Sources and sinks on single neurons

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The source

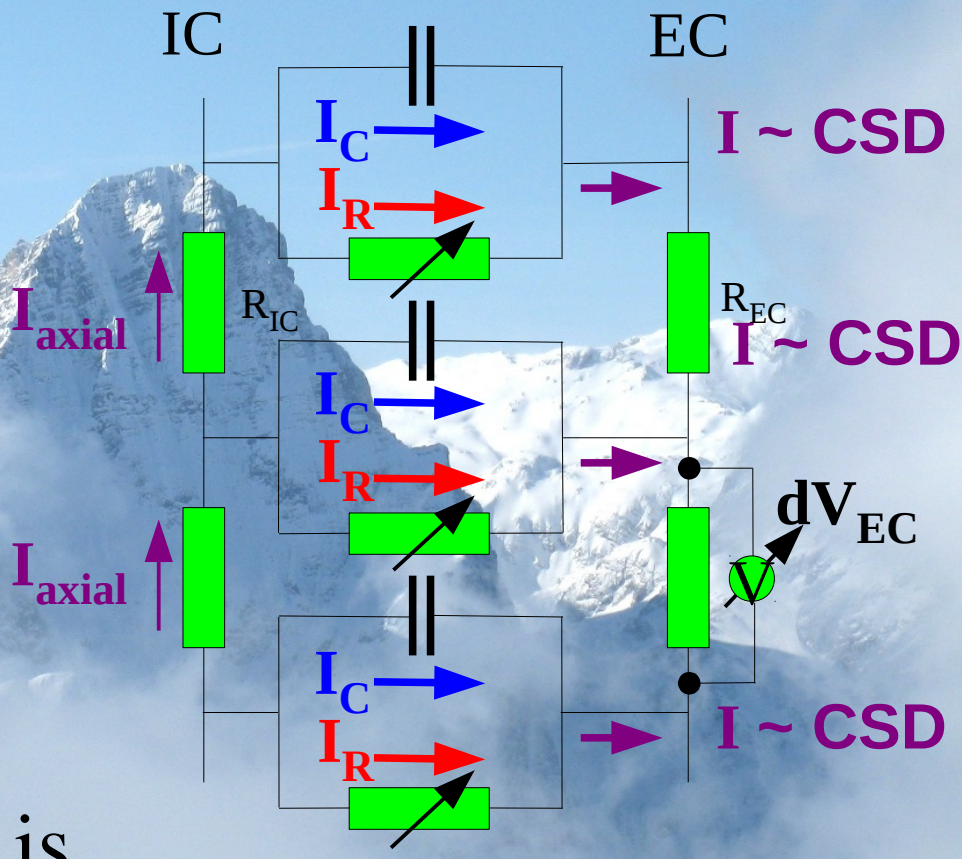
What is the source of the extracellular potential?

The membrane current!

Which membrane current?

$I(r, t) = I_R(r, t) + I_C(r, t)$

The source of the EC potential is the sum of the capacitive and resistive currents



The source

The capacitive current is:

$$I_C = C_m \frac{dV_m}{dt}$$

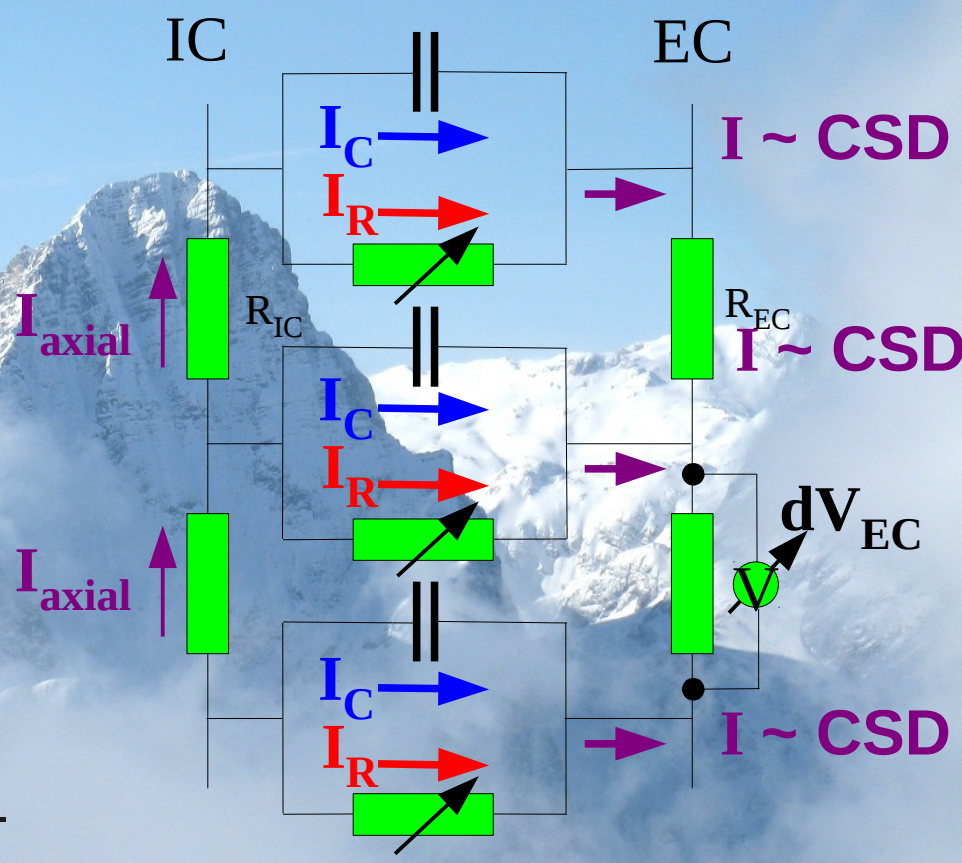
Substituting back :

$$C_m \frac{dV_m}{dt} = -I_R + I$$

Thus:

$$I = \frac{\partial I_{axial}}{\partial x} \approx \frac{\partial^2 V_m}{\partial x^2} \approx \frac{-\partial^2 V_{EC}}{\partial x^2}$$

Assuming sealed ends: $\sum I = 0$



The source

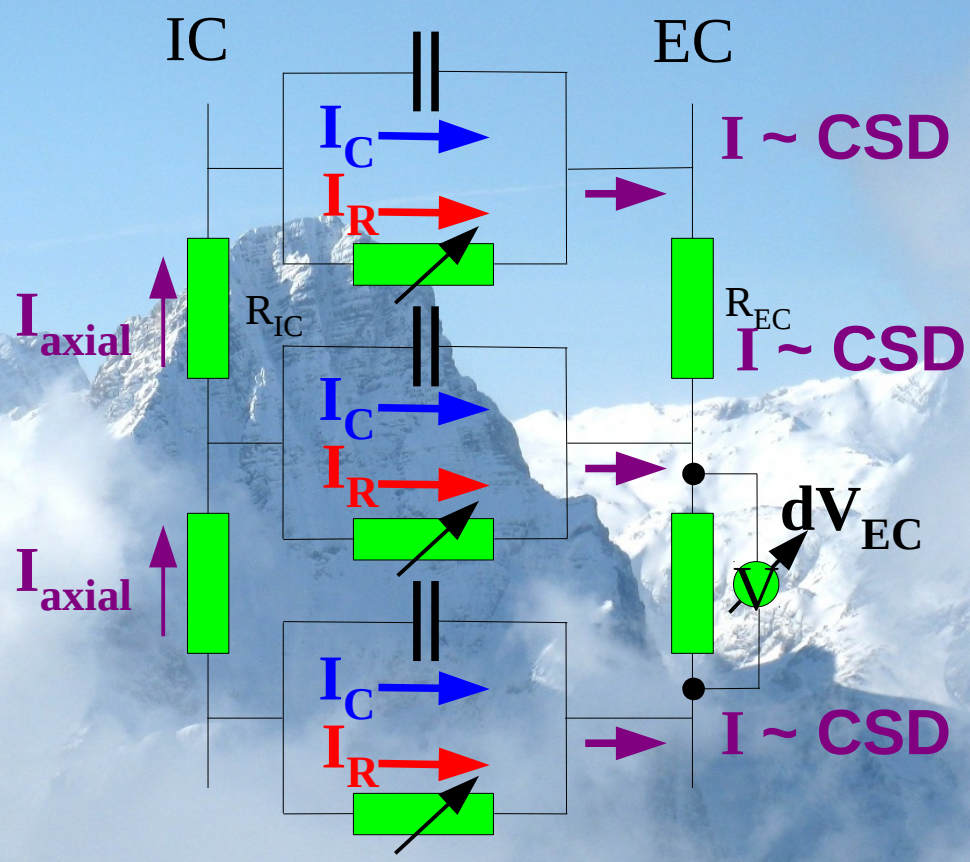
In voltage clamp:

$$C_m \frac{dV_m}{dt} = I_C = 0$$

Thus,

$$I = I_R$$

In voltage clamp, I_R is measurable, but the extracellular potential is generated by the net membrane current I not I_R



The sum of I_R is not zero, but the sum of I is zero for the whole cell!

The rule

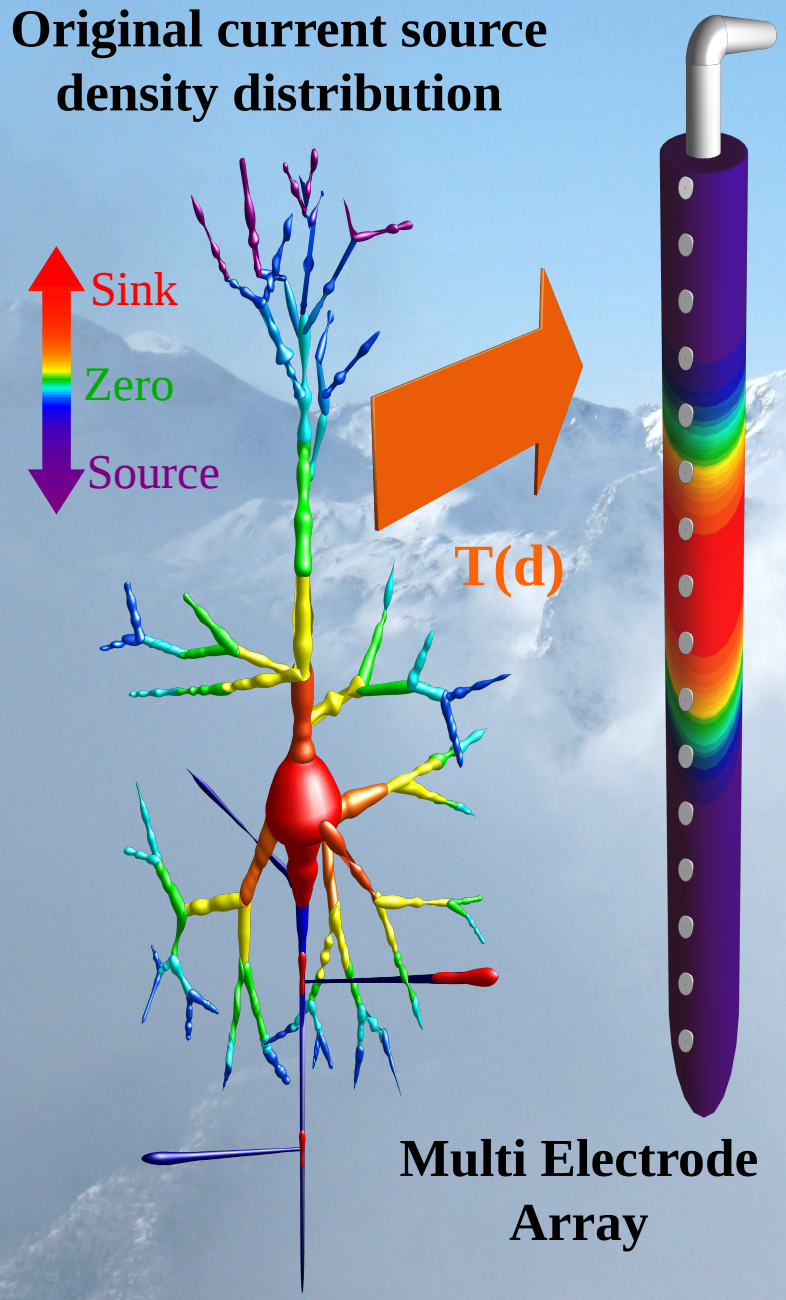
Generation of the extracellular potential patterns is governed by the Poisson equation:

$$\nabla^2 V(r) = \frac{\partial^2 V(r)}{\partial x^2} + \frac{\partial^2 V(r)}{\partial y^2} + \frac{\partial^2 V(r)}{\partial z^2} = \frac{-I(r)}{\sigma_e}$$

The forward problem:
Calculating *V* while *I* is known: modelling

The inverse problem:
Calculating *I* while *V* is known: analysis

The forward problem



The Green-function method provides the solution.
The discretised form:

$$V_i = \frac{1}{4\pi\sigma_e} \sum_{j=1}^{N} \frac{I_j}{|\boldsymbol{r}_i - \boldsymbol{r}_j|}$$

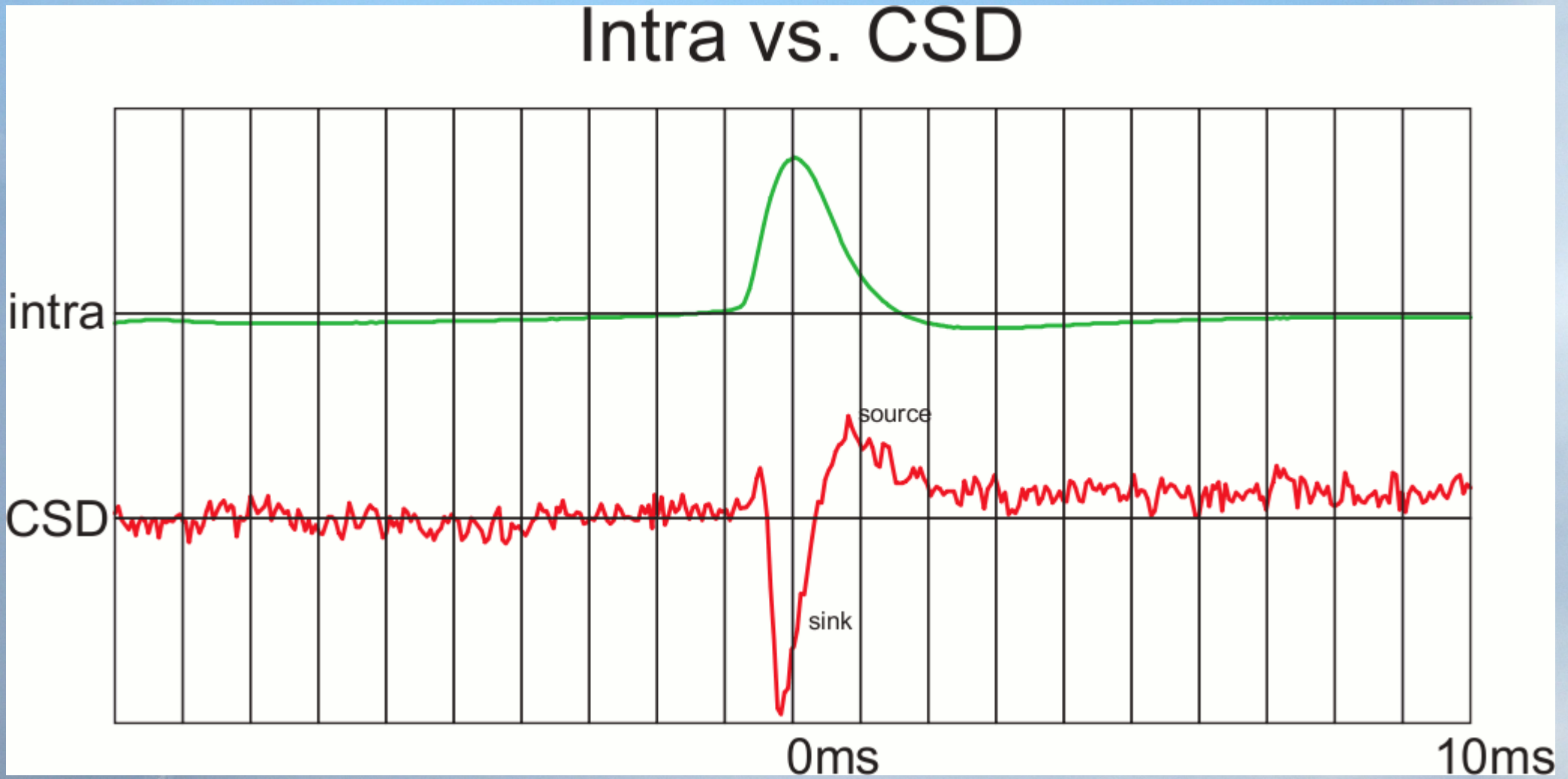
In matrix formalism:

$$V = \boldsymbol{T}\, I$$

In case of a linear probe and cell $\boldsymbol{T}$ can be calculated as:

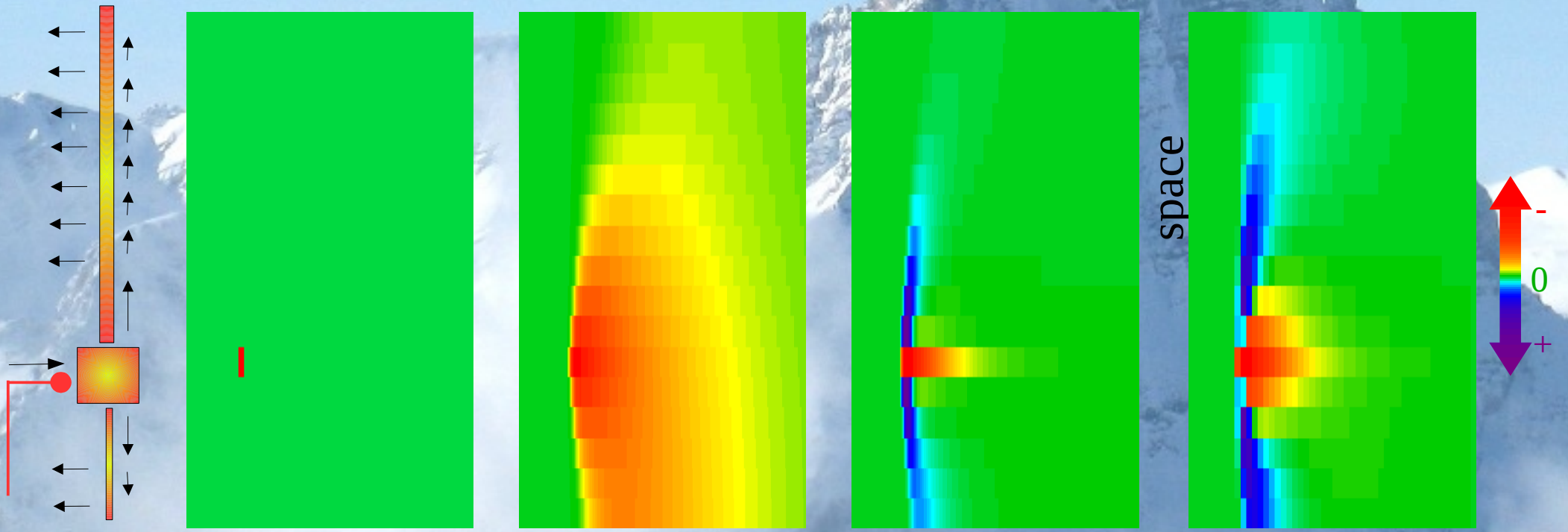
$$T_{ij} = \frac{1}{4\pi\sigma_e} \frac{1}{\sqrt{(x_i - x_j)^2 + d^2}}$$

