Implantable Biomedical Microelectromechanical Systems

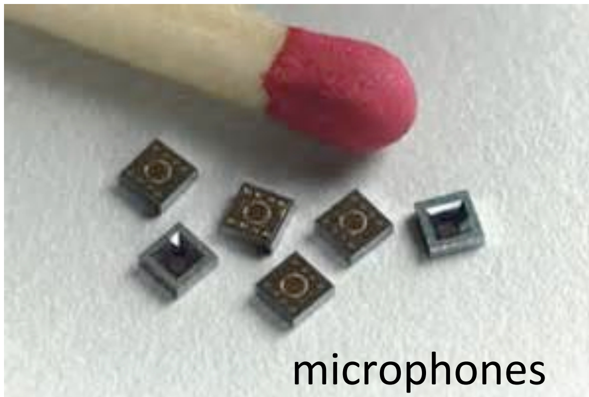
Mark G. Allen

Moore Professor of Electrical and Systems Engineering; and
Director, Singh Center for Nanotechnology
University of Pennsylvania
mallen@upenn.edu
http://mems.seas.upenn.edu

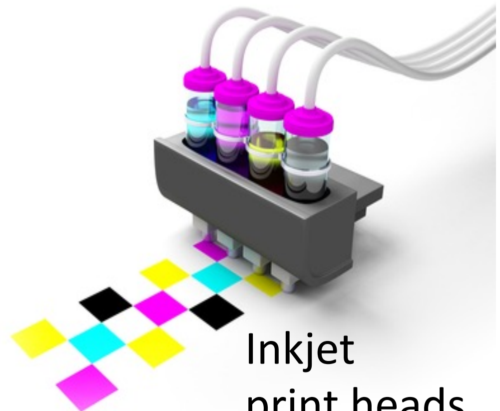
Outline

- Some historical perspectives on MEMS
- Medical microsystems and medical needs
- Implantable sensor examples
- Conclusions and acknowledgements

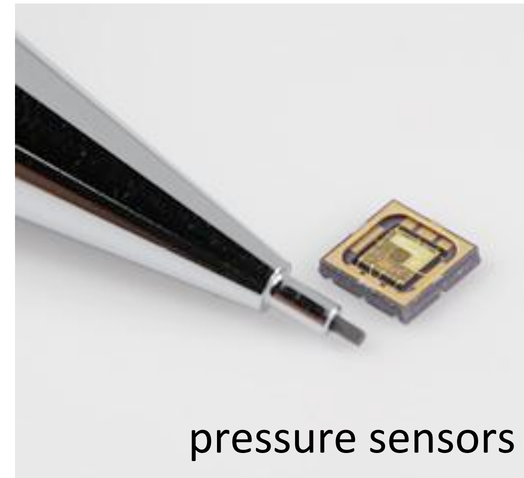
MEMS: Using Microfabrication to Produce Mechanical Structures and Transducers



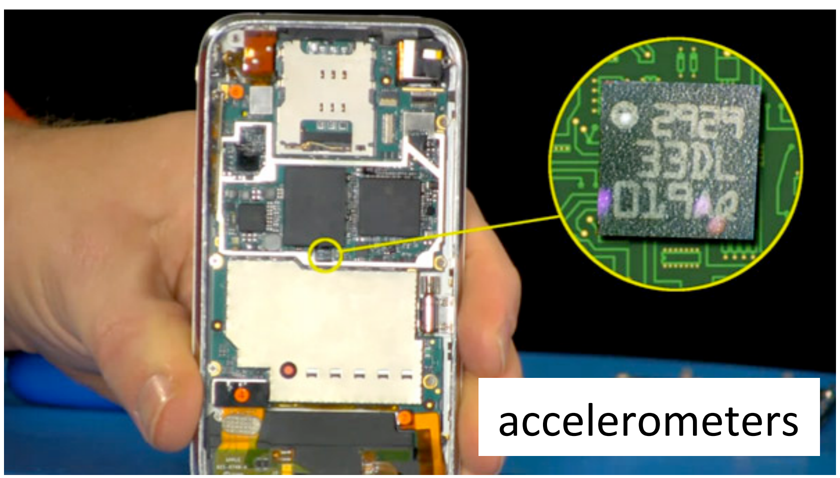
microphones



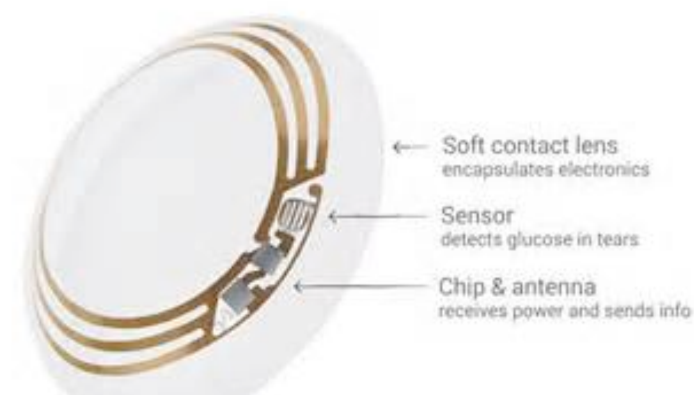
Inkjet
print heads



pressure sensors



accelerometers



chemical sensors

Medical Microsystems/MEMS

Microsystems based on the use of microfabrication and nanofabrication techniques to create mechanical structures, sensors, and actuators that can interface with parts of the human body, either *in-vitro* or *in-vivo*, to diagnose or treat disease

The Origins of MEMS

PROCEEDINGS OF THE IEEE, VOL. 70, NO. 5, MAY 1982

Silicon as a Mechanical Material

KURT E. PETERSEN, MEMBER, IEEE

Abstract—Single-crystal silicon is being increasingly employed in a variety of new commercial products not because of its well-established electronic properties, but rather because of its excellent mechanical properties. In addition, recent trends in the engineering literature indicate a growing interest in the use of silicon as a mechanical material with the ultimate goal of developing a broad range of inexpensive, batch-fabricated, high-performance sensors and transducers which are easily interfaced with the rapidly proliferating microprocessor. This review describes the advantages of employing silicon as a mechanical material, the relevant mechanical characteristics of silicon, and the processing techniques which are specific to micromechanical structures. Finally, the potentials of this new technology are illustrated by numerous detailed examples from the literature. It is clear that silicon will continue to be aggressively exploited in a wide variety of mechanical applications complementary to its traditional role as an electronic material. Furthermore, these multidisciplinary uses of silicon will significantly alter the way we think about all types of miniature mechanical devices and components.

I. INTRODUCTION

miniaturized mechanical devices and components must be integrated or interfaced with electronics such as the examples given above.

The continuing development of silicon micromechanical applications is only one aspect of the current technical drive toward miniaturization which is being pursued over a wide front in many diverse engineering disciplines. Certainly silicon microelectronics continues to be the most obvious success in the ongoing pursuit of miniaturization. Four factors have played crucial roles in this phenomenal success story: 1) the active material, silicon, is abundant, inexpensive, and can now be produced and processed controllably to unparalleled standards of purity and perfection; 2) silicon processing itself is based on very thin deposited films which are highly amenable to miniaturization; 3) definition and reproduction of the device shapes and patterns are performed using photographic

Petersen, 1982

The Origins of MEMS

NSF, 1987

**SMALL MACHINES,
LARGE OPPORTUNITIES:
A REPORT ON THE EMERGING
FIELD OF MICRODYNAMICS**

Report of the Workshop on Microelectromechanical
Systems Research

Workshop was held in three sessions:
Salt Lake City, Utah, July 27, 1987
Hyannis, Massachusetts, November 12, 1987
Princeton, New Jersey, January 28 - 29, 1988

Sponsored by the National Science Foundation

Any opinions, findings, conclusions, or recommendations expressed in this report are those of the workshop and do not necessarily reflect the views of the National Science Foundation or the employers of the panel members.

NSF, 1987

The Origins of MEMS

microdynamics. Microdynamical components and systems will use their own technologies in their own manufacture and thereby lead to improvements in the process or in the equipment. Microdynamical systems manufacture might also lead to advances in the microelectronics used to make the systems themselves, and could be used as a supplement to the batch fabrication of microelectronics parts. The snowballing effect of increased knowledge and more sophisticated microdynamics can only prove beneficial to the whole of microtechnology.

Below is a list of applications of microdynamical devices that appear feasible. These applications will result from systems and components that are likely to be demonstrated in laboratories during early research programs or that may appear as the initial product offerings in the next few years.

- Prosthetic devices, made lighter, cheaper, better articulated, with a greater range of function; or even prosthetic/artificial organs.
- Ingestible or implantable "smart pills" that have sensors and are combined with dose regulating drug dispensers. By actively dispensing the drugs these would differ from current passive devices; the receptacle would also be the dispenser.
- Connectors for repairing blood vessels. Silicon has the advantage of being inert in biological systems.
- Micro-manipulation of biological materials: for example, sorting of individual cells in order to make diagnostic tests, such as counting the number of white blood cells, or in order to perform artificial insemination.
- Catheter-based medical diagnosis. The flexible fiberoptics-based imaging systems already developed are limited by the inability of visible light to penetrate solid tissues. Researchers are now working on mechanical sector ultrasonic imaging systems that will form high-resolution, two-dimensional images of the tissues surrounding the catheter or endoscope. Scaling down these systems, which currently measure about 4 mm in diameter, will require microactuators. The imaging systems will extend the usefulness of current catheter-based instruments, and will provide

- Prosthetic devices, made lighter, cheaper, better articulated, with a greater range of function; or even prosthetic/artificial organs.
- Ingestible or implantable "smart pills" that have sensors and are combined with dose regulating drug dispensers. By actively dispensing the drugs these would differ from current passive devices; the receptacle would also be the dispenser.
- Connectors for repairing blood vessels. Silicon has the advantage of being inert in biological systems.
- Micro-manipulation of biological materials: for example, sorting of individual cells in order to make diagnostic tests, such as counting the number of white blood cells, or in order to perform artificial insemination.
- Catheter-based medical diagnosis. The flexible fiberoptics-based imaging systems already developed are limited by the inability of visible light to penetrate solid tissues. Researchers are now working on mechanical sector ultrasonic imaging systems that will form high-resolution, two-

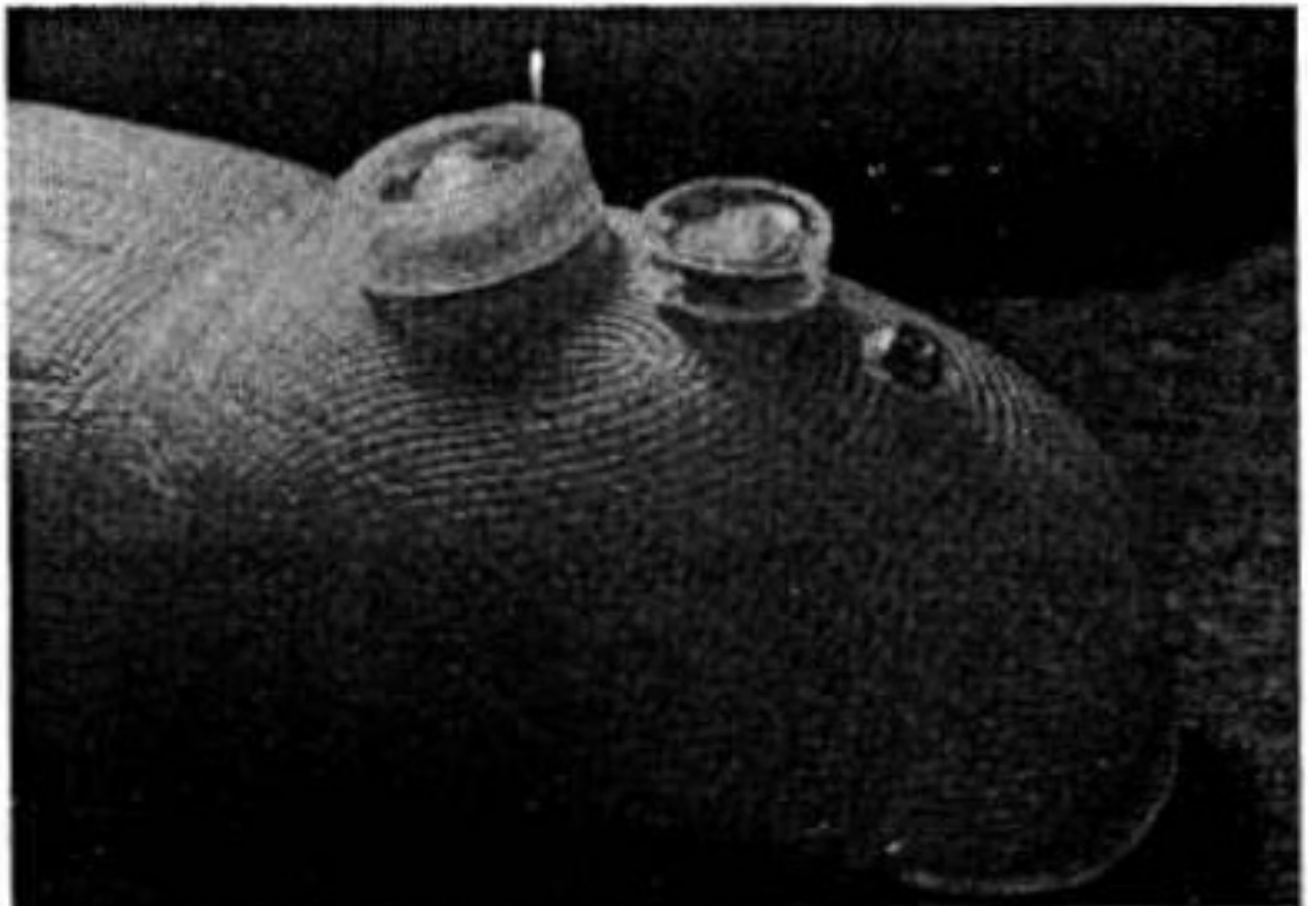
A Few Observations…

- People are living longer and longer
- Maintaining quality of life and independence as average age increases is demanded
- Disease states are becoming more complex (a consequence of success?)

