Chemical Sensing Based on Biomimetic Principles

Larisa Florea, Wayne Francis and **Dermot Diamond**

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

Invited lecture presented at

***4th International Symposium on Sensor Science* (*I3S2015*)**

Biocenter/PharmaCenter, Universität Basel
Switzerland

NAPES Consortium

DCU

institut Curie

TelLab

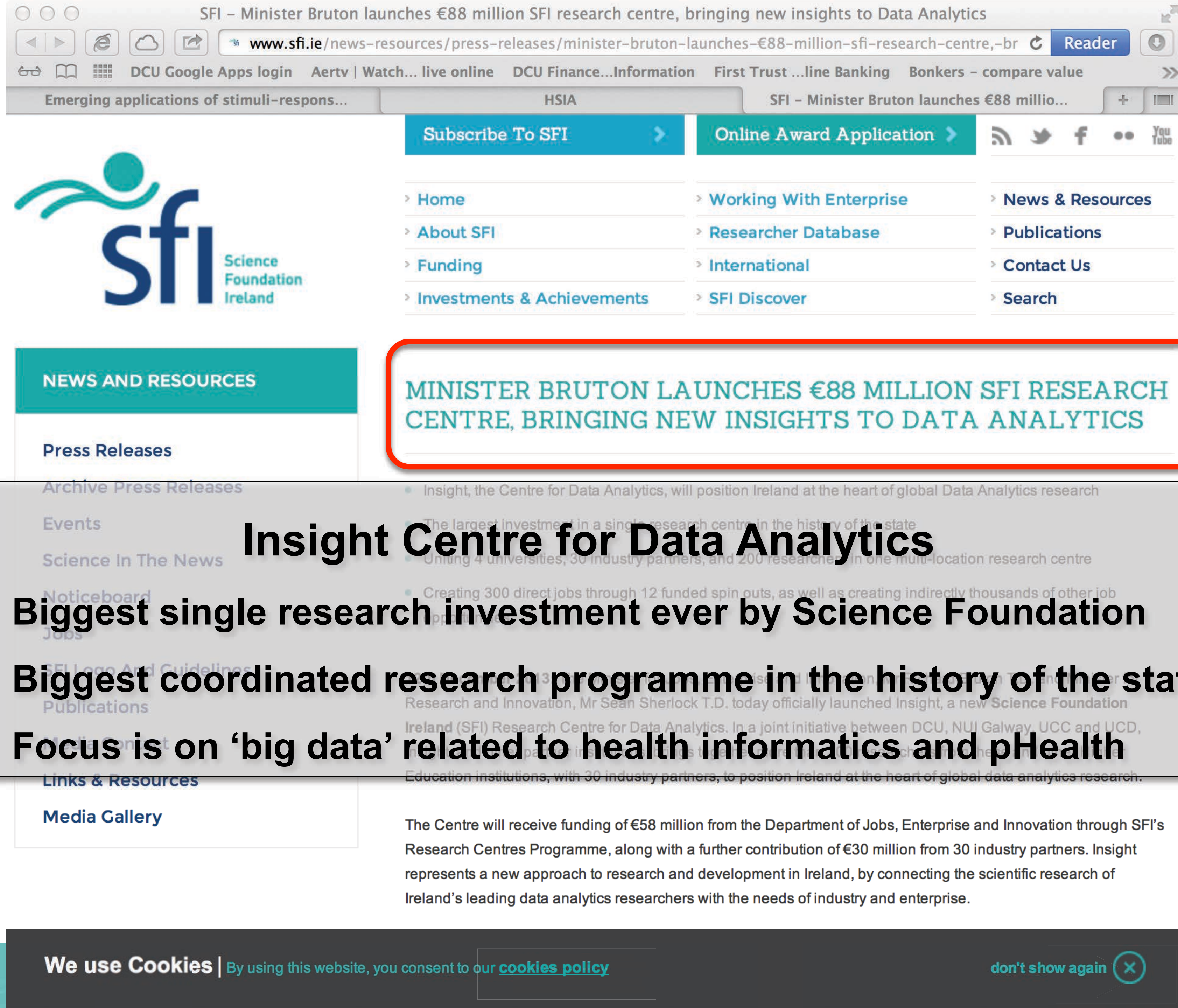
WIS
Williams Industrial Services

TU/e

CIC microGUNE
Microtechnologies Cooperative Research Center

UNIVERSITÀ DEGLI STUDI DI MILANO

Aquila Bioscience



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

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.

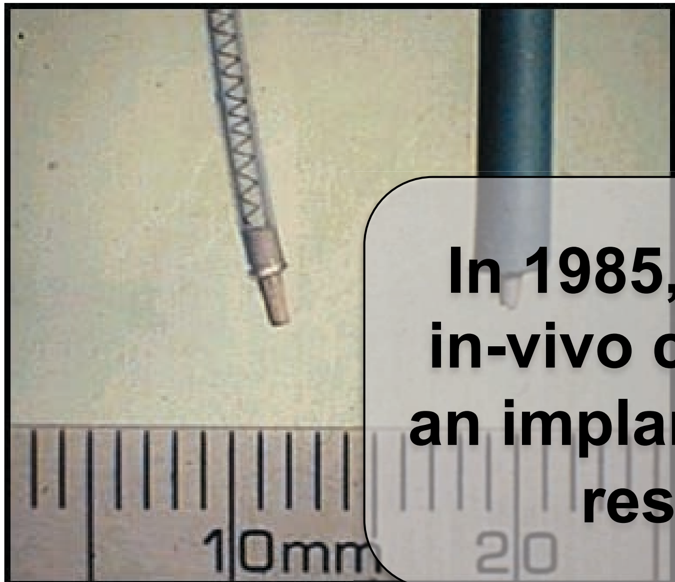
Digital communications networks are at the heart of modern society. The digitization of communications, the development of the Internet, and the availability of relatively inexpensive but powerful mobile computing technologies have established a global communications network capable of linking billions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

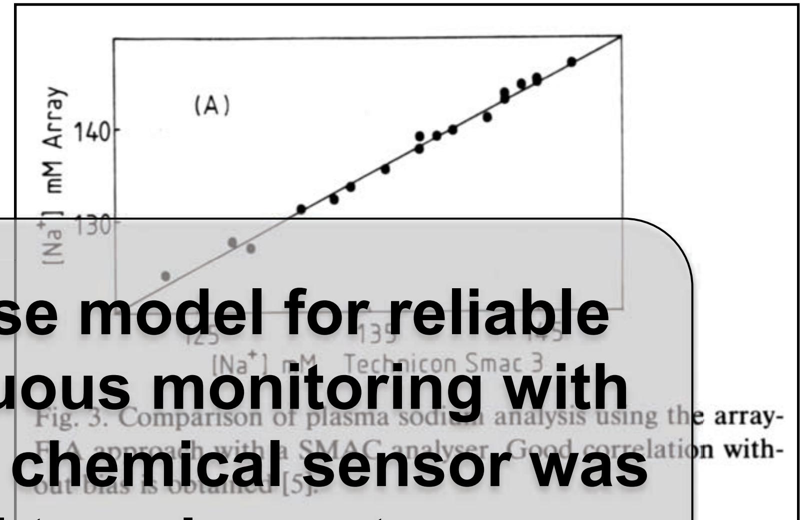
Blood Analysis; Implantible Sensors

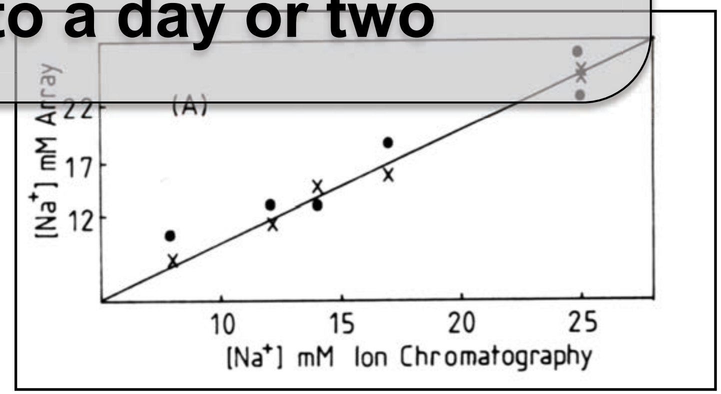
In 1985, the use model for reliable in-vivo continuous monitoring with an implantable chemical sensor was restricted to a day or two



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

Dr. David Band, St Thomas's Hospital London

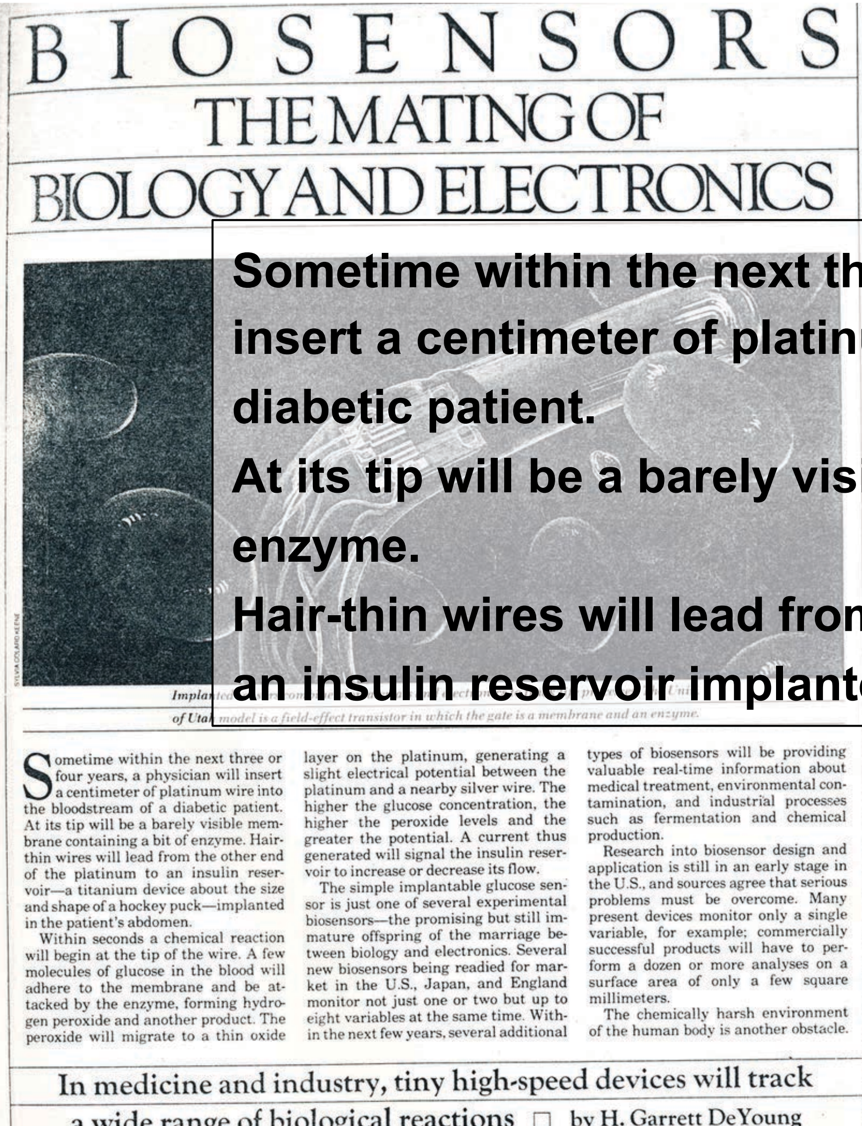




Anal. Chem., *64 (1992) 1721-1728.*

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

The promise of biosensors…..



BIOSENSORS

THE MATING OF BIOLOGY AND ELECTRONICS

Implant… of Utah … model is a field-effect transistor in which the gate is a membrane and an enzyme.

