Frontiers of More than Moore in Bioelectronics and the Required Metrology Needs

Anthony (Tony) Guiseppi-Elie

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Frontiers of Characterization and Metrology for Nanoelectronics

May 23-26, 2011 MINATEC Campus, Grenoble, France


2011 International Conference on Frontiers of
Characterization and Metrology for Nanoelectronics
MINATEC Campus, Grenoble, France
23 - 26 May 2011
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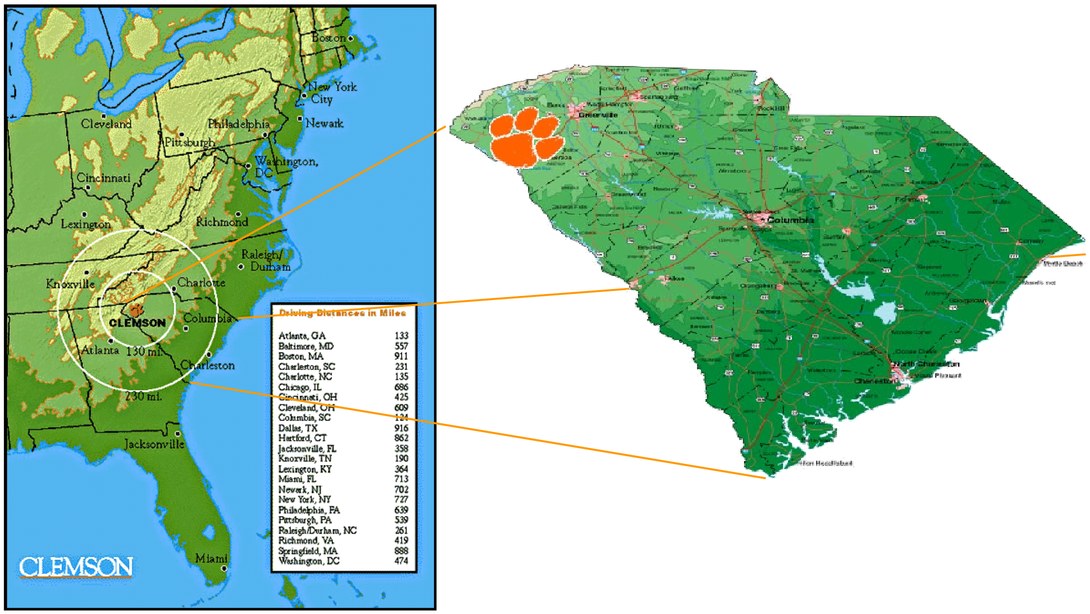


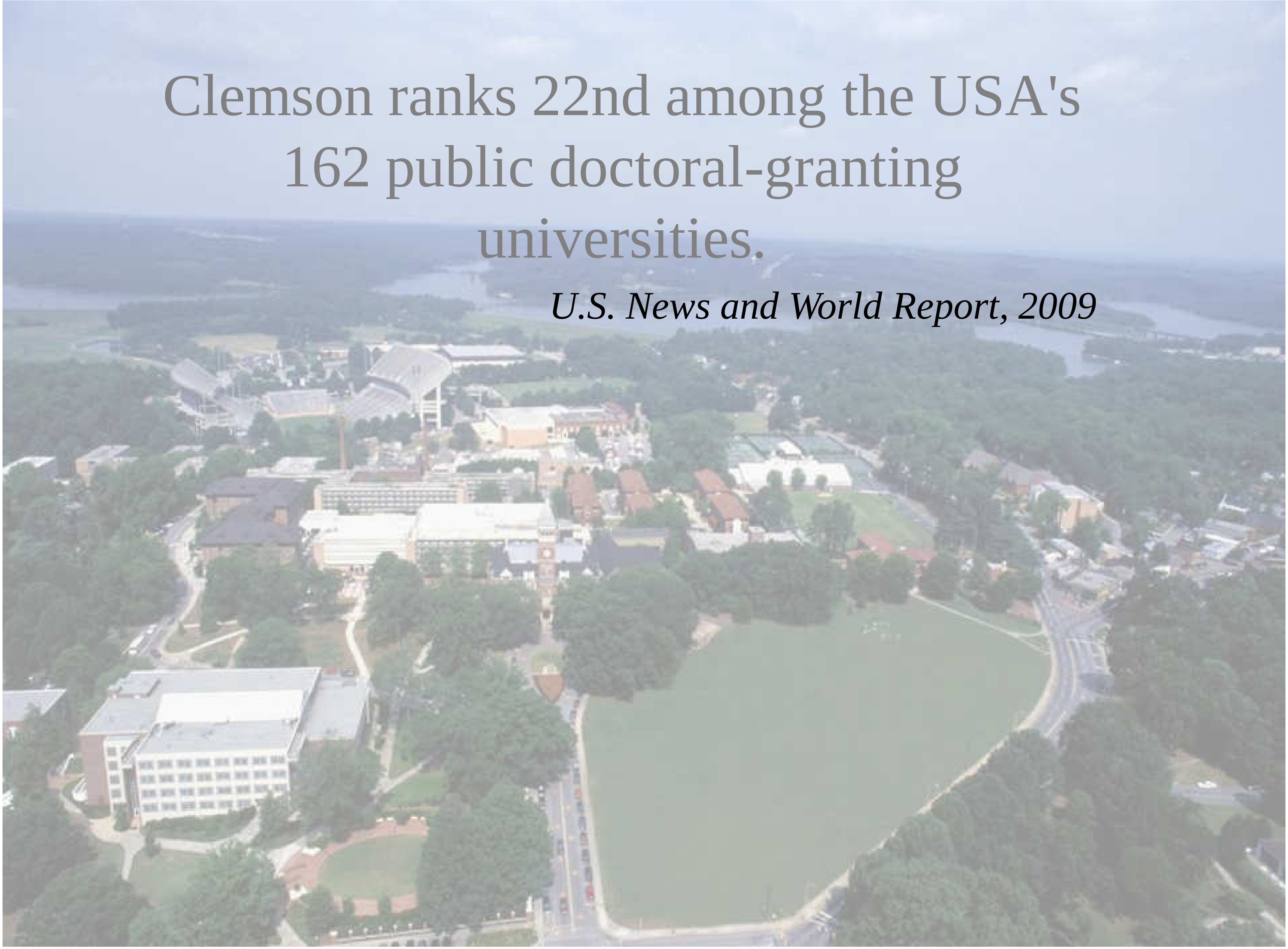
Founded in 1889, Clemson University is a South Carolina land-grant institution dedicated to teaching, research, and public service, and to improving the quality of life through education.

Clemson's 1,400-acre main campus, located in the Northwestern corner of South Carolina on the shores of Lake Hartwell, is surrounded by 17,000 acres of University farms and woodlands devoted to research.

Approximately 17,165 students, including 3,096 graduate students are enrolled in five colleges offering Baccalaureate and Graduate degrees in over 70 fields of study.

Clemson ranks 22nd among the USA's 162 public doctoral-granting universities.

U.S. News and World Report, 2009



Disclosure

Anthony Guiseppi-Elie, Sc.D.
Founder, President and Scientific Director

Founded 1995 - near-patient molecular diagnostic products of clinical significance

ABTECH

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Improving Human Health Through Nano-Bio-Technology:

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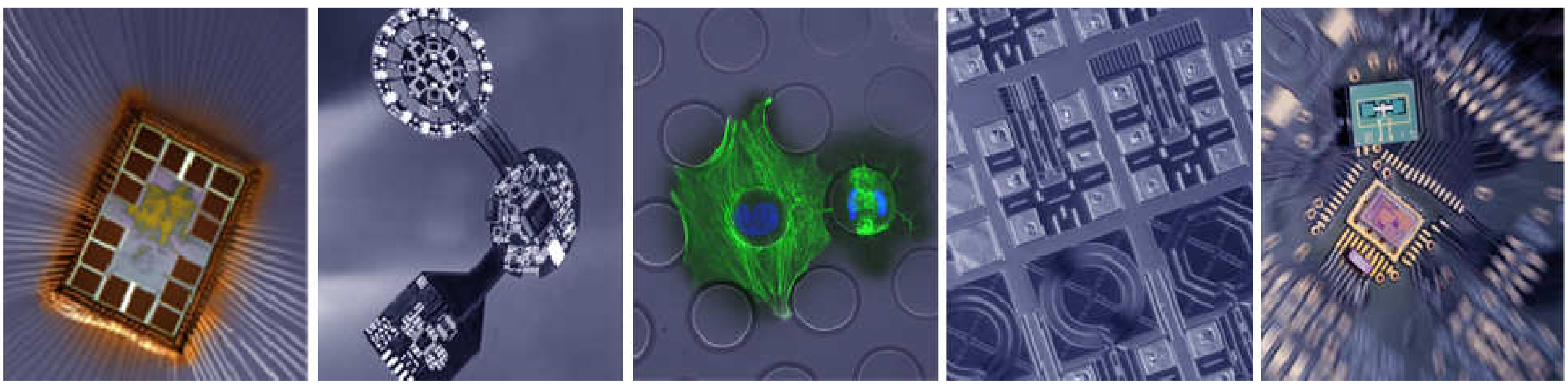
The CU-C3B is a national model for advanced nano-bio electronics



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Grand Challenge Problems

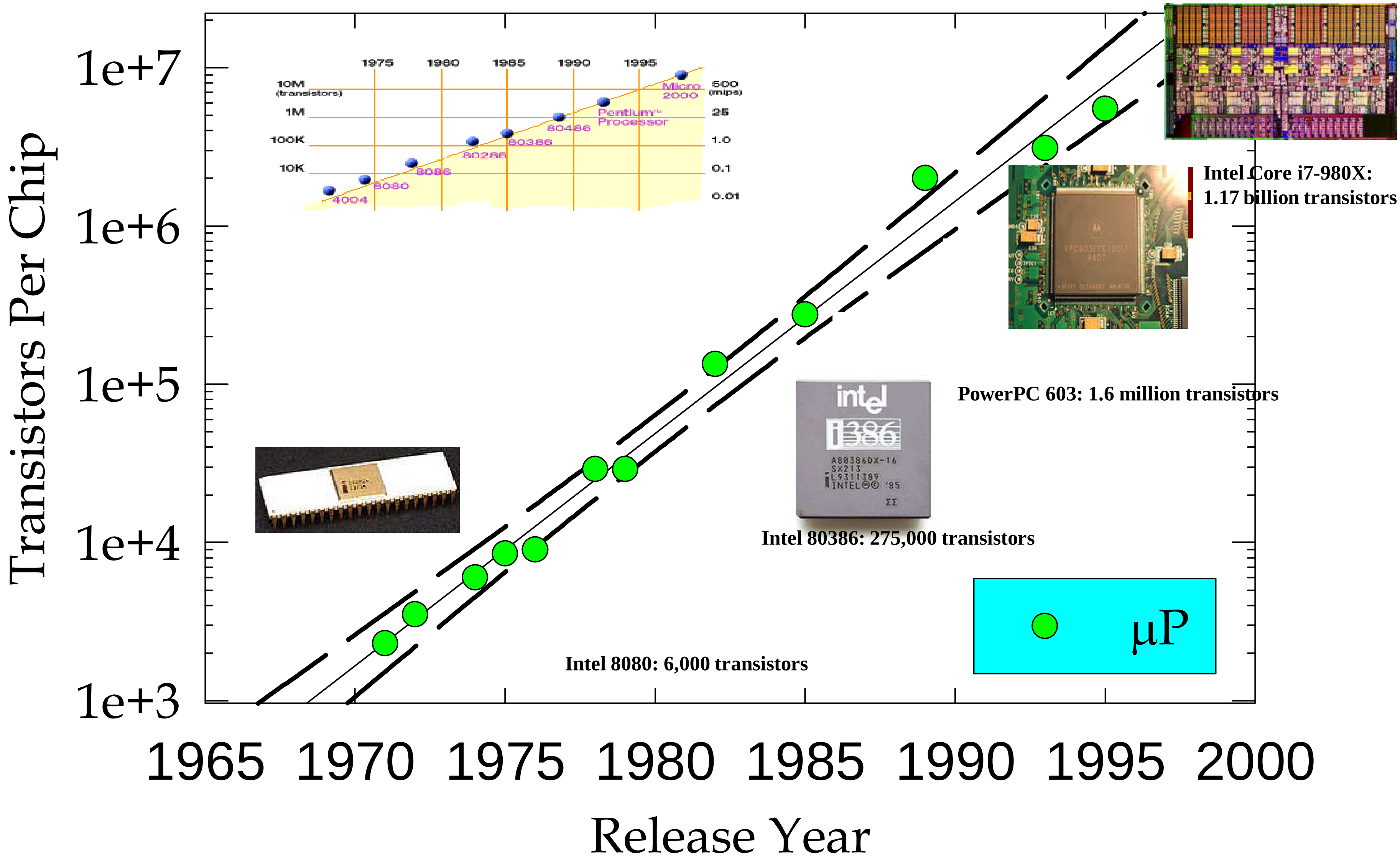
The Bio-materials Interface: Enabling chronically implantable bioanalytical devices - **Bionics**

Bioelectronics: Enabling direct electronic communication between electronic solid state devices and the biology -- **More than Moore**

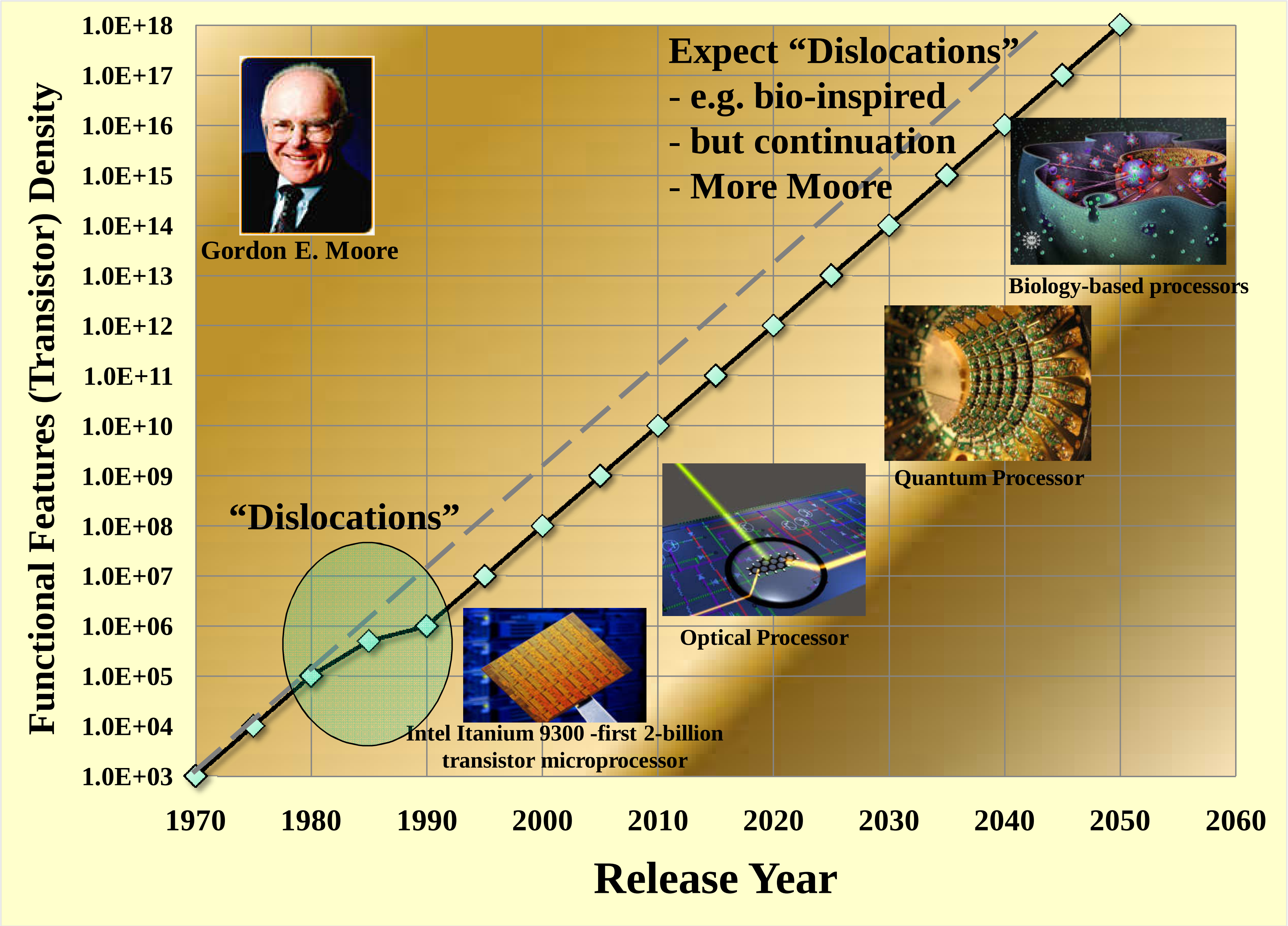
Moore's Law

Milestones in Microprocessing Power

Adapted from: PC Magazine -- December 17, 1996; Intel's Web Site 1998.



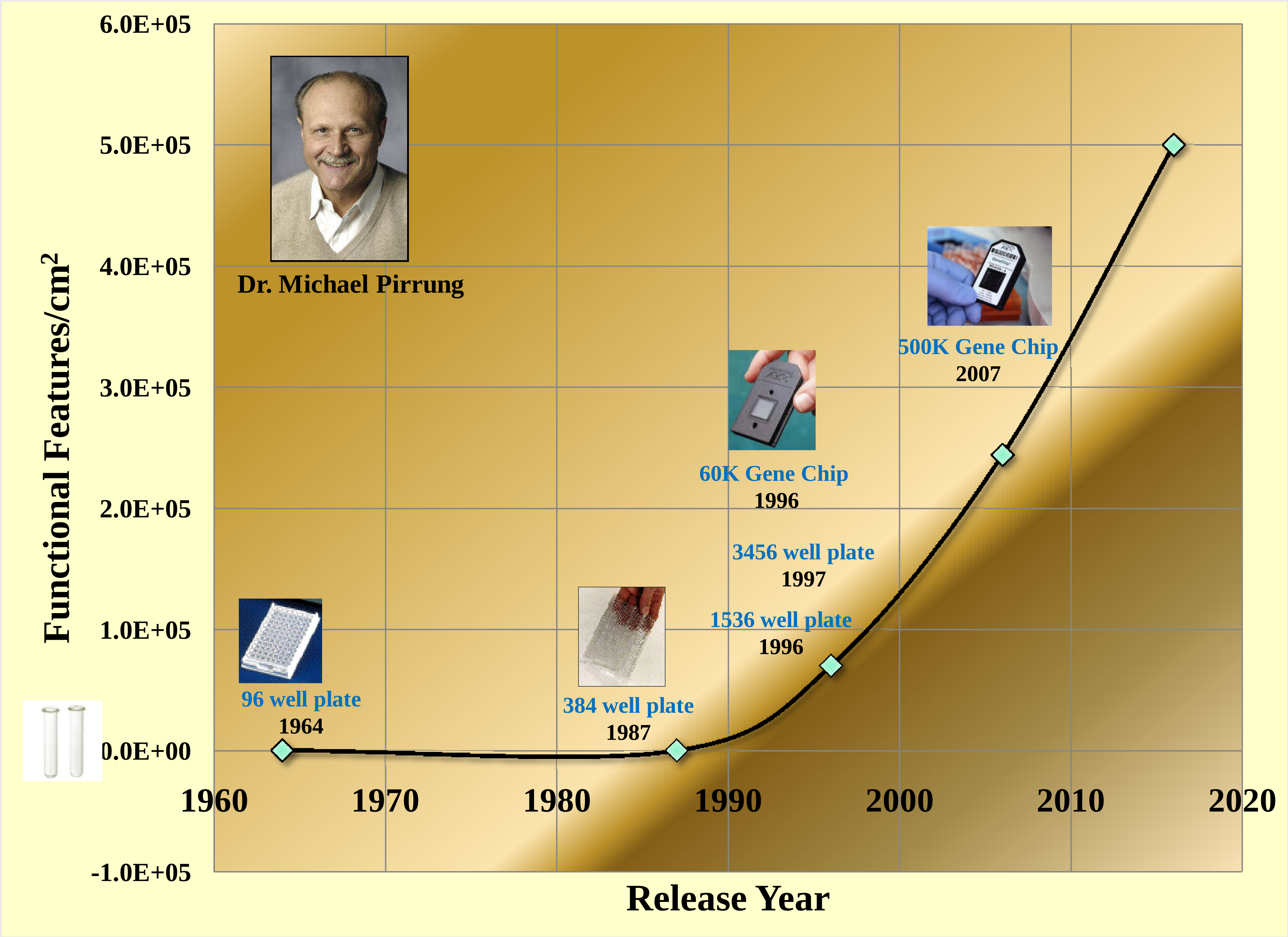
Moore's Law "Prediction": Future of Microprocessors



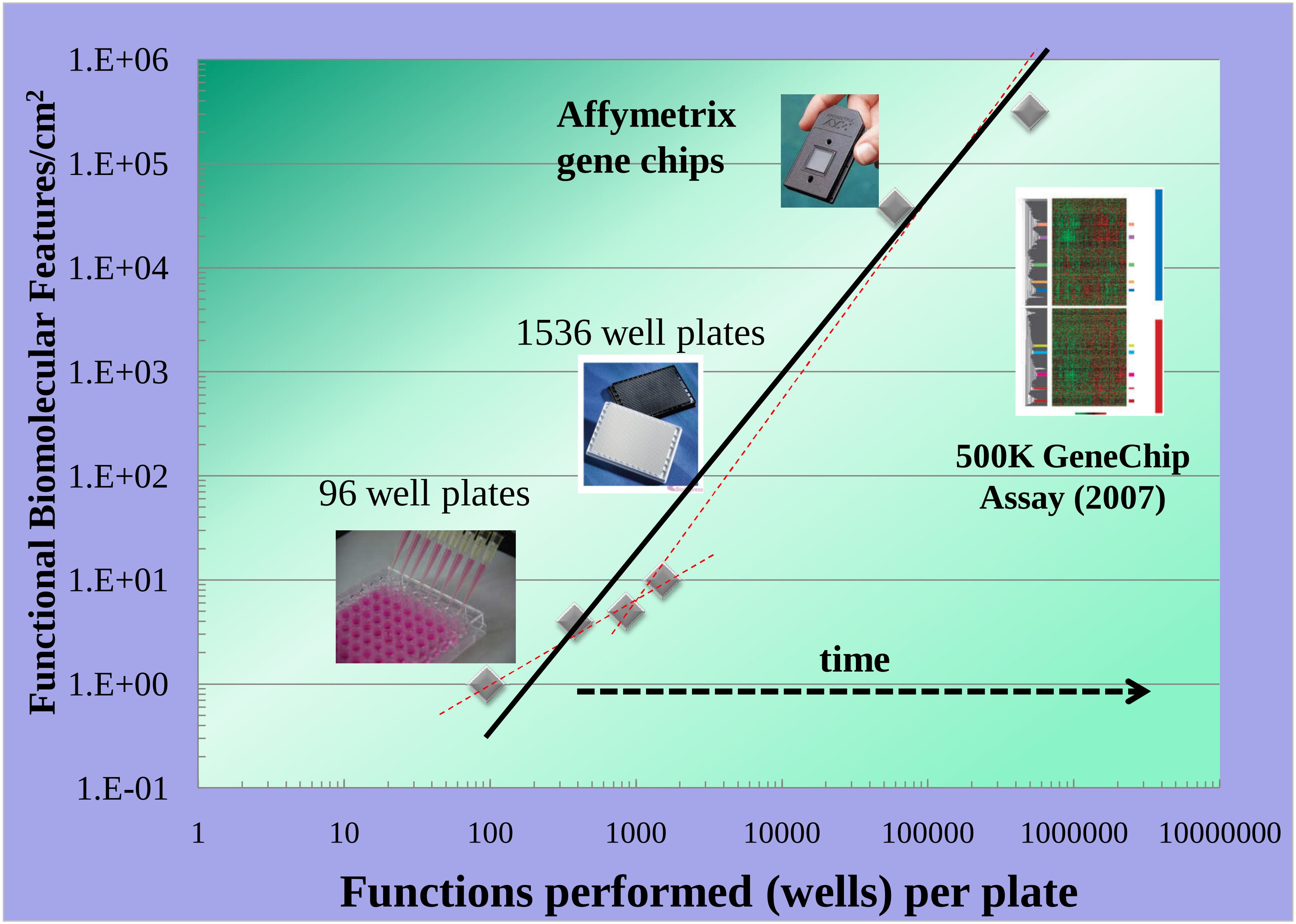
Similar Trends in Biomolecular Engineering?

- Biological experimentation
  - Becoming more efficient and quantitative
  - Discovery Science – Post processing of data
- The # of possible simultaneous assays has increased over time
- Follows similar trend to Moore's law
- Prof. Guiseppi's prediction…

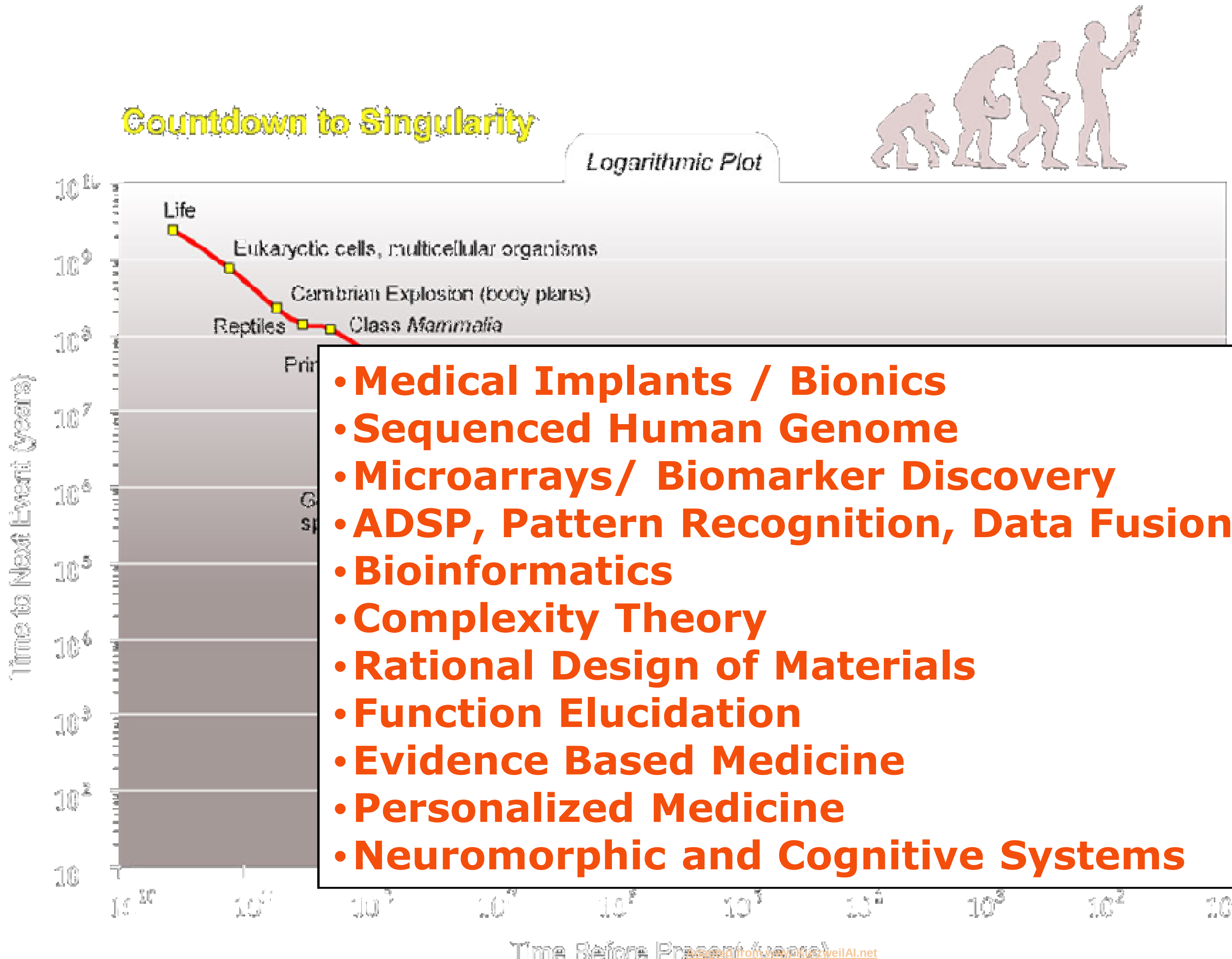
Guiseppi's Prediction: Future of Bioevent Density



Guiseppi's "Prediction": Future of Bioevent Throughput



Has Bio Field Reached that Critical Mass?

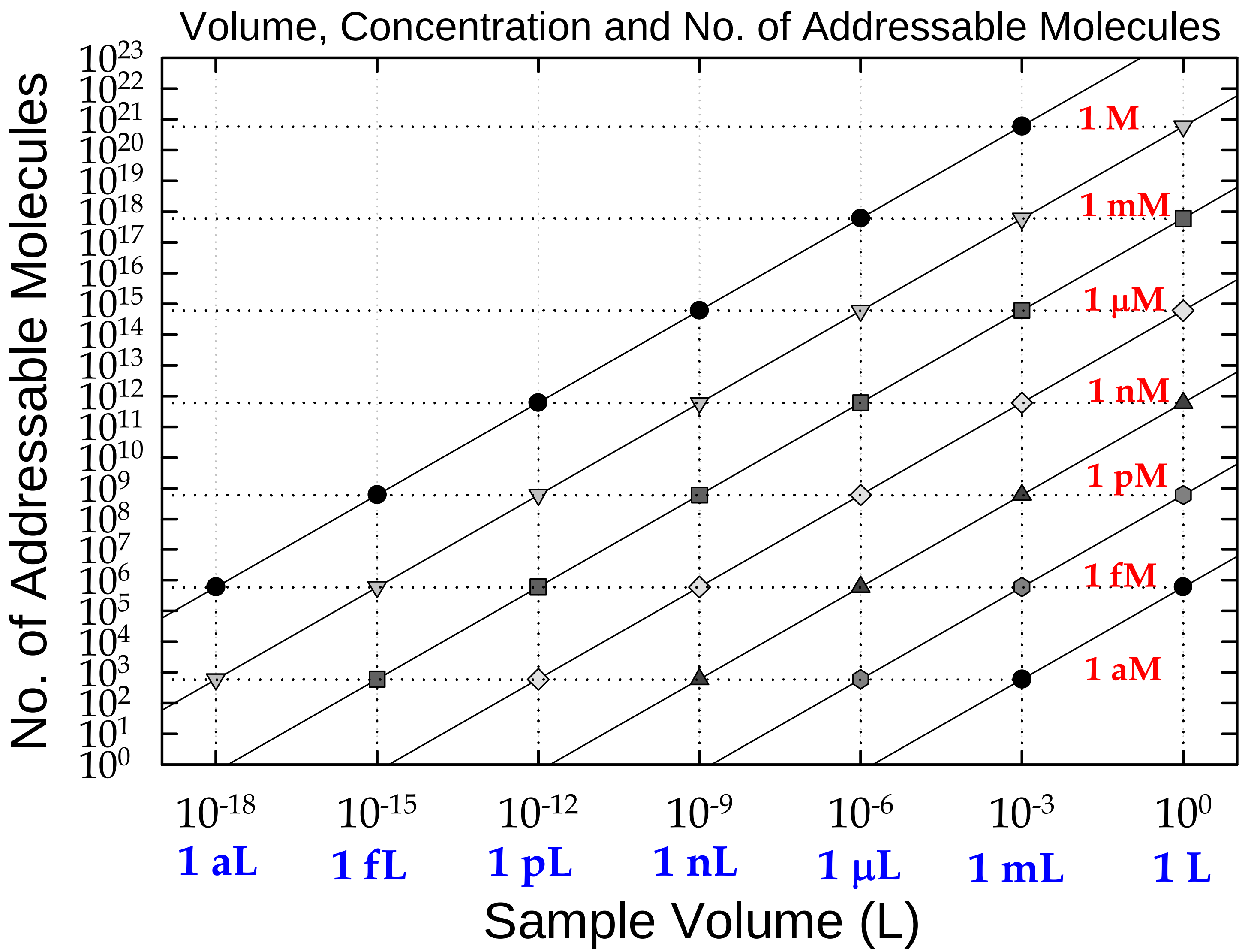


- Medical Implants / Bionics
- Sequenced Human Genome
- Microarrays/ Biomarker Discovery
- ADSP, Pattern Recognition, Data Fusion
- Bioinformatics
- Complexity Theory
- Rational Design of Materials
- Function Elucidation
- Evidence Based Medicine
- Personalized Medicine
- Neuromorphic and Cognitive Systems

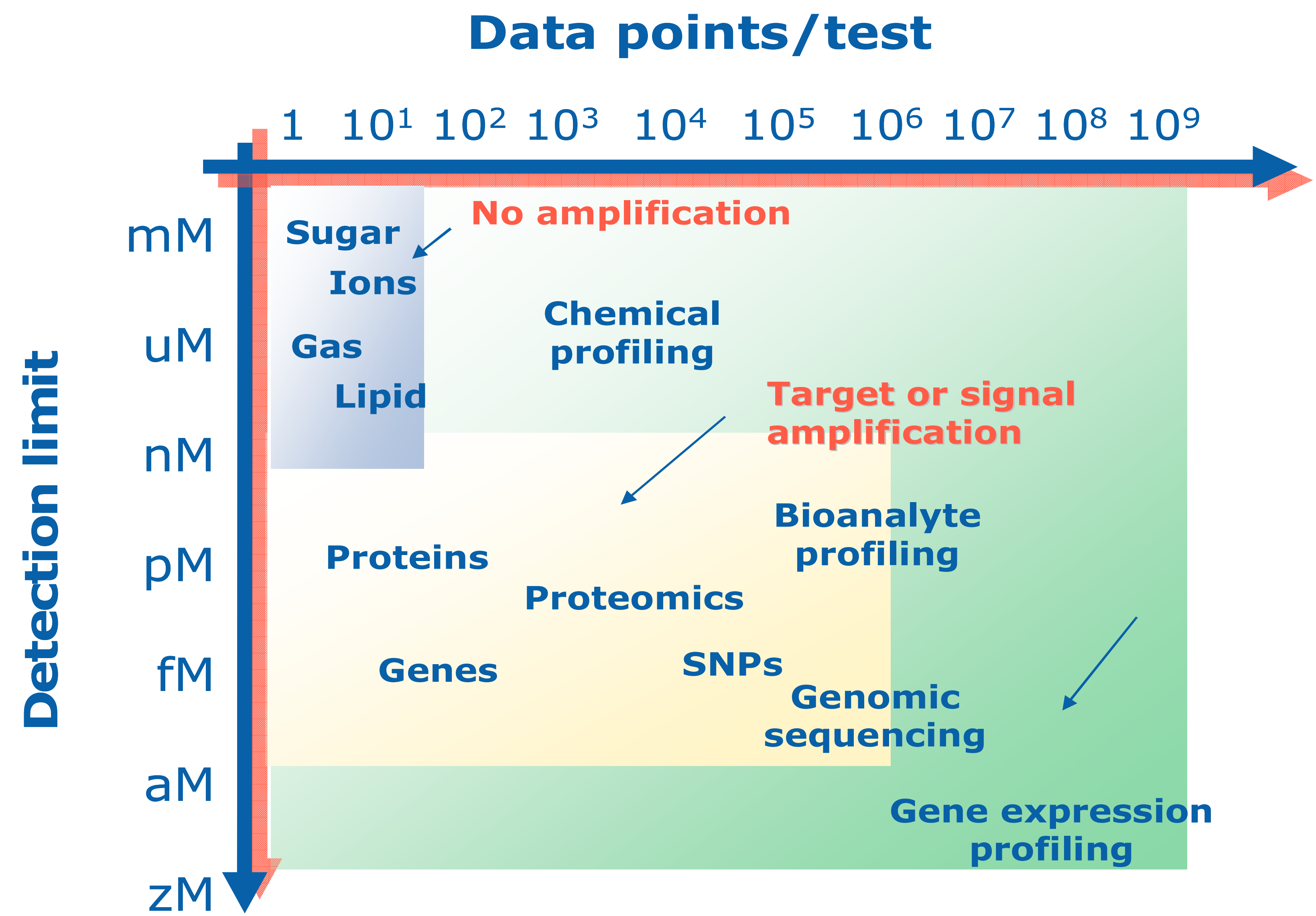
Addressing Single Molecules?

