From transmembrane currents to extracellular potentials and back

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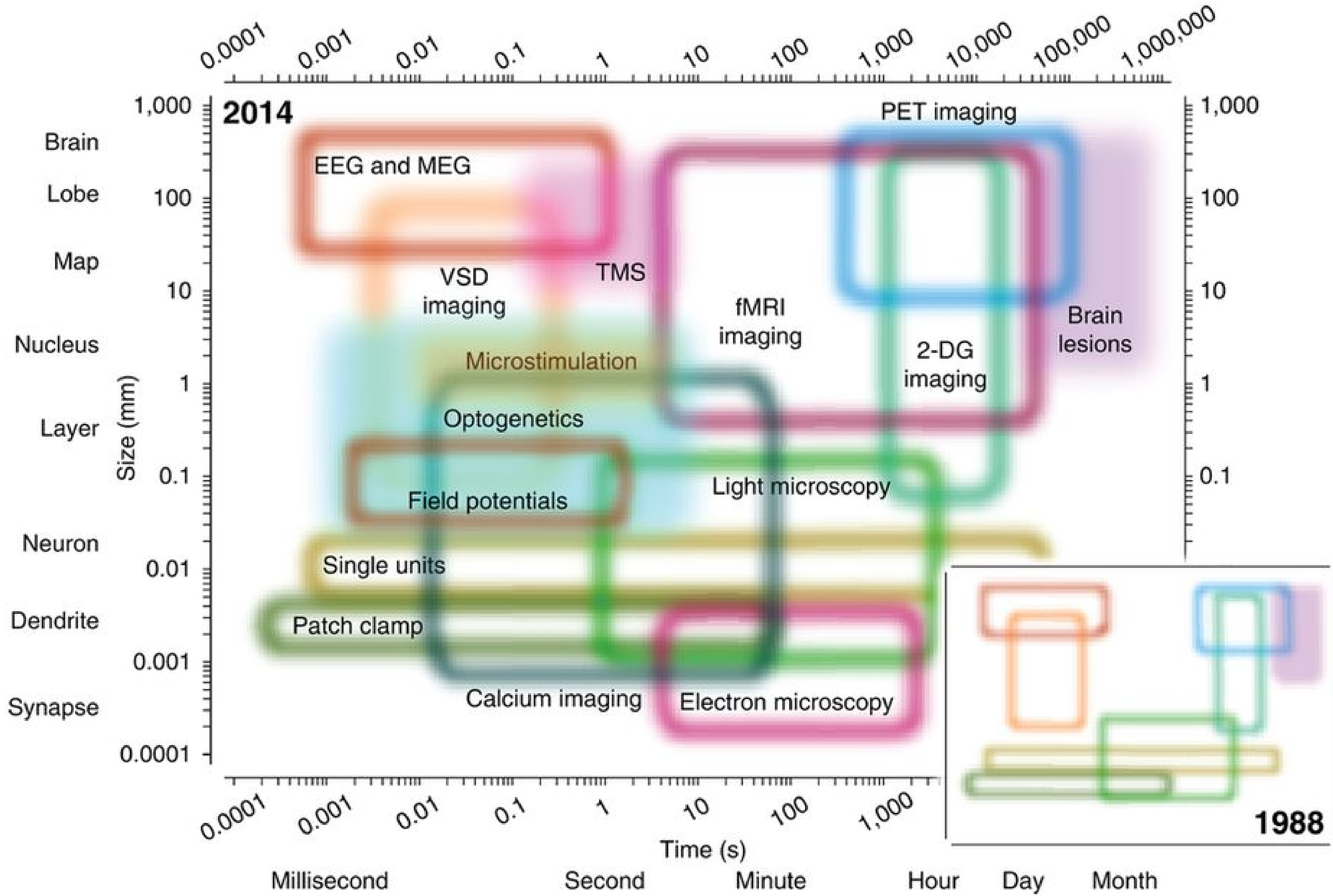
LVIII Cracow School of Theoretical Physics 2018, Zakopane

Techniques to study brain function

Temporal and spatial scales

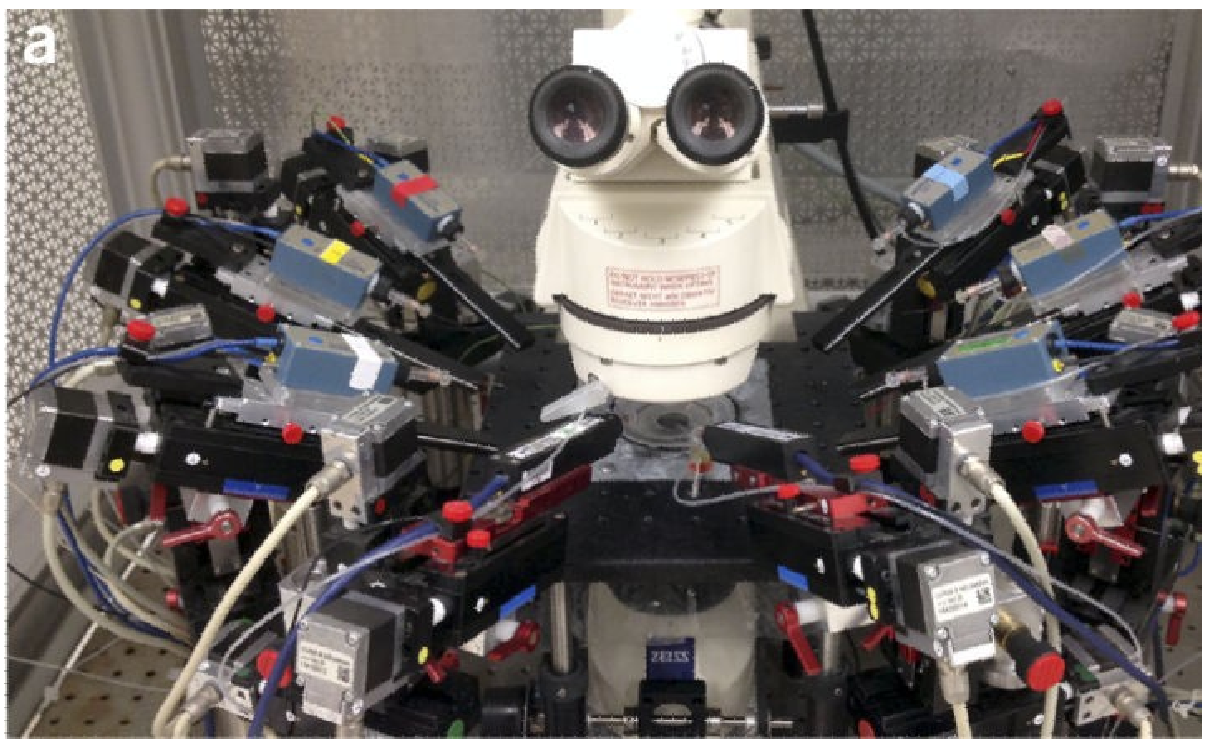


Churchland, Sejnowski 2014

Extracellular potential

Electrodes through the ages

- Intracellular recordings
  - Glass microelectrodes
    (Umrath, 1930; Hodgkin & Huxley, 1939)
  - Pulled glass electrodes for mammalian cells
    (Ling & Gerard, 1949)
  - Patch clamp (Neher & Sakmann, 1976)

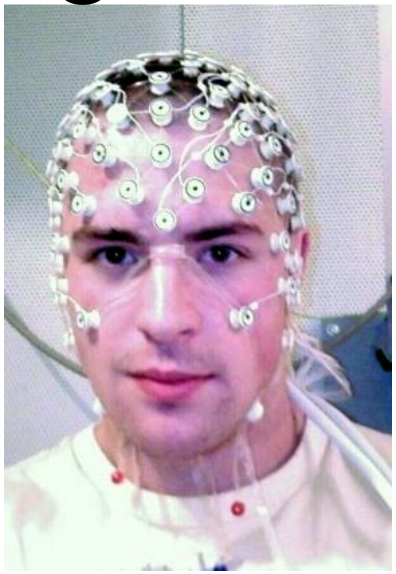


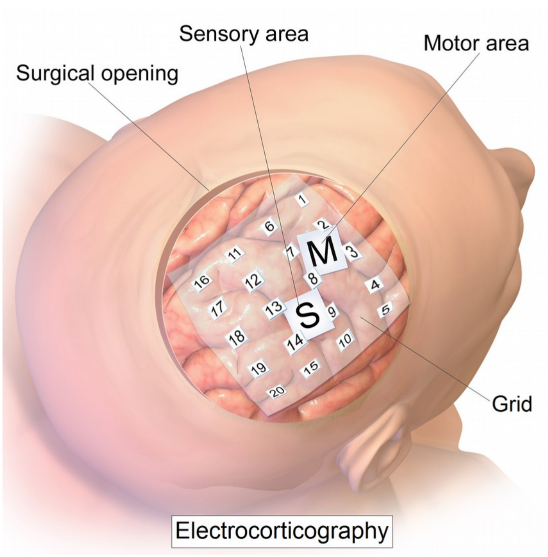
Wang et al., 2015
8 patch-clamps

up to ~12

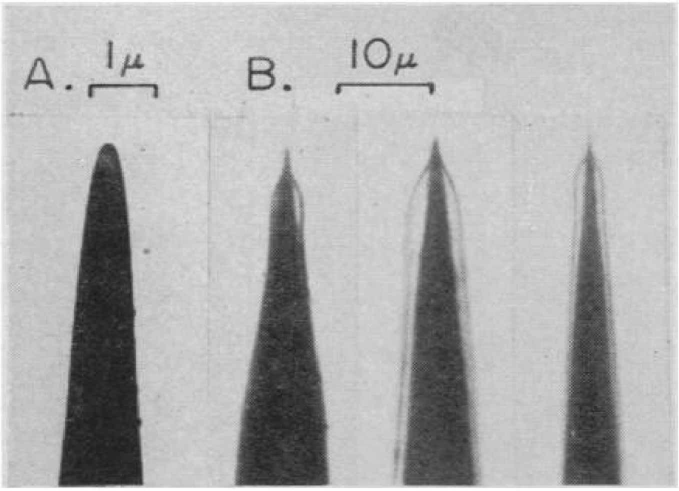
Electrodes through the ages

- Extracellular recordings
  - EEG (Berger, 1924)
  - ECoG (Penfield & Jasper, 1950s)
  - Depth recordings (single units, MUA, LFP)
    - Glass microelectrodes (1940s)
    - Wires (1950s)
  - In vitro methods (MEAs for slices and cultures)

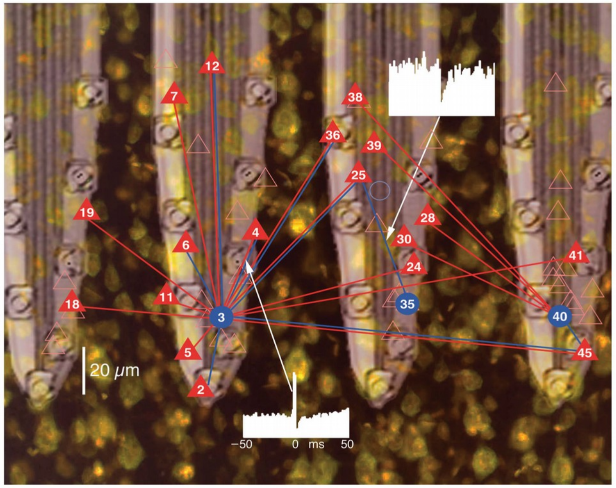




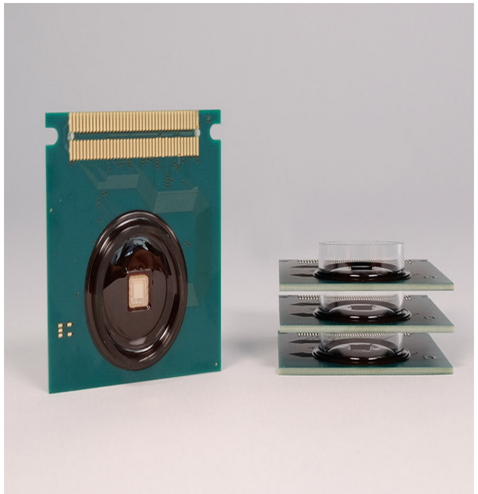
Wikipedia



Tungsten wires, Hubel, 1957

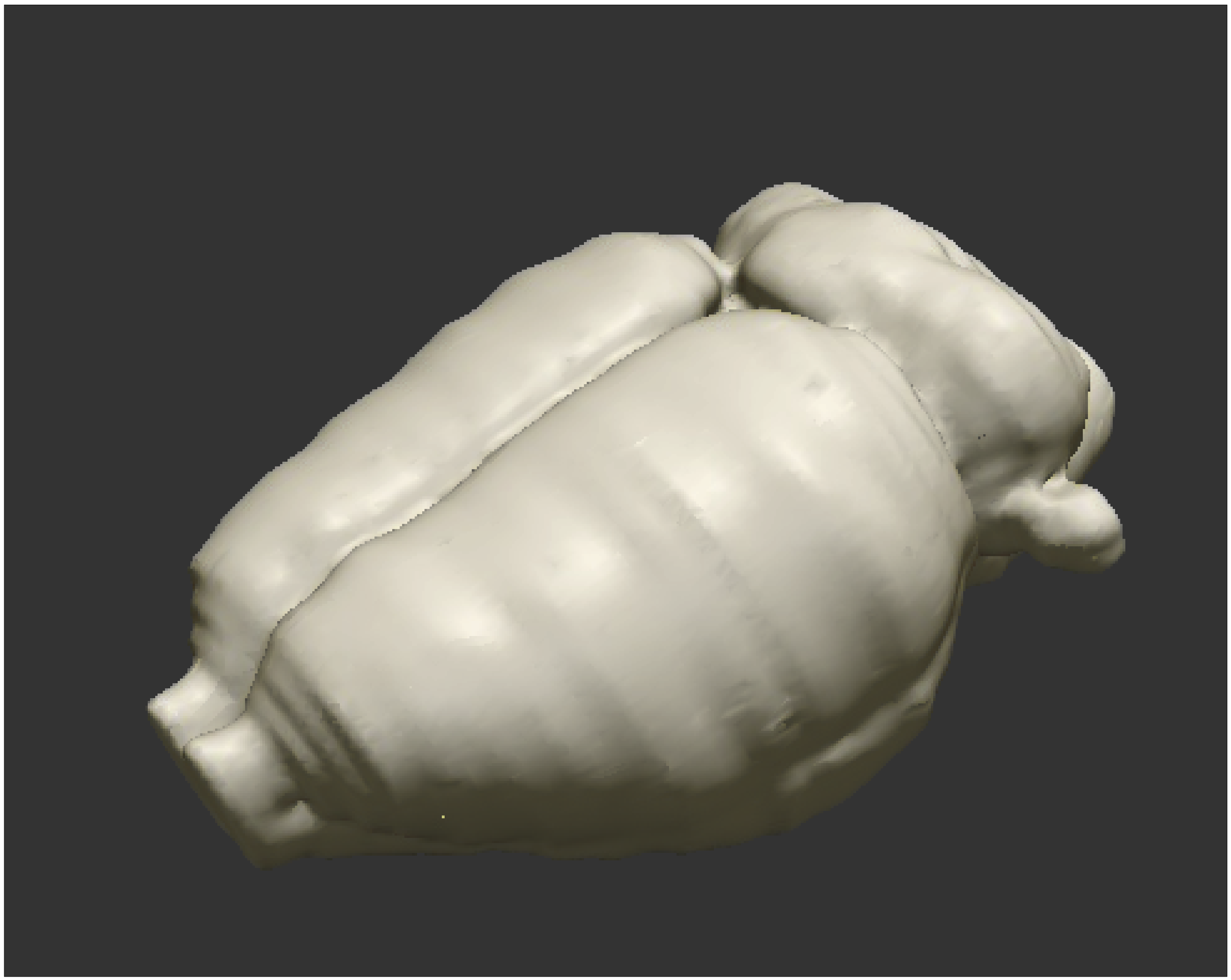


Silicon probes, Buzsaki 2004



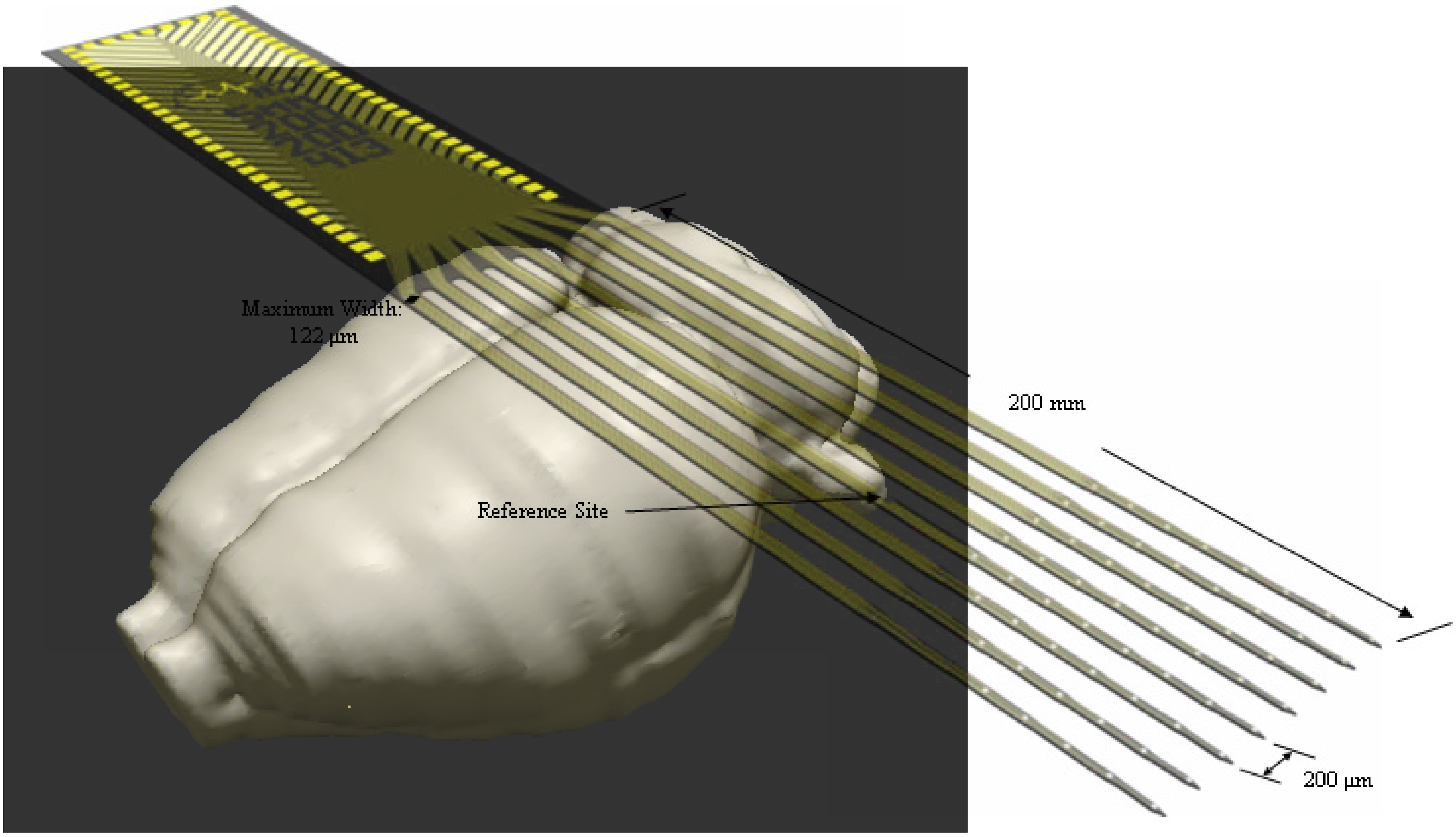
4096 ch. CMOS MEA, 3brain

Electric potential in the brain



http://service.3dbar.org

Electric potential in the brain



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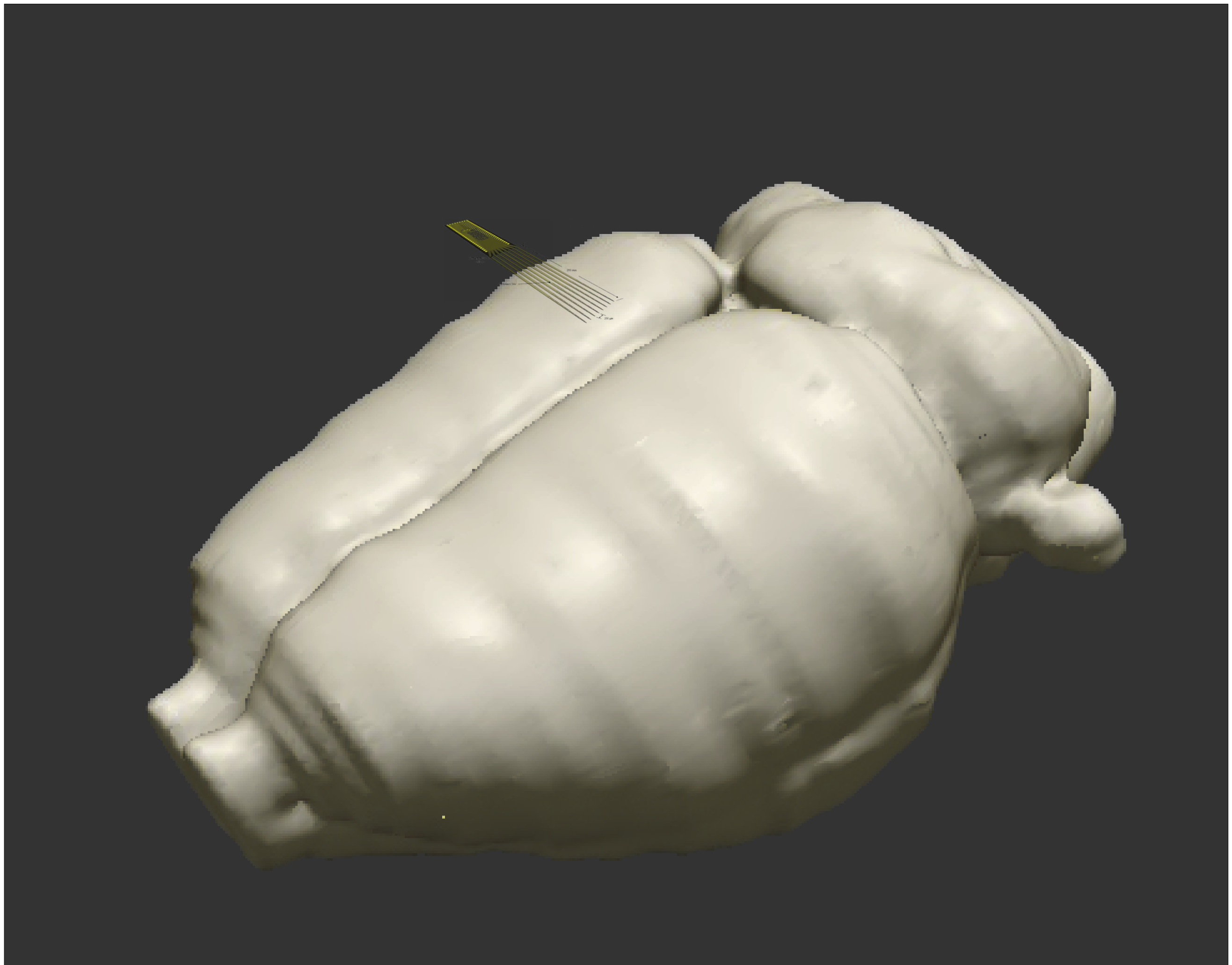
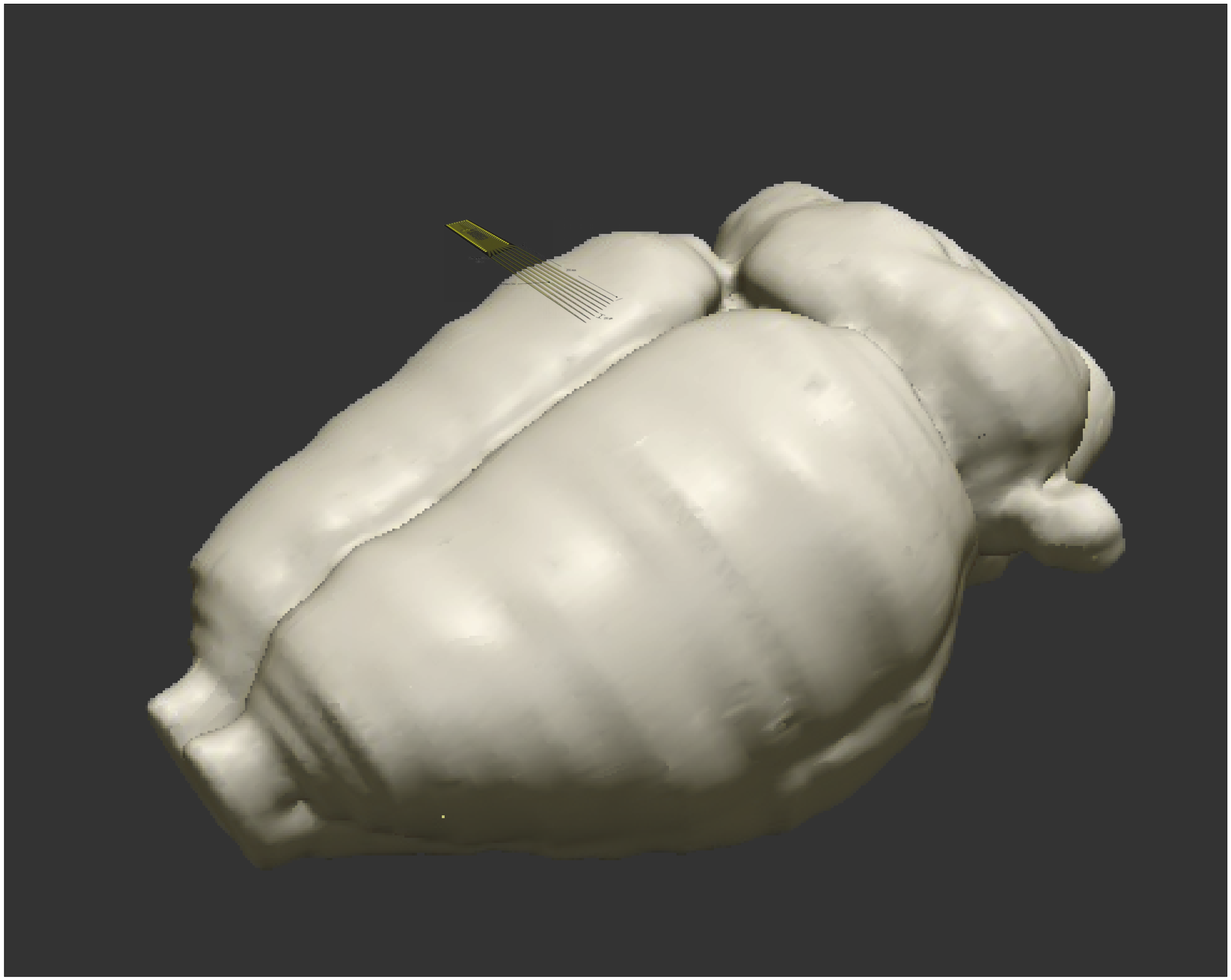
Electric potential in the brain

