UNIVERSITÀ DEGLI STUDI DI PADOVA

DIPARTIMENTO DI INGEGNERIA DELL'INFORMAZIONE

Closed-Loop Deep Brain Stimulation

Department of Information Engineering - DEI

Telemedicine's Course Project

Students: *Matilde Boschiero, Umberto Michieli*

Supervisor: *Giulia Cisotto*

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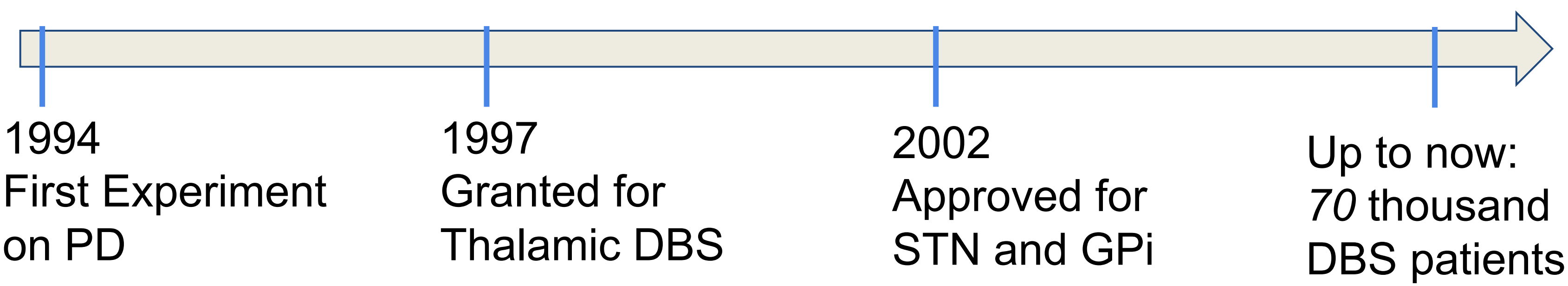
DBS: What is it about?

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

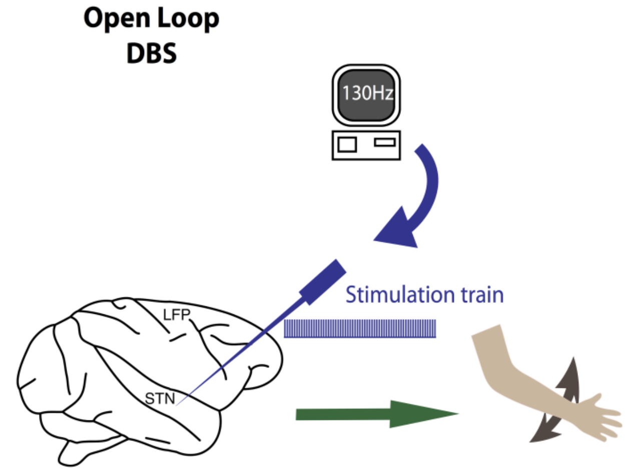


[1] *Adaptive Deep Brain Stimulation in Advanced Parkinson Disease*, Little et. al, Annals of Neurology, 2013
[2] *History, Applications, and Mechanism of Deep Brain Stimulation*, Miocinovic et. al., Neurological Review, 2013

