NCSR
National Centre for Sensor Research

Insight

# Can futuristic sensing platforms based on biomimetic microfluidics provide opportunities in bioprocess monitoring?

**Dermot Diamond, Akshay Shinde, Aleksander Glaz, Andrew Donohoe, Ruairi Barret, Margaret McCaul,**

**INSIGHT Centre for Data Analytics, National Centre for Sensor Research, School of Chemical Sciences, Dublin City University**

**Invited Lecture presented at**

**Trends in Environmental Biotechnology Symposium "Bio-hydrogen and bio-chemical production for Ireland's circular economy"**

**NUI-Galway, 31st October 2019**

THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
HORIZON 2020
HoliFAB

**Jean Louis Viovy (Fluigent-Curie), Mark Bowkett (TE Laboratories), Laurent Malaquin (LAAS-CNRS)**

HoliFAB

sfi DCU UCC OÉ Gaillimh NUI Galway UCD DUBLIN

# The Insight Centre for Data Analytics


Insight is one of the biggest data analytics centres in Europe. It undertakes high-impact research, seeks to derive value from Big Data and provides innovative technology solutions for industry and society by enabling better decision-making.

With **€88 million (ca.50% Industry)** in funding, Insight has 400 researchers across areas such as connected health, decision analytics, social media analytics, smart cities and the semantic web.

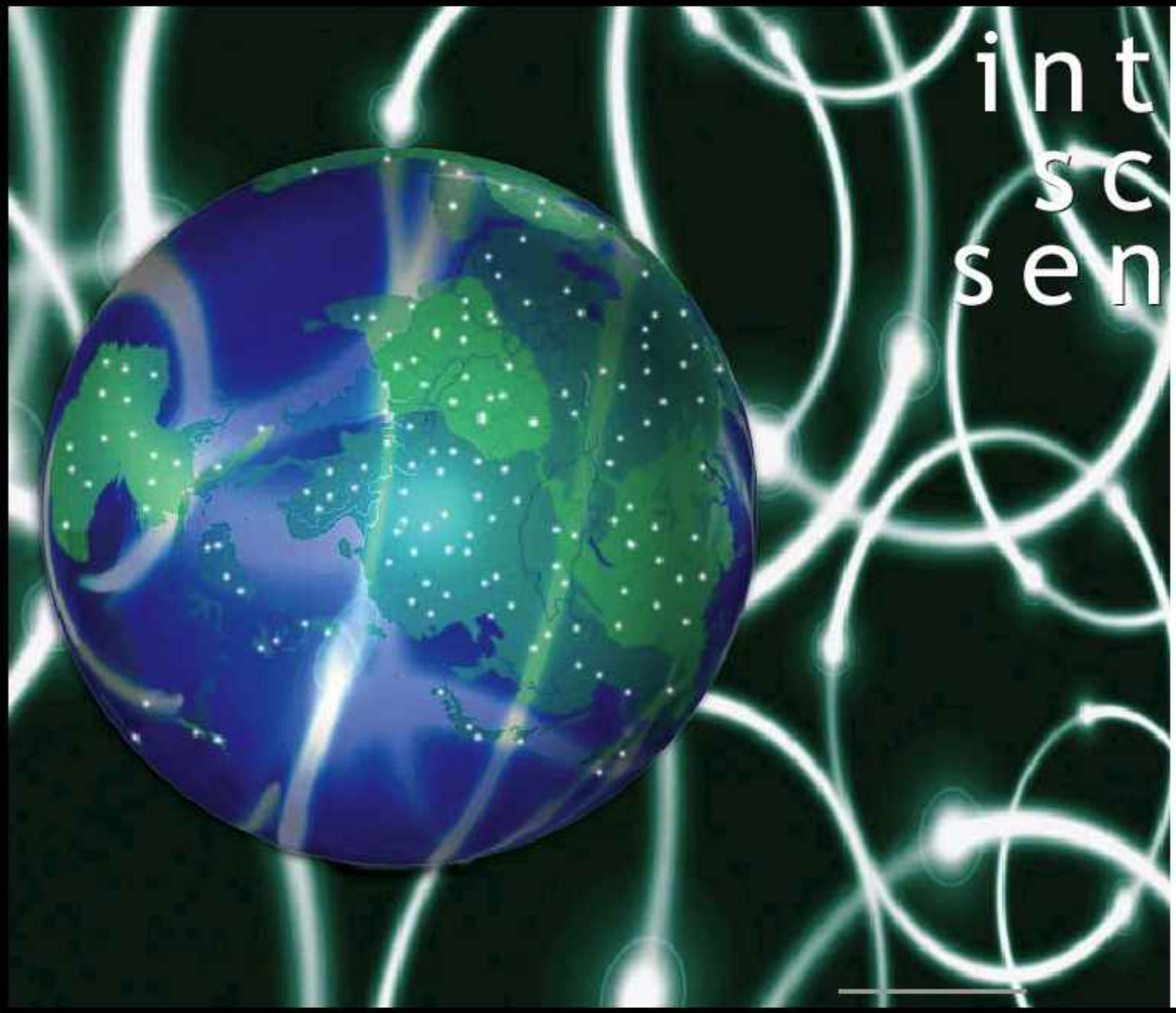
http://www.sfi.ie/sfi-research-centres/insight/

**2nd Phase funding approved (ca. €50 million SFI) commencing autumn 2019**

# Internet of (Biochemical) Things IO$_{BC}$T

- **Bridging the Molecular and Digital Worlds**
  - Emergence of 'Internet of Analytical Things', Internet of 'Molecular Things', 'Internet of Biochemical Things'
- **Long-Term "Deploy and Forget" use model**
  - Embedded 'smartness'
    - Sensing (temperature, light-level, imaging, vibration)
    - Communications (wireless)
    - Power (10-year battery life-time, energy scavenging capability)
  - Awareness of
    - Surrounding environment
    - Internal (functional) condition

# Keynote Article: Anal. Chem., 76 (2004) 278A-286A



## 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.

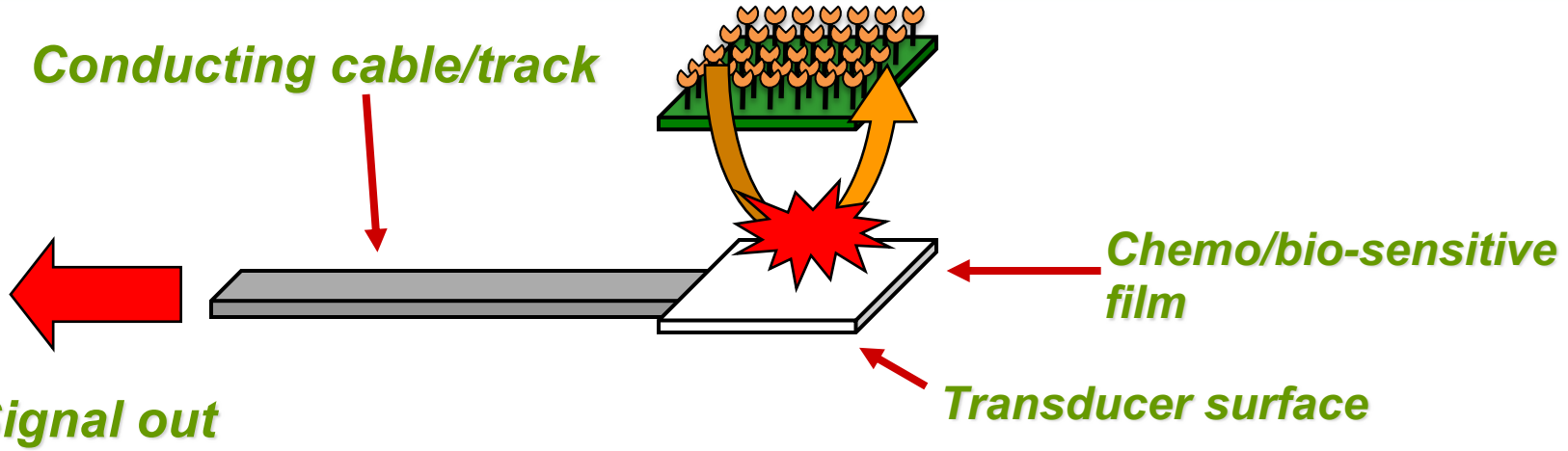
Digital communications networks are at the heart of modern society. The digitization of communications, the development of the Internet, and the availability of relatively inexpensive but powerful mobile computing technologies have established a global communications network capable of linking billions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

Ron Ambrosio & Alex Morrow, IBM TJ Watson

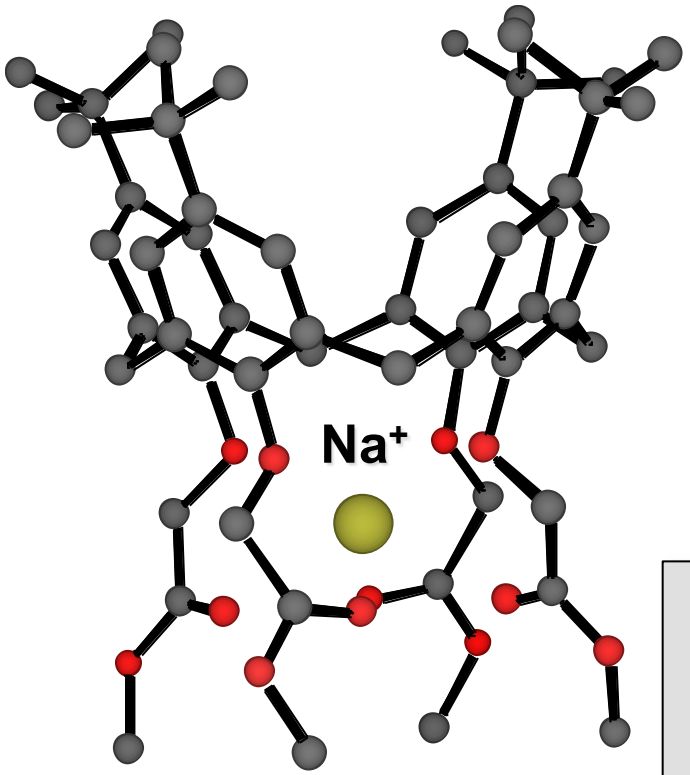
# What is a 'Bio/Chemical Sensor?