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.

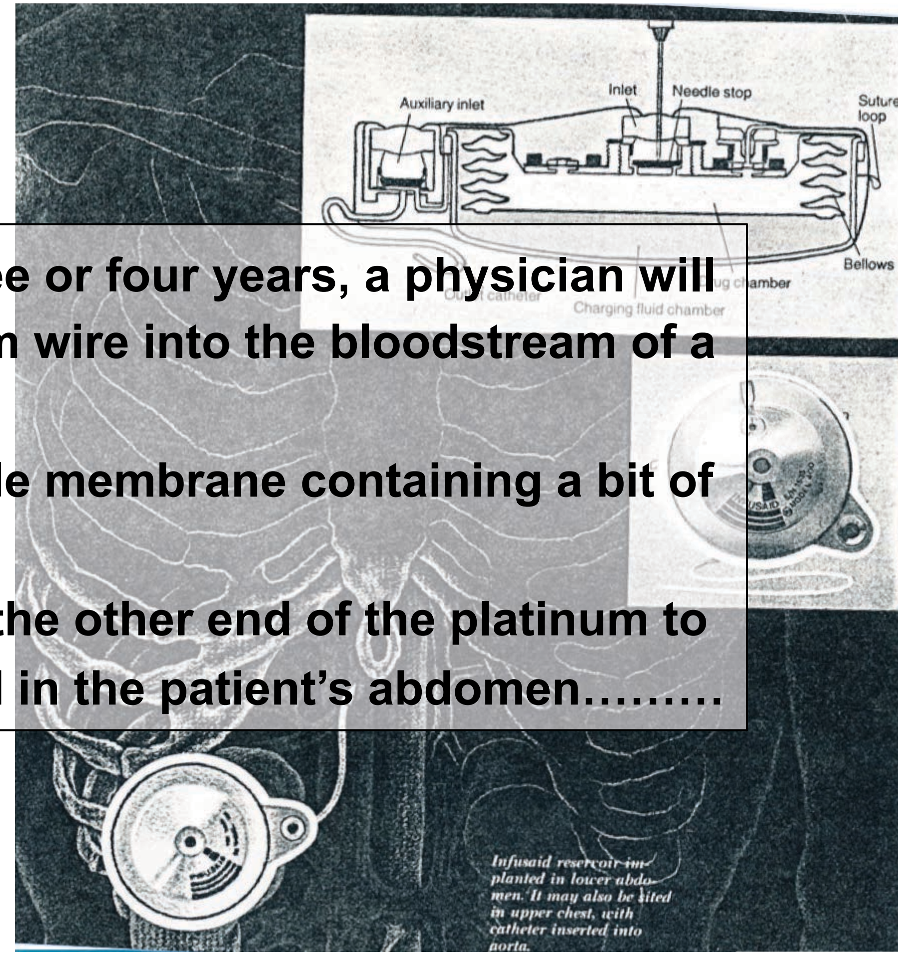
Within seconds a chemical reaction will begin at the tip of the wire. A few molecules of glucose in the blood will adhere to the membrane and be attacked by the enzyme, forming hydrogen peroxide and another product. The peroxide will migrate to a thin oxide layer on the platinum, generating a slight electrical potential between the platinum and a nearby silver wire. The higher the glucose concentration, the higher the peroxide levels and the greater the potential. A current thus generated will signal the insulin reservoir to increase or decrease its flow.

The simple implantable glucose sensor is just one of several experimental biosensors—the promising but still immature offspring of the marriage between biology and electronics. Several new biosensors being readied for market in the U.S., Japan, and England monitor not just one or two but up to eight variables at the same time. Within the next few years, several additional types of biosensors will be providing valuable real-time information about medical treatment, environmental contamination, and industrial processes such as fermentation and chemical production.

Research into biosensor design and application is still in an early stage in the U.S., and sources agree that serious problems must be overcome. Many present devices monitor only a single variable, for example; commercially successful products will have to perform a dozen or more analyses on a surface area of only a few square millimeters.

The chemically harsh environment of the human body is another obstacle.

In medicine and industry, tiny high-speed devices will track a wide range of biological reactions □ by H. Garrett DeYoung



Infusaid reservoir implanted in lower abdomen. It may also be sited in upper chest, with catheter inserted into aorta.

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 implanted in the patient's abdomen………

High Technology, Nov. 1983, 41-49

Freestyle Navigator

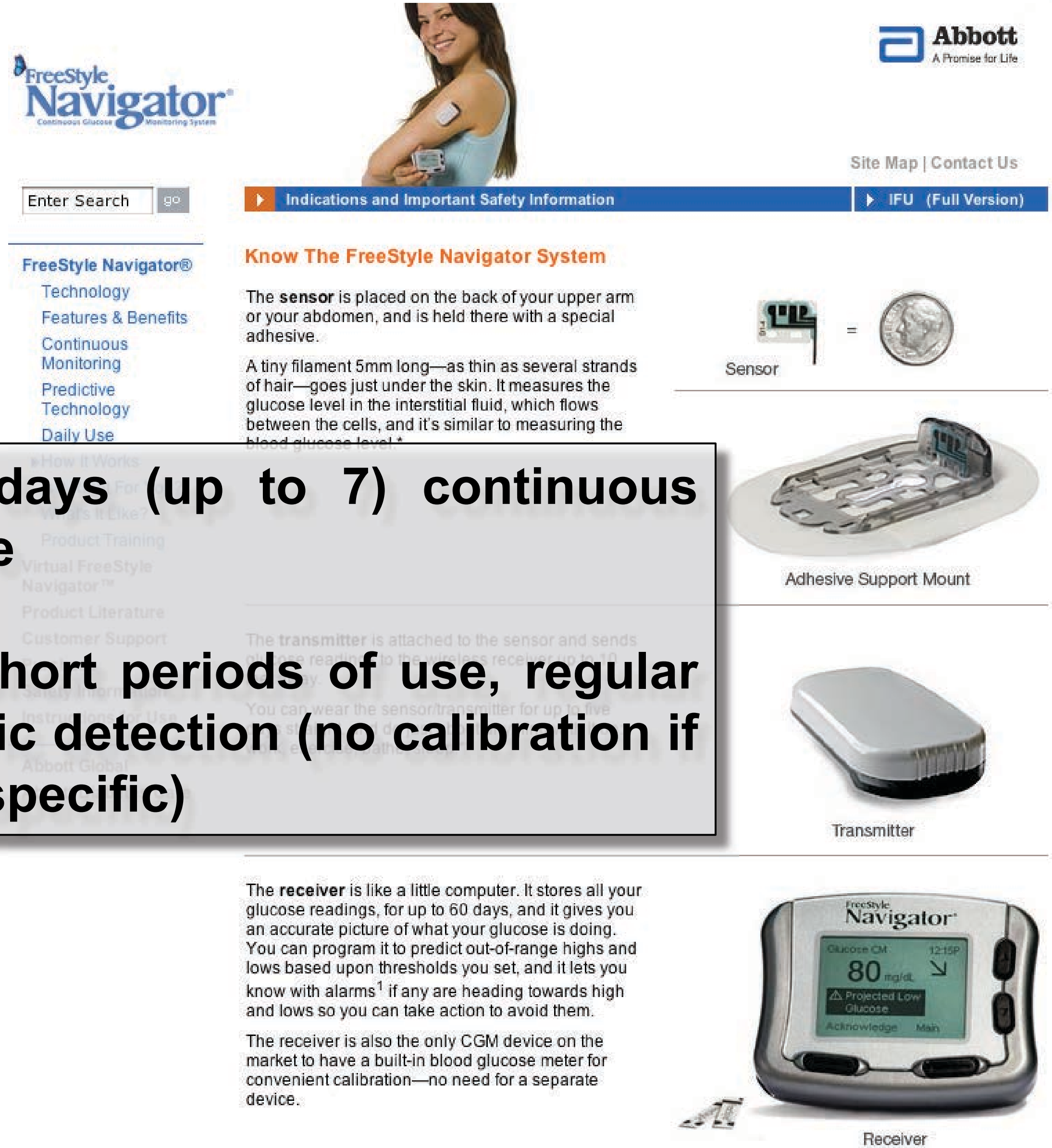
- Combines microfluidics with a micro-dimensioned filament sampling unit which is designed to minimise incidence of infection (the sensor can be left in place for 5 days)

- 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.**

Google Smart Contact Lenses Move Closer to Reality

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

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

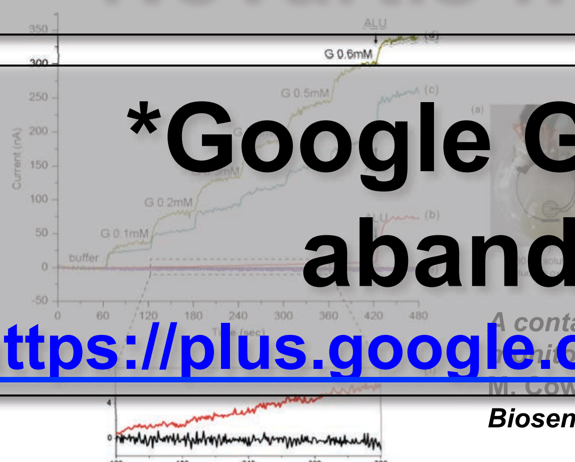


Fig. 2. Images of the sensor as it goes through surface functionalization and the related measured responses: (a) sequential images of sensor pre-treatment with GOD/titania/Nafion®; (b) measured amperometric response for the sensor just incubated with GOD; (c) measured amperometric response for the sensor prepared with GOD/titania sol–gel film; (d) measured amperometric response for the sensor prepared with GOD/titania/Nafion®; (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 ... 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