DBS: Open vs Closed Loop

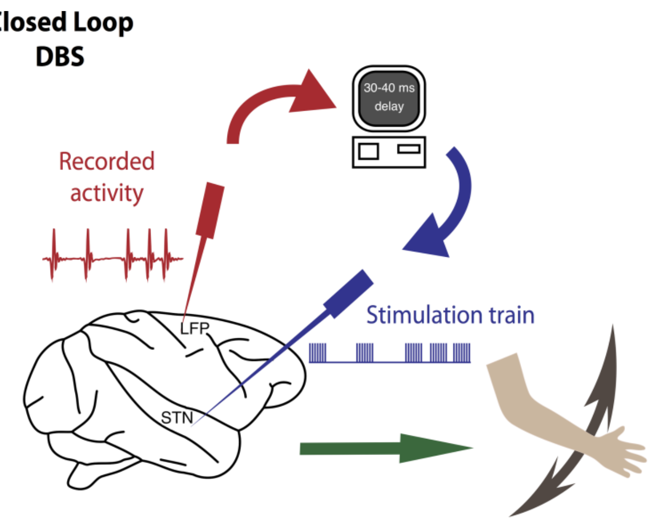
Open Loop: *continuous* (cDBS) or *random* (rDBS) stimulation [1]

- 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
- Biomarker as feedback: LFP, Action Potential [4]
- Less power consumption

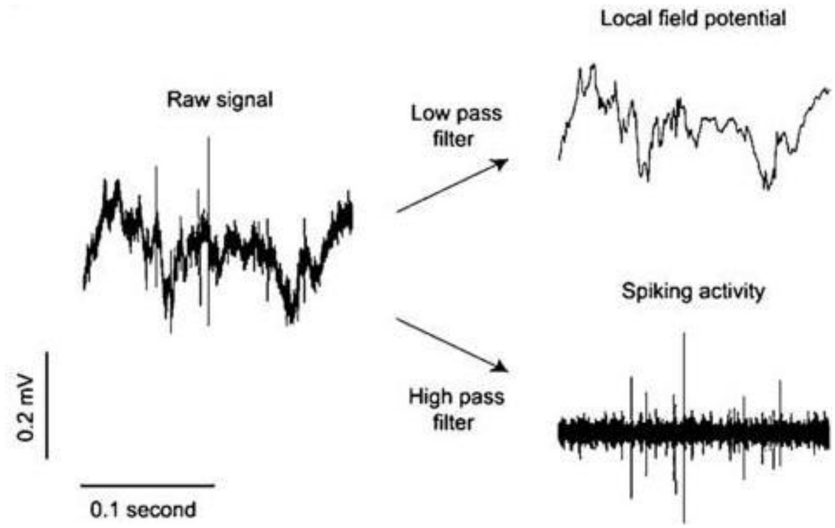


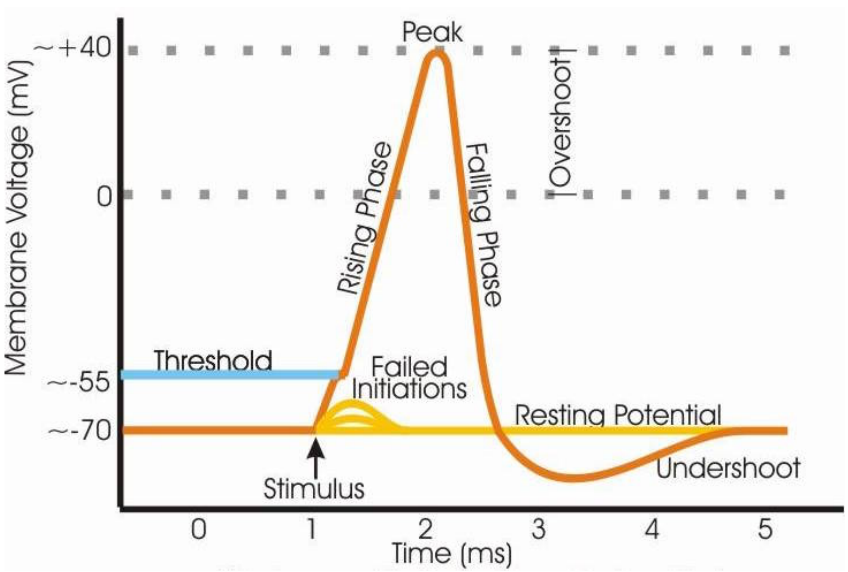
[1] *Adaptive Deep Brain Stimulation in Advanced Parkinson Disease,* Little et. al, Annals of Neurology, 2013
[2] *Stimulation on Demand: Closing the Loop on Deep Brain Stimulation,* Santos et. al., Cell Press , 2011.
[3] *History, Applications, and Mechanism of Deep Brain Stimulation,* Miocinovic et. al., Neurological Review, 2013
[4] *A Miniature Low-Power Multi-Biomarker-Based Brain Sensor for Closed-Loop DBS,* Parastarfeizabadi M., IEEE Sensors Journal, 2017