***'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'***

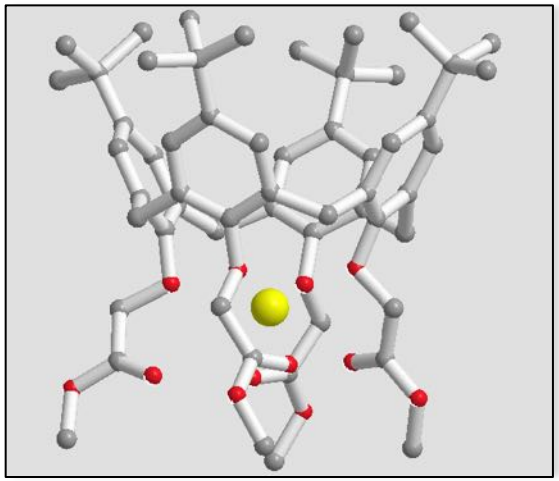



Chemo/Bio-sensing involves selective **BINDING** & **TRANSDUCTION** on the device surface; this also implies the target analyte MUST meet the device surface (**LOCATION** & **MOVEMENT**). It provides a signal observable in the macroscopic world (**COMMUNICATION**)

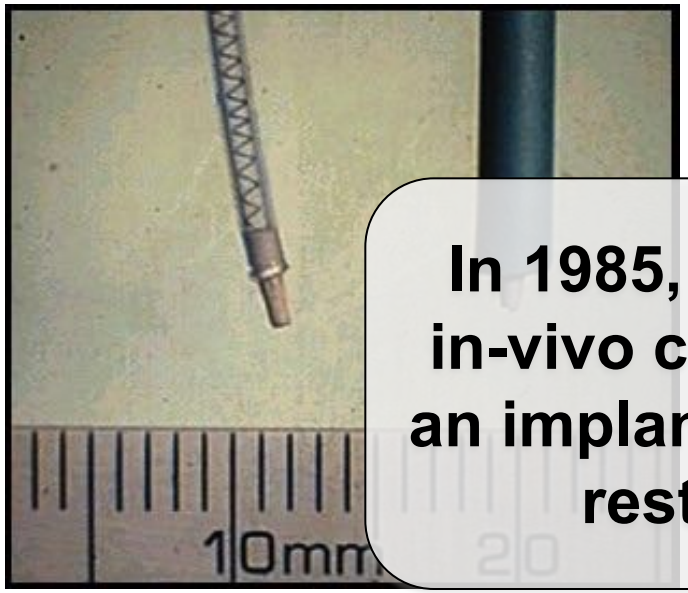
# Calixarene Ionophores – controlling the selectivity





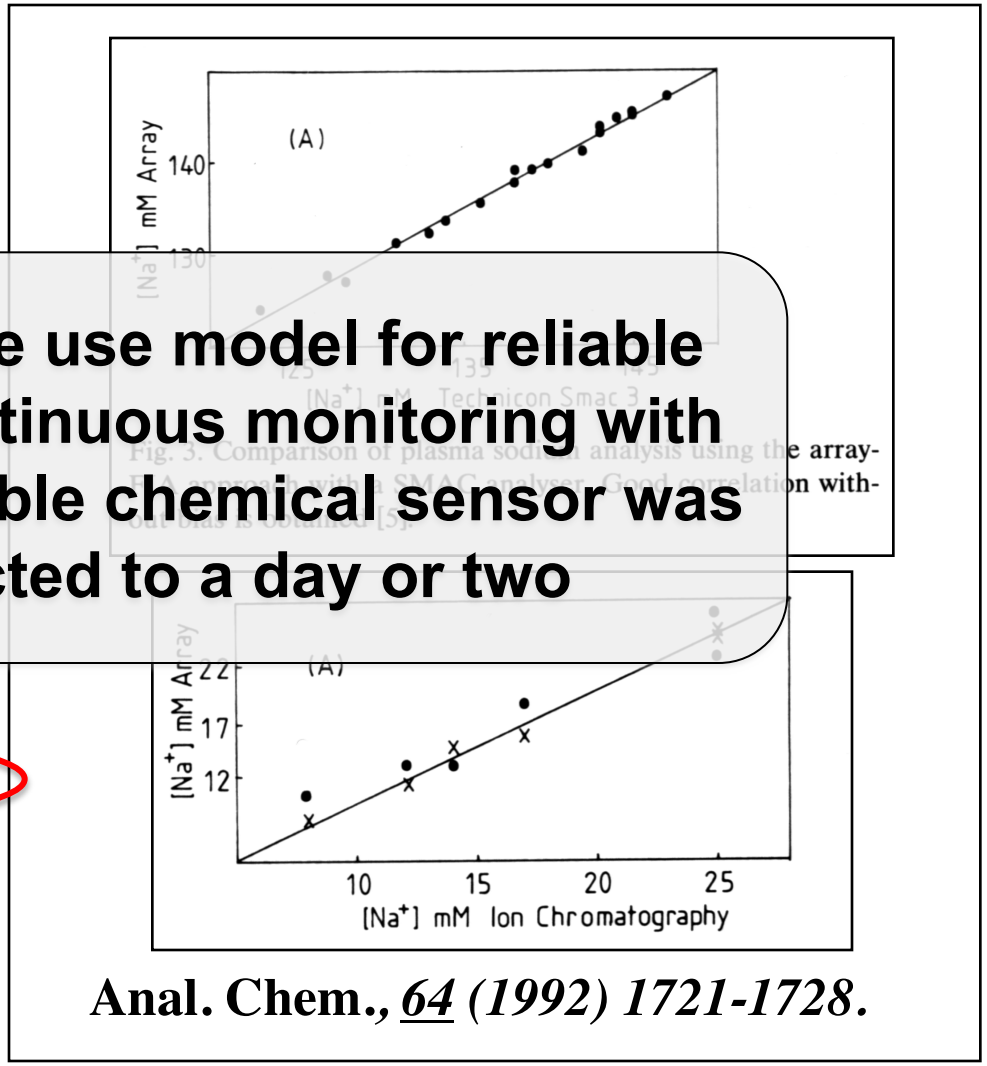
# Blood Analysis; Implantible Sensors




**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**

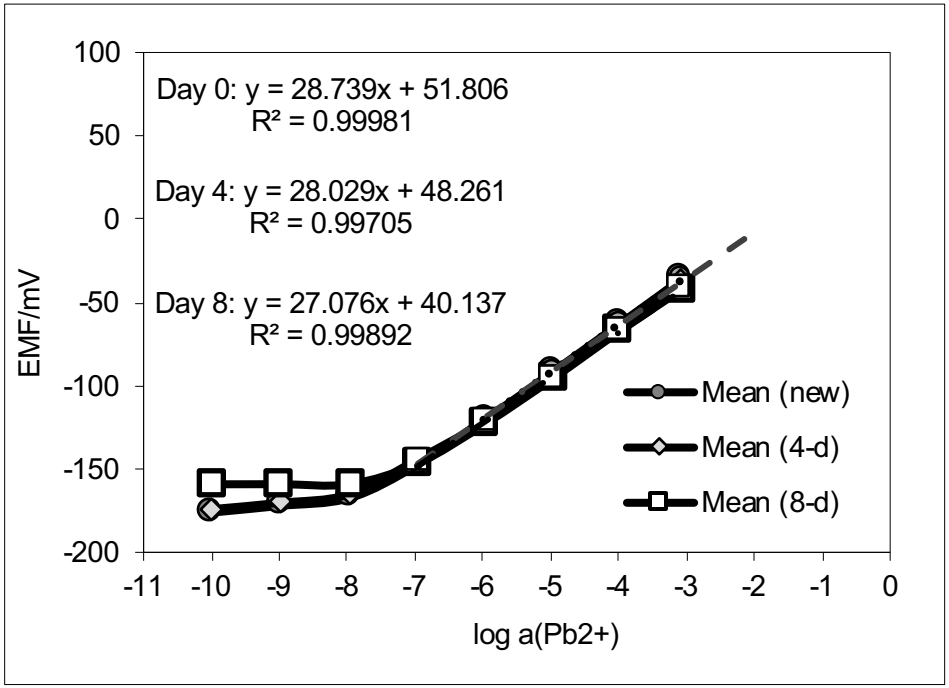
**Dr. David Band, St Thomas's Hospital London**