6.023 x 10^{23} molecules = I mole

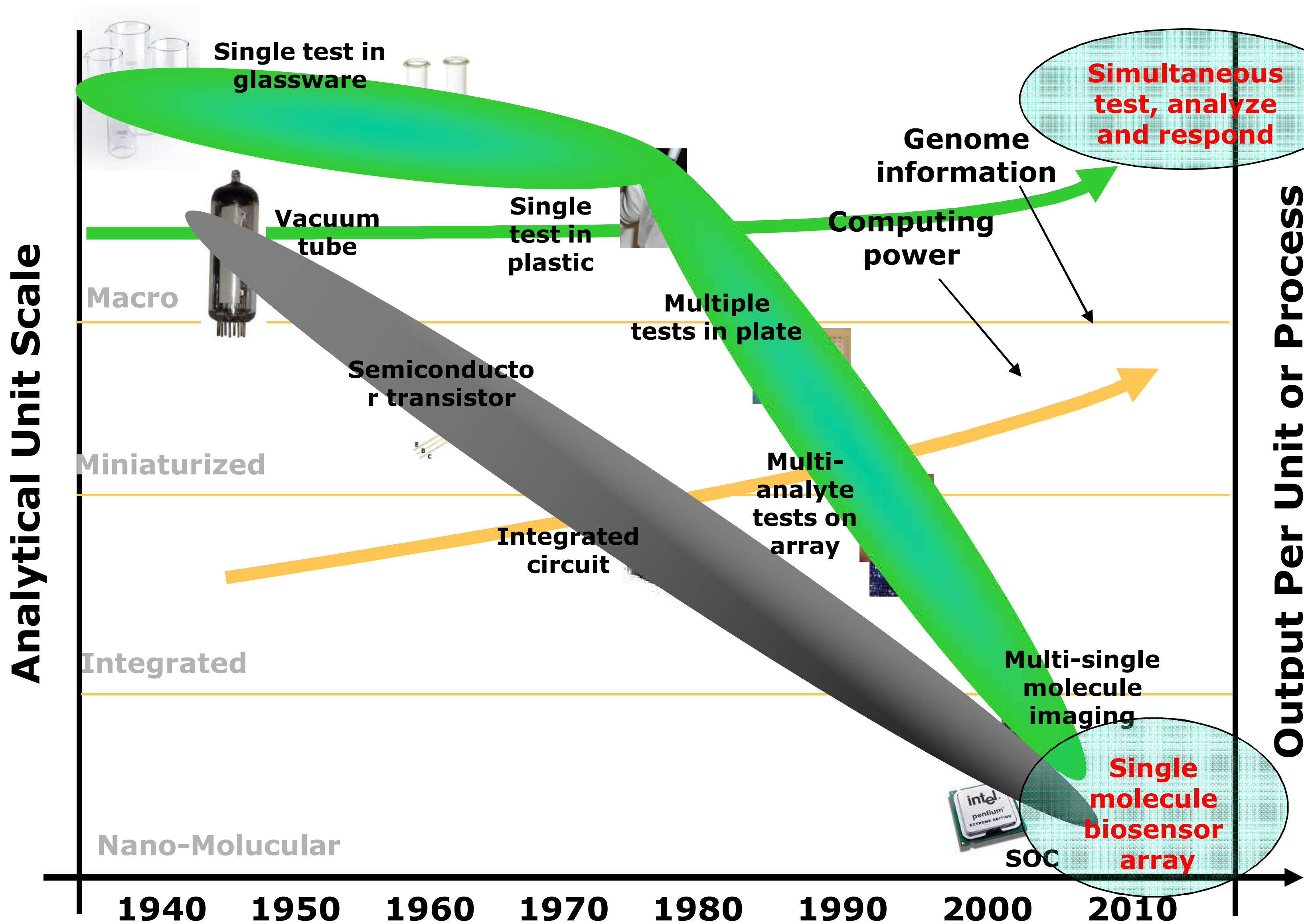
Sample Size



Molecules to be Addressed In Bioanalytical Biosensor Applications

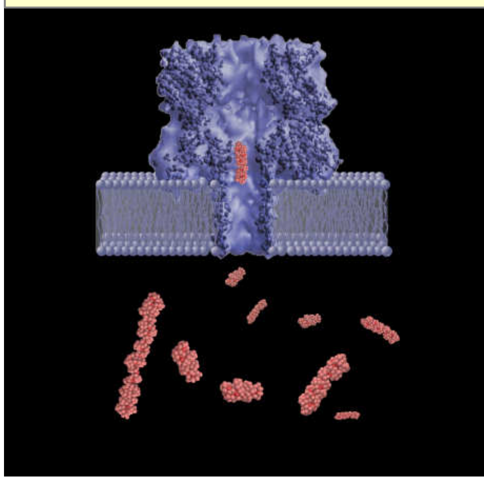


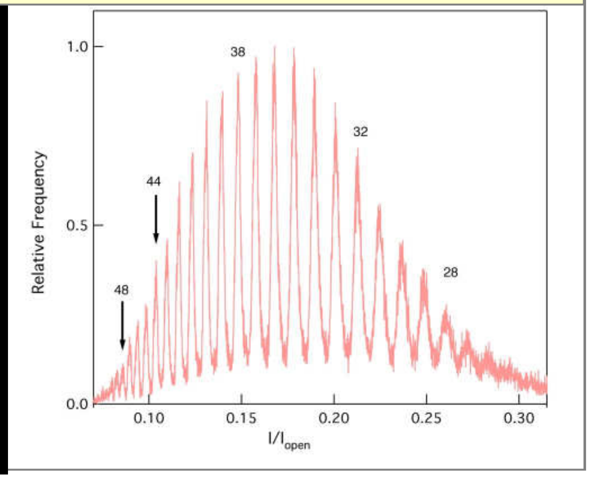
Opportunity for Convergence



Supported nanopore membranes

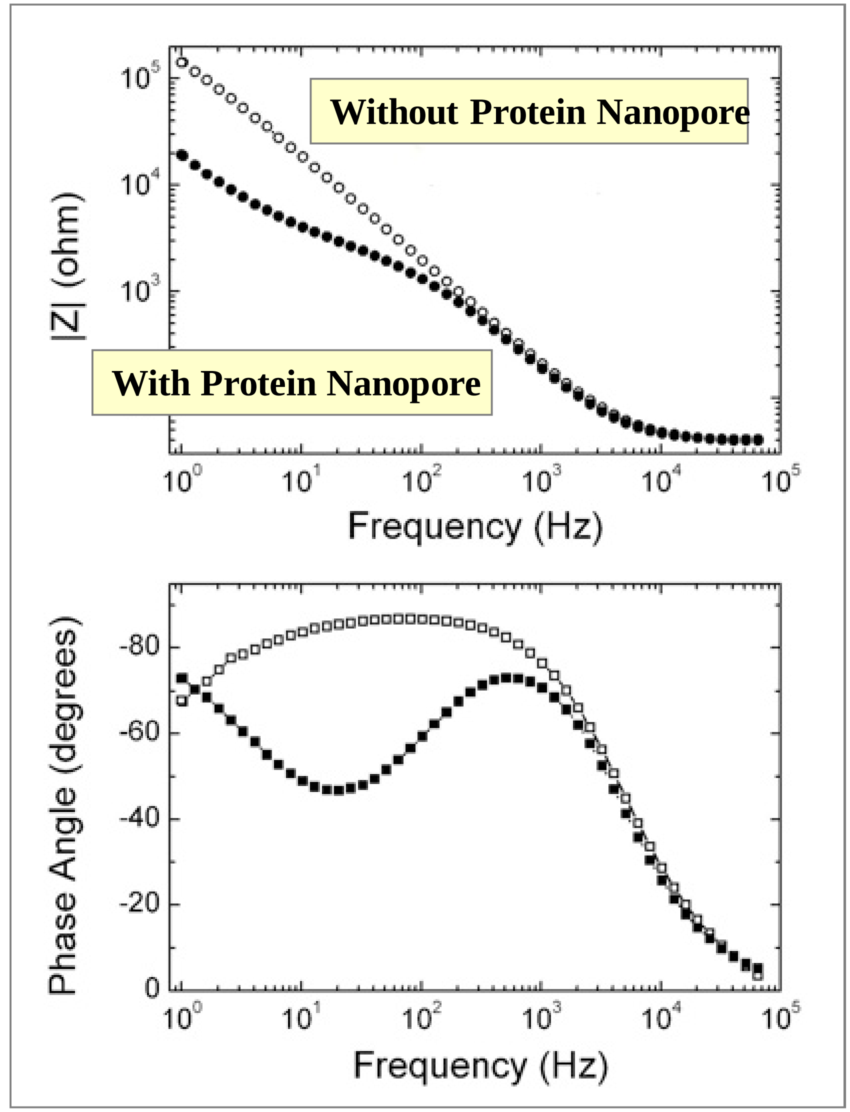
Sorting and counting molecules using electrical impedance through molecular nanopores



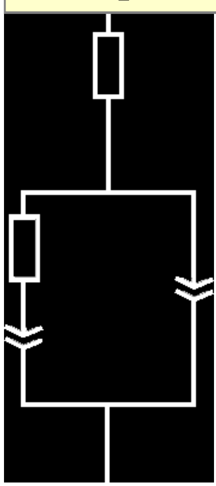


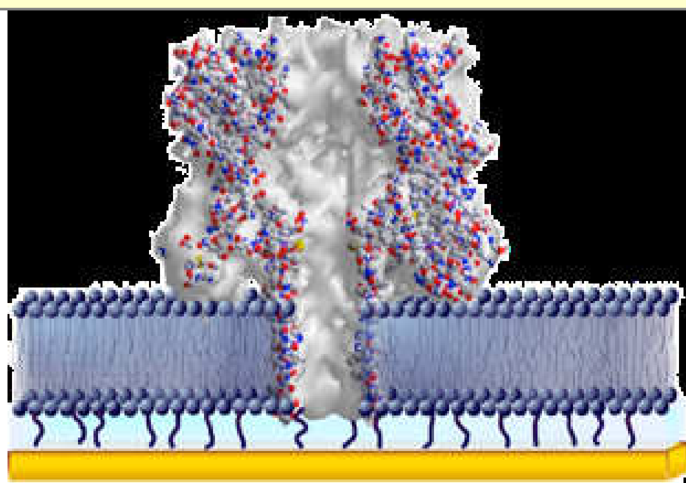
Reiner1 & Kasianowicz et al. *PNAS* (**2010**)*107(27)* 12080–*12085*

Electrochemical Impedance Spectroscopy



Equivalent circuit model of an electrode-supported, nanopore-containing membrane



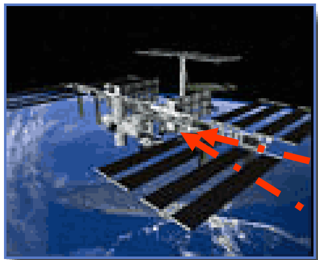


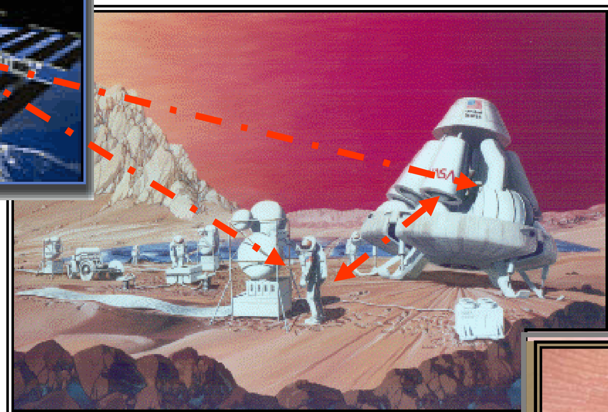
What I Wish to Tell You!

- **Bio-compatibility:** understanding molecular, nano- meso- and micro- surface interactions at the intersection of biology and silicon
- **Designing for manufacturability:** Compatibility with standard CMOS fabrication methods
- **Bioelectronics:** Enabling direct electronic communication between electronic solid state devices and "the biology"
- **Manufacturing paradigms:** Modularity, parallelism, redundancy, complexity, cost/volumes for intended applications - modularity

OPPORTUNITIES FOR *IN-VIVO* BIOSENSORS

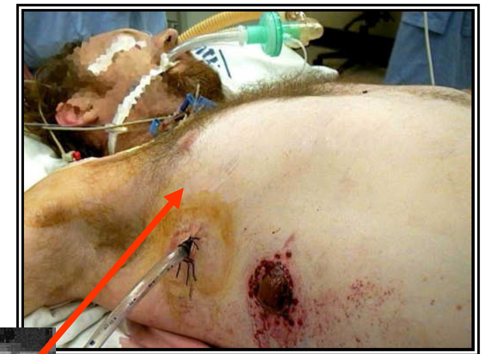
Lactate and Glucose Monitoring

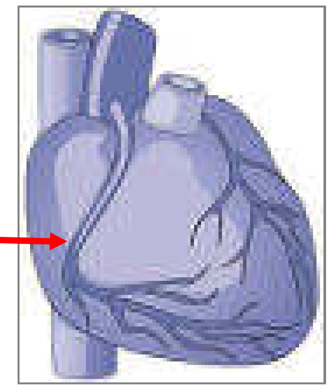




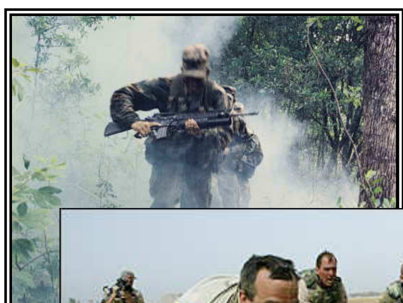
Manned
Space
Flights
Diagnostics

Trauma
Management

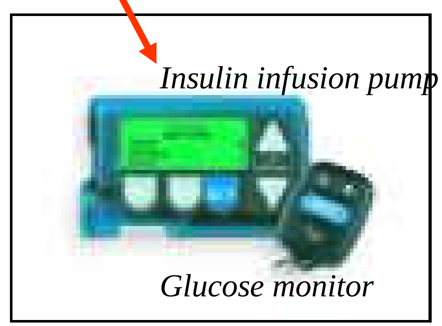




Congestive Heart Failure and
Transplanted Organ Health



Battlefield
Trauma outcomes



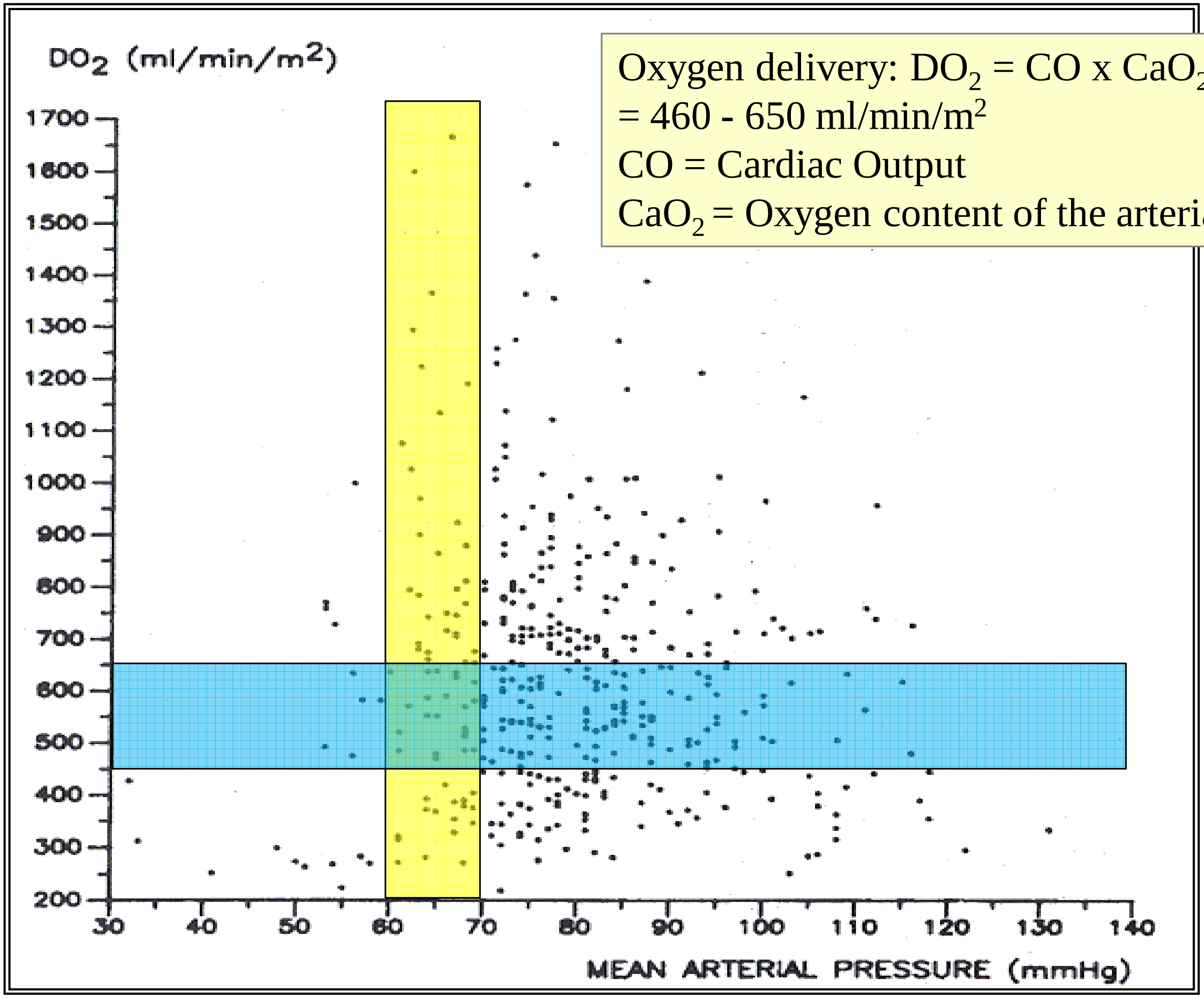
Chronic Diabetes Care

The Case for Monitoring

- ✦ Trauma - the No.1 killer of persons < 50 yrs old.
- ✦ Death from hemorrhage is implicated in 50-68% of battlefield trauma cases (Col. Erin Edgar)
- ✦ During hemorrhage induced trauma and following surgery, hemodynamics and physiology are delicate and can change rapidly
- ✦ Need to initiate *immediate* and *continuous* monitoring of **molecular indicators** of global physiologic stress.

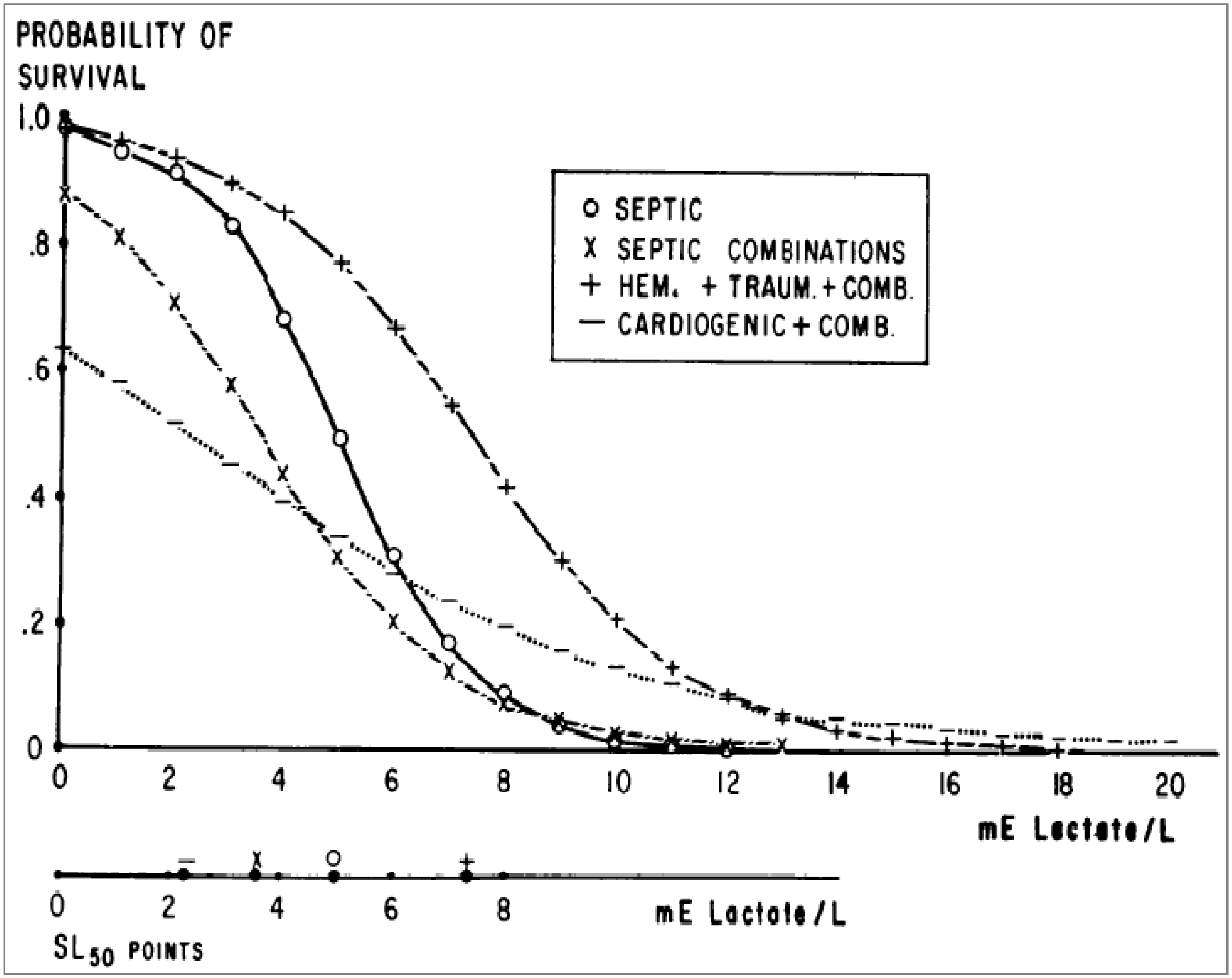
Being Fooled by Vital Signs (e.g. Blood Pressure)

Oxygen Delivery: $DO_2 = CO \times C_aO_2$
460 - 650 ml/min/m^2



Oxygen delivery: $DO_2 = CO \times CaO_2$
= 460 - 650 ml/min/m^2
CO = Cardiac Output
CaO_2 = Oxygen content of the arterial blood

Lactic Acidosis: A Prognosticator in Trauma



Huckabee, W. E. (1963) "LACTIC ACIDOSIS." The American Journal Of Cardiology 12: 663-666

Vitek, V. and R. A. Cowley (1971) "Blood lactate in the prognosis of various forms of shock." Annals Of Surgery 173(2): 308-313

Broder, G. and M. H. Weil (1964) "EXCESS LACTATE: AN INDEX OF REVERSIBILITY OF SHOCK IN HUMAN PATIENTS" Science 143: 1457-1459

What motivates our focus on lactate?

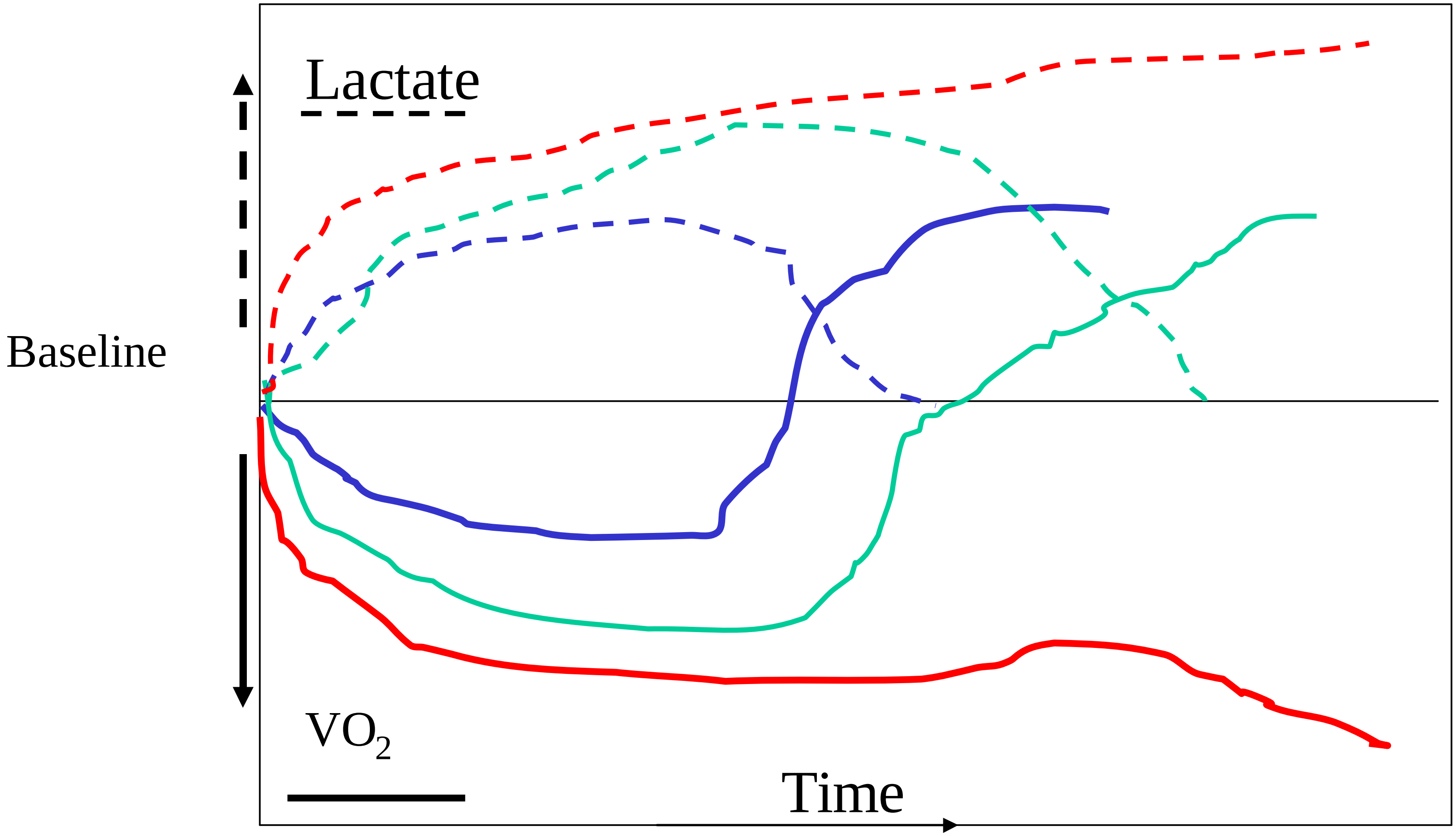
- **Mortality/Morbidity**
  - Patients who have an arterial lactate level of more than 5 mmol/L and a pH of less than 7.35 are critically ill and have a very poor prognosis. The multicenter trials have shown a mortality rate of 75% in these patients.
- **However, if lactate levels normalize in:**
  - 24 hrs = 90-100% survival
  - 24-48 hrs normalization = 75% survival
  - >48 hrs = 13%

Kyle J. Gunnerson, MD and Sat Sharma, MD, FRCPC, e-Medicine WebMD, April 14, 2010
http://emedicine.medscape.com/article/167027-overview

Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Crit Care*. Feb 10 2006;10(1):R22

HYPOTHESIS: Clinical Outcomes Related to Peripheral Perfusion Following Trauma:

The case for continuous lactate monitoring



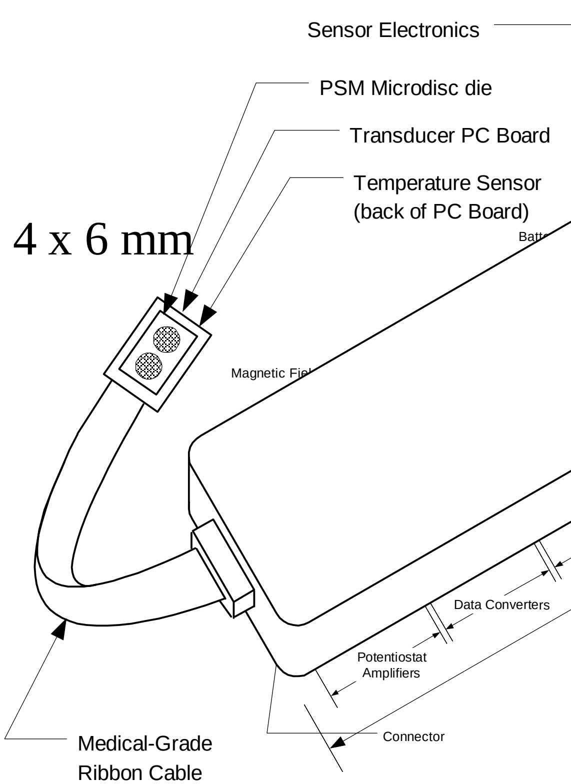
Survivors without Complications | Survivors with Multisystem Organ Failure | Nonsurvivors

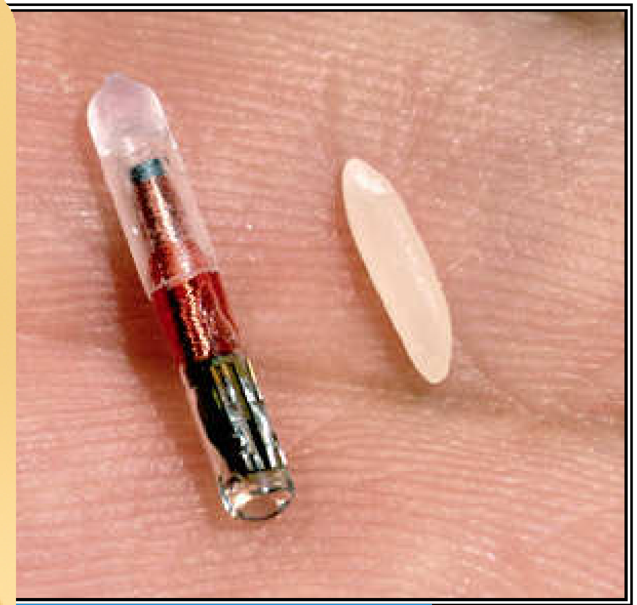
PSMBioChip System

(Physiologic Status Monitoring)

Discrete Prototype Device

ASIC Device





Digital Angel Corporation

VeriChip

An Implantable Biochip for Physiologic Status Monitoring

Glucose, Lactate, pH and Temperature

Implantable Biochips

IEEE SENSORS JOURNAL, VOL. 5, NO. 3, JUNE 2005 345

Design of a Subcutaneous Implantable Biochip for Monitoring of Glucose and Lactate

Anthony Guiseppi-Elie, Sean Brahim, Gymama Slaughter, and Kevin R. Ward

1856 IEEE SENSORS JOURNAL, VOL. 9, NO. 12, DECEMBER 2009

Fabrication and Packaging of a Dual Sensing Electrochemical Biotransducer for Glucose and Lactate Useful in Intramuscular Physiologic Status Monitoring

Abdur Rub Abdur Rahman, Gusphyl Justin, Adilah Guiseppi-Wilson, and Anthony Guiseppi-Elie, *Member, IEEE*

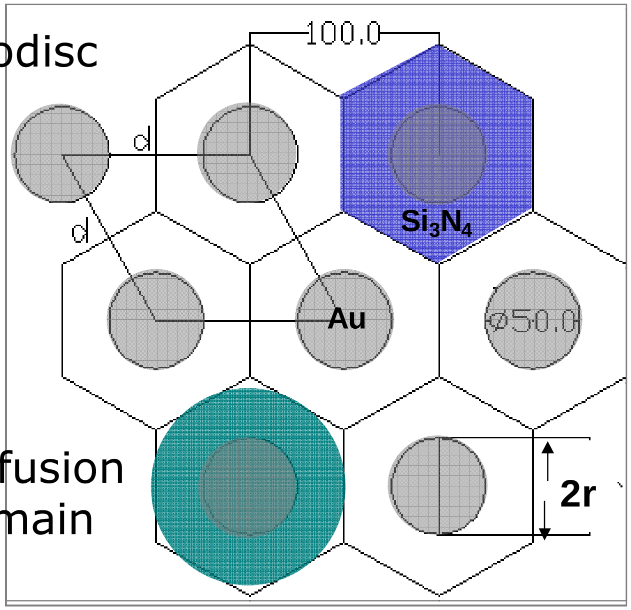
Anal Bioanal Chem
DOI 10.1007/s00216-010-4271-x

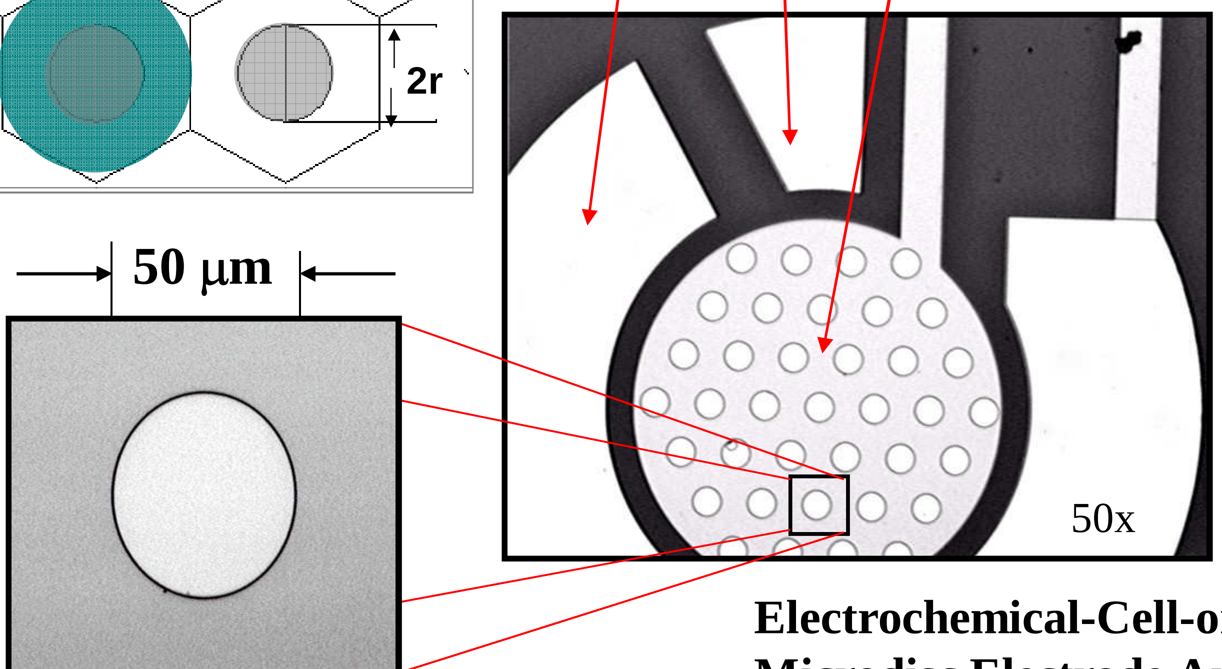
ORIGINAL PAPER

An implantable biochip to influence patient outcomes following trauma-induced hemorrhage

Anthony Guiseppi-Elie

Front-end biotransducer for discrete component prototyping of the PSMBioChip

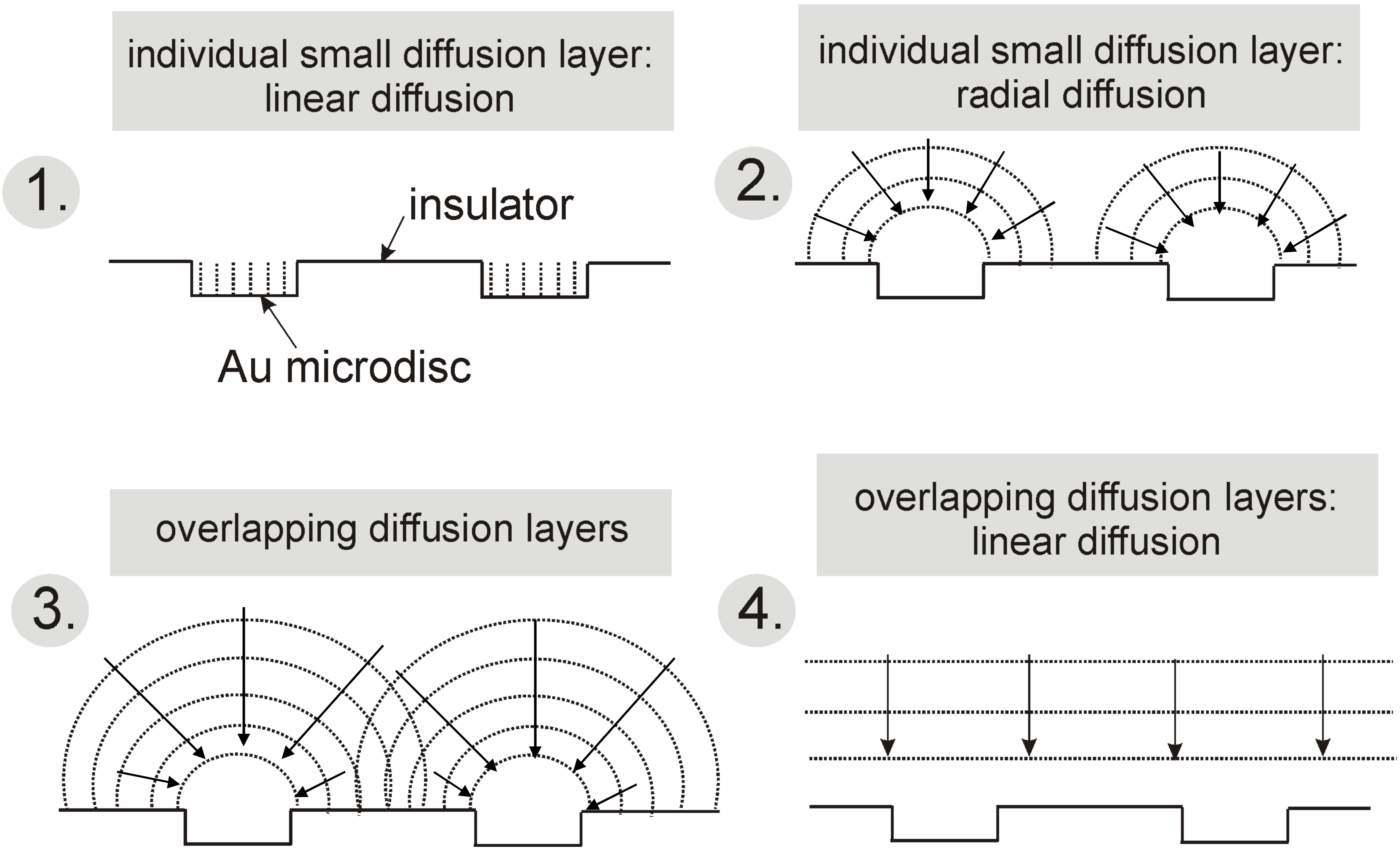




Electrochemical-Cell-on-a-Chip
Microdisc Electrode Array (ECC MDEA 5037)

A. Guiseppi-Elie, S. Brahim, G. Slaughter and K. R. Ward, "Design of a Subcutaneous Implantable Biochip for Monitoring of Glucose and Lactate", (**2005**) *IEEE Sensor Journal*, 5(3), pp. 345-355.

