Abstracts

Random Structures on the Brain

Monday 4 December 2017

Cortical connectivity: quantitative anatomical data from mouse, man and monkey

Almut Schüz

The most characteristic feature of the cerebral cortex is its rich connectivity in itself, based predominantly on excitatory connections. These are comprised of short- and middle-range connections within the grey matter and long-range connections, mainly via the white matter. Together with the fact that the connections are modifiable in strength, this qualifies the cortex for all kinds of associative functions [1]. Here I will briefly summarize quantitative data on short- and middle-range connections [1,2] and then deal with cortico-cortical long-range connectivity. I will show data on the global connectivity of the mouse cortex, based on tracer injections [3], and then focus on the human cortical white matter. The number of fibers in the deep intrahemispheric bundles, connecting the different lobes is similar to the number of fibers connecting the two hemispheres. Both of them constitute, however, only a small percentage of the total number of long-range connections via the white matter [4]. Electron microscopic data show the large range of axonal diameters in these bundles, indicating a large range of conduction velocities in cortico-cortical axons [5]. Such data are relevant for understanding functional interactions within the cortical network and the role of conduction times in it. They are also be useful for testing diffusion weighted imaging methods for tractography and for measuring axonal diameters in vivo.

[1] Braitenberg V, Schüz A (1998) Cortex: Statistics and Geometry of Neuronal Connectivity, 2nd edition, Springer Berlin, Heidelberg
[2] Voges N, Schüz A, Aertsen A, Rotter S (2010) A modeler's view on the spatial structure of intrinsic cortical connectivity in the neocortex. Progress in Neurobiology 92, 277-292
[3] Schüz A, Chaimow D, Liewald D, Dortenmann M (2006) Quantitative aspects of corticocortical connections: a tracer study in the mouse. Cerebral Cortex 16, 1474-1486
[4] Schüz A, Braitenberg V (2002) The human cortical white matter: quantitative aspects of cortico-cortical long-range connections. In: Cortical Areas: Unity and Diversity, A. Schüz and R. Miller (eds) Taylor & Francis, London, New York
[5] Liewald D, Miller R, Logothetis N, Wagner H-J, Schüz A (2014) Distribution of axon diameters in the cortical white matter: an electron-microscopic study in three human brains and a macaque. Biological Cybernetics 108(5) 541-557

Aspects of the multi-scale hierarchical organization of macaque visual cortex

Markus Diesmann

The cortical network exhibits organization on multiple levels, from motifs in the connections of nearby neurons, to the layers of the cortical microcircuit and the spatial structure of cortical areas, to the network of areas. These levels have been extensively characterized individually, but an integrated view is missing. In particular, it has been known for a long time that cortical architecture, the area-specific cellular and laminar composition of the network, is related to the connectivity between areas, forming a hierarchical and recurrent network at the brain scale. Based on our work on the cortical microcircuit [1], our recent study [2] integrates data on cortical architecture and axonal tracing data into a multi-scale framework describing one hemisphere of macaque vision-related cortex. The model is a random structure as connections are specified by probabilistic rules on the level of neuronal populations. Statistical regularities estimate connection strength where measurements are unavailable. The connectivity matrix is therefore a combination of experimental data and statistical predictions.

