Rethinking On/In-Body Biochemical Sensing Strategies to Achieve Long-Term Functionality

Dermot Diamond, Akshay Shinde, Aleksander Glaz, Andrew Donohoe, Ruairi Barrett, and Margaret McCaul

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

presented at

Department of Biomedical Engineering
UNC-Chapel Hill and NC State University
North Carolina, USA
5th December 2019

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

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.

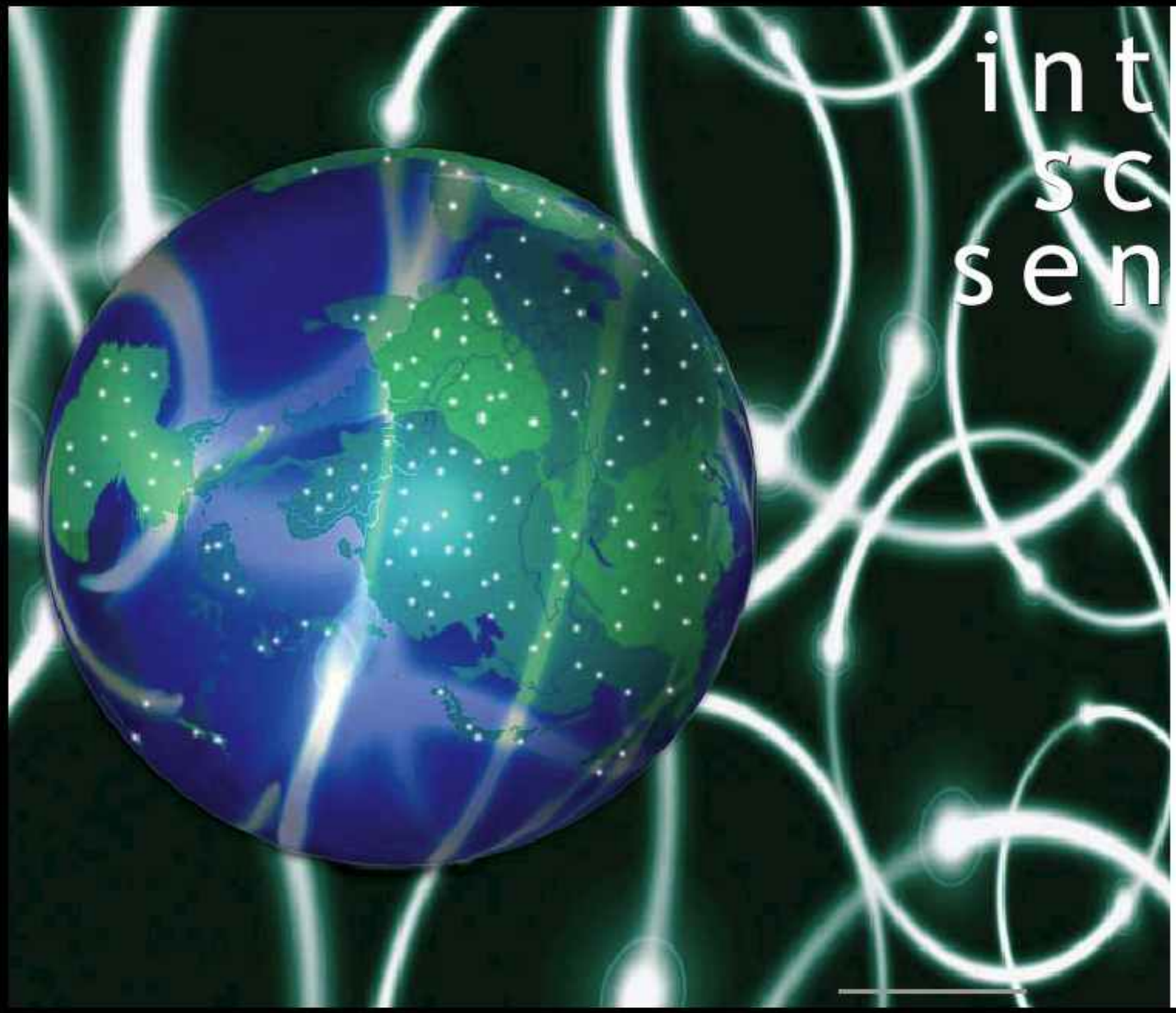
http://www.sfi.ie/sfi-research-centres/insight/

2nd Phase funding approved (ca. €49 million SFI); 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)
  - Critical Need: 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.

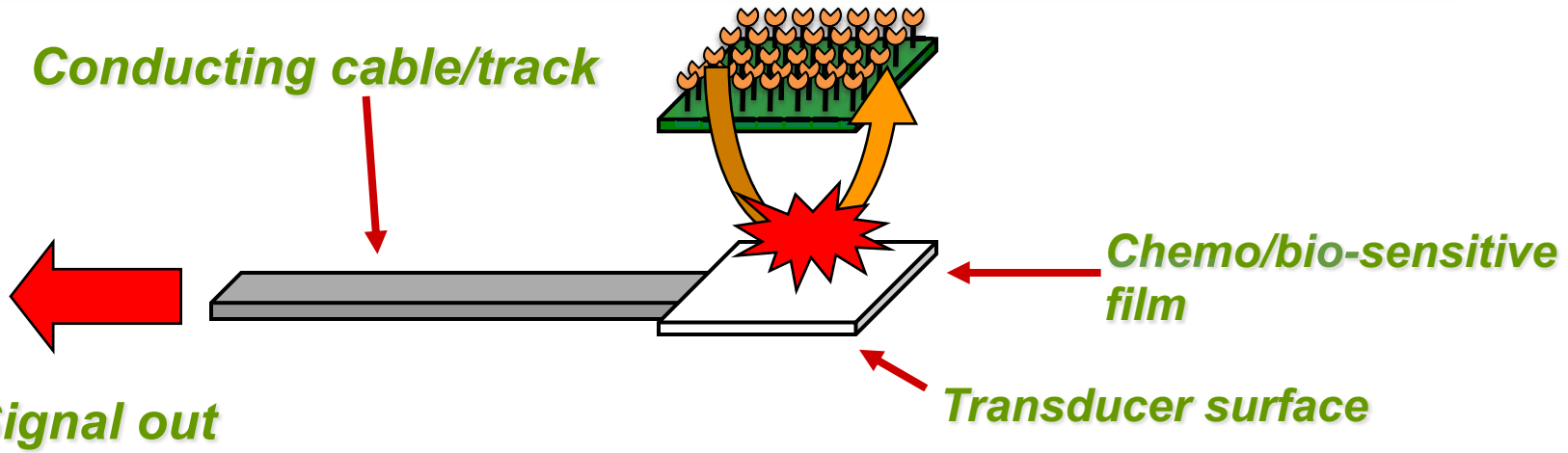
Digital communications networks are at the heart of modern society. The digitization of communications, the development of the Internet, and the availability of relatively inexpensive but powerful mobile computing technologies have established a global communications network capable of linking billions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

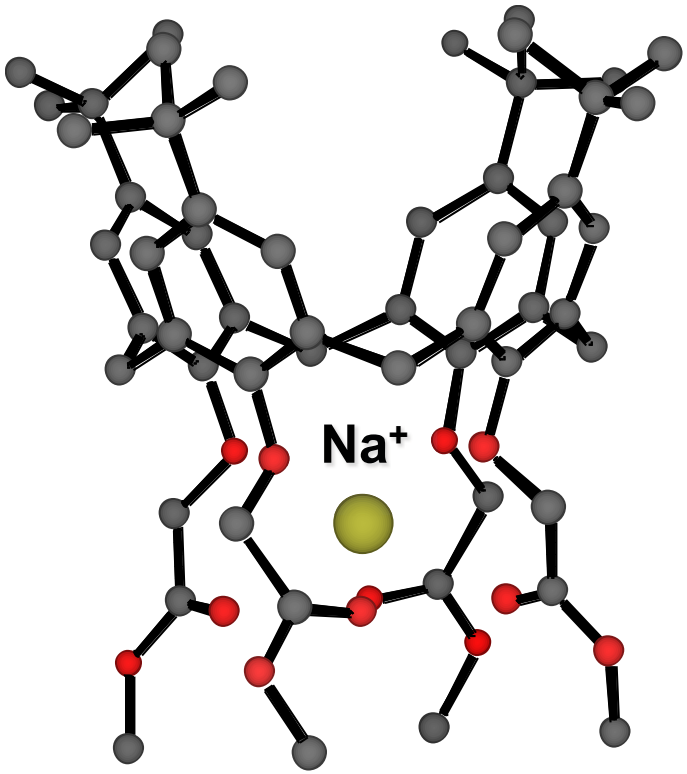
What is a 'Bio/Chemical Sensor?