Design of the microdisc electrode array (MDEA)

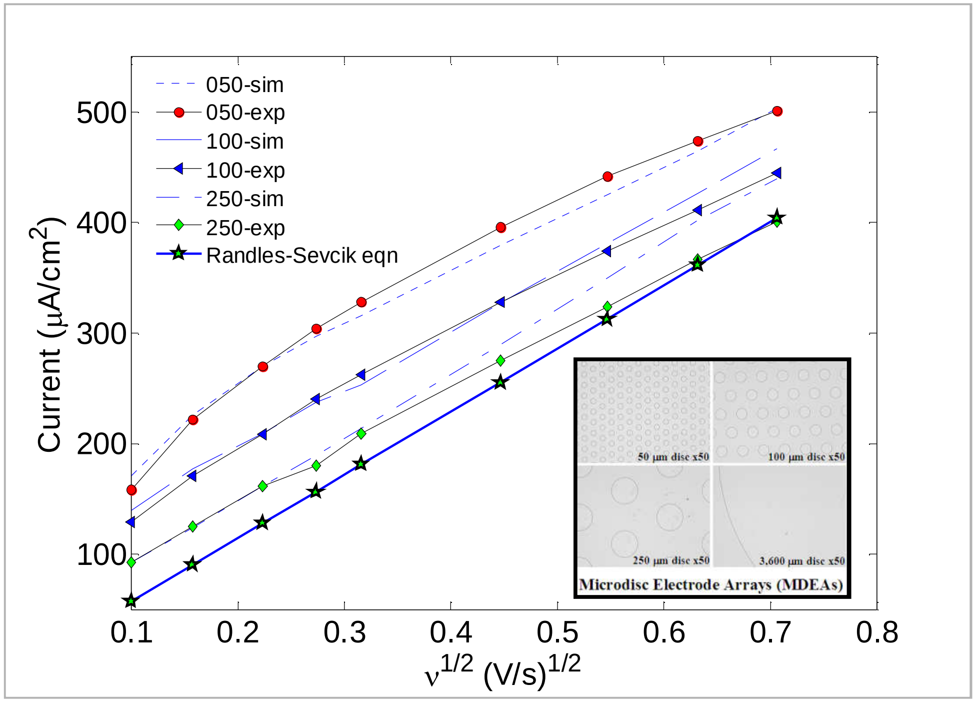


Abdur Rub Abdur Rahman and Anthony Guiseppi-Elie "Design Considerations in the Development and Application of Microdisc Electrode Arrays (MDEAs) for Implantable Biosensors" *Biomedical Microdevices* (**2009**) 11:701-710.

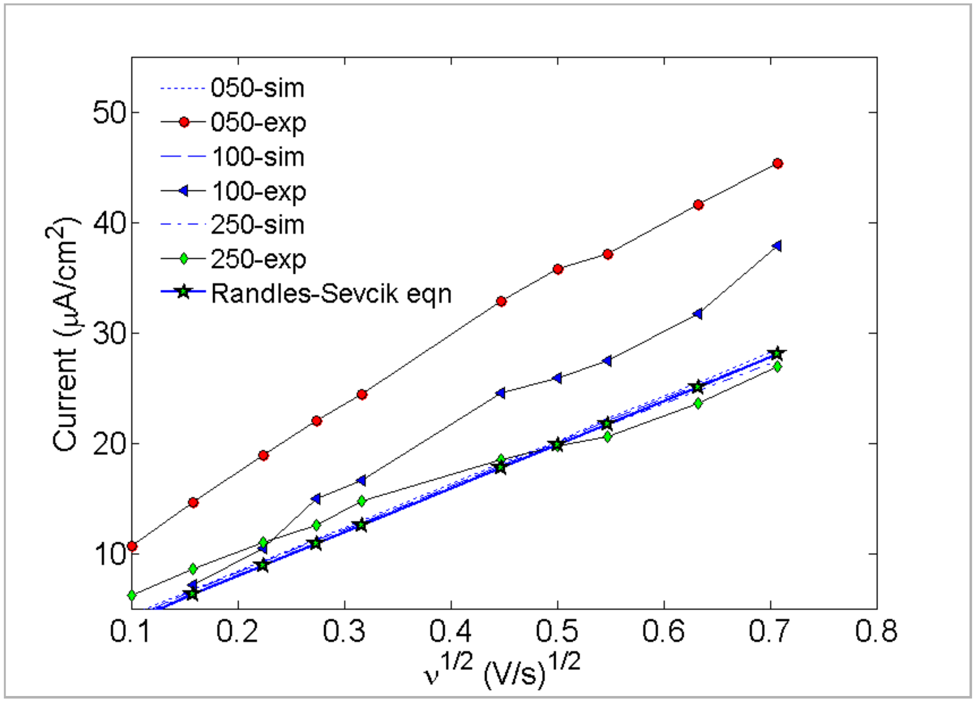
Performance enhancement of the microdisc electrode array format of the PSMBioChip

$$I_p = 2.687 \times 10^5 n^{3/2} v^{1/2} D^{1/2} A C_{ox}$$

Un-Coated



Hydrogel Coated

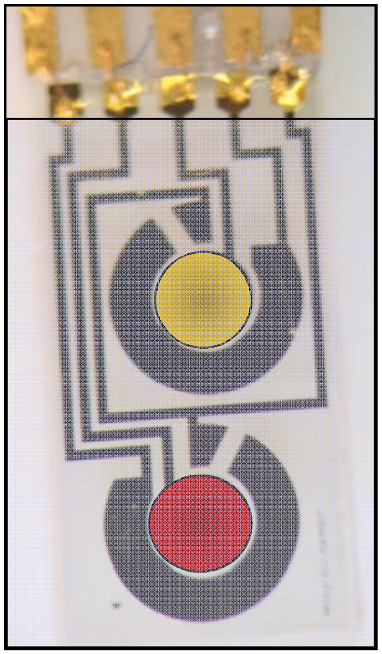


Enhanced effective area with reduction of disc diameter

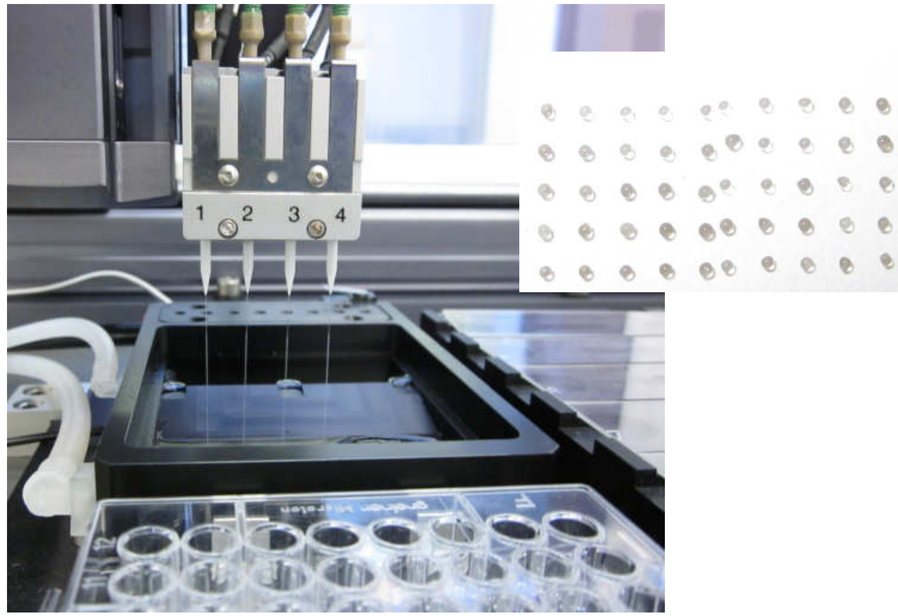
Enhancement maintained for 50 μm device beneath hydrogel

G. Justin, A. R. Abdur Rahman, and A. Guiseppi-Elie, "Bioactive Hydrogel Layers on Microdisc Electrode Arrays: Cyclic Voltammetry Experiments and Simulations," *Electroanalysis* (**2009**) (accepted)

Conferring biological specificity to a multi-analyte bioanalytical biochip – How?



MDEA
5037



- **Micro-solenoid, non-contact printing**
- **Micro-contact printing**
- **Ink-jet printing**
- **Spin-coating and electropolymerization**

Electroconductive Hydrogels

556

Full Paper

Electroconductive Hydrogels:
Properties of Polypyrrole-Poly

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Molecularly engineered p(HEMA)-based hydrogels for implant biochip biocompatibility

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[a]*Center for Bioelectronics, Biosensors and Biochips (C3B), Virginia Commonwealth University, P.O. Box 843038, 601 West Main Street, Richmond, Virginia 23284-3038, USA*
[b]*Department of Emergency Medicine, Virginia Commonwealth University, Richmond, Virginia 23284-3038, USA*

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Review

Electroconductive hydrogels: Synthesis, characterization and biomedical applications

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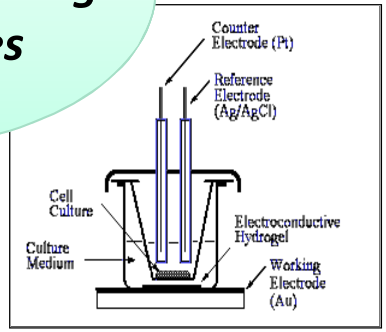
[a] *ABTECH Scientific, Inc., Biotechnology Research Park, 800 East Leigh Street, Richmond, VA 23219, USA*
[b] *Center for Bioelectronics, Biosensors and Biochips (C3B), Clemson University Advanced Materials Center, 100 Technology Drive, Anderson, SC 29625, USA*
[c] *Department of Chemical and Biomolecular Engineering, Department of Bioengineering, Department of Electrical and Computer Engineering, Clemson University, Clemson, SC 29634, USA*

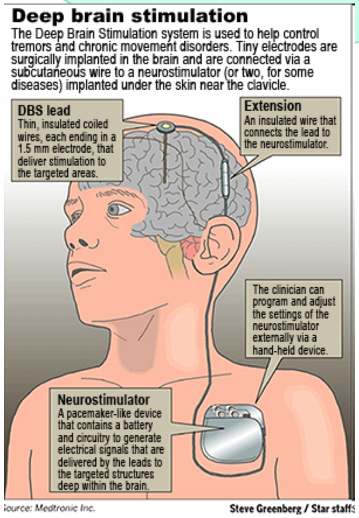
In vivo Physiological Status Monitoring biosensors

Electrostimulated drug delivery devices

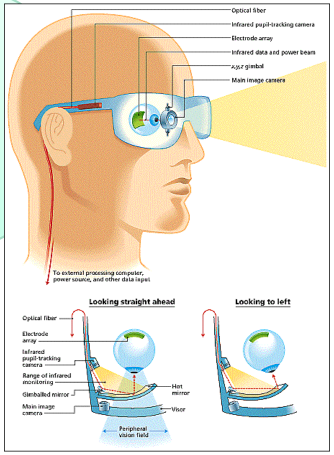


Clinical Applications for Electroconductive Hydrogels

Deep Brain Stimulation Devices

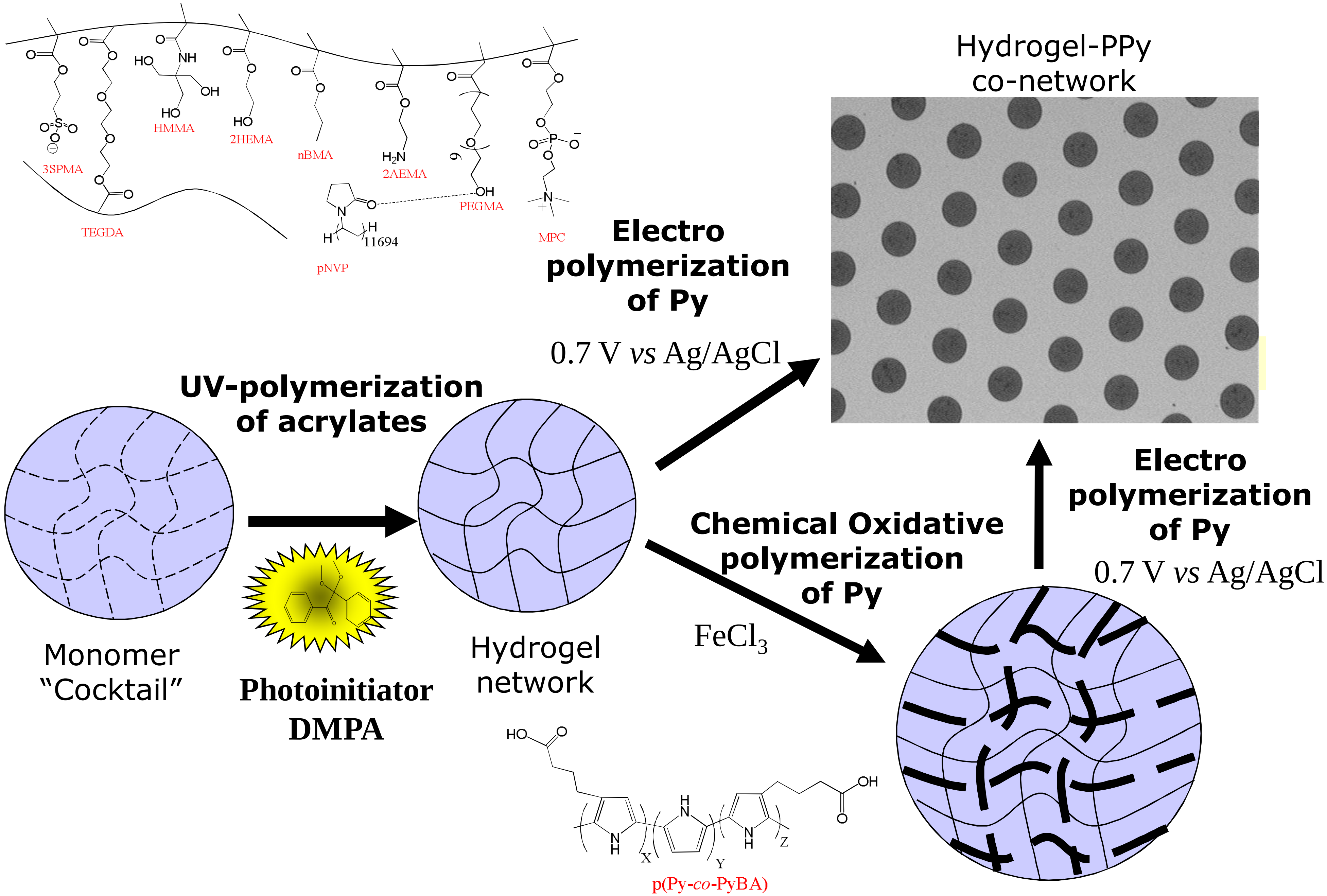


Neural prostheses

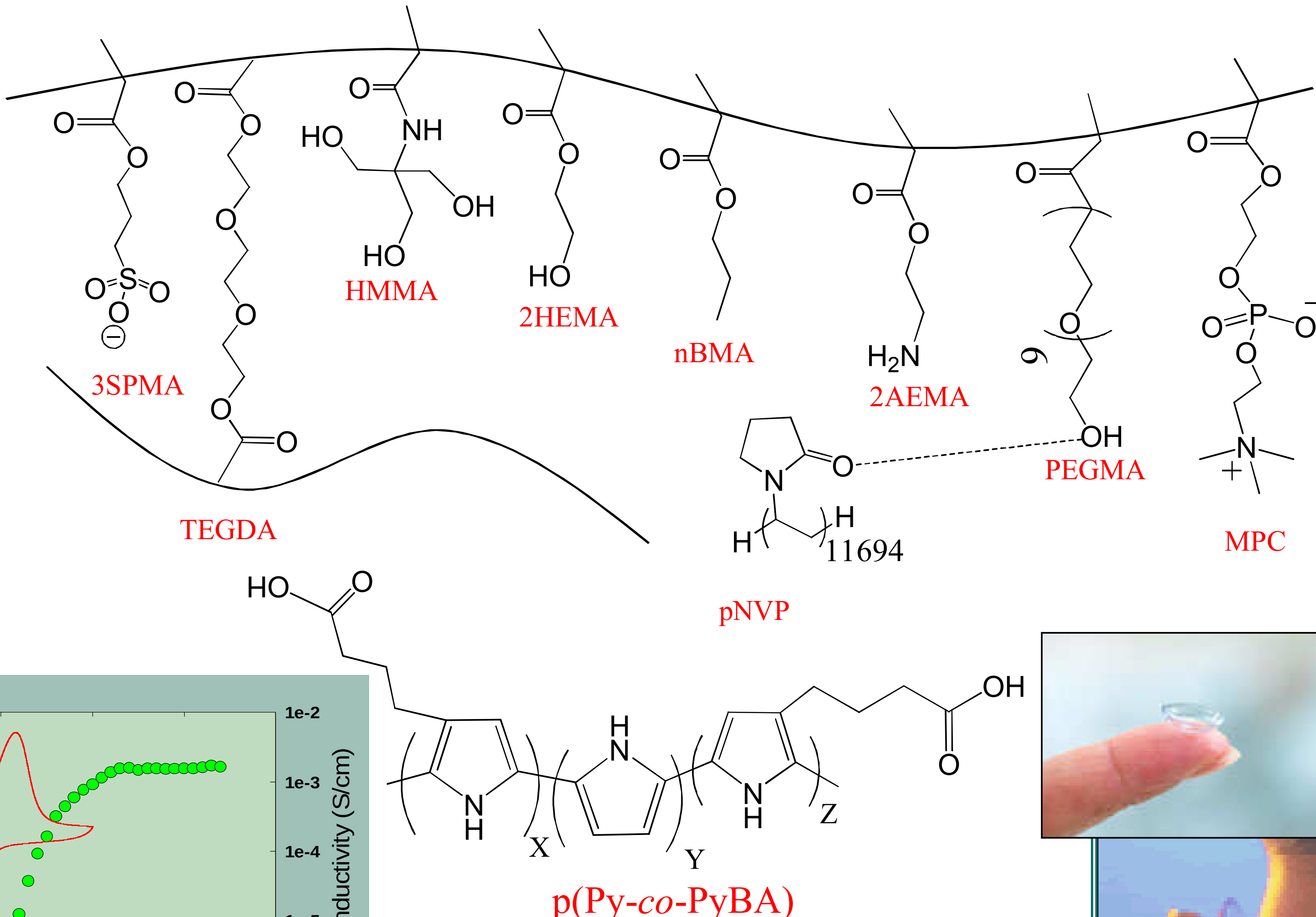


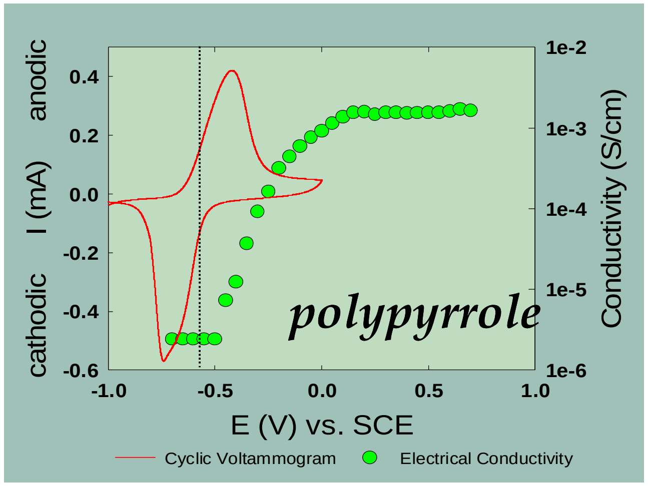
Implantable Biofuel Cells

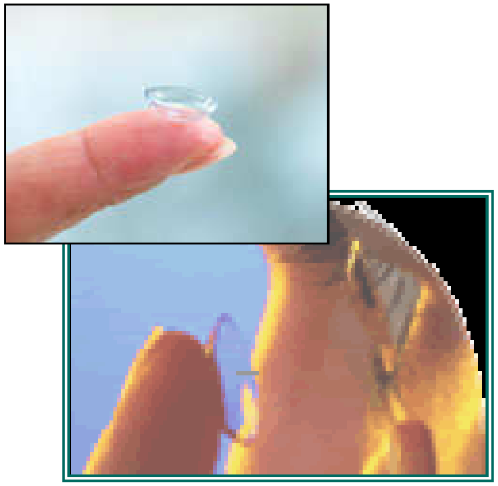
Generalized Synthesis of Electroconductive Hydrogels



p(HEMA)-based Electroconductive Hydrogel

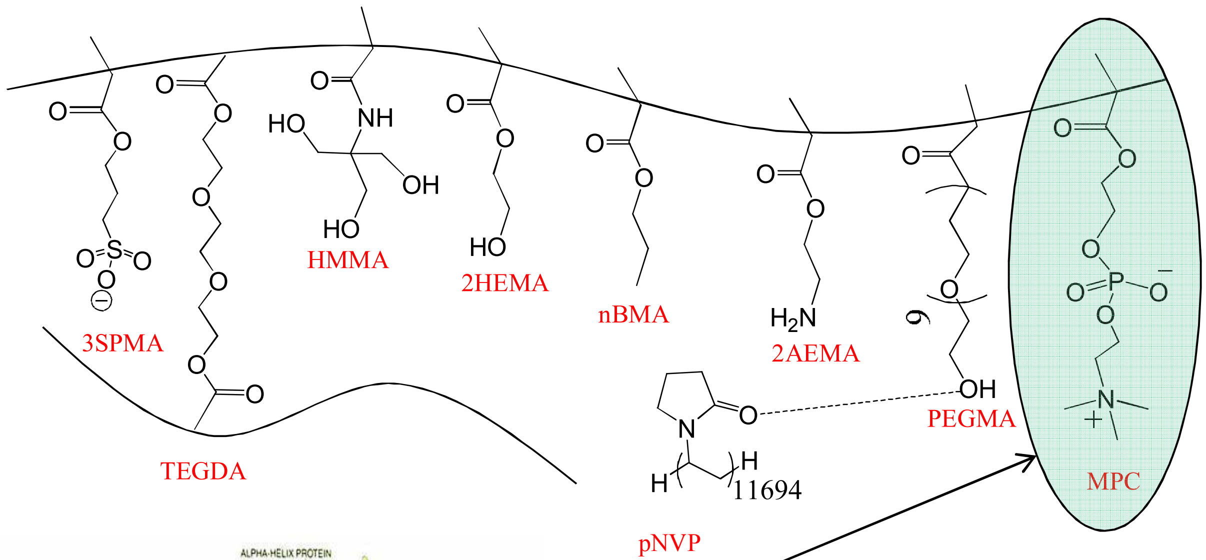




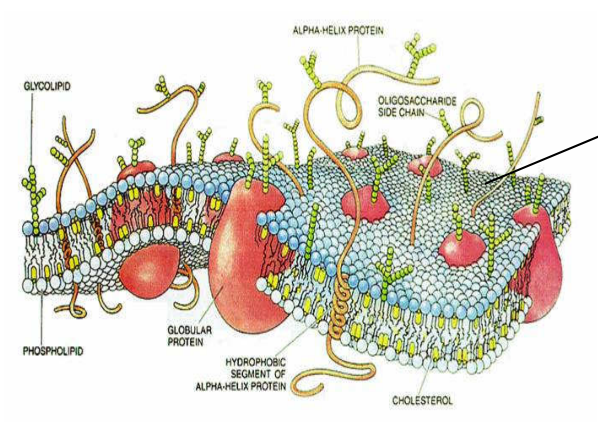


Molecularly Engineered p(HEMA)-based Hydrogel

In-vitro and *in-vivo* Biocompatibility



Bio-inspired synthetic polymer

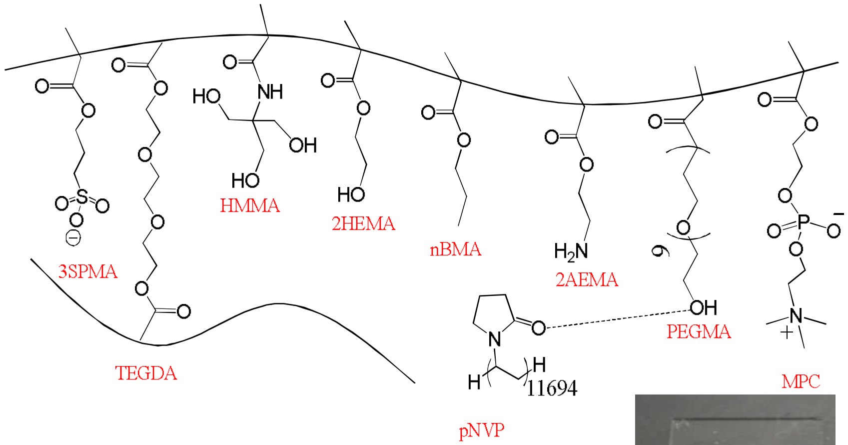


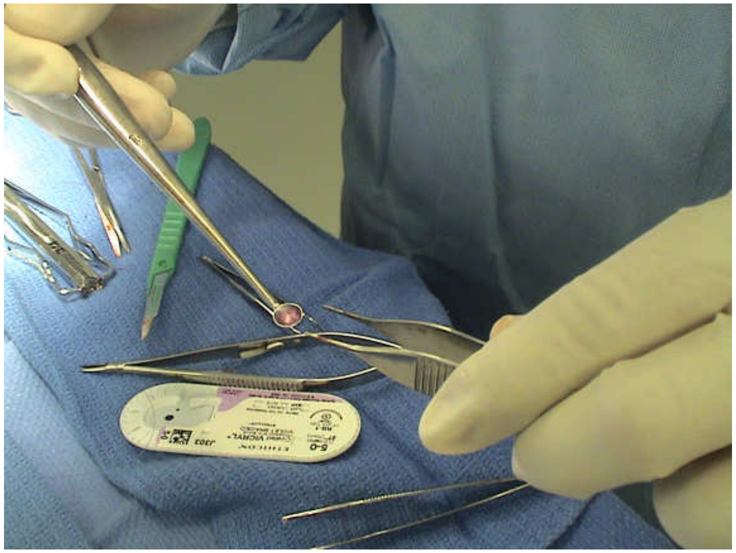
Cell membrane dynamics

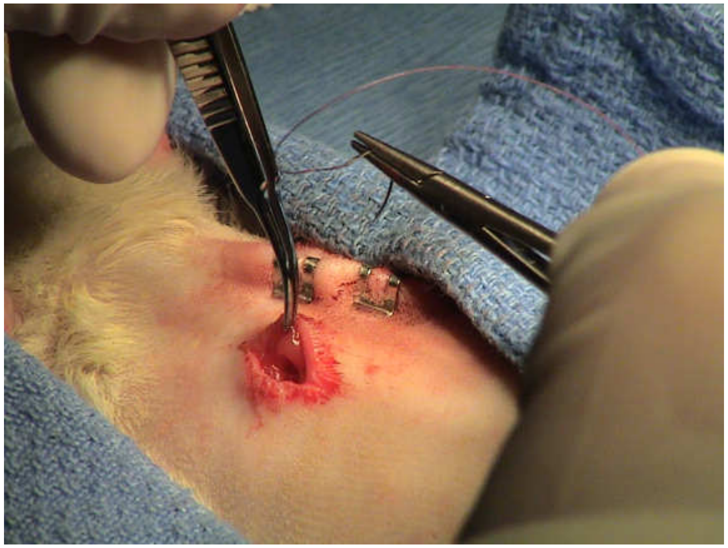
- Hydrophilic p(HEMA) resistant to protein adsorption and cell attachment
- Hydrogel high water content and suitable mechanical properties less irritation to tissue
- Biomimetic chemistry by MPC and PEGMA
  - PEG anti-fouling
  - Phosphoryl choline of cell membrane

Cross-linker TEGDA altered 1, 3, 5, 7, 9 and 12 mole%

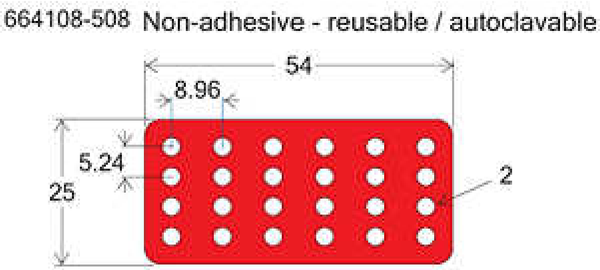
Molecularly Engineered p(HEMA)-based Hydrogel
In-vitro and *in-vivo* Biocompatibility

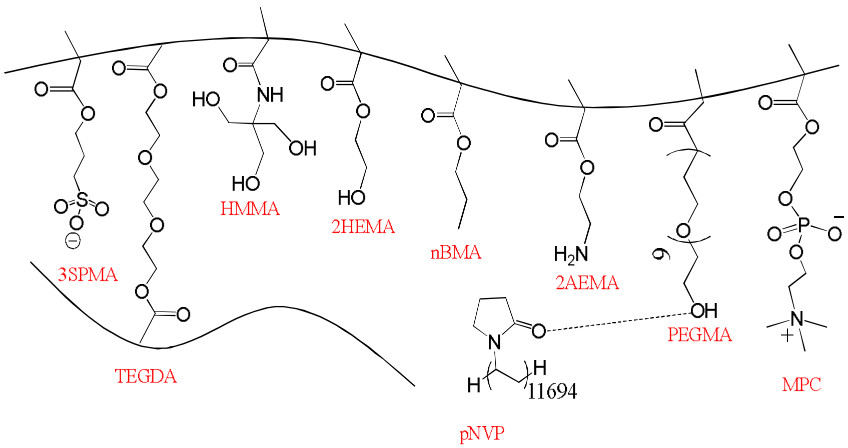


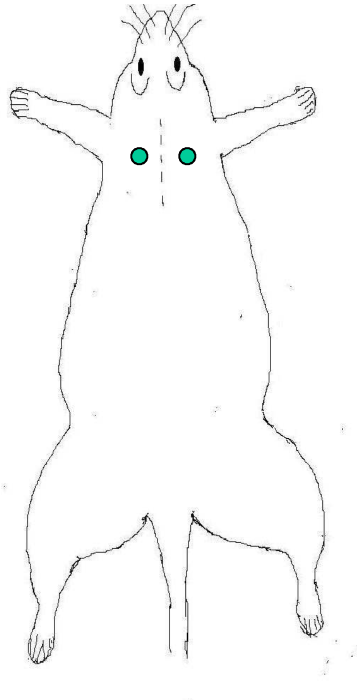


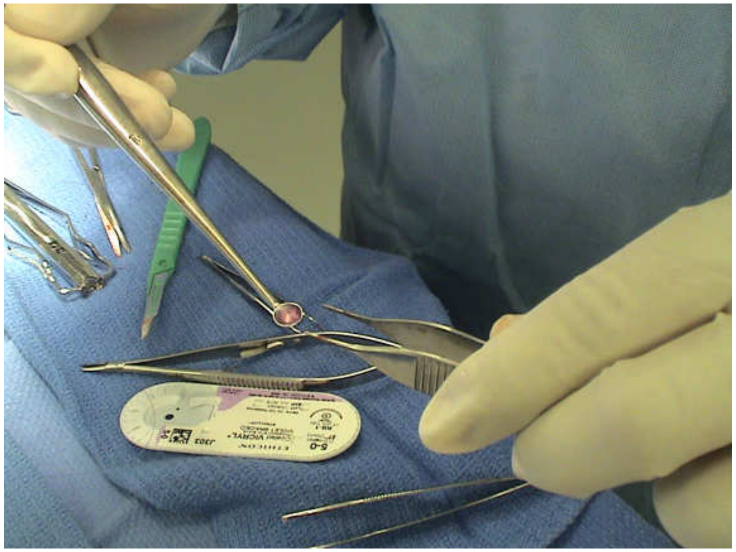


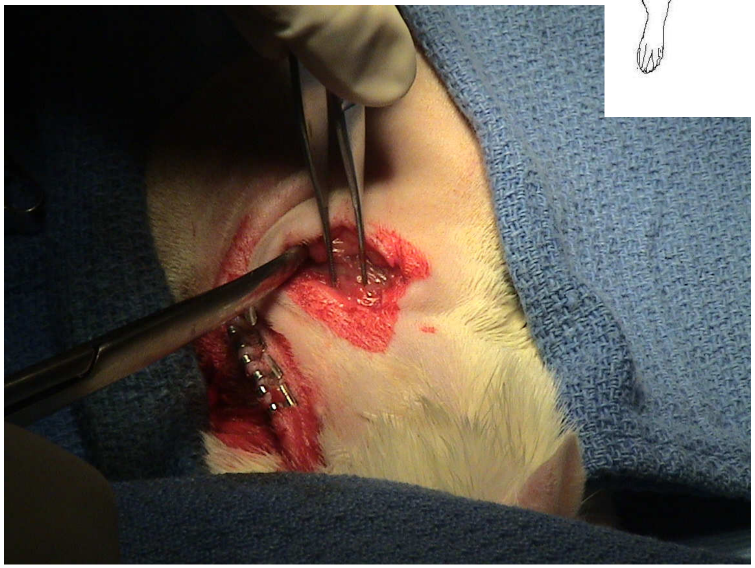
Molecularly Engineered p(HEMA)-based Hydrogel
In-vitro and *in-vivo* Biocompatibility





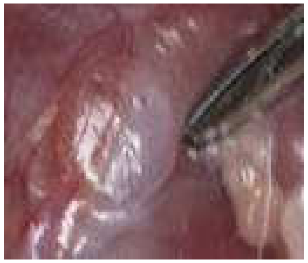


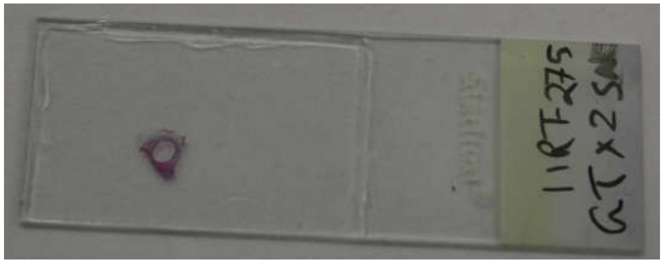




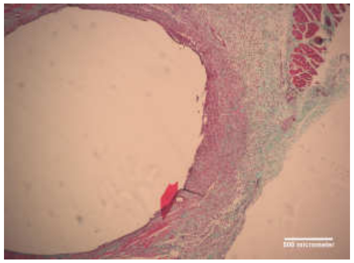
Molecularly Engineered p(HEMA)-based Hydrogel
In-vitro and *in-vivo* Biocompatibility

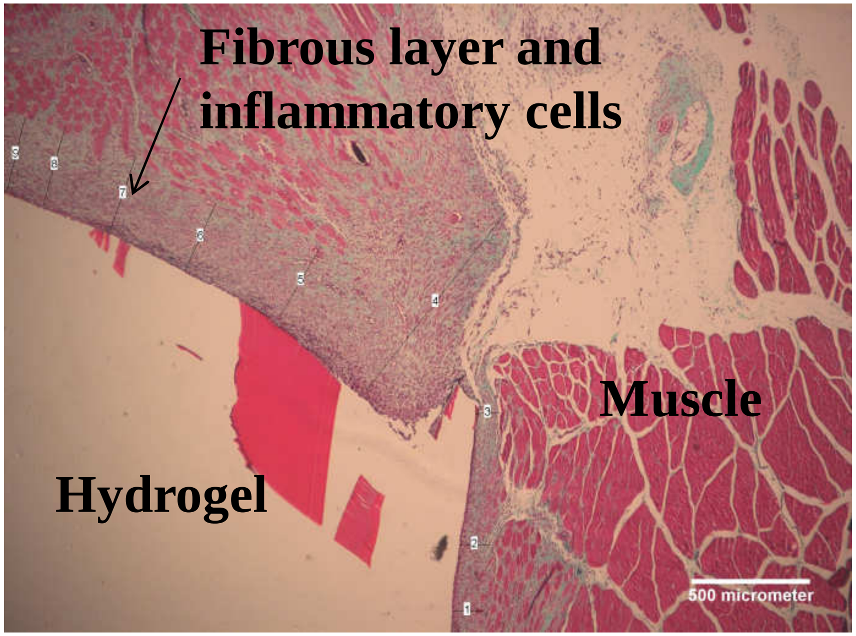
Implant **Resect** **Mount**





Image





ImageJ Software

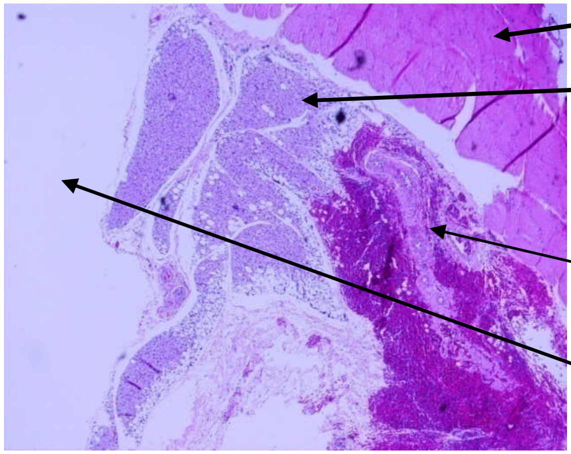
In-vivo Implantation in Sprague Dawley Hemorrhage Model

