Real-Time Monitoring of Sweat Electrolyte Composition

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ACES Tutorial presented at

11th Annual International Electromaterials Science Symposium

Deakin University, Burwood Campus, Melbourne, Australia, 10–12 February **2016**

Why Now?

- ICT Corporations like Google and Apple intend to develop new services based on time-series data related to health and other application domains.
- This implies moving beyond the mature offerings in exercise, sports etc. based on physical sensing (location, movement, heart rate, respiration..)
- Linking with Pharma and Medical Devices Companies – potentially huge resources
- But these services will require access to biochemical information obtained from sensors

HYPEwatch: Apple, iWatch & Health Monitoring

Apple Inc CEO Tim Cook

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

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.

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.

Google Smart Contact Lenses Move Closer to Reality

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

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

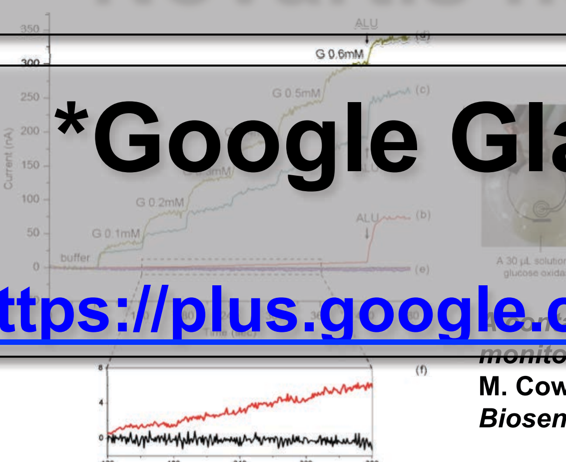

Fig. 2. Images of the sensor as it goes through surface functionalization and the related measured responses: (a) sequential images of sensor pre-treatment with GOD/titania/Nafion®; (b) measured amperometric response for the sensor just incubated with GOD; (c) measured amperometric response for the sensor prepared with GOD/titania/Nafion®; (d) measured amperometric response for the sensor prepared with GOD/titania sol–gel film; (e) three controls (signals for buffer) for the same pre-treatment of (b), (c), and (d); (f) the enlarged view of curve (b) and control of (b) for 120–360 s.

A contact lens with embedded sensor for monitoring tear glucose level, H. F. Yao, A. J. Shum, M. Cowan, I. Lahdesmaki and B. A. Parviz, *Biosensors & Bioelectronics*, **2011**, **26**, 3290-3296.

Known among scientists as "Ophthalmic Electrochemical Sensors," these contact lenses will feature flexible electronics that include sensors and an antenna. The sensors are designed to read chemicals in the tear fluid of the wearer's eye and alert her, possibly through a little embedded LED light, when her blood sugar falls to dangerous levels.

"Human tear fluid contains a variety of inorganic electrolytes (e.g., Ca.sup.2+, Mg.sup.2+, Cl.sup.-), organic solutes (e.g., glucose, lactate, etc.), proteins, and lipids. A

http://www.gmanetwork.com/news/story/360331/scitech/technology/google-s-smart-contact-lenses-may-arrive-sooner-than-you-think

ACS Nano Cover and Editorial

'Grand Plans for Nano', (9) 12 December 2015

EDITORIAL

Grand Plans for Nano

This year, nanoscience and nanotechnology have been called front and center to help address the grand challenges that the world faces. Our community has been asked to suggest future challenges, and the first such crowd-sourced grand challenge has been announced by the White House Office of Science and Technology Policy.[1−5] As we have said on these pages, we believe that nanoscientists and nanotechnologists around the world have special roles to play in bringing together expertise from diverse fields in order to tackle important tasks both large and small.[2] Indeed, our higher perspectives and communication across fields have great value globally in key areas such as devices, energy, health, and safety.[6−10]

As these Grand Challenge projects and other opportunities emerge, we will work with the leading and rising researchers in the relevant and potentially impacted communities to lay out the challenges and opportunities for nanoscience, nanotechnology, and other fields.[7−10] We see key roles for *ACS Nano* as a community forum to guide both nanoscience and nanoscience policy, to improve the impact of research by coordinating how it is reported,[11,12] and to showcase innovative work from around the world.

We are looking forward to an exciting year in 2016, which will mark *ACS Nano*'s tenth volume. It has already been quite an adventure, and much more is to come. We note that you will see some changes in our "look" next year. We will keep our forward-looking posture, our in-depth science and engineering, and the identifying markings that let you know right away when you are reading an article in *ACS Nano*. We have made subtle design changes that will enable us to speed up production in order to accelerate our already fast turn-around times of your work. We want to thank our production team and staff for this collaboration and all of the iterations that went into this optimization effort.

Finally, we want to thank you, our readers, authors, and referees for moving *ACS Nano* and our field to ever higher impact on our world. We wish you a safe and peaceful holiday season and look forward to hearing from you and working with you in the year and years ahead.

Disclosure: Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

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Printable Ultrathin Metal Oxide Semiconductor-Based Conformal Biosensors

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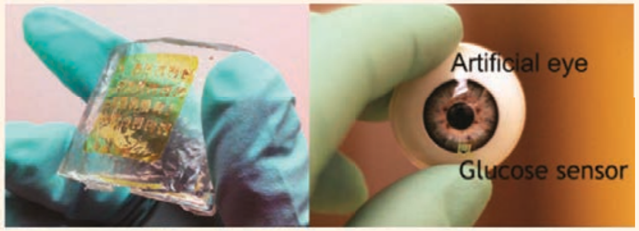
[†]California NanoSystems Institute, [‡]Department of Materials Science and Engineering, [§]Department of Pharmacology, [||]Department of Chemistry and Biochemistry, and [⊥]Department of Psychiatry, Hatos Center for Neuropharmacology, and Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, California 90095, United States. [#]These authors contributed equally.

ABSTRACT Conformal bioelectronics enable wearable, noninvasive, and health-monitoring platforms. We demonstrate a simple and straightforward method for producing thin, sensitive In_2O_3-based conformal biosensors based on field-effect transistors using facile solution-based processing. One-step coating *via* aqueous In_2O_3 solution resulted in ultrathin (3.5 nm), high-density, uniform films over large areas. Conformal In_2O_3-based biosensors on ultrathin polyimide films displayed good device performance, low mechanical stress, and highly conformal contact determined using polydimethylsiloxane artificial skin having complex curvilinear surfaces or an artificial eye. Immobilized In_2O_3 field-effect transistors with self-assembled monolayers of NH_2-terminated silanes functioned as pH sensors. Functionalization with glucose oxidase enabled D-glucose detection at physiologically relevant levels. The conformal ultrathin field-effect transistor biosensors developed here offer new opportunities for future wearable human technologies.



KEYWORDS: biosensor · aqueous process · metal oxide semiconductor · conformal · flexible · field-effect transistor

Materials – great! Sensing - ????

- FET configuration (same as 1984 paper)
- Amine and hydroxy terminated surface groups respond to pH
- Attachment of GOX enables glucose sensing via pH changes due to formation of gluconic acid
- Poor kinetics
- pH response not stable
- Glucose sensor responds to pH – selectivity issue
- No integrated reference or counter electrodes

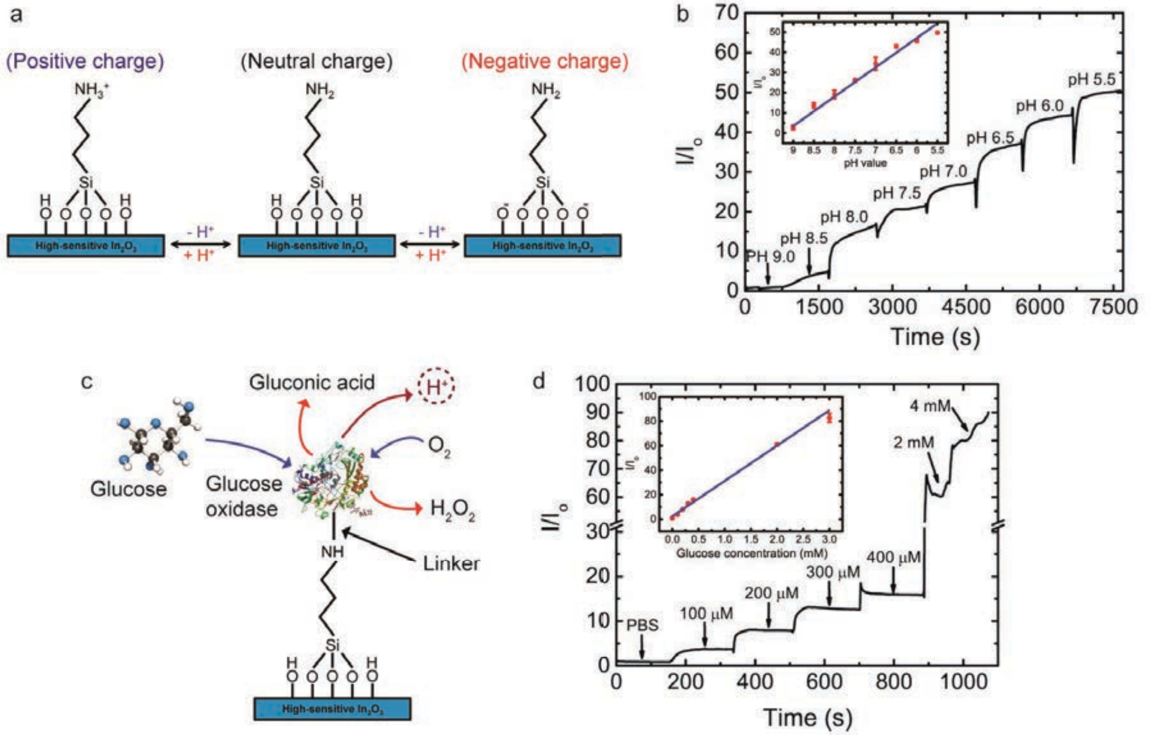
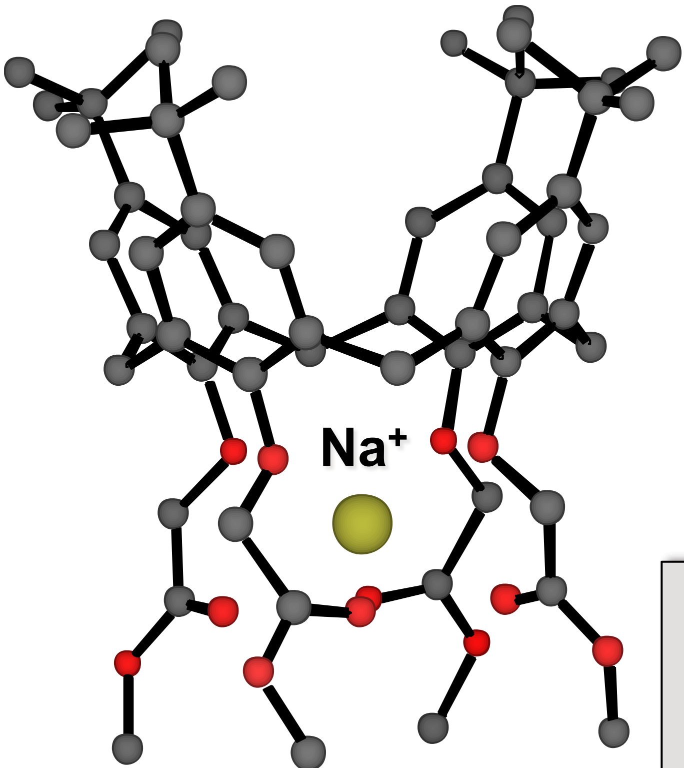
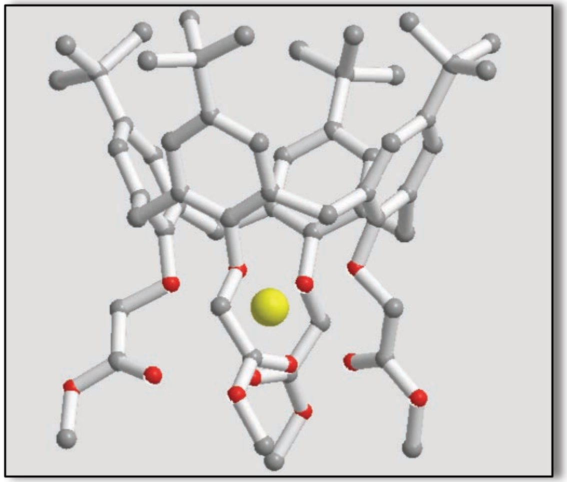


