Convergence: Impacting Engineering Curricula, Patient Care & Implantable Microanalytical Systems

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url=https://www.biochips.org

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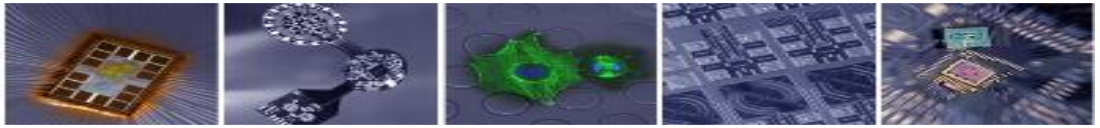
AMERICAN INTERNATIONAL INSTITUTE OF MEDICAL SCIENCES, ENGINEERING & INNOVATION

AIIMSEI.org

TECHNISCHE UNIVERSITÄT DRESDEN

Institute of Materials Science
Chair of Materials Science and Nanotechnology

NanoSeminar Series | TU-Dresden | May 23rd, 2024



C3B®

Improving Human Health
Through Nano-BioTechnology:
Research in Bioelectronics, Biosensors and Biochips (C3B®)

Disclosures

SYNC.MD

Collect, store and share health information securely

Improvia Health

Functional neurostimulation for improved health outcomes

ABTECH

Diagnostic biosensors for the management of hemorrhagic trauma

CHAPMAN UNIVERSITY

UNICITI
INTERNATIONAL EDUCATION HUB

CLARK ATLANTA UNIVERSITY

UNITED Scientific Group
A non-profit organization

MDPI

Thank you!

TEES | Texas A&M Engineering Experiment Station

PROTECT - SUSTAIN

CLEMSON UNIVERSITY SOUTH CAROLINA 1889

C3B®

UNITED STATES ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

My High-level Motivations

Grand Challenge Problems

Organic Electronics: Enabling/improving biomedical devices using organic materials – **More of Moore** – *for biology*

Bioelectronics: Enabling direct electronic communication between solid state devices and the biology – **More than Moore** – *the abo-bio interface.*

My Guiding Axiom

Grand Challenge Problems

ENGINEERING: “You cannot control that which you cannot measure.”

BIOMEDICAL SCIENCES: “Biological systems are far too complicated to control.”

Outline

Convergence in the Academy

EnMed and Liberal Arts-Engineering

Convergence in Research

- **Electroconductive Hydrogels**

  Biosensors and Bioelectronics

- **Microanalytical Systems**

  Hemorrhagic Trauma and Allotransplantation

- **ElectOMICS**

  Polymers, Fields, and Genes

Summary

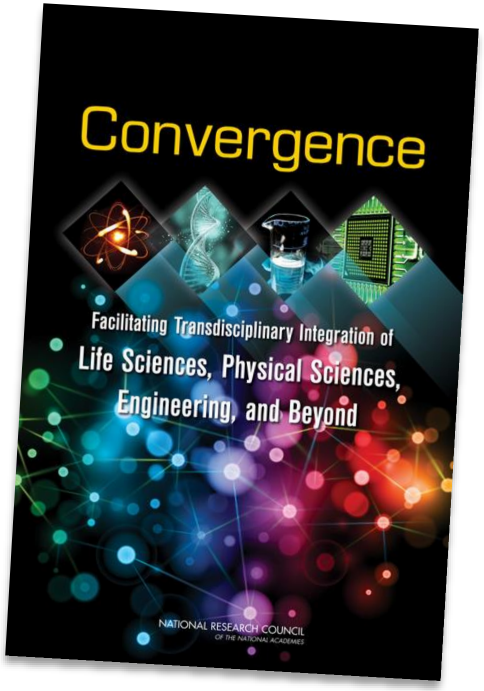
Convergence

... the integration of historically distinct fields or disciplines that leads to the emergence of a new and unified whole to address need and create transformative impact.

Marcia K. McNutt

Dan Mote, Jr.,

Victor J. Dzau



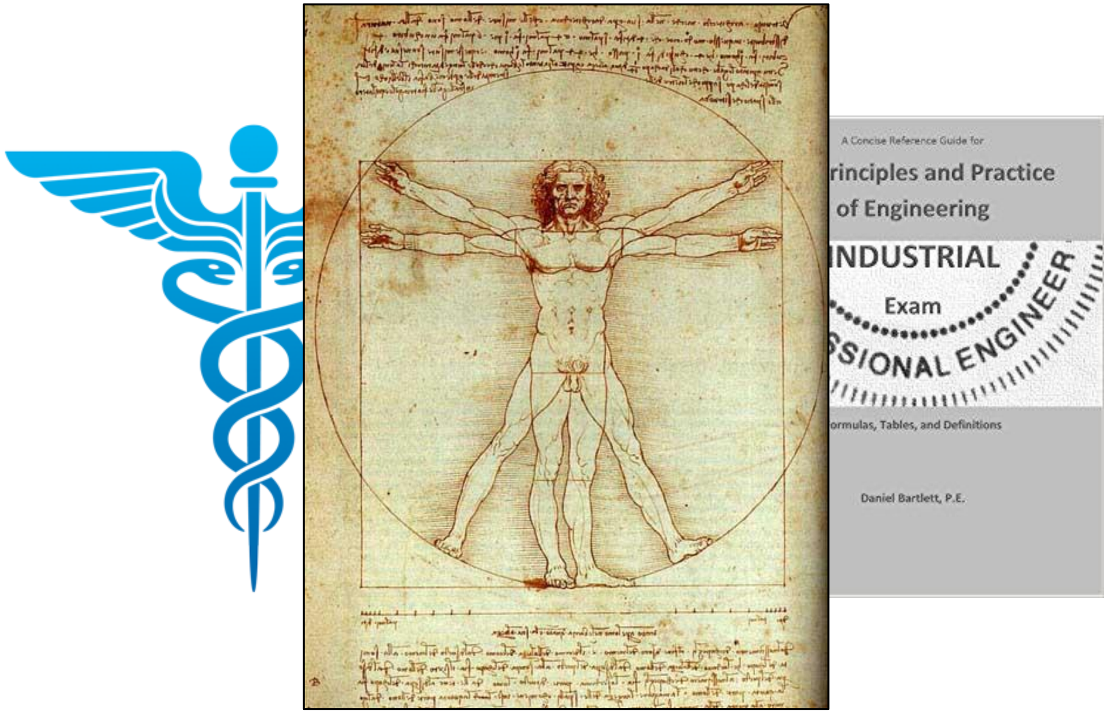
Convergence: Facilitating Transdisciplinary Integration of Life Sciences, Physical Sciences, Engineering, and Beyond (**2014**)

Committee on Key Challenge Areas for Convergence and Health; Board on Life Sciences; Division on Earth and Life Studies; National Research Council.

Washington (DC): National Academies Press (US); 2014 Jun 16.ISBN-13: 978-0-309-30151-0ISBN-10: 0-309-30151-3

Convergence: Engineering-Medicine

- Defining “Transformative Impact” – Example of Biomedical Engineering.
- Create a “Biomedical Engineer”.



The Whitaker Foundation

710 million USD Expended on BME

- 1,500 faculty grants awarded
- 400 graduate fellowships
- 75 BME departments
- 13 BME buildings built

Katona PG. Biomedical engineering and the Whitaker foundation: a thirty-year partnership. *Ann Biomed Eng.* **2006** Jun;34(6):904-16. doi: 10.1007/s10439-006-9087-7.

Convergence

… the integration of historically distinct fields or disciplines that leads to the emergence of a new and unified whole to address need and create transformative impact.

Convergence: Engineering-Medicine

Convergence: Liberal Arts-Engineering

ENMED
ENGINEERING & MEDICINE

EnMed is an innovative engineering medical school option created by Texas A&M University

Program Objectives

new kind of doctor who will create transformational technology for health care.

Produce a

Physicianeer

EnMed Working Group

ENMED
ENGINEERING & MEDICINE

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John E. Hurtado
Assoc. Dean, Academic Affairs

Timothy Jacobs
Director, Interdisciplinary Engineering Programs

Victor Ugaz
TEES Director of Research Development

ENMED PROGRAM OBTAINS LCME APPROVAL

- April 2018
- Track approved for the HM Campus
- Inaugural class to matriculate in July 2019

LCME®
LIAISON COMMITTEE ON MEDICAL EDUCATION
www.lcme.org

NEW PARALLEL CURRICULUM (TRACK) NOTIFICATION FORM

ENGINEERING TO MEDICINE TRACK (ENMED)
TEXAS A&M COLLEGE OF MEDICINE
TEXAS A&M COLLEGE OF ENGINEERING

Please use this form to notify the Liaison Committee on Medical Education (LCME) of the creation of a new parallel curriculum (track). See white paper defining a parallel curriculum on the LCME website for background information (http://lcme.org/publications/#White-Papers).

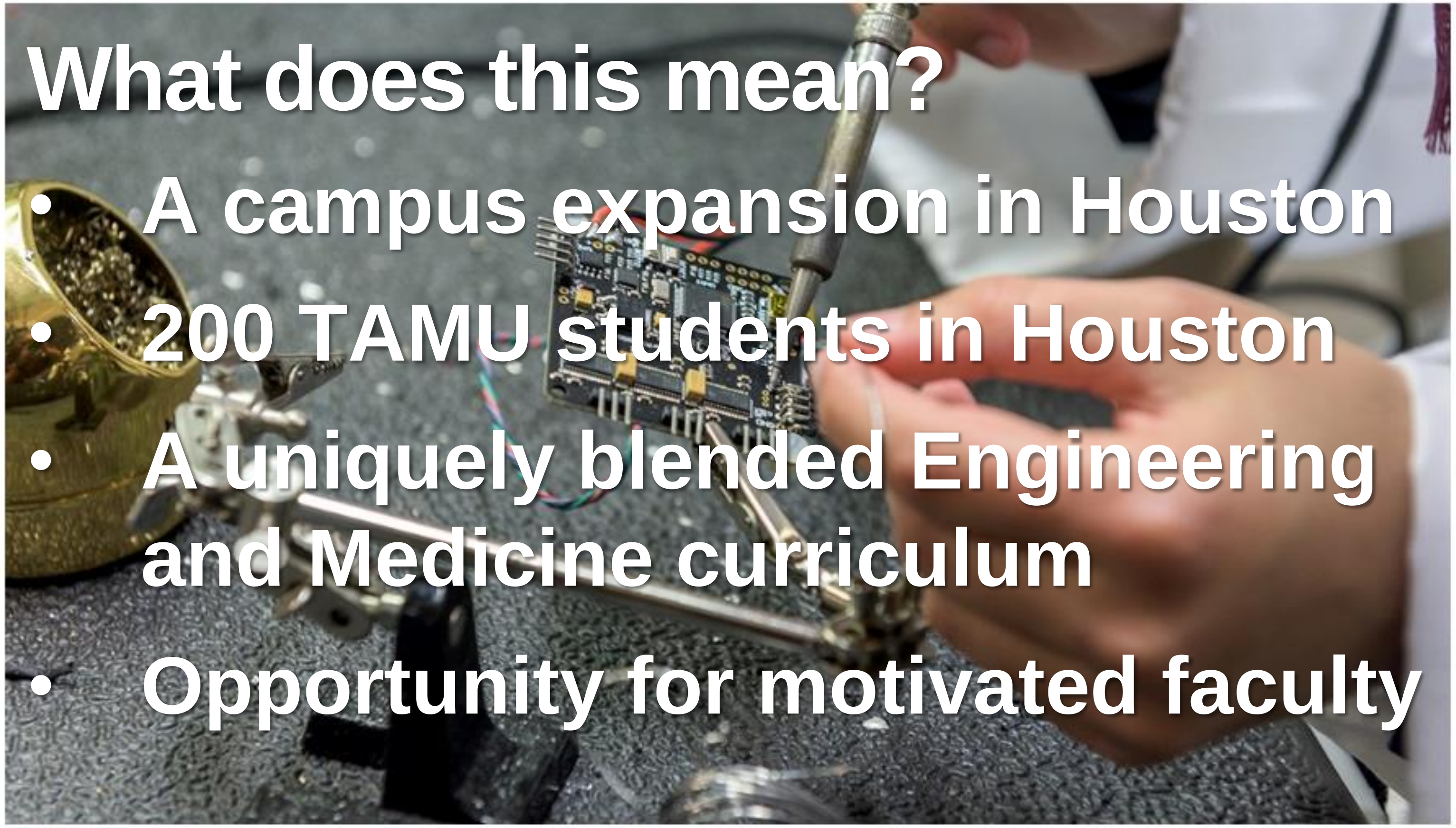
SUBMISSION INSTRUCTIONS

Please submit the completed notification form as a PDF to lcmesubmissions@aamc.org. Notification forms must be submitted by **December 1st, one year before the expected implementation.**

Date of Submission	December 1, 2017
School Name	Texas A&M University College of Medicine
Date or academic year change will become effective	Summer 2019
Name and title of the program official submitting the information	Carrie Byington, MD Dean of Medicine

LCME* Approval

ENMED
ENGINEERING & MEDICINE



What does this mean?

- A campus expansion in Houston
- 200 TAMU students in Houston
- A uniquely blended Engineering and Medicine curriculum
- Opportunity for motivated faculty

ENMED PROGRAM OBTAINS LCME APPROVAL

**Liaison Committee on Medical Education*

Academic Program – From Engineer to Physicianeer

ENMED
ENGINEERING & MEDICINE

Program Requirements

MD-MEng

Every EnMed admit will have

- A BS in Engineering, Computer Science or equivalent undergraduate preparation

Program Outcomes

Every EnMed graduate will earn an MD and MEng

- Expert at life science and technology
- Invent something transformational
- Understand research and commercialization
- Be prepared to be early adopters and thought leaders

Ramping to…

50

EnMed students / year

Leadership

ENMED
ENGINEERING & MEDICINE

Best to Lead

- A world-class physician-scientist
- Internationally recognized leader in biomedical imaging and bioengineering
- Member of National Academy of Medicine and the National Academy of Engineering

RODERIC I. PETTIGREW, PHD, MD

CEO of EnHealth and Executive Dean for EnMed

Founding Director, National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health (NIH)

Academic Program –
From Engineer to Physicianeer

ENMED
ENGINEERING & MEDICINE

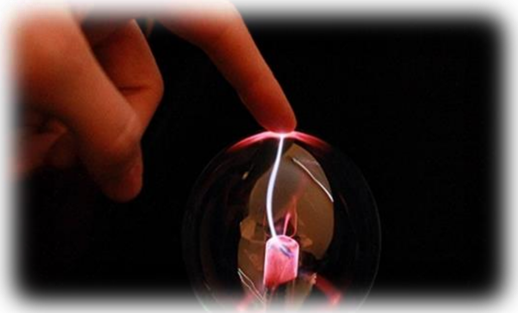
MD-MEng

Medicine Content Sequence

- Duration 18 months
- **Course titles and duration same as regular curriculum**
- Weekly theme and case relevant learning activities
- Mapped to USMLE Step 1 Content

Engineering Content Sequence

- Four-course sequence
- **Students will learn to view the human body as an integrated <u>engineered</u> system.**
- Presented from a new perspective that values the confluence of engineering principles and its problem-solving approach with those taught during medical training.



Academic Program –
From Engineer to Physicianeer

ENMED
ENGINEERING & MEDICINE

EY 2019 EnMed Curriculum Concept Model — Revised 6.28.17

Jun '19	July '19	Aug '19	Sept '19	Oct '19	Nov '19	Dec '19	Jan '20	Feb '20	Mar '20	Apr '20	May '20	Jun '20
Engineering Prematriculation program	Orientation; POM	Foundations of Medicine I		POM; Foundations of Medicine II		Exams	Neuroscience	POM; Introduction to Disease		Cardiovascular	Repiratory	Exams
		Gross Anatomy		Gross Anatomy			EC III[1]	Engineering Content III (2 sch)[1]				
		POM		POM								
		Engineering Content I (1 sch)		Engineering Cont. II (1 sch)								

July '20	Aug '20	Sept '20	Oct '20	Nov '20	Dec '20	Jan '21	Feb '21	Mar '21	Apr '21	May '21	Jun '21
						Block 1	Block 2	Block 3	Block 4	Block 5	Block 6
Heme/Onc	Renal/GU	GI/ Nutrition	EBMSR	Endo/Repro; Integument/ MS	Exams	IMED		Surgery		Step 1 Prep and Examination	Electives
Engineering Content IV (2 sch)[1]				Eng Cont IV (2 sch)		Engineering Innovation I (1 sch)[2]					

July '21	Aug '21	Sept '21	Oct '21	Nov '21	Dec '21	Jan '22	Feb '22	Mar '22	Apr '22	May '22	Jun '22
Block 7	Block 8	Block 9	Block 10	Block 11	Block 12	Electives	Electives	Electives	Electives	Electives	Step 2 Prep and Exam
Pediatrics	Ob-Gyn		Psychiatry		FMED						
Engineering Innovation II (2 sch)[2]											

July '22	Aug '22	Sept '22	Oct '22	Nov '22	Dec '22	Jan '23	Feb '23	Mar '23	Apr '23	May '23	Jun '23
Engineering Innovation III Required Elective[3] (4 sch)	Engineering Innovation III Required Elective[3] (4 sch)	Engineering Innovation IV Required Elective[3] (4 sch)	Engineering Innovation IV Required Elective[3] (4 sch)	Emergency Medicine, Acting Internship, ICU, Electives						Graduation	

Notes:
[1] Engineering Content III and IV - 1 sch for CSIE and 1 sch for Grand Rounds
[2] Engineering Innovations I and II will deliver a clerkship-specific needs statement at the end of each clerkship
[3] Engineering Innovations III and IV Required Electives may be taken any time after completion of clerkships. Flexibilty for interviews and other off-campus academic programs will be allowed.

- Engineering Content
- Preclincial Content
- Clerkships
- Examinations
- Electives, AI, ICU, EM

From Engineer to Physicianeer

ENMED
ENGINEERING & MEDICINE

Cannon Woodbury
UT Dallas
Biomedical Engineering

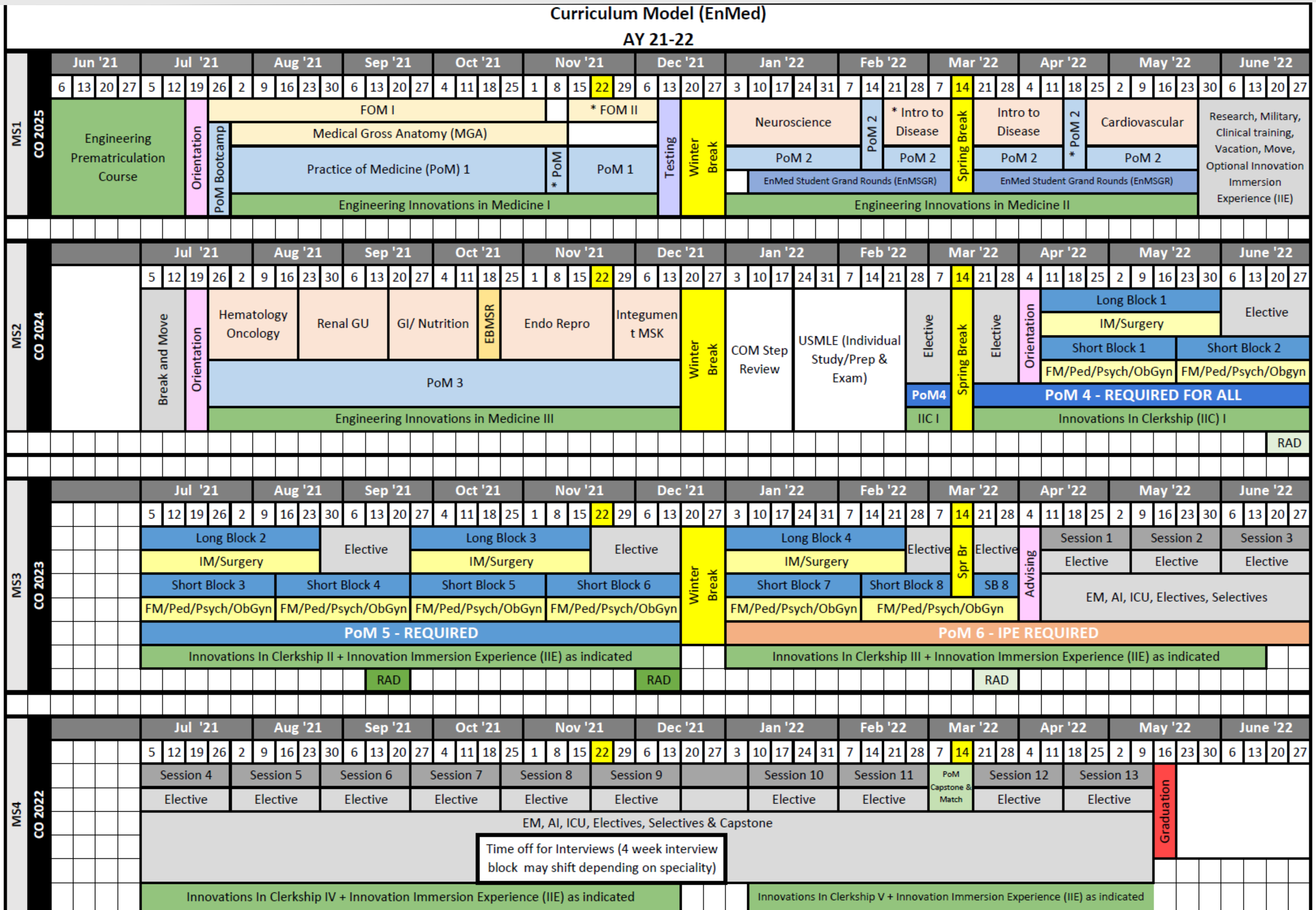
Lamees Elnihum
Texas A&M University
Chemical Engineering
(minors in Aerospace and Chemistry)

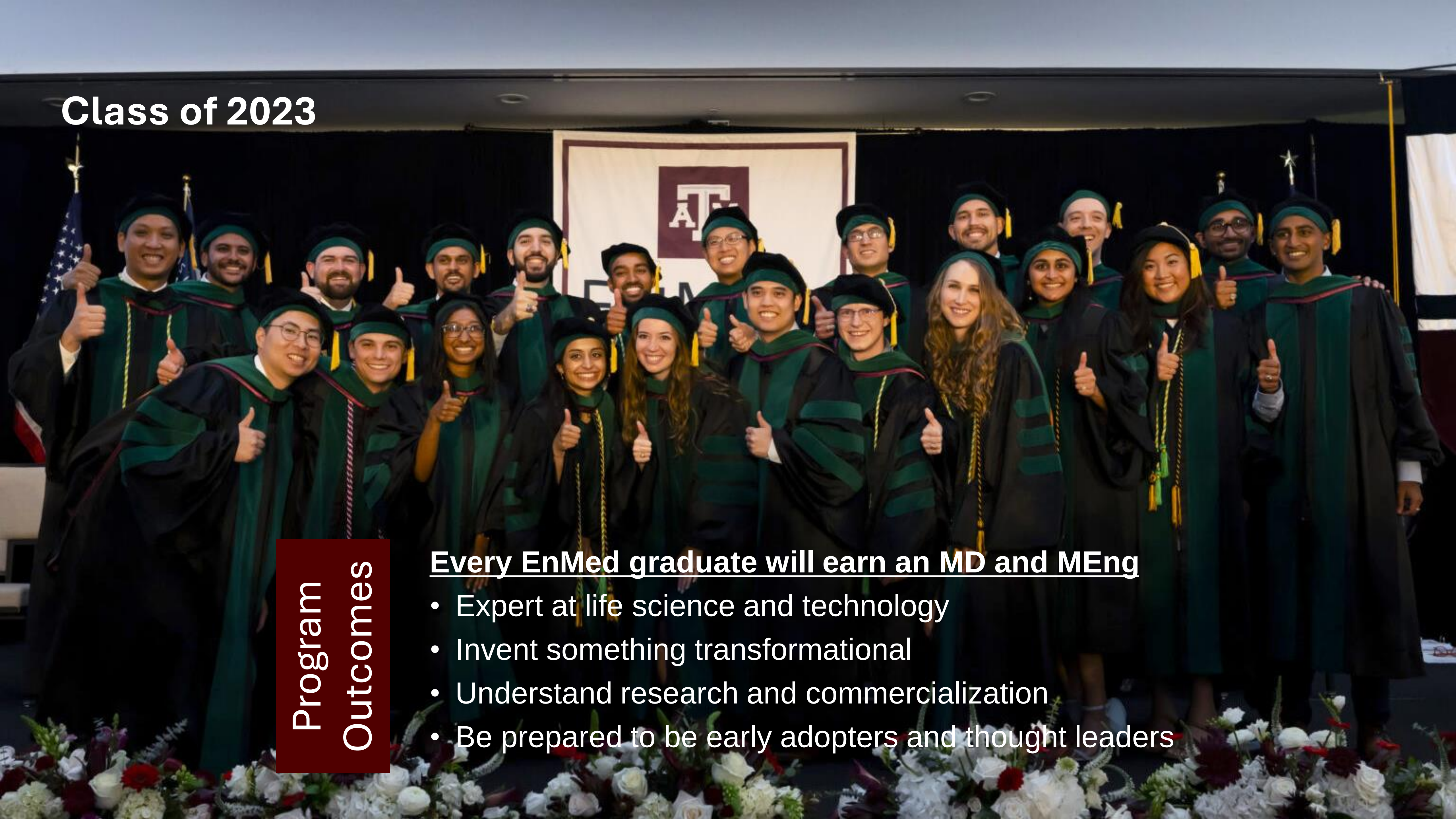
Kenneth Livingston
UT Dallas
Electrical Engineering

2017-18 Pilot Cohort

2018-19 Pilot Cohort

EnMed Curriculum - at a glance





Class of 2023

Program Outcomes

Every EnMed graduate will earn an MD and MEng

- Expert at life science and technology
- Invent something transformational
- Understand research and commercialization
- Be prepared to be early adopters and thought leaders

Dual Medicine-Engineering degree

OLLSCOIL NA GAILLIMHE
UNIVERSITY OF GALWAY

MB, BCh, BAO, and BE
8 years

School of Medicine and Advanced Medical Engineering

ASU
Arizona State University

MD/MS
? years

Dual Medicine-Engineering Degrees

UIC
UNIVERSITY OF ILLINOIS
COLLEGE OF MEDICINE

MD/MS (BIOE)
5 years

An M.D. Program Built at the Nexus of Engineering and Innovation

Carle Illinois
COLLEGE OF MEDICINE
Carle
UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN

MD
4 years

Convergence

… the integration of historically distinct fields or disciplines that leads to the emergence of a new and unified whole to address need and create transformative impact.

