Current mass-manufacturing challenges in integrated Lab-on-Chip devices and the Lab-on-PCB concept

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5-7/7/2017
NCSR "Demokritos", Athens, Greece

Overview

- Background
- Early research: Lab-on-Chip technology
- NCSRD $\longrightarrow$ UK : Integration challenges and mass-manufacturable Lab-on-PCB
- University of Bath: State-of-the-art research challenges
- Industrial engagement and Innovation

Background

M. Eng. Electrical and Computer Engineering (2005):

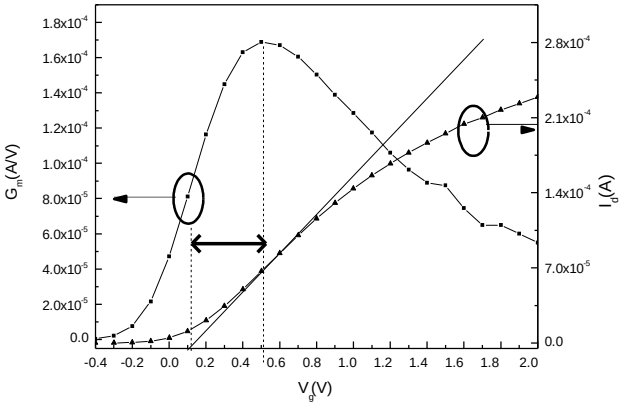
microelectronic circuit design (N.T.U.Athens, Greece)

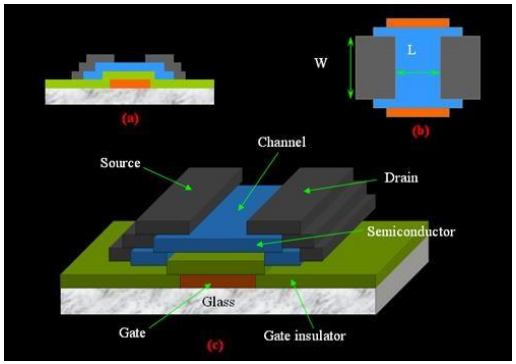
National Technical University of Athens

PhD in microelectronics (2009):

TFT fabrication, N.C.S.R Demokritos (Athens, Greece)

SHARP LABORATORIES OF AMERICA, INC.



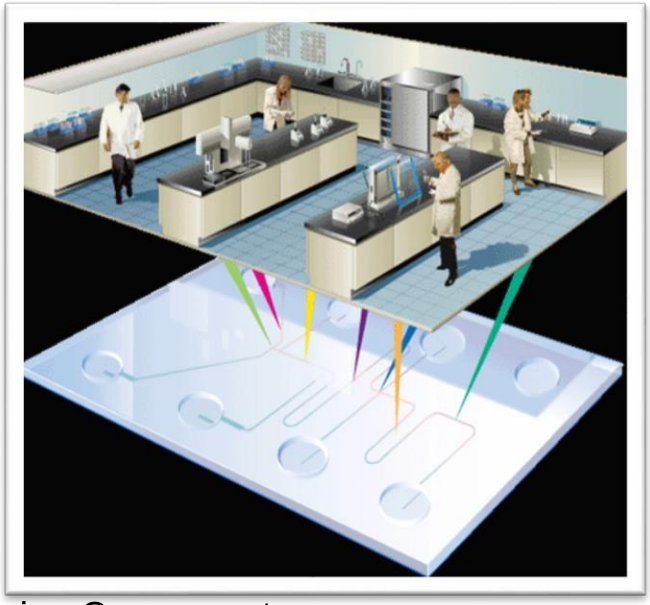


Post-Doctoral Researcher, Lab-on-Chip technology: 2009-2013: N.C.S.R Demokritos (Athens, Greece)

Trend for smarter multi-functional microchips → μTAS (micro Total Analysis Systems) aka LoC (Lab-on-a-Chip)
= Systems of reduced size and weight, performing sample handling steps together with analytical measurements

Democratize healthcare for everybody

In one sentence: We can clearly expect lab-on-a-chip to save numerous lives.



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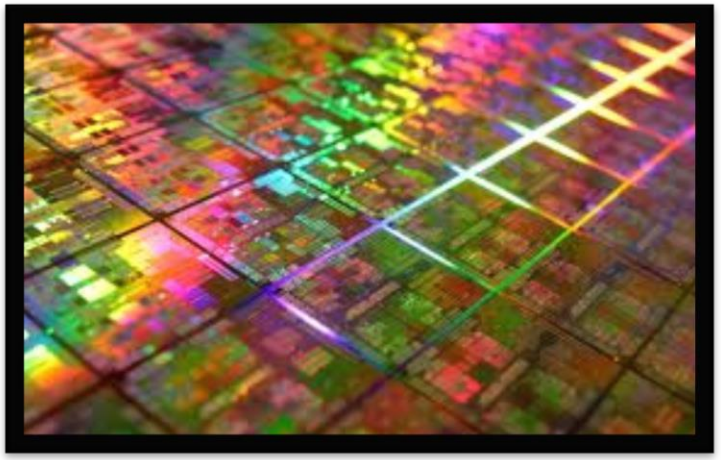

microComponents:

μfluidic channels

μvalves

μpumps

+ …….

Chem/bio detectors/sensors

separators

μmixers

IC Components:

Transistors

Diodes

Capacitors

Inductors

+ ……..

Manz et al., “Miniaturized total chemical analysis systems: A novel concept for chemical sensing”, Sensors and Actuators B: Chemical, vol 1, 1990, 244-248
A. Tudos et al. , Lab on a Chip, 2001, 1, 83-95

Lab-on-a-chip impact

Unique adva

- Miniat
- Low r
- Rapid
- Auton

Indicative

- Poin
- Envi
- Defe
- Fooc
- Rege
- Cher
- Drug
- ……

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THE CONVERSATION

MEDICAL & BIOTECH

How Close Are We to a Real *Star Trek*–Style Medical Tricorder?

Vital signs information and images aren't enough for a fully automated device that can tell you what's actually wrong with a patient

By Despina Moschou, The Conversation US on June 16, 2017

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5.7 billion
nostics

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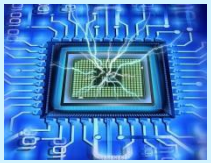
Roche

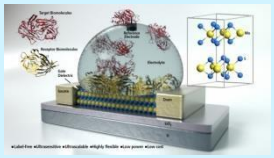
Alere ™

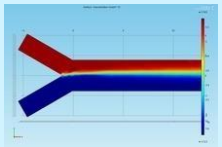
Whitesides G.., "The origins and the future of microfluidics", Nature, vol 442, 2006, 368-373
Volpatti et al, "Commercialization of microfluidic devices", Trends in Biotechnology July 2014, Vol. 32, No. 7

Multi-disciplinary field (@%#!)

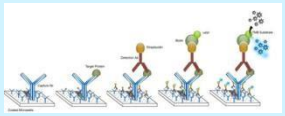


Microelectronics





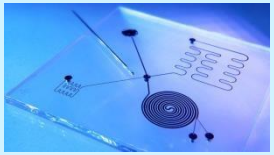
Microscale fluid mechanics



Biochemistry

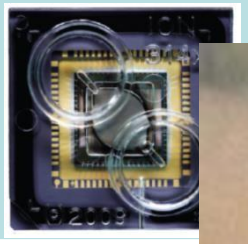
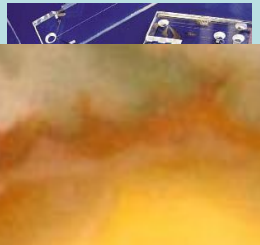
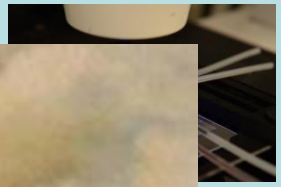
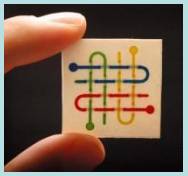
Biology/medicine

Chemistry-surface modifications



Microfabrication

Why isn't LOC here???

CMOS	Glass	Polymers	Paper
			
Semiconductor fabrication techniques (cleanrooms)			Cost-effective
Sophisticated circuits			Printable
Commercialized components			Stackable, filtering
µfluidics integration			Few µfluidics demonstrated
Overall cost	Expensive	Mass manufacturing?	Detection sensitivity

Lab-on-PCB???

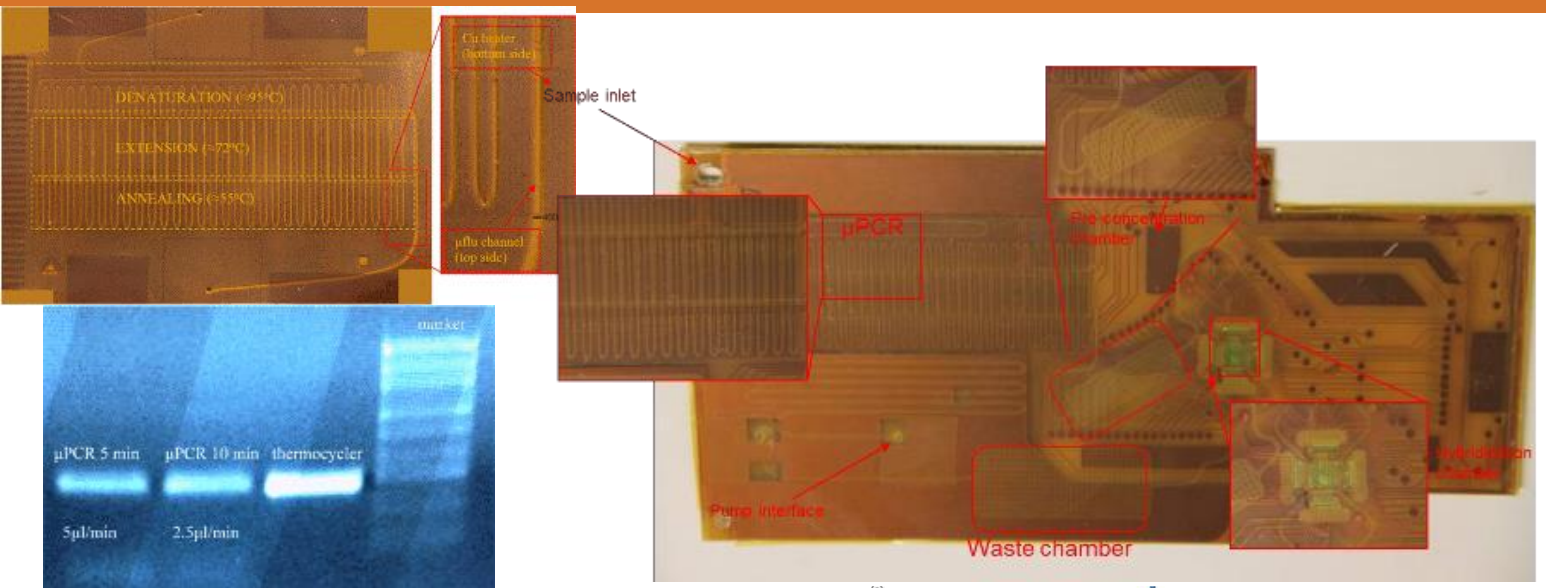
First suggested in the ‘90s, however **side-lined by easier microfluidic fabrication processes** (soft lithography, glass/polymer processing)

