On-Body Chem/Bio-Sensing - Opportunities and Challenges

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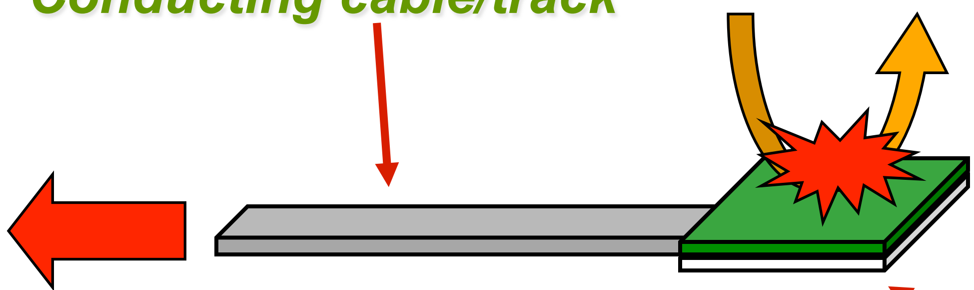
What is a Chemo/Bio-Sensor?

'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'



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**)

History: Calixarenes, 1984/5

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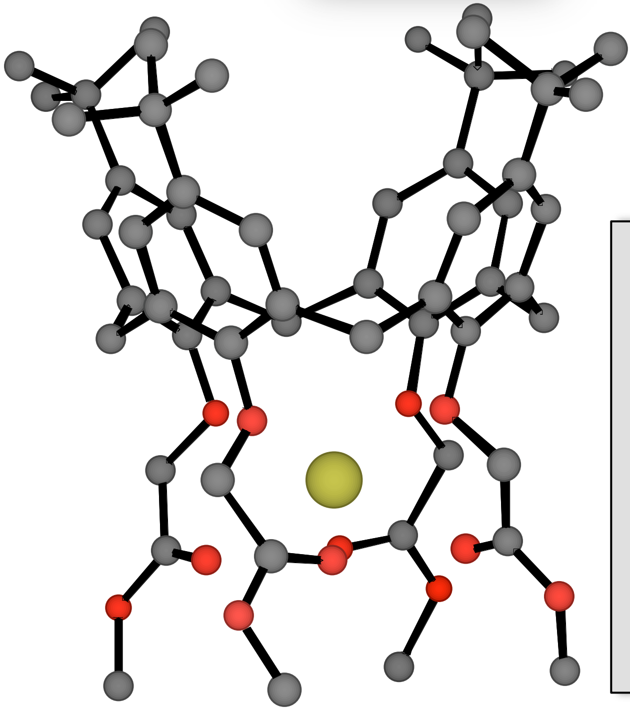
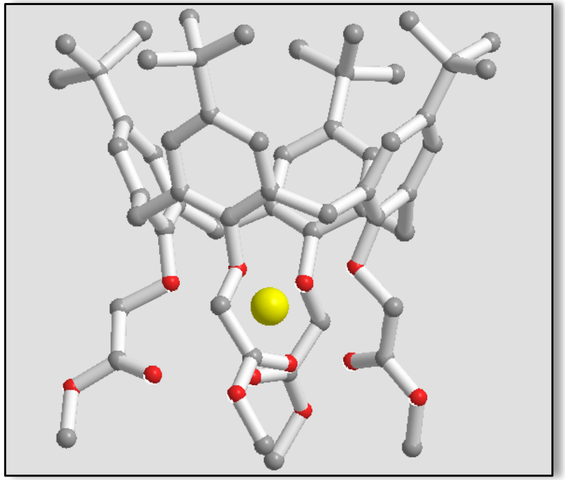
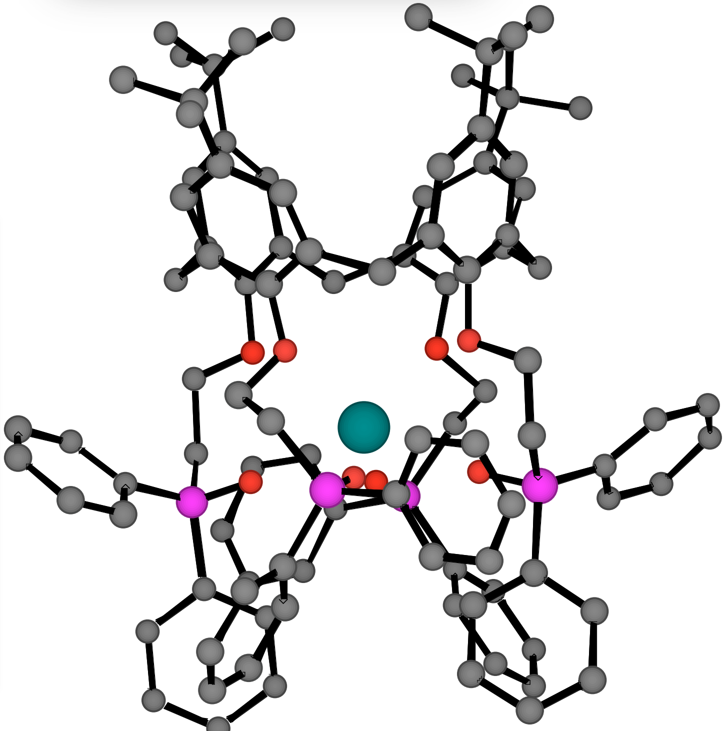