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

Physical Transducers

Chemical Sensors

Biosensors

Increasing difficulty & cost

Increasing scalability

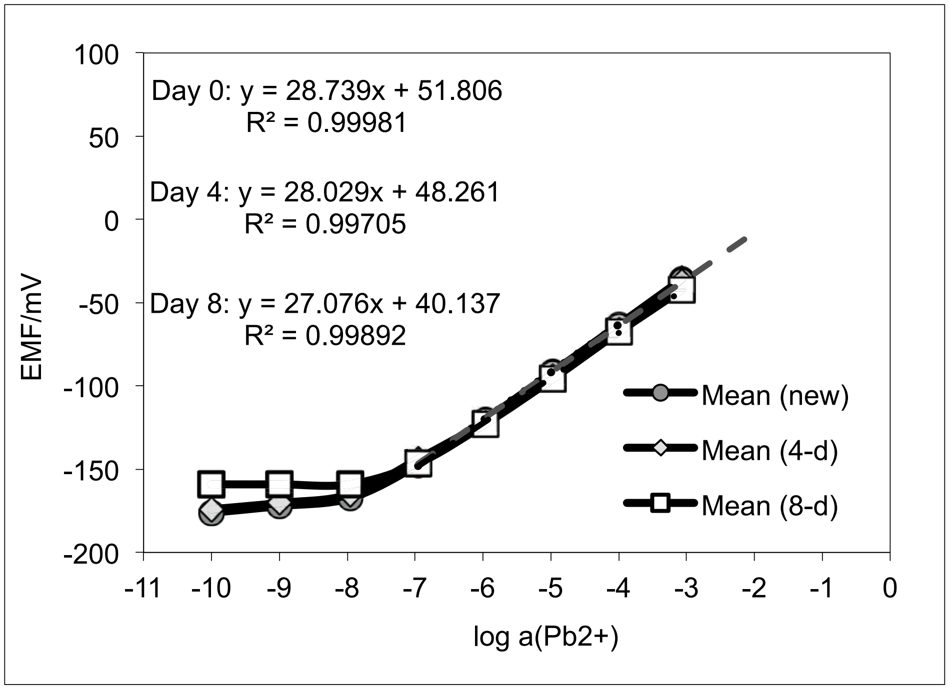
Air/Gas

Terrestrial (lake, river, waste, ground) Water

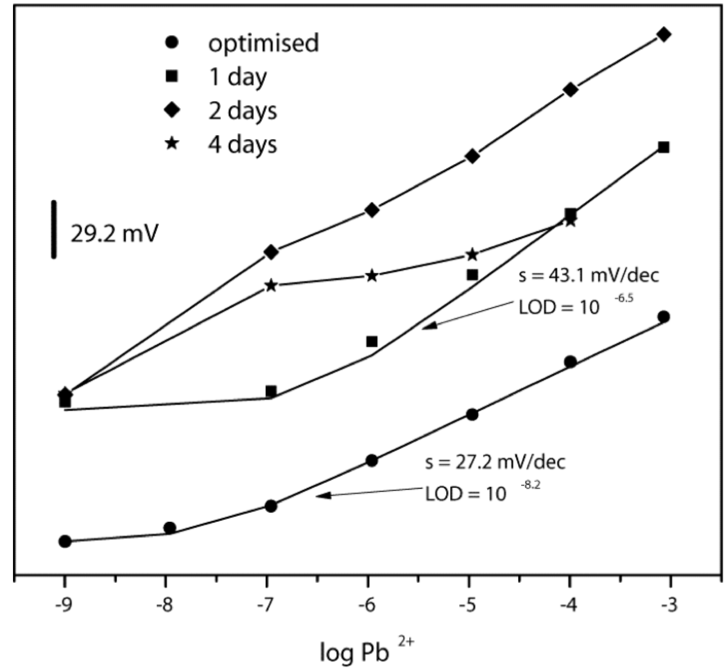
Marine Waters

Change in Electrode Function over Time

See Electrochimica Acta 73 (2012) 93–97



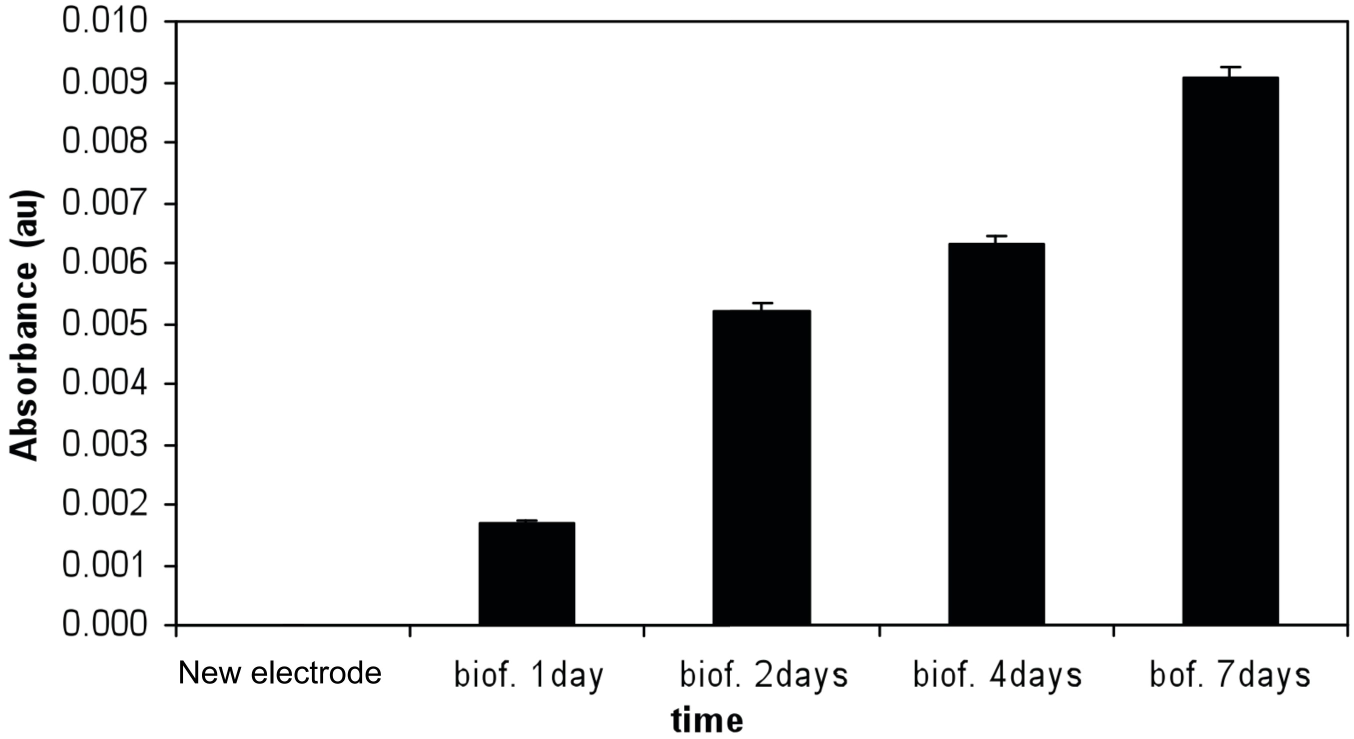
stored in 10^{-9}M Pb^{2+}, pH=4



Continuous contact with river water

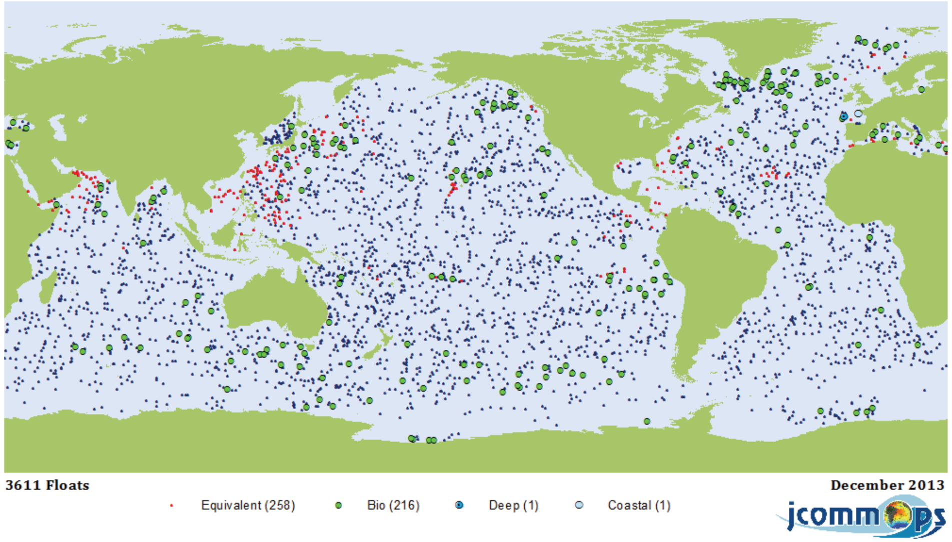
PVC-membrane based Solid-State Screen Printed ISEs

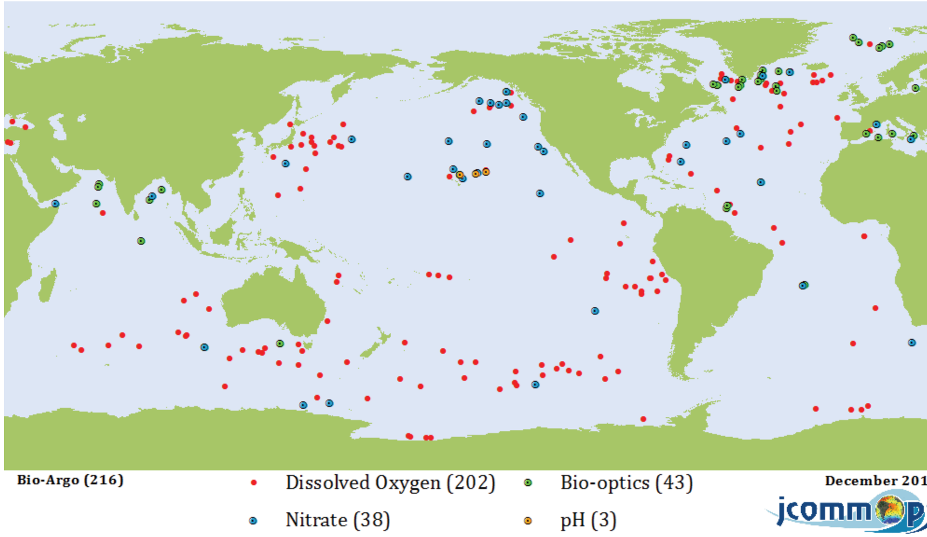
Biofilm Formation on Sensors



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

Argo Project (accessed March 9 2014)





- **Ca. 3,600 floats: temperature and salinity**
- **Only 216 reporting chem/bio parameters (ca. 6%)**
- **Of these nitrate (38), DO (202), Bio-optics (43), pH (3)**

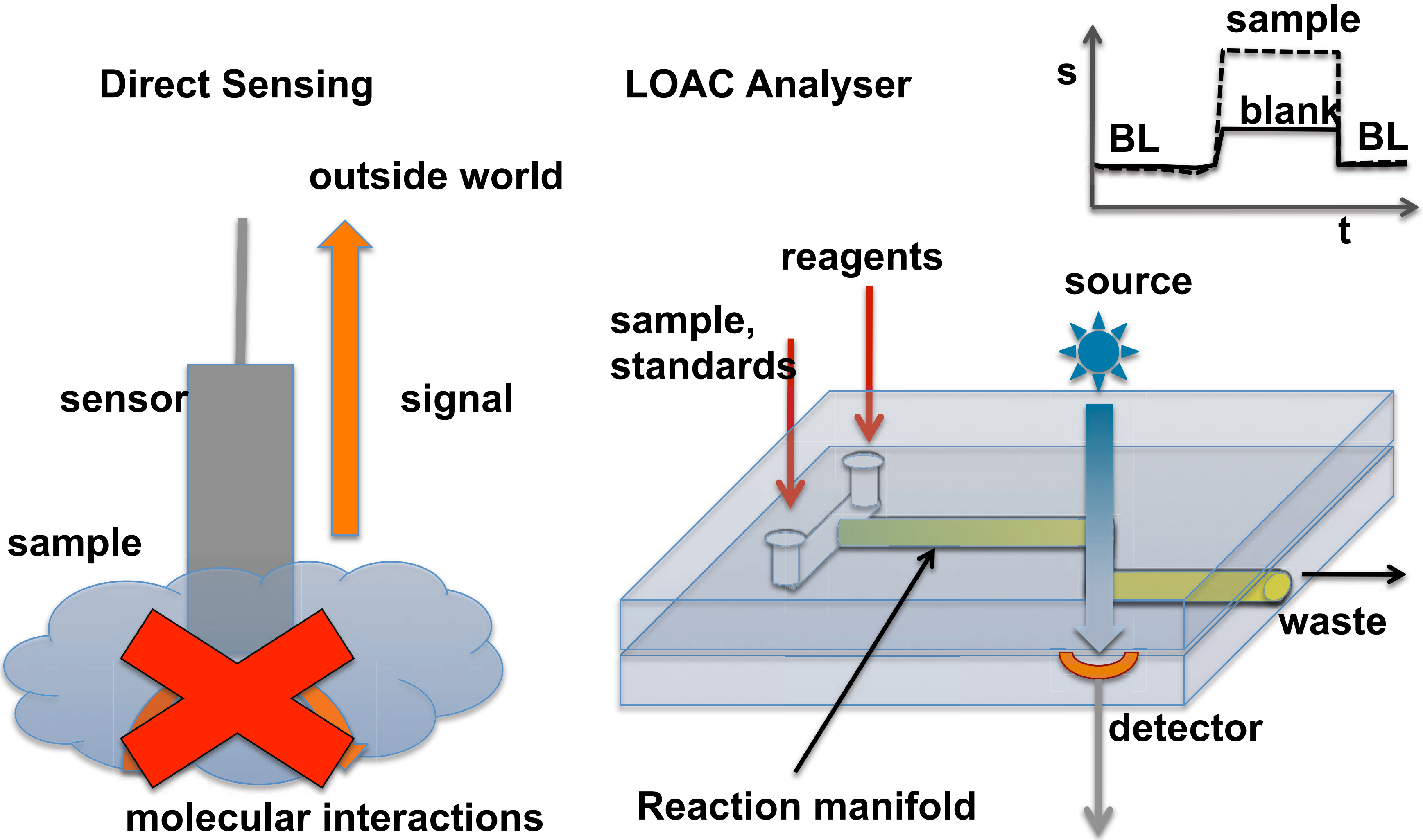
@€60K ea!

