Overview

Abstract (1/10):
Summary of the summary. A short introduction with results stated clearly.

Introduction (1/10):
Introduce the topic, the problem and how the problem is being solved. The target audience are other master students.

Theory:

- Basic information about neurons and the cell membrane. (7/10)
- Basic information about different types of neurons, how they serve different purposes and have different functions. (0/10)
- Turning the neuron into a electronic circuit, explaining ion pumps and channels. (5/10)
- Detailed explanation of action potentials and the generation of action potentials with a the hudgekin and huxley model. (1/10)
- Explanation of the principle of compartmental models with diagrams. There are many kinds. Not too long. (0/10)
- Detailed explanation of electrodes, how they are used, what they measure, how tetrodes work. (1/10)
- Mentioning that neurons measured from the same electrode must be seperated. Cocktail party problem, source seperation. (0/10)
- Detailed explanation of extracellular potential, the physics behind the problem, dipole effect, how it can be calculated, etc.(4/10)
- Discussion of the difference between intracellular and extracellular spike shape. Some say the extracellular spike is the derivative. (0/10)
- Explanation of Neuron and LFPy. How they work, the principle behind them, what they are intended to calculate. (2/10)
- (Detailed?) Explanation of the current state of cell classification. Why is it important, how is it done. Mentioning most influential work from early to current work. (0/10)
- Detailed explanation of the Blue Brain cell database, how it was made, why is it useful, what were the focus of the models, models are public. (0/10)

Note to self, mention the most influential work that has been done on all topics mentioned in the theory. I should show I know all the basic important work that has been done in these fields.

Methods

Everything here is work which I have done myself. Show what I have done, make sure it understood as a lot.

- Explanation of the basis of differentiating spikes, how does one measure how spikes are different. Meantion spike width and ampltiude. (0/10)
- Explain different definitions of spike width and amplitude measurements. (1/10)
- Detailed explanation about the simulation environment. What does LFPyUtil solve and how does it solve it. (3/10)
- Showing a minimum working example of LFPyUtil, show what it makes easier. (0/10)
- Detailed explanation of each simulation, what are the parameters. (3/10)
- How did I use the BlueBrain models, which models are used, why are they used. (0/10)

Results:

State the results in such a way they clearly show what I want to show, but does not "jump to conclusions". State the results without bias. Include figures with text, at a glance the figures will be read seen and read first.

- Detailed explanation of the replication of Pettersen and Einevoll, show that the simulation environment can be trusted. (6/10)
- Show which definition is best for differentiating spikes from different kinds of neurons. (0/10)
- Show that interneurons and pyramidal neurons can be classified. (0/10)
- Explain why spikes look differnt, what are the physical processes that does this? (0/10)

Discussion:

The discussion is important, make it of high quality and maybe long.

- Explain any deviations from Pettersen and Einevoll in the replication. (5/10)
- Create a conclusion of the results from Pettersen and Einevoll. (0/10)
- Using spike width have already been used for differentiate neurons, show how current results backs up this statement. (0/10)
- Research has shown that thin spikes can also come from measuring near axons of pyramidal cells. (0/10)
- Spike widths from blue brain does not match real spikes, the model ones are too long. Argue that even though the models does not match real spikes there is still a large difference between interneurons and pyramidal neurons. (0/10)

Note to self, when trying to explain a method first show the problem clearly then propose the solution to the problem. Engage the reader by showing the problem in such a way they can become curious for a solution.

Abstract

The physical processes that creates electrical signals in neurons are well understood, but how the signals are processed into actions and thoughts has yet to receive a scientifically robust answer Cell type classification is of high importance because the function of different neurons is still largely a mystery.

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1 | Introduction

Since the conception of neuroscience the neurons function have been studied on many levels from the properties of the cell membrane to clustered networks of neurons.

There are several types of neurons and it was early noticed that different kind of neurons gave different types of signals.

This was of much interest because

Modern types of classification uses genotype?, the structure of the neuron and the electric signal.

It is useful to seperate interneurons from pyramidal neurons as pyramidal neurons are excitatory and interneurons are inhibitory.

