CNS 2011

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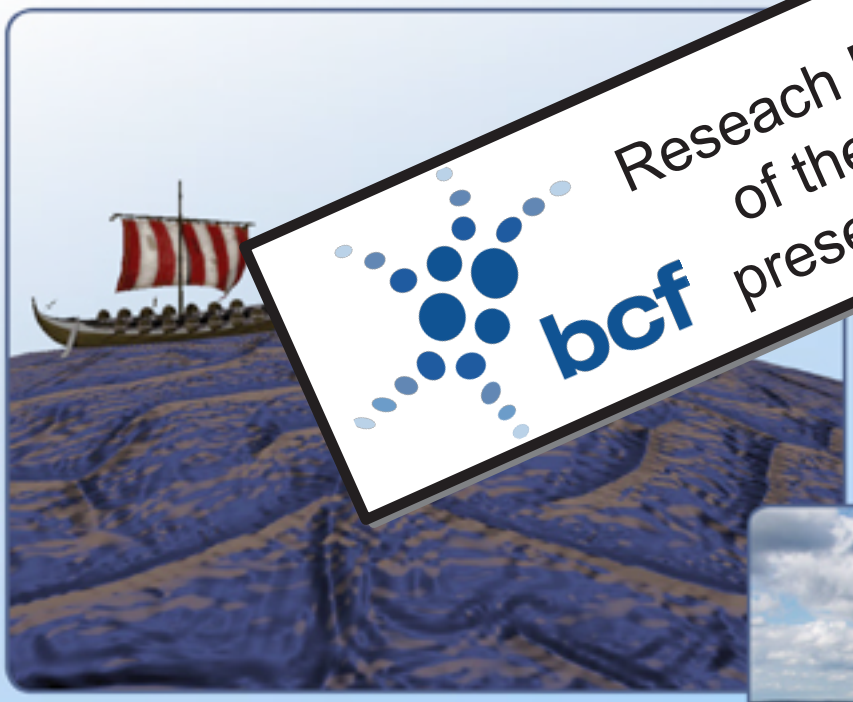

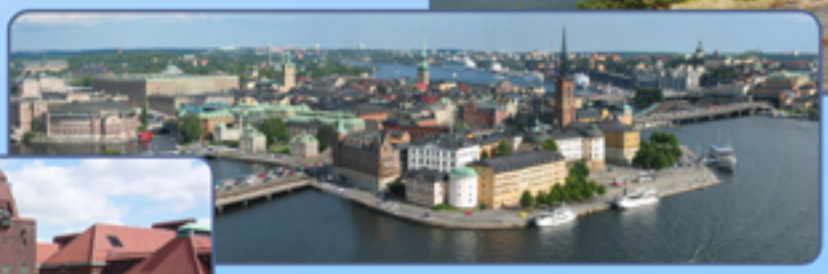

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Deger et al. BMC Neuroscience 2011, 12(Suppl 1):P273
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BMC Neuroscience

POSTER PRESENTATION Open Access

Effective neuronal refractoriness dominates the statistics of superimposed spike trains

Moritz Deger[1*], Moritz Helias[2], Clemens Boucsein[1], Stefan Rotter[1]

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The pooled spike trains of populations of neurons are typically modeled as Poisson processes [2]. It is known, though, that the superposition of point processes is a Poisson process if and only if all components are Poisson processes [3]. However, neocortical neurons spike more regularly [1]. Partly this is because they often have a refractory period, but also because the membrane potential is hyperpolarized after each spike, as illustrated in Figure 1A. Here we analyze neuronal spike trains recorded intracellularly *in vivo* from rat somatosensory cortex. We match them with a Poisson process with dead-time [4], which is the simplest model of neuronal activity that incorporates refractory effects. The dead-time here models the effective refractoriness of the neuron, which can be larger than the refractory period due to channel kinetics alone. From the spike train recordings we construct independent superpositions (see Figure 1B) and compare their statistics to our analytical results for the model processes. We find that the effective refractoriness of the neurons dominates the second-order statistics of the superposition spike trains. We uncover profound statistical differences as compared to Poisson processes, which considerably affect the dynamics of the membrane potential of neurons that receive such superpositions, as we further show in numerical simulations (see also [5]).