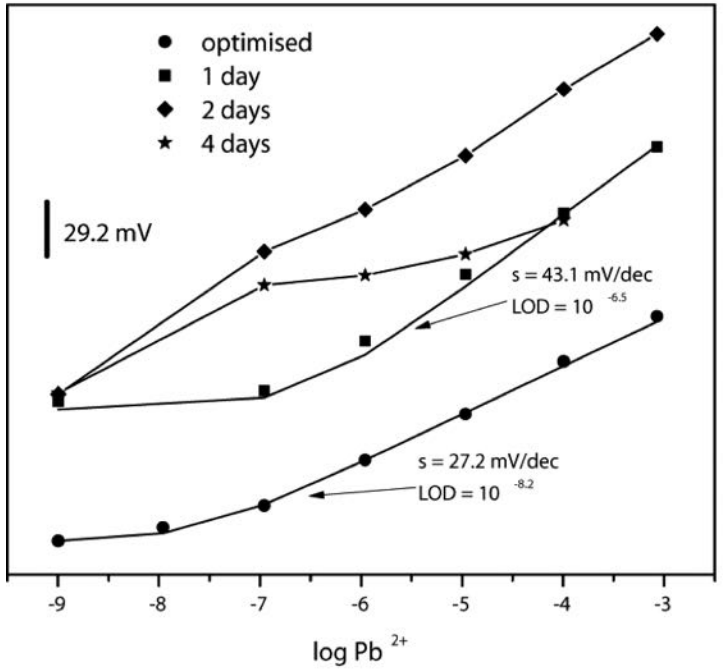



Anal. Chem., *64 (1992) 1721-1728.*

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

# Continuous Use: $Hg^{2+}$ in River Water



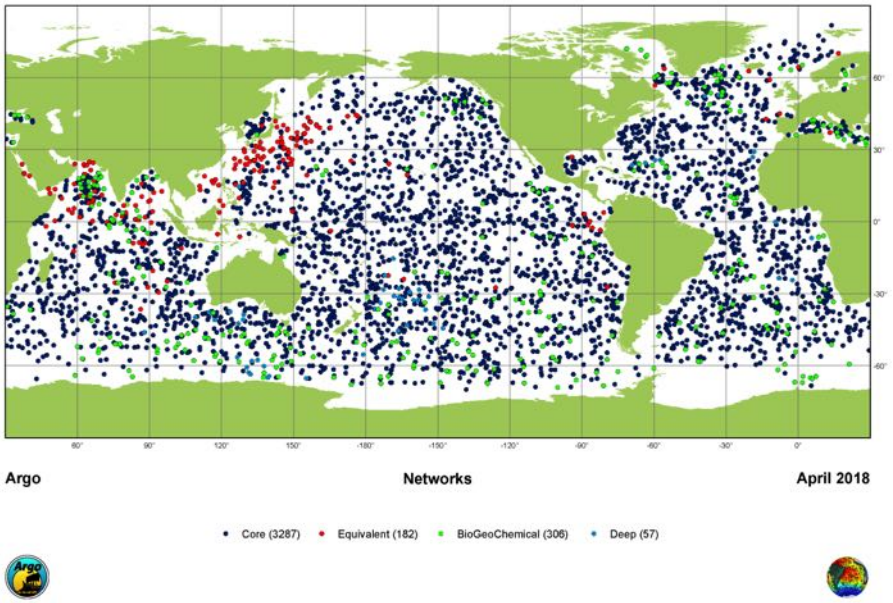



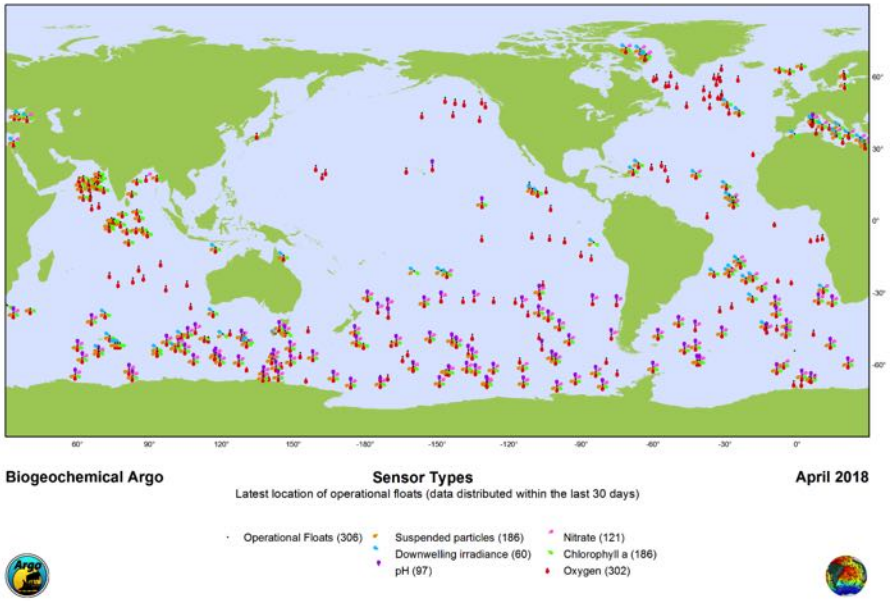

**stored in $10^{-9}$M $Pb^{2+}$, pH=4, in the lab**

**Continuous contact with river water**


**Anastasova, S.; Radu, A.; Matzeu, G.; Zuliani, C.; Mattinen, U.; Bobacka, J.; Diamond, D.; Disposable Solid-Contact Ion-Selective Electrodes for Environmental Monitoring of Lead with PPB Limit-of-Detection. *ELECTROCHIMICA ACTA* 2012, *73*, 93–97.**

# Argo Project (accessed May 2018)

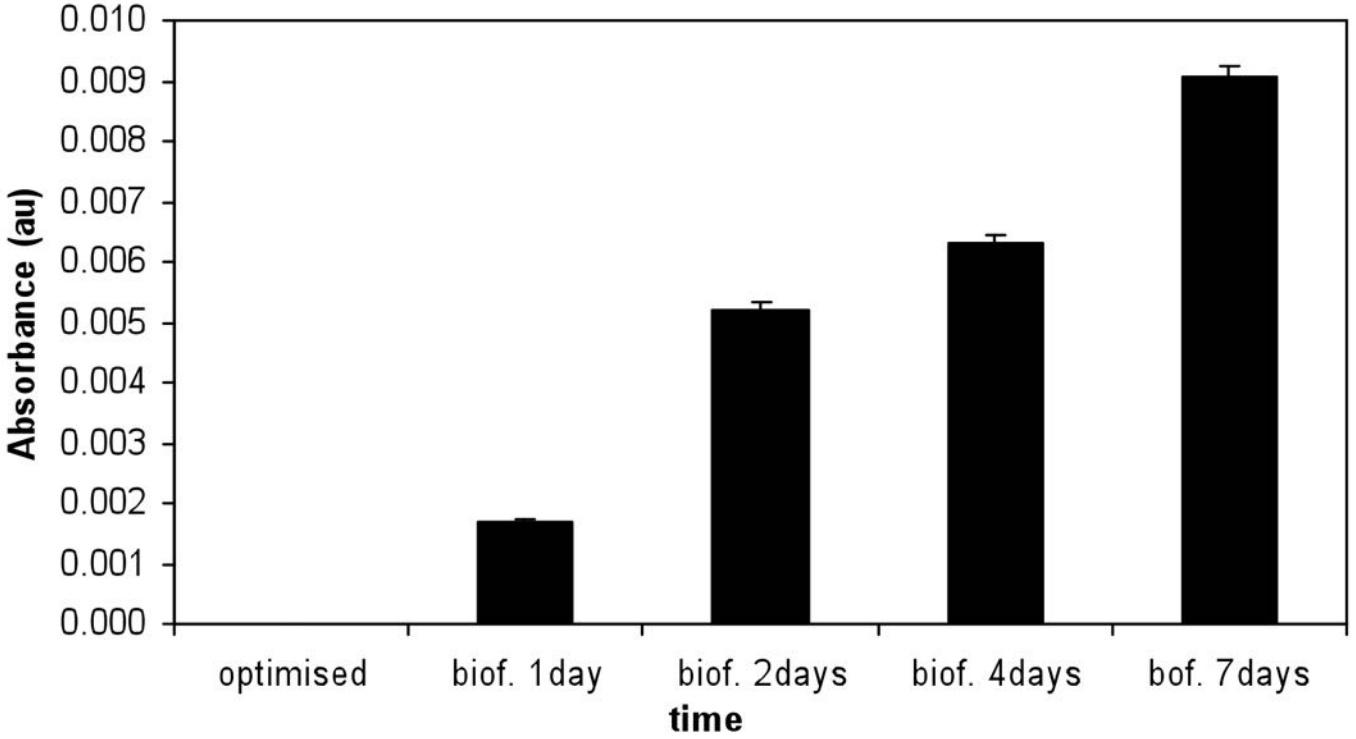



Argo (2000). Argo float data and metadata from Global Data Assembly Centre (Argo GDAC) http://doi.org/10.17882/42182

