Biomimetic Microfluidics based on Stimuli-Responsive Soft Polymers

Dermot Diamond*, Aishling Dunne, Danielle Bruen, Colm Delaney, Peter McCluskey, Gareth Lacour, Andrew Donoghue, Ruairi Barrett, Margaret McCaul and Larisa Florea

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

Invited Lecture presented at

CIMTEC 2018 Session FL-4

'Biomedical Devices with Biological and Bioinspired Materials'

Perugia, Italy, June 14, 2018.

Fundamental Challenge: (4d!)

Can we deliver platforms (nano to macro scale) with advanced functionalities capable of long-term (months, years) autonomous operation in remote (hostile) environments (implants, environment) at a reasonable cost?

‘Deploy and Forget’ long-term use model

Functions…..

Chem/biosensing, communications, programmed uptake & release, movement, redundancy ‘death’ (biodegrade) and regeneration, self-awareness & self-maintenance…

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.

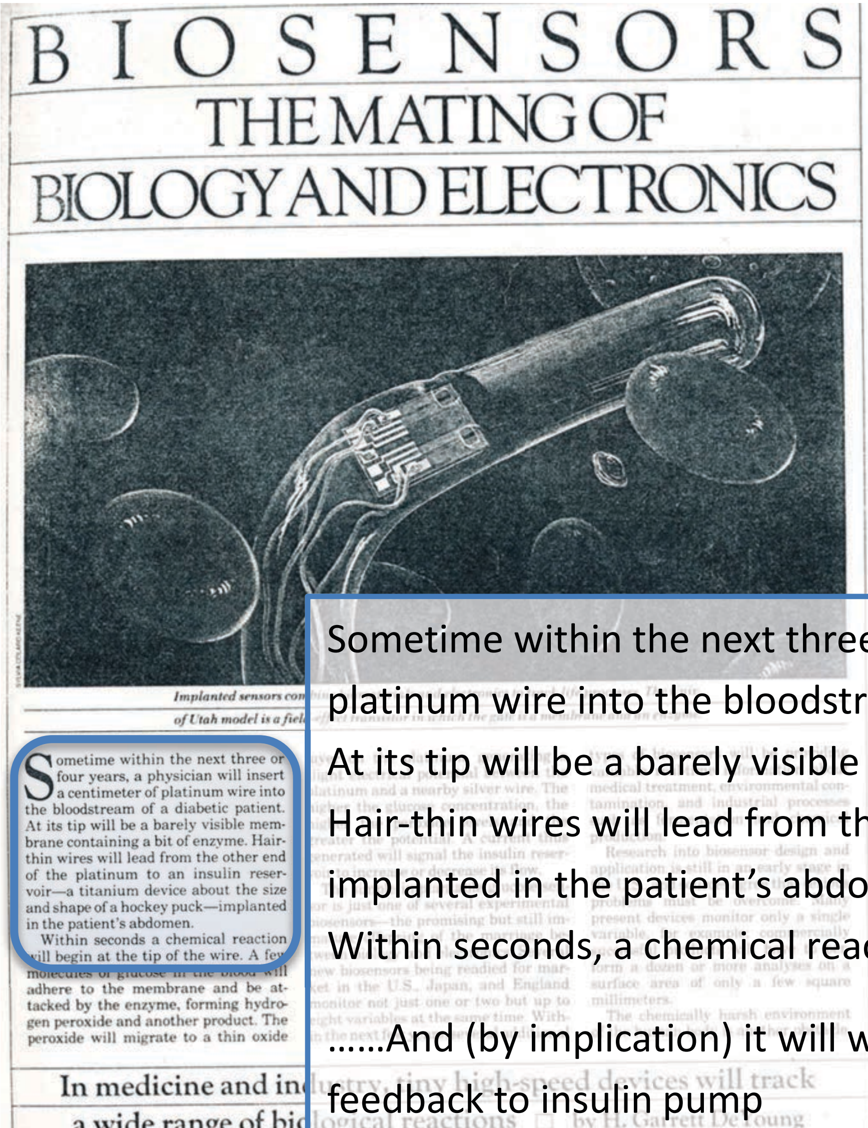
Digital communications networks are at the heart of modern society. The digitization of communications, the development of the Internet, and the availability of relatively inexpensive but powerful mobile computing technologies have established a global communications network capable of linking billions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

The (broken) promise of biosensors…..

High Technology, Nov. 1983, 41-49

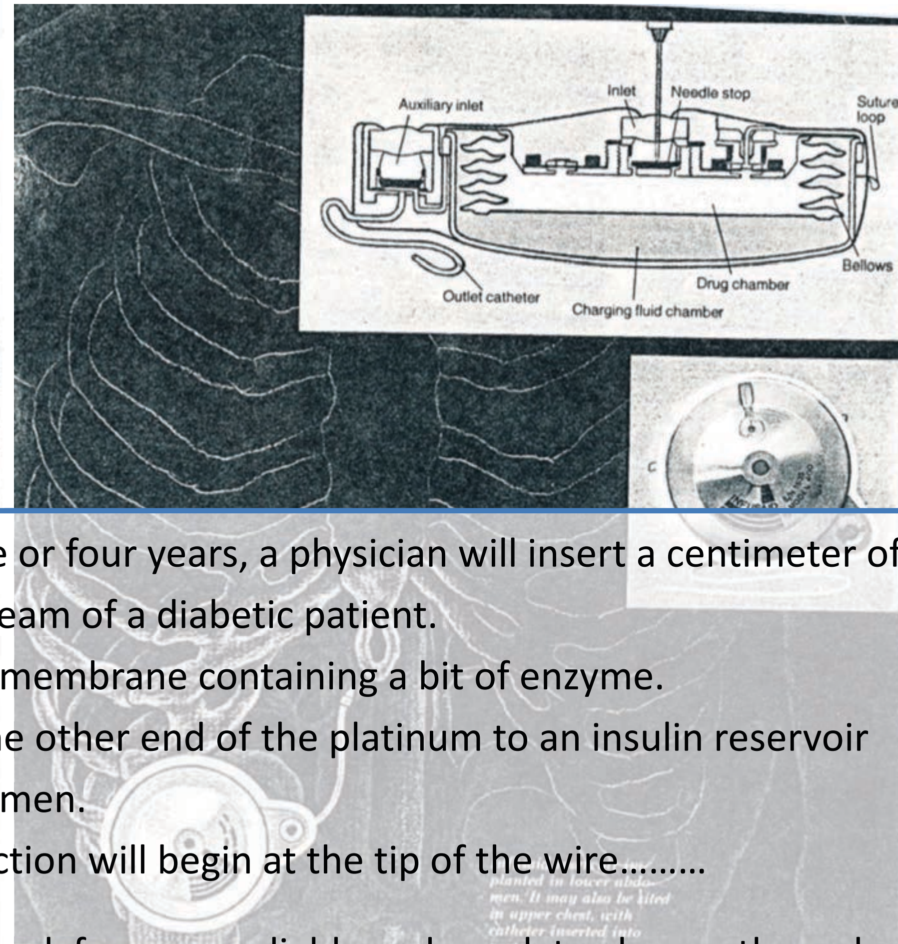

BIOSENSORS

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 □ by H. Garrett DeYoung



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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

Adam Heller

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

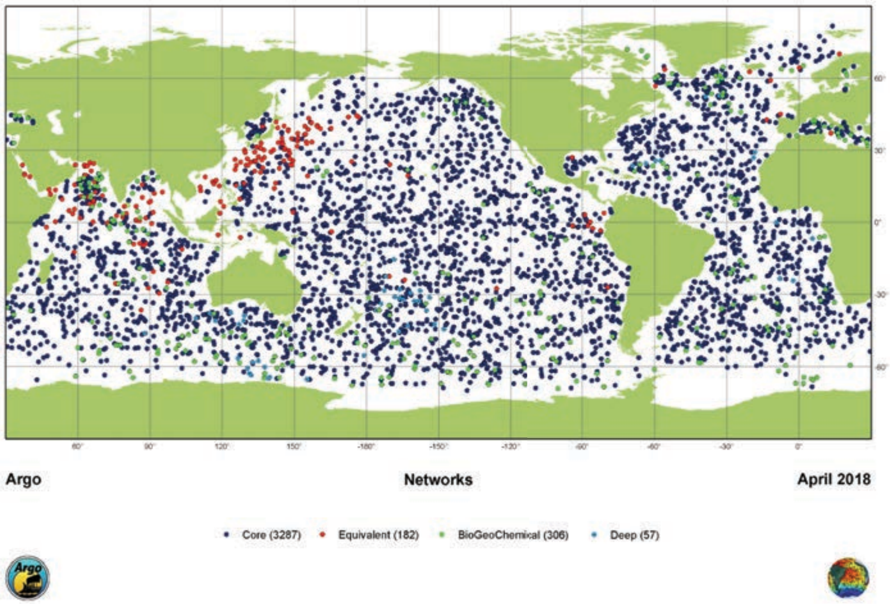
San Francisco Business Times; Tuesday, April 6, 2004

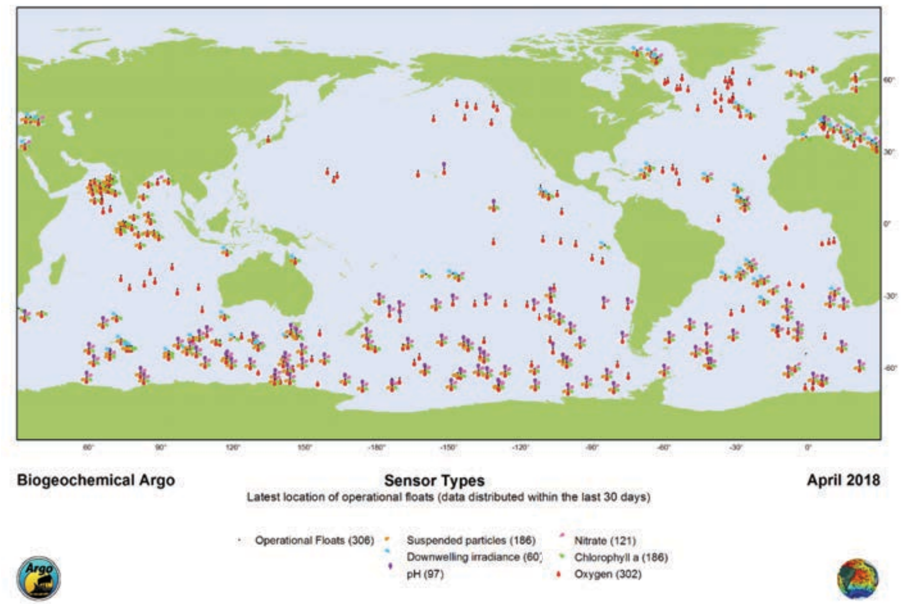
'Abbott completes TheraSense acquisition'

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.

Argo Project (accessed May 2018)





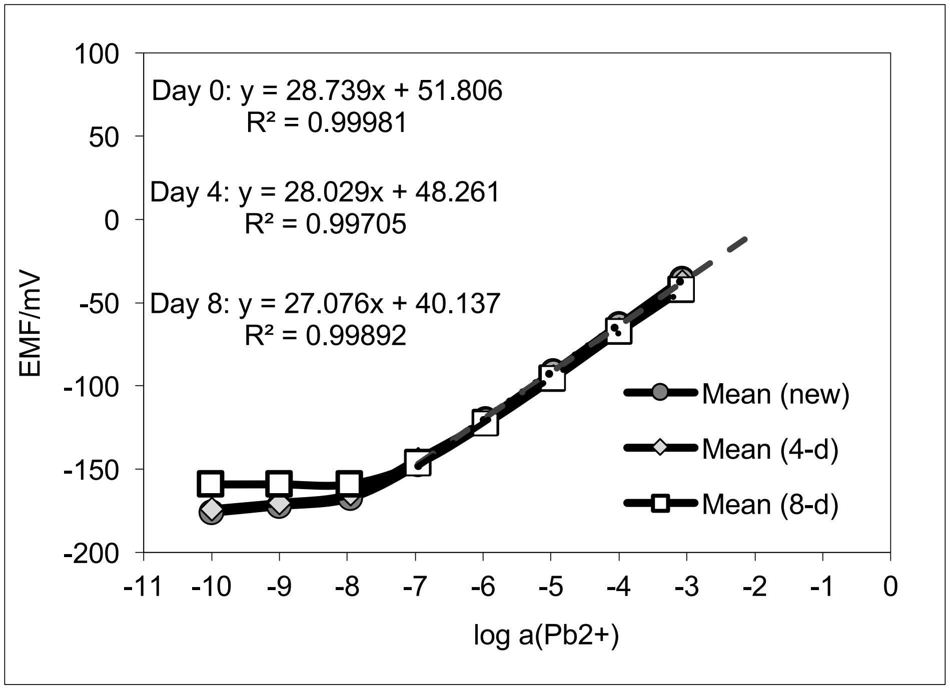
Argo (2000). Argo float data and metadata from Global Data Assembly Centre (Argo GDAC) http://doi.org/10.17882/42182

Core: 3287 (temperature, flow, salinity, depth….)

