“Calixarenes as ionophores in ion-selective electrodes: The Past and The Future of Chemical Sensing”

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Dublin & DCU Location
Battle of Clontarf (1014)
Insight Centre for Data Analytics

- Biggest single research investment ever by Science Foundation
- Biggest coordinated research programme in the history of the state
- Focus is on ‘big data’ related to health informatics and eHealth
- Materials science will play a central role in the practical realisation of new concepts in chemical sensing and biosensing
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.

Dermot Diamond
Dublin City University
(Ireland)

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. E-mail can instantaneously 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, the 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
Grand Challenge

• To develop a **scalable model** for chemical sensing in remote, hostile locations (e.g., inside the body, in the environment)
  – Completely autonomous devices
  – Must provide reliable, high quality data
  – Capable of long-term (months, years) independent operation

**Surely we can do this already — can’t we?**

I’m afraid not. There are no examples of long-term implantable chem/bio-sensors;
In the environment (water), units cost typically €20K++
Artificial Pancreas

Used a Technicon segmented flow colorimetric glucose analyser

Sugar levels: sub-cutaneous insulin

Sugar levels: artificial pancreas

Insulin addition

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)
Impantable Artificial Pancreas.. 1980


Medical and Biological Engineering and Computing, July 1980, Volume 18, Issue 4, pp 527-537

‘Intravascular blood glucose sensing is difficult owing to the complex technology involved and the foreign body reaction of blood.’

‘The measurement of glucose in tissue would be easier to handle, but it has not been established whether the extravascular tissue concentration of glucose is sufficiently significant to serve as an input signal for a closed-loop system.’

‘..several groups are working on the development of.. an implantable glucose sensor’
Adam Heller

Subcutaneous sampling of interstitial fluid using microneedles to access the fluid through the skin without causing bleeding

San Francisco Business Times; Tuesday, April 6, 2004

‘Abbott completes TheraSense acquisition’

Abbott Laboratories said Tuesday it completed its $1.2 billion acquisition of Alameda-based TheraSense Inc. after a majority of shareholders approved the transaction a day earlier.


Abbott Park, Illinois — Adam Heller, Ph.D., a professor at the University of Texas in Austin who created the technology that led to the development of Abbott’s FreeStyle Blood Glucose Monitoring Systems® and FreeStyle Navigator® Continuous Glucose Monitoring System, today received the 2007 National Medal of Technology and Innovation from President George W. Bush in an award ceremony at the White House.
Freestyle Navigator

- Combines microfluidics with a micro-dimensioned filament sampling unit which is designed to minimise incidence of infection (therefore can be left in place for 5 days).

- Measures glucose in interstitial fluid (not blood). Diabetics have poor peripheral blood supply; therefore this is a major advance.

- Wireless communications used to harvest data continuously, and relay to carers and specialists. Enables trending, aggregation, warning...

Target was for 7 days continuous monitoring using a patch-type platform, then replace;

Freestyle Navigator appears to have been withdrawn from the US market (2012); Rumours of relaunch with 14-day continuous use model

Reasons unclear but likely to be issues related to device stability, skin irritation, negative user response (YouTube videos);

Biocompatibility is still a huge issue!
Apple hiring medical device staff, shares break $600 mark

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.

‘Healthkit’ personal health information platform developed in collaboration with Mayo Clinic
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.

• Use model is 24 hours max, then replace;
• likely to leverage Google Glass infrastructure;
• Novartis now working with Google.


pH sensing – wasn’t that solved by Nikolskii in the 1930’s?

<table>
<thead>
<tr>
<th>EVENT</th>
<th>DATE</th>
</tr>
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<tbody>
<tr>
<td>Launch (San Francisco)</td>
<td>September 2013</td>
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<tr>
<td>PHASE 1: Innovation Phase</td>
<td></td>
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<tr>
<td>Registration opens</td>
<td>January 1, 2014</td>
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<td>Early-bird Registration deadline</td>
<td>March 2014</td>
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<tr>
<td>OA Solutions Fair and Kick-Off Event</td>
<td>March 2014</td>
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Wendy Schmidt Ocean Health XPRIZE

$2,000,000 up for grabs!
Task is to provide a way to do reliable measurements of pH in the ocean environment

The winner will almost certainly be a reagent based platform, not a conventional chemical sensor
• Ca. 3,600 floats: temperature and salinity
• Only 216 reporting chem/bio parameters (ca. 6%)
• Of these nitrate (38), DO (202), Bio-optics (43), pH (3)

DO is by Clark Cell (Sea Bird Electronics) or Dynamic fluorescence quenching (Aanderaa)

