NIPS2011 Satellite Meeting

CAUSAL GRAPHS:
LINKING BRAIN STRUCTURE TO FUNCTION

Talks Abstracts

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Causality analysis in information flow from cortical time series

I will describe an approach that we developed for a robust estimation of transfer entropy from time series of simultaneously recorded extracellular cortical recordings. I will also describe the application of these methods to evaluate the role of synchronization of neural activity in the gamma (40-100 Hz) frequency range in the spatial propagation of cortical information.

<u>NOTES:</u>

Bert Kappen

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The binary Garrote

In this talk, I present a new model and solution method for sparse regression. The model introduces binary selector variables s_i for the features i in a way that is similar to Breiman's Garrote model. I refer to this method as the binary Garrote (BG). The posterior probability for s_i is computed in the variational approximation. The BG is compared numerically with the Lasso method and with ridge regression. Numerical results on synthetic data show that the BG yields more accurate predictions and more accurately reconstructs the true model than the other methods. The naïve implementation of the BG requires the inversion of a modified covariance matrix which scales cubic in the number of features. We indicate how for sparse problem the solution can be computed linear in the number of features.

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Causal effects between brain regions: existence and quantification

A simulation study was set up to replicate the findings by Guo et al [1]. In that paper, conditional and partial G-causality were compared using an extensively applied toy model in Granger tests that was extended in a way that each time series had an exogenous input and a latent variable to them. The influence of these exogenous inputs and latent variables was examined on the performance of conditional and partial G-causality in retrieving the true underlying network. The conclusion of the authors was that, although partial G-causality could only theoretically fully eliminate the influence of latent variables and exogenous inputs in the case where this influence is equal over all variables, it outperformed conditional G-causality in many other cases. Our replication tries to find an answer why the authors found negative partial Granger causality estimates and what the influence on the results was of using a model based parametric bootstrap to construct confidence intervals. We analyzed our results using a non-parametric bootstrap on the one hand and classical parametric inference on the other. First of all, we did not find any negative estimates for the partial G-causality measure and support this finding theoretically. Based on the bootstrap method we found that, although partial G-causality better controls for false positives than conditional G-causality in some cases, it does not always outperform the latter method. Based on the classical parametric inference, partial G-causality holds exactly the same results as conditional G-causality. We argue that the (non) parametric method that is used to analyze G-causality has more influence on the results than the choice between partial and conditional G-causality. This reduces the importance of partial G-causality for the applied user.

[1] Guo, S. et al., J Neurosci Meth, 172:79-93, 2008

NOTES:

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New methods for EEG source connectivity analysis

The EEG-based analysis of directed ("causal") information flow between brain regions is hindered by the fact that the signals related to electrical activity in source brain regions are mixed into the EEG sensors due to a process called volume conduction. We here assess relevant approaches to EEG based connectivity analysis on simulated EEG data, which are realistically generated as linear mixtures of interacting sources. We observe that most of the tested methods are not able to determine the connectivity structure of the underlying sources because either the effect of source mixing is neglected or the assumptions made to estimate the underlying sources are inappropriate for source connectivity analysis. We present two novel approaches to obtain source estimates that overcome theoretical and practical shortcomings of existing approaches. S-FLEX [1] is an inverse source reconstruction methodology, which is able to recover multiple source of arbitrary shape and depth, and is applicable to entire time series. SCSA [2] is a blind source separation (BSS) technique, which estimates the underlying brain sources and their mixing patterns jointly under the assumption of a sparse connectivity structure of the sources. We demonstrate that the specific assumption made by S FLEX and SCSA are the key to correct source connectivity determination in our simulation. Finally, we analyze information transfer between sources of the human alpha rhythm during rest. Here we observe that neither the strength of the sources nor the corresponding interaction patterns are exclusively symmetric, which supports the hypothesis of a consistent dominant laterality in the studied population.

[1] S. Haufe et al., NeuroImage, 54:851-859, 2011
[2] S. Haufe et al., IEEE Trans Biomed Eng, 57:1954-1963, 2010

NOTES:

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Causal information approach to coping with a large number of variables

Granger causality has become the method of choice to determine whether and how two time series exert causal influences on each other. This approach is based on prediction: if the prediction error of the first time series is reduced by including measurements from the second one in the linear regression model, then the second time series is said to have a causal influence on the first one. From the beginning it has been known that if two signals are influenced by third one that is not included in the regressions, this leads to spurious causalities, so an extension to the multivariate case is in order. Conditional Granger causality analysis (CGCA) has been proposed to correctly estimate coupling in multivariate data sets. Sometimes though, a fully multivariate approach can entrain problems which can be purely computational but even conceptual: in presence of redundant variables the application of the standard analysis leads to under-estimation of causalities. We will address the problem of partial conditioning to a limited subset of variables, in the framework of information theory. We will show that, in many instances, conditioning on a small number of variables, chosen as the most informative ones for the driver node, leads to results very close to those from the multivariate analysis. This is particularly relevant when the pattern of causalities is sparse.

