# Biomimetic Microfluidics and Stimuli-responsive Materials: The Key to Realising Chemical Sensing Platforms with Revolutionary Capabilities

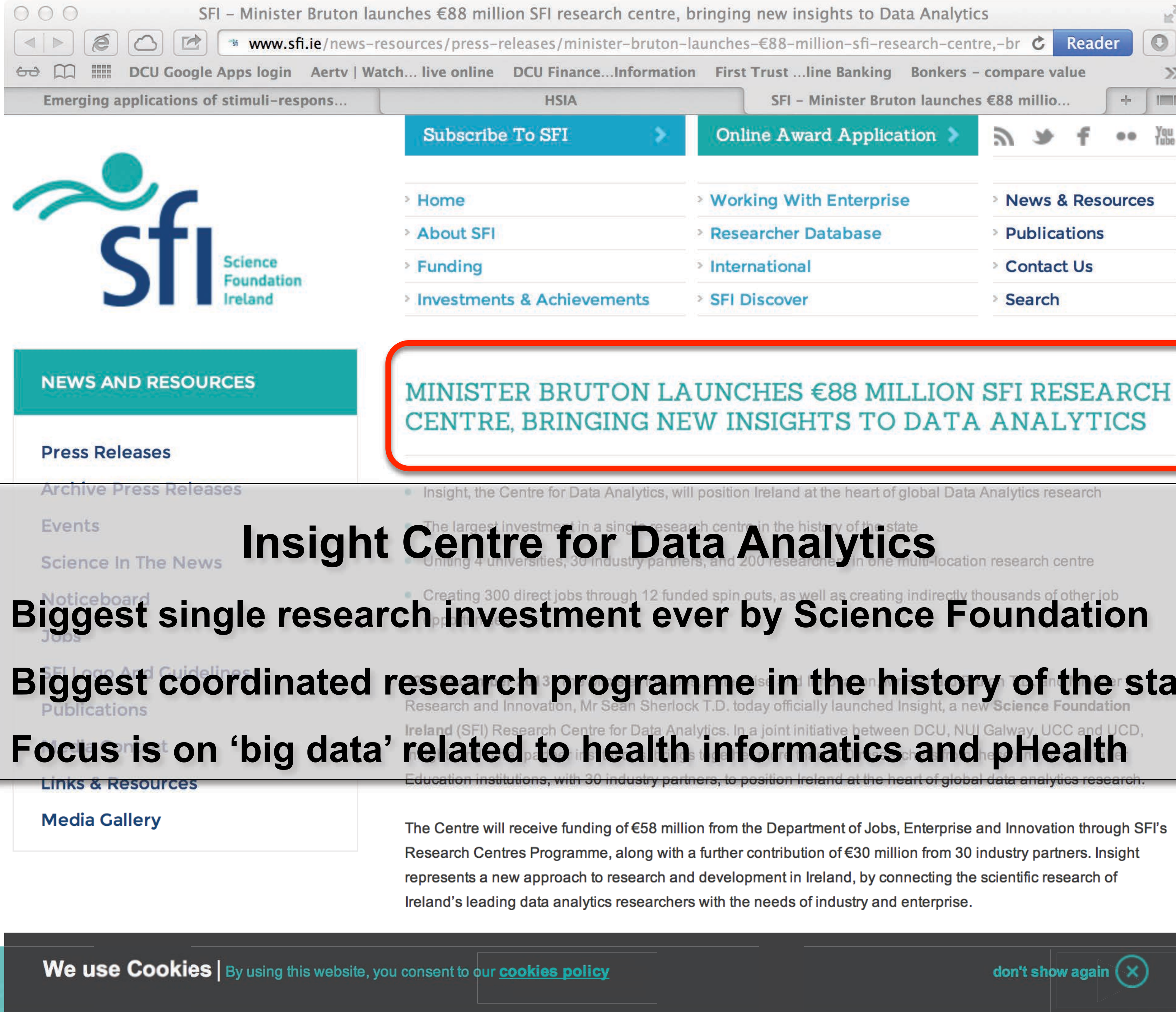
Larisa Florea, Wayne Francis, Simon Coleman, Aishling Dunne, Danielle Bruen, Alex Tudor and **Dermot Diamond**,

**SFI INSIGHT Centre for Data Analytics, National Centre for Sensor Research, Dublin City University, Dublin 9, Ireland**

**Invited lecture presented at**

**Royal Society of Chemistry 'Analytical Research Forum 2015'**

**Burlington House, London, 3 July 2015**




# Insight Centre for Data Analytics

- Biggest single research investment ever by Science Foundation
- Biggest coordinated research programme in the history of the state
- Focus is on 'big data' related to health informatics and pHealth

# NAPES Consortium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Microtechnologies Cooperative Research Center

UNIVERSITÀ DEGLI STUDI
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Aquila
Bioscience

# Keynote Article: August 2004, Analytical Chemistry (ACS)

# internet scale sensing

Dermot Diamond
Dublin City University
(Ireland)

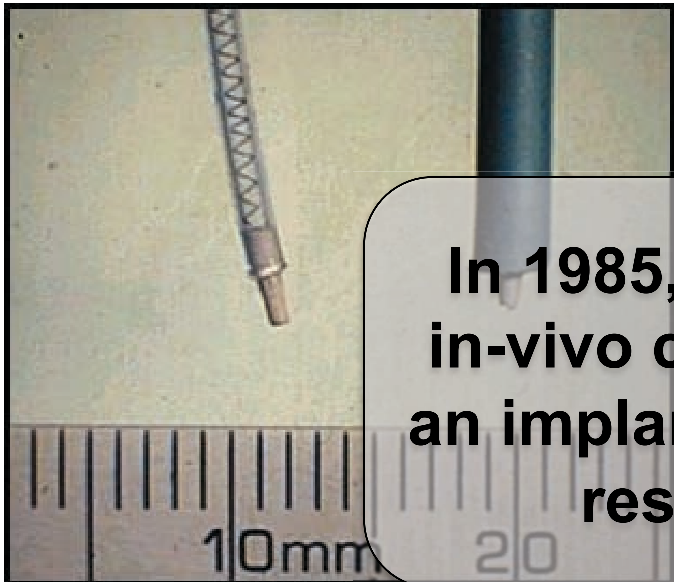
Incredible advances in digital communications and computer power have profoundly changed our lives. One chemist shares his vision of the role of analytical science in the next communications revolution.

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

Dermot Diamond, Anal. Chem., 76 (2004) 278A-286A
(Ron Ambrosio & Alex Morrow, IBM TJ Watson)

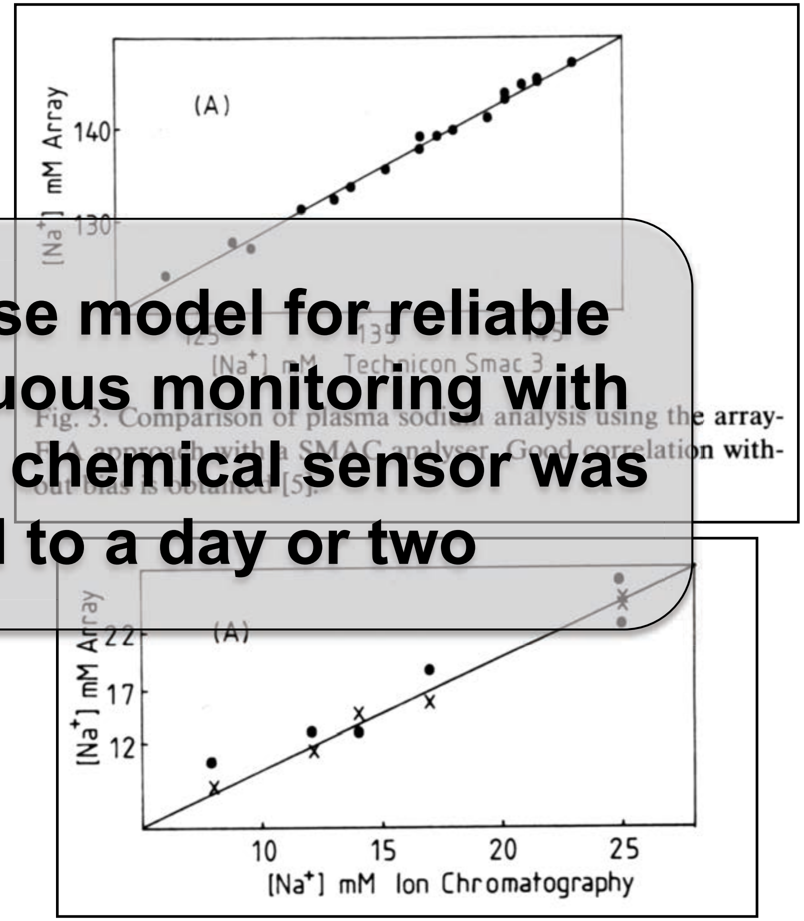
# Blood Analysis; Implantible Sensors




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

**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**

# Apple, iWatch & Health Monitoring


Independent.ie Wednesday 7 May 2014

News | Sport | Business | Woman | Entertainment | Lifestyle | Videos

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Apple hiring medical device staff, shares break $600 mark

0 Comments | Recommend 7 | Tweet 89 | 8+1 3 | Share

Apple Inc CEO Tim Cook


## May 7th 2014

**‘Over the past year, Apple has snapped up at least half a dozen prominent experts in biomedicine**, according to LinkedIn profile changes.

