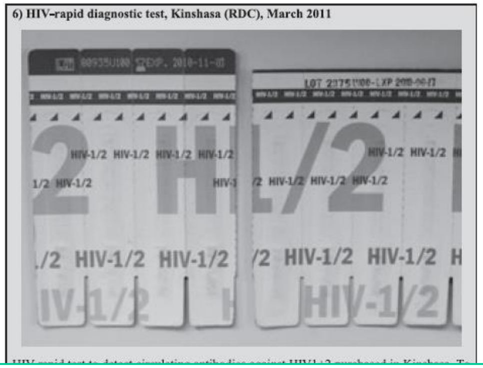
Calcutta-based Govind Sarda and his brother Ghanshyam say the kits were mistakenly distributed after a consignment of what were believed to be HIV/Aids testing kits were delivered to India from China.

The pair were denied bail at their court appearance on Monday.

'Past expiry dates'

Calcutta police detective Gyanwant Singh said nearly 90,000 blood diagnostic and pregnancy testing kits, all in use well beyond their expiry dates, had been seized from various blood banks and hospitals in West Bengal during the past 20 days.

He added that police inquiries had revealed that the faulty kits may have been supplied to at least eight other Indian states.



Introduction

A reliable diagnosis is critical in the management of visceral leishmaniasis (VL). Early case detection and treatment improve prognosis for the patient and can reduce transmission, especially in *Leishmania donovani* areas as there is no animal reservoir.

Rapid diagnostic tests (RDTs) for VL are amongst the most important innovations in the control of VL. These tests allow for patients to be diagnosed closer to their homes. The demand for RDTs was such that counterfeit products began circulating in the Indian subcontinent soon after they were adopted in the VL elimination initiative.

www.who.int/tdr/publications/documents/vl-rdts.pdf

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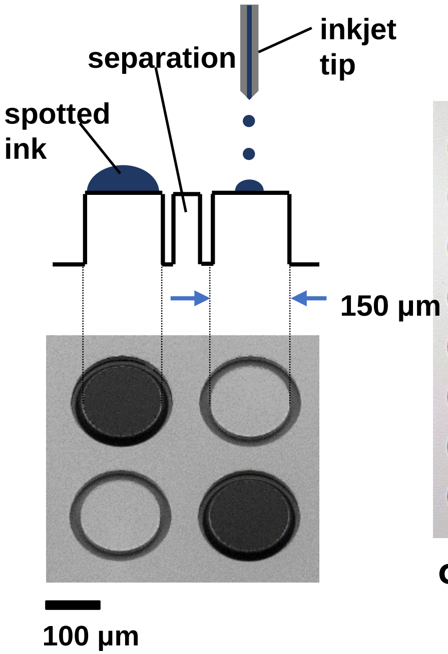
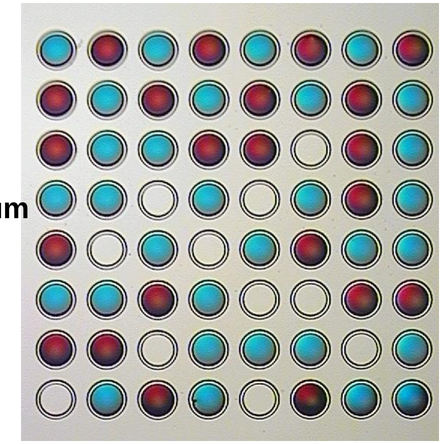
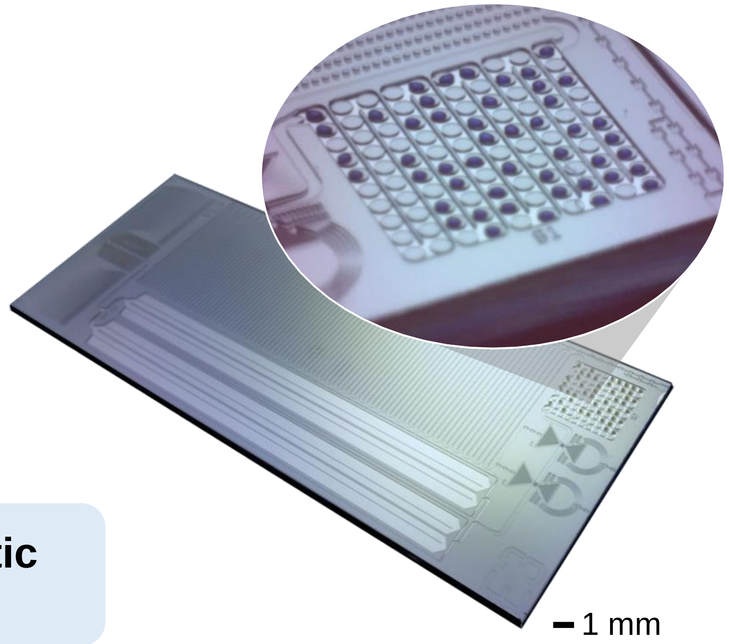
Embedding dynamic optical security codes to silicon microfluidic chips