- **More information** is required for <u>cost-effective</u> prevention and treatment of disease

Can medical microsystems help?

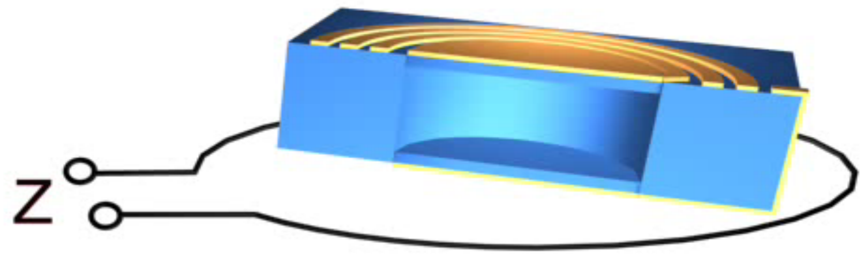
Implantable Sensors for Physiological Parameter Measurement: The Promise

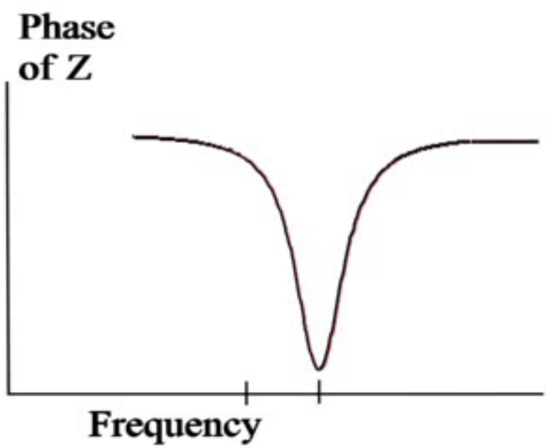


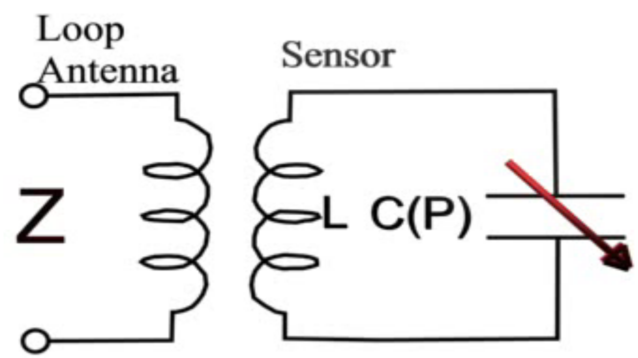
C. Collins, IEEE Trans. Biomedical Engineering April, 1967

Sensor Operational Concept

$$f = \frac{1}{2\pi\sqrt{L\,C(P)}}$$







Device Readout

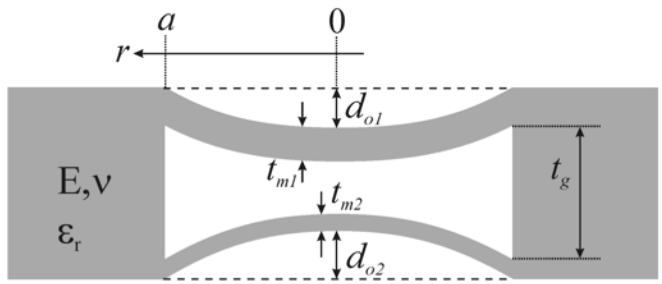
$$\frac{d_o}{t_m} + 0.488\left(\frac{d_o}{t_m}\right)^3 = \frac{3P(1-\nu^2)}{16E}\left(\frac{a}{t_m}\right)^4$$ d_0

$$C_o = \frac{\varepsilon_o \partial a^2}{t_g + 0.5 t_{m1}\varepsilon_r^{-1}} + \frac{\varepsilon_o \varepsilon_r \partial (a_e^2 - a_c^2)}{t_g + 0.5 t_{m1}}$$ $C(P_0)$

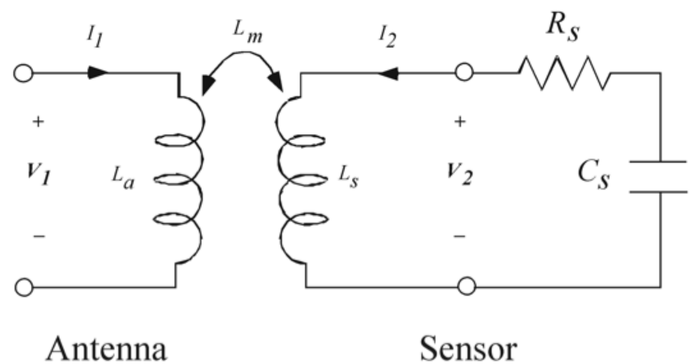
$$C_s(P) = C_o \sum_{i=0}^{\infty} \frac{1}{2i+1}\left(\frac{d_{o1} + d_{o2} + d_{i1} + d_{i2}}{t_g + 0.5 t_{m1}\varepsilon_r^{-1}}\right)^i$$ $C(P)$

$$f_o(P) = f_o(P=0)\left(\sum_{i=0}^{\infty} \frac{1}{2i+1}\left(\frac{d_{o1} + d_{o2} + d_{i1} + d_{i2}}{t_g + 0.5 t_{m1}\varepsilon_r^{-1}}\right)^i\right)^{-\frac{1}{2}}$$ $f_0(P)$

$$Z_1 = \frac{V_1}{I_1} = j2\pi f L_a \left[1 + k^2 \frac{\left(\frac{f}{f_o}\right)^2}{1 - \left(\frac{f}{f_o}\right)^2 + \frac{1}{Q} j \frac{f}{f_o}}\right]$$



$$f_0 = \frac{1}{2\pi}\left(\frac{1}{\sqrt{L_s C_s(P)}}\right)$$



Fabrication - Pre-MEMS

- ‘Substrate’: Short (1-2mm), thin-walled (250 µm) glass tube
- Flat spiral coil hand-wound on teflon sheet and shellac used to hold in place
- Coils transferred to studs and mounted on mylar diaphragms
- Coil-bearing diaphragms stretched across glass tube
- Heat-sealing with polyethylene tubing

COLLINS: PRESSURE TRANSENSOR FOR EYE IMPLANTATION

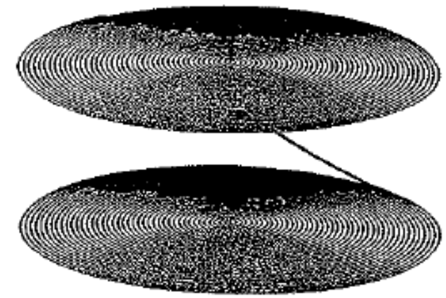


Fig. 1. A pair of flat spiral coils constitutes a distributed resonant circuit. Both stray capacity and mutual inductance are altered, making the resonant frequency vary sensitively with coil spacing (exaggerated in diagram).

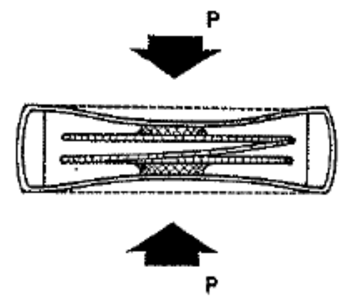
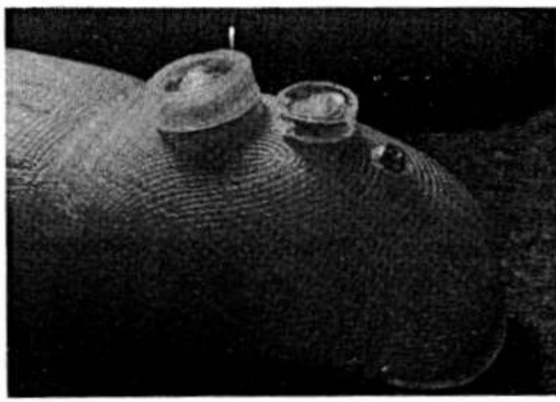


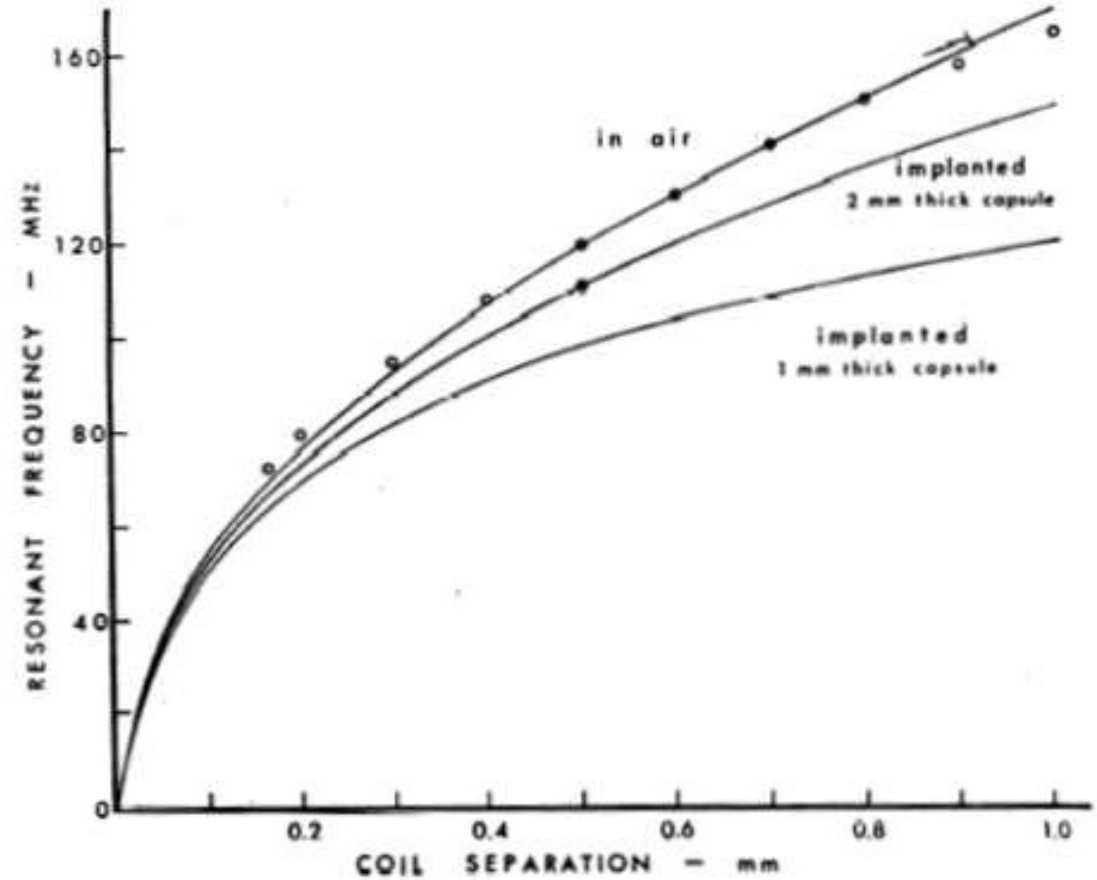
Fig. 2. Cross section showing the plastic bubble tonometer consisting of a small hermetically sealed pillbox with tightly stretched drumhead diaphragms bearing on the spiral transensor coils within. Pressure forces the coils closer together, thus lowering the pill frequency.