Convergence: Engineering-Medicine

Convergence: Liberal Arts-Engineering

Convergence: Liberal Arts-Engineering

- Provide a well-rounded education that combines technical skills with a broader understanding of social, cultu [illegible]

Program Objective

- Premium value on fostering creativity, critical thinking, and effective communication skills alongside engineering expertise.

Produce a

Socratic Engineer

ANDERSON UNIVERSITY

College of Engineering

- *Christian (Southern Baptist Convention)*
- *Liberal Arts*
- *Regional serving*
- *~4,117 students ('22-'23)*

College of Engineering

Design. Build. Sustain.

"Conv
scient
condu f
know uter
science to engineering design..."

Phillip Sharp, MIT Institute Professor and Nobel Laureate (2011)

Genome Engineering

Ecosystem Engineering

Outline

Convergence in the Academy

EnMed and Liberal Arts-Engineering

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- **Electroconductive Hydrogels**

  Biosensors and Bioelectronics

- **Microanalytical Systems**

  Hemorrhagic Trauma and Allotransplantation

- **ElectOMICS**

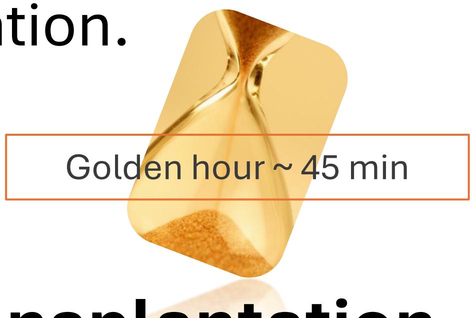
  Polymers, Fields, and Genes

Summary

Biomedical Problems of Interest

Hemorrhagic Trauma

Physiologically informed patient resuscitation and reanimation.



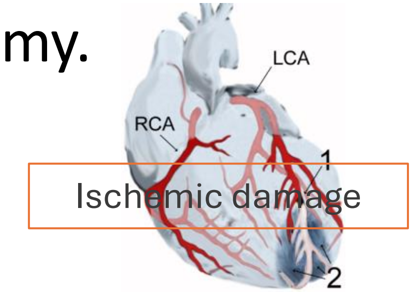
Allotransplantation

Physiologically informed allograft stratification.

National Trauma Institute. (**2018**). Trauma Statistics & Facts https://www.nattrauma.org/what-is-trauma/trauma-statistics-facts/
Kauvar D.S. et al. (**2006**) *Journal of Trauma and Acute Care Surgery*, *60*(6), S3-S11.

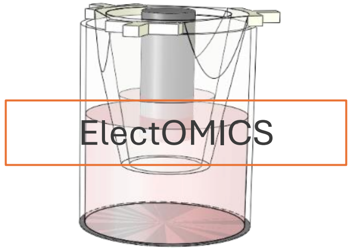
Wound Healing

Traumatic defects in electrical tissue from cardiac infar or axomy.



Electrobiology

Exogenous and endogenous electric fields in biology.



Cao et al. "Electrical and mechanical strategies to enable cardiac repair and regeneration." *IEEE Reviews in Biomedical Engineering* (**2015**)

Drug Delivery

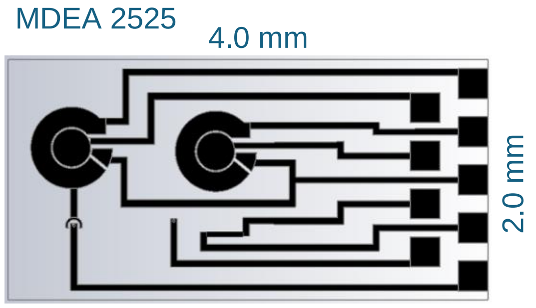
Bio-responsive drug delivery to address homeostasis.

Q.-X. A. Sang et al. *Biochem. Biophys. Res. Commun.* (**2000**), 274, 780.
Wilson and Guiseppi-Elie *Int. J. of Pharmaceutics* (**2014**) 461(1-2) 214-222.
Chu, David S., et al., *Biomat. Sci.* (**2015**) 3.1: 41-45.

Biomedical Solutions Under Development

Hemorrhagic Trauma

Allograft Stratification

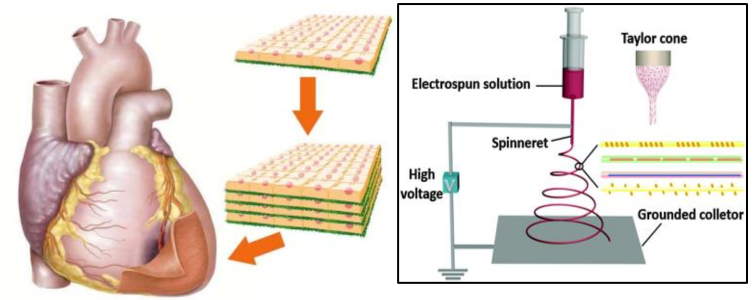


Minimally invasive Physiological Status Monitoring **(PSM) Biochip** – Five metabolite biomarkers.

Aggas et al. (**2023**) *Bioengineering MDPI* 2023, 10(4), 434.
Bhat et al. (**2020**) *Journal of Translational Medicine* **18,** 348.
Kotanen, et al. (**2012**) *Biosensors and Bioelectronics* 35(1), pp. 14-26.
Guiseppi-Elie, et al. (**2011**) *Analytical and Bioanalytical Chemistry, 399*(1), 403-419.

Wound Healing

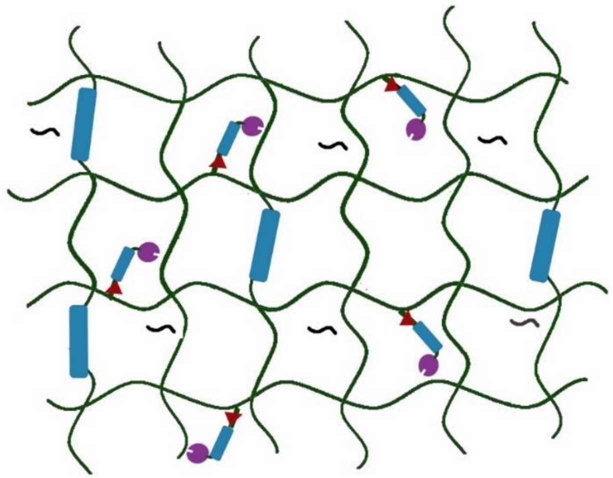
Electrobiology



Micro and nano- fabrication (electrospinning, 3D printing, microlithography) of **electroconductive polymers**: fibers, films and microforms.

Mancino et al. (**2022**), *Nanomedicine* 44, 102567.
Abasi et al. (**2019**) *IEEE Xplore* 875-878.
Abasi et al. (**2019)** *Mat. Sci. and Eng.: C* 99 1304-1312.
Aggas et al. (**2018**) *Bioengineering* 5(4) 87.
Li Yao, et al. (**2003**) *Chem. Mater.* 15(9) 1860 – 1864.

Drug Delivery



Sensing, Measuring, and Actively Responding Technical (**SMART**) Hydrogels.

Whitney et al. (**2024**) Adv. Sensor Res. (Accepted)
Bhat et al. (**2020**) *ACS Sensors* 5, 2, 500–509.
Wilson and Guiseppi-Elie (**2013**) *Adv. Healthcare Mat.* 2(4) 520-532.
Wilson et al. (**2012**) *Journal of Controlled Release* 160.1: 41-47.
Guiseppi-Elie et al., *J. Bioact. Compat. Polym.,* (**2010**), 25(2) 121-140.

Impact of hemorrhage on trauma

- Hemorrhage is the primar plication of trauma
  - Leading cause of deat USA
  - Accounts for 62% of es 15-24
  - High contribution to e first 24 h

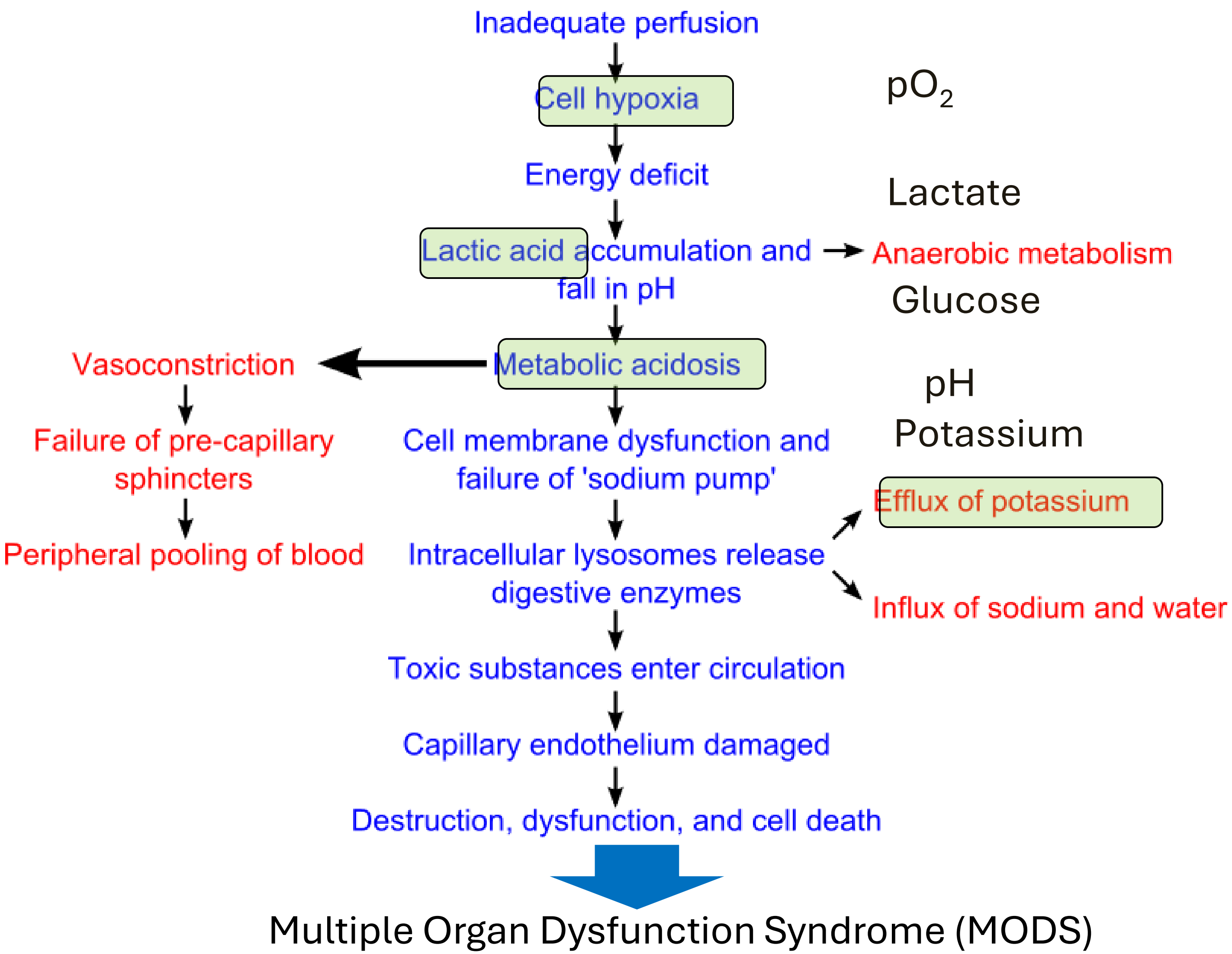
Golden hour period ~ 45 minutes

National Trauma Institute. (12/2018). Trauma Statistics & Facts
https://www.nattrauma.org/what-is-trauma/trauma-statistics-facts/
Kauvar D.S. et al. (2006) *Journal of Trauma and Acute Care Surgery* , *60*(6), S3-S11.

Pathophysiology of Hemorrhage and Hemorrhagic Shock

- Vasoconstriction
- Reduced peripheral blood flow
- High oxygen demand

Peripheral muscles are most systemically affected during hemorrhage



Guiseppi-Elie, A., et al. (2011) *Analytical and Bioanalytical Chemistry*, *399*(1), 403-419.

Patent – Indwell a biochip within a major muscle

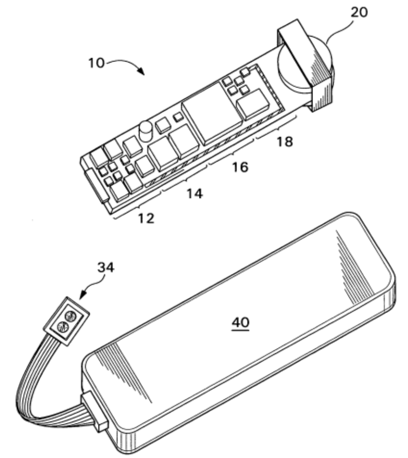


Fig. 1

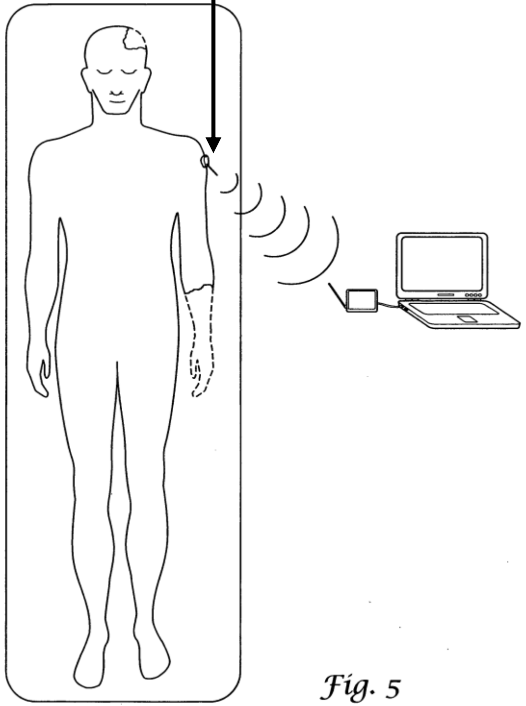


Fig. 5

US 20120088997A1

(19) **United States**
(12) **Patent Application Publication** (10) **Pub. No.: US 2012/0088997 A1**
Guiseppi-Elie (43) **Pub. Date: Apr. 12, 2012**

(54) **IMPLANTABLE BIOCHIP FOR MANAGING TRAUMA--INDUCED HEMORRHAGE**

(76) Inventor: **Anthony Guiseppi-Elie**, (US)

(21) Appl. No.: **13/317,236**

(22) Filed: **Oct. 12, 2011**

Related U.S. Application Data

(60) Provisional application No. 61/404,904, filed on Oct. 12, 2010.

Publication Classification

(51) **Int. Cl.**
A61B 5/145 (2006.01)
C12M 1/34 (2006.01)
G01N 33/48 (2006.01)

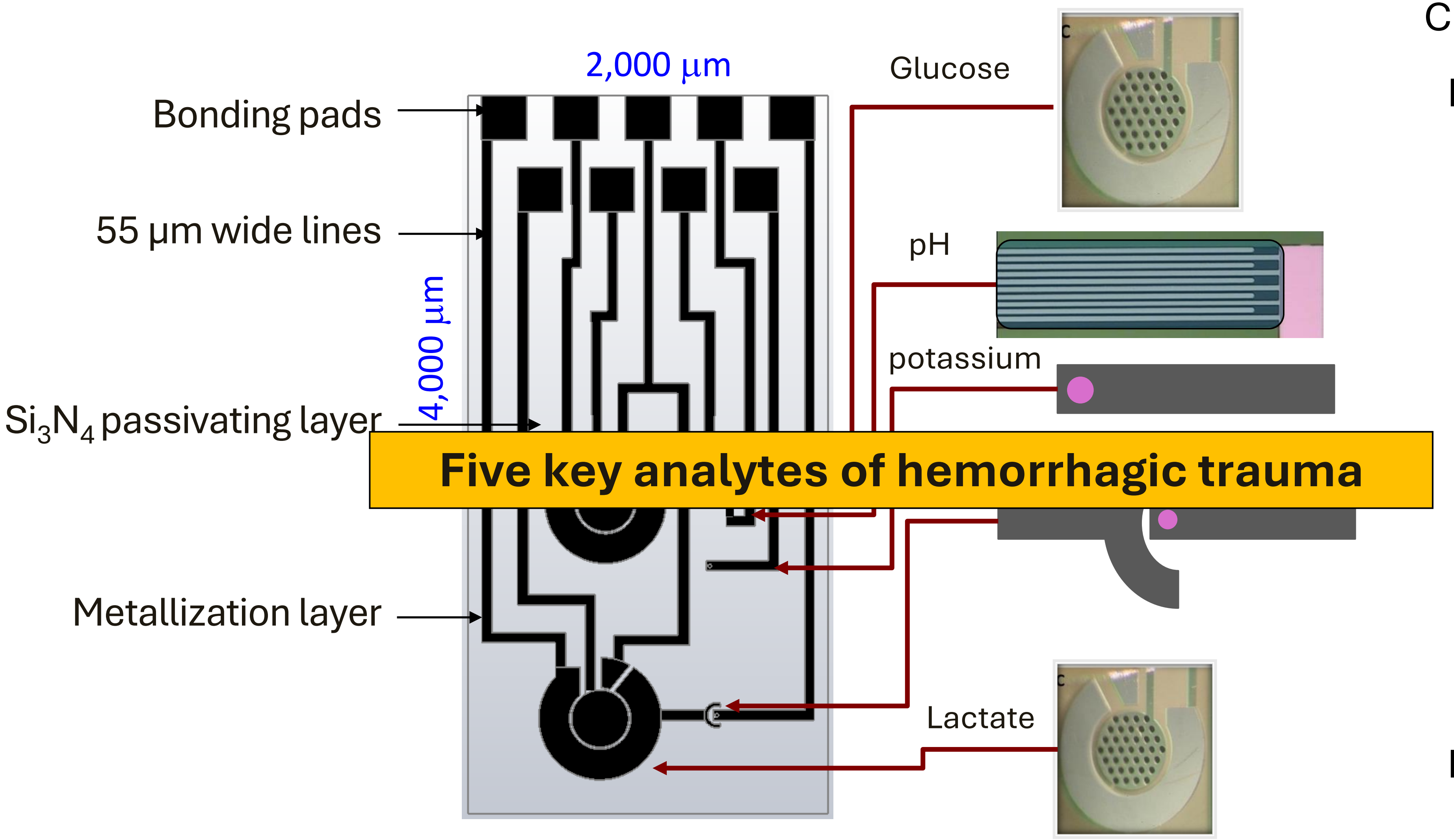
(52) **U.S. Cl.** **600/364**; 422/68.1; 435/287.1; 435/287.2; 600/309; 600/365

(57) **ABSTRACT**

A biocompatible biosensor and transmitter device for temporary implantation prior to, during and following trauma-induced hemorrhaging detects the presence and level of at least one analyte and transmits detected data to a second, external device. Thus, a method for managing post-trauma patient outcomes includes providing such a biosensor and transmitter device, temporarily implanting the biocompatible biosensor and transmitter device intramuscularly in a trauma victim; and monitoring the presence and level of the at least one analyte detected by the biocompatible biosensor and transmitter device and transmitted to the external data receiving means.

A. Guiseppi-Elie, (2012) *US Patent Application* US 13/317,236

Design of a penta-analyte biosensor – PSM Biochip



Critical Feature Size

MDEA ϕ = 25 µm

IME = 1.0 µm

MDE ϕ = 10 µm

MDE ϕ = 10 µm

MDEA ϕ = 25 µm

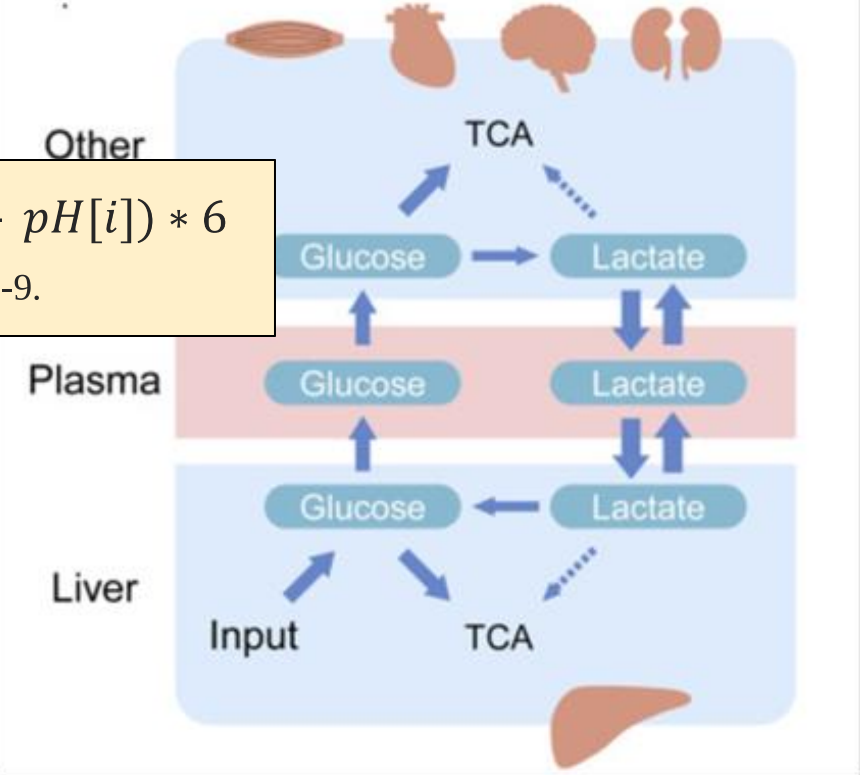
Pathophysiological Intravascular Ranges: Metabolic Indicators

Analytes	Pathophysiological range		
	LOW	NORMAL	HIGH
Glucose	**Hypoglycemia** **<3.88 mM** **<70 mg/dL**	Euglycemia 3.88 – 5.5 mM 70-99 mg/dL	Hyperglycemia >5.5 – 10 mM 99
Lactate	Hypolactatemia < 0.5 mM	Eulactatemia 0.5 – 2.0 mM	**Hy** **>2**
Potassium	Hy (<3		
pH	**Acidosis** **(<7.35)**	7.35 - 7.45	Al
pO_2	**Hypoxia** **<5.18 mM** **<100 mmHg**	5.18 - 6.22 mM While breathing in, 160 mmHg, gradient 100-120 mmHg	Hy >1

$$[K^+]_i = random([K^+]_{normal}) + (7.35 - pH[i]) * 6$$

Burnell et al. *J Clin Invest* 1956;35(9):935-9.