Simulating multi-area models at the level of resolution of neurons and synapses still taxes the largest supercomputers available [3], but downscaling entails the danger of perturbing the higher-order statistics of neuronal activity [4]. The latter is relevant because correlations drive the fluctuations observed in mesoscopic measures like the local-field potential (LFP) and the EEG. As a compromise between these two constraints, we investigate a model where each area is represented by the network below a square millimeter of cortical surface. These circuits capturing the majority of the local connections are modelled at full density, i.e., with their natural number of neurons and synapses. The resulting network contains a few million neurons and can be simulated on common high-performance computing systems using NEST [5]. The dynamics of the network unfolds in a physiologically realistic regime after adjustments of the connectivity within the margins of error [6]. At a sufficiently large coupling between the areas, spike patterns, the distribution of spike rates, and the power spectrum of spiking activity are compatible with in-vivo resting-state data. Furthermore, the matrix of correlations between the activities of areas is more similar to the experimentally measured functional connectivity of resting-state fMRI than the anatomical matrix. This correspondence on multiple spatial scales is achieved in a metastable state of activity where neuronal populations exhibit fluctuations of activity on time scales much larger than the time constants of the single-neuron dynamics.
As previously done for our microcircuit model [1], we are presently working on a machine-readable formal model description so that we can make the multi-area model [2] available as an open-source platform and building block for further studies.
The open development of NEST is guided by the NEST Initiative. Partial funding comes from the Human Brain Project through EU grants 604102 and 720270.
[1] Potjans TC., Diesmann M. (2014). The cell-type specific cortical microcircuit: relating structure and activity in a full-scale spiking network model. Cerebral Cortex 24:785–806
[2] Schmidt M, Bakker R, Hilgetag CC, Diesmann M, van Albada SJ (2017) Brain Structure and Function, in press
[3] Kunkel S, Schmidt M, Eppler JM, Plesser HE, Masumoto G, Igarashi J, Ishii S, Fukai T, Morrison A, Diesmann M, Helias M (2014) Front in Neuroinform 8:78
[4] van Albada SJ, Helias M, Diesmann M (2015). PLOS Comput Biol 11:e1004490
[5] Gewaltig M-O & Diesmann M (2007) NEST (Neural Simulation Tool) Scholarpedia 2(4):1430
[6] Schuecker J, Schmidt M, van Albada SJ, Diesmann M, Helias M (2017). PLOS Comput Biol 13:e1005179

Interplay between network architecture and single neuron dynamics in shaping the spontaneous activity of cortical models

Antonio C. Roque

The spontaneous cortical population activity is characterized by irregular firing of individual neurons and population oscillations with a broad frequency range. A question which arises in this context is whether and how these activity patterns depend on the interplay between the structural organization of the network and the intrinsic characteristics of the cortical neurons. To approach this problem, we have used computer simulations of cortical network models with hierarchical modular architecture composed of mixtures of excitatory and inhibitory neurons with different intrinsic firing behaviors. The neurons belonged to the five main electrophysiological cell classes found in the cortex: the excitatory regular spiking, chattering and intrinsically bursting neurons, and the inhibitory fast spiking and low threshold spiking neurons. In the region of the parameter space where the inhibitory synaptic strength exceeds the excitatory synaptic one, we observed spontaneous activity states with spiking characteristics similar to the ones observed experimentally. In the absence of intrinsic synaptic noise, these states have finite lifetimes (are transient) and display population activity oscillations with alternating high and low global-activity epochs followed by abrupt unpredictable decay toward the resting state. The lifetime expectancy depended on network modularity, on mixture of neurons of different types, and on excitatory and inhibitory synaptic strengths. For fixed network parameters the lifetimes of the transient states obey exponential distributions. Introducing noise into the dynamics of synaptic variables, we observe that the noise-affected network activity, which is no longer transient, displays alternations between collective oscillations and quiescent states with irregular transitions between them. We explain the observed dynamic patterns by using a

phenomenological global description of the network state combined with local descriptions of individual neurons in their single-neuron phase space. By dissecting the model we are able to determine network and intrinsic neuronal mechanisms responsible for the spontaneous activity patterns observed in the simulations. This provides a way to bridge between network and neuronal activity states and how they influence each other.

Randomness and determinism in the shape of the brain
Julien Levèvre

Thinking about the appearance of the human brain, a clear image comes to mind with a lot of folds that give a labyrinthine aspect. Since the first steps of neuroanatomy, researchers have been puzzled by the organization of sulci and gyri and their underlying relationships with brain functions. Like fingerprints, cortical folding pattern are unique to everyone, in particular for monozygotic twins, and are the result of a developmental process and a coordinated action of a genetic program and environmental factors. There are also increasing evidences that neurodevelopmental diseases can have an impact in the way the cortical folds appear, from massive effects in microcephaly or corpus callosum agenesis to more subtle ones in autism or psychiatric disorders.

Modeling of the cortical folding pattern and its morphogenesis is therefore of great interest, both in a clinical perspective and in a more fundamental approach. I will illustrate those points by several results obtained in the five past years. In particular I will insist on two key aspects:
1) the intriguing relationship between global features of the brain (size, growth) and more local ones (cortical folds).
2) the constant need of new mathematical tools from Geometry, Partial Differential Equations or Harmonic Analysis to tackle those neuroanatomical questions.