Implantable Sensors for Physiological Parameter Measurement: The Promise



3. Bubble tonometers 6, 4, and 2 mm in diameter. The sm
onometer displayed here was detected when implanted i
nterior chamber of the eye, but requires further develop
The larger models are used when pressures are desired from
ressively deeper structures.

TRANSACTIONS ON BIO-MEDICAL ENGINEERING, APRIL 1967



So Why Wasn't This Adopted?
Issues in Long-Term Human Implantation of Sensors

- Stability
  - Hermetic sealing of pressure reference
  - Overgrowth of tissue on sensor affecting calibration
  - Corrosion and Fatigue
- Biocompatibility
  - restricts materials set
- Readout Distance
  - Some applications require sensors deep within body (30 cm requires 10x improvement)
  - Attenuation by lossy medium of surrounding tissue
- But: something happened…

The Technology Convergence

MEMS Fabrication Technology

New materials for MEMS

Reasonable manufacturing precision

Micromanufacturing Infrastructure

Low Power Circuitry

A milliwatt is a lot!

Energy harvesters

Advanced batteries

Wireless Implantable Microsystems

Wireless Electronics Technology

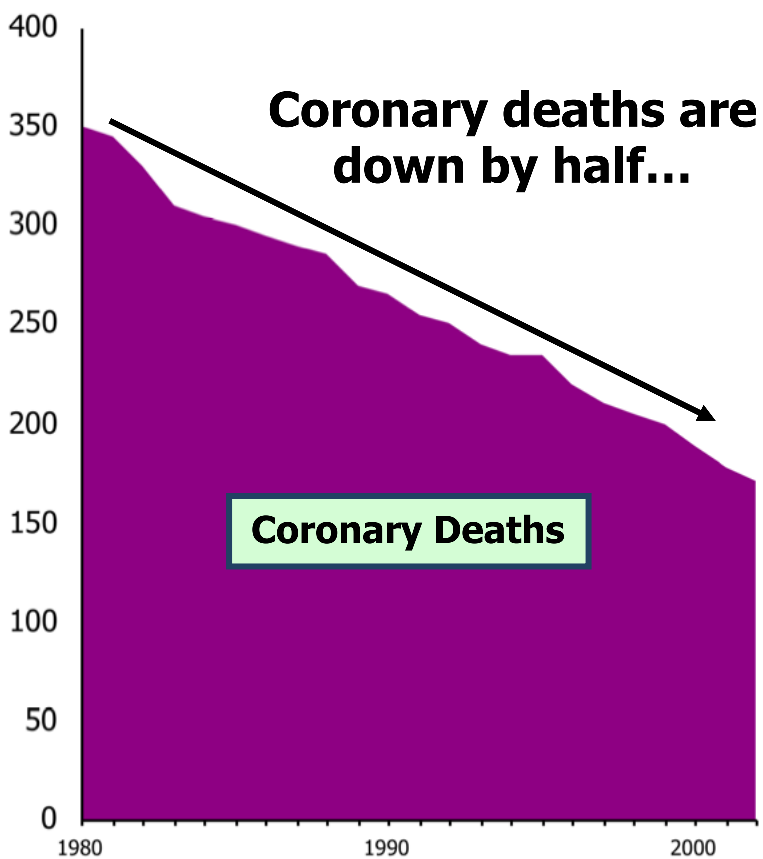
Miniaturization of communication technology

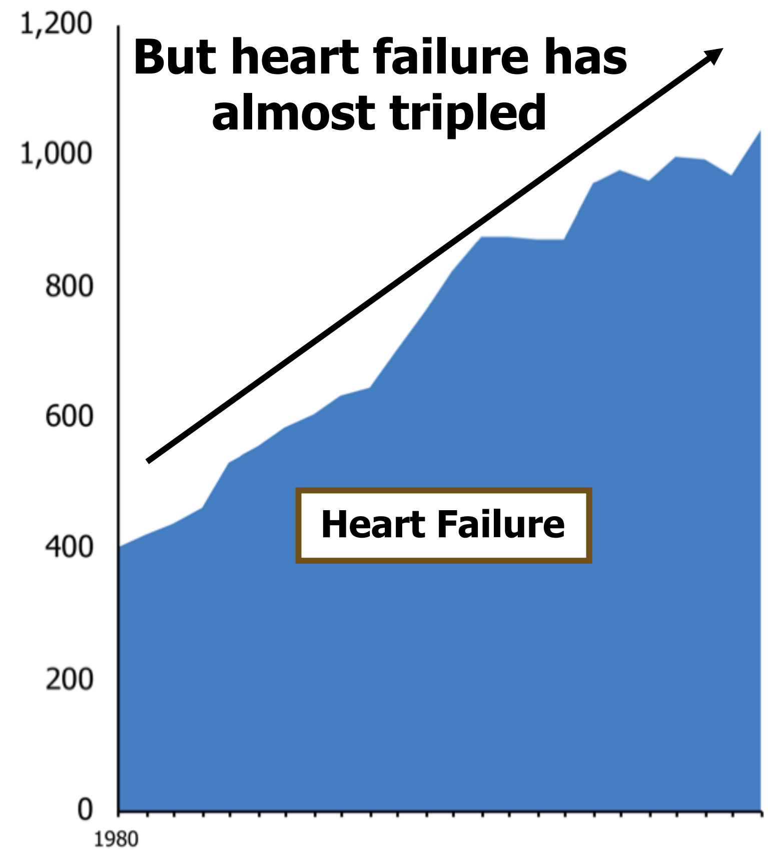
Unprecedented sensitivity to signal levels

Advanced signal processing

Globe-spanning net for information transfer

An Application: Heart Disease Is Transitioning From An Acute To A Chronic Disease





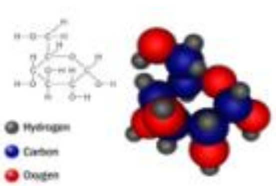
Source: National Hospital Discharge Survey, CDC/NCHS and NHLBI.

Proactively Managing Cardiovascular Pressure Is Critical to Chronic Disease Management

