NCSR
National Centre for Sensor Research

Insight

From Finger Prick Sampling to On-Body and Ultimately Implantable Chem/Bio-Sensors: The Key Role of Active Fluidics in Realising the Long-Term Functional Platforms of the Future

*Larisa Florea, Danielle Bruen, Wayne Francis, Aishling Dunne, Simon Coleman, Aymen BenAzouz and Dermot Diamond**

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

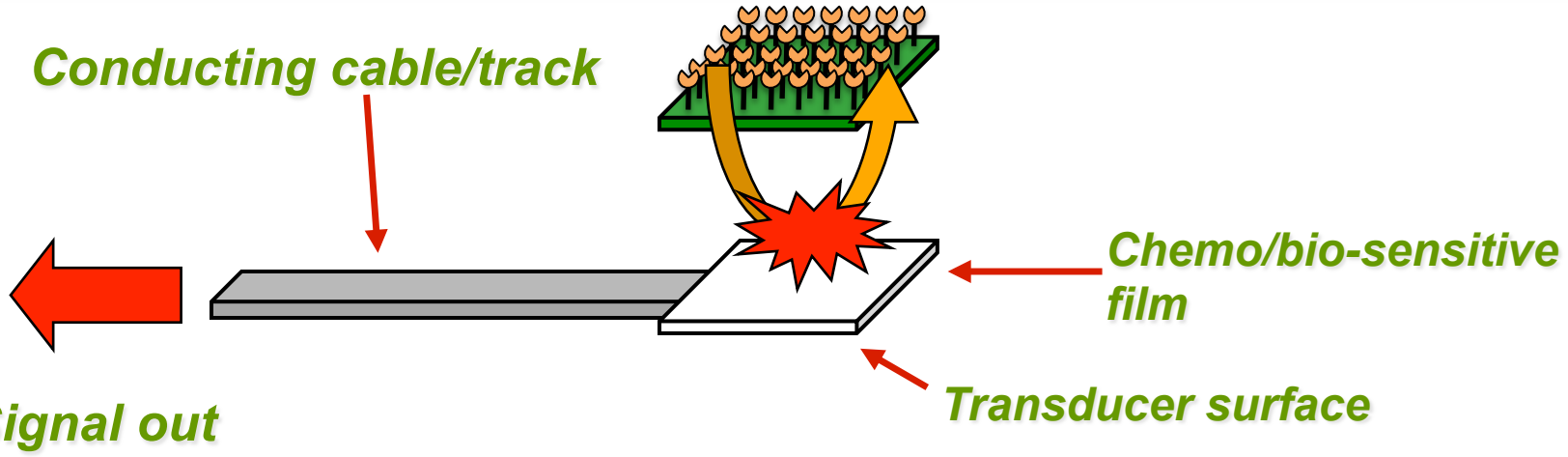
Invited Lecture presented at

CIMTEC2016

Perugia, Italy, 8th June 2016

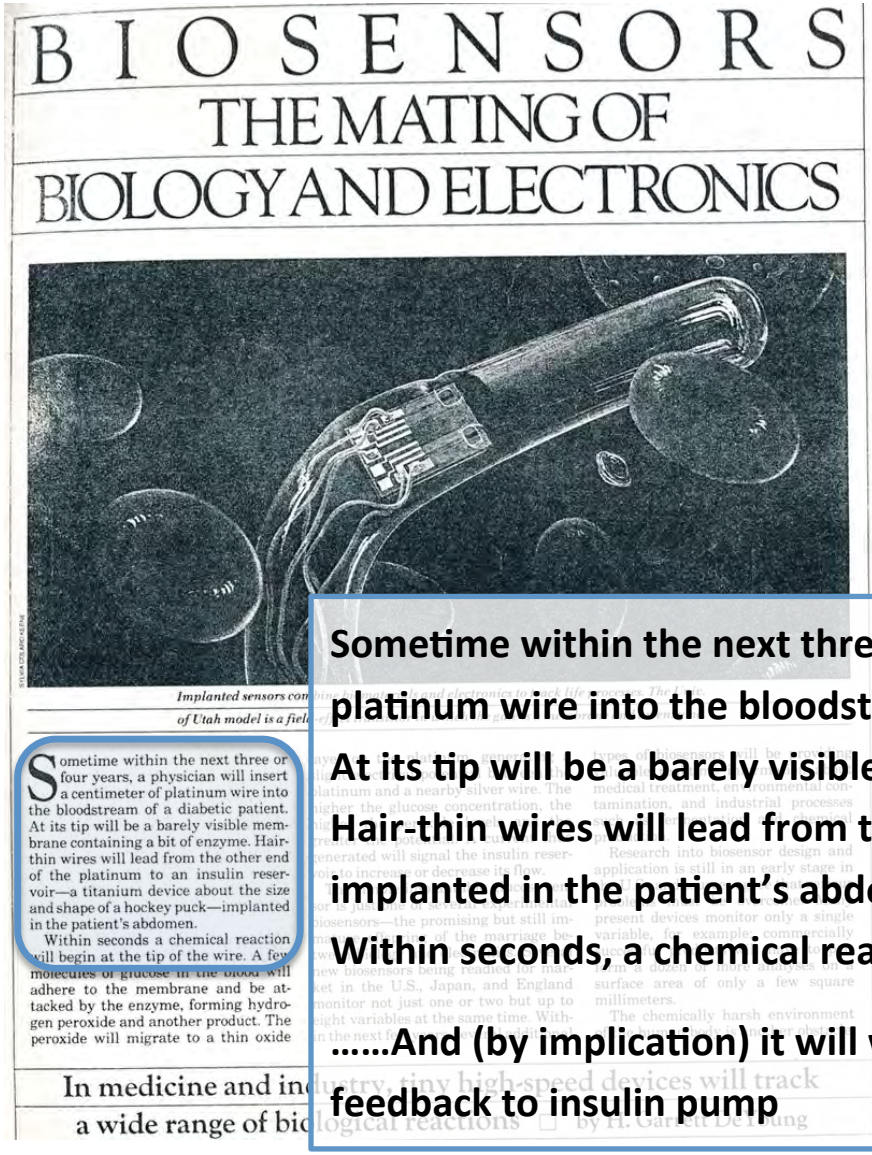
What is a Chemo/Bio-Sensor?

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



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

The (broken) promise of biosensors…..


BIOSENSORS

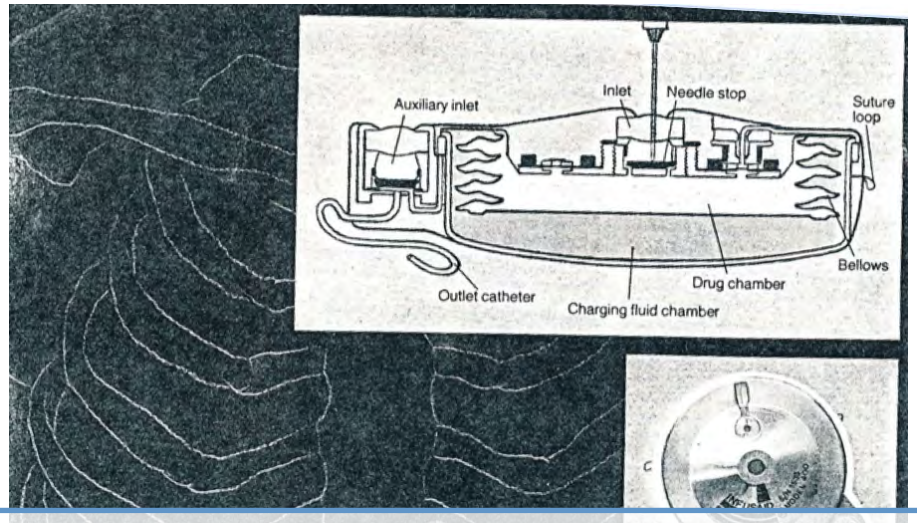
THE MATING OF BIOLOGY AND ELECTRONICS

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

Current Approach: Finger Prick Sampling

- e.g. Diabetes: ca. 7% of world population
- USA: population 300 million
- Ca. 20 million diabetics
- Personal control of condition using finger prick test => blood sample + glucose biosensor

- Say four measurements per day = 80 million/day
- Per year = ca. 30 Billion measurements/yr
- Each sensor used ONCE

Abbott Freestyle ‘Libre’

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

Welcome to flash glucose monitoring!

How to use the FreeStyle Libre System

The FreeStyle Libre system utilises advanced technology that is easy to use.

