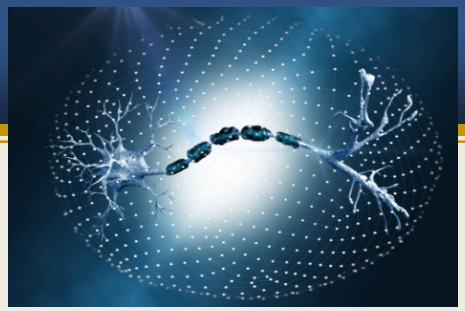


SPARC

Closing the Loop

Considerations for Human Studies

Biomedical Engineering
FLORIDA INTERNATIONAL UNIVERSITY

Ranu Jung
rjung@fiu.edu

February 25-26, 2015

NIH National Institute of Biomedical Imaging and Bioengineering

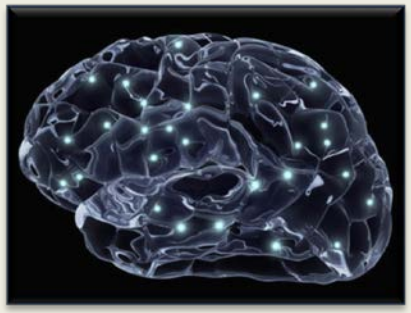
NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

NeuroDesign

Influence:
Immediate modification of activity patterns

[Neurocontrol]

Patterns of Neural Activity



Access:
Tap into endogenous activity patterns

[Neurosignatures]

Plasticity:
Alter pattern formation mechanisms

[Neurotherapies]

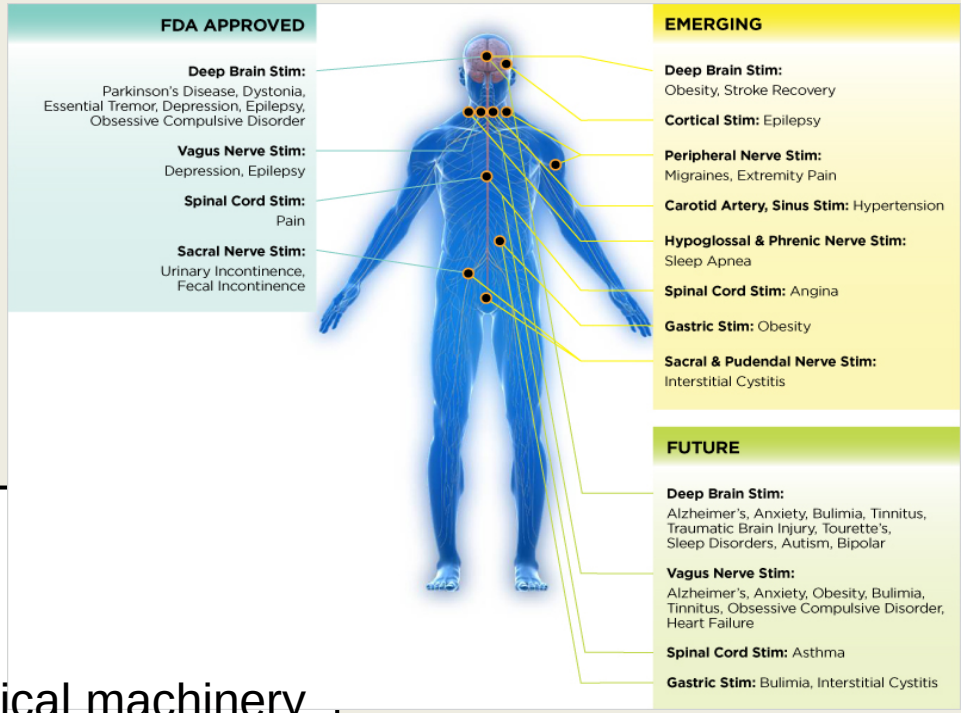
Jung, R,. Biohybrd Systems: Nerves, Interfaces and Machines, 2011

Closing the Loop

address key issues in design, development and delivery of safe and robust biohybrid adaptive systems

Important trends for closing the loop:

- neurotechnology to provide targeted neural sensing and activation
- neurotechnology with adaptive capabilities
- neurotechnology that is increasingly integrated with biological systems
- neurotechnology for personalized precision treatment



- Limited spatiotemporal sampling
- Adaptive biological system
- Punctate intervention
- Precision control of core bio-chemical machinery

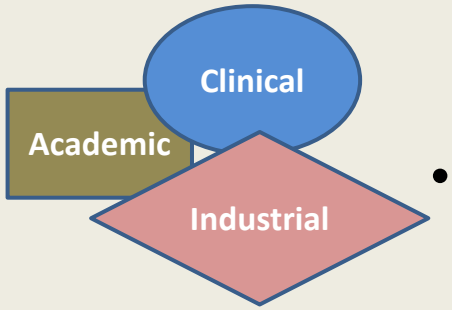
http://www.qiggroup.com/neurostimulation-market.aspx

Investigational Device Exemption (IDE)

to conduct studies with your New Device

IRB

FDA



CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

- Overview of Clinical Plans
  - Experimental Plan
    - Study Design
    - Sample Size
    - Outcome Measures
    - Expected Results
- Prior Investigations
  - Non-Clinical Test Data
  - Clinical Test Data
- Investigational Plan
  - Purpose
  - Clinical Protocol
  - Risk Analysis
  - Monitoring
  - Records and Reports
- Methods, Facilities and Controls
  - Device Manufacturer and Suppliers
  - Manufacturing Process Info
  - Manufacturing Compliance Info
  - Device Design and Manufacturing
    - Design Inputs
    - Design Outputs
    - Design Verification
    - Design Validation
    - Manufacturing Controls
    - Packaging and Usage
- Investigator Agreements
- IRB information
- Labeling

Closing the Loop

address key issues in design, development and delivery of safe and robust biohybrid adaptive systems