In the same way that…

Blood Glucose

Diabetes

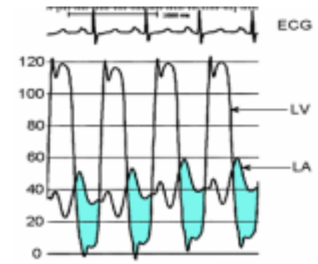


DRIVES

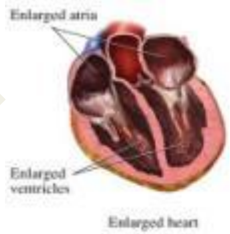
We know that…

Intracardiac Pressure

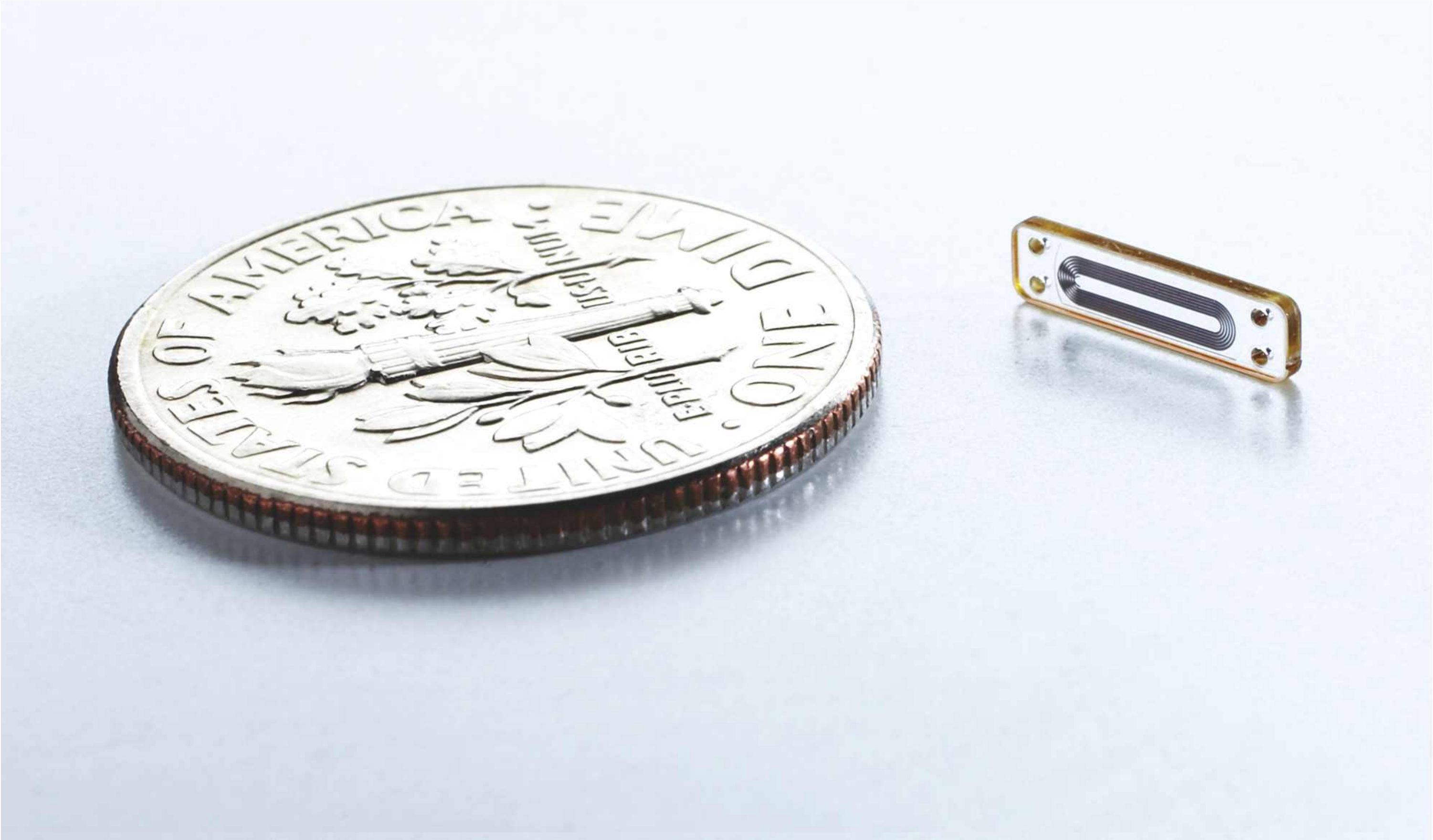
Heart Failure



DRIVES

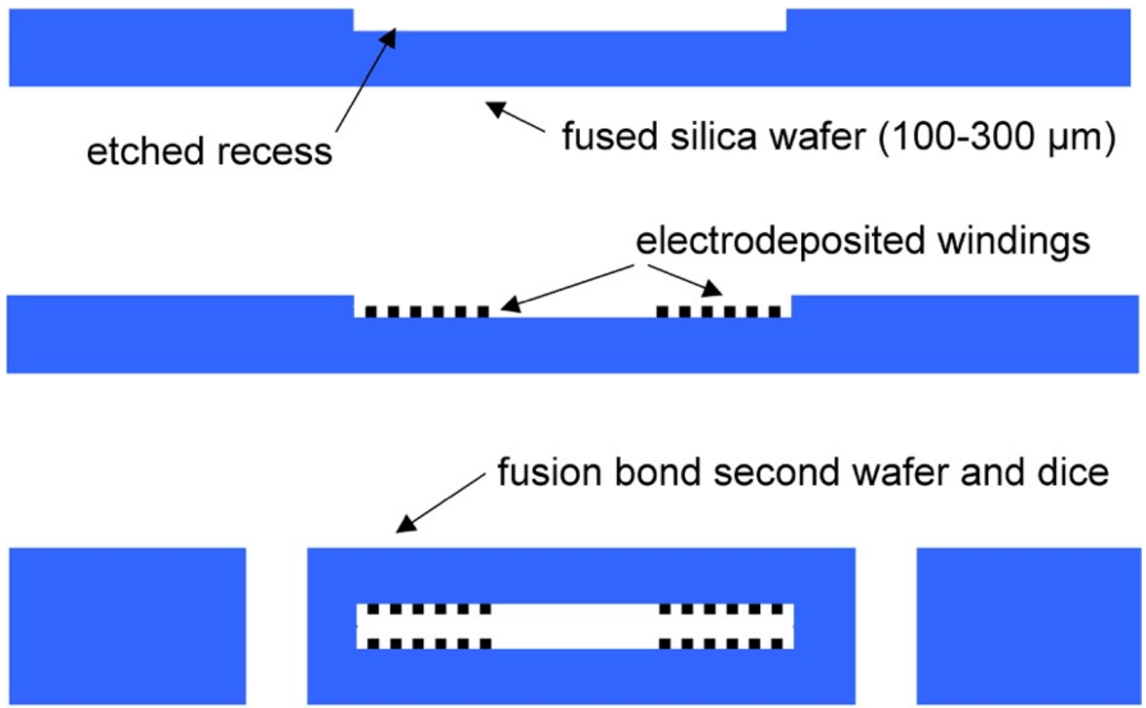


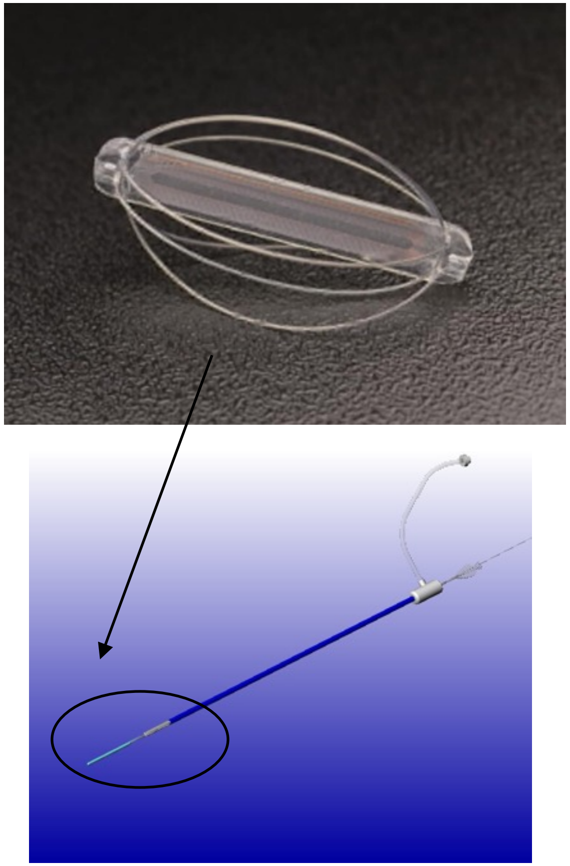
Goal: An Implantable Sensor



100 Years At The Bottom

Sensor Structure

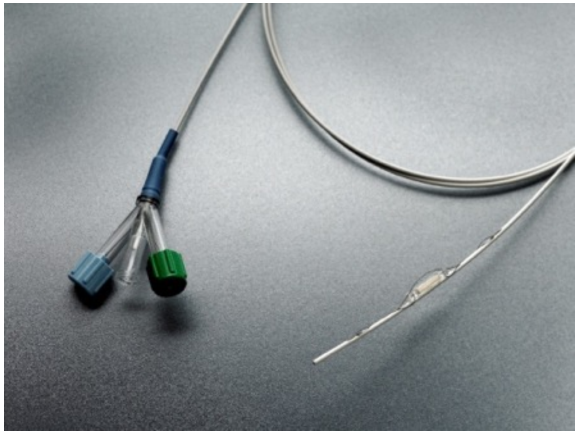




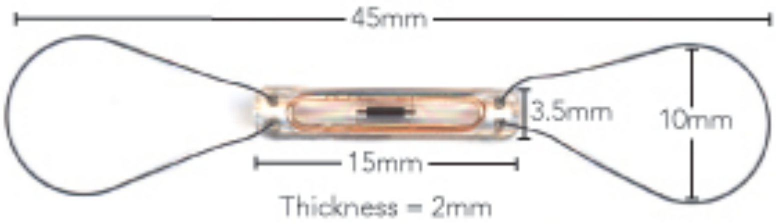
Install in delivery catheter

The CardioMEMS Pressure Measurement System

Catheter-based delivery system

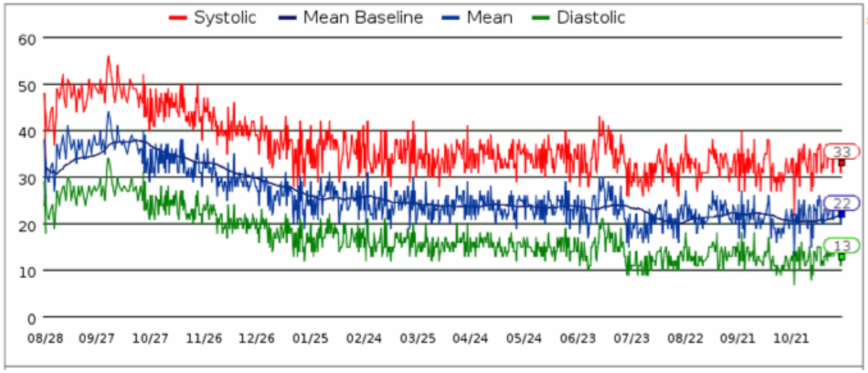


MEMS-based pressure sensor



Readout electronics

Measurement database

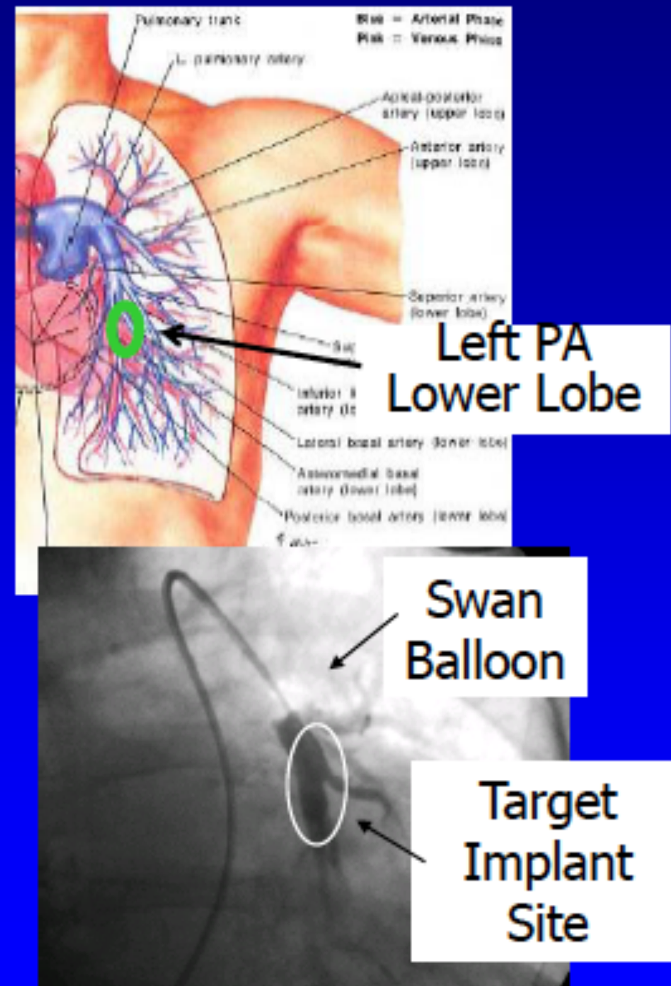


CHAMPION Clinical Trial

- The objective of the study is to evaluate the safety and efficacy of the HF Pressure Measurement System in reducing heart-failure-related hospitalizations in a subset of subjects suffering from heart failure (n=550)
- Primary efficacy will be measured by comparing the rate of HF-related hospitalizations during the 6 months following implant in the TREATMENT group (standard of care HF management plus HF management based upon hemodynamic information obtained from the HF Presure Management System) with that of the CONTROL group (standard of care HF management).
- Results of trial presented at 2010 European Heart Failure Conference (PIs: W. Abraham, MD and P. Adamson, MD)

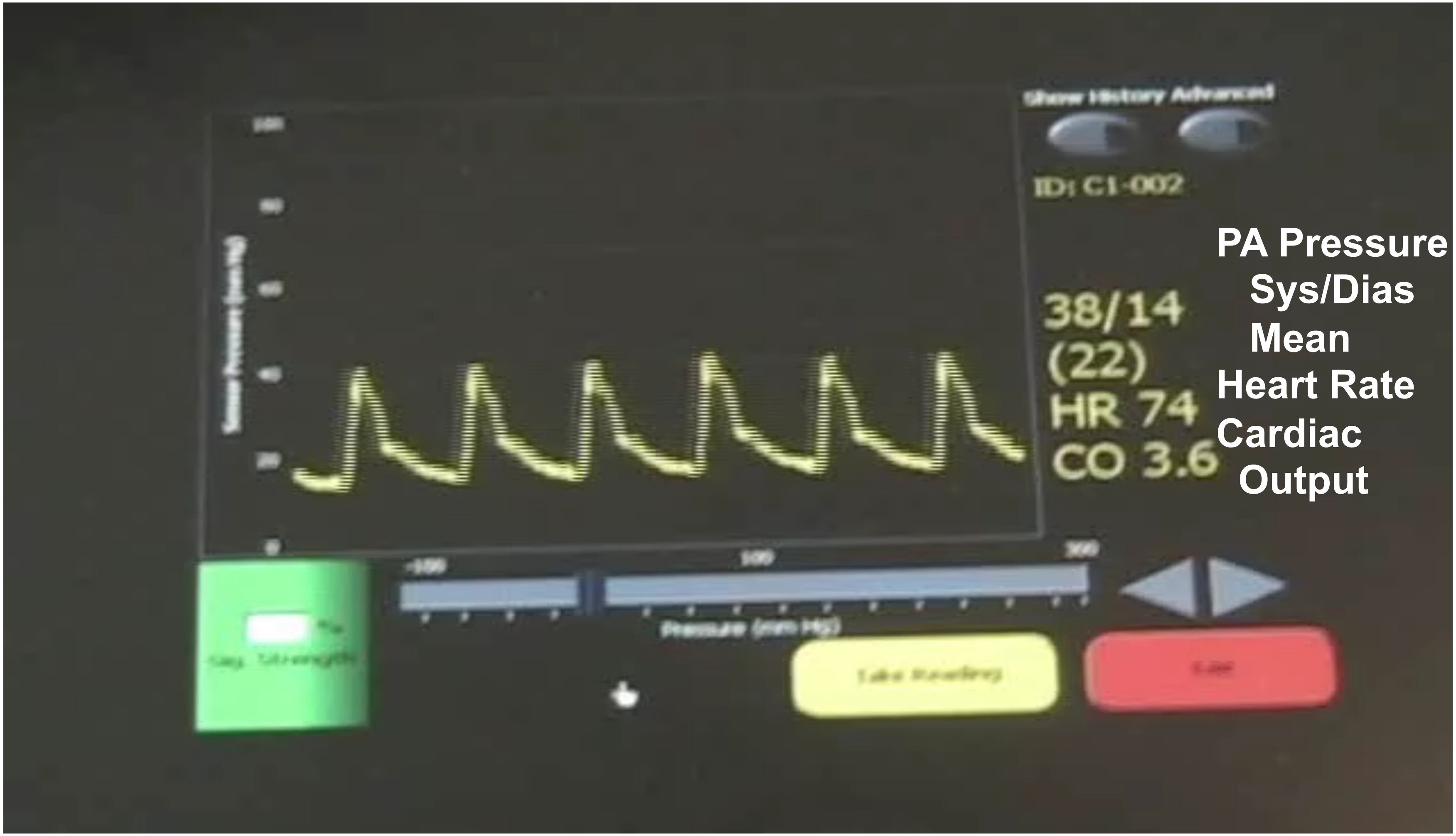
PA Sensor Placement

- RHC with selective pulmonary angiogram
- Right or left PA branch, basal (lower) lobe, descending branch, pre-bifurcation
- Vessel Lumen ID: 10 mm (7-15mm)
- The Sensor and nitinol loops allow placement in the pulmonary artery in a distal location without injury to artery
- Clopidogrel/ASA combination 1 month post-implant or previous warfarin therapy