1 **Apply sensor**
with applicator

●○○

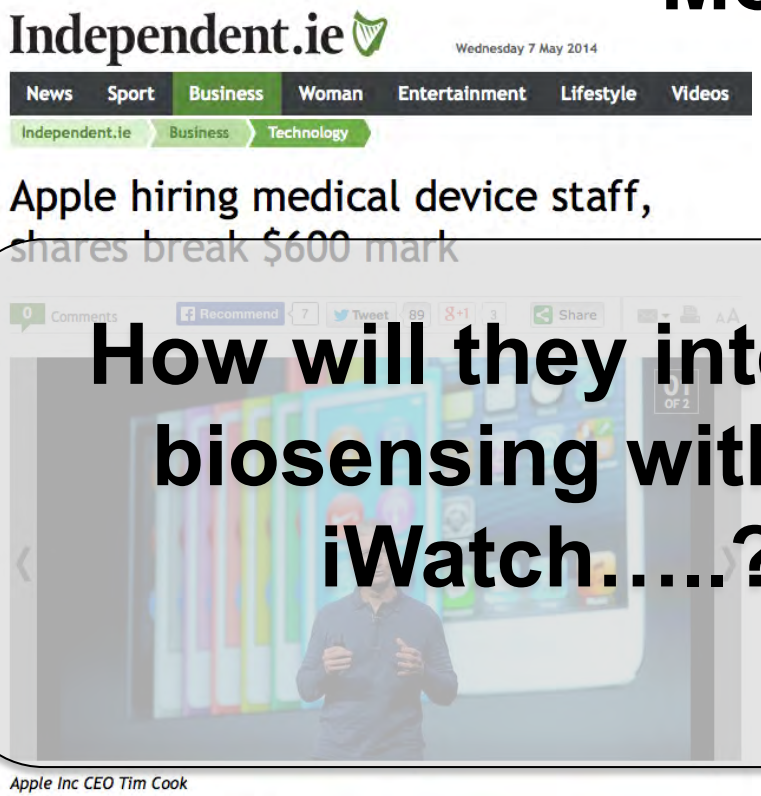
- A thin flexible sterile fibre (5mm long) is inserted just below the skin. Most people reported that applying the sensor was painless[6]
- The 14-day sensor stays on the back of your upper arm and automatically captures glucose readings day and night.
- The sensor is water resistant and can be worn while bathing, swimming and exercising[7]

[6] Most people did not feel any discomfort under the skin while wearing the FreeStyle Libre sensor. In a study conducted by Abbott Diabetes Care, 93.4% of patients surveyed (n=30) strongly agree or agree that while wearing the sensor, they did not feel any discomfort under their skin. [29 persons have finished the study; 1 person terminated the study after 3 days due to skin irritations in the area where the sensor touched the skin.]
[7] Sensor is water-resistant in up to 1 metre (3 feet) of water for a maximum of 30 minutes

- ‘Small fibre’ used to access interstitial fluid
- Data downloaded at least once every 8 hr via 1s contactless scan (1-4 cm)
- Waterproof to 1 metre
- Replace every 2 weeks

Current state-of-the-art for patch based glucose sensing is 2-weeks use outside the body Implants require 10 years inside the body

HYPEwatch: Apple, iWatch & Health Monitoring



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.

…e hiring is in sensor technology, an area Chief Executive Tim Cook singled out last …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.

Current Strategies

- Keep the sensor OUTSIDE the body (patches, wearables, contact lenses, ….)
- Replace the sensor regularly

Even with these strategies there still are significant issues (albeit at a reduced level) ;

- **Biofouling leading to surface effects and sensor drift**
- **Calibration may still be required (coulometry?)**
- **Liquid handling may still be required**
- **Maintaining the integrity of the sensor/body fluid interface**
- **Minimising Infection**

What's the Problem?

- **There has been no success in solving the core issues**
- **For long-term implantable biosensors, these can be summarised as;**
  - Lack of stability of devices over time/limited lifetime
  - Need to calibrate at regular intervals
  - This requires a liquid handling (microfluidic) system along with the sensor, electronics, power…..
  - For implants, these components must continue to function for years; all reagents and standards must be stable

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SWEATCH: Sweat Analysis

Insight

- SWEATCH: A Wearable Platform for Harvesting and Analysing Sweat Sodium Conten [1]
- Na^+ selective potentiometric sensing in a fully integrated platform
- Potential to be further developed to analyze a variety of electrolytes and other relevant analytes.
- Collaboration between
  - Insight Centre of Data Analytics, DCU
  - ARC Centre of Excellence for Electromaterials Science (ACES), Australia
  - Shimmer, DCU Innovation Campus

ARC Centre of Excellence for Electromaterials Science

shimmer DISCOVERY IN MOTION

SEVENTH FRAMEWORK PROGRAMME

MARIE CURIE ACTIONS

MASK
Project no: 269302
Materials and Advanced Sensor Knowledge Exchange

[1] Tom Glennon, Conor O Quigley, Margaret McCaul, Giusy Matzeu, Stephen Beirne, Gordon G. Wallace, Florin Stroiescu, Niamh O Mahoney, Paddy White, and Dermot Diamond, **'SWEATCH': A Wearable Platform for Harvesting and Analysing Sweat Sodium Content, Electroanalysis, 28 (2016) DOI: 10.1002/elan.201600106.**

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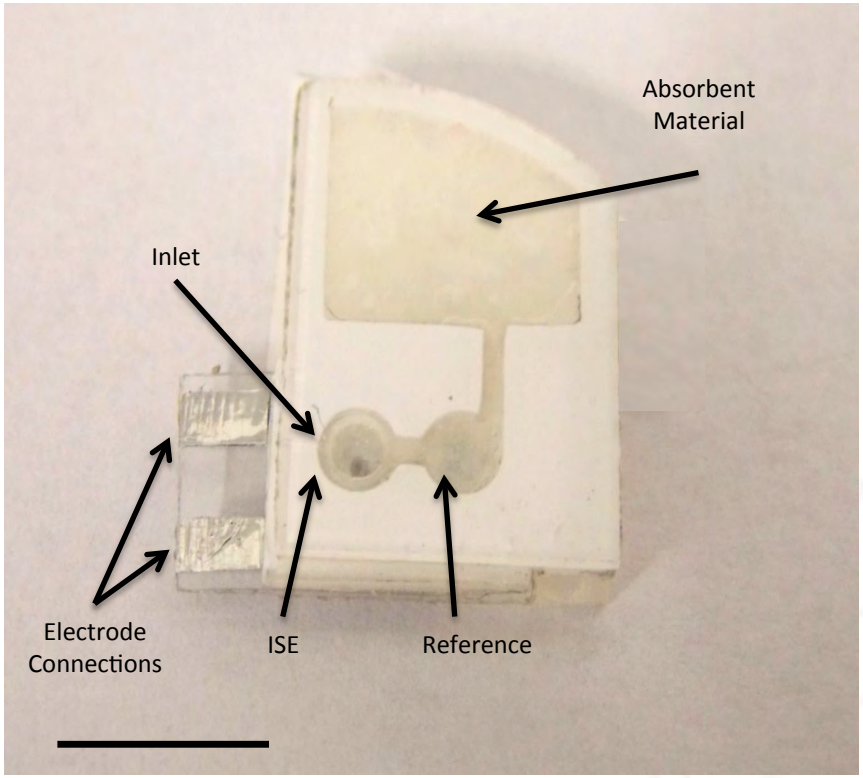
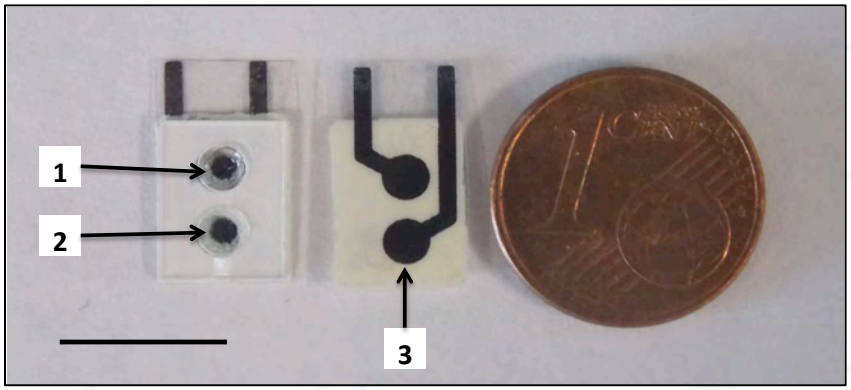
Na^+ Sensing in Sweat

