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NCI Southwest

NACK Network
Building College-University Partnerships for Nanotechnology Workforce Development

NSF
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Managing Director, NACK Network

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Assistant Professor, Penn State
NEURAL INTERFACES: NANOSCIENCE AND MATERIALS TECHNOLOGY

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NACK/NCI-SW Webinar 31 January 2019
OUTLINE - MACROSCOPIC

• Healthcare Challenge – Why neural implants?
• SiC Biotechnology – the niche we are pioneering
  • \textit{In vitro} studies (biochemistry, nanoscale phenomenon)
  • SiC biosensors – glucose and myoglobin
  • BMI and related technologies
  • SiC \textit{in vivo} performance
• Education Opportunities and Challenges
NEURAL IMPLANTS

ElectRx

CONCEPT

Precise and intelligent modulation of nerve-organ circuits to provide new treatments for restoring physical and mental health

NERVOUS SYSTEM

ORGANS

PHYSIOLOGICAL HEALTH STATUS

GOALS

Develop new high-precision, minimally invasive technologies for monitoring and regulating peripheral nerve signals to adaptively control organ functions

http://www.kurzweilai.net/darpa-selects-research-teams-for-its-electrx-neuron-sensing-stimulation-program
MOTIVATION

http://spectrum.ieee.org/biomedical/bionics/goodbye-wheelchair-hello-exoskeleton
DEKA bionic arm – 3 DARPA programs to achieve long-term (70+) year function
MOTIVATION

Neurostimulation device activates peripheral nerve(s)

Neuromodulators boost synaptic plasticity

Neuronal connections are tuned to improve cognitive skills

https://www.youtube.com/watch?v=wZZ4Vf3HinA
MOTIVATION

https://youtu.be/7-NKUbsT6Y0
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• Education Opportunities and Challenges
PRESENT NEURAL INTERFACES CAUSE SEVERE DAMAGE

W/ parylene C DBS probes

- Si arrays (Michigan and Utah) ~ 1 month
- Polymer-coated Si arrays ~ 6-24 months
- Novel coatings ~ 4 years MAX
- A new strategy is clearly needed!
- Cubic SiC → excellent bio and hemocompatibility
- In-vitro and In-vivo (1 month) data → solution?

Severe tissue death with W DBS probes

In-vivo challenge – suitable materials for 25+ year operation in the human body
WHY SEMICONDUCTORS?

Polymers
- Soft elastic material
- Short-term use
- Disposable/Inexpensive
- Biodegradable
- Time release
- Normally insulating

Metals
- Conductors
- Hard, strong, durable
- Non-smart
- Shed particles/chemically reactive

Semiconductors
- Hard material
- Long-term use (ceramic-like)
- Complex electronics
  - Sensors
  - Drug delivery (wet chips)
  - Diagnostics
  - Biocompatible?
  - Hemocompatible?
Start with a Si wafer (4"

SiC film on Si
5 µm/hour

Note reflection of ceiling tiles in photograph

CVD @ 1350 °C
SiC needle with impedance sensors for myocardial monitoring

SiC coated heart stent

SiC coated hip prosthesis

Polyimide-based peripheral nerve electrode coated with a-SiC
SOME SiC BIOMEDICAL APPLICATIONS

Fig. 2: Left – Polymeric microdialysis probe (CMA/20, CMA Microdialysis, Chelmsford MA) prior to and after (inset) protein exposure to the 6-protein test mix for approximately six days. Right – Columnar SiC membrane prior to and after (inset) exposure to the 6-protein mix for five days.

Bone cells on porous SiC

3C-SiC QD’s After the uptake by human fetal osteoblast cells.

Bone Cells on Uncoated Si

Microdialysis, fluorescent Detection, bone scaffold
Cell interaction with 3C-SiC superior to top biomedical polymer Parylene C
Graphene is planar layer of sp² bonded C atoms packed into 2D honeycomb lattice.

- Thermal processing of SiC at elevated temp → epitaxial graphene on SiC surfaces.
- Advantages → non-metallic electrodes for SiC devices (higher $\sigma$, lower $A/cm^2$)

Mono, bi and tri-layer graphene possible.
H intercalation → no covalent bonds to support

IN-VITRO EXPERIMENT: HACAT’S ON GRAPHENE

- Focal Point Proteins
- Actin Mesh
- Cell nucleus
BIO- AND HEMO-COMPATIBILITY OF 3C-SiC

Biocompatibility

Hemocompatibility

Only 3C-SiC passed all ISO 10993 tests (chem stability, bio- and hemo-compat.)