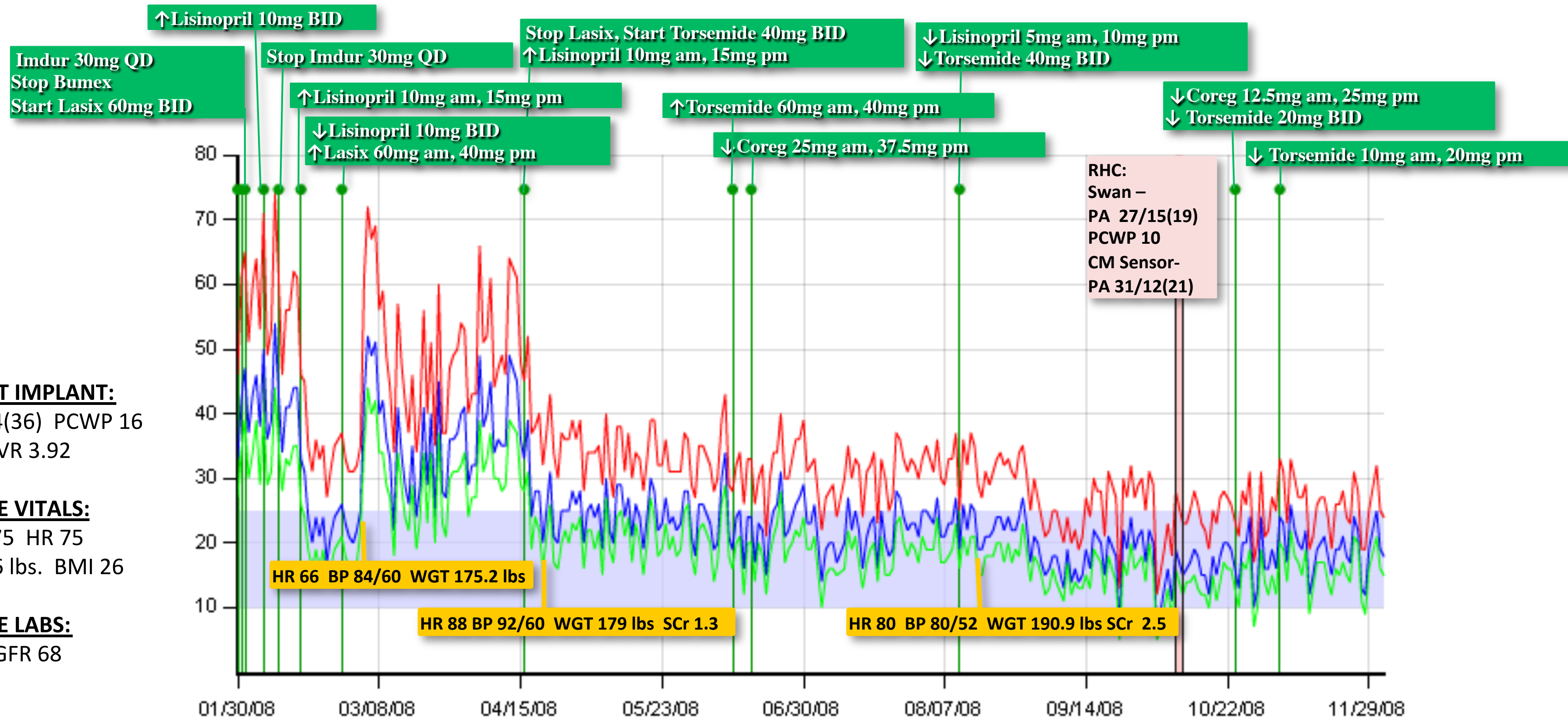


Caution – Investigational device. Limited by United States law to investigational use

Wireless Measurement of PA Pressure



A Case Study



SWAN AT IMPLANT:
PA 51/24(36) PCWP 16
CO 5.1 PVR 3.92

BASELINE VITALS:
BP 127/75 HR 75
WGT 176 lbs. BMI 26

BASELINE LABS:
SCr 1.2 GFR 68

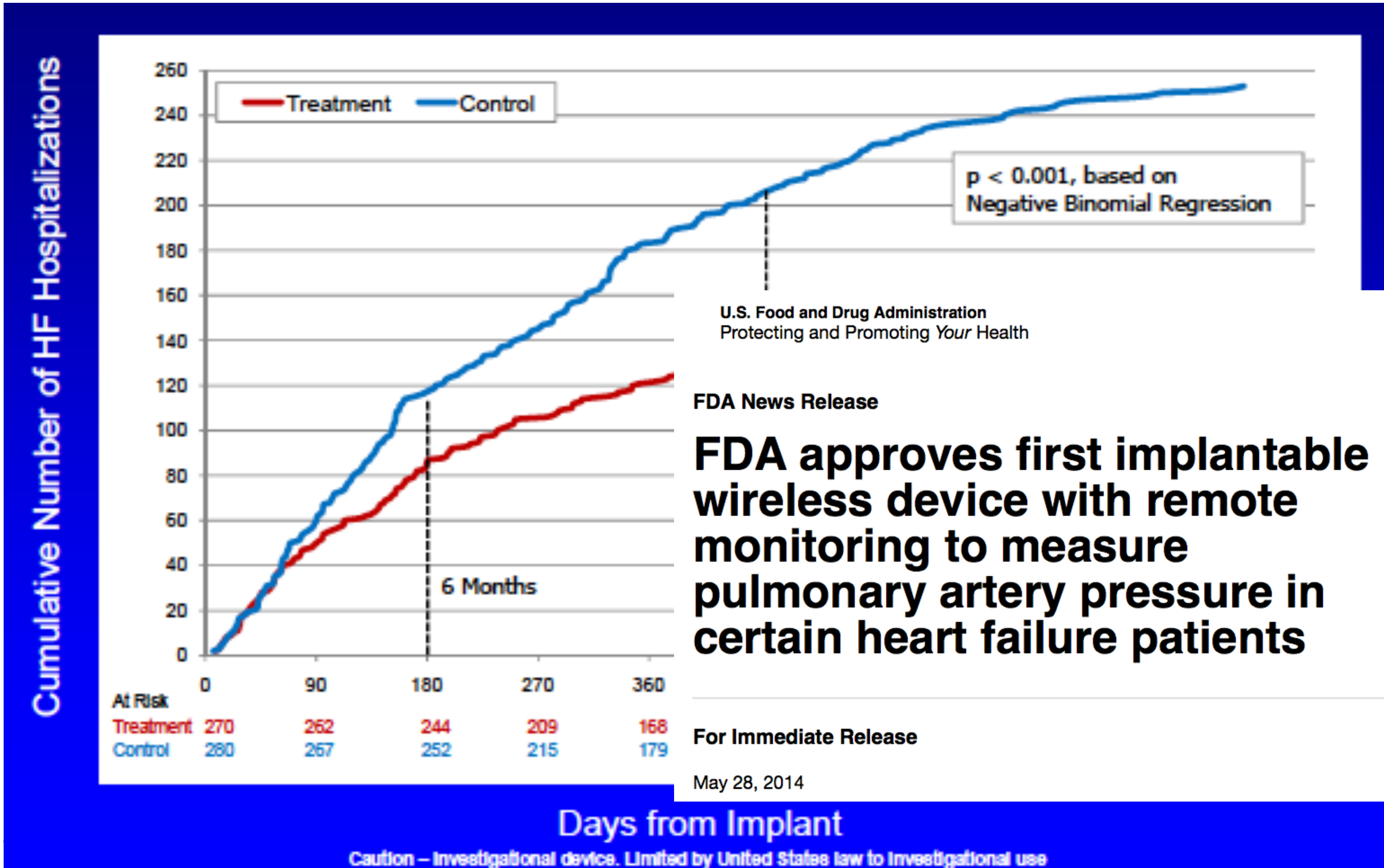
MEDICAL HISTORY

- Familial Dilated Cardiomyopathy
- ICD with CRT
- HTN
- Paroxysmal Atrial Fibrillation
- Hyperlipidemia
- Gout
- Sleep Apnea
- Depression
- Osteoarthritis
- Insomnia

BASELINE MEDICATIONS

Carvedilol 37.5mg BID
Lisinopril 10mg QD
Eplerenone 25mg QD
Digoxin 0.125mg QD
Bumetanide 1mg BID
KCL 10 meq BID
Amiodarone 200mg BID
Coumadin as directed
Aspirin 81mg QD

Cumulative HF Hospitalizations Over Entire Randomized Followup Period



U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA News Release

FDA approves first implantable wireless device with remote monitoring to measure pulmonary artery pressure in certain heart failure patients

For Immediate Release

May 28, 2014

But it takes some time…

WIRELESS MICROMACHINED CERAMIC PRESSURE SENSORS

Jennifer M. English and Mark G. Allen
School of Electrical and Computer Engineering
Georgia Institute of Technology, Atlanta, GA 30332, USA

IEEE MEMS '99

ABSTRACT

In high temperature applications, such as pressure sensing in turbine engines and compressors, high-temperature materials and data retrieval methods are required. The microelectronics packaging infrastructure provides well-developed, high temperature ceramic materials, processing tools, and processing techniques that have the potential for applicability in high temperature sensors. A completely passive wireless telemetry scheme, which relies on a frequency shift output, has been

fired to form a ceramic structure. In general, this type of tape is referred to as low temperature co-fireable ceramic (LTCC) as the typical curing (firing) temperature is 900°C [4]. Ceramic tapes made solely from alumina particles are also available and have curing temperatures above 1600°C. These high temperature characteristics indicate that the ceramic tape may be an excellent choice for the fabrication of pressure sensors for high temperatures.

BACKGROUND

The microelectronics packaging infrastructure has developed

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA News Release

FDA approves first implantable wireless device with remote monitoring to measure pulmonary artery pressure in certain heart failure patients

For Immediate Release

May 28, 2014

Posted: 1:53 p.m. Wednesday, May 28, 2014

St. Jude Medical to acquire CardioMEMS

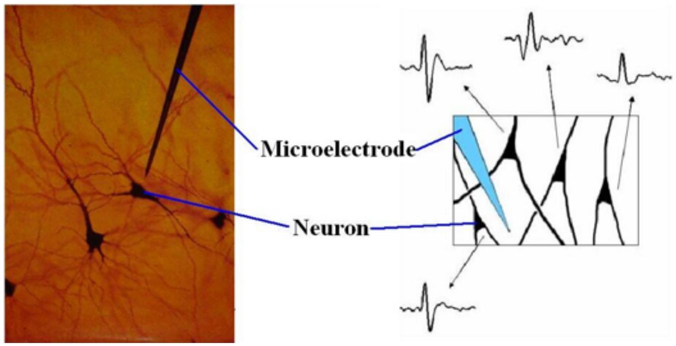
Related

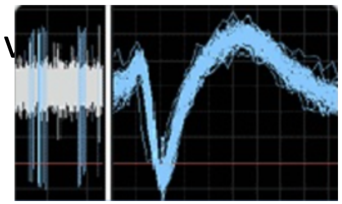
By Christopher Seward

The Atlanta Journal-Constitution

St. Jude Medical Inc., a medical device company, said it plans to exercise an option to a has received U.S. Food and Drug Administration approval.

Why Implantable Neural Microelectrodes?