1st order challenges:

placing the neural interface at the appropriate location and keeping it there

2nd order challenges:

delivering meaningful stimuli, interpreting neural codes

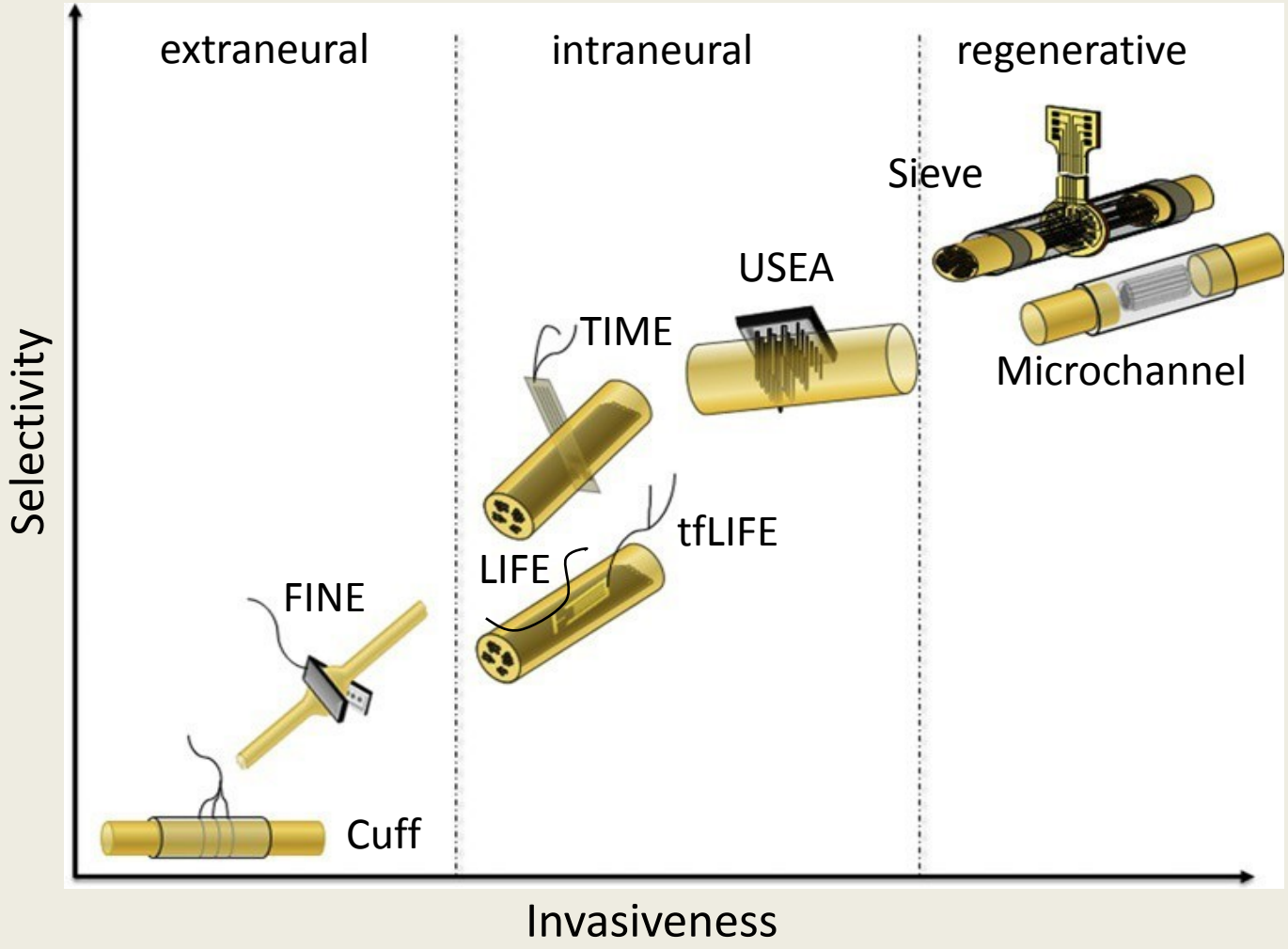
3rd order challenges:

dealing with variability, complexity, plasticity

1st order challenges:
placing the neural interface at the appropriate location and keeping it there

- placement at a location that enables selective communication with the target tissue
  - proximity
  - practical surgical procedures
  - stability of the interface
- biocompatibility
  - chemical properties
  - biological effects
  - mechanical
  - charge/charge density

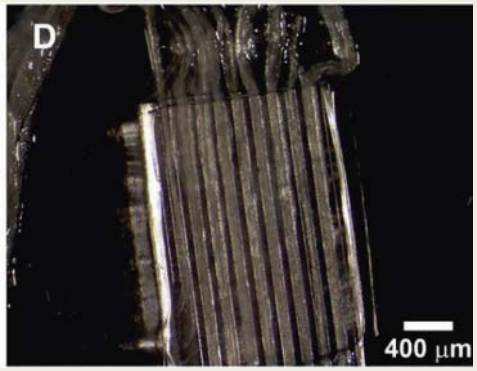
Proximity to Target

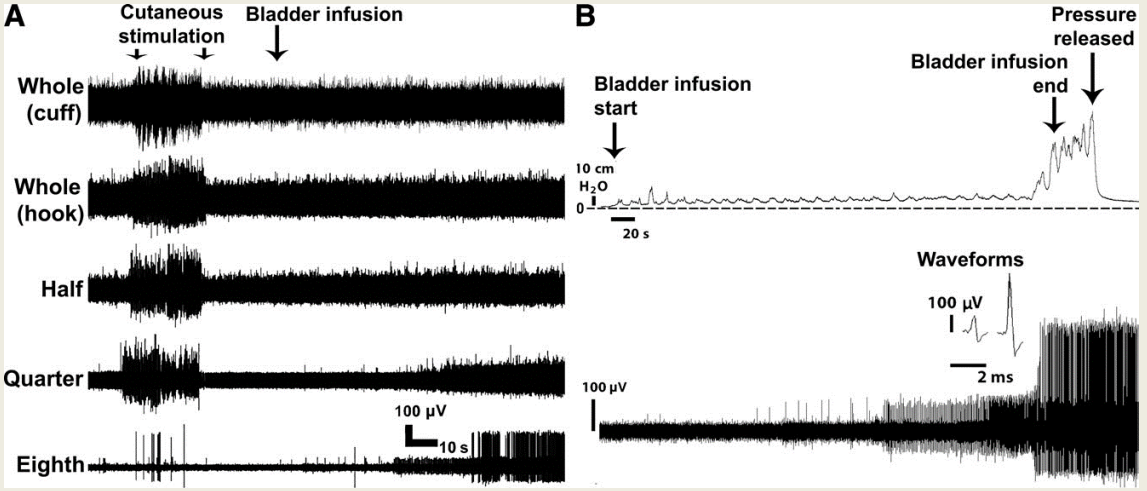


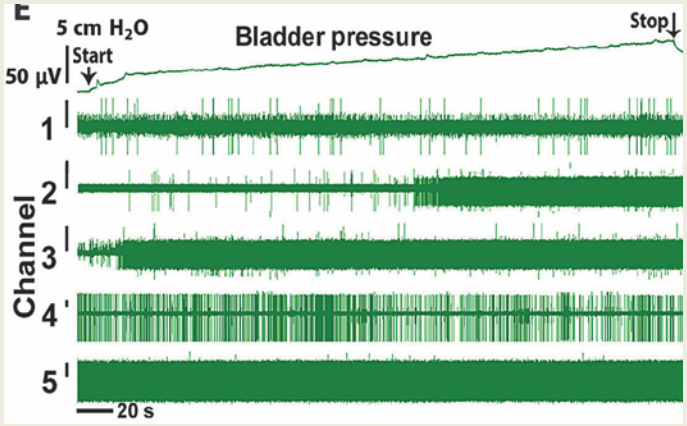
Modified from DelValle & Navarro, Int Rev Neurobiol 2013

