

# **2nd Nordic Neuroinformatics Workshop**

*SKIPHELLE, SEPTEMBER 17th-19th, 2004*

## **PROGRAM**

## **LIST OF PARTICIPANTS**

## **ABSTRACTS**

## **ORGANIZERS**

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## **SPONSORS**

Nordic Institute for Theoretical Physics (NORDITA)  
University of Oslo  
Agricultural University of Norway

## PROGRAM

### Friday, September 17th

- 18:30-18:45 **Opening of meeting, welcome address**  
18:45-19:30 Erik De Schutter, U. Antwerp: *Modeling excitability and plasticity in cerebellar Purkinje cells*  
20:00 DINNER

### Saturday, September 18th

- 08:00 BREAKFAST  
09:00-09:45 Nicolas Brunel, CNRS-URD, Paris: *Dynamics of local cortical networks*  
09:45-10:05 Anders Lansner, KTH, Stockholm: *A large-scale biophysically detailed cortical attractor network model with a mini- and hypercolumnar organization*  
10:05-10:25 Erik Fransén, KTH, Stockholm: *Ionic mechanisms in working memory and information processing in the entorhinal cortex of the medial temporal lobe*  
10:25-10:45 Jeanette Hellgren Kotaleski, KTH, Stockholm: *Temporal computation by biochemical networks – classical conditioning and reinforcement learning*  
10:45-11:10 COFFEE BREAK  
11:10-11:30 John Hertz, NORDITA, Copenhagen: *Neocortical circuitry as a dynamical spin glass*  
11:30-11:50 Gaute T. Einevoll, NLH, Ås: *Measuring and modelling cortical population dynamics from laminar-electrode data*  
11:50-12:10 Patrik Hoyer, Univ. of Helsinki: *A sparse coding network learns both V1 receptive fields and topography from natural images*  
12:10-12:30 Hans E. Plesser, NLH, Ås: *Simulating large neuronal networks with NEST*  
12:30 LUNCH BREAK  
15:00-15:45 Rolf Kötter, Heinrich-Heine Univ., Düsseldorf: *The CoCoMac project (www.cocomac.org): Background, status, directions*  
15:45-16:05 Jan G. Bjaalie, Univ. of Oslo: *Databases of brain systems and connectivity: FACCS -- Functional Anatomy of the rat Cerebro-Cerebellar System*  
16:05-16:25 Trygve B. Leergaard, Univ. of Oslo: *Spatial distribution of promoter gene activity in the mouse brain: Computerized imaging for investigation of disease models*  
16:25-16:45 Finn Årup Nielsen, National Hospital, Copenhagen: *Databasing molecular imaging*  
16:45-17:15 COFFEE BREAK  
17:15-17:35 Ulla Ruotsalainen, Tampere Univ. of Technology: *Questions in archiving and exchange of emission tomography research data*  
17:35-17:55 Anu Kivimäki, Tampere Univ. of Technology: *Monte Carlo study of automated MRI-PET image registration with brain images having pathological defects*  
17:55-18:15 Ricardo N. Vigário, Helsinki Univ. of Tech.: *Blind source separation of MEG and fMRI*  
18:15-18:35 Pål G. Larsson: Norwegian Nat. Centre for Epilepsy, Oslo: *Utilisation of neuroinformatics in clinical neurophysiology*  
19:00 DINNER

## Sunday, September 19th

- 08:00 BREAKFAST
- 09:00-09:45 Henry Markram, EPFL Lausanne: *Reconstructing neocortical microcircuits*
- 09:45-10:05 Johan Storm, Univ. of Oslo: *Computational and experimental analysis of intrinsic electrical signalling in single hippocampal pyramidal neurons*
- 10:05-10:30 COFFEE BREAK
- 10:30-10:50 Tiina Manninen, Tampere Univ. of Technology: *Simulation models of signal transduction in neurons*
- 10.50-11.10 Hans Liljenström, SLU, Uppsala: *Density dependent effects in neural systems - from ion channels to networks*
- 11:10 **Discussion, closing of meeting**
- 12:00 LUNCH