Insight

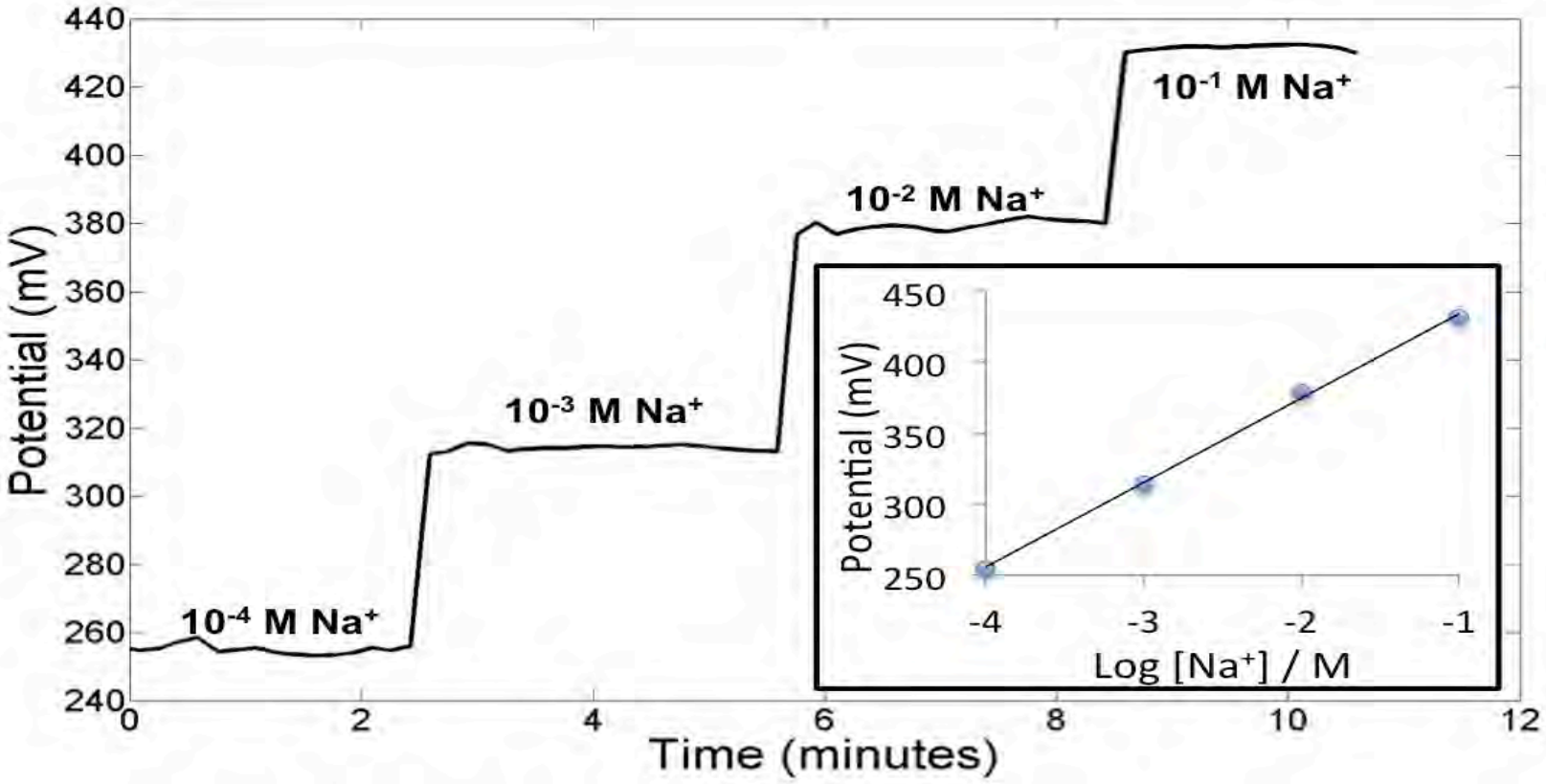




- Front (left) and back (right) of the electrochemical sensor showing:
  1. The Ion Selective Electrode (ISE)
  2. The reference electrode (RE)
  3. The screen-printed conductive carbon layer.
- Scale bar = 1 cm

- Sensor integrated into a fluidic chip for sweat analysis and sampling
- Laser cut absorbent material incorporated to maintain flow for real-time monitoring and to collect sweat for further analysis

Sensor Calibration



- Calibration of a Na^+ SS-ISE and SS-RE output signal using the Shimmer board, giving a slope of 56.98mV and an R2 value of 0.99.

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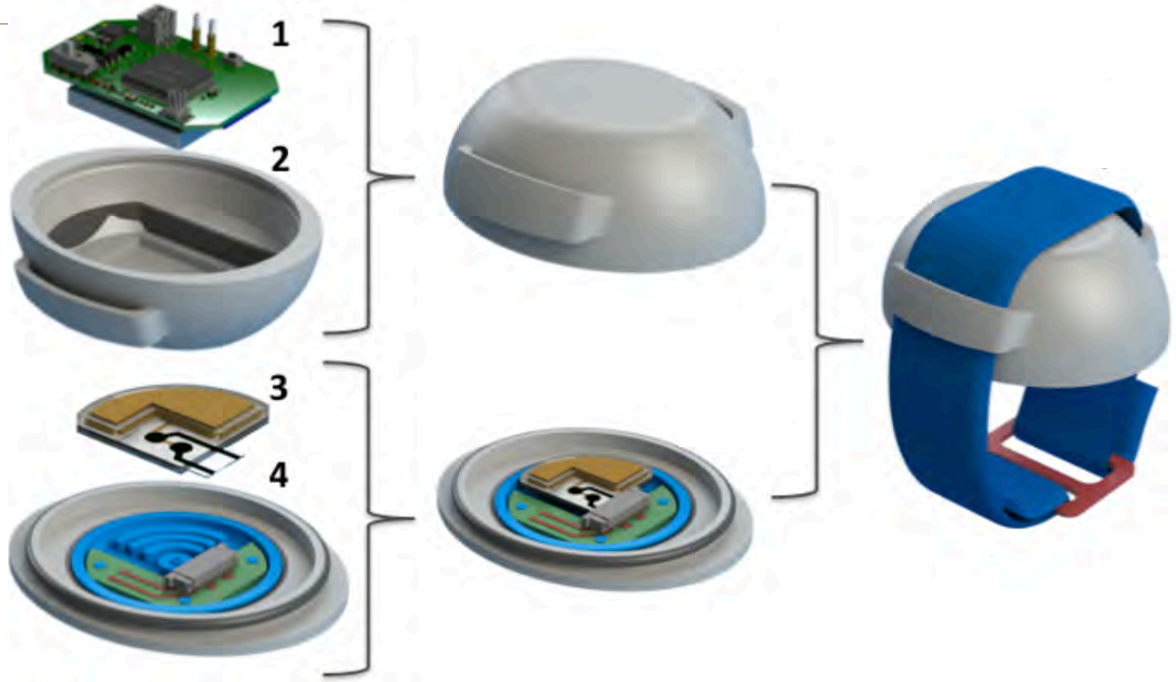
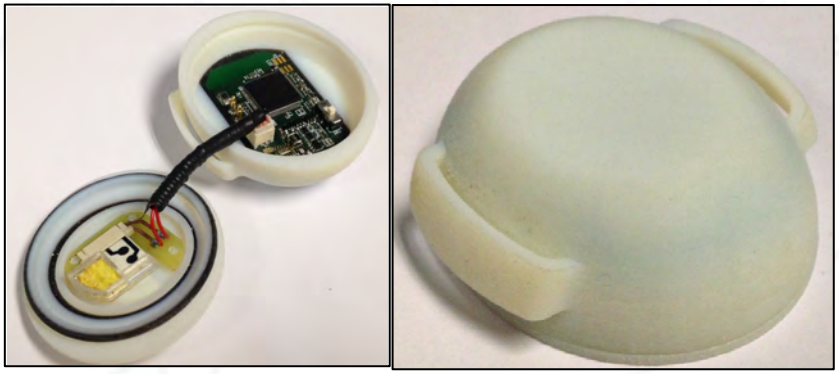
SWEATCH Device

Insight

1. Custom-built electronics with wireless communication (Shimmer)
2. 3D printed casing
3. Microfluidic chip + ISE
4. 3D printed sweat harvester and sensor connections



- Rapid prototyping techniques such as laser ablation and 3D printing are utilised to custom build various components including casing and sweat harvesting device ***(the Australian National Nanofabrication Facility – Materials node and the Nano-Bioanalytical Research Facility (NRF) in Dublin City University)***



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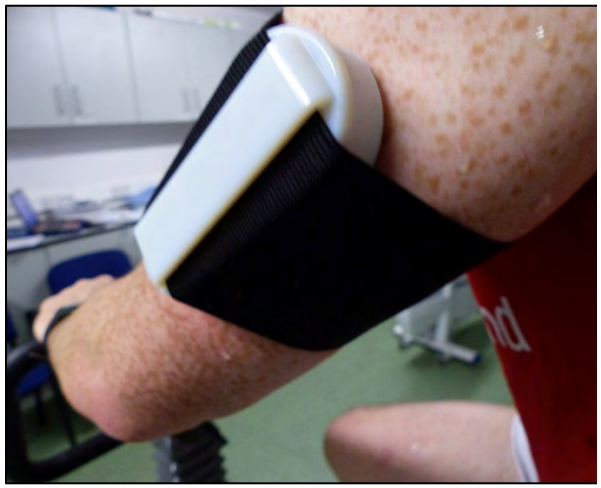
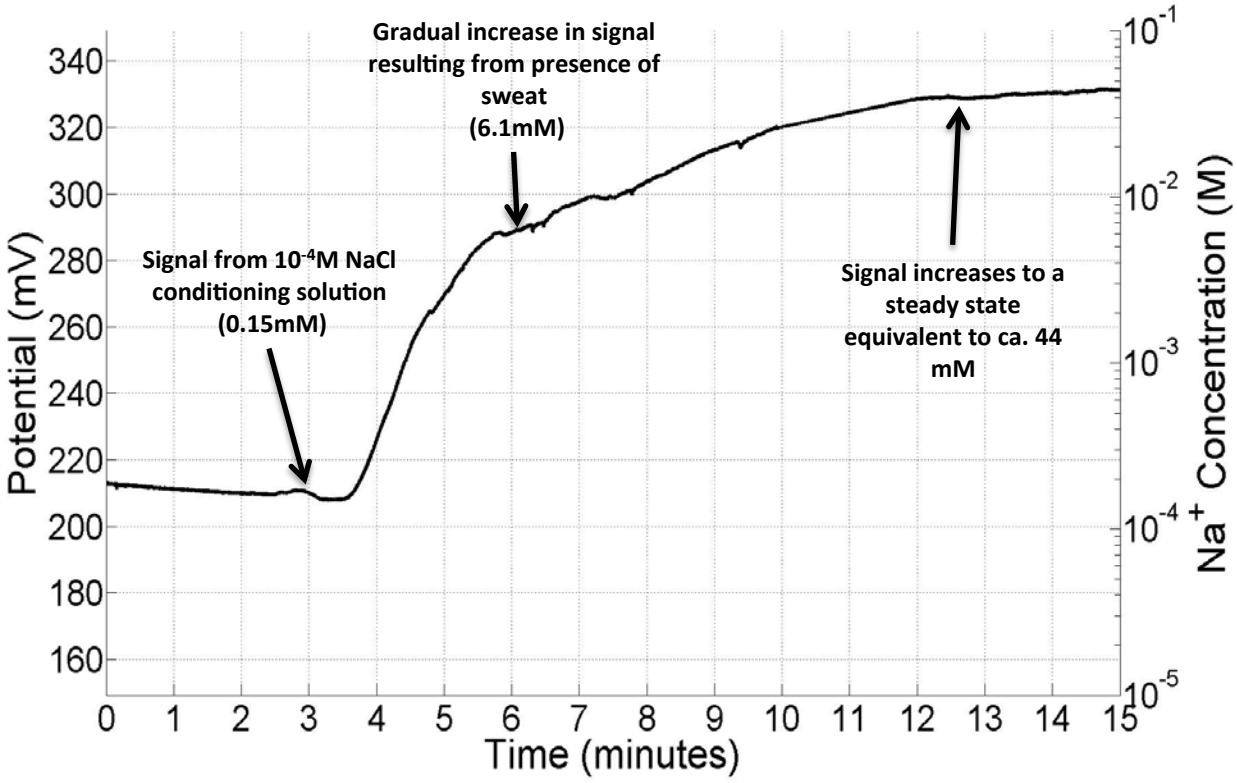
On Body Trials