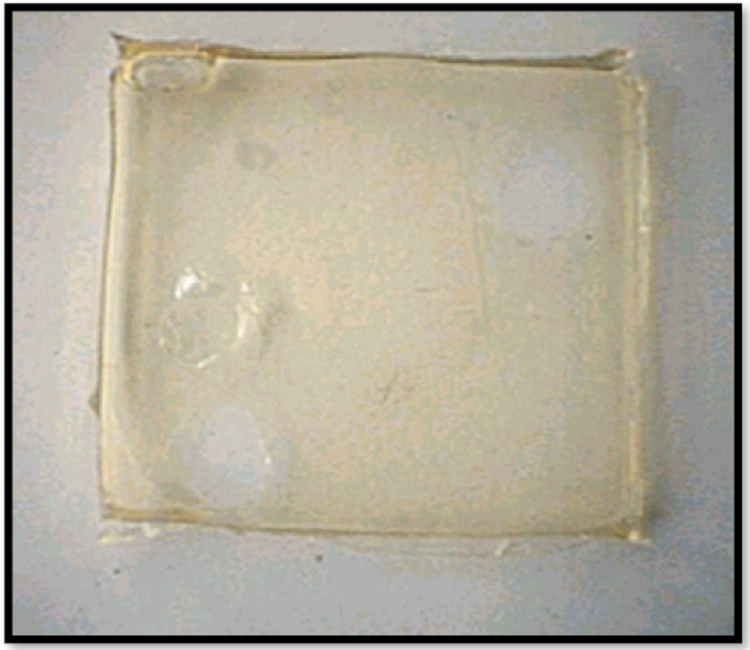


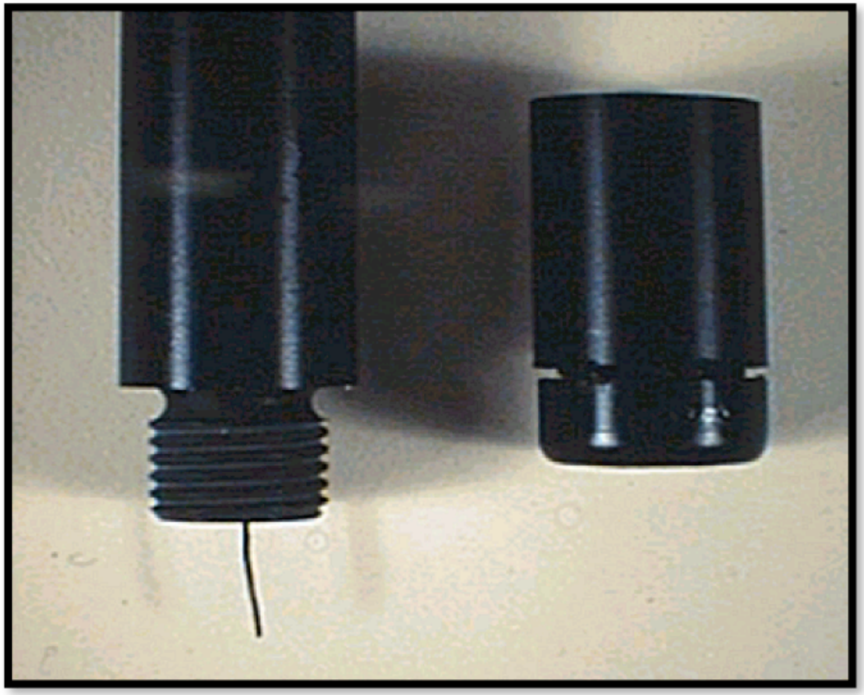


Tetraester - Na+ selective

Tetraphosphine oxide - Ca^{2+} selective

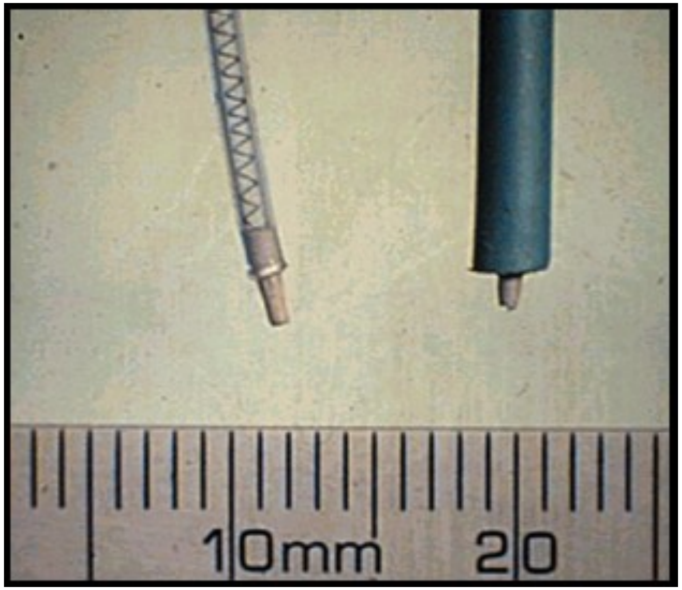
PVC - Membrane ISEs





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; In-Vivo Sensing



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

Dr. David Band, St Thomas's Hospital London

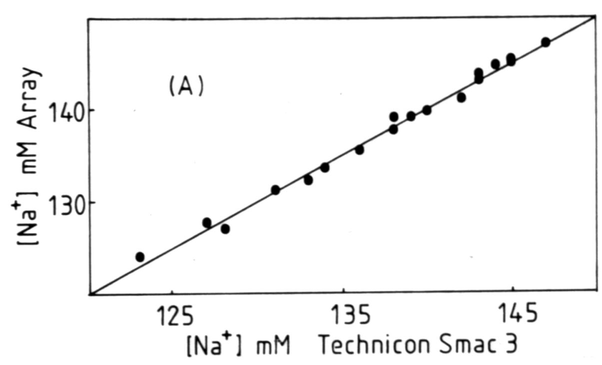
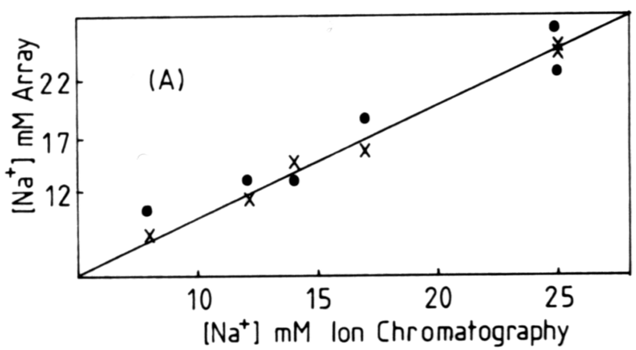


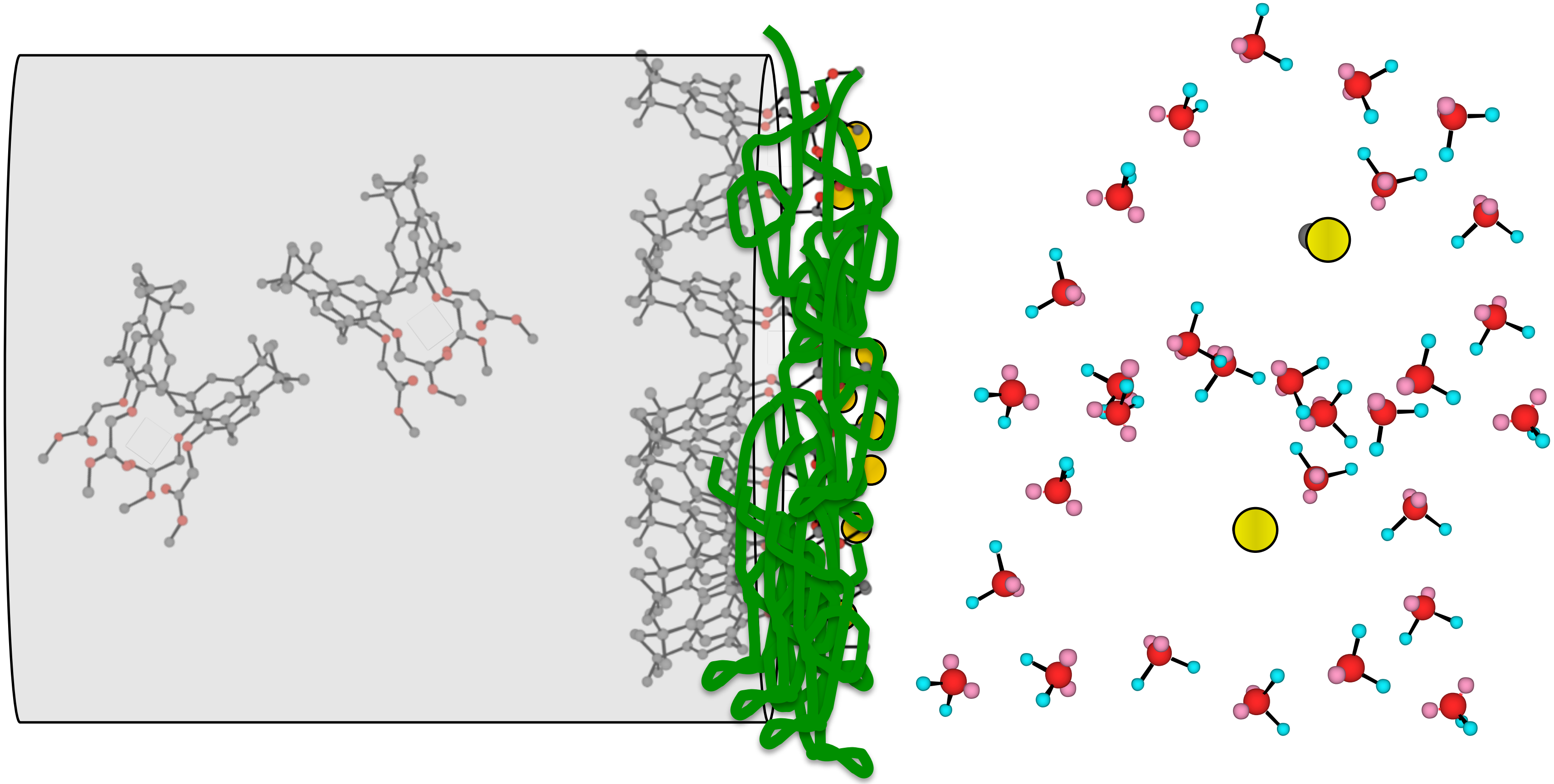
Fig. 3. Comparison of plasma sodium analysis using the array-FIA approach with a SMAC analyser. Good correlation without bias is obtained [5].



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

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

Control of membrane interfacial exchange & binding processes



Remote, autonomous chemical sensing is a tricky business!

Implantable sensors e.g. The Artificial Pancreas….

- Implantable unit comprising a glucose sensor (based on enzyme glucose oxidase) coupled with insulin reservoir
- Effective lifetime – many years (5-yr minimum target)
- Problem: glucose biosensor will not function reliably for more than a few days when implanted
- How to remotely calibrate
- Stability of reagents/calibrants

But the concept of the artificial pancreas has been around for decades;
SUGAR ELECTRODE SENSOR FOR ARTIFICIAL PANCREAS
By: BESSMAN, SP; SCHULTZ, RD
HORMONE AND METABOLIC RESEARCH Volume: 4 Issue: 6 Pages: 413-417 Published: 1972

