Futuristic Microfluidics Incorporating Bioinspired Functionalities

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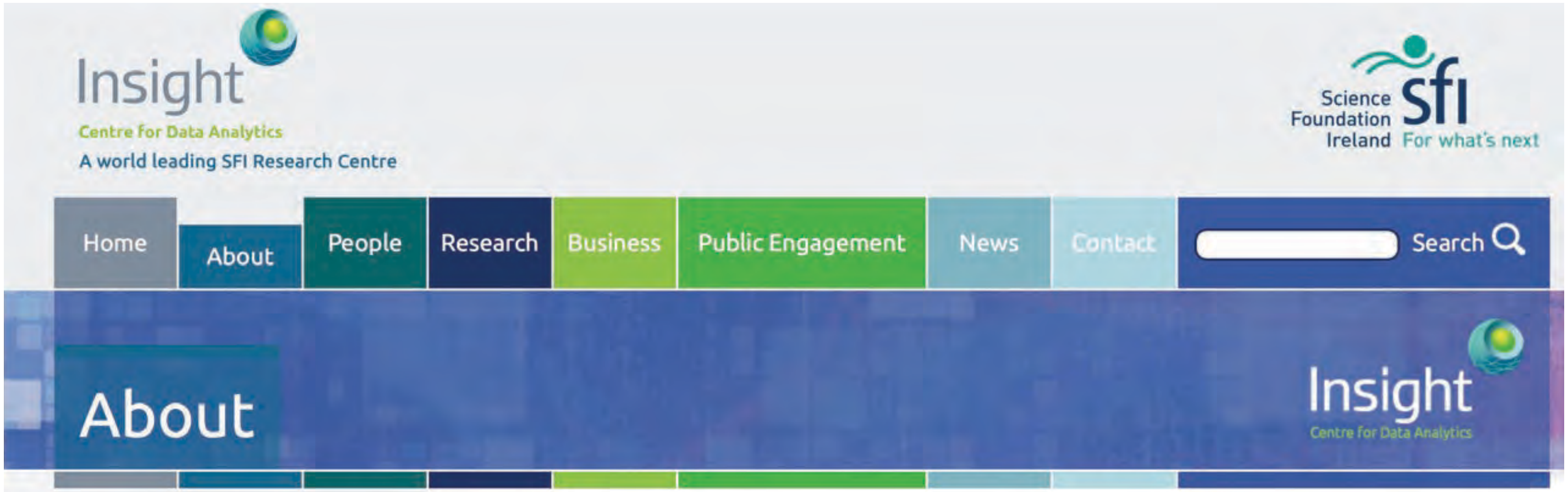
Faculty of Pharmacy, Vitoria-Gasteiz, Spain
30th January 2020

THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
HORIZON 2020
HoliFAB

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

HoliFAB

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.

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

2nd Phase funding approved (ca. €49 million SFI); 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)
  - Critical Need: 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.

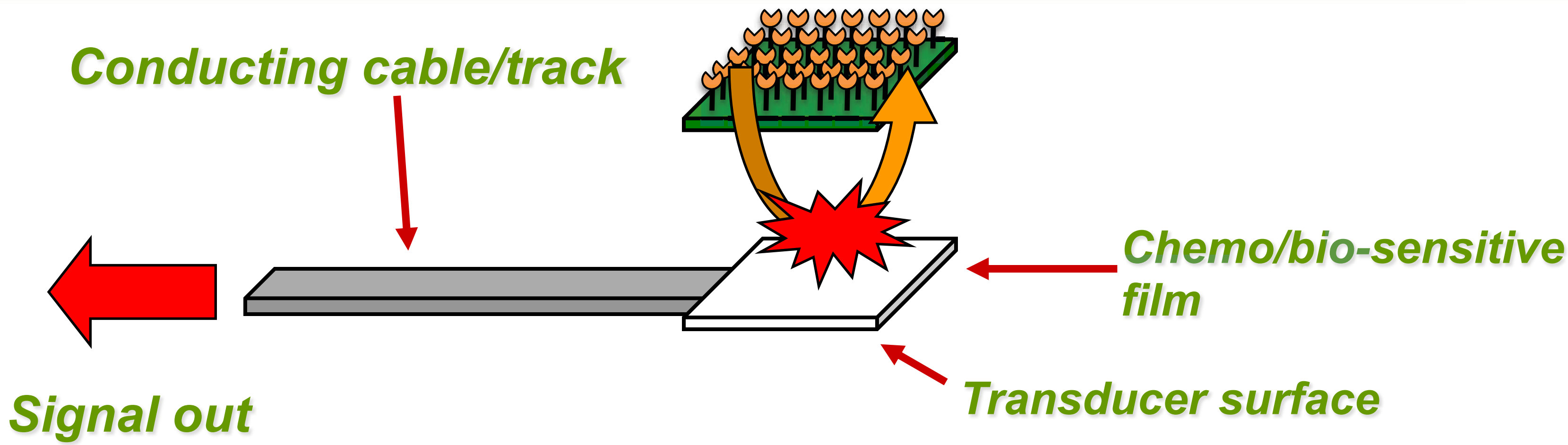
Digital communications networks are at the heart of modern society. The digitization of communications, the development of the Internet, and the availability of relatively inexpensive but powerful mobile computing technologies have established a global communications network capable of linking billions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

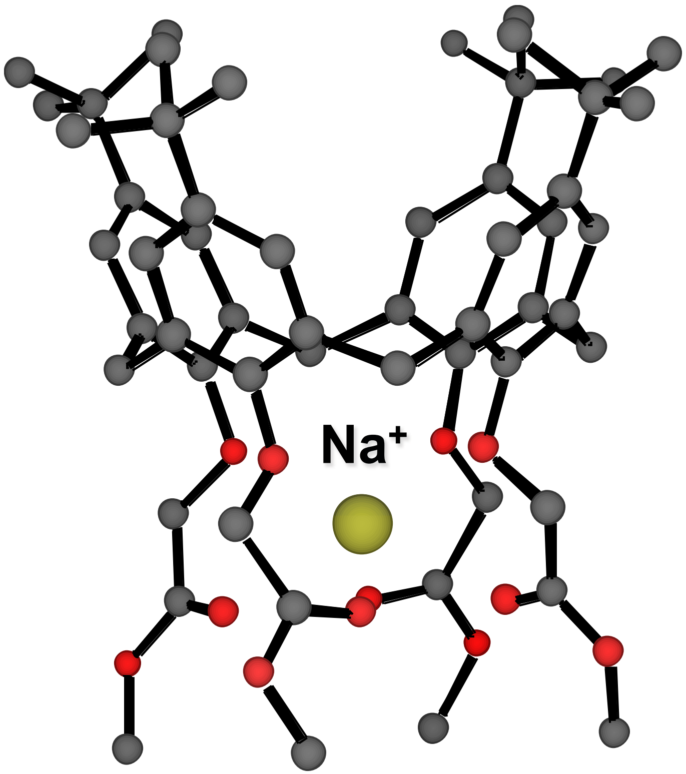
What is a ‘Bio/Chemical Sensor?

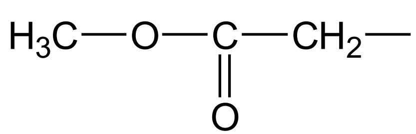
‘a device, consisting of a transducer and a chemo/bio-sensitive film/membrane, that generates a signal related to the concentration of particular target analyte in a given sample’

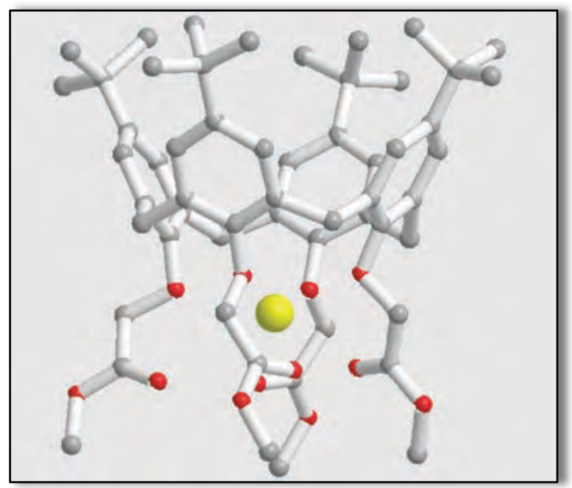


Chemo/Bio-sensing involves selective BINDING & TRANSDUCTION on the device surface; this also implies the target analyte MUST meet the device surface (LOCATION & MOVEMENT). It provides a signal observable in the macroscopic world (COMMUNICATION)

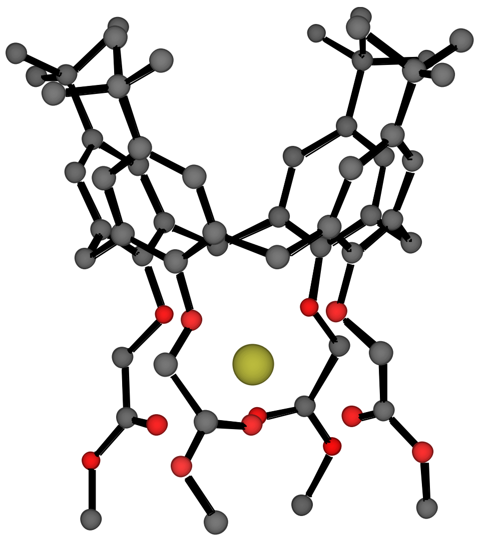
Calixarene Ionophores – controlling the selectivity

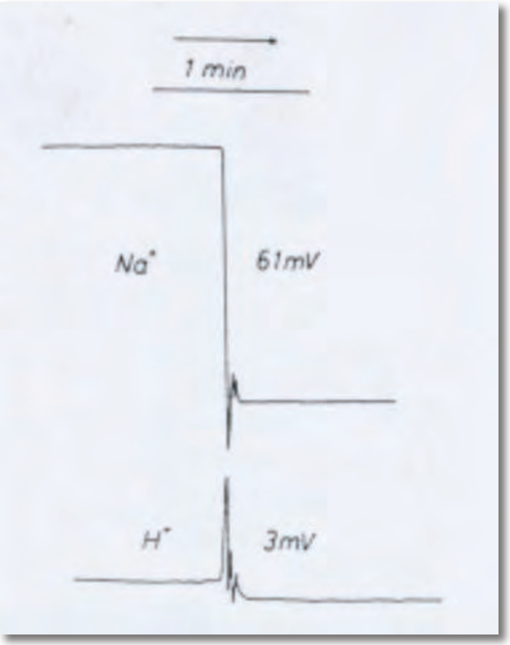


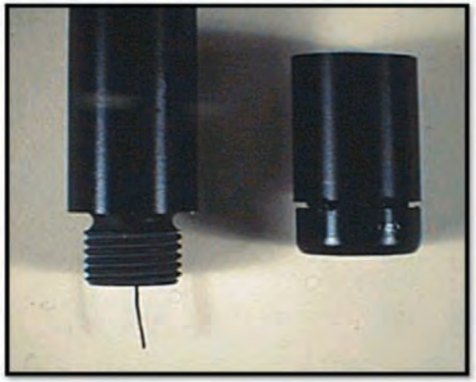




And…….



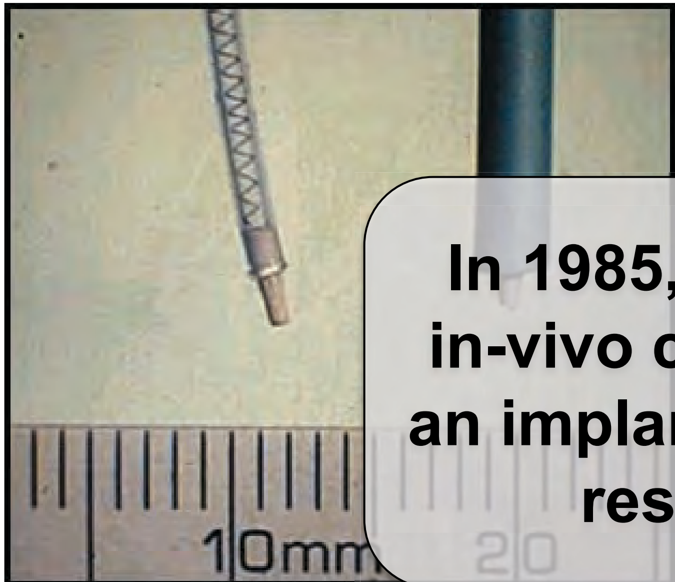




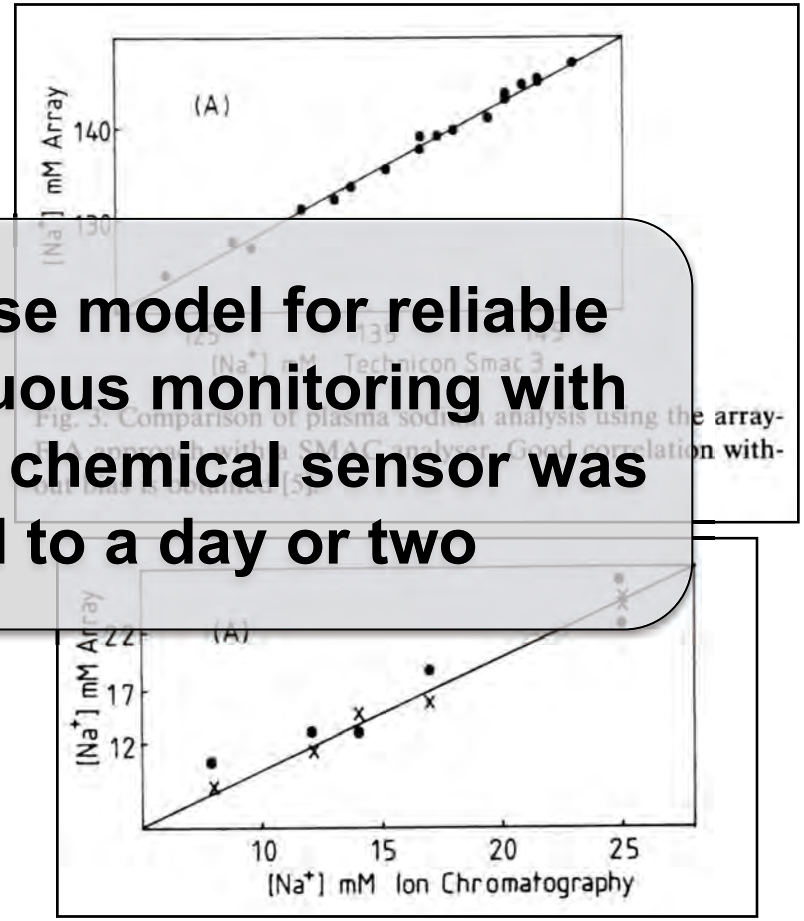
Neutral Carrier Based Ion-Selective Electrodes, D.Diamond, Anal. Chem. Symp. Ser., 25 (1986) 155.

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



Anal. Chem., *__64__ (1992) 1721-1728.*

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

Dr. David Band, St Thomas's Hospital London

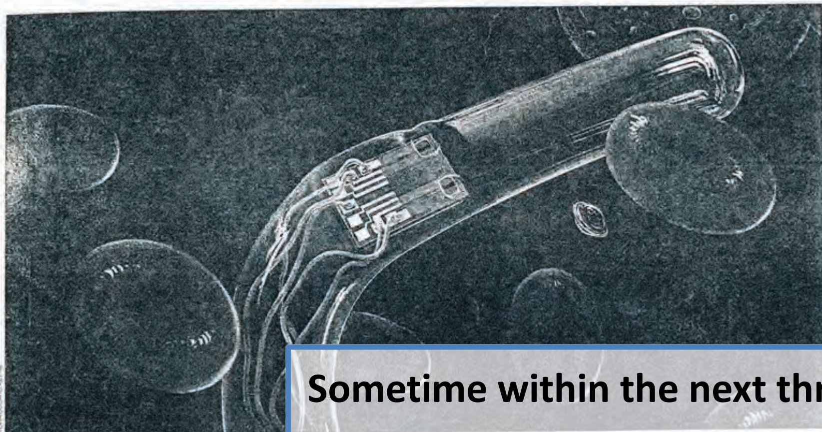
Ligand (and variations of) used in many clinical analysers for blood Na^+ profiling

The (broken) promise of biosensors…..