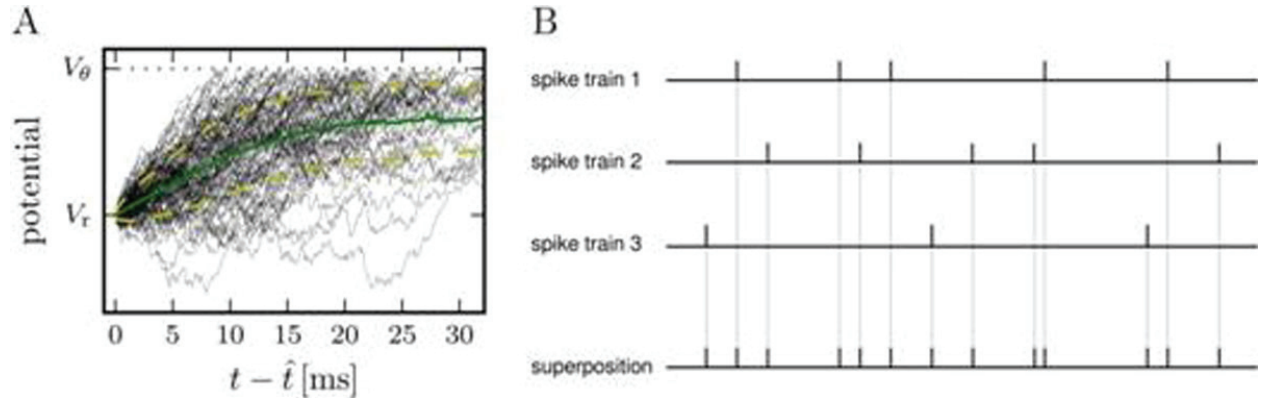

Figure 1 A: Membrane potential trajectories of a simulated neocortical neuron. After each spike, the potential has to charge up until spikes can be initiated by input fluctuations, leading to an effective refractoriness. Green line shows the mean subthreshold trajectory, yellow lines show mean +/- standard deviation. B: Scheme of the independent superposition of three spike trains. Adapted from [6].

* Correspondence: deger@bcf.uni-freiburg.de
[1]Bernstein Center Freiburg & Faculty of Biology, Albert-Ludwig University, 79104 Freiburg, Germany
Full list of author information is available at the end of the article

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Author details
[1]Bernstein Center Freiburg & Faculty of Biology, Albert-Ludwig University, 79104 Freiburg, Germany. [2]Laboratory for Computational Neurophysics, RIKEN Brain Science Institute, Wako City, Saitama 351-0198, Japan.

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Effect of network structure on spike train correlations in networks of integrate-and-fire neurons

Volker Pernice*, Benjamin Staude, Stefano Cardanobile, Stefan Rotter

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Balanced networks of excitatory and inhibitory neurons are a popular paradigm to describe the ground state of cortical activity. Although such networks can assume a state of asynchronous and irregular activity with low firing rates and low pairwise correlations, recurrent connectivity inevitably induces correlations between spike trains [1]. To elucidate the influence of network topology on correlations, we have recently employed the framework of linearly interacting point processes [2] as an analytically tractable model for network dynamics [3]. A power series of the connectivity matrix can be used to disentangle the different contributions to pairwise correlations from direct and indirect interactions between neurons.

In the present study we show that this framework can be applied to approximate dynamics of networks of integrate-and-fire neurons, if the reset after each spike is formally described as self-inhibition. The reset then effectively decreases overall correlations. We study ring networks, where we are able to derive analytical expressions for the distance dependence of correlations and fluctuations in population activity. Rates and correlations in simulated networks are predicted accurately, provided that spike train correlations are reasonably small and the linear impulse response of single neurons is known.

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* Correspondence: pernice@bcf.uni-freiburg.de
Bernstein Center Freiburg and Faculty of Biology, Albert-Ludwig-University, 79104 Freiburg, Germany

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POSTER PRESENTATION Open Access

Fail-safe detection of threshold crossings of linear integrate-and-fire neuron models in time-driven simulations

Susanne Kunkel[1,2*], Moritz Helias[3], Markus Diesmann[3,4,5], Abigail Morrison[1,2,3]

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Stockholm, Sweden. 23-28 July 2011

The characteristics of time-driven simulation are a fixed-size simulation step and a fixed-size communication interval [1]. The former defines update-and-check points, which are the discrete points in time when all neurons update their state variables and check for a super-threshold membrane potential. The latter defines the discrete points in time when all neurons communicate their spikes. The communication interval is a multiple of the simulation step size and limited only by the minimum synaptic transmission delay in the network.

The time-driven environment of the simulator NEST [2] provides an 'on-grid' and an 'off-grid' framework that handle spikes differently. In the on-grid framework, spikes are incorporated, detected and emitted only at the pre-defined update-and-check points. In the off-grid framework, spikes can be incorporated and emitted at any point in time [3]. For each neuron the arrival times of incoming spikes introduce additional update-and-check points. Hence, the simulation step can be increased up to the size of the communication interval. The detection of a threshold crossing can only take place at a check point, but the timing of the referring spike is estimated with precision limited only by the limits of double representation.