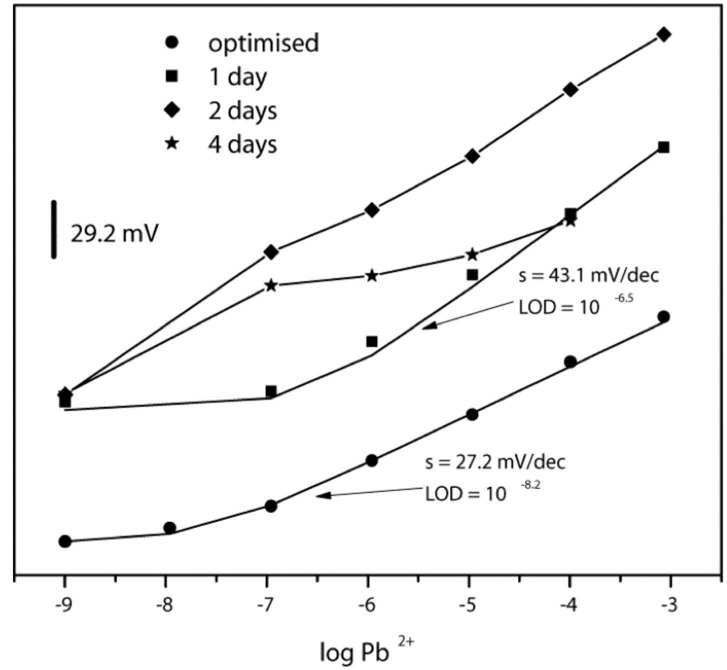
Biochemical:306
Suspended particles: 186; Nitrate: 121; Chlorophyll: 186; pH: 97; DO: 302

Change in Electrode Function over Time

See Electrochimica Acta 73 (2012) 93–97



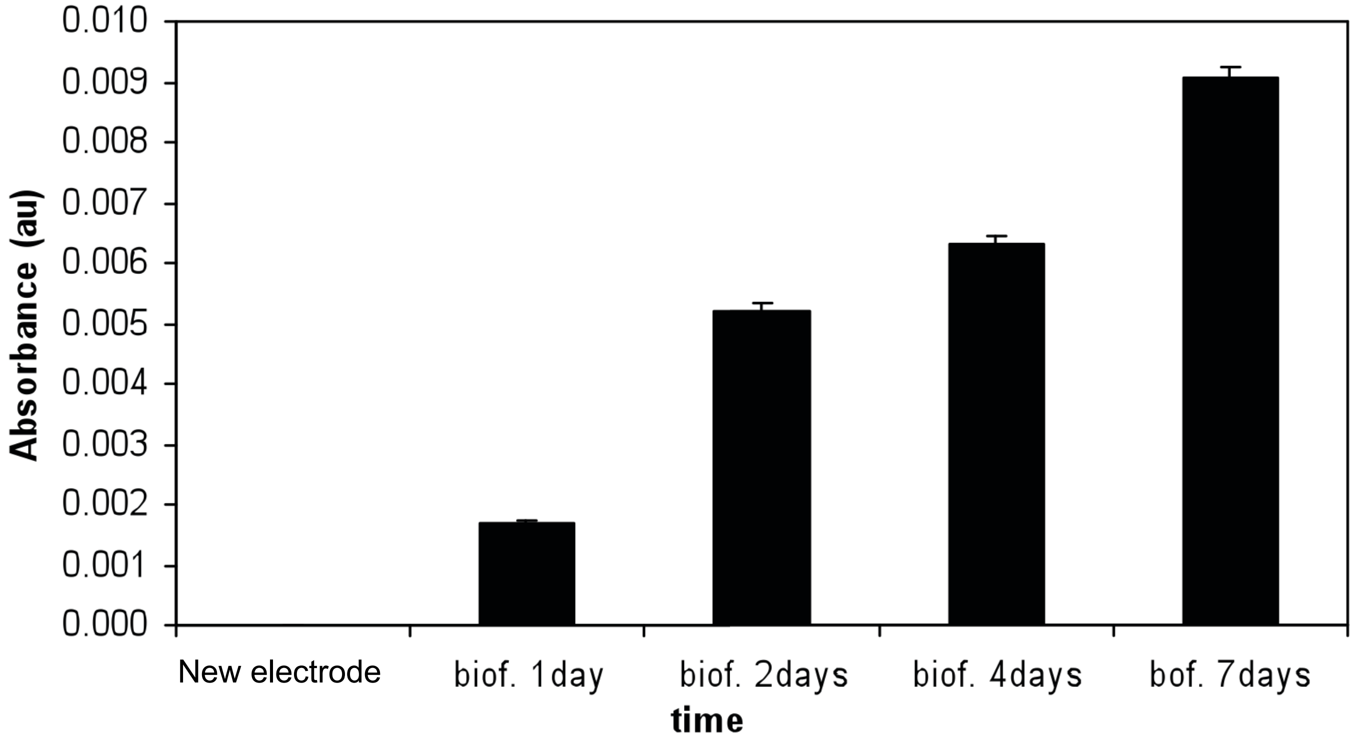
stored in 10^{-9}M Pb^{2+}, pH=4



Continuous contact with river water

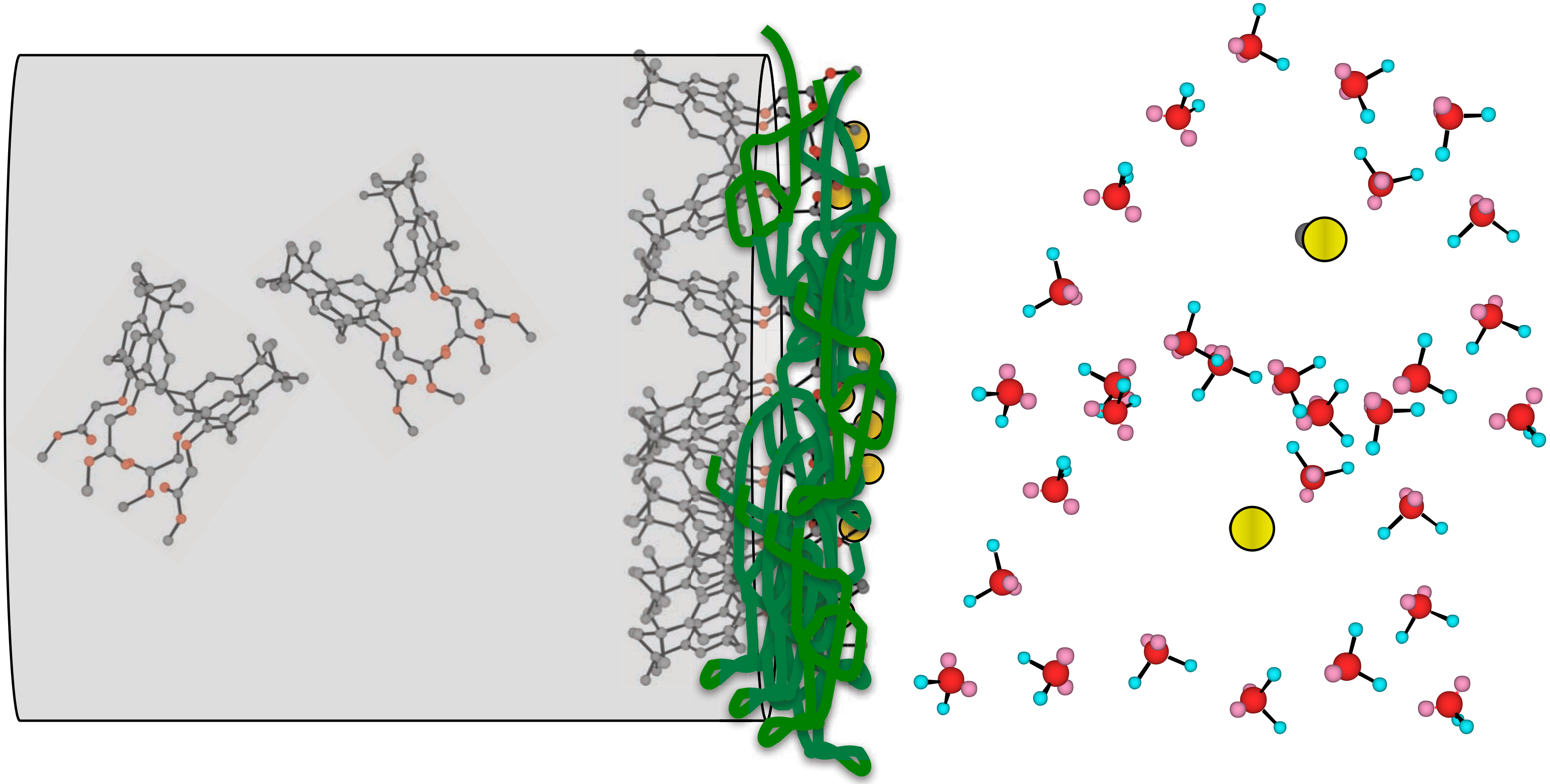
Conventional PVC-membrane based ISEs

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

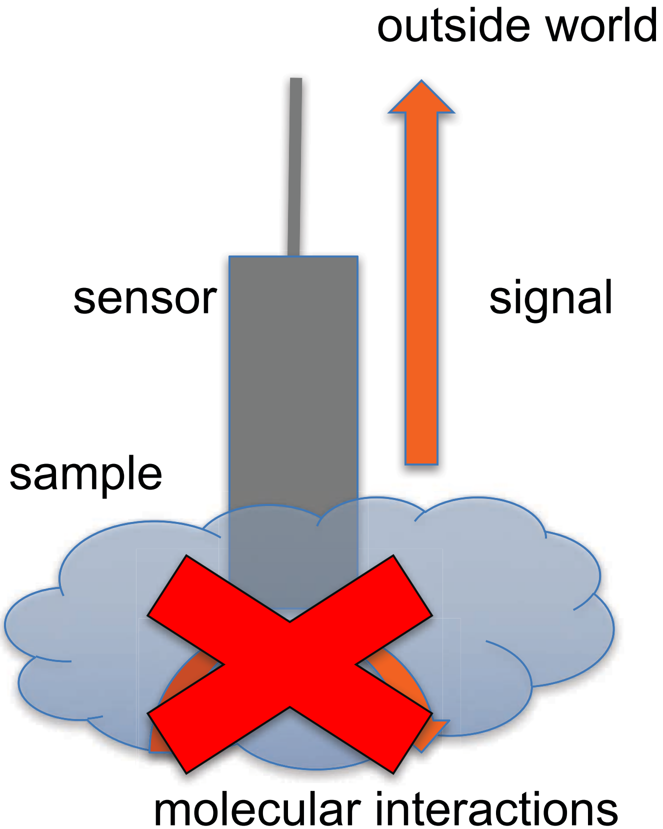


Remote, autonomous chemical sensing is a tricky business!

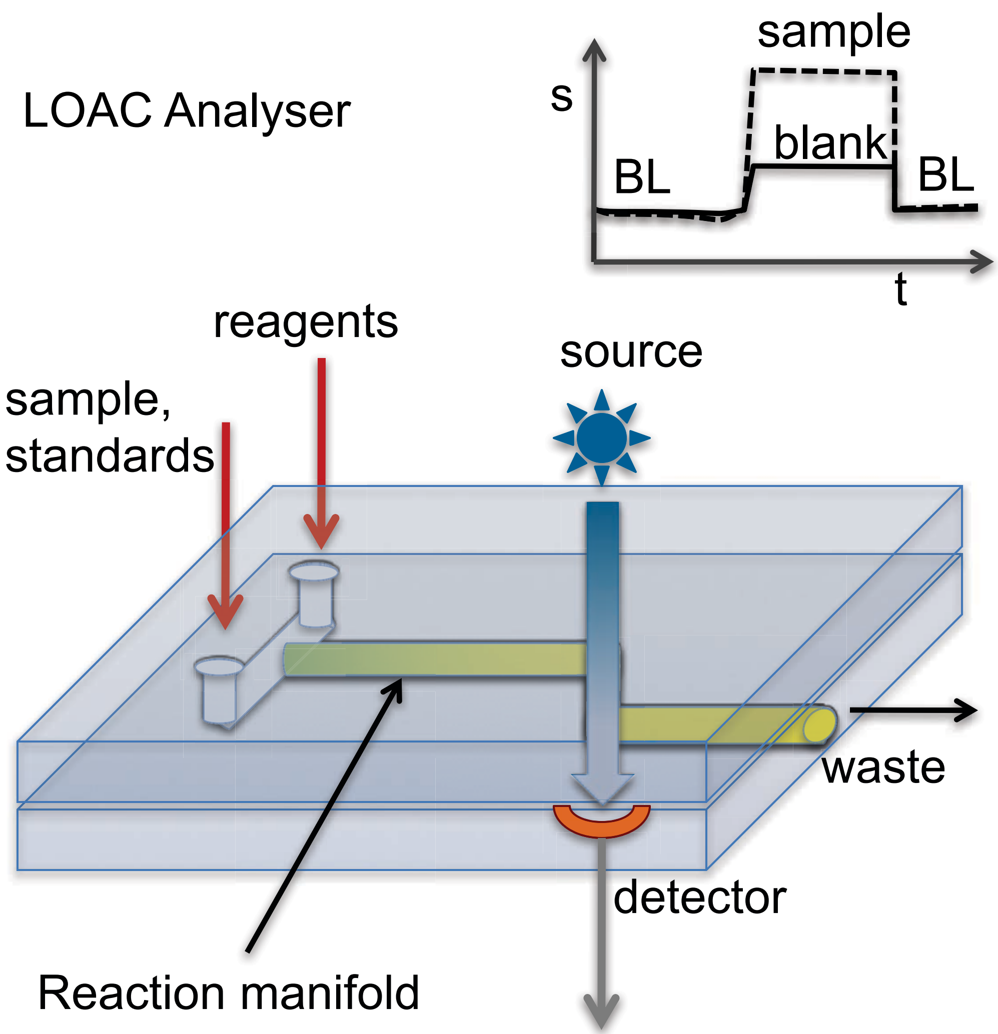
Osberstown – 3 week deployment

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!!!!

