’Monitoring Biochemical Parameters - Diagnostics, Wearables and Implants’

Professor Dermot Diamond
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National Centre for Sensor Research
Dublin City University

Invited Keynote Lecture Presented at
Neuroengineering Workshop
Weetword Hall
University of Leeds
September 22\textsuperscript{nd} 2015
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 pHealth
NAPES Consortium

Funded under grant agreement No. 604241 of the European Union’s Seventh Framework Programme
(Ron Ambrosio & Alex Morrow, IBM TJ Watson)
Dimensions of a Synapse

The promise of biosensors.....

In medicine and industry, tiny high-speed devices will track a wide range of biological reactions.

by H. Garrett DeYoung

High Technology, Nov. 1983, 41-49
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


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


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.’
\( \mu \text{-TAS: The Original Concept} \)

Integrate all operations required to obtain an analytical measurement

- Take samples
- Add reagents
- Process samples
- Perform analysis
- Perform calibrations

Microdimensioned channels leads to dramatic reductions in reagent consumption, waste generation, energy demand, sample turnaround.

Microdialysis sampling via arterio-venus shunt


Real Time Blood Glucose and Lactate

System functioned continuously for up to three hours!
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 Press Release
September 29, 2008

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 is for several days (up to 7) continuous monitoring; then replace**

**Use model is good – short periods of use, regular replacement, coulometric detection (no calibration if the enzyme reaction is specific)**

Freestyle Navigator appears to have been withdrawn from the US market (2012)

Reasons unclear but may be related to low rates of user uptake – there are many reasons why this can happen...
Apple, iWatch & Health Monitoring

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.

How will they integrate biosensing with the iWatch.....?
**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.

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

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**Google Glass project has been abandoned!** (Jan 15 2015) see [https://plus.google.com/+GoogleGlass/posts/9uiwXY42tvc](https://plus.google.com/+GoogleGlass/posts/9uiwXY42tvc)

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Series of papers by Ramachandram Badugu, Joseph R. Lakowicz, and Chris D. Geddes [1] & Jin Zhang of the University of Western Ontario [2] based on boronic acid quinolinium receptors: Under alkaline conditions (pH9) saccharide diols bind to form the B⁻ centre which interacts strongly with the N⁺ centre, quenching the fluorescence emission.


After decades of intensive research, our capacity to deliver chemo/bio-sensors capable of long-term autonomous use for in-vivo monitoring is still very limited.

Blood is by far the best diagnostic medium, but no chem/bio-sensor will function acceptably for more than a few days continuous exposure to blood without calibration.

The trend is to try and measure key markers from outside or from peripheral locations.
Argo Project (accessed March 9 2014)

- 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
Change in Electrode Function over Time

See Electrochimica Acta 73 (2012) 93–97

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

Continuous contact with river water

PVC-membrane based ISEs
• Electrodes exposed to local river water (Tolka)
• ‘Slime test’ shows biofilm formation happens almost immediately and grows rapidly
Control of membrane interfacial exchange & binding processes

Remote, autonomous chemical sensing is a tricky business!
Direct Sensing vs. Reagent Based LOAC/ufluidics

Direct Sensing

outside world

sensor

signal

sample

molecular interactions

LOAC Analyser

reagents

sample, standards

source

Reaction manifold

detector

waste

BL

 sample

blank

BL

s

t
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.

Phosphate: The Yellow Method

**Mixture (Reagent)**

\[(\text{NH}_4\text{VO}_3) + (\text{NH}_4)_6\text{Mo}_7\text{O}_{24}.4\text{H}_2\text{O}, \text{HCl conc.}\]

**Sample**

\[\text{H}_2\text{PO}_4^-\]

\[
(\text{NH}_4)_3\text{PO}_4.\text{NH}_4\text{VO}_3.16\text{MoO}_3
\]

- Yellow vanaomolybdophosphoric acid is formed when ammonium metavanadate and ammonium molybdate (mixture) reacts with phosphate (acidic conditions).

- In conventional (molybdate) method, ascorbic acid is used to generate the well-known deep blue complex (v. fine precipitate).

