

The Internet of (Biochemical) Things: Disruptive Concepts based on Fundamental Advances in Materials Science and 3D Fabrication Technologies

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Invited Lecture Presented at
**CFF2019 - Chemistry for the Future
International Conference
July 3-5, 2019**

Dipartimento di Chimica e Chimica Industriale
Via Giuseppe Moruzzi, 13 - Pisa



The Insight Centre for Data Analytics



[Insight](#) is one of the biggest data analytics centres in Europe. It undertakes high-impact research, seeks to derive value from Big Data and provides innovative technology solutions for industry and society by enabling better decision-making.

With **€88 million (ca.50% Industry)** in funding, Insight has **400 researchers** across areas such as connected health, decision analytics, social media analytics, smart cities and the semantic web; see <http://www.sfi.ie/sfi-research-centres/insight/>

2nd Phase funding approved (ca. €50 million SFI) commencing autumn 2019



Internet of (Biochemical) Things IO_{BC}T

- **Bridging the Molecular and Digital Worlds**
 - Emergence of ‘Internet of Analytical Things’, Internet of ‘Molecular Things’, ‘Internet of Biochemical Things’
- **Long-Term “Deploy and Forget” use model**
 - Embedded ‘smartness’
 - Sensing (temperature, light-level, imaging, vibration)
 - Communications (wireless)
 - Power (10-year battery life-time, energy scavenging capability)
 - Awareness of
 - Surrounding environment
 - Internal (functional) condition



internet scale sensing

Dermot Diamond
Dublin City University
(Ireland)

Incredible advances in digital communications and computer power have profoundly changed our lives. One chemist shares his vision of the role of analytical science in the next communications revolution.

Digital communications networks are at the heart of modern society. The digitalization of communications, the development of the Internet, and the availability of relatively inexpensive but powerful mobile computing technologies have established a global communications network capable of linking billions of people, places, and objects. Email can instantly transmit complex documents to multiple remote locations, and websites provide a platform for instantaneous notification, dissemination, and exchange of information globally. This technology is now pervasive, and those in research and business have multiple interactions with this digital world every day. However, this technology might simply be the foundation for the next wave of development that will provide a seamless interface between the real and digital worlds.

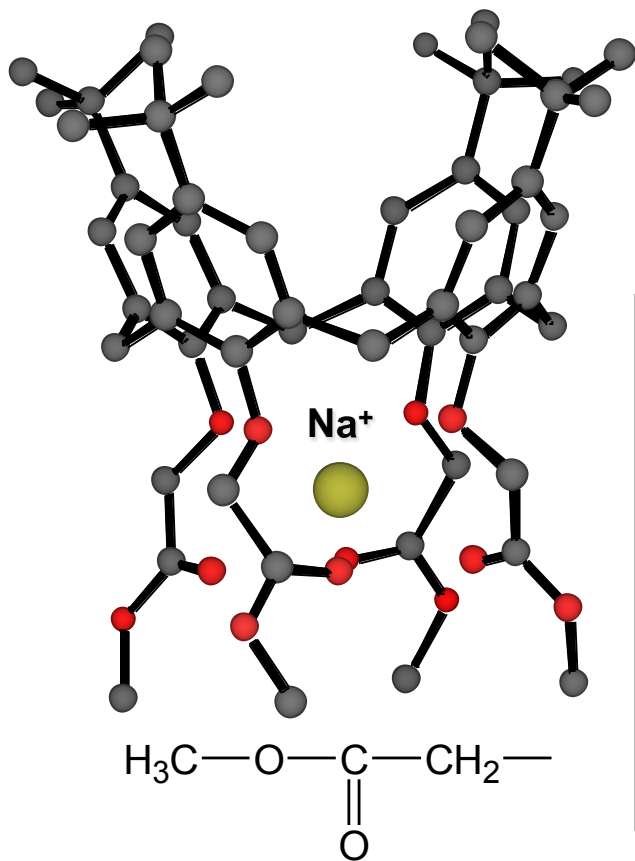
The crucial missing part in this scenario is the gateway through which these worlds will communicate. How can the

Ron Ambrosio & Alex Morrow, IBM TJ Watson

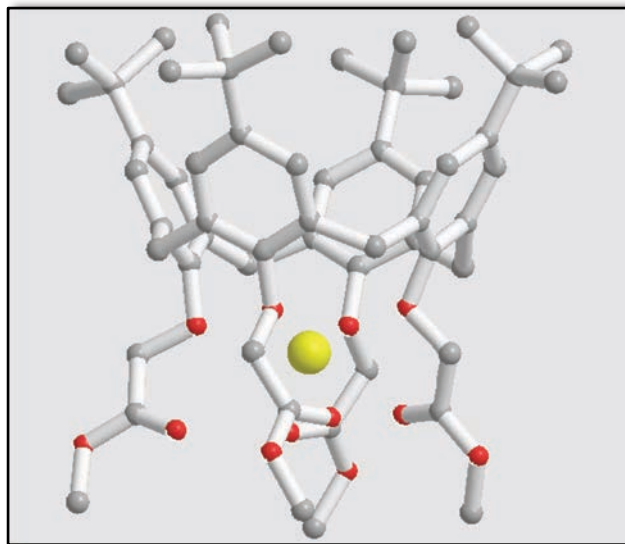




Calixarene Ionophores – controlling the selectivity

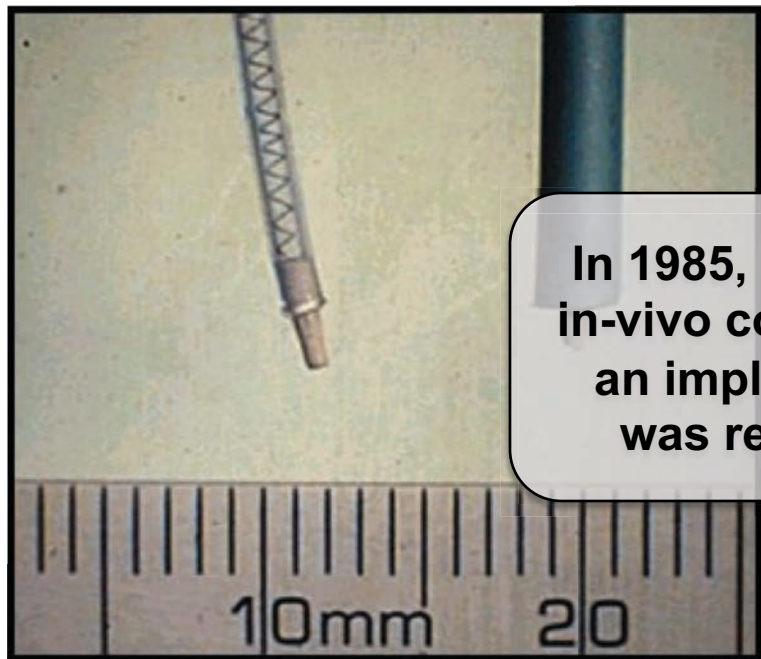
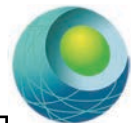


Gyula Svehla





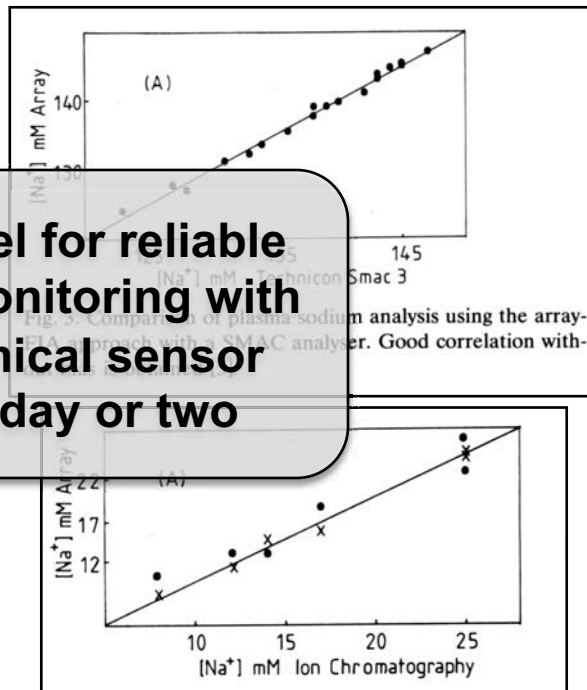
Blood Analysis; Implantable Sensors



1985: Catheter Electrodes for intensive care
– function for 24 hrs

Dr. David Band, St Thomas's Hospital London

In 1985, the use model for reliable in-vivo continuous monitoring with an implantable chemical sensor was restricted to a day or two



Anal. Chem., 64 (1992) 1721-1728.

Ligand (and variations of) used in many clinical analysers for blood Na⁺ profiling



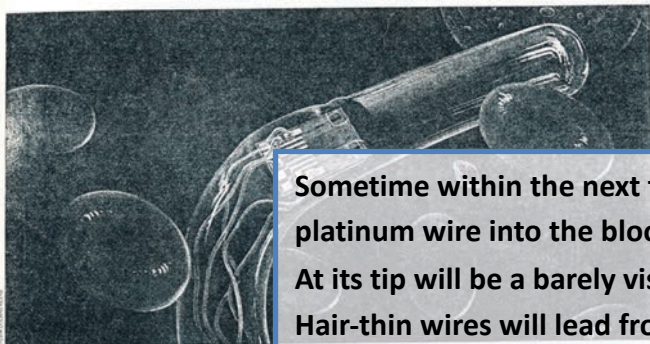


The (broken) promise of biosensors.....



High Technology, Nov. 1983, 41-49

BIOSENSORS THE MATING OF BIOLOGY AND ELECTRONICS



Implanted sensors combine biology and electronics to track life processes. The 1 cm. of Utah model is a field-effect transistor.

Sometime within the next three or four years, a physician will insert a centimeter of platinum wire into the bloodstream of a diabetic patient. At its tip will be a barely visible membrane containing a bit of enzyme. Hair-thin wires will lead from the other end of the platinum to an insulin reservoir—a titanium device about the size and shape of a hockey puck—implanted in the patient's abdomen.

Within seconds a chemical reaction will begin at the tip of the wire. A few minutes or so later, the reaction will adhere to the membrane and be attacked by the enzyme, forming hydrogen peroxide and another product. The peroxide will migrate to a thin oxide

layer on the platinum wire, which will generate a current. The current will be proportional to the glucose concentration, the peroxide levels and the potential. A current thus generated will be sent to a computer, which will process the data and send it to a pump. The pump will then release insulin into the bloodstream. The sensor is just one of many experimental biosensors being developed.

Between two and three new biosensors being ready for market in the U.S., Japan, and England monitor not just one or two but up to eight variables at the same time. Within the next few years, several additional

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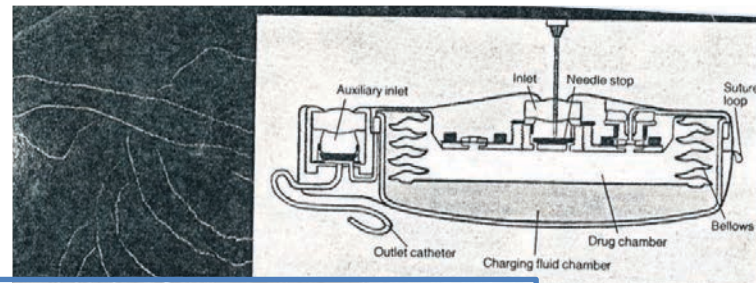
At its tip will be a barely visible membrane containing a bit of enzyme.

Hair-thin wires will lead from the other end of the platinum to an insulin reservoir implanted in the patient's abdomen.

Within seconds, a chemical reaction will begin at the tip of the wire.....

.....And (by implication) it will work for years reliably and regulate glucose through feedback to insulin pump

In medicine and industry, tiny high-speed devices will track a wide range of biological reactions ☐ by H. Garrett DeYoung



Infusoid reservoir implanted in lower abdomen. It may also be fitted in upper chest, with catheter inserted into aorta.





After Ca. 40 years – Dominant Use Model is Still Finger Prick Sampling

- e.g. Diabetes: ca. 7% of world population
- USA: population 300 million
- Ca. 20 million diabetics
- Personal control of condition using finger prick test => blood sample + glucose biosensor
- Say four measurements per day
= 80 million/day
- Per year = ca. 30 Billion
measurements/yr
- Each sensor used ONCE





Adam Heller



Subcutaneous sampling of interstitial fluid using microneedles to access the fluid through the skin without causing bleeding

Measurement by coulometry



San Francisco Business Times; Tuesday, April 6, 2004

'Abbott completes TheraSense acquisition'

Abbott Laboratories said Tuesday it completed its \$1.2 billion acquisition of Alameda-based TheraSense Inc. after a majority of shareholders approved the transaction a day earlier.

Abbott Press Release September 29, 2008

Abbott Park, Illinois — Adam Heller, Ph.D., a professor at the University of Texas in Austin who created the technology that led to the development of Abbott's FreeStyle Blood Glucose Monitoring Systems® and FreeStyle Navigator® Continuous Glucose Monitoring System, today received the 2007 National Medal of Technology and Innovation from President George W. Bush in an award ceremony at the White House.



Abbott Freestyle 'Libre'

The days of routine glucose testing with lancets, test strips and blood are over.²

Welcome to flash glucose monitoring!



How to use the FreeStyle Libre System

The FreeStyle Libre system utilises advanced technology that is easy to use.