Artificial Pancreas

A. M. ALBISSER, M.A.SC., PH.D., AND ASSOCIA

Used a Technicon segmented flow colorimetric glucose analyser

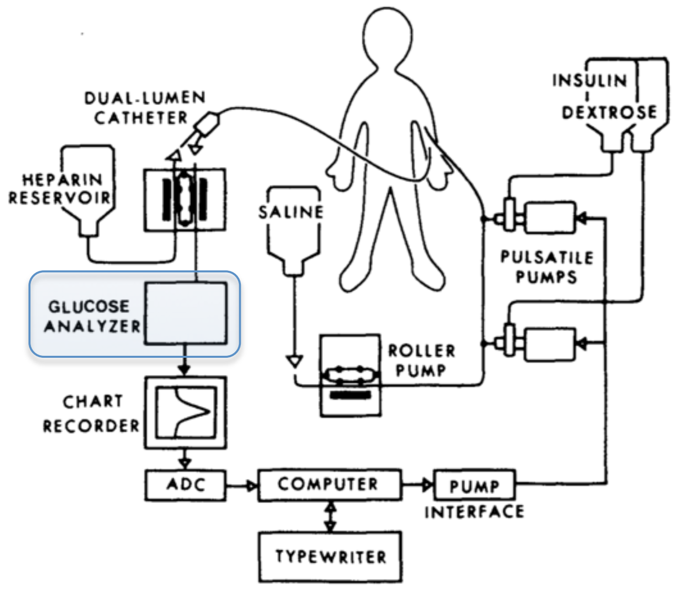
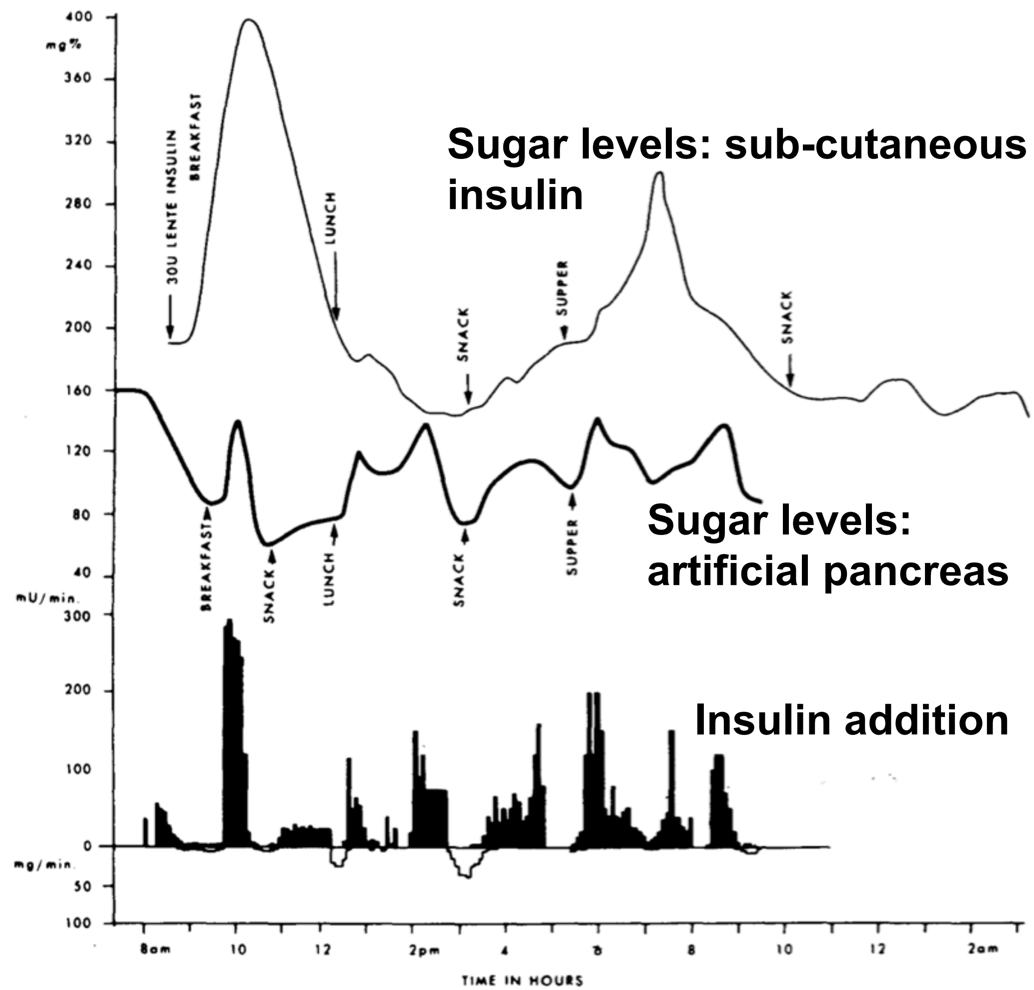


FIG. 1. Schematic diagram of apparatus used for monitoring and automatic regulation of blood sugar.



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

Up to now, implantable pumps for clinical application and suitable for the delivery of insulin have not been developed. However several groups are working on the development of both implantable dosing units and an implantable glucose sensor. 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. Only when these questions have been answered and a suitable pumping and dosing unit have been developed, can the closed-loop system for the control of blood glucose be realised and miniaturised for implantation.

An implantable artificial pancreas, W. Schubert, P. Baurschmidt, J. Nagel, R. Thull, M. Schaldach;

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**’

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

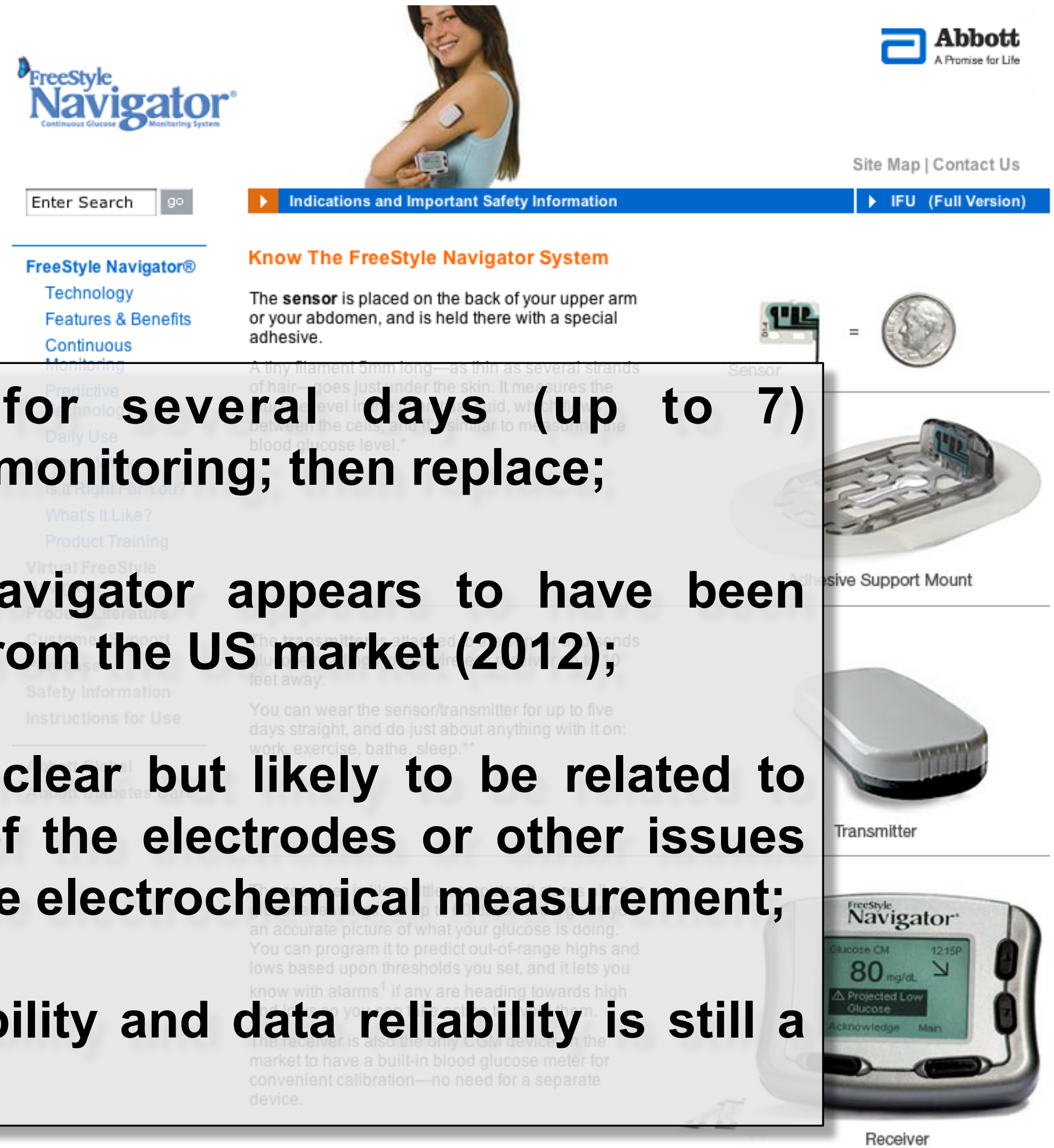
‘Abbott completes TheraSense acquisition’

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 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 minimize 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 and data reliability is still a huge issue!

So where are we?

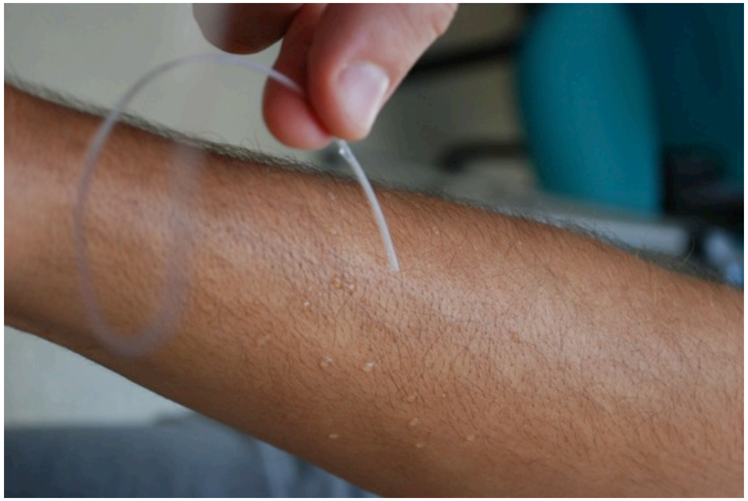
- **The dominant model for success (outside specialised laboratories) in clinical applications for chemical sensors and biosensors is primarily based on 'single shot' or at best short-term use (hours, days), employing disposable devices.**
- **Long-term chemo/bio-sensor implants are still a long way off.**
  - Fundamental breakthroughs are required to make progress
- **In the meantime, on-body sensing (non- or minimally-invasive…..) offers opportunities.**

What sample do we go for?
blood, sweat, tears………..

