2024

Bayesian inference of causal relations between dynamical systems [1].

From ancient philosophers to modern economists, biologists, and other researchers, there has been a continuous effort to unveil causal relations. The most formidable challenge lies in deducing the nature of the causal relationship: whether it is unidirectional, bidirectional, or merely apparent — implied by an unobserved common cause [2]. While modern technology equips us with tools to collect data from intricate systems such as the planet's ecosystem or the human brain, comprehending their functioning requires the identification and differentiation of causal relationships among the components, often without external interventions. In this context, we introduce a novel method capable of distinguishing and assigning probabilities to the presence of all potential basic causal relations between two or more time series within dynamical systems. The efficacy of this method is verified using synthetic datasets (Fig. 1.) and applied to EEG (electroencephalographic) data recorded from epileptic patients. Given the universal applicability of our method, it holds promise for diverse scientific fields.

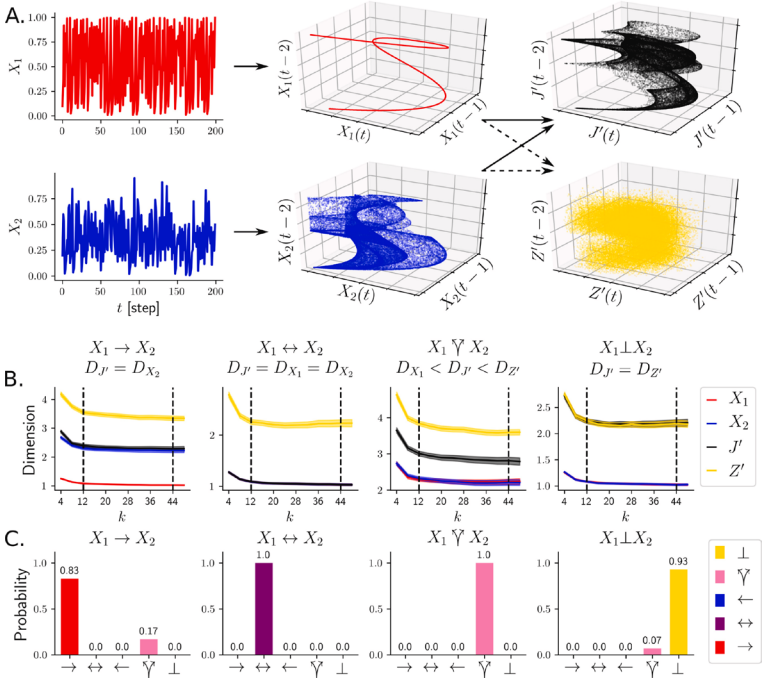


Figure 1. The workflow and testing of our method on coupled logistic map systems. (A) Time series (left) of the driver and the driven time series. Next to them, the state spaces of the systems are reconstructed by time delay embedding of the two time series (red) and (blue), resulting in the red and blue manifolds. Then, the joint of the two datasets, and their time-shuffled version are also embedded, resulting in a reconstruction of the joint state space of the two subsystems (black manifold) and their independent joint (yellow). On (B, C) the test of our method on the four simulated examples of five possible causal interactions (one of the unidirectional, bidirectional:, unidirectional backward, common cause and independence) are demonstrated. (B) The intrinsic dimensionality of each manifold is estimated for different neighborhood sizes. The plateau of dimension-estimates identifies where the estimates can be considered reliable (between dashed lines). Note the match between the actual causal and dimensional relationships: the dimension of the joint manifold relative to the others. (C) Posterior probabilities of the possible causal relationships. The method correctly assigned the highest probability to the actual causal relation in each case.

Validation of dimensional causality on EEG data (Fig 2.). — we aim to assess our approach under real-world conditions, where the true dimensionality and the properties of the noise are unknown. While the precise causal relationships between time series in these systems are

not known, external factors can induce changes in the internal causal relationships that our analysis method can detect. Notably, the standard epilepsy-diagnostic photo-stimulation procedure, where patients are exposed to flashing light at different frequencies in a standardized test, serves as an ideal model for an external common cause affecting the two brain hemispheres.

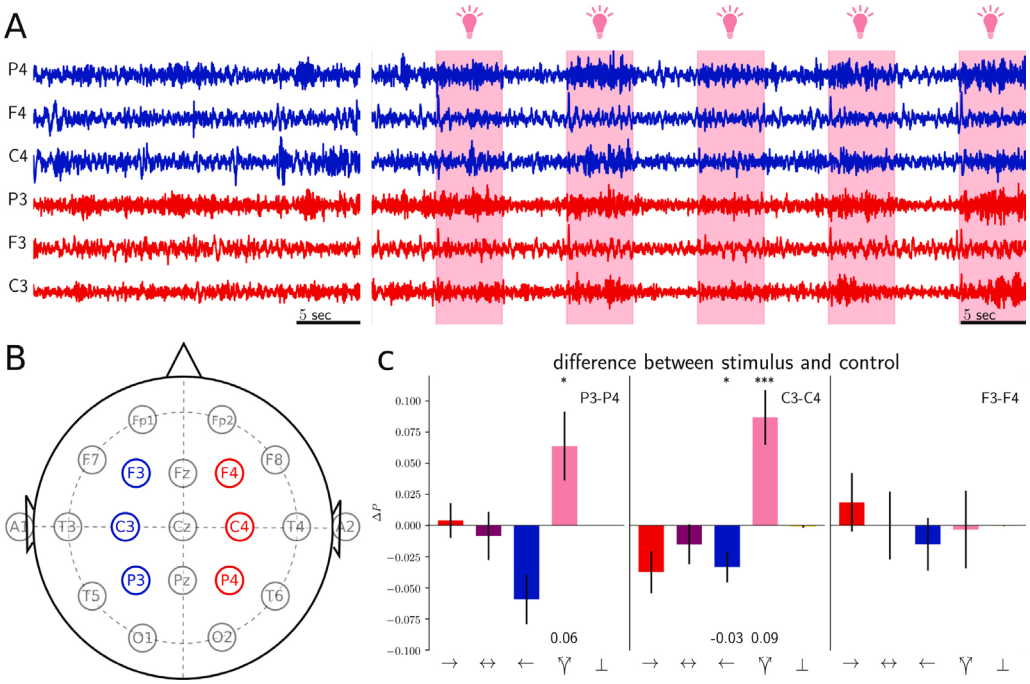


Figure 2. Inter-hemispherical interactions during photo-stimulation. (A) CSD signal in control condition and photo-stimulation periods (light bulbs) at the six analyzed recording-channels. (B) Electrode positions on the scalp. Causal relations were computed between P3–P4, C3–C4 and F3–F4 channel pairs. (C) Difference in probabilities of causal relations between stimulation and control (mean and SE). The probability of the existence of common cause is significantly higher during stimulation periods for P3–P4 and C3–C4 channel-pairs but not for F3–F4.

References:

[1] https://doi.org/10.1016/j.chaos.2024.115142

[2] https://doi.org/10.3390/e26030185

[3] https://doi.org/10.1088/1751-8121/ad6224

[4] https://doi.org/10.48550/arXiv.2407.20694

[5] https://doi.org/10.48550/arXiv.2410.19469

2023.

Application of our word association method - We utilized our method [1] that discerns frames of opinions through the maximal modularity partitioning of networks based on free word associations, three distinct studies showcase its effectiveness in various healthcare contexts. The first study delved into mental representations of substance use and potentially addictive behaviors among 661 participants, revealing four distinct emotional categories. Notably, different representations were associated with substances versus other addictive behaviors, suggesting varied cognitive evaluations underlying these activities [2]. The second study, involving 216 primary care physicians in Switzerland, employed the method to understand mental representations of bariatric surgery. It identified three key perspectives: indication-focused, treatment-focused, and outcome-focused, with the treatment-focused mindset leading to higher patient referrals for surgery [3]. Finally, the third study focused on the attitudes and perceptions towards endocrine endometriosis therapy among 3348 women. It uncovered predominantly negative mental associations and emotions, highlighting a pre-therapeutic information deficit [4]. This method's application across these studies demonstrates its utility in extracting nuanced insights into public opinions and mental representations on diverse health-related topics.