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# A large-scale biophysically detailed cortical attractor network model with a mini- and hypercolumnar organization

Anders Lansner<sup>a</sup>, Mikael Lundqvist<sup>b</sup>, and Alexander Kozlov<sup>b</sup>

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Abstract attractor network models of cortical associative memory have been extensively explored and analysed theoretically [1]. Continuous learning connectionist type networks with adapting units and synaptic depression have demonstrated the real-time palimpsest memory capabilities of such networks and their ability to serve as long-term as well as a fast learning and forgetting working memory [4]. Network models with biophysically detailed neurons and synapses have indicated that the attractor memory paradigm is biologically reasonable [3]. In order to gain a deeper insight into the biological plausibility of recurrent attractor network models of cortex we have extended a previous network model of cortical layers II/III based on a horizontal network of minicolumns to one that is also modularised in terms of hypercolumns (macrocolumns). The extended model includes pyramidal cells together with two different kinds of inhibitory interneurons (basket cells and double bouquet cells). This structure is based on observed cortical microcircuitry and modularity, most prominent in primates (see e.g. [2]). Some initial results regarding attractor memory properties, dynamics etc. of such a network model will be presented and discussed.

- [1] Amit, D. (1989). "Modeling Brain Function: The world of attractor neural networks". New York, Cambridge University Press.
- [2] DeFelipe, J., L. Alonso-Nanclares and J. I. Arellano (2002). "Microstructure of the neocortex: Comparativ aspects." *J Neurocytology* **31**: 299-316.
- [3] Fransén, E. and A. Lansner (1998). "A model of cortical associative memory based on a horizontal network of connected columns." *Network: Computation in Neural Systems* **9**: 235-264.
- [4] Sandberg, A., A. Lansner and J. Tegnér (2003). "A working memory model based on fast Hebbian learning." *Network: Computation in Neural Systems* **14**: 789-802.

# **Ionic mechanisms in Working Memory and Information Processing in the Entorhinal Cortex of the Medial Temporal Lobe**

*Erik Fransén*

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Our learning and memory system has the challenge to work in a world where items to learn are separated in space and time. Using the information extracted by the perceptual systems, the learning system must select and combine information. Both these operations may require a temporary storage where i.e. evaluation of significance or statistical correlation may be performed. This work builds on the common hypothesis that hippocampus and subicular, entorhinal and parahippocampal/posrhinal areas are essential for these functions. We bring up two examples of models, one [1] modeling *in vivo* and *in vitro* data from delay match-to-sample working memory experiments of entorhinal cortex layer II [2], the second one [3] modeling slice data from entorhinal cortex layer V [4] showing cellular "integrator-like" intrinsically generated stable graded levels of spiking activity. On the basis of lesions and imaging studies, it has been suggested that while working memory operations in prefrontal cortex may be important for monitoring familiar stimuli, the medial temporal lobe may be more important for matching and maintenance of novel stimuli [5]. Indeed, the intrinsic persistent activity displayed by these layer V cells represent an ideal mechanism for sustaining information about a novel stimulus for memory-guided responses in behavioral tasks. In both modeling cases we discuss how cationic currents might be involved and relate their activation by calcium, kinetics of activation and inactivation as well as pharmacology to behavioral and cellular experimental results.

- [1] E. Fransén, A. Alonso, M. Hasselmo *J Neurosci* **22** 1081-97 (2002)
- [2] T. Otto, H. Eichenbaum *Behav. Neurosci.* **106** 763-76 (1992)
- [3] E. Fransén, A. Egorov, M. Hasselmo, A. Alonso *Soc Neurosci Abstr* **29** 557.6 (2003)
- [4] A. Egorov, B. Hamam, E. Fransén, M. Hasselmo, A. Alonso *Nature* **420** 173-8 (2002)
- [5] C. Stern, S. Sherman, B. Kirchhoff, M. Hasselmo *Hippocampus* **11** 337-46 (2001)

# Temporal computation by biochemical networks – classical conditioning and reinforcement learning

Jeanette Hellgren Kotaleski<sup>a</sup>, Mia Lindskog<sup>a</sup> and Kim T Blackwell<sup>b</sup>

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Information processing, such as temporal computation, may take place in the biochemical signaling pathways activated by different synaptic inputs [1,2]. This might also be associated with potentiation or depression of the synaptic responses. We have explored the possible role of temporal computation in two biochemical networks known to be involved in learning in the brain: classical conditioning of the eyeblink response in the cerebellum, and reinforcement learning in the basal ganglia.

