Bioinspired Microfluidics

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Murray Edwards College, Cambridge, UK

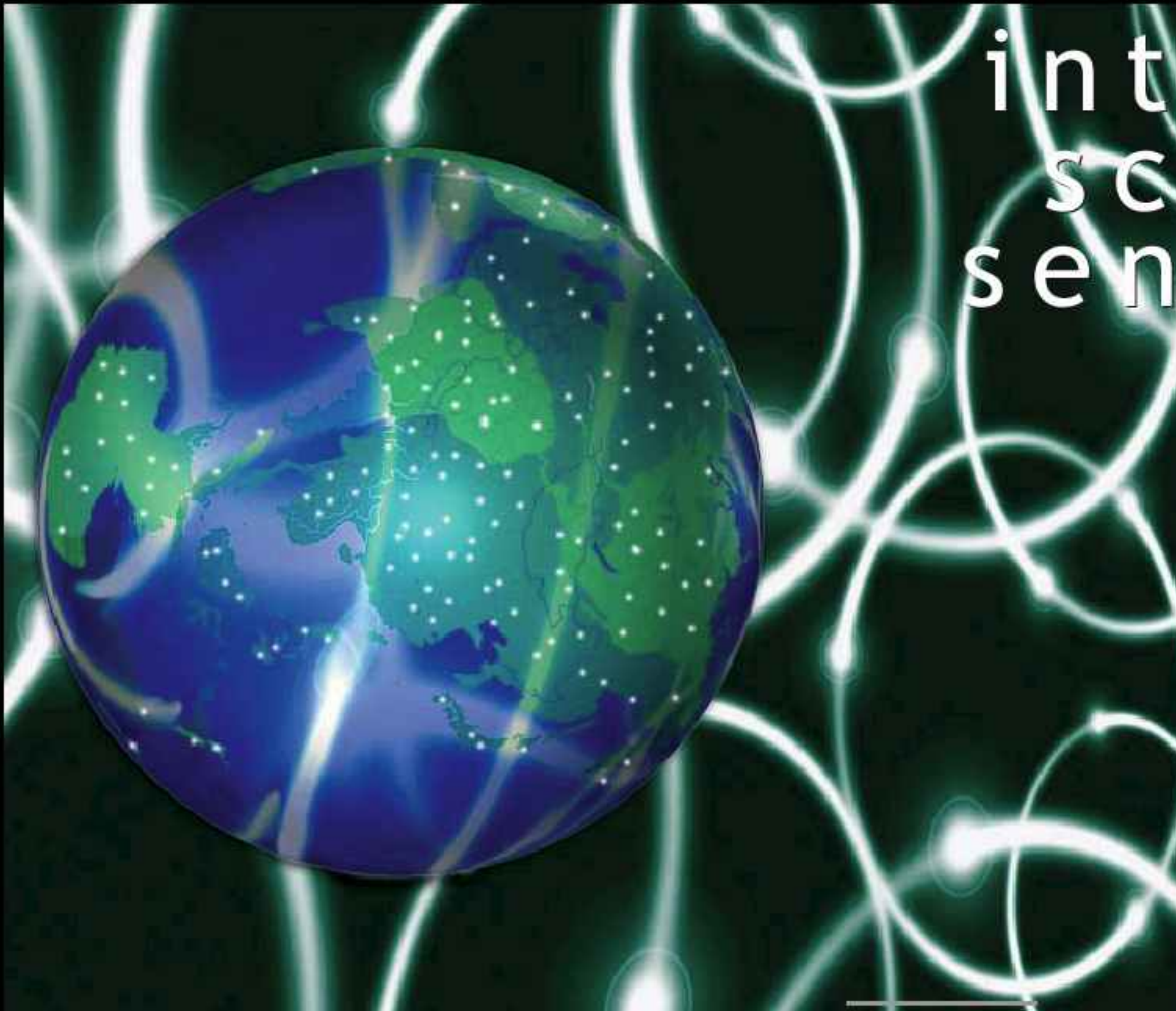
10-11 October 2017

Question:

Can we deliver chem/bio-sensing platforms capable of long-term autonomous operation in remote (hostile) environments at a reasonable cost?

'Deploy and Forget' long-term use model

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



internet scale sensing

Dermot Diamond
Dublin City University
(Ireland)

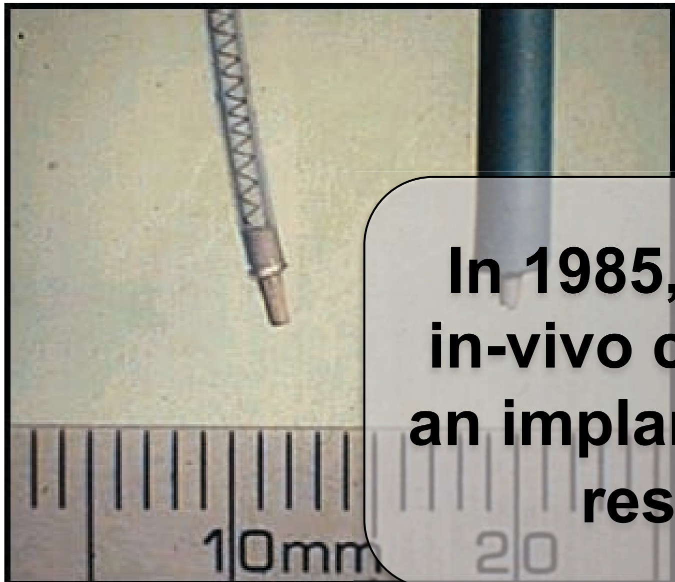
Incredible advances in digital communications and computer power have profoundly changed our lives. One chemist shares his vision of the role of analytical science in the next communications revolution.

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.

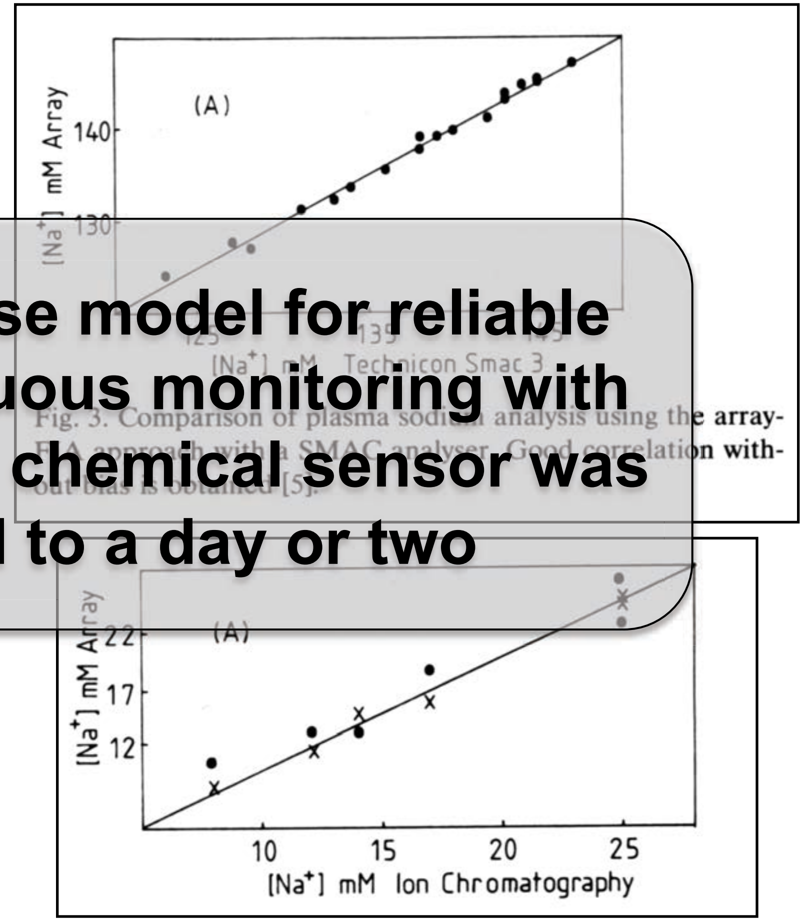
The crucial missing part in this scenario is the gateway through which these worlds will communicate: How can the digital world sense and respond to changes in the real world? Analytical scientists—particularly those working on chemical sensors, biosensors, and compact, autonomous instruments—are

Ron Ambrosio & Alex Morrow, IBM TJ Watson

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



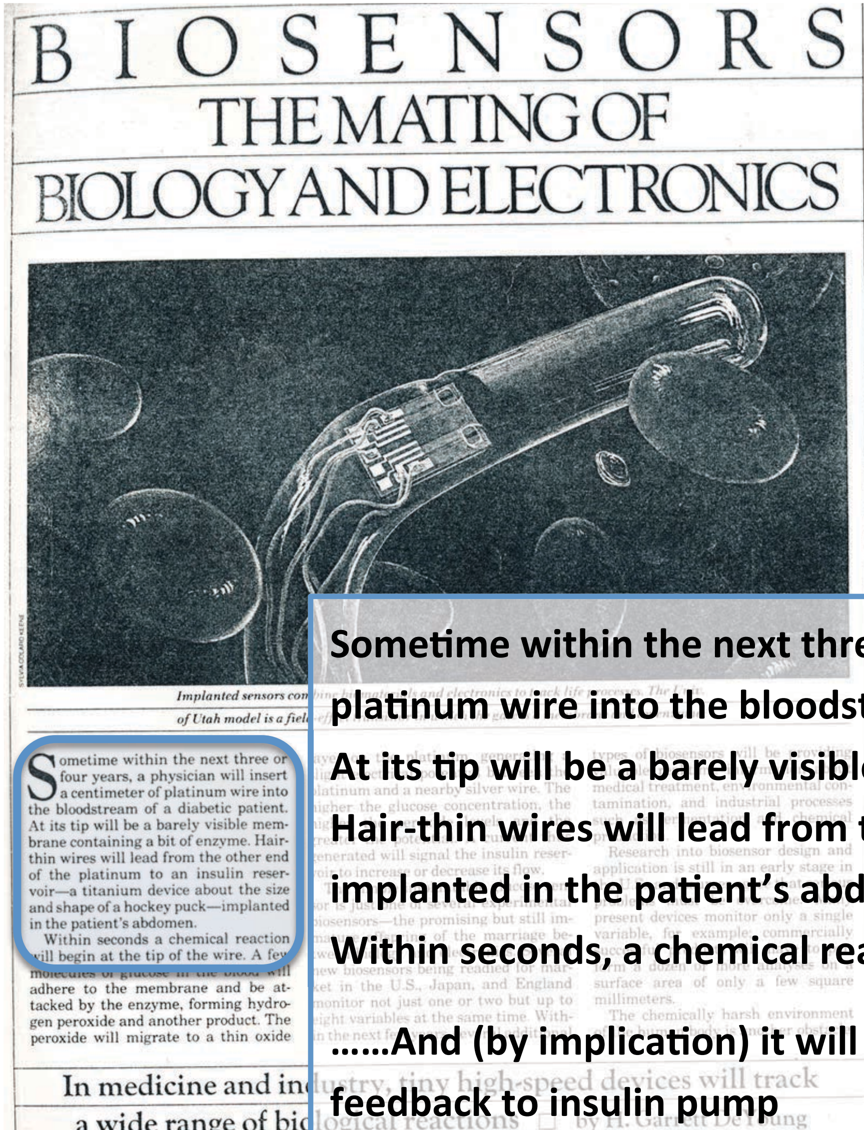
Anal. Chem., *64* (1992) 1721-1728.