**Core: 3287 Biochemical:306**
**Suspended particles: 186; Nitrate: 121 Chlorophyll: 186 pH: 97 DO: 302**

# Biofilm Formation on Sensors



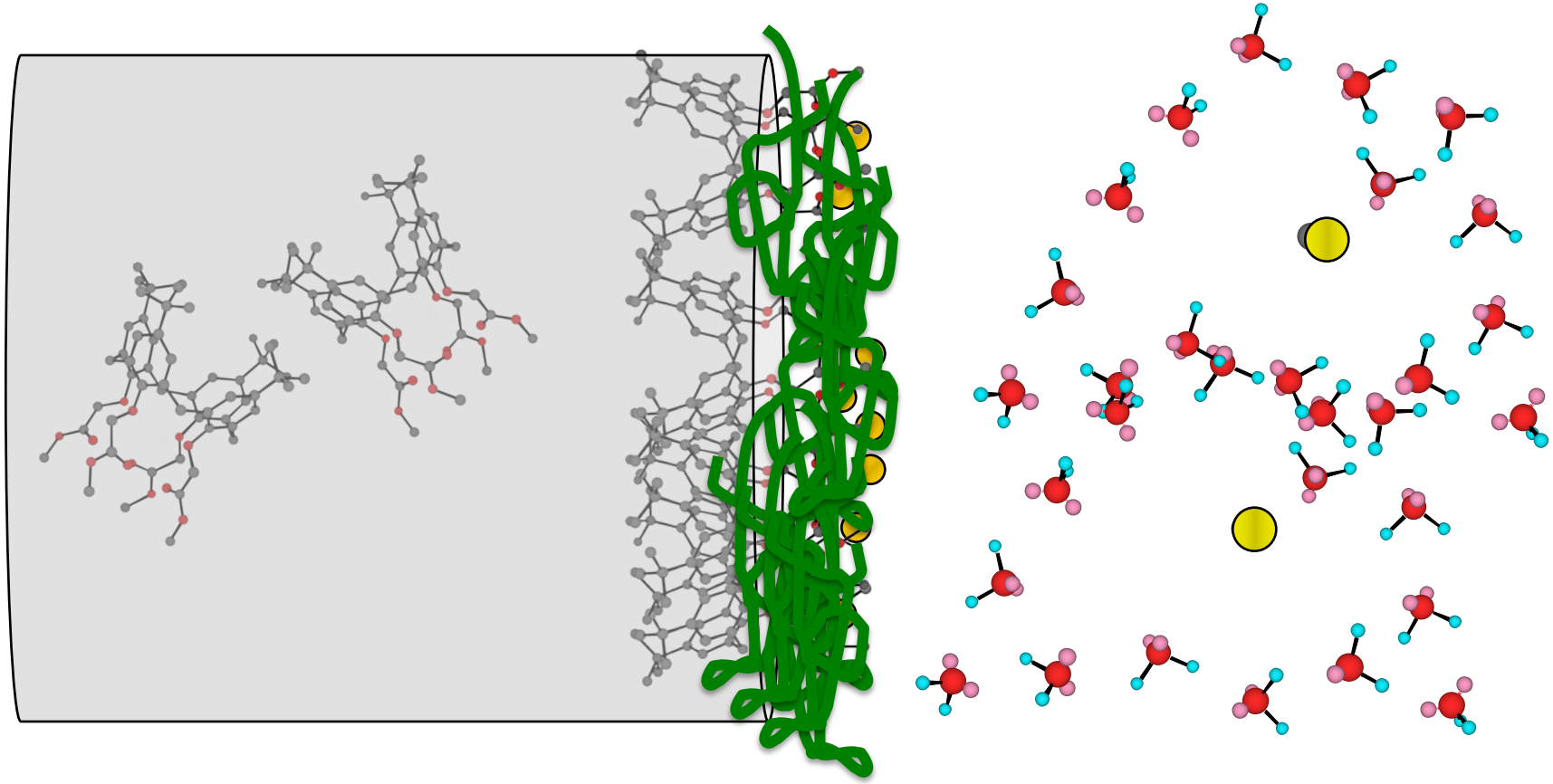

New electrode

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

**Anastasova, S.; Radu, A.; Matzeu, G.; Zuliani, C.; Mattinen, U.; Bobacka, J.; Diamond, D.; Disposable Solid-Contact Ion-Selective Electrodes for Environmental Monitoring of Lead with Ppb Limit-of-Detection. *ELECTROCHIMICA ACTA* 2012, *73*, 93–97.**

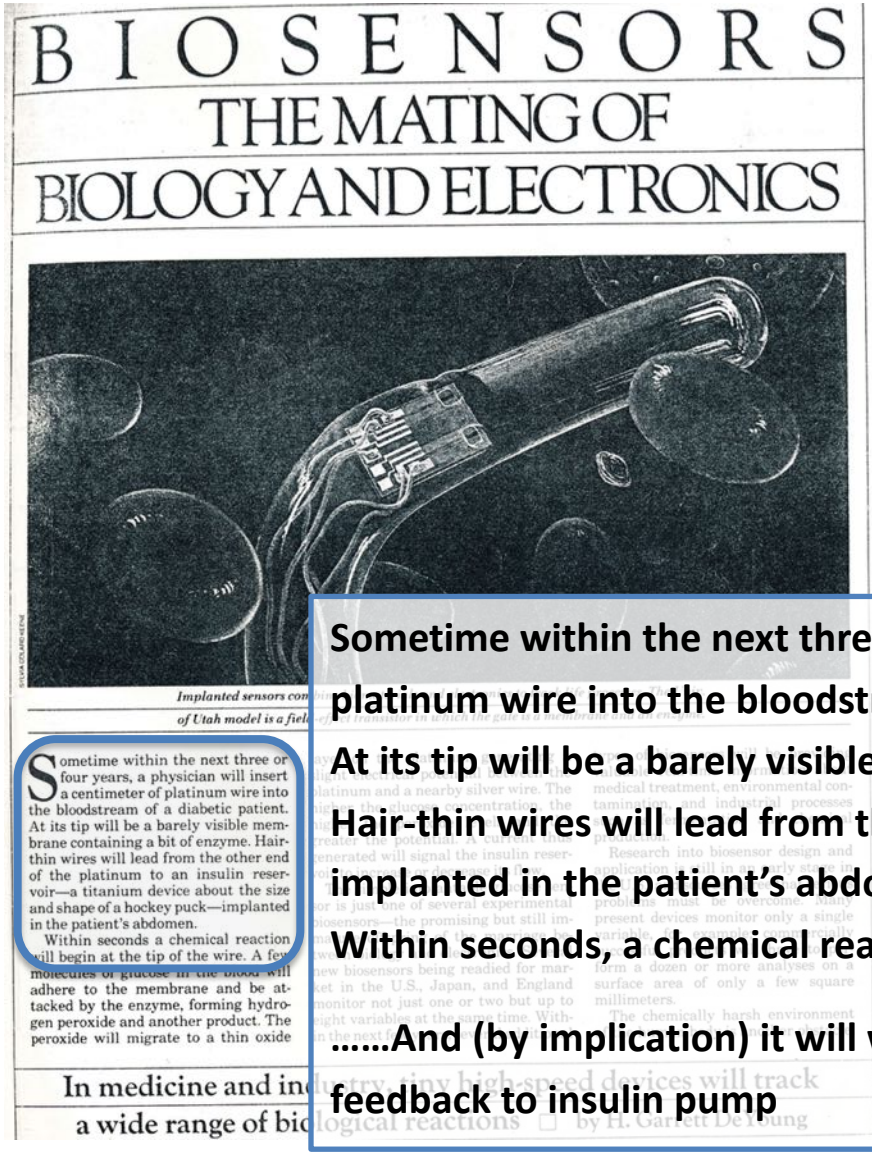
# Osberstown – 3 week deployment

# Control of membrane interfacial exchange & binding processes



**Remote, Long-term, autonomous chemical sensing is a tricky business! Regular calibration is essential.**

# 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.

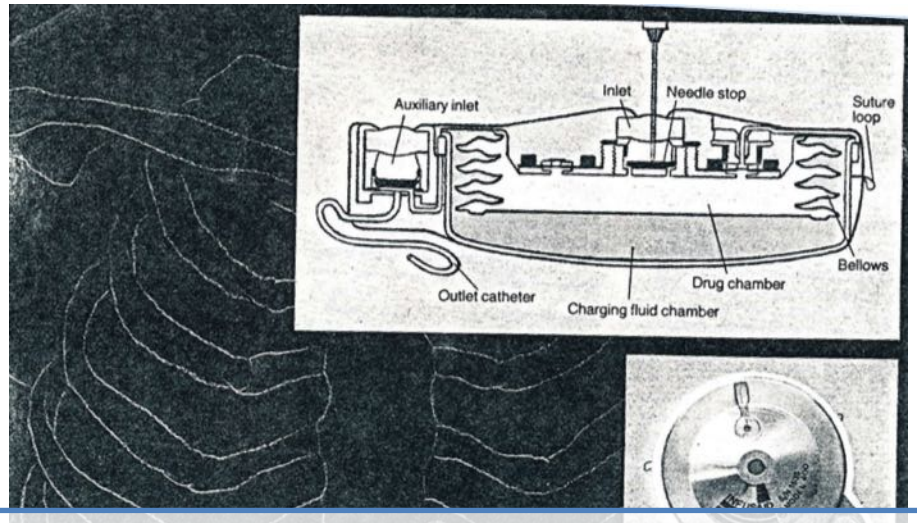
Within seconds a chemical reaction will begin at the tip of the wire. A few molecules of glucose in the blood will adhere to the membrane and be attacked by the enzyme, forming hydrogen peroxide and another product. The peroxide will migrate to a thin oxide

In medicine and in… a wide range of bio…

…try, tiny high-speed devices will track …logical reactions

by H. Garrett De Young

**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**

# After Ca. 40 years – Dominant Use Model is 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

# Sensor Research Activity

**WOS Search 26/08/2019**
**"Graphene AND Biosensor OR Chemical Sensor"**
**= 6,178 papers**

**This research will not advance the lifetime and stability issues that inhibit the broader use of Biochemical Sensors**

# What is happening?

- To publish in top journals it is not enough to present really interesting fundamental research
- There must be an application!!