Saddow et al, IEEE NMDC, Catania, Sicily (IT) October 2014
QUESTIONS?
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The antenna sensor’s response is almost linear and shows similar trend of frequency shifting for both mimicking liquid and pig blood.

*Blood glucose levels: American Diabetes Association
Myocardial infarction detection via impedance spectroscopy

Changes in the space charge region (flatband potential) of SiC

Possible applications:
- CHEMFET
- ISFET (pH sensors)

Interdigitated electrodes on amorphous SiC (a-SiC)

Detection of myoglobin via impedance spectroscopy

Dr. A. Oliveros PhD Dissertation, USF © 2013
MYOCARDIAL INFARCTION DETECTION USING IMPEDANCE SPECTROSCOPY

Functionalisation of SiC NanoWire Field Effect Transistors (NWFETs) for advanced biosensor applications

E. Bano, R. Bange and V. Stambouli

IMEP-LAHC, LMGP
Grenoble INP, France

11th ECSCRM 2016 Halkidiki, Greece, 25-29 September 2016

S. E. Saddow, visiting professor spring 2017
Requirements and challenges:

- Semiconductor nanowire → High surface over volume ratio

- Low doping level → highest field effect

- Stable !!! → resistant to liquid functionalization steps: saline solutions
Si NWs : STABILITY ISSUES (*Peled et al. Nanobiotech. 2014*)

Immersion of Si NWs in Saline buffer solution (pH 7) at 37°C

Contrary to Si NWs, no diameter reduction of SiC NWs → proof of chemical inertness of SiC NW
SiC NWs: from VLS GROWTH to INTEGRATION in NW FET

M. Bossi
F. Rossi
IMEM, Parma, Italy

Ultasonic bath
Transfer
Intégration of SiC NW on the chip by e-beam lithography

Electronic detection of DNA demonstrated – moving to SiC coating on Si NWs
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3C-SiC FOR NEURAL INTERFACES

3C-SiC has properties useful for many biomedical devices, such as neural interfaces:

- 3X hardness and 3X flexibility of Si → thinner probes for less surgical trauma
- Biocompatible: in-vitro data → as good as parylene C and Polyimide
- Can be micromachined like Si → all Si devices proven in 3C-SiC
NEURAL CELL MTT VIABILITY ASSAY RESULTS

- H4’s
  - NCD > PCD
  - 3C ~ Si

- PC12’s
  - PCD > NCD
  - 3C > NCD
  - 3C > Si

- Cortical
  - 3C ~ Polyimide

Results charge Dependent (not shown)

- Note: Tested materials uncoated

C. Frewin et al, Chap. 6 in Sic Biotechnology, S. E. Saddow, Editor © 2012 Elsevier
3C-SiC probes vs. coated Si probes

Si and 3C-SiC probes fabricated using same technology
3C-SiC 3X as hard and 3X as flexible:

**Measured Mechanical Properties**

<table>
<thead>
<tr>
<th>Material Type</th>
<th>Hardness [GPa]</th>
<th>Elastic Mod. [GPa]</th>
<th>Fracture tough. [MPa·m$^{1/2}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(100)Si</td>
<td>12.46 ± 0.78</td>
<td>172.13 ± 7.76</td>
<td>1.59 ± 0.21</td>
</tr>
<tr>
<td>(100)3C-SiC</td>
<td>31.19 ± 3.7</td>
<td>433 ± 50</td>
<td>4.6</td>
</tr>
<tr>
<td>Poly-3C-SiC</td>
<td>33.54 ± 3.3</td>
<td>457 ± 50</td>
<td>2.18</td>
</tr>
</tbody>
</table>

* Measured via nanoindentation.
** Crack lengths used to calculate the film fracture toughness.

