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Representation Of Stimuli As Neural Activity

UCM: Universidad Complutense de Madrid
UAM: Universidad Autonoma de Madrid
FhG-IBMT: Fraunhofer Institute for Biomedical Engineering
IBMC: Institute for Molecular and Cell Biology of Porto
UEx: Univ. of Exeter

“Perception”

“Internal Representation” of the external world

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Understand the fundaments of perception

↑

Determine the principles of coding of sensory stimuli

↑

Interactions sensory inputs - activity of CNS neurons

↓

we will be able to reproduce the same spatiotemporal pattern of activity

"Perception"
Oscillations and Information processing

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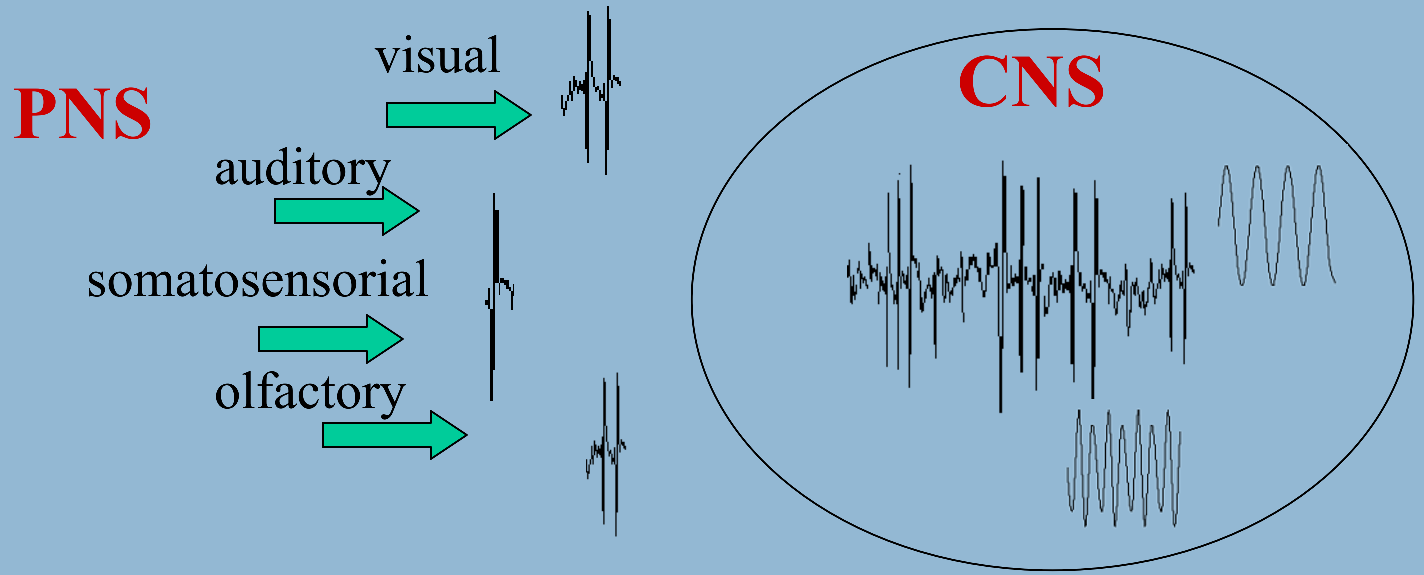

- Record the neural activity in PNS and CNS
- Develop mathematical models using experimental data

Our Experiment

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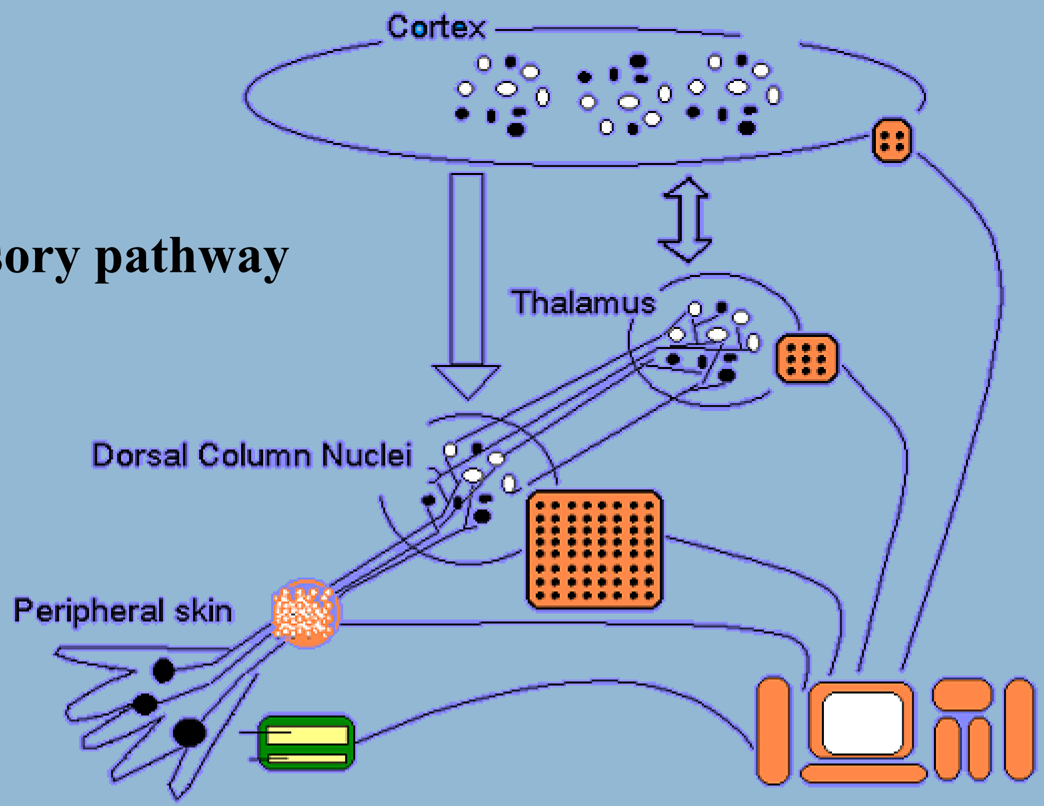
Lemniscal sensory pathway



Methodology

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- Sieve microelectrodes
- Skin stimulator
- Sieve electrodes implantation
- Histological – quantification of nerve regeneration
- Simultaneous recordings from the PNS – CNS
- Data analysis
- Mathematical models

Sieve electrode design

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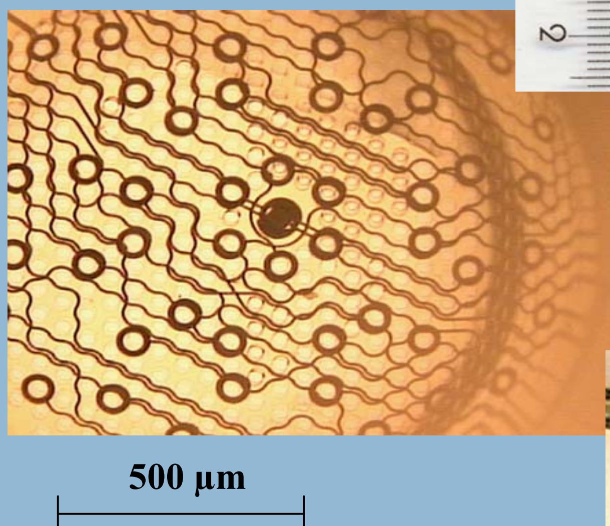

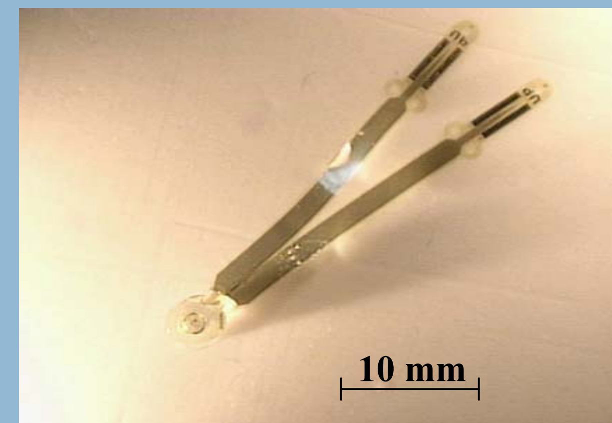

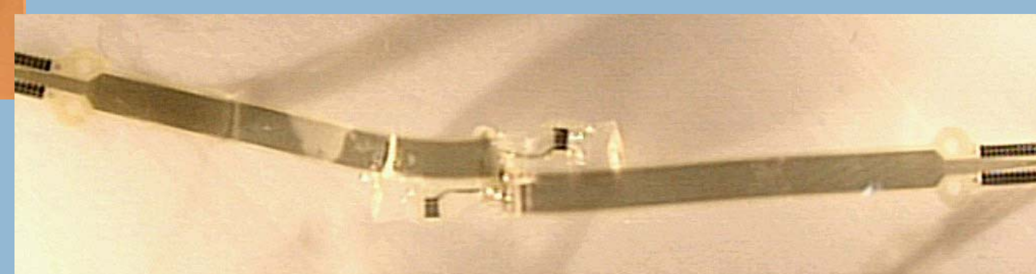

- **54 ring electrodes (50/90 µm)**
- **Electrodes material with platinum-black**
- **Easy to contact the electrodes**
- **Big stimulation counter electrodes distal and proximal**
- **2 mm tubes as nerve channels**