In eyeblink conditioning a specific temporal interval is required between the conditioned (CS) and unconditioned stimulus (US) for learning to occur. This is associated with an increase in Protein Kinase C (PKC) activation in Purkinje cells. To evaluate to what extent biochemical interactions within the Purkinje cell may explain this temporal sensitivity, a model of PKC activation by calcium, diacylglycerol (DAG) and arachidonic acid (AA) was developed. Simulations predicted increased PKC when CS preceded US by 0.1-3 s [3].

To begin to explore the requirements for learning in the basal ganglia, as during reinforcement learning, we have developed a model of the biochemical pathways activated by glutamate and dopamine in Spiny Projection Neurons in the striatum [4].

The intracellular phosphoprotein DARPP-32, is an important signaling molecule in this respect because of its role in modulating neuronal excitability as well as synaptic strength. The phosphorylation state of DARPP-32 is regulated by e.g. glutamate and dopamine. The biochemical pathways leading from these neurotransmitters to DARPP-32 phosphorylation have been delineated, but the interactions between them is not well understood. To investigate the dynamics of the interactions, and the effect of temporal pattern of stimulation on DARPP-32 modulation, we have simulated the biochemical reactions involved in the phosphorylation of DARPP-32. Results show that the activation of DARPP-32 needs either a sustained stimulation or repetitive short stimulations of the dopamine type 1 receptor (D1). Pairings of D1 stimulation with calcium elevation (such as caused by NMDA stimulation), with different delays in between, were investigated and compared with reinforcement learning scenarios.

[1] U.S. Bhalla, *J.Comput Neurosci* **13** 49-62 (2002)

[2] U.S. Bhalla, *J.Chem Neuroanat* **26** 81-86 (2003)

[3] J. Hellgren Kotaleski, *et al.*, *Integr. Physiol Behav Sci*, **37** 265-292 (2002)

[4] M. Lindskog, *et al.*, *Soc Neurosci Abstract* (2002)

# Neocortical Circuitry as a Dynamical Spin Glass

*John Hertz, Alex Lerchner, and Mandana Ahmadi*

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Neocortical circuitry is highly connected, and, at the sub-mm length scale, quite random. This makes it an ideal system to study using methods from mean-field spin glass theory. One thus reduces the network problem to a single-neuron one with a Gaussian noisy input, the mean and correlations of which have to be determined self-consistently from the neuron's firing statistics. This reduction can be performed for any kind of model neuron and model synapse; in the investigations I will describe we used leaky integrate-and-fire ones and the simplest synaptic model: a presynaptic spike causes a brief current pulse, of fixed strength, to be injected into the postsynaptic neuron. Because of the asymmetry of the synaptic connections, the retarded self-interaction present in the spin glass problem is absent. Moreover, this asymmetry also violates detailed balance, so equilibrium statistical mechanics can not be used for this "dynamical glass" system.

A simple ansatz for the form of the correlation function can describe general states with asynchronous irregular firing. While the firing rates in such a state can be found to a very good approximation by simple algebra, the full problem, including calculating the correlations self-consistently, requires numerical treatment. From our solution, we have been able to see how the observed features of the firing statistics depend on single-neuron and synaptic parameters. In particular, for suitable parameters, the calculated Fano factor (spike count variance/mean spike count) is greater than 1 and increases with firing rate, in agreement with experiments in primary visual cortex. We have extended the model in several ways: (1) to include improved models of the synapses, and (2) to couple a number of different such networks together to model a slightly bigger piece of cortex, in a way based on the known anatomy of primary visual cortex.