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Characterization of epileptogenic networks by means of Granger Causality

In epileptogenic networks, it is relatively common that the onset and peak times of epileptic discharges show systematic temporal shifts across brain regions. This phenomenon suggests the spread of the discharges between regions, and that it could be possible to use methods that are based on predicting the behavior of one time-series from another to both identify and characterize epileptogenic networks. We applied Granger Causality (GC) on intracranial EEG data, recorded from 4 patients during multiple seizures (3-8 across patients), to evaluate the patterns of causal influences across the recording sites. We found that significant GC occurred systematically across distant brain regions during epileptic discharges, and that this phenomenon was reproducible across both seizures and patients. Moreover, we found that the evaluation of GC across all possible recording sites led to reliable identification of the key regions of the epileptogenic networks, in agreement with the expert clinical evaluation. These findings suggest that GC could be a useful measure in determining epileptogenic networks and also help to identify brain regions critical for seizure onset.

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Causal effects between brain regions: existence and quantification

The causal influence one brain region exerts over another has been studied using approaches such as Granger Causality and Dynamic Causal Modeling. These approaches provide principled ways to infer the existence of causal interactions and to model these interactions, respectively. However, none of these methodologies specifically consider the results of the causal interactions, that is, they do not consider the actual dynamic impact of the causal interactions (i.e. the causal effects). We argue that the causal effects should constitute the basis for quantification of the causal influence between brain regions. Here we build on the interventional definition of causal effect introduced by Judea Pearl to suggest a definition of causal effect appropriate for causal interactions between brain regions. Using this definition, we indicate that the structure of the causal graph imposes constraints on the existence of such causal effects. An important conclusion from this work is that the inference of the causal structure and the quantification of causal effects are different tasks with different requirements. Importantly, we show that only under particular circumstances can the question "Which is the causal effect of region X on region Y" be given a meaningful answer.

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Band-limited Granger causality analysis of human electrocorticography (EcoG)

Frequency bands in electrical brain signals are believed to represent different underlying neural processes, possibly correlating with distinct mental states. As contemporary neuroimaging research concentrates on investigating functional networks in the brain, an analysis method that identifies the direction of information processing (i.e. causal relation) within and between the networks in specific frequency bands is in demand. Granger causality (G-causality) analysis, a statistical concept of causality based on prediction which was originally developed for economics, has, in the last few years, become popular as a tool for exploring causal relations in brain signals. While G-causality was initially used on unfiltered EEG data, the next natural step was to extend this method to specific frequency bands. However, attempts to employ G-causality to band-limited EEG data exposed serious reliability issues as discussed in recent work [1]. The authors further suggested an alternative method termed band-limited G-causality, though have not demonstrated it empirically. We investigate the use of this new approach, confronting various implementation issues, and apply it to ECoG data acquired in epileptic patients. Specifically, we demonstrate the causal relations, in the gamma and alpha bands, between electrodes situated in the lateral and the medial pre-frontal cortex with regard to internally vs. externally generated action planning.

[1] Barnett, L., Seth, A.K.: Behaviour of Granger causality under filtering: Theoretical invariance and practical application. Journal of Neuroscience Methods 201(2), 404-419 (Oct 2011)

NOTES:

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Measuring long-range neuronal coupling with Magnetoencephalography and intracranial EEG: From basic neuroscience to clinical applications
Local and long-distance neural synchronization play a key role in mediating behavior. Although neuroimaging studies continue to play a fundamental role in the study of large-scale networks, the fine-scale temporal and oscillatory properties of such networks need to be investigated with high (millisecond) temporal resolution. I will present data using invasive and non-invasive electrophysiological techniques that investigate oculomotor behavior and visuomotor control. First, using Magnetoencephalography (MEG) we address the role of cerebral oscillations and long-range cortico-cortical coupling in mediating continuous visuomotor control. Beyond providing direct links between cortical activity and hand movement kinematics, our data reveal task-specific modulations of large-scale parieto-frontal activations across multiple frequency bands. In a separate study, we used intracranial EEG (iEEG) to record directly from various brain structures in implanted epilepsy patients while they performed a delayed saccade paradigm. Our findings suggest that local high gamma (60 140 Hz) power and long-range coupling in the alpha range (8-12 Hz) might play a fundamental role in oculomotor planning and saccade execution. Finally, I will present recent findings from our group that illustrate the utility of using Granger Causality to examine the propagation of epileptic discharges throughout epileptogenic networks during seizures.