1 Apply sensor with applicator



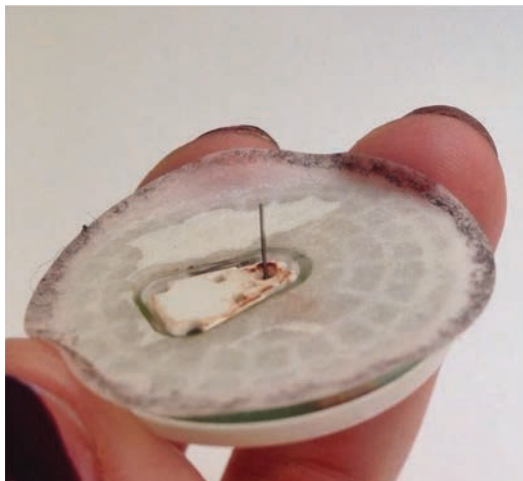
- A thin flexible sterile fibre (5mm long) is inserted just below the skin. Most people reported that applying the sensor was painless¹
- The 14-day sensor stays on the back of your upper arm and automatically captures glucose readings day and night.
- The sensor is water resistant and can be worn while bathing, swimming and exercising²

¹ Most people did not feel any discomfort under the skin while wearing the FreeStyle Libre sensor. In a study conducted by Abbott Diabetes Care, 93.4% of patients surveyed (n=30) strongly agree or agree that while wearing the sensor, they did not feel any discomfort under their skin. [29 persons have finished the study; 1 person terminated the study after 3 days due to skin irritations in the area where the sensor touched the skin.]
² Sensor is water-resistant in up to 1 metre (3 feet) of water for a maximum of 30 minutes.



- 'Small fibre' used to access interstitial fluid
- Data downloaded at least once every 8 hr via 1s contactless scan (1-4 cm)
- Waterproof to 1 metre
- Replace every 2 weeks

Significant Advance – but not ‘ideal’



- ‘Microfibre’ is punched into the skin to access sample fluid
- This may be accessing blood rather than interstitial fluid
- Allergic reactions in some cases



Abbott to add 500 new jobs at Donegal healthcare plant

US healthcare giant employs almost 3,000 people in the Republic

Mon, Jul 23, 2018, 15:35 | Updated: Mon, Jul 23, 2018, 20:33

Peter Hamilton



Abbott's Donegal site manufactures test strips used in its FreeStyle blood glucose-monitoring meters. Photograph: Tim Boyle/Bloomberg

Abbott Jobs in Donegal



Macromolecules 1990, 23, 4372–4377

Synthesis, Characterization, and Properties of a Series of Osmium- and Ruthenium-Containing Metallopolymers

Robert J. Forster and Johannes G. Vos*

School of Chemical Sciences, Dublin City University, Dublin 9, Ireland

Received November 27, 1989; Revised Manuscript Received February 16, 1990

- 1989: Forster and Vos series of papers on Os/Ru bipy/PVP
- 1990s: Heller develops foundational ideas
- 2004: Abbott acquires Therasense (\$1.2bn)
- 2018: Abbott Jobs announcement



NIGHTSCOUT

#WeAreNotWaiting

<http://www.nightscout.info> <https://www.dexcom.com>

Welcome to Nightscout

What is the Nightscout project?



Nightscout (CGM in the Cloud) is an open source, DIY project that allows real time access to a CGM data via personal website, smartwatch viewers, or apps and widgets available for smartphones.

Nightscout was developed by parents of children with Type 1 Diabetes and has continued to be developed, maintained, and supported by volunteers. When first implemented, Nightscout was a solution specifically for remote monitoring of Dexcom G4 CGM data. Today, there are Nightscout solutions available for Dexcom G4, Dexcom Share with Android, Dexcom Share/G5 with iOS, and Medtronic. Nightscout also provides browser-based visualization for #openAPS users and Loop users. The goal of the project is to allow remote monitoring of a T1D's glucose level using existing monitoring devices.

Search ...

Disclaimer

All information, thought, and code described here is intended for informational and educational purposes only. Nightscout currently makes no attempt at HIPAA privacy compliance. Use of code from github.com is without warranty or support of any kind. Please review the LICENSE found within each repository for further details. Use Nightscout at your own risk, and do not use the information or code to make medical decisions.

Support Nightscout

Your contributions help the developers purchase test equipment, webspace, cables, and other tools that drive this project forward. Received donations are managed by The Nightscout Foundation. Click [here](#) to donate.

Please consult with your tax professional regarding deducting donations.

Nightscout



Developed by coders & engineers within the T1 Diabetes Community & friends

Developing APPs

Accessing real-time data from diabetes monitors (Dexcom, wearable glucose sensors)

User groups formed, self-funded

Use disclaimers, no warranty, not for making therapeutic decisions



February 8, 2019: Nano Magazine....



www.nano-magazine.com email
announcing

**‘The graphene biosensor that
could provide early lung cancer
diagnosis’**

**‘The wonder-material graphene
could hold the key to unlocking
the next generation of advanced,
early stage lung cancer
diagnosis’**

nano
THE MAGAZINE FOR SMALL SCIENCE

Weekly News Round-up: The graphene biosensor that could provide early lung cancer diagnosis, plus much more.



MON, FEB 04

The graphene biosensor that could provide early lung cancer diagnosis

The wonder-material graphene could hold the key to unlocking the next generation of advanced, early stage lung cancer diagnosis.



Fig. 2 Characterization of the graphene films. SEM images of the top view of the f-MLG (a) and p-MLG (b) samples on PVC. Raman spectra of the f-MLG (c) and p-MLG (d) performed using a 532 nm laser excitation system with a 40x microscope objective, and 10 s integration time for the single scan.

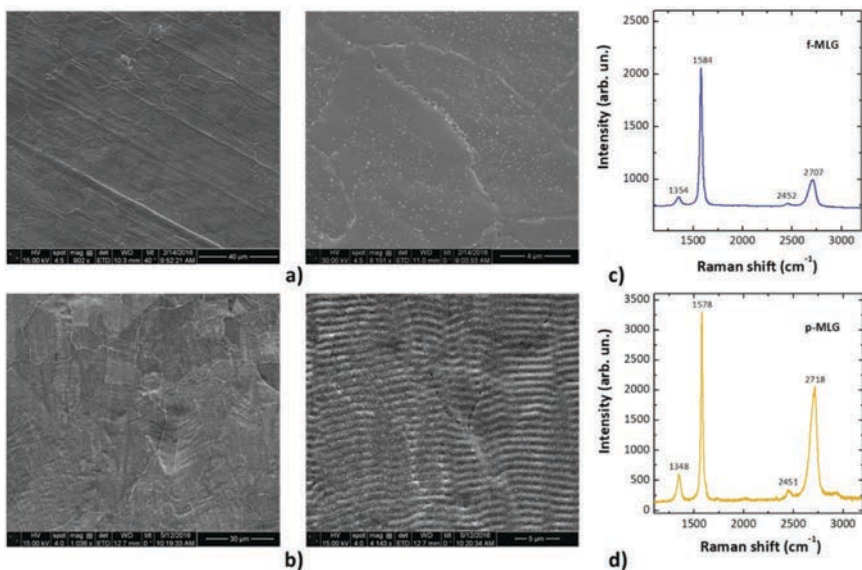
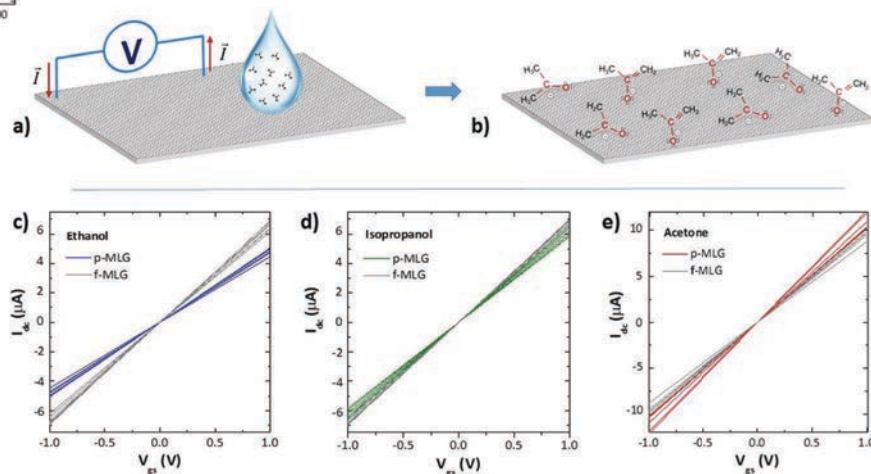


Fig. 3 The schematic representation of the two-point measurement concept (a) for the in situ electrical characterization of VOC-induced graphene electrodes (c, d); electron-induced reorientation of acetone while applying ± 1 V (b). The I_{dc} versus V_{gs} curves of the flat and patterned graphene electrodes influenced with exposure to **1.4–3.3x10⁵ ppm** of VOC solutions: ethanol (c), isopropanol (d) and acetone (e).

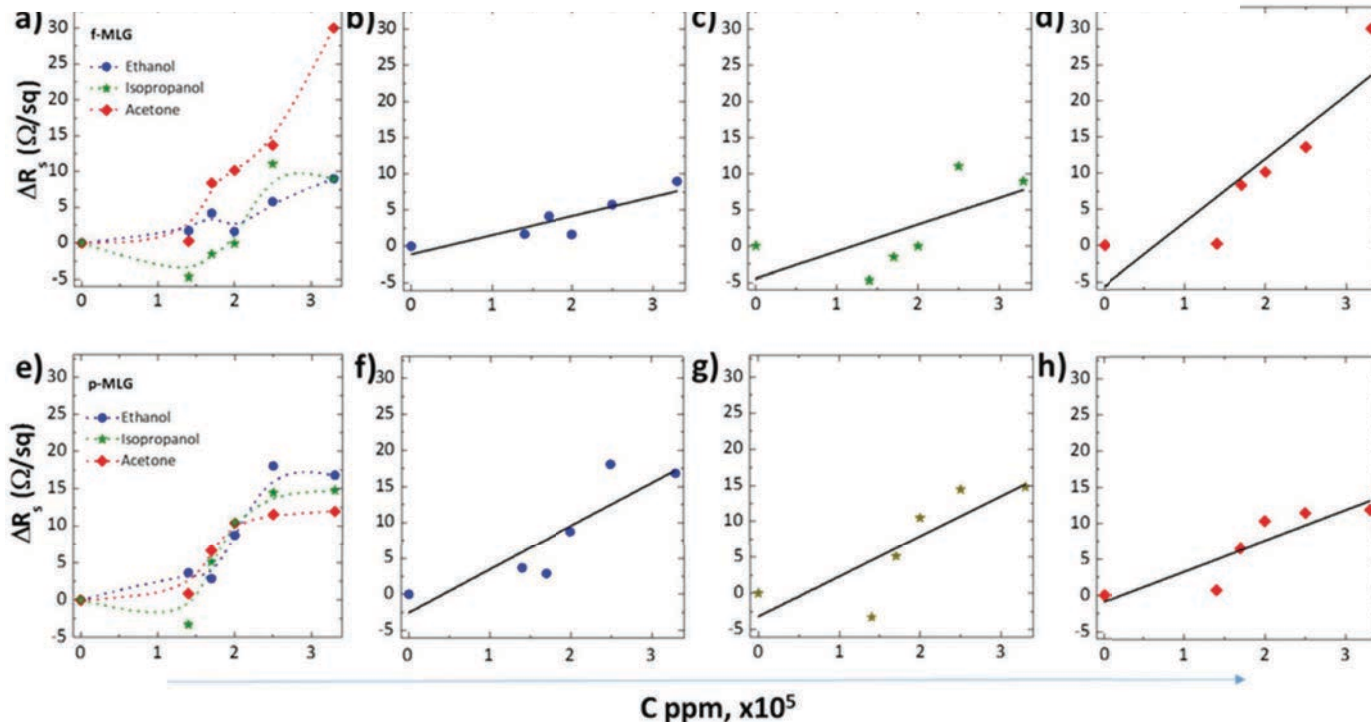




Response Curves to 'cancer marker' VOCs in breath (e-Nose)



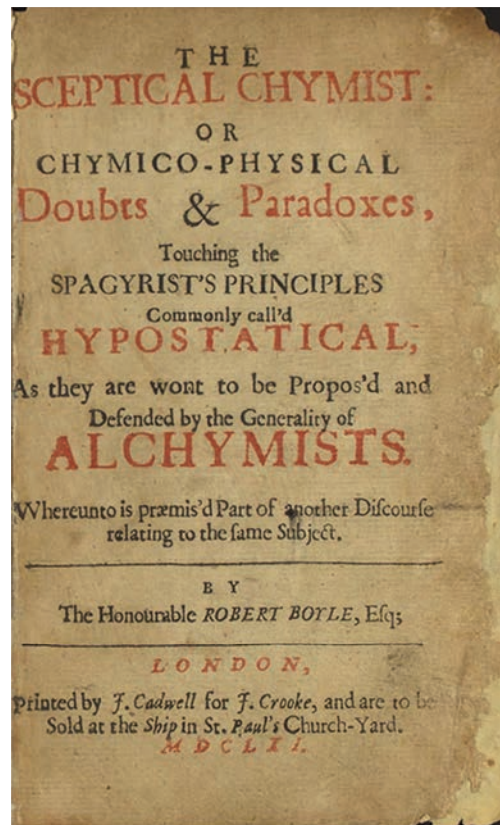
Fig. 4 Sensitivity identification of f-MLG (a) and p-MLG (e) electrodes at various concentrations of cancer marker solutions (ethanol – ◆, isopropanol – ★, and acetone – ◆). Changes in the value of sheet resistance (ΔR_s) for f-MLG (b–d) and p-MLG (f–h) as a function of CM concentration.]



Massive concentrations (0-30%!), no selectivity, bare graphene (no surface functionalization), no humidity studies.....



