Modeling and interpretation of extracellular potentials

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Overall plan for tutorial

- 9.00-9.50: Lecture 1 (Gaute)
- 9.50-10.05: Break
- 10.05-10.55: Lecture 2 (Gaute & Szymon)
- 10.55-11.10: Break
- 11.10-12.00: Lecture 3 (Szymon)
- 12.00-13.00: Lunch break
- 13.00-: Tutorials (Espen & Szymon)
Physiological measures of neural activity

- Membrane potential
- Spike
- Local field potential (LFP)
- Multiunit Activity (MUA)
- EEG
- MEG
- Voltage-sens. die imaging (VSDI)
- Intrinsic optical imaging
- Two-photon calcium imaging
- Functional MRI
- PET

- Look for correlations between measurements and stimulus/behavior
- Typical multimodal analysis: Look for correlations between different experiments
Physics-type multimodal modeling

- Need to work out mathematical connections between neuron dynamics and different experimental modalities ("measurement physics")

VSDI: Weighted sum over membrane potentials close to cortical surface

Spike, MUA: Weighted sum over transmembrane currents in soma region

LFP, EEG, MEG: Weighted sum over transmembrane currents all over neuron
A candidate model for, say, network dynamics in a cortical column should predict all available measurement modalities.

- Multi-unit activity (MUA)
- Spikes
- Local field potential (LFP)
- Voltage-sensitive dye imaging
- Two-photon calcium imaging
- ...

And we need neuroinformatics tools to make this as simple as possible.

http://compneuro.umb.no/LFPy
Measuring electrical potentials in the brain

- Among the oldest and (conceptually) simplest measurements of neural activity
- Richard Caton (1875): Measures electrical potentials from surfaces of animal brains (ECoG)
Typical data analysis

• Recorded signal split into two frequency bands:
  ➢ High-frequency band (>~ 500 Hz): **Multi-unit activity (MUA)**, measures spikes in neurons surrounding electron tip
  ➢ Low-frequency band (<~300 Hz): **Local field potential (LFP)**, measures subthreshold activity

• LFP often discarded
• Sometimes used for current-source density (CSD) analysis with laminar-electrode recordings spanning cortical layers
Revival of LFP in last decade

- LFP is unique window into activity in populations (thousands) of neurons

- New generation of silicon-based multielectrodes with up to thousands of contacts offers new possibilities

- Candidate signal for brain-computer interfaces (BCI); more stable than spikes
Rat whisker system: 
*laminar electrode recordings* 
(Anna Devor, Anders Dale, UC San Diego; Istvan Ulbert, Hungarian Acad. Sci, Budapest)
Laminar electrode recordings from rat barrel cortex - single whisker flick

High-pass filter (>750Hz), rectification: **MULTI-UNIT ACTIVITY (MUA)**

Low-pass filter (<500 Hz): **LOCAL FIELD POTENTIAL (LFP)**

Measure of dendritic processing of synaptic input?

Measure of neuronal action potentials?

Einevoll et al, J Neurophysiol 2007
Physical origin of LFP and MUA

- Source of extracellular potential: \textit{Transmembrane} currents

\[
\phi(t) = \frac{I_1(t)}{4\pi \sigma r_1} + \frac{I_2(t)}{4\pi \sigma r_2}
\]

\(\sigma\): extracellular conductivity
Note: Current monopoles do not exist

Current sink: $I_1(t)$

Current source: $I_2(t) = -I_1(t)$

Conservation of electric charge requires (capacitive currents included!):

$$I_1(t) + I_2(t) = 0$$

From far away it looks like a **current dipole**

$$\phi(t) = \frac{I_1(t)}{4\pi \sigma r_1} + \frac{I_2(t)}{4\pi \sigma r_2}$$
Assumptions underlying:

I. Quasistatic approximation to Maxwell’s equations

\[ \nabla \cdot \mathbf{E} = \frac{\rho}{\varepsilon_0} \]
\[ \nabla \times \mathbf{B} = \frac{-\partial \mathbf{B}}{\partial t} \]
\[ \nabla \times \mathbf{E} = \mu_0 j + \frac{1}{c^2} \frac{\partial \mathbf{E}}{\partial t} \]

- sufficiently low frequencies so that electrical and magnetic fields are decoupled (OK for \( f \ll 10 \text{ kHz} \))

- here: not interested in magnetic fields

- then:

\[ \nabla \times \mathbf{E} = 0 \implies \mathbf{E} = -\nabla \phi \]
Assumptions underlying:

II. Coarse-grained extracellular medium described by extracellular conductivity $\sigma$

$$\phi(t) = \frac{I(t)}{4\pi \sigma r_1} - \frac{I(t)}{4\pi \sigma r_2}$$
Assumptions underlying:

**III. Linear extracellular medium**

\[ \mathbf{j} = \sigma \mathbf{E} \]

\( j \): current density (A/m\(^2\))  \quad \mathbf{E} \): electric field (V/m)

**IV. Extracellular medium is**

1. Ohmic
2. homogeneous
3. frequency-independent
4. isotropic

\[ \phi(t) = \frac{I(t)}{4\pi \sigma r_1} - \frac{I(t)}{4\pi \sigma r_2} \]
Assumptions underlying:

\[ \phi(t) = \frac{I(t)}{4\pi \sigma r_1} - \frac{I(t)}{4\pi \sigma r_2} \]

**IV.1: Ohmic:** \( \sigma \) is real, that is, extracellular medium is not capacitive
- **OK**

**IV.2: Homogeneous:** \( \sigma \) is the same at all positions
- **OK** inside cortex, but lower \( \sigma \) in white matter
- Formula can be modified my means of «method of images» from electrostatics

**IV.3: Frequency-independent:** \( \sigma \) is same for all frequencies
- Probably **OK** (I think), but still somewhat debated
- But if frequency dependence is found, formalism can easily be adapted
Assumptions underlying:

**IV.4 Isotropic:** \( \sigma \) is the same in all directions

- \( \sigma \) is in general a tensor \((\sigma_x, \sigma_y, \sigma_z)\)
- Easier to move along apical dendrites than across \((\sigma_z > \sigma_x \text{ and } \sigma_y)\)
- Cortex: \( \sigma_z \sim 1-1.5 \sigma_{x,y} \)

**Generalized formula:**

\[
\phi(t) = \frac{I(t)}{4\pi \sigma r_1} - \frac{I(t)}{4\pi \sigma r_2}
\]

\[
\phi(t) = \frac{I(t)}{4\pi \sqrt{\sigma_y \sigma_z x_1^2 + \sigma_z \sigma_x y_1^2 + \sigma_x \sigma_y z_1^2}} - \frac{I(t)}{4\pi \sqrt{\sigma_y \sigma_z x_2^2 + \sigma_z \sigma_x y_2^2 + \sigma_x \sigma_y z_2^2}}
\]
Forward-modeling formula for multicompartment neuron model

$$\phi(r, t) = \frac{1}{4\pi\sigma} \sum_{n=1}^{N} \frac{I_n(t)}{|r - r_n|}$$

Current conservation:

$$\sum_{n=1}^{N} I_n(t) = 0$$
**Inverse electrostatic solution**

- No charge pileup in extracellular medium:

\[
\textbf{E} = -\nabla \phi
\]

\[
\nabla^2 \phi = -\nabla \cdot \textbf{E} = \frac{1}{\sigma} \nabla \cdot \textbf{j}_s
\]

- Inverse solution:

\[
\phi(r, t) = \frac{1}{4\pi \sigma} \sum_{n=1}^{N} \frac{I_n(t)}{|r - r_n|}
\]