Insight





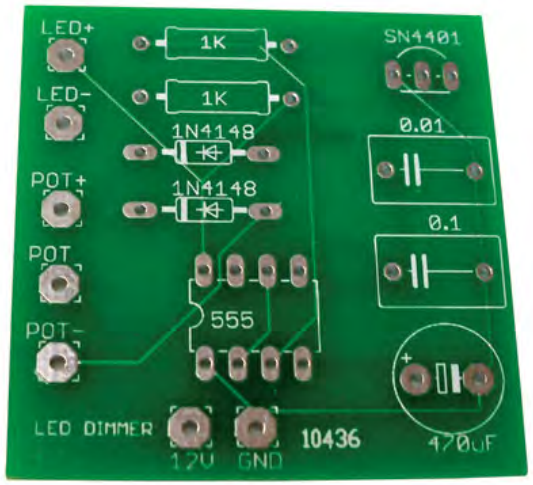
Tom Glennon, Conor O Quigley, Margaret McCaul, Giusy Matzeu, Stephen Beirne, Gordon G. Wallace, Florin Stroiescu, Niamh O Mahoney, Paddy White, and Dermot Diamond, 'SWEATCH': A Wearable Platform for Harvesting and Analysing Sweat Sodium Content, Electroanalysis, 28 (2016) DOI: 10.1002/elan.201600106

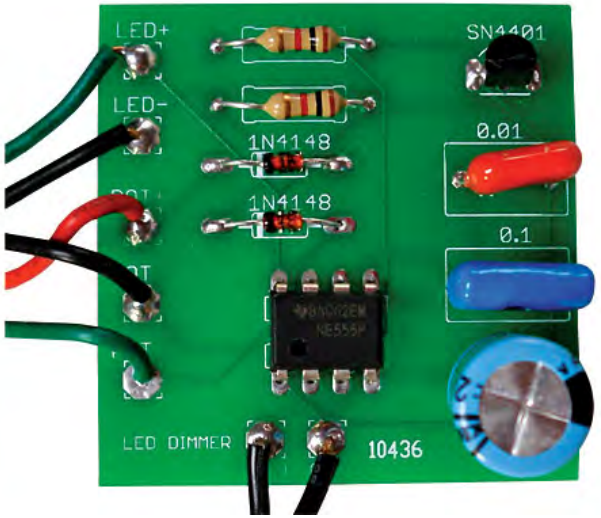
Microfluidics, to date, has been largely focused on the development of science and technology, and on scientific papers, rather than on the solution of problems

Editorial 'Solving Problems', George Whitesides, Lab Chip 10 (2010) 2317-2318

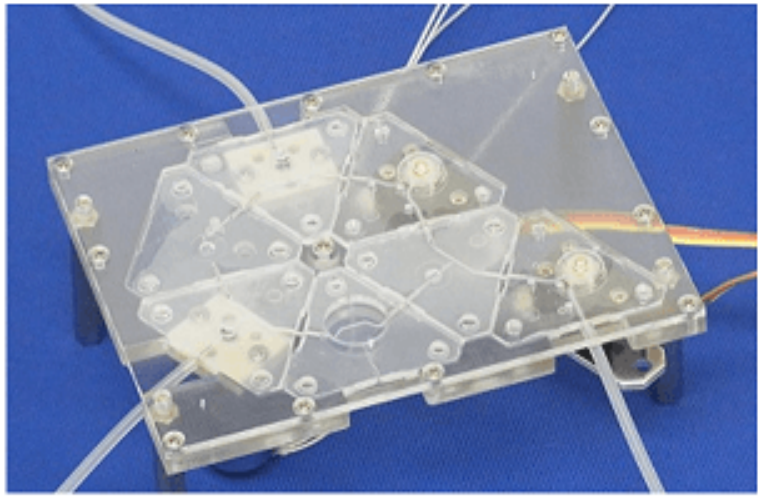
Origins of microfluidics: Inspired by Electronic 'Chips'

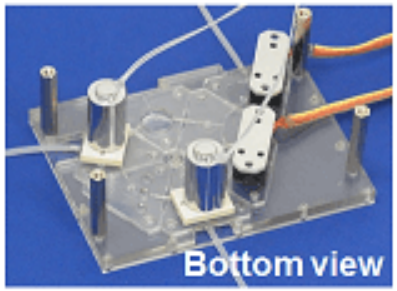
- Tremendous success of 'integrated circuits' in 1960s 1970s
- Integrated Fluidics would do the same for Analytical Science
- 'Lab on a Chip': inherently 2D!



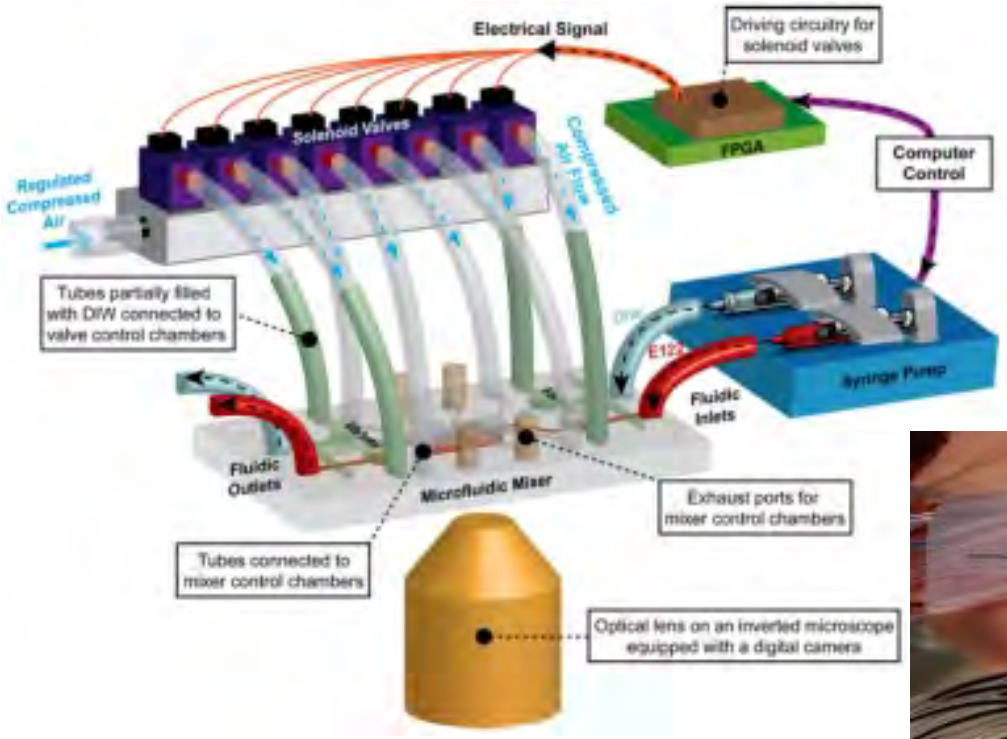


www.gesundheitsindustrie-bw.de





But not everything is integrated…..