See https://picasaweb.google.com/JCOMMOPS/ArgoMaps?authuser=0&feat=embedwebsite

‘calibration of the DO measurements by the SBE sensor remains an important issue for the future’, Argo report ‘Processing Argo OXYGEN data at the DAC level’, September 6, 2009, V. Thierry, D. Gilbert, T. Kobayashi
After decades of intensive research, our capacity to deliver successful long-term deployments of chemo/bio-sensors in remote locations is still very limited.
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’

Conventionally, chem/Bio-sensors employ selective BINDING & TRANSDUCTION at the device surface, which is pre-functionalised with binding sites selective for a chosen analyte. Binding events at the surface provide a signal observable in the macroscopic world (COMMUNICATION)
PVC - Membrane ISEs

Typical membrane cocktail (%w/w); PVC:33%, NPOE (plasticiser):66%; ionophore/exchanger: 1% (ratio at least 2:1 by mole); dissolve in a volatile solvent e.g. THF and cast membrane from this solution
Blood Analysis; Implantable Sensors

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


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

• Best ionophore for sodium
Real time monitoring of Sodium in Sweat through screen printed potentiometric strips:
• Monitoring of athletes during exercise
• Monitoring clinical conditions e.g. Cystic Fibrosis patients

Macroduct sweat sampling unit (Wescor Corporation) Speed x4

Pilocarpine based sweat sampling  Exercise based sweat sampling  Sensor calibration
Na⁺ monitoring in sweat using wearable sensor

• Measurements successfully made with CF-positive and normal volunteers
  • clear difference between CF+ and normal levels
• Elevated levels of Na⁺ found in sweat of CF+ volunteers as expected
• Enables electrolyte loss to be estimated when combined with sweat rate/volume data
• Important for rehydration
• Interesting observations
  • elevated viscosity of sweat of CF+ volunteers
  • sweat rate much lower – in some cases no sweating occurred
  • could not exercise as long as normal volunteers

• Diagnostic CF threshold >60mM [Na⁺] reached
• Issue with initial delay
  • arises from inherent delay in onset of sweating
  • contribution from device ‘dead-volume’

Next Generation: Watch Fluidic Sensor Concept
Ca\textsuperscript{2+} - complexes of PO tetramers

Not Ca\textsuperscript{2+} selective

Ca\textsuperscript{2+} selective

methyl (short)

Ethyl (long)
Response of TPOL Electrode

Lowering the LOD of ISEs (1999)


Lowering the Detection Limit of Solvent Polymeric Ion-Selective Electrodes. 1. Modeling the Influence of Steady-State Ion Fluxes

Tomasz Sokalski,*†§ Titus Zwickl,† Eric Bakker,*‡ and Ernö Pretsch*†

Department of Organic Chemistry, Swiss Federal Institute of Technology (ETH), Universitatsstrasse 16, CH-8092 Zurich, Switzerland, and Department of Chemistry, Auburn University, Auburn, Alabama 36849
ISEs: Low Limit of Detection

- See series of papers by Pretsch, Bakker and Sokalski

![Diagram showing ion transfer and filling solution](image)

- Lower limits of detection should be possible if the primary ion concentration in the internal filling solution is kept low.
- Ion transfer across membrane OCCURS IN BOTH DIRECTIONS!
- At low sample concentrations, outer boundary region rapidly becomes saturated due to ion transport from internal filling solution.
Lead in Zurich Tap Water


Figure 2. Measurement procedure of potentiometric trace level determinations of Pb$^{2+}$ by calibrating with a series of lead ion solutions at higher concentration. Shown are the emf responses as a function of the sample activity for each of the separate measurements. The slopes for each of the five-point calibrations are, from top to bottom, 28.5, 28.4, 28.6, 28.6, 28.5, and 28.9 mV/decade.

Figure 6. Potentiometric determination of Pb$^{2+}$ in unspiked Zurich tap water at different pH values (see also Figure 5). Horizontal dotted lines: measurement of free lead in the native sample (lower value) and of total lead after buffering the pH to 4.0 (higher value). Vertical arrow: lead concentration obtained with ICPMS.
Response of electrodes based on tetra-, penta- and hexa-phosphine oxides to increasing concentration of Pb$^{2+}$ in a background of 0.01M Ca$^{2+}$ - evidence of ‘best-fit’ mechanism as response to Pb$^{2+}$ is enhanced as the cavity size increases (size selectivity). The hexamer produces excellent ISEs for Pb$^{2+}$, and also Hg$^{2+}$ (pH < 3.0).
Lead-Selective Electrodes Based on Calixarene Phosphine Oxide Derivatives, Francis Cadogan, Paddy Kane, M. Anthony McKervey, and Dermot Diamond, Anal. Chem. 1999, 71, 5544-5550
Planar ISE arrays for blood profiling
(with Matt Leader, Sendx)