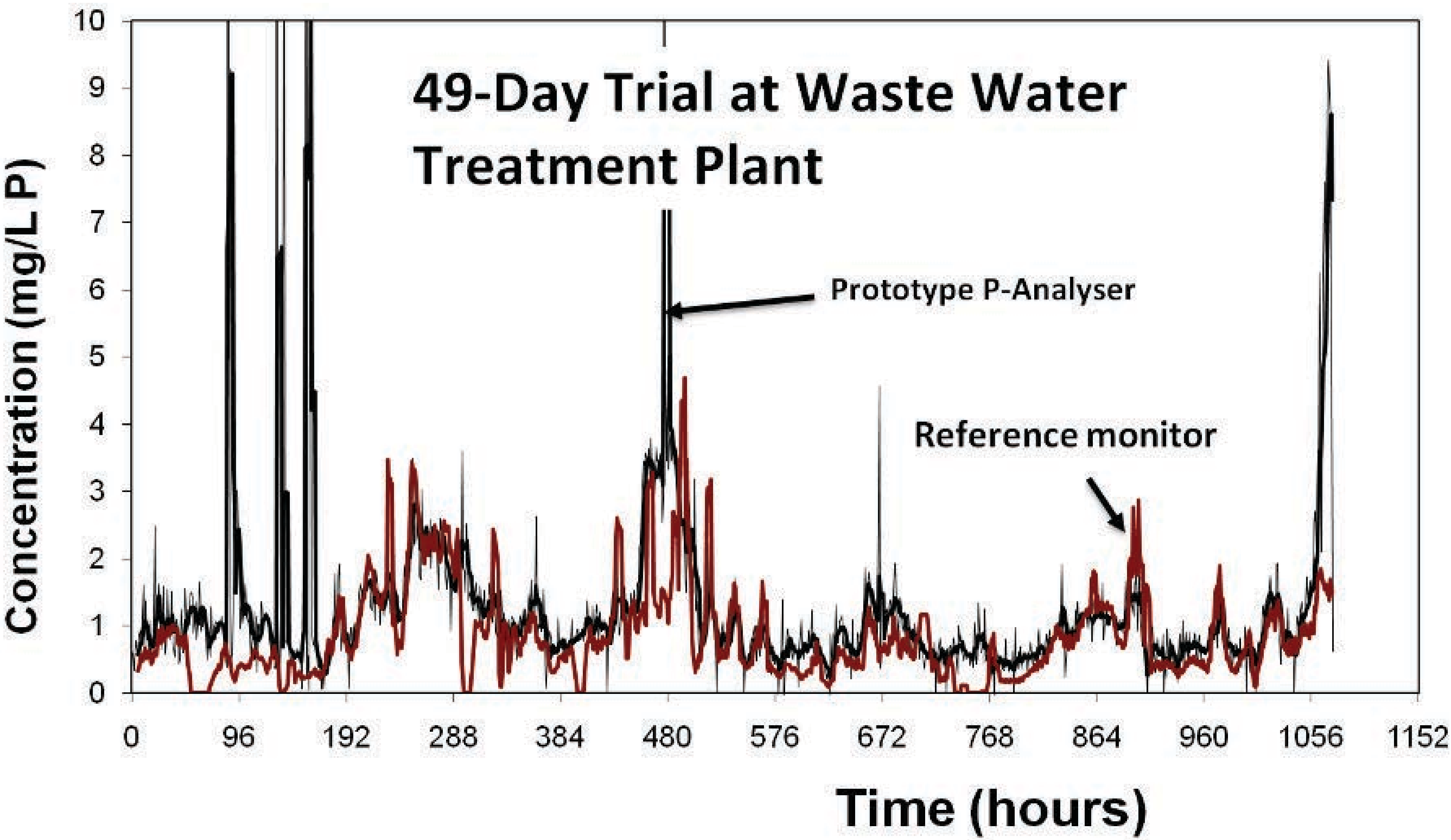
Prototype Testing – Generation 3

Milano San Rocco WWTP

Available Sampling Points:

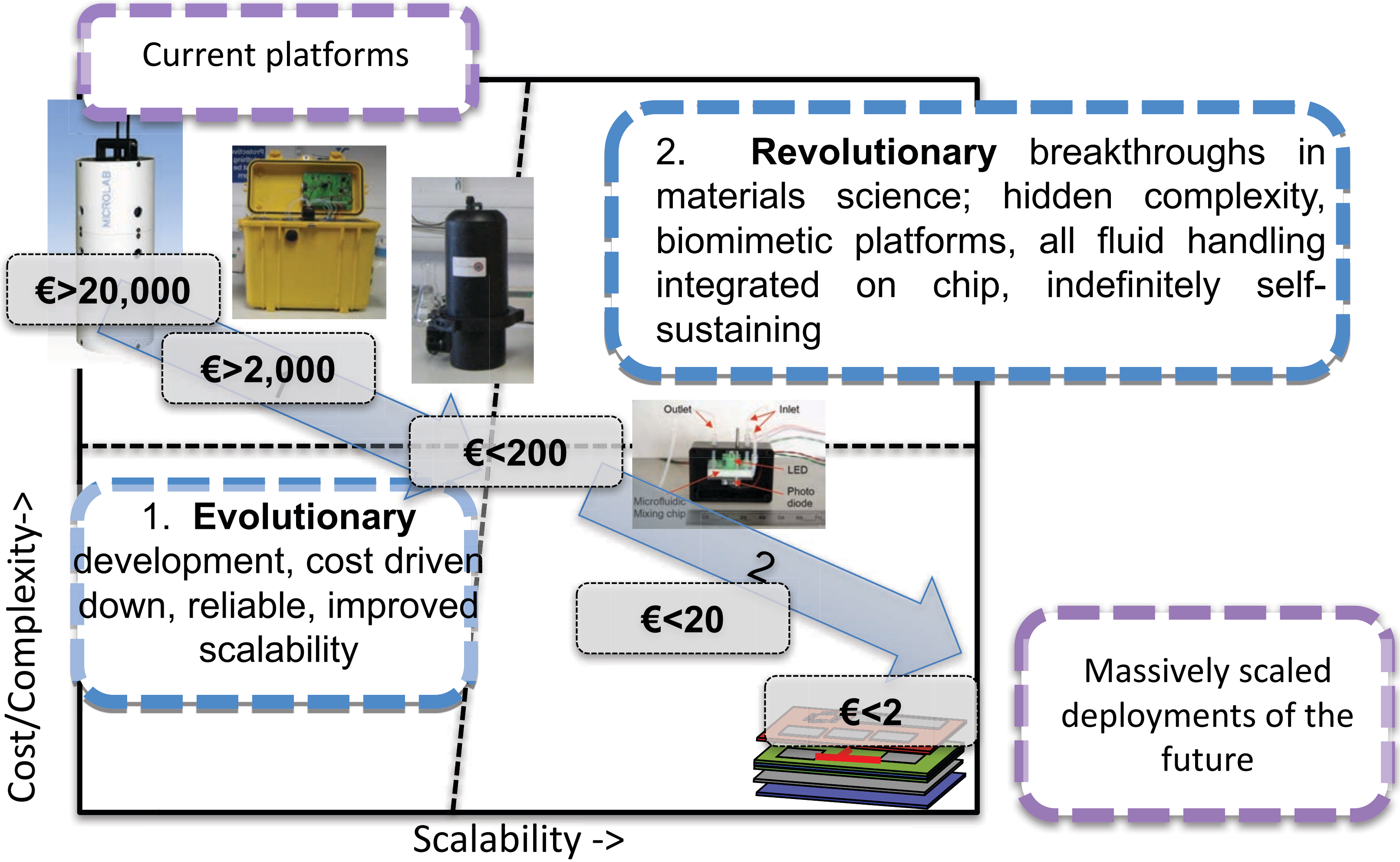
1. Output water after Sand Filtration
2. Output water after the Clarifier
3. Activated Sludge (Biological Tank)
4. Input Water

Autonomous Chemical Analyser



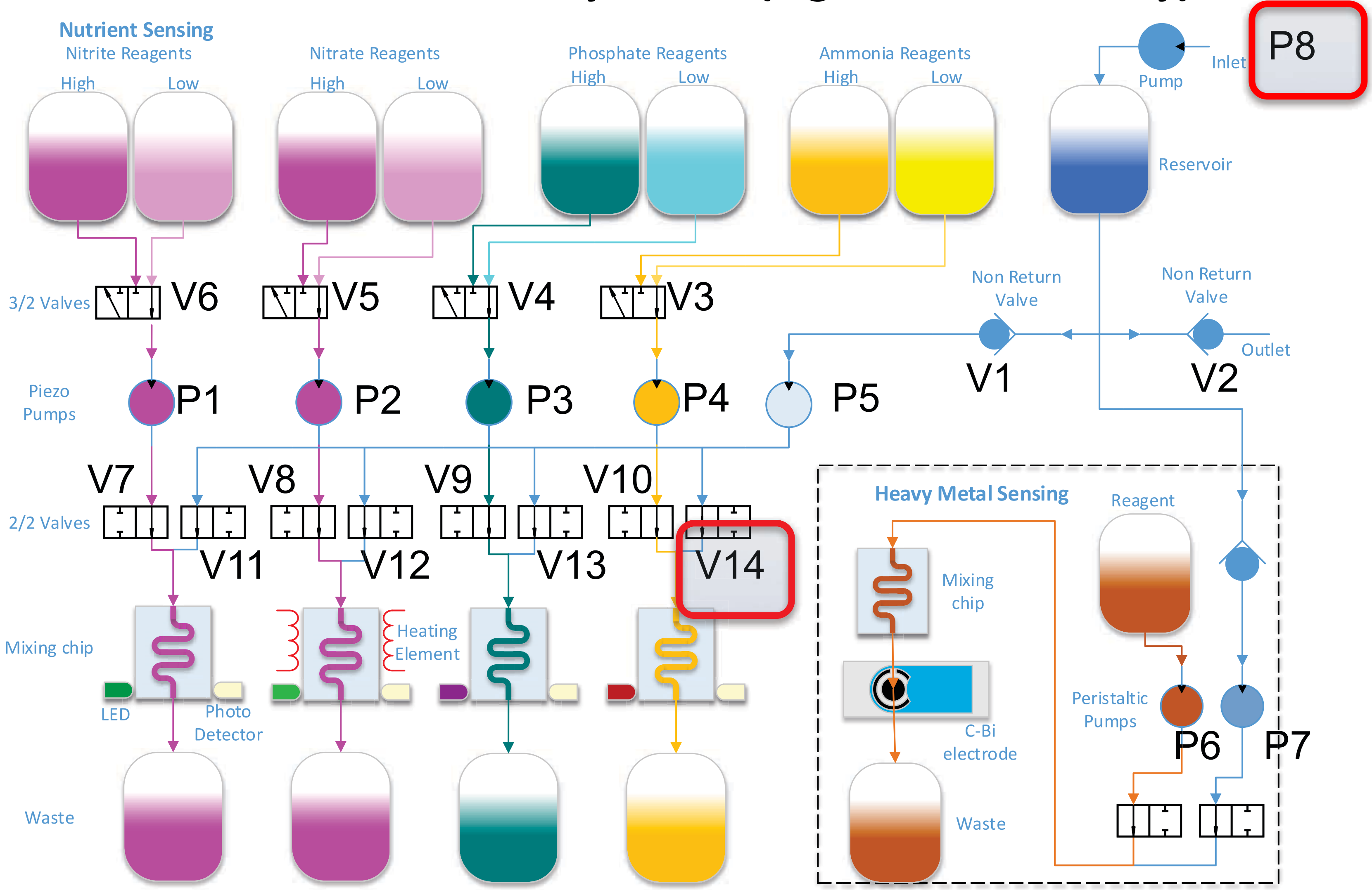
J. Cleary, C. Slater, D. Diamond, Analysis of phosphate in wastewater using an autonomous microfluidics-based analyser, World Academy of Science, Engineering and Technology. 52 (2009) 196–199.