**Why is Bioprocess Monitoring so poorly connected as a potential application for emerging sensors??**

# Bioprocess Monitoring

- **Real-time monitoring requirement**
- **Limited time duration?**
- **Constrained molecular environment**
- **Need to maintain sterile conditions?**
- **Tethered vs. Untethered Sensing?**
- **What should be monitored?**
  - Physical parameters: temperature, colour, pressure
  - Chemical (1): Headspace composition, pH, DO, ions..
  - Chemical (2): Organics – in-situ vs. sampling
  - Biologicals: ?????

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

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

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

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

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

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

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

Increasing difficulty & cost

Increasing scalability

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

Reliable sensors available, relatively low cost

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

**On-land Water/ Monitoring**

More accessible locations

Target concentrations tend to be higher

Infrastructure available

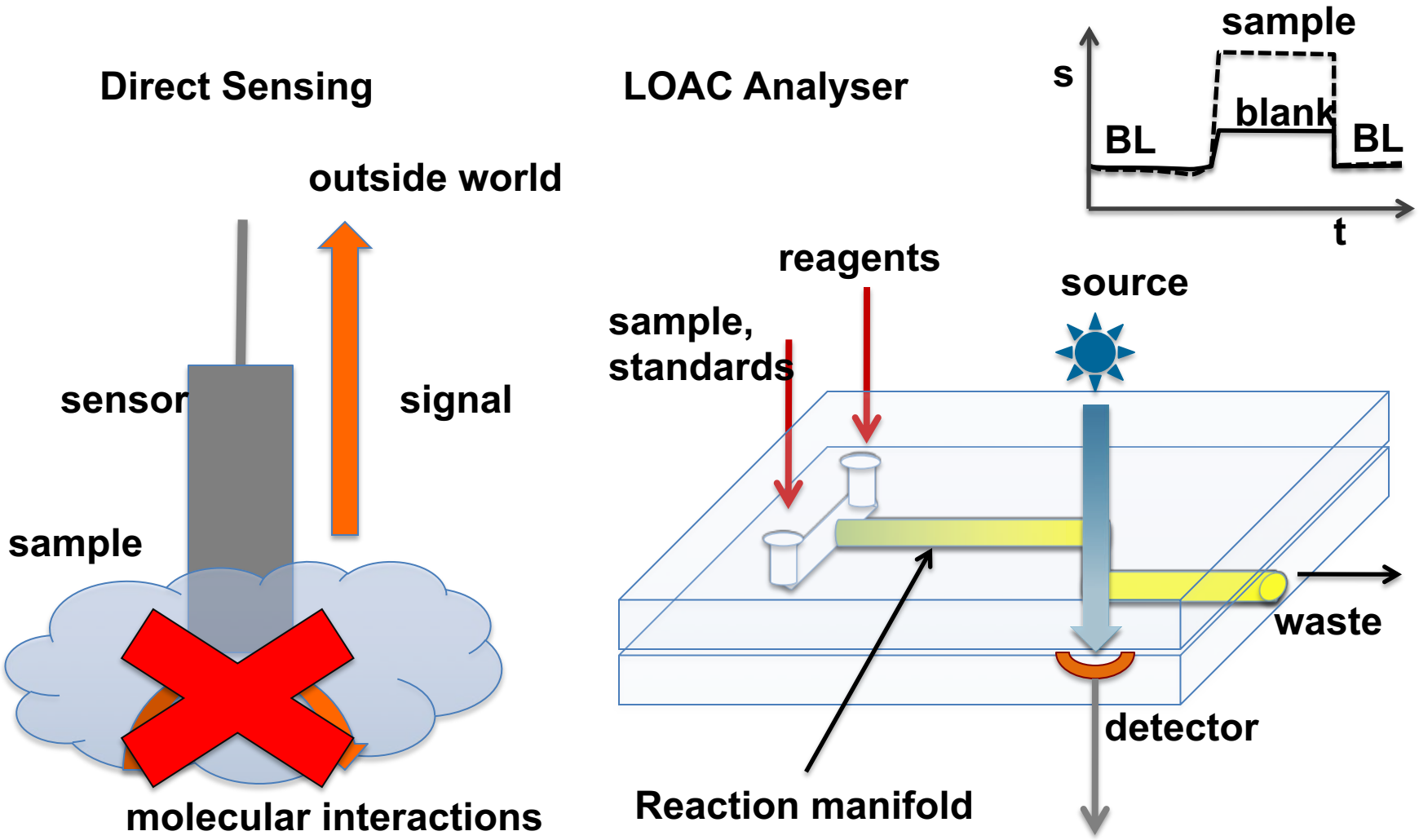
**Marine Water**

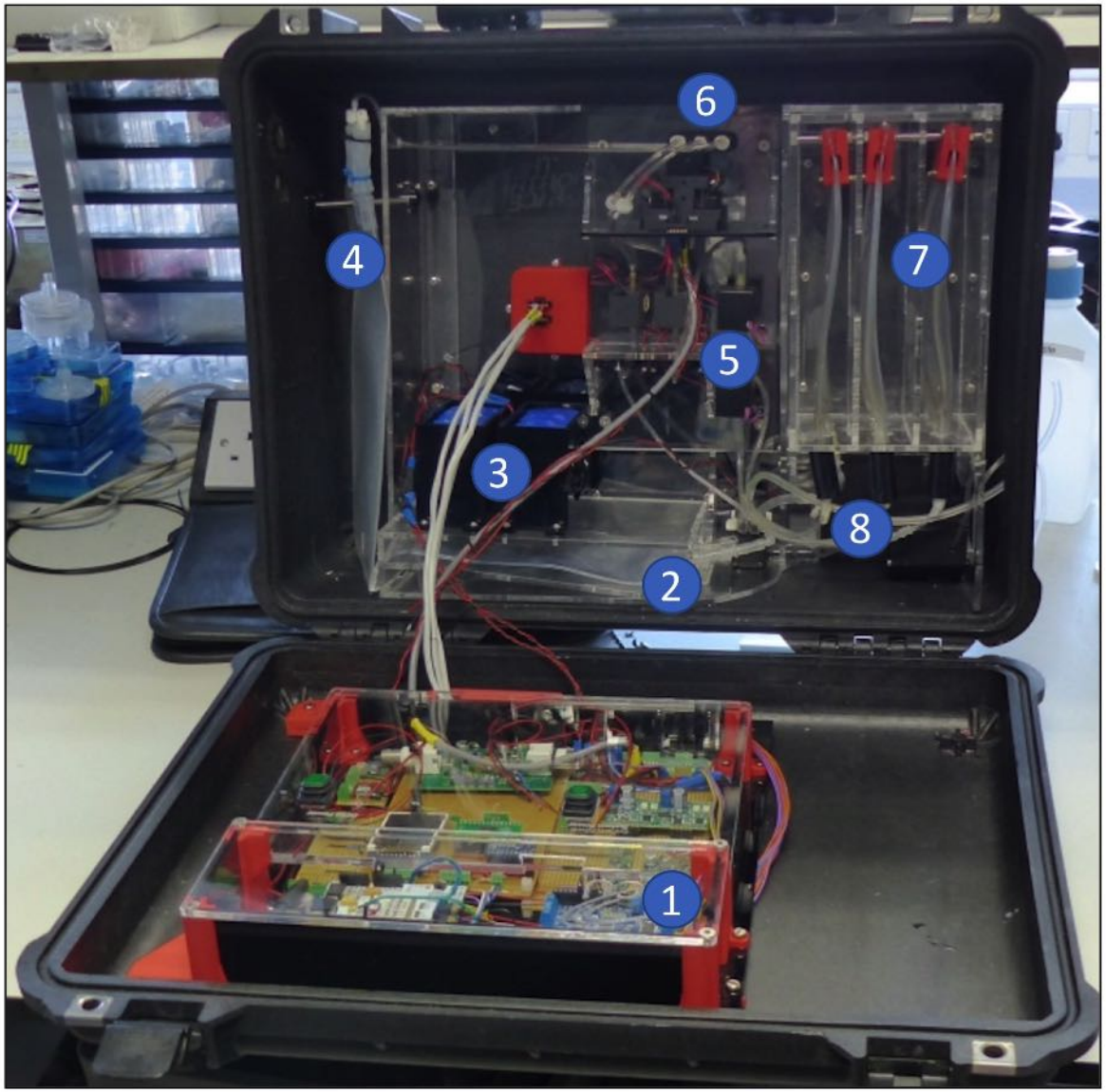
Challenging conditions

Remote locations & Limited infrastructure

Concentrations tend to be lower and tighter in range

# Direct Sensing vs. Reagent Based LOAC/ufluidics






# Nutrient Platform
## (Phosphate $PO_4^{3-}$)

1. Electronics for Autonomous operation, Detection and Data Transmittance
2. Reagent Bag
3. Battery
4. Waste Bag
5. Pumps and Valves for Fluid Handling
6. Microfluidic Chip, LED (375nm) and Photodiode
7. Sample, High and Low Calibration standard bags
8. Inlet System

