

# 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

$\mu$ EEG: processing and evaluation methods

$\mu$ EEG

$\mu$ EEG recording of patient data

Processing  $\mu$ EEG

Conversion of  $\mu$ 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



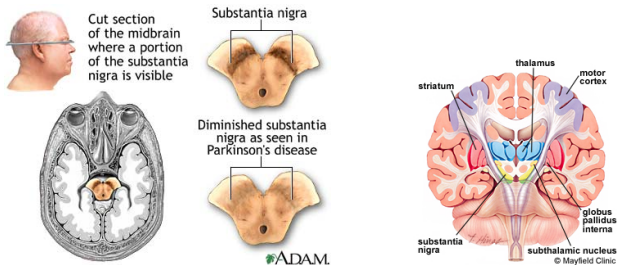
## Characteristic Problems

- ▶ 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**

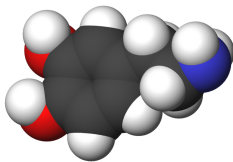
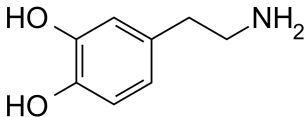
# Patophysiology

- ▶ 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**



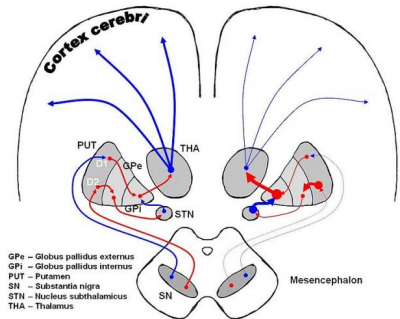
# Dopamine

- ▶ 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

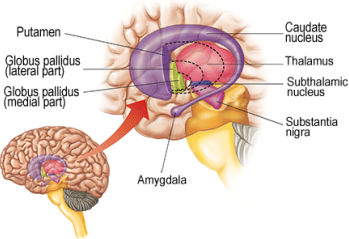


Dopaminergic pathways of the human brain in normal condition (left) and Parkinson's disease (right). Red Arrows indicate **suppression** of the target, blue arrows indicate **stimulation** of target structure.

# Basal Ganglia II

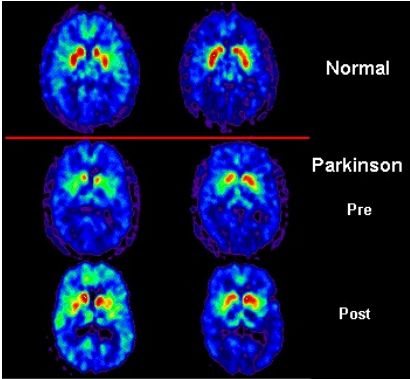
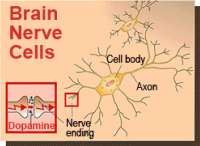
18F PET scan(right) shows decreased dopamine activity in the basal ganglia

## The Human Basal Ganglia



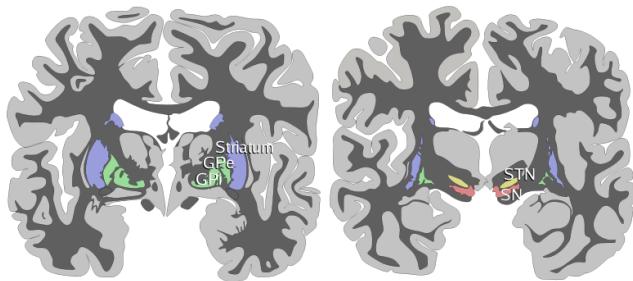
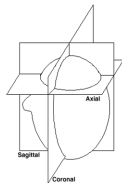
Near the base of the brain is a small area called the substantia nigra which contains cells that produce dopamine.

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

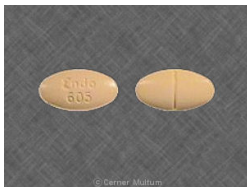
- ▶ **No no definitive cure known**  
(=no possibility to stop or revert the process)
- ▶ Current therapies only suppress symptoms

## 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)

# 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”





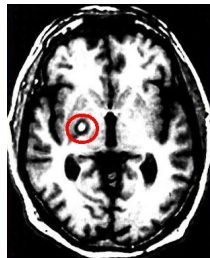
## ”On/Off switching”

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...