Main advantage to using 3C-SiC instead of polymer-coated Si is the thinner probe thickness (6 um vs. 15 um for Si)

---

*C. Locke, G. Kravchenko, P. Waters, J. Deva Reddy, A. A. Volinsky, C. L. Frewin, S. E. Saddow, ECSCRM ‘08*
IN-VIVO PERFORMANCE OF 3C-SiC – MOUSE

Micromachining process – similar to Si probes

- 3C-SiC film growth
- Step 2: Neuroprobedevice fabrication
- Step 3: Neuroprobedevice patterning
- Step 4: Neuroprobedevice Etching
- Step 5: Bonding of device wafer to handle wafer
- Step 6: Backside etching of tab structure
- Step 7: Release of fabricated neuroprobedevice

- Test material, tissue reaction
  - ~ 20 µm thick, 250 µm W, 7 mm L
- 3C-SiC compared with Si

---

MEAS AND PROBES FOR FUNCTIONAL RECORDING/SENSING

- 3C-SiC base material
  - Ti/Au or other metals
  - Carbon-electrodes being studied (graphene)
  - Insulator (SU-8, parylene, polyimide, etc.)
  - a-SiC coated → ‘self aligned’ process on Au

- Neuronexus probe design
  - 5 um thick vs. 15 um for NNx (less tissue damage)
  - Implanted in rats at GMU (3C-SiC only)
  - Use conductors and insulators proven in MEAs
SOLUTION

Osseointegrated – lets integrate with a robust, long-term neural interface!

http://www.jhuapl.edu/newscenter/pressreleases/2016/160112.asp

All-SiC neural probe concept preliminary mask design for the 16 electrode implant + PCB board design to connect to an Omnetics 18 pin nanoconnector.
ALL-SIC INI

4H-SiC Electrodes, resistors, diodes

Cyclic Voltammetry in PBS 7.4 pH 50 mV/s

- TIN
- Pt
- SIROF
- 4H-SiC

Current Density mA/cm²

Potential V vs. Ag/AgCl

All Electrodes 35 µm diameter
SiC 25 µm diameter
Test 11 : échantillon 1

- Lithographie e-beam
- Dépôt Ni 45nm / Cr 5 nm
- Lift-off
- Gravure du SiC dans ICP Oxford pendant 1 min
- Observations MEB

Base process → 150 nm tall pillars. Need to optimize
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In vivo materials study

Surface Functionalization of Glucose Sensor

(a) Ti/Au antenna on Si 4H-SiC substrate

(b) SiO$_2$ Ti/Au electrode

(c) PEG brush

(d) a-SiC

The antenna response with coatings:
- SiO$_2$
- a- SiC
IN-VIVO PERFORMANCE OF 3C-SiC – PIG SUB-Q

Bare Ti/Au On 4H-SiC

Si

SiO$_2$/Si

PEG

a-SiC

“All SiC”

3C-SiC and a-SiC on back

No implant tissue block

- Si and SiO$_2$ → inflammatory response with fibrous encapsulation surrounding implants
- Some inflammatory signs found on bare Ti/Au on 4H-SiC antenna
- PEG coated, the ‘all-SiC’ (poly-3C-SiC), a-SiC coated and single crystal 3C-SiC sensors → NO inflammatory immune response

8.5 x 11.5 mm in-vivo Glucose sensor (RF)
**IN-VIVO PERFORMANCE OF 3C-SiC – MOUSE**

<table>
<thead>
<tr>
<th>CD45 – Indicator of Microglia/ Macrophage</th>
<th><strong>GREEN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>GFAP – Indicator of Astrocyte Activity</td>
<td><strong>RED</strong></td>
</tr>
<tr>
<td>MAP2 – Indicator of Microtubule (Dendrite/ Axon)</td>
<td><strong>BLUE</strong></td>
</tr>
</tbody>
</table>

Two (2) 30 days in-vivo tests

Implants in wild-type mice

<table>
<thead>
<tr>
<th>Silicon</th>
<th>3C-SiC</th>
</tr>
</thead>
</table>

Dr. C. Frewin NIH Fellowship
**COMPARISON WITH PT/IR DBS IMPLANT (MRI)**

- Implanted commercial* “MRI compatible” electrodes into rat model and exposed to a 2T field
  - MRI field induces current in probe → imaging artifact observed
  - No imaging artifact observed for SiC probe!
- Heat conductivity issue
  - SiC thermal conductivity ~ copper at RT acts as heat spreader
  - Plastic coated metal probe → no heat dissipation (acts as heat concentrator)

*http://www.plastics1.com/PCR/Catalog/Item.php?item=691
SAR* SIMULATION IN HEAD PHANTOM