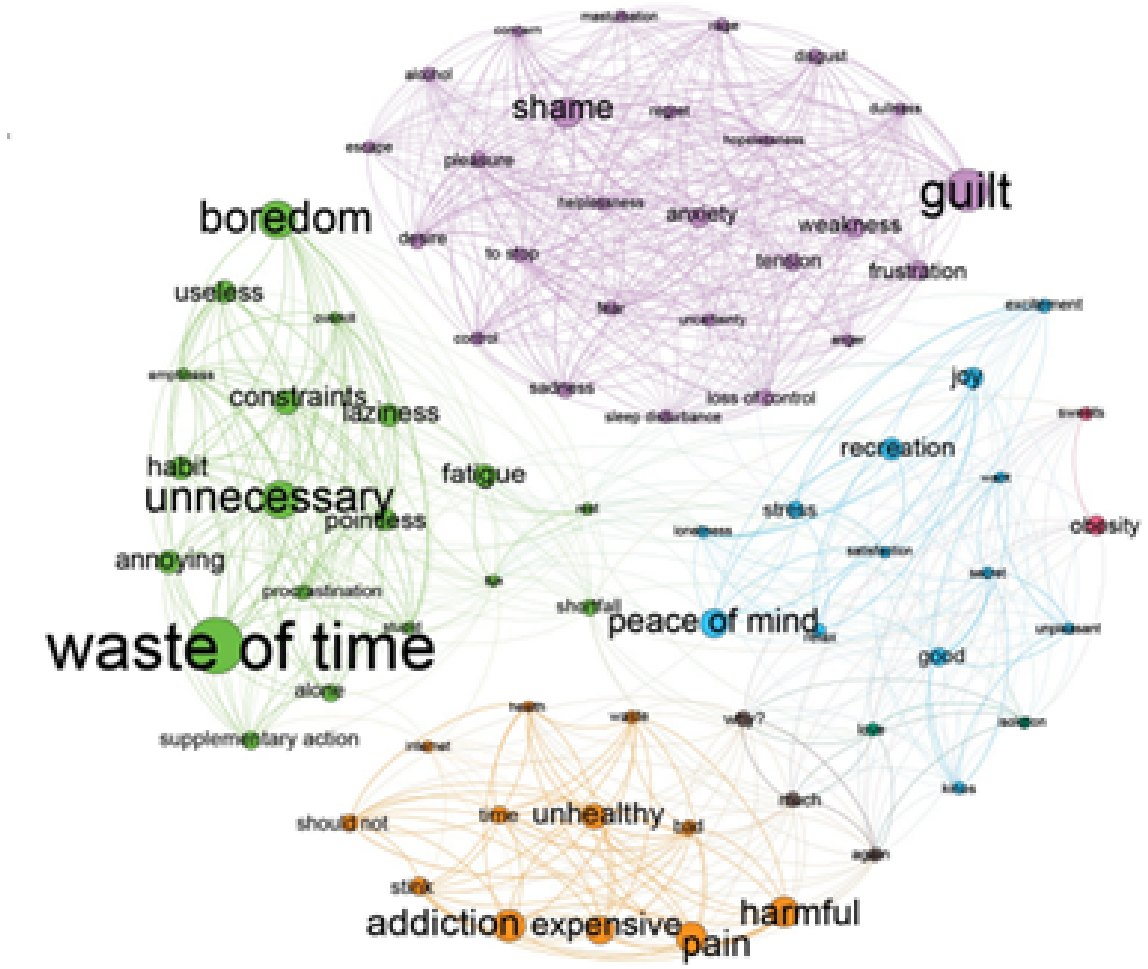


Figure 1: Mental representations of the CoOp networks. Each MR is visualized with different colors (purple: Guilt-Shame; blue: Relaxation; orange: Addiction-Health, green: Waste-of-time). The sizes of a node and its label are proportional to the frequency of the given association. An edge means that two associations fall into a common MR in the consensus-partitioning procedure at least 40%.

Classification of ADHD with machine learning - In this study, EEG-based event-related potential (ERP) indices were analyzed using machine learning techniques, specifically linear support vector machines, to identify biomarkers for ADHD in 306 adolescents. The ERPs, reflecting neural responses to reward anticipation and response, effectively distinguished between various ADHD presentations and predicted substance use within the ADHD group. These results highlight the efficacy of combining EEG data with machine learning in ADHD diagnosis and prognosis, demonstrating a significant advancement in neuroscientific methods [5].

Complexity based Causal Discovery of Hidden common cause - A novel concept and a corresponding causality analysis method were introduced to uncover the presence of a hidden common driver linking two observed time series derived from dynamical systems. The Complexity-based Causal Discovery of Hidden Common Cause (CCDH) method employs a symbol series compression technique to estimate the complexity of

each time series. Following our previously established approach, it then compares the complexity of the two observed time series to that of the joint series of symbols. The identification of a hidden common cause is inferred from the relationships between the joint and the individual complexities. The significance of this new method was exemplified through its application to deep bilateral EEG measurements taken near the hippocampi of an epileptic patient. The method successfully deduced the time periods of directed driver-driven relations between the two hippocampi, as well as the characteristic time periods influenced by a hidden common driver during an epileptic seizure [6].

References:
[1] DOI: https://doi.org/10.3758/s13428-018-1090-z
[2] DOI: https://doi.org/10.1371/journal.pone.0287564
[3] DOI: https://doi.org/10.1016/j.soard.2023.05.015
[4] DOI: https://doi.org/10.1093/humrep/dead221
[5] DOI: https://doi.org/10.1016/j.psychres.2023.115139
[6] DOI: https://doi.org/10.1016/j.chaos.2023.114054.

2022

Reconstructing the complete spatiotemporal membrane potential distribution on individual neurons — We showed that it is possible to reconstruct the complete spatiotemporal distribution of the membrane potential of a single neuron, with the spatial resolution of an extracellular probe, by combining single-channel somatic patch-clamp and multi-channel extracellular potential recordings during action potential generation. The model-based membrane potential reconstruction utilized the detailed morphology of the neuron and allowed for distinguishing between the two major but previously hidden components of the current source density (CSD) distribution: the resistive and the capacitive currents. This distinction provided a clue to the clear interpretation of the CSD analysis, as the resistive component corresponds to transmembrane ionic currents: all the synaptic, voltage-sensitive, and passive currents; while capacitive currents are considered the main contributors of counter-currents. In perspective, the estimation of the spatial distribution of resistive membrane currents makes possible the localization of the synaptic input currents, which make the neuron fire [1].