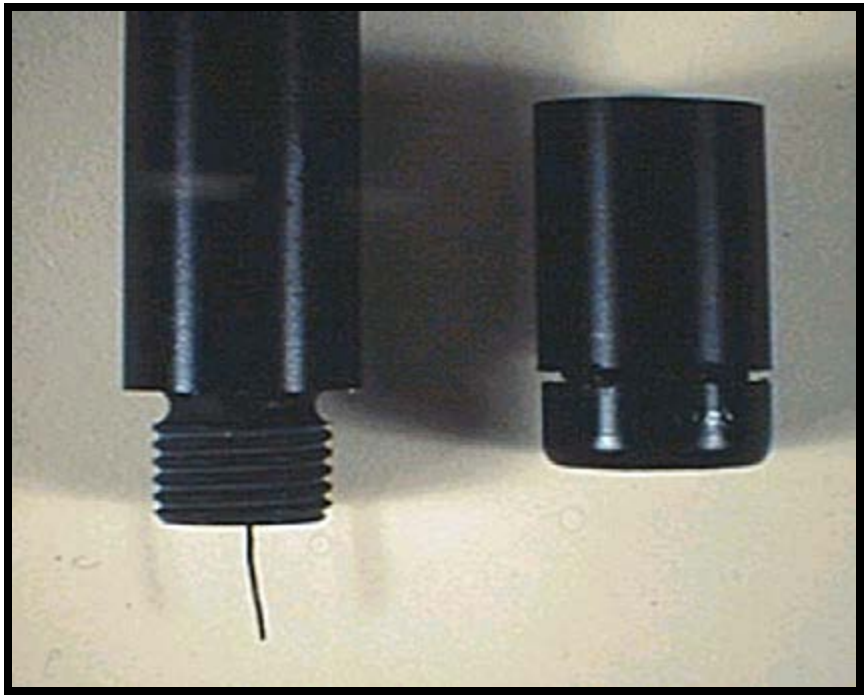
Figure 4. Chemical sensing *via* In_2O_3 FET-based conformal biosensors. (a) The pH-sensing mechanism occurs by protonation of In_2O_3 surface hydroxyl groups and primary amines of APTES at decreasing pH (increasing proton concentrations). (b) Representative responses of an In_2O_3-based FET biosensor to a biologically important pH range (pH 5.5–9). Inset shows data from five devices. (c) Enzymatic oxidation of D-glucose *via* glucose oxidase to produce gluconic acid and hydrogen peroxide. Protons are generated during this oxidation and protonation of the In_2O_3 surfaces is manifested. (d) Representative responses of In_2O_3 sensors to physiologically relevant D-glucose concentrations found in human diabetic tears (lower range) and blood (upper range). Inset shows data from five devices. Error bars represent standard deviations of the means.

Calixarene Ionophores – controlling the selectivity



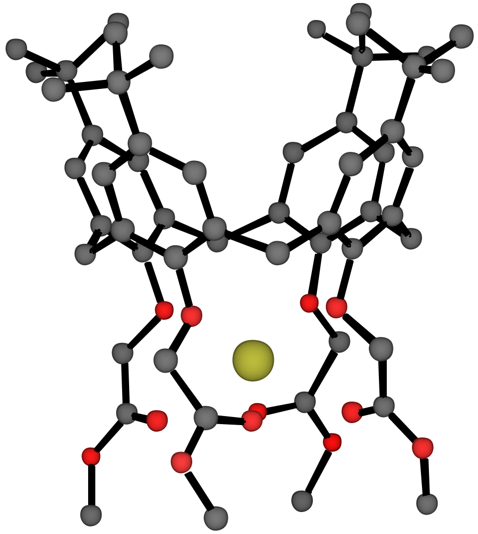


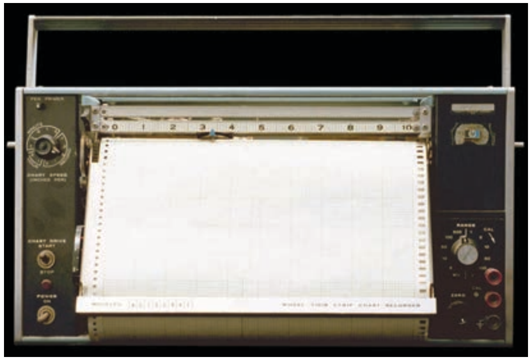
PVC - Membrane ISEs

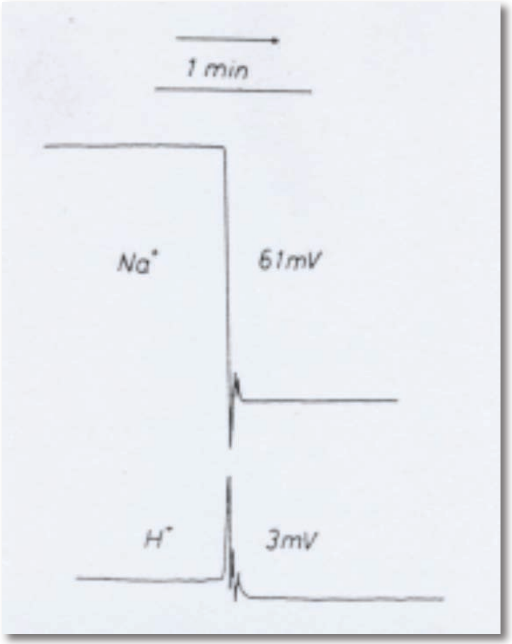


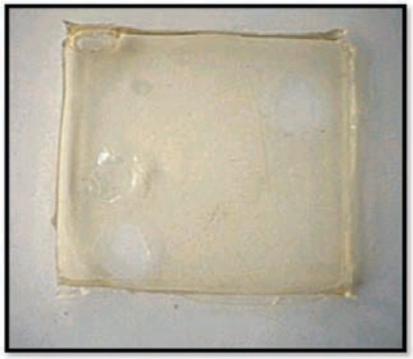
- Typical membrane cocktail (%w/w); PVC:33%, NPOE (plasticiser):66%; ionophore/exchanger (tpClPB): 1% (ratio at least 2:1 by mole); dissolve in a volatile solvent e.g. THF and cast membrane from this solution
- Ag/AgCl reference electrode
- Fill with 0.1 M solution of the primary (analyte) ion

