Disclosures and Support

• Donation from Medtronic (this work is investigator initiated), and other gift funds
• Support of NSF Engineering Research Center for Sensorimotor Neural Engineering
• NDSEG Fellowship
• NIH Training Grant (Computational Neuroscience)
• Some of this work involves off-label use of DBS
• Work conducted under FDA IDEs (and institutional IRBs)
Essential Tremor

• Estimated at more than 5 million patients in the US
• Primarily affects the elderly
• Localized rhythmic movement
• Most common is upper limb kinetic
• Other tremors appear as disease progresses

Mechanism not understood
What is Deep Brain Stimulation?

• A “Brain Pacemaker”

• Constant electrical stimulation to deep brain structures

• Used to treat a variety of neurological disorders
  • Stimulation target varies by disorder being treated
  • Movement Disorders:
    Essential Tremor, Parkinson’s Disease
Clinical DBS

• Originally based off of cardiac pacemaker technology
  – Battery and stimulation generator implanted in chest

• “Open-Loop”
  – Delivers therapy constantly

• Lead targets determined by disorder and symptoms
DBS Target Sites

• Ventral Intermediate (VIM) Thalamic Nucleus
  – Reduces PD tremor, **ET target**

• Subthalamic Nucleus (STN)
  – Effective at treating all motor symptoms
  – Can worsen other PD Symptoms

• Globus Pallidus Internus (Gpi)
  – Alternative to STN, not as effective but no symptom worsening
DBS for Essential Tremor

Normal Physiological Tremor

1 m/s²
acceleration

.1 mV
extensor

flexor

500 ms
RMS = .04 cm
ApEn = .71
Freq = 7 Hz

Essential Tremor OFF-DBS

40 m/s²
acceleration

.2 mV
extensor

flexor
RMS = 10.89 cm
ApEn = .4043
Freq = 4 Hz

Essential Tremor ON-DBS

15 m/s²
acceleration

.1 mV
extensor

flexor
RMS = 1.51 cm
ApEn = .52
Freq = 5 Hz

[Vaillancourt, 2003]
DBS Shortcomings

Current Issues:

• Battery replacement requires surgery

• Clinicians manually balance:
  – Minimizing power
  – Minimizing side-effects
  – Minimizing tremor

• An Open Loop Solution to a Closed Loop Problem
A Solution: Closed-Loop DBS

Sensors allow for adaptive DBS algorithms that control when and how stimulation will occur.

Image Credits: Medtronic and Microsoft Research
Closed-loop DBS will:

- Increase battery life
- Reduce side-effect exposure
- Provide an important research tool
- Require new hardware platforms

Image Credits: Medtronic and Microsoft Research
Closed-Loop DBS System Design
Our Approach

Leveraging Investigational Devices from Medtronic

- Shortcut to fully implanted systems in humans
- Gives a straightforward regulatory process to use

Activa PC+S: Sensing and stimulation

Nexus-D: Real-time communication
The Nexus-D Extension

Designed and built a new Nexus adapter
- Enables a wireless & ambulatory Nexus-D with Bluetooth
- Microcontroller expands command set for ease of mobile development
Nexus C# DLL

Enables quick and iterative prototyping without worrying about abstracted hardware
Now designing the closed-loop algorithm and how to make use of these components

Publications:


Wearable Closed-Loop DBS

Use wearable sensors to demonstrate closed-loop DBS

• Evaluate stimulation power efficiency improvements
• Investigate side-effect mitigation

Image Credits: Medtronic and Microsoft Research
Wearable Sensors

- **Inertial Sensing Watch**
  9 axis IMU: accelerometer, gyroscope, and compass

- **Electromyography**
  Muscle activity sensed via electrodes on the arm

Worn systems allow for ambulatory data collection for long-term monitoring and diagnosis
Wearable CLDBS for Tremor

1. Patient begins to experience tremor
2. Wearable sensor senses the arm’s tremor motions.
3. Sensor wirelessly transmits data to computer
4. Experimental algorithm determines new stimulation parameters
5. Wirelessly updates stimulation parameters to Activa PC+S using the NexDEx and Nexus-D.