Tuesday 5 December 2017

On oscillating systems of interacting neurons
Eva Löcherbach

We consider multi class systems of interacting nonlinear Hawkes processes, modeling several large families of neurons. We prove propagation of chaos for such systems and associated central limit theorems. Moreover, we discuss situations in which the limit system exhibits oscillatory behavior. Finally, we show how these results can be related to certain PDMP's (piecewise deterministic Markov processes) and the study of their longtime behavior. This is a joint work with Susanne Ditlevsen.

On age dependent Hawkes processes modeling spike trains of neurons
Mads Bonde Raad

In the last decade, Hawkes processes (also sometimes called self-exciting point processes) have received a lot of attention in the neuroscience community as good models for functional connectivity in neural spiking networks. In this talk I will consider a variant of this process, which is the age dependent Hawkes process

incorporating individual post-jump behavior into the frame of the usual Hawkes model and allowing, e.g. to model a refractory period. I will speak about two topics. Firstly, when the interactions between neurons are of mean field type, I study large network limits and establish the propagation of chaos property of the system. Second, I discuss how classical stability results for Hawkes processes can be improved by introducing age into the system.

On periodic signals in stochastic Hodgkin-Huxley models
Reinhard Höpfner

We consider a stochastic Hodgkin-Huxley model where dendritic input –modelled as an autonomous SDE which depends on a deterministic T-periodic signal $t \to S(t)$ encoded in its drift– is the only source of noise. This amounts to a 5d random system driven by 1d Brownian motion. We do have criteria to prove positive Harris recurrence (ergodicity) for systems of this type ([2], [3], [1]). As a consequence, we dispose of strong laws of large numbers for the system. In particular, we can describe the spiking activity of the neuron in the long run using strong laws of large numbers.

Let τn denote the beginning of the n-th spike. Whereas successive interspike times $\xi n := \tau n+1 - \tau n$ have no reason to be independent, there is a Glivenko-Cantelli theorem ([2]) for the sequence $(\xi n) n \geq 1$: empirical distribution functions Fn converge as $n \to \infty$ to some honest limit distribution function F. This limit F characterizes the spiking behaviour of the neuron in the long run. It depends on the modelization of the dendritic input, in particular on the signal $t \to S(t)$ encoded in its drift.
We are interested in statistical inference on the unobserved deterministic signal $t \to S(t)$, assuming that the Hodgkin Huxley neuron can be observed over a long time interval.
Large parts of the talk are joint work with Eva Löcherbach and Michèle Thieullen.

[1] R. Höpfner, E. Löcherbach, M. Thieullen: Ergodicity for a stochastic Hodgkin-Huxley model driven by Ornstein-Uhlenbeck type input. AIHP **52** (2016), 483–501
[2] R. Höpfner, E. Löcherbach, M. Thieullen: Ergodicity and limit theorems for degenerate diffusions with time periodic drift ... stochastic Hodgkin-Huxley model. ESAIM P+S **20** (2016), 527–554
[3] R. Höpfner, E. Löcherbach, M. Thieullen: Strongly degenerate time inhomogeneous SDEs: Densities and support properties. Bernoulli **23** (2017), 2587–2616
[4] S. Holbach: Local asymptotic normality for shape and periodicity in the drift of a time inhomogeneous diffusion. SISP (2017+) DOI 10.1007/s11203-017-9157-5

Building an Understanding of the Cortical Rich Club Through Model Simulations
Mario Senden

