RWTH Aachen University
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Bachelor Thesis/Master Thesis/Seminar Paper

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The present work was submitted to the Chair of Software Engineering

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I hereby declare in lieu of an oath that I have completed the present Bachelor's thesis/Master's thesis* entitled

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independently and without illegitimate assistance from third parties. I have use no other than the specified sources and aids. In case that the thesis is additionally submitted in an electronic format, I declare that the written and electronic versions are fully identical. The thesis has not been submitted to any examination body in this, or similar, form.

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Kurzfassung

Eine kurze Zusammenfassung der Arbeit.

Abstract

A short abstract of this thesis.

Inhaltsverzeichnis

Kapitel 1

Introduction

-Neuropathic pain as basis
-comes with many diseases

-pain as electric signals
-goal to understand the firing patterns in nerve fibers
-microneurography as recording technique
-needle in vitro in patients
-action potentials as spikes
-animal data
-does not need fiber separation

-OpenMNGlab
-currently only good for loading the data
-want to add analysis capabilities
-compute quantifiers for spike trains and recordings
-discuss results

Software:
-working on jupyter notebook
-automate the spike analysis process
-integrate analysis into openMNGlab
-get requirements for spike analysis software

There are many unsolved problems in the medical sciences. One of which is neuropathic pain that often occurs as a side effect of other diseases such as Diabetes for example.
-TODO: Do more research on neuropathic pain
Pain is transmitted as electric signals through the nerves inside our bodies. Because of this fact in order to understand different types of pain such as neuropathic pain for one we need to understand the transmission of electrical signals in nerve fibers.
Measuring electrical signals can be done in different ways. One of which is called microneurography. This is a technique that is used to record nerve activity in peripheral nerves. With this technique typically a needle gets inserted into a nerve fiber which then detects the electrical current in the fiber. Additionally, we can stimulate the nerve fiber to get certain responses.
Nerve fibers transmit data with the use of action potentials, short AP or spike. It has been

shown in previous research that information is not transmitted by the shape or amplitude of the spikes, but the frequency and timings (look the exact papers up again).

[www10]

Kapitel 2

Data

Because human nerve data is hard to obtain, we can also use animal data instead as a proxy. Animal data is usable as proxy because we can observe the nerve fibers in vitro but can better separate one single nerve fiber from others. In human data an additional step of fiber separation is necessary to differentiate between individual fibers. We can use the same experimental protocols on Animals as we would on humans. This way we can understand firing patterns of spikes and quantify them. The results can then be applied to human data.
In the case of this thesis, we are using the data from wistar rats. The data was recorded from 2011 to 2012 by Roberto de Col and was published in a paper (put reference). The goal of the paper was to evaluate the effects of spiking activity on the response to mechanical stimulation.

-How much of the exact experimental details are supposed to go here as far as methodology goes, since this is a computer science thesis

The experiments were done in vitro on peripheral nerve fibers. The fibers were mechanically and electrically stimulated via a custom made electromechanostimulator. The nerve activity was recorded using an electrode. The electrical stimulation consists of small electrical pulses that come in a controlled frequency. The mechanical force is applied in a sinusoidal shape.
For single recordings the mechanical force that is applied throughout stays at approximately the same level for most of the files (put for how many files this is the case), but there are exceptions where the mechanical stimulation changes in amplitude and length during one recording.

The experimental software used for these experiments is called Spike2 and is described further in the background chapter.

Kapitel 3

Background

-Available spike analysis frameworks
-fieldtrip
-elephant
-Why they are not sufficient
-problem with the relays? maybe windows updates

-openMNGlab as a solution
-acquisition frameworks we need to handle
-Current status of openMNGlab, including Neo
-go into detail on different data acquisition softwares
-Dapsys, OpenEphys, Spike2
-why does dapsys not work in the future

When deciding with which software to analyze the data there were multiple possibilities.

There are the existing FieldTrip and Elephant tools, as well as the Software framework openMNGlab, that all offer different analysis opportunities for electrophysiology data.

Fieldtrip (fieldtriptoolboX.org) is a software developed at the Radboud University, Nijmegen, the Netherlands and offers a wide variety of analysis functions. The main problem with this software is its programming language. It is a MATLAB toolkit, however it would be preferred to use a software package in python or another programming language that slots better in the already existing structure within the chair for medical informatics. In addition to that it is not only speficied for spike trains software, dealing with MEG, EEG and iEEG analysis.

Elephant (https://elephant.readthedocs.io/en/latest/index.html) is a python module which offers some high-level analysis functions for spike trains specifically. The main problem with this software is the lack of basic functionalities. It relies more on highly specified analysis tools that are not necessarily viable in our use-case. For the use in this thesis I want to start with the basic signal from the spikes, try out different quantifiers and look at the data from a fresh perspective.

In the end I decided on using the software framework openMNGlab. It is a python framework being developed at the chair of medical informatics RWTH. It offers some basic import and analysis functionalities that are ideal for using in this Bachelor thesis. With this framework I can start from the beginning and develop my own quantifiers.