aDBS: Biomarker Choice

Local Field Potential (LFP) [1,2]

- Bandwidth: [*0.01* - *300*] Hz
- F_S > 1 kHz
- Amplitude: [*5*µ - *5*m] V
- Quantization: *8* - *12* bits
- Metal or glass electrodes





Action Potential (AP) [2]

- Bandwidth: [*0.01* - *10*k] Hz
- F_S > 40 kHz
- Amplitude: [-*80* - *40*] mV
- Quantization: *8* - *12* bits
- New optical imaging techniques

[1] *Extrapolating meaning from local field potential recordings*, Bozer H. et. al., Extracellular Space, 2016.
[2] *Multi-channel in vivo recording techniques: signal processing of Aps and LFPs*, Xu J. M. et al. Acta physiologica Sinica, 2014, pp. 349-357.

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

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

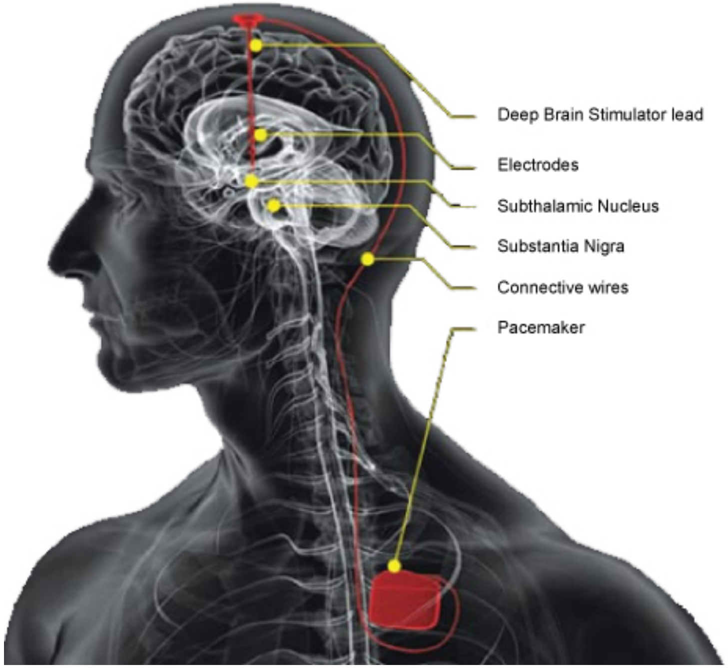
[1] *Adaptive Deep Brain Stimulation in Advanced Parkinson Disease*, Little et.al., Annals of Neurology, 2013

aDBS: System Setup

<u>High Frequency</u>
Stimulation: f ≥ *130* Hz

Target regions:

- <u>STN</u> and Post STN
- GPi
- Bilateral Thalamus

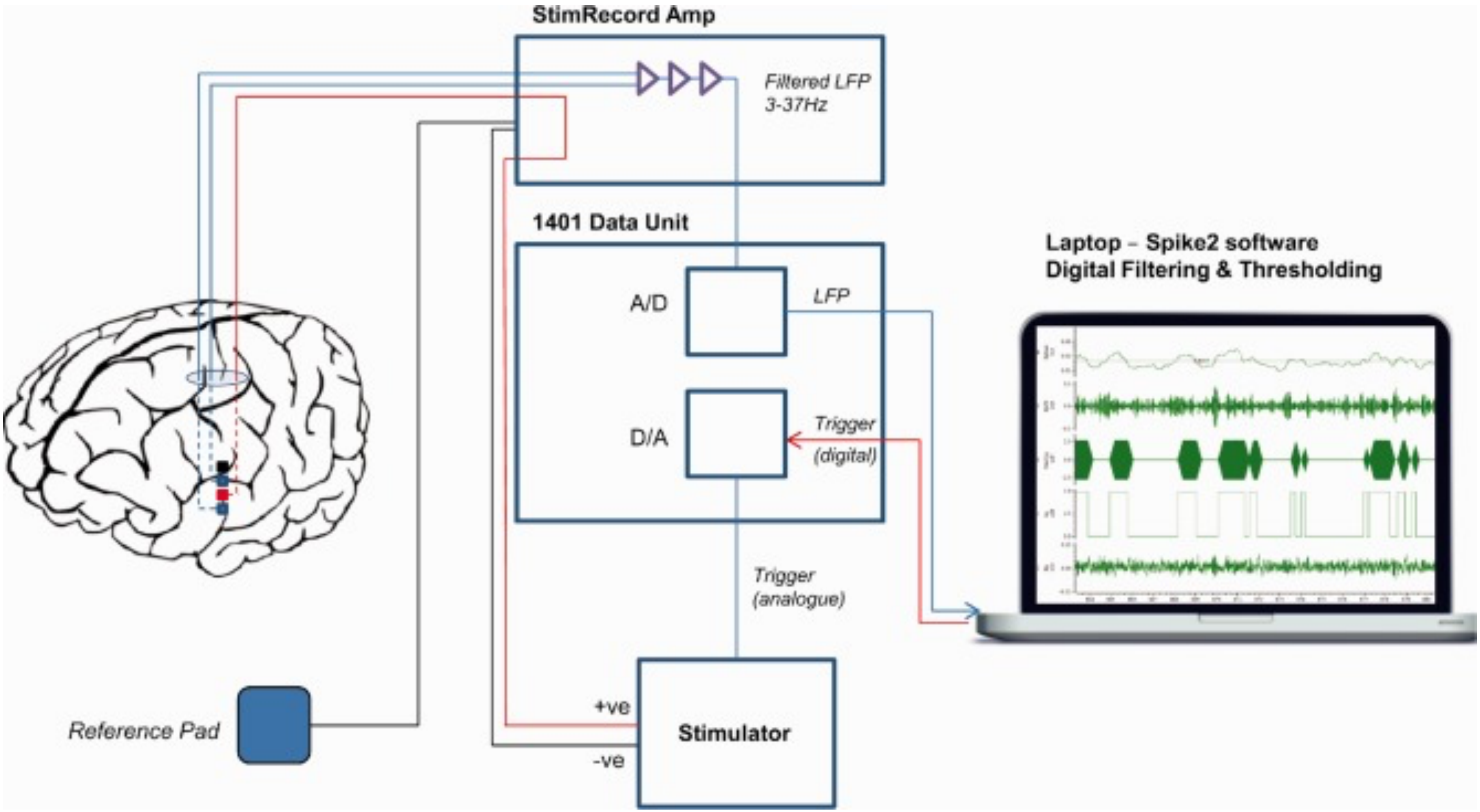


<u>Electrodes</u>: quadripolar electrode with 4 contacts [(*0*-*2*), (*1*-*3*)] by Medtronic ®

<u>Unilateral</u> vs Bilateral Stimulations

A posteriori verification of electrodes placement through <u>MRI</u> or <u>CT</u>

aDBS: Technical Aspects (1)



[1] *Adaptive Deep Brain Stimulation in Advanced Parkinson Disease*, Little et.al., Annals of Neurology, 2013

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 (x*9100*)