**Much of the hiring is in sensor technology, an area Chief Executive Tim Cook singled out last year as primed "to explode."**

Industry insiders say the moves telegraph a vision of **monitoring everything from blood-sugar levels to nutrition, beyond the fitness-oriented devices now on the market.’**

**"This is a very specific play in the bio-sensing space,"** said Malay Gandhi, chief strategy officer at Rock Health, a San Francisco venture capital firm that has backed prominent wearable-tech startups, such as Augmedix and Spire.

**How will they integrate biosensing with the iWatch…..?**

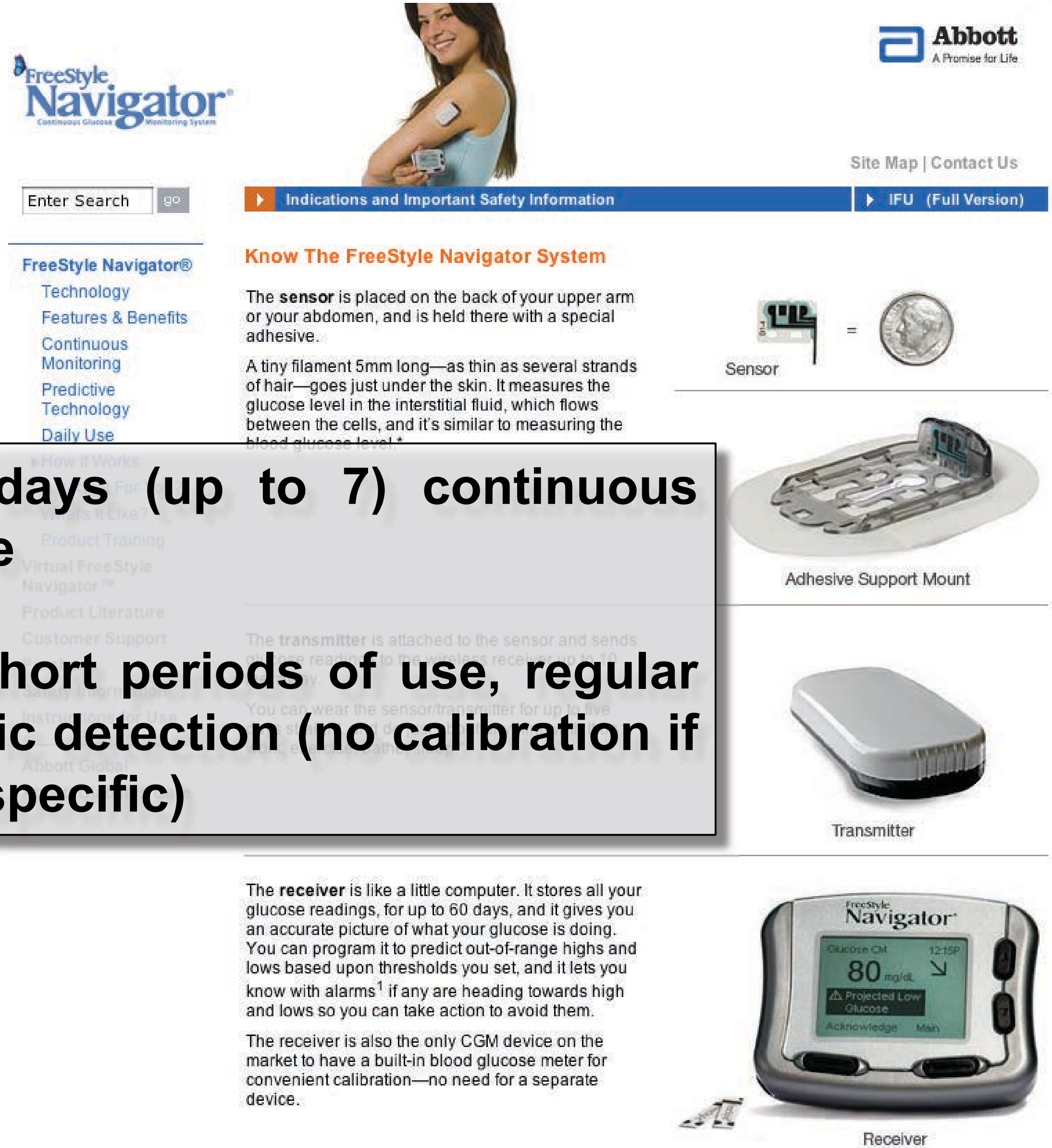
DCU UCC UCD DUBLIN

# Freestyle Navigator

- Combines microfluidics with a micro-dimensioned filament sampling unit which is designed to minimise incidence of infection (therefore can be left in place for 5 days).
- Measures glucose in interstitial fluid (not blood). Diabetics have poor peripheral blood supply; therefore this is a major advance.
- Wireless communications used to harvest data continuously, and relay to carers and specialists. Enables trending, aggregation, warning….

Target is for several days (up to 7) continuous monitoring; then replace

Use model is good – short periods of use, regular replacement, coulometric detection (no calibration if the enzyme reaction is specific)



# Google Contact Lens

United States Patent Application 20140107445
Kind Code A1 Liu; Zenghe April 17, 2014
Microelectrodes in an Ophthalmic Electrochemical Sensor

Abstract

An eye-mountable device includes an electrochemical sensor embedded in a polymeric material configured for mounting to a surface of an eye. The electrochemical sensor includes a working electrode, a reference electrode, and a reagent that selectively reacts with an analyte to generate a sensor measurement related to a concentration of the analyte in a fluid to which the eye-mountable device is exposed.

- Use model is 24 hours max, then replace;
- likely to leverage Google Glass* infrastructure;
- Novartis now working with Google.

Google Smart Contact Lenses Move Closer to Reality


***Google Glass project has been abandoned! (Jan 15 2015) see https://plus.google.com/+GoogleGlass/posts/9uiwXY42tvc**

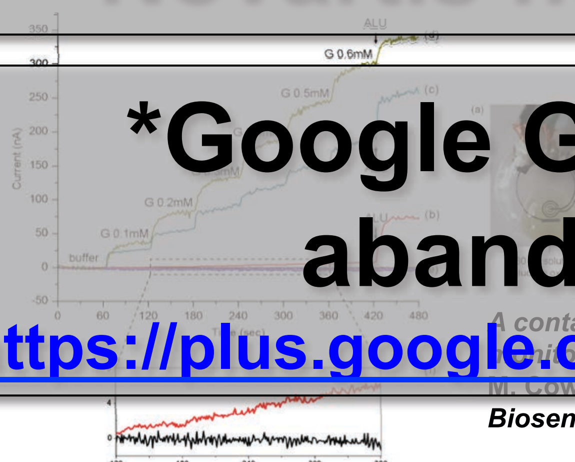


Fig. 2. Images of the sensor as it goes through surface functionalization and the related measured responses: (a) sequential images of sensor pre-treatment with GOD/titania/Nafion®; (b) measured amperometric response for the sensor just incubated with GOD; (c) measured amperometric response for the sensor prepared with GOD/titania/Nafion®; (d) measured amperometric response for the sensor prepared with GOD/titania sol–gel film; (e) three controls (signals for buffer) for the same pre-treatment of (b), (c), and (d); (f) the enlarged view of curve (b) and control of (b) for 120–360 s.

*A contact lens with embedded sensor for monitoring tear glucose level*
M. Cowan, I. Landesmaki and B. A. Parviz,
***Biosensors & Bioelectronics*, 2011, 26**, 3290-3296.

**http://www.gmanetwork.com/news/story/360331/scitech/technology/google-s-smart-contact-lenses-may-arrive-sooner-than-you-think**

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# Remote (Continuous) Sensing Challenges: Platform and Deployment Hierarchies

**Physical Transducers –low cost, reliable, low power demand, long life-time**

Thermistors (temperature), movement, location, power,, light level, conductivity, flow, sound/audio, ……

**Chemical Sensors – more complicated, need regular calibration, more costly to implement**

Electrochemical, Optical, .. For metal ions, pH, organics…

**Biosensors – the most challenging, very difficult to work with, die quickly, single shot (disposable) mode dominant use model**

Due to the delicate nature of biomaterials enzymes, antibodies….