Simulated SAR* vs. implant probe material

<table>
<thead>
<tr>
<th>Material</th>
<th>Whole Head</th>
<th>Inside the box</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max 10 g</td>
<td>Max 1 g</td>
</tr>
<tr>
<td>Ref.</td>
<td>2.55</td>
<td>5.83</td>
</tr>
<tr>
<td>All-3C-SiC</td>
<td>2.54</td>
<td>5.91</td>
</tr>
<tr>
<td>3C-SiC Tip</td>
<td>2.55</td>
<td>5.87</td>
</tr>
<tr>
<td>iridium</td>
<td>2.55</td>
<td>6.01</td>
</tr>
<tr>
<td>titanium</td>
<td>2.54</td>
<td>5.98</td>
</tr>
<tr>
<td>platinum</td>
<td>2.54</td>
<td>5.97</td>
</tr>
<tr>
<td>IrO$_2$</td>
<td>2.55</td>
<td>6.00</td>
</tr>
<tr>
<td>TiN</td>
<td>2.55</td>
<td>5.98</td>
</tr>
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</table>

*SAR Specific Absorption Rate (W/kg)
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• Education Opportunities and Challenges
  • first examples of cool stuff to set the stage
Deep-Tissue Cancer Treatment
Peter Choyke, Ádám Gali, Giancarlo Salviati, Stephen Saddow

- Use SiC Nanostructures to effect X-ray excited optical luminescence (XEOL)
- Near IR light shown to be effective at eliminating surface cancers

Scheme to apply SiC NPs for energy transfer toward IR700. IR700 (red) overlaps with NIR emission from SiC NPs as shown.
Why SiC Nanowires

Nanowires (NWs) based on cubic silicon carbide (3C-SiC) are chemically inert and compatible in the biological environment (Cacchioli et al and G. Salviati, NANO LETTERS 2014).

Figure 3: left - Cartoon of core-shell structure. Right - TEM image of the real NW core-shell structure. Orange square delineates NW shape after milling.
The mission of 2D Materials Engineering is to synthesize, investigate, and tailor two-dimensional materials and their heterostructures for advanced electronics, optoelectronics and biosensings.

https://www.iit.it/research/lines/2d-materials-engineering
Bio-graphene activities

Graphene potential for peripheral neuron regeneration:
- Primary neurons do well on non-coated graphene
- 35% longer axons on graphene than controls
- Possible electrical stimulation

Convertino et al., under review

Biosensing for early cancer detection:
- Analysis of body fluids
- High sensitivity and versatility than controls
- Handiness, non-destructive testing

Voliani, Coletti et al., Italian Patent (PT140236)

Gliomics Project
EDUCATION CHALLENGES – ALL LEVELS

• Today’s technology is extremely cross-discipline:
  • Materials, Science, Engineering, Cyber, etc.

• We must do the following (warning, no easy task!):
  • Provide sufficient depth in a given field to be effective
  • Provide sufficient breadth in technology to be able to produce products
  • Work in diverse teams to achieve common objectives
  • Be savvy in terms of marketing, sales, business systems
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• Educating the next-generation workforce is like creating a collage –
  • Each component must provide value
  • The sum total of all components must lead to the desired outcome
  • Depth in one area (i.e., core competency) must be achieved, but not at the expense of the other areas!

• How to do this? Top down? Bottom up? Not everyone learns the same way, but all must arrive at the same destination to be effective, productive members of the new technology workforce!
**EDUCATION CHALLENGES – ALL LEVELS**

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ACKNOWLEDGMENTS

SiC Bio/Materials Studies
C. Coletti (Tissue)
N. Schettini (Blood)
C. Frewin (Brain)

Glucose Sensing
S. Afroz, F. Cespedes, G. Mumcu

Biosensors
S. Iannota, IMEM-CNR
R. Bange, E. Bano, V. Stambouli (DNA)

Simulations
M. Beygi

Deep-Tissue Cancer (NIH R21)
P. Choyke, NCI
A. Gali, Wigner (Budapest)
G. Salviati, IMEM-CNR

Implantable Neural Interfaces
E. Bernardin (all-SiC)
C. Frewin, J. Pancrazio UTD
J. Hassan, E. Janzen, LIU
M. Beygi, MRI compatible interfaces

Fabrication and Processing
R. Everly, NREC
F. La Via, IMM-CNR, 3C-SiC epi
K. Zekentes, E. Bano, V. Stambouli,
IMEP & FORTH, nanopillars

Financial support: DARPA, USF UNI (Crete), NIH R21 (Cancer), USF PEG (Neural Interfaces)
QUESTIONS?