Achieving Scale-up for Environmental Sensor Networks



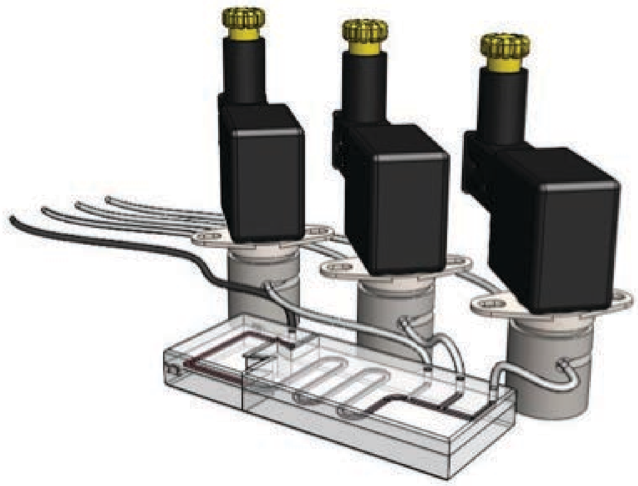
D. Diamond, R. Byrne, F.B. Lopez, J. Cleary, D. Maher, J. Healy, C. Fay, J. Kim, K.-T. Lau, Biomimetics and Materials with Multiple Personalities - The Foundation of Next Generation Molecular Sensing Devices, in: Proceedings IEEE Sensors Conference, Kona, HawaiI, 2010: pp. 1079–1082. doi:10.1109/ICSENS.2010.5690729.

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



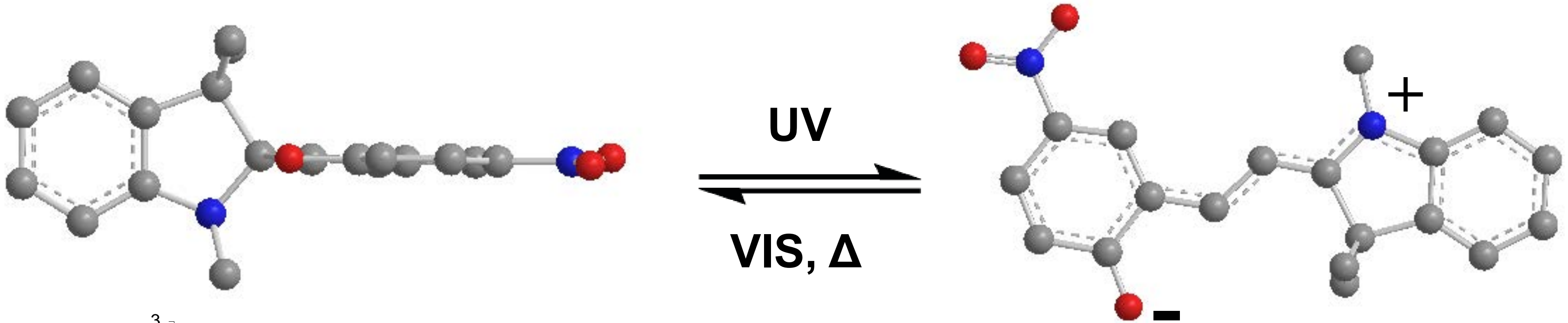
How to advance fluid handling in LOC platforms: re-invent valves (and pumps)!

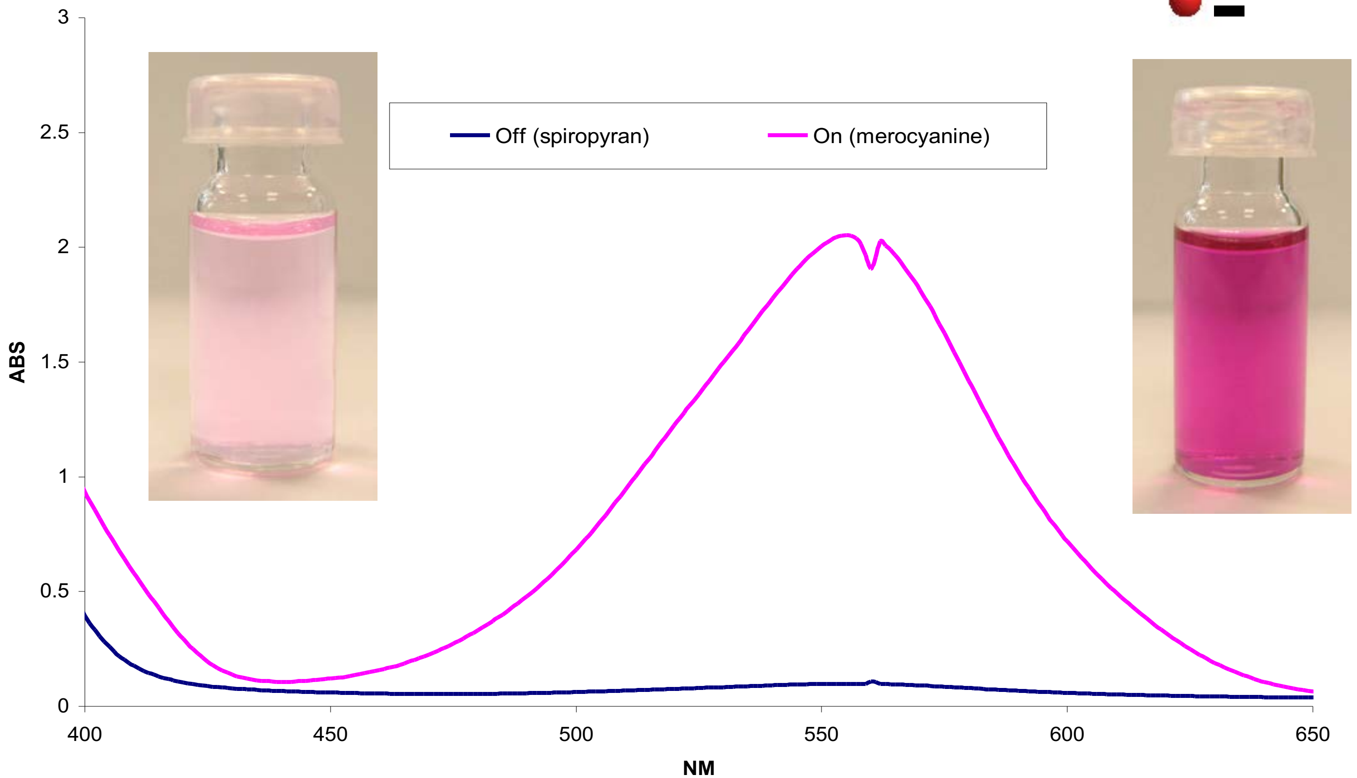
- **Conventional valves cannot be easily scaled down - Located off chip: fluidic interconnects required**
  - Complex fabrication
  - Increased dead volume
  - Mixing effects
- **Based on solenoid action**
  - Large power demand
  - Expensive



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

Photoswitchable Soft Actuators

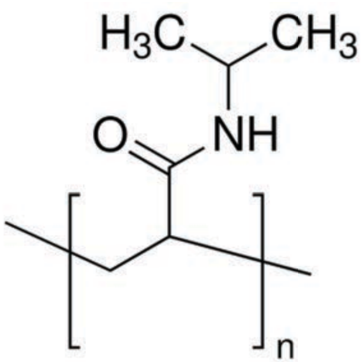




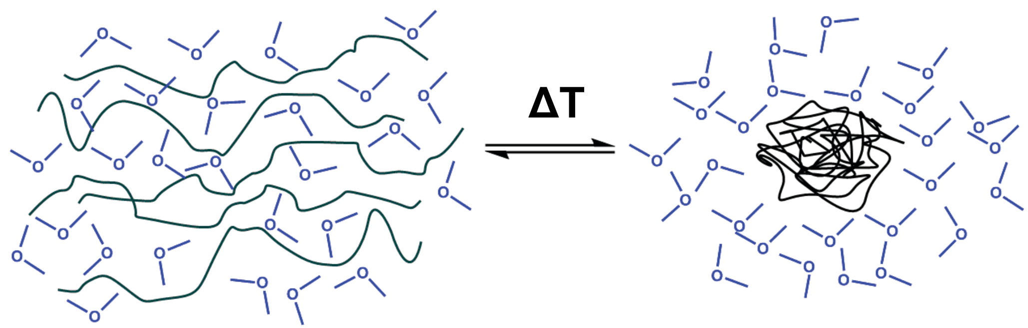
Poly(*N*-isopropylacrylamide)

- 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



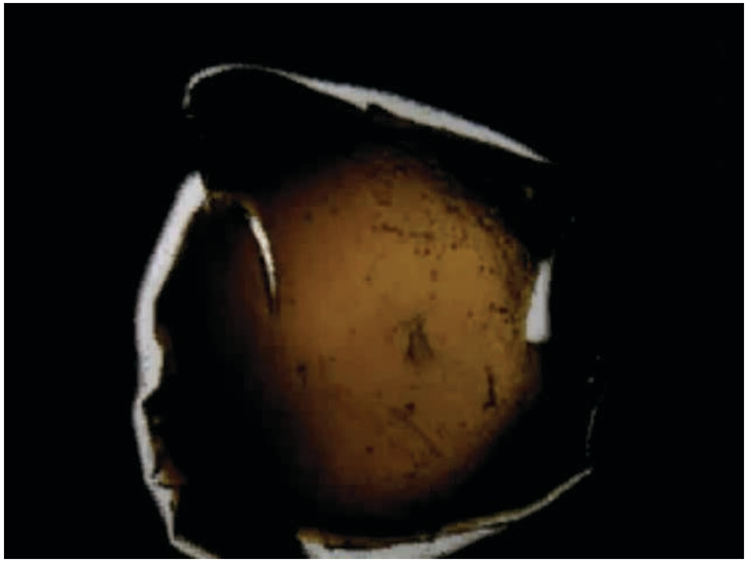
Hydrophilic **Hydrophobic**

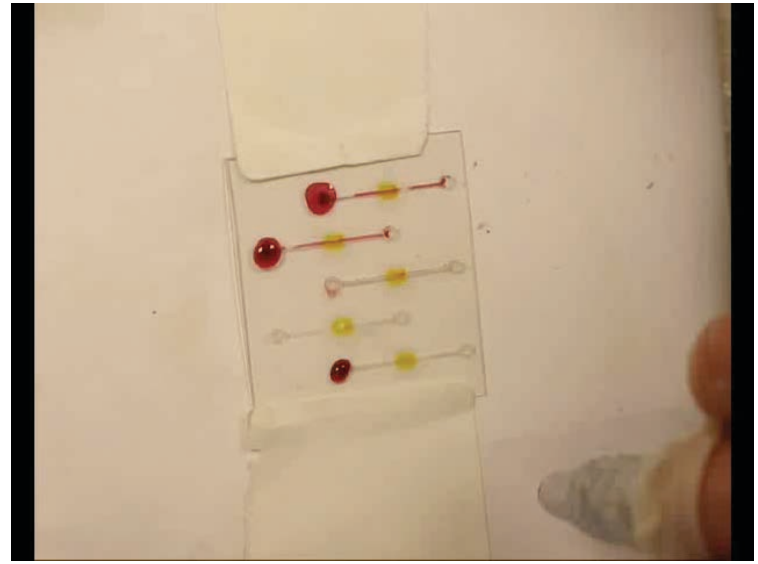


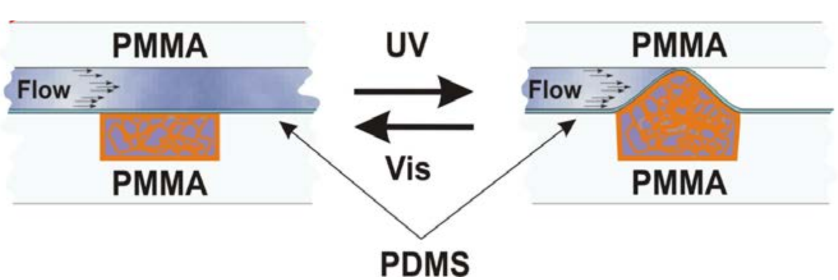
Hydrated Polymer Chains

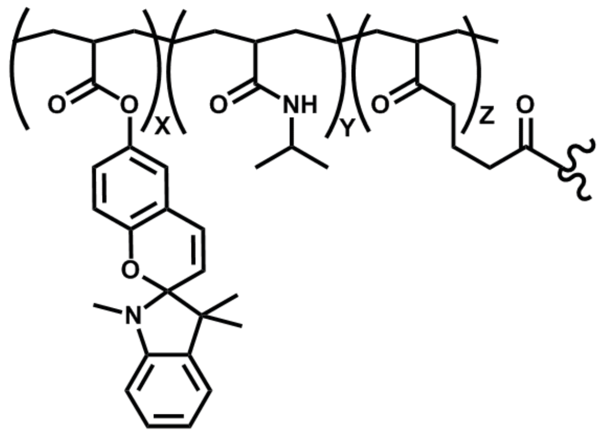
Loss of bound water -> polymer collapse

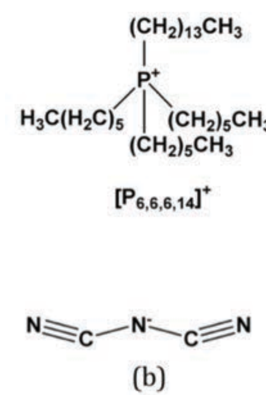
Photo-actuator polymers as microvalves in microfluidic systems











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.