Is it possible to seperate interneurons from pyramidal neurons soly based on the shape of the action potental.

Knowing the neuron type is important for research. While doing single cell recordings on alive subjects the researchers are recording in the dark. The electrodes only pick up on electrical signals from the brain, so the researcher does not know exactly what they cell they are recording.

Surely the different types of neurons are specialized at certain functions

In this article we show that interneurons can be seperated from pyramidal neurons based on data and models from the Blue Brain project. The program makes an easy way to do the same analysis on future models as long as the models can be loaded with LFPy.

2 | Theory

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2.1 The Neuron

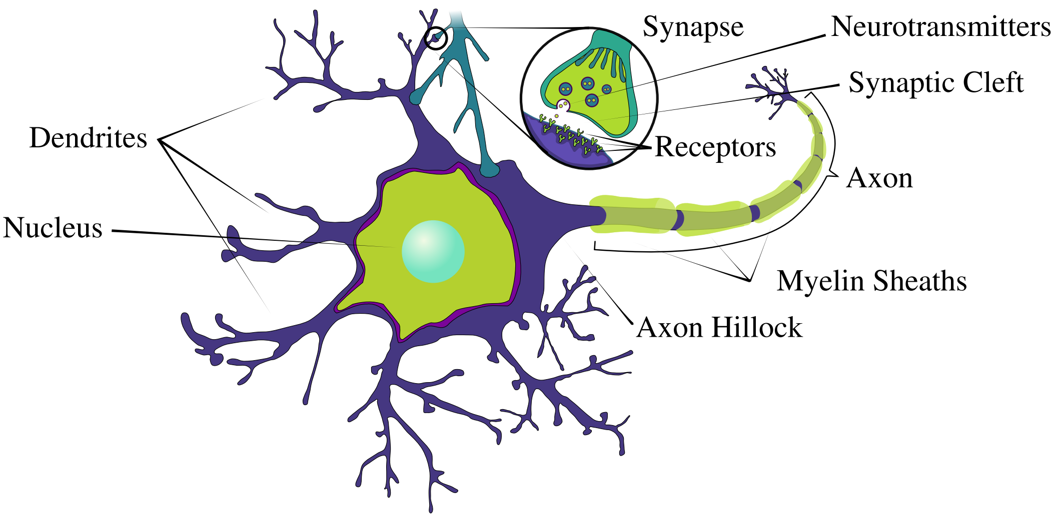

Figure 2.1: Stuff about this neuron.

Neurons are electrically excitiable cells that are a fundamental part of all brain functions. Other names include nerve cells, neurone or more colloquially brain cells. Neurons form in big networks which process information, and in the human brain there is an estimated 10^{11} neurons.

Special proteins in the cell membrane enables the neuron to fire action potentials when it is electrically excited. These action potentials are sharp voltage changes that propagates through the full structure of the neuron. The same properties that makes the neuron able to fire makes the action potential regenerative, meaning it will propagate without decay.

The body of the neuron, the soma, has dendrites and the axon attached to it. The dendrites and the axon are very thin branching structures with a width usually in the order of $1\,\mu\mathrm{m}$. While neurons often have many dendrites directly attached to the soma there is only one axon attached through the axon hillock. The axon can branch several times before it ends and usually connects to the dendrites of other neurons via synapes.

The synapes are electrically sensitive which allows information to pass between neurons. Though the majority of all synapes are axo-dendritic (axon to dendrite), other junctions are also possible. Other junctions include but are not limited to, dendrite to dendrite, axon to axon and axon to blood vessel. When an action potential reaches a synapse it will activate the synapse and pass information to the connect neuron. The information that is passed along depends on the type of synapse, and if it is of a chemical or electrical type.

