SPP 1665:

Resolving and manipulating neuronal networks in the mammalian brain – from correlative to causal analysis

Newsletter, second edition, December 2014

1) Publications

There are some new publications related to the SPP 1665:

a) Messer M, Kirchner M, Schiemann J, **Roeper J**, Neininger R, **Schneider G**: A multiple filter test for the detection of rate changes in renewal processes with varying variance. arXiv: stat.AP/1303.3594. Annals of Applied Statistics, accepted for publication.

http://arxiv.org/pdf/1303.3594v5.pdf

Abstract:
Non-stationarity of the event rate is a persistent problem in modeling time series of events, such as neuronal spike trains. Motivated by a variety of patterns in neurophysiological spike train recordings, we define a general class of renewal processes. This class is used to test the null hypothesis of stationary rate versus a wide alternative of renewal processes with finitely many rate changes (change points). Our test extends ideas from the filtered derivative approach by using multiple moving windows simultaneously. To adjust the rejection threshold of the test we use a Gaussian process, which emerges as the limit of the filtered derivative process. We also develop a multiple filter algorithm, which can be used when the null hypothesis is rejected in order to estimate the number and location of change points. We analyze the benefits of multiple filtering and its increased detection probability as compared to a single window approach. Application to spike trains recorded from dopamine midbrain neurons in anesthetized mice illustrates the relevance of the proposed techniques as preprocessing steps for methods that assumerate stationarity. In over 70% of all analyzed spike trains classified as rate non-stationary, different change points were detected by different window sizes.

b) **Gärtner M**, Brodbeck V, Laufs H, **Schneider G** (2015): A stochastic model for EEG microstate sequence analysis. Neuroimage 104: 199-208.

http://www.ncbi.nlm.nih.gov/pubmed/?term=A+stochastic+model+for+EEG+microstate+sequence+analysis.

Abstract:
The analysis of spontaneous resting state neuronal activity is assumed to give insight into the brain function. One noninvasive technique to study resting state activity is electroencephalography (EEG) with a subsequent microstate analysis. This technique reduces the recorded EEG signal to a sequence

of prototypical topographical maps, which is hypothesized to capture important spatio-temporal properties of the signal. In a statistical EEG microstate analysis of healthy subjects inwakefulness and three stages of sleep, we observed a simple structure in the microstate transition matrix. It can be described with a first order Markov chain in which the transition probability from the current state (i.e., map) to a different map does not depend on the current map. The resulting transition matrix shows a high agreement with the observed transition matrix, requiring only about 2% of mass transport (1/2 L1-distance). In the second part, we introduce an extended framework in which the simple Markov chain is used to make inferences on a potential underlying time continuous process. This process cannot be directly observed and is therefore usually estimated from discrete sampling points of the EEG signal given by the local maxima of the global field power. Therefore, we propose a simple stochastic model called sampled marked intervals (SMI) model that relates the observed sequence of microstates to an assumed underlying process of background intervals and thus, complements approaches that focus on the analysis of observable microstate sequences.

2) Poster contributions

The promotion of young students is one very important issue of the SPP 1665 work. It can therefore be taken as a very good sign that already some students did take the chance to contribute in poster presentation and did actively participated in meetings and workshops.

a) **Ehinger BV**, **König P**, Ossandón J, 2014, "Robust and Explorative Analysis of EEG / How to cope with a Messy Design?" , "Statistical Challenges in Neuroscience", 3 – 5 September, Warwick University, UK
The poster contributions can be read under the following link:
http://www2.warwick.ac.uk/fac/sci/statistics/crism/workshops/neuroscience/posters

b) **Ehinger BV**, **König P**, Ossandón J, 2014, "Robust and Explorative Analysis of EEG", " Donders Discussion – A conference for PhD students in cognition and neuroscience", 30 – 31 October 2014, Nijmegen, The Netherlands
More information on the poster and the meeting is available under the following link:
http://www.ru.nl/dondersdiscussions/archive/poster/

c) **Bitzenhofer S**, Sieben K, Siebert K, **Hanganu-Opatz IL**, 2014, " Glutamatergic and GABAergic synaptic interplay underlies the theta-gamma network oscillations in the prefrontal cortex of neonatal rats", Society for Neuroscience annual meeting 15 – 19 November 2014, Washington, US

d) Albert S, Messer M, Neininger R, **Roeper J**, **Schneider G**, "Multiple filtering for the detection of rate and variance changes in point processes", Workshop Time Dynamic Change Point Models and its Applications, October 2014, Göttingen

3) Other publications

Wolfgang Krautschneider from the TUHH kindly provided two outcomes of his work to be published in our newsletter.