Increasing difficulty & cost

Increasing scalability

**Gas/Air Sensing – easiest to realise**

Reliable sensors available, relatively low cost

Integrate into platforms, develop IT infrastructure, GIS tools, Cloud Computing

**On-land Water/ Monitoring**

More accessible locations

Target concentrations tend to be higher

Infrastructure available

**Marine Water**

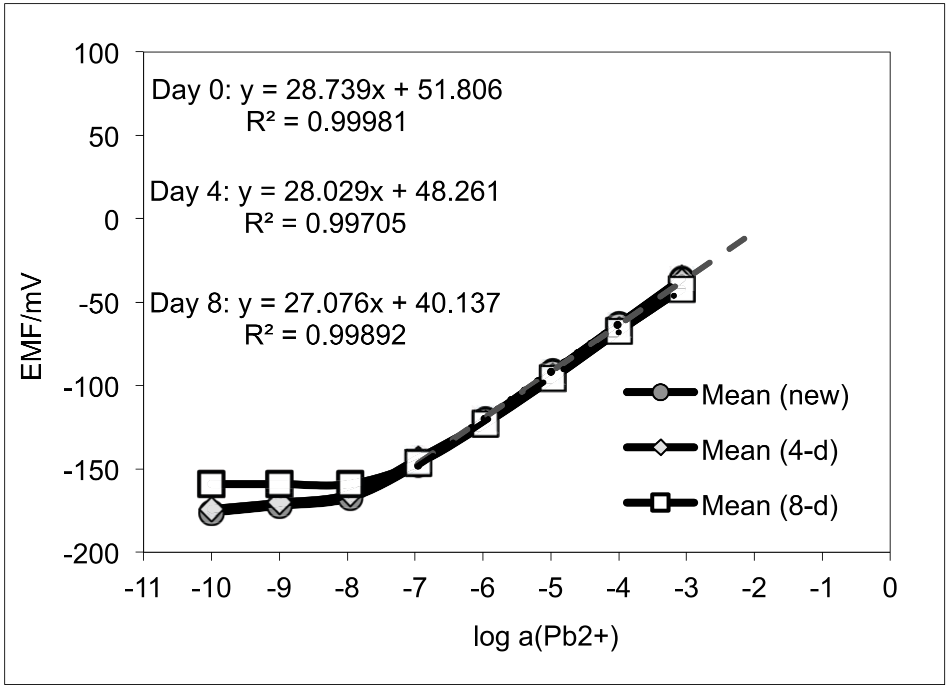
Challenging conditions

Remote locations & Limited infrastructure

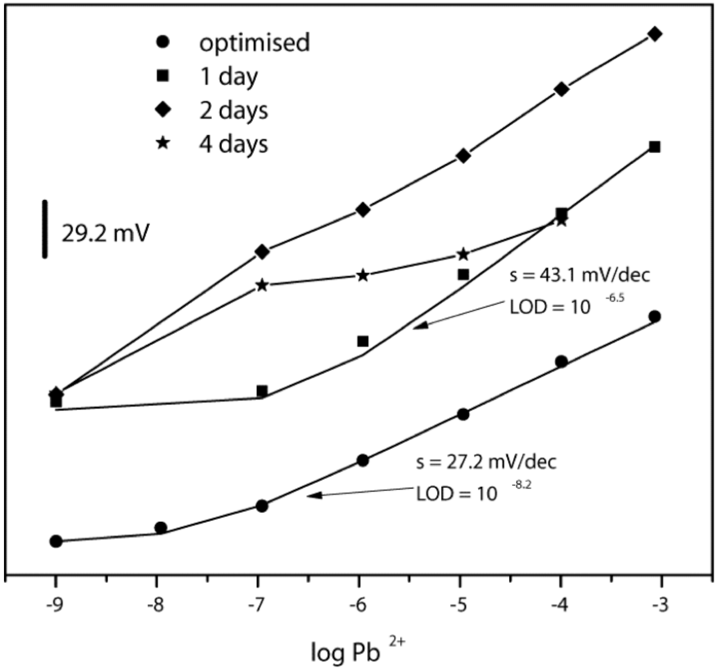
Concentrations tend to be lower and tighter in range

# Change in Electrode Function over Time

See Electrochimica Acta 73 (2012) 93–97




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



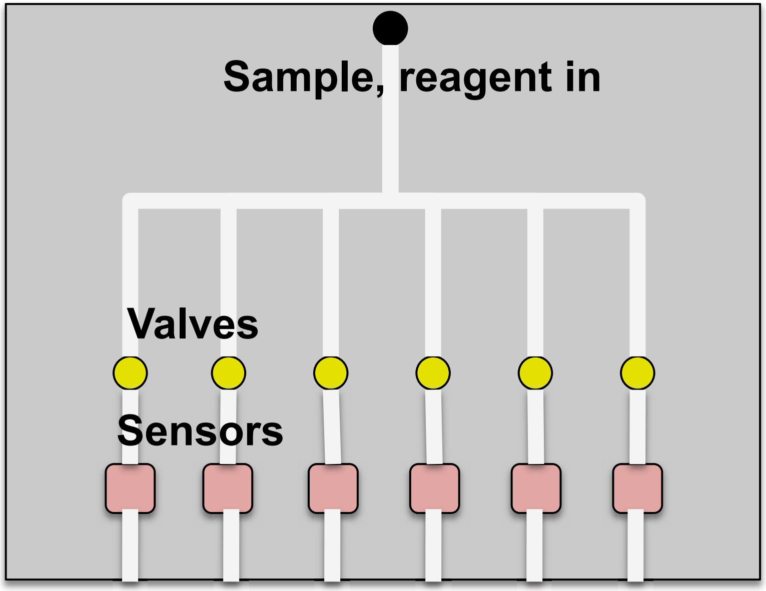

Continuous contact with river water

PVC-membrane based ISEs

# Current Analyser Design

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

- If each sensor has an in-calibration lifetime of 1 day….
- And these sensors are very reproducible….
- And they are very stable in storage (up to several years) ….

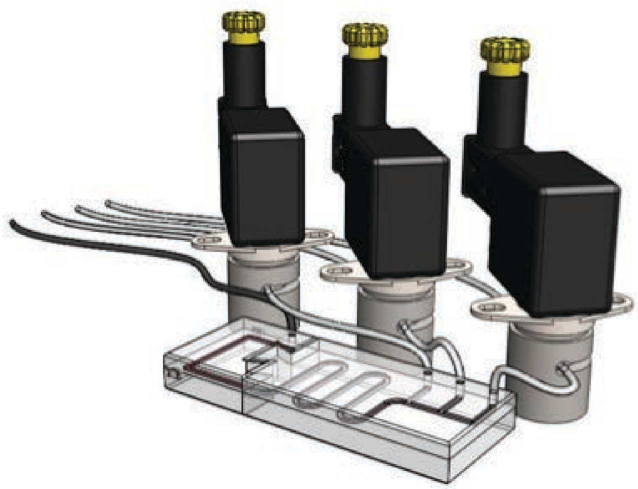



**Then 100 sensors when used sequentially could provide an aggregated in-use lifetime of around 3 months**

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

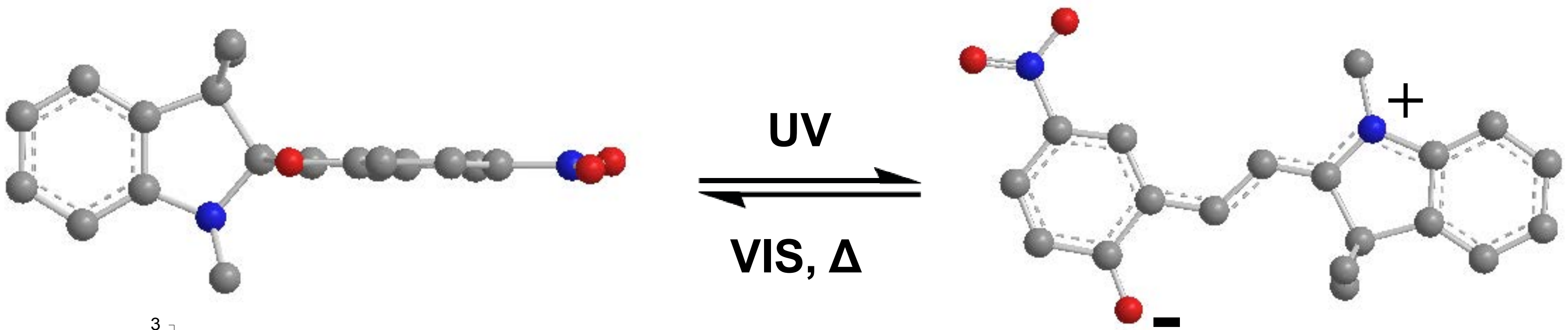
# How to advance fluid handling in LOC platforms: re-invent valves (and pumps)!