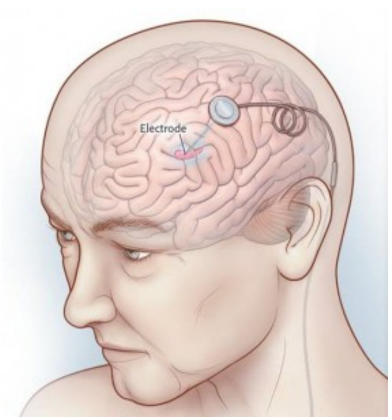




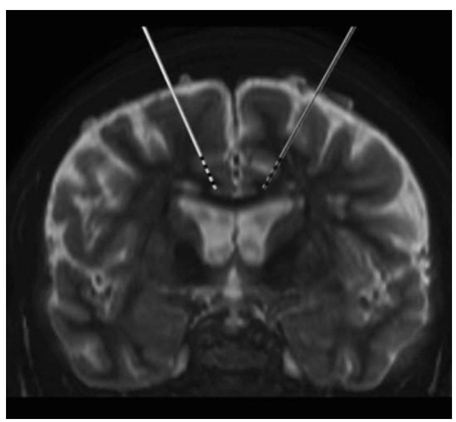
Reconnect brain to peripheral nervous system

Picture downloaded from www.cyberkineticsinc.com

Treat diseases and relieve symptoms

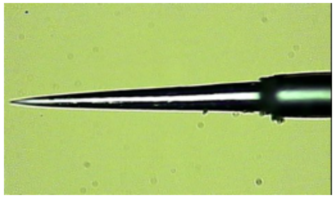


Neurosurgery 73:86–93, 2013

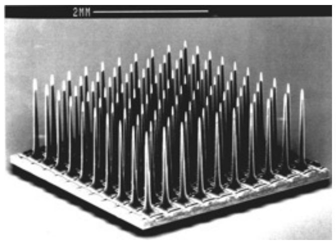


Neurosurgery 74:628–637, 2014

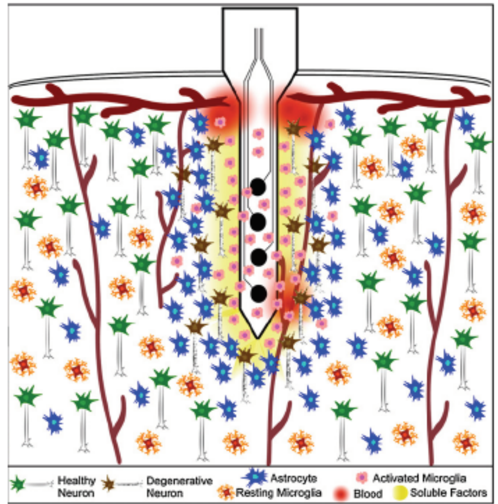
Neural Microelectrodes for interfacing with neural cortex



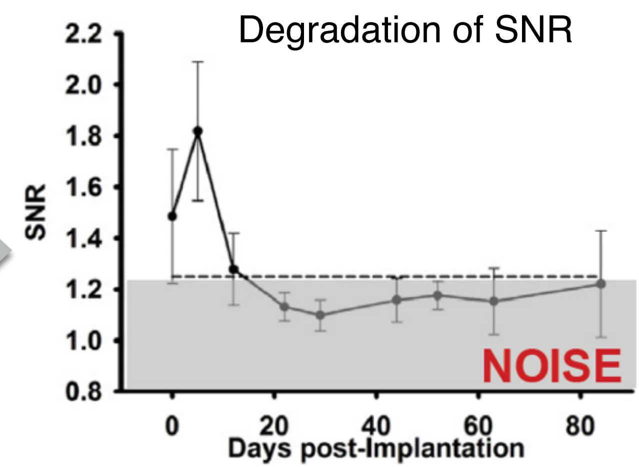
Microwire (MW) NEs



Si-based NEs



Potter, Capadona et al. J. Neuroscience Meth. 2012



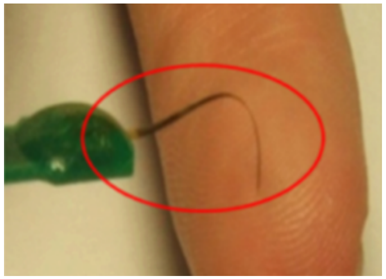
Karumbaiah, Bellamkonda et al. Biomaterials 2013

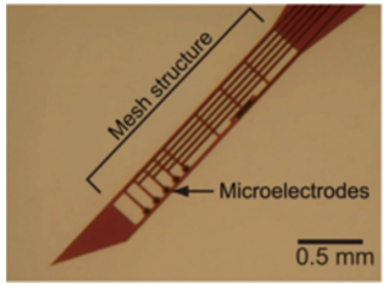
Challenges with stiff neural microelectrodes:

- Immune rejection
- Macrophage or neutrophil mediated degradation
- Mechanical failure
- Chronic inflammation
- Capacity of implants to be integrated into the host system

Improving Flexibility and Biocompatibility

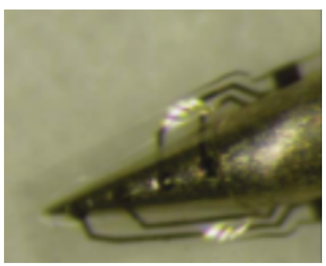
Improving flexibility

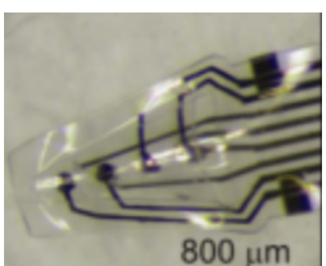




Challenges with flexible neural microelectrodes:
- Insertion tool that causes minimum injury
- Biocompatible with host environment

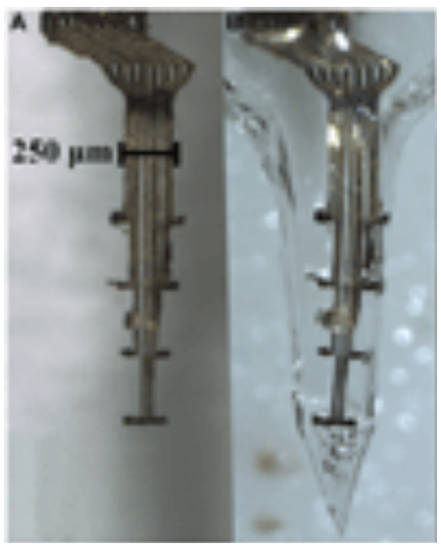
Stiff delivery tool for NEs





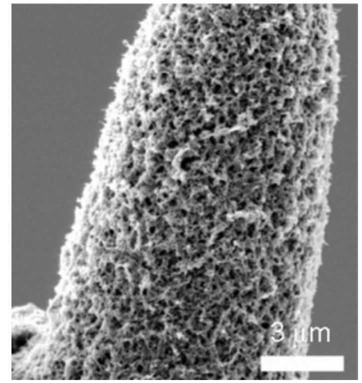
E. Meng et al., Lab Chip, 2013

Dissolvable shuttle for NEs

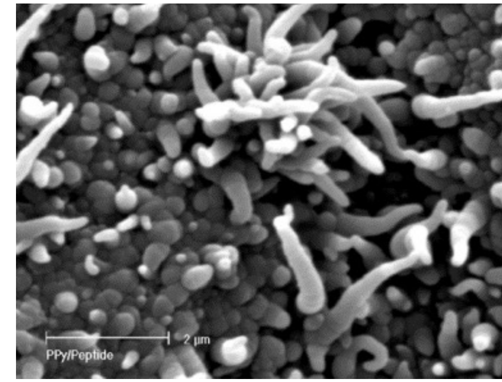


J. Agorelius et al., Front. Neurosci., 2015

Improving Biocompatibility

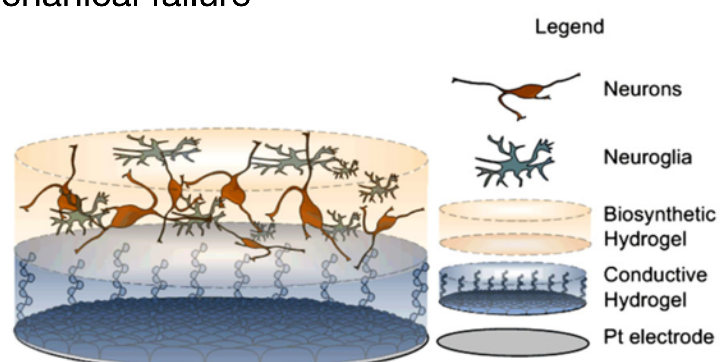


PEDOT/MWCNT/Dex-coated Pt/Ir microelectroded (*T. Cui et al. Biosensors, 2015*)



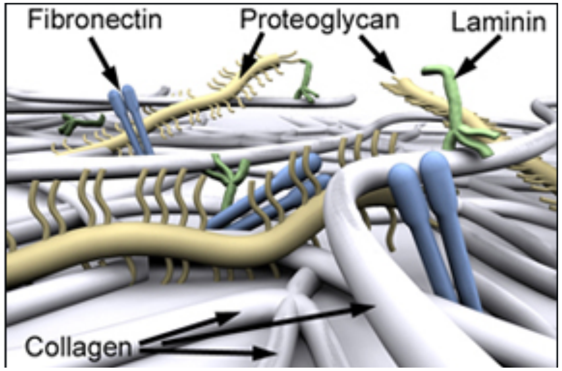
PPy/DCDPGYIGSR on a neural microelectrode site (*T. Cui et al. Biomaterials, 2003*)

Challenges with protein-coated neural microelectrodes:
- Coatings are not sustainable
- Mechanical failure



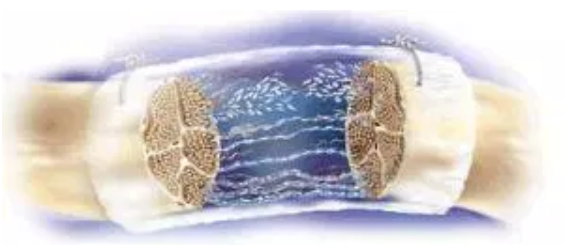
Proposed scheme of tissue engineered electrode interface (R. Green *et al. Front. Neuroeng., 2014*)

The Extracellular Matrix (ECM) Choice



- ECM comprises a notable portion of the central nervous system.
- Composition: ECM of brain tissue mainly comprises laminin, fibronectin, and collagen; these proteins **form the interstitial matrix and the basement membrane**.
- Biocompatibility/Non-immunogenicity: ECM **supports critical functions in normal neuronal physiology**. It is ideal for the deposition of cells, guide fibroblasts and attract fibrogenic cells.
- Mechanical and structural properties: **Provides major structural support for the neural tissue**.
- Bioresorbability/biodegradability: degradation rate of ECM proteins **can be tuned depending on the degree of cross-linking**.

NeuralFlex

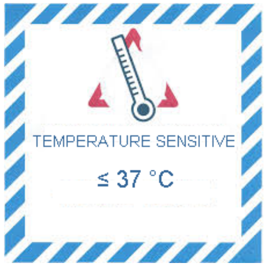


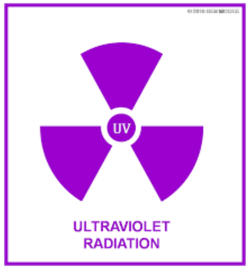
NeuralGen

NeuralMatrix

Challenges with fabrication of ECM-Microelectrodes

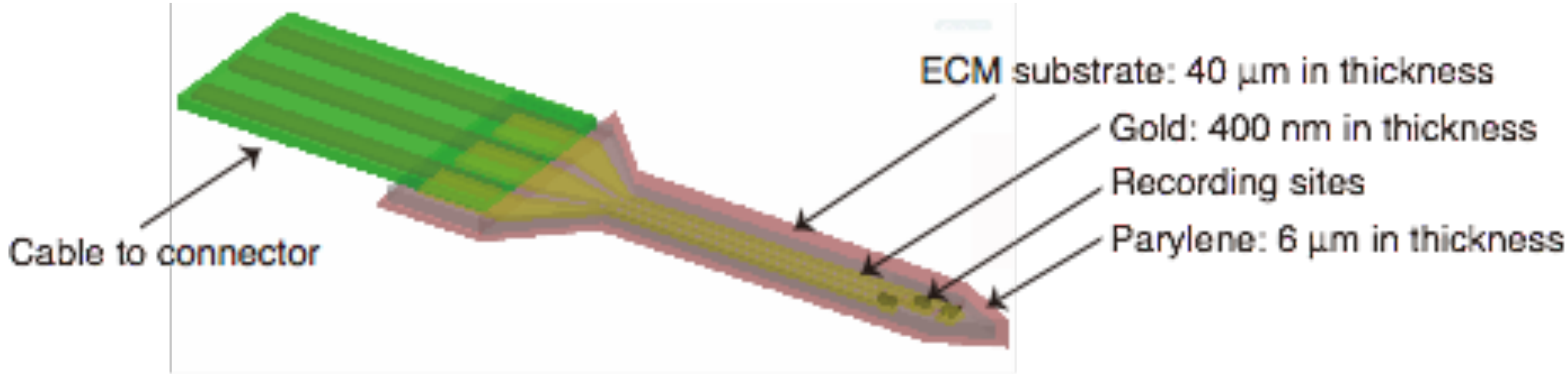
- Temperature sensitive:
  - Processing temperature for collagen and laminin should not exceed 37 °C
  - High temperature generated during E-beam deposition and dry etching processes degrades ECM proteins
- Light sensitive:
  - UV exposure from lithography induce cross-linking of collagen
- Chemical sensitive:
  - pH should be kept at 7.4 after forming ECM microstructures. Increasing or decreasing pH will disrupt the structure of ECM proteins.
  - Solvents used in the photolithography process can disrupt the structure of ECM proteins.
  - O2 plasma used in dry etching process degrades proteins.



