‘Can Biomimetic Principles Coupled with Advanced Fabrication Technologies and Stimuli-Responsive Materials Drive Revolutionary Advances in Wearable and Implantable Biochemical Sensors?’

Dermot Diamond, Larisa Florea, Aishling Dunne, Alex Tudor, Aymen BenAzouz and Simon Coleman

Insight Centre for Data Analytics, National Centre for Sensor Research

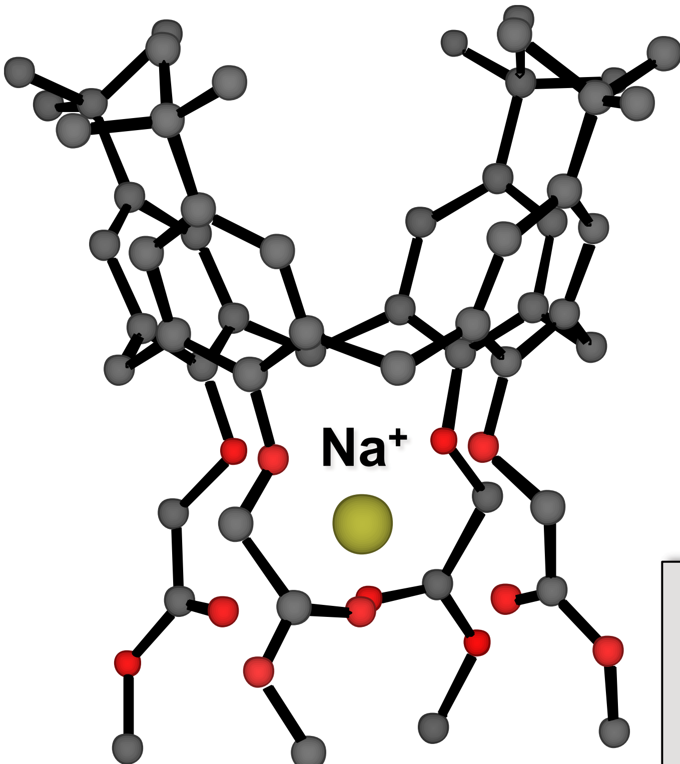
Dublin City University, Dublin 9, Ireland

Invited Seminar Presented at

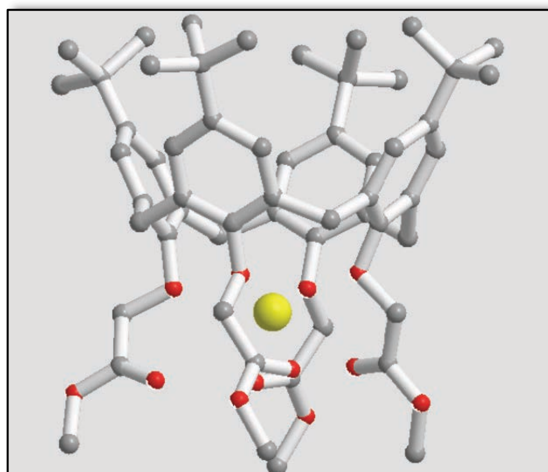
Tyndall Institute, Cork

21st January 2016

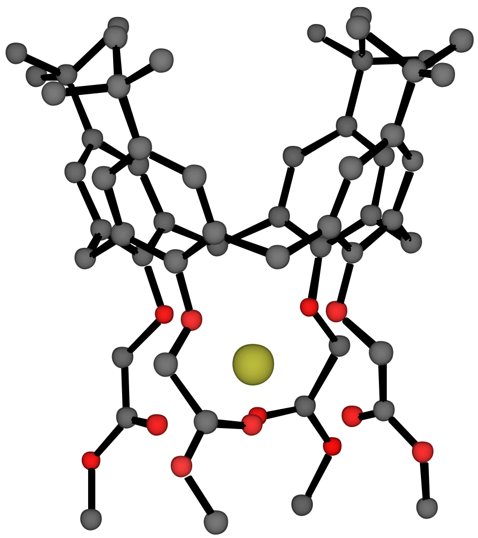
Calixarene Ionophores – controlling the selectivity

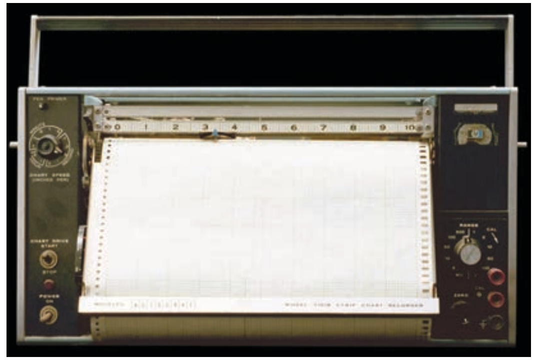


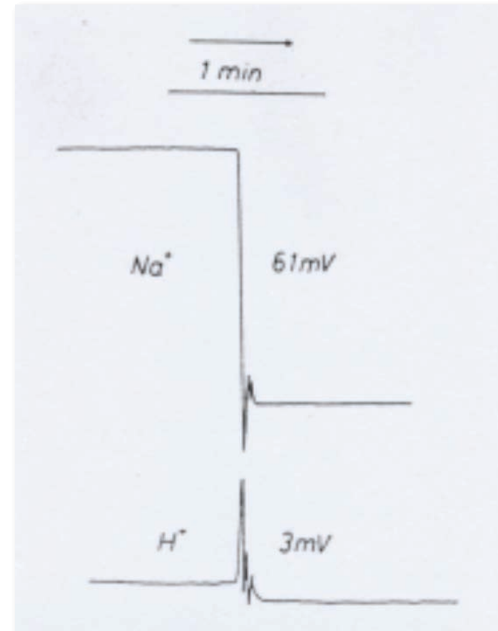
$H_3C-O-C(=O)-CH_2-$



Selectivity, Response Time, Stability…



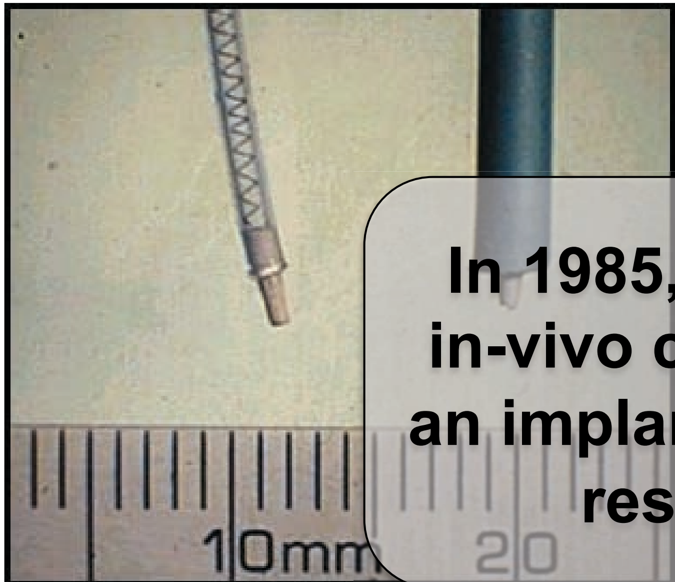




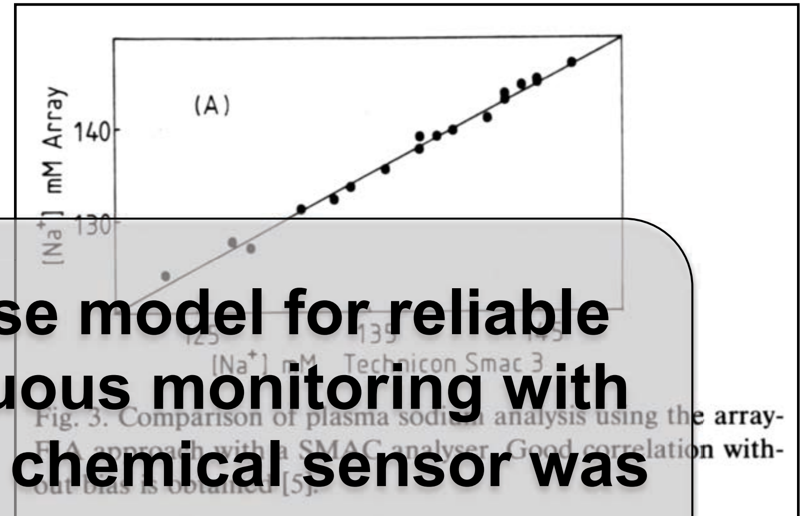
Neutral Carrier Based Ion-Selective Electrodes, D.Diamond, Anal. Chem. Symp. Ser., 25 (1986) 155.

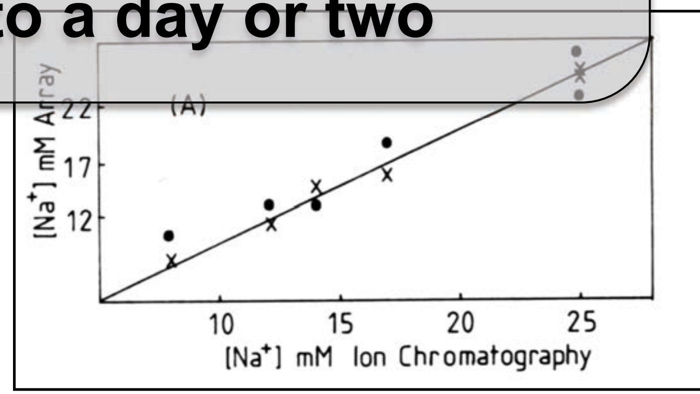
A sodium Ion-Selective Electrode based on Methyl p-t-Butyl Calix[4]aryl Acetate as the Ionophore, D.Diamond, G.Svehla, E.Seward,and M.A.McKervey, Anal. Chim. Acta., 204 (1988) 223-231

