Theoretical neuroscience

Lectures
Vincent Hakim vincent.hakim@ens.fr
Gianluigi Mongillo gianluigi.mongillo@univ-paris5.fr
Jean-Pierre Nadal nadal@lps.ens.fr
Srdjan Ostojic srdjan.ostojic@ens.fr

TDs/Exercise sessions

Francesca Mastrogiuseppe francesca.mastrogiuseppe@ens.fr
Where and when

- Lectures every Thursday, 13h-16h30, ENS, L363/365
- TDs every Thursday with Francesca, 17h-18h30, same room.
- Exam: written Jan 25th + study/presentation one paper.

Website:
http://www.lps.ens.fr/~risc/CA6/

Register! Whether you take the course for credit or not (« auditeur libre »), send an email to mastere@cogmaster.net with copy to nadal@lps.ens.fr (giving name, status, and, if appropriate, name and email of the administrative person to whom the final grade will have to be sent) – bonus: you will be on the course mailing list.
What is this course about?
Theoretical neuroscience

(also computational neuroscience, brain theory, neural modeling,...)

Using tools from mathematics/physics/computer/science
to help analyze/understand how the brain work:
- processes information (see, hear smell,...)
- takes decision
- guides movements
- remembers

......

Very complex questions:
Experiments (biology, psychophysics) crucial to see what is going on
Theory very helpful to guide and analyze experiments, suggest new ones,...
The brain: a network of $10^{11}$ neurons connected by $10^{15}$ synapses
## Spatial scales of the brain

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>~10cm</td>
<td>Whole brain</td>
</tr>
<tr>
<td>~1cm</td>
<td>Brain structure/cortical areas</td>
</tr>
<tr>
<td>100µm-1mm</td>
<td>Local network/‘column’/‘module’</td>
</tr>
<tr>
<td>10µm-1mm</td>
<td>Neuron</td>
</tr>
<tr>
<td>100nm-1µm</td>
<td>Sub-cellular compartments</td>
</tr>
<tr>
<td>~10nm</td>
<td>Channel, receptor, intracellular protein</td>
</tr>
</tbody>
</table>
The brain is a network of different areas

Lesions show the specialization of different brain areas
Imaging by positron emission tomography (PET)

Naming different categories of word activate distinct regions of the temporal cortex
The area level

- Experimental tools (in vivo, invasive): optical imaging (VSD), intrinsic imaging, electrophysiology, neuroanatomy
The area level: interconnected local networks

- Areas are interconnected networks of local networks
The local network level

- Experimental tools (in vivo, invasive): calcium imaging, electrophysiology; (in vitro) calcium imaging, electrophysiology, electron microscopy

Extracellular recordings

de Solages,...,Léna
Neuron 2008

Csicvari et al, J Neursci 1999
Local networks: interconnected ensembles of neurons

- Size $\sim$ cubic mm
- Total number of cells $\sim$ 100,000
- Types of cells:
  - pyramidal cells - excitatory (80%)
  - interneurons - inhibitory (20%)
- Total number of synapses $\sim$ $10^9$ (10,000 per neuron)
- Cells connect potentially to all other cell types ($E \rightarrow E$, $E \rightarrow I$, $I \rightarrow E$, $I \rightarrow I$)
- Connection probability $\sim$ 10%

Lefort,...,Petersen Neuron (2009)
The neuron level: different compartments and sub-compartments

- Experimental tools (in vivo, invasive): calcium imaging, electrophysiology; (in vitro) calcium imaging, electrophysiology, electron microscopy
Neuron = complex tree-like structures with many compartments (e.g. dendritic spines).

Two sub compartment: synapses and dendritic spines.
The subcellular compartment level

Experimental tools: high resolution imaging, electron microscopy.

The molecular level

Membrane, channels,.....

Complex intracellular networks of molecular interactions

Dendritic spine
The molecular level

Experimental tools:
- patch clamp recording of individual channel,
- molecular biology (fusion proteins, ...)