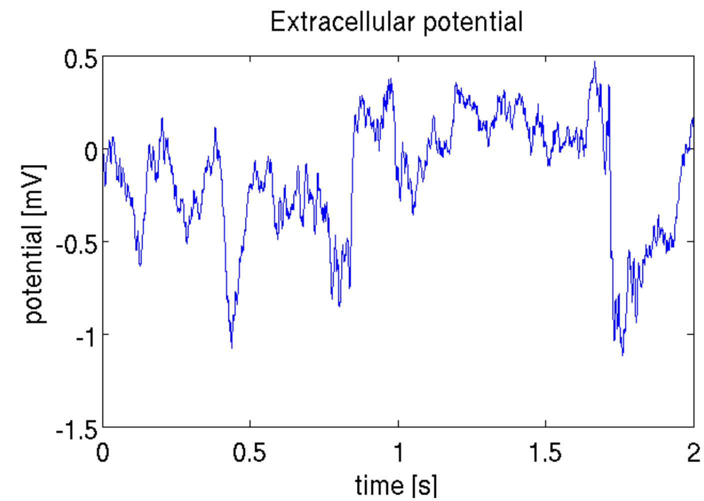


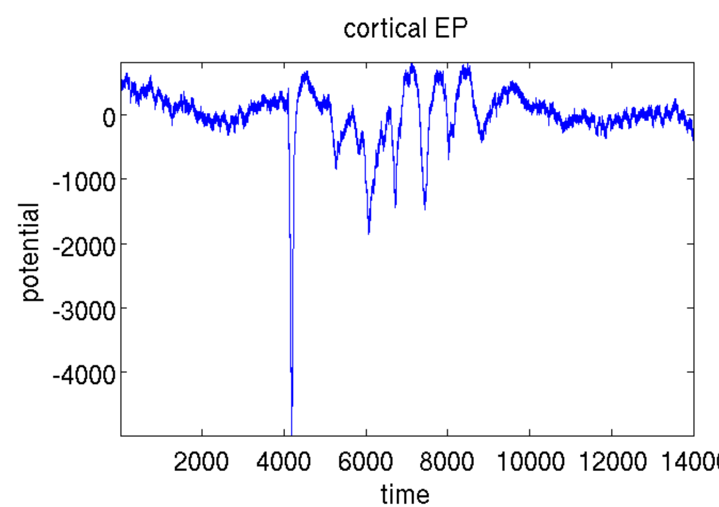
http://service.3dbar.org

Electric potential in the brain

Mark Hunt







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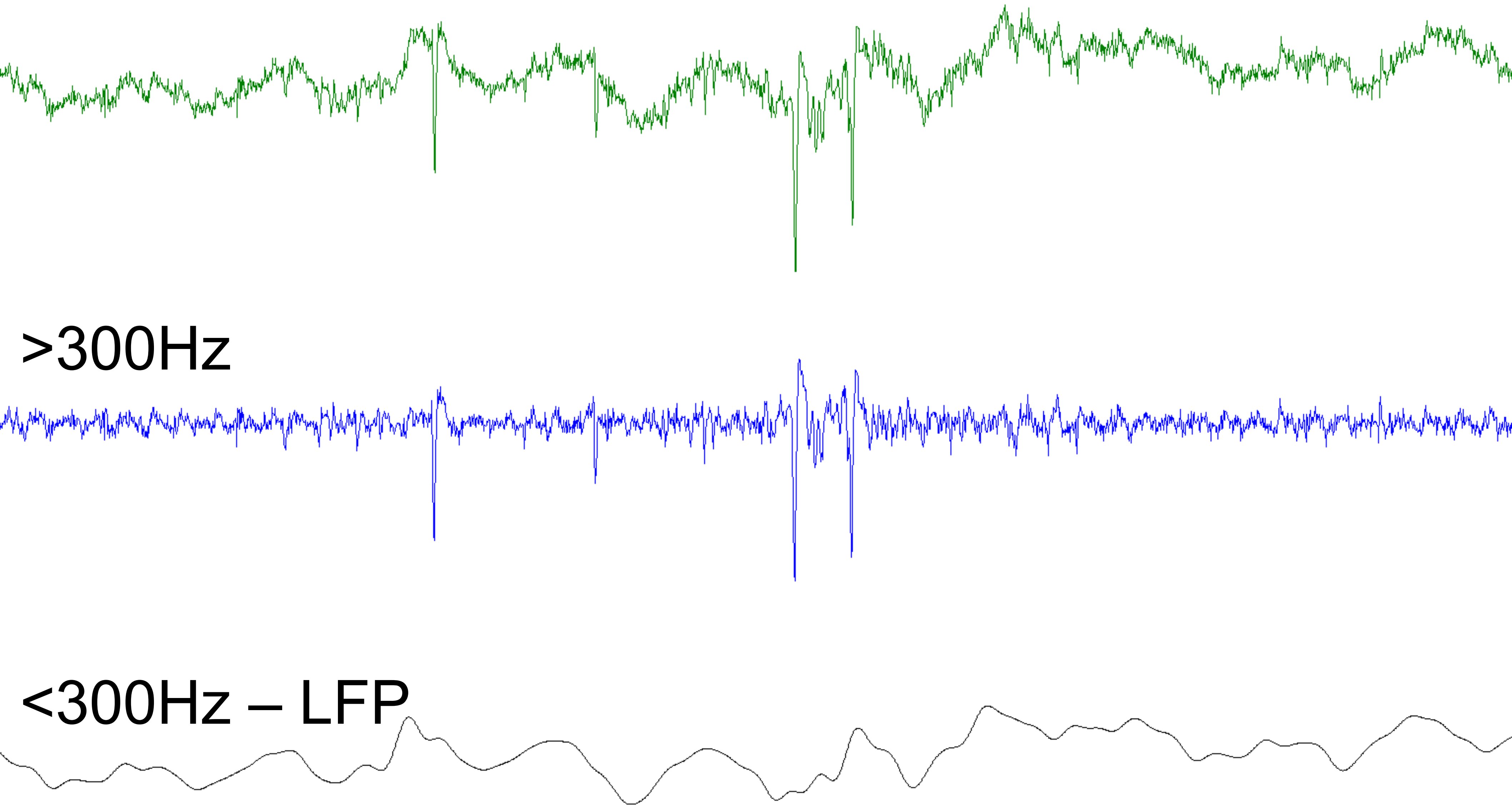
Ewa Kublik

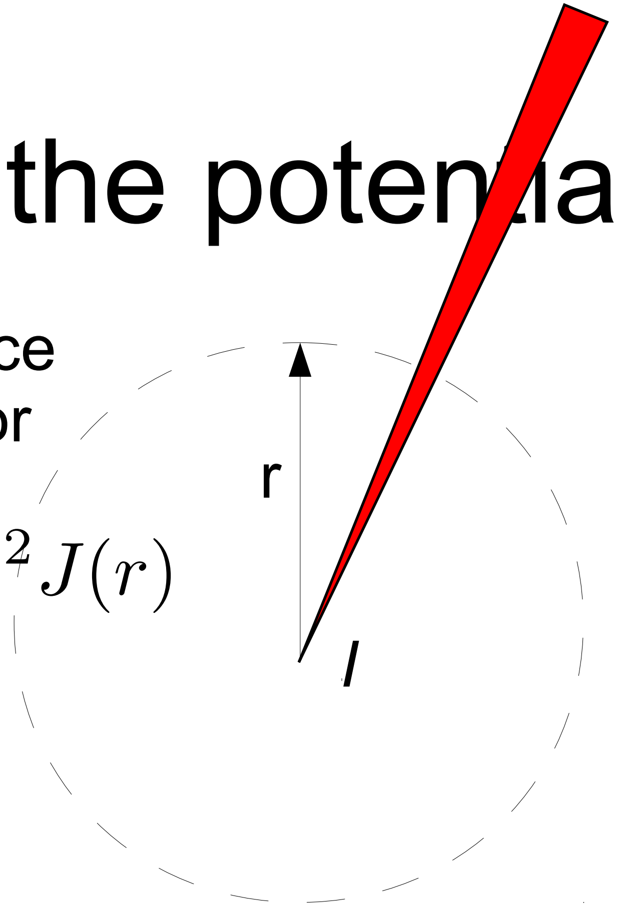

>300Hz
<300Hz – LFP

Where does the potential come from?

Where does the potential come from?

Assume a point source
in a volume conductor

$$I = \int_S \vec{J}(r) d\hat{S} \frac{I}{4\pi r^2} \hat{r} r^2 J(r)$$



Ohm's law

$$\vec{J} = \sigma \vec{E} = -\sigma \nabla V$$

$$\vec{\nabla} V = -\frac{I}{4\pi\sigma r^2}\hat{r}$$

$$\nabla V(r,\theta,\phi) = \frac{\partial V}{\partial r}\hat{r} + \frac{1}{r}\frac{\partial V}{\partial \theta}\hat{\theta} + \frac{1}{r\sin\theta}\frac{\partial V}{\partial \phi}\hat{\phi}$$

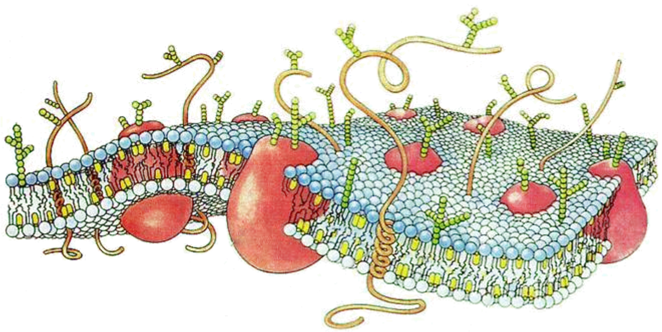
But V is spherically symmetric: V = V(r)

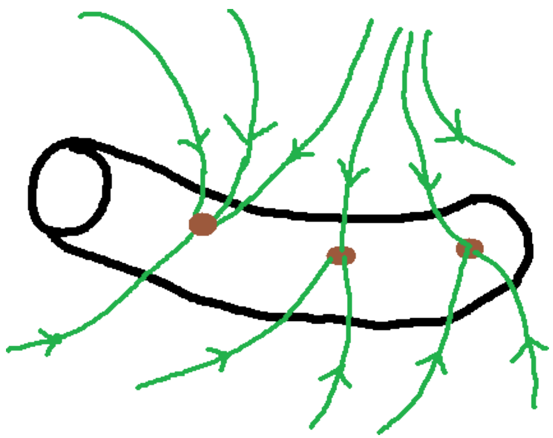
$$\frac{\partial V}{\partial r} = -\frac{I}{4\pi\sigma r^2}$$

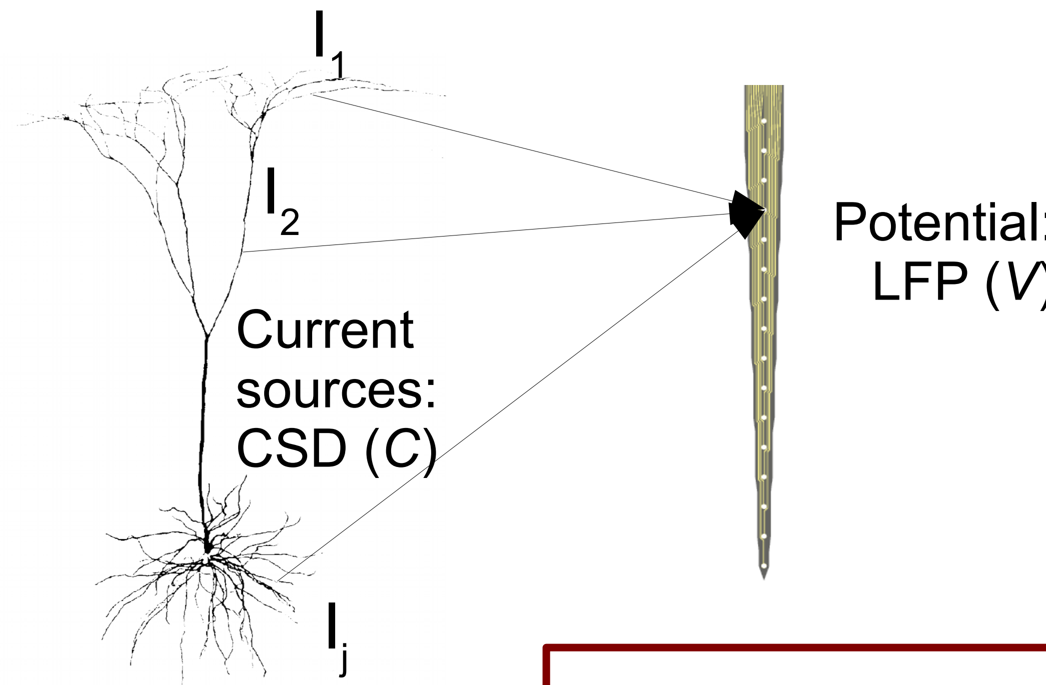
$$V(r) = \frac{I}{4\pi\sigma r}$$

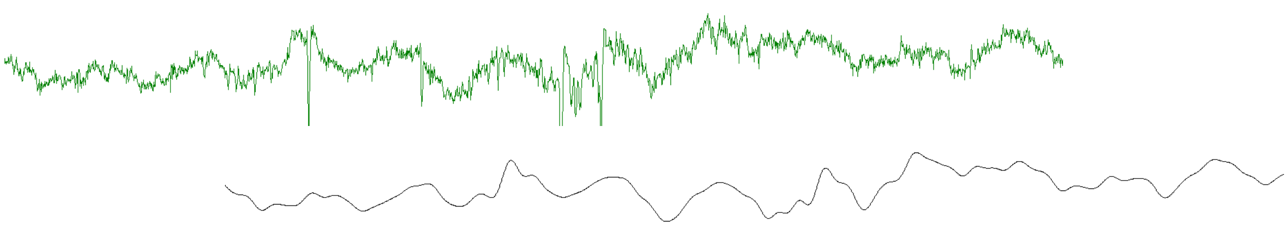
Tranquillo „Quantitative neurophysiology”

Origin of extracellular potential









$$V(r) = \frac{I}{4\pi\sigma r}$$

$$V(r) = \sum_j \frac{I_j}{4\pi\sigma|\vec{r} - \vec{r}_j|} = \frac{1}{4\pi\sigma}\int d^3\vec{r'}\ \frac{C(\vec{r'})}{|\vec{r} - \vec{r'}|}$$

Current Source Density

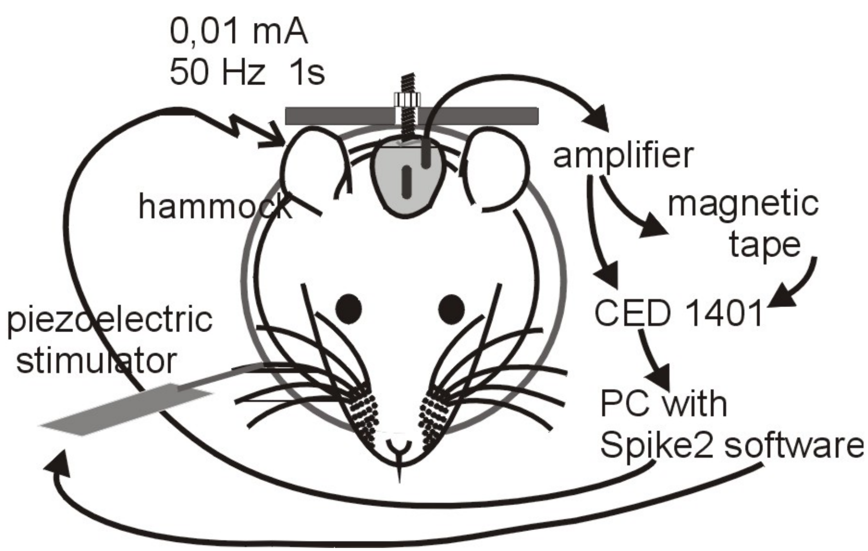
$$V(\vec{r},t) = \frac{1}{4\pi\sigma}\int \frac{C(\vec{r'},t)}{|\vec{r}-\vec{r'}|} d^3\vec{r'}$$

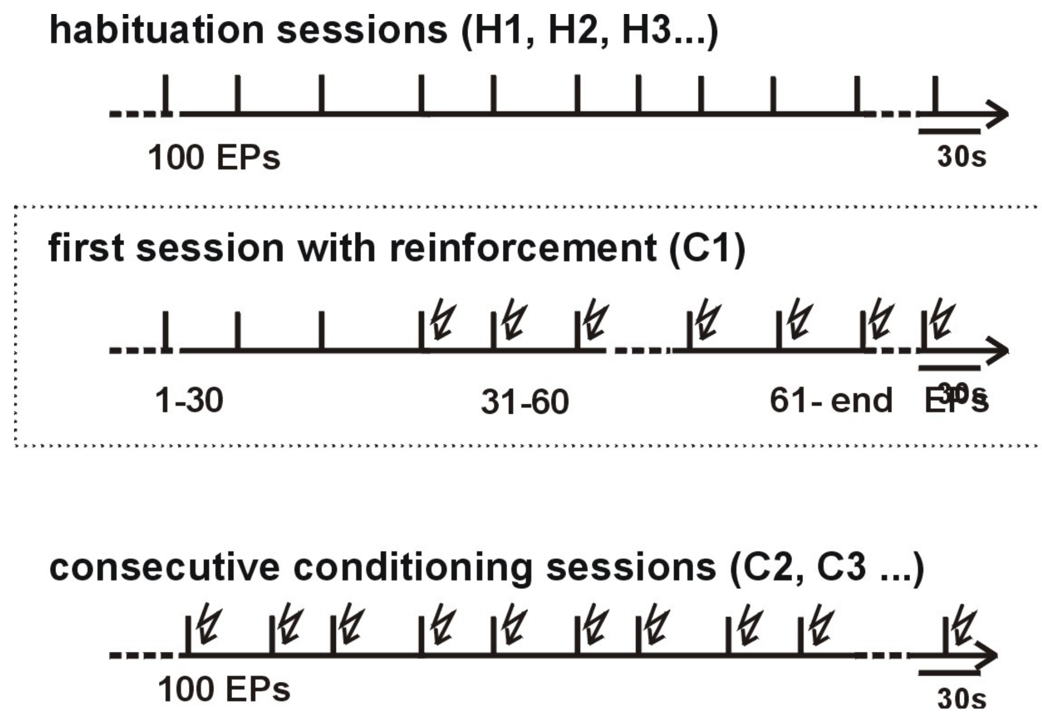
$$C = -\sigma \Delta V$$

C – current source density

σ – conductivity tensor; here: a constant (homogeneous and isotropic medium)

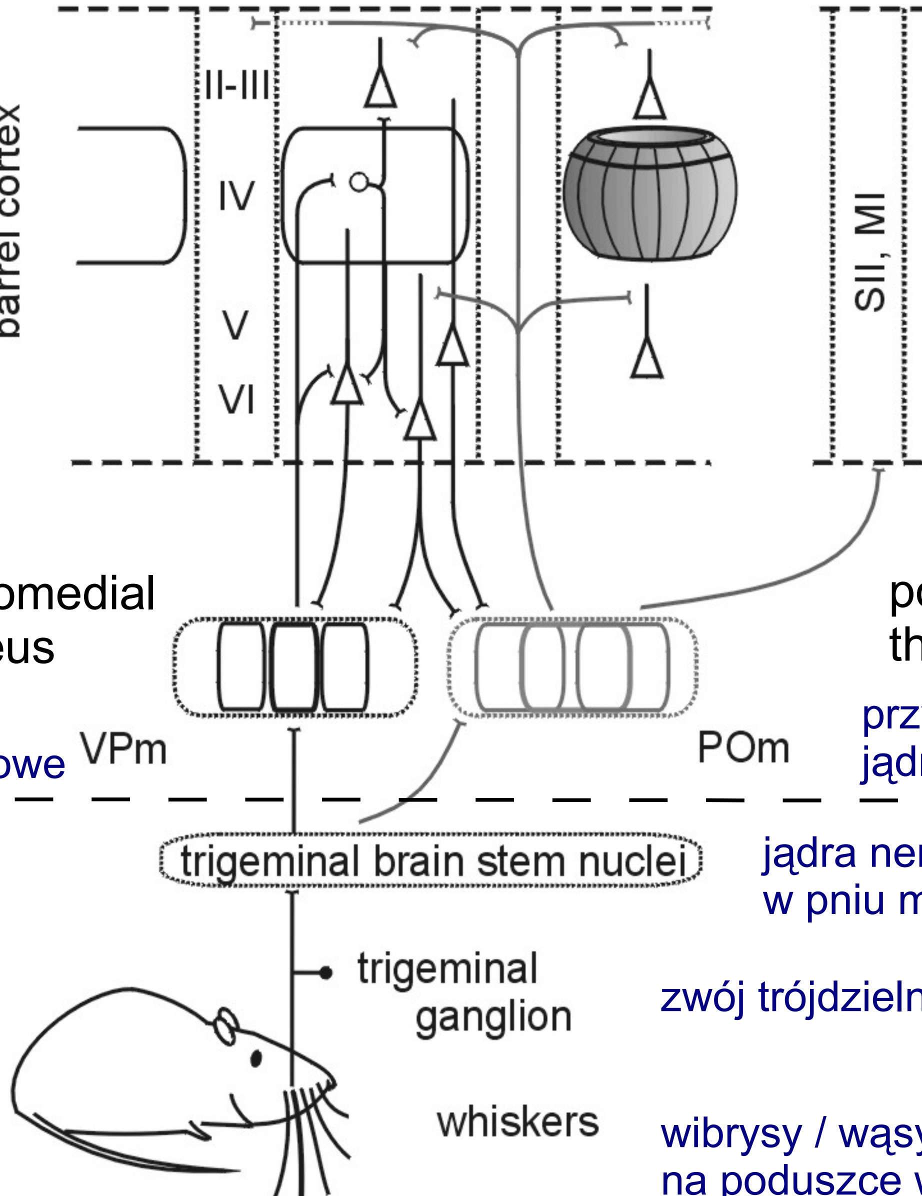
Experimental paradigm:



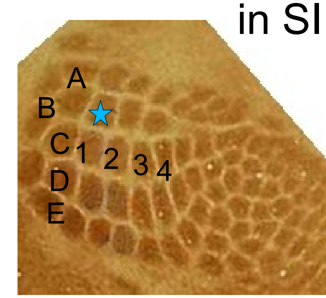


Vibrissa – barrel system of the rat

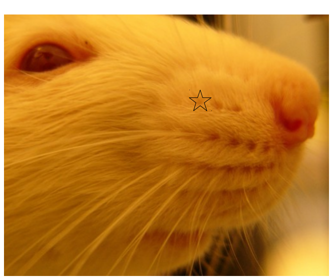
E. Kublik



barrel field in SI cortex



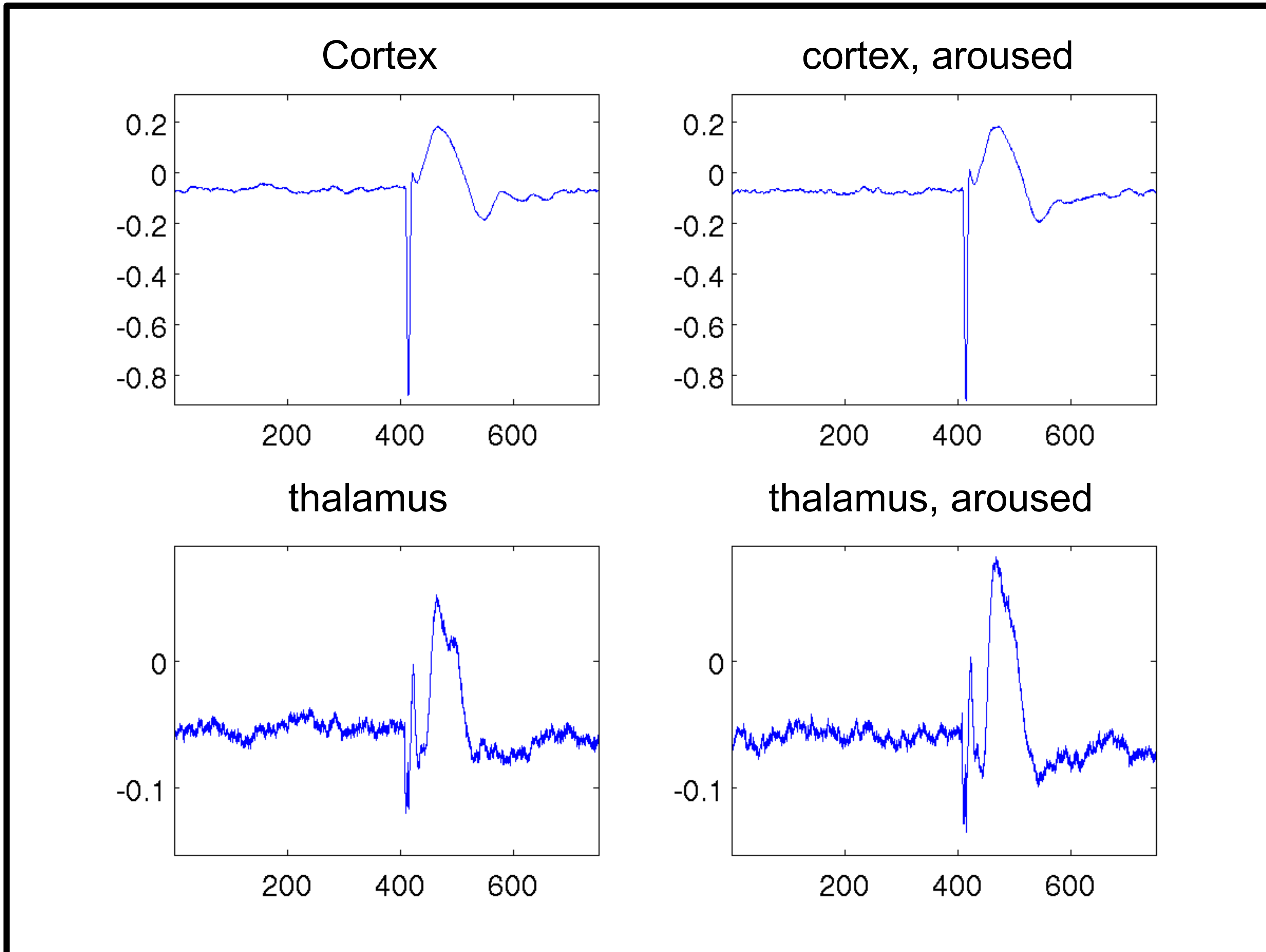
poduszka wibrysowa



Data: evoked potentials

cortex

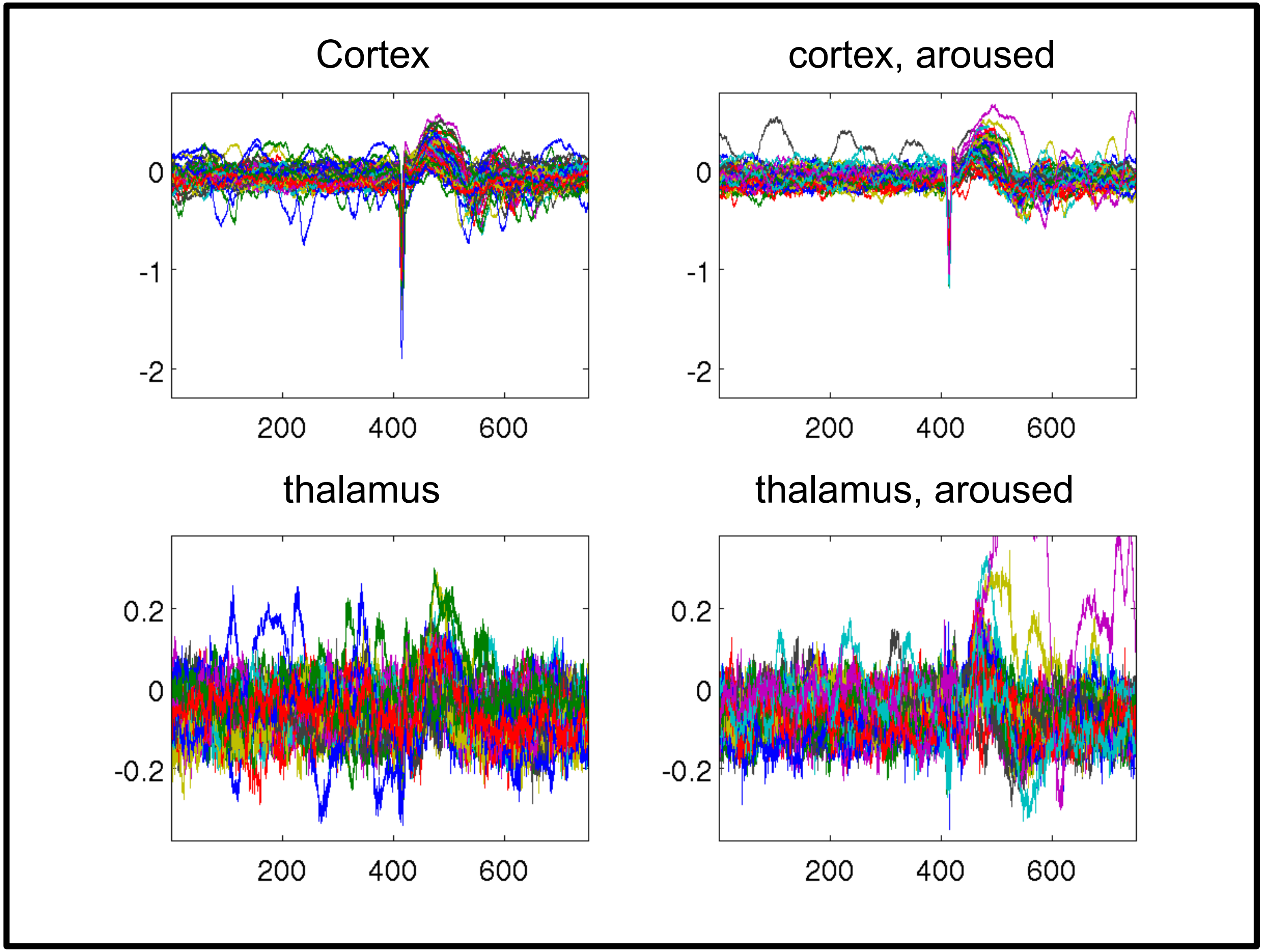
thalamus

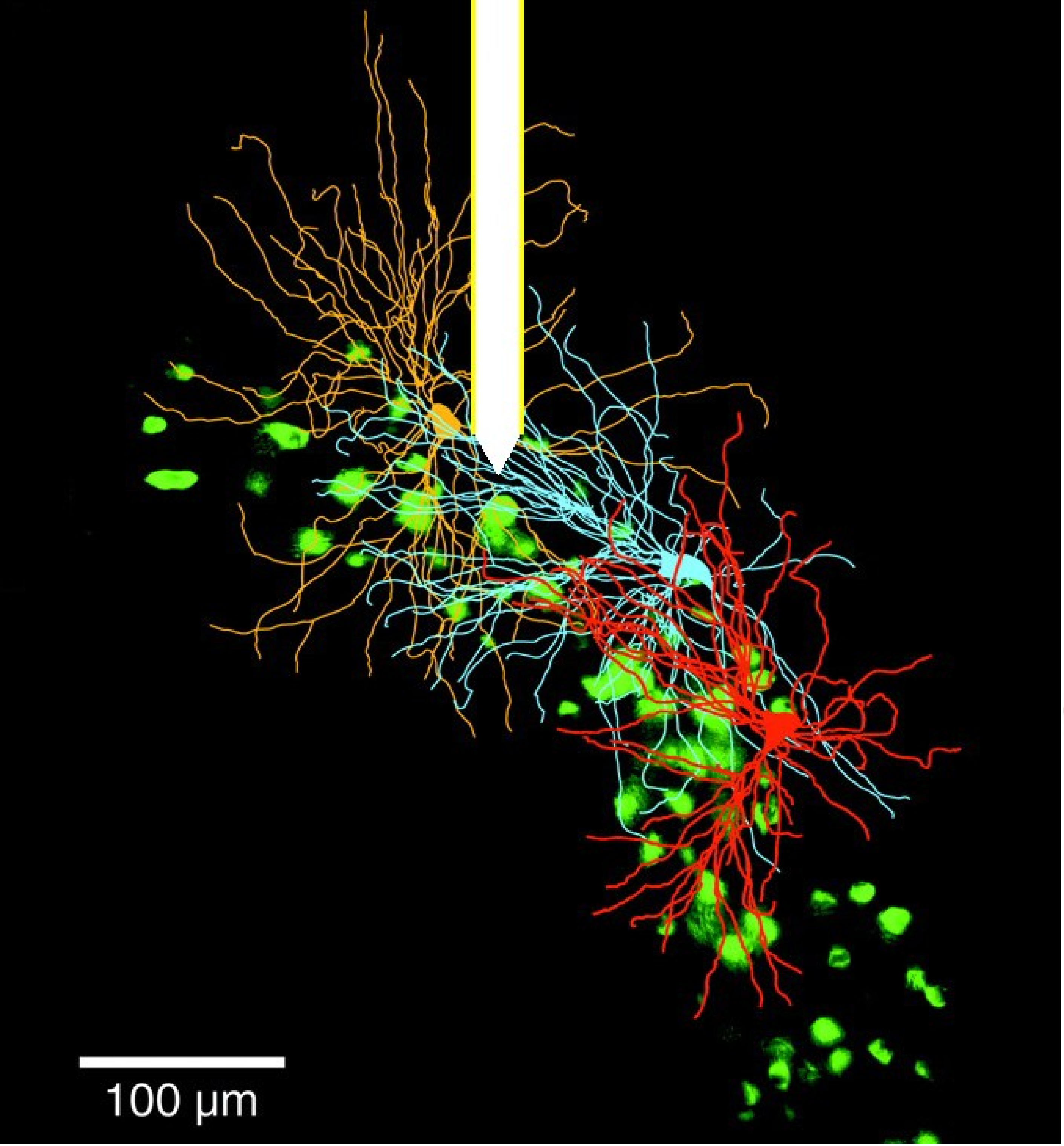


Data: evoked potentials

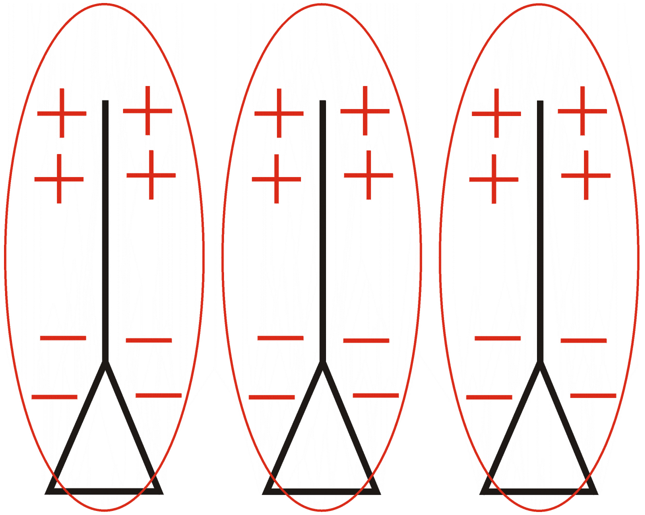
cortex

thalamus

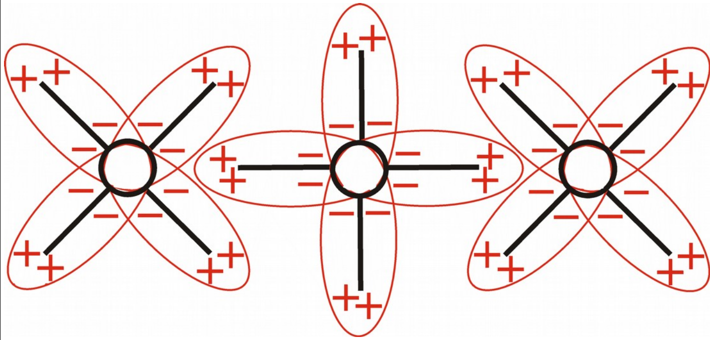




from Varga et al (2002) modified

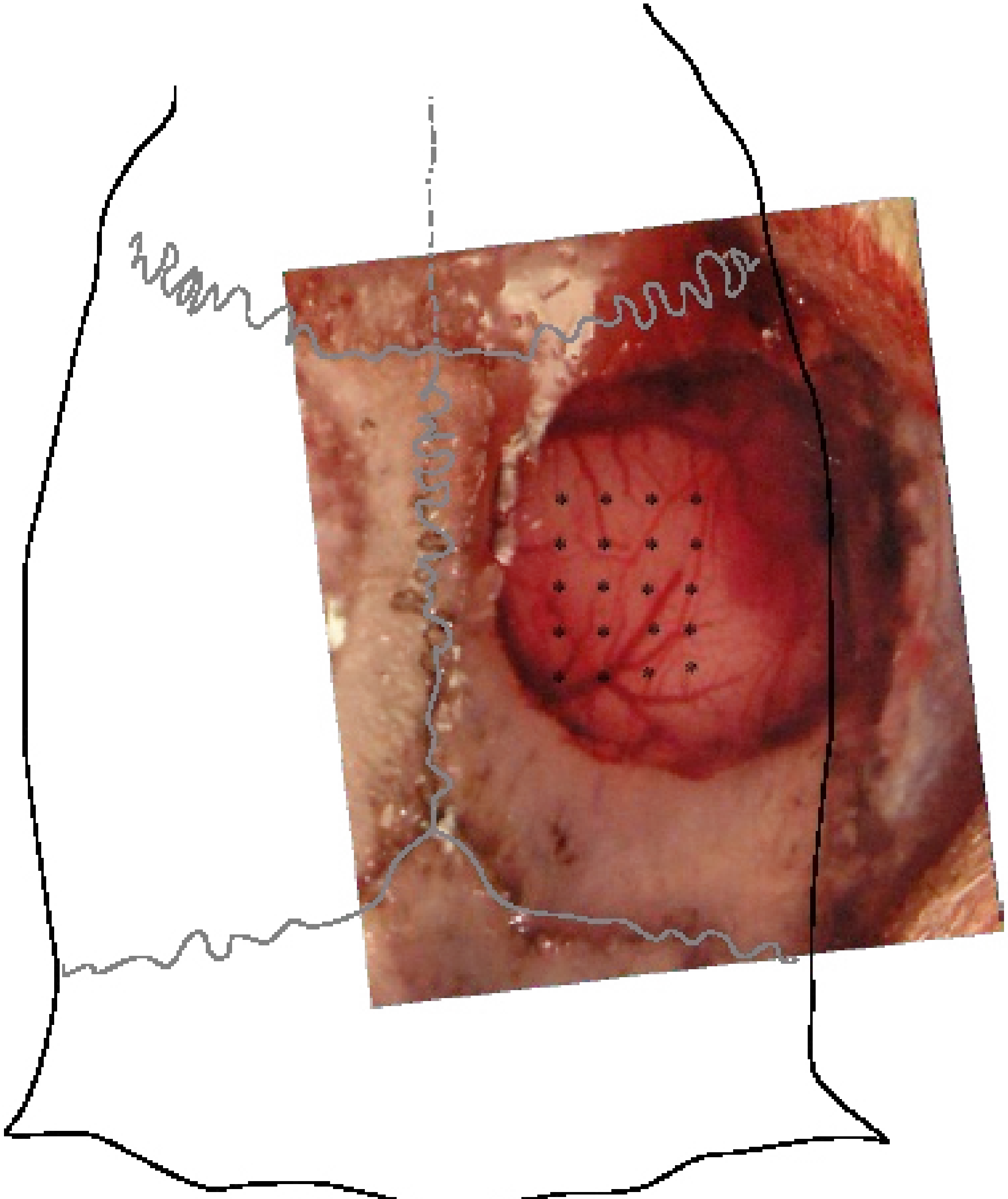


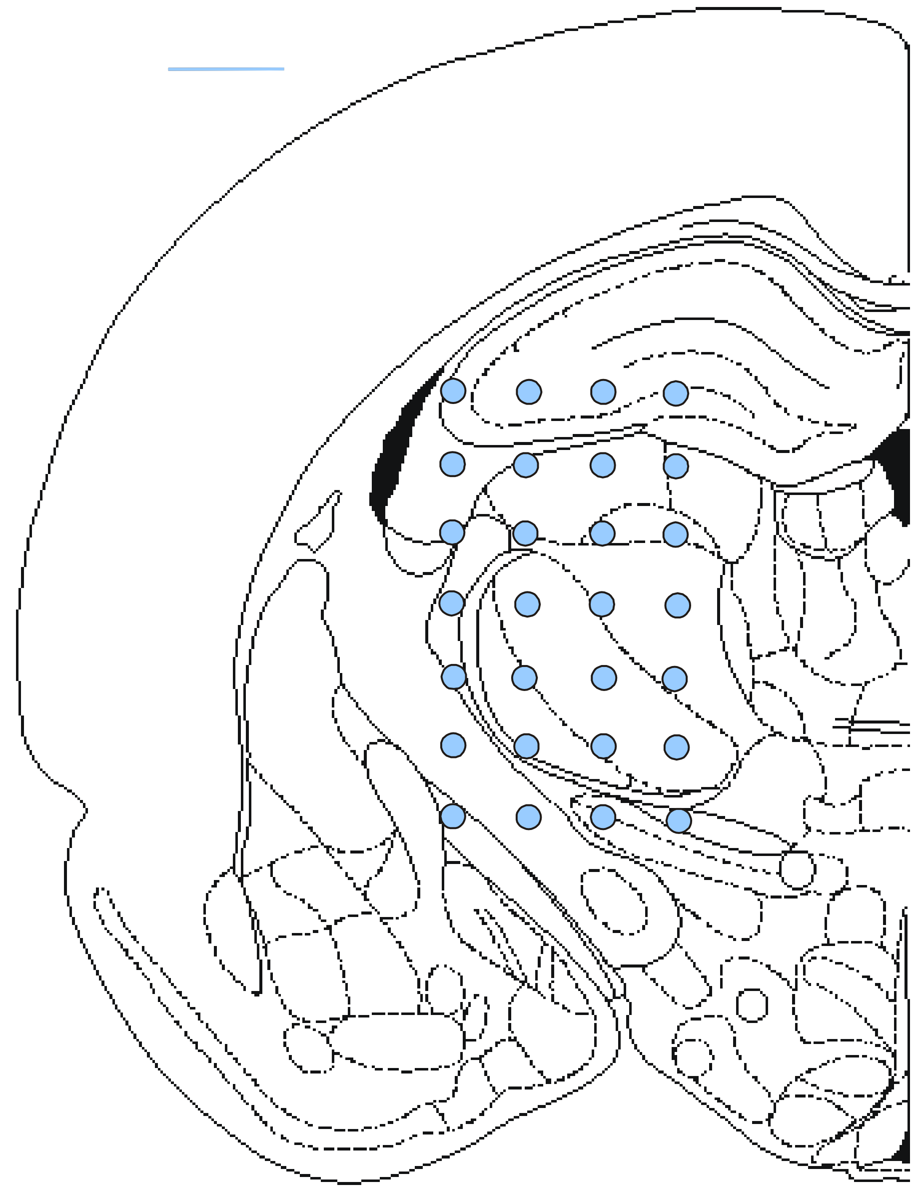
Open field



Closed field

Experimental setup





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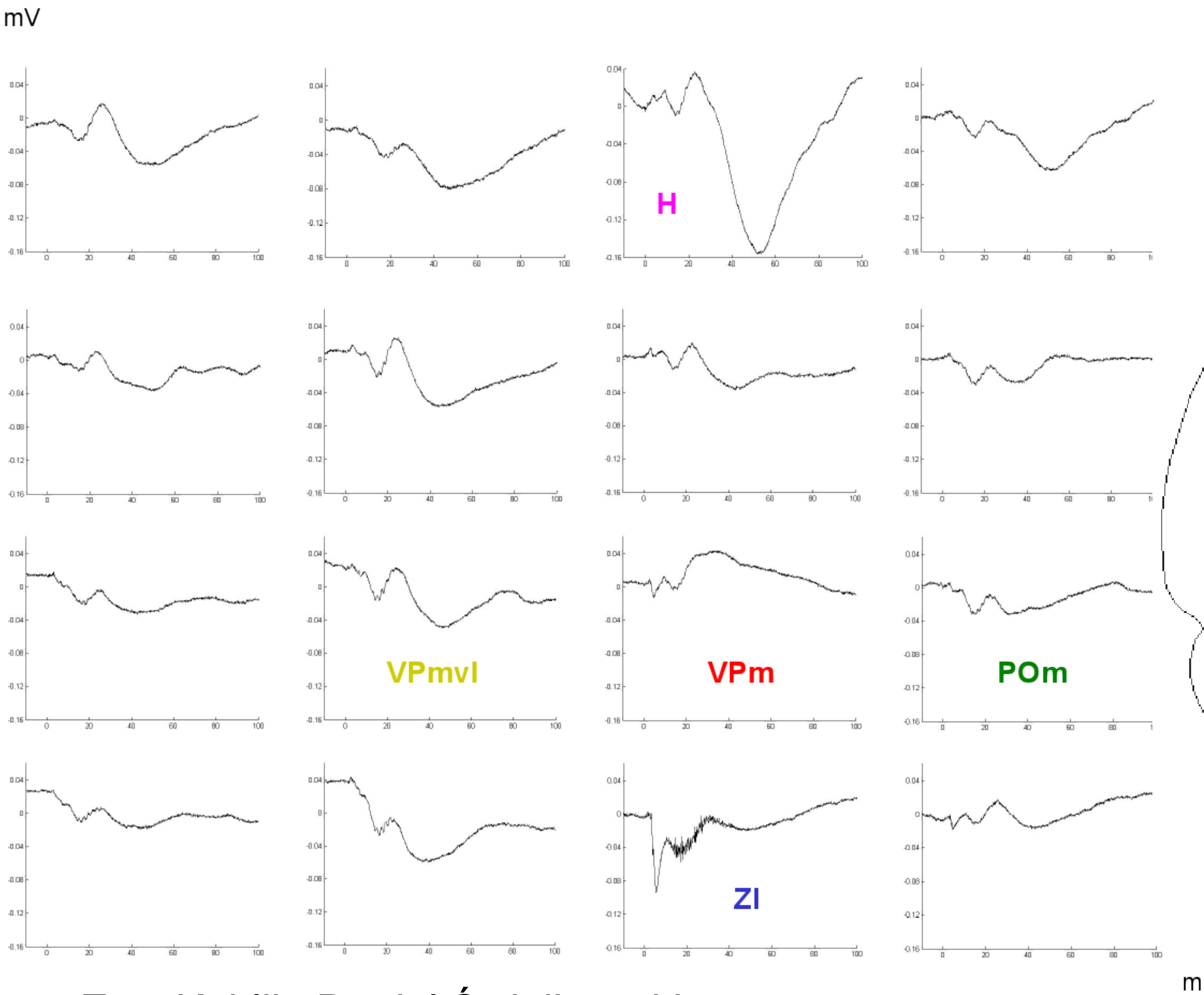
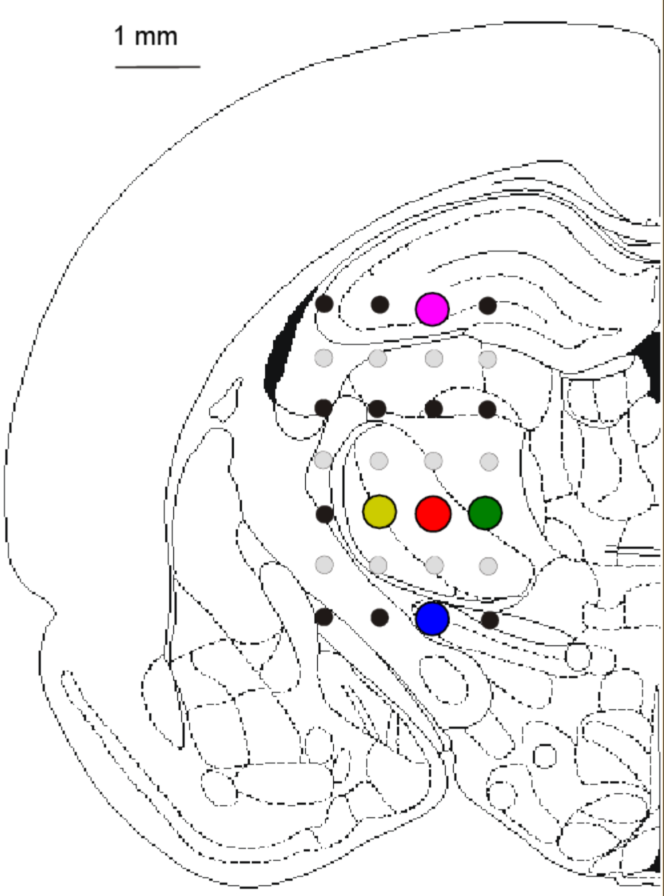
Example LFP
recorded in the rat forebrain



D. Świejkowski



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LFP

LFP = ~~Local Field Potential~~

LFP = Low Frequency Part
of the extracellular potential

How to deal with LFPs?

- Forward modeling:

  Find out LFPs in a model and connect them with network activity

- Inverse modeling:

  Find the sources of the potentials from data
  Current Source Density analysis [CSD]

CSD reconstruction methods

- Traditional CSD method

  Pitts, W.H. (1952) Investigations on synaptic transmission. In *Cybernetics*
  Freeman, J. A., & Nicholson, J. Neurophysiol. C. (1975), 38(2), 369–382.
  Mitzdorf, U. Physiol. Rev. (1985), 65, 37

- iCSD (inverse CSD method)

  Pettersen et al., J.Neurosci. Methods (2006)154(1–2), 116–133
  Łęski et al., Neuroinformatics (2007) 5, 207-222
  Łęski et al., Neuroinformatics(2011) Doi:10.1007/s12021-011-9111-4

- kCSD (kernel CSD method)

  Potworowski et al., Neural Computation (2012)24:541-575

Traditional CSD

$$C = -\nabla \cdot [\sigma \nabla V]$$

- Numerical second derivative in 1D (three-point formula)

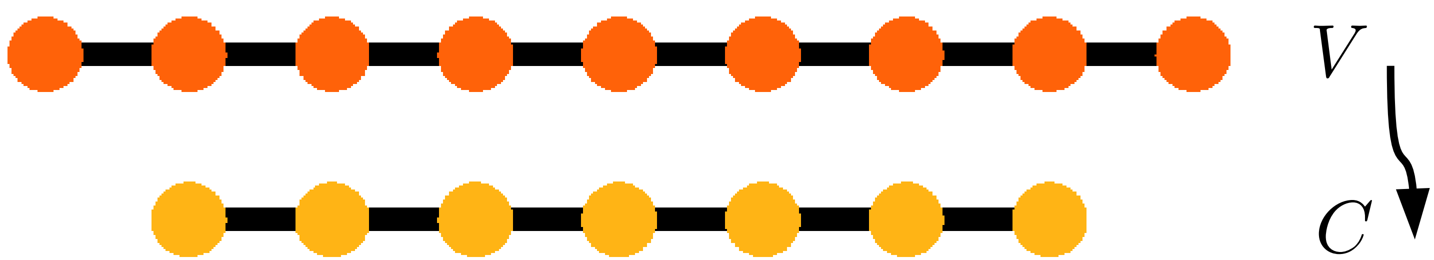
$$\frac{\partial^2 f}{\partial x^2} \simeq \frac{f(x+h) - 2f(x) + f(x-h)}{h^2}$$

- Problems:
  - Assumes homogeneity in y, z
  - Difficult to adapt to specific situation
  - Can't use at the boundary

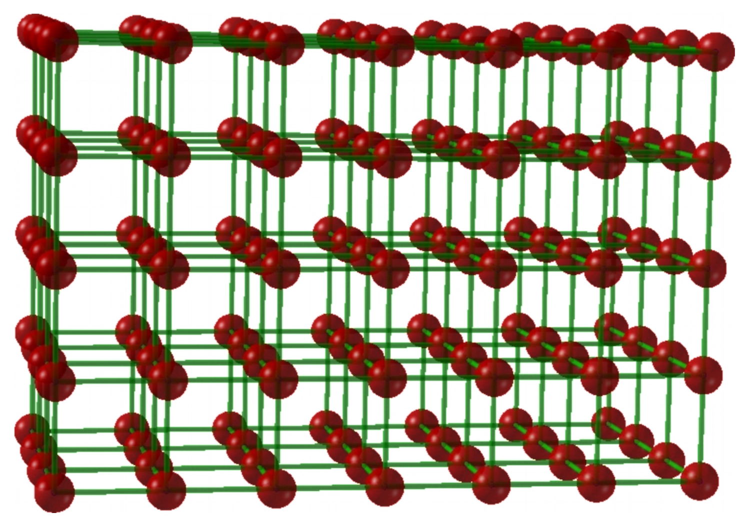
“Traditional” CSD method

$$C = -\sigma \frac{\partial^2 V}{\partial x^2} \approx -\sigma \frac{V(x+h) - 2V(x) - V(x-h)}{h^2}$$

In “traditional” CSD we lose points on the boundary:



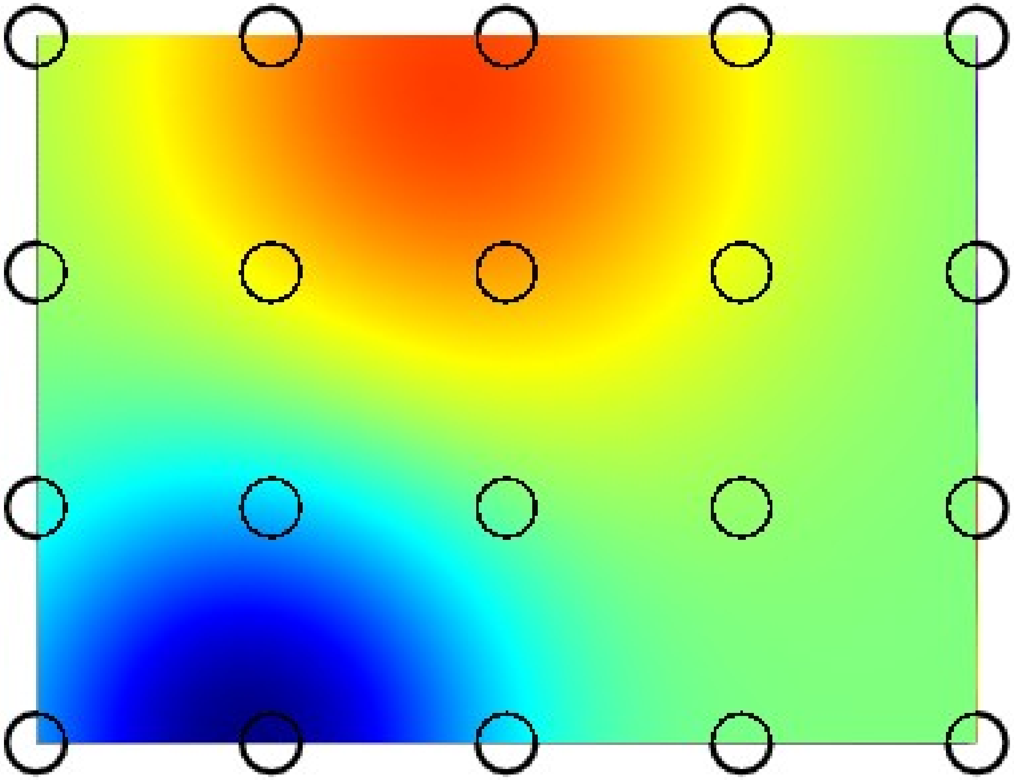
In 3D setup we considered (4x5x7)
inside: 2x3x5 = 30
boundary: 110 out of 140 points



Inverse current source density (iCSD)

Pettersen et al. 2006

- Assume N-parameter model of CSD e.g. interpolated on a grid



$$CSD(x) = \sum_{i=1}^{N} a_i \, \tilde{b}_i(x)$$

$$V_j = \sum_i L_{ji} a_i, L_{ji} = \tilde{b}_i(x_j)$$

$$\vec{a} = L^{-1}\vec{V}$$

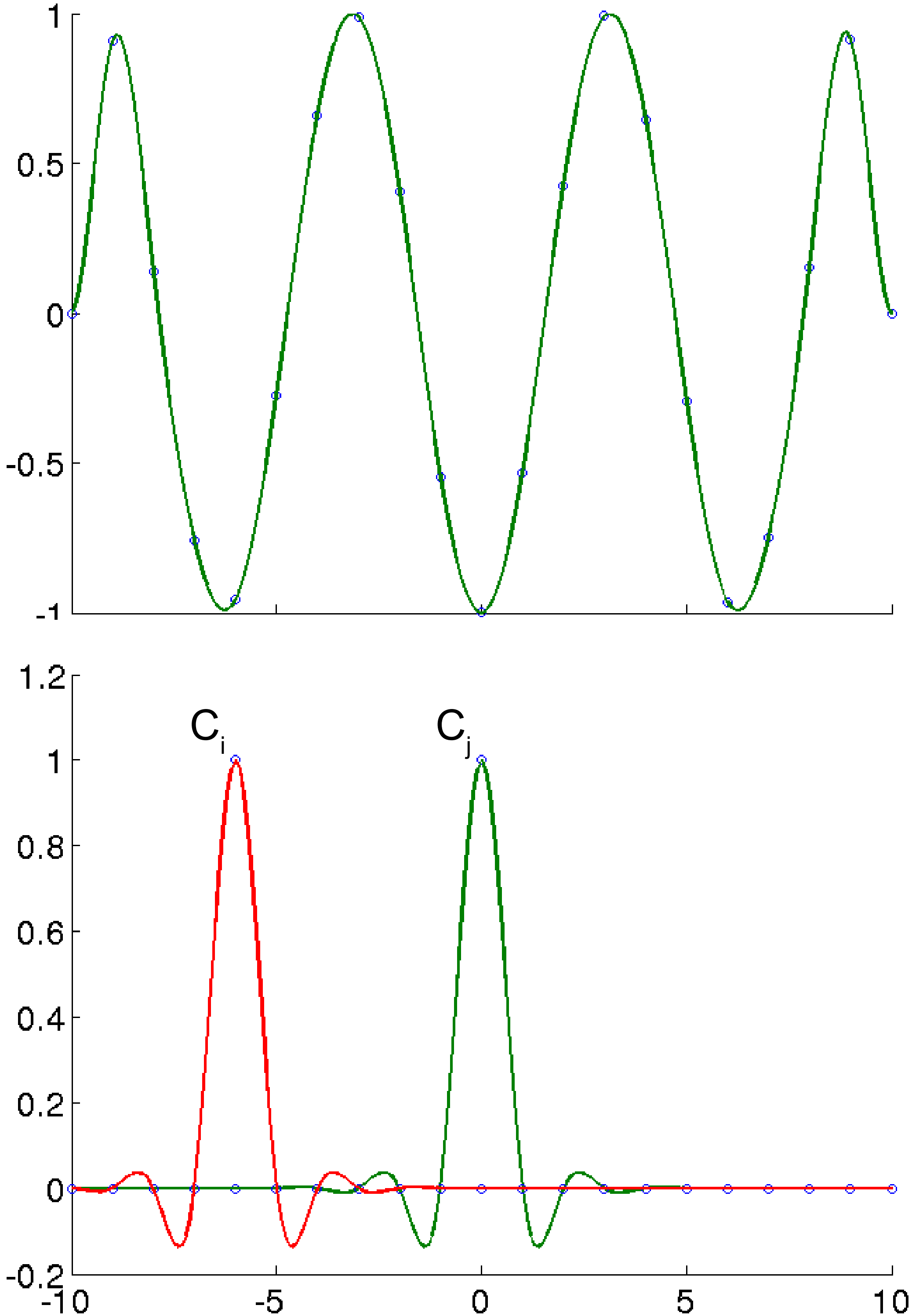
- Evaluate potentials on the grid by forward modeling

  V at grid points = F[N parameters of CSD]

- Invert F

  N parameters of CSD = F^{-1}[*V* at grid points]

Example



Inverse Current Source Density (iCSD)

$$C(\mathrm{x}) = \sum_{i=1}^{N} a_i \, \tilde{b}_i(\mathrm{x})$$

Family of CSD distributions

basis in the CSD space

$$b_i(x,y,z) = \mathcal{A}\widetilde{b}_i(x,y,z) = \frac{1}{4\pi\sigma} \int \mathrm{d}\mathbf{x}' \, \frac{\widetilde{b}_i(\mathbf{x}')}{|\mathbf{x}-\mathbf{x}'|}.$$

basis in the space of potentials

$$V(\mathrm{x}) = \mathcal{A}C(\mathrm{x}) = \sum_{i=1}^{N} a_i \, b_i(\mathrm{x})$$