Parallel EC and IC recordings in a hippocampal slice



Relation between EC and IC

Simulated spatio-temporal patterns, generated by a single synaptic pulse



I_R resistive membrane current

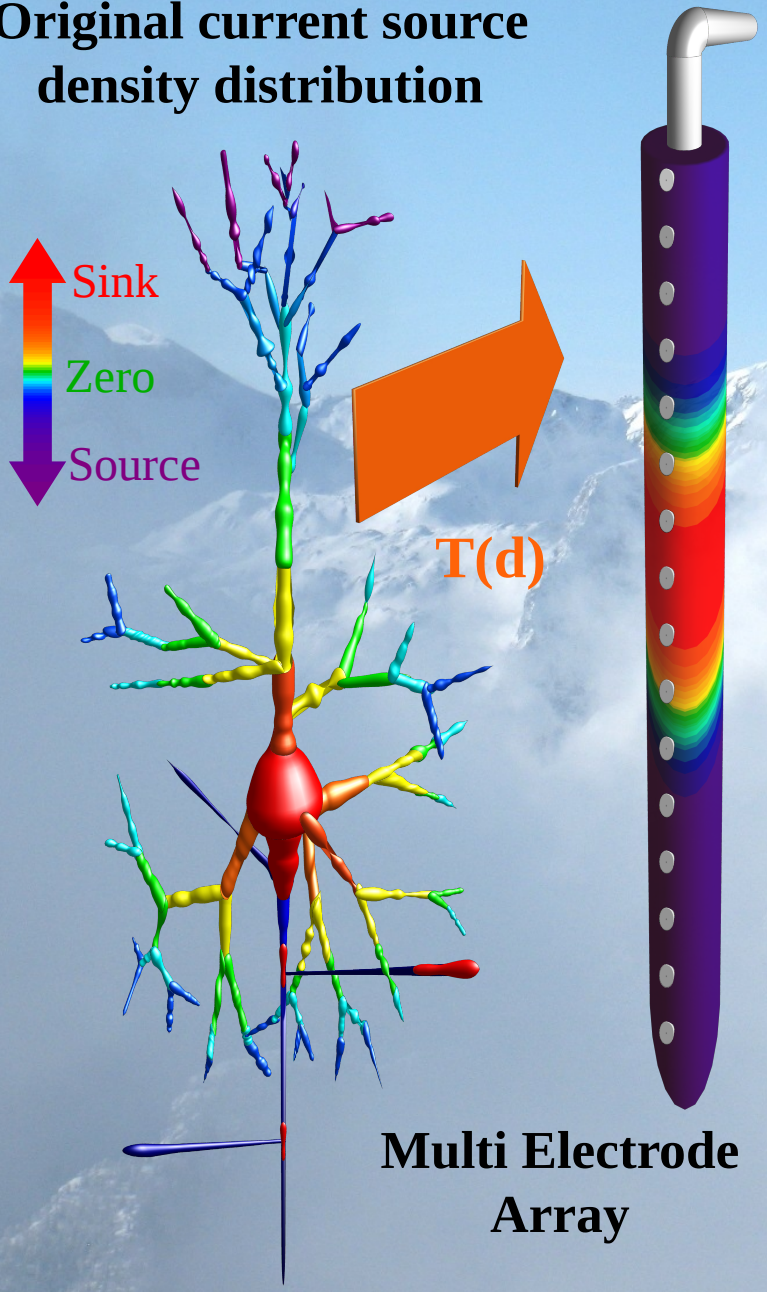
V_m membrane potential

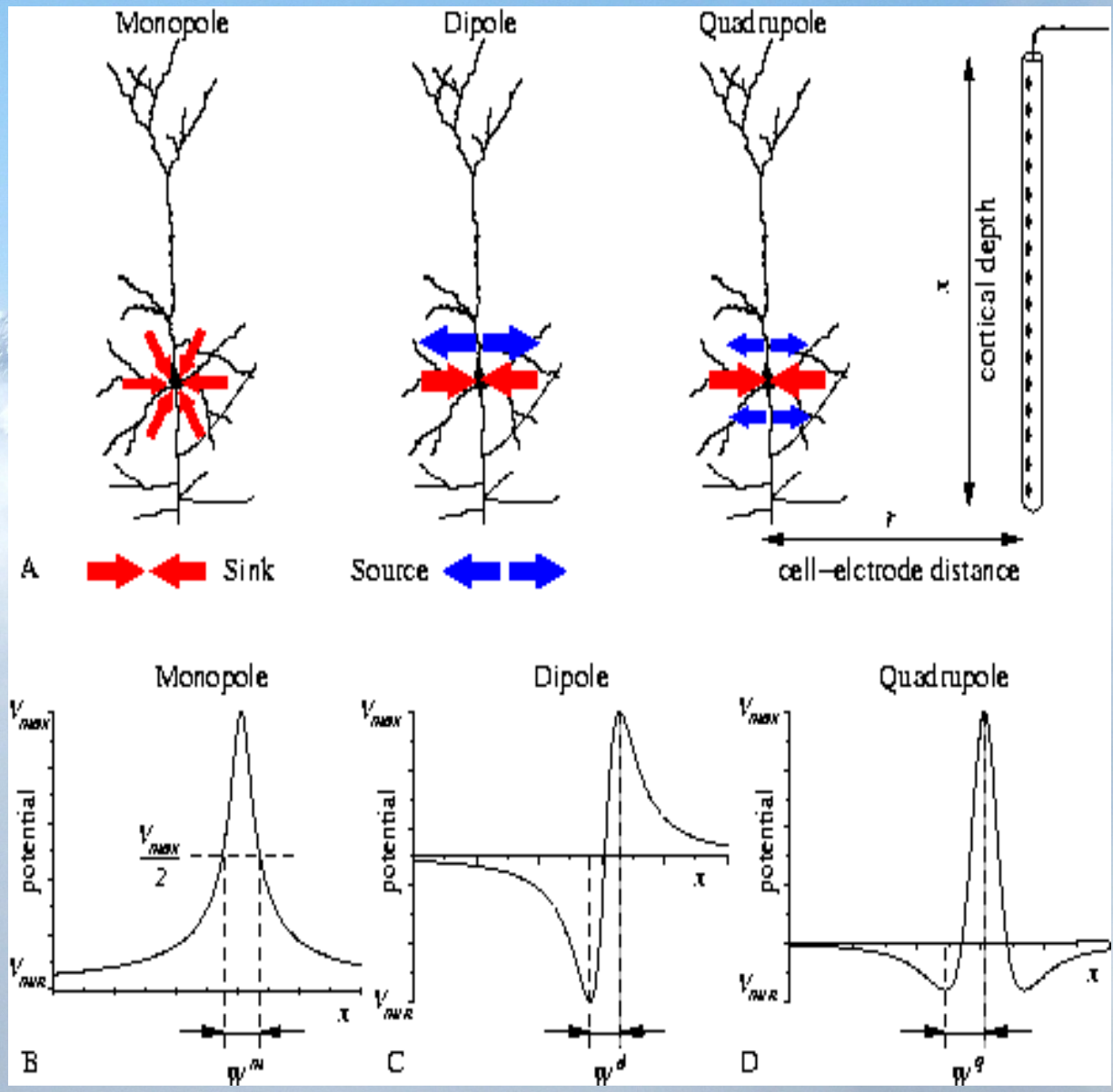
I_m net membrane current, CSD

V_{EC} extracellular potential

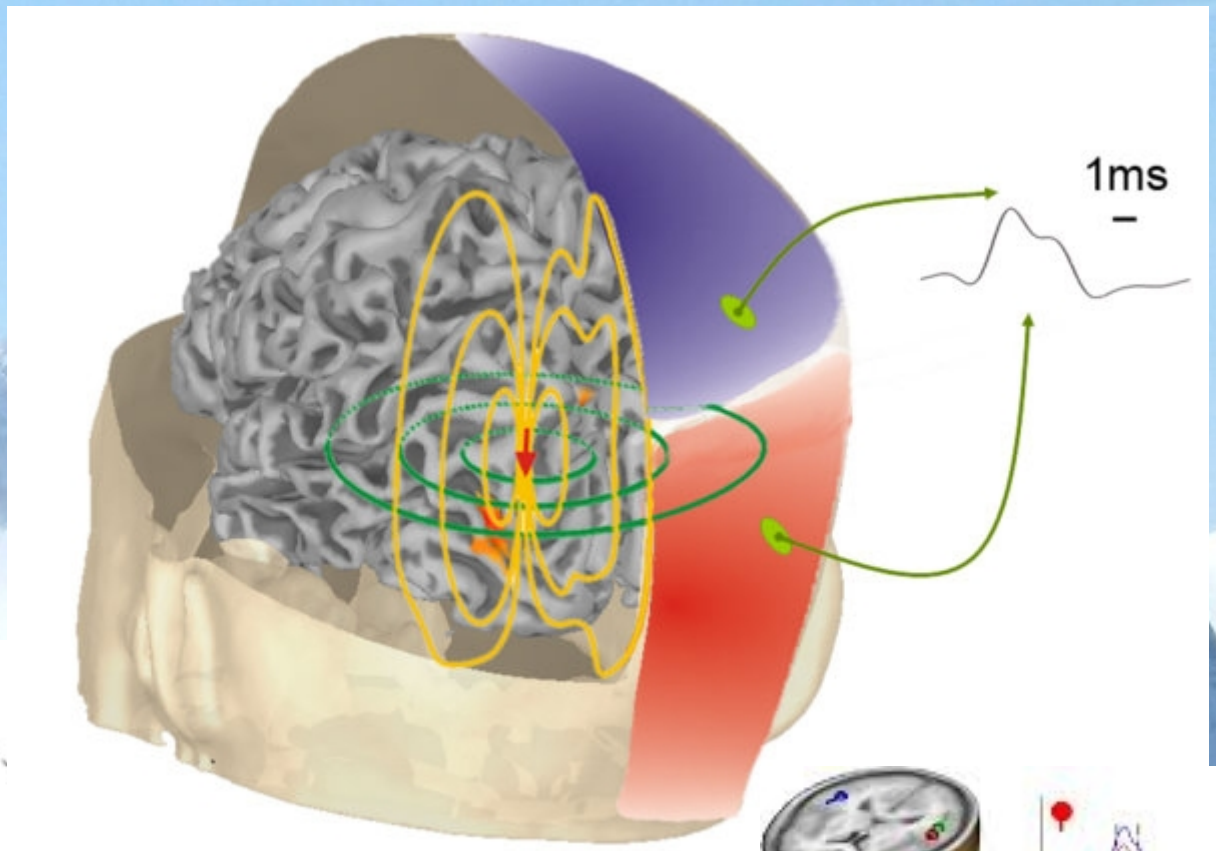
The forward problem

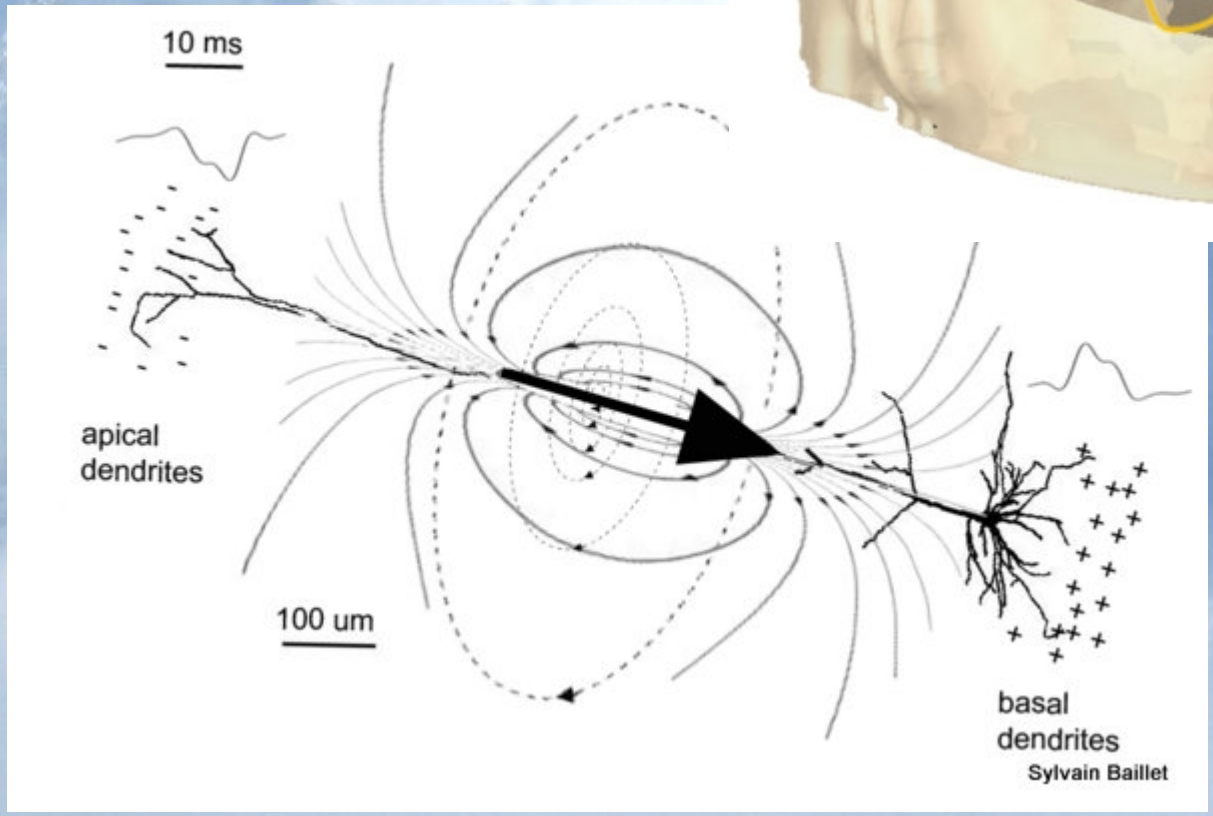
Original current source density distribution

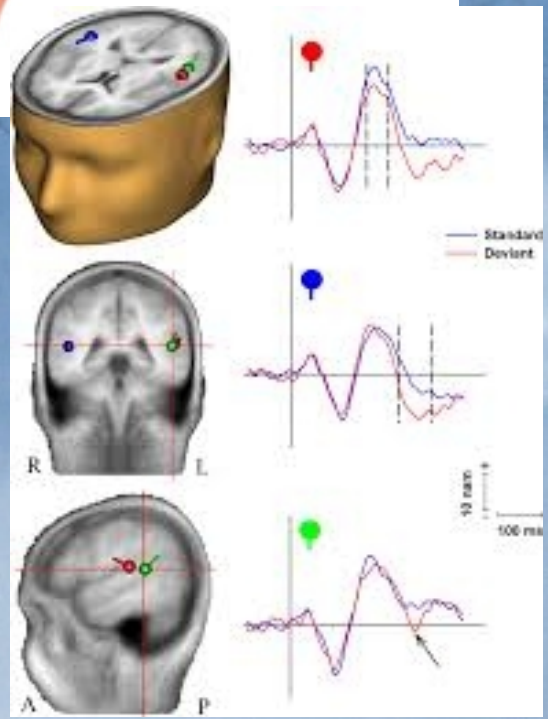




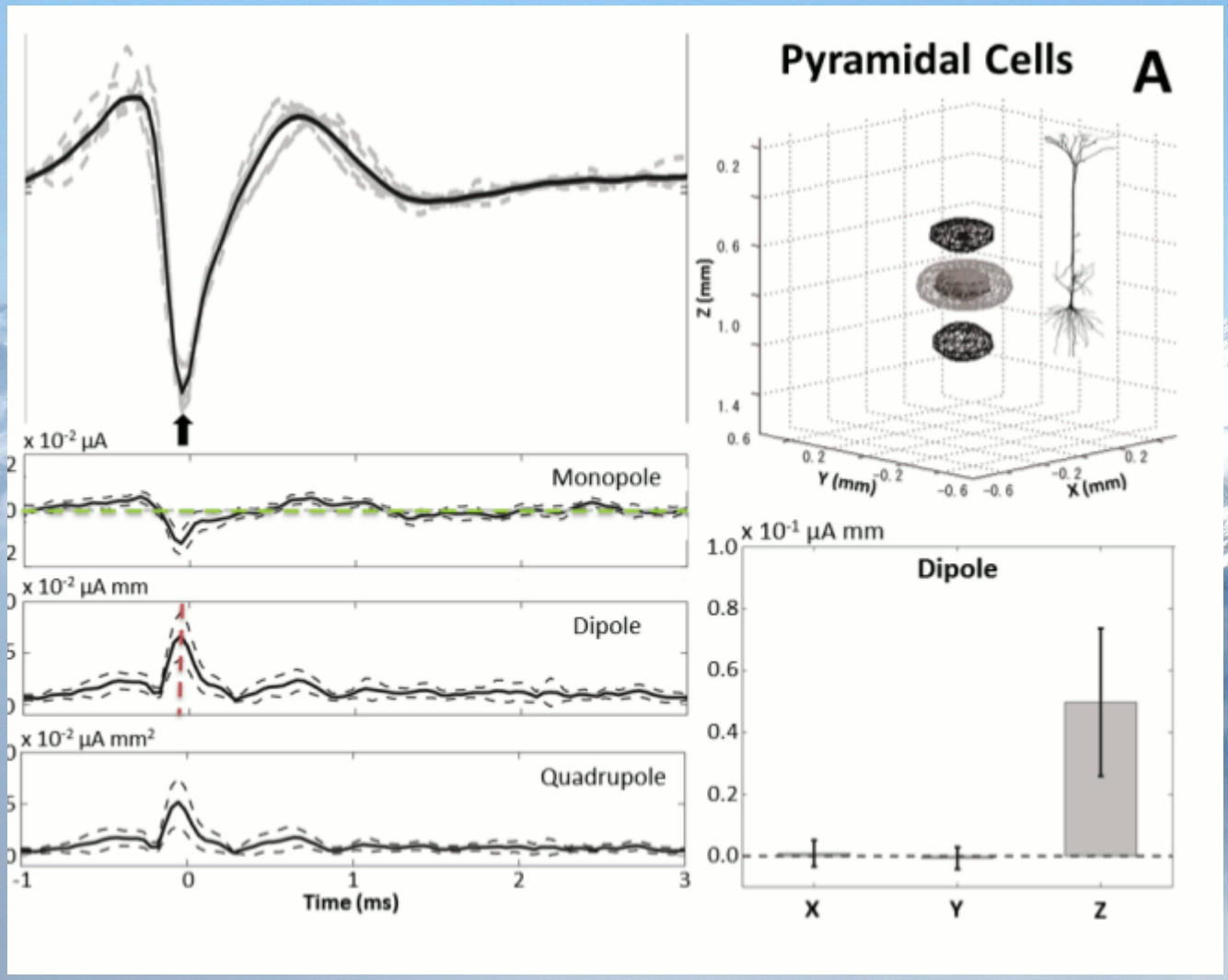
Equivalent dipole modeling







Are neural monopole currents are possible?



