

Neuroinformatics

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Lecture 4: Case study - Deep brain stimulation for Parkinson's
disease

Overview

Why this lecture?

Because...

Parkinson's disease

Disease basics

Symptoms

Pathophysiology

Therapy

Deep brain Stimulation (DBS)

Basics

Stimulators

Targetting

μ EEG: processing and evaluation methods

μ EEG

μ EEG recording of patient data

Processing μ EEG

Conversion of μ EEG to a spike train

Statistics

Spike train statistics

Applications

Mechanism of DBS STN

Why this lecture?

We included this in order to

- ▶ Show you a case study:
 - ▶ how can the methods you will learn be applied?
 - ▶ are they good for basic research of brain function?
 - ▶ are there some applications?
- ▶ Show you how we came to computational neuroscience
- ▶ Give you some insight into what we do

Parkinson's disease (PD)

Review of Pathophysiology, Diagnosis and Therapy

Historical perspective

Dr. James Parkinson (1755-1828)

1817:

- ▶ "involuntary tremulous motion"
- ▶ "pass from a walking to a running pace"
- ▶ "shaking palsy"



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

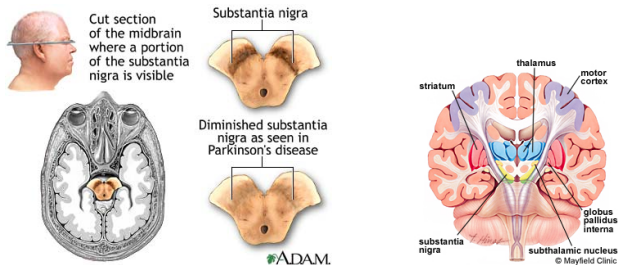
- ▶ Hypomimia - decreased facial animation
- ▶ Hypophonia - soft speech
- ▶ Dysarthria - unclear pronunciation
- ▶ Dyspnea - labored breathing
- ▶ Festination - Shuffling gait
- ▶ Micrographia - small handwriting

- ▶ 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

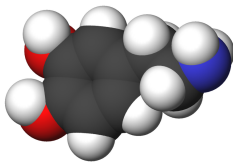
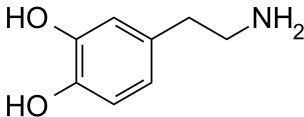
Patophysiology

- ▶ 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** neurotransmitter **Dopamine**.
- ▶ **Cause** of this neurodegenerative process **unknown**



Dopamine

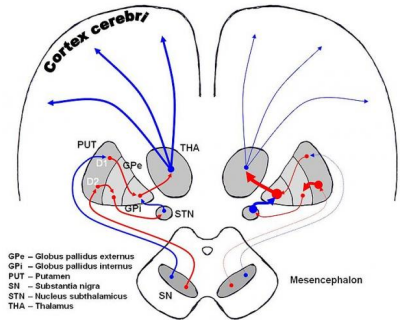
- ▶ Neurotransmitter (chemical information transmission at synapses)
- ▶ Role in reward-motivated behavior
- ▶ Role in motor control
- ▶ Levels increased by stimulants (incl. drugs: cocaine, amphetamine)
- ▶ Probably connected with schizophrenia
- ▶ Dopaminergic neurons rather rare (est. 400 000 in human brain)



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

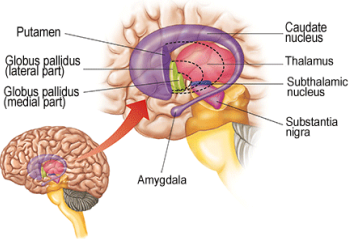


Neuronal pathways of the human brain in normal condition (left) and Parkinson's disease (right). Red Arrows indicate **suppression** of the target (GABA), blue arrows indicate **stimulation** of target structure (glutamate).

Basal Ganglia II

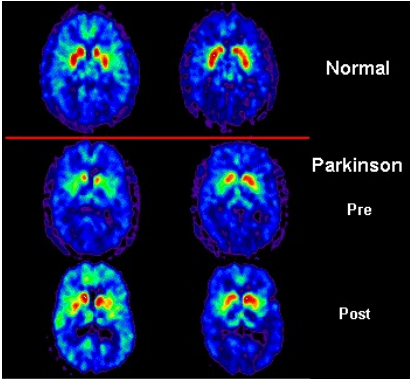
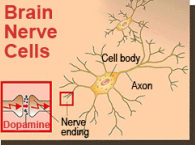
18F PET scan(right) shows decreased dopamine activity in the basal ganglia