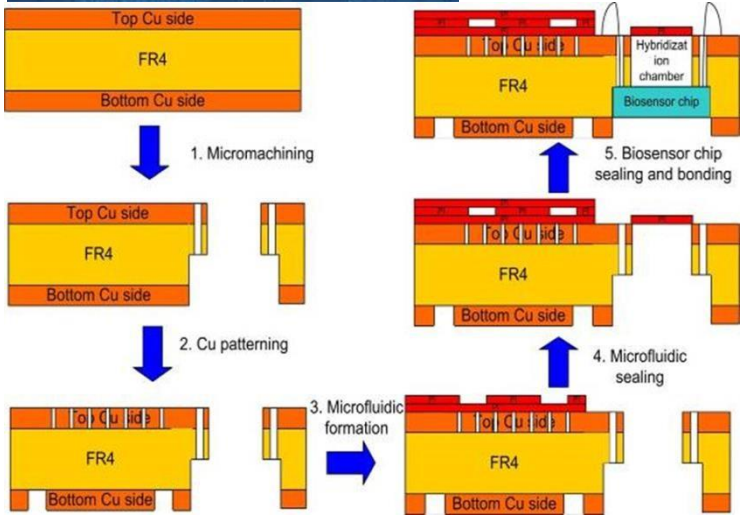
Recently LOC **integration main focus** → PCBs (Printed Circuit Boards) ideal integration platform:

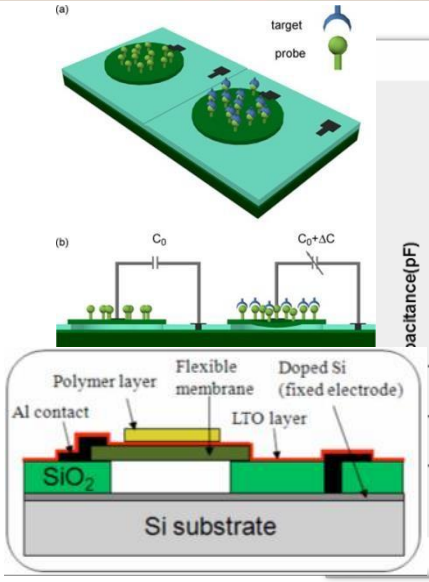
- Long-standing industrial infrastructure (low-cost upscaling, projected mass-fabrication cost < £5)
- Adequate microfabrication capabilities
- Intuitive integration of electronics

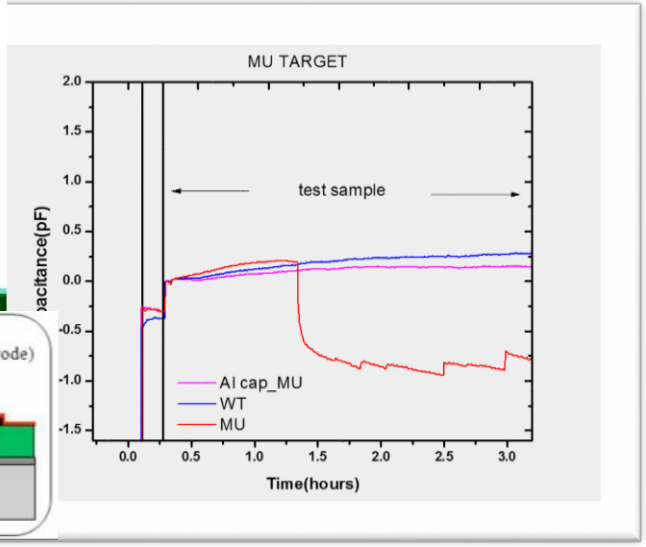
D. Moschou and A. Tserepi, “The lab-on-PCB approach: tackling the μTAS commercial upscaling bottleneck”, Sensors and Actuators B: Chemical, Lab on a Chip - Miniaturisation for Chemistry and Biology, 17(8), pp. 1388-1405
Lammerink et al, “Modular concept for fluid handling systems a demonstrator micro analysis system”, 1996, Proceedings of the IEEE Micro Electro Mechanical Systems (MEMS), pp. 389-394.

Integrated μicro-PCR on PCB







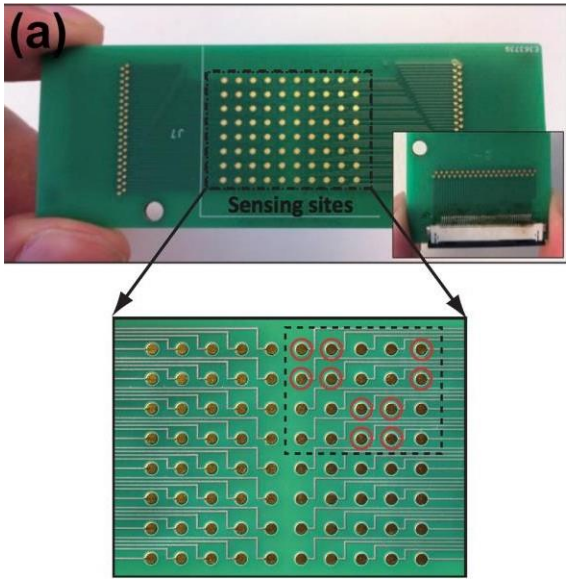


Moschou et al., “All-plastic, low-power, disposable, continuous-flow PCR chip with integrated microheaters for rapid DNA amplification”, Sensors and Actuators B: Chemical, 2014, vol 199, pp. 470

Moschou et al., “Integrated biochip for PCR-based DNA amplification and detection on capacitive biosensors”, Progress in Biomedical Optics and Imaging - Proceedings of SPIE, 8765,87650L

Southampton, UK (2013)

Extended Gates
PCB-based pH sensors

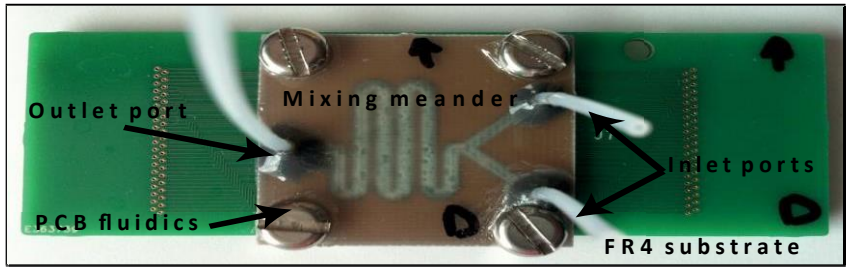


Enzyme-linked immunosorbent assay (ELISA): clinical “gold standard” for reliably detecting and quantifying (antigens, mainly proteins and polypeptides)

eμ-ELISA project (EPSRC)

Goals:

- PoCTB cartridges (sensors+μflu)
- Portable instrumentation
- Exclusively PCB manufacturing techniques



- Imperial College NHS Trust (Immunology department- Clinical testing)
- Newbury Electronics (Commercial upscaling)

Relocating…


Wolverhampton
Leicester
Birmingham
Northampton
Gloucester
Oxford
Luton
Swindon
Swansea
Cardiff
London
Bexley
Bristol
Woking
Maidstone
Southampton
Exeter
Bournemouth
Portsmouth
Plymouth