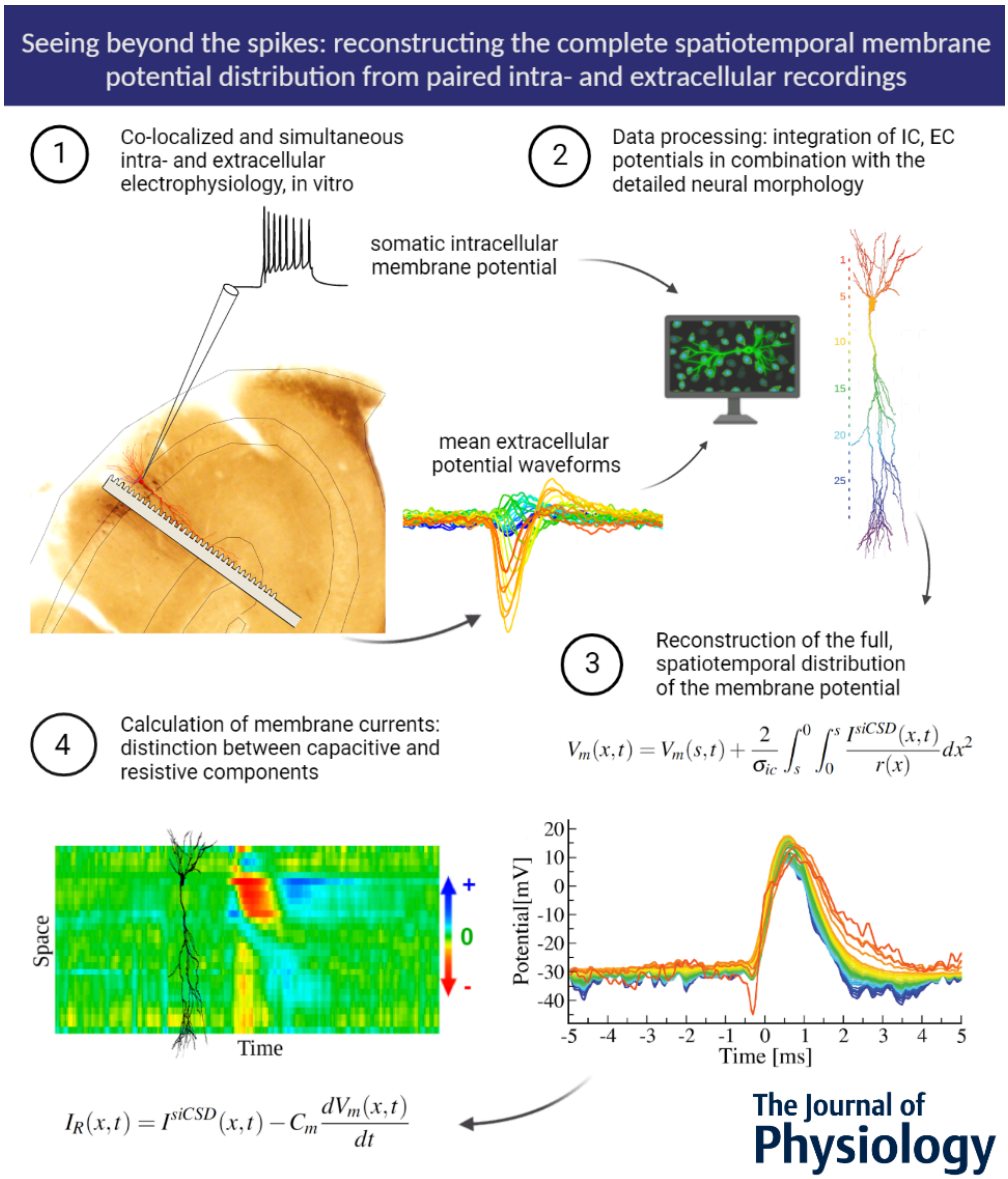


Figure 1: Outline of our new analysis method for reconstruction of the spatio-temporal distribution of the membrane potential on individual neurons.

Signal transmission modularity in the cerebral cortex. — Axons of neighboring neurons that transmit information between regions of the cerebral cortex form synapses in a diffuse and clustered pattern. These two domains of axon terminations support different signal processing schemes. To better understand the functional roles of the two axonal domains individual and collective structural properties of the axons were studied. We found that synapse spacing is the best predictor of the two axonal domains (Fig. 2). Higher synapse density within clusters can promote concerted neuronal actions via convergence whereas diffuse termination pattern can diversify neuronal responses across the cortical mantle. Our findings provide evidence that spatial proximity of the neurons is a major determinant of cortical functional organization [2].

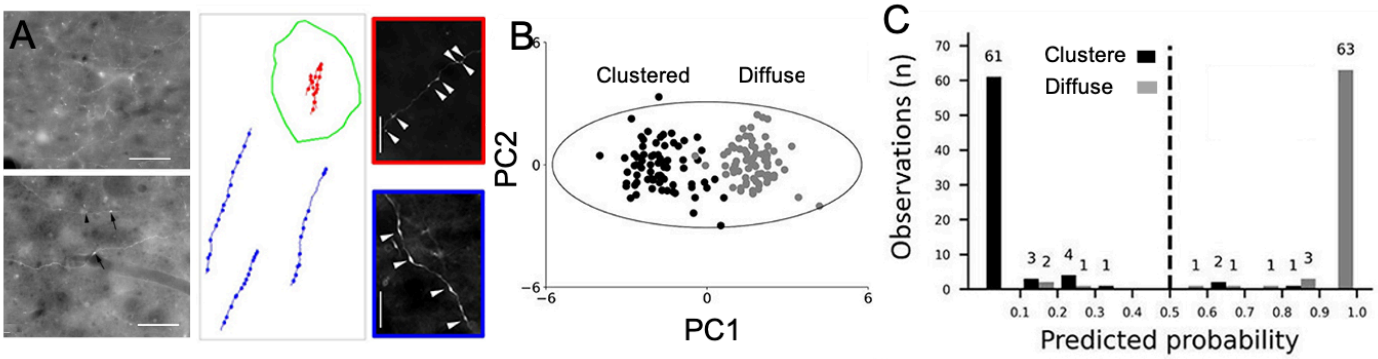


Figure 2. Multivariable analyses of the axons. A) Light microscopic images (left and right panels) and drawings (middle panel) of axons in the clustered (upper panels, red) and diffuse (lower panels, blue) axonal domains. Arrows and arrowheads point to possible sites of synaptic contacts. B) Structural properties clearly distinguish axons with clustered and diffuse termination patterns by using principal component analysis (PCA). C) Among the

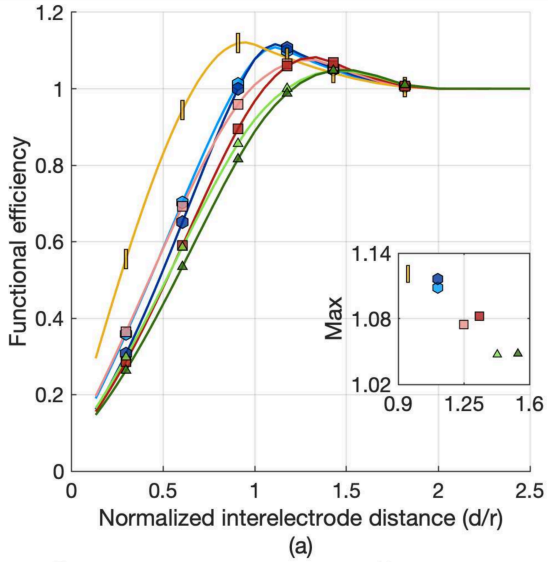
variables examined those related to synapse spacing were the best predictors of the two axonal domains in a stepwise logistic regression model [2].

Analysis of microstructure of ingestive behavior. — The drinkometer is a promising device for the study of ingestive behavior of liquid meals in humans. It can be used to investigate behavior in different target populations. However, ingestive behavior has a great variability across study participants. Therefore, a new analytical approach is required for the extraction and analysis of drinkometer-derived data that could account for this variability. We developed an optimized protocol to predict an optimal burst-pause criterion (PC) for the extraction of PC-dependent microstructural parameters of ingestive behavior. These describe the microstructure of bursts, while PC-independent parameters describe the microstructure of sucks. Therefore, a PC is required to analyze separately two physiologically different parts of behavior. To accomplish this burst-pause criterion derivation (BPCD), a Gaussian Mixture Model (GMM) was built for estimation of two probability density functions (PDFs). These model the distribution of inter-suck intervals (ISIs) and inter-burst intervals (IBIs), respectively. The PC is defined at the intersection point of the two density functions. A Kaplan-Meier (KM) survival analysis was performed for post-hoc verification of the fit of the predicted optimal PC to the ISI distribution [3,4,5].