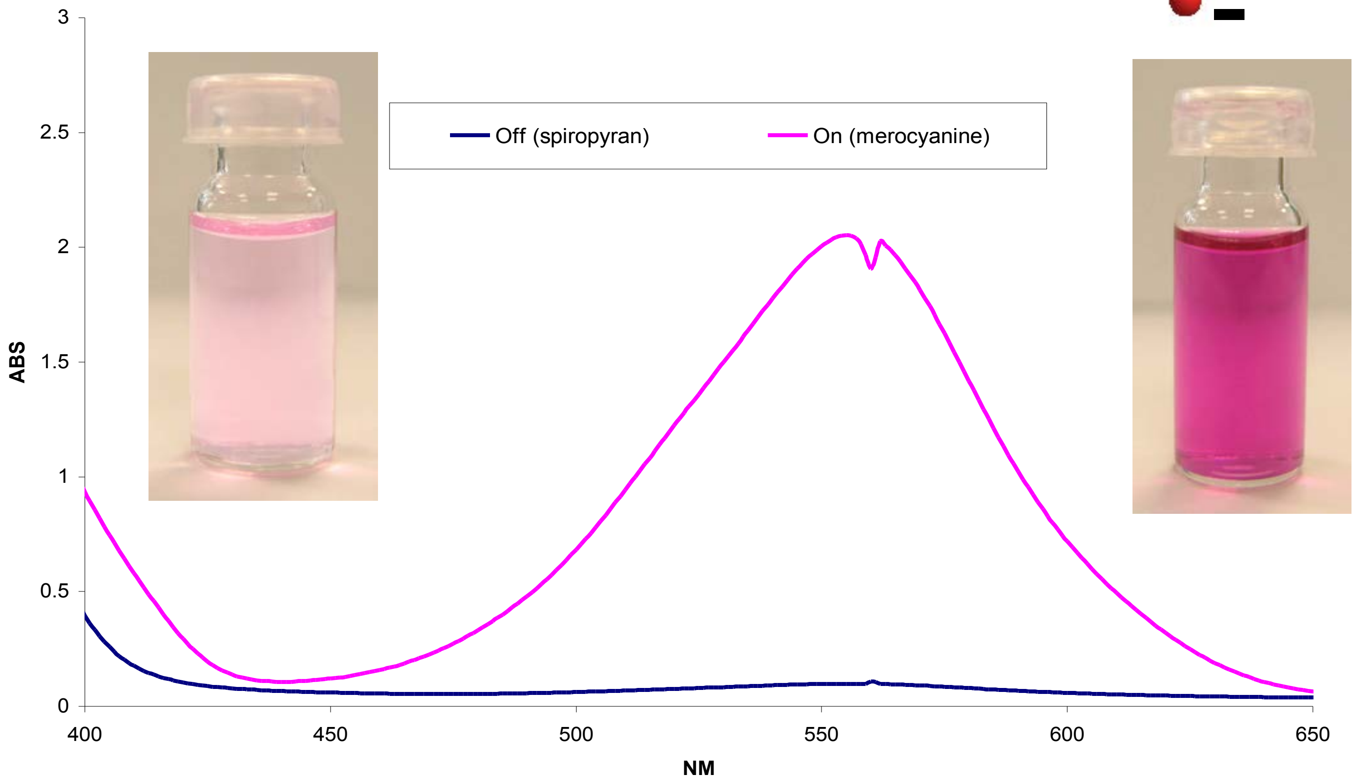
- **Conventional valves cannot be easily scaled down - Located off chip: fluidic interconnects required**
  - Complex fabrication
  - Increased dead volume
  - Mixing effects
- **Based on solenoid action**
  - Large power demand
  - Expensive



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

# Photoswitchable Actuators

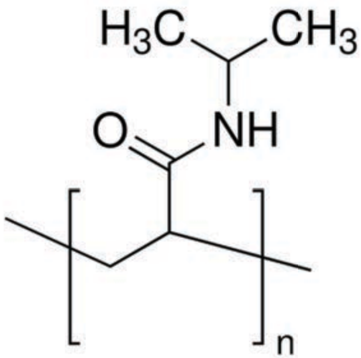


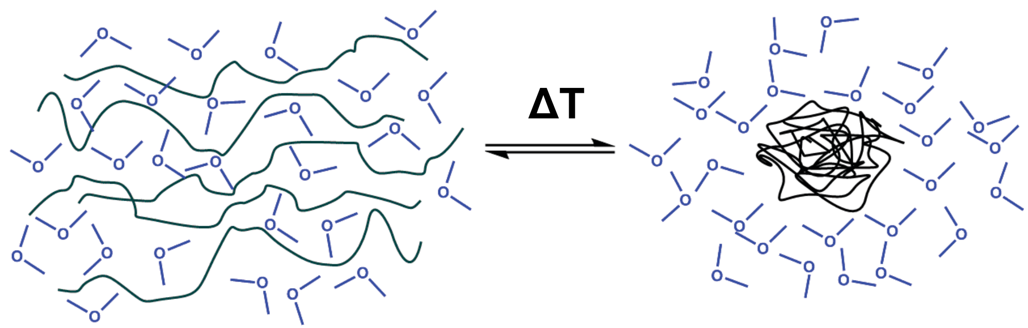
# Poly(*N*-isopropylacrylamide)