Flexible Electrodes for Electrobiological Signal Acquisition

To Project: High-resolution characterization of functional connectivity and behavior in healthy and transgenic mice from the neonatal period through adulthood

U. Schmidt, R. Starbird* and W.H. Krautschneider
Institute of Nano and Medical Electronics, Hamburg University of Technology
*R. Starbird is now with Instituto Tecnologico de Costa Rica, Cartago, Costa Rica

We are implementing a process for manufacturing of flexible electrodes for acquisition of electrobiological signals. The electrodes are covered with a special coating of Polyethylenedioxythiophene (PEDOT) to reduce their impedance.

Main fabrication steps are [1]

- Mask design with standard software
- Gold deposition
- Monomer deposition
- Polymerization

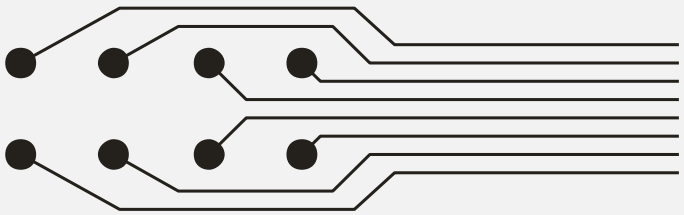

Fig. 1 Mask design for the electrodes. Seven different layouts can be placed on a mask set to be processed in parallel.

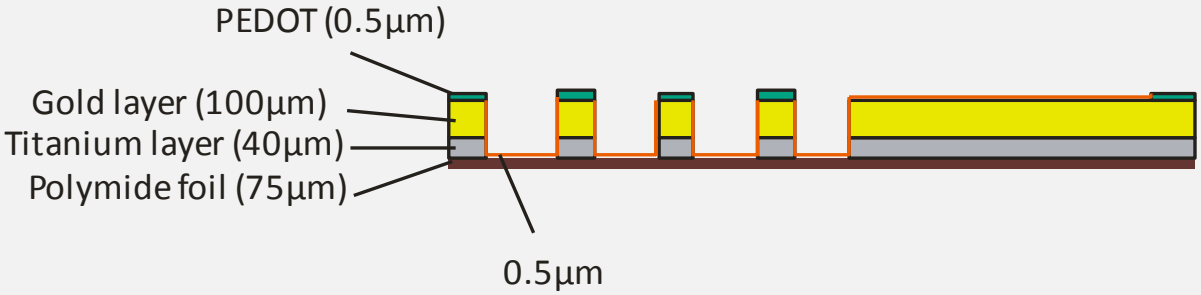

Fig. 2 Cross section of flexible electrode using a polymide foil as a substrate.

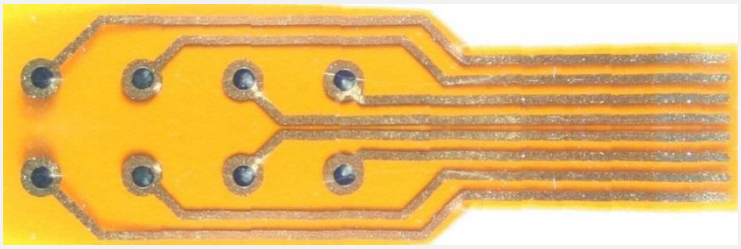

Fig. 3 Metallization level and PEDOT deposition (Black circles) for electrodes with reduced impedance

Figs 1 shows the mask designs, Fig. 2 a cross section of the different layers of the flexible electrodes and Fig. 3 a photograph of a foil with 8 electrodes.