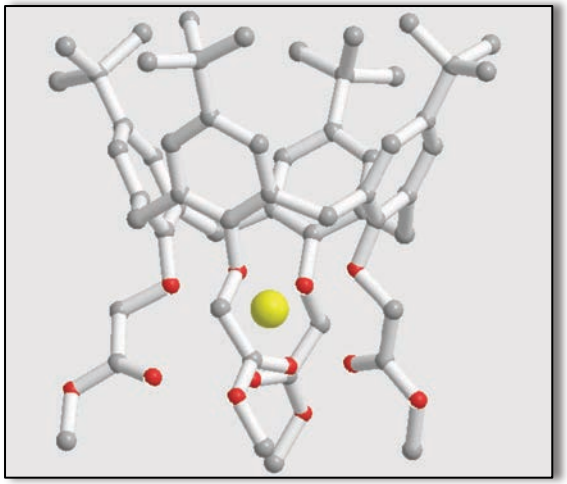
'a device, consisting of a transducer and a chemo/bio-sensitive film/membrane, that generates a signal related to the concentration of particular target analyte in a given sample'

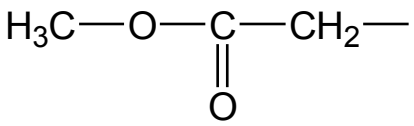


Chemo/Bio-sensing involves selective BINDING & TRANSDUCTION on the device surface; this also implies the target analyte MUST meet the device surface (LOCATION & MOVEMENT). It provides a signal observable in the macroscopic world (COMMUNICATION)

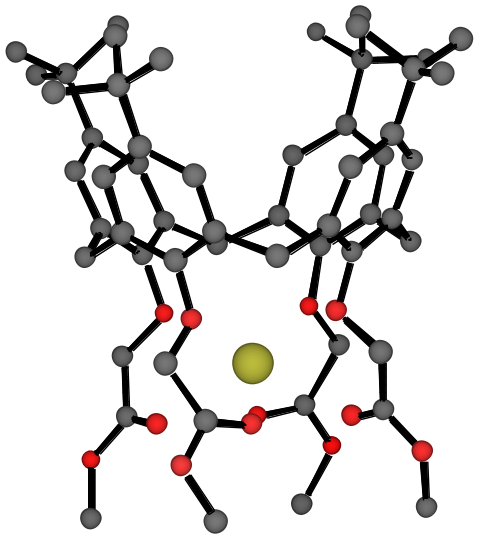
Calixarene Ionophores – controlling the selectivity

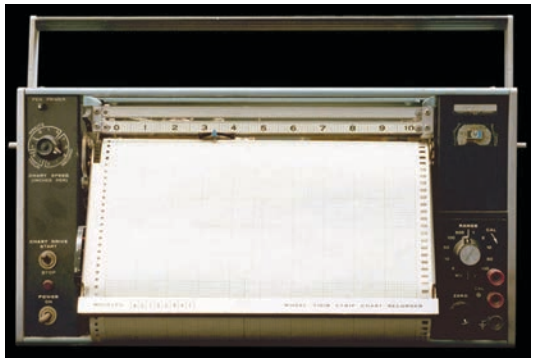


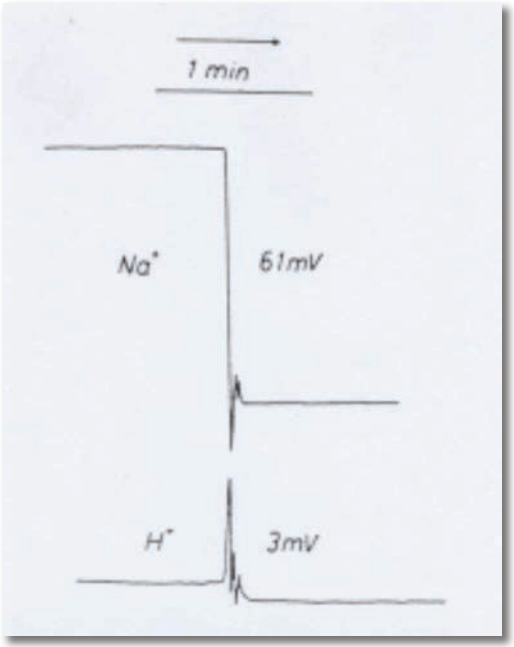


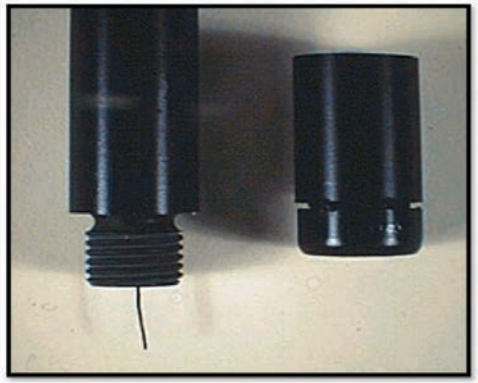


And…….





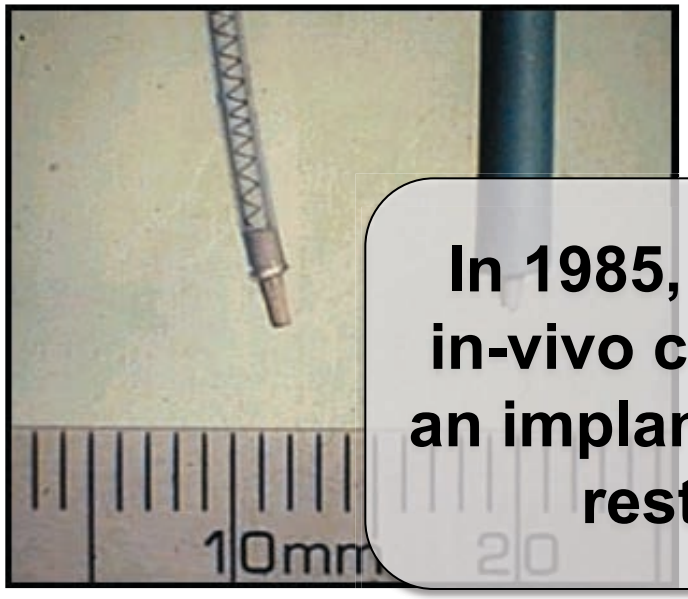




Neutral Carrier Based Ion-Selective Electrodes, D.Diamond, Anal. Chem. Symp. Ser., 25 (1986) 155.

