‘From Molecules to Devices: Can we Create Disruptive Technologies based on 3D Functionality at Multiple Dimensions to Solve Global Challenges?’

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

Insight Centre for Data Analytics, National Centre for Sensor Research

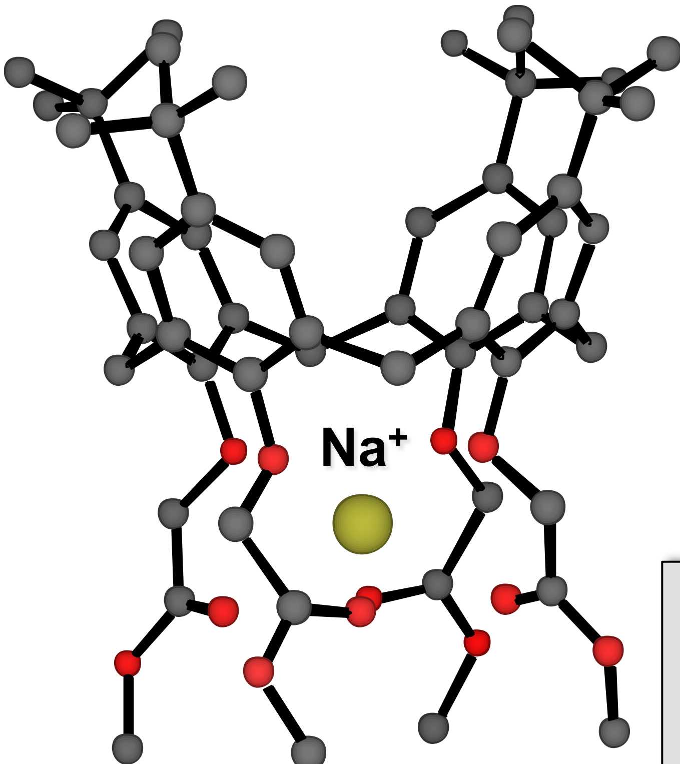
Dublin City University, Dublin 9, Ireland

Invited Seminar Presented at

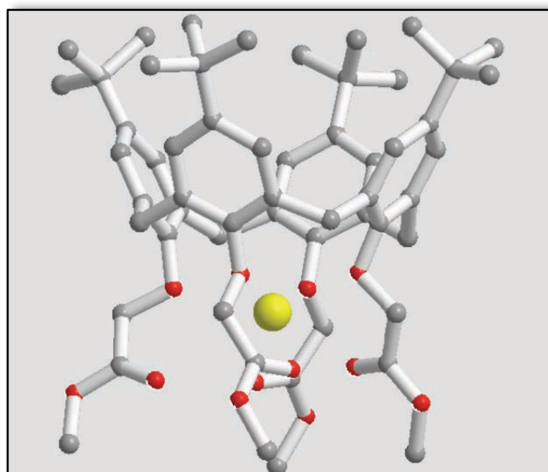
Henkel Ireland

26th January 2016

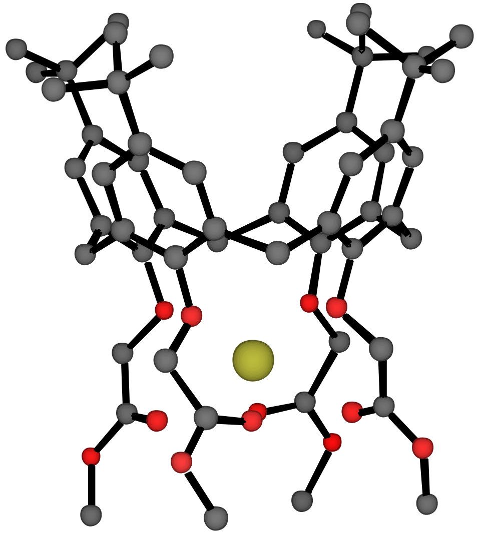
Calixarene Ionophores – controlling the selectivity

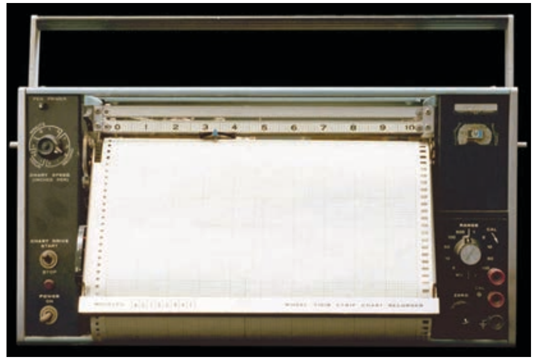


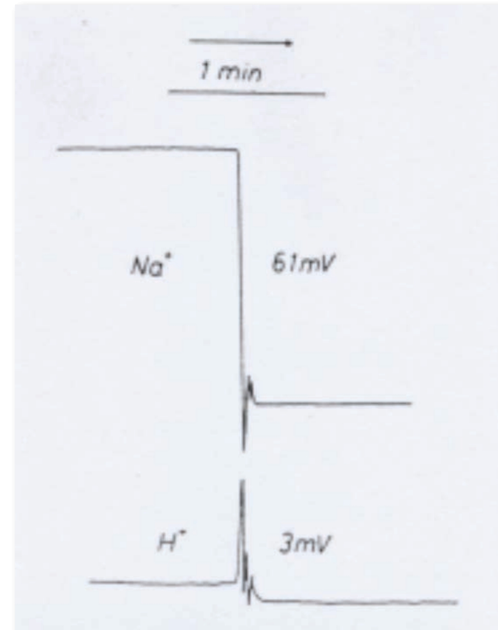
$H_3C-O-C(=O)-CH_2-$



Selectivity, Response Time, Stability…



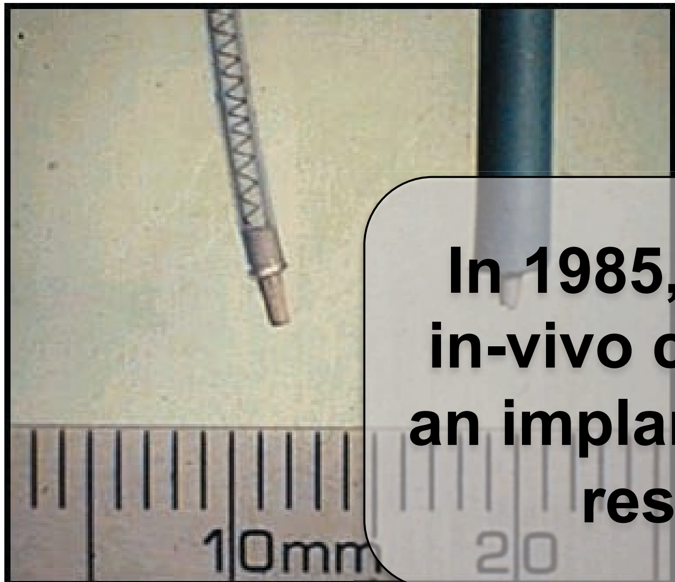




Neutral Carrier Based Ion-Selective Electrodes, D.Diamond, Anal. Chem. Symp. Ser., 25 (1986) 155.

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

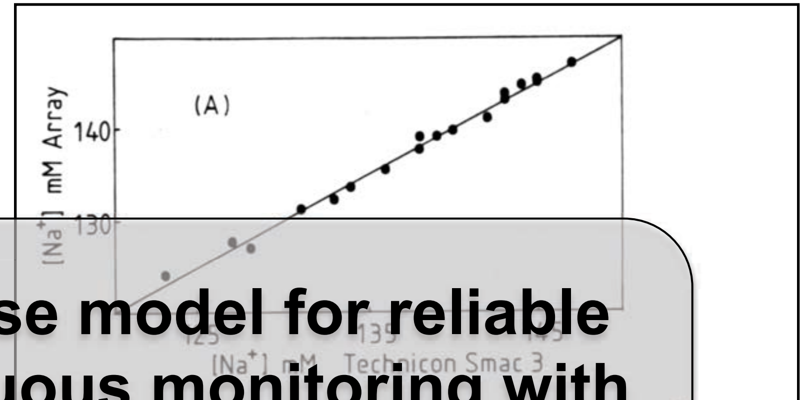
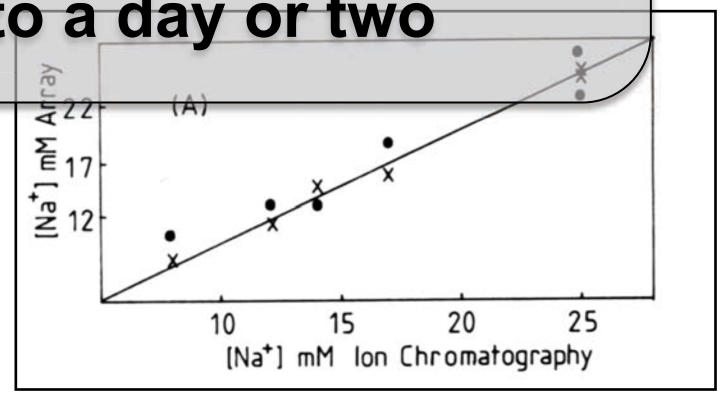


Fig. 3. Comparison of plasma sodium analysis using the array-FIA approach with a SMAC analyser. Good correlation without bias is obtained [5].



