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# Scientific Programme Overview

# Saturday, September 29, 2007

09:00 a.m. Registration

- 10:15 a.m. Orientation and Introductory Remarks
- 10:45 a.m. The Importance of Seizure Prediction A Patient's View
- 11:00 a.m. Keynote Lecture

01:30 p.m. Session 1: Seizure Prediction I – Assessment and Statistics

04:00 p.m. Session 2: From Single Cells to Complex Networks I – Theoretical Approaches, Modeling Single Cells and Small Networks 06:15 p.m. Get Together

# Sunday, September 30, 2007

08:30 a.m. Session 3: From Single Cells to Complex Networks II – Experimental Approaches, Single Cells and Small Networks in Slices
11:00 a.m. Session 4: Seizure Detection – State of the Art and Applicability for Alarm and Intervention Systems
02:00 p.m. International EEG-Database Project
03:00 p.m. The Unpredictable Concert
04:00 p.m. Leisure Activities

# Monday, October 1, 2007

09:00 a.m. Session 5: Interictal / Ictal Transitions – Animal Models and Human Recordings 11:00 a.m. Session 6: Seizure Control I

02:00 p.m. Technical Implementation of Closed Loop Intervention Systems

02:30 p.m. Session 7: Seizure Prediction II – Recent Developments

05:00 p.m. Session 8: The Seizure Prediction Competition

07:30 p.m. Poster Session

Short presentations of the best posters and poster awards

# Tuesday, October 2, 2007

09:00 a.m. Session 9: Seizure Control II

11:00 a.m. Session 10: Thoughts about Seizure Prediction and its Future 02:00 p.m. Discussion

03:00 p.m. Invitation to the Next Seizure Prediction Meeting 03:15 p.m. Conclusion

For the detailed programme see pp. 12-19.

# Welcome to the 3<sup>rd</sup> International Workshop on Seizure Prediction in Epilepsy!

It is a great honour for us to host this Workshop in Freiburg. Following the first and second Workshop of this kind in Bonn in 2002 and Bethesda in 2006, we are pleased to welcome you to the 3rd International Workshop on Epileptic Seizure Prediction in the heart of the Black Forest. The Workshop takes place in the year of the 550th anniversary celebrations of the Albert-Ludwigs-University Freiburg.

Seizure prediction has had its ups and downs over the last years. While public perception of this field has grown and awareness has increased of the usefulness of a clinical system based on seizure prediction for warning and for new intervention strategies, rigorous statistical evaluations demonstrated that the performance of present-day available prediction methods has to be improved considerably to warrant a clinical applicability.

There is therefore reason to reflect on our understanding of the mechanisms underlying interictal-ictal transitions and to analyse the factors limiting the present-day performance of algorithms. The hope is that a better understanding of mechanisms contributing to the variability of cerebral dynamics will offer new chances to improve prediction methods. Parallel to this, new intervention devices are being developed which could greatly profit from the effectiveness of closed-loop systems based on seizure prediction. The analysis of intervention techniques resetting the dynamics of the preictal and early ictal period may also offer opportunities to better understand preictal and ictal dynamics, thereby giving impetus to the development of new prediction approaches.

The wide scope of contributions presented at this Workshop reflects the ongoing state of discussion. We would like to express our deepest gratitude for your overwhelming interest in the Workshop. More than 120 participants have registered for the Workshop and we received more than 50 contributions for poster presentations. We greatly appreciate the fact that leading scientists from various fields including electrophysiology, computational neuroscience, mathematics, statistics, time series analysis, engineering, physics as well as companies and clinical experts have agreed to come to Freiburg and contribute to this meeting. We particularly welcome the significant number of young investigators participating at the Freiburg workshop. The great interest of participants from all over the world and the high number of original contributions presented as posters instils confidence in us that seizure prediction is a promising field for the years to come.

We wish all participants stimulating sessions, and we hope that everybody will enjoy their stay in Freiburg.

Andreas Schulze-Bonhage, Jens Timmer, Björn Schelter





# Scientific Advisory Board

- Gregory Bergey (Johns Hopkins University, Baltimore, USA)
- Piotr J. Franaszczuk (Johns Hopkins University, Baltimore, USA)
- Mark Frei (Flint Hills Scientific, Lawrence, Kansas, USA)
- Bruce Gluckman (Pennsylvania State University, USA)
- Jean Gotman (Montreal Neurological Institute, Canada)
- Claudia Hemmelmann (University of Jena, Germany)
- John Jefferys (University of Birmingham, UK)
- Klaus Lehnertz (University of Bonn, Germany)
- Michel Le Van Quyen (Centre National de la Recherche Scientifique, Paris, France)
- Brian Litt (University of Pennsylvania, Philadelphia, USA)
- Fernando Lopes da Silva (University of Amsterdam, The Netherlands)
- Florian Mormann (California Institute of Technology, USA)
- Ivan Osorio (University of Kansas, USA)
- Steven J. Schiff (Pennsylvania State University, USA)
- Demetrios Velis (Epilepsy Institute of The Netherlands, Heemstede, The Netherlands)
- Richard Wennberg (University of Toronto, Canada)
- Gregory Worrell (Mayo Clinic, Rochester, USA)

# The Organizing Team

The 3rd International Workshop on Seizure Prediction in Epilepsy is organized as a joint project of the Epilepsy Center of the University Hospital Freiburg, the Freiburg Center for Data Analysis and Modeling (FDM) and the Bernstein Center for Computational Neuroscience (BCCN) Freiburg, Germany.



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# **NIH Support**

The following investigators were nominated for travel and accomodation support by the National Institutes of Health, USA:

- Anna Korzeniewska (Johns Hopkins University, Baltimore, USA)
- Sandeep Nair (Allegheny-Singer Research Institute, Pittsburgh, USA)
- Jonathan Mason (Pennsylvania State University, USA)
- William Stacey (University of Pennsylvania, Philadelphia, USA)
- Dominique Duncan (Yale University, USA)
- Justin Sanchez (University of Florida, USA)
- Marom Bikson (The City College of New York, USA)
- Catherine Schevon (Columbia University, USA)

The following invited speakers are funded for travel and accomodation by the National Institutes of Health, USA:

- Anatol Bragin (UCLA, Los Angeles, USA)
- Steven Rothman (University of Minnesota, USA)
- Roger Traub (SUNY Downstate Medical Center, New York, USA)
- Michal Zochowski (University of Michigan, Ann Arbor, USA)

We like to thank Hitten Zaveri and Ivan Osorio for all their effort in applying for the NIH grant. Moreover, we like to thank the following people for contributing to the grant application:

Brian Litt, Bruce Gluckman, Chris Sackellares, David Rudrauf, Kaspar Schindler, Fabrice Wendling, Fernando Lopes da Silva, Florian Mormann, Gregory Bergey, Gregory Worrel, Javier Echauz, Jean Gotman, Klaus Lehnertz, Leonidas Iasemidis, Mark Frei, Markus Muller, Pawel Kudela, Piotr Franaszczuk, Ralph Andrzejak, Roger Traub, Steven Rothman, Steven Schiff, Stiliyan Kalitzin, Yitzhak Schiller.

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# Funding Organizations and Sponsors

We express our gratefulness for supporting the workshop to:

Deutsche Forschungsgemeinschaft DFG

Deutsche Forschungsgemeinschaft (German Research Foundation)



National Institutes of Health



Deutsche Gesellschaft für Epileptologie

bccr

Bernstein Center for Computational Neuroscience Freiburg



epilepScio

Pfizer







Cyberonics, Inc.



UCB Pharma GmbH

NeuroVista Corporation

# Scientific Programme

# Saturday, September 29, 2007

09:00 a.m.	REGISTRATION - HAUS "ZUR LIEBEN HAND"
	Conference venue address: Löwenstr. 16 (cf. the map on the back side of this booklet).
	<b>ORIENTATION AND INTRODUCTORY REMARKS</b>
10:15 a.m 10:45 a.m.	<b>Welcome and Introductory Remarks</b> Andreas Schulze-Bonhage (University Hospital Freiburg, Germany) and Jens Timmer (University of Freiburg, Germany)
10:45 a.m 11:00 a.m.	<b>THE IMPORTANCE OF SEIZURE PREDICTION -</b> <b>A PATIENT'S VIEW</b> Natascha Dunker
11:00 a.m 12:00 p.m.	<b>KEYNOTE LECTURE</b> <b>Principles of Interictal-Ictal Transitions and Precursors of Seizures</b> <i>Fernando Lopes da Silva (University of Amsterdam, The Netherlands)</i>
12:00 p.m 01:30 p.m.	Lunch (on your own)

01:30 p.m 03:30 p.m.	Session 1: Seizure Prediction I – Assessment and Statistics
	organized by: Florian Mormann (California Institute of Technology, USA) and Claudia Hemmelmann (University of Jena, Germany)
	<b>Designing a Prediction Algorithm: Definitions and Caveats</b> <i>Hitten Zaveri (Yale University, USA)</i>
	<b>Testing a Prediction Algorithm: Assessment of Performance</b> <i>Kevin Kelly (Allegheny-Singer Research Institute, Pittsburgh, USA)</i>
	<b>Testing a Prediction Algorithm: Stastistical Validation</b> Ralph Andrzejak (Universitat Pompeu Fabra, Barcelona, Spain)
	Seizure Prediction in Epilepsy: Does a Combination of Methods Help? Hinnerk Feldwisch genannt Drentrup (University of Freiburg, Germany)
03:30 p.m 04:00 p.m.	Coffee Break
~	Session 2: From Single Cells to Complex Networks I - Theoretical Approaches, Modeling Single Cells and Small Networks
	organized by: Piotr J. Franaszczuk (Johns Hopkins University, Baltimore, USA) and Fernando Lopes da Silva (University of Amsterdam, The Netherlands)
04:00 p.m	<b>Gap Junctions, Fast Oscillations, and the Initiation of Seizures</b> <i>Roger Traub (SUNY Downstate Medical Center, New York, USA)</i>
06:00 p.m.	Interictal to Ictal Transition in Temporal Lobe Epilepsy: Insights from Mean Field Models Fabrice Wendling (University of Rennes, France)
	<b>Network Models of Epileptiform Activity:</b> <b>Modification via Cortical Stimulation?</b> <i>Pawel Kudela (Johns Hopkins University, Baltimore, USA)</i>
	<b>Stochastic Resonance in Neuron Models</b> Marie-Therese Horstmann (University of Bonn, Germany)
	Get Together
06:15 p.m.	It will take place in the "Peterhofkeller" which is located in the vicinity of the conference venue (cf. the map on the back side of this booklet).

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Sunday,	September 30, 2007	12:30 02:00
	Session 3: From Single Cells to Complex Networks II – Experimental Approaches, Single Cells and Small Networks in Slices	
08:30 a.m. – 10:30 p.m.	organized by: Steven J. Schiff (Pennsylvania State University, USA) and Demetrios Velis (Epilepsy Institute of The Netherlands, Heemstede, The Netherlands)	02:0 03:0
	Intrinsic Cortical Mechanisms which Oppose Epileptiform Activity: Implications for Seizure Prediction Andrew Trevelyan (Newcastle upon Tyne, UK)	
	<b>Evaluation and Modulation of Neuronal Excitability in Local</b> <b>Epileptic Circuits</b> <i>Wytse Wadman (University of Amsterdam, The Netherlands)</i>	
	Cortical Network Activity and its Influence on Synaptic Communication Yousheng Shu (Chinese Academy of Sciences, Shanghai, China)	03:00 03:4
	From Neural Dynamics to Macroscopic Pattern Formation during Ictogenesis Michal Zochowski (University of Michigan, Ann Arbor, USA)	03:4
10:30 a.m. – 11:00 a.m.	Coffee Break	04:00
	SESSION 4: SEIZURE DETECTION – STATE OF THE ART AND APPLICABILITY FOR ALARM AND INTERVENTION SYSTEMS organized by: Jean Gotman (Montreal Neurological Institute, Canada) and Mark Frei (Flint Hills Scientific, Lawrence, Kansas, USA)	04:00 oper
11:00 a.m. – 12:30 p.m.	Seizure Detection, Past and Present Jean Gotman (Montreal Neurological Institute, Canada)	
	Computing Constraints of an Implanted Device Compared to a Traditional Computer Jon Werder (Medtronic, Minneapolis, USA)	

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**Seizure Detection Algorithms Adapted to an Implanted Device** *Javier Echauz (BioQuantix, Atlanta, USA)* 

LUNCH (ON YOUR OWN)		
INTERNATIONAL EEG-DATABASE PROJECT		
organized by: Brian Litt (University of Pennsylvania, Philadelphia, USA) and Andreas Schulze-Bonhage (University Hospital Freiburg, Germany)		
<b>Standards for EEG-Data for Evaluation of Seizure Prediction Algorithms</b> Brian Litt (University of Pennsylvania, Philadelphia, USA)		
Integration of Clinical Data in a Seizure Database – The Freiburg Experience Carolin Gierschner (University Hospital Freiburg, Germany)		
<b>Sharing Mass Storage in Global Collaborations</b> <i>Volker-Henning Winterer (University of Freiburg, Germany)</i>		
<b>The International EEG Database Project – Interim Report</b> Brian Litt (University of Pennsylvania, Philadelphia, USA)		
The Unpredictable Concert I:		
<b>Music Performed by Participants of the Meeting – World Premiere</b> B. Litt, S. Schiff, M. Gotman, A. Schulze-Bonhage, F. Mormann, J. Echauz		
The Unpredictable Concert II:		
<b>The EEG as Music</b> Gerold Baier, Thomas Hermann and Ulrich Stephani		
Leisure Activities		
The meeting point is the conference venue, Haus "Zur Lieben Hand". First we will visit a local "Sektkellerei" in the city Breisach, where spar- kling wine is produced. A bus transfer for all participants is organized. Afterwards, the conference dinner will be served at the "Schlossberg- restaurant Dattler". If you want to go there directly, the address is Am Schlossberg 1. We will be glad to provide you with more information at the registration desk.		

