Rethinking On/In-Body Biochemical Sensing Strategies to Achieve Long-Term Functionality

Dermot Diamond

INSIGHT Centre for Data Analytics, National Centre for Sensor Research, School of Chemical Sciences, Dublin City University

ACS Fall 2019 National Meeting
San Diego
August 26th, 2019

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

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.

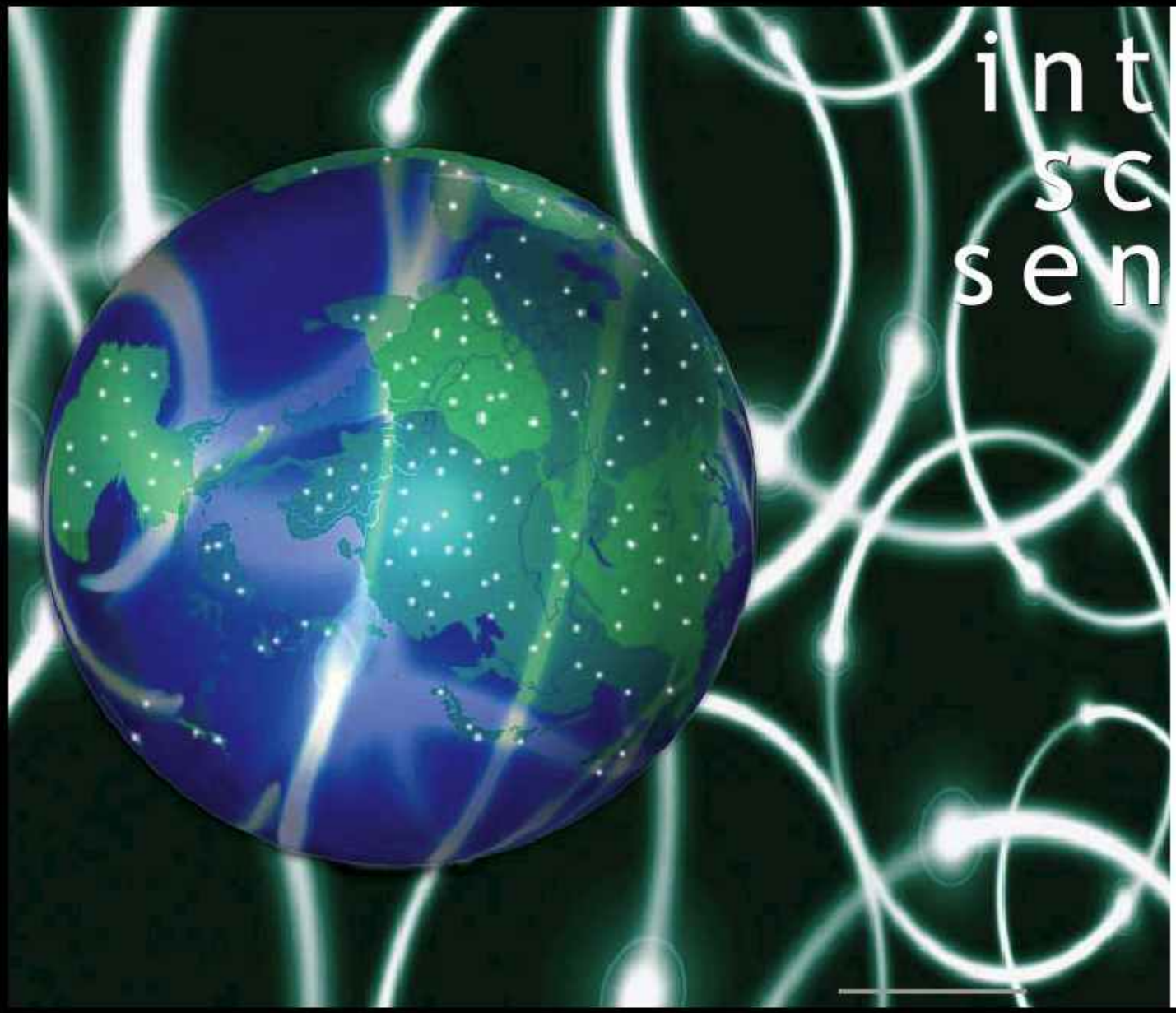
http://www.sfi.ie/sfi-research-centres/insight/

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

Keynote Article: Anal. Chem., 76 (2004) 278A-286A



internet scale sensing

Dermot Diamond
Dublin City University
(Ireland)

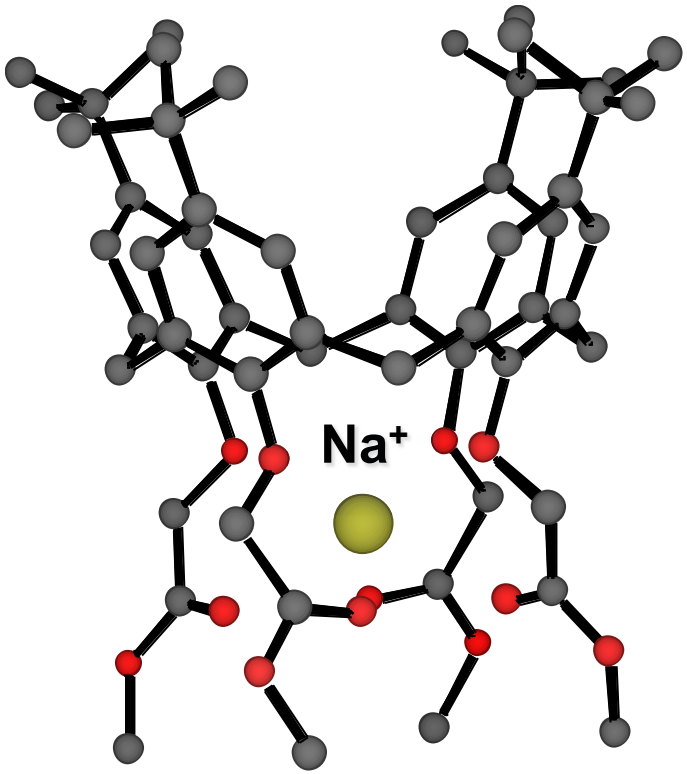
Incredible advances in digital communications and computer power have profoundly changed our lives. One chemist shares his vision of the role of analytical science in the next communications revolution.

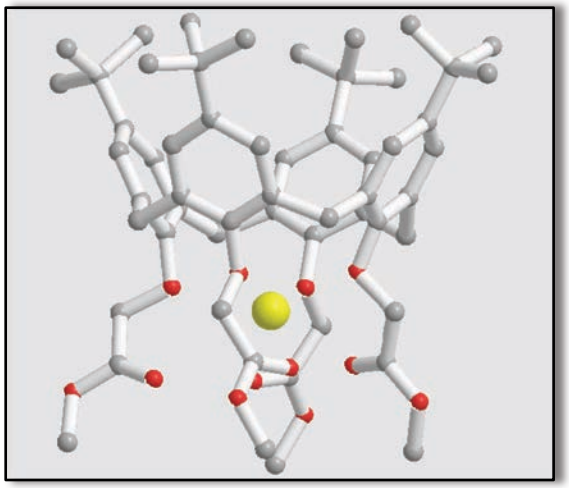
Digital communications networks are at the heart of modern society. The digitization of communications, the development of the Internet, and the availability of relatively inexpensive but powerful mobile computing technologies have established a global communications network capable of linking billions 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.

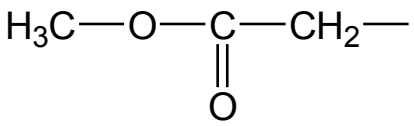
The crucial missing part in this scenario is the gateway through which these worlds will communicate: How can the digital world sense and respond to changes in the real world? Analytical scientists—particularly those working on chemical sensors, biosensors, and compact, autonomous instruments—are

Ron Ambrosio & Alex Morrow, IBM TJ Watson

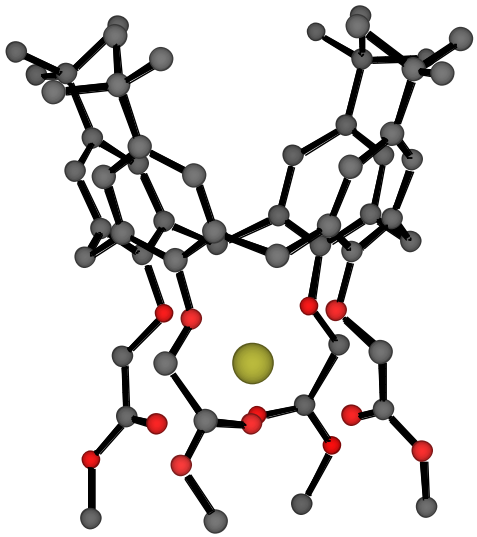
Calixarene Ionophores – controlling the selectivity

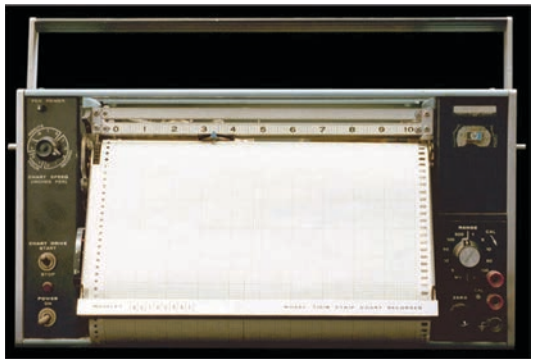


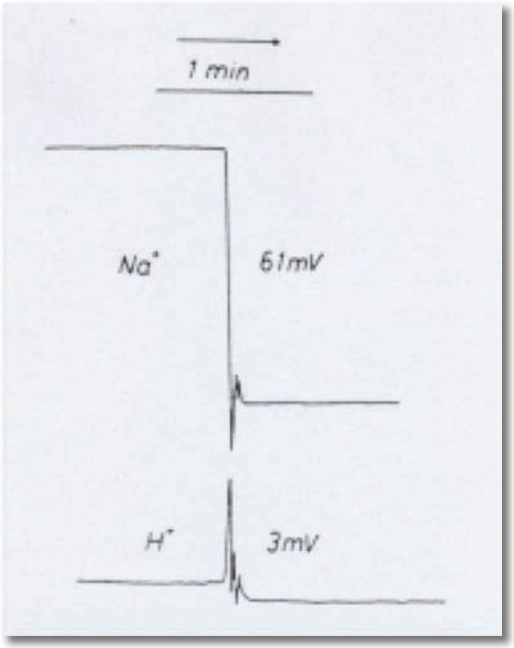


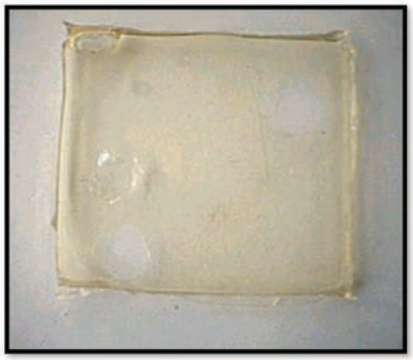


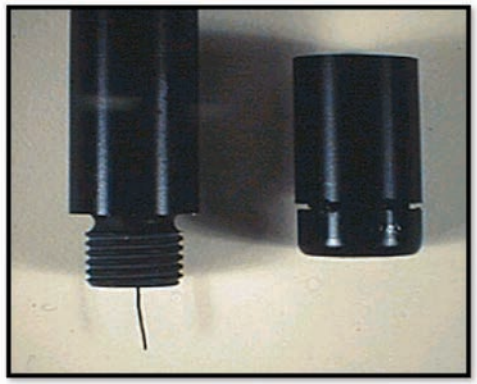
And…….







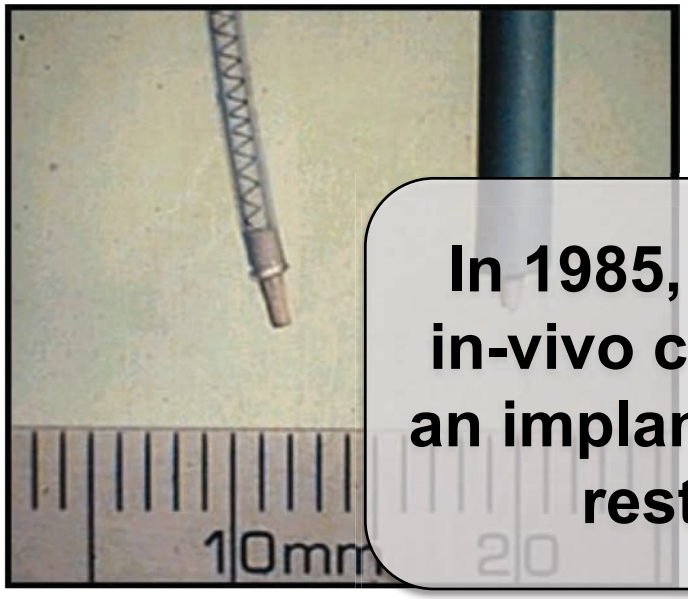




Neutral Carrier Based Ion-Selective Electrodes, D.Diamond, Anal. Chem. Symp. Ser., 25 (1986) 155.