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

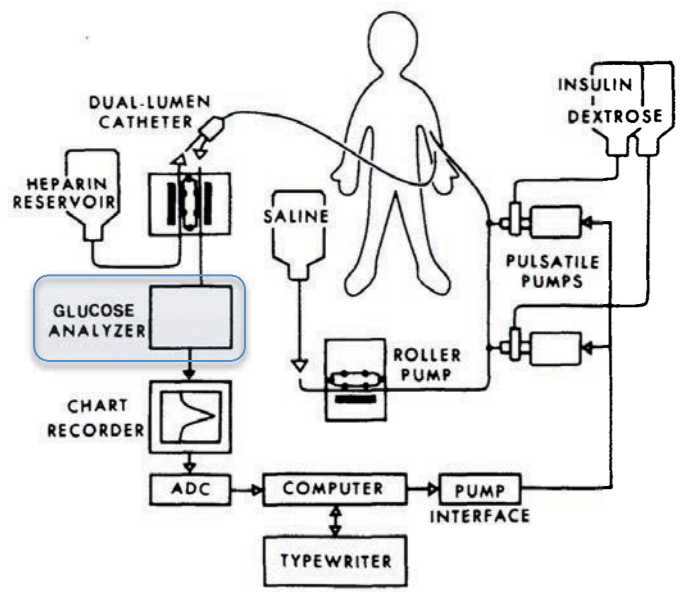
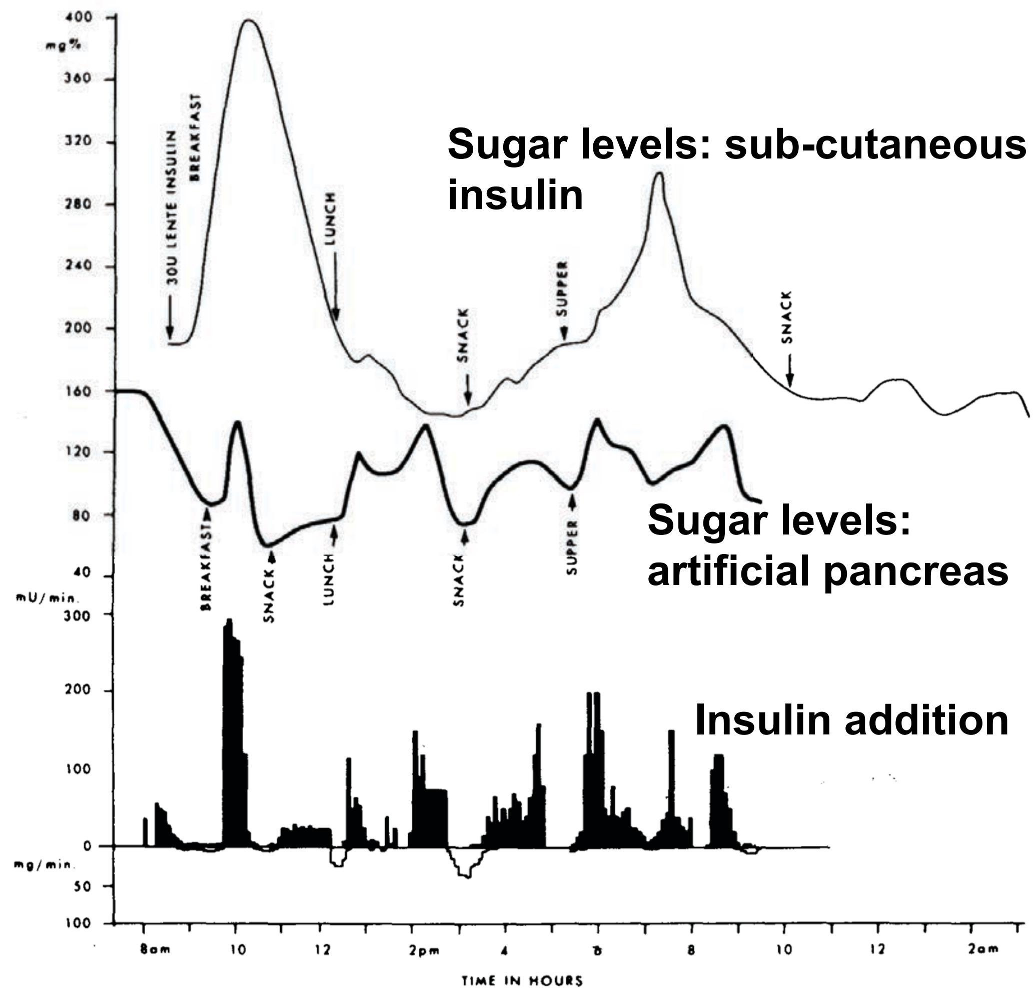
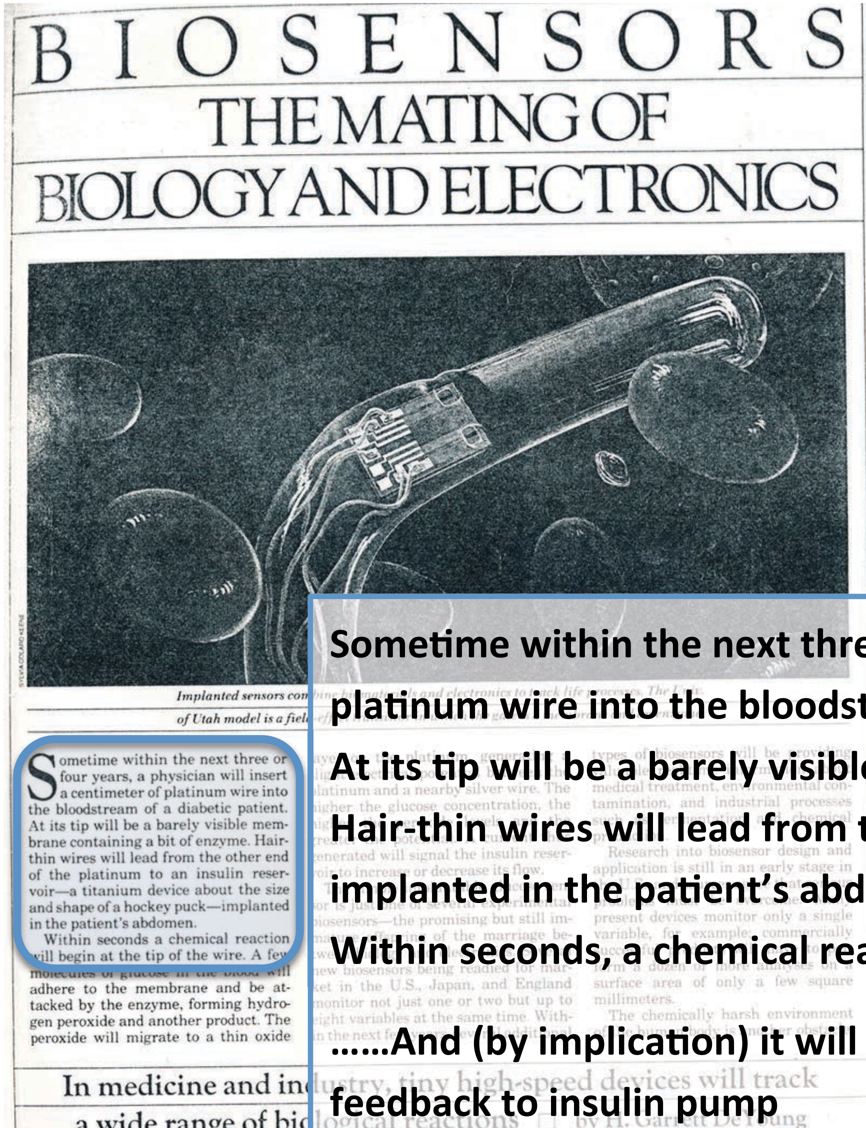


FIG. 1. Schematic diagram of apparatus used for monitoring and automatic regulation of blood sugar.



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

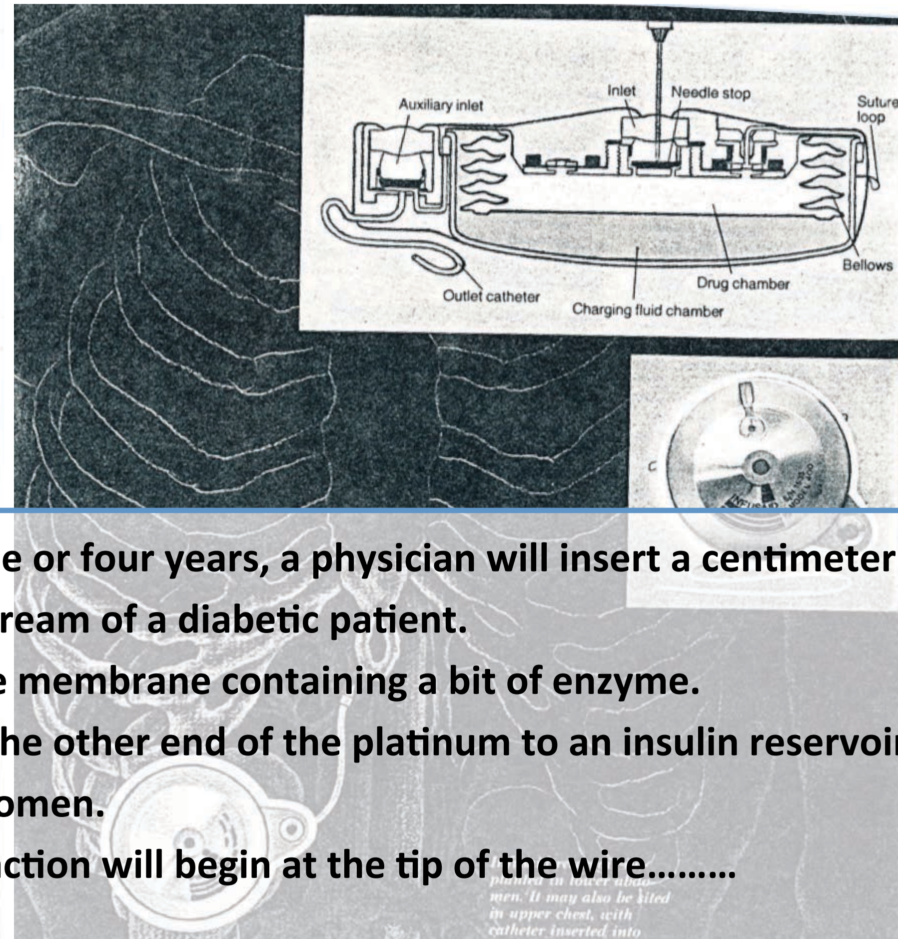
Implanted sensors com…
of Utah model is a fiel…

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 in…
a wide range of bio…

High Technology, Nov. 1983, 41-49



Sometime within the next three or four years, a physician will insert a centimeter of platinum wire into the bloodstream of a diabetic patient.

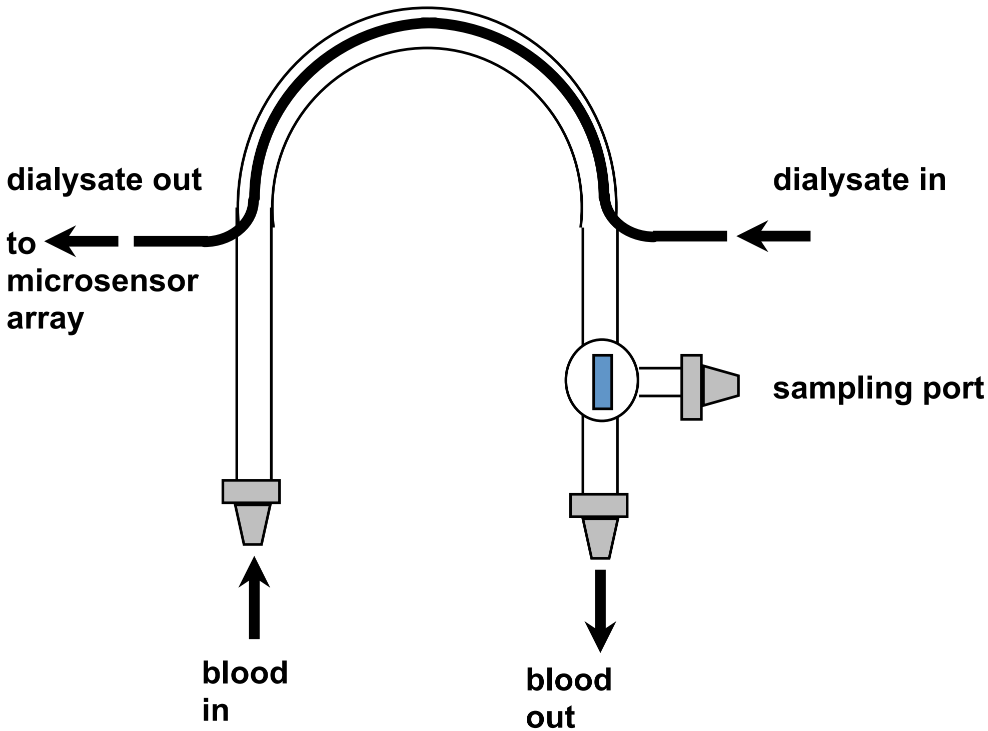
At its tip will be a barely visible membrane containing a bit of enzyme.