In general, a time-driven simulator that supports the off-grid framework performs neural network simulations with the same precision and faster than an event-driven simulator [4]. However, time-driven simulation still bears the risk of missing a threshold crossing as a very brief excursion of the membrane potential above threshold may not be detected at the next check point. In the off-grid framework, this problem is more pronounced in networks with low connectivity and strong coupling as well as in the case of low firing rates. The on-grid framework is even more affected due to fewer check points and the synchronized arrival of spikes.

Here, we present algorithms which are guaranteed to detect all threshold crossings by supplementing the standard test for a super-threshold membrane potential at each check point and that exploit the information about the neuronal state at nearby check points. These additional tests need to be invoked whenever the membrane potential is sub-threshold, which means at virtually all check points. We develop sub-tests of increasing complexity and specificity, starting with simple sifting methods and ending up with a complex expression that faithfully indicates the existence of a threshold crossing between the last and the current check point. An analysis of the test specificities and computational costs results in a cascade of tests which locates all threshold crossings at a low computational cost.

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Author details
[1]Functional Neural Circuits Group, Faculty of Biology, Albert-Ludwig University of Freiburg, Germany. [2]Bernstein Center Freiburg, Albert-Ludwig University of Freiburg, Germany. [3]RIKEN Brain Science Institute, Wako, Japan. [4]Institute of Neuroscience and Medicine (INM-6), Computational and Systems Neuroscience, Research Center Jülich, Germany. [5]RIKEN Computational Science Research Program, Wako, Japan.

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* Correspondence: kunkel@bcf.uni-freiburg.de
[1]Functional Neural Circuits Group, Faculty of Biology, Albert-Ludwig University of Freiburg, Germany
Full list of author information is available at the end of the article

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Identification of striatal cell assemblies suitable for reinforcement learning

Carlos Toledo-Suárez[1,2,4*], Man Yi Yim[2,3], Arvind Kumar[2,3], Abigail Morrison[1,2]

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Both in vivo [1] and in vitro [2] experimental data suggest that medium spiny neurons in striatum participate in the formation of sequentially firing cell assemblies, at a timescale relevant for the presumed involvement of basal ganglia in reinforcement learning. Computational models argue that such cell assemblies are a feature of a minimal network architecture of the striatum [3]. This suggests that cell assemblies can be a potential candidate for representation of the 'system states' in the framework of reinforcement learning.

Spike patterns associated with cells assemblies can be identified by clustering the spectrum of zero-lag cross-correlation between all pairs of neurons in a network [3]. Other methods based on the dimensionality reduction of the similarity matrix of the spike trains have also been used [2,4].

Here we investigate how the identification of cell assemblies is dependent on the methodology chosen, and to what extent the statistical properties of the cell assemblies make them suitable for representation of system states in the striatum during reinforcement learning.

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Author details
[1]Functional Neural Circuits Group, Faculty of Biology, University of Freiburg, 79104, Germany. [2]Bernstein Center Freiburg, University of Freiburg, 79104, Germany. [3]Neurobiology and Biophysics, Faculty of Biology, University of Freiburg, 79104, Germany. [4]Dept. Computational Biology, School of Computer Science and Communication, KTH, Stockholm, 10044,Sweden.

* Correspondence: carlos.toledo@bcf.uni-freiburg.de
[1]Functional Neural Circuits Group, Faculty of Biology, University of Freiburg, 79104, Germany
Full list of author information is available at the end of the article

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The impact of structural embeddedness of neurons on network dynamics

Ioannis Vlachos[1*], Ad Aertsen[1,2], Arvind Kumar[1,2]

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It is a common practice in experimental neuroscience to assess the statistical significance of spiking activity variations, measured from single or multiple neurons. For instance, in behavioral experiments, the probability of an increase in firing rate or correlation strength among a group of neurons is estimated under the assumption that an appropriately chosen null-hypothesis were true. If the probability for observing the experimental results under the null-hypothesis is small, the results are deemed statistically significant and the neural activity is assumed to be functionally related to the task. Thus, it is also implicitly assumed that the statistically significant neural activity must have some effect on the network dynamics. However, this tacit inference is not warranted a priori. That is, the fact that the recorded neuronal activity is not a chance event does not necessarily imply that it will have an impact on local or downstream network activity, particularly when the network is not homogeneously random. Therefore, any strong, or even causal association to behavior is not justified either.

We illustrate this largely ignored point by systematically analyzing the responses of 100 simulated spiking neuron networks, each composed of 10,000 neurons, to external stimulation. All networks had different topologies, however, the average connectivity parameters were kept constant. We measured the population activity and related it to network properties that characterize the way in which the stimulated neurons are embedded in their local environment. To estimate the embeddedness of neurons, we used known metrics from graph theory such as centrality and k-shell decomposition. Our results indicate that the impact neuronal events have on local or downstream network dynamics strongly depends on the *structural embeddedness* of participating neurons. We discuss potential implications of our findings for the analysis of neuronal activity. We also point out additional hurdles that need to be overcome in extracting network function, which go beyond knowledge of the structure and dynamics.