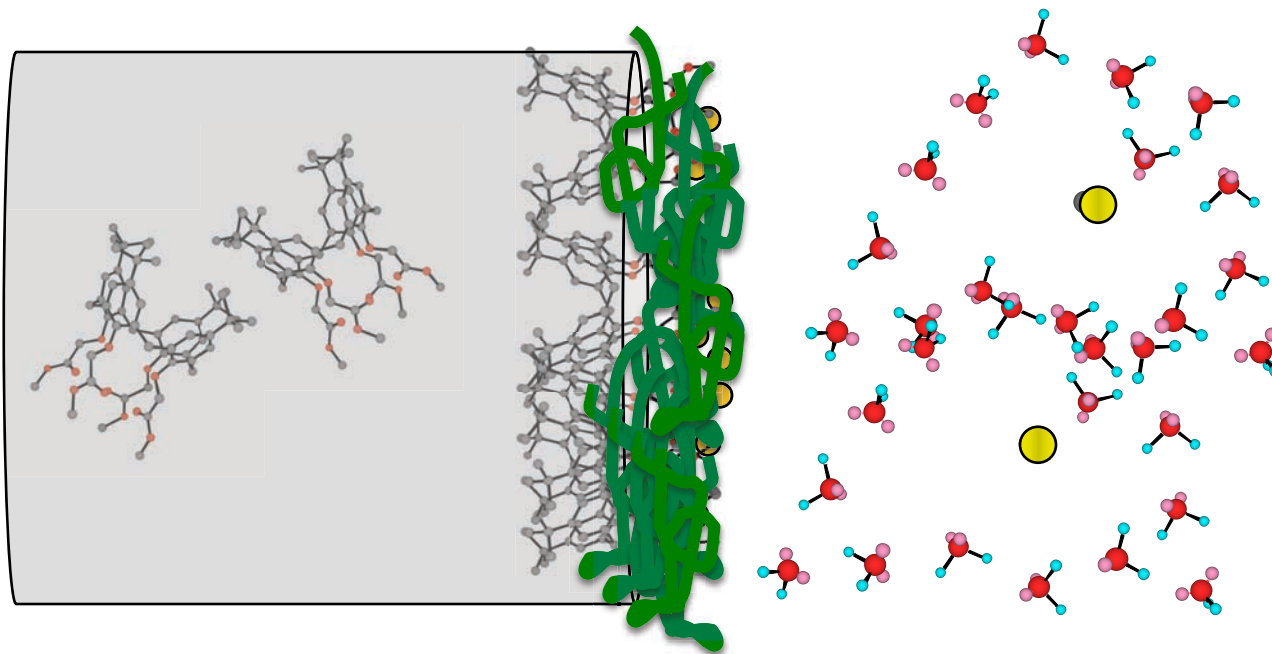
'The Sceptical Chemist' (1661) 'Chymico-Physical Paradoxes'



**Robert Boyle: b.
Lismore Castle,
Waterford, Ireland,
1621**



Control of membrane interfacial exchange & binding processes



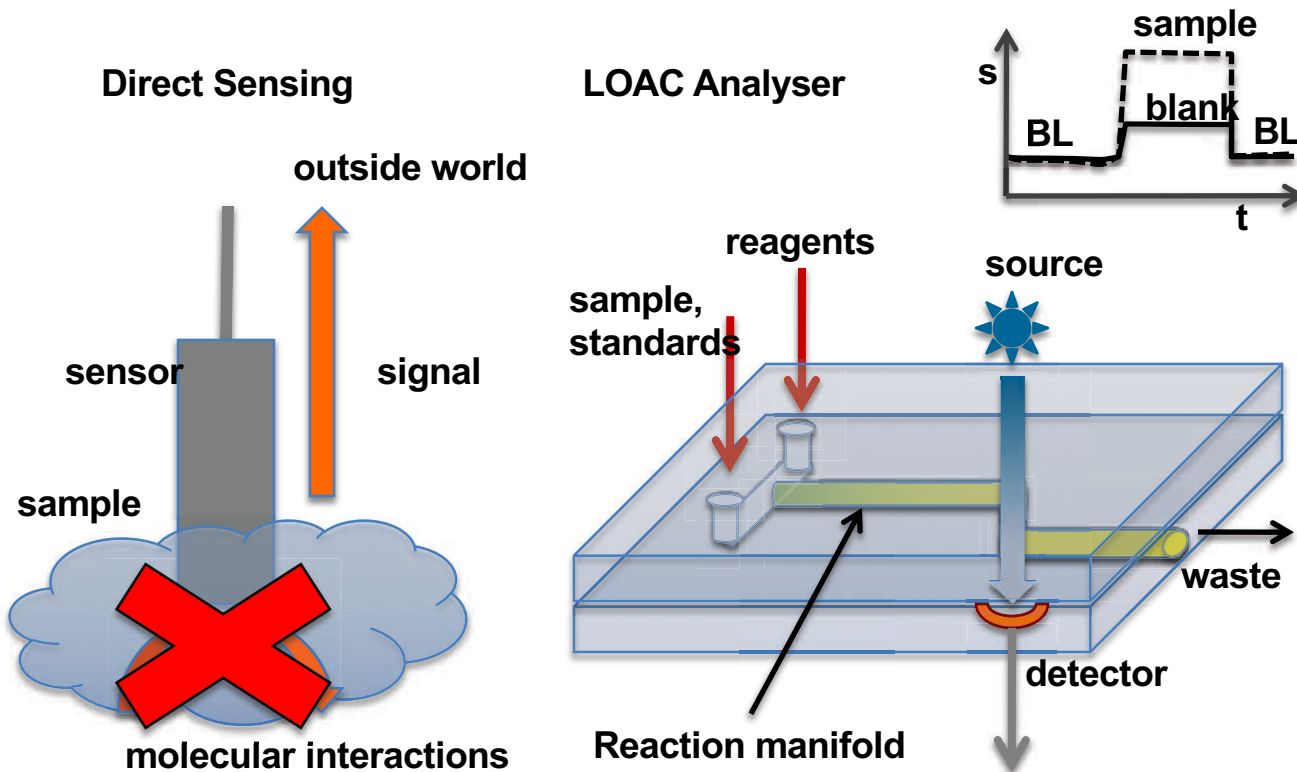
Remote, autonomous chemical sensing is a tricky business!



Osberstown Waste Water Treatment Plant – 3 week deployment



Direct Sensing vs. Reagent Based LOAC/ufluidics





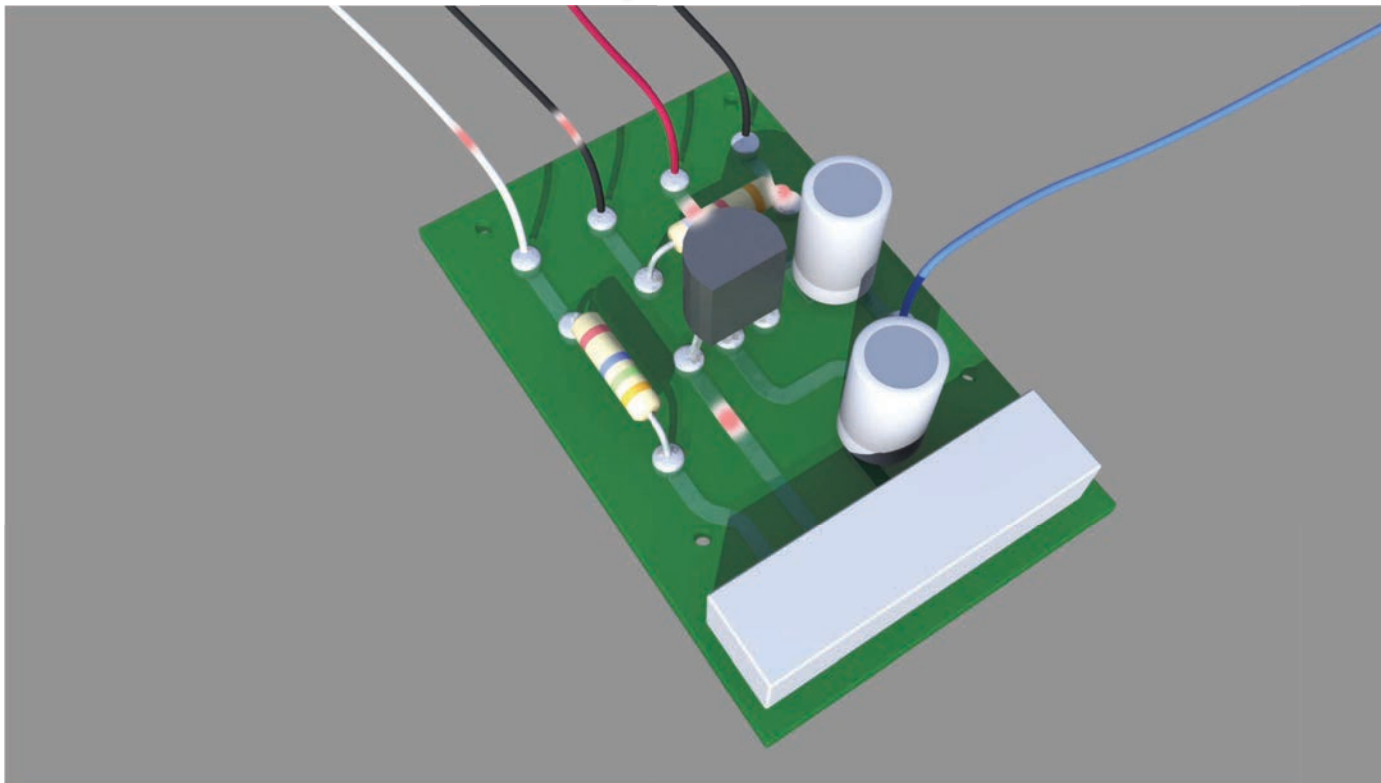
Microfluidics – Evolution....



Electronics Inspired

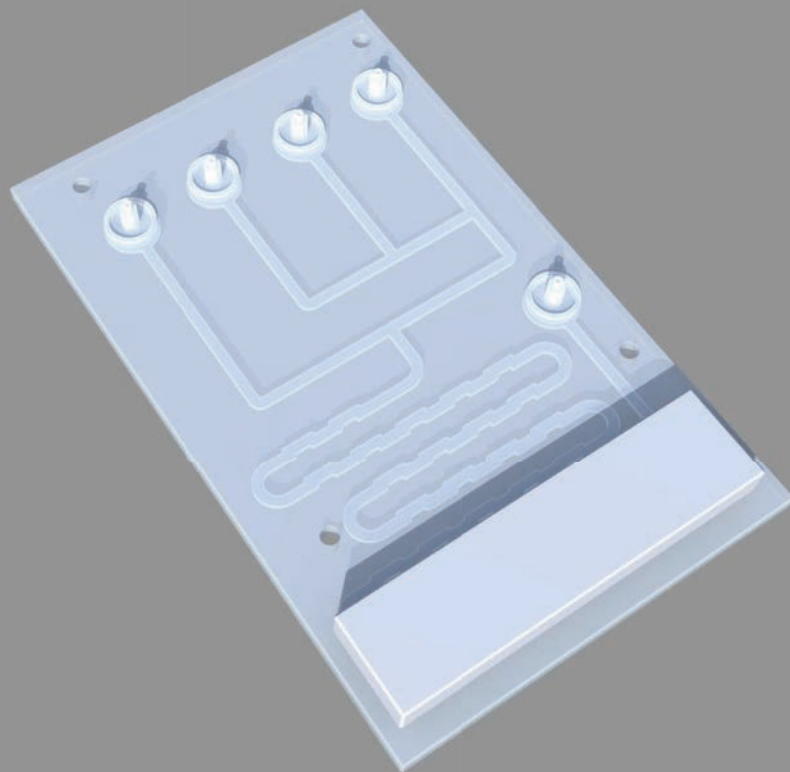


Modeled on an integrated circuit



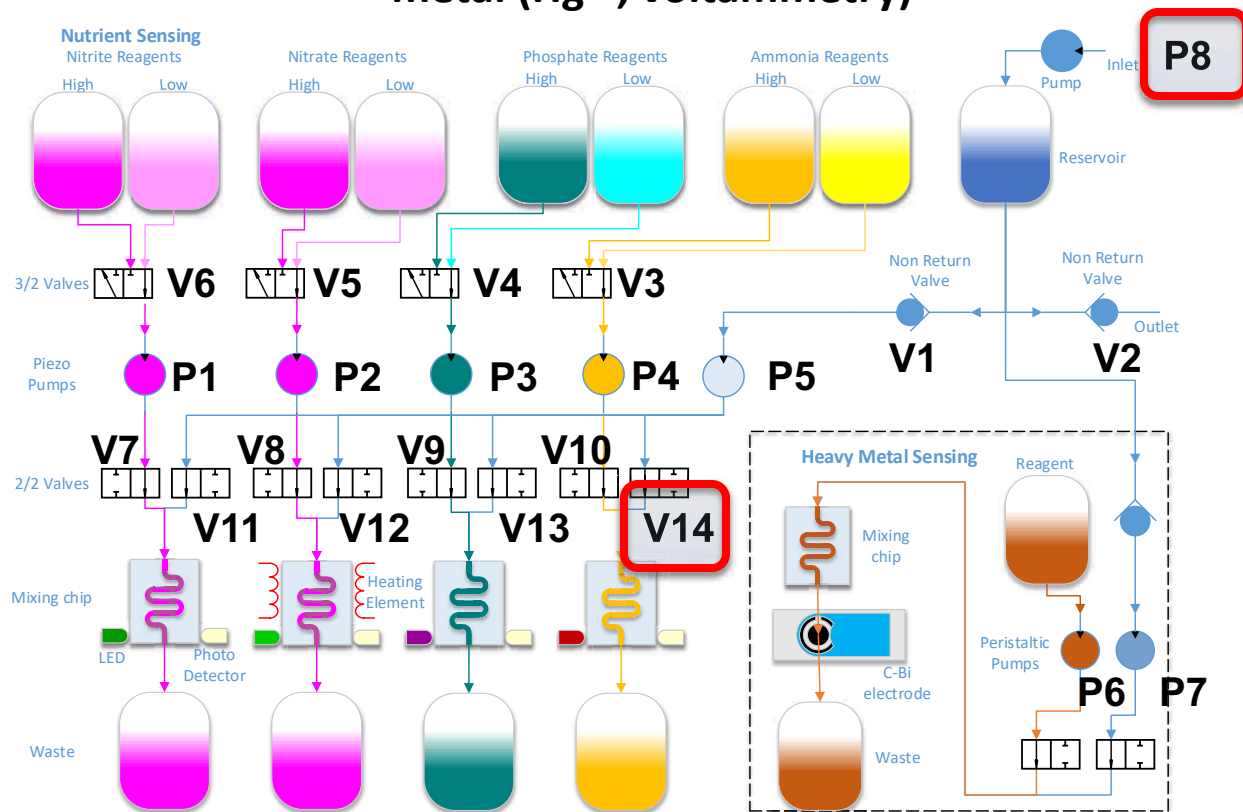


But not everything is integrated.....