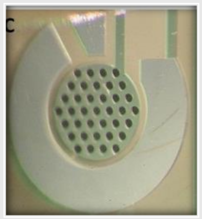
Liu et al. *Cell Metabolism*, 32(4) 2020, 619-628.e21



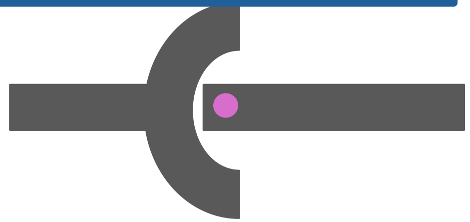
Glucose: Hirshberg, Eliotte et al. (2008), *Pediatric Critical Care Medicine, 9(4), 361-366*
Potassium: Viera, Anthony J., (2015) *American family physician, 58(4), 777-782*
Lactate and pH: Andersen, Lars W., et al, (2013) *Mayo Clinic Proceedings,* Vol. 88, No. 10, pp. 1127-1140
pO_2: de Jonge, Evert, et al.(2008), *Critical care,* 12(6), R156

Physiologically relevant analytes and the electrochemical techniques and device structures used in their measurement

Analyte	Motivation	Method	Technique	Transducer
Glucose	Levels fall during trauma-associated hemorrhage	Glucose Oxidase Biosensor	Amperometry (Apply voltage measure current)	Microdisc Electrode Array (MDEA) ϕ = 25 μm
Lactate	Levels rise during trauma trauma-associated hemorrhage	Lactate Oxidase Biosensor	Amperometry (Apply voltage measure current)	Microdisc Electrode Array (MDEA) ϕ = 25 μm
Potassium	Hyperkalemia	Ion Specific Electrode (ISE)	Potentiometry (Measure voltage vs. REF)	Microdisc Electrode (MDE) ϕ = 10 μm
pH	Lactate in the tissues causes acidosis	pH Responsive Hydrogel	Impedimetry (Apply V sin(wt) Measure I sin(wt+θ)	Interdigitated Microelectrodes (IME) ϕ = 1 μm
pO_2	Hypoxia in the muscle bed	Electrocatalytic Layer	Voltammetry (Sweep voltage measure peak current)	Microdisc Electrode (MDE) ϕ = 10 μm







Electroconductive Hydrogels

Full Paper

Electroconductive Hydrogels: Electrical and Electro
Properties of Polypyrrole-Poly(HEMA) Composites

Sean Brahim,[a] *Anthony Guiseppi-Elie*[a,b*]

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Box 843038, 601 West Main Street, Richmond, Virginia
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Molecularly engineered p(HEMA)-based hydrogels for

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13-8656, Japan

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Biosensors and Bioelectronics

Volume 176, 15 March 2021, 112889

On the intersection of molecular bioelectronics and biosensors: 20Years of C3B

John R. Aggas [a b 1], Brandon K. Walther [a c 1], Sara Abasi [a b 1], Christian N. Kotanen [a b d], Olukayode Karunwi [a e], Ann M. Wilson [a f g], Anthony Guiseppi-Elie [a b c g]

Hydrogels: The Effects
arge Density on the Storage
d Biosensor

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jour

Amperometric glucose bi

Christian N. Kotanen [a,b], Chaker Tlili [a,c], Anthony Guiseppi-Elie [a,b,c,d]

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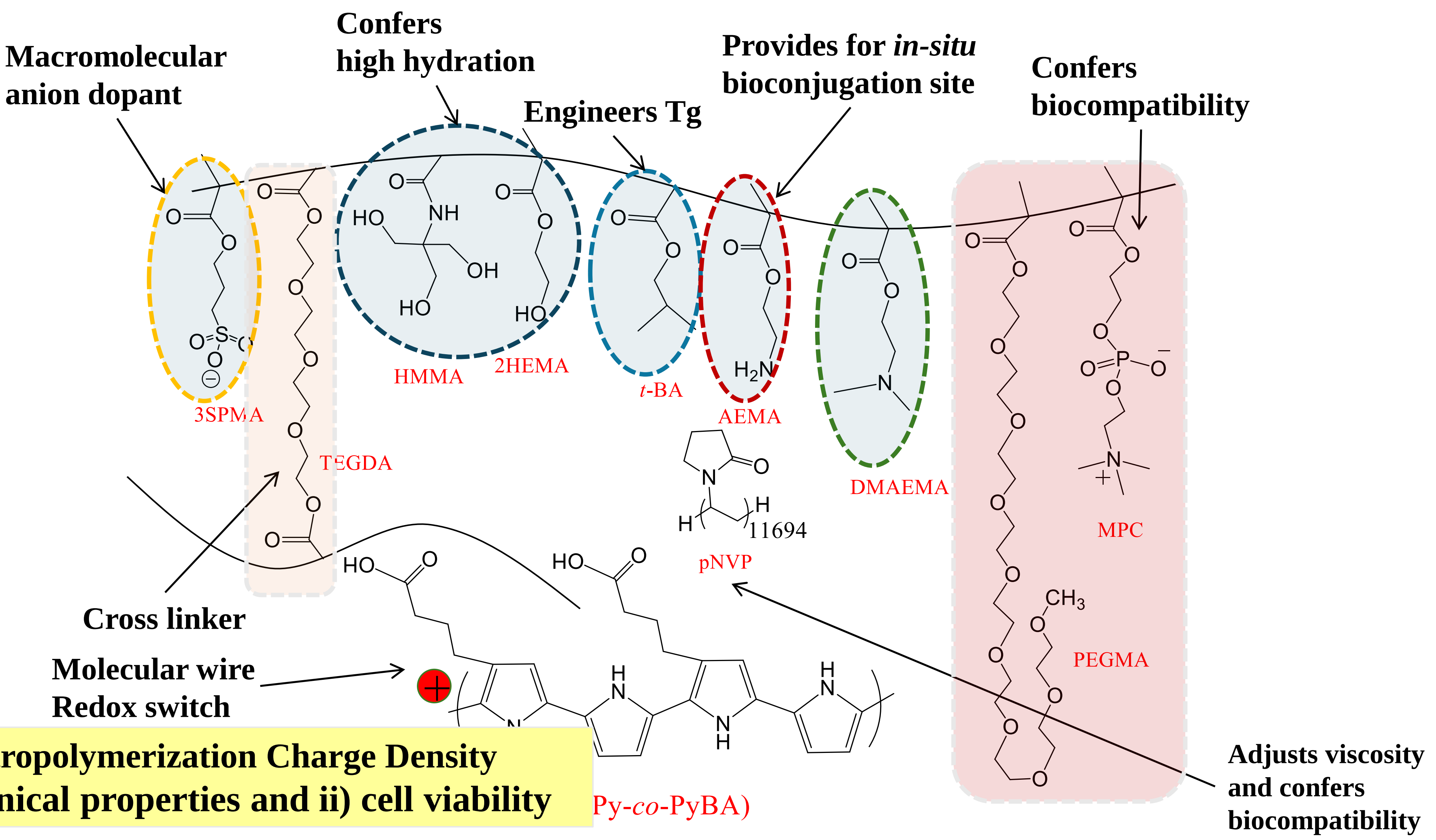
Received: 11 September 2011 / Accepted: 29 November 2011 /
Published online: 3 January 2012

p(HEMA)-based Electroconductive Hydrogel

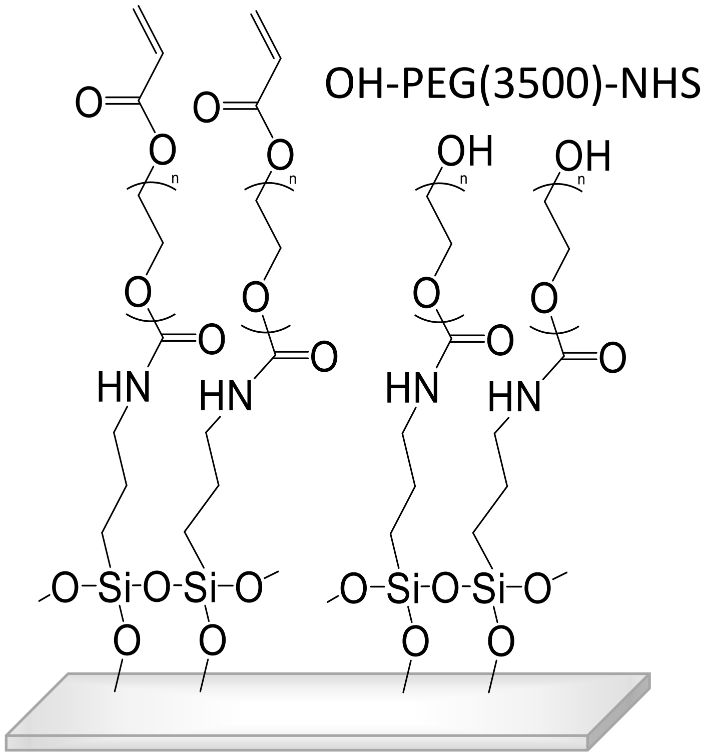
Dr. Gusphyl
JUSTIN



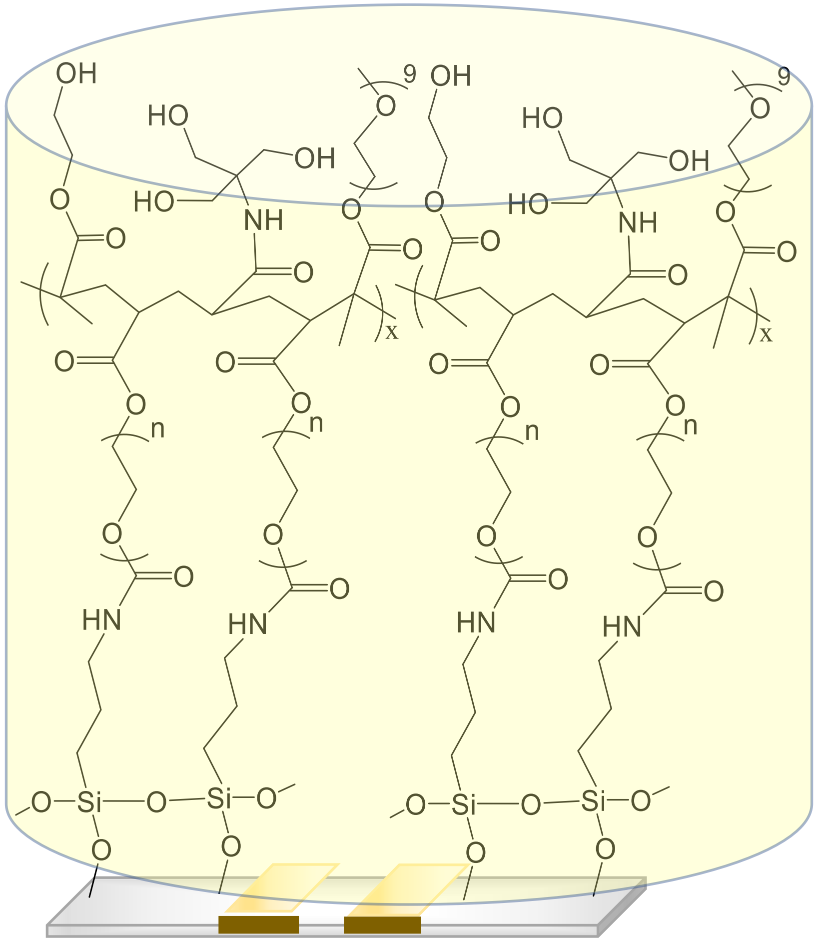
Δ Py-*co*-PyBA – Electropolymerization Charge Density
…effect on i) mechanical properties and ii) cell viability

Gusphyl Justin and Anthony Guiseppi-Elie*, "**An Electroconductive Blend of p(HEMA-*co*-PEGMA-*co*-HMMA-*co*-SPMA) Hydrogels and p(Py-*co*-PyBA): In Vitro Biocompatibility**" *Journal of Bioactive and Compatible Polymers* (**2010**), 25(2) 121-140.

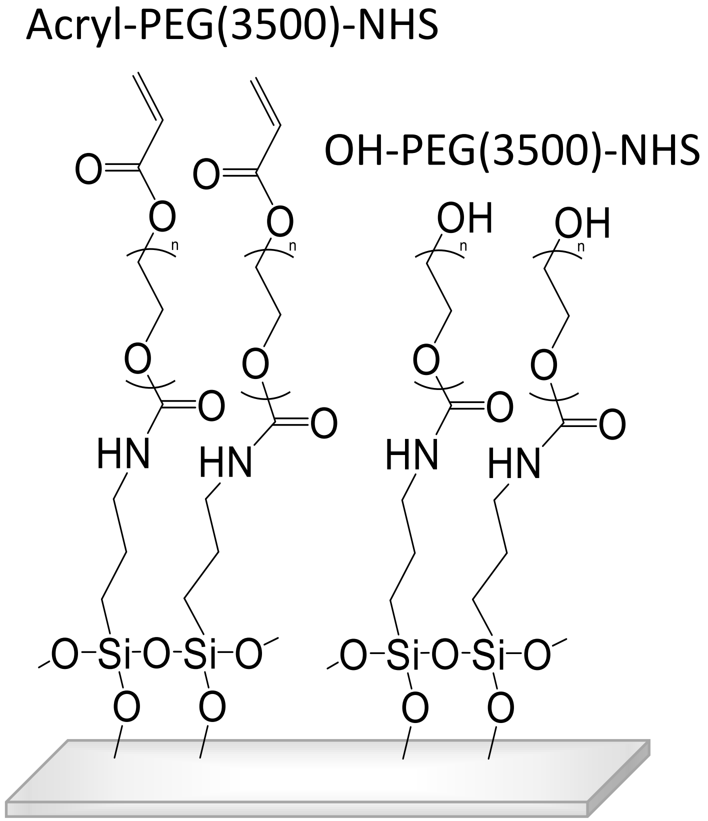
Hydrogels on solid surfaces

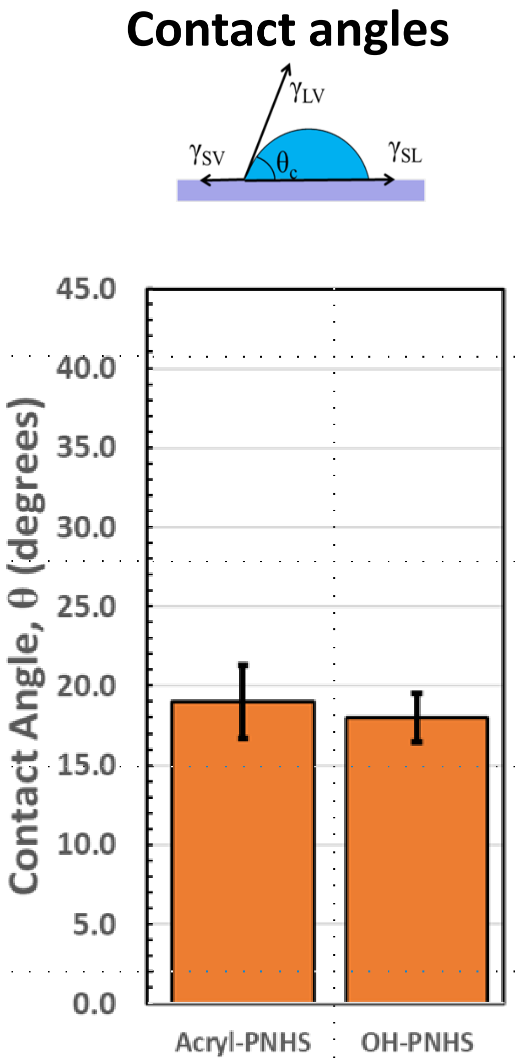


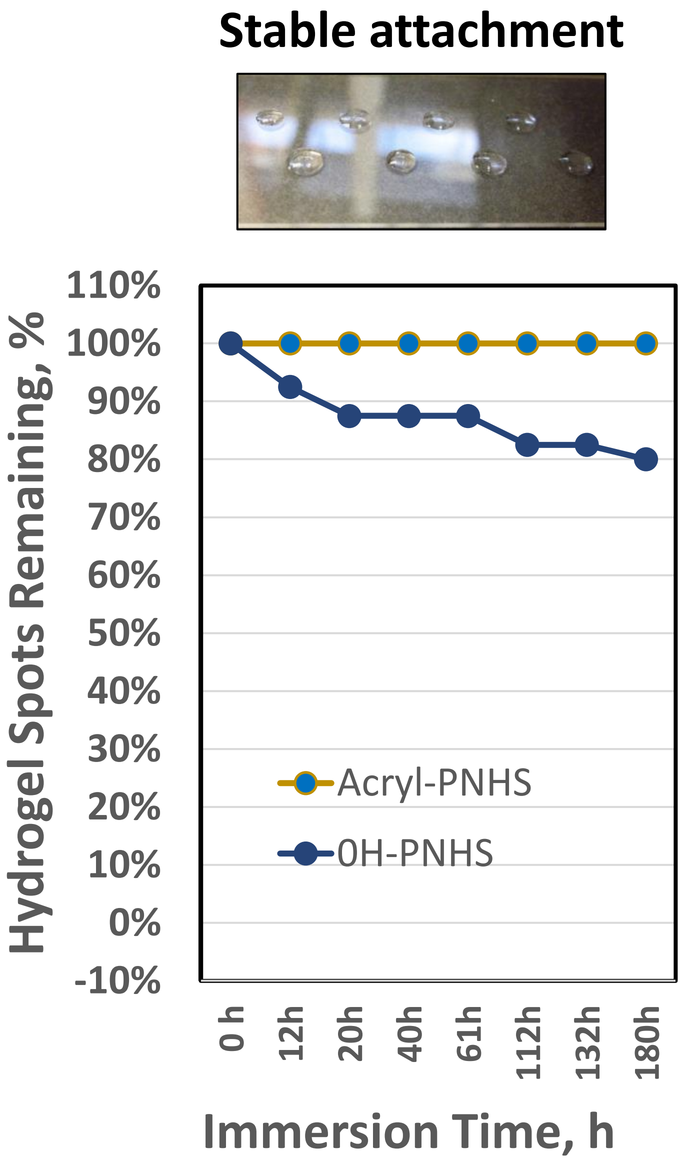
p(HEMA-*co*-PEGMA-*co*-HMMA)
Hydrogel Membrane

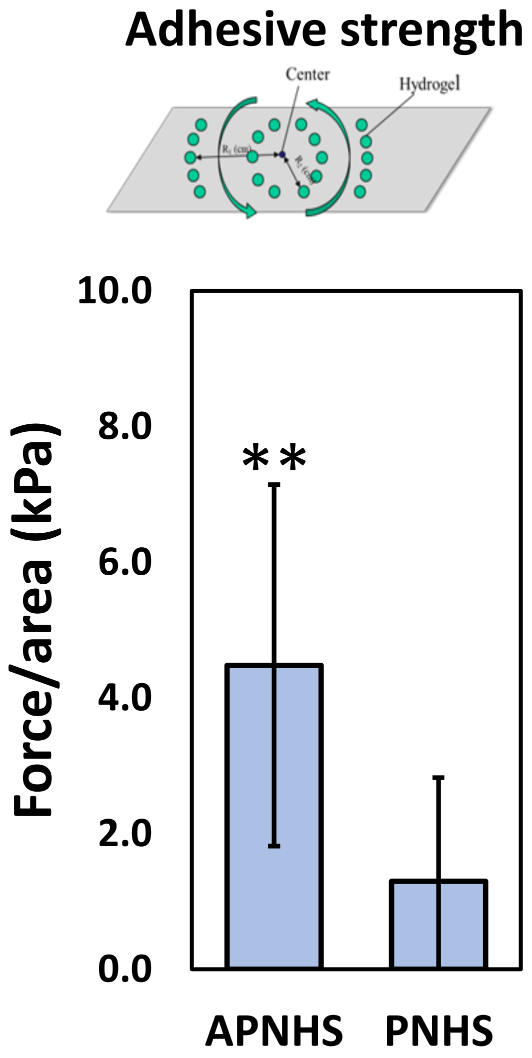


The role of the ω-functionality in attachment vs adhesion

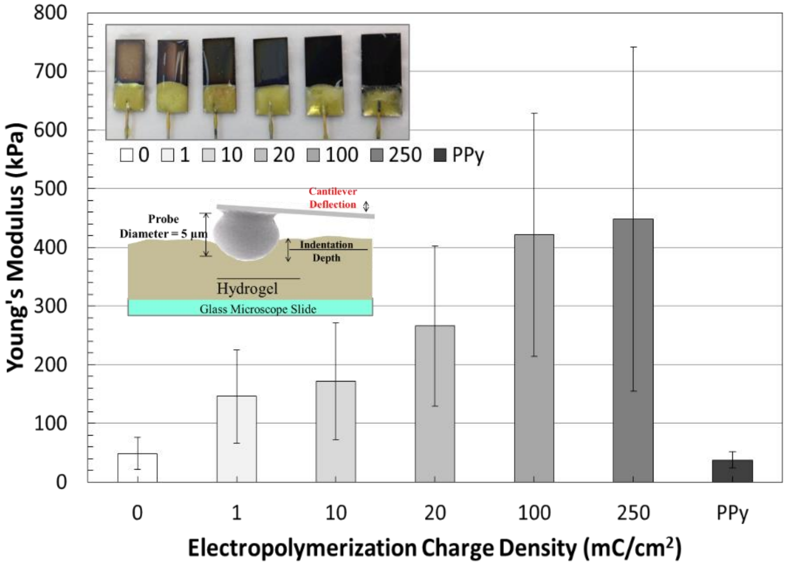


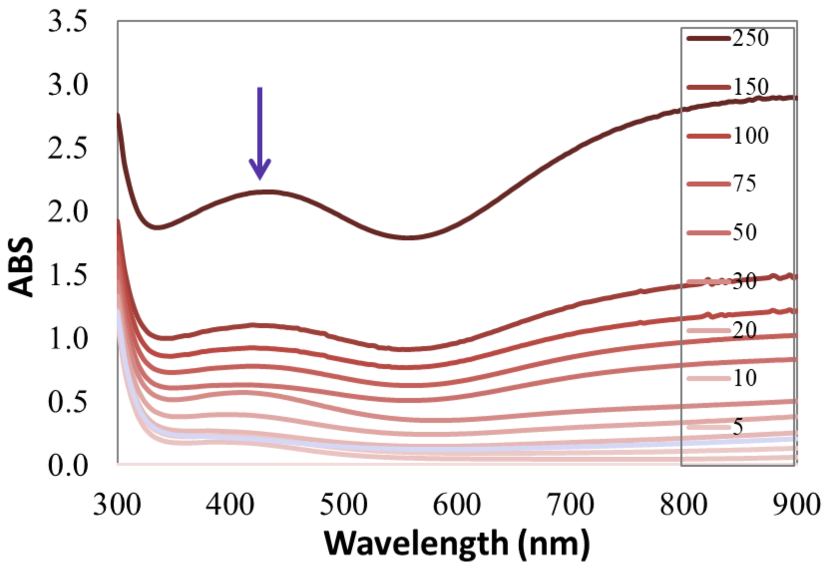


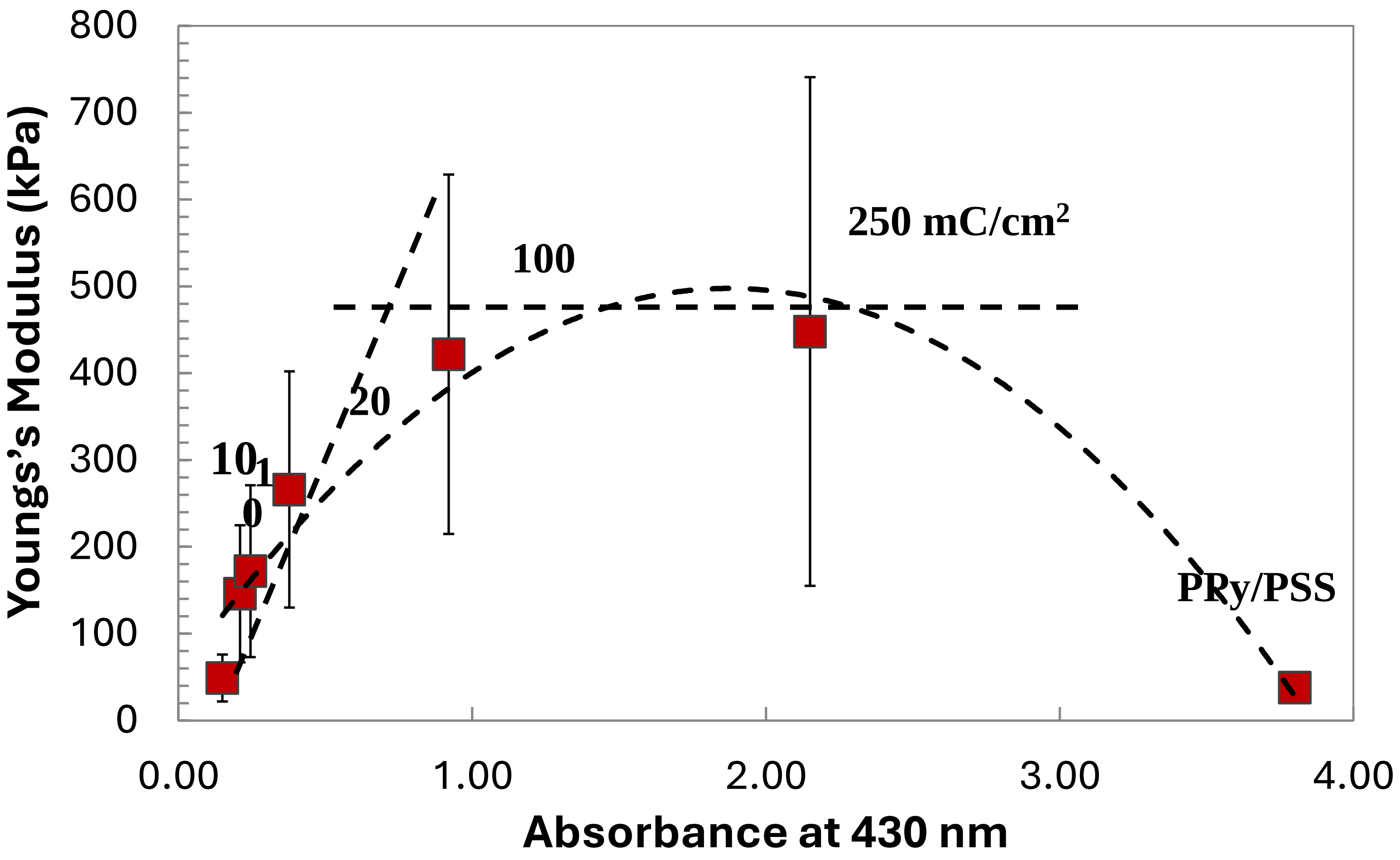




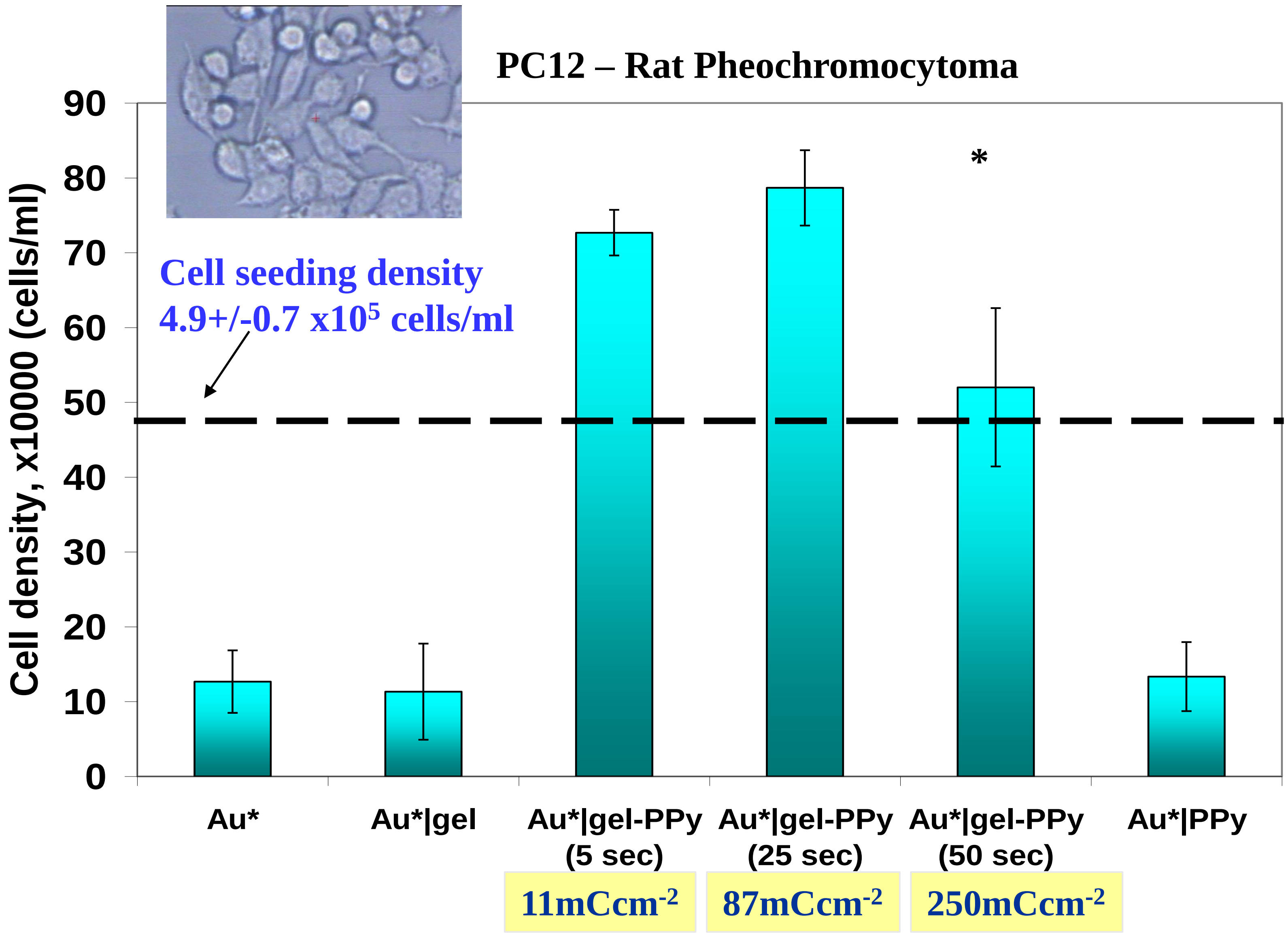
Elastic modulus measured by nano-indentation of Au*|hydrogel-PPy (electropolymerization charge densities)



