Intelligent Data Analysis for MEA Neurochip Data

Barbara Priwitzer, Stefan Dornbrach, Sebastian Elger, Kerstin Lenk, Martin Tangermann

Abstract

We present the research topics of the project “Intelligent Data Analysis for MEA Neurochip Data” at the Hochschule Lausitz (FH), which is funded by the German Federal Ministry of Education and Research since June 2009 within the program “IngenieurNachwuchs”.

1 Introduction

Analysis of neuronal signals is a well-established field of computational neuroscience [1]. Research is mainly focused on analysing changes of neuronal activity caused by external, short-term stimuli. In contrast, the project “Intelligent Data Analysis for MEA Neurochip Data” at Hochschule Lausitz (FH) funded by the German Federal Ministry of Education and Research deals with data from long-term in-vitro experiments leading to quasi-stable spike patterns. In this article we present the topics considered in this project and some results so far.

2 Background

Data for the project are generated by NeuroProof GmbH in Warnemünde and kindly provided for the project.

2.1 Experimental Setup

Neurons extracted from embryonic mice are cultivated on multielectrode-array neurochips (MEA neurochip) with 64 electrodes [2]. This in-vitro neuronal network shows spontaneous activity after three to four days and its activity stabilizes after 21 days, at which age the cultures are used for experiments. The activity at each electrode is recorded and can be separated into activity of up to four neurons. Experiments are carried out for long periods: A standard experiment consists of one native episode, and nine further episodes where a neuro-active substance is applied in stepwise growing concentration. For each episode a stable phase of at least 20 minutes is selected for evaluation.

The main aim of these experiments is to assist high-throughput screening in pharmaceutical research, allowing conclusions on the pharmaceutical effect of candidate substances at an early stage of product development as well as hints for possible side effects.

2.2 Evaluation of MEA data

The standard evaluation of MEA data developed within the last years [2], [3] consists of:

- calculation of approximately 200 features describing various aspects of the neuronal activity, as spike rate, burst rate, features describing the burst structure etc.;
- computation of concentration response curves and determination of EC50 values;
- substance classification of neuronal activity patterns using machine learning methods.

3 Research at Hochschule Lausitz (FH)

Within the above mentioned project research is carried out at Hochschule Lausitz (FH) in order to enhance the standard evaluation of MEA data. All of the below mentioned developments are work in progress.

3.1 Concentration Response Curves (Kerstin Lenk)

Concentration (or dose) response curves (CRC) are a standard method for examining the influence of a substance on activity parameters of the system [4]. In the context of MEA neurochip data a
sigmoid shape can generally not be assumed for the CRC (see fig. 1) as several mechanisms involving several binding sites of different receptors might be in action in case of pharmaceutica. There does not exist a standard method for calculating CRCs which can be carried out automatically for such curves. Within the project important steps towards the development of such a method have been undertaken.

Figure 1: Multiphasic CRC which suggests that different receptors are binding.

In addition to computing CRCs first steps have been undertaken to develop a phenomenological spiking neuron model suitable to simulate CRCs. The INEX model itself is a cellular automaton based on the assumption that spiking of neurons can be described as a Poisson process (see [5]).

3.2 Features from Phase Diagrams (Martin Tangermann)

A common approach in nonlinear time series analysis is to explore the phase space of the particular dynamical system [6]. A phase space reconstructs the characteristics of a system in a purely spatial way, e.g. the phase space for a sinusoid signal is a circle.

Two-dimensional phase diagrams or return plots for spike trains, i.e. neuronal activity, have been examined earlier [7], [8]. Within the project a systematic approach to generating and examining return plots for MEA neurochip data has been made [9].

Due to noise in the data smoothing is necessary; the so obtained 1-dimensional curve, which has the additional advantage of making data with few spikes feasible, can be transformed into a return plot. We observe different classes of return plots depending on the state of the network, see fig. 2

Figure 2: Spike trains of single neurons and the corresponding return plot. Each spike train consists of 198 spikes.
A: Frontal cortex tissue.
B: Same neuron as in A but with $2 \times 10^{-5}$ mol/l Bicucullin applied.
C: Hypothalamus tissue.