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

Artificial Pancreas

A. M. ALBISSER, M.A.SC., PH.D., AND ASSOCIA

Used a Technicon segmented flow colorimetric glucose analyser

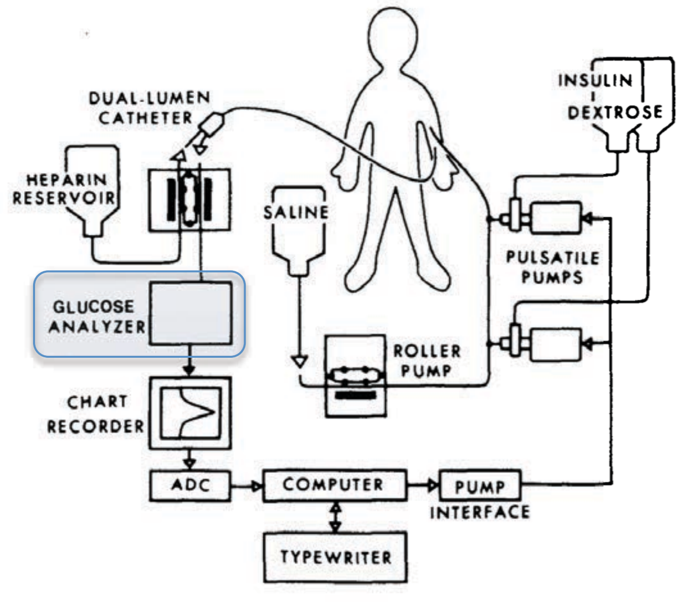
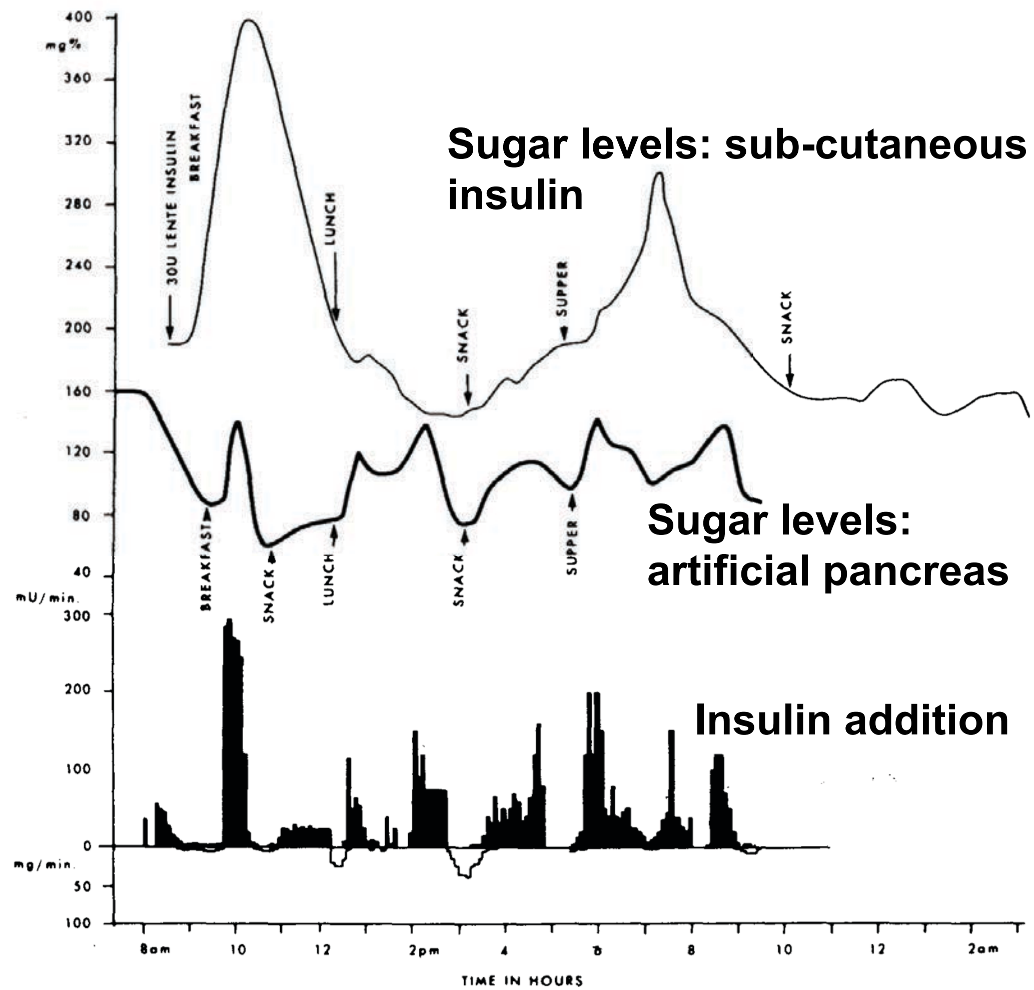
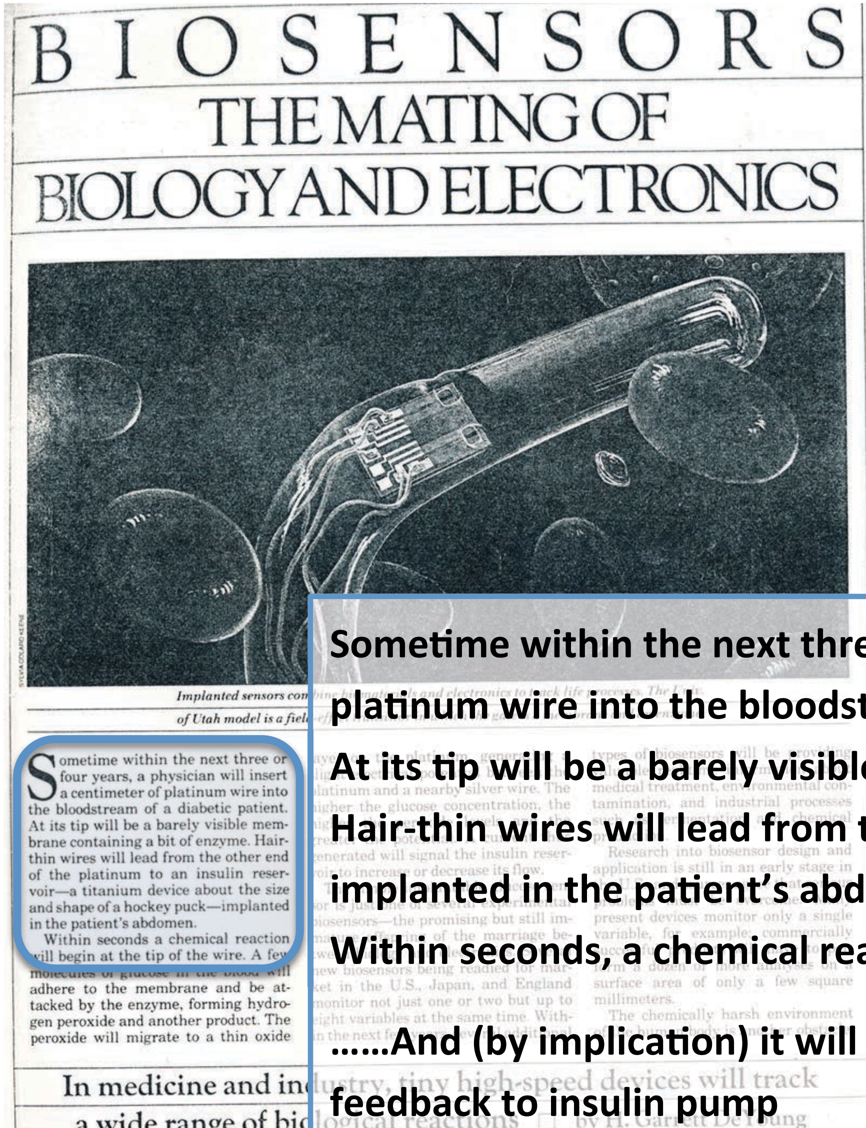


FIG. 1. Schematic diagram of apparatus used for monitoring and automatic regulation of blood sugar.



A M Albisser, B S Leibel, T G Ewart, Z Davidovac, C K Botz, W Zingg, H Schipper, and R Gander
Clinical Control of Diabetes by the Artificial Pancreas
Diabetes May 1974 23:5 397-404; doi:10.2337/diab.23.5.397 1939-327X (Toronto)

The (broken) promise of biosensors…..


BIOSENSORS
THE MATING OF BIOLOGY AND ELECTRONICS

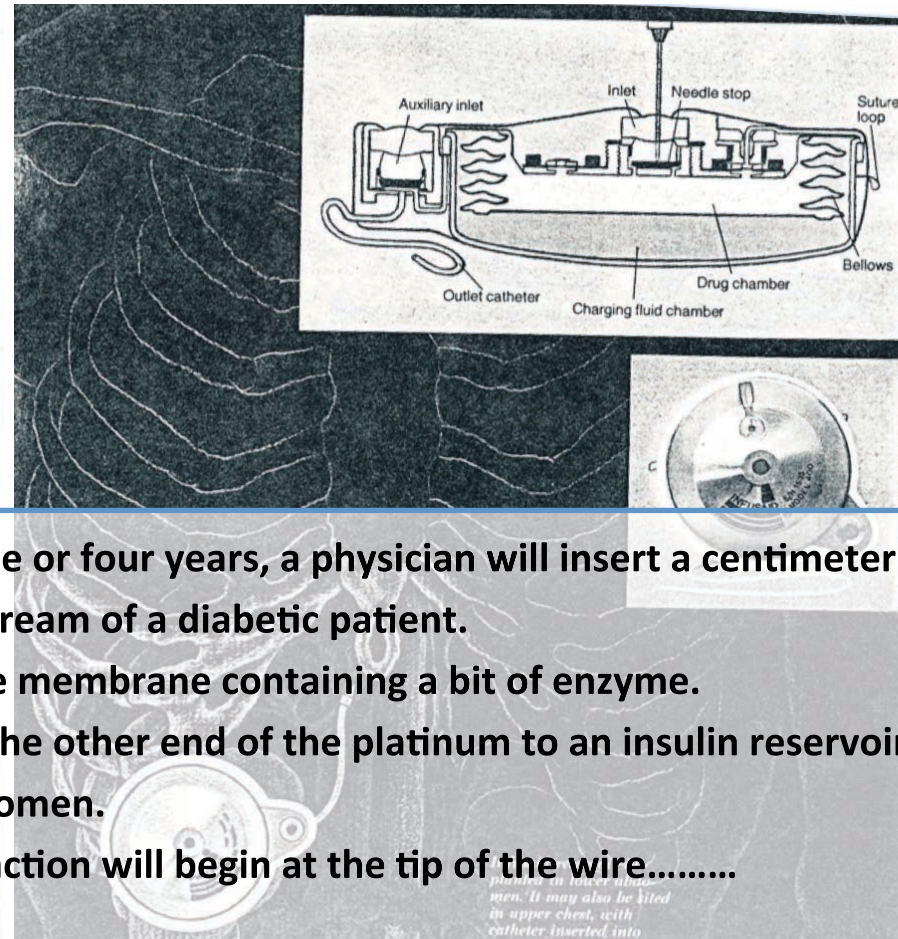
Sometime within the next three or four years, a physician will insert a centimeter of platinum wire into the bloodstream of a diabetic patient. At its tip will be a barely visible membrane containing a bit of enzyme. Hair-thin wires will lead from the other end of the platinum to an insulin reservoir—a 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 in

a wide range of bio

High Technology, Nov. 1983, 41-49



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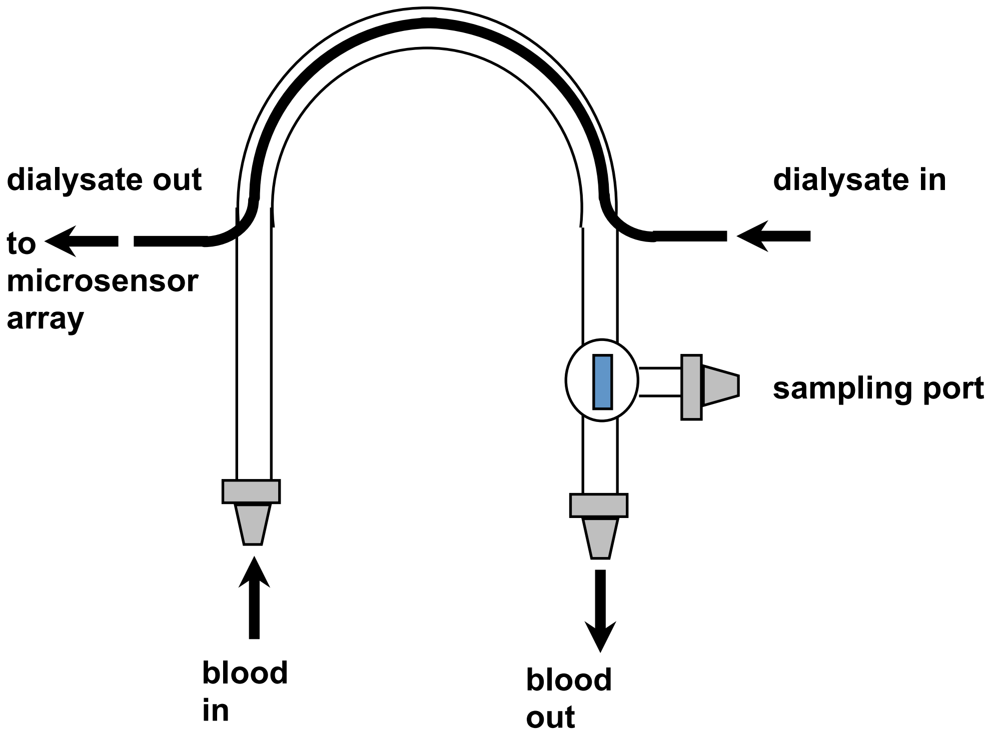
At its tip will be a barely visible membrane containing a bit of enzyme.