Kernel Current Source Density (kCSD)

$$C(\mathrm{x}) = \sum_{i=1}^{M} a_i \, \tilde{b}_i(\mathrm{x})$$

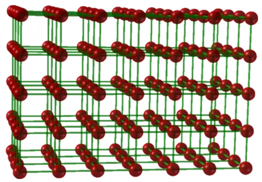
Family of CSD distributions
(think M large, M ≫ N)

basis in the CSD space

$$b_i(x, y, z) = \mathcal{A}\widetilde{b}_i(x, y, z) = \frac{1}{4\pi\sigma} \int \mathrm{d}\mathbf{x}' \, \frac{\widetilde{b}_i(\mathbf{x}')}{|\mathbf{x} - \mathbf{x}'|}.$$

basis in the space of potentials

$$V(\mathrm{x}) = \mathcal{A}C(\mathrm{x}) = \sum_{i=1}^{M} a_i \, b_i(\mathrm{x})$$

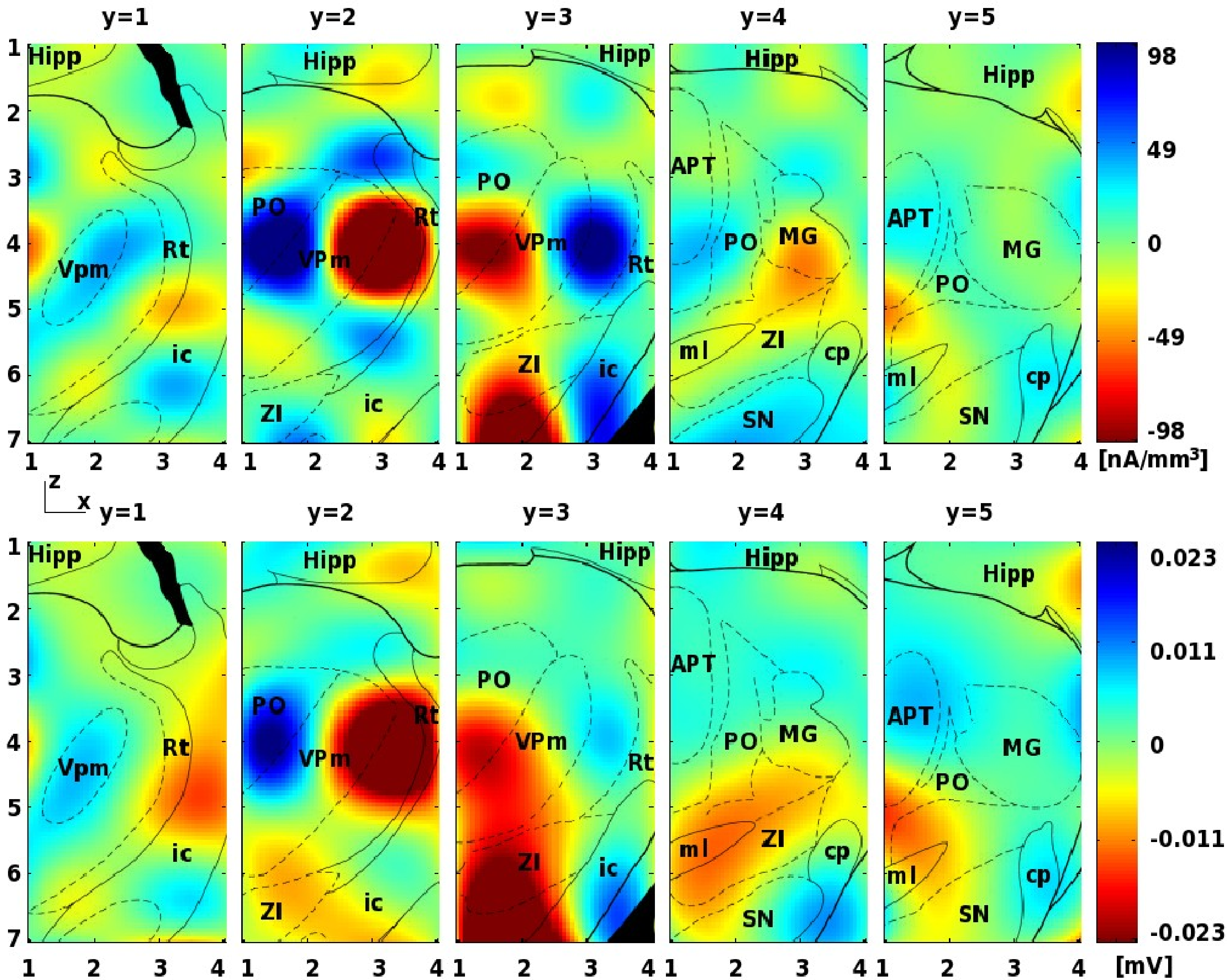


iCSD in 3D

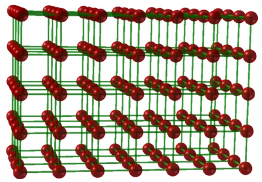
Daniel Świejkowski, Ewa Kublik, Andrzej Wróbel

Current Source Density

Interpolated field potential



Łęski et al. (2007) Neuroinformatics



iCSD in 3D

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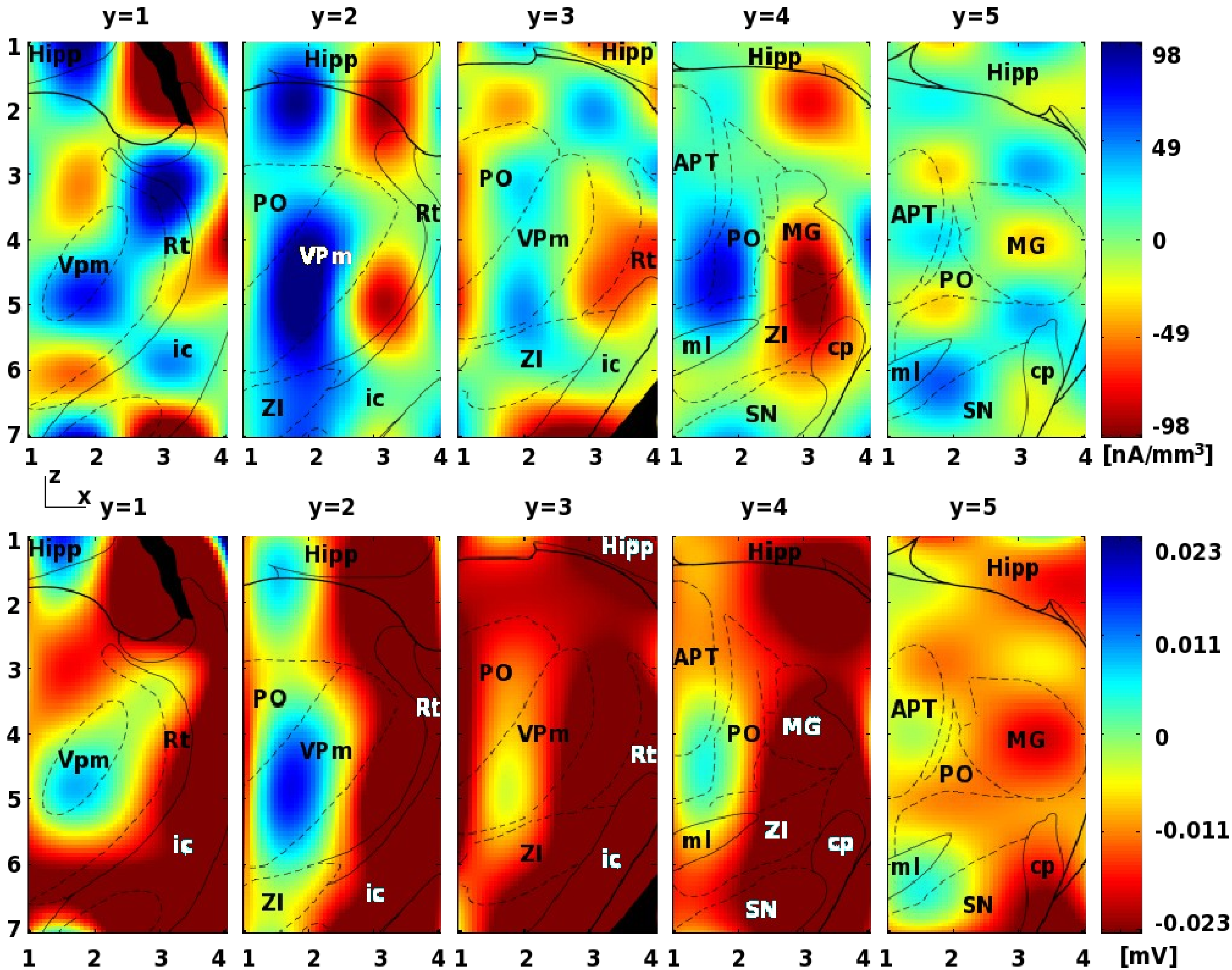
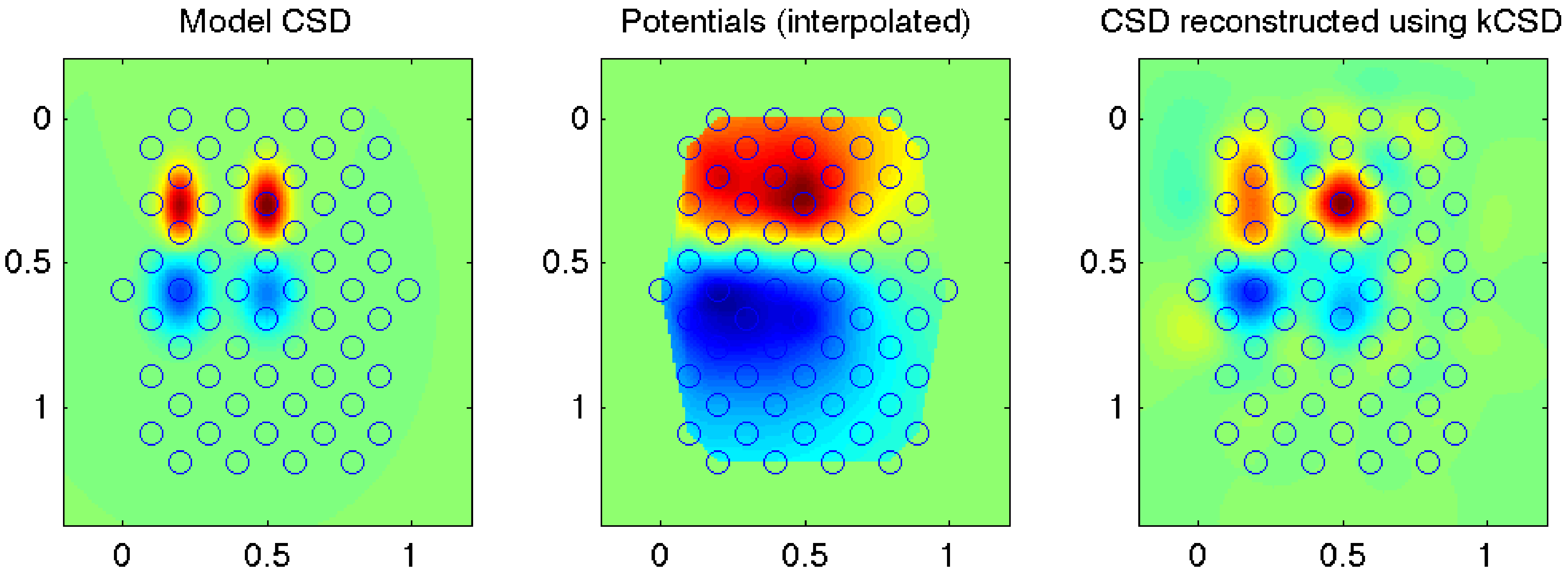


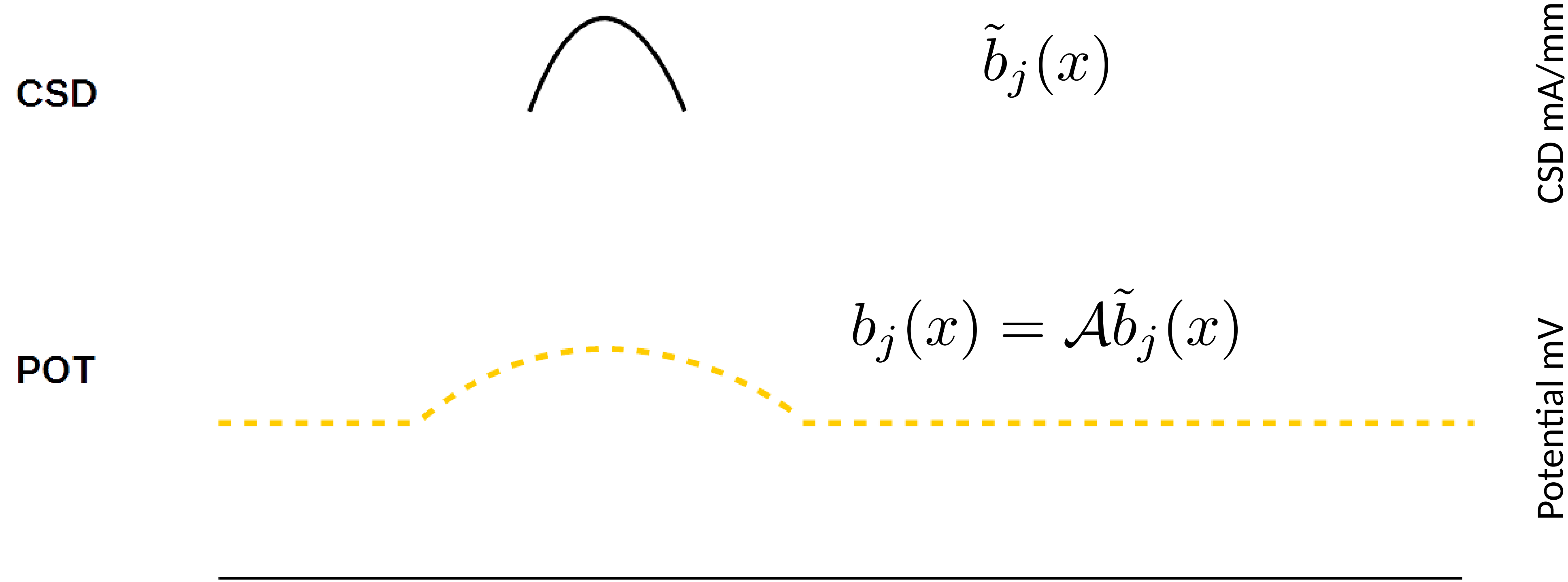
Łęski et al. (2007) Neuroinformatics

Kernel Current Source Density: kCSD

- Nonparametric method
- Use overcomplete bases
- Arbitrary distribution of contacts
- Deals with noise



Potworowski et al. (2012) Neural Comp.



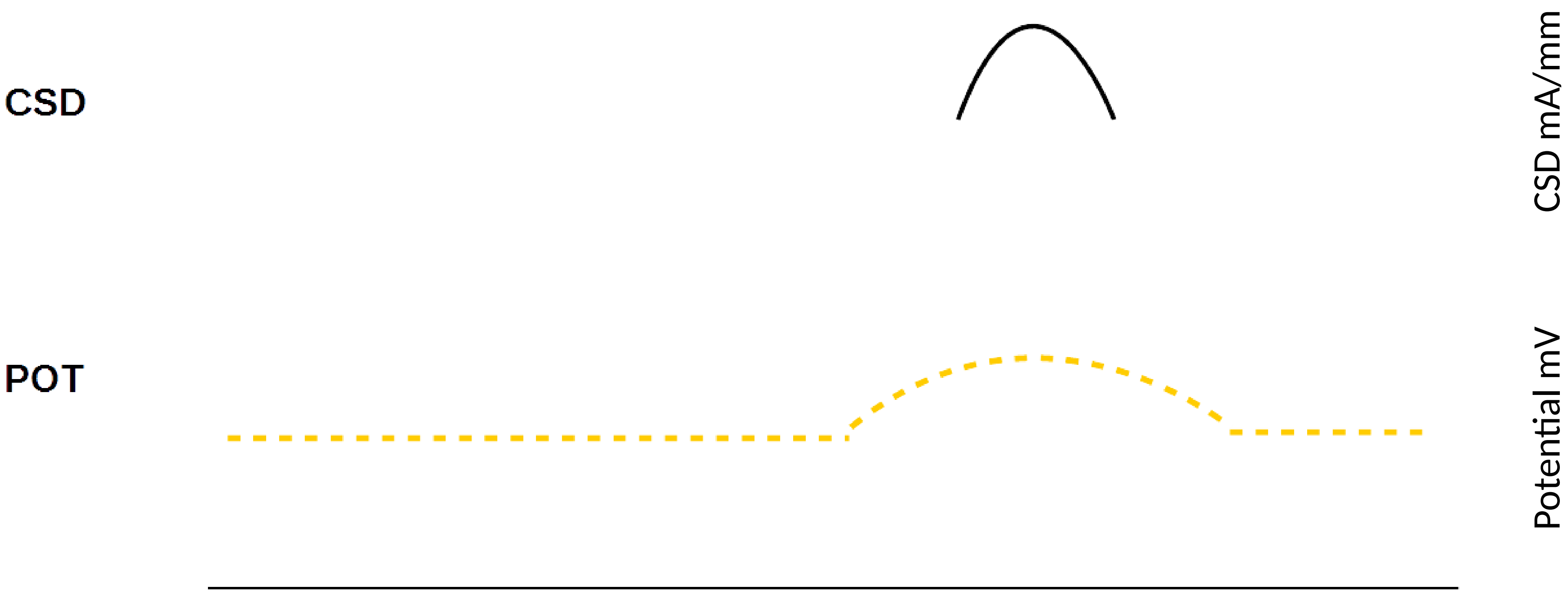
$$\tilde{b}_j(x)$$

$$b_j(x) = \mathcal{A}\tilde{b}_j(x)$$

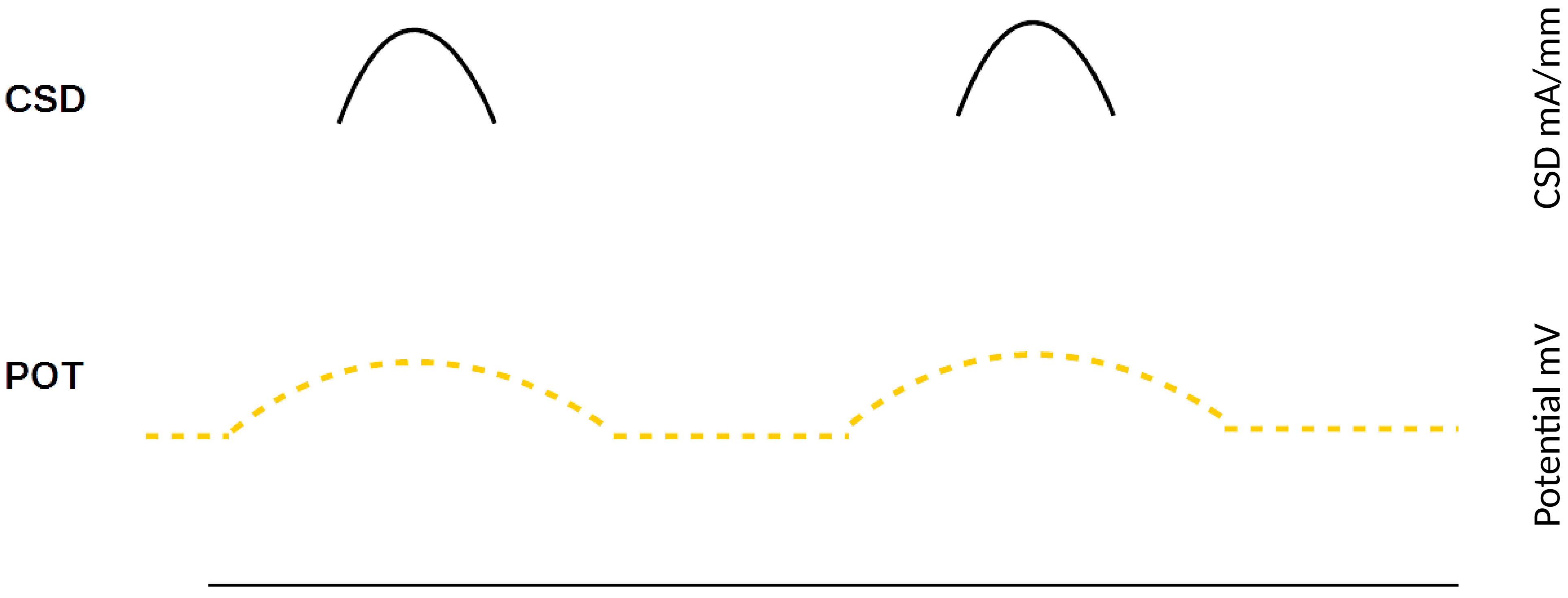
In 3D:

$$b_j(x) = \mathcal{A}\tilde{b}_j(x) = \frac{1}{4\pi\sigma}\int dx' \frac{\tilde{b}_j(x')}{|x - x'|}$$

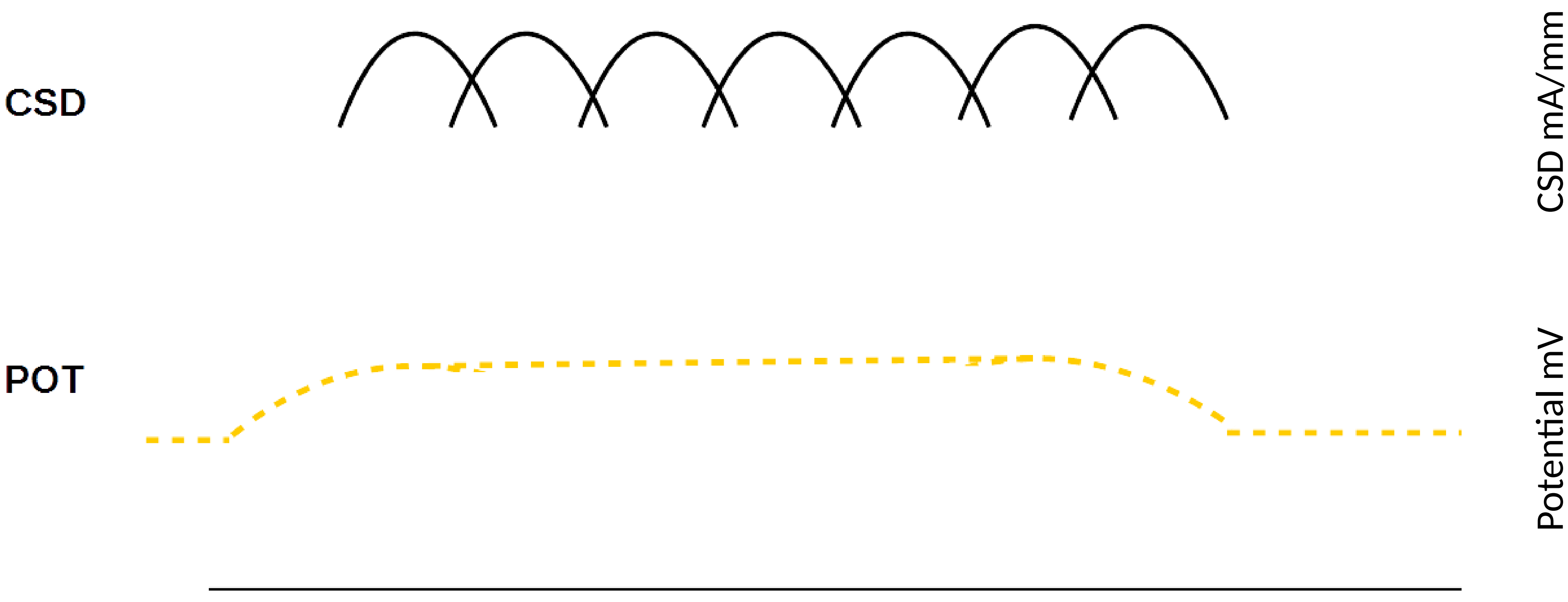
(Chaitanya Chintaluri)



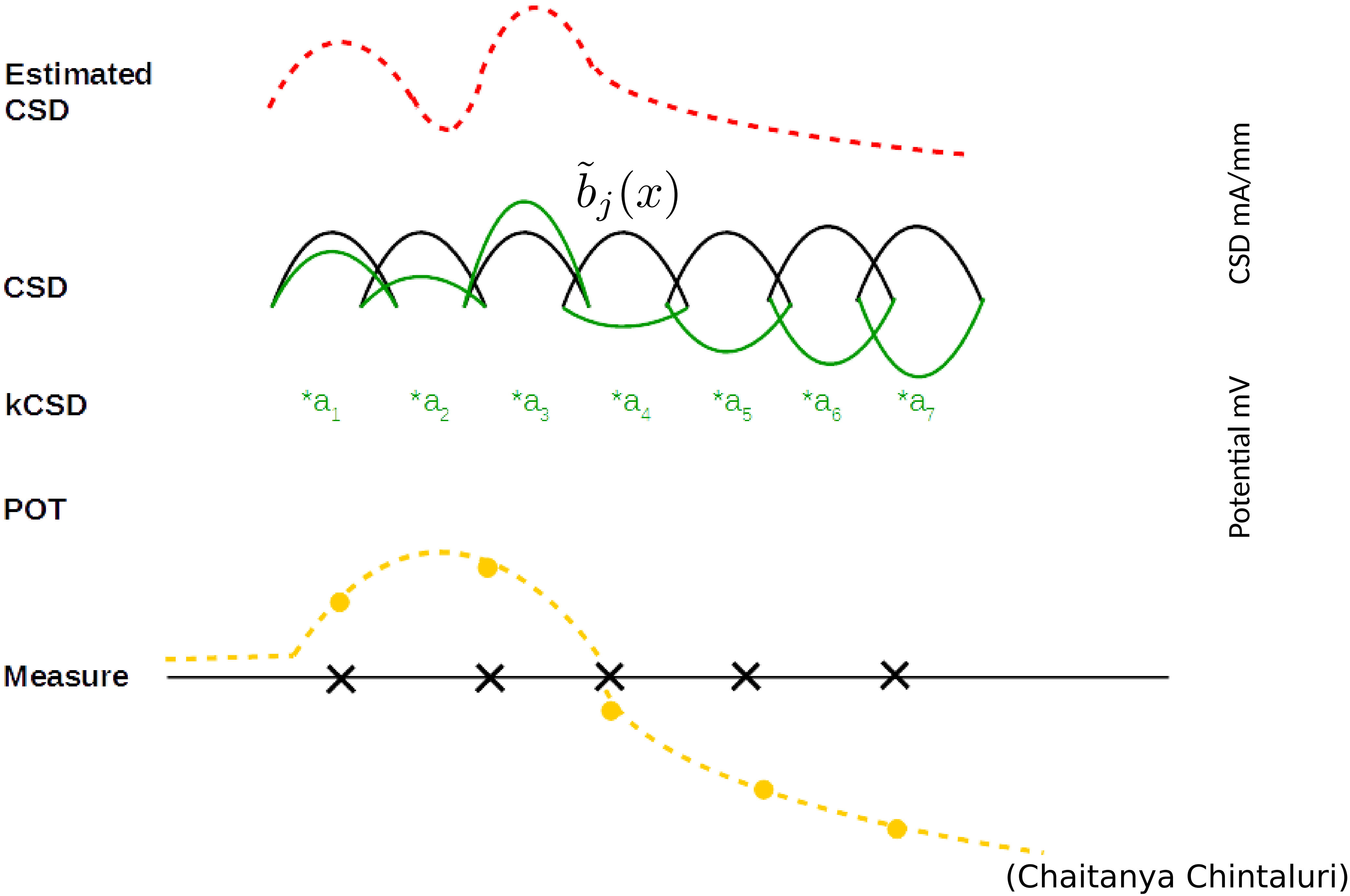
(Chaitanya Chintaluri)



(Chaitanya Chintaluri)



(Chaitanya Chintaluri)


Estimated CSD
$\tilde{b}_j(x)$
CSD
kCSD
*a1
*a2
*a3
*a4
*a5
*a6
*a7
POT
Measure
CSD mA/mm
Potential mV
(Chaitanya Chintaluri)

Challenge

How to estimate 1000 parameters
from 10 measurements?