The PEDOT coating results in a significant reduction of the impedance of the electrodes. For larger electrodes (1 mm²), up to two orders of magnitude compared to gold electrodes have been reached at a frequency of 100 Hz.

Next step for improvement of the electrodes will be the reduction of the minimum structure size of the electrodes down to 10 µm. For small electrode areas, the PEDOT deposition will require further optimization to keep the electrode impedance at a low level.

[1] R. Starbird, W. Krautschneider, G. Blume and W. Bauhofer, In Vitro biocompatibility study and electrical properties of the PEDOT coat, PEDOT Collagen-coat, PEDOT nanotubes and PEDOT aerogels for neural electrodes. In: Biomedical Engineering (BioMed 2013), DOI: 10.2316/P.2013.791-072. AISTED 2013. S. 320-326.

nME Institut für Nano- und Medizinelektronik

TUHH Technische Universität Hamburg-Harburg

A Small Area 16 Channel Low Power Neural Recording ASIC

To Project: High-resolution characterization of functional connectivity and behavior in healthy and transgenic mice from the neonatal period through adulthood

L. Abu-Saleh, A. Bahr, D. Schroeder and W.H. Krautschneider

We have developed an application specific integrated circuit (ASIC) for recording EEG signals in the cortex of mice. The ASIC consists of 16 analog channels for recording signals within an input range of +/- 8 mV. The signals are digitized by a 10 bit SAR analog digital converter and accessible via a parallel digital output. A measured signal of one of the channels is shown in Fig. 1. The ASIC is designed for small chip area, low power consumption (about 3.5 mW) and low noise.

Technology	UMC 130nm CMOS technology
# Analog Inputs	16
Dimensions	1,5 x 1,5 mm²
Input range	+/- 8mV
Bandwidth	2 Hz – 10 kHz
ADC Type	10 bit SAR ADC
Tape Out Date	July 14, 2014
Delivery date	Dec. 02, 2014

Table 1: Key Parameter

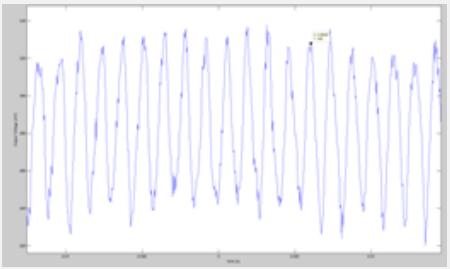

Figure 1: First recorded signal

The process of ASC development consists of the design and specification of several thousands of MOS transistors and capacitors. Firstly, all of these components are simulated after having wired them to specific function blocks and, secondly, after having composed these function blocks to a complete system. By this way, it can be checked, whether the desired functionality can be achieved. Then, the complete system is layouted for an area of 1.5 x 1.5 mm² and, thirdly, simulated again, as now the parasitic effects of the wiring, of the substrate etc. can be taken into consideration.

The key parameters of the ASIC are shown in Table 1.

Special focus of this ASIC project is devoted to low area and low power consumption. The analog frontends are designed in a very symmetrical way to achieve balanced transfer characteristics of the individual channels.

A block diagram with the main components of the ASIC is shown in Fig. 2.

Fabrication of the ASIC started in July at United Manufacturing Corporation (UMC) foundry in Taiwan, the ASIC was delivered to Hamburg early December.

Next Steps:

All the functionality of the ASIC will be thoroughly tested. First test results are looking promising (Fig. 1). Extended test measurements by the troika are planned for January 2015.

Main feature for January 2015 Update Design: Addition of a Data SPI Interface for directly connecting data stream from ASIC with existing OpenEphys and Intan interface boards and software.

