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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



• Look for correlations between measurements and stimulus/behavior

• Typical multimodal analysis: Look for <u>correlations</u> between different experiments

Physics-type multimodal modeling



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

'Modeling what you can measure'

• A candidate model for, say, network dynamics in a cortical column should predict <u>all</u> available measurement modalities



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



Measuring electrical potentials in the brain



• Among the oldest and (conceptually) simplest measurents 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 siliconbased multielectrodes with up to thousands of contacts offers new possibilities

• Candidate signal for braincomputer 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



Physical origin of LFP and MUA

• Source of extracellular potential: <u>*Transmembrane*</u> currents



 σ : extracellular conductivity

Note: Current monopoles do not exist



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

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

• From far away it looks like a <u>current dipole</u>

Assumptions underlying:

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

I. Quasistatic approximation to Maxwell's equations

$$\nabla \cdot \mathbf{E} = \frac{\rho}{\epsilon_0}$$

$$\nabla \cdot \mathbf{B} = 0$$

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

$$\nabla \times \mathbf{B} = -\mu_0 \mathbf{j} + \frac{\partial \mathbf{E}}{c^2 \partial t}$$

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

- here: not interested in magnetic fields

- then:

$$\nabla \times \mathbf{E} = 0 \Rightarrow \mathbf{E} = -\nabla \phi$$



II. Coarse-grained extracellular medium described by extracellular conductivity σ





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

III. Linear extracellular medium



IV. Extracellular medium is

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

Assumptions underlying:

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

IV.1: Ohmic: σ is real, that is, extracellular medium is <u>not</u> capacitive

- **OK**
- IV.2: Homogeneous: σ is the same at all <u>positions</u>
 - OK inside cortex, but lower σ in white matter
 - Formula can be modified my means of «method of images» from electrostatics
- IV. 3: Frequency-independent: σ is same for all <u>frequencies</u>
 - Probably OK (I think), but still somewhat debated
 - But if frequency dependence is found, formalism can easily be adapted

Assumptions underlying:

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

IV.4 Isotropic: σ is the same in all <u>directions</u>



- σ is in general a <u>tensor</u> (σ_x , σ_y , σ_z)
- Easier to move along apical dendrites than across ($\sigma_z > \sigma_x$ and σ_y)

- Cortex:
$$\sigma_z \sim 1-1.5 \sigma_{x,y}$$

• Generalized formula:

$$\phi(t) = \frac{I(t)}{4\pi\sqrt{\sigma_y\sigma_z x_1^2 + \sigma_z\sigma_x y_1^2 + \sigma_x\sigma_y z_1^2}} - \frac{I(t)}{4\pi\sqrt{\sigma_y\sigma_z x_2^2 + \sigma_z\sigma_x y_2^2 + \sigma_x\sigma_y z_2^2}}$$

Forward-modeling formula for multicompartment neuron model

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

Current conservation: $\sum_{n=1}^{N} I_n(t) = 0$



Inverse electrostatic solution



Current source density

- Neural tissue is a spaghettilike 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 $[A/m^3]$

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 $\boldsymbol{\sigma}$

• Generalized Poisson equation:

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

- Can always be solved with Finite Element Modeling (FEM)
- Example use: Modeling of MEA experiments (slice, cultures)





New book





• Chapter on modeling of extracellular potentials:

4

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

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

Current conservation: $\sum_{n=1}^{N} I_n(t) = 0$



Multicompartmental modeling scheme



 Kirchhoff's current law ("currents sum to zero"):

CURRENTS TO

SEGMENTS

• Example dendritic segment [non-branching case]:



Forward modelling of spikes

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

[neuron model from Mainen & Sejnowski, 1996]





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



Spike sorting problem

- Electrodes pick up signals from many spiking neurons; must be sorted
- At present spike so

 labor intensive
 unreliable

• Need automated sp sorting methods whic

o accurate
 o reproducible
 o reliable
 o validated
 o fast
 take advantage

to take advantage of generation of multiel



Steps in spike sorting



Einevoll et al, Current Opinion Neurobiology 2012





- Can make test data of abitrary 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 algoritms needed

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



http://www.g-node.org/spike



Available online at www.sciencedirect.com

Current Opinion in Neurobiology

Towards reliable spike-train recordings from thousands of neurons with multielectrodes

Gaute T Einevoll¹, Felix Franke², Espen Hagen¹, Christophe Pouzat³ and Kenneth D Harris^{4,5}

Current Opinion in Neurobiology, 2012

• Poster on Tuesday: P143

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

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Example LFP from multicompartment model



Basal excitation gives "inverted" LFP pattern compared to apical excitation

Linden et al, Journal of Computational Neuroscience 2010

Generated LFP depend on morphology



LFP dipole from single L5 pyramidal neuron

1 Hz oscillatory current into apical synapse:



Frequency dependence of LFP dipole



1 Hz

¹⁰⁰ Hz



Origin of low-pass filtering effect of LFP

• Depth profiles of return 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:

o spatial reach set by spatial range of correlations of synaptic input
 o effect of correlations depends sensitively on synaptic input distribution

Poster on «Frequency dependence of spatial reach», Tuesday: P143

Simplified model of the frequency dependence of the LFP's spatial reach

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