Challenge

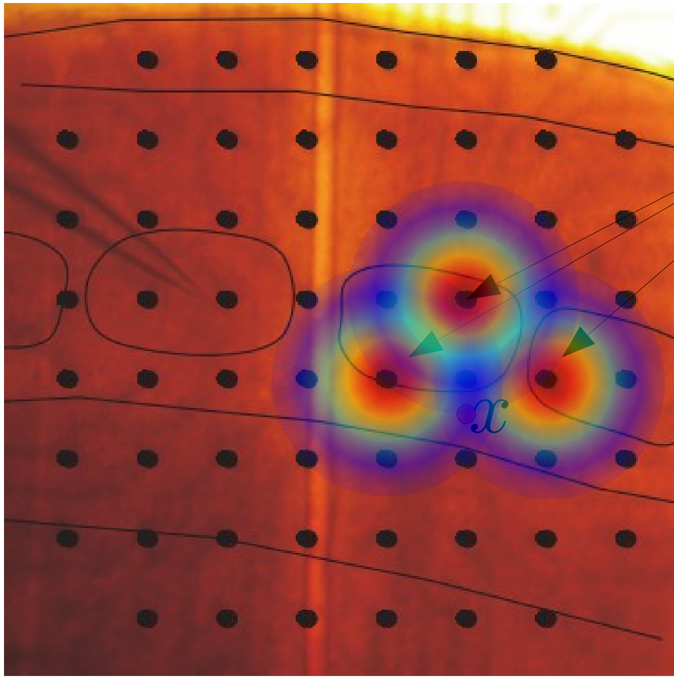
How to estimate 1000 parameters
from 10 measurements?

How to solve Poisson equation when C and V are not known, we only know V at 10 points

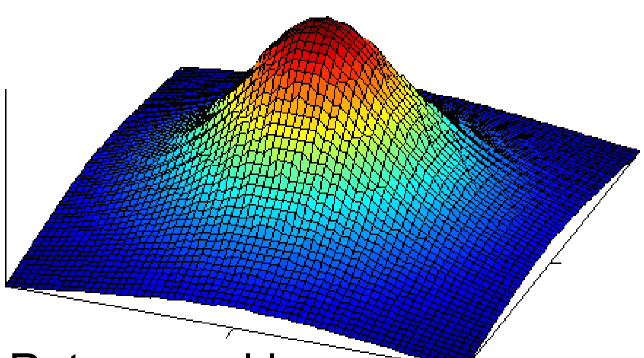
$$C = -\nabla \cdot [\sigma \nabla V]$$

Step 1: Kernel Interpolation of Potential

$x_1, \ldots, x_n \quad V_1, \ldots, V_n \quad V(x) = ?$



$K(x_i, x)$



Jan Potworowski

$$K(\mathbf{x}, \mathbf{x}') = \sum_{i=1}^{M} b_i(\mathbf{x}) b_i(\mathbf{x}')$$

$$V(x) = \sum_{i=1}^{N} \beta_i K(x_i, x)$$

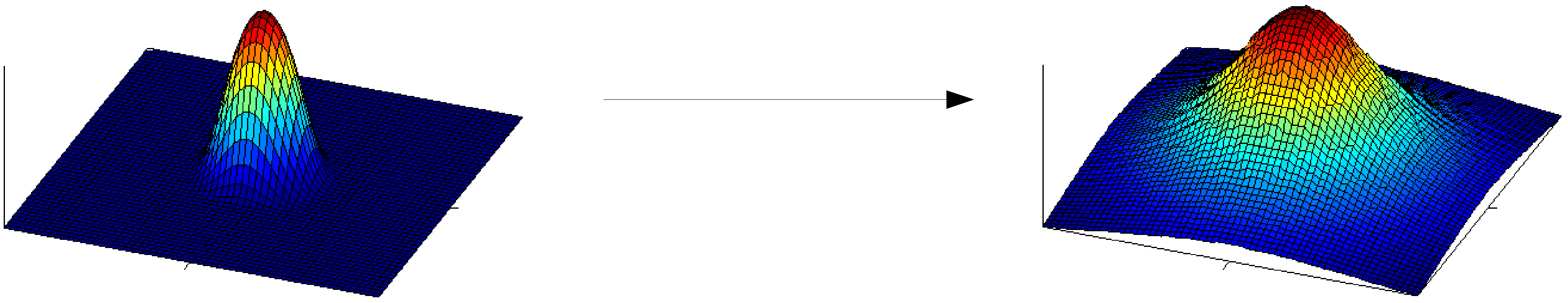
$$err\left(\hat{V}\right) = \sum_{i=1}^{N} \left(\hat{V}(x_i) - V_i\right)^2$$

$$\boldsymbol{\beta} = \mathbf{K}^{-1} \cdot \mathbf{V}$$

Tichonow Regression

Step 2: From potential to the CSD

$$C(\vec{r},t) = \mathcal{A}^{-1} V(\vec{r},t) \qquad V(\vec{r},t) = \mathcal{A} C(\vec{r},t)$$

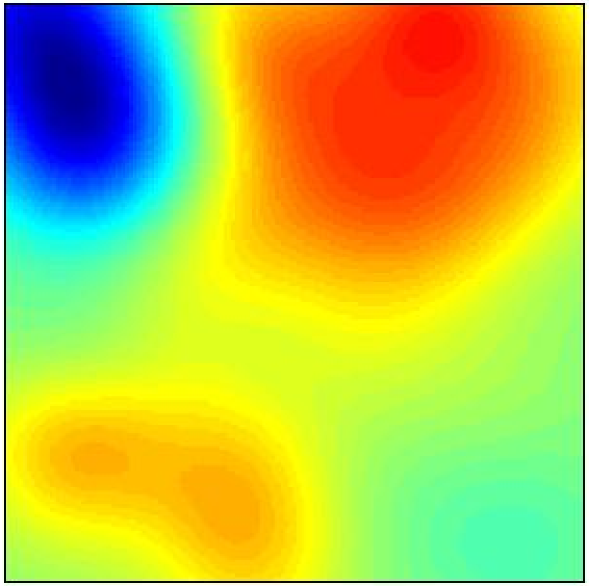


$$C^*(\mathbf{x}) = \widetilde{\mathbf{K}}^T(\mathbf{x}) \cdot \mathbf{K}^{-1} \cdot \mathbf{V}$$

$$\tilde{K}(\mathbf{x},\mathbf{x}') = \mathcal{A}^{-1} K(\mathbf{x},\mathbf{x}') = \sum_{i=1}^{M} \tilde{b}_i(\mathbf{x}) b_i(\mathbf{x}')$$

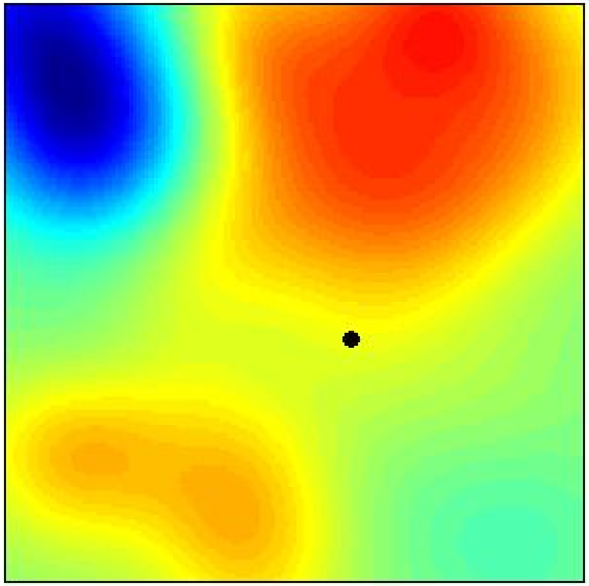
Jan Potworowski

CSD in the tissue



Jan Potworowski

CSD in the tissue

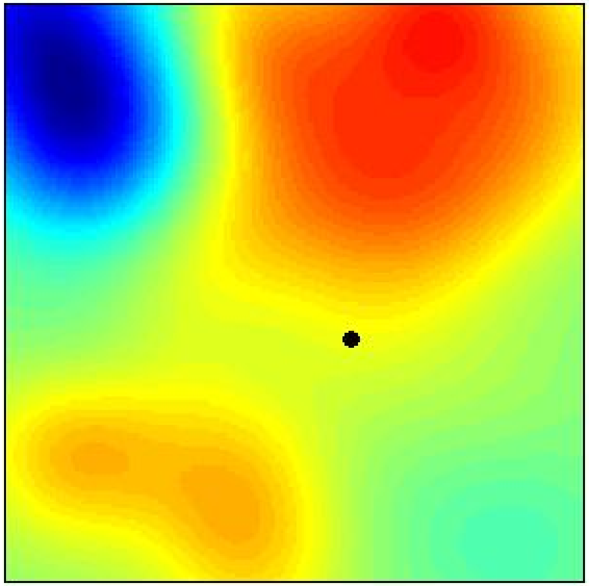


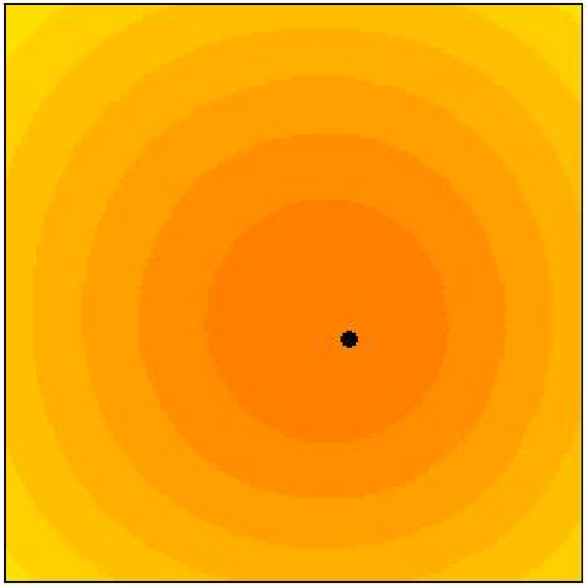
1 electrode

Jan Potworowski

CSD in the tissue

Interpolated potential

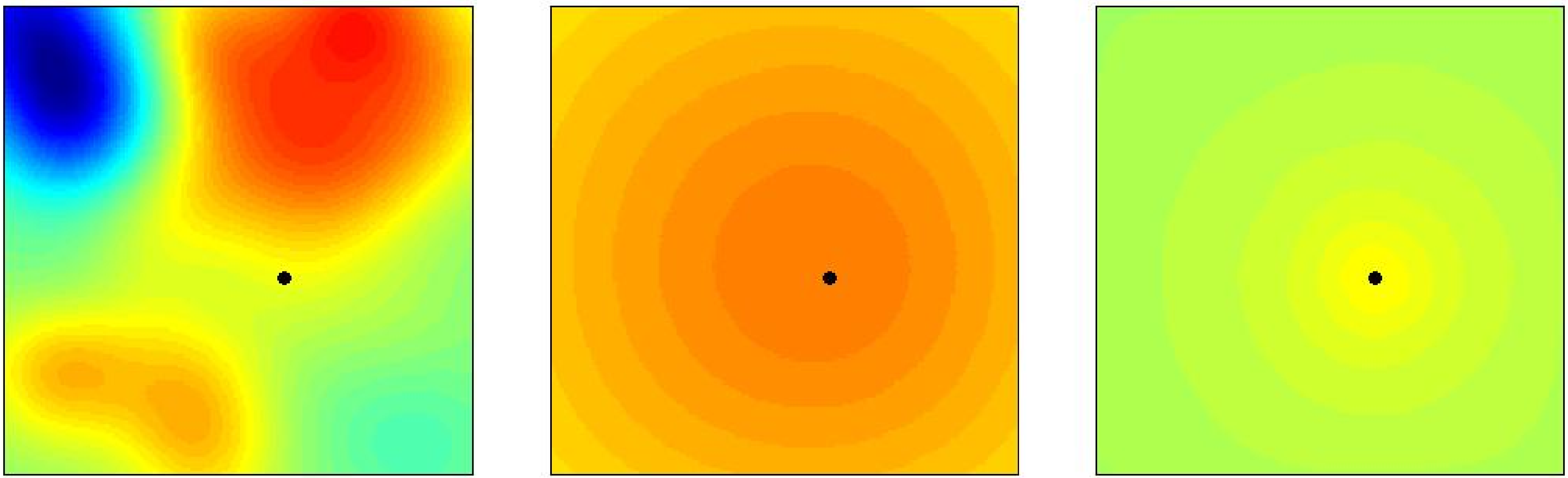




1 electrode

Jan Potworowski

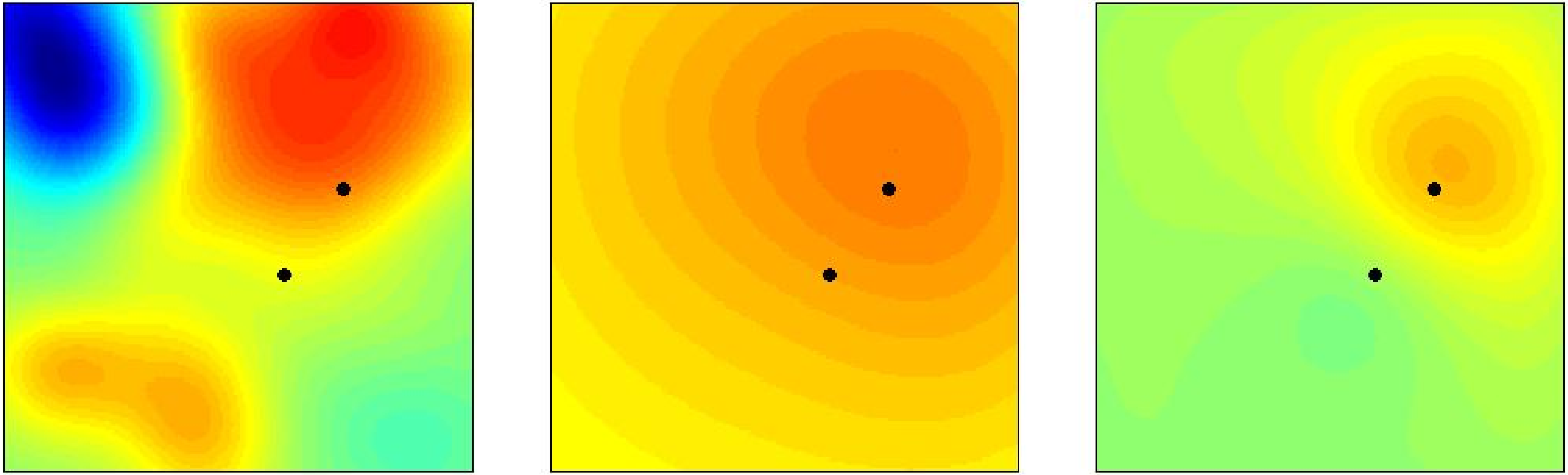
CSD in the tissue | Interpolated potential | Reconstructed CSD



1 electrode

Jan Potworowski

CSD in the tissue | Interpolated potential | Reconstructed CSD



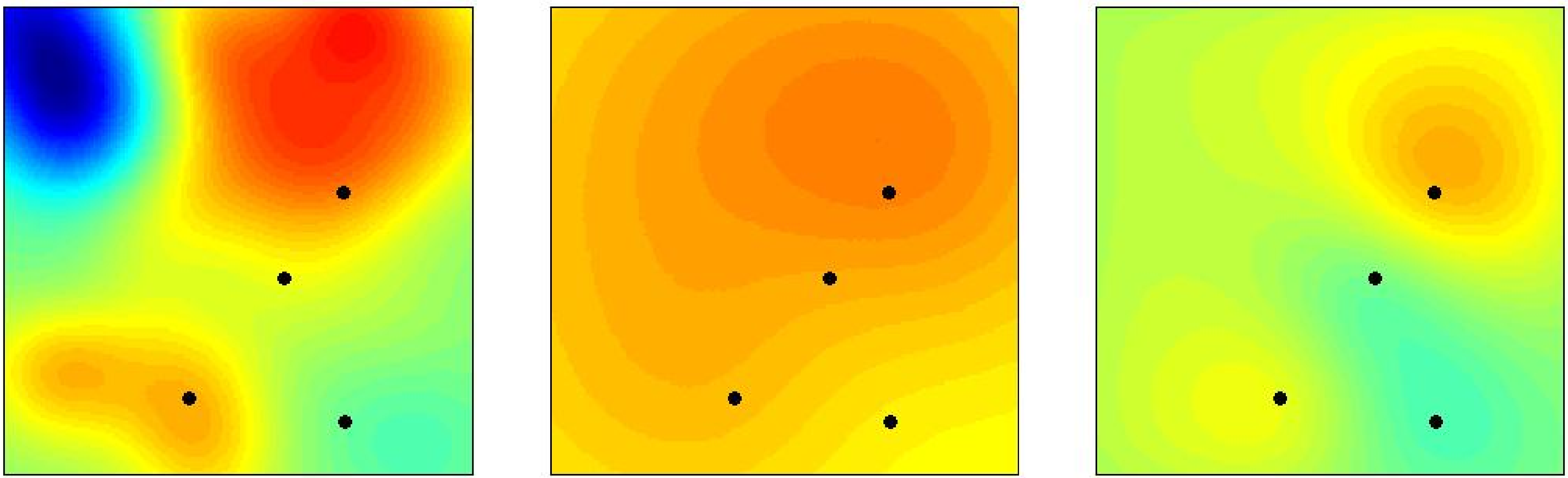
2 electrodes

Jan Potworowski

CSD in the tissue

Interpolated potential

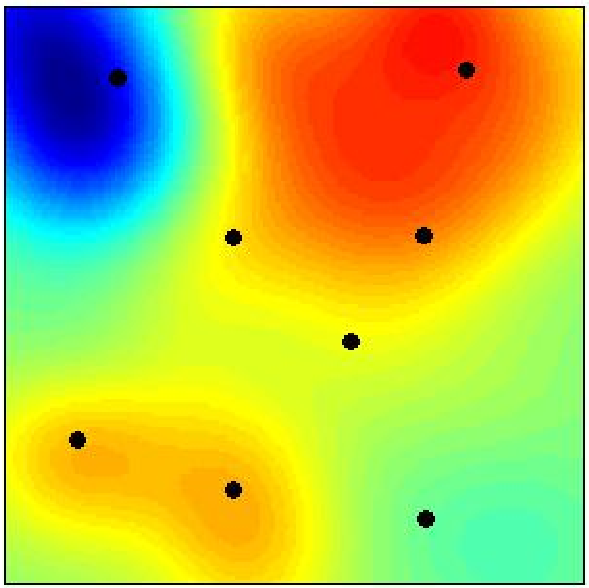
Reconstructed CSD



4 electrodes

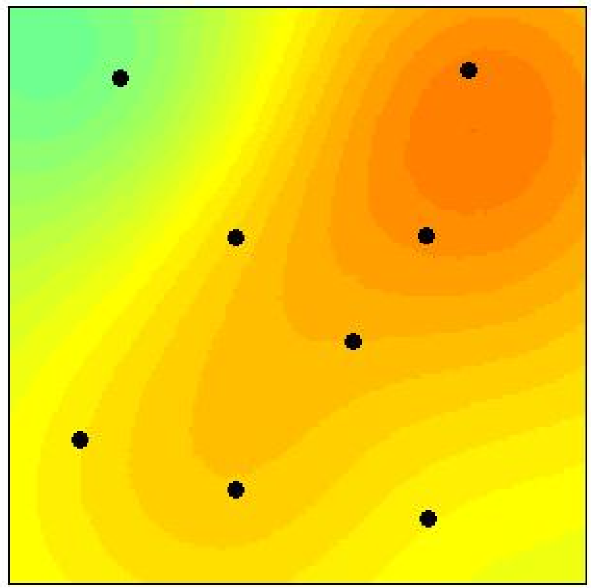
Jan Potworowski

CSD in the tissue

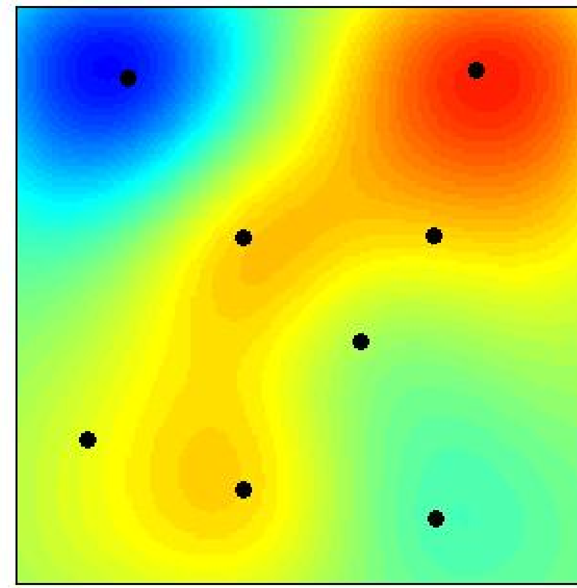


8 electrodes

Interpolated potential

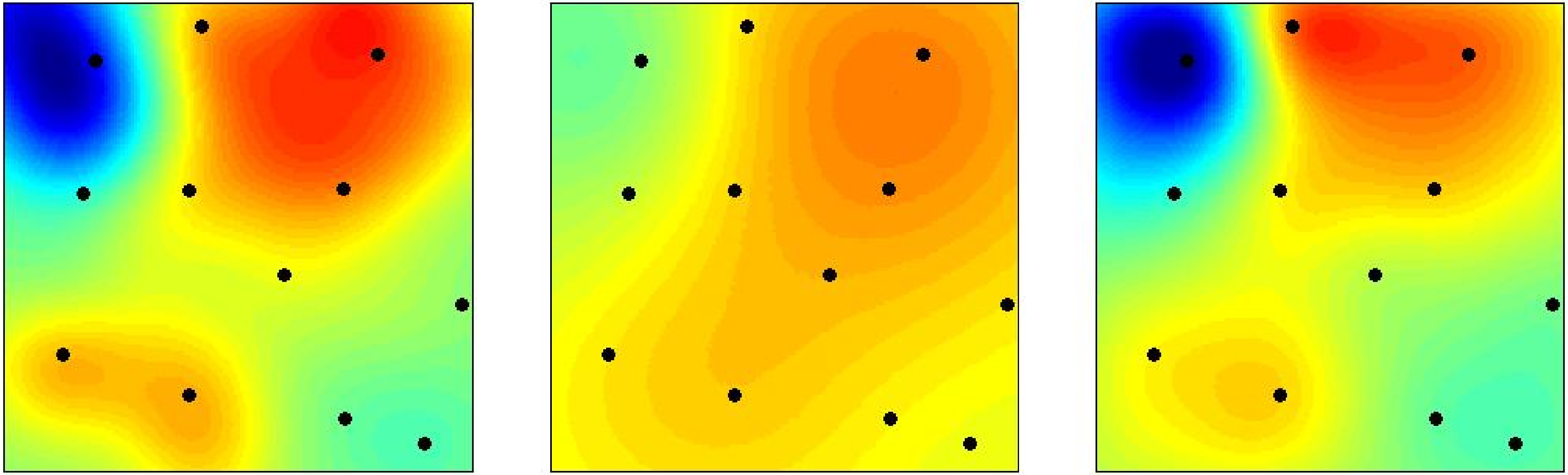


Reconstructed CSD



Jan Potworowski

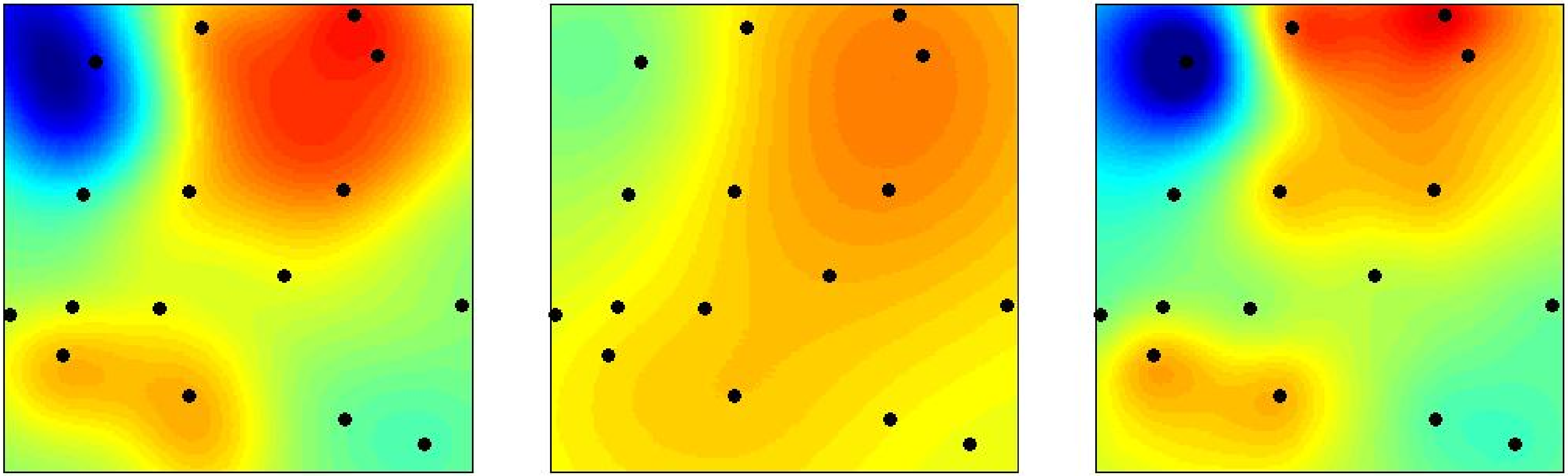
CSD in the tissue | Interpolated potential | Reconstructed CSD



12 electrodes

Jan Potworowski

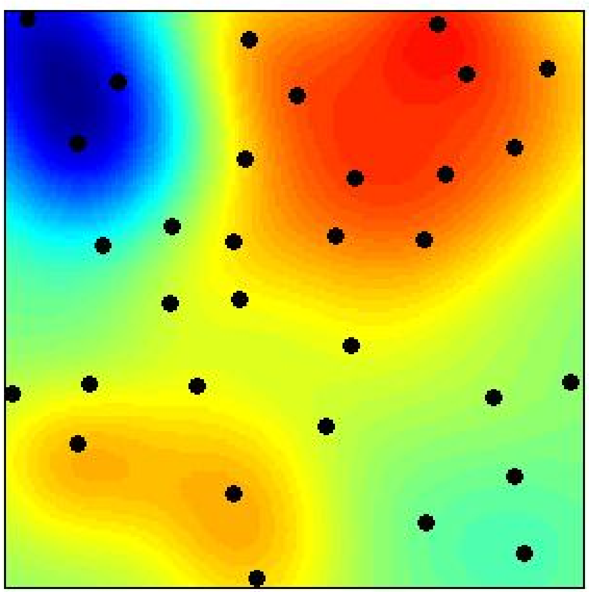
CSD in the tissue | Interpolated potential | Reconstructed CSD



16 electrodes

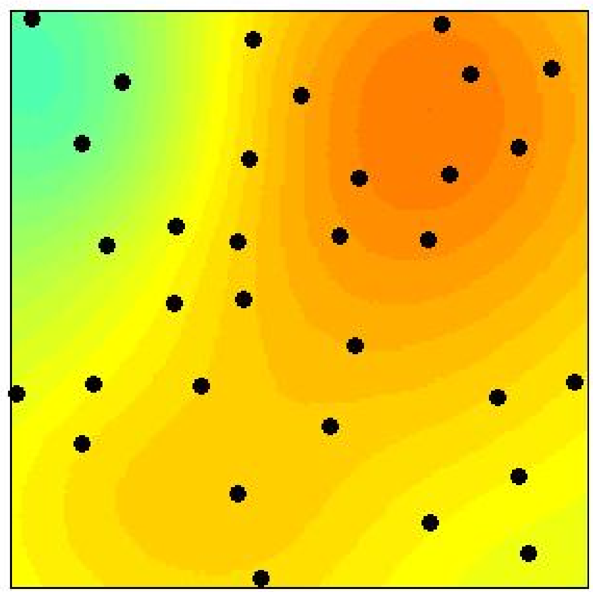
Jan Potworowski

CSD in the tissue

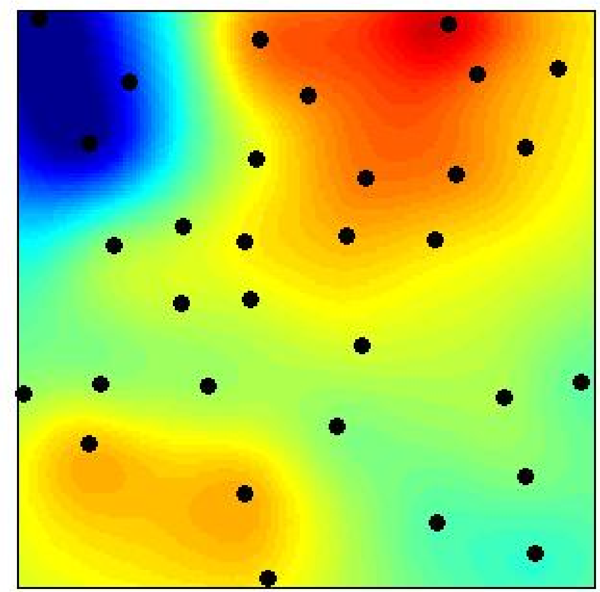


32 electrodes

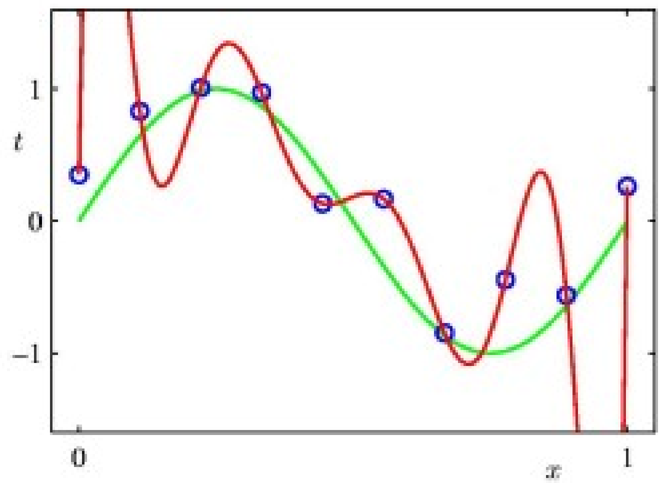
Interpolated potential



Reconstructed CSD



Jan Potworowski



kCSD – regularization

$$\sum_{i=1}^{N}\left(\underbrace{\sum_{j=1}^{N}\beta_j K(\mathbf{x}_j,\mathbf{x}_i)}_{V^*(\mathbf{x}_i)} - V_i\right)^2 = 0.$$

minimize

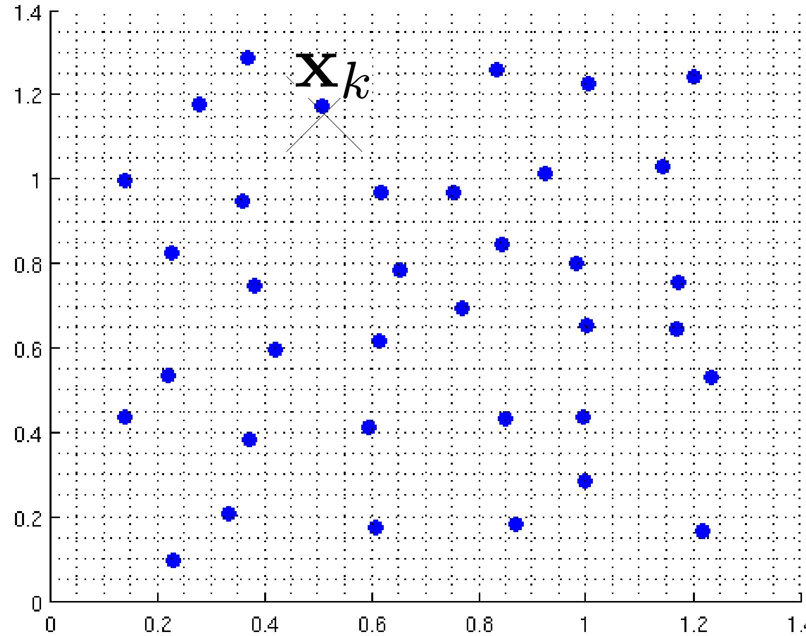
$$\sum_{i=1}^{N}(V^*(\mathbf{x}) - V_i)^2 + \lambda\sum_{i=1}^{N}\|V(x)\|^2$$

$$\beta = (\mathbf{K} + \lambda\mathbf{I})^{-1}\cdot\mathbf{V}$$

$$C^*(\mathbf{x}) = \widetilde{\mathbf{K}}^T(\mathbf{x})\cdot(\mathbf{K} + \lambda\mathbf{I})^{-1}\cdot\mathbf{V}$$