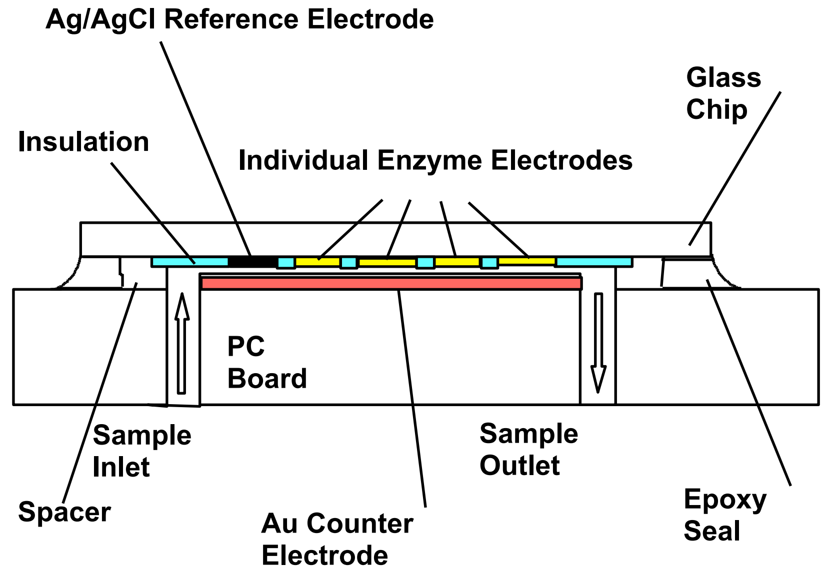
Hair-thin wires will lead from the other end of the platinum to an insulin reservoir implanted in the patient's abdomen.

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



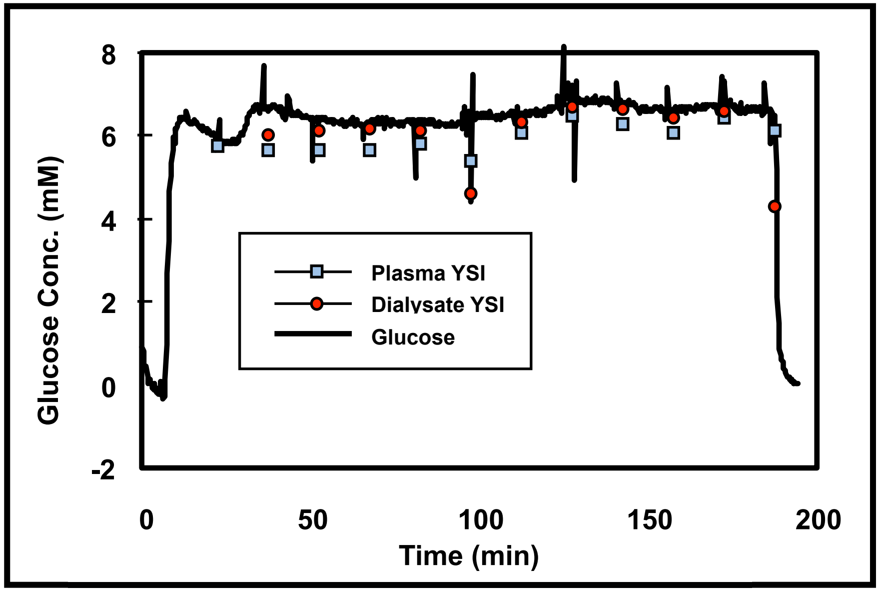


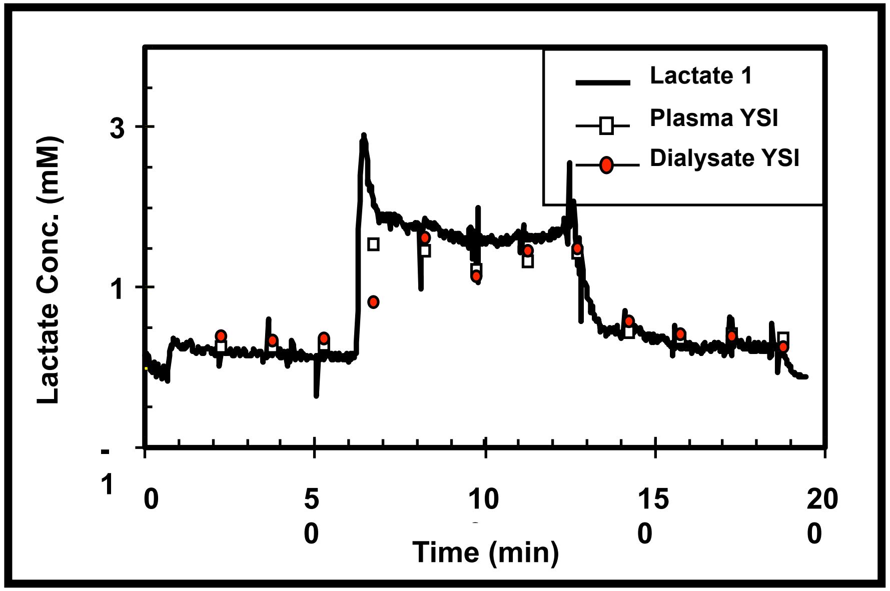
Novel Instrumentation for Real-Time Monitoring Using Miniaturised Flow Cells with Integrated Biosensors, R. Freaney, A. McShane, T.V. Keavney, M.McKenna, K. Rabenstein, F.W. Scheller, D. Pfeiffer, G. Urban, I. Moser, G. Jobst, A. Manz, E. Verpoorte, M.W. Widmer, D. Diamond, E. Dempsey, F.J. Saez de Viteri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

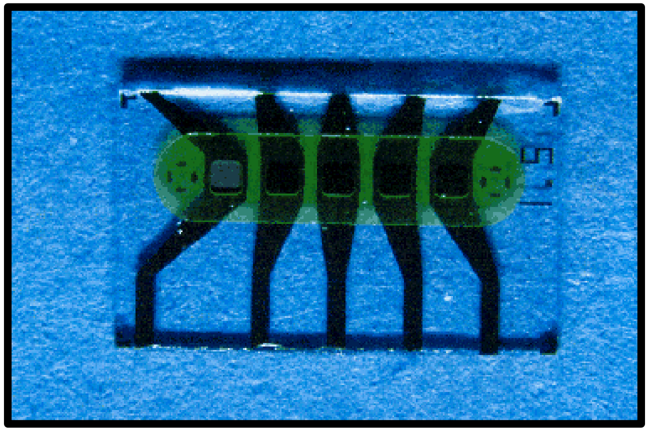
In Vitro Optimisation of a Microdialysis System with Potential for On-Line Monitoring of Lactate and Glucose in Biological Samples, E. Dempsey, D. Diamond, M.R. Smyth, M. Malone, K. Rabenstein, A. McShane, M.McKenna, T.V. Keavney and R Freaney, Analyst, 122 (1997) 185-189.

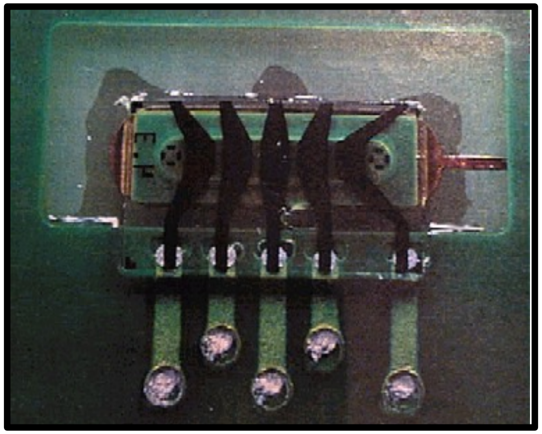
Design and Development of a Miniaturized Total Chemical-Analysis System for Online Lactate and Glucose Monitoring in Biological Samples, Ethna Dempsey, Dermot Diamond, Malcolm R. Smyth, Gerald Urban, Gerhart Jobst, I. Moser, Elizabeth MJ Verpoorte, Andreas Manz, HM Widmer, Kai Rabenstein and Rosemarie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

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

HYPEwatch: Apple, iWatch & Health Monitoring


Independent.ie

Wednesday 7 May 2014

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Apple hiring medical device staff, shares break $600 mark

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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.

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.

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

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, H. F. Yao, A. J. Shum, M. Cowan, I. Lahdesmaki and B. A. Parviz, *Biosensors & Bioelectronics*, **2011**, **26**, 3290-3296.

"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

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!

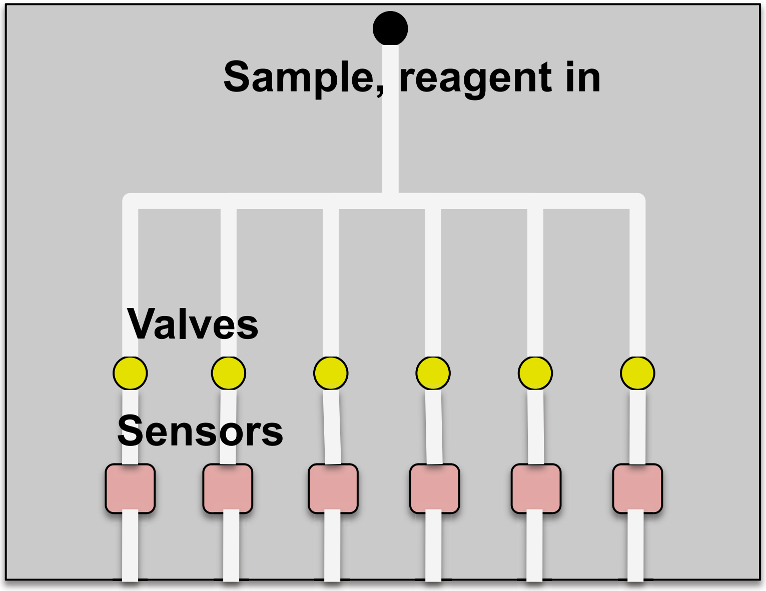
GRAND CHALLENGE
(man on the moon!)

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.

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)

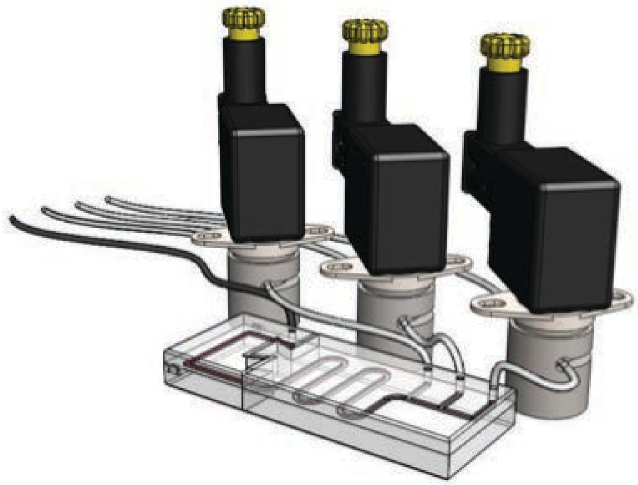


Then 50 sensors when used sequentially could provide an aggregated in-use lifetime of around 1 year

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

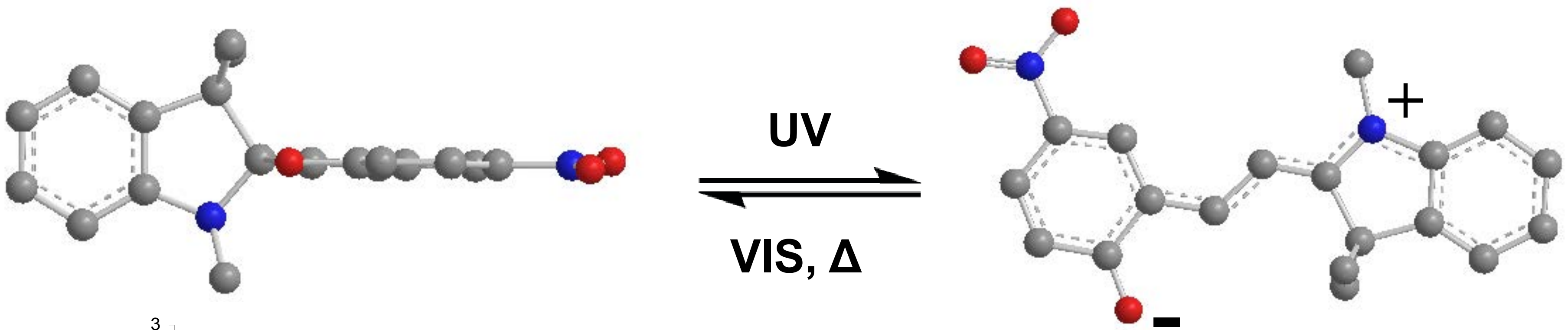
How to advance fluid handling in LOC platforms: re-invent valves (and pumps)!