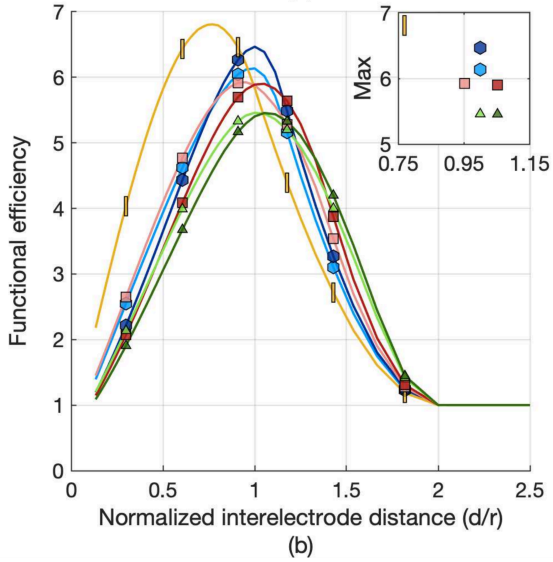
Model-free detection of unique events in time series — Recognition of anomalous events is a challenging but critical task in many scientific and industrial fields, especially when the properties of anomalies are unknown. In this paper, we introduce a new anomaly concept called “unicorn” or unique event and present a new, model-free, unsupervised detection algorithm to detect unicorns. The key component of the new algorithm is the Temporal Outlier Factor (TOF) to measure the uniqueness of events in continuous data sets from dynamic systems. The concept of unique events differs significantly from traditional outliers in many aspects: while repetitive outliers are no longer unique events, a unique event is not necessarily an outlier; it does not necessarily fall out from the distribution of normal activity. The performance of our algorithm was examined in recognizing unique events on different types of simulated data sets with anomalies and it was compared with the Local Outlier Factor (LOF) and discord discovery algorithms. TOF had superior performance compared to LOF and discord detection algorithms even in recognizing traditional outliers and it also detected unique events that those did not. The benefits of the unicorn concept and the new detection method were illustrated by example data sets from very different scientific fields. Our algorithm successfully retrieved unique events in those cases where they were already known such as the gravitational waves of a binary black hole merger on LIGO detector data and the signs of respiratory failure on ECG data series. Furthermore, unique events were found on the LIBOR data set of the last 30 years [6].

2021

Optimal electrode design for spike sorting. — We examined how the geometrical arrangement of electrodes influences spike sorting efficiency, and formalised the principles for the design of electrode systems enabling optimal spike sorting performance. The clustering performance of KlustaKwik, a popular toolbox, was evaluated using semi-artificial multi-channel data, generated from a library of real spike waveforms recorded in the CA1 region of mouse Hippocampus in vivo. Based on spike sorting results under various channel configurations and signal levels, a simple model was established to describe the efficiency of different electrode geometries. Model parameters can be inferred from existing spike waveform recordings, which allowed quantifying both the cooperative effect between channels and the noise dependence of clustering performance. Based on the model, analytical and numerical results can be derived for the optimal spacing and arrangement of electrodes for one- and two-dimensional electrode systems (Fig. 1), targeting specific brain areas [1].


Functional efficiency
Normalized interelectrode distance (d/r)
Max
1.14
1.08
1.02
0.9
1.25
1.6
0
0.2
0.4
0.6
0.8
1
1.2
0.5
1.5
2
2.5

(a)


Functional efficiency
Normalized interelectrode distance (d/r)
Max
7
6
5
0.75
0.95
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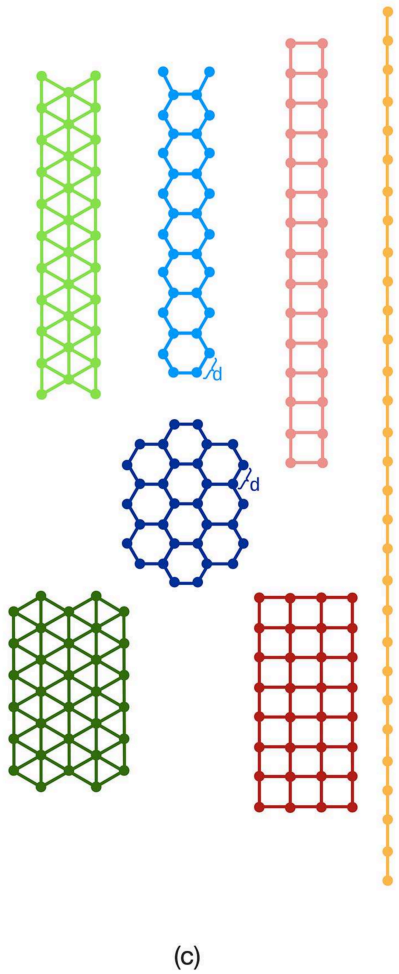
(b)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(c)

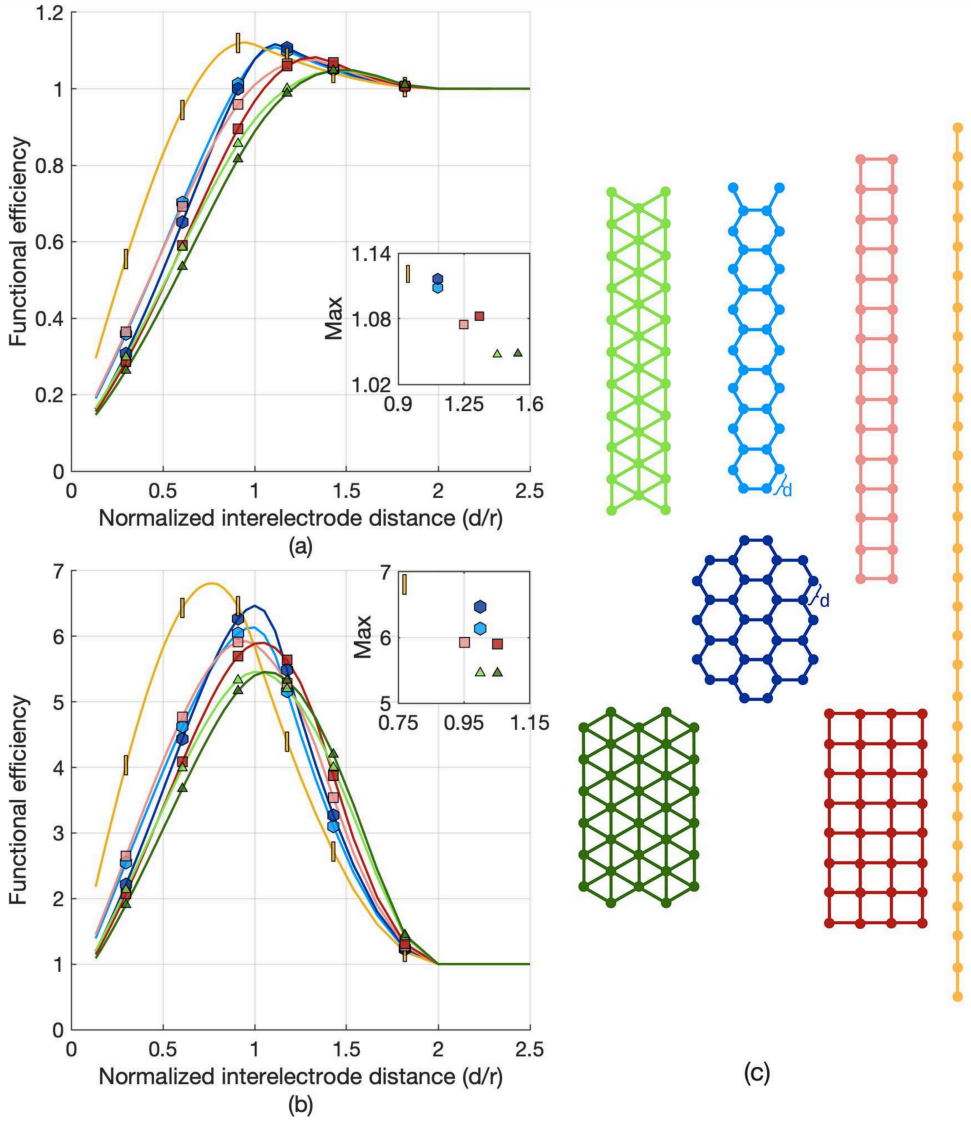


Figure 1. Functional efficiency of 32-channel electrode grids, as a function of the normalized inter-electrode distance: a) Original sinal to noise ratio (SNR range 8.3 – 47.7) b) SNR = 37.5 for all spikes. While the linear probe showed the highest efficiency at its maximum, its performance depends heavily on the inter-electrode distance and SNR.