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

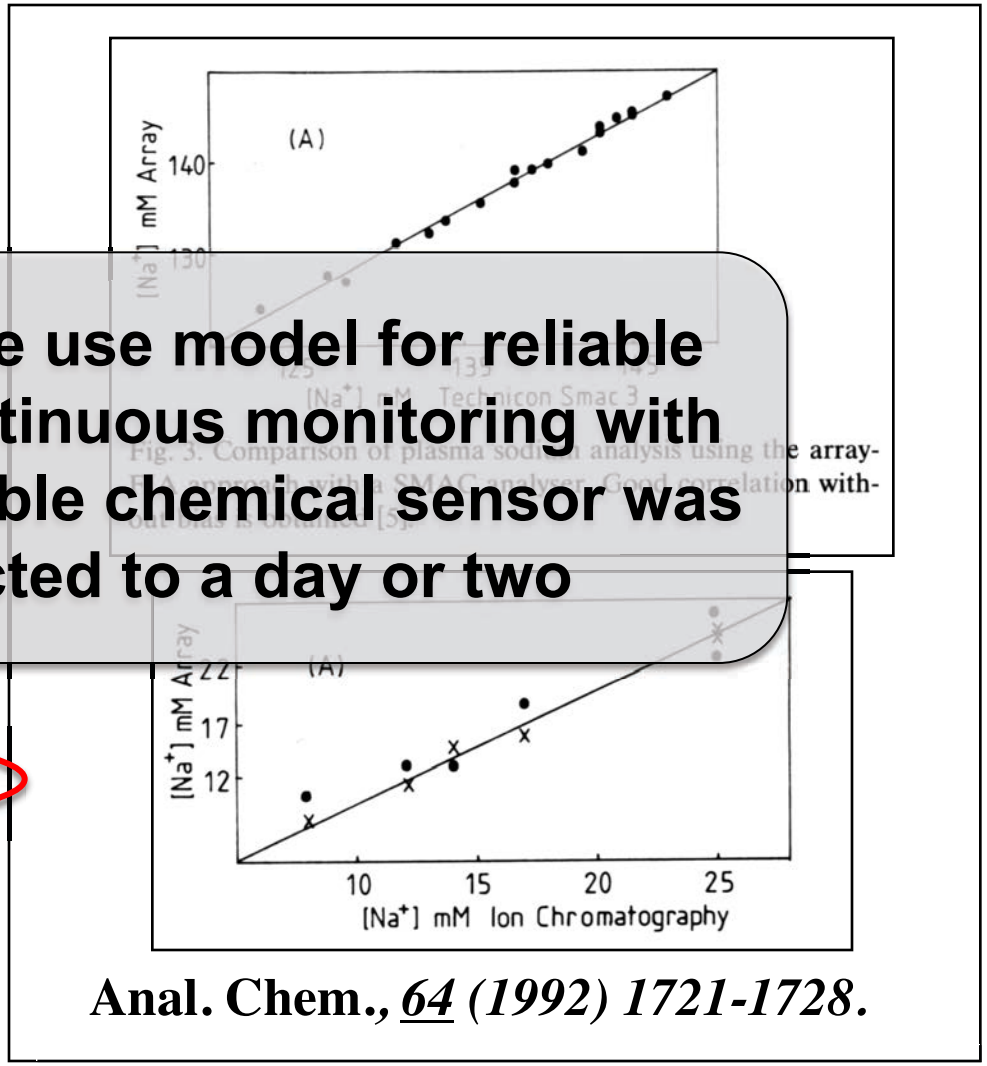
Blood Analysis; Implantible Sensors



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

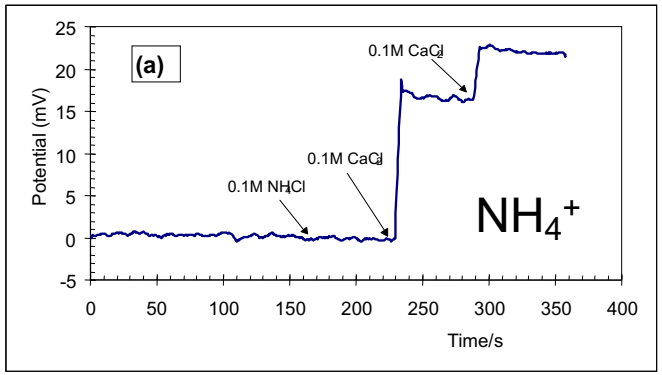
1985: Catheter Electrodes for intensive care – function for 24 hrs

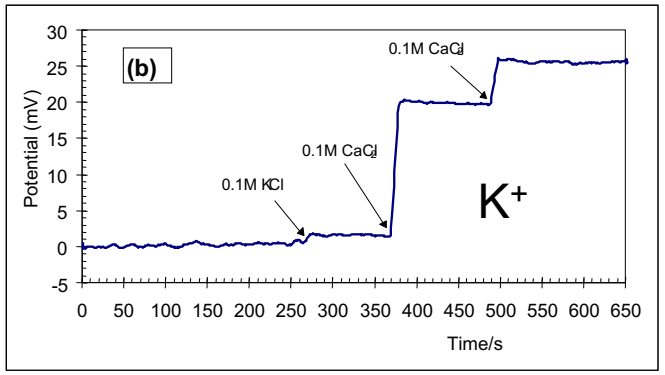
Dr. David Band, St Thomas's Hospital London

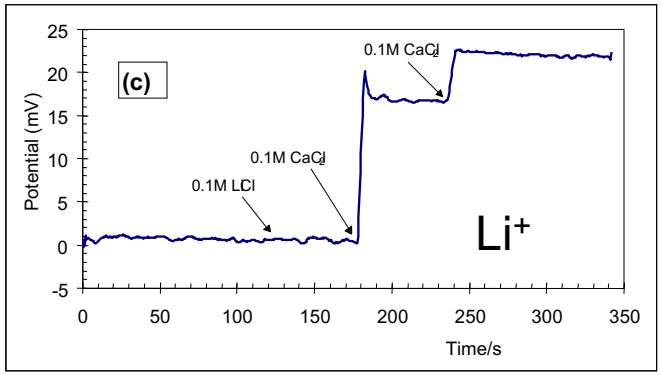


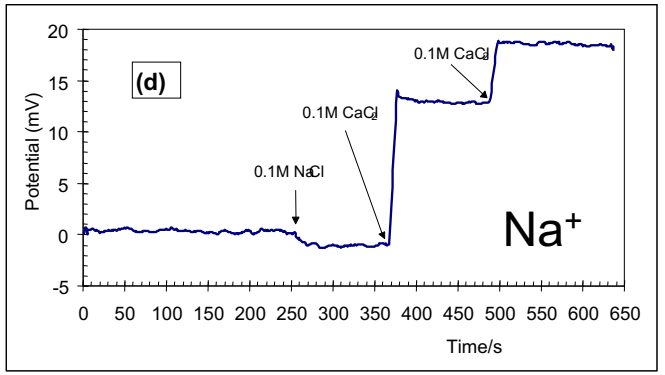
Anal. Chem., *64* (1992) 1721-1728.

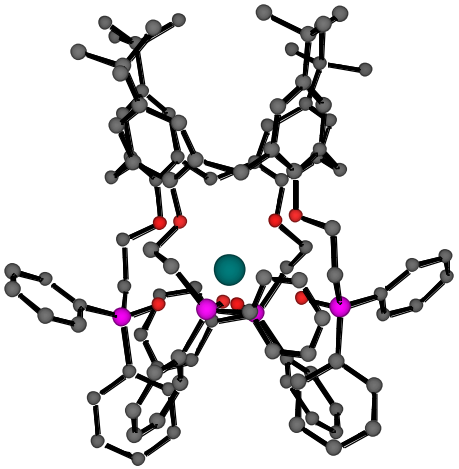
Ligand (and variations of) used in many clinical analysers for blood Na^+ profiling

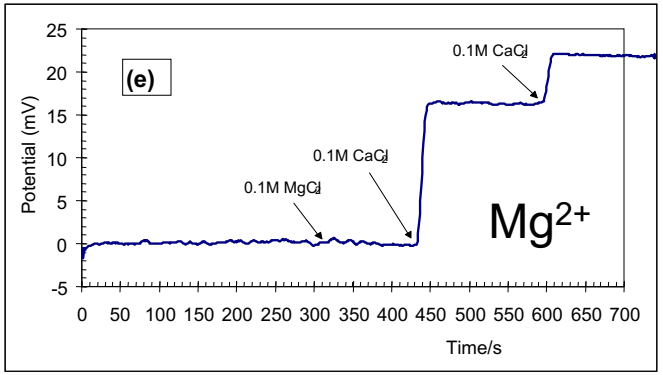








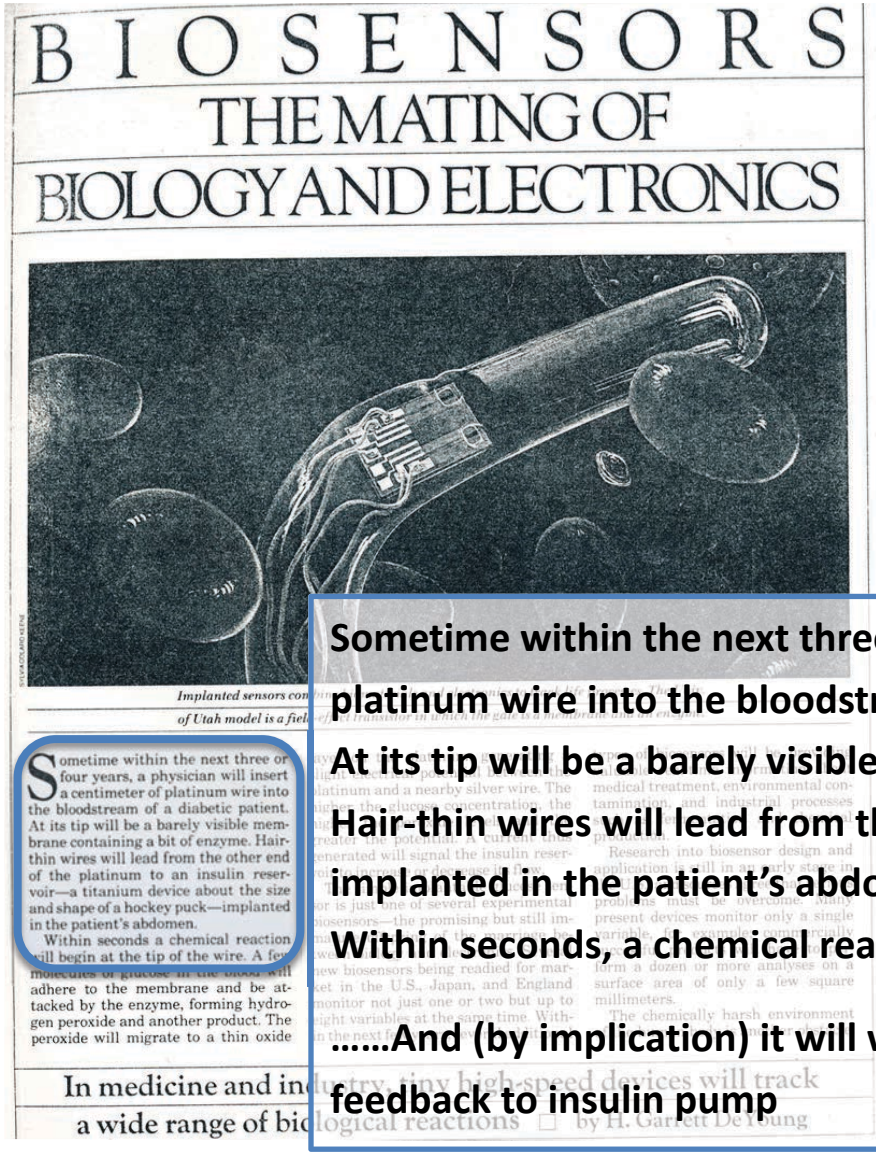




tetra-phosphine oxide electrode

Talanta 43 (1996) 1145–1148

The (broken) promise of biosensors…..