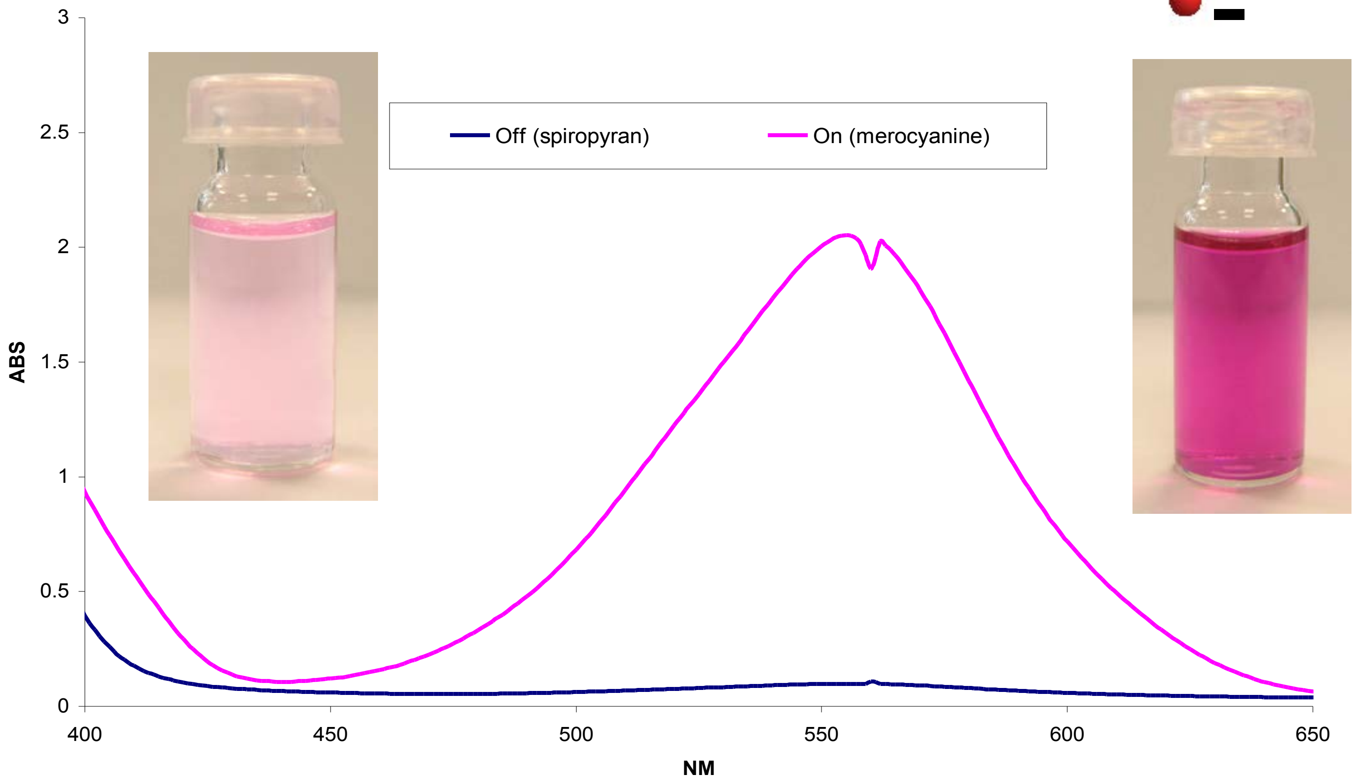
- **Conventional valves cannot be easily scaled down - Located off chip: fluidic interconnects required**
  - Complex fabrication
  - Increased dead volume
  - Mixing effects
- **Based on solenoid action**
  - Large power demand
  - Expensive



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

Photoswitchable Actuators

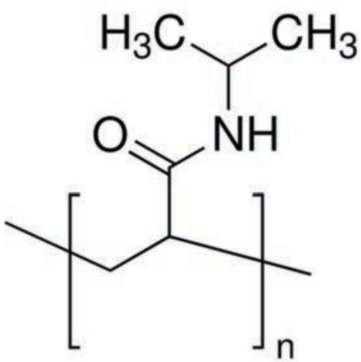




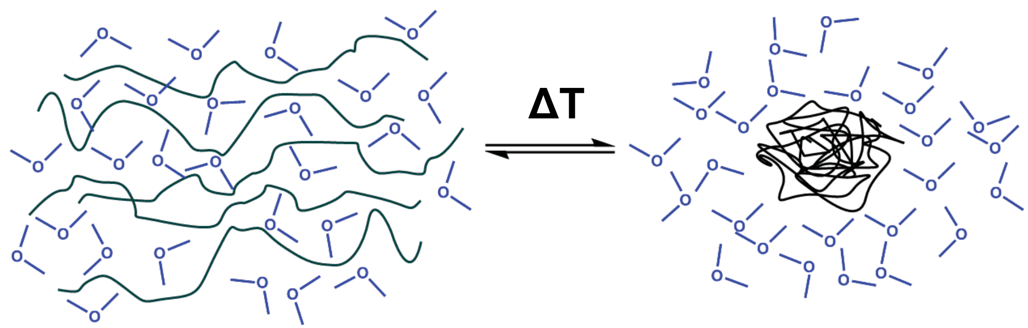
Poly(*N*-isopropylacrylamide)

- **pNIPAAM exhibits inverse solubility upon heating**
- **This is referred to as the LCST (Lower Critical Solution Temperature)**
- **Typically this temperature lies between 30-35°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



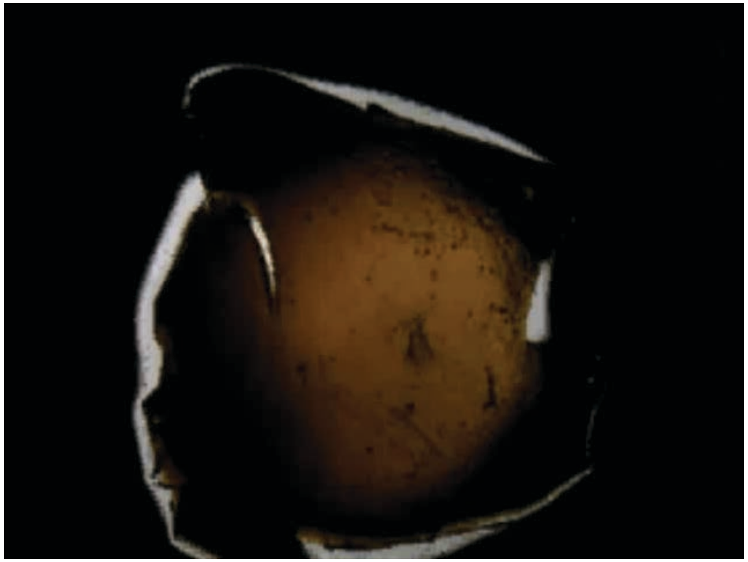
Hydrophilic **Hydrophobic**

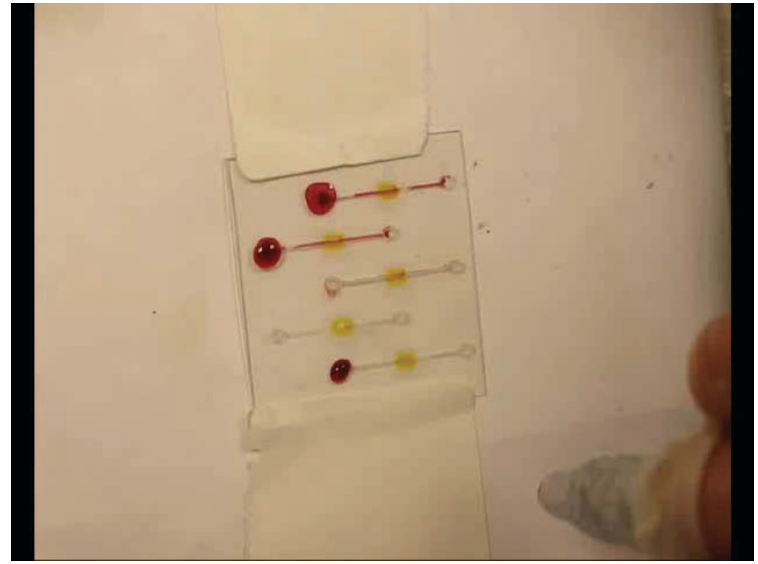


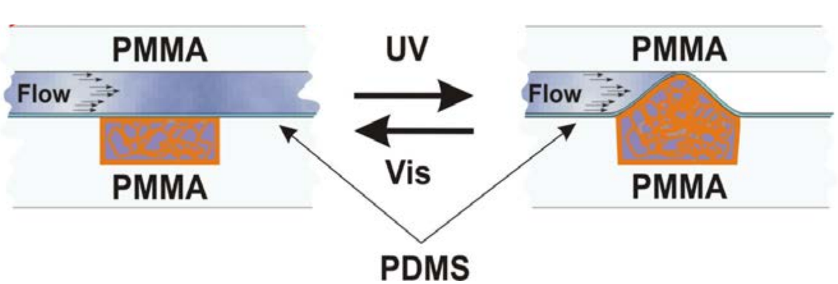
Hydrated Polymer Chains

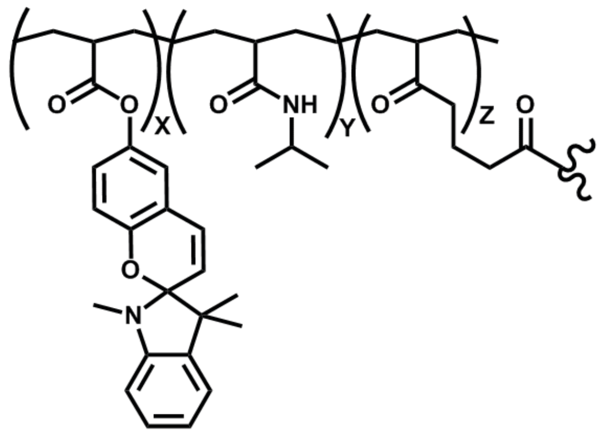
Loss of bound water -> polymer collapse

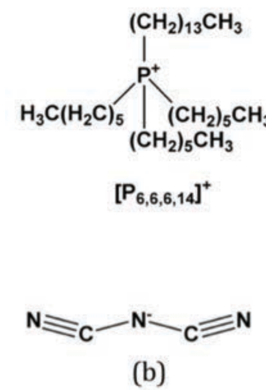
Photo-actuator polymers as microvalves in microfluidic systems