High Technology, Nov. 1983, 41-49

BIOSENSORS

THE MATING OF BIOLOGY AND ELECTRONICS

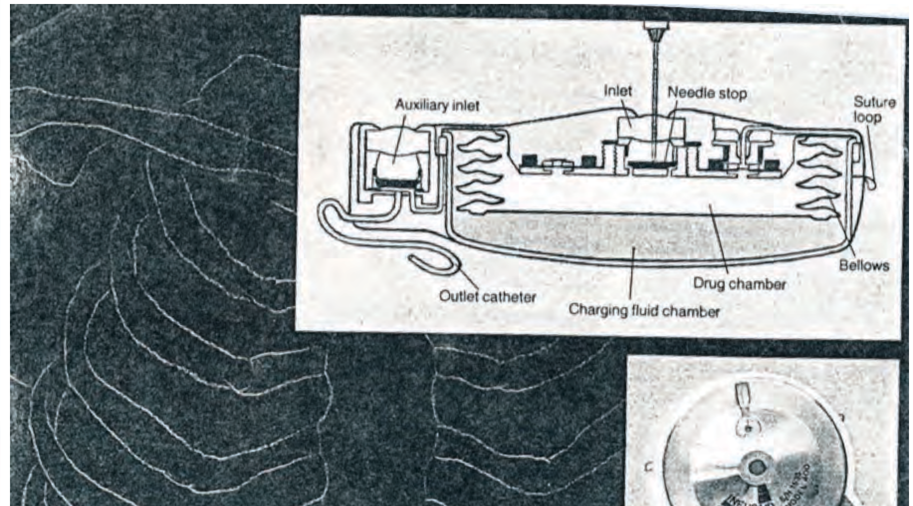


Implanted sensors com… of Utah model is a fiel…

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



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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

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

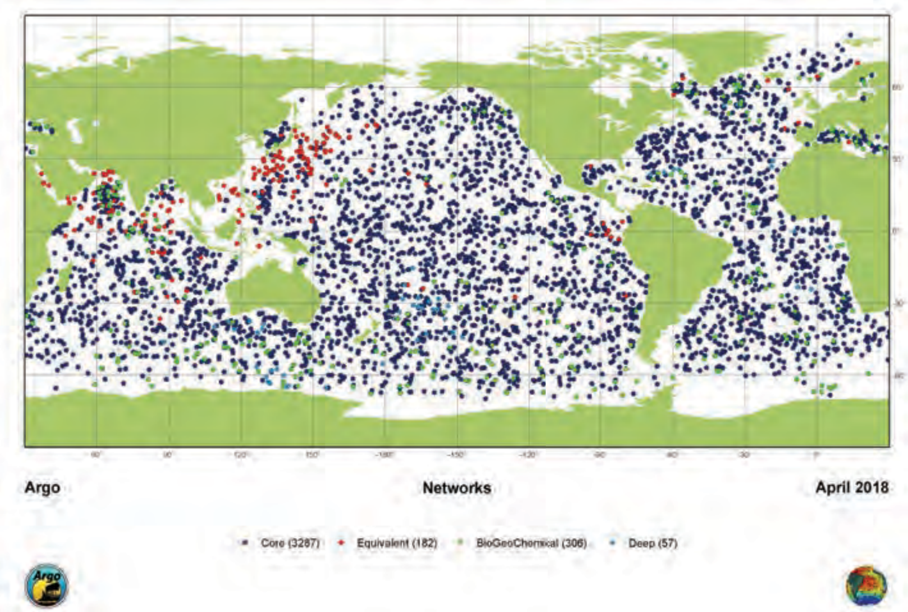
Developing APPs

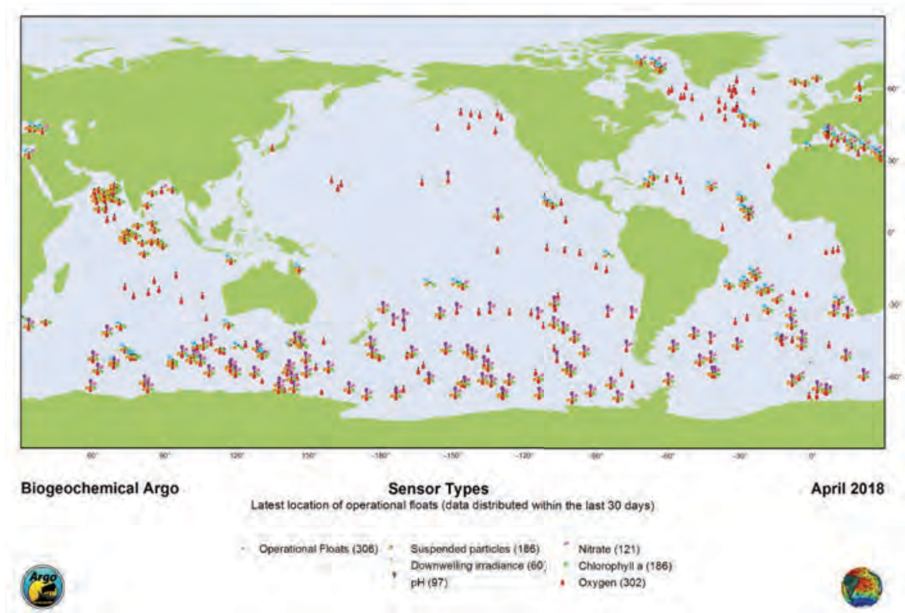
Accessing real-time data from diabetes monitors (Dexcom, wearable glucose sensors)

User groups formed, self-funded

Use disclaimers, no warranty, not for making therapeutic decisions

Argo Project (accessed May 2018)



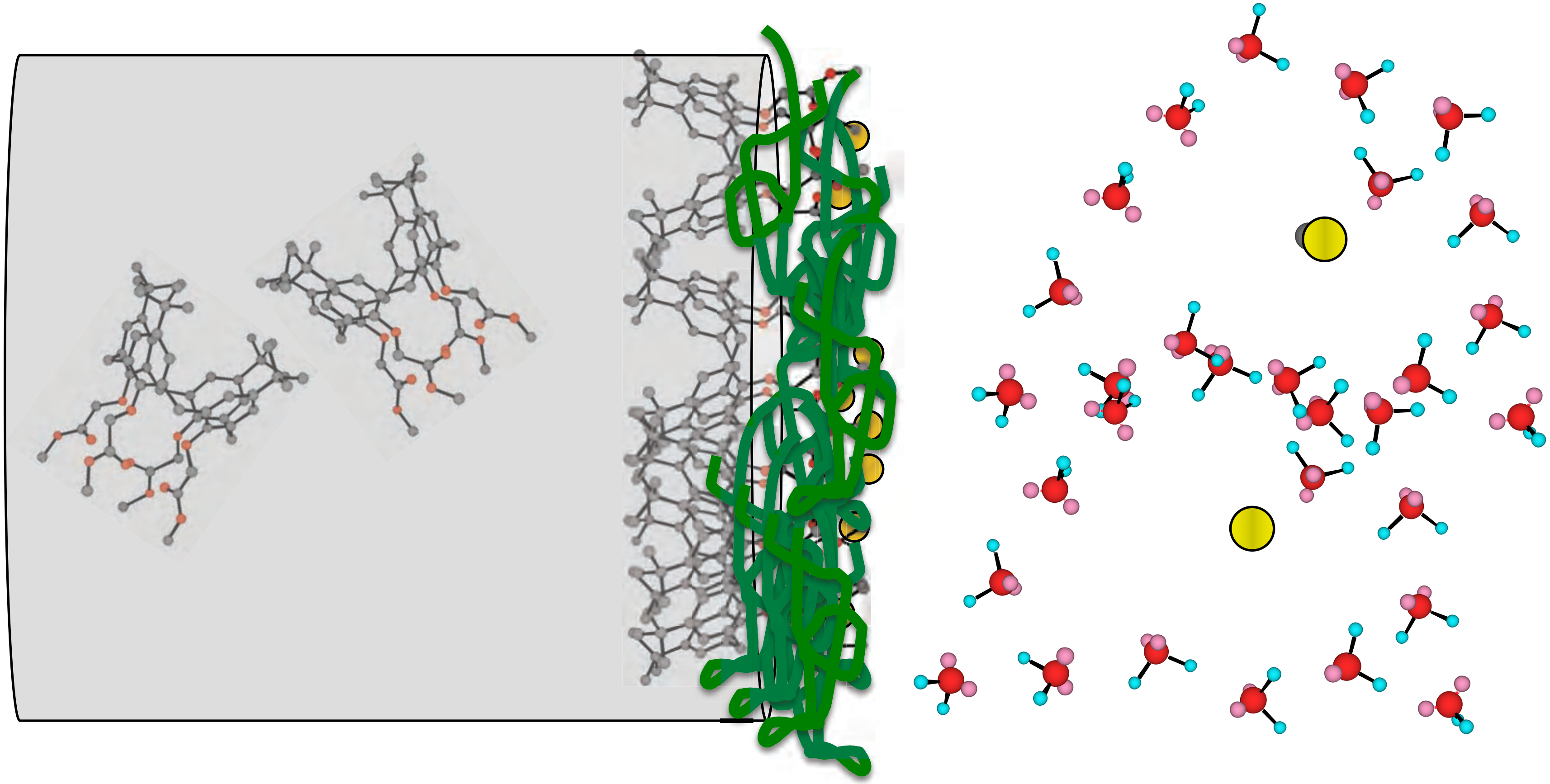


Argo (2000). Argo float data and metadata from Global Data Assembly Centre (Argo GDAC) http://doi.org/10.17882/42182

Core: 3287 Biochemical:306

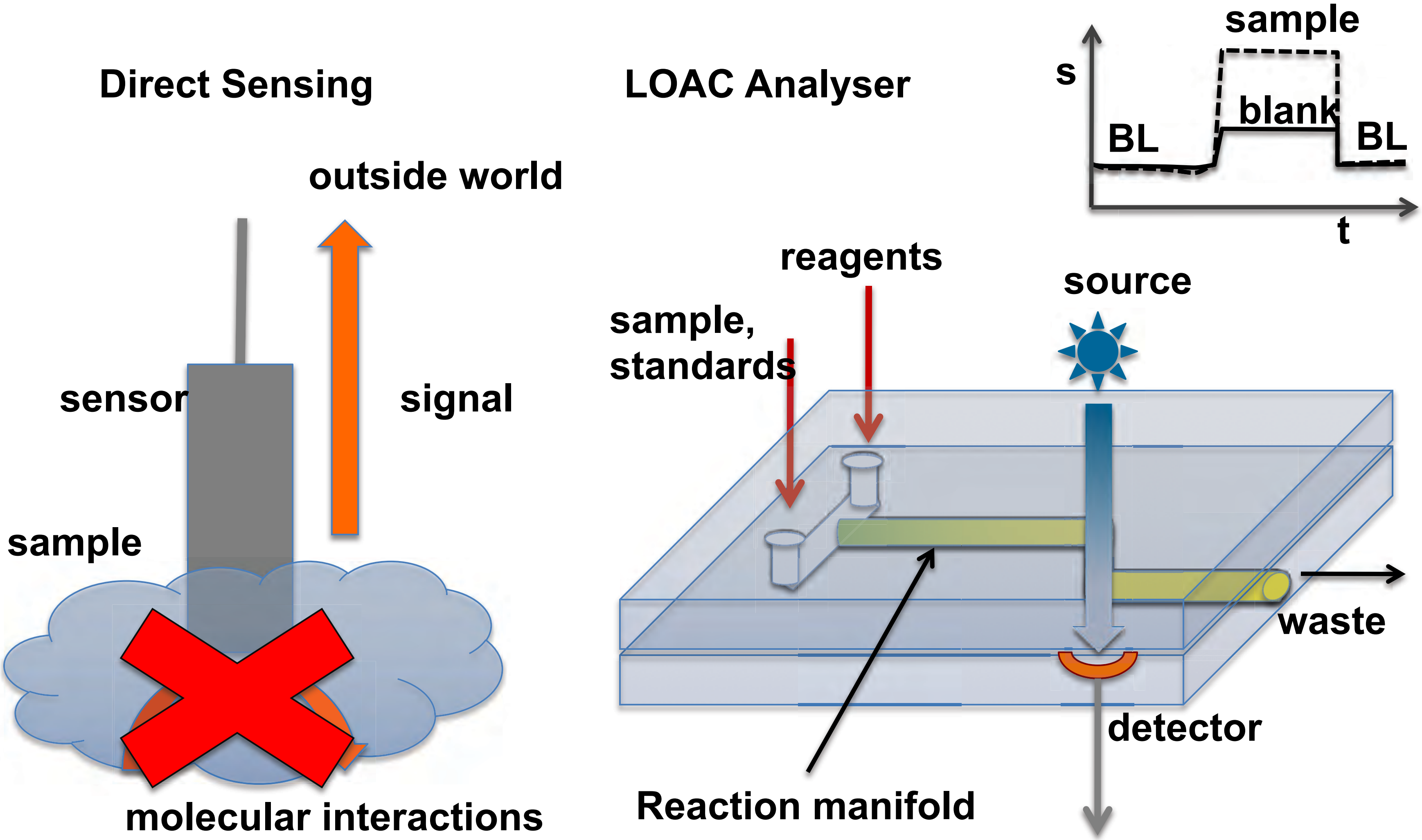
Suspended particles: 186; Nitrate: 121 Chlorophyll: 186 pH: 97 DO: 302

Control of membrane interfacial exchange & binding processes



Remote, autonomous chemical sensing is a tricky business!

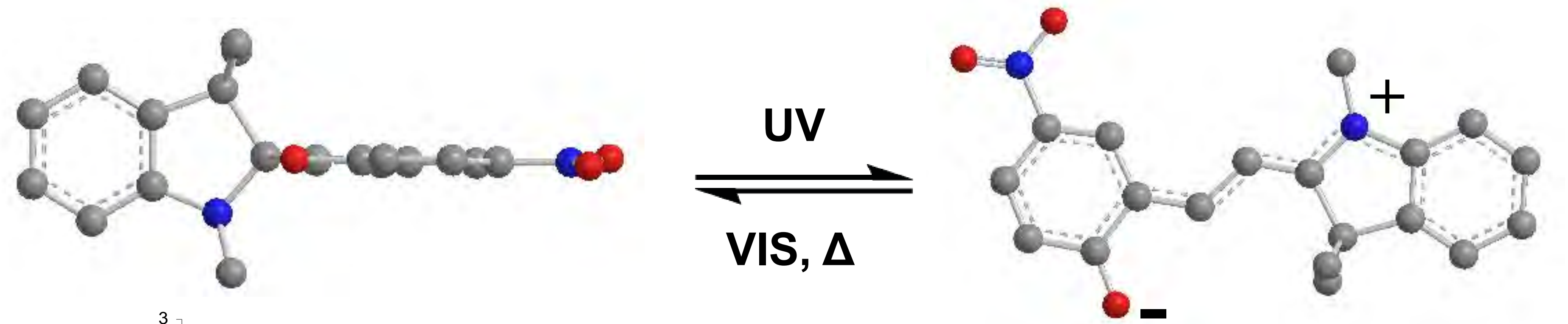
Direct Sensing vs. Reagent Based LOAC/ufluidics