Proximity to Target

Bladder Control- Closed Loop (Access- Dorsal roots; Control - Sacral root stim)
Surgical reduction in rat of L6 dorsal root into 100μm rootlets



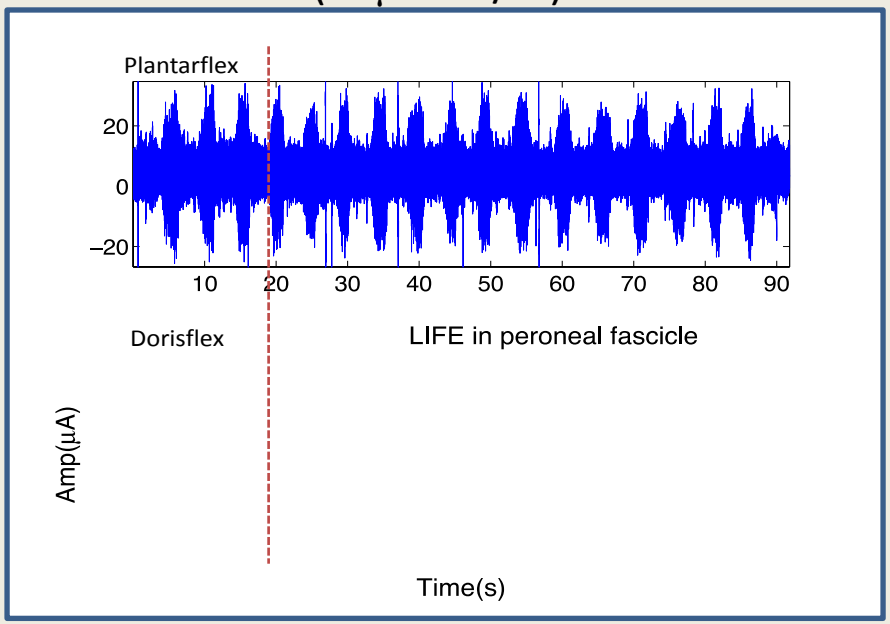




Chew et al., Sci Transl Med 2013

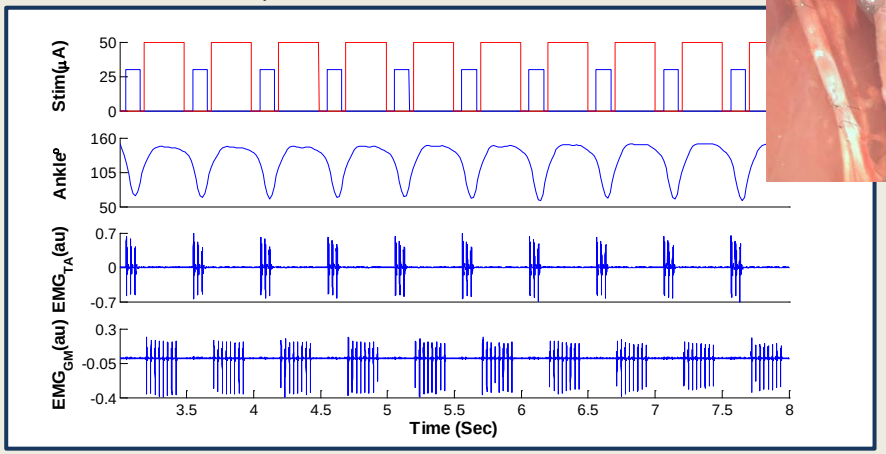
Proximity to Target

LIFE afferent recordings from Rabbit sciatic nerve fascicles (25µm Pt/IR)



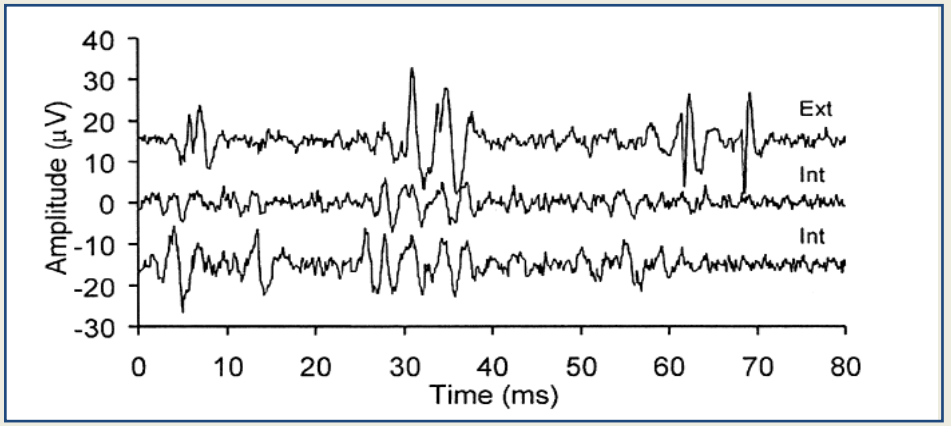
R Jung (Unpublished)

Stimulation of fascicles in Rat sciatic nerve with LIFEs (25µm Pt/IR)



R Jung (Unpublished)