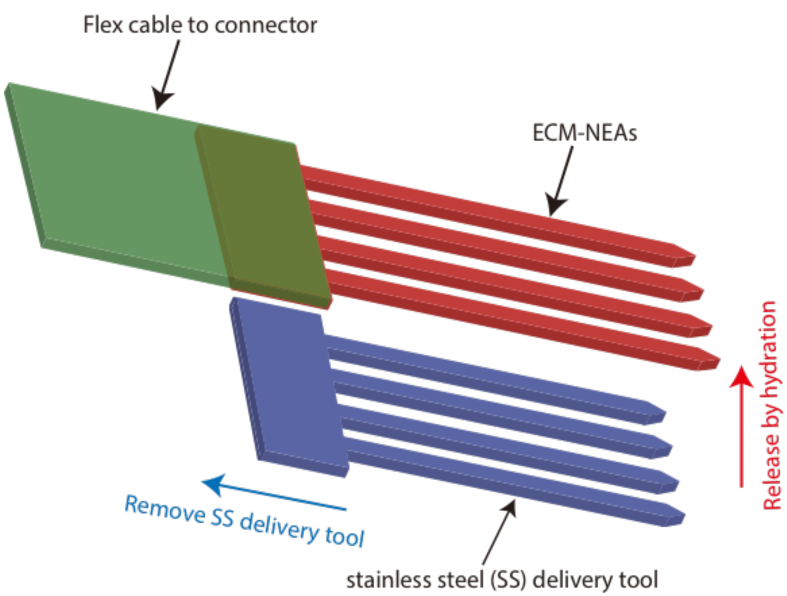


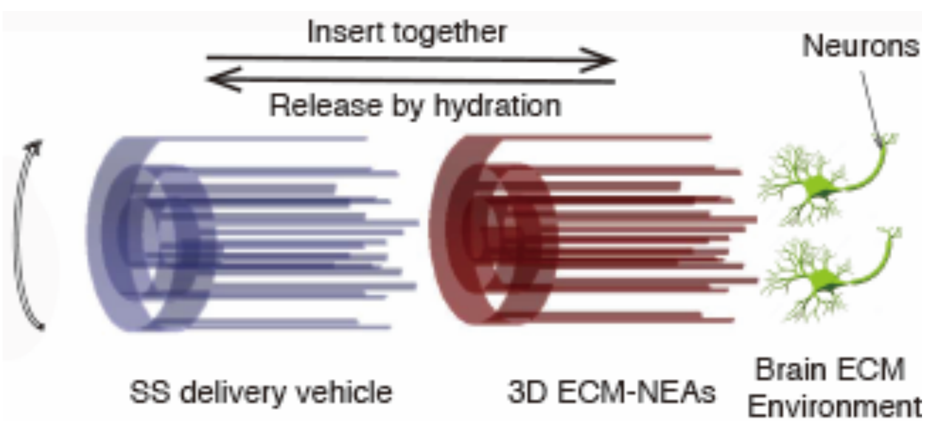
Chemical Sensitivity

ECM-Neural Microelectrodes Design



ECM-NEs

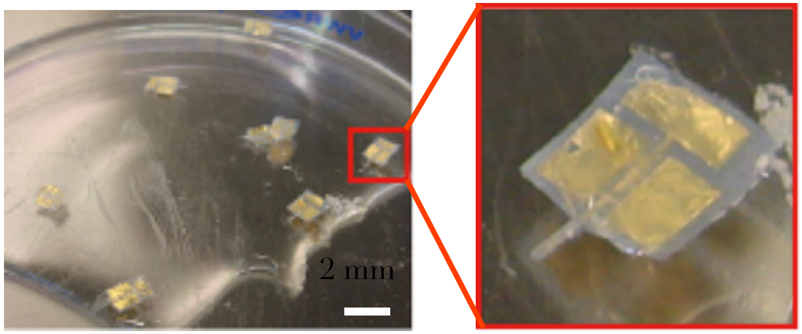




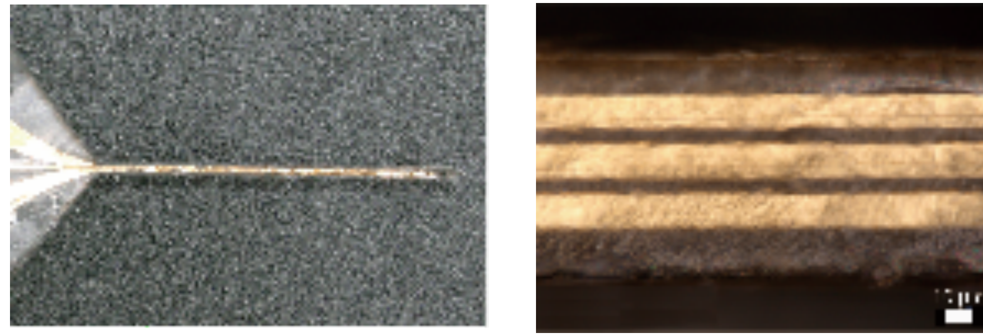
Delivery of ECM-NEs

Delivery of ECM-NEAs

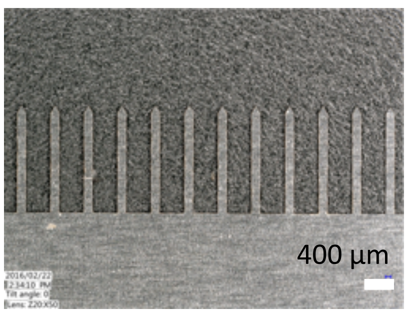
Fabricated ECM-Neural Microelectrodes



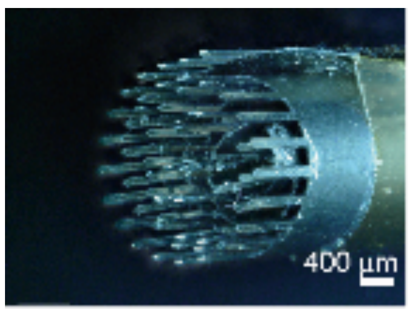
Individual Collagen-NEs



A 100 µm-wide Collagen-Laminin-NE



Planar array



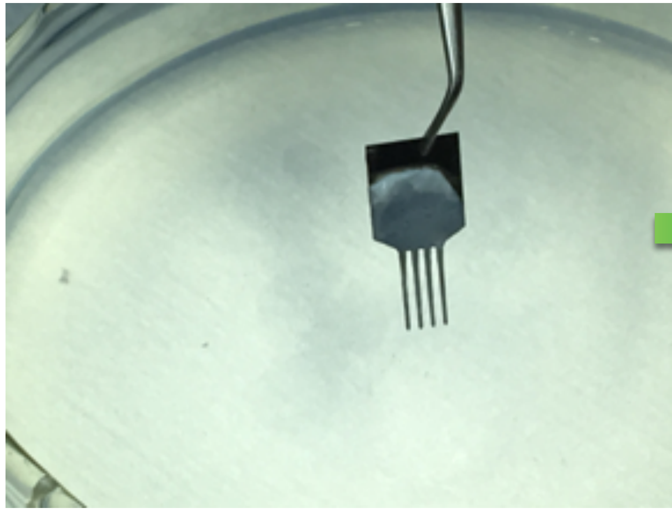
3D array

Stainless Steel Delivery tools

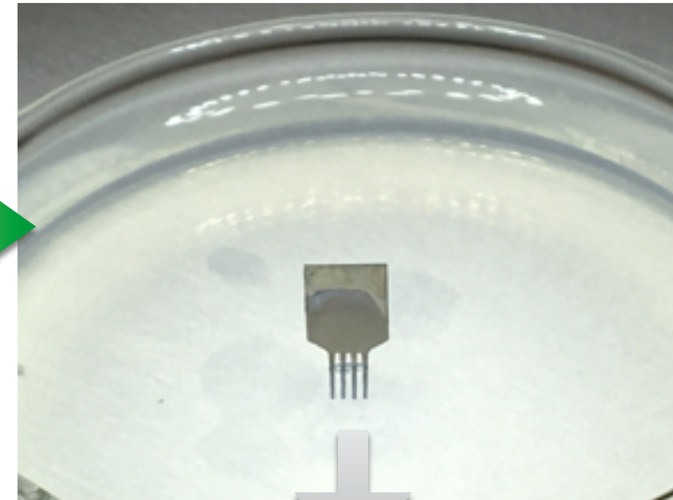
- Minimized dimensions:
  - Electrode area: 400 µm^2
  - Shank width: 100 µm
  - Shank length: 5 mm
  - Linear array spacing: 500 µm
- 3D array achieved with inner diameter approximately 450 µm.
- Roll spacing determined by spacer materials coated at the base of the linear array.

Insertion of ECM-Microelectrodes

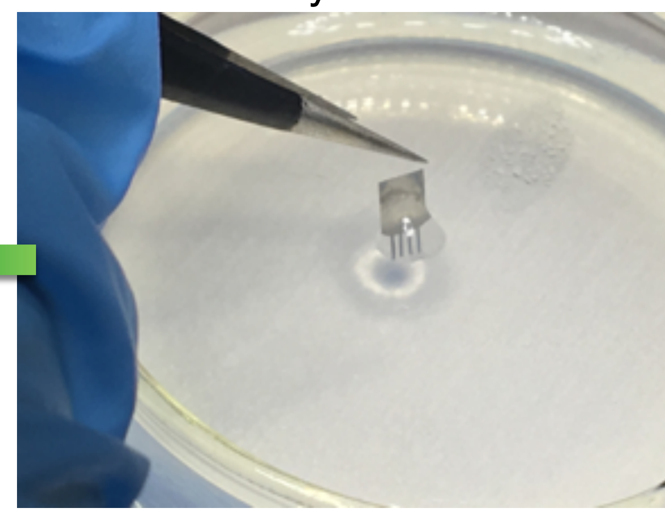
ECM-NE/SS



Insert



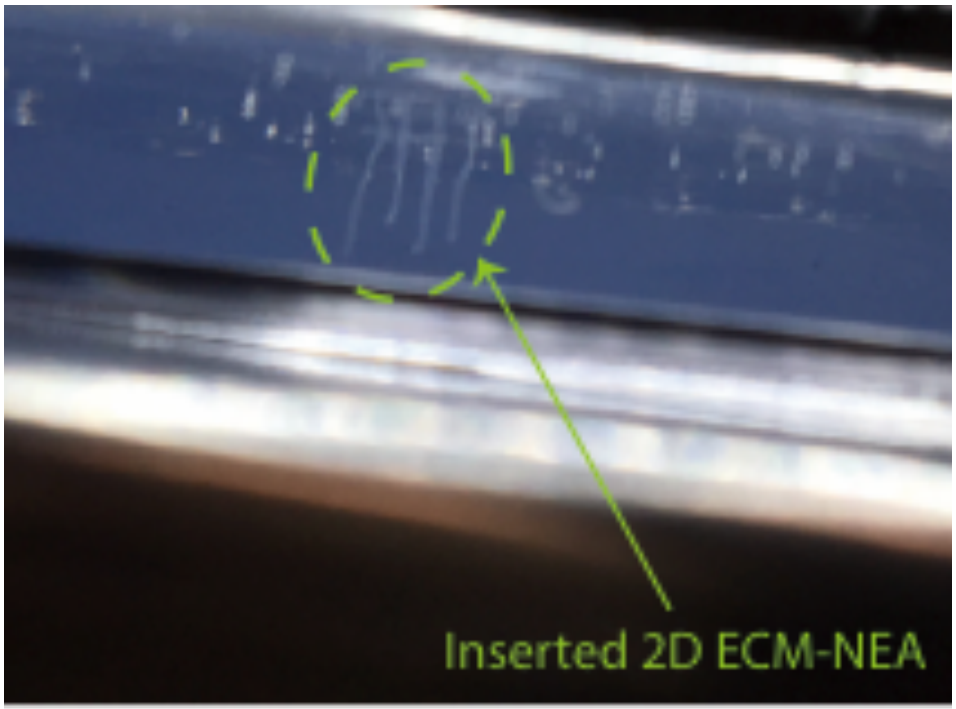
Hydrate

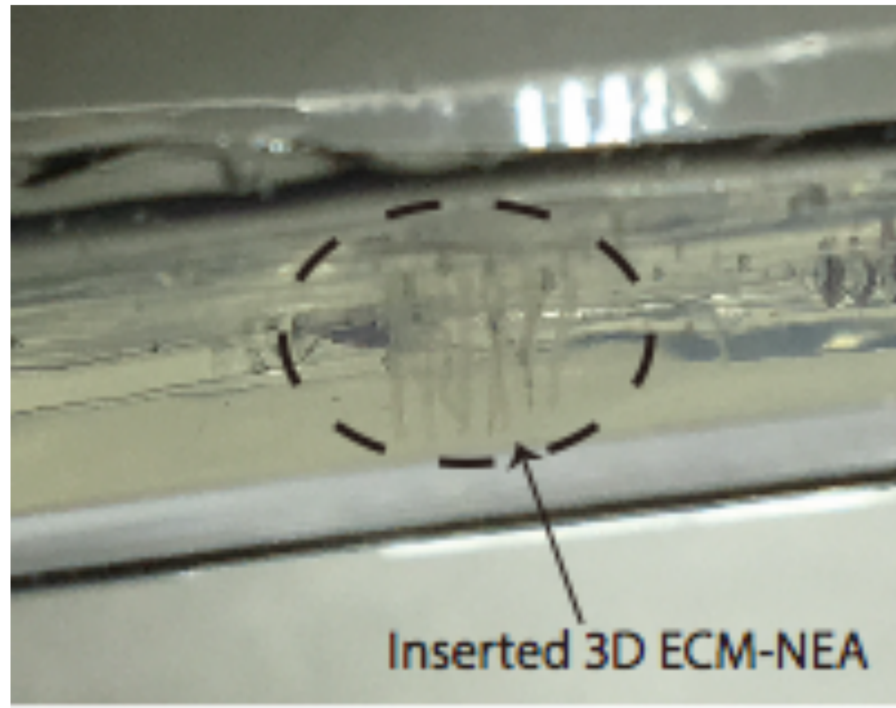


Removal of SS delivery needle

Inserted ECM-Microelectrodes

- 2D and 3D ECM-NEAs are successfully implanted into a brain mechanical model (2% agarose gel).