Experimental set up for PID Control

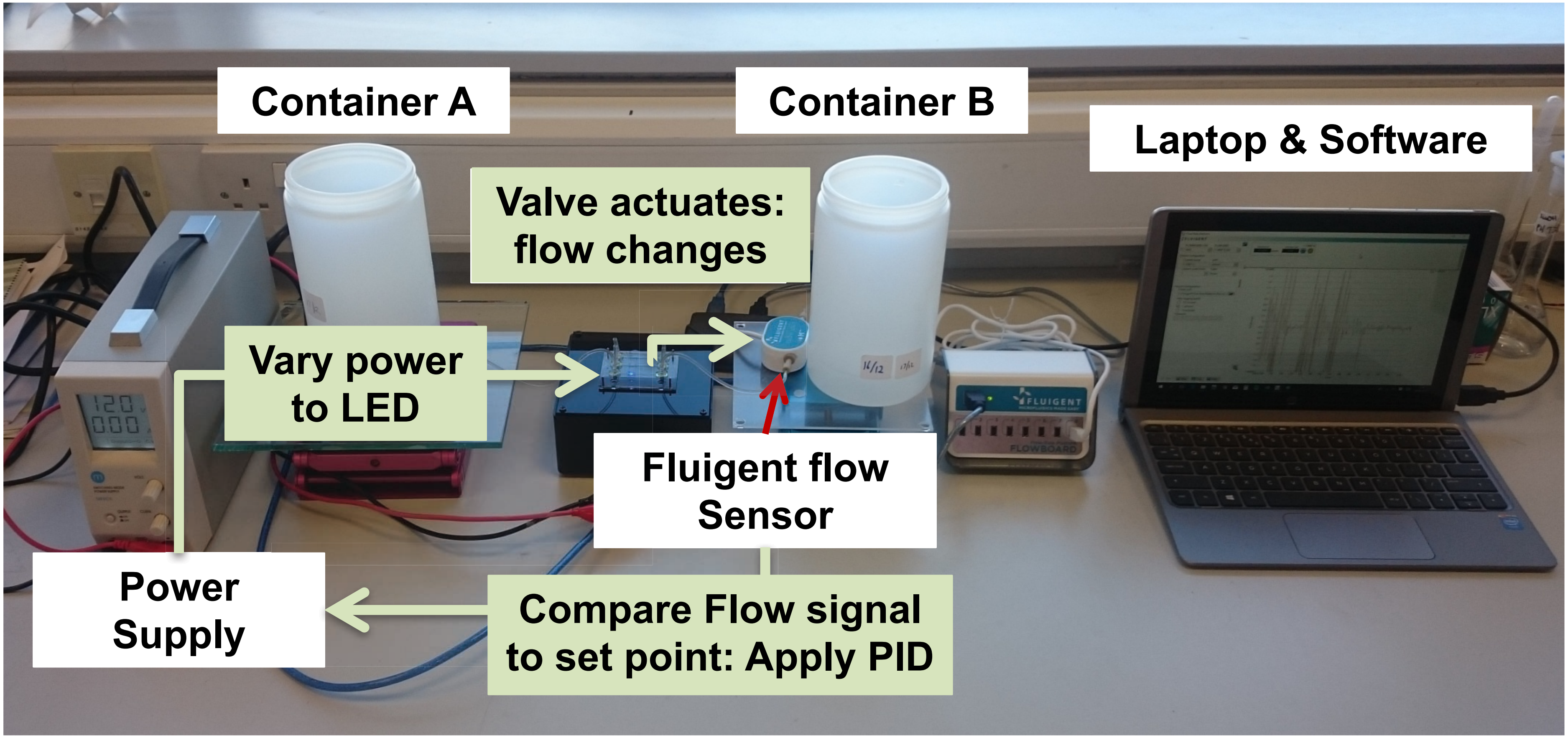
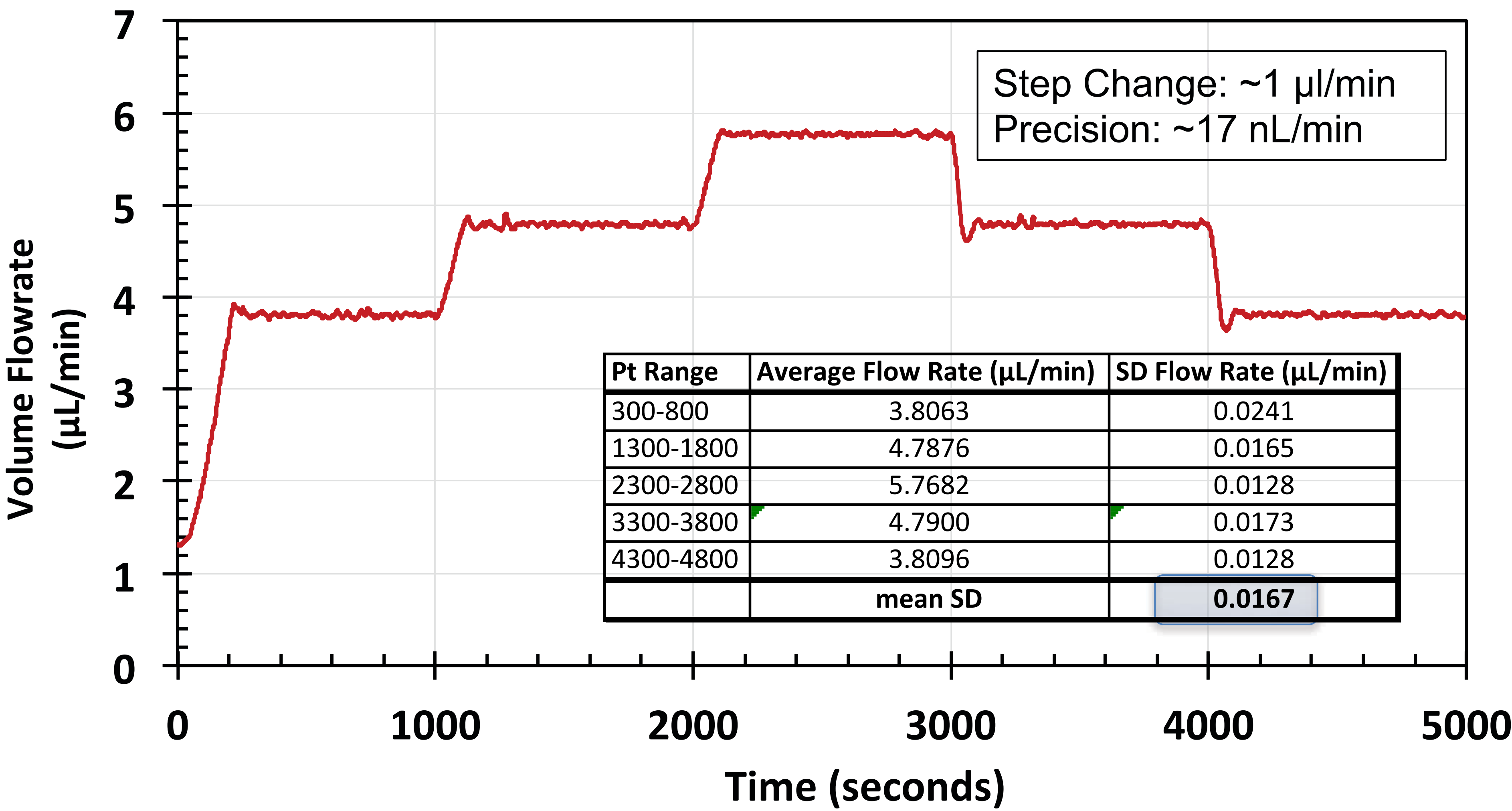


Photo-Controlled Flow Rate

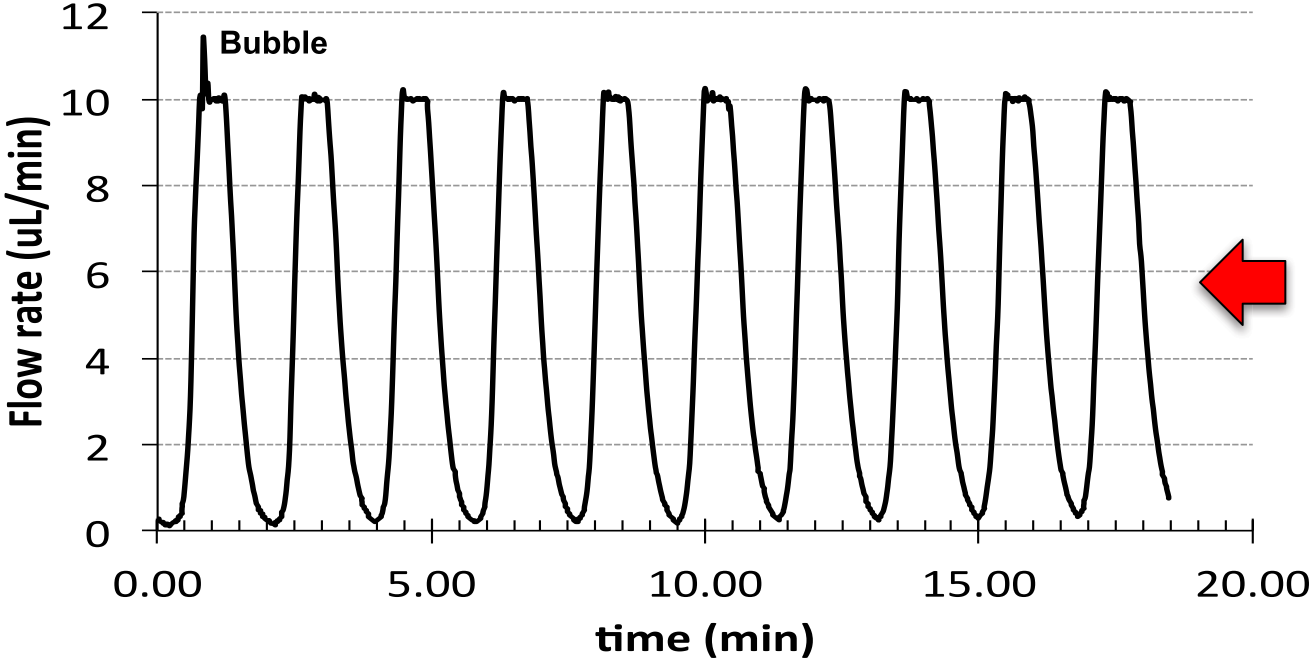


Pt Range	Average Flow Rate (µL/min)	SD Flow Rate (µL/min)
300-800	3.8063	0.0241
1300-1800	4.7876	0.0165
2300-2800	5.7682	0.0128
3300-3800	4.7900	0.0173
4300-4800	3.8096	0.0128
	mean SD	**0.0167**

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.