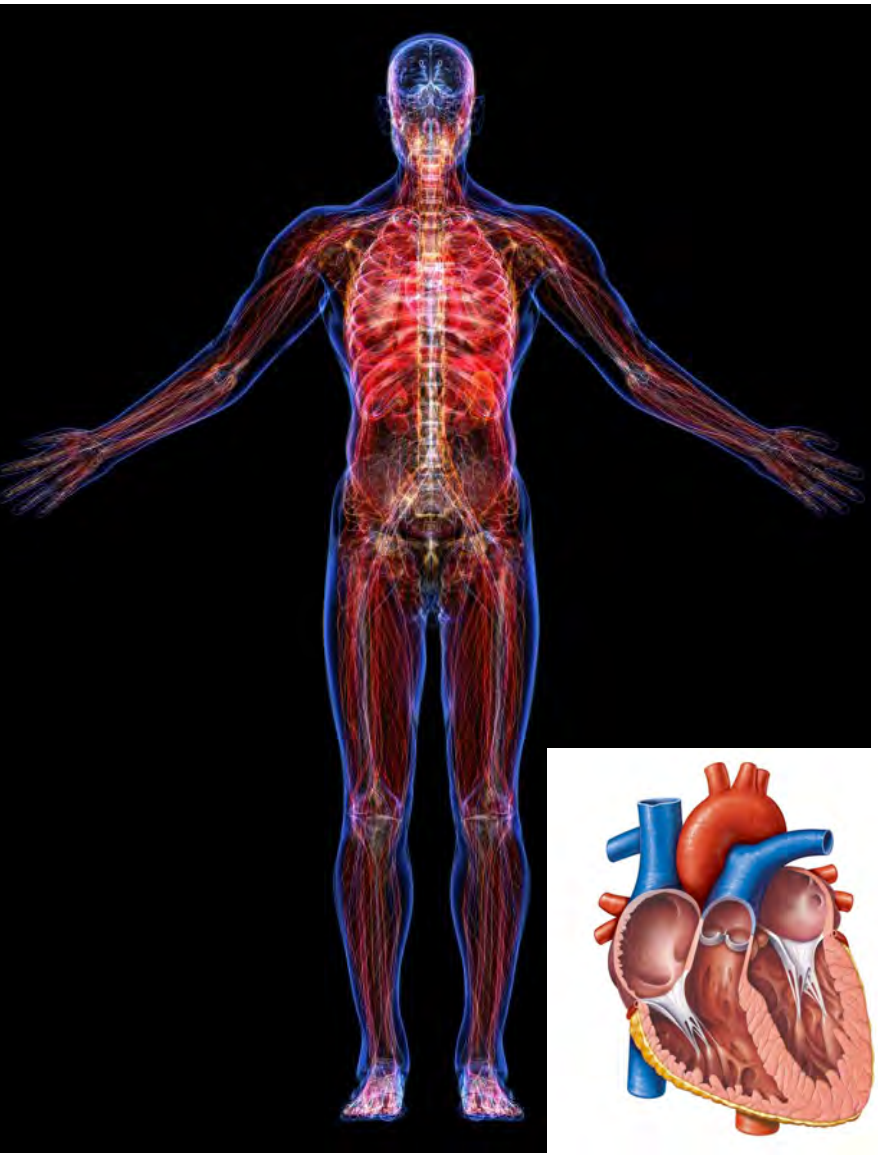


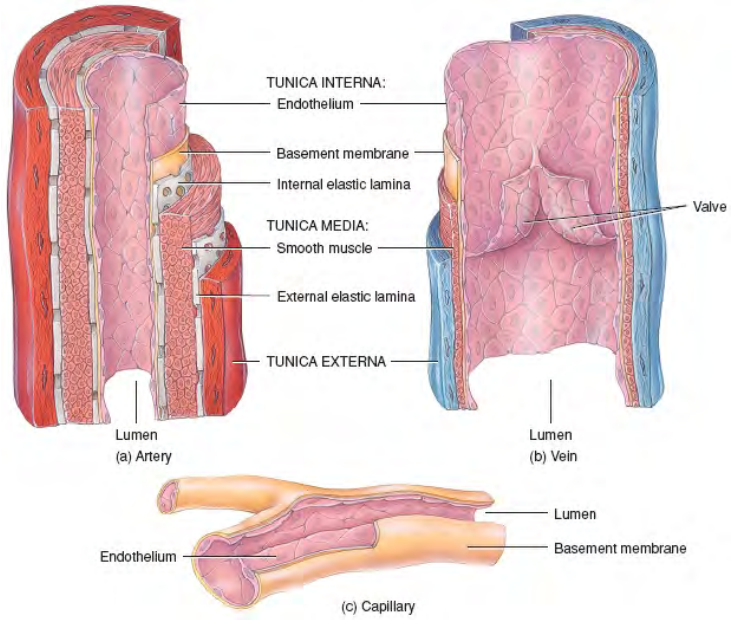
- Many components are located off-chip
- Detectors, pumps, valves….
- Hard Materials

http://www.eetimes.com/document.asp?doc_id=1171478

- Fluidic Interconnects can get very messy
- Most of the ‘Chip’ has no function

How does Biology do it?



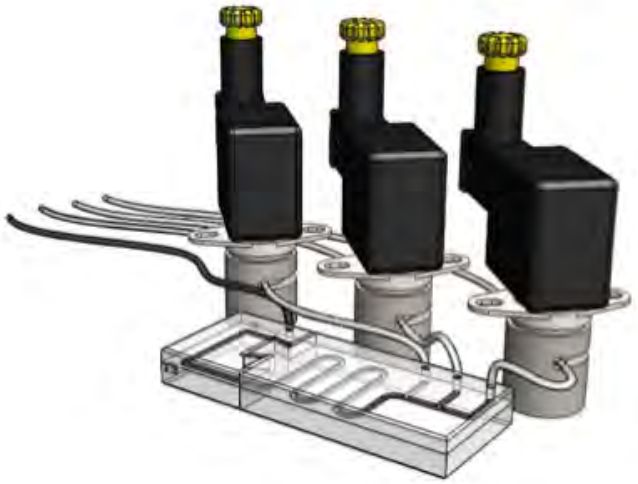


- Inherently 3D
- Soft, flexible materials
- Everything is fully integrated
- All available space is functional
- Channel walls play an active role

http://www.wisegeek.org/what-is-an-open-circulatory-system.htm

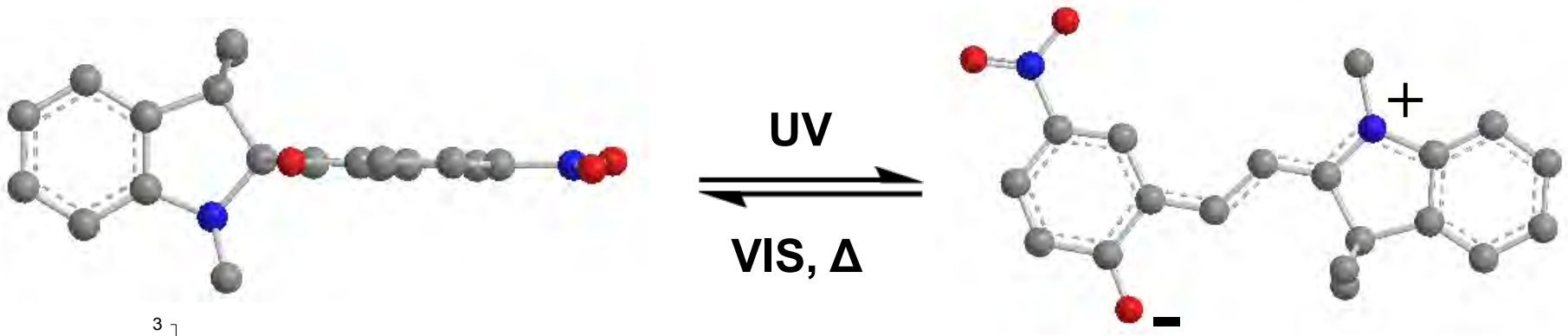
How to advance fluid handling in LOC platforms: re-invent valves (and pumps)!

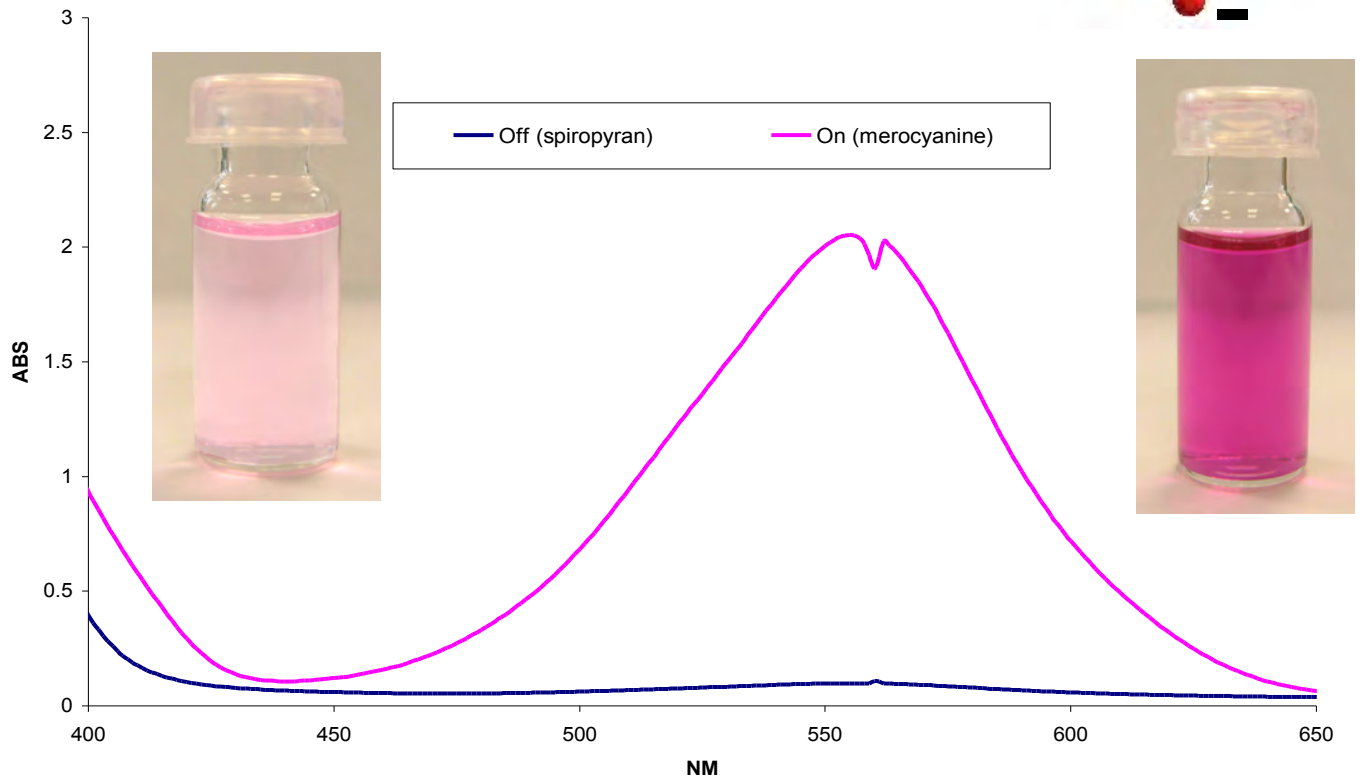
- **Conventional valves cannot be easily scaled down - Located off chip: fluidic interconnects required**
  - Complex fabrication
  - Increased dead volume
  - Mixing effects
- **Based on solenoid action**
  - Large power demand
  - Expensive