# Measuring and modelling cortical population dynamics from laminar-electrode data

*Gaute T. Einevoll<sup>1</sup>, Klas Pettersen<sup>1</sup>,  
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Non-invasive imaging methods such as fMRI, PET, EEG and MEG have provided lots of information about the brain at the systems level. However, the spatial and/or temporal resolutions of these techniques are limited, and it has been difficult to firmly link the observed systems-level activity with electrical activity of the underlying neuronal circuitry. On the microscopic level single-unit electrophysiological recordings have (combined with mathematical modeling) for more than half a century given significant insights into the function of single neurons. However, attempts at "bridging the gap" between the microscopic single-unit and the macroscopic systems level have so far had limited success. Multi-electrode recordings and imaging with voltage-sensitive dyes are maybe the two most promising experimental techniques for studying neural circuits at the mesoscopic level (~0.1-1 mm) since they measure electrical activity directly.

In laminar-electrode recordings of cortical activity the extracellular potential is measured at ~20 different cortical depths with a typical spacing of 50-100  $\mu\text{m}$ . The high-frequency part (Multi-Unit Activity; MUA) of such data reflects firing of action potentials in cortical populations, while the low-frequency part (Local Field Potential; LFP) are thought to be dominated by the slower dendritic processing of synaptic inputs. The mathematical analysis of such data has been limited to standard statistical methods such as principal components analysis where the interpretation of the data in terms of firing activity in cortical populations and their synaptic connections is difficult.

We present a new scheme for analysis of laminar-electrode data where physiological constraints are explicitly incorporated in the mathematical model: The MUA-data is modeled as a sum over contributions from firing activity of several cortical populations, while the LFP-data is assumed to reflect the dendritic processing of the synaptic inputs stemming from this firing activity. The method is applied to stimulus-averaged laminar-electrode data from anesthetized rat barrel cortex following single-flick whisker stimulation.

The presented example data, comprising numerous experimental repetitions with 27 different stimulus flick conditions, seems to be well accounted for by a model with four cortical populations: one granular, one supragranular and two infragranular. From the optimization procedure the temporal ordering of stimulus-evoked firing activity in the populations is predicted. We also obtain predictions for spatial LFP signatures following action-potential firing in the different populations. We interpret these signatures in terms of pre-calculated LFP-templates based on anatomically reconstructed model neurons [using the program package NEURON and Maxwell's equations], and predictions are made for the spatial organization of the synaptic connections between the cortical populations. Our results are compared with previous experimental findings.

# A sparse coding network learns both V1 receptive fields and topography from natural images

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The receptive fields of neurons in the primary visual cortex have been characterized as localized, oriented and bandpass, and neurons with similar position, orientation and frequency preferences are grouped together, forming a topographic map. Numerous neural network models have been proposed that learn some of these properties from natural image data, but to our knowledge no model has been able to learn all these properties.

Olshausen and Field [1] showed how the single principle of sparseness of a linear representation leads to realistic simple-cell receptive fields when trained on natural image data. We extend this model by seeking sparseness of local energies instead of linear outputs. This straightforward extension leads to a topographic representation in many ways similar to that observed in V1, while maintaining realistic receptive fields.

In addition to emerging the topography, the same principle also helps explain the principal properties of complex cells. Most local energies behave in many ways similar to complex cells: they tend to show phase and (limited) shift invariance, in addition to orientation and frequency selectivity. This supports the notion that the topography seems to define the pooling into complex cells.

[1] Olshausen and Field, *Nature* **381** 607-609 (1996)

# Simulating Large Neuronal Networks with NEST

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Because of the immense difficulties involved in observing neuronal activity in an intact brain, experimental data exists mostly for single or small numbers of neurons, or for very large populations. As a consequence, scientists increasingly employ theoretical and computational methods in order to assess the dynamical properties of individual and populations of neurons and to come up with testable predictions. *Computational neuroscience* is thus a fast growing research field, dedicated to the investigation of the nervous system with the help of computer simulations.