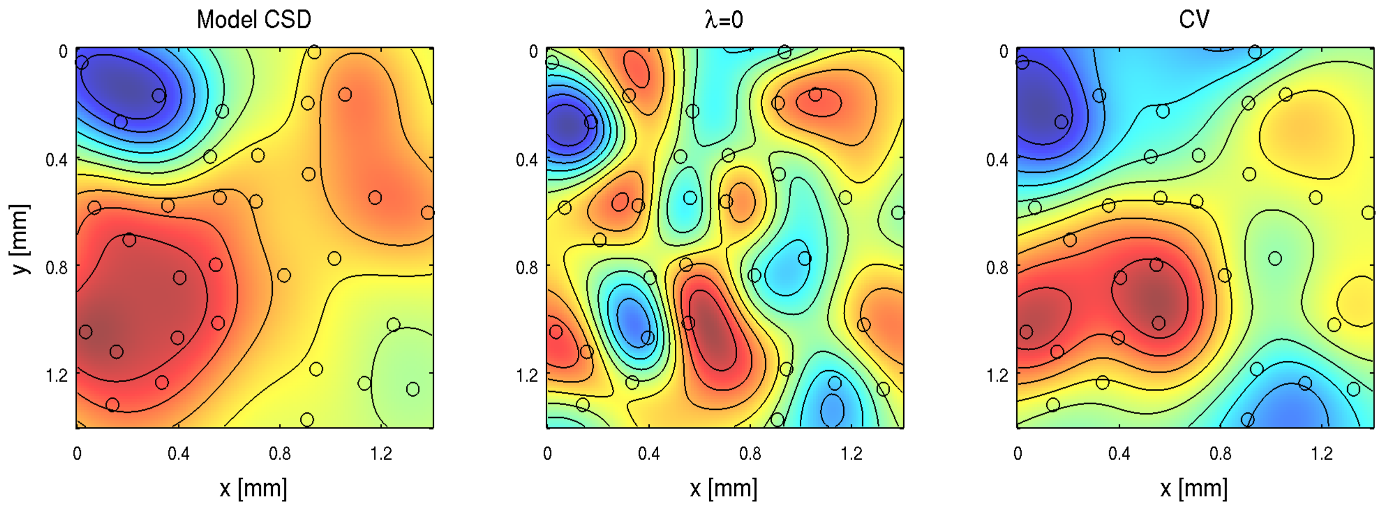
kCSD – choosing λ

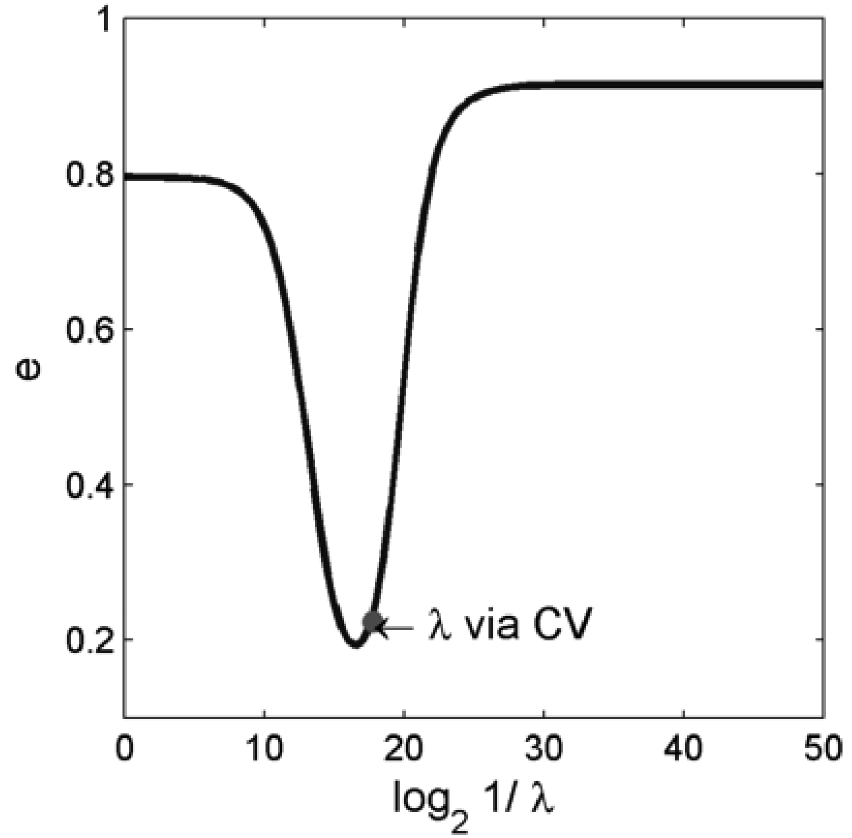
- Overfit (λ too small) vs underfit (λ too large)
- Leave-one-out cross-validation:
  - Choose λ
  - Use all but one data points to estimate CSD
  - Calculate V at the point left out
  - Average over all possible missing points



$$C^*(\mathbf{x}) = \widetilde{\mathbf{K}}^T(\mathbf{x}) \cdot (\mathbf{K} + \lambda \mathbf{I})^{-1} \cdot \mathbf{V}$$

How well is λ chosen?

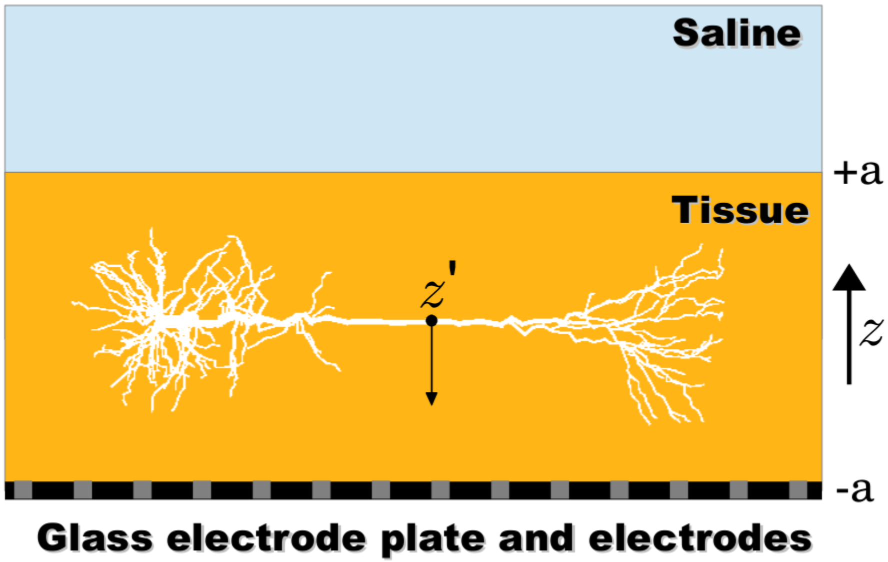


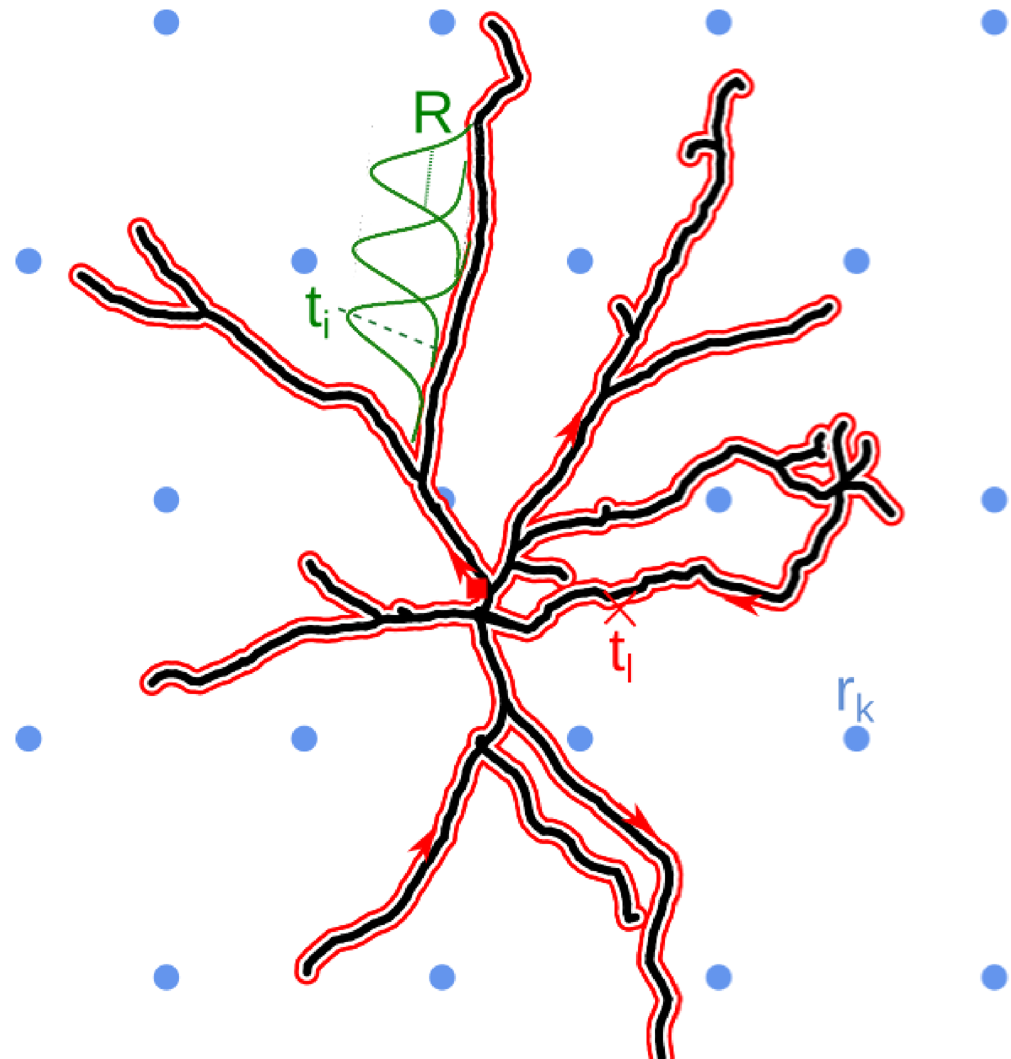


Single cells

Cserpan et al., eLife, 2017

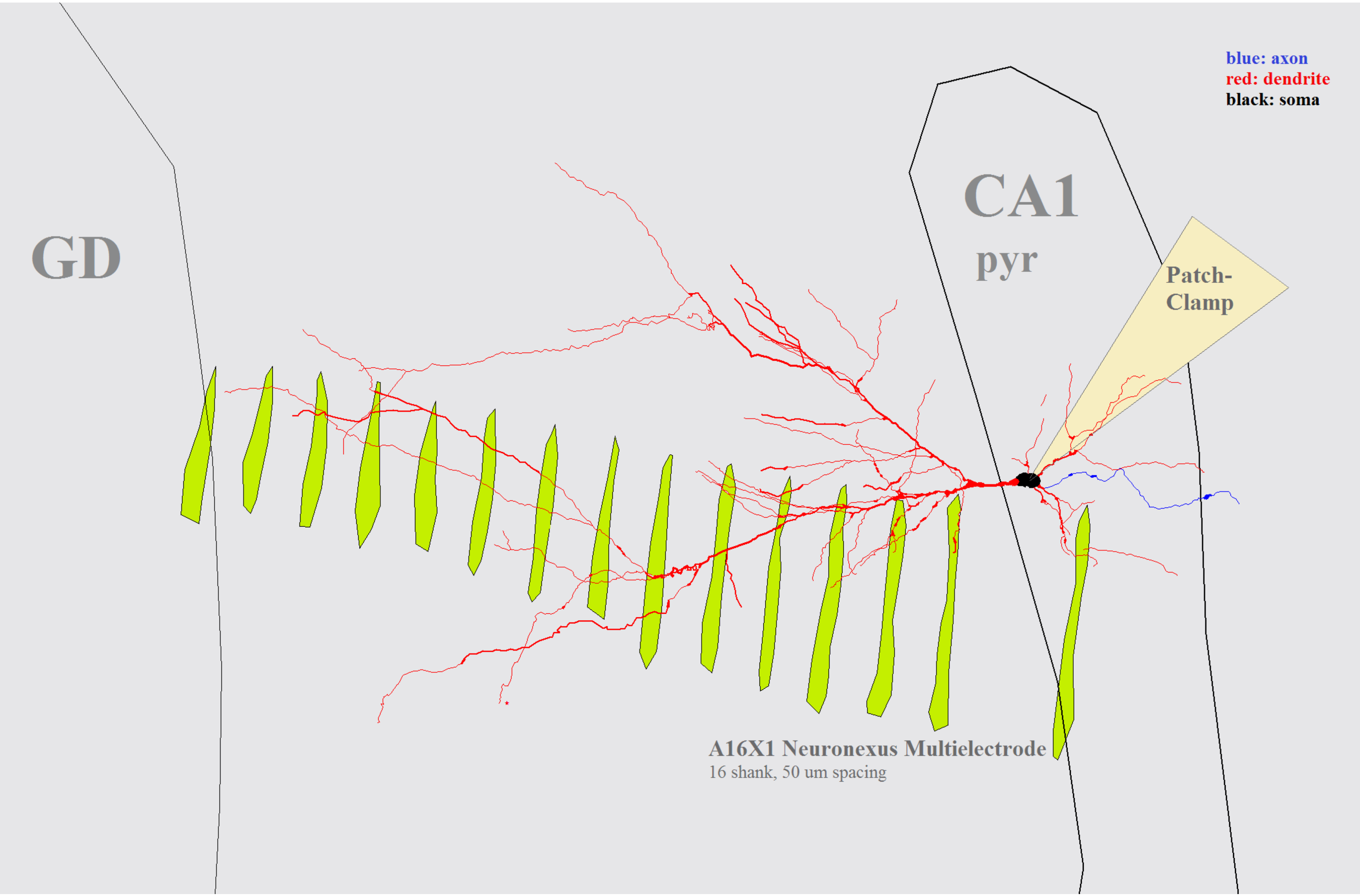
Single cell kCSD



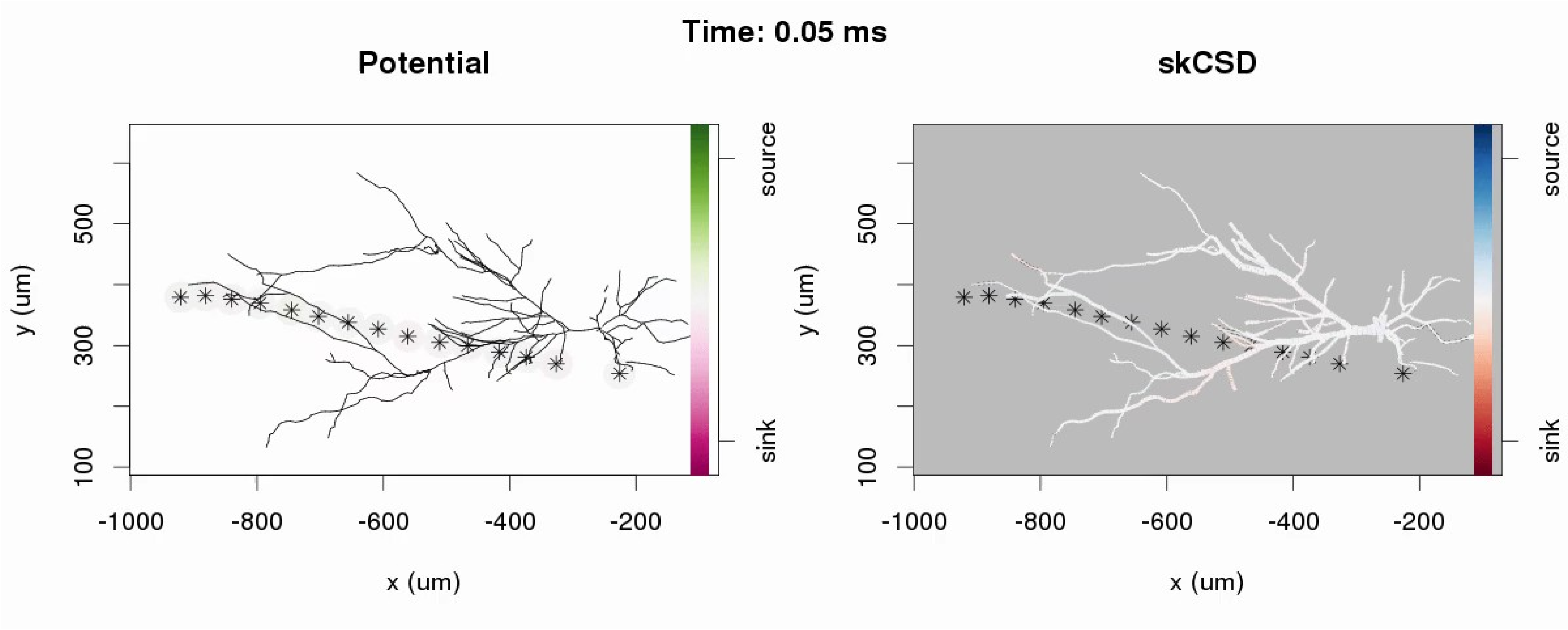


Dorottya Cserpan

Dorottya Cserpan



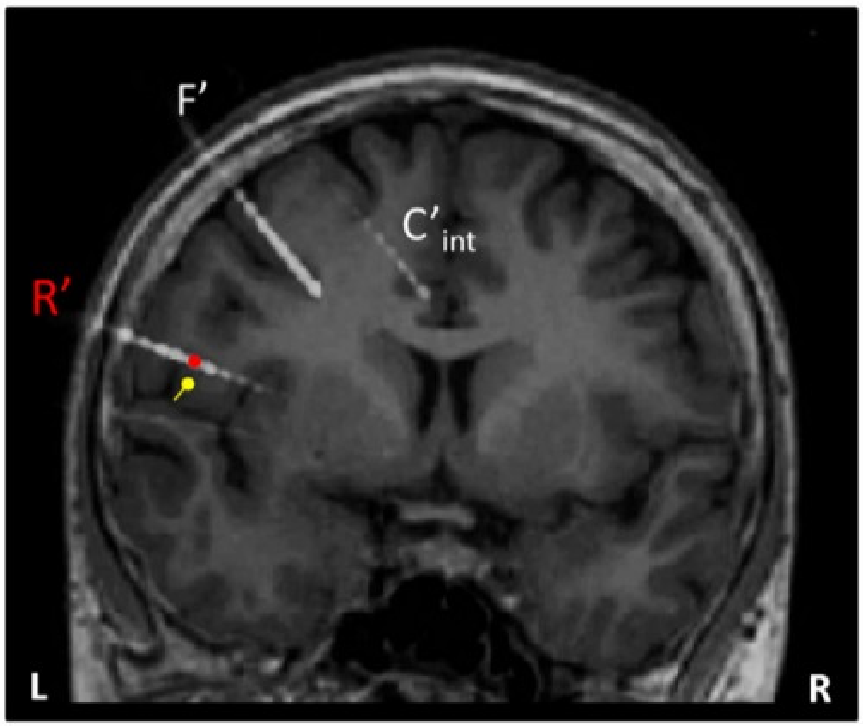
Domokos Meszéna, Lucia Wittner
Istvan Ulbert

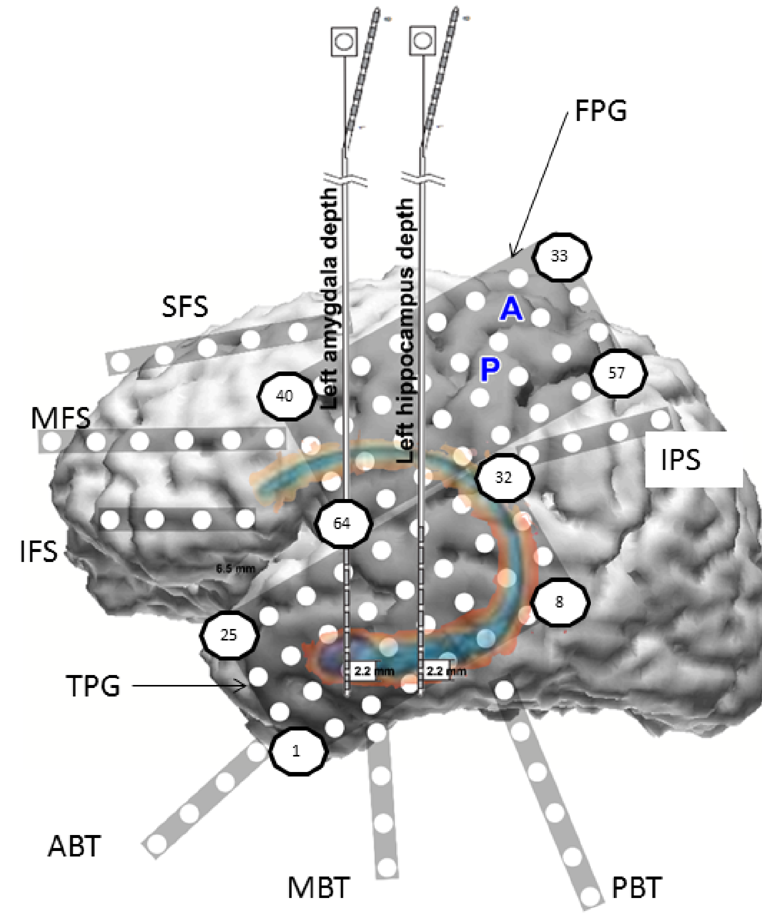


Preprocessing: Zoltan Somogyvari
Analysis: Dorottya Cserpan

Whole brains

In vivo (towards human)





*V. Caune et al., NeuroImage, 2014

* Urszula Malinowska & Anna Korzeniewska, Johns Hopkins University School of Medicine

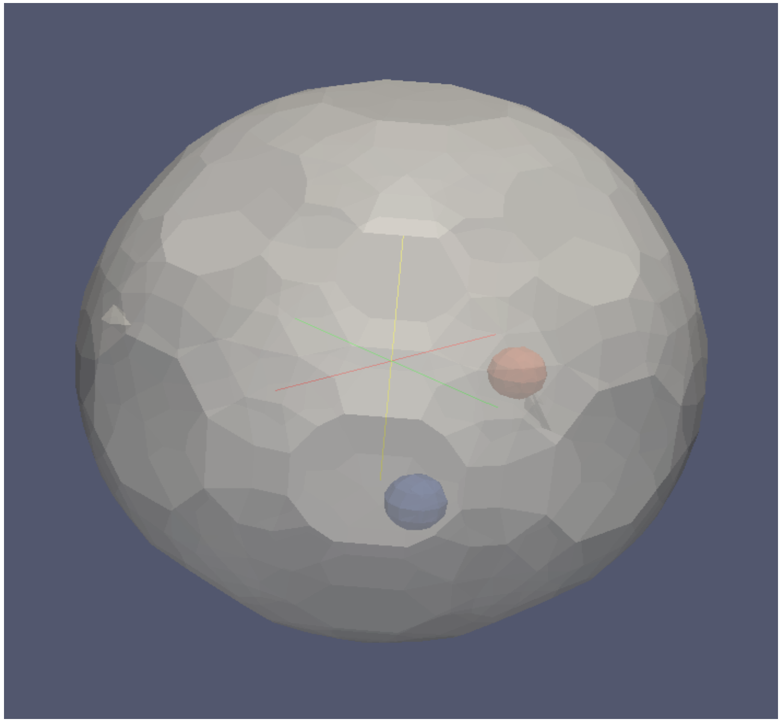
Modelling scheme

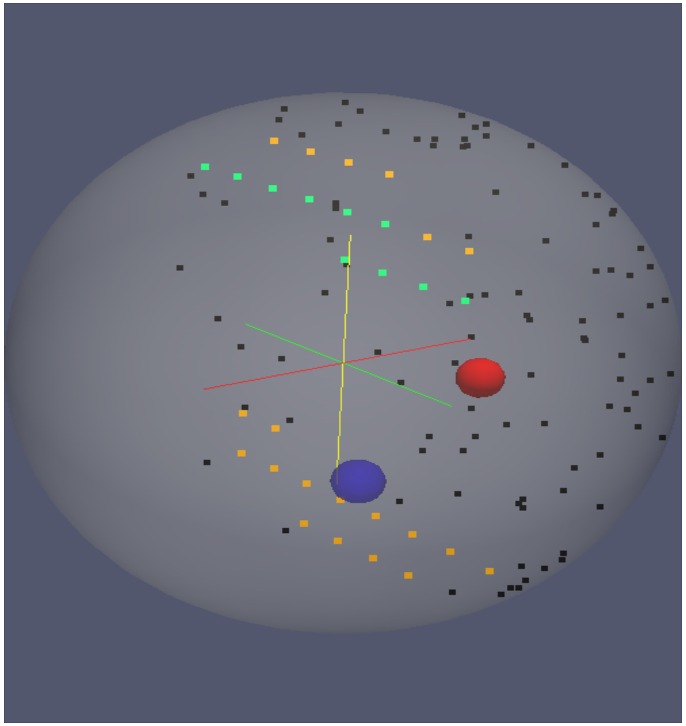
Kernel Electric source imaging (kESI) – Method based on kCSD 3D with non-trivial electrodes placement, and non-trivial electrical conductivity.

Requires both forward model & inverse model.

- Simple brain model – Spherical head
- Rat head model – Experimentally verifiable
- Human head model – Pre-surgical evaluation tool

Distributed dipolar source





Brain as a sphere.