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

Photoswitchable Soft Actuators

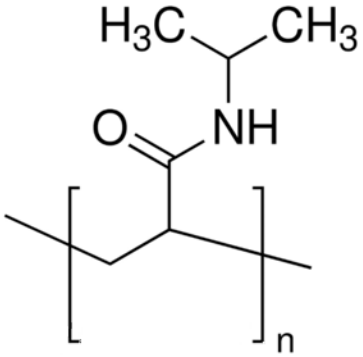




Poly(*N*-isopropylacrylamide)

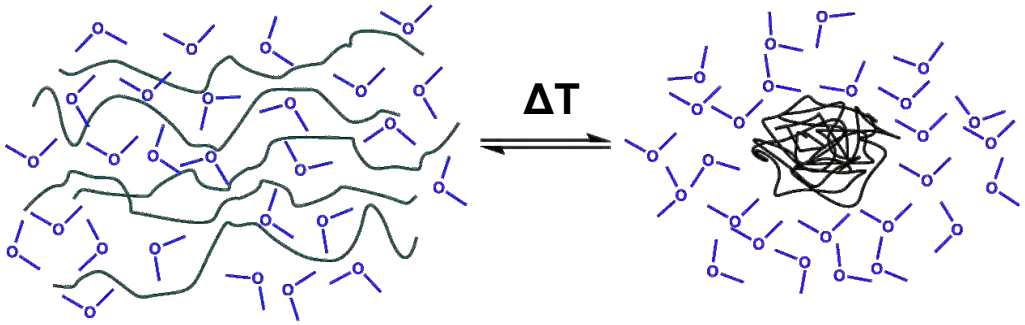
- pNIPAAM exhibits inverse solubility upon heating
- This is referred to as the LCST (Lower Critical Solution Temperature)
- Typically this temperature lies between 30-35^{o}C, but the exact temperature is a function of the (macro)molecular microstructure
- Upon reaching the LCST the polymer undergoes a dramatic volume change, as the hydrated polymer chains collapse to a globular structure, expelling the bound water in the process

pNIPAAM



Hydrophilic

Hydrophobic

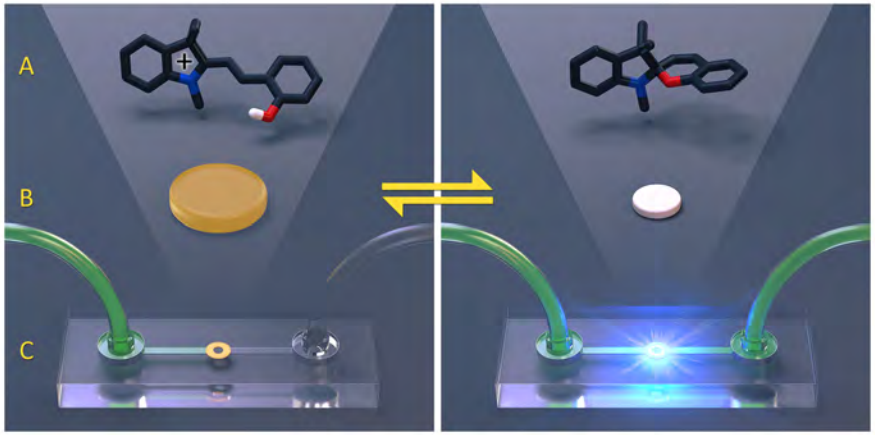


Hydrated Polymer Chains

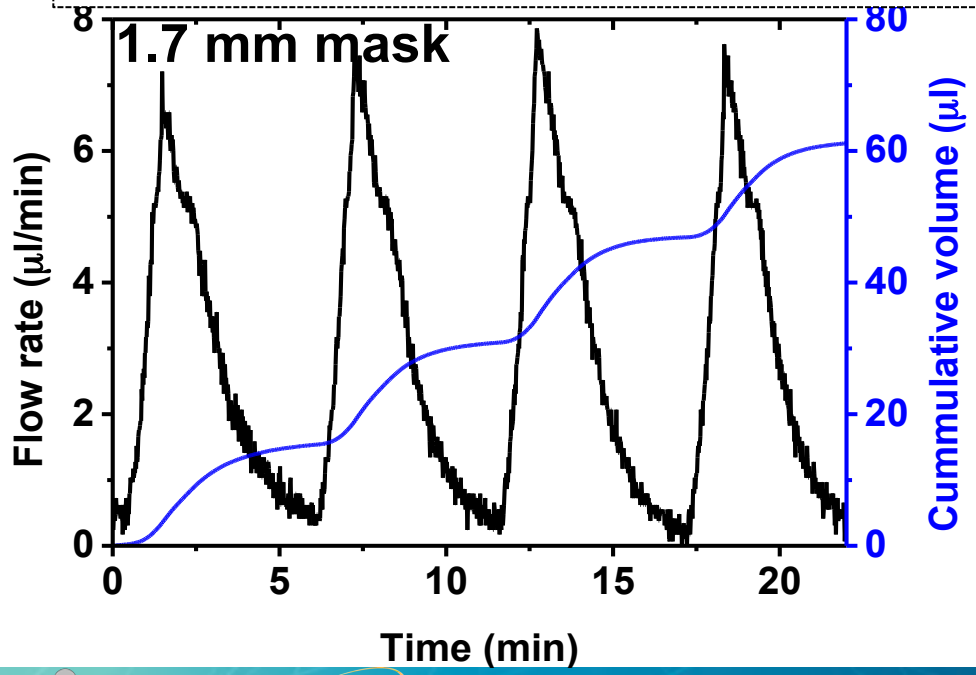
Loss of bound water -> polymer collapse

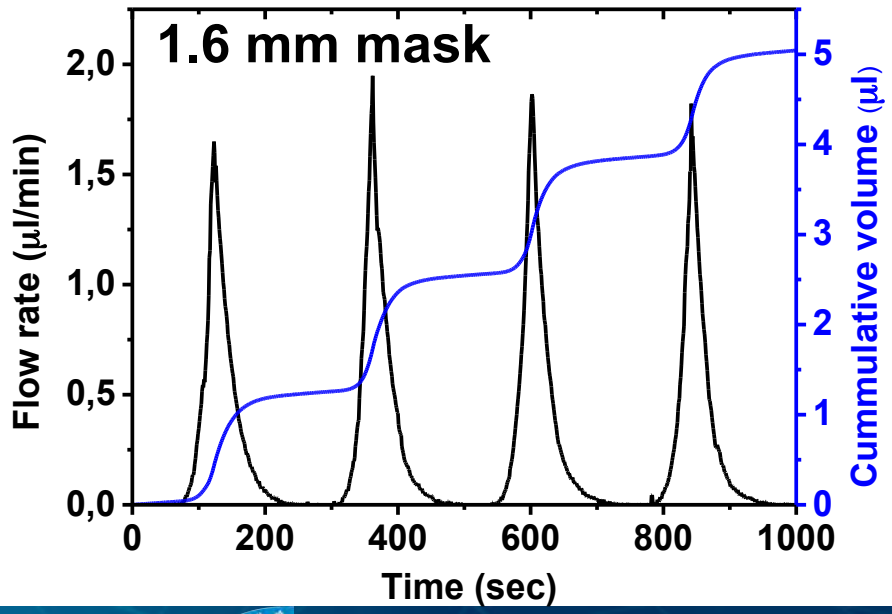
Valve Optimisation

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



From *'Molecular Design of Light-Responsive Hydrogels, For in Situ Generation of Fast and Reversible Valves for Microfluidic Applications'*, J. ter Schiphorst, S. Coleman, J.E. Stumpel, A. Ben Azouz, D. Diamond and A. P. H. J. Schenning, Chem. Mater., 27 (2015) 5925−5931. **(cover article)**





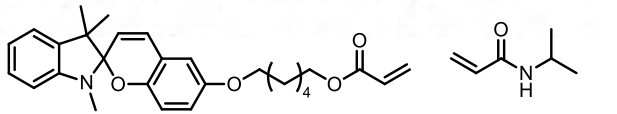
Photocontrol of Surface Features – Channel Surfaces Become 'Active'

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

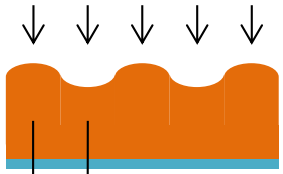
Jelle E. Stumpel,[†] Bartosz Ziółkowski,[‡] Larisa Florea,[‡] Dermot Diamond,[‡] Dirk J. Broer,*[,†,§] and Albertus P. H. J. Schenning*[,†,§]

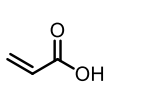


SPA, 1 mol%

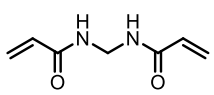
NIPAAM, 91-92 mol%

a)