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

Dr. David Band, St Thomas's Hospital London

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

The (broken) promise of biosensors…..



BIOSENSORS

THE MATING OF BIOLOGY AND ELECTRONICS

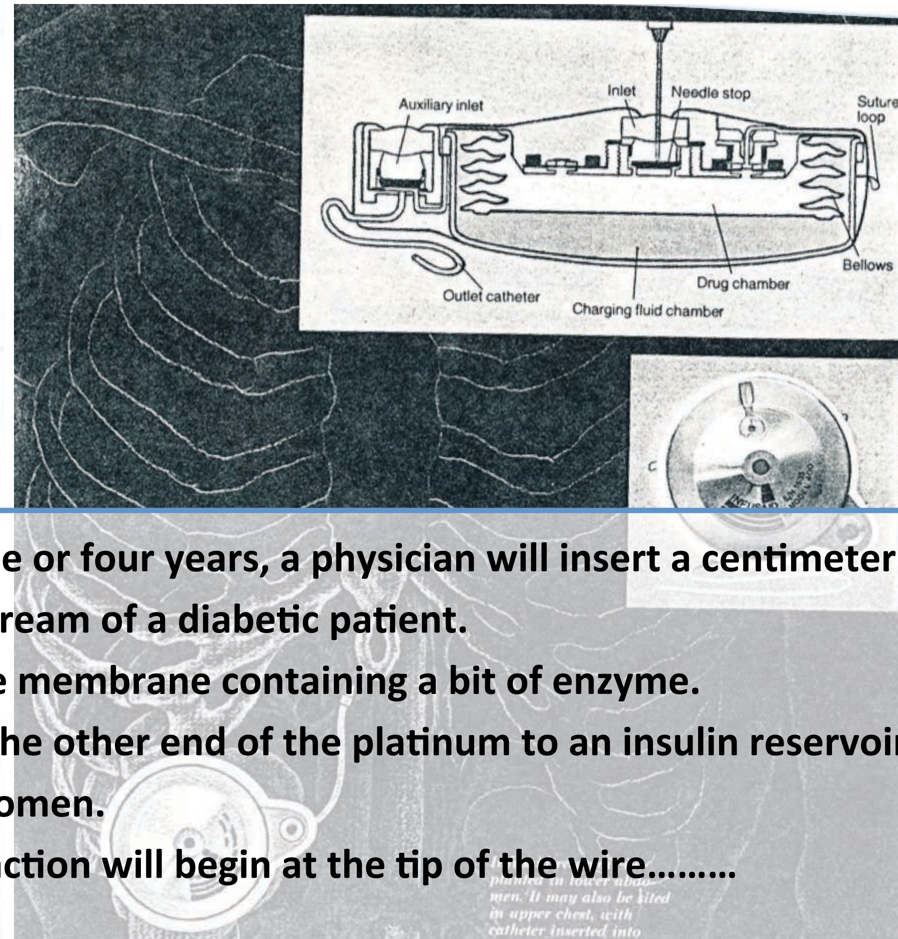
Implanted sensors com… of Utah model is a fiel…

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 □ by H. Garrett DeYoung

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!

How to use the FreeStyle Libre System

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

1 Apply sensor
with applicator

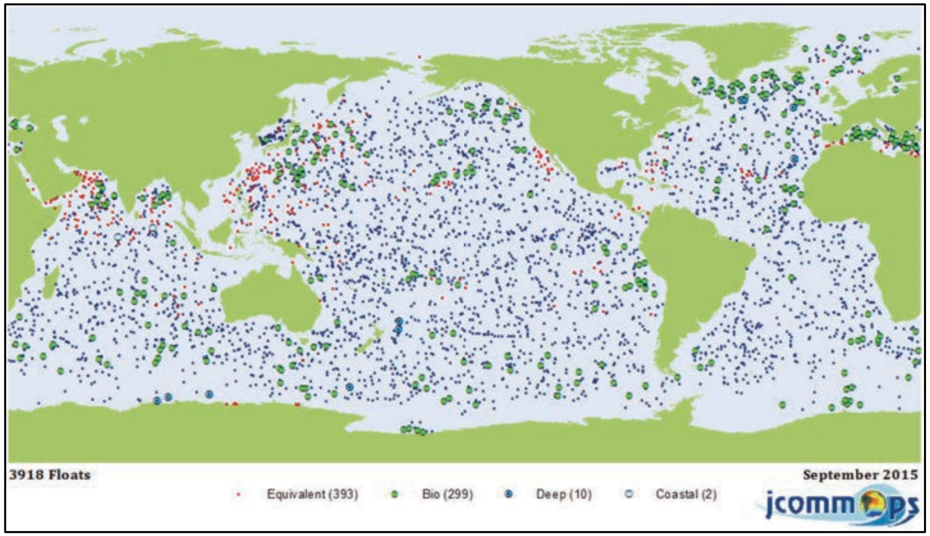
- A thin flexible sterile fibre (5mm long) is inserted just below the skin. Most people reported that applying the sensor was painless[6]
- The 14-day sensor stays on the back of your upper arm and automatically captures glucose readings day and night.
- The sensor is water resistant and can be worn while bathing, swimming and exercising[7]

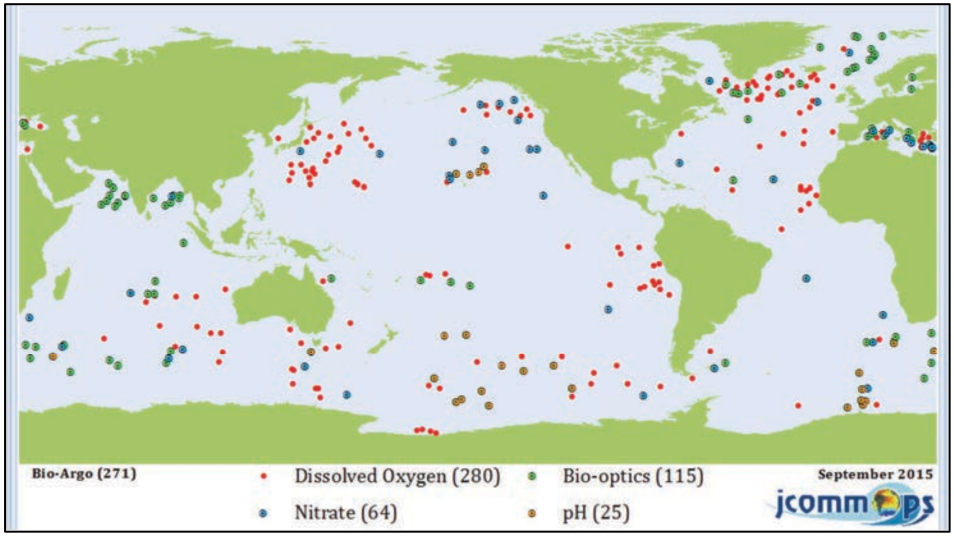
[6] Most people did not feel any discomfort under the skin while wearing the FreeStyle Libre sensor. In a study conducted by Abbott Diabetes Care, 93.4% of patients surveyed (n=30) strongly agree or agree that while wearing the sensor, they did not feel any discomfort under their skin. [29 persons have finished the study; 1 person terminated the study after 3 days due to skin irritations in the area where the sensor touched the skin.]
[7] 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

Current state-of-the-art for patch based glucose sensing is 2-weeks use outside the body: Implants require 10 years inside the body

Argo Project (accessed March 20 2016)





- **Ca. 4,000 (3918) floats: temperature and salinity**
- **Bio/Chem: Nitrate (64), DO (280), Bio-optics (115), pH (25)**

DO is by Clark Cell (Sea Bird Electronics) or Dynamic fluorescence quenching (Aanderaa)

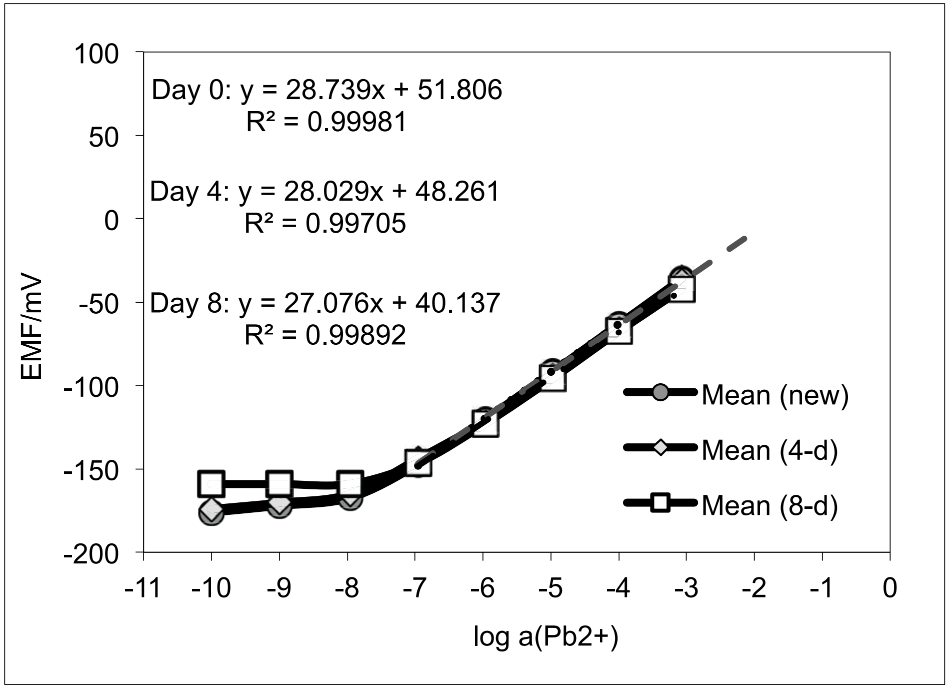
@€60K ea!