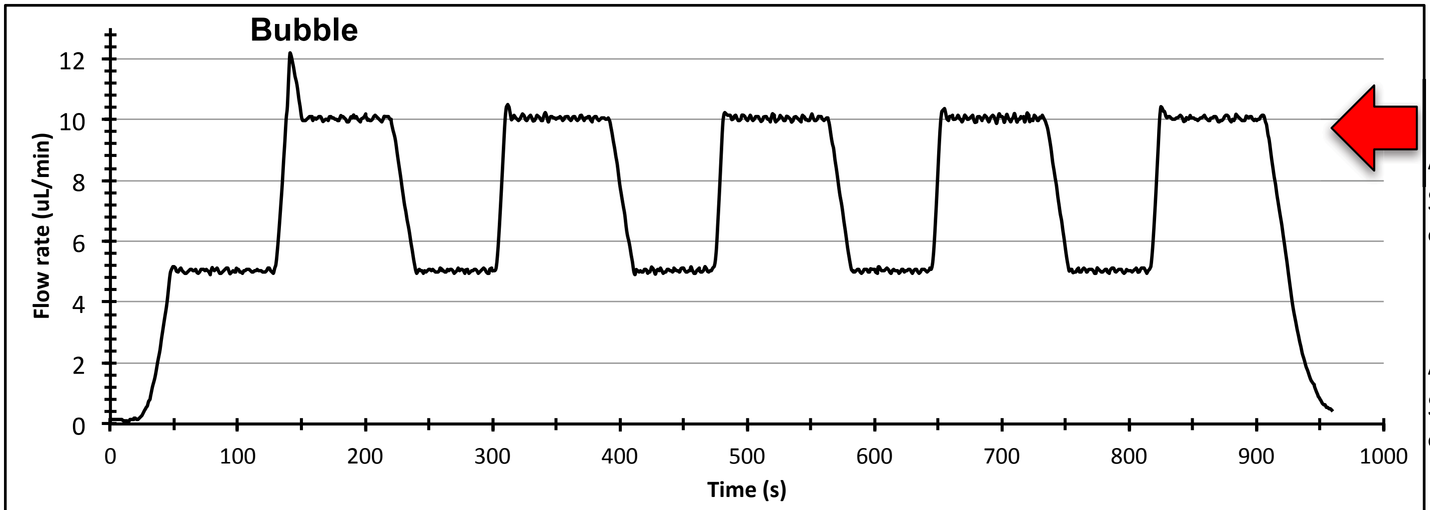
sfi DCU UCC OÉ Gaillimh NUI Galway UCD DUBLIN

Some figures of merit



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

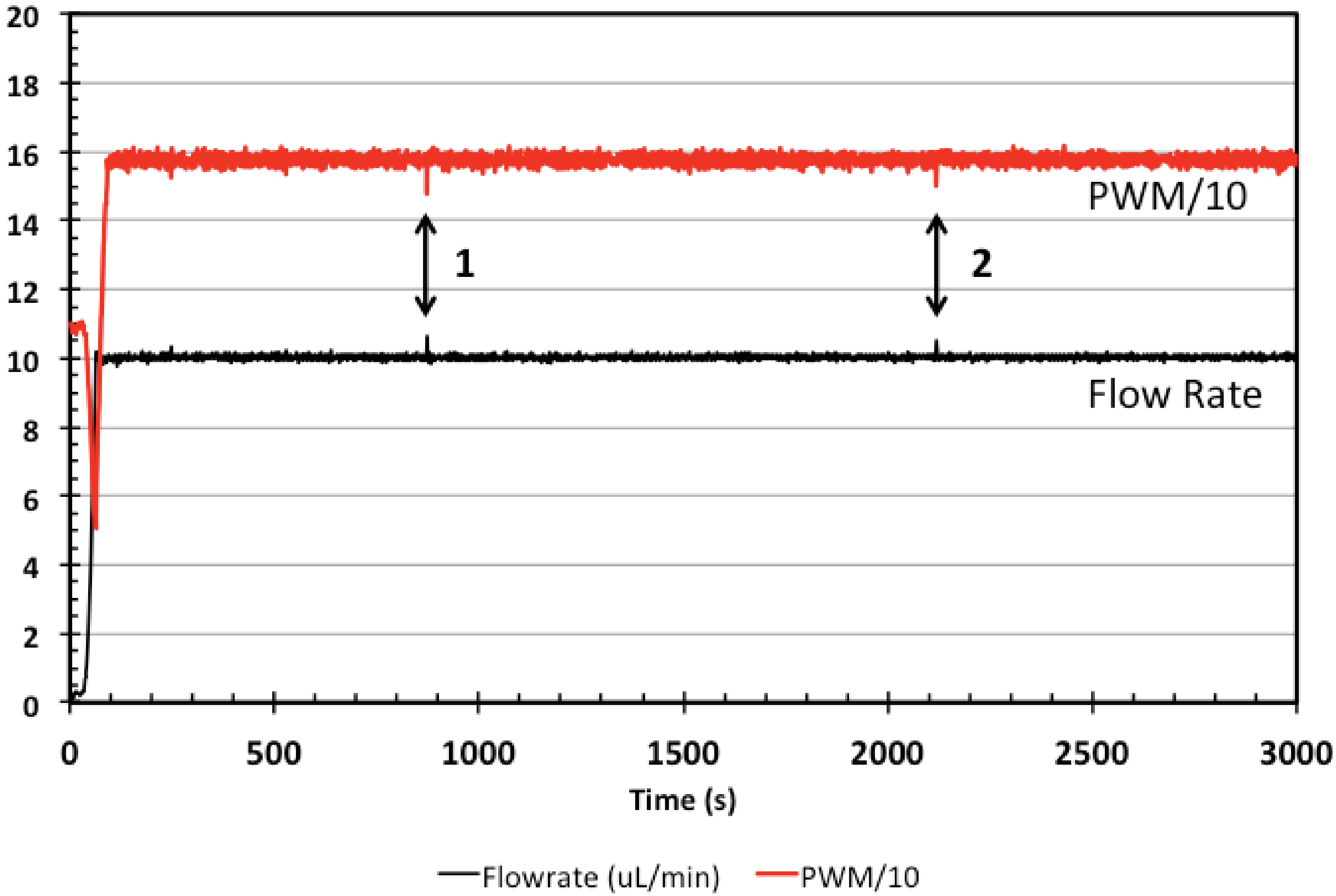
Averages (n=10)	
mean	10.0028
Mean SD	0.0323
Error Mean	0.0028
%RSD	0.3235
%RE mean	0.0279



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

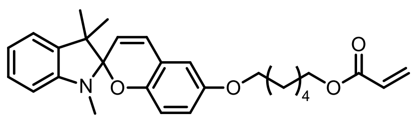
Photocontrol of Assembly and Subsequent Switching of Surface Features

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

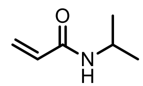
ACS applied materials & interfaces, 6 (2014) 7268-7274

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[*,†,§]

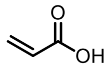


SPA, 1 mol%

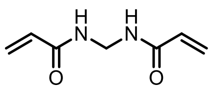


NIPAAM, 91-92 mol%

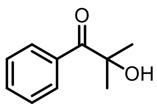
a)



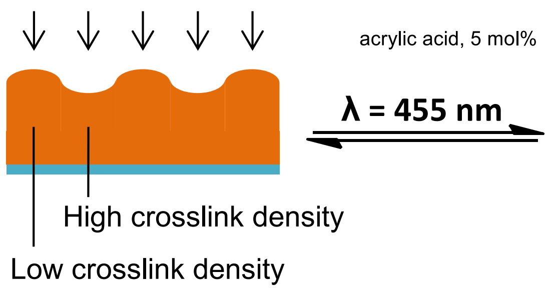
acrylic acid, 5 mol%



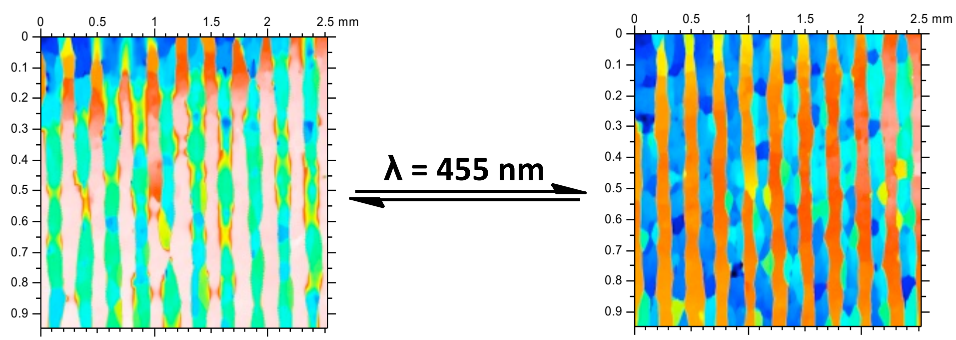
MBIS, 1-2 mol%

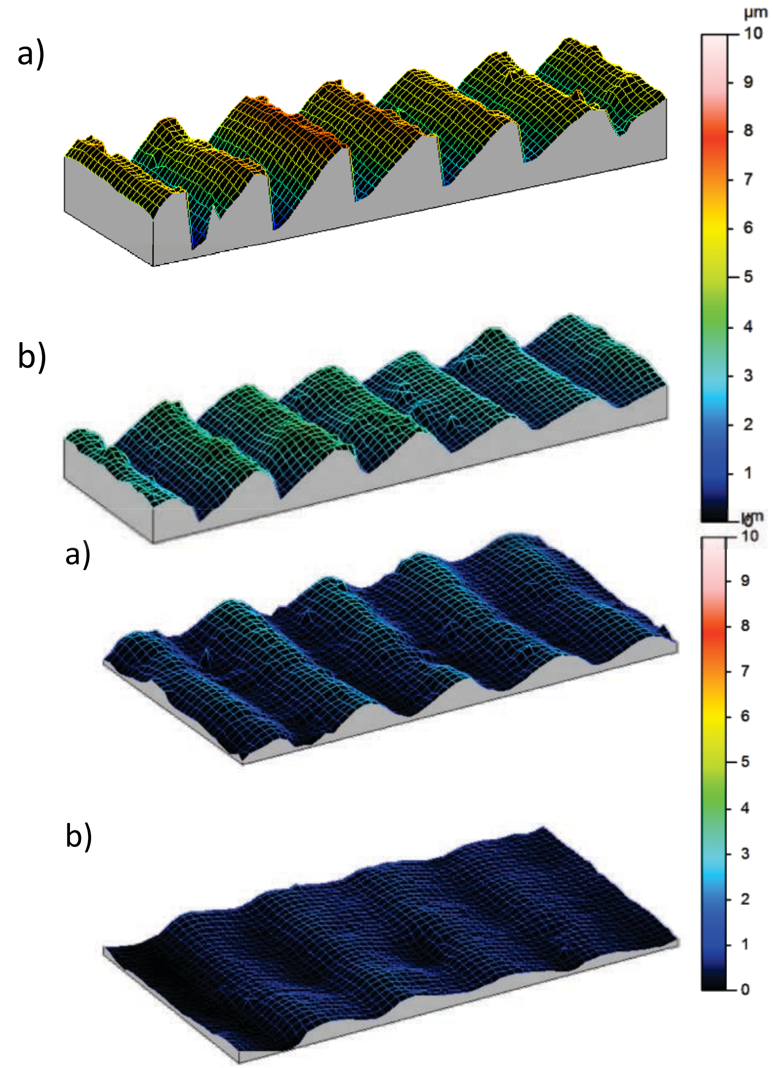


Darocur 1173, 1 mol%

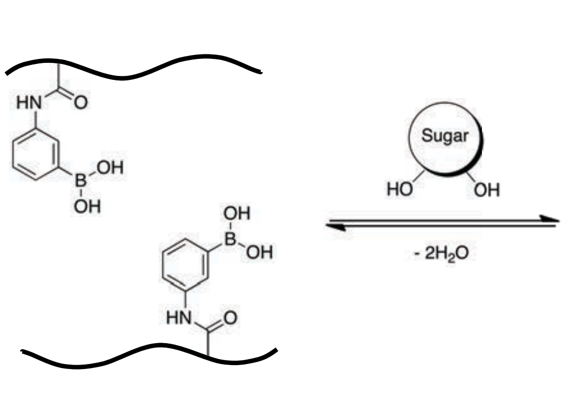


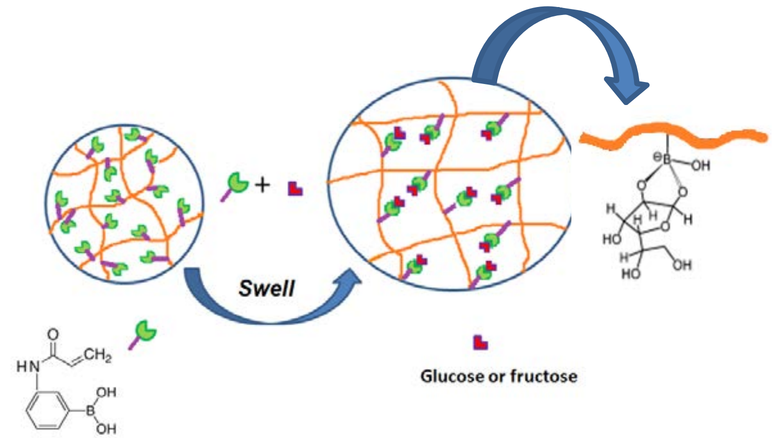
b)