Centre for Hybrid Biodevices

3 UK patents filed

A SENSOR FOR USE IN ANALYSING BIOMOLECULES

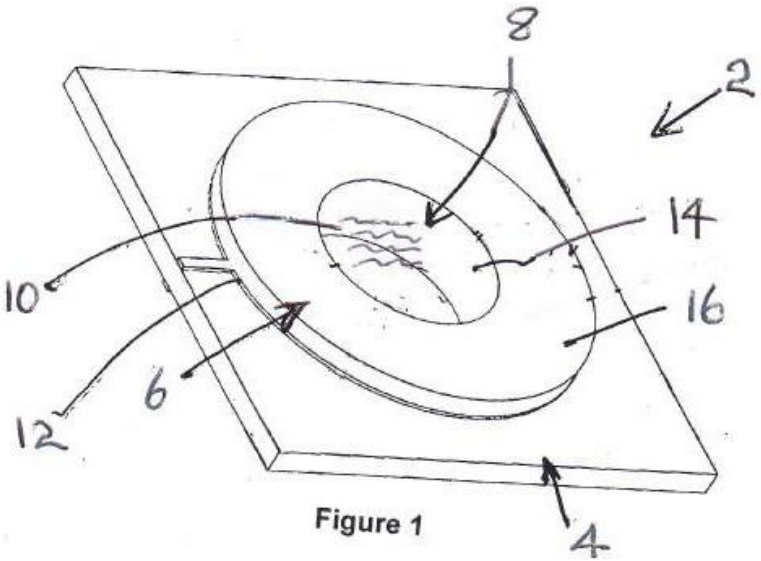


Figure 1

A PCB INTEGRATED REFERENCE ELECTRODE

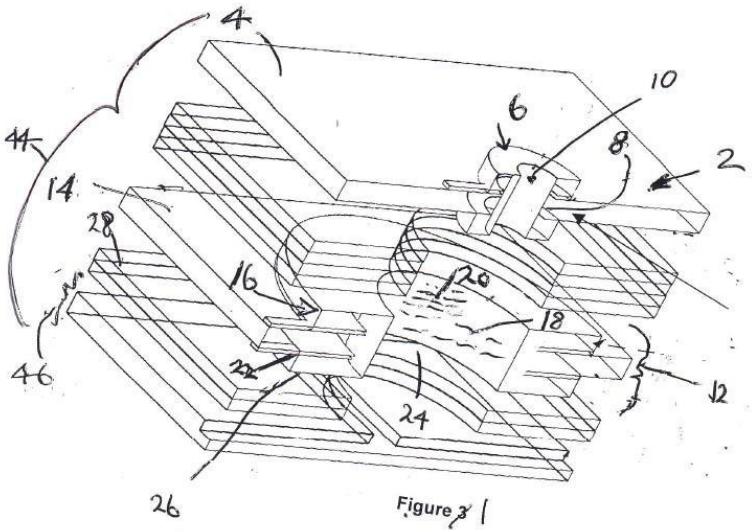


Figure 3

A MICROFLUIDIC CHIP CONNECTOR ASSEMBLY

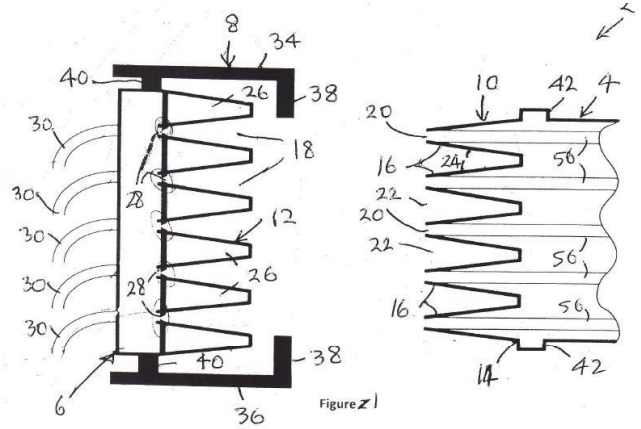


Figure 5

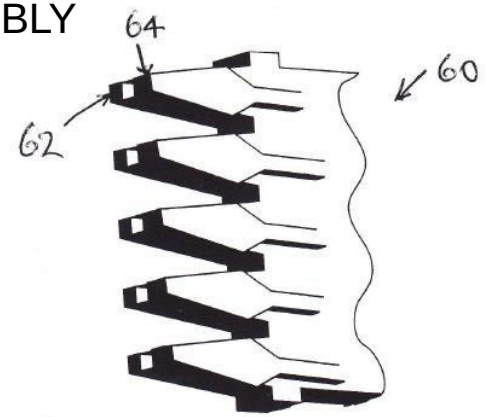


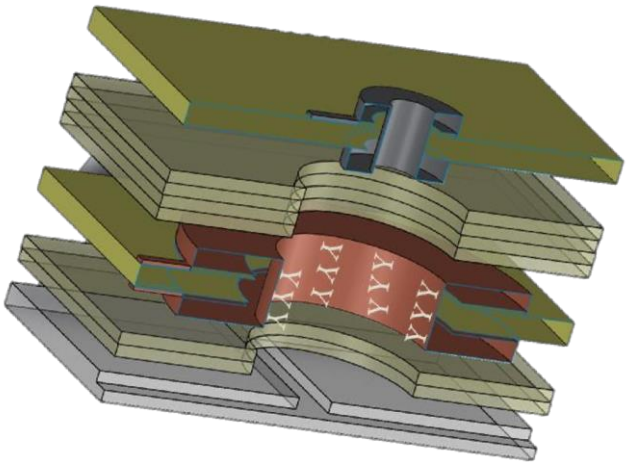
Figure 6

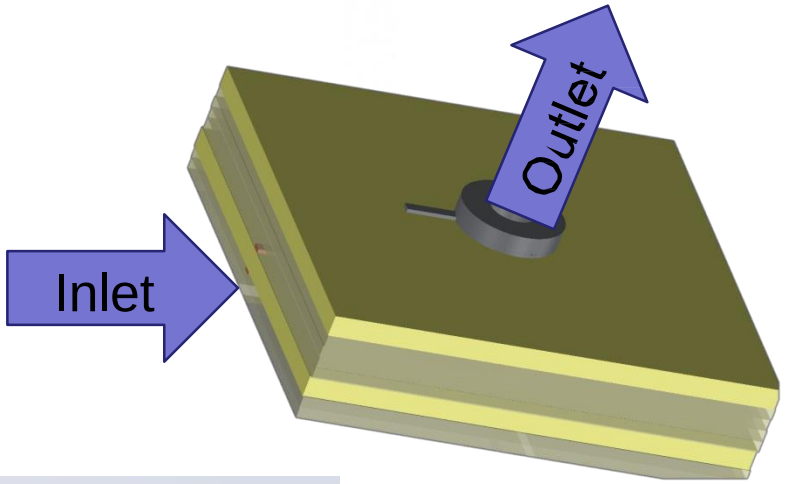
Multi-layer PCB concept

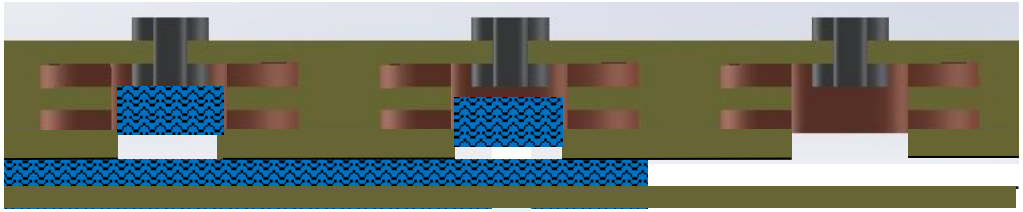
Reference electrodes Layer#1: (Ag/AgCl)

Sensing electrodes Layer #2: (Au)

Microfluidics Layer #3

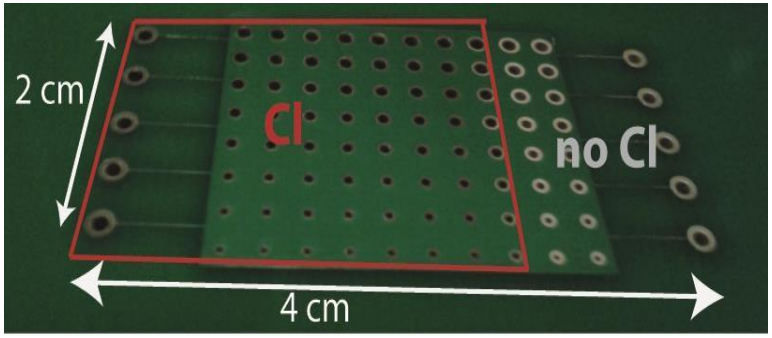




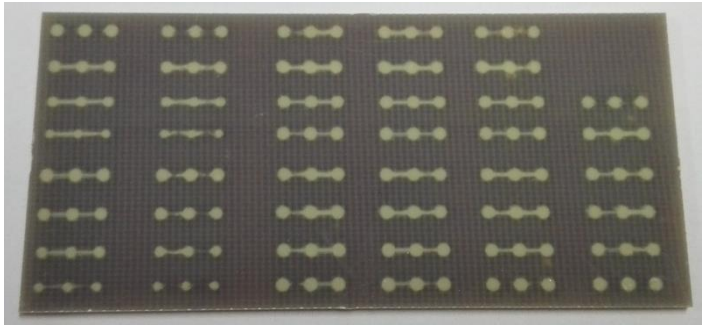


NEWBURY ELECTRONICS

Prototyped PCB reference electrodes



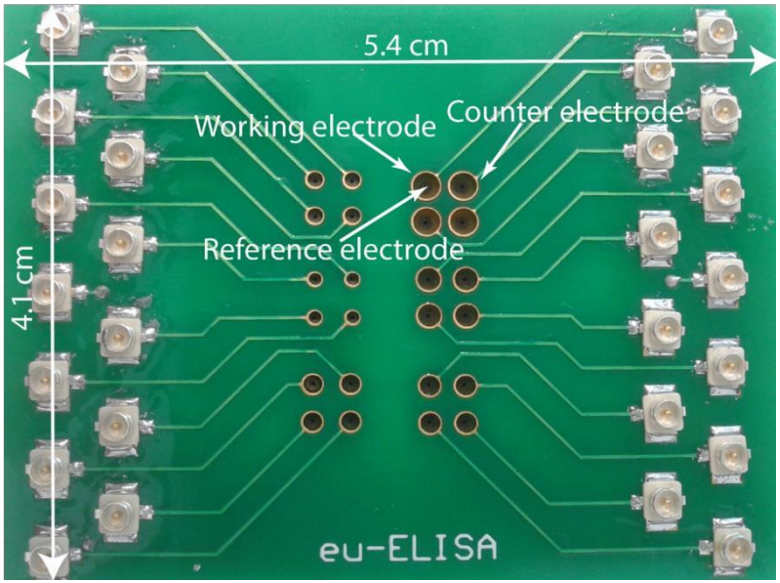
Prototyped 3-layer PCB microfluidics



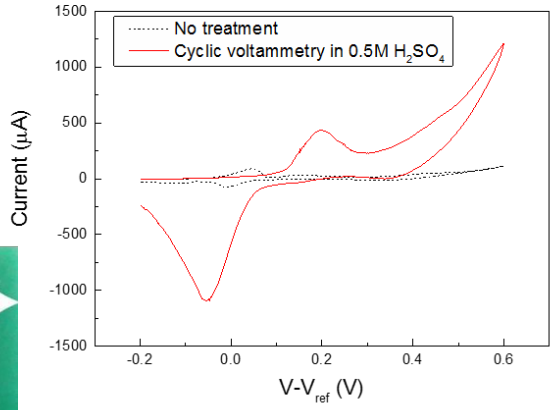
Moschou et al., Sensors 2015, 15(8), 18102-18113.
Prodromakis, T.; Moschou, D., UK Patents GB 1415405.8, GB1415406.6, GB 1415404.1, 29 August 2014.