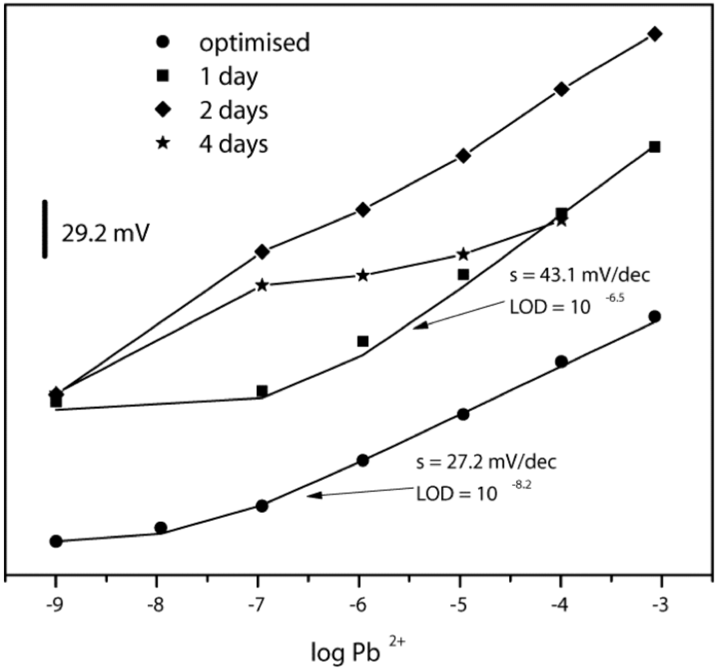
See https://picasaweb.google.com/JCOMMOPS/ArgoMaps?authuser=0&feat=embedwebsite

'calibration of the DO measurements by the SBE sensor remains an important issue for the future', Argo report 'Processing Argo OXYGEN data at the DAC level', September 6, 2009, V. Thierry, D. Gilbert, T. Kobayashi

Change in Electrode Function over Time

See Electrochimica Acta 73 (2012) 93–97



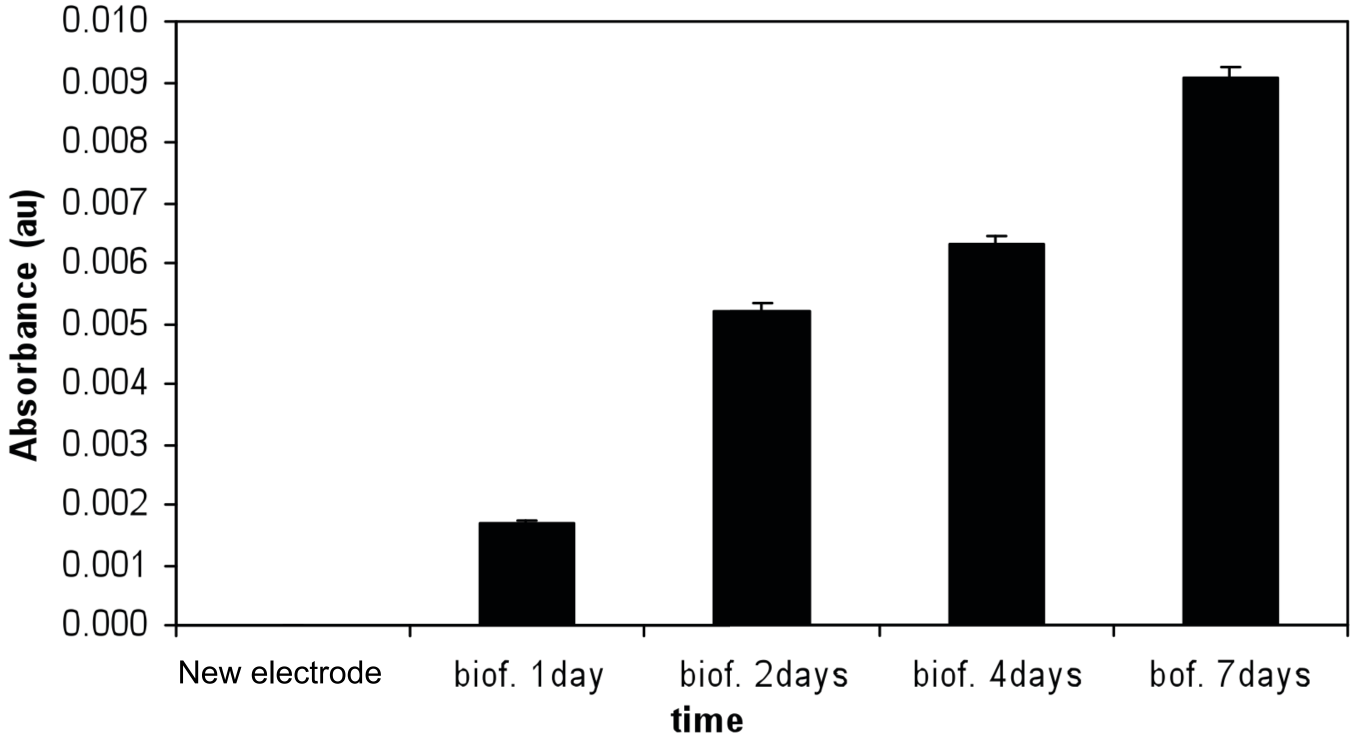


stored in 10^{-9}M Pb^{2+}, pH=4

Continuous contact with river water

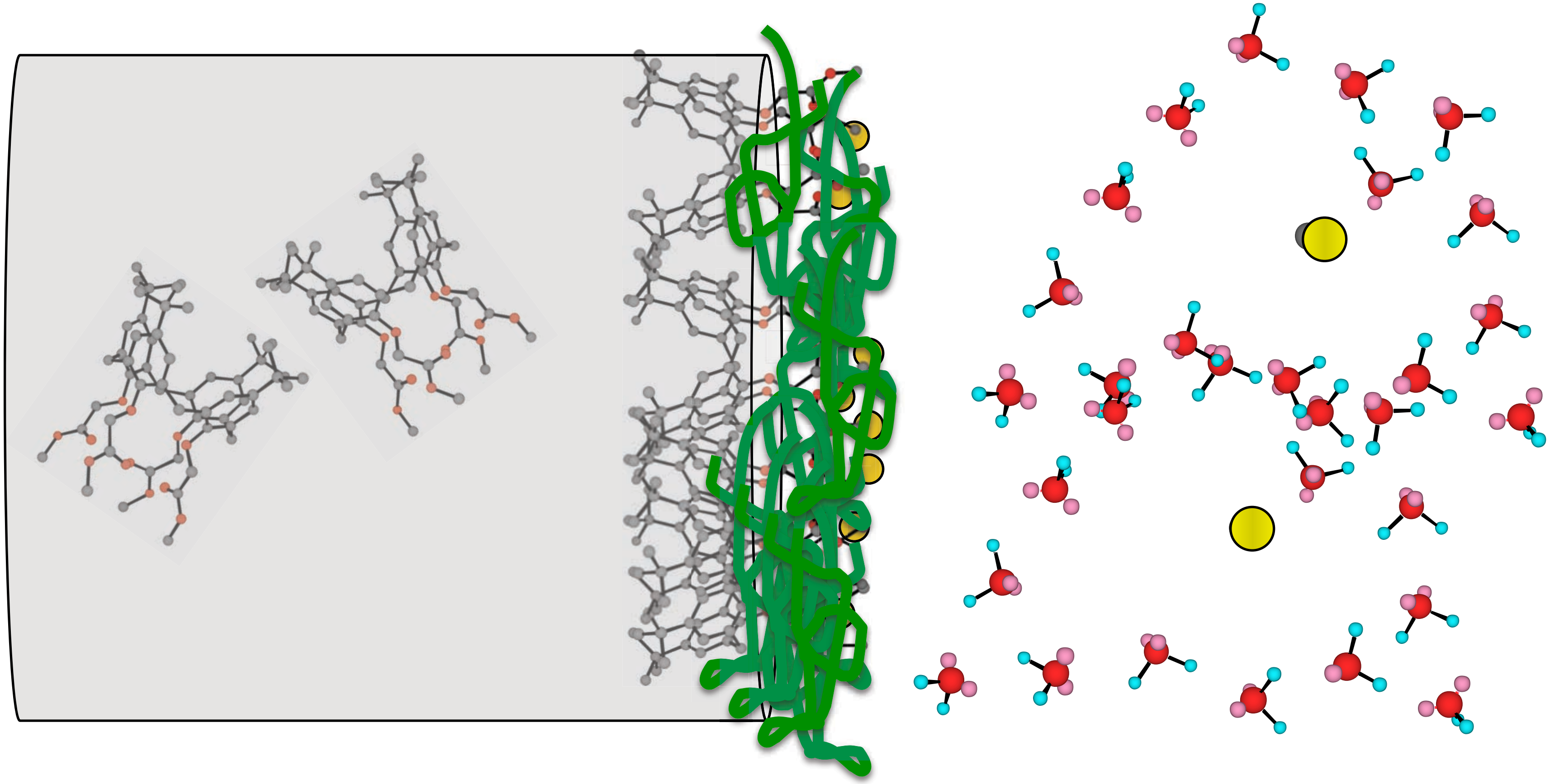
Conventional PVC-membrane based ISEs

Biofilm Formation on Sensors



- **Electrodes exposed to local river water (Tolka)**
- **'Slime test' shows biofilm formation happens almost immediately and grows rapidly**

Control of membrane interfacial exchange & binding processes

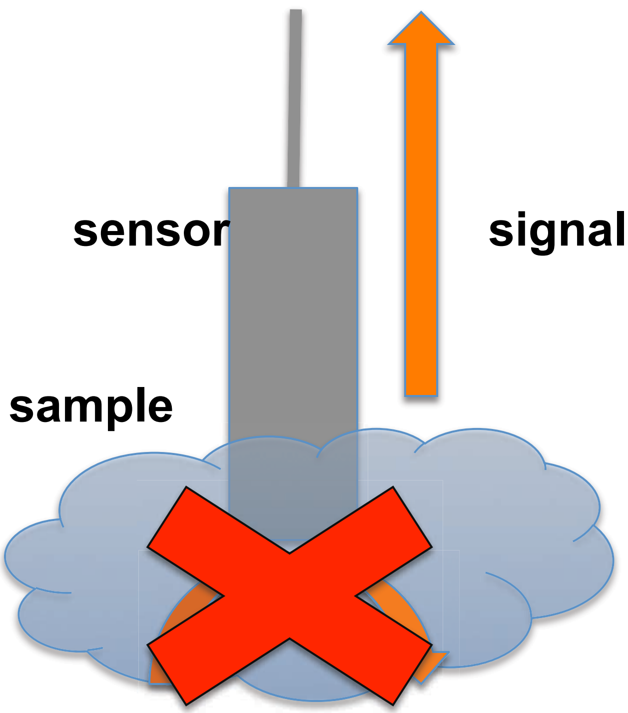


Remote, autonomous chemical sensing is a tricky business!

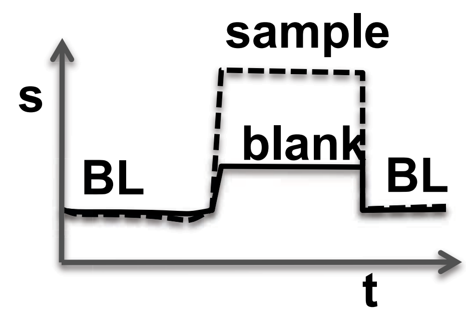
Osberstown – 3 week deployment

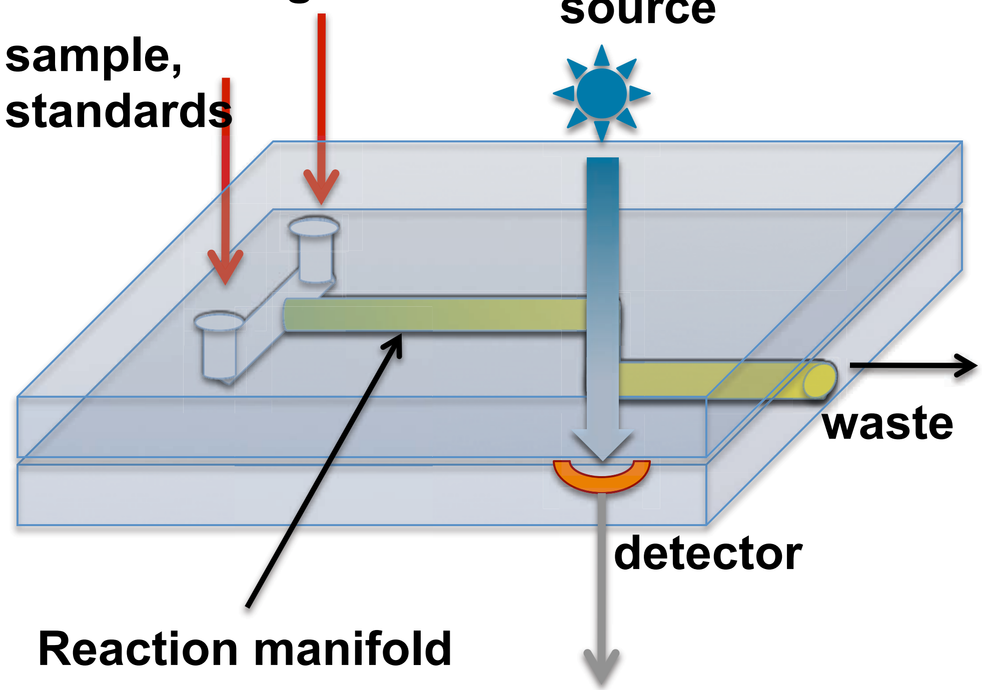
Direct Sensing vs. Reagent Based LOAC/ufluidics

Direct Sensing



LOAC Analyser





Phosphate: The Yellow Method

Mixture (Reagent)

$(NH_4VO_3) + (NH_4)_6Mo_7O_{24}.4H_2O$, HCl conc.