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Author details
[1]Bernstein Center Freiburg, University of Freiburg, Germany. [2]Neurobiology & Biophysics, Faculty of Biology, University of Freiburg, Germany.

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* Correspondence: vlachos@bcf.uni-freiburg.de
[1]Bernstein Center Freiburg, University of Freiburg, Germany
Full list of author information is available at the end of the article

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Uncorrelated inputs enhance signal representation in the inhibitory striatum network

Man Yi Yim[1*], Ad Aertsen[1,2], Arvind Kumar[1,2]

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Medium spiny neurons (MSNs) are the principal neurons in the striatum. The recurrent connections among them mediate weak feedback inhibition, whereas fast-spiking interneurons (FSIs) project extensively to the MSNs and provide strong feedforward inhibition. The striatum is innervated by massive excitatory afferents from various regions of the neocortex via the corticostriatal projection neurons. Interestingly, despite their strong convergence, corticostriatal projections are structured in such a way that neighboring MSNs in the striatum are not likely to share their presynaptic inputs [1].

To understand the functional consequences of such a corticostriatal connectivity structure we studied the representation of cortical inputs in a spiking neural network model of the striatum. Activation of a fraction of MSNs resulted in a corresponding decrease in the spiking of unstimulated neurons, due to the overall inhibitory nature of the striatum network. This was similar to the neuronal activity recorded in behaving rats [2]. Further, we found that correlations in the cortical inputs strongly influenced the transfer function of the striatum. Weak pairwise correlation within the input pool of individual striatal neurons enhanced the representation by increasing the signal-to-noise ratio (activity of stimulated vs. unstimulated neurons) in the striatum. By contrast, correlation among the input pools of different neurons weakened the representation, because the resulting synchronized inhibition was less efficient to silence the unwanted background activity. Interestingly, the structure of corticostriatal projections provides the conditions that minimize the correlation among the input pools of different MSNs.

MSNs can display short epochs of rapid firing, which may change their overall response to cortical inputs. Our simulation results suggest that the bursting activity of the MSNs did not affect the correlation dependence of the signal representation. Rather, it modulated the representation in a qualitative manner. In addition to the correlation of the excitatory inputs, synchrony within the inhibitory striatal network also influenced the signal representation. Specifically, we show that correlated feedforward inhibition mediated by FSIs, which might arise due to gap junction couplings, impaired the signal representation in the striatum. To date, experimental [3] and computational [4] studies suggest that feedforward inhibition is not correlated. According to our model, this supports an optimal representation of cortical inputs in the striatal network.

In summary, we showed that uncorrelated excitation and uncorrelated inhibition in the striatum support optimal signal representation, which, based on the anatomical and physiological findings, may be utilized by the striatum to enhance the encoding of cortical information for the execution of different cognitive functions.

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Author details
[1]Bernstein Center Freiburg, University of Freiburg, Freiburg, 79104, Germany. [2]Neurobiology & Biophysics, Faculty of Biology, University of Freiburg, Freiburg, 79104, Germany.

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* Correspondence: yim@bcf.uni-freiburg.de
[1]Bernstein Center Freiburg, University of Freiburg, Freiburg, 79104, Germany
Full list of author information is available at the end of the article

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Shaping corticostriatal connectivity with STDP

Jyotika Bahuguna[1,3*], Man Yi Yim[1,2], Ad Aertsen[1,2], Arvind Kumar[1,2]

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The striatum, the main input nucleus of the basal ganglia, is one of the major sites for learning and decision making. The striatum receives massive convergent inputs from the cortex. Task related cortical activity show weak pairwise correlations, thus, individual medium-sized spiny neurons (MSNs) in the striatum are very likely to receive correlated activity from the cortex. Surprisingly, although cortical neurons outnumber MSNs and each MSN receives around 10,000 cortical inputs, neighboring medium-sized spiny neurons (MSNs) in the striatum are not likely to share their presynaptic inputs [1]. This special arrangement of corticostriatal projections and their inputs is thought to be important to obtain a better signal representation in the striatum [2].

How does this specific anatomical structure of the corticostriatal projection come about? Corticostriatal synapses show a gamut of spike-time-dependent plasticity (STDP) rules which can influence the structure of these projections [3]. Therefore, here, we explored the functional consequences of different STDP rules in shaping the structure of the corticostriatal projections.

