Chapter 1

Introduction

- Problem statement
- Opportunity of voltage imaging, core idea of inverting the causal 'presynaptic spike → postsynaptic PSP' relation
- Overview of thesis

1.1 Connectomics

- Motivation
- Ground-truth connectomics: tracing of electron microscopy and fluoresent injection imaging
- Necessity of connection inference
- Mention 'invasive' connection testing (stimulate one cell, record possible neighbours)
- Limitations of 'connectomics', and of inferred vs 'actual' connectomics.
  Terminology, e.g. 'functional connectomics'

1.2 Voltage imaging

- Technologies (from dyes to GEVIs)
- Specs: cell yield, tissue depth, recording duration, SNR, species
- ..and growth of these over time, and comparison with calcium imaging.
  To extrapolate how these might advance in the future
- Comparison with other recording techniques: ephys, calcium imaging, (and briefly mention coarser methods)

1.3 Network inference

- Working with events/spikes only, versus working with continuous signals; or a hybrid as here.
- Overview of the spikes-only methods
- The connectomics competition, and the findings about the best methods
- Mention other application domains, like gene regulatory networks
- 'Spike-triggered voltage regression' of Zhou/Cai

Chapter 2

The neuron model

In this chapter, we decribe our experimental setup: the neuron model we simulate, its inputs, and how we simulate voltage imaging.

2.1 Neuron model

We choose to simulate the 'AdEx' neuron model, or the 'adaptive exponential integrate-and-fire' neuron. This is a leaky-integrate-and-fire (LIF) neuron model, with two additions. First, the full upstroke of each spike is simulated, as an exponential runoff. Second, an extra dynamic variable is added: the adaptation current. This allows the simulation of many non-linear effects of real neurons, like spike-rate adaptation and post-inhibitory rebound. (Note however that we do not focus on any of these effects in this thesis).

The AdEx model consists of two differential equations, one to simulate the membrane voltage V, and one for the adaptation current w:

$$\mathrm{d}V/\mathrm{d}t =$$
$$\mathrm{d}w/\mathrm{d}t =$$

We solve these equations using first-order (Euler) integration.

In addition to the two differential equations, the AdEx model also consists of an instantaneous reset condition. When the membrane voltage V reaches a certain threshold, a spike is recorded, V is reset, and w is increased:

$$\text{if } V > \theta \text{ then: } V \leftarrow V_r$$
$$w \leftarrow w + \Delta w$$

2.2 Input spikes

In our simplest experimental setup, we simulate just one AdEx neuron. Its input is provided by an array of N Poisson neurons, i.e. they each generate spike trains according to a Poisson process. We call this the 'N-to-1' setup.

The inter-event intervals of a Poisson process follow an exponential distribution. We use that fact to generate spike trains: we draw samples from $\text{Exp}(\lambda)$ (with λ the desired firing rate), and cumulatively sum up these intervals to obtain spike times. This is done until we have reached the desired input train duration.

2.3 Voltage imaging

The signals detected by a light microscope in a voltage imaging setup are not the same as the real membrane voltage signals of which they are a reflection.

We model this lossy transformation by simply adding Gaussian noise to our simulated membrane voltage. As in the voltage imaging literature, we quantify the amount of this noise by a 'spike-SNR' measure (spike signal-to-noise ratio). This is defined as the height of an average spike relative to the standard deviation of the noise.

A more realistic model of the voltage-imaging transformation would also incorporate the exponential decay over time of the SNR, and the short-term 'smearing in time' of voltage indicators. The latter could be done by passing the voltage signal through a linear filter with non-instantaneous impulse response.

Chapter 3

Spike-triggered averaging

- Principle, example STAs
- Influence on STA of E/I balance, output firing rate, reversal potentials
- Use as connection test: shuffled spike trains and height of STA, p-values, and the 'area-over-start' heuristic for E vs I classification.
- Evaluation of a connection test: 'ternary' classification, summary measures, AUROC
- Performance of the simple STA-height test, for different N
- Influence of window length

Chapter 4

New connection inference methods

4.1 STA Template correlation

- Idea for the two-pass test
- Template examples. Both ideal and template found with first-pass (STA height-only)
- Peformance for different N, & comparison with previous method

4.2 Linear regression of the upstroke

- Non-STA method: concatenated individual windows as (X, y)
- Examples of pooled windows, and fits
- Mention the problem of unknown transmission delays
- Perfomance for different N, & comparison with previous methods

4.3 Fitting a full STA model

- Model design
- Iterative model fitting
- Problem of overfitting, and parameter-constraints to solve it
- An advantage: fit parameters (like transmission delay and time constants) are biologically meaningful
- Perfomance for different N, & comparison with previous methods

4.4 Clustering, & Hierarchical model fitting

- (Time-permitting)

4.5 Zhou/Cai's 'Spike-triggered regression'

- (Time-permitting)

4.6 Computational cost

- Timings of each method, extrapolation for larger number of tested connections

4.7 Summary

- Conclusions of the N-to-1 experiment
- Leadup to the network experiments: what we could not yet test (the problem of indirect connections, as e.g. identified in the connectomics challenge)

Chapter 5

Network model

- Network connectivity, E/I balance, raster plots
- Too many possible connections to test them all → Subsampling
- Performance of last chapter's methods
- If time: experiment with a network that is less densely connected than our current fully-random one. Why? To better examine the effect of indirect connections / colliders (For the current connectivity, there are too many of those. But in a more realistic, 'localized' network, there are less, and so it seems easier to isolate and examine their effect).

Chapter 6

Discussion

6.1 Summary & conclusions

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6.2 Future work

- Test on real data
- Direct comparison with spikes-only methods
- More complexity in the testing setup: different transmission delays and time constants per synapse / neuron, plus:
- Short term synaptic plasticity. Bursting. Oscillations.
- Simulate different brain areas (different cell types and connectivity patterns). Simulate the same area, but in different states (up vs down, e.g.)
- New connection test method to try: something deep learning-based (we have infinite training data, given our simulation)