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

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

Direct Sensing vs. Reagent Based LOAC/ufluidics



Current Analyser Design

Phosphate: The Yellow Method

Mixture (Reagent)

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

\+

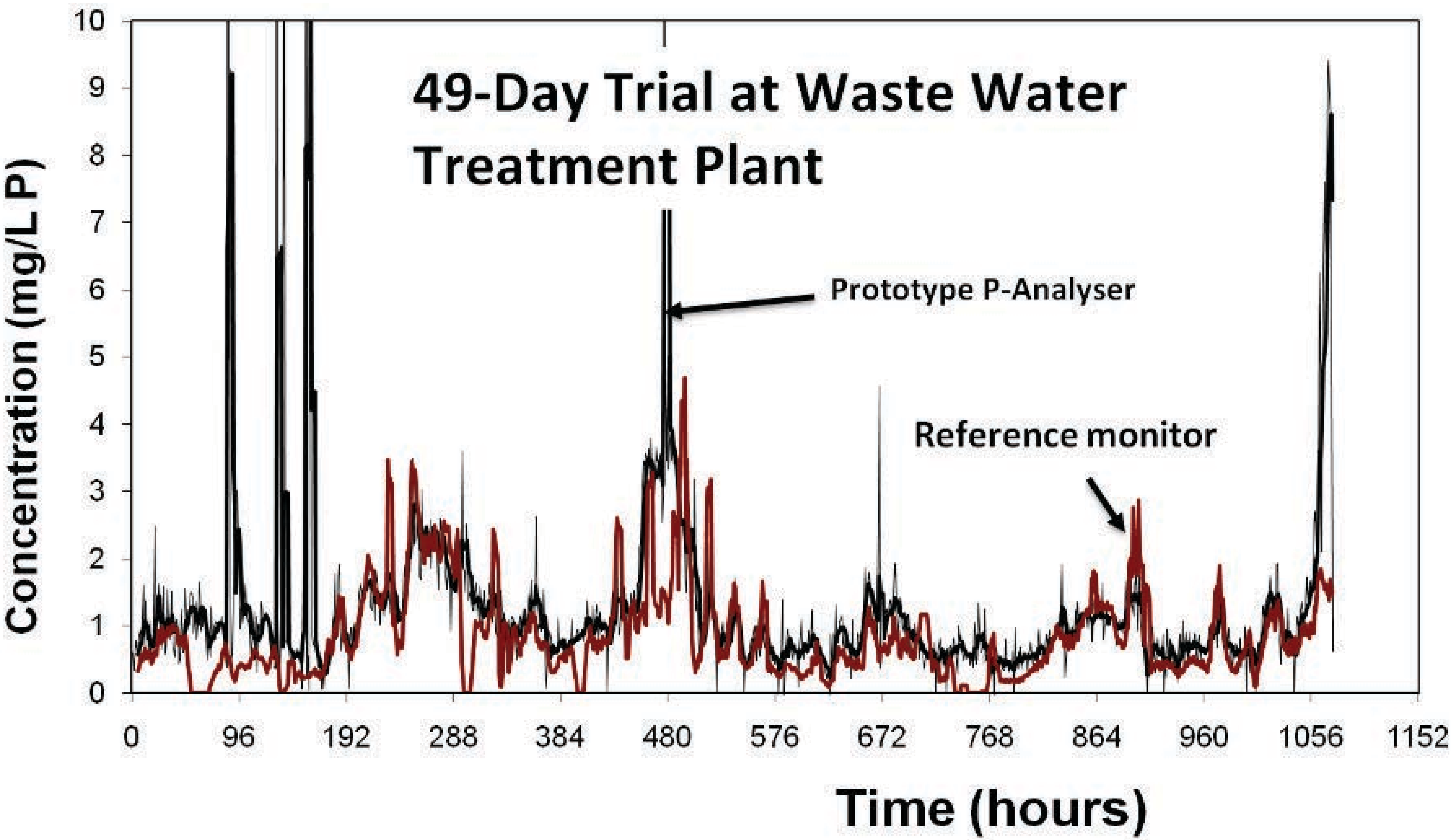
Sample

(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!!!!

Autonomous Chemical Analyser



Phosphate monitoring using the Yellow Method

Osberstown – 3 week deployment

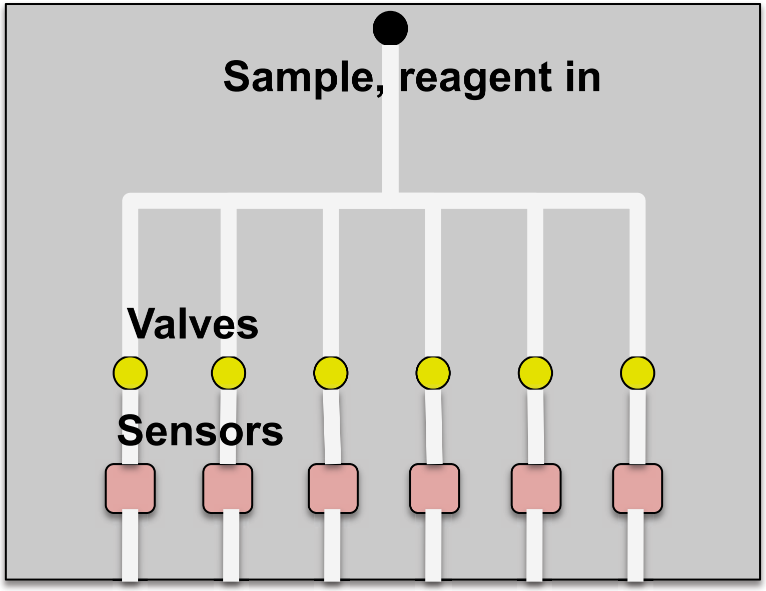
Biofouling of sensor surfaces is a major challenge for remote chemical sensing – both for the environment and for implantable sensors

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

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

OR…..

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

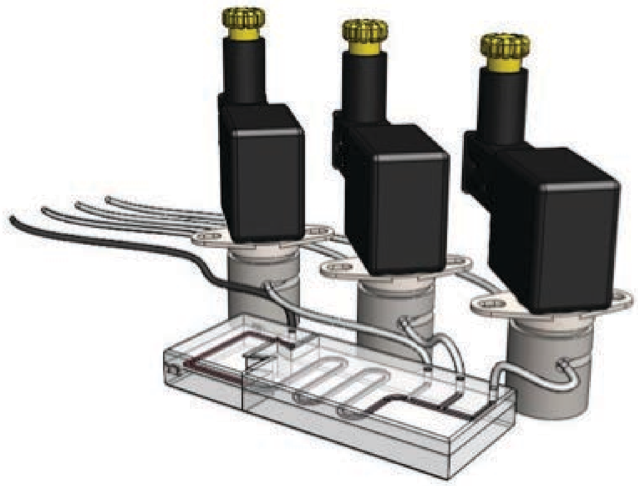


Then 100 short-life (1-day) sensors used sequentially could provide an aggregated use model of ~3 months

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

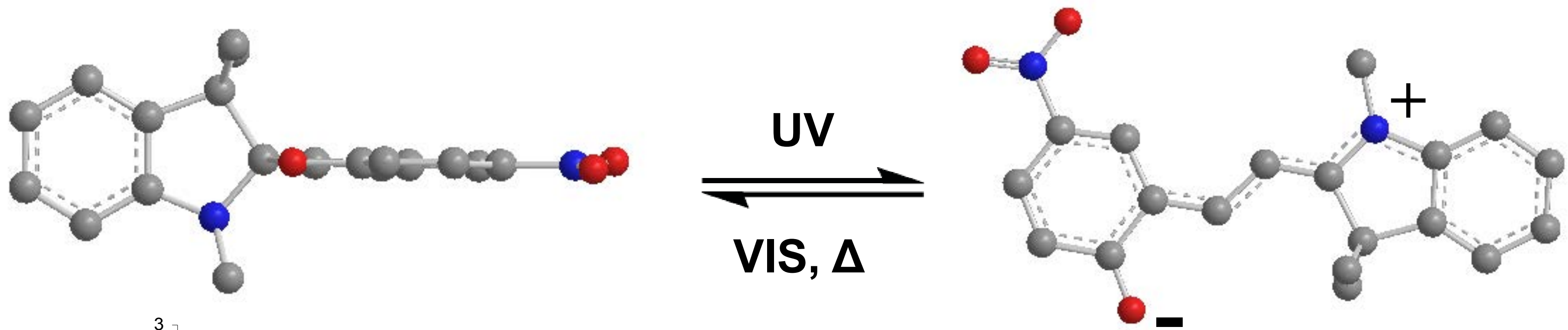
How to advance fluid handling in LOC platforms: re-invent valves (and pumps)!

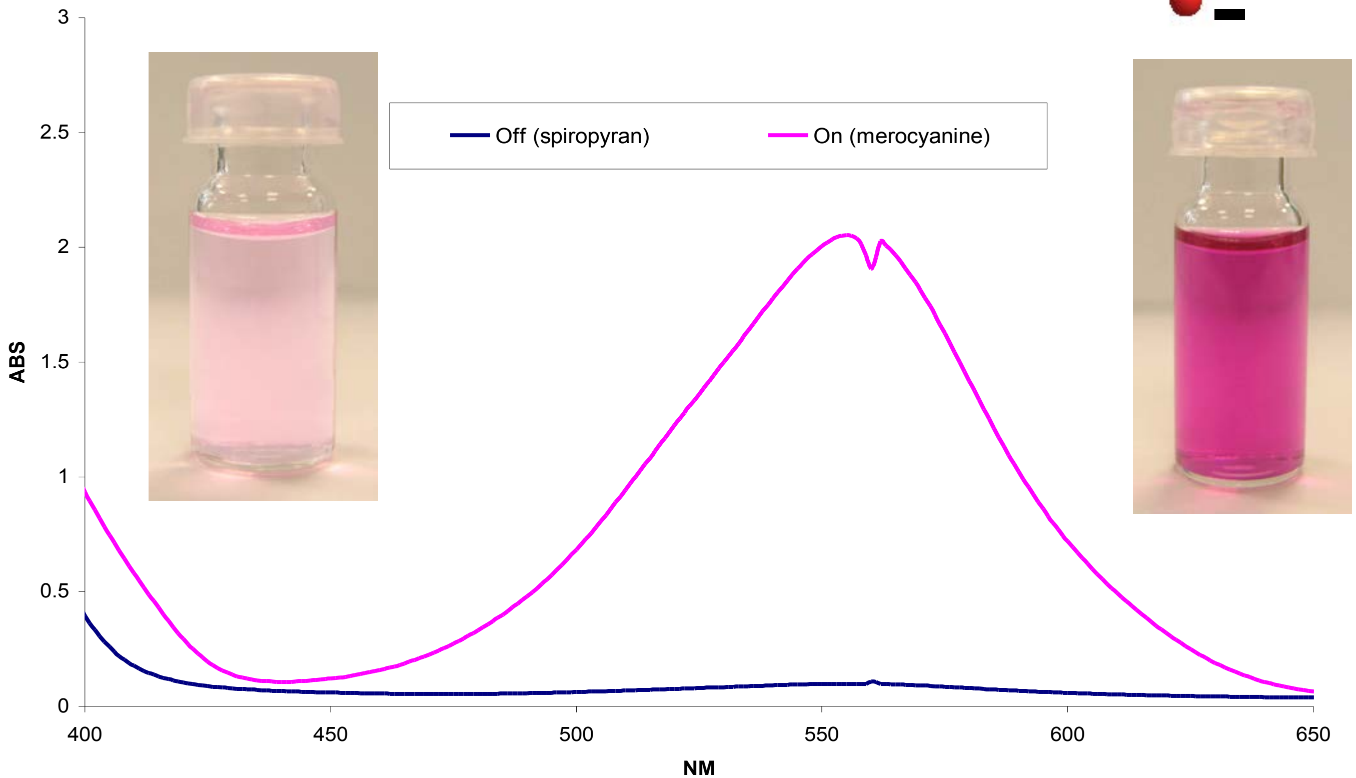
- **Conventional valves cannot be easily scaled down - Located off chip: fluidic interconnects required**
  - Complex fabrication
  - Increased dead volume
  - Mixing effects
- **Based on solenoid action**
  - Large power demand
  - Expensive