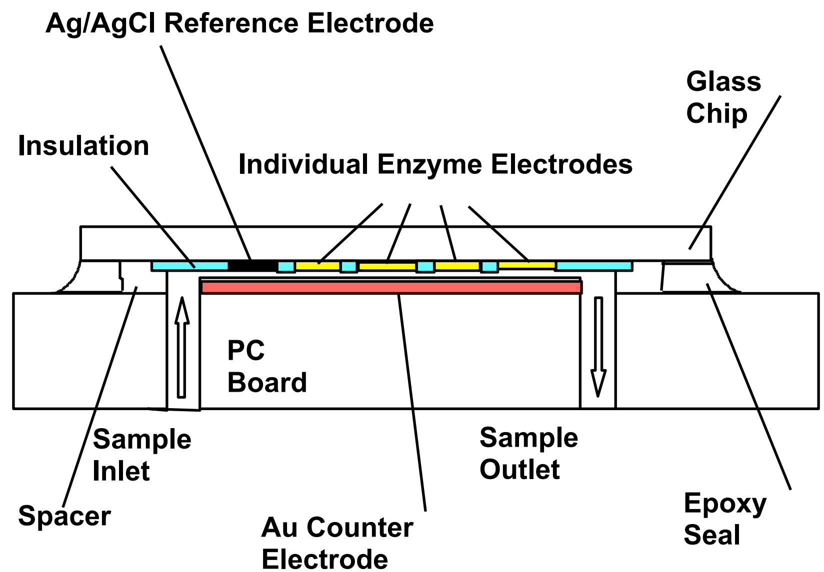
Hair-thin wires will lead from the other end of the platinum to an insulin reservoir implanted in the patient's abdomen.

Within seconds, a chemical reaction will begin at the tip of the wire………

……And (by implication) it will work for years reliably and regulate glucose through feedback to insulin pump

Microdialysis sampling via arterio-venus shunt



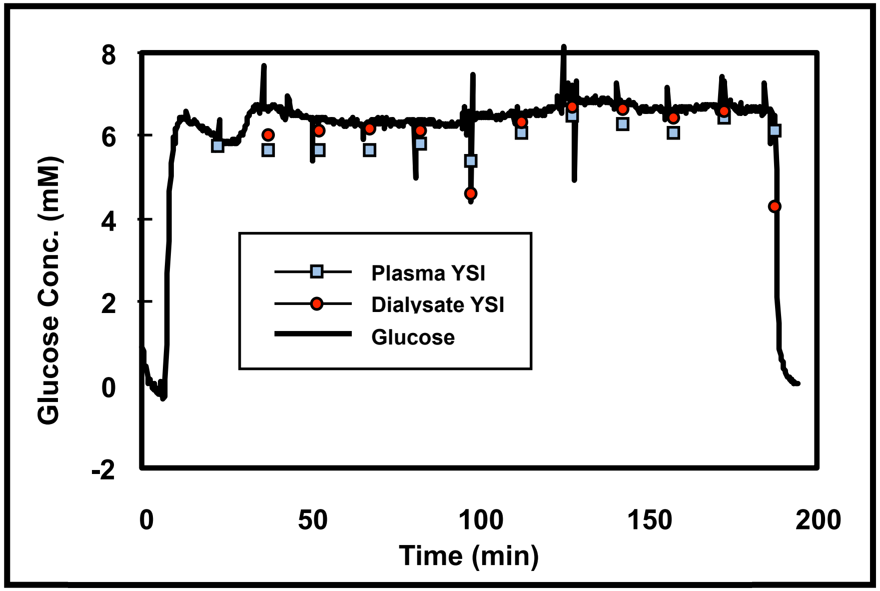


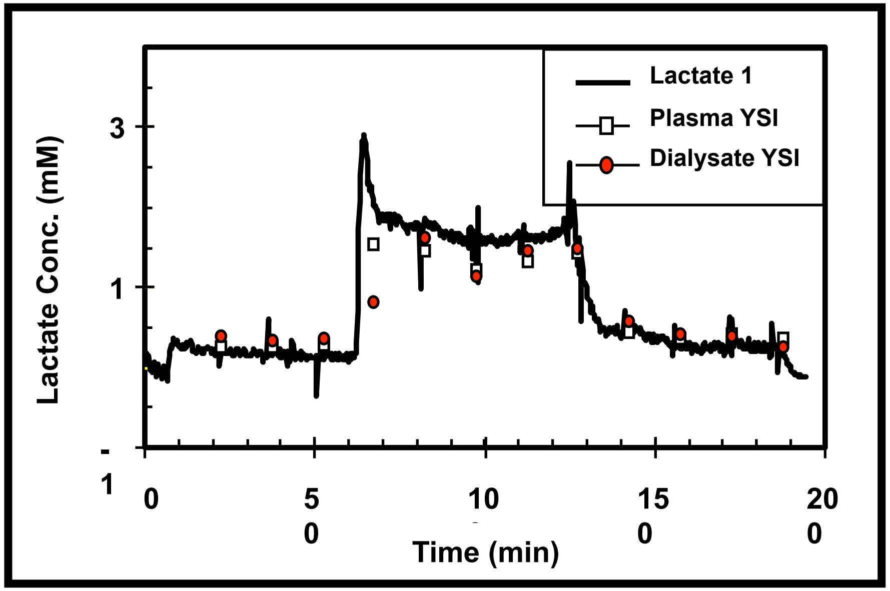
Novel Instrumentation for Real-Time Monitoring Using Miniaturised Flow Cells with Integrated Biosensors, R. Freaney, A. McShane, T.V. Keavney, M.McKenna, K. Rabenstein, F.W. Scheller, D. Pfeiffer, G. Urban, I. Moser, G. Jobst, A. Manz, E. Verpoorte, M.W. Widmer, D. Diamond, E. Dempsey, F.J. Saez de Viteri and M. Smyth, Annals of Clinical Biochemistry, 34 (1997) 291-302.

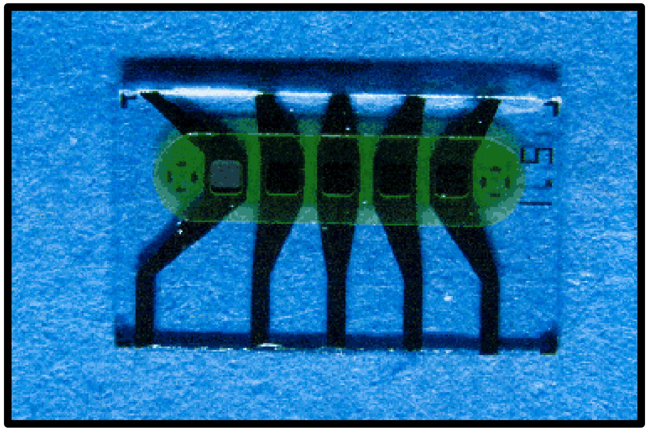
In Vitro Optimisation of a Microdialysis System with Potential for On-Line Monitoring of Lactate and Glucose in Biological Samples, E. Dempsey, D. Diamond, M.R. Smyth, M. Malone, K. Rabenstein, A. McShane, M.McKenna, T.V. Keavney and R Freaney, Analyst, 122 (1997) 185-189.

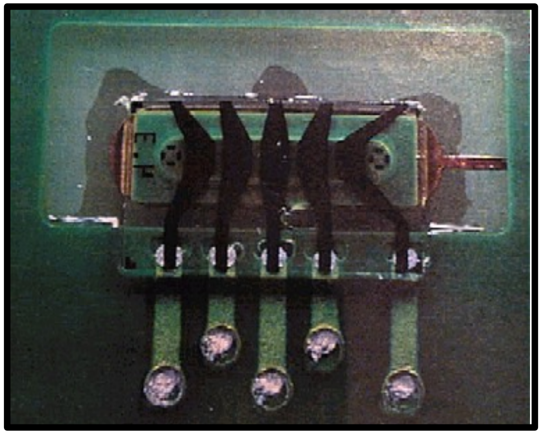
Design and Development of a Miniaturized Total Chemical-Analysis System for Online Lactate and Glucose Monitoring in Biological Samples, Ethna Dempsey, Dermot Diamond, Malcolm R. Smyth, Gerald Urban, Gerhart Jobst, I. Moser, Elizabeth MJ Verpoorte, Andreas Manz, HM Widmer, Kai Rabenstein and Rosemarie Freaney, Anal. Chim. Acta, 346 (1997) 341-349.

Real Time Blood Glucose and Lactate









System functioned continuously for up to three hours!

Abbott Freestyle 'Libre'

The days of routine glucose testing with lancets, test strips and blood are over.[2]

Welcome to flash glucose monitoring!

- '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

HYPEwatch: Apple, iWatch & Health Monitoring

Independent.ie

Wednesday 7 May 2014

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Independent.ie > Business > Technology

Apple hiring medical device staff, shares break $600 mark

Apple Inc CEO Tim Cook

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

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.

[illegible]e 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.

Google Contact Lens

United States Patent Application ***20140107445***

Kind Code A1 Liu; Zenghe April 17, 2014

Microelectrodes in an Ophthalmic Electrochemical Sensor

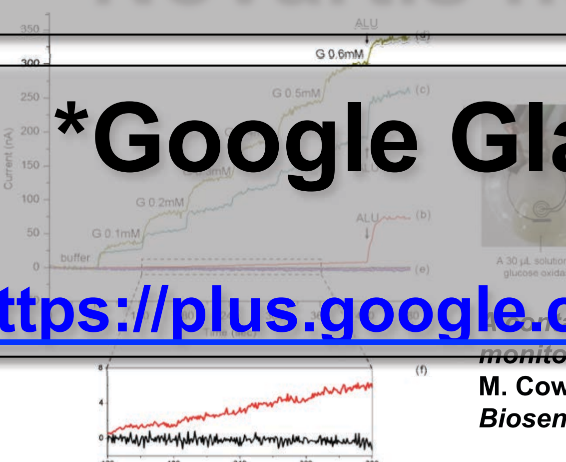
Abstract

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



Known among scientists as "Ophthalmic Electrochemical Sensors," these contact lenses will feature flexible electronics that include sensors and an antenna. The sensors are designed to read chemicals in the tear fluid of the wearer's eye and alert her, possibly through a little embedded LED light, when her blood sugar falls to dangerous levels.