Sieve electrode design

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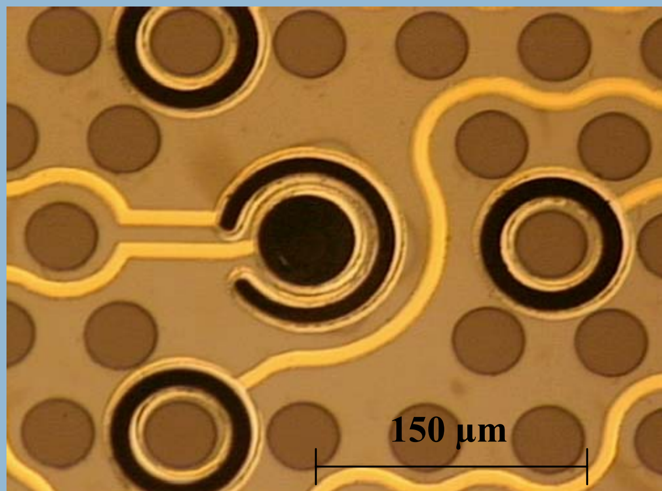

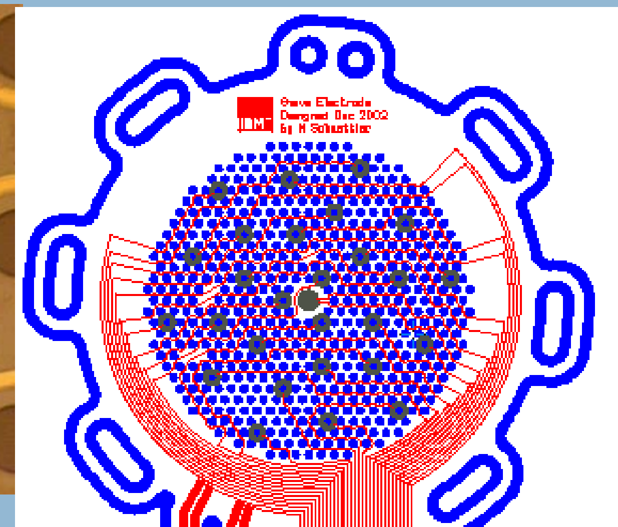

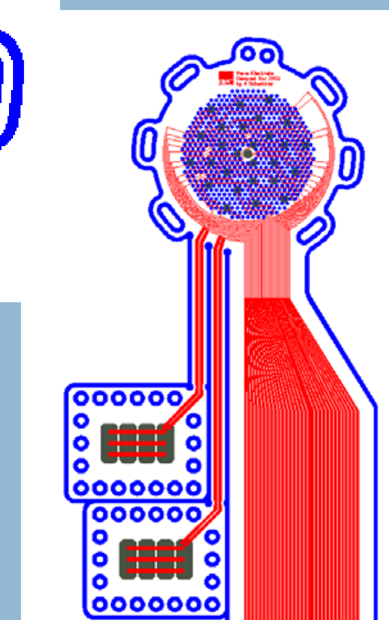

- **Improved mechanical fixation between electrode and silicone tube**
- **570 regeneration holes (40 µm)**
- **Recording reference electrodes with no holes around the electrodes to reduce crosstalk**
- **Two possible sizes for recording reference (ring and circle)**

Electrode impedance for production and implantation controlling

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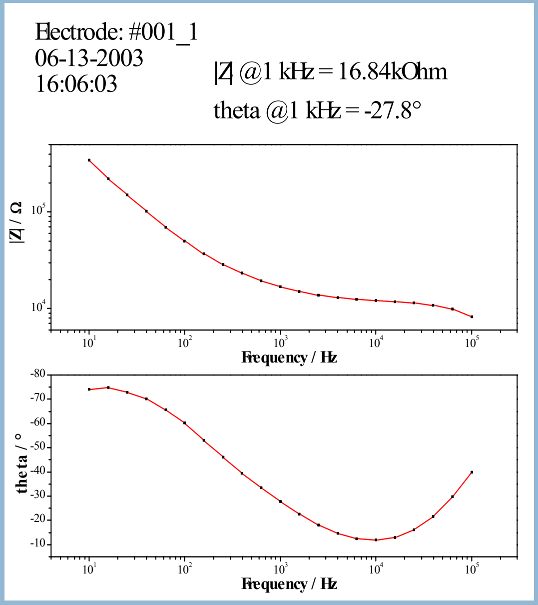
Electrode impedance at 1 kHz (N=20)

Defect	**Absolute Value / kOhm**		**Phase / °**	
	Mean	SD	Mean	SD
Demolished	1196	26	-77	0,78
Line crack	2218	50	-89,3	1,0
No connector contact	44 510	26 443	-92	27
Wet connector	1,65	1,02	-23	9,4
Non defect	16,8	1,4	-28,7	2,9

Electrode Impedance



Electrode check:

Electrode impedance have to be between

5 kOhm and 50 kOhm at 1 kHz

Tools for electrode handling

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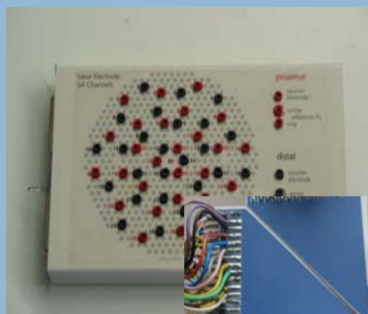

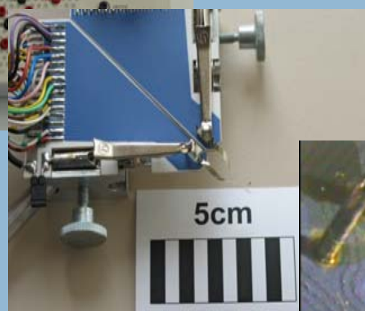

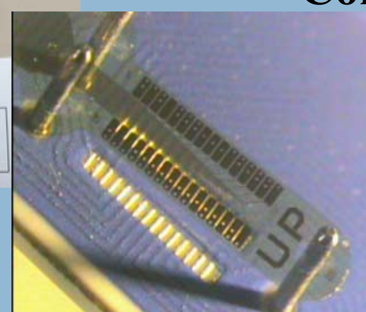

Connection of the electrodes

- Positioning tool with guide pins and labelling
- Connectionbox for distal and proximal electrodes
- Connector for 54 electrodes

Hand held stimulator

- Current or voltage controlled
- Bipolar rectangular pulse shape
- Amplitude 0.05 mA - 5 mA
  0.1 V - 10 V
- Frequency 1 Hz - 60 Hz
- Pulse width 10 µs - 500 µs

Stimulator

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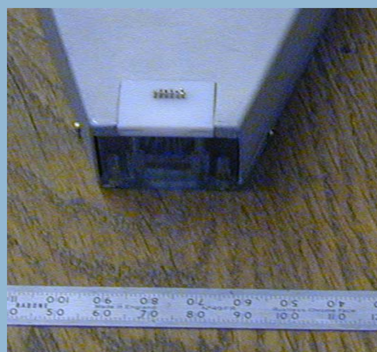
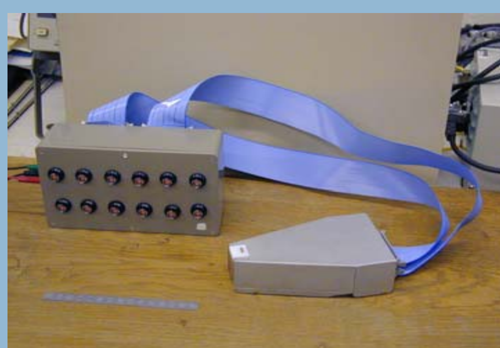
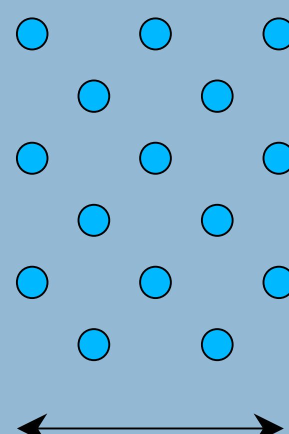


- 12 pins (6 x 2 grid) spacing 1.2 mm
- 0.6 mm diameter individually retractable pins (up to 3 mm)
- Piezoelectric bimorph actuators





4 mm

- Array of 15 pins with 1 mm row spacing
- Range of movement increased to 5 mm
- Variable drive voltage will allow variable movement

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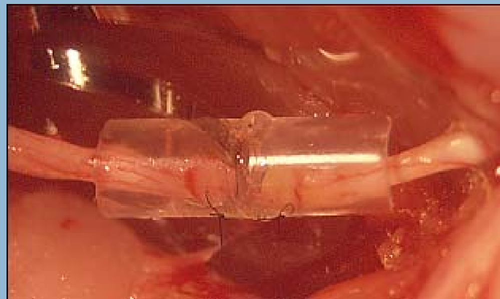

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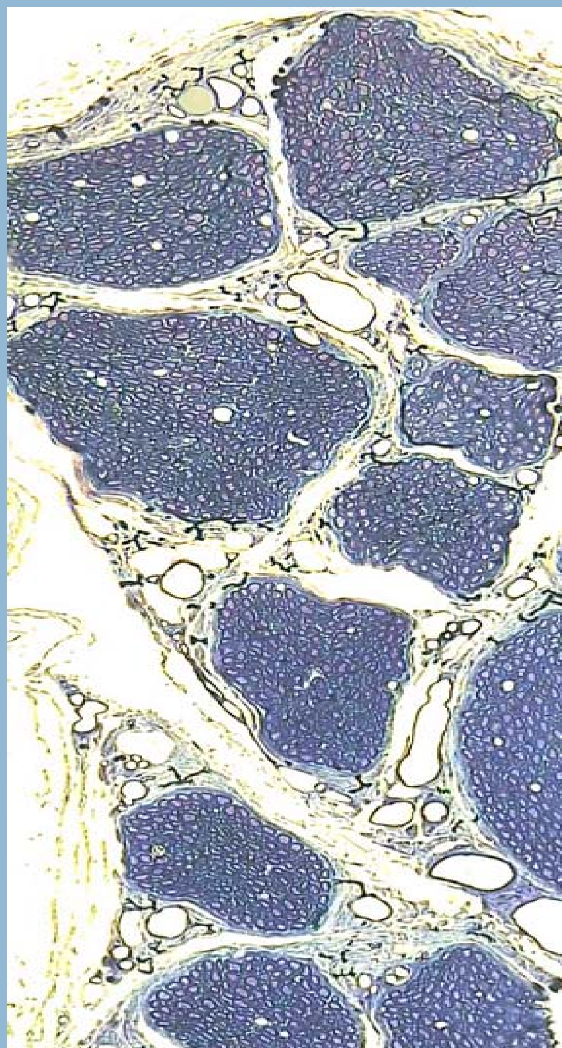
Cat median nerve (Toluidine blue)