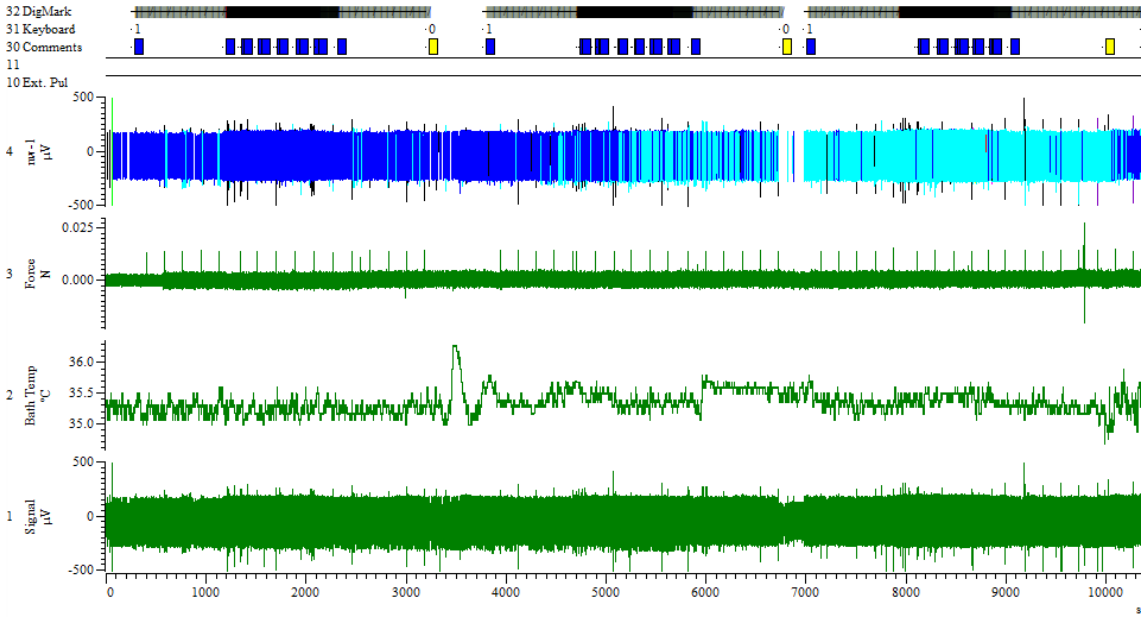

Abbildung 3.1: Typical mechanically and electrically stimulated recording in Spike2

3.1 Data acquisition software

There are many different data acquisition software packages for electrophysiological data.

3.1.1 Spike2

"Spike2 is a multi-channel continuous data acquisition and analysis package" (https://ced.co.uk/products/spko
produced by Cambridge electronic design limited.
-Used for the experiments I am analysing by Roberto
-records data in multiple channels
-channel for raw signal
-channel for mechanical force
-channel for event markers
-channel for temperature (not used by me)
-channel for comments (used for marking when chemicals are applied)
-spikes can be separated into own channels (done by experimenters)
-software offers a graphical representation of the data
-channels are separated
-was used for confirmation of what the data should output in terms of basic quantifiers
-can export csv files from the data
-has direct importer in openMNGlab

Spike2 is a data acquisition and analysis software produced by Cambridge electronic design limited. It is a flexible tool that can be used in a variety of different ways.