+

Sample

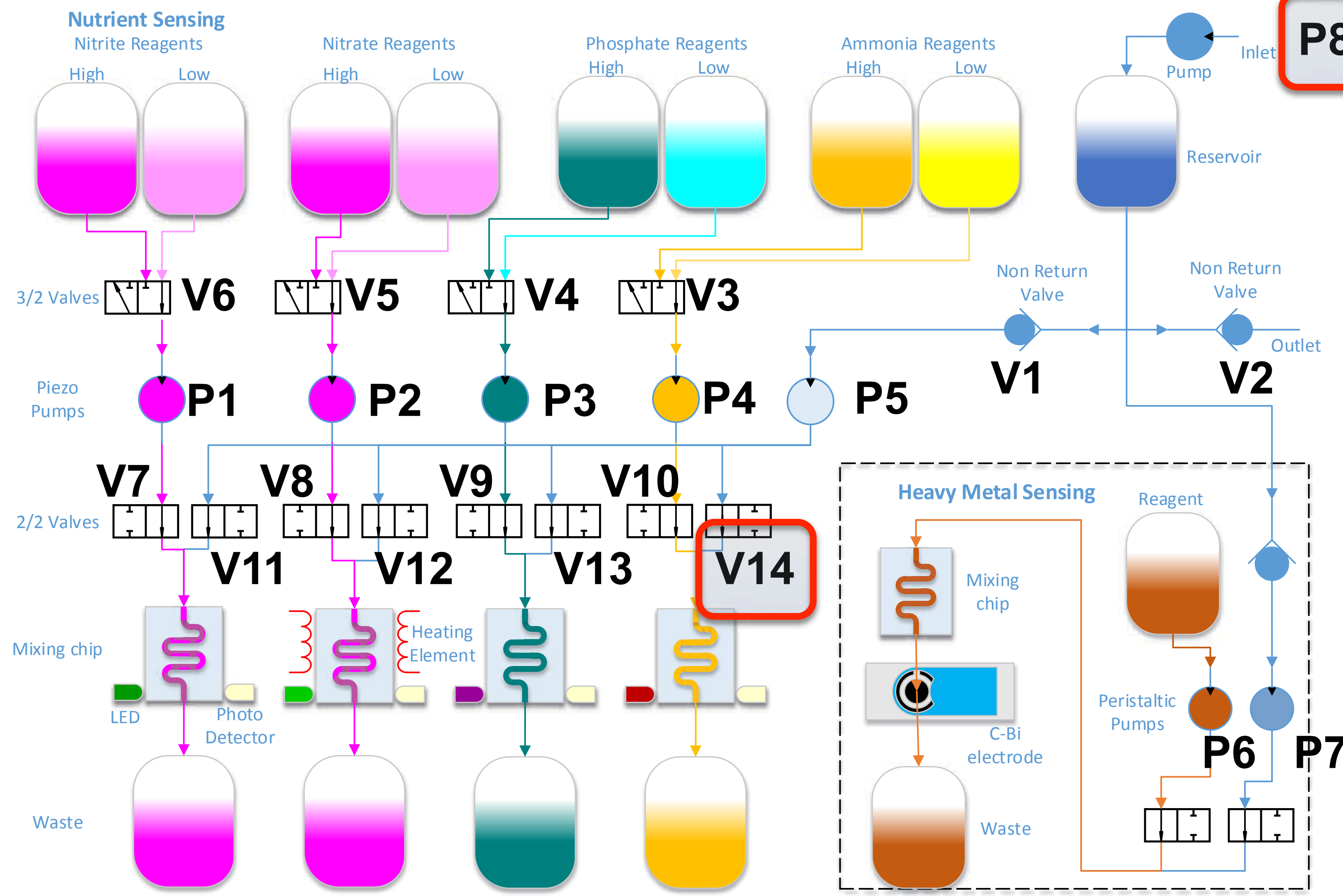
(KH_2PO_4)

$$(NH_4)_3PO_4.NH_4VO_3.16MoO_3$$

- yellow vanaomolybdophosphoric acid is formed when ammonium metavanadate and ammonium molybdate (mixture) reacts with phosphate (acidic conditions)
- In conventional (molybdate) method, ascorbic acid is used to generate the well-known deep blue complex (v. fine precipitate)
- Could not be exploited in LOAC devices until UV-LEDs became available!!!!

Microfluidics – Problem Solved?

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

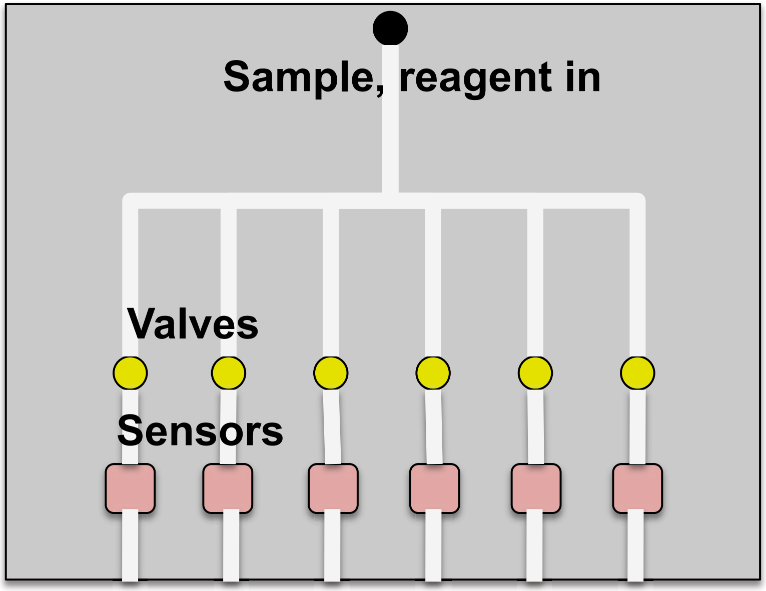


Chem/Bio-sensors do not stay in calibration long enough

- **Reusable - Incorporate regular calibration**
  - Fluidics, reagents, pumps, valves

OR…..single use

- **use arrays of sensors**
  - Must be very stable **in storage** (up to several years)

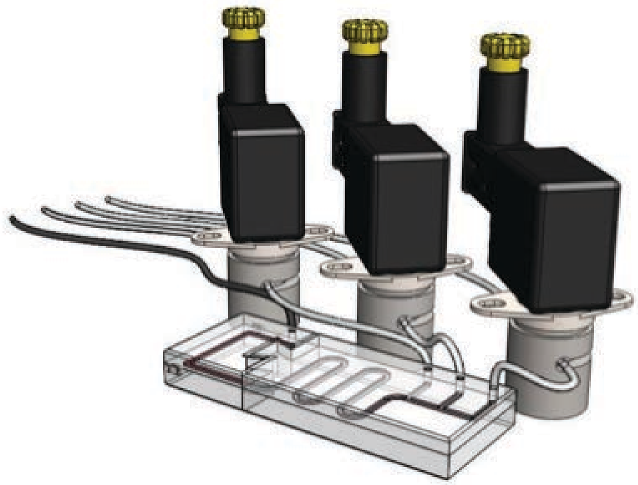


Then 100 short-life (1-day) sensors used sequentially could provide an aggregated use model of ~3 months

But now we need multiple valves integrated into a fluidic platform to select each sensor in turn

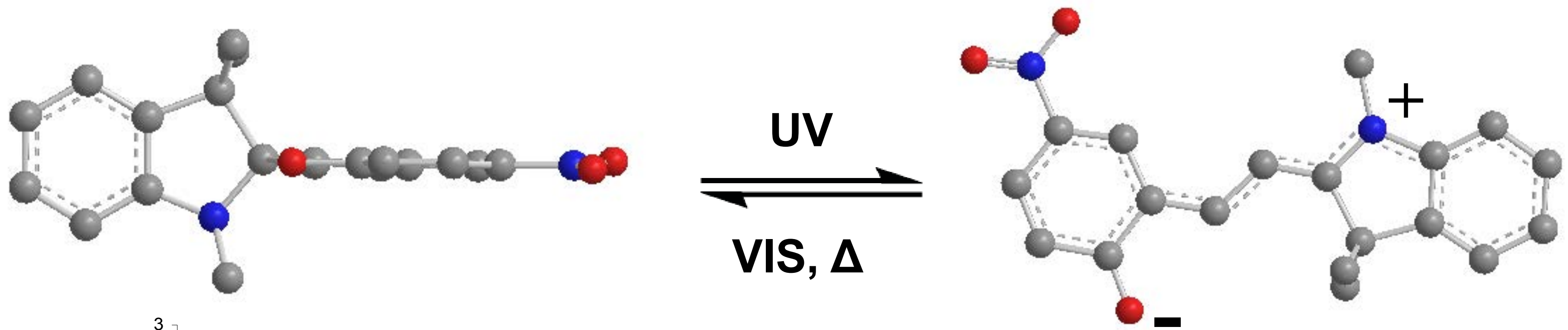
How to advance fluid handling in LOC platforms: re-invent valves (and pumps)!