The Human Basal Ganglia



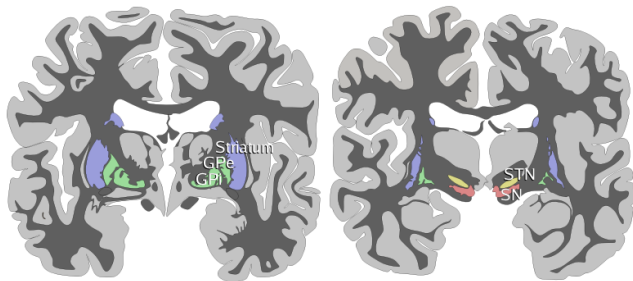
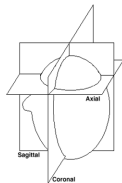
Near the base of the brain is a small area called the substantia nigra which contains cells that produce dopamine.

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

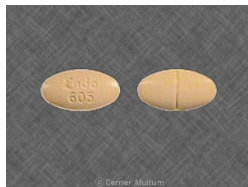
- ▶ **No no definitive cure known**
(=no possibility to stop or revert the process)
- ▶ Current therapies only suppress symptoms

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)

Levodopa (L-dopa)

- ▶ **Increasing the synthesis of dopamine**
- ▶ Introduced in the late 1960s
- ▶ “Gold Standard” in drug therapy
- ▶ Crosses the blood-brain barrier
- ▶ **Adverse effects:** nausea, vomiting, postural hypotension, involuntary movements, restlessness, and cardiac arrhythmias
 - ▶ Behavioral disturbances in 20 to 25% of population
 - ▶ Trouble in thinking (cognitive effects)
 - ▶ L-dopa can induce: Psychosis, Confusion, Hallucination, Anxiety, Delusion
- ▶ Some Individuals develop hypomania (inappropriate sexual behavior); “Dirty Old Man”, “Flashers”



”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...

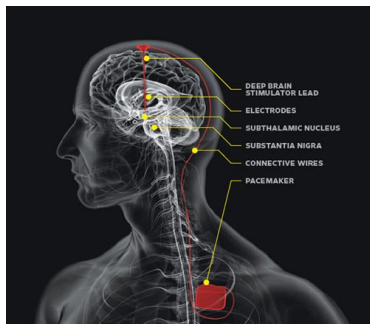
- ▶ **Genetic engineering:**

- ▶ 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)

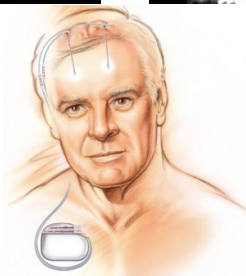
Overview of the therapeutical technique

DBS basics



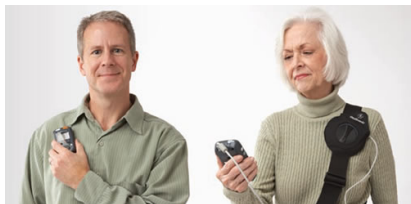
- ▶ Modern **treatment technique for Parkinson's disease** (PD), Essential tremor, clinical depressions and other.
- ▶ **Stimulation electrodes** implanted into patient's brain
- ▶ Supports or replaces medication when insufficient or contraindicated
 - ▶ Typical case: patient with long-term progressive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



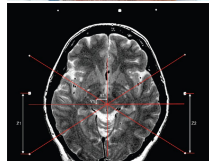
Targetting

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: processing and evaluation methods

Tomáš Sieger (updates: E. Bakštein)

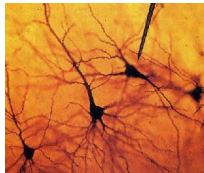
μ EEG

EEG



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

μ EEG



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

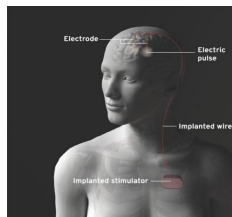
▶ microelectrodes

- ▶ neuron $\sim 10\mu\text{m}$ (10-25 μm)
- ▶ electrode tip $\sim 1\div 10\mu\text{m}$
- ▶ one / more conacts (tetrodes)
- ▶ bipolar / unipolar
- ▶ recording / stimulatory