2.2 Electrical Activity

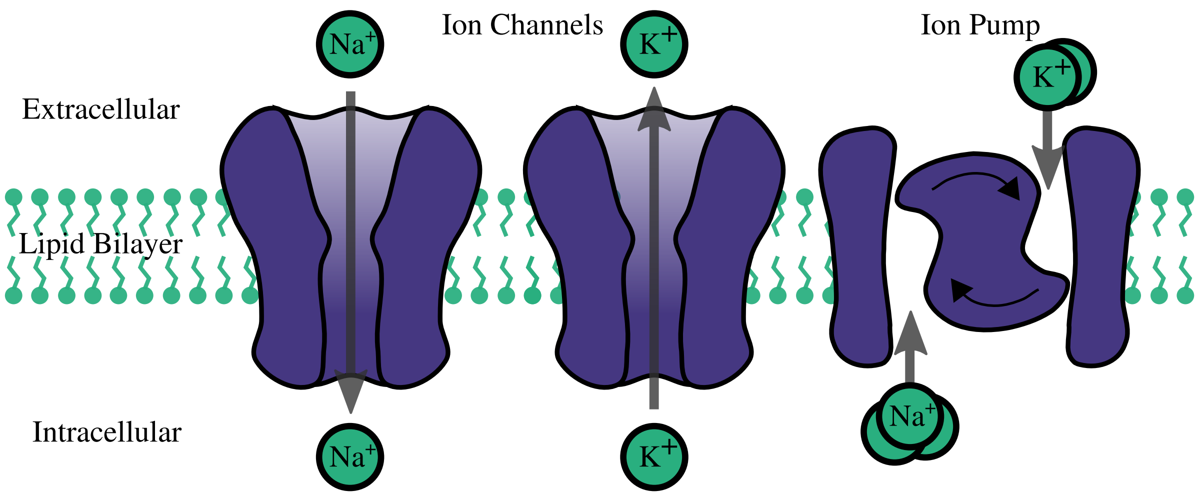

Figure 2.2: Something about ion pumps and channels.

The potential difference between the inside and outside the neurons are caused by different concentrations of ions in the extracellular and intracellular medium. The ions cannot pass through the cell membrane as it consists of a $5\,\mathrm{nm}$ lipid bilayer which is mostly impenetrable to ions.

In the membrane sits diffrent ion channels and ion pumps which can have selective permeability to ions, this creates a potential gradient across the membrane. The most significant ions in this process are Sodium (Na^+), Potassium (K^+), Calcium (Ca^{2+}), Magnecium (Mg^{2+}) and Chloride (Cl^-). Ion channels are divided between passive channels and active channels where the active channels can change permeability under certain conditions while passive channels have a constant permeability.

The ion pumps differ from the channels by activly transporting certain ions through the membrane. For instance, the Sodium-Pottasium exchanger pushes two K^+ ions out of the cell for every three Na^+ it pushes into the cell. Doing this creates a net loss of charge inside the cell and the pump is therefore electrogenic. Not all pumps are electrogenic, the Sodium-Hydrogen exchanger transports H^+ and Na^+ without effecting the net charge. For each H^+ ion out of the cell the pump pushes one Na^+ into the cell.

To understand the electrical activity of neurons it is useful to view the neuron as an electronic circuit where the ion channels, ion pumps and the membrane serve as different electronic components.

Hodgkin & Huxley [5], Connor & Stevens [1], and Sterratt et al. [9]

2.3 Action Potential

Action potentials are sharp increases in the membrane potential followed by a less sharp decrease towards the resting potential. In the the depolarization phase the potential rises towards the peak magnitude, while in the repolarization phase the potential decreases towards the cells resting potential. When the potental is below the resting potential it reaches the afterhyperpolarization phase before it returns to its resting potential.

2.4 Neuron Models

There are multiple models for neurons, some of the main groups are point models and compartmental models. List many models? Multi-compartmental models can be useful to understand the processing of neurons with complex morphological structures

2.5 Electrodes

2.6 Calculating Extracellular Potential

The extracellular potential is the electric potential generated from the transmembrane currents in the neurons. When a neuron fires this can be seen from the extracellular potential which will have a spike which is similar to the intracellular spike.