Motor activity recorded using LIFEs from amputee

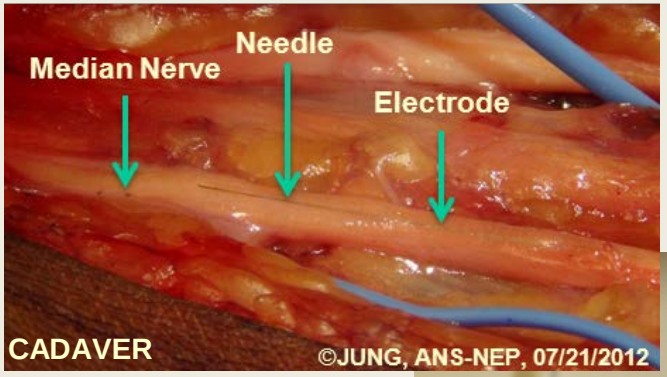


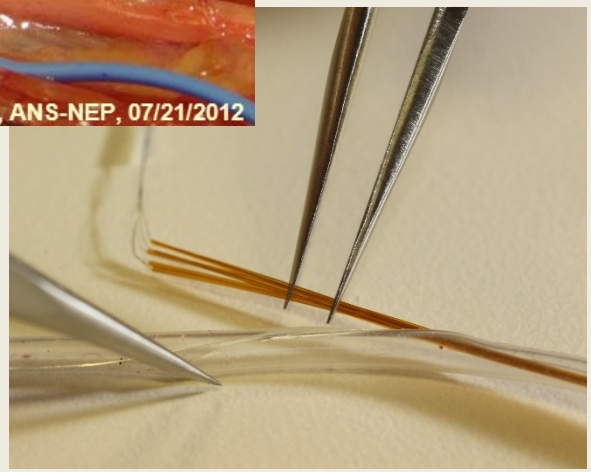
Dhillon et al. J Hand Surg 2004

Surgical Procedures

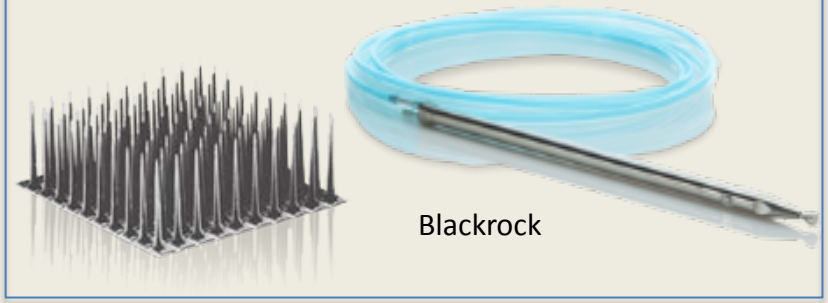
- Surgical tools and procedures for electrode and lead management

LIFE implanted with tungsten needle (cadaver study)

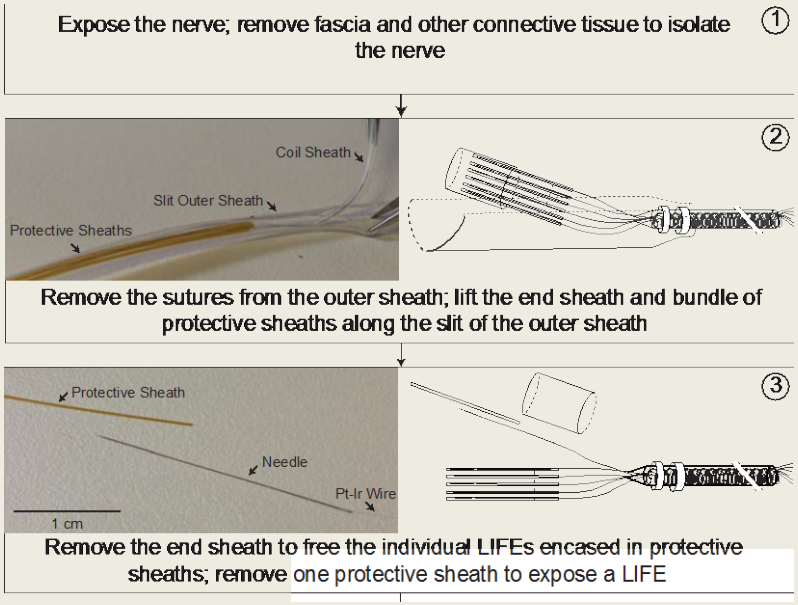




Utah Array and Array Inserter



Multi Lead Multi Electrode management system

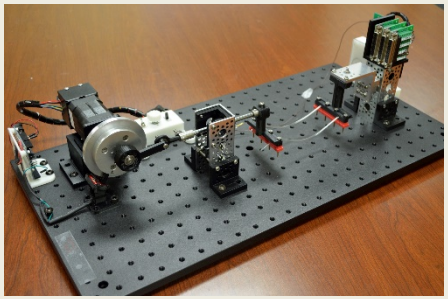


Thota et al, J Neurosc Meth 2014

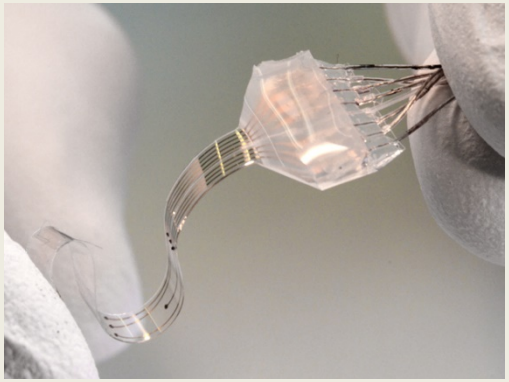
Stability of the Interface

- Anchoring the electrode
- Mechanical Stress
  - Effect on tissue
  - Effect on electrodes

mechanical testing (FIU)



e-dura (EPFL)

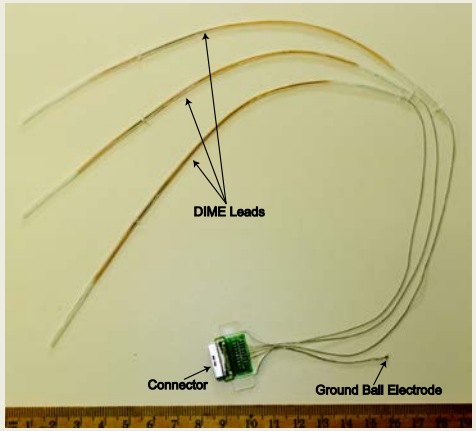


IEEE Spectrum, Jan 2015

- Distributed sensing and recording
  - Multiple sites on one lead
  - Multiple leads
    - Need robust management system

DIME (FIU)