Deep distributed dipolar source

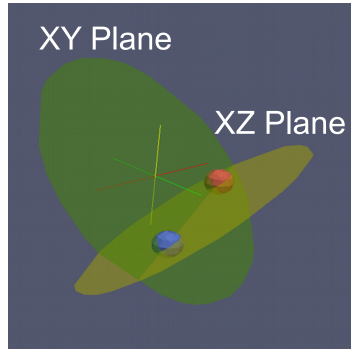
Distribution of electrodes

Black – 100 ECoG (random placement)
Colored – SEEG electrodes (regular)

ECoG + SEEG

652 Electrodes

Prior information

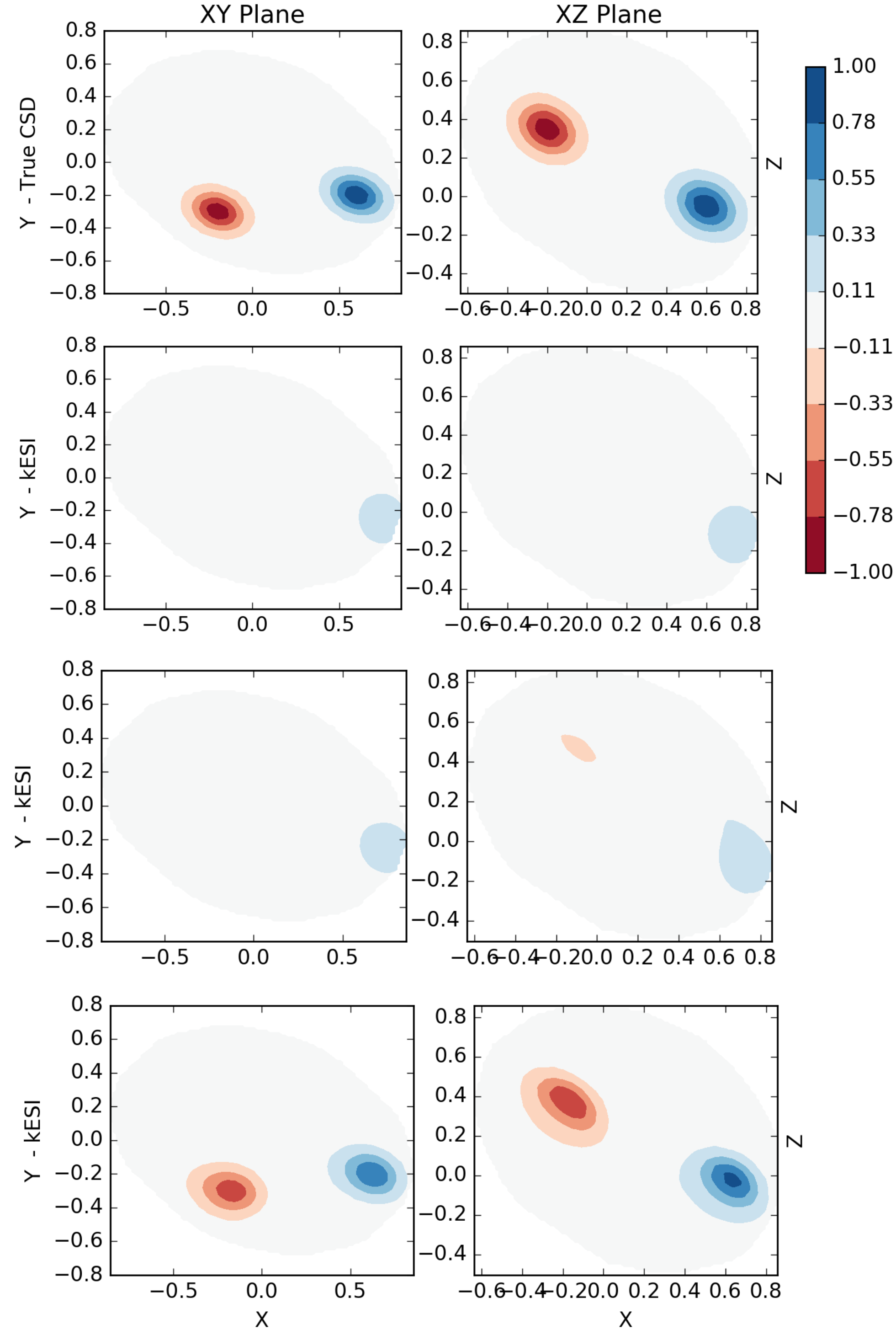


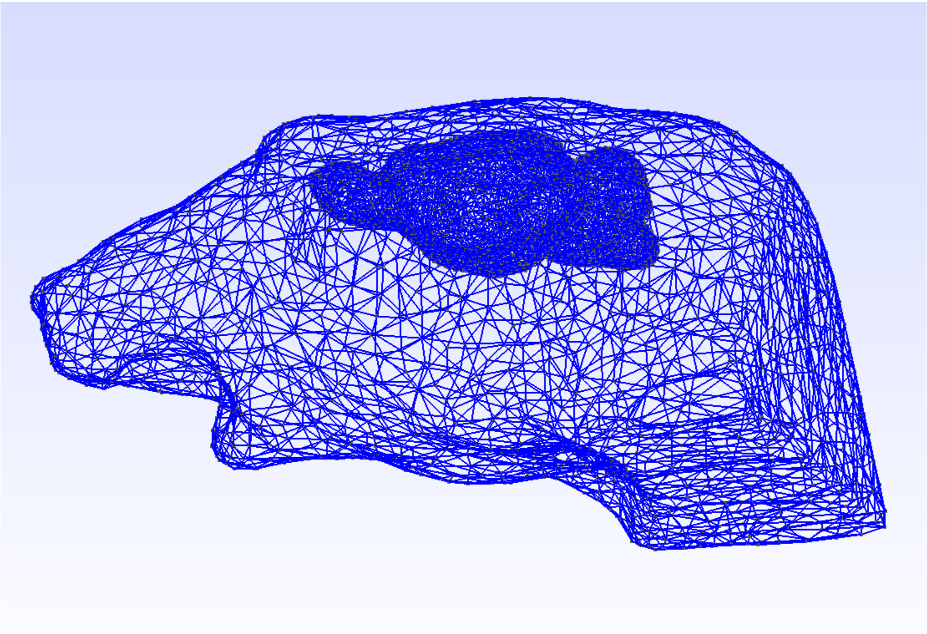
61432
0.903

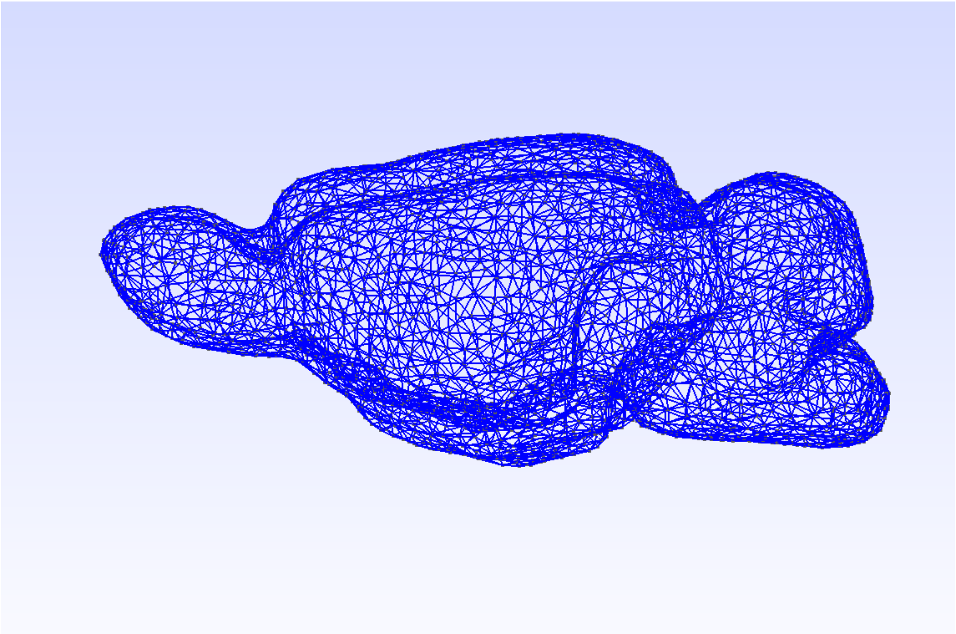
17918
0.855

Improved reconstruction

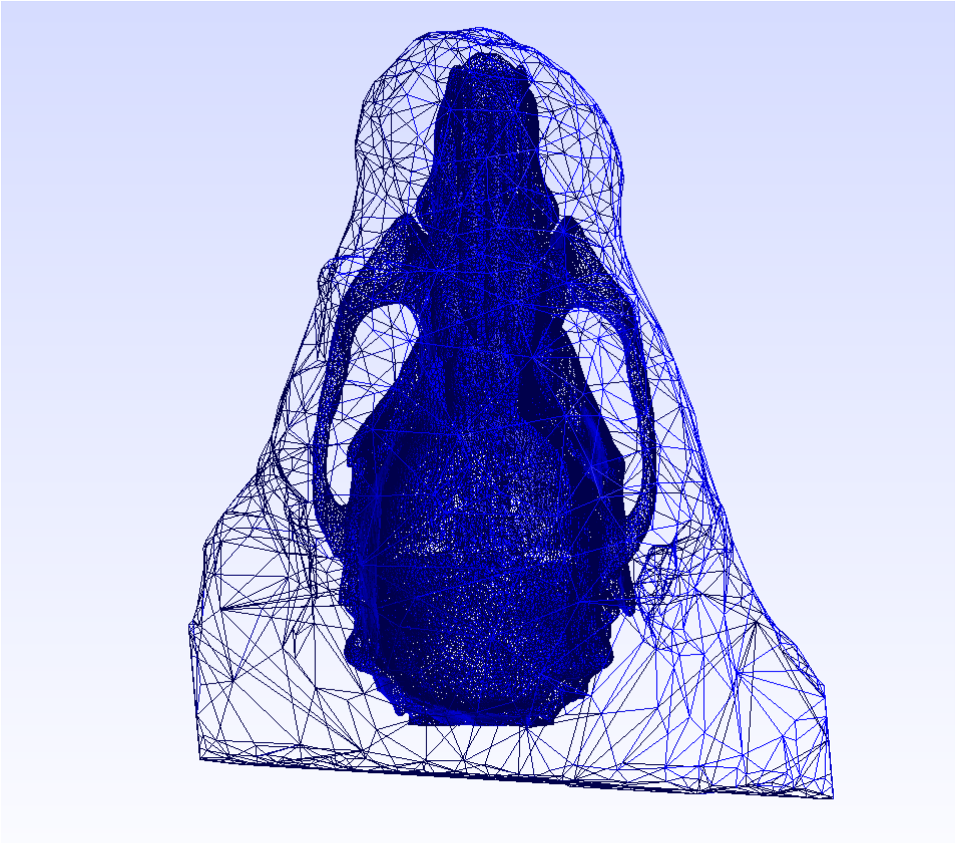
4581
0.248







Rat brain model



Top left: rat's head (scalp)
Top right: rat's brain (unsegmented)

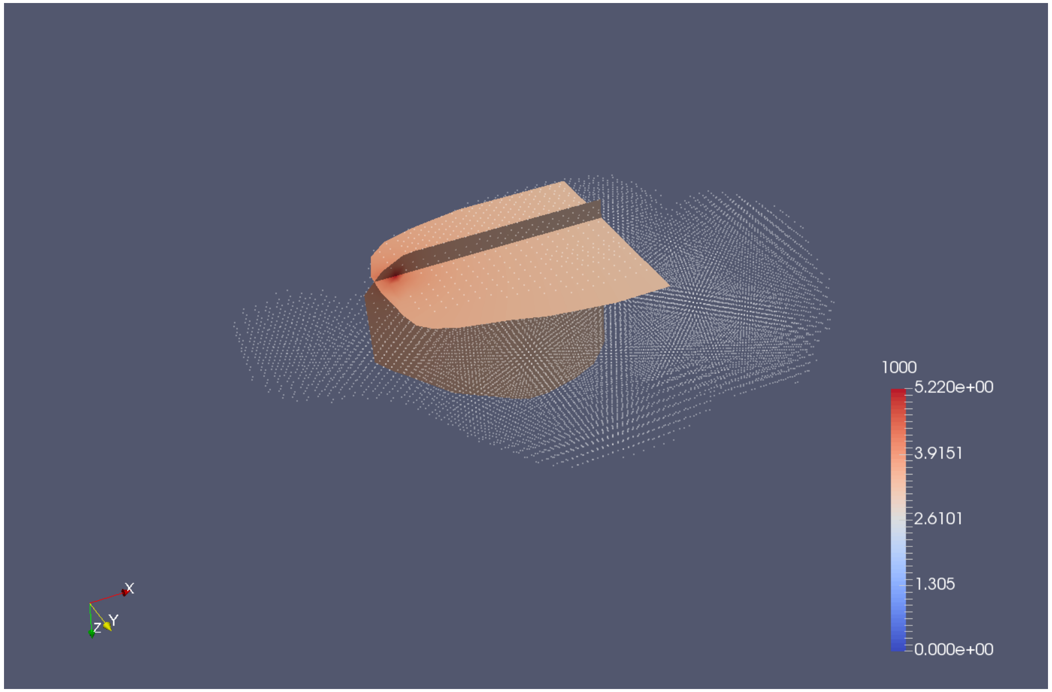
Meshes by Uli Hofmann, Freiburg

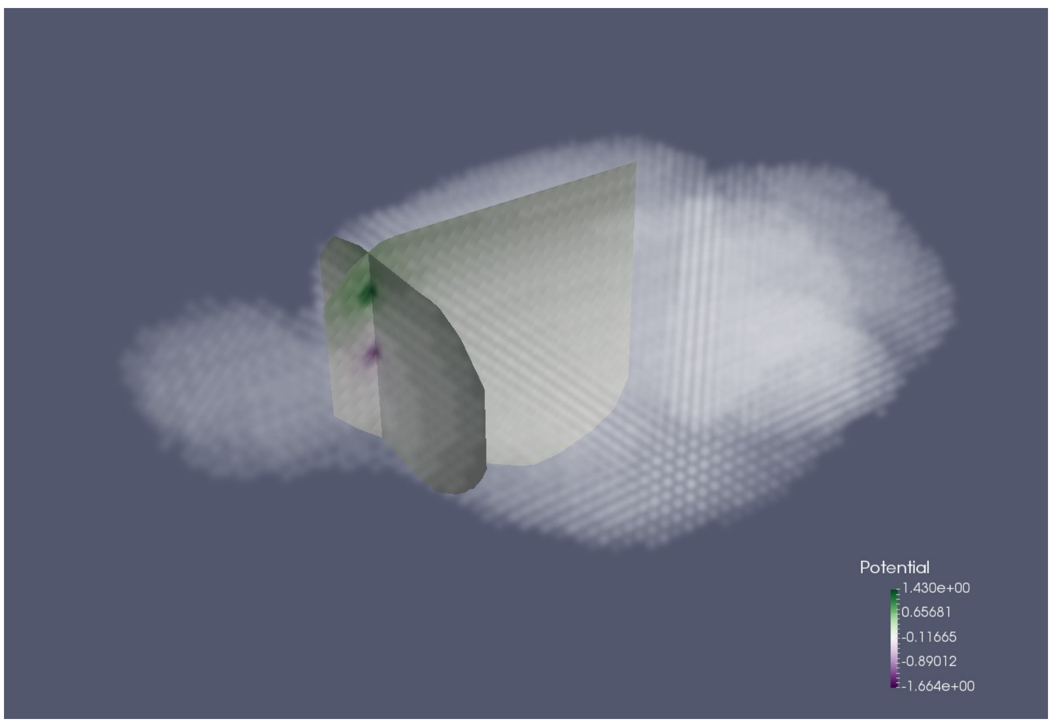
Right: Rat's head and skull

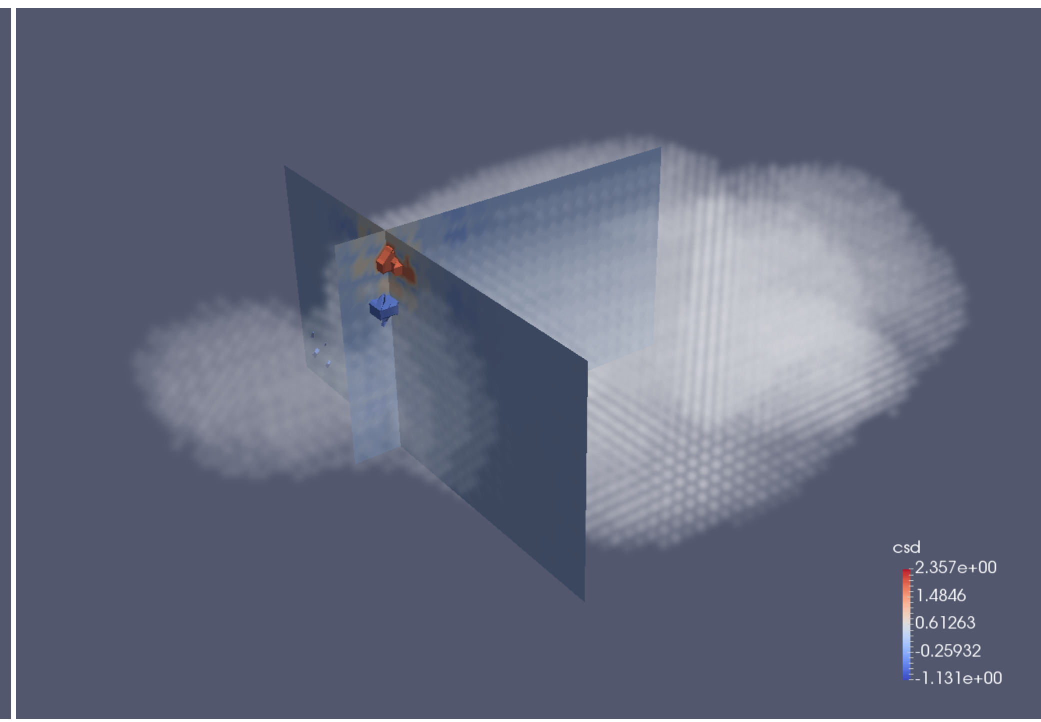
kESI in rat

Left: point current injection –
FEM computed electrical potential

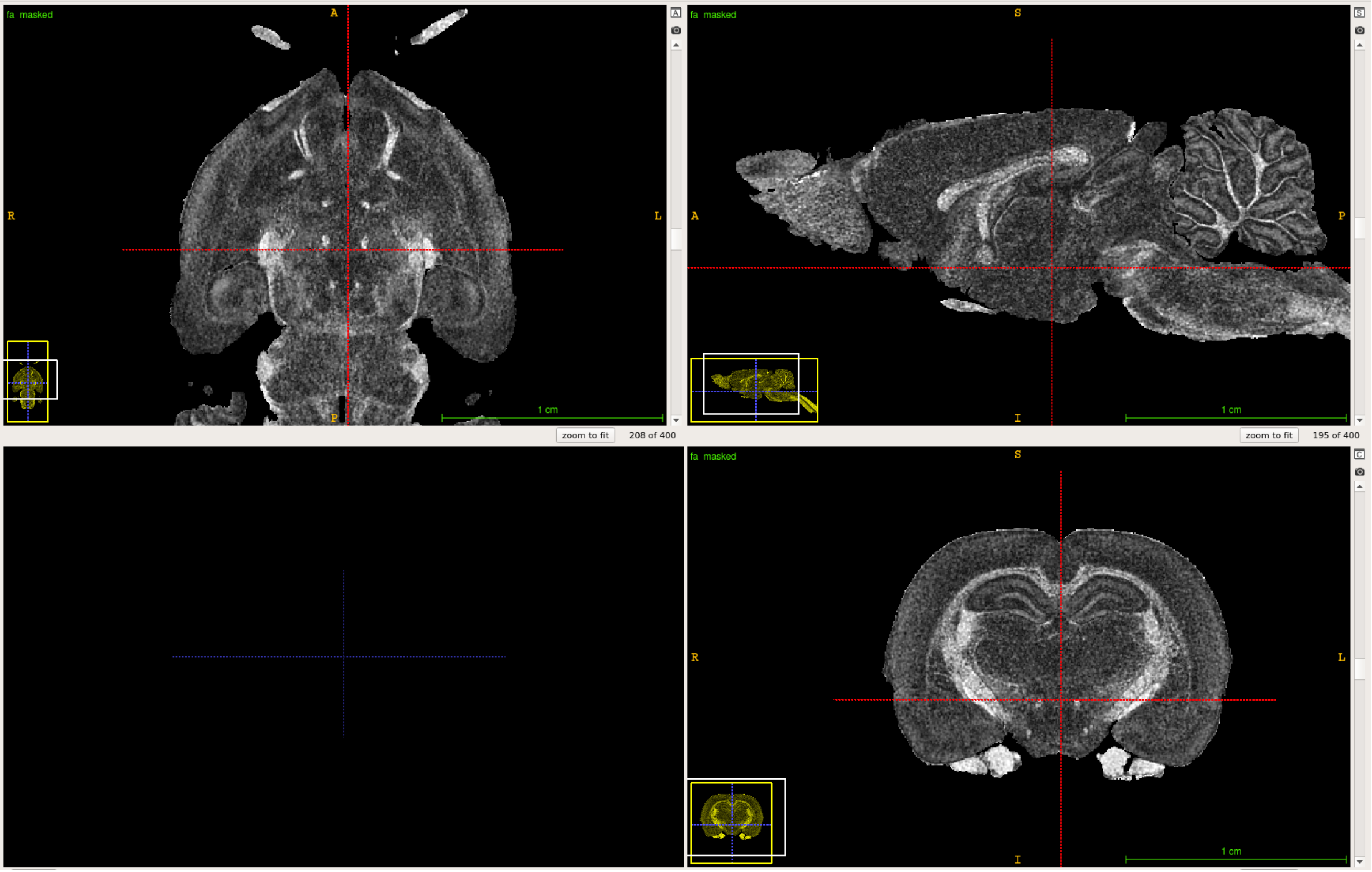
Ground truth: a dipole
Bottom left: reconstructed potential
Bottom right: reconstructed CSD







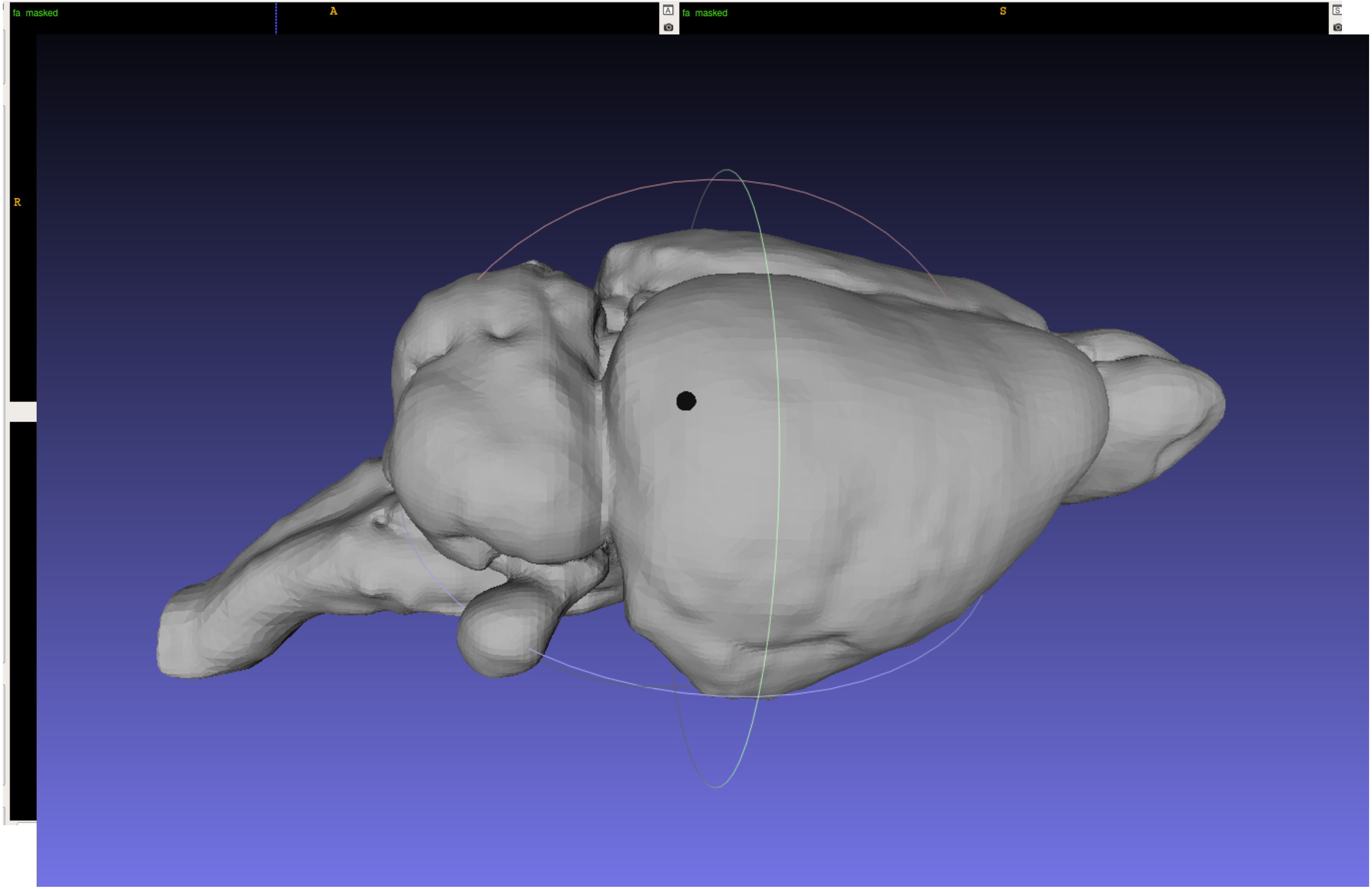
Chaitanya Chintaluri



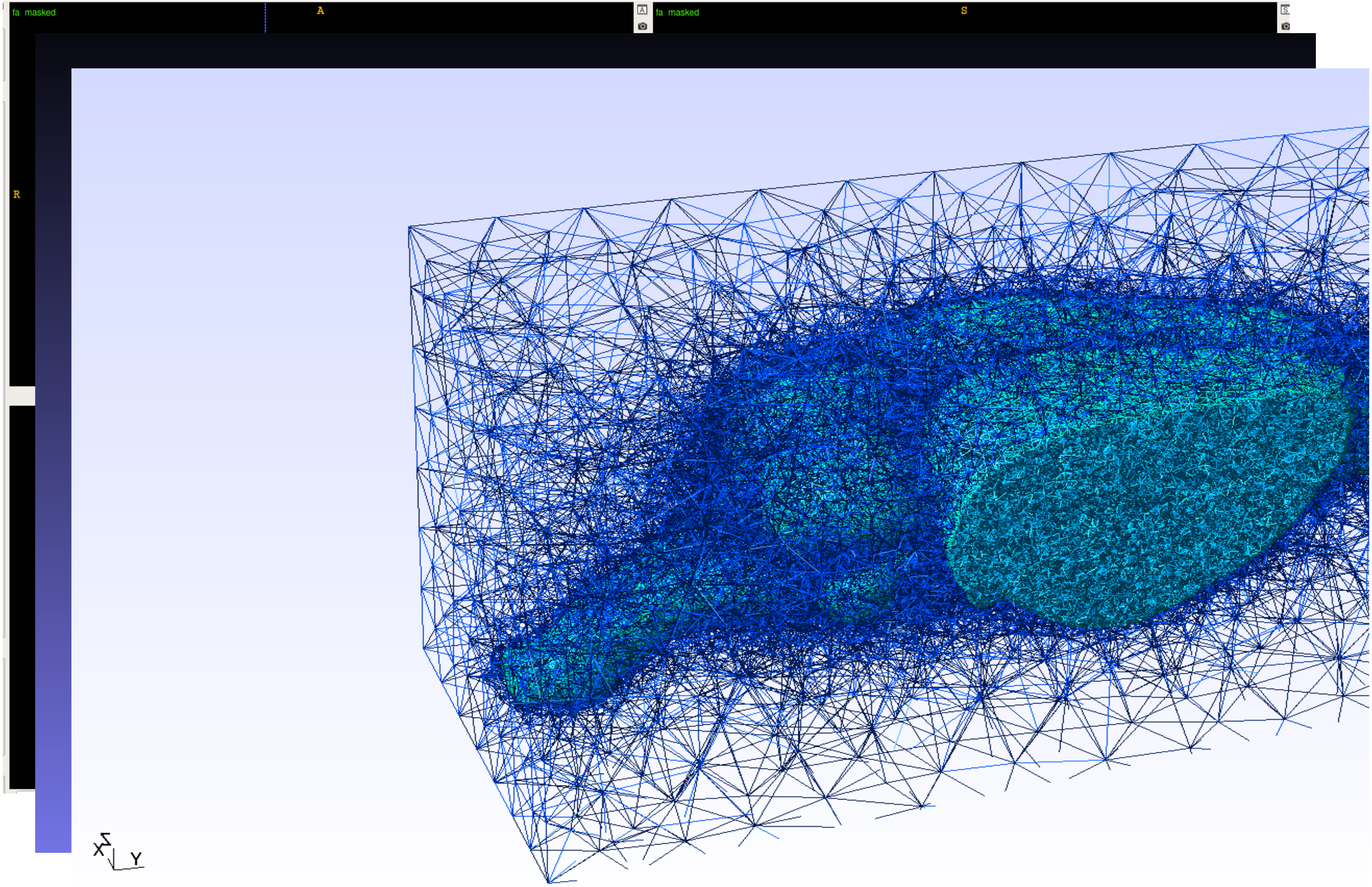
*

G. Allan Johnson et al., NeuroImage, 2012
“A multidimensional magnetic resonance histology atlas of the Wistar rat brain”

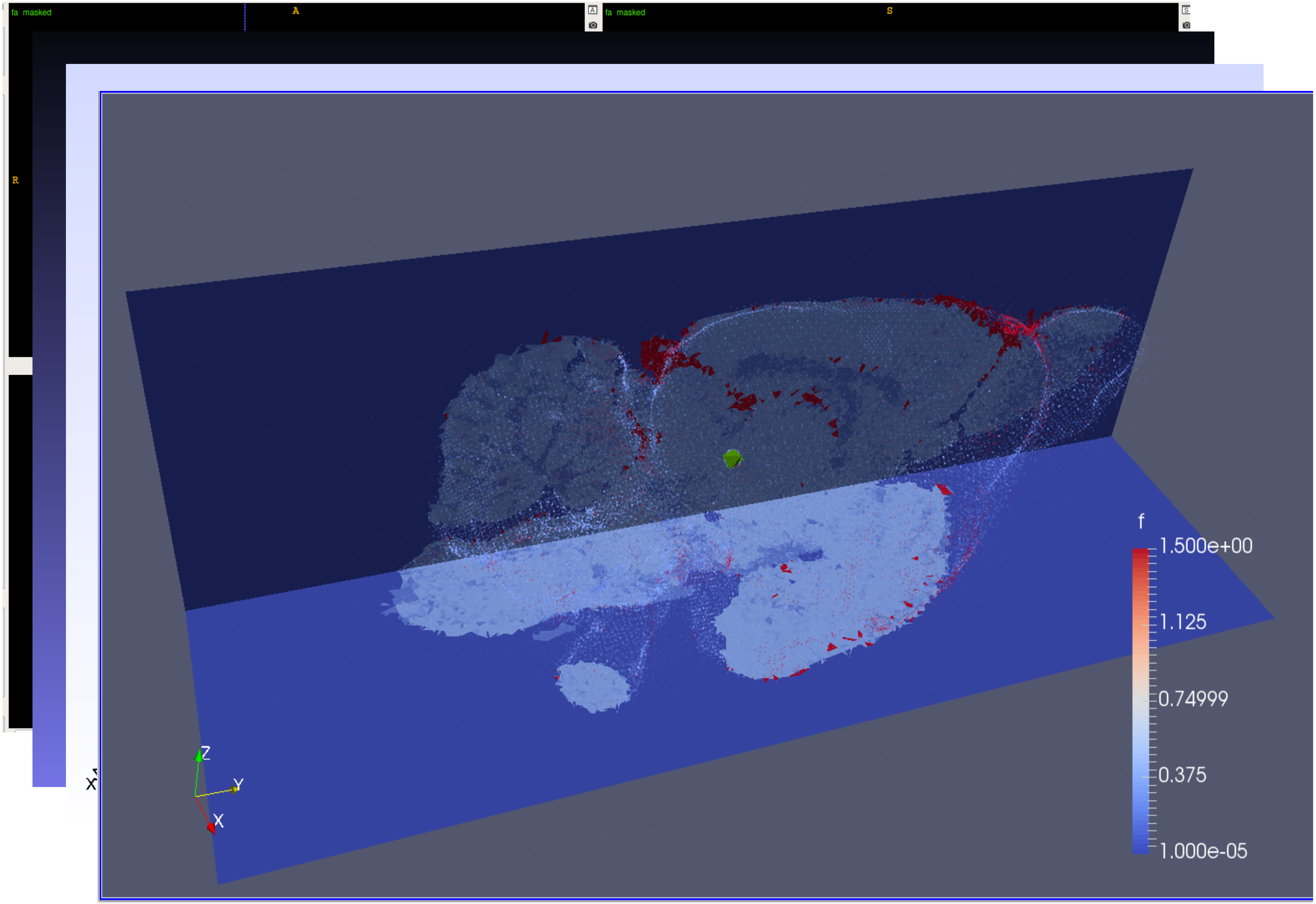
Piotr Majka, Laboratory of Neuroinformatics,
Co-registration with Waxholm's brain atlas, masking.