Riera et al.: Pitfalls in the dipolar model for the neocortical EEG sources, Journal of Neurophysiology, 108(4):956-75, 2012

The inverse problem

Determination of transmembrane currents, flowing on the neurons, based on the extracellular potential patterns.

$$\nabla^2 V(r) = \frac{\partial^2 V(r)}{\partial x^2} + \frac{\partial^2 V(r)}{\partial y^2} + \frac{\partial^2 V(r)}{\partial z^2} = \frac{-I(r)}{\sigma_e}$$

This requires the solution of the Poisson inverse problem. In order to perform the second derivation, the full 3D potential distribution should be known, with spatial resolution comparable to the size of the sources.

The inverse problem

The 3D potential distribution can not be measured, since a 3D electrode array would cause significant tissue damage.

Without this, the inverse solution is not unique!

What could be done?

Based on a priory knowledge about the source, the proper solution could be chosen among the infinitely many possible ones.

The traditional CSD method

Discretising and neglecting the derivatives in the unknown dimensions leads to the traditional CSD method:

$$I_i = \frac{-V_{i+1} + 2V_i - V_{i-1}}{dx^2 \sigma_e}$$

Implicitly we assumed, that the orthogonal derivatives are negligible, i.e. there are large homogeneous laminar sources.

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Micro-electro imaging: Determination of cortical and synaptic layers and synaptic dynamics based on extracellular multi-electrode potential measurements

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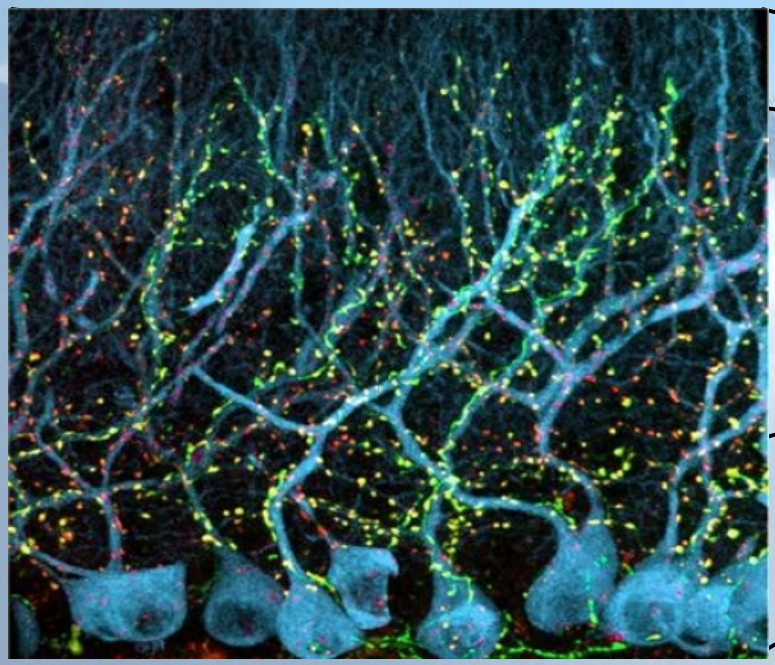
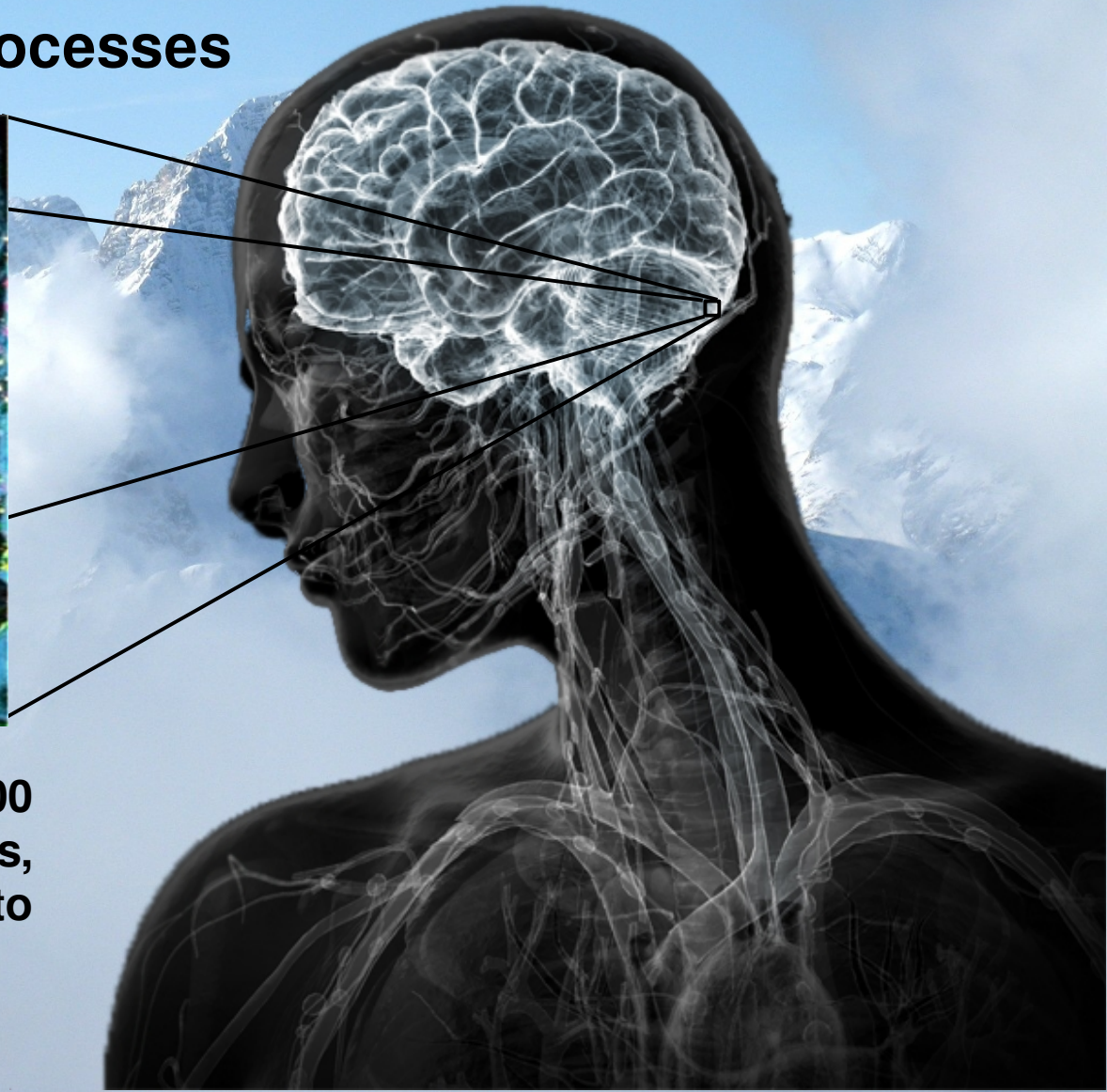
Micro-electro imaging

The gray mater of the brain

Dense tissue of the neural processes



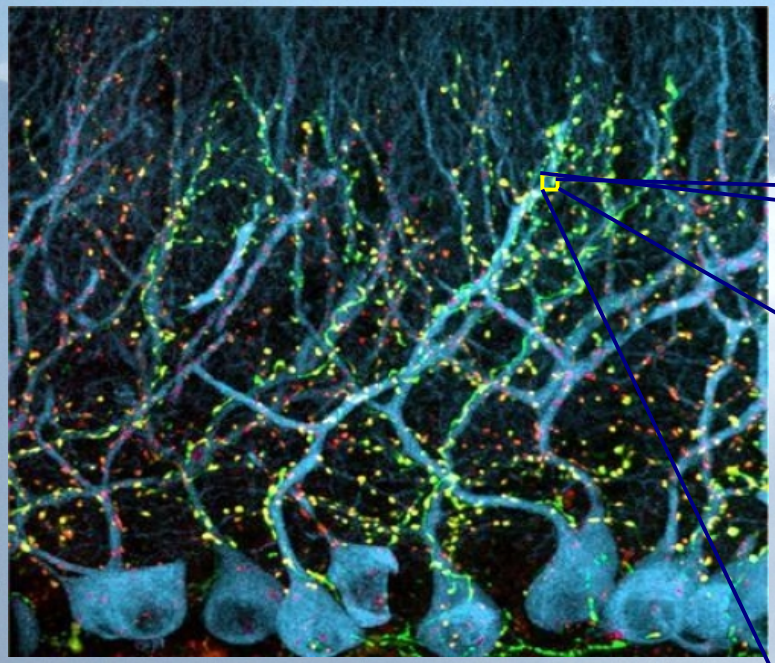


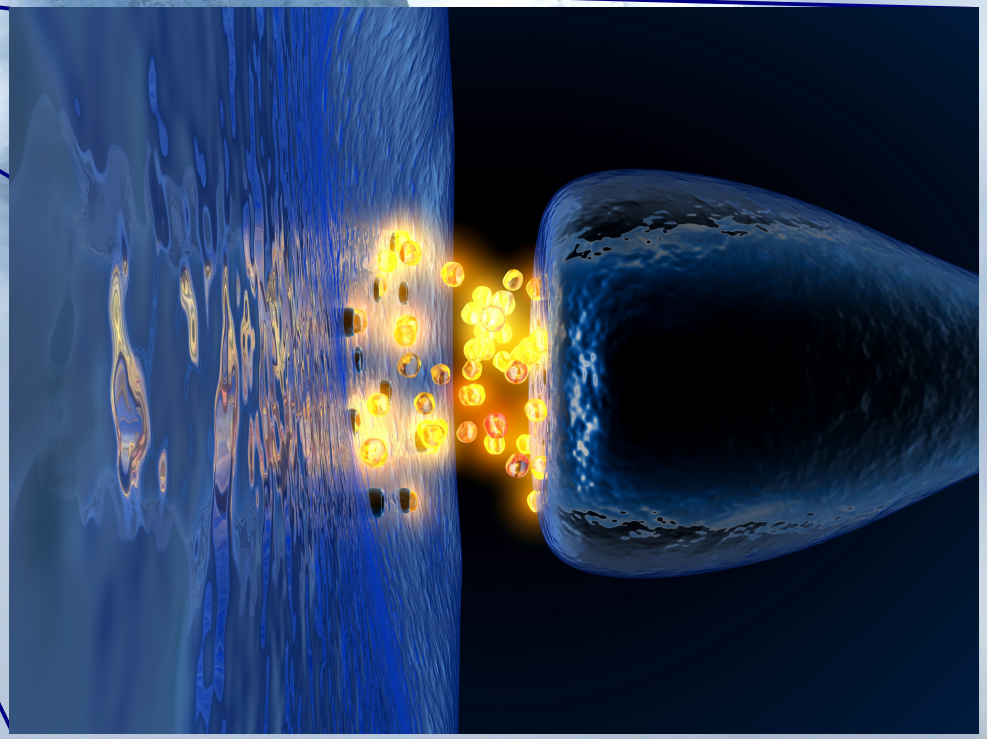
An average neuron receives 15000 input synapses from other neurons, but in some cases it grows up to 500000.

Micro-electro imaging

Synapse: communications between neurons

Opening of the ion channels due to binding of the neurotransmitter molecules initiates a wave of currents on the membrane.

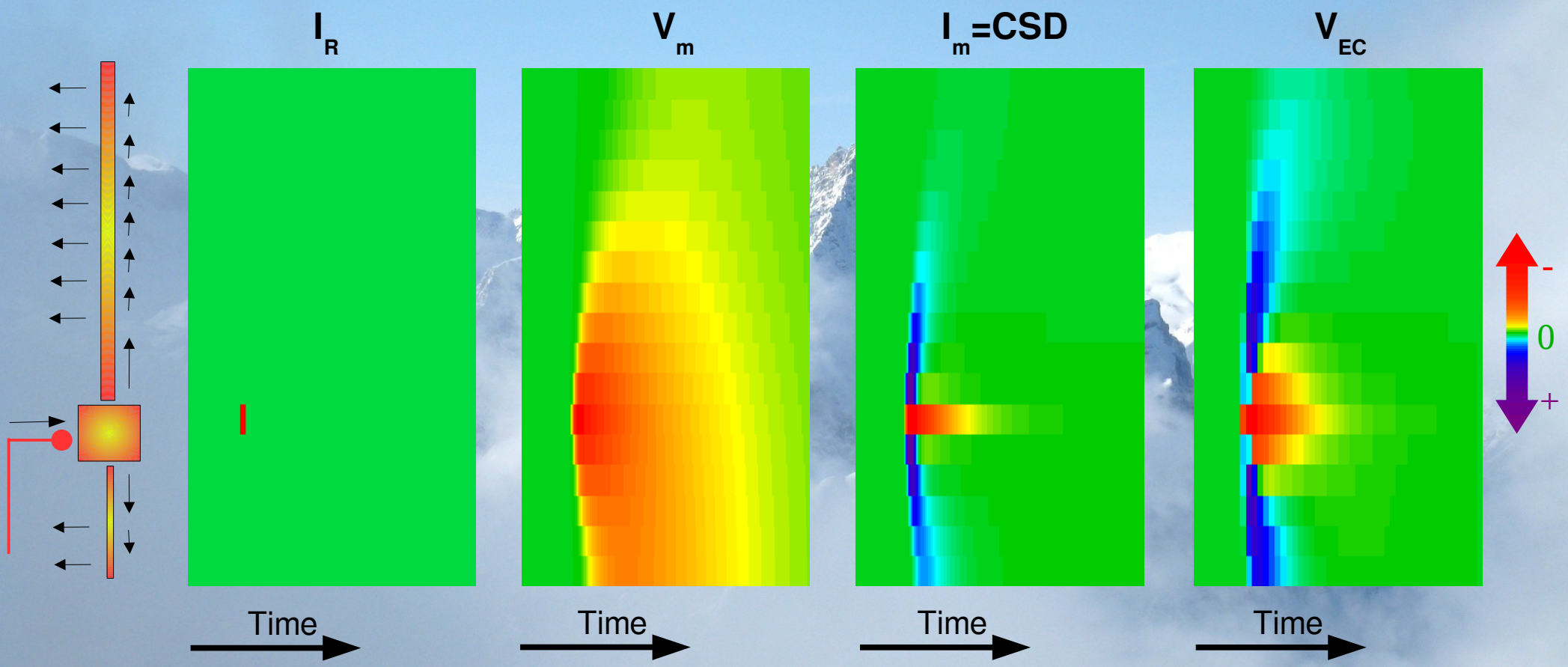




An average neuron receives 15000 input synapses from other neurons, but in some cases it grows up to 500000.

Micro-electro imaging

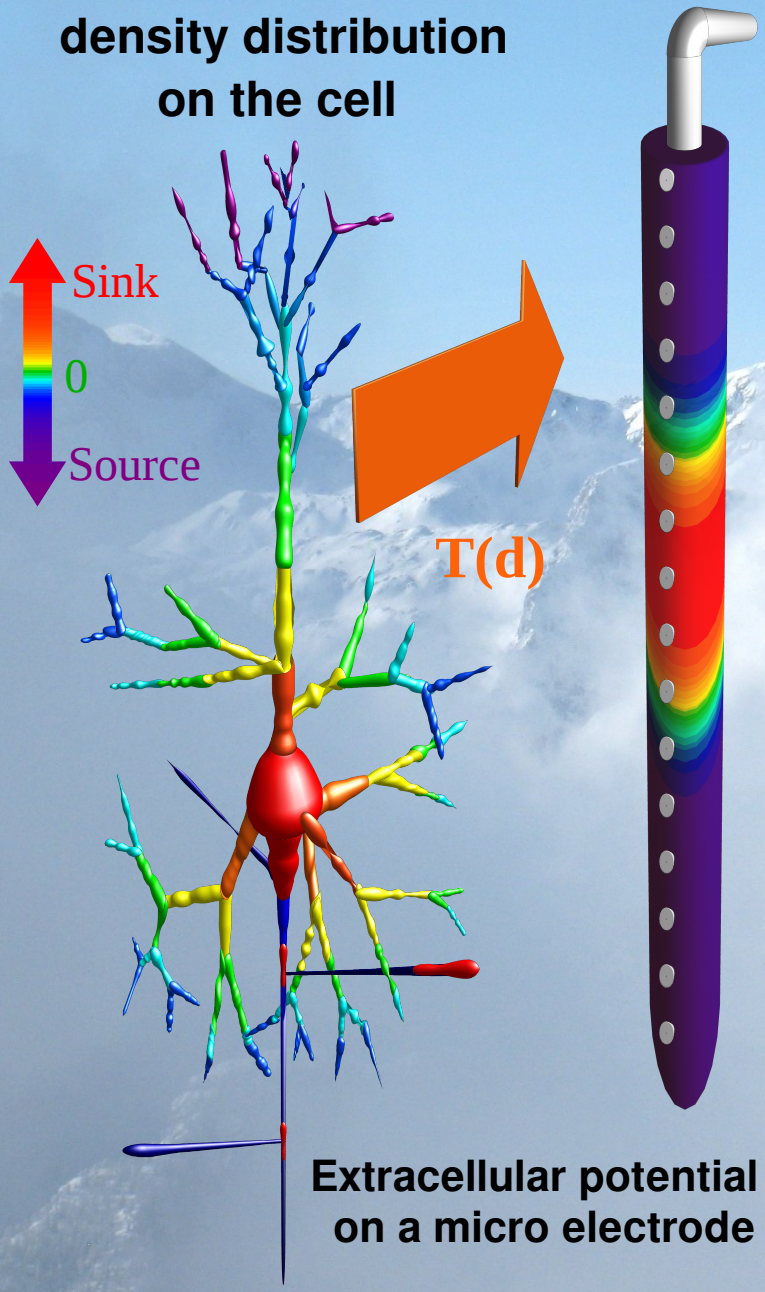
A single simulated synaptic pulse



Even a single current pulse into the simulated neuron generates quite complex spatio-temporal pattern of extracellular potential