Application: research of DBS STN mechanisms in Parkinson's disease

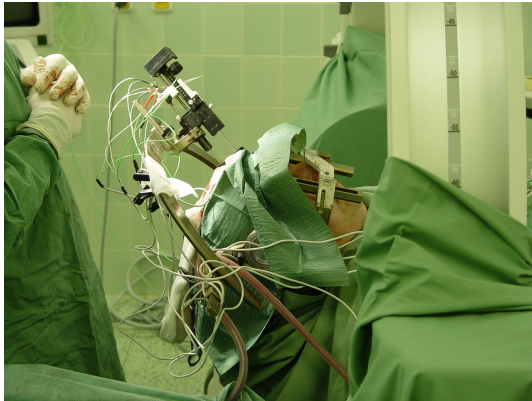
- ▶ Parkinson's disease: neurodegenerative disorder
- ▶ Deep brain stimulation (DBS)



- ▶ non-motoric side effects: depression, emotional lability
- ▶ hypothesis: STN neurones are connected to cognitive processes

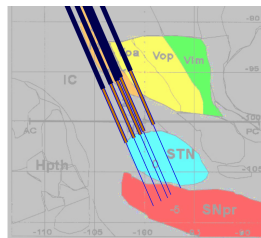
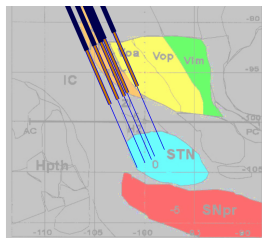
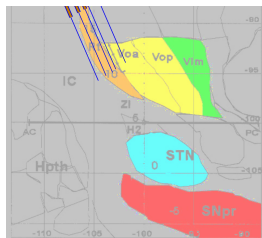
μ EEG - recording of patient data

- ▶ 5 parallell mikroelektrodes (cross), 2mm apart
- ▶ sampling rate 24kHz

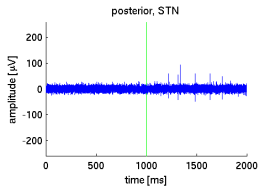
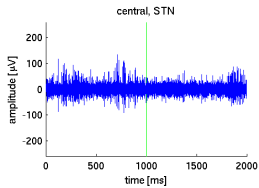
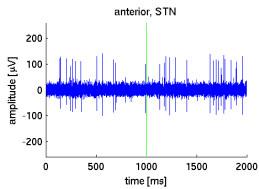


Microregistration - shifting electrodes

- ▶ 3 recording positions:

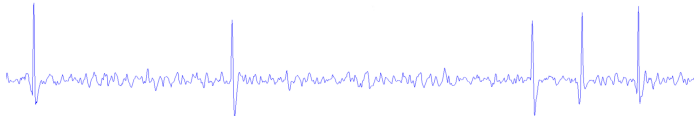


μ EEG example



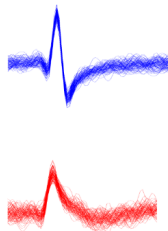
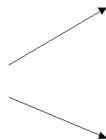
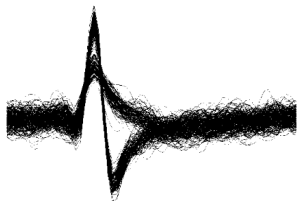
Spike detection and spike sorting

- ▶ μ EEG

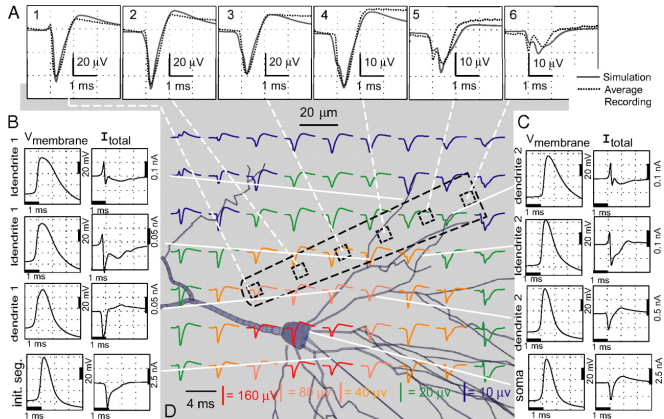


- ▶ spike detection

- ▶ sorting of detected spikes to neurons



Recorded spike shape depends on the neuron-electrode positioning



- ▶ 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.