BIOSENSORS

THE MATING OF BIOLOGY AND ELECTRONICS

Implanted sensors con… 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

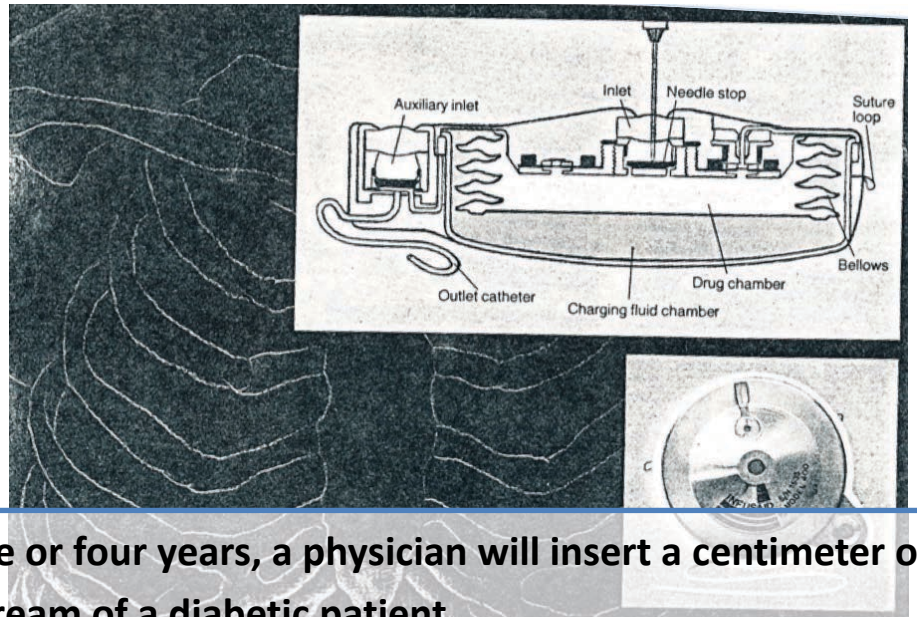
…platinum and a nearby silver wire. The… medical treatment, environmental con… taminants, and industrial processes…

Research into biosensor design and application is still in an early stage in… or is just one of several experimental… problems must be overcome. Many… present devices monitor only a single… variable, requiring frequent recalibration… biosensors—the promising but still im… form a dozen or more analyses on a… new biosensors being readied for mar… surface area of only a few square… ket in the U.S., Japan, and England… millimeters.

monitor not just one or two but up to… The chemically harsh environment… eight variables at the same time. With… in the next…

In medicine and in… try, tiny high-speed devices will track a wide range of bi… logical reactions □ by H. Garrett DeYoung

High Technology, Nov. 1983, 41-49



planted in lower abdo… men. It may also be sited in upper chest, with catheter inserted into

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

Nightscout

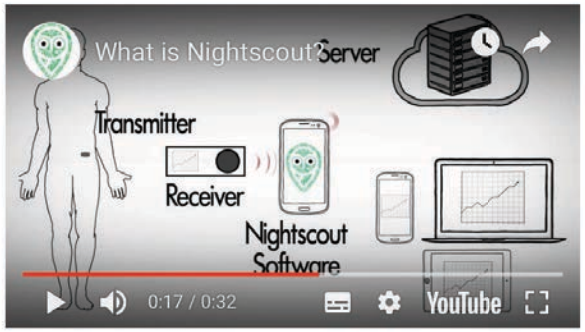
Welcome to Nightscout | Setup Guides | FAQs | Links | Map | Labs | Privacy | Nightscout Foundation | Contact

NIGHTSCOUT
#WeAreNotWaiting

http://www.nightscout.info https://www.dexcom.com

Welcome to Nightscout

What is the Nightscout project?



Nightscout (CGM in the Cloud) is an open source, DIY project that allows real time access to a CGM data via personal website, smartwatch viewers, or apps and widgets available for smartphones.

Nightscout was developed by parents of children with Type 1 Diabetes and has continued to be developed, maintained, and supported by volunteers. When first implemented, Nightscout was a solution specifically for remote monitoring of Dexcom G4 CGM data. Today, there are Nightscout solutions available for Dexcom G4, Dexcom Share with Android, Dexcom Share/G5 with iOS, and Medtronic. Nightscout also provides browser-based visualization for #openAPS users and Loop users. The goal of the project is to allow remote monitoring of a T1D's glucose level using existing monitoring devices.

Search ...

Disclaimer

All information, thought, and code described here is intended for informational and educational purposes only. Nightscout currently makes no attempt at HIPAA privacy compliance. Use of code from github.com is without warranty or support of any kind. Please review the LICENSE found within each repository for further details. **Use Nightscout at your own risk, and do not use the information or code to make medical decisions.**

Support Nightscout

Your contributions help the developers purchase test equipment, webspace, cables, and other tools that drive this project forward. Received donations are managed by The Nightscout Foundation. Click here to donate.

Please consult with your tax professional regarding deducting donations.

- Developed by coders & engineers within the T1 Diabetes Community & friends
- Developing APPs
- Accessing real-time data from diabetes monitors (Dexcom, wearable glucose sensors)
- User groups formed, self-funded
- Use disclaimers, no warranty, not for making therapeutic decisions

Abbott Jobs

THE IRISH TIMES

Mon, Feb 11, 2019

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Companies › Health & Pharma | Financial Services | Agribusiness & Food | Energy & Resou

Abbott to add 500 new jobs at Donegal healthcare plant

US healthcare giant employs almost 3,000 people in the Republic

Mon, Jul 23, 2018, 15:35 | Updated: Mon, Jul 23, 2018, 20:33

Peter Hamilton

Abbott's Donegal site manufactures test strips used in its FreeStyle blood glucose-monitoring meters. Photograph: Tim Boyle/Bloomberg

US healthcare giant Abbott plans to create 500 jobs in Donegal as it expands its existing manufacturing facility there.

With nearly 3,000 employees across nine sites in the Republic, Abbott's operations here include manufacturing nutritional products and creating diagnostic tools for physicians.

Macromolecules **1990,** *23,* 4372–4377

Synthesis, Characterization, and Properties of a Series of Osmium- and Ruthenium-Containing Metallopolymers