Computational neuroscientists use simulation to investigate models of the nervous system at functional or process levels. Great effort has been devoted to developing appropriate simulation tools and techniques, and several systems for the simulation of single neurons or small networks are available today (Neuron, Genesis [1,2]). Beyond facilitating simulations in the first place, these models allow researchers to share models across lab boundaries, allowing for more productive collaborations.

Recently there has been growing interest in large scale simulations, involving tens of thousands of neurons and upward of 100 million synapses, while maintaining an appropriate degree of biological detail. Entirely new simulation software is required for the efficient simulation of these networks.

Within the framework of the Neural Simulation Technology Initiative, we have developed the NEST simulator as a tool for large network simulations [3]. NEST provides support for the construction of hierarchical networks, so that brain architecture (laminae, columns, nuclei) can be represented directly in NEST. The parallel design of the simulation core permits the efficient simulation of very large networks ( $10^5$  neurons,  $10^9$  synapses) [4]. NEST has recently been released to the community under an open source license [5].

We will present the key features of the NEST simulator as a simulation tool, and will demonstrate its application to the simulation of the early visual pathway.

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[1] M.L. Hines and N.T. Carnevale, *Neural Comput* **9** 1179-1209 (1997).

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[4] A. Morrison *et al.*, Advancing the boundaries of high connectivity network simulation with distributed computing, submitted (2004).

[5] <http://www.nest-initiative.org>.

## The CoCoMac project ([www.cocomac.org](http://www.cocomac.org)): Background, status, directions

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The CoCoMac project (*Collation of Connectivity data of the Macaque brain*) [1, 2] aims to reconstruct the large scale wiring diagram of the primate brain from the fractionated anatomical tracing data that have been published over the last 50 years. Identification of brain structures is based on microstructural delineations, which are independent of spatial coordinate systems [3]. The database is freely accessible via the internet [2] and provides primary data from the literature, processed connectivity data and extensive mapping information based on 390 publications with a focus on the cerebral cortex of adult macaques. Current work extends the database to subcortical structures, provides tools for visualization and analysis [2], and investigates the links between structural and functional connectivity [4,5]. Major future directions include links with other data resources including ontologies and coordinate-based atlases, extensions to additional data modalities, such as receptor [6] and microcircuitry data [7], and the application of connectivity data to computer simulations [8] and systems analyses [4,9], particularly in the context of functional imaging data [10].

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## **Databases of brain systems and connectivity: FACCS -- Functional Anatomy of the rat Cerebro-Cerebellar System**

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Integration of the dispersed and complicated information arrays from the brain that will be needed to build new knowledge is demanding and will require new approaches. The present project addresses some of the fundamentals of this challenge by producing a coordinate based digital atlas and database for selected regions of the rat brain. It employs 1) automatic and semi-automatic data acquisition and software for 3-D reconstruction, 2) a relational database (Oracle) in the context of a three tier architecture based on J2EE infrastructure, and 3) a suite of associated Java tools. The database presently includes connectivity data from a large number of experimental animals, describing detailed three-dimensional topography in one of the largest projection systems in the brain, the cerebro-ponto-cerebellar system. All data were transformed to a standardized coordinate system, to facilitate across-animal comparisons. The database allows users to search for corticopontine and / or pontocerebellar projection data, freely combine data from different animals, and visualize and analyse the chosen data sets in Java and Java3D based viewers. Graphic search tools allow ‘in computo’ experiments to be performed. The long term goal is to expand the database to other brain regions and systems, and to include other data categories.

