From transmembrane currents to extracellular potentials and back

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Techniques to study brain function
Temporal and spatial scales
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)
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)

Tungsten wires, Hubel, 1957
Silicon probes, Buzsaki 2004
4096 ch. CMOS MEA, 3brain

Wikipedia
Electric potential in the brain

http://service.3dbar.org
Electric potential in the brain

http://service.3dbar.org
Electric potential in the brain

http://service.3dbar.org
Electric potential in the brain

Mark Hunt

Extracellular potential

Cortical EP

http://service.3dbar.org

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

Potential: LFP ($V$)

Current sources: CSD (C)

Currents: $I_1, I_2, I_j$

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

\( \sigma \) – conductivity tensor; here: a constant (homogeneous and isotropic medium)
Experimental paradigm:

habituation sessions (H1, H2, H3...)

100 EPs

30s

first session with reinforcement (C1)

1-30
31-60
61-end

100 EPs

30s

consecutive conditioning sessions (C2, C3 ...)

100 EPs

30s
Vibrissa – barrel system of the rat

E. Kublik

barrel field in SI cortex

wzgórze (bareloidy)

ventral posteromedial thalamic nucleus

jądro brzuszne tylno-przyśrodkowe

VPm

POm

posteromedian thalamic nucleus

przyśrodkowa część jądra tylnego

jądra nerwu trójdzielnego w pniu mózgu (baryłeczki)

zwój trójdzielny

wibrysy / wąsy czuciowe / wąsy zatokowe na poduszce wibrysowej
Data: evoked potentials

cortex

Cortex

thalamus

thalamus, aroused

Cortex

cortex, aroused

thalamus

thalamus, aroused
Data: evoked potentials

cortex

thalamus

Cortex

cortex, aroused

thalamus

thalamus, aroused
from Varga et al (2002) modified
Experimental setup

Ewa Kublik, Daniel Świejkowski
Example LFP recorded in the rat forebrain

D. Świejkowski

Ewa Kublik, Daniel Świejkowski
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*

- **iCSD (inverse CSD method)**
  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)

\[
\frac{\partial^2 f}{\partial x^2} \approx \frac{f(x + h) - 2f(x) + f(x - h)}{h^2}
\]

• 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)

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

- Evaluate potentials on the grid by forward modeling
  \[ V_j = \sum_i L_{ji} a_i, L_{ji} = \tilde{b}_i(x_j) \]

- Invert F
  \[ \tilde{a} = L^{-1} \tilde{V} \]

- Evaluate potentials on the grid by forward modeling
  \( V \text{ at grid points} = F[N \text{ parameters of CSD}] \)

- Invert F
  \( N \text{ parameters of CSD} = F^{-1}[V \text{ at grid points}] \)
Example
Inverse Current Source Density (iCSD)

\[ C(x) = \sum_{i=1}^{N} a_i \tilde{b}_i(x) \]

Family of CSD distributions

basis in the CSD space

\[ b_i(x, y, z) = \mathcal{A} \tilde{b}_i(x, y, z) = \frac{1}{4\pi\sigma} \int dx' \frac{\tilde{b}_i(x')}{|x - x'|}. \]

basis in the space of potentials

\[ V(x) = \mathcal{A}C(x) = \sum_{i=1}^{N} a_i b_i(x) \]
Family of CSD distributions (think $M$ large, $M \gg N$)

basis in the CSD space

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

basis in the space of potentials

$$b_i(x, y, z) = \tilde{A} \tilde{b}_i(x, y, z) = \frac{1}{4\pi\sigma} \int dx' \frac{\tilde{b}_i(x')}{|x - x'|}.$$
iCSD in 3D
Daniel Świejkowski, Ewa Kublik, Andrzej Wróbel

Current Source Density

Interpolated field potential

Łęski et al. (2007) Neuroinformatics
iCSD in 3D
Daniel Świejkowski, Ewa Kublik, Andrzej Wróbel

Current Source Density

Interpolated field potential

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.
In 3D:

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

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

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

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

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

\[ \beta = K^{-1} \cdot V \]

Tichonow Regression
Step 2: From potential to the CSD

\[ C(\vec{r}, t) = \mathbf{A}^{-1}V(\vec{r}, t) \]

\[ V(\vec{r}, t) = \mathbf{A}C(\vec{r}, t) \]

\[ C^*(\mathbf{x}) = \tilde{\mathbf{K}}^T(\mathbf{x}) \cdot \mathbf{K}^{-1} \cdot \mathbf{V} \]

\[ \tilde{\mathbf{K}}(\mathbf{x}, \mathbf{x}') = \mathbf{A}^{-1}K(\mathbf{x}, \mathbf{x}') = \sum_{i=1}^{M} \tilde{b}_i(\mathbf{x})b_i(\mathbf{x}') \]
CSD in the tissue
CSD in the tissue

1 electrode
CSD in the tissue

Interpolated potential

1 electrode
CSD in the tissue

Interpolated potential

Reconstructed CSD

1 electrode
CSD in the tissue

Interpolated potential

Reconstructed CSD

2 electrodes

Jan Potworowski
4 electrodes

CSD in the tissue

Interpolated potential

Reconstructed CSD
CSD in the tissue

Interpolated potential

Reconstructed CSD

8 electrodes

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CSD in the tissue

Interpolated potential

Reconstructed CSD

12 electrodes

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16 electrodes

CSD in the tissue  Interpolated potential  Reconstructed CSD

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32 electrodes

CSD in the tissue

Interpolated potential

Reconstructed CSD

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kCSD – regularization

\[
\sum_{i=1}^{N} \left( \sum_{j=1}^{N} \beta_j K(x_j, x_i) - V_i \right)^2 = 0.
\]

minimize

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

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

\[
C^*(x) = \bar{K}^T(x) \cdot (K + \lambda I)^{-1} \cdot V
\]
kCSD – choosing \( \lambda \)

- Overfit (\( \lambda \) too small) vs underfit (\( \lambda \) too large)

- Leave-one-out cross-validation:
  - Choose \( \lambda \)
  - Use all but one data points to estimate CSD
  - Calculate \( V \) at the point left out
  - Average over all possible missing points

\[
C^*(x) = \tilde{K}^T(x) \cdot (K + \lambda I)^{-1} \cdot V
\]
How well is $\lambda$ chosen?
Single cells

Cserpan et al., eLife, 2017
Single cell kCSD

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

Improved reconstruction
Rat brain model

Top left: rat’s head (scalp)
Top right: rat’s brain (unsegmented)
Right: Rat’s head and skull

Meshes by Uli Hofmann, Freiburg
kESI in rat

Left: point current injection – FEM computed electrical potential

Ground truth: a dipole
Bottom left: reconstructed potential
Bottom right: reconstructed CSD
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
Point current source, forward model
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

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