Distributed intrafascicular multielectrode lead



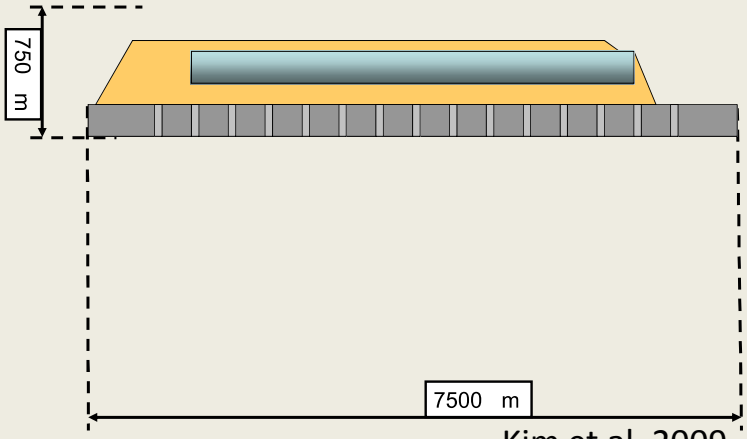
Thota et al, J Neurosci Meth 2014

http://professional.medtronic.com/pt/ion3

Stability of the Interface

Integrating electronics with the electrode

stretchable electronics

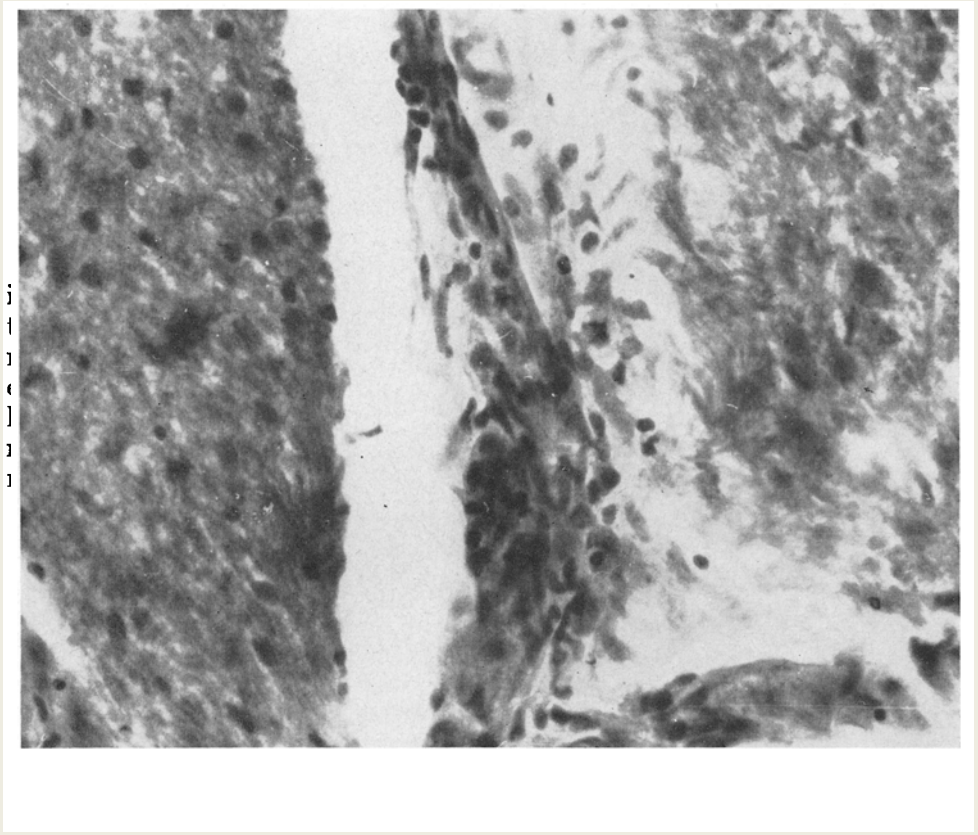


Kim et al, 2009

- New opportunities present new challenges
  - mass, heat …..
  - wireless-location under skin
  - durability

Kim et al, 2009

Biocompatibility



Collias & Manuelidis, J Neurosurgery, 1957

local tissue (brain) response to the electrode

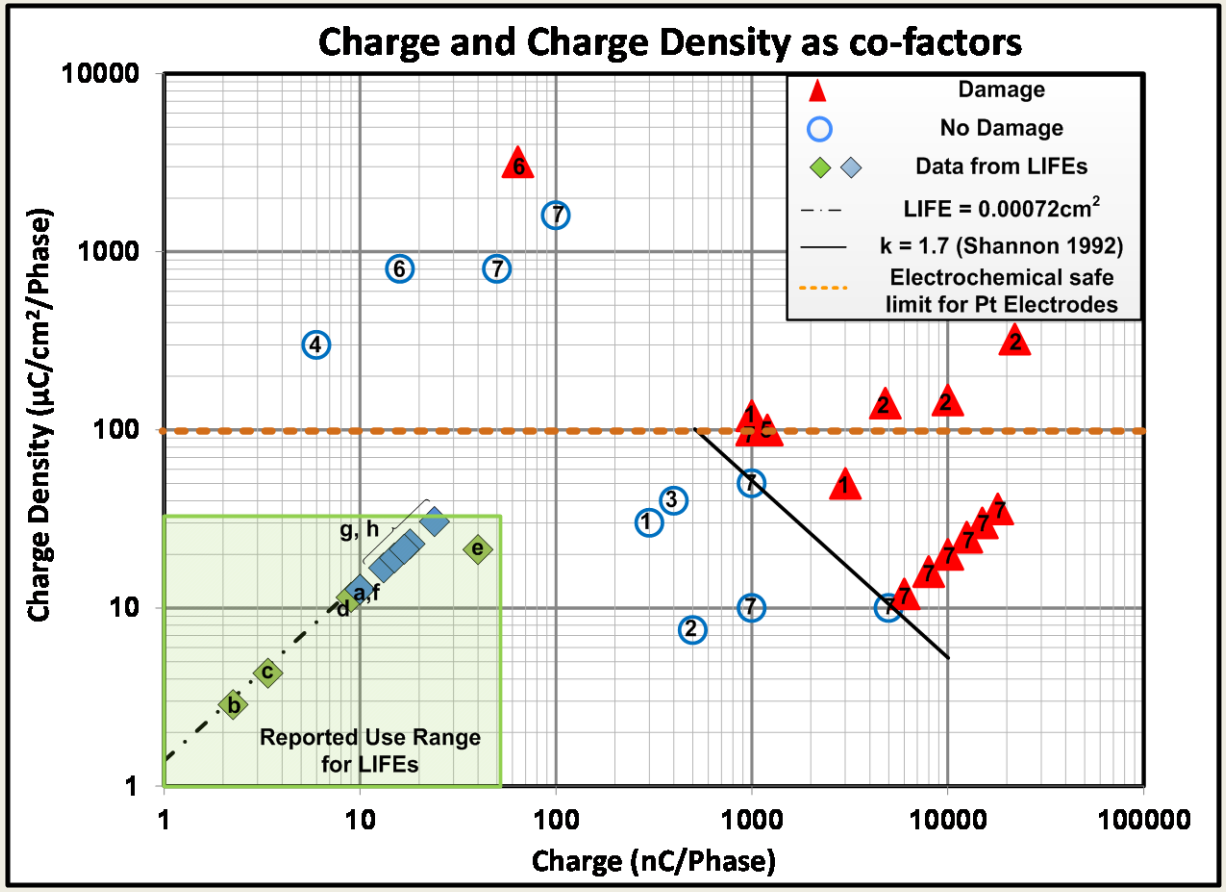
concerns:

- systemic damage
- local damage
- encapsulation

factors:

- size
- location
- materials
- charge transfer
- mechanical compliance
- coatings
- manufacturing processes
- implantation techniques

Biocompatibility: stimulation-related concerns



Kuntaegowdanahalli & Jung (Unpublished)

Preclinical prolonged stimulation with Pt-Electrodes in brain (▲ ○)

1 – Pudenz et al. 1975
2 – Brown et al. 1977
3 – Yuen et al. 1981
4 – Bullara et al. 1983
5 – Agnew et al. 1983
6 – Agnew *et al.* 1986
7 – McCreery et al. 1988, 1990

Preclinical (◆) and Clinical (◆) Data from Pt-LIFEs in peripheral nerves

a – Nannini *et al.* 1991
b – Yoshida *et al.* 1993a
c – Yoshida *et al.* 1993b
d – Yoshida *et al.* 1996
e – Zheng et al. 2008 (Electrode Area= 0.0018cm^2)
f – Dhillon *et al.* 2004
g – Dhillon *et al.* 2005
h – Unpublished data from Dr. Ken Horch's lab

