Microfluidic Platforms based on Biomimetic Materials and Principles

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AllIM Facility, Innovation Campus, Squires Way, North Wollongong
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 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
pH sensing – wasn’t that solved by Nikolskii in the 1930’s?

<table>
<thead>
<tr>
<th>EVENT</th>
<th>DATE</th>
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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>
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<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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<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
And for nutrients....
Personal health Monitoring....

Implantable artificial organs, medical devices, sensors....capable of functioning autonomously and reliably for years....constantly monitoring our health status and reporting to cloud databases....
Artificial Pancreas

Used a Technicon segmented flow colorimetric glucose analyser

Sugar levels: sub-cutaneous insulin

Sugar levels: artificial pancreas

Insulin addition


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

- 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.

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.
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;**

Freestyle Navigator appears to have been withdrawn from the US market (2012);

Reasons unclear but likely to be related to biofouling of the electrodes or other issues related to the electrochemical measurement;

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
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.

**Abstract**

**Microelectrodes In An Ophthalmic Electrochemical Sensor**

**Kind Code**

**A1**

**Liu; Zenghe**

**April 17, 2014**

**United States Patent Application**

**20140107445**

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**Google Contact Lens**

**Google Smart Contact Lenses Move Closer to Reality**

- 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

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**Biosensors & Bioelectronics, 2011, 26, 3290-3296.**
After decades of intensive research, our capacity to deliver successful long-term deployments of chemo/bio-sensors in remote locations is still very limited
MicroTAS/Lab on a Chip/Microfluidics

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.

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 (spiropyran)
On (merocyanine)

UV

VIS

ABS

Off (spiropyran)
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
Polymer based photoactuators based on pNIPAAm

Formulation as by Sumaru et al


X:Y:Z = 1:99:5

poly(N-isopropylacrylamide) (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.
Photo-actuator polymers as microvalves in microfluidic systems

Photoswitchable Binding

UV

VIS, Δ

Off (spiropyran)
On (merocyanine)

ABS

NM

400 450 500 550 600 650

Slide 20
Spiropyran and Metal Ions

The binding of many metals, such as Cu$^{2+}$ and Co$^{2+}$, to the phenolate of the MC form has been demonstrated.

Increase in absorbance below ~460 nm due to formation of MC$_{2}$-Cu$^{2+}$ complex.

Decrease at 540 nm as free MC concentration decreases.
Characterisation

Uptake and Release – ‘Post Column’ Detection

\[ \text{Co}^{2+} + \text{PAR} \rightarrow \text{PAR-Co}^{2+} \]

410 nm \hspace{1cm} 510 nm
Published on Web 11/01/2010 (speed ~x4): channels filled with KOH (pH 12.0-12.3 + surfactant; agarose gel soaked in HCl (pH 1.2) sets up the pH gradient; droplets of mineral oil or DCM containing 20-60% 2-hexyldecanoic acid + dye. Droplet speed ca. 1-10 mm/s; movement caused by convective flows arising from concentration gradient of HDA at droplet-air interface (greater concentration of HDA towards lower pH side); **HDA <-> H⁺ + DA⁻**.

**Maze Solving by Chemotactic Droplets;** Istvan Lagzi, Siowling Soh, Paul J. Wesson, Kevin P. Browne, and Bartosz A. Grzybowski; *J. AM. CHEM. SOC.* 2010, **132**, 1198–1199

Photo-modulation of pH

Channel Solution: Spiropyran Sulfonic Acid 10^{-3}M (H_2O)

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<tr>
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<th>pH</th>
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<tr>
<td>H_2O</td>
<td>6.5</td>
</tr>
<tr>
<td>MCH^{+}-SO_3^-</td>
<td>4.8</td>
</tr>
<tr>
<td>SP-SO_3^-</td>
<td>3.4</td>
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Movement of Droplets in Channels using Light

- We use light to create a localised pH gradient
- This disrupts an ion pair at the droplet interface
- Surfactant is expelled and movement of the droplet occurs
- Interested in exploring how to use droplets for sensing and for transport & release of active components
Mechanism of Photo-Stimulated Droplet Movement (with David Officer, UOW)

We can do the same with IL Droplets

Trihexyl(tetradecyl)phosphonium chloride ([P\textsubscript{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\textsuperscript- ion which is created using a polyacrylamide gel pad soaked in 10\textsuperscript{-2} M HCl; A small amount of NaCl crystals can also be used to drive droplet movement.

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.
Background

Stereolithography

- Single photon absorption
- 2D patterns

Two-photon polymerisation

- Two photon absorption
- 3D structures
Background

http://www.nanoscribe.de/
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!