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	Session 5: Interictal / Ictal Transitions – Animal Models and Human Recordings	02:00 ] 02:30 ]
09:00 a.m 10:30 a.m.	organized by: Bruce Gluckman (Pennsylvania State University, USA) and John Jefferys (University of Birmingham, UK)	
	Interictal/Ictal Transition in Human Mesial Temporal Lobe Epilepsy and a Rat Model of this Condition Anatol Bragin (UCLA, Los Angeles, USA)	
	<b>Prediction of Preictal State or Seizures?</b> Steven L. Weinstein (George Washington University, Washington DC, USA)	
	<b>Dynamics of a Chronic Limbic Epilepsy Model</b> Paul Carney (University of Florida, USA)	02:30
10:30 a.m 11:00 a.m.	Coffee Break	04:30
	Session 6: Seizure Control I	
	organized by:	
	Gregory Worrell (Mayo Clinic, Rochester, USA) and	
	Ivan Osorio (University of Kansas, USA)	
	Light Up and Chill: Potential Nondestructive Techniques for Terminating Focal Seizures	
11:00 a.m 12:30 p.m.	Steven Rothman (University of Minnesota, USA)	
	Cellular Mechanisms Underlying Antiepileptic Effects of Cortical Electrical Stimulation in Acute Models of Epilepsy in-Vitro and in-Vivo	04:30 05:00
	Yitzhak Schiller (Rambam Medical Center, Haifa, Israel)	05:00
	Controlling the Unpredictable	06:00
	Stiliyan Kalitzin (Epilepsy Institute of The Netherlands,	
10.20 m m	Heemstede, The Netherlands)	06:00 07:30
12:30 p.m 02:00 p.m.	Lunch (on your own)	01.00
		07:30

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02:00 p.m	Contributions from industrial companies involved in detection- or prediction-based intervention systems
02:30 p.m.	Does Seizure Prediction Require Discretely Localized Onset? A Comparison of Mesial Temporal Seizures and Neocortical Seizures with Regional Onset NeuroVista Corporation (Seattle, USA)
	Session 7: Seizure Prediction II – Recent Developments
02:30 p.m	organized by: Klaus Lehnertz (University of Bonn, Germany) and Michel Le Van Quyen (Centre National de la Recherche Scientifique, Paris, France)
	<b>Multivariate Approaches Based on Random Matrix Theory</b> <i>Markus Müller (Autonomous University of Morelos,</i> <i>Cuernavaca, Mexico)</i>
04:30 p.m.	<b>Multivariate Synchronization Approaches</b> Stephan Bialonski (University of Bonn, Germany)
	Small-World Dynamics and Human Epilepsy Kaspar Schindler (University of Bern, Switzerland)
	<b>Frequency Flows and the Time-Frequency Dynamics of</b> <b>Multivariate Phase Synchronization in Brain Signals</b> <i>Frederique Amor (Centre National de la Recherche Scientifique, Paris, France)</i>
04:30 p.m 05:00 p.m.	Coffee Break
	Session 8: The Seizure Prediction Competition
05:00 p.m 06:00 p.m.	organized by: Jean Gotman (Montreal Neurological Institute, Montreal, Canada) and Björn Schelter (University of Freiburg, Germany)
06:00 p.m 07:30 p.m.	Dinner (on your own) & Mounting of posters
	Poster Session
07:30 p.m 10:30 p.m.	Short presentations of the best posters
	Poster awards

TECHNICAL IMPLEMENTATION OF CLOSED-LOOP

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**INTERVENTION SYSTEMS** 

# Tuesday, October 2, 2007

Session 9: Seizure Control II
organized by: Gregory Bergey (Johns Hopkins University, Baltimore, USA) and Richard Wennberg (University of Toronto, Canada)
<b>Vagus Nerve Stimulation and Hippocampal Deep Brain Stimulation</b> <i>Paul Boon (Reference Centre for Refractory Epilepsy, Gent, Belgium)</i>
<b>Thalamic Deep Brain Stimulation</b> Richard Wennberg (University of Toronto, Canada)
<b>Responsive Brain Stimulation</b> Gregory Bergey (Johns Hopkins University, Baltimore, USA)
Coffee Break
SESSION 10: THOUGHTS ABOUT SEIZURE PREDICTION AND ITS FUTURE organized by: Brian Litt (University of Pennsylvania, Philadelphia, USA) and Andreas Schulze-Bonhage (University of Freiburg, Germany) from a physicist's perspective Florian Mormann (California Institute of Technology, USA) from the perspective of a clinical neurophysiologist Demetrios Velis (Epilepsy Institute of The Netherlands,
Heemstede, The Netherlands) from a physician's perpective Christian Elger (University of Bonn, Germany)
from an external view Leonard A. Smith (London School of Economics & Political Science, UK)
Lunch (on your own)
LUNCH (UN IUUR UWN)
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# Invitation to the Next Seizure Prediction Meeting

03:00 p.m	
03:15 p.m.	Ivan Osorio (University of Kansas, USA)
-	Hitten Zaveri (Yale University, USA)

- 03:15 p.m. -04:00 p.m. Conclusion
- 04:00 p.m. ADJOURNMENT

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# **General Information**

# Public Transport in Freiburg

Freiburg has an excellent public transport network consisting of four tram lines and several bus lines. A single-ride ticket through the whole city amounts to 2 EUR, a ticket for 24 hours to 5 EUR (8 EUR for five persons, "REGIO24 Preisstufe 1"). For a trip, e.g. to Breisach or to the Black Forest, we recommend using a "REGIO24 Preisstufe 3" ticket, which is valid for 24 hours. It amounts to 10 EUR for one person (16 EUR for five persons). All tickets for public transport can be purchased directly on the tram or bus. A detailed public transport map can be found in the tourist leaflet which is available at the registration desk. Public transport closes at about 0:30 midnight. Taxis are available 24 hours per day. A taxi ride in the city area is 5 to 15 EUR, a taxi can be ordered at the number +49 - (0)761 - 555 555.

# Freiburg Münster

The Freiburg Münster, built in three stages from 1120 to 1515, is the cathedral of Freiburg. It is located on the site of an older parish church. The church became seat of the Bishop of Freiburg and was officially recognised as a cathedral in 1827. On Saturday 29th there will be an organ recital in the Münster Freiburg from 11:30 a.m. to 11:55 a.m. (free entrance). Catholic church service will be held on sunday 10:00 a.m. accompanied by the girl's choir. Another service will be in St. Peter (Black Forest) for the 200th anniversary of the local church choir on Sunday at 10 a.m.

# In Case of Emergencies

In case of an emergency please use the nation-wide numbers for police 110 or ambulance 112. In case of minor problems of all kinds please contact the registration desk or call the conference-intern service number (24h per day) +49 176 282 124 51.

# Abstracts for Poster Presentation

# 1. Seizure Prediction and Closed-Loop Intervention

1.1) Seizure Prediction: Measuring Generalized Synchronization and Directionality with Cellular Nonlinear Networks

Dieter Krug (1,2), Hannes Osterhage (1,2), Christian E. Elger (1), Klaus Lehnertz (1,2,3)

 Dept. of Epileptology, Univ. Bonn;
 Helmholtz-Institute for Radiation and Nuclear Physics, Univ. Bonn;
 Interdisciplinary Center for Complex Systems, Univ. Bonn

Anticipation of epileptic seizures is, among others, the most challenging aspect in epileptology. Recent findings indicate that particularly synchronization measures show a promising performance that exceeds chance level if tested by statistical validation. Estimators for generalized synchronization offer the possibility for detecting driver-responder relationships and are thus highly attractive to identify interacting brain structures involved in ictogenesis. Despite the conceptual simplicity of nonlinear interdependency measures, real-time applications are currently limited by calculations for the large number of electrode combinations. Promising systems for measuring generalized synchronization while minimizing space and energy consumption

are cellular nonlinear networks (CNN) as they offer a massive computing power, are capable of universal computation, and are already available as analogue integrated circuits. Studying coupled model system (structurally identical and non-identical) we show the ability of our software CNN to approximate both symmetrical and asymmetrical interdependency measures with a sufficient accuracy (~ 90 %; out-ofsample validation). A subsequent analysis of multi-day, multi-channel intracranial EEG recordings from up to now two patients undergoing presurgical evaluation shows that a long-lasting pre-ictal state (duration: ~ 4 hours) can be detected using our CNN-based approach to measure generalized synchronization. At present, the computation times for a CNN-based estimation and a numerical calculation of interdependency measures are comparable. Hardware implementations will provide a speed-up of orders of magnitudes making complex real-time applications possible. This work was supported by the Deutsche Forschungsgemeinschaft.

#### 1.2) INTERACTIONS IN STOCHASTIC Dynamical Systems: Possible Applications to Seizure Prediction

Jens Prusseit (1,2), Klaus Lehnertz (1,2,3)

(1) Department of Epileptology, University of Bonn; (2) Helmholtz-Institute for Radiation and Nuclear Physics, University of Bonn; (3) Interdisciplinary Center for Complex Systems, University of Bonn

We propose a data-driven approach to measure coupling between stochastic processes. Extending a method proposed

by Siegert et al. (Phys. Lett. A 243, 275, 1998) we estimate deterministic and stochastic parts of the dynamics and define measures that both detect the direction and quantify the strength of the coupling. We numerically test the method using time series from coupled stochastic model systems. Applying our method to intracranially recorded EEG time series from patients suffering from focal epilepsies, we observe interdependencies between EEG signals from different contacts that allow one to identify the epileptic focus even during the interictal state. We discuss possible applications for the detection of pre-seizure states.

#### 1.3) A Cluster Computing System for Rapidly Evaluating Seizure Prediction Algorithms

Kent Leyde, Mike Bland, Khaled Boulos, Gregory Dunn, David Himes, Frederick Hood, Ryan Seghers, David Snyder, Jim Stearns

#### NeuroVista Corporation

Introduction: Seizure prediction algorithms are often computationally complex and require the use of large multi-patient intracranial EEG data sets. Measures employed to avoid in-sample testing necessitate partitioning data and separating training and testing computations. Rigorous methods are required to characterize algorithm performance. The computational burden of these tasks is a barrier to developing and evaluating seizure prediction algorithms. Methods: A cluster computing system was designed specifically for seizure prediction research. Storage requirements were derived from the desire to study a meaningful population of 50 to 100 patients, with a typical record length of 100 to 200 gigabytes per subject. Computational requirements were derived from the need to execute and assess

the results from hundreds of candidate algorithms, comprising signal processing, feature extraction, classification, cross-validation, and performance metric calculation tasks. The resulting system includes 120 computing nodes comprising 675 gigaflops of processing power and 40 terabytes of on-line storage. Custom software supports automated preparation and management of large quantities of clinical data, rapid implementation and execution of algorithms, rigorous performance analysis, and management of cluster hardware. Results: Over an 18 month period, the cluster computing system was used to analyze approximately 500 candidate algorithms and variants, involving the processing of approximately 5 million patient-hours from a data set of 76 patients. Conclusions: Rapid, rigorous, evaluation of candidate seizure prediction algorithms using large data sets and cross-validation methods is beyond the capability of presently available individual personal computers, but may be accomplished using cluster computing techniques.