Network Path Convergence Shapes Low-Level Processing in the Visual Cortex. — Hierarchical counterstream via feedforward and feedback interactions is a major organizing principle of the cerebral cortex. The counterstream, as a topological feature of the network of cortical areas, is captured by the convergence and divergence of paths through directed links. So defined, the convergence degree (CD) reveals the reciprocal nature of forward and backward connections, and also hierarchically relevant integrative properties of areas through their inward and outward connections. We asked if topology shapes large-scale cortical functioning by studying the role of CD in network resilience and Granger causal coupling in a model of hierarchical network dynamics. Our results indicate that topological synchronizability is highly vulnerable to attacking edges based on CD, while global network efficiency depends mostly on edge betweenness, a measure of the connectedness of a link. Furthermore, similar to anatomical hierarchy determined by the laminar distribution of connections, CD highly correlated with causal coupling in feedforward gamma, and feedback alpha-beta band synchronizations in a well-studied subnetwork, including low-level visual cortical areas. In contrast, causal coupling did not correlate with edge betweenness. Considering the entire network, the CD-based hierarchy correlated well with both the anatomical and functional hierarchy for low-level areas that are far apart in the hierarchy (Fig 2). Conversely, in a large part of the anatomical network where hierarchical distances are small between the areas, the correlations were not significant. These findings suggest that CD-based and functional hierarchies are interrelated in low-level processing in the visual cortex. Our results are consistent with the idea that the interplay of multiple hierarchical features forms the basis of flexible functional cortical interactions [2].

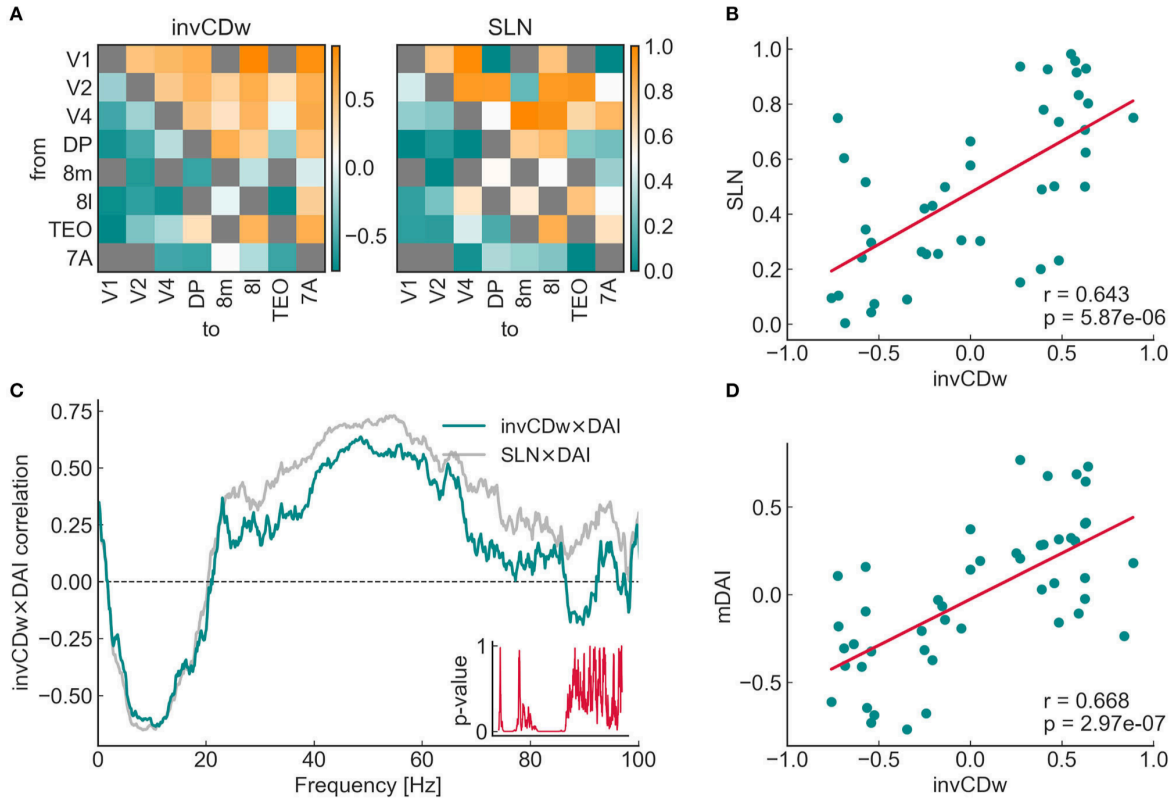


Figure 2. Relationship of the additive inverse of the weighted convergence degree (invCDw) with the SLN (fraction of supragranular labeled neurons) and the DAI (directed influence asymmetry index) in the 8 × 8 subgraph od labellad anatomical areas. (A) The invCDw shows a significant negative correlation in the alpha-band and a significant positive correlation in the gamma-band similar to that found for the SLN. Interestingly, the invCDw shows almost the exact level of correlation in the alpha-band (for feedback connections) as the SLN, whereas in the gamma-band (for feedforward connections) it is somewhat lower. (D) There is a significant positive correlation between the invCDw and the multifrequency DAI (mDAI, p < 10 −6).

2020

Reorganization of Large-Scale Functional Networks During Low-Frequency Electrical Stimulation of the Cortical Surface. — In a research carried out with the National Institute of Clinical Neuroscience, we examined the rearrangement of the functional brain network of epileptic patients undergoing brain surgery under the influence of direct, cortical stimulation with graph theory parameters. Our most important finding is that a more integrated network topology appears when stimulating the seizure onset zone than when stimulating outside the the seizure onset zone. This difference is more pronounced in patients who have been suffering from the disease for more time, so presumably the brain lesions associated with epilepsy are more conserved in their functional network (Fig. 1).

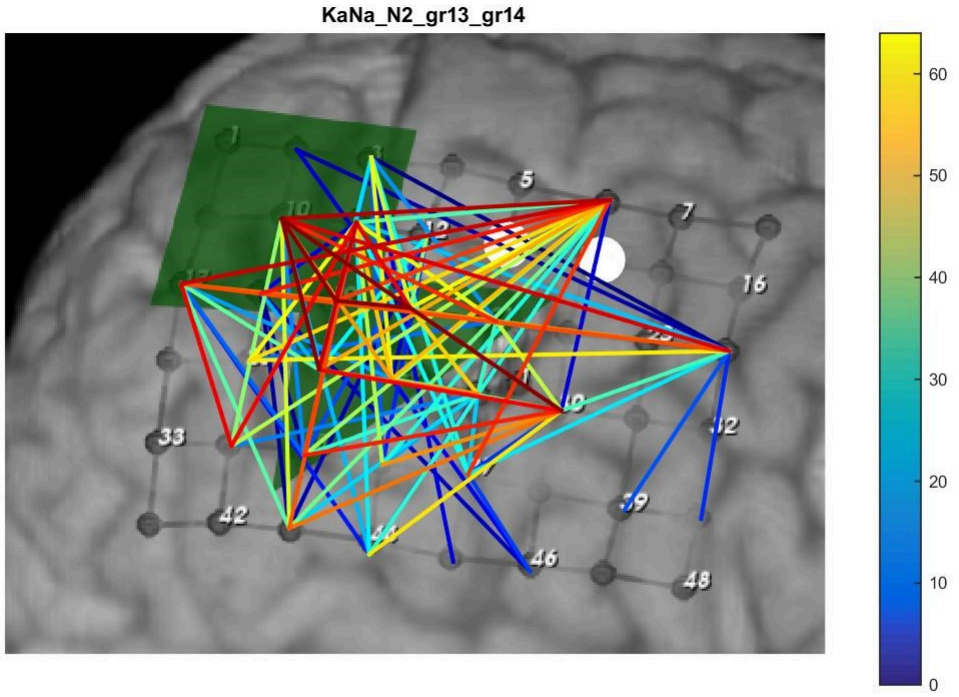


Figure 1. *Network of the propagating response to an electric stimulation. White circles and the orange flash sign between them denote the two electrodes used for the stimulation. Green area shows the resection area on the surface of the brain.*