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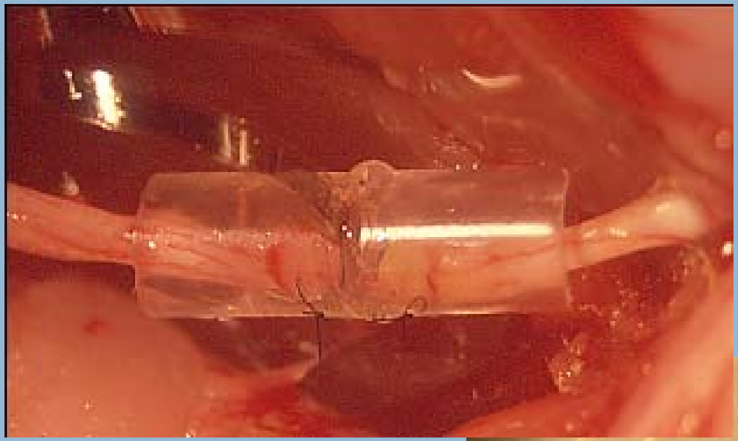

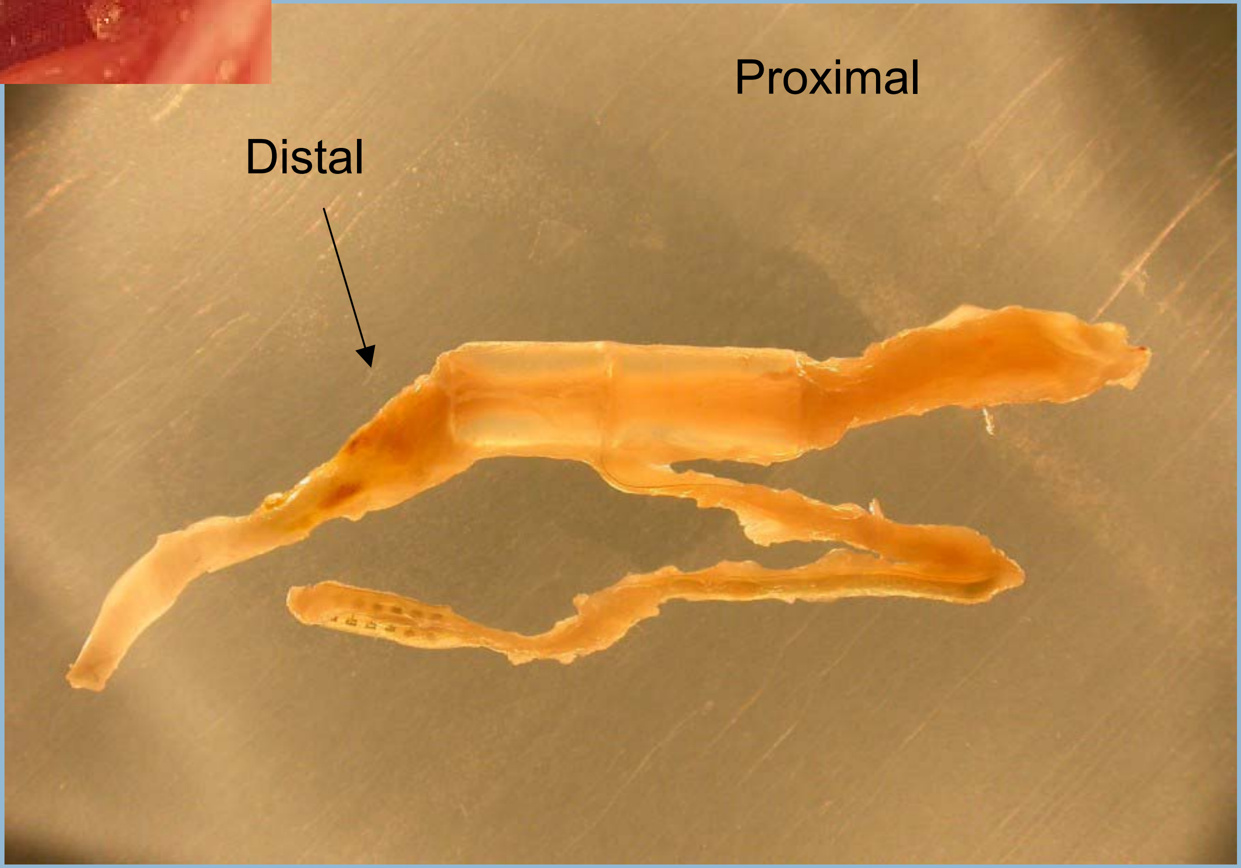

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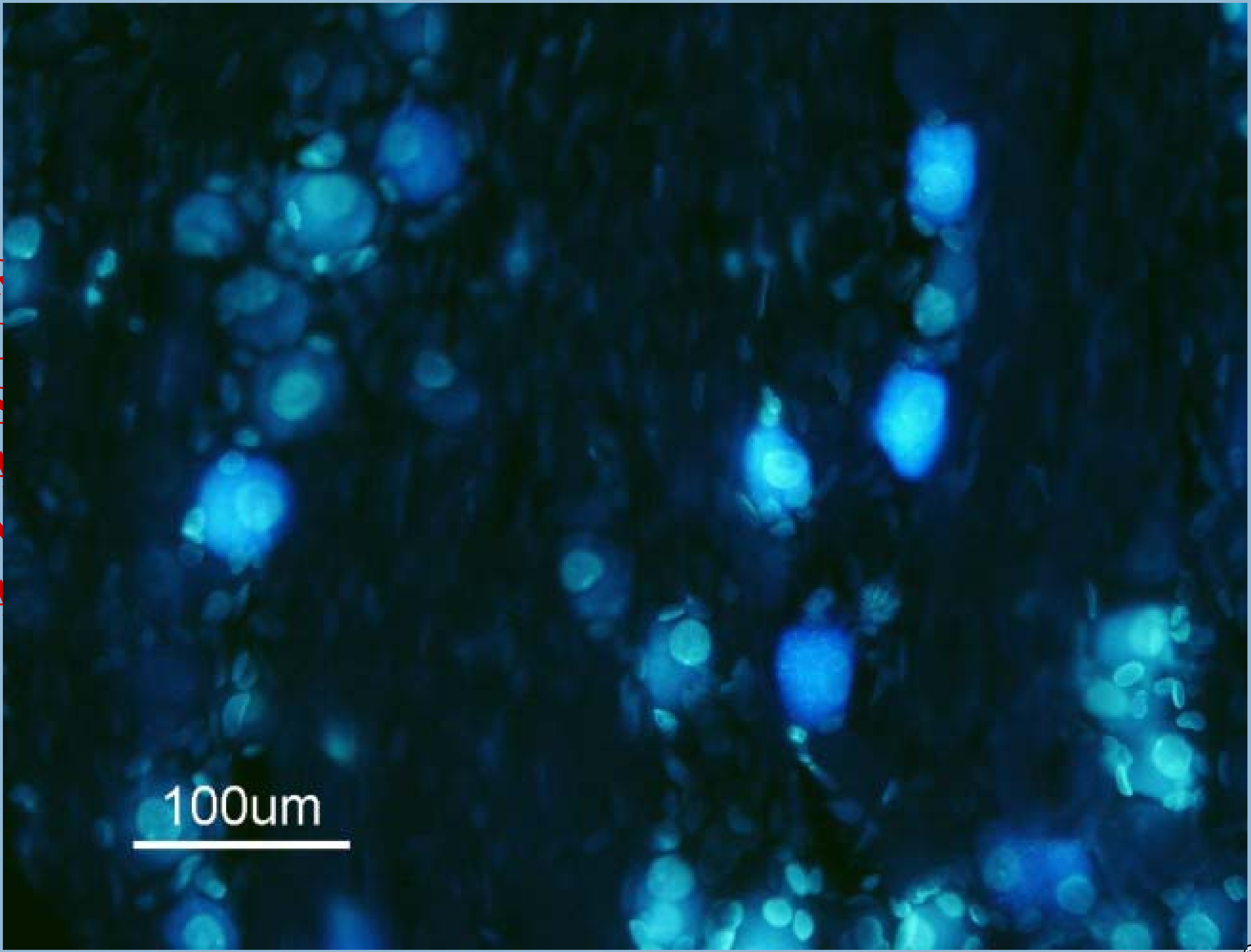
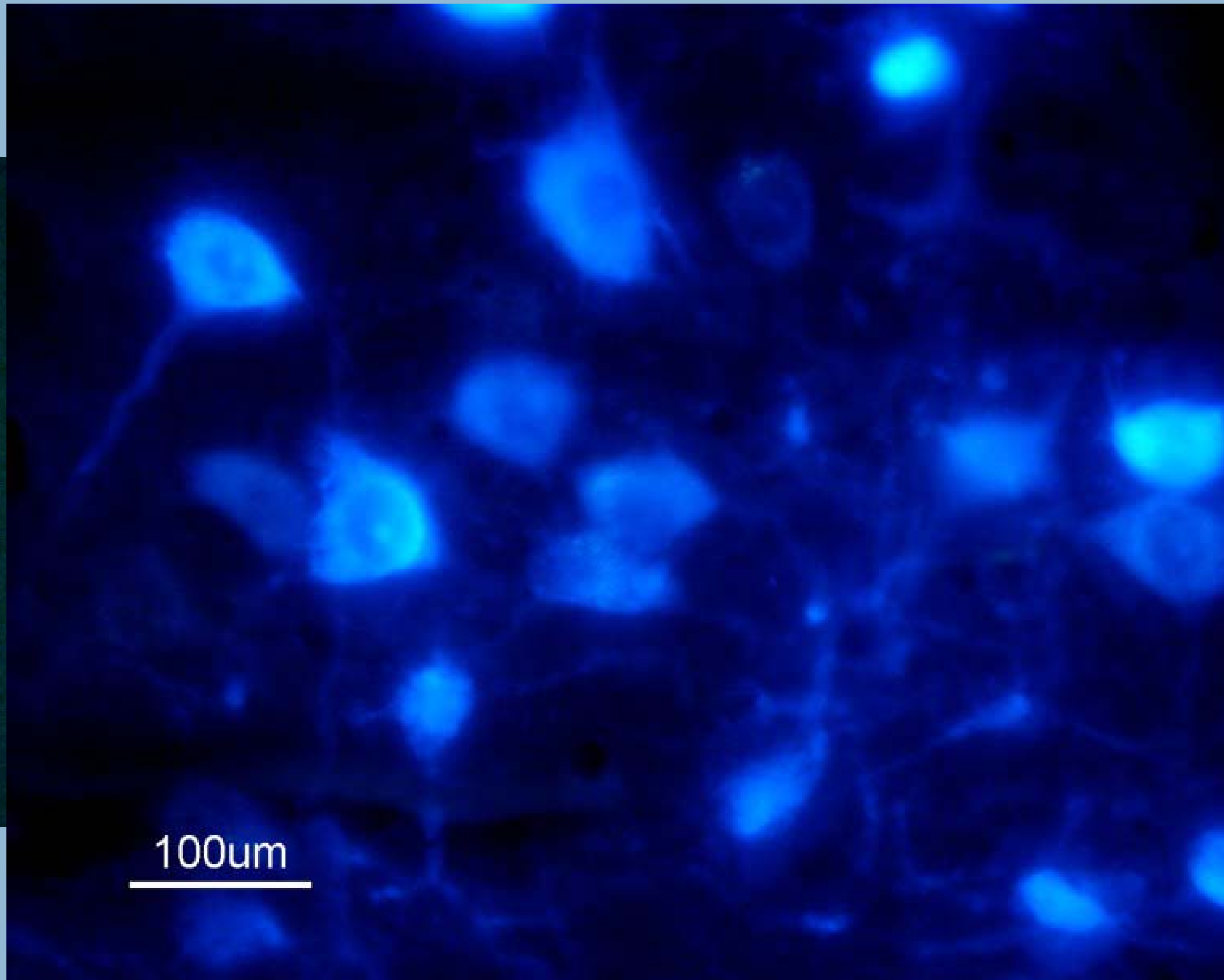