A sodium Ion-Selective Electrode based on Methyl p-t-Butyl Calix[4]aryl Acetate as the Ionophore, D.Diamond, G.Svehla, E.Seward,and M.A.McKervey, Anal. Chim. Acta., 204 (1988) 223-231

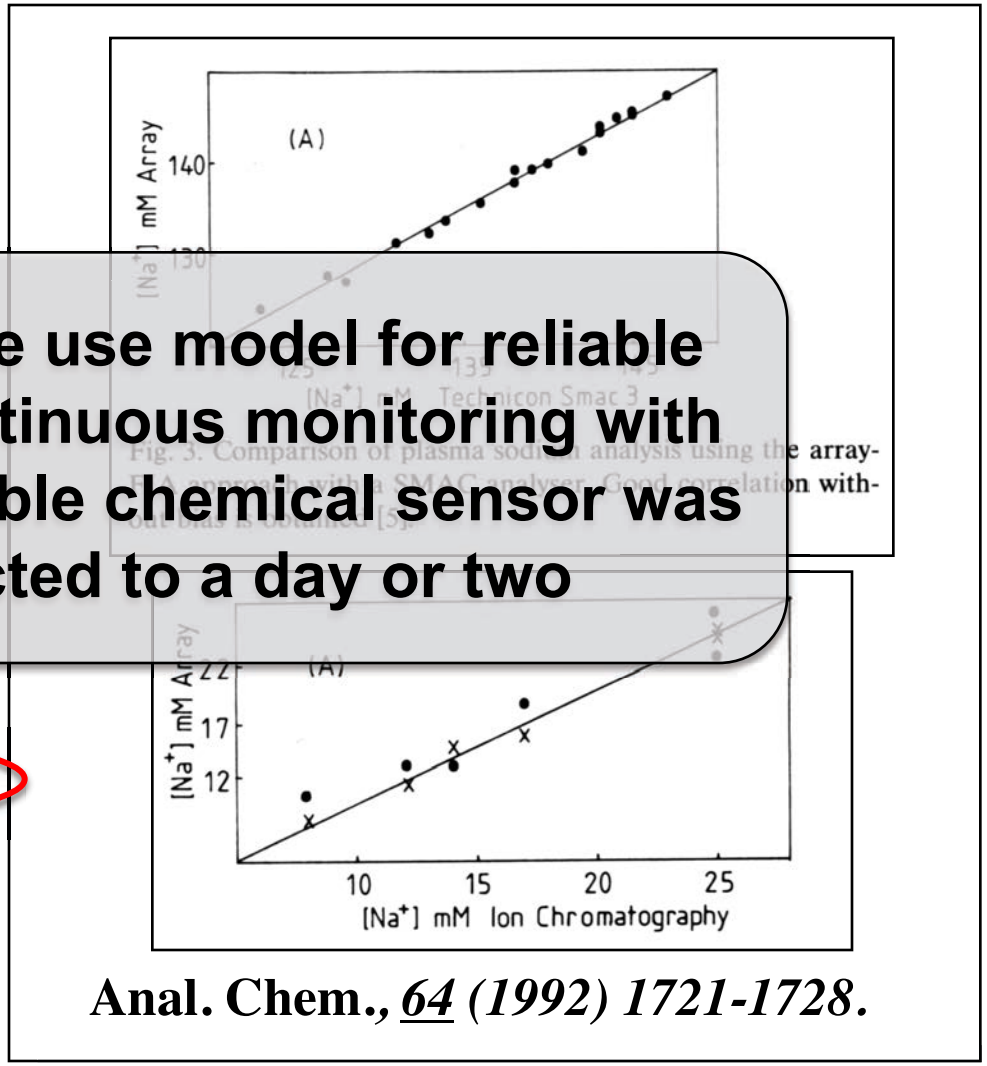
Blood Analysis; Implantible Sensors



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

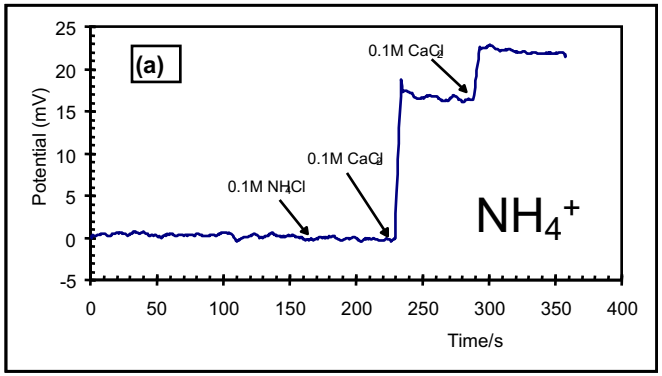
1985: Catheter Electrodes for intensive care – function for 24 hrs

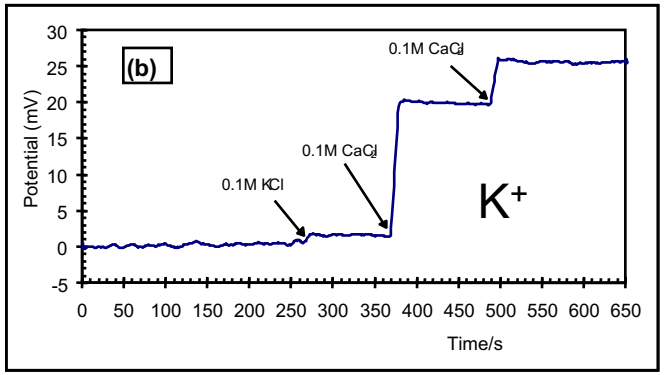
Dr. David Band, St Thomas's Hospital London

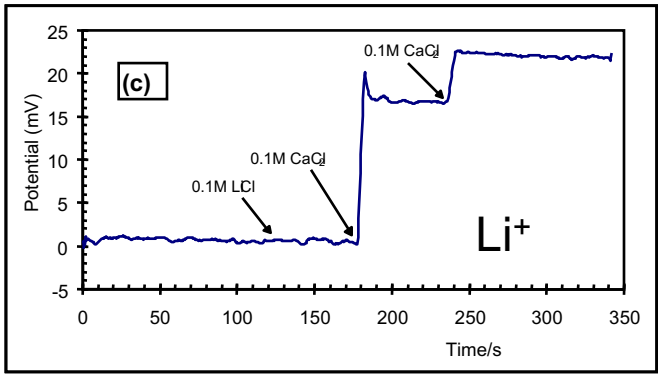


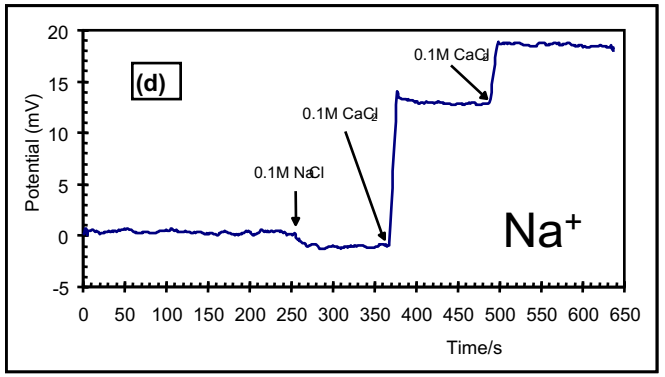
Anal. Chem., *64 (1992) 1721-1728.*

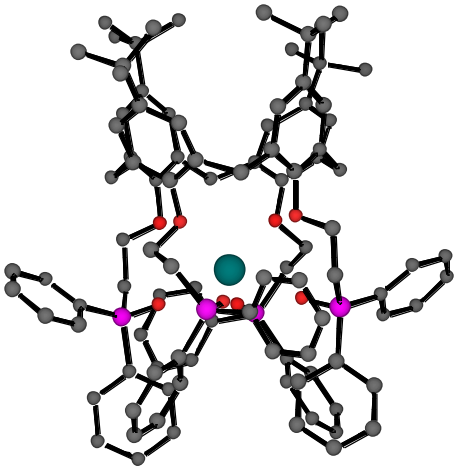
Ligand (and variations of) used in many clinical analysers for blood Na^+ profiling

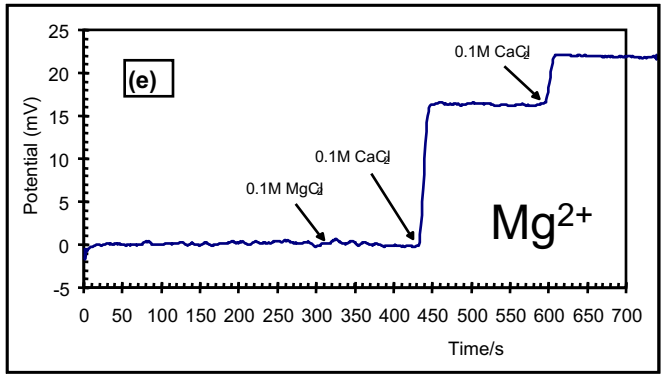








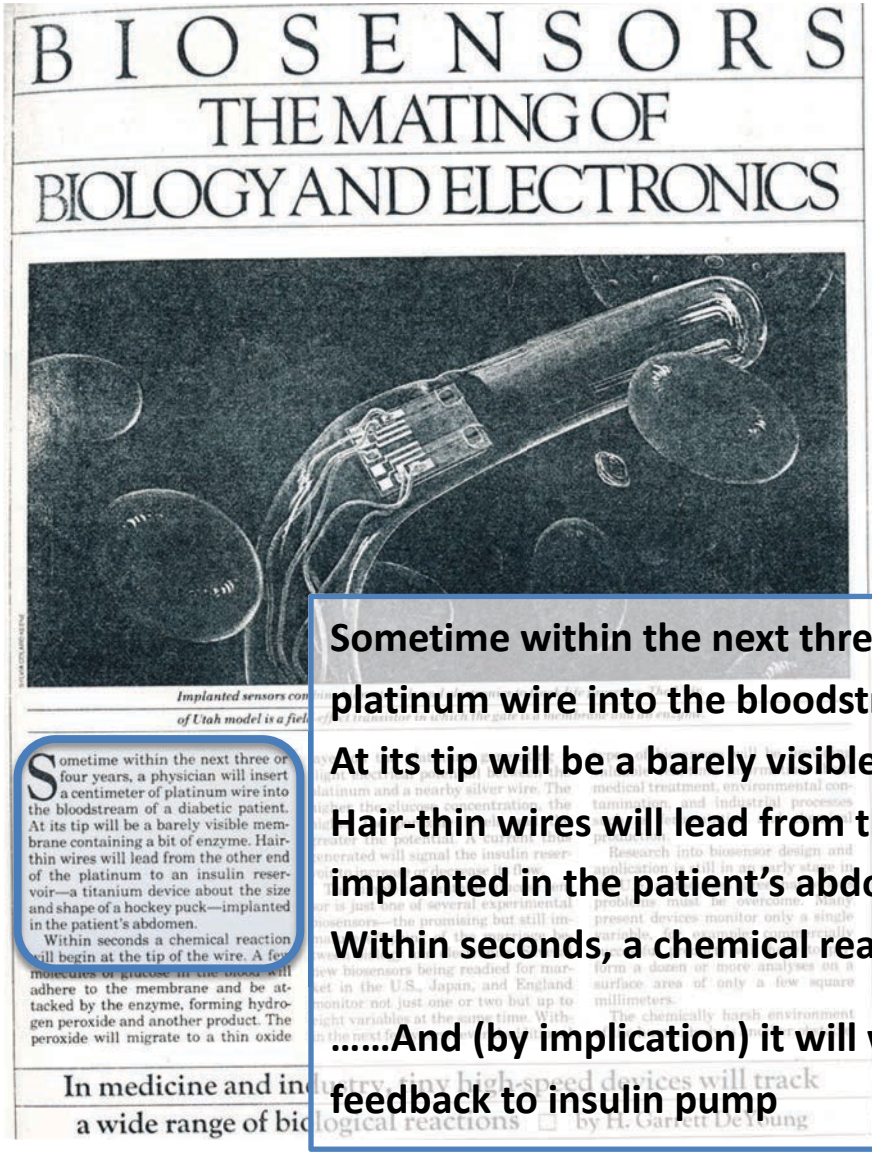




tetra-phosphine oxide electrode

Talanta 43 (1996) 1145–1148

The (broken) promise of biosensors…..