Wearable Chemical sensors
What to measure? What sample?

- BODY FLUIDS – BLOOD, SWEAT, TEARS, URINE, SALIVA, INTERSTITIAL FLUID (MICRONEEDLE SAMPLING PATCHES)

- BREATH ANALYSIS

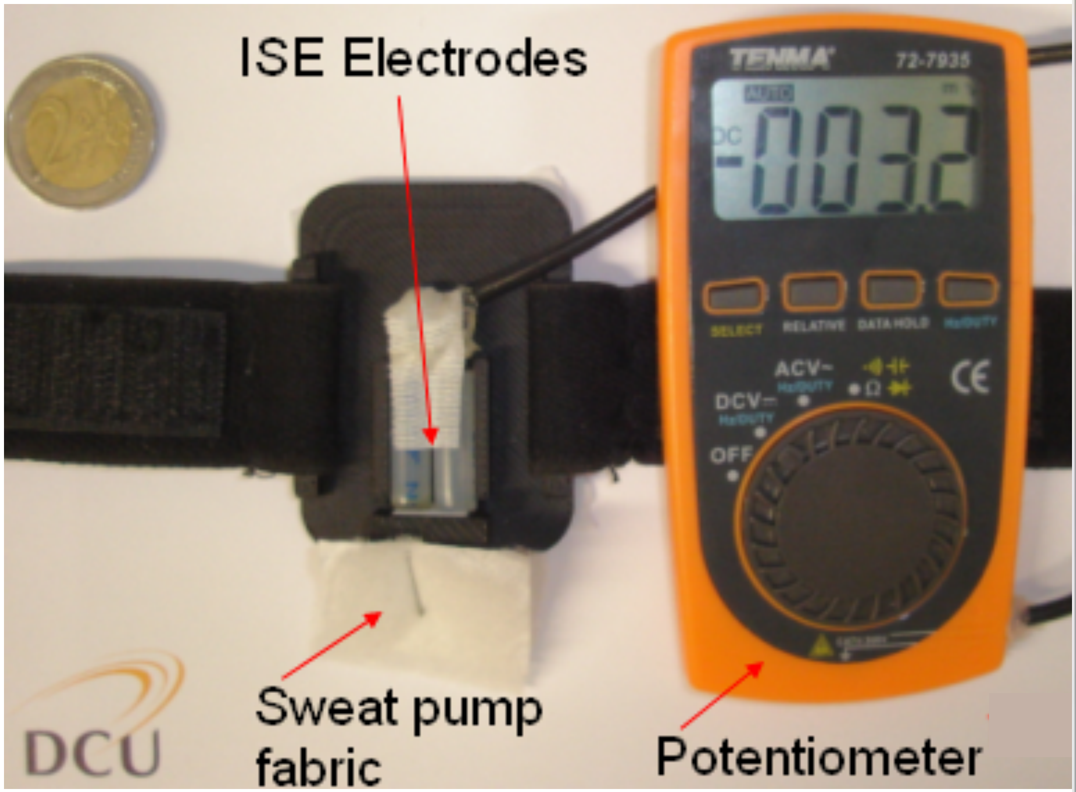


SWEAT IS ACCESSIBLE, BUT RELATIONSHIP TO SYSTEMIC PHYSIOLOGY (BLOOD) NOT WELL UNDERSTOOD;

SAMPLING IS AN ISSUE

- PLATFORM CONFIGURATION
  - PATCH; WATCH; BAND; TEXTILE INTEGRATED

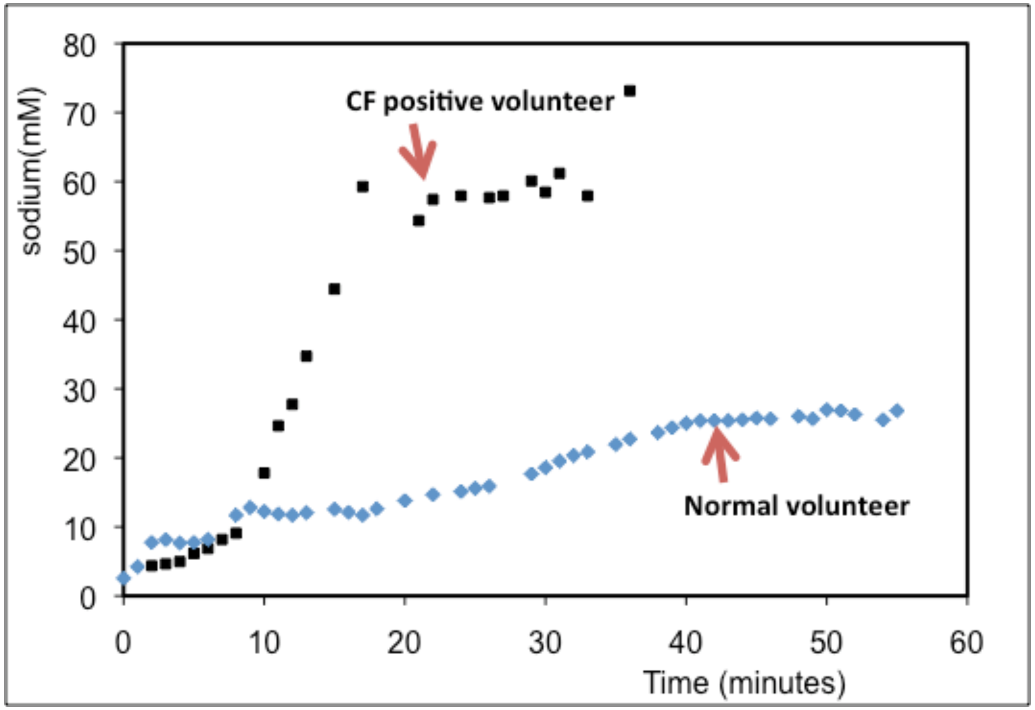
Na+ sensor: Sodium Sensor Belt (SSB)



Schazmann, B., et al., Analytical Methods, 2010, 2(4): p. 342-348.

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

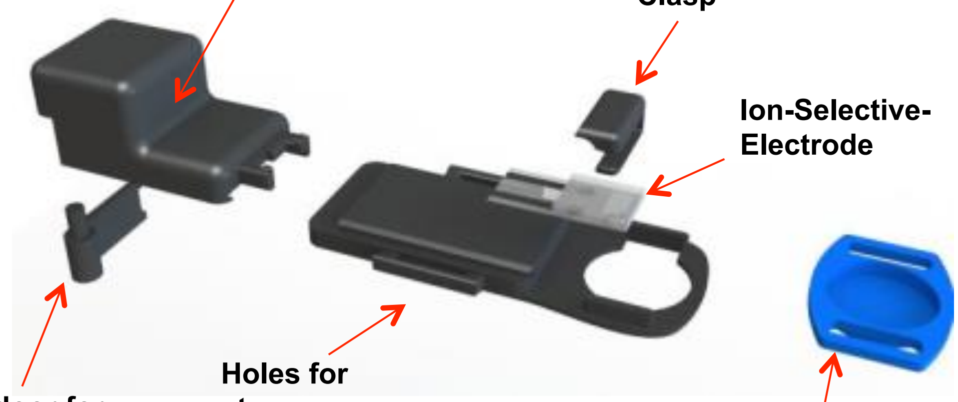


- **Diagnostic CF threshold >60mM [Na^+] reached**
- **Issue with initial delay**
  - arises from inherent delay in onset of sweating
  - contribution from device ‘dead-volume’

Na^+ Monitoring in Sweat

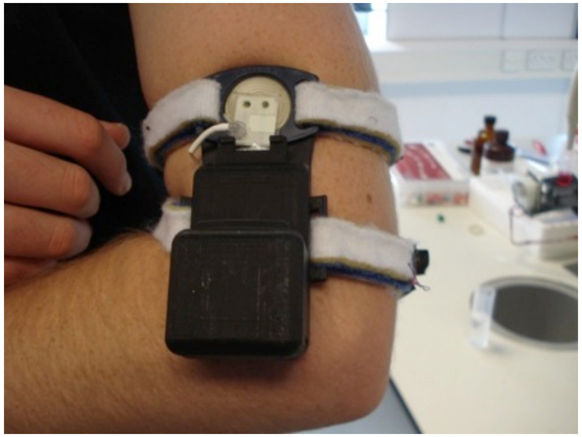
Real time monitoring of Sodium in Sweat through screen printed potentiometric strips:

- **Monitoring of athletes during exercise**
- **Monitoring clinical conditions e.g. Cystic Fibrosis patients**