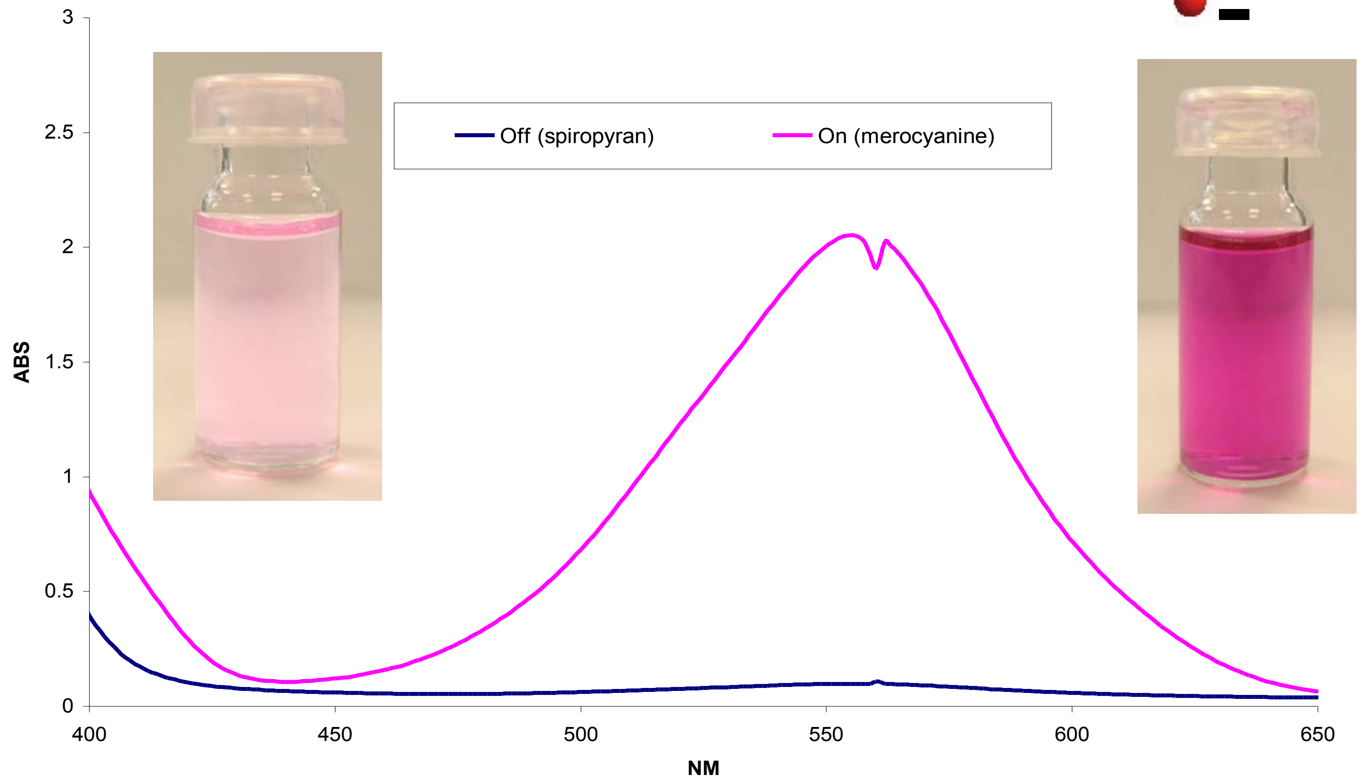
- **Conventional valves cannot be easily scaled down - Located off chip: fluidic interconnects required**
  - Complex fabrication
  - Increased dead volume
  - Mixing effects
- **Based on solenoid action**
  - Large power demand
  - Expensive



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

Photoswitchable Soft Actuators

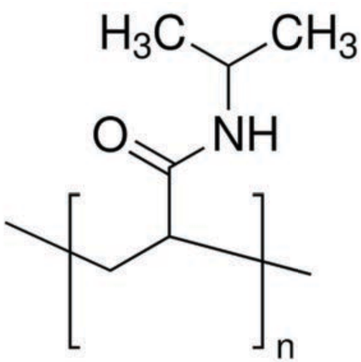




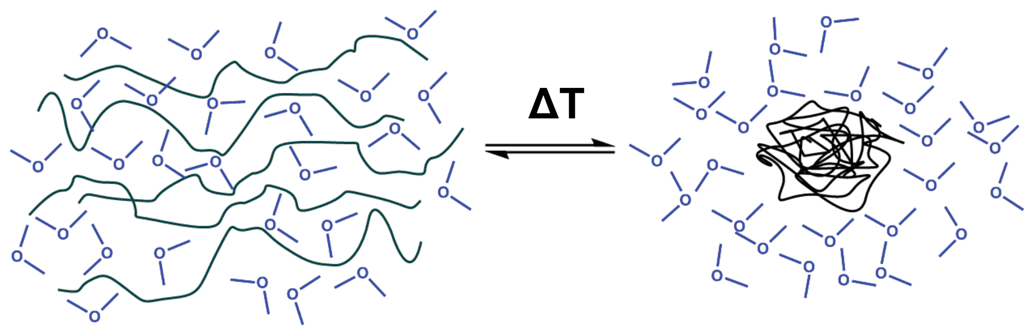
Poly(*N*-isopropylacrylamide)

- pNIPAAM exhibits inverse solubility upon heating
- This is referred to as the LCST (Lower Critical Solution Temperature)
- Typically this temperature lies between 30-35^{o}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



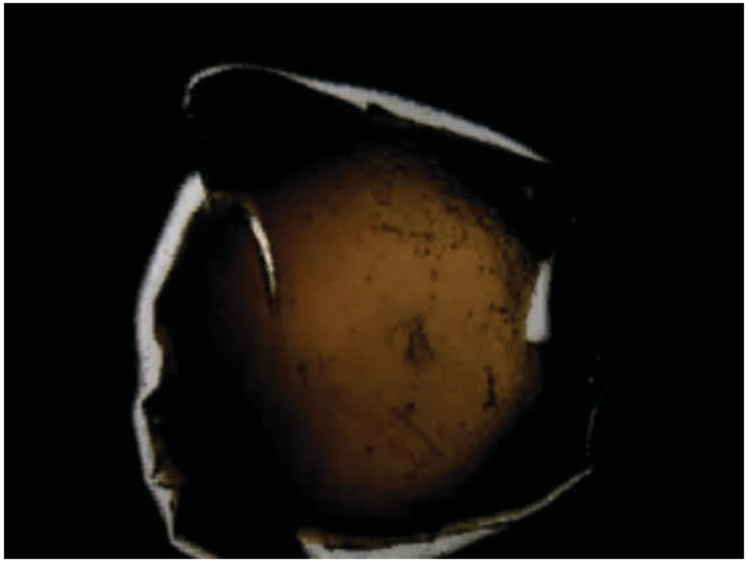
Hydrophilic **Hydrophobic**

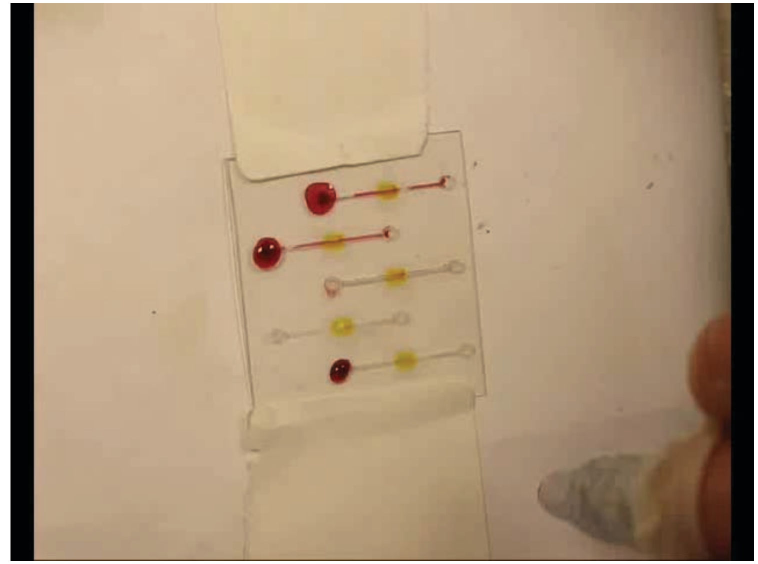


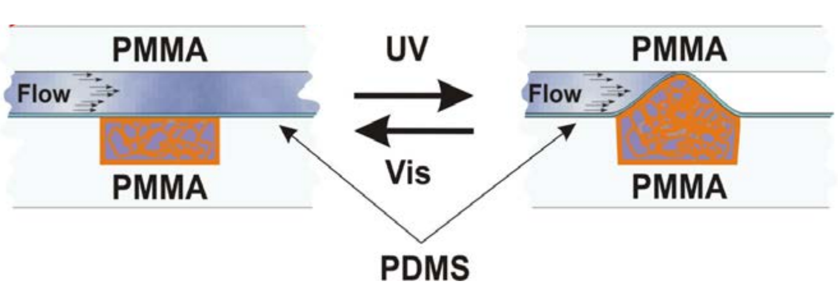
Hydrated Polymer Chains

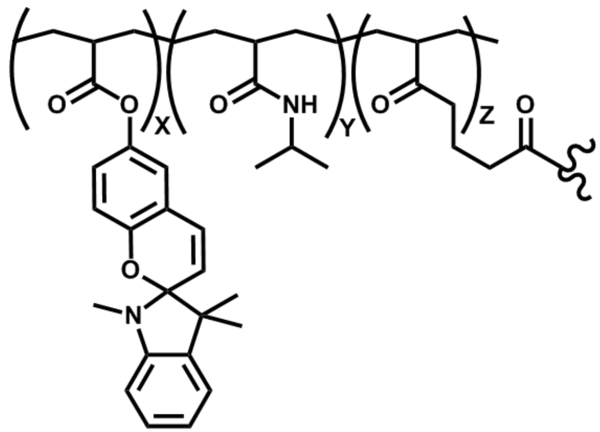
Loss of bound water -> polymer collapse

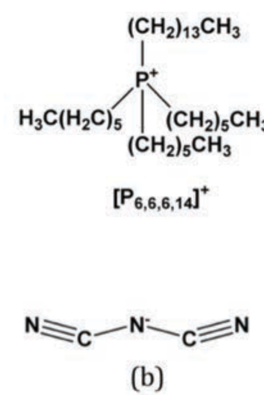
Photo-actuator polymers as microvalves in microfluidic systems









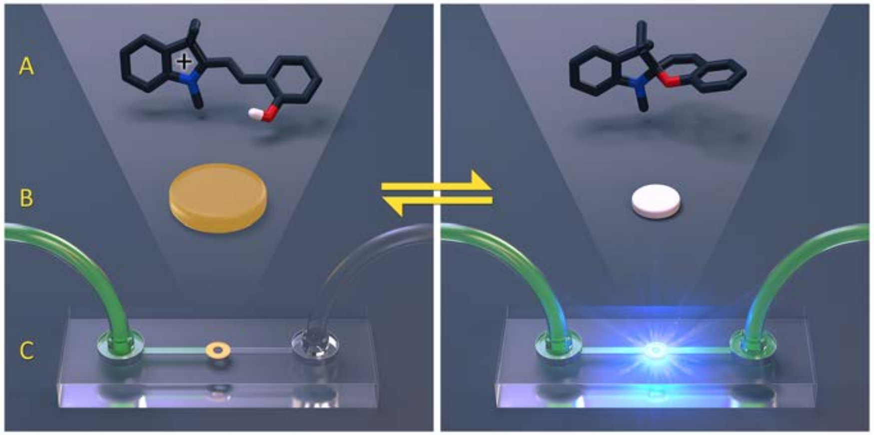


trihexyltetradecylphosphonium dicyanoamide $[P_{6,6,6,14}]^+[dca]^-$

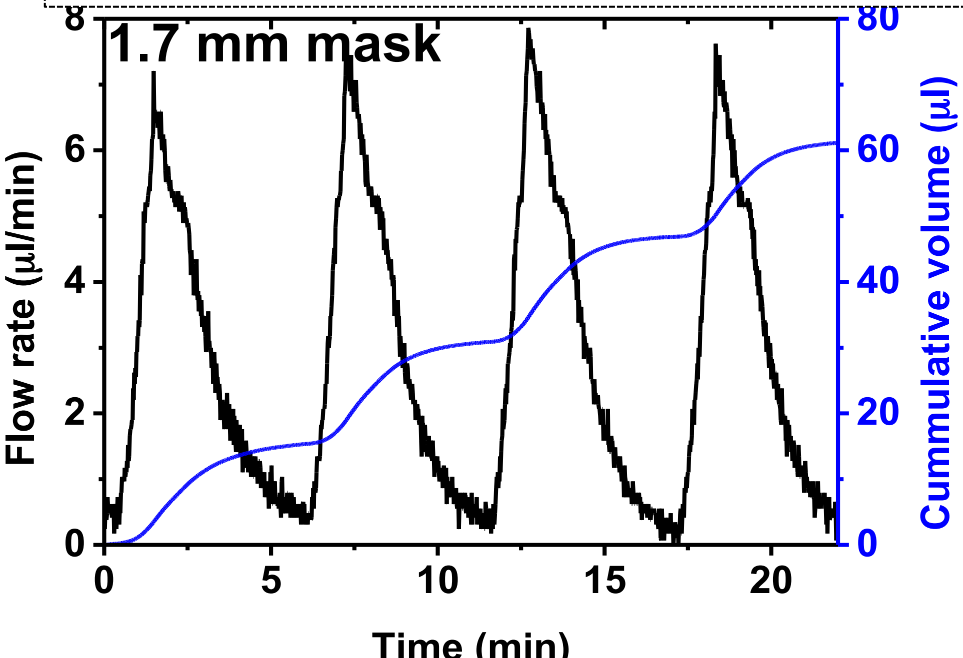
Ionogel-based light-actuated valves for controlling liquid flow in micro-fluidic manifolds, Fernando Benito-Lopez, Robert Byrne, Ana Maria Raduta, Nihal Engin Vrana, Garrett McGuinness, Dermot Diamond, Lab Chip, 10 (2010) 195-201.