BIOSENSORS

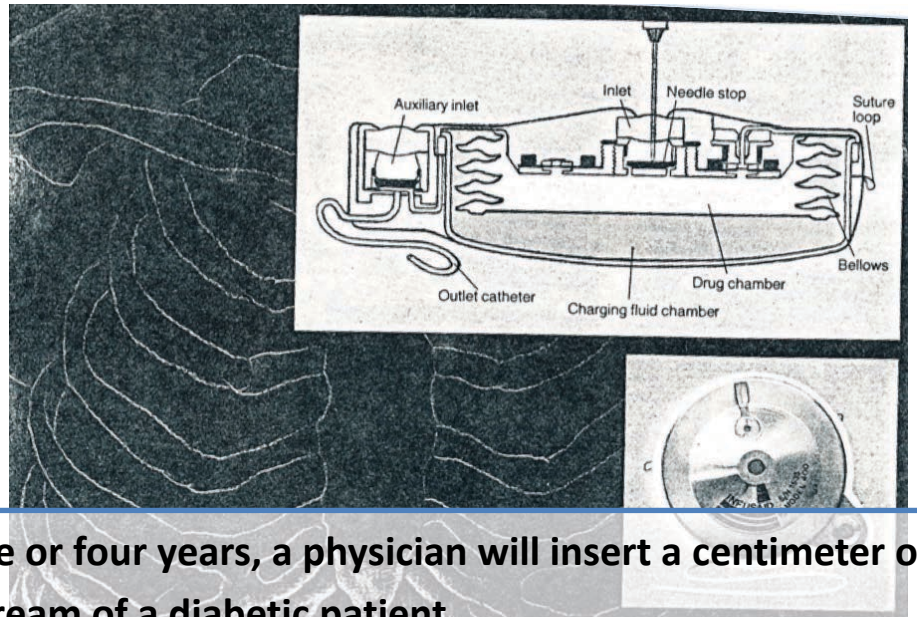
THE MATING OF BIOLOGY AND ELECTRONICS

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 molecules of glucose in the blood 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

In medicine and industry, tiny high-speed devices will track a wide range of biological reactions

High Technology, Nov. 1983, 41-49



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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

After Ca. 40 years – Dominant Use Model is 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

Abbott Freestyle ‘Libre’

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

Welcome to flash glucose monitoring!

- ‘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

Nightscout

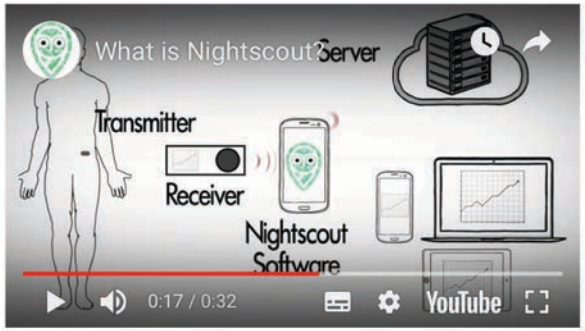
Welcome to Nightscout | Setup Guides | FAQs | Links | Map | Labs | Privacy | Nightscout Foundation | Contact

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.

- 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

Abbott Jobs

THE IRISH TIMES Mon, Feb 11, 2019

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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

US healthcare giant Abbott plans to create 500 jobs in Donegal as it expands its existing manufacturing facility there.

With nearly 3,000 employees across nine sites in the Republic, Abbott's operations here include manufacturing nutritional products and creating diagnostic tools for physicians.

Macromolecules **1990,** *23,* 4372–4377

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

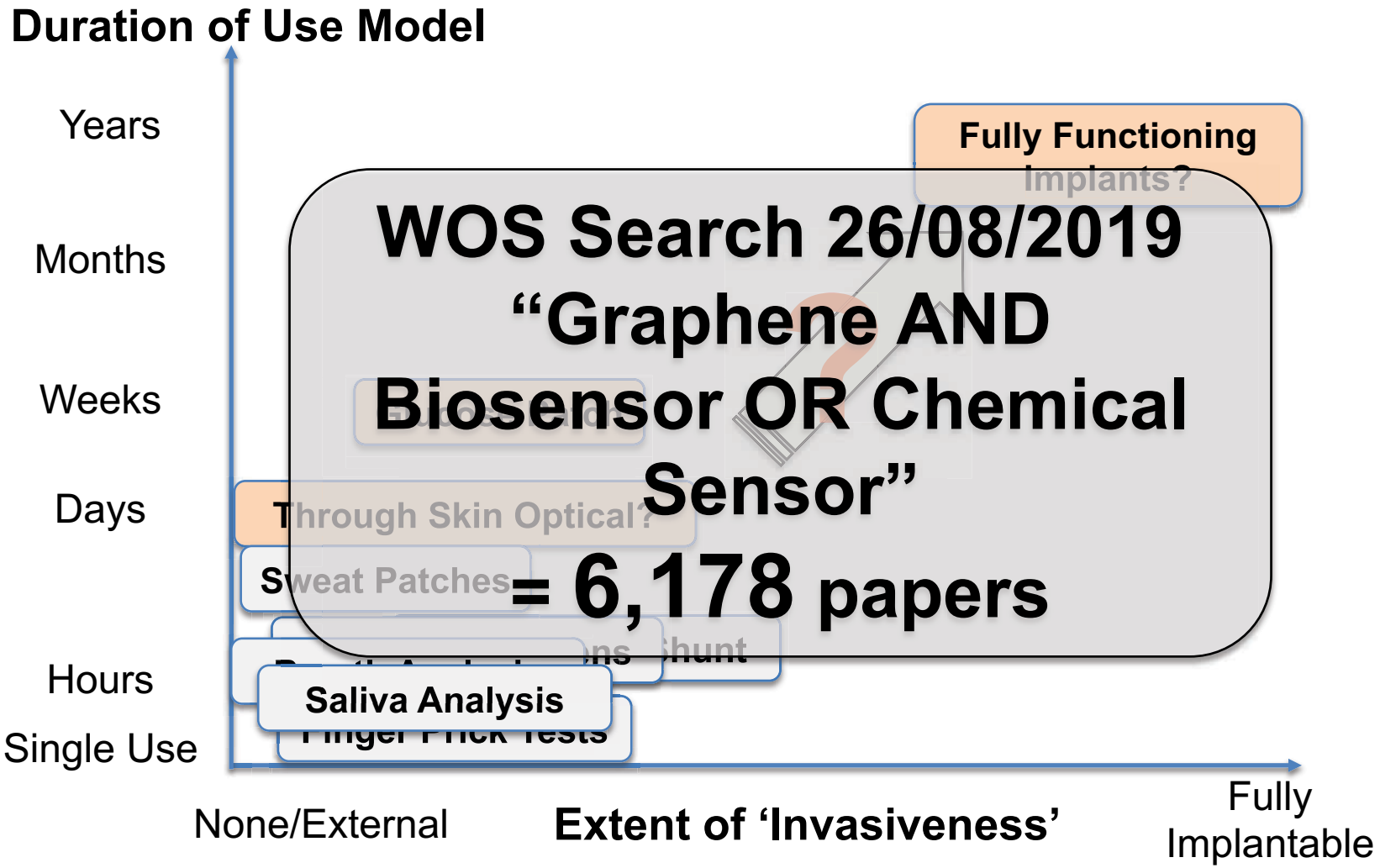
Robert J. Forster and Johannes G. Vos*

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

Long-Term Biochemical Monitoring?



WOS Search 26/08/2019 "Graphene AND Biosensor OR Chemical Sensor" = 6,178 papers

February 4, 2019

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’

Nanoscale, 2019, 11, 2476

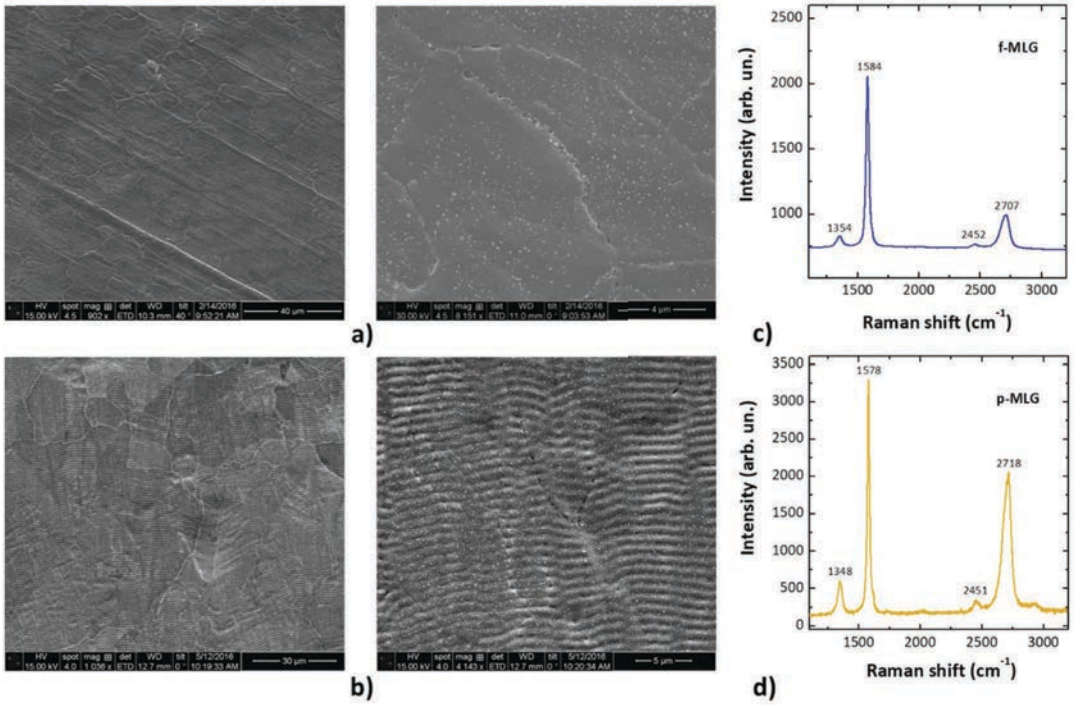


Fig. 2 Characterization of the graphene films. SEM images of the top view of the f-MLG (a) and p-MLG (b) samples on PVC. Raman spectra of the f-MLG (c) and p-MLG (d) performed using a 532 nm laser excitation system with a 40x microscope objective, and 10 s integration time for the single scan.