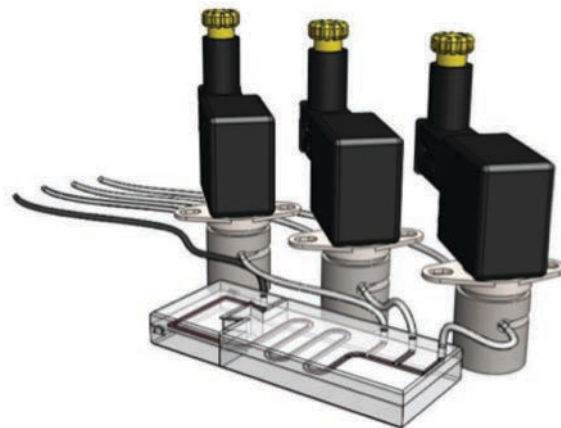
Fluidic Schematic: Multi-Analyte - Nitrite, nitrate, phosphate, ammonia, heavy metal (Hg^{2+} , voltammetry)





How to advance fluid handling in LOC platforms: re-invent valves (and pumps)!

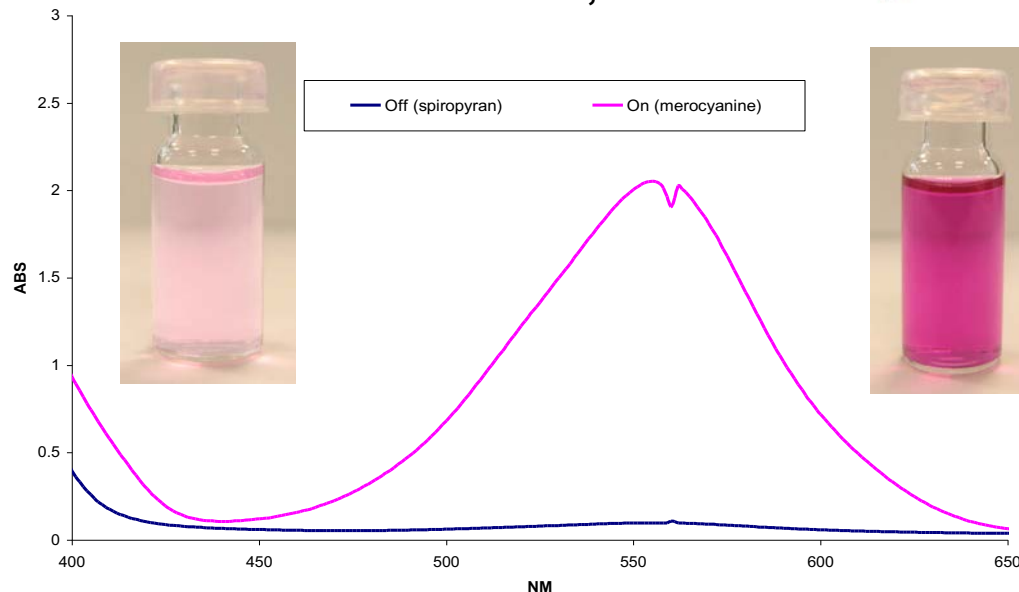
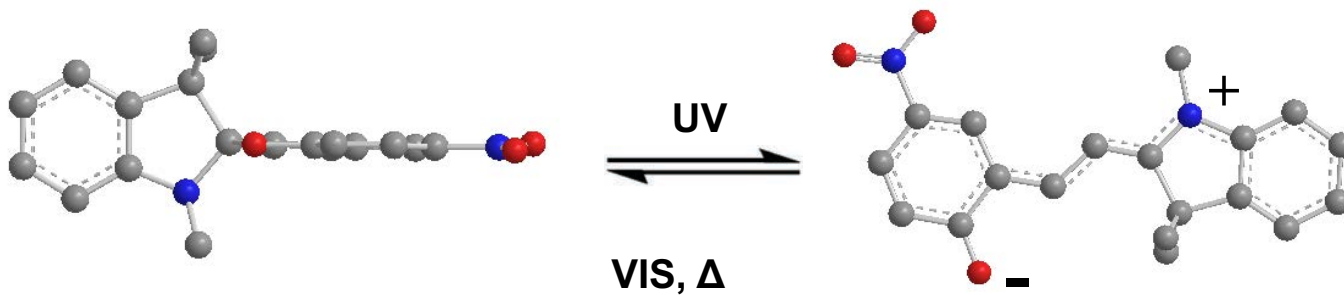
- **Conventional valves cannot be easily scaled down - Located off chip: fluidic interconnects required**
 - Complex fabrication
 - Increased dead volume
 - Mixing effects
- **Based on solenoid action**
 - Large power demand
 - Expensive



Solution: soft-polymer (biomimetic) valves fully integrated into the fluidic system



Molecular Photoswitches: Spiropyans & Merocyanine

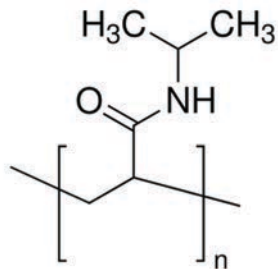




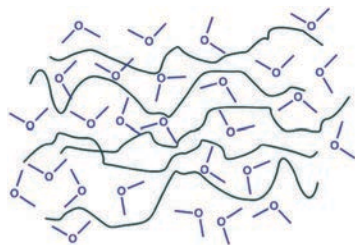
Poly(*N*-isopropylacrylamide)

- pNIPAAm exhibits inverse solubility upon heating
- This is referred to as the LCST (Lower Critical Solution Temperature)
- Typically this temperature lies between 30-35°C, but the exact temperature is a function of the (macro)molecular microstructure
- Upon reaching the LCST the polymer undergoes a dramatic volume change, as the hydrated polymer chains collapse to a globular structure, expelling the bound water in the process

pNIPAAm

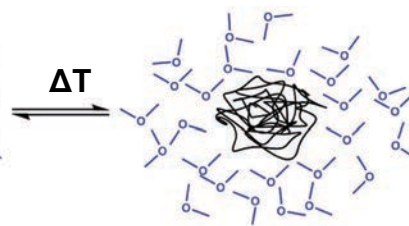


Hydrophilic



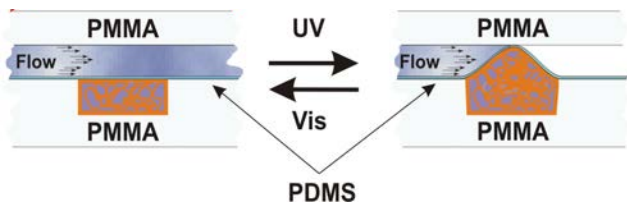
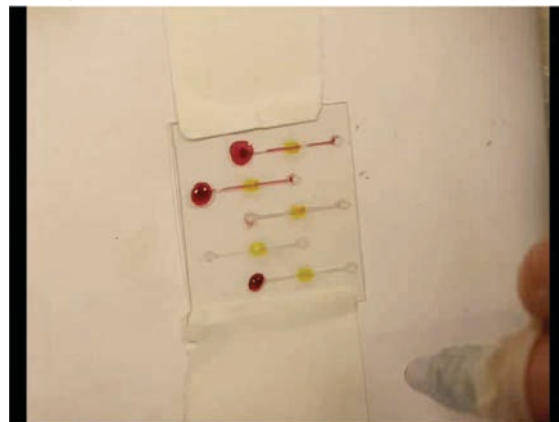
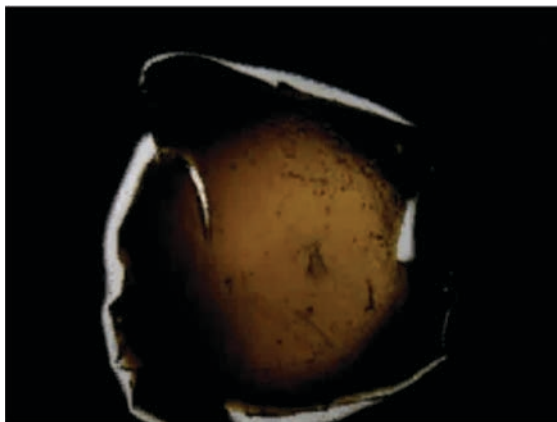
Hydrated Polymer Chains

Hydrophobic

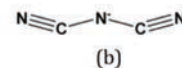
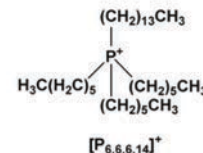
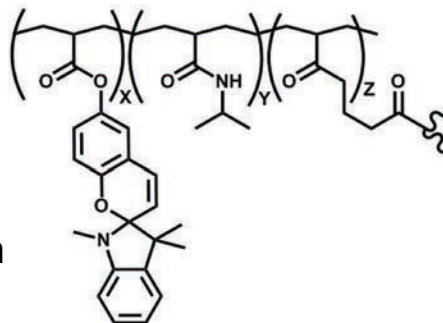


Loss of bound water
→ polymer collapse

Photo-actuator polymers as microvalves in microfluidic systems



**trihexyltetradecylphosphonium
dicyanoamide $[P_{6,6,6,14}]^+[dca]^-$**



Ionogel-based light-actuated valves for controlling liquid flow in micro-fluidic manifolds, Fernando Benito-Lopez, Robert Byrne, Ana Maria Raduta, Nihal Engin Vrana, Garrett McGuinness, Dermot Diamond, Lab Chip, 10 (2010) 195-201.

Experimental set up for PID Control

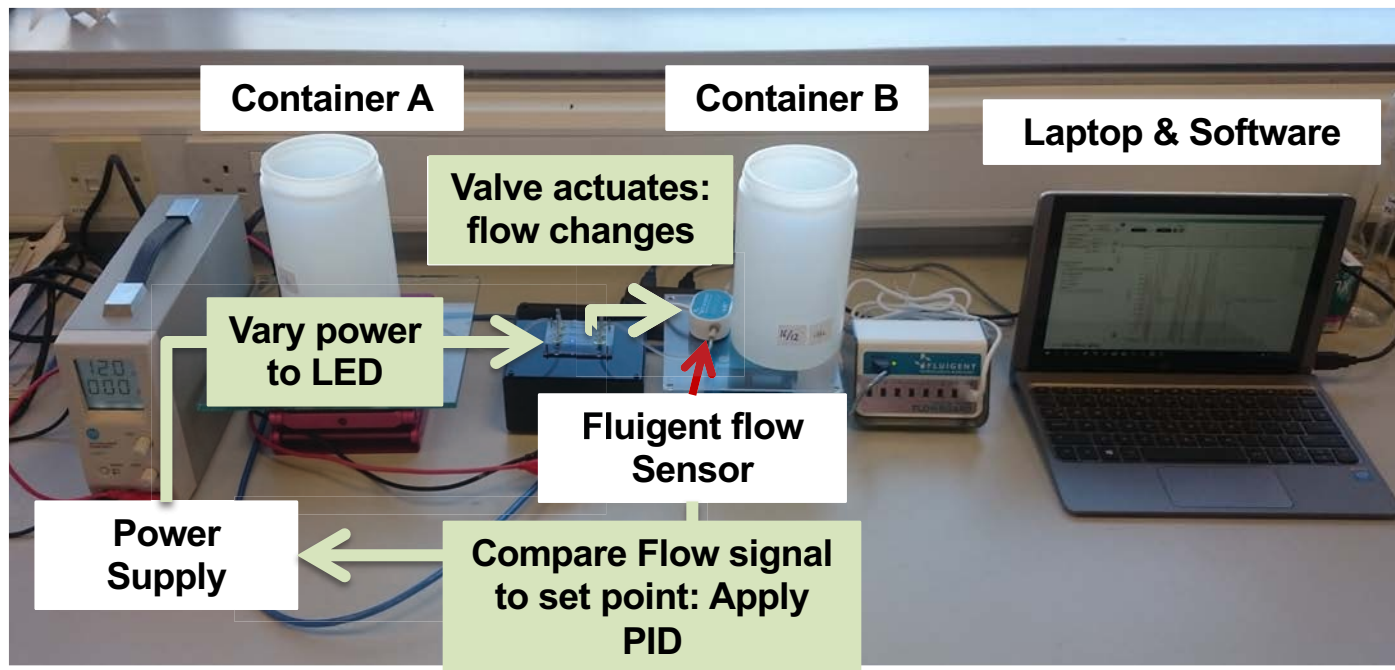
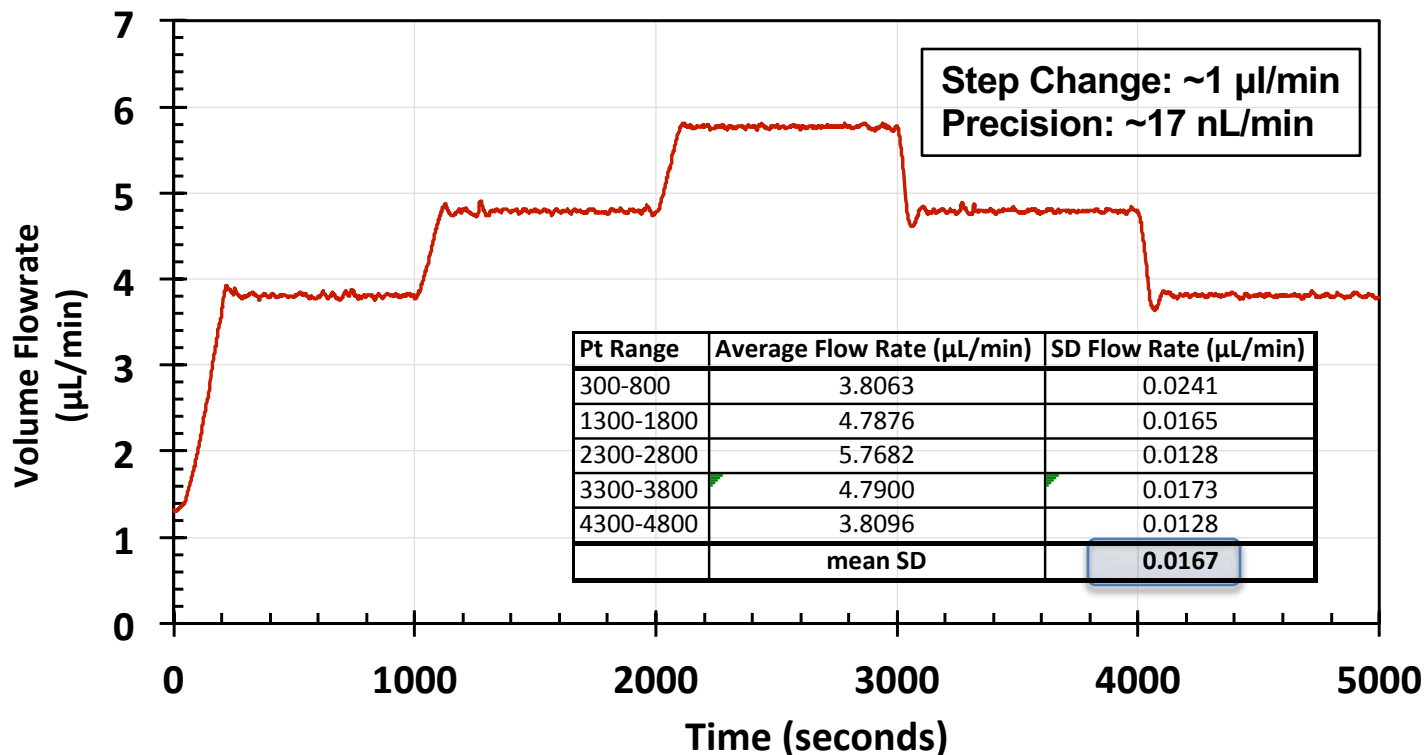