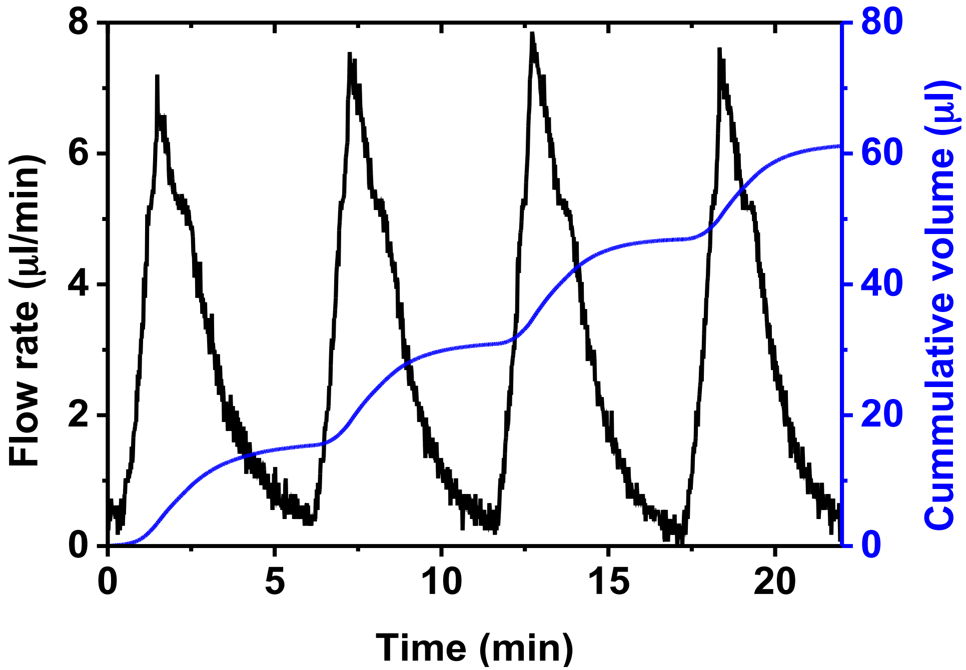




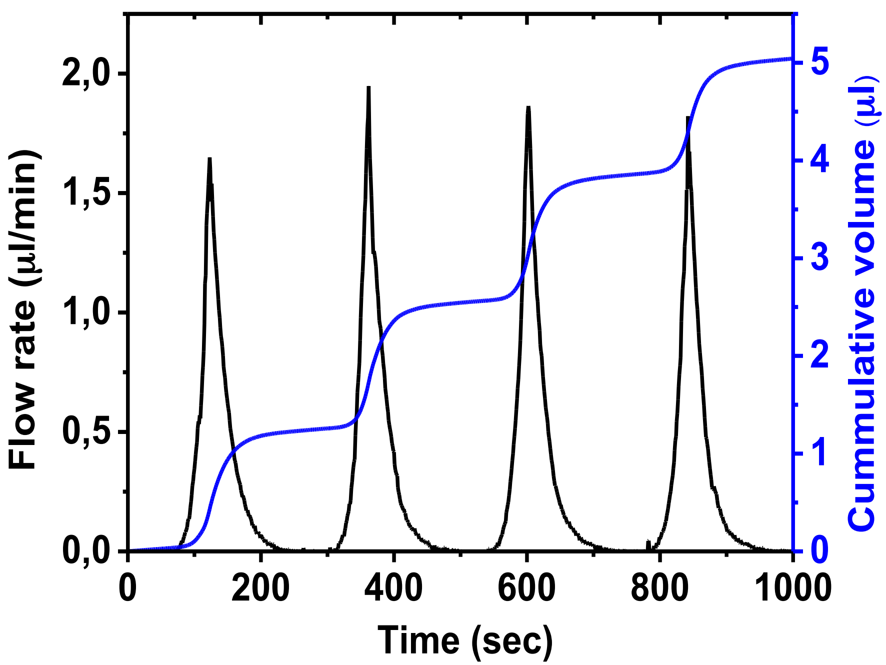
trihexyltetradecylphosphonium dicyanoamide $[P_{6,6,6,14}]^+[dca]^-$

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.

Optimisation of valve dimensions



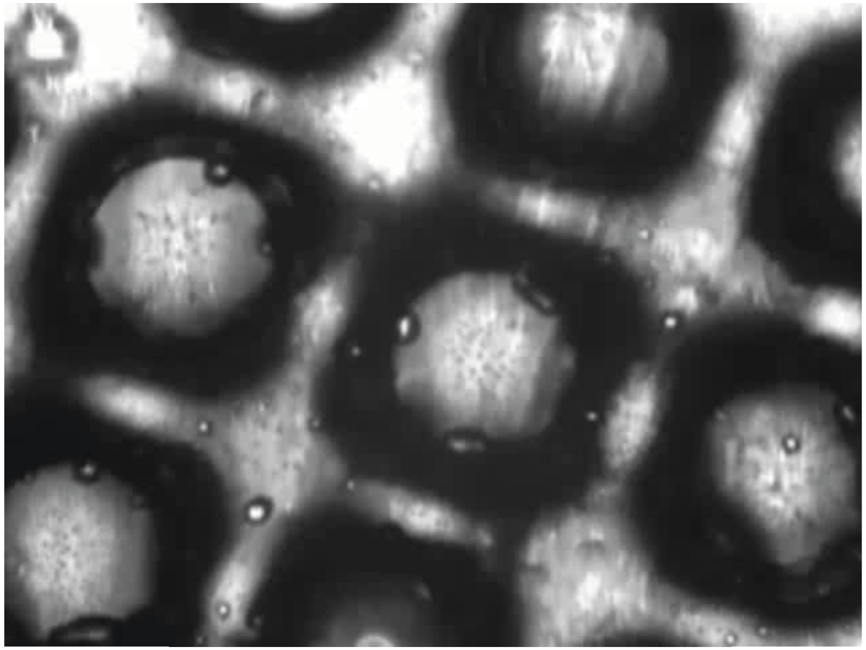
1.7 mm mask



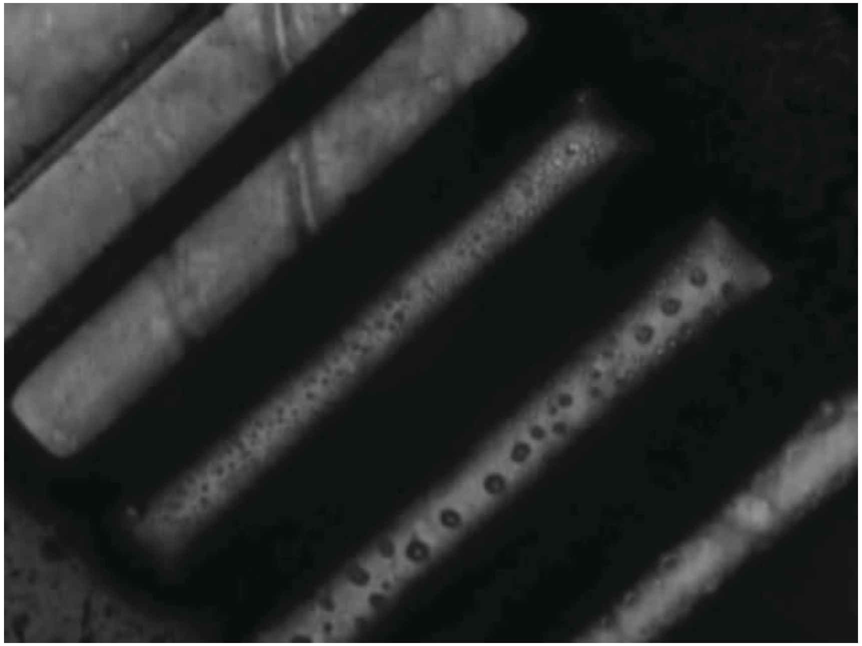
1.6 mm mask

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

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

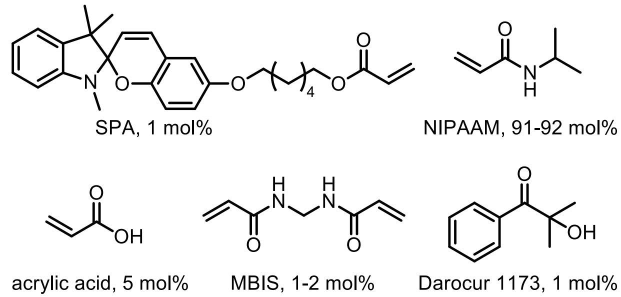
Photocontrol of Assembly and Subsequent Switching of Surface Features

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

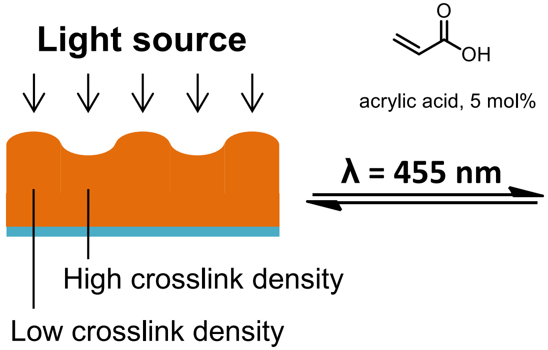
ACS applied materials & interfaces, 6 (2014) 7268-7274

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

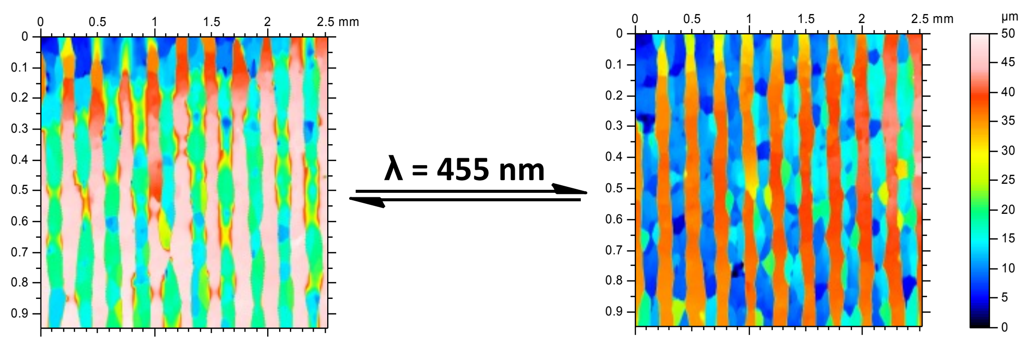
Jelle E. Stumpel,[†] Bartosz Ziółkowski,[‡] Larisa Florea,[‡] Dermot Diamond,[‡] Dirk J. Broer,[*,†,§] and Albertus P. H. J. Schenning[*,†,§]

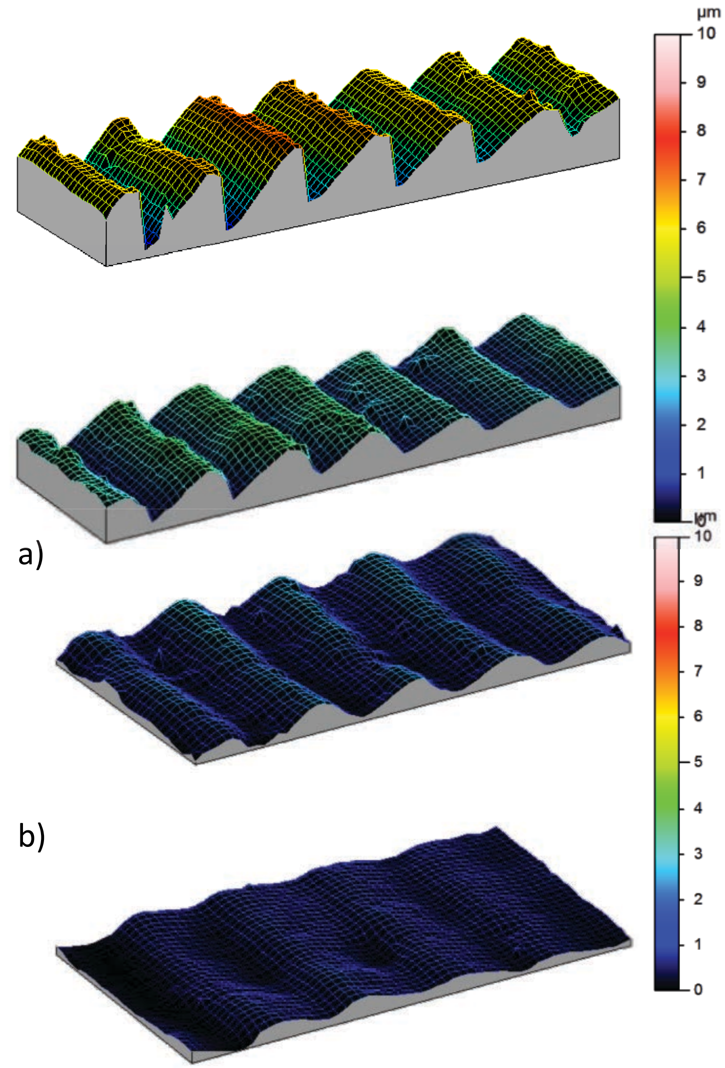


a)