"THE COMPUTER SAYS I NEED TO UPGRADE MY BRAIN TO BE COMPATIBLE WITH ITS NEW SOFTWARE."

Thank you for your kind attention!
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February 28, 2019
1 PM Eastern

Strategies to Build Enrollments in Your Nanotechnology and STEM Programs
PLEASE TAKE OUR BRIEF SURVEY
ADDITONAL SUPPLEMENTAL SLIDES FOLLOW
SiC surfaces can be functionalized in the same way as Si
Used to create biosensors with specific targets (specificity)
SAM PERMISSIVENESS TO NEURAL CELL LINES

- Only 25% with PC12 cells and 44% proliferation with H4 cells on bare 6H-SiC (0001).
- Slight increase in cell proliferation with Octadecene
- 5-7X increase in cell proliferation with APDEMS and APTES on both cell lines!!!!!!

<table>
<thead>
<tr>
<th>Substrate</th>
<th>6H-SiC (0001) H2 etched</th>
<th>6H-SiC (0001) Octadecene</th>
<th>6H-SiC (0001) APDEMS</th>
<th>6H-SiC (0001) APTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact angle (º)</td>
<td>19±2</td>
<td>110±5</td>
<td>48.2±4</td>
<td>54.1±2</td>
</tr>
</tbody>
</table>
SAM SYNTHESIS ON 3C-SIC

Figure 8. (a) Wettability contrast image of a micropatterned ODTMS modified 3C-SiC surface by optical microscopy. Water droplets condense preferentially in hydrophilic oxygen plasma-exposed regions. (b) Fluorescence optical micrograph (50× magnification) of a 3C-SiC surface following micropatterning of the ODTMS layer and immobilization of fluorescently labeled BSA protein.

Platelet rich plasma (PRP)
- Healthy 45 kg female farm pigs
- Centrifuged at 200 g, 20’
- Buffered sodium citrate → blue stopper
- 15 min exposure
- No anticoagulants used
Higher adhesion than SiC and low activation.

Lowest adhesion and activation of all the samples.

Higher adhesion than 3C-SiC and high activation.

*Oil immersion lens
DYNAMIC PLATELET ADHESION STUDY

Hemocompatibility fluorescence micrographs using Rothamin as a fluorescence tag.

- 3C-SiC
- a-SiC
- SiO\(_2\)
- Si (100)

3C-SiC passed ISO 10993-4 standards, other films failed.

Scale bar 100 μm.

Dynamic PRP exposure to surfaces → results same as static: 3C-SiC
3C-SiC and Si probes in PBS

Probes then immersed in PBS
VIDEO OF PROBE SNAP

Video courtesy of Dr. J. Pancrazio, GMU, Fairfax, VA
3C-SiC probe bends 90° when dry! Result replicated in 70% ethanol & in 1x PBS
SILICON CARBIDE (SiC)

- A semiconductor and a ceramic
- More than 220 crystal forms (3C-, 4H-, 6H-SiC, etc.)
  - Different polytypes have different properties
- Very strong covalent bonds
- Thermal conductivity ~ copper
- Wide band gap → low carrier concentration
- Optically transparent – UV/blue light source
- Chemically inert – not attacked by acids and bases
- Does not shed particles or absorb water
- SiC shows evidence of hemo- and biocompatibility
- High hardness and elastic modulus
TOWARDS APPLICATIONS: BIO-INTERFACES/BIO-SENSING

**Biosensing for early cancer detection:**
- Analysis of body fluids
- High sensitivity and high versatility
- Non-destructive testing
- Handiness

*Voliani et al., Patent Pending (PT140236)*

**Biocompatibility evaluation:**
Coating with poly-D-lysine. There is not a clear decrease in cell viability for primary cortical neurons when grown on graphene supports (on both Si- and C-side).

*Collaboration with F. Benfenati within Flagship*

**Electrodes for neuronal prosthetics**
*Collaboration with USF, DARPA Project*

*Frewin et al., US Patent 8,751,015 (2014)*
ALL-SiC MEA: ROBUST INI SOLUTION

- In NNx technology parallel metal electrodes are densely packed using an insulating layer between the Si shank, and then coated in parylene-C (or some variant of this insulation strategy).
- In all-SiC technology, a pn diode blocks current flow and an amorphous SiC (a-SiC) insulator caps the metallic-like electrodes: