

Neuroinformatics

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Lecture 8: Case study - Deep brain stimulation for Parkinson's disease

Overview

Parkinson's disease

- Disease basics
- Symptoms
- Patophysiology
- Therapy

Deep brain Stimulation (DBS)

- Basics
- Stimulators
- Targetting

μ EEG: metody zpracování a vyhodnocování

- μ EEG

- Sběr patientského μ EEG

- Zpracování μ EEG

- Převod μ EEG na sled akčních potenciálů

- Statistiky

- Statistiky nad sledy akčních potenciálů

- Aplikace

- Mechanismus DBS STN

Parkinson's disease (PD)

Review of Pathophysiology, Diagnosis and Therapy

Epidemiology

- ▶ Average incidence is 20 per 100,000 in North America
- ▶ 1 Million affected in the United States, about the same in Europe
- ▶ 50,000 new cases per year
- ▶ Cost estimated to exceed \$5.6 Billion annually

- ▶ Average age of onset around 60
- ▶ Men affected slightly more than women
- ▶ Genetic Link
- ▶ African-Americans and Asians slightly less likely than Caucasians to develop PD
- ▶ Caffeine and smoking shows some protective effects

- ▶ **Continuous Progressive Neurological Disease**, thereby causing increasing disability of movement
- ▶ **no cure**

Symptoms

- ▶ Four cardinal symptoms
 - ▶ Tremor
 - ▶ Rigidity
 - ▶ Akinesia and bradykinesia
 - ▶ Postural instability
- ▶ **Tremor** - Usually tremor at rest, when person sits, arm shakes, tremor stops when person attempts to grab something
- ▶ **Rigidity** - Increased muscle tone and increase Resistance to movement (arms and legs stiff)
- ▶ **Akinesia and Bradykinesia** - Lack of movement or slowness in initiation and execution of voluntary movements
- ▶ **Postural instability** - Abnormal fixation of posture (stoop when standing), equilibrium, and righting reflex
- ▶ **Gait disturbances** - shuffling feet

Characteristic Problems

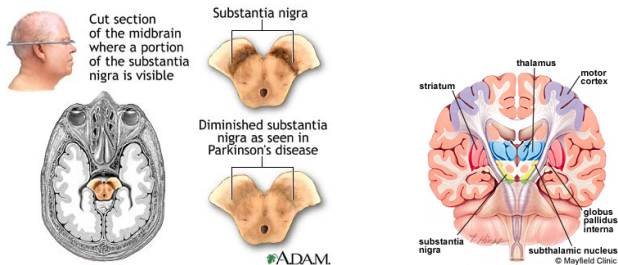
- ▶ Hypomimia - decreased facial animation
- ▶ Hypophonia - soft speech
- ▶ Dysarthria - unclear pronunciation
- ▶ Dyspnea - labored breathing
- ▶ Festination - Shuffling gait
- ▶ Micrographia - small handwriting

- ▶ Change in facial expression (staring, lack of blinking)
- ▶ Failure to swing one arm when walking
- ▶ Flexion (stooped) posture
- ▶ "Frozen" painful shoulder
- ▶ Limping or dragging of one leg
- ▶ Numbness, tingling, achiness or discomfort of the neck or limbs
- ▶ Subjective sensation of internal trembling
- ▶ Resting tremor

Most symptoms may affect one or both sides of the body

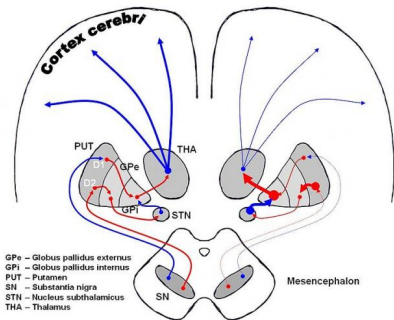
Patophysiology

- ▶ Loss of dopaminergic cells located in Substantia Nigra in Basal Ganglia
- ▶ Most symptoms do not appear until striata dopamine levels decline by at least 70-80%
- ▶ **imbalance** primarily between the **excitatory** neurotransmitter **Acetylcholine** and **inhibitory** neurontransmitter **Dopamine**.
- ▶ **Cause** of this neurodegenerative process **unknown**



Basal Ganglia I - Movement control

- ▶ The Basal Ganglia Consists of Five Large Subcortical Nuclei That Participate in Control of Movement:
 - ▶ Caudate Nucleus
 - ▶ Putamen
 - ▶ Globus Pallidus
 - ▶ Subthalamic Nucleus
 - ▶ Substantia Nigra

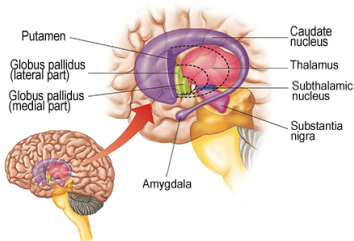


Dopaminergic pathways of the human brain in normal condition (left) and Parkinson's disease (right). Red Arrows indicate **suppression** of the target, blue arrows indicate **stimulation** of target structure.