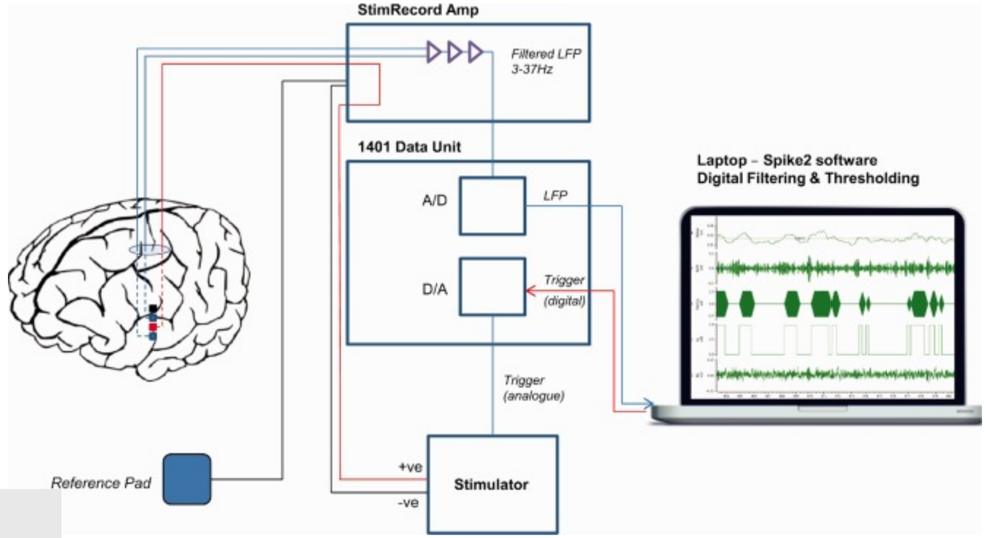


Figure (from left to right) : Activa SC, Activa RC and Activa PC Deep Brain Stimulation Systems by Medtronic ® [1]

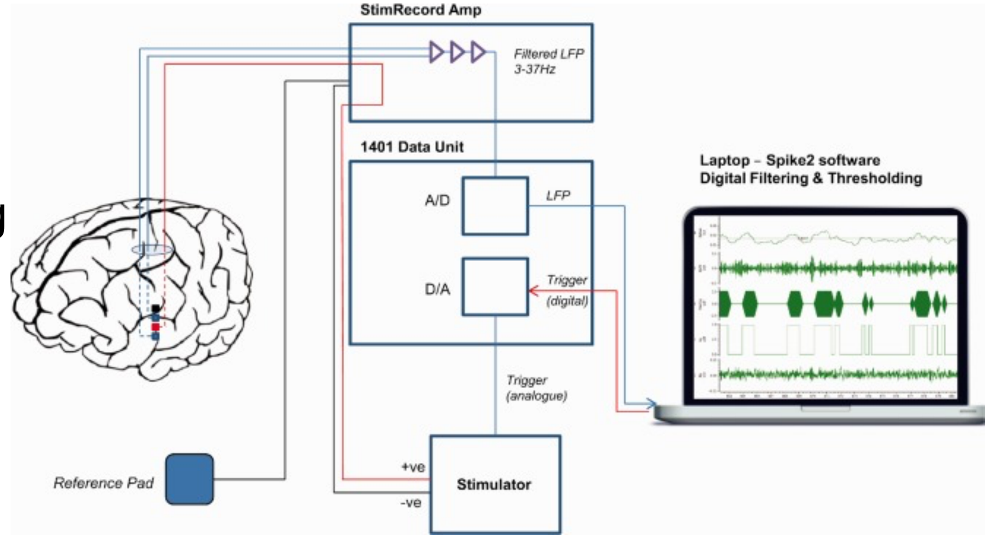
Beta signal:
- Choice of contacts with greater beta in [*13-35*] Hz
- Extract frequency of beta peak in the spectrum of LFP
- Filter the signal around this peak
- Correlates with motor tasks