After implantation for 2 weeks in the trapezius muscle

A

un-modified p(HEMA)

Significant encapsulation and accumulation of foreign body material



Muscle

Area of Moderate Fibrosis and inflammation with foamy histocytes around the site where hydrogel was placed

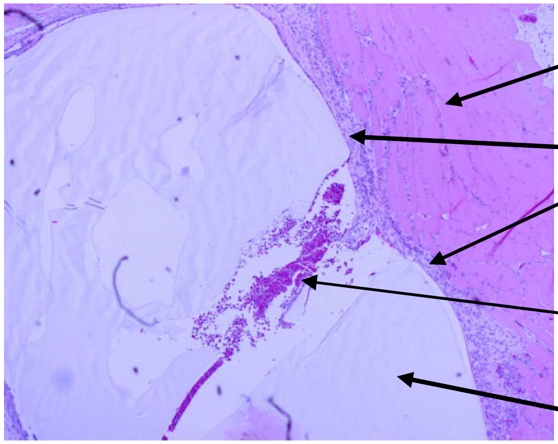
Residual area of Hemorrhage

Area where hydrogel existed

B

1 mol % MPC

Thin band of encapsulation and much reduced residual inflammation



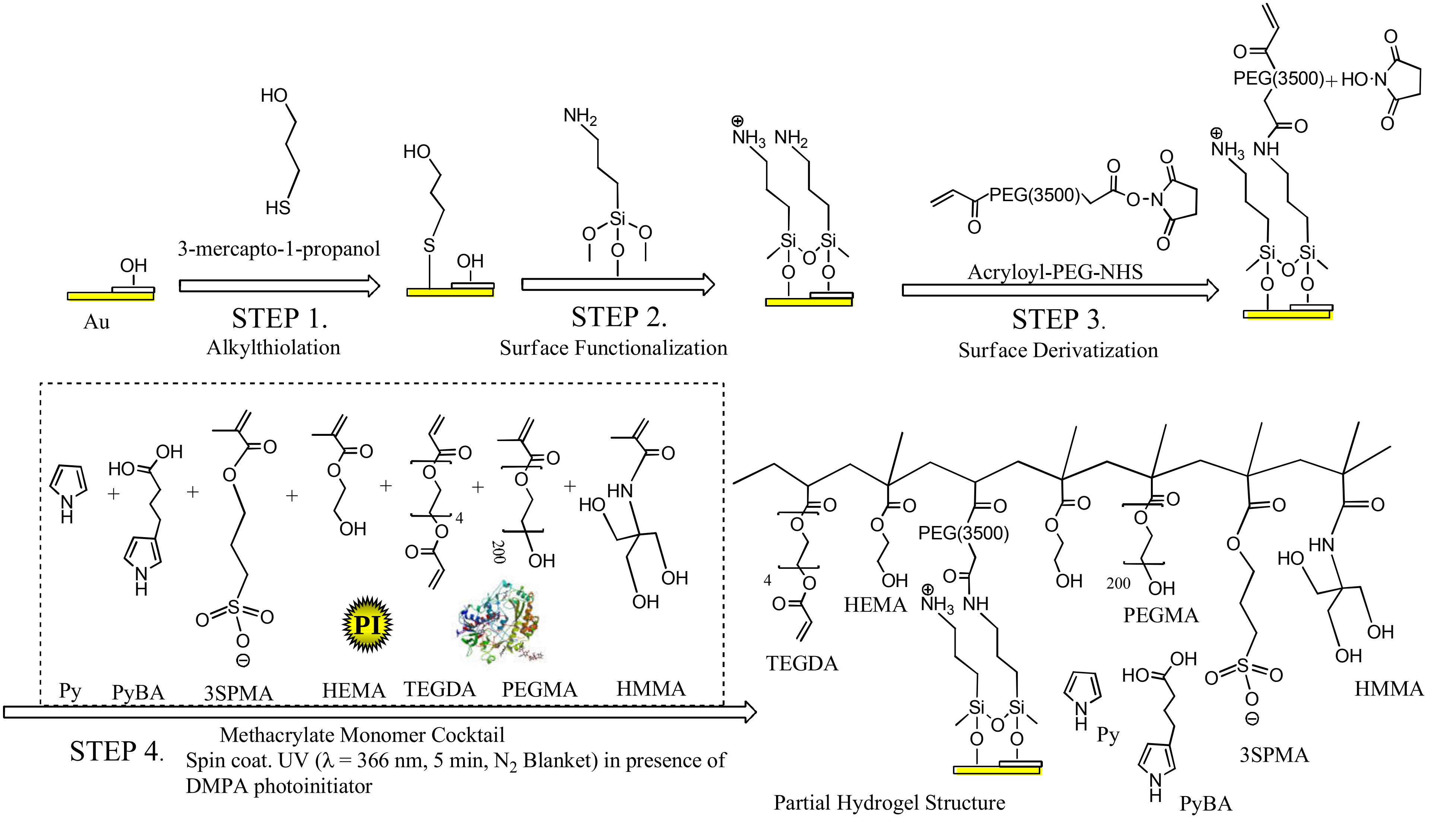
Muscle

Rim of new connective tissue forming a capsule and some residual inflammation around hydrogel

Residual area of Hemorrhage

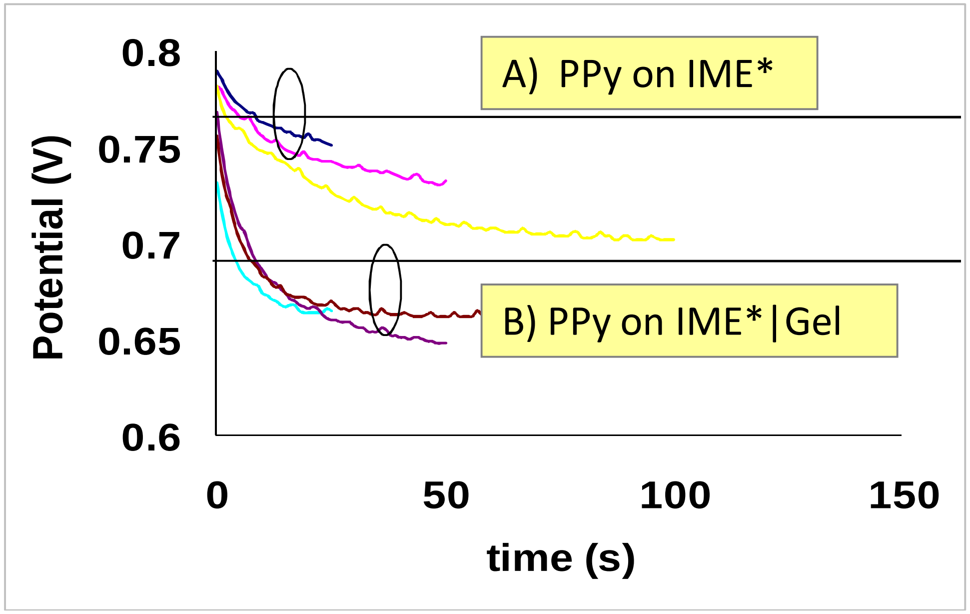
Hydrogel

Substrate surface modification, derivatization, monomer casting and electroconductive hydrogel synthesis

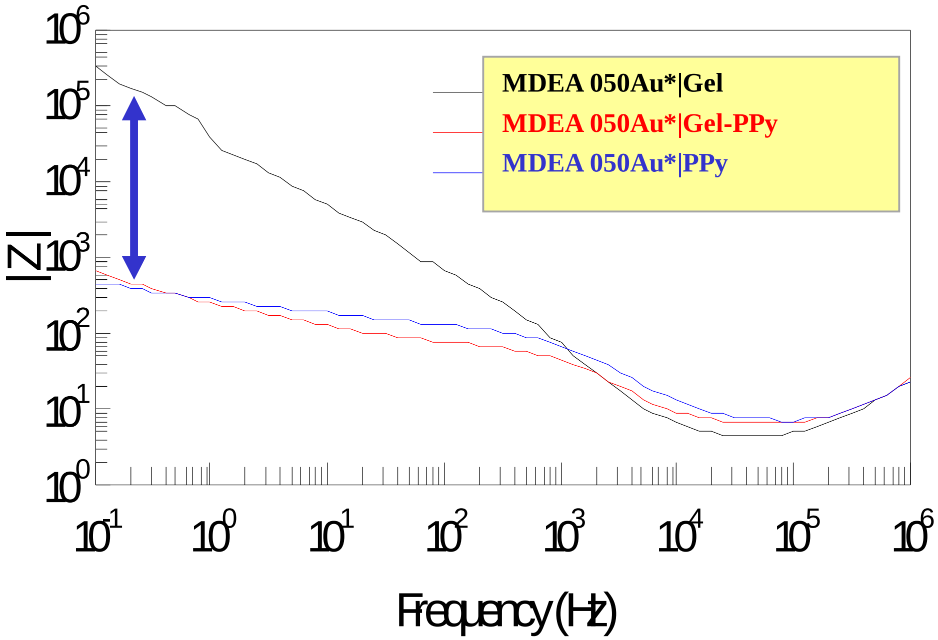


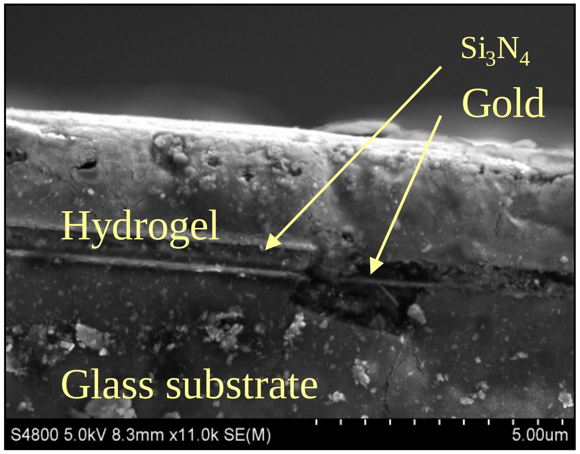
Electroconductive hydrogel p(HEMA-*co*-PEGMA-co-MPC-*co*-HMMA-*co*-SPMA)–P(Py-*co*-PyBA) hydrogel co-network

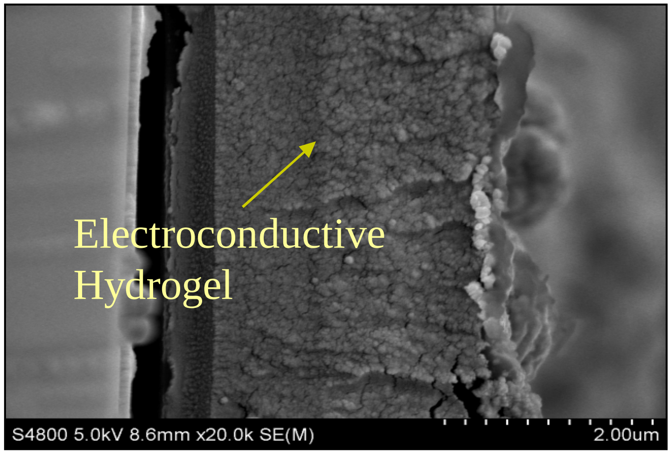
Galvanostatic electropolymerization of Py

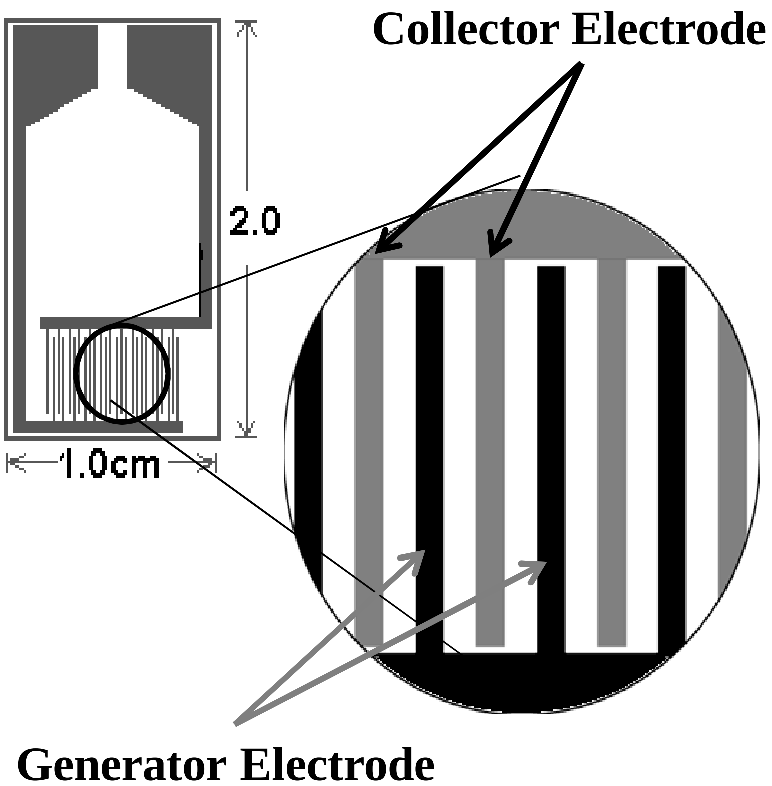


Electrochemical impedance magnitude, |Z|,

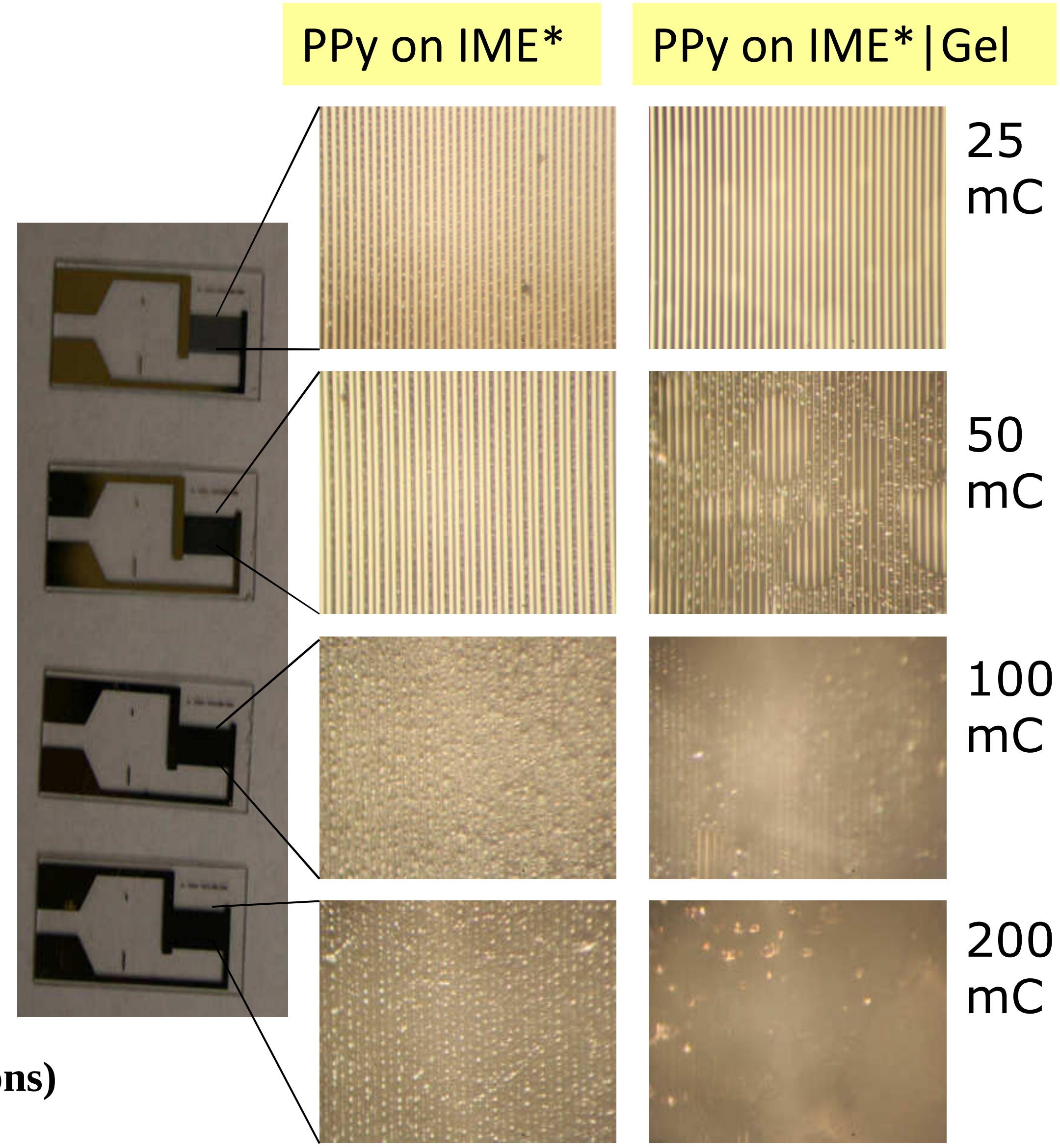






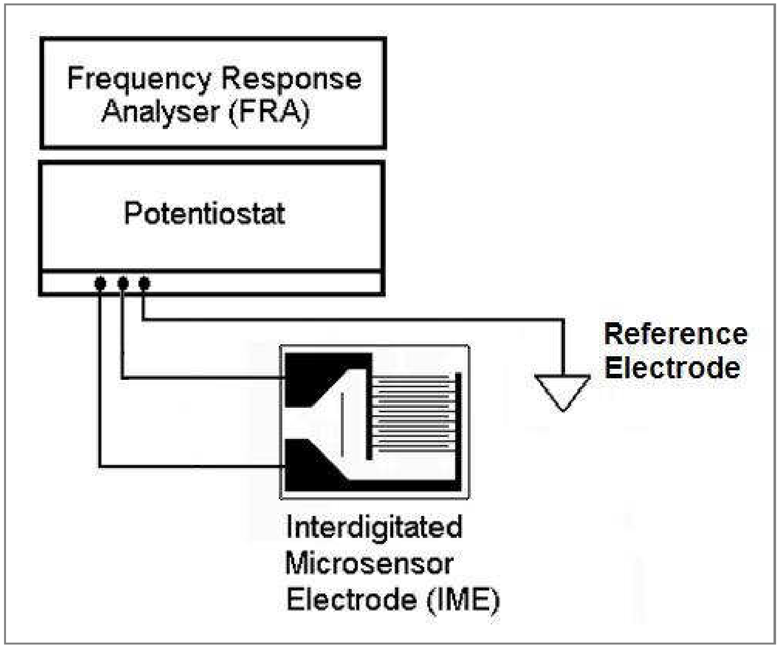


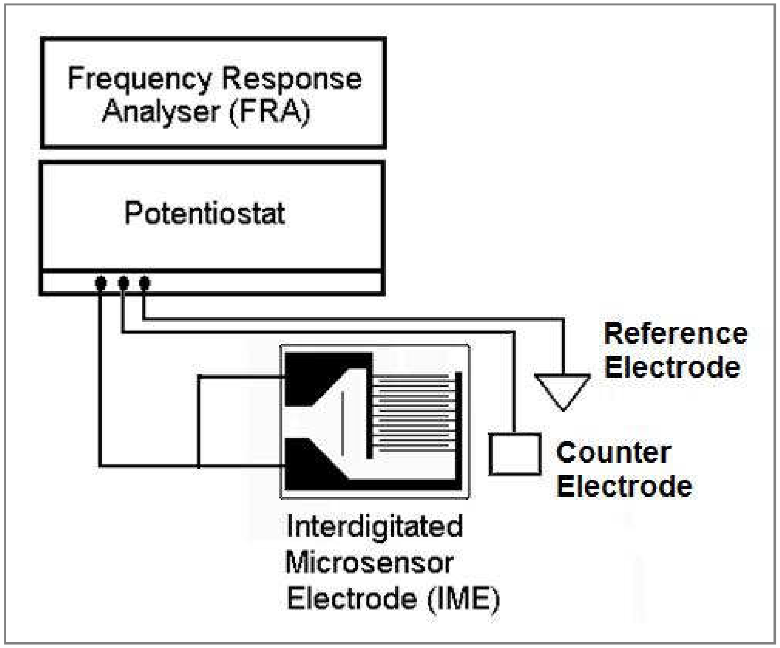
Digit width = spacing = 5, 10, 15 & 20 microns)

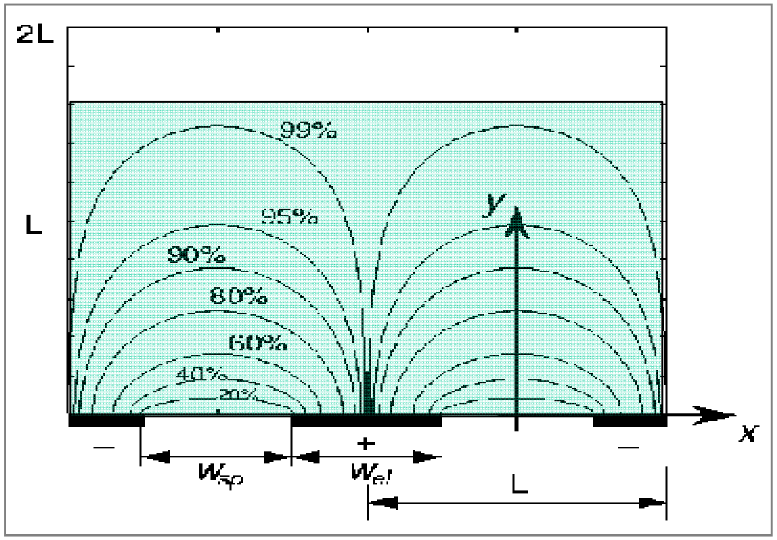


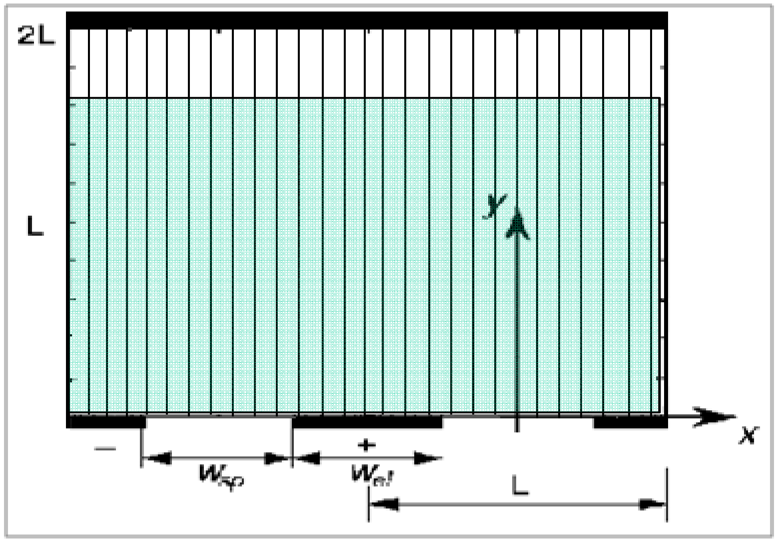
Electropolymerized PPy films grown on IME* (left) and on IME*|Gel devices (right).

Electrochemical Impedance of Electroconductive Hydrogels – Planar and Transverse Interrogation

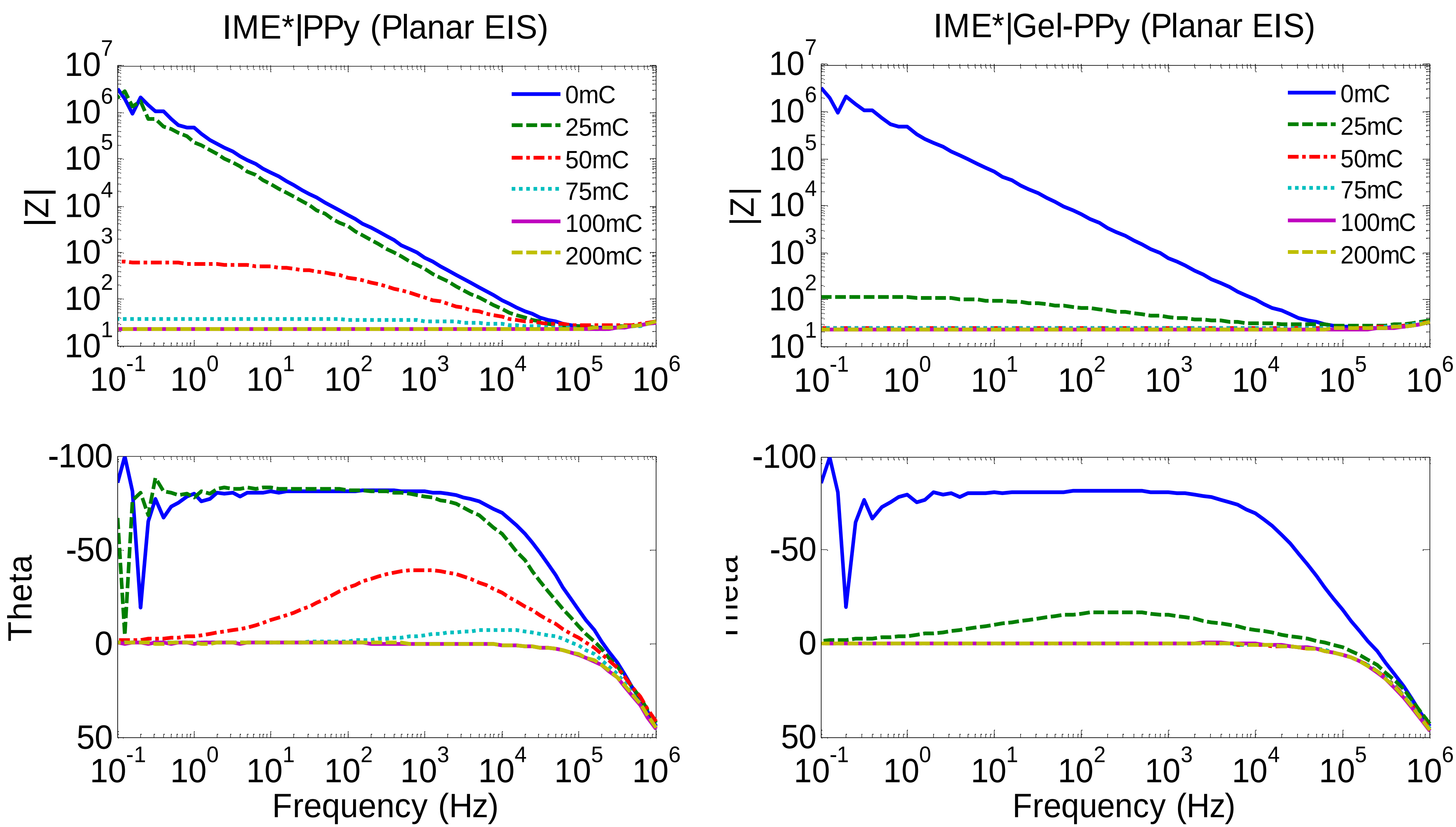






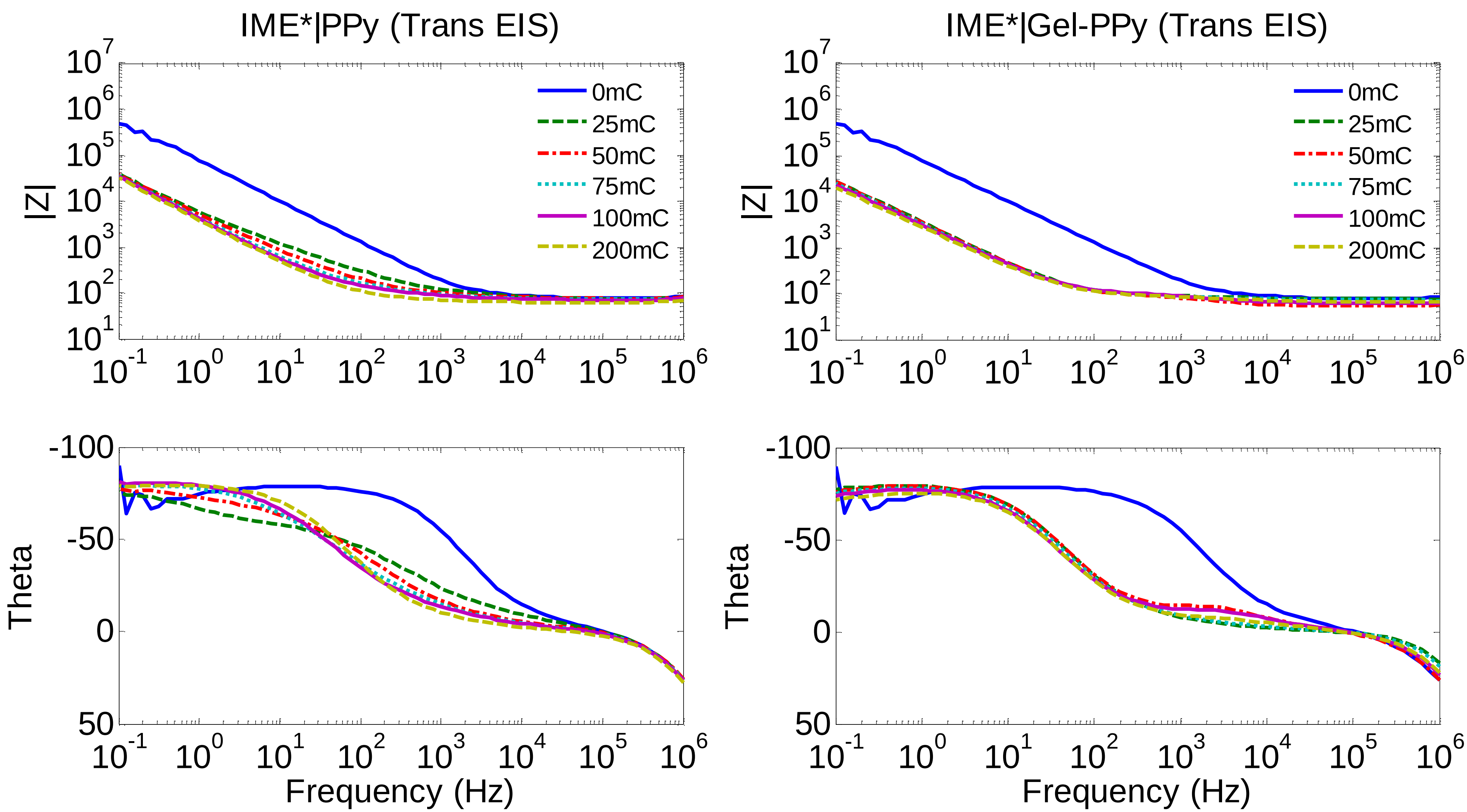


Electrochemical Impedance of Electroconductive Hydrogel of P(Py-co-PyBA) vs. PPy - Planar

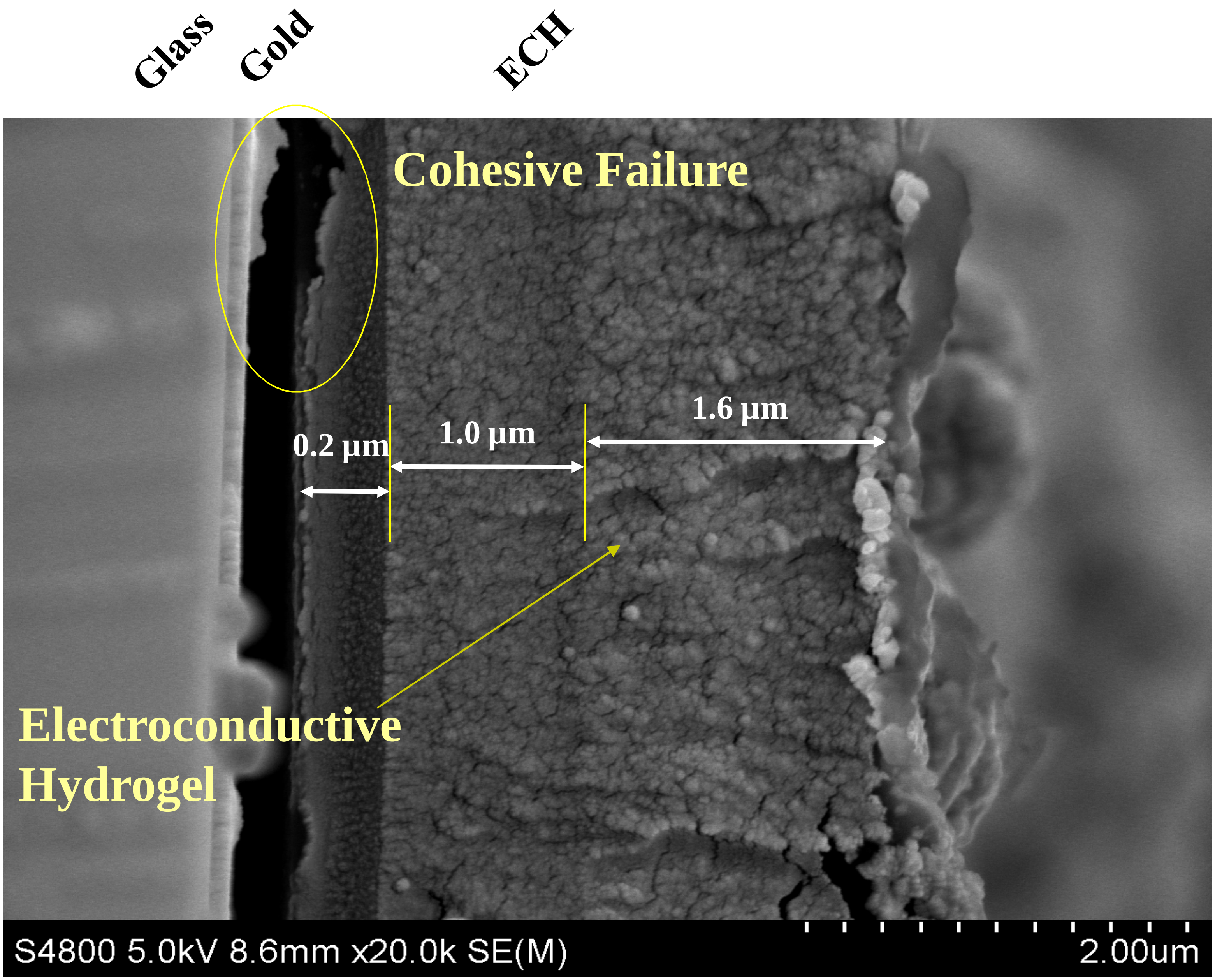


IME*|PPy and IME*|Gel-P(Py-*co*-PyBA) : Planar EIS (co-planar counter and working electrodes). Bode impedance magnitude and phase plots for the IME*|PPy (left) and IME*|Gel-P(Py-*co*-PyBA) (right) measured using the co-planar arrangement of counter and working electrodes.

Electrochemical Impedance of Electroconductive Hydrogel of P(Py-co-PyBA) vs. PPy - Transverse

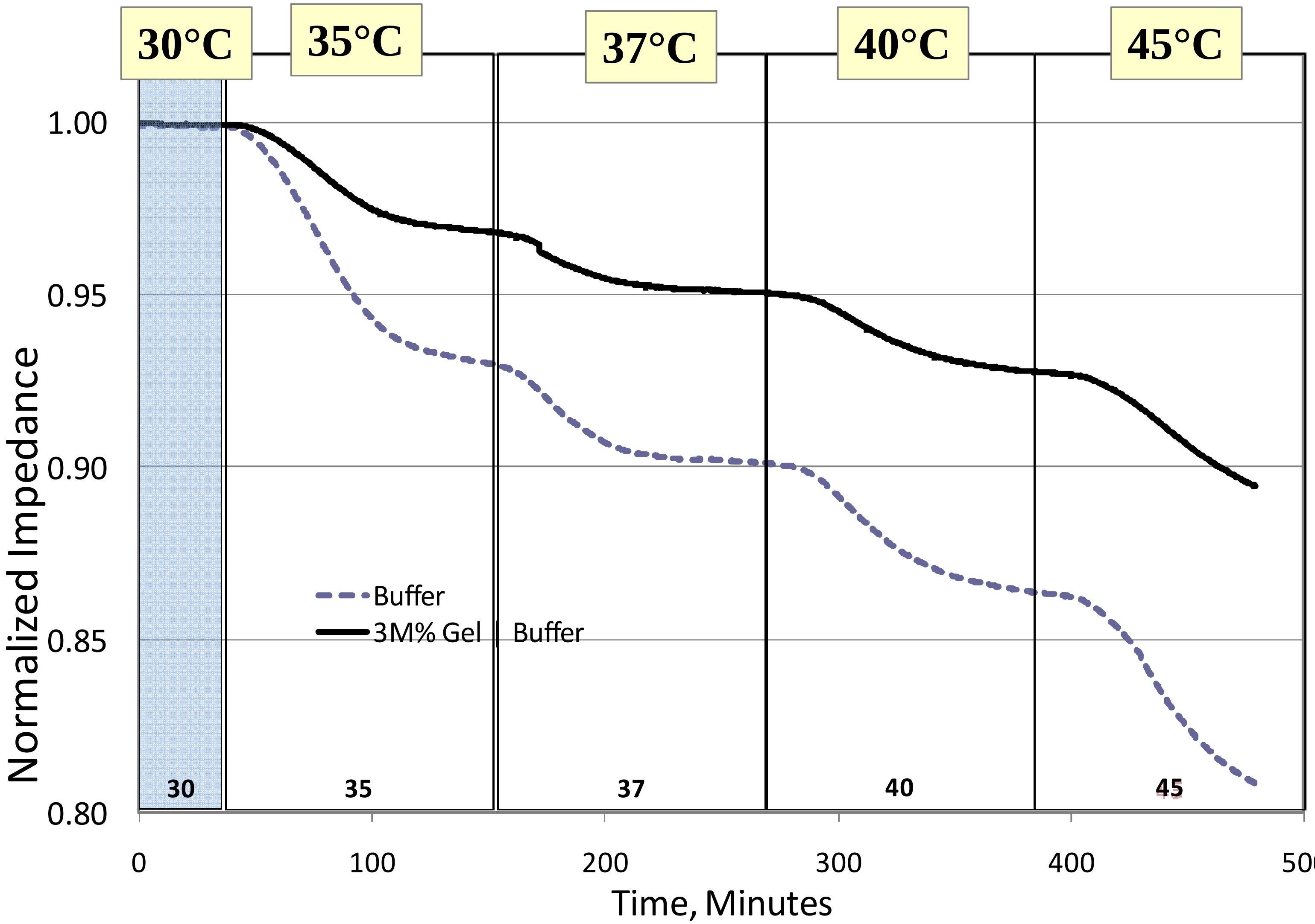


IME*|PPy and IME*|Gel-P(Py-*co*-PyBA): Trans EIS (external counter electrode). Bode impedance magnitude and phase plots for the IME*|PPy (left) and IME*|Gel-P(Py-*co*-PyBA) (right) measured using an external counter electrode.