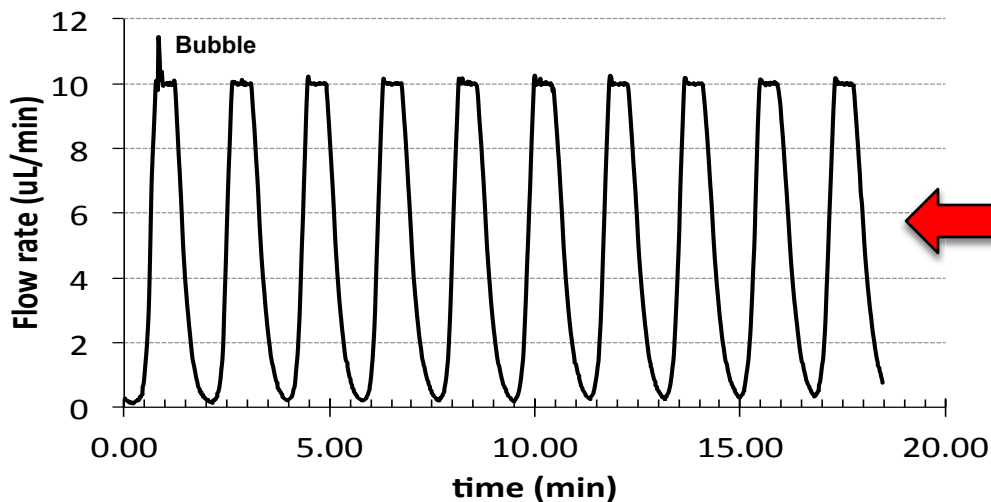
Photo-Controlled Flow Rate



C. Delaney, P. McCluskey, S. Coleman, J. Whyte, N. Kent, D. Diamond, Precision control of flow rate in microfluidic channels using photoresponsive soft polymer actuators, LAB ON A CHIP. 17 (2017) 2013–2021. doi:[10.1039/c7lc00368d](https://doi.org/10.1039/c7lc00368d).



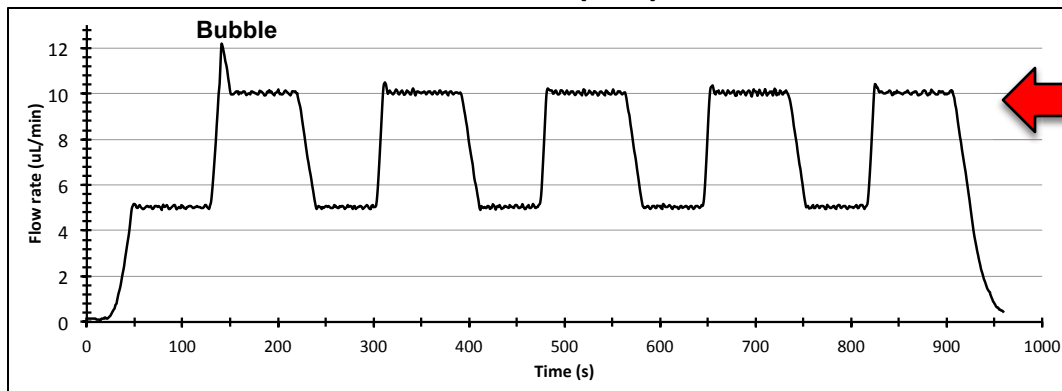
Some figures of merit



Switching 0.0-10.0 $\mu\text{L}/\text{min}$
 $n = 15$ points sampled behind the initial small overshoot

Averages ($n=10$)

mean	10.0028
Mean SD	0.0323
Error Mean	0.0028
%RSD	0.3235
%RE mean	0.0279

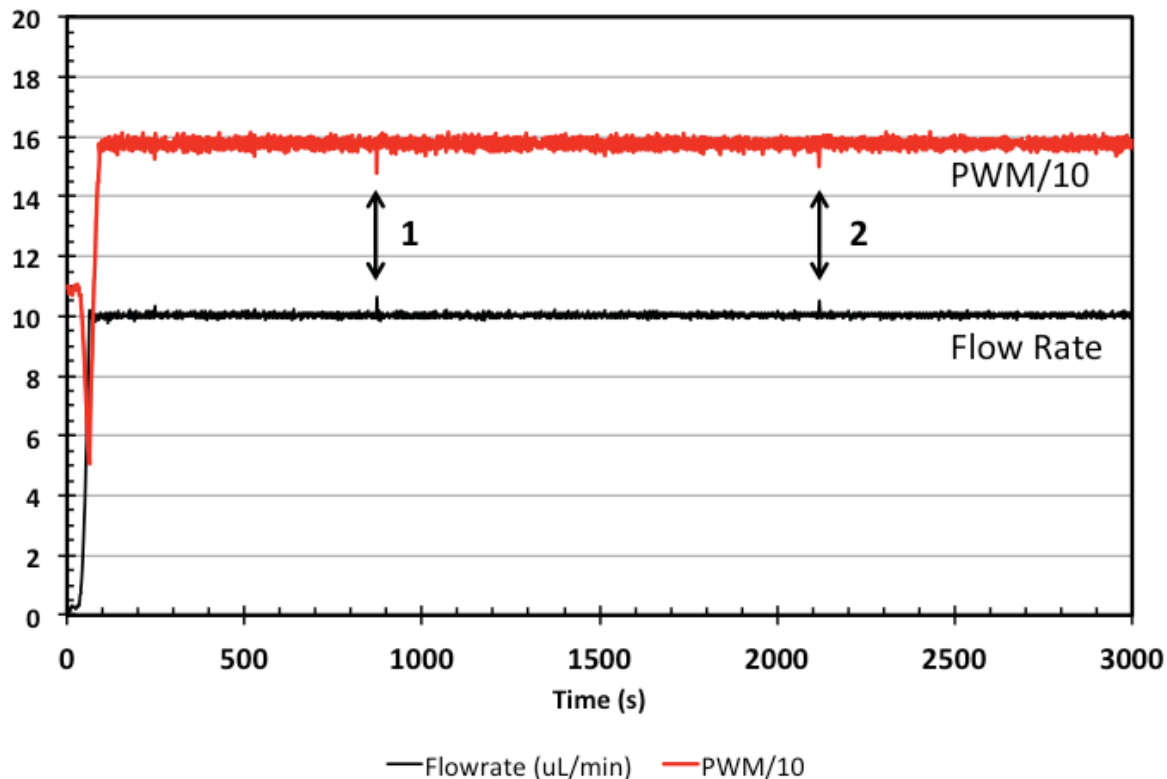


Switching 5.0-10.0 $\mu\text{L}/\text{min}$
 $n = 30$ points sampled

Mean %RE (5=true)	0.780
Mean %RE (5.039=true)	0.098
Average of mean	5.039
SD Mean	0.006
%RSD	0.120
Mean %RE (10=true)	0.372
Mean %RE (10.037=true)	0.102
Average of mean	10.037
SD Mean	0.012
%RSD	0.124



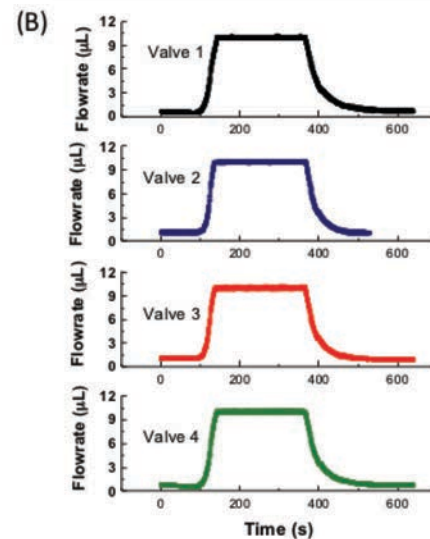
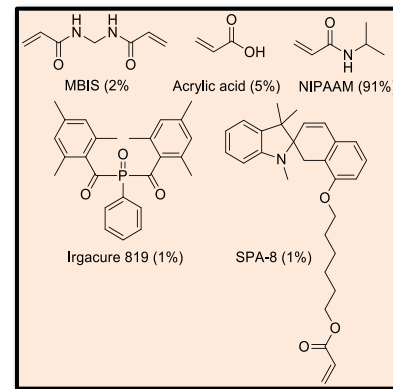
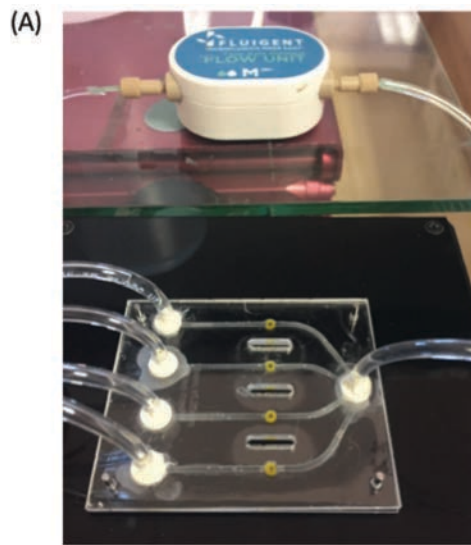
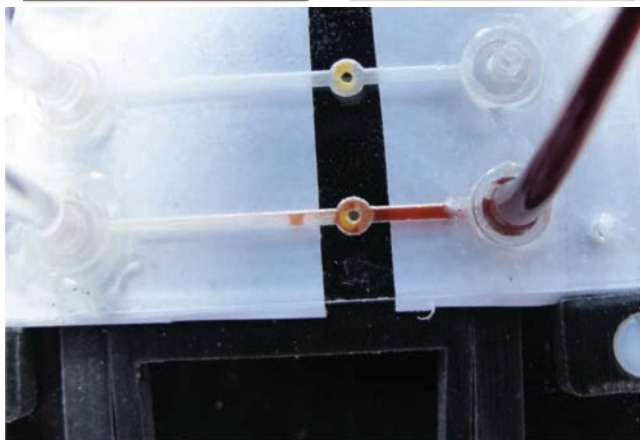
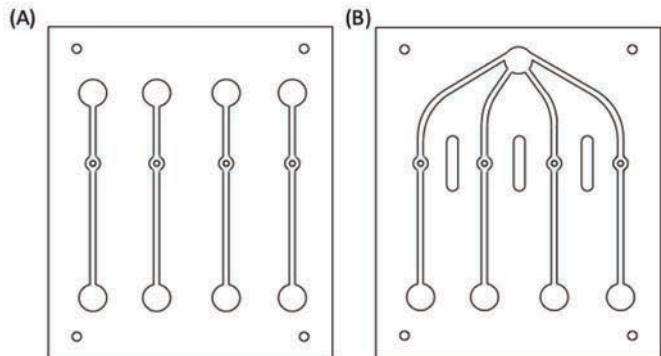
Power Supply to LED



Over a period of 50 min constant maintenance of 10 $\mu\text{L}/\text{min}$ flow rate there is no discernable change in LED power \rightarrow diagnostic information



Multiplexing: Valve Arrays





Impact of 3d Printing



Minimum thickness

- Assembled chip 4.25 mm
- 3D Printed Chip 1.58 mm

Advantages:

- No Assembly
- No Bonding necessary
- Integrated barbs (1/16")
- Chip thickness reduced by 63%
- Automated manufacturing

Assembled Chip



Printed Chip



Printed Chip



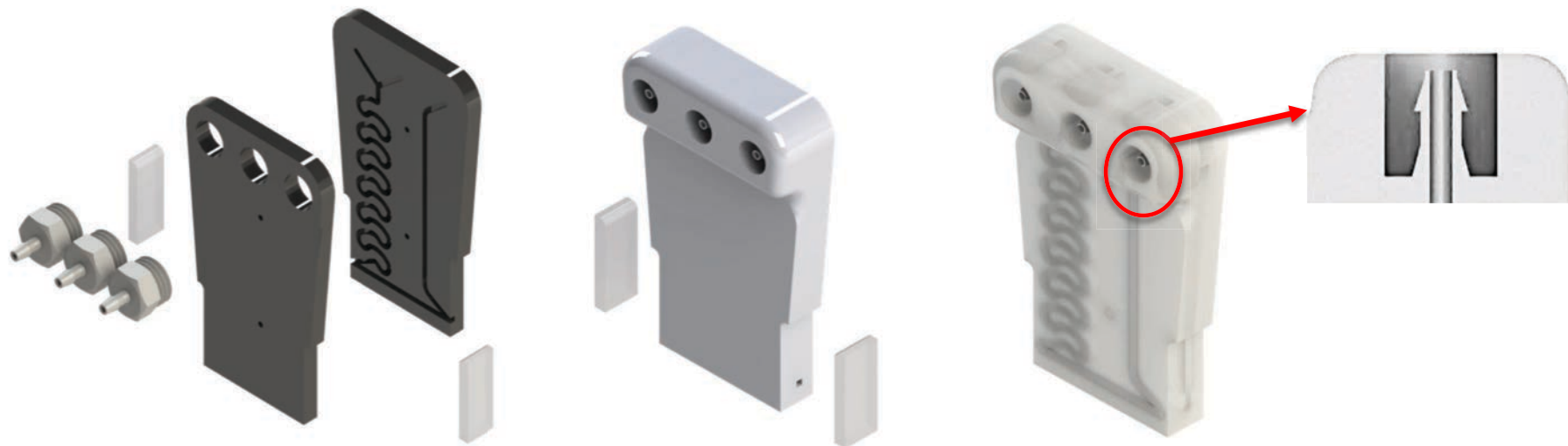
Rendered Chip



Holifab H2020 Project; Laurent Malaquin, LAAS-CNRS, Margaret McCaul (DCU)