The brain's structural connectivity contains a set of densely interconnected hub regions, collectively termed the rich club. These regions mediate a majority of all anatomical paths between pairs of brain regions and have been hypothesized to form a central high-capacity backbone for brain communication. As such they could play a crucial role for the integration of functionally specialized (peripheral) brain regions into transient functional networks. In order to investigate this putative role of the rich club it is necessary to establish that a structural rich club can affect functional network formation in a meaningful way and to suggest potential mechanisms through which it might do so. The former requires systematic manipulation of structural connectivity to identify which aspects of functional network formation might be the result of the rich club phenomenon as compared to other network properties of the brain (such as small-worldness). The latter requires an investigation of local dynamics exhibited by rich club regions as well as their contribution to information propagation within the brain network. Whole-brain computational models serve as invaluable tools in each of these cases. Not only are they fully manipulable but able to distinguish

between the contribution of local dynamics and network effects to the behavior of the system as a whole. Furthermore, their parameters can have mechanistically meaningful interpretations.
Like with any other modeling approach, the application of whole-brain models to study the cortical rich club involves three consecutive steps. The first step, denotation, establishes a representation relation between the target system and the model of choice. This involves a validation of the ability of the model to serve as a proxy for the target system such that the question of interest about the target can be meaningfully addressed within the model. The second step, demonstration, involves a thorough investigation of the model in order to address the aforementioned question and demonstrate an effect. The final step, interpretation, converts what has been learned about the model back to the target system such that conclusions about the model ought to constitute conclusions about the target system.
In my talk, I will present three modeling studies on the contribution of the rich club phenomenon to functional network formation and cortex-wide communication. I will pay specific attention to the denotation, demonstration, and interpretation stages in each of these studies. The first study uses a steady-state attractor model to investigate to what extent the rich club phenomenon contributes to the diversity of the brain's functional repertoire over and above the effects produced by other network topologies. The second study investigates the local dynamics the rich club as well as other brain regions need to exhibit in order to fit (dynamic) network behavior empirically observed for resting and a range of task states. Specifically, I will raise the question whether low-frequency oscillations exhibited by rich-club regions can contribute to functional coupling among peripheral brain regions. The third study analyzes task-dependent input and output effective connectivity of the rich club and relates these to information exchange among peripheral brain regions.

Wednesday 6 December 2017

Modeling structure and function of complex networks and the brain

Remco van der Hofstad

Since 1999, network science has clearly established itself as one of the most interdisciplinary fields in science. In this talk, we discuss the structure of complex networks in general, before zooming into their recent applications to the brain.

Empirical findings have shown that many real-world networks share fascinating features. Indeed, many real-world networks are small worlds, in the sense that typical distances are much smaller than the size of the network. Further, many real-world networks are scale-free in the sense that there is a high variability in the number of connections of the elements of the networks. Therefore, such networks are highly inhomogeneous.

Spurred by these empirical findings, random graph models have been proposed for such networks. In this course, we discuss several empirical findings of real-world networks such as the Internet and the World-Wide Web, and describe some of the models proposed for them. We then focus on some of the topological features of these models, such as their small-world behavior and clustering, and compare the results to the empirical evidence.

Arguably the largest and least understood complex network is the brain viewed as a collection of interconnected neurons. We discuss some of the network representations of the brain, as well as models that have been proposed for it. Then we speculate on key aspects of models to be used for the structure and functioning of the brain.

Dynamical neuronal networks of the biological clock

Jos Rohling

Understanding how neurons and brain regions communicate, coordinate, synchronize, and collectively respond to signals and perturbations is one of the most intriguing, yet unsolved problems in neuroscience. We investigate one brain area that is involved in time regulation of the body.

The biological clock is a relatively small brain network containing approximately oscillating 20,000 neurons, of which the output on all levels can be captured solely by its phase, period and amplitude. For the clock, experimental data is available for different levels of organization, from behavioural data to ensemble electrical activity data of groups of neurons, to single cell molecular data. Using our groups' ability to measure at all levels of organization (behaviour, in vivo electrical activity, ex vivo electrical activity, ex vivo calcium imaging, ex vivo gene expression), we are able to link the (rest-activity) behaviour of the animal with the activity of the single neurons.
The controllable output parameters of phase, period and amplitude characterize the clock completely, providing the perfect opportunity for research on brain networks on the microscopic neuronal level, as opposed to macroscopic brain network research that investigates networks between brain regions connected by bundles of axon fibers. Whereas it is difficult to define the nodes for macroscopic brain networks, we are able to identify single neurons and define them as nodes in the network. The challenge is to obtain functional and anatomical methods to identify connections between these nodes, and define the edges in the network. We have used a number of analytical methods to identify network properties of the clock, such as clustering methods based on random matrix theory, and detrended fluctuation analysis to determine temporal power-law characteristics.
A complicating factor is that this functional network is not static during its oscillatory cycle: for example, the network appears to be different between day and night time. The dynamical nature of the network is normally not taken into account in network studies. I will discuss our latest results, highlighting the advances that were made in recent years, but also discuss the challenges we still face in this field.