500um

100um

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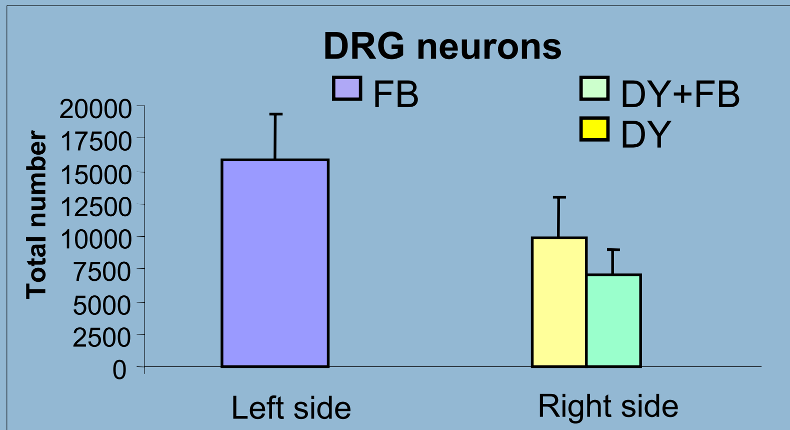
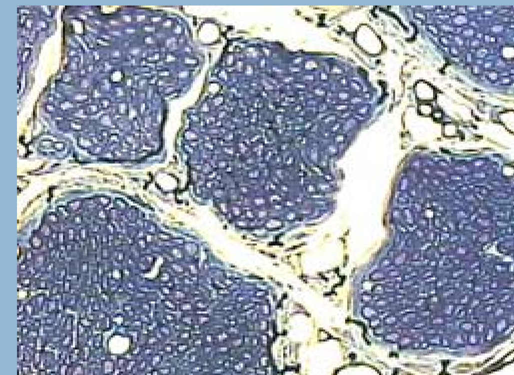
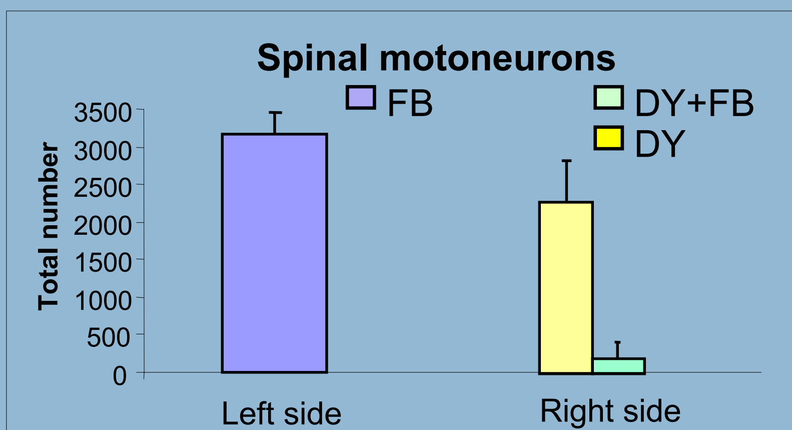
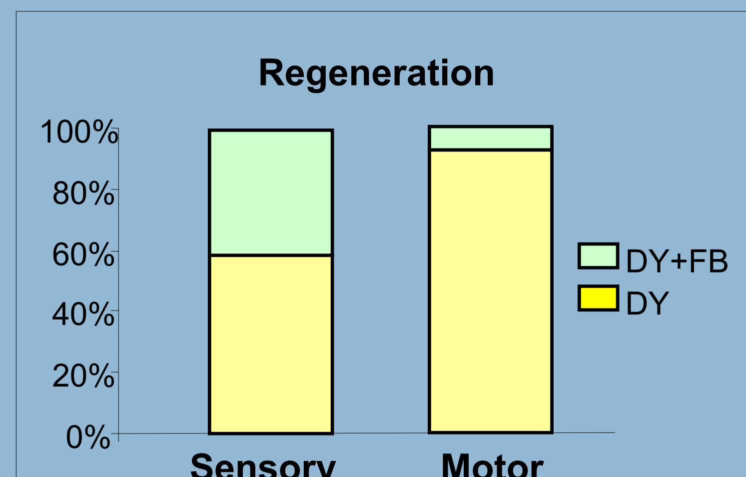

DRG neurons
FB
DY+FB
DY
Total number
20000
17500
15000
12500
10000
7500
5000
2500
0
Left side
Right side




Spinal motoneurons
FB
DY+FB
DY
Total number
3500
3000
2500
2000
1500
1000
500
0
Left side
Right side


Regeneration
100%
80%
60%
40%
20%
0%
Sensory
Motor
DY+FB
DY

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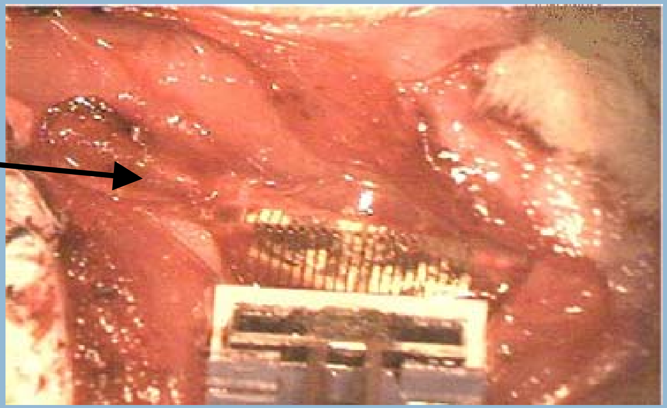
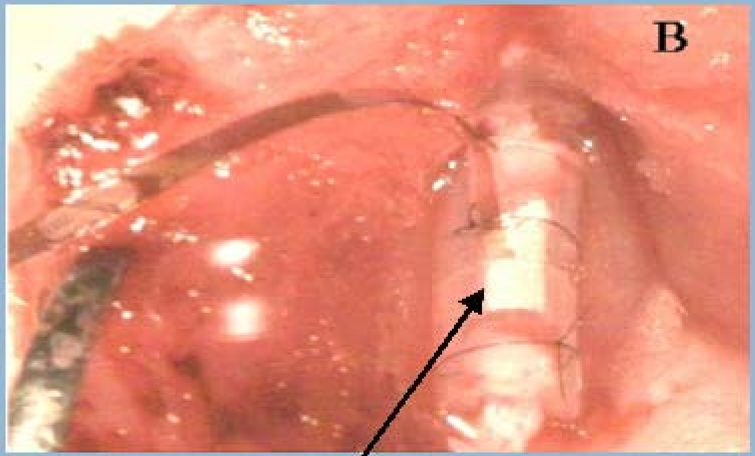
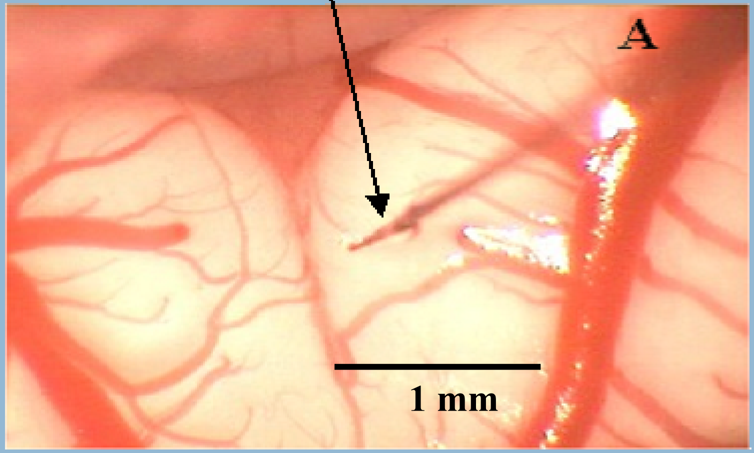
Active Microelectrode during an experiment