Acute blockade of NR2C/D subunit-containing NMDA receptors modifies sleep and neural oscillations in mice. — We found that NR2C/D blockade changed the slep structue as the time spent in slow-wave and rapid eye movement sleep decreased, but the time spent in quiet wakefulness increased. Furthermore, there was a significant decrease of sleep spindle oscillation density. These findings highlight the importance of NR2C/D-containing NMDARs and take a step towards establishing a link between electrophysiological correlates of psychiatric disorders and underlying synaptic dysfunctions.

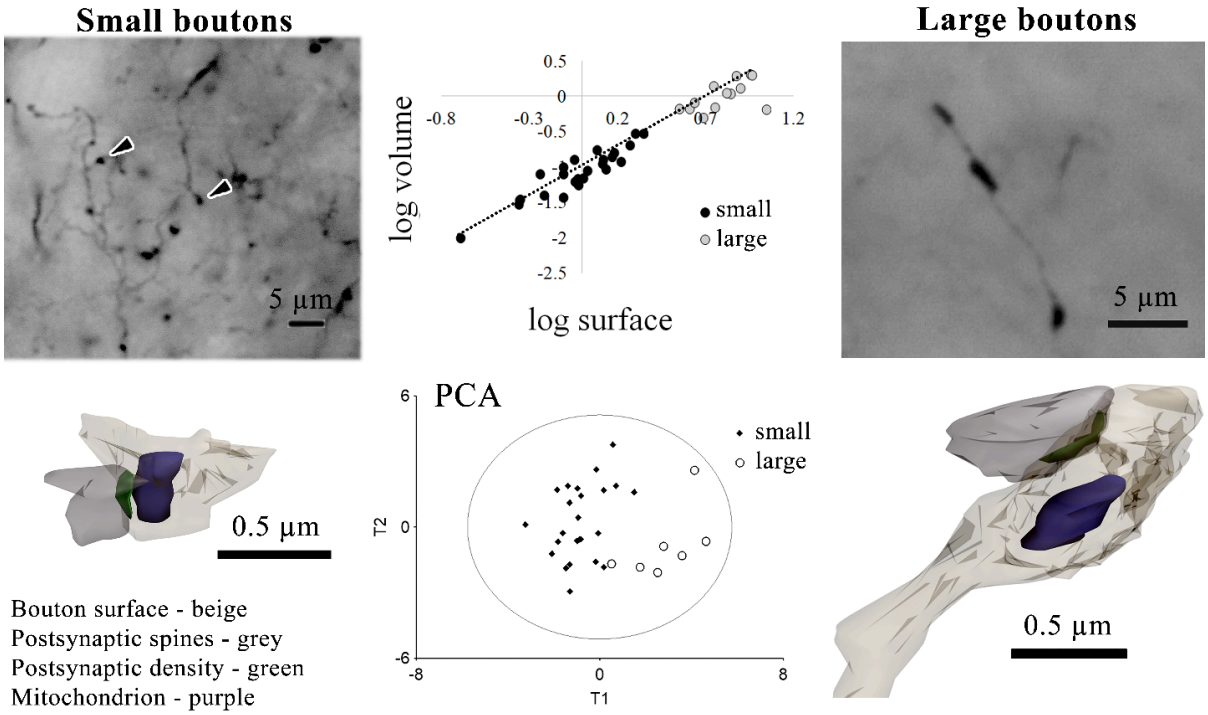
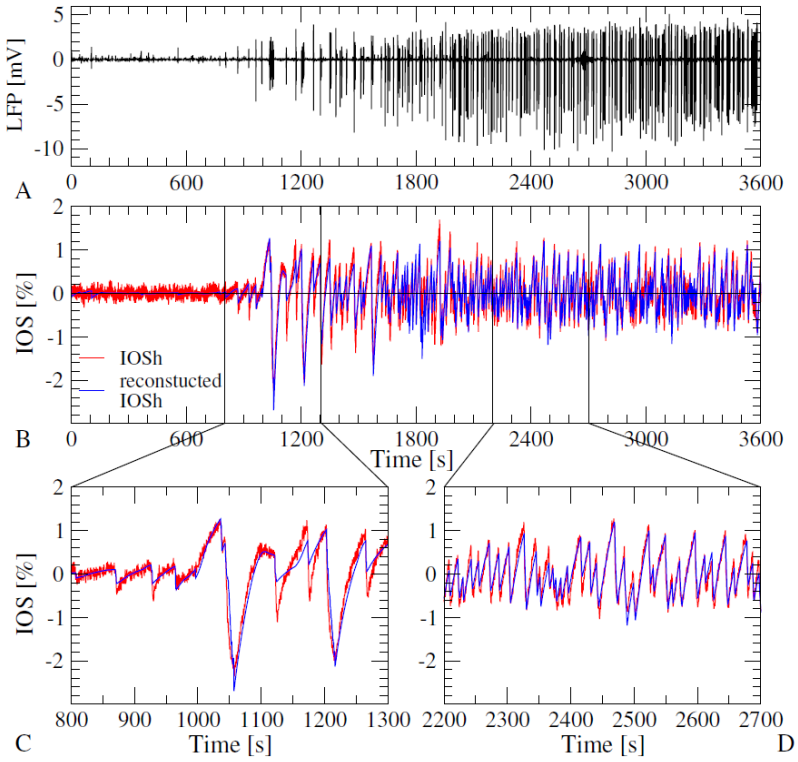


Figure 2. *Small and large synaptic buttons in primate cortex. The two types can be distinguished by their surface and volume as well as along the principal components of their ultrastructural features.*

Synaptic organization of cortico-cortical communication in primates. — We have shown that in primates, including humans, in the cerebral cortex, axon terminals can be grouped into small and large types based on their three-dimensional ultrastructural properties. Using three-dimensional electron microscopic serial section reconstruction, we found a strong correlation between surface and volume, so that it also separated the two types of axon ends. Multivariate principal component analysis of ultrastructural features confirmed the applicability of the above categorization. Based on our results, it can be assumed that interactions in the cerebral cortex in primates also occur basically through two channels: 1) strong but rapidly decaying signaling through large axon terminals and 2) weak, long-decay modulating signaling through small axon terminals (Fig. 2).