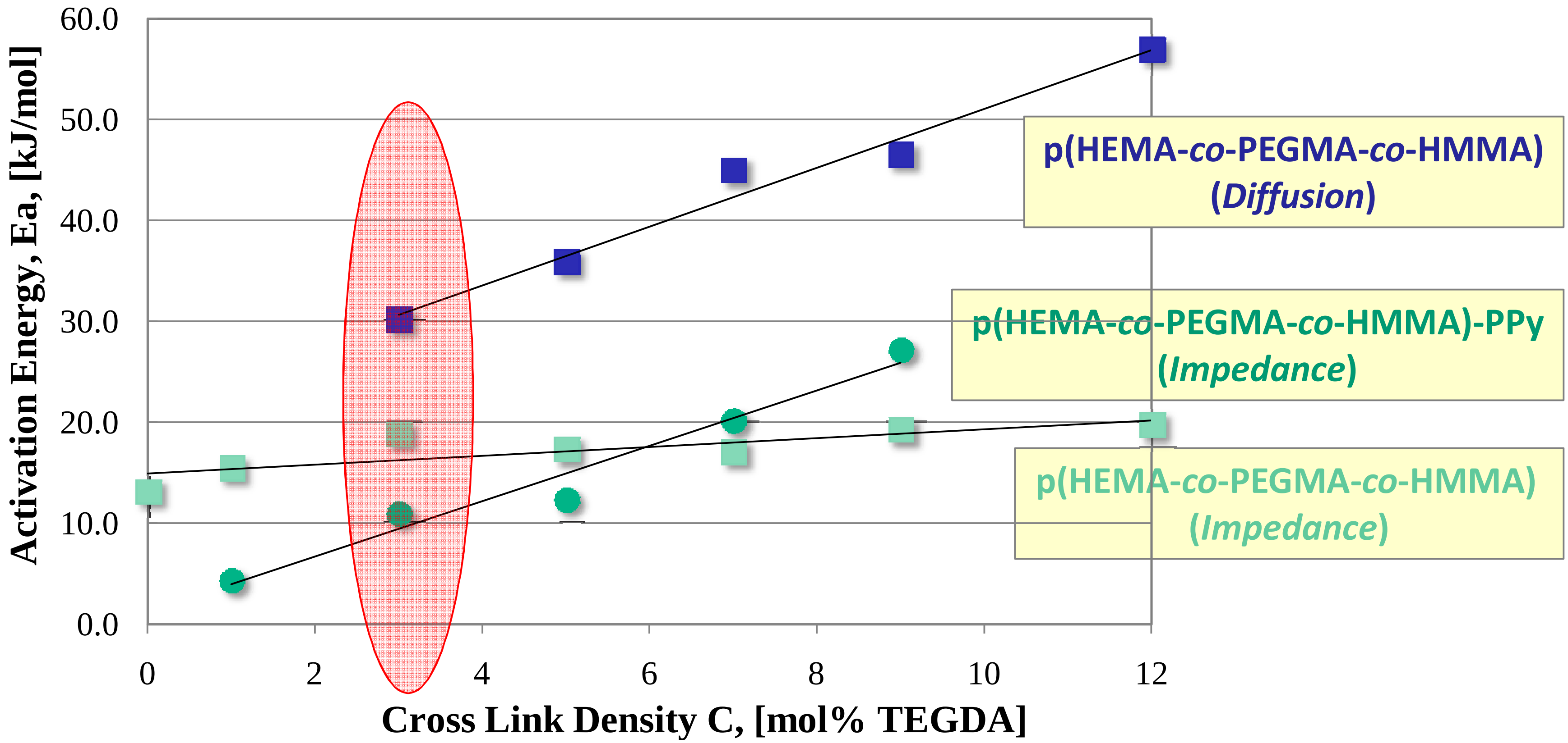


Freeze-fracture SEM of a cross section of an electroconductive hydrogel (ECH) membrane following electropolymerization of Py on MDEA and within the hydrogel.

Normalized impedance magnitude |Z| *vs.* time at 64 kHz for the 0.1M Tris/0.1M KCL buffer (pH=7.4) (- - - -) and for the 3 M% cross linked p(HEMA-*co*-PEGMA-*co*-HMMA) hydrogel in 0.1M Tris/0.1M KCL buffer (pH 7.4) (-----).



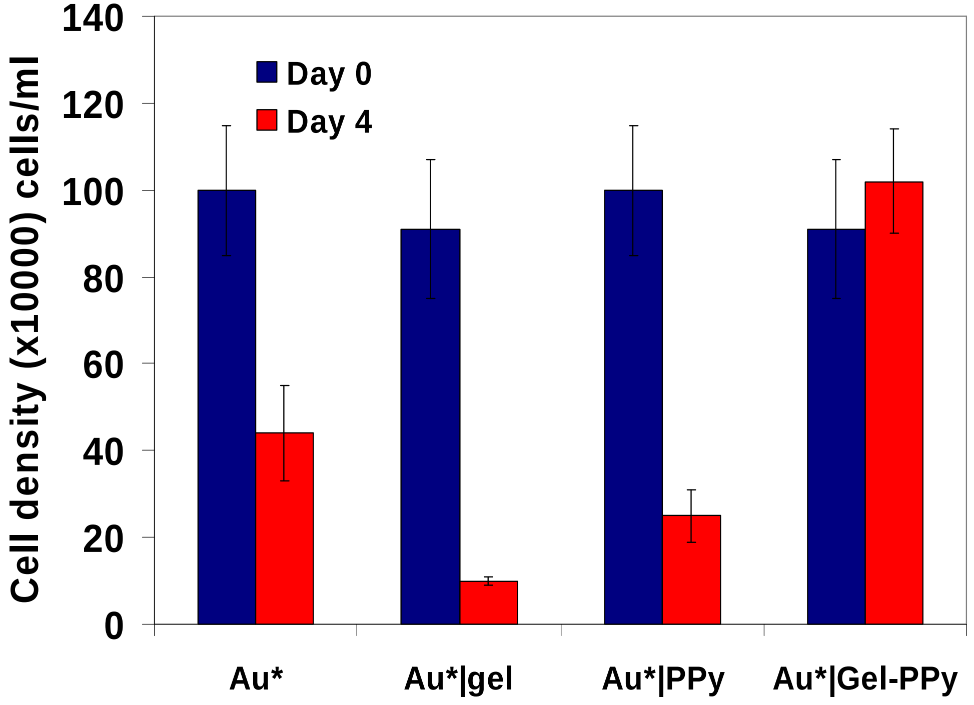
Comparison of the activation energies (E*, kJ/mol) for impedimetric transport within p(HEMA-*co*-PEGMA-*co*-HMMA) hydrogels and p(HEMA-*co*-PEGMA-*co*-HMMA)-PPy electroconductive hydrogels as a function of M% cross linker, TEGDA, as measured at 64 kHz in 0.1M Tris/0.1M KCL buffer (pH=7.4).

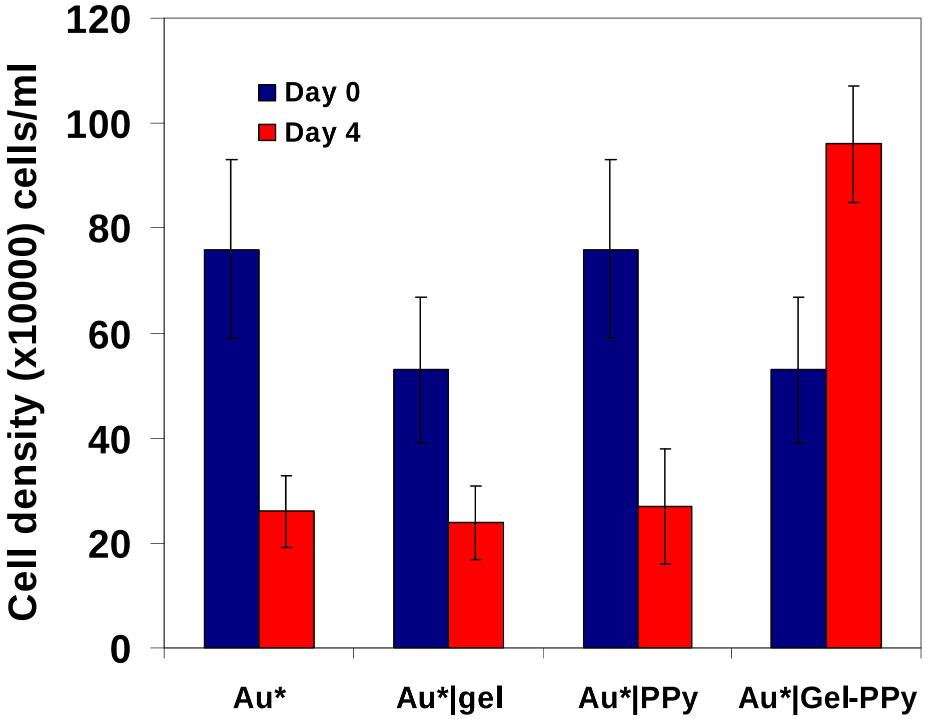


Cell viability as a function of Au electrode surface composition (after 4 days)

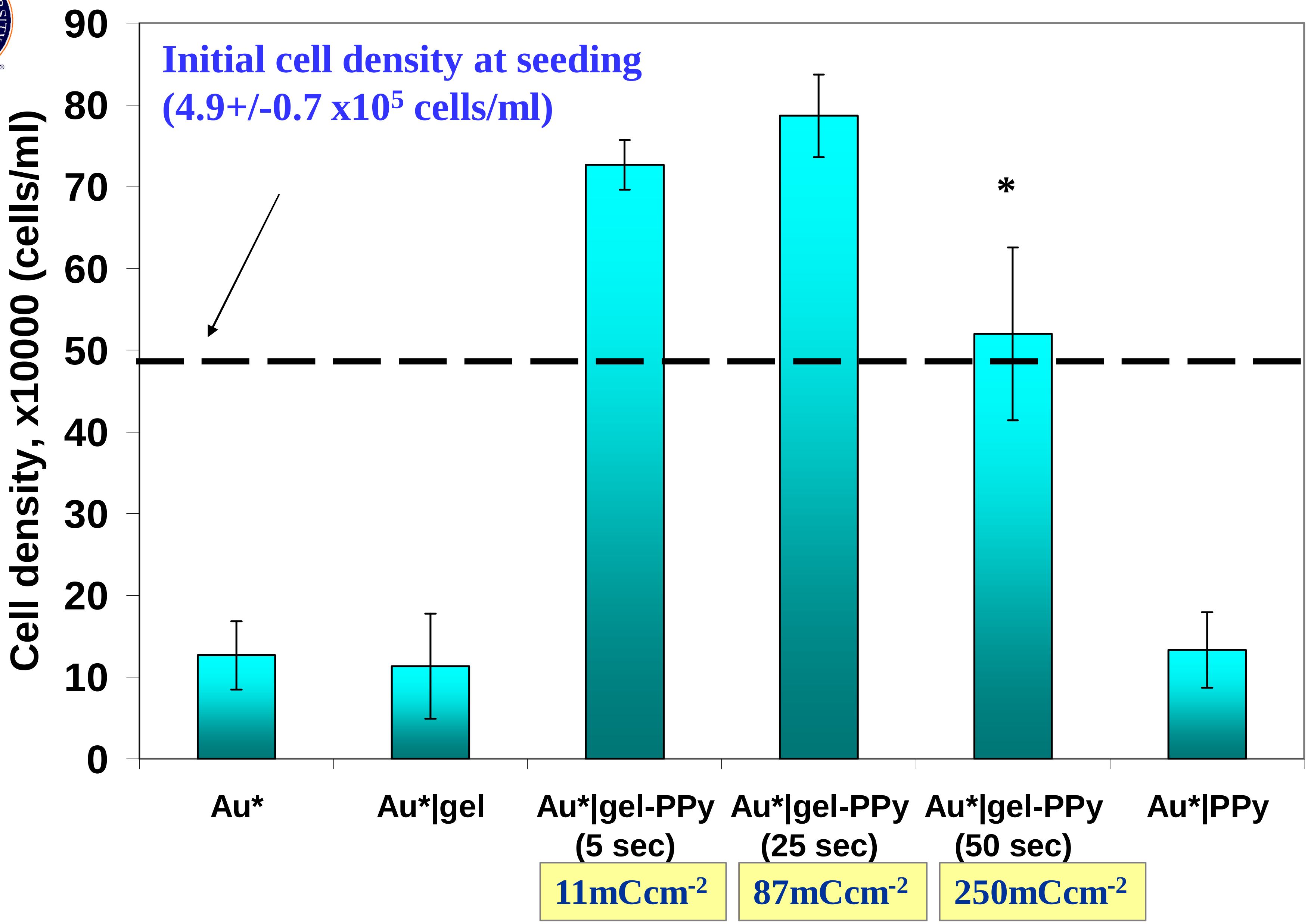
PC12 - Pheochromocytoma

RMS 13 – Human Muscle fibroblasts





Cell densities following trypsinization (5 min) and enumeration of RMS13 and PC12 pre- (blue bars) and post- (red bars) incubation for 4 days on Au*, Au*|hydrogel, Au*|PPy, Au*|hydrogel-PPy surfaces

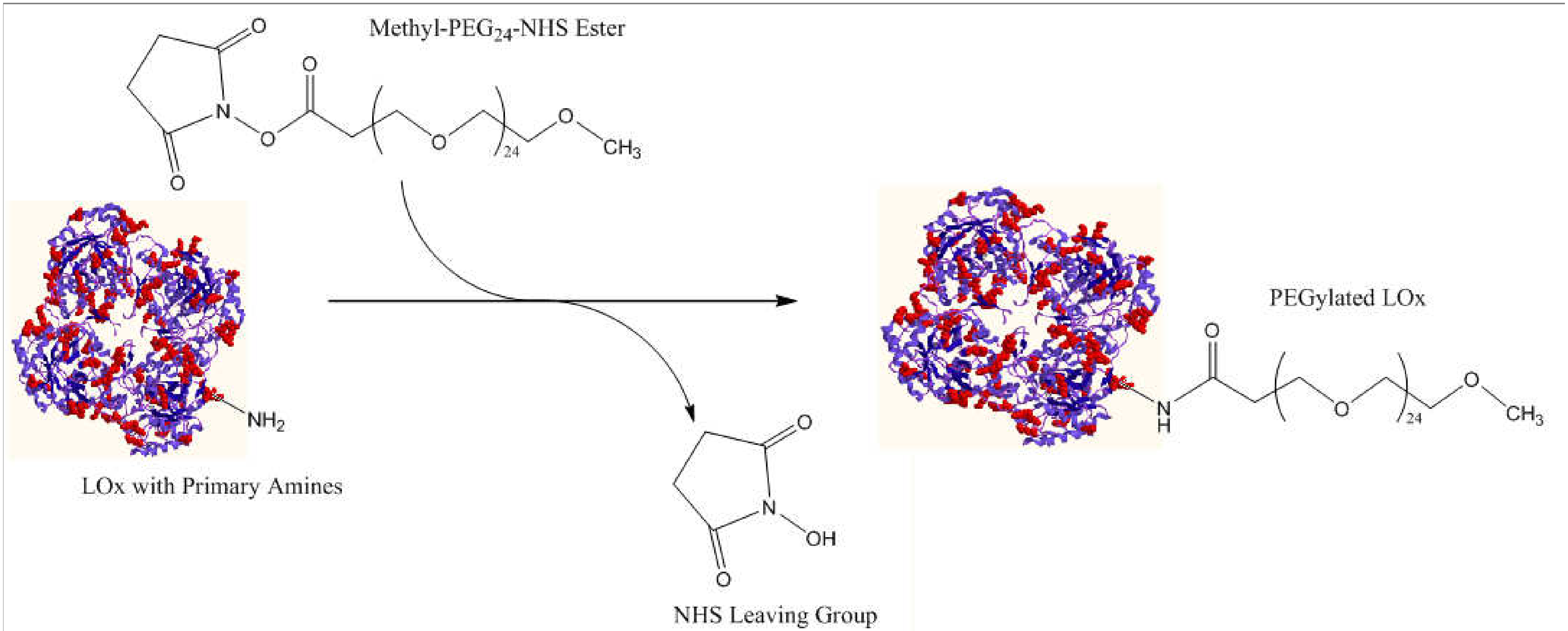


Comparison of PC12 cell densities post-incubation (for 4 days) on Au*, Au*|hydrogel, Au*|PPy, Au*|hydrogel-PPy (5, 25 and 50 second electropolymerization times). Initial seeding cell density was 4.9+/-0.7 x10^5 cells/ml (broken line). * Indicates a p-value greater than 0.05.

Grand challenge issues in electrode-tissue interfaces

- ✦ Overcoming the limitations of the disciplines
- ✦ Materials by design. …Not just one property.
- ✦ Integrating length scales - modeling of molecule-to-system architectures.

PEGylation of LOx at Lysine Residues

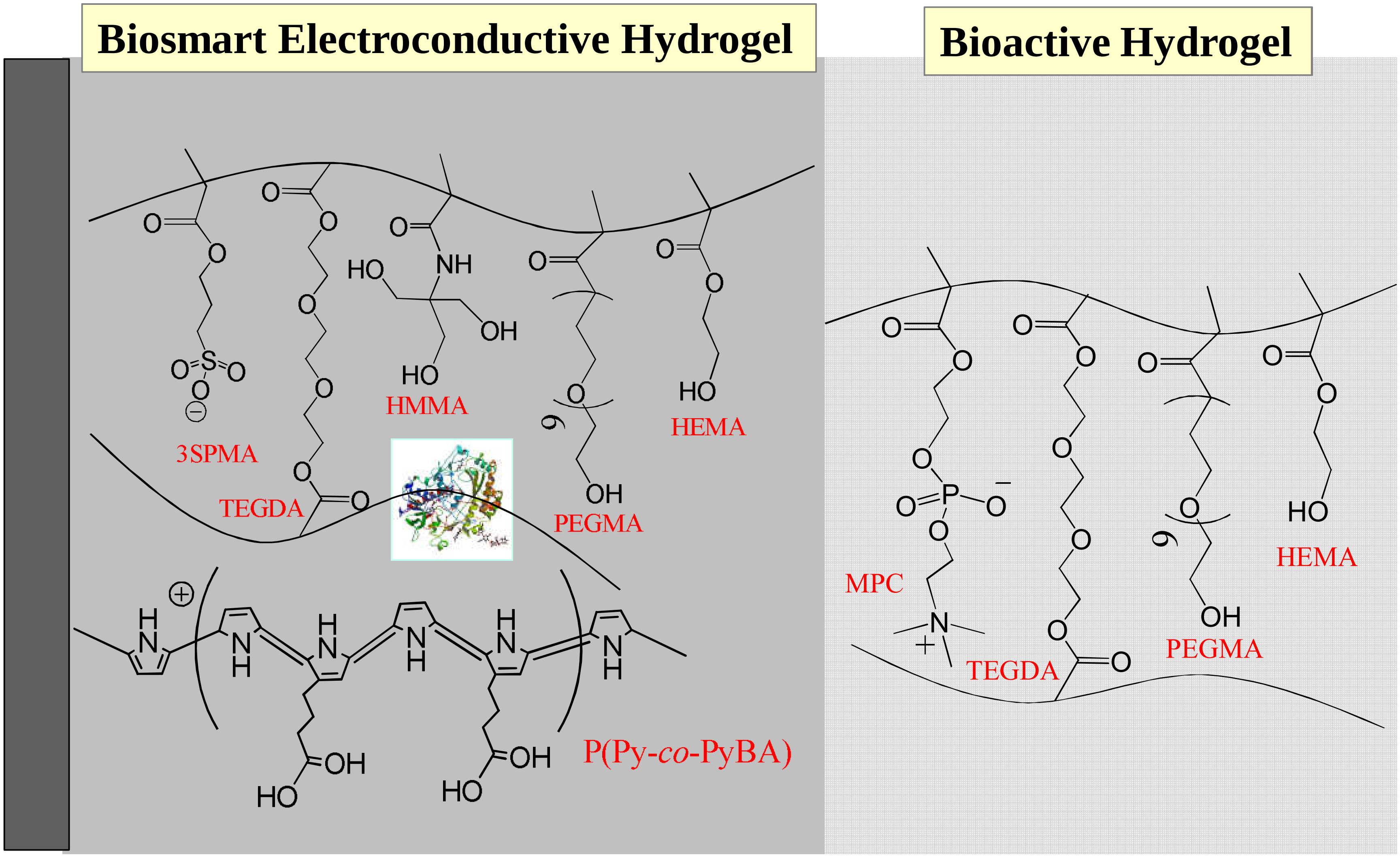


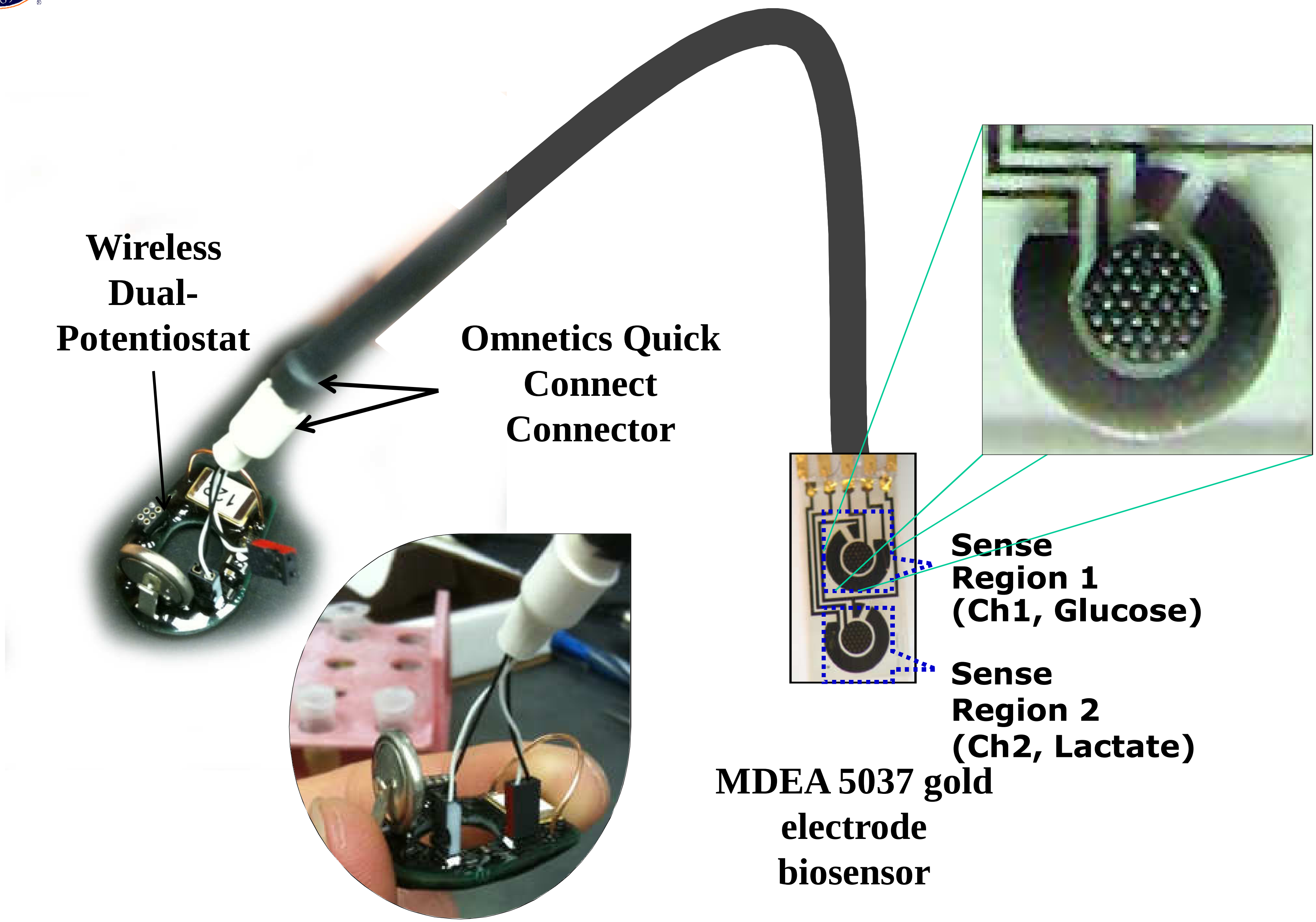
$$\text{L-Lactate} + O_2 \longrightarrow \text{Pyruvate} + H_2O_2$$

$$\beta\text{-D-glucose} + O_2 \longrightarrow \text{glucono-}\delta\text{-lactone} + H_2O_2$$

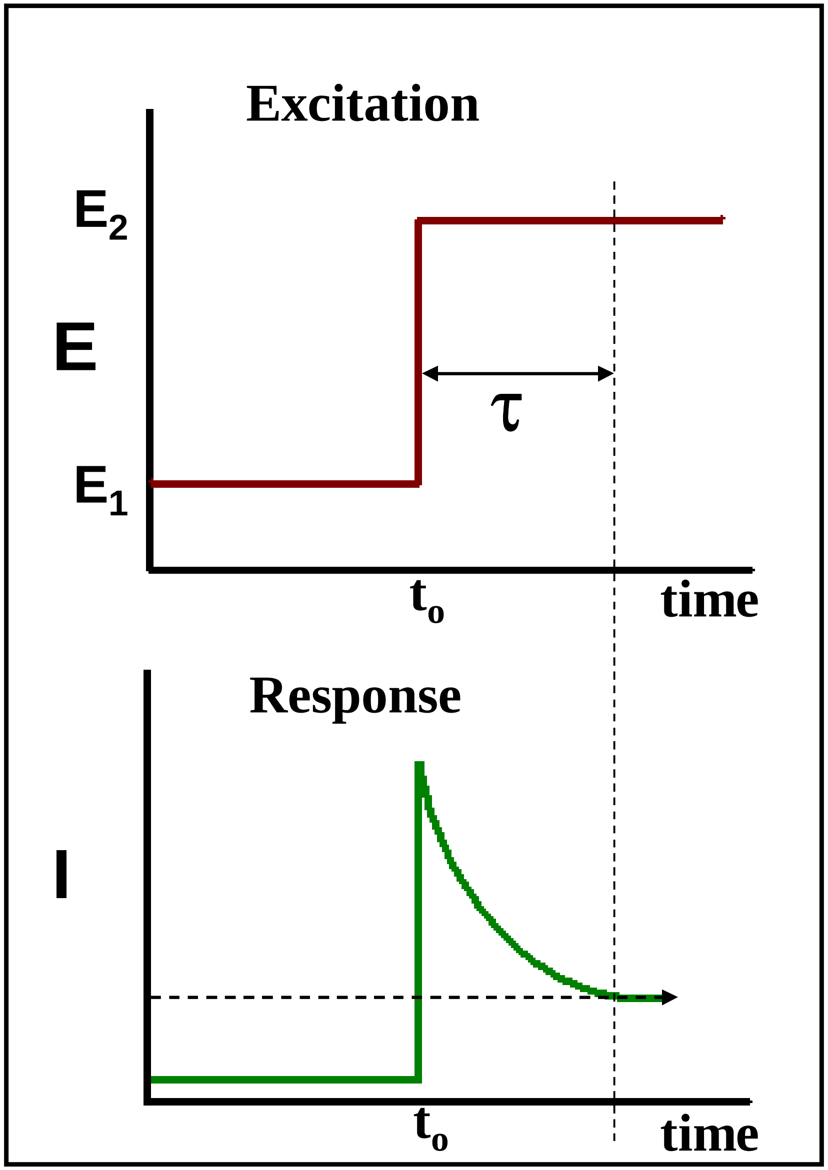
- Enzyme activity via kinetic assay: v_{max}, K_M, k_{cat}, k_{cat}/K_M
- MW and MW distribution via capillary gel electrophoresis:

Schematic illustration of the molecular constituents of a poly(HEMA-*co*-PEGMA-*co*-HMMA-*co*-SPMA)/P(Py-*co*-PyBA) electroconductive hydrogel containing an oxidoreductase enzyme and bioactive hydrogel topcoat containing phosphoryl choline (MPC).




Wireless Dual-Potentiostat
Omnetics Quick Connect Connector
Sense Region 1 (Ch1, Glucose)
Sense Region 2 (Ch2, Lactate)
MDEA 5037 gold electrode biosensor

Principle of operation of the amperometric biotransducer



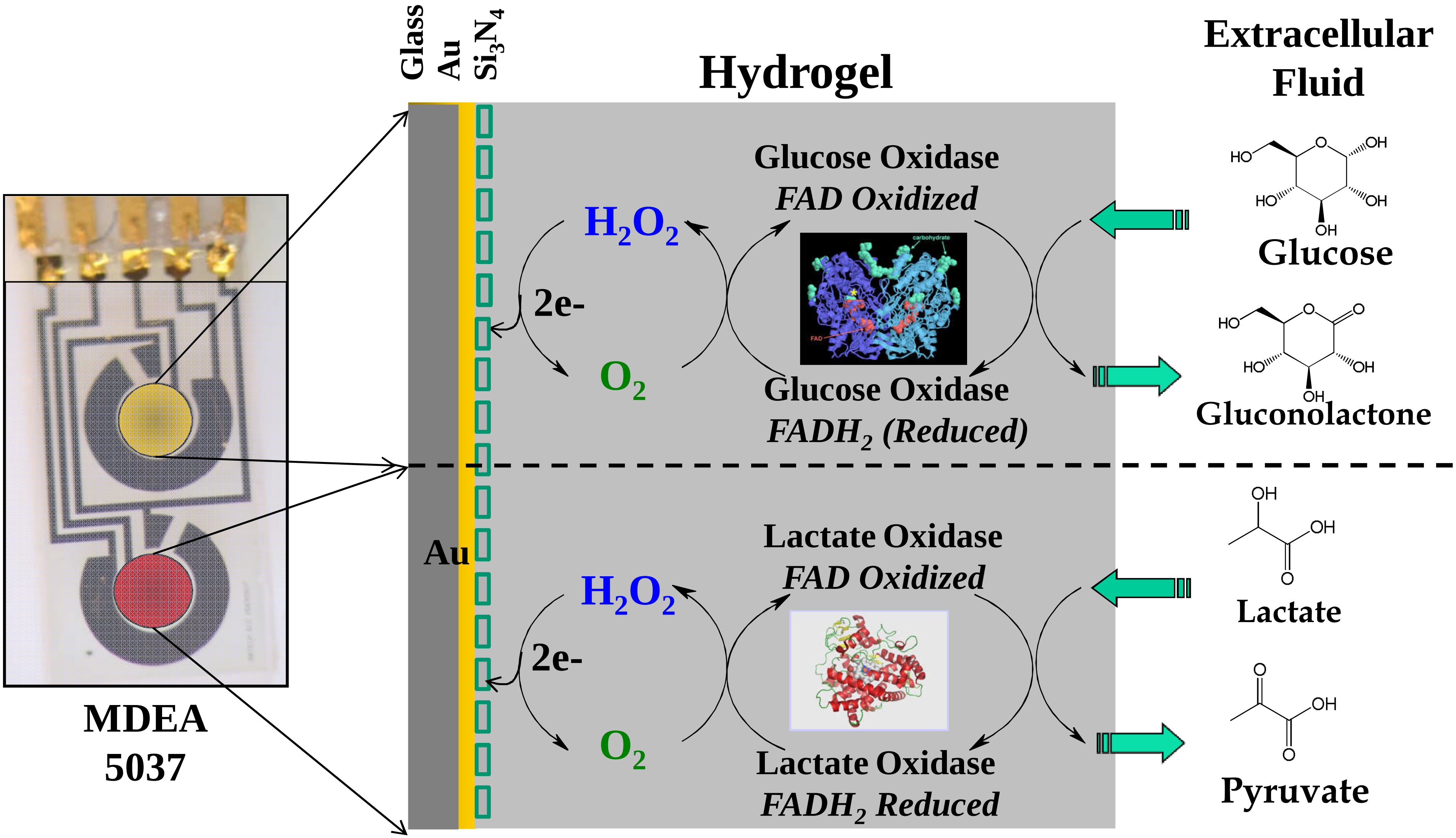
Chronoamperometry (CA)

- Cottrell's Equation

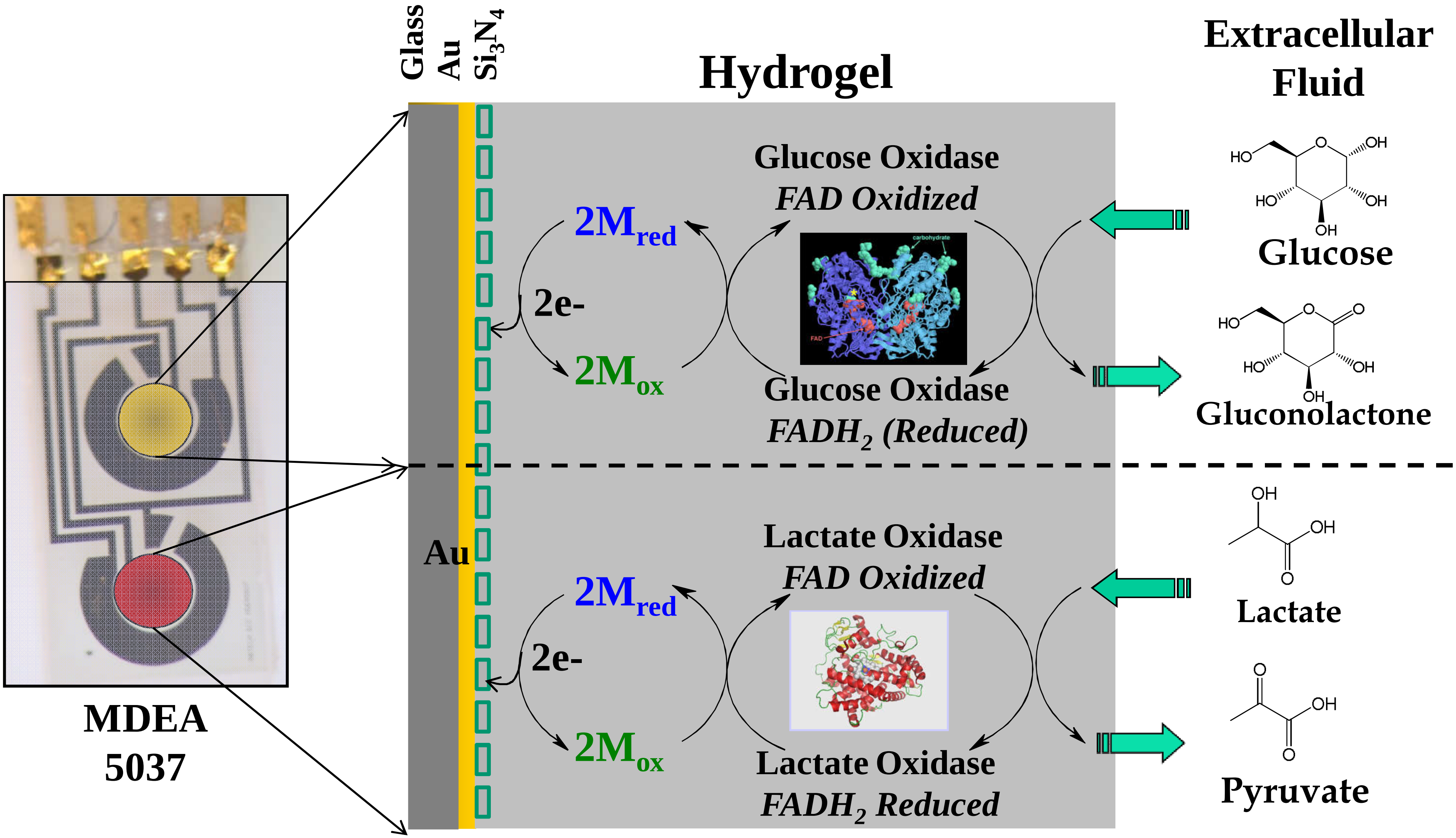
$$i(t) = \frac{\mathrm{nFA}\, D_o^{1/2} C_o^{*}}{\pi^{1/2} t^{1/2}}$$