Micro-electro imaging

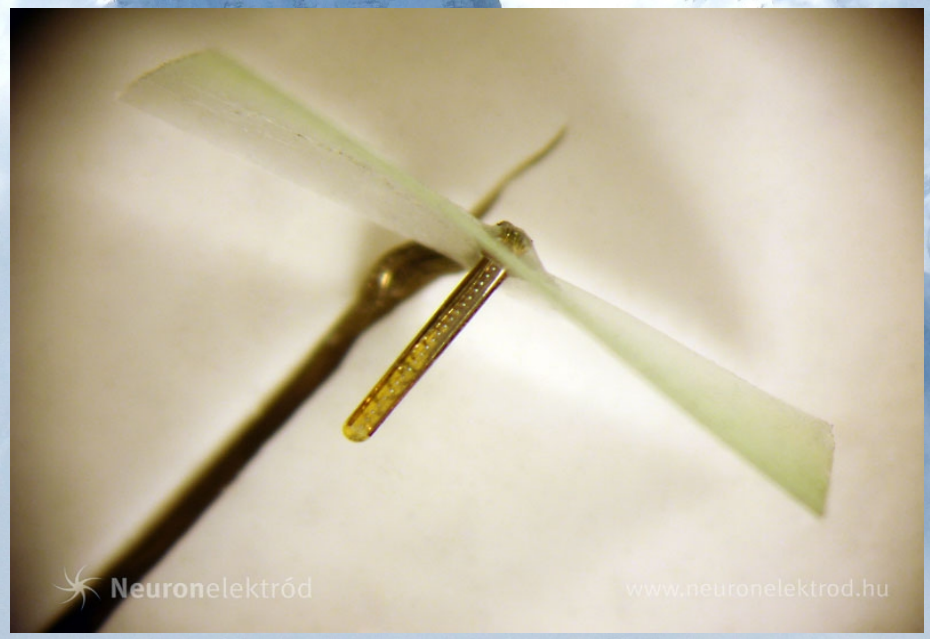
Current source density distribution on the cell



Extracellular potential pattern on a micro electrode array

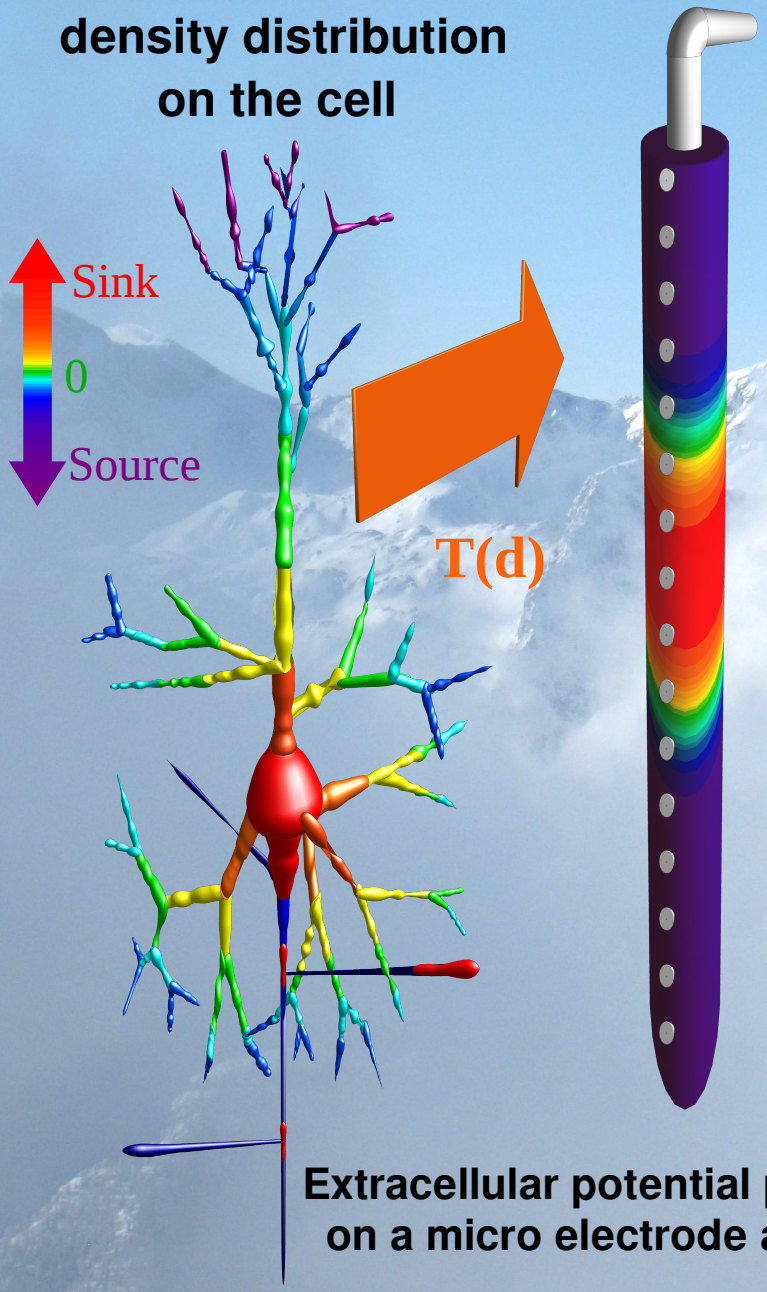
Micro electrode arrays

By chronically implanted micro electrode arrays, the EC potential of the neurons can be monitored during awake behaving animals.



Micro-electro imaging

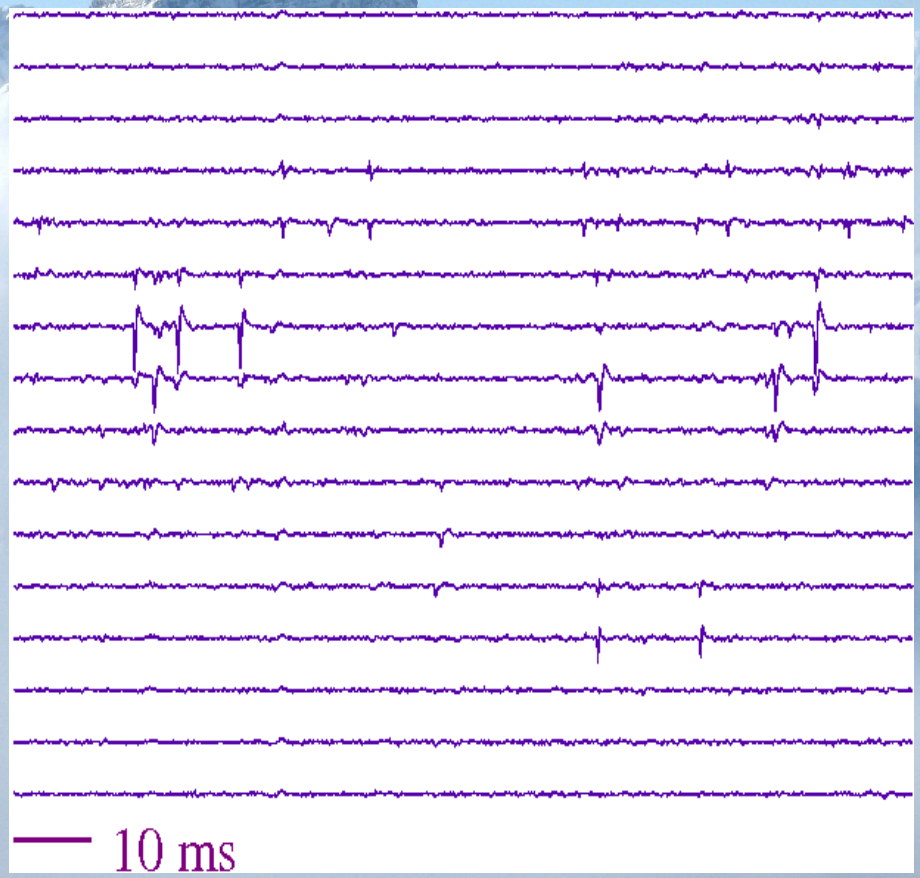
Current source density distribution on the cell



Extracellular potential pattern on a micro electrode array

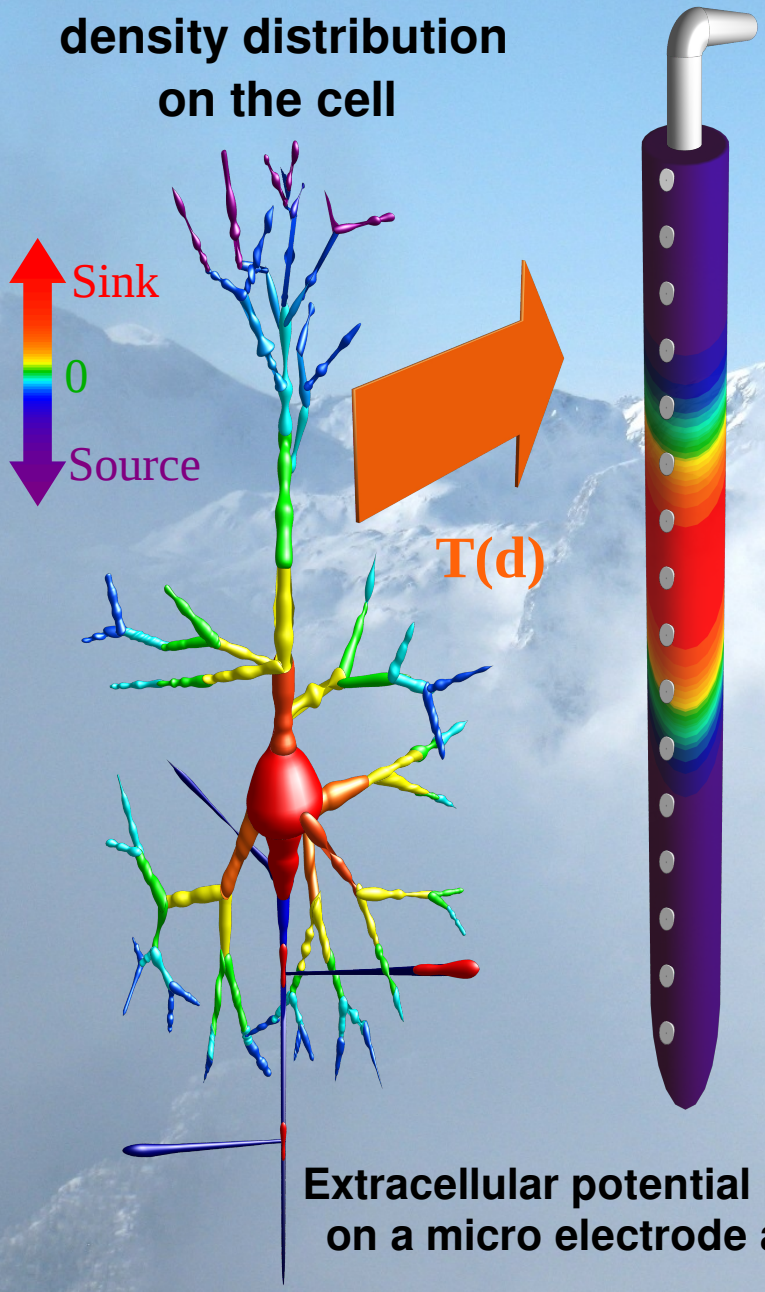
The output of the neurons

The EC potentials of the individual neurons are easily recognizable on the high pass filtered recordings, representing the output of the neurons.



Micro-electro imaging

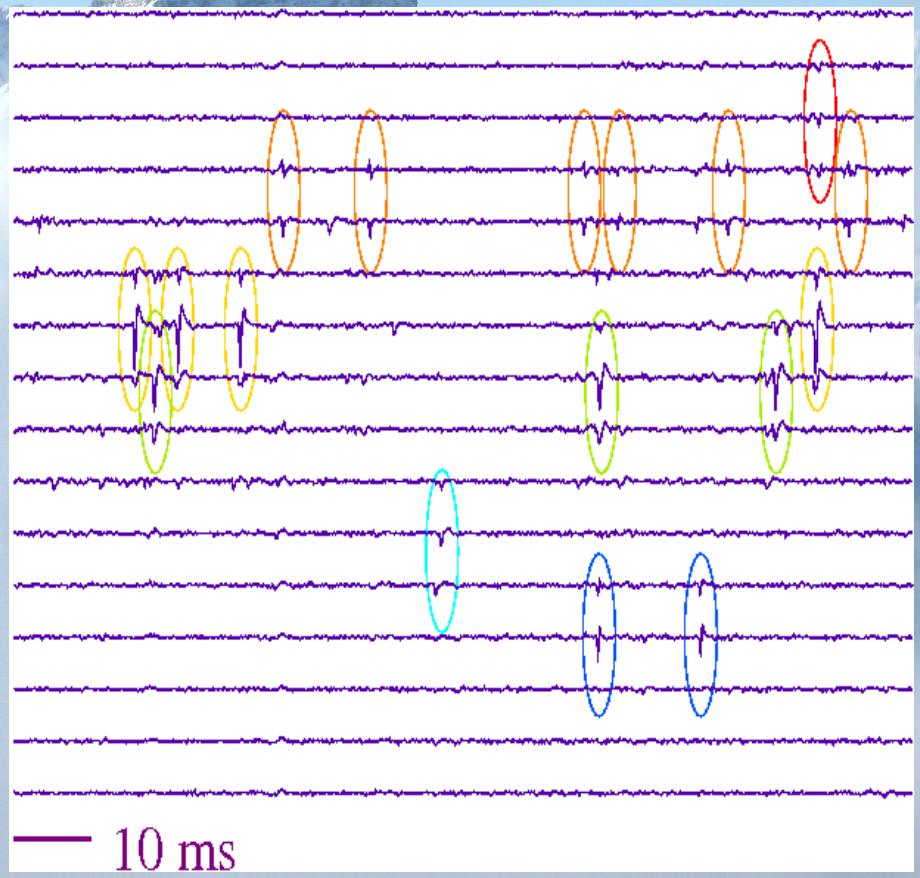
Current source density distribution on the cell



Extracellular potential pattern on a micro electrode array

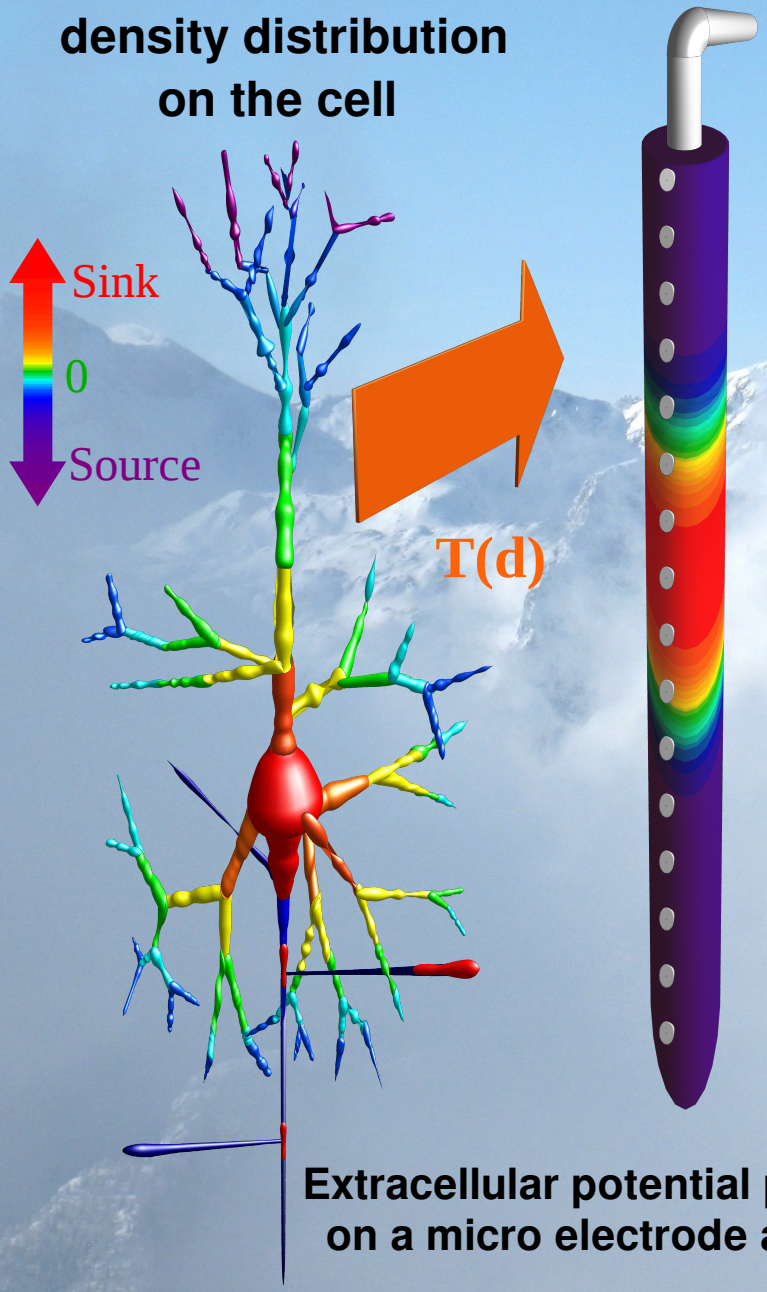
The output of the neurons

The spikes of the individual neurons can be distinguished based on the different signal form and relative amplitudes.