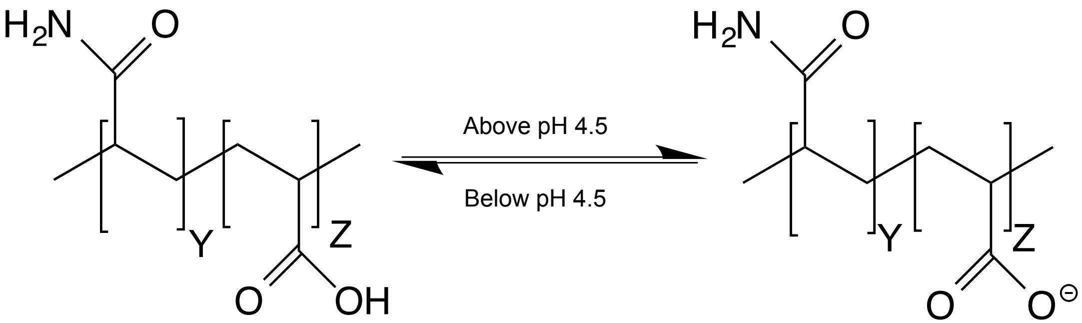


b)

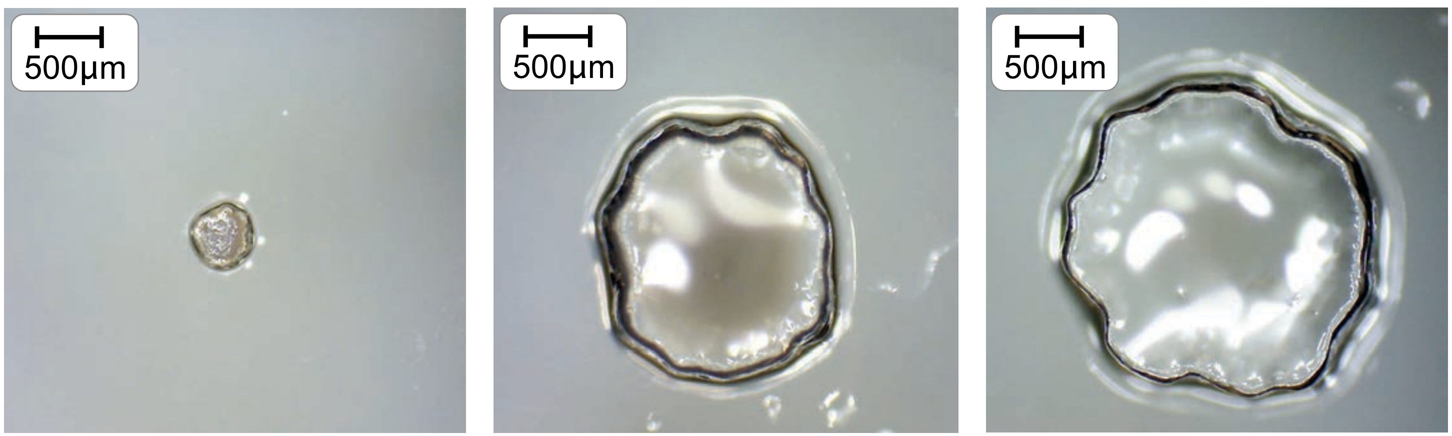




pH Responsive Gel Actuation



Y=Z acrylic acid/acrylate



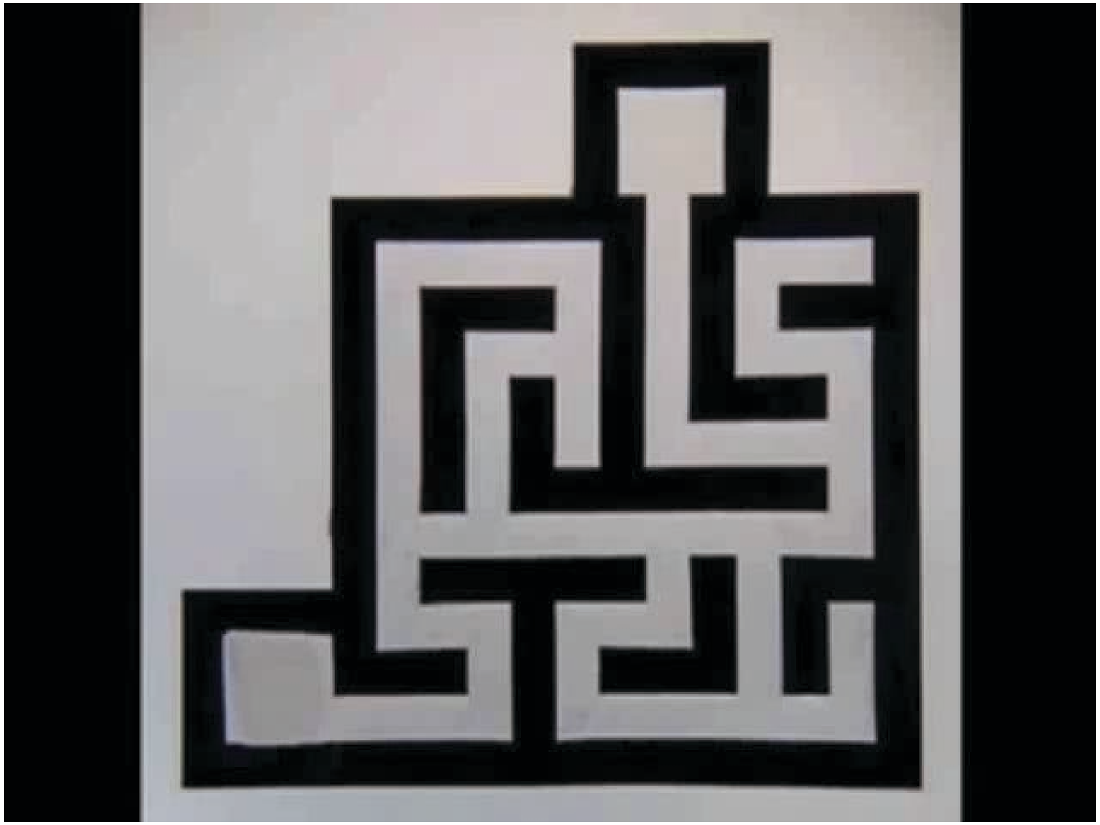
pH 3 | pH 5.5 | pH 11

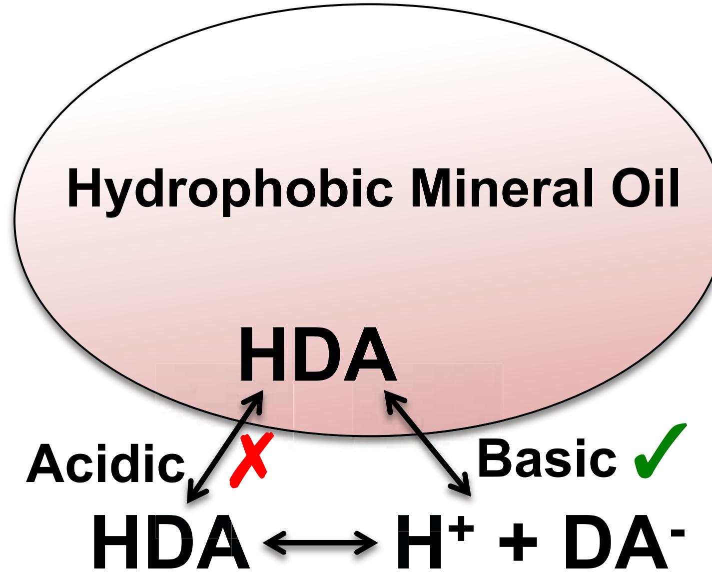
Ca. 400% change in volume (Aishling Dunne and Larisa Florea)

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





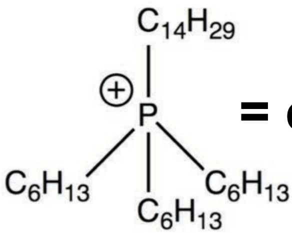
In a pH gradient, DA^- is preferentially transferred to the aqueous phase at the more basic side of the drop.

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^-**

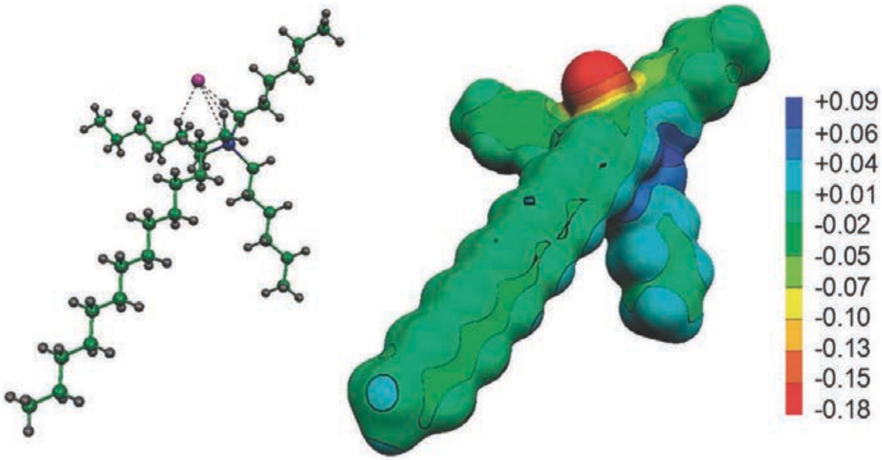
Maze Solving by Chemotactic Droplets; Istvan Lagzi, Siowling Soh, Paul J. Wesson, Kevin P. Browne, and Bartosz A. Grzybowski; **J. AM. CHEM. SOC. 2010, *132, 1198–1199***

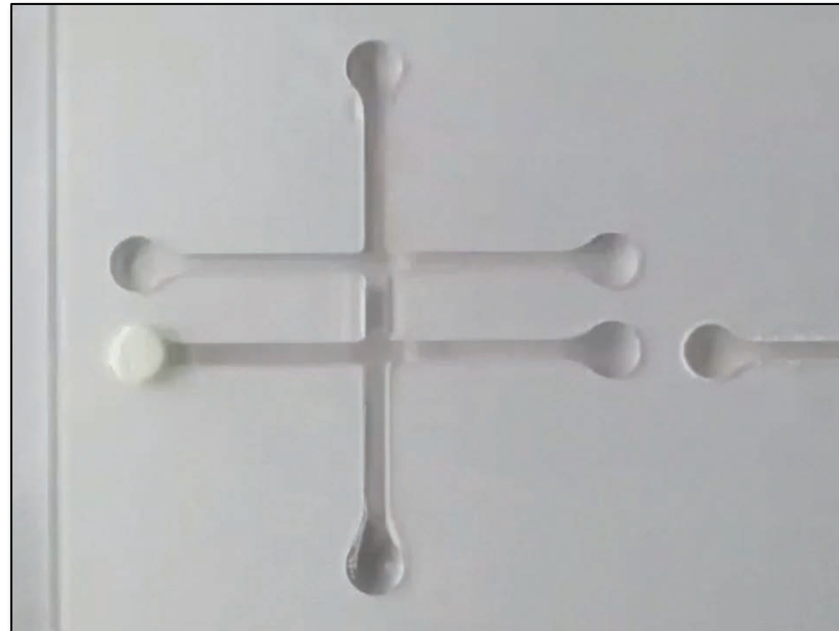
Fuerstman, M. J.; Deschatelets, P.; Kane, R.; Schwartz, A.; Kenis, P. J. A.;Deutch, J. M.; Whitesides, G. M. *Langmuir 2003, 19, 4714.*