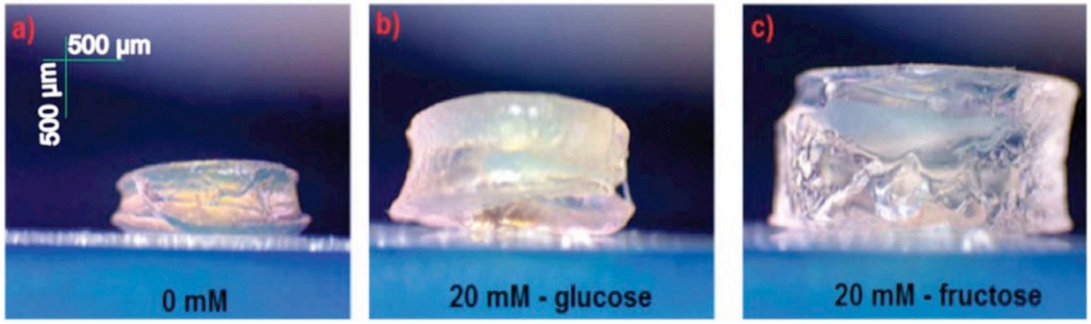


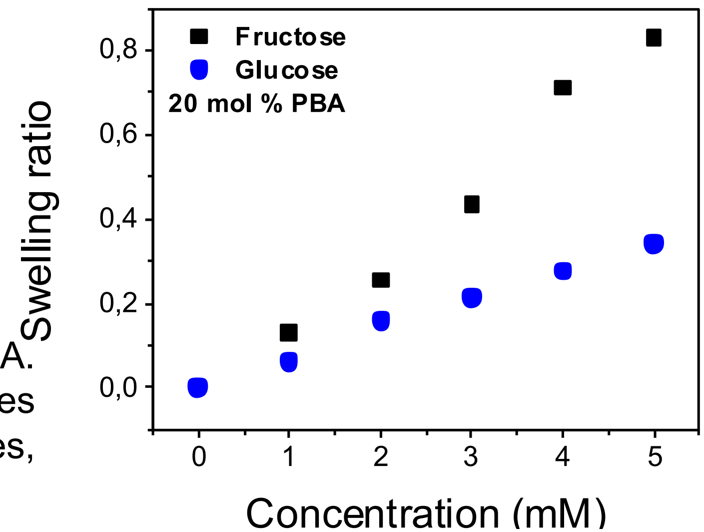
Sugar-Responsive Soft Hydrogels





Acrylamide-*co*-PBA Polymer

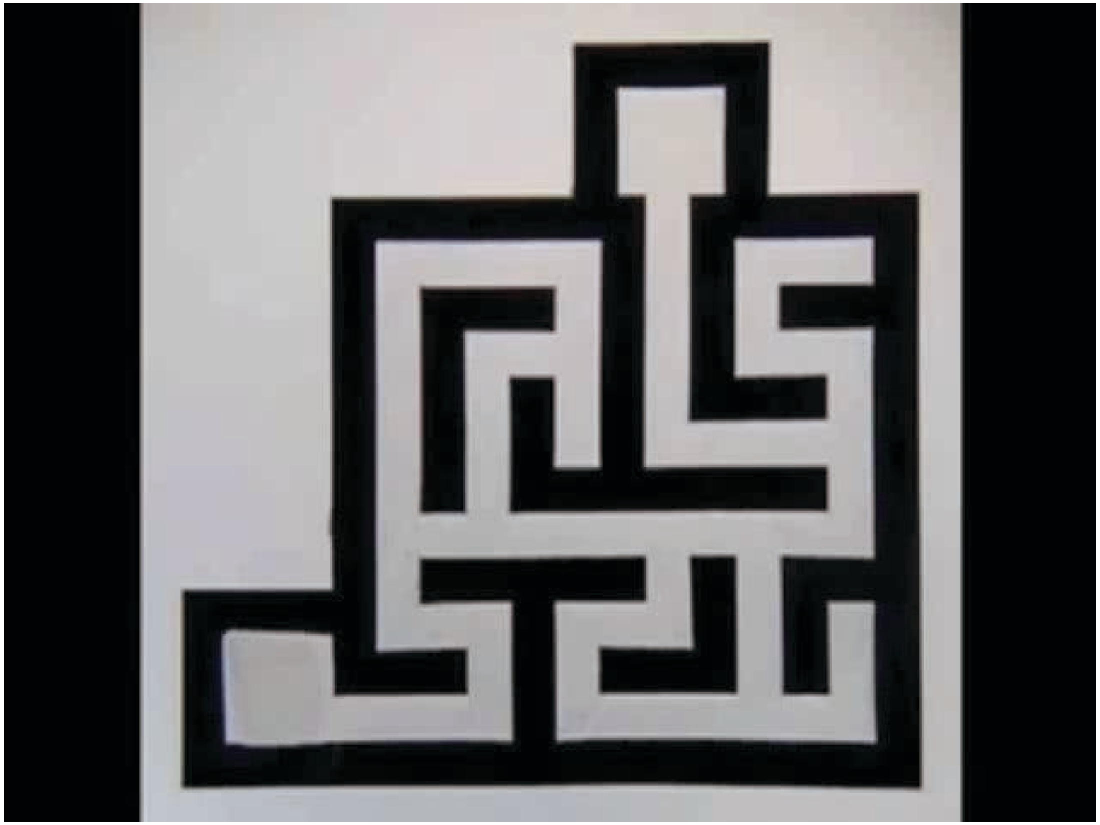


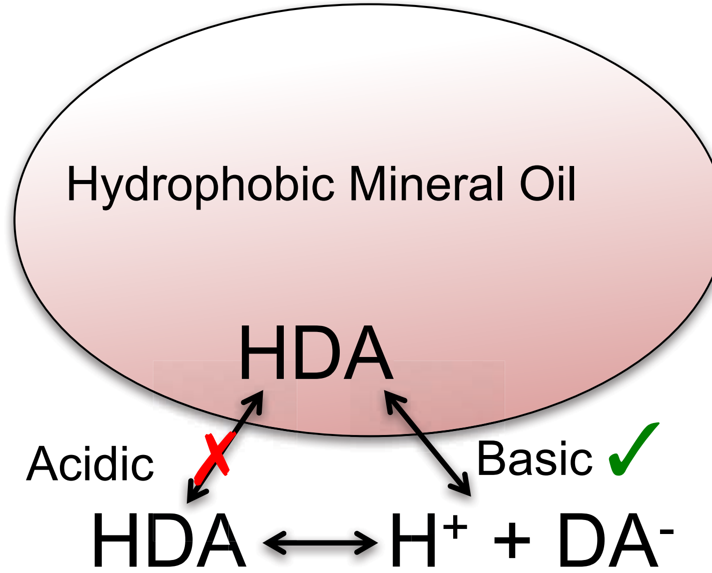


C.M. Daikuzono, C. Delaney, H. Tesfay, L. Florea, O.N. Oliveira, A. Morrin, D. Diamond, Impedance spectroscopy for monosaccharides detection using responsive hydrogel modified paper-based electrodes, Analyst. 142 (2017) 1133–1139. doi:10.1039/c6an02571d.

Detect, Migrate, Repair..

Chemotactic Systems





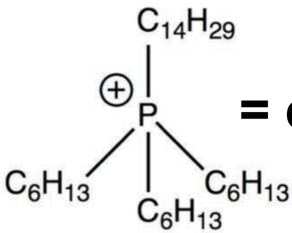
In a pH gradient, DA^- is preferentially transferred to the aqueous phase at the more basic side of the drop.

Published on Web 11/01/2010 (speed ~x4): 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); HDA <-> H^+ + DA^-

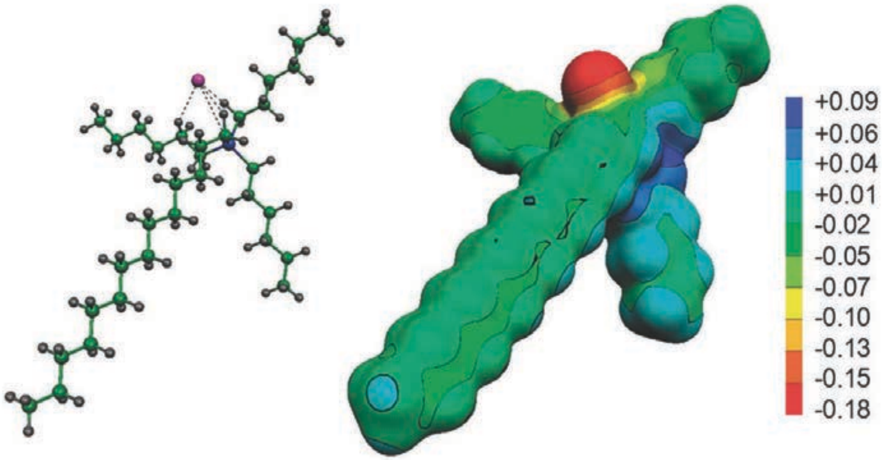
Maze Solving by Chemotactic Droplets; Istvan Lagzi, Siowling Soh, Paul J. Wesson, Kevin P. Browne, and Bartosz A. Grzybowski; J. AM. CHEM. SOC. 2010, *132, 1198–1199*

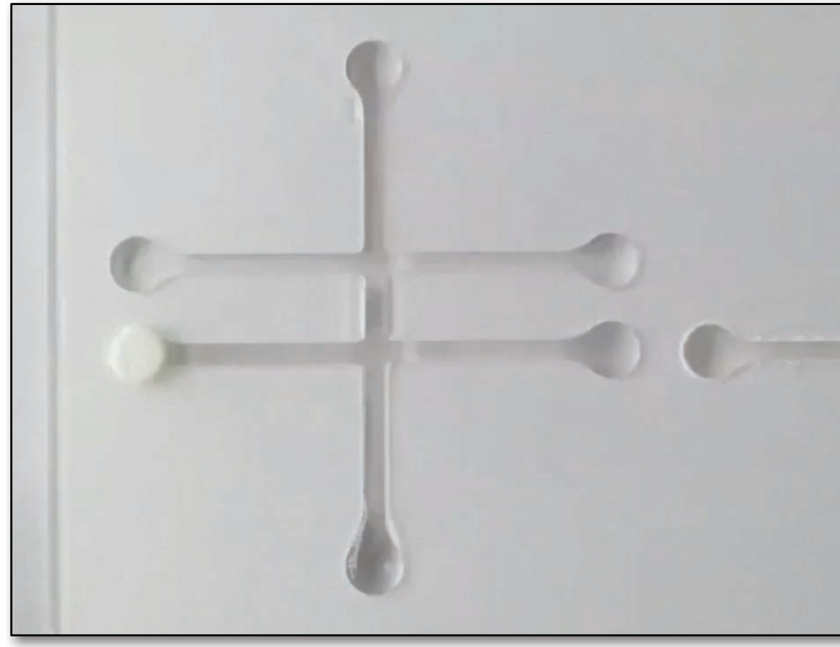
Fuerstman, M. J.; Deschatelets, P.; Kane, R.; Schwartz, A.; Kenis, P. J. A.;Deutch, J. M.; Whitesides, G. M. *Langmuir 2003, 19, 4714.*