- 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**



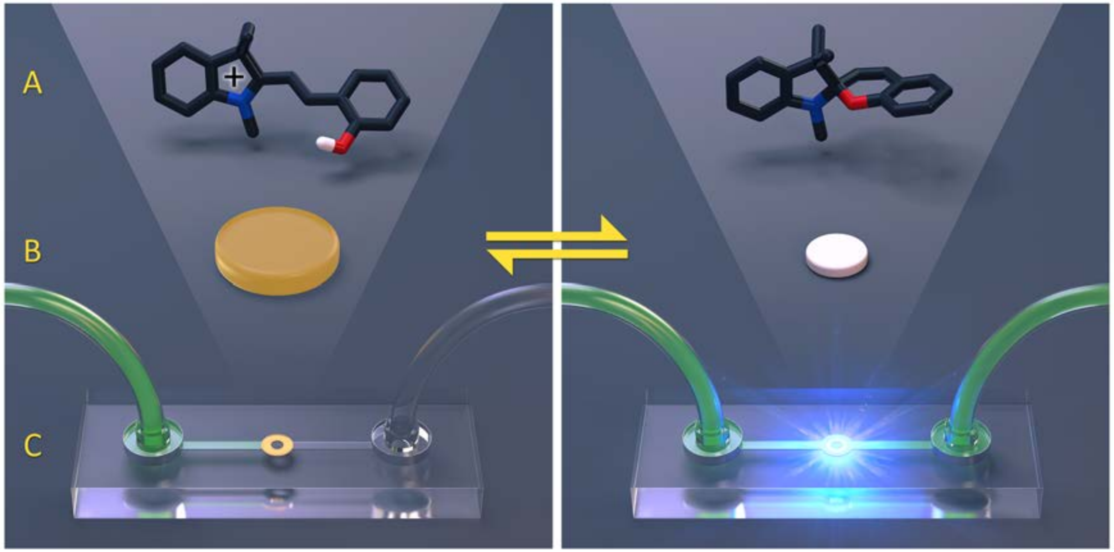

**Hydrophilic** **Hydrophobic**

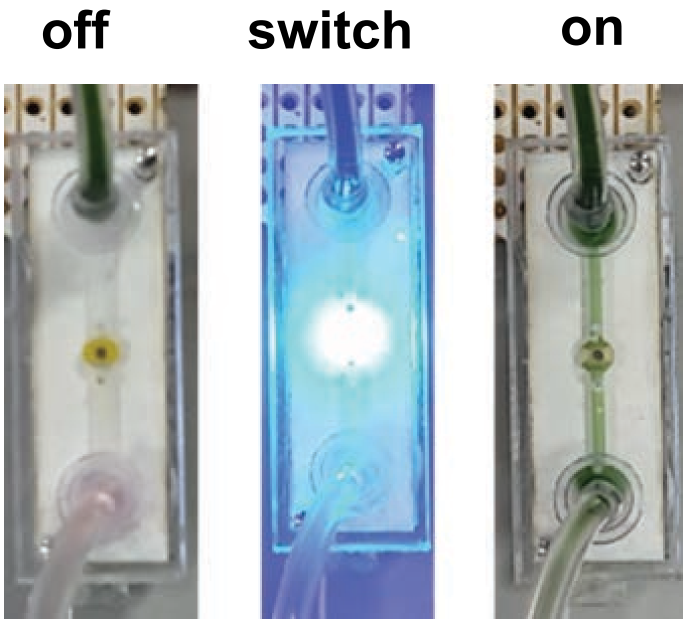



**Hydrated Polymer Chains**

**Loss of bound water -> polymer collapse**

# Reversible Photo-Switching of Flow

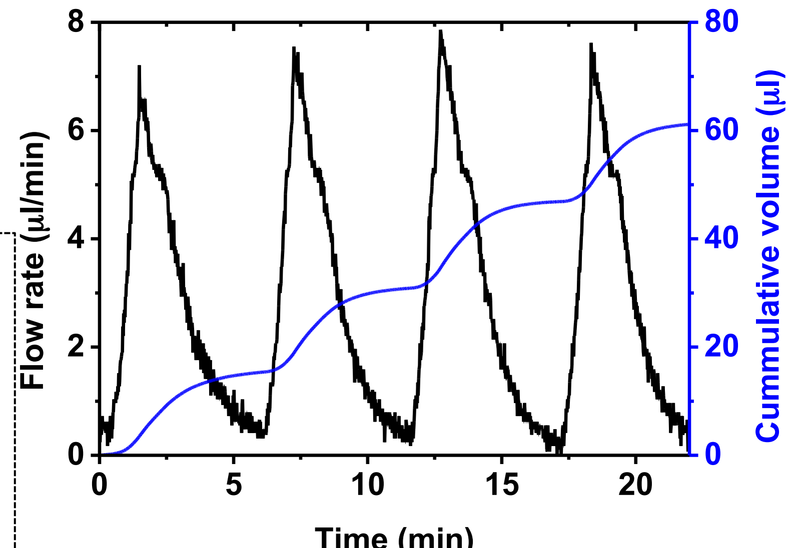



**Above:** scheme showing switching process protonated MC-H$^+$ photoswitched to SP triggering p(NIPAAM-*co*-AA-*co*-SP) gel contraction and opening of the channel.

**Right, Top:** Photos of the valve in operation before (flow OFF) and after (flow ON) one minute of blue light irradiation.

**Right, Bottom:** Flowrate and cumulative volume measurements showing repeated opening and closing of microvalve: 1 min blue light irradiation opens valve followed by ~5.5 min thermal relaxation to close.




**From: 'Molecular design of light-responsive hydrogels, for in-situ generation of fast and reversible valves for microfluidic applications ' Chemistry of Materials (2015), accepted.**

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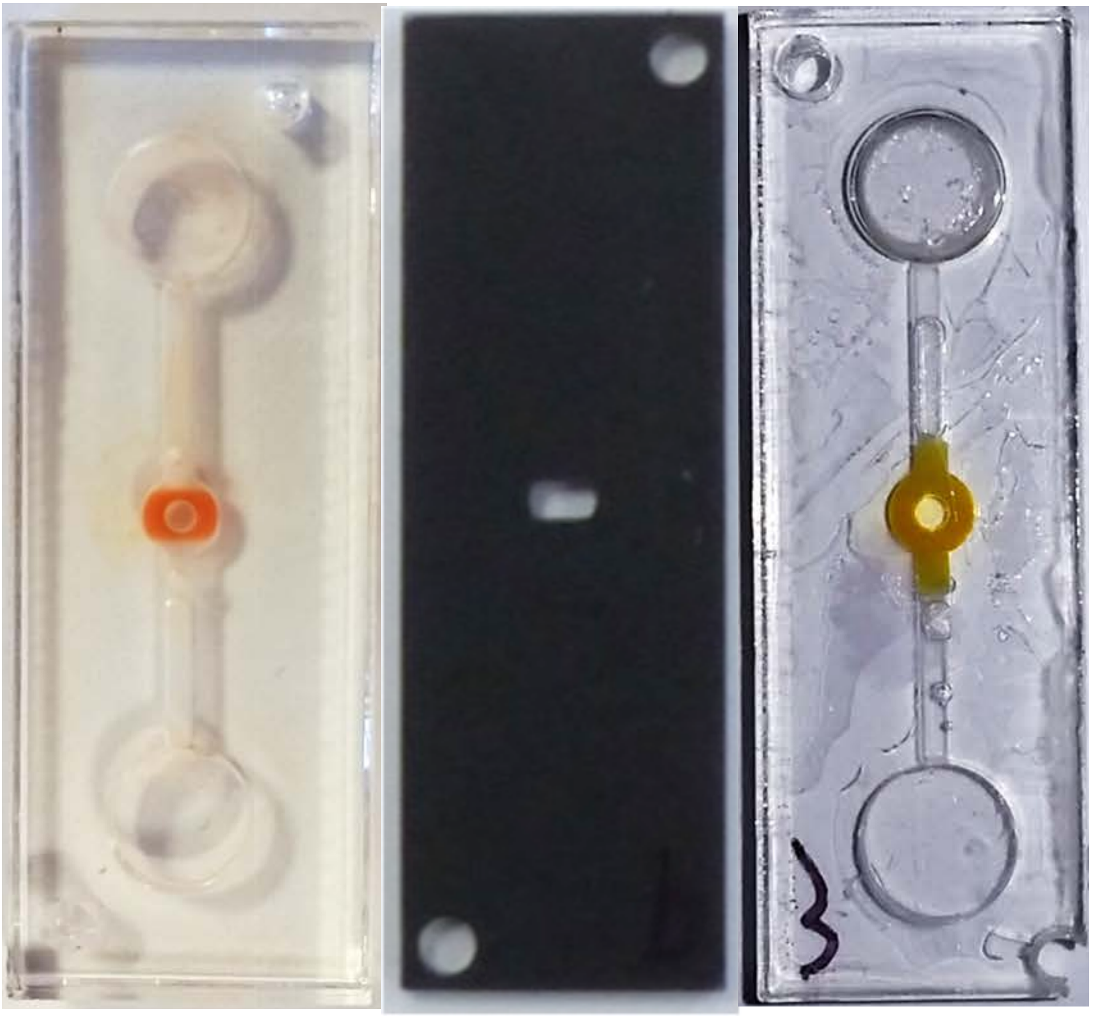
**†Functional Organic Materials and Devices, §Institute for Complex Molecular Systems, Eindhoven University of TechnologyEindhoven, The Netherlands**

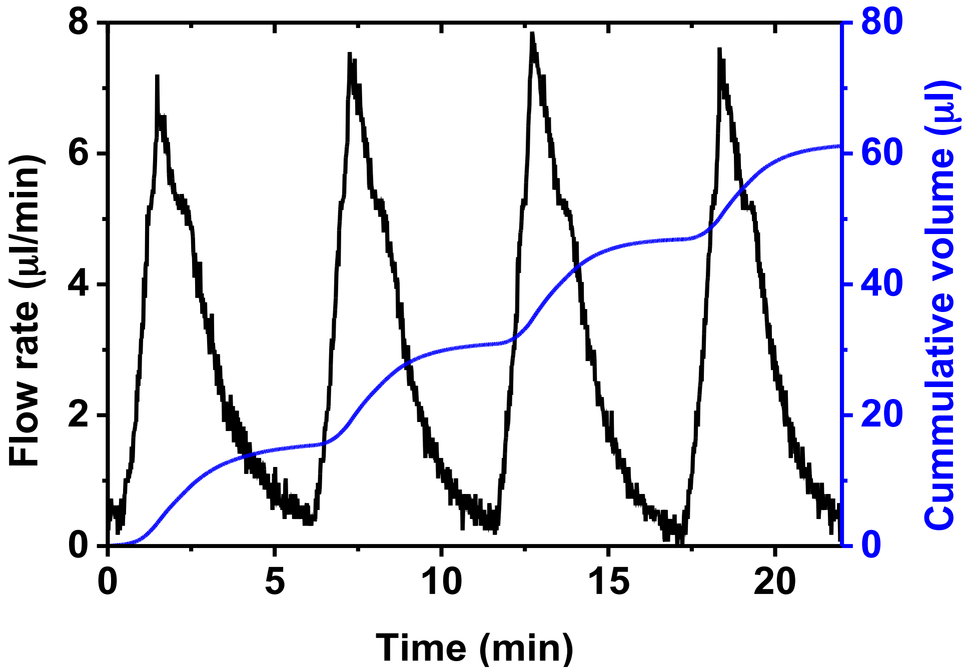
**‡ INSIGHT Centre for Data Analytics, National Center of Sensor Research, Dublin City University, Ireland**