Micro-electro imaging

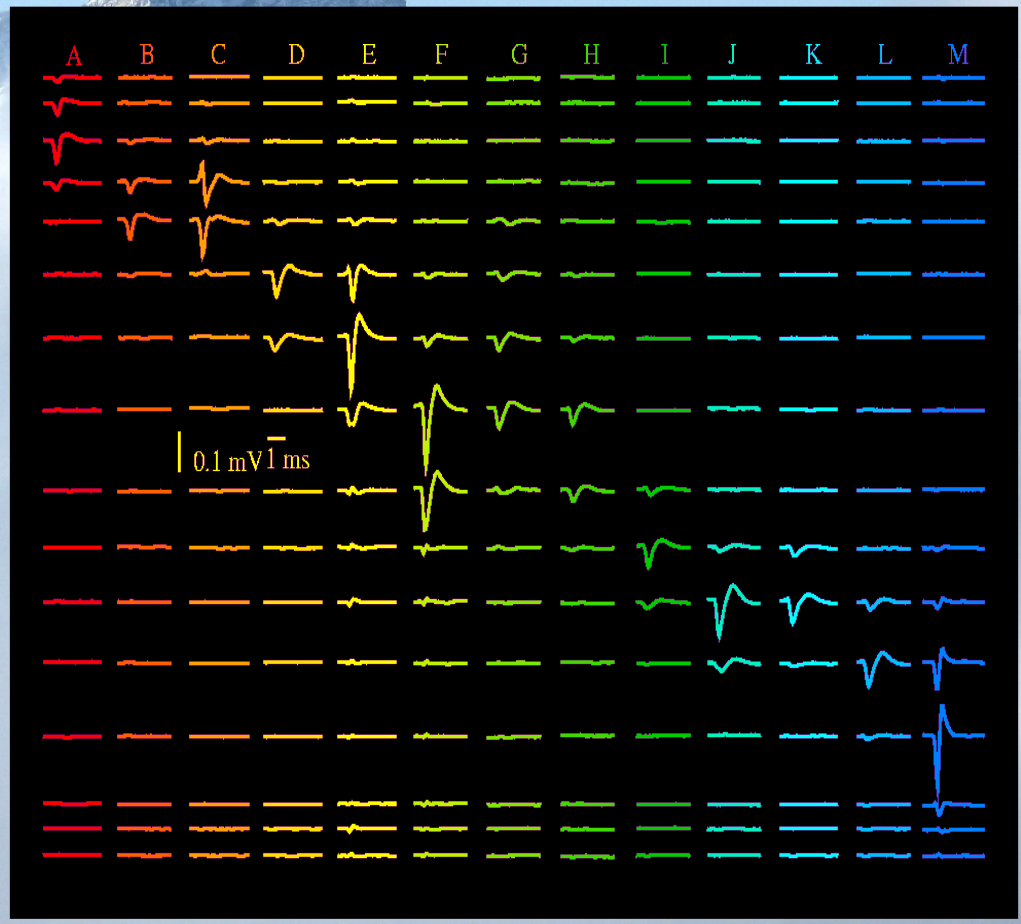
Current source density distribution on the cell



Extracellular potential pattern on a micro electrode array

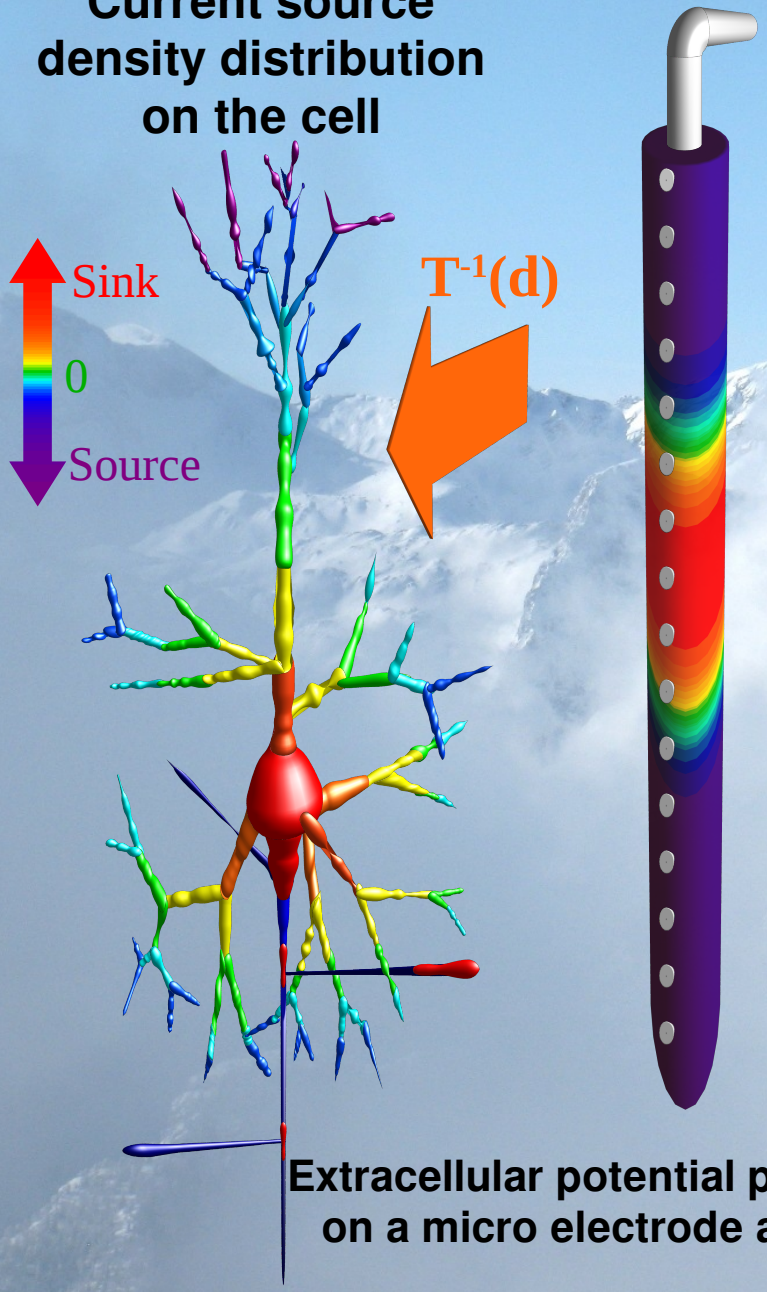
The output of the neurons

Each neuron generates a specific spatio temporal potential pattern (marked with different colors)



Micro-electro imaging

Current source density distribution on the cell



Extracellular potential pattern on a micro electrode array

The problem

The dendritic integration is relatively well understood.

It is possible to measure and identify the output of the individual neurons.

BUT

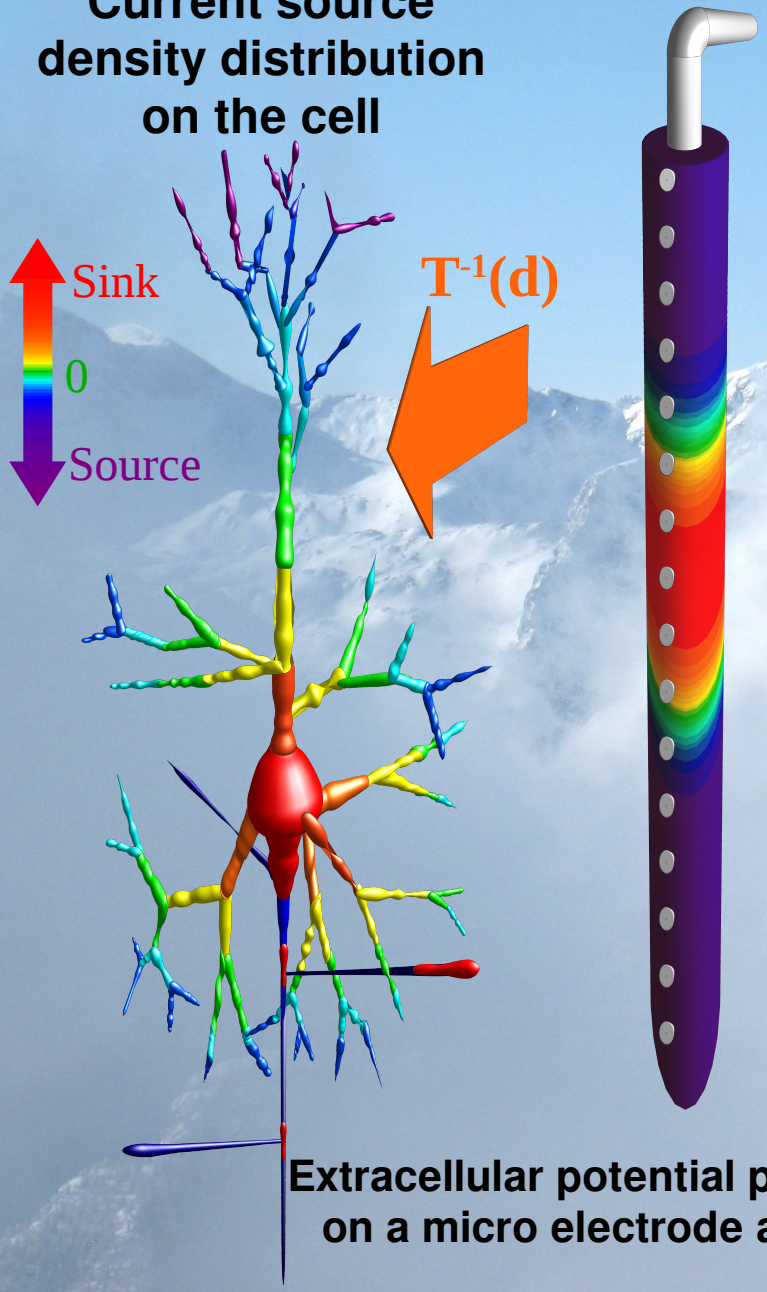
We have no clue of that what spatio temporal synaptic current pattern emerges on the dendrites from the integration of enormous number synaptic input impulses.

There is no proper measuring technique!

Without knowing the inputs, understanding the elementary computation performed by individual synapses is hopeless.

Micro-electro imaging

Current source density distribution on the cell



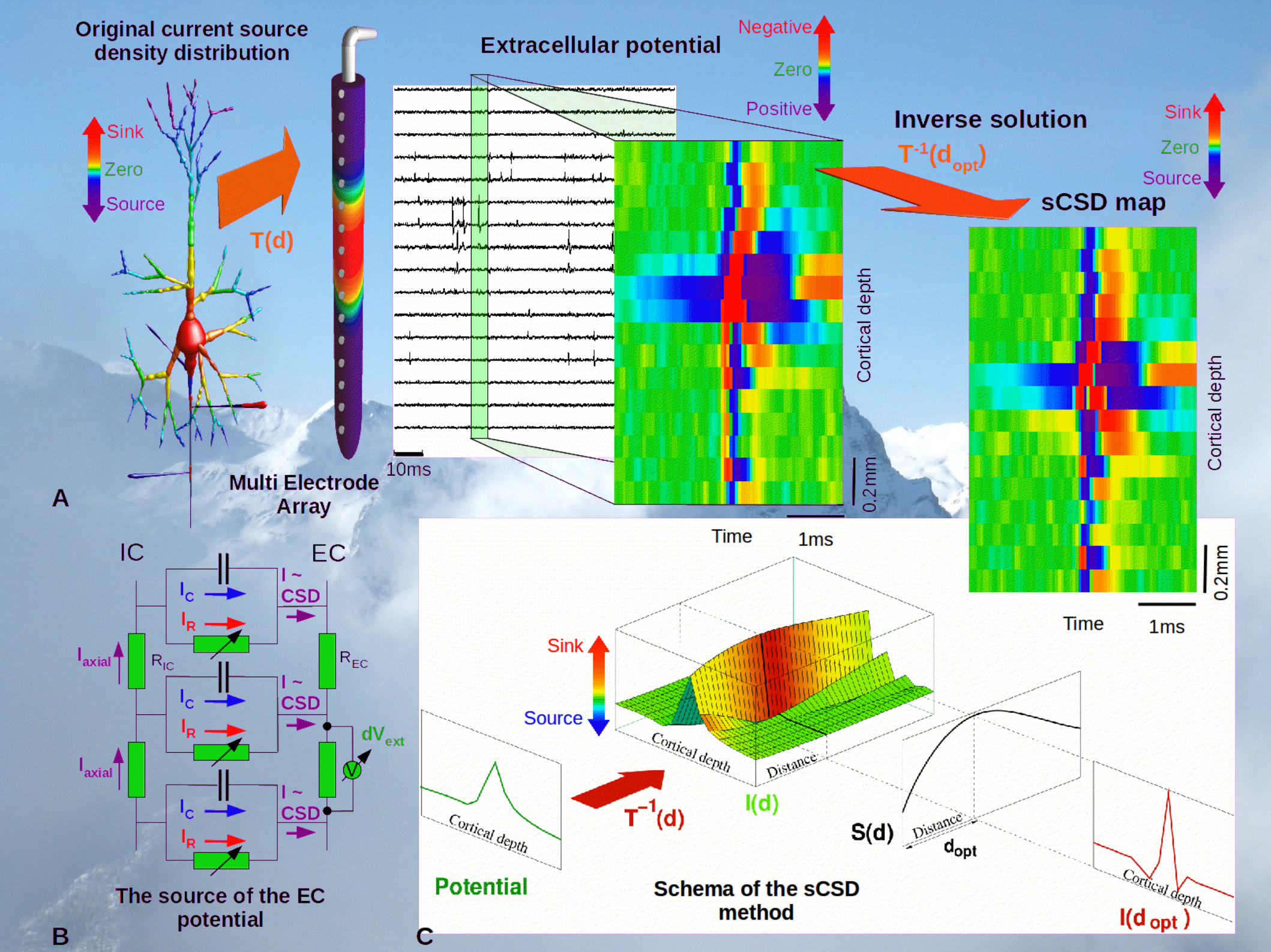
Extracellular potential pattern on a micro electrode array

The idea

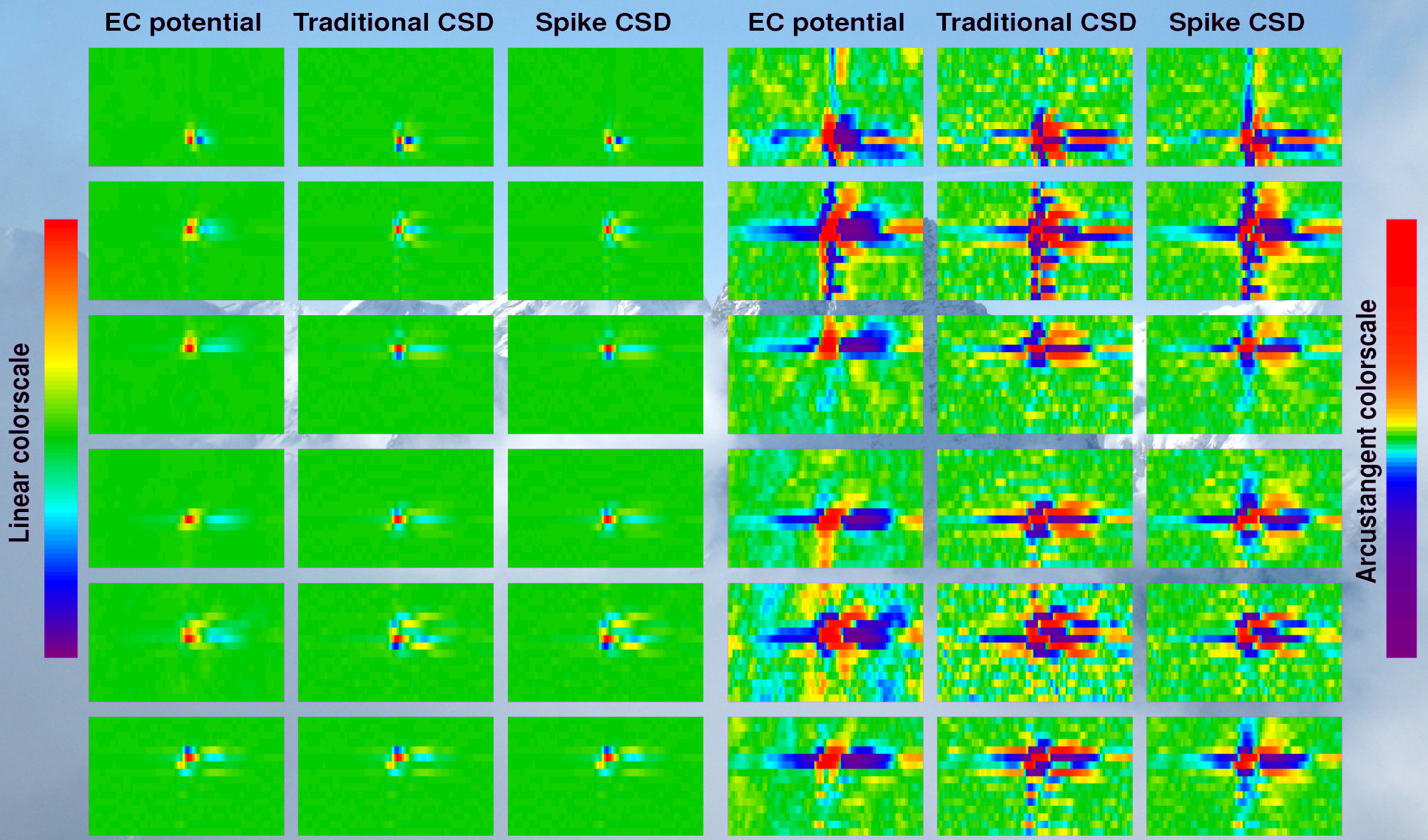
Source reconstruction by inverse methods: Inverse solution of the Poisson-equation under special constrains which incorporates our a priori knowledge to the solution and makes it unique.