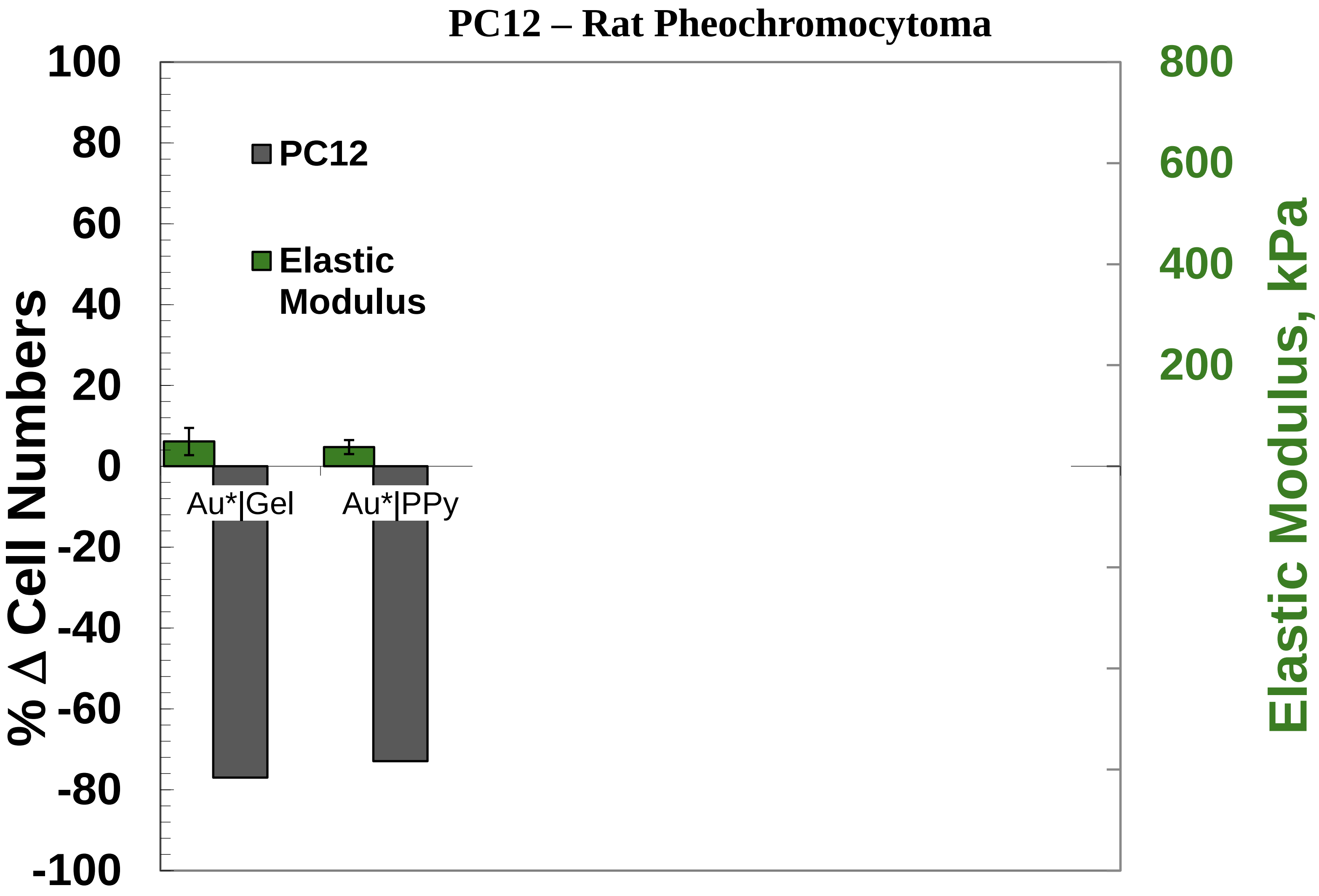




PC12 cell densities post-incubation (4 days) on Au*, Au*|hydrogel, Au*|PPy, Au*|hydrogel-PPy (5, 25 and 50s electropolymerization times)

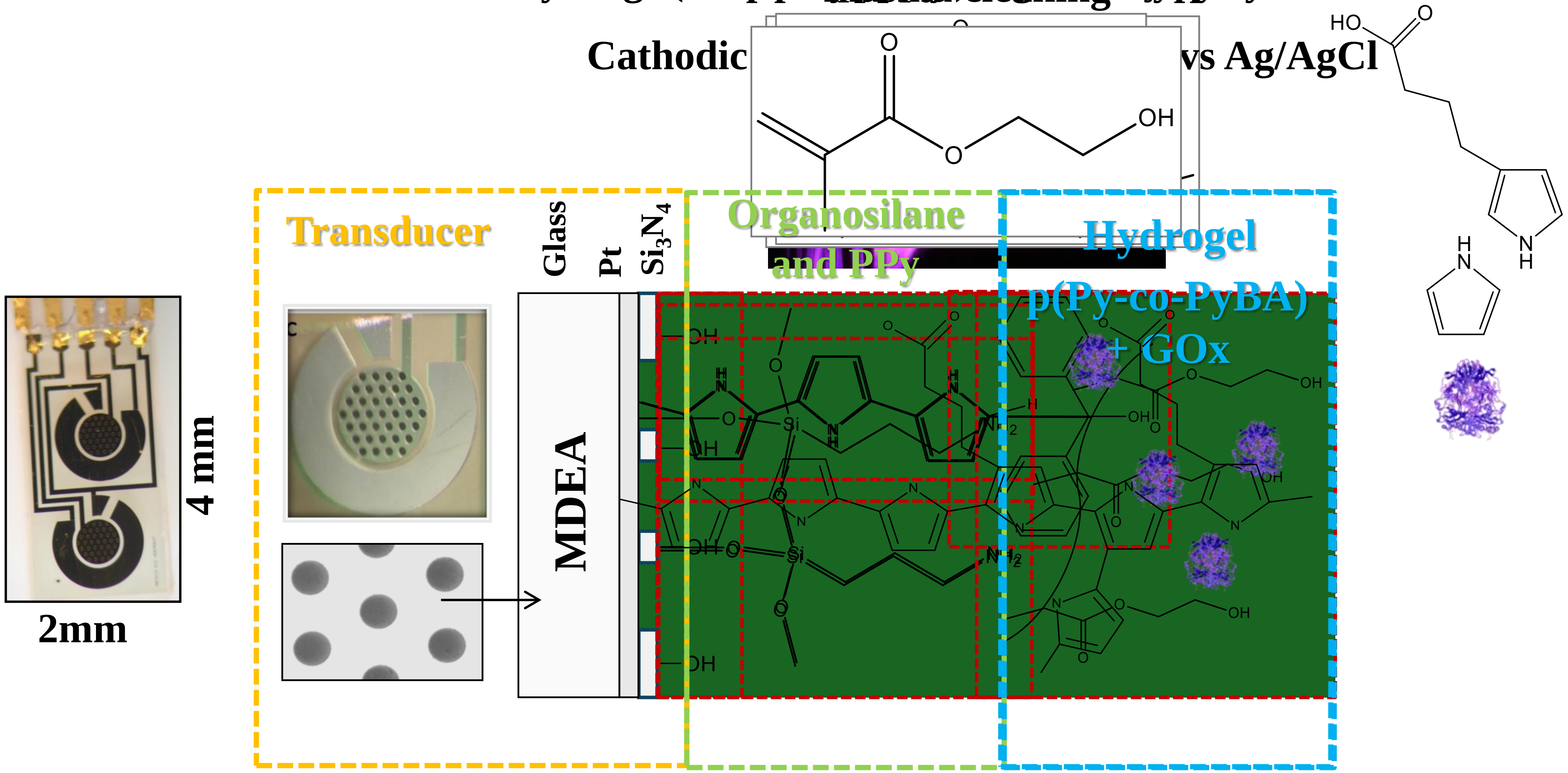


PC12 cell viability and elastic modulus of Au*|hydrogel-PPy (electropolymerization times)



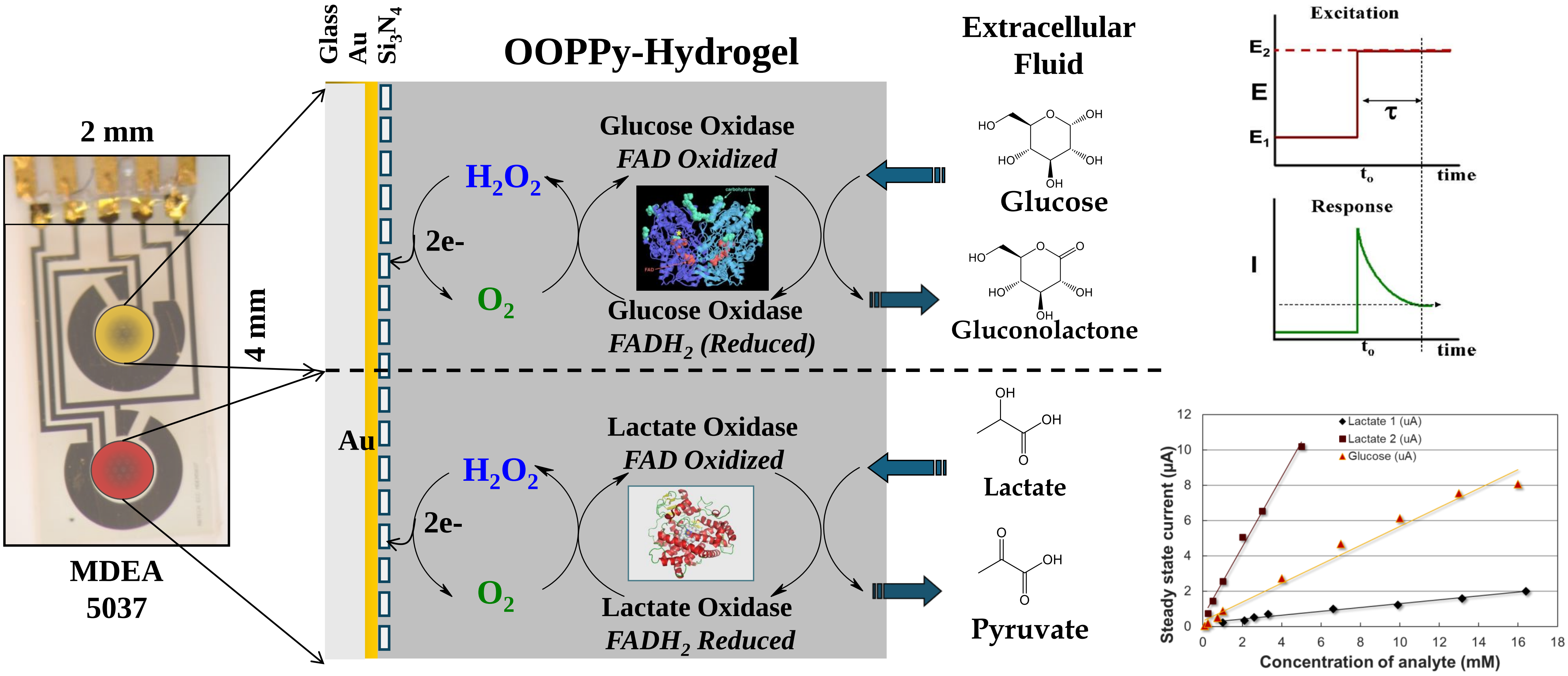
Anthony Guiseppi-Elie, Chenbo Dong and Cerasela Zoica Dinu "**Crosslink Density of a Biomimetic Poly(HEMA)-based Hydrogel Influences Growth and Proliferation of Attachment Dependent RMS 13 Cells**" *J. Mater. Chem.* (**2012**) 22 (37), 19529 – 19539

Bioactive Electroconductive Hydrogels
Electropolymerization to entrap GOx

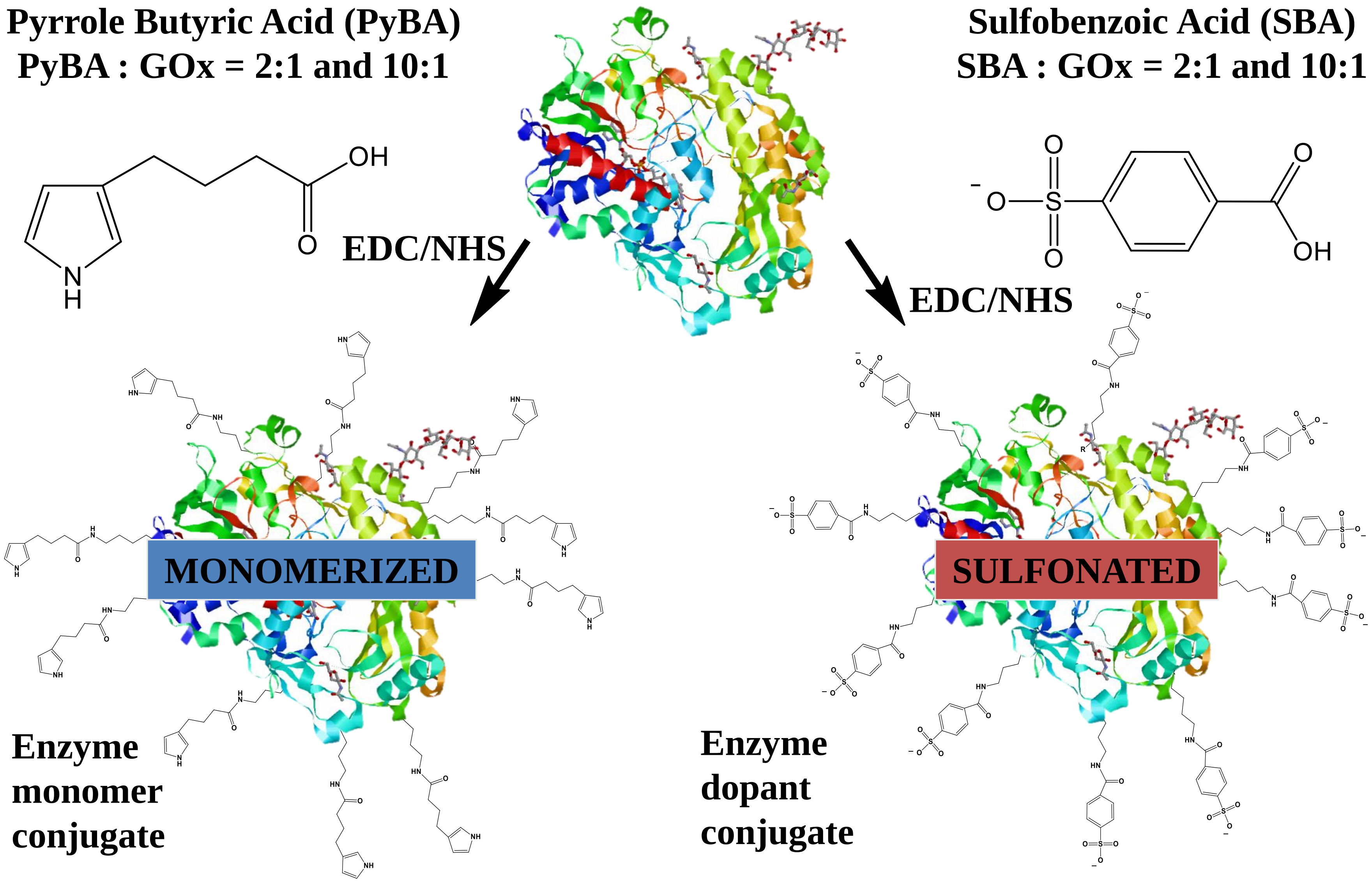


Karunwi, O., et al., Engineering the abio-bio interface to enable more than Moore in functional bioelectronics. *Journal of The Electrochemical Society*, **2013.** 160(4): p. B60-B65.

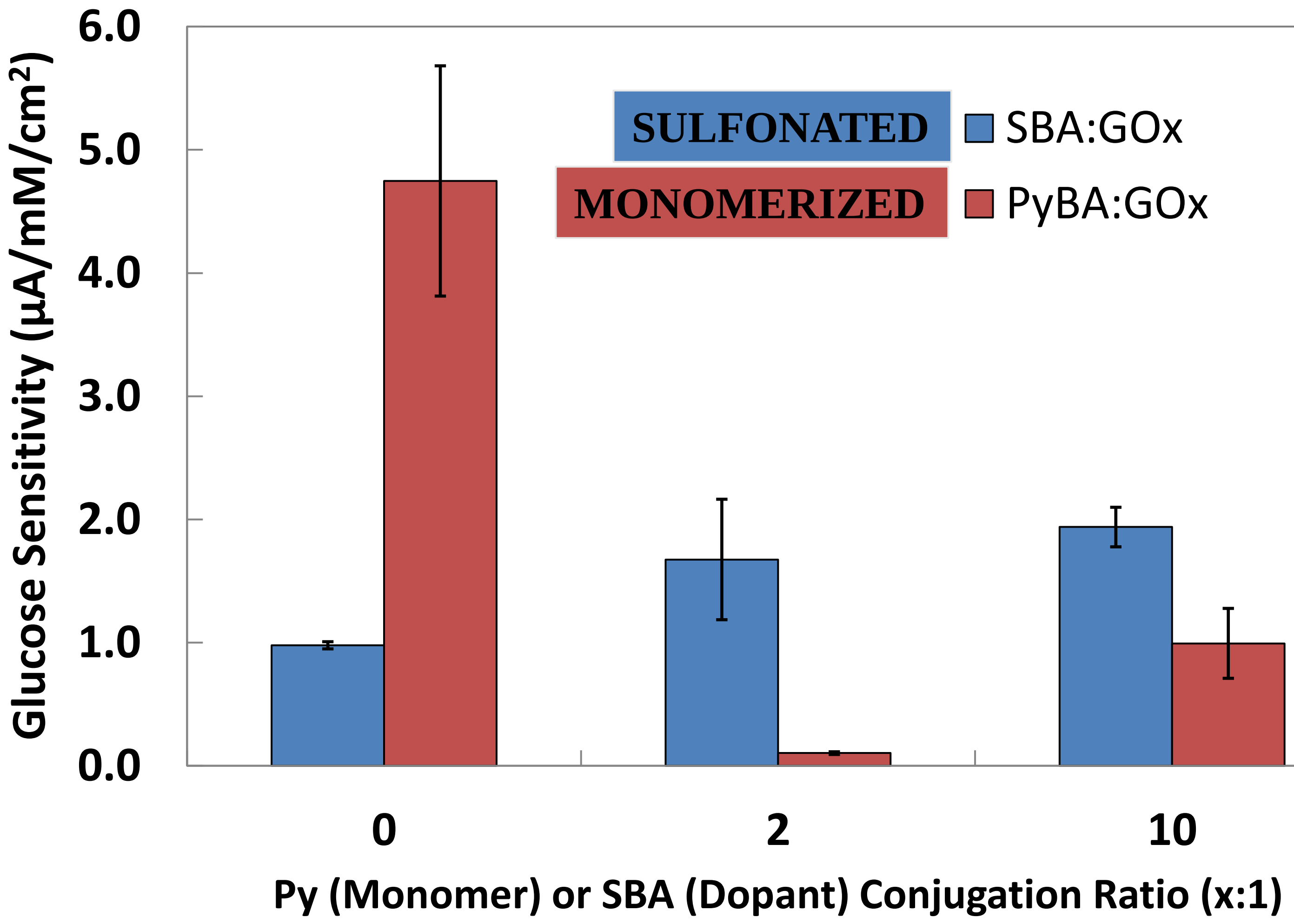
Fabrication of the electrochemical Glucose and Lactate GEN I biotransducers



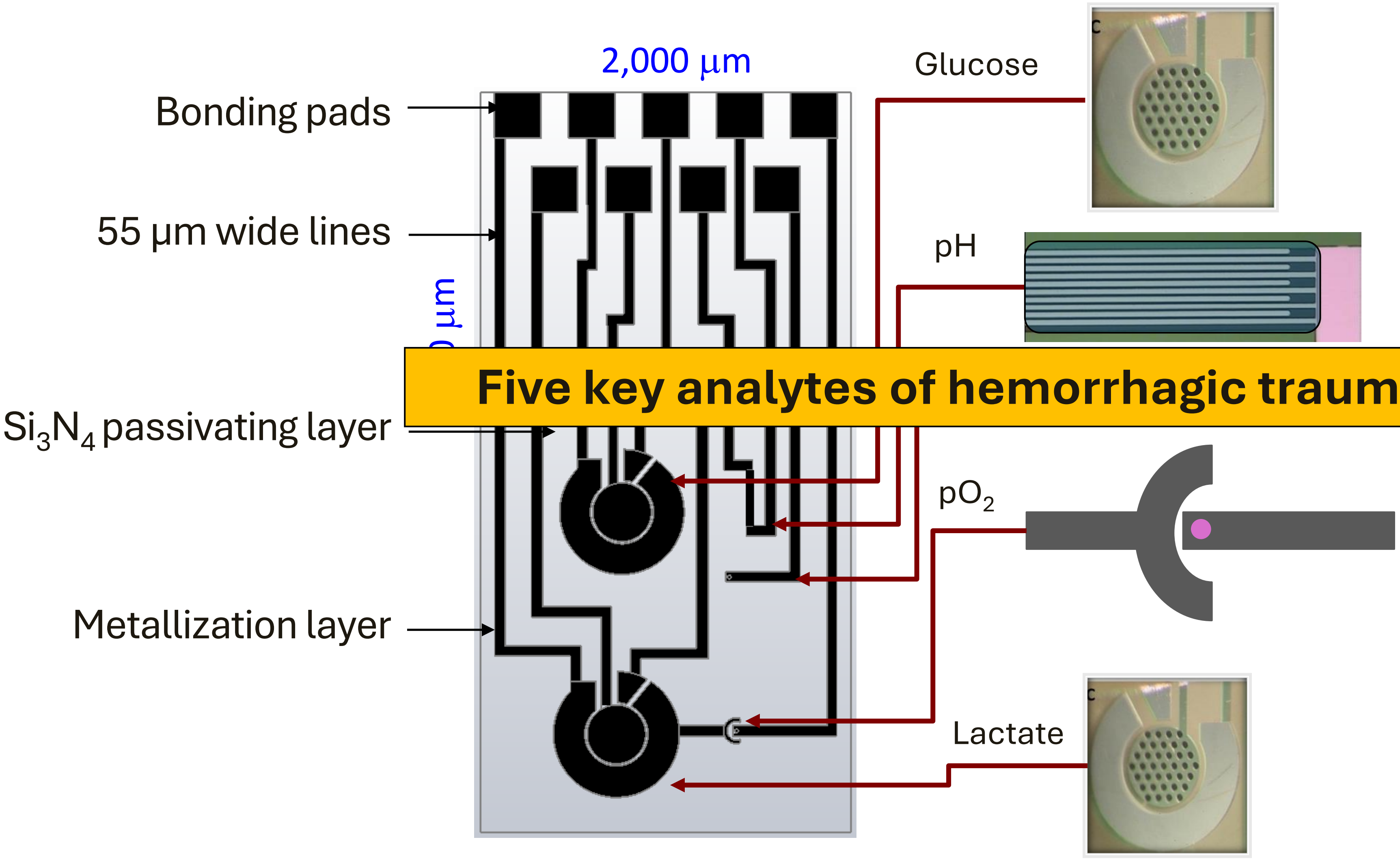
Experimental Approach II - Enzyme Engineering