#### 1.4) Developing Seizure Prediction Algorithms Based Upon EMU Recordings: Data Challenges and Solutions

David Himes, Mike Bland, Khaled Boulos, Kent Leyde

#### NeuroVista Corporation

Introduction: Assembling a database for developing and evaluating seizure prediction algorithms requires data from multiple centers to be converted to a common format and validated. Differences in data collection practices and equipment must be addressed. Methods: In the process of collecting and pre-processing patient data, inconsistencies were identified, catalogued, and corrected using a flexible

pre-processing system. Results: Issues that required correction were: Lead changes within subject - due to headbox limitations, investigators sometimes exchanged leads for a given channel within the same recording session. Dropped samples some EEG manufacturers allow system pausing or account for time drift by assigning clock times to sample times, creating discontinuities within the binary data. Labeling inconsistencies – physicians and technicians frequently used different channel names within subjects, complicating electrode identification. Non-integer sampling frequencies - some EEG systems account for clock/sample drift by assigning fractional sampling frequencies, making resampling difficult. Time zone inconsistencies - it is not uncommon for data within differing portions of a manufacturer's file set (EEG, video, annotations, patient demographics) to employ differing time standards, potentially causing desynchronization. Anonymization - patient information is embedded across many data file types, complicating deidentification efforts. Calibration factor changes within session - investigators infrequently alter their headbox gain within sessions, requiring recalibration of binary data to provide a uniform amplitude scale. Conclusions: Significant data pre-conditioning is required to facilitate use in algorithm development. The aforementioned system supports mass processing, while allowing a dynamically growing library of corrective measures to be applied to subject files.

1.5) DOES SEIZURE PREDICTION REQUIRE DISCRETELY LOCALIZED ONSET? A Comparison of Mesial Temporal and Regional Onset Neocortical Seizures

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Introduction: Seizure prediction studies have focused primarily on patients with well-localized seizures, and electrodes proximate to the ictal onset zone. Whether seizure prediction is more challenging for patients with extra-temporal and/or regional seizure onset remains unexplored. Methods: Continuous subdural EEG recordings of 76 EMU patients were analyzed with a seizure prediction algorithm. The dataset comprises 7452 hours of data, with 301 primary seizures (clusters excluded). Of these patients, seizure onsets were regional neocortical in 7, unilateral mesial temporal in 18, and multi-focal and/or extra-temporal in the remainder. A block-wise (90 minute) statistical model employing k-fold crossvalidation was used to compute prediction sensitivity and the false positive rate for each patient. The Wilcoxon signed ranks test was used to examine algorithm performance versus a chance predictor (paired rate of alerts), and the Kruskall-Wallis test for differences by seizure onset pattern. Results: Mean sensitivity was 79% (p < 0.0001 vs. chance), with a false positive rate of 0.08/hr (2.2/seizure). Sensitivity did not differ by onset pattern (p = 0.77) with 80% for mesial temporal, 88% for regional, and 77% for all others. False positive rate was similarly unaffected (p = 0.72) with rates of 0.08/hr for mesial temporal, 0.07/hr for regional, and 0.08/hr for all others (2.6, 2.4, 2.0/seizure, respectively). Conclusions: High sensitivity seizure prediction with clinically acceptable false alert rates has been demonstrated in

a population of 76 EMU patients. Performance for patients with mesial temporal or regional neocortical onsets did not differ from the population as a whole.

1.6) IMPLEMENTATION OF CLOSED-LOOP, EEG-TRIGGERED VAGUS NERVE STIMULAtion using Patient-Specific Seizure Onset Detection from Scalp EEG

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In a clinical study currently underway at the Beth Israel Deaconness Medical Center in Boston, Massachusetts we are demonstrating the feasibility of automatically triggering the Vagus Nerve Stimulator Therapy System (Cyberonics Inc.) in response to real-time detection of a neurologist-specified (ictal or interictal) abnormality in the scalp EEG. We recently enrolled our first patient, and confirmed that our computerized system reliably and automatically activated the subject's vagus nerve stimulator whenever the patient experienced an inter-ictal epileptiform burst that was pre-specified by a neurologist. Future results form the study will be presented at the meeting. Our computerized system relies on a patientspecific detection algorithm to differentiate the neurologist-specified (ictal or interictal) epileptiform abnormality from the remaining activity in a subject's EEG. The patient-specific algorithm classifies a subject's EEG as being consistent or inconsistent with the neurologist-specified abnormality using the support-vector machine learning algorithm and feature vectors derived from spectral analysis of the EEG. Prior to our clinical study of

closed-loop, EEG-triggered vagus nerve stimulation, we retrospectively evaluated the sensitivity, specificity, and detection latency of our patient-specific algorithm using 536 hours of continuously recorded scalp EEG from 16 pediatric epilepsy subjects. We noted that our patient-specific algorithm detected 132/143 seizures with a 6.8+/-2.4 second detection latency and 0.2+/-0.7 false alarms per hour. For comparison, the Reveal algorithm (a commercial, patient non-specific detector) evaluated on the same data detected 94/143 seizures with a 17.8+/-10.0 second detection latency and 2.0+/-5.3 false alarms per hour.

#### 1.7) SIGNAL PREDICTION ALGORITHM BY Cellular Nonlinear Networks (CNN)

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The derivation and analysis of EEG signal feature extraction methods has been treated in several investigations. Although, the results of recent studies indicate that a pre-ictal transition to a seizure can be detected, up to now the sensitivity and specificity of the applied methods are not sufficient for an automated seizure prediction. In this contribution we will present recent results obtained by applying a signal prediction algorithm to segmented EEG-signals of long-term recordings obtained in ECoG and SEEG measurements. The prediction performance of autonomous single-layer delay-type discrete time CNN (DTCNN) has been analysed for different cell coupling structures and several feedback delays. Firstly, nonlinear feedbacks have been assumed which have been represented by polynomial weight functions of different order. By taking the assumption that for

each EEG data segment a certain DTCNN predictor can be applied, a series of different prediction coefficients and errors results in an EEG analysis. We observed distinct changes of these quantities in our investigations by considering data of different patients. A detailed discussion of all results will be given in the paper.

#### 1.8) Developing an Alarm System for Epileptic Seizures using Neuro-Fuzzy Models and Spectral Analysis

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The time-varying dynamics of epileptic seizures and the high inter-individual variability make their detection difficult. EEG (electroencephalograph) has been an important clinical tool for the evaluation and treatment of epilepsy. Epileptic seizures occur when a massive group of neurons in the cerebral cortex suddenly begin to discharge in a highly organized rhythmic pattern and exotic phenomena happen during and epileptic seizure which make the long-term prediction of seizures very difficult. On the other hand, neural networks and neuro-fuzzy models are well-known mathematical methods for describing the complex and chaotic forms in nature. In this study, a combination of singular spectrum analysis and the neuro-fuzzy interpretation of locally linear models is proposed to make accurate long term prediction of EEG signals for alarming epileptic seizures. The principal components obtained from spectral analysis have narrow band frequency spectra and definite linear or nonlinear trends and periodic patterns, hence they are predictable in large prediction horizon. The incremental learning algorithm initiates a model for each of the components as an optimal linear least squares estimation, and adds the nonlinear neurons if they help to reduce error indices over training and validation sets. Therefore the algorithm automatically constructs the best linear or nonlinear model for each of the principal components to achieve maximum generalization, and the long term prediction of the original time series is obtained by recombining the predicted components. Results depict the power of the proposed method in long term prediction EEG signals during epileptic seizures.

#### 1.9) MODIFICATIONS OF THE EEG SIGNAL FOR DELAY RECONSTRUCTION BASED SEIZURE PREDICTION METHODS

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Recent approaches to epileptic seizure prediction have utilised nonlinear analysis tools, with many methods such as Dynamical similarity index [1] based on delay reconstruction. Although delay reconstruction is a powerful tool, the EEG is ultimately an unsuitable signal for analysis within its current framework. Delay reconstruction theoretically applies to noiseless time-series data, recorded from an autonomous and lowdimensional system. However, the EEG is a noisy signal, recorded from a nonautonomous system - our brains are both non-stationary and input driven. Furthermore, there is little evidence that the brain is low-dimensional. This

work investigates if a signal more suited to delay reconstruction can be generated from EEG data through some adaptions to the DSI method. Firstly, we analyse a time-series that is the difference between two closely spaced intracranial recordings. This has the advantage that both the common electrode noise (e.g. 50Hz) and the effect of far away dynamics are reduced. This attempts to create a timeseries representation of the underlying local system by cancelling the common input from far away brain dynamics. Secondly, given the hypothesis that the brain is lower dimensional during the pre-ictal period [2] we propose that the template of reference dynamics used is formed from the pre-ictal (rather than inter-ictal) period. Preliminary findings on the Freiburg competition dataset show sensitivity of 25%-100% across patients, with high false positive rates (FPR) of 1-6.6 FP/hr. Further analysis is required to investigate if the FPR can be reduced and to verify if this can offer any improvement over traditional DSI. The high FPR of preliminary results suggests that perhaps future epilepsy prediction research should concentrate on non-reconstruction based methods. [1] M. Le Van Quyen, J. Martinerie, M. Baulac, and F. Varela. Anticipating epileptic seizures in real time by a nonlinear analysis of similarity between EEG recordings. NeuroReport, 10(10):2149-2155, 1999. [2] K. Lehnertz and C.E. Elger. Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. Physical Review Letters, 80(22):5019-5022, 1998.

1.10) HIGH FREQUENCY OSCILLATIONS AND EPILEPTIC SEIZURE PREDICTION

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Purpose: High frequency oscillations (HFOs) have recently proven to be useful in examining epileptic transients. It is thought that these HFOs are specific to epileptic pathologies and may aid diagnosis in terms of localization and provide further understanding of underlying mechanisms. Here we investigate the role of HFOs in terms of seizure prediction. Method: Intracranial EEG was recorded from several patients who were undergoingpre-surgical assessment from subdural ECoG grid electrodes or depth electrodes. The EEG was sampled at 4kHz. Spectral content was examined in the time-frequency domain during interictal, preictal and ictal time periods. Results: Results from the data analysis demonstrated high frequency spectral power changes in relation to epileptic events. These spectral power changes were compared to synchronization/desynchronization event related data that were recorded from nonepileptogenic tissue, that also demonstrate significant HFO components above 250 Hz. Conclusion: HFOs are a possible common factor within a diverse range of epileptic etiologies. If this is confirmed by future work, this may provide a method of non-patient-specific seizure anticipation within a desirable time range for focal therapeutic intervention.

1.11) Epileptic Seizure Prediction and the Open Source Software Project BioSig.

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Seizure prediction is a very challenging topic in EEG processing. Same of these difficulties are caused by the fact, that the results of different studies can not be easily compared or reproduced. Partly, there are technological reasons and a lack of standardization. Different data formats, sampling rates and filter settings make it difficult to compare the data. Often, only univariate or bivariate signal processing methods are used, which limit the number of parameters to one or two. Furthermore, no single unambiguous performance measure is available, and the various performance metrics can not be easily compared. BioSig is an open source software library for biomedical signal processing. BioSig supports the reading of over 40 different biomedical signal data formats; BioSig contains various methods for quality control and artifact processing [1], many feature extraction and classification methods are supported, and long list of various evaluation criteria are supported. BioSig is free/libre open source software (FLOSS), licensed with the GNU GPL. BioSig provides a common framework, that supports the comparison of different methods and approaches. Parts of BioSig were developed for the Brain-Computer interface research which requires single trial EEG classification. Many of these tools could be useful for developing and comparing methods on seizure prediction and detection, for investigating the interictal-ictal transition, and for modeling the dynamics of epileptic processes. Recently support for the database of the epileptics seizure prediction contest was

added and we are investigating how Bio-Sig can contribute best to the challenge of epileptic seizure prediction.