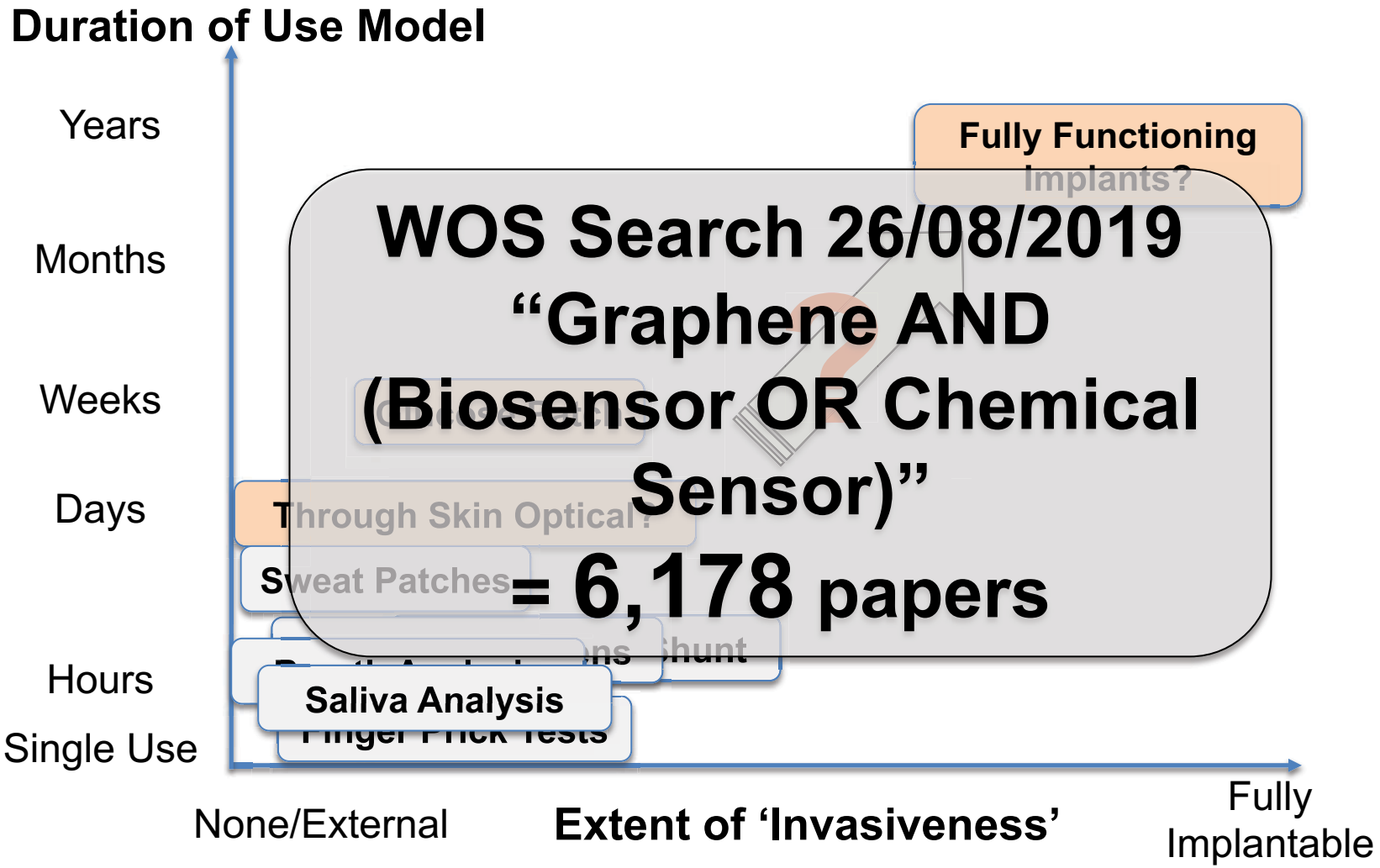
Robert J. Forster and Johannes G. Vos*

School of Chemical Sciences, Dublin City University, Dublin 9, Ireland

Received November 27, 1989; Revised Manuscript Received February 16, 1990

- 1989: Forster and Vos series of papers on Os/Ru bipy/PVP
- 1990s: Heller develops foundational ideas
- 2004: Abbott acquires Therasense ($1.2bn)
- 2018: Abbott Jobs announcement

Long-Term Biochemical Monitoring?



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

February 4, 2019

www.nano-magazine.com
email announcing

‘The graphene biosensor that could provide early lung cancer diagnosis’

‘The wonder-material graphene could hold the key to unlocking the next generation of advanced, early stage lung cancer diagnosis’

nano
THE MAGAZINE FOR SMALL SCIENCE

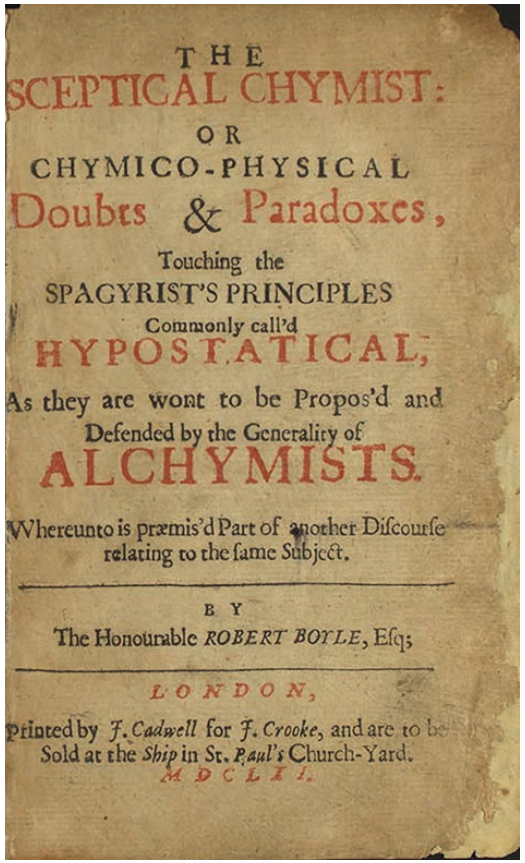
Weekly News Round-up: The graphene biosensor that could provide early lung cancer diagnosis, plus much more.

MON, FEB 04

The graphene biosensor that could provide early lung cancer diagnosis

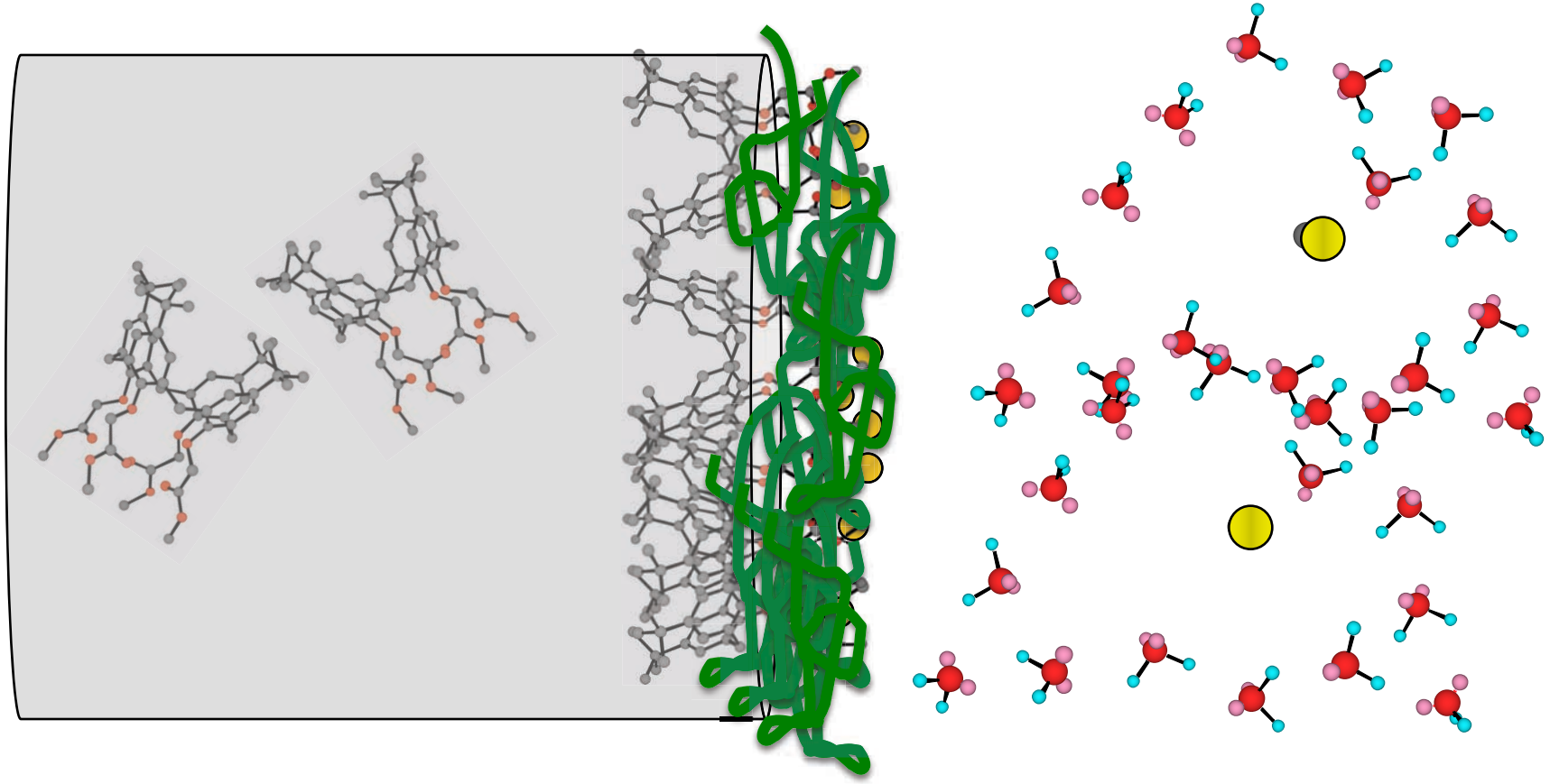
The wonder-material graphene could hold the key to unlocking the next generation of advanced, early stage lung cancer diagnosis.

‘The Sceptical Chemist’ (1661)
‘Chymico-Physical Paradoxes’


THE
SCEPTICAL CHYMIST:
OR
CHYMICO-PHYSICAL
Doubts & Paradoxes,
Touching the
SPAGYRIST'S PRINCIPLES
Commonly call'd
HYPOSTATICAL,
As they are wont to be Propos'd and
Defended by the Generality of
ALCHYMISTS.
Whereunto is præmis'd Part of another Discourse
relating to the same Subject.
BY
The Honourable ROBERT BOYLE, Esq;
LONDON,
Printed by J. Cadwell for J. Crooke, and are to be
Sold at the Ship in St. Paul's Church-Yard.
MDCLXI.