Specifically, we studied how the synaptic connections change when a striatal neuron receives a mixture of correlated and uncorrelated synaptic input spikes. Because a neuron is more likely to elicit a spike in response to coincident inputs, the synapses receiving correlated inputs are expected to strengthen over time, whereas those receiving uncorrelated inputs are expected to undergo long-term depression, due to the depression-dominated features of the STDP rule. Furthermore, recurrent inhibition among MSNs implies that STDP would also organize corticostriatal projections such as to reduce the input correlations and sharing of presynaptic neurons among MSNs coupled with recurrent inhibitory synapses. The detailed structure of corticostriatal projections, therefore, depends on the intricate statistics of the cortical inputs, recurrent connectivity and activity within the striatum.

In summary, here we show that standard STDP may explain the observed anatomical structure of the corticostriatal projections. Thus, an interplay of different corticostriatal STDP rules, together with the interactions in the network of MSNs and striatal interneurons, may encode signals from the cortex and modulate the activity of striatal neurons, in particular, the MSNs, which provide the striatal output to the downstream nuclei of the basal ganglia.

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Author details
[1]Bernstein Center Freiburg, University of Freiburg, Germany. [2]Neurobiology & Biophysics, Faculty of Biology, University of Freiburg, Germany. [3]Computational Biology, School of Computer Science and Communication, KTH, Stockholm, Sweden.

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* Correspondence: jyotika.bahuguna@bcf.uni-freiburg.de
[1]Bernstein Center Freiburg, University of Freiburg, Germany
Full list of author information is available at the end of the article

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Burst initiation and propagation in cortical cultures requires an inhomogeneous connectivity distribution and synaptic rescaling

Sarah J Jarvis[1,2*], Stefan Rotter[1,3], Ulrich Egert[1,2]

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Dissociated cortical cultures grown on microelectrode arrays (MEA) have been established as a useful biological model in the analysis of network dynamics. Their network dynamics are dominated by periods of strongly synchronized spiking, termed 'bursting', whose role is currently not understood. It has been demonstrated that bursts have different motifs and contain structure, refuting the possibility that they are merely chaotic activity. Of particular interest are the conditions required for bursting to initiate and propagate throughout the entire network. Within cultures, initiation sites can be well localized, even under varying experimental conditions such as cell density and network size. Propagation waves display fairly regular patterns of neuron recruitment within the network burst. However, in order to minimize bursting and promote closed-loop communication with the disassociated culture, it is of interest to understand what conditions are necessary for bursting to arise.

Interestingly, the propagation of bursts has been observed to be faster than can be accounted for by only local connectivity. While paired intracellular recordings have revealed some clues as to the local structure and short range connectivity, they were unable to clarify the contribution of long-range connectivity of neurons to burst propagation. Additionally, pharmacological studies which result in freezing of synaptic plasticity and impaired cell migration have demonstrated that modifications to connectivity can greatly alter the pattern of burst propagation.

As network structure has been established to strongly affect dynamics, we investigate the contribution of network features that can account for experimentally observed burst initiation and propagation patterns. Specifically, we examine the contribution of long-range connections within a 2D model network of spiking neurons representing a mature dissociated cortical culture. We previously demonstrated with networks of rate-based units that within clustered topologies, the relative number of long-range connection to cluster size greatly affects the robustness of the network to noise and ability to sustain activity [1], while including highly recurrent activity is required for fast ignition of activity from low-level background activity. Here, we extend these networks to a population of Integrate and Fire neurons and chart the effect of introducing inhomogeneities and a non-uniform distribution of connections, specifically the numbers and location of post-synaptic connections of each neuron. By driving the network with low levels of background activity, we observe the emergence of burst initiation sites and chart how different cluster configurations act to alter their location while simultaneously inspecting the velocity of burst propagation as it spreads throughout the network. Then, in keeping with recent evidence of synaptic reorganization in cortical cultures [2], we compensated the synaptic strength of neurons that received fewer presynaptic connections and noted how this increased the likelihood of inducing bursting. We compare burst profiles obtained in these simulations against their biological equivalents to identify the necessary topological features required.

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* Correspondence: jarvis@bcf.uni-freiburg.de
[1]Bernstein Center Freiburg, Freiburg 79104, Germany
Full list of author information is available at the end of the article

Author details
[1]Bernstein Center Freiburg, Freiburg 79104, Germany. [2]Biomicrotechnology, Department of Microsystems Engineering - IMTEK, University of Freiburg, 79110 Freiburg, Germany. [3]Computational Neuroscience, Faculty of Biology, University of Freiburg, 79104, Germany.

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Network inhomogeneity supports burst initiation in vitro

Samora Okujeni[1,2,3*], Nila Moenig[2], Steffen Kandler[1,2,3], Oliver Weihberger[1,2,3], Ulrich Egert[1,3]

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The emergence of spontaneous bursting events in developing neuronal networks likely depends on the evolving network connectivity. Theoretical models have shown that hierarchical network structures embedding clusters of strongly inter-connected neurons are optimal for initiating and sustaining spontaneous activity [1]. It is conceivable that activity-dependent wiring could innately support the formation of similar network structures.