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

Photoswitchable Actuators

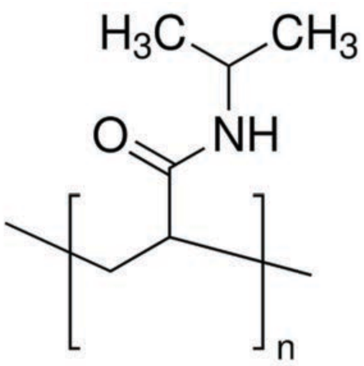




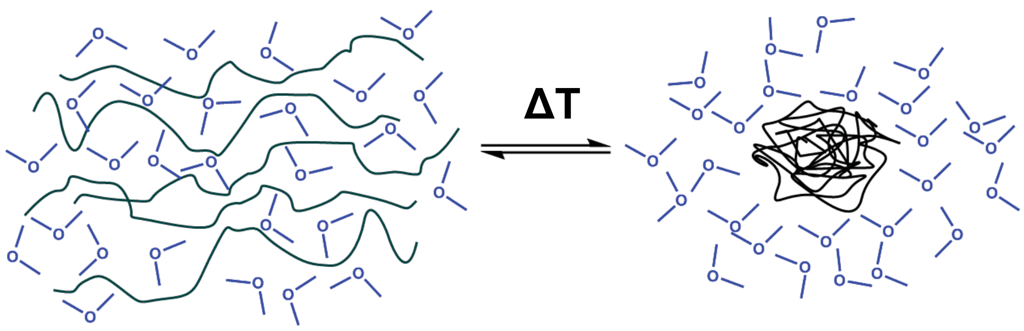
Poly(*N*-isopropylacrylamide)

- **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

Polymer based photoactuators based on pNIPAAm

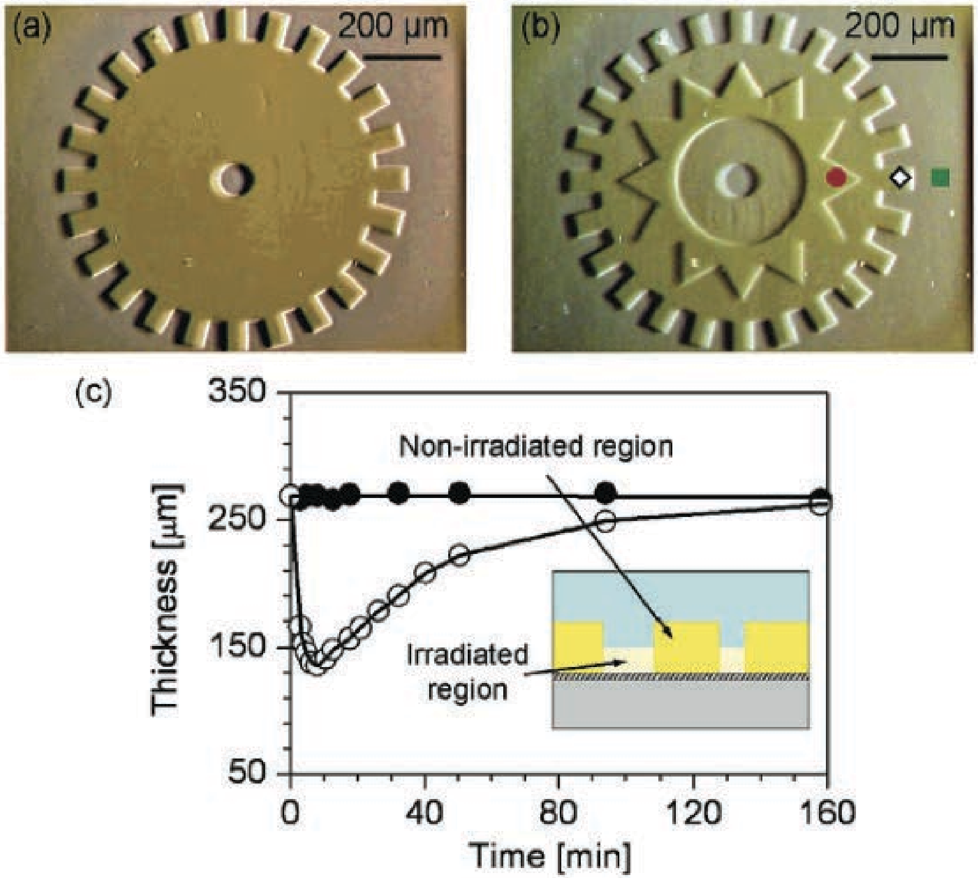
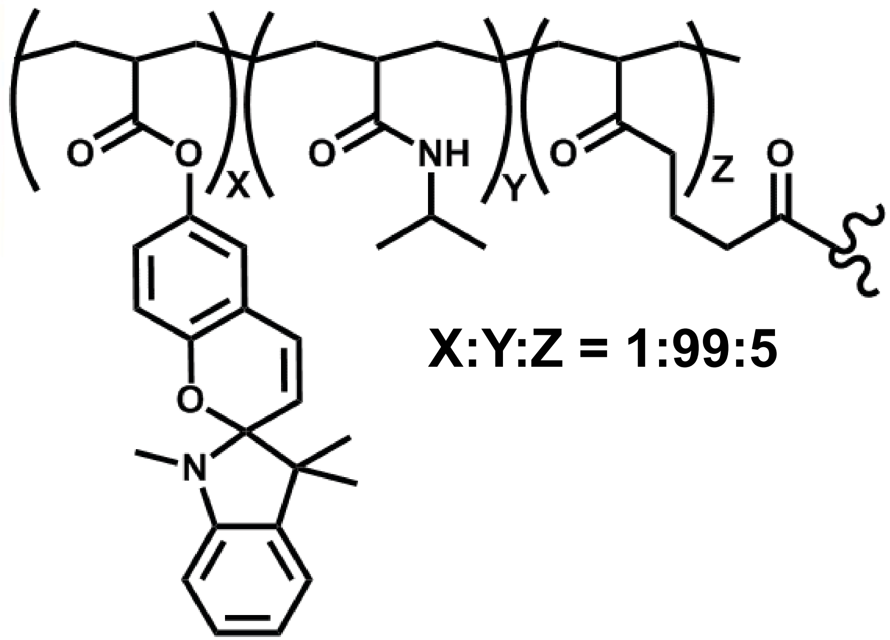


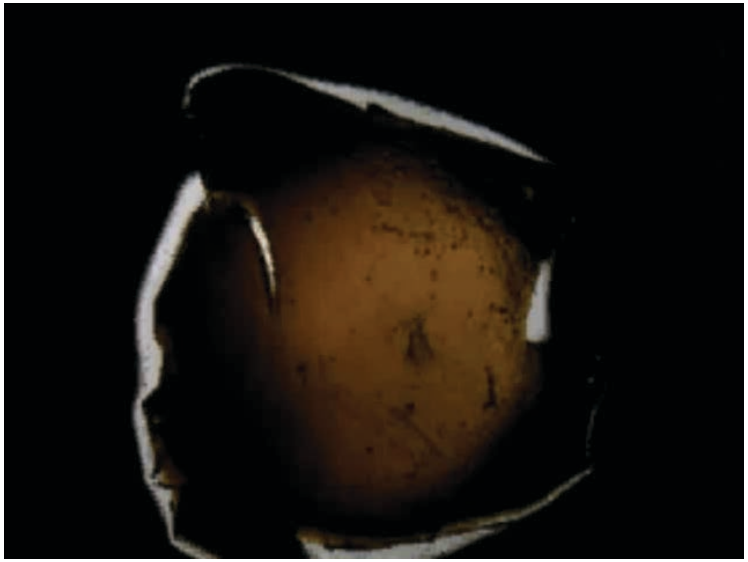
Figure 3. (a, b) Images of the pSPNIPAAm hydrogel layer just after the micropatterned light irradiation. Duration of irradiation was (●, red) 0, (◇) 1, and (■, green) 3 s. (c) Height change of the hydrogel layer in (●) non-irradiated and (○) irradiated region as a function of time after 3 s blue light irradiation.

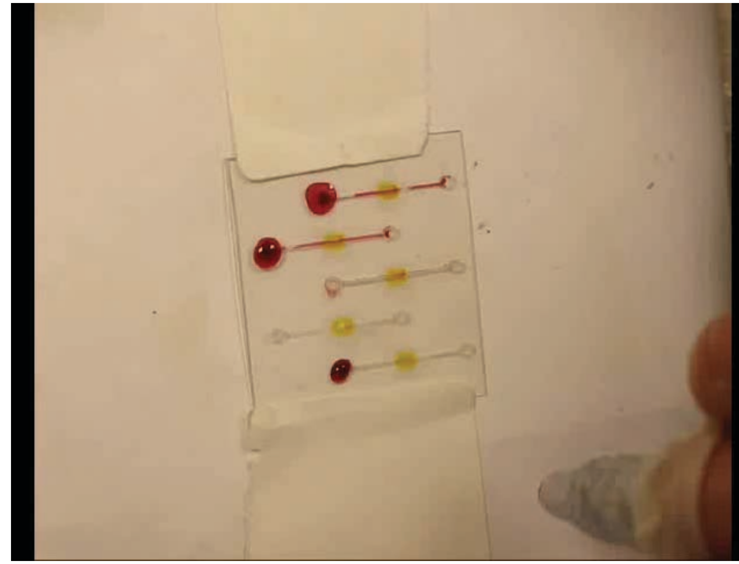


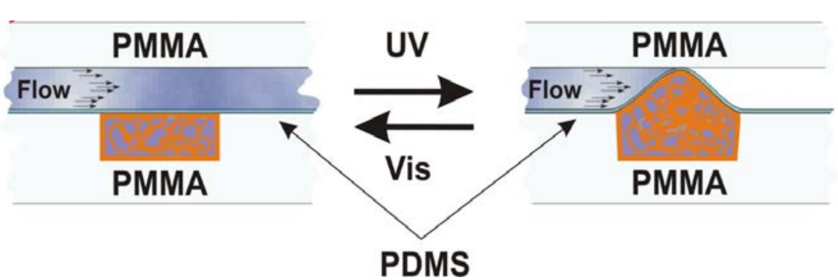
X:Y:Z = 1:99:5

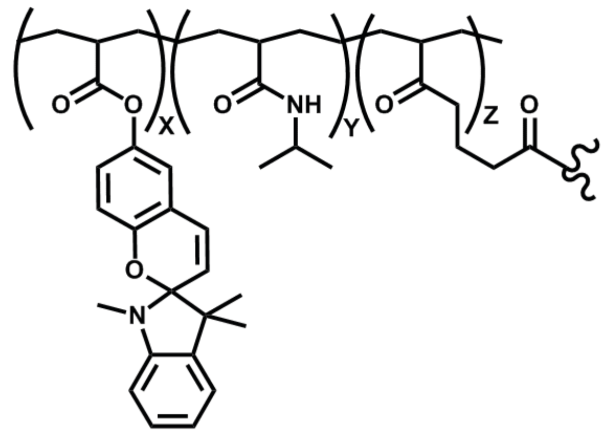
poly(N-isopropylacrylamide) (PNIPAAm)
Formulation as by Sumaru et al[1]
***1) Chem. Mater.*, 19 (11), 2730 -2732, 2007.**

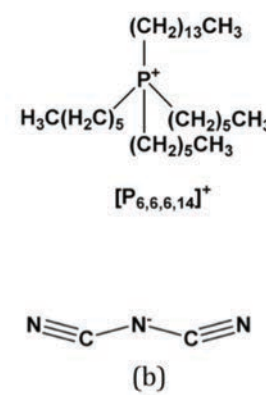
Photo-actuator polymers as microvalves in microfluidic systems











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.