1.12) AUTOMATED MULTIBAND DETECtion of High-Frequency Oscillations in Intracranial EEG and Evaluation of their Prediction Performance

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Automated detection of high-frequency oscillations (HFOs) in intracranial recordings of human epileptic EEG has become an interesting research topic. Those HFOs have been shown to occur localized in space at the seizure onset zone as well as localized in time before an upcoming seizure [1]. We analyzed recordings of 4 patients suffering from a pharmacoresistant focal epilepsy. They underwent implantation of subdural grid and depth electrodes for presurgical long-term EEG monitoring with a sampling rate of 1024 Hz. For all patients we selected 3 intrafocal, 3 extrafocal, and a reference channel. Each channel has been processed with a multiband extension of the automated HFO detection algorithm described in [2]. The EEG signals have been bandpass filtered by a dyadic filterbank (wavelet analysis). The frequency bands of interest are 32-64, 64-128, 128-256, and 256-512 Hz. From these four bands, we extracted the features "HFO density" and "HFO duration" and we statistically evaluated

them with the seizure prediction characteristic [3]. The sensitivity of the feature "HFO density" is significantly higher than the one of "HFO duration" (paired Wilcoxon rank sum test, p < 1e-5). For the "HFO density" the sensitivity values observed exceed the critical value of the random predictor for some patients. A multiband method for HFO detection, which is able to find HFOs of specified intensity and minimal duration, has been introduced. These preliminary results show that HF features can be used as a predictor for epileptic seizures and encourages to further investigations.[1] G. A. Worrell et al., "High-frequency oscillations and seizure generation in neocortical epilepsy," Brain 2004: 127, pp. 1496–1506.[2] A. B. Gardner et al., "Human and automated detection of high-frequency oscillations in clinical intracranial EEG recordings," Clin Neurophysiol 2007: 118, 1134-1143.[3] M. Winterhalder et al., "The seizure prediction characteristic: A general framework to assess and compare seizure prediction methods," Epilepsy Behav 2003: 4(3), 318-325.

# 2. Seizure and Waveform Analysis and Detection

2.1) Low Power Interictal Detection Algorithm to Facilitate Long Term and Wireless AEEG Monitoring

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Traditional seizure and interictal detection techniques aim to quantify the amount of activity present. To do this they must have a high sensitivity (to correctly detect all of the events) and few false detections (high specificity). These requirements are difficult to fulfil simultaneously. An alternative approach, termed data selection, is presented here. This method is a different view on the detection problem: A detection procedure is used to select which sections of data are saved-a fixed amount on either side of an automated detection-and which are discarded. A high sensitivity is still required, but false detections are not as significant as they are rejected by a human interpreter in the same way as background signals are when a standard continuous EEG trace is analysed. The method only allows data reduction, not event quantification, but this is still significant in reducing the analysis time required and in facilitating wireless ambulatory EEG units. Ordinarily there is too much raw EEG data to transmit without compromising battery life and so online, low power, data reduction is required. The data selection algorithm's tolerance to false detections simplifies the algorithm design making it very suitable for this low power implementation. The

data selection method presented here is based upon the Continuous Wavelet Transform and can offer a 50% reduction in the amount of data to be transmitted whilst correctly recording 95% of expert marked interictal events. All of the algorithm blocks are also suitable for ultra low power VLSI implementation.

#### 2.2) Improved Temporal Lobe Epileptic Event Detection through Inclusion of Cardiac Fluctuations.

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Due to the activation of the central autonomic network, neurovegetative signs are commonly observed during epileptic seizures either as the primary seizure manifestation or as an accompaniment to other seizure symptoms. Autonomic changes (cardiovascular changes, respiratory manifestations, gastrointestinal symptoms, cutaneous manifestations, pupillary symptoms and genital and sexual manifestations) give valuable information on the topographic origin of the epileptiform discharge. The cardiovascular autonomic symptoms induced by temporal lobe epilepsy seizures mainly consist of tachycardia often with an increase of blood pressure; rarely they consist of bradycardia, dramatic decrease of blood pressure; and irregular pulse. The role of epileptiform discharges localised to temporal lobe structures in the induction of neurovegetative heart arrhytmias has been demonstrated: on stimulation of the human left insular cortex bradycardia and depressor responses were more frequently obtained than tachycardia and pressor effects whereas the converse applied for the right insular cortex. The analysis

of the R-R intervals variability from electrocardiographic recordings has been used as a measure of autonomic control over the cardiovascular system to detect periods of increased seizure likelihood. We consider the Brain-Heart system as a coupled system in which bioenergetic processes in the brain have an autonomic influence on the heart. We specifically investigate temporal lobe epilepsy and its correlation to cardiac arrhythmias to develop a probabilistic model fusion approach applied to simultaneously recorded EEG and ECG data for both ictal and interictal episodes and provide evidence that epileptic event detection is improved through the inclusion of a probabilistic description of the cardiac fluctuations.

#### 2.3) Automatic Detection and Ictal Pattern Recognition of Epileptic Seizures in Long-Term Human EEG

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Epileptic seizures are reflected in human EEG by multiple ictal patterns. Recently, the prospect of warning and potential intervention systems based on the reliably, early detection of ictal EEG patterns have attracted increasing interest. Moreover, since the workload involved in the detection of seizures by human experts is quite formidable, several attempts have been made to develop automatic seizure detection systems. Here we present a novel procedure for generic, online and real-time automatic detection of multi-morphological ictal-patterns in the human longterm EEG and its validation in continuous. routine clinical EEG recordings from 57 Patients with a duration of approximately

43h. We analysed 91 seizures representing the 6 most common ictal morpgologies (Alpha, Beta, Theta and Delta- rhythmic activity, Amplitude depression and Polyspikes). We found that taking the seizure morphology into account plays a crucial role in optimization of the detection performance. Moreover, besides enabling a reliable (mean false alarm rate <0.5/h, for specific ictal morphologies <0.25/h), early and accurate detection (average correct detection rate >96%) within the first few seconds (average latency of approx. 2s) of ictal patterns in the EEG, this procedure facilitates the automatic categorization of the prevalent seizure morphologies without the neccessity to adapt the proposed system to specific patients. Acknowledgements: We thank Armin Brandt, Carolin Gierschner and Heike Dittrich from the Freiburg Epilepsy Center. Partial funding for this research was supplied by the Committee for Research, University Clinics, Freiburg and the German Federal Ministry for Education and Research (BMBF, grant 01GQ0420 to BCCN Freiburg).

#### 2.4) Analysis of the Dynamics of Human Epileptic Seizures from Scalp EEG

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Results in literature show that the convergence of the STLmax time series, extracted from intracranial EEG recorded from patients affected by intractable temporal lobe epilepsy, is linked to the seizure onset: when the convergence of STLmax profiles of critical electrode

sites reaches a critical level, a seizure is likely to occur. Moreover, the behaviour of this convergence over time allows for the automatic detection of the electrodes involved in the process leading to the seizure. This prediction technique is called ASPA and was presented by Iasemidis et al. in 2003. In order to analyse the predictability of seizures from scalp EEG, this prediction technique was here implemented and tested over three scalp EEG recordings: One from a patient affected by partial frontal lobe epilepsy (patient A) and two from a patient affected by absence seizures (patient B). The algorithm exploits the first seizure in each recording for selecting the groups of critical electrodes to be monitored, this process takes 10min after the seizure onset. After the initialization, the technique succeeded in issuing a warning before every seizure, with an average horizon of 5.43min, that is a good result since the average monitoring time was 6.17min. The technique also automatically detected as critical the electrodes in the focal area, for patient A, and in the frontal area, for patient B. In conclusion, ASPA seems to be able to detect changes also in the dynamics of scalp EEG as well as to infer information about the critical area, even for absence seizures.

#### 2.5) Seizure Detection Enhanced by Seizure Prediction

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Seizure detection involving seizure probability estimation has been applied to intracranial data in a patient non-specific manner (Clinical Neurophysiology 116 (2005) 2460–2472). This method has been shown to give performance levels acceptable for clinical use. Here this method

is combined with a seizure prediction method based on phase synchronization (Physical Review E 67 (2003) 021912), in order to boost its detection performance. The seizure predictor is tuned to have a very low false positive rate (FPR), and hence low sensitivity. Despite this low sensitivity, any prediction is likely to lead to a seizure because of the low false positive rate. Thus when a prediction signal is given one can temporarily lower the seizure detection probability threshold, in order to increase the likelihood of detecting a seizure. The feasibility of this method was tested on the contest data for the Freiburg Seizure Prediction Workshop. In order for prediction to enhance detection, the predictor needs to predict seizures that the detector cannot detect, and this was difficult to do given the low sensitivity of the seizure predictor and the small number of seizures in the contest data. The feasibility of this method will need to be evaluated on a larger data set.

#### 2.6) Multiscale Electrophysiology in Human Epileptogenic Brain: Microseizures, DC-Fluctuations, and High Frequency Oscillations

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RATIONALE: Human brain oscillations span a wide range of spatiotemporal scales. The spatial organization of neuronal assemblies range from small neuronal clusters to centimeter scale networks. Similarly, the frequencies span a wide range from DC to high frequency oscillations. METHODS: We studied 10 patients with hybrid electrodes containing microwires and macroelectrodes. The EEG was acquired using a DC capable broadband amplifier (Neuralynx Inc.). RESULTS: Broadband recordings demonstrated oscillations extending from DC to 700 Hz. Slow oscillations and DC fluctuations were often spatially diffuse, but also occurred in sub-millimeter regions within the seizure onset zone. Fast oscillations (>80 Hz) were primarily localized, and most prominent within the seizure onset zone. In the seizure onset zone frequent sub-millimeter domain seizures were recorded (microseizures) on the microwires, but not apparent on clinical macroelectrodes. The microseizure activity was spatially and temporally correlated with large-scale clinical seizure activity. CON-CLUSIONS: Multiscale EEG recordings demonstrate oscillations and seizures occur over a range of spatiotemporal scales. The microwires demonstrate independent microdomains of seizure activity occurring throughout the epileptogenic zone. Remarkably, microseizures are not detected with standard macroelectrodes. We propose that the generation of focal seizures may occur by the coalescence of microseizure islands, and only become apparent on macroelectrodes after sufficient tissue has been recruited.

#### 2.7) Spread of Ictal Activity in Focal Epilepsy of Frontal and Temporal Origin

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Objective: Latencies between seizure onset, propagation of ictal activity, and initial clinical symptoms and signs are critically important for the successful implementation of detection-based intervention

systems in the treatment of epilepsy. This study analyzes intracranial EEG-recordings for temporal characteristics of ictal spread and its dependence on focus localization. Methods: Intracerebral EEG recordings of 215 seizures from 43 patients with pharmacoresistant focal epilepsy were evaluated based on site of first propagation, latencies between EEG seizure onset, early propagation, and clinical seizure onset. Seizure onset was mesial temporal in 15 patients, neocortical temporal in 15 patients, and frontal in 13 patients. Results: Periods during which ictal activity remained confined to the seizure onset area were significantly different between the patient groups. Median latencies between electrographic seizure onset and early propagation were significantly longer for patients with mesial temporal (10 s) as compared to neocortical temporal (5 s) and frontal seizure focus (2 s; p<0.01). Concordantly, median latencies to onset of clinical symptomatology were significantly longer for patients with mesial temporal (19 s) as compared to neocortical temporal (17 s) and frontal seizure focus (6 s; p<0.01). Conclusions: The speed of propagation of ictal activity and the latencies until initial clinical seizure symptoms differ significantly depending on focus localization. Extended spread often occurred within the time window during which current detection systems operate. This suggests that inclusion criteria of patients suitable for testing the efficacy of detection-based seizure intervention strategies should be based on focus localization and patient-individual propagation patterns.

2.8) Interictal High Frequency Oscillations (>200 Hz) Recorded with Intracranial Depth Macroelectrodes: A Marker of Mesial Temporal Lobe Epilepsy?

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Interictal surrogate markers may provide an accurate mean of localizing the epileptogenic region during the presurgical evaluation of refractory partial epilepsies. In this context, microelectrode recordings from patients with mesial temporal lobe epilepsy (MTLE) have revealed that interictal high-frequency oscillations (HFOs) from 200 to 500Hz, termed fast ripples, are specific of ictogenic structures. Our aim is to use conventional intracranial EEG recordings to characterize these pathological HFOs. Sixteen patients with intractable partial seizures undergoing investigation with intracranial macroelectrodes were recruited prospectively and consecutively. 52 minutes on average of interictal EEG sampled at 1024Hz was analyzed for each patient. HFOs (>200Hz) were detected according to an original semi automatic strategy that consisted in a full automated high sensibility detection followed by a visual validation. This selection was assisted by a wavelet decomposition based time frequency map. Our strategy permits a high sensibility and specificity detection of HFOs. They had a mean frequency of  $242 \pm 40$ Hz, were of short duration (10ms) and low amplitude (16µV). HFOs were mostly nested with a sharp wave and were recorded by one or very few nearby contacts. HFOs were recorded only for each of the nine

patients suffering from MTLE, especially in the ictogenic zone. Interictal HFOs > 200Hz can be recorded from conventional depth macroelectrodes. They were recorded specifically in the ictogenic zone in MTLE, suggesting that they could have valuable diagnostic utility for routine invasive presurgical localization of these epileptic foci.