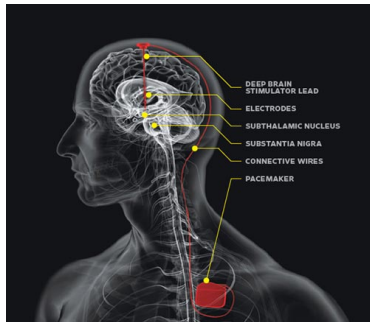
- ▶ **Genetic engineering:**

- ▶ 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)

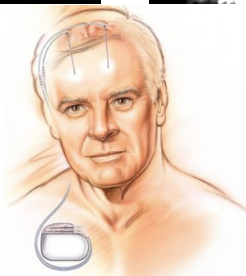
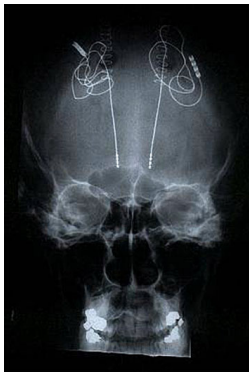
Overview of the therapeutical technique

# DBS basics



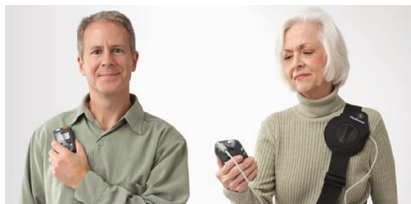
- ▶ Modern **treatment technique for Parkinson's disease** (PD), Essential tremor, clinical depressions and other.
- ▶ **Stimulation electrodes** implanted into patient's brain
- ▶ Supports or replaces medication when insufficient or contraindicated
  - ▶ Typical case: patient with long-term progressive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





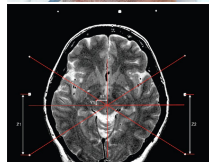
# Targetting

**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**

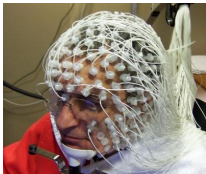
- ▶ Set of microelectrodes shifted through patient's brain
- ▶ Electrophysiological properties along trajectory recorded
- ▶ Activity evaluated by trained physician
- ▶ Accurate location of target nucleus boundaries identified.

# $\mu$ EEG: processing and evaluation methods

Tomáš Sieger (updates: E. Bakštein)

# $\mu$ EEG

EEG



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

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

$\mu$ EEG



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

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

## ▶ microelectrodes

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

▶ electrode tip  $\sim 1\div 10\mu\text{m}$

▶ one / more contacts (tetrodes)

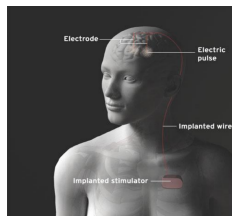
▶ bipolar / unipolar

▶ recording / stimulatory



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

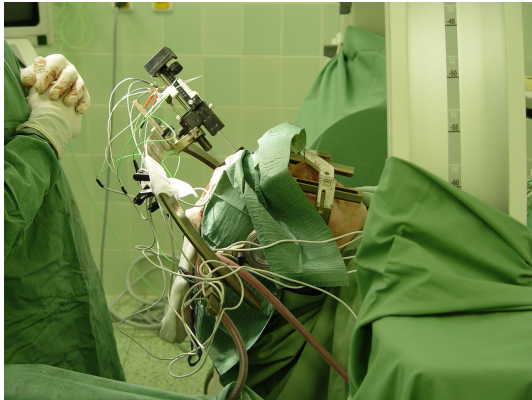
- ▶ Parkinson's disease: neurodegenerative disorder
- ▶ Deep brain stimulation (DBS)



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

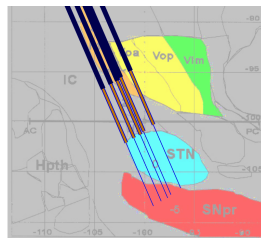
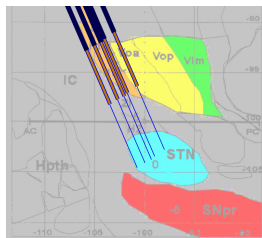
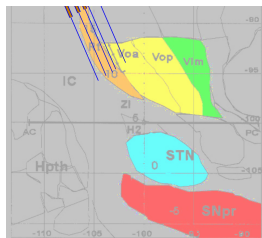
# $\mu$ EEG - recording of patient data