"Human tear fluid contains a variety of inorganic electrolytes (e.g., Ca.sup.2+, Mg.sup.2+, Cl.sup.-), organic solutes (e.g., glucose, lactate, etc.), proteins, and lipids. A

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; (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 monitoring tear glucose level, H. F. Yao, A. J. Shum, M. Cowan, I. Lahdesmaki 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

What is the core issue??

- Simple, bare chem/biosensors do not function reliably EXCEPT as single shot short-term use devices – regular recalibration required (if they manage to keep functioning)
- Sensor surfaces change as soon as they are exposed to the real world – biofouling, interferents, leaching of components….
- Current systems work for days (after decades of research)
- Implants must work for 10 years!

What should the grand (man on the moon) challenge be?

Can we develop the scientific knowledge and technology required to deliver self-aware, self-maintaining and sophisticated implantable devices that will function reliably for a minimum of 10 years inside the body?

That's great – but we need specific, focused projects that can deliver tangible outputs in a reasonable timeframe. These projects should be consistent with advancing knowledge towards the ultimate goal, and also leverage knowledge from fundamental advances into the projects.

ACS Nano Cover and Editorial

‘Grand Plans for Nano’, (9) 12 December 2015

EDITORIAL

Grand Plans for Nano

This year, nanoscience and nanotechnology have been called front and center to help address the grand challenges that the world faces. Our community has been asked to suggest future challenges, and the first such crowd-sourced grand challenge has been announced by the White House Office of Science and Technology Policy.[1−5] As we have said on these pages, we believe that nanoscientists and nanotechnologists around the world have special roles to play in bringing together expertise from diverse fields in order to tackle important tasks both large and small.[2] Indeed, our higher perspectives and communication across fields have great value globally in key areas such as devices, energy, health, and safety.[6−10]

As these Grand Challenge projects and other opportunities emerge, we will work with the leading and rising researchers in the relevant and potentially impacted communities to lay out the challenges and opportunities for nanoscience, nanotechnology, and other fields.[7−10] We see key roles for *ACS Nano* as a community forum to guide both nanoscience and nanoscience policy, to improve the impact of research by coordinating how it is reported,[11,12] and to showcase innovative work from around the world.

We are looking forward to an exciting year in 2016, which will mark *ACS Nano*'s tenth volume. It has already been quite an adventure, and much more is to come. We note that you will see some changes in our “look” next year. We will keep our forward-looking posture, our in-depth science and engineering, and the identifying markings that let you know right away when you are reading an article in *ACS Nano*. We have made subtle design changes that will enable us to speed up production in order to accelerate our already fast turn-around times of your work. We want to thank our production team and staff for this collaboration and all of the iterations that went into this optimization effort.

Finally, we want to thank you, our readers, authors, and referees for moving *ACS Nano* and our field to ever higher impact on our world. We wish you a safe and peaceful holiday season and look forward to hearing from you and working with you in the year and years ahead.

Disclosure: Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

Warren W. C. Chan
Associate Editor

Paula T. Hammond
Associate Editor

Sharon Glotzer
Associate Editor

Mark C. Hersam
Associate Editor

Associate Editor

The ‘grand challenge’ concept is rapidly growing in importance as a focusing mechanism for large scale R&D initiatives e.g. EU Brain, Graphene -> FET next phase

nline December 22, 2015
nano.5b07280

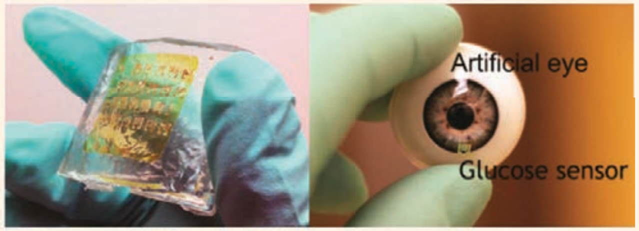
Cover Article: ACS Nano 9 (12) (2015) 12174–12181

Printable Ultrathin Metal Oxide Semiconductor-Based Conformal Biosensors

You Seung Rim,[*,†,‡,#] Sang-Hoon Bae,[†,‡,#] Huajun Chen,[†,‡] Jonathan L. Yang,[†,§] Jaemyung Kim,[†,∥] Anne M. Andrews,[∥,⊥] Paul S. Weiss,[†,‡,∥] Yang Yang,[†,‡] and Hsian-Rong Tseng[*,†,§]

[†]California NanoSystems Institute, [‡]Department of Materials Science and Engineering, [§]Department of Pharmacology, [∥]Department of Chemistry and Biochemistry, and [⊥]Department of Psychiatry, Hatos Center for Neuropharmacology, and Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, California 90095, United States. [#]These authors contributed equally.

ABSTRACT Conformal bioelectronics enable wearable, noninvasive, and health-monitoring platforms. We demonstrate a simple and straightforward method for producing thin, sensitive In_2O_3-based conformal biosensors based on field-effect transistors using facile solution-based processing. One-step coating *via* aqueous In_2O_3 solution resulted in ultrathin (3.5 nm), high-density, uniform films over large areas. Conformal In_2O_3-based biosensors on ultrathin polyimide films displayed good device performance, low mechanical stress, and highly conformal contact determined using polydimethylsiloxane artificial skin having complex curvilinear surfaces or an artificial eye. Immobilized In_2O_3 field-effect transistors with self-assembled monolayers of NH_2-terminated silanes functioned as pH sensors. Functionalization with glucose oxidase enabled D-glucose detection at physiologically relevant levels. The conformal ultrathin field-effect transistor biosensors developed here offer new opportunities for future wearable human technologies.



KEYWORDS: biosensor · aqueous process · metal oxide semiconductor · conformal · flexible · field-effect transistor

Materials Handling – great! Sensor Aspect - ????

- FET configuration (same as 1984 paper)
- Amine and hydroxy terminated surface groups respond to pH
- Attachment of GOX enables glucose sensing via pH changes due to formation of gluconic acid
- Poor kinetics
- pH response not stable
- Glucose sensor responds to pH – selectivity issue
- No integrated reference or counter electrodes

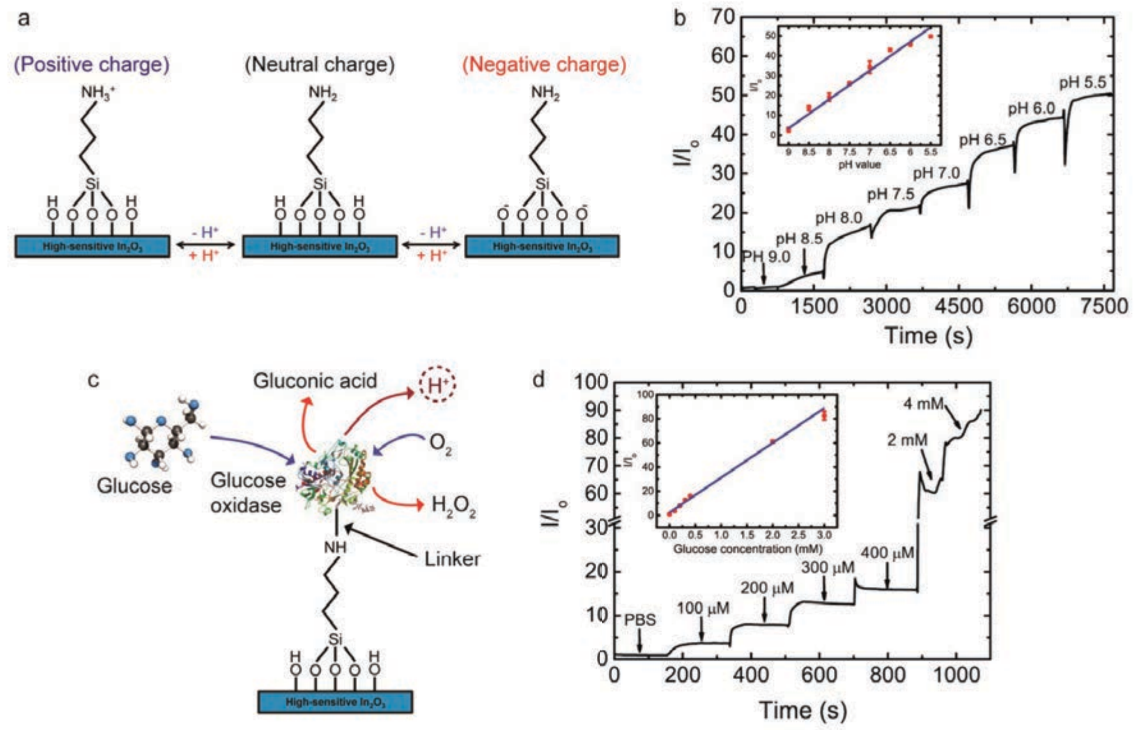


Figure 4. Chemical sensing *via* In_2O_3 FET-based conformal biosensors. (a) The pH-sensing mechanism occurs by protonation of In_2O_3 surface hydroxyl groups and primary amines of APTES at decreasing pH (increasing proton concentrations). (b) Representative responses of an In_2O_3-based FET biosensor to a biologically important pH range (pH 5.5–9). Inset shows data from five devices. (c) Enzymatic oxidation of D-glucose *via* glucose oxidase to produce gluconic acid and hydrogen peroxide. Protons are generated during this oxidation and protonation of the In_2O_3 surfaces is manifested. (d) Representative responses of In_2O_3 sensors to physiologically relevant D-glucose concentrations found in human diabetic tears (lower range) and blood (upper range). Inset shows data from five devices. Error bars represent standard deviations of the means.

Convergence of Materials, Fabrication & Characterisation

Basic → **Applied**

Materials Science

- Biomaterials & Materials chemistry
  - Chem/bio-recognition
  - Transduction/signalling
  - Chem/bio-polymers
- Rapid protoyping & fab
- Materials characterisation
  - Spectroscopies
  - Electrochemistry
  - Separations?
  - Imaging and microscopies
- (Bio)Microfluidics

Prototype devices & platforms

- Incorporating bioinspired functionalities, biomimetic characteristics
- Self-aware, self-healing/ repair, self-replicating..
- Capable of self- or externally controlled movement

Applications

- Personal Health
  - Wearables/on-body devices – minimally or non-invasive
  - (micro) robotics and micro surgical tools
  - Implantable sensors for in-situ, real-time monitoring
  - Imaging and spatially resolved data for tissue mapping and location verification

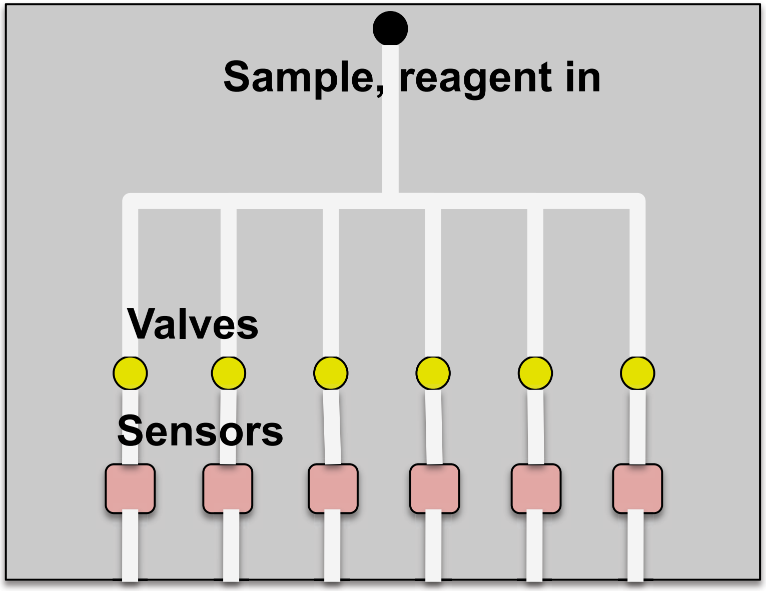
Fundamental/Futuristic Concepts & Thinking

IMPACT

Industry links, Research networks, community engagement

Extend Period of Use via Multiple short-use Sensors….?