# In-situ Creation of Valve Structures

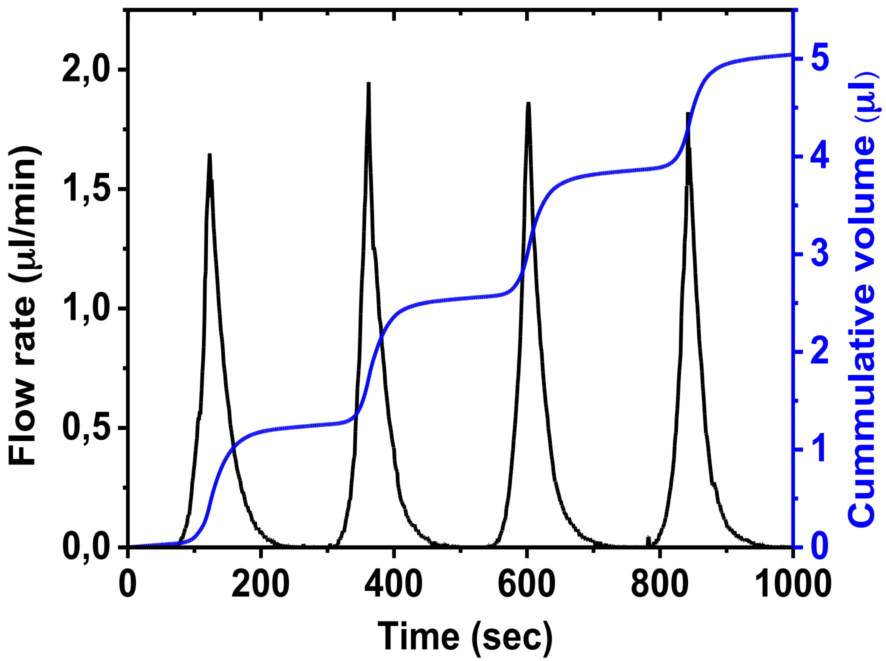
- **Monomer mixture passed through the microfluidic system**
- **Blue light (450nm) surface mount LED causes in-situ polymerisation of photoresponsive gel around central pillar support (left)**
- **Mask design (centre) optimised to prevent swelling into channels from chamber (right).**



# Optimisation of valve dimensions




1.7 mm mask




1.6 mm mask

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

'Micro-Rose'
2 µm
EHT = 14.64 kV
WD = 10.5 mm
Signal A = SE1
Photo No. = 9753
Date :23 Jan 2015
Time :12:31:01
ZEISS
2 µm
EHT = 14.64 kV
WD = 10.5 mm
Signal A = SE1
Photo No. = 9755
Date :23 Jan 2015
Time :12:33:11
ZEISS
'Micro-Stoma'
2 µm
EHT = 14.64 kV
WD = 11.0 mm
Signal A = SE1
Photo No. = 9763
Date :23 Jan 2015
Time :12:39:59
ZEISS
2 µm
EHT = 14.64 kV
WD = 11.0 mm
Signal A = SE1
Photo No. = 9764
Date :23 Jan 2015
Time :12:40:59
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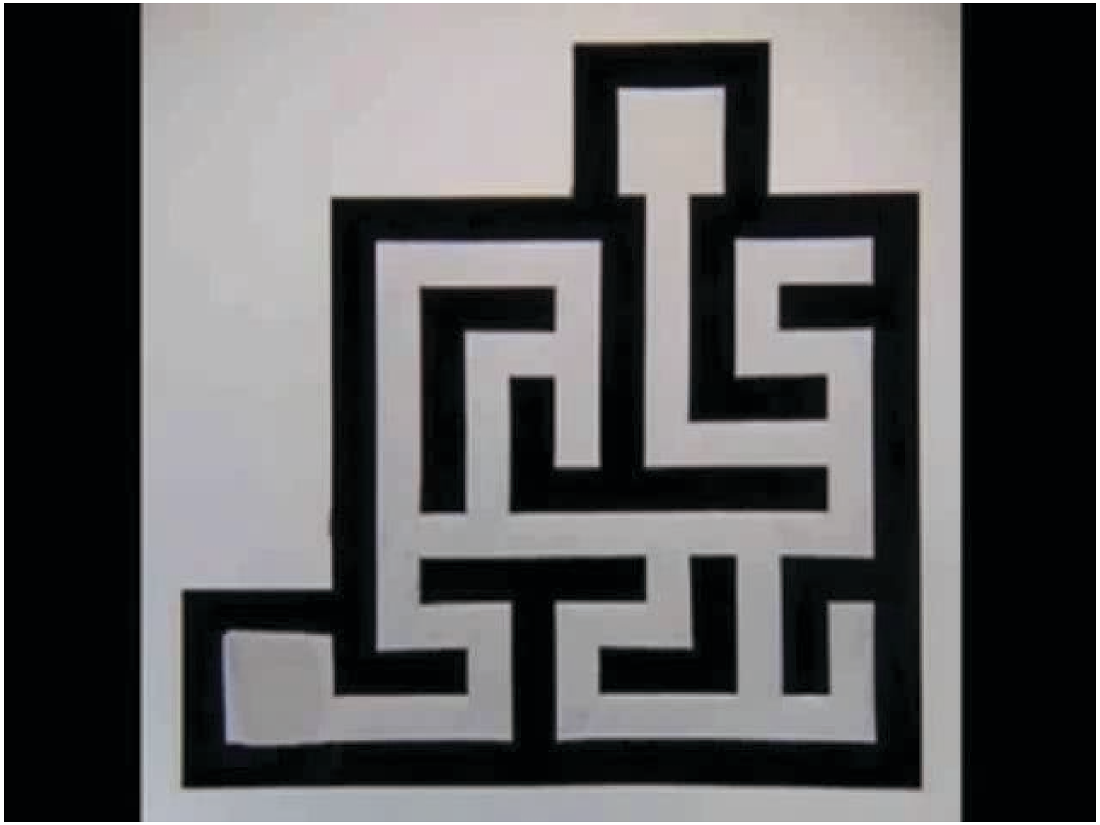
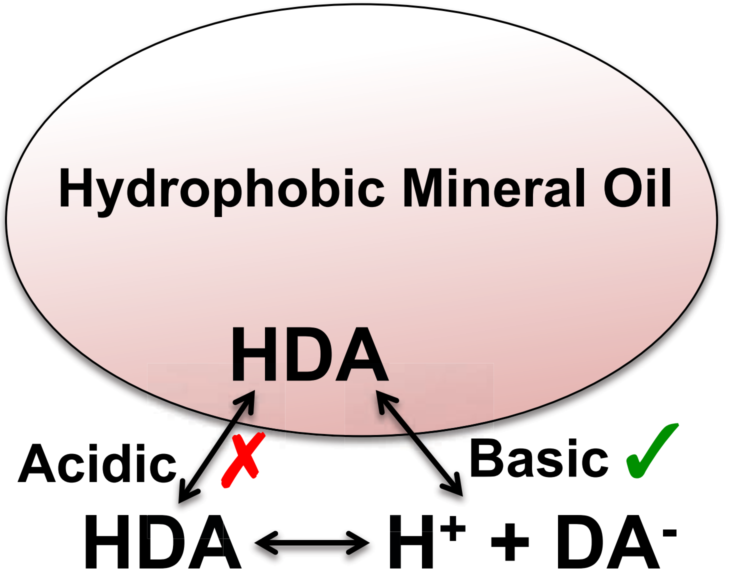
# Chemotactic Systems





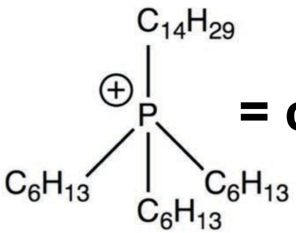

**In a pH gradient, $DA^-$ is preferentially transferred to the aqueous phase at the more basic side of the drop.**

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

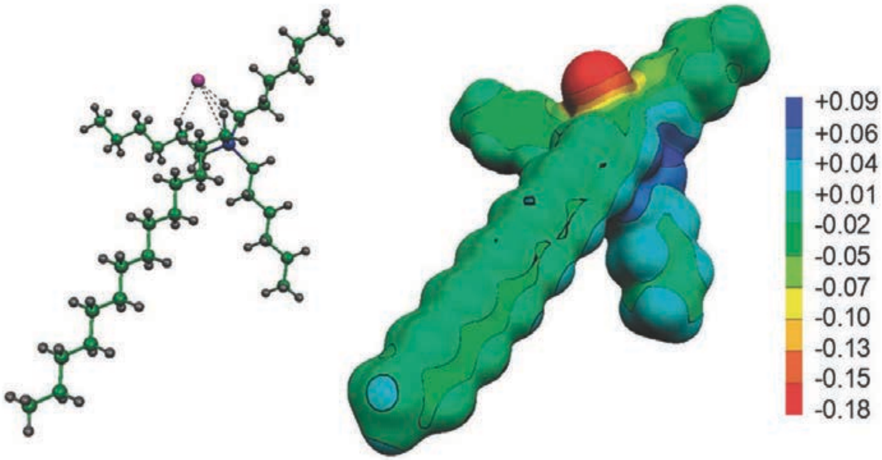
**Maze Solving by Chemotactic Droplets**; Istvan Lagzi, Siowling Soh, Paul J. Wesson, Kevin P. Browne, and Bartosz A. Grzybowski; **J. AM. CHEM. SOC. 2010, *132, 1198–1199***