peripheral nerve recodings

DCN recordings



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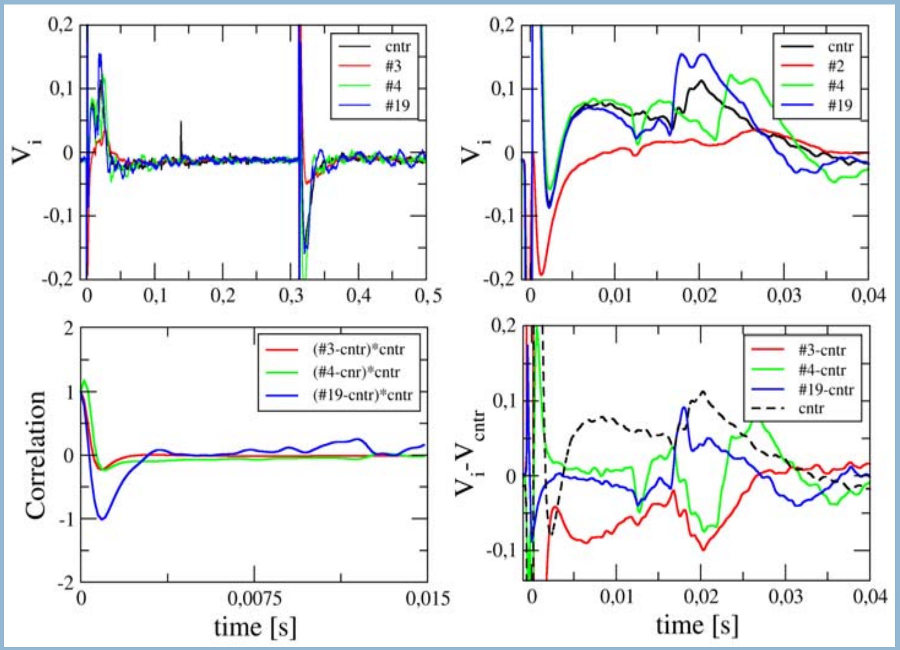
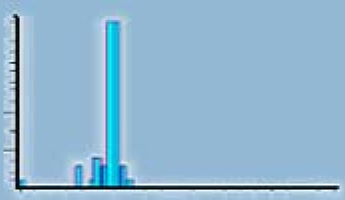
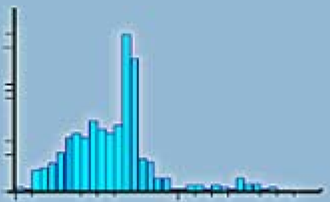
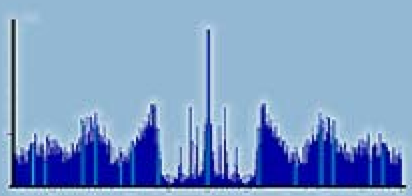




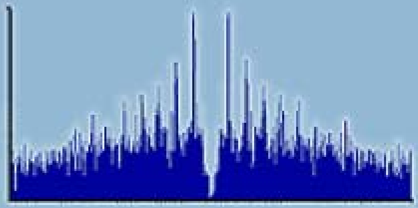
20 ms



100 ms



0 500 ms



0 500 ms

RATE HISTOGRAMS

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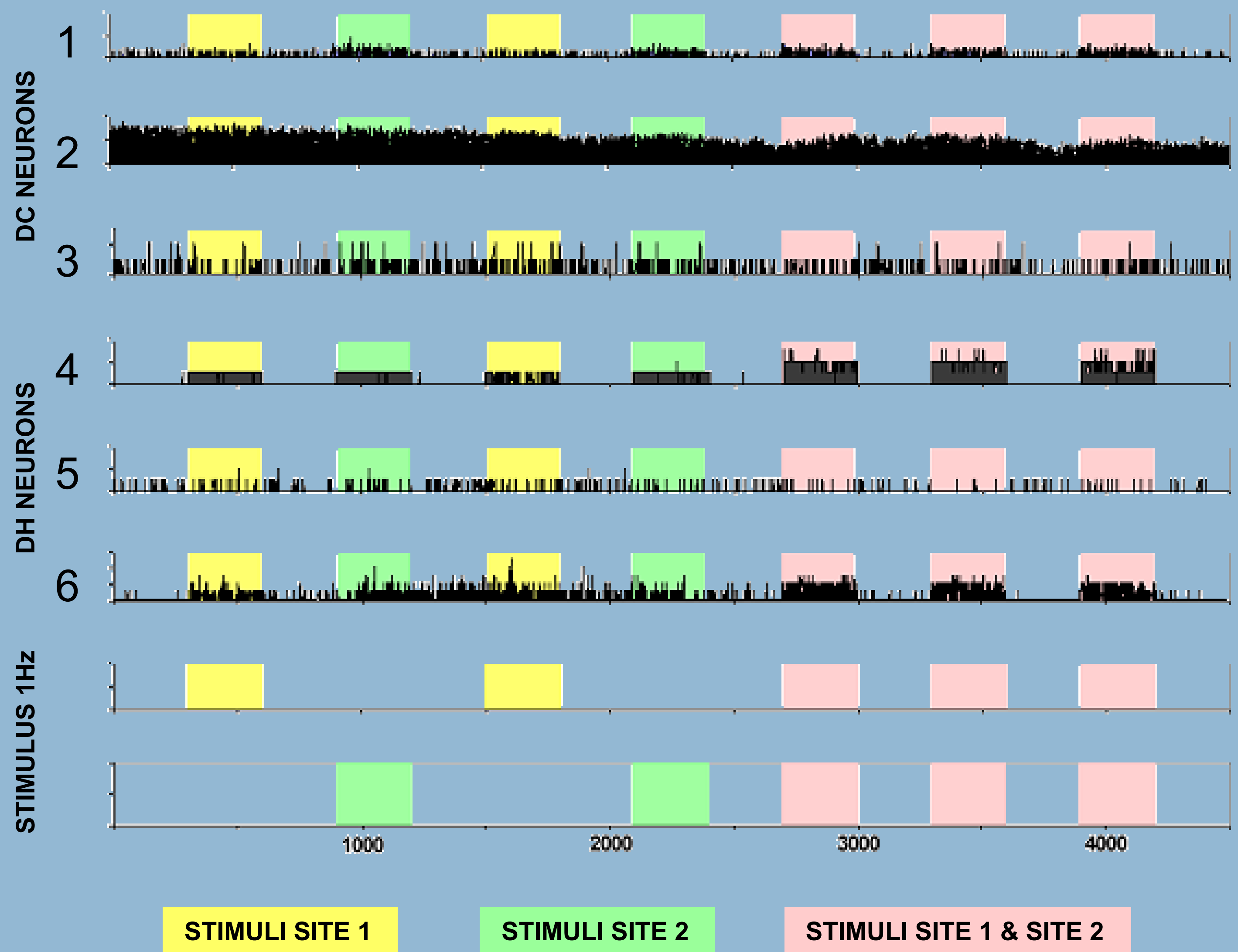

PERIEVENT HISTOGRAMS

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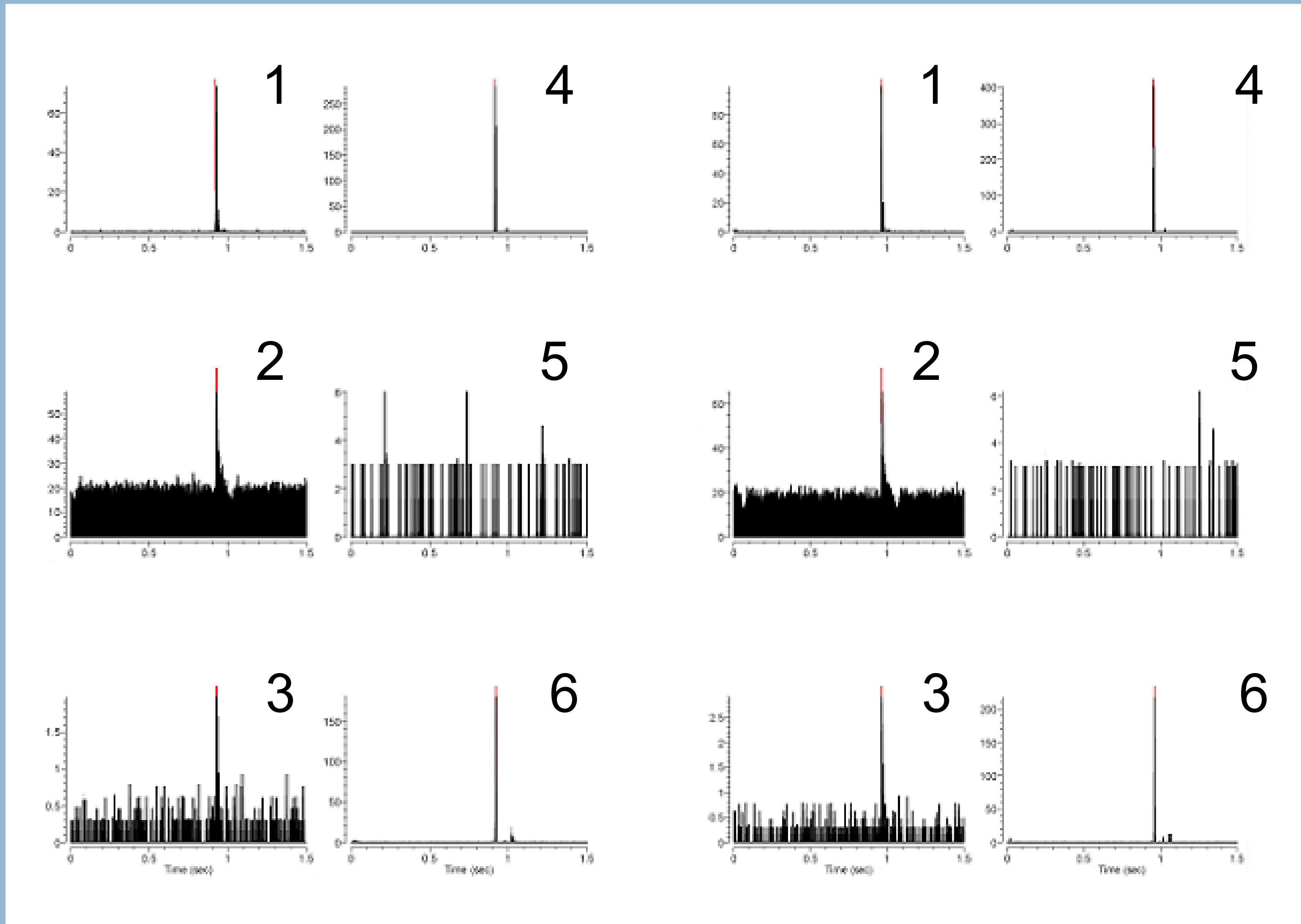
Frequency (imp/sec)