2nd order challenges:
delivering meaningful stimuli, interpreting neural code

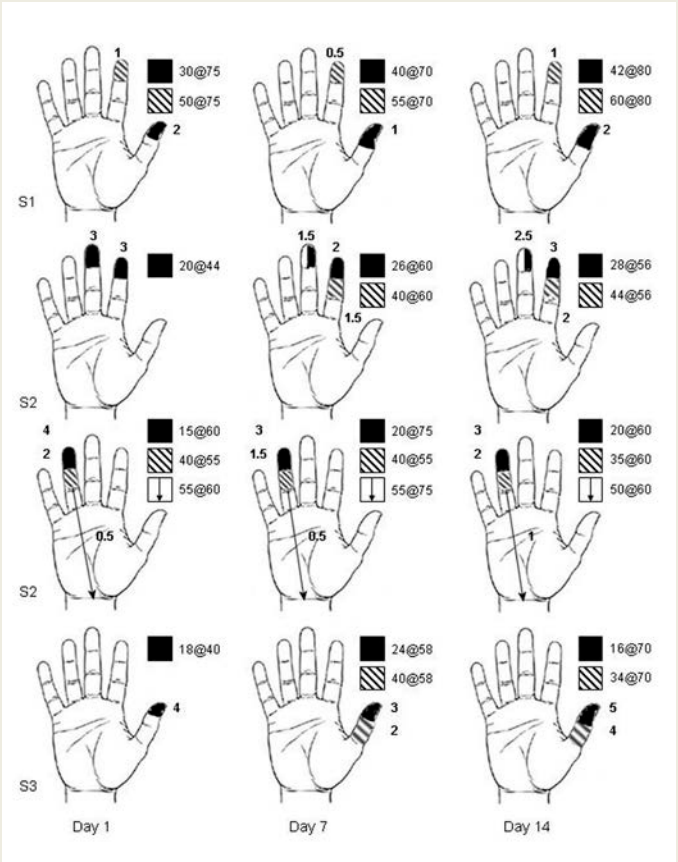
Stimulation

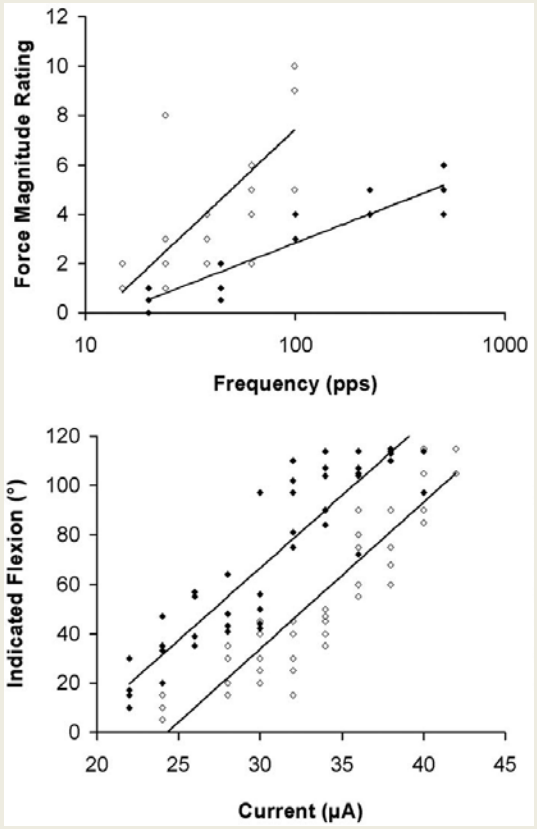
Recording

- spatially distributed
- temporally complex
- mismatch in timescales between neurons and physiological processes
- interconnectivity enables context dependence

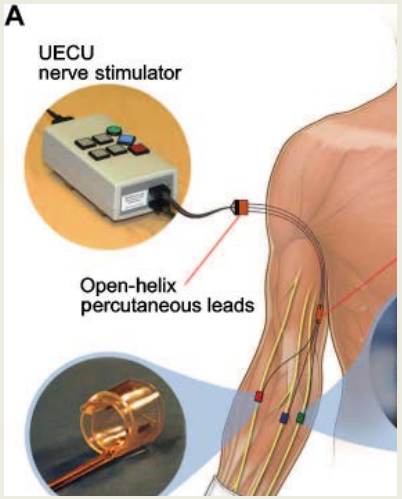
Delivering Meaningful Stimuli

- vary location, frequency, amplitude
  ➔ discrete, graded, stable sensations
- freq and amplitude ➔ naturalistic





Dhillon & Horch, 2005 (LIFE)