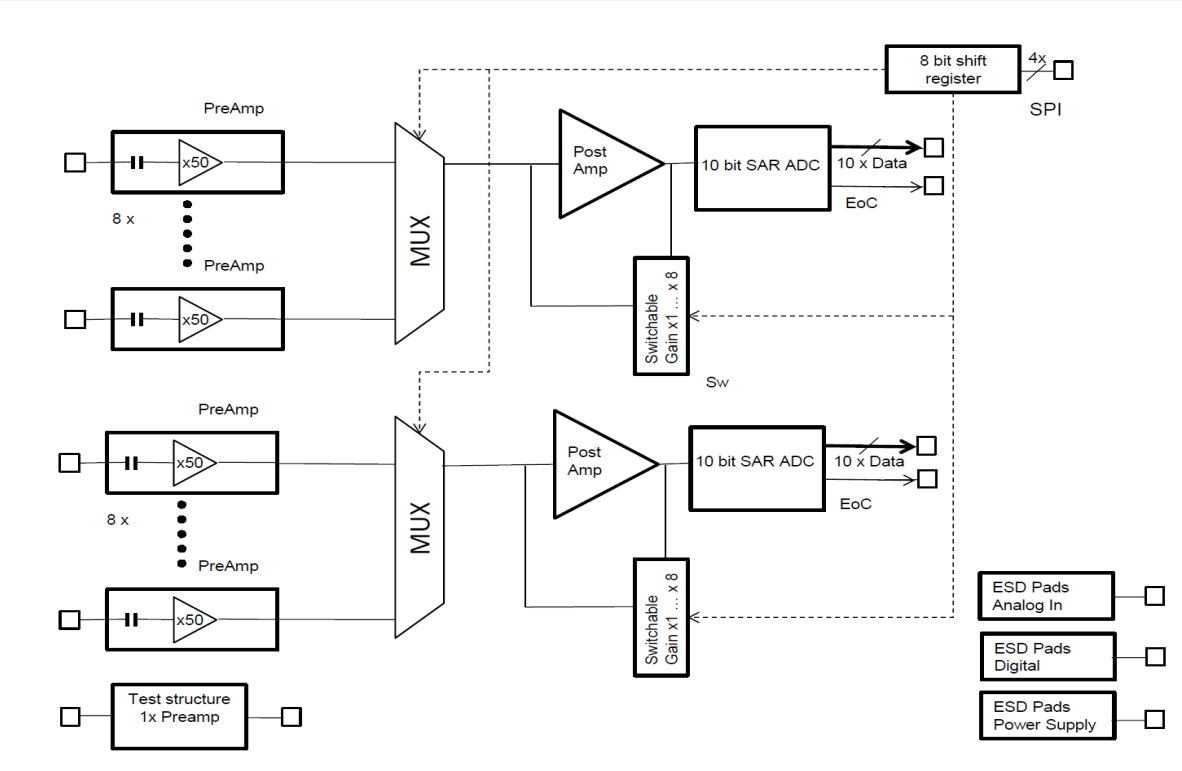

Figure 2: Block Diagram ECoG3 Chip

Chip description

The ASIC consists of low noise analog frontends, which record the signals in unipolar configuration. The input is capacitively coupled and, then, the signals are amplified by 34dB. Eight preamplifiers are connected via a multiplexer to a post amplifier. This post amplifier has been designed for low noise. It has a configurable gain with the steps 1, 2, 4 and 8. A 10 bit SAR-ADC is connected to the post amplifier, delivering the data to a parallel output. The structure consisting of multiplexer, post amplifier and ADC is placed twice on the chip, so that in total 16 analog input channels can be supported.

4) Troika work and co-operations

Again, the co-operational work between and within the troikas have been in the focus. The group of Gaby Schneider offered during the summer semester 2014 a research-orientated and SPP-related lecturer series on spike train analysis for students of mathematics. More detailed information on this is available under the following link:

http://www.math.uni-frankfurt.de/~ismi/schneider/StatPrakt14.html

On the 4th of November the groups of Christoph Herrmann and Carsten Wolters did meet with their co-workers and discussed the use of HD-tACS. During this meeting several half-hour presentations were held by the students Sven Wagner ("Newest results with regard to tCS optimization"), Britte Agsten ("Comparison of complete electrode model (CEM) and point-electrode model (PEM) in tCS"), Simon Homölle ("Newest results with regard to ferret head modeling and tCS simulations"), Heiko-Ivo Stecher ("New technology in Oldenburg") and Toralf Neuling ("Phantom head recordings").