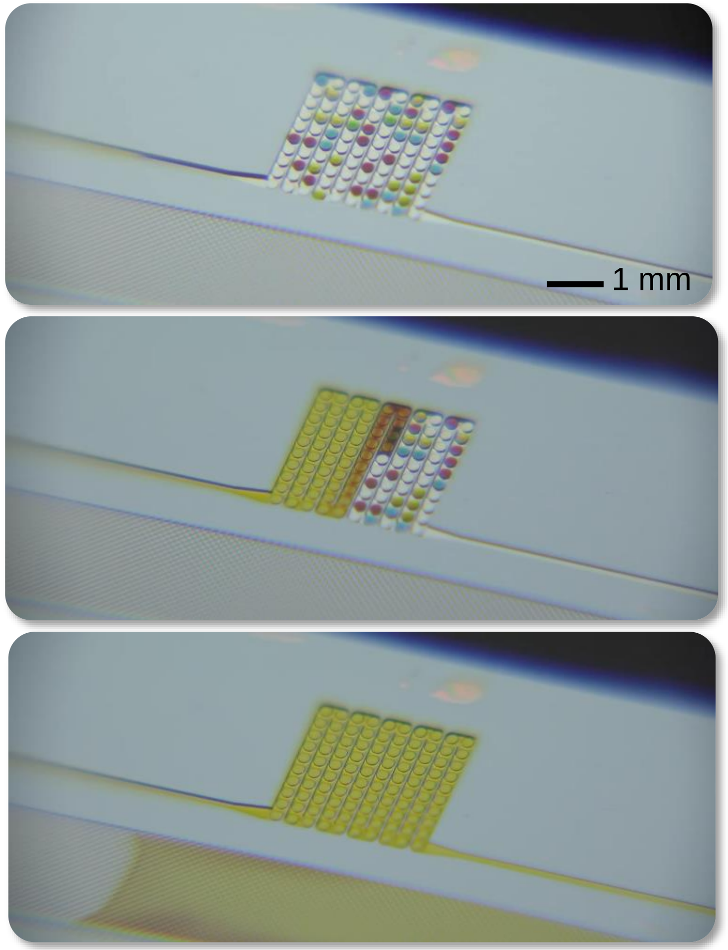




optical code on “islets”



erasable code on a microfluidic device



the code can be **embedded on the diagnostic device**, not just be present on the package

O. Gokce, C. Mercandetti, and E. Delamarche, *Anal. Chem.*, 90, 2018

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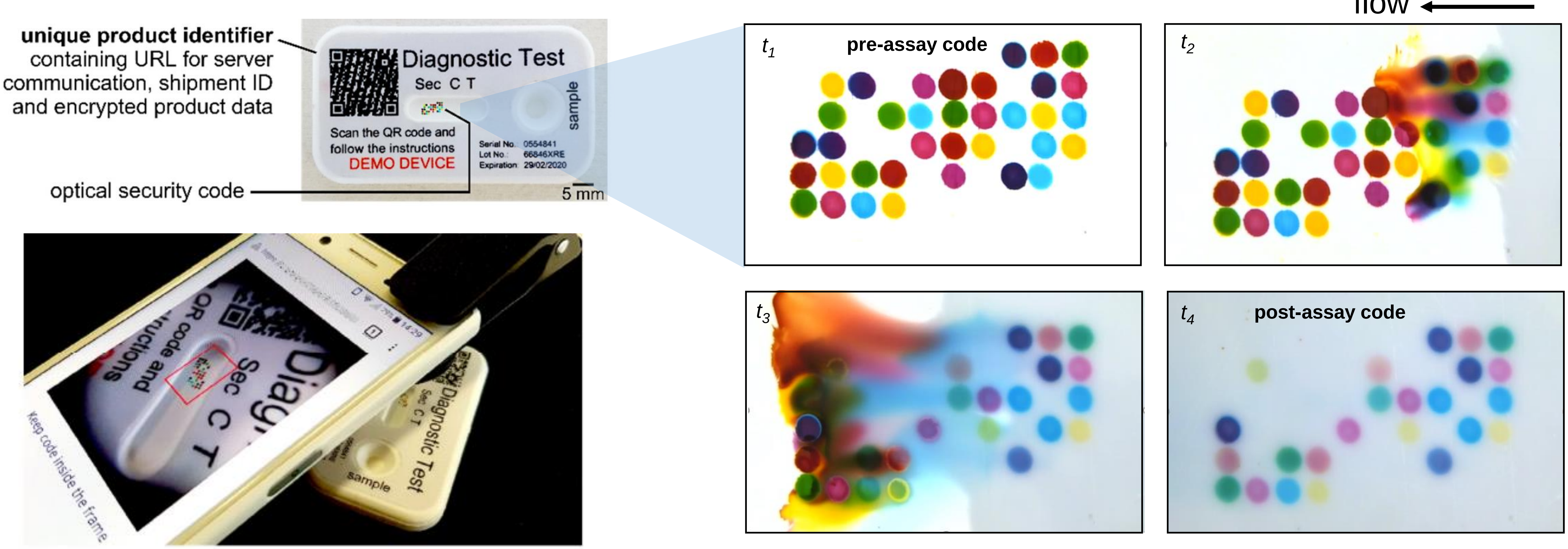
Dynamic codes implemented on conventional materials used for rapid diagnostic tests

dynamic optical codes written on a nitrocellulose membrane and read out using smartphone's camera



- 152 bits of information (at least **10^{45} combinations**)
- Dynamic codes have a **hidden layer of information** compared to static codes

O. Gokce, C. Mercandetti, and E. Delamarche, *Anal. Chem.*, 90, 2018

Electronic peripherals and smartphone towards connected diagnostics

bi-directional communication between microfluidic chips and a smartphone using compact and portable peripherals

- trapping particles using dielectrophoresis
- flow control using a protocol uploaded from smartphone
- continuous flow monitoring in sub-nL precision
- real-time failure detection
- guiding the user (when to pipette, end of test)
- compact/portable readers for optical detection
- reading security features using smartphone