PCB sensing electrode pre-treatment

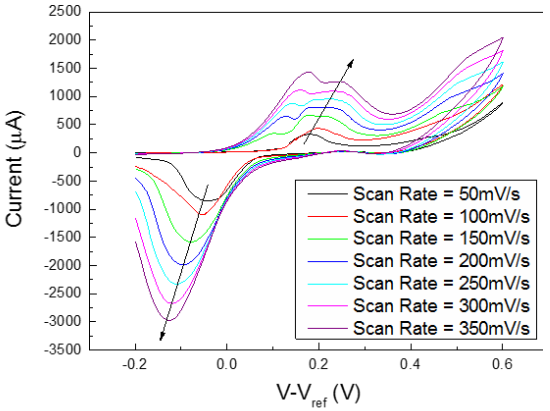
Prototyped 2-layer PCB sensing electrode structure (Integrated Ag/AgCl reference and Au working, counter electrodes)



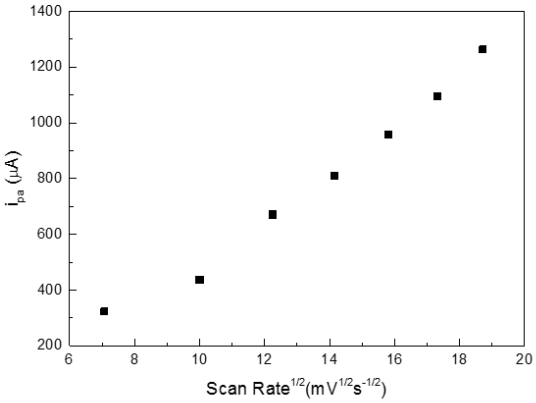
Electrochemical sensing electrode cleaning



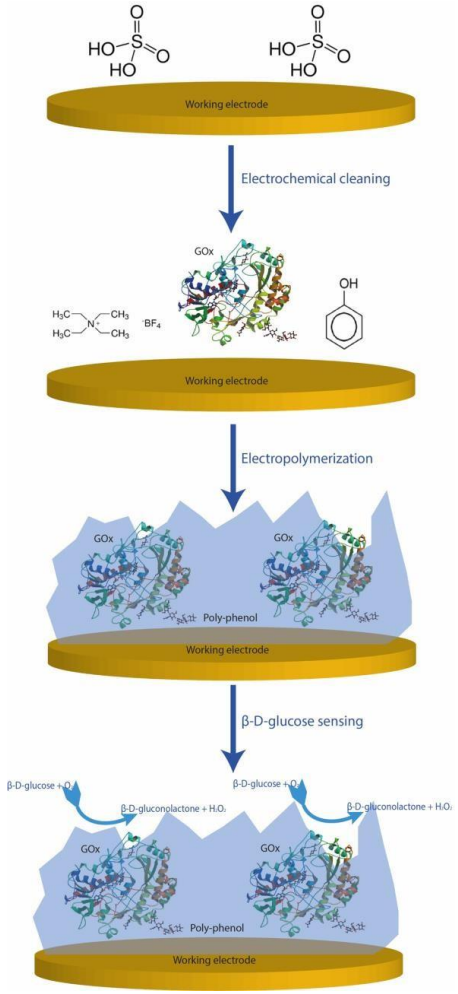
Cyclic voltagrams in $K_3Fe(CN)_6$



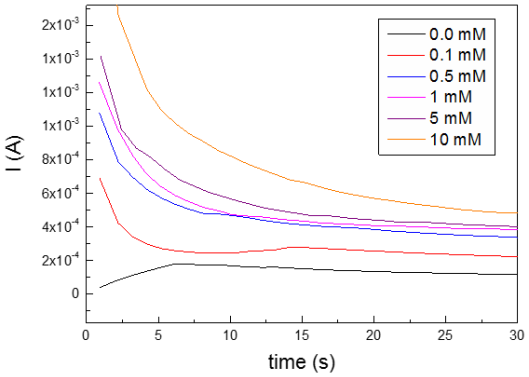
Anodic current dependence on cyclic voltammetry scan rate



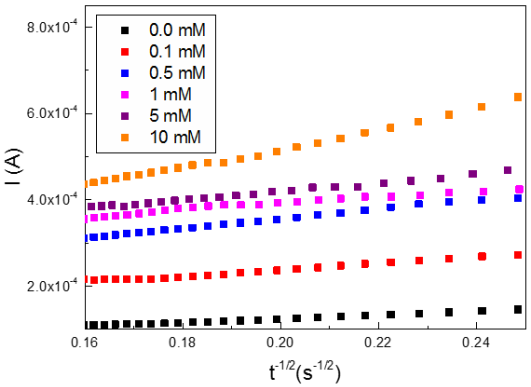
Glucose sensing



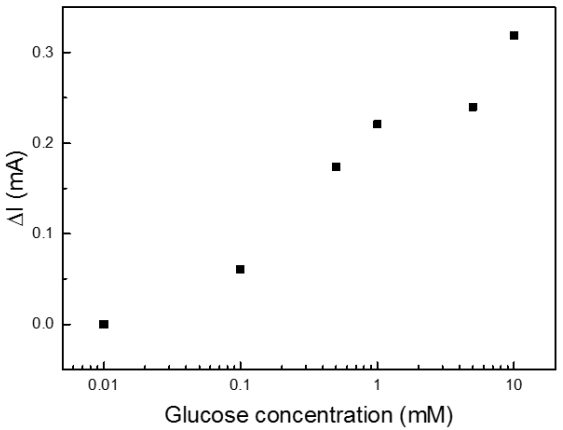
Chronoamperometric curves for varying glucose concentrations



Cottrel plots (i(t)=nFACsqrt(D/πt))

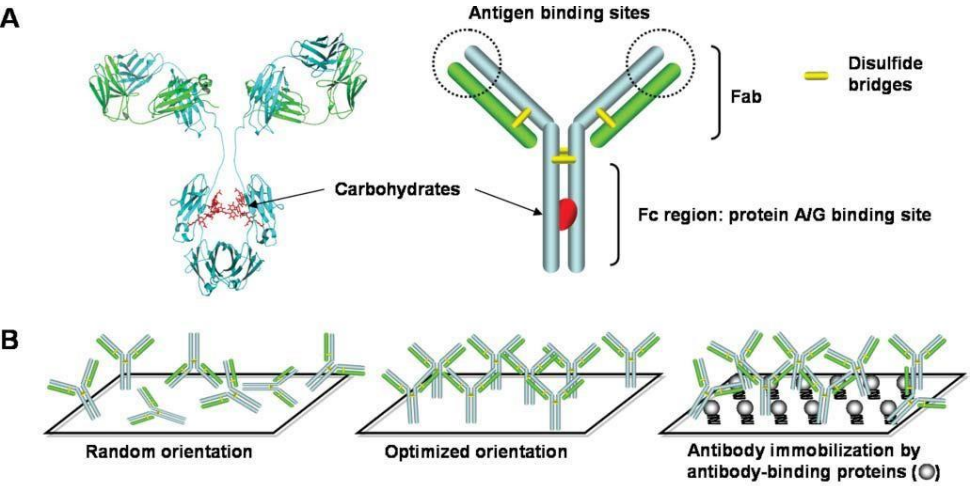


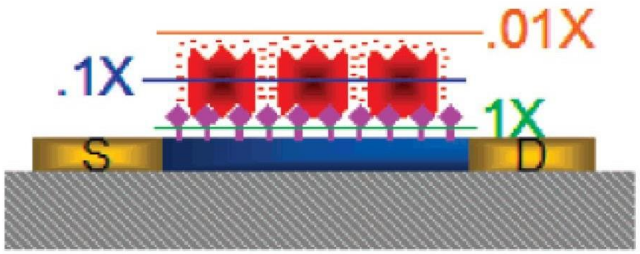
Glucose sensing calibration curve



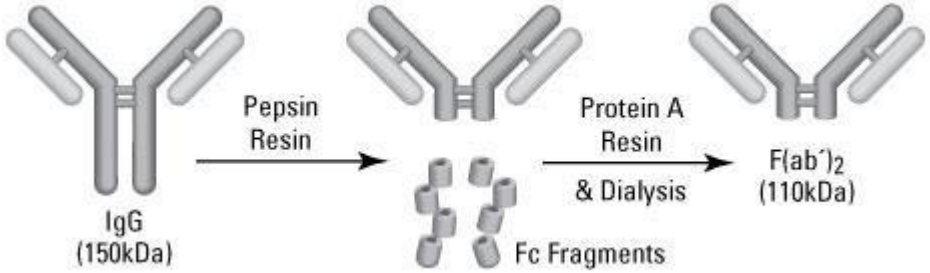
Moschou et al., "A PCB-based electrochemical glucose biosensing platform", 20th International Conference on Miniaturized Systems for Chemistry and Life Sciences, MicroTAS 2016, pp. 1047-1048