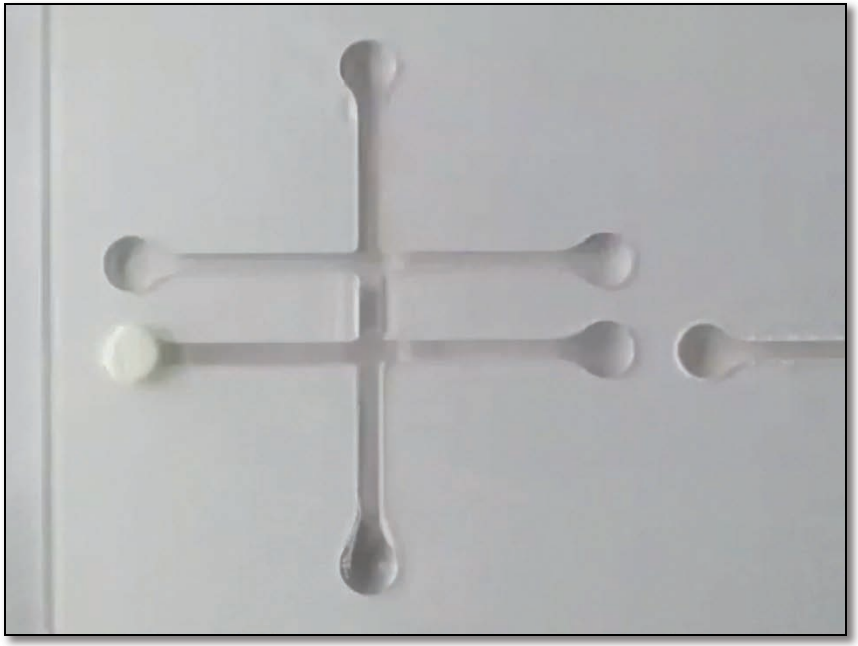
Fuerstman, M. J.; Deschatelets, P.; Kane, R.; Schwartz, A.; Kenis, P. J. A.;Deutch, J. M.; Whitesides, G. M. *Langmuir 2003, 19, 4714.*

# We can do the same with IL Droplets




= cationic surfactant

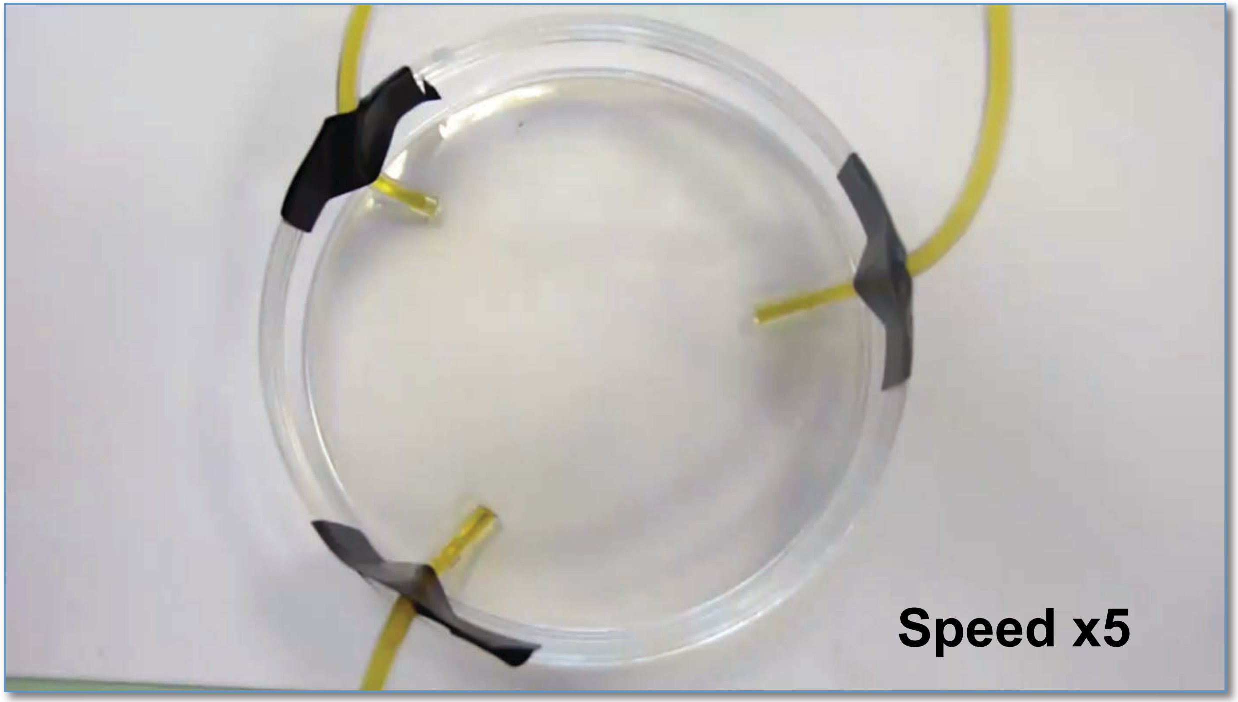


**Trihexyl(tetradecyl)phosphonium chloride ([$P_{6,6,6,14}$][Cl]) droplets with a small amount of 1-(methylamino)anthraquinone red dye for visualization. The droplets spontaneously follow the gradient of the $Cl^-$ ion which is created using a polyacrylamide gel pad soaked in $10^{-2}$ M HCl; A small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

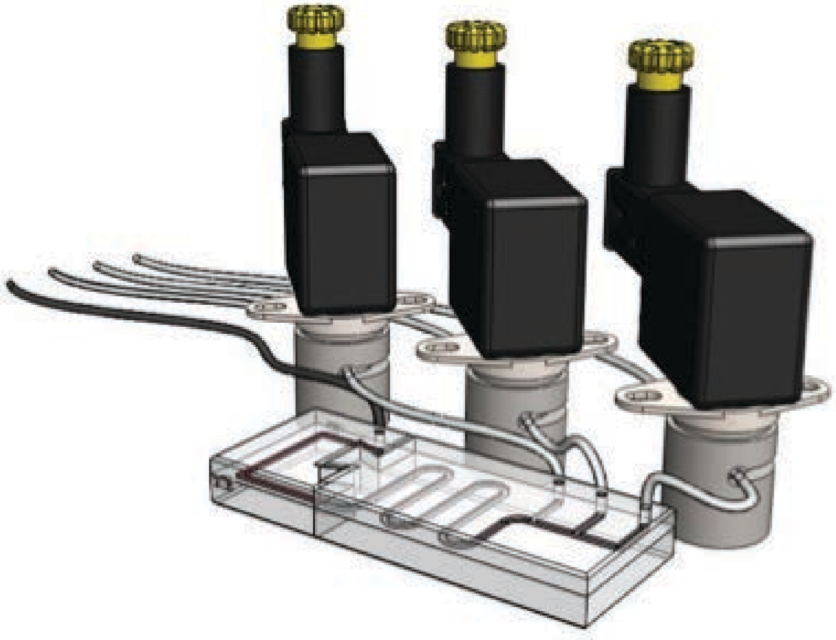
*Electronic structure calculations and physicochemical experiments quantify the competitive liquid ion association and probe stabilisation effects for nitrobenzospiropyran in phosphonium-based ionic liquids*, D. Thompson et al., *Physical Chemistry Chemical Physics*, 2011, 13, 6156-6168.

# 2D chemotactic droplet movement

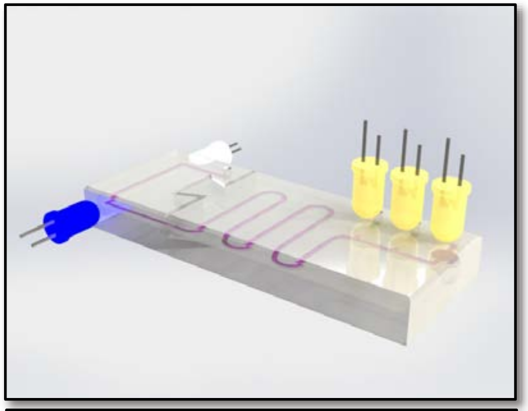


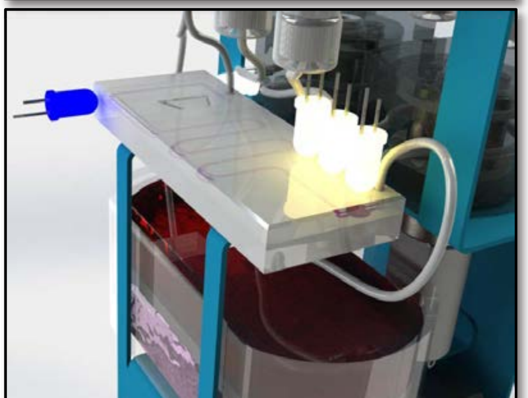

- NaOH in petri dish; HCl with indicator dye added from tubes in sequence
- Droplet moves spontaneously towards acidic locations
- In 2/3 cases, the droplet enters the source tube
- Droplets can be loaded with monomeric units that polymerise inside the tubing sealing off the source of the 'leak'