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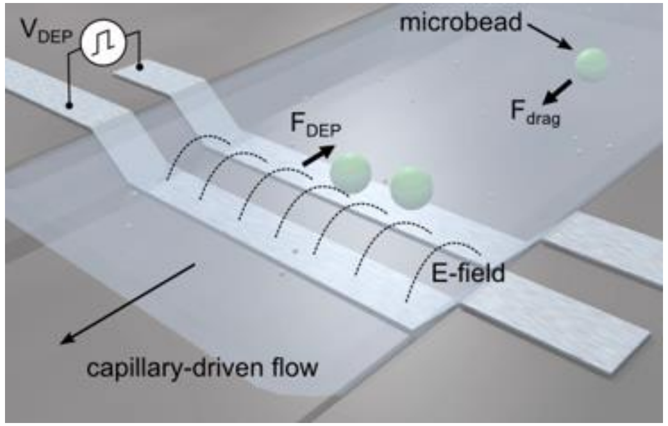
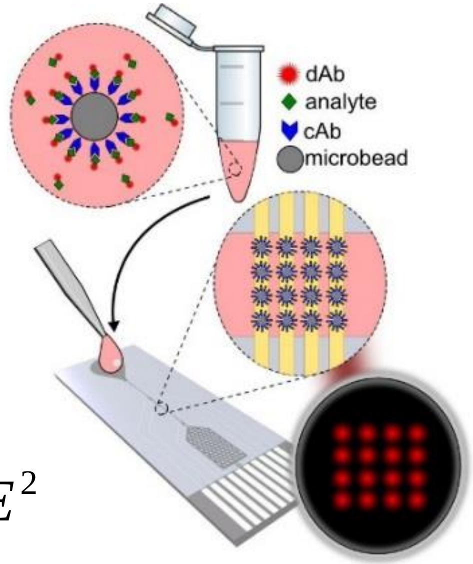
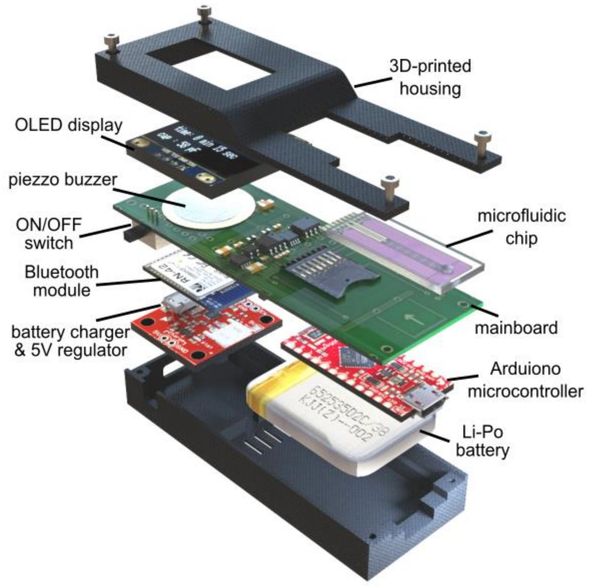
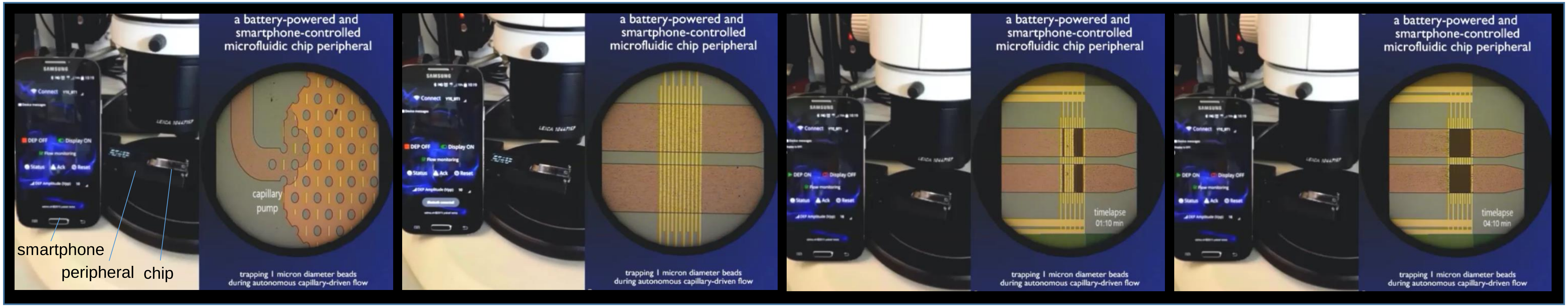
Dielectrophoretic trapping of microbeads using a smartphone-controlled peripheral







$$\langle F_{DEP} \rangle = 2\pi\varepsilon_m R^3 \,\mathrm{Re}(CM^*)\nabla E^2$$



capillary-driven flow | DEP OFF (0 min) | DEP ON (after 1 min) | DEP ON (after 4 min)

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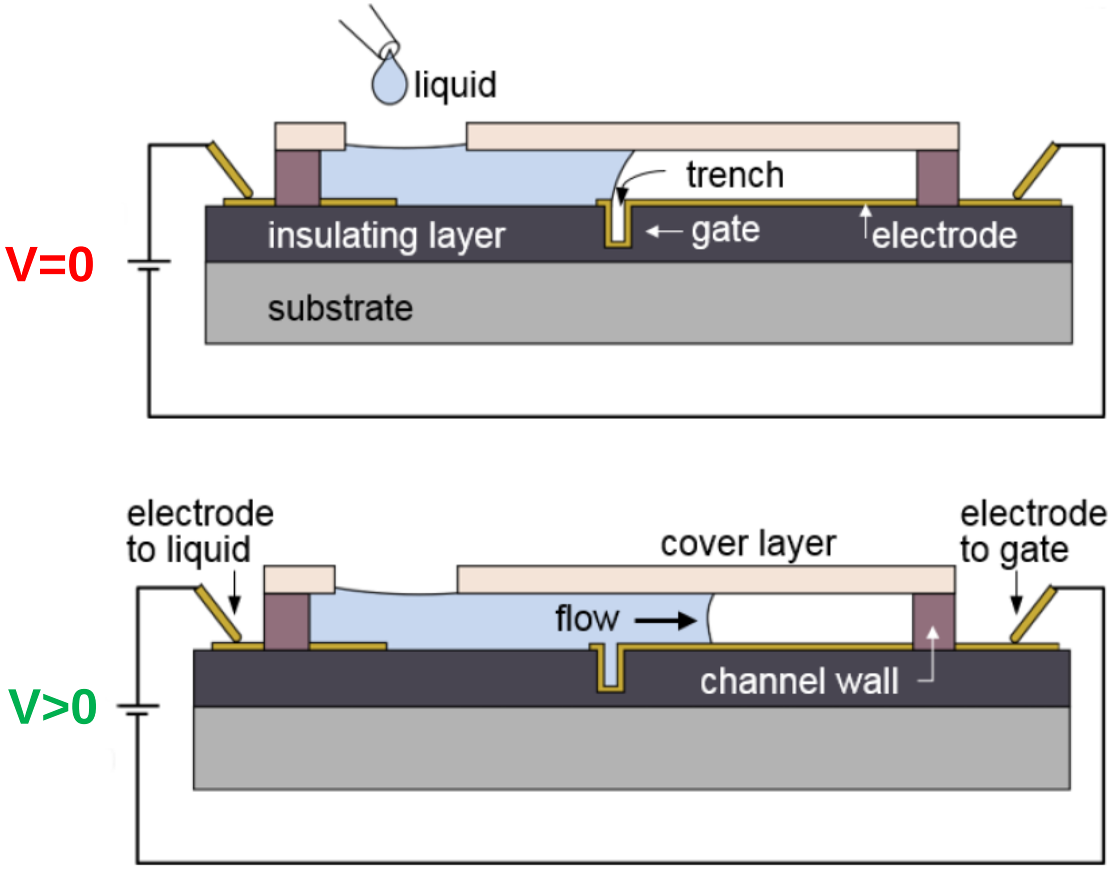
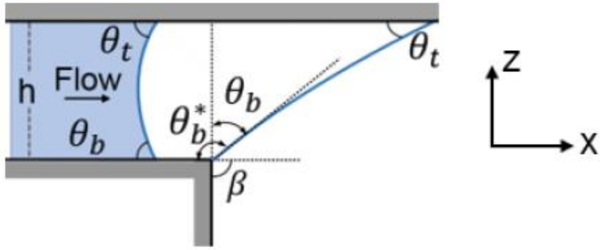
Stop-and-Go control of flow using “Electrogates”: towards a universal microfluidic chip