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The human connectome

The human brain consists of connections between neurons at the local level and of connections between brain regions at the global level (Kaiser, 2011) . The study of the entire network, the connectome, has become a recent focus in neuroscience research. Using routines from physics and the social sciences, neuronal networks were found to show properties of scale-free networks, making them robust towards random damage, and of small-world systems leading to better information integration. First, I will describe novel results concerning the hierarchical and modular organization of neural networks. Second, I will report on the role of hierarchical modularity on activity spreading. Importantly, low connectivity between modules can provide bottlenecks for activity spreading. Limiting activity spreading is crucial for preventing epileptic seizures. Indeed, connectivity between modules is increased in epilepsy patients which could explain the rise of large-scale synchronization. Finally, unlike other networks, the nodes and edges of brain networks are organized in three-dimensional space. This organization is non-optimal concerning wiring length minimization but more optimal concerning the reduction of path lengths and thus delays for signal propagation (Kaiser & Hilgetag, 2006). Together, these findings indicate that multiple constraints drive brain evolution leading to non-optimal solutions when only single factors are observed. I will discuss how these structural properties influence neural dynamics and how they arise during evolution and individual brain development (Varier & Kaiser, 2011).

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Combining interaction-latency reconstruction based on transfer entropy with graph-theoretical approaches to prune neural connectivity graphs

Transfer entropy (TE) is an information-theoretic, model-free way to determine directed interactions between signals. Its inherently non-linear nature makes it especially suitable for the analysis of complex dynamical systems such as neural networks. Here, we suggest a novel TE-estimator that takes neuronal interaction delays into account explicitly. We demonstrate that this estimator together with optimization of the delay embedding based on the local constant predictor described by Ragwitz and Kantz (Phys Rev E, 2002) is capable of recovering interaction delays for a large variety of interaction types such as threshold and quadratic coupling and also multiplicative modulatory coupling. Under certain constraints these reconstructed delays can be combined in a graph-theoretical approach to indicate putative indirect connections in bivariate analyses. We present data on detection accuracy and the scaling behavior of the graph-theoretical approach. We also demonstrate the application of the proposed method to indicate indirect interactions in simulated data, LFP data from the turtle brain, and reconstructed neuronal source signals from Magnetoencephalographic (MEG) recordings. Last, we present the open source toolbox TRENTOOL, that packages parameter and TE estimation functions with statistical routines and the graph-timing algorithms in a user-friendly way.

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Explaining the causal link between place cells and grid cells with Category Theory

Graph theory is an imperialistic tool that is pervasively used in a number of scientific fields ranging from financial economy to genomics and ecology. It allows to represent pairwise correlations among variables as edges connected to nodes. However, graph theory might fall short to understand the underlying causal principles which produce the correlation network. Tools for causal analysis like Bayesian networks or linear regression models still rest on graphs to describe causal relations. Category theory and graph theory are strongly intricated. Ehresmann [1] has demonstrated that a category is a (directed) graph plus an internal composition of arrows; and conversely a graph generates the category of its paths, obtained just by adding its paths as new edges (with the convolution as composition). Here we propose a new theoretical framework based on category theory, aiming to shed some light on the causal link between place cells in the hippocampus and grid cells in the medial entorhinal cortex. The theory developed by the authors in [2], is implemented in a computational model that simulate and predict the emergence of place fields. The paper's rationale is to study the effect in injecting the concepts of co-product and colimit from category theory, providing an alternative to orthodox computational models of spatial representation in the hippocampus.

[1] A.C. Ehresmann and J-P. Vanbremeersch. Memory Evolutive Systems; Hierarchy, Emergence, Cognition. Elsevier, 2007.
[2] J Gomez-Ramirez and R Sanz. Hippocampal categories: A mathematical foundation for navigation and memory. In C Hernandez, Ricardo S, J Gomez-Ramirez, L Smith, A Hussain, A Chella, and I Aleksander, editors, From Brains to Systems, volume 718 of Advances in Experimental Medicine and Biology, pages 149–164. Springer New York

NOTES:

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Variational Bayesian Causal Connectivity Analysis for fMRI

The ability to accurately estimate effective connectivity among brain regions from neuroimaging data could help answering many open questions in neuroscience. In this talk, we present a Bayesian method based on causality to obtain a measure of effective connectivity from fMRI data. The method uses a vector autoregressive model for the latent variables describing neuronal activity in combination with a linear observation model based on a convolution with a hemodynamic response function. We show that due to this modeling, it is possible to efficiently estimate all latent variables of the model using a variational Bayesian inference algorithm. The computational efficiency of the method enables us to apply it to large scale problems with high sampling rates and several hundred regions of interest, which are commonly encountered in practical settings. We provide comprehensive empirical evaluations with synthetic fMRI data to evaluate the performance of the method under various conditions, and in comparison with existing methods.