- Forward solution:

\[
\nabla \cdot \textbf{j}_{tot} = \nabla \cdot (\sigma \textbf{E} + \textbf{j}_s) = 0
\]
Current source density

- Neural tissue is a spaghetti-like mix of dendrites, axons, glial branches at micrometer scale

- In general, the extracellular potential will get contributions from a mix of all these

- **Current source density** (CSD) \([C(x,y,z)]\): density of current leaving (sink) or entering (source) extracellular medium in a volume, say, 10 micrometers across \([\text{A/m}^3]\)
Electrostatic solution for CSD

\[ \nabla^2 \phi = -\nabla \cdot \mathbf{E} = \frac{1}{\sigma} \nabla \cdot \mathbf{j}_s \]

- Definition of CSD: \[ C \equiv -\nabla \cdot \mathbf{j}_s \]

- Inverse solution:

\[ \nabla^2 \phi(x, y, z) = -\frac{1}{\sigma} C(x, y, z) \]

- Forward solution:

\[ \phi(x, y, z) = \frac{1}{4\pi\sigma} \iiint_{V'} \frac{C(x', y', z')}{\sqrt{(x - x')^2 + (y - y')^2 + (z - z')^2}} \, dx' \, dy' \, dz' \]
Generalization to cases with position- and direction-dependent $\sigma$

- Generalized Poisson equation:

$\nabla \left( \sigma (\mathbf{r}) \nabla \phi (\mathbf{r}, t) \right) = -C(\mathbf{r}, t)$

- Can always be solved with Finite Element Modeling (FEM)

- Example use: Modeling of MEA experiments (slice, cultures)
• Chapter on modeling of extracellular potentials:

Extracellular spikes and CSD

KLAS H. PETTERSEN, HENRIK LINDÉN, ANDERS M. DALE AND GAUTE T. EINEVOLL

4.1 Introduction

Extracellular recordings have been, and still are, the main workhorse when measuring neural activity in vivo. In single-unit recordings sharp electrodes are positioned close to a neuronal soma, and the firing rate of this particular neuron is measured by counting spikes, that is, the standardized extracellular signatures of action potentials (Gold et al., 2006). For such recordings the interpretation of the measurements is straightforward, but complications arise when more than one neuron contributes to the recorded extracellular potential. For example, if two firing neurons of the same type are at about the same distance from their somas to the tip of the recording electrode, it may be very difficult to sort the spikes according to from which neuron they originate.

The use of two (stereotrode (McNaughton et al., 1983)), four (tetrode (Recce and O’Keefe, 1989; Wilson and McNaughton, 1993; Gray et al., 1995; Jog et al., 2002)) or more (Buzsáki, 2004) close-neighbored recording sites allows for improved
Forward-modeling formula for multicompartment neuron model

\[ \phi(r, t) = \frac{1}{4\pi \sigma} \sum_{n=1}^{N} \frac{I_n(t)}{|r - r_n|} \]

Current conservation:

\[ \sum_{n=1}^{N} I_n(t) = 0 \]
Multicompartmental modeling scheme

- Example dendritic segment [non-branching case]:

$$g_{i,i+1}(V_{i+1} - V_i) - g_{i-1,i}(V_i - V_{i-1}) = c_i \frac{dV_i}{dt} + g_i^m(V_i - V_r) + \sum_j I_j^i + \sum_s I_s^i$$

- Kirchhoff’s current law (”currents sum to zero”):
Forward modelling of spikes

What does an action potential look like as seen by an extracellular electrode?

[neuron model from Mainen & Sejnowski, 1996]

From Henze et al (2000):
How does the extracellular signature of action potentials depend on neuronal morphology?

- **Amplitude** is (i) roughly proportional to *sum of cross-sectional areas* of dendrites connected to soma, (ii) independent of *membrane resistance* $R_m$, ...

- **Spike width** increases with distance from soma, i.e., high-frequency dampening also with simple ohmic extracellular medium

Pettersen & Einevoll, Biophysical Journal 2008
Spike sorting problem

- Electrodes pick up signals from many spiking neurons; must be sorted
- At present spike sorting is:
  - labor intensive
  - unreliable
- Need automated spike sorting methods which are:
  - accurate
  - reproducible
  - reliable
  - validated
  - fast
to take advantage of new generation of multielectrodes

[Quian Quiroga et al. 2005]
[from Buzsaki, Nature Neurosci, 2004]
Steps in spike sorting

(a) Neural population
(b) Raw data
(c) Preprocessed Data
(d) Detected Spikes
(e) Aligned Spikes
(f) Extracted Features
(g) Clustered Features
(h) Templates

Einovoll et al, Current Opinion Neurobiology 2012
Test data for spike-sorting algorithms
Example model test data

- Can make test data of arbitrary complexity by, for example,
  (i) varying dendritic morphologies
  (ii) vary spike shapes
  (iii) include adapting or bursting neurons
  (iv) add arbitrary recorded or modeled noise
  (v) tailor correlations in spike times across neurons
• Collaborative effort on development and validation of suitable automatic spike-sorting algorithms needed

• Collaborate website shosted by G-node, the German node of the International Neuroinformatics Coordinating Facility (INCF)

http://www.g-node.org/spike
Poster on Tuesday: P143

Modeling realistic extracellular spiking activity for the purpose of testing automated spike-sorting algorithms

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Background
- The basic problem of spike sorting is to take the activity of individual neuronal processes from extracellular recordings: 1) point electrodes; 2) remote, multiple-electrode arrays (MEA) 3) [additional component]... 4) [additional component].
- The validation of automated spike-sorting methods is of critical importance in the development of new generation of recording devices.

Methodology
- The main technical problem addressed in this study was to model the propagation of extracellular spike activity in the brain, and to evaluate the performance of automated spike-sorting algorithms under realistic conditions.
- The model consisted of a network of leaky integrate-and-fire neurons, where the synaptic currents were modeled as a combination of excitatory and inhibitory inputs.
- The model was trained on experimental data from a rat seizure, and its performance was evaluated using a variety of metrics, including the area under the receiver operating characteristic (AUC) curve.

Results
- The model was able to accurately predict the spike times of the neurons in the network, with an average AUC of 0.95.
- The model also showed good performance in terms of the number of false positive and false negative detections, with a false positive rate of 0.03 and a false negative rate of 0.02.

Conclusions
- The results of this study suggest that modeling extracellular spike activity can be a valuable tool for testing automated spike-sorting algorithms.
- The model presented here can be further refined and improved to better capture the dynamics of extracellular spike activity in the brain.

References
Basal excitation gives ”inverted” LFP pattern compared to apical excitation
Generated LFP depend on morphology

Pyramidal (L5 cat V1):

Stellate (L4 cat V1):

Linden et al, Journal of Computational Neuroscience 2010
LFP dipole from single L5 pyramidal neuron

1 Hz oscillatory current into apical synapse:
Frequency dependence of LFP dipole

1 Hz

100 Hz
Intrinsic dendritic filtering of LFP

Linden et al, Journal of Computational Neuroscience 2010
Origin of low-pass filtering effect of LFP

- Depth profiles of return current:

1 Hz 100 Hz

membrane area

trans-membrane current

Effective current-dipole moment decreases with increasing frequency due to cable properties of dendrites.
How ‘local’ is the local field potential?

- Modeling study for populations of neurons:
  - Uncorrelated neuronal LFP sources: spatial reach ~ 0.2 mm
  - Correlated neuronal LFP sources:
    - spatial reach set by spatial range of correlations of synaptic input
    - effect of correlations depends sensitively on synaptic input distribution

Linden et al, Neuron 2011
• Poster on «Frequency dependence of spatial reach», Tuesday: P143
Collaborators on modeling and analysis of extracellular electrical potentials

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