Basal Ganglia II

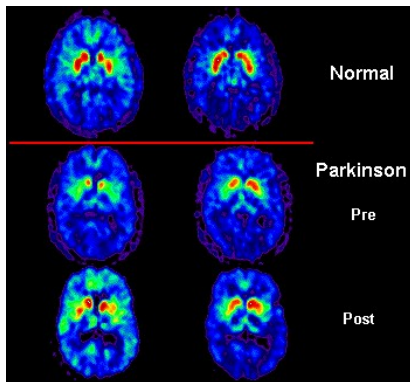
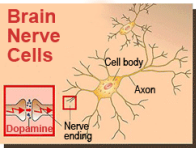
18F PET scan(right) shows decreased dopamine activity in the basal ganglia

The Human Basal Ganglia



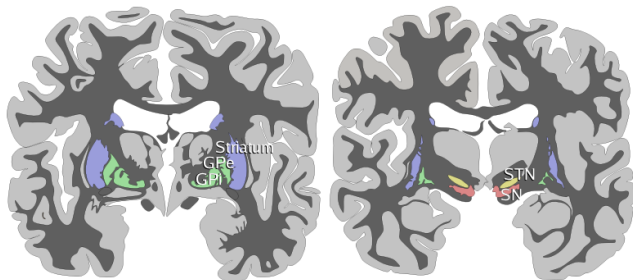
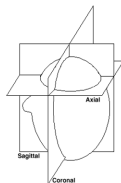
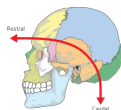
Near the base of the brain is a small area called the substantia nigra which contains cells that produce dopamine.

Dopamine acts as a transmitter between the nerve endings.



Subthalamic nucleus (STN)

- ▶ Subthalamic nucleus:
 - ▶ small lens-shaped nucleus (several mm in size)
 - ▶ ventral to the thalamus
 - ▶ function not well understood
- ▶ Below: Coronal slices of human brain showing the basal ganglia.
 - ▶ ROSTRAL: striatum, globus pallidus (GPe and GPi)
 - ▶ CAUDAL: subthalamic nucleus (STN), substantia nigra (SN)



Therapy

- ▶ **No no definitive cure known**
(=no possibility to stop or revert the process)
- ▶ Current therapies only suppress symptoms

Therapeutic options

1. Drug treatment
 - ▶ **Levodopa** - dopamine precursor
 - ▶ Dopamine agonists - stimulate dopamine receptors directly
2. Pallidotomy - destruction of cells in the GP
3. **Deep brain stimulation** - application of electrical pulses to STN or GP
4. Nerve cell transplantation (Experimental, research only)
5. Genetic engineering (Experimental, research only)

”On/Off switching”

After long-term therapy with levodopa:

- ▶ **”On/off”Effect:** like a switch ; without warning, suddenly person goes from full control back to bradykinesia tremor etc. Lasting 30min to several hours, then gets control again.
- ▶ ”On/off”Effect usually after 2 or more years on L Dopa
- ▶ related to denervation hypersensitivity

Pallidotomy

- ▶ **Destruction of cells in the globus pallidus (GP)**
- ▶ Until the late 1990s, most common type of PD surgery. DBS is now being performed more often (reversible)
- ▶ May help to restore the balance in basal ganglia.
- ▶ **Procedure:**
 1. Position of GP located using medical imaging techniques (such as MRI and/or CT)
 2. Insertion of a wire probe into the GPI.
 3. Placement confirmed by electrical tests (microrecording)
 4. Tissue surrounding the Probe heated by emission of electromagnetic field. The heat destroys nearby tissue.



Pallidotomy II - effects

- ▶ Almost immediate effect
- ▶ Improvements:
 - ▶ 70% to 90% reduction of dyskinesias and dystonia
 - ▶ 25% to 50% for tremor, rigidity, bradykinesia, and gait disturbance
 - ▶ Levodopa dose may be reduced after the surgery, and dyskinesia improvement is based partly on this reduction.
- ▶ **Adverse side effects:** hemorrhage, weakness, severe visual and speech deficits and confusion
- ▶ **Irreversible!** Not much performed anymore...

Experimental techniques

Possible future techniques under research include:

- ▶ **Neural tissue transplants:**

- ▶ Researchers are studying ways to implant neural tissues from fetal pigs into the brain to restore the degenerate area.
- ▶ In a clinical trial conducted in part at Boston University School of Medicine, three patients out of 12 implanted with the pig tissues showed significant reduction in symptoms.
- ▶ Connected with risks and side effects...