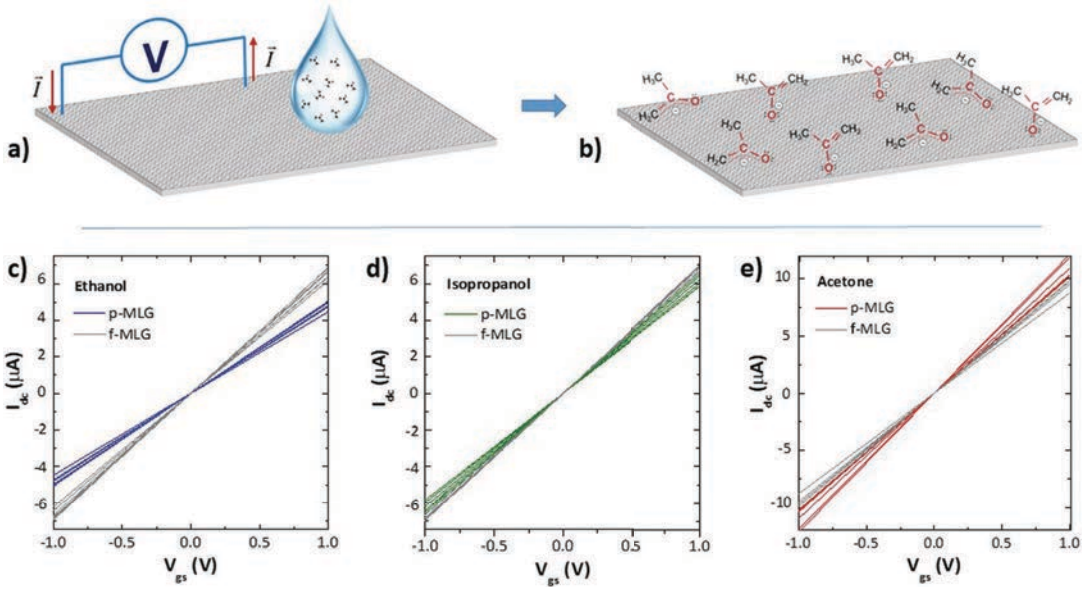
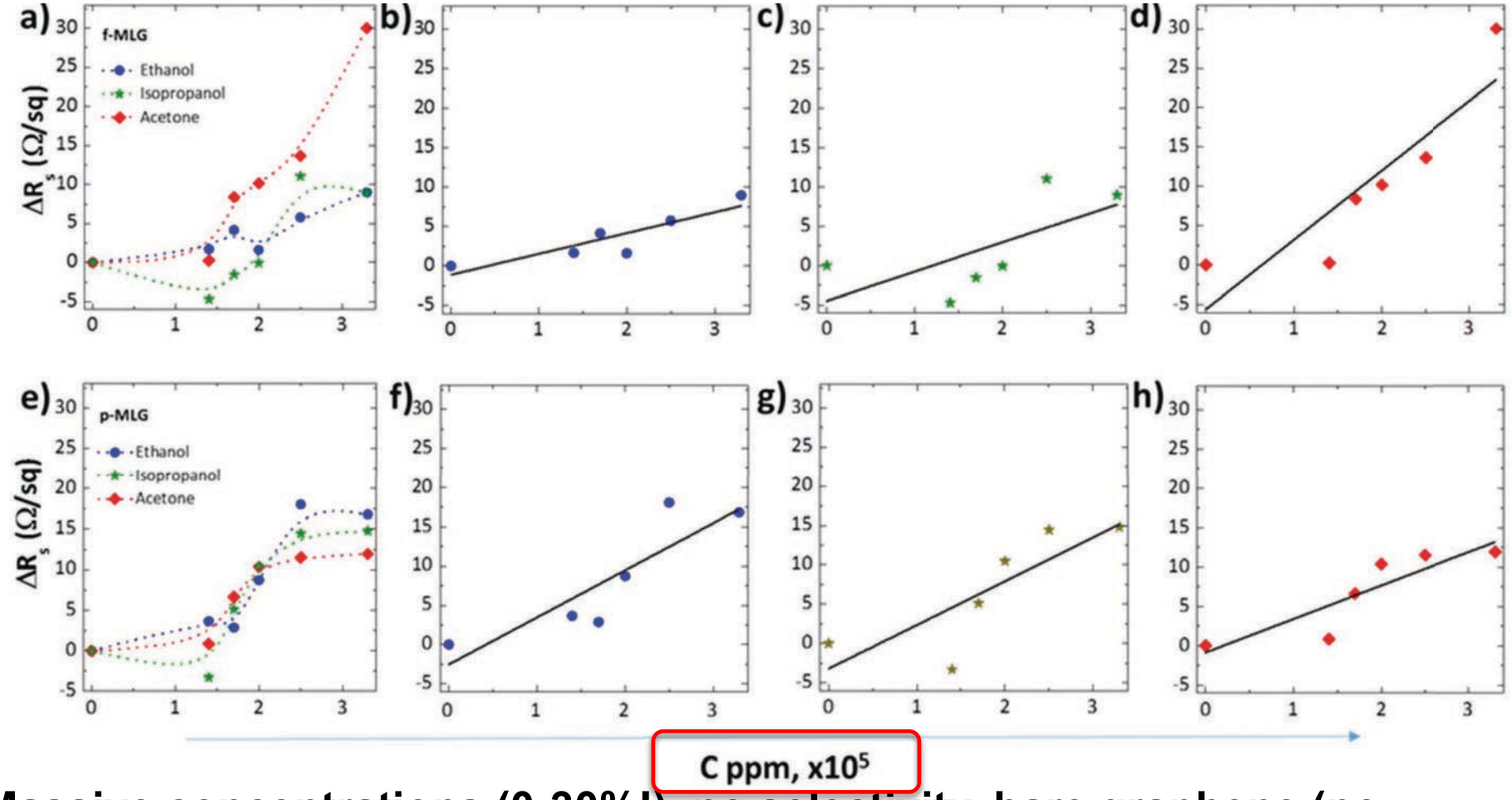


Fig. 3 The schematic representation of the two-point measurement concept (a) for the in situ electrical characterization of VOC-induced graphene electrodes (c, d); electron-induced reorientation of acetone while applying ±1 V (b).
The I_{dc} versus V_{gs} curves of the flat and patterned graphene electrodes influenced with exposure to **1.4–3.3x10^5 ppm** of VOC solutions: ethanol (c), isopropanol (d) and acetone (e).

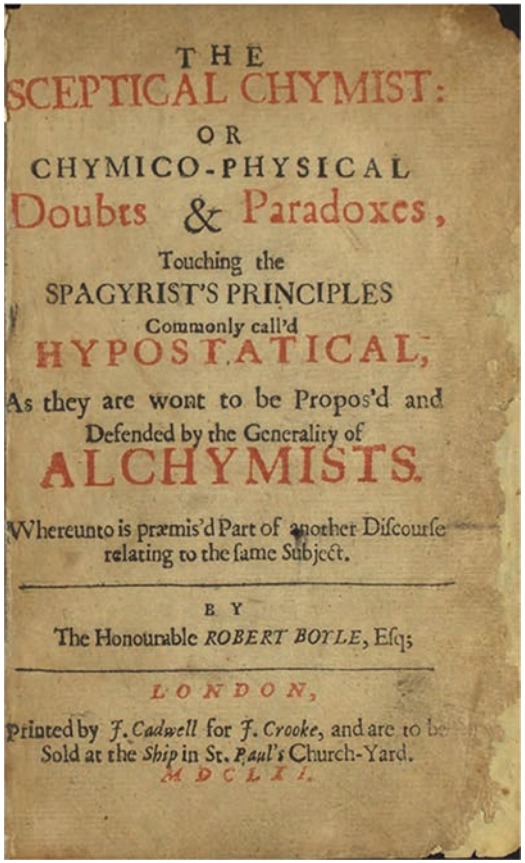
Response Curves to ‘cancer marker’ VOCs in breath (e-Nose)

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…….

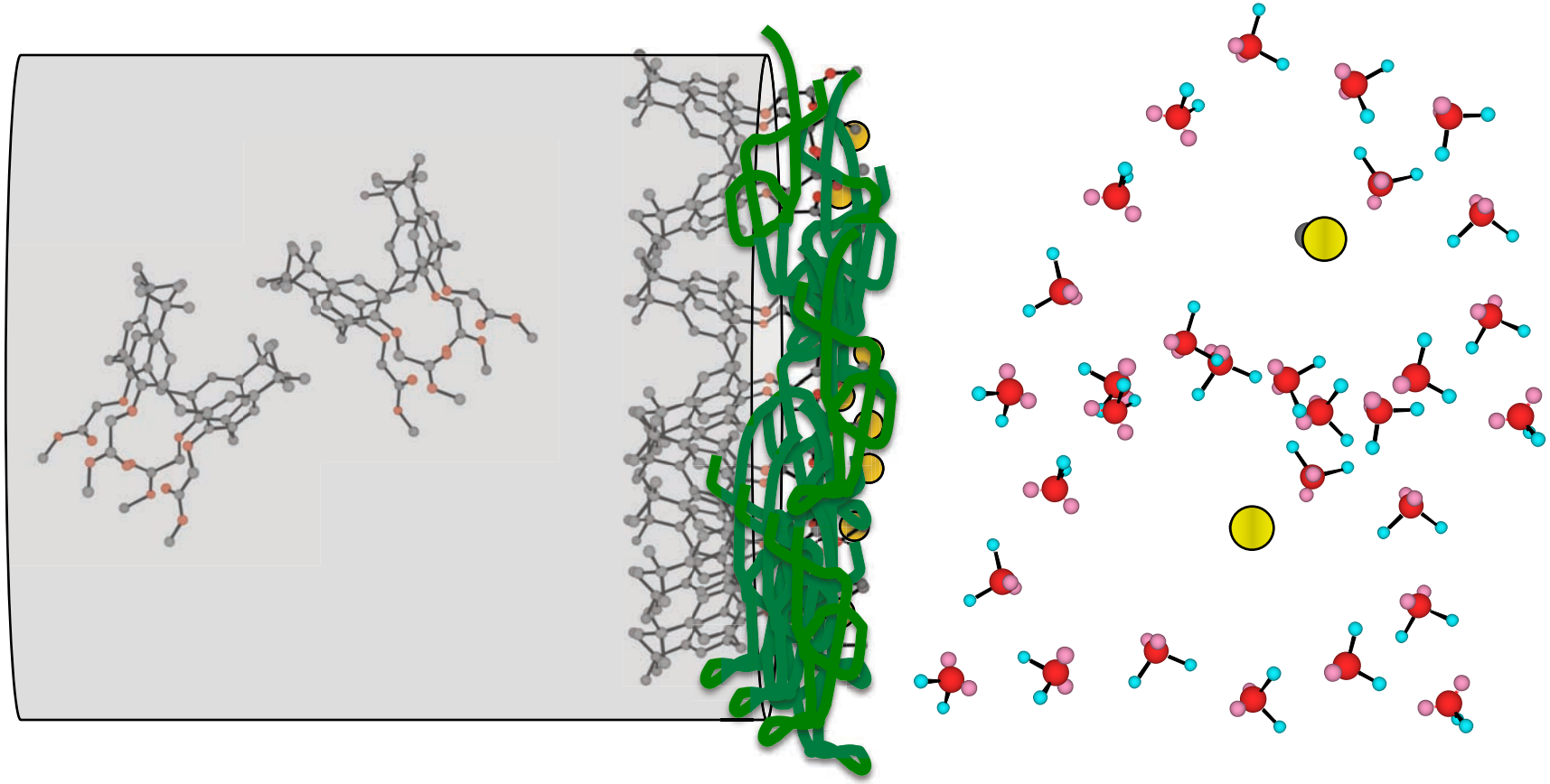
‘The Sceptical Chemist’ (1661)
‘Chymico-Physical Paradoxes’



THE
SCEPTICAL CHYMIST:
OR
CHYMICO-PHYSICAL
Doubts & Paradoxes,
Touching the
SPAGYRIST'S PRINCIPLES
Commonly call'd
HYPOSTATICAL,
As they are wont to be Propos'd and
Defended by the Generality of
ALCHYMISTS.
Whereunto is præmis'd Part of another Discourse
relating to the same Subject.
BY
The Honourable *ROBERT BOYLE*, Esq;
LONDON,
Printed by *J. Cadwell* for *J. Crooke*, and are to be
Sold at the *Ship* in St. *Paul's* Church-Yard.
MDCLXI.

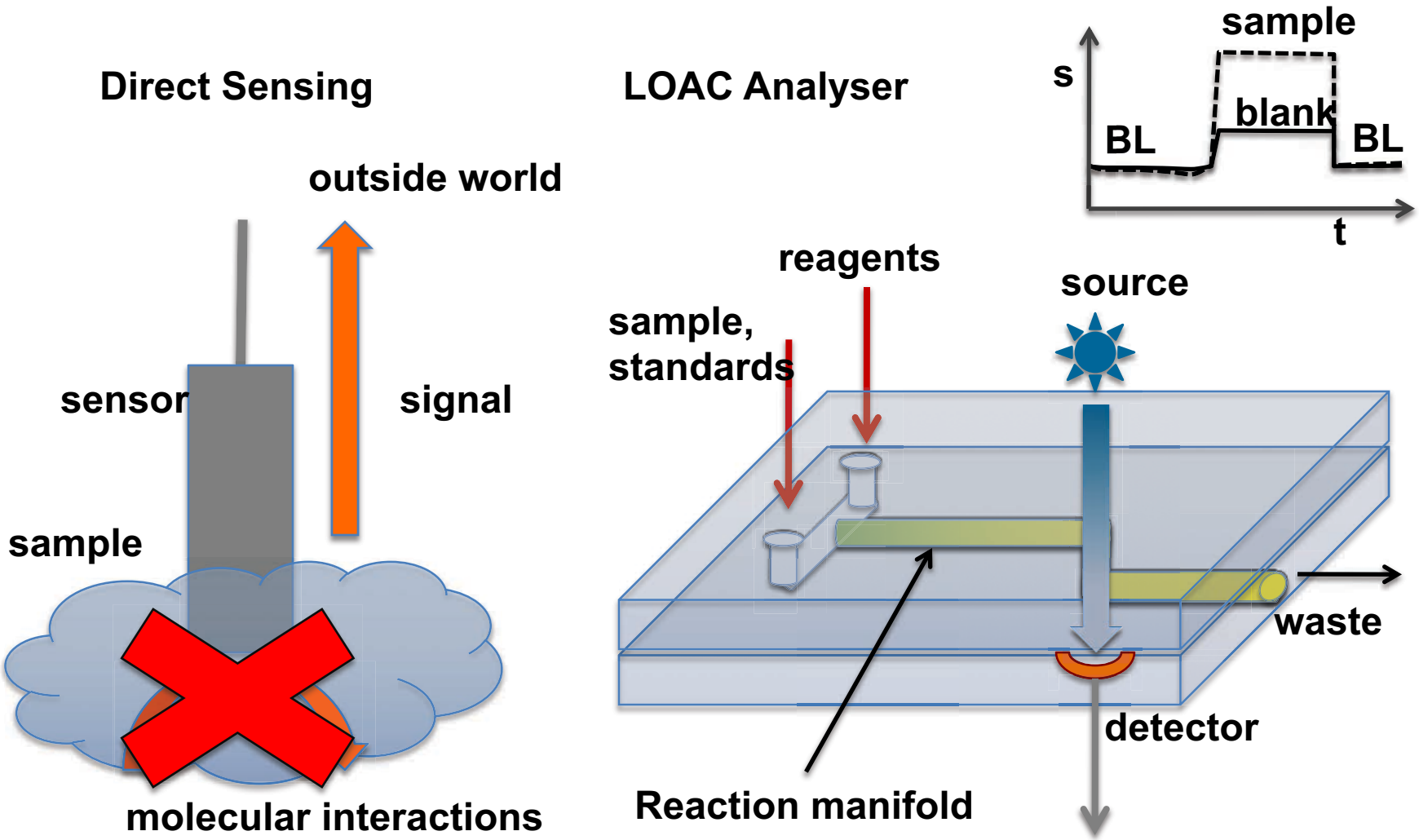
Robert Boyle: b. Lismore Castle, Waterford, 1621

Control of membrane interfacial exchange & binding processes



Remote, autonomous chemical sensing is a tricky business!