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

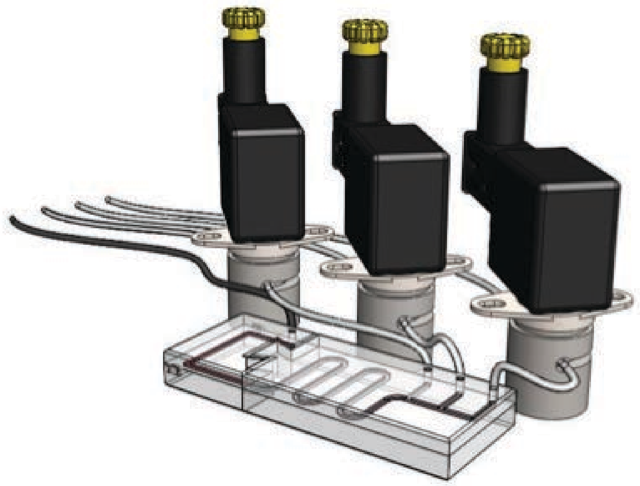


Then 50 sensors when used sequentially could provide an aggregated in-use lifetime of around 1 year

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

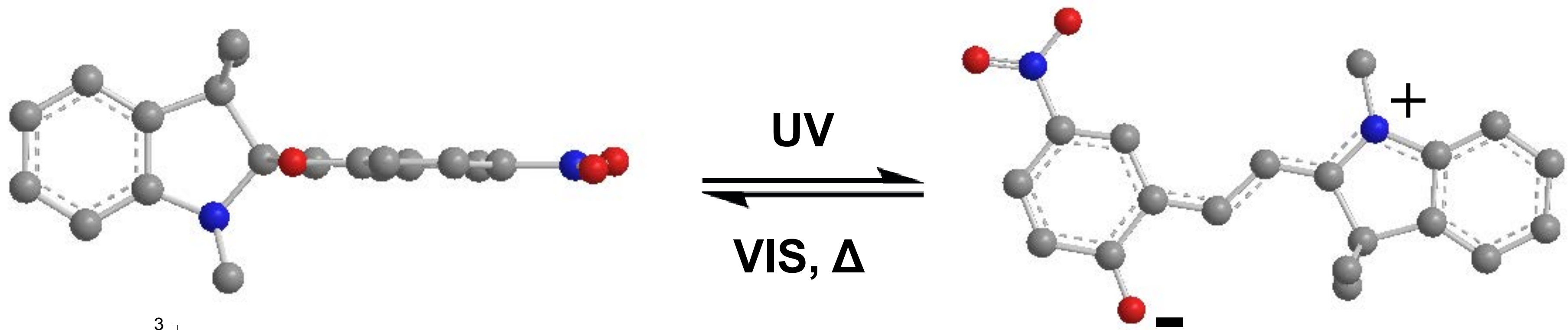
How to advance fluid handling in LOC platforms: re-invent valves (and pumps)!

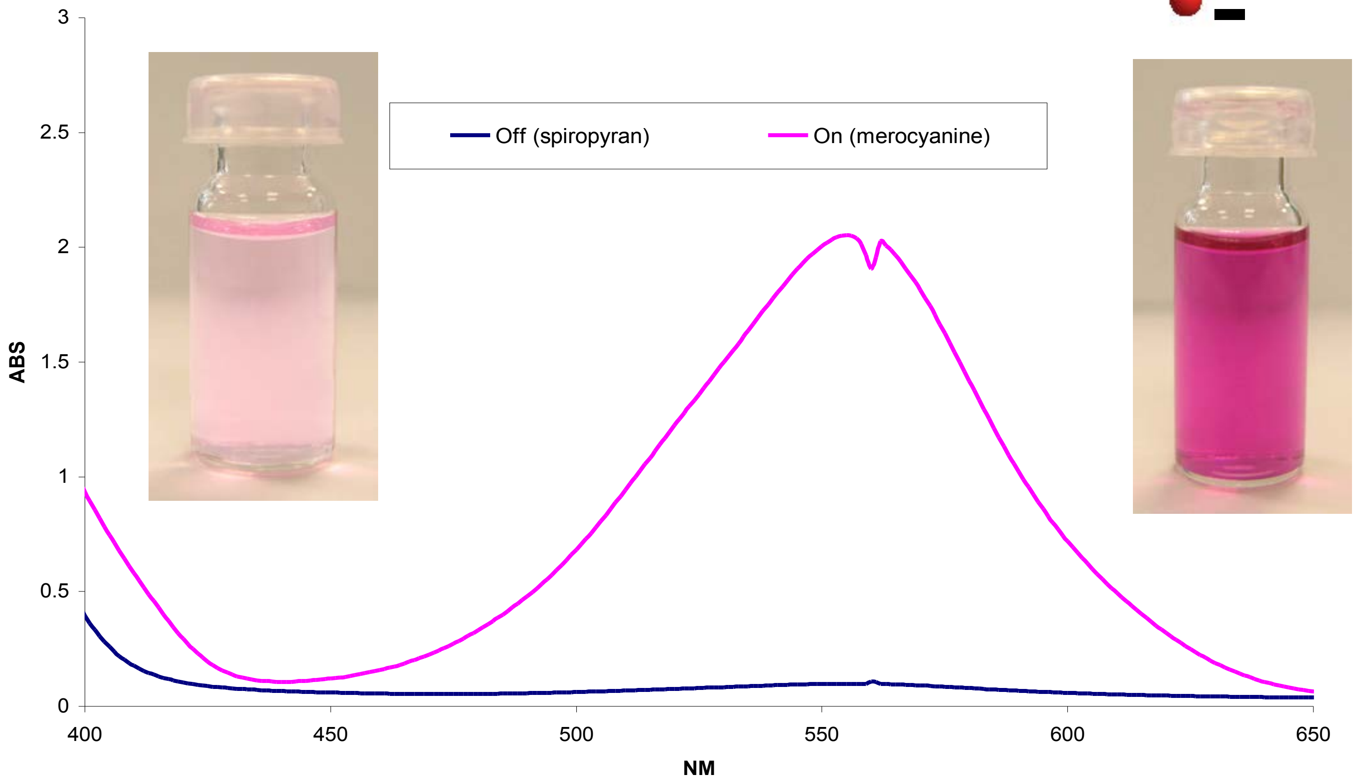
- **Conventional valves cannot be easily scaled down - Located off chip: fluidic interconnects required**
  - Complex fabrication
  - Increased dead volume
  - Mixing effects
- **Based on solenoid action**
  - Large power demand
  - Expensive



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

Photoswitchable Actuators





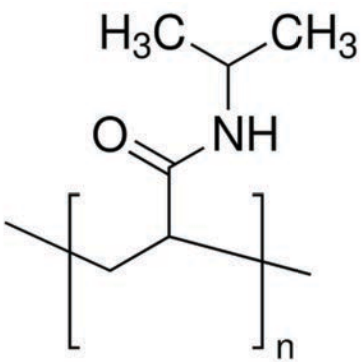
Famous Molecule….

From Prof. Thorfinnur Gunnlaugsson, TCD School of Chemistry
Spotted on Nickelodeon Cartoons February 2015

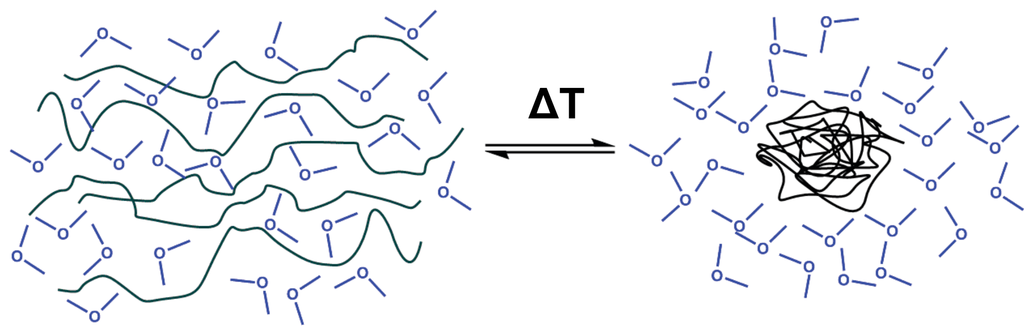
Poly(*N*-isopropylacrylamide)