Phase Computation in the Motor System

Mario Negrello

Despite being at the core of the brain and at the core of brain function, not much is known about the processing schemes of the essential mesencephalic nuclei. In terms of neuro-architecture they are generally simpler than cortices, with fewer cell types and more homogeneous connectivity. This poses challenges to a standard computational view of their function.

We have undertaken to discover the capabilities of the inferior olivary nucleus of the cerebellum, known to be essential to limb coordination, motor timing and smooth movements. The inferior olive is a center piece of the cerebellar system and is thought to produce teaching signals to for cerebellar motor learning. It is composed of intrinsic oscillator cells which receive converging glutamatergic and gabaergic input, from the cerebellum, and the diencephalic junction respectively. These inputs encounter the ongoing dynamics of the inferior olivary neurons, which they shape and modulate through phase shifts and resets.

From a detailed computational model of olivary tissue, strongly constrained by anatomical and physiological data this research focuses on the interaction between the spiking streams as they arrive differentially on the somata, dendrites and glomeruli of the inferior olivary neurons. The Hodgkin-Huxley type network model includes all neurons in one half of the inferior olive nuclei, with somata positions, dendritic fields and gap junctions derived from large-scale anatomical reconstructions of both the inferior olivary neurons, as well as the descending axonal arborizations from gabaergic and glutamatergic projections.

The modeling experiments, which inquire on the interaction between these input streams, produce strong predictions about a cohort of enigmatic aspects of olivary dynamics, i.e., the low firing rates (~1Hz), unreliable response to sensory stimulus(<<50% of trials), the unexpectedly synchronous firing of olivary spikes, as well as the shape of the olivary Calcium spike (i.e., spikelets).

Through dynamical systems modeling and anatomical measurement, we believe to have uncovered fundamental operational potentialities of the inferior olivary nucleus, one of the three main components of the cerebellar system. Due to its cellular properties and arrangement, the inferior olive can transiently store and maintain phase differences in subpopulations of the nucleus, in dynamically organized clusters. The model is embedded within a view of cerebellar function that purports to explain motor function of inferior olive on the scales of motor behavior and adaptation. The results allow me to propose integrative hypotheses about the most clinically relevant aspects of cerebellar dysfunction represented by hypertonias, hypotonias and intentional tremors.

Thursday 7 December 2017

Multiscale modeling for brain disease

William W. Lytton

Abstract: Multiscale modeling has arisen as a focus of computational systems biology, with the realization that genome, proteome, connectome, etceteromes, will only become comprehensible once placed in the context of explicit computer simulations.
Measurements and activity patterns at one scale must be understood dynamically in the context of patterns at higher and lower scales. Nowhere is this more apparent than in the domain of brain disease, where manipulations at molecular levels
(drugs) are used to change, licitly or illicitly, behavior and thought. We have begun to study schizophrenia and other brain dysfunctions with an eye towards connecting these levels in order to reveal functional and dysfunctional dependencies.
Rather than only thinking hierarchically up the great chain of embeddings (e.g. from molecule to spine to dendrite to cell to circuit to area to behavior), it will be valuable to transform to other representational frames to connect across multiple scales.

On a toy network of neurons interacting through nonlinear dendritic compartments

Romain Veltz (with N. Fournier and E. Tanré)

The dendrites of many neurons are endowed with active mechanisms which confer them properties of excitability and enable the genesis of local dendritic spikes. In this work, we consider the propagation of dendritic spikes in a dendrite composed of a single branch. These local dendritic spikes are due to voltage dependent ion channels (i.e. sodium, calcium or NDMA spikes). Because the dendritic compartments are connected through a linear cable equation, dendritic spikes propagate in both sides, although with possibly different speeds. Two dendritic spikes propagating in opposite directions will cancel out when they collide as in the case of the axon because of the refractory period.