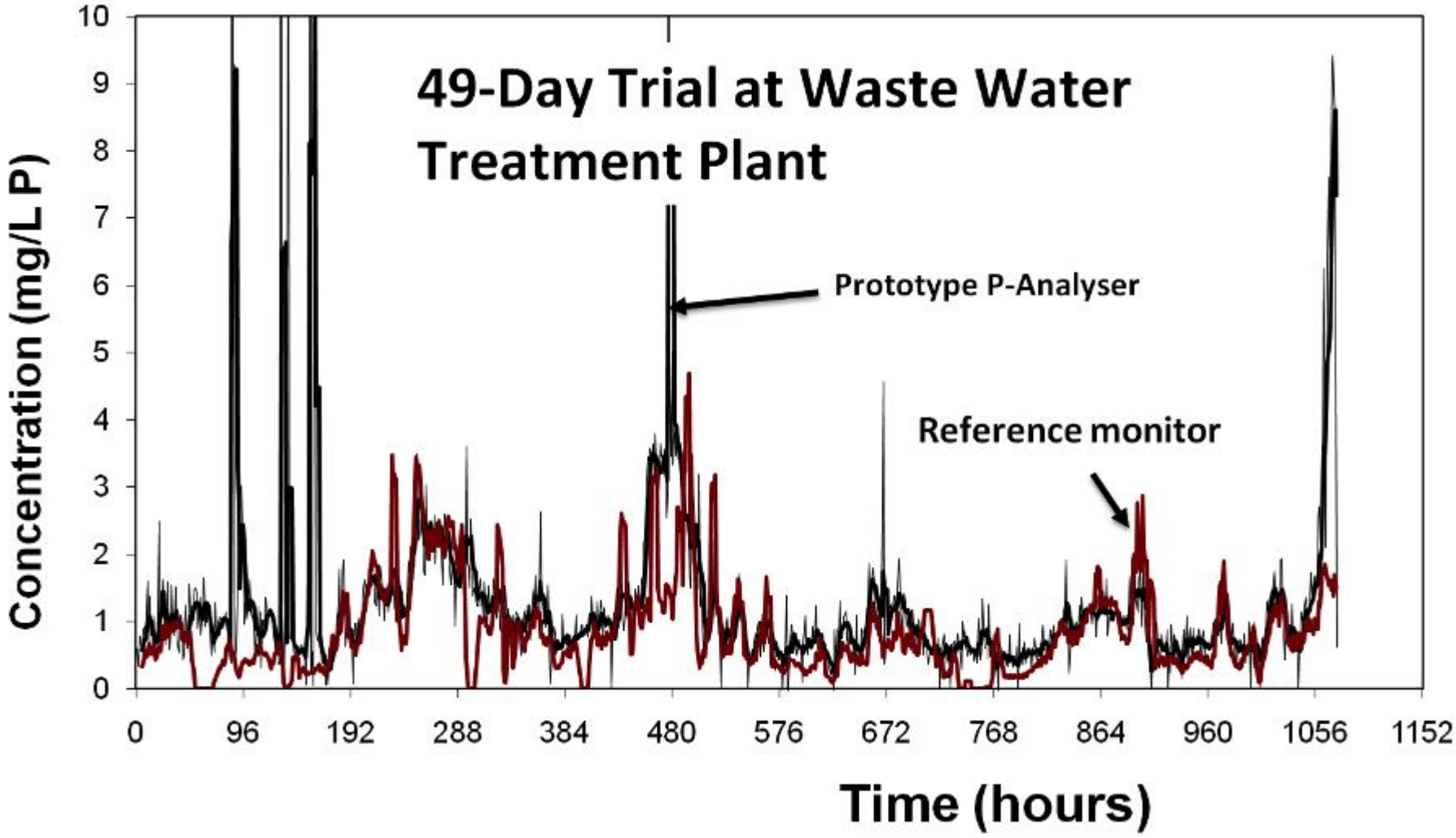
# Prototype Testing – Generation 3

## Milano San Rocco WWTP

Available Sampling Points:

1. Output water after Sand Filtration
2. Output water after the Clarifier
3. Activated Sludge (Biological Tank)
4. Input Water