We can do the same with IL Droplets



= cationic surfactant



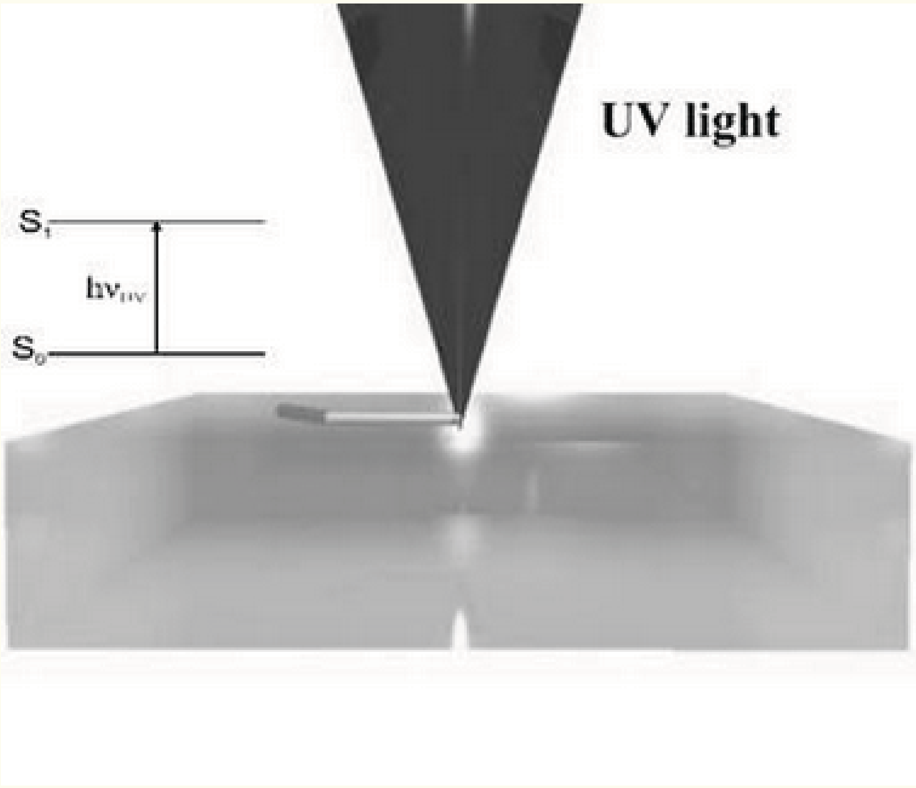


Trihexyl(tetradecyl)phosphonium chloride ($[P_{6,6,6,14}][Cl]$) droplets with a small amount of 1-(methylamino)anthraquinone red dye for visualization. The droplets spontaneously follow the gradient of the Cl^- ion which is created using a polyacrylamide gel pad soaked in 10^{-2} M HCl; A small amount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

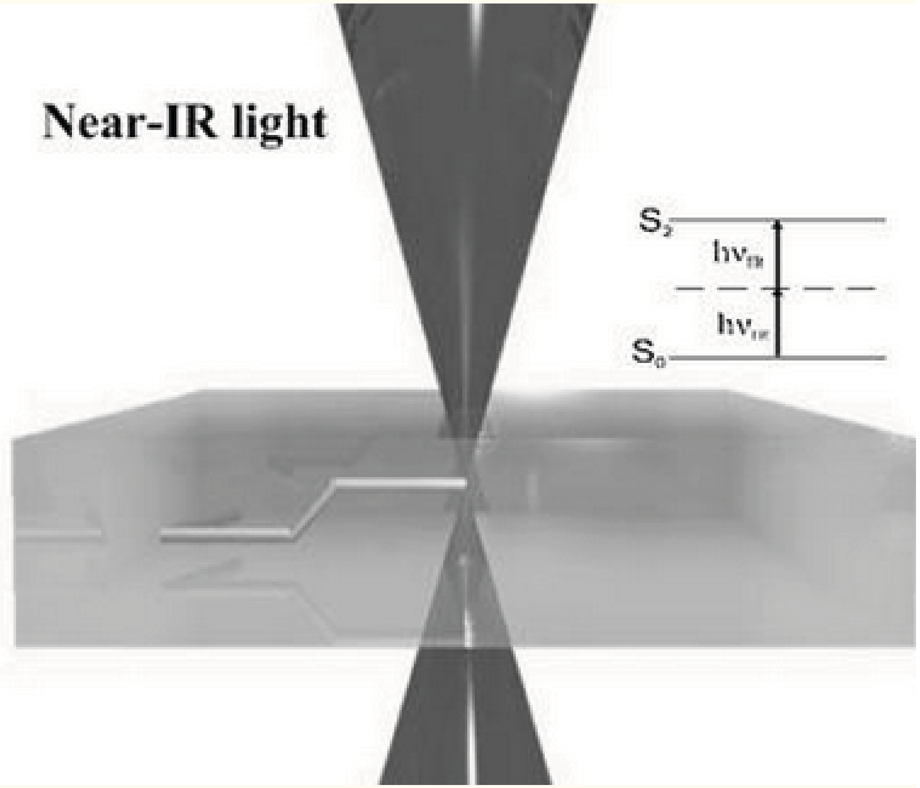
Background

Stereolithography



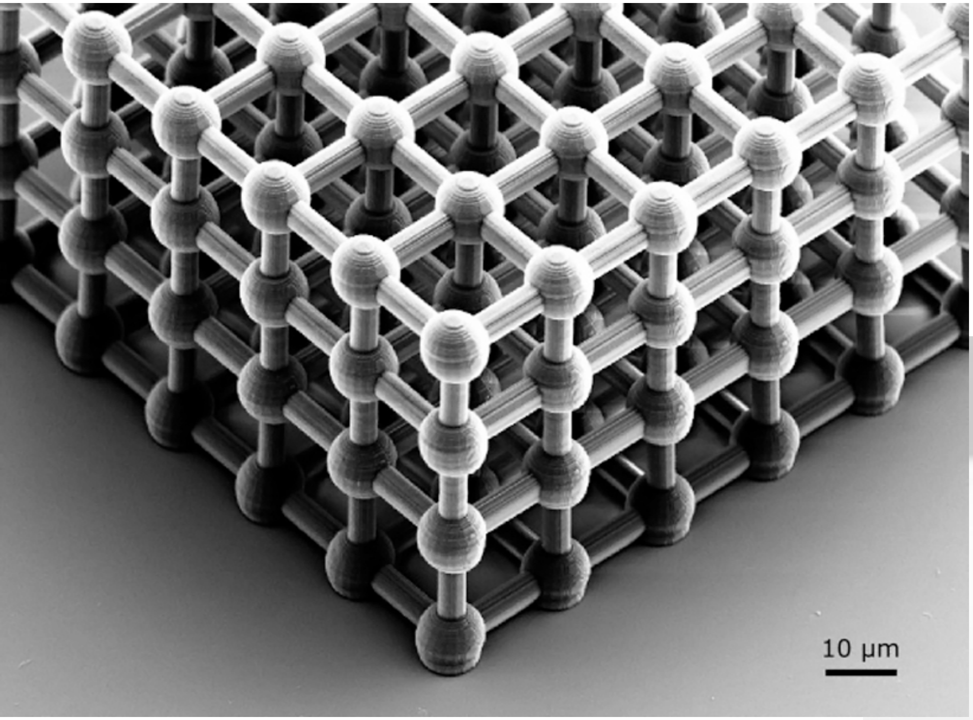
- Single photon absorption
- 2D patterns