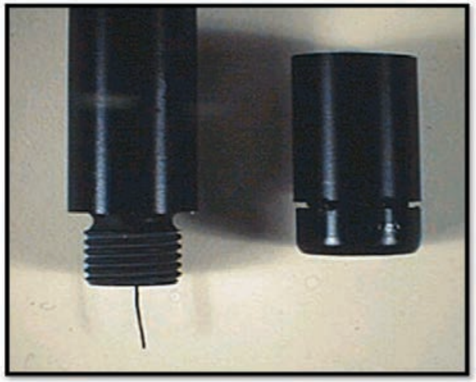
Selectivity, Response Time, Stability…







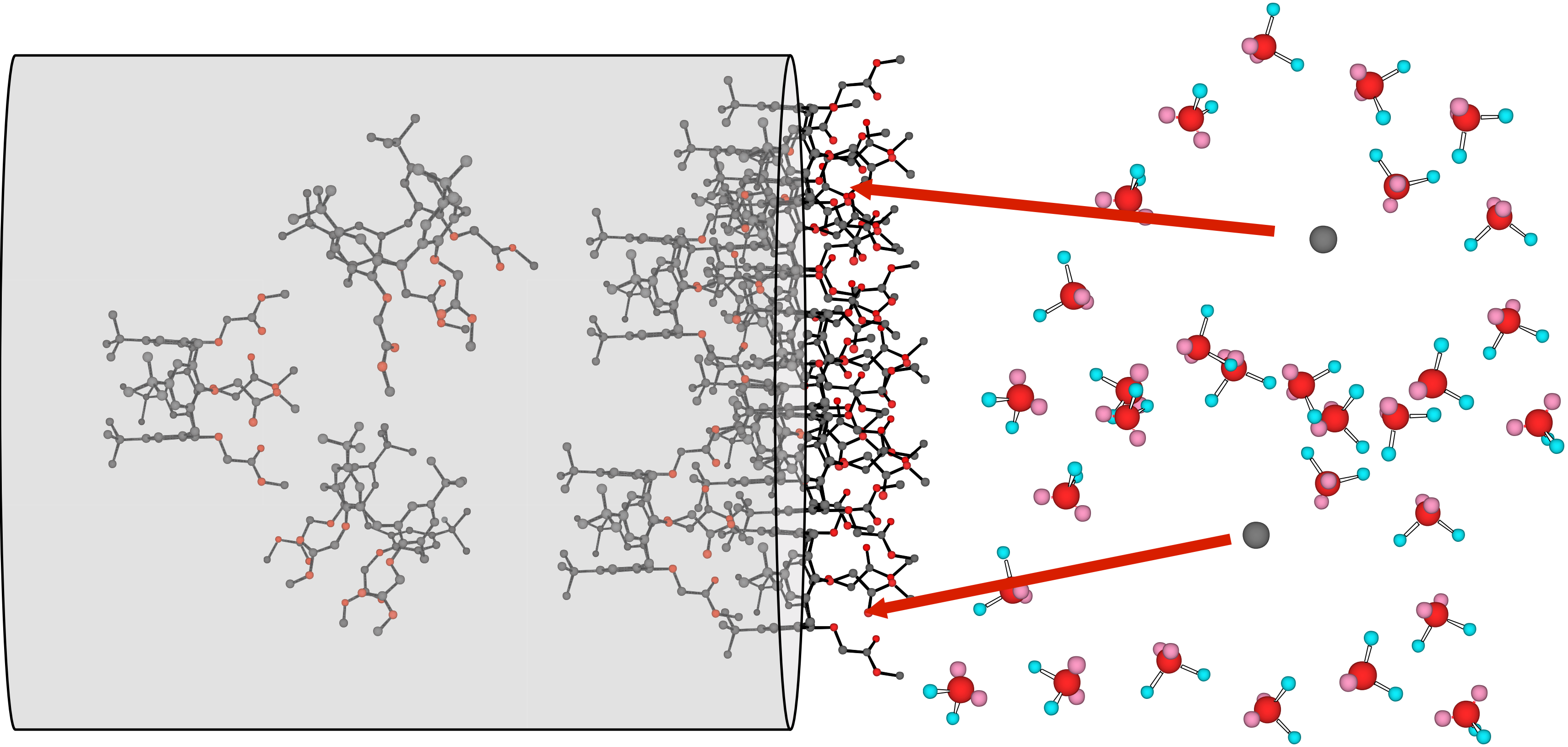




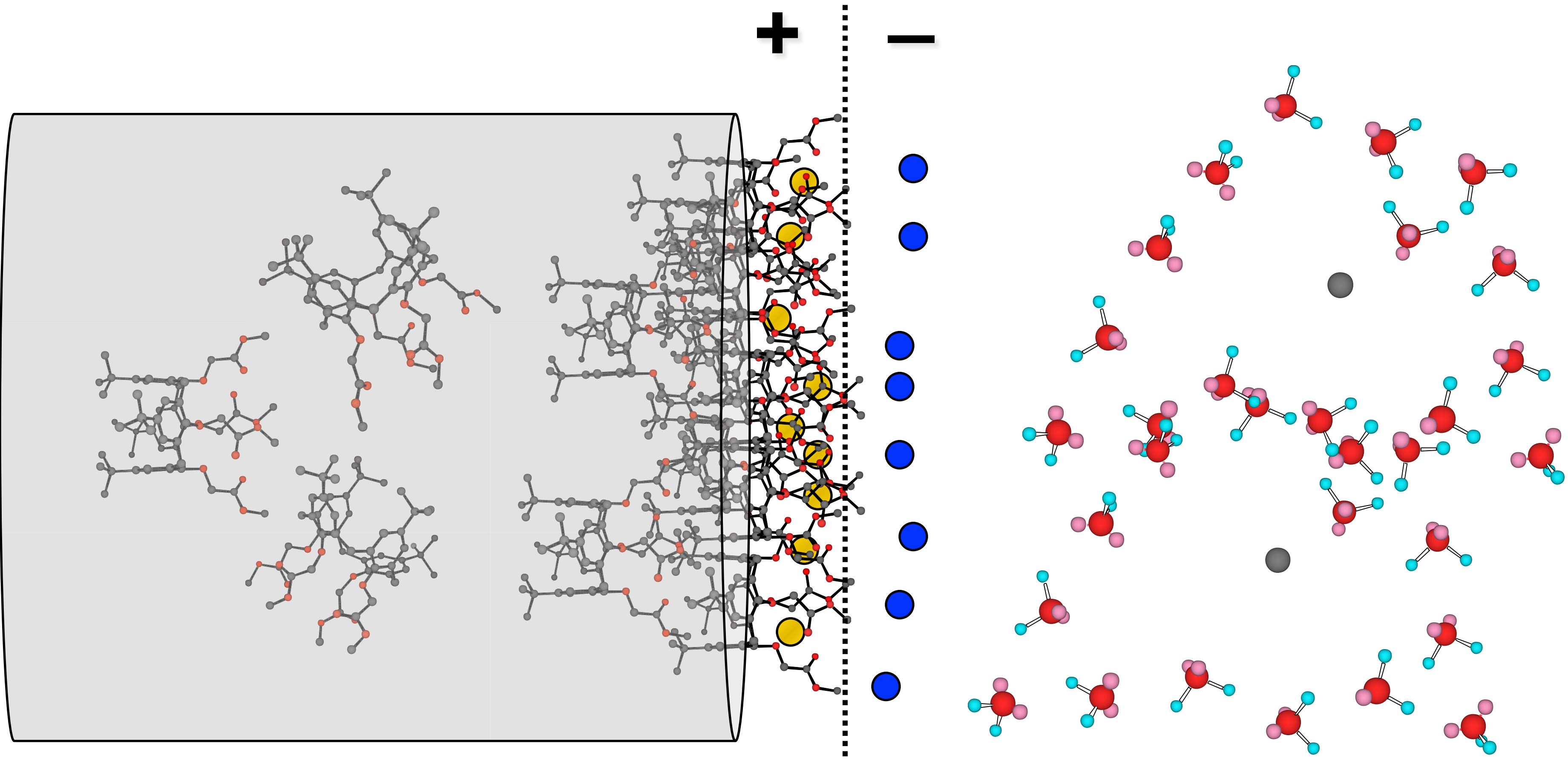
Neutral Carrier Based Ion-Selective Electrodes, D.Diamond, Anal. Chem. Symp. Ser., 25 (1986) 155.

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

Principle of Signal Generation in PVC Membrane Electrodes

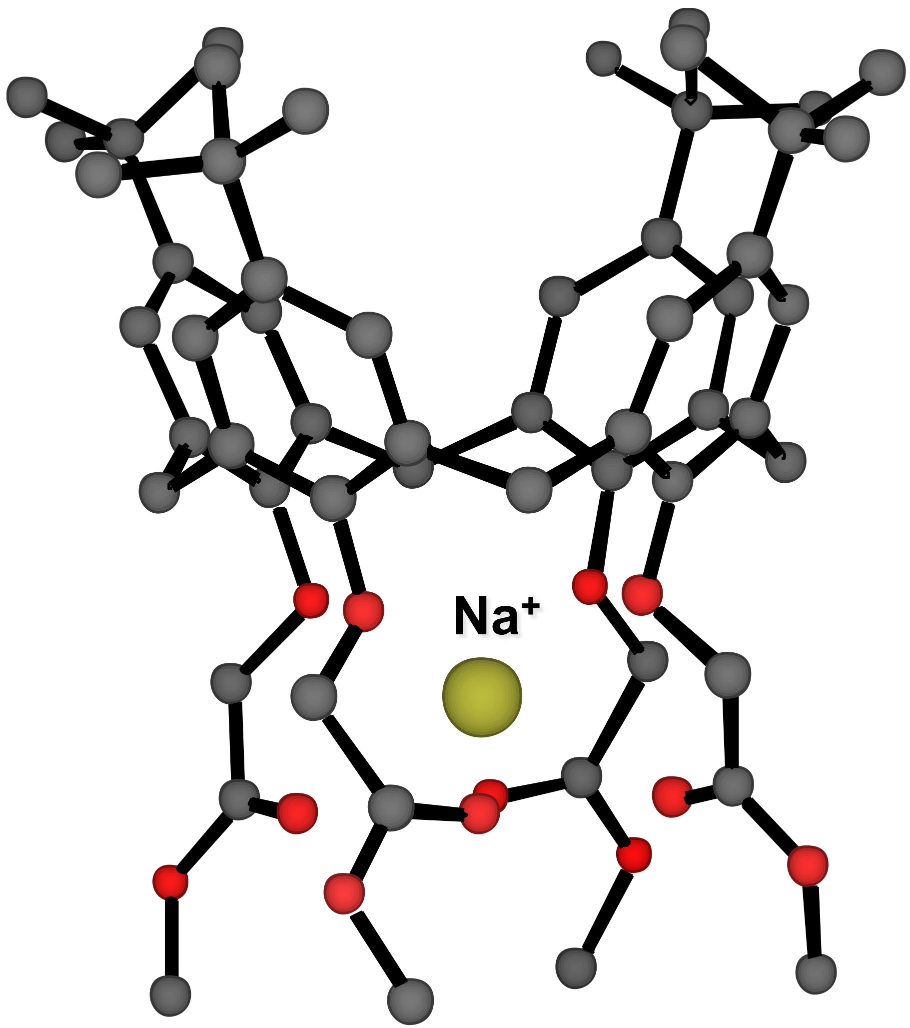


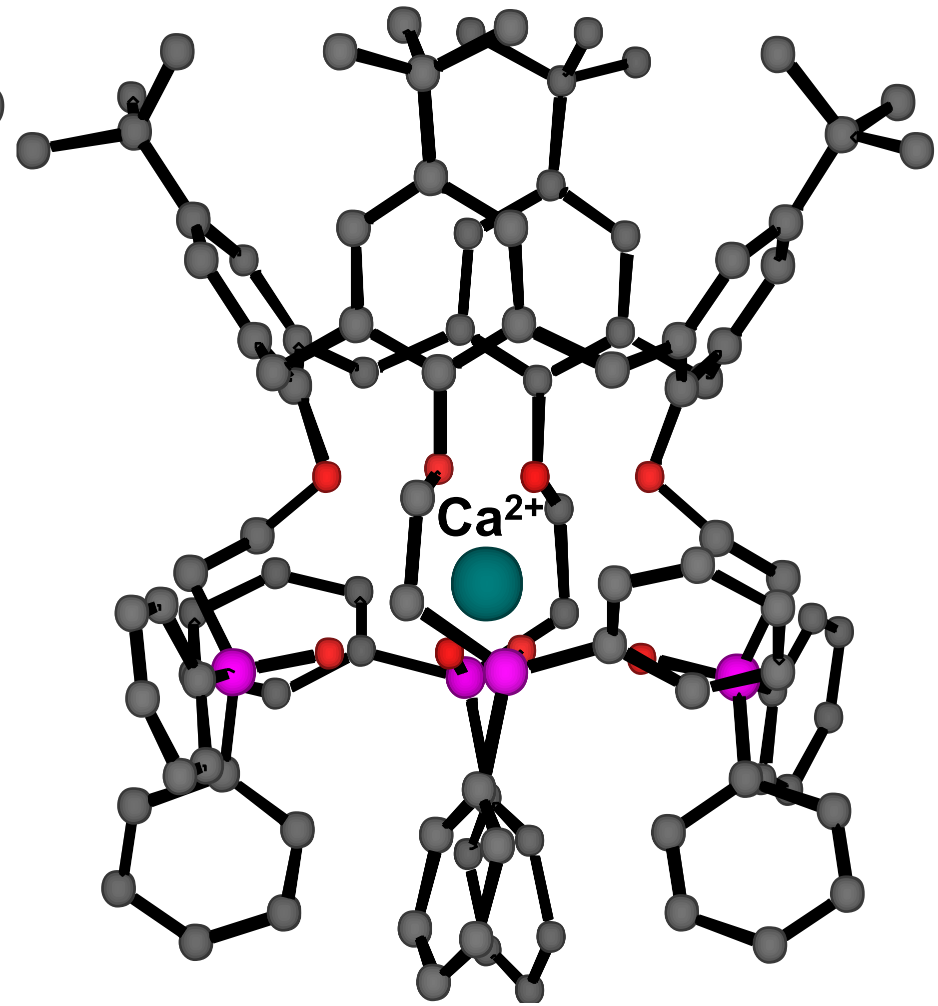
Principle of Signal Generation in PVC Membrane Electrodes



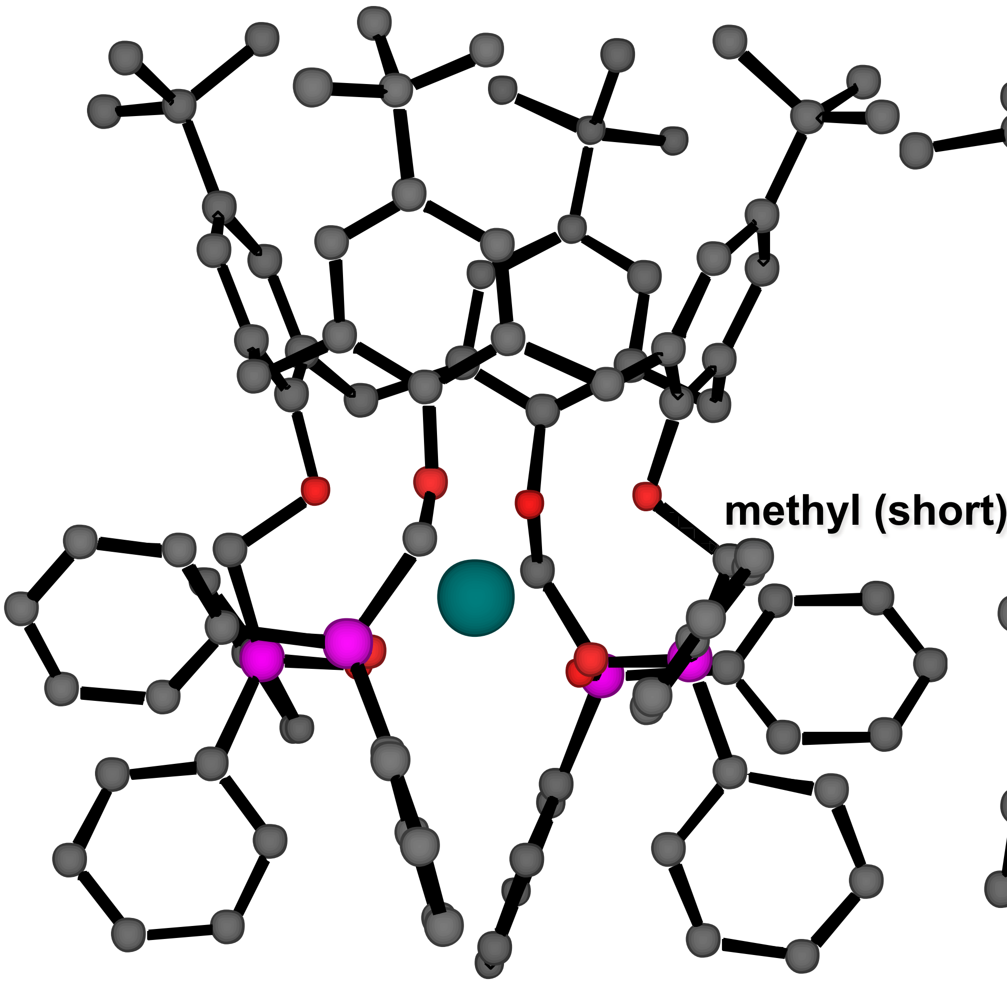
- A charged double layer spontaneously forms at the sample-membrane boundary which gives rise to an interfacial boundary potential whose magnitude depends on the stability constant of the complex formed. Selectivity therefore depends on relative stability constant values