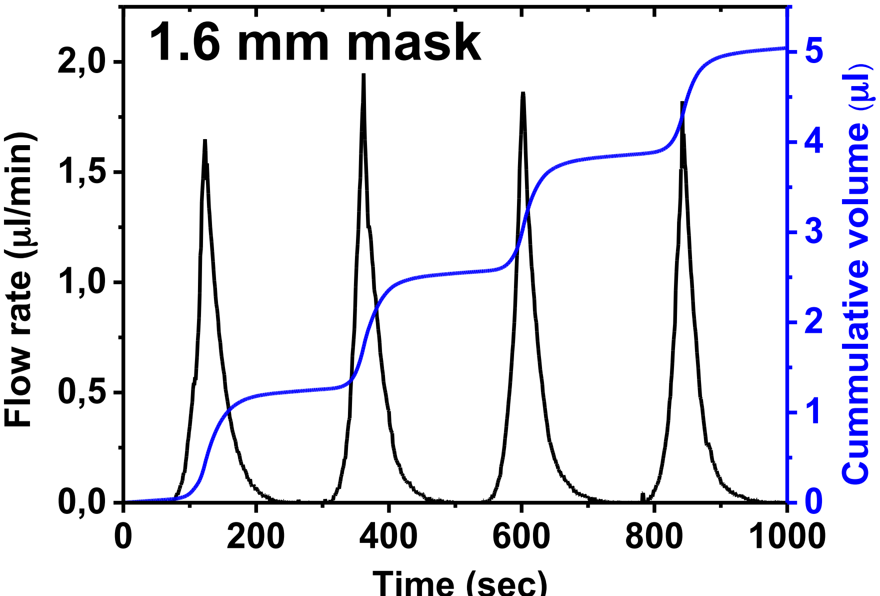
Valve Optimisation

First example of actuating polymer gels as reusable valves for flow control on minute time scales
(> 50 repeat actuations)



From '*Molecular Design of Light-Responsive Hydrogels, For in Situ Generation of Fast and Reversible Valves for Microfluidic Applications*', J. ter Schiphorst, S. Coleman, J.E. Stumpel, A. Ben Azouz, D. Diamond and A. P. H. J. Schenning, Chem. Mater., 27 (2015) 5925−5931. **(cover article)**





Experimental set up for PID Control

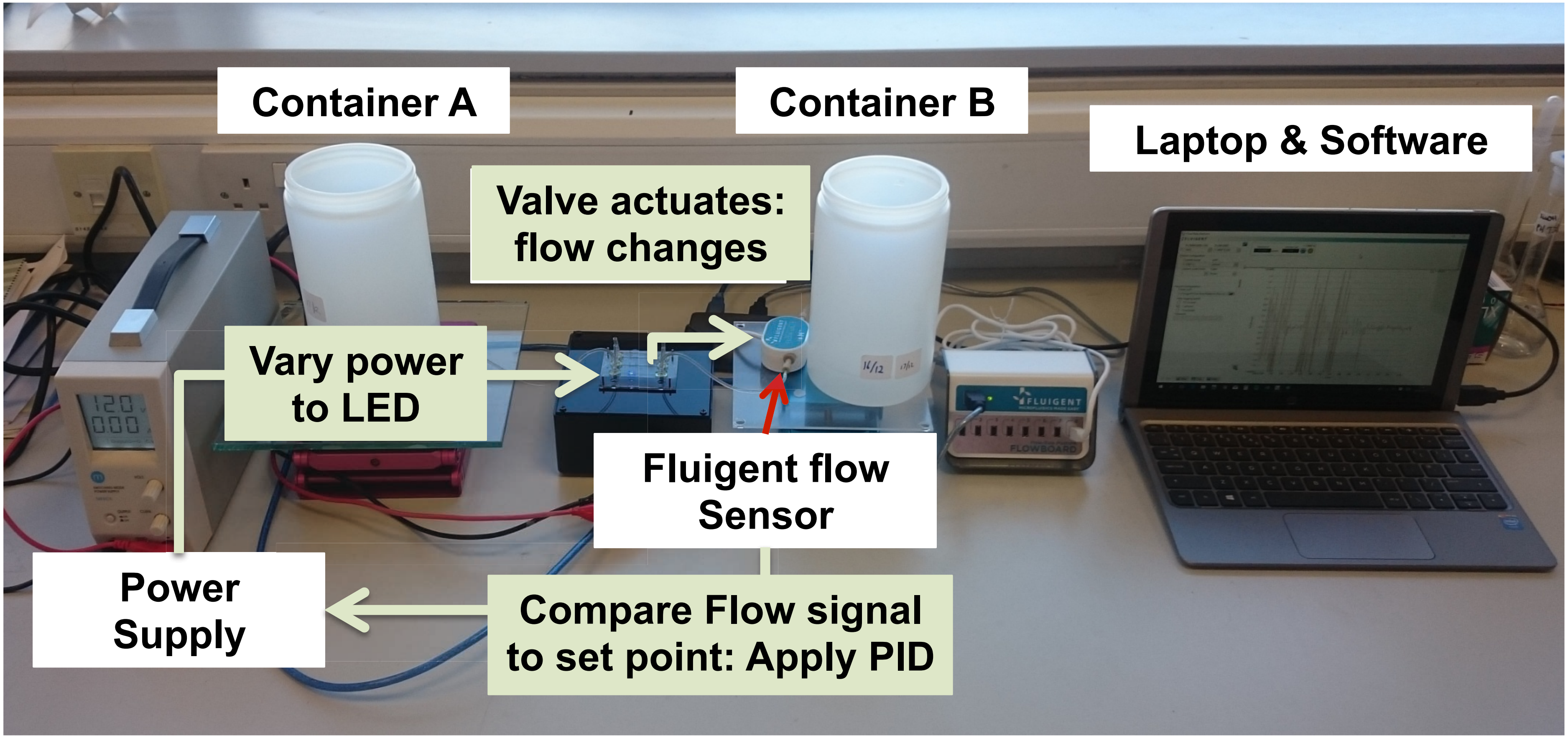
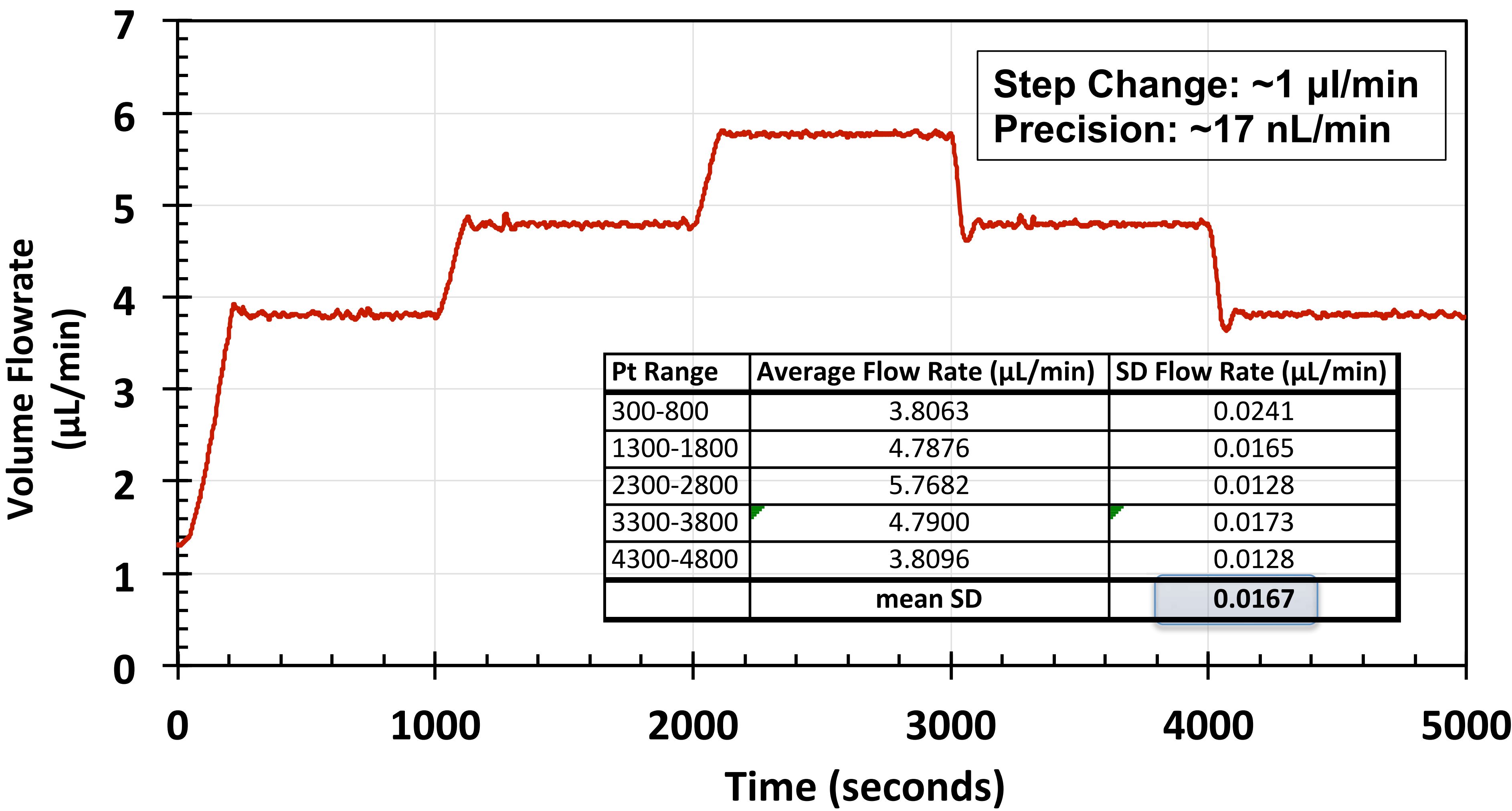