Actuation Mechanism

SPIRO
(contracted-colourless)

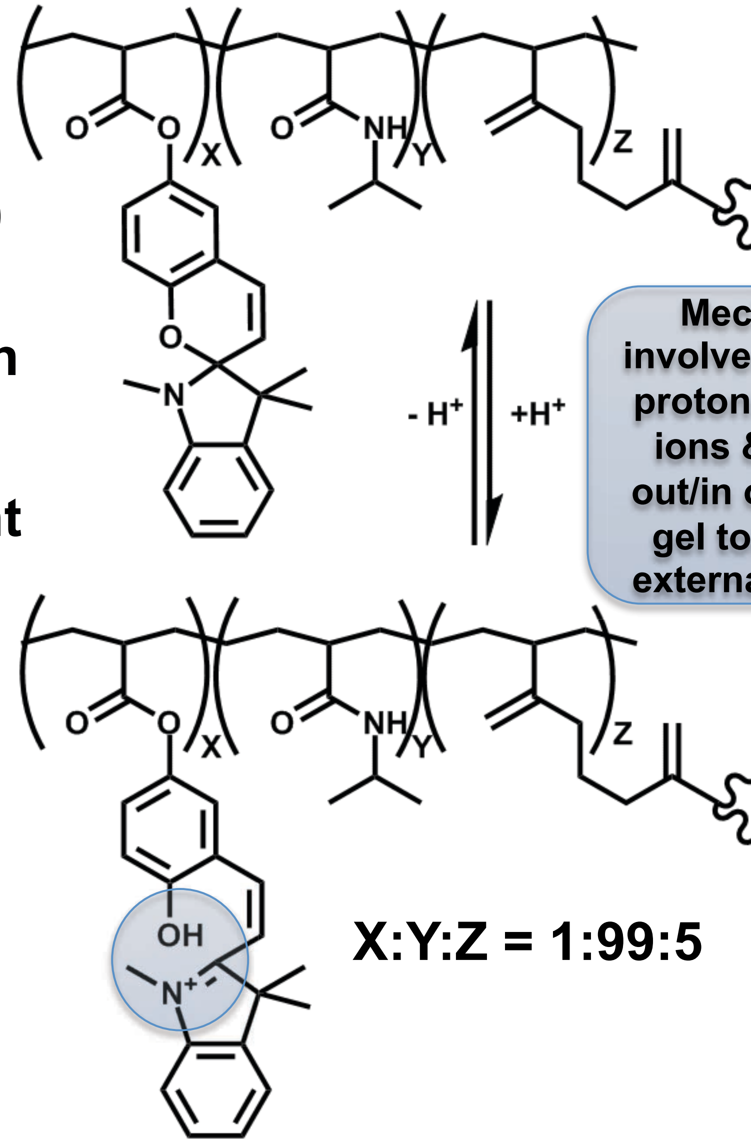
H^+, X^-, solvent

acidic solution

H^+, X^-, solvent

white light

MERO-H^+
(expanded-yellow)

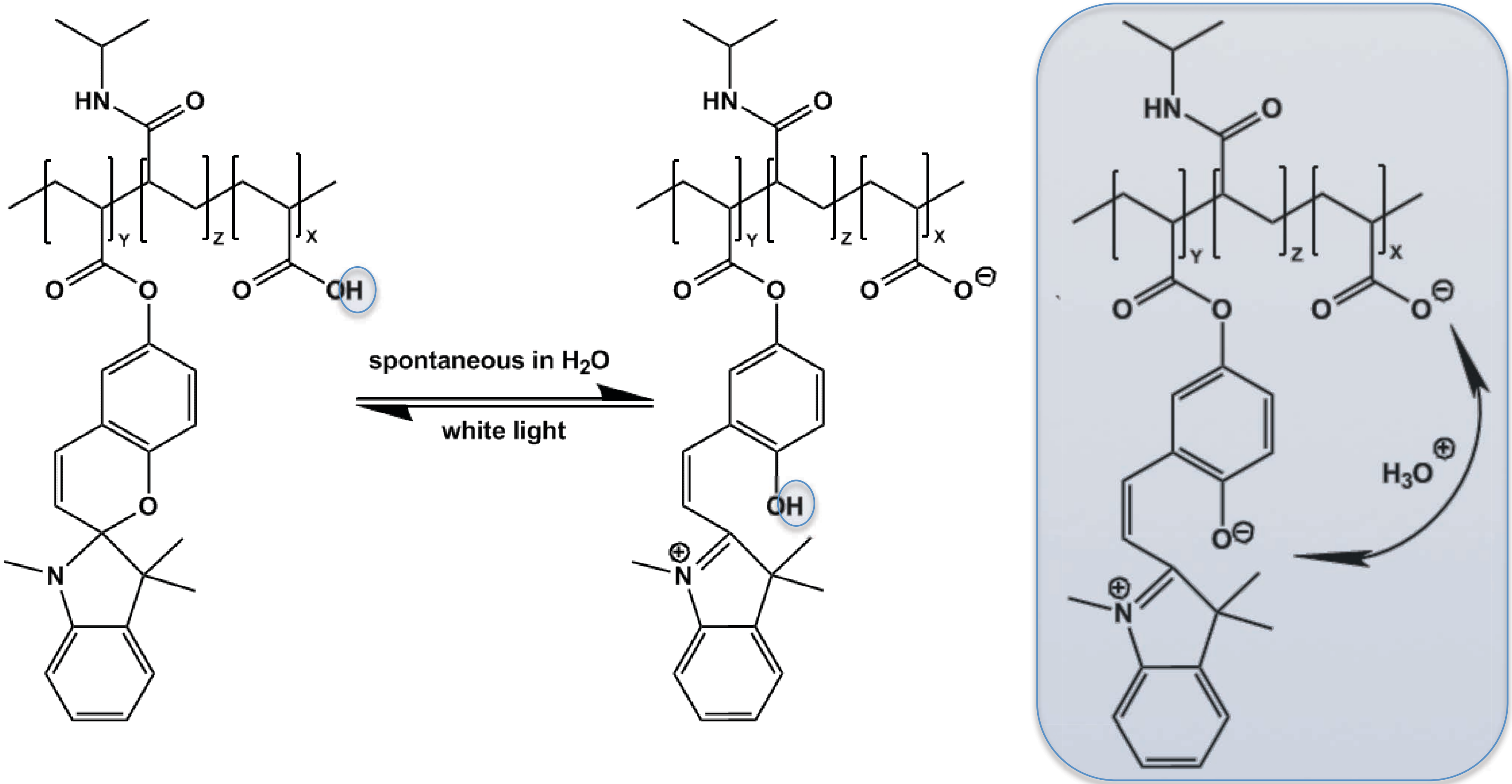


Mechanism involves diffusion protons, counter ions & solvent out/in of the bulk gel to/from the external solution

X:Y:Z = 1:99:5

Self protonating photoresponsive gel

Ziolkowski *et al.*, Soft Matter, 2013, 9, 8754–8760



Previously proton source was external (acidic soln. required)
Protons, counter ions & solvent diffuse into/out of the gel

Now the proton exchange is 'internalised'
The proton population is essentially conserved

Effect of AA-modification on Actuation Cycling in non-acidified water

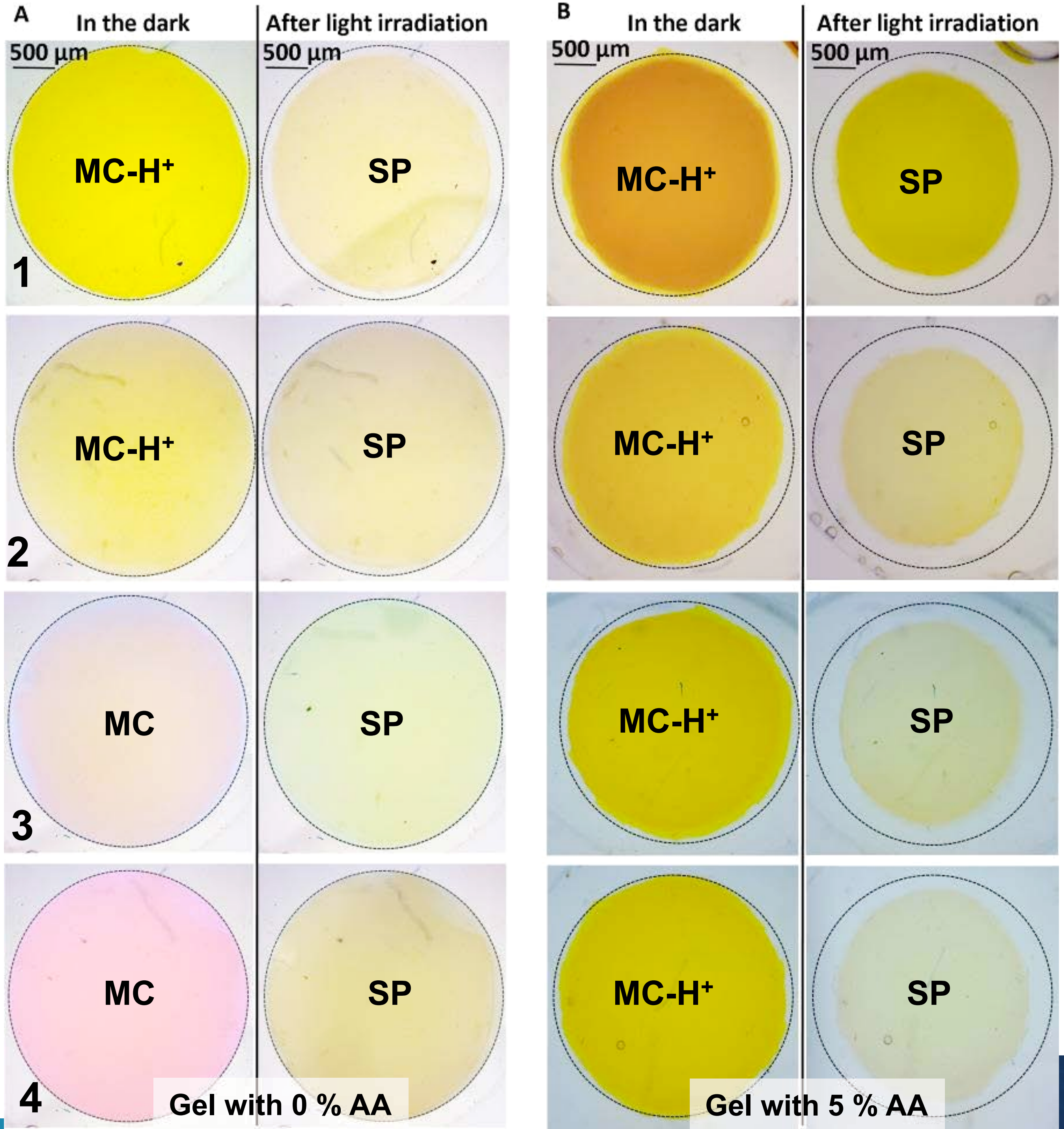
A: Un-modified Gel (left): Colour gradually changing from yellow to purple as H^+ leaves the gel on each cycle.