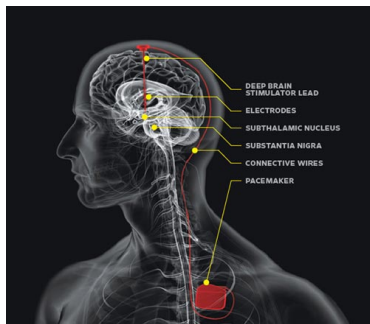
- ▶ **Genetic engineering:**

- ▶ Scientists are modifying the genetic code of individual cells to create dopamine-producing cells from other cells, such as those from the skin.

Deep brain Stimulation (DBS)

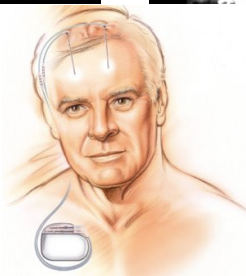
Overview of the therapeutical technique

DBS basics



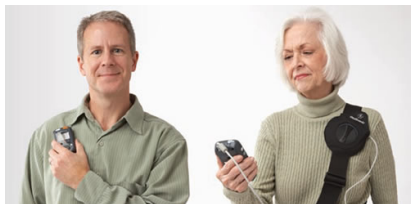
- ▶ Modern **treatment technique for Parkinson's disease** (PD), Essential tremor, clinical depressions and other.
- ▶ **Stimulation electrodes** implanted into patient's brain
- ▶ Supports or replaces medication when insufficient or contraindicated
 - ▶ Typical case: patient with long-term progressive PD.

DBS implants



Stimulator device

- ▶ Device similar to heart pacemaker
- ▶ Implanted in the chest cavity
- ▶ Leads below skin to top of the head
- ▶ Battery-operated
- ▶ Remote-controlled
 - ▶ Most devices need to be reoperated once in every 2-5 years
 - ▶ Some devices remotely rechargeable



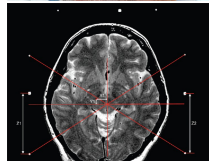
Targetting

Problem: locate and implant the target structure accurately

- ▶ Target structure very small (STN - several mm)
- ▶ Far away from head surface
- ▶ Soft tissue (may shift + hard to see on CT)

Procedure:

1. Fitting patient with stereotactic frame (→ patient coordinate system)
2. Imaging using MRI and CT (low accuracy)
3. Planning trajectory
4. **Microrecording** (→ accurate identification of target position)
5. Implantation of stim. electrode
6. Implantation of dbs device (few days after)



Microrecording

Aim: refine on position of the target structure

- ▶ Set of microelectrodes shifted through patient's brain
- ▶ Electrophysiological properties along trajectory recorded
- ▶ Activity evaluated by trained physician
- ▶ Accurate location of target nucleus boundaries identified.

μ EEG: metody zpracování a vyhodnocování

Tomáš Sieger

EEG



$\sim 10\,000\mu\text{m}$

$\sim 1\div 100\text{Hz}$

μ EEG

EEG



$\sim 10\,000\mu\text{m}$
 $\sim 1\div 100\text{Hz}$

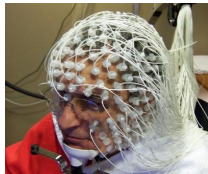
μ EEG



$\sim 1\mu\text{m}$
 $\sim 10\,000\text{Hz}$

μ EEG

EEG



$\sim 10\,000\mu\text{m}$
 $\sim 1\div 100\text{Hz}$

μ EEG



$\sim 1\mu\text{m}$
 $\sim 10\,000\text{Hz}$

- ▶ mikroelektrody

μ EEG

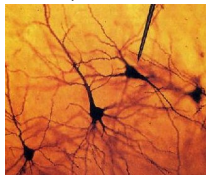
EEG



$\sim 10\,000\mu\text{m}$

$\sim 1\div 100\text{Hz}$

μ EEG



$\sim 1\mu\text{m}$

$\sim 10\,000\text{Hz}$

- ▶ mikroelektrody
 - ▶ neuron $\sim 10\mu\text{m}$ (10-25 μm)

μ EEG

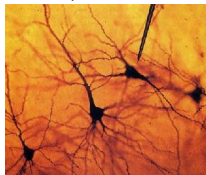
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 - ▶ hrot $\sim 1\div 10\mu\text{m}$

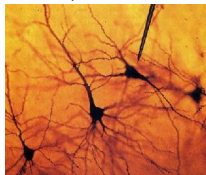
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μ EEG



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▶ jeden / více kontaktů (tetrody)