- 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



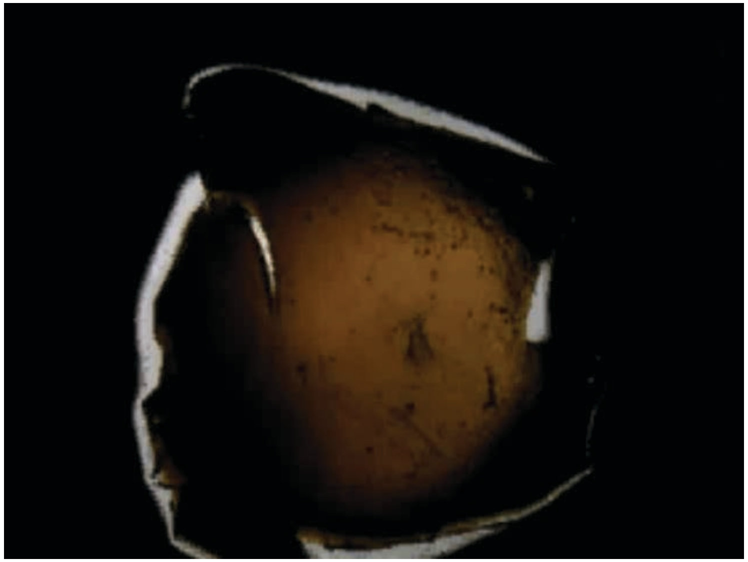
Hydrophilic **Hydrophobic**

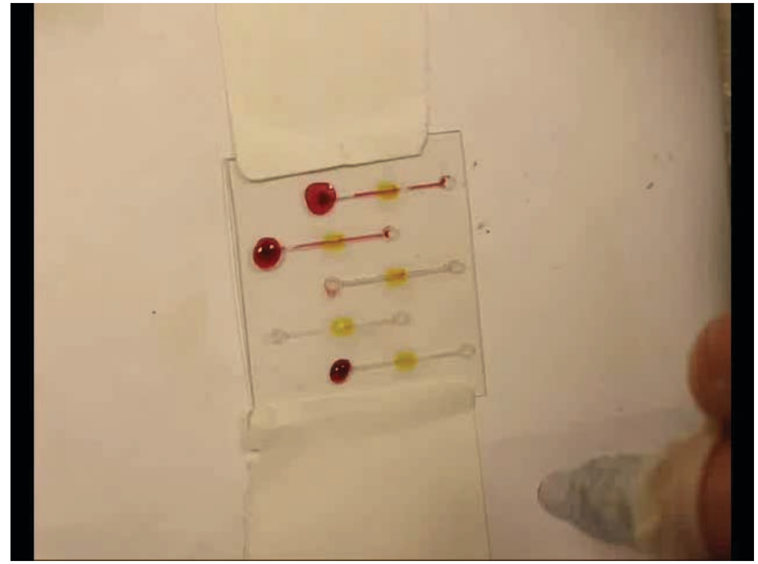


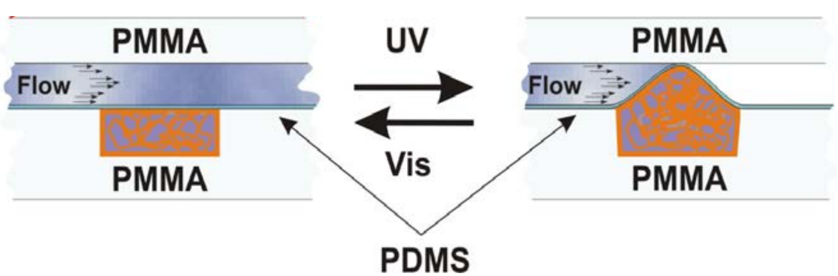
Hydrated Polymer Chains

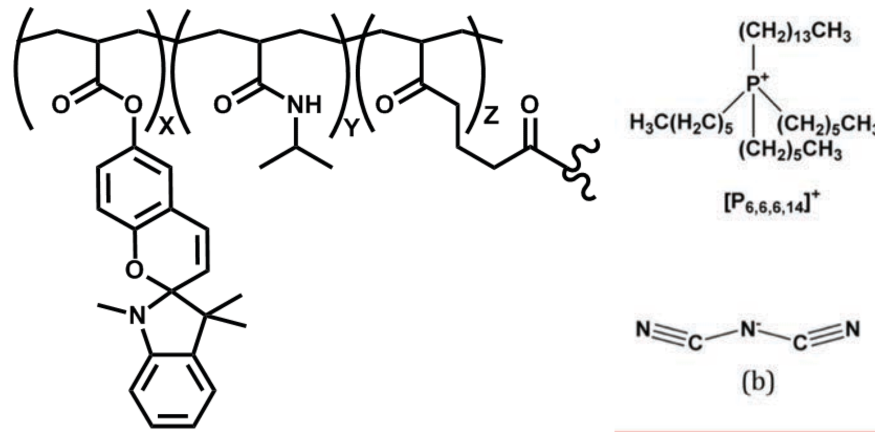
Loss of bound water -> polymer collapse

Photo-actuator polymers as microvalves in microfluidic systems





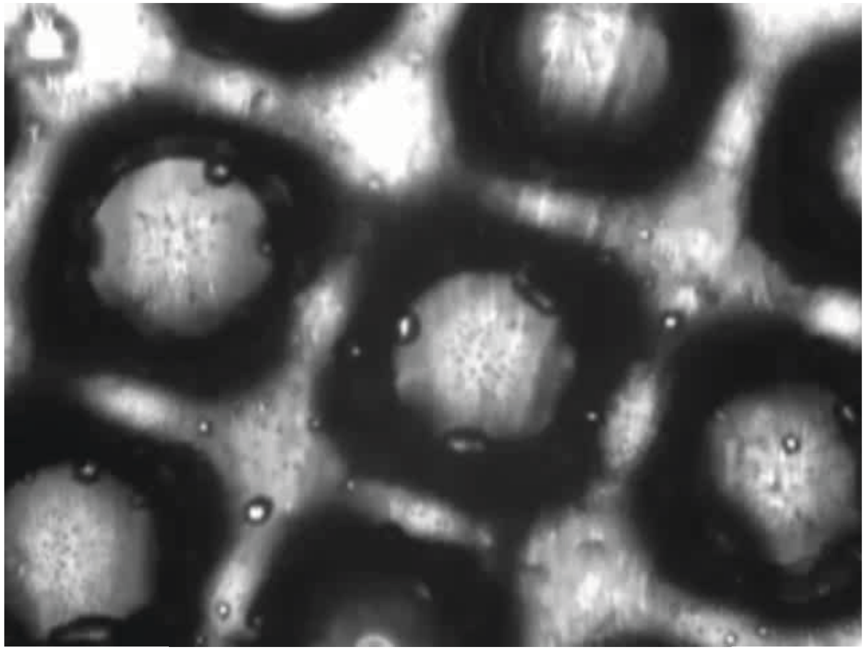




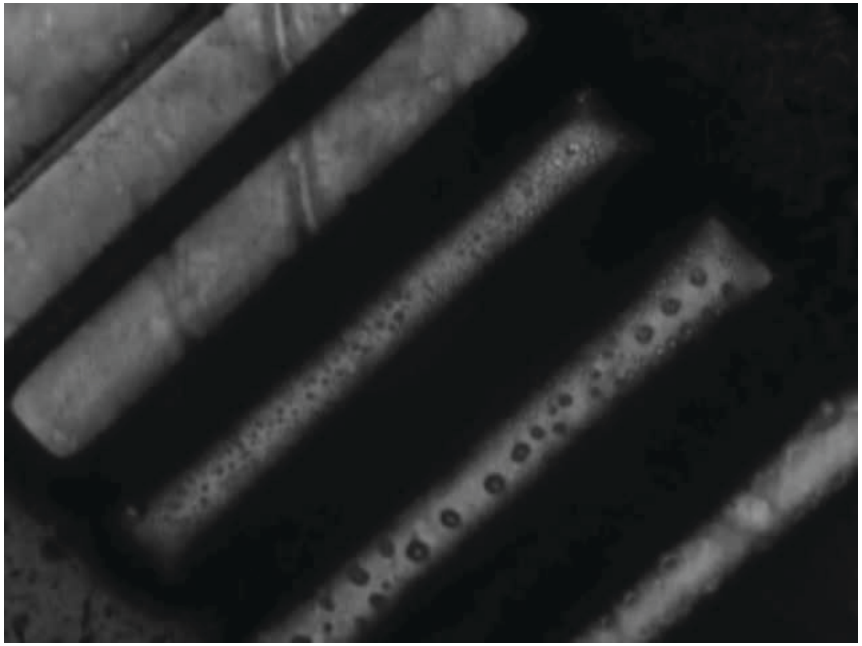
trihexyltetradecylphosphonium dicyanoamide $[P_{6,6,6,14}]^{+}[dca]^{-}$

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.

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



Ntf2 pillars speed x3



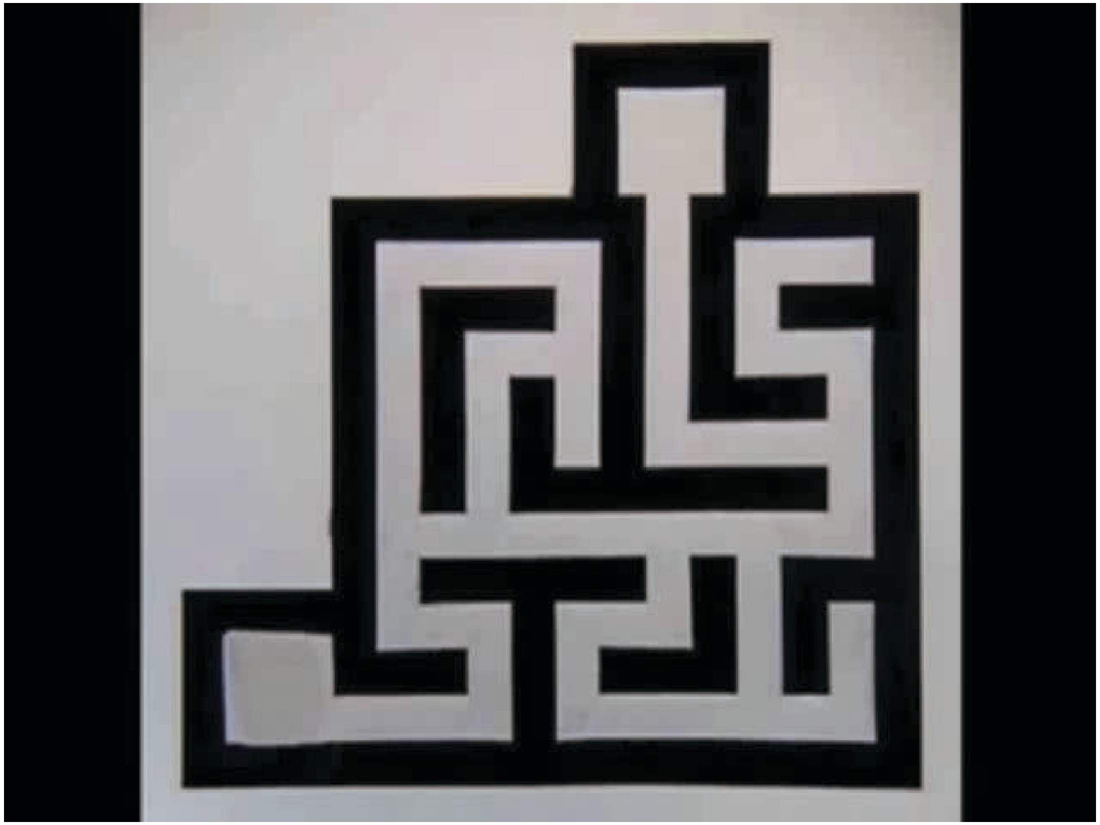
DCA lines speed x4

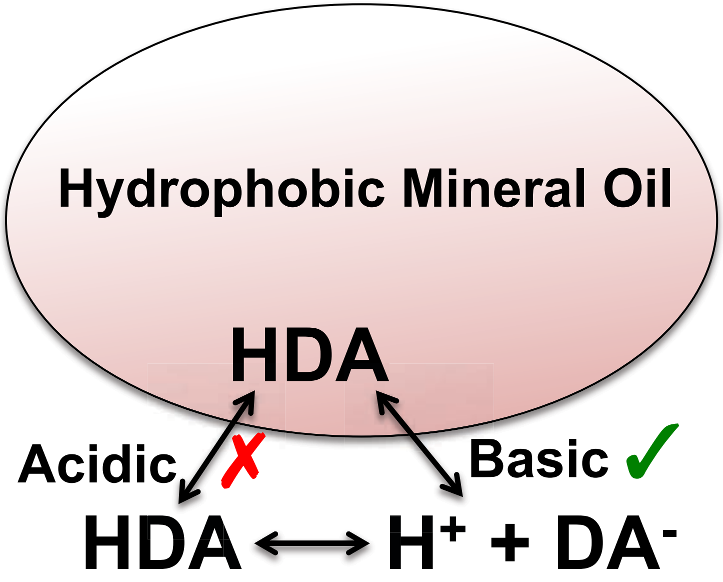
With Dr Peer Fischer, Fraunhofer-Institut für Physikalische Messtechnik (IPM), Freiburg

Multi-Functional Bio-Inspired Fluidics!

- **At present, the fluidic system's function is to;**
  - Transport reagents, samples, standards to the detector
  - Perform relatively simple (but important) tasks like cleaning, mixing
  - Switching between samples, standards, cleaning solutions
- **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 preferred locations

Chemotactic Systems



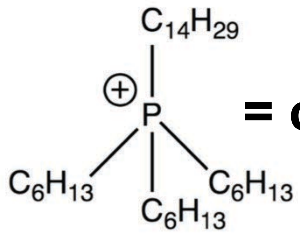


In a pH gradient, DA$^-$ is preferentially transferred to the aqueous phase at the more basic side of the drop.