From Multi-Part to Single Part Fluidic Chips



7 Parts : 3
days
~€50/chip

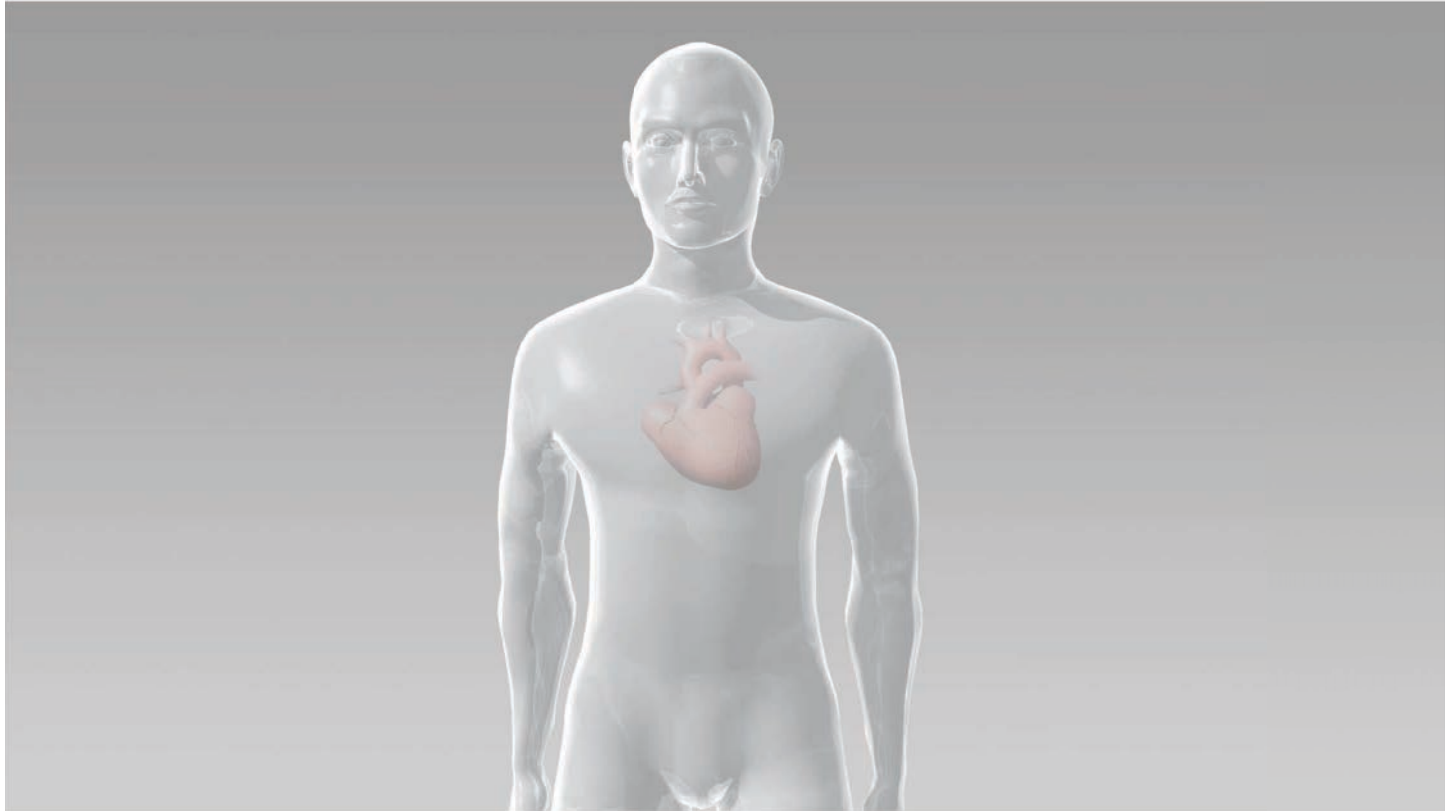
3 Parts : 1 day

1 Part : 1 hour
~€1/chip

Margaret McCaul (DCU) and Laurent Malaquin (LAAS-CNRS)



Bioinspired Fluidics





Photocontrol of Assembly and Subsequent Switching of Surface Features



ACS APPLIED MATERIALS
& INTERFACES

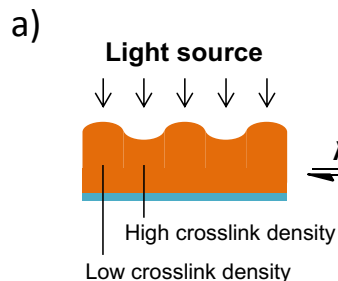
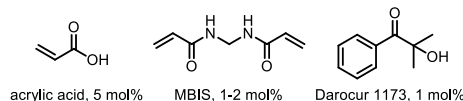
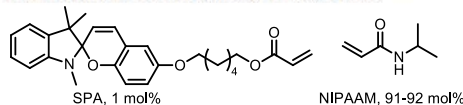
Research Article

www.acsami.org

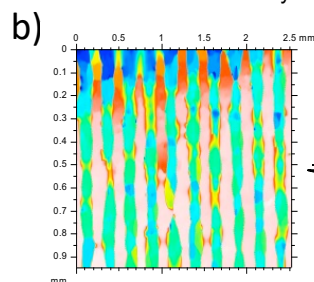
ACS applied materials & interfaces, 6 (2014) 7268-7274

Photoswitchable Ratchet Surface Topographies Based on Self-Protonating Spiropyran–NIPAAm Hydrogels

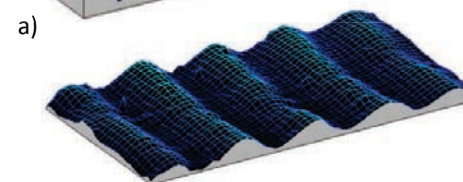
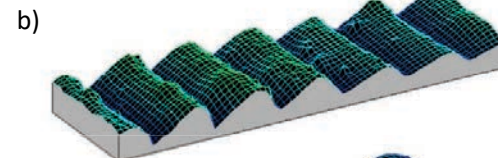
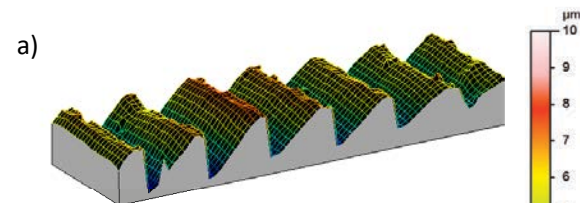
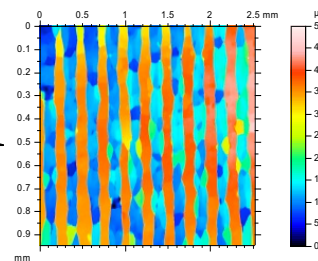
Jelle E. Stumpel,[†] Bartosz Ziolkowski,[‡] Larisa Florea,[‡] Dermot Diamond,[‡] Dirk J. Broer,^{*†,§}
and Albertus P. H. J. Schenning^{*†,§}



$\lambda = 455 \text{ nm}$

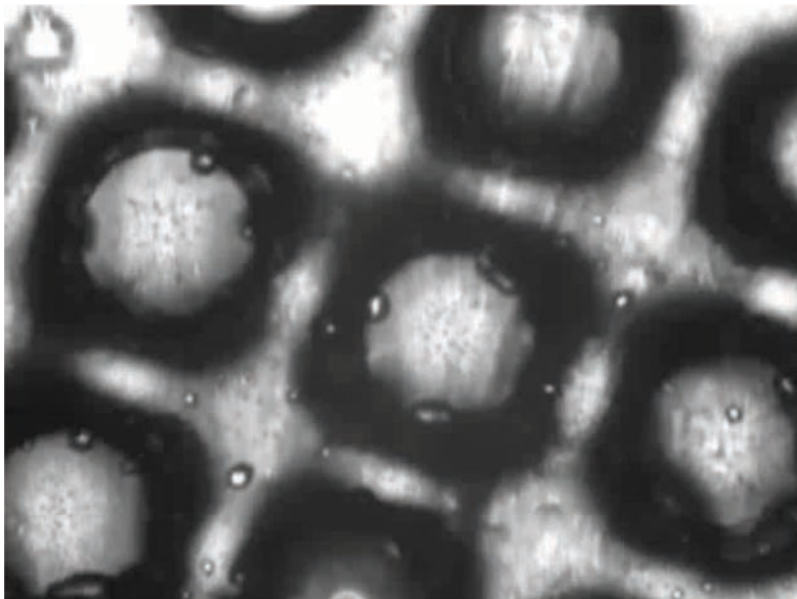


$\lambda = 455 \text{ nm}$

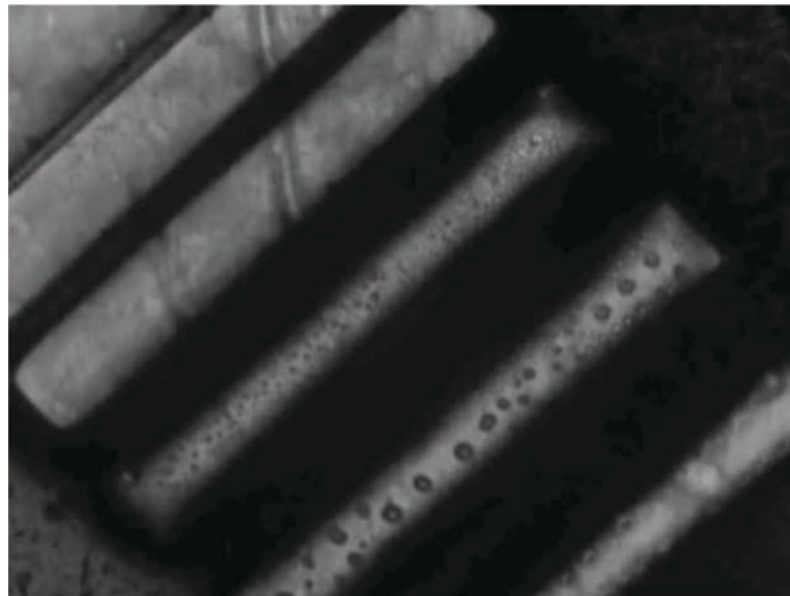




Flexible creation of μ -dimensioned features in flow channels using in-situ photo-polymerisation



Ntf2 pillars speed x3

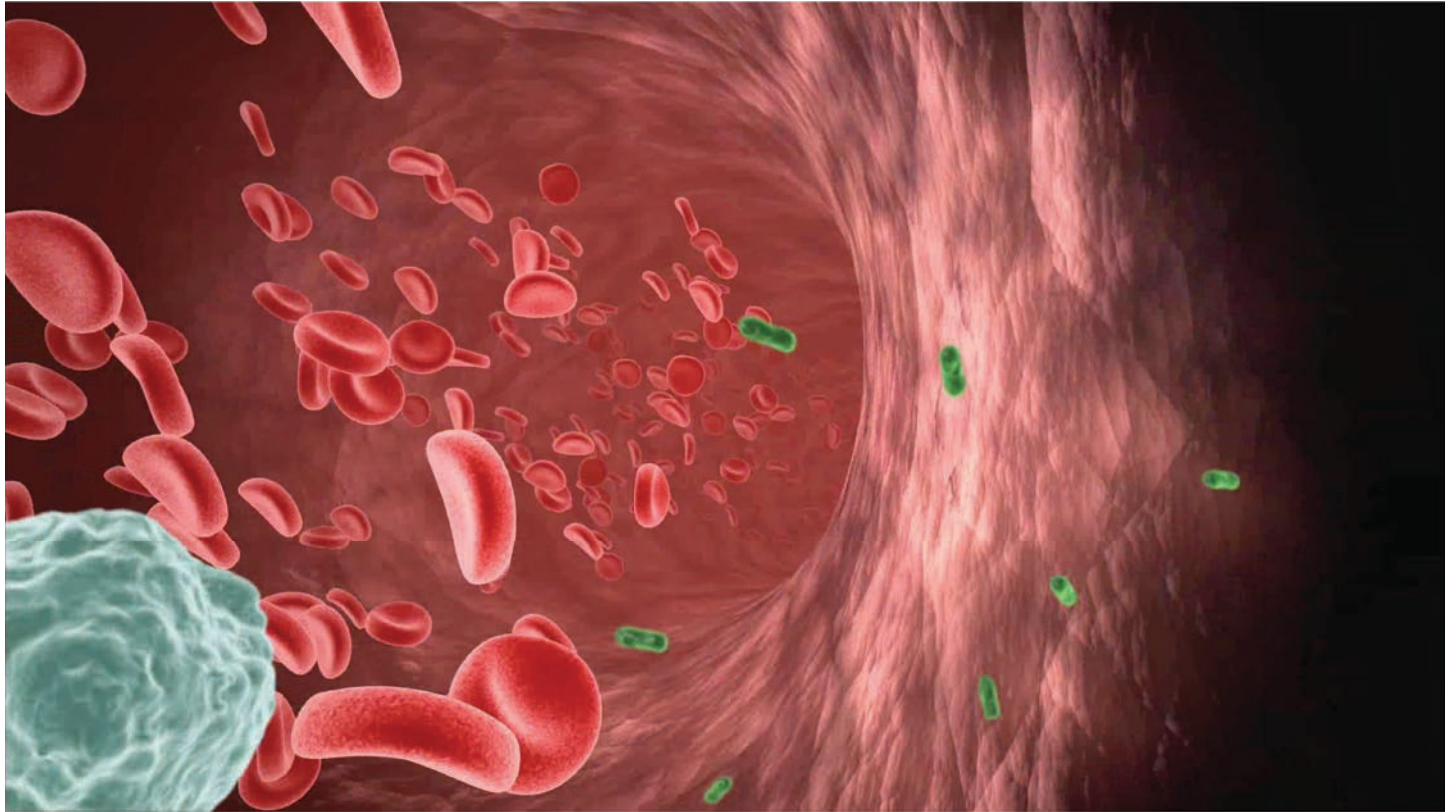


DCA lines speed x4

With Dr Peer Fischer, Fraunhofer-Institut für Physikalische Messtechnik (IPM), Freiburg