- adding **flow control** to capillary-driven microfluidic chips by combining **liquid pinning** and **electrowetting**





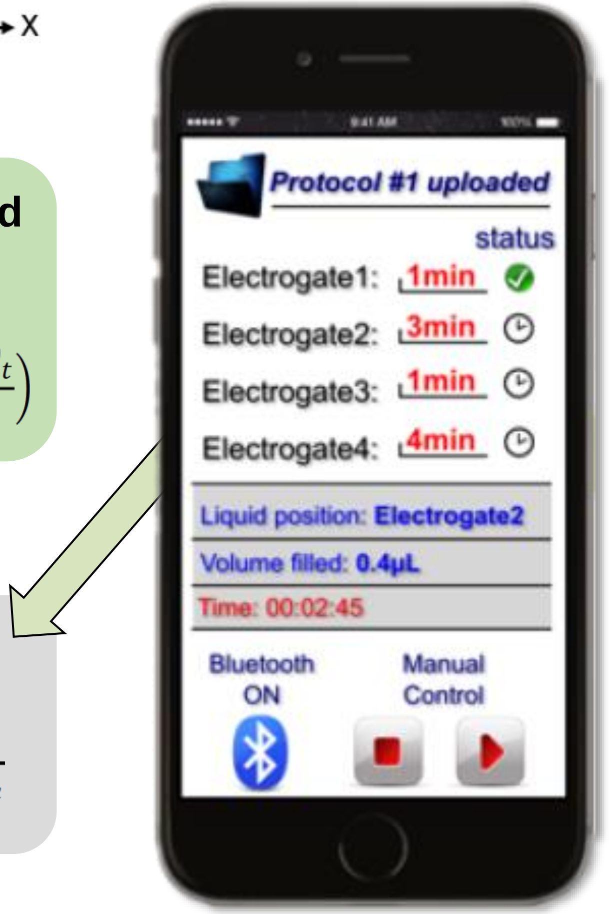
Laplace pressure and meniscus pinning

$$\Delta P = \gamma_{LG}\left(\frac{2\cdot\cos\theta_s}{w}+\frac{\cos\theta_b^* + \cos\theta_t}{d}\right)$$