TODO: go into detail

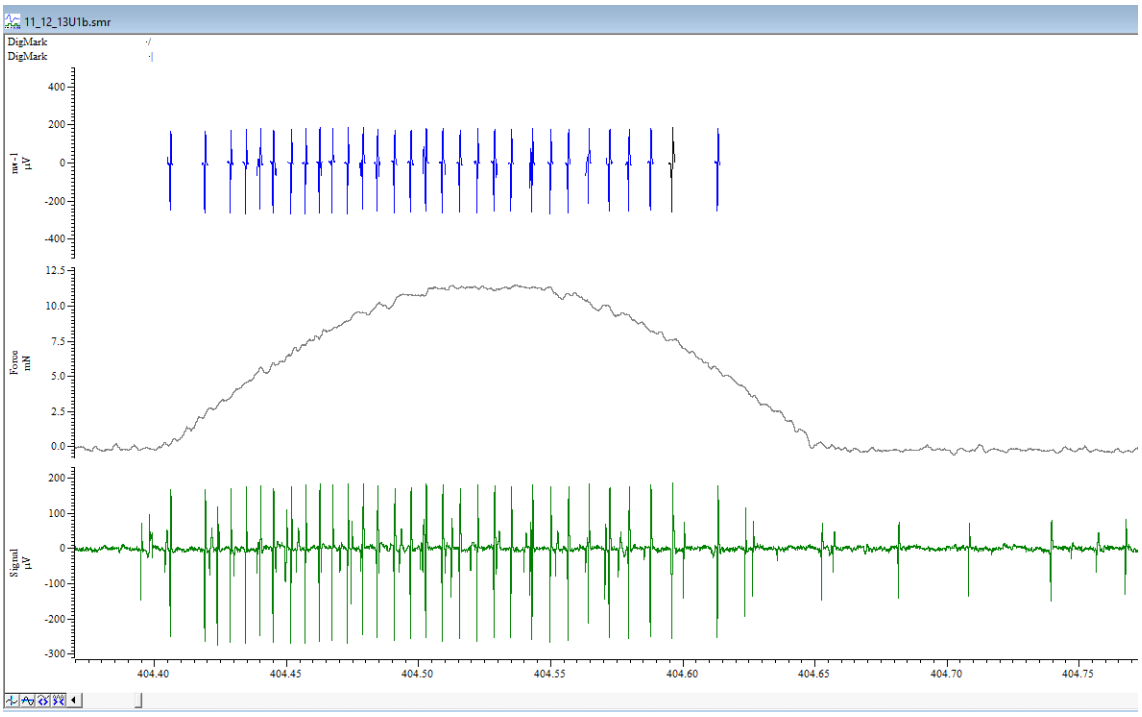

Abbildung 3.2: A single spike train in spike2

The software can record multiple channels simultaneously. An example screenshot from a recording can be seen in Figure 3.1. This depicts a typical recording used for analysis in this bachelor thesis. The recording contains data from nerve fibers of rat cranial dura mater. The nerve fibers were stimulated using a mechanoelectrostimulator applying electaical and mechanical stimulation.

First of all it contains a channel for the recorded raw signal at the bottom. The next channel contains the temperature during the recording. In this example it fluctuates between 35°C and 36.5°C. In channel 3 we can observe the mechanical force that was applied to the nerve fibers. In Figure 3.1 there are spikes in mechanical force whenever a mechanical stimulation occurs to evoke a spike train. For this experiment we want to collect the data of single nerve fibers. It is diffucult, to record just a single nerve fiber in vitro, however. This is why in this experiment spike templates are applied to the raw signal to filter out specific fibers. These filtered fibers are then displayed in channel 4, where only the action potentials of selected shapes are collected.
The topmost channel in Figure 3.1 contains markers for the electrical and mechanical stimuli. Additionally there is a channel containing comments regarding the experiment. Comments can represent the experimental protocol and are filled in by the experimenters. In this example there are comments denoting a change electrical stimulation frequency. In other experiments for example, these could also denote the application of certain chemicals towards the recorded subject.

A more detailed view of a single spike train can be seen in Figure 3.2. Here the difference in electrical and mechanical event markers in the topmost chanel can be seen. Mechanical markers are represented by a slash, while electrical markers are represented by a vertical line. Another thing that can be seen here is the channel containing only the spikes. This channel is ideal for the extraction of the spikes for later analysis as there is no noise in the

channel anymore and the spikes can also be interpreted as simple events with a timestamp.

3.1.2 Dapsys

"DAPSYS is a combined hardware and software system designed for real-time acquisition and display of data and synchronous control of stimulators." (http://www.dapsys.net/)
-Used by Barbara for her experiments
-used for mng-experiments with human patients
-also has a graphical representation of the data
-has importer in openMNGlab
-needs to export specific templates for the importer to work
-Dapsys has problem in the future
-it gets harder to set up experimental protocols
-maybe it has something to do with newer windows updates
-that means this will probably not be used much in the future

3.1.3 OpenEphys

OpenEphys
-open-source electrophysiology
-based in Cambridge, Massachusetts
-Used in experiments in Bristol cooperation

Kapitel 4

Software

My steps in analysis:

First, I used a jupyter notebook from Radomir. For this the data needed to be extracted from Spike2 directly in the Software. This export step leads to a single csv file for one recording with 5 channels: Time, Signal, Force, DigMark(stimulation events), Spikes

Using the cev files I could extract the spike trains for each mechanical stimulation. The detection of the spike train worked as follows: The start of the spike train gets determined by the stimulation event. The length of the spike train is a previously set amount of time (in most cases 500ms). During this timeframe all spikes in the spike channel get put into a list that keeps track of the spike trains. This pretty basic detection of spike trains works well in this specific use case but has its limits when it comes to other kinds of data with other experimental protocols or just simply recordings without any protocols. Then because we do not have the exact starting points of the trains or bursting patterns this method of detection falls flat.

This first jupyter notebook already made use of what later became openMNGlab. The import of the data was handled by the software framework. However, openMNGlab got some updates soon after which made some significant changes to how the importers work. In the new and improved framework, the importer worked on the original Spike2 files instead of the extracted csv files. This allows for more detailed representation of the data since much of the information was lost in the extraction before this update. However, with this new way of importing the data the mechanical stimulation was not able to be extracted. I still needed the information of the mechanical stimulation which was only contained in the extracted csv file. For this reason, in my analysis from here on, I used a hybrid of the old and new versions of openMNGlab until I was able to fix the new importer to also include the mechanical stimulation channel.

Kapitel 5

Conclusion

Abbildung 5.1: Das SE Logo

Literaturverzeichnis

[www10] Software Engineering website http://www.se-rwth.de/, june 2010.

Anhang A

z. B. Programmdokumentation