NOTES:

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Epileptogenic focus localization through functional connectivity analysis of the intracranial EEG

Epilepsy is a chronic neurological disorder characterized by recurrent seizures. Around 1% of the worldwide population has epilepsy. Approximately 30% of the patients cannot be adequately cured with anti-epileptic drugs. These patients have, so called, refractory epilepsy. Alternatively these patients can be rendered seizure free by removing the epileptogenic focus, i.e. the brain region responsible for causing the epileptic seizures. This implies the need for accurate localization of the epileptogenic focus. During the pre-surgical evaluation the neurologist identifies the epileptogenic focus through visual inspection of the intracranial electroencephalographic (IEEG) signals. An algorithm was developed to localize the epileptogenic focus more accurately based on connectivity analysis of the IEEG signals. Causality analysis was performed on the ictal IEEG in 5 patients. A time variant multivariate autoregressive (TVAR) model was estimated out of the IEEG signals by using Kalman filtering. The full-frequency Adaptive Directed Transfer Function was calculated out of these TVAR-coefficients [1]. The out-degree of the IEEG channels was visualized over time and the epileptogenic focus was identified. The IEEG channel with the maximal out-degree is pinpointed as the driver behind the seizures. In the 5 patients we found a high correlation between the estimated epileptogenic focus and the resected brain area. The proposed method is capable to localize the epileptogenic focus through the analysis of IEEG signals without prior knowledge of electrode positions in the 5 investigated patients. The results are concordant with post-operative results. This implies that the time-variant connectivity analysis of seizure onsets may add valuable information during the pre-surgical evaluation of a patient.

[1] van Mierlo P et al. , Accurate epileptogenic focus localization through time-variant functional connectivity analysis of intracranial electroencephalographic signals. Neuroimage. 2011 Jun 1;56(3):1122-33.

NOTES:

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Brain connectivity associated with different damages of the visual system

In this work we analyze electroencephalographic (EEG) data of patients having different visual field defects. As it has been shown in the literature, a damaged human connectome shows significant differences from an intact one regarding functional connectivity. Due to this we assume that there are significant correlations of both certain clinical parameters describing visual field defects and measures describing functional connectivity graphs. To answer this question we used EEG data from 43 patients from three different studies. Functional brain connectivities were computed using, e.g. synchronization likelihood, in the typical frequency bands. Graph measures like average path length, clustering coefficient, network density were tested for significant correlations against clinical parameters. We found out that different clinical parameters significantly correlate with typical graph measures of small world networks. This effect was prominent in all examined frequency bands to different degrees. We conclude that brain connectivity from EEG significantly correlates with damages of the visual system.

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Causality in neuroscience

For decades, the main ways to study the effect of one part of the nervous system upon another have been either to stimulate or lesion the first part and investigate the outcome in the second. A fundamentally different approach to identifying causal connectivity in neuroscience is provided by a focus on the predictability of ongoing activity in one part from that in another. This approach has been made possible by the pioneering work of Wiener (1956) and Granger (1969). The Wiener–Granger method, unlike stimulation and ablation, does not require direct intervention in the nervous system. Rather, it relies on the estimation of causal statistical influences between simultaneously recorded neural time series data, either in the absence of identifiable behavioral events or in the context of task performance. Causality in the Wiener–Granger sense is based on the statistical predictability of one time series that derives from knowledge of one or more others. I will define and illustrate Wiener Granger causality (WGC) with a pragmatic focus on application to neural time-series data, including electroencephalographic and local field-potential signals, spike trains, and functional MRI signals. I will compare the method with contrasting approaches such as 'dynamic causal modeling'. Returning to theory, I will introduce some novel network-level concepts based on WGC including multivariate causality, causal density, Granger-autonomy, and Granger-emergence, and I will try to show how these concepts can shed new light on multi-scale neural causality. I will finish with some thoughts about what one should require of a measure of causality, in the specific context of the relation between network structure and network dynamics.

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