- E_1- No redox activity
- E_2- $|E| > E°'$
- τ - step size (determined experimentally)
- Quiescent solution

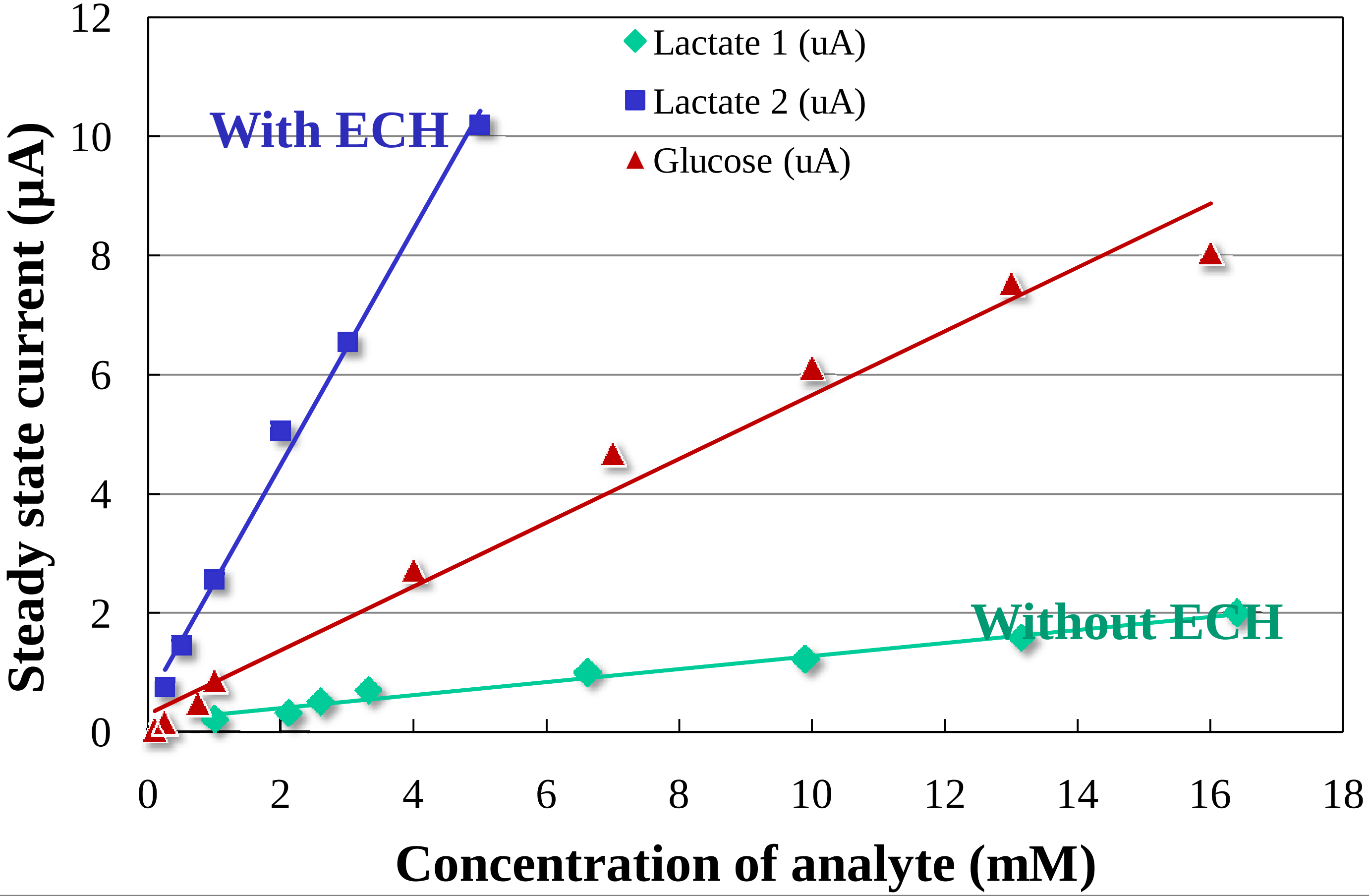
Fabrication of the electrochemical p(HEMA)/Glucose and Lactate TYPE I biotransducers



Fabrication of the electrochemical p(HEMA)/Glucose and Lactate TYPE II biotransducers

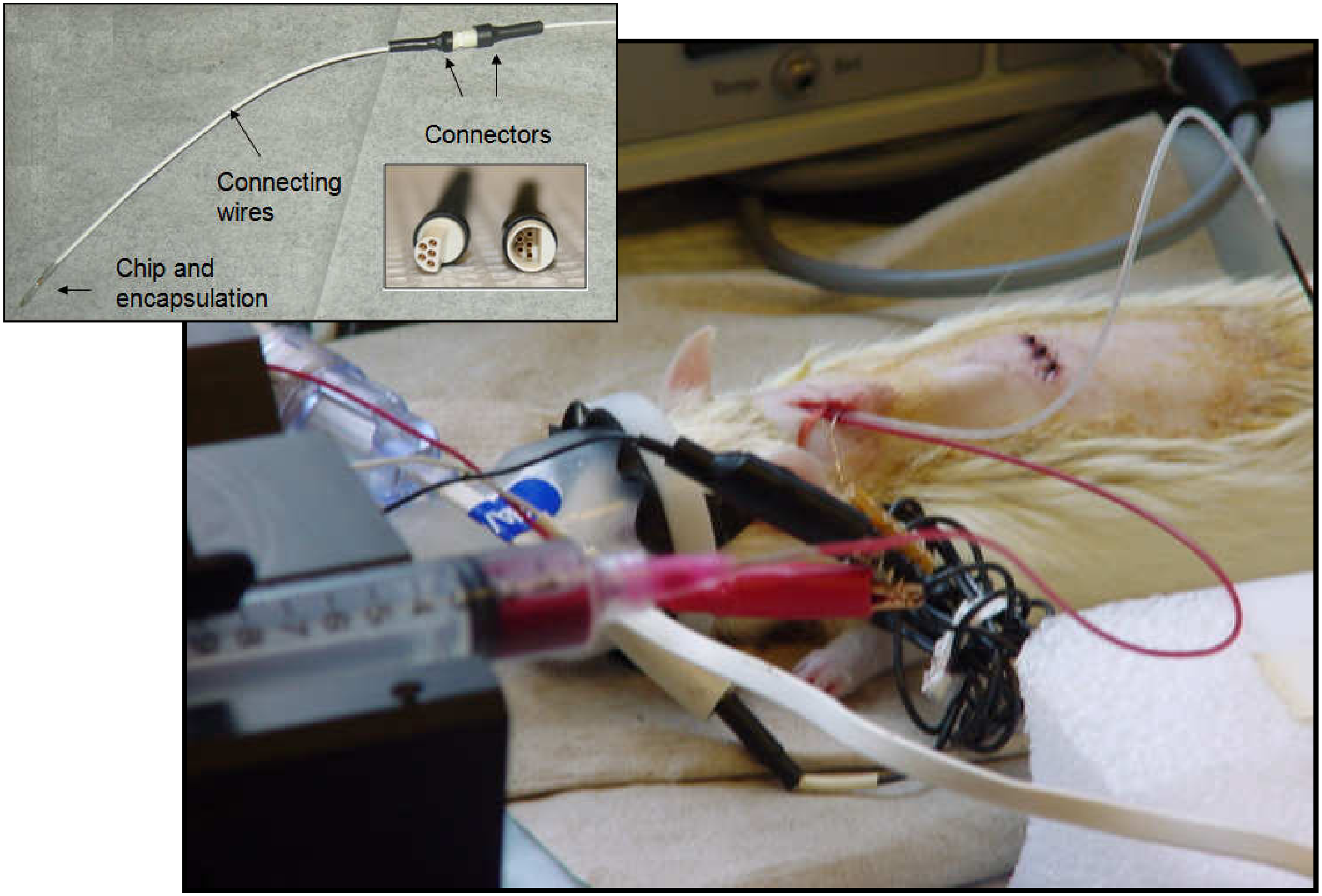


In vitro calibration of the dual responsive glucose and lactate biotransducer – different lactate sensitivities



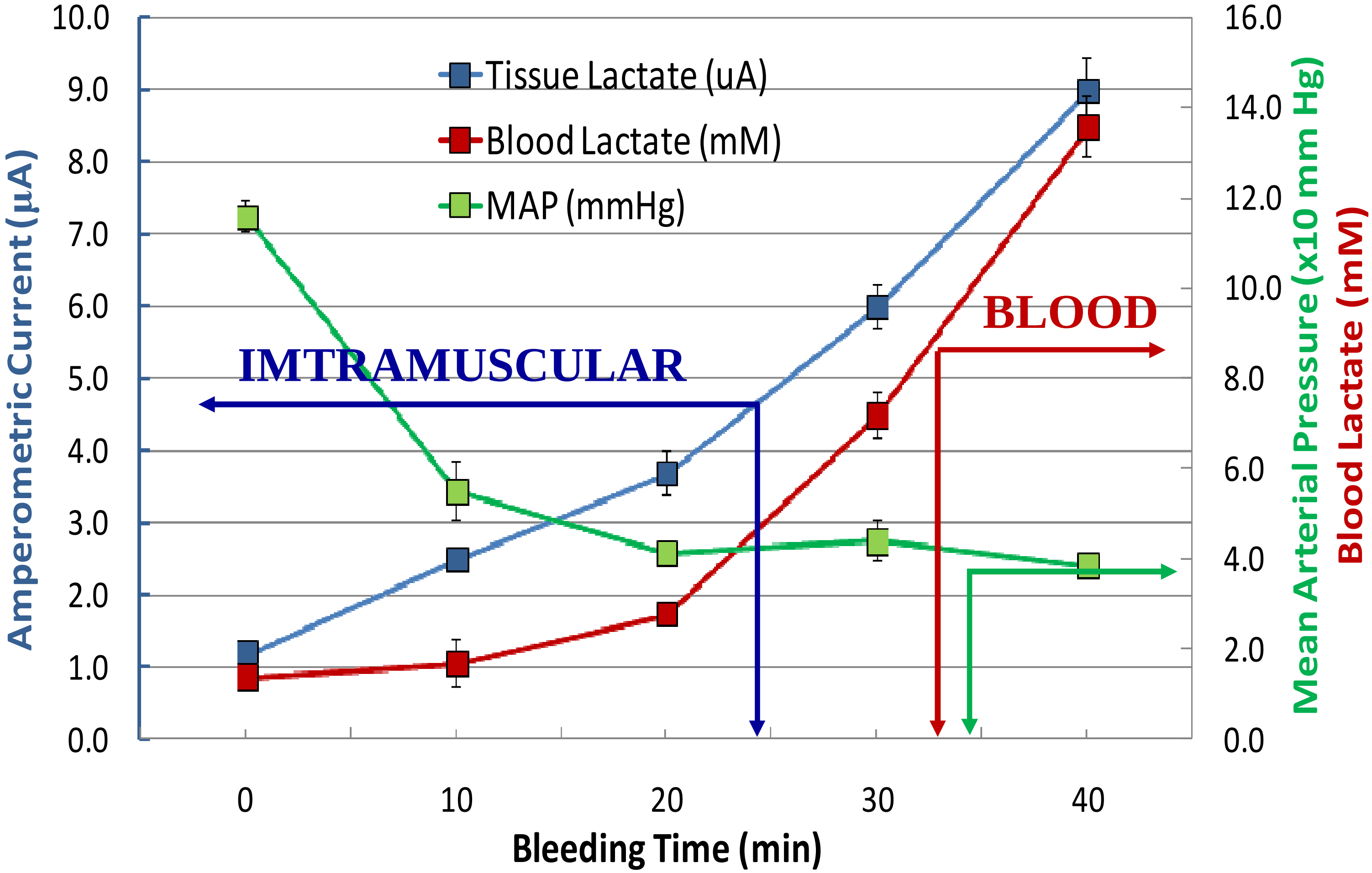
MDEA 5037 lactate and glucose biosensor incorporating electroconductive polymer bio-smart hydrogel membrane of composition 80:10:2.5:2.5:5.0 mol% (HEMA:TEGDA:PEGMA:MPC:Py) in 0.1 M PBKCl, pH 7.0 at RT.

A catheterized and instrumented Sprague Dawley rat under controlled hemorrhage conditions with intramuscularly (trapezius) implanted PSM Biochip.



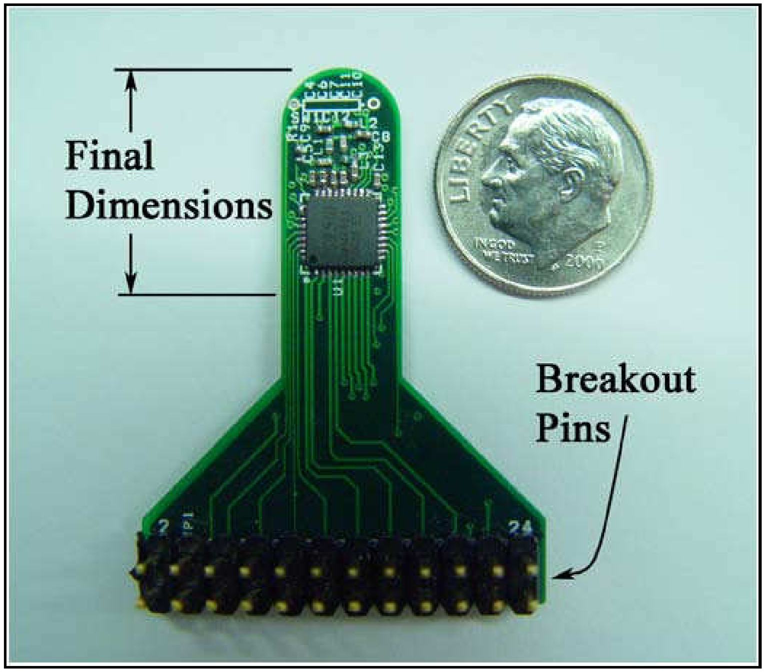
In vivo amperometric performance of the implanted PSMBioChip during hemorrhage – Sprauge Dawley rat model.

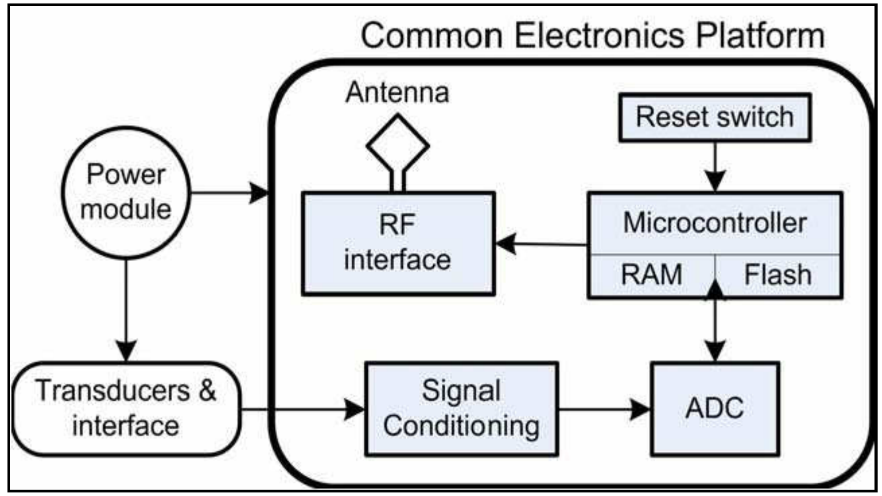
Amperometric response of an intramuscularly implanted lactate biosensor during hemorrhage, the mean arterial pressure (MAP) and the systemic blood lactate obtained using a YSI Biostat Bioanalyzer.

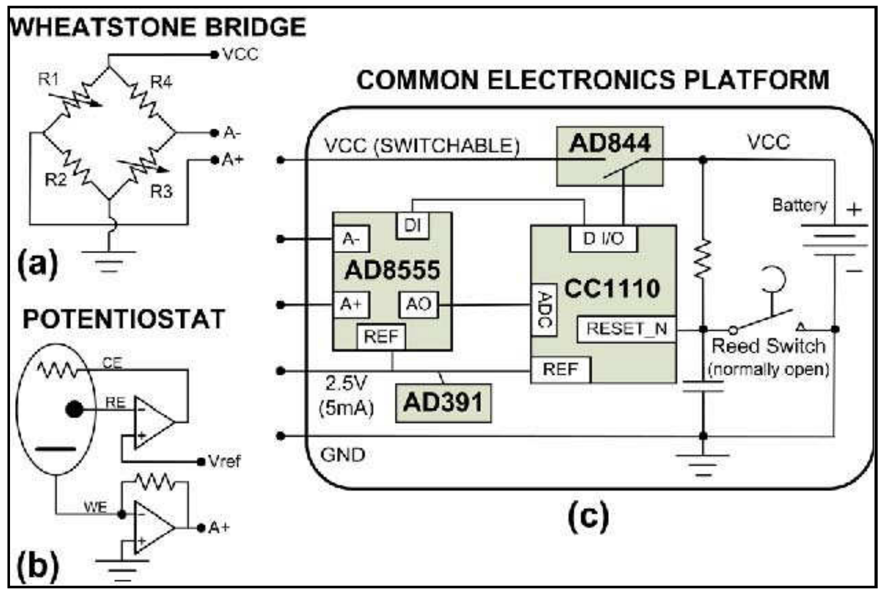


Anthony Guiseppi-Elie "An Implantable Biochip to Influence Patient Outcomes Following Trauma-induced Hemorrhage" *Journal Analytical and Bioanalytical Chemistry* (**2011**) 399(1), 403-419.

Discrete component prototyping of the PSMBioChip





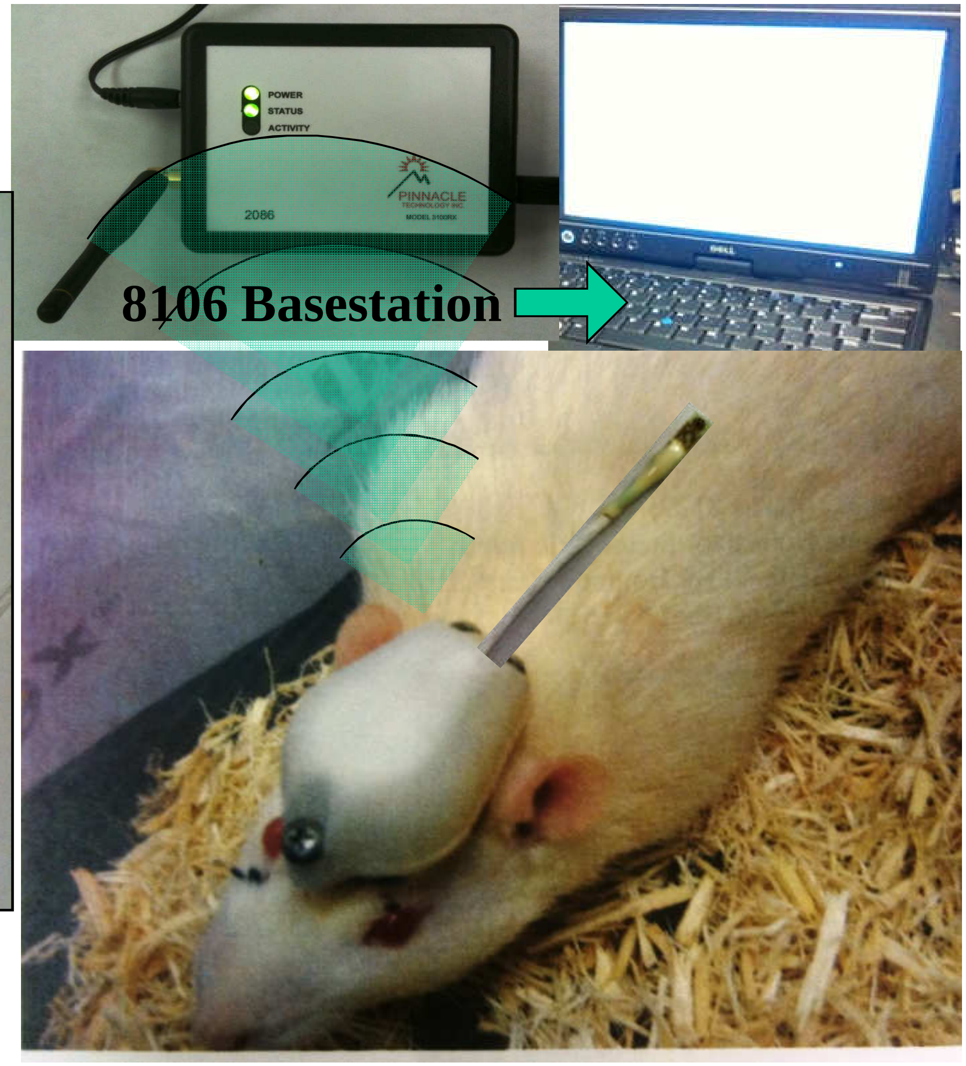


TI /ChipCon CC1110

- 8051 Microprocessor
- 9-14 bit ADC
- RF Transcever
  - MICS: 402-405 MHz

R. H. Farahi, T. L. Ferrell, A. Guiseppi-Elie and P. Hansen, “Integrated Electronics Platforms for Wireless Implantable Biosensors” *IEEE Transactions L***ife Science Systems and Applications Workshop** **(2007) IEEE/NIH, p 27–30.**

A Sprague Dawley rat equipped with a head mounted wireless transmitting dual potentiostat to support intramuscular bioanalytical measurements of lactate and glucose in the trapezious muscle.



CLEMSON UNIVERSITY SOUTH CAROLINA 1889

Status

- CDMRP funded small vertebrate animal studies ongoing at Clemson University

CLEMSON UNIVERSITY

- IP ownership released by Clemson University to Guiseppi-Elie, successfully transferred to ABTECH Scientific, Inc.

ABTECH

- Collaborative program established with Tripler Army Medical Center – Dr. Catherine Uyehara, Chief, Dept. Clinical

U.S.ARMY

PACIFIC REGIONAL MEDICAL COMMAND
TRIPLER ARMY MEDICAL CENTER

Grand challenge issues in implantable biochips

- Power
- Biocompatibility
- Mixed signal electronics
- Bioactive interfaces

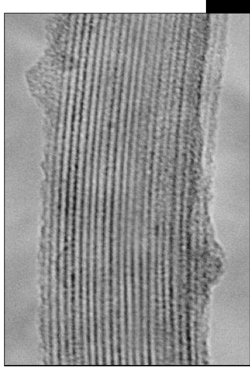
Molecular Bioelectronics: Direct Electronic Control of Enzyme Kinetics Enabled by Compatibility of Scales – TYPE III Biotransducers

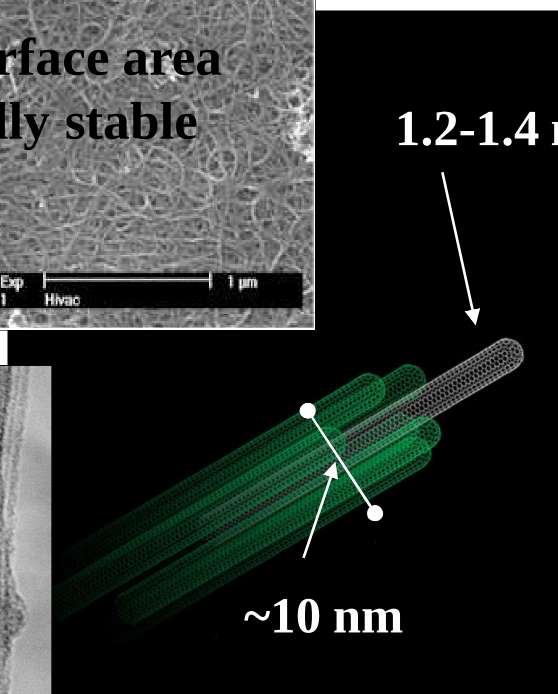
Nanotube filaments penetrate the glycoprotein shell and attain tunneling proximity to the cofactor. Impact on bioactivity via denaturation is minimum.

- Highly conductive
- Strong
- Large surface area
- Chemically stable
- Inert

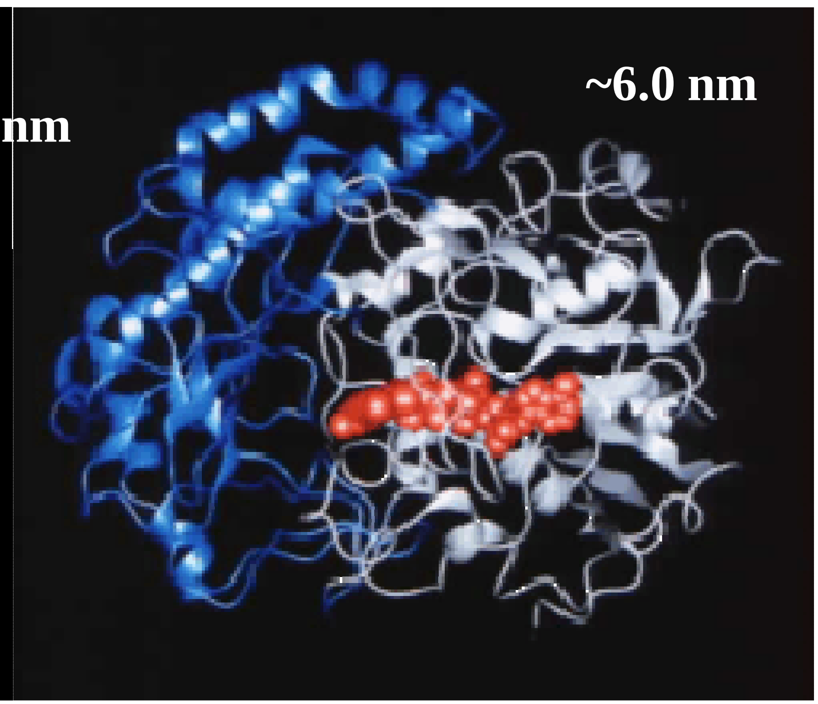
n nanotube

Enzyme subunit





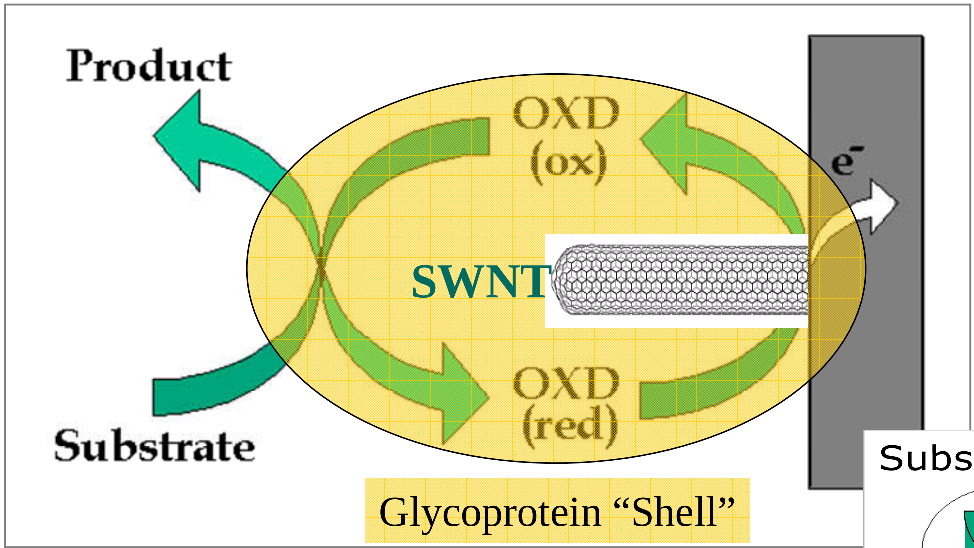
Carbon nanotubes
Courtesy: CNST



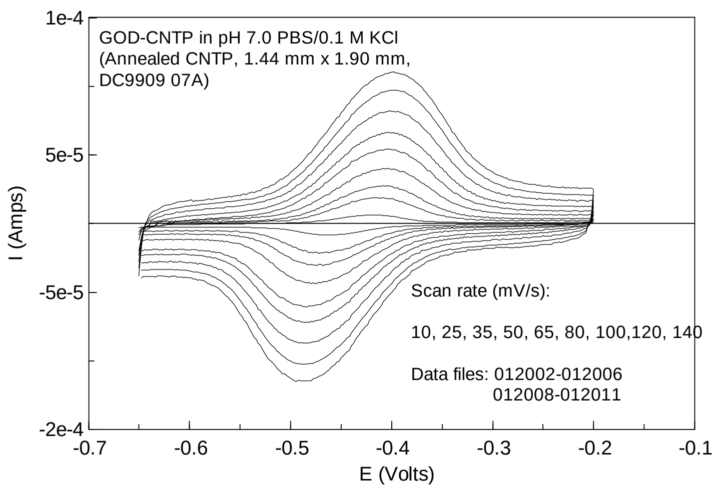
Glucose oxidase
Courtesy: NCBI

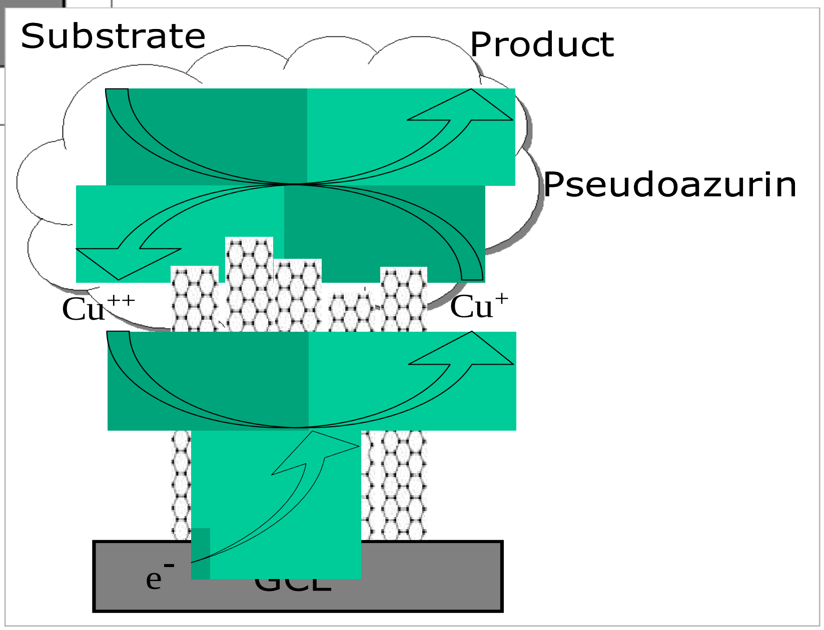
A sphereoidal shape:
6.0 nm x 5.2 nm x 3.7 nm

Amperometric enzyme biosensor - *Direct*



Direct Biosensor
No mediator molecule needed
Oxidation possible
Reduction possible

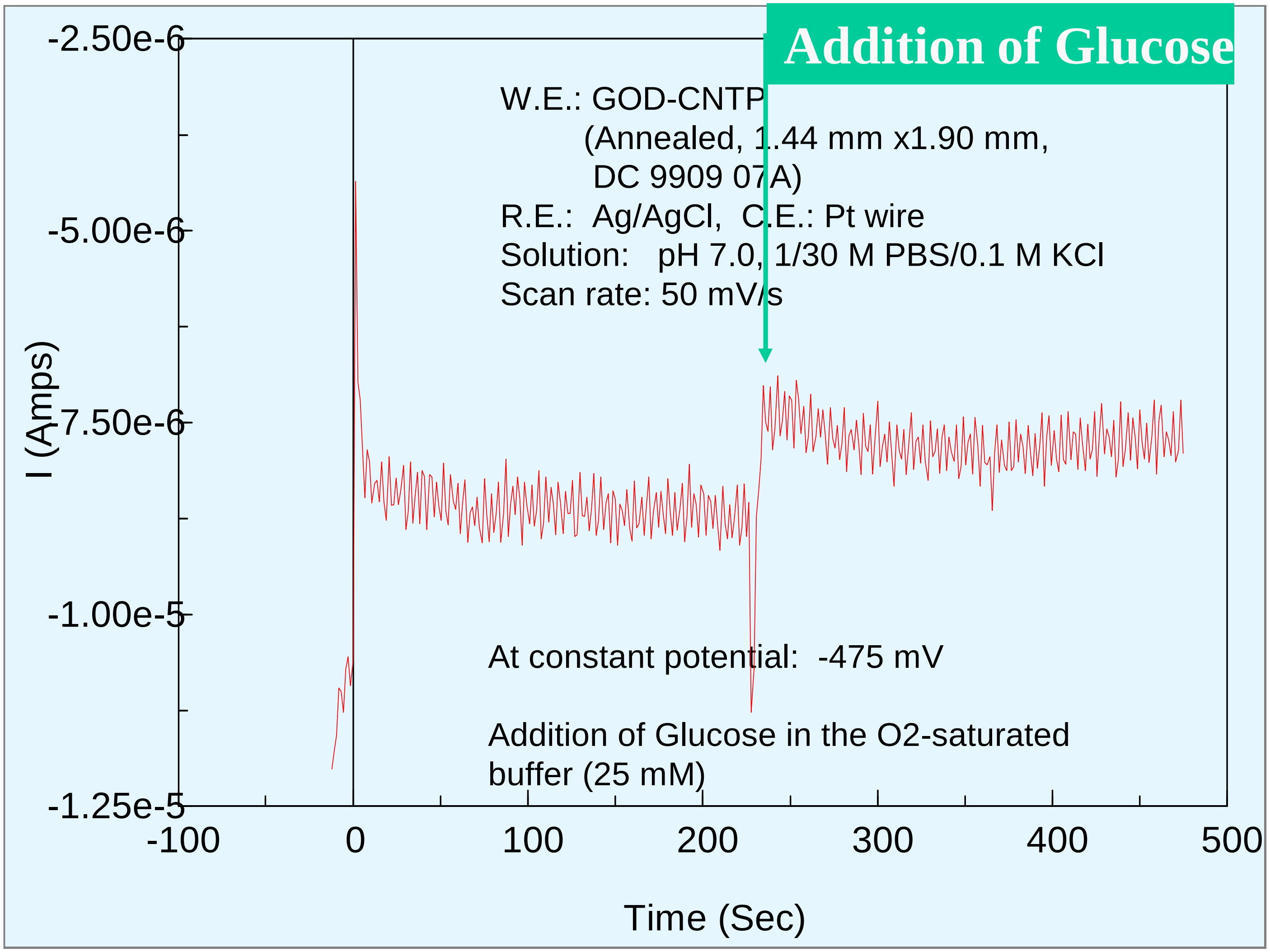




S. Brahim, N. K. Shukla and A.Guiseppi-Elie “Nanobiosensors: Carbon Nanotubes in Bioelectrochemisty” In *Nanotechnology in Biology and Medicine* (**2006**), Tuan Vo-Dinh, Ed.; CRC Press, New York.

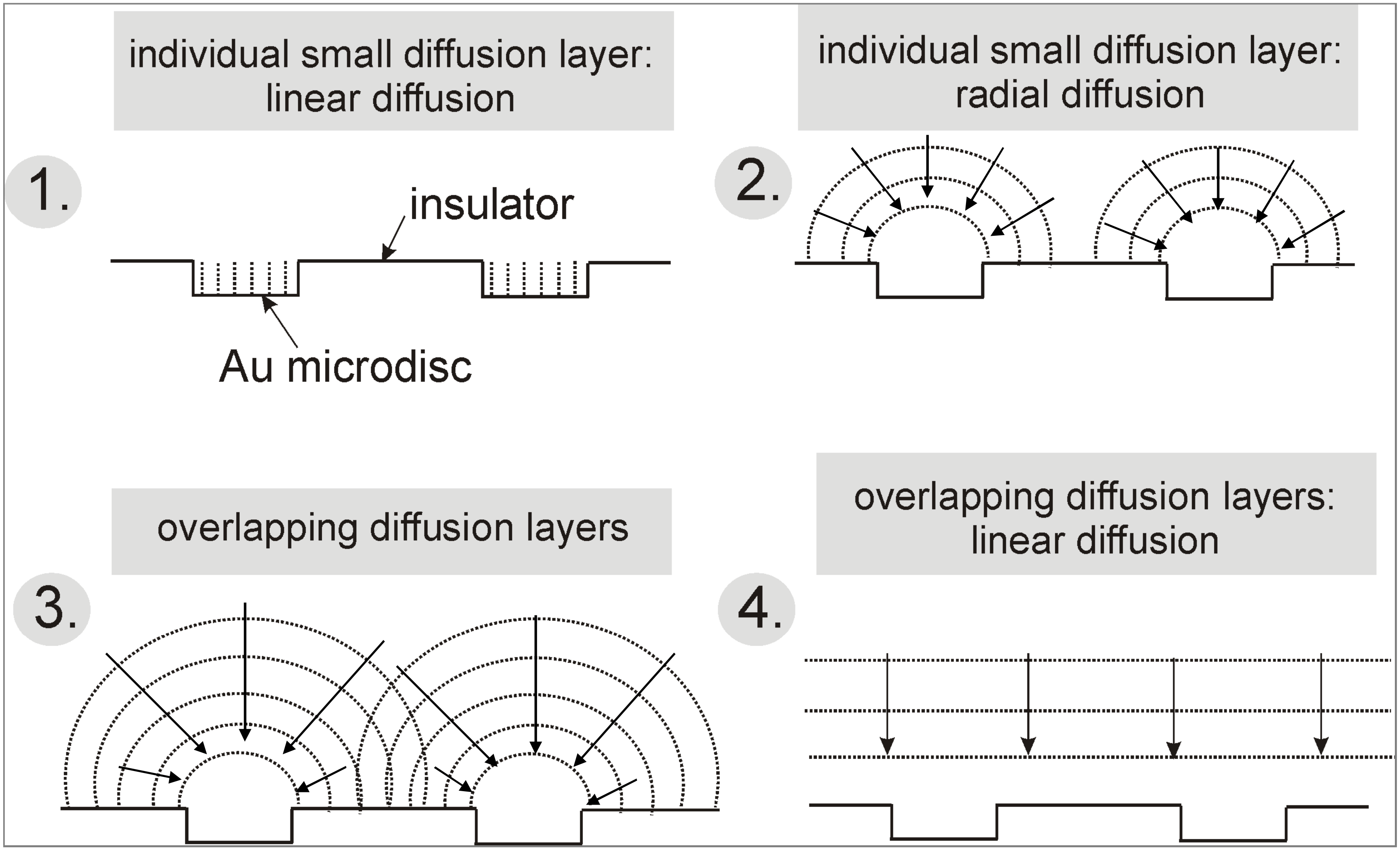
Anthony Guiseppi-Elie, Sean Brahim, Gary Wnek, Ray Baughman, “Carbon Nanotube Modified Electrodes for the Direct Bioelectrochemistry of Pseudoazurin” *NanoBiotechnology* (**2005**), 1(1) 83.