References:
[1] DOI: 10.1142/S0129065719500229
[2] DOI: 10.1111/jsr.13257
[3] DOI: 10.1111/ejn.14905

2019



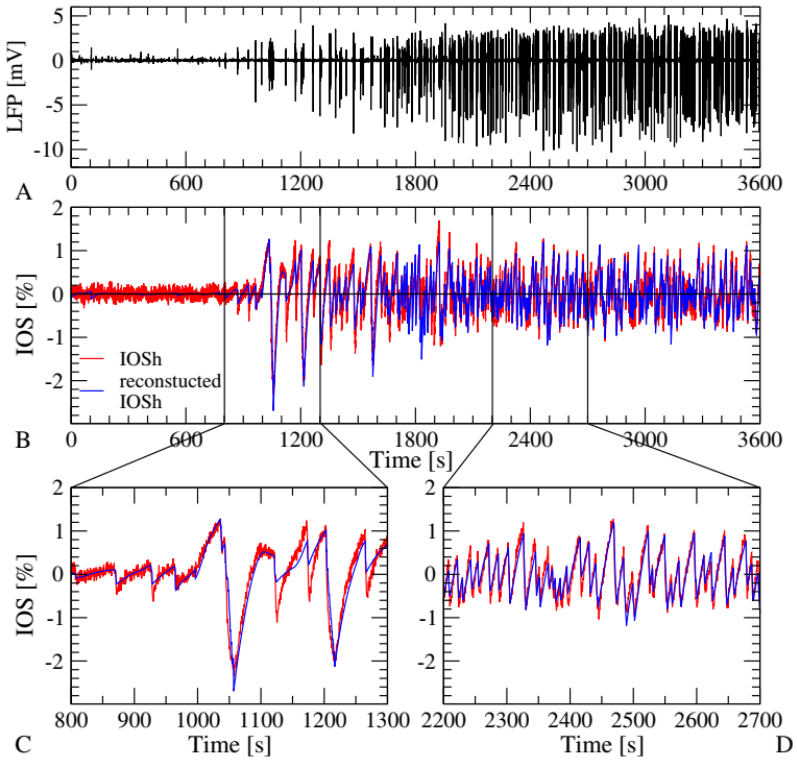


Figure 1. Reconstruction of the Intrinsic Optical Signal (IOSh) based on the measured Local Field Potential (LFP). A: The temporal evolution of the LFP during evoked epileptic activity of the brain slice. B-D: Comparison of the measured (red) and the reconstrucetd IOSh signal (blue). The reconstruction follows the measurement through different dynamic regimes.

Causality analysis between electrical signals of neural activity and the intrinsic optical signal of the neural tissue. — Causal relationship between local field potential (LFP) and intrinsic optical signal (IOS) in evoked epileptiform activity in vitro brain slices was investigated. The parallel IOS and LFP recordings were performed by Sándor Borbély and Ildikó Világi (Eötvös Loránd University). As far as we know, this work was the first conclusive application of the Sugihara's new causality method, the cross-convergent mapping (CCM) in neuroscience. As CCM is the first causality analysis method which can reliably detect the circular connection, we were in the position of investigating the question, whether only the evoked epileptic activity causes the intrinsic optical signal IOS, or there is a feedback mechanism as well, and the ion concentration changes measured by the IOS influence the termination or the renewal of the epileptic activity.During preprocessing, two components of the IOS signal have been distinguished: a faster, activity dependent component (IOSh) which changes its sign between transmitted and reflected light measurements thus it is related to the reflectance or the dispersion of the tissue and a slower component (IOSl), which is negative in both cases, thus can be attributed to the increase of the absorption of the tissue. We found only unidirectional causal drive from the electric towards the optical signal, but this work demonstrated several phenomena which are instructive for further investigation: We found, that the correlation was small between the LFP and the IOSh at the time of the actual causal effect and the peaks of the cross correlation function did not reflect the actual causal dependency in this case. In stead, the temporal derivative of the IOSh was correlated with the LFP power at the time delay of the causal peak. Based on these observations, a simple model have been set up to describe the dependency of the IOSh on the LFP power and IOSh was reconstructed, based on the LFP signal (Fig. 1.). Besides the actual results, we believe that this study demonstrates, that it is possible to calculate the causality between two data series with drastically different time scales and provides useful know-how for application of causality analysis for any field of science [1].

Emergence of polarized opinions from free association networks. — We developed a method that can identify polarized public opinions by finding modules in a network of statistically related free word associations. Associations to the cue "migrant" were collected from two independent and comprehensive samples in Hungary ($N_1 = 505$, $N_2 = 505$). The co-occurrence-based relations of the free word associations reflected emotional similarity, and the modules of the association network were validated with well-established measures. The positive pole of the associations was gathered around the concept of "Refugees" who need help, whereas the negative pole associated asylum seekers with "Violence" (Fig. 2). The results were relatively consistent in the two independent samples. We demonstrated that analyzing the modular organization of association networks can be a tool for identifying the most important dimensions of public opinion about a relevant social issue without using predefined constructs) [2].

2018

Analysis of complex systems in the brain and beyond

We showed by using 3D electron microscopic reconstructions and quantitative comparisons that each pathways of the hierarchical circuitry of the somatosensory cortex forms two kinds of synaptic contacts: one exhibiting structural properties, which permit signal transmission at high fidelity, and another with morphological properties of the modulatory type. These findings are crucial in understanding the dynamics of interactions of the different hierarchically organized cortical pathways. The manuscript summarizing these findings is about submission.

The directed interactions have been determined among the variables of a lake ecosystem, via a new causality analysis method. Causality analysis indicated that the observed eutrophication signals were induced by climate change, which altered the phosphate, the fito- and the zooplacton interactions.

A new data analysis method has been developed to generate an electric imaging, based on parallel recordings on intrinsic optical and local field potential by a transparent electrode array. The new method makes possible the fusion of the two methods, by exploiting the advantages of bot, the excellent spatial resolution of the optical imaging and the excellent temporal resolution of the electric signal (Fig. 1).

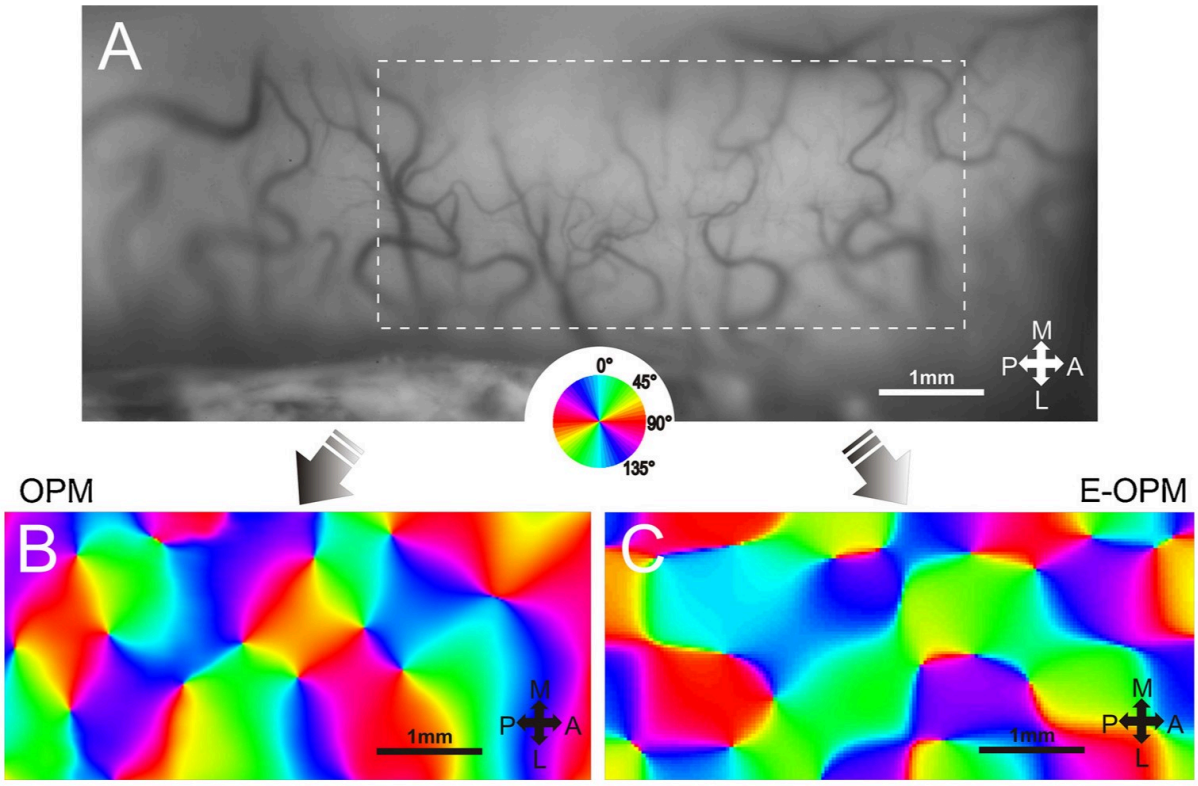


Figure 1. *Comparison between optically and electrically derived orientation preference maps. The white dashed frame on the grayscale vascular image (A) shows the position of the 32-channel microelectrode array inside the investigated A17 region. Traditionally processed orientation preference map (B) and electrical orientation preference map derived from the evoked ECoG responses to the visual stimuli (C) are shown.*