Spike sorting

Selected methods

method	spike detection	spike sorting	
		features	clustering
WaveClus ¹	amplitude	koef. WT AP	superparamg.
KlustaKwik ²	N/A	ad hoc	Gauss mix fit + AIC
OnlineSort ³	energy	AP	min. LS of AP differences, threshold
Spike2 ⁴	amplitude manual	ad hoc	manual / 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>

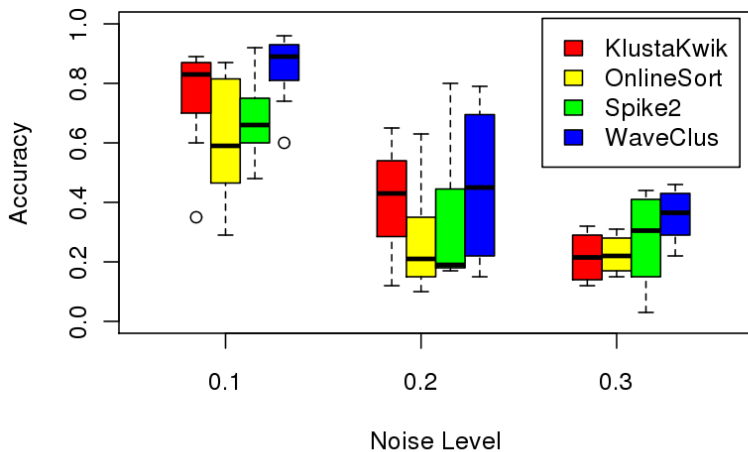
Spike sorting

Problems

- ▶ guarantee?
 - ▶ did we detect all true spikes?
 - ▶ did we include noise spikes (false positives)?
 - ▶ were the spikes sorted correctly?
- ▶ which method should we choose?
 - ▶ how should we set the parameters?
- ▶ method comparison:
 - ▶ processing of artificial/simulated signal
 - ▶ problem: how to generate signal, sufficiently similar to real one

Spike sorting

Methods: comparison of accuracy

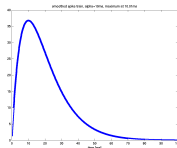


Spike train statistics

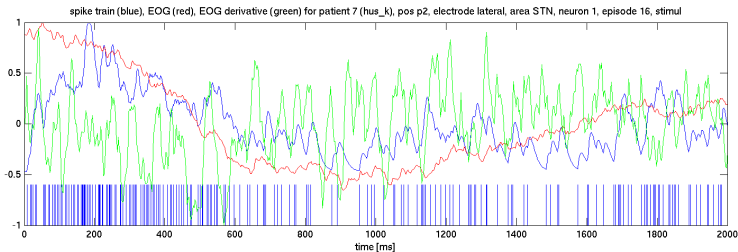
- ▶ tasks:
 - ▶ compare spike train to other quantity:
 - ▶ single number
 - ▶ continuous signal
 - ▶ compare two spike trains
- ▶ how to characterize a spike train?
 - ▶ mean firing rate
 - ▶ median ISI
 - ▶ ISI coefficient of variance
 - ▶ ISI index of assymetry
 - ▶ Fano faktor
 - ▶ ...
 - ▶ the spike train itself!
 - ▶ holds most information

Comparing spike train to continuous signal

- ▶ spike train \rightarrow continuous function (instantaneous firing rate)
 - ▶ convolution of spiketrain with alpha function $w(\tau) = \alpha^2 \tau e^{-\alpha \tau}$



- ▶ Compute relation between signal and instantaneous firing rate

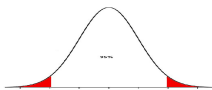


Comparing spike train to continuous signal (2)

- ▶ Compute relation between signal and instantaneous firing rate
 - ▶ correlation (Pearson, Spearman)
 - ▶ mutual information
- ▶ statistical significance
 - ▶ correlation coefficients
 - ▶ watch out for assumptions (normality)
 - ▶ watch out for degrees of freedom
- ▶ Monte-Carlo simulation: bootstrap
 - ▶ repeat many times (5000x):
 - ▶ generate artificial signals
 - ▶ compute correlation coefficient

▶ result: distribution of correlation coefficients

▶ we deem coefficients outside of 95% interval significant

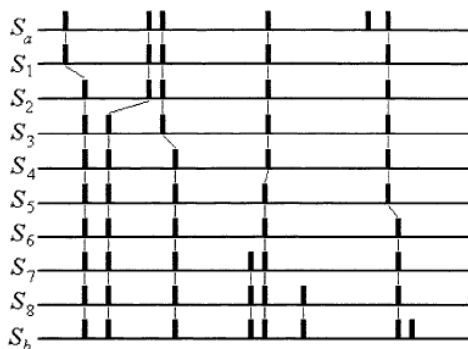


Comparing two spike trains

- ▶ ad-hoc methods
 - ▶ spike train metrics (Victor, Purpura)
 - ▶ comparison of spike train features
- ▶ Statistical tests
 - ▶ testing difference in spiketrain intensities (testing frequency coding)
 - ▶ testing difference in spiketrain distribution (testing temporal coding)
 - ▶ advantage: statistical significance