5) Workshops

Analytical Workshop "Analysis and Management of Electrophysiological Activity Data", November 24 – 27 2014, Jülich

The SPP1665 workshop series has launched on Nov. 24-27, 2014 with the first SPP 1665 Analytical Workshop on "Analysis and Management of Electrophysiological Activity Data" organized by Prof. Dr. Sonja Grün and Dr. Michael Denker of the Institute of Neuroscience and Medicine (INM-6) and the Institute for Advanced Simulation (IAS-6) of the Jülich Research Center. 13 students coming from various experimental and theoretical backgrounds, who are to large part directly involved in SPP1665 troikas, had the opportunity to gain hands-on experience in how to practically apply a wide range of different analysis methods for electrophysiological data, including diverse topics such as LFP analysis, spike-LFP correlation, characterization of single neuron activity, spike correlations, or the search for higher order patterns in massively parallel spike trains. Each day started with two lectures by experts in the respective field, including Prof. Dr. Martin Nawrot of the FU Berlin as a guest speaker. In the afternoon, students worked on exercises in the form of newly designed IPython notebooks, which combine scientific explanations, exercise task descriptions, and runnable, modifiable Python code into a single teaching module. In addition, 3 tutors were present during each exercise session in order to help students with technical and scientific advice. While little advance programming experience was required to attend the course, a second aim of the workshop was to stress the usefulness and importance of embracing advanced software tools developed and provided by the Neuroinformatics community for writing better code, increasing the reproducibility of research, and ultimately also initiating new collaborations in a smoother fashion. To this end, on the first day students were presented with a full-immersion experience aimed at introducing concepts of Python programming, version control, and current software projects aimed at data analysts of electrophysiological data. After a long day's work, students would return to their large shared apartments in the town of Jülich, which provided opportunities to establish new contacts and interactions across the project's troikas in an informal setting. (Text by Michael Denker)

The feedback of the workshop was very positive. Here are some of the responses:

“Despite a group with a heterogeneous background, the organizers succeeded to cover the main analysis methods for electrophysiology data without forgetting the basics. From an initiation to python programming to the analysis of spike trains correlation, they not only presented us the theory but also gave us the opportunity to get some practical experience in the analysis of neural data. In short, this workshop was very beneficial for me and it will help me for the analysis of my own data." (Florian Aspart, Berlin)

“The workshop was very exciting and helpful. The scope (from LFP to higher-order coherence analysis of spike-trains) was ambitious, but the organizers succeeded to put up a understandable, nice and diverse workshop with just enough material to continue own studies at home. The lectures were of high quality and the exercises were very interactive and data oriented. Discussions commonly prolonged through lunch and in the evenings, with the lecturers readily available for questions (also about own problems/data). The social parts were fun and it was very inspiring to talk and discuss the projects with other PhDs, Postdocs and members of the SPP.” (Benedikt Ehinger, Osnabrück)

Some visualized impressions:

6) Gender Equality

The Priority Program is aiming at promoting young female scientists. To have the best made-to-measure arrangements, coaching and individual chosen seminars (e.g. by the "Deutsche Hochschulverband" and "DECHEMA") are a being offered. We are very optimistic that this kind of support is one of the bits to increase the percentage of female scientists in leading positions.

7) Upcoming events

Events 2015			
Date	**Place**	**Event**	**Organization**
March, 18 - 21	**Göttingen**	**Progress report (during the NWG meeting in Göttingen)**	**Ileana Hanganu-Opatz**
April, 20 – 24	**Bochum**	**Optogenetics Workshop**	**Ilka Diester, Stefan Herlitze, Jochen Röper, Peter Hegemann**
Mai	**Hamburg**	**Analytical Workshop (II)**	**Andreas Engel**
October, 8 - 10	**Hamburg**	**Annual Meeting**	**Ileana Hanganu-Opatz**

Next newsletter:

To be expected for June 2015.