By modelling the neuron as compartments and approximating each compartment as a spherical volume current source at position $\mathbf{r_0}$, the potential at at position $\mathbf{r}$ at time t will be,

$$\mathbf{E}(\mathbf{r}, \mathbf{t}) = \frac{1}{4\pi\sigma} \frac{I_0(t)}{|\mathbf{r} - \mathbf{r_0}|} \tag{2.1}$$

$$\mathbf{E}(\mathbf{r}, \mathbf{t}) = \sum_{n=1}^{N} \frac{1}{4\pi\sigma} \frac{I_n(t)}{|\mathbf{r} - \mathbf{r_0}|} \tag{2.2}$$

Potential from compartments modelled as line sources.

$$\begin{aligned}\mathbf{E}(\mathbf{r}, \mathbf{t}) &= \frac{1}{4\pi\sigma} \sum_{n=1}^{N} I_n(t) \frac{dr_n}{|\mathbf{r} - \mathbf{r_0}|} && (2.3)\\ &= \frac{1}{4\pi\sigma} \sum_{n=1}^{N} I_n(t) \frac{1}{\Delta s_n} \log \left| \frac{\sqrt{h_n^2 + \rho_n^2} - h_n}{\sqrt{l_n^2 + \rho_n^2} - l_n} \right| && (2.4)\end{aligned}$$

Taken from Lindén et al. [6]

This equation rests on two assumptions,

1. The permeability μ of the extracellular medium is the same as that of vacuum μ_0.
2. The quasistatic approximation which lets the time derivatives, $\partial E/\partial t$, be ignored as source terms. See ??

The extracellular potential can be calculated using Maxwell's equations and the continuity equation if the spatial distribution (morphology) of transmembrane currents and the extracellular conductivity is known.

In the quasistatic approximation, since $\nabla \times \mathbf{E} = \mathbf{0}$, the electric field can be expressed with a scalar potential.

Forward problem = calculate the potential from the current source, inverse problem is used in magnetoenchephalography (important). The amplitude of a spike in the extracellular potential is usually in the magnintude of $< 200\mu$V. The noise of electrodes vary, but can be as much as 20μV. This limits the range electrodes can record from.

The currents sum to zero, while the spike is very visible, there are many small currents in the dendrites with opposite current. ([4])

The extracellular spike width tend to increase with distance from soma because of the neuronal morphology. This article used a passive neuron model with different morphologies to show that the spike width increases with distance to soma. The spike amplitude also decreases with distance to soma and seems to follow a power law. ([8]).

The shape of extracellular spikes are mainly depedent on the membrane currents and the morphology of the cell. Some of the effects from the morphology of the cell are increased spike width and decreased amplitude from distance to soma.

Many things here from around page 245. When the conductivity σ and the current generators are know, Maxwell's equations and the continuity equation equation can be used to calculate the electric field E and magnetic field B. (TODO: Copied text) ([4])

Background

Recording is usually done using electrodes, this makes recording the membrane potential more challenging than recording from the extracellular medium as the electrode has to be very close or inside the cell. At the time of writing, recording the membrane potential of a concious subject is nearly impossible, this makes understanding extracellular potentials vital for current research.

Early calculations was done by Rall 1962 investigating the interaction between action potentials and synapes using cylinders as the current source. (TODO: Read article, make more understandble.) Holt and Koch 1999 added comparmental models to reconstruct pyramidal neurons.

The information about the transmembrane current is usually difficult to obtain, as well as the morphology.

2.7 Neuron & LFPy

LFPy is a Python module that uses Neuron and the mentioned methods to calculate the electric field outside the neuron. [6]

Background

3 | Methods

Methods mentioned here have been developed spesifically for this research.

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3.1 Blue Brain

The Blue Brain project released XXX models based upon neurons from the hind-limb somatosensory cortex from 2-week-old Wistar Han rats. The models were used The extracellular potential was calculated using "TODO: Insert parameters here".

Use the models. Write code to capture one action potential. Bursting neurons often hav adapting action potential, what to do there.

3.2 Spike Width Measurement

Many different definitions of spike width has been used to differentiate neurons, but to date it is not clear which definition is best suited for neuron classification.

Width Type I - Peak-to-peak:

Width is measured as the time from the minimum potential to the maximum. This is the time from the polarization phase to the afterhyperpolarization phase.

Width Type II - Width at Half Amplitude:

Width is measured as the duration the spike is below half amplitude of the signal measured from the baseline at the start of the signal.