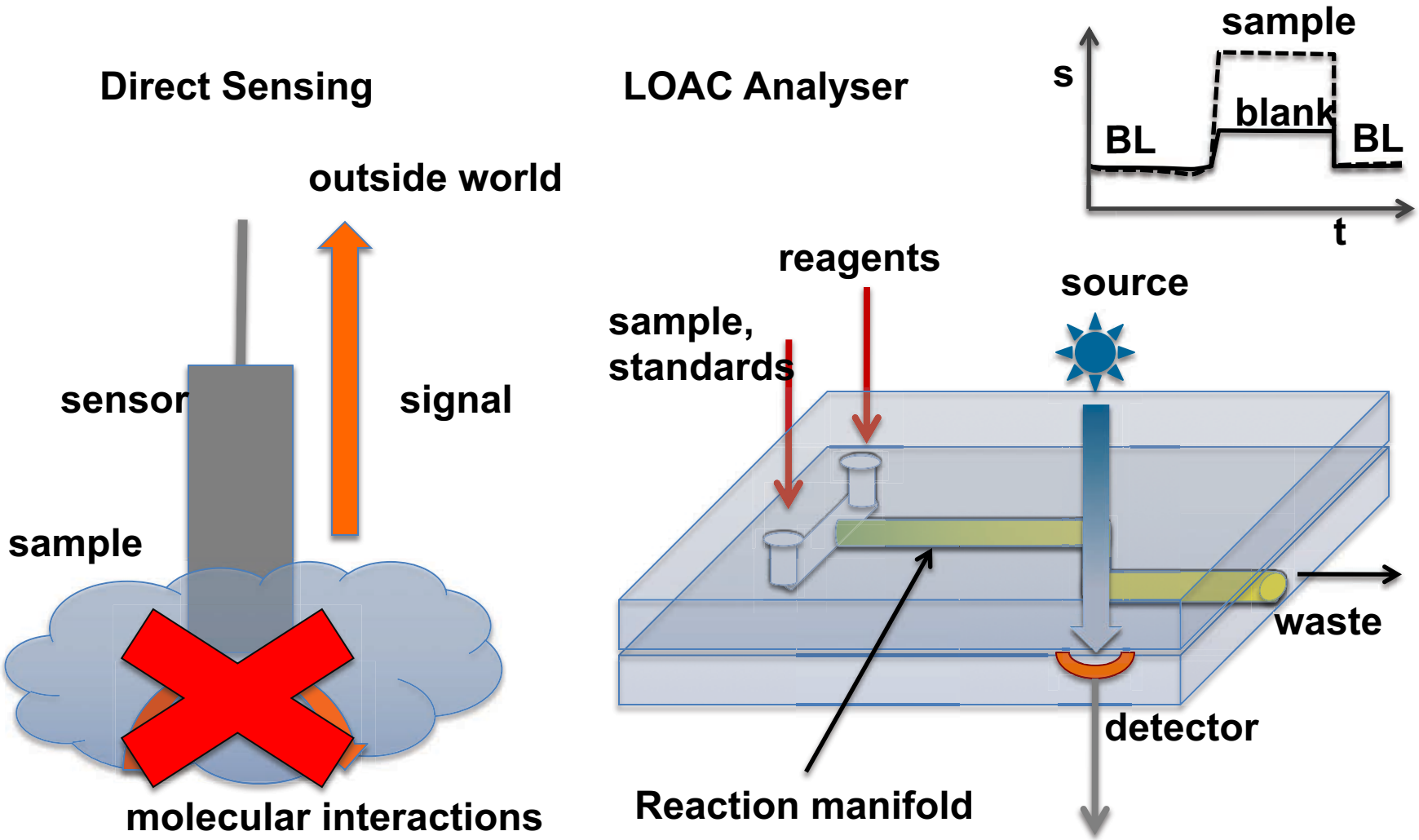
Robert Boyle: b. Lismore Castle, Waterford, 1621

Control of membrane interfacial exchange & binding processes



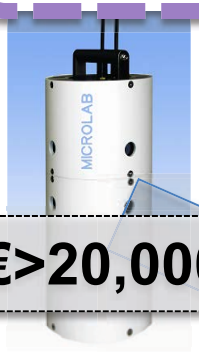
Remote, autonomous chemical sensing is a tricky business!

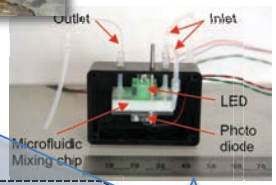
Direct Sensing vs. Reagent Based LOAC/ufluidics



Achieving Scale-up

Current platforms





€>20,000

1

€>2,000

€<200

2

€<20

€<2

2. **Revolutionary** breakthroughs in materials science; hidden complexity, biomimetic platforms, all fluid handling integrated on chip, indefinitely self-sustaining

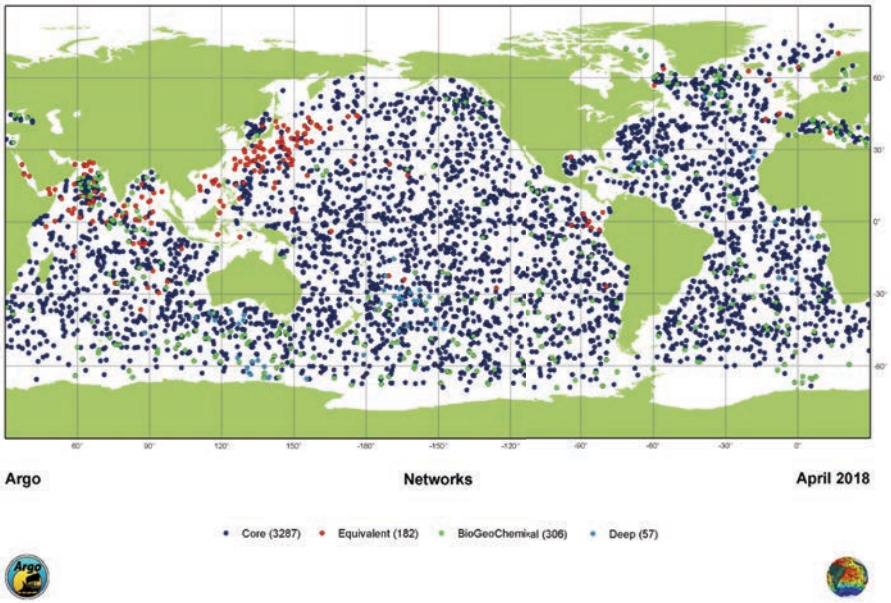
1. **Evolutionary** development, cost driven down, reliable, improved scalability

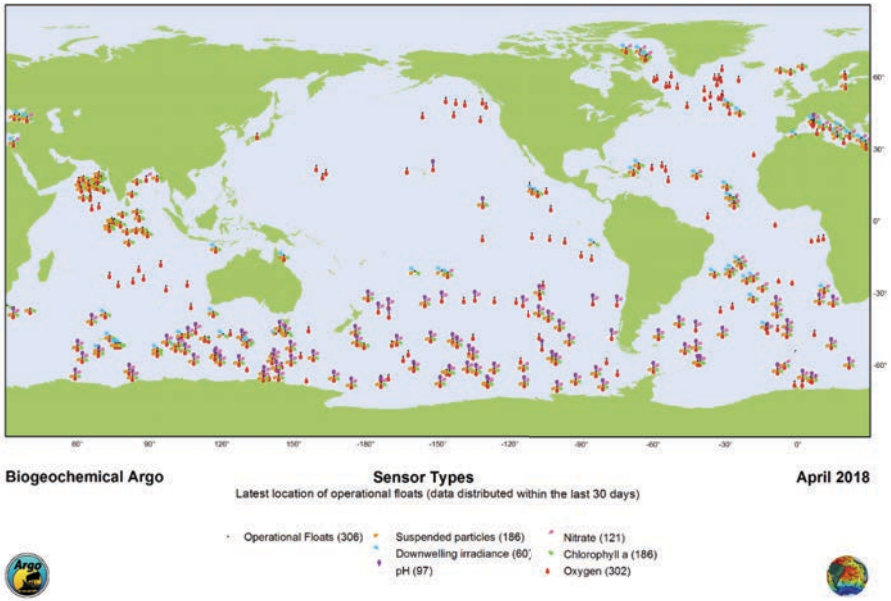
Massively scaled deployments of the future?