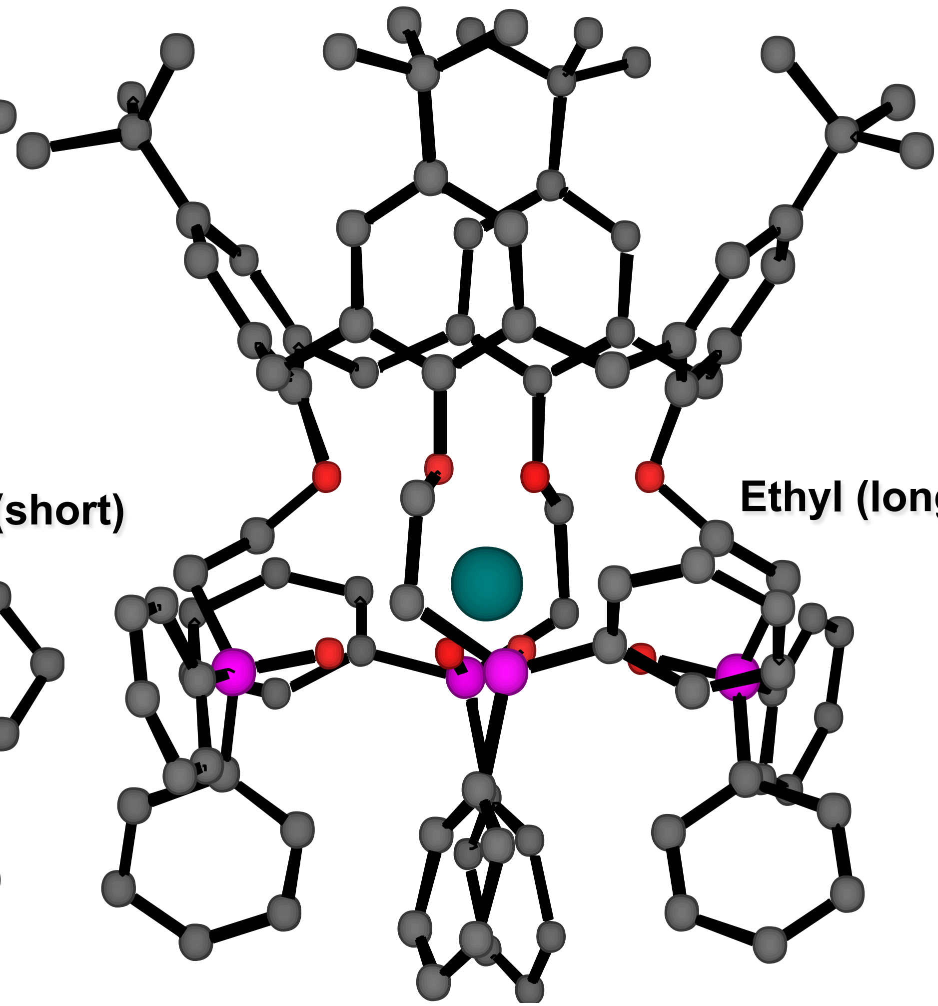
Tetraester vs. tetraphosphine oxide





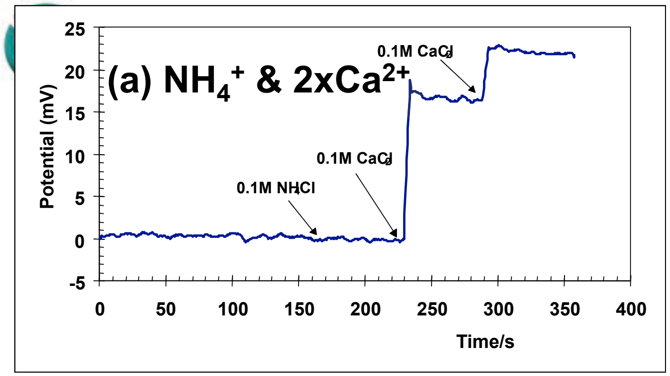
Ca^{2+} - complexes of PO tetramers

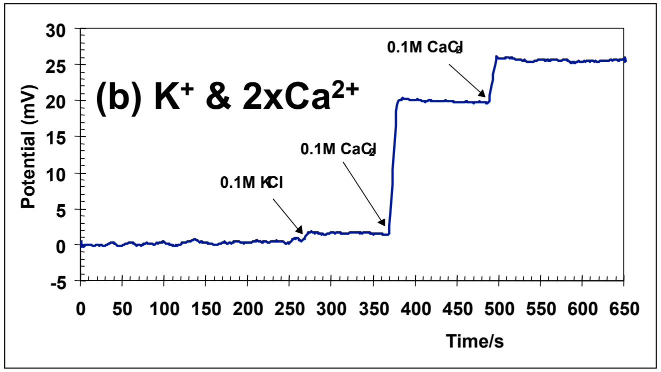


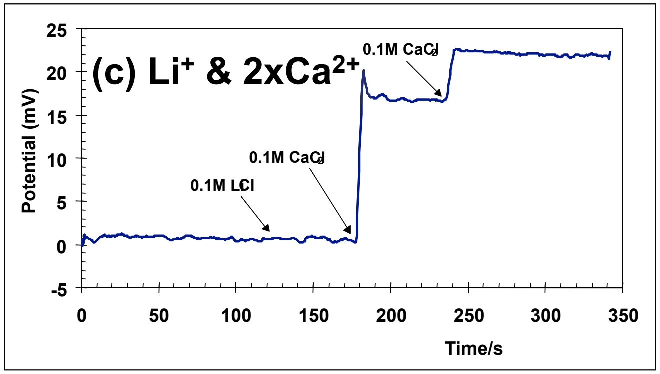


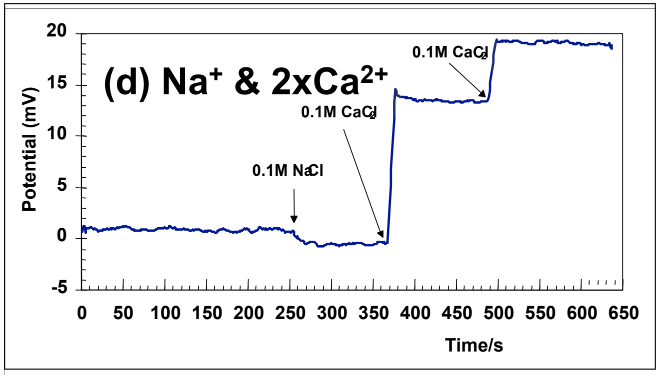
Not Ca^{2+} selective

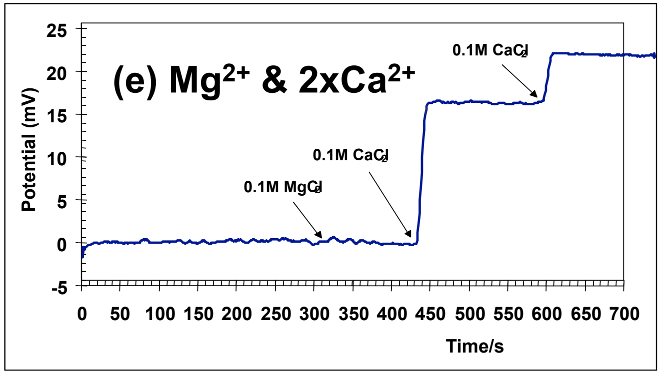
Ca^{2+} selective



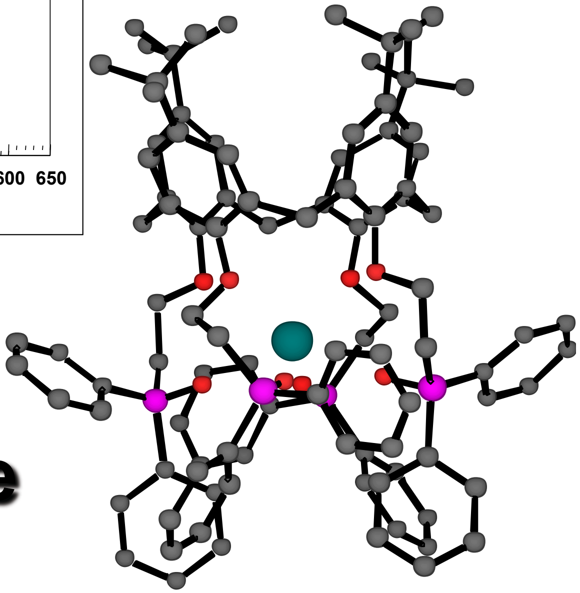








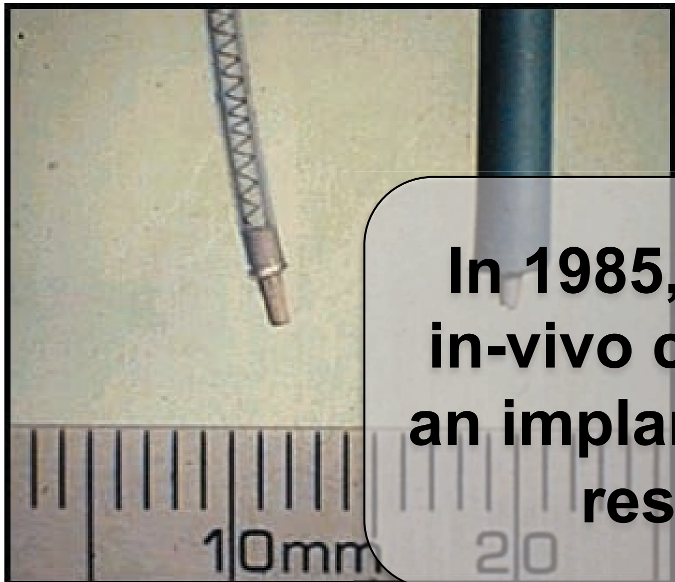
Response of TPOL Electrode



Calcium-selective Electrode based on a Calix[4]arene Tetraphosphine Oxide, Tom McKittrick, Dermot Diamond, Debbie J. Marrs, Paul O'Hagan and M.Anthony McKervey, Talanta 43 (1996) 1145-1148.