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



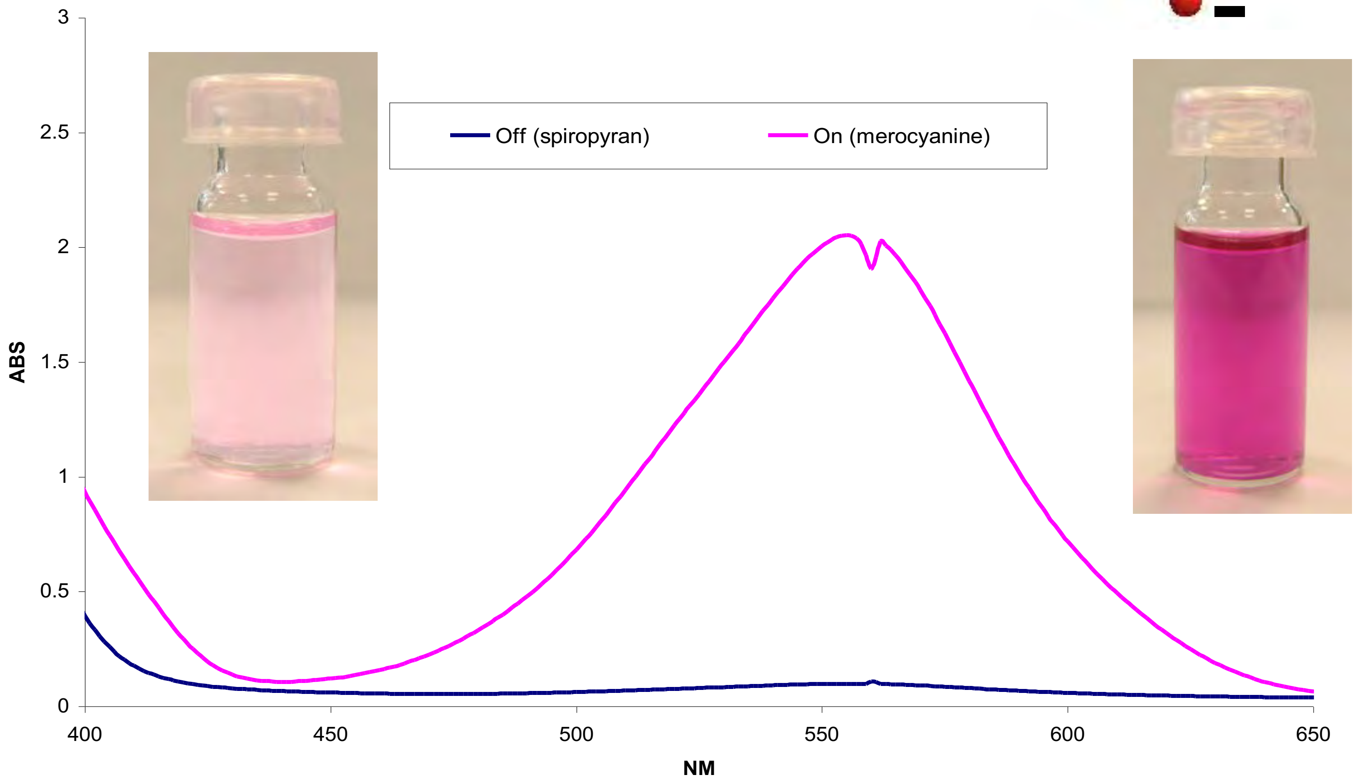
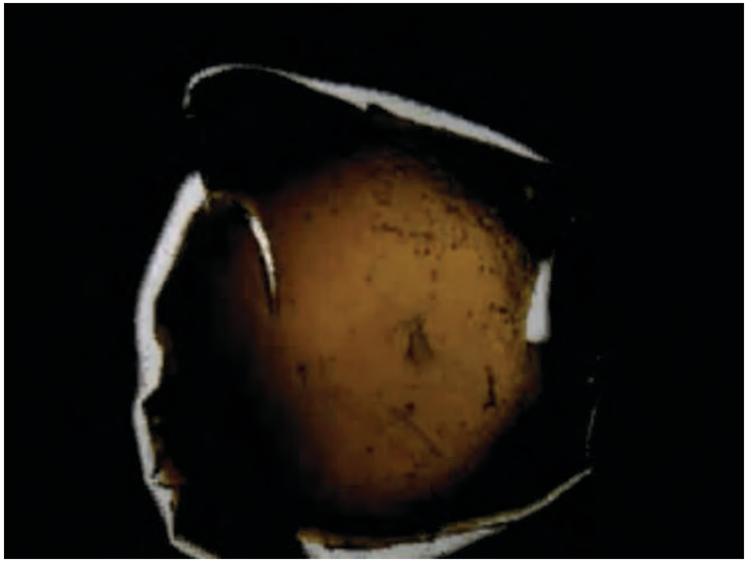
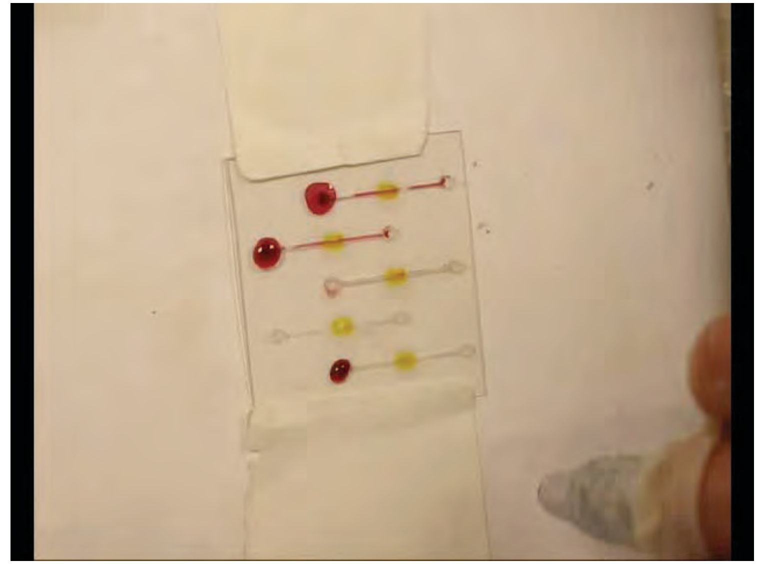
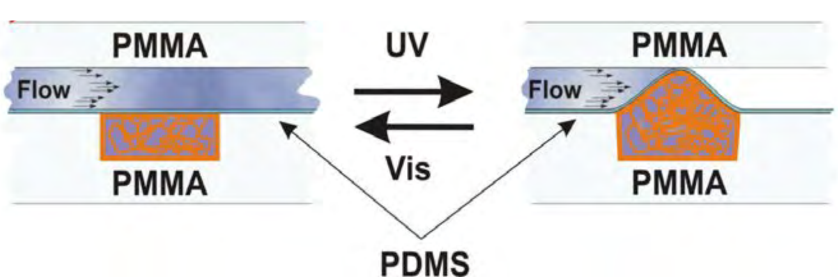
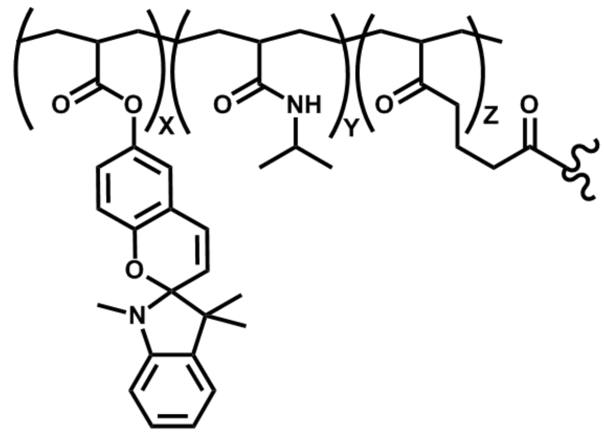


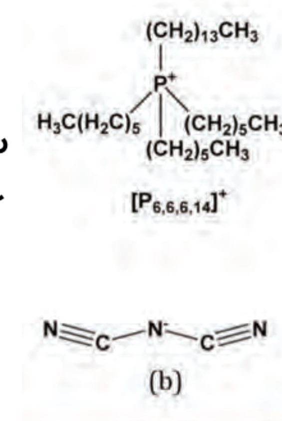
Photo-actuator polymers as microvalves in microfluidic systems











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

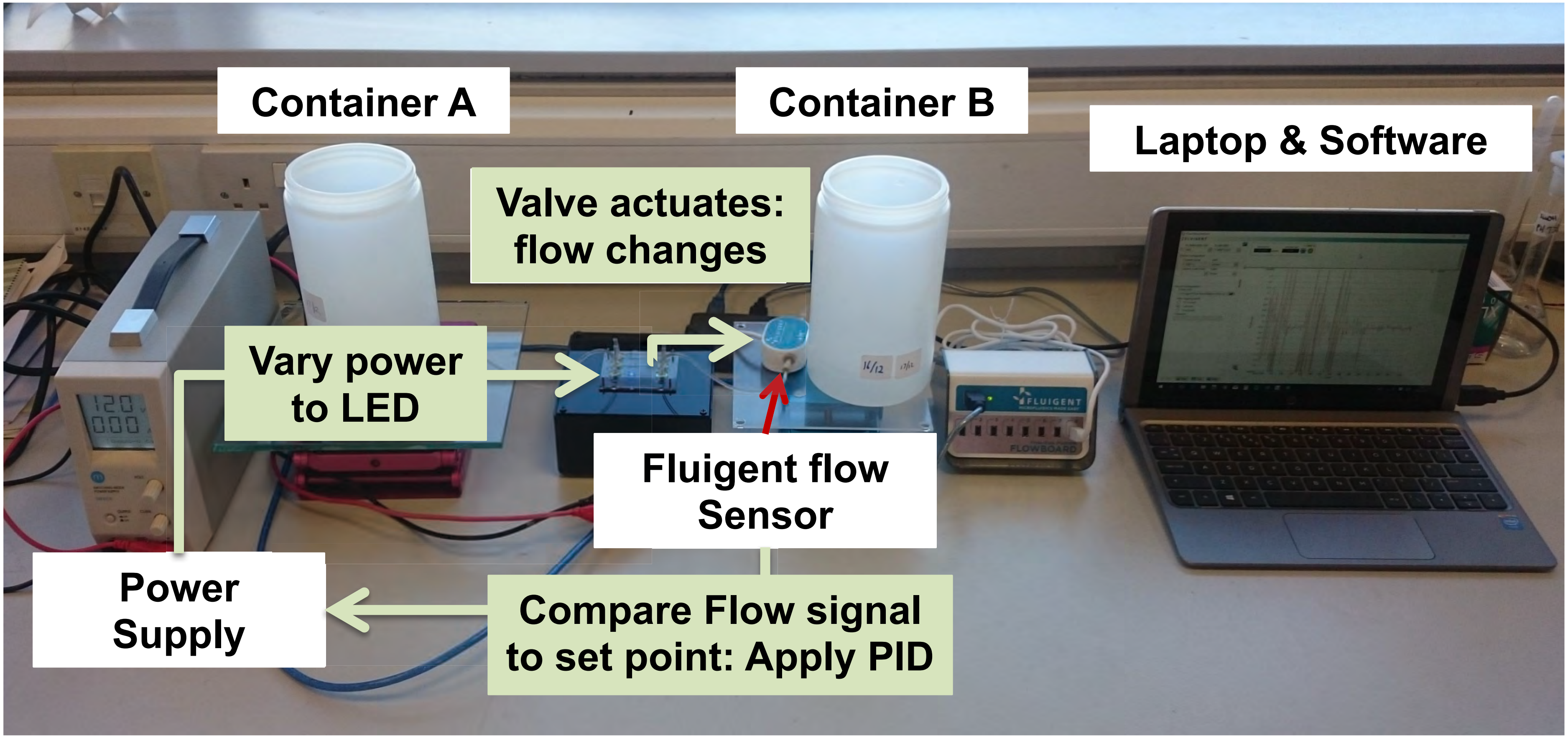
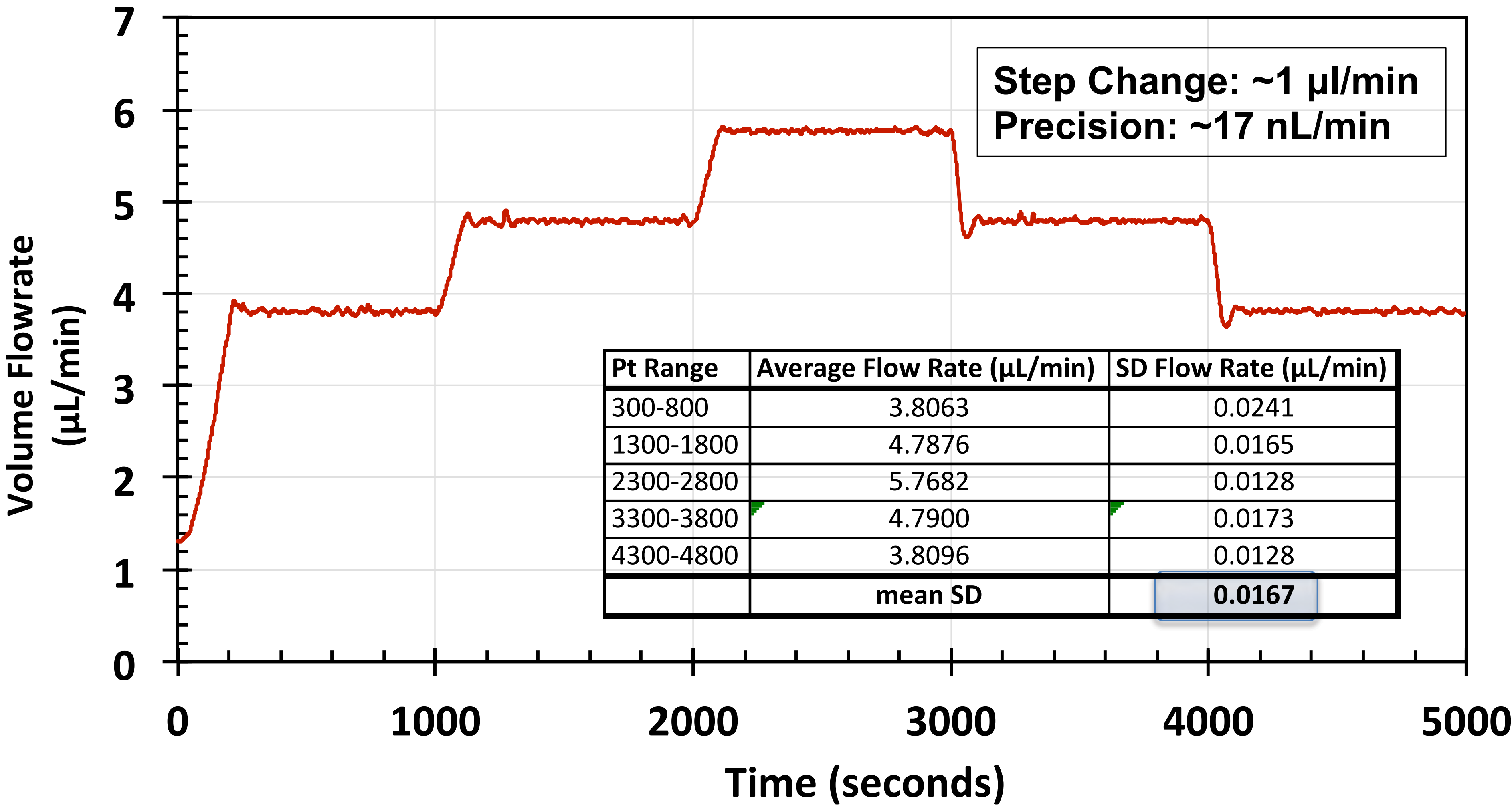


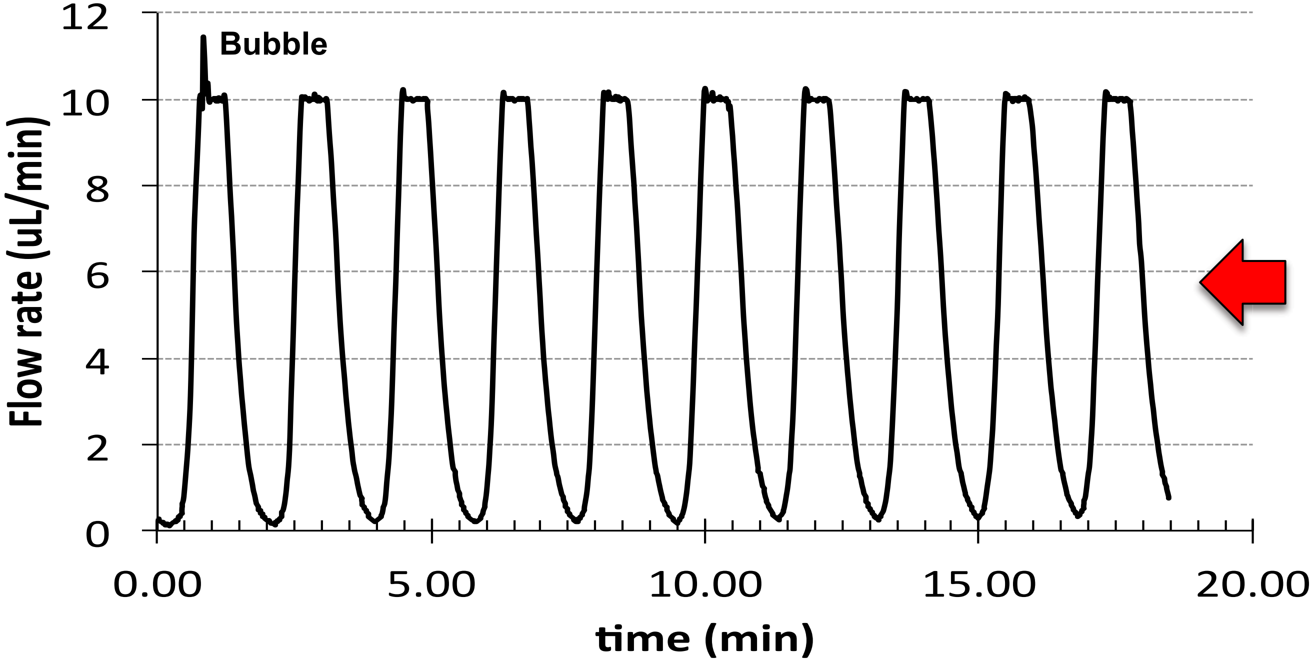
Photo-Controlled Flow Rate



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**

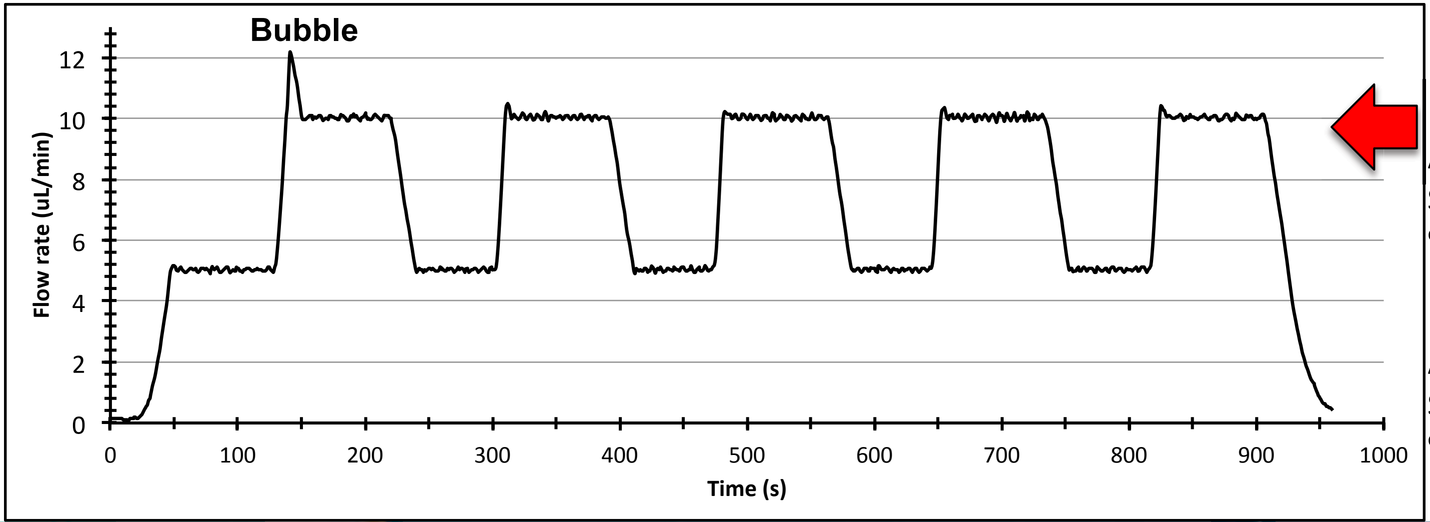
C. Delaney, P. McCluskey, S. Coleman, J. Whyte, N. Kent, D. Diamond, Precision control of flow rate in microfluidic channels using photoresponsive soft polymer actuators, LAB ON A CHIP. 17 (2017) 2013–2021. doi:[10.1039/c7lc00368d](10.1039/c7lc00368d).