'Autofocus' algorithm for position estimation of the neurons

Analogous to the ultra resolution microscopy, where objects can be resolved beyond the Nyquist limit


Original current source density distribution
Sink
Zero
Source
T(d)
Multi Electrode Array
A
Extracellular potential
Negative
Zero
Positive
10ms
Cortical depth
0.2mm
Inverse solution
$T^{-1}(d_{opt})$
Sink
Zero
Source
sCSD map
Cortical depth
0.2mm
Time
1ms
IC
EC
I_C
I_R
I ~ CSD
I_{axial}
R_{IC}
R_{EC}
dV_{ext}
The source of the EC potential
B
Time
1ms
Sink
Source
Cortical depth
Distance
I(d)
$T^{-1}(d)$
Potential
S(d)
Distance
d_{opt}
Cortical depth
$I(d_{opt})$
Schema of the sCSD method
C

What is essential, is invisible to the eye

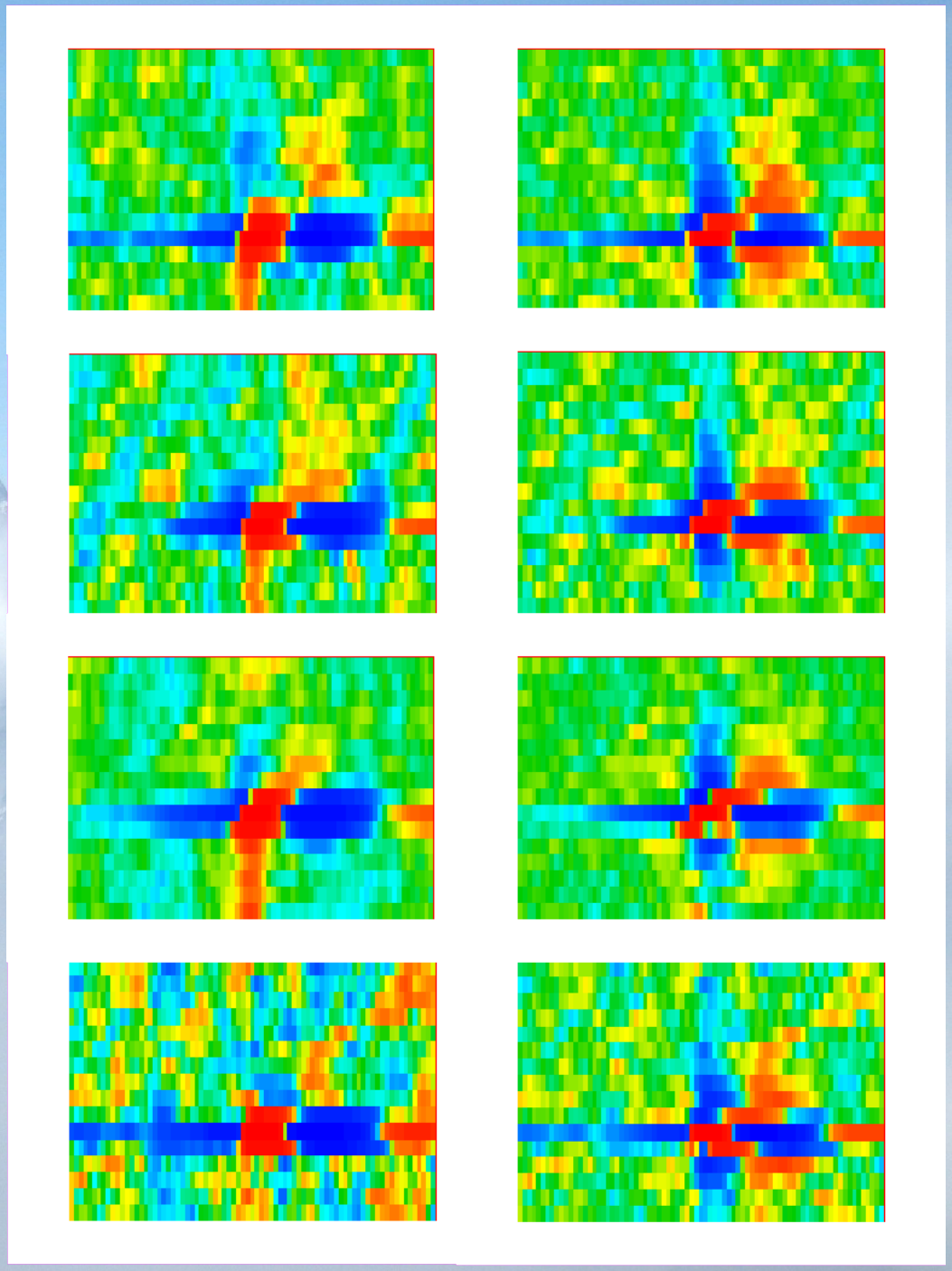


1-5% relative amplitudes are typically significant

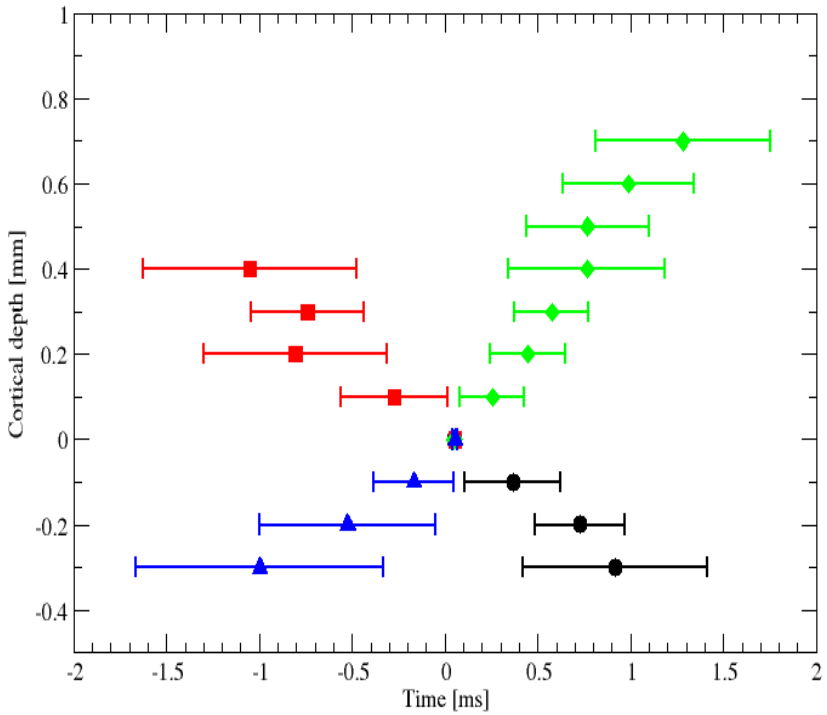
Spatio- temporal dynamics of the action potentials

New fine details revealed by the application of the new SCSD method

Besides apical, basal back-propagation became observable.

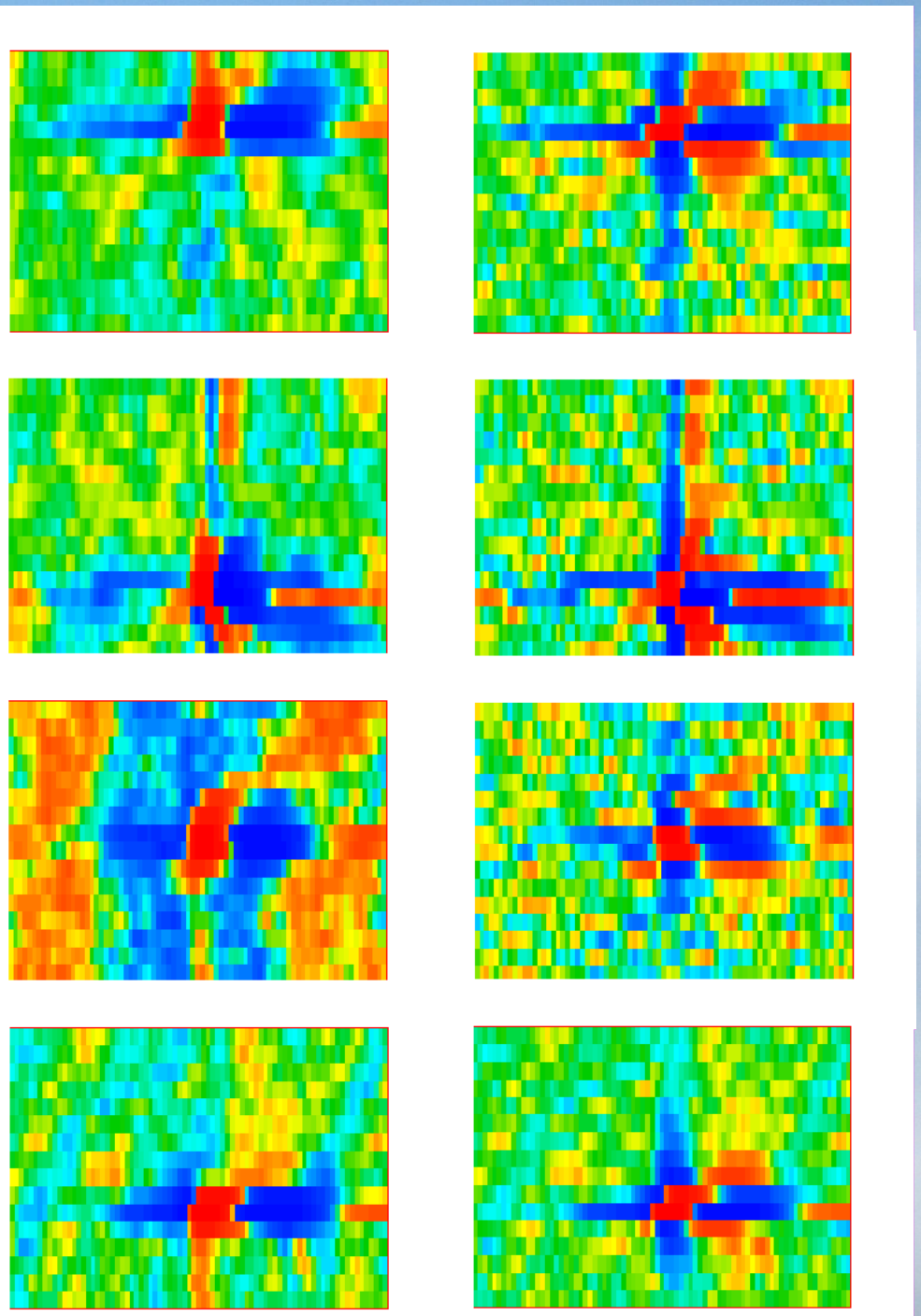


Some signs of forward propagation appears

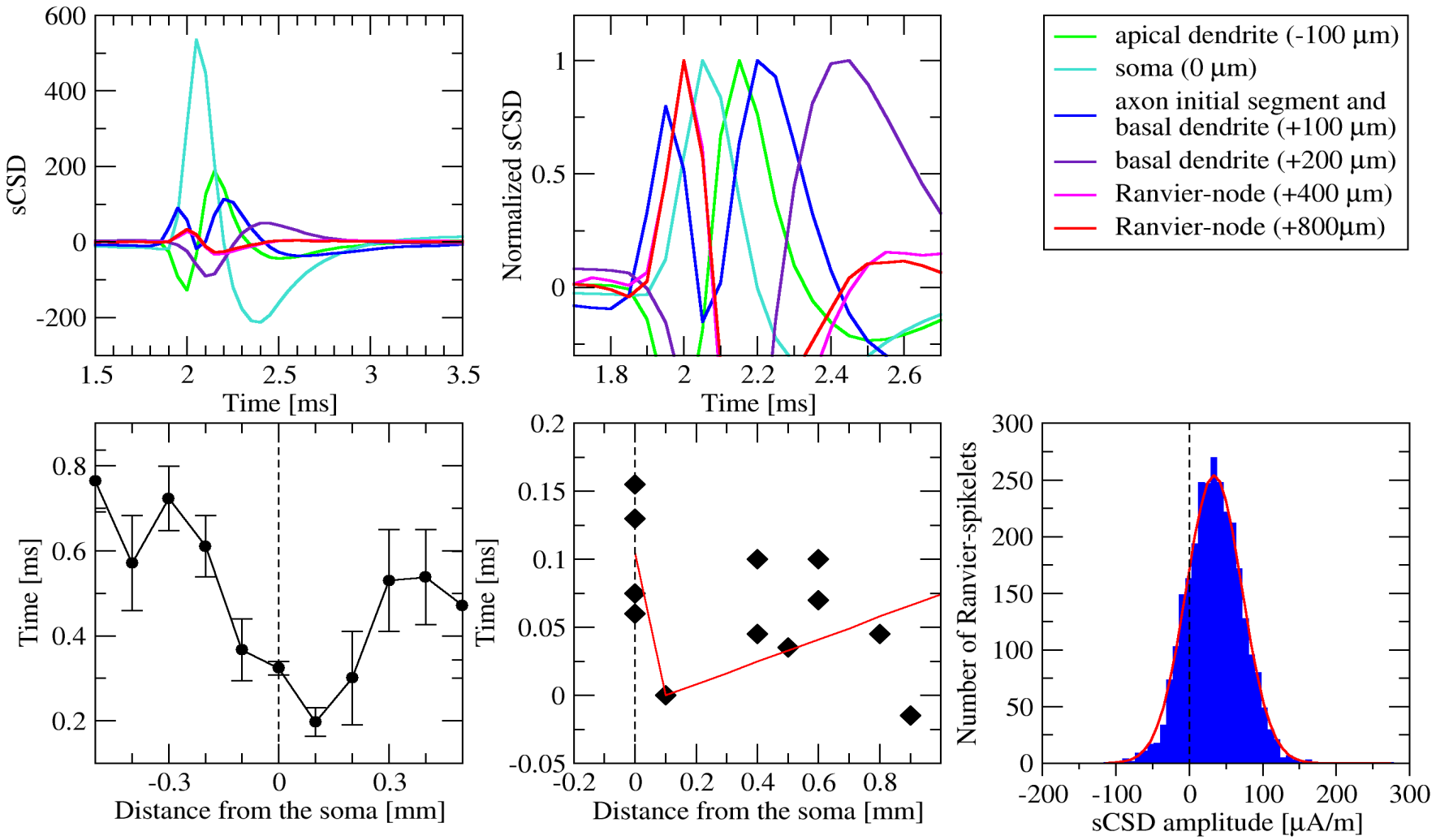


Potential

sCSD



Initiation and spreading of the action potential

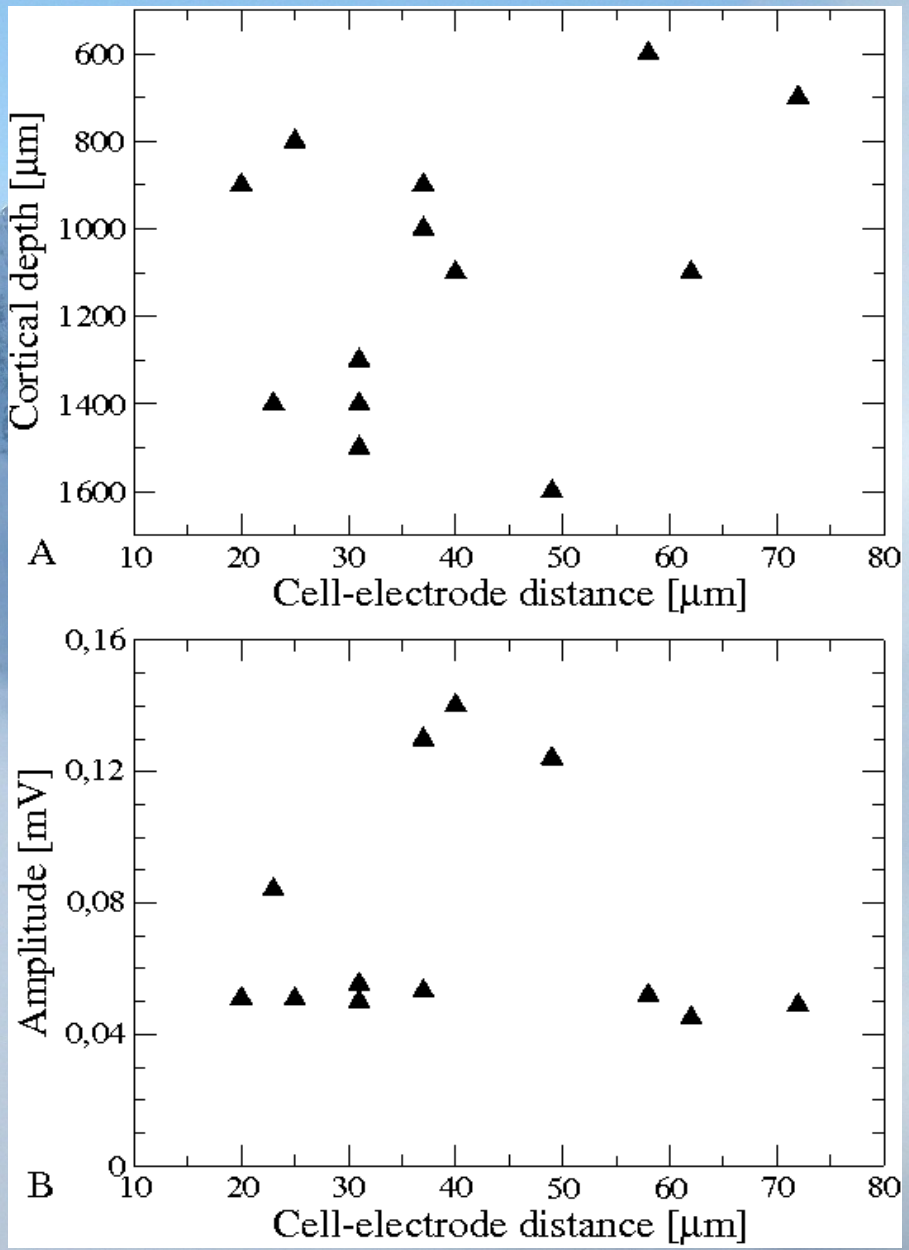


An opportunity for indirect verification

Henze et al. J. Neurophysiol. 2000: Action potentials can be measured from 200µm distance, but reaches the 60 µV amplitude only in 60µm vicinity, which is required for the successful spike sorting.