Hints on electrochemical sensing

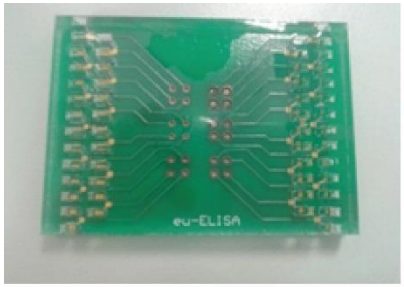


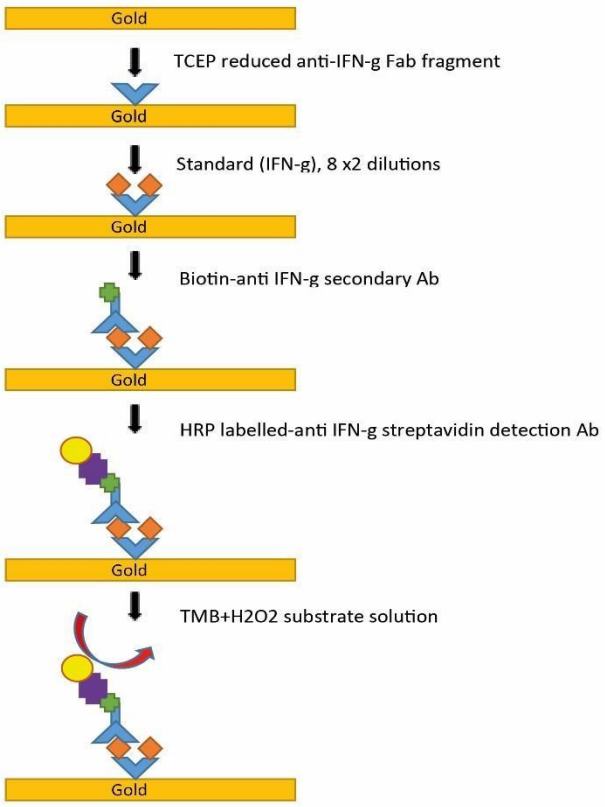


Debye length ($\propto$ buffer ionic strength) defines sensing sensitivity



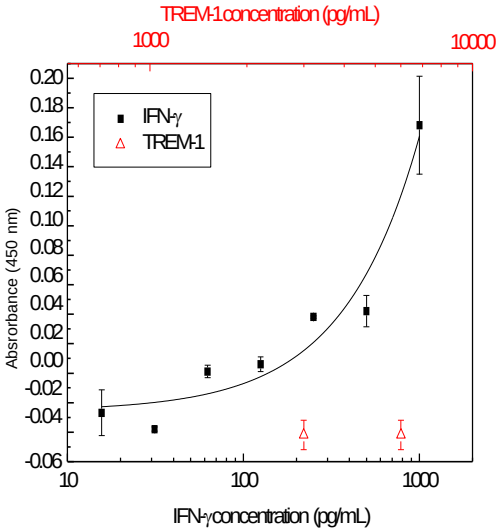
euELISA IFN-gamma assay



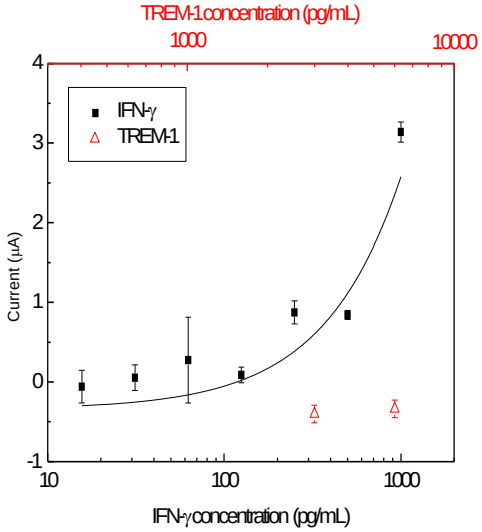


- Clinical ELISA assay (IFN-gamma commercial Duoset kit)
- Thiol terminated Fab fragments used instead of kit capture Ab (42ug/ml in PBS)
- Bi-sulphide bond immobilization on PCB gold surface
- SPR measurements

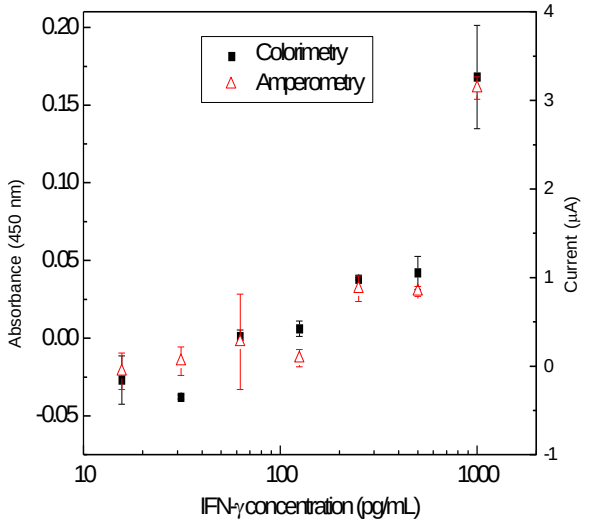
Electrochemical sensing results



Optical detection

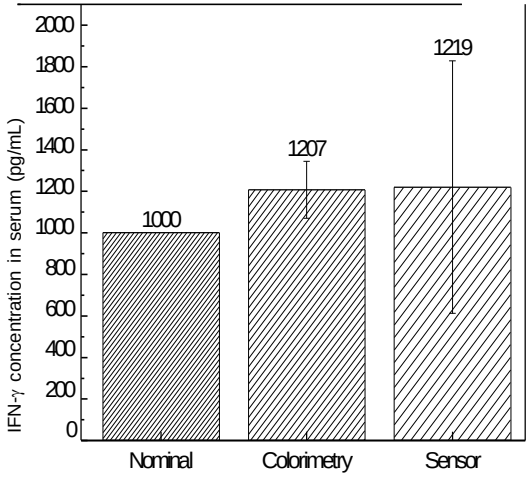


Electrochemical detection



$LOD_{colorimetry}$=28.22pg/mL

$LOD_{amperometry}$=126.75pg/m



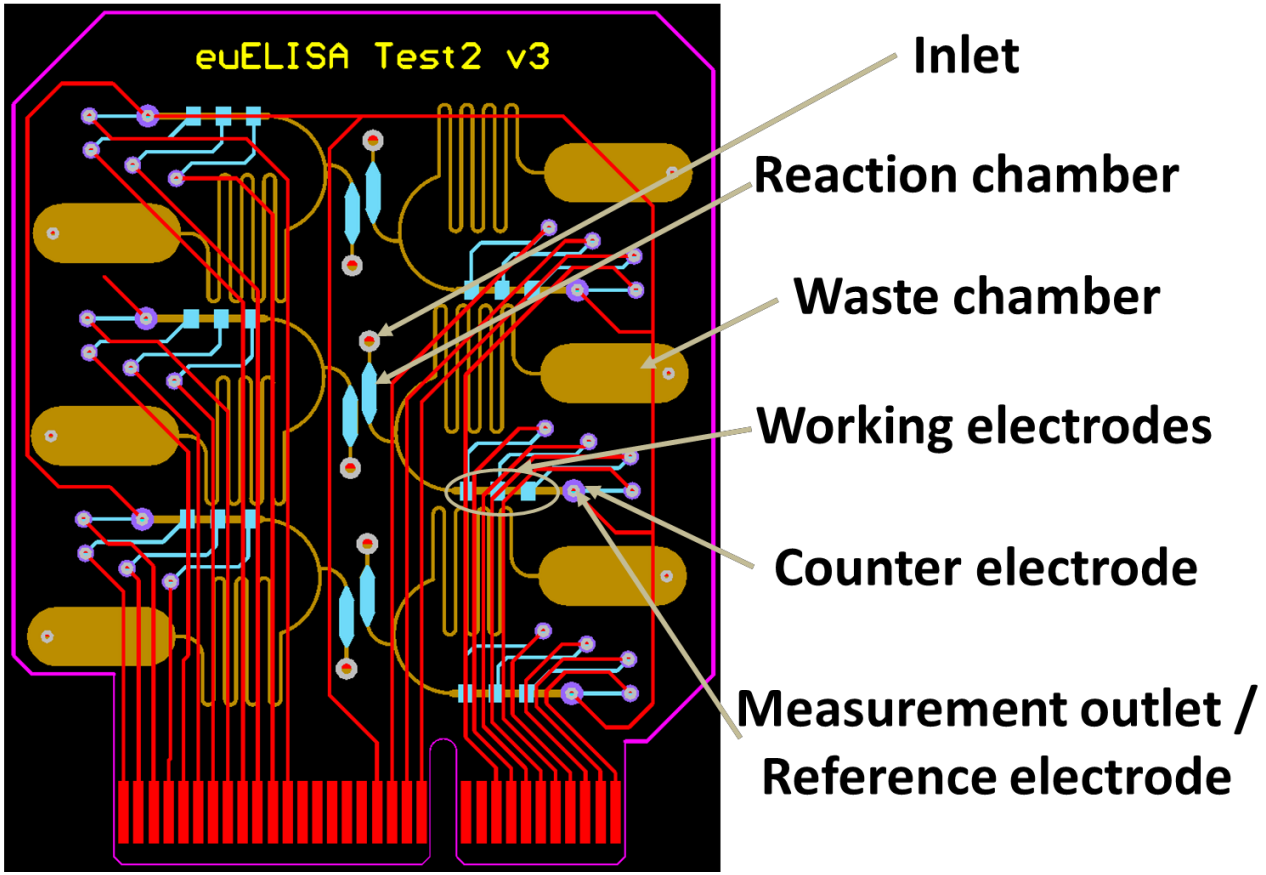
IFN-γ recovery in human serum

Despina Moschou et al, "Amperometric IFN-γ immunosensors with commercially fabricated PCB sensing electrodes" , 2016, Biosensors and Bioelectronics, 86, pp. 805-810