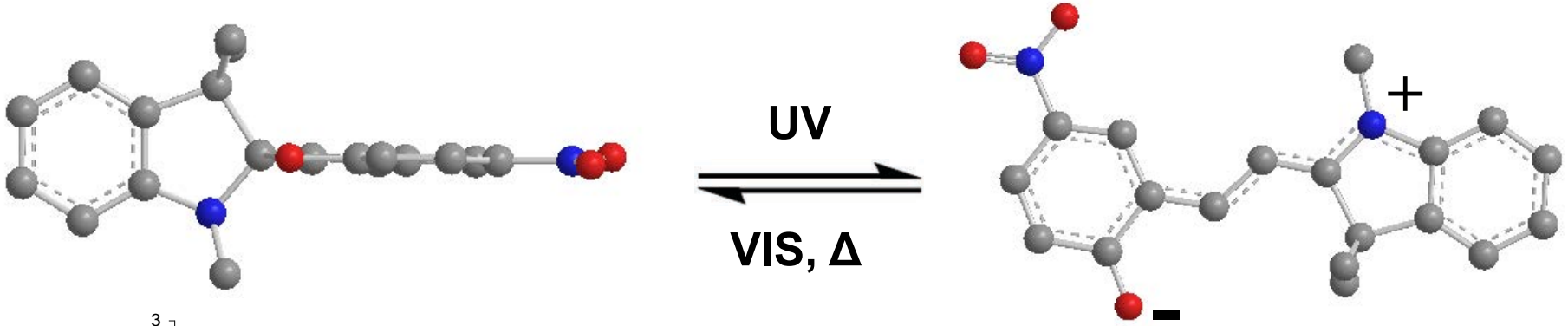
Direct Sensing vs. Reagent Based LOAC/ufluidics



Bioinspired Devices

- **Functional (Bio)Materials OR Materials that can mimic characteristics of biological systems**
  - **Self-awareness of condition**
  - **Some capacity for self-maintenance/self repair**
- **Hierarchy of behaviours**
  - Routine internalized maintenance for minor issues
  - Escalation to external intervention for more serious issues (detect, report, request intervention)

Photoswitchable Soft Actuators



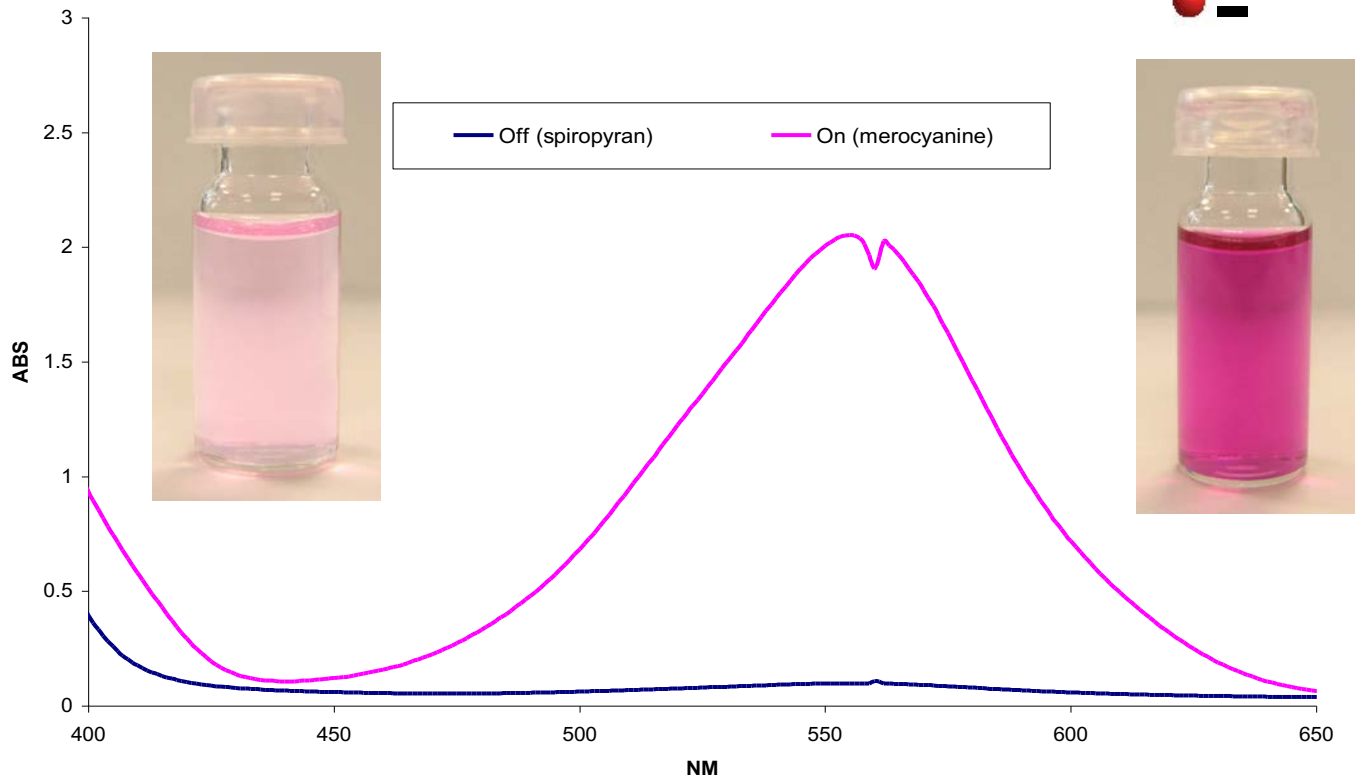
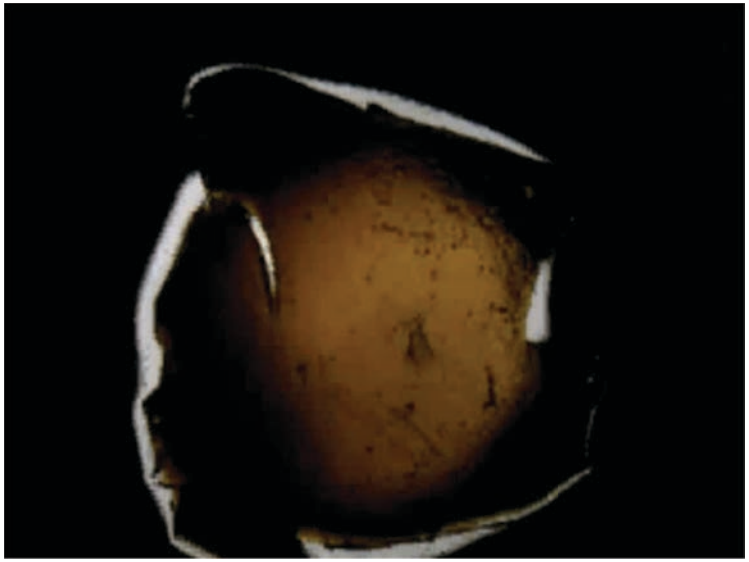
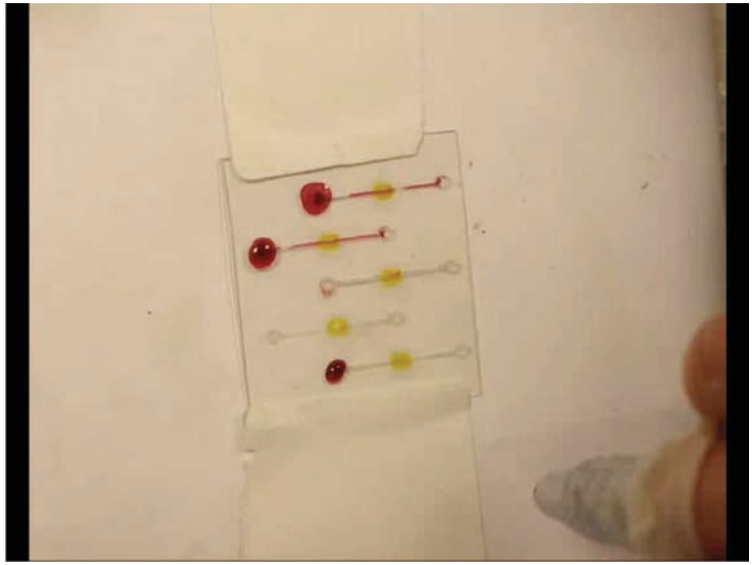
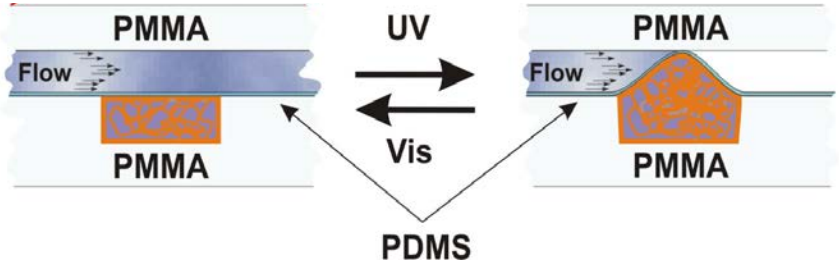
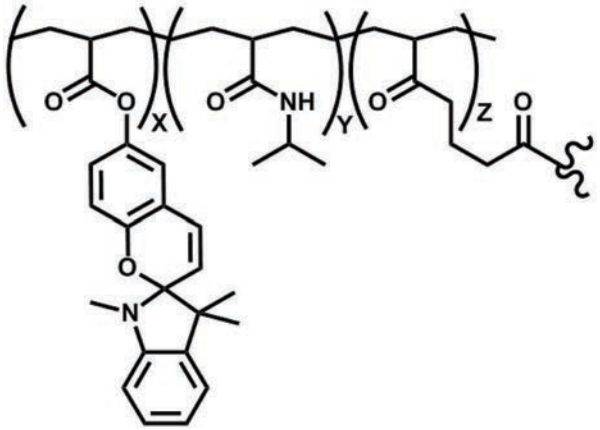


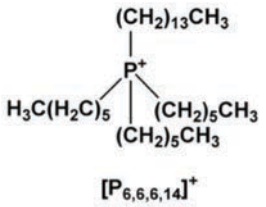
Photo-actuator polymers as microvalves in microfluidic systems