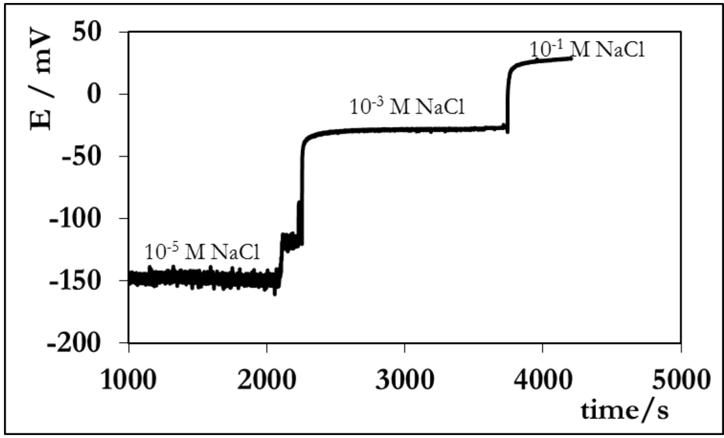


Macroduct sweat sampling unit (Wescor Corporation) Speed x5

Pilocarpine based sweat sampling

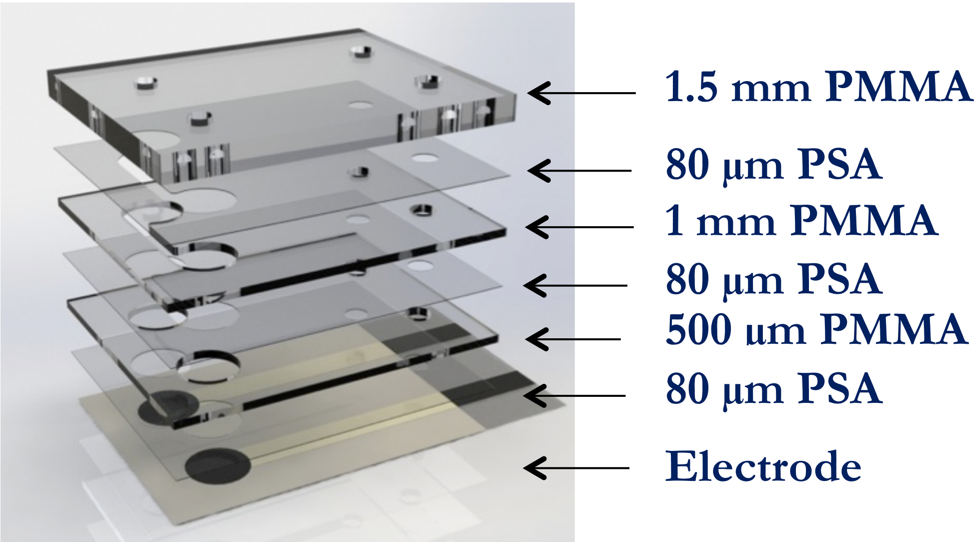


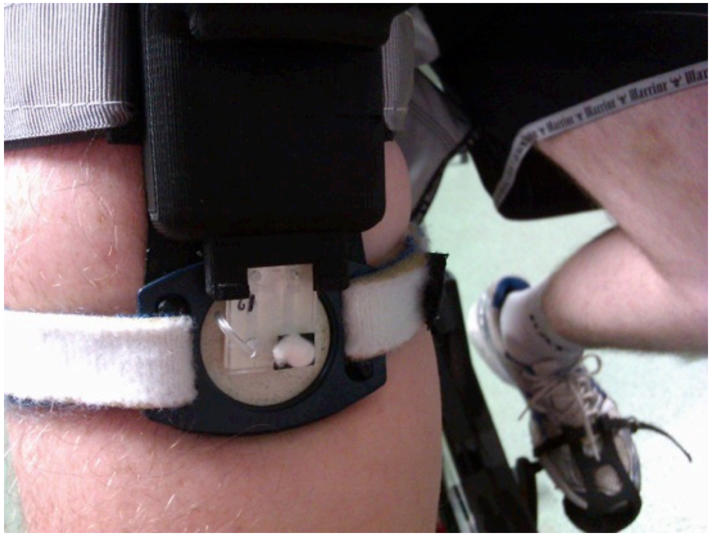
Exercise based sweat sampling

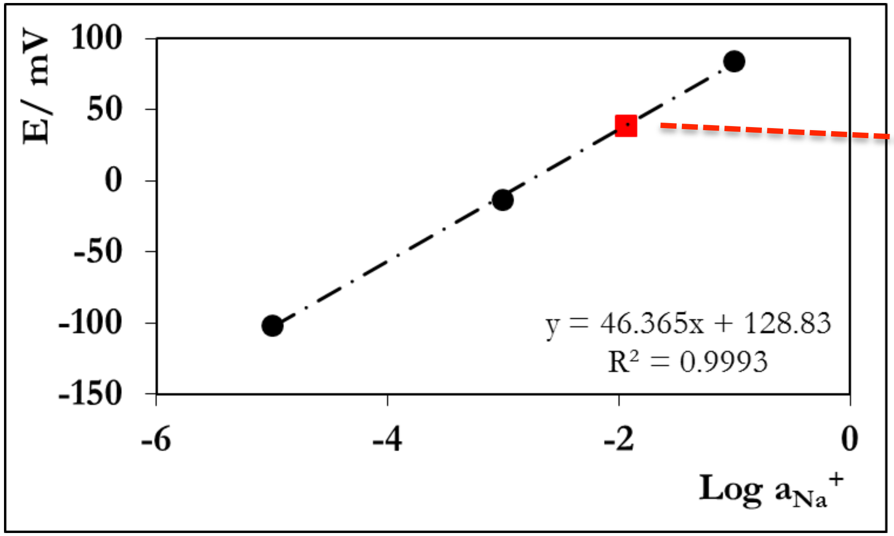


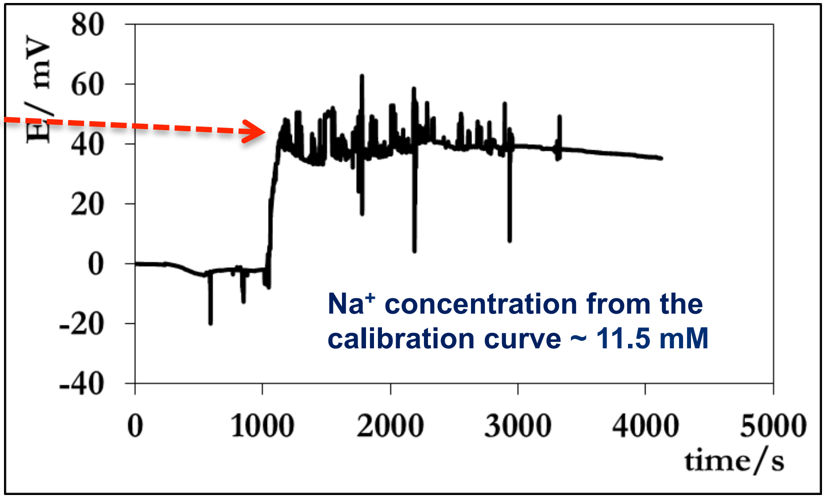
Sensor calibration

On-Body Sweat Analysis

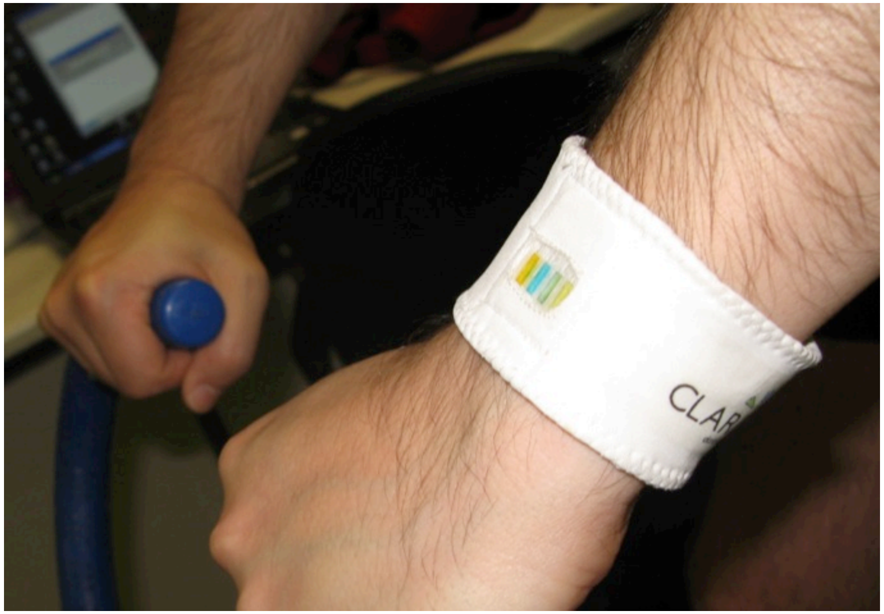


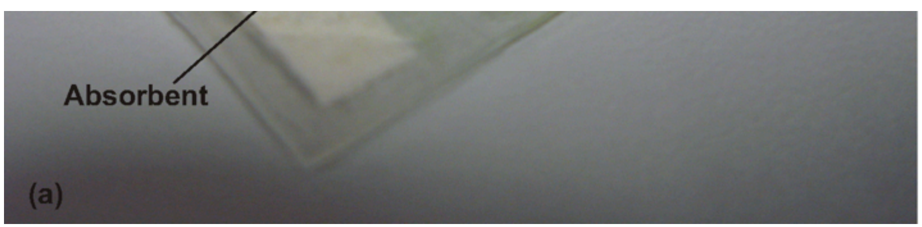


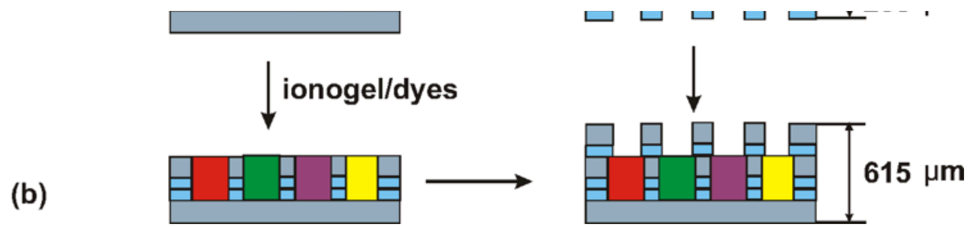




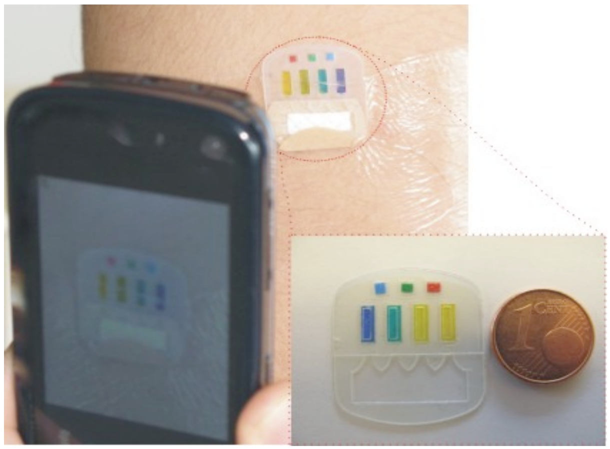
Microfluidic pH Sensor fabrication



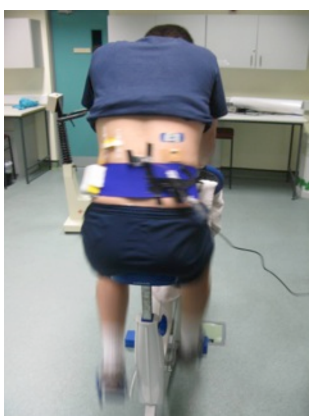




pH Monitoring via Smart Phone App



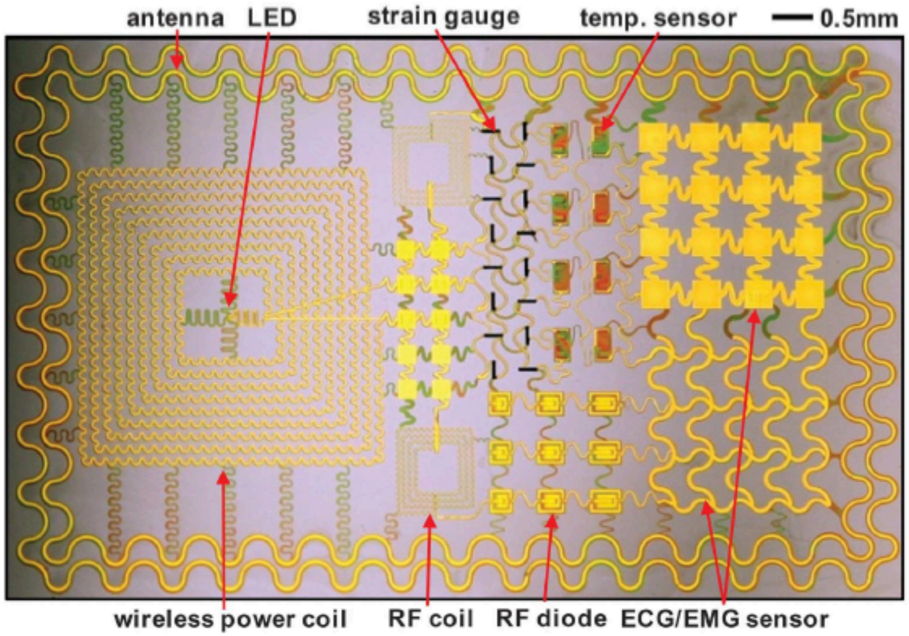
- COLOUR CHANGE VISIBLE BY EYE
- SMARTPHONE APP TO DETECT pH AUTOMATICALLY
- REAL TIME VIDEO ANALYSIS IS POSSIBLE



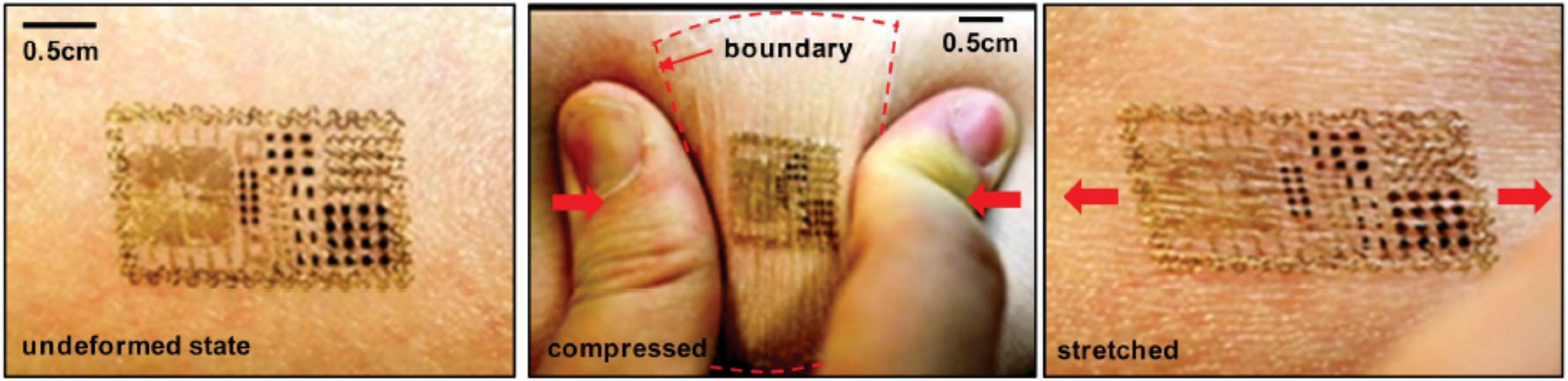
Time [min]	pH Meter	Dyes Prediction (pH)	% RE
20	6.38	5.89	7.68
30	5.8	5.56	4.14
40	5.67	5.67	0.00
50	5.95	5.63	5.38

SWEAT pH DETERMINATION USING THE BARCODE IN AN ATHLETE DURING A 50 MIN TRAINING PERIOD

Latest Trends – Tattoo format sensors



Prof. John Rogers @ University of Illinois



Wearable Cameras

- **Large marketspace potential**
  - The market for Google Glass hardware alone is estimated to be worth $11B by 2018
  - Global market for wearables in health and fitness could reach 170 million devices by 2017, an annual growth of 41% (AIB research)

ACS Breakthrough Science Videos

Immunochromatographic Diagnostic Test Analysis Using Google Glass
Steve Feng, Romain Caire, Bingen Cortazar, Mehmet Turan, Andrew Wong, and Aydogan Ozcan
DOI: 10.1021/nn500614k

Using Google Glass for Diagnostics

Terms of Use

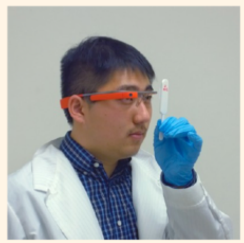
ARTICLE

Immunochromatographic Diagnostic Test Analysis Using Google Glass

Steve Feng,[†,‡] Romain Caire,[†,‡] Bingen Cortazar,[†,‡] Mehmet Turan,[†,‡] Andrew Wong,[†,‡] and Aydogan Ozcan[†,‡,§,⊥,*]