In order to quantify the various types of return plots observed for MEA neurochip
data, 80 features have been developed and implemented. The algorithms include fill factor and entropy measures, area recognition methods, winding numbers calculation, curvature analysis, shape parameters, convexity measures, intersecting and overlapping observations. These features have been successfully applied for substance classification.

Many of the actually used features describing neuronal activity are based on so-called bursts, i.e. cascades of spikes. Some tissues as hypothalamus do not reveal a clear burst structure [10], the method of return plots offers the great advantage of delivering many meaningful features without defining bursts.

3.3 Network Structure: Inhibited and Excited Neurons (Sebastian Elger)

The neurons cultivated on MEAs form an in-vitro system of a neuronal network. There are about 10,000 different types of neurons, which cannot be discriminated on the MEA neurochip. Nevertheless, observations of neuronal activity changes to application of neuronal substances suggest that the recorded activity belongs to different types of neurons, namely two types seem to be recognizable: Inhibited neurons which react to application of Bicucullin (BCC), a GABA_A antagonist, by reduction of the spike rate, while excited neurons will show more activity in the same scenario, cp. fig 3.

For most systems the number of excited neurons is larger than the number of inhibited neurons. Aim of this part of the project is to recognize the type of the neurons, whose activity is recorded during the experiment. It is expected that the neuron type itself is an important feature for the network activity and that the different types of neurons do not only show different reaction on BCC, but also on other neuro-active substances.

Work done so far includes the categorization of the neurons, application of machine learning methods in order to determine the neuron type and selection of relevant features for the categorization of neurons.

Figure 3: Spike Rate of an excited (top) and an inhibited neuron (bottom) under BCC application.

A major problem here is the categorization of the training set: Many neurons show neither clear up- or down-going of the activity. We hope that cluster analysis will lead to better discrimination. Cross-validation results obtained so far are very promising, ca. 95% of the neurons are classified correctly, but feature selection is not yet stable.

3.4 Fourier coefficients for quasi stable spike patterns (Stefan Dornbrach)

A standard method in signal processing is Fourier analysis. Fourier analysis for spike trains is often used to reveal activity changes due to external stimuli [11], [12].

In the special case of MEA neurochip data Fourier coefficients are supposed to be important features for classifying
neuro-active substances. Up to now no systematic investigation for Fourier coefficients of MEA neurochip data have been undertaken.

Within the project a tool has been developed which estimates the relevant Fourier coefficients and calculates values for frequency bands, see fig 4. The tool uses Discrete Fourier Transformation with padding and tapering to produce periodograms. These are the basis for calculating new features which shall subsequently be used for substance and unit classification.

4 Summary

The work done so far within the project is focused on developing new features especially for single neurons in order to get more detailed information on the neuronal patterns observed in MEA neurochip experiments. These features shall contribute to better classification of neuro-active substances and to better understanding of the mechanisms involved in these experiments. The INEX model developed within the project shall confirm assumptions gained from data analysis.

Further work has to be done in order to establish the results obtained so far, especially by classification of substances, mechanisms or unit types.

5 References


About the Authors

Barbara Priwitzer is the head of the research group “Intelligent Data Analysis for MEA Neurochip Data” at Hochschule Lausitz (FH) and holds a doctoral degree in mathematics. Since 2007 she is teaching in the computer science department of Hochschule Lausitz (FH).

Kerstin Lenk is currently working on her doctoral dissertation in computational neuroscience. She graduated from Hochschule Lausitz (FH) as Diplom-Informatikerin in 2009 with focus on medical informatics.

Stefan Dornbrach, Sebastian Elger and Martin Tangermann are currently master students in computer science at Hochschule Lausitz (FH) and all three of them hold a Bachelor’s degree in Computer Science.