## **Spatial distribution of promoter gene activity in the mouse brain: Computerized imaging for investigation of disease models**

*Jana Boy<sup>1</sup>, Trygve B. Leergaard<sup>2</sup>, Thorsten Schmidt<sup>1</sup>, Marc Niwar<sup>1</sup>, Ulrike Bichelmeier<sup>1</sup>, Silke Nuber<sup>1</sup>, Francis Odeh<sup>2</sup>, Carsten Holzmann<sup>3</sup>, Stefan Haas<sup>4</sup>, Stanley Prusiner<sup>5</sup>, Andreas Wree<sup>4</sup>,  
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The ability to turn the expression of particular genes on or off represents a powerful tool for the investigation of many biological processes, from complex developmental biology to the pathophysiology of disease. In binary transgenic systems, such as the tetracycline dependant regulatory system (TetR) developed by Gossen and Bujard [1], specific target genes may be activated or silenced by the interaction of an effector transgene on a target transgene. In order to construct animal disease models in which the responder gene expression is targeted to tissues known to be afflicted in the disease in question, detailed knowledge about the spatial distribution of promoter activity is needed. We have conducted a detailed mapping of promoter location throughout the brain of double transgenic mouse lines (Prp/LacZ and CamKII/LacZ) by visualizing promoter activity using LacZ reporter gene and X-Gal staining in serial sections from whole brains. To facilitate the assignment of anatomical localization to the data, section quality, angle and position was carefully controlled. High-resolution mosaic images of sections were obtained through a Olympus Bx52 microscope, equipped with a high-precision Märzhäusser motorized stage, an Optronics MicroFire digital camera, and the Neurolucida software package. With use of this system, mosaic images (consisting of as much as 136 individual frames) were constructed from entire coronal brain sections (~ 150 x 100 mm) using a 20 x lens. The resulting images (tiff files of 300-400 MB) provided a nearly seamless overview of entire sections with sufficient resolution to distinguish individual cell morphology. Preliminary analyses show that promoter induced reporter gene expression is heterogeneously distributed in the brain, suggesting that these promoter lines may be suitable for generating inducible animal disease models for several neurodegenerative diseases.

# Databasing Molecular Neuroimaging

*Finn Årup Nielsen*

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Positron emission tomography allows for molecular neuroimaging, e.g., for mapping human neurotransmitter systems. Many such studies are performed as either "voxel-based" or "region-based". Voxel-based studies are usually reported with reference to the Talairach stereotaxic system [1] and appear with tables listing "hot spot" foci indicating the centers of areas with significant difference between two groups of scans. The voxel-based approach is widely used in the cognitive functional neuroimaging literature. Databasing such studies has been advanced with the BrainMap database (Research Imaging Center, San Antonio, TX). The newest version of this database contains data from over 500 studies, but the interface only allows for preprogramed access to the data. To allow for a more flexible access we have constructed the Brede database which presently records data from 126 studies. Apart from cognitive studies the Brede database also contains data from molecular neuroimaging studies. The experiments in the Brede database are associated with items in an ontology. The ontology contains items for, e.g., cognitive functions and neuroreceptors. Some of the items are linked with corresponding MeSH terms, items from SenseLab (<http://senselab.med.yale.edu/-senselab/>) and other biomedical databases. The items are organized in a directed graph (a causal network) with the most general concepts (e.g., "neuroreceptor") at the roots of the graph, while more specialized concepts (e.g., the 5-HT<sub>2A</sub> receptor) are at the leafs. The representation of the hot spots centers in standardized coordinate space together with the ontology enables the statistical modeling of the distribution of the Talairach coordinates conditioned on, e.g., function and neuroreceptor type. So far we have implemented a line of multivariate analysis methods as well as volume-based similarity metrics that work on these distributions [2].

Only few molecular imaging studies are analyzed and reported with respect to the voxel-based Talairach system. Most studies appear as region-based where specific variables, such as the "binding potential", are reported for a series of brain regions. The regions for which variables are reported will typically vary between studies. To handle this variability we have constructed a second ontology for the description of brain regions. When results from region-based studies are entered they are annotated with items from this ontology. Current development focuses on building tools for the analysis of region-based studies and their integration with the voxel-based studies.

The published database is available as XML files in the Brain Neuroinformatics Toolbox and on the Internet on the address <http://hendrix.imm.dtu.dk/services/jerne/brede/>. The Internet edition also features results from automated web-page generation.