Glucose biotransducer sensitivity as a function of enzyme conjugation ratio



Design of a penta-analyte biosensor – PSM Biochip



Five key analytes of hemorrhagic trauma

Critical Feature Size

MDEA ϕ = 25 μm

IME = 1.0 μm

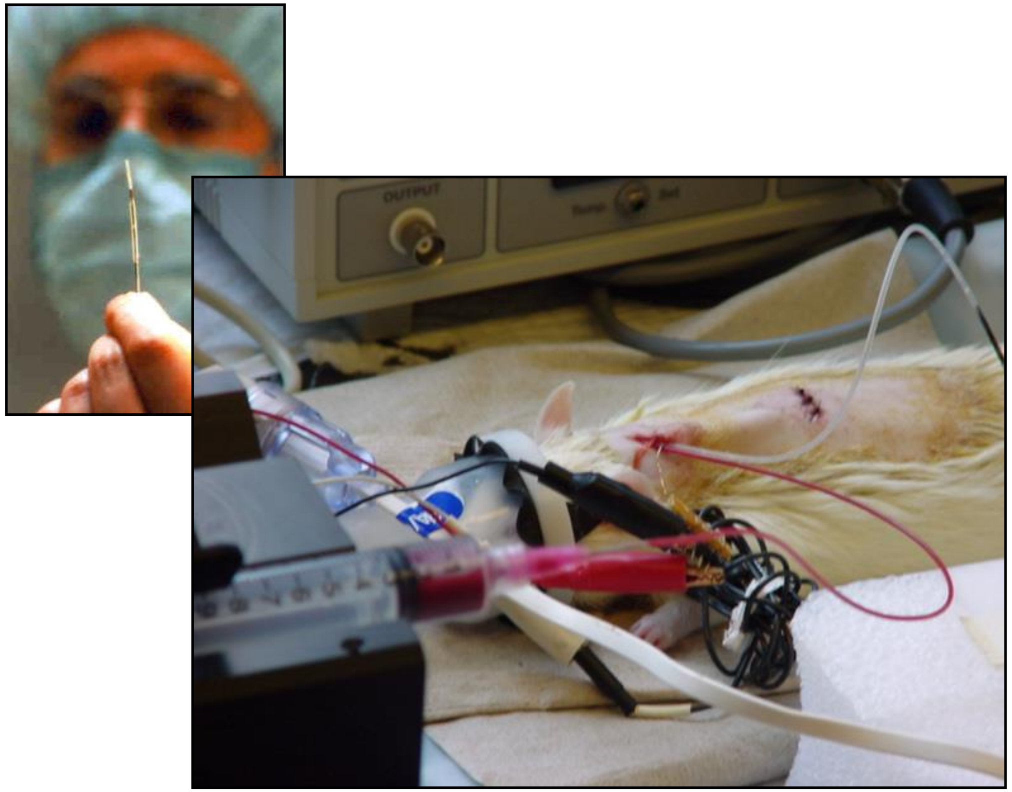
MDE ϕ = 10 μm

MDE ϕ = 10 μm

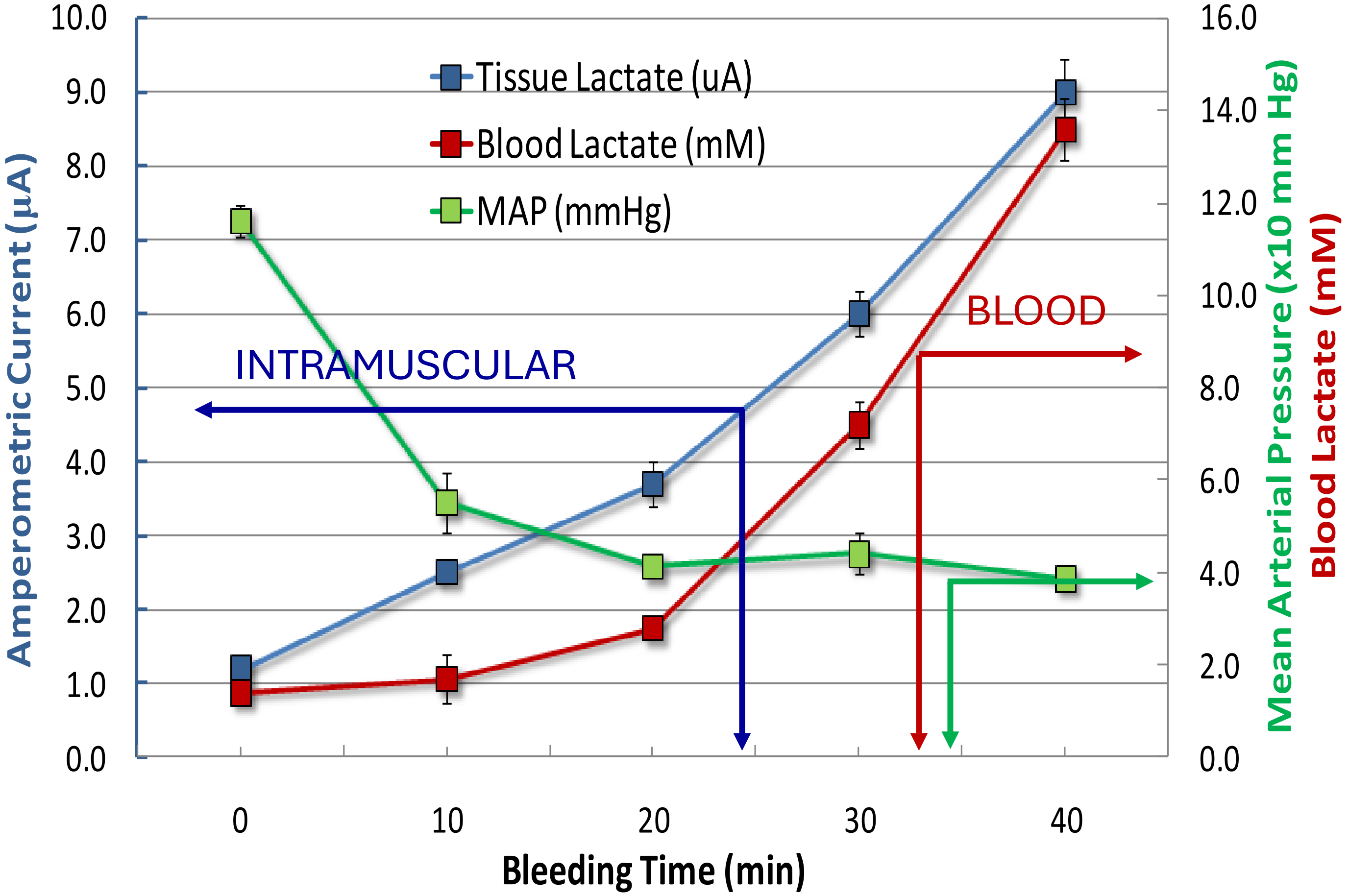
MDEA ϕ = 25 μm

In vivo amperometric performance of the implanted PSM BioChip 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.

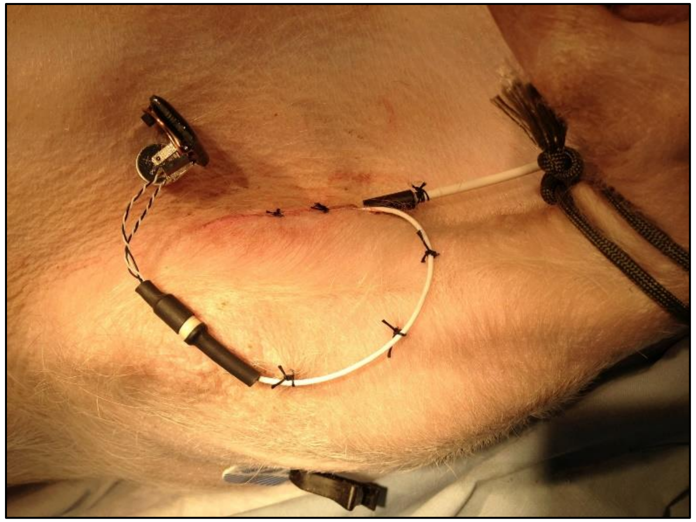


Sprauge Dawley

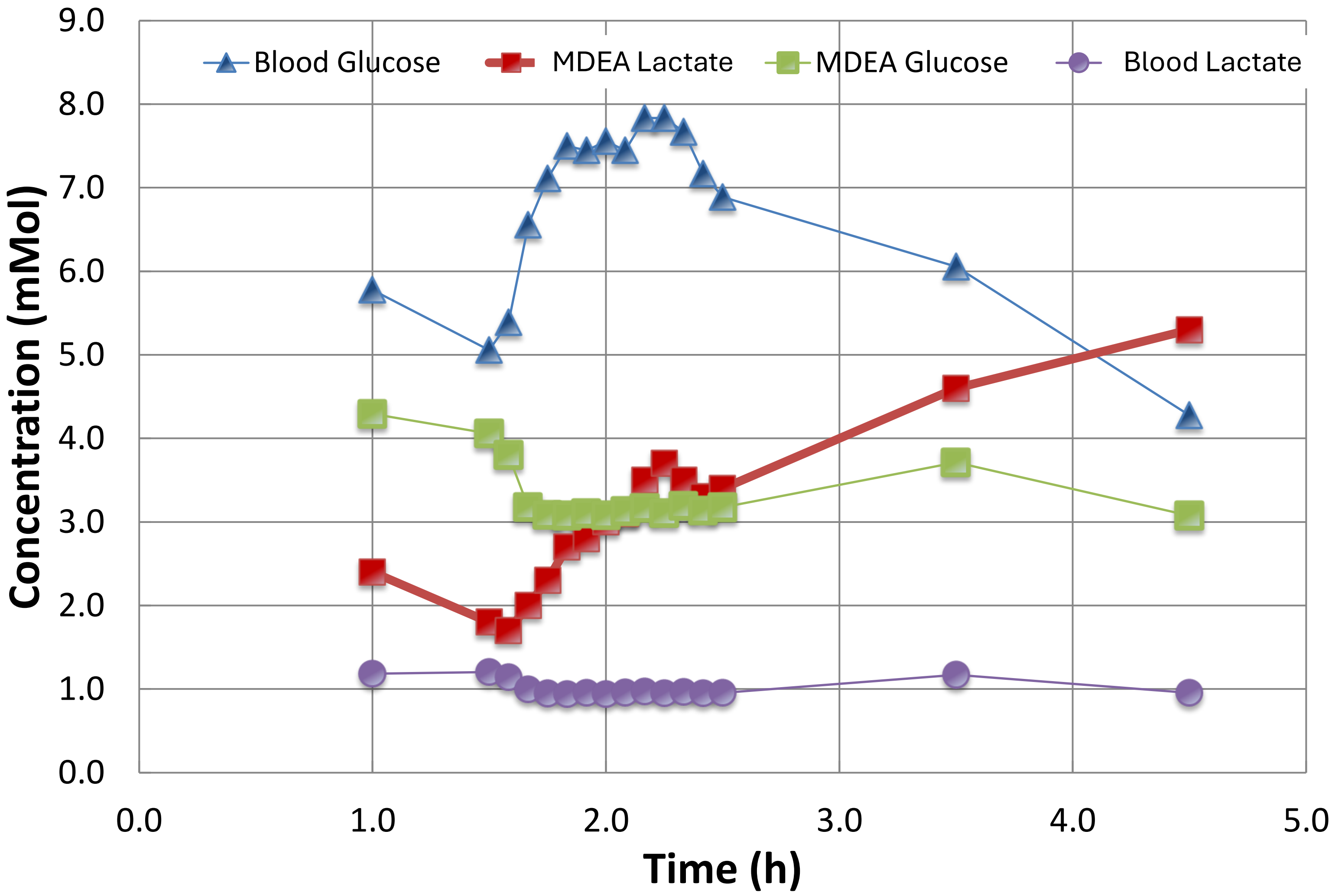


Anthony Guiseppi-Elie "An Implantable Biochip to Influence Patient Outcomes Following Trauma-induced Hemorrhage" *Journal Analytical and Bioanalytical Chemistry* (**2011**) 399(1), 403-419.

In vivo amperometric performance of the implanted PSMBioChip during hemorrhage – *Sus scrofa* – pig model.

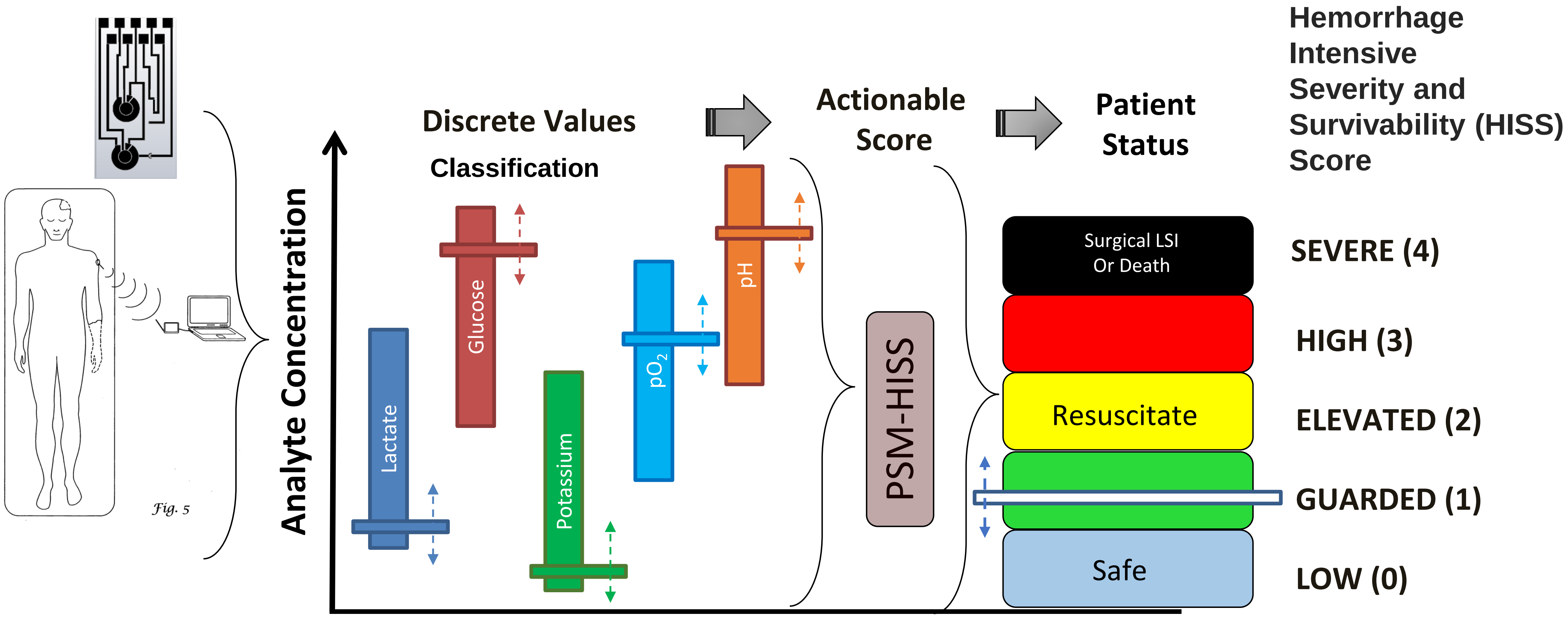


Sus scrofa



Unpublished

Patient stratification for improving hemorrhagic trauma outcomes



PSM Biochip Data To Hemorrhage Intensive Severity and Survivability (**HISS**) Score

Guiseppi-Elie et al. (**2013**) *Biomed Microdevices*, 15(3), 561-577

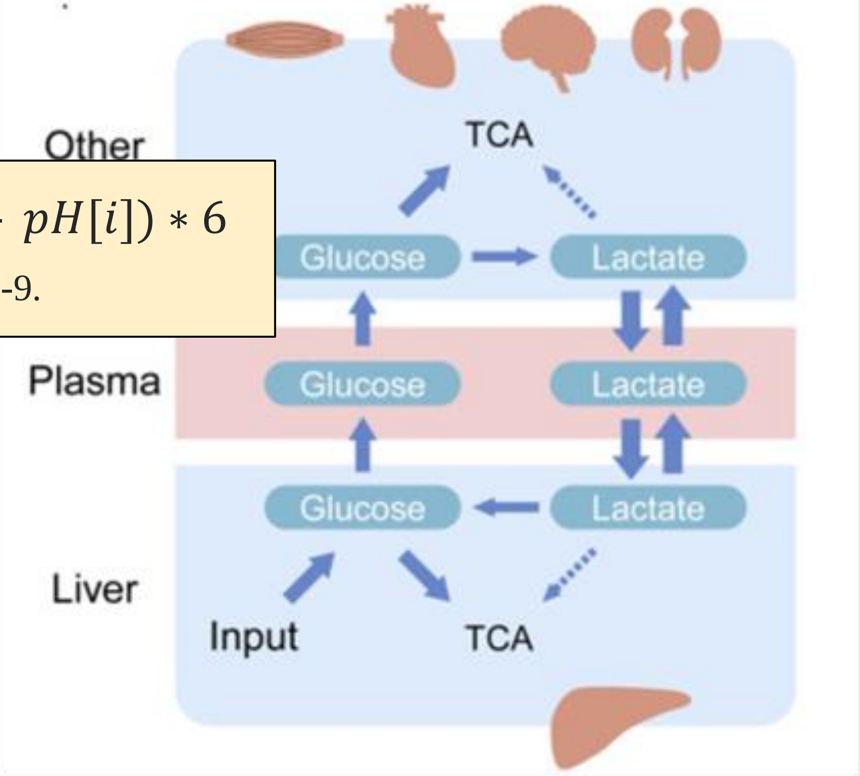
Pathophysiological Intravascular Ranges: Metabolic Indicators

Analytes	Pathophysiological range		
	LOW	NORMAL	HIGH
Glucose	**Hypoglycemia <3.88 mM <70 mg/dL**	Euglycemia 3.88 – 5.5 mM 70-99 mg/dL	Hyperglycemia >5.5 – 10 mM 99
Lactate	Hypolactatemia < 0.5 mM	Eulactatemia 0.5 – 2.0 mM	**Hy >2**
Potassium	Hy (<3		
pH	**Acidosis (<7.35)**	7.35 - 7.45	Al
pO_2	**Hypoxia <5.18 mM <100 mmHg**	5.18 - 6.22 mM While breathing in, 160 mmHg, gradient 100-120 mmHg	Hy >1

$$[K^+]_i = random([K^+]_{normal}) + (7.35 - pH[i]) * 6$$

Burnell et al. *J Clin Invest* 1956;35(9):935-9.

Liu et al. *Cell Metabolism*, 32(4) 2020, 619-628.e21



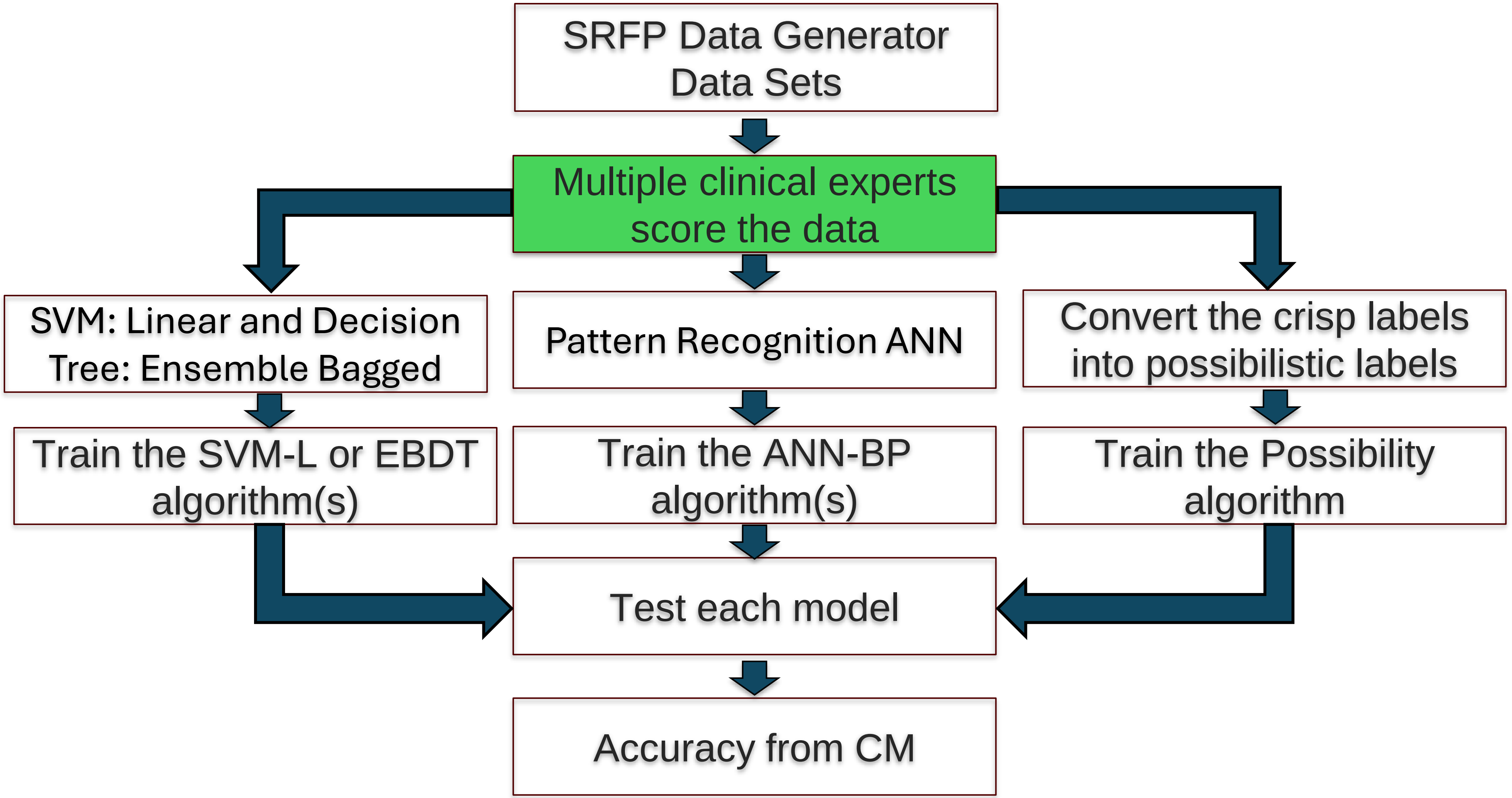
Glucose: Hirshberg, Eliotte et al. (2008), *Pediatric Critical Care Medicine, 9(4), 361-366*
Potassium: Viera, Anthony J., (2015) *American family physician, 58(4), 777-782*
Lactate and pH: Andersen, Lars W., et al, (2013) *Mayo Clinic Proceedings,* Vol. 88, No. 10, pp. 1127-1140
pO_2: de Jonge, Evert, et al.(2008), *Critical care,* 12(6), R156

Patient Data Sets for Key Metabolites

1. Sensibly Rationalized Fictitious Patient (SRFP) Data for deep learning model

- Unavailability of adequate clinical **stat** data
- Unavailability of adequate clinical **temporal** data
- Need to establish proof of concept for the approach
- Low-cost digital equivalent of large patient data sets
- Possibility for data engineering

Flowchart for classification, pattern recognition and possibility analysis to produce accuracy from the confusion matrix (CM).