Width Type II - Width at Half Amplitude:

Width is measured as the duration the spike is below half amplitude of the signal measured from the baseline at the start of the signal.

3.3 Simulations with LFPyUtil

LFPyUtil is a python package that was created for this project with the purpose to simplify the simulation pipeline for multiple neurons and creating and easy to use interface when developing new simulations. LFPyUtil extends and uses the package LFPy to accomplish this.

The main feature of the python package LFPy is enable the calculation of extracellular potentials, but another major feature is the simplification of simulations with the simulation engine Neuron. Using Neuron requires a good understanding of the programming language hoc which creates many challanges as hoc is outdated and is no longer maintained by the developers. To use Neuron with python one has to use the python interface to Neuron which has been implemented in such a way that runs hoc code directly "under the hood". A common situation is that one must write hoc code inside strings and pass them to the python-hoc interpreter. This has the unfortunate consequence that the two programming langues are very intertwined and also does not follow common python coding conventions. This also makes it harder for users to troubleshoot errors as problems can occur either in python, hoc or between the two. To solve this the package LFPy has attempted to wrap the cell model and electrodes from the Neuron engine into python objects, such as the `LFPy.Cell` and `LFPy.StimIntElectrode` classes.

When running a simulation with Neuron there is no inherent support for running simulations simultaniously. Because LFPy is an extension to Neuron this is also lacking in LFPy. LFPyUtil attempts to solve this by starting each simulation in independent processes. This does not speed up a single simulation but rather speeds up the simulation of multiple neurons and simulations that must be run multiple times with different parameters. The major difficulties of running independent processes with Neuron is that there is no reset function which can make the state of the previous simulation effect the state of the next simulation.

In all simulations the extracellular conductivity was set to $\sigma = 0.3\,\Omega\,\mathrm{m}$ based upon data from experimental measurements.

All stimulus electrodes uses the `LFPy.StimIntElectrode` with a custom made electrode named ISyn. With the default stimulus all transmembrane currents will be summed equal the input current, using ISyn prevents this and the currents are correctly summed to 0.

The following items are python objects in LFPyUtil.

SphereRand

SphereRand places electrodes placed in uniformly distributied locations around the soma within a default radius of $50\,\mu\mathrm{m}$. Spike timing is detected by thresholding the soma membrane potential. That timing is applied to all electrodes such that all electrodes measure the same part of the simulation. If the signal has several spikes the spike index must be supplied, the default setting uses the first spike.

4 | Results

In figure ?? the spike width from interneurons and pyramidal neurons have been plottet seperatly. Neurons in the pyramidal group are the type TTPC1 and TTPC2 The groups suggests that interneuron can be seperated from pyramidal neurons depending on their spike shape.

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4.1 Pettersen & Einevoll (2008) Reproduction

To verify that the simulation environment could be trusted some results from Pettersen & Einevoll [8] was replicated. Spesifically the spike width and amplitude dependency in relation to the distance from soma was compared to current results.

4.1.1 Simulation

Cell: The Mainen & Sejnowski [7] cell was used with a passive model, which is the same model used in Pettersen & Einevoll [8]. It is not clear in which plane the measurements was taken from so the cell was rotated using PCA (principal component analysis) on the compartment positions. This rotates the cell so most of the dendrites are along the y and x-axis.

Spike Generation: An action potental was generated using the Connor-Stevens model [1, 2] using the same parameters as Dayan & Abbott [3]. This had an amplitude of $107.6mV$ from baseline with the peak at $48.21mV$. These values are similar (TODO: how similar?) to Dayan & Abbott [3], but not with Pettersen & Einevoll [8] which had an amplitude of $83mV$ from baseline. To compensate for the difference the action potental was normalized to $83mV$ manually (fig. 4.1).

Parameters: Parameters are the same as Pettersen & Einevoll [8] and Dayan & Abbott [3] . Membrane resistance $R_m = 3 \cdot 10^4 \Omega/cm^2$, membrane capacitance $C_m = 1\mu F/cm^2$, axial resistance $R_a = 150\Omega/cm^2$, time resolution $dt = 2^{-6}ms$. The reversal potential was set to zero. The action potental was imposed in all soma sections using the "play" vector function in Neuron.