We can do the same with IL Droplets



= cationic surfactant

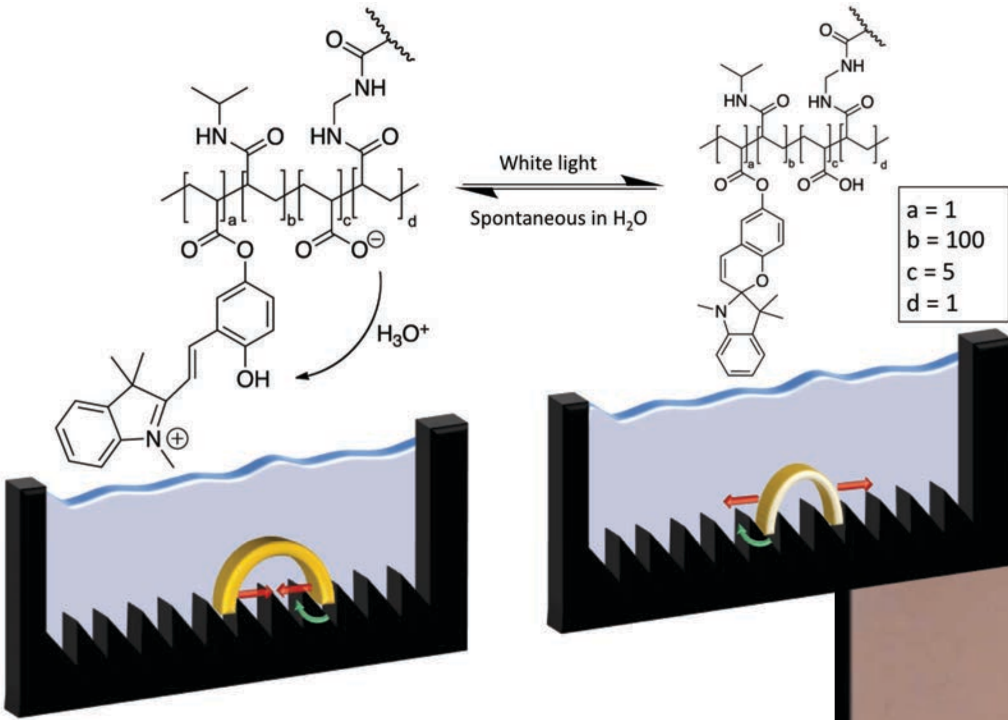




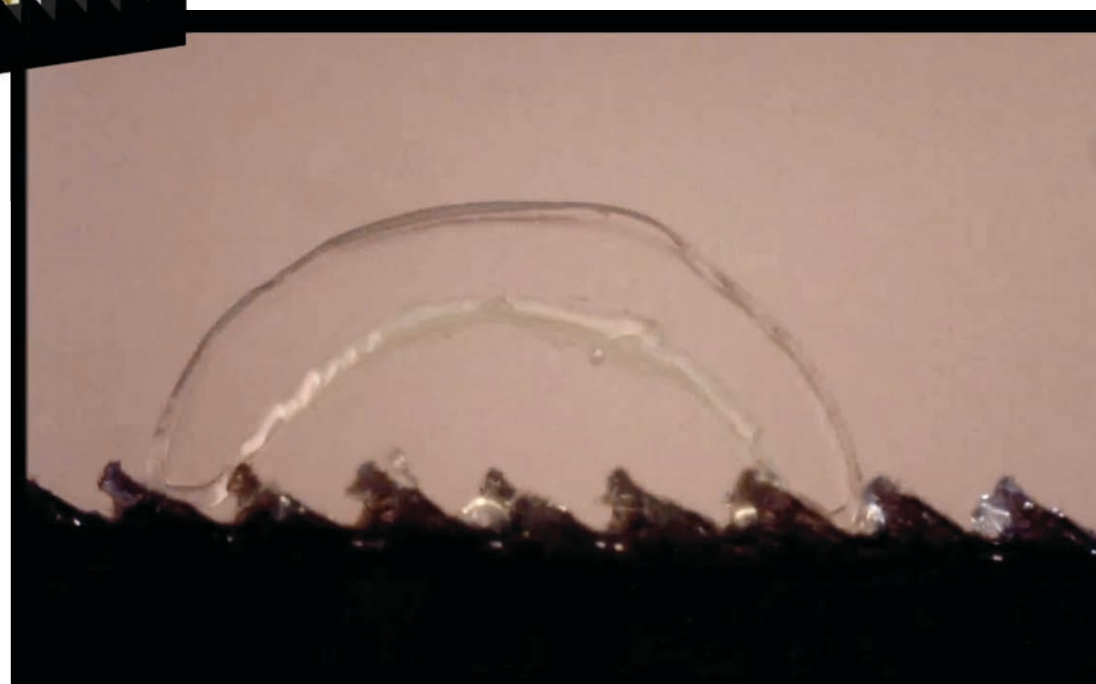
Trihexyl(tetradecyl)phosphonium chloride ([$P_{6,6,6,14}$][Cl]) droplets with a small amount of 1-(methylamino)anthraquinone red dye for visualization. The droplets spontaneously follow the gradient of the Cl^- ion which is created using a polyacrylamide gel pad soaked in 10^{-2} M HCl; A small amount 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.

Photo-Responsive Soft Hydrogels



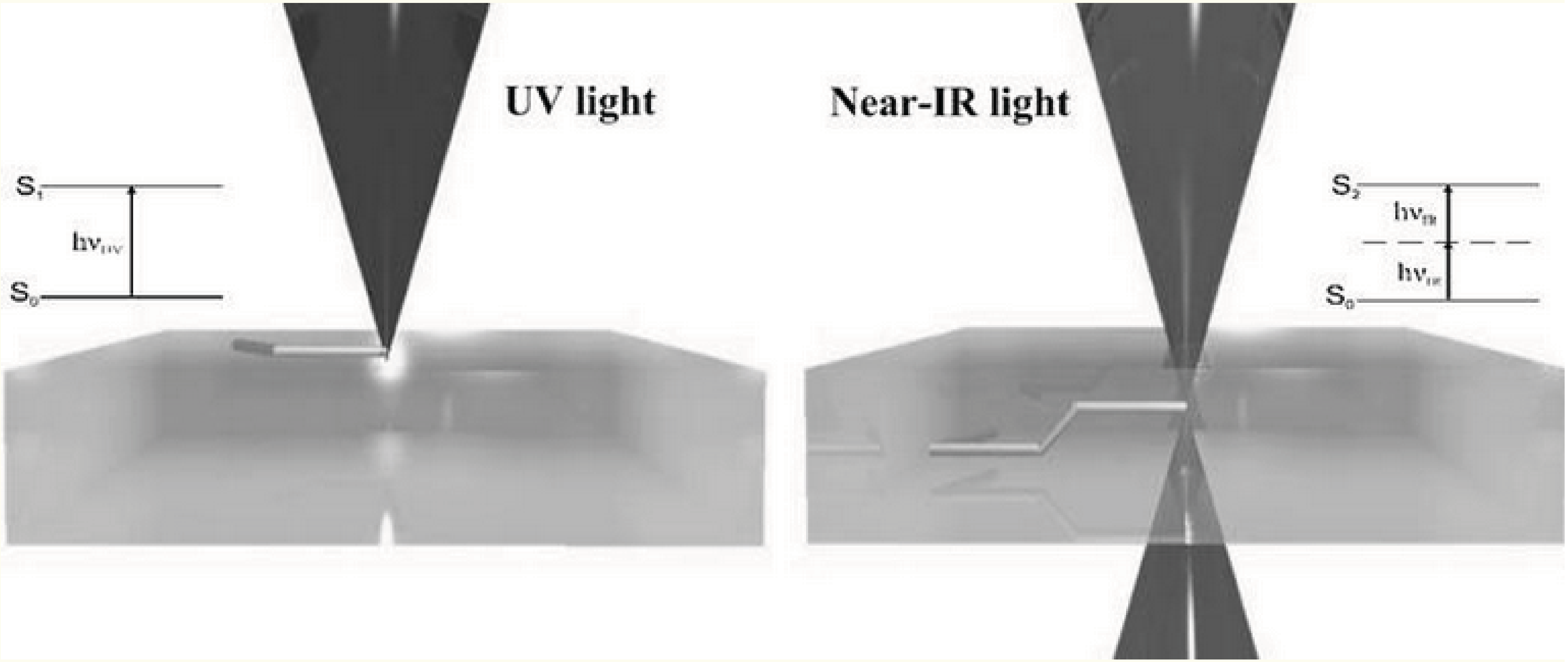
'Walking towards the light'



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

Background

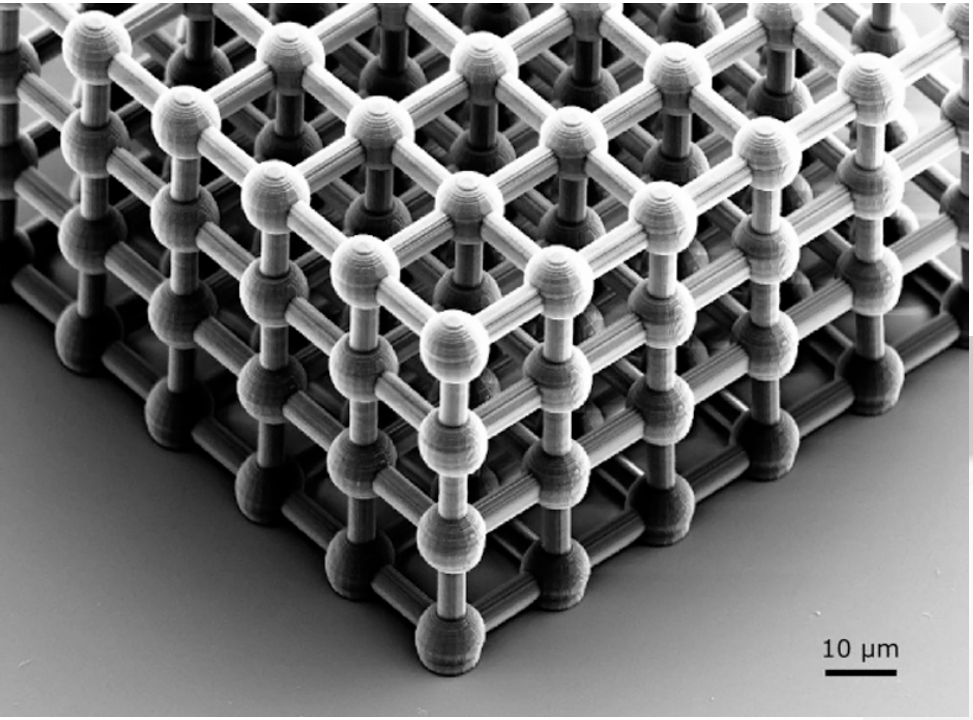
Stereolithography | **Two-photon polymerisation**

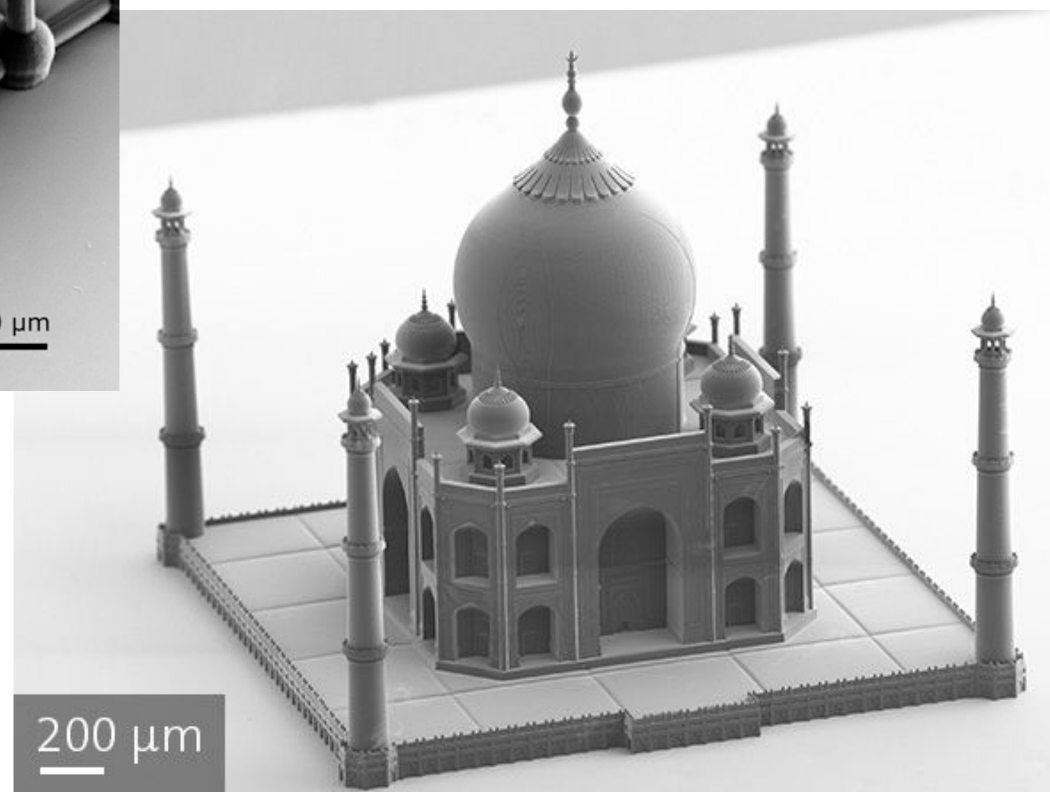


- Single photon absorption
- 2D patterns

- Two photon absorption
- 3D structures

Background





http://www.nanoscribe.de/

Merging of Materials, Devices and Data

Data and Information; IOT

Outside: On-Body

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

Inside: Implants/In-vivo

- Smart Stents
- Self-Aware Transplant Implants
- 3D Tissue Platforms and Implants
- Post-Operative IC (days)
- Medium term Convalescence (weeks)

Devices and Platforms

MATERIALS

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

sfi DCU UCC OÉ Gaillimh NUI Galway UCD Dublin

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- Enterprise Ireland (IPP Shimmer, IPP TELLABs)
- Research Partners – academic and industry
- EU Projects: NAPES, CommonSense, Aquawarn, Holifab

MASK
Project no: 269302
Materials and Advanced Sensor
Knowledge Exchange