Some figures of merit



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

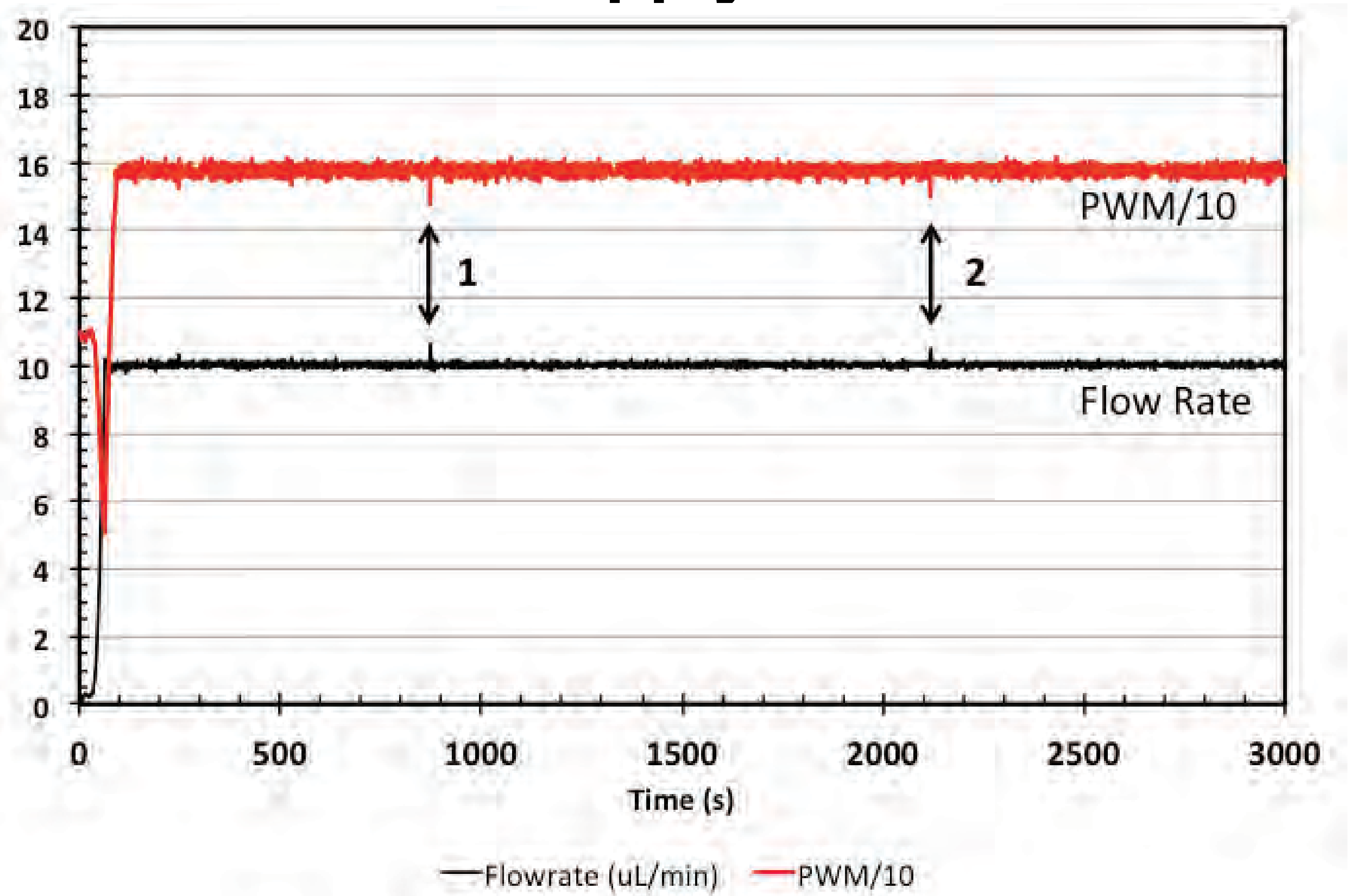
Averages (n=10)	
mean	10.0028
Mean SD	0.0323
Error Mean	0.0028
%RSD	0.3235
%RE mean	0.0279



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

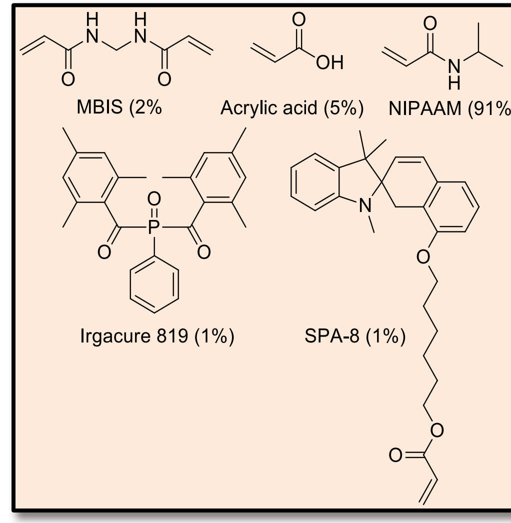
Mean %RE (5=true)	0.780
Mean %RE (5.039=true)	0.098
Average of mean	5.039
SD Mean	0.006
%RSD	0.120
Mean %RE (10=true)	0.372
Mean %RE (10.037=true)	0.102
Average of mean	10.037
SD Mean	0.012
%RSD	0.124

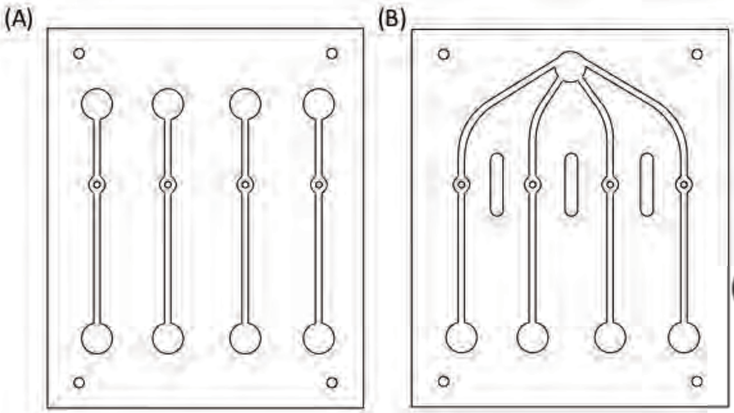
Power Supply to LED

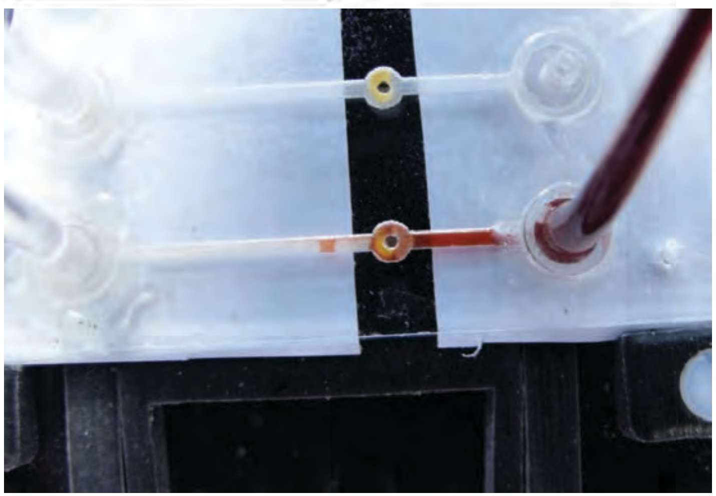


Over a period of 50 min constant maintenance of 10 µL/min flow rate there is no discernable change in LED power ➔ diagnostic information

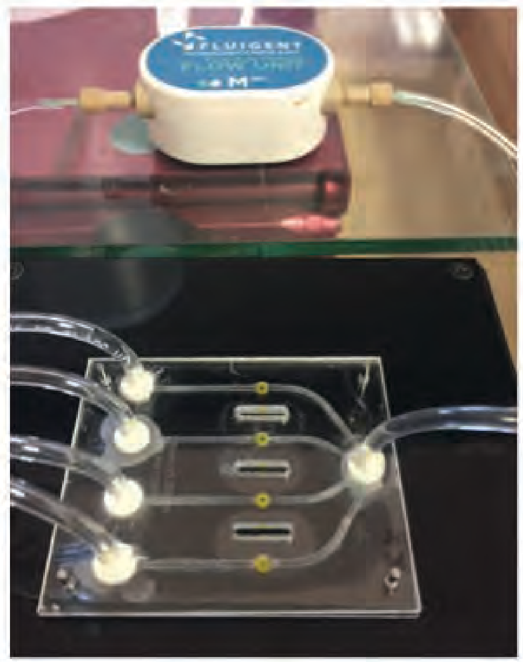
Multiplexing: Valve Arrays



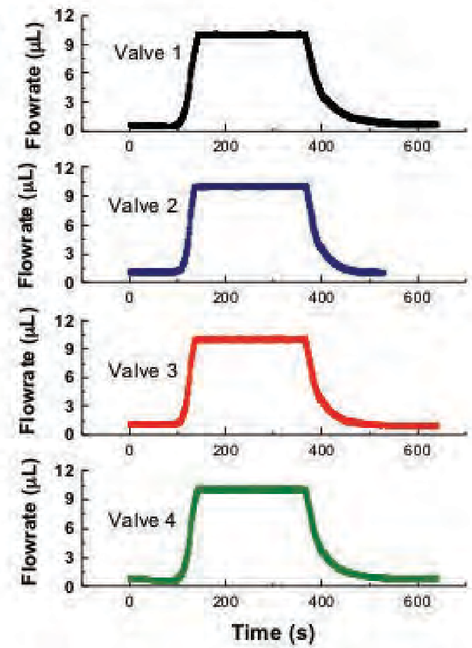




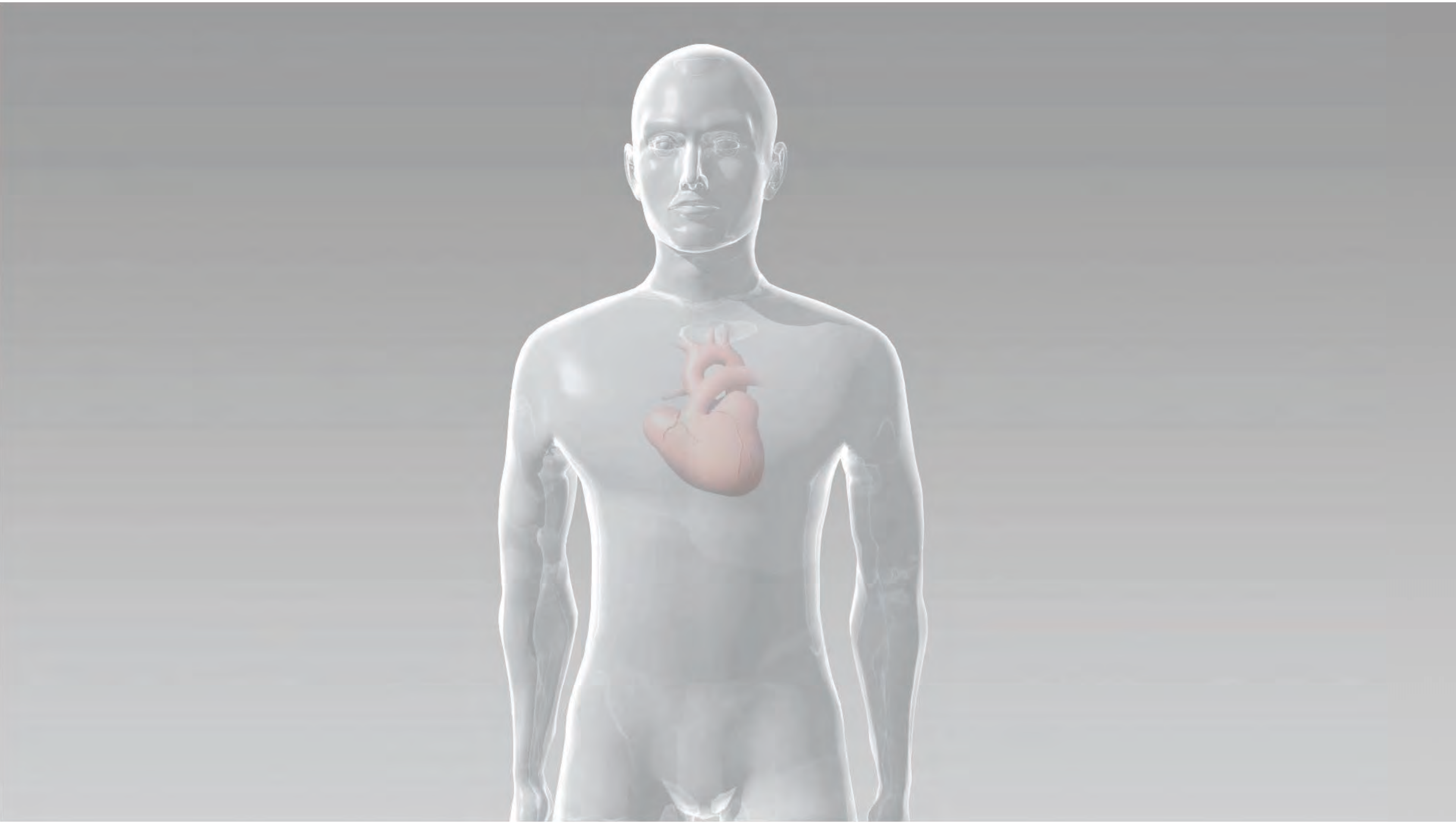
(A)



(B)



Bioinspired Fluidics



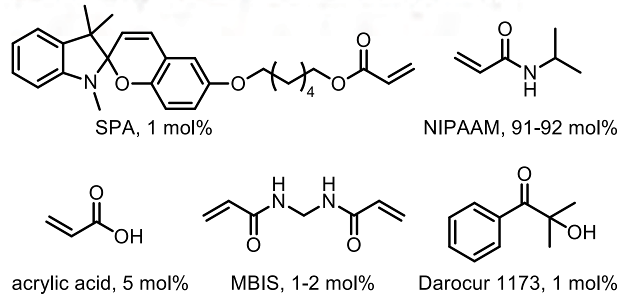
Photocontrol of Assembly and Subsequent Switching of Surface Features

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

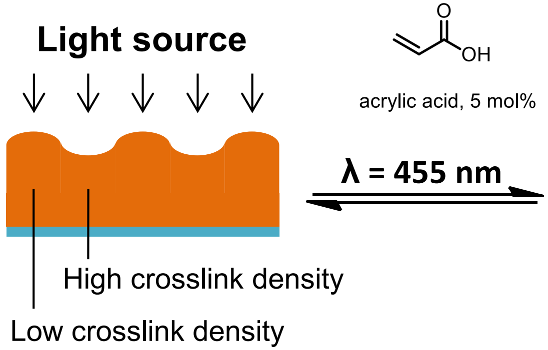
ACS applied materials & interfaces, 6 (2014) 7268-7274

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

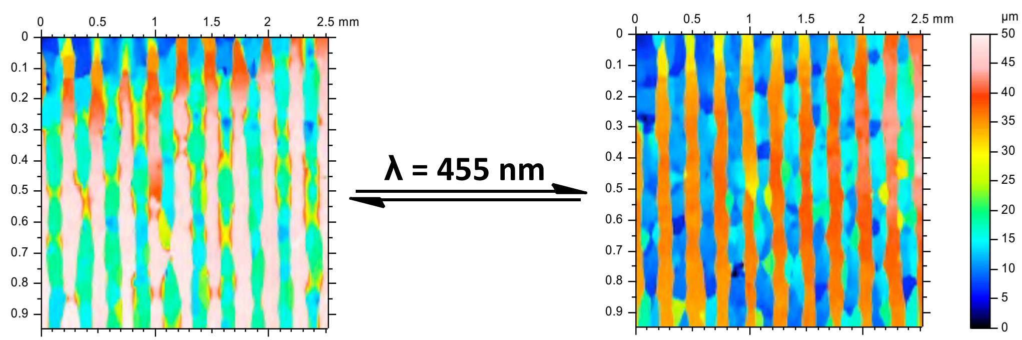
Jelle E. Stumpel,[†] Bartosz Ziółkowski,[‡] Larisa Florea,[‡] Dermot Diamond,[‡] Dirk J. Broer,[*,†,§] and Albertus P. H. J. Schenning[*,†,§]