# 3. Interictal-Ictal Transitions

#### 3.1) THE SPATIO-TEMPORAL EVOLUTION OF EEG CORRELATION CLUSTERS

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Epileptic seizures represent changes in the correlation structure of brain activity. For a deeper understanding of seizure dynamics it is important to gain information about how strong different parts of the brain co-act in the respective phases. This information could be obtained from algorithms that were able to reliably detect the time evolution of correlation clusters. We present a multivariate approach to the detection of clusters in complex spatio-temporal systems that is based on eigenvectors of the equal-time correlation matrix. Instead of the largest eigenvectors themselves suitable linear combinations are exploited that are obtained systematically by maximization of a distance measure. These Cluster Participation Vectors (CPV) eliminate the disturbing effect of inter-cluster correlations and their components allow for improved conclusions on the involvement of channels in clusters. In model data the algorithm is able to correctly identify up to four clusters even in the presence of strong inter-cluster correlations and noise contamination. We demonstrate the usefulness of a running window application of the concept of CPV to EEG recordings at the example of standard surface EEG as well as ECoG with inter-ictal and ictal activity.

#### 3.2) Correlation Changes During Ictal Activity

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Epileptic activity in the EEG is often characterized by specific correlation patterns in part or all of the electrodes. Using a recently introduced correlation matrix formalism and measures from random matrix theory we investigate the multivariate correlation patterns before, during, and after ictal activity. Using the spectrum of relative eigenvalues and the individually unfolded P(s) distribution [1,2] we describe the correlation changes in data from 8x8 cortical grids placed over a frontal lobe seizure onset zone. It is found that the correlation patterns are in qualitative agreement with previous studies obtained with all intracranially implanted electrodes [3]. There is a strong correlation increase that accompanies the termination of the ictal activity (c.f. [3]) and which is carried over into the postictal period, predominantly in low-frequency

components. During ictal activity, there are typical alterations of correlation decrease and correlation increase. The results are compared with the eigenvalue patterns of matrices composed of mutual information coefficients. The mutual information spectrum of eigenvalues characterises the onset of the ictal activity as a decrease in the subdelta components. The termination of the seizure is best marked by a strong increase in mutual information of components faster than 1 Hz. We discuss the differences between the two multivariate measures which may be due to nonlinear correlations present in the data. [1] M. Müller, Y. López, C. Rummel, G. Baier, A. Galka, U. Stephani, H. Muhle, Localized Short Range Correlations in the Spectrum of the Equal Time Correlation Matrix. Phys. Rev. E 74, 041119 (2006). [2] G. Baier, M. Müller, U. Stephani, H. Muhle, Characterizing Correlation Changes of Complex Pattern Transitions: the Case of Epileptic Activity. Phys. Lett. A 363, 290 (2007). [3] K. Schindler, H. Leung, C.E. Elger, K. Lehnertz, Assessing Seizure Dynamics by Analysing the Correlation Structure of Multichannel intracranial EEG. Brain, 130, 65 (2007).

3.3) Activation of the Thalamus and Deactivation of the Caudate Nucleus and Cortex Precede Generalized Cortical Epileptiform Discharges

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The pathophysiology of generalized epileptiform discharges (GED) is not completely understood. Thalamus, basal ganglia, and neocortex have been implicated in the generation of GED, yet the specific role of each structure remains to be clarified. In children with idiopathic generalised epilepsy (IGE), we performed combined EEG functional MRI (fMRI) to identify GED-related changes in blood oxygen level-dependent (BOLD) signal in the striato-thalamo-cortical network. In the six patients with a sufficient number of GEDs during fMRI, within-subject analysis demonstrated BOLD signal changes that preceded the GED. An increase in BOLD signal in the medial thalamus started 6 seconds before the onset of the GED. Decreases in cortical BOLD signal were mainly found in frontoparietal cortical areas and the precuneus and started 6 to 3 seconds before the GED. All patients showed a decrease in BOLD signal in the head of the caudate nucleus. The onset of deactivation was, however, quite variable. The temporospatial pattern of BOLD signal changes suggests that GED on the cortical surface is preceded by a sequence of neuronal events in the thalamo-cortical-striatal network. First there is an increase in thalamic activity that starts approx 6 seconds prior to the GED followed by a deactivation of the cortex and caudate nucleus. We propose that these early changes in BOLD signal reflect changes in neuronal activity that contribute to the generation of interictal GED and might play a crucial role in the transition from a normal to a generalized hypersynchronous pattern of neuronal activity.

#### 3.4) Estimating the Average Amount of Common Information in Scalp EEG Recordings Towards Preictal State Discrimination

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There is an interest in EEG synchronization studies, towards preictal vs interictal state discrimination and the ultimate goal of seizure prediction (Mormann et al., Clinical Neurophysiology 2005; 116:569-587). Mainly intracranial EEG recordings have been used for this purpose, although the use of surface EEG would be more realistic for therapeutic intervention in the future. In this work we propose a technique for estimating the common information between adjacent channels of scalp EEG recordings, in order to pursue preictal vs interictal state discrimination. We use Moddemeijer's estimator (Moddemeijer, Internal report paper no. 1588, Twente University, Department of Electrical Engineering, The Netherlands, 1986) of the Average Amount of Mutual Information (AAMI) statistic, which quantifies the amount of common information between two random variables (i.e., two EEG channels). We analyse data from 3 patients undergoing presurgical evaluation for epilepsy surgery, all suffering from temporal lobe epilepsy. The analysis is performed on a desktop computer, using a time-windowing method in different EEG frequency bands, for at least 3 hours before and 1 hour after each of the 12 seizures analysed, wherever available. Results indicate that during the preictal period (first 20-min), in temporal EEG channels where the seizure is first observed, a statistically significant decrease or increase in AAMI values exists, compared to AAMI values during the interictal period (interval, with minimum duration of 30-min, taken from the EEG record at least 3 hours before and 1 hour after any seizure), in 11/12 (0.5 - 30 Hz), 10/12 (0.5 - 8 Hz), 11/12 (8 - 14 Hz), 11/12 (14 - 30 Hz) seizures. The observed decreases in AAMI are predominant, possibly reflecting specific electrode position relative to the epileptogenic area.

3.5) LONG-TERM EVALUATION OF PREICTAL STATE IDENTIFICATION BY ECG CHANGES IN PARTIAL EPILEPSY

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Objectives: Long-term interactions between epileptic discharges and the neuroautonomic regulation of the heart are studied. Depending on their localisation, epileptic focus may be highly related to autonomic control centers in the brain so an epileptic activity could influence the autonomic system behaviour. We focus our interest on specific, autonomic changes which could be product of an epileptic activity during inter-ictal, preictal and ictal states. Additionally, we determine the existence of particular signatures of impending seizures presented in the autonomic regulation the heart, useful for anticipation purposes. Materials: Analyses are performed on long-term intracranial-EEG/ECG recordings of 5 patients with refractory partial epilepsy and evaluated for up to 7-14 days. Methods: Autonomic activity is assessed through oscillations from R-R intervals of ECG using time-frequency analysis. Discrete Windowed Fourier Transform (DWFT) and Wavelet Transform (WT) are used to determine the influence of epileptic discharges on the autonomic activity. Statistical analysis is preformed in order to evaluate the existence of relevant information relating specific epileptic and autonomic activities. Results: Significant changes in autonomic activity can be detected during recurrent, specific-located epileptic discharges. Furthermore, patient-specific recurrent patterns preceding seizures are observed, indicating a possible pre-ictal signature of the autonomic system activity. Our results suggest that an on-line version of the analyses, trained on each patient's peri-ictal ECG, could serve as a basis for a seizure alarm system.

#### 3.6) LONG-RANGE DEPENDENCE OF EPILEPTIC SEIZURES

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Considering spike trains it was found that there are long term correlations among interspike intervals. A fractal spike train process is statistically self-similar, which means that fluctuations and other properties over brief times are proportional to those measured over a longer period. EEG signals arise from cellular activities and can be considered as top of the hierarchy above field potentials. Due to this, we assumed that signals recorded by subdural and intracerebral macro electrodes keep the aforementioned properties at least for short intervals. These can be considered stationary. Fitting of self-similar process to EEG time series can provide a very concise description of the system. The selfsimilarity parameter - the Hurst exponent (HE) - is a hidden parameter. It describes the long-range dependence of the process. We implemented a method based on the rescaled adjusted range or R/S statistic for estimation of the HE. Preliminary analysis on patients suffering from temporal lobe epilepsy (21-patient database from Epilepsy Center Freiburg) showed

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that HE produces distinct changes during seizures. In this recent work we assessed different types of seizures from the same database and from National Institute of Neurosurgery, Budapest, Hungary. Other types of seizures can be also detected as well as temporal lobe seizures. In the preictal interval a gradual increase, in the postictal state a decrease of the HE can be observed for several seizures. This can provide more accurate modeling of EEG signals and the dynamics of epileptic seizures using stochastic processes.

#### 3.7) INCREASING TRENDS OF PHASE Synchrony and Correlation of Microwire Channels before Seizure Onset

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RATIONALE: A hypothesis for focal seizure generation involves the progressive coalescence of microdomain islands of seizure activity. Study of quantitative metrics such as phase synchrony and correlation between microwire channels before macroscale seizure onset is therefore of fundamental interest. METHODS: We studied 10 patients with custom hybrid depth and subdural electrodes containing arrays of microwires and clinical macroelectrodes. The EEG was acquired using a broadband amplifier operating in parallel with the clinical EEG acquisition system. Phase synchrony and correlation between microwire electrodes was investigated. RESULTS: Broadband measures of phase synchrony and correlation between microwire channels show variable behavior prior to macroseizure onset. However, in some patients the phase

synchrony and correlation between highpass filtered (>70Hz) microwire data increases seconds before macroseizure onset. CONCLUSIONS: Increasing trends of phase synchrony and correlation between microwires before macroscale seizure onset supports a model of seizure generation involving the coalescence of microdomain islands. We speculate that the trend in phase synchronization and correlation between microdomains continues to some threshold value, beyond which macroscale seizure occurs. We demonstrate that neuronal oscillations and seizures occur over a wide range of spatial and temporal scales, and that microseizures are likely important in the generation of macroscale seizures.

#### 3.8) Analysis of Activity Flows During Preictal and Ictal Periods

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Better understanding and description of processes leading to onset and spread of epileptic seizure may help in prevention or early termination of seizure. Multichannel methods provide tools for analysis of interactions between different regions of brain but they often are not well suited for nonstationary epileptiform signals. In many epileptic patients, seizures originating from the same focus often produce very similar EEG signals, particularly recorded intracranially. Using information from multiple seizures improves the statistical properties of estimators, allowing for analysis of shorter stationary window. The short-time direct directed transfer function (SdDTF) method, recently developed to investigate the directions and intensities of activity flow between cortical regions during cognitive tasks with multiple trials, was applied to intracranial recordings of several patients with multiple seizures (5-80). A multichannel autoregressive model (MVAR) was fitted simultaneously to all recorded seizures. The seizures were aligned according to their ictal onsets, judged by visual inspection. Preictal intervals of 60 sec, as well as ictal segments of 60 sec were analyzed. The SdDTF method showed flow of activity from the ictal onset zone. During the preictal period significant flows of low frequency activity could be observed in the vicinity of the focus. These flows may reflect underlying processes of synchronization leading to seizure onset. Supported by: NINDS R01 NS40596 and NS48222

#### 3.9) Spatial and Temporal Identification of Seizure Precursor Dynamics using a Phase Modeling Approach

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Recent studies have indicated a significant predictive performance for bivariate EEG analysis techniques, allowing one to discriminate the pre-ictal from the interictal period above chance level. In addition, some studies reported that the site selected as best for prediction was not in close vicinity to the epileptic focus but could be located in remote or even contralateral brain structures. This seemingly counterintuitive finding may indicate the importance of brain outside of the ictalonset zone but within the "epileptic network" in generating clinical seizures. Addressing this issue we studied directional relationships - in the driver-responder sense - in multi-day, multi-channel invasive EEG recordings using a phase modeling approach (Rosenblum & Pikovsky, Phys Rev E 64, 045202, 2001). Inter-ictally, we observed two distinct regions that exhibit a pronounced dynamical dependence on the surrounding brain regions both on the side of the epileptic focus and in the opposite hemisphere. Using a priori knowledge as to the localization of the epileptic focus we were able to assign the focal region to one of these structures, which, however, is driven by surrounding brain regions. Interestingly, the other structure, which is a driving structure and is located in almost homologous contralateral brain regions, exhibited dynamical aspects that allowed us to discriminate the pre-ictal from the inter-ictal period at a high performance. If proven significantly, our findings indicate the high relevance of brain structures outside the epileptic focus in ictogenesis. Measuring directionality in multi-channel EEG recordings may help to identify target brain structures with potential precursor dynamics, particularly in prospective seizure prediction studies.