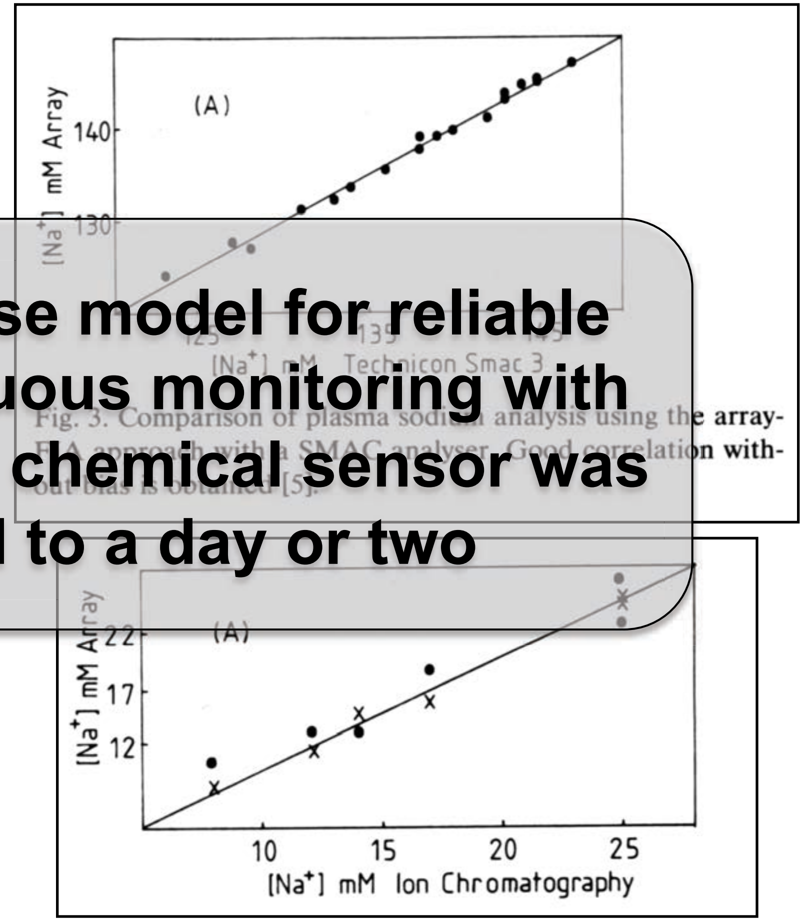
Blood Analysis; Implantible Sensors

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

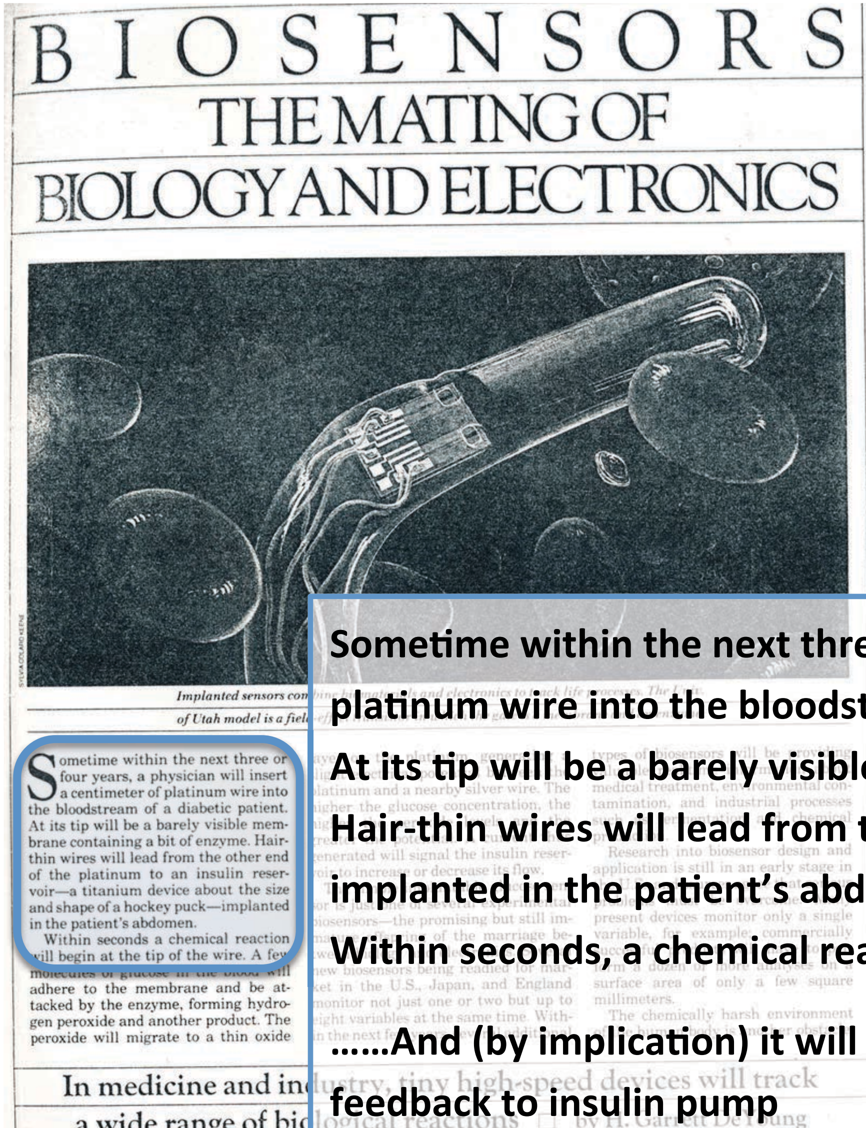
Dr. David Band, St Thomas's Hospital London



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

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

The (broken) promise of biosensors…..

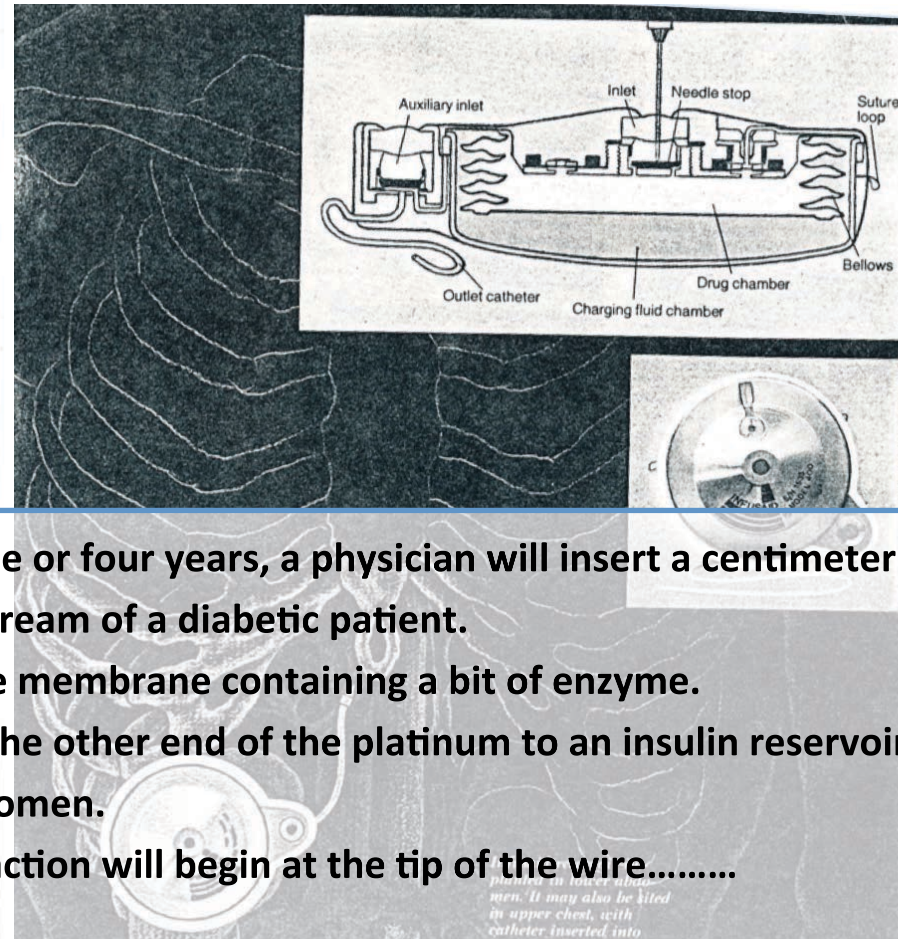

BIOSENSORS
THE MATING OF
BIOLOGY AND ELECTRONICS

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

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



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.

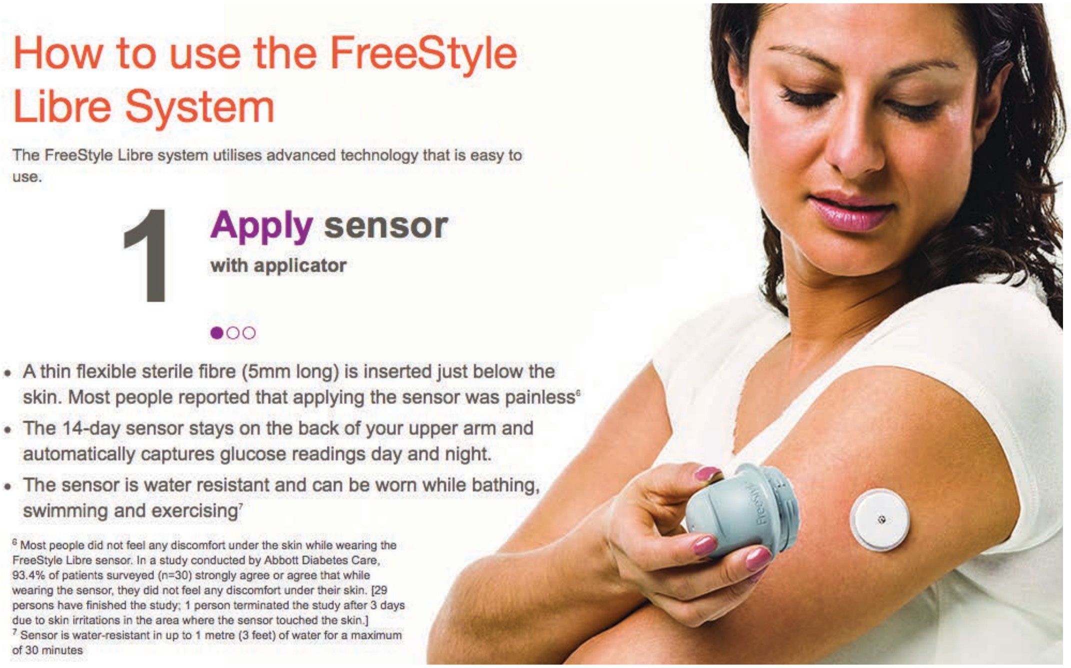
Within seconds, a chemical reaction will begin at the tip of the wire………

……And (by implication) it will work for years reliably and regulate glucose through feedback to insulin pump

Abbott Freestyle 'Libre'

The days of routine glucose testing with lancets, test strips and blood are over.[2]