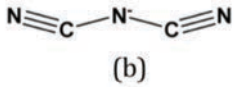












trihexyltetradecylphosphonium dicyanoamide $[P_{6,6,6,14}]^+[dca]^-$

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

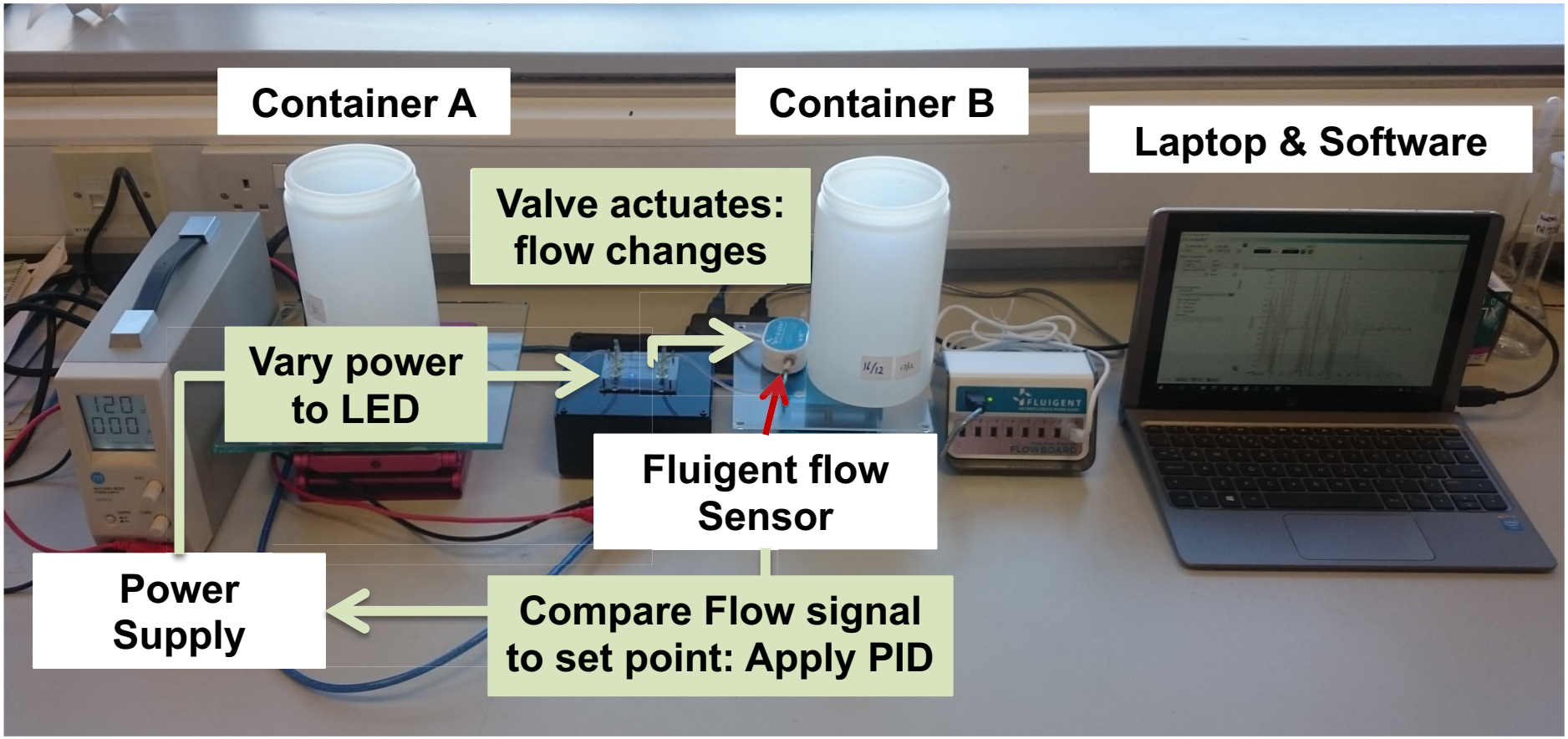
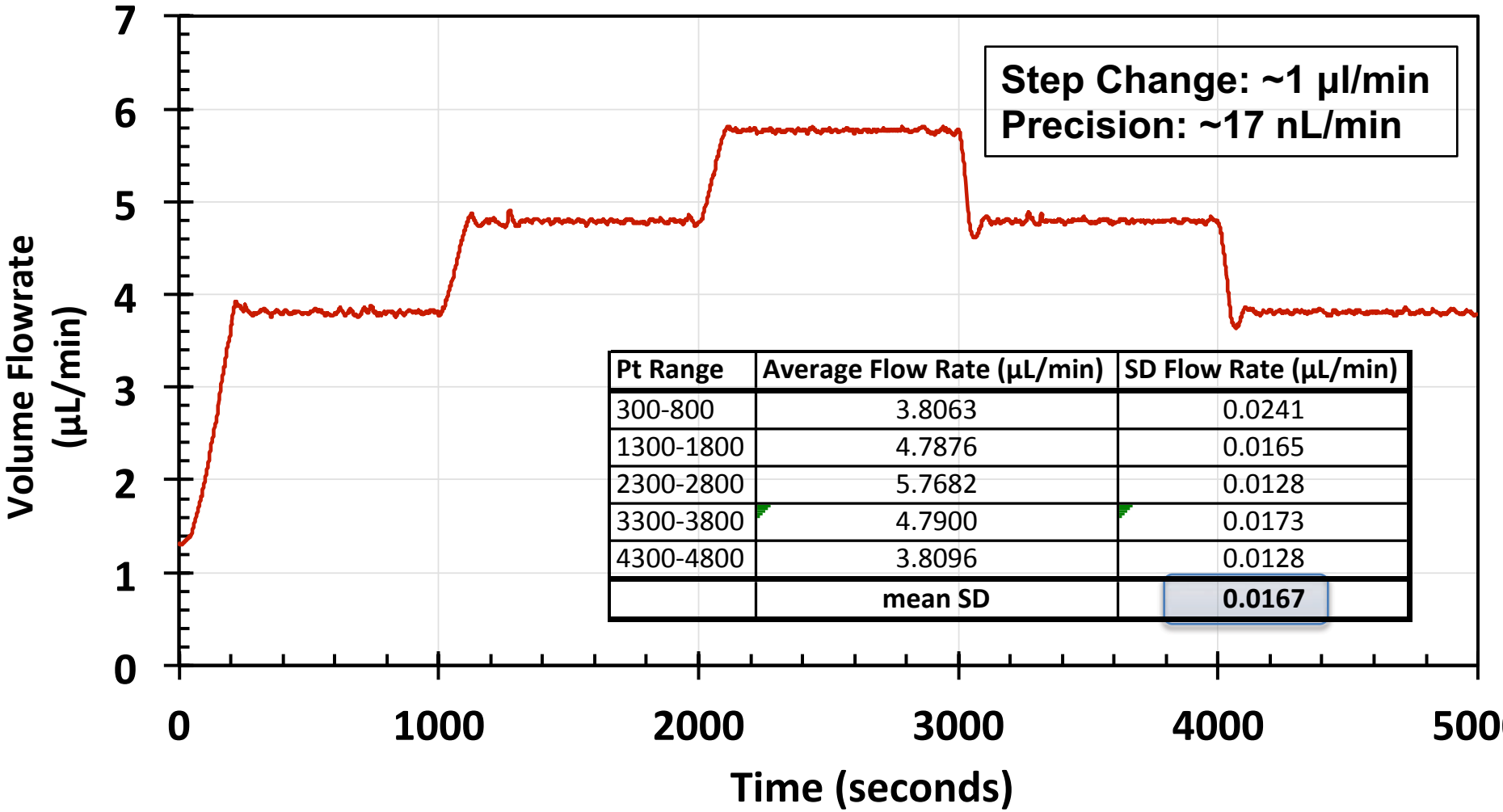


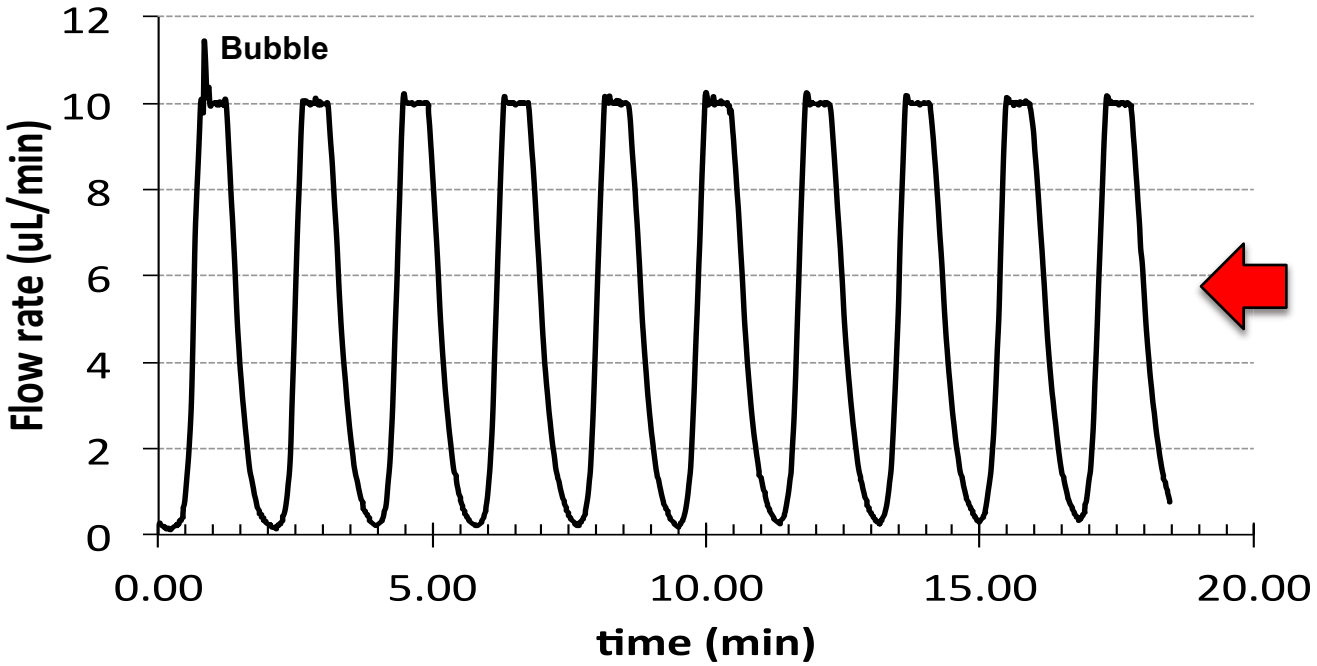
Photo-Controlled Flow Rate



Pt Range	Average Flow Rate (µL/min)	SD Flow Rate (µL/min)
300-800	3.8063	0.0241
1300-1800	4.7876	0.0165
2300-2800	5.7682	0.0128
3300-3800	4.7900	0.0173
4300-4800	3.8096	0.0128
	mean SD	**0.0167**

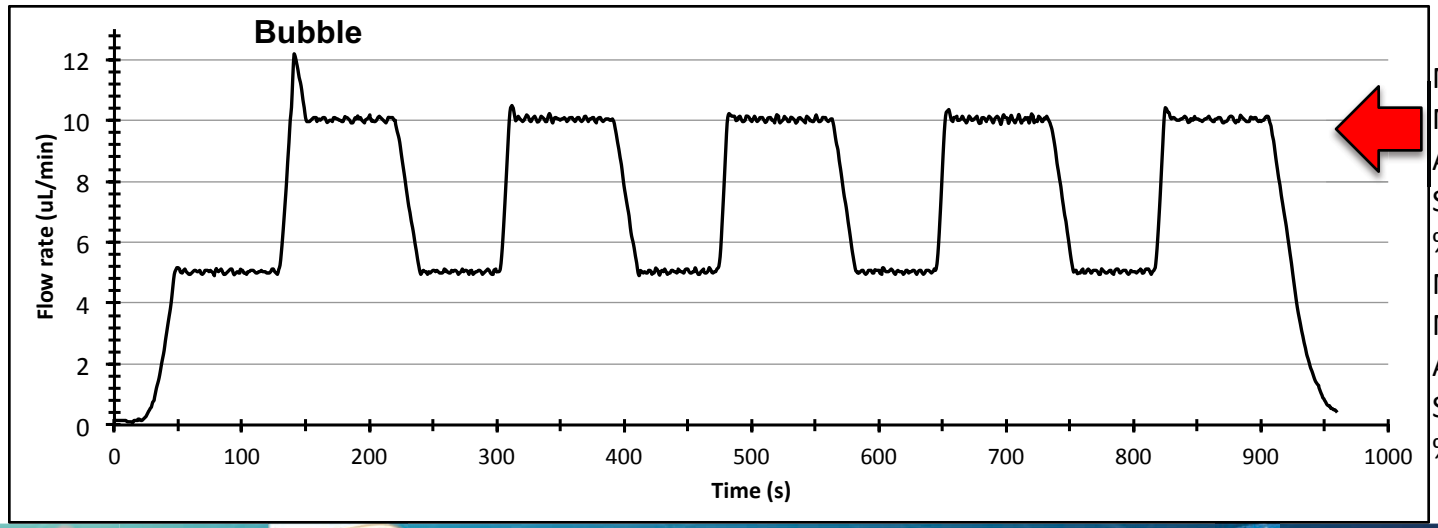
C. Delaney, P. McCluskey, S. Coleman, J. Whyte, N. Kent, D. Diamond, Precision control of flow rate in microfluidic channels using photoresponsive soft polymer actuators, LAB ON A CHIP. 17 (2017) 2013–2021. doi:10.1039/c7lc00368d.

