Treating Epilepsy via Adaptive Neurostimulation

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Learning objectives

- Review the neurostimulation hypothesis for treating epilepsy.
- Understand the basic principles of adaptive neurostimulation.
- Study a mathematical framework for optimizing the choice of neurostimulation parameters.
- Observe results from applying adaptive neurostimulation \textit{in vitro}.
Disclosure statement

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Epilepsy

- **Epilepsy is a neurological disorder marked by spontaneous seizures.**
  - Affects ~1% of world's population.
  - Up to 20-25% of those do not benefit from standard treatments (anti-convulsants, surgery).

- **Causes are varied** (pre-disposition, head trauma, fever, tumor, etc.)

- **What is a seizure?**
  - Abnormal electrical activity in the brain, may produce physical convulsions, or other symptoms.
Anatomy of a seizure \textit{(in vitro)}
Neurostimulation hypothesis

External perturbation of an epileptic neural system can alter dynamics away from excitability.
Deep brain stimulation (DBS)

- Implanted electrodes electrically stimulate brain tissue.

- Recent clinical trials of DBS:
  - Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTÉ)
    » 157 people; 17 sites in US; 2003-2008; sponsored by MedtronicNeuro
  - Randomized Controlled Trial of Hippocampal Stimulation for Temporal Lobe Epilepsy (METTLE)
    » 90 people; 1 site in Canada; 2008-2011; sponsored by U. of Calgary
  - RNS™ System Long-Term Treatment Clinical Investigation:
    » 280 people; 28 sites in US; 2006-2013; sponsored by NeuroPace
    » Closed-loop stimulation “detect-then-stimulate”

Many parameters to control: stimulation site, stimulation frequency/intensity, stimulation pattern, …
Electrophysiology results from *in vitro* model

The literature repeatedly shows 1Hz, 10-200µA, fixed stimulation successfully suppresses seizures in vitro. [D’Arcangelo et al., Neurobiology of Disease. 2005].

![Graph showing electrophysiological results](image-url)
A few interesting open questions

• What parameter settings (stimulation site, frequency, intensity, pattern) achieve maximal suppression?

• Can we reduce the number and/or intensity of stimulations, while maintaining suppression efficacy?

• How can we customize parameters for different subjects?
Adaptive neurostimulation paradigm

Objective: create a stimulation device which is

1. **Optimal**: maximize seizure reduction + minimize stimulation.
2. **Responsive**: strategy evolves as a function of the observation.
3. **Automatic**: stimulation strategy learned from data.
Adaptive neurostimulation example
Methods: Data collection *in vitro*

- Electrophysiological recording in the Entorhinal Cortex (B), with stimulation at fixed frequencies in the Subiculum (A).
Methods: Data collection and labeling

Experimental protocol:
• Control (min. 3 seizures)
• Periodic pacing at 0.2Hz (min. 20 minutes).
• Recovery (until interval between ictal events stabilizes).
• Etc. with 0.5Hz, 1.0Hz, 2.0Hz.

Then, manually identify:
• Seizure occurrences
• Neurostimulation parameters:
  {0Hz, 0.2Hz, 0.5Hz, 1.0Hz, 2.0Hz}
Methods: Signal processing

- Select **decision window** duration: 1 sec.

- Select **observation window** duration: 13 sec.

- Extract **observation features** using signal processing techniques:
  - Range, energy, multi-scale Fourier transform
Methods: Training data

- Form an input vector, $x_t$, for each decision window, $t$:
  \[ x_t = \{z_t, a_t, c_t, z_{t+1}\} \]
  where $z_t$ = observation features at $t$
  $a_t$ = neurostimulation parameters at $t$
  $c_t$ = cost function at $t$

- The cost function depends on the occurrence of seizures and stimulation delivered:
  \[ c_t = c_t^{seizure} + \alpha c_t^{stim} \]
  where $c_t^{seizure} = \begin{cases} 1 & \text{if seizure occurred at time } t, \\ 0 & \text{otherwise} \end{cases}$
  $c_t^{stim} = \begin{cases} 1 & \text{if stimulation occurred at time } t, \\ 0 & \text{otherwise} \end{cases}$
  $\alpha$ is a free parameter.
Methods: Minimizing the cost function

• The objective is to select actions such as to minimize the expected cumulative cost:
  \[ E [ c_t + c_{t+1} + c_{t+2} + \ldots + c_T | z_t ] \]

• Use regression analysis to estimate the cost for different action choices from the training data:
  \[ Q_k(z_p, a_t) = c_t + \max_{a \in A} Q_{k-1}(z_{t+1}, a) \]

• Select the action which minimizes the expected cost:
  \[ a_t := \arg\max_{a \in A} Q_k(z_p, a) \]
Experimental protocol for validation

1. Control period (min. 3 seizures).
2. Periodic pacing at 1.0 Hz (min. 20 minutes).
3. Recovery period.
4. Adaptive stimulation strategy (min. 20 minutes).
5. Recovery period, no stimulation.
6. Periodic pacing at effective frequency \( f = n_s/T \)

where \( n_s = \) number of stimulations during adaptive protocol

\( T = \) duration of adaptive protocol
Proportion of time spent in seizure

- Proportion of time spent in seizure, averaged over N=11 slices.

* = statistically significant at $p=0.05$
Effective frequency of the adaptive protocol
Suppression efficacy for slices with \( eff > 1 \text{Hz} \)

\[\text{N} = 11 \quad \text{N} = 4\]

* = statistically significant at \( p = 0.1 \)
Adaptive protocol example #1

(a) Adaptive controller suppresses a seizure by increasing the frequency of stimulation.
Adaptive protocol example #2

(a) Adaptive controller suppresses a seizure by increasing the frequency of stimulation.

(b) A short seizure develops, stimulation is applied to shorten its duration.
Adaptive protocol example #3

(a) *Adaptive controller suppresses a seizure by increasing the frequency of stimulation.*

(b) *A short seizure develops, stimulation is applied to shorten its duration.*

(c) *Adaptive controller increases frequency to suppress seizure, then decreases frequency.*
### In vivo: Challenges

<table>
<thead>
<tr>
<th>In vitro model</th>
<th>In vivo model</th>
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<tbody>
<tr>
<td>Limited slice-to-slice variation.</td>
<td>Larger variance between subjects.</td>
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<td>Short lifespan.</td>
<td>Longer lifetime; disease can evolve over time.</td>
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<td>In vitro model has known periodic pacing strategy.</td>
<td>No known open-loop strategies.</td>
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<td>Restricted parameter space.</td>
<td>Higher-dimensional action space (more electrodes, intensity settings, etc.)</td>
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Discussion

• Animal models of epilepsy provide a rich framework for investigating adaptive neurostimulation strategies.

• Most adaptive neurostimulation approaches adopt a “detect-then-stimulate” paradigm.

• Our work leverages techniques from the control literature.
  – Goal is to directly minimize a cost function.
  – Explicit seizure prediction (or detection) is not required.

• Results show good suppression in vitro, in some cases using significantly less stimulation than periodic pacing.

• Preliminary evidence suggests that neurostimulation can be used to probe the excitability of the system.
References