3.10) STATISTICAL EVALUATION OF Measures of Scalar Time Series in Discriminating Preictal EEG States

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We consider a large number of measures used in the statistical and nonlinear analysis of univariate time series and EEG in particular. We include measures of correlation (autocorrelation, bicorrelation, mutual information), entropy, spectral energy, complexity (largest Lyapunov exponent, algorithmic complexity, Hurst exponents), dimension (point density, false nearest neighbors), and goodness of fit from linear and nonlinear models. In addition, the following feature time series are extracted from the oscillations of each EEG channel: local minima and maxima and the time between them, minimum to maximum magnitude difference and interspike intervals. The measures are applied to the original and the feature time series for selected values of the methodspecific parameters, giving a total of 284 measures. The measures are estimated on subsequent segments of 30sec of multichannel EEG at preictal stage of several hours as well as interictal stage. The objective of this study is two-fold: a) to assess whether some of the measures can discriminate between early and late preictal stages, and b) to find the measures with the best discriminating power. For this, statistical analysis of the measure values grouped in different preictal stages has been applied using receiver operating characteristic (ROC) curves and statistical testing. The results on 10 epileptic EEG

records show that simple measures have the same, and at cases better, power in discriminating preictal stages than other more sophisticated measures.

#### 3.11) MICROANATOMY OF Epileptiform Activity in Human Multielectrode Recordings

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Uncovering the role of microcircuits in seizure origin and development requires fine-scale observation of neuronal activity in the ictal region. We report the use of a dense 2D microelectrode array (MEA) to provide new details of interictal and ictal electrophysiological disturbances in human epileptogenic cortex in vivo. A 4mm square MEA (96 microelectrodes in a 10 x 10 grid, 400 micron spacing, 1 mm long, 3-5 micron diameter recording tips) (NeuroPort<sup>™</sup>, Cyberkinetics Neurotechnology Systems, Foxboro, MA) was implanted in six patients with medically intractable focal epilepsy undergoing intracranial EEG (iEEG) monitoring at the Columbia University Medical Center. Chronic recordings of 2 – 14 days were obtained. In five of the six patients, the interictal uEEG revealed highly focal waveforms that resembled conventional epileptiform discharges ("focal µEDs") or electrographic seizures ("micro-ictal appearing discharges", or µIADs). These features were topographically restricted to areas spanning 0.2 to 4 mm2 and were not evident

in the iEEG. Additionally, the presence of focal  $\mu$ EDs and  $\mu$ IADs correlated with the location of the MEA with respect to the epileptogenic zone. These early findings suggest that  $\mu$ EDs and  $\mu$ IADs are specific markers of epileptogenic cortex, suggesting a structure of sparsely distributed tiny epileptogenic foci, and that they may serve as precursors to seizures. The interictal-ictal transitions seen in two of the patients suggest that  $\mu$ IADs play a prominent role in the development and propagation of seizures.

# 4. Dynamic Modeling and Statistical Analysis

# 4.1) INFORMATION FLOW IN INTRACRANIAL EEG Recordings of Epilepsy Patients

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Mechanisms leading to the occurrence of epileptic seizures are still poorly understood. We analyzed EEG recordings using an information theoretic approach combined with concepts from symbolic dynamics in order to investigate intraand interhemispheric interactions as well as processes of seizure generation. We here studied continuous multi-day multichannel EEG recordings of up to now 15 patients suffering from unilateral medically intractable mesial temporal lobe

epilepsy. All patients underwent invasive presurgical diagnostics and are postoperatively seizure free. EEG signals were recorded from bilateral intrahippocampal depth electrodes, each equipped with 10 contacts and implanted stereotactically along the longitudinal axis of the hippocampal formation. The transfer entropy, which quantifies the directionality of the flow of information was calculated for all channel combinations using a moving window technique. During seizure activity, we observed the mesial temporal structures in one hemisphere to be more active and driving homologous structures in the opposite hemisphere. These active structures, however, not necessarily coincided with the epileptic focus and were frequently observed in the contralateral hemisphere. During the interictal state a comparable active-passive relationship could be observed again indicating more active contralateral structures. Moreover, in many patients interactions between brain structures allowed to identify longlasting preictal states. Measuring directionality in the human epileptic brain may provide relevant information about the location of the epileptic focus. In addition, our findings indicate the importance of brain outside of the ictal onset zone but within the epileptic network in seizure generation.

4.2) INFLUENCE OF NETWORK Topology on Global Synchronization in a Network of Model Neurons

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We study the transition to global synchronization in a network of integrateand-fire-neurons, which are coupled diffusively over a given network topology, as a model for seizure generation. The network dynamics is driven stochastically by a probability for spontaneous firing for each neuron. We derive criteria for the coupling strength, for which synchronization emerges in the mean network activity. We propose a necessary condition for global synchronization by requiring that each firing neuron gives rise to enough activity for at least one other neuron to fire. For low leakage currents, low refractory times, and sufficiently connected network topologies (i. e., regular networks) this condition determines a threshold for the coupling strength. At this threshold the peak heights of the mean network activity grow abruptly. We investigate the influence of different network topologies (in particular lattices, small-world and scale-free networks) on the transition to global synchronization and discuss how the coupling strength relates to general network characteristics such as mean path length or clustering coefficient.

4.3) STATISTICAL METHODS FOR Developing and Evaluating Preictal Classifiers

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Introduction: Evaluation of seizure prediction algorithms present many challenges. Statistical methods must prevent in-sample testing, guard against accidental correlations, and provide flexibility with respect to the timing of prediction events. To enable the development of increasingly higher performance algorithms, the methods must also provide for direct statistical comparison of alternate implementations. Methods: We propose a block-wise statistical model capable of capturing continuous as well as intermittent prediction events. Prediction alerts may be of any duration, unrestricted by the temporal block size. The test statistic is population-based and allows hypothesis testing without bias toward patients with high seizure count. Algorithm candidates may be compared either against a chance predictor, or directly against each other in a paired test using parametric or non-parametric methods. Evaluation is conducted within a k-fold cross-validation framework (k seizures) to prevent in-sample testing. Results: Utility of the model is demonstrated by comparison of algorithm candidates based on wellknown EEG feature calculations. The evaluation database is comprised of continuous subdural EEG recordings of 76 EMU patients encompassing 7452 hours of data, with 301 primary seizures (clusters excluded). Algorithm superiority compared to chance prediction is demonstrated (p < 0.0001), and the distribution of alert durations shown to be approximately log-normal with median of 156 minutes. Conclusions: A block-wise

temporal model allows direct statistical comparison of alternative seizure prediction algorithms, without making assumptions regarding prediction alert duration. Such a model may facilitate the ongoing development of improved algorithms.

#### 4.4) A Computational Model of Epilepsy and Response to Electrical Stimulation

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We aim to develop robust control algorithms for implantable electrical stimulation devices. For this purpose we require a computational model that mimics key characteristics of the biological models we wish to use for further study. We present a simple model of a neural network that exhibits epileptiform activity. This network consists of an array of leaky integrate and fire neurons connected in a "small world" topology. We include a noise current tuned to achieve a small random spiking rate. We add an explicit representation of postictal depression effects, as well as a simple model of a stimulating electrode and a recording sensor. We demonstrate that this network responds to simulated electrical stimulation in a manner consistent with the behavior seen in biological models. We plan to use this model as a minimal-cost method for evaluation of electrical stimulation methods for epileptic seizure suppression.

#### 4.5) A Computational Model of Glia-Mediated Seizure Induction

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There is an increasing amount of evidence supporting a causal relation between chronic inflammation and seizures. Several proinflammatory cytokines have been studied in the context of seizure susceptibility and neuronal damage, including tumor necrosis factor alpha. It is believed that, in certain conditions, TNF-alpha can increase neural excitability and facilitate infection-related seizures [1]. The effect is potentially related to a recent discovery that links TNF-alpha to homeostatic synaptic plasticity. Specifically, acute application or long-term glial production (during chronic activity blockade) of TNF-alpha increases AMPA receptor surface expression in hippocampal neurons [2], [3]. The regulation resembles synaptic scaling, a homeostatic mechanisms which globally adjusts synaptic strengths to maintain a certain synaptic drive to neurons. It is thought to ensure the stability of the cortex throughout development and during learning. Despite having a generally beneficial role, homeostatic mechanisms were proposed in models as a cause of neural hyperexcitability and epileptogenesis [4]. We have developed a computational model of gliamediated synaptic scaling, in a network of spiking neurons interacting with the glial tissue. It is the first model to consider the mechanisms underlying synaptic scaling and the spatial effects that can arise from the diffusion of neuromodulators. Our model reproduces experimental findings linking chronic overexpression, systemic infection, or lesions to hyperexcitability and network bursts and is consistent with the idea that chronic inflammation can increase seizure predisposition.

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#### 4.6) RANDOMIZED EEG ANALYSIS

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The electroencephalogram (EEG) is a useful tool in the diagnosis of many disorders, including epilepsy. Typically, EEG signals are taken from multiple locations around the head, and collected for many hours. The amount of data produced by an EEG can be sizable; in the Freiburg data set, the EEG signal from a single patient amounted to approximately eleven billion samples. One practical problem to such a large dimensional signal is to extract the relevant information. Many potential models for brain dynamics have been presented, and none fully reconstruct brain dynamics. However, recent developments in random projections, underpinned by the Johnson-Lindenstrauss Lemma [1, 2], indicate that a generically chosen projection maintains the total energy (i.e. Euclidean norm) of a generic signal. This is an amazing result, as the corresponding projections are easy

to compute, are not tied to any model of the brain, and significantly reduce the dimensionality of data. This work focuses on demonstrating various properties of random projection in preserving the total energy within the EEG signal with a sparse method as proposed in [3]. Specifically, we form a random projection matrix where each of the values in a projection matrix are independent, identically distributed binary random variables. In theory, the total energy of a randomly projected signal will be preserved to within a multiplicative factor of  $(1\pm)$ , independent of the original dimension. Preliminary results indicate that random projections do maintain the total energy in portions of the EEG signal, even when different numbers of channels are used. Within this work, I demonstrate approximate energy conservation between different patients and different time horizons. Furthermore, I note some potential future applications for such random projections. [1] Johnson, William and Lindenstrauss, Joram. "Extensions of Lipschitz Mappings into a Hilbert Space." In Proceedings of the Conference in Modern Analysis and Probability. New Haven, CT. 1982. pp 189-206. [2] Dasgupta, Sanjoy and Gupts, Anupam. "An Elementary Proof of the Johnson-Lindenstrauss Lemma." ICSI Technical Report TR-99-006. March, 1999. [3] Achliotas, Dimitris. "Database-friendly random projections: Johnson-Lindenstrauss with binary coins." Journal of Computer and System Sciences. Vol. 66. pp. 671-687. 2003.

4.7) Emergence of Spreading Hyperexcitability in Diffusively Coupled FitzHugh-Nagumo Systems

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We investigate the emergence of excitability in diffusively coupled FitzHugh-Nagumo systems and demonstrate how to protect neurons adjacent to a hyperexcitable core against recruitment into this pathological state. Our efforts focus on spatially extended systems and on two coupled discrete neural populations. We determine the parameter regime in which transient wave forms emerge in the spatially extended system and show how control can minimize the volume of invaded tissue. In the discrete population model, we investigate effects of time-delayed feedback schemes on noise-induced cooperative dynamics of the ensemble of neural populations.

#### 4.8) ORDINAL EEG ANALYSIS

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Ordinal time series analysis is a new approach to the qualitative investigation of long and complex time series. The idea behind it is to consider the order relation between the values of a time series instead of the values themselves. Roughly speaking, a given time series is transformed into a series of so called ordinal patterns describing the up and down in the original series. Then the distribution of ordinal patterns obtained is the base of the analysis. Here we discuss applicability of ordinal time series analysis to the analysis of EEG data. In particular, we demonstrate how Cluster Analysis (CA) of distributions of ordinal patterns in EEG time series can be used for the classification and discrimination of basic brain states.