Some figures of merit



Switching 0.0-10.0 µL/min
n= 15 points sampled behind the initial small overshoot

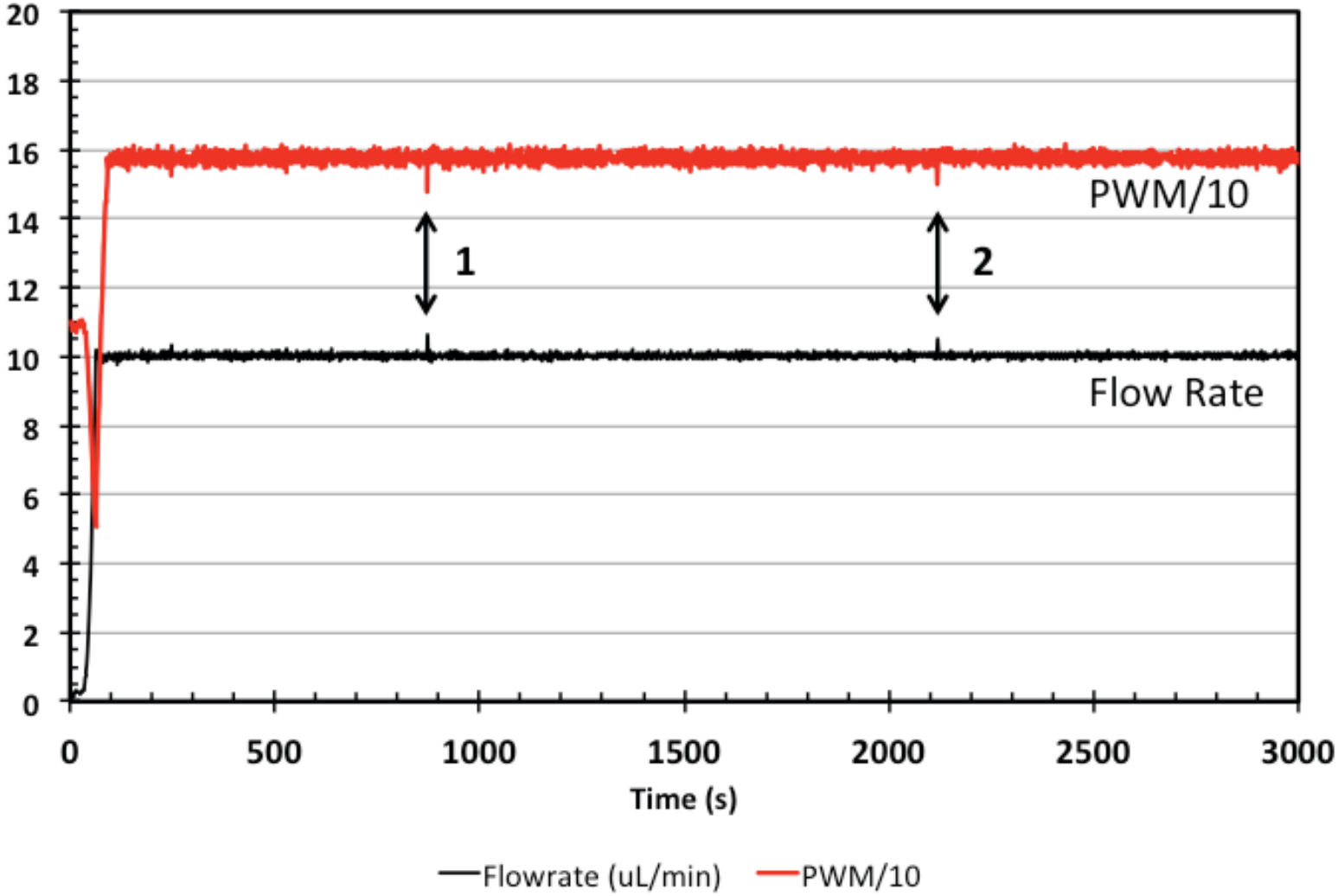
Averages (n=10)	
mean	10.0028
Mean SD	0.0323
Error Mean	0.0028
%RSD	0.3235
%RE mean	0.0279



Switching 5.0-10.0 µL/min
n= 30 points sampled

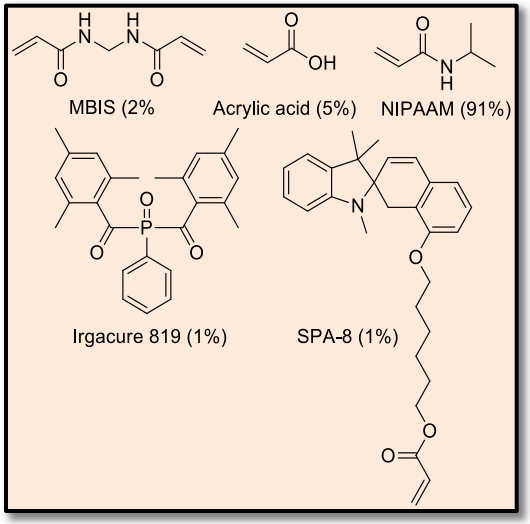
Mean %RE (5=true)	0.780
Mean %RE (5.039=true)	0.098
Average of mean	5.039
SD Mean	0.006
%RSD	0.120
Mean %RE (10=true)	0.372
Mean %RE (10.037=true)	0.102
Average of mean	10.037
SD Mean	0.012
%RSD	0.124

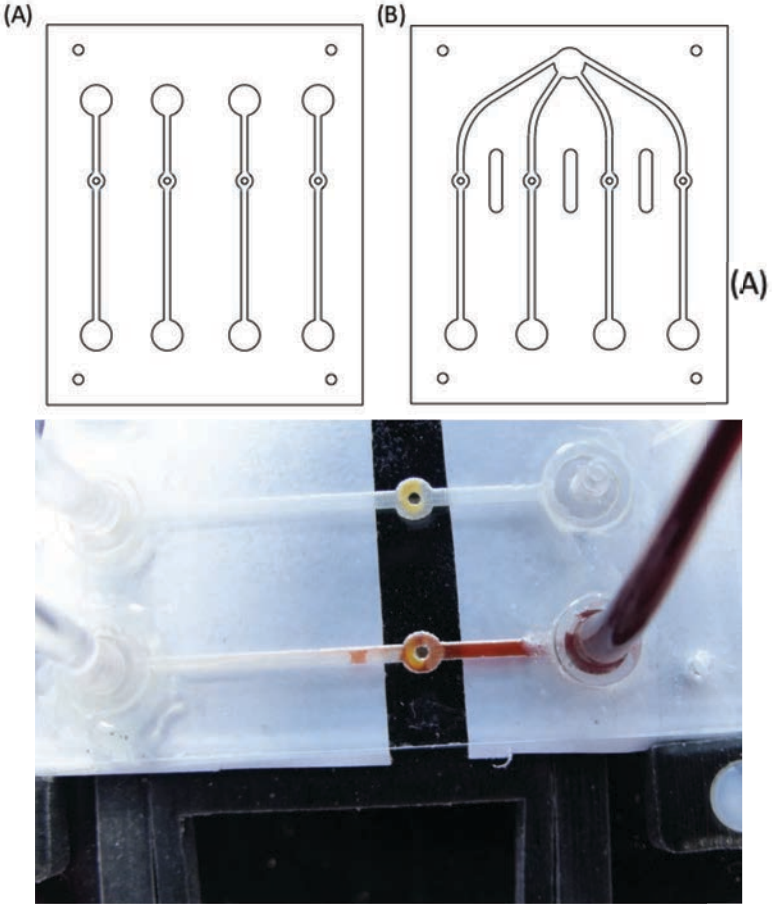
Power Supply to LED

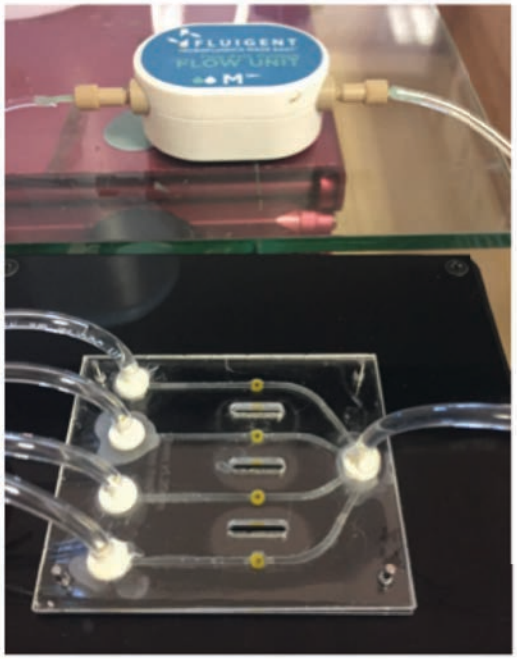


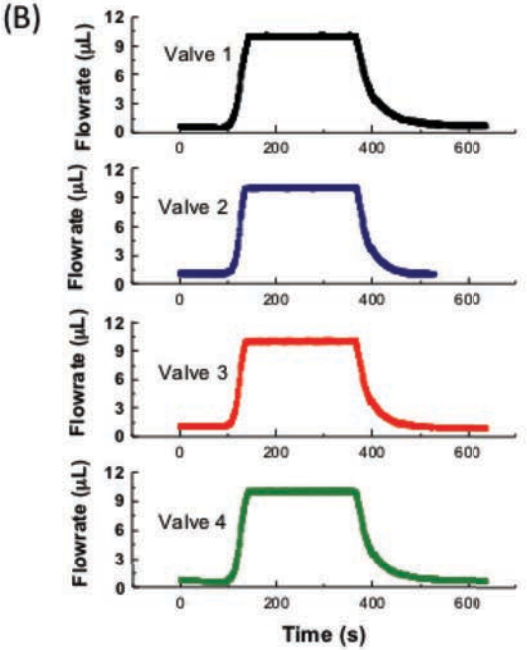
Over a period of 50 min constant maintenance of 10 µL/min flow rate there is no discernable change in LED power ➔ diagnostic information

Multiplexing: Valve Arrays









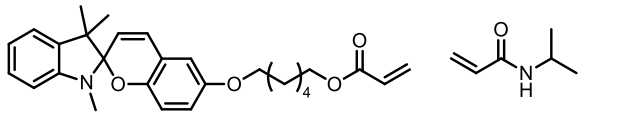
Photocontrol of Assembly and Subsequent Switching of Surface Features

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

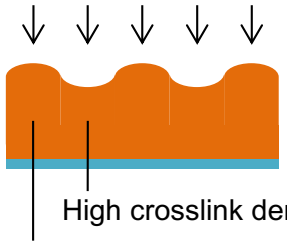
Jelle E. Stumpel,[†] Bartosz Ziółkowski,[‡] Larisa Florea,[‡] Dermot Diamond,[‡] Dirk J. Broer,*[,†,§] and Albertus P. H. J. Schenning*[,†,§]

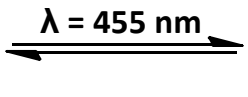


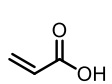
SPA, 1 mol%

NIPAAM, 91-92 mol%

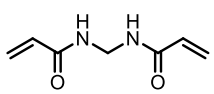
a)



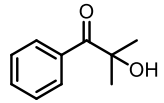




acrylic acid, 5 mol%

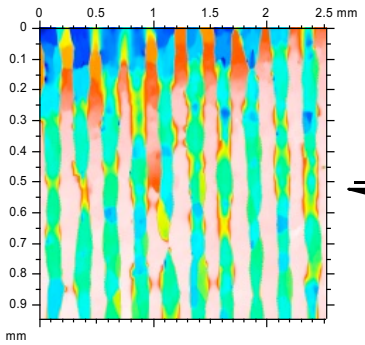


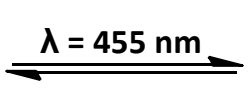
MBIS, 1-2 mol%

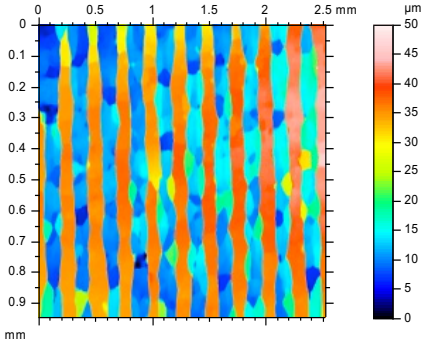


Darocur 1173, 1 mol%

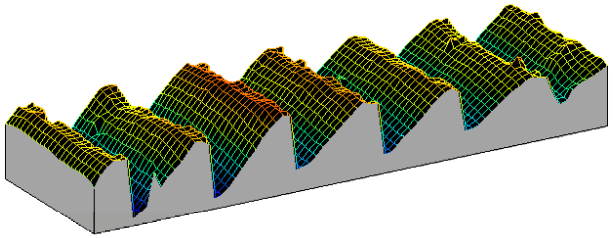
b)







a)



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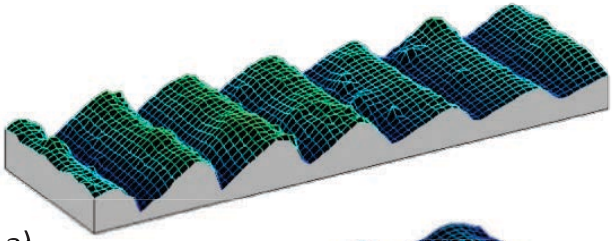
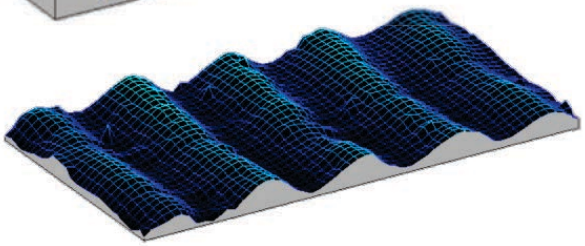
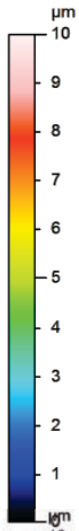
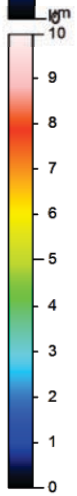


a)