STIMULI SITE 1

STIMULI SITE 2

Experimental procedure

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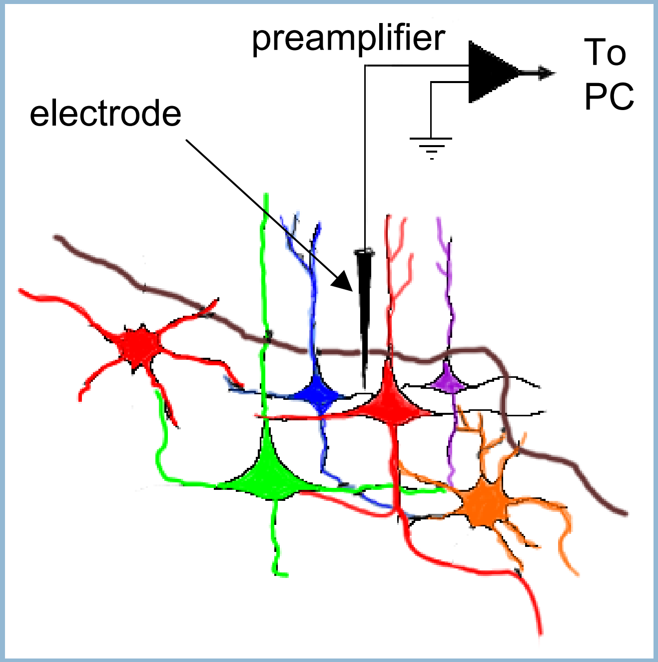
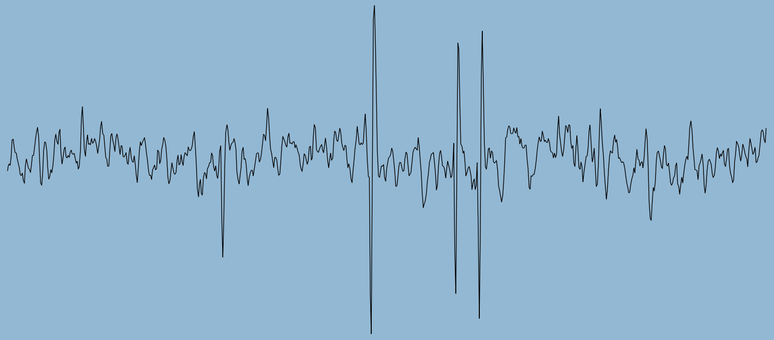


Raw experimental data



- **Simultaneous monitoring of several nearby neurons**
- **Wide band noise**
- **Detection & Separation problems**

Professional operators sorting spikes manually with tetrode electrodes do typically **from 10 to 30% errors!!!**

Performance using a single electrode is **even lower (up to 50%)!!!!!**

Objective: Extract time stamps of spiking events and assign them to different neurons (the more the better)

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Ideal Solution

- Takes a raw data file and produces time stamps of spiking events of prominent cells (as much as possible)
- Fast
- Efficient in memory use
- Automatic
- Accounts for spike shape variation
- Resolve spike superimposition
- Reliable!!!

- Signal denoising
- Spike extraction independent of operator mistakes
- Spike shape recovering
- Automatic spike sorting with subset resorting

Developed packages:

- FilterSpikes (ver. 0.23*)
- DetectSpikes (ver. 0.35*)
- SortSpikes (ver. 0.52*)

FilterSpikes & DetectSpikes packages results:

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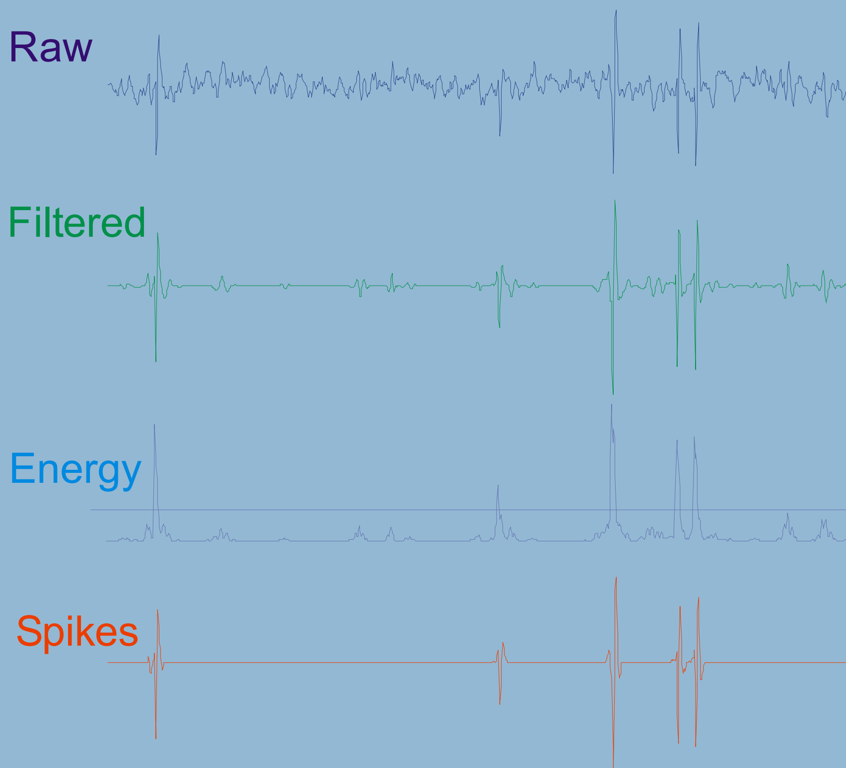


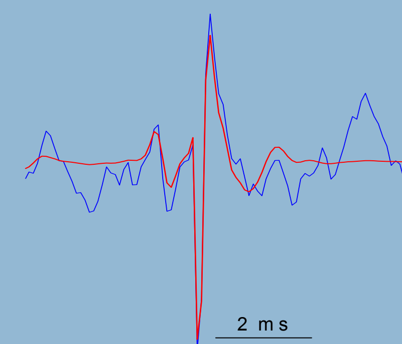
FilterSpikes

- **High Pass Filtering**

F_{stop}= 400Hz and F_{pass}= 600Hz

2. Wavelet denoising

Undecimated DWT with hard thresholding.



DetectSpikes

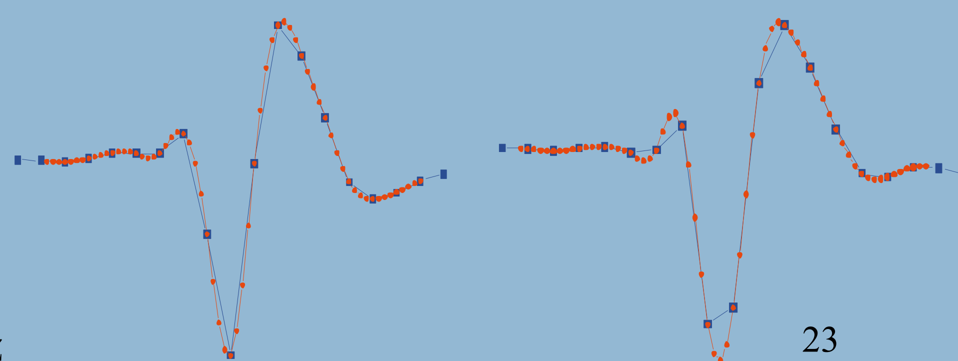
1. Spike extraction methods

A). Windowed Power

B). Nonlinear Energy Operator

2. Thresholding: T = M + K*STD

3. Spike reconstruction at 40 kHz



SortSpikes package

Spike waveform with 64 points at 40 kHz rate
Automatic classification with KlustaKwik
May often over split or merge clusters.