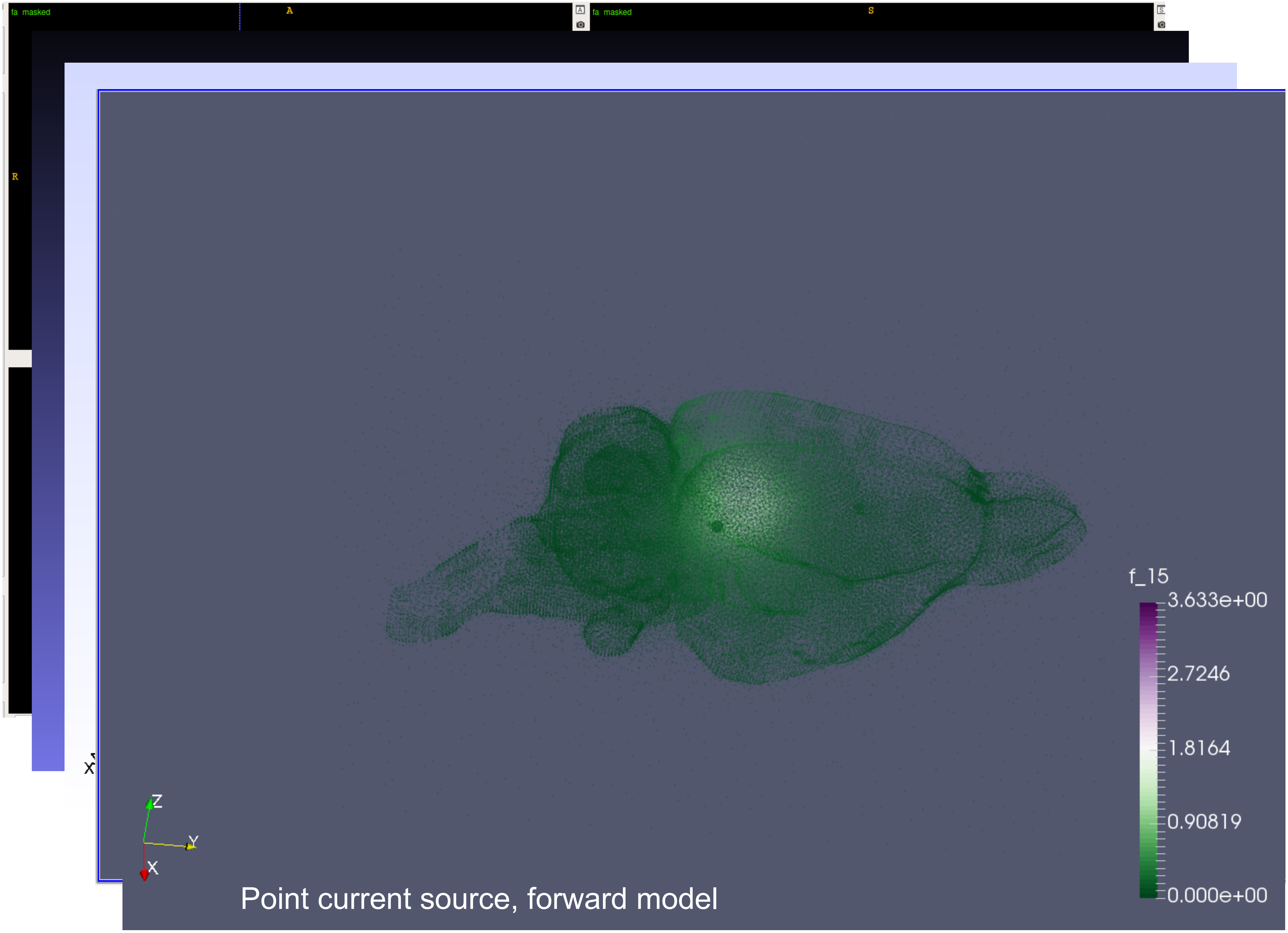
Closed surface, with reference electrode

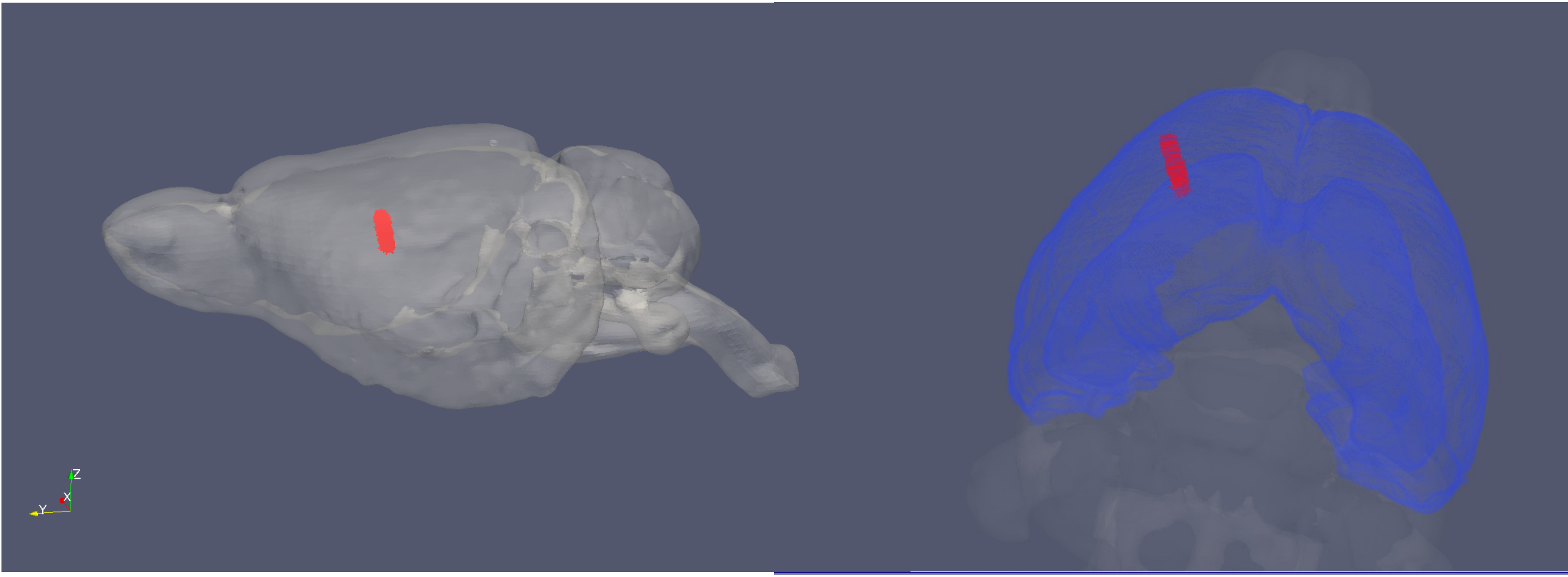


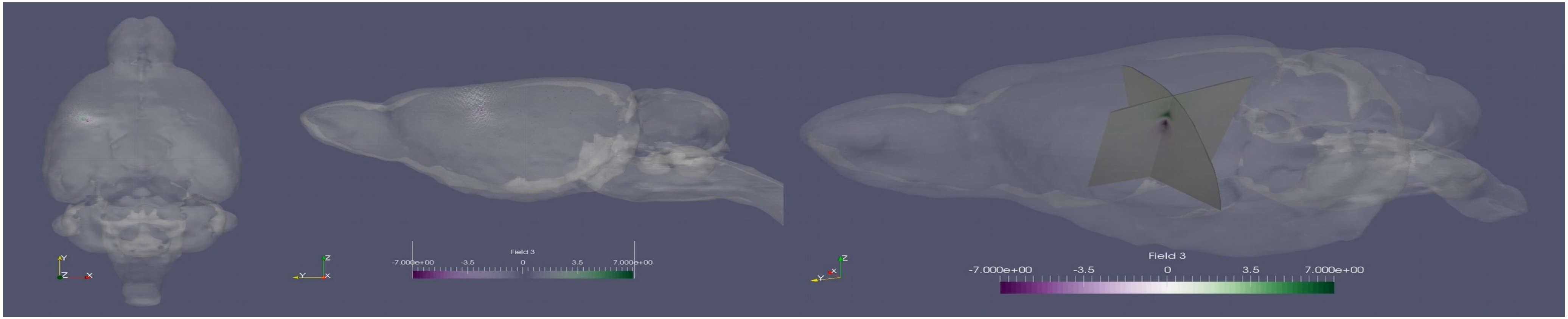
3 dimensional mesh



Assign anisotropic electrical conductivity

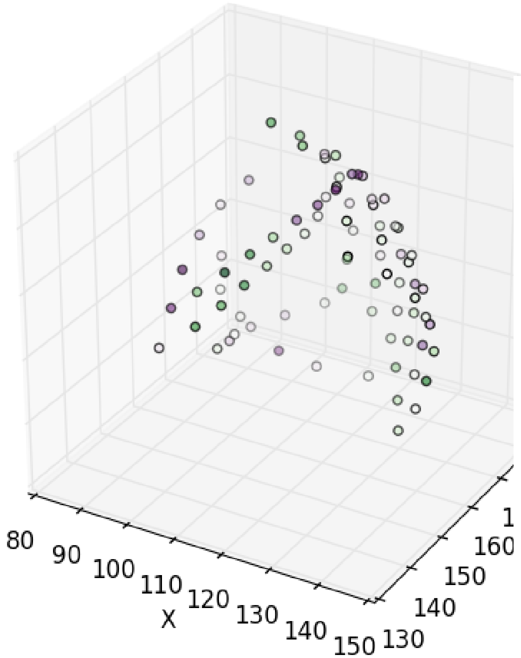

fa masked
A
fa masked
S
R
f_15
3.633e+00
2.7246
1.8164
0.90819
0.000e+00
Z
Y
X
Point current source, forward model

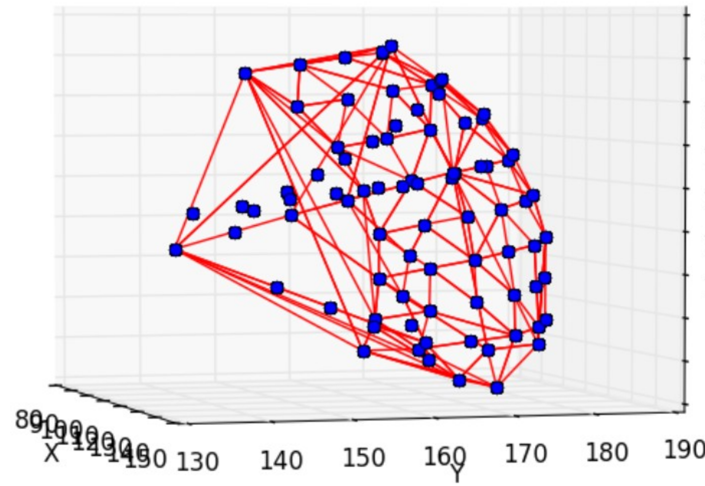

Z
X
Y

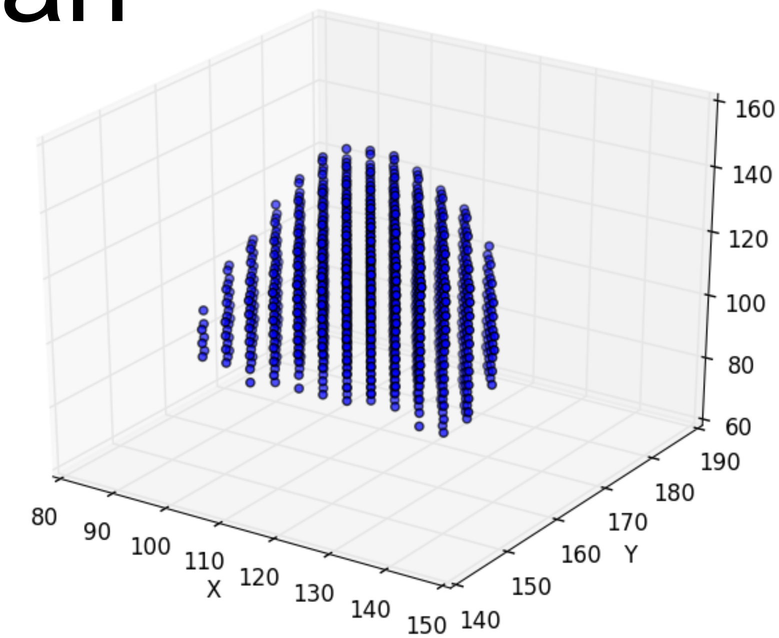


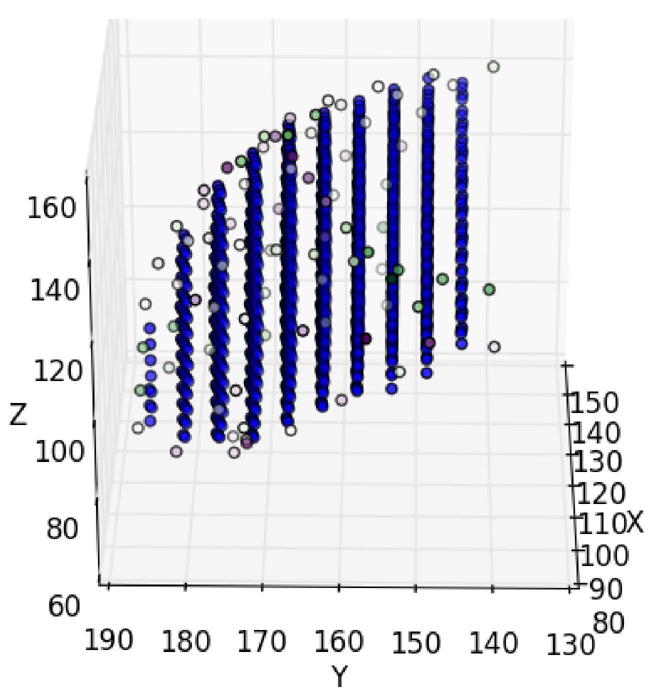
Y
Z
X
Z
Y
X
Field 3
-7.000e+00
-3.5
0
3.5
7.000e+00
Z
X
Y
Field 3
-7.000e+00
-3.5
0
3.5
7.000e+00

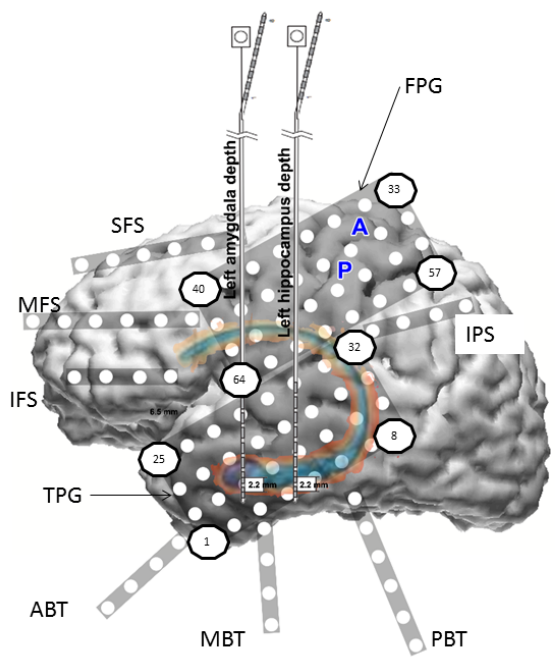
KESI in human

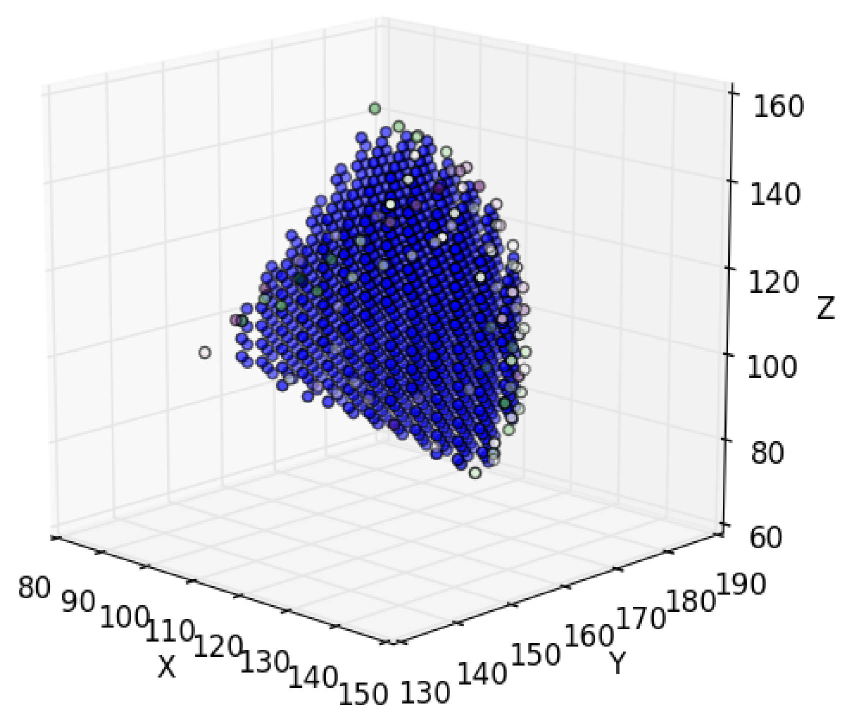




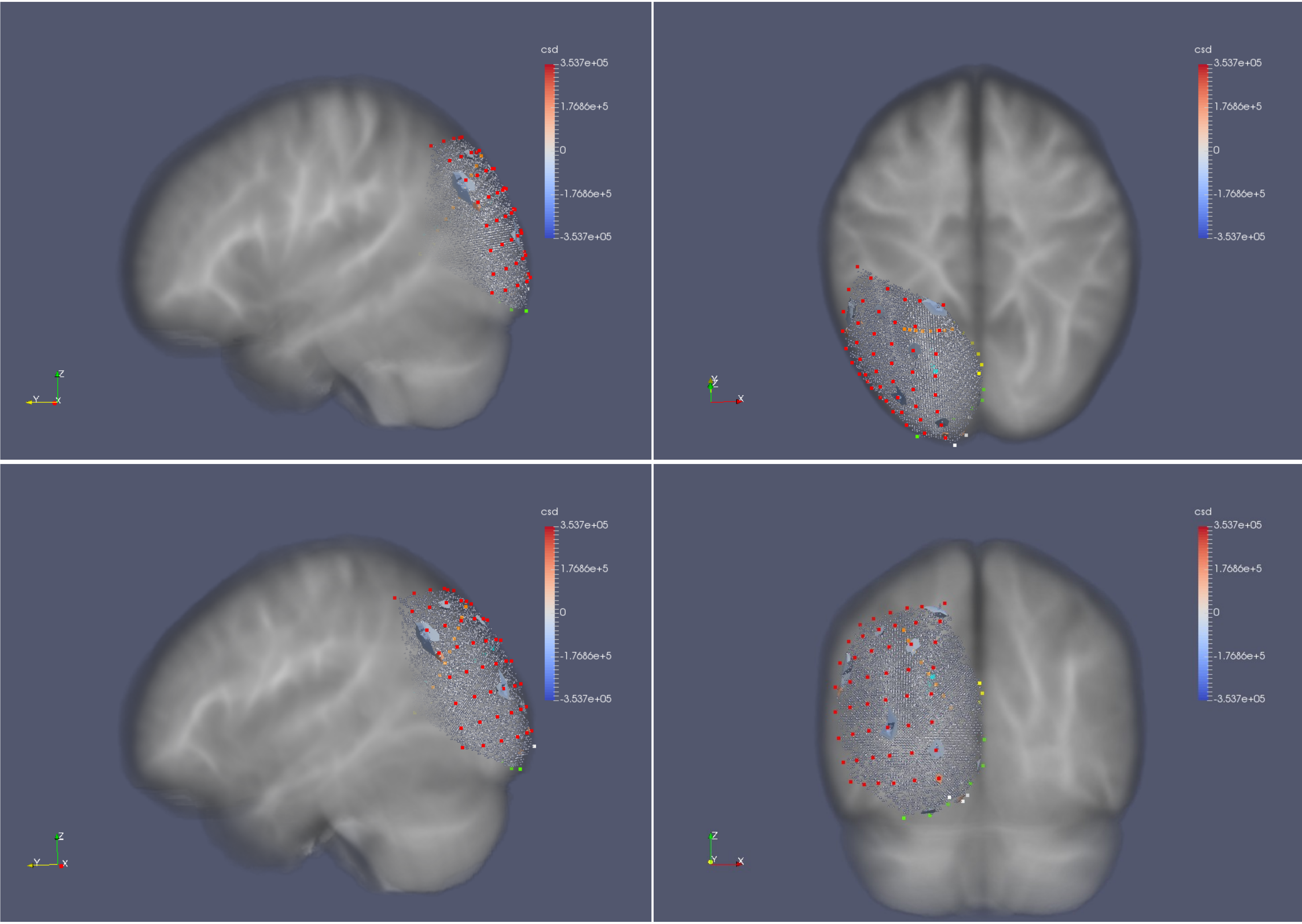








Marta Kowalska
Data – Johns Hopkins



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-1.7686e+5
-3.537e+05
Z
Y
X
csd
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1.7686e+5
0
-1.7686e+5
-3.537e+05
Y
Z
X
csd
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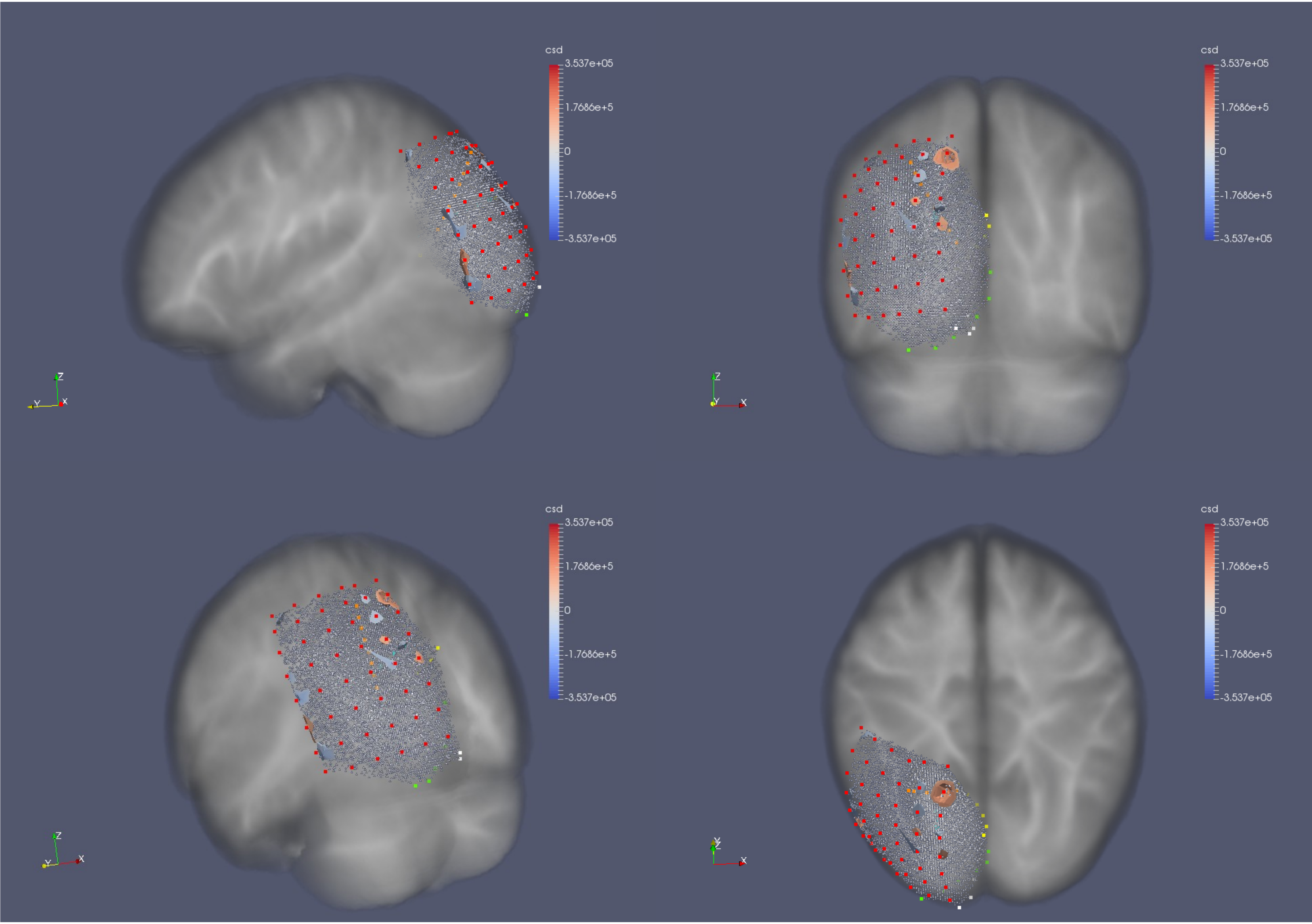
csd
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1.7686e+5
0
-1.7686e+5
-3.537e+05
Z
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X
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Z
Y
X
csd
3.537e+05
1.7686e+5
0
-1.7686e+5
-3.537e+05
Y
Z
X

Tools

- LFPy https://lfpy.github.io/
- H. Głąbska, H.C. Chintaluri, D.K. Wójcik Collection of simulated data from a thalamocortical network model, Neuroinformatics 15:87 (2017)
- kCSD https://github.com/Neuroinflab/kCSD-python

Open position

We are looking for a postdoc
for kESI project

http://neuroinflab.pl/jobs

Thanks for your attention

Experiments

- Daniel Świejkowski
- Ewa Kublik
- Andrzej Wróbel

- Szymon Łęski
- Wit Jakuczun
- Jan Potworowski
- Helena Głąbska
- Chaitanya Chintaluri
- Marta Kowalska

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POiG „POWIEW”
IBD PAN, ICM UW

- Klas Pettersen
- Torbjoern Ness
- Gaute Einevoll

Aas, Oslo, Norway

- Dorottya Cserpan
- Zoltan Somogyvari
- Istvan Ulbert

Budapest, Hungary