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

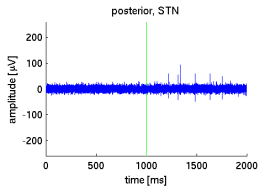
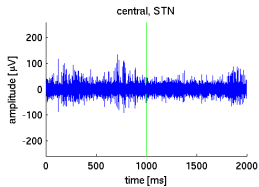
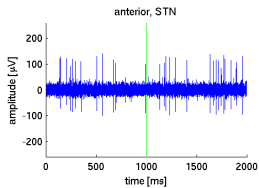


# Microregistration - shifting electrodes

- ▶ 3 recording positions:



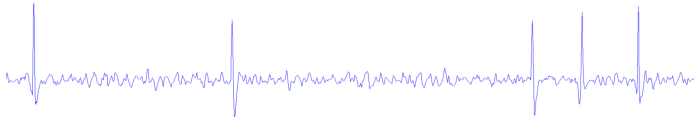
# $\mu$ EEG example





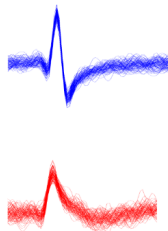
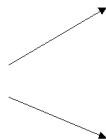
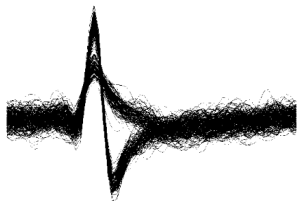
# Spike detection and spike sorting

- ▶  $\mu$ EEG

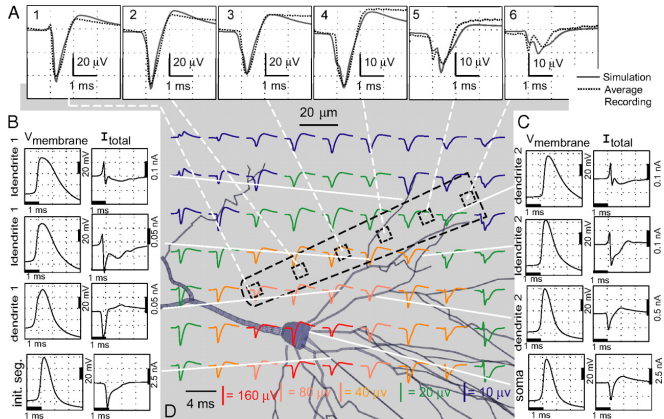


- ▶ spike detection

- ▶ 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 <sup>1</sup>	amplitude	koef. WT AP	superparamg.
KlustaKwik <sup>2</sup>	N/A	ad hoc	Gauss mix fit + AIC
OnlineSort <sup>3</sup>	energy	AP	min. LS of AP differences, threshold
Spike2 <sup>4</sup>	amplitude manual	ad hoc	manual / k-means

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

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

<sup>3</sup>Ueli 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.

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

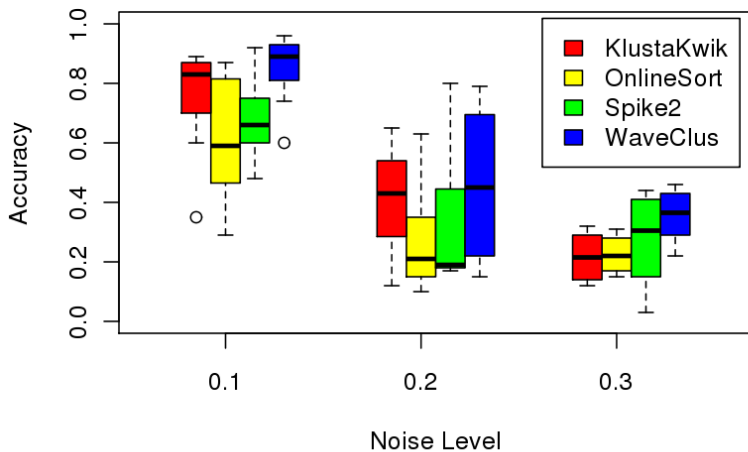
# Spike sorting

## 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

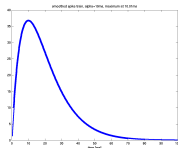


# Spike train statistics

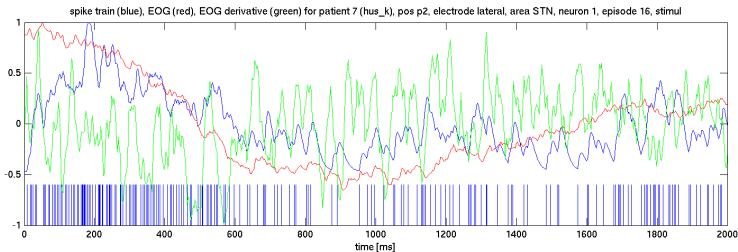
- ▶ tasks:
  - ▶ compare spike train to other quantity:
    - ▶ single number
    - ▶ continuous signal
  - ▶ compare two spike trains
- ▶ how to characterize a spike train?
  - ▶ mean firing rate
  - ▶ median ISI
  - ▶ ISI coefficient of variance
  - ▶ ISI index of assymetry
  - ▶ Fano faktor
  - ▶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