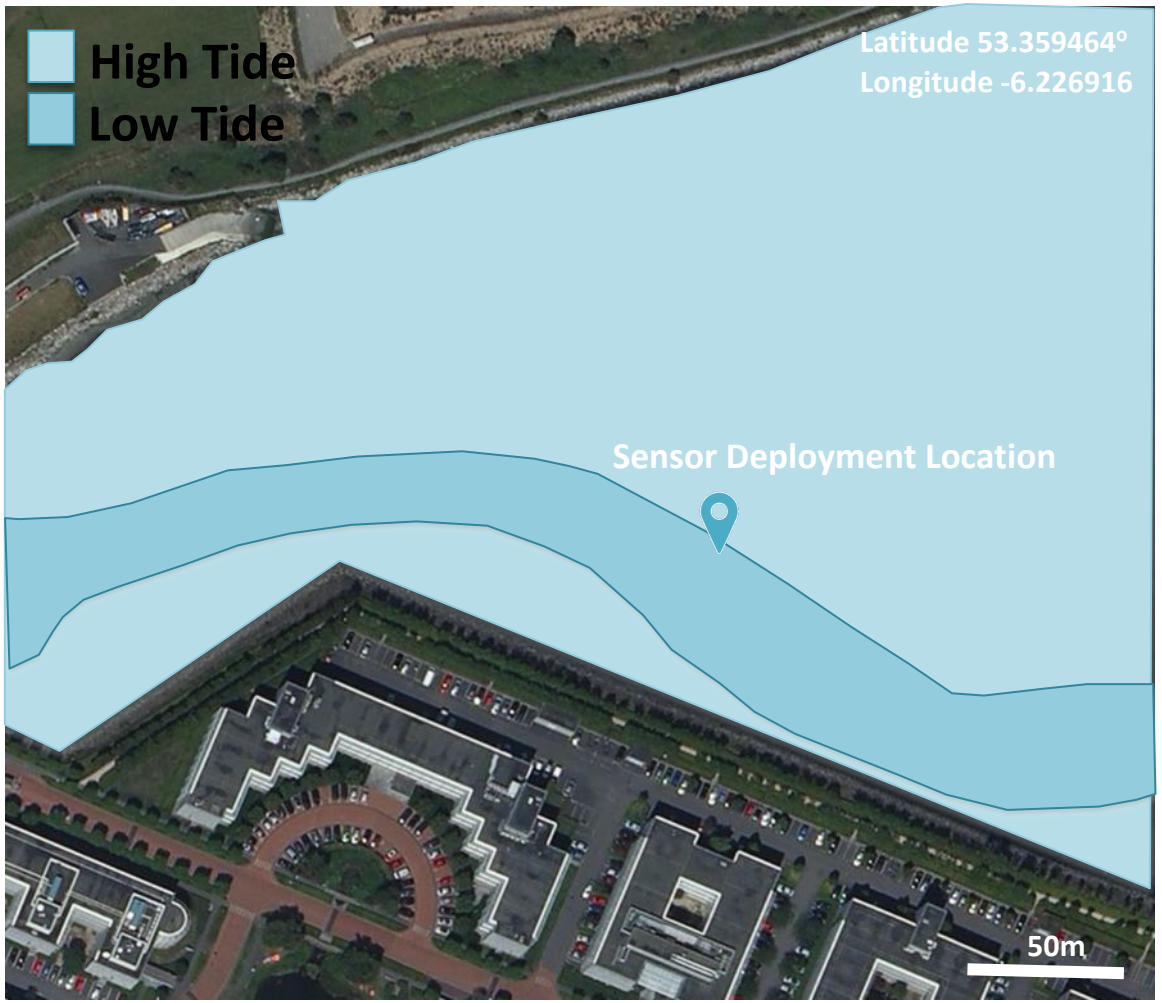
# Autonomous Chemical Analyser



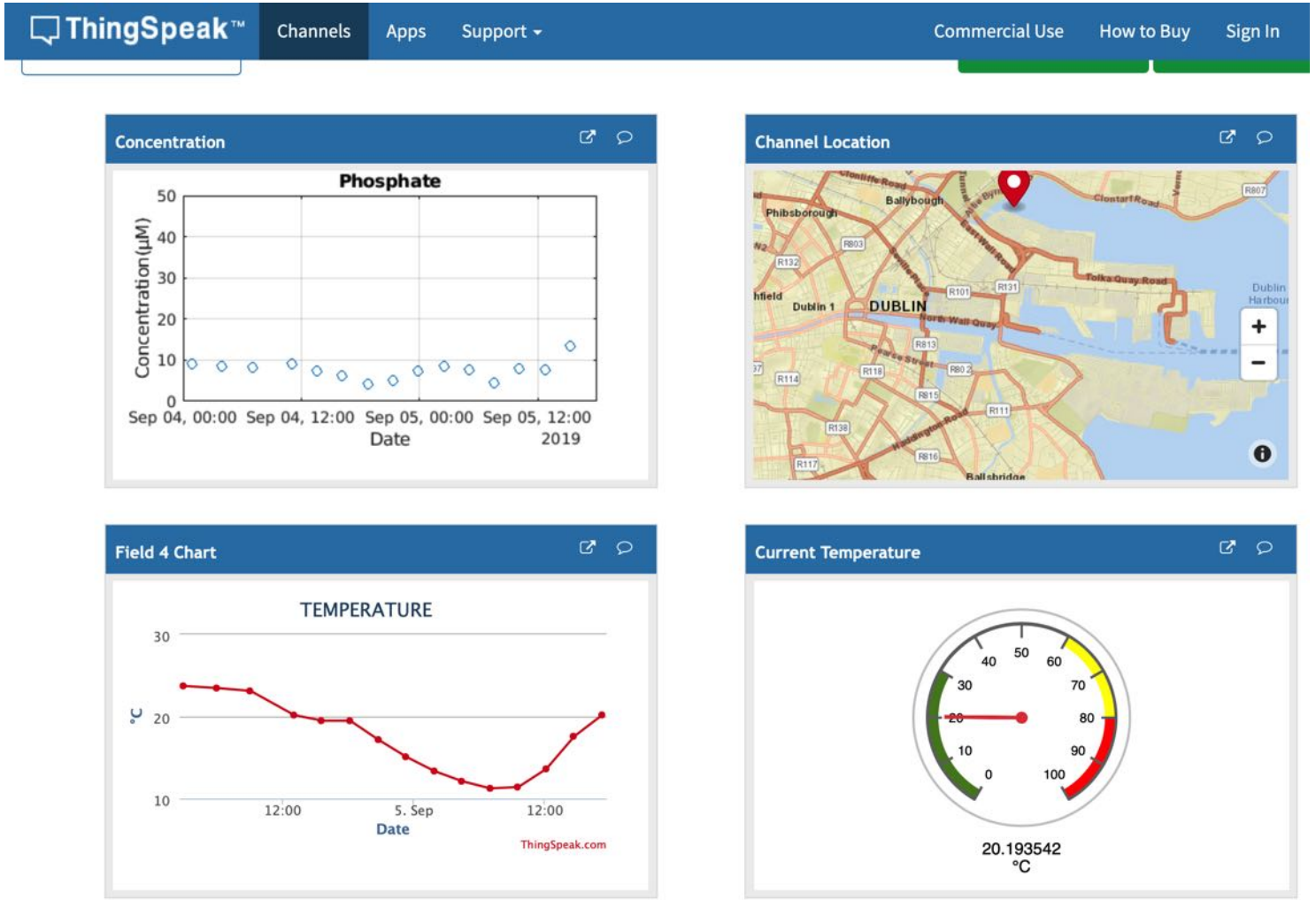

J. Cleary, C. Slater, D. Diamond, Analysis of phosphate in wastewater using an autonomous microfluidics-based analyser, World Academy of Science, Engineering and Technology. 52 (2009) 196–199.


High Tide


Low Tide


High Tide
Low Tide
Latitude 53.359464°
Longitude -6.226916
Sensor Deployment Location
50m

# 3D Printed Chip – Live Feed




https://thingspeak.com/channels/786279

# Water Quality – Dublin Bay

## Failure of Ringsend tank led to sewage discharge into Dublin Bay

An investigation into the cause of the incident is ongoing, Irish Water says

Tue, Feb 26, 2019, 06:00

**Kevin O'Sullivan** Environment & Science Editor

An aerial photograph taken at Poolbeg, Dublin, shows a large discharge was continuing at 5.45pm on Sunday evening. Photograph: Eoin O'Shaughnessy/ DublinCityShots

THE IRISH TIMES

LATEST NEWS MOST READ MEDIA IRELA

## Swimming banned at every south Dublin beach after overflow at treatment plant

Dún Laoghaire-Rathdown and city councils issue notices expected to last seven days

File image of Dollymount beach in Dublin. Photograph: Dara Mac Dónaill/The Irish Times

**Mark Hilliard**

Updated: about an hour ago

https://www.irishtimes.com/news/environment/swimming-banned-at-every-south-dublin-beach-after-overflow-at-treatment-plant-1.3917229

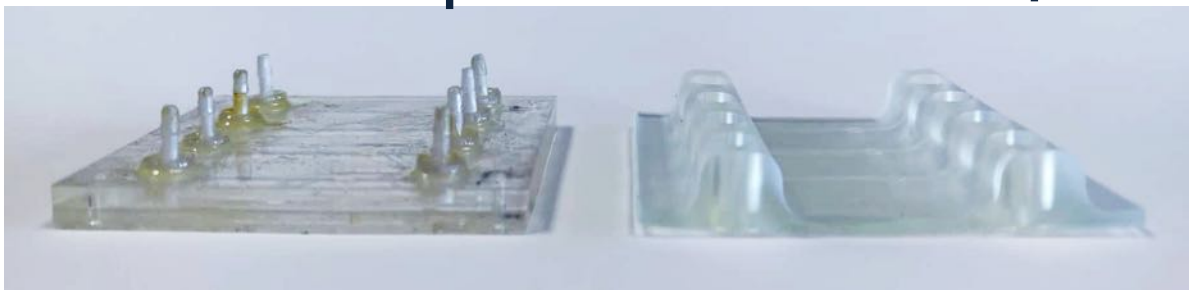
**Date Accessed 6th June 2019**

# Impact of 3d Printing

**Minimum thickness**

- Assembled chip 4.25 mm
- 3D Printed Chip 1.58 mm

**Assembled Chip** **Printed Chip**



**Advantages:**

- No Assembly
- No Bonding necessary
- Integrated barbs (1/16”)
- Chip thickness reduced by 63%
- Automated manufacturing

**Rendered Chip**

**Printed Chip**

# From Multi-Part to Single Part Fluidic Chips

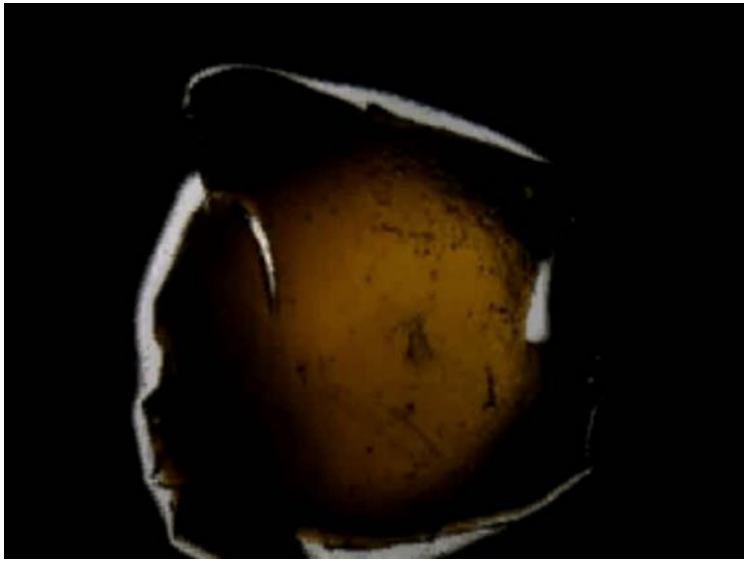
7 Parts : 3 days
~€50/chip

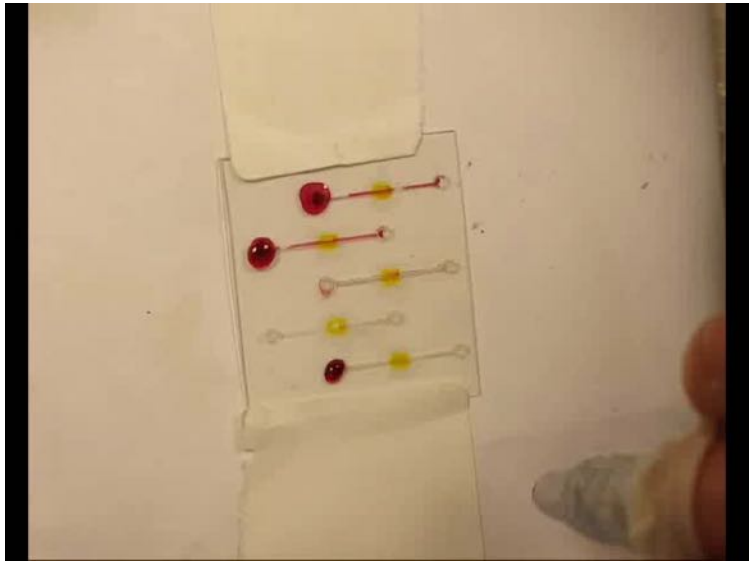
3 Parts : 1 day

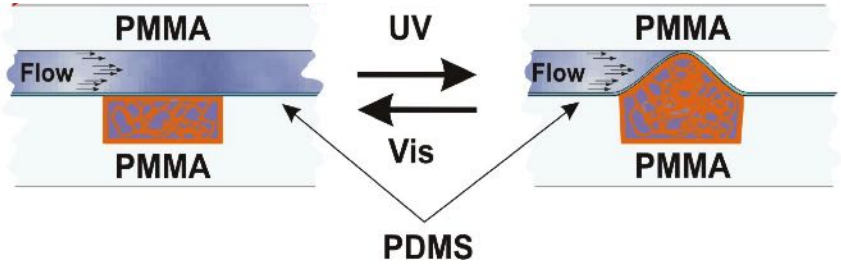
1 Part : 1 hour
~€1/chip

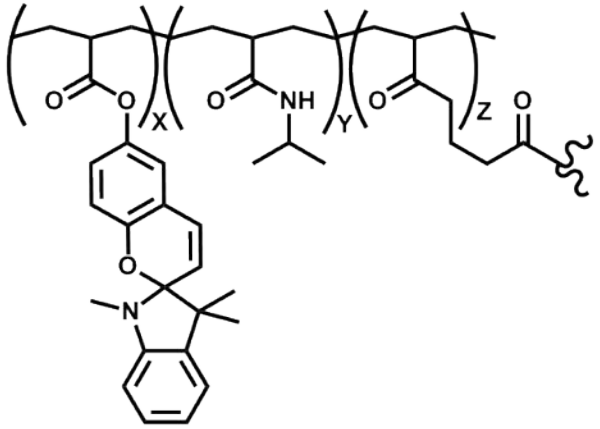
**With Laurent Malaquin (LAAS-CNRS)**

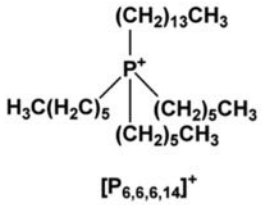
# Photo-actuator polymers as microvalves in microfluidic systems