Molecular Bioelectronics
Direct Electronic Control of Enzyme Function



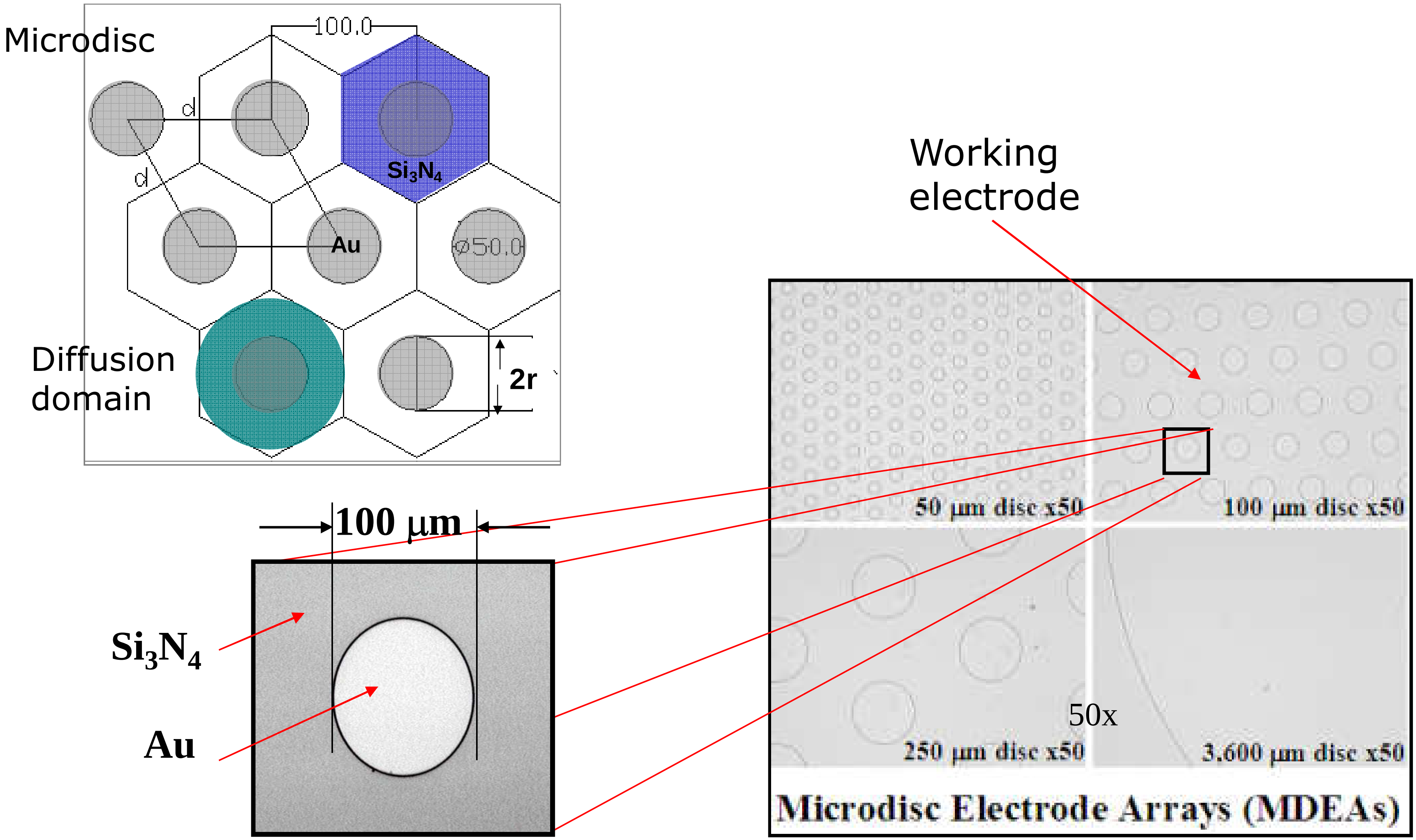
Anthony Guiseppi-Elie, Chenghong Lei and Ray H. Baughman "Direct electron transfer to glucose oxidase using carbon nanotubes" *Nanotechnology* (**2002**) 13 (5) 559-564.

Design of the microdisc electrode array (MDEA)



Abdur Rub Abdur Rahman and Anthony Guiseppi-Elie "Design Considerations in the Development and Application of Microdisc Electrode Arrays (MDEAs) for Implantable Biosensors" *Biomedical Microdevices* (**2009**) 11:701-710.

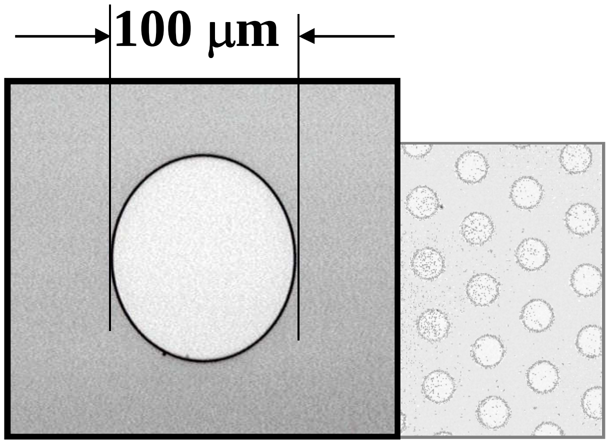
Microdisc electrode arrays for biotranducers

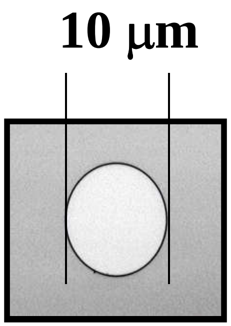


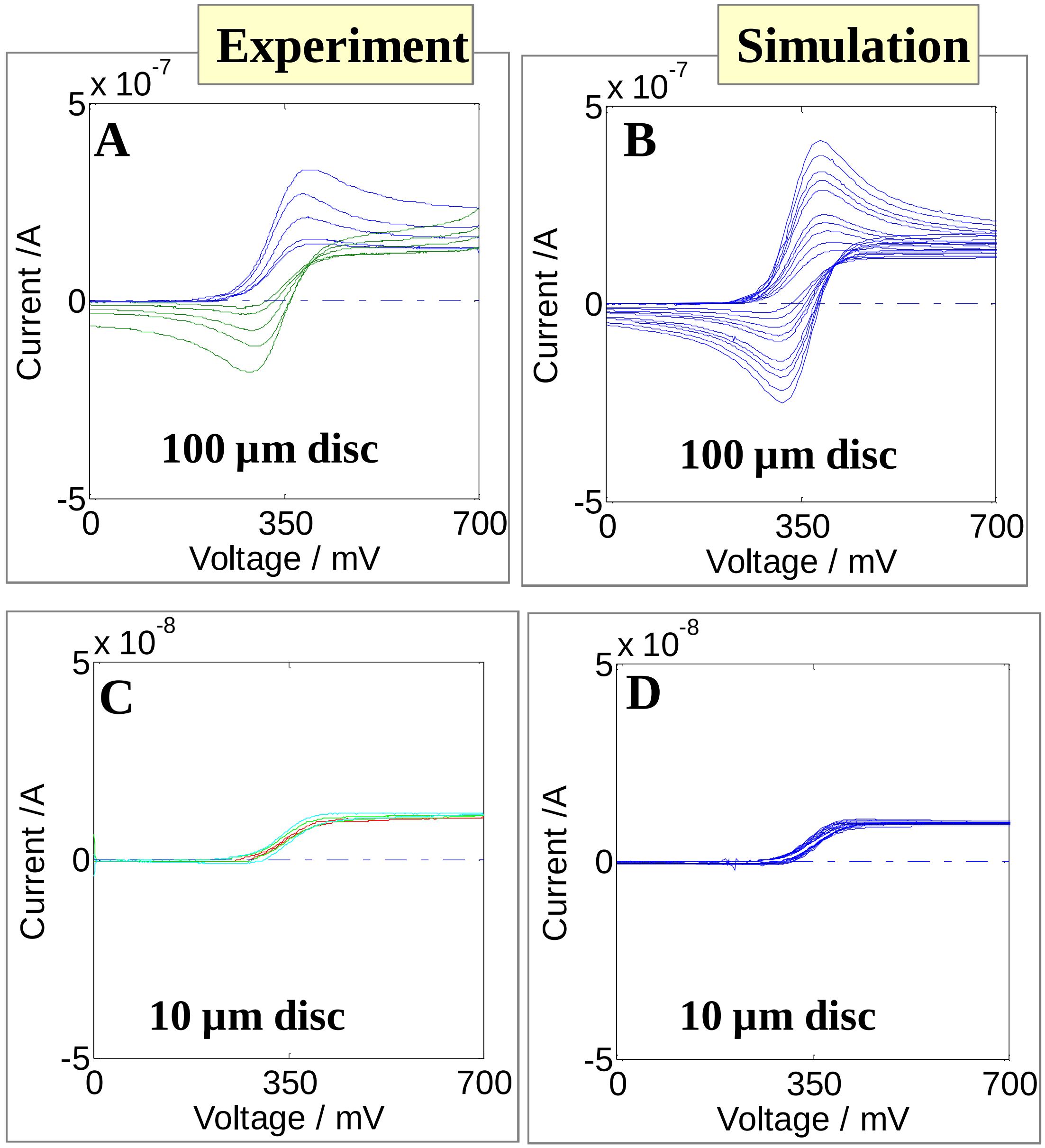
Microdisc Electrode Arrays

A. Guiseppi-Elie, S. Brahim, G. Slaughter and K. R. Ward, "Design of a Subcutaneous Implantable Biochip for Monitoring of Glucose and Lactate", (**2005)** *IEEE Sensor Journal*, 5(3), pp. 345-355.

Multiple scan rate cyclic voltammetry (MSRCV) of microdisc- (A and B = 100 μm) and ultramicro- (C and D = 10 μm) electrodes.

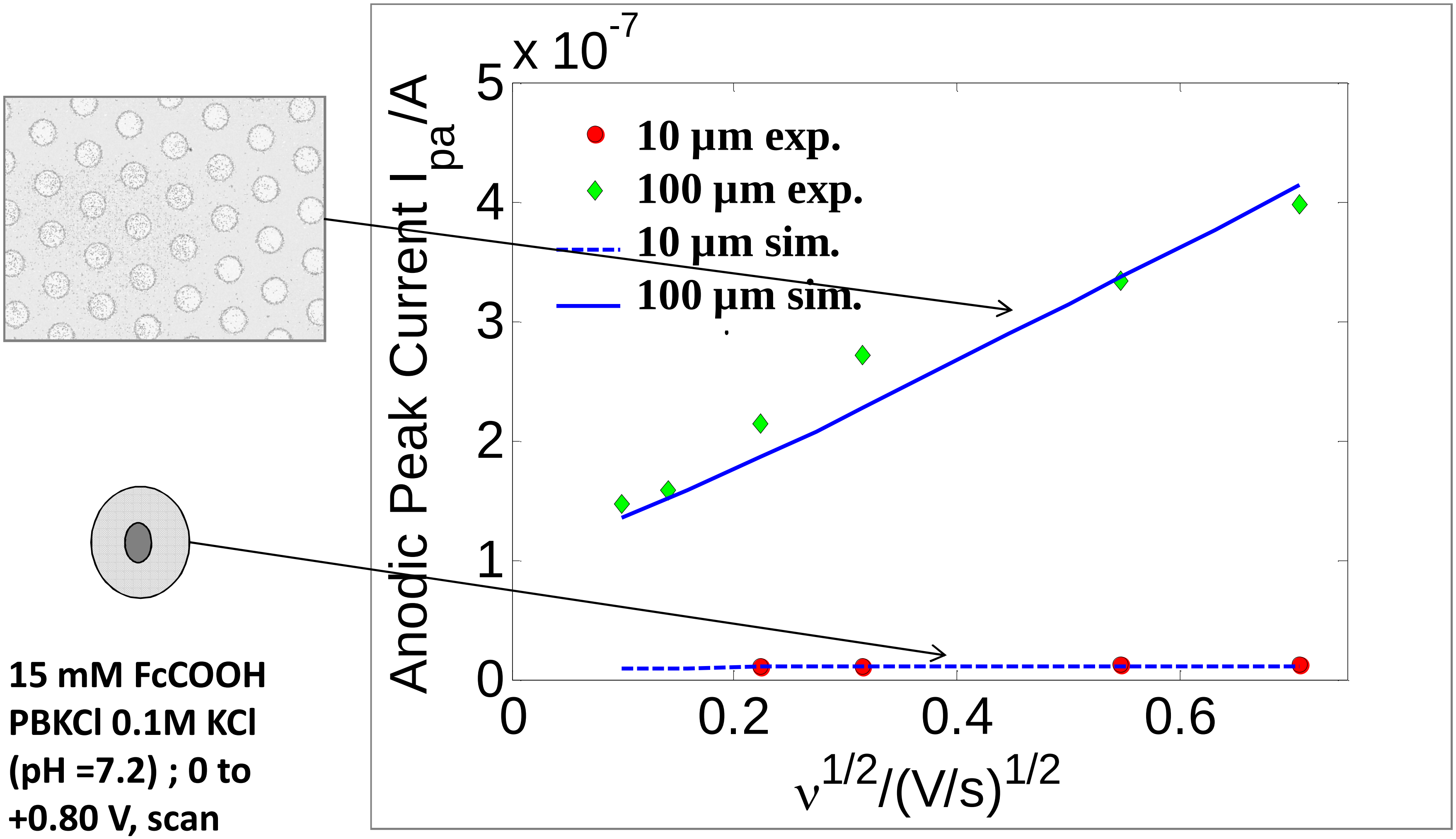






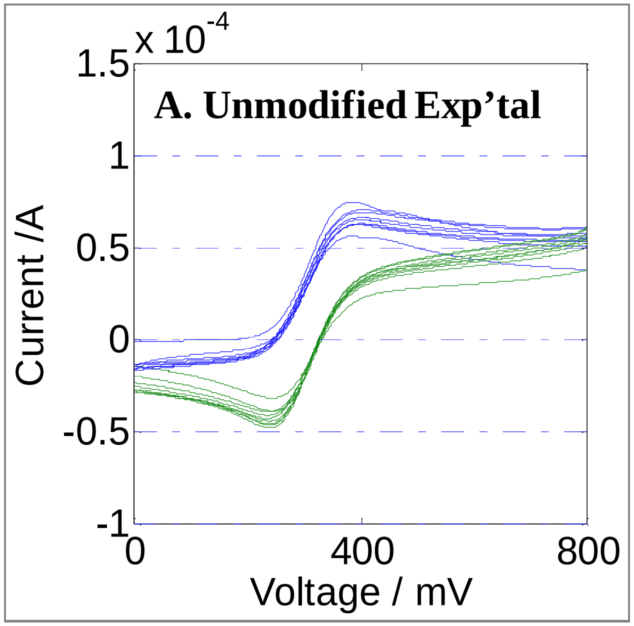
15 mM FcCOOH PBKCl 0.1M KCl (pH =7.2) ; 0 to +0.80 V, scan rates 10 – 100 mV/s.

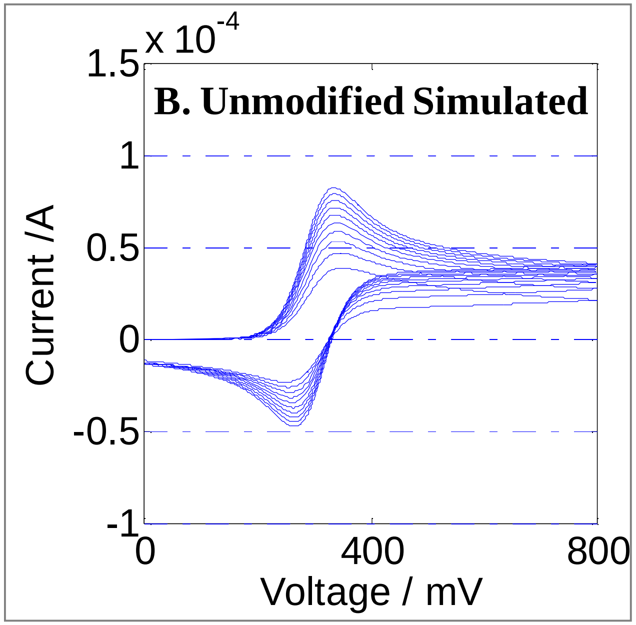
Anodic peak current, Ip_a, as a function of the square root of the voltammetric scan rate for microdisc- (A and B = 100 μm) and ultramicro- (C and D = 10 μm) electrodes.

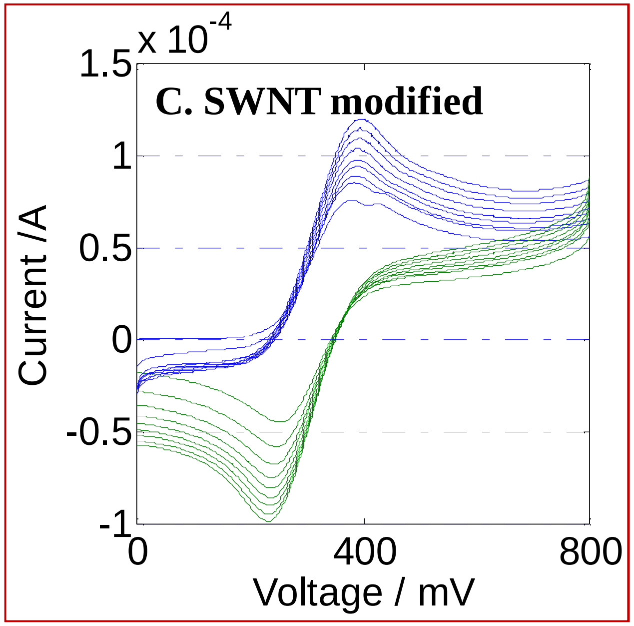


15 mM FcCOOH PBKCl 0.1M KCl (pH =7.2) ; 0 to +0.80 V, scan rates 10 – 100 mV/s.

Multiple scan rate cyclic voltammetry (MSRCV) of microdisc electrodes MDEA 100 Au with adsorbed SWNTs.

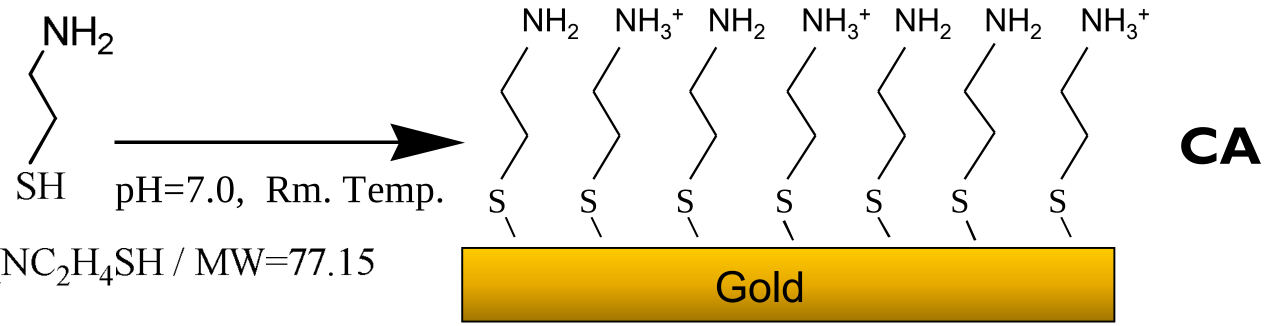






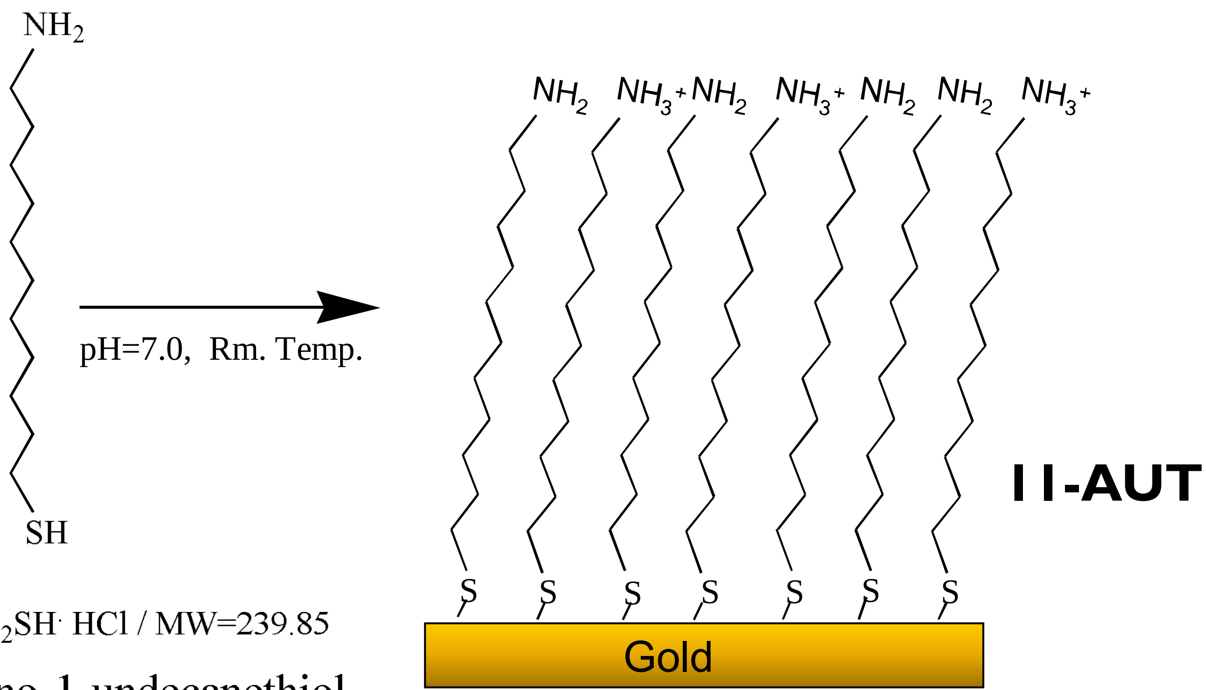
CVs were obtained in 15 mM FcCOOH prepared in phosphate buffered 0.1M KCl solution (pH =7.2) over the range 0 to +0.80 V at scan rates 10 – 100 mV/s at RT.

Cysteamine modified MDEA-Au 100 mm electrode (MDEA-Au|CA) and11-AUT modified MDEA-Au 100 mm electrode (MDEA-Au|11-AUT).



$H_2NC_2H_4SH$ / MW=77.15

2-Aminoethanthiol (Cysteamine)

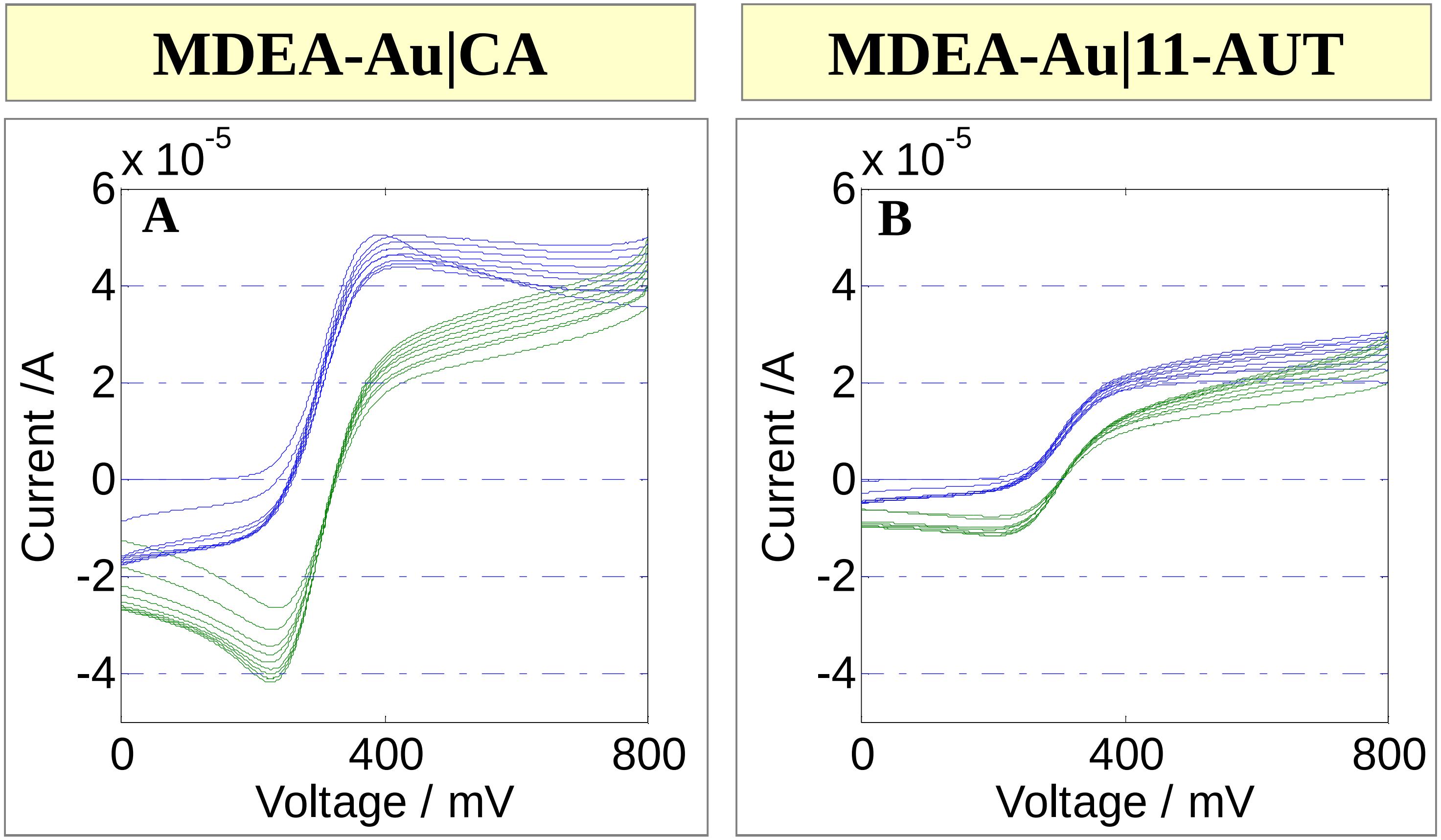


$H_2NC_{11}H_{22}SH \cdot HCl$ / MW=239.85

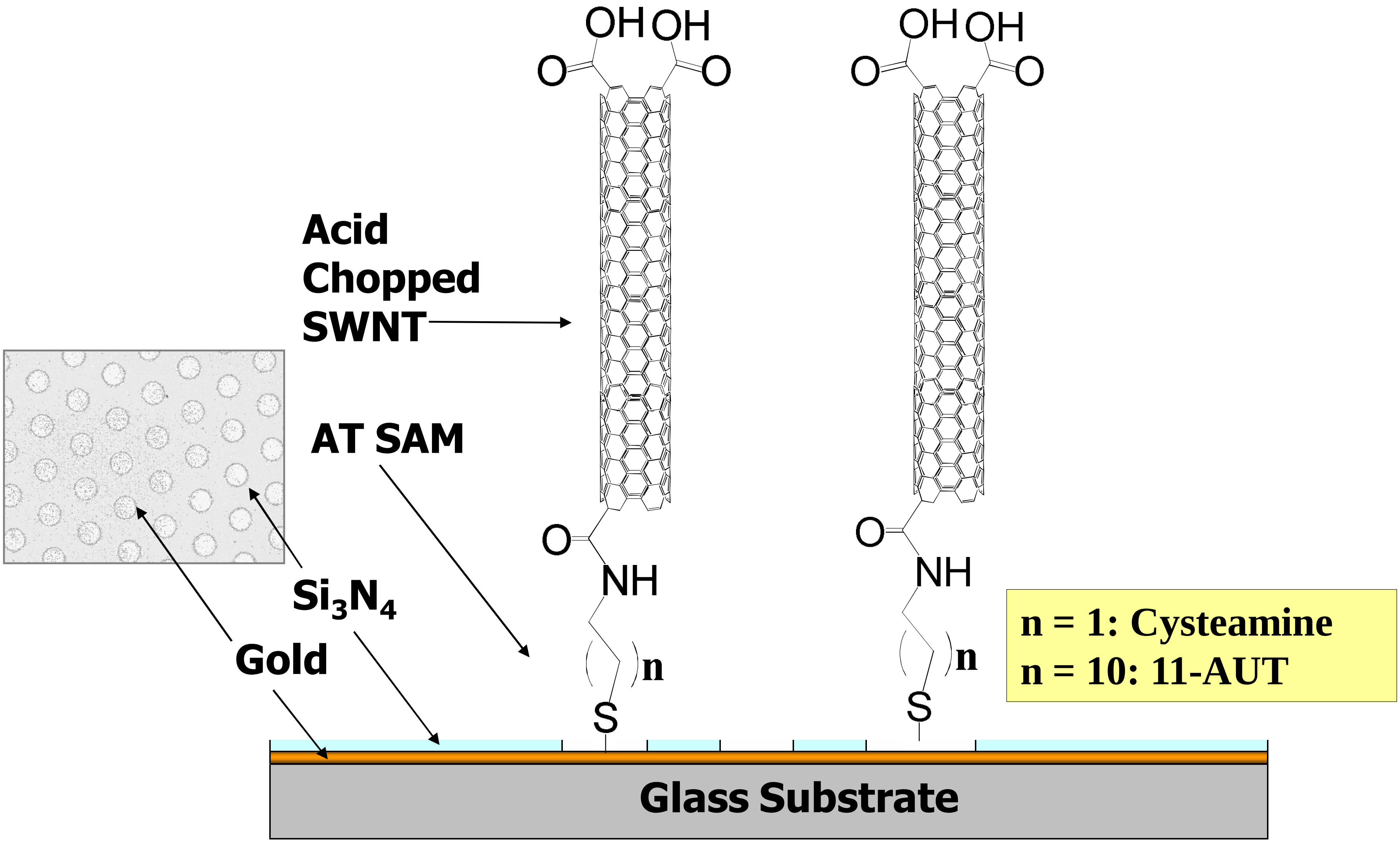
11-Amino-1-undecanethiol, hydrochloride

Gymama E. Slaughter, Erhard Bieberich, Gary E. Wnek, Kenneth J. Wynne and Anthony Guiseppi-Elie "Improving Neuron-to-electrode Surface Attachment (NESA) Via Alkane Thiol Self-assembly: An AC Impedance Study" *Langmuir* (2004), 20(17), 7189-7200.

Multiple scan rate cyclic voltammetry (MSRCV) of (A) Cysteamine modified MDEA-Au 100 µm electrode (MDEA-Au|CA) and (B) 11-AUT modified MDEA-Au 100 µm electrode (MDEA-Au|11-AUT).



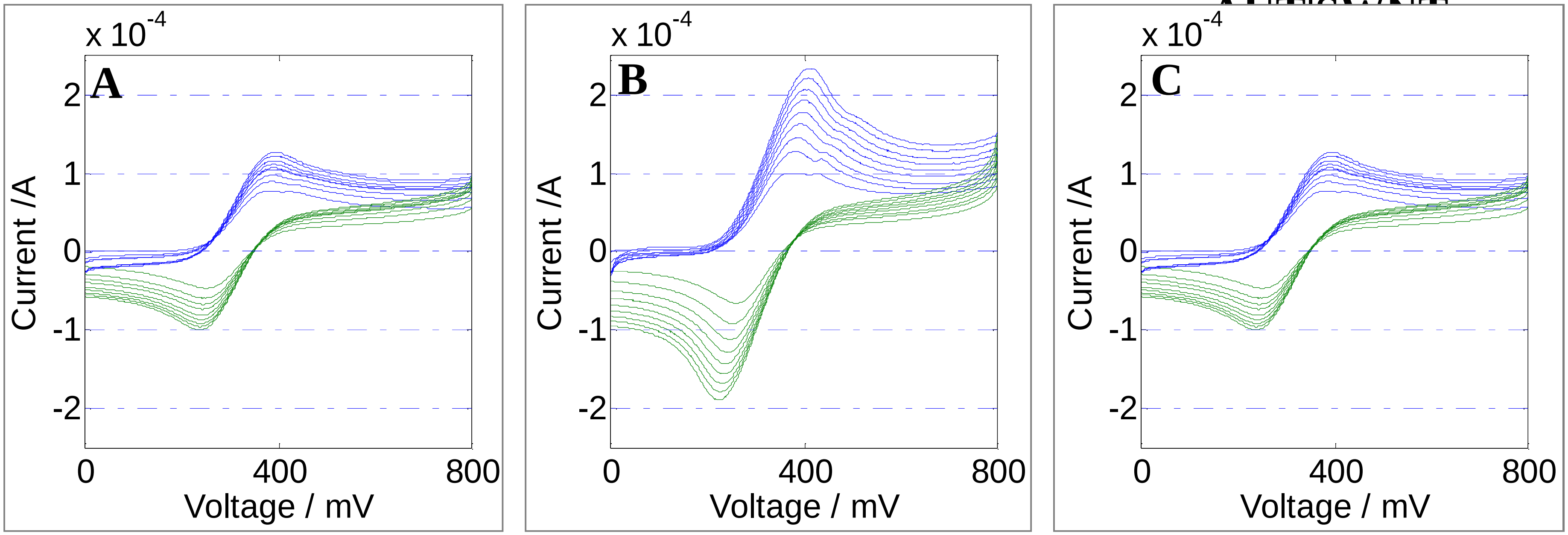
CVs were obtained in 15 mM FcCOOH prepared in phosphate buffered 0.1M KCl solution (pH =7.2) over the range 0 to +0.80 V at scan rates 10 – 100 mV/s at RT.



Anthony Guiseppi-Elie, Abdur Rub Abdur Rahman and Nikhil K. Shukla "SAM-modified Microdisc Electrode Arrays (MDEAs) With Functionalized Carbon Nanotubes" *Elctrochimica Acta* **(2010) 55(14), 4247-4255**

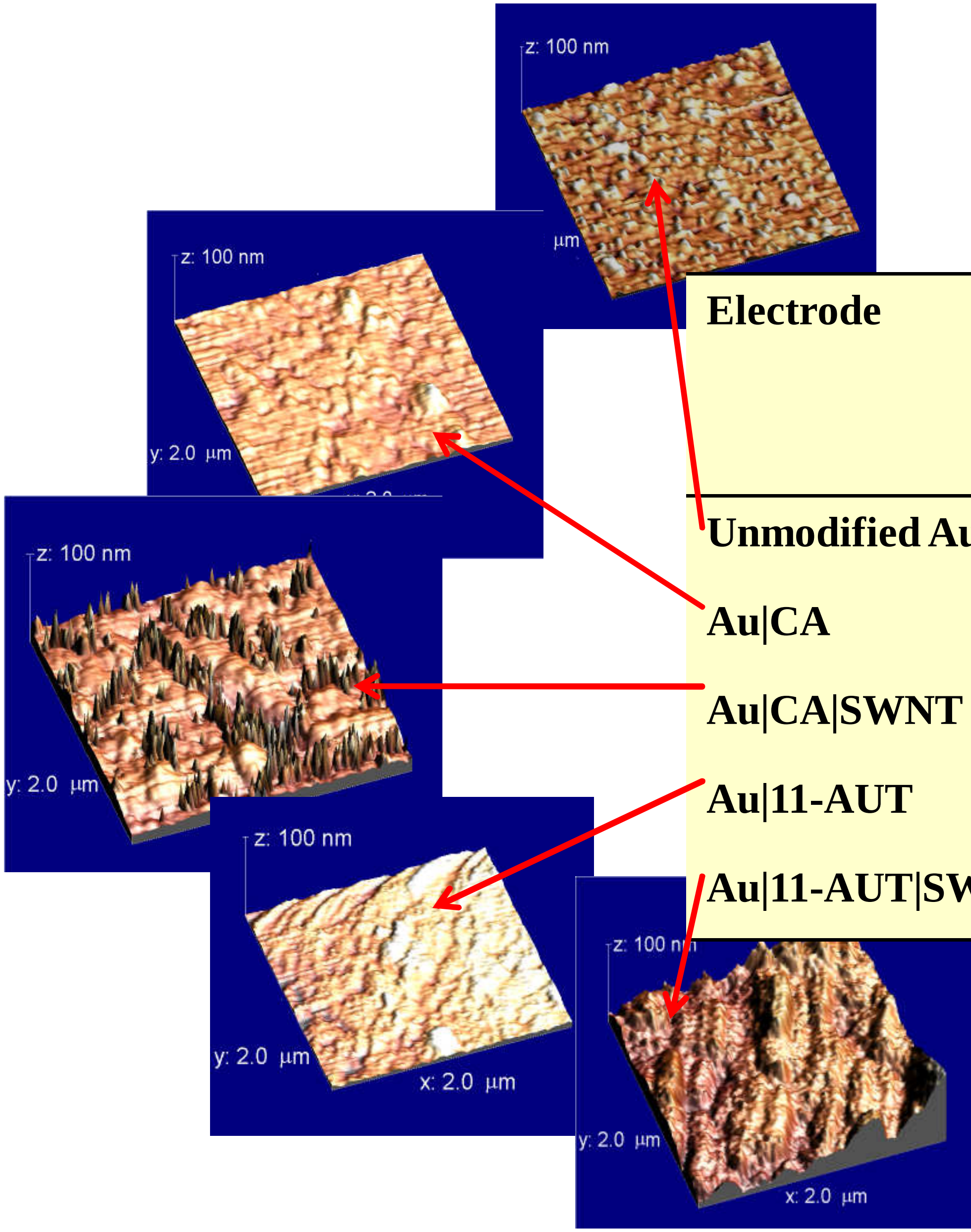
Multiple scan rate cyclic voltammetry (MSRCV) of: (A) Unmodified MDEA-Au 100 μm electrode with adsorbed acid-chopped SWNT, (B) Cysteamine modified MDEA-Au 100 μm electrode conjugated to acid-chopped SWNT (MDEA-Au|CA|SWNT), and (C) 11-AUT modified MDEA-Au 100 μm electrode conjugated to acid-chopped SWNT (MDEA-Au|11-AUT|SWNT).