Actuation stops after initial cycle

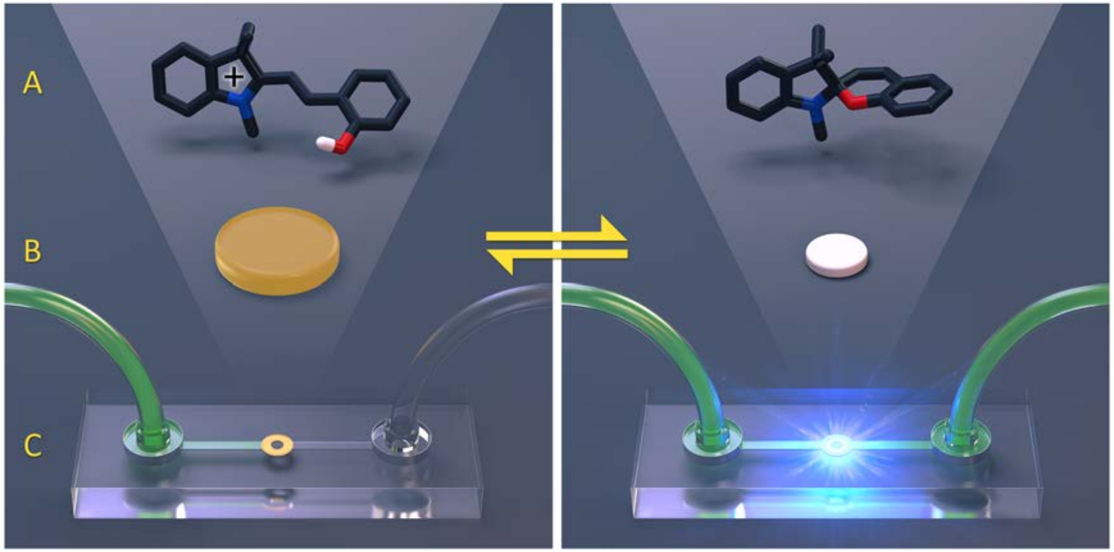
B: Modified Gel (Right) Colour remains essentially the same, as H^+ stays in the gel during cycling

Actuation efficiency is retained over multiple cycles

Ziolkowski *et al.*, Soft Matter, 2013, 9, 8754–8760



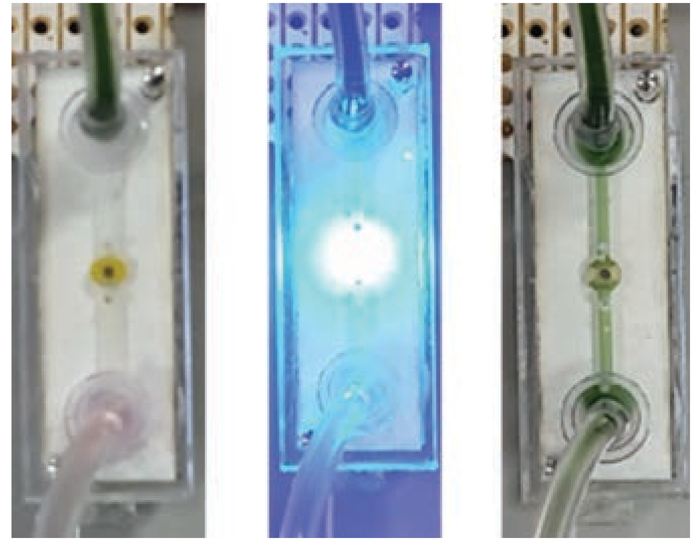
Reversible Photo-Switching of Flow

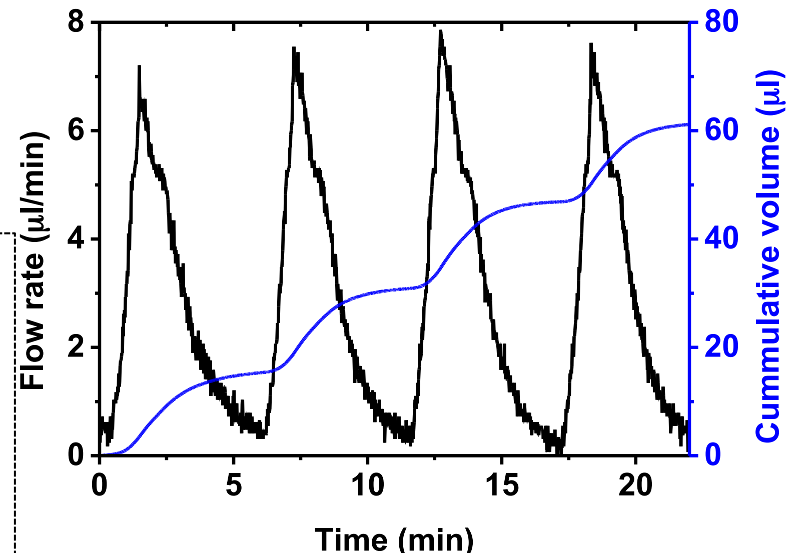


Above: scheme showing switching process protonated MC-H$^+$ photoswitched to SP triggering p(NIPAAM-*co*-AA-*co*-SP) gel contraction and opening of the channel.

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.





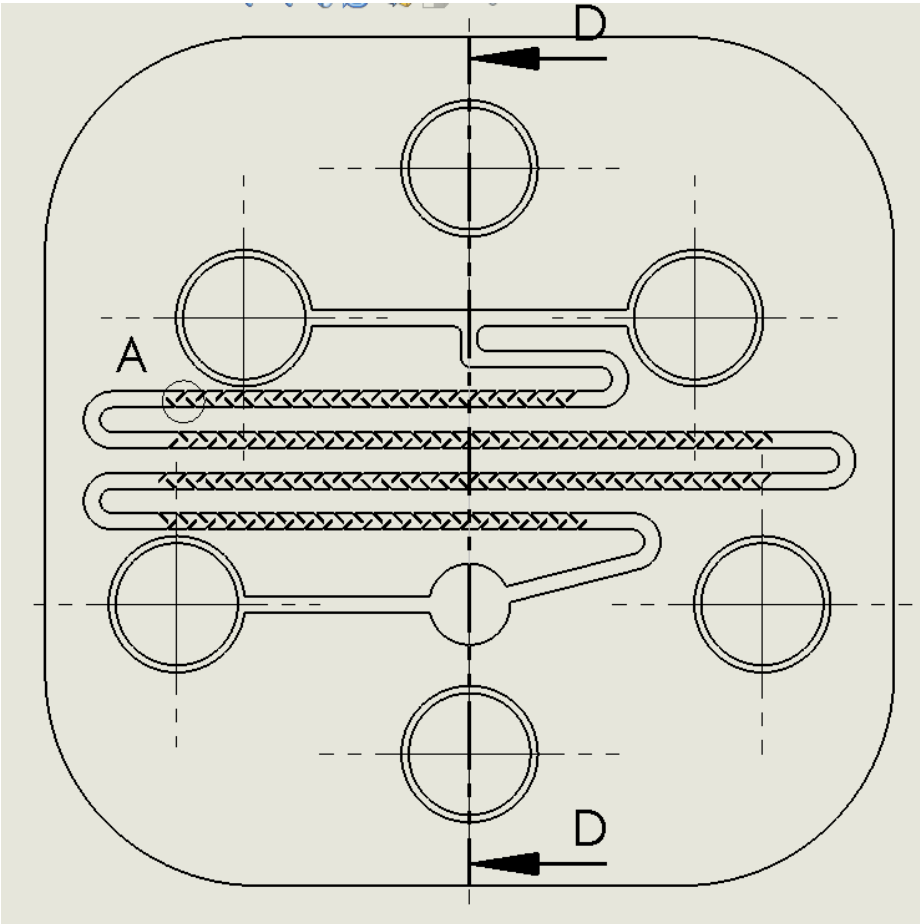
From: 'Molecular design of light-responsive hydrogels, for in-situ generation of fast and reversible valves for microfluidic applications ' Chemistry of Materials (2015), accepted.

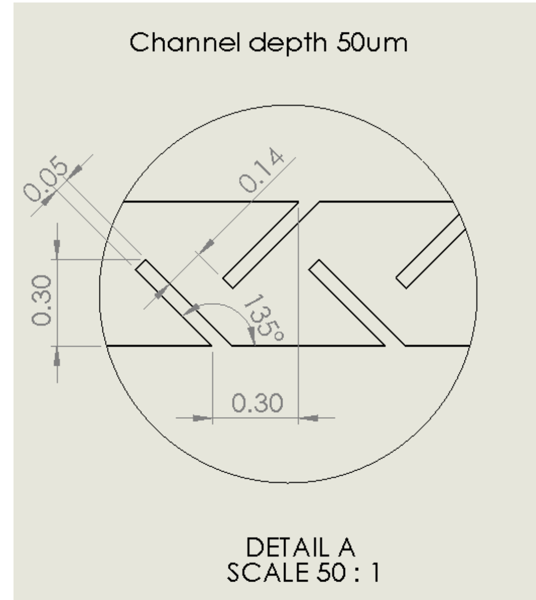
Jeroen ter Schiphorst,[†,#] Simon Coleman,[‡,#] Jelle E. Stumpel,[†] Aymen Ben Azouz,[‡] Dermot Diamond[*,‡] and Albertus P.H.J. Schenning[*,†,§]

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

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

Mixing Baffles





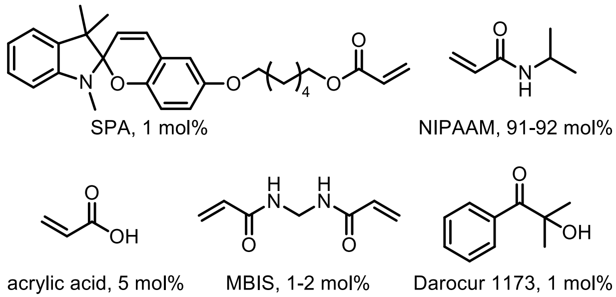
Photocontrol of Assembly and Subsequent Switching of Surface Features

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

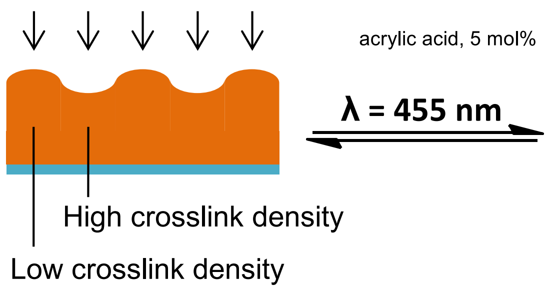
ACS applied materials & interfaces, 6 (2014) 7268-7274