We focus on an abstract description of this nonlinear behaviour which is more amenable to analysis. This description reveals a rich mathematical structure that we study through the use of combinatorics. This also provide an algorithm for an efficient simulation. In passing, we link this description to the famous Ulam problem opening the door for a mean field model.

Whenever a dendritic spike reaches the soma, it triggers a depolarization. For simplicity, we put a spiking mechanism in the soma as a generalised integrate and fire model. We call such model, a Ball-and-Stick (BaS) neuron. We then study the large N limit of networks of N excitatory BaS neurons. Among other findings, we are able to extract the right scaling for the synaptic weights which allows to have a large N limit which we derive. Numerical simulations are presented for cases not covered by our mathematical results.

This is one of the first work on mean field limits of networks of spiking neurons with a dendritic branch.

Statistical analysis of retinal responses
Bruno Cessac

The retina, located at the back of the eye, converts the light coming from a visual scene into sequences of impulses (spikes) conveyed to the brain by the optic nerve, and interpreted by the visual cortex. This process involves multi scale biophysical dynamics: molecular level, cellular level (neurons), network of neurons. Recent technological advances allow to record simultaneously the spiking activity of thousands of neurons in the retina. This is a step toward understanding how the retina encodes a visual stimulus in a parallel stream of spikes.
The statistical analysis of these data requires however elaborated methods. I will present examples of such methods constructed from variable length markov chains, non equilibrium statistical physics and information geometry with applications to real data analysis.

Causal inference on brain networks using Gaussian processes with causal kernels (GP CaKe)
Max Hinne

Causal inference on brain networks, i.e. determining effective connectivity, typically outputs a graph with edge weights indicating the evidence for the presence of a connection. However, causal interactions between brain regions are not instantaneous, but can have interesting temporal patterns. For example, an interaction may be absent, then weakly inhibitory, then excitatory and finally dampening out. In this talk, I will present a novel framework for effective connectivity based on Gaussian processes with appropriately constructed causal kernels (with the tasty acronym of GP CaKe). The method can be seen as a nonparametric generalization of dynamic causal modelling, while retaining the flexibility and efficiency of autoregressive models. In the talk I will explain how kernels may be constructed to enforce interactions to be localized in time, be causal and be temporally smooth, and demonstrate the method on EEG alpha oscillations.

Friday 8 December 2017

Exact simulation of the jump times for a class of Piecewise Deterministic Markov Processes. Application to the exact simulation of the spiking times for a class of stochastic Hodgkin-Huxley models

Michèle Thieullen

In my talk I will consider stochastic Hodgkin-Huxley models which belong to the family of Piecewise Deterministic Markov Processes (PDMP). These models are built on the gating properties of an Hodgkin-Huxley neuron with a finite number of channels. I will focus on the exact simulation of the jump times and in particular of the spiking times. We propose different numerical schemes and we compare them in terms of their efficiency. Our results are general and apply to a large class of PDMP.
This is joint work with my colleagues Vincent Lemaire and Nicolas Thomas at LPMA, UPMC.

Fitting a stochastic neural network model to real data

Christophe Pouzat (Ludmila Brochini, Pierre Hodara and Guilherme Ost)

The first relay of the insect olfactory system–the /antennal lobe/–is now a well-established model of first olfactory relays in general: its synaptic organization as well as neuronal types diversity are very similar to what is found in vertebrates. But it is much easier to get stable recordings /in vivo/ from insects than from vertebrates and recording of the order of 1% of the active neurons in the antennal lobe can be done routinely. We will use here freely available datasets containing /extracellular recordings/ from the locust, /Schistocerca americana/ ([https://zenodo.org/record/21589]). These datasets contain both spontaneous and odor evoked activity from many (5 to 10) neurons recorded simultaneously. Since the data give access to the output of the recorded neurons: the /spike trains/, as opposed to the membrane potential–provided by other recording techniques–, estimating the spike rate or intensity of each neuron makes sense. We will show how stochastic intensity models belonging to a class introduced by D. Brillinger (1998) and enjoying a recent surge of analytical results (starting with Galves and Löcherbach, 2013) can be specified and fitted by likelihood maximization, both in the spontaneous and odor evoked regimes. The principle and results of the goodness of fit tests for spike train data will also be presented and the problems posed by the interpretation of the model components will be discussed.