To test this we chronically manipulated activity-dependent structural plasticity by inhibition of protein

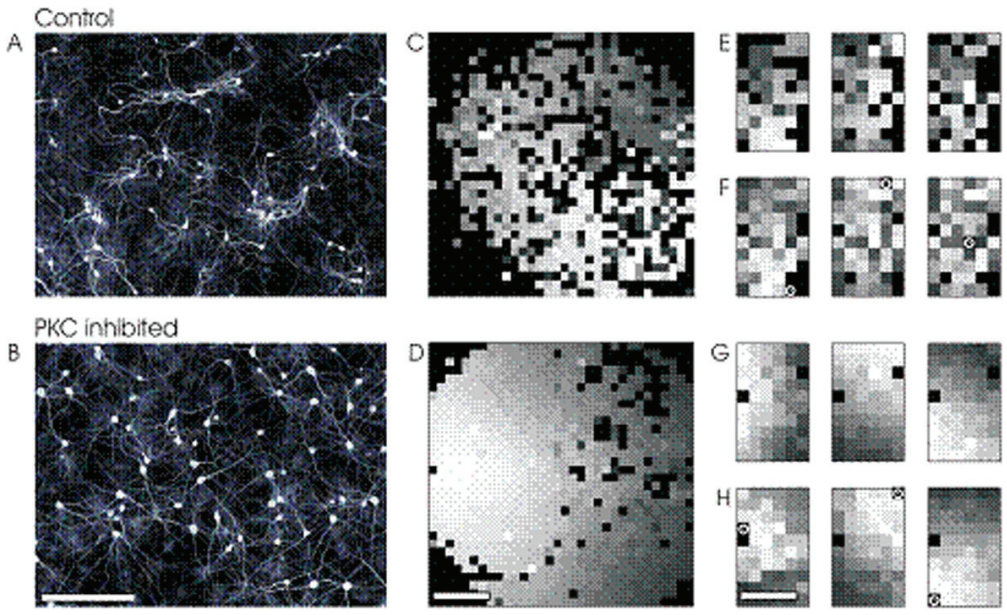

Figure 1 MAP2 staining of dendrites and somata: control networks (A) display characteristic features of an activity-dependent wiring process including fasciculation and ramification of dendrites within clusters. Developmental inhibition of PKC (B) generates more homogeneous networks in which neurites grow out ignoring neuronal neighbors. Propagation of activity in spontaneous and stimulation-induced bursts was analyzed in micro-electrode recordings (first spike rank order from light to dark gray; black: no activity; white circles indicate stimulation sites): bursts in control networks (C) display irregularities in the spatial propagation pattern indicating complex underlying structure. Homogeneous networks developing under impaired PKC activity (D) show highly isotropic propagation patterns. Spontaneous (E) and elicited (F) propagation patterns in controls are hardly comparable. Stimulation of homogeneous networks elicits highly isotropic propagation patterns (H) similar to those in spontaneous bursts (G). Scale bars: 2mm.

* Correspondence: okujeni@bcf.uni-freiburg.de
[1]Bernstein Center Freiburg, Univ. Freiburg, Freiburg, Germany
Full list of author information is available at the end of the article

kinase C (PKC) in developing networks of cortical neurons in vitro. Previous studies showed that PKC inhibition in developing cerebellum promotes dendritic outgrowth and arborization of Purkinje cells and impairs pruning of climbing fibers. We found that developmental inhibition of PKC in cortical cell cultures increased dendritic outgrowth, impaired neurite fasciculation and clustering and abolished network pruning. This resulted in more homogeneous and potentially better connected networks (fig. 1A-B). As a result, propagation of activity within bursts was faster and occurred in strongly isotropic waves (fig. 1C-D). Interestingly, bursts in these networks were triggered from fewer sites and at much lower rates suggesting that the homogeneous networks forming under blockade of activity-dependent wiring processes embed fewer burst initiation zones.

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Author details
[1]Bernstein Center Freiburg, Univ. Freiburg, Freiburg, Germany. [2]Fac. Biol., Univ. Freiburg, Germany. [3]Fac. Engineer. – IMTEK, Univ. Freiburg, Germany.