Victor metric

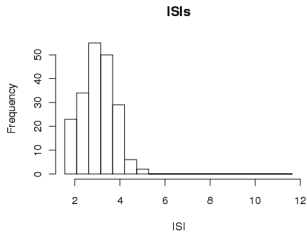
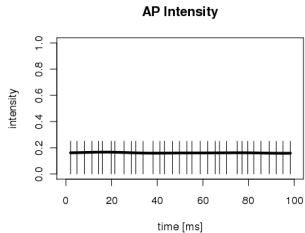
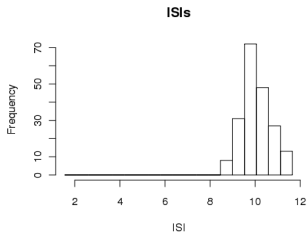
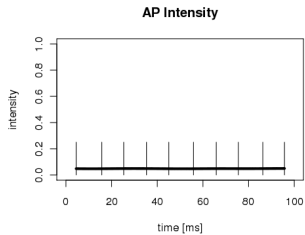
- ▶ Jonathan D. Victor and Keith Purpura. [Metric-space analysis of spike trains: theory, algorithms, and application](#). Network 8,



127-164 (1997)

Testing spiketrain intensities

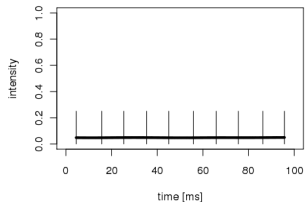
Wilcoxon 2-sample test



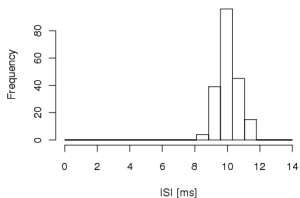
Testing ISI distribution

Kolmogorov-Smirnov 2-sample test

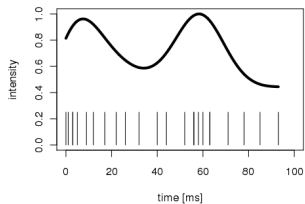
AP Intensity



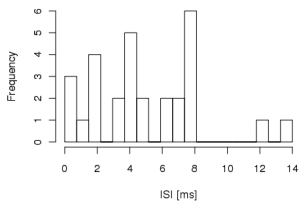
ISIs



AP Intensity



ISIs

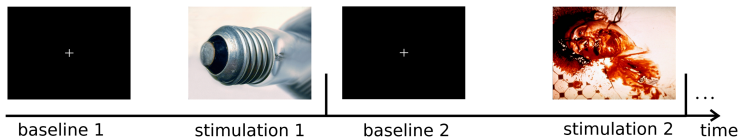


Test of spike train differences

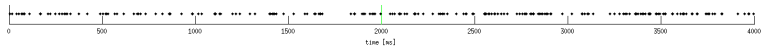
- ▶ combination of previous two tests
 - ▶ we want a single test at significance level α
- ▶ procedure:
 1. test of AP intensities at significance level $\frac{\alpha}{2}$
 2. test of ISI distribution at significance level $\frac{\alpha}{2}$
- ▶ the resulting test yields a significance level α

Visual stimulation + recording μ EEG

▶ visual stimulation



▶ recorded μ EEG



Statistics

- ▶ data
 - ▶ 10 patients
 - ▶ 43 recording positions
 - ▶ 141 recordings (74 in STN)
 - ▶ 173 recording minutes (89 minutes in STN)
 - ▶ 176 neurons (101 in STN)
- ▶ results: counts of identified **significant** neurons
 - ▶ by comparing spiketrain characteristics: 6
 - ▶ by comparing spiket trains: 20

Team

- ▶ Department of Cybernetics, Faculty of Electrical Engineering, Czech Tech. University, Prague
 - ▶ Doc. Ing. Daniel Novák, PhD.
 - ▶ Mgr. Tomáš Sieger, PhD.
 - ▶ Ing. Eduard Bakštein
 - ▶ Ing. Jakub Schneider
 - ▶ Ing. Jiří Wild, PhD.
- ▶ Department of neurology, 1st Faculty of Medicine, Charles University
 - ▶ Prof. MUDr. Robert Jech, PhD.
 - ▶ MUDr. Tereza Serranová, PhD.
 - ▶ MUDr. Filip Růžička, PhD.
- ▶ Na Homolce hospital, Prague
 - ▶ MUDr. Dušan Urgošík, CSc.

Thank you for your attention!