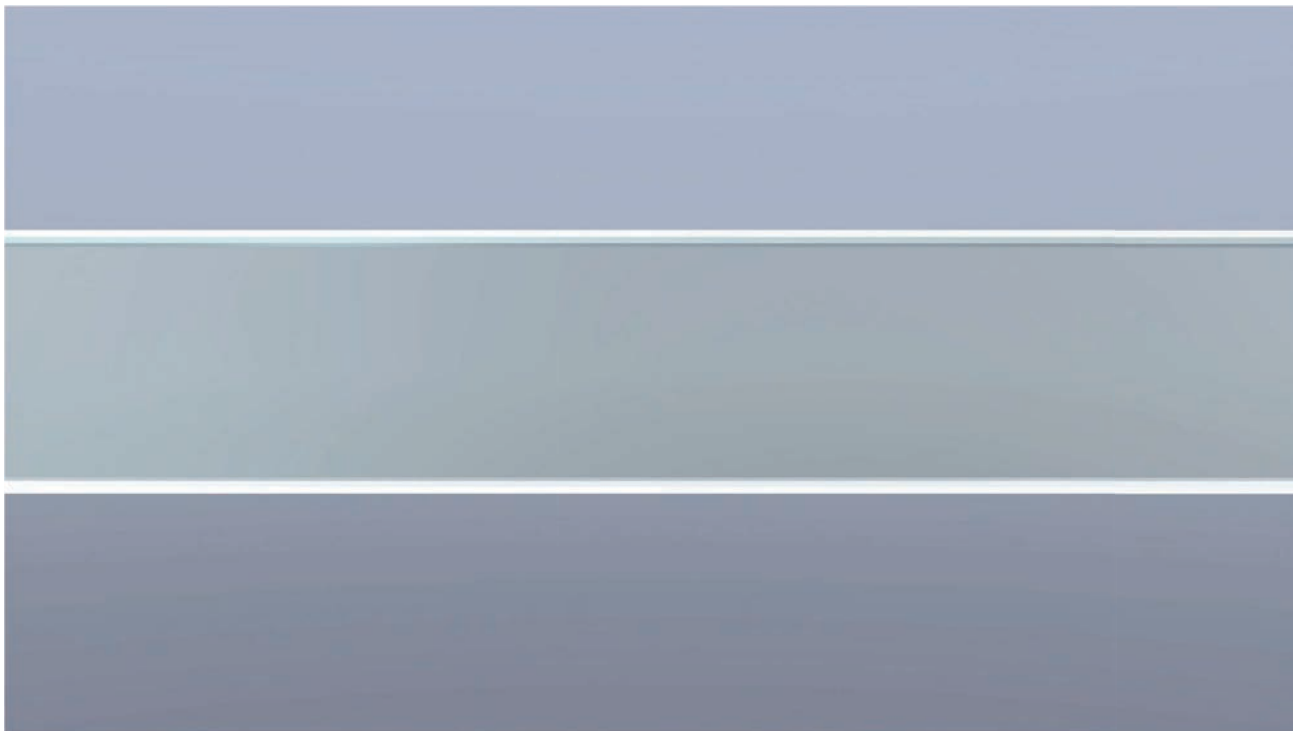


The Immune System



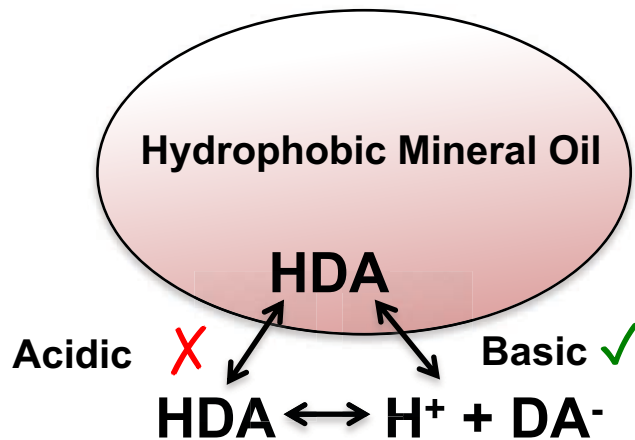
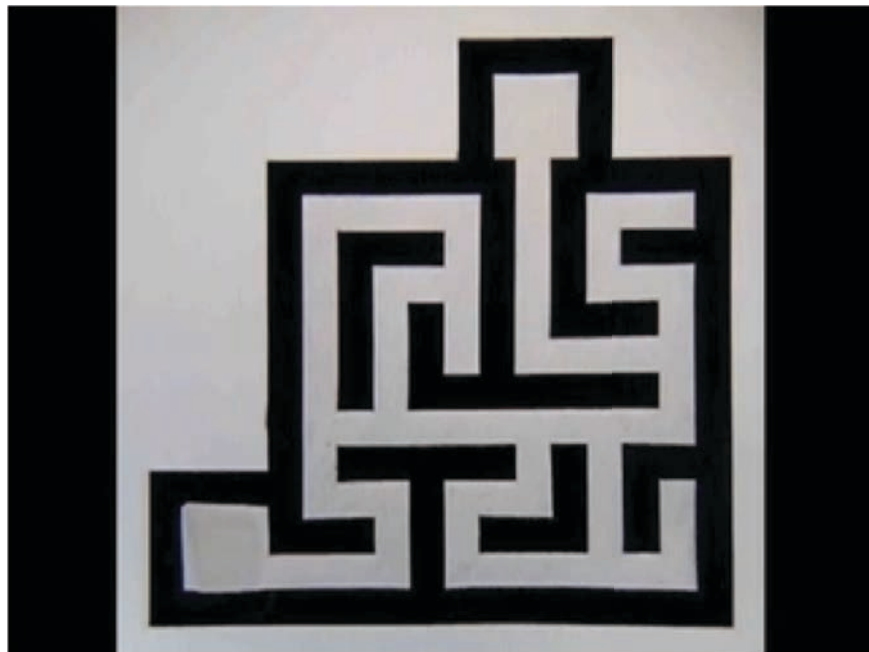


Detect, Migrate, Repair..





Chemotactic Systems



In a pH gradient, DA^- is preferentially transferred to the aqueous phase at the more basic side of the drop.

Published on Web 11/01/2010 (speed $\sim \times 4$): channels filled with KOH (pH 12.0-12.3 + surfactant; agarose gel soaked in HCl (pH 1.2) sets up the pH gradient; droplets of mineral oil or DCM containing 20-60% 2-hexyldecanoic acid + dye. Droplet speed ca. 1-10 mm/s; movement caused by convective flows arising from concentration gradient of HDA at droplet-air interface (greater concentration of DA^- towards higher pH side); $\text{HDA} \leftrightarrow \text{H}^+ + \text{DA}^-$

Maze Solving by Chemotactic Droplets; Istvan Lagzi, Siowling Soh, Paul J. Wesson, Kevin P. Browne, and Bartosz A. Grzybowski; **J. AM. CHEM. SOC.** 2010, **132**, 1198–1199

Fuerstman, M. J.; Deschatelets, P.; Kane, R.; Schwartz, A.; Kenis, P. J. A.; Deutch, J. M.; Whitesides, G. M. *Langmuir* 2003, **19**, 4714.



Marangoni Effect; 'Tears of wine'



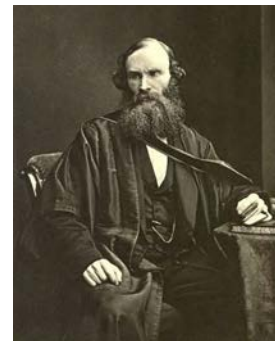
The mass transfer along an interface between two fluids due to surface tension gradient

The general effect is named after Italian physicist **Carlo Marangoni** (1840-1925), who studied it for his doctoral dissertation at the **University of Pavia** and published his results in **1865**.

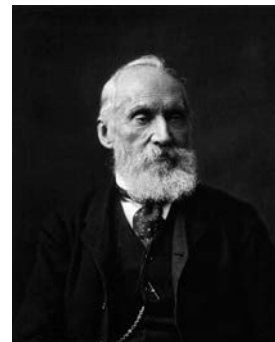


Carlo Marangoni

Enrnestina Marangoni (1876-1972)



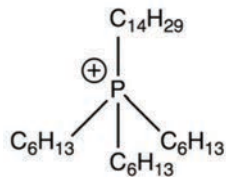
James Thompson



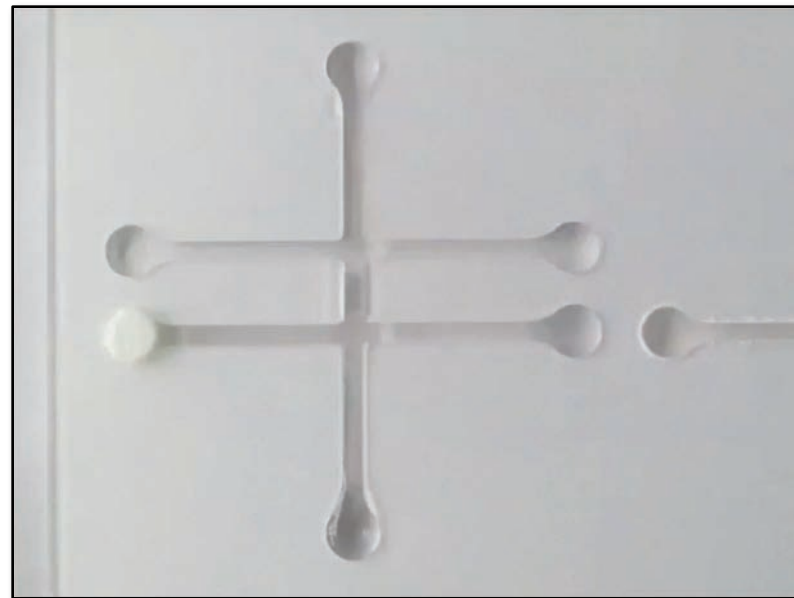
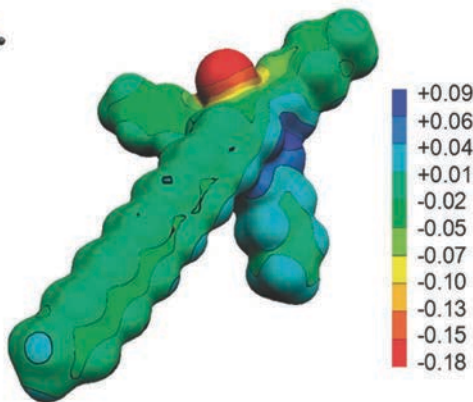
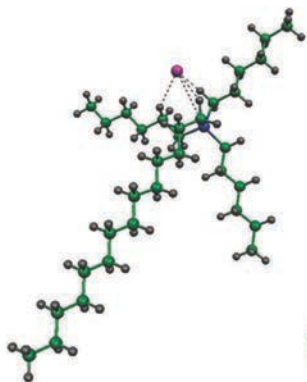
William Thompson

See <http://web.mit.edu/1.63/www/Lec-notes/Surfacetension/Lecture4.pdf>

Chemotactic IL Droplets



= cationic surfactant



Trihexyl(tetradecyl)phosphonium chloride ($[\text{P}_{6,6,6,14}][\text{Cl}]$) droplets with a small amount of 1-(methylamino)anthraquinone red dye for visualization. The droplets spontaneously follow the gradient of the Cl^- ion which is created using a polyacrylamide gel pad soaked in 10^{-2} M HCl; A small amount of NaCl crystals can also be used to drive droplet movement.

Electronic structure calculations and physicochemical experiments quantify the competitive liquid ion association and probe stabilisation effects for nitrobenzospirropyran in phosphonium-based ionic liquids, D. Thompson et al., Physical Chemistry Chemical Physics, 2011, 13, 6156-6168.