Sensibly Rationalized Fictitious Patient (SRFP) Data to Hemorrhage Intensive Severity and Survivability (**HISS**) Score

Fictitious Patient	Sensibly Rationalized Fictitious Patient (SRFP) Data					**HISS Score**				
	Glucose (mg/dL)	Lactate (mmol/L)	pH	Potassium (mmol/L)	pO_2 (mmHg)	D1	D2	D3	D4	D5

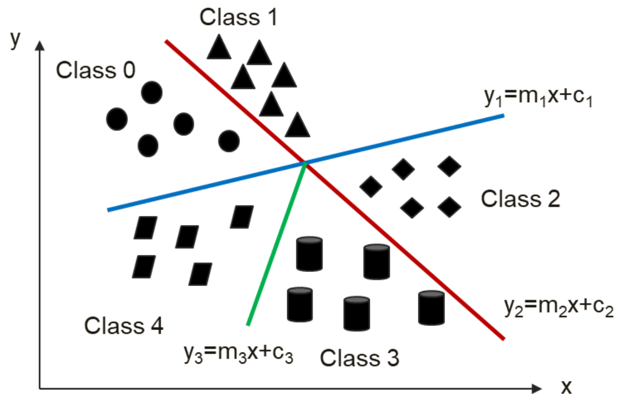
LOW (0) **GUARDED (1)** **ELEVATED (2)** **HIGH (3)** **SEVERE (4)**

Total patient data set size is 100

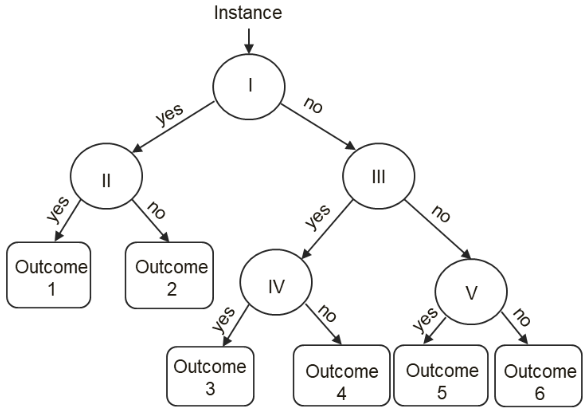
http://people.tamu.edu/~guiseppi/resources-HISS.html

Questions addressed

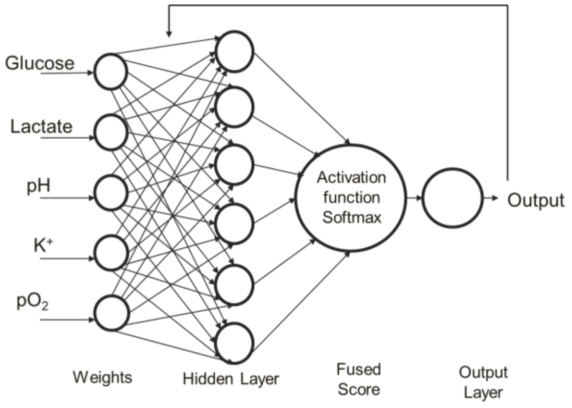
- Which classification algorithm is best suited to the challenge of fusion scoring?
- What is the minimum data set needed to achieve 99% and 99.9% accuracy in patient stratification



Support Vector Machine - Linear



Decision Tree: Ensemble Bagged

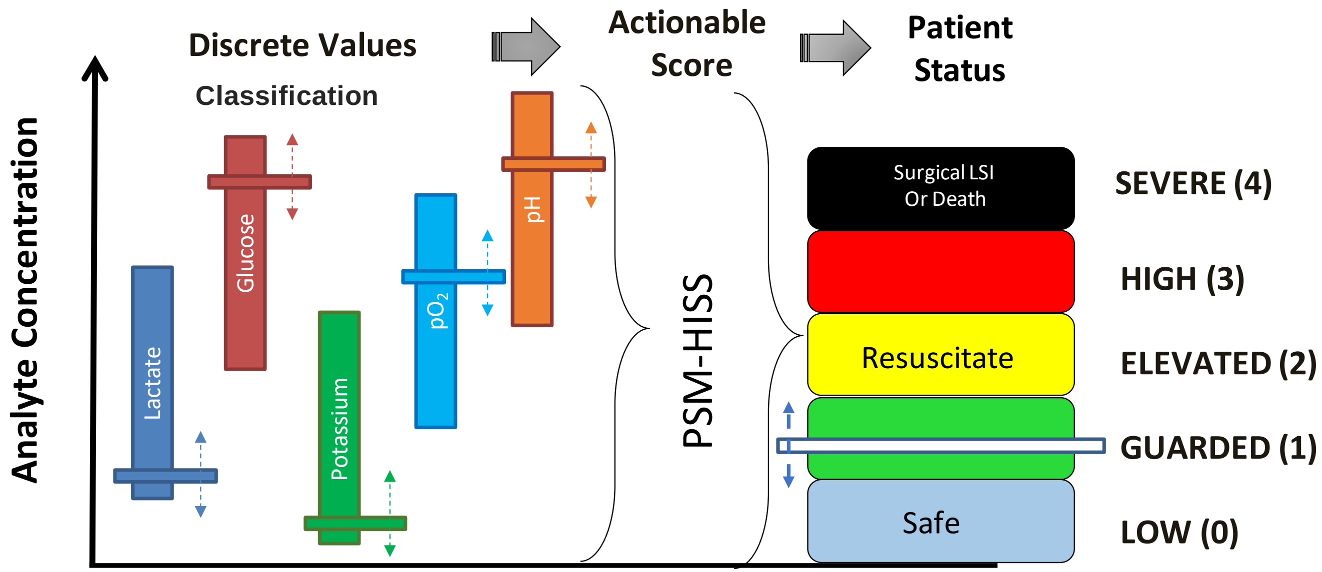


Artificial Neural Network with Bayesian Regularization (ANN:BR)

Mean Test and Training Accuracy

Class		Frequency [%]				
		[100]D1	[100]D2	[100]D3	[100]D4	[100]D5
LOW (0)	0	56	43	37	43	53
GUARDED (1)	1	14	20	27	18	17
ELEVATED (2)	2	5	18	7	15	13
HIGH (3)	3	19	17	11	24	17
SEVERE (4)	4	6	2	18	0*	0*
SVM-L accuracy [%]		78.3±0.5	92.7±0.5	78.3±2.4	88.3±0.5	86.7±0.9
EBDT accuracy [%]		83.3±1.2	96.3±0.9	72.3±0.9	90.0±0.0	87.7±1.2
Class with the highest confusion (TPR – sensitivity for EBDT)		4 (17%)	4 (0%)	2 (14%)	2 (60%)	2 (77%)

Summary



Algorithm	Accuracy
SVM-L	0.91±0.06
EBDT	0.93±0.04
ANN:BR	0.92±0.07
PRBF	0.92±0.03

Projection

[147]7 (99%)

[154]9 (99.9%)

Bhat, A., Podstawczyk, D., Walther B. K., Aggas J.R., Machado-Aranda D., Ward K.R., & Guiseppi-Elie, A.). **Toward a hemorrhagic trauma severity score: fusing five physiological biomarkers** *Journal of Translational Medicine* (**2020**) 18(1)384.

Collaborators

Collaborative program established with Tripler Army Medical Center – **Catherine Uyehara, Ph.D.**, Chief, Dept. Clinical Investigation: **Implantation In Piglet Trauma Model**

U.S. ARMY
PACIFIC REGIONAL MEDICAL COMMAND
TRIPLER ARMY MEDICAL CENTER

Collaborative program established with Medical University of South Carolina – **Edward C. Jauch, M.D. M.S., FACEP, FAHA**, Former Director, Division of Emergency Medicine: **Role of First Responders**

MUSC Health
MEDICAL UNIVERSITY of SOUTH CAROLINA

Collaborative program established with University of Michigan – **Lt. Col. Kevin R. Ward, M.D.**, Professor, Emergency Medicine and Exec. Director, Michigan Center for Integrative Research in Critical Care: **PSM Biochip and HISS Score**

Stratification of Vascularized Composite Allografts

The next slide contains surgically graphic images

Vascularized Composite Allografts

Allotransplantation ...the transfer of anatomical structures containing multiple tissue types including skin, bone, fat, muscle, and connective tissue from one individual to another.

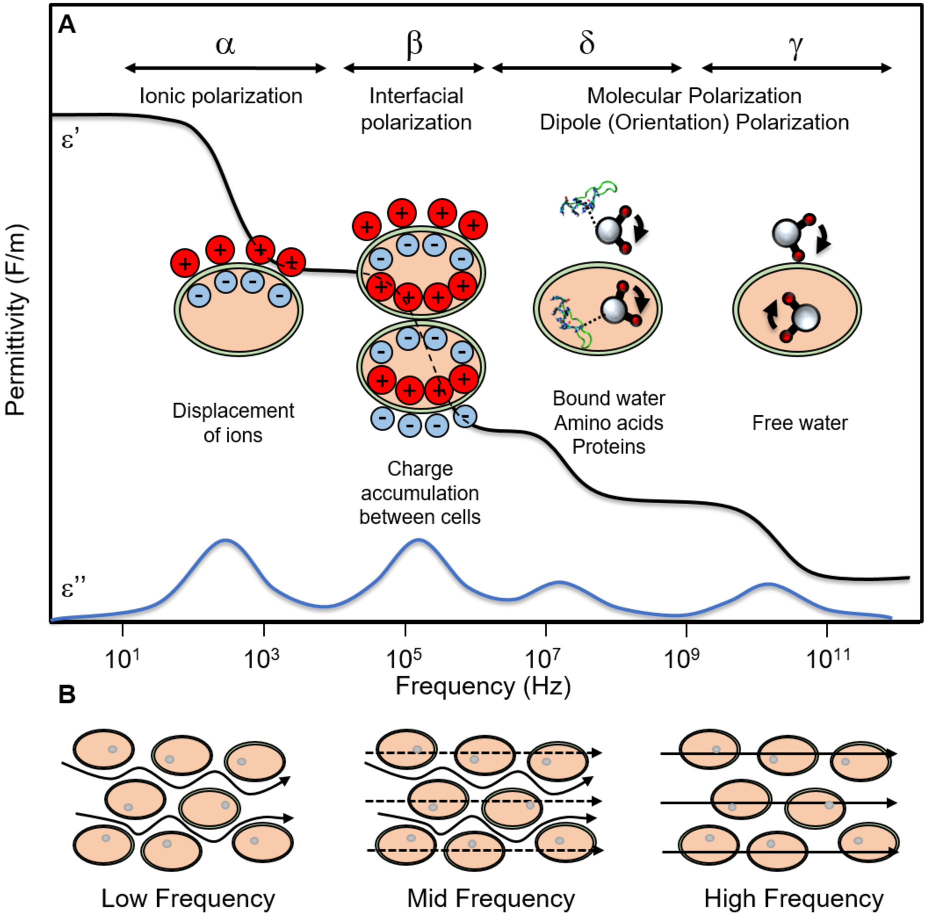
Face Transplant

Hand Transplant

Edema (swelling due to fluid retention) is the main clinical Indicator of acute rejection in VCA

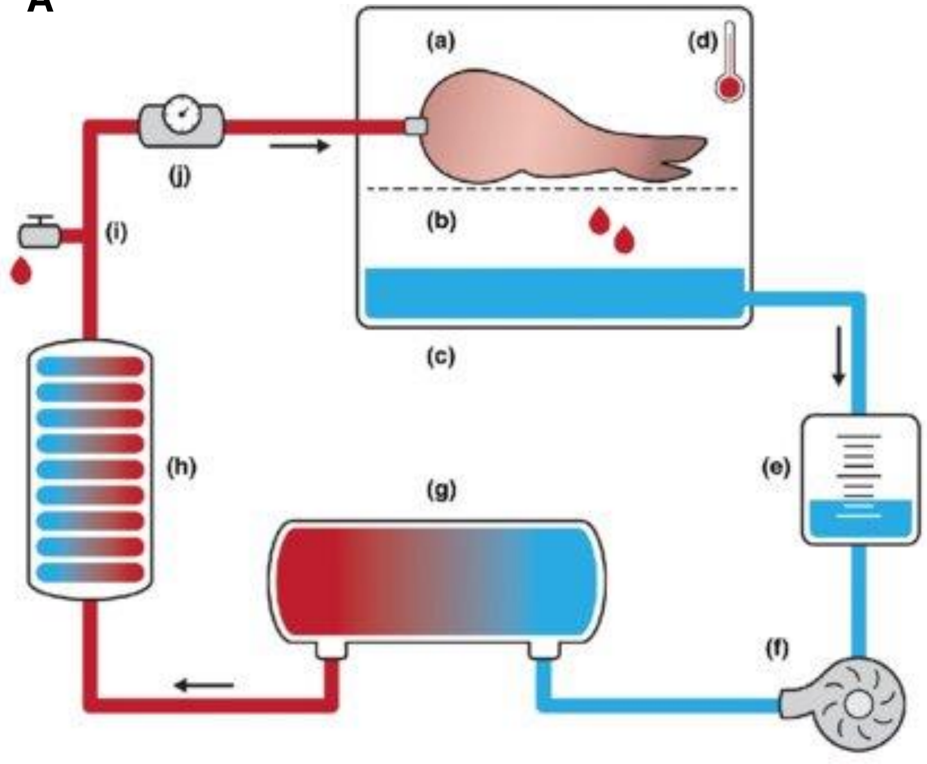
Edema may be measured and monitored by **Bioimpedance Spectroscopy (BIS)**

Bioimpedance Monitoring

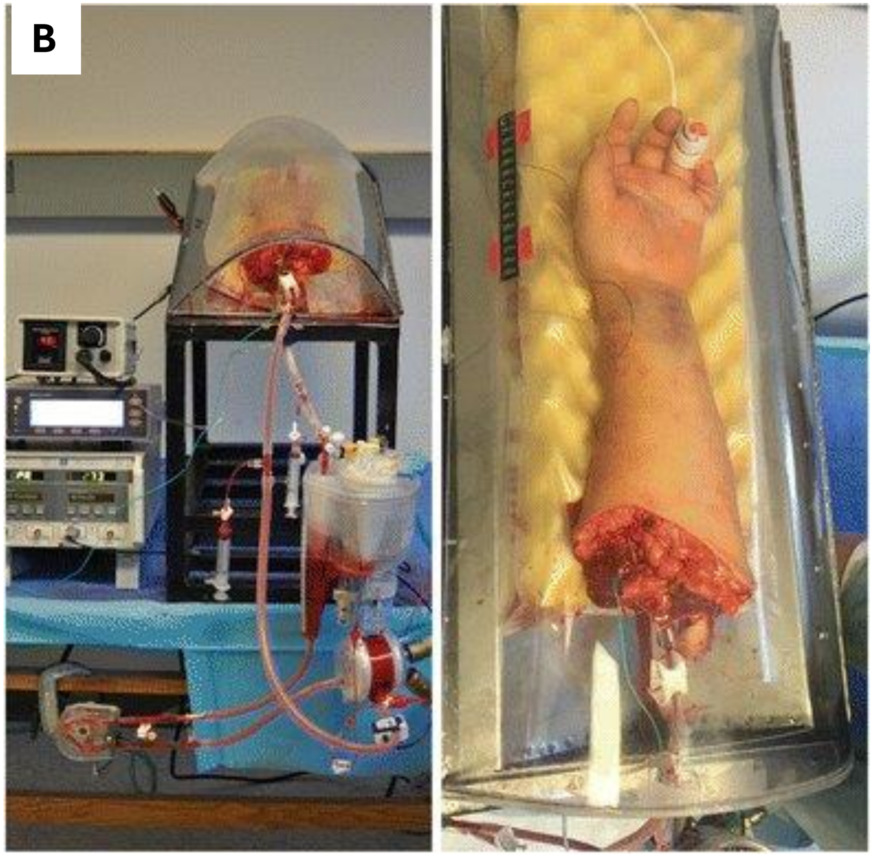


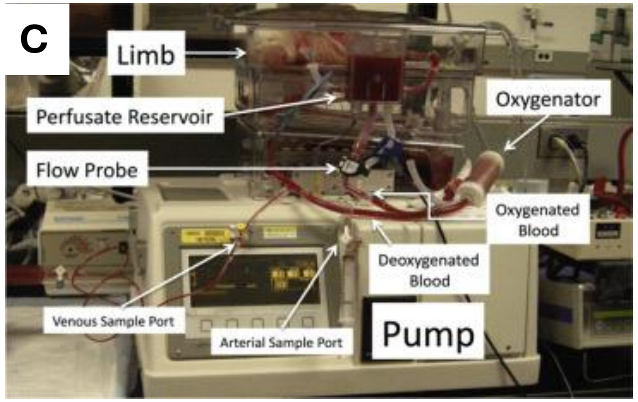
Abasi, Aggas, Garayar-Leyva, Walther and Guiseppi-Elie* "Bioelectrical Impedance Spectroscopy for Monitoring Mammalian Cells and Tissues under Different Frequency Domains: A Review" *ACS Measurement Science Au* (**2022**) 2, 6, 495–516.

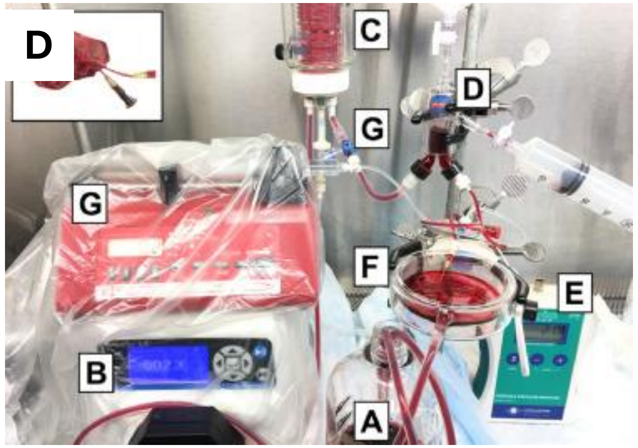
Extracorporeal System used in VCA *ex-vivo* Perfusion



Kruit et al. (2021), *Transpl Int,* 34: 365-375



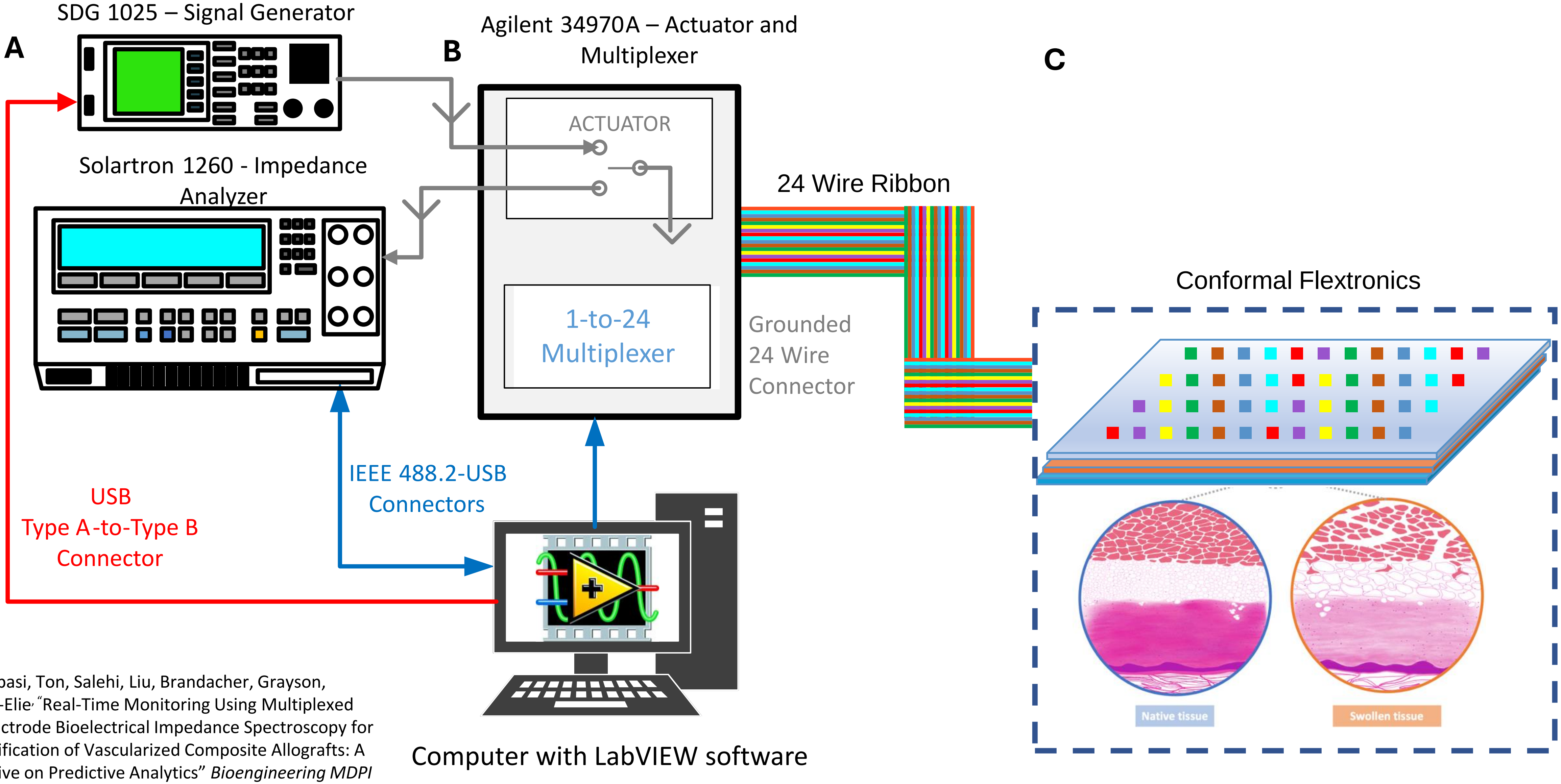




Banff classification of acute rejection in skin-containing allografts

Grade	Classification	Comments
Grade 0	None	No or rare inflammatory infiltrates.
Grade I	Mild	Mild perivascular infiltration. No involvement of the overlying epidermis.
Grade II	Moderate	Moderate-to-severe perivascular inflammation with or without mild epidermal and/or adnexal involvement (limited to spongiosis and exocytosis. No epidermal dyskeratosis or apoptosis.
Grade III	Severe	Dense inflammation and epidermal involvement with epithelial apoptosis, dyskeratosis, and/or keratinolysis.
Grade IV	Necrotizing acute rejection	Frank necrosis of epidermal or other skin structures.

Multielectrode Multiplexed Bioimpedance Spectroscopy (MMBIS) for Monitoring of Edema in VCA

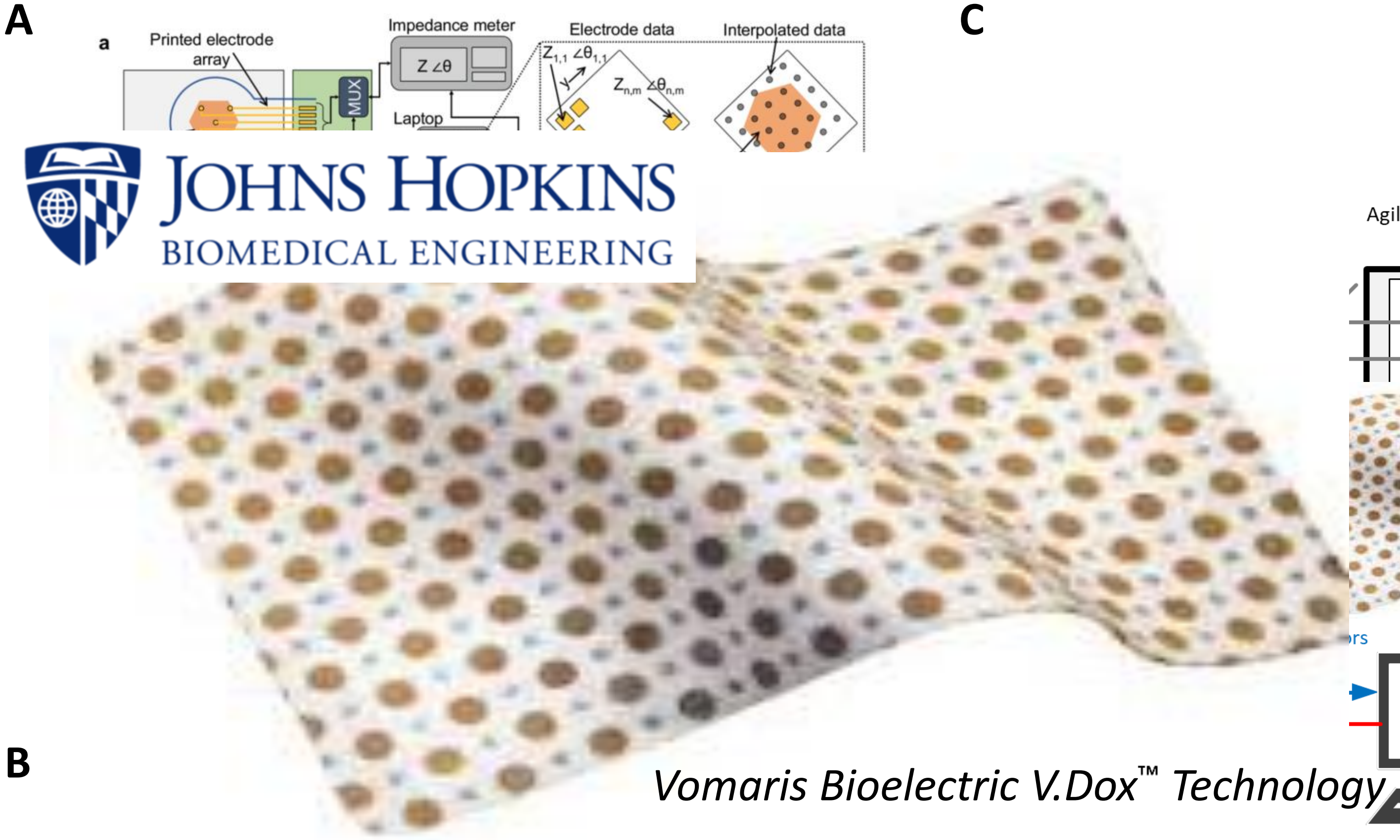


Aggas, Abasi, Ton, Salehi, Liu, Brandacher, Grayson, Guiseppi-Elie, "Real-Time Monitoring Using Multiplexed Multi-electrode Bioelectrical Impedance Spectroscopy for the Stratification of Vascularized Composite Allografts: A Perspective on Predictive Analytics" *Bioengineering MDPI* **2023**, *10*(4), 434.