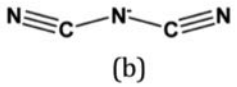






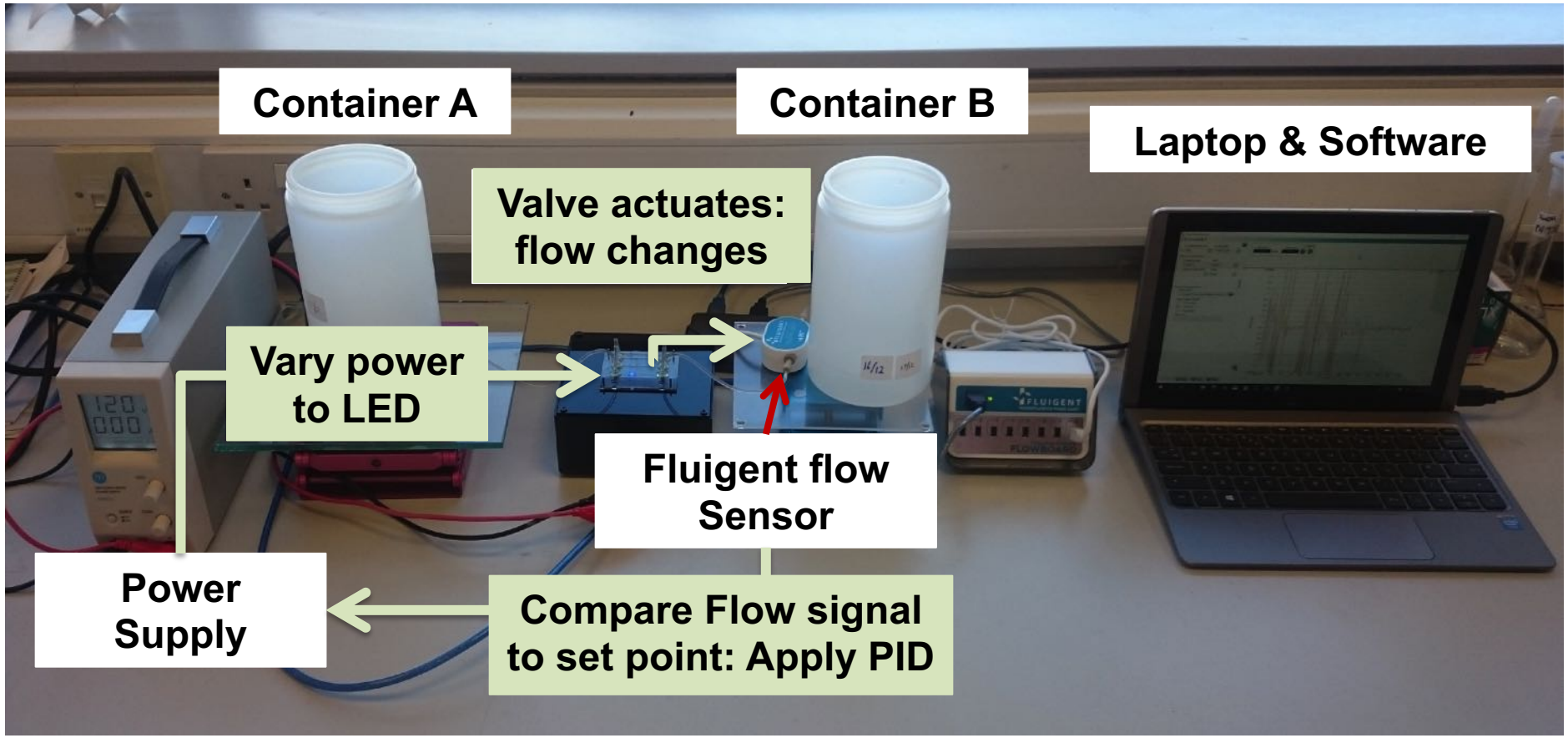



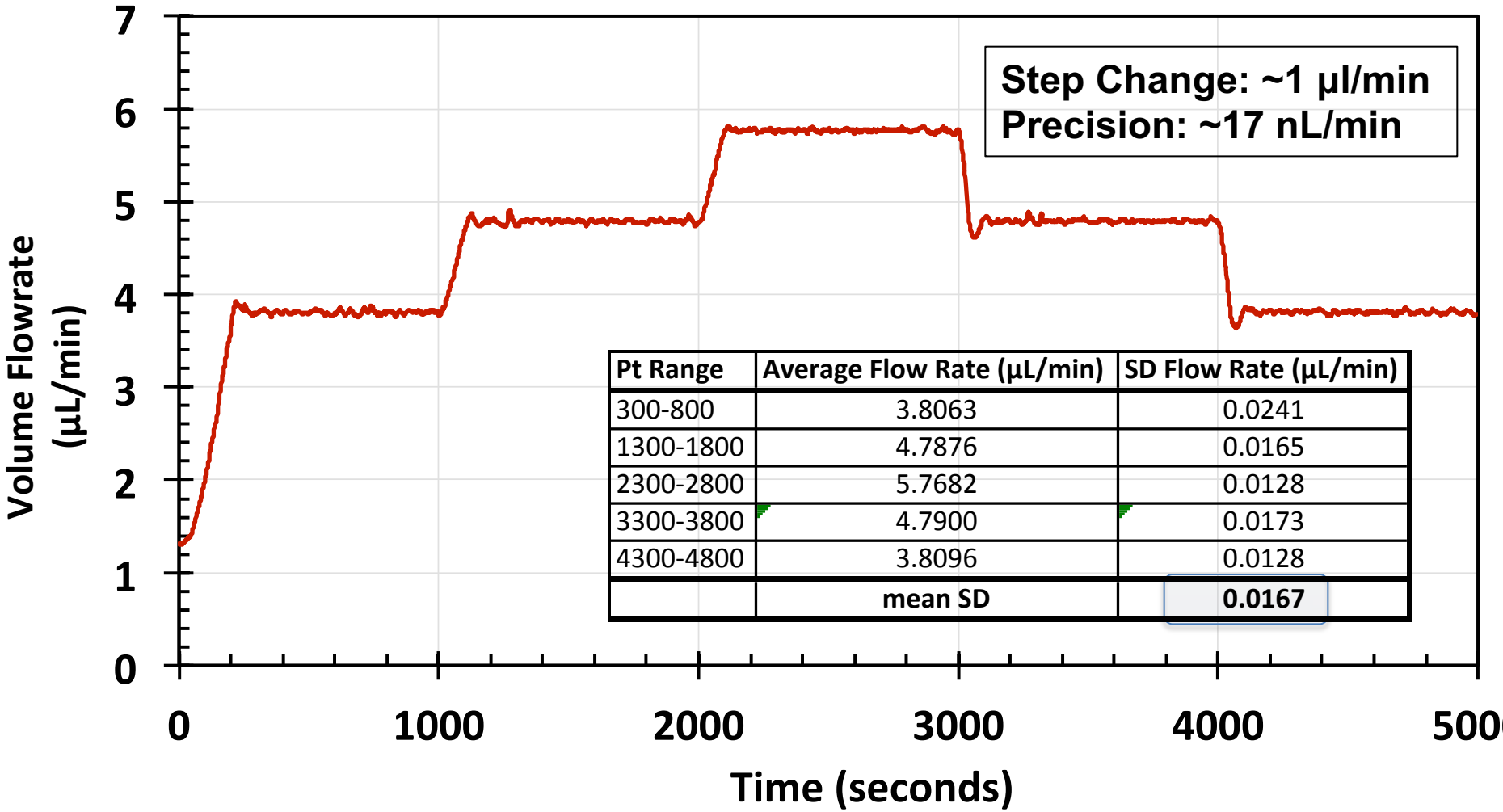

**trihexyltetradecylphosphonium dicyanoamide $[P_{6,6,6,14}]^+[dca]^-$**

**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.**

# Experimental set up for PID Control



# Photo-Controlled Flow Rate




| Pt Range | Average Flow Rate (µL/min) | SD Flow Rate (µL/min) |
|---|---|---|
| 300-800 | 3.8063 | 0.0241 |
| 1300-1800 | 4.7876 | 0.0165 |
| 2300-2800 | 5.7682 | 0.0128 |
| 3300-3800 | 4.7900 | 0.0173 |
| 4300-4800 | 3.8096 | 0.0128 |
| | **mean SD** | **0.0167** |

C. Delaney, P. McCluskey, S. Coleman, J. Whyte, N. Kent, D. Diamond, Precision control of flow rate in microfluidic channels using photoresponsive soft polymer actuators, LAB ON A CHIP. 17 (2017) 2013–2021. doi:10.1039/c7lc00368d.

# Concluding Thoughts

- **Start with lower risk measurements accessible via reliable sensing technologies;**
  - Temperature, pressure already available
  - pH, DO, ions, glucose, lactate…..
  - Infrared/RAMAN probes for headspace/liquid phase
  - Adapt existing platforms e.g. skin-patch sensors
- **Knowledge gained on sensor reliability is transferrable to other application domains**

**Need for more dialog between the Biochemical Sensing and Bioprocessing communities**

# Thanks to…..

- NCSR, SCS, DCU
- Science Foundation Ireland & INSIGHT Centre
- Enterprise Ireland
- Research Partners – academic and industry
- H2020: Holifab Project

**Thanks for the invitation!**