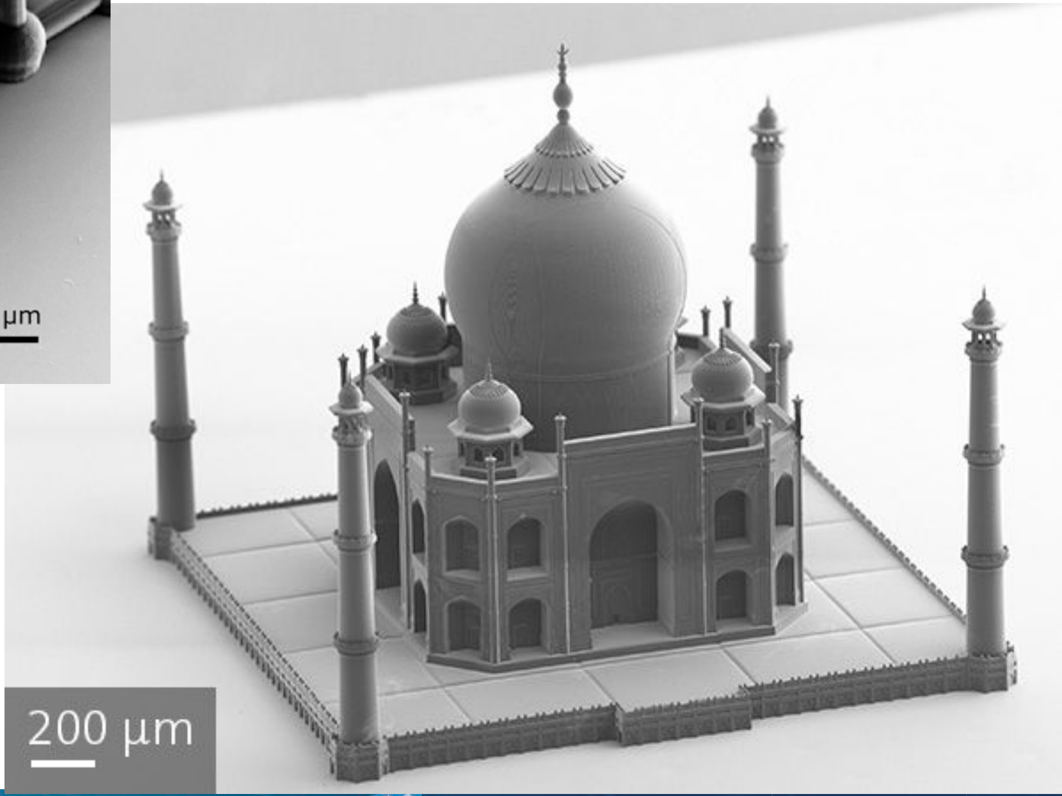
Two-photon polymerisation



- Two photon absorption
- 3D structures

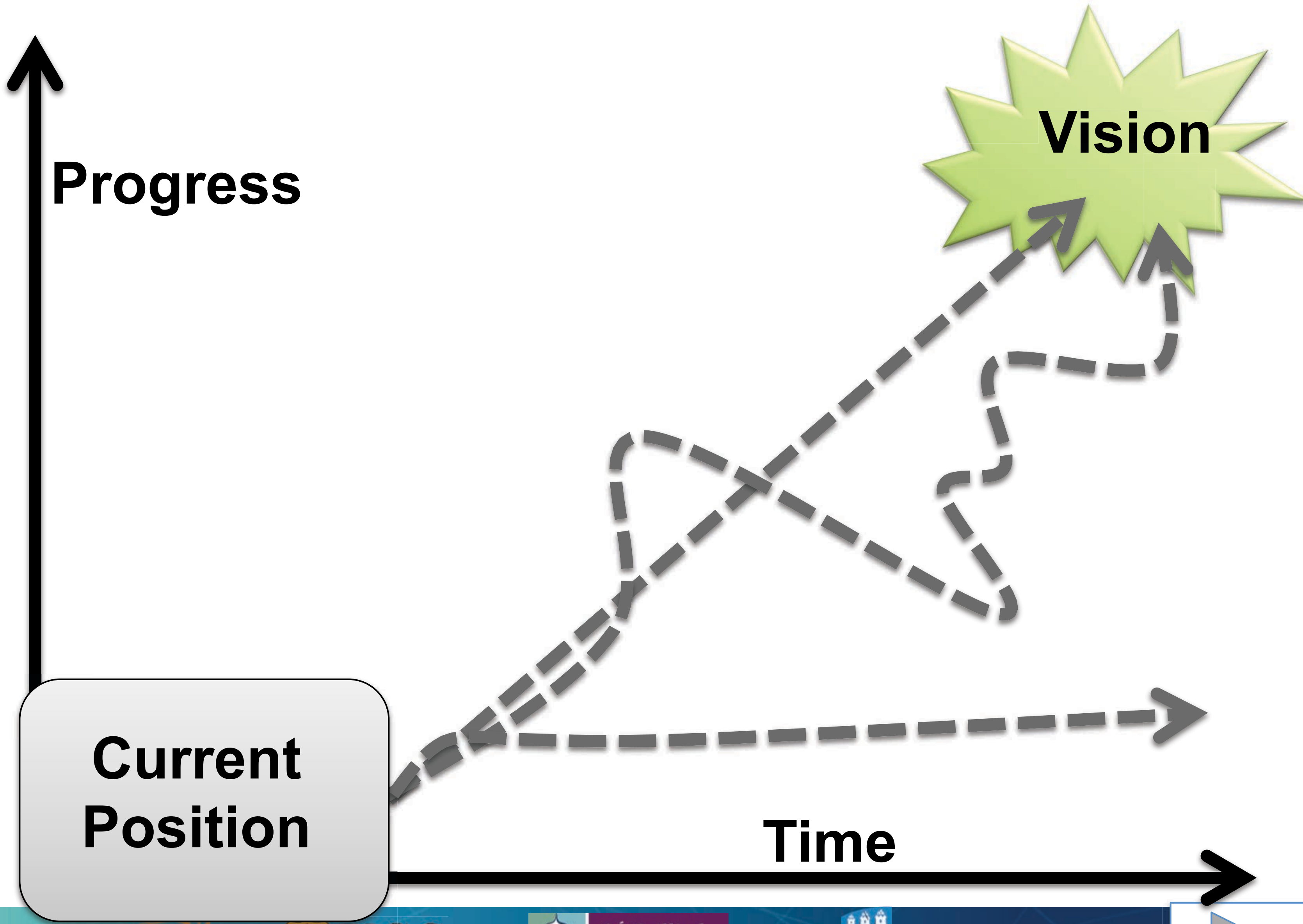
Background



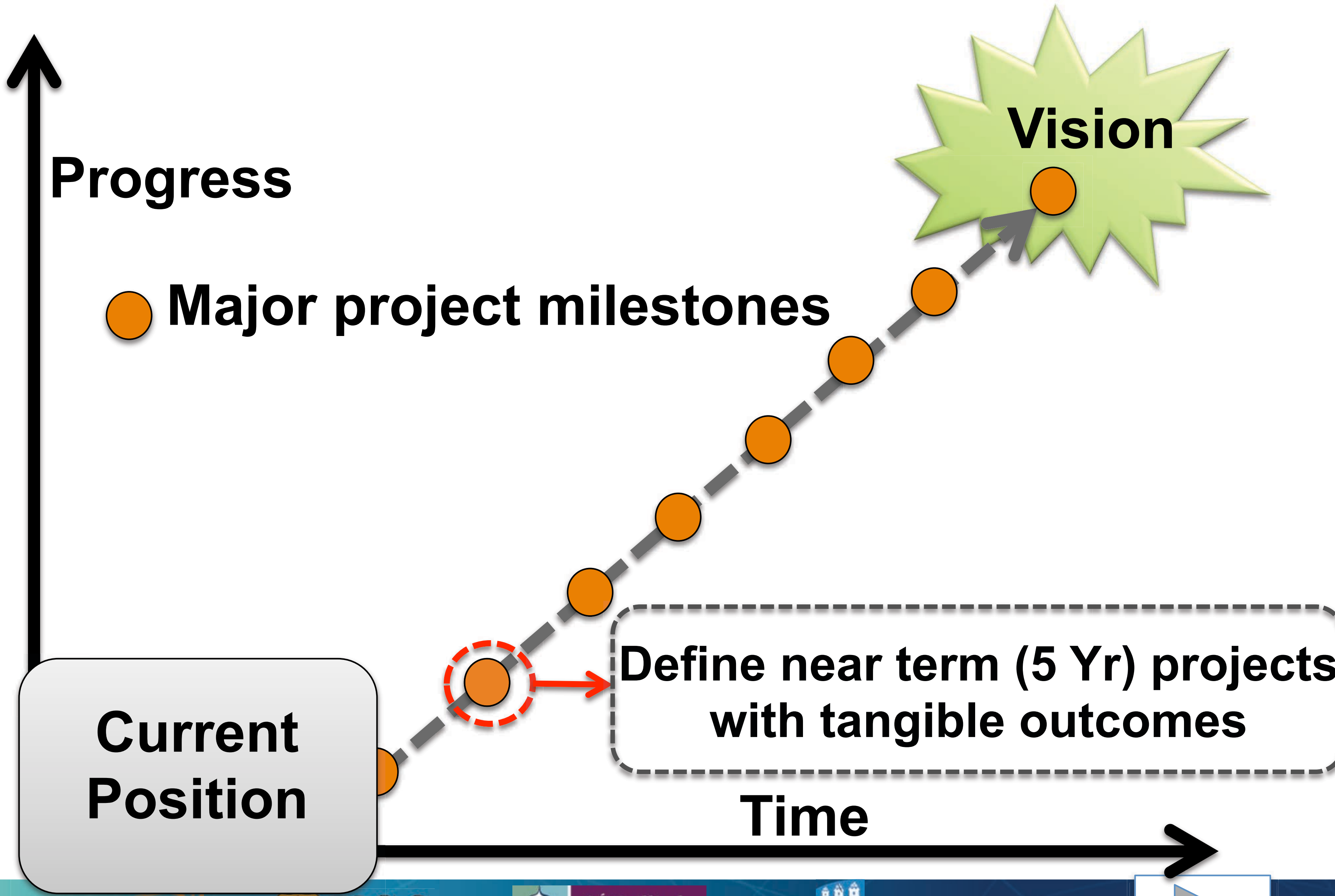


http://www.nanoscribe.de/

Roadmap?



Roadmap?


Vision
Progress
Major project milestones
Define near term (5 Yr) projects with tangible outcomes
Current Position
Time

Near Term Goals (5Years)

Outside: On-Body

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

Inside: Implants/In-vivo

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

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

'STEP': Shared access to major facilities and equipment

- Open to internal and external users
- Transparent cost
- Generate new revenue streams
- Trained user base
- Maintenance

‘STEP’ 3D Printing Suite

DUBLIN CITY UNIVERSITY | EXPLORE DCU | STUDY AT DCU | RESEARCH & ENGAGEMENT | INFO & SERVICES

Research and Innovation

- Research and Innovation
- Key R&I Areas
- Facts & Figures
- R&I Strategy
- Collaborate with DCU
- News & Events
- Research by Faculty
- Research by Institute/Centre
- Research Infrastructure
- Graduate Research
- International
- Research Support
- Technology Transfer
- Contact

3D PRINTING FACILITIES

DCU's 3D printing facility contains a suite of printers that can print using a broad range of materials, have a range of printing techniques and can also print to low micron resolution.

Pricing:

Academic: €45 per hour
Industry: €90 per hour

NOTE: Prices may vary depending on CAD modifications, material costs and technical intervention required. Quotations can be provided for all jobs.

Contact:

Technical: lorcan.kent@dcu.ie

Instruments:

Stratasys Objet260 Connex 1 — Managed By STEP

The Objet260 Connex1 allows us build three-material models as large as 255 x 252 x 200 mm.

The instrument has 16-micron layer accuracy and 14 photopolymers to simulate a range of material properties.
The Objet260 Connex1 offers 14 base materials including:

- Rigid Opaque (VeroWhitePlus, VeroBlackPlus, VeroGray and VeroBlue)
- Rubber-like (Tango family)
- Transparent (RGD720 & VeroClear)
- Simulated Polypropylene (Endur and Durus)
- Biocompatible (MED610)
- High Temperature (RGD525)

Request Access | Booking System

Stratasys Dimension SST 768 — Managed By STEP

Stratasys Dimension 3D printer, capable of printing 3-dimensional fundamental structures, as well as highly-resolved pre-commercial prototype structures.

This printer has a large build envelope to print models up to 254 x 254 x 305 mm. It uses Stratasys' Fused Deposition Modeling (FDM) Technology to create models in ABSplus thermoplastic.
It uses CAD STL files and with two layer resolution settings, 0.254mm or 0.330mm slices,we can build a part quickly for design verification, or choose the finer setting for higher quality surface detail.The system builds the parts by extruding a bead of ABS plastic through an extrusion head, producing high quality parts that are ready to use immediately after completion.

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Stratsys Dimension uPrint — Managed By STEP

The uPrint is a workhorse printer producing high quality parts as large as 203 x 152 x 152mm produced in 0.254mm slices. It uses soluble support material which means the finished parts are quickly cleaned with the built in wavewash system.

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Smart 3D - MiiCraft+ HR — Managed By STEP

MiiCraft+, SLA-based DLP pico 3D printer, offers resolution as high as 30 microns in the Z-axis and 56 microns in the XY-plane. Very good printer for smaller items printed in a short time frame

- X and Y resolutions: 25 micron (slow speed) and 40 microns (fast build speed)
- Z resolution: 30/50/100 microns with MiiCraft Resin
- Build area: X = 25 mm, Y= 45mm, Z=180m
- Materials - Photocurable polymer resins – blue and transparent

Request Access | Booking System

Asiga - Freeform Pico Plus 27 — Currently Unavailable

The Freeform Pico is a 3D printing system which uses Asiga's Slide-And-Separate technology to achieve very low fabrication forces for an upside-down stereolithography system. This results in minimal
support structures and very high accuracy. It can build at up to 12mm per hour at 25 micron slice resolution and 48mm per hour at 100 micron slice resolution

- X and Y resolutions: 27 micron
- Z resolution: 1 micron step size, approx 30 micron layer depth
- Light source: UV LED
- Build area: X = 35 mm, Y= 21.8mm, Z=76m

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 for 'self-aware' sensing devices!

Henkel could play a leading role – unique core knowledge of polymer and materials chemistry

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

SEVENTH FRAMEWORK PROGRAMME
MARIE CURIE ACTIONS
MASK
Project no: 269302
Materials and Advanced Sensor Knowledge Exchange
OrgBIO
NAPES
NEXT GENERATION ANALYTICAL PLATFORMS FOR ENVIRONMENTAL SENSING
COMMON SENSE
MARINE SENSORS - MARINE MONITORING
aquawarn
sfi
DCU
UCC
OÉ Gaillimh
NUI Galway
UCD DUBLIN

Thanks for listening