Cost/Complexity->

Scalability ->

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

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)

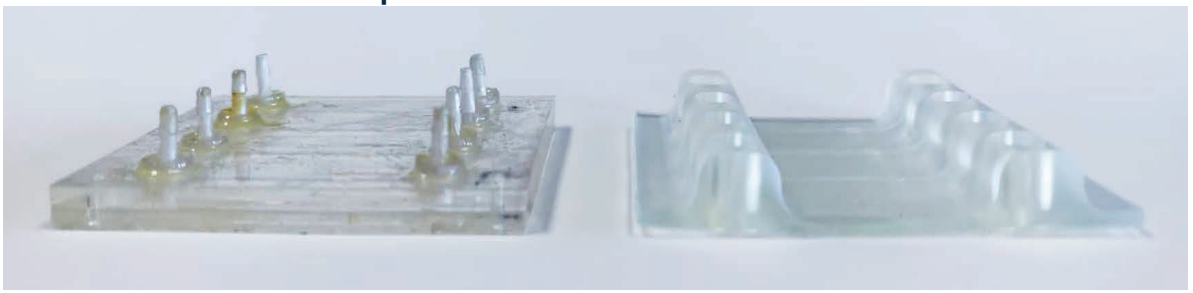
Impact of 3d Printing

Minimum thickness

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

Assembled Chip

Printed Chip



Advantages:

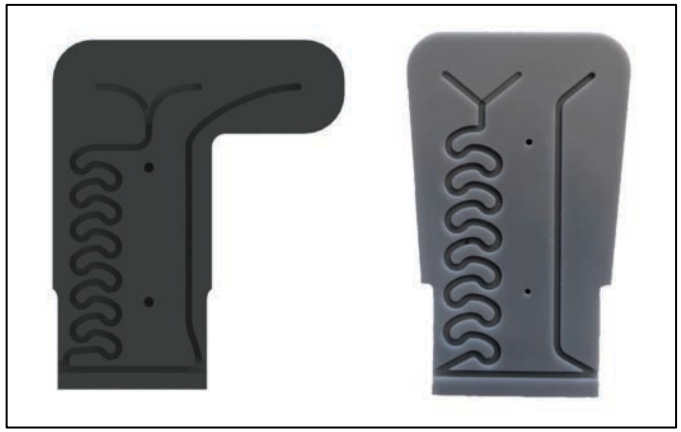
- **No Assembly**
- **No Bonding necessary**
- **Integrated barbs (1/16”)**
- **Chip thickness reduced by 63%**
- **Automated manufacturing**

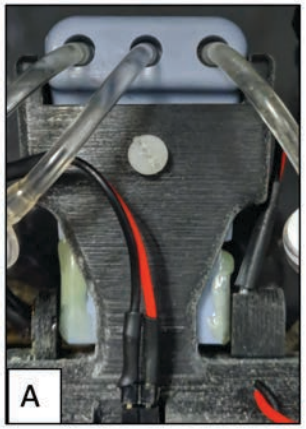
Rendered Chip

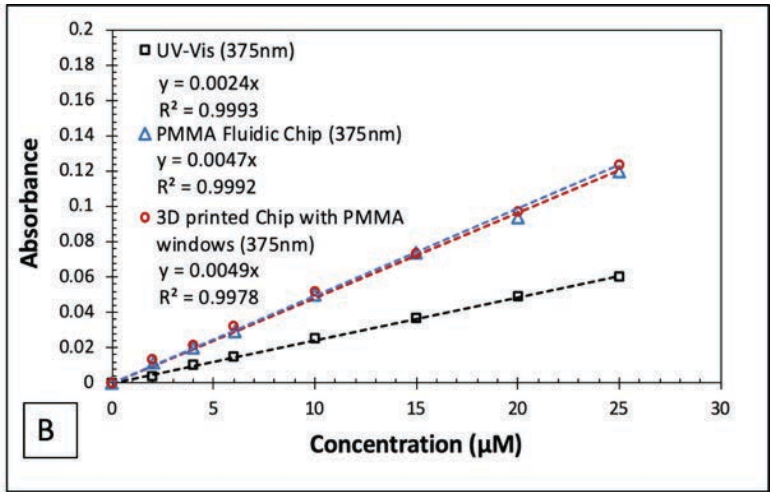
Printed Chip

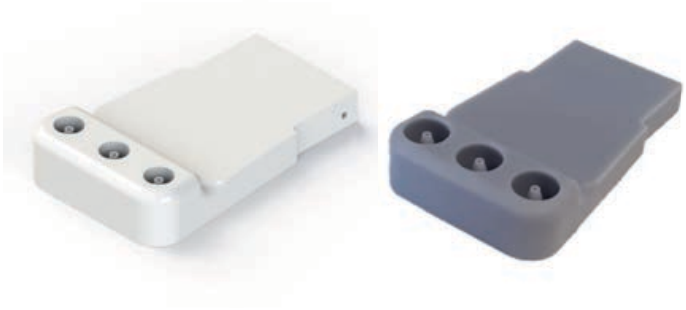
See Poster – McCaul et al. “3D Printed Chips for Environmental Applications

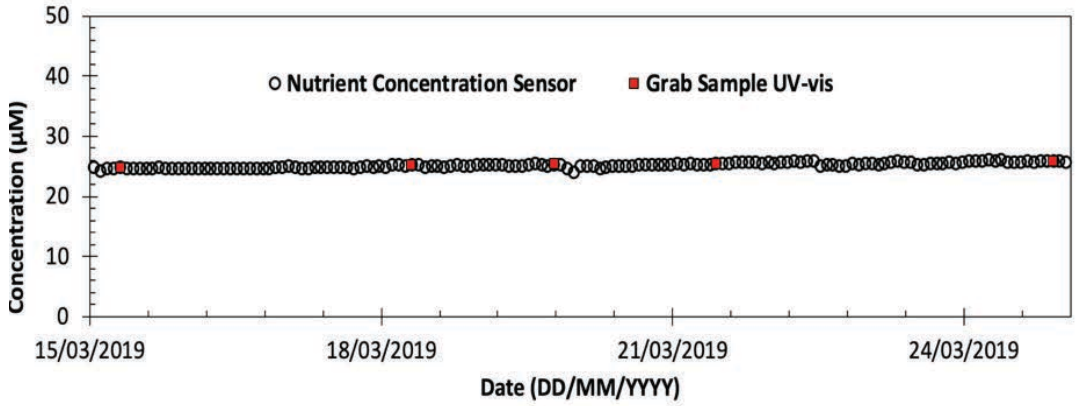
3d Printed Microfluidics







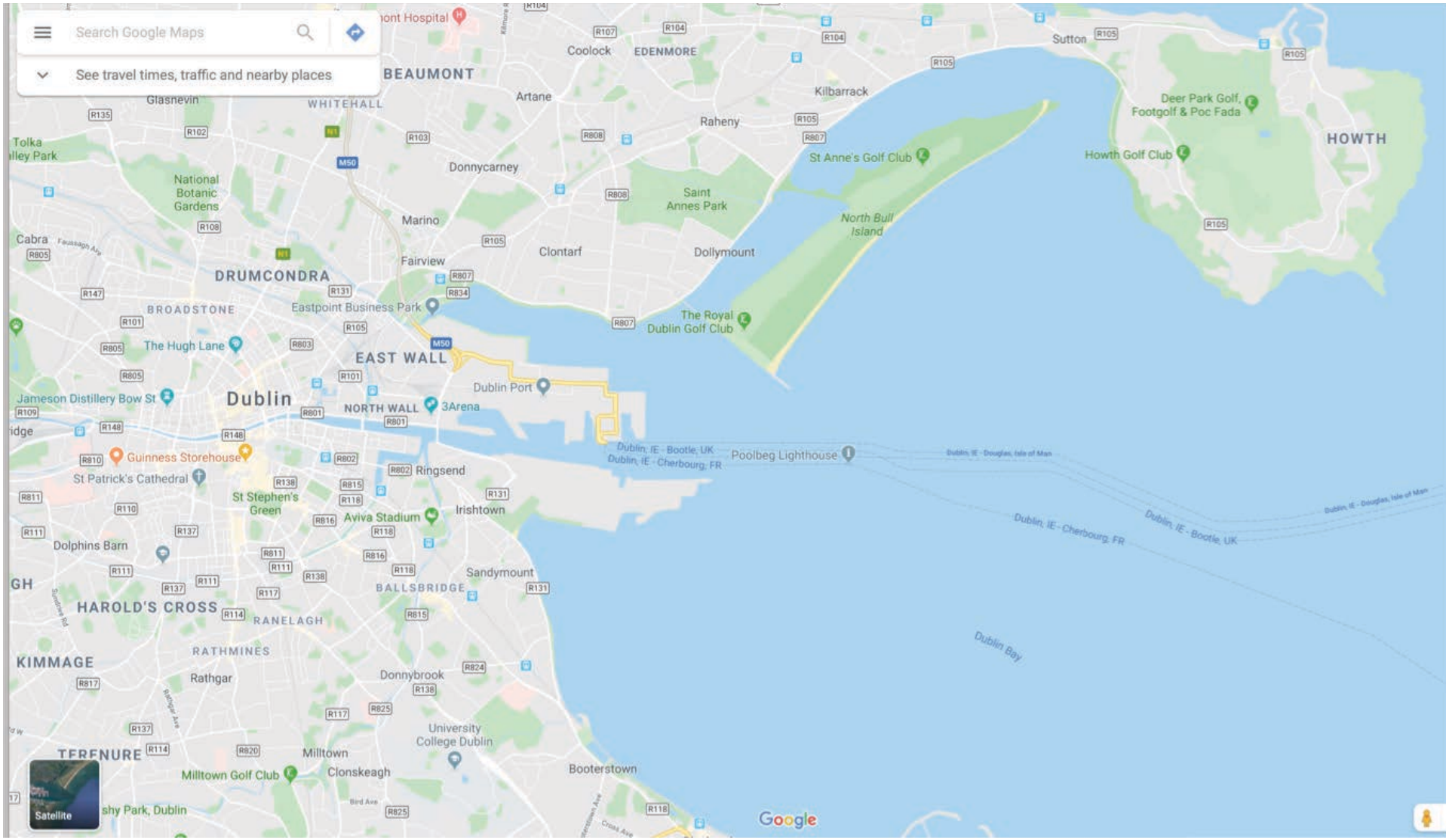




Rendered images and 3-d printed parts showing
Top: lower chip layer (3-d printing stopped);
Bottom: finished chip
Top right: calibration plots of 3-d printed and micro-machined chips and UV-VIS reference method