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BMC Neuroscience

POSTER PRESENTATION Open Access

High-resolution mapping of single neurons provides insight into neuron structure and LFP generation

Patrick Dini[1,2,3*], Maxime Ambard[1], Ulrich Egert[1,3], Urs Frey[4], Andreas Hierlemann[4]

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Recent modeling [1] has suggested that the spatial structure of single neurons, especially the orientation and the shape of their dendritic trees, is of great importance in the understanding of the properties of the LFP generated (for example, a low-pass filtering effect has been shown in remote neurites [2]). In order to test these predictions, high-density microelectrode arrays (MEAs) featuring 11'011 electrodes are a valuable tool [3]. They provide detailed information about the external electrical field potentials of cultured neurons, from which the relevant information about single neurons properties must be extracted. We developed an on-line software allowing us to track neurites of single neurons (Figure 1A-K, footprint of a neuron), which provides information about their spatial structure and their activity dynamics leading to predictions on their morphology (Figure 1L). These allow us to elucidate additional properties of LFP generation, such as, multi-polar potentials

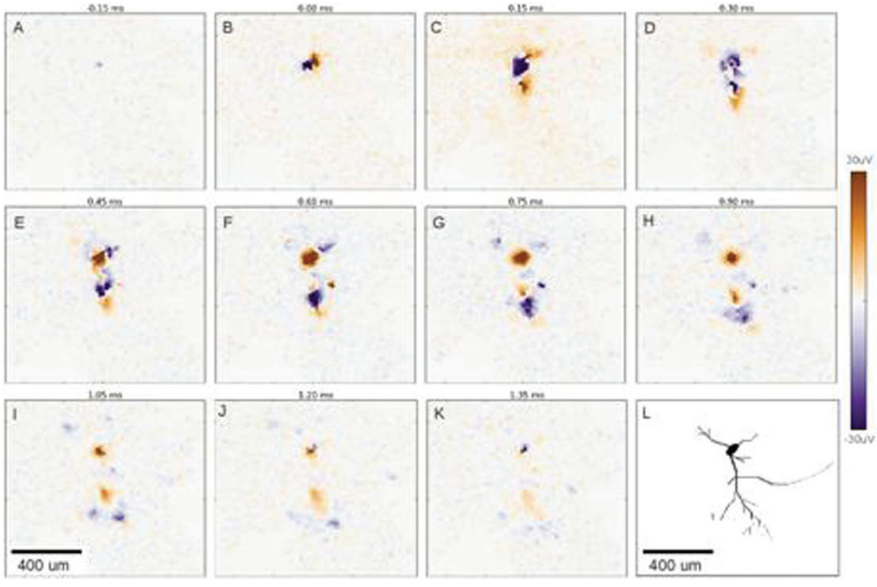

Figure 1

* Correspondence: patrick.dini@bcf.uni-freiburg.de
[1]Bernstein Center Freiburg, Albert-Ludwigs-University Freiburg, Freiburg 79100, Germany
Full list of author information is available at the end of the article

related to the morphology of the studied cell. Moreover, reconstruction of the morphology of different cells was performed based on footprints and compared with imaging from GFP-stained neural cultures.

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Author details

[1]Bernstein Center Freiburg, Albert-Ludwigs-University Freiburg, Freiburg 79100, Germany. [2]Institute of Biology III, Albert-Ludwigs-University Freiburg, Freiburg 79100, Germany. [3]Biomicrotechnology, Department of Microsystems Engineering, Albert-Ludwigs-University Freiburg, Freiburg 79100, Germany. [4]Bio Engineering Laboratory, Department of Biosystems Science and Engineering, ETH Zurich, Basel 4058, Switzerland.

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ORAL PRESENTATION Open Access

How local is the local field potential?

Henrik Lindén[1*], Tom Tetzlaff[1], Tobias C Potjans[2,3], Klas H Pettersen[1], Sonja Grün[2,4], Markus Diesmann[2,3,4], Gaute T Einevoll[1]

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The local field potential (LFP), usually referring to the low-frequency part of an extracellularly recorded potential (< 500 Hz), is nowadays routinely measured together with the spiking activity. The LFP is commonly believed to mainly reflect synaptic activity in a local population surrounding the electrode [1] but how large this population is, i.e. how many neurons contribute to the signal, is still debated. In this modeling study we investigate which factors influence the spatial summation of contributions that generate the LFP signal. A better understanding of this is crucial for a correct interpretation of the LFP, especially when analyzing multiple LFP signals recorded simultaneously at different cortical sites.

4We use a simplified two-dimensional model of a cortical population of neurons where the LFP is constructed as a weighted sum of signal contributions from all cells within a certain radial distance to the recording electrode. First we consider a general formulation of the model: if the single-cell LFP contributions can be viewed as current dipole sources [2], the single-cell amplitude will decay as $1/r^2$ with distance r to the electrode. On the other hand, for the two-dimensional geometry considered here, the number of neurons at a given distance increases linearly with r. In addition to these two opposed scaling factors the amplitude of the summed LFP signal also depends on how correlated the single-cell LFP sources are. We calculate the LFP amplitude as a function of the population radius and relate it to the above factors. We show that if the single-cell contributions decay as dipole sources or more steeply with distance, and if the sources are uncorrelated, the LFP is originating from a small local population. Cells outside of this population do not contribute to the LFP. If, however, the different LFP sources are uniformly correlated, cells at any distance contribute substantially to the LFP amplitude. In this case the LFP reach is only limited by the size of the region of correlated sources. This result highlights that the spatial region of the LFP is not fixed; rather it changes with the dynamics of the underlying synaptic activity.