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# Questions in archiving and exchange of emission tomography research data

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Emission tomography, positron emission tomography (PET) and single photon emission tomography (SPECT), are very important methods for brain research and development of pharmaceuticals for neurological disorders. With these imaging methods it is possible to investigate metabolic functions in brain and other organs, but especially interesting is the possibility to have insight in the regional receptor occupancy of a tracer in brain. The image data can be analyzed quantitatively with PET. Although these imaging methods are very interesting they also produce some problems for archiving and data exchange because of their special nature. The image content varies not only between individuals but also within an individual in different acquisitions and especially during medication.

The emission tomography data is originally collected and saved as measurement profiles of radioactivity. For research purposes the data is mostly collected as time sequence scans. The measurement profiles are reconstructed as images showing the distribution of the tracer during each measurement time-frame. The final result is then calculated either regionally or through the whole image with physiological models to end up with biologically meaningful values like blood flow, glucose metabolism or receptor density. If the archiving of the data is based on images, as it is mostly for clinical purposes, there are a lot of limitations when comparing data from different research groups or in multi-center pharmacological studies because:

1. *Initial corrections for the data are different (scatter correction, body movement)*
2. *Image reconstruction methods are varying (FBP, OSEM, MRP)*
3. *Image registration to anatomical images are varying (AIR, surface based methods)*
4. *Model calculation methods are different, and the data, for which the model calculations have been done (region, pixel by pixel), is different*
5. *Definition of the interesting regions or structures is different for different purposes.*
6. *All the collected data can probably be re-used when the biological knowledge increases.*

All the methodology within the emission tomography imaging has been under constant development until now, and because of the development of new scanners it is obvious that there will be improvements also in the future. The cost and value of this kind of metabolic data is high, and it is often very difficult to collect at one imaging site enough data for certain research purposes. This leads to acute need for definition of data format for archiving and exchange. At the moment there are two realistic possibilities either to store the data as raw data (sinograms and other measurements) or as physiological parameters calculated from the data together with the tools, which were used. The latter would lead to less data but the tools should be in open use and a lot of automation should be included in the analysis, especially in the regional analysis. The raw data would be optimal for archiving because the processing of the data could be done always with the newest methods available for the certain purpose. With this approach the amount of the data is huge and problems with the various data formats can make the analysis difficult. Both of these two approaches would benefit of development of automatic analysis tools and opening of the data structures.

# Monte Carlo Study of Automated MRI-PET Image Registration with Brain Images having pathological defects

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Different imaging modalities offer possibility to gather large amount of multidimensional functional and anatomical information from the brain for comparisons and statistical analysis. The comparison of images obtained from single subject using different imaging modalities requires that the images have been mapped to same space. One way to do the mapping is to register the functional images like positron emission tomography (PET) to anatomical image like Magnetic Resonance Image (MRI). Automated image registration (AIR) method is widely applied to this task [1]. To perform automatically the registration, the method should also work with different pathological situations. In this study the quantitative performance of AIR method in pathology is studied using Monte Carlo simulated FDG brain data.

For the evaluation of the automated MRI-PET image registration with pathological brain images we used realistic simulated data based on Zubal phantom and Monte-Carlo based simulation tool [2]. Numerical simulators are able to produce realistic phantom images where the ground truth is available and the performance of automated image analysis algorithms can be quantified. The Zubal phantom is based on a MR image from which it was created by manual segmentation. This allows us to use it as a base for rigid MRI-PET registration. The PET data was simulated based on F-18 labeled FDG. For testing of the performance of AIR method in pathology we generated images with three types of pathology (hypermetabolic tumor, epilepsy and hemisphere difference). We consider two cases where the orientations and positions of the brain were moved between MRI and PET images.

The results showed that AIR method managed to register the simulated MRI and PET images with good quality. The results for pathological cases were similar to healthy ones. Especially the translation parameters found by AIR were accurate. The maximum difference between found parameters and ground truth was around 1 mm, less than length of the voxel side. However, there were more relevant errors in the rotation parameters (around 1 degree). This could have meaning if we would be interested in a smaller brain structures. The competing strategy to registration could be to extract the volumes of interesting brain structures automatically and directly from PET images. We have tested the DM-DSM (deformable model with dual surface minimization) method for this task and we have achieved promising results [3]. The advantage of this strategy is that we do not need the anatomical image to define the position of the objects of interest.