[1] http://www.medtronic.com/us-en/healthcare-professionals/products/neurological/deep-brain-stimulation-systems.html

aDBS: Technical Aspects (3)

1401 Data Unit:

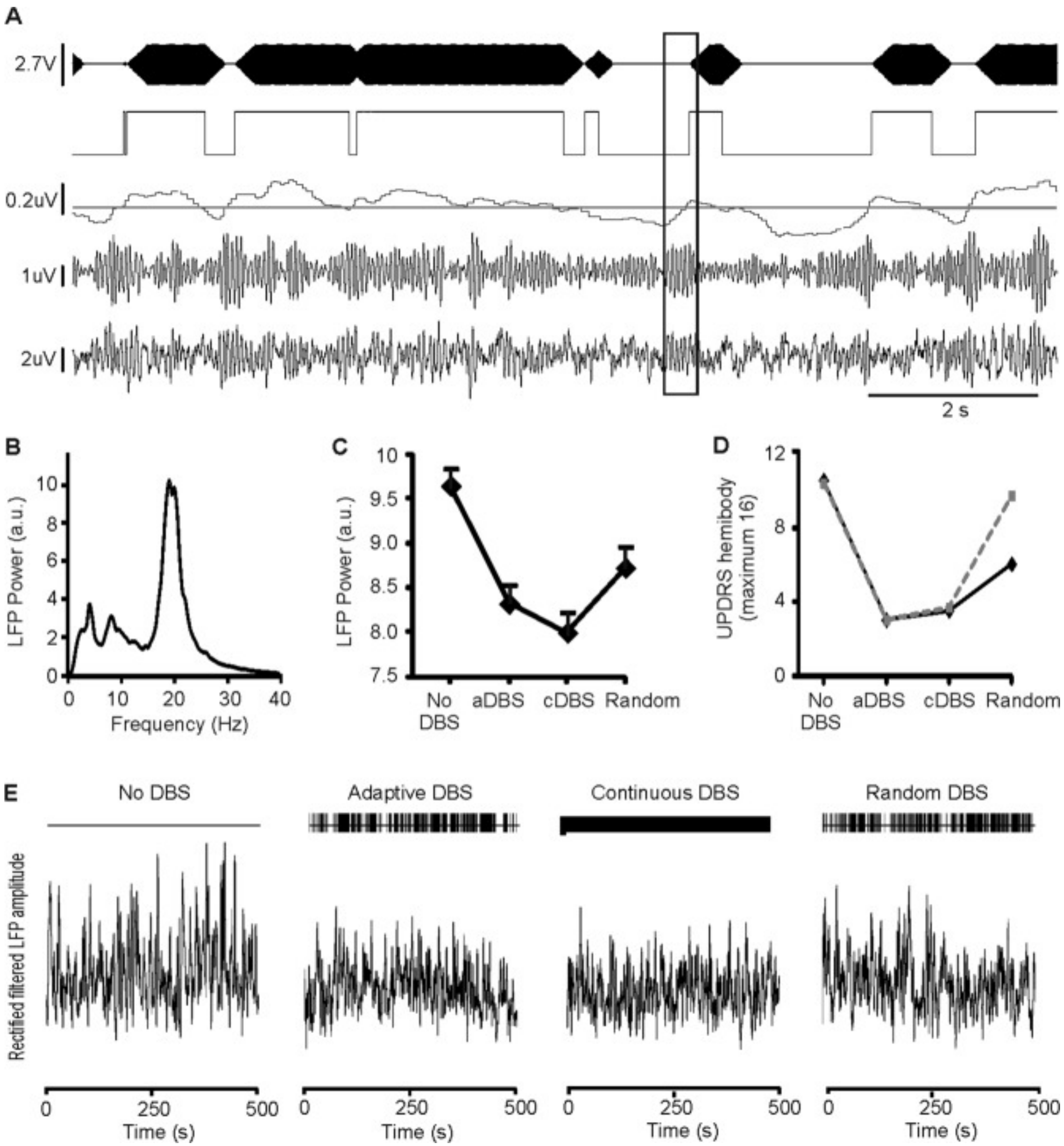
- LFP → A/D (usually *12* bits)
- Spike2 Software:
  - Filtering: rectification + smoothing MA filter of *400* ms duration
  - User-defined threshold
- Processed LFP → D/A