[†]Electrical Engineering Department, [‡]Bioengineering Department, [§]California NanoSystems Institute, and [⊥]Department of Surgery, David Geffen School of Medicine, University of California, Los Angeles, California 90095, United States

ABSTRACT We demonstrate a Google Glass-based rapid diagnostic test (RDT) reader platform capable of qualitative and quantitative measurements of various lateral flow immunochromatographic assays and similar biomedical diagnostics tests. Using a custom-written Glass application and without any external hardware attachments, one or more RDTs labeled with Quick Response (QR) code identifiers are simultaneously imaged using the built-in camera of the Google Glass that is based on a hands-free and voice-controlled interface and digitally transmitted to a server for digital processing. The acquired JPEG images are automatically processed to locate all the RDTs and, for each RDT, to produce a quantitative diagnostic result, which is returned to the Google Glass (*i.e.*, the user) and also stored on a central server along with the RDT image, QR code, and other related information (*e.g.*, demographic data). The same server also provides a dynamic spatiotemporal map and real-time statistics for uploaded RDT results accessible through Internet browsers. We tested this Google Glass-based diagnostic platform using qualitative (*i.e.*, yes/no) human immunodeficiency virus (HIV) and quantitative prostate-specific antigen (PSA) tests. For the quantitative RDTs, we measured activated tests at various concentrations ranging from 0 to 200 ng/mL for free and total PSA. This wearable RDT reader platform running on Google Glass combines a hands-free sensing and image capture interface with powerful servers running our custom image processing codes, and it can be quite useful for real-time spatiotemporal tracking of various diseases and personal medical conditions, providing a valuable tool for epidemiology and mobile health.