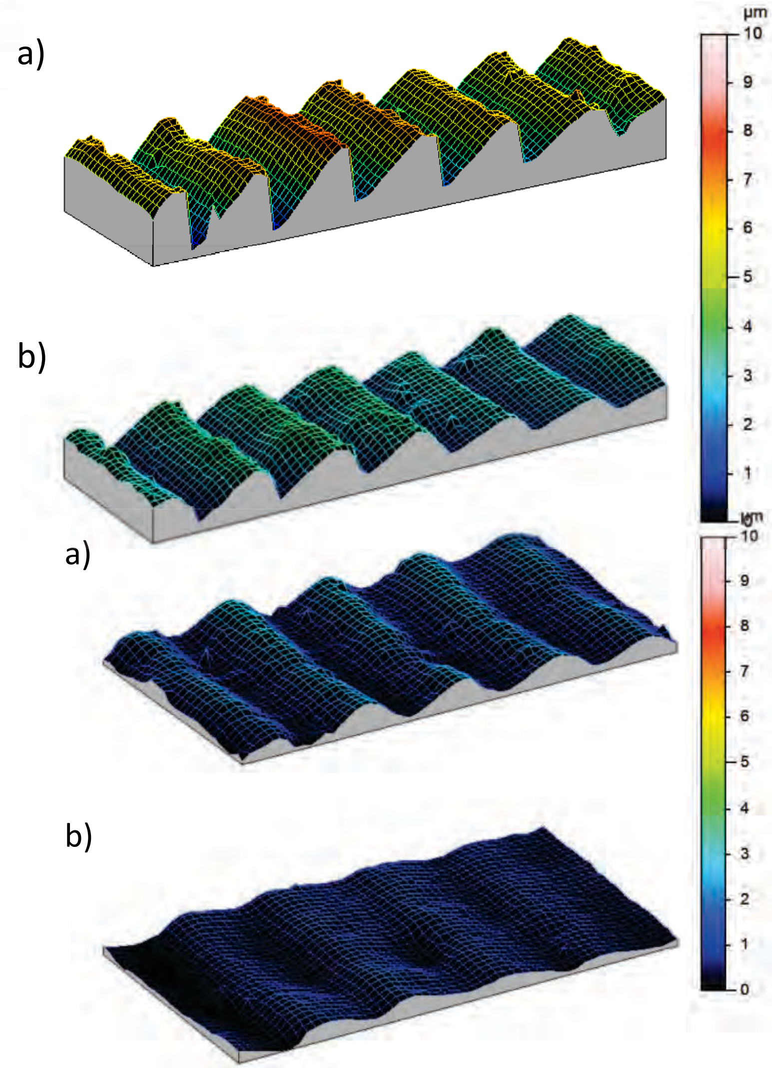


a)

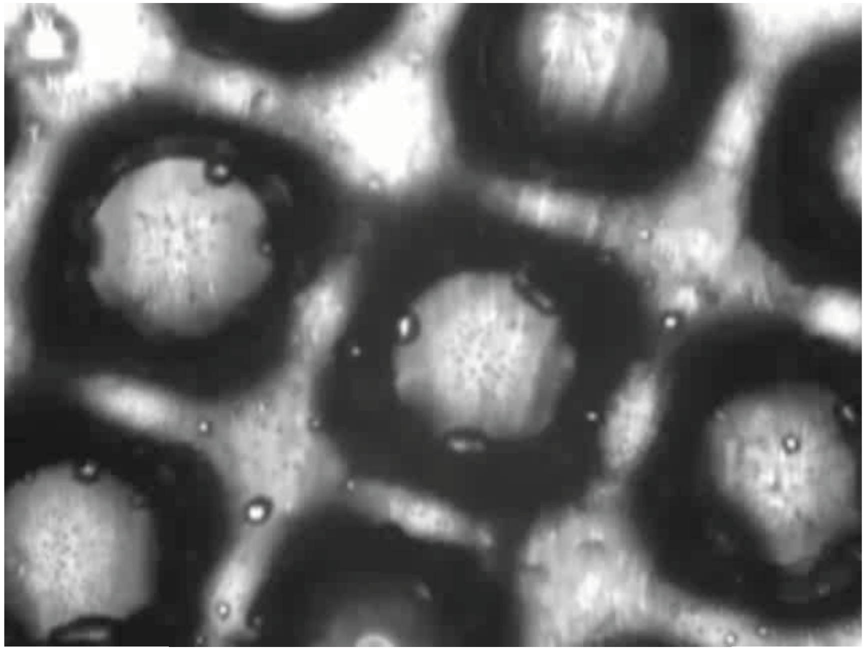


b)

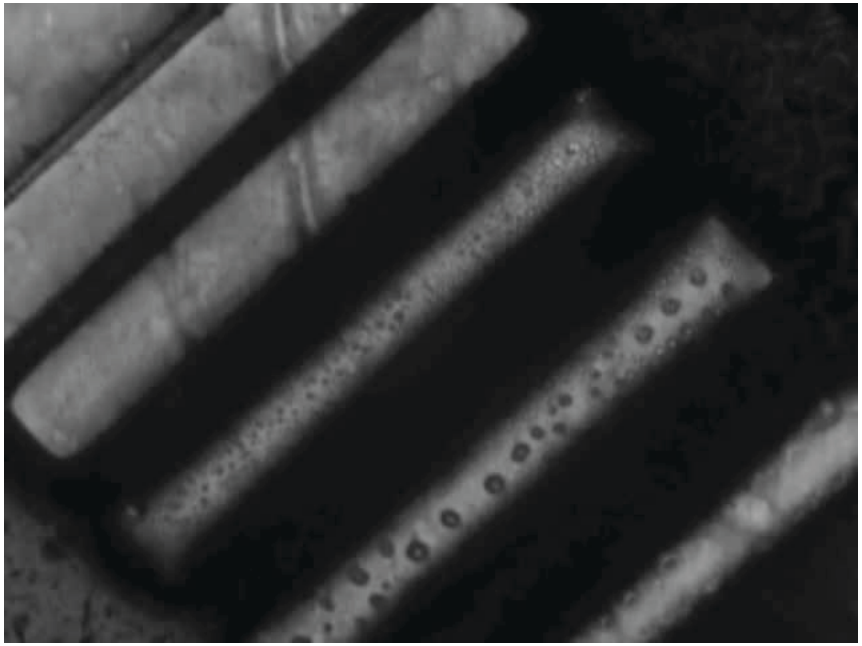




Flexible creation of µ-dimensioned features in flow channels using in-situ photo-polymerisation



Ntf2 pillars speed x3

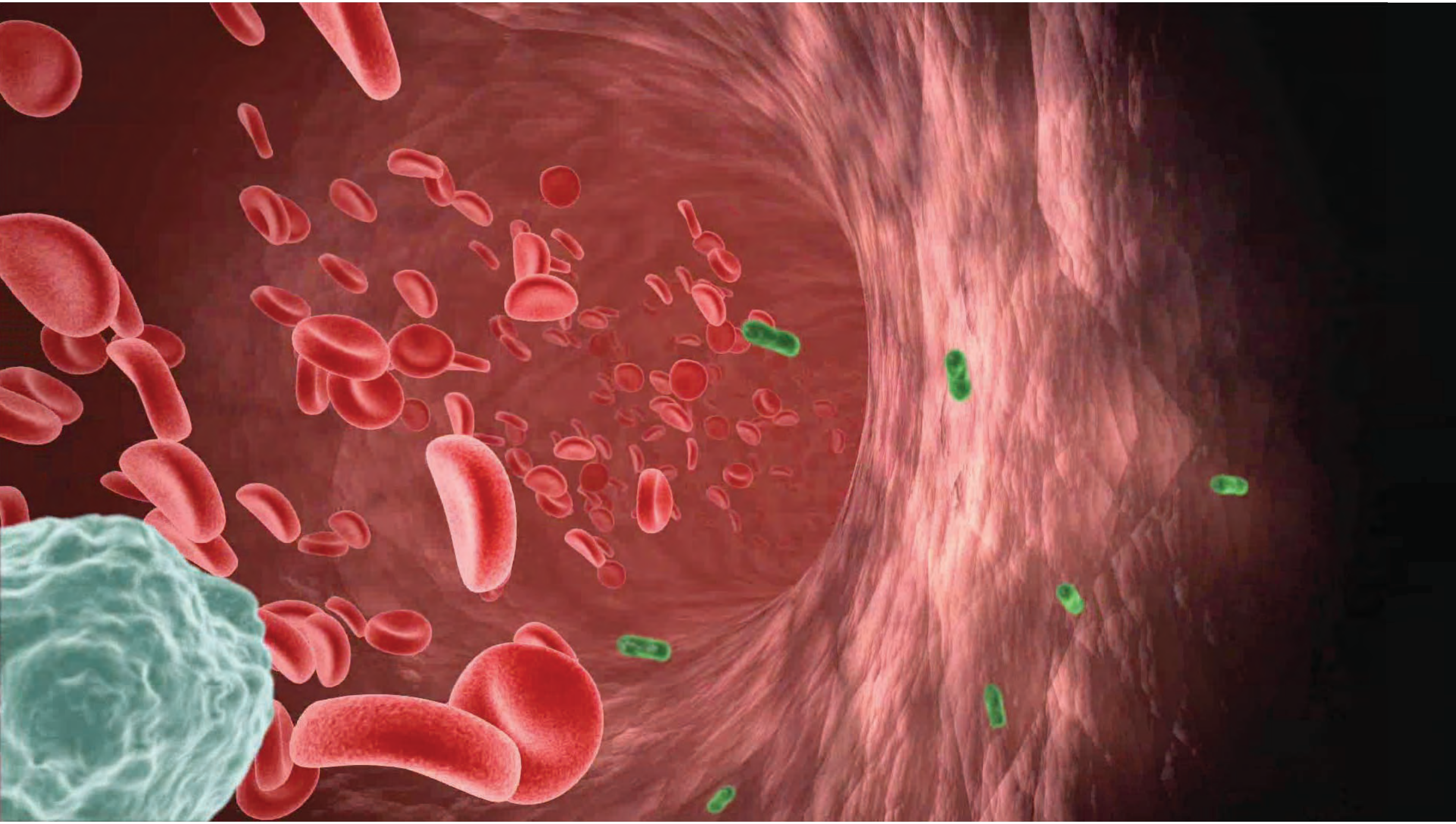


DCA lines speed x4

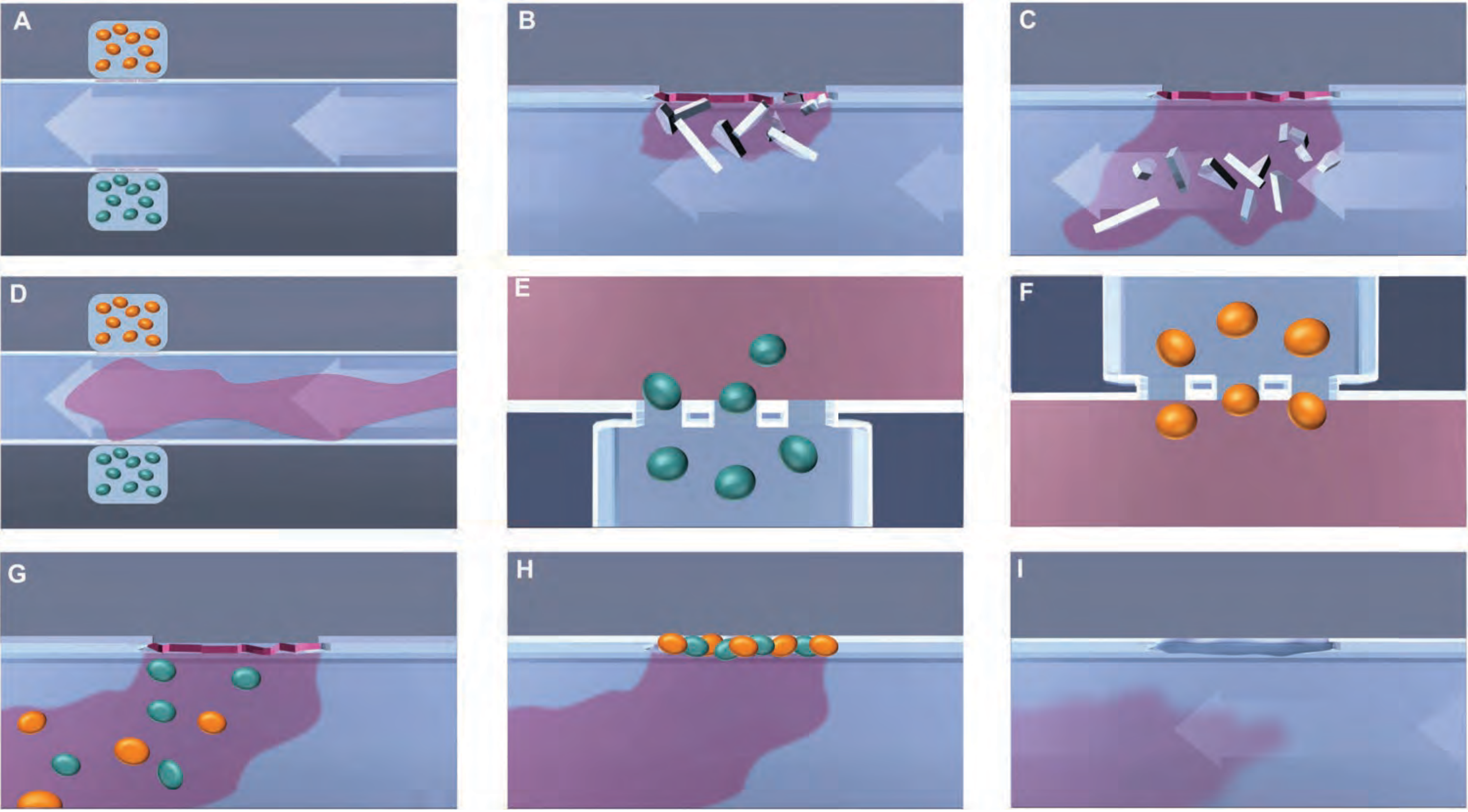
With Dr Peer Fischer, Fraunhofer-Institut für Physikalische Messtechnik (IPM), Freiburg

Binding behavior can also be modulated using light

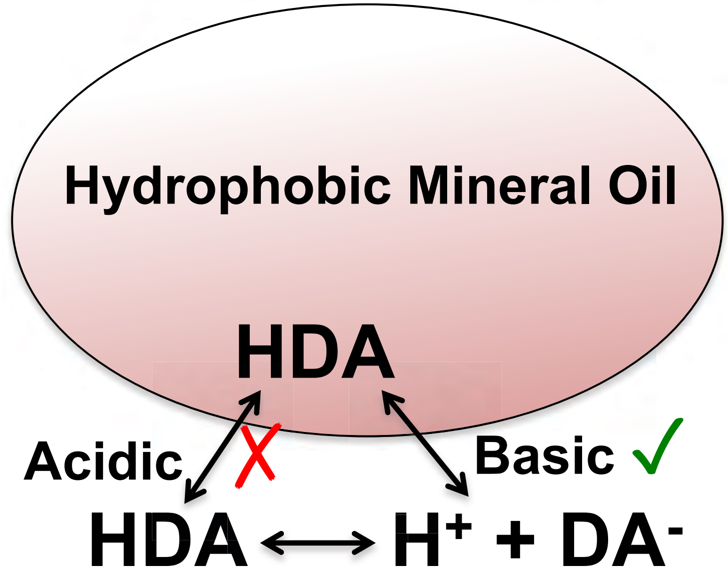
The Immune System



We have all the sub units.....



Chemotactic Systems



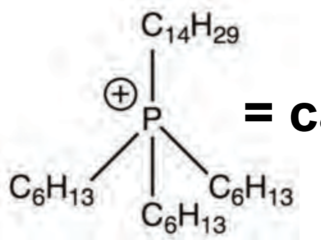
In a pH gradient, DA^- is preferentially transferred to the aqueous phase at the more basic side of the drop.