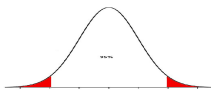


## Comparing spike train to continuous signal (2)

- ▶ 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



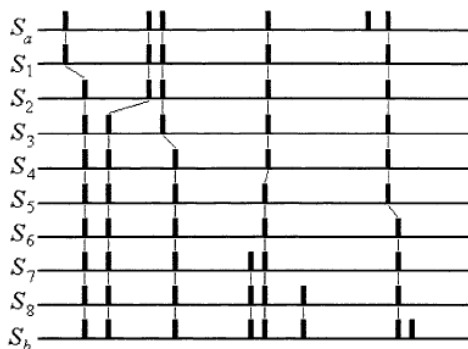


# Comparing two spike trains

- ▶ 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

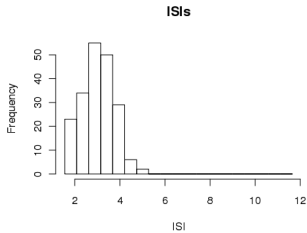
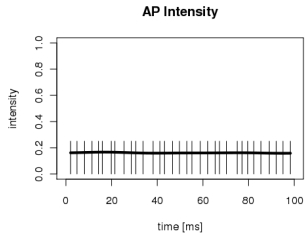
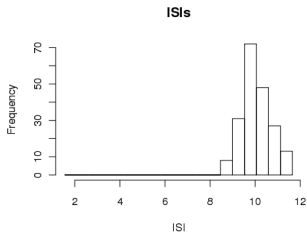
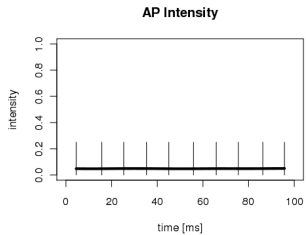
- ▶ Jonathan D. Victor and Keith Purpura. [Metric-space analysis of spike trains: theory, algorithms, and application](#). Network 8,



127-164 (1997)

# Testing spiketrain intensities

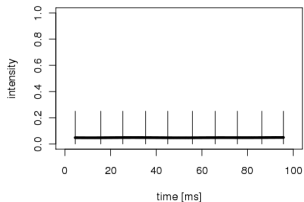
Wilcoxon 2-sample test



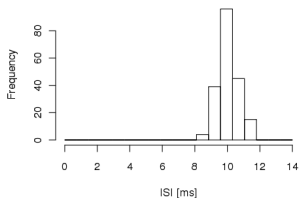
# Testing ISI distribution

Kolmogorov-Smirnov 2-sample test

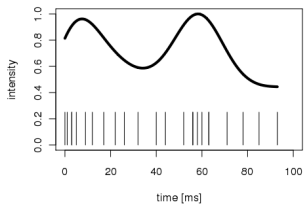
**AP Intensity**



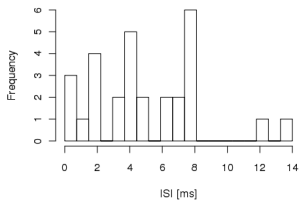
**ISIs**



**AP Intensity**



**ISIs**

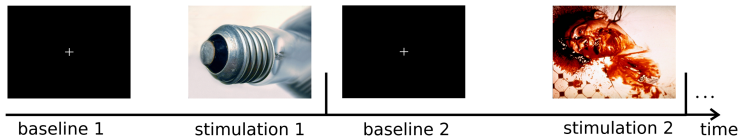


# Test of spike train differences

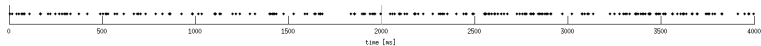
- ▶ combination of previous two tests
  - ▶ we want a single test at significance level  $\alpha$
- ▶ procedure:
  1. test of AP intensities at significance level  $\frac{\alpha}{2}$
  2. test of ISI distribution at significance level  $\frac{\alpha}{2}$
- ▶ the resulting test yields a significance level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

# Visual stimulation + recording $\mu$ EEG

## ▶ visual stimulation



## ▶ recorded $\mu$ 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

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Děkuji za pozornost