Electrowetting

$$\cos\theta_b = \cos\theta_0 + \frac{cV^2}{2\gamma_{LG}}$$

assay protocol applied from a smartphone application



Y. Arango, Y. Temiz, O. Goekce, E. Delamarche, *Appl. Phys. Lett.*, 112, 2018

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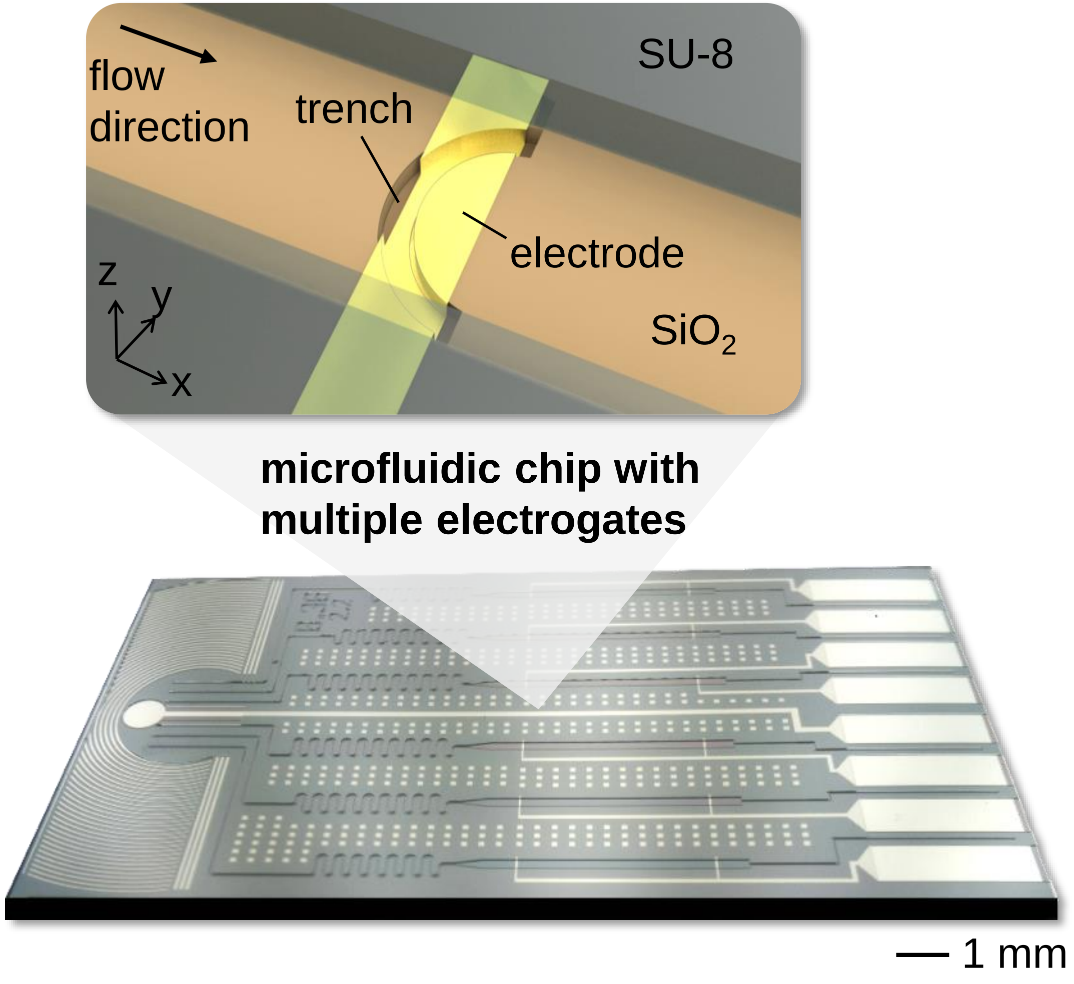
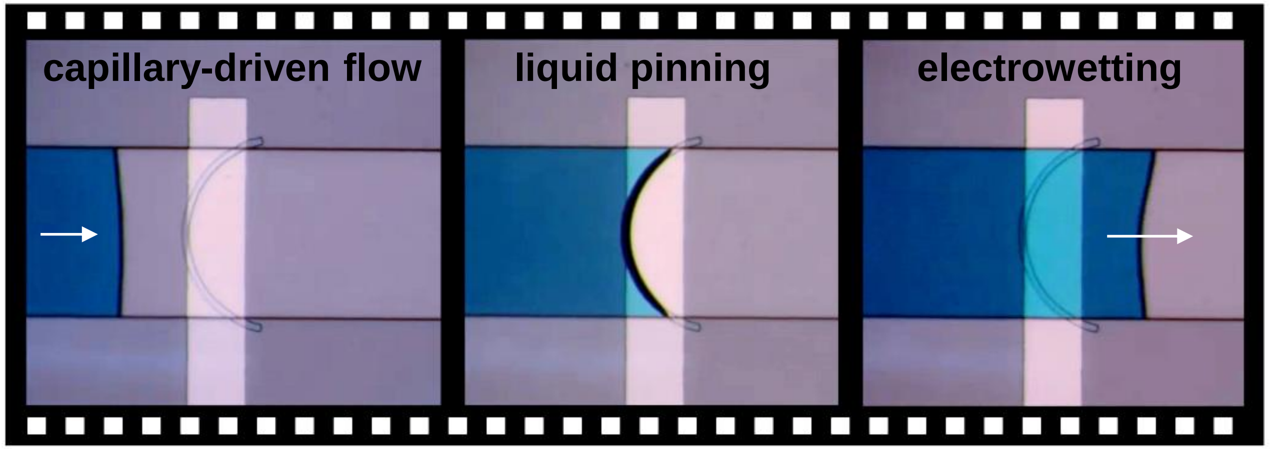
Characteristics of electrogates





- compatible with autonomous **capillary-driven flow**
- low actuation voltage **(< 10 V**), **smartphone control**
- long retention time (**> 30 min**)
- fast actuation (**<1 s**)
- compatible with biological buffers and **human serum**
- 4 different fabrication processes developed

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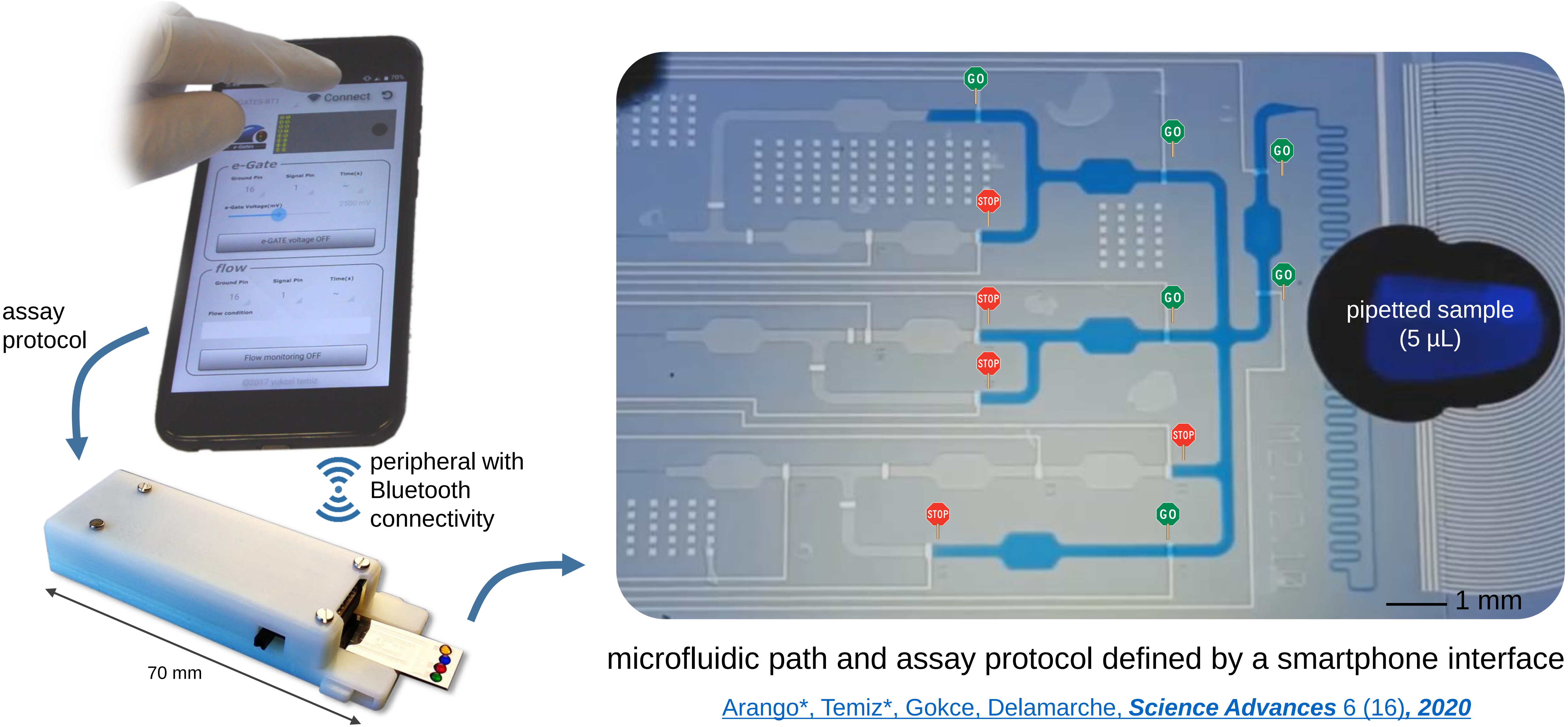
Programming microfluidic path and flow conditions from smartphone