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 <-> $H^+ + DA^-$**

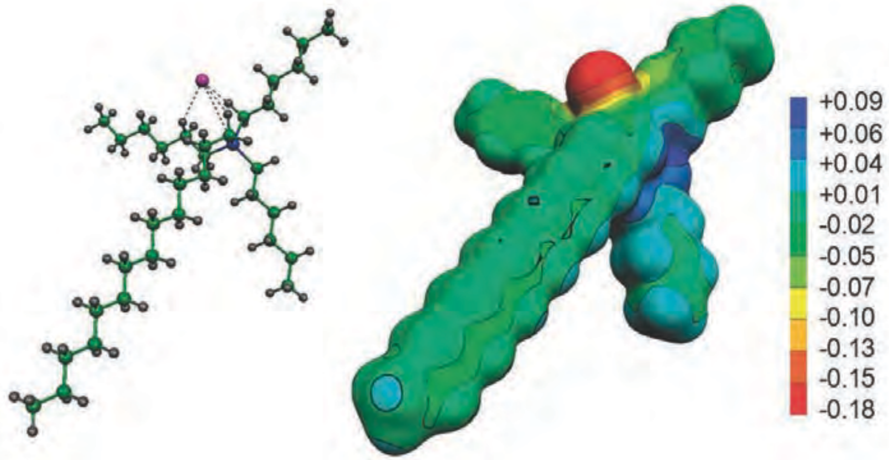
Maze Solving by Chemotactic Droplets; Istvan Lagzi, Siowling Soh, Paul J. Wesson, Kevin P. Browne, and Bartosz A. Grzybowski; **J. AM. CHEM. SOC. 2010, *132, 1198–1199***

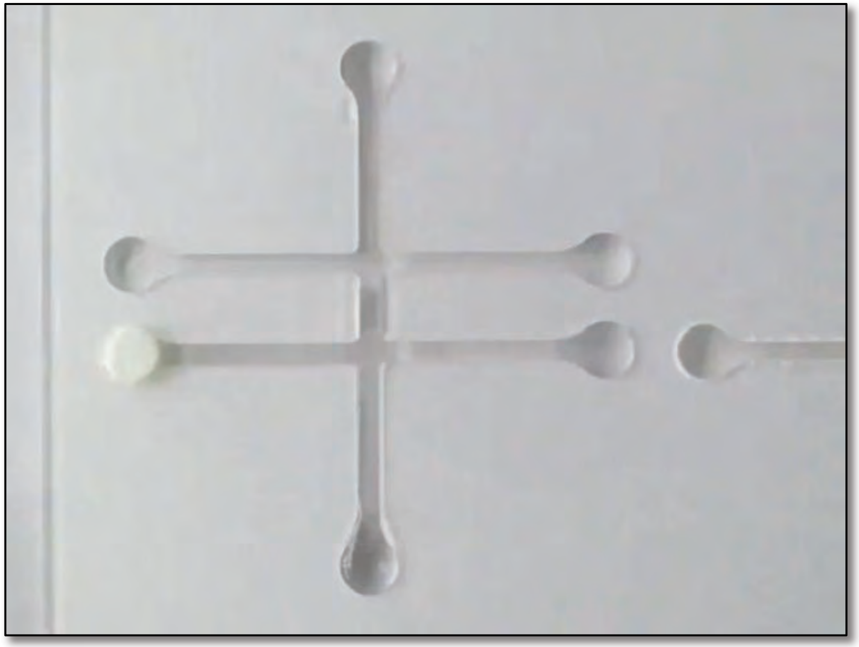
Fuerstman, M. J.; Deschatelets, P.; Kane, R.; Schwartz, A.; Kenis, P. J. A.;Deutch, J. M.; Whitesides, G. M. *Langmuir 2003, 19, 4714.*

Chemotactic IL Droplets



= cationic surfactant



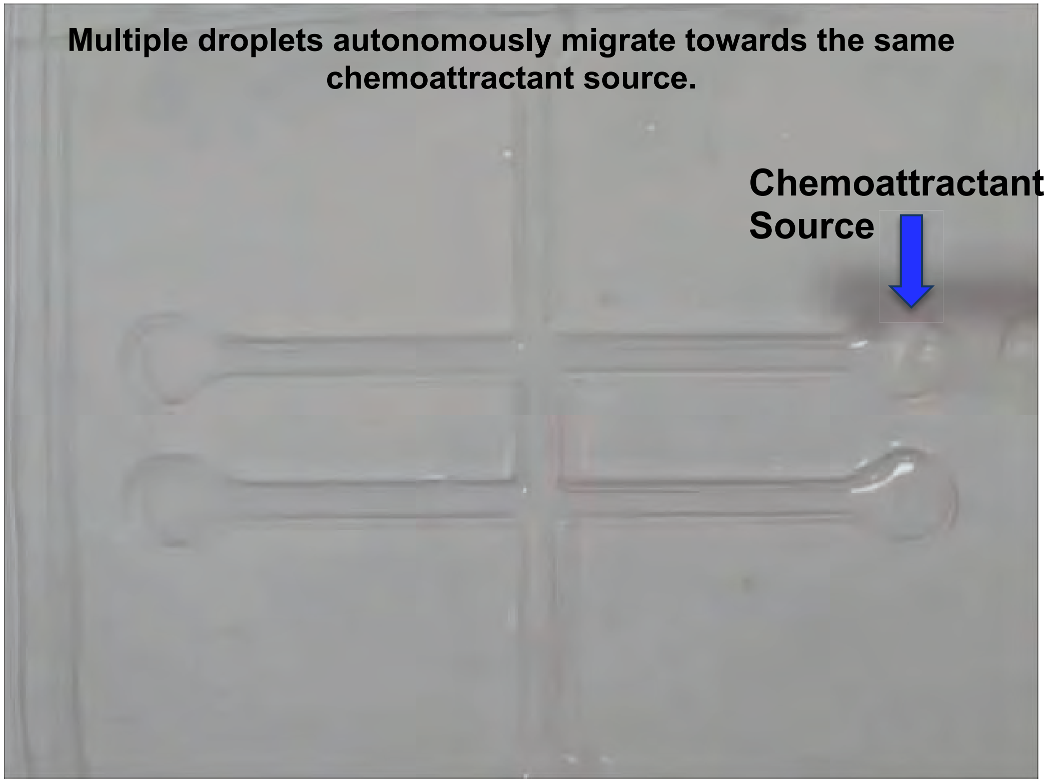


Trihexyl(tetradecyl)phosphonium chloride ($[P_{6,6,6,14}][Cl]$) droplets with a small amount of 1-(methylamino)anthraquinone red dye for visualization. The droplets spontaneously follow the gradient of the Cl^- ion which is created using a polyacrylamide gel pad soaked in 10^{-2} M HCl; A small amount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

From 2D to 3D Movement

2D Movement



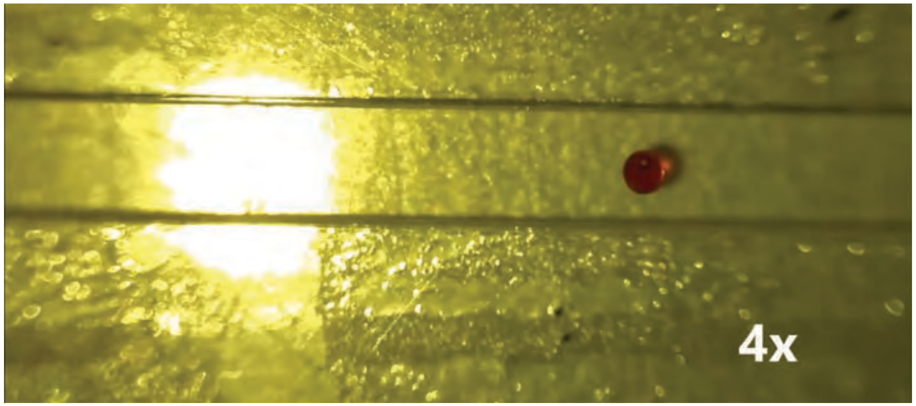
L. Florea et al. Chem. Comm. 51 (2015) 2342.

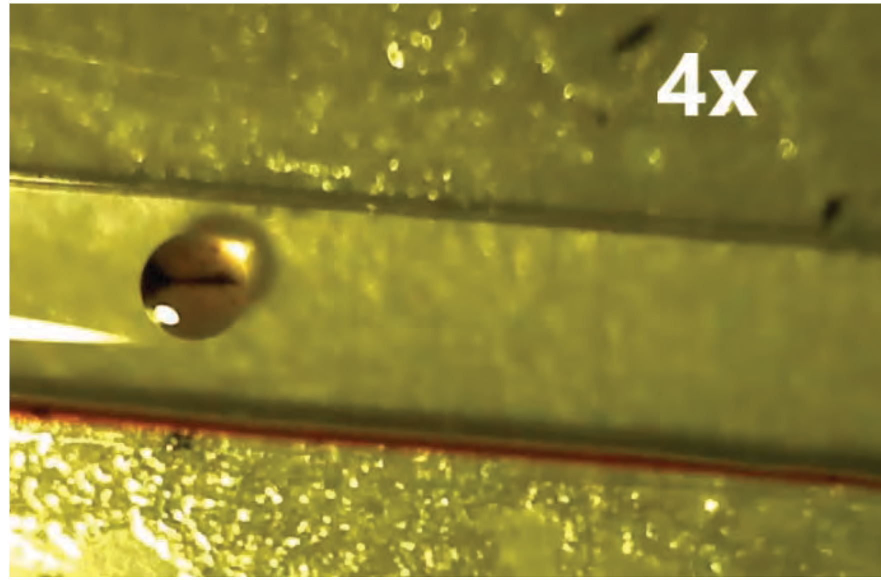
L. Florea et al. Sens. Actuators B 239 (2017) 1069.

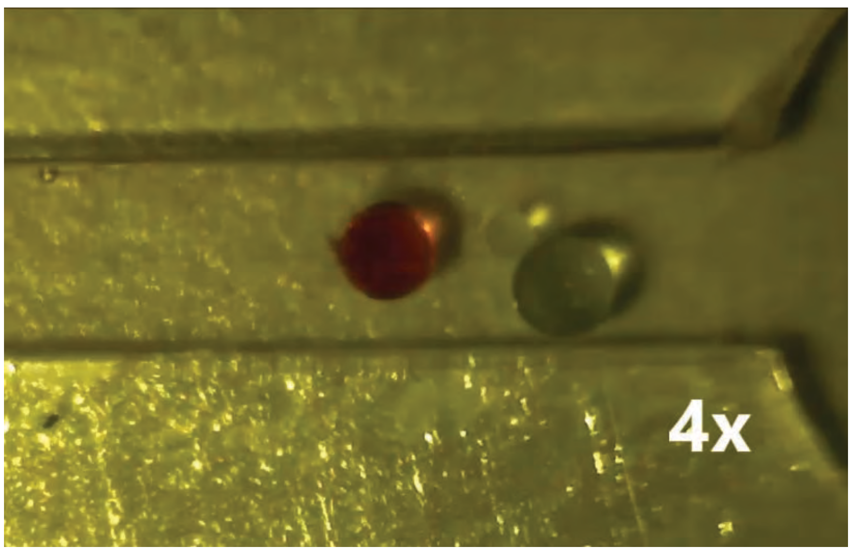
3D Movement

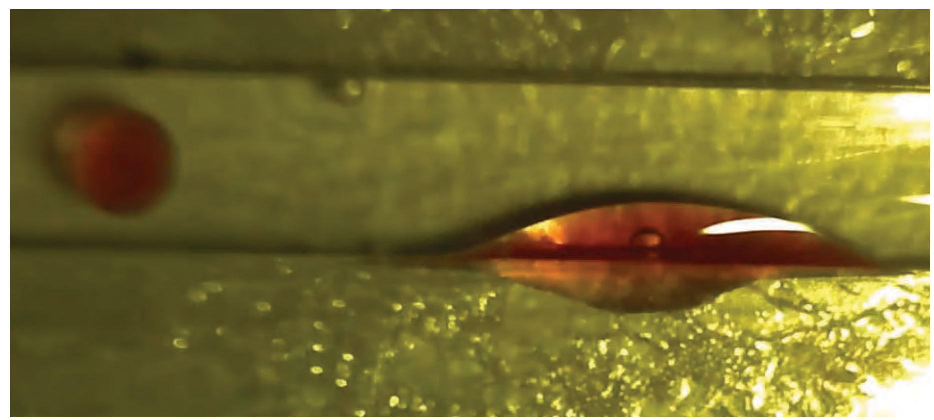
With David Officer, Adv Mater. 2018
doi: 10.1002/adma.201801821

Fun with Droplets and Dynamic Electro-Ionic Gradients



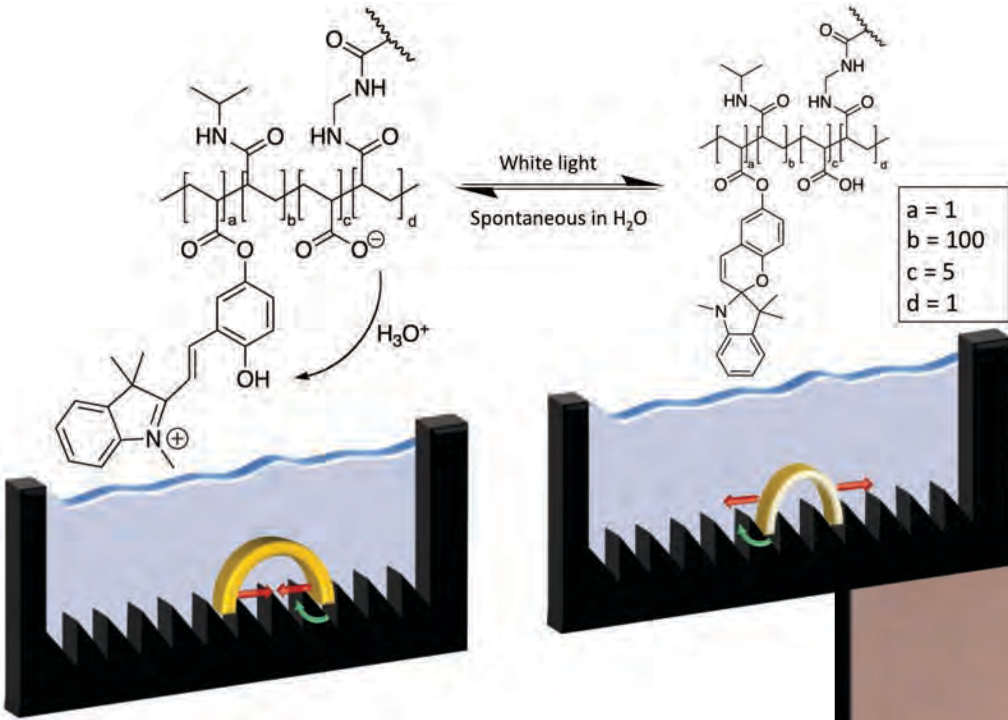




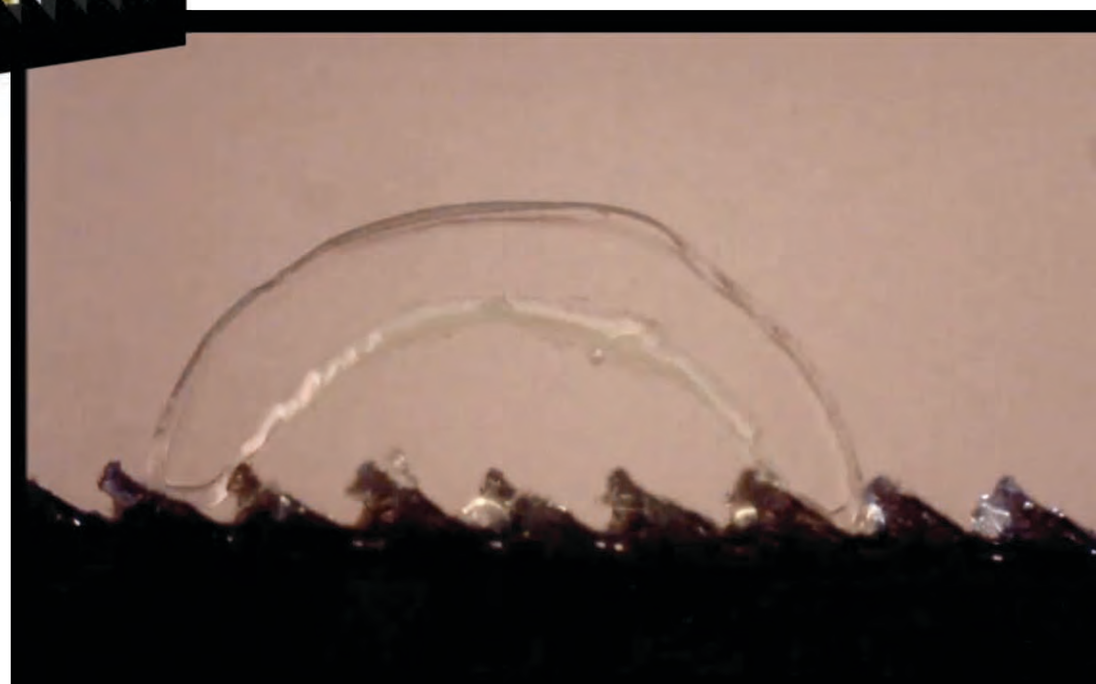


Joan Cabot, Brett Paull (UTAS), Larisa Florea

Photo-Responsive Soft Hydrogels



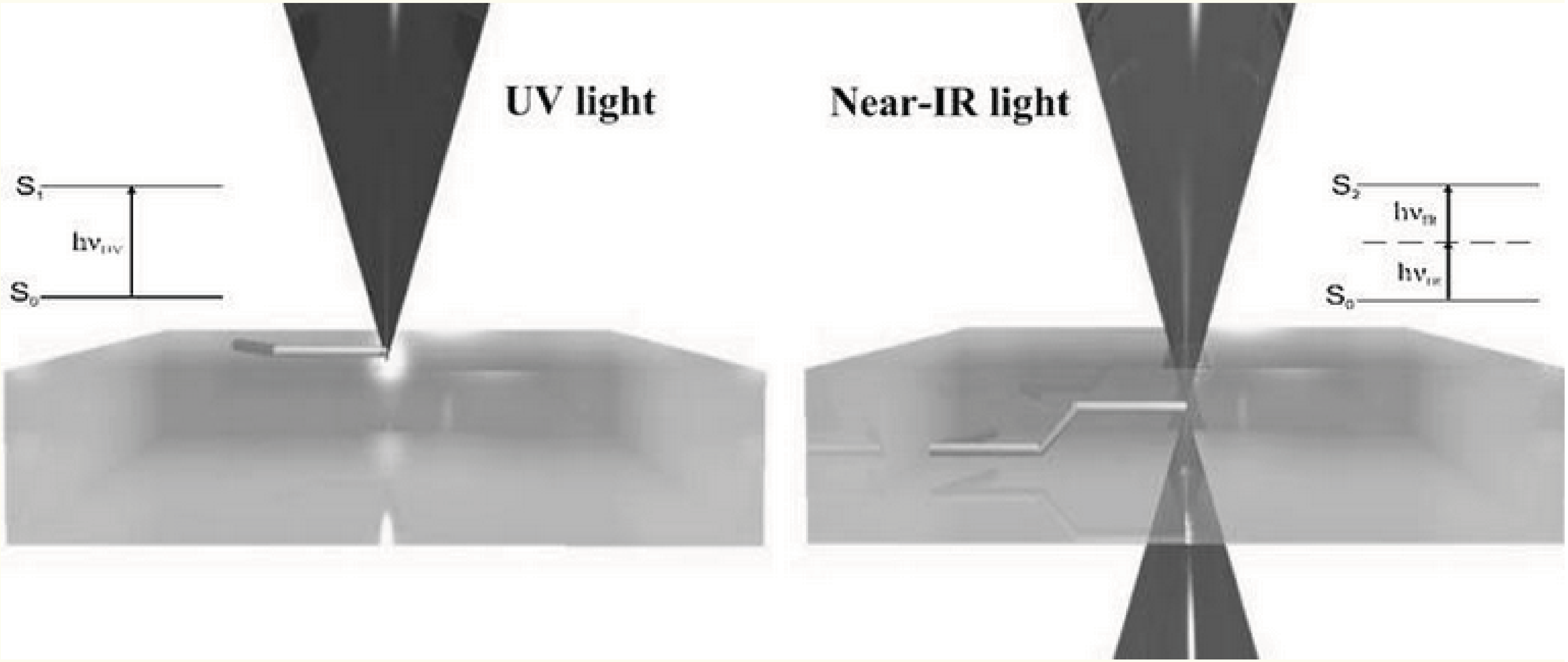
‘Walking towards the light’