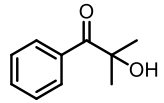




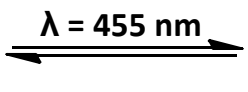
acrylic acid, 5 mol%



MBIS, 1-2 mol%



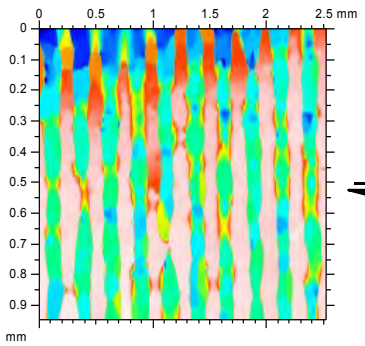
Darocur 1173, 1 mol%

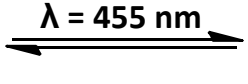


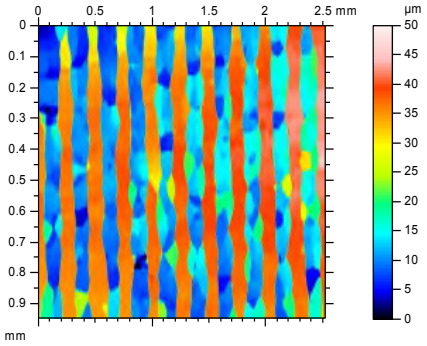
High crosslink density

Low crosslink density

b)







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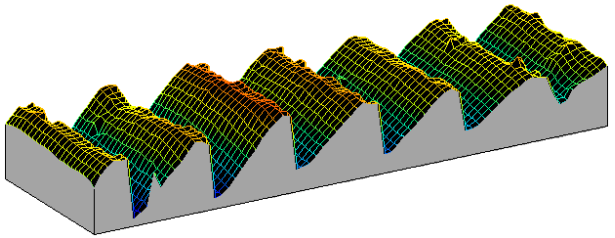

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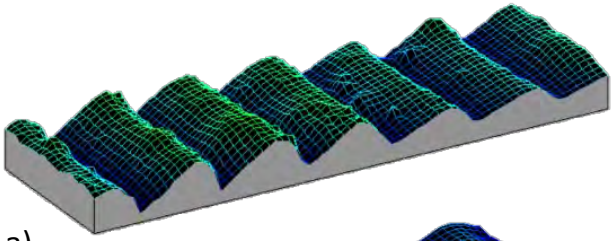

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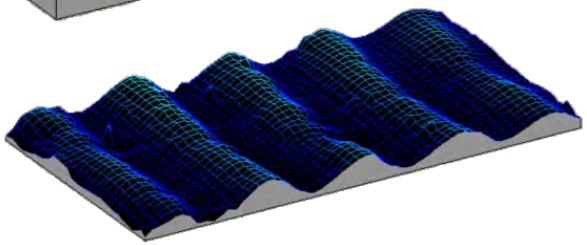
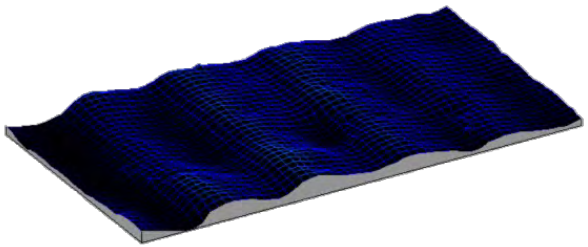
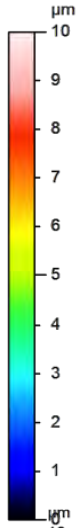
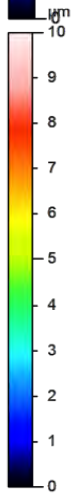


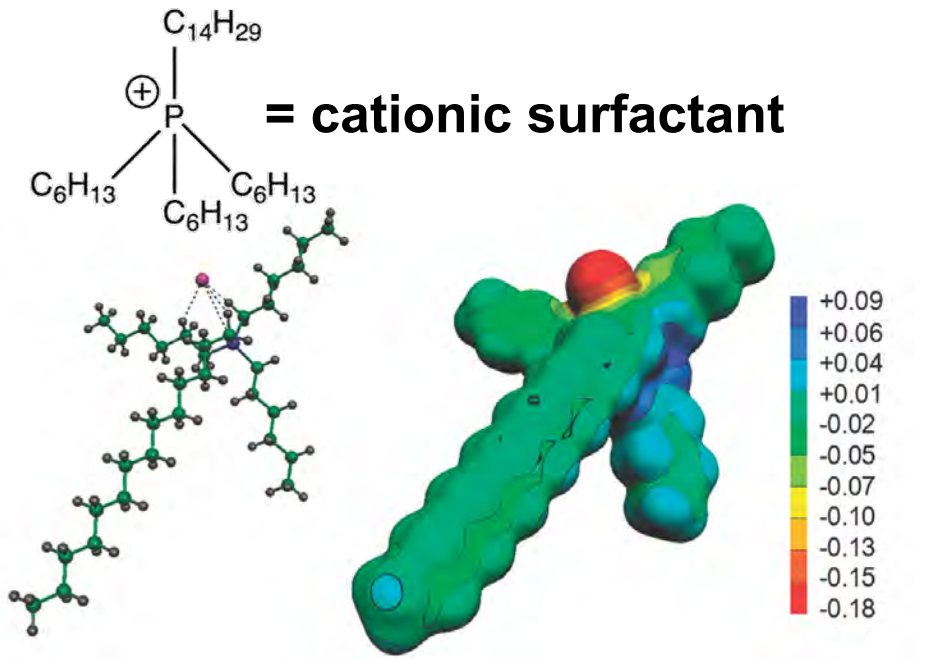
b)

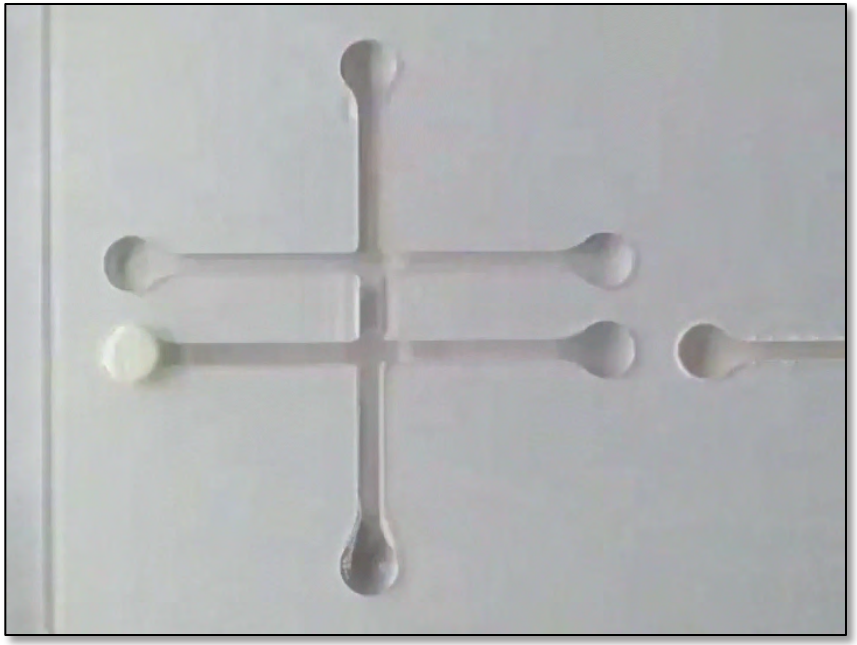






We can do the same with IL Droplets





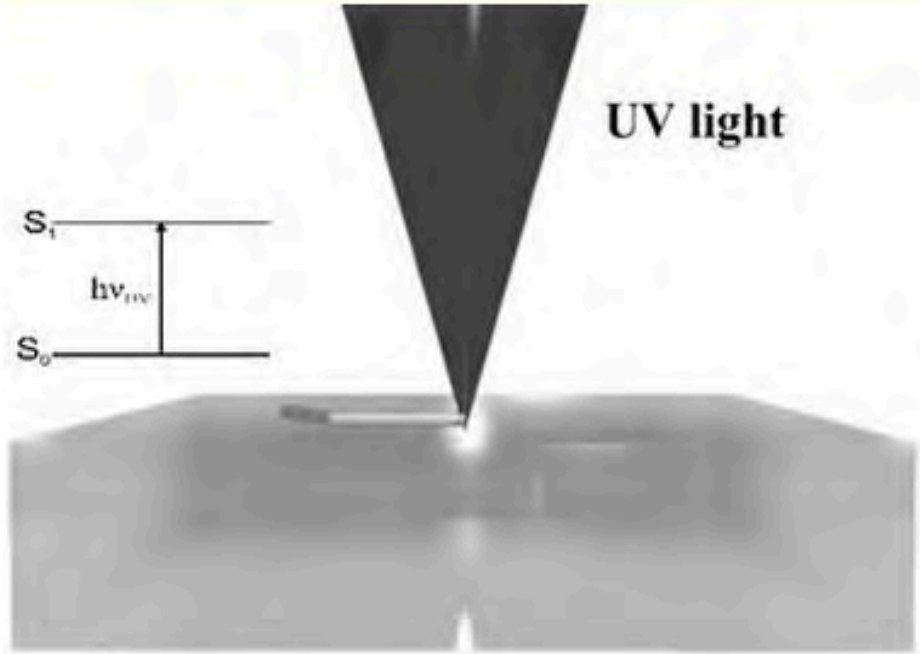
Trihexyl(tetradecyl)phosphonium chloride ($[P_{6,6,6,14}][Cl]$) droplets with a small amount of 1-(methylamino)anthraquinone red dye for visualization. The droplets spontaneously follow the gradient of the Cl^- ion which is created using a polyacrylamide gel pad soaked in 10^{-2} M HCl; A small amount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

Self-propelled chemotactic ionic liquid droplets, W. Francis, C. Fay, L. Florea, D. Diamond, Chemical Communications, 51 (2015) 2342-2344.

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.