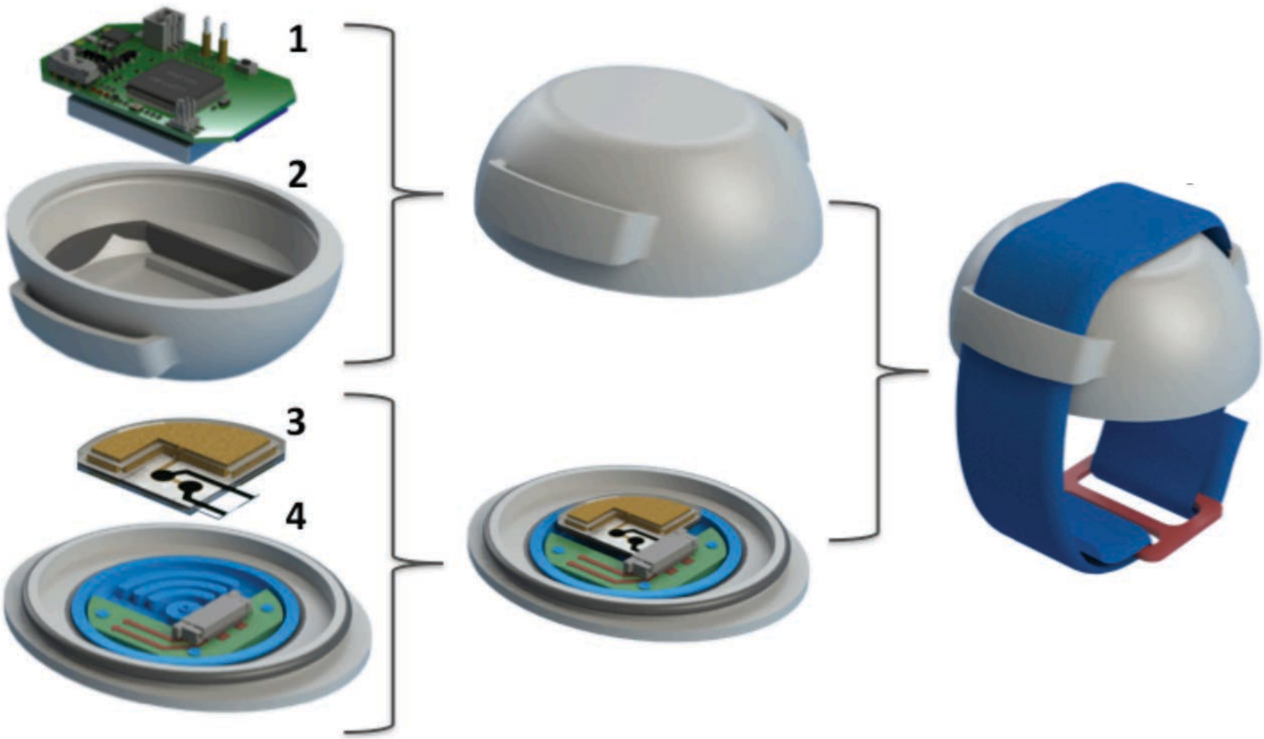
Welcome to flash glucose monitoring!



- '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

Sweatch Device

1. Electronics
2. 3D printed casing
3. Microfluidic chip + ISE
4. 3D printed sweat harvester and sensor connections

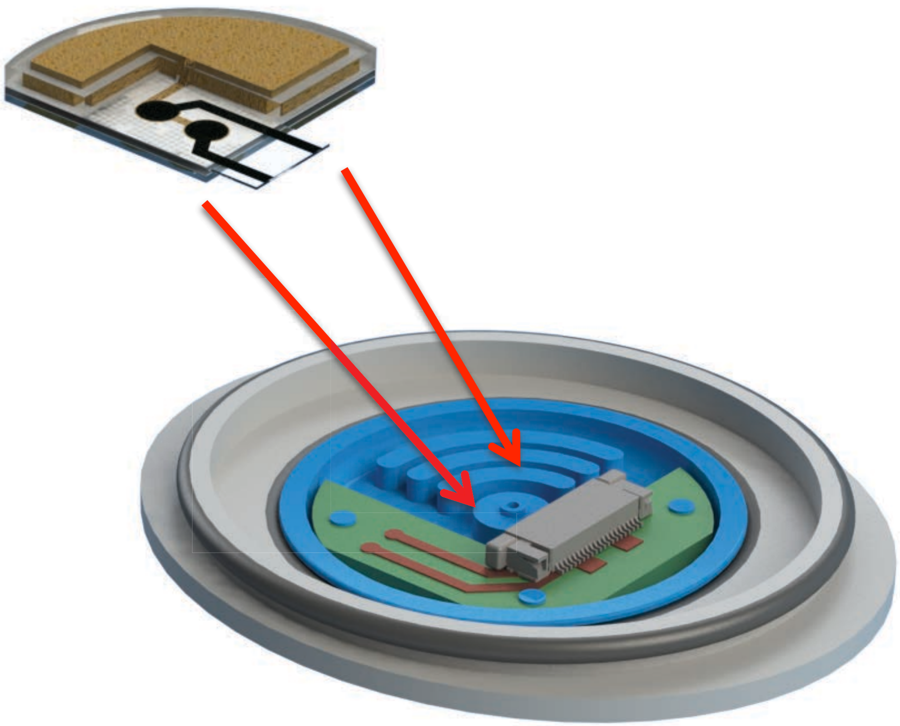


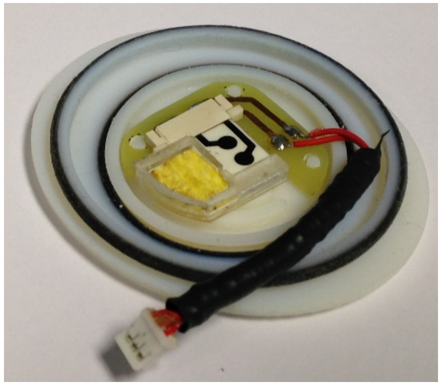
SFI | DCU | UCC | OÉ Gaillimh NUI Galway | UCD DUBLIN

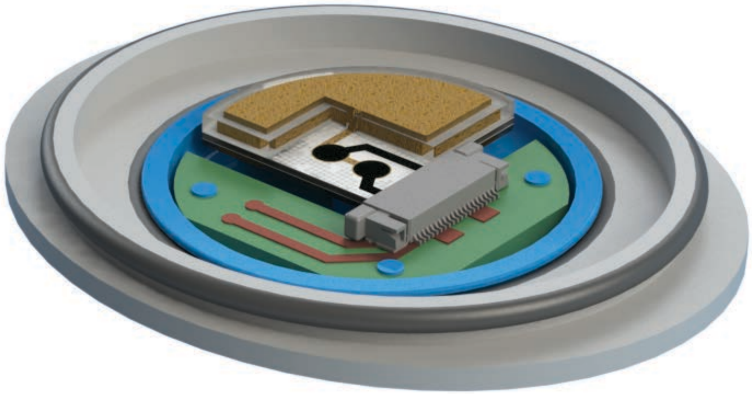
Printing of Multiple Materials – Integrated Fluidic Sealing Layer

1: Pop Macro-duct into elliptical ring from below

Integration of Fluidic System and Electrodes

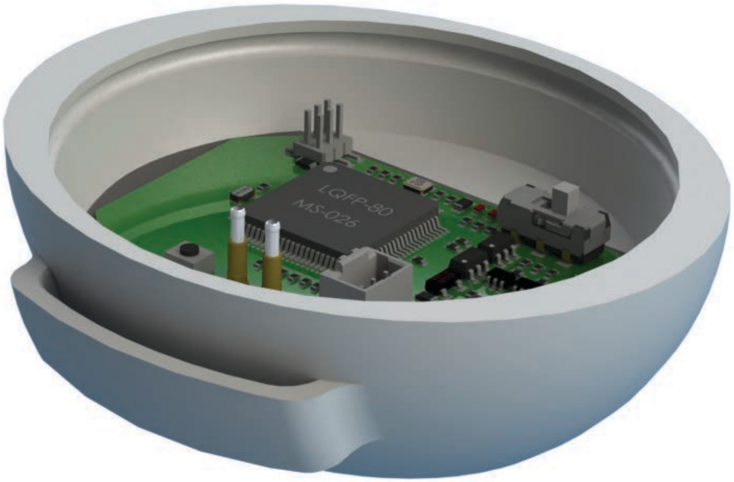


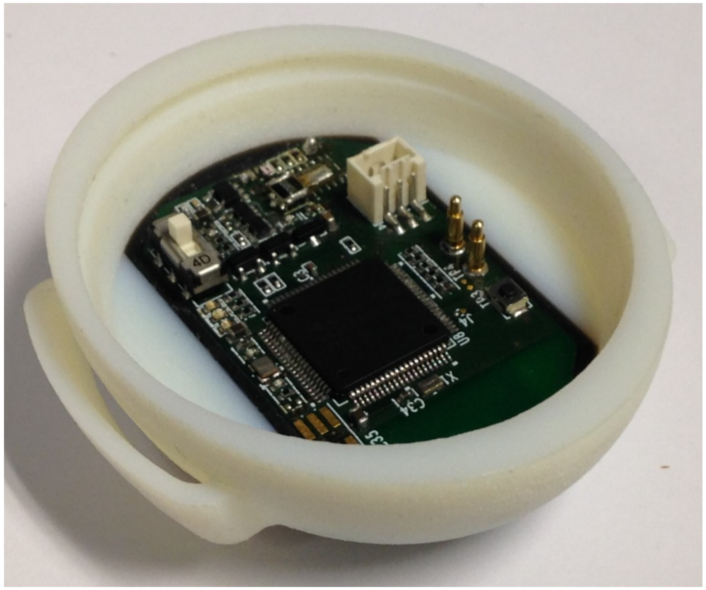




3a: Open FFC Connector by pulling tab forward with tweezers
3b: Place microfluidic chip + sensor assembly into FFC Connector
3:c Close FFC Connector

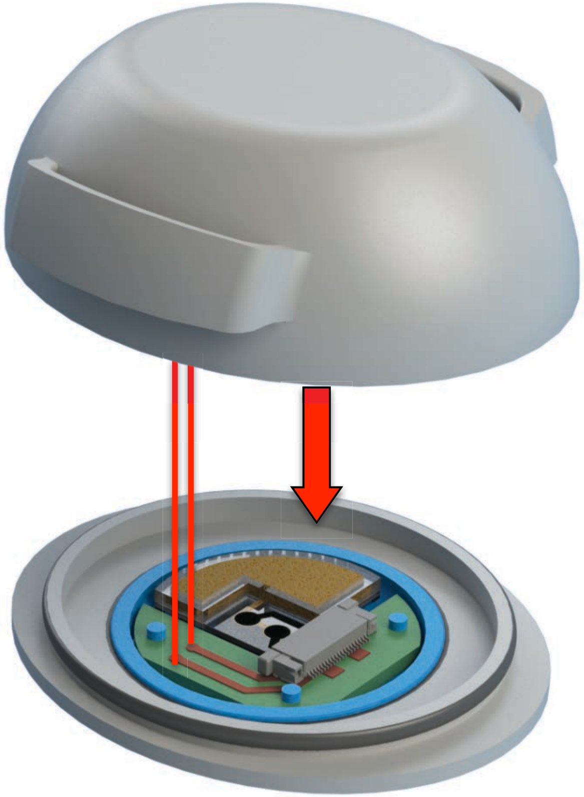
Assembly Manual





4: Place Shimmer board and Battery Combination into enclosure making sure Shimmer board fits snug into black rubber-like material