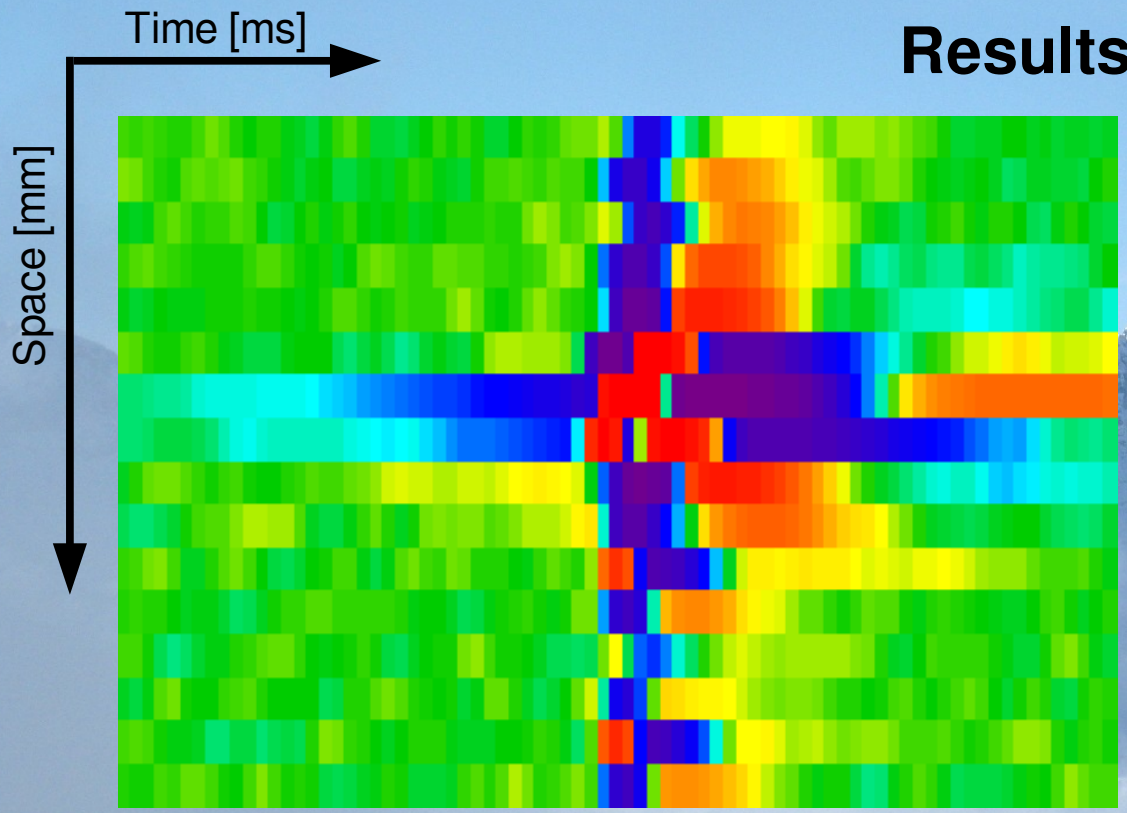
We assumed a priori, that d<200 µm

The result: max(d)=72 µm



Micro-electro imaging

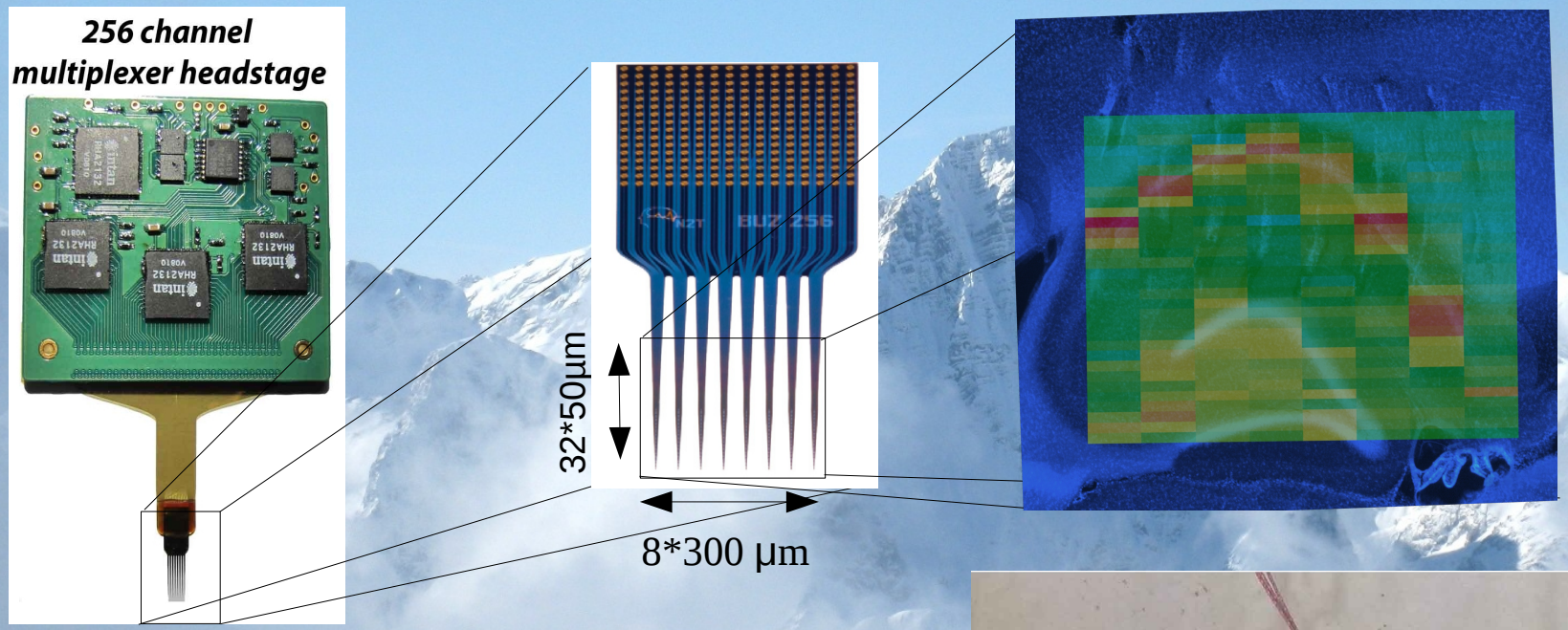
Results



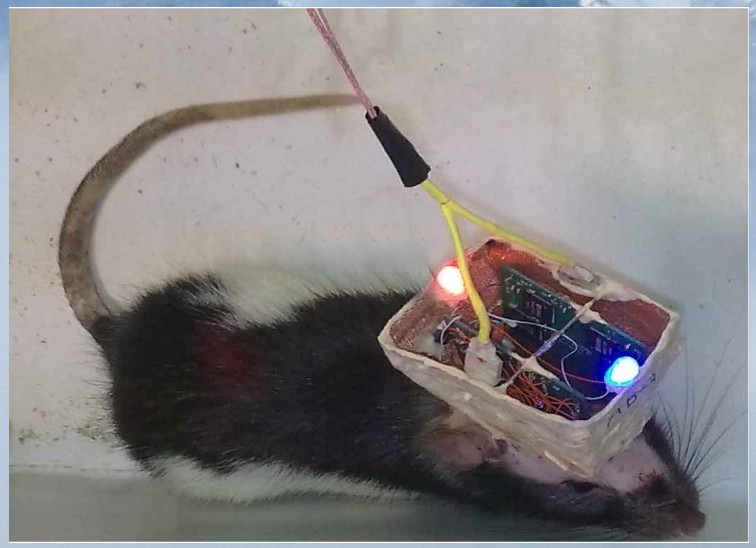
We showed, how the action potential is generated and spread back to the apical and basal dendrites and propagates along the myelinated axon.

Micro-electro imaging

2 dimensional, 256 channel electrode system

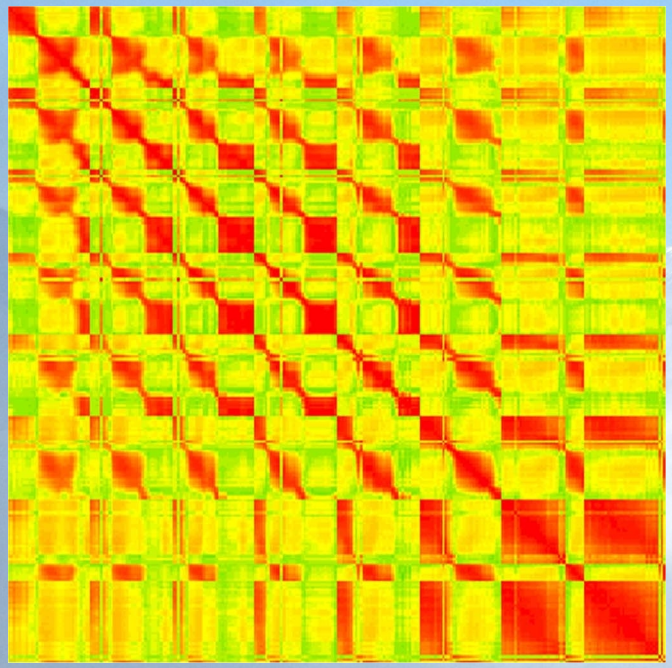


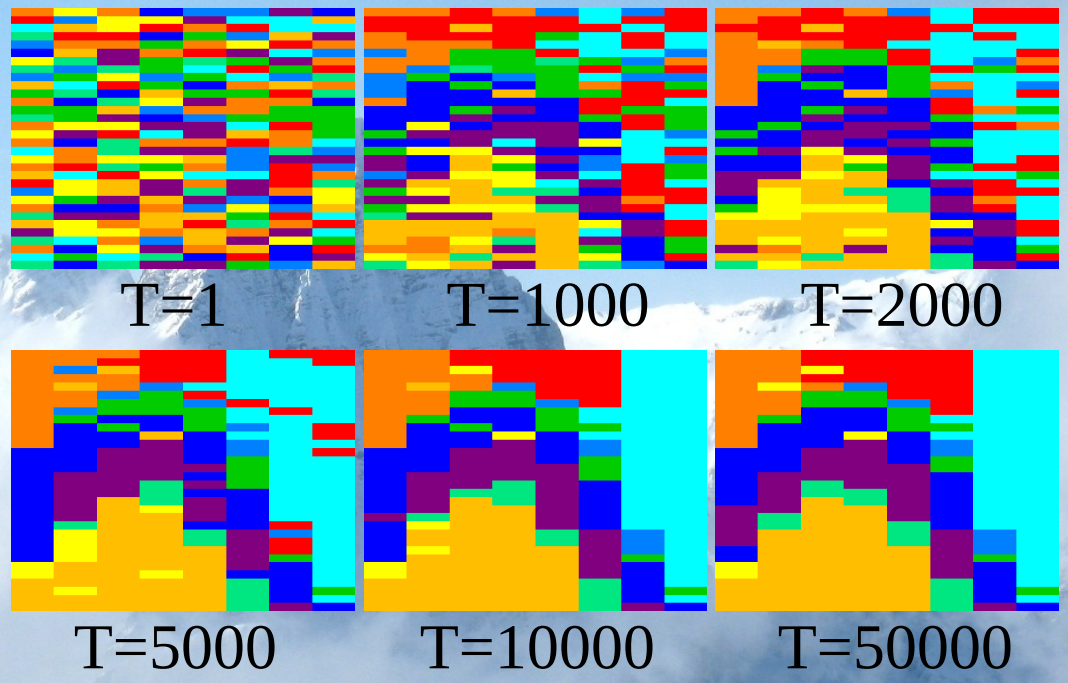
Made possible parallel monitoring of the many subareas of the hippocampus and cc. 100 sorted and identified neurons.



Micro-electro imaging

Micro-electro anatomy





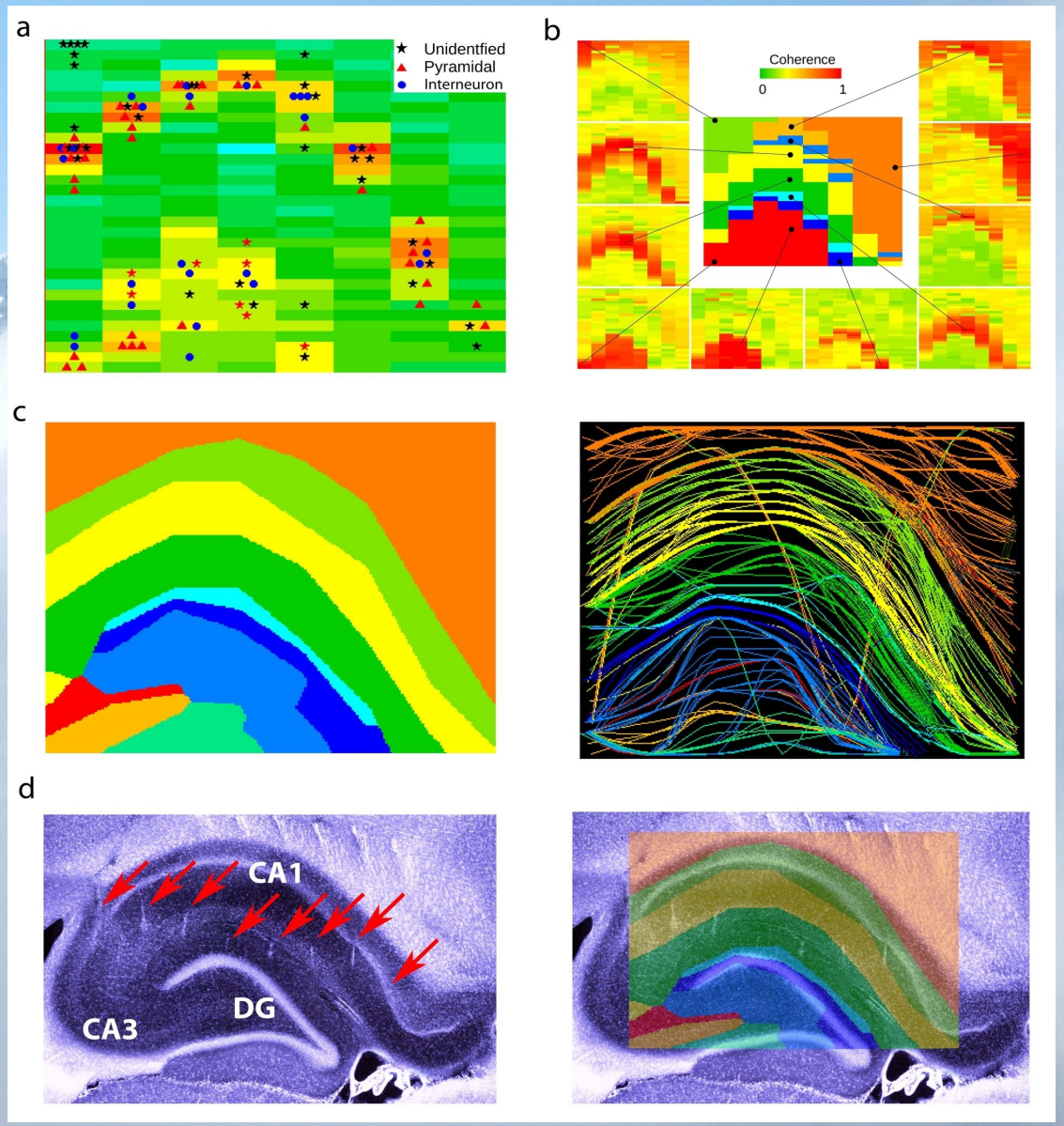
Layer structure of the hippocampus are revealed under the assumption, that the channels in the same layer receive similar synaptic inputs, but with different temporal delays. Thus coherence and the coherence based clustering could reveal the anatomical layers.

Micro-electro imaging

Micro-electro anatomy

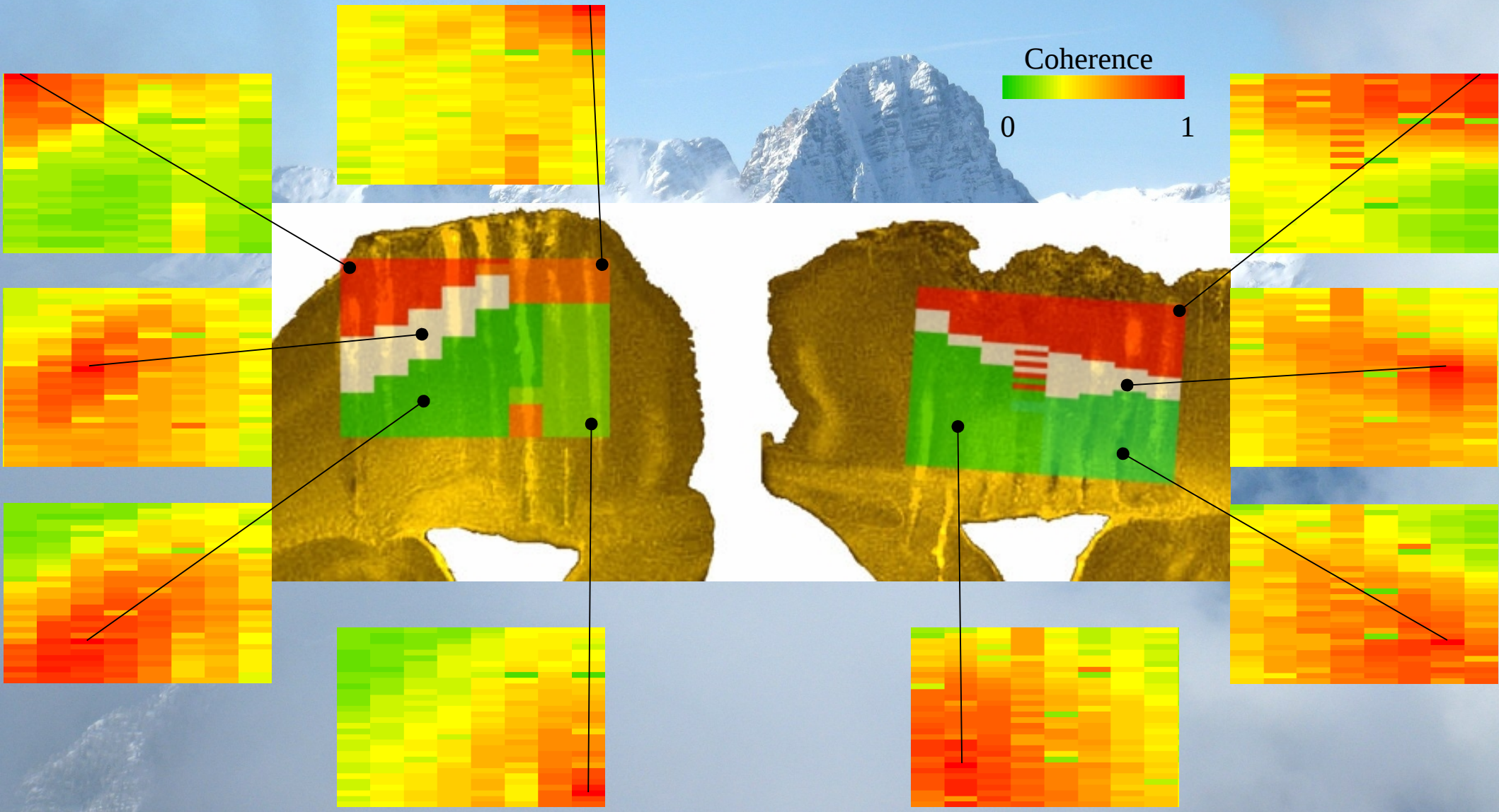
The high frequency power map show the somatic layers, which corresponds to the positions of the sorted individual neuros. The fusion of this high frequency power map with the result of the coherence clustering resulted a detailed layering map of the hippocampus. This electro-anatomical map corresponded well to the tissue histology.