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

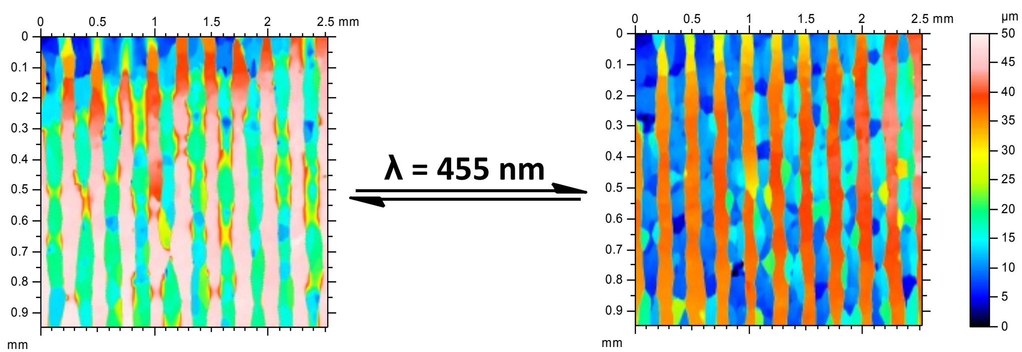
Jelle E. Stumpel,[†] Bartosz Ziółkowski,[‡] Larisa Florea,[‡] Dermot Diamond,[‡] Dirk J. Broer,[*,†,§] and Albertus P. H. J. Schenning[*,†,§]

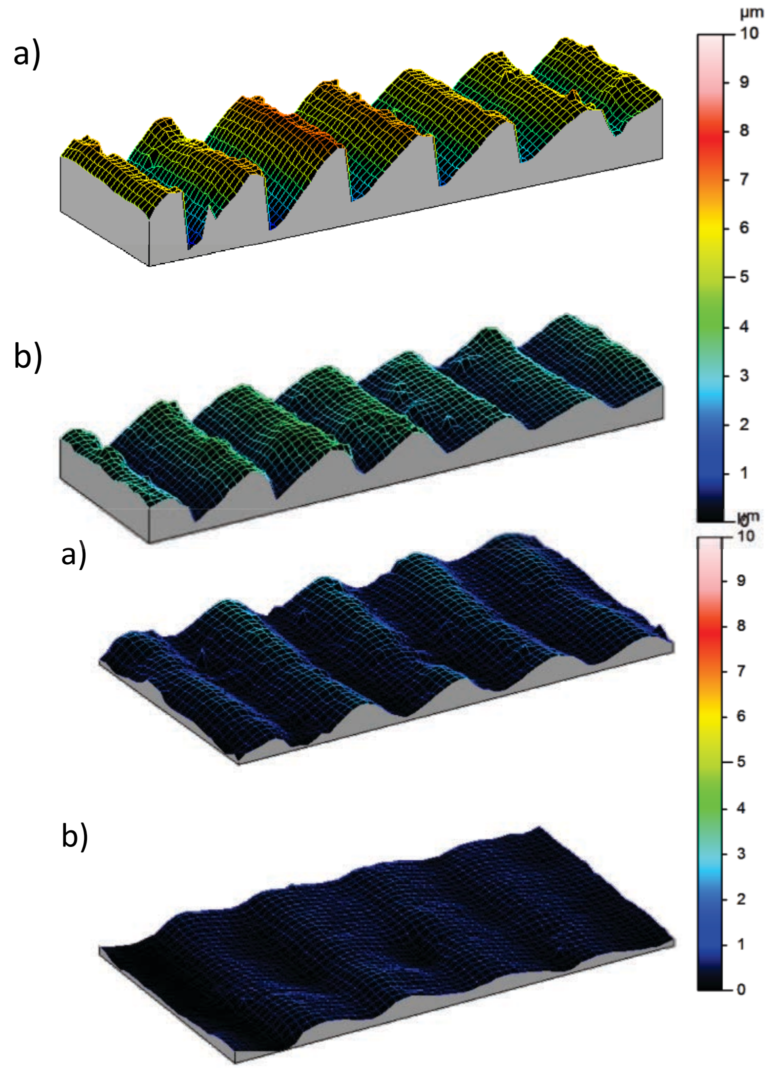


a)



b)





Chemotaxis

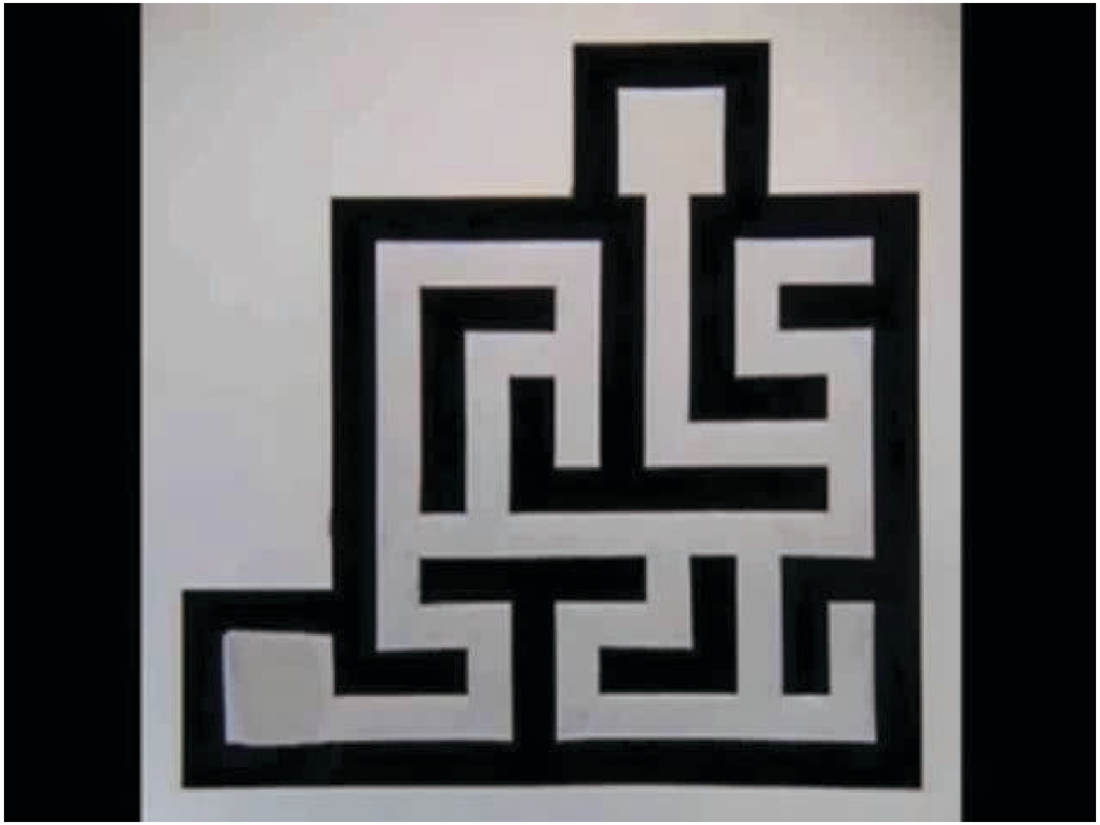
Chemotaxis of a Single cell to cAMP

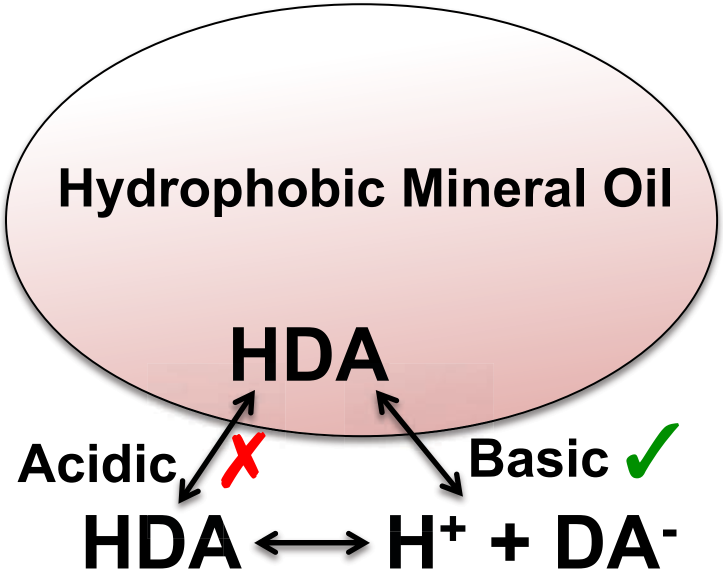
Time-lapse video microscopy (DIC optics, 60X objective) of a single cell moving toward a micropipette containing the chemoattractant cAMP. Note that the cell changes direction in response to movement of the micropipette by extending a new pseudopod in the direction of the pipette tip

.

Source: *www.dnatube.com/video/257/Chemotaxis-of-a-Single-cell-to-cAMP*

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.*

µ-TAS or Lab on a Chip - The Original Concept

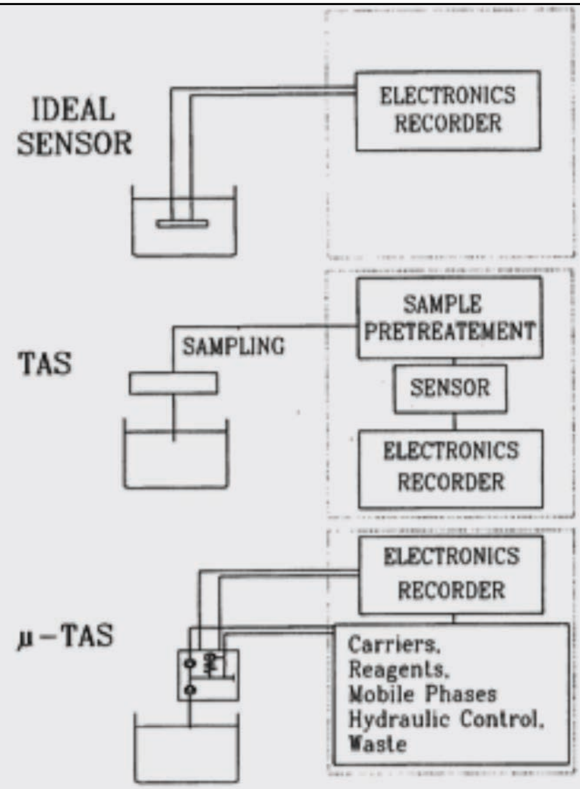


Fig. 3. Schematic diagram of an ideal chemical sensor, a 'total chemical analysis system' (TAS) and a miniaturized TAS (µ-TAS).

Integrate all operations required to obtain an analytical measurement

- Take samples
- Add reagents
- Process samples
- Perform analysis
- Perform calibrations

Microdimensioned channels leads to dramatic reductions in reagent consumption, waste generation, energy demand, sample turnaround….

Miniaturized Total Chemical Analysis Systems: A Novel Concept for Chemical Sensing; A Manz, N. Graber and H.M. Widmer, Sens. Actuator, B1 (1990) 244-248 (almost 3,000 citations July 2015).

The Future: 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!

The European Sensor Systems Cluster (ESSC)

Eurosensors 2015
Freiburg (Germany),
6-9 September 2015
Two ESSC sessions

European Sensor Systems Cluster - *ESSC*

Vision, Objectives, Strategies, Priorities and Challenges of EU Cluster

Cluster launched at Preparatory Workshop on 27 November 2014 in Brussels

sponsored and observed by EC DG Research and Innovation

Room Tunis, Session Time: 12:00 - 13:30

Vision, Objectives and Position Paper

Michele Penza - Chairman of the ESSC
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ENEA, Materials Technologies, Brindisi - Italy

AGENZIA NAZIONALE PER LE NUOVE TECNOLOGIE, L'ENERGIA E LO SVILUPPO ECONOMICO SOSTENIBILE

European Commission

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Thanks to…..

Thanks for listening

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