#### 4.9) Symbolic Analysis of Multivariate Data

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Many natural systems exhibit complex patterns in their output signals that reflect the underlying dynamics. By symbolization, raw signals can be transformed into a series of discretized symbols that - being a considerably simplified representation of the data - might still contain enough information about the underlying dynamics. By utilizing information-theoretic measures (entropy rate, mutual information, and transfer entropy) we analyze statistical correlations of spatiotemporal binary patterns derived from multivariate signals. In many cases, such an extremely simplified representation suffices to identify changes in the system dynamics. To illustrate our approach we study a network of coupled chaotic oscillators that contains two interacting clusters with a time-varying degree and direction of interaction. We show that our approach allows to qualitatively identify the induced changes in the simulated dynamics. Using our approach, we analyzed intracranial multi-channel, multi-day EEG recordings from epilepsy patients who underwent presurgical evaluation. Preliminary findings indicate that changes in the degree and direction of inter(intra)-hemispheric interactions appear to be related to

ictogenesis. If findings can be validated for a larger patient group, the underlying simplicity of a binary representation of multivariate data may enable the development of a miniaturized analysis device using special-purpose digital signal processors (DSP) or analog hardware such as Cellular Neural Networks (CNN).

#### 4.10) SIMULTANEOUS ANALYSIS OF Population Spikes and Single Neuron Activity In Vivo at the Onset of Seizure

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We present here an analysis of the underlying mechanisms related to interictal spikes (IS) and their contribution to the process of seizure onset. Since the role of population discharges for impending seizures is still largely unknown, we have developed a technique to simultaneously monitor and correlate the activity of single neurons and ISs using chronic microelectrode array electrophysiology. The firing rates of ISs and single neurons (interneurons and pyramidal cells) in the CA3 region of the hippocampus was compared 1.5 hr prior to seizure onset for 10 seizures in rats with stimulation induced spontaneous temporal lobe seizures. During this interval, both cell types exhibited burst-like neuromodulations with the interneurons producing the highest firing rate (mean 1.357 spikes/s), with a statically significant peak in activity 490 s before seizure onset and the pyramidal cells producing a lower firing rate (mean 0.566 spikes/s), with a peak in activity 170 s before seizure onset. Cross-correlation

between neuronal firing and ISs indicated that the increases in firing were not synchronous with the population spikes possibly indicating one is driving the other. The cross-correlation between pyramidal cell and IS modulation yielded a periodic trend with first maxima at an IS lag of 600 s while interneurons produced a maxima in correlation at an IS lag of 520 s. Interestingly, no ISs occurred within 160 s of seizure onset while single neuron modulation was still elevated. The multiscale analysis presented here may provide new markers for seizure prediction.

# 5. Animal Models of Epilepsy

#### 5.1) DYNAMICS OF SPIKE-WAVE Discharges in Young Adult and Aged Fischer 344 Rats

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Several studies with animal models of aging, including studies in our laboratory (Kelly et al, 2001), have shown an age-related increase in the incidence and duration of7-9 Hz generalized spike-wave discharges (SWDs; absence seizures) as the animal ages. In an effort to elucidate the mechanisms underlying aging-related changes in the expression of SWDs, we studied the dynamical electroencephalographic

(EEG) properties associated with spontaneously occurring SWDs in young (4 month) and aged (20 month) Fischer 344 rats. The short term maximum Lyapunov exponent (STLmax), a measure of chaoticity, and the pattern match regularity statistic (PMRS), a measure of signal complexity based on the likelihood of signal pattern similarity, were utilized to extract a dynamical profile of the EEG signal. A statistical comparison of preictal dynamical values (2 min before a SWD) showed no significant difference between the two age groups in either STLmax (p=0.18) or PMRS (p=0.19). However, the same statistical test performed on postictal dynamical values (2 min after a SWD) revealed a significant difference between the two groups in both STLmax (p=0.009) and PMRS values (p=0.01). A comparison of the difference between average preictal and postictal dynamical values suggested that brain "resetting" to its normal interictal state was more effective in the 4 month cohort compared to the 20 month cohort by both STLmax (p=0.007) and PMRS (p=0.008) values. These preliminary results suggest that brain recovery following SWDs was more sustained in young adult animals compared to aged animals. Supported by a Targeted Research Initiative for Seniors grant from the Epilepsy Foundation to S Nair.

5.2) INSIGHTS INTO EPILEPTIFORM Activity using Phase Resetting Curves

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Oscillatory coordinated cellular activity is a major characteristic of brain function. In this study, we focus on the characterization of the dynamics of epileptiform activity, based on seizures that manifest themselves with very periodic activity, termed absence seizures. Taking advantage of this long-lasting periodic activity, our approach consists in obtaining experimentally the phase response curves (PRC), which describe the alteration of the phase due to an input at each point of the cycle, and incorporating these into models of coupled oscillators. We use a rat model of absence seizures that results from injection with gamma-hydroxybutyric acid (GHB). As a result, rhythmic synchronized spike-and-wave (SWD) discharges occur in the neocortex and thalamus. Intracerebral recordings are obtained from the cortex and thalamus. PRCs were obtained by stimulating either the thalamus or the cortex, and evaluating the alteration of the oscillation. The electrical stimuli used were the minimal that did not alter profoundly the oscillation. In addition, larger stimulations were tested for their ability to halt the SWD. Only brief stopping (desynchronization) of the SWD was observed in some cases (55%) at large stimulation intensities, phenomenon for which no specific phase of the perturbation was noted. The experimentally obtained PRCs, for the cortex and thalamus, were approximated by polynomials. Incorporating these functions into a Kuramoto-like system of two coupled

differential equations representing the time evolution of the phases, we study the phase preferences of the stationary states and their stability, and the results from the model are compared with the experimental recordings.

#### 5.3) The Generation of Epileptic Seizures Requires Interaction of Sclerotic and Intact Networks - A Study in a Mouse Model for Temporal Lobe Epilepsy

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Network structures and dynamics initiating epileptic seizures in mesial Temporal Lobe Epilepsy (MTLE) are still not fully understood. MTLE is accompanied by severe changes of the hippocampal histology, especially cell loss in CA1 and the hilus, granule cell dispersion and mossy fiber sprouting. Excision of those sclerotic areas is necessary to stop epileptic seizures and the development of less invasive therapy options requires the knowledge which brain areas participate in seizure generation. To determine, whether seizures are initiated by the sclerotic hippocampal areas or if a larger network participates in those processes, we used a model for MTLE in mice. A single unilateral injection of kainate into the dorsal hippocampus induced histological changes comparable to hippocampal sclerosis. Recordings of epileptiform events (EE) in-vivo indicated that hypersynchronous spiking involved not only the sclerotic areas of the injected hippocampus but also the temporal hippocampus, although histologically unchanged. To investigate whether initiation of EEs occurred in those sclerotic areas, we recorded slices from this region on multielectrode arrays. Surprisingly, it was impossible to induce EEs there. In contrast, in slices from the temporal hippocampus without obvious histological damage we could induce EEs (bicuculline) with the same rate of recurrence as in controls. Analysis of the coherence between MEA electrodes revealed, however, that slices from epileptic mice showed a changed activity structure within the dentate gyrus. Although apparently structurally intact, the network dynamics in these slices thus differed. The network necessary for EE initiation therefore likely consists of subnetworks with various degrees of degeneration.

5.4) Evolution of Correlations and High Frequency Components in Multi-Channel EEG Recordings from Rat Kindling and Kainate Models of Temporal Lobe Epilepsy

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We assessed multi-channel correlations and high frequency (HF, 100-500 Hz) content in EEG recordings from two animal models of temporal lobe epilepsy, hippocampal kindling and intra-hippocampal kainate injection. We found that in the

kindling model, HF discharges (ripples, 100-400 Hz) developed over subsequent days and were not limited to the kindling site, but also extended to the contralateral hippocampus with high correlation. In contrast, the HF discharges of the kainate model (fast ripples, 400-500 Hz) occurred only in the lesioned hippocampus. During the afterdischarge (AD) of the kindling model, a behavioral seizure (Racine 5) was observed after 18-25 days of stimulation in all rats. The HF power was always high before and during the initial phase of the seizure, but similar ripples were present in the AD many days before seizures appeared (seizures occurred during the primary AD in most cases). The correlation between all pairs of channels increased during the AD from the first kindling day onwards. We did not find a clear difference when behavioral seizures first appeared. During the AD, sudden inversions of the sign of the correlation occurred between pairs of contacts placed in the right hippocampus as well as between pairs placed in both hippocampii. Overall, our data support a key role of HF discharges and enhanced correlations during the epileptogenic process in both, the kindling and kainate models of temporal lobe epilepsy.

5.5) Changes in Inter-Hippocampal Coherence Precede Epileptiform Activity in Mice with Induced Epilepsy

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The Mesial Temporal Lobe Epilepsy (MTLE) syndrome is among the most prevalent forms of focal epilepsies, however, network structures and understanding of the dynamics involved in the generation of seizures are still elusive. Thus, there is an urgent need to investigate on the time scale of processes initiating epileptic seizures, allowing for more detailed examination of seizure initialization mechanisms. We addressed these questions using the in vivo intrahippocampal kainate model for induced MTLE in mice. These mice show histological changes comparable to human hippocampal sclerosis in the injected hippocampus. We recorded recurrent epileptiform activity (EA) in the injected and in the contralateral, intact hippocampus. We investigated on changes in inter-hippocampal coherence preceding the onset of epileptiform events to determine ongoing seizure generation processes on a timescale suitable for acute intervention. We found, that inter-hippocampal coherence decreased significantly in high frequency bands (> 80 Hz) up to 12 seconds before the onset of EA. This indicates an early decoupling of the ipsilateral hippocampus from the contralateral, intact hippocampus during the seizure initiation phase. Additionally, this time scale limits the possible range for cellular and mechanisms leading to increased synchronicity in the network, ulitmately initiating the seizure.

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#### 5.6) A MARKOV SOURCE MODEL OF SEIZURE PROGRESSION

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Seizures can have onset, middle and terminal stages with distinctive dynamics, but are usually treated as monolithic events. We are employing the rodent tetanus toxin model of temporal lobe epilepsy to test-bed closed-loop seizure control with low frequency electrical field modulation. In this model, seizures have been characterized (Finnerty and Jefferys, J. Neurophys 2000) to have five distinct stages characterized by the frequency of field postsynaptic potential (FPSP) "spikes". The fourth stage (~9-16Hz) is strongly correlated with secondary generalization (rearing and myoclonus). Seizures start in 2-3 days, and achieve a maximal seizure rate of ~30/day in a week. We have implemented an automated quantitative model of seizure evolution and dynamics with a hidden Markov model (HMM). A HMM is a stochastic model in which the observed time series reflects transitions between discrete underlying states. A HMM comprises "hidden" states with

fixed probabilities, state transition probabilities, and state-dependent measurement distributions. With only the number of states prespecified, a HMM was trained on the FPSP spike frequency time series (1/4s bins) derived from sampled data segments that include baseline and seizures. When this trained HMM was then used to determine the most likely state sequence of other seizures, it identified a seizure progression through discrete stages consistent with published descriptions. Notably, a model-identified state with 9-16Hz discharges often preceded clonic behavior. Because seizure patterns vary over time and between animals, such a model and analysis tool will be useful for comparison of different treatment protocols. (Support: NIH R01EB001507, K02MH01493 and R01MH50006.)