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

2-Photon vs. Stereolithography

Stereolithography | **Two-photon polymerisation**



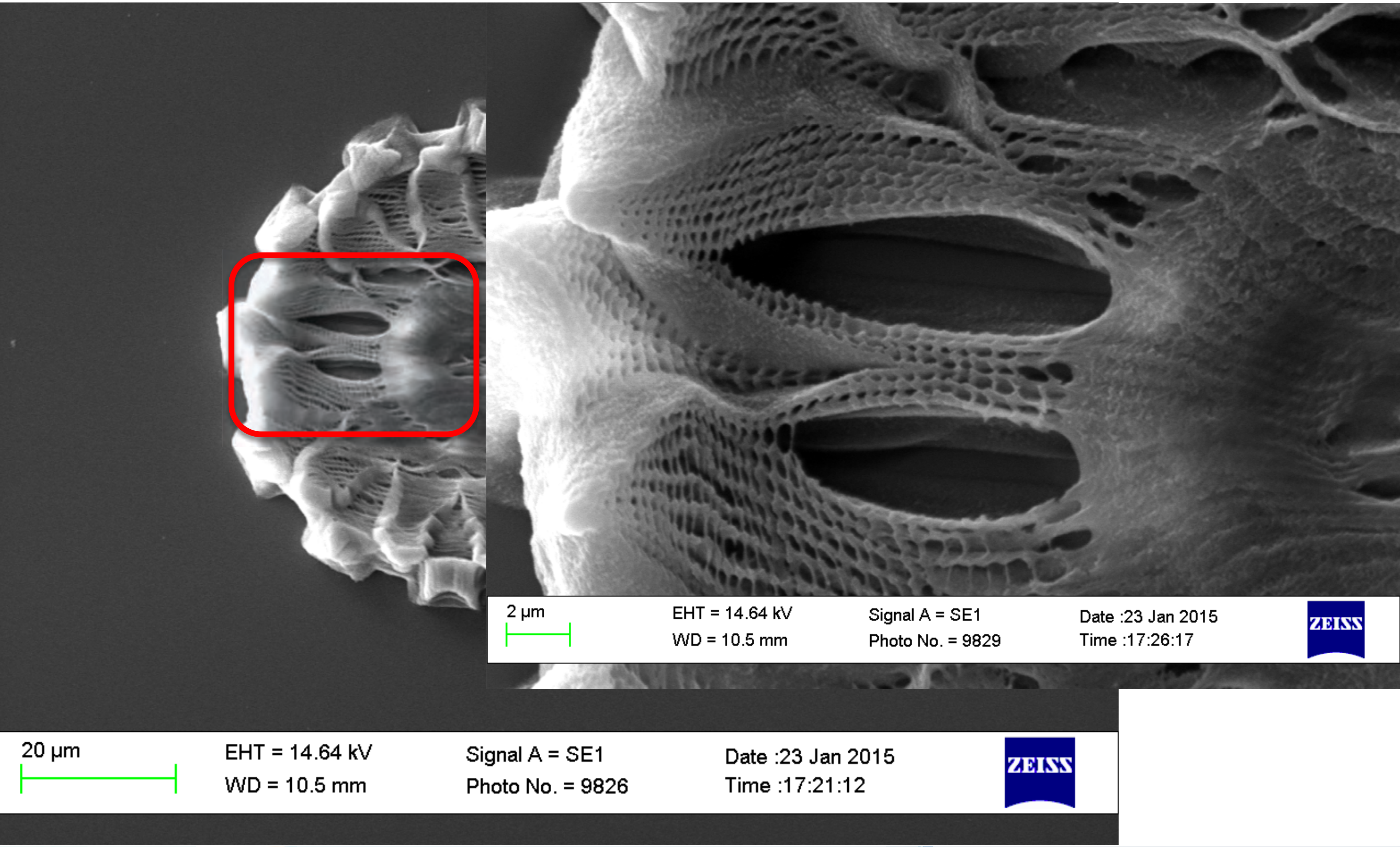
Stereolithography:

- Single photon absorption
- 2D patterns

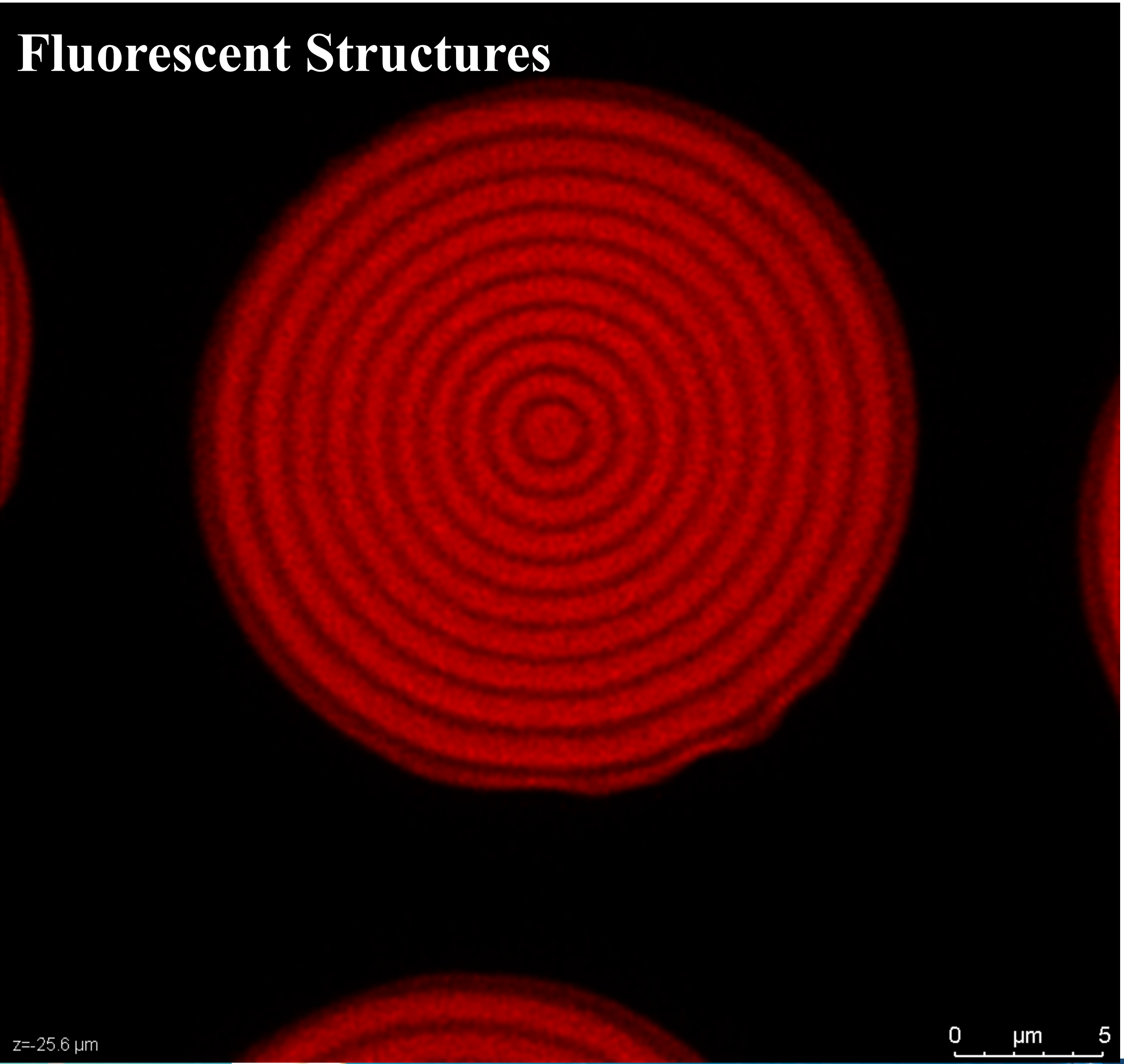
Two-photon polymerisation:

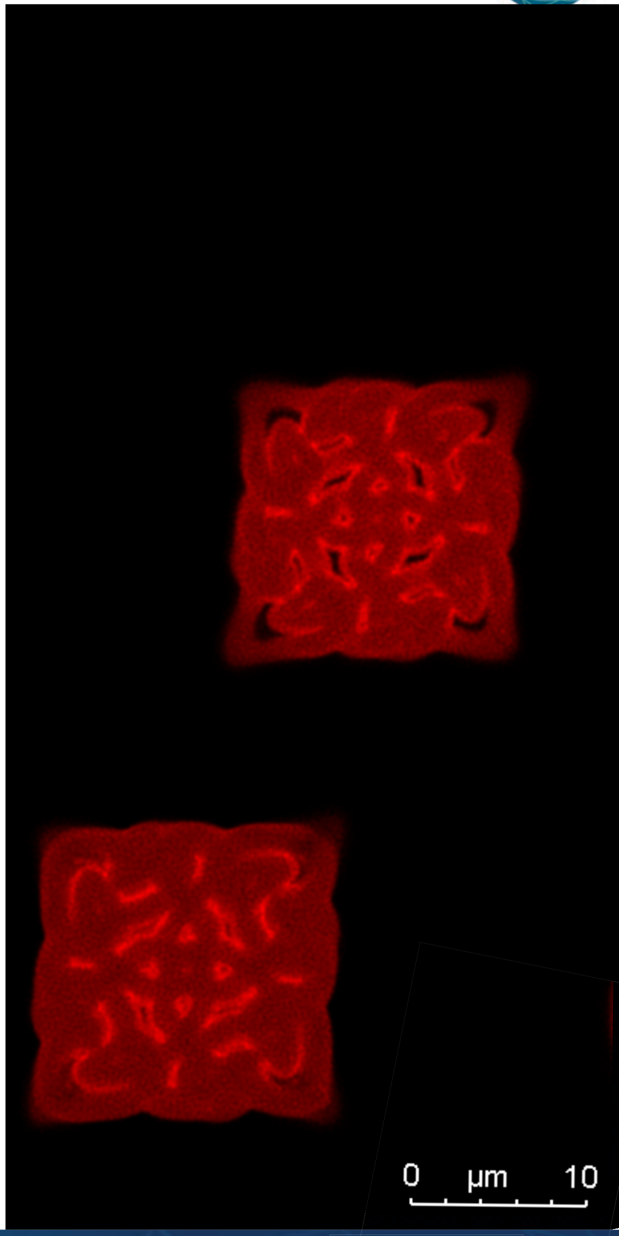
- Two photon absorption
- 3D structures

‘Daisy’ – Micro/Nano Scaled Porous Structure
(with Guang Zhong Yang, Imperial College London)

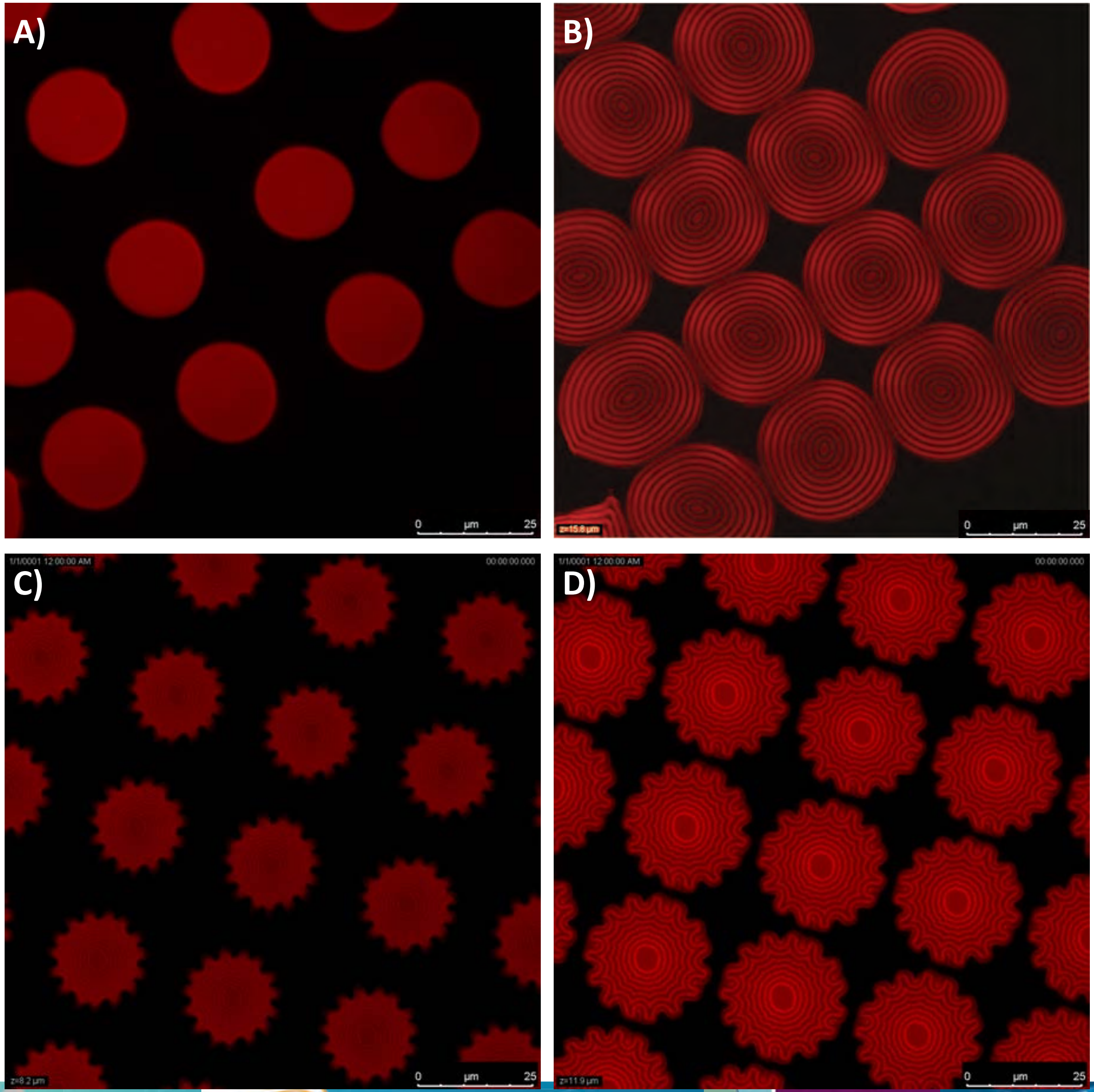


Rhodamine labeled gels (STED Microscopy)