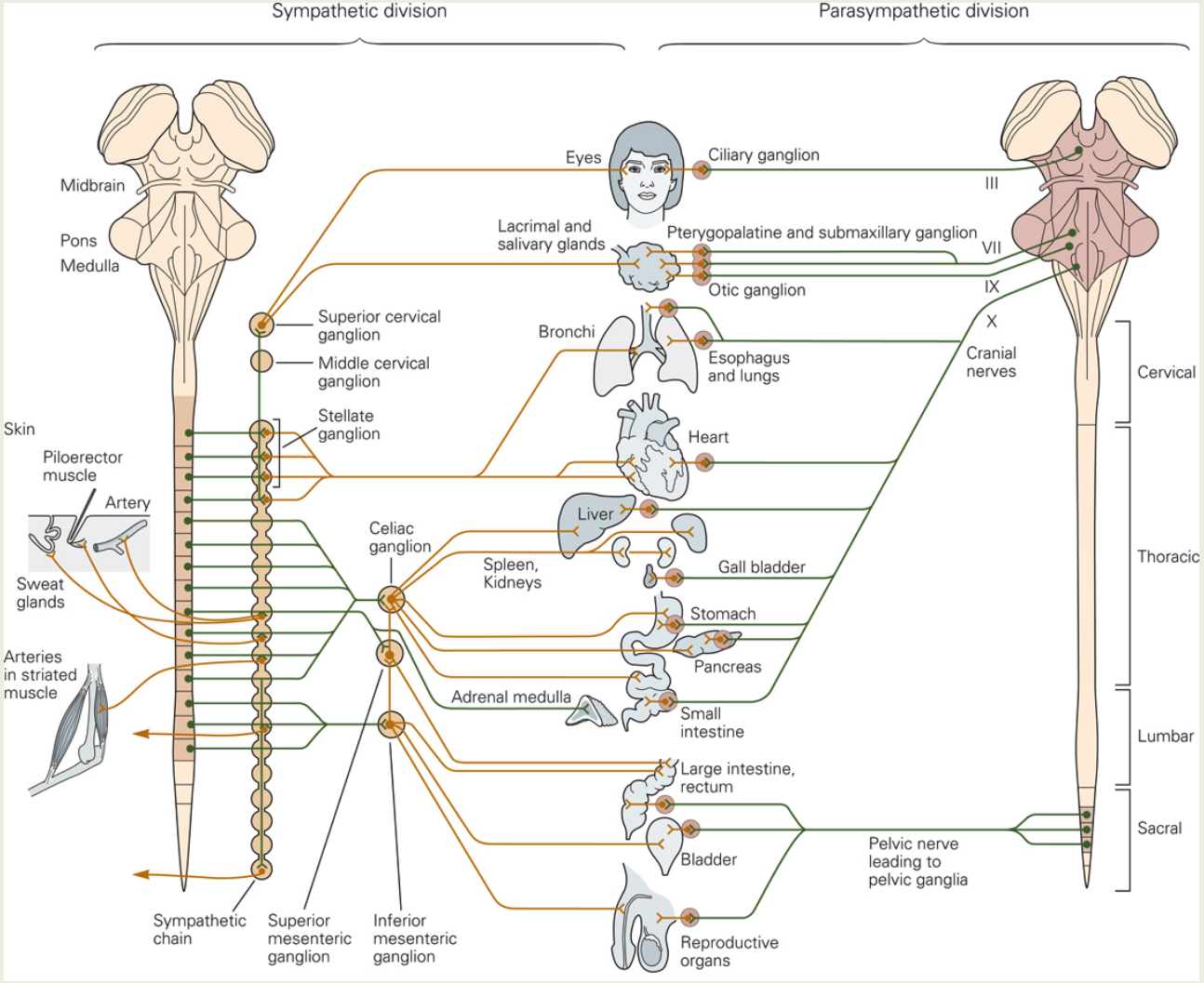


Tan et al, 2014
(cuff)

Delivering Meaningful Stimuli

Autonomic innervation:

- complex codes
- timescale mismatch
- State/context dependence

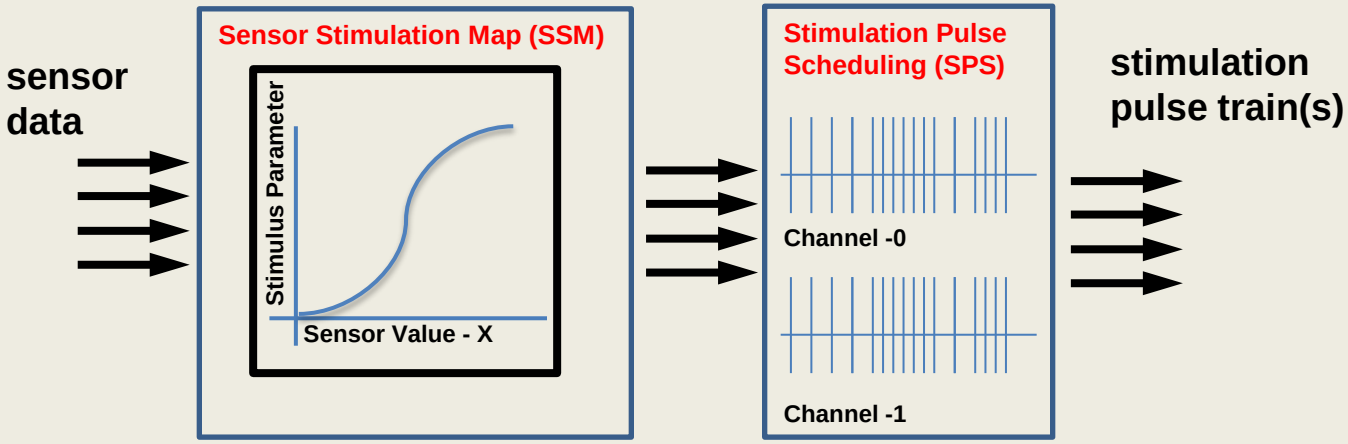


Kandel et al. Principles of Neuroscience

delivering meaningful stimuli; interpreting neural code

control system complexities:

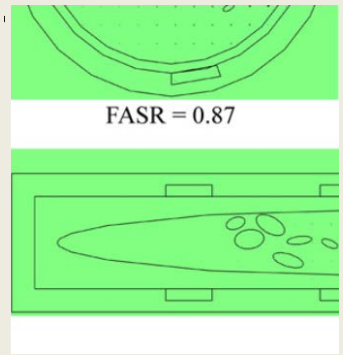
- multiple-input multiple-output MIMO control
- nonlinear mappings
- multi-channel stimulation pulse coordination

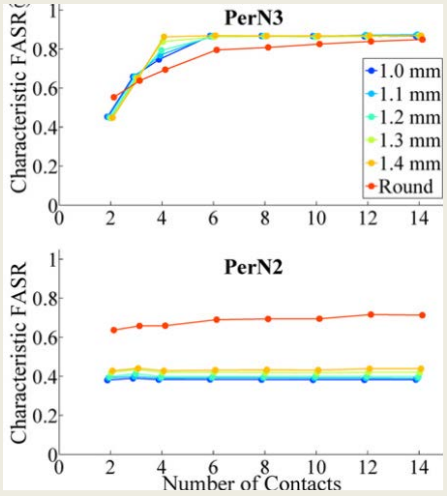


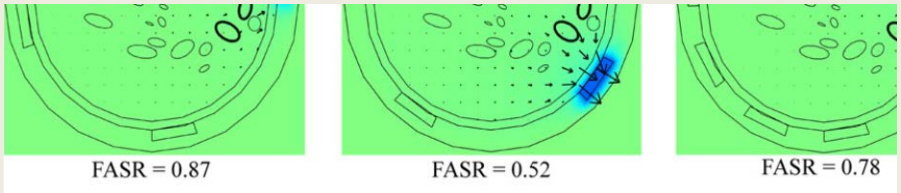
delivering meaningful stimuli; interpreting neural code

Using computational models to design electrodes and algorithms

computational models to investigate effects of cuff design on fascicle selectivity