A. Lynch, D. Diamond and M. Leader, Analyst, 2000, 125, 2264-2267.
Mass production of SCISEs and SCREs
(Alek Radu and Salzitsa Anastasova)

- Using Screen Printer DEK 248 silver paste was printed on plastic sheets.
- Next, carbon was printed twice, with 15 minutes of curing in oven at 200°C between successive prints.
- After finishing carbon, the insulating layer was printed and UV-cured.
- Conducting polymer Poly (3-octylthiophene) (10^{-2} M in Chloroform) was dropcast (initially) or grown electrochemically (later) on printed platforms.
- The CP is covered with a PVC membrane cocktail containing active components for ISEs and reference electrodes (Fluka)
Improving sensor reproducibility

Manual fabrication, conventional design

SP fabrication, manual deposition of CP layer (POT) and sensing layer

After zero point correction, slopes are virtually identical: single point calibration for each sensor
EC-deposition of CP Layer -> highly Reproducible Sensors

6 calibration curves superimposed!

SP fabrication, **electrochemical deposition of CP (PEDOT)**, manual deposition of sensing layer;
Applied to analysis of river water samples

Would it be possible to use these electrodes in a remote autonomous instrument?

**Screen Printed ISEs**
- V. low cost (cents), mass-produced
- Almost perfect reproducibility -> calibrate 1 per batch!
- V. high sensitivity -> LOD in low PPB for Pb\(^{2+}\); better than ICP-MS!, ..... & V. selective
- Each ISE used once; unknown estimated using 4-point standard additions

\[ y = 0.9705x + 0.0947 \]
\[ R^2 = 0.9912 \]
Change in Electrode Function over Time

See Electrochimica Acta 73 (2012) 93–97

Day 0: $y = 28.739x + 51.806$
$R^2 = 0.99981$

Day 4: $y = 28.029x + 48.261$
$R^2 = 0.99705$

Day 8: $y = 27.076x + 40.137$
$R^2 = 0.99892$

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

Continuous contact with river water

Conventional PVC-membrane based ISEs
Biofilm Formation on Sensors

- Electrodes exposed to local river water (Tolka)
- ‘Slime test’ shows biofilm formation happens almost immediately and grows rapidly
Remote, autonomous chemical sensing is a tricky business!
Direct Sensing vs. Reagent Based LOAC/ufluidics

Direct Sensing

- Sensor
- Signal
- Sample
- Molecular interactions

outside world

LOAC Analyser

- Sample, standards
- Reagents
- Source
- Reaction manifold
- Detector
- Waste
- BL
- Blank
- s
- t

Direct Sensing LOAC Analyser
Many people, myself included, expected that the ability to manipulate fluid streams, in microchannels, easily, would result in a proliferation of commercial LoC systems, and that we would see applications of these devices proliferating throughout science. In fact, it has not (yet) happened.

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.

Autonomous platform – water Analysis

Sampling port
Deployment at Osberstown WWTP

- Phosphate monitoring unit deployed
- System is fully immersed in the treatment tank
- Wireless communications unit linked by cable
- Data transmitted to cloud
Biofouling of sensor surfaces is a major challenge for remote chemical sensing – both for the environment and for implantable sensors.
Autonomous Chemical Analyser

49-Day Trial at Waste Water Treatment Plant

- Prototype P-Analyser
- Reference monitor

Concentration (mg/L P)

Time (hours)
Achieving Scale-up

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

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

Scalability ->

- Current platforms
  - €>20,000
  - €>2,000
  - €<200

- Massively scaled deployments of the future
  - €<20
  - €<2
Cost Comparison Analyser (€)

The €20 analyser

- Fluidics
- Electronics
- Housing
Use Arrays of Sensors....?

- If each sensor has an in-use 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 Materials

UV

VIS, Δ

Merocyanine Spiropyran

Off (spiropan)
On (merocyanine)

ABS

400 450 500 550 600 650

NM

Off (spiropan)
On (merocyanine)
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

![Chemical structure of pNIPAAm](image)

**Hydrophilic**

Hydrated Polymer Chains

**Hydrophobic**

Loss of bound water -> polymer collapse

$\Delta T$
Photo-actuator polymers as microvalves in microfluidic systems

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
Thanks to…

Thanks Johan for the invitation