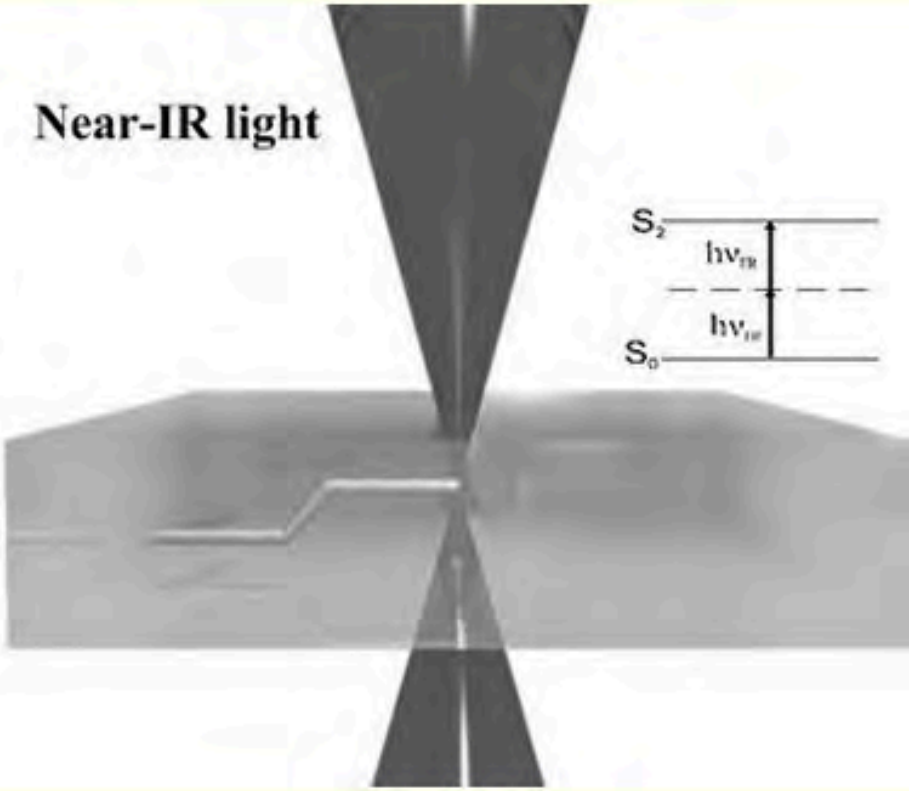
2-Photon Polymerisation

Stereolithography



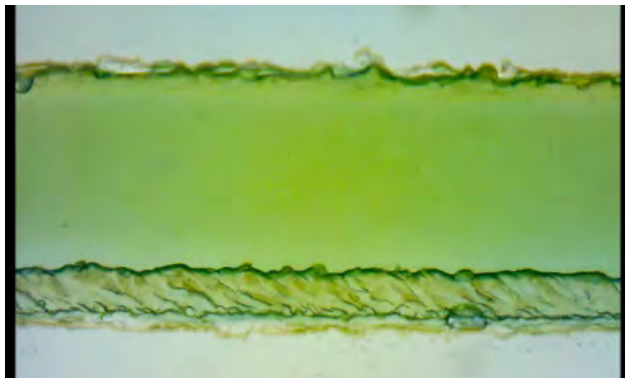
- Single photon absorption
- 2D patterns

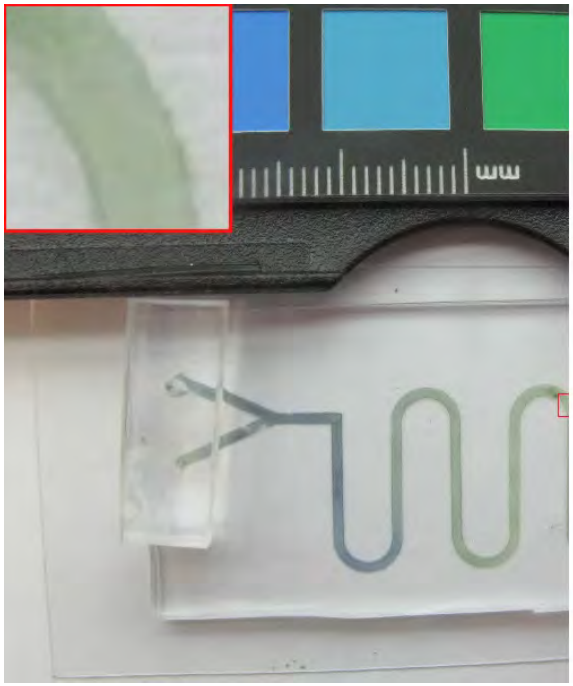
Two-photon polymerisation

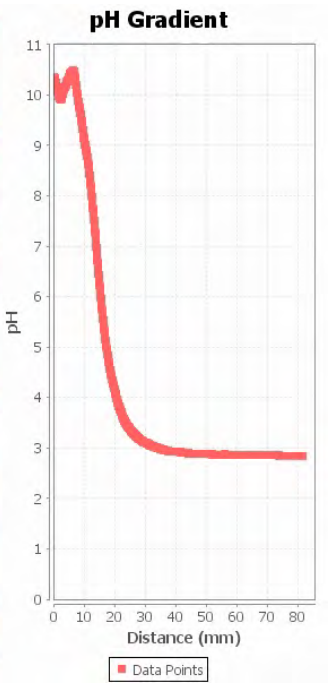


- Two photon absorption
- 3D structures

Channels that can sense…

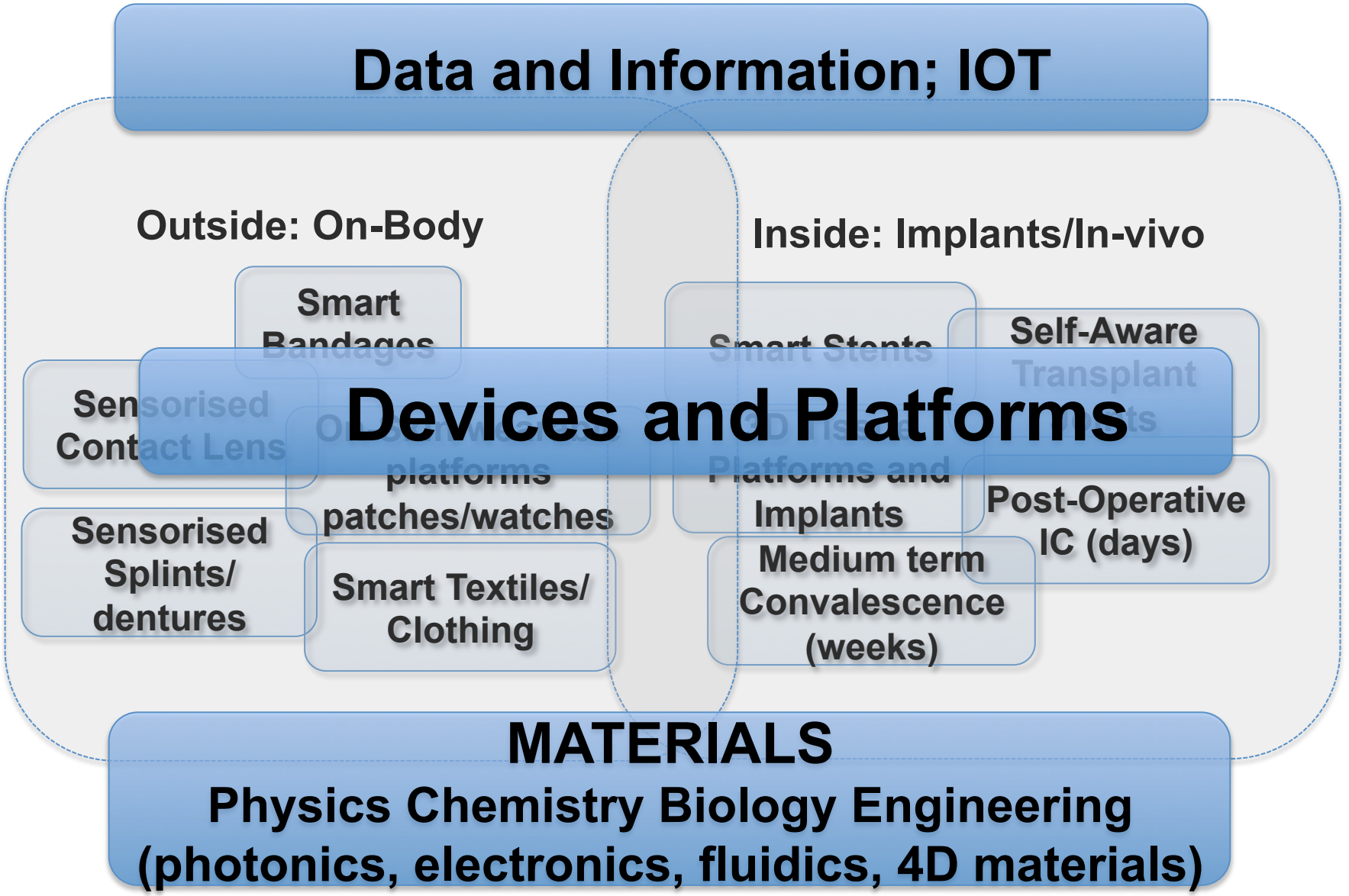






- PANi deposited on channel walls - Channels are now inherently responsive e.g. pH sensitive
- Status can be determined at any location within the channels using low cost digital imaging
- Presented at: μTAS 2011 (MicroTAS) Conference, Seattle, October 2-6, 2011

Near Term Applications (5Years)



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- Enterprise Ireland
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MASK
Project no: 269302
Materials and Advanced Sensor Knowledge Exchange