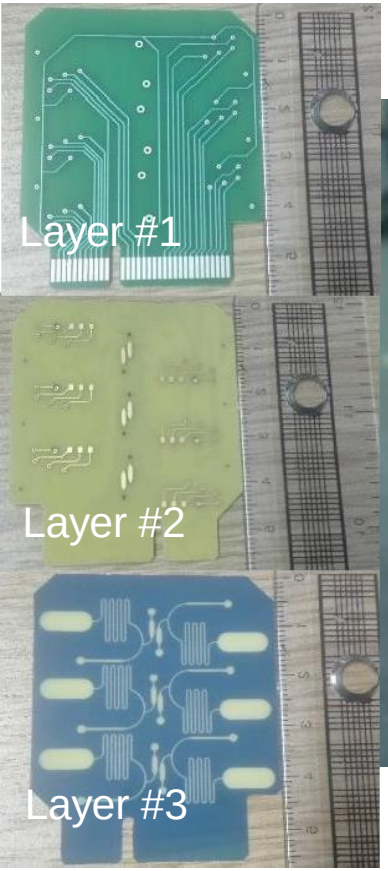
LoPCB chip (4.6cm x 5.7cm)

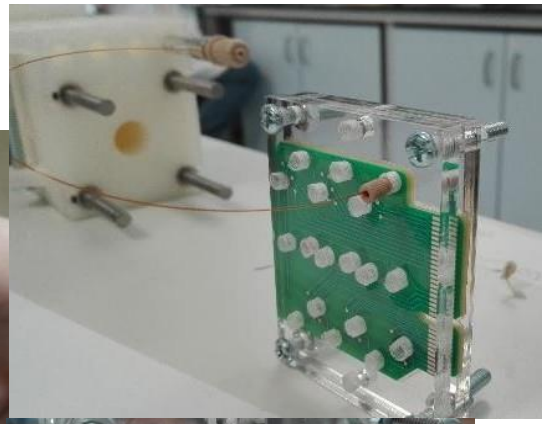
Fully integrated cartridge
(Reference, sensing electrodes, microfluidics)

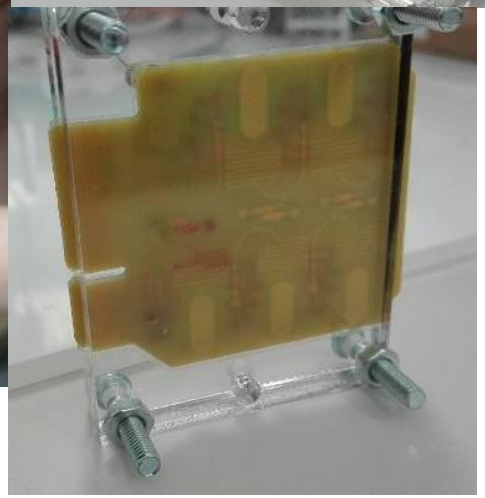
- PCI express interfacing
- 6 channel (4 standard curve points within clinical range, 1 negative control, 1 sample)
- 10 µL reaction chambers
- 3 amperometric sensors per channel
- Full assay implementation on chip

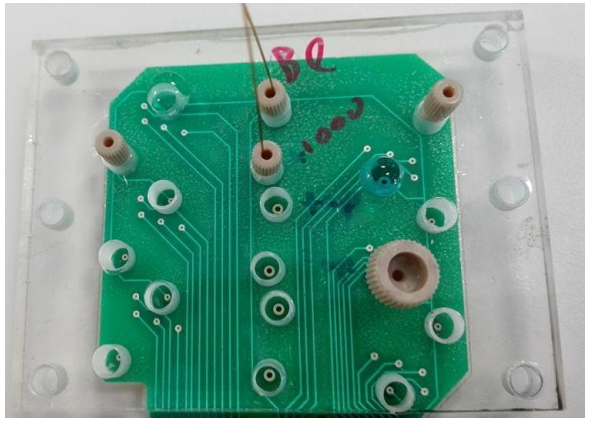


euELISA commercially fabricated ☺

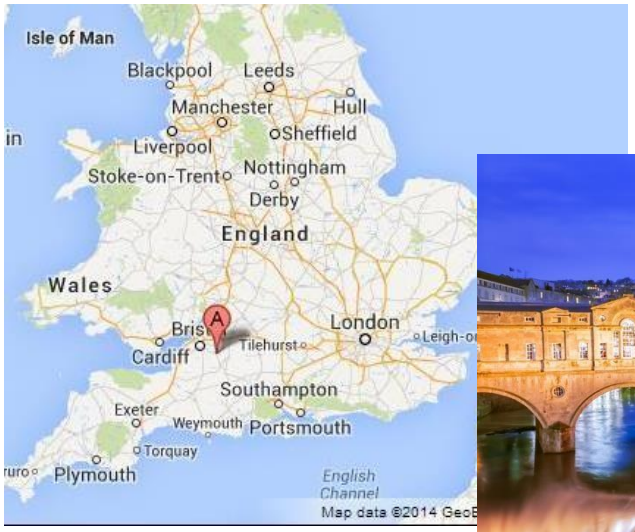


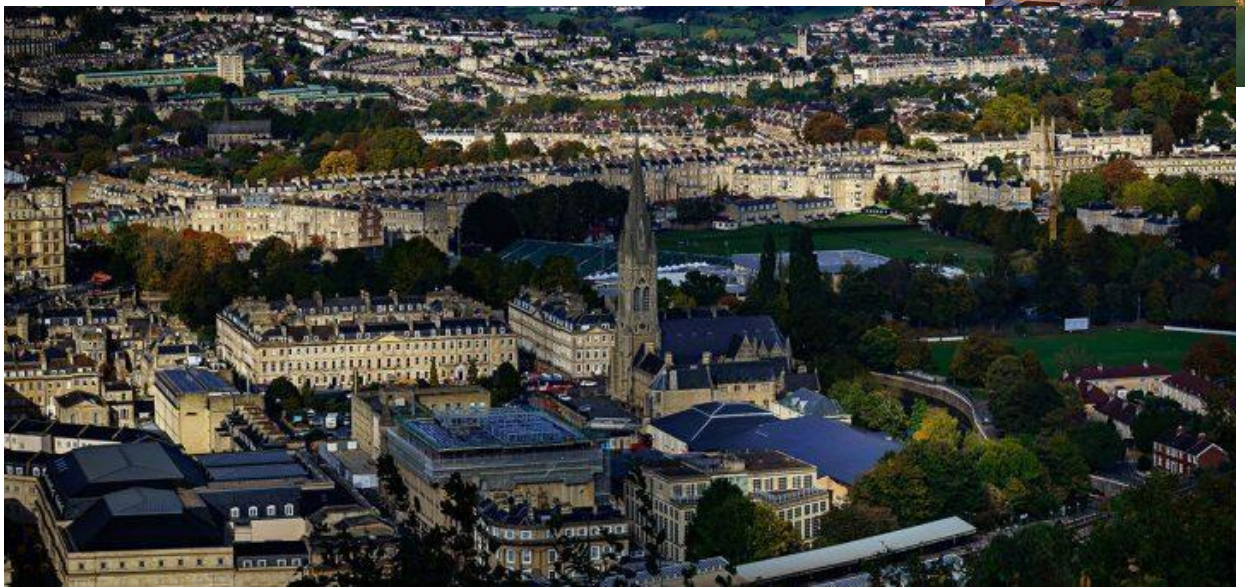






Prize Fellow / Lecturer, Bioelectronics:
2016-Now: University of Bath, UK





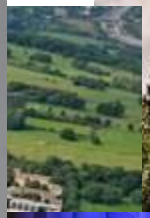
University of Bath

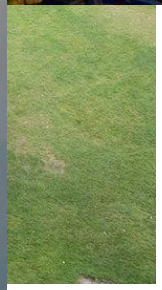
BUCKINGHAM PALACE

I send my best wishes to the staff, students, alumni and supporters of the University of Bath who are present in Bath Abbey to commemorate the Fiftieth Anniversary of the University's establishment by Royal Charter.

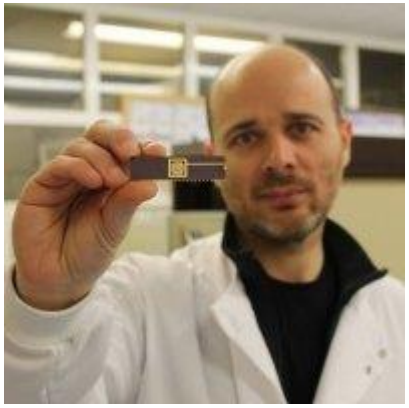
As you celebrate your achievements in research and education over the last fifty years, I have pleasure in conveying my congratulations to you all on this most significant anniversary.

ELIZABETH R.





CAST group in Bath

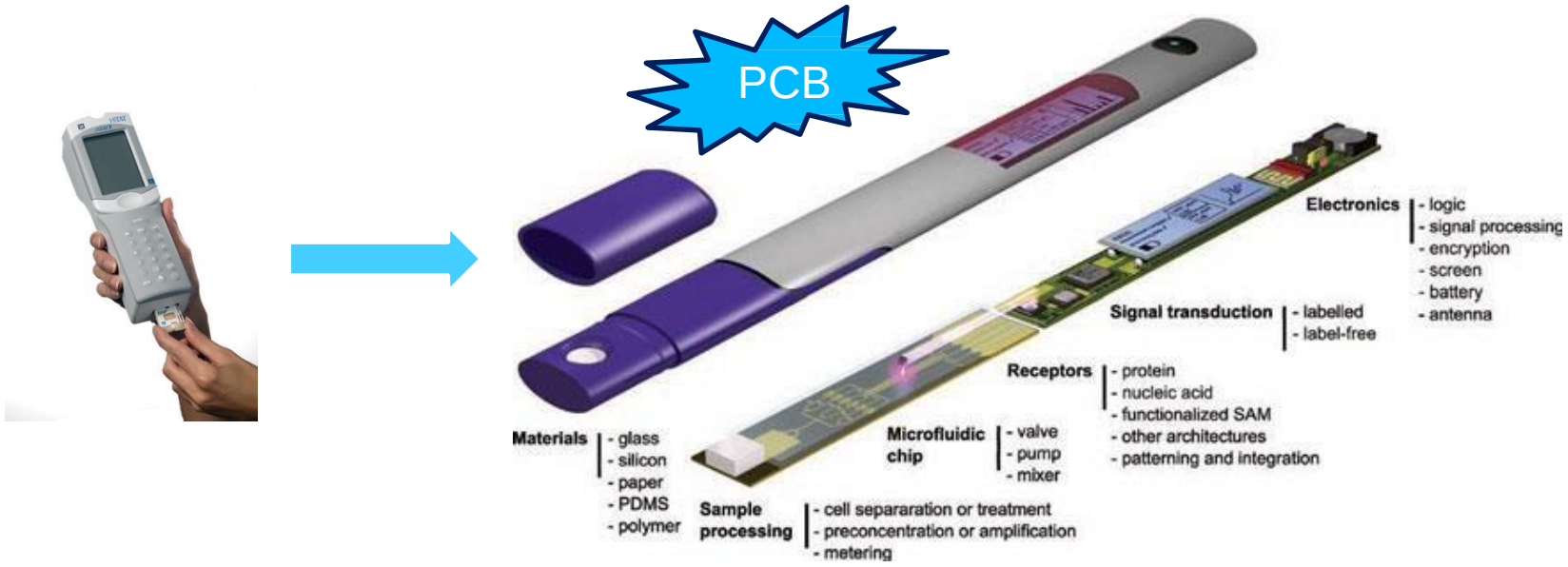


The Centre's interdisciplinary research focuses on highly accurate sensors, devices and related technologies, including:

- electronic circuit and systems
- wide bandgap semiconductors
- LEDs
- devices for medical applications
- implantable systems
- sensor and actuator materials
- nanotechnology
- biosensors and chemical sensors.