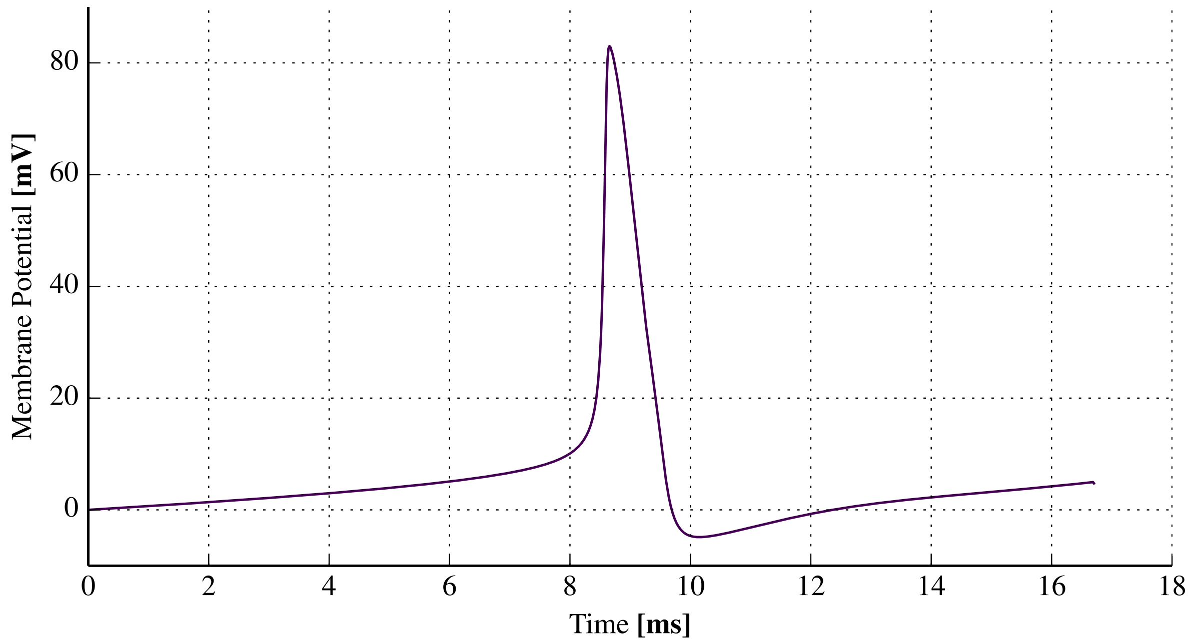

Figure 4.1: Soma membrane voltage.

Electrode Positions: Recording sites were placed in the xz plane at 11 linearly spaced positions along 36 lines with equal angular spacing. (TODO: Show the electrode positions.)

Spike Width & Amplitude: A baseline was set as the value at the start of the signal. Amplitude was calculated as the difference between maximum absolute value and the baseline. The spike width was calculated at half width at maximum amplitude.

Spike width was recorded at $0.5625ms$ for $dt = 2 \cdot 10^{-5}$, similar to $0.55ms$ from Pettersen & Einevoll [8]. When increasing the resolution to $dt = 2 \cdot 10^{-6}ms$ the spike width rose to $0.625ms$.

4.1.2 Results

The action potental that was used in Pettersen & Einevoll [8] is similar to the one used here. The amplitude of the fourier transform is displayed in fig. 4.2 , which is in close resemblance to the standard action potential in Fig. 3 in the paper.

The spike width increases with the distance from soma as seen in fig. 4.3 . These results are lower than the widths reported in Pettersen & Einevoll [8]. (Use more time on editing the Connor-Stevens model to come closer to an max.amplitude on 20mV?).

Sudden changes in spike width was experienced with increased distance from soma. Above $200\mu V$ the spikes shapes are not well defined. This was also reported in Pettersen & Einevoll [8].