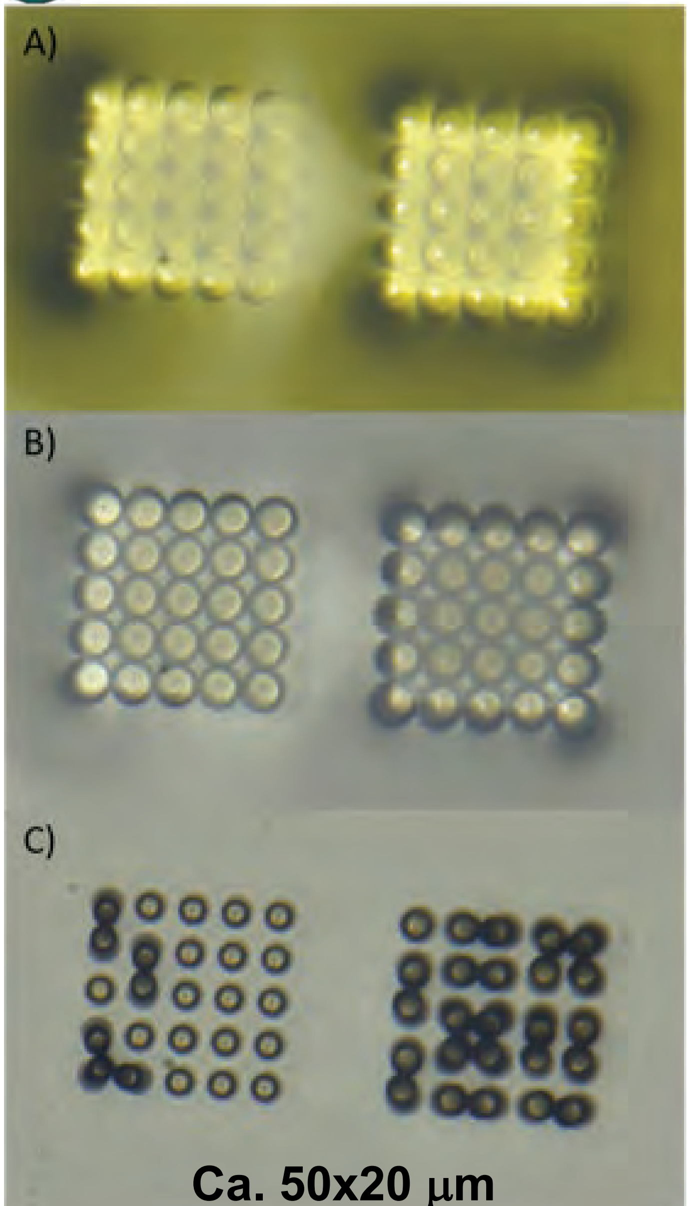
Endo-Skeleton Controlled Actuation

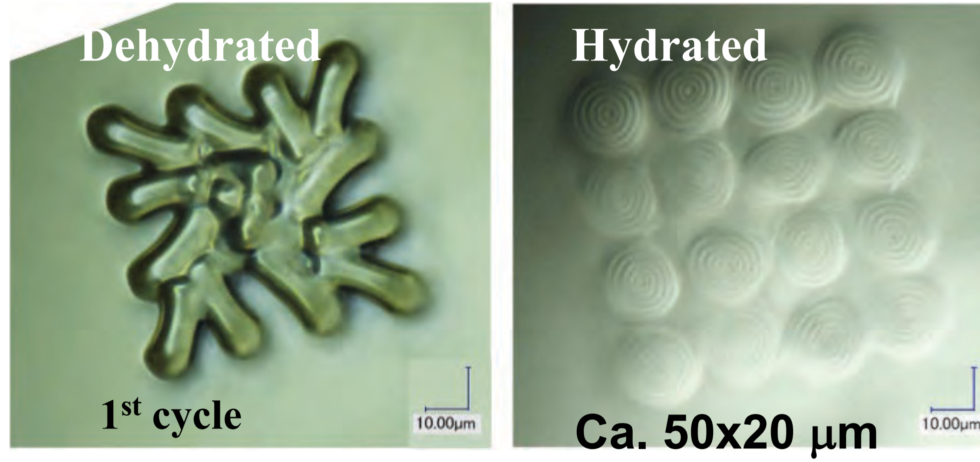


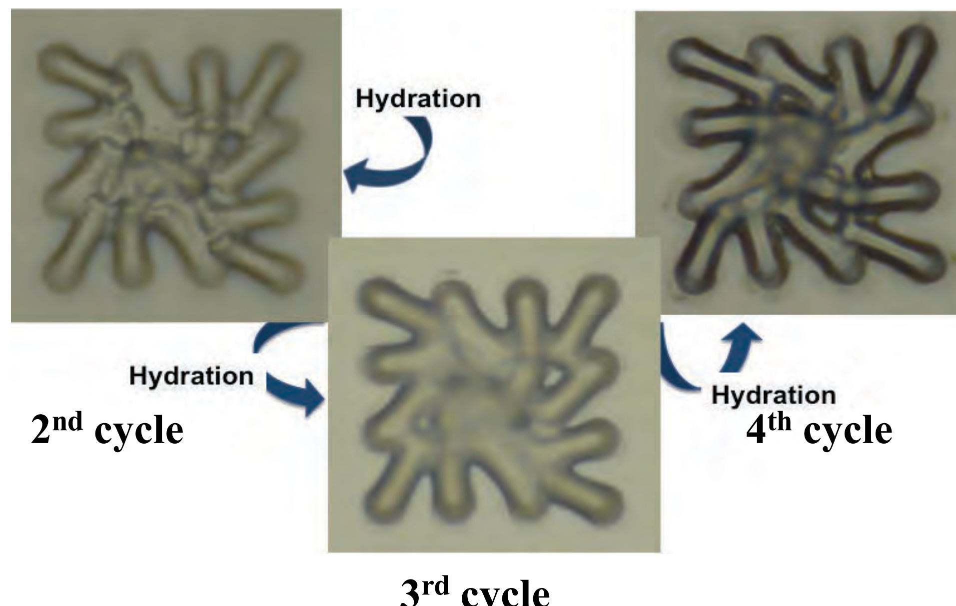
Microscope images of micro-scale pillar array fabricated in PIL hydrogels by 2-PP showing the collapsed pillars before hydration (left) and after hydration (middle and right). The concentric contour slicing pattern used to create the microstructure is visible in the swollen hydrated structures and are very clear in the high resolution STED image (right) of rodamine modified hydrogels. The hydration process is fully reversible and shows shape-memory behaviour.

Tudor, C. Delaney, H. Zhang, A.J. Thompson, V.F. Curto, G.-Z. Yang, M.J. Higgins, D. Diamond, L. Florea, Fabrication of soft, stimulus-responsive structures with sub-micron resolution via two-photon polymerization of poly(ionic liquid)s, **Materials Today. 21 (2018) 807–816. doi:10.1016/j.mattod.2018.07.017.**

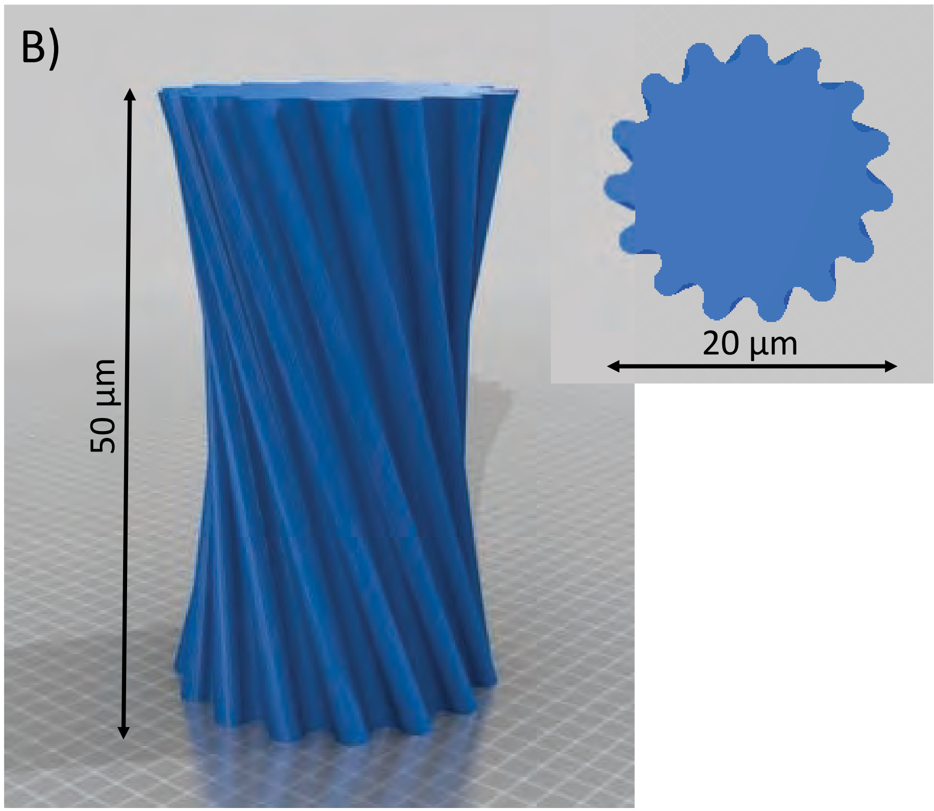
Endo-Skeletal effects within PIL Micropillars?

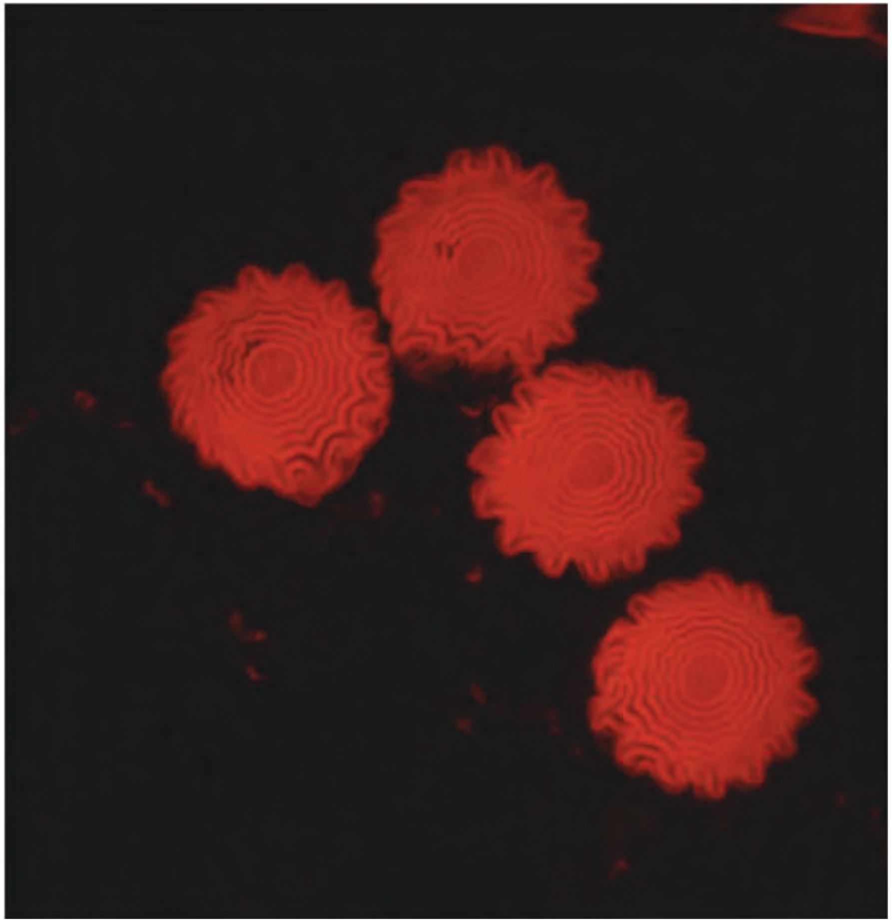






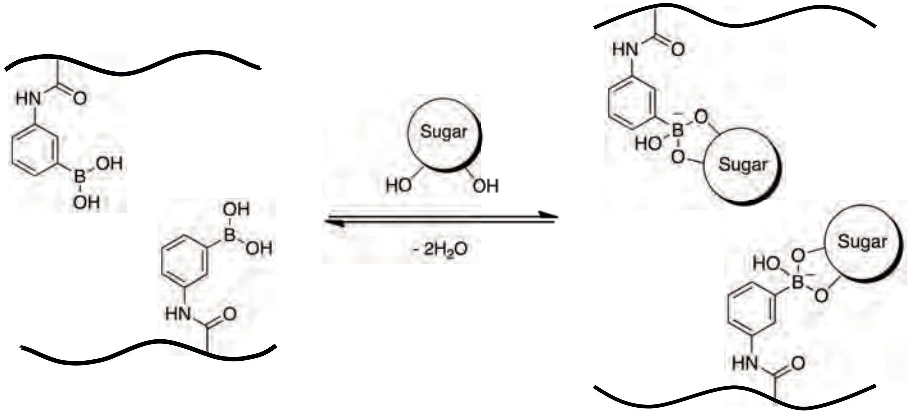
Twisting Motion from Spiral Ratchet Structure

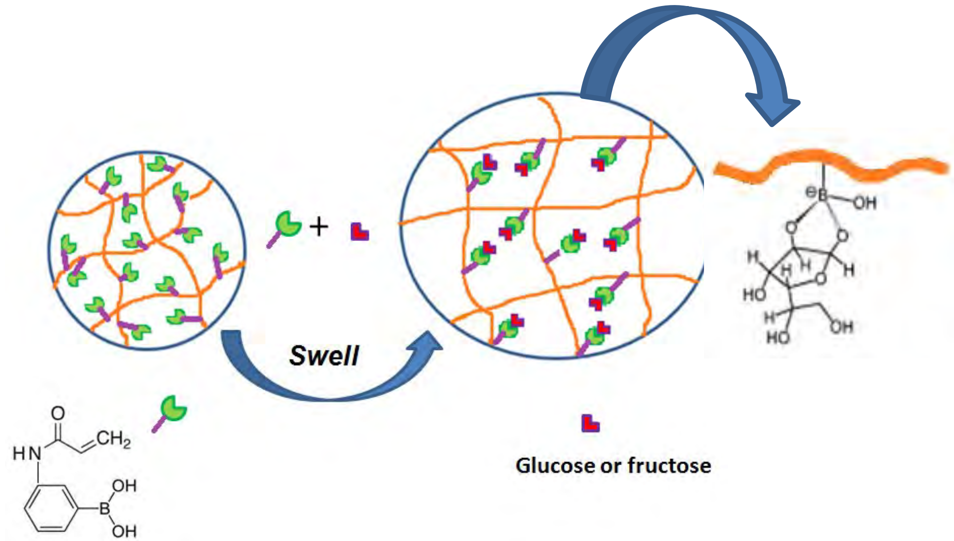




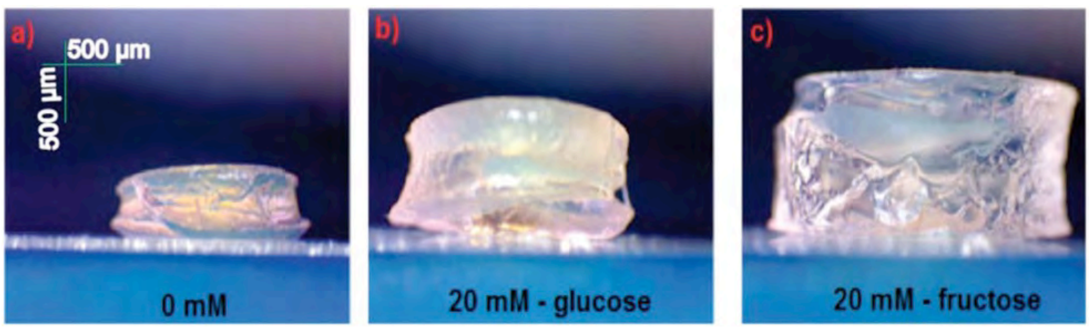
Materials Today. 21 (2018) 807–816. doi:[10.1016/j.mattod.2018.07.017](https://doi.org/10.1016/j.mattod.2018.07.017).

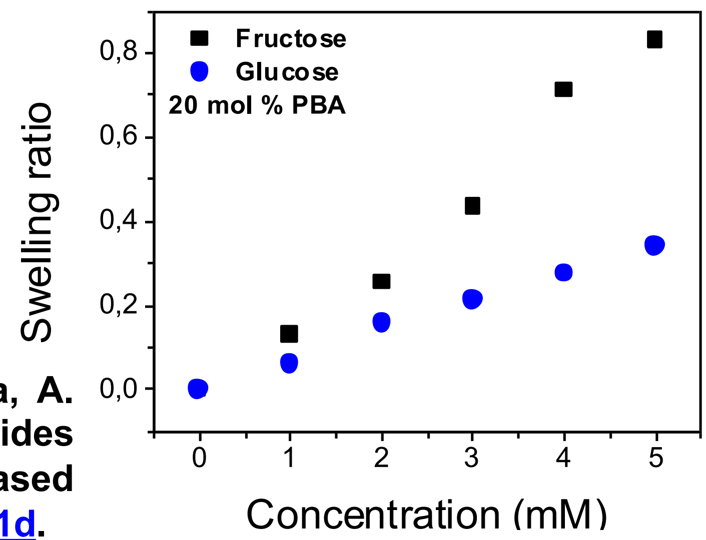
Sugar-Responsive Soft Hydrogels





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

Data and Information; IOT

Outside: On-Body

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

Inside: Implants/In-vivo

- Smart Stents
- Self-Aware Transplant …nts
- 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)

Thanks to…..

- NCSR, SCS, DCU
- 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)

THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
HORIZON 2020
HoliFAB

HoliFAB

Thanks for the invitation!