microfluidic path and assay protocol defined by a smartphone interface

Arango*, Temiz*, Gokce, Delamarche, ***Science Advances*** 6 (16), ***2020***

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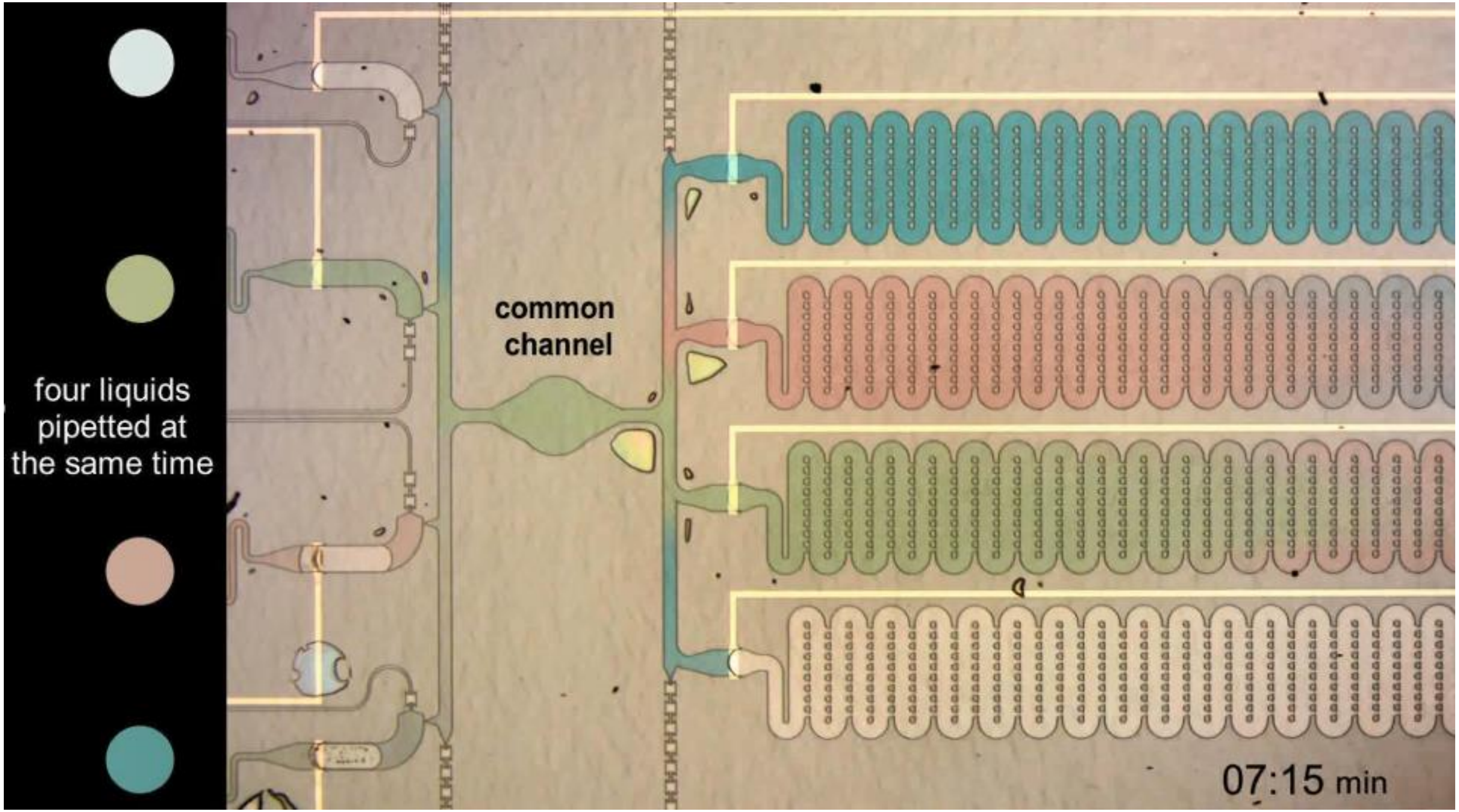
Sequential delivery of liquids has been a long-lasting challenge in capillary-driven microfluidics