KEYWORDS: Google Glass · rapid diagnostic test reader · colorimetric sensor · lateral flow immunochromatographic assays · HIV testing · prostate-specific antigen (PSA) test · mobile health

ACS Nano 8 (3) 3069-3079, 2014

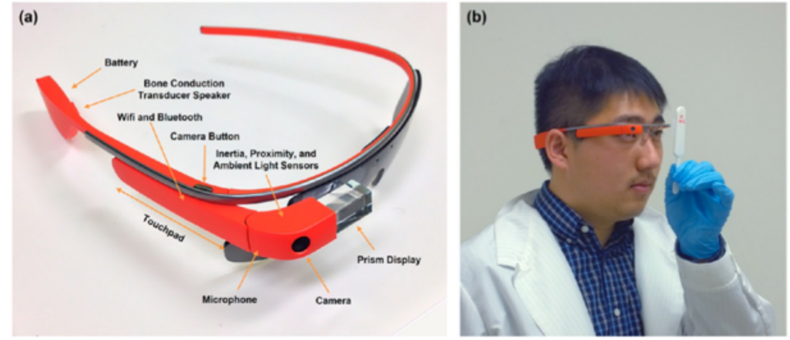


Figure 1. Labeled Google Glass and demonstration of imaging a rapid diagnostic test (RDT). (a) Front-profile view of the Google Glass with various hardware components[36] labeled. (b) Example of using the Glass for taking an image of an RDT as part of our RDT reader application.

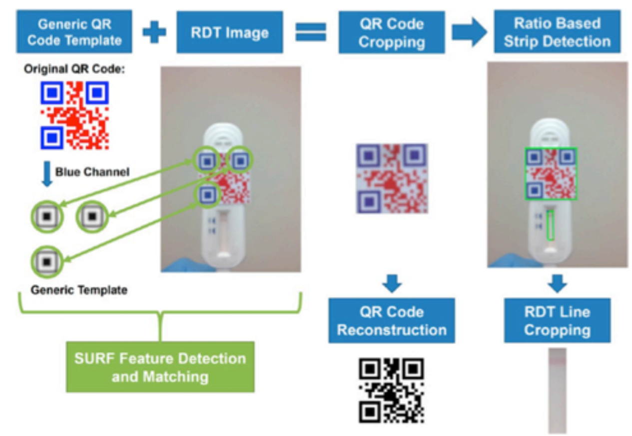


Figure 7. Methodology for finding QR code in a Glass image scene and segmenting the test strip region. Using a generic QR code template, we match location modules across the image using SURF.[67] Detected QR codes are then reconstructed and processed, and the location is used for ratio-based segmentation of the rapid diagnostic test strip region.

Contact lens for diabetics

- **Optically responsive contact lenses for diabetes**
  - **Series of papers by Ramachandram Badugu, Joseph R.Lakowicz, and Chris D. Geddes; e.g.[1]**
  - **Jin Zhang of the University of Western Ontario[2].**

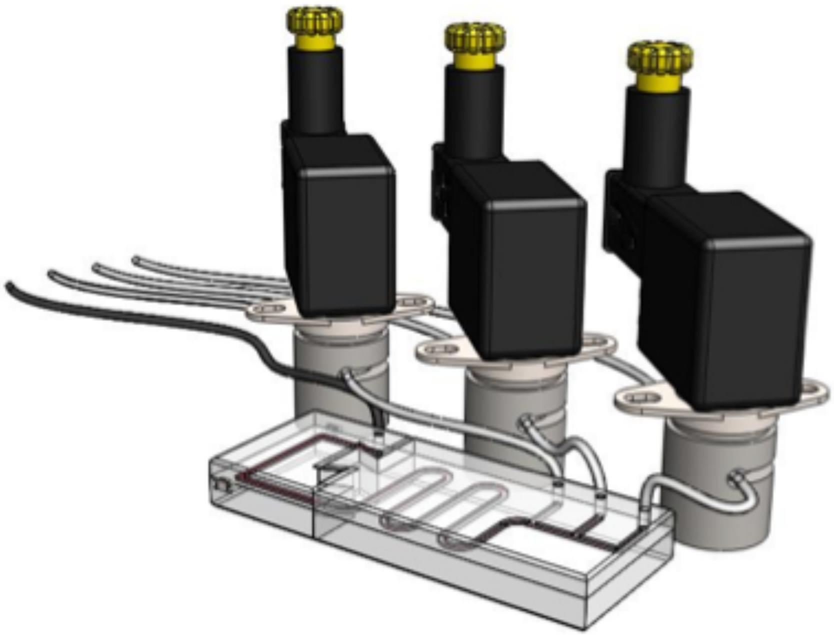
[1] Noninvasive continuous monitoring of physiological glucose using a monosaccharide-sensing contact lens, R. Badugu, J.R. Lakowicz, C.D. Geddes, Analytical Chemistry, 76 (2004) 610-618.

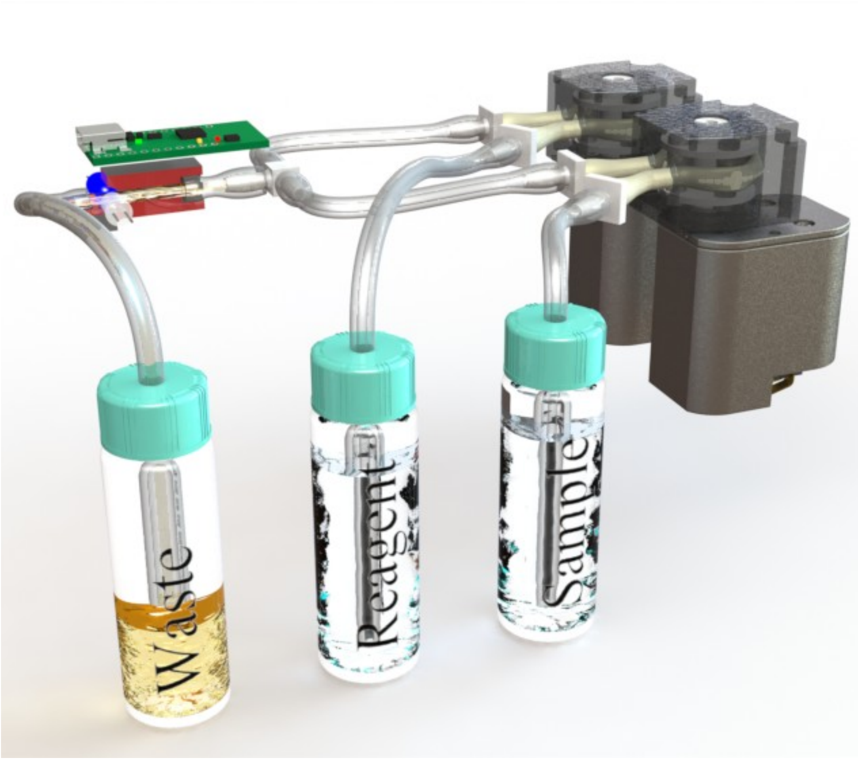
[2] Jin Zhang*, William Hodge, Cindy Hutnick, and Xianbin Wang, "Non-invasive diagnostic technology for diabetes through monitoring ocular glucose", J. Diabetes Sci. Tech. 5,166, (2011)

Conclusions

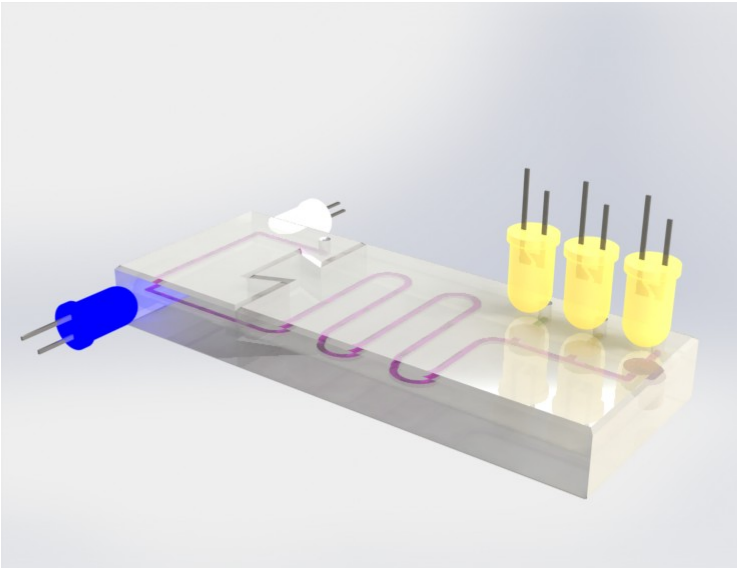
- Invasive/implantable chem/bio-sensors that function for 5 or more years (target for pancreas) are still well beyond the state-of-the-art
- Real-time in-situ Chem/Bio monitoring for 8-10 days is possible
- Use model that involves regular changing of the sensor is the key to success with current technologies
- Breakthroughs will emerge from multi-partner collaborations across industry and academia
- Arrays of short-term use sensors are possible, provided low cost liquid handling approaches can be realised
-