Time series showing over 150 measurements of Phosphate (PO_4^{3-} µM) generated in lab by the Prototype Nutrient platform sampling from a tank containing 25 µM phosphate in fully autonomous mode

Dublin Bay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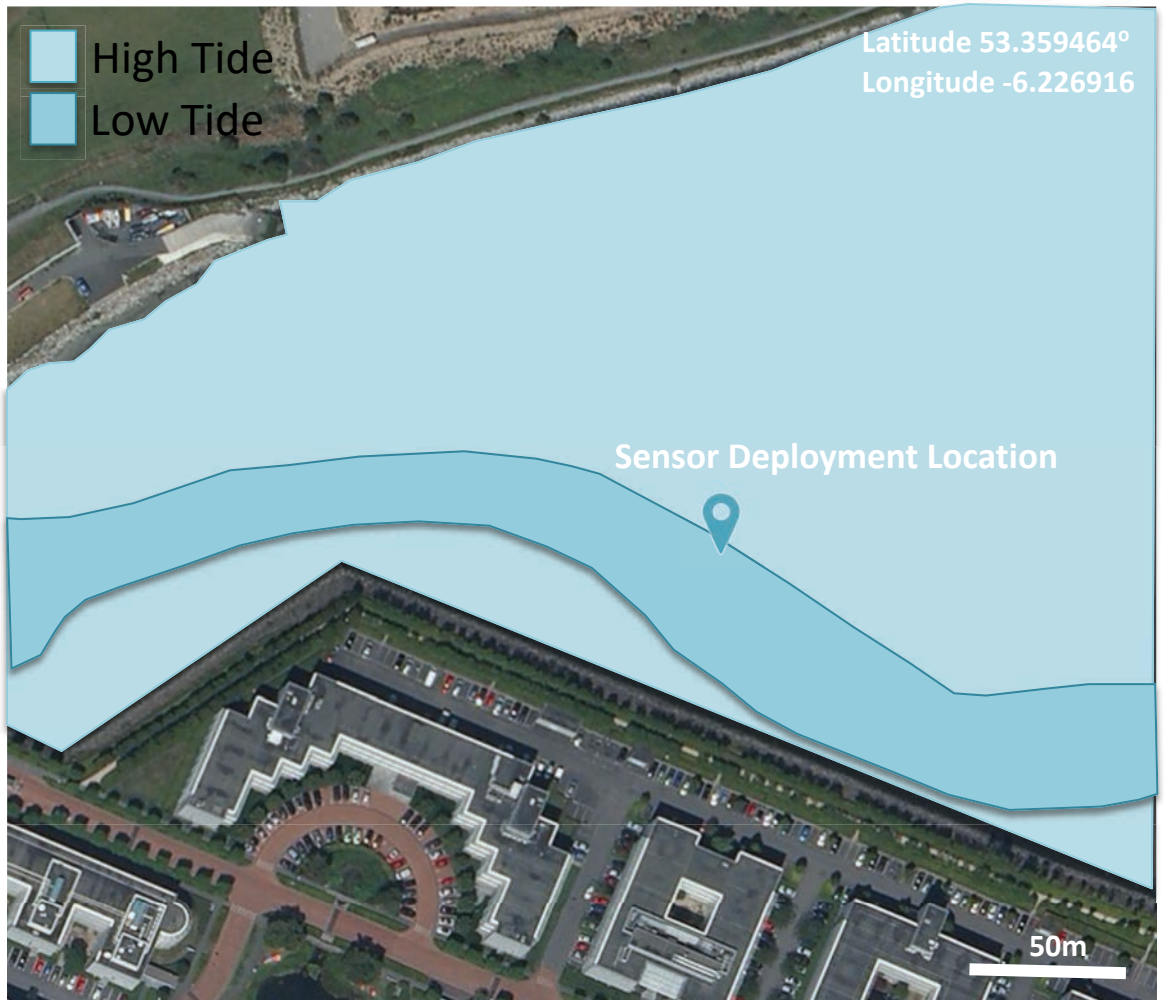
Deployment Location



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

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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

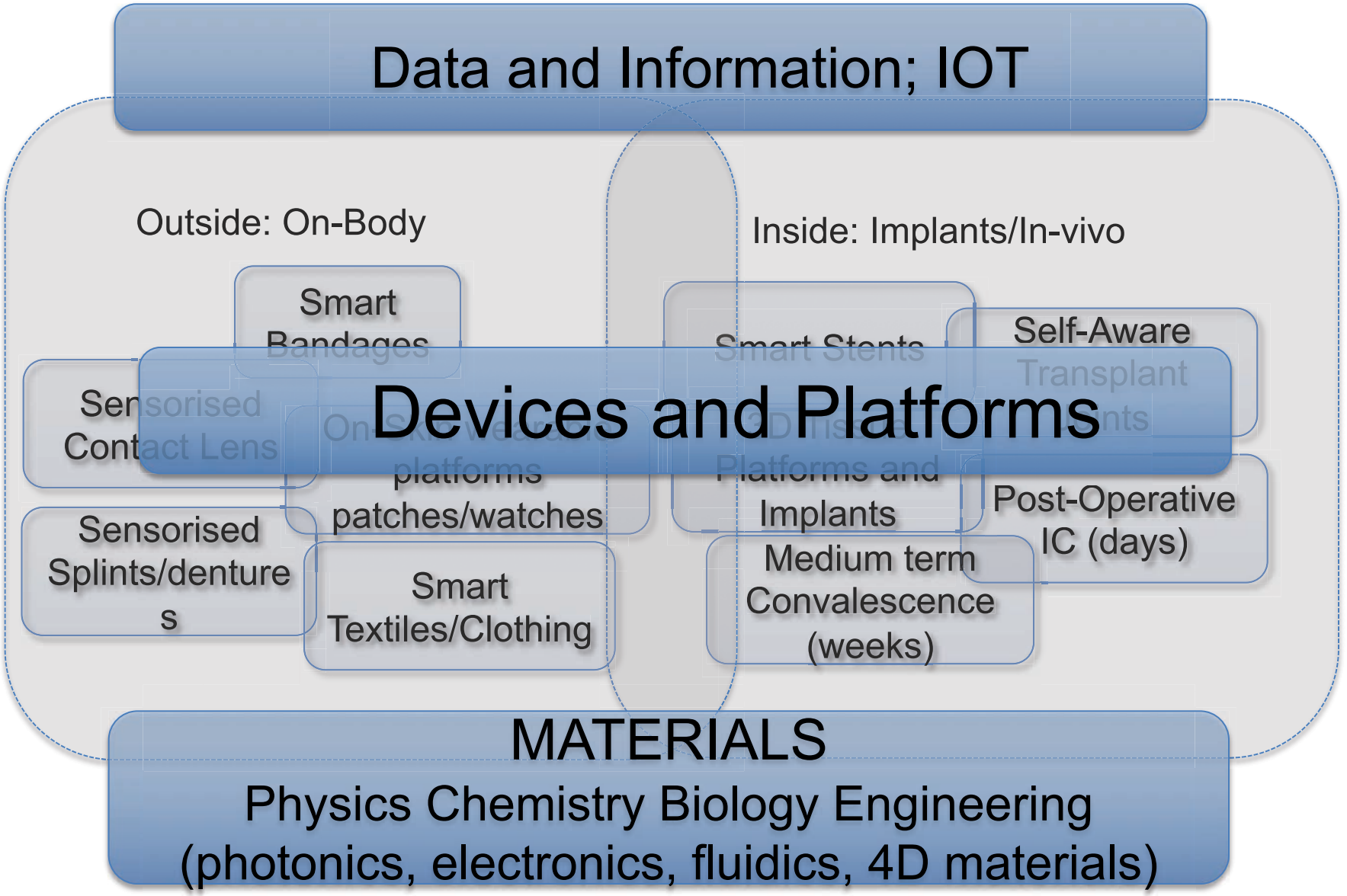
File image of Dollymount beach in Dublin. Photograph: Dara Mac Dónaill/The Irish Times

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

Merging of Materials, Devices and Data



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HoliFAB

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Thanks for the invitation!