Closed-Loop Deep Brain Stimulation

Department of Information Engineering - DEI

Telemedicine’s Course Project

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Deep Brain Stimulation (DBS) is a procedure involving implantation of neurostimulator electrodes sending electrical impulses to specific targeted regions.

- **Treatment** of movement and neuropsychiatric disorders [1,2]:
  - Parkinson Disease (PD)
  - Tourette Syndrome
  - Obsessive-Compulsive Disorder
  - Treatment-Resistant Depression (TRD)

- **Open Loop vs Closed Loop** DBS

1994
First Experiment on PD

1997
Granted for Thalamic DBS

2002
Approved for STN and GPi

Up to now:
70 thousand DBS patients

**DBS: Open vs Closed Loop**

**Open Loop:** *continuous* (cDBS) or *random* (rDBS) stimulation [1]
- cDBS → first attempt of DBS
- rDBS → random train of stimulations

**Closed Loop:** *adaptive* (aDBS) stimulation [1,2,3]
- Automatically adapt to the dynamic of the disease → Less side effects & more clinical benefits
- Less power consumption

aDBS: Biomarker Choice

Local Field Potential (LFP) [1,2]
- Bandwidth: [0.01 - 300] Hz
- $F_S > 1$ kHz
- Amplitude: $[5 \mu - 5m]$ V
- Quantization: 8 - 12 bits
- Metal or glass electrodes

Action Potential (AP) [2]
- Bandwidth: [0.01 - 10k] Hz
- $F_S > 40$ kHz
- Amplitude: [-80 - 40] mV
- Quantization: 8 - 12 bits
- New optical imaging techniques

aDBS: Clinical Trial

**Clinical Trials Studied:** [1]

- **Patients →** 8 PD cases
- **Mean Age →** 59.1 yrs old
- **Mean Disease Duration →** 9.4 yrs
- **UPDRS →** Off/On Stimulation and Medication

<table>
<thead>
<tr>
<th>Case</th>
<th>Age Duration (yr)</th>
<th>UPDRS Off</th>
<th>UPDRS On</th>
<th>DBS Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case1</td>
<td>59 - 12</td>
<td>42</td>
<td>20</td>
<td>On/Off fluctuations, tremor bradykinesia</td>
</tr>
<tr>
<td>Case2</td>
<td>62 - 10</td>
<td>20</td>
<td>8</td>
<td>On/Off fluctuations, tremor</td>
</tr>
<tr>
<td>Case3</td>
<td>67 - 7</td>
<td>43</td>
<td>14</td>
<td>On/Off fluctuations, dyskinesias</td>
</tr>
<tr>
<td>Case4</td>
<td>49 - 10</td>
<td>42</td>
<td>6</td>
<td>Tremor</td>
</tr>
<tr>
<td>Case5</td>
<td>49 - 10</td>
<td>58</td>
<td>23</td>
<td>On/Off fluctuations, tremor</td>
</tr>
<tr>
<td>Case6</td>
<td>63 - 3</td>
<td>18</td>
<td>8</td>
<td>Tremor/Bradykinesia</td>
</tr>
<tr>
<td>Case7</td>
<td>67 - 14</td>
<td>63</td>
<td>24</td>
<td>On/Off fluctuations</td>
</tr>
<tr>
<td>Case8</td>
<td>57 - 8</td>
<td>43</td>
<td>17</td>
<td>Severe Off periods, On/Off fluctuations</td>
</tr>
<tr>
<td>Mean</td>
<td>59.1 - 9.4</td>
<td>41.1</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>2.5 - 1.3</td>
<td>5.6</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

aDBS: System Setup

Target regions:
- STN and Post STN
- GPi
- Bilateral Thalamus

High Frequency Stimulation: \( f \geq 130 \text{ Hz} \)

Electrodes: quadripolar electrode with 4 contacts \([(0-2), (1-3)]\) by Medtronic®

Unilateral vs Bilateral Stimulations

A posteriori verification of electrodes placement through MRI or CT
aDBS: Technical Aspects (1)


Closed-Loop DBS

Matilde Boschiero, Umberto Michieli
aDBS: Technical Aspects (2)

**LFP acquisition:**
- From contacts 0-2 and 1-3
- Recording from STN

**StimRecord Amplifier:**
- Band pass filter [3-37] Hz
- 3-stage common mode rejection amplifier (x9100)

**Beta signal:**
- Choice of contacts with greater beta in [13-35] Hz
- Extract frequency of beta peak in the spectrum of LFP
- Filter the signal around this peak
- Correlates with motor tasks