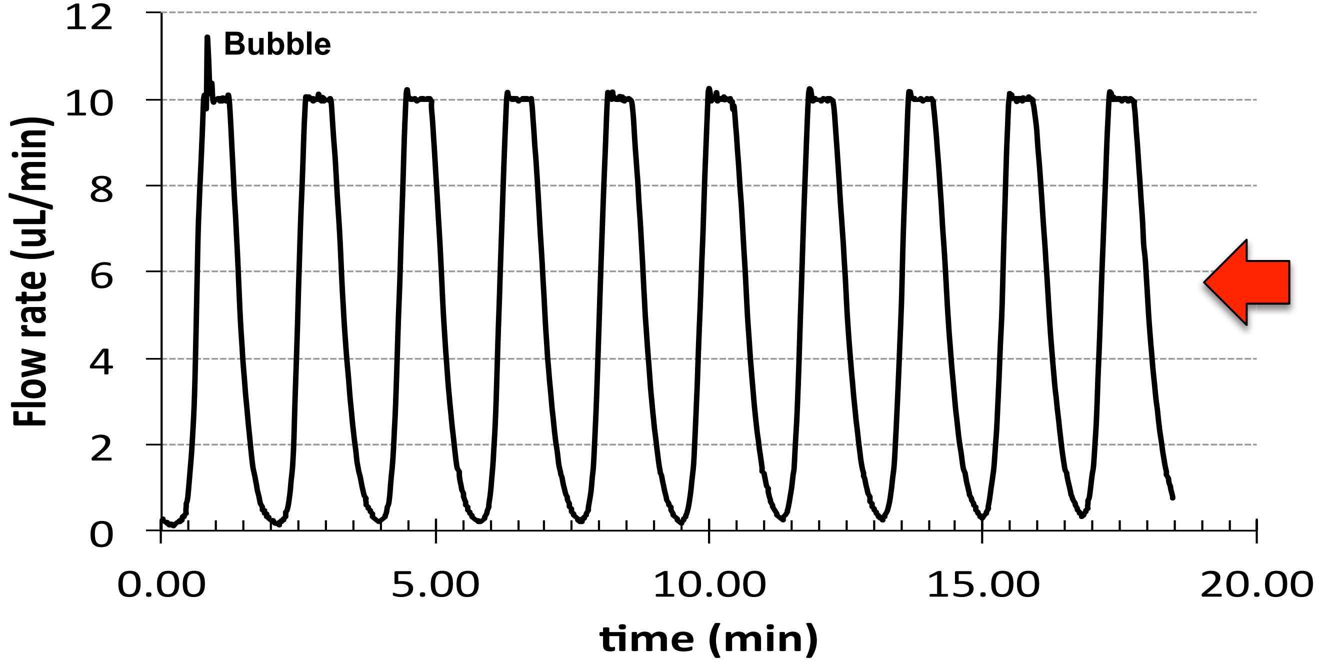
Photo-Controlled Flow Rate



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.J. Kent, D. Diamond, Precision Control of Flow Rate in Microfluidic Channels Using Photoresponsive Soft Polymer Actuators, Lab Chip. (2017). doi:10.1039/C7LC00368D.

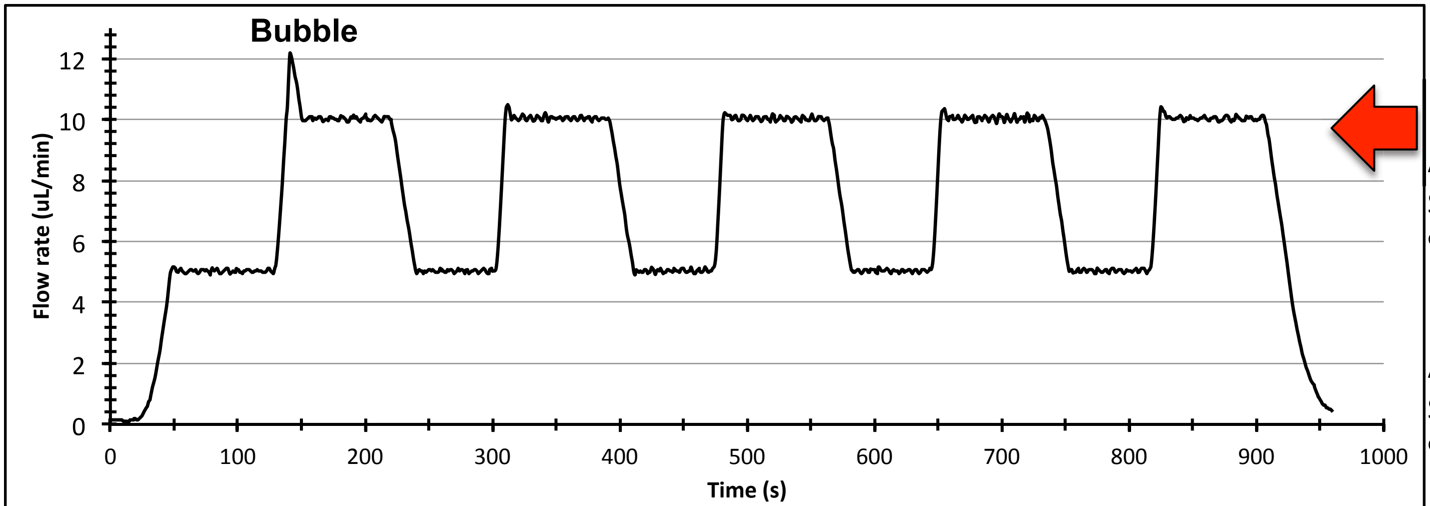
Some figures of merit



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

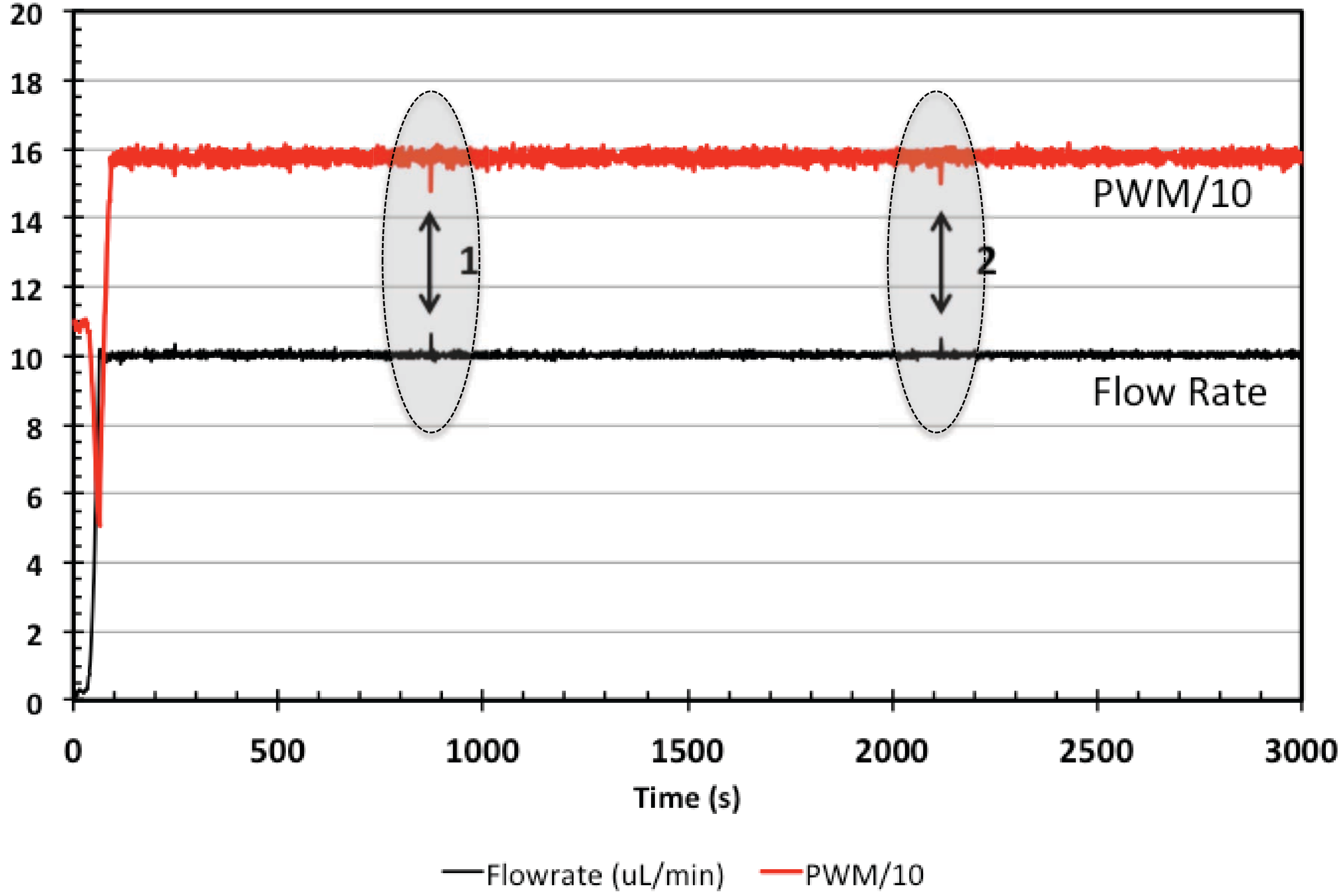


Switching 5.0-10.0 µL/min
n= 30 points sampled

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

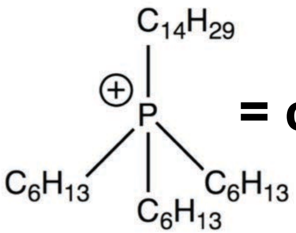
sfi DCU UCC OÉ Gaillimh NUI Galway UCD DUBLIN

Power Supply to LED

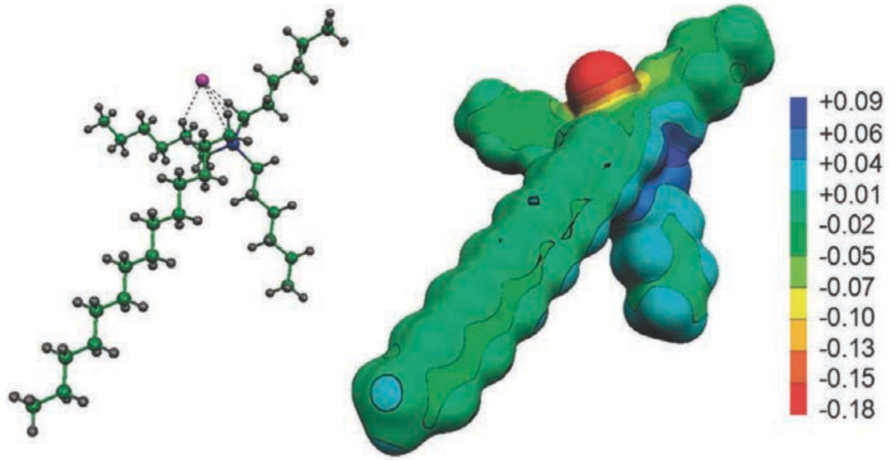


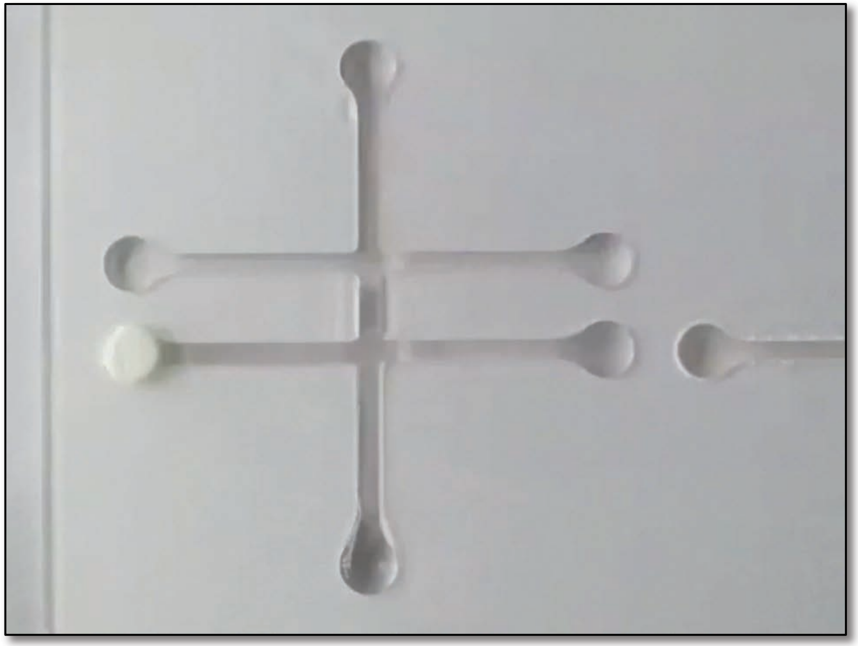
Over a period of 50 min constant maintenance of 10 µL/min flow rate there is no discernable change in LED power ➔ diagnostic information

We can do the same with IL Droplets



= cationic surfactant





Trihexyl(tetradecyl)phosphonium chloride ($[P_{6,6,6,14}][Cl]$) 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 nitrobenzospiropyran in phosphonium-based ionic liquids, D. Thompson et al., *Physical Chemistry Chemical Physics*, 2011, 13, 6156-6168.