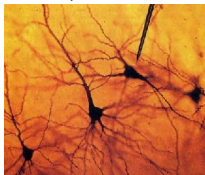
EEG



$\sim 10\,000\mu\text{m}$

$\sim 1\div 100\text{Hz}$

μ EEG



$\sim 1\mu\text{m}$

$\sim 10\,000\text{Hz}$

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▶ jeden / více kontaktů (tetrody)

▶ bipolární / unipolární



EEG



$\sim 10\,000\mu\text{m}$

$\sim 1\div 100\text{Hz}$

μ EEG



$\sim 1\mu\text{m}$

$\sim 10\,000\text{Hz}$

▶ mikroelektrody

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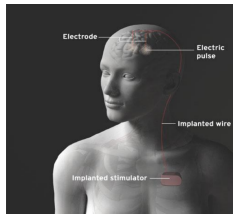
▶ bipolární / unipolární

▶ nahrávací / stimulační



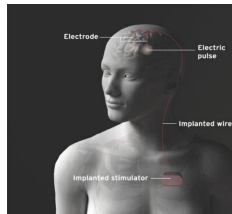
Aplikace: výzkum mechanismu DBS STN u Parkinsonovy nemoci

- ▶ Parkinsonova nemoc: neurodegenerativní onemocnění
- ▶ Hluboká mozková stimulace (DBS)



Aplikace: výzkum mechanismu DBS STN u Parkinsonovy nemoci

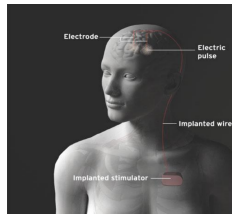
- ▶ Parkinsonova nemoc: neurodegenerativní onemocnění
- ▶ Hluboká mozková stimulace (DBS)



- ▶ vedlejší non-motorické účinky: deprese, emoční labilita

Aplikace: výzkum mechanismu DBS STN u Parkinsonovy nemoci

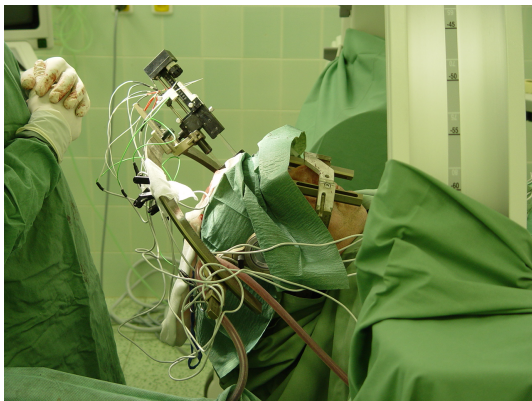
- ▶ Parkinsonova nemoc: neurodegenerativní onemocnění
- ▶ Hluboká mozková stimulace (DBS)



- ▶ vedlejší non-motorické účinky: deprese, emoční labilita
- ▶ hypotéza: neurony STN zapojeny do procesu vnímání

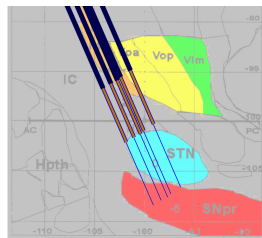
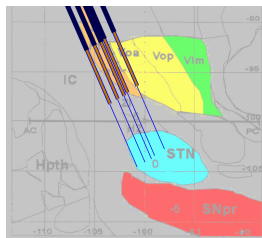
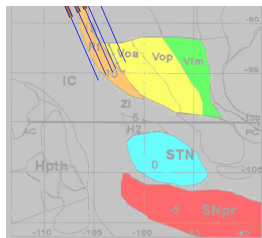
μ EEG - sběr patientských dat

- ▶ 5 paralelních mikroelektrod (kříž), rozteč 2mm
- ▶ vzorkování 24kHz

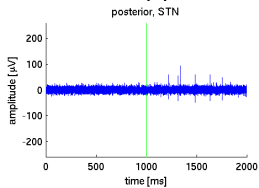
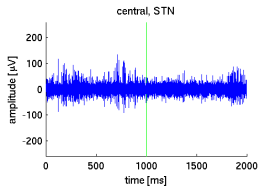
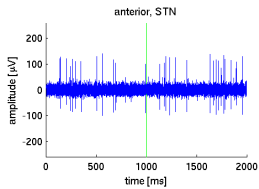


Mikroregistrace - průstup elektrod

- ▶ 3 nahrávací pozice:

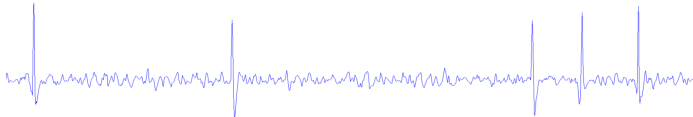


Ukázka μ EEG



Detekce a třídění akčních potenciálů

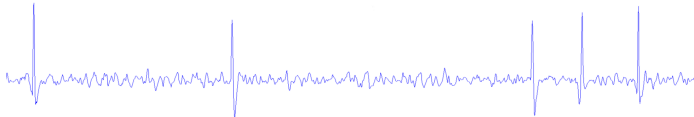
- ▶ μ EEG



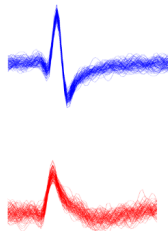
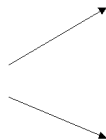
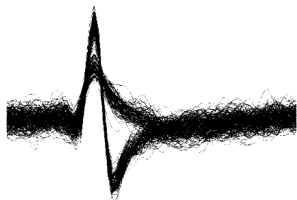
- ▶ detekce akčních potenciálů

Detekce a třídění akčních potenciálů

- ▶ μ EEG



- ▶ detekce akčních potenciálů
- ▶ třídění detekovaných akčních potenciálů



Třídění akčních potenciálů

Vybrané metody

metoda	detekce AP	třídění AP	
		příznaky	klastrování
WaveClus ¹	amplitudová	koef. WT AP	superparamg.
KlustaKwik ²	N/A	ad hoc	Gauss mix fit + AIC
OnlineSort ³	energetická	AP	min. LS rozdílů AP, prahy
Spike2 ⁴	amplitudová ruční	ad hoc	ruční / k-means

¹R. Quian Quiroga, [Unsupervised Spike Detection and Sorting with Wavelets and Superparamagnetic Clustering](#). *Neural Computation* 16, 1661–1687 (2004)

²Kenneth D. Harris, [Accuracy of Tetrode Spike Separation as Determined by Simultaneous Intracellular and Extracellular Measurements](#). *Neurophysiol* 84:401-414, 2000.

³Ueli Rutishauser, [Online detection and sorting of extracellularly recorded action potentials in human medial temporal lobe recordings, in vivo](#). *Journal of Neuroscience Methods* 154 (2006) 204–224.

⁴CED Spike2 SW, <http://www.science-products.com/Products/CatalogC/Acq&AnaSoftware/Spike2/Spike2.html>

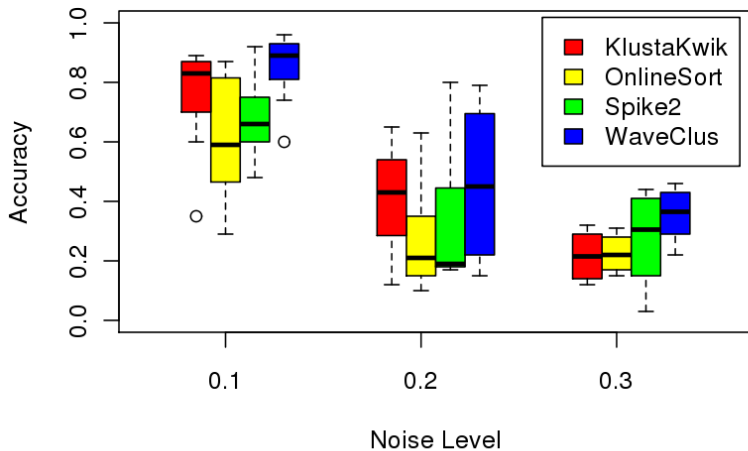
Třídění akčních potenciálů

Problémy

- ▶ záruka?
 - ▶ byly zachyceny skutečné AP?
 - ▶ nebyly zachyceny šumové AP?
 - ▶ byly AP správně rozříděny?
- ▶ jakou metodu zvolit?
 - ▶ a jak nastavit parametry?
- ▶ srovnání metod:
 - ▶ zpracování umělého signálu
 - ▶ problém: jak vygenerovat umělý signál podobný reálnému?

Třídění akčních potenciálů

Srovnání úspěšnosti metod



Statistiky nad sledy akčních potenciálů (AP)

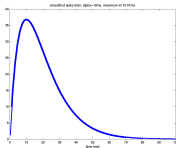
- ▶ úlohy:
 - ▶ srovnat sled AP s jinou veličinou
 - ▶ jediným číslem
 - ▶ spojitým signálem
 - ▶ srovnat sledy AP mezi sebou

Statistiky nad sledy akčních potenciálů (AP)