Figure (from left to right) : Activa SC, Activa RC and Activa PC Deep Brain Stimulation Systems by Medtronic® [1]

**aDBS: Technical Aspects (3)**

**1401 Data Unit:**
- LFP → A/D (usually 12 bits)
- Spike2 Software:
  - Filtering: rectification + smoothing MA filter of 400 ms duration
  - User-defined threshold
- Processed LFP → D/A

**Stimulator:**
- Stimulation starts at 0.5 V with delay of 30/40 ms after threshold’s crossing and increases of 0.5 V every 3/4 minutes.
- Battery powered: ± 9 V
- Output: biphasic charge balanced symmetrical pulse waveform of 100 μs ramped 250 ms up/down onset/offset
aDBS: Technical Aspects (4)

A. From bottom to top [1]:
   a. Bipolar analogue LFP
   b. LFP digitally filtered around the beta peak
   c. MA output of rectified and beta filtered LFP + amplitude threshold of triggering
   d. Stimulation trigger
   e. 130 Hz and 100 µs stimulation at contact 1

B. LFP power spectrum without DBS

C. LFP power change in different stimulation modes

D. UPDRS trend, solid line = blinded, dashed = unblinded

E. 500 s of rectified beta-filtered LFP amplitude

But why does DBS work? [1]

- Regularization of neuronal patterns → decreases output from stimulated site

- Pathological bursts and oscillatory activities prevented
  - Improved processing of sensorimotor information
  - Reduction of disease symptoms

- Underlying physiological causes are multiple and controversial.

### aDBS: Results (1)

<table>
<thead>
<tr>
<th></th>
<th>Age - Disease Duration (yr)</th>
<th>UPDRS</th>
<th>DBS Indications</th>
<th>Online Filter Range (Hz)</th>
<th>Stimulation</th>
<th>Time on Stimulation %</th>
<th>Time between Stimulation Bursts (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Off</td>
<td>On</td>
<td></td>
<td>V</td>
<td>Site</td>
<td>Contact</td>
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<td>Case1</td>
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<td>2.7</td>
<td>L</td>
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<td>20</td>
<td>8</td>
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<td>19 - 25</td>
<td>1.8</td>
<td>R</td>
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<td>1.8</td>
<td>0.2</td>
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Results adopted and integrated from [1]

SEM=σ/N  Standard Error of the Mean
p: parametric statistical analysis

aDBS: Results (2)

- Reduce the overly synchronized activity of motor cortex
- Efficacy and Resource Optimization (*energy consumption*)
- Benefits on all the cardinal signs of PD: *Rest tremor, Bradykinesia* and *Rigidity*
- On-time periods drop as beta bursts become less frequent
- Unilateral vs Bilateral (*recovery improvement*): 30% vs 10% [1]

<table>
<thead>
<tr>
<th>Mean Reduction in UPDRS Motor Scores (blinded and unblinded)</th>
<th>cDBS</th>
<th>rDBS</th>
<th>aDBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42.5 %</td>
<td>20.2 %</td>
<td>58 %</td>
</tr>
<tr>
<td>On-Time Period (%)</td>
<td>100 %</td>
<td>43.3 ± 1.5 %</td>
<td>44.2 ± 2.4 %</td>
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<td>Delivered Energy per Unit Time</td>
<td>270 ± 7 μW</td>
<td>/</td>
<td>132 ± 21 μW</td>
</tr>
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</table>

[1] Depressione resistente ai farmaci: speranze dalla stimolazione magnetica, Repubblica - Salute, Prof. Stefano Pallanti on DBS, 2010
aDBS: Issues

1. Not mass therapy (affordability, frequent follow-up visits and battery replacements)

2. Simultaneous sensing and stimulation

3. Biomarker Choice: LFP, AP, etc.

4. More complex circuitry than cDBS

5. Side effects: Paresthesias, Headache, Dysarthria, Paresis, Ataxia, Hemorrhages, Infections

6. Ethical issues (psycho-social impact, effects on personal identity, treatment of children) [1]

aDBS: Conclusions and Future Directions

★ Minimize patient risks (e.g. surgical, side effects, etc)

★ (Possible multiple) biomarkers optimization for every symptoms

★ Optimal anatomical target location

★ Optimal smoothing to beta activity

★ Optimal on-stimulation time/delay/threshold

★ Real-time and lightweight algorithm

★ Applicability to other neurological disorders

★ Ad-personam parameters setting

★ Optogenetic technique