Image Credit: UW BRL
CLDBS with Wearables for ET

In collaboration with Andrew L. Ko at UW Medical Center:

Two algorithms tested

1. Tremor-modulated IMU Stimulation
   - (direct) presence/absence of tremor to changes stimulation

2. Movement-triggered EMG Stimulation
   - (indirect) sensing of movement or rest changes stimulation

ET Wearable CLDBS Trial

Gyro Magnitude (sqrt(gx^2 + gy^2 + gz^2))

EMG Magnitude (sum of absolute values from 4 leads: 2 forearm, 2 upper arm)

Stim Delivered

No Stimulation Open-Loop IMU-Triggered EMG-Triggered
Experimental Results

Both approaches resulted in a decrease in stimulation power and an increase in tremor band power when compared to open-loop stimulation

- IMU system had lower power
- EMG system had lower tremor

Need a means of comparing algorithms ....
Performance Metrics

• Tremor Difference Term
  o Use total tremor band power in with:
    No stim (BP_{NO}), Open-Loop (BP_{OL}), and Closed-Loop (BP_{CL})
  o Final value represents the increase in tremor due to closed-loop algorithm, normalized against open-loop tremor

\[ Trem = \frac{BP_{CL}}{BP_{NO}} - \frac{BP_{OL}}{BP_{NO}} \]

• Stim. Power Reduction Term
  o Assuming impedance is constant, power is proportional to amplitude squared
  o Square CLDBS amplitude (V_{CL}) area under the curve, divide by total CLDBS duration (T), divide by OLDBS amplitude squared
  o Final value is the stimulation power reduction that the closed-loop system provides compared to open-loop DBS

\[ Pwr = 1 - \frac{\sum V_{CL}(t)^2}{T \times V_{OL}^2} \]
Performance Metrics

\[ M = \frac{P_{wr}}{100 \times T_{rem}} \]

Can use these two terms to determine the algorithm’s power-tremor tradeoff

Metric value represents the algorithm’s percentage decrease in stimulation power per 1% increase in tremor
Experimental Algorithm Performance

**IMU Tremor-Modulated System**
- Tremor Difference: 36%
- Power Reduction: 84%
- Trade-Off: **2.3%**

**EMG Movement-Trigger System**
- Tremor Difference: 8.2%
- Power Reduction: 53%
- Trade-Off: **6.5%**
Wearable Closed-Loop DBS
For PD Rest Tremor Patients

Work done in collaboration with Dr. Helen Bronte-Stewart at Stanford University.
I built experimental systems for their use, participated in data collection, analyzed data

Two algorithms tested – both using the IMU

1. Tremor-Modulated Stimulation
   - Same algorithm as ET-IMU tremor-modulated trial

2. Moving-Baseline Stimulation
   Two control loops based off of thresholding logic:
   -“Fast Loop” treats tremor quickly as it is sensed
   -“Slow Loop” inhibits return of tremor over long-term

Publications:
Tremor Modulated: Patient 1, Limb 1

Tremor Diff: 12%  Power Red: 83%  Trade-Off: 7.2%
Tremor Modulated: Patient 1, Limb 2

Tremor Diff: 26.7%  Power Red: 72%  Trade-Off: 2.7%
Wearable Summary

• Demonstrated dynamic closed-loop DBS using different sensors and algorithms (in PD)
• Algorithm performance can vary across patients and across limbs in same patient
  – Need to develop patient-specific algorithms
  – Requires patient system identification and modelling
Neural Sensing for BCI
Why Neural Sensing?

Neural Sensing for DBS
• Neural sensing may be useful for determining when a patient is suffering from symptoms
• Can determine when a patient is moving to deliver therapy when needed

Neural Sensing for Brain-Computer Interfacing
• Neural sensing may allow implanted patients to control devices with their mind
Sensing Electrodes

**DBS Electrodes**
- Standard DBS Electrode with four contacts
- Deep brain structures targeted for therapy

**Cortical Strip Electrodes**
- Using a four-electrode strip for cortical sensing
- Placement is flexible, can target motor cortex

Electrode Image
Credits: Medtronic
PD STN Data with the Nexus-D

- With Stanford, collected first Nexus-D streamed data from a human
- From PD STN during rest and movement
Neural Sensing and Brain-Computer Interfaces in ET Patients

Two Experimental Tasks

1. Cortical sensing during overt and imagined movement
   - Using neural signals to determine when patient is moving
2. Constant Velocity Brain Computer Interface Experiment
   - Training patient to volitionally manipulate cursors with his brain
Activa PC+S Cortical Sensing

Overt Power Spectral Density (1s to 3s after prompt)