- ▶ úlohy:
 - ▶ srovnat sled AP s jinou veličinou
 - ▶ jediným číslem
 - ▶ spojitým signálem
 - ▶ srovnat sledy AP mezi sebou
- ▶ jak charakterizovat sled AP?
 - ▶ průměrná frekvence pálení
 - ▶ medián ISI
 - ▶ koeficient variace ISI
 - ▶ index asymetrie ISI
 - ▶ Fano faktor
 - ▶ ...
 - ▶ **samotný sled AP!**
 - ▶ nese nejvíce informace

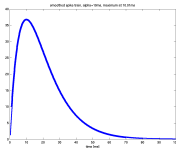
Srovnání sledu AP se spojitým signálem

- ▶ sled AP \rightarrow spojitá funkce (okamžitá frekvence pálení)
 - ▶ konvoluce sledu AP s kauzálním oknem $w(\tau) = \alpha^2 \tau e^{-\alpha \tau}$

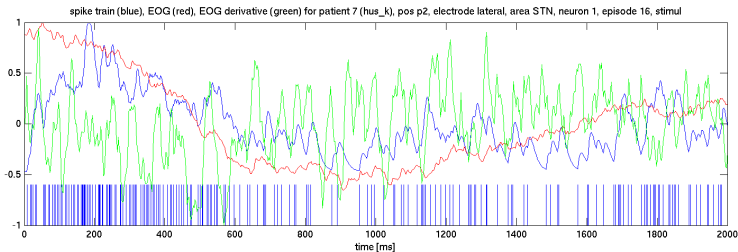


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 - ▶ konvoluce sledu AP s kauzálním oknem $w(\tau) = \alpha^2 \tau e^{-\alpha \tau}$



- ▶ spočítat vztah daného signálu a okamžitou frekvenci pálení



Srovnání sledu AP se spojitým signálem (2)

- ▶ spočítat vztah daného signálu a okamžité frekvence pálení
 - ▶ korelace (Pearson, Spearman)
 - ▶ vzájemná informace

Srovnání sledu AP se spojitým signálem (2)

- ▶ spočítat vztah daného signálu a okamžité frekvence pálení
 - ▶ korelace (Pearson, Spearman)
 - ▶ vzájemná informace
- ▶ statistická významnost
 - ▶ u korelací
 - ▶ pozor na předpoklady (normalita)
 - ▶ pozor na stupně volnosti

Srovnání sledu AP se spojitým signálem (2)

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 - ▶ u korelací
 - ▶ pozor na předpoklady (normalita)
 - ▶ pozor na stupně volnosti
- ▶ Monte-Carlo simulace: bootstrap

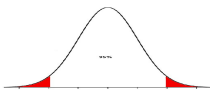
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 - ▶ korelace (Pearson, Spearman)
 - ▶ vzájemná informace
- ▶ statistická významnost
 - ▶ u korelací
 - ▶ pozor na předpoklady (normalita)
 - ▶ pozor na stupně volnosti
- ▶ Monte-Carlo simulace: bootstrap
 - ▶ mnohokrát (5000x):
 - ▶ vytvořit umělé signály
 - ▶ spočítat korelační koeficient

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- ▶ výsledek: distribuce korelačních koeficientů

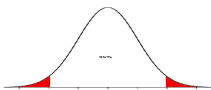


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▶ výsledek: distribuce korelačních koeficientů

▶ koeficienty mimo centrální 95% interval prohlásíme za významné

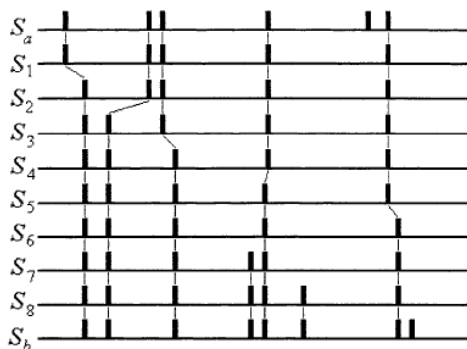


Srovnání sledů akčních potenciálů

- ▶ ad-hoc metody
 - ▶ metriky nad sledy AP (Victor, Purpura)
 - ▶ srovnání příznaků sledů AP
- ▶ statistické testy
 - ▶ test rozdílu intenzit AP (test frekvenčního kódování)
 - ▶ test rozdílné distribuce AP (test časového kódování)
 - ▶ výhoda: statistická významnost

Victorova metrika

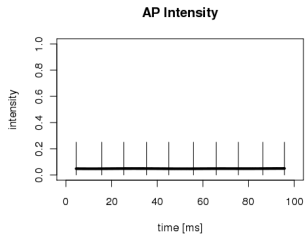
- ▶ Jonathan D. Victor and Keith Purpura. [Metric-space analysis of spike trains: theory, algorithms, and application](#). Network 8,



127-164 (1997)