Electrochemical Generation of Cl^- gradients on demand

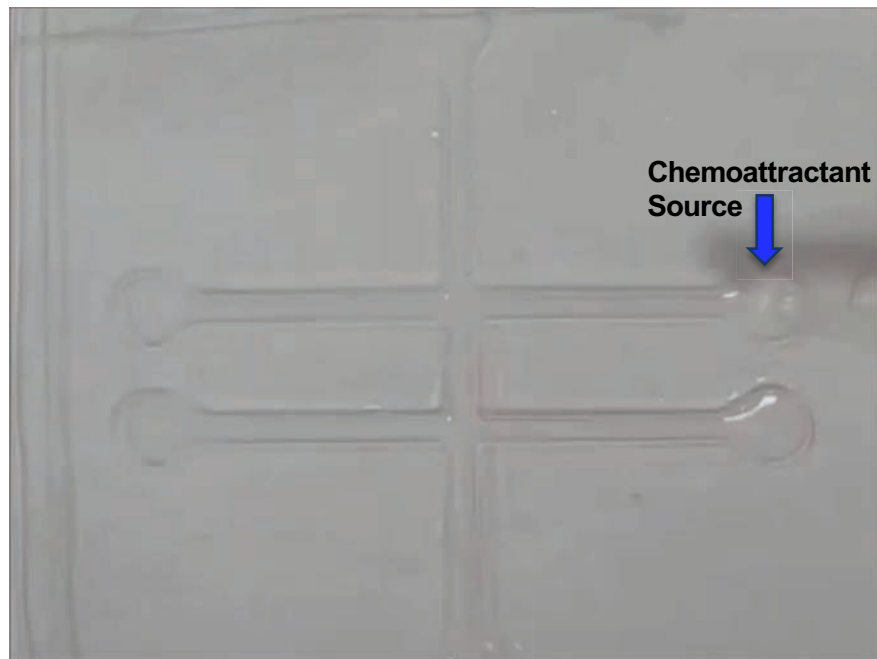




From 2D to 3D Movement



2D Movement



L. Florea et al. Chem. Comm. 51 (2015) 2342.

L. Florea et al. Sens. Actuators B 239 (2017) 1069.

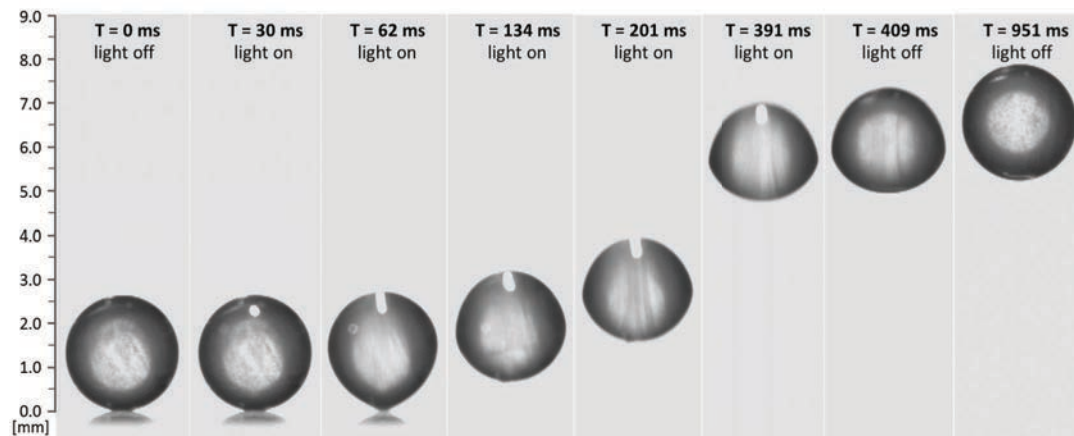
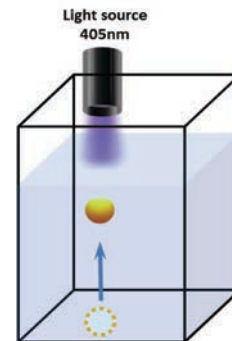
3D Movement



With David Officer, Adv Mater. 2018; doi: 10.1002/adma.201801821



Light Induced Movement, Marangoni Flows and Droplet Distortion

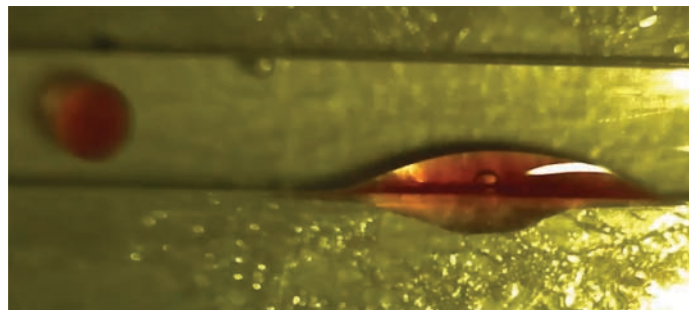
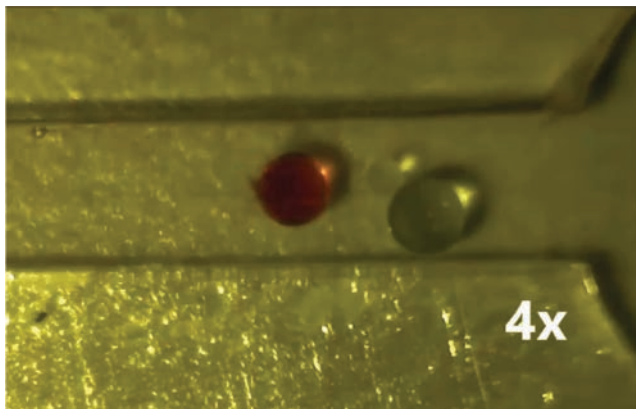
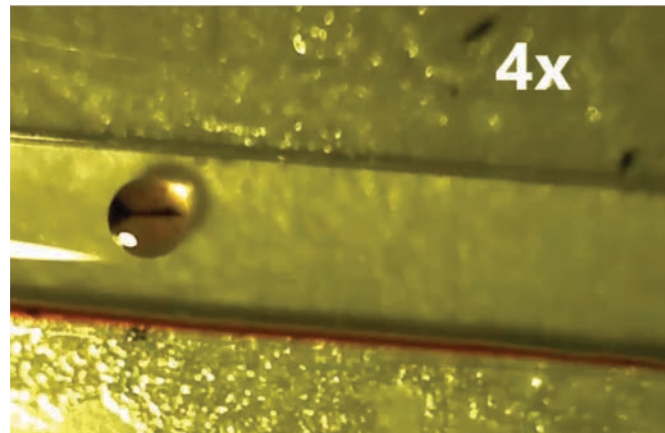
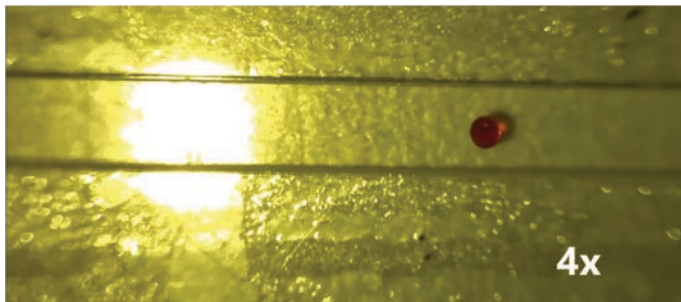


Prof. David Officer, University of Wollongong





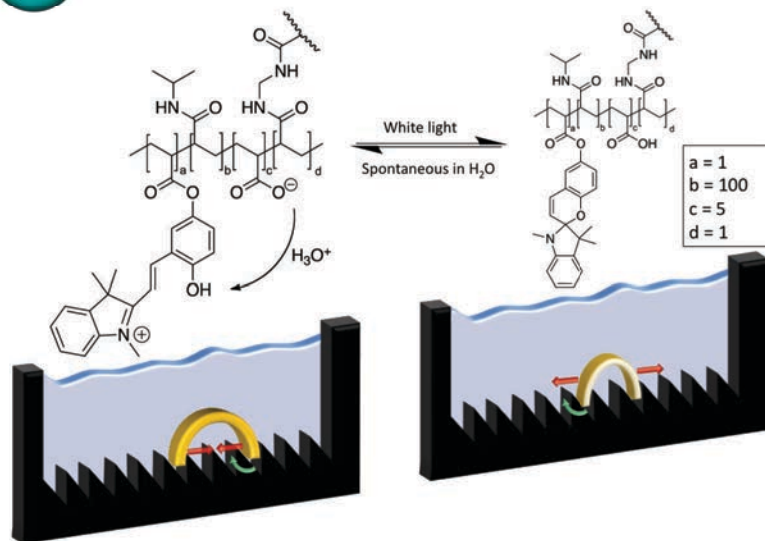
Fun with Droplets and Dynamic Electro-Ionic Gradients



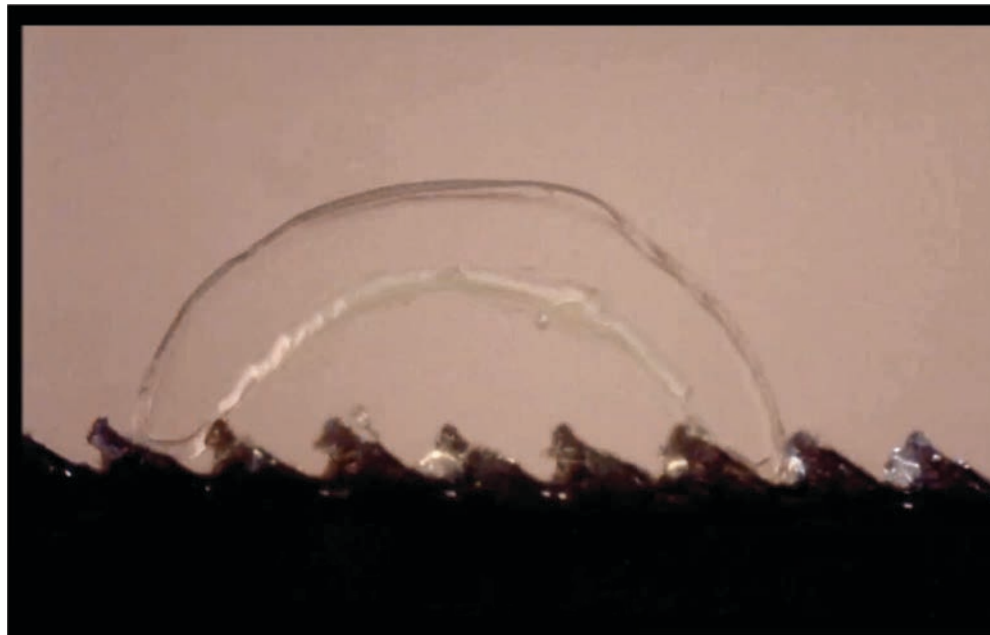
Joan Cabot, Brett Paull (UTAS), Larisa Florea



Photo-Responsive Soft Hydrogels



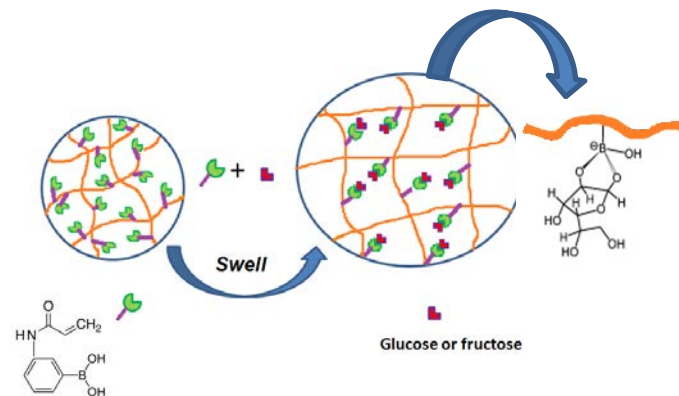
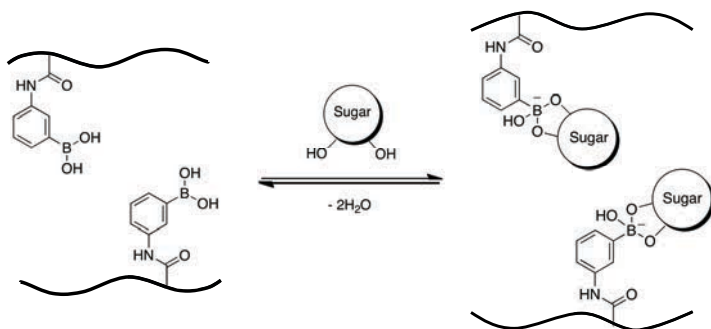
‘Walking towards the light’



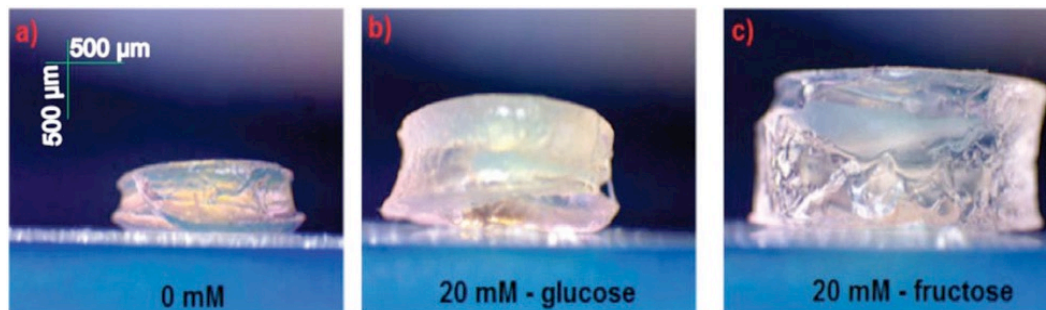
W. Francis et al. / Sensors and Actuators B 250 (2017) 608–616



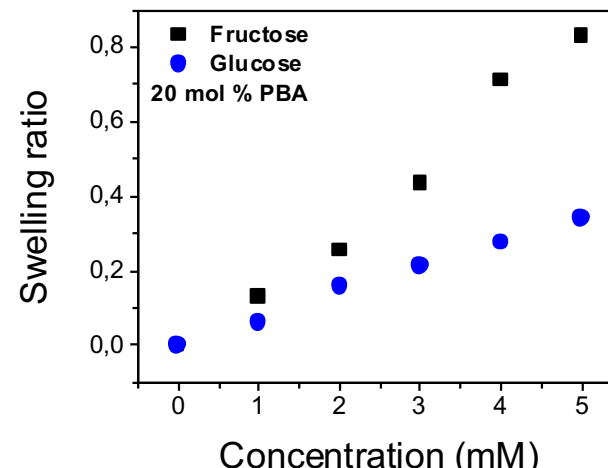
Sugar-Responsive Soft Hydrogels

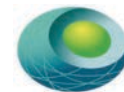


Acrylamide-co-PBA Polymer



C.M. Daikuzono, C. Delaney, H. Tesfay, L. Florea, O.N. Oliveira, A. Morrin, D. Diamond, Impedance spectroscopy for monosaccharides detection using responsive hydrogel modified paper-based electrodes, *Analyst*. 142 (2017) 1133–1139. doi:[10.1039/c6an02571d](https://doi.org/10.1039/c6an02571d).





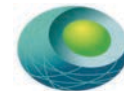
Merging Fundamental Science with Emerging Technologies and End-User Experience

Functional
(hybrid)
Materials

Precise Control
of 3D Structure
Nano->Micro->
Meso->Macro

Unraveling the
Molecular
Basis of
Disease
Mechanisms

Targeted and
Personalised
Clinical
Interventions



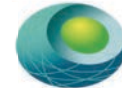
Thanks to.....

- NCSR, SCS, DCU
- Science Foundation Ireland & INSIGHT Centre
- Enterprise Ireland
- Research Partners – academic and industry
- EU H2020: Holifab Project



Jean Louis Viovy (Fluigent) , Mark Bowkett (TE Laboratories), Laurent Malaquin (LAAS)





Thanks for the invitation!