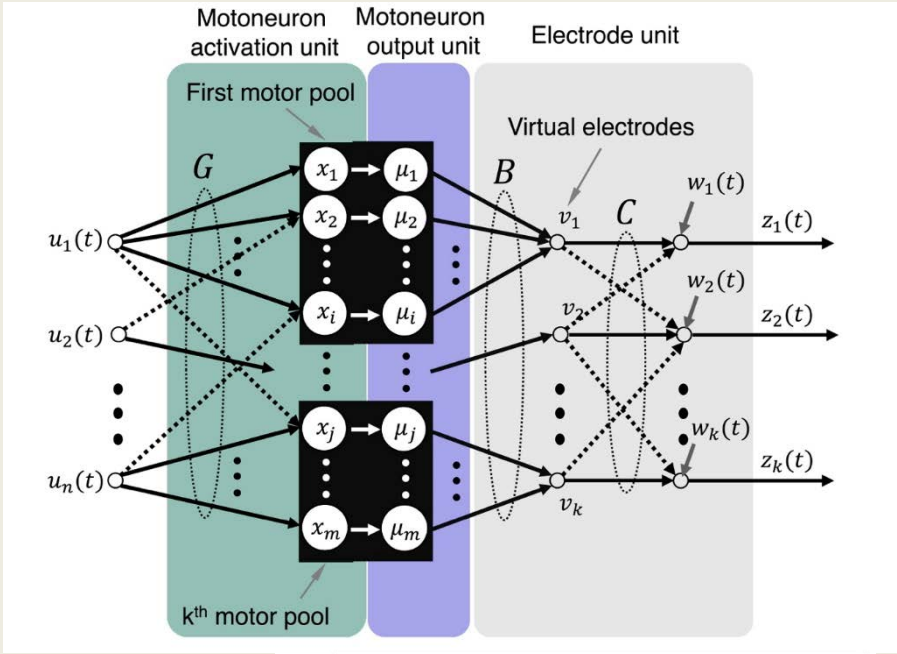


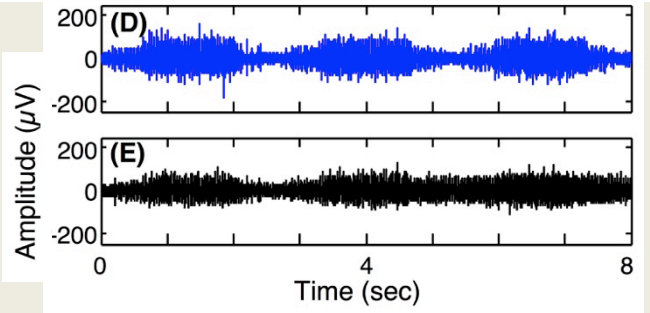




Kent & Grill, 2014.

simulations of neural recordings to assess efficacy of decoding algorithms:





Abdelghani et al, 2014.

3rd order challenges:
variability and human factors

- variability
  - across users
    - may be enhanced by impairment
  - across time
    - circadian rhythms
    - potentiation, habituation
    - adaptation, fatigue
  - across tissues
    - neural
    - target organ

3rd order challenges:
variability and human factors

- human factors
  - personal capabilities
    - affected by age, impairment, tolerance for technology
    - ease of use
    - need for training
  - personal needs (self-dosing)
    - at home, at work, …
    - comfort
  - personal preferences
    - activities, style, …

Hardware Programming/ User Fitting / Data Management

Hardware/Firmware

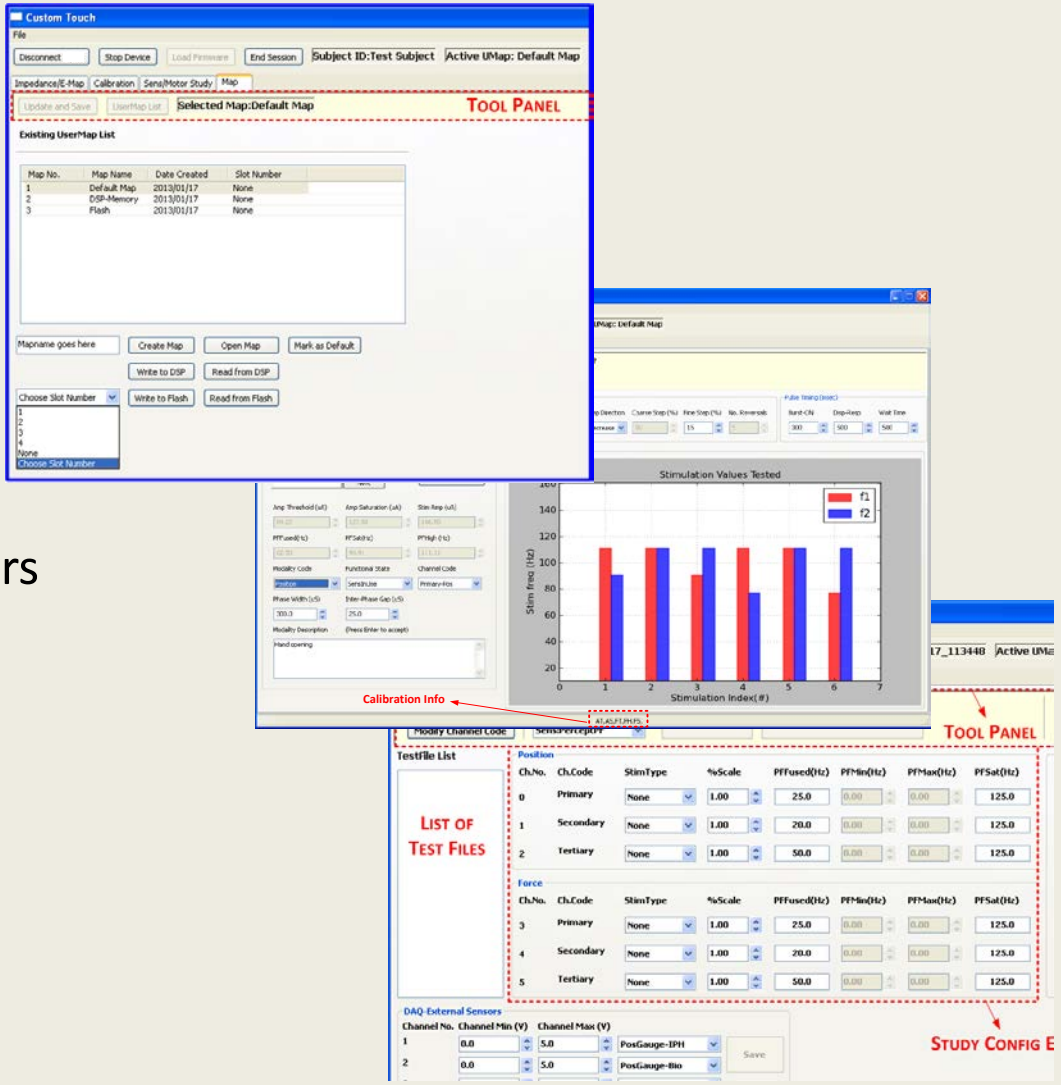
- Create new Stim programs
- View/Modify Programs

User Fitting

- Calibrate electrodes
- Determine stimulation parameters
- Set channel modality

Experimental/Test Panels

- Determine Maps
- Conduct Studies
- Annotate and Store Data



Closing the Loop

safely and effectively address user needs

Important trends for closing the loop:

- neurotechnology to provide targeted neural sensing and activation
- neurotechnology with adaptive capabilities
- neurotechnology that is increasingly integrated with biological systems
- neurotechnology for personalized precision treatment

1st order challenges:

- placing the neural interface at the appropriate location and keeping it there

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3rd order challenges:

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