Towards an ideal POC diagnostic device

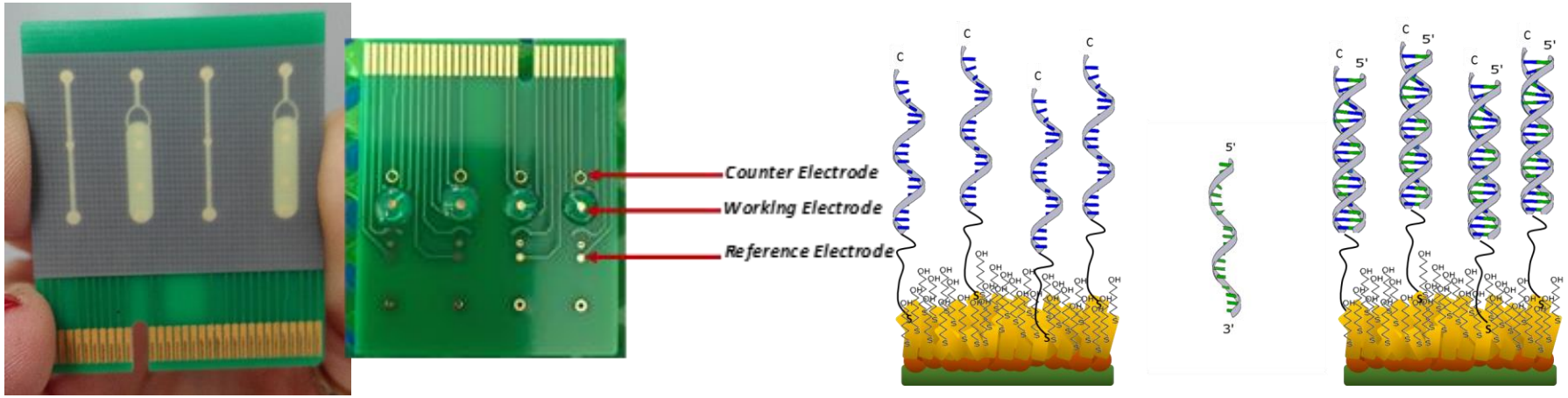
Affordable by those at risk of infection
Sensitive with very few false-negatives
Specific with very few false-positives
User-friendly tests that are simple to perform and require minimal training
Rapid, to enable treatment at first visit, and Robust, for example not requiring refrigerated storage
Equipment-free
Delivered to those who need it

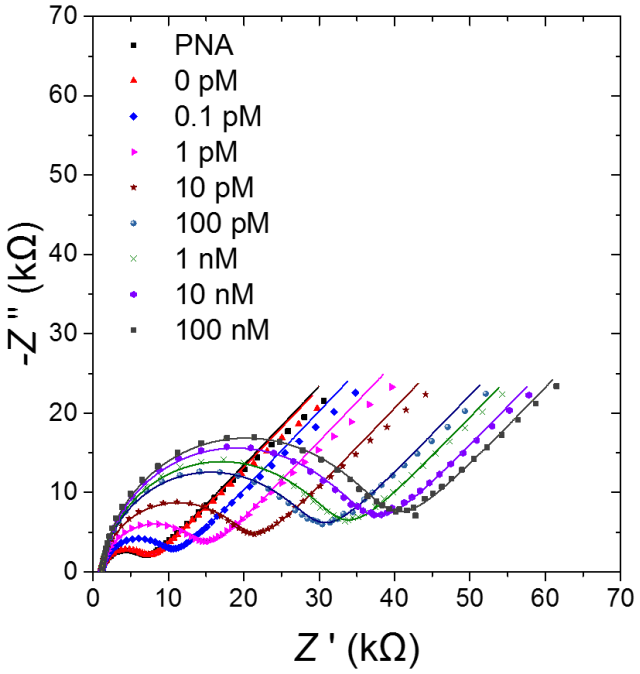


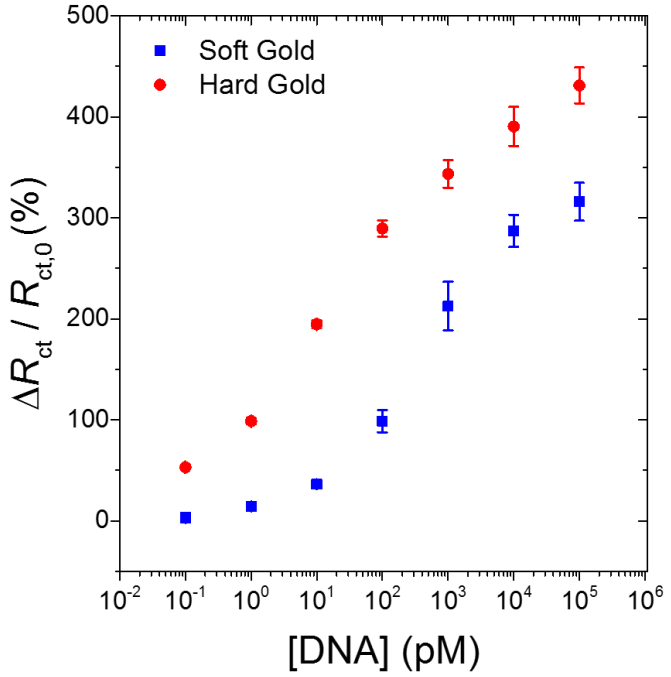
https://www.i-sense.org.uk/infectious-diseases/assured-diagnostics

Gervais et al, "Microfluidic Chips for Point-of-Care Immunodiagnostics", Adv. Mater. 2011, 23, H151–H176

DNA electrochemical detection

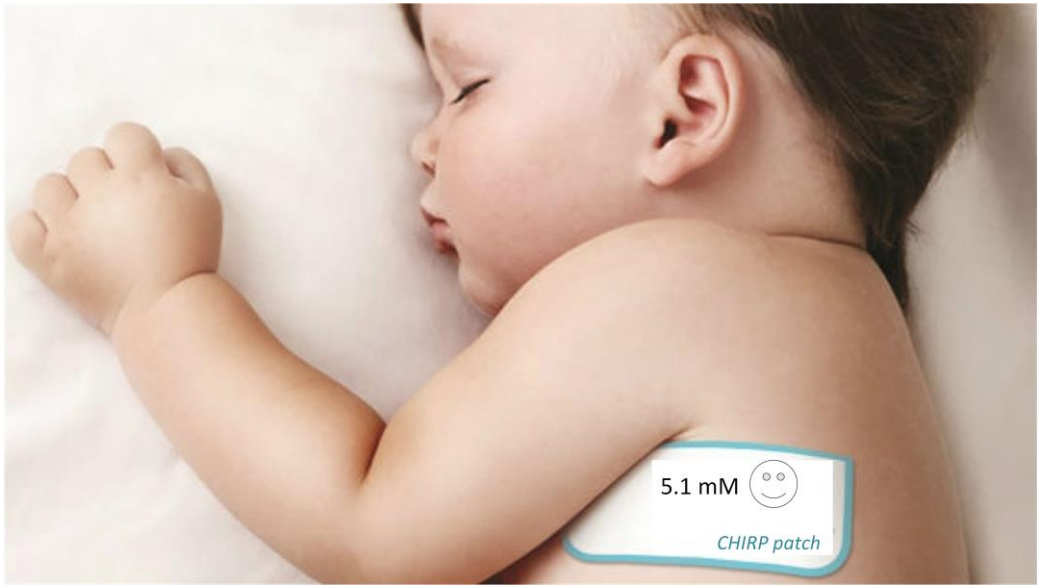






The CHIRP project

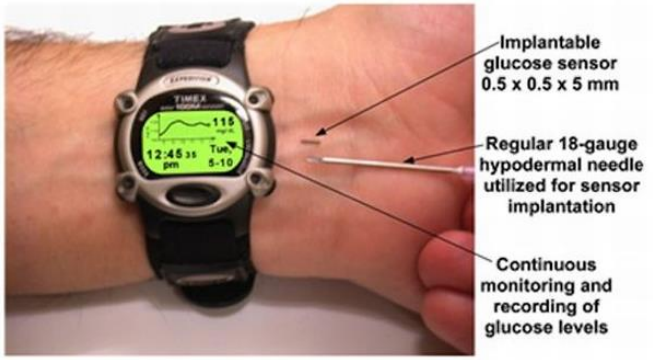
- Increasing sugar consumption → global diabetes epidemic
- Diabetes prevalence rapidly increasing in low/middle-income countries (Turkey: 13.6%, double the global average)
- Turkey: increased childhood obesity, very young population (0-14 year olds: 25.5% of population)
- CHIRP vision: make a pre-diabetes diagnostic test for mass population preventative screening of children
- Painless, reliable, disposable patch



Currently available solutions for diabetes screening

Low-cost, but invasive

Non-invasive, high-cost



Non-invasive, disposable

???