Pettersen & Einevoll [8] reports a spike amplitude above $150\mu V$ at $20\mu m$, this does not match current findings. fig. 4.4 shows spike amplitude with logarithmic axes. (TODO: Is numbers on the power law decays necessaryy?) Although the data does not match Pettersen & Einevoll [8], it is comparable with what is expected in the near and far limit field of a ball and

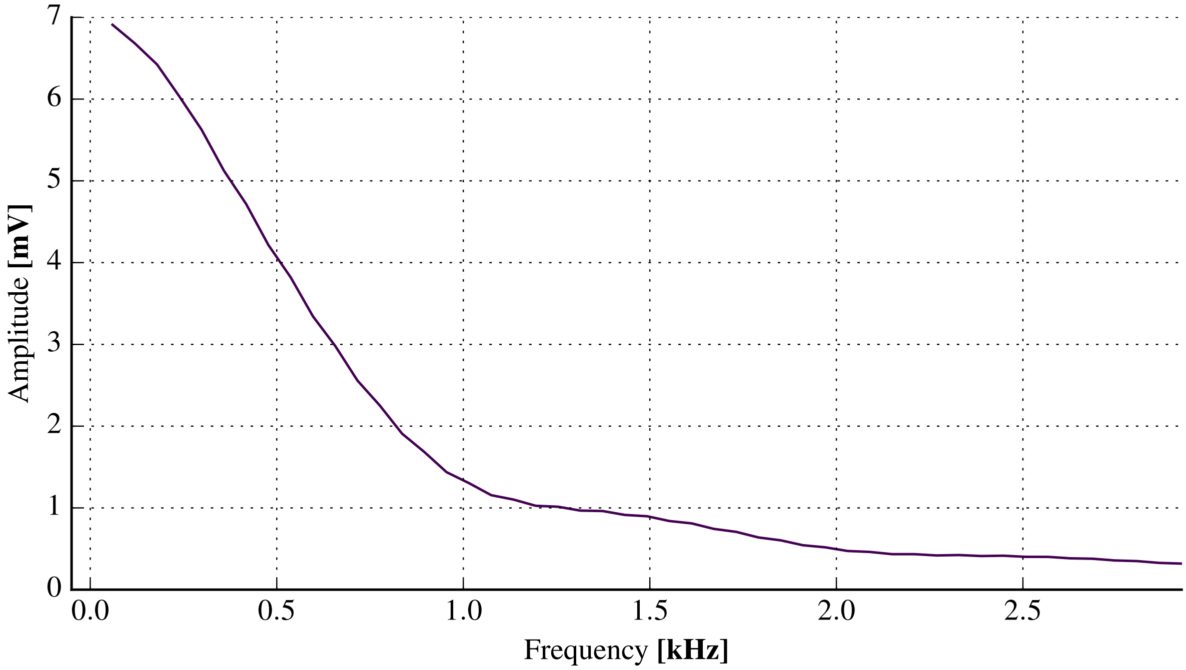

Figure 4.2: Frequency specter of simulated somatic membrane potential.