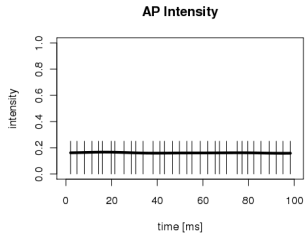
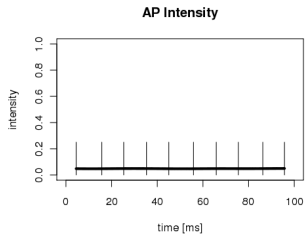
Test intenzit AP

Wilcoxonův 2-výběrový test



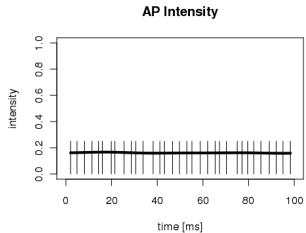
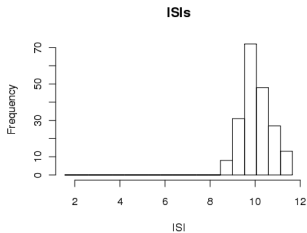
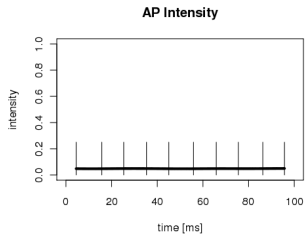
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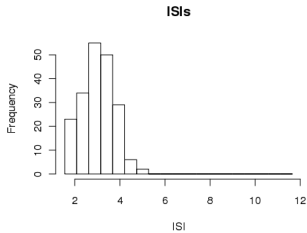
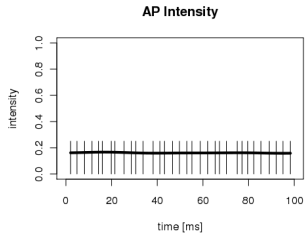
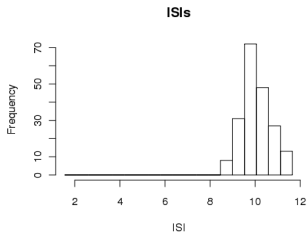
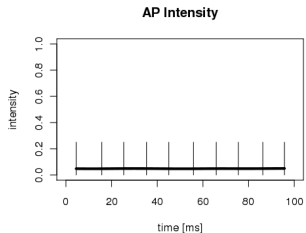
Test intenzit AP

Wilcoxonův 2-výběrový test



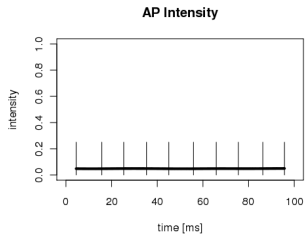
Test intenzit AP

Wilcoxonův 2-výběrový test



Test distribuce ISI

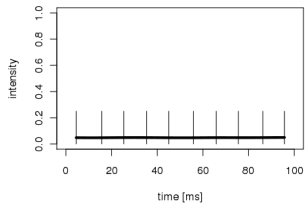
Kolmogorovův-Smirnovův 2-výběrový test



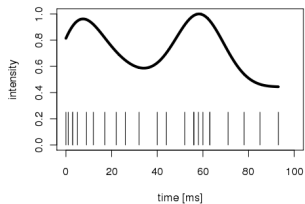
Test distribuce ISI

Kolmogorovův-Smirnovův 2-výběrový test

AP Intensity

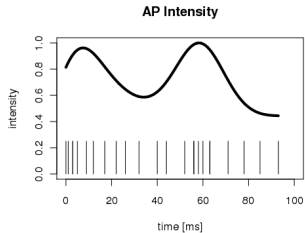
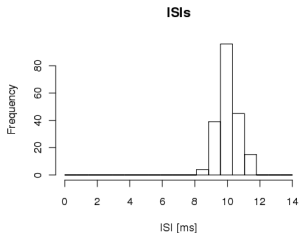
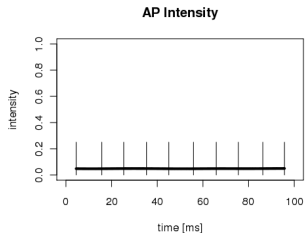