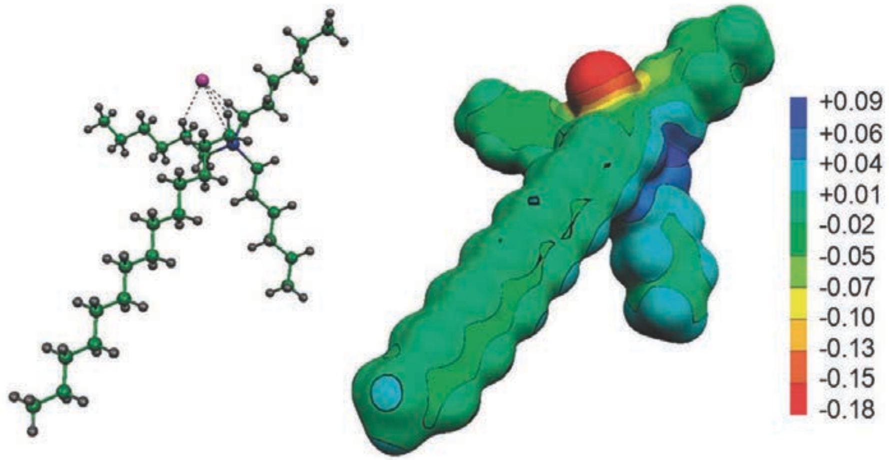
Published on Web 11/01/2010 (speed ~x4): channels filled with KOH (pH 12.0-12.3 + surfactant; agarose gel soaked in HCl (pH 1.2) sets up the pH gradient; droplets of mineral oil or DCM containing 20-60% 2-hexyldecanoic acid + dye. Droplet speed ca. 1-10 mm/s; movement caused by convective flows arising from concentration gradient of HDA at droplet-air interface (greater concentration of DA$^-$ towards higher pH side); **HDA <-> H$^+$ + DA$^-$**

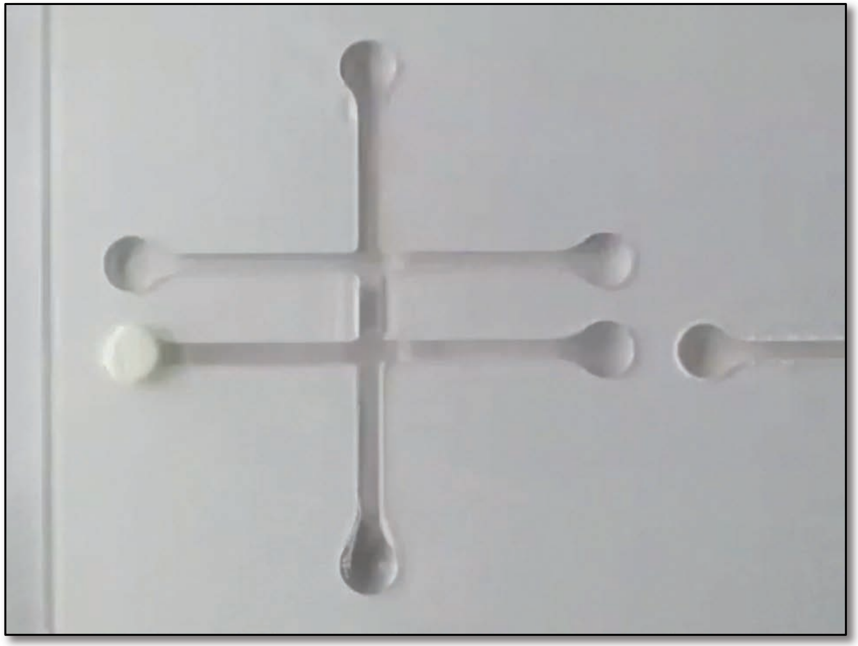
Maze Solving by Chemotactic Droplets; Istvan Lagzi, Siowling Soh, Paul J. Wesson, Kevin P. Browne, and Bartosz A. Grzybowski; **J. AM. CHEM. SOC. 2010, *132, 1198–1199***
Fuerstman, M. J.; Deschatelets, P.; Kane, R.; Schwartz, A.; Kenis, P. J. A.;Deutch, J. M.; Whitesides, G. M. *Langmuir 2003, 19, 4714.*

We can do the same with IL Droplets



= cationic surfactant





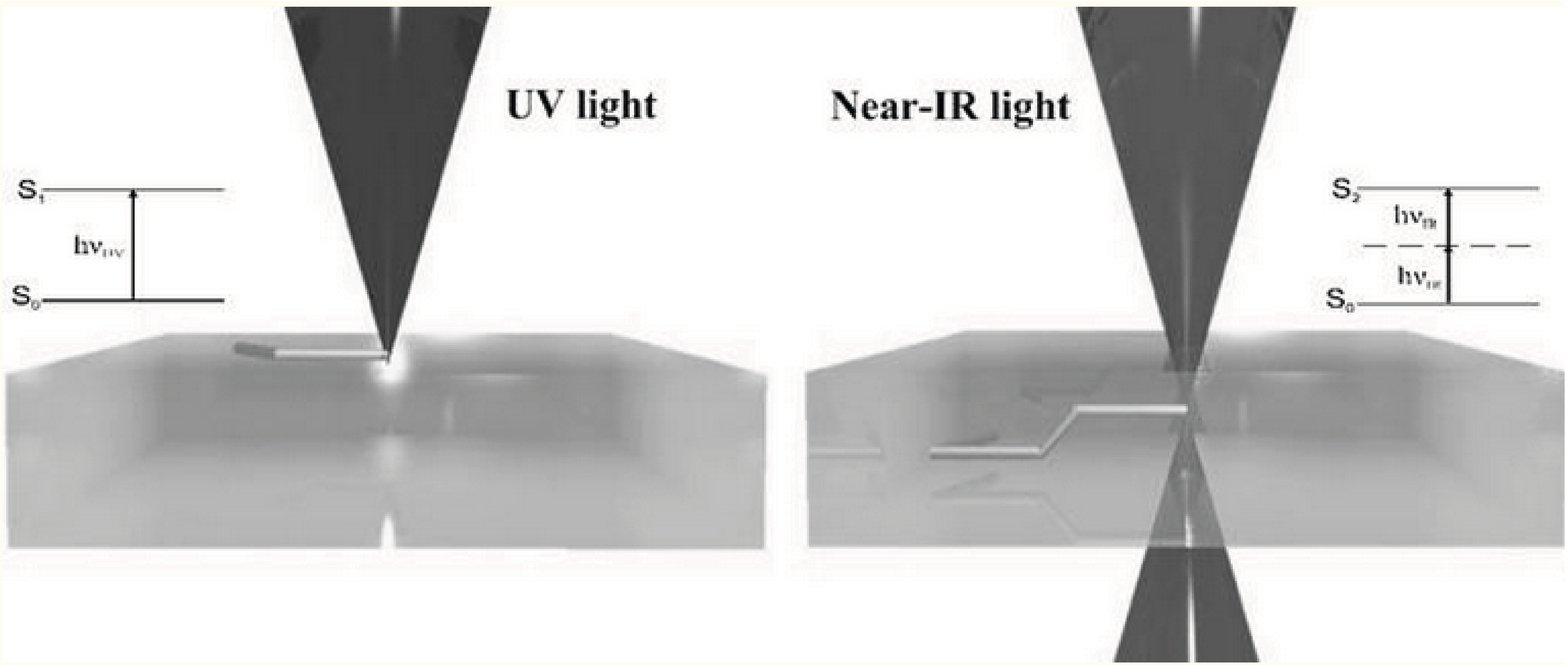
Trihexyl(tetradecyl)phosphonium chloride ($[P_{6,6,6,14}][Cl]$) droplets with a small amount of 1-(methylamino)anthraquinone red dye for visualization. The droplets spontaneously follow the gradient of the Cl^- ion which is created using a polyacrylamide gel pad soaked in 10^{-2} M HCl; A small amount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

Electrochemical Generation of Cl- gradients on demand…

Background

Stereolithography | **Two-photon polymerisation**



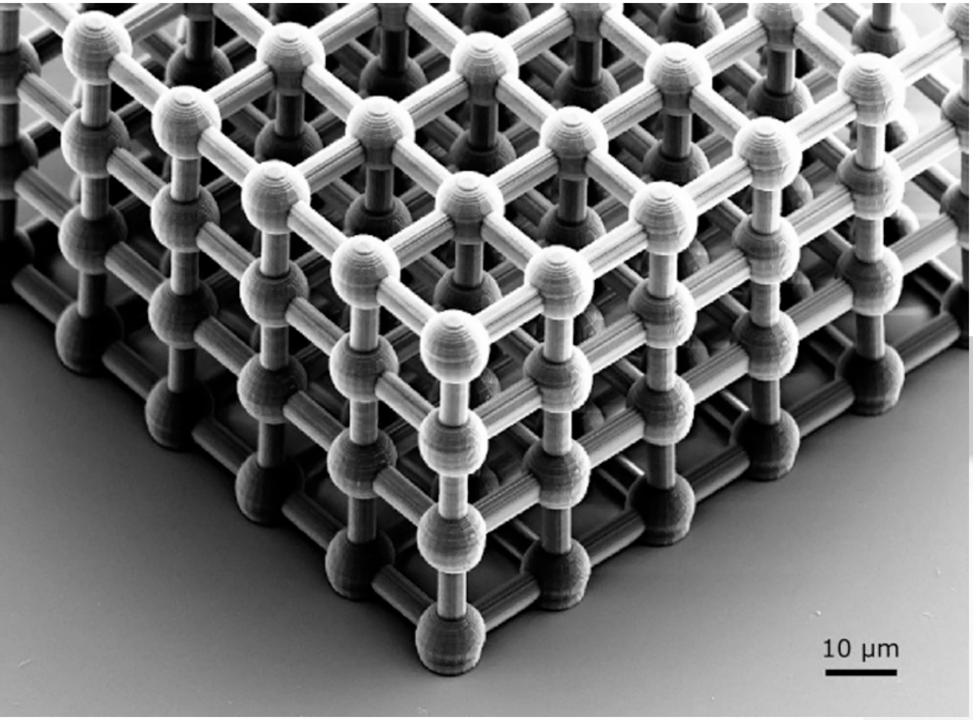
Stereolithography

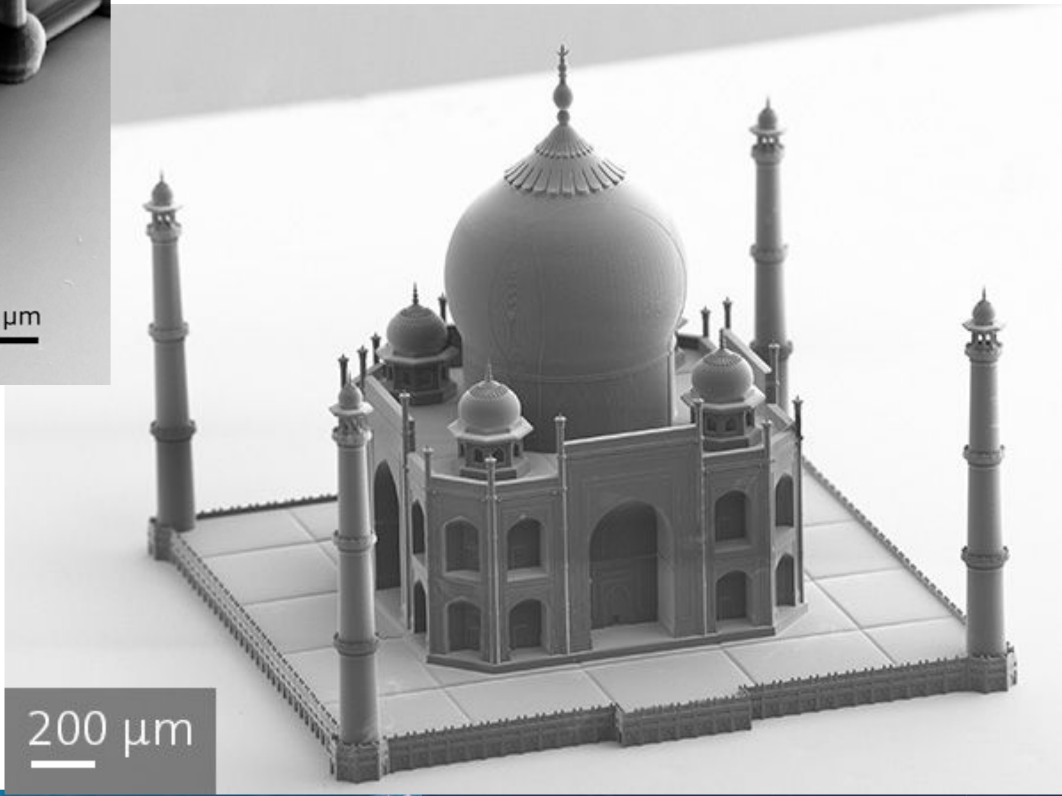
- Single photon absorption
- 2D patterns