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# Martins da Silva, Prof. Antonio

Hospital Santo Antonio and ICBAS-University of Porto (Porto, Portugal) Neurophysiology - Hospital S. António, 4099-001 Porto, Portugal Email: ams{at}icbas.up.pt Phone: + 351 22 207 75 47

# Mason, Dr. Jonathan

Pennsylvania State University (State College, PA, USA) 359 Toftrees Ave, #303, State College, PA, 16803, USA Email Address: jpm35{at}psu.edu Phone: +1 404-273-0939 *Abstract no 5.6* 

# Meier, Dr. Ralph

Bernstein Center for Computational Neuroscience Freiburg (Freiburg, Germany) Schänzlestrasse 1, 79104 Freiburg, Germany Email: meier{at}biologie.uni-freiburg.de Homepage: http://find.bccn.uni-freiburg.de Phone: +49 761 203 2864 *Abstracts no 2.3, 5.3, 5.4, 5.5* 

# Mirmomeni, Masoud

University of Tehran (Tehran, Iran) N. Kargar Ave, Campus II Fanni, School of ECE, Postcode: 1439957131, Iran Email: m.mirmomeni{at}ece.ut.ac.ir Phone: +98-21-88027756 *Abstract no 1.8* 

# Mormann, Dr. Florian

California Institute of Technology (Pasadena, CA, USA) 1200 E California Blvd, MC 216-76, Pasadena CA, USA Email: fmormann{at}yahoo.de Homepage: http://www.meb.uni-bonn.de/epileptologie/ staff/mormann/mormann\_en.htm Phone: +1-626-395-8962 Organizer of Session 1 Invited talk in Session 10 Musician in The Unpredictable Concert I

# Müller, Dr. Markus

Facultad de Ciencias, UAEM (Cuernavaca, Mexico) Facultad de Ciencias, UAEM, Avenida Universidad 1001,62290 Cuernavaca, Morelos, Mexico Email: muellerm{at}buzon.uaem.mx Phone: +52-777-3297020 Invited talk in Session 7

Abstracts no 3.1, 3.2

# Nair, Dr. Sandeep

Allegheny Singer Research Institute, Allegheny General Hospital (Pittsburgh, USA) 940 S. Tower, Allegheny General Hospital, 320 E. North Ave, Pittsburgh 15212, USA Email: snair{at}wpahs.org Phone: +1-412-359-4221 *Abstract no 5.1* 

# Nawrath, Jakob

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Freiburg Center for Data Analysis and Modeling (Freiburg, Germany) Eckerstr. 1, 79104 Freiburg, Germany Email: nawrath{at}fdm.uni-freiburg.de Homepage: http://epilepsy.uni-freiburg.de Phone: +497612037706 *Abstract no 1.12* 

# Niederhöfer, Christian

Johann Wolfgang von Goethe University (Frankfurt, Germany) Max von Laue Str. 1, 60438 Frankfurt, Germany Email: niederhoefer{at}iap.uni-frankfurt.de Phone: +49 69 798 47462 *Abstract no 1.7* 

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## Osorio, Prof. Ivan

University of Kansas, Medical Center, Department of Neurology (Kansas City, USA) Landon Center of Aging, 3599 Rainbow Boulevard, Mailstop 2012, Kansas City, KS 66160, USA Email: iosorio{at}kumc.edu Homepage: http://www2.kumc.edu/neurology/osorio.html Phone: +1 913-588-6970 Organizer of Session 6

# Osterhage, Hannes

Department of Epileptology, University of Bonn (Bonn, Germany) Sigmund-Freud-Str. 25, 53105 Bonn, Germany Email: h.osterhage{at}web.de Phone: +49 228 287 1 9379 *Abstracts no 1.1, 3.9, 4.1* 

# Perez Velazquez, Dr. Jose Luis

University of Toronto (Toronto, Canada) 555 University Avenue, Toronto, Canada Email: jose-luis.perez-velazquez{at}sickkids.ca Phone: +11438137715 *Abstract no 5.2* 

#### Pineau, Dr. Joelle

McGill University (Montreal, Canada) 3480 University st, Montreal QC Canada H3A 2A7 Email: jpineau{at}cs.mcgill.ca Homepage: http://www.cs.mcgill.ca/~jpineau Phone: +1-514-398-5432 Abstract no 4.4

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Abstract no 1.2

# Reichau, Hermine

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# Robertson, Prof. Richard

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# Rothkegel, Alexander

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#### Rothman, Prof. Steven

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Department of Pediatrics (Clinical Neuroscience), University of Minnesota (Minneapolis, Minnesota, USA) Mayo Mail Code 486, 420 Delaware Street, SE, Minneapolis, MN 55455-0323, USA Email: srothman{at}umn.edu Phone: +1 612-625-7466 *Invited talk in Session 6* 

# Rummel, Dr. Christian

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### Sanchez, Dr. Justin

University of Florida (Gainesville, USA) P.O. Box 100296, Gainesville, USA Email: jcs77{at}ufl.edu Homepage: http://nrg.mbi.ufl.edu Phone: 352-846-2180 *Abstract no 4.10* 

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Abstract no 4.6

# Savin, Cristina

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#### Schachinger, Daniela

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# Schelter, Dr. Björn

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Organizer of Session 8

Abstract no 1.12

### Schevon, Dr. Catherine

Columbia University (New York City, NY, USA) 710 West 168th Street, New York, NY 10032, USA Email: cas2044{at}columbia.edu Phone: +1 212 305-1742 *Abstract no 3.11* 

# Schiff, Dr. Steven J.

The Pennsylvania State University (University Park, USA) 212 Earth & Engineering Sciences Building, University Park, USA Email: sjs49{at}engr.psu.edu Homepage: http://www.esm.psu.edu/schiff Phone: +1 814-863-4210 Organizer of Session 3 Musician in The Unpredictable Concert I Abstract no 5.6

# Schiller, Dr. Yitzhak

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#### Schindler, Dr. Kaspar

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Abstract no 3.2

# Schlögl, Dr. Alois

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# Schulze-Bonhage, Prof. Andreas

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# Serletis, Dr. Demitre

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# Shoeb, Ali

Electrical Engineering and Computer Science Departement Massachusetts Institute of Technology (Boston, Massachusetts, USA) 7 Conant Road Unit #38, Winchester Massachusetts 01890, USA Email: ashoeb{at}mit.edu Phone: +1 781 258 4661 *Abstract no 1.6* 

# Shu, Dr. Yousheng

Institute of Neuroscience, Chinese Academy of Sciences (Shanghai, China) 320 Yueyang Road, Shanghai, 200031, China Email: shu{at}ion.ac.cn Homepage: http://www.ion.ac.cn Phone: +86-21-54921759 Invited talk in Session 3

# Smith, Prof. Leonard A.

London School of Economics & Political Science (London, UK) Centre for the Analysis of Time Series, London School of Economics & Political Science, Houghton Street, London, WC2A 2AE, UK Email: l.smith{at}lse.ac.uk Homepage: http://www.lse.ac.uk/collections/cats/Lennypage.htm Phone: +44 (0)20 7955 7626 Invited talk in Session 10

# Snyder, David

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# Soss, Dr. Jason

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# Suffczynski, Dr. Piotr

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# Tang, Prof. Feng Ru

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# Traub, Prof. Roger

SUNY Downstate Medical Center (Brooklyn, New York, USA) SUNY Downstate Medical Center, 450 Clarkson Ave., Box 31, Brooklyn, NY 11203, USA Email: Roger.Traub{at}downstate.edu Phone: +1-718-270-6762 Invited talk in Session 2

# Trevelyan, Dr. Andrew

Newcastle University (Newcastle upon Tyne, UK) School of Neurology, Neurobiology and Psychiatry, University of Newcastle upon Tyne, Medical School, Framlington Place, Newcastle upon Tyne, UK Email: andytrev{at}gmail.com Phone: +44-191-222-8935 *Invited talk in Session 3* 

# Triantis, Dr. Iasonas

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# Valderrama, Mario

Cognitive Neurosciences and Brain Imaging, LENA, CNRS UPR 640 (Paris, France) 50 Boulevard de l'Hôpital, 75013 Paris, France Email: mvalderm{at}yahoo.com Phone: +33 629323349 *Abstract no* 3.5

# van Putten, Dr. Michel

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# Vincent, Robert D.

McGill University School of Computer Science (Montreal, Quebec, Canada) 3480 University St. #318, Montreal, Quebec, H3A 2A7, Canada Email: bert{at}cs.mcgill.ca Homepage: http://www.cs.mcgill.ca/~rvince3 Phone: +1 514 945-9485 *Abstract no 4.4* 

# Viventi, Jonathan

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# Wadman, Prof. Wytse

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# Wagner, Tobias

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# Wang, Lei

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#### Weinstein, Dr. Steven

Children's Hospital, George Washington University (Washington, DC, USA) 111 Michigan Ave. 20817, Washington, DC, USA Email: slweinste{at}earthlink.net Phone: +1 202-884-2120 Invited talk in Session 5 Abstract no 5.6

# Weiss, Bela

Faculty of Information Technology, Peter Pazmany Catholic University (Budapest Hungary) 1083 Budapest, Prater u. 50/a, Hungary Email: weiss{at}itk.ppke.hu Phone: +36702986411 Abstract no 2.6

Abstract no 3.6

### Wendling, Dr. Fabrice

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# Wennberg, Dr. Richard

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# Werder, Jon

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# Worrell, Dr. Gregory

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Abstracts no 2.6, 3.7

#### Worth, Dr. Robert M

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### Zaveri, Dr. Hitten

Yale University (New Haven, USA) Department of Neurology, 333 Cedar Street, New Haven, CT 06520-8018, USA Email: hitten.zaveri{at}yale.edu Phone: +12037375407 Invited talk in Session 1

### Zochowski, Dr. Michal

Department of Physics, University of Michigan (Ann Arbor, USA) 450 Church St, Ann Arbor, MI 48109, USA Email: michalz{at}umich.edu Phone: +1 734-647-5552 Invited talk in Session 3

# Workshop Book

Related to the Workshop a book entitled

"Seizure Prediction in Epilepsy -From Basic Mechanisms to Clinical Applications" will be published by Wiley in the beginning of 2008.

# Invitation to the Fourth Seizure Prediction Meeting

The Fourth International Seizure Workshop will be held at the Big Cedar Lodge in the Ozark Mountains, Missouri, USA. Ivan Osorio and Mark G. Frei will lead the Organizing Committee. The date of this meeting will be decided after consultation with the Organizing Committee and participants of the Freiburg meeting.

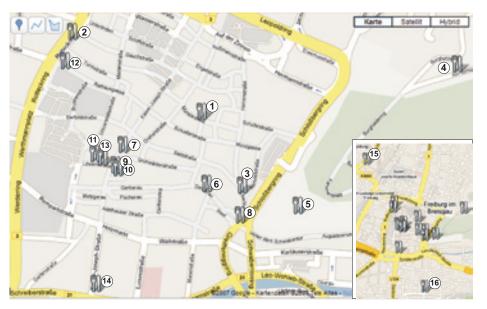


Notes

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# Map of Restaurants in Freiburg



- 1. Hotel Oberkirch, Münsterplatz 22: Local gastronomic specialties, fine dining
- 2. Colombi Hotel, Rotteckring 16: Local gastronomic specialties, fine dining
- 3. Ringhotel Zum Roten Bären, Oberlinden 12: Local gastronomic specialties, fine dining
- 4. Schlossbergrestaurant Dattler, Am Schlossberg 1: Local gastronomic specialties, fine dining
- 5. Greiffenegg-Schlössle, Schloßbergring 3: Local gastronomic specialties, fine dining
- 6. Hausbrauerei Feierling, Gerberau 46: Brewery and local gastronomic specialties, casual dining
- Osteria Kühnel und Scaglia, Grünwälderstr. 2: Italian wine tavern, casual dining
- 8. Storchen La Cicogna, Schwabentorplatz 7: Italian gastronomic specialties, casual dining

- 9. Markthalle Freiburg, Kaiser-Joseph-Str. 237: International specialties, casual dining
- 10. Martin's Bräu Freiburg, Kaiser-Joseph-Str. 237: brewery and local gastronomic specialties, casual dining
- 11. Maria, Löwenstr. 3-7: Low priced restaurant
- 12. Pizzeria La Piazza, Rathausgasse 50: Low priced restaurant
- 13. Schlappen, Löwenstr. 2: Low priced restaurant
- 14. Pizzeria Laubfrosch, Kaiser-Joseph-Str. 273: Low priced restaurant
- 15. Paradies, Mathildenstr. 28: Local and international gastronomic specialties, casual dining
- 16. Omas Küche, Hildastrasse 66: Local gastronomic specialties, casual dining

# Map of the Conference Venue and Hotels in Freiburg



- Conference Venue Haus "Zur Lieben Hand" Löwenstraße 16 79098 Freiburg
- 2. Railway Station Bismarckallee 7c
- Ringhotel Zum Roten Bären Oberlinden 12 79098 Freiburg im Breisgau Phone: +49 761 387 87-0
- 4. Colombi Hotel Rotteckring 16 79098 Freiburg Phone: +49 761 21060
- 5. Hotel Oberkirch Münsterplatz 22 79098 Freiburg Phone: + 49 761 2026868
- 6. Hotel am Rathaus Rathausgasse 4-8 79098 Freiburg Phone: +49 761 296160

- Park Hotel Post Eisenbahnstraße 35/37 79098 Freiburg Phone: +49 761 385480
- Hotel Barbara Poststraße 4
   79098 Freiburg im Breisgau Phone: +49 761 296250
- 9. City Hotel Weberstr. 3 79098 Freiburg Phone: +49 761 388070
- 10. Hotel Rheingold Eisenbahnstr. 47 79098 Freiburg Phone: +49 761 28210
- 11. Hotel Schiller Hildastr. 2 79102 Freiburg Phone: +49 761 703370
- 12. Peterhofkeller (Get-Together) Niemensstr. 10

In case of any problems, please call the conference hotline +49 176 282 124 51.