Improved Biocompatibility with ECMs

Standard Petri-dish

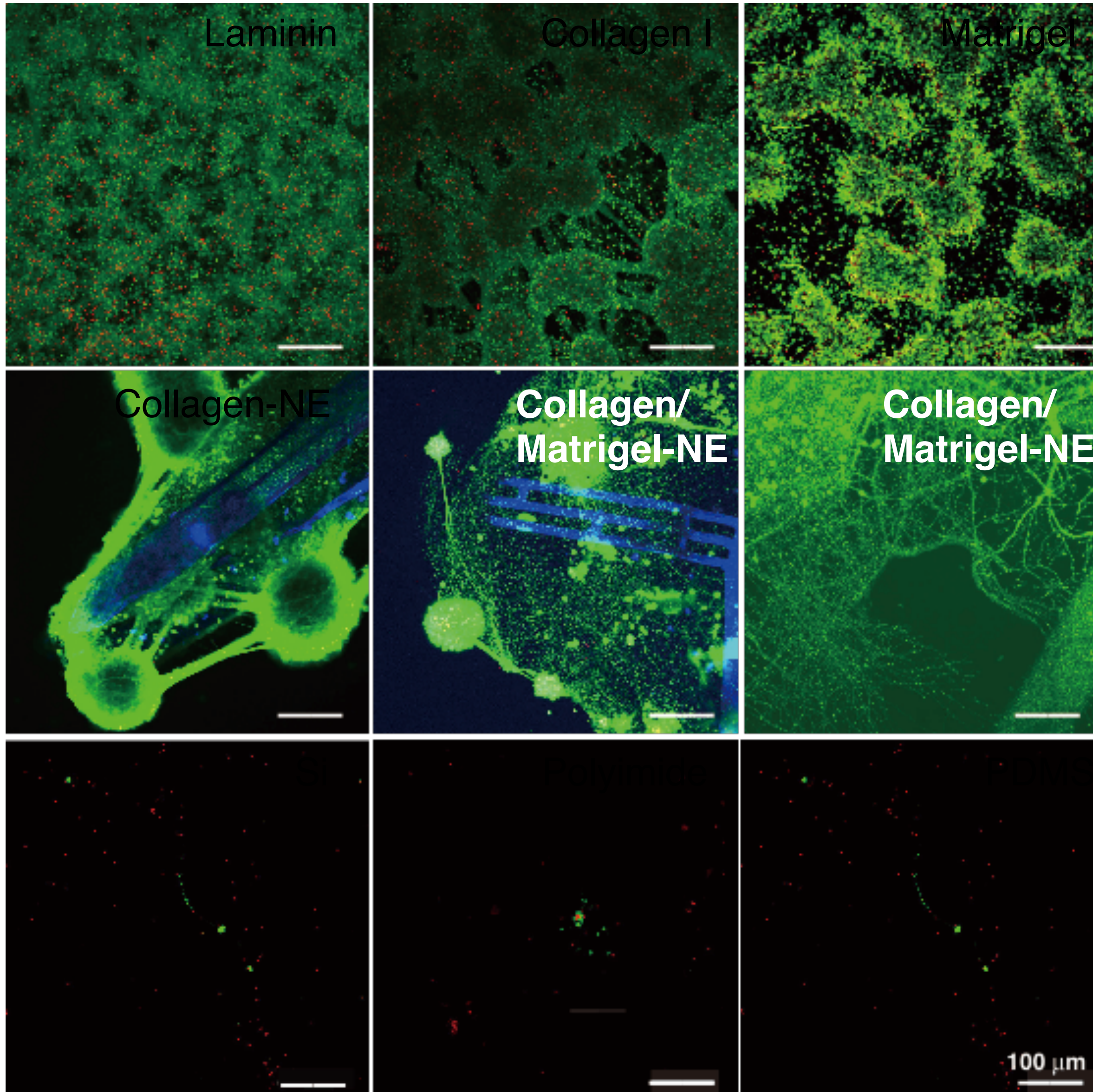
Healthy growth on positive controls

ECM-NEs

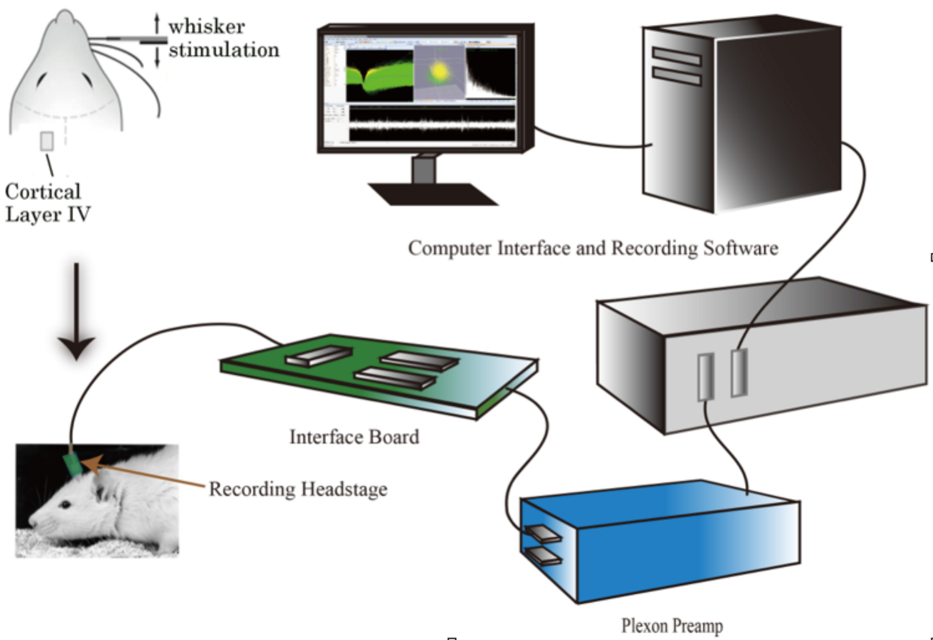
Healthy growth within ECM-NEs

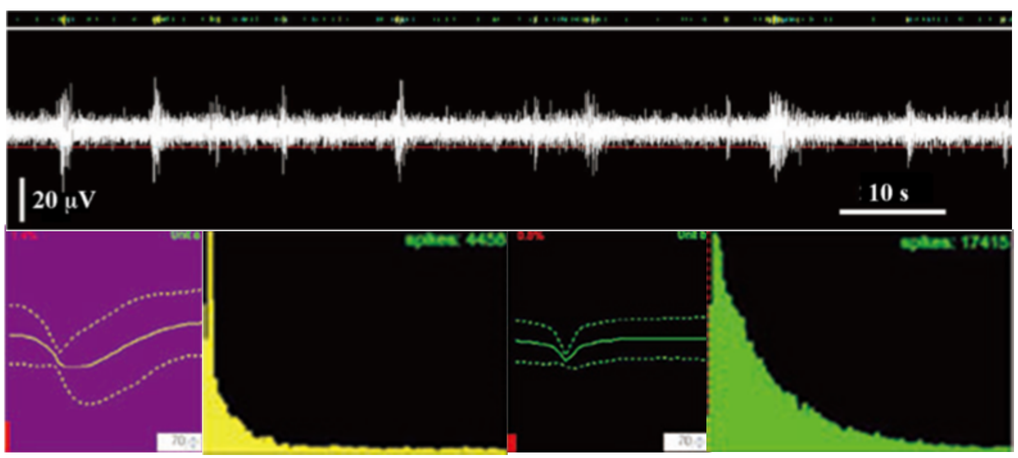
Non-biological-NEs

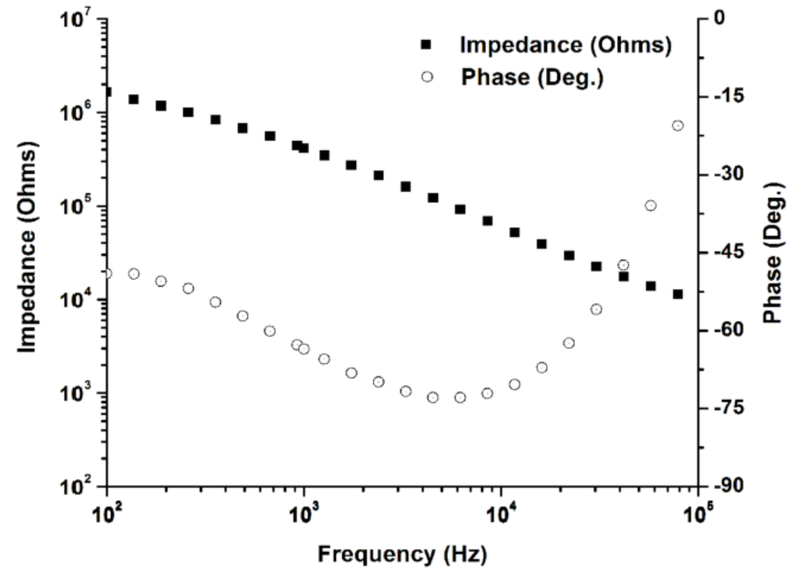
Reduced growth on bare synthetic materials

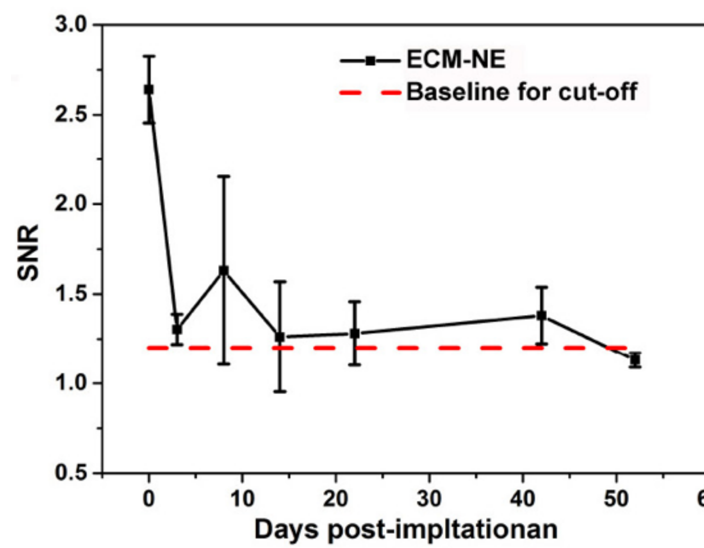


Electrical Functionality









Conclusions and Acknowledgements

- Medical treatment is greatly augmented by new information
  - Implantable devices a key tool
- New materials, even biological materials, can be harnessed as implants
- Technology convergence has made MEMS-based implantable transducers of multiple material types inevitable!

CardioMEMS, Inc.

Dr. Michael Fonseca

Dr. Wen Shen

MSMA Group at Georgia Tech and Penn

mems.seas.upenn.edu