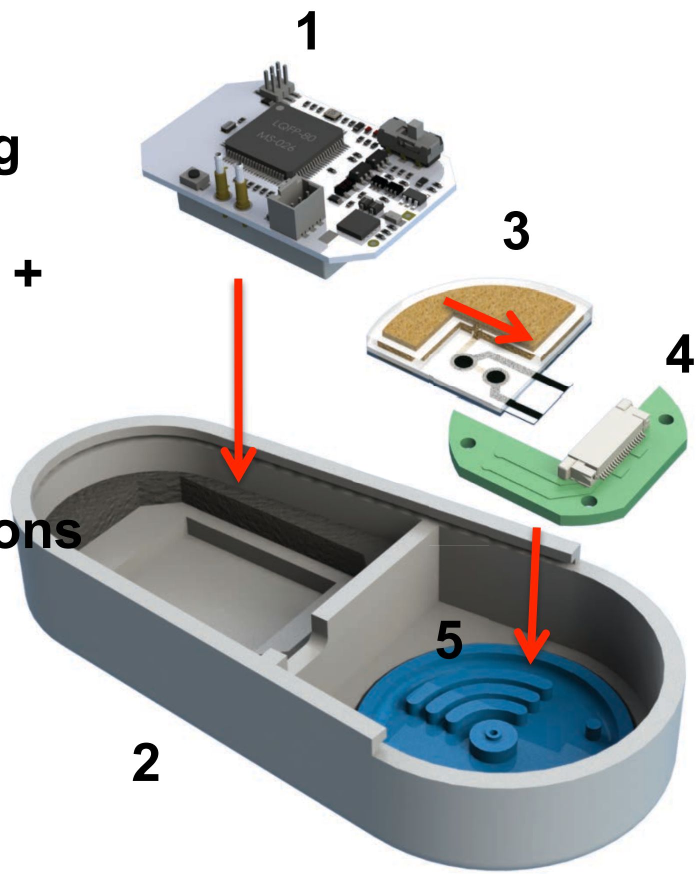
Assembly Manual



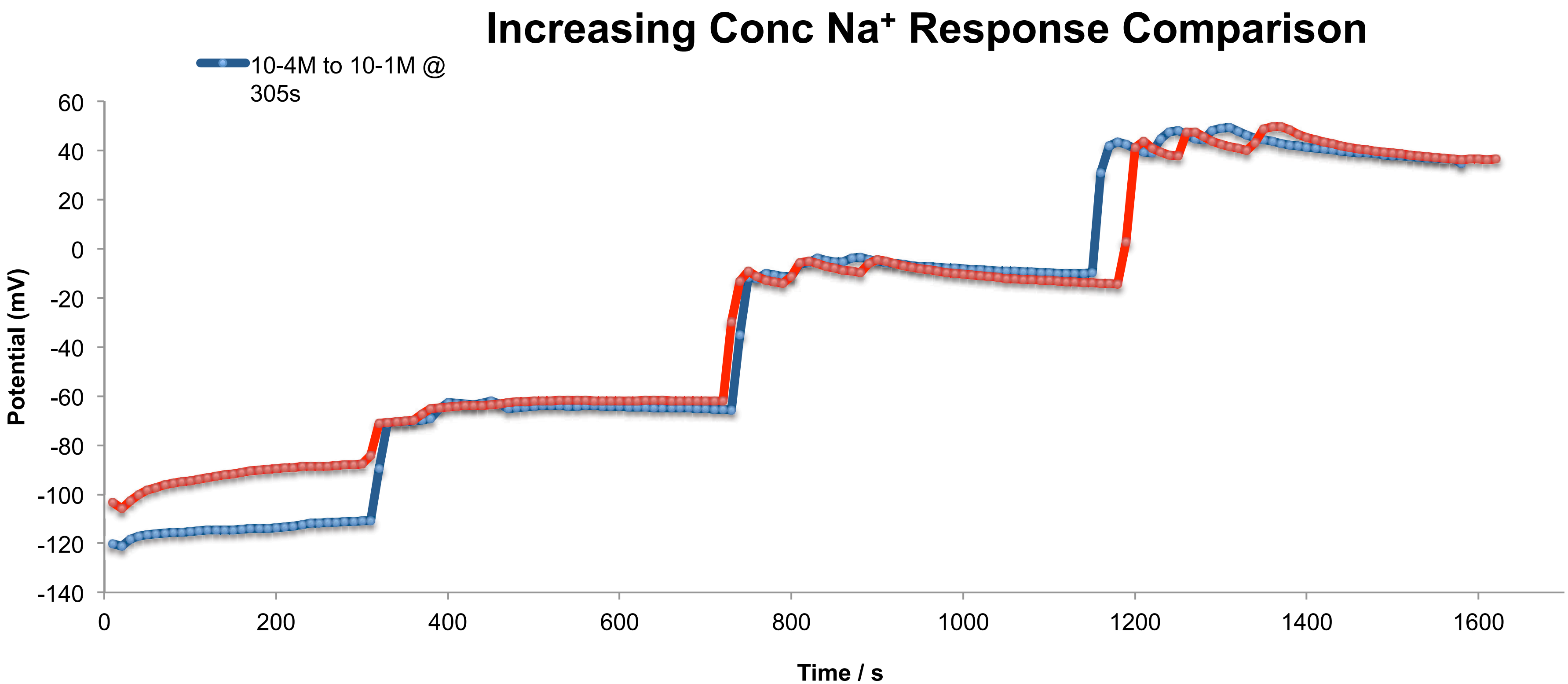
6: Push enclosure down onto bottom assembly carefully aligning elliptical shapes of both parts.
Make sure edges are fully secure

Sweatch Device

1. Electronics
2. 3D printed casing
3. Microfluidic chip + ISE
4. Sensor connections
5. 3D printed sweat harvester

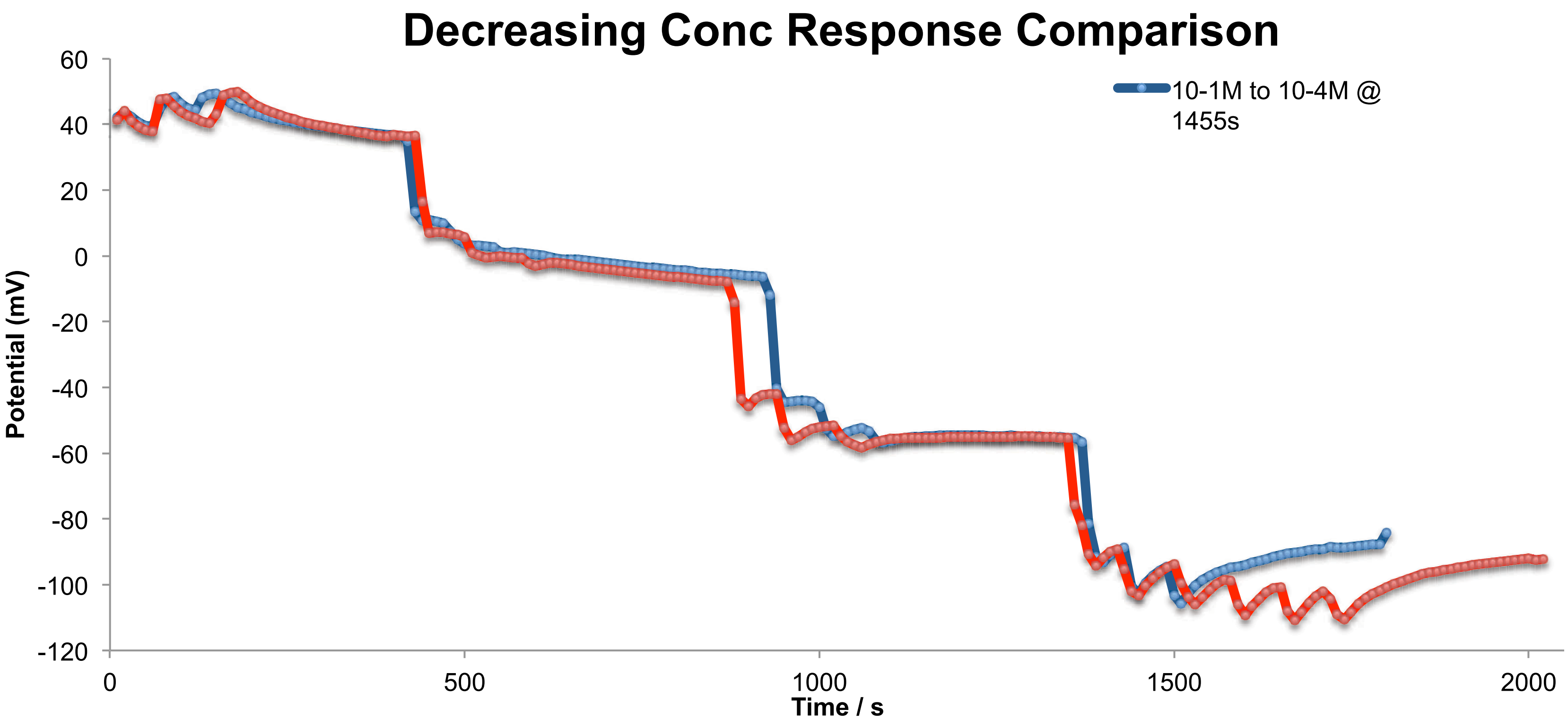


Chip 10 Sensor and Fluidic Test



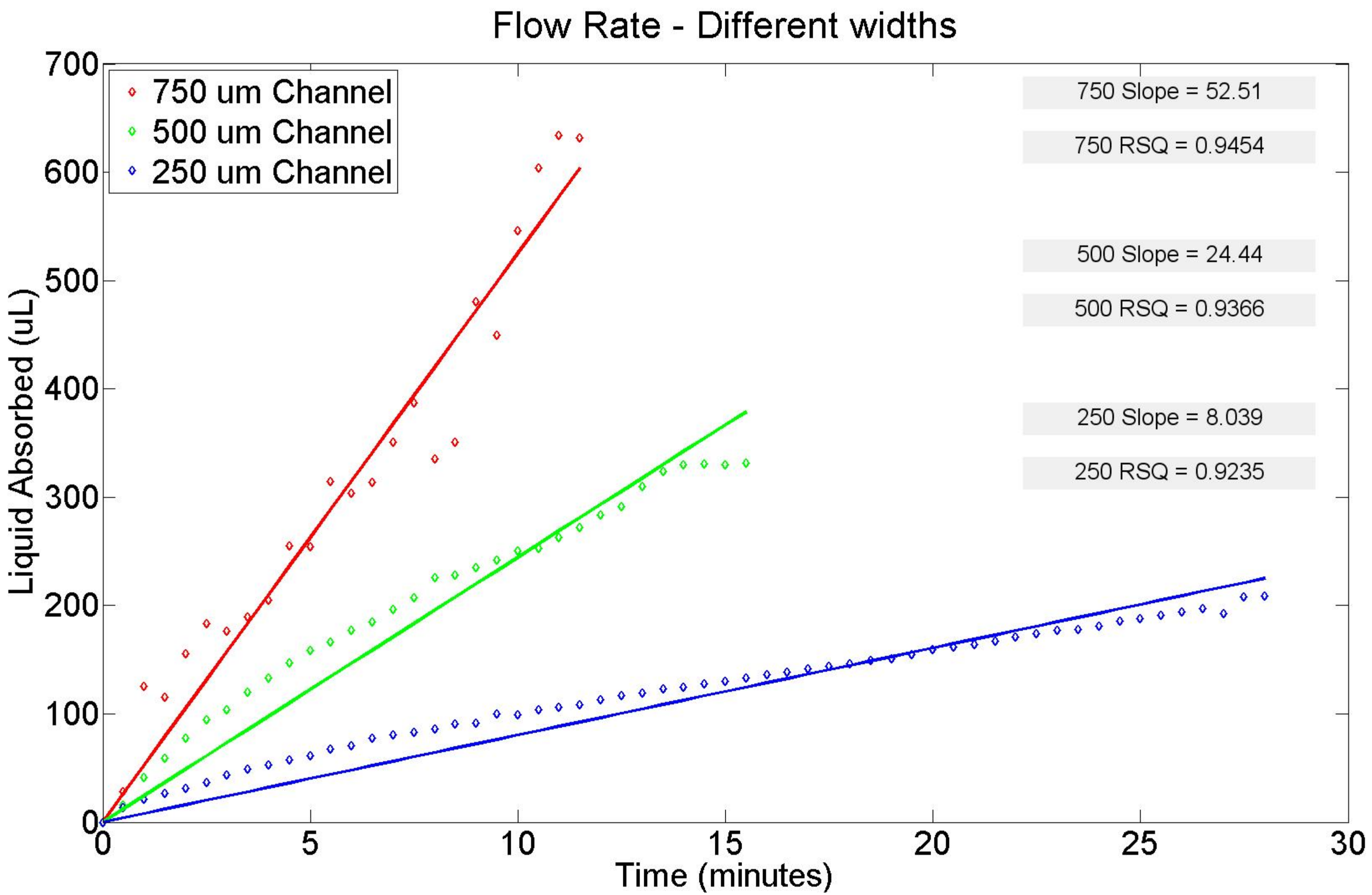
- Very similar responses
- On returning to 10-4M higher response noted
  - May be attributed to retained Na+ in the absorbent material from the higher concentrations