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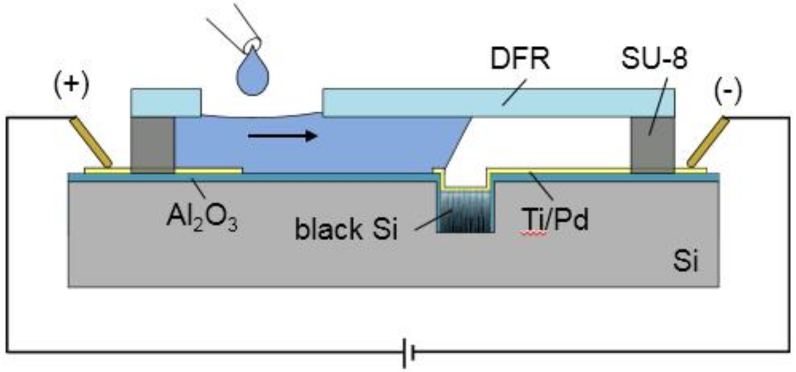
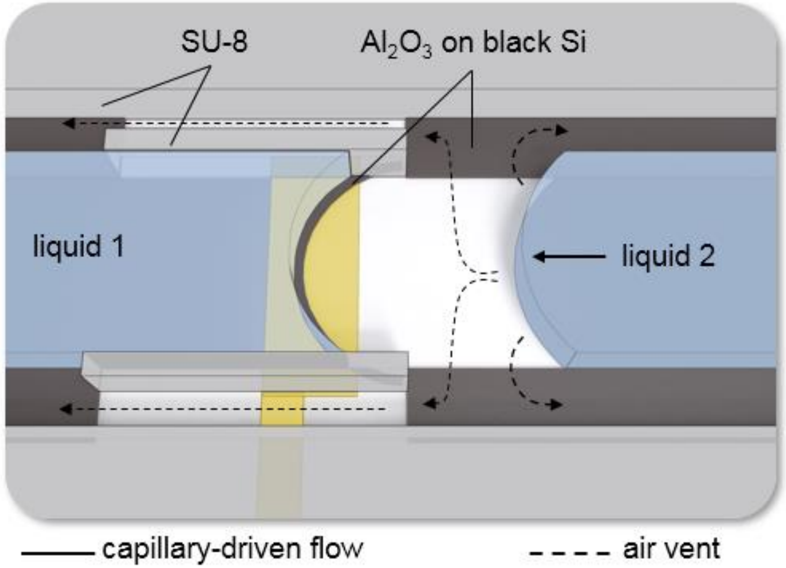
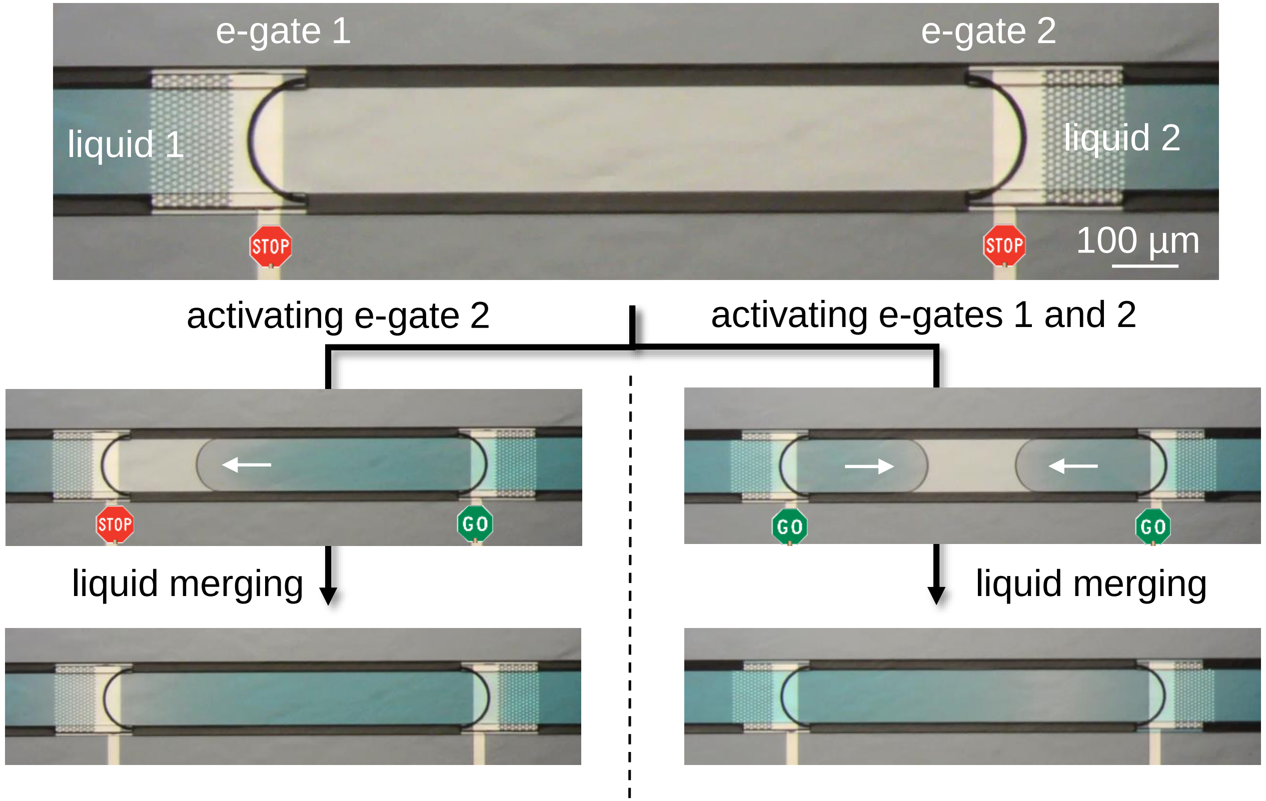
Synchronized merging of multiple liquids without trapping air







[Arango*, Temiz*, Gokce, Delamarche, ***Science Advances*** 6 (16), ***2020***]

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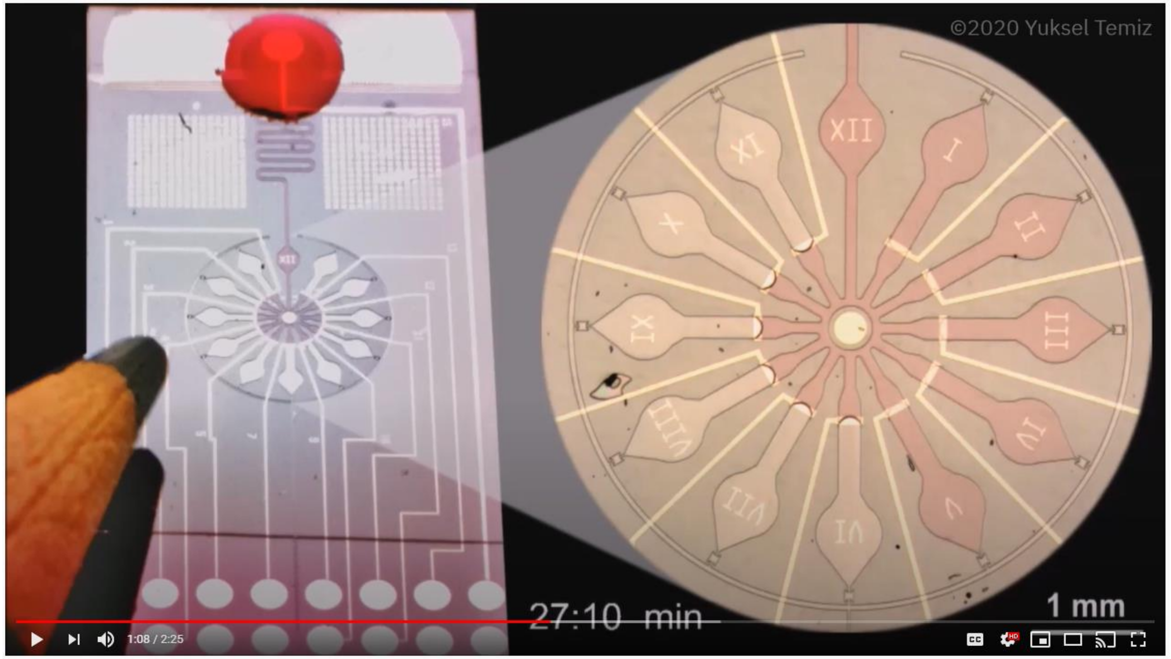
Concluding remarks