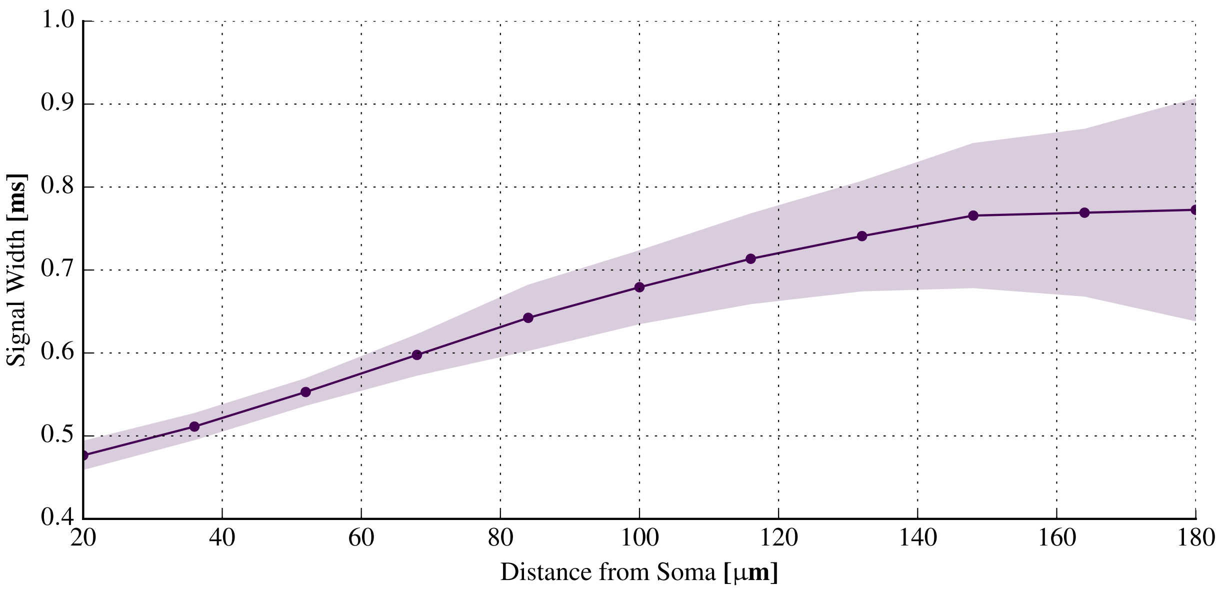

Figure 4.3: Spike width over distance. Mean +/- 1 std.

stick neuron. In the near field the the expectation is a $1/r$ decay and in the far field it is $1/r^2$ or $1/r^3$ depending on distance. (TODO: Clearify this, put reference back to theory chapter.)

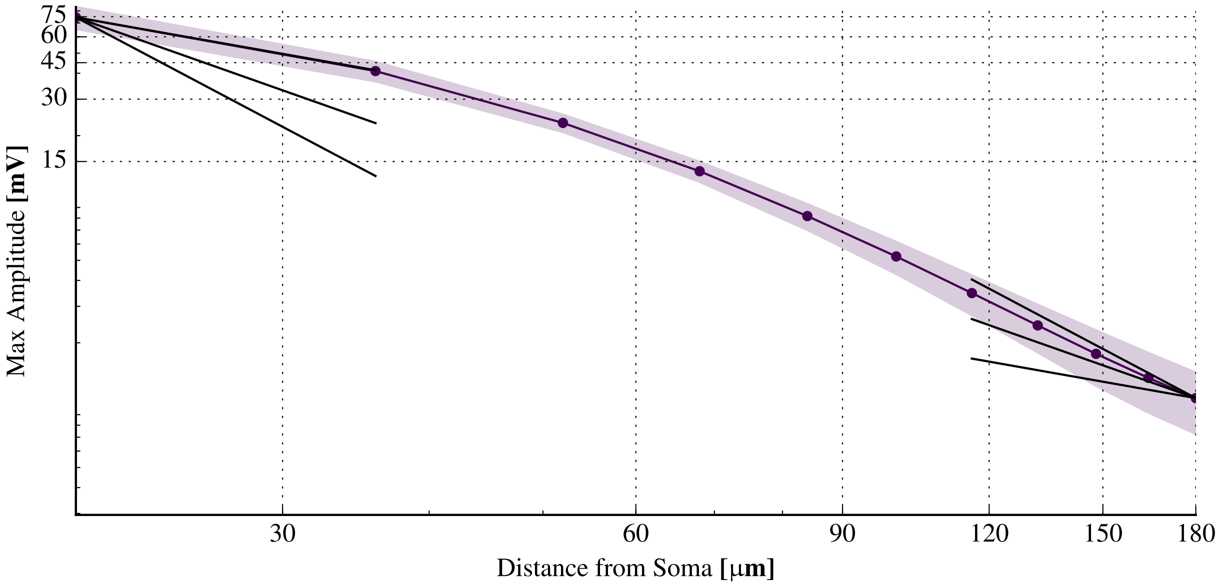

Figure 4.4: Spike amplitude over distance. Mean +/- 1 std. The power law decays $1/r$, $1/r^2$ and $1/r^3$ are shown at the leftmost and rightmost data points.

4.1.3 Discussion

5 | Discussion

Nothing here yet.

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