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 changs in different stimulation modes

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

E. 500 s of rectified beta-filtered LFP amplitude

[1] *Adaptive Deep Brain Stimulation in Advanced Parkinson Disease*, Little et. al., Annals of Neurology, 2013

aDBS: Technical Aspects (5)

Band Pass Filter	[3-37] Hz	**Amplifier**	X9100
ADC	8-12 bits	**Delay**	30-40 ms
Battery	± 9 V	**MA windows**	400 ms
No Distortion at	0.5 kΩ	**Charge Densities**	$< 30\ \mu\text{Q/cm}^2$
Stimulation Frequency	130 Hz	**Stimulation Voltage**	0.5 V + 0.5 V/(3 or 4 minutes)
Sim. Pulse Duration	100 μs	**Ramp interval**	250 ms

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.

[1] *History, Applications, and Mechanism of Deep Brain Stimulation,* Miocinovic et. al., Neurological Review, 2013

aDBS: Results (1)

	Age - Disease Duration (yr)	UPDRS		DBS Indications	Online Filter Range (Hz)	Stimulation			Time on Stimulation %		Time between Stimulation Bursts (s)	
		Off	On			V	Site	Contact	aDBS	Random	aDBS	Random
Case1	59 - 12	42	20	On/Off fluctuations, tremor bradykinesia	16 - 22	2.7	L	1	44.2	44.5	1.09	1.19
Case2	62 - 10	20	8	On/Off fluctuations, tremor	19 - 25	1.8	R	1	35.5	34.1	0.64	0.75
Case3	67 - 7	43	14	On/Off fluctuations, dyskinesias	23 - 29	1.8	R	2	43.4	42.6	0.47	0.69
Case4	49 - 10	42	6	Tremor	17 - 24	1.6	L	2	46.4	46.5	0.45	0.50
Case5	49 - 10	58	23	On/Off fluctuations, tremor	16 - 18	2.1	L	1	42.1	45.2	0.94	0.86
Case6	63 - 3	18	8	Tremor/Bradykinesia	28 - 34	2.6	R	1	57.7	45.8	0.73	0.64
Case7	67 - 14	63	24	On/Off fluctuations	17 - 22	2.4	R	2	37.1	40.8	0.64	0.65
Case8	57 - 8	43	17	Severe Off periods, On/Off fluctuations	16 - 20	2.7	R	1	47.6	46.7	1.75	1.53
Mean	59.1 - 9.4	41.1	15		22	2.1			44.3	43.3	0.84	0.85
SEM	2.5 - 1.3	5.6	2.5		1.8	0.2			2.4	1.5	0.2	0.1
p										0.58		0.81

Results adopted and integrated from [1]

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

[1] *Adaptive Deep Brain Stimulation in Advanced Parkinson Disease,* Little et.al., Annals of Neurology, 2013

aDBS: Results (2)

	cDBS	rDBS	aDBS
Mean Reduction in UPDRS Motor Scores (blinded and unblinded)	42.5 %	20.2 %	58 %
On-Time Period (%)	100 %	43.3 ± 1.5 %	44.2 ± 2.4 %
Delivered Energy per Unit Time	$270 \pm 7\ \mu$W	/	$132 \pm 21\ \mu$W

- 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]

[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]

[1] *Ethical issues in deep brain stimulation*, Schermer M., Front Integr Neurosci., 2011.

aDBS: Conclusions and Future Directions

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- ★ 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