- **Capillary flow –** can be programmed very precisely in miniaturized assays to encode flow on nL s^{-1} levels
- **Flow control –** electrogates can be triggered by a smartphone app for defining flow paths and temporarily stopping flow at pre-determined locations
- **Flexible design -** library of functional elements combined for specific applications + smartphone protocol
- **Security -** counterfeit diagnostic tests are a reality – embedded optical or electrical security codes can help

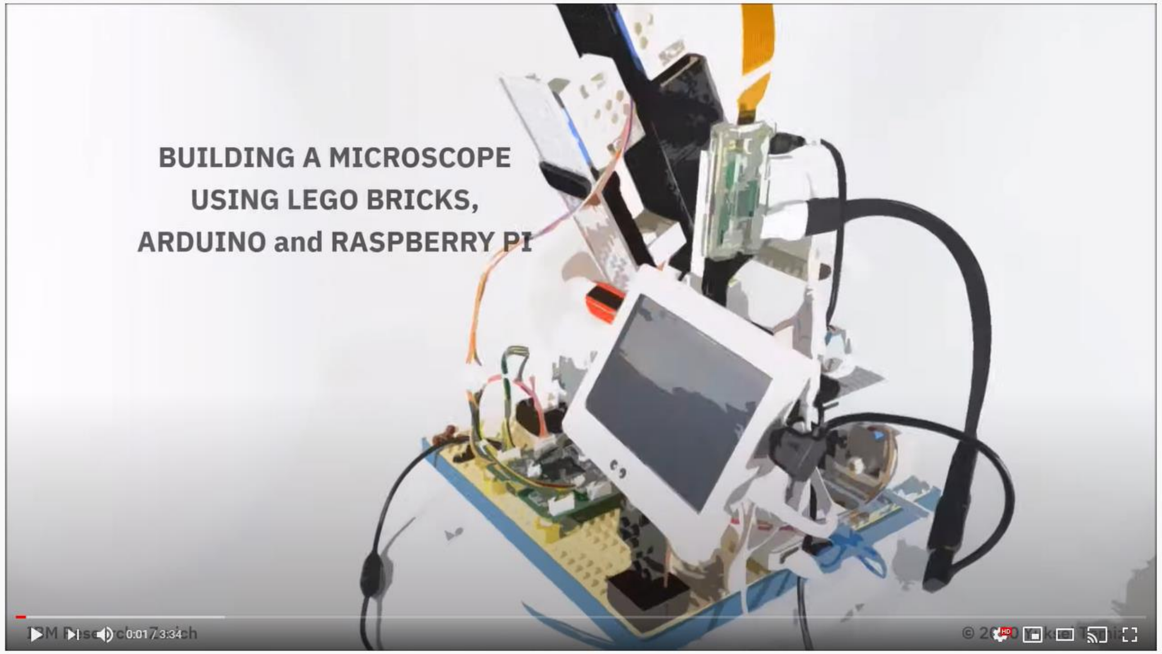
Programmable liquid circuits



World's smallest liquid "clock" - programmable liquid circuits

https://youtu.be/iel4a4HiDss

An open-source microscope



IBM open sources $300 fully-functional LEGO® microscope design

https://youtu.be/PBSYnk9T4o4

https://github.com/IBM/MicroscoPy

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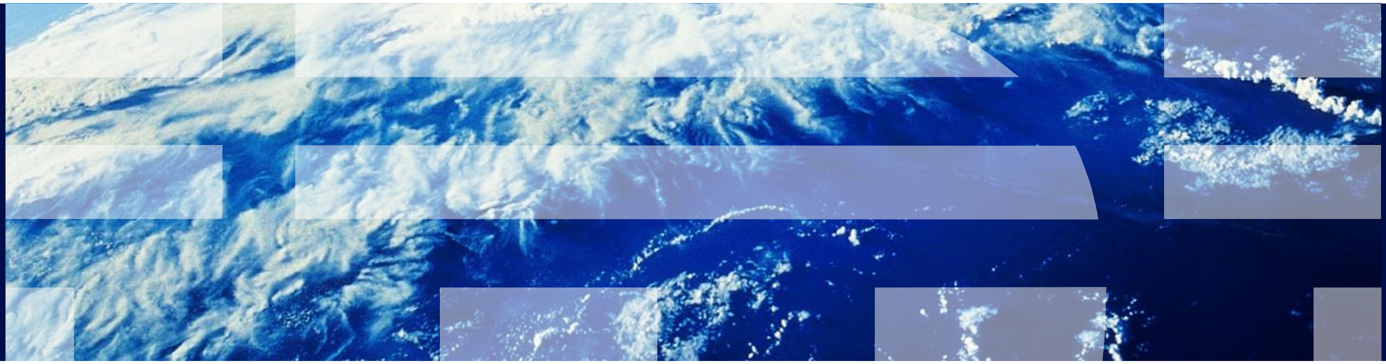
THANK YOU!



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