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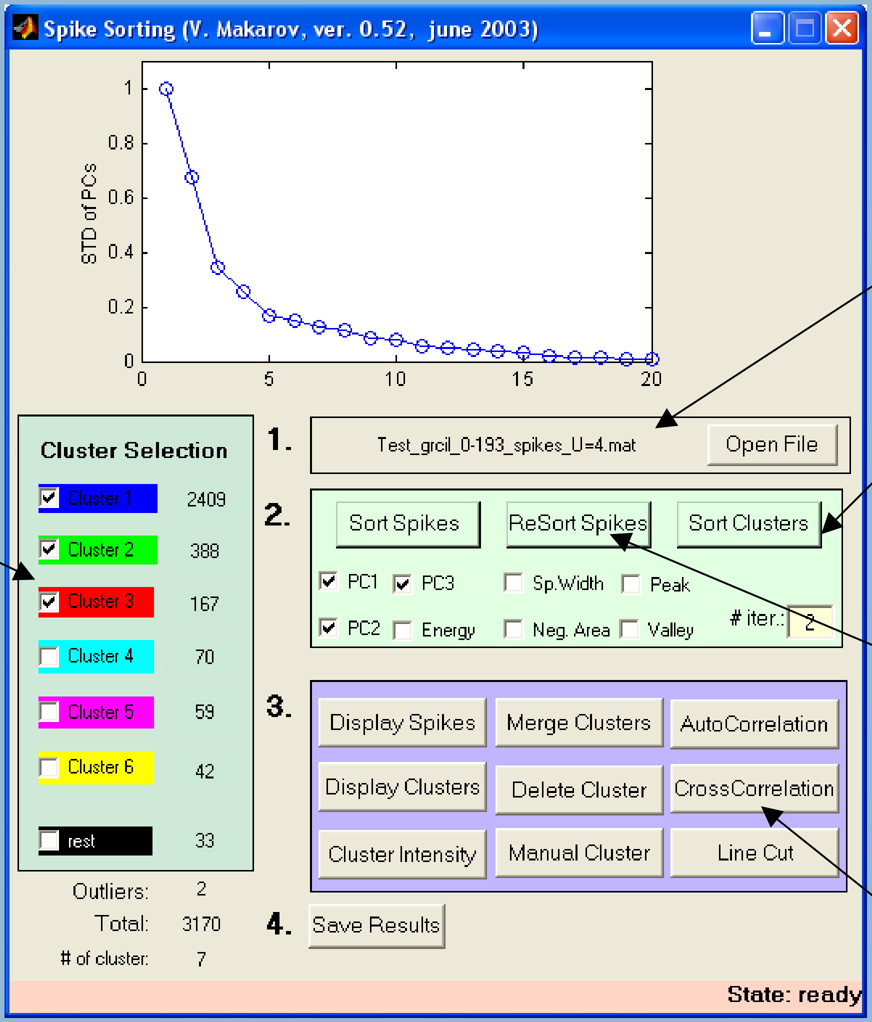
Cluster selection, color representation, and number of spikes



File with spikes and time stamps (after DetectSpikes)

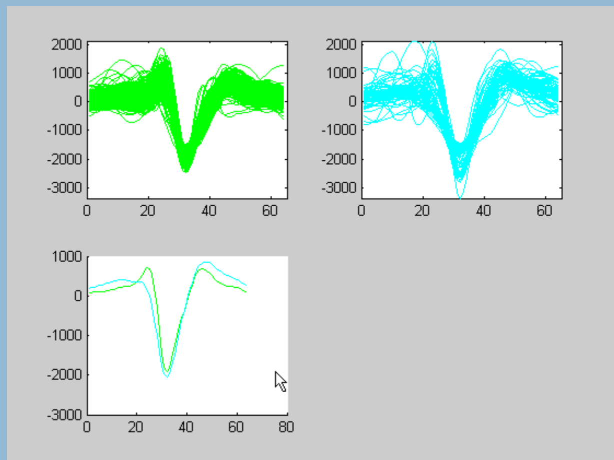
Sorting buttons and features selection

Resort button, allows To perform secondary sorting on a subset of spikes

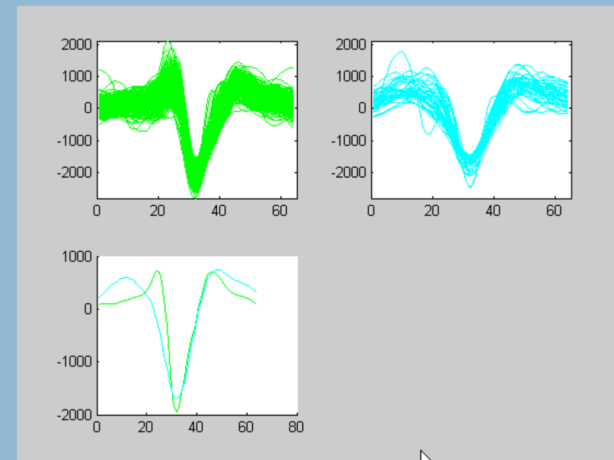
Clusters and spikes Manipulation buttons

Sorting on a subset improves performance

Badly separated spikes after **1st run**



Improved cutting. 2nd run on **the subset**



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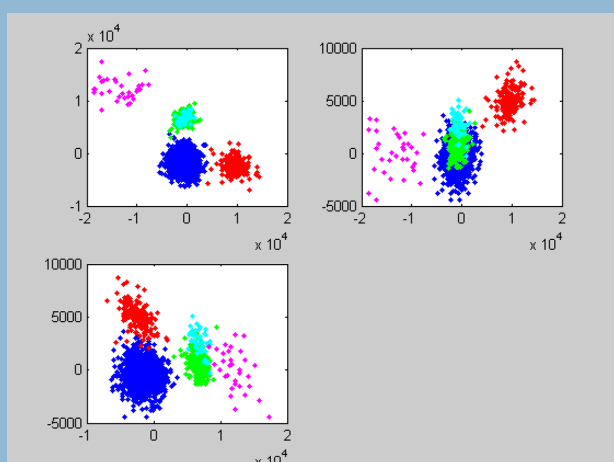
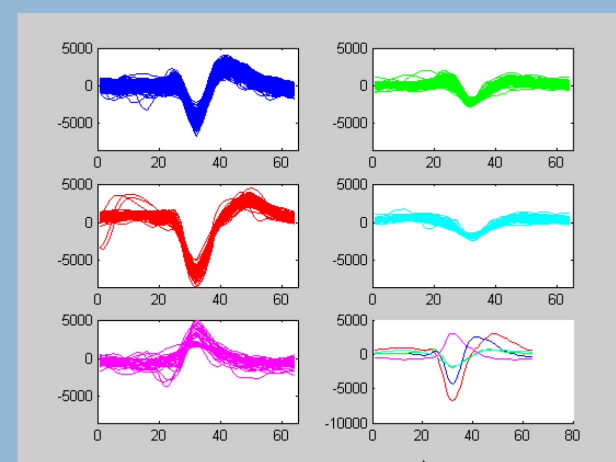
Example of final classification



Feature space



Spike wave forms

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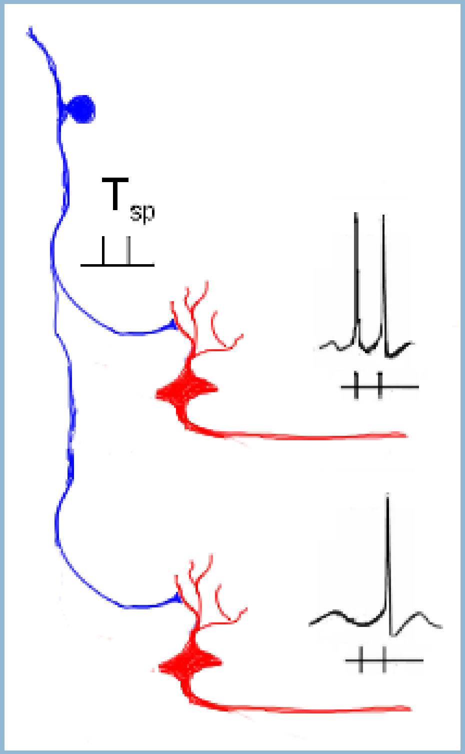
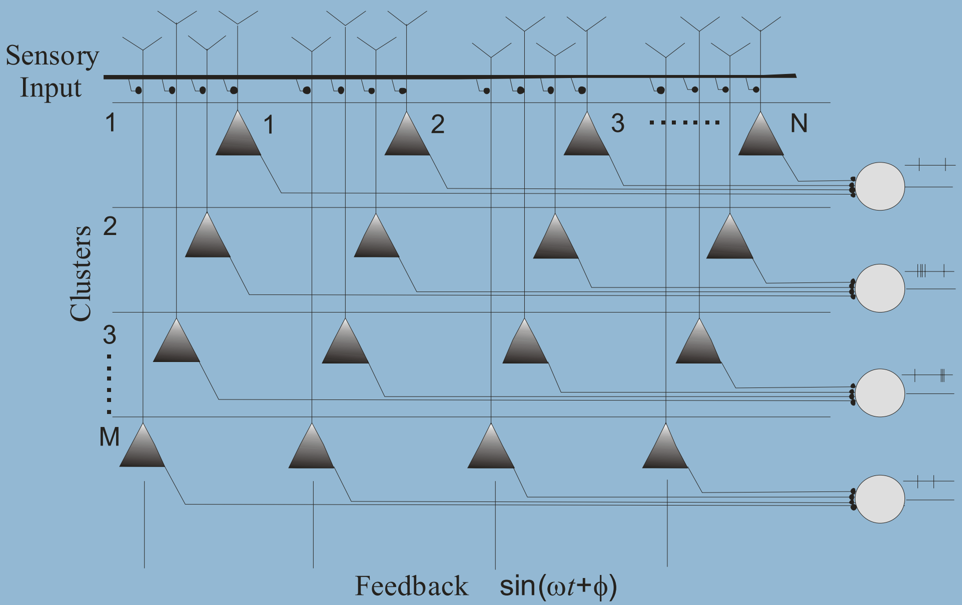
Mathematical modelling of neural networks

1. Role of subthreshold oscillations in the stimuli processing
2. Delay induced oscillatory phenomena (stability loss)



Network Organization



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Minimal number of neurons in a cluster $N = \frac{1}{f_m \tau_m}$

Optimal cluster frequency distribution: $f_m = \frac{(N+1)^m}{N(N-1)^{m-1}} F_{\min}$ (not linear!)