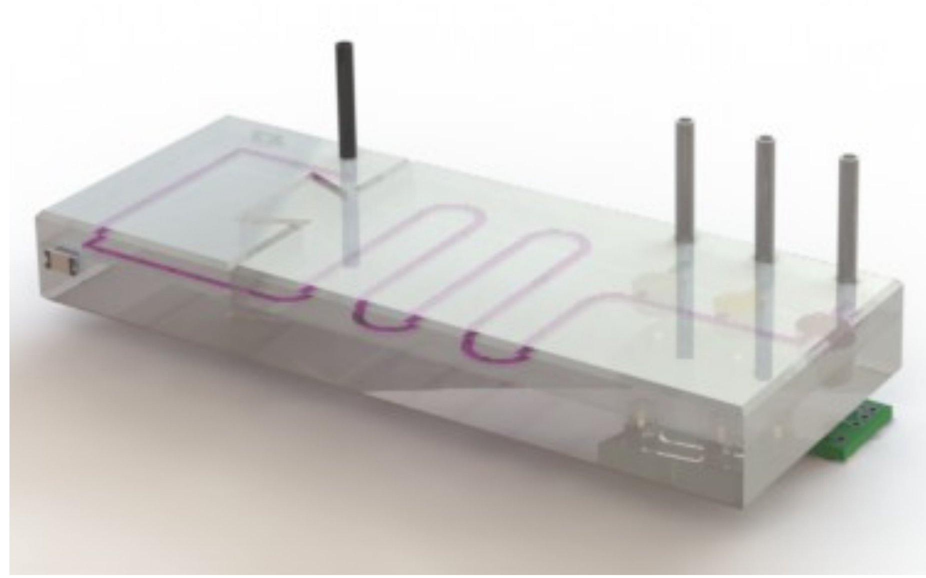
Can we go from this:

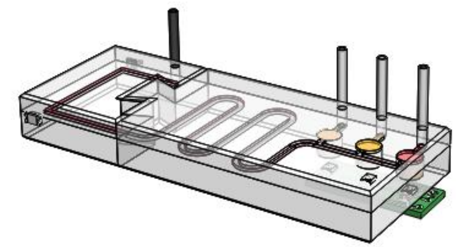


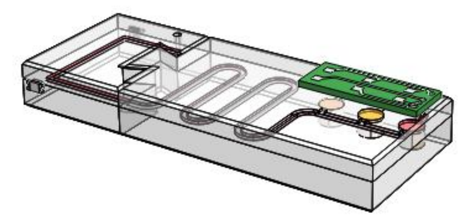


To Photo-Fluidics & Detection



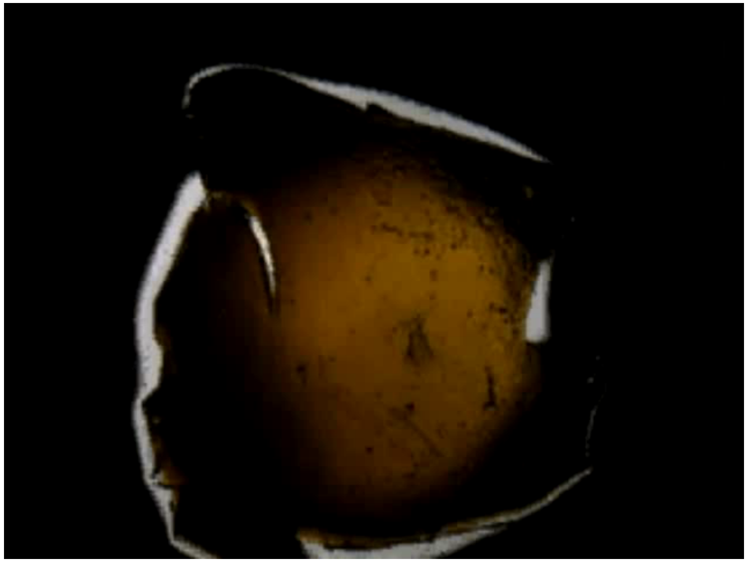


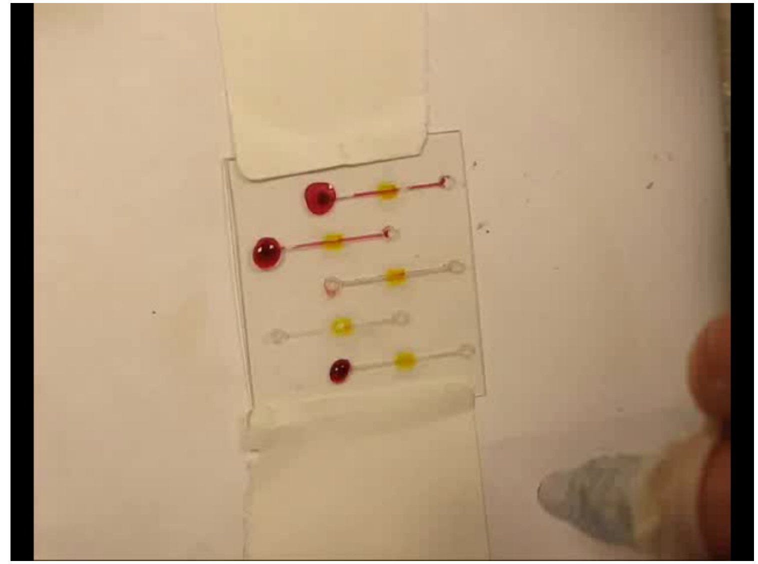


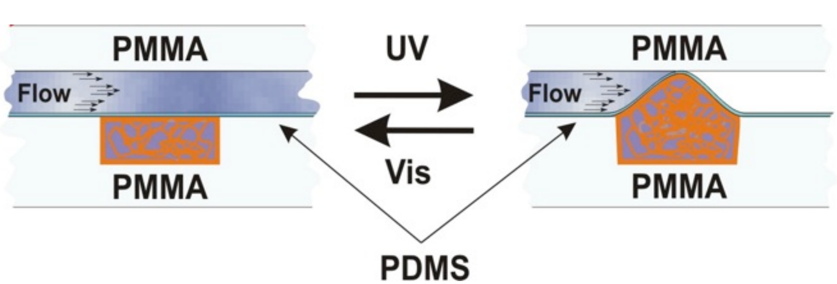


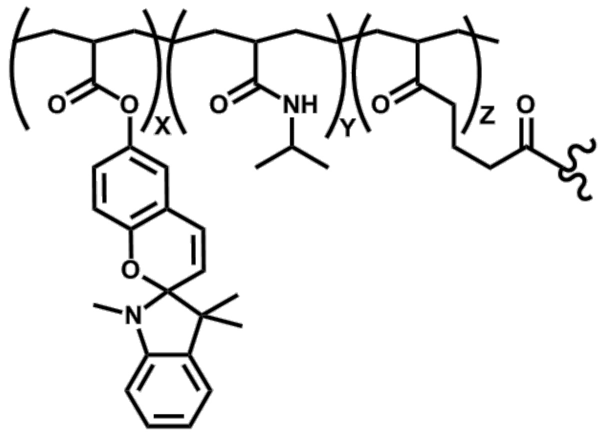
- Fluidic handling completely integrated into the microfluidic chip
- Valves actuated remotely using light (LEDs)
- Detection is via LED colorimetric measurements

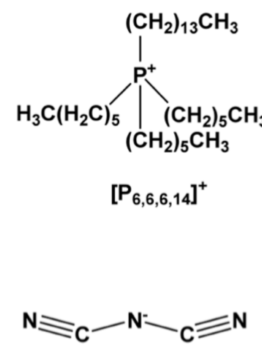
Photo-actuator polymers as microvalves in microfluidic systems











(b)

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.

Related Contributions to CIMTEC 2014

- *FO-8.2:L03* **Reversible Photochromic Polynorbornenes Bearing Spiropyran Side Groups for layer-by-layer coatings;**
  L. FLOREA[1], C. MOLONEY[1], D. NIXON[1], S. MOULTON[2], G.W. WALLACE[2], F. BENITO-LOPEZ[1,3], D. DIAMOND[1], [1]INSIGHT, National Centre for Sensor Research, Dublin City University, Dublin, Ireland; [2]ARC Centre of Excellence for Electromaterials Science and Intelligent Polymer Research Institute, University of Wollongong; [3]CIC Microgune, Arrasate-Mondragón, Spain

- *FO-8:P01* **Photo-Responsive Soft Actuators Based on Spiropyran Functionalised Hydrogels; A. DUNNE**, L. FLOREA, D. DIAMOND, INSIGHT, National Centre for Sensor Research, School of Chemical Sciences, Dublin City University, Dublin, Ireland

- *FO-8:P09* **Stimuli-Controlled Movement of Droplets and Polymeric "Vehicles", W. FRANCIS**, L. FLOREA, D. DIAMOND, INSIGHT, National Centre for Sensor Research, School of Chemical Sciences, Dublin City University, Dublin, Ireland

- *FO-9:P01* **Wearable Chemical Sensing - Sensor Design and Sampling techniques for Real-time Sweat Analysis; J.A. DEIGNAN**, S. COYLE, G. MATZEU, C. O'QUIGLEY, C. ZULIANI, D. DIAMOND, INSIGHT, National Centre for Sensor Research, Dublin City

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