Two-photon polymerisation

- Two photon absorption
- 3D structures

Background





http://www.nanoscribe.de/

The Exciting Potential of Stimuli-responsive Materials and Biomimetic Microfluidics

Larisa Florea[1], Vincenzo Curto[2], Alexander J. Thompson[2], Guang-Zhong Yang[2], and Dermot Diamond[1]*

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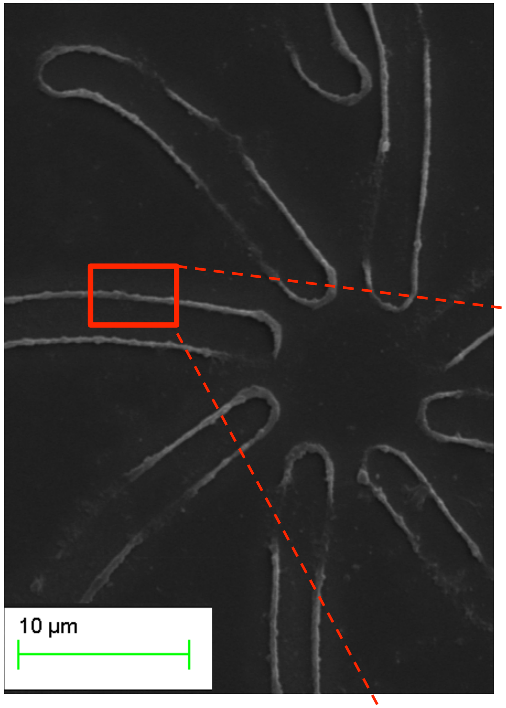
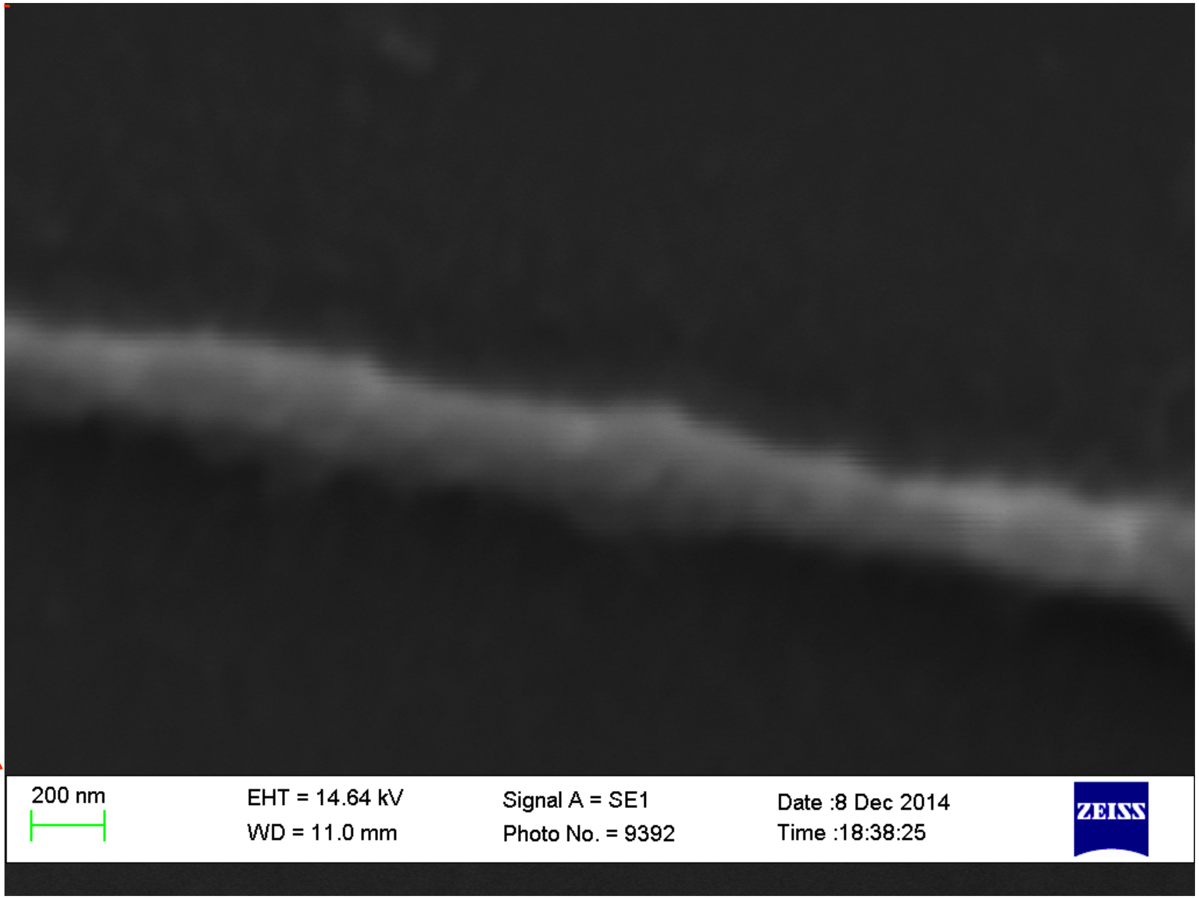
[2]The Hamlyn Centre for Robotic Surgery, Imperial College London, London, SW7 2AZ

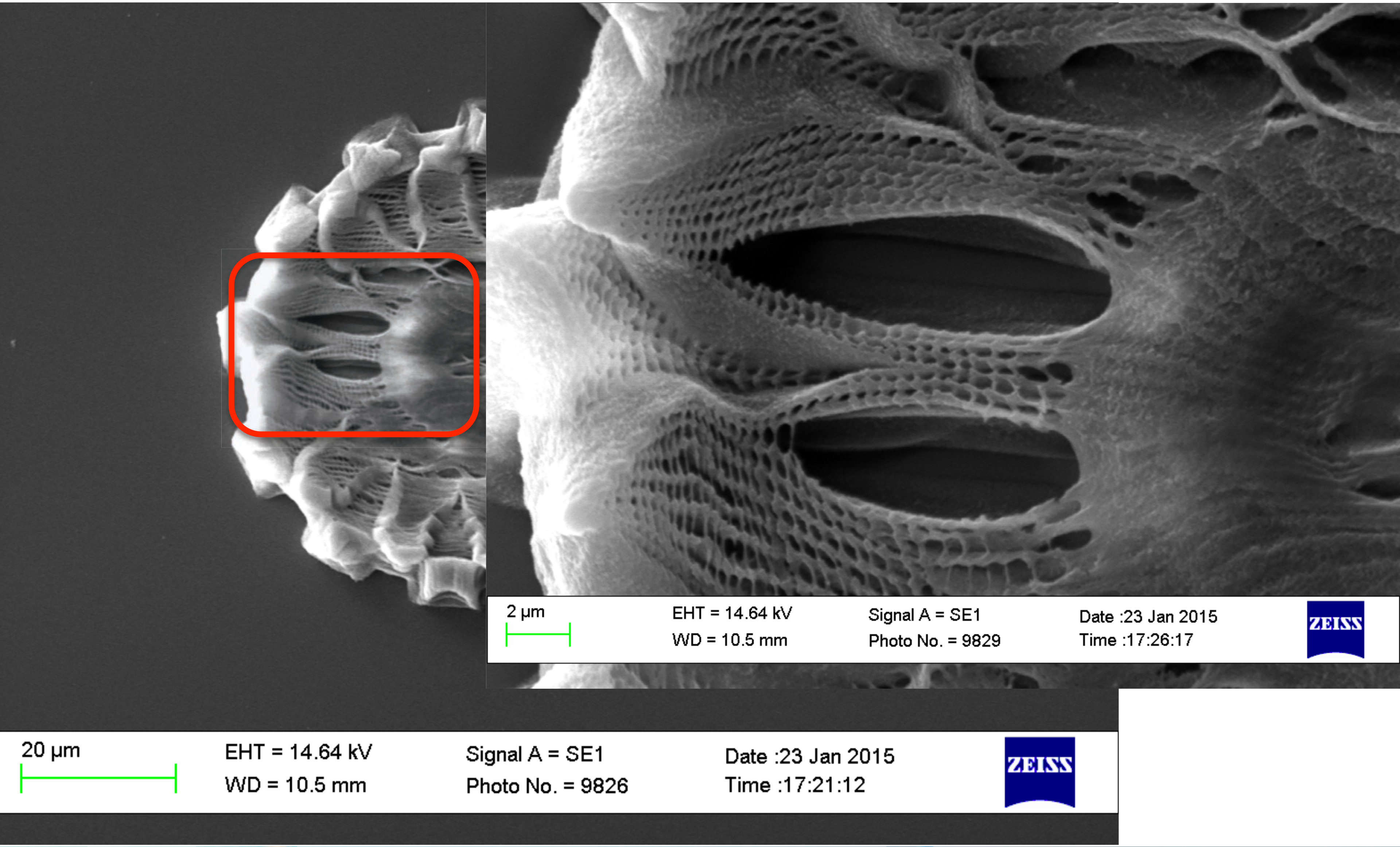
Submitted to Euronanoforum, Riga, Latvia, June 2015





Creating 3D soft gel structures with a line resolution of ca. 200 nm

‘Daisy’ – Micro/Nano Scaled Porous Structure



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**
- **Learn from nature – e.g. more sophisticated circulation systems in sensing devices!**

We have the tools – now we need a strategy to unleash **'informed creativity'!**

Thanks to…..

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

MASK
Project no: 269302
Materials and Advanced Sensor Knowledge Exchange

NAPES
NEXT GENERATION ANALYTICAL PLATFORMS FOR ENVIRONMENTAL SENSING

COMMON SENSE
MARINE SENSORS - MARINE MONITORING

aquawarn

SEVENTH FRAMEWORK PROGRAMME

MARIE CURIE ACTIONS

sfi DCU UCC OÉ Gaillimh NUI Galway UCD DUBLIN

Thanks for listening