Condition for number of clusters: $\left(\frac{N+1}{N-1}\right)^M = \frac{F_{\max}}{F_{\min}}$

Example: For $F_{\min}$=5Hz, $F_{\max}$=15Hz, N=8 and M=7

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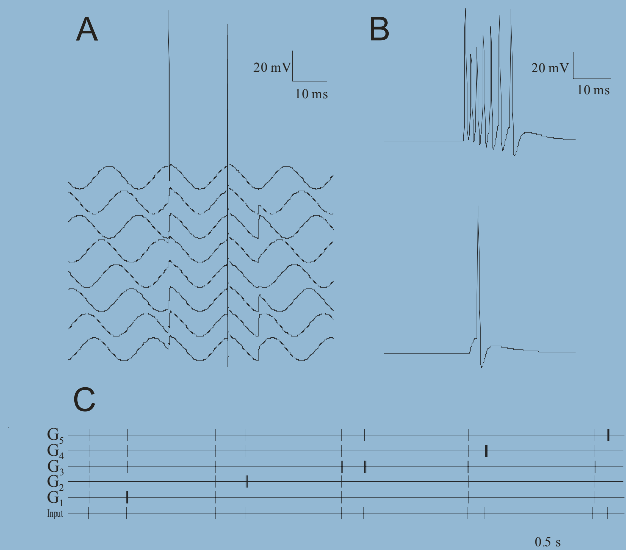
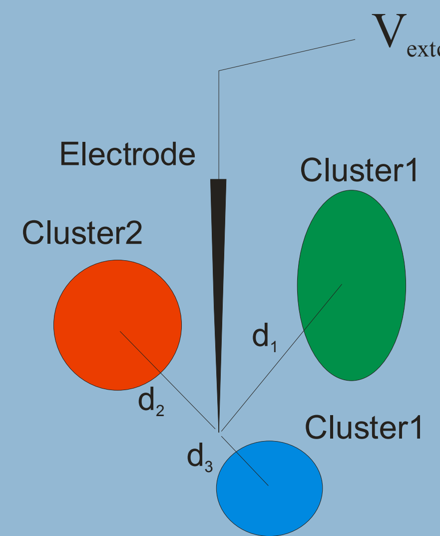
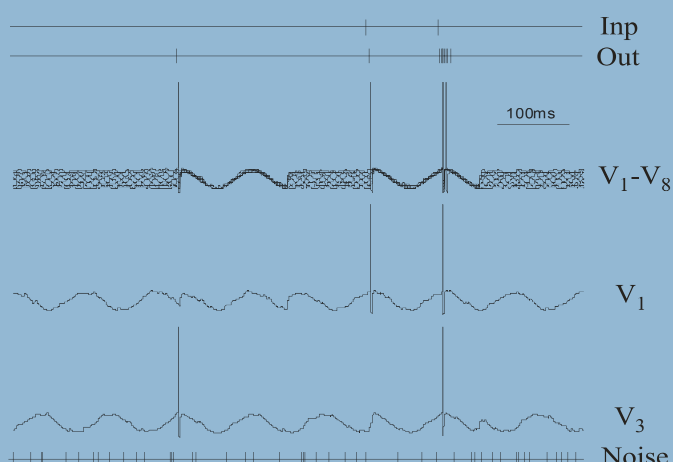
Network Response to stimulations with doublets

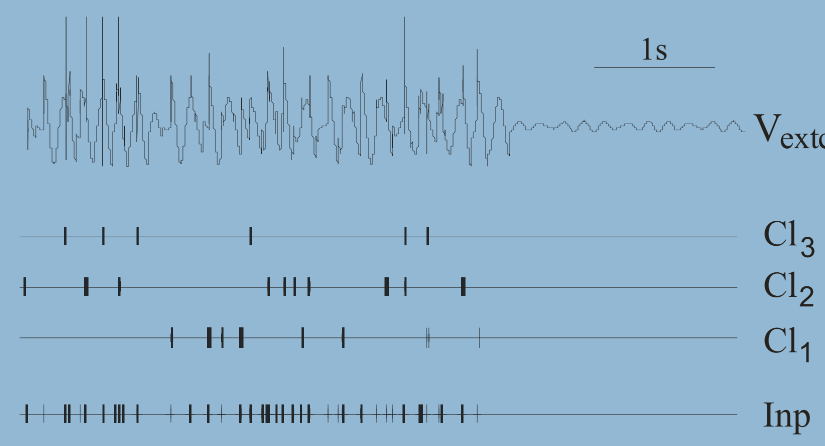


Synchronization of Extra-cellular activity



Robustness of interspike interval measurement





Oscillatory Phenomena and Stability of Periodic Solutions in a Simple Neural Network with Delay*

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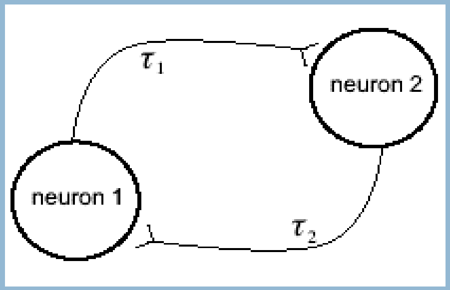
Delays occur:

1. In the signal transmission
2. In synaptic transmission

How does delay change the stability of neural network states?



$$\dot{u}_1(t) = -\mu_1 u_1(t) + aF(u_2(t-\tau_2))$$
$$\dot{u}_2(t) = -\mu_2 u_2(t) + bG(u_1(t-\tau_1))$$

Bifurcation parameters:

1. Global delay: $\tau = \tau_1 + \tau_2$

2. Composite coupling: $\nu = -abF'(0)G'(0)$

Positive sign - excitatory-inhibitory coupling
Negative sign - couplings of the same type

*J. Wei, M.G. Velarde, V.A. Makarov, Nonlinear Phenom. Complex Syst., 5:4 (2002) 407 - 417

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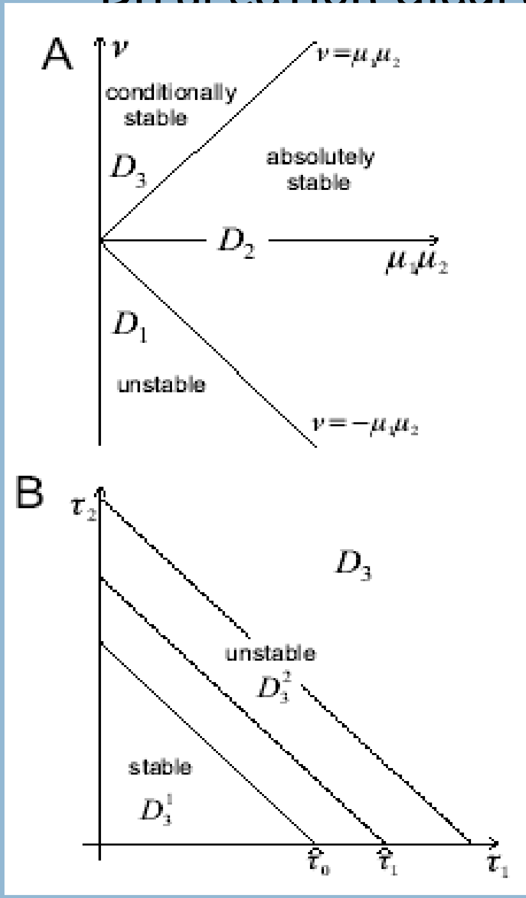
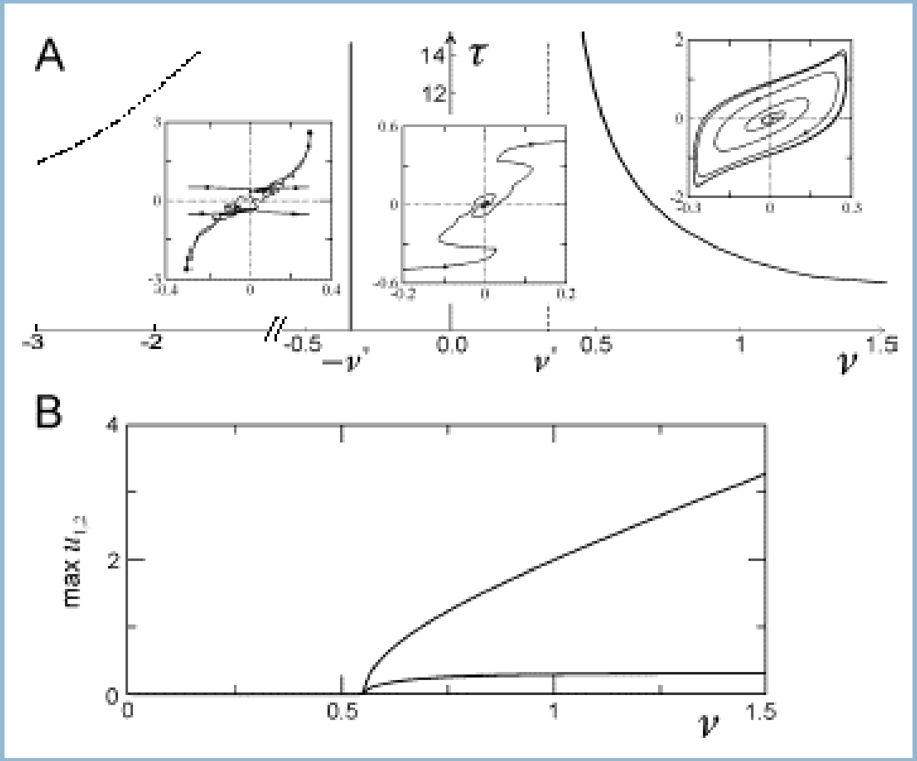
Bifurcation diagram



Global existence of periodic solutions



- Delays can change the stability of neural network states
- Delay can cause delay-controlled periodic behavior
- Only composite coupling and global delay affect the system
- Periodic solution appears when the delay is large enough
- Most radical changes can occur for the excitatory-inhibitory configuration

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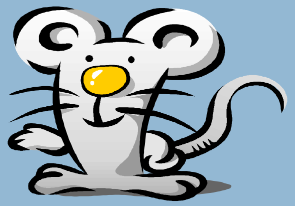

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