Chip 10 Sensor and Fluidic Test



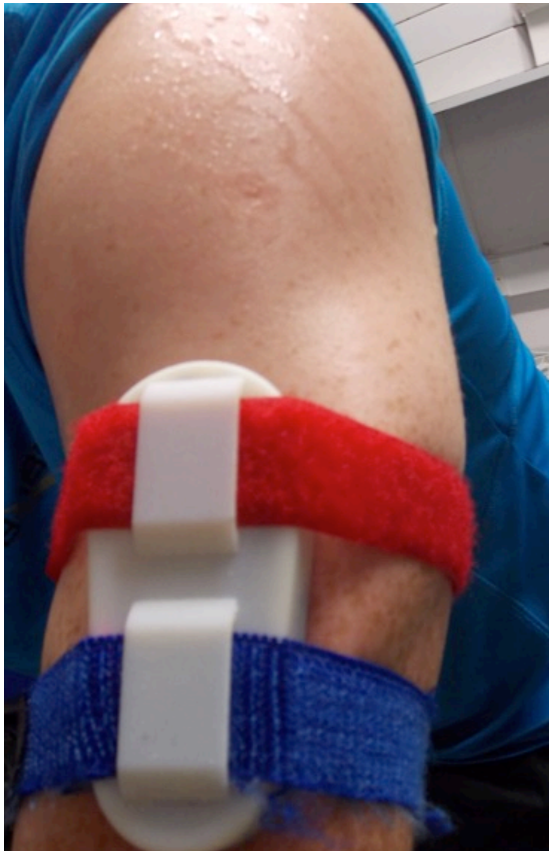
- Very similar responses

Fluidic Testing

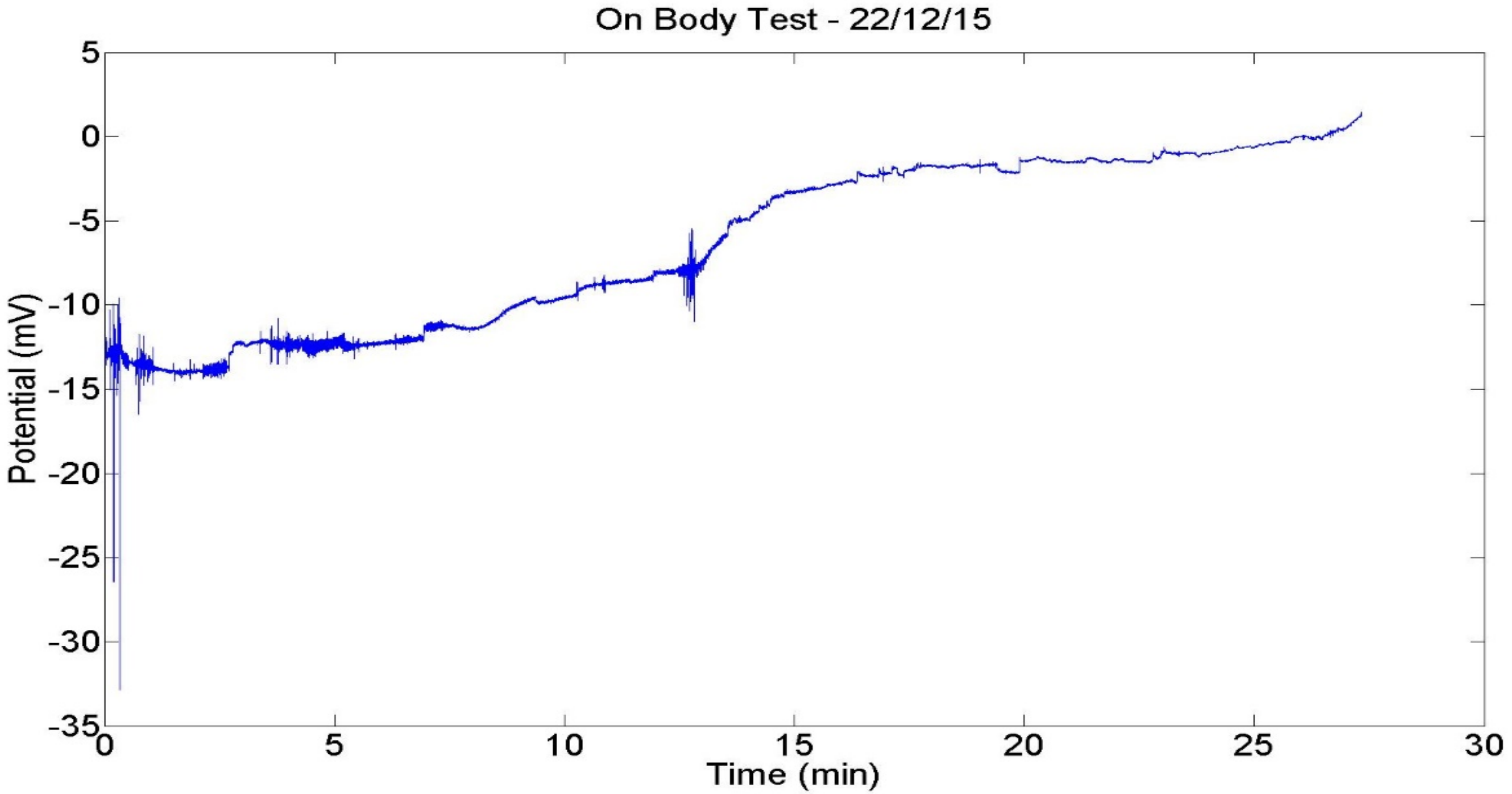


Trial 1 Sweat Sampling

- Male volunteer cycled for 30 mins on a stationary bicycle.
- 143ul sweat collected from arm after duration of the test.
- Large amounts of sweat observed after 12 minutes.



Trial 1 Data



On Body Test - 22/12/15
Potential (mV)
Time (min)
5
0
-5
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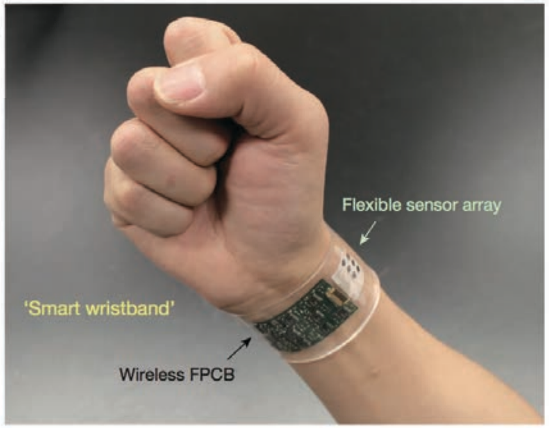
a



LETTER

doi:10.1038/na

Fully integrated wearable sensor arrays for multiplexed *in situ* perspiration analysis

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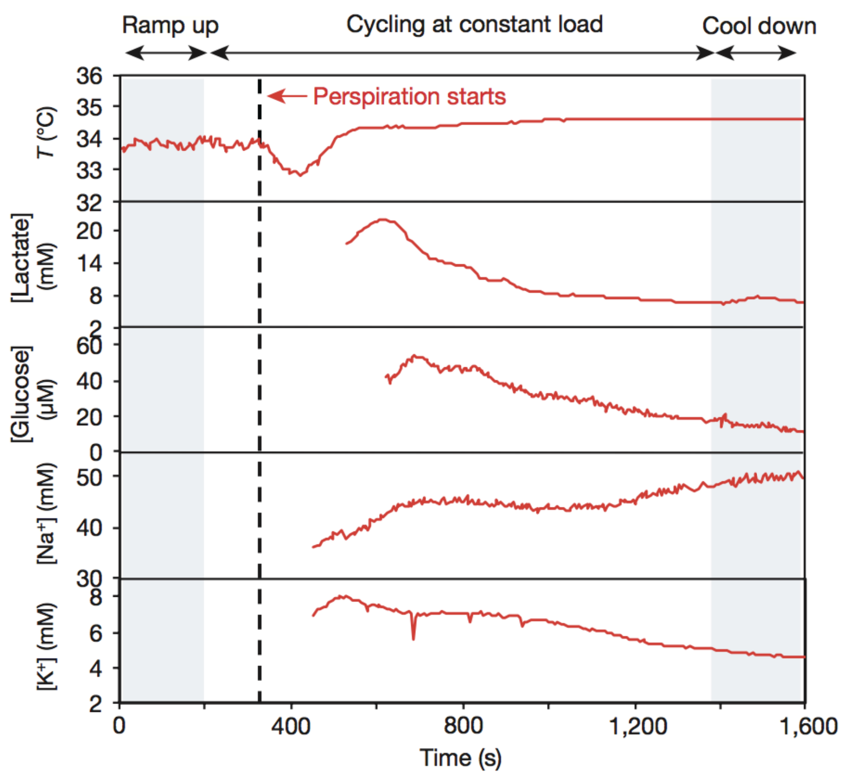
Gao, W. *et al*. *Nature* http://dx.doi.org/10.1038/nature16521 (2016).

d



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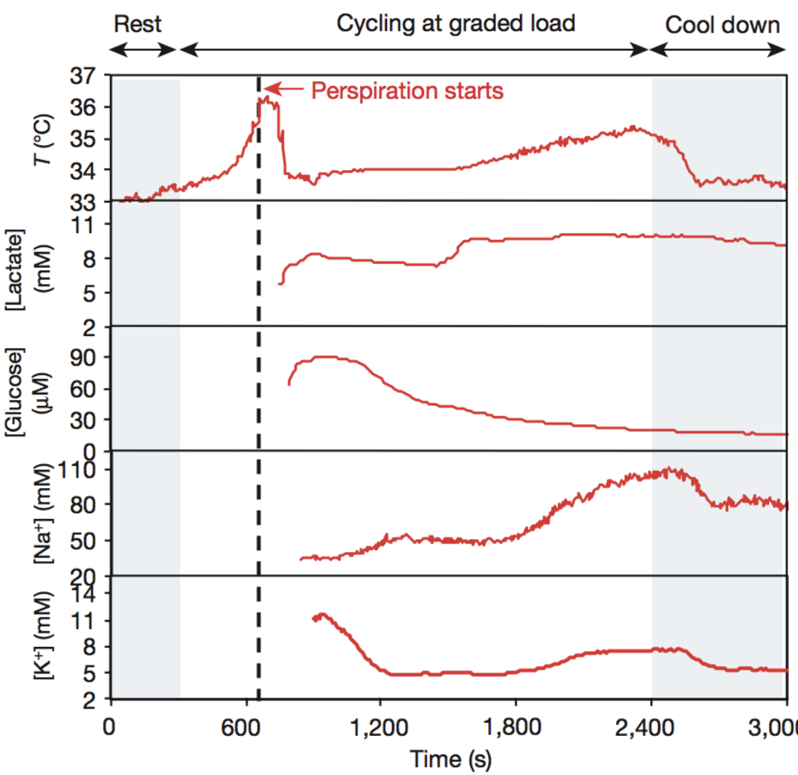

Time to re-think the game!!!

- 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
- Learn from nature – e.g. more sophisticated circulation systems for 'self-aware' sensing devices!

Need for creativity to move centre stage!

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Materials and Advanced Sensor Knowledge Exchange