MDEA-Au|SWNT | **MDEA-Au|CA|SWNT** | **MDEA-Au|11-AUT|SWNT**



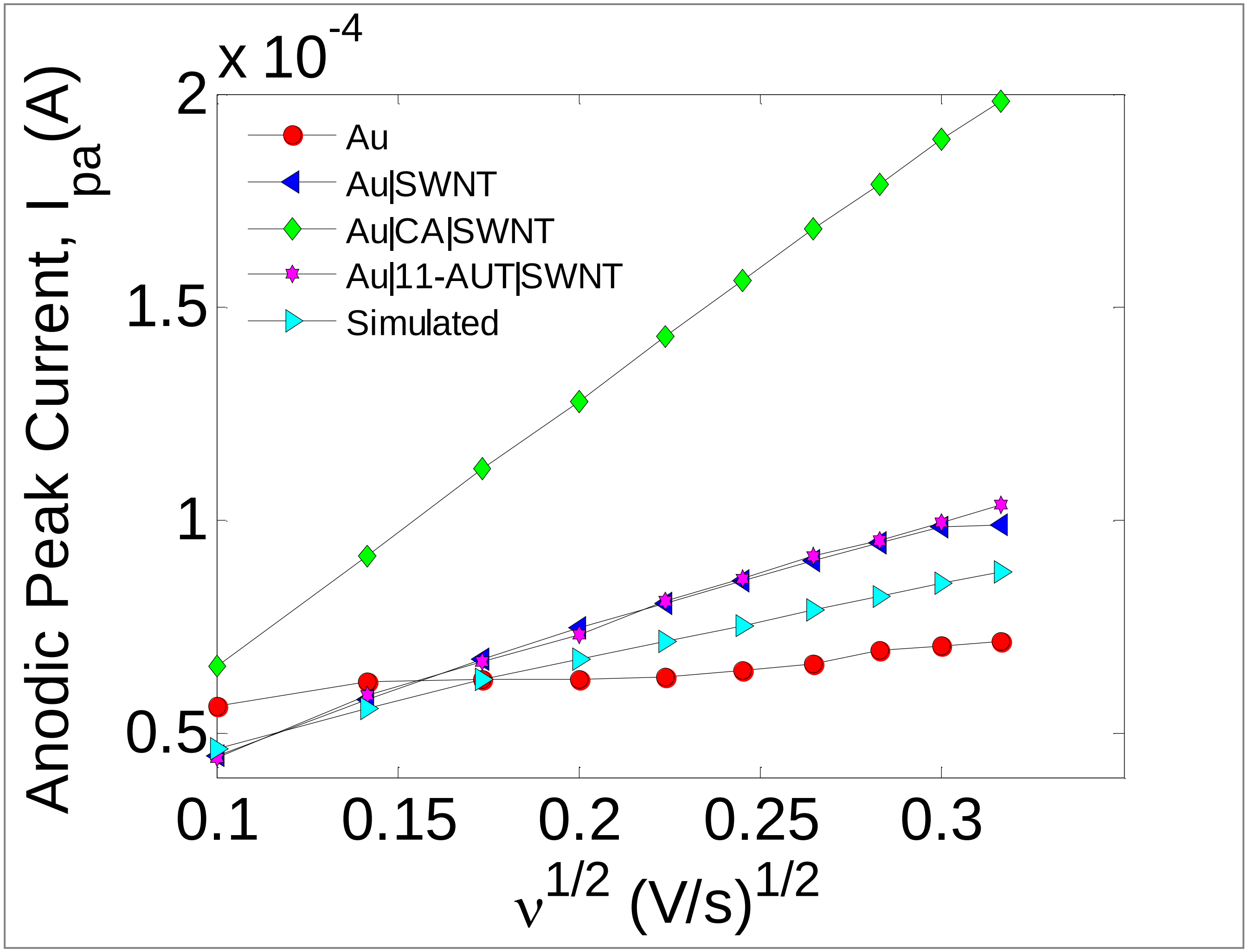
CVs were obtained in 15 mM FcCOOH prepared in phosphate buffered 0.1M KCl solution (pH =7.2) over the range 0 to +0.80 V at scan rates 10 – 100 mV/s at RT.

Tapping mode AFM images



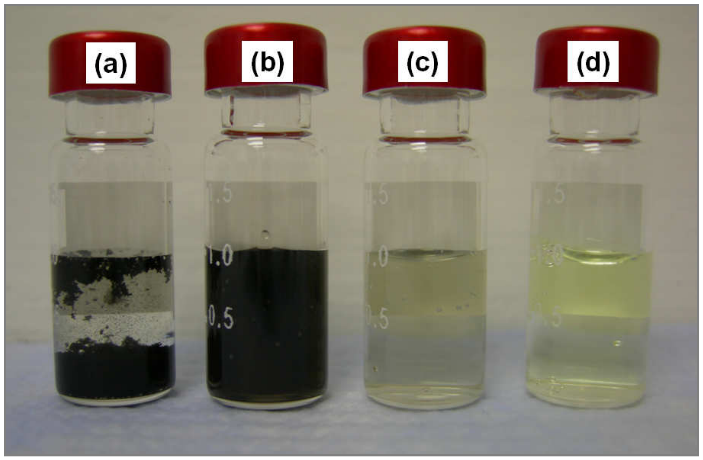
Electrode	grain size /feature hts. (nm)	Rms Roughness (nm)	Average Roughness (nm)
Unmodified Au	5.1 ± 1.7	1.63	6.5
Au|CA	2.8 ± 0.8	0.97	9.7
Au|CA|SWNT	24.0 ± 4.9	6.4	15.2
Au|11-AUT	4.8 ± 2.9	1.8	8.9
Au|11-AUT|SWNT	25.5 ± 6.7	9.5	28.7

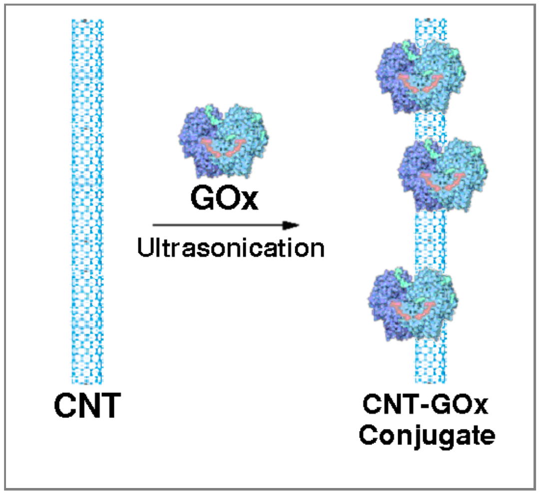
Plots of the anodic peak current, Ip_c, as a function of the square root of the voltammetric scan rate

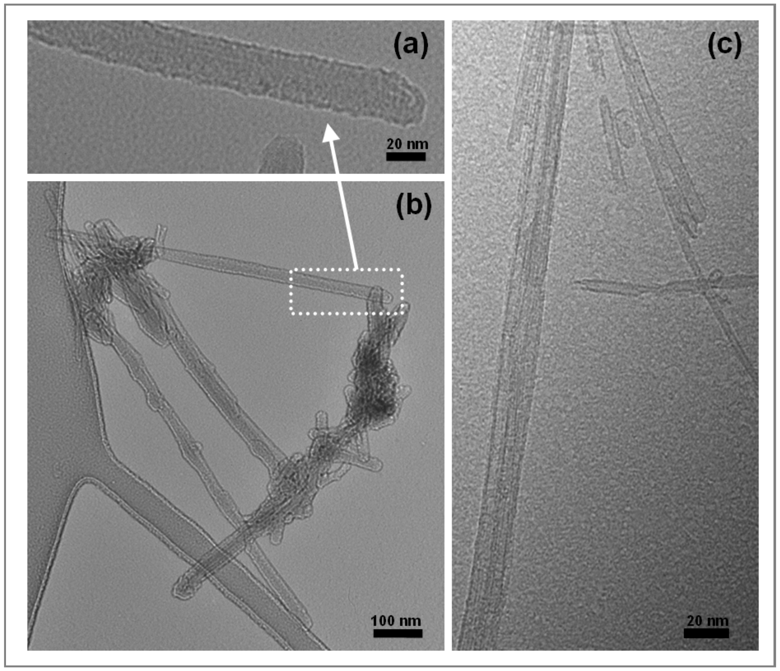


CVs were obtained in 15 mM FcCOOH prepared in phosphate buffered 0.1M KCl solution (pH =7.2) over the range 0 to +0.80 V at scan rates 10 – 100 mV/s at RT.

Supra-molecular complex formation via ultrasonic processing and ultracentrifugation

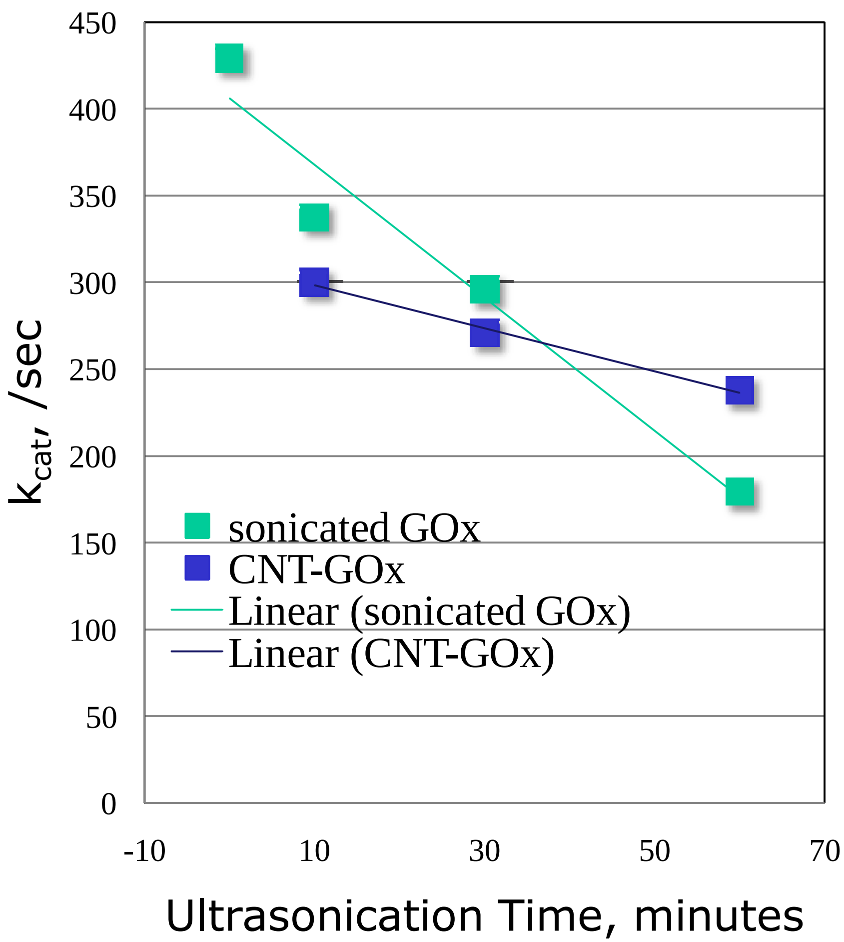


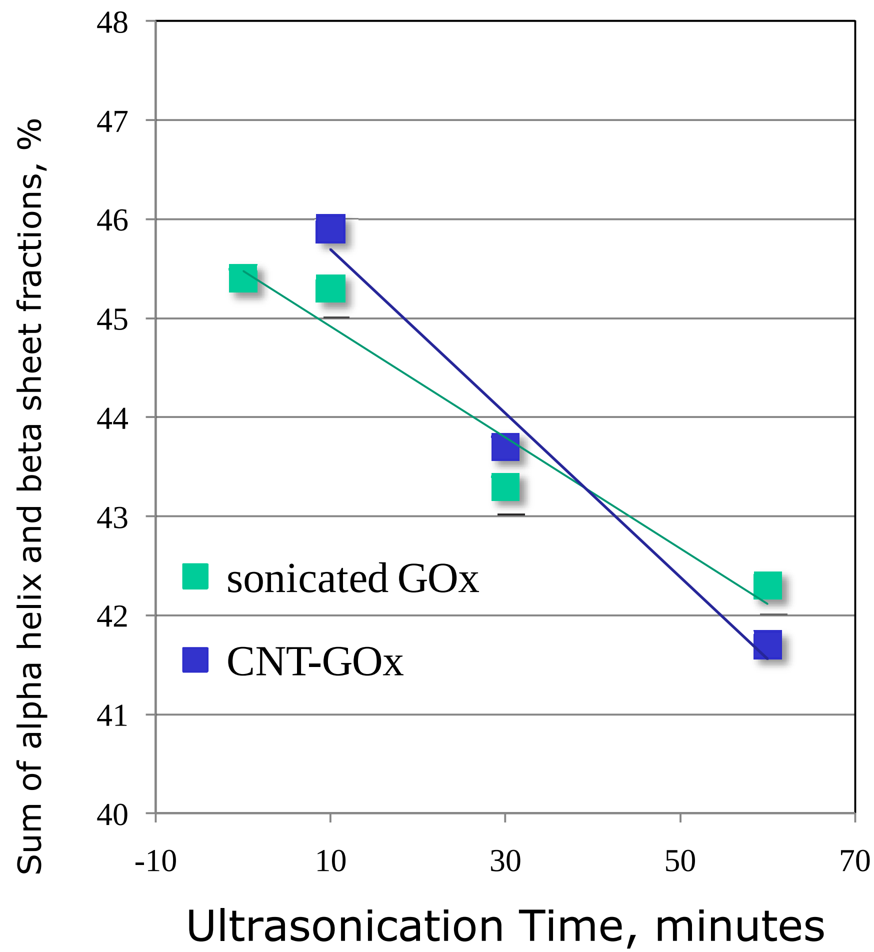




Anthony Guiseppi-Elie*, Sung-Ho Choi, Kurt E. Geckeler, Balakrishnan Sivaraman, and Robert A. Latour "Ultrasonic Processing of Single-Walled Carbon Nanotube-Glucose Oxidase Conjugates: Interrelation of Bioactivity and Structure" *NanoBiotechnology (***2008),** 4, 9-17.

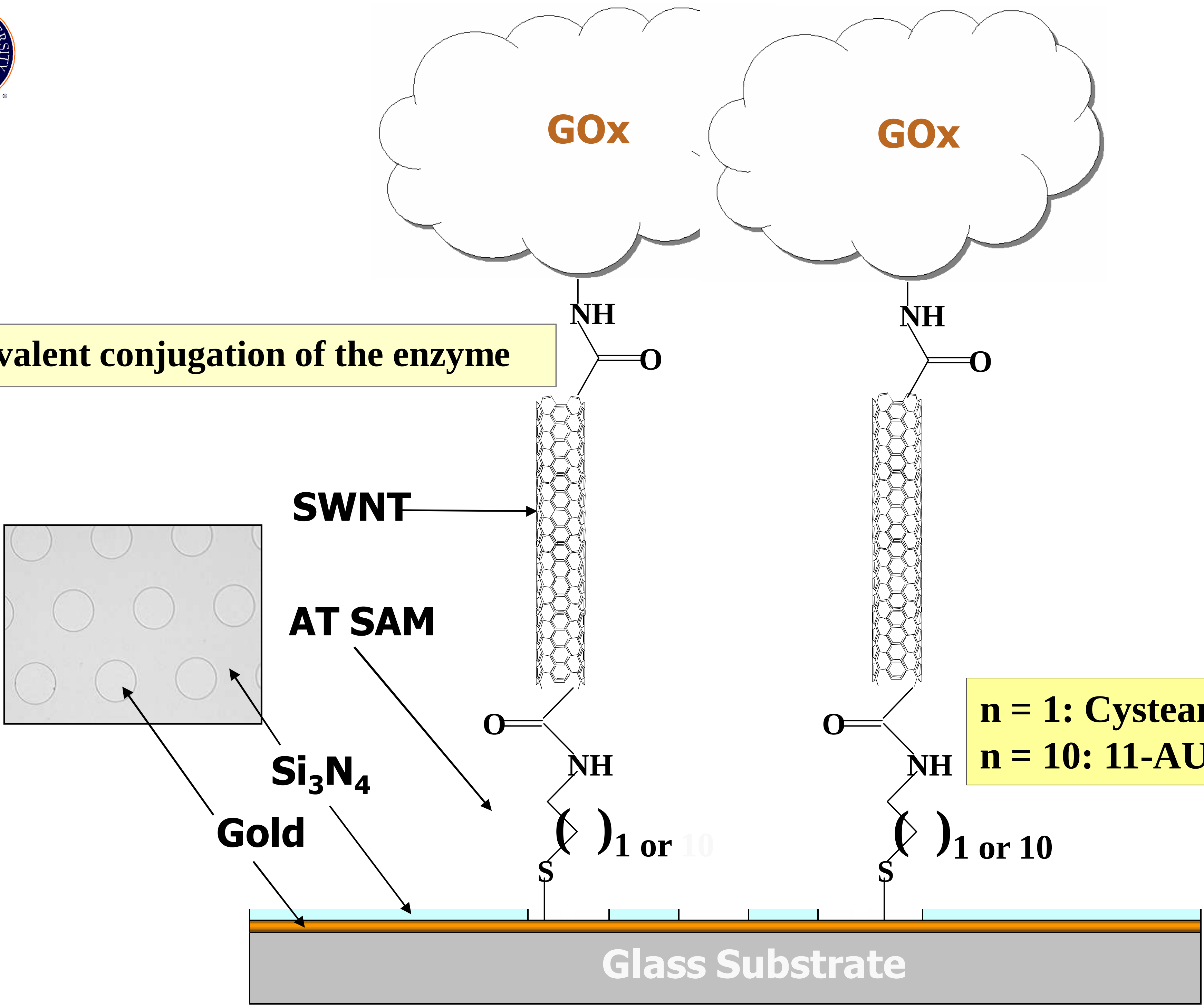
Kinetic activity and structural changes following ultrasonication of GOx and CNT-GOx





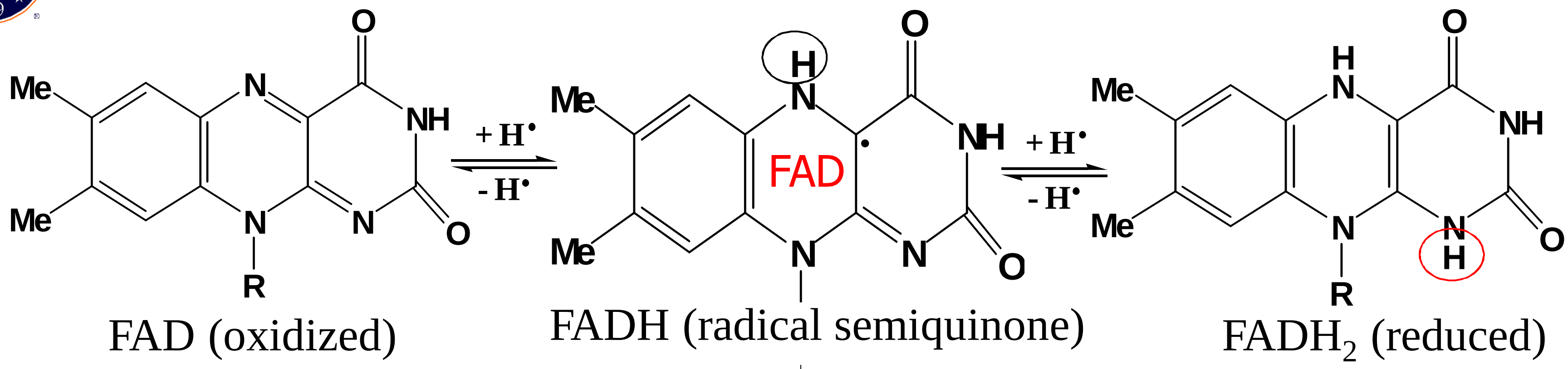
Anthony Guiseppi-Elie, Sung-Ho Choi and Kurt E. Geckeler "Ultrasonic Processing of Enzymes: Effect on Enzymatic Activity of Glucose Oxidase" *Journal of Molecular Catalysis B: Enzymatic* (**2009**) 58, 118–123.

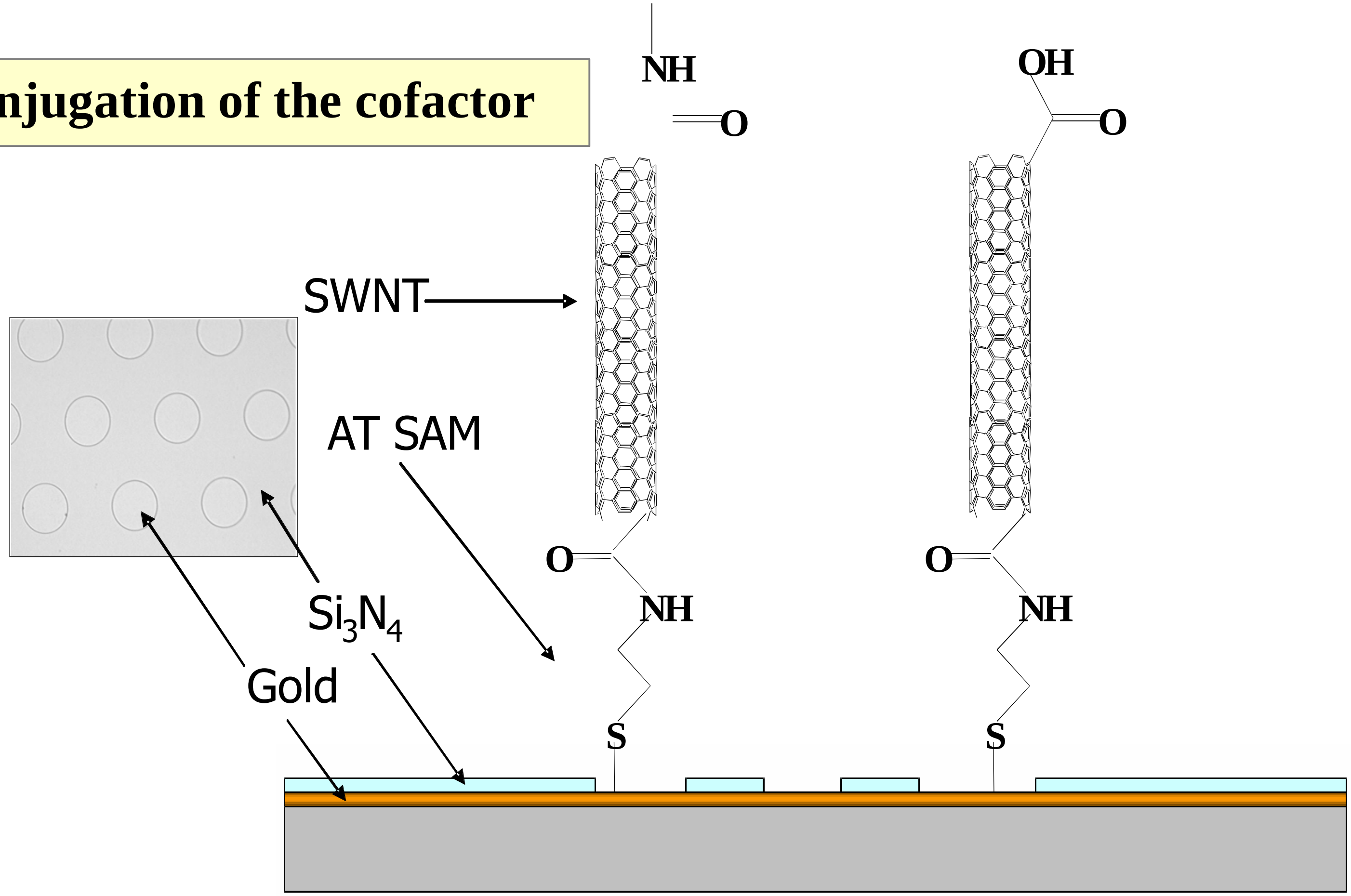
Covalent conjugation of the enzyme



n = 1: Cysteamine
n = 10: 11-AUT

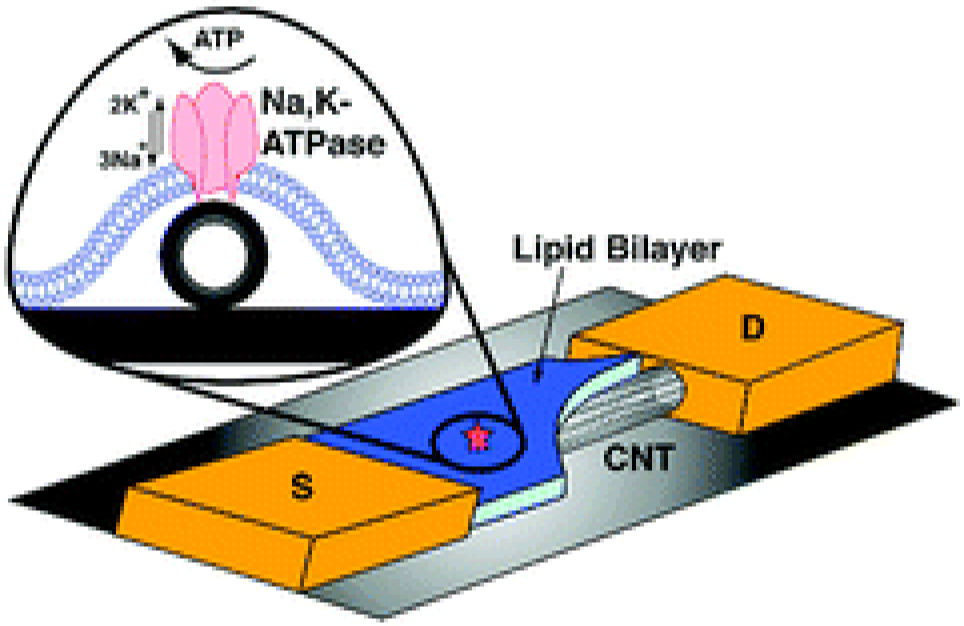
Covalent conjugation of the cofactor

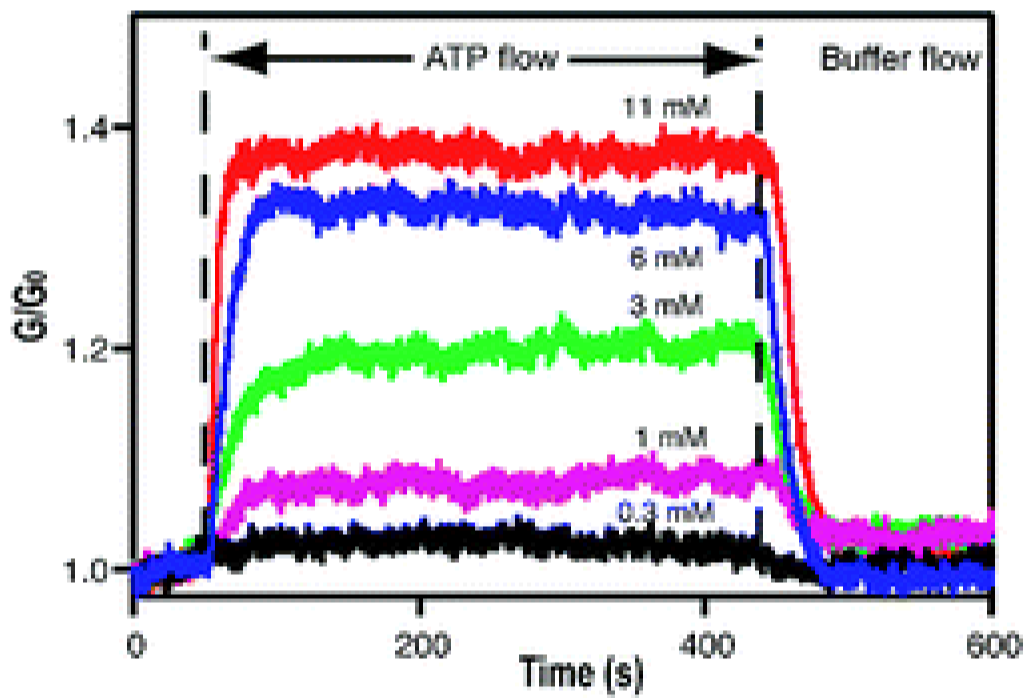




Biomolecular Recognition Events Gate SWNT FinFET

Vg controlled by Na^+/K^+ pump

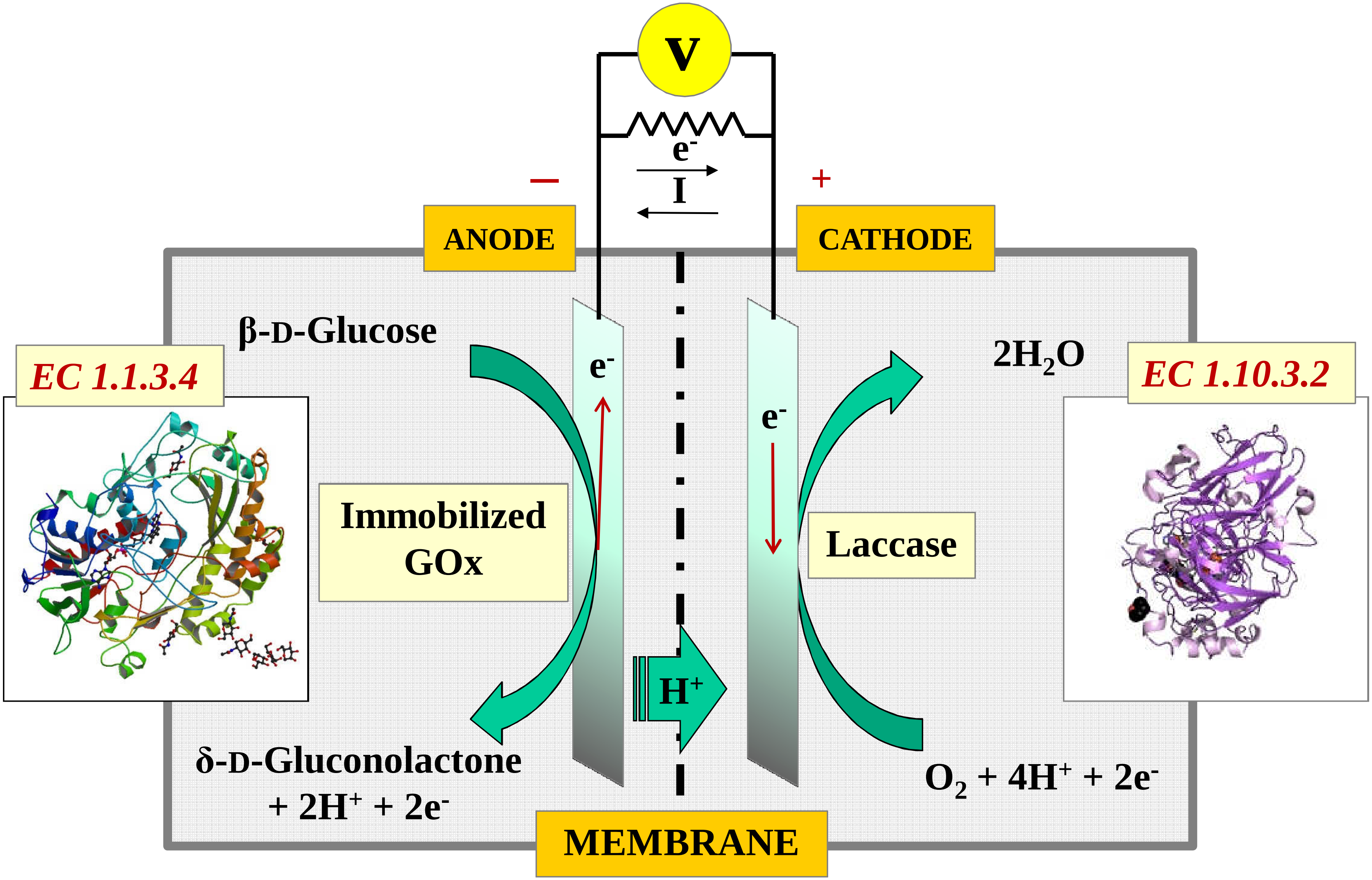




- **Proof of concept for other ion transport proteins to couple to single walled carbon nanotubes for logic gates**

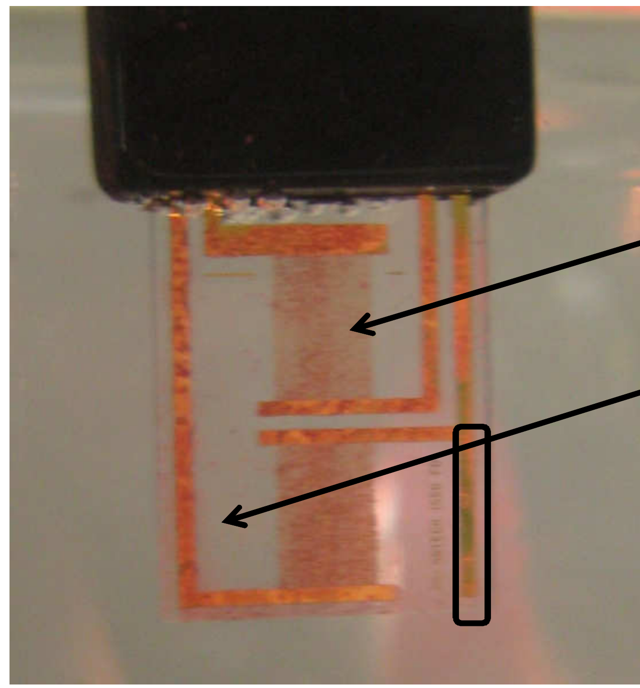
S-C J Huang *et al*, *Nano Lett.*, (**2010**), 10 (5), 1812–1816

The Prototypical Enzyme Biofuel Cell



Microbial Biofuel Research

Direct electron transfer between bacterial biofilms and microfabricated electrodes
Lenny Tender, Naval Research Laboratory
Anthony Guiseppi-Elie, Clemson University



Grand Challenge Problems

The Bio-materials Interface: Enabling chronically implantable bioanalytical devices - **Bionics**

Bioelectronics: Enabling direct electronic communication between electronic solid state devices and "the biology" **-- More than Moore**

Grand Challenge Metrology Opportunities

The Bio-materials Interface - BIONICS:

1. Standard Reference Biomaterials
    - Genomic testing - Total RNA, m-RNA
    - Biocompatibility Testing - Biomaterials
2. Standard Methods for the Quantitative Assessment of Biocompatibility
    - Acute tissue response
    - Chronic tissue response

Grand Challenge Opportunities

Bioelectronics -- More than Moore in biology:

Power

- external sources; internal sources, management

Bioactive and smart materials for "the Biology"

Integration science

New manufacturing paradigms

- bottom up; self assembly; redundancy; parallelism

New manufacturing paradigms

Customer as part of the product

- neuromorphic; cognitive systems; adaptive; conforming

Summary

- "Bio-smart" materials by design; combining molecular biorecognition (enzymes), biocompatibility (PEG and MPC), interference shielding (PPy) and redox mediation (M) within p(HEMA)-based hydrogel
- Polymers are non-cytotoxic and support excellent viability and restricted proliferation
- *In vitro* measures of biocompatibility are highly correlated with extent of hydration.
- Biotransducer design using E'Cell-on-a-Chip (ECC) microlithographically fabricated microdisc arrays
- Systems integration and form-factor
- Demonstrated physiologic status monitoring

Thank you!
Merci!