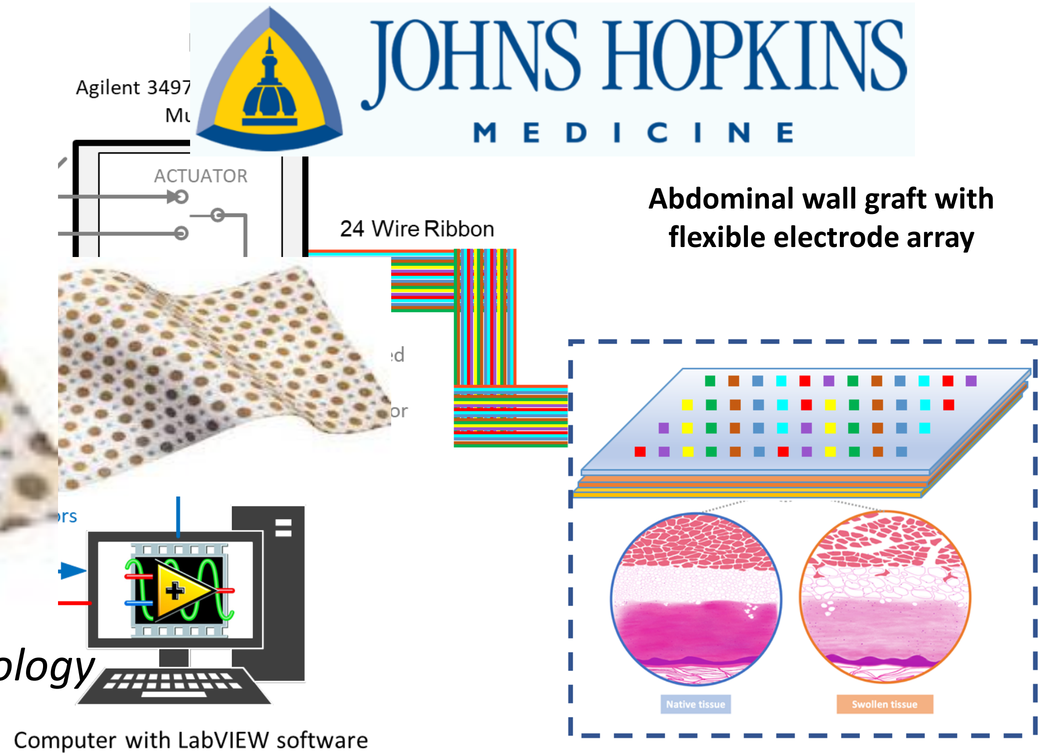
AI-enabled Predictive Analytics

Diagnostic Monitoring and Prognostics for Vascularized Allographs

A



C



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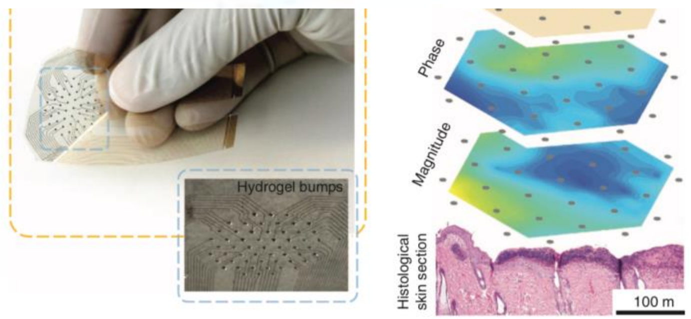


A) Inkjet-printed gold electrode array for impedimetric analysis of surfaces with imprinted insulation, from Khan et al. 2016.
B) Electrode array used to generate tomographical impedance map of collapsed tissue, from Swisher et al. 2015.
C) Application of multiplexed electrode arrays to abdominal wall VCA graft and subsequent data analysis from Guiseppi-Elie et al. 2020.

Pathophysiological Intravascular Ranges: MMBIS Profiles

Multielectrode Multiplexed Bioimpedance Spectroscopy (MMBIS)

	Pathophysiological Range			
Tissue Under Test	LOW	NORMAL (L)	NORMAL (H)	HIGH
Tissue Type:	**Blood Plasma**	**Muscle**	**Bone** (Cancellous)	**Fat**
Permittivity, ε_{100MHz} (S/m)	**????**	**6.60E+1**	**2.76E+1**	**1.27E+1**
Conductivity Av±SD (S/m)	**1.41E+0 ±2.14E-1**	**4.61E-1 ±2.44E-1**	**8.05E-2 ±9.42E-2**	**7.76E-2 ±9.31E-2**
Time Constant (τ) (ms) $\tau = [(R_0 - R_\infty)C]^{1/\alpha}$	**2.30E-4**	**9.84E-4**	**3.19E-3**	**2.23E-1**

https://itis.swiss/virtual-population/tissue-properties/database/

Pathophysiological Intravascular Ranges: Cytokine Profiles

Analyte	Pathophysiological range		
	LOW	NORMAL	HIGH
IL-1α	< 5 pg/mL (1)	5-50 pg/mL (1)	> 50 pg/mL (1)
IL-6	< 5 pg/mL (1) <4.3 pg/mL (7)	5-30 pg/mL (1) 1.2+/-0.6 pg/mL (2) 0-43.5 pg/mL (6) 0-1.8 pg/mL (8) <5 pg/mL (9) <14.8 pg/mL (11) 5-15 pg/mL (13)	> 30 pg/mL (1) >35 pg/mL (12)
IL-10	< 1 pg/mL (1) <10 pg/mL	1-10 pg/mL(1) 1.9+/- 1.1 pg/mL (2) <2 pg/mL (11)	> 10 pg/mL (1) >10 pg/mL (7)
TNF-α	< 5 pg/mL (1) <0.55 pg/mL (5)	5-20 pg/mL (1) 5.11-7.23 pg/mL (3) 0.55 – 1.65 pg/mL (5) <5.6 pg/mL (11) 0-16 pg/mL (13)	> 20 pg/mL (1) > 7.79 pg/mL (3) > 8.1 pg/mL (4) >1.65 pg/mL (5)
IFN-γ	< 5 pg/mL (1)	5-50 pg/mL (1) <2.2 pg/mL (11)	> 50 pg/mL (1) >19.5 pg/mL (10)

Patient Data Sets for Key Metabolites, Cytokines, and MMBIS

2. Sensibly Rationalized Fictitious Patient (SRFP) Data for deep learning model

- Unavailability of adequate clinical **stat** data
- Unavailability of adequate clinical **temporal** data
- Need to establish proof of concept for the approach
- Low-cost digital equivalent of large patient data sets
- Possibility for data engineering

Clinical Expert Data

	Sensibly Rationalized Fictitious Patient (SRFP) Data											VCA Score (0,1,2,3)		
DP	**Glucose (mg/dL)**	**Lactate (mmol/L)**	**pH**	**K^+ (mmol/L)**	**pO_2 (mmHg)**	**IL-1α**	**IL-6**	**IL-10**	**TNF-α**	**IFN-γ**	**MMBIS**	**CE-1**	**…**	**CE-N**
1	70	2.7	7.42	5.10	78	22	28	4	22	40	2.219E-3	1	0	1
2	160	6.0	7.11	6.14	44	45	22	15	40	32	4.521E-4	2	0	3
n	41	9.7	7.26	4.84	97									
..	..	..	..	..	..									
n+1	123	3.3	7.41	5.00	86									
n+2	49	8.7	7.13	5.92	53									
..	..	..	..	..	..									
n+25	220	8.6	7.23	4.52	92									

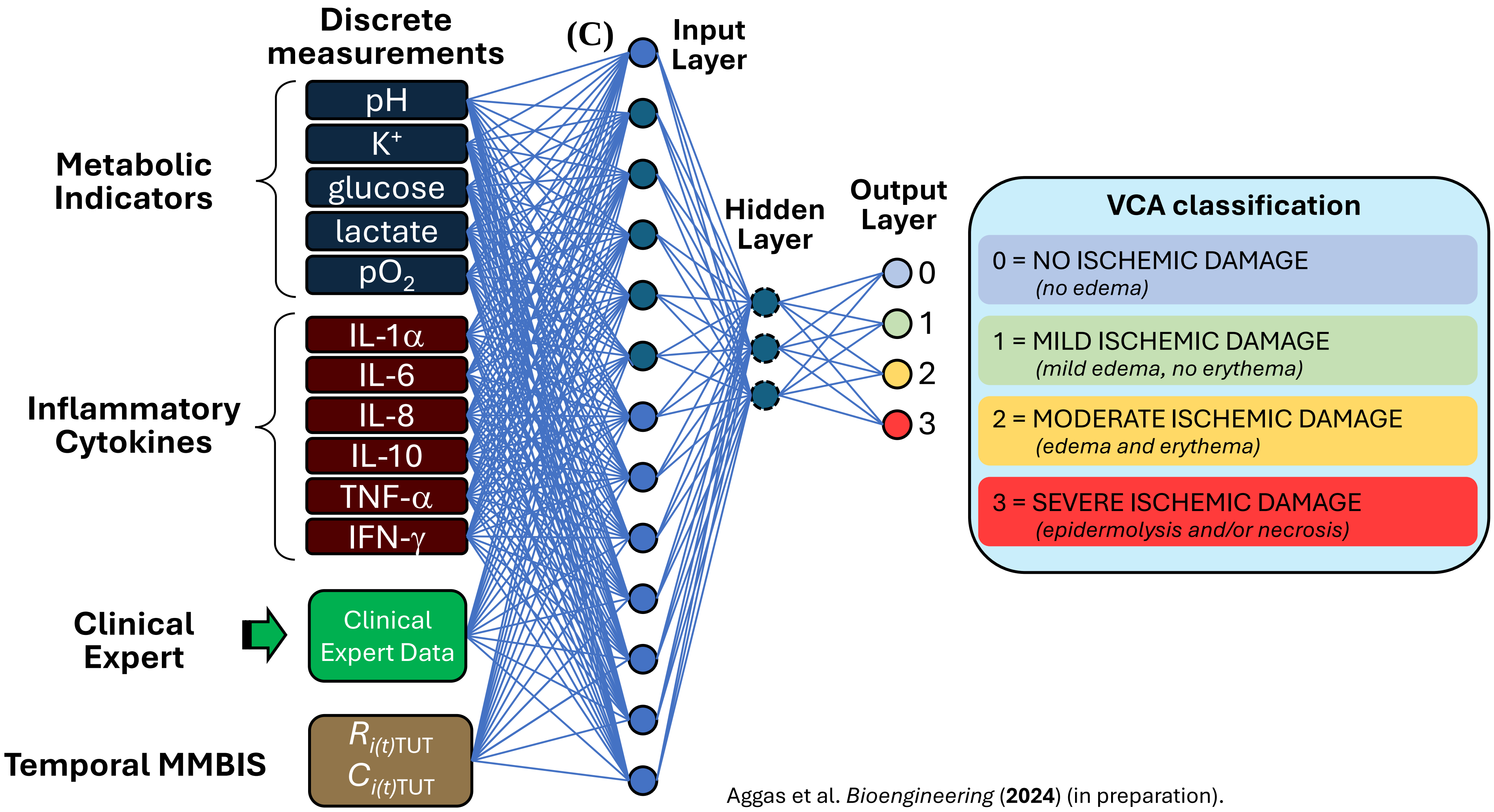
0 = NO ISCHEMIC DAMAGE
(no edema)

1 = MILD ISCHEMIC DAMAGE
(mild edema, no erythema)

2 = MODERATE ISCHEMIC DAMAGE
(edema and erythema)

3 = SEVERE ISCHEMIC DAMAGE
(epidermolysis and/or necrosis)

Accessing and/or Building Data Sets



Aggas et al. *Bioengineering* (**2024**) (in preparation).

Aggas et al. *Bioengineering* (**2023**) Mar 29;10(4):434.

Collaborators

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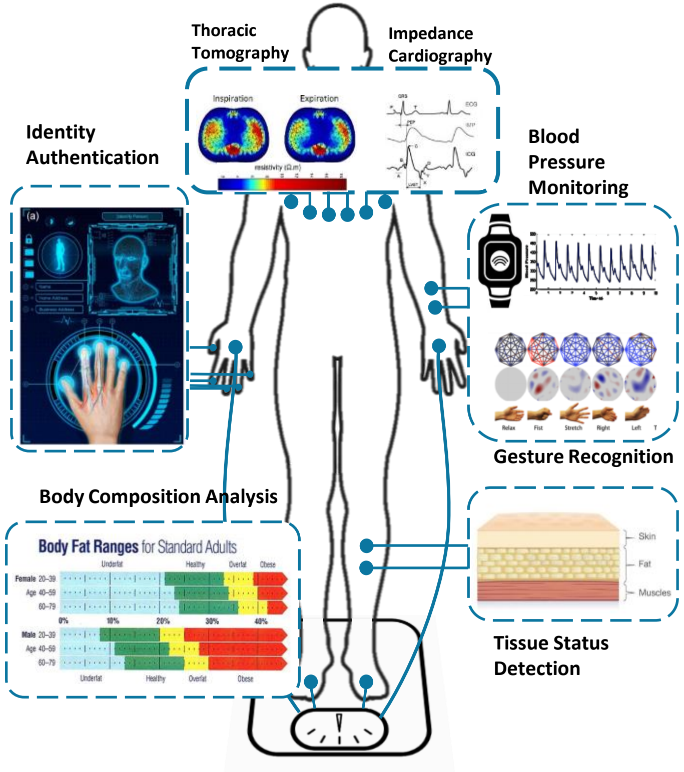
Warren L Grayson, PhD
Professor and Vice-Chair
Department of Biomedical Engineering
Transplantation Tissue Engineering Center
JOHNS HOPKINS BIOMEDICAL ENGINEERING



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bioengineering — MDPI

Perspective

Real-Time Monitoring Using Multiplexed Multi-Electrode Bioelectrical Impedance Spectroscopy for the Stratification of Vascularized Composite Allografts: A Perspective on Predictive Analytics

John R. Aggas [1,2,†], Sara Abasi [1,3,†], Carolyn Ton [4,5], Sara Salehi [4,5], Renee Liu [4,5], Gerald Brandacher [5,6], Warren L. Grayson [4,5,7,8,9,*] and Anthony Guiseppi-Elie [1,10,11,*]

Aggas§ and Abasi§, et al. *Bioengineering MDPI* **2023**, *10*(4), 434. https://doi.org/10.3390/bioengineering10040434

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ACS MEASUREMENT SCIENCE Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/measureau — Review

Bioelectrical Impedance Spectroscopy for Monitoring Mammalian Cells and Tissues under Different Frequency Domains: A Review

Sara Abasi,¶ John R. Aggas,¶ Guillermo G. Garayar-Leyva, Brandon K. Walther, and Anthony Guiseppi-Elie*

Abasi§ and Aggas§, et al. *ACS Measurement Science Au* (**2022**) 2, 6, 495–516. https://doi.org/10.1021/acsmeasuresciau.2c00033.

JOHNS HOPKINS BIOMEDICAL ENGINEERING — BIOMEDICAL ENGINEERING TEXAS A&M UNIVERSITY

BMC Part of Springer Nature

Journal of Translational Medicine

Methods of ex vivo analysis of tissue status in vascularized composite allografts

Carolyn Ton, Sara Salehi, Sara Abasi, John R. Aggas, Renee Liu, Gerald Brandacher, Anthony Guiseppi-Elie & Warren L. Grayson

Ton and Salehi et al. *BMC J. Transl. Med.* (**2023**) 21, 609. https://doi.org/10.1186/s12967-023-04379-x

CDMRP DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS
W81XWH-17-1-0630 (Grayson)
W81XWH-16-RTRP-IIRA (Grayson)
W81XWH-13-0409 (Guiseppi-Elie)

TEES Texas A&M Engineering Experiment Station
TEES-246413 (Guiseppi-Elie)

Electomics

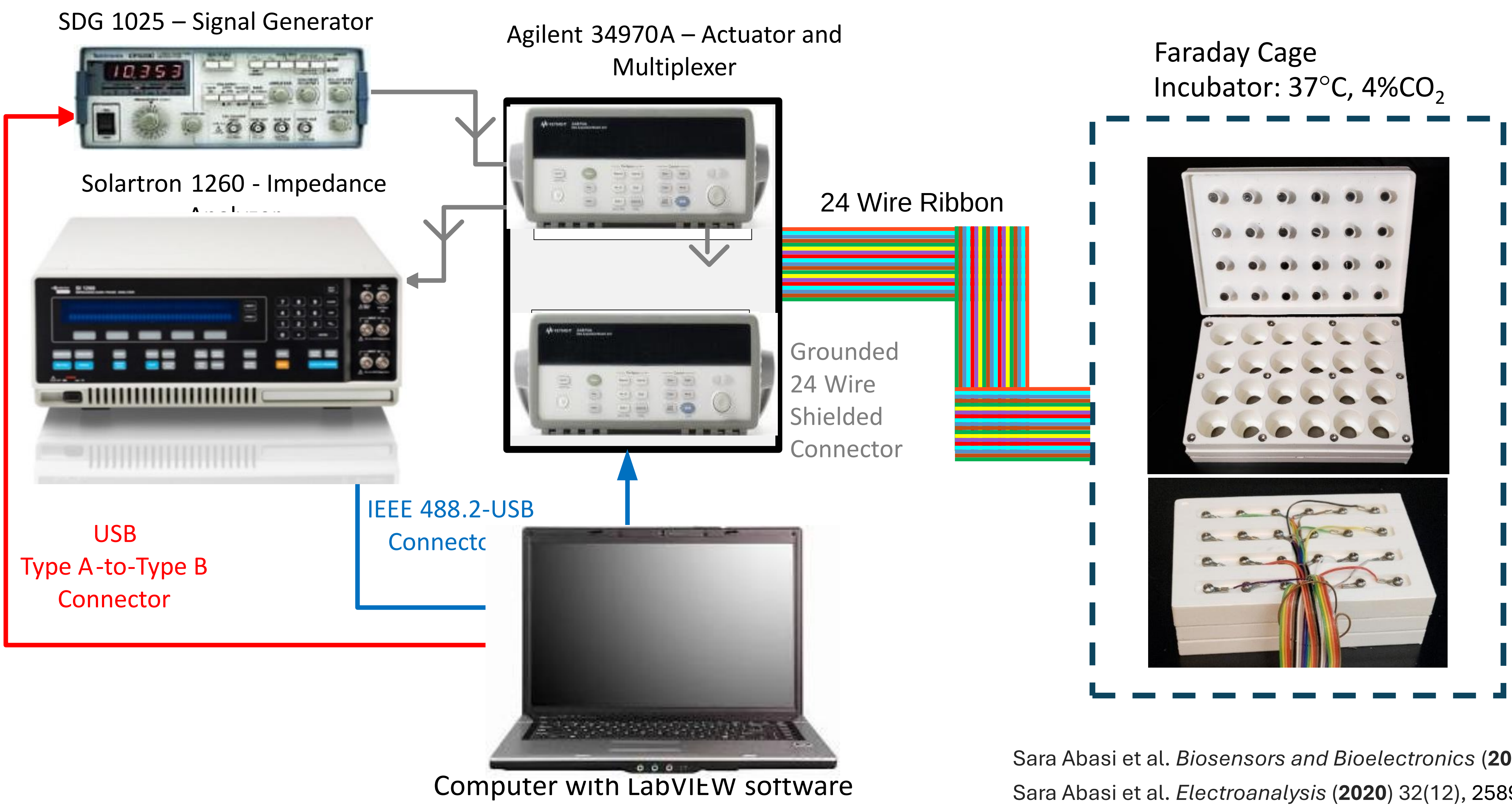
Gene Expression Under an Exogenous Electric Field

- Cellular gene expression and cell proliferation are known to be affected by electric fields (EF)[1].

- An apparatus (ECSARA) has been fashioned for concomitant application of EFs and multiplexed multi-frequency bioelectrical impedance spectroscopy (MMBIS) for isolating the effects of EF on cell biology[2].

- Trans Endothelial Electrical Resistance (TEER), cell proliferation and gene expression were examined under EF stimulation, with specific attention to a uniquely physically responsive yes-associate protein: YAP.

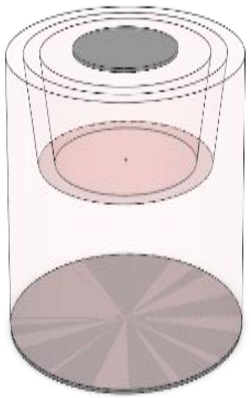
Electric Cell Stimulation And Recording Apparatus (ECSARA)



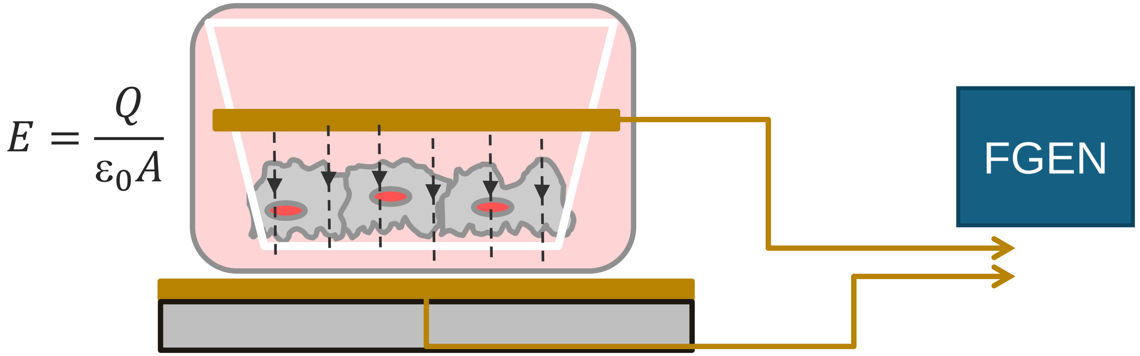
Sara Abasi et al. *Biosensors and Bioelectronics* (**2020**) 147, 111793

Sara Abasi et al. *Electroanalysis* (**2020**) 32(12), 2589-3188

Electric Cell Stimulation And Recording Apparatus (ECSARA)

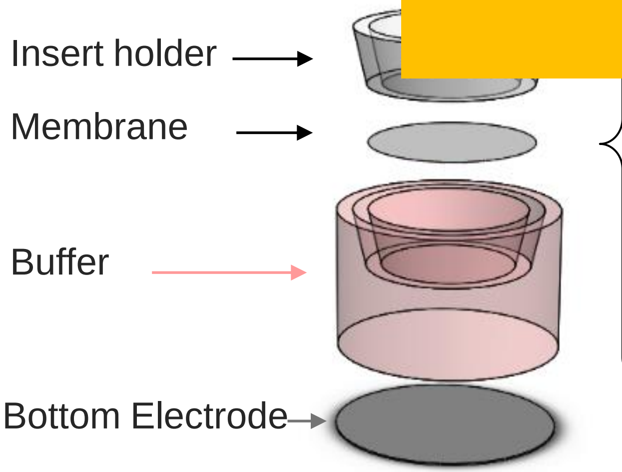


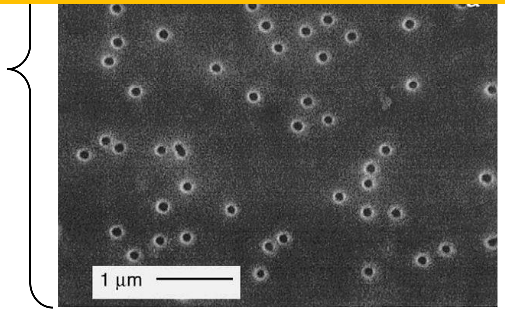
Cell Culture Insert

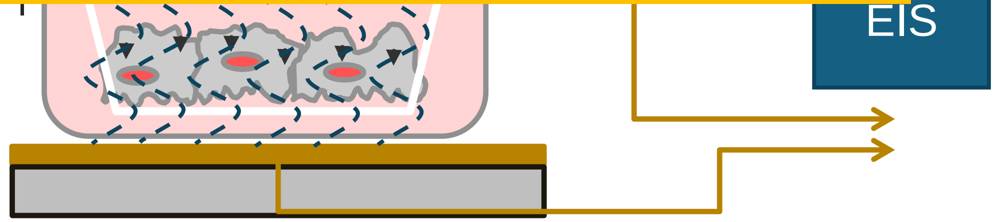


Electric Field Stimulation

Application of a uniform electric field to cells + in situ impedance measurement

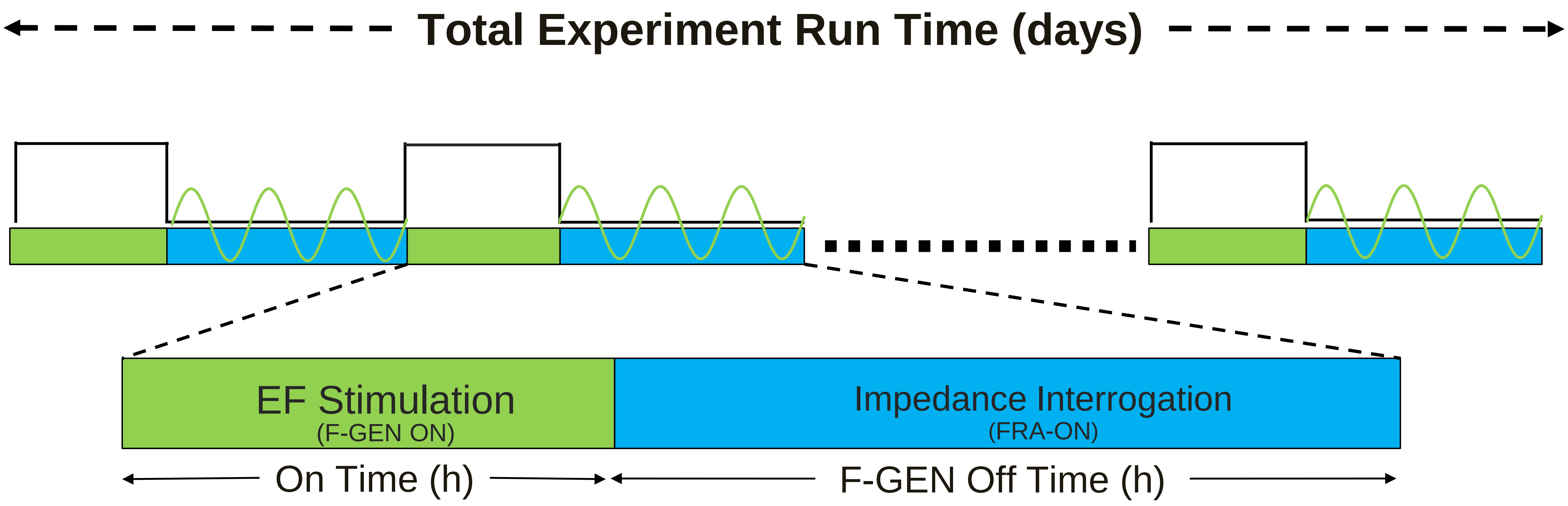






***In Situ* Multiplexed Multifrequency Bioelectrical Impedance Spectroscopy (MMBIS)**

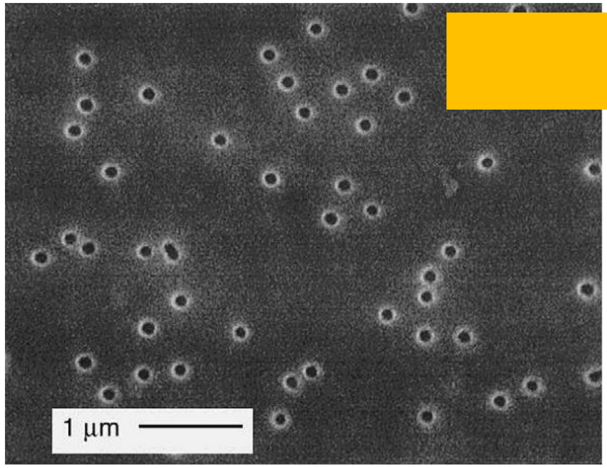
Typical Experiment Timeline



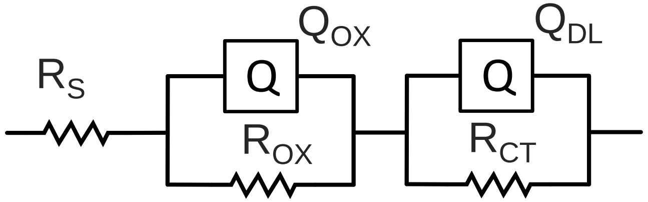
Selected E-Field signal applied to selected wells.