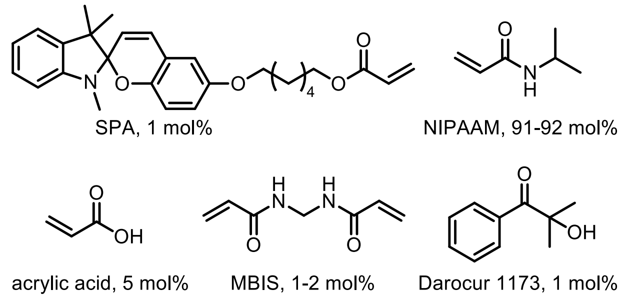
Photocontrol of Assembly and Subsequent Switching of Surface Features

ACS APPLIED MATERIALS & INTERFACES
Research Article
www.acsami.org

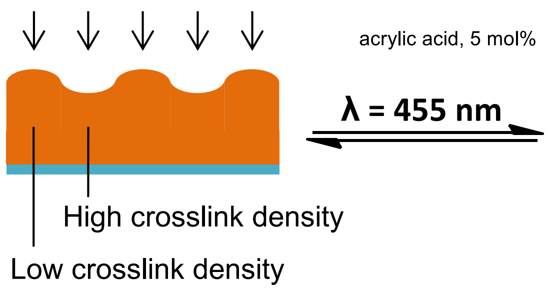
ACS applied materials & interfaces, 6 (2014) 7268-7274

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

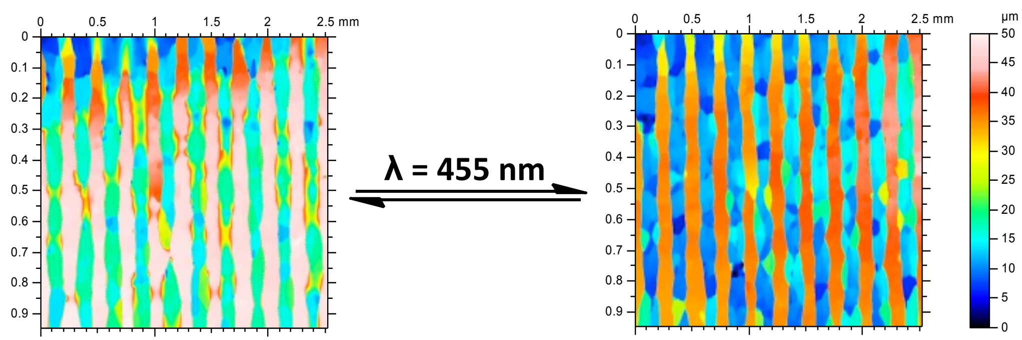
Jelle E. Stumpel,[†] Bartosz Ziółkowski,[‡] Larisa Florea,[‡] Dermot Diamond,[‡] Dirk J. Broer,[*,†,§] and Albertus P. H. J. Schenning[*,†,§]

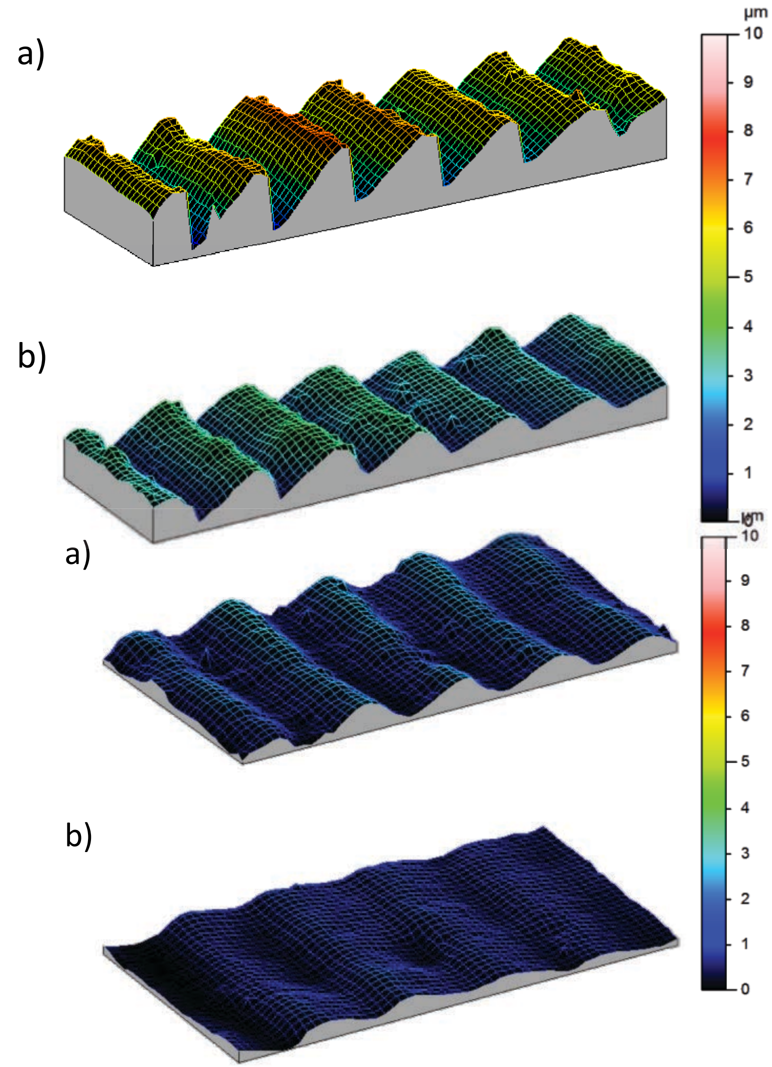


a)



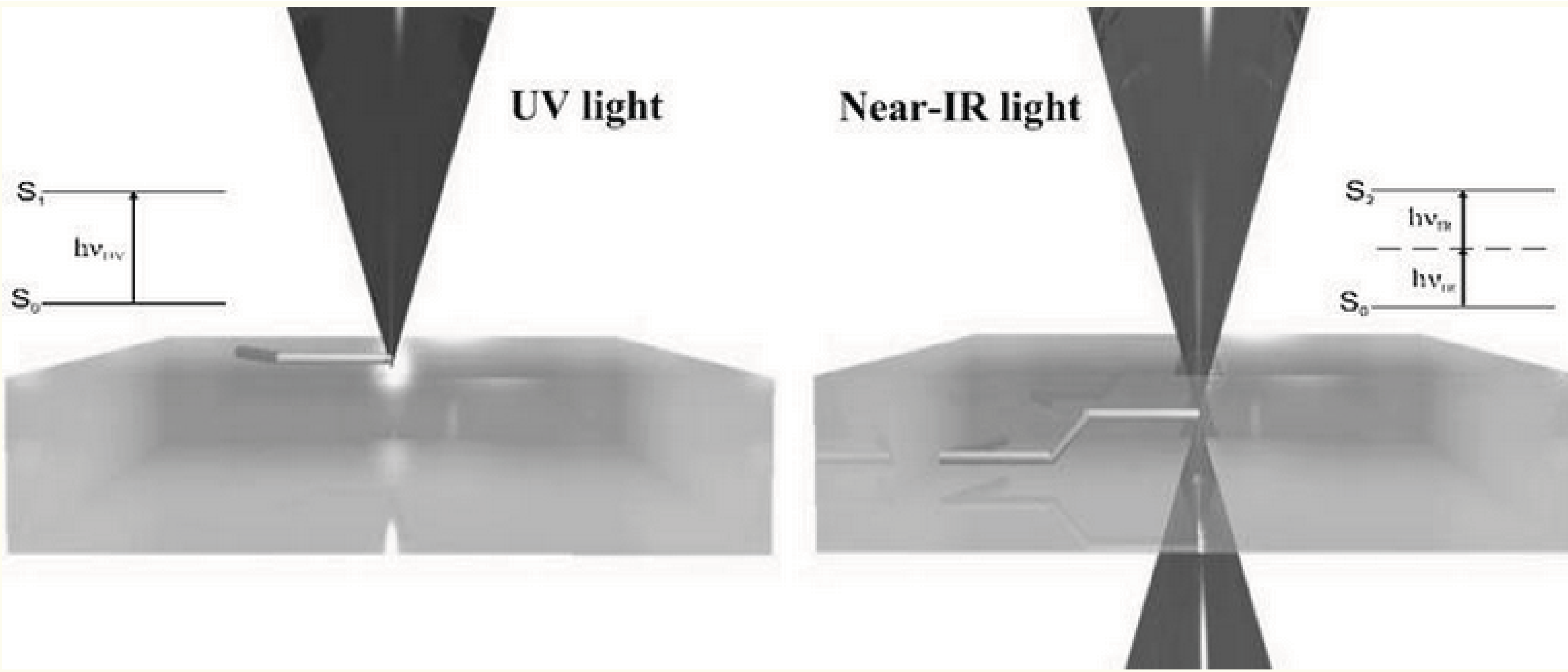
b)





Background

Stereolithography | **Two-photon polymerisation**



- Single photon absorption
- 2D patterns

- Two photon absorption
- 3D structures

Merging of Materials, Devices and Data

Data and Information; IOT

Outside: On-Body

- Smart Bandages
- Sensorised Contact Lens
- platforms patches/watches
- Sensorised Splints/ dentures
- Smart Textiles/ Clothing

Inside: Implants/In-vivo

- Smart Stents
- Self-Aware Transplant
- Platforms and Implants
- Post-Operative IC (days)
- Medium term Convalescence (weeks)

Devices and Platforms

MATERIALS

Physics Chemistry Biology Engineering (photonics, electronics, fluidics, 4D materials)

Thanks to…..

- NCSR, DCU
- Science Foundation Ireland & INSIGHT Centre
- Enterprise Ireland
- Research Partners – academic and industry
- EU Projects: NAPES, CommonSense, Aquawarn, MASK-IRSES, OrgBio

MASK
Project no: 269302
Materials and Advanced Sensor Knowledge Exchange