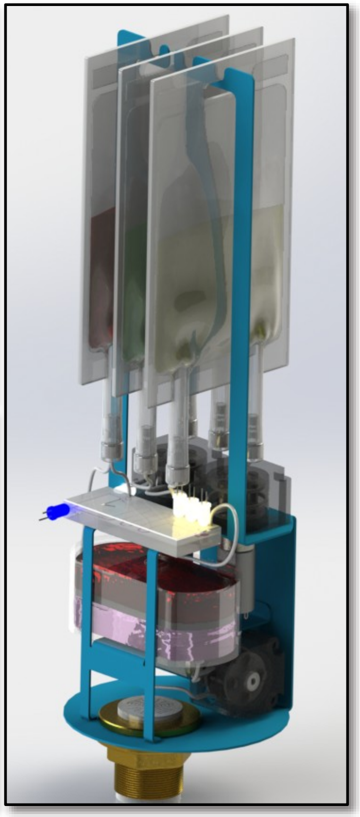
# We must go from this:

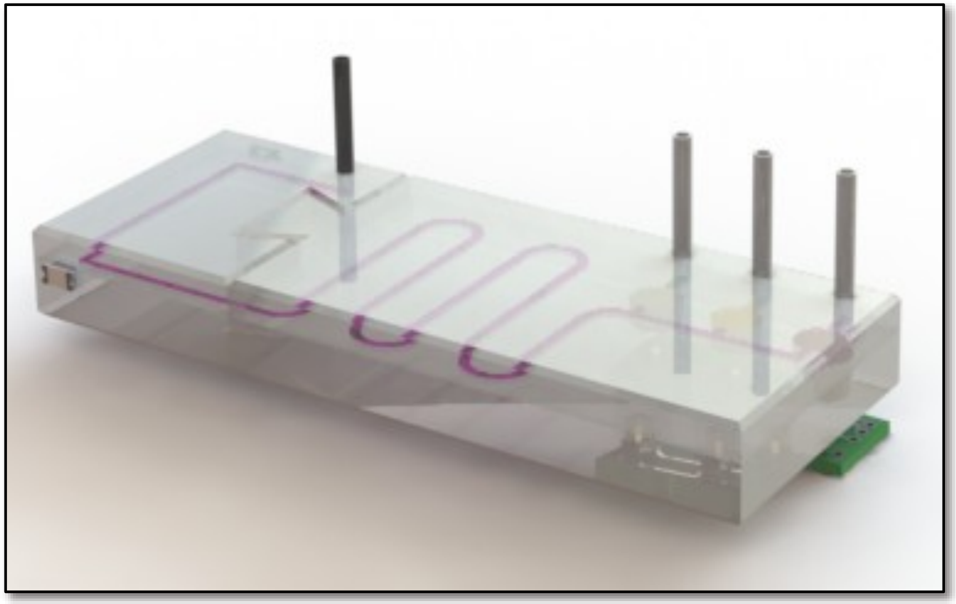



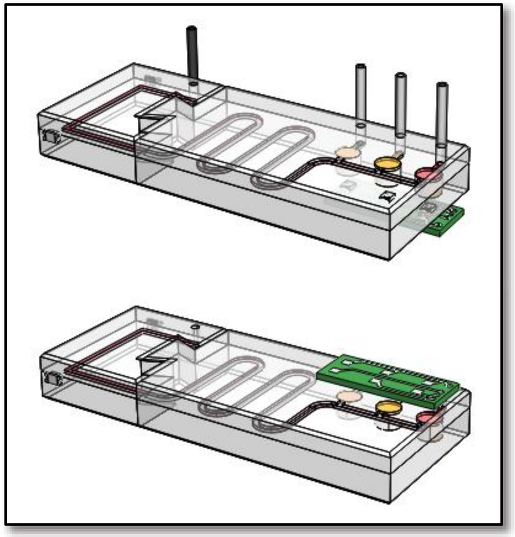
# To Photo-Fluidics & Detection











- **Fluidic handling completely integrated into the microfluidic chip**
  - **Valves actuated remotely using light (LEDs)**
  - **Detection is via LED colorimetric measurements**
  - **Photo-controlled uptake and release**

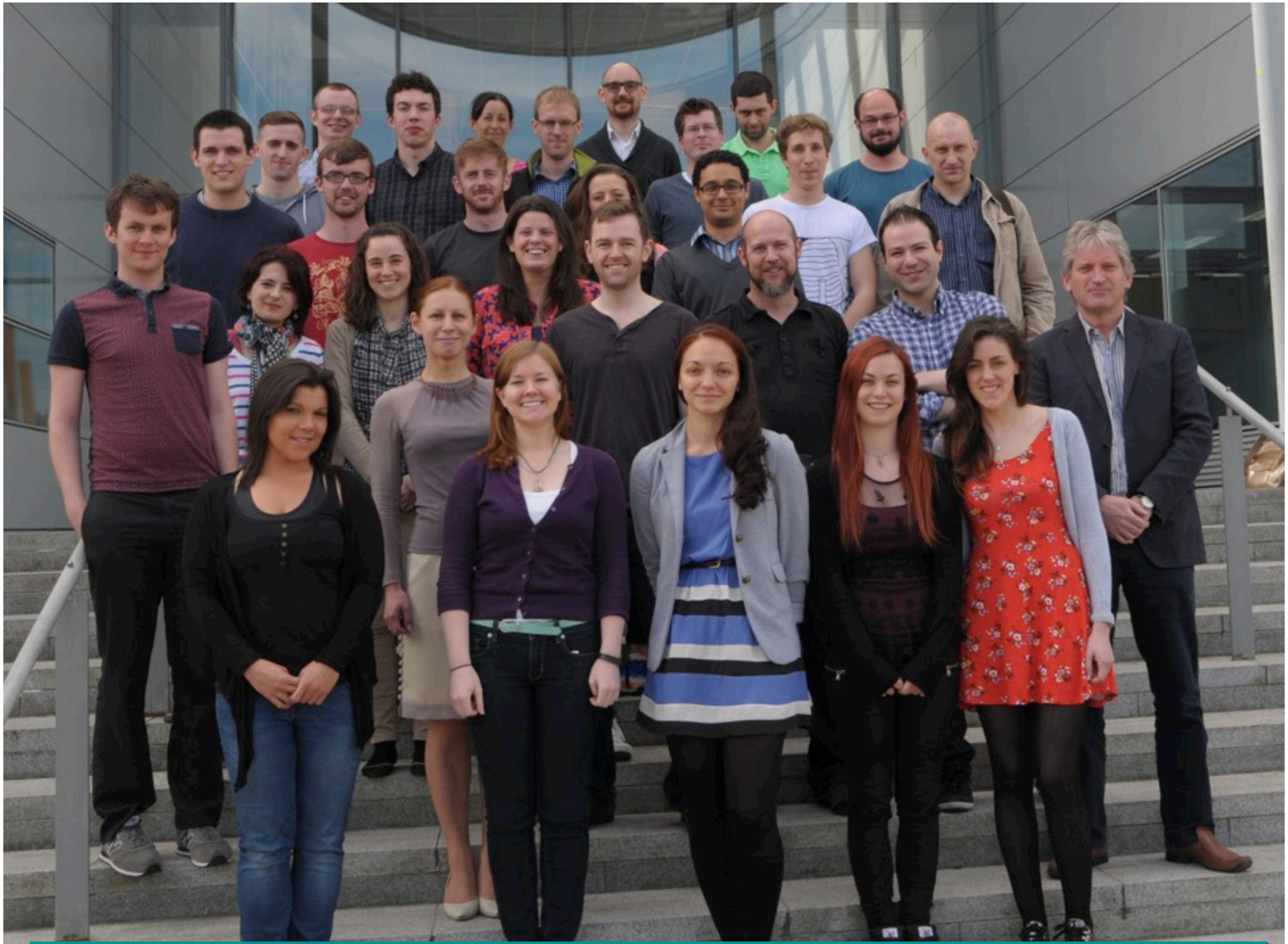
# And Ultimately – to Bioinspired Multi-Functional Fluidics

- **In the future, the fluidic system will perform much more sophisticated 'bioinspired' functions**
  - System diagnostics, leak/damage detection
  - Self-repair capability
  - Switchable behaviour (e.g. surface roughness, binding/release),
- **These functions will be inherent to the channels and integrated with circulating smart micro/nano-vehicles**
  - Spontaneously move under an external stimulus (e.g. chemical, thermal gradient) to specific locations

# Time to re-think the game!!!

- New materials with exciting characteristics and unsurpassed potential…
- Combine with emerging technologies and techniques for exquisite control of 3D morphology
- And greatly improved methods for characterisation of structure and activity

**We have the tools – now we need creativity!**



# Thanks for listening