Imagined Power Spectral Density (1s to 3s after prompt)

Overt Movement

Imagined Movement
Stability of Cortical Recordings

In hand motor area, beta-band across 1-4 months

Rest Overt Movement

Rest Power Spectral Density (Contacts 8-10)

Overt Power Spectral Density (Contacts 8-10)

Publications:
Neural Sensing of Movement Summary

• Sensing with the Activa PC+S with cortical strips on the motor cortex can easily distinguish hand and arm movements from rest
• This has been stable over four monthly sessions, demonstrating the chronic sensing possibilities
• Imagined movements are more difficult with only a small change in a small band.
Implanted BCI

Utilize implanted electrodes as signal sources for a Brain-Computer Interface (BCI)

• Demonstrate use of brain signals for command and control of devices
• Compare efficacy of different signal locations for BCI

Image Credit: Phys.org
Integration with Unity

- Proof of concepts for Activa PC+S BCI games prototyped in Unity
- Allows easy configuration of trial geometries and tasks
BCI Training: Overt Movement Trials
BCI: Imagined Movement Trials

Lead 3 spectrogram (dB)

Beta Control Signal

Cursor Trajectory
Neural Triggered Closed Loop DBS
Hand to Mouth Task: Stimulation Off

Note tremor present through the entire duration of movement
Note high beta band power during rest
Hand to Mouth Task: CLDBS Trial 3 (Final Tuning)

Latency 2.5 sec (from telemetry, classifier averaging)
Note tremor present only at beginning of movement due to system delays
Patient FTM Tasks in order:
1) Draw spiral
2) Connect Dots (three times)
3) Handwriting

Durations indicated in brown

Patient rested between dots and handwriting while researcher switched pages

Promising performance in real life cases
Closed-Loop DBS for ET: Therapeutic Effect

Activa PC+S, and cortical strip electrodes

3 ET subjects at UW, ~12 months


Houston, Thompson, Ojemann, Ko, Chizeck, *IEEE NER’17*
Closed-Loop DBS for ET: Prompted Movement Task

With CL DBS


Houston, Thompson, Ojemann, Ko, Chizeck, IEEE NER’17
Neuroethics
Patients with DBS have reported problems post-op (Agid, et. al. 2006):

Changes in self-perception.
- “I don’t seem to recognize myself without the problems I had before.”
- “I’m an electronic doll”—“I feel like a ‘Robocop’”—“I’m under remote control”
- “Even though I know my motor state is perfectly normal, I just can’t get rid of the thoughts I used to have, when I was ill.”

Changes to interpersonal relationships.
- “Since the operation, he wants to live like a young man […] I prefer him as he was before, always nice and quiet.”
- “During all the years he was ill, I had to grin and bear it […] but I can’t stand it any more. […] He just sits there and expects me to do everything.”

Neuroethics
The Psychosocial Impact of DBS
Explaining Psychosocial Effects

Theories from the literature—DBS may:

- Make patients feel *alienated* from or *inauthentic* to themselves. (Kraemer, 2011 & 2013)
- Challenge or clash with the patient’s *self-narratives*. (Baylis, 2011)
- Impair the user’s ability to be *autonomous* (Mackenzie 2014).

Two questions:

- *What are the psychosocial effects of closed-loop DBS?*
- *Would closed-loop control make DBS easier to accept from any of these perspectives?*
Closed-Loop DBS User Interviews

• Semi-structured interviews—an on-going conversation with each patient.
• Open-ended questions on a wide range of topics:
  ✓ “Has ET changed how you get along with people?”
  ✓ “Do you ever forget that you have a brain implant?”
  ✓ “How often do you turn your stimulator on or turn it off?”
• Interviews conducted while the patient tests the experimental platform.

Submitted Publications:
Preliminary Results (1st ET Subject)

Initial body image issues (post-op):

- Initial worries about others being able to see implanted leads.
- “I feel like I’ve got a conduit going down the back of my neck. I’m always rubbing on it.”
- He is constantly aware that the implant is there.


Results (1st ET Subject)

Battery conservation is a high priority:
  o He keeps his stimulator turned off “95% of the time.”
  o Why conserve battery?
    ✓ Avoid surgery.
    ✓ Medical costs after retirement.
    ✓ Looking ahead: a thinner stimulator unit.

Mixed reactions to closed-loop control:
  o Excited to have it
  o Worries about hard-to-use system.