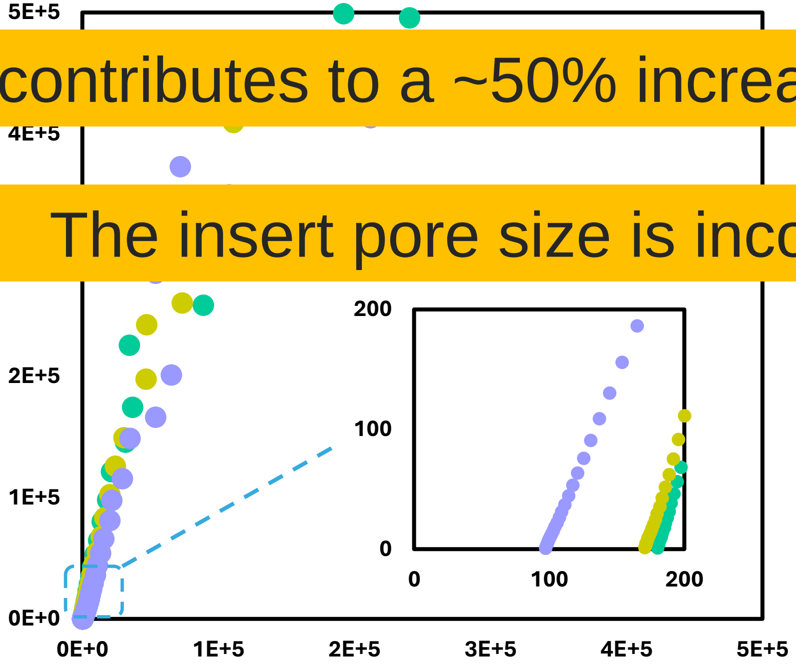
Multiplexed, serial Z-Interrogation of selected cells

Effect of cell culture insert pore size on trans-membrane impedance



Pore size = 0.4, 3.0 µm
Porosity = 12.6%, 14.0%

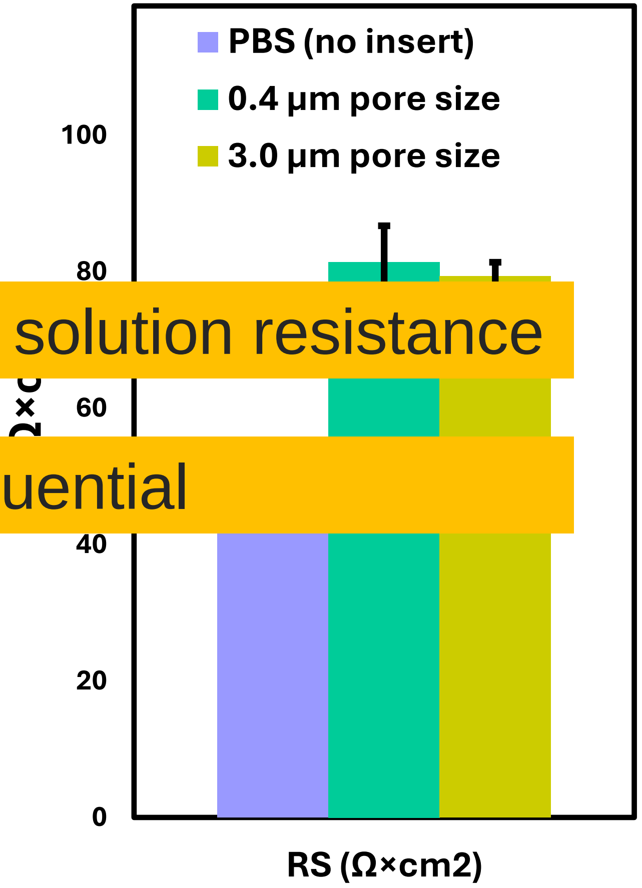




The insert contributes to a ~50% increase in solution resistance

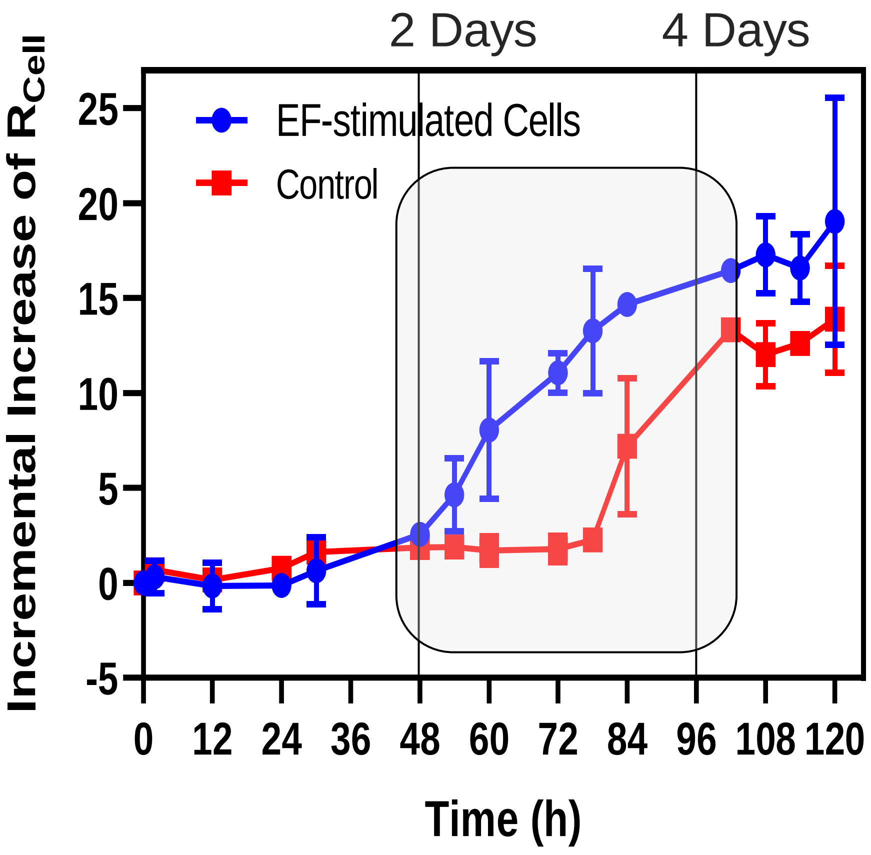
The insert pore size is inconsequential

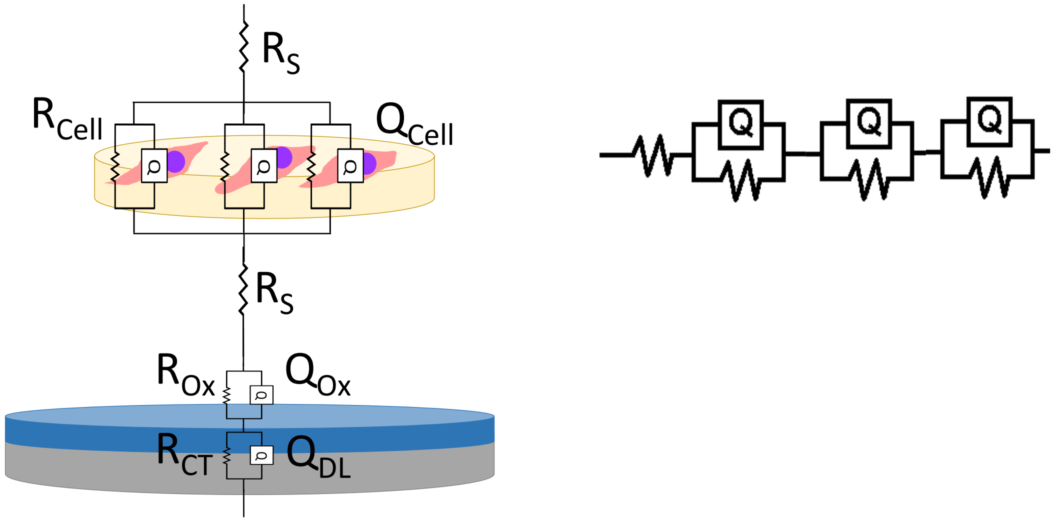
n=3



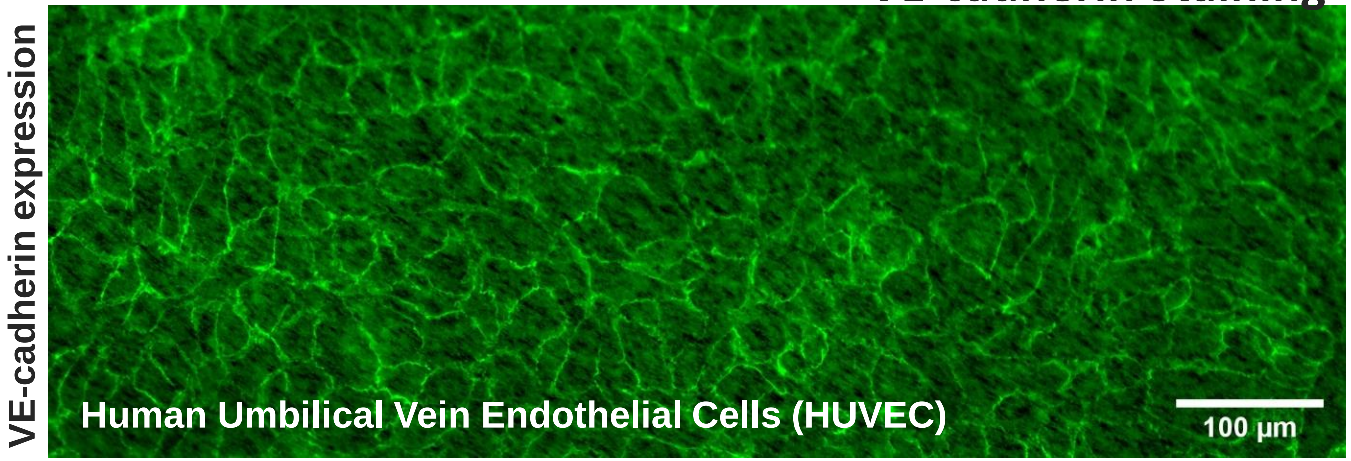
Human Umbilical Vein Endothelial Cells (HUVEC) - TEER

Cell Seeding:
5 x10^4 cells/mL or 3 x10^4 cells/cm^2





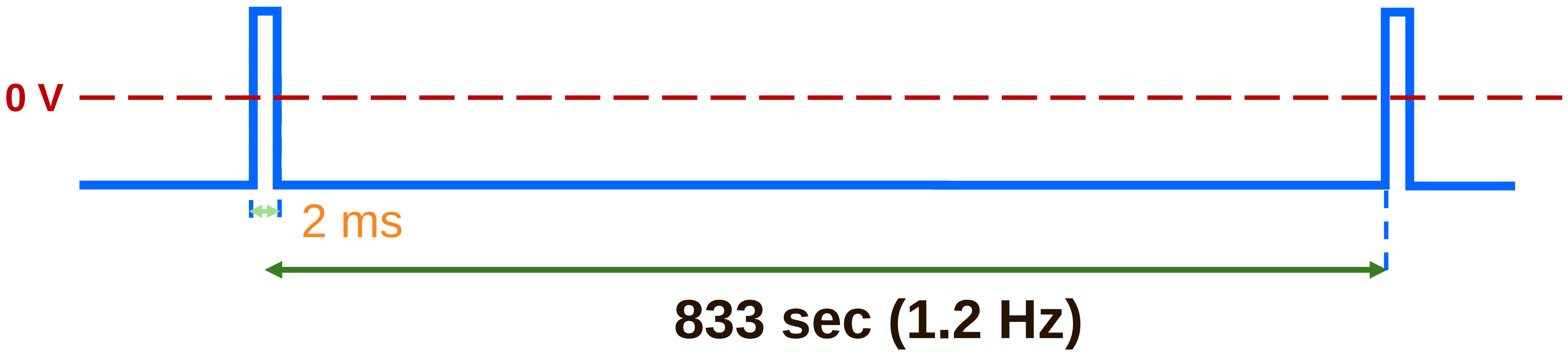
VE-cadherin Staining



Electrical Stimulation

Three EF stimulation conditions were explored:

- **T1** : Amp: 0.6V Freq.: 1.2 Hz Pulse Width: 2mS - 81 mV/mm
- **T2**: Amp: 1.2V Freq.: 1.2 Hz Pulse Width: 2mS - 162 mV/mm
- **T3**: Amp: 1.2V Freq.: 0.6 Hz Pulse Width: 2mS - 162 mV/mm
- **CTRL**: No stimulation



Sara Abasi and Brandon Walter et al. *BMES 2020* (**2020**) abstract on-line

Growth: Viability and Impedance Monitoring

- **Viability Assay:**
  - 10% Alamarblue® was added to the cells at predefined times and the absorbance of the supernatant was measured.

- **Impedance Spectroscopy:**
  - At predefined time, ES was stopped and MMBIS was performed using an interrogation voltage of **20mV p-t-p** over freq. range of **0.01 Hz – 1.0 MHz**.

Immunostaining and RT-PCR

Confocal Microscopy:

- YAP + VE-Cadherin stain – analysis of nuclear to total YAP ratio:

$$\boldsymbol{YAP\ Partition = \frac{Nuclear\ YAP}{Total\ YAP}}$$

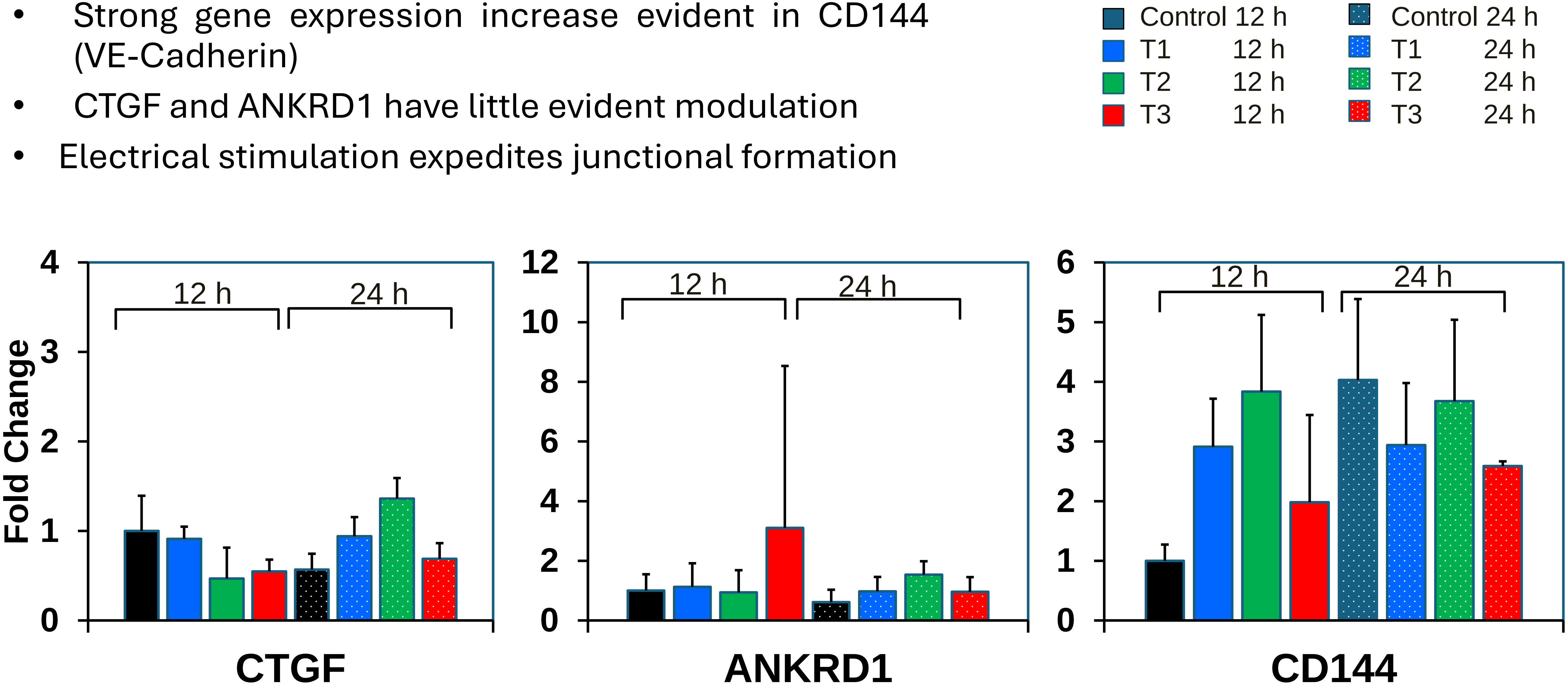
- This value is between 0 and 1, normalizing relative YAP activity across conditions and cell morphology
- Maximum Z projection used for all analysis

Gene Expression:

- Downstream YAP targets (CTGF and ANKRD1) and junctional marker (VE-Cadherin/CD144) using RTqPCR

Gene Expression

- Strong gene expression increase evident in CD144 (VE-Cadherin)
- CTGF and ANKRD1 have little evident modulation
- Electrical stimulation expedites junctional formation

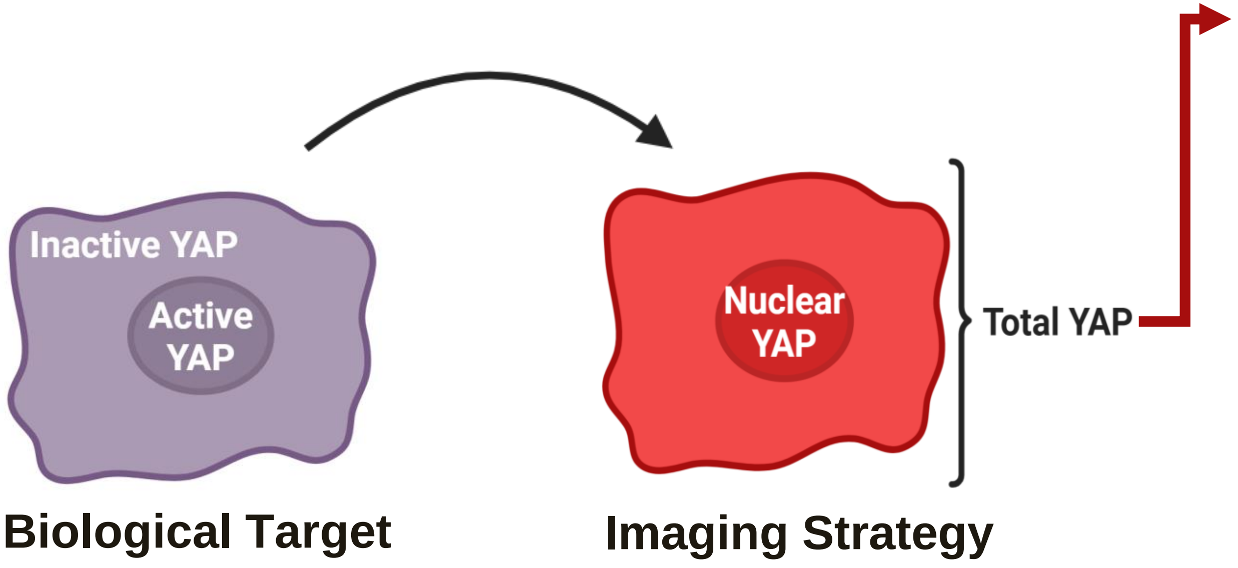


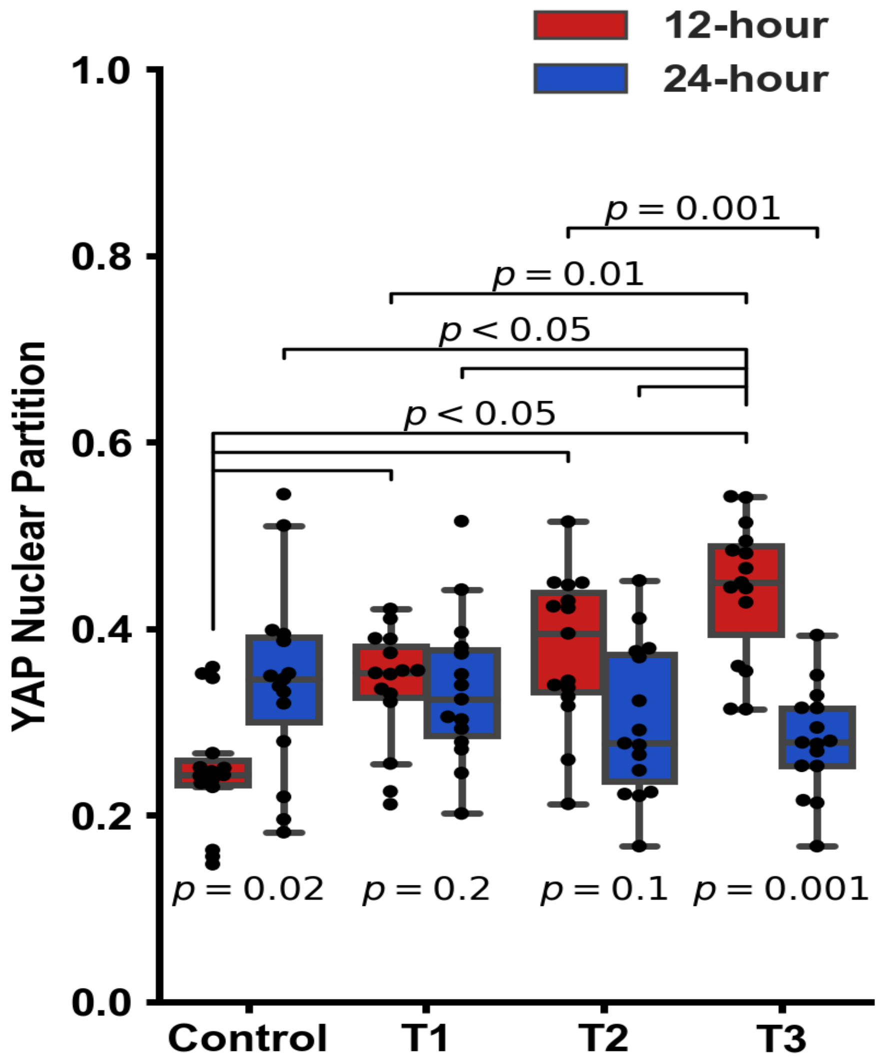
Yes-Associated Protein-1 (YAP) Localization

- 12-hour general upward trend of YAP nuclear partitioning with electrical stimulation (activation **RED**)
- General downward trend of YAP partitioning at 24 hours with electrical stimulation (deactivation **BLUE**)

OVERALL:

Electrical stimulation activates YAP, accelerating HUVEC proliferation





Key Findings

- Mild electrical stimulation can be used to turn on/off genes expressed by endothelial cells.
- Electrical stimulation has a proliferative effect, evidenced by accelerated junctional formation and increased YAP partitioning.
- EF seems a promising external stimulus where vasculogenesis and formation of endothelial cell monolayer are sought such as in tissue and regenerative engineering.

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Founding Editor-in-Chief, *Bioengineering*, President and Sr. Fellow, AIIMSEI

Dr. Rossana Madrid
Bioengineering Department, National University of Tucumán, Argentina

Plenary Speakers

Prof. Dr. Luke Pyung-Se Lee
Harvard Medical School, Harvard University, Brigham and Women's Hospital, Boston, USA.

Prof. Dr. Molly Shoichet
Institute of Biomedical Engineering, University of Toronto, Toronto, Canada.

Prof. Dr. Wai Yee Yeong
School of Mechanical & Aerospace Engineering, Nanyang Technological University, Singapore.

Prof. Dr. Kristala L. Jones Prather
Head of the Department of Chemical Engineering, Massachusetts Institute of Technology (MIT), Cambridge, USA.

Prof. Dr. Chuanbin Mao
Department of Biomedical Engineering, The Chinese University of Hong Kong, Hong Kong.


Danke


Thank you!