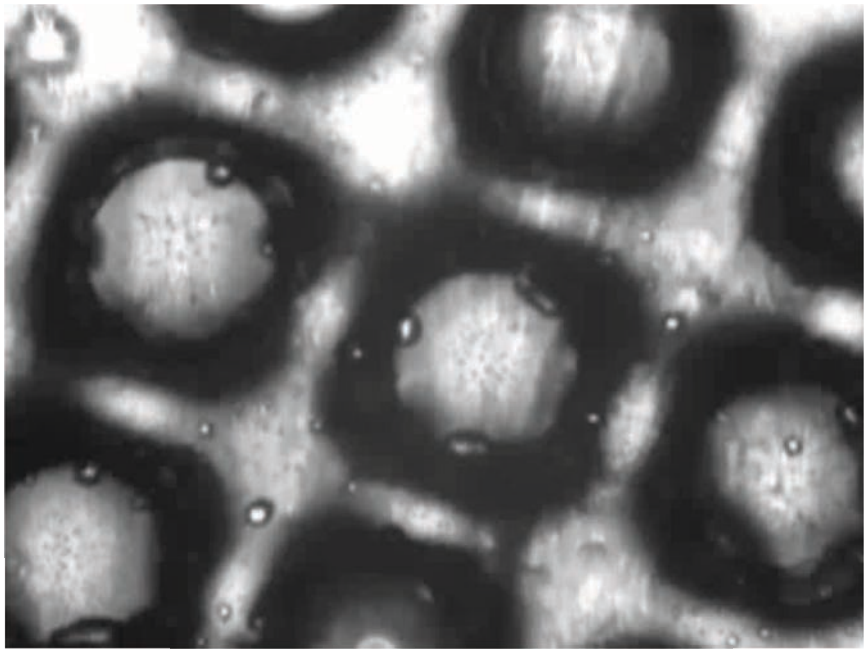


b)

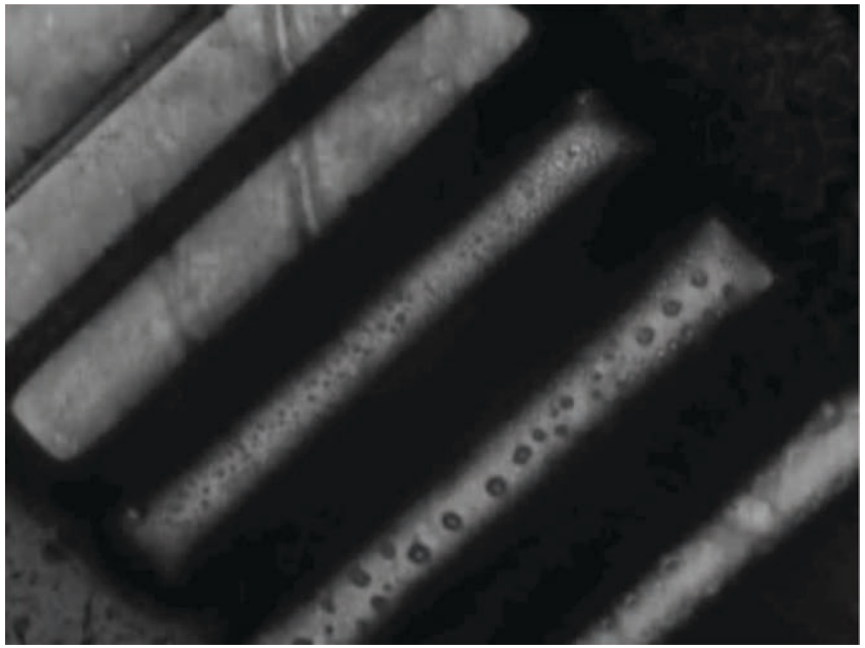




Flexible creation of μ-dimensioned features in flow channels using in-situ photo-polymerisation



Ntf2 pillars speed x3

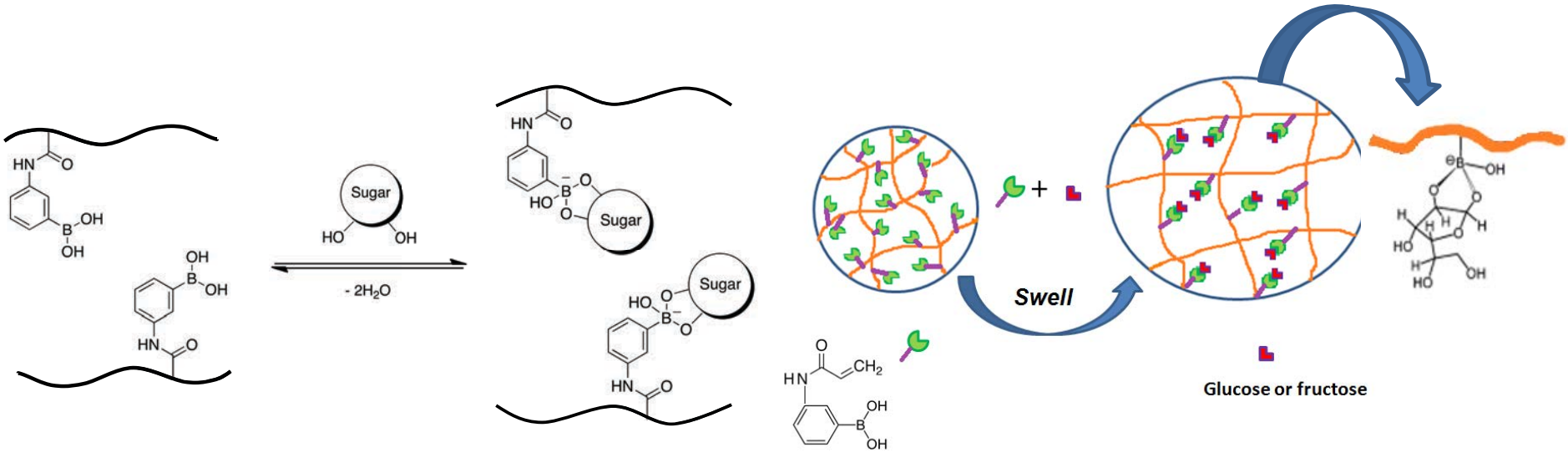


DCA lines speed x4

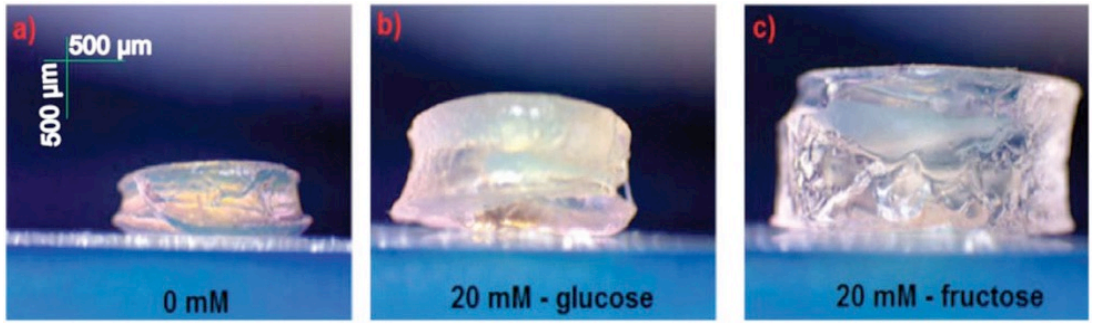
With Dr Peer Fischer, Fraunhofer-Institut für Physikalische Messtechnik (IPM), Freiburg

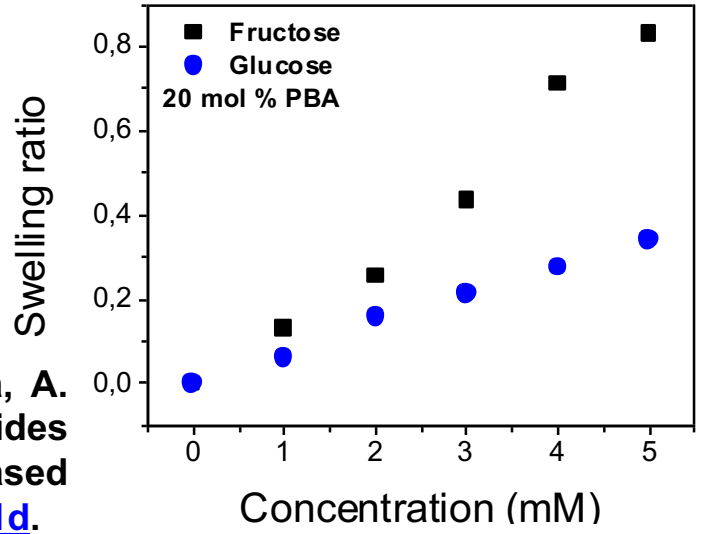
Binding behavior can also be modulated using light

Sugar-Responsive Soft Hydrogels



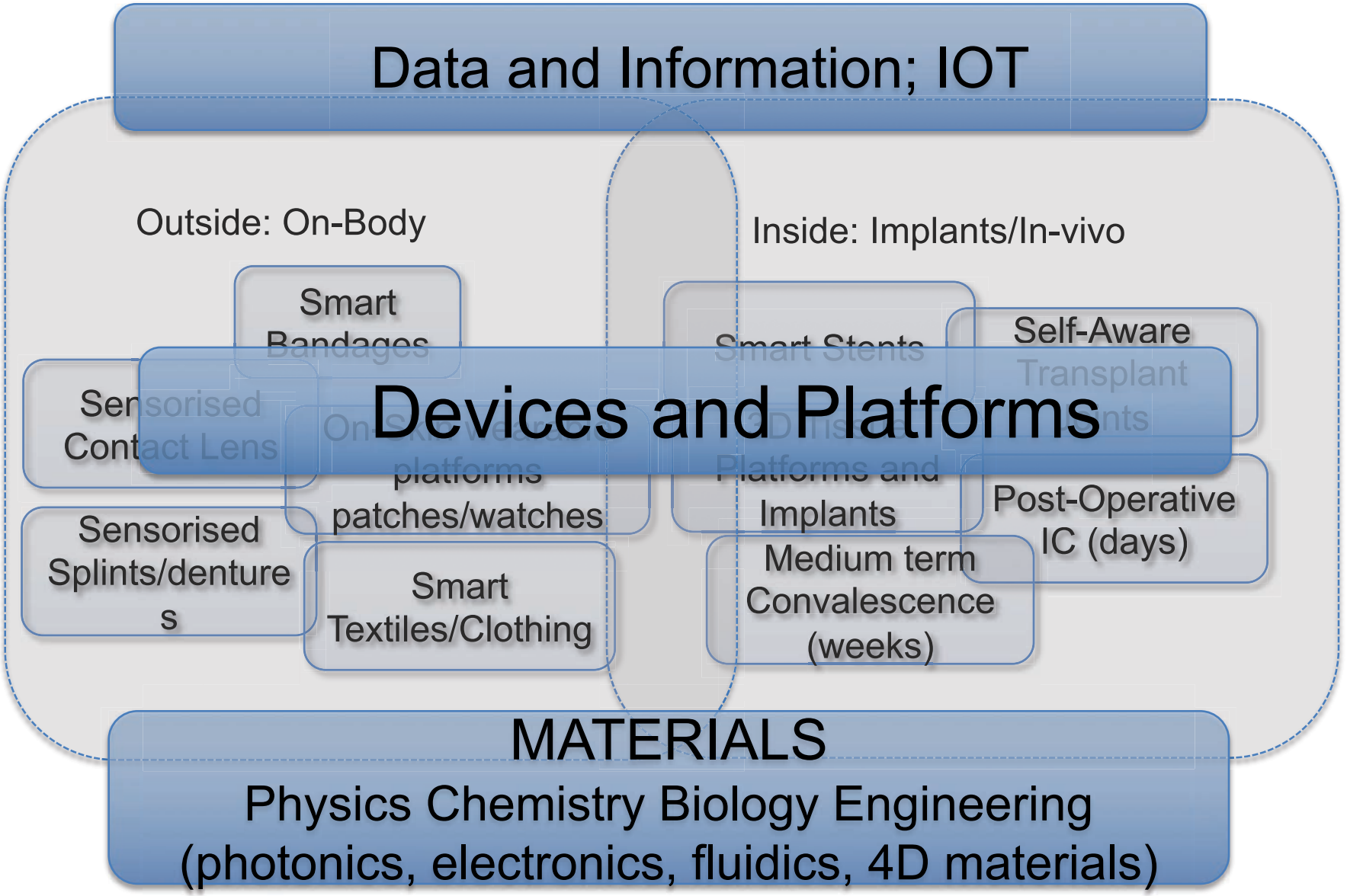
Acrylamide-*co*-PBA Polymer





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.

Merging of Materials, Devices and Data



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- Science Foundation Ireland & INSIGHT Centre
- Enterprise Ireland
- Research Partners – academic and industry
- H2020: Holifab Project

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

HoliFAB

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