Berényi et al. J Neurophysiology 2014



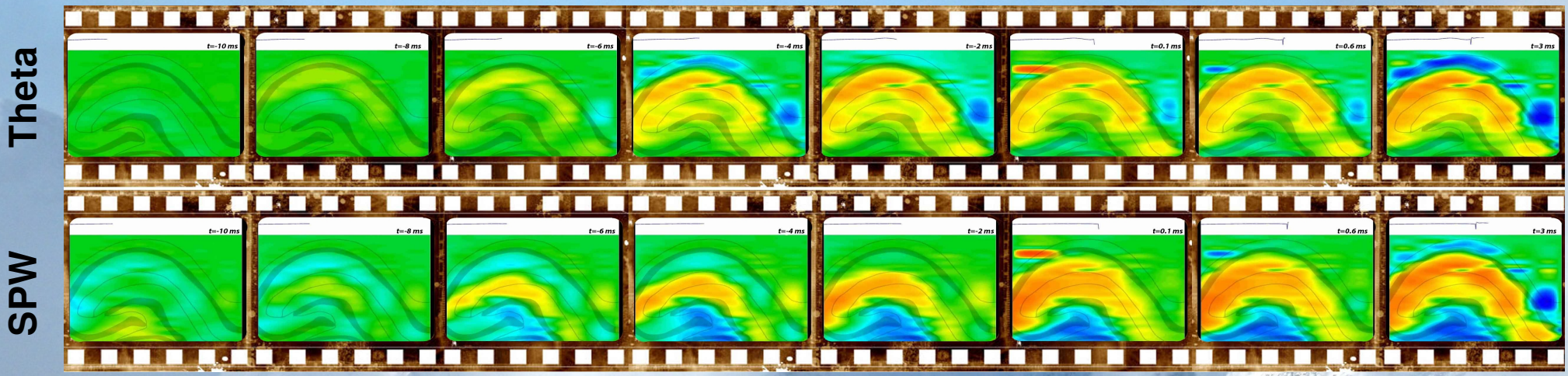
Micro-electro imaging

Micro-electro anatomy:
512 channel electrode system in the neocortex



Micro-electro imaging

Two inputs of one neuron



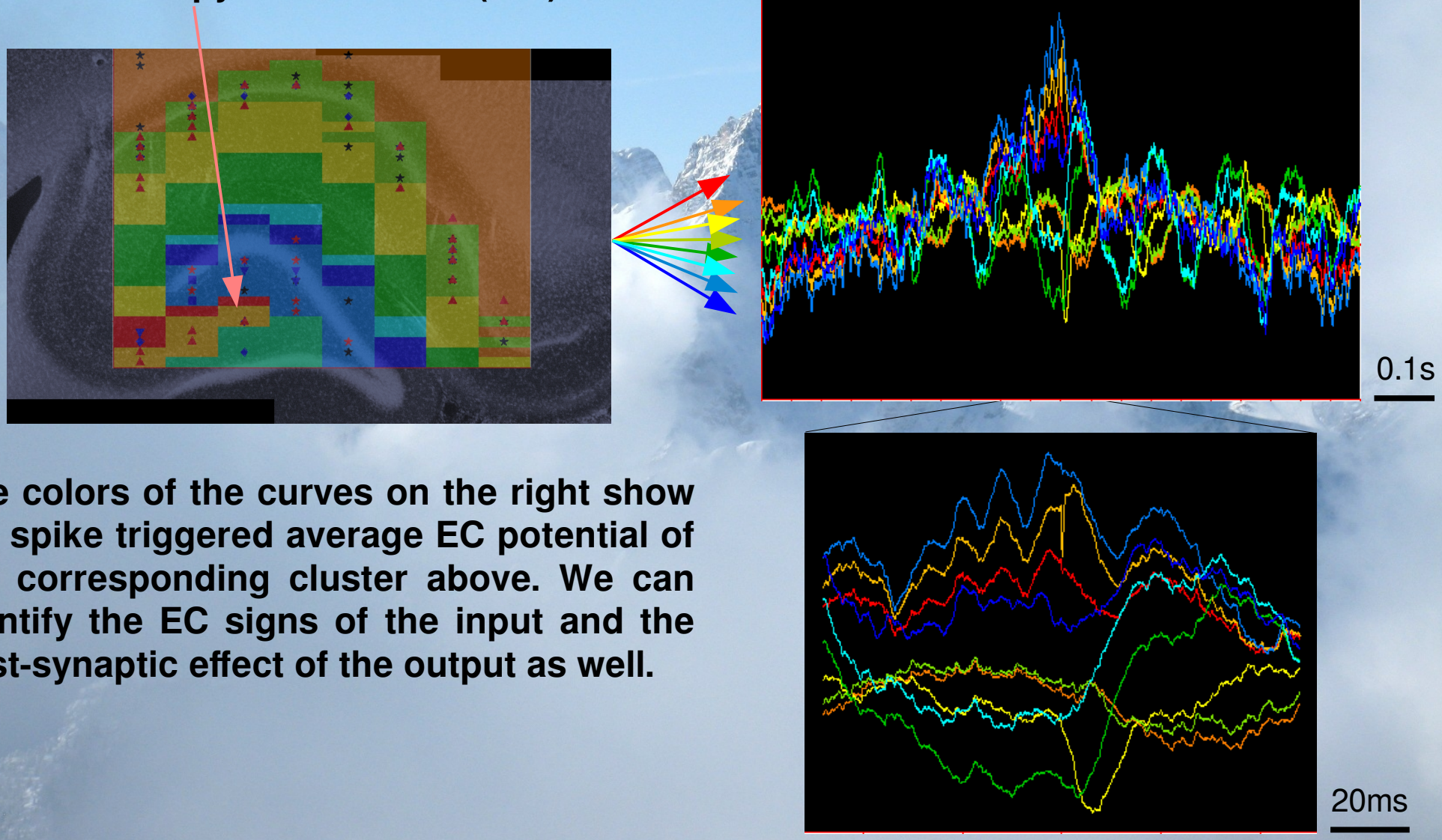
We have first demonstrated directly, that the same (inter)neuron receives synaptic inputs on different pathways during two different oscillatory (and information processing) stages of hippocampus.

Nat. Reviews Neurosci. 2012, 13(6) 407-20

Micro-electro imaging

Inputs of a neurons from different layers

A CA3 pyramid neuron (#56)



The colors of the curves on the right show the spike triggered average EC potential of the corresponding cluster above. We can identify the EC signs of the input and the post-synaptic effect of the output as well.

Micro-electro imaging

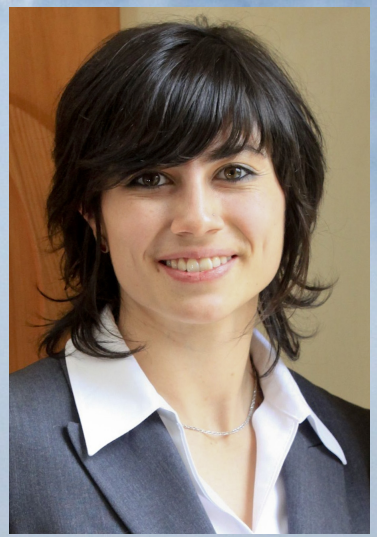
Acknowledgement

István Ulbert, MTA TTK

György Buzsáki, NYU

Antal Berényi, NYU
Szegedi Egyetem

Lisa Roux, NYU



John Long, NYU

Micro-electro imaging

Acknowledgement

Péter Érdi

Fülöp Bazsó

László Négyessy

Dorottya Cserpán

László Zalányi

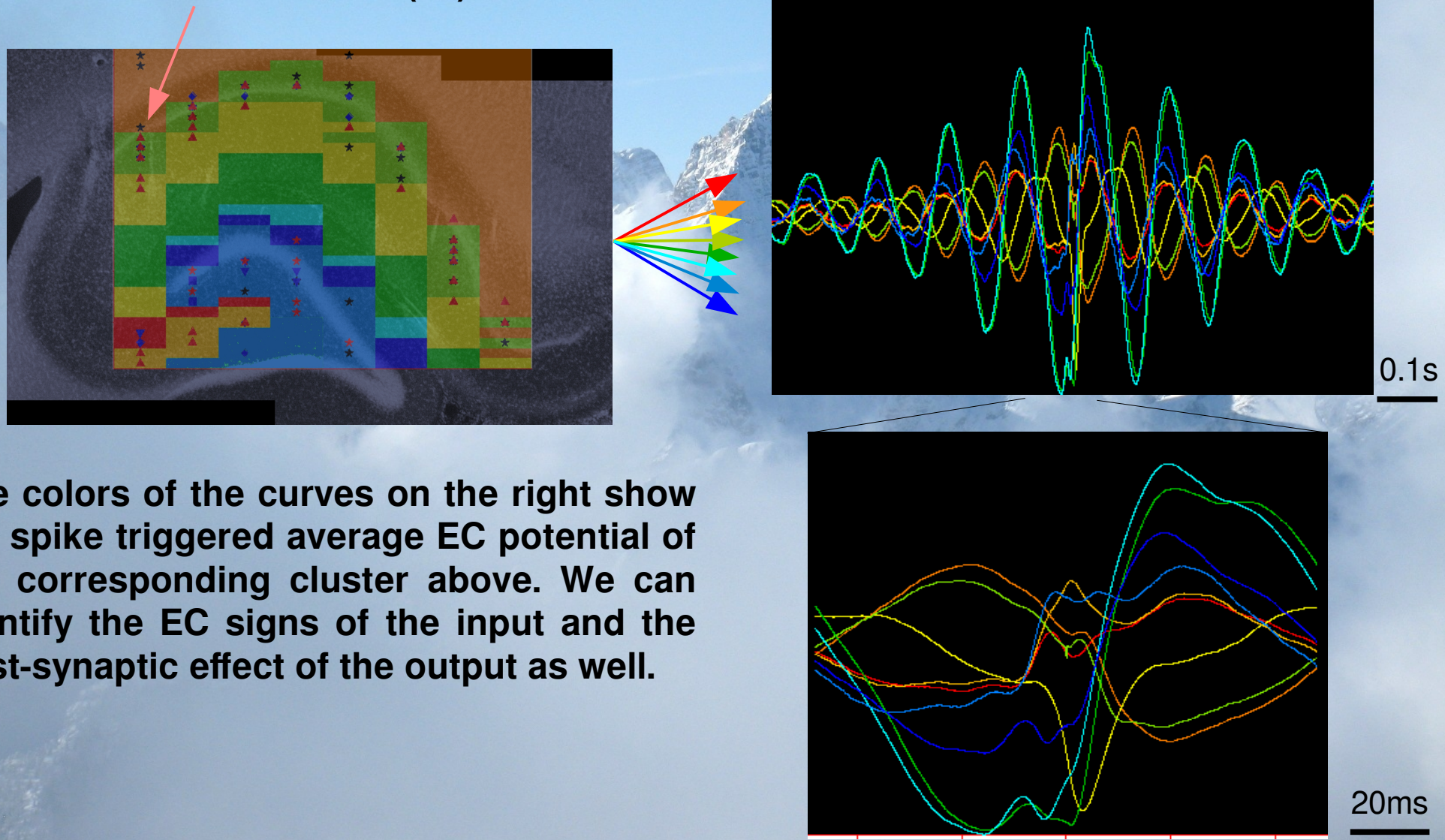
Zsigmond Benkő

Theoretical Neuroscience and Complex Systems Research Group

Micro-electro imaging

Inputs of a neurons from different layers

A CA1 interneuron (#8)

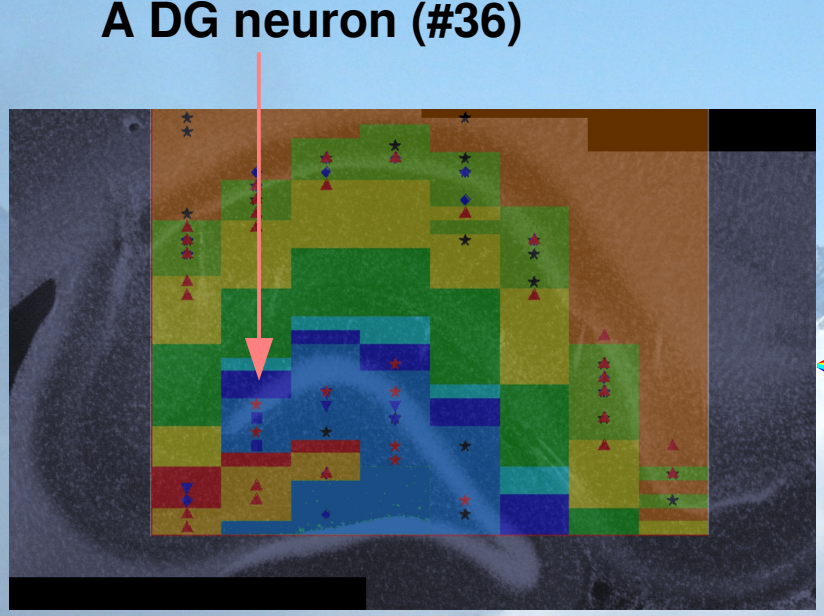


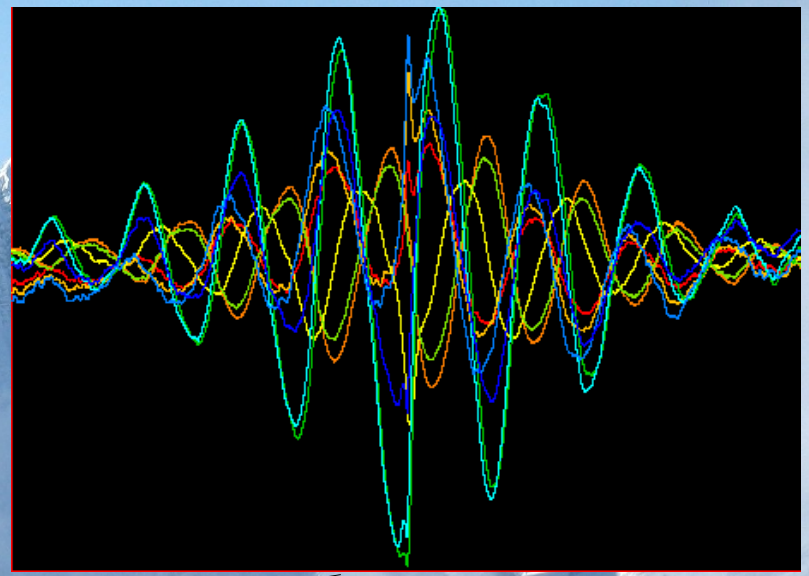
The colors of the curves on the right show the spike triggered average EC potential of the corresponding cluster above. We can identify the EC signs of the input and the post-synaptic effect of the output as well.

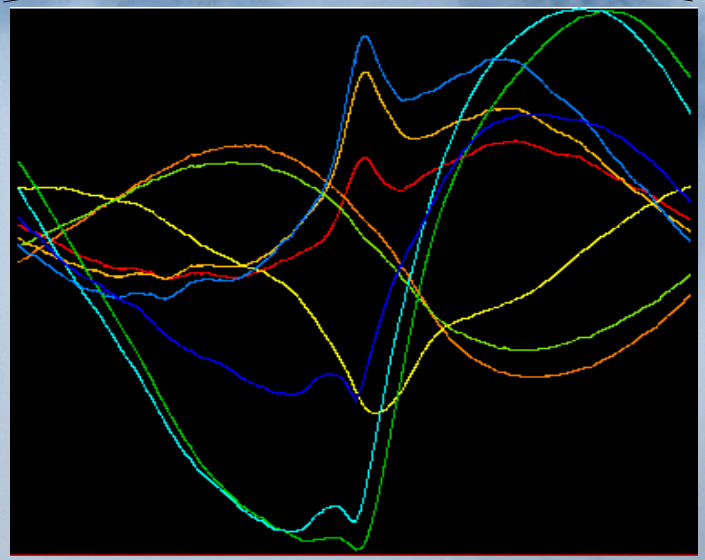
Micro-electro imaging

Inputs of a neurons from different layers

A DG neuron (#36)





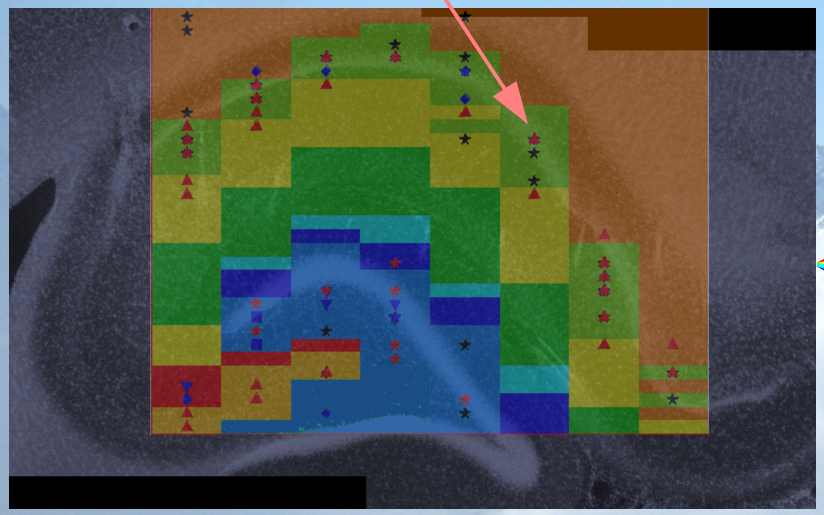


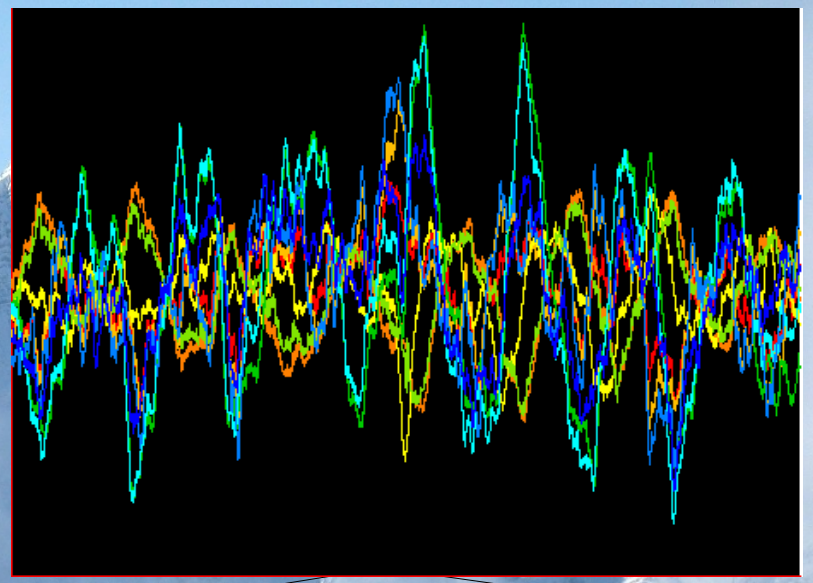
The colors of the curves on the right show the spike triggered average EC potential of the corresponding cluster above. We can identify the EC signs of the input and the post-synaptic effect of the output as well.

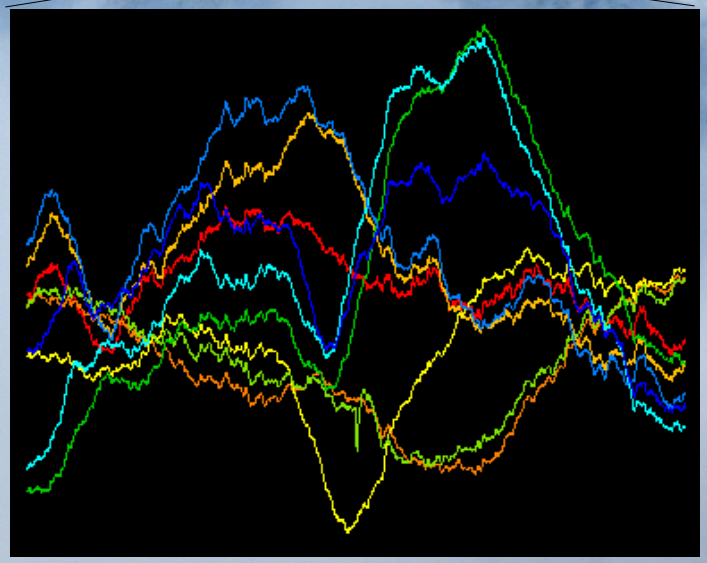
Micro-electro imaging

Inputs of a neurons from different layers

A CA1 pyramid neuron (#86)







The colors of the curves on the right show the spike triggered average EC potential of the corresponding cluster above. We can identify the EC signs of the input and the post-synaptic effect of the output as well.