CHIRP project

CHIRP concept

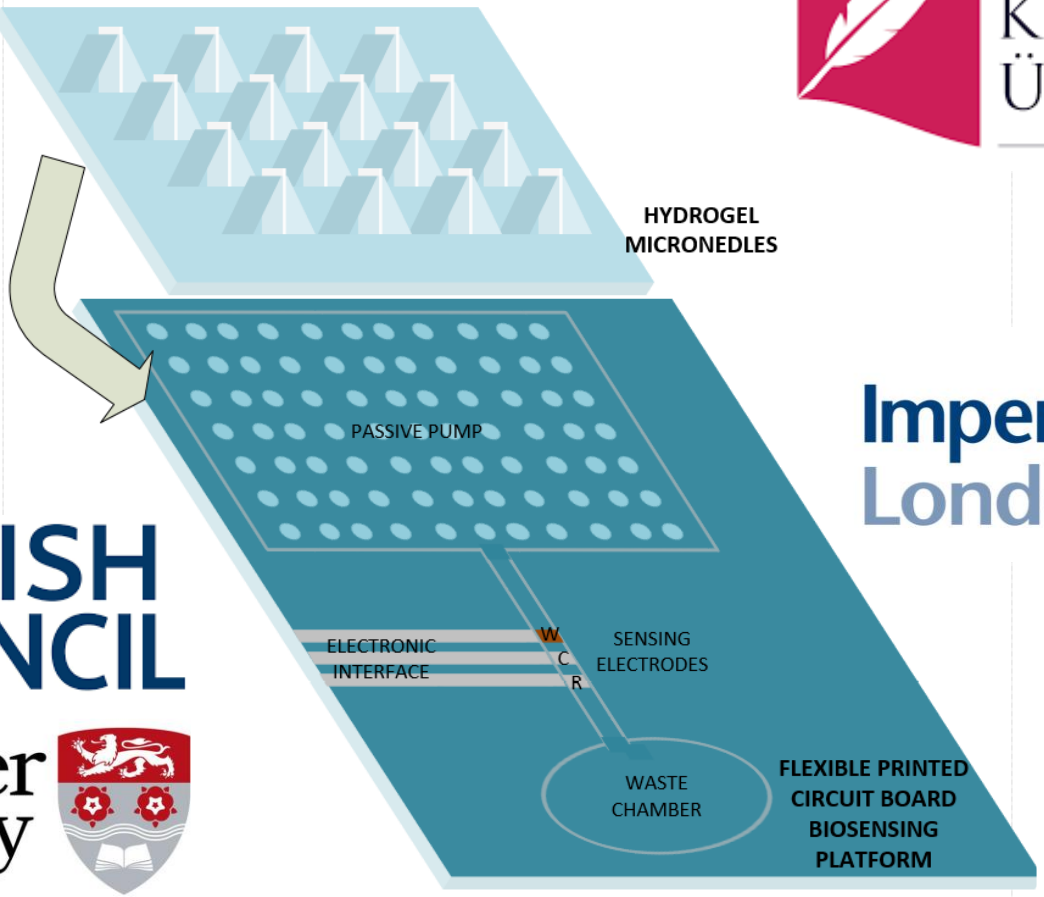
UNIVERSITY OF BATH

4 partners (UK-Turkey)

2 year project

Project budget: £279,898.86

İZMİR KÂTİP ÇELEBİ ÜNİVERSİTESİ 2010



Imperial College London

BRITISH COUNCIL

Lancaster University

TÜBİTAK

Adding functionality...

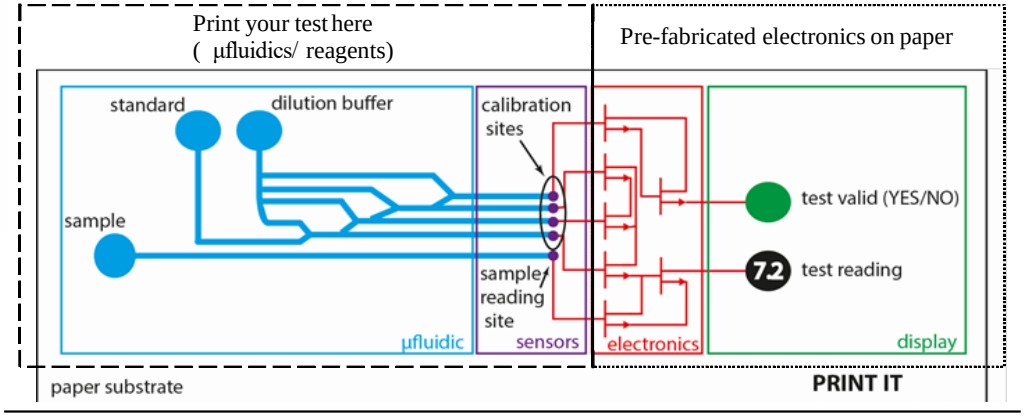
PRINTing Integrated diagnostic Tests: decentralizing health diagnostic test manufacturing

Printing on-demand (chemist's, GP office) the required diagnostic test

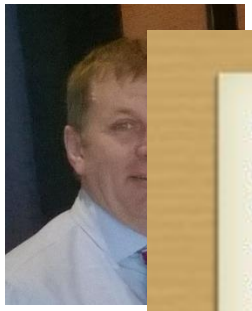
Printable biosensors/microfluidics on paper

Integrated TFT electronic circuitry (no reader required)

Highly ambitious, yet game-changing…



Industrial engagement



SPIR
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Many eu
academi
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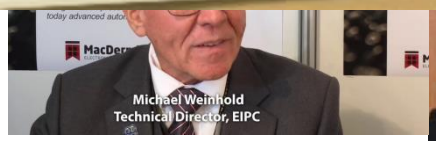
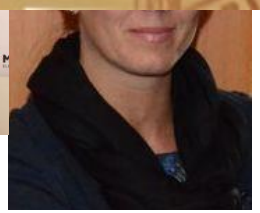
prototypes…





Industrial collaborations

Viking

SPIRIT CIRCUITS
Serious About PCBS

GRAPHIC

Optiprint
Innovative PCB Solutions

SES
SCHOELLER ELECTRONICS SYSTEMS

ventec
INTERNATIONAL GROUP
騰輝電子

isola

Adeon

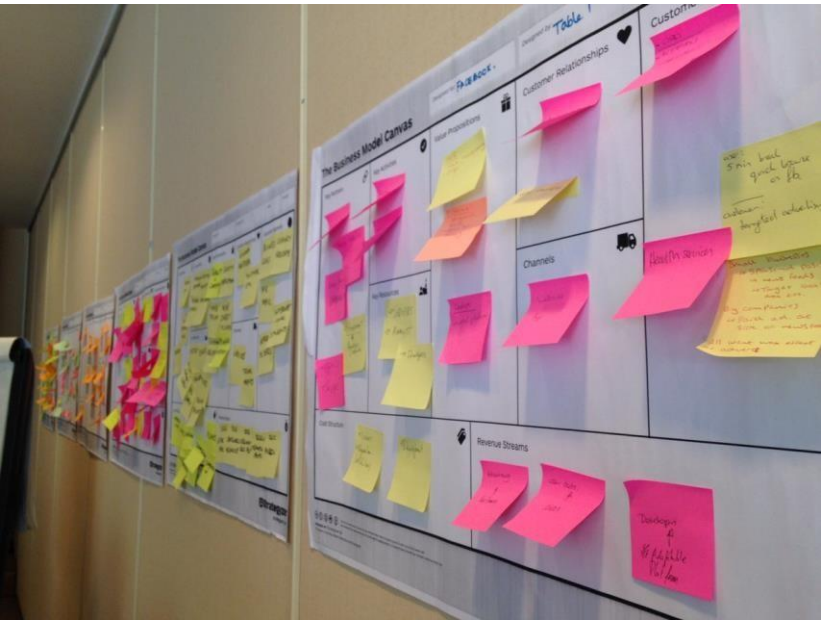
Bringing together PCB and microfluidics industry?

Global PCB market:$59.2 billion
Europe sharing a 4.1% market share
Mostly aimed at high specification products (aerospace, automotive applications).
Top 74 largest european PCB companies: $1 billion in turnover in 2015.

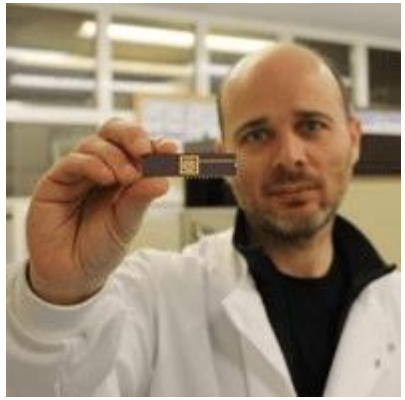
MF-8

LoC market growth at 18-29%
Reaching $3.6-5.7billion by 2018

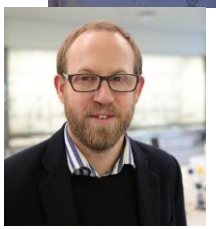
Research to innovation…

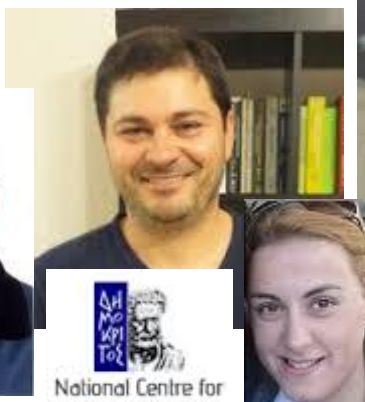


Acknowledgements







British Council, Newton Fund Institutional Links, UK-Turkey , project: 336872

Ένα Μεγάλο Ευχαριστώ !