AP Intensity



Test distribuce ISI

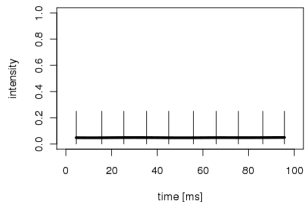
Kolmogorovův-Smirnovův 2-výběrový test



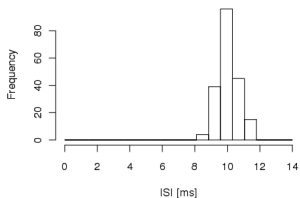
Test distribuce ISI

Kolmogorovův-Smirnovův 2-výběrový test

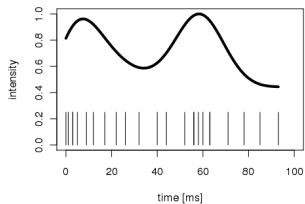
AP Intensity



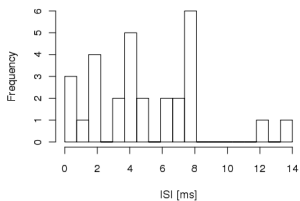
ISIs



AP Intensity



ISIs

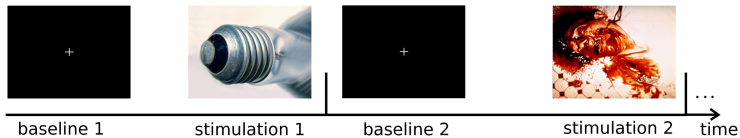


Test nepodobnosti sledů akčních potenciálů

- ▶ kombinace předchozích 2 testů
 - ▶ chceme jediný test na hladině významnosti α
- ▶ postup:
 1. test rozdílu intenzit AP na hladině $\frac{\alpha}{2}$
 2. test rozdílu distribucí ISI na hladině $\frac{\alpha}{2}$
- ▶ výsledný test pracuje na hladině α

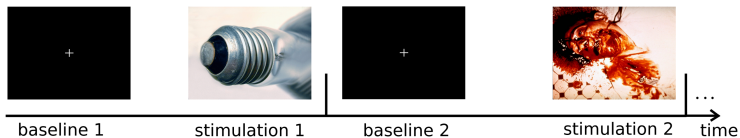
Vizuální stimulace + nahrávání μ EEG

▶ vizuální stimulace

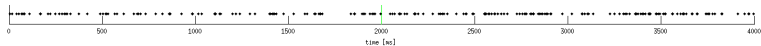


Vizuální stimulace + nahrávání μ EEG

▶ vizuální stimulace



▶ nahrané μ EEG



Statistiky

- ▶ data
 - ▶ 10 pacientů
 - ▶ 43 nahrávacích pozic
 - ▶ 141 záznamů (74 z STN)
 - ▶ 173 minut záznamu (89 minut z STN)
 - ▶ 176 neuronů (101 v STN)
- ▶ výsledky: počet nalezených **významných** neuronů
 - ▶ srovnáním charakteristik AP: 6
 - ▶ srovnáním sledů AP: 20

Tým

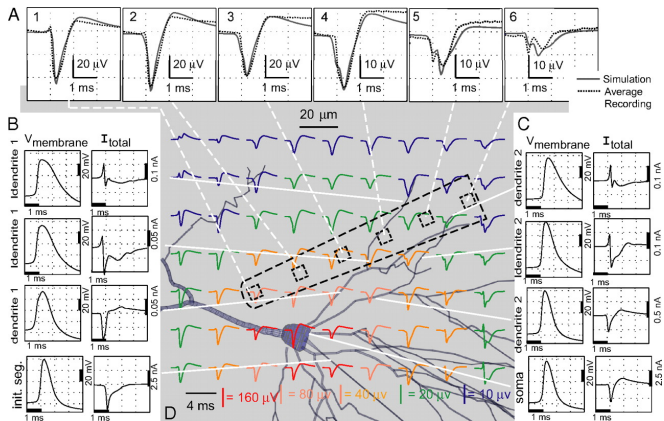
- ▶ Katedra kybernetiky, FEL ČVUT, Praha
 - ▶ Ing. Daniel Novák, PhD.
 - ▶ Mgr. Tomáš Sieger
 - ▶ Ing. Jiří Wild
 - ▶ Ing. Eduard Bakštein
- ▶ Neurologická klinika, 1.LF UK, Praha
 - ▶ Doc. MUDr. Robert Jech, PhD.
 - ▶ MUDr. Tereza Serranová
 - ▶ MUDr. Filip Růžička
- ▶ Nemocnice Na Homolce, Praha
 - ▶ MUDr. Dušan Uργοšík, CSc.

Shrnutí

- ▶ μ EEG
- ▶ srovnání metod třídění akčních potenciálů
 - ▶ nejlepší WaveClus (KlustaKwik)
- ▶ doporučení: používat celé sledy akčních potenciálů
- ▶ DAO - jednoduchá a robustní práce s daty

Děkuji za pozornost

Tvaru akčných potenciálů v závislosti na poloze elektrody



- ▶ Carl Gold, D.A. Henze, Ch. Koch and G. Buzsáki, [On the Origin of the Extracellular Action Potential Waveform: A Modeling Study](#). *J. Neurophysiol* 95:3113-3128, 2006.