We further validate these results through LFP simulations of morphologically reconstructed cortical cells [2-4] where we study the effects of neuronal morphology on the size of the region contributing to the LFP. Finally, we show the laminar dependence of the reach measure used here and discuss potential implications of the interpretation of experimentally recorded LFPs.

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Author details
[1]Dept. of Mathematical Sciences and Technology, Norwegian University of Life Sciences, Ås, 1432, Norway. [2]Institute of Neuroscience and Medicine, Computational and Systems Neuroscience (INM-6), Research Center Jülich, Jülich, 52425, Germany. [3]Brain and Neural Systems Team, RIKEN Computational Science Research Program, Wakoshi, Saitama, 351-0198, Japan. [4]RIKEN Brain Science Institute, Wakoshi, Saitama, 351-0198, Japan.

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* Correspondence: henrik.linden@umb.no
[1]Dept. of Mathematical Sciences and Technology, Norwegian University of Life Sciences, Ås, 1432, Norway
Full list of author information is available at the end of the article

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BMC Neuroscience

ORAL PRESENTATION Open Access

State-dependent modulation of stimulus-response relations in cortical networks in vitro

Oliver Weihberger[1,2,3*], Ayal Lavi[4], Samora Okujeni[1,2,3], Uri Ashery[4], Ulrich Egert[1,3]

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Variable responses of neuronal networks to repeated identical electrical or sensory stimuli reflect the interaction of the stimulus' response with ongoing activity and its modulation by adaptive mechanisms such as cognitive context, network state, cellular excitability or synaptic transmission capability. To identify the rules that underlie the modulation of stimulus-response relations we set up a state-dependent stimulation paradigm in generic neuronal networks *in vitro*.

Extracellular neuronal activity was recorded and stimulated from rat cortical cell cultures on microelectrode arrays at 60 sites. Spontaneous and evoked network activity was examined under control conditions, under blockage of $GABA_A$-receptors as well as under overexpression of the synaptic protein DOC2B [1]. We were interested in the interactions that arise between spontaneous and stimulus-evoked activity dynamics and how these shape and modulate stimulus-response relations.

Spontaneous network activity consisted of recurring periods of globally synchronized burst firing, so-called network bursts. The duration of intervals that preceded network bursts best predicted the length of the following network burst. This supported a process of network depression to a low threshold during bursts followed by subsequent recovery [2]. Facilitation of synaptic transmission by overexpressing DOC2B yielded ~30 % more spikes per network burst. The intervals between bursts increased by ~ 75 %, suggesting interdependence between resource activation and the time it needs for them to be recovered.

Response length and delay depended on the timing of stimulation relative to preceding bursting. Response length increased exponentially and saturated with increasing duration of pre-stimulus inactivity t, $y(t) = A(1-e^{-\alpha t})$. Response delay, in turn, decreased exponentially and saturated at a low level, $y(t) = Be^{-\beta t} + C$. The rate constant β describes the coupling between recovery from depression and response delay. We found activity-dependent recovery dynamics with longer spontaneous bursts yielding smaller β and vice versa.

Stimulus-response modulation persisted under the blockage of inhibition, that introduced overall longer responses and shorter delays. Longer network bursts with more spikes occurred less frequently and recovery rates concomitantly decreased. The average firing rate was, however, unchanged, supporting a pool of available resources that is repeatedly used and replenished during and between network bursts, respectively.

Conclusion

The timing of stimulation relative to spontaneous bursting modulates stimulus-response relations in cortical networks *in vitro* following distinct rules. The interrelation between resource depletion and replenishment determines the temporal evolution of the network's excitability state. Our findings can be explained by short-term synaptic depression and activity-dependent adaptation of excitability as underlying mechanisms.

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Author details
[1]Bernstein Center Freiburg, University of Freiburg, Freiburg, 79104, Germany. [2]Faculty of Biology, Neurobiology and Biophysics, University of Freiburg, 79104 Freiburg, Germany. [3]IMTEK – Dept. of Microsystems Engineering, University of Freiburg, Freiburg, 79110, Germany. [4]Deptartment of Neurobiology, Tel Aviv University, Tel Aviv, 69978, Israel.

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* Correspondence: weihberger@bcf.uni-freiburg.de
[1]Bernstein Center Freiburg, University of Freiburg, Freiburg, 79104, Germany
Full list of author information is available at the end of the article

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