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves, putting significant burden on caregivers and society. The goal of our research is to identify druggable molecular targets in a hope to ameliorate the life of people suffering from this disease. A new project targeting the fundamental question of molecular, system and functional level causes of Schizophrenia was started in 2018 in collaboration with Semmelweis University funded by Gedeon Richter Plc. During this year a new experimental laboratory was set up and preliminary results generated to elaborate on a possible role of NR2C containing NMDA receptors in generating sleep disturbances underlying decreased memory performance, a key symptom of Schizophrenia.

2017

We have published a new data analysis method, called skCSD, to reveal membrane currents on single neurons, based on extracellular multichannel electrode array measurements. The new method provides higher precision in membrane current source density reconstruction due to the inclusion of the morphology information into the calculation. We have applied the new method to the first available parallel extracellular and intrancellular data and showed the spatial propagation of the currents during action potential generation on the dendritic branches of the cell. (Fig. 1) The scripts for the analysis, written in R, were tested and made publicly available as an open source program package.

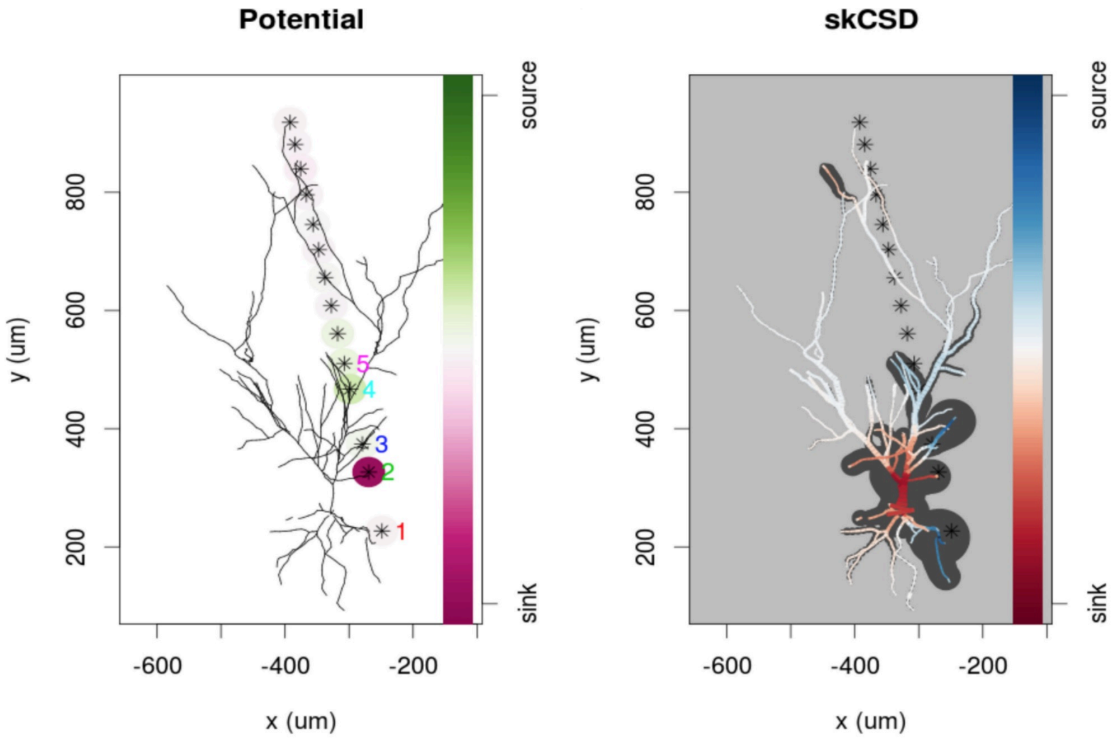


Figure 1: *Left: Electrode positions (stras) and reconstructed morphology of the pyramid cell from the CA1 region of the rat hippocampus. The color coded circles on the electrodes show the measured momentary electric potential at the moment of the peak of an action potential generated by the neuron. Right: The reconstructed current source density distribution along the dendritic tree of the neuron. Warm colors mark inward positive currents to the neuron (sink) cold colors mark the outward currents from the neuron (sources).*

We have published the first results on the analysis of the parallel recordings on intrinsic optical and local field potential by a transparent electrode array. The new method makes possible the fusion of the two methods, by exploiting the advantages of both, the excellent spatial resolution of the optical imaging and the excellent temporal resolution of the electric signal.

We applied our coherence clustering method, to determine the cortical structures and areas from the measurements with the transparent cortical surface electrode grid, parallel to the intrinsic optical signal measurement. The methodology and the first results were published on a conference and in a proceedings journal.

We created a new feedback model of the dynamics of gene expression and protein synthesis on the basis of experimental findings. We built a stochastic kinetic model to investigate and compare the “traditional” and the feed-back model of genetic expression processes. Qualitative and quantitative changes in the shape and in the numerical characteristics of the stationary distributions of proteins and RNA molecules suggest that more combined experimental and theoretical studies should be done to uncover the details of the kinetic mechanisms of gene expressions.

We showed that in the somatosensory cortical circuitry, which is largely responsible for tactile perception, lateral interactions mostly depend on the intra-areal connections complemented by the neuronal feedback originating from areas with higher order functional representations. In contrast, feedforward connections from lower order areas exhibit spatially restricted lateral spread indicating higher functional specificity. Our results also suggest that the population activity is mostly determined by the target regions of the feedforward connections overlapping the strong local input within an area. The manuscript including these findings has been submitted for publication and is now under major revision.

To better understand somatosensory, and in general cortical communication, we studied the synaptic organization of the above mentioned connections in 3D by way of electron microscopy. Using state of the art data analyses techniques we found that the size of axon terminals is an important distinguishing morphological feature of the cortical synapses. We also found that the size of the mitochondria and postsynaptic densities (the active zone of the signal transmission) relative to the size of the axon terminals also exhibit important distinguishing characteristics and that their positive correlation can be explained by the energy need of synaptic transmission. The manuscript summarizing these findings is going to be submitted soon.

Our ongoing studies show that the robustness and synchronizability of the network of cortical areas is especially sensitive to targeted removal of the network edges on the basis of their convergence degree introduced previously by our group.

By including a Bayesian evaluation algorithm, the development of our new causality analysis method, now we call it dimensional causality method (DC), has been completed. The DC method has been tested on various simulated systems, such as coupled Lorentz systems, coupled logistic maps and coupled Hindmarsh-Rose models. These simulated dynamical systems pose different challenges towards the DC algorithm but we found, that all the DC method was able to infer all possible causal relations (unidirectional, circular, independent and hidden common cause) in all the three model cases. Preliminary applications were made on neurophysiological data from epileptic patients, during photostimulation experiment and during epileptic seizure.

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