- Could not be exploited in LOAC devices until UV-LEDs became available!!!
2nd Generation Analyser: Design

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 web
Phosphate monitoring using the Yellow Method
Osberstown – 3 week deployment

Biofouling of sensor surfaces is a major challenge for remote chemical sensing – both for the environment and for implantable sensors
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

Current platforms

Massively scaled deployments of the future

Cost/Complexity -> Scalability ->
Cost Comparison Analyser (€)

Gen1 Gen2 Future

Fluidics Electronics Housing

The €20 analyser
Extend Period of Use via 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 Actuators

UV

VIS, Δ

Off (spiropyran)
On (merocyanine)

![Graph showing absorbance (ABS) vs. wavelength (NM)]

- Blue line: Off (spiropyran)
- Pink line: On (merocyanine)
Famous Molecule....

From Prof. Thorfinnur Gunnlaugsson, TCD School of Chemistry
Spotted on Nickelodeon Cartoons February 2015
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

\[
\text{Hydrophilic} \quad \xrightarrow{\Delta T} \quad \text{Hydrophobic}
\]

Hydrated Polymer Chains

Loss of bound water -> polymer collapse
Polymer based photoactuators based on pNIPAAm

Figure 3. (a, b) Images of the pSPNIPAAm hydrogel layer just after the micropatterned light irradiation. Duration of irradiation was (●, red) 0, (○) 1, and (■, green) 3 s. (c) Height change of the hydrogel layer in (●) non-irradiated and (○) irradiated region as a function of time after 3 s blue light irradiation.

poly(N-isopropylacrylamide) (PNIPAAm)
Formulation as by Sumaru et al

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
Actuation Mechanism

SPIRO (contracted)

H⁺, X⁻, solvent

acidic solution

H⁺, X⁻, solvent

white light

MEROD+ (expanded)

X:Y:Z = 1:99:5

Mechanism involves diffusion of protons, counter ions & solvent out/in of the bulk gel to/from the external solution.
Photo-actuator polymers as microvalves in microfluidic systems

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

Reversible Photo-Switching of Flow

Above: scheme showing switching process protonated MC-H⁺ photoswitched to SP triggering p(NIPAM-co-AA-co-SP) gel contraction and opening of the channel.

Right, Top: Photos of the valve in operation before (flow OFF) and after (flow ON) one minute of blue light irradiation.

Right, Bottom: Flowrate and cumulative volume measurements showing repeated opening and closing of microvalve: 1 min blue light irradiation opens valve followed by ~5.5 min thermal relaxation to close.

From: ‘Molecular design of light-responsive hydrogels, for in-situ generation of fast and reversible valves for microfluidic applications ‘ (submitted for publication)

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Background

Stereolithography

- Single photon absorption
- 2D patterns

Two-photon polymerisation

- Two photon absorption
- 3D structures
Background

http://www.nanoscribe.de/
Creating 3D soft gel structures with a line resolution of ca. 200 nm
Globular Porous Structure
3D Scanning meets 3D Printing: Impact on Implant Surgery

Example: Conor Hurson, Consultant Orthopaedic Surgeon, St. Vincent’s University Hospital & Cappagh National Orthopaedic Hospital; working with Engineers at IT Tallaght
What is the state of the art?

- Highly conformable PEDOT-PSS organic polymer electrode arrays (OECTs)
- Placement of a 64-channel NeuroGrid on rat somatosensory cortex
- Functioned continuously for up to 10 days

NeuroGrid: recording action potentials from the surface of the brain
Conformable electrodes and electronics
Rogers Group, University of Illinois

Figure 3. Soft, Conformal Electronics for EEG
(A) Images of skin-like, or epidermal, electronics that exploit electrodes and semiconductor components in open, filamentary mesh architectures with fractal inspired geometries (left). These devices can softly laminate onto and peel away from (middle) the surface of the skin for stable, non-irritating, long-lived measurement interfaces. Spectrograms of representative EEG data (right) show characteristic alpha rhythm behavior when the eyes are closed (Kim et al., 2011).
(B) Image of a stretchable electronic system that integrates chip-scale components and a free-floating interconnect network for wireless EEG. Data acquired from the forehead (green; middle and right) are quantitatively similar to those simultaneously acquired using a wired commercial device (blue). The large deflections correspond to blinking of the eyes as the subject shifts from performing mental math to resting (Xu et al., 2014).

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

We have the tools – now we need creativity!
Thanks to

• Members of my research group
• NCSR, DCU
• Science Foundation Ireland & INSIGHT Centre
• Research Partners – academic and industry
• NAPES, CommonSense, Aquawarn EU Projects

Thanks for listening