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# **Blind source separation of MEG and fMRI**

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The problem of blind source separation (BSS) consists in extracting unknown source signals from their mixed observations. This is an important problem in the analysis of many different biomedical systems. With no a priori information on the mixing process or the nature of the sources, it is impossible to solve the BSS problem. Yet, it is often the case that we know the mixing to be approximately instantaneous and linear, and the sources to be independent. Then, it has been shown that independent component analysis (ICA) constitute a very suitable tool for such analysis.

This presentation, based on published work by the author, aims at illustrating the use of ICA and temporal decorrelation methods to solve the BSS problem in different biomedical data modalities. A first example will focus on the analysis of brain responses, evoked by multimodal stimuli, collected via magnetoencephalograms (MEG). We will further use these methods to the identification of cortical control of voluntary movements, which is evidenced through coherence couplings between MEG measured over the sensorimotor cortex and the surface electromyograms. On a last example, we will see preliminary results of the use of ICA to the analysis of functional magnetic resonance images (fMRI), collected during brain response to spoken texts.

# Utilisation of Neuroinformatics in Clinical Neurophysiology

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In presurgical work-up for epilepsy surgery a crucial point is to find the epileptic focus to a degree of certainty making brain surgery acceptable. The presurgical methods include seizure semiology, Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) and Electroencephalography (EEG). Due to small foci and fast cortical spreads, EEG is still the most important method. However, the method has a low spatial resolution, which to some extent also blurs the temporal resolution. This has driven the work of implementing new methods to increase the yield of the recordings. This talk will give examples of use of coherence calculations from scalp EEG to analyse connectivity at the macro level and the use of intralaminar recording during surgery to analyse local generation and spread of activity.

## Simulation models of signal transduction in neurons

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Computational Systems Biology (CSB) research group at Tampere University of Technology (<http://www.cs.tut.fi/sgn/csb/>) works on applications of signal processing, image analysis, and various computational and machine learning methods for the systems biology field, most importantly in functional genomics and cell signaling. CSB group develops modeling and simulation tools for studying complex biological phenomena. Computational studies of neuronal cell signaling is one of the research topics.

In this study, systems biological philosophy is employed to study the complex interactions of intracellular signaling on the behavior of single neurons. Signal transduction is mediating information between the cell membrane and various intracellular compartments in neurons. Specifically, changes in the localized concentrations of intracellular  $\text{Ca}^{2+}$  ions ( $[\text{Ca}^{2+}]_i$ ) in response to external or internal stimuli influence the neuronal signal transduction, including the effects on gene expression. We have a special interest in calcium-mediated protein kinase C (PKC) signaling which has been shown to be important in long-term potentiation and memory formation.

We utilize the database of Quantitative Cellular Signaling to obtain signal transduction models (<http://doqs.ncbs.res.in>; [1]). We derive the mathematical model for the PKC signaling pathway in neurons. The model is implemented in the GENESIS/Kinetikit neuronal simulator [2], which makes it possible to integrate the simulation models of signal transduction with the models of neuronal excitability [3]. To study the behavior of the PKC model,  $\text{Ca}^{2+}$ , arachidonic acid (AA), and diacyl glycerol (DAG) components of the model are perturbed with different kinds of functions which mimic the realistic stimuli for the PKC pathway [4]. In most cases studied, the model output follows the  $\text{Ca}^{2+}$  stimulus. However, we find that the larger the amplitudes of the AA and DAG stimuli, the clearer their effects on model output. Furthermore, sensitivity analysis is applied to study the variations in the values of model parameters to produce the desired output. In future, the results of the sensitivity analysis form the basis of simplifying the models as well as developing parameter estimation for signal transduction and neuronal models.

The present study is a part of the larger project in which we evaluate the performance and usability of simulation tools for biochemical networks using the PKC signaling pathway model as a test case [5].

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