Figure 11-32. Patch-clamp measurements for a single voltage-gated Na\(^+\) channel. A tiny patch of plasma membrane was detached from an embryonic rat muscle cell, as in Figure 11-31. (A) The membrane was

Neher and Sakmann 1976,...
The many temporal scales of the brain

<table>
<thead>
<tr>
<th>Days-Years</th>
<th>Long-term memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seconds-Minutes</td>
<td>Short-term (working) memory</td>
</tr>
<tr>
<td>100ms - 1s</td>
<td>Behavioral time scales/Reaction times</td>
</tr>
<tr>
<td>~ 10ms</td>
<td>Single neuron/synaptic time scales</td>
</tr>
<tr>
<td>~ 1ms</td>
<td>Action potential duration; local propagation delays</td>
</tr>
<tr>
<td>&lt;&lt; 1ms</td>
<td>Channel opening/closing</td>
</tr>
</tbody>
</table>
Submillisecond

- Molecular time scales (channel opening/closing; diffusion of neurotransmitter in synaptic cleft; etc)
Millisecond

- Width of action potentials; axonal delays in local networks
Tens of ms

- Synaptic decay time constants; membrane time constant of neurons; axonal delays for long-range connections
Hundreds of ms

- Behavioral time scales (e.g. motor response to a stimulus)
Seconds-minutes

- Short-term memory, working memory

Delayed response match-to-sample task

Funahashi et al
Days - years

- Long term memory
New exciting tools and data that bridges across scales

- Reconstruction from serial electron microscopy images: **connectomics**

- Excitation/inhibition of specific neurons in vivo: **optogenetics**
Before discussing imaging techniques per se, we need to address the issue of selective staining, which is essential for all reconstruction efforts. Contrast in electron micrographs depends on the accumulation of heavy electron-dense (heavy metal) atoms on the structures of interest.

For the purposes of circuit reconstruction, a stain selective for neuron plasma (but not internal) membranes, synaptic vesicles, and post-synaptic densities would be ideal. Standard EM staining protocols rely on various combinations of osmium tetroxide, uranyl acetate, lead citrate and a number of other compounds to stain sub-cellular structures, but these techniques are not selective for the plasma membrane. The identification of single neurons within tissue sections historically relied on the Golgi-EM method. Modern techniques enable the intracellular filling of neurons that were first characterized electrophysiologically by injecting biocytin, biotinylated dextran amine (BDA) or horseradish peroxidase (HRP). In all cases it is ultimately HRP that catalyses, through the creation of free oxygen radicals from hydrogen peroxide, the oxidation-assisted polymerization of a chromogen, usually diaminobenzidine (DAB). Subsequent heavy-metal intensification of DAB yields an electron density. DAB polymerization has also been used to 'photo-convert' fluorescent probes into electron-dense products. Photo-conversion of chromophores such as resorufin-based arsenical hairpin binder (ReAsh) thus enables correlation between structures observed in living tissue with the same structures in electron micrographs. Quantum dots of different size and shape can also be discriminated in the transmission electron microscope (TEM), further aiding correlations between light microscopy and EM studies.

Towards neural circuit reconstruction with volume electron microscopy techniques, Briggman and Denk 2006 also recent book, S Seung « Connectome: How the Brain's Wiring Makes Us Who We Are »
How optogenetics works

A light-sensitive protein from algae

Take the gene for this protein...

...and insert the DNA into specific neurons in the brain

This protein is an ion channel that opens in response to blue light

Neurons communicate by “firing.” This is an electrical signal created by opening & closing ion channels.

So now you can cause neurons to fire just by flashing blue light!

With the right combination of neurons, you can activate an entire brain circuit to control specific behaviors (like movement)

G Miesenbrock, K Deisseroth, E Boyden, ....,2005-...
Ju Lu & Yi Zuo, New and Views (same issue)
Theoretical neuroscience

**What?** Describe in a mathematically compact form a set of experimental observations.

**How?** Understand how a neural system produces a given behavior.

**Why?** Understand why a neural system performs the way it does, using e.g. tools from information theory.
Methods

Numerical simulations

• write your own code (Matlab, C, C++,...)

• Use dedicated software
  -single neuron (Neuron,...)
  -Network simulations (Nest, Brian/R Brette)
Methods

Analytical calculations

- Single neuron/synapse models: systems of coupled differential equations. Tools of dynamical systems (linear stability analysis, bifurcation theory)
- Noise: ubiquitous at all levels of the nervous system. Probability theory, stochastic processes.
- Coding: information theory.
Course outline

Basic notions and tools

1. Neurons
2. Synapses
3. Networks
4. Learning
5. Coding

Specific computations and systems

1. Vision
2. Navigation
3. Memory
4. Decision
Most useful books

Dayan and Abbott, "Theoretical Neuroscience" (MIT Press, 2001)

Ermentrout and Terman, "Mathematical foundation of neuroscience" (Springer 2010)

Gerstner et al, "Neuronal dynamics : from single neurons to networks and models of